Kent Lewandrowski *Editor*
Patrick M. Sluss *Associate Editor*

Utilization Management in the Clinical Laboratory and Other Ancillary Services

Springer

Editors
Kent Lewandrowski and Patrick M. Sluss

Utilization Management in the Clinical Laboratory and Other Ancillary Services

Editors

Kent Lewandrowski
Division of Laboratory Medicine Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

Patrick M. Sluss (Associate Editor)
Pathology Service Core Laboratories, Massachusetts General Hospital, Boston, Massachusetts, USA

ISBN 978-3-319-34197-2 e-ISBN 978-3-319-34199-6
DOI 10.1007/978-3-319-34199-6

Library of Congress Control Number: 2016955239

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

The rising cost of health care in the United States and most developed countries is creating increasing pressure to control medical care expenditures. This is true regardless of whether the payer is a government agency or a private sector insurance company. In the United States, millions of citizens lack health insurance altogether. These “self-pay” patients face financial ruin if they become seriously ill, and many must forgo even basic medical services including preventative care. The Affordable Care Act (ACA) of 2010 was intended to expand coverage for the uninsured and to reduce projected health-care expenditures by restructuring the way in which medical care was reimbursed. Previously the American health-care system was largely based on a fee-for-service arrangement wherein providers were paid for each unit of service. This encouraged hospitals and physicians to provide more care than was sometimes necessary and resulted in a misalignment of incentives between payers and the providers. As described in Chap. 1 , the ACA includes provisions to shift reimbursement from the traditional fee-for-service system that encourages increasing the volume of care to value-based contracts utilizing bundled payments for episodes of care (or even entire populations). The ACA also includes quality metrics and risk sharing arrangements to better align the incentives between payers and providers. Whether the intended outcomes of the ACA are eventually realized or not will take some years to be determined. Regardless of the eventual fate of the ACA, the pressure to contain health-care costs will continue to increase. Similar pressures will be experienced in other developed countries including those with largely government-financed health-care systems.

Ancillary services including the clinical laboratory, radiology, and pharmacy are common targets of utilization management programs. This is because these services are frequently perceived to be overutilized and because they can be easily quantified in terms of the units of service provided and their attendant costs. The available menu of laboratory tests continues to expand including the rapid introduction of high-cost genetic and molecular diagnostic assays. As well, the number of pharmaceuticals and radiological procedures is also steadily expanding with many new high-cost drugs and scans becoming available. The growth in technologies available to medical providers will continue to drive increases in health-care costs. When this is

combined with the aging populations in most developed countries and increasing life spans, the prospects for relentless and potentially ruinous increases in the cost of medical care are drawing increasing concern.

There are a number of approaches that can be employed to reduce health-care expenditures including:

1. Reducing reimbursements to providers for individual units of service

2. Arbitrarily reducing (or delaying) the amount of care that is provided

3. Improving the efficiency of the health-care system such that units of care can be provided at a lower unit cost

4. Implementing evidence-based utilization management programs to reduce or eliminate unnecessary care

There is an extensive literature on utilization management of ancillary services as is illustrated by the bibliographies accompanying many of the chapters in this book. However, the literature has been spread across multiple journals and other published sources spanning several decades. It is therefore difficult for individuals who are exploring utilization management initiatives to compile and assimilate what has been previously published as a starting point for implementing a utilization management program. We realized the need for a textbook dedicated to providing medical professionals with a concise but comprehensive review of utilization management in the clinical laboratory. We also chose to include chapters on utilization management in the pharmacy and in radiology. One chapter provides an international perspective Canada. In an effort to achieve as broad a representation of the topic as possible, we asked a number of colleagues to contribute chapters reflecting their own expertise and personal experiences. The chapters included in the book are as follows:

"Health-Care Reform and Its Impact on Medical Reimbursement"

"Utilization Management in the Clinical Laboratory: An Introduction and Overview"

"Effective Governance Structure and Management of Utilization Programs"

"Informatics and Decision Support in Utilization Management"

“Utilization Management Employing Test Interpretations and Algorithms”

“Calculating Costs and Savings in Utilization Management”

“Benchmarking and Management Metrics in Utilization Management”

“Laboratory Formularies”

“Utilization and Other Resource Management in Clinical Chemistry”

“Utilization Management in Routine Hematology”

“Patient Blood Management”

“Utilization Management of Blood Derivatives”

“Utilization Management in the Clinical Microbiology Laboratory”

“Utilization Management in a Large Community Hospital”

“Utilization Management: The Role of Reference Laboratories”

“Utilization Management in Anatomic Pathology”

“Utilization Analysis in Hematopathology”

“Test Utilization: Controlling Cost in Reference Laboratory Testing”

“Utilization Management of Genetic Testing”

“The Use of Physician Profiling and Prior Approval (Gatekeeping) in Utilization Management in the Clinical Laboratory”

“Test Utilization: The Essential Role of the Clinical Consultant”

“The Role of the Genetic Counselor in Utilization Management”

“Utilization Management in Radiology”

“Strategies for the Clinical and Financial Management of Drug Utilization”

“Laboratory Utilization Management in Canada”

“Utilization Management Initiatives That Can Be Imported into Healthcare Systems”

We wish to thank the authors for their willingness to contribute to this special edition and hope that the information contained in the articles is both educational and of practical use to those who are engaged in utilization management activities.

Kent Lewandrowski
Patrick M. Sluss
Boston, MA, USA

Contents

About the Editor and Contributors

About the Editor

Kent Lewandrowski, MD

is the director of Pathology, Laboratories and Molecular Medicine, and associate chief of pathology at the Massachusetts General Hospital. He is also director of the hospital point-of-care program and the quality chair of the Department of Pathology. He is a professor at Harvard Medical School with research interests in the evaluation of point-of-care technologies and outcomes studies concerning implementation of point-of-care testing. Dr. Lewandrowski was trained in anatomic and clinical pathology at the Massachusetts General Hospital and has been on the staff of the Department of Pathology since 1991. He is also editor in chief of the medical journal *Point of Care: The Journal of Near Patient Testing Technologies* .

Patrick M. Sluss, PhD, MA

is one of the five associate directors of the central laboratory core that provides roughly 11 million test results per year for clinicians at the Massachusetts General Hospital. He also directs the clinical pathology laboratory at Spaulding Rehabilitation Hospital and is an Associate Professor of Pathology at Harvard Medical School. Dr. Sluss received his PhD in Physiology and Biophysics from the Colorado State University (1981) and completed his NIH postdoctoral training in Biochemistry at Albany Medical College in New York (1984). Dr. Sluss joined the faculty at Massachusetts General Hospital in 1991. His clinical and research interests have focused on the development and clinical implementation of methods for the measurement of protein and steroid biomarkers.

Contributors

Rodney C. Arcenas
Microbiology, Molecular Microbiology Laboratory, Department of Clinical Pathology, Memorial Regional Hospital, Pathology Consultants of South Broward, LLP, Hollywood, FL, USA

Jason Baron
Department of Pathology, Massachusetts General Hospital, Boston, MA, USA
Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

Ida Bixho
Department of Pathology and General Internal Medicine/Primary Care, Brigham and Women's Hospital, Boston, MA, USA

Evan M. Bloch
Department of Pathology Transfusion Medicine Division, Johns Hopkins University School of Medicine, Baltimore, MD, USA

John A. Branda
Department of Pathology, Massachusetts General Hospital, Boston, MA, USA

Kelly Branda
Informed DNA, St. Petersburg, FL, USA

Garry Choy
Department of Radiology, Massachusetts General Hospital, Boston, MA, USA

Jessie H. Conta
Department of Laboratories, Seattle Children's Hospital, Seattle, WA, USA

Elizabeth M. Van Cott
Massachusetts General Hospital, Boston, MA, USA

Jane A. Dickerson
Department of Laboratories, Seattle Children's Hospital, Seattle, WA, USA

Anand Dighe
Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Christopher Fortier
Department of Pharmacy, Massachusetts General Hospital, Boston, MA, USA

Brian Jackson
ARUP Laboratories, University of Utah, Salt Lake City, UT, USA

Cyril Jacquot
Departments of Laboratory Medicine and, Hematology, Children's National Medical Center, Washington, DC, USA

Petr Jarolim
Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Stephan Kadauke
Department of Pathology, Massachusetts General Hospital, Boston, MA, USA

Frederick L. Kiechle
Department of Clinical Pathology, Memorial Regional Hospital, Pathology Consultants of South Broward, LLP, Hollywood, FL, USA

Annette S. Kim
Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA

Kent Lewandrowski
Division of Laboratory Medicine, Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Christina M. Lockwood
Laboratory Medicine, University of Washington, Seattle, WA, USA

Stacy E. F. Melanson
Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA

Claudio A. Mosse
Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, TN, USA

Christopher Naugler
Departments of Pathology and Laboratory Medicine and Family Medicine, Cumming School of Medicine, University of Calgary, C414, Diagnostic and Scientific Centre, Calgary, AB, Canada

Valerie L. Ng
Department of Laboratory Medicine, School of Medicine, University of California, San Francisco, San Francisco, CA, USA
Department of Laboratory Medicine and Pathology, Alameda Health System/Highland Hospital, Oakland, CA, USA

Andy Pulvemacher
University of Wisconsin Hospital and Clinics, Madison, WI, USA

Prabashni Reddy
Center for Drug Policy, Partners Healthcare, Boston, MA, USA

Eric S. Rosenberg
Department of Pathology, Massachusetts General Hospital, Boston, MA, USA

Joseph Rudolf
Division of Laboratory Medicine, Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Alexander Ryu
Department of Radiology, Massachusetts General Hospital, Boston, MA, USA

Adam C. Seegmiller
Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, TN, USA

Aaron C. Shaver
Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, TN, USA

Patrick M. Sluss
Pathology Service Core Laboratories, Massachusetts General Hospital, Boston, MA, USA

Elizabeth Stewart
Department of Medicine, Alameda Health System/Highland Hospital, Oakland, CA, USA

Nathan Thompson
Department of Pharmacy, John Hopkins Medicine, Baltimore, MD, USA

Luis Ticona
Department of Medicine, Massachusetts General Physician Organization, Massachusetts General Hospital, Boston, MA, USA

Jeffrey S. Warren
Department of Pathology, University of Michigan Medical School, Ann Arbor, MI, USA

Alan H. B. Wu
Department of Laboratory Medicine, University of California, San Francisco, CA, USA
Clinical Laboratories, San Francisco General Hospital, San Francisco, CA, USA

Daniel Dante Yeh
Trauma Emergency Surgery Surgical Critical Care, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_1

1. Health-Care Reform and Its Impact in Medical Reimbursement

Luis Ticona[1]

(1) Department of Medicine, Massachusetts General Physician Organization, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA

Luis Ticona
Email: lticona@partners.org

Keywords Health-care reform – Accountable care organization – Health policy – Payment reform – Medical reimbursement

Health-care costs in the USA grew at an alarming rate during the 1990s, doubling from $858 billion dollars in 1992 to $1638 billion dollars in 2002. By 2012 costs reached $2793 billion dollars [1], peaking at approximately 17 % of the gross domestic product (GDP). This exceeded the proportion of GDP spent by all other industrialized countries, with the Netherlands a far second at 11.8 % of its GDP in 2012 [2]. Currently, the USA spends $8713 dollars per patient per year, more than twice the average of most industrialized countries in the world as shown in Fig. 1.1 [3].

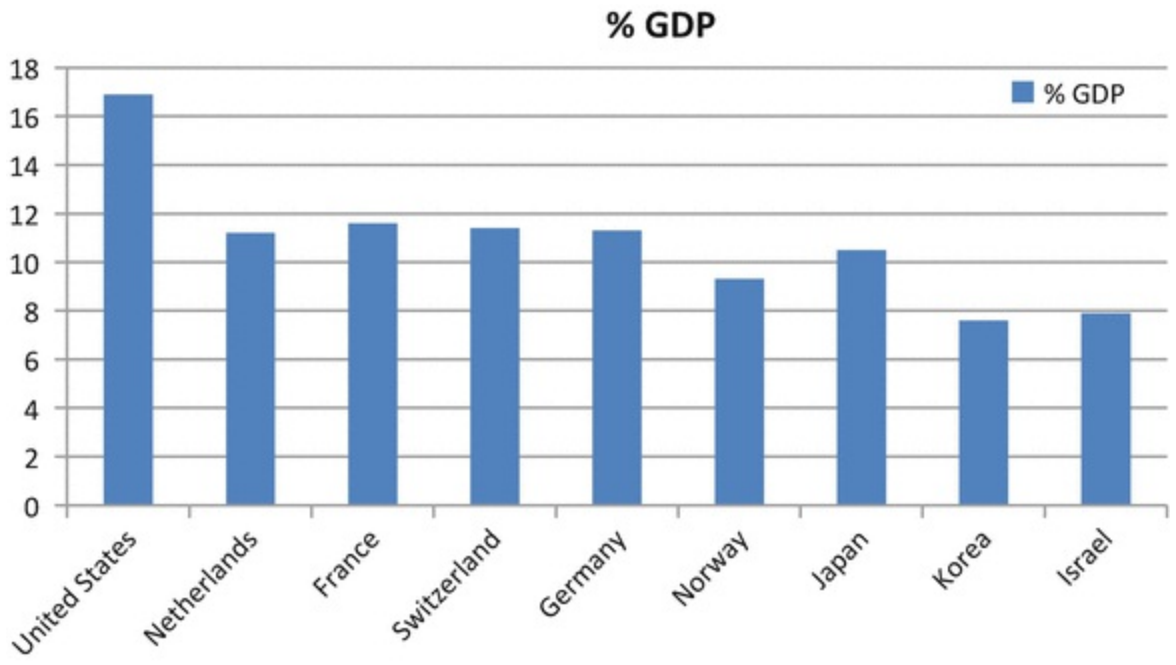


Fig. 1.1 Health expenditures as a percentage of gross domestic product (GDP) in 2014 in different countries. *X*-axis shows the percent of GDP. *Y*-axis shows different countries. *Source*: Organization for Economic Cooperation and Development (OECE)

Policy-makers noted growing US health-care costs in the 1970s, but a robust economy could withstand, and at times support, this rate of growth. By the early 2000s, however, the rate of health-care spending growth sharply outpaced overall GDP growth. Coupled with an economic recession that decreased private sector revenue and available public funding, financing the US health-care system became an almost permanent fixture in the contemporary political discourse. This increased scrutiny continues to be relevant; the growth of health-care costs continued to outpace overall GDP growth until recently, inciting fears of mounting government debt, crowding out within the public sector, and increasing cost-shifting to individuals [4].

Throughout the late 1990s and early 2000s, amidst mounting evidence of high variability in health outcomes and services across geographic, racial, and socioeconomic groups in the USA, the health-care sector primarily focused on the standardization and delivery of high-quality care [5]. This often translated into the development of screening systems for primary and secondary prevention of chronic disease and avoidable outcomes. Moreover, as the tools and evidence to diagnose, cure, and manage acute and chronic conditions increased in number, health-care utilization increased. Payment schemes , for the most part, accommodated this growth in utilization through

fee-for-service models developed through imprecise actuarial and pricing methodology.

It is important to note that during this time, the number of hospital beds was decreasing, the number of physicians remained stable, and the number of doctor visits per capita was lower than in most industrialized countries: trends that continue to this day [6]. Nevertheless, overall costs continued to rise through this decade, with hospital-associated costs, often linked with expensive drugs and procedures, accounting for the majority of this growth [7]. This pattern likely reflected the increased prices negotiated by hospitals and physician organizations, often driven by the increased fixed costs of technology acquisition (MRI machines, CT scanners, catheterization facilities, etc.), subspecialty care, or purely strategic maximization of profit, rather than a pure increase in utilization for all patients. For example, Fig. 1.2 shows the variation in cost for total hip replacement in different regions and localities across the USA [8]. The cost varies by a factor of fourfold depending on the location in which the service is provided, without discernible differences in patient demographics or quality outcomes.

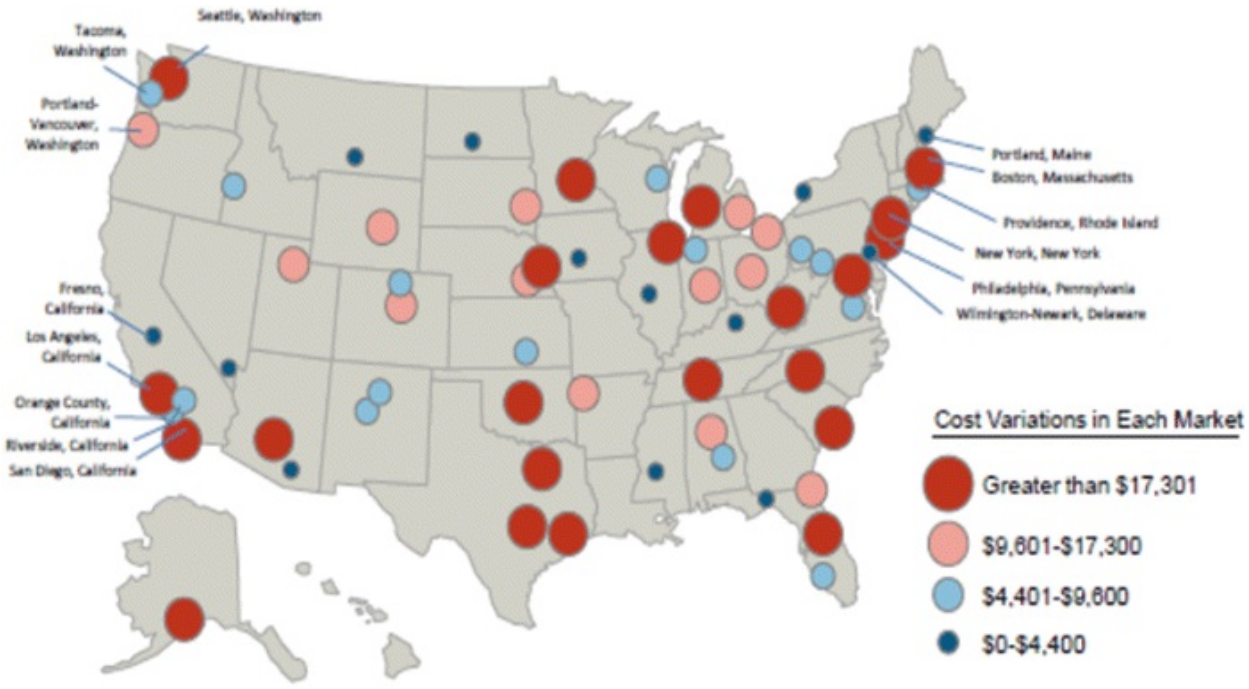


Fig. 1.2 Variation in cost for hip replacement in different regions and localities. *Colored circles* show the cost (to the payer) of the procedure in different areas of the USA. *Source*: ©2015 Blue Cross Blue Shield Association/Blue Health Intelligence

The pressing need for improved quality overshadowed rising costs, and health delivery systems responded by investing more resources in the development of programs to address the identified gaps in clinical care. But the fee-for-service system also created an incentive for providers to increase their patient throughput, provide more services to increase their margins, and consolidate to increase their bargaining power to negotiate higher prices with payers while growing their market share. Even as Medicare reduced payments to physicians during the late 1980s and early 1990s, the majority of these costs were passed on to private payers in the form of increased negotiated prices, which subsequently led to increased insurance premiums [9]. Widespread cost-containment measures in the form of managed care were often overlooked during this time as a reaction to previous efforts with health management organizations (HMOs) by the private sector. HMOs were widely considered failures after the enactment of restrictive practices led to longer wait times, service denial, very narrow networks, and prior authorizations for certain pharmaceuticals and procedures causing outcry and derision from patients and providers.

US health-care outcomes remained unevenly distributed even after a large increase in spending. By the end of the 2010s, there was higher in-hospital mortality for heart attacks and strokes when compared with that of other industrialized nations but lower rates of cancer mortality [7]. Several other important outcomes were also lower or equivalent to nations that spent less money on health care. Moreover, steep-patient level cost variability, underscored by Fig. 1.3 [10], became an organizing principle of health-care reform [11]. Current projections forecast health costs that will continue to increase, approaching 20 % of GDP by 2025 [12] due to the aging US population, the increasing burden of chronic disease and obesity, and the increasing availability and number of high-cost pharmaceuticals and medical technology.

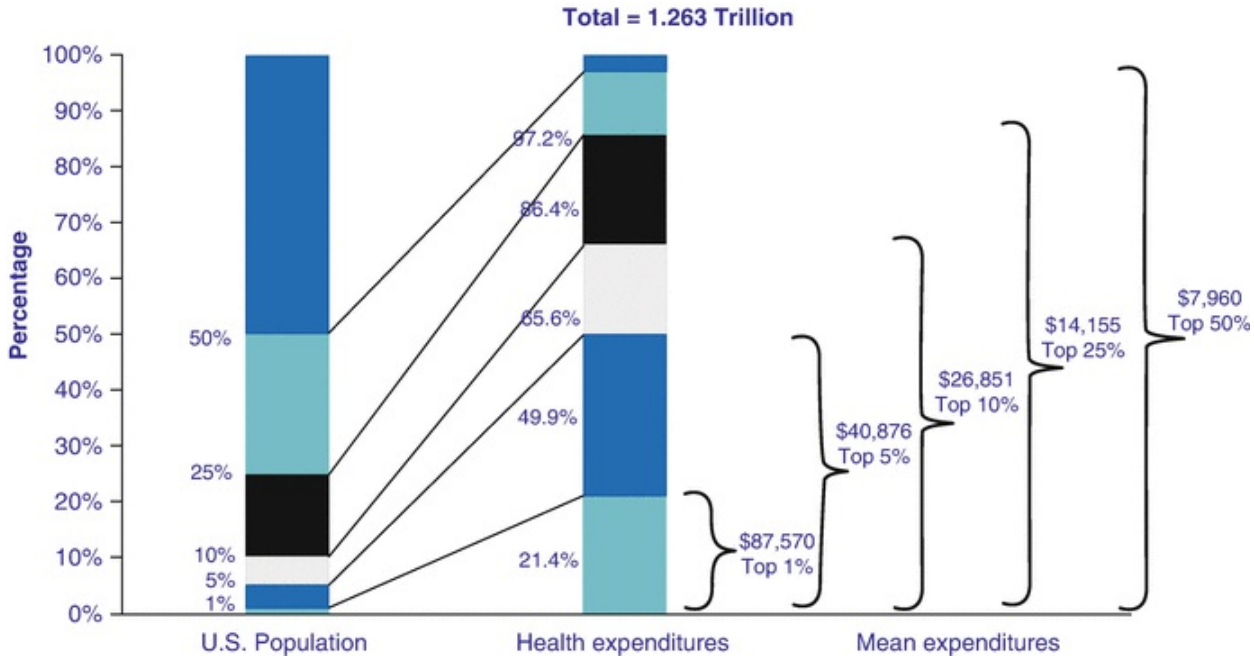


Fig. 1.3 Distribution of health expenditures ' (US) population by magnitude of expenditure and mean expenditure. For example, 1 % of the population consumes 21.4 % of the health-care expenditures with a mean cost per patient of $87,570. *Source*: Center for Financing, Access, and Cost Trends, AHRQ (Agency for Healthcare Research and Quality)

By the mid-2000s, the US health-care delivery system had firmly adapted and responded to the incentives for increased throughput. Physician salaries, hospital payments, and pharmaceutical reimbursement were largely a product of the quantity of services or treatments delivered, at negotiated prices that were at times unrelated to quality or outcomes and often higher than adjusted prices in other industrialized nations. This paradigm shifted toward the concept of value in the mid-2000s. Value in health care is defined as the incremental improvement in measured health outcomes achieved by a specific intervention divided by its cost [13]. This concept folded quality, cost, and often appropriateness of care into the analysis of health-care delivery systems. Most payers, both private and public, began using the concept of "high value care" as a way to communicate their shift in priorities toward quality, which focused on improved health outcomes, as a product of cost.

The hybrid model of health-care financing in the USA meant that rising health-care costs affected both the public sector and the private sector almost equally. About half of the current per-person costs of care ($3507/year) are financed by the public sector, with the other half financed by employers

($3119/year) and individual out-of pocket spending ($912/year) [14]. By the mid-2000s there was an increasing number of Medicare beneficiaries dependent on federal assistance, unsustainably high insurance premiums paid by employers, and cost-sharing schemes that increasingly shifted costs of care to individuals. As a result health-care costs and reform became one of the most important issues of the 2008 US presidential election [15]. While the main point of debate was coverage expansion, there was a large emphasis on "bending the cost curve." This meant decreasing the growth rate of health-care costs as they related to the growing US deficit, rising health insurance premiums, and the subsequent impact on individual contributions to health-care services amidst a recent recession where employers could no longer afford increasing insurance premiums.

The passage of the Affordable Care Act (ACA) in 2010, although contentious, was rooted in projected health-care cost reductions despite a promise of expanded coverage. Cost-containment measures included greater oversight of health insurer practices, increased price transparency in insurance policies, payment reduction for hospital-acquired infections and readmissions by Medicare, and a higher emphasis on comparative effectiveness research and patient-centered care. Other tangentially related features include a much larger role of health-care informatics, with a promise of more accountability through usage analytics.

The ACA expressly introduced provisions that shifted from volume to value by allowing Medicare to enter into "value-based purchasing" contracts, creating financial incentives to form "accountable care organizations" (ACOs) with a financial stake in terms of health outcomes and cost growth and novel-bundled payment schemes covering whole episodes of care [16]. Whether these initiatives will fully deliver in their promise to reduce costs and improve quality is still to be seen, but the law expressly placed an unprecedented emphasis in cost and quality. The creation of the Center for Medicaid and Medicare Innovation (CMMI) , which serves as a laboratory for the development of novel payment schemes using Medicare reimbursements to pilot programs across the country, is another transformative feature of the ACA.

The overall goal of payment reform is threefold. First, novel payment models seek to reward systems that hold health-care providers and organizations accountable for quality metrics and health-care outcomes for whole populations rather than individuals. This population health

management approach allows for the financing of prevention and the development of new risk mitigation strategies as opposed to purely reactionary care. Second, most novel payment models encourage competition on the quality of services rather than specific negotiated prices or cost-shifting strategies. Third, these new models standardize agreements in the form of contracts between payers and providers that outline specific quality goals allowing for bargaining and prioritization of the reform agenda. Early results show hope; the Department of Health and Human Services (HHS) reported $417 million in savings to Medicare as a result of ACO programs and reduced hospital readmissions of 8 %, or 150,000 admissions, between January 2012 and December 2013, only a few years after ACO contracts went into effect [17].

The ACO experiment is currently underway, and it illustrates the challenge of changing payment schemes in the US health-care system. Thirty-two provider organizations joined the Medicare pioneer ACO program in 2012. This pilot had a shared savings component that depended on each organization's performance on 33 quality measures. Thirteen members of the original cohort discontinued their involvement with the Medicare Pioneer ACO program after 2 years stating that the model penalized already efficient organizations through their quality assessment methodologies. Overall performance of the organizations in terms of savings was mixed, although on average most achieved modest reductions in spending and mostly no major changes in performance on quality measures [18]. Nevertheless, the number of ACOs continues to grow, with 744 organizations in public and private contracts for a total of 25 million covered lives by 2015. This mix of private and public buy-in for payment reform is critical for the spread and implementation of innovative payments throughout the country and underscores the health-care sector's hunger for change.

Other payment reform initiatives include episode-based payments that provide single bundled payments for specific health-care events, from acute hospitalizations to longitudinal cancer care. Overall, this highlights the strategy adopted by the Department of Health and Human Services (HHS) to transition from fee-for-service payments to other agreements. HHS was explicit in its goal to transition 30 % of traditional fee-for-service Medicare payments to ACOs or bundled payment arrangements by the end of 2016 and 50 % by the end of 2018. HHS also set a goal of tying 85 % of all traditional Medicare payments to quality or value by 2016 and 90 % by 2018 through

programs such as the Hospital Value-Based Purchasing and the Hospital Readmissions Reduction Programs . This is the first time in the history of the Medicare program that HHS has set explicit goals for alternative payment models and value-based payments [19]. It is important to note that private payers arguably led the development of many of these models, creating their own agreements such as the Alternative Quality Contract developed by Blue Cross Blue Shield of Massachusetts in 2009, which became a model for other private insurers in the state to negotiate global payments with providers.

State governments, given increasing fiscal pressure , have also increased their own legislative efforts to control costs. In 2012, Governor Deval Patrick of Massachusetts signed a bill that benchmarked health-care cost growth rates to match the state's gross state product growth rate. It expressly encouraged providers to enter global payments, among other initiatives. Other state-level initiatives have included Vermont's single-payer system experiment as a means to "control health care costs, not just by cutting fees to doctors and hospitals, but by fundamentally changing the state's healthcare system" [20]. Vermont abandoned this experiment in December of 2014 after projections of tax increases reaching up to 10 % for individuals and businesses in the state in order to fund the single-payer system.

Overall, payment reform is here to stay. Both private and public payers understand that high costs are a product of aggressive pricing, technological advances that include novel pharmacologic agents, and overutilization. The shift to risk-sharing schemes that link quality and cost payments, both for the care of populations and to cover episodic care, is just the beginning. Health-care organizations will have to redesign systems to carefully account for the resources they deploy in the care of patients, deploy them at the right time, and make use of established utilization management strategies to help control costs and usage in order to remain viable and thrive through the transformation of the US health-care system. In the case of ancillary services including the clinical laboratory, radiology, and pharmacy, there will be increasing pressure to implement effective utilization management programs. The chapters that follow review the current literature on utilization management in these areas and provide numerous examples of successful utilization management initiatives along with strategies to facilitate successful implementation.

References

1. California Healthcare Foundation. Health care costs 101: 2014 edition. California Health Care Almanac. 2014. http://www.chcf.org/~/media/MEDIA%20LIBRARY%20Files/PDF/H/PDF%20HealthCareCosts14.pdf. Accessed 30 Aug 2015.

2. OECD. OECD health Statistics 2014. How does the United States Compare? http://www.oecd.org/unitedstates/Briefing-Note-UNITED-STATES-2014.pdf. Accessed 30 Aug 2015.

3. Anderson C. Multinational comparisons of health systems data. The Commonwealth Fund. 2014. http://www.commonwealthfund.org/~/media/files/publications/chartbook/2014/nov/pdf_1788_anderson_multinational_comparisons_2014_oecd_chartpack_v2.pdf. Accessed 30 Aug 2015.

4. Johnson T. "Healthcare costs and U.S. competitiveness" council on foreign relations. 2012. http://www.cfr.org/competitiveness/healthcare-costs-us-competitiveness/p13325. Accessed 3 Sept 2015.

5. IOM (Institute of Medicine). Crossing the quality chasm: a new health system for the 21st century. Washington, DC: National Academy Press; 2001.

6. Squires D. Explaining high healthcare spending in the united states: an international comparison of supply, utilization, prices and quality. Issues in international health policy. 2012. Commonwealth Fund Pub. 1595. Volume 10.

7. Squires D. The U.S healthcare system in perspective: a comparison of twelve industrialized nations. Issues in international health policy. 2011. Commonwealth Fund Pub 1532. Volume 16. http://www.commonwealthfund.org/~/media/Files/Publications/Issue%20Brief/2011/Jul/1532_Squires_US_hlt_sys_comparison_12_nations_intl_brief_v2.pdf. Accessed 30 Aug 2015.

8. Blue Cross Blue Shield Association/Blue Health Intelligence. A study of cost variations for knee and hip replacement surgeries in the U.S. Blue Cross Blue Shield. The Health of America Report dated Jan 21, 2015. http://www.bcbs.com/healthofamerica/BCBS_BHI_Report-Jan-_21_Final.pdf. Accessed 10 Sept 2015.

9. Cutler D. Tax policy and the economy. Cost shifting or cost cutting? The incidence of reductions in medicare payments. MIT; 1998. pp. 1–28. http://www.nber.org/chapters/c10911.pdf. Accessed 1 Sept 2015.

10. Cohen S, Uberoi N. Differentials in the concentration in the level of health expenditures across population subgroups in the U.S., 2010. Statistical Brief #421. Rockville, MD: Agency for Healthcare Research and Quality; 2013. http://meps.ahrq.gov/mepsweb/data_files/publications/st421/stat421.shtml

11. The high concentration of U.S. health care expenditures: research in action. Rockville, MD: Agency for Healthcare Research and Quality; 2006. Issue 19. http://archive.ahrq.gov/research/findings/factsheets/costs/expriach/index.html. Accessed 3 Sept 2015.

12. Carey MA. Health care spending forecast to increase modestly in next decade. Kaiser Health News. 2014. http://www.khn.org/news/health-costs-inflation-cms-report/. Accessed 3 Sept 2015.

13. Porter M, Lee T. The strategy that will fix health care. Harv Bus Rev. 2013. https://hbr.org/2013/10/the-strategy-that-will-fix-health-care/. Accessed 1 Sept 2015.

14. Squires D. The U.S healthcare system in perspective: a comparison of twelve industrialized nations. Issues in international health policy. July 2011. Commonwealth Fund Pub 1532. Vol 16. http://www.commonwealthfund.org/~/media/Files/Publications/Issue%20Brief/2011/Jul/1532_Squires_US_hlt_sys_comparison_12_nations_intl_brief_v2.pdf. Accessed 30 Aug 2015.

15. Collins SR, Nicholson JL, Rustgi SD, Davis K, The 2008 presidential candidates' health reform proposals: choices for America. The Commonwealth Fund. 2008.

16. Accountable Care Organizations. 2015. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ACO/index.html?redirect=/aco. Accessed 31 Aug 2015.

17. HHS Press Office. Efforts to improve patient safety result in 1.3 million fewer patient harms, 50,000 lives saved and $12 billion in health spending avoided. 2014. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ACO/index.html?redirect=/aco. Accessed 2 Sept 2015.

18. McWilliams JM, Chernew ME, Landon BE, Schwartz AL. Performance differences in year 1 of Pioneer accountable care organizations. N Engl J Med. 2015;372:1927–36. [CrossRef][PubMed][PubMedCentral]

19. HHS Press Office. Better, Smarter, Healthier: in historic announcement, HHS sets clear goals and timeline for shifting Medicare reimbursements from volume to value. 2015. http://www.hhs.gov/news/press/2015pres/01/20150126a.html. Accessed 3 Sept 2015.

20. Shumlin P. The economic urgency of healthcare reform. Huffington Post. Politics blog [Internet]. Posted 2011. http://www.huffingtonpost.com/gov-peter-shumlin/health-care-reform-shumlin_b_919900.html. Accessed 3 Sept 2015.

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_2

2. Utilization Management in the Clinical Laboratory: An Introduction and Overview

Kent Lewandrowski[1] ✉, Jason Baron[2] ✉ and Anand Dighe[2] ✉

(1) Division of Laboratory Medicine, Department of Pathology, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street, Boston, MA 02114, USA
(2) Department of Pathology, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street, Boston, MA 02114, USA

✉ **Kent Lewandrowski (Corresponding author)**
Email: KLEWANDROWSKI@mgh.harvard.edu
Email: klewandrowski@partners.org

✉ **Jason Baron**
Email: jmbaron@partners.org

✉ **Anand Dighe**
Email: asdighe@mgh.harvard.edu

Keywords Utilization management – Literature review – Clinical laboratory – Utilization toolbox

Introduction and Discussion

Health-care systems in developed nations are facing continuing pressure to improve quality and efficiency and to reduce costs. This is particularly true in the USA where health-care expenditures comprise a larger percentage of gross domestic products than any other country. For example, in 2010, the total annual health-care expenditure in the USA was $2.6 trillion dollars or more than ten times the amount spent in 1980 [1]. Advances in medical technologies and therapeutics, combined with an aging population, virtually assures that this trend will continue unless there are major changes to the health-care system. Recent legislation including the Affordable Care Act (Obamacare) will have a major impact on reimbursement for medical care . The formation of accountable care organizations (ACO's) and similar risk-sharing approaches such as the Massachusetts Blue Cross Blue Shield Alternative Quality Contract will progressively eliminate the traditional fee-for-service system of reimbursement in favor of global payments for entire episodes of care and even global payments for entire populations of patients. In addition, quality measures and other metrics are being introduced as part of pay-for-performance systems wherein physicians and hospitals have a portion of their payment withheld pending acceptable achievement of performance goals (e.g., proper management of diabetes care, reducing readmissions, reducing hospital-acquired infections). These so-called "value-based" payment systems will hold providers accountable for both quality and cost [1]. Collectively these developments will only increase pressure on providers to improve outcomes while reducing cost.

Utilization management has been a traditional approach to control costs in health-care systems. This is particularly true for ancillary services such as the clinical laboratory, pharmacy, and radiology. These services are often targeted because they are generally perceived to be significantly overutilized (or miss-utilized) and because they are usually readily quantifiable. Volume and unit cost data can be easily obtained to estimate the aggregate savings resulting from individual utilization management initiatives. Overutilization of laboratory services has been documented for several decades. For example, in one study from 1982, the authors undertook chart reviews by pathologists and primary care physicians on medical service inpatients. The pathologists identified 26.5 % of tests as being unnecessary and the primary care physicians 42.8 %. The ten most frequently ordered tests showed the worst rate of overutilization [2]. This finding has been consistently confirmed in the literature especially for high-volume automated tests. A number of

articles and reviews have appeared in the literature over the years highlighting the need for utilization management in the clinical laboratory and outlining strategies for successful implementation (see [2–11] and supplemental references).

The clinical laboratory usually accounts for approximately 4 % of the typical hospital budget. Therefore, at first glance, it would not appear that much money could be saved by reducing expenditures for laboratory services. However, the operating budgets of most hospital laboratories are still substantial. For example, in our hospital the total operating budget for pathology services is roughly $ 94 million dollars per year divided among the clinical laboratories (50 %), blood transfusion (29 %), and anatomic pathology (21 %). Another important aspect concerning laboratory services is that test results have a major impact on the downstream costs of medical care. It has been estimated that over 70 % of clinical decisions (and their attendant costs) are based on the results of laboratory testing [3]. To the extent that a significant percentage of laboratory tests may be unnecessary, the impact of these tests on the overall cost of care is substantial. Furthermore most laboratories define the reference range for common tests as the mean plus or minus 2 standard deviations of the normal population. Therefore 5 % of tests will be abnormal (either low or high) by statistical chance alone. For a laboratory performing five million tests per year, this translates into 250,000 falsely abnormal test results. A significant percentage of these will require time on the part of the physician to assess whether the abnormality is significant and may result in unnecessary follow-up testing and specialist consultations. To the extent that 20–50 % of these tests were unnecessary to begin with, significant downstream costs may be incurred from tests that never should have been ordered in the first place.

Utilization management has other benefits beyond reducing costs in the laboratory. Eliminating unnecessary tests frees up technologists' time allowing these resources to be reassigned to more important duties such as performing STAT testing thus reducing turnaround time for tests on critically ill patients. In addition, the time spent by phlebotomists or nursing assistants collecting blood specimens is also reduced. Finally repetitive blood drawing on hospitalized patients has been associated with hospital-acquired anemia (HAA). For example, Salisbury et al. reported an outcome study in patients with acute myocardial infarction and HAA. They found that patients with HAA had higher mortality rates (hazard ratio 1.82) and a worse health status

1 year after hospitalization [4]. Other studies on HAA have reached similar conclusions.

Utilization management usually implies reducing unnecessary testing as shown in Table 2.1. However, there are tests that have traditionally been underutilized such as cholesterol screening, testing for diabetic management, and human immunodeficiency virus screening. Also there are tests where the appropriate level of utilization is unclear or controversial. A case example is screening for prostate cancer using prostate-specific antigen (PSA) . In 2012 the US Preventive Services Task Force recommended against routine screening using PSA and concluded that there is moderate certainty that the benefits of screening do not outweigh the harms (morbidity arising from biopsies and subsequent treatment of low-grade tumors) [5]. In contrast the American Urological Association (AUA) has taken a different perspective. The AUA has recommended against PSA screening in men under 40 years of age, and it does not recommend screening in men between 40 and 54 years of age. However, for men between 55 and 69 years of age, the AUA recommends "shared decision-making for men aged 55–69 years that are considering PSA screening and proceeding based on a man's values and preferences."

Table 2.1 Overutilization versus underutilization : some examples

Overutilization	Routine chemistry panels
	Complete blood counts
	Blood components
	Some esoteric tests
Underutilization	Screening for cervical HPV infection
	Cholesterol screening
	Testing for diabetes and dyslipidemia management
	HIV screening
Controversial utilization	Prostate-specific antigen testing
	High sensitivity C-reactive protein
	Lipoprotein $_{a}$ (Lp(a))

HPV human papilloma virus, *HIV* human immunodeficiency virus

A final goal of utilization management should be to ensure that patients receive the right tests that are needed without necessarily reducing testing

costs. For example, we recently banned serologic testing for Babesiosis which is neither optimally sensitive nor specific for diagnosis of this infection. In its place we substituted the thick and thin blood smear as the preferred test.

When deciding how to approach utilization management, it is important to consider the incentives that may be influencing physicians, the hospital, and the laboratory. From the perspective of the laboratory, the incentives may be very different depending on whether the testing is performed on outpatients or inpatients. In the United States, inpatient testing is typically reimbursed using a global payment based on the diagnostic-related group (DRG) . The hospital gets a single payment for the entire admission regardless of how many (or few) tests are ordered. There is a strong incentive to reduce inpatient testing as excess tests incur additional costs without generating any revenue. On the other hand, outpatient testing is, for the moment, reimbursed directly. The more tests that are performed, the more revenue is generated. This is one reason many hospitals have set up outreach programs to bring more billable tests into the laboratory. There is little incentive to aggressively target outpatient test utilization. This of course will change dramatically if outpatient testing reimbursement is reconfigured into a single global payment for the entire episode of outpatient care. Likewise physicians may have different incentives depending on the specific situation. For example, some physician practices have set up physician's office laboratories (POLs) where they can bill directly for the tests originating from the practice. There is no incentive to reduce this source of profitable revenue for the practice. Independent practitioners who send their patients to a hospital or commercial laboratory for phlebotomy and testing also have little incentive to control utilization. The practice gets paid for the office visit and is not held accountable for the costs of the testing that they have ordered. With global payment systems , this incentive structure will change dramatically. Physicians who are subject to capitated reimbursement or those in accountable care organizations will have a strong incentive to reduce unnecessary testing as the practice is at financial risk if the cost of care is excessive.

A recurring theme in laboratory utilization management is determining, from an evidence-based perspective, what constitutes overutilization. In many cases there is no consensus on what testing is, or is not, appropriate. Although clinical guidelines exist for some types of testing, often there is no

peer-reviewed literature defining appropriate test utilization. For example, how often should a typical patient hospitalized with community-acquired pneumonia have a complete blood count test? Walraven performed a systematic literature review of studies that provided and applied criteria for inappropriate utilization. They concluded that many studies used implicit or explicit criteria that did not meet acceptable methodological standards and that alternative evidence-based standards should be developed for measuring appropriateness [6]. In a follow-on study by Hauser, the authors commented that in the past, many studies used subjective or locally defined definitions of appropriate. However, literature consensus of what is appropriate has improved, and advances in database technologies, as opposed to chart reviews, have facilitated utilization audits [7]. In our experience, determining what is inappropriate utilization is often impossible or, when there is data, it is often inconclusive. In most cases we rely on local clinical experts to provide guidance or meet with clinicians to try to reach a consensus. Invariably this process is based more on intuition and experience rather than true evidence, but we have nonetheless had a number of successes.

A key concept in utilization management concerns who will take overall leadership for the program. Ideally physicians are in the best position to assume leadership as they have the medical knowledge to make judgments about what is in the best interests of patient care. Lacking physician leadership other parties are likely to fill the void such as administrators and third-party payers. Indeed, in some specialties, this is already becoming the case. Recently a number of insurance companies have begun requiring prior authorization before patients can receive expensive genetic and molecular pathology tests. These requirements usually involve multiple administrative barriers that can place a significant burden on the time of the clinician and the patient. An article by Grumet published as far back as 1989 highlighted the onerous strategy often employed by third-party payers with the quote “But another feature has crept into the managed care formula that has been largely overlooked: that of slowing and controlling the use of services and payment for services by impeding, inconveniencing and confusing providers and consumers alike” [8]. In the article he described, eight of these approaches including:

1. Procedural complexity: Requirements for multiple forms and procedure codes

2. Exotic terms: The use of unique or exotic procedures, codes, and terms (e.g., corridor deductibles)

3. Slowdowns: Slowing authorization for procedures and claims

4. Shifting of procedures: Frequent changes to codes, forms, and policies

5. Fail-safe payment systems: Protocols designed to inhibit approving claims where any negative condition will stop fulfilling the claim

6. Overlapping coverage: Systems designed to shift coverage to other payers

7. Fragmentation of transactions: Systems requiring the provider to interact with multiple offices within the insurance carrier

8. Uncertainty of coverage: Ambiguity about whether certain services will be covered

With regard to laboratory utilization management, we believe pathologists and laboratory directors are the most logical individuals to take a leadership role. While many clinicians are interested in improving utilization, they are often consumed with their clinical duties and are not compensated for this activity. However, as described by Zhao et al. [9], there have been historical reasons why pathologists have not been leaders in utilization management. Included among these are:

1. Pathologist contributions not clearly defined

2. Pathologist contributions not compensated (particularly a problem in community hospitals)

3. Lack of recognition of pathologists' role among hospital administrators, managed care, and pathologists themselves

National pathologist professional organizations have recognized these issues and have been encouraging pathologists to redefine their roles in the health-care delivery system. Among these new roles is utilization management. As shown in Table 2.2, pathologists have a number of assets to bring to the table. While it is true that pathologists will not have as good an understanding as medical specialists of the clinical applications of many laboratory tests, this fund of knowledge can be developed over time. Furthermore knowing the intricacies of every test on the menu is not necessary to be a leader of the utilization management program so long as the pathologist has access to clinical advisors in the different medical specialties. Many pathologists have experience directing complex organizations (laboratories) and often serve on hospital and medical staff committees. A number have developed roles as physician executives. In the case of clinical pathologists, most are salaried physicians who are accountable to their hospital and physician's organization. Utilization management is part of their expected professional duties. Finally pathologists understand the cost and reimbursement structure for laboratory tests and have access to test volumes, trends, and ordering patterns through the laboratory information system. Pathologists by virtue of their role as laboratory directors are thus in a much better position to lead the utilization management program than most clinicians particularly those practicing in narrow specialties. The pathologist can thus serve as the hub of a wheel connecting to physicians across different specialties and coordinating the overall program.

Table 2.2 Why pathologists and laboratory directors should take a leadership role in utilization management

Executive leadership experience
• Experience directing organizations (laboratories)
• Frequently serve in role as physician executives
• Frequently serve on hospital and physicians organization committees
Identified professional responsibilities
• Professional duties include utilization management, budgeting, and cost containment
• Accountable to the hospital and health-care system
Knowledge and experience
• Understands the use and limitations of laboratory testing
• Understands laboratory operations
• Understands cost and reimbursement structure for laboratory testing

• Access to laboratory test volumes, trends, and ordering patterns
• Understanding of informatics

A number of publications have described the organizational structure of hospital utilization management programs [10]. A former organizational structure for utilization management in our hospital is shown in Fig. 2.1 (as described in [10]). The major governing body in the hospital is the General Executive Committee (GEC). Its membership includes clinical chiefs of service (including the Chief of Pathology) and senior hospital administration. The Medical Policy Committee (MPC) reports to the GEC and is responsible for oversight of all clinical activities in the hospital. Its membership includes the Chief Medical Officer, a cross section of clinicians and representatives from nursing and other departments. The Clinical Laboratory Advisory Committee (CLAC) was a subcommittee of the Medical Policy Committee charged with coordinating utilization management and other laboratory-related issues. Membership of the CLAC included representatives from pathology, who chaired the committee, and a cross section of physicians from different clinical specialties. Utilization management initiatives that were approved by the CLAC were forwarded to the MPC for final approval. The Transfusion Committee serves in a similar capacity as the CLAC and is responsible for utilization management and other policies concerning the use of blood components. Initially the CLAC served its purpose and a number of utilization-related initiatives were accomplished. However, as the pace of our utilization management activities expanded, we found that a committee that met once per month was unable to effectively manage the program. We also found that the clinician members were hesitant to make a judgment about tests outside of their specialties. For example, a transplant surgeon would not feel qualified to approve a proposal to eliminate Babesia antibody testing from our laboratory menu. For this reason we reorganized our program to include a core group of clinical pathologists one of whom has advanced informatics training to serve as a coordinating committee. The committee generates utilization management ideas, collects data (e.g., test volumes, test results, ordering providers), and prepares the data for presentations to groups of physicians from the relevant specialty(s). The committee therefore relies on the use of multiple ad hoc specialty group meetings (e.g., infectious disease, transplant, cardiology, medicine house officers) rather than a standing committee with a cross section of physicians. This approach allows

multiple issues to be vetted in semi-real time, does not waste the time of the clinicians who only need to review topics in their specialty, and allows the committee to move more rapidly on multiple initiatives.

Fig. 2.1 Former organizational structure for Utilization Management at the Massachusetts General Hospital (circa 2008). Committees with pathologist leadership include the Clinical Laboratory Advisory Committee and the Transfusion Committee

When starting a utilization management program, it is helpful to establish benchmarking data to determine how your organization compares to other health-care systems and to assess your internal performance over time. External benchmarking data can sometimes be obtained from national professional organizations or by performing a survey of one's peers in other health-care systems. The data should be normalized in some way such as tests per outpatient visit or the number of tests per inpatient discharge. Analysis of test numbers alone is not sufficient as it does not take into account the volume of patients being cared for. Two key points concerning external benchmarking data are as follows.

First it is important to make certain that the "peer" group to which you are being compared is appropriate. For example, a large academic medical center should not be compared to a mid-sized community hospital as the scope of medical services and patient acuity of the two will be completely different rendering the analysis essentially worthless. Second, all organizations in the peer group should count tests in the exact same way. For example, one organization might report each of the tests in a basic metabolic panel as individual tests whereas other organizations may roll them up into a single panel scored as one test. Molecular diagnostic tests can be reported using a number of individual elements or as reported as a single test. When

properly performed, external benchmarking can give the utilization management program a sense of where their organization stands relative to its peers. This may help to assess the scope of opportunity both globally and within specific laboratory specialties. On the other hand, internal benchmarking data allows the organization to evaluate its progress in managing utilization over time. In the past we monitored the total tests per inpatient discharge over time as described in [10]. In doing so we were able to track a 26 % decrease in inpatient tests per discharge over a 6-year period. More recently we have been benchmarking individual services and clinical units within the hospital (e.g., intensive care units, neurology service). This approach allows us to share the information with the individual services so they can see the specific data that is relevant to them.

One of the major reasons to manage utilization is to control costs in the laboratory. For this reason it is important to understand how to calculate cost savings resulting from utilization management activities. The literature contains a number of examples where the cost analysis was not performed correctly. In most cases these studies used laboratory test charges rather than actual costs, or they used average unit costs of tests rather than marginal costs. Charges for laboratory tests often bear little relationship to the actual cost to perform the tests. Charges are often greatly inflated as part of a strategy to improve revenues. The concept of average versus marginal cost is especially important with high-volume automated tests. Assume a laboratory performs a million tests per year with an annual operating budget of $5 million per year. Therefore the average unit cost is $5 per test. Next assume a utilization management initiative eliminates 100,000 tests per year. Using an average unit cost of $5, one could calculate an annual savings of $500,000. But this calculation is completely incorrect. In the laboratory there are two types of cost, fixed and variable. Fixed costs do not change with the volume of tests and include such elements as space, overhead, equipment, and management. Reducing test volumes by 100,000 (2 %) will have no impact on these costs. Then there are variable costs. These change with the volume of tests and include such elements as reagents and other consumables. When automated tests are removed from a preexisting laboratory, only the variable costs are actually saved. In the case of automated testing, the variable costs are typically quite low. In a study by Winkelman, it was shown that it would take an approximate 10 % reduction in automated testing volume to achieve only a 2 % reduction in cost [11]. Therefore, with automated testing, most of

the true savings occur from reductions in specimen collection and eliminating the downstream costs of testing as described above. For laboratory tests with a high variable cost, such as molecular diagnostics and many esoteric tests, significant money can be saved by reducing test volumes. A second category concerns reference laboratory testing . Virtually all hospitals send a significant number of tests out to reference laboratories. In this case the hospital gets billed for every test that is performed. Therefore reference laboratory charges are all variable costs and significant savings can be achieved by reducing utilization of these tests. However, laboratories should also be aware of the potential impact of reducing test volumes on revenues. In most cases, tests on hospital inpatients do not generate any revenue because the admission is paid using a global fee such as a diagnostic-related group (DRG) . The hospital gets paid the same for the admission regardless of how many tests are, or are not, performed. In most cases outpatient tests generate revenue: reducing the test volume will correspondingly reduce revenues.

A number of medical professional societies are beginning to take an active interest in utilization management. Often this involves the publication of practice guidelines or consensus statements. One of the most visible of these initiatives is the National Physicians Alliance “Promoting Good Stewardship in Medicine Choosing Wisely” campaign [12, 13]. In this program various medical specialties have designated their “Top 5 List” of tests, procedures, and therapies that should not be performed. Predictably a number of these involve laboratory testing. The American Society for Clinical Pathology has summarized the recommendations that relate to the clinical laboratory as shown in Fig. 2.2. In our institution the “Choosing Wisely” recommendations are often cited by clinicians who are working on utilization management. These recommendations represent a good start for guiding utilization management and will no doubt continue to expand. However, there are many areas of laboratory testing that are not covered by the guidelines. For this reason it is important to consult practice guidelines from other professional societies and to develop locally generated consensus standards.

TYPE OF TEST	TEST RECOMMENDATION	RECOMMENDING ORGANIZATION
Immunology	Don't perform unproven diagnostic tests, such as immunoglobulin (IgE) testing of an indiscriminate battery of immunoglobulin E (IgE) tests, in the evaluation of allergy.	American Academy of Allergy, Asthma & Immunology (AAAAI)
	Don't routinely do diagnostic testing in patients with chronic urticaria.	
	Don't test ANA sub-serologies with a positive ANA and clinical suspicion of immune-mediated disease.	American College of Rheumatology
	Don't test for Lyme disease as a cause of musculoskeletal symptoms without an exposure history and appropriate exam findings.	
	Don't order autoantibody panels unless positive antinuclear antibodies (ANA) and evidence of rheumatic disease.	American College of Rheumatology – Pediatric Rheumatology
	Don't test for Lyme disease as a cause of musculoskeletal symptoms without an exposure history and appropriate exam findings.	
	Don't repeat a confirmed positive ANA in patients with established juvenile idiopathic arthritis (JIA) disease activity or systemic lupus erythematosus (SLE).	
	Don't perform immunological testing as part of the routine infertility evaluation.	American Society for Reproductive Medicine
Chemistry	Don't routinely measure1,25-dihydroxyvitamine D unless the patient has hypocalcaemia or decreased kidney function.	The Endocrine Society and the American Association of Clinical Endocrinologists
	Don't order a total or freeT3 level when assessing levothyroxine (T4) dose in hypothyroid patients	
	Don't perform population based screening for 25-OH-Vitamin D deficiency.	ASCP
	Don't routinely screen for prostate cancer using a prostate-specific antigen (PSA) test [or digital rectal exam].	American Academy of Family Physicians (AAFP)
	Don't perform repetitive [CBC and] chemistry testing in the face of clinical and lab stability.	Society of Hospital Medicine (Adult Hospital Medicine)
Toxicology	Don't administer a chelating agent prior to testing urine for metals, a practice referred to as "provoked" urine testing.	The American College of Medical Toxicology and the American Academy of Clinical Toxicology
	Don't perform methotrexate toxicity labs more often than every 12 weeks on stable doses.	American College of Rheumatology – Pediatric Rheumatology

Microbiology	Don't obtain a urine culture unless there are clear signs and symptoms that localize to the urinary tract.	AMDA
	Avoid [antibiotics and] wound cultures in emergency department patients with uncomplicated skin and soft tissue abscesses after successful incision and drainage and with adequate medical follow-up.	American College of Emergency Physicians
Hematology	Don't perform repetitive CBC [and chemistry] testing in the face of clinical and lab stability.	Society of Hospital Medicine (Adult Hospital Medicine)
Blood Banking	Don't administer packed red blood cells (PRBCs) in a young healthy patient without ongoing blood loss and hemoglobin of ≥6g/dL unless symptomatic hemodynamically unstable.	American Society of Anesthesiologists
	Avoid transfusions of red blood cells for arbitrary hemoglobin or hematocrit thresholds and in the absence of symptoms of active coronary disease, heart failure or stroke.	Society of Hospital Medicine (Adult Hospital Medicine)
	Do not transfuse more than the minimum number if red blood cells (RBC) units necessary to relieve symptoms of anemia or to return a patient to a safe hemoglobin range (7 to 8 g/dL in stable, non-cardiac, in-patients).	American Society of Hematology (ASH)
	Do not administer plasma or prothrombin complex concentrates for non-emergent reversal of vitamin K antagonists (i.e. Outside of the setting of major bleeding, intracranial hemorrhage or anticipated emergent surgery).	
	Don't transfuse red blood cells in hemodynamically stable, non-bleeding ICU patients with a hemoglobin concentration greater than 7 g/dl.	Critical Care Societies Collaborative – Critical Care
Coagulation	Don't use bleeding time test to guide patient care.	ASCP
	Don't do work up for clotting disorder (order hypercoagulable testing) for patients who develop first episode of deep vein thrombosis (DVT) in the setting of a known cause.	Society for Vascular Medicine
	Don't routinely order thrombophillia testing on patients undergoing a routine infertility evaluation.	American Society for Reproductive Medicine
	Don't do an inherited thrombophillia evaluation for women with histories of pregnancy loss, intrauterine growth restriction (IUGR), preeclampsia and abruption.	Society for Maternal-Fetal Medicine

Cytology	Don't perform Pap smears on women younger than 21 or who have had a hysterectomy for non-cancer disease. Don't screen women older than 65 years of age for cervical cancer who have had adequate prior screening and are not otherwise at high risk for cervical cancer. Don't screen women younger than 30 years of age for cervical cancer with HPV testing, alone or in combination with cytology.	American Academy of Family Physicians (AAFP)
	Don't perform routine annual cervical cytology screening (Pap tests) in women 30-65 years of age.	The American College of Obstetricians and Gynecologists
	Don't perform Pap tests for surveillance of women with a history of endometrial cancer.	Society of Gynecologic Oncology
Molecular Pathology	Don't screen for ovarian cancer [with CA-125] in asymptomatic women at average risk.	The American College of Obstetricians and Gynecologists
	Don't screen low risk women with CA-125 [or ultrasound] for ovarian cancer	Society of Gynecologic Oncology
	Don't perform low risk HPV testing.	ASCP
	Only order Methylated Septin 9 (SEPT9) to screen for colon cancer on patients for whom conventional diagnostics are not possible.	
Pre-Op Battery	Don't perform preoperative medical tests for eye surgery unless there are specific medical indications.	American Academy of Ophthalmology
	Don't obtain baseline laboratory studies in patients without significant systemic disease (ASA I or II) undergoing low-risk surgery – specifically complete blood count, basic or comprehensive metabolic panel, coagulation studies when blood loss (or fluid shifts) is/are expected to be minimal.	American Society of Anesthesiologists
	Avoid routine preoperative testing for low risk surgeries without a clinical indication.	ASCP
Non-Pre-Op Battery	Don't perform routine pre-operative testing before low-risk surgical procedures.	Society of General Internal Medicine (SGIM)
	Don't order diagnostic tests (arterial blood gases, blood chemistries, blood counts) at regular intervals (such as everyday), but rather in response to specific clinical questions.	Critical Care Societies Collaborative – Critical Care

Screening Tests	Don't perform routine cancer screening for dialysis with limited life expectancies without signs or symptoms.	American Society of Nephrology
	Don't perform routine general health checks for asymptomatic adults.	Society of General Internal Medicine (SGIM)
	Don't recommend cancer screening in adults with life expectancy of less than 10 years.	
	Do not perform PSA testing for prostate cancer screening in men with no symptoms of the disease when they are expected to live less than 10 years.	The American Society of Clinical Oncology (ASCO)
	Don't recommend screening for breast or colorectal cancer, nor prostate cancer with the PSA test, without considering life expectancy and the risks of testing, overdiagnosis and overtreatment.	American Geriatrics Society (AGS)
	Don't offer noninvasive prenatal testing (NIPT) to low-risk patients or make irreversible decision based on the results of this screening test.	Society for Maternal-Fetal Medicine
Anatomic Pathology	Don't perform sentinel lymph node biopsy or other diagnostic tests for the evaluation of early, thin melanoma because they do not improve survival.	American Academy of Dermatology (AAD)
Fertility	Don't perform advanced sperm function testing, such as sperm penetration or hemizona assays, in the initial evaluation of the infertile couple.	American Society for Reproductive Medicine
Biopsy	Don't perform surgery to remove a breast lump for suspicious findings unless needle biopsy cannot be done.	Commission on Cancer (COC)
CBC (WBC)	Don't use white cell stimulating factors for primary prevention of febrile neutropenia for patients with less than 20 percent risk for this complication.	American Society of Clinical Oncology (ASCO)
Cardiac Markers	Don't perform stress cardiac imaging or advanced non-invasive imaging in the initial evaluation of patients without cardiac symptoms unless high-risk markers are present.	American College of Cardiology
D-dimer	Don't perform chest computed tomography (CT angiography) to evaluate for possible pulmonary embolism in patients with a low clinical probability and negative results of a highly sensitive D-dimer assay.	American College of Chest Physicians American Thoracic Society (ATS)
Hemoglobin	Don't administer erythropoiesis-stimulating agents (ESAs) to chronic kidney disease (CKD) patients with hemoglobin levels ≥ 10 g/dL without symptoms of anemia.	American Society of Nephrology
Hemoglobin A1c	Avoid using medications to achieve hemoglobin A1c<7.5% in most adults age 65 and older; moderate control is generally better.	American Geriatrics Society
Pap Test	Don't perform colposcopy in patients treated for cervical cancer with Pap tests of low grade squamous intraepithelial lesion (LGSIL) or less.	Society of Gynecologic Oncology

PSA	A routine bone scan is unnecessary in men with low - risk prostate cancer (patients with newly diagnosed prostate cancer who have a PSA < 20.0 ng/ml and a Gleason score of 6 or less unless the patient's history or clinical examination suggests bony involvement)	American Urological Association
	Don't treat an elevated PSA with antibiotics for patients not experiencing other symptoms.	
Testosterone	Don't prescribe testosterone to men with erectile dysfunction who have normal testosterone levels.	American Urological Association
	Don't prescribe testosterone therapy unless there is biochemical evidence of testosterone deficiency.	The Endocrine Society and American Association of Clinical Endocrinologists
Thyroid Function Tests	Don't routinely order a thyroid ultrasound in patients with abnormal thyroid function tests if there is no palpable abnormality of the thyroid gland.	The Endocrine Society and American Association of Clinical Endocrinologists
Urinalysis/ Urine Culture	Don't use antimicrobials to treat bacteriurua in older adults unless specific urinary tract symptoms are present.	American Geriatrics Society (AGS)
TYPE OF TEST	TEST -RELATED RECOMMENDATION	RECOMMENDING ORGANIZATION
Glucose	Don't recommend daily home finger glucose testing in patients with Type 2 diabetes mellitus not using insulin.	Society of General Internal Medicine (SGIM

Fig. 2.2 American Society for Clinical Pathology summary of laboratory-related recommendations of the National Physicians alliance promoting good Stewardship in medicine choosing Wisely Campaign. Reproduced with permission

A Toolbox for Implementing Utilization Management Initiatives

A number of strategies (tools) for addressing utilization management have been described in the literature as shown in Table 2.3. For any given utilization management initiative , it is important to select the right utilization management tool to implement it. A number of factors will influence this decision including:

Table 2.3 Strategies to approach laboratory utilization management: a toolbox

Physician education and feedback
Presentations at medical conferences
Distributing literature on test guidelines
Develop an electronic laboratory handbook with recommended laboratory workups
Practice guidelines
Identify and monitor “sound alike” tests (e.g., 25OH and 1–25OH vitamin D)
Posting test costs or charges
Retaining a laboratory-based genetic counselor
Physician profiling and variation analysis
Post “pending” tests to the electronic medical record
Restrictions on testing
Discontinue obsolete tests (banning)
Use of gatekeepers or prior authorization systems
Restrict selected tests that can only be ordered by specific specialists
Develop a list of tests that should never be ordered more than once (e.g., genetic tests)
Restrict inpatient sendout tests that are not relevant to the current hospitalization
Capture and eliminate same-day duplicate tests
Restrict the use of automatic orders for daily laboratory testing
Establish a laboratory formulary
Requisition design
Validate and refine reference intervals to eliminate falsely abnormal tests
Develop admission templates
Order entry design[a]
Decision support
Use of “pop-ups”
Develop algorithms and reflex testing protocols
Benchmarking against peer organizations
Clinical pathology consultative and interpretive services
Financial motivation including risk sharing and pay-for-performance

[a]Order entry systems may be used to support many of the strategies listed in this table

1. Who is the target audience (e.g., primary care, subspecialty practices, inpatients versus outpatients, residents)? For example, using a gatekeeping mechanism to control utilization of high-volume automated

testing will be doomed to fail due to the sheer volume of test requests. Impacting these tests is best approached by physician education coupled with controls built into the order entry system. In contrast testing performed by specialists can often be evaluated by meeting with the physicians during regular staff meetings or with leaders in the specialty practice to develop evidence-based guidelines.

2. What is the test volume (e.g., occasional test, low volume (20–50 per month), moderate volume or high volume (thousands per month)? For example, a low-volume test can be easily subjected to gatekeeping without undue inconvenience for the physicians and the laboratory.

3. What infrastructure is available to assist implementation (e.g., order entry systems, laboratory middleware, requisition design, admission templates, laboratory formulary)?

4. Indications for the test. Some tests should essentially never be ordered (ban), whereas others are useful in certain situations but are overutilized. The latter situation precludes an outright ban but could be subjected to gatekeeping or allowing only certain specialists to order the test.

5. Outpatient versus inpatient testing: Testing on inpatients should be limited to those tests that are required for the management of the patient's acute episode leading to hospitalization. Tests that will not be required for immediate patient management may best be restricted and will not be reimbursed beyond the global DRG payment. On the other hand, outpatient tests generate revenue which will be lost if test volumes are reduced. Although lost revenue should not be a reason to avoid utilization management on outpatients, it is, nonetheless, a factor that needs to be acknowledged.

6. Testing that is ordered predominantly by one or a few physicians but not by others in the same area of medical specialty. This situation is not uncommon and can pose significant challenges. In some cases this reflects the unique patient population that is seen by the specialist. For

example, one neurologist may specialize in seeing patients with seizure disorders whereas other neurologists may see other types of patients (e.g., movement disorders, Alzheimer's disease). This alone could explain what initially might appear to be a peculiar test ordering pattern. In other cases a particular physician may be the only one ordering a certain test with no clear explanation. In our experience these physicians are often uncooperative or outright obstinate. There are a variety of approaches to dealing with this situation. These include forcing the physician to justify the test to a laboratory utilization committee (or medical policy committee), enlisting assistance from the physician's chief of service or the chief medical officer, having the physician develop his/her own guidelines followed by ongoing monitoring and feedback, or subjecting the test to a gatekeeping mechanism or a prior approval strategy. An alternative approach is simply to wait out the physician until testing strategies change or the physician leaves the health-care organization either through retirement or by moving to a different practice. In our hospital this has actually occurred on a number of occasions.

In the discussion that follows, we will review some of the utilization management tools listed in Table 2.3 and provide specific examples where these tools were used to implement utilization management initiatives. Many of these tools are discussed in detail in other chapters of this book and will not be further described here. These include:

1. Retaining a laboratory-based genetic counselor
2. Physician profiling
3. Establishing a laboratory formulary
4. Order entry design: decision support
5. Benchmarking
6. Clinical pathology consultative services

7. Prior authorization

Physician Education

Physician education to control utilization management has frequently been regarded as a weak intervention, and its impact is often of limited duration. However, depending on the specific educational objective, physician education can be very effective in a number of situations. There are many venues in which physician education can be delivered depending in part on the target audience, the complexity of the presentation, and the need to allow for discussion and feedback. Physician turnover can limit the longevity of the educational intervention especially in hospitals with large numbers of resident/fellow trainees or in services that rely on locum tenens coverage. Some of the available approaches to providing education include:

1. National medical conferences, hospital grand rounds, or morbidity and mortality rounds

2. Continuing education webinars and podcasts (includes internal webinars and those offered nationally)

3. Web-based written guidelines

4. Distributing literature and guidelines on subject areas

5. Developing websites with recommended approaches to laboratory testing

6. Emails sent to target physicians

7. In-person discussions such as attending resident hospital rounds or peer-to-peer discussions

8. Use of order entry pop-ups with educational content

The key is to first decide whether the utilization initiative can reasonably be expected to be successful using education alone and to plan on mechanisms to ensure its longevity. It is also necessary to develop metrics to monitor the effectiveness and persistence of the intervention. In most cases physician education involves developing practice guidelines or evidence-based approaches to clinical problems with the educational component being to disseminate and gain acceptance of the recommendations. In most cases it is best for the laboratory to enlist the aid of local clinical experts who are recognized by their peers. Educational materials arising exclusively from the laboratory will usually be regarded with skepticism. In one study, Thakkar et al. reported on the results of an educational intervention targeting the frequency of daily blood test orders in hospitalized patients [14]. The intervention involved education through flyers placed in providers' offices and email communications. They documented a mean decrease in complete blood counts from 1.46 to 1.37 tests per day and a decrease in basic metabolic panels from 0.91 to 0.83 tests per day. They did not report on the effectiveness of the intervention over the long term. In our hospital we attempted a similar intervention in which we required medical house staff to specifically decide which tests were needed each day as opposed to writing orders for tests as "daily until discontinued." We observed a significant decrease in test orders, but the number of orders rapidly returned to baseline after we stopped active management of the intervention. Similar issues with recidivism were also reported by May et al. [15].

Another approach we have used to educate physicians for selected esoteric tests (e.g., testing for tick-borne infections) employs personalized email communications to the providers. Many esoteric tests have a limited number of physicians who order the test with any frequency. First we do a computer search to identify the providers and the volume of tests that they order. We then send them an email with educational content. An example of a recent email is shown below.

Email to individual providers . Good day. You are probably aware that

the hospital is facing significant budget challenges. The clinical laboratories have been working with a number of medical services to identify tests of low or marginal clinical utility that can be eliminated from the test menu. One such test is serology IgG and IgM for Babesiosis. You are receiving this email because you have ordered two or more Babesia serologies based on a recent audit. Infectious disease specialists have concluded that the most appropriate test to detect active infection with Babesia is the thick and thin blood smear. Serologic tests cannot differentiate current from past infection and suffer from false negative and positive results. For this reason Babesia serology will no longer be offered by the clinical laboratory as the blood smear is the preferred approach. The MGH Medical Policy Committee has approved this change to the testing menu. We recognize that there may be occasional situations where the serologic test offers clinical value. The Pathology Core Laboratory resident on-call is available to approve these requests. The MGH Core Lab resident on call can be reached by paging 2–1827.

Physician Feedback

Physician feedback provides an interactive method to educate physicians about their test ordering patterns and may allow opportunities for one-on-one interactions. Typically the term “physician feedback” implies physician profiling (see chapter on physician profiling). However, this is not always the case. Feedback can take many forms such as posting test costs (or charges), gatekeeping of tests, creating order entry pop-ups with an educational component, performing physician-blinded variation analysis, or even simple interventions such as posting pending tests in the electronic medical record to alert the physician that the test has already been ordered. For example, Fig. 2.3a shows an electronic order entry pop-up screen that appears whenever a physician orders testing for creatine kinase MB isoenzyme (CK-MB). Note that the pop-up includes educational information on the updated rule out of myocardial infarction protocol. If the clinician decides to order the test anyway, a second screen pops-up requiring a reason for the test request. The success of the pop-up screen was monitored along with the reason given for the test by the clinician. Over time we observed an 80 % decrease in orders for CK-MB. Figure 2.3b shows the impact of the pop-up on CK-MB test orders over time. Inappropriate test orders could be monitored and individualized education provided to the physician .

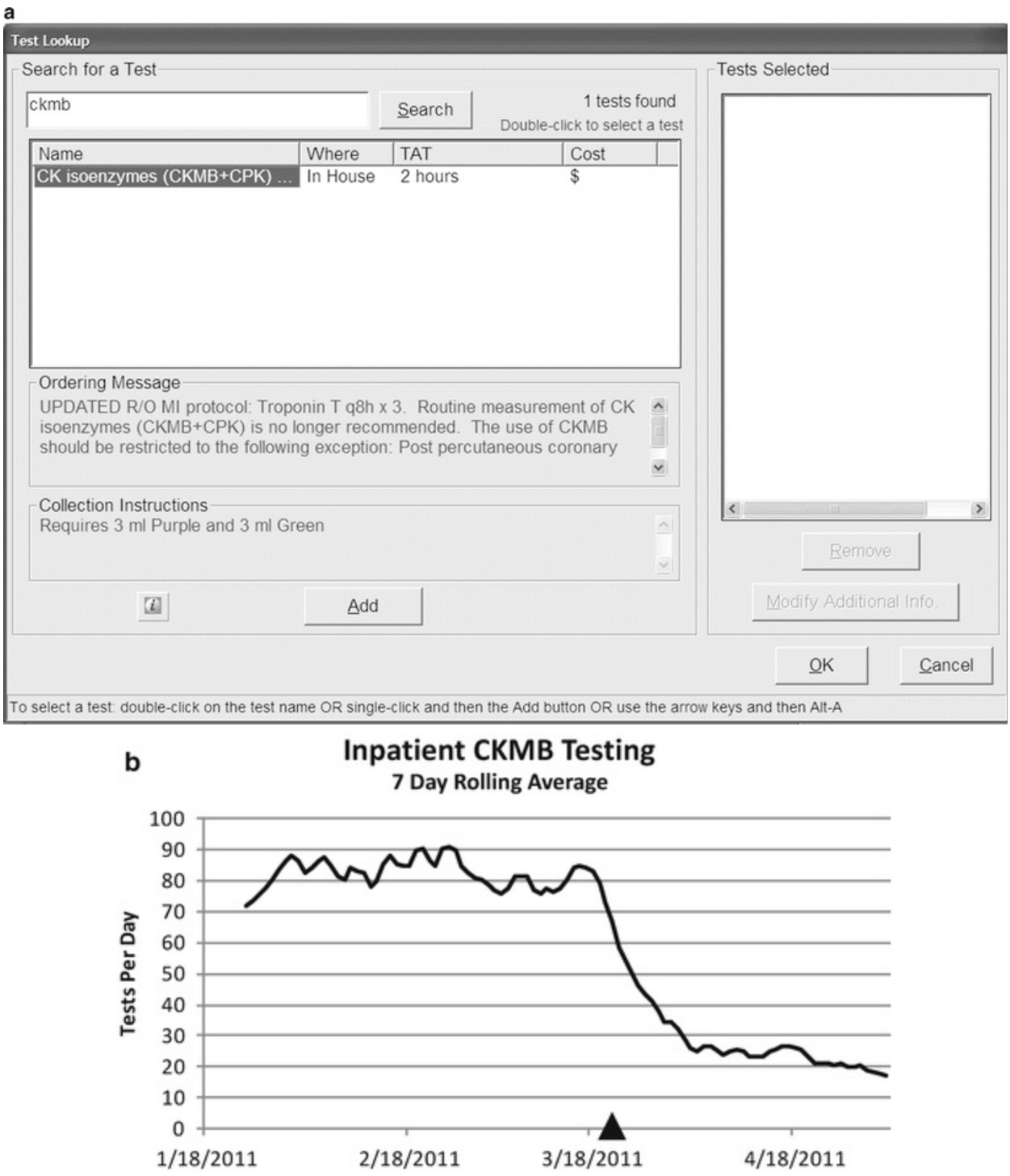


Fig. 2.3 (**a**) Order entry pop-up screen that appears when a physician requests testing for creatine kinase MB isoenzyme. When the test is requested, an ordering message is displayed describing the new rule out myocardial infarction (R/O MI) protocol and reminding the clinician that creatine kinase MB isoenzyme (CK-MB) and total creatine kinase enzyme (CPK) is no longer recommended. (**b**) Volume of creatine kinase MB isoenzyme test orders over time after implementation of an order entry pop-up screen. The pop-up was implemented in late March of 2011. The graph shows a significant decline in the test volume following implementation of the intervention

Another example of physician feedback is shown in Fig. 2.4. In this case we were attempting to determine which physicians were ordering genetic tests and their medical specialty. As shown in Fig. 2.4, there was significant variation in the dollar amount of genetic test orders among different providers. In addition, most of the top test ordering physicians by dollar volume were in pediatric genetics. The “profiling “data was provided to the pediatric genetics physicians with the identities of the individual providers blinded from the data set. We arranged a meeting with the pediatric genetics group to develop guidelines for appropriate test orders in different clinical scenarios. The result was an approximate $ 10,000 per month decrease in expenses for these tests .

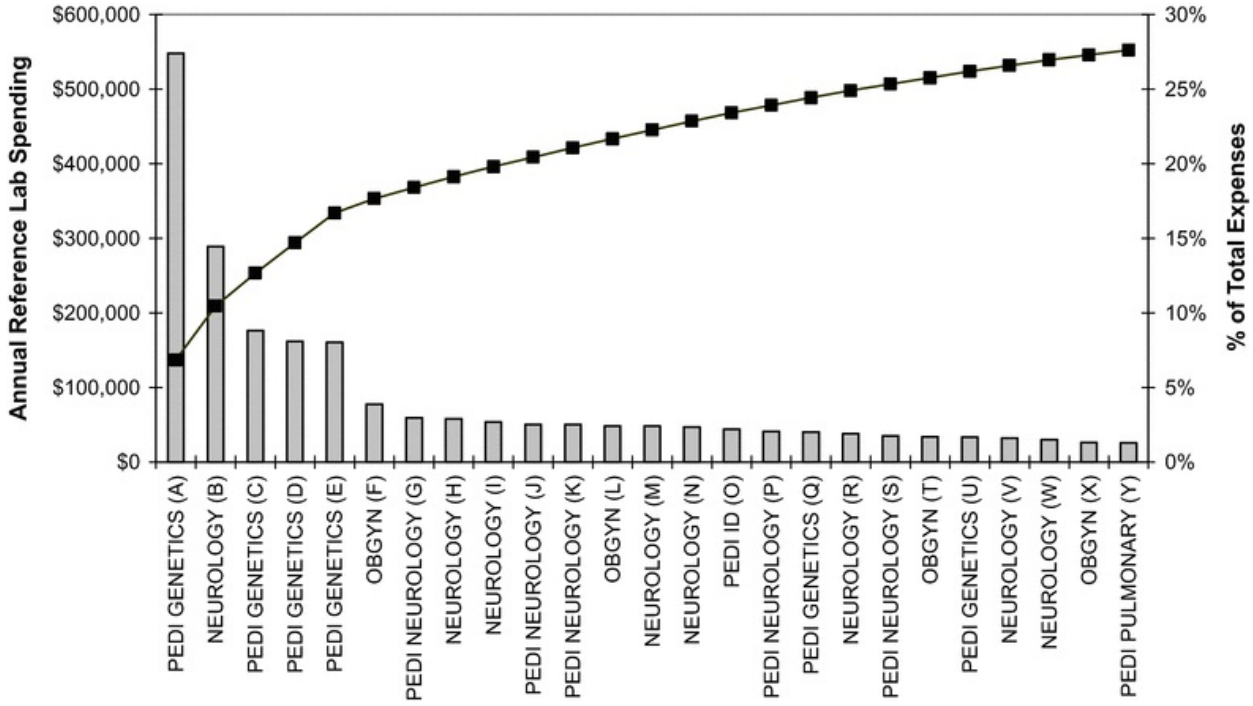


Fig. 2.4 Genetic testing ordered by different providers and their medical specialty. The graph shows the annual expense of genetic tests ordered by different providers and the *line* with *boxes* shows the cumulative expense across all providers. *Key*: individual providers are designated by letters A–Y, *Pedi* pediatric

Posting Laboratory Costs or Charges

Physicians are often unaware of the cost (or charges) for laboratory tests that they order. Posting the cost of laboratory tests may be complicated because

laboratories often do not know their true unit costs for many of the tests that they offer. Also when tests are eliminated, the laboratory does not save the average unit cost but rather only the variable cost as described earlier. An alternative approach is to post laboratory charges in the provider order entry system. In a study by Feldman et al., the authors reported the results of posting laboratory charges for 60 randomly assigned tests [16]. Following posting of the charges, there was a modest reduction in testing from an average of 3.72–3.40 tests per patient day. In our hospital we implemented a somewhat simpler strategy in which we post relative costs as $, $$, or $$. We have not evaluated the impact of this on test ordering patterns.

Requisition and Order Entry Screen Design

It has long been known that the design of a laboratory requisition (or order entry test screen) can have a significant positive or negative impact on laboratory test utilization. This may include:

1. Removing a test
2. Adding a test
3. Grouping of tests in a logical order
4. Adding an opportunity to order an automated algorithm (e.g., thyroid algorithm)

For example, several years ago we were receiving a number of test requests for celiac disease including anti-tissue transglutaminase, anti-gliadin, and anti-endomysial antibodies. Working with our clinical immunologists and gastroenterologists, we developed a celiac disease screening algorithm comprised of sequential testing of total IgA and tissue transglutaminase (IgA and/or IgG) levels. Gliadin antibodies would sometimes be added depending on the results of the TTG testing . Of note, endomysial antibody was an expensive test that had been sent out to a reference laboratory. A box for checking the new celiac algorithm was added to our outpatient order requisition. The gliadin and endomysial antibodies could still be requested as

"write-in" tests but were not specifically listed on the requisition. The impact on total testing volumes for celiac disease is shown in Fig. 2.5. Over time there was a significant reduction of testing for endomysial and gliadin antibodies without a corresponding increase in tissue transglutaminase antibodies.

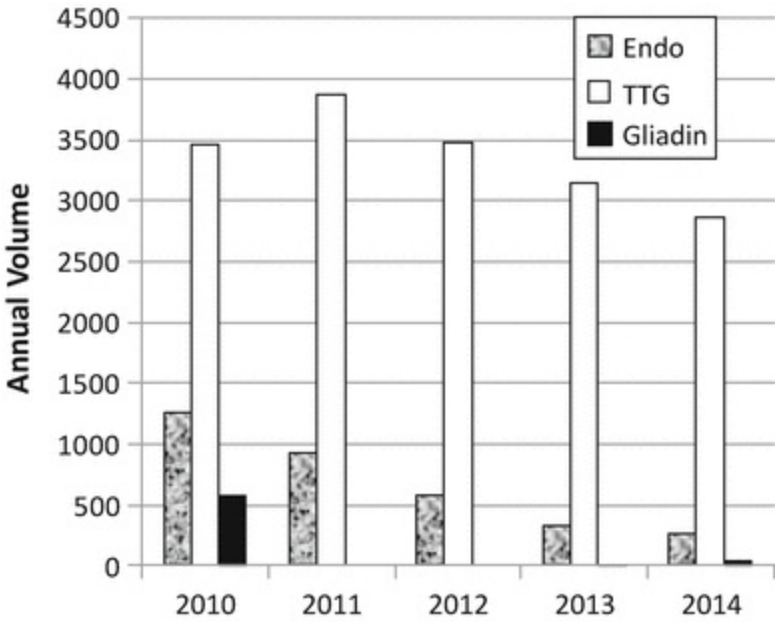


Fig. 2.5 Annual test volumes for celiac disease tests . *Key*: *Endo* anti-endomysial antibody, *TTG* anti-tissue transglutaminase antibody

In 1998 van Walraven reported the results of a multi-prolonged intervention strategy combining requisition changes, clinical guidelines, and changes to funding policy (Canada) that targeted testing for erythrocyte sedimentation rate, urine microscopic examination, renal function, iron stores, and thyroid function testing. They observed significant decreases in requests for these tests following the intervention [17].

In another example we reviewed our inpatient provider order entry (POE) system for opportunities to reduce unnecessary utilization. One feature of the POE system is a "quick pick" screen where common laboratory tests are displayed to make test ordering more convenient for the provider (Fig. 2.6). However, this also creates opportunities for overutilization as tests are easy to order and are visually presented to the clinician. We removed several tests from the quick pick screen that we thought were being overutilized including lactate dehydrogenase (LDH) and total creatine kinase (CPK). In the case of

LDH , there was a 54 % decrease in test orders following removal of the test from the screen.

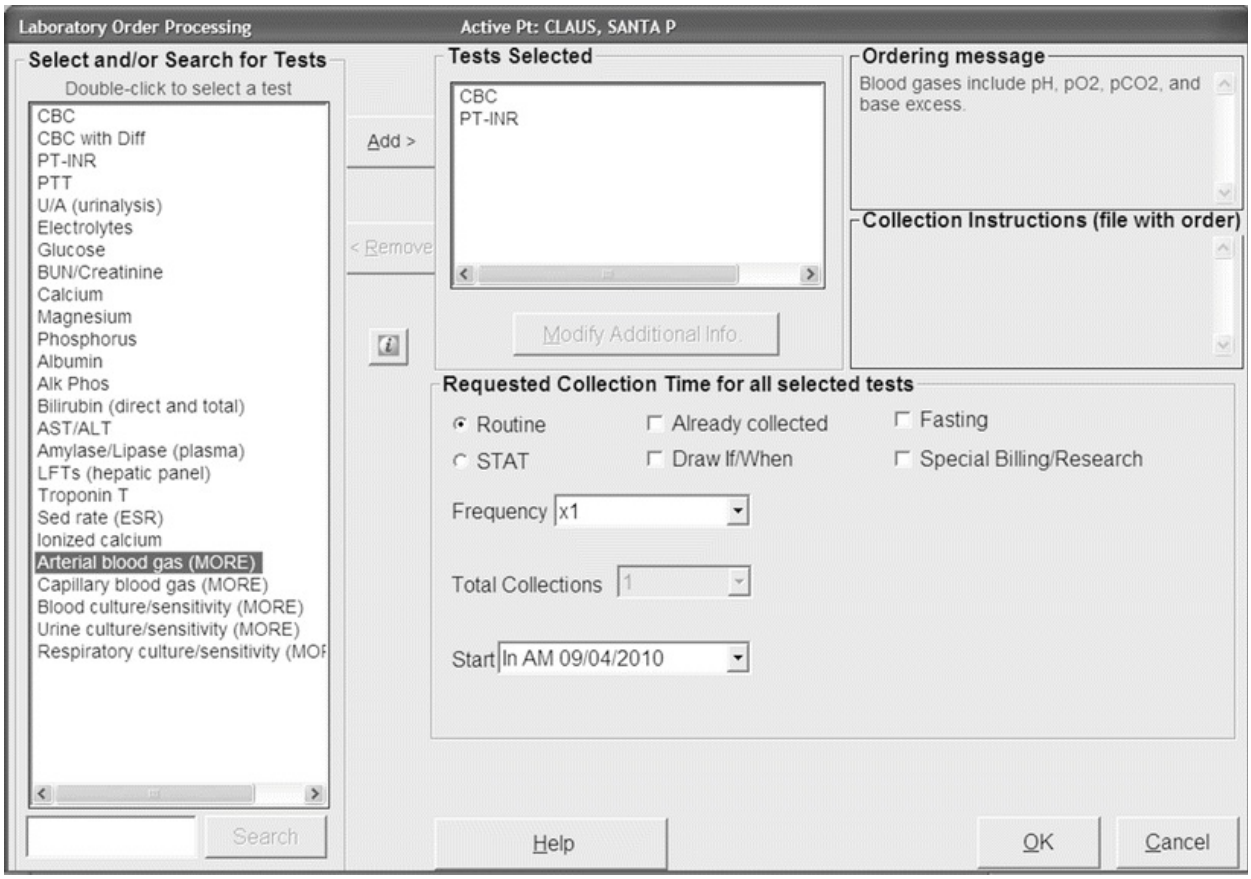


Fig. 2.6 Provider order entry "quick pick" screen: common tests that are ordered are displayed in the *box* on the *left*. Selected tests appear in the *center box*. Other ordering information is displayed in other locations on the screen

Develop an Electronic Laboratory Handbook

In the past many laboratories printed laboratory handbooks that could be distributed to physicians and staff. These books contained various information including the test menu, normal reference ranges, expected turnaround time, and specimen collection requirements. Although useful in their time, these books rapidly become out of date and are therefore unreliable. They also lack a user interface such as a search function to find test information and look for guidance in test selection and interpretation. Several years ago we developed an electronic online laboratory handbook that could be easily updated to incorporate changes in our laboratory services (Fig. 2.7). Because the handbook is readily available online in our hospital applications menu, it provides convenient access to testing information throughout our health-care network. Through the use of a search function, the clinician cannot only find test information but also guidance on what is the most appropriate test to order. For example, if the clinician types “CMV” into the search box, all of the related tests on our menu are shown along with which test is recommended in different clinical situations. This function eliminates unnecessary testing and also helps to ensure that the patient gets the right test.

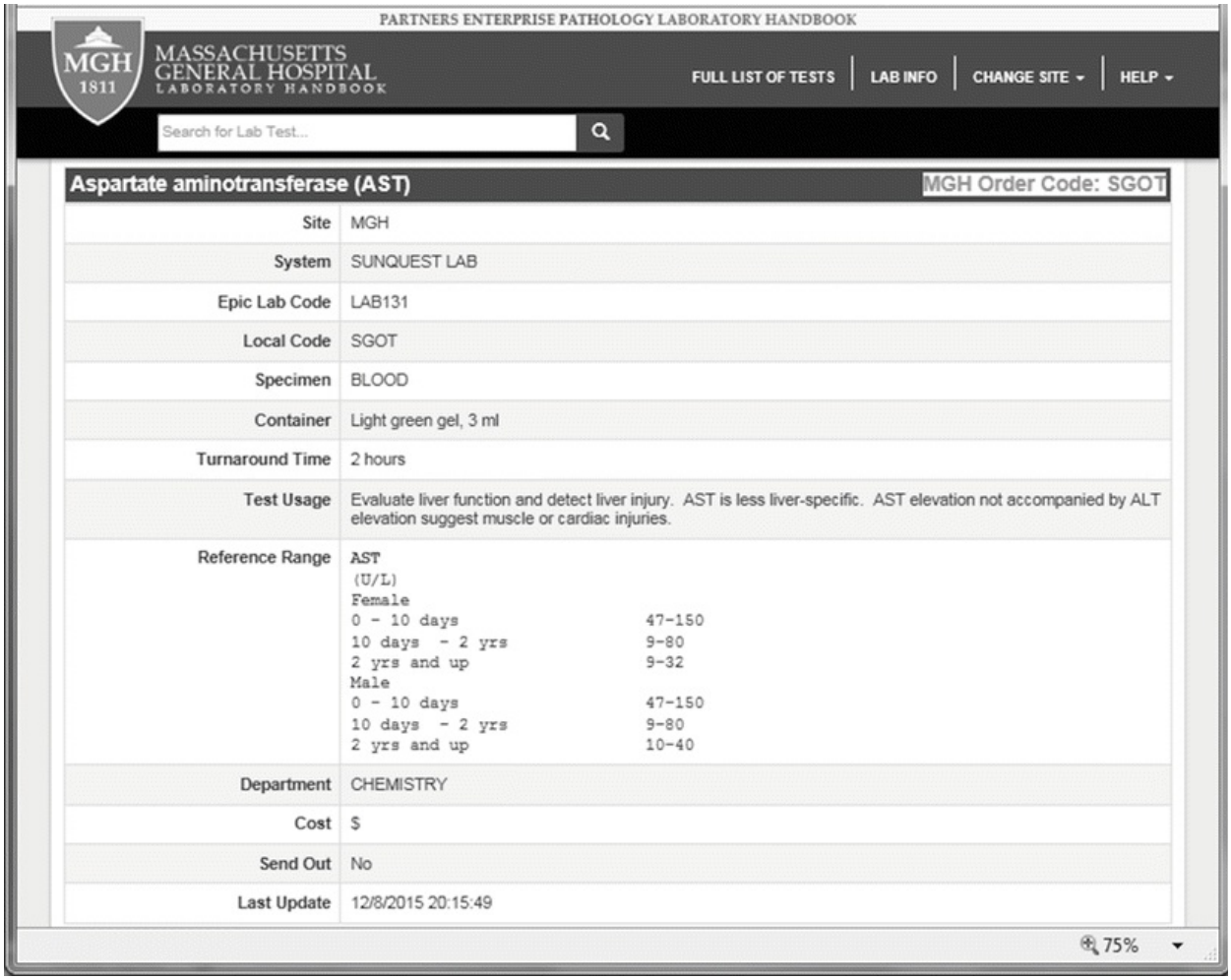


Fig. 2.7 Screen shot of the Massachusetts General Hospital On-Line Laboratory Handbook . Various information can be accessed from the screen such as critical values, reference ranges, reflex protocols, and laboratory policies

"Sound Alike" Tests Another use of the online handbook is to identify "sound alike" tests. For example, if the clinician types "vitamin D" into the search box, the following message appears.

Test Name	**Lab**	**Comment**
1–25-OH Vitamin D	*Chemistry* (*Sendouts*)	Please note that 1,25 OH vitamin D is in general NOT the test of choice for assessment of vitamin D deficiency. Please order 25-OH vitamin D if that is the intent
25-OH Vitamin D	*Core Lab*	25-OH vitamin D is the test of choice for evaluation of vitamin D deficiency. Test measures total 25-OH vitamin D (D2 and D3) by tandem mass spectrometry

In most situations 25-OH vitamin D is the preferred test to evaluate vitamin D status. However, clinicians often get confused by the “look alike” test, 1–25 OH vitamin D. The decision support function aids clinicians in test selection and also provides educational content at the time of the test order. This approach is much more effective than “after the fact” education once an error in test selection has already occurred.

Develop Practice Guidelines

Practice guidelines may be developed by national physician’s organizations, government agencies, or at the local level within an individual hospital or practice. Locally developed guidelines (even if modeled on national guidelines) tend to be the most effective as the relevant stakeholders will have provided input. The problem with guidelines is that they are usually voluntary and they may also fail to capture the nuances of real-world clinical practice. One of the earliest guidelines developed for laboratory testing is the now near universal thyroid screening algorithm as shown in Fig. 2.8. This screening guideline was highly effective because, in most cases, the patient only requires one test (thyroid-stimulating hormone). In the absence of the guideline, many physicians ordered multiple tests up front to ensure that all of the necessary results would be available with one blood draw. The algorithm is managed within the laboratory and can be automated on most immunoassay platforms. Over the years a large number of guidelines have been published. For example, in 1995 Kelly reported that more than 1700 clinical practice guidelines by national organizations were available [18]. That number has increased substantially since that time. He also noted that many complex issues occur in the development, dissemination, and implementation of guidelines. The most notable recent example of a practice guideline is the “Choosing Wisely” guidelines discussed earlier. However, other guidelines are potentially controversial, or there may be disagreement between different organizations as described above for screening for prostate cancer using prostate-specific antigen. Following the prostate screening guidelines issued by the United States Preventative Services Task Force, we began monitoring our PSA test volumes over time as shown in Fig. 2.9. Clearly there has been some decrease in the test volume but nowhere near as much as we had initially expected. This example illustrates the major problem with guidelines in that, for various reasons, physicians may choose

not to follow them, or they may be unaware of them. Requiring physicians to search online for guidelines is inconvenient and is usually ineffective. To help solve this problem, our hospital maintains an intranet website that lists a large number of practice guidelines and suggested approaches to various clinical problems. The site is called the Primary Care Office Insite (PCOI) . Most of our physicians are aware of the website. The Department of Veterans Affairs and Department of Defense has employed a similar approach which can be accessed on their website (http://www.healthquality.va.gov/). As one final example, our blood transfusion committee developed guidelines for the appropriate use of blood components including red blood cells, platelets, fresh frozen plasma, and cryoprecipitate. The guidelines contain a lot of detail and are impossible for the average physician to remember. The solution was to print plastic cards that could be attached to a physician's identification badge holder which made them readily available. Subsequently our blood bank set up a computer algorithm that can pull laboratory data to determine if individual transfusions were meeting the guidelines. In cases that they do not meet the guidelines, an email is sent to the ordering provider reminding them of the guidelines and provides ongoing education.

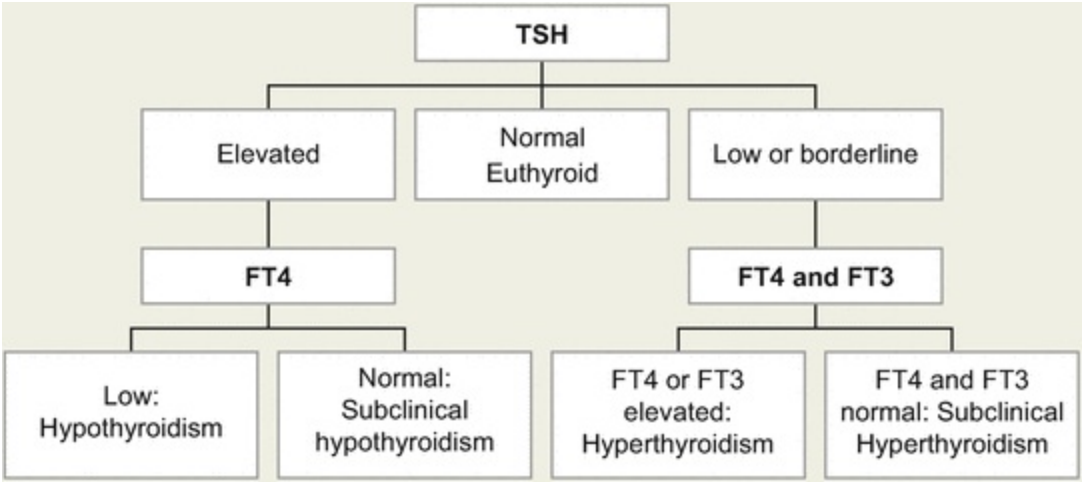


Fig. 2.8 Example of a thyroid screening algorithm . When a thyroid screen is ordered, only the initial test (TSH) is performed. Based on the result of the TSH test, other tests may be added. In most cases the TSH is normal and no further testing is required. *Key*: *TSH* thyroid-stimulating hormone, *FT4* free T4, *FT3* free T3

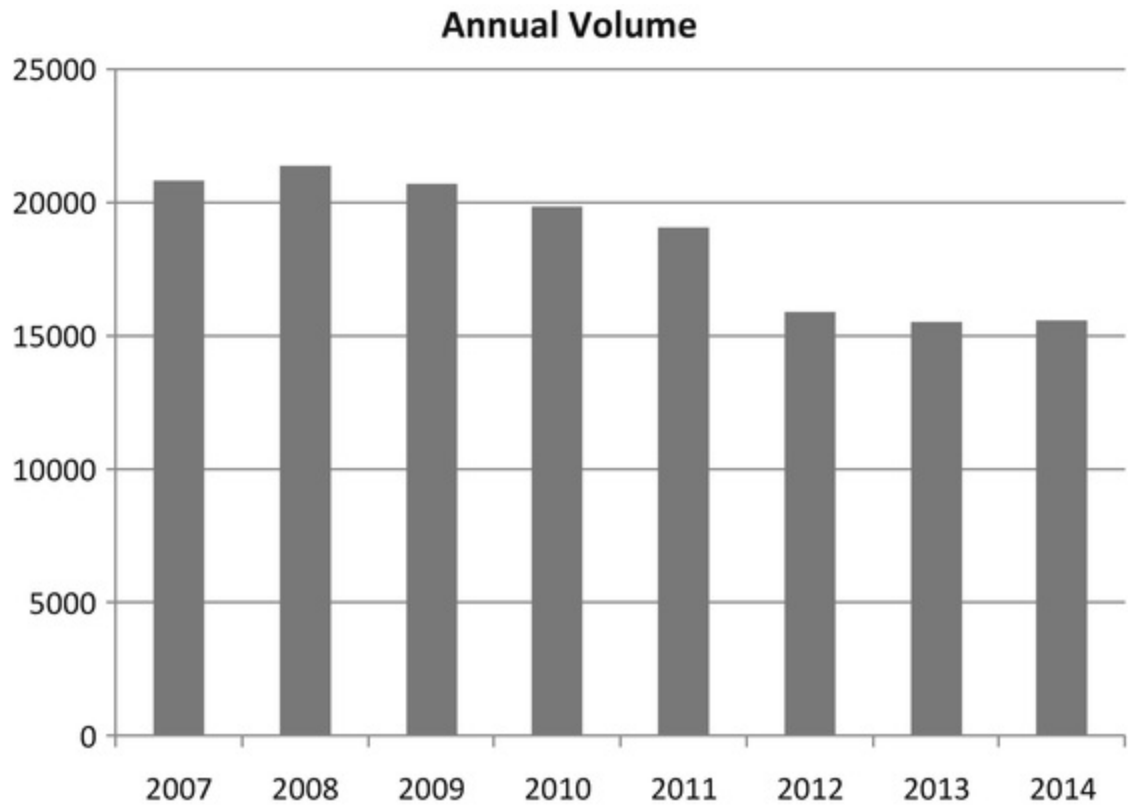


Fig. 2.9 Annual test volume for prostate-specific antigen . A modest decline in the test volume was observed over time

Regardless of their source, the keys to practice guidelines include the following:

1. They must be convenient to access during the course of clinical care.

2. They must be endorsed by key local clinicians and/or national physician's organizations.

3. Physicians must be made aware of them.

4. They must be clear, simple, and easy to understand.

Capture and Eliminate Same-Day Duplicate Tests

In most hospitals, especially academic medical centers, the medical team

caring for the patient may inadvertently order duplicate tests on the same day. In one study Bridges et al. evaluated the rate of duplicate orders for six tests (acute hepatitis panel, antinuclear antibody, vitamin B12 and folate, thyroid-stimulating hormone, and ferritin with iron/TIBC) [19]. The overall rate of duplicate tests was 7.7 %. In another study May et al. [15] described an intervention to reduce redundant test ordering utilizing the laboratory information system to capture duplicate orders and cancel them. They reported a 12 % decrease in inpatient tests.

Gatekeeping

Gatekeeping has long been utilized by third-party payers to restrict access to medical services [20]. In the past this activity rarely involved laboratory testing. However, the recent availability of high-cost genetic and molecular testing has led to a number of payers setting up prior approval requirements (gatekeeping) for these tests. However, gatekeeping has also been employed for the purpose of physician education by laboratory directors as a means to control utilization as described earlier in this chapter. In most cases this involves moderate- to high-cost tests that are requested in relatively low volume. Attempts to gatekeep higher-volume tests by direct human interaction will be logistically impossible. Electronic order entry can be employed in this situation. The gatekeeping strategy is basically an extension of what many hospitals currently do to control the use of expensive antibiotics which is usually managed by infectious disease physicians. Reports of gatekeeping initiatives in the clinical laboratory go back several decades. For example, in 1987 our hospital set up a mandatory laboratory approval for requests for lactic dehydrogenase isoenzyme analysis (LDH isoenzymes), a marker for myocardial infarction that was being supplanted by assays for creatine kinase MB isoenzyme. The gatekeeping effort reduced requests for LDH isoenzymes from approximately 2000 per month to 7 per month (>99 %). A number of studies have reported on similar successes. For example, Fryer et al. reported an 83 % decrease following a gatekeeping initiative for toxicology screens [21] and Hutton et al. an 85 % reduction in C-reactive protein testing [22]. Gatekeeping is an effective approach to utilization management on two fronts: first it imposes a barrier to ordering the test and, second, it creates an opportunity for physician education. Over time if the gatekeeping strategy with education is effective, the number of tests

that need to be reviewed should decline.

Restricting Inpatient Sendout Tests

A number of tests that are sent out to reference laboratories will not reasonably be expected to have a result during the time of the patient's hospital admission or will not contribute actionable information to impact treatment. This is particularly true for molecular genetic tests. Hospitals are beginning to gatekeep these tests or even ban their use on inpatients altogether. The test can then be deferred to the outpatient setting if it is truly needed. In another example, tests may be ordered up front in the context of the working differential diagnosis without knowledge by the physician of the turnaround time. However, once the diagnosis becomes clear, some of these may, in retrospect, not have been necessary. Kyle et al. reported an intervention targeting a paraneoplastic panel with a unit cost of $ 1757.50 and an expected turnaround time of 14–21 days. Panels that were requested on inpatients were reviewed with the ordering physician who frequently was unaware of the turnaround time. Overall 60 % of the requests were canceled [23].

Develop Admission Templates

A number of hospitals have implemented admission templates . Usually these are developed by interdisciplinary teams to specify physician's orders based on the admitting diagnosis. For example, we have templates for a variety of diagnoses such as heart failure, acute myocardial infarction, and pneumonia. The templates include nursing orders, pharmacy, laboratories, and other orders. The main purpose of the templates is threefold:

1. To standardize patient care across the hospital

2. To ensure that required tests, drugs, etc. are ordered and not forgotten

3. To assist in utilization management

In our hospital the laboratory and pharmacy reviews all templates to ensure good practice and assess opportunities for utilization management. On

a number of occasions , we have removed unnecessary tests and made other modifications to the templates.

Validate and Refine Reference Intervals

Many physicians, especially interns and junior residents , place considerable faith in the normal reference values published by their laboratories. Frequently values that are even slightly outside of the reference range prompt a clinical response which may include repeat or additional testing, specialist consultations, or other maneuvers. In some cases clinical laboratories have not made an adequate effort to ensure the accuracy of their reference ranges including considerations such as gender, ethnicity, and age. In other cases reference ranges are determined in a sloppy manner such as carrying over historical ranges to new assays or performing only a limited normal value study. For example, a laboratory might take 20 samples from volunteers in their lab. Given the current demographics of the medical technologist labor force, this approach will usually result in a sampling of a generally older population with a greater representation of females. It also assumes that all of the volunteers are indeed normal and healthy. Another approach that has been used is to take samples from presumptively healthy blood donors, but this also introduces certain population biases. If a reference range is not properly established, normal patients will exhibit abnormal laboratory values which may prompt further testing and intervention. Also, truly abnormal test results may be inappropriately designated as normal. As one illustration of this, we had long experienced a higher than expected rate of borderline hypokalemia . As a result, many fruitless clinical workups were occurring on an ongoing basis. Despite our best efforts, we could not identify the source of the problem. Eventually we were notified that the manufacturer was recalibrating their assay which would add 0.2 mol/L to each potassium result. The problem was immediately solved. As one follow-up we checked with the pharmacy who reported a significant decrease in potassium supplementation in our hospitalized inpatients. While this was a calibration issue and not a reference range issue, it does demonstrate the impact of reporting erroneous abnormal results. In another example, the reference range for our plasma chloride was not properly set with the lower end of the range set at 100 mmol/L. A number of clinicians complained about seeing too many patients with low chloride values compelling them to figure out what next steps to do. This represented

a significant waste of the physician's time. A survey of other hospitals using the same instrument as ours showed a different reference range prompting us to reassess our range and change it.

Develop Algorithms and Reflex Testing Protocols

In our hospital we have implemented over 200 reflex testing protocols . Some of these represent basic standards of practice (e.g., a negative rapid strep A test is reflexed to a throat culture), whereas others were designed with utilization management in mind. In some cases the optimal laboratory workup of a clinical problem is beyond the scope of knowledge of the typical clinician. In a study by Laposata et al., the authors reviewed the rate of inappropriate test orders in groups of physicians who either did or did not have access to our special coagulation testing algorithms. Physicians who did not have access to the algorithms averaged 3.56 test ordering errors per laboratory requisition compared to 1.62 errors for those who did [24]. In addition a significant percentage of physicians stated that the algorithms and laboratory interpretations saved them time, reduced the number of tests ordered, and helped prevent a misdiagnosis.

Often a physician is faced with a differential diagnosis that may require a number of laboratory tests. However, based on the results of an initial test, the differential diagnosis is narrowed thereby eliminating the need for many of the other tests. Algorithms ensure that the correct tests are performed and eliminate those that are not, even though this could not be foreseen in advance. Another example is the anemia algorithm described in the chapter on utilization management in hematology.

Restrict Orders for "Daily Until Discontinued" Laboratory Testing

In many hospitals, especially academic medical centers, physicians (interns and residents) order laboratory tests as "daily until discontinued ." Usually this includes a complete blood count (CBC), basic metabolic panel, and calcium/phosphorus/magnesium. There are several reasons for this practice:

1. Many hospital patients are very ill and may require frequent monitoring.

2. The resident may be afraid of criticism if laboratory values are not available during patient rounds.

3. Convenience: Most residents are very busy and must work within required duty hours. By putting the common laboratory tests on "autopilot," there is one less item to have to think about.

This practice is obviously wasteful and contributes to iatrogenic anemia. In the past we attempted to reduce this practice with the exceptions of the CBC in oncology patients, immunosuppressant drug levels, and coagulation testing on patients on heparin or Coumadin. In most cases the preferred approach is to assess each patient on a regular basis and determine what tests will be required for that day. We attempted various educational activities at house officer conferences and performed a short pilot project (described above) with little long-term success. Subsequently we implemented an order entry pop-up screen as shown in Fig. 2.10 and began an audit of who was ordering "daily labs." Any physician who ordered four or more "daily labs" in a 1-week period received an email as shown in below:

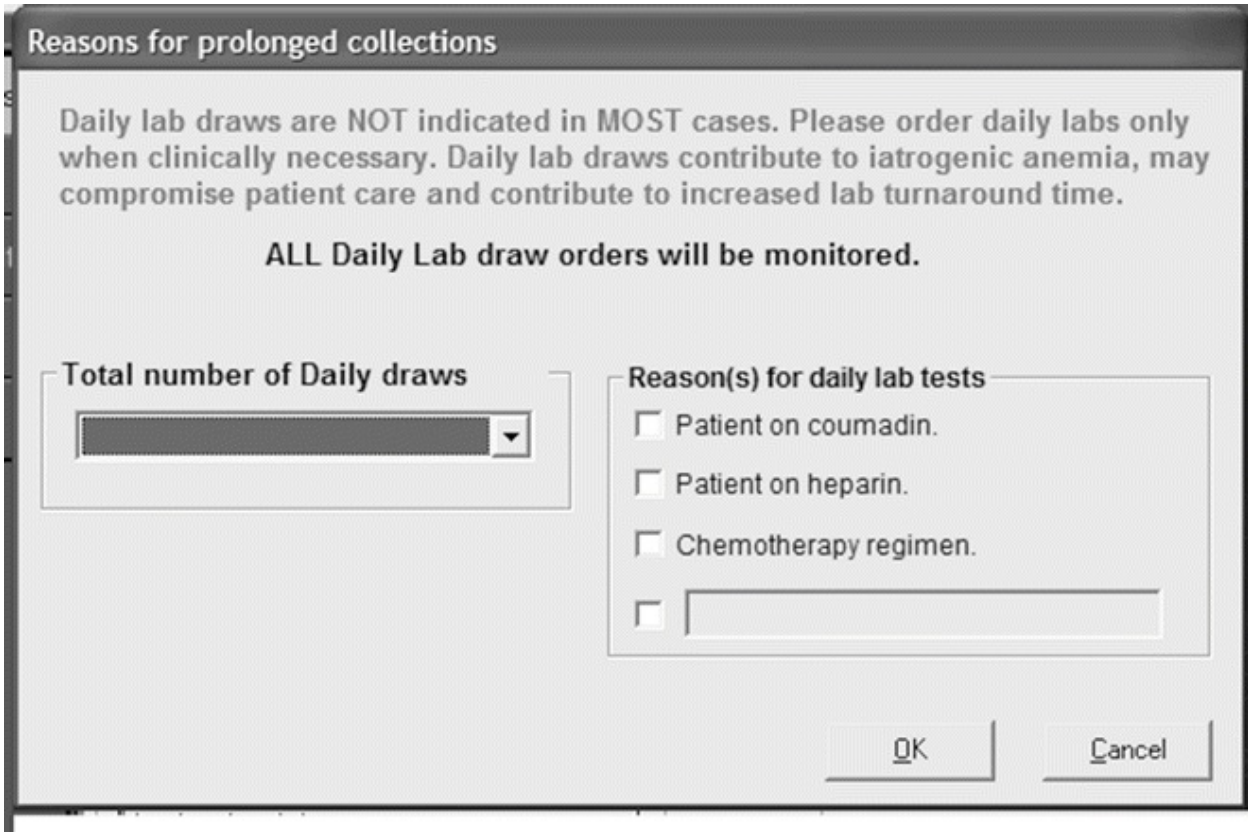


Fig. 2.10 Order entry "pop-up" screen for "daily labs ." If a request is made for "daily labs," a pop-up screen appears stating the hospital policy and a reason for the request is required

You are receiving this e-mail because during the past week, you placed 4 or more orders for recurrent daily labs without an apparent approved indication.

Inappropriate use of recurrent laboratory orders can inadvertently lead to unnecessary testing. Excess laboratory testing places patients at increased risk for hospital acquired anemia. Moreover, unneeded testing can also reduce patients' experience of care, waste nursing and laboratory resources and lead to increased turnaround-time for needed laboratory tests.

Per MGH ordering guidelines, orders for recurrent daily labs should only be used in the following five situations:

1. To monitor PTT in patients receiving heparin

2. To monitor PT/INR in patients receiving Coumadin

3. To monitor labs needed to safely manage or treat chemotherapy patients

4. For immunosuppressant monitoring

5. For reasons included on approved MGH order templates, if tests are ordered using the template

This policy has been approved by the MGH Medical Policy Committee.

Over time we have achieved a significant reduction in "daily lab" orders as shown in Fig. 2.11. The progress we observed suggests a slow but steady culture change is occurring among the residents who order the majority of the testing on hospital inpatients. In the future we plan to block all daily orders in our order entry system with the exception of the indications mentioned above.

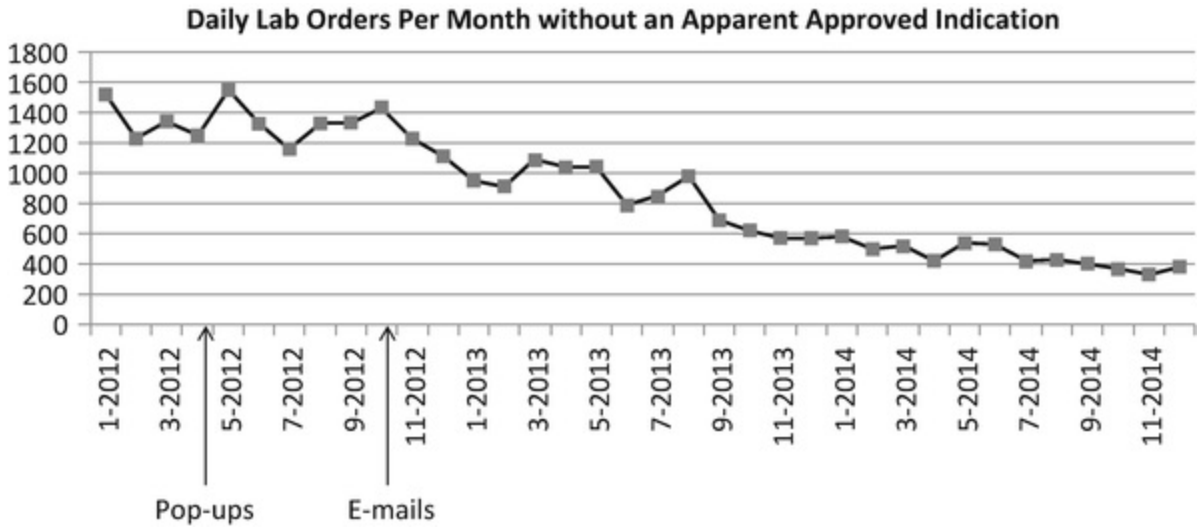


Fig. 2.11 Number of "daily lab" orders per week without an apparent approved indication. Over time following multiple interventions the number of non-approved requests for "daily labs" showed a significant and steady decline

Restrict Which Physicians or Specialists Can Order

Expensive Tests

A number of hospitals have set up systems where only certain physician specialists can order expensive tests. In most cases these restrictions target tests in genetics, neurology, and infectious disease. The strategy recognizes that these tests may be important for some patients but that most nonspecialists lack an adequate understanding of when the tests are appropriate or should be avoided. For example, a patient with a complex presentation may generate a long differential diagnosis that would require many diverse tests to be ordered. However, a specialist can often narrow the differential diagnosis and select only those tests that are most likely to be informative. This strategy can be built into hospital laboratory formularies as discussed in a subsequent chapter.

Restrict Orders for Tests That Should Never Be Ordered More Than Once

Delivery of care is often fragmented across a health-care network. A test may be ordered by one physician, but the result may not be widely available or may be difficult to find in the electronic medical record. In addition, many physicians may fail to look at what tests are already available resulting in duplicate orders. For obvious reasons genetic tests should never be ordered more than once on an individual patient. However, some nongenetic tests should also not be ordered more than once in the course of a patient's workup for a given clinical problem. When a patient is seen by multiple clinicians and specialists, duplicate tests may be ordered. The laboratory can use the order entry system or the laboratory information system to identify and cancel redundant orders for tests that should only be ordered once during a given clinical evaluation. At a minimum, tests that are already pending in the system should be identified clearly in the electronic medical record so that clinicians are aware that the test is in the system awaiting a result.

Conclusion

Increasing pressures to contain costs in the American health-care system will continue to drive efforts to manage the utilization of medical resources including the clinical laboratory. Physicians should be leaders in this process

to ensure that the quality of patient care is not compromised. In the case of laboratory medicine, clinical pathologists are ideally suited to lead the utilization management program while working in collaboration with clinicians and administrators. Many examples of utilization management initiatives have been described in the literature. Successful implementation of such initiatives can be accomplished using a variety of strategies (tools) so long as the most appropriate strategy is selected to match the individual initiative. More detail concerning many of the topics described in this manuscript can be found in the chapters that follow.

References

1. Rao S. Utilization management in a changing healthcare environment. Clin Chim Acta. 2014;427:109–10.
[CrossRef][PubMed]

2. McConnell T, Berger P, Dayton H, Umland B, Skipper B. Professional review of laboratory utilization. Human Pathol. 1982;13:399–403.
[CrossRef]

3. Weinstein M, Smith G. Automation in the clinical pathology laboratory. N C Med J. 2007;68:130–1.
[PubMed]

4. Salisbury A, Alexander K, Reid K, Masoudi F, Rathore S, et al. Incidence, correlates, and outcomes of acute, hospital acquired anemia in patients with myocardial infarction. Circ Cardiovasc Qual Outcomes. 2010;3:337–46.
[CrossRef][PubMed][PubMedCentral]

5. U.S. Preventive Services Task Force. Final recommendation statement: prostate cancer: screening. 2014. http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/prostate-cancer-screening.

6. Walraven C, Naylor D. Do we know what inappropriate laboratory utilization is: a systematic review of laboratory clinical audits. JAMA. 1998;280:550–8.
[CrossRef][PubMed]

7. Hauser R, Shirts B. Do we know what inappropriate laboratory utilization is: an expanded systematic review of laboratory clinical audits. Am J Clin Pathol. 2014;141:774–83.
[CrossRef][PubMed]

8. Grumet G. Health care rationing through inconvenience. NEJM. 1989;321:607–11.
[CrossRef][PubMed]

9. Zhao J, Liberman A. Pathologists role in clinical utilization management: a financing model for managed care. Am J Clin Pathol. 2000;113:336–42.

[CrossRef][PubMed]

10. Kim J, Dzik W, Dighe A, Lewandrowski K. Utilization management in a large urban academic medical center: a 10-year experience. Am J Clin Pathol. 2011;135:108–18.
[CrossRef][PubMed]

11. Winkelman J. Less utilization of the clinical laboratory produces diproportionately small true cost reductions. Hum Pathol. 1984;15:499–501.
[CrossRef][PubMed]

12. National Physicians Alliance Promoting Good Stewardship in Medicine. http://npalliance.org/promoting-good-stewardship-in-medicine-project/. Accessed 23 Mar 2015.

13. Good Stewardship Working Group. The "top 5" lists in primary care: meeting the responsibility of professionalism. Arch Intern Med. 2011;171:1385–90.
[CrossRef]

14. Thakkar R, Kim D, Knoght A, Riedel S, Vaidya D, Wright S. Impact of an educational intervention on the frequency of daily blood test orders for hospitalized patients. Am J Clin Pathol. 2015;143:393–7.
[CrossRef][PubMed]

15. May T, Clancy M, Critchfield J, Ebling F, Enriguez A, et al. Reducing unnecessary inpatient laboratory testing in a teaching hospital. Am J Clin Pathol. 2006;126:200–6.
[CrossRef][PubMed]

16. Feldman L, Shihab H, Thiemann D, Yeh H, Ardolino M, Mandell S, Brotman D. Impact of providing fee data on laboratory test ordering. JAMA Intern Med. 2013;173:903–8.
[CrossRef][PubMed]

17. van Walraven C, Goel V, Chan B. Effect of population-based interventions on laboratory utilization. JAMA. 1998;280:2028–33.
[CrossRef][PubMed]

18. Kelly J. Role of clinical practice guidelines and clinical profiling in facilitating optimal laboratory use. Clin Chem. 1995;41:1234–6.
[PubMed]

19. Bridges S, Papa L, Norris A, Chase S. Duplicate laboratory tests: a hospital audit. Clin Chem. 2012;58:1371–2.
[CrossRef][PubMed]

20. Wickizer T, Lessler D. Utilization management: issues, effects and future prospects. Annu Rev Public Health. 2002;23:233–54.
[CrossRef][PubMed]

21. Fryer A, Smellie W. Managing demand for laboratory tests: a laboratory toolkit. J Clin Pathol. 2013;66:62–72.
[CrossRef][PubMed]

22. Hutton H, Drummond H, Fryer A. The rise and fall of C-reactive protein: managing demand within clinical biochemistry. Ann Clin Biochem. 2009;45:155–8.

[CrossRef]

23. Kyle A, Petterson L, Reed K. Reducing laboratory costs through education-based gatekeeping. Arch Pathol Lab Med. 2014;138:301.
[CrossRef]

24. Laposata M, Laposta M, Van Cott E, Buchner D, Kashalo M, Dighe A. Physician survey of laboratory medicine interpretive service and evaluation of the influence of interpretations on laboratory test ordering. Arch Pathol Lab Med. 2004;128:1424–7.
[PubMed]

Supplemental References Not Cited in Text Complied by Amelia Huck, MD

Smellie WSA. Demand management and test request rationalization. Ann Clin Biochem. 2012;49:323–36.
[CrossRef][PubMed]

Jackson BR. Managing laboratory test use: principles and tools. Clin Lab Med. 2007;27:733–48.
[CrossRef][PubMed]

Ezzie ME, Aberegg SK, O'Brien JM. Laboratory testing in the intensive care unit. Crit Care Clin. 2007;23:435–65.
[CrossRef][PubMed]

Rao GG, Crook M, Tillyer ML. Pathology tests: is the time for demand management ripe at last? J Clin Pathol. 2003;56:243–8.
[CrossRef][PubMed]

Larsson A, Palmer M, Hultén G, Tryding N. Large differences in laboratory utilisation between hospitals in Sweden. Clin Chem Lab Med. 2000;38:383–9.
[CrossRef][PubMed]

van Walraven C, Naylor CD. Do we know what inappropriate laboratory utilization is? A systematic review of laboratory clinical audits. JAMA. 1998;280:550–5.
[CrossRef][PubMed]

Benson ES. The responsible use of the clinical laboratory. Clin Biochem. 1986;19:262–70.
[CrossRef][PubMed]

Lewandrowski K. Managing utilization of new diagnostic tests. Clin Leadersh Manag Rev. 2003;17:318–24.
[PubMed]

Young DW. Improving laboratory usage: a review. Postgrad Med J. 1988;64:283–9.
[CrossRef][PubMed][PubMedCentral]

Wickizer TM, Lessler D. Utilization management: issues, effects, and future prospects. Annu Rev Public Health. 2002;23:233–54.

[CrossRef][PubMed]

Fryer AA, Smellie WSA. Managing demand for laboratory tests: a laboratory toolkit. J Clin Pathol. 2013;66:62–72.
[CrossRef][PubMed]

Emerson JF, Emerson SS. The impact of requisition design on laboratory utilization. Am J Clin Pathol. 2001;116:879–84.
[CrossRef][PubMed]

Miyakis S, Karamanof G, Liontos M, Mountokalakis TD. Factors contributing to inappropriate ordering of tests in an academic medical department and the effect of an educational feedback strategy. Postgrad Med J. 2006;82:823–9.
[CrossRef][PubMed][PubMedCentral]

Tierney WM, Miller ME, McDonald CJ. The effect on test ordering of informing physicians of the charges for outpatient diagnostic tests. N Engl J Med. 1990;322:1499–504.
[CrossRef][PubMed]

Wang TJ, Mort EA, Nordberg P, Chang Y, Cadigan ME, Mylott L, Ananian LV, Thompson BT, Fessler M, Warren W, Wheeler A, Jordan M, Fifer MA. A utilization management intervention to reduce unnecessary testing in the coronary care unit. Arch Intern Med. 2002;162:1885–90.
[CrossRef][PubMed]

Qureshi AI, Suri FK, Guterman LR, Hopkins N. Ineffective secondary prevention in survivors of cardiovascular events in the US population: report from the third national health and nutrition examination survey. Arch Intern Med. 2001;161:1621–8.
[CrossRef][PubMed]

McConnell TS, Berger PR, Dayton HH, Umland BE, Skipper BE. Professional review of laboratory utilization. Hum Pathol. 1982;13:399–403.
[CrossRef][PubMed]

Forsman RW. Why is the laboratory an afterthought for managed care organizations? Clin Chem. 1996;42:813–6.
[PubMed]

Lundberg GD. The modern clinical laboratory: justification, scope, and directions. JAMA. 1975;232:528–9.
[CrossRef][PubMed]

Salisbury AC, Reid KJ, Alexander KP, Masoudi FA, Lai SM, Chan PS, Bach RG, Wang TY, Spertus JA, Kosiborod M. Diagnostic blood loss from phlebotomy and hospital-acquired anemia during acute myocardial infarction. Arch Intern Med. 2011;171:1646–53.
[CrossRef][PubMed]

Salisbury AC, Alexander KP, Reid KJ, Masoudi FA, Rathore SS, Wang TY, Bach RG, Marso SP, Spertus JA, Kosiborod M. Incidence, correlates, and outcomes of acute, hospital-acquired anemia in patients with acute myocardial infarction. Circ Cardiovasc Qual Outcomes. 2010;3:337–46.
[CrossRef][PubMed][PubMedCentral]

Winkelman JW. Less utilization of the clinical laboratory produces disproportionately small true cost

reductions. Hum Pathol. 1984;15:499–501.
[CrossRef][PubMed]

Good Stewardship Working Group. The ‘top 5’ lists in primary care: meeting the responsibility of professionalism. Arch Intern Med. 2011;171:1385–90.
[CrossRef]

Five things physicians and patients should question. http://www.choosingwisely.org/doctor-patient-lists. Accessed 24 Apr 2013.

Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2012;157:120–34.
[CrossRef][PubMed]

Catalona WJ, D’Amico AV, Fitzgibbons WF, Kosoko-Lasaki O, Leslie SW, Lynch HT, Moul JW, Rendell MS, Walsh PC. What the U.S. Preventive Services Task Force missed in its prostate cancer screening recommendation. Ann Intern Med. 2012;157:137–8.
[CrossRef][PubMed]

Wong ET, McCarron MM, Shaw Jr ST. Ordering of laboratory tests in a teaching hospital: can it be improved? JAMA. 1983;249:3076–80.
[CrossRef][PubMed]

Larsson A, Blom S, Wernroth M, Hultén G, Tryding N. Effects of an education programme to change clinical laboratory testing habits in primary care. Scand J Prim Health Care. 1999;17:238–43.
[CrossRef][PubMed]

Kumwilaisak K, Noto A, Schmidt UH, Beck CI, Crimi C, Lewandrowski K, Bigatello LM. Effect of laboratory testing guidelines on the utilization of tests and order entries in a surgical intensive care unit. Crit Care Med. 2008;36:2993–9.
[CrossRef][PubMed]

Bunting PS, van Walraven C. Effect of a controlled feedback intervention on laboratory test ordering by community physicians. Clin Chem. 2004;50:321–6.
[CrossRef][PubMed]

Solomon DH, Hashimoto H, Daltroy L, Liang MH. Techniques to improve physicians’ use of diagnostic tests: a new conceptual framework. JAMA. 1998;280:2020–7.
[CrossRef][PubMed]

Warren JS. Laboratory test utilization program: structure and impact in a large academic medical center. Am J Clin Pathol. 2013;139:289–97.
[CrossRef][PubMed]

Kim JY, Dzik WH, Dighe AS, Lewandrowski KB. Utilization management in a large urban academic medical center: a 10-year experience. Am J Clin Pathol. 2011;135:108–18.
[CrossRef][PubMed]

MacMillan D, Lewandrowski E, Lewandrowski K. An analysis of reference laboratory (send out) testing: an 8-year experience in a large academic medical center. Clin Leadersh Manag Rev. 2004;18:216–9.
[PubMed]

Liu Z, Abdullah A, Baskin L, Lewis G, Kelter G, Naugler C. An intervention to reduce laboratory utilization of referred-out tests. Lab Med. 2012;43:164–7.
[CrossRef]

Durand-Zaleski I, Roudot-Thoraval F, Rymer JC, Rosa J, Revuz J. Reducing unnecessary laboratory use with new test request form: example of tumour markers. Lancet. 1993;342:150–3.
[CrossRef][PubMed]

Grisson R, Kim JY, Brodsky V, Kamis IK, Singh B, Belkziz SM, Batra S, Myers HJ, Demyanov A, Dighe AS. A novel class of laboratory middleware promoting information flow and improving computerized provider order entry. Am J Clin Pathol. 2010;133:860–9.
[CrossRef][PubMed]

Thomas Hindmarsh J, Lyon AW. Strategies to promote rational clinical chemistry test utilization. Clin Biochem. 1996;29:291–9.
[CrossRef]

Kratz A, Laposata M. Enhanced clinical consulting—moving toward the core competencies of laboratory professionals. Clin Chim Acta. 2002;319:117–25.
[CrossRef][PubMed]

Laposata ME, Laposata M, Van Cott EM, Buchner DS, Kashalo MS, Dighe AS. Physician survey of a laboratory medicine interpretive service and evaluation of the influence of interpretations on laboratory test ordering. Arch Pathol Lab Med. 2004;128:1424–7.
[PubMed]

Health care costs: a Primer—Kaiser Family Foundation. http://www.kff.org/insurance/7670.cfm. Accessed 24 Apr 2013.

Song Z, Safran DG, Landon BE, He Y, Ellis RP, Mechanic RE, Day MP, Chernew ME. Health care spending and quality in year 1 of the alternative quality contract. N Engl J Med. 2011;365:909–18.
[CrossRef][PubMed][PubMedCentral]

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_3

3. Effective Governance Structure and Management of Utilization Programs

Jeffrey S. Warren[1]

(1) Department of Pathology, University of Michigan Medical School, 1301 Catherine Street, Ann Arbor, MI 48109, USA

Jeffrey S. Warren
Email: warren@med.umich.edu

Keywords Governance – Utilization management – Reference testing – Cost curve – Personalized medicine – Precision medicine – Whole-genome sequencing – Esoteric tests – Prospective payment

Effective governance is fundamentally important to the operation of a successful utilization management program . To ensure success in the context of pathology and laboratory utilization management, the governance structure must foster both institutional and institution-wide goals . Implicit in this statement is the idea that without careful attention to alignment, the overarching goals of an institution may clash with the disparate activities and goals of the many constituencies across an institution. There is a paucity of literature that systematically addresses the particular relationship between governance structure and effectiveness of laboratory utilization management; analysis of both failed and successful programs can provide insight into the critical importance of this relationship. Perusal of agendas from recent laboratory industry conferences, chapter titles from laboratory medicine texts, and content from online continuing education vehicles provides clear-cut

evidence that effective resource utilization is a high priority. Formal leadership development and the broad application of advanced management practices to the provision of pathology and laboratory services were largely neglected prior to the past two decades. Effective leadership and management require sharp organizational skills, consistent communication, tenacity, and persistence. Ongoing measurement and communication of progress are critical attributes of successful programs.

The causes and ramifications of the stratospheric—and still-rising—cost of health care in the United States continue to be discussed in the lay press, general medical literature, and laboratory medicine-specific practice publications [1–5]. The first two chapters of this text provided an important contextual framework for understanding the "high cost of health-care challenge." This chapter provides an overview of governance structure and management, a framework that considers how a utilization management program can effectively function within an institution at large. The remaining chapters describe key strategies and tools that underpin effective comprehensive utilization management programs. Many of the specific approaches to effective management are influenced by setting whether type of institution, type of laboratory (e.g. hospital-based, reference), or particular laboratory discipline.

It should be emphasized that utilization management is only one facet of an overarching strategy to better utilize pathology and laboratory services resources. Maximally efficient provision of pathology and laboratory services also requires:

> rational laboratory organization (e.g., optimal layout of work flow, flexible space design, grouping of like technologies), horizontal integration of laboratory-related activities (e.g., specimen procurement and transport, oversight of point-of-care and sendout reference laboratory testing), consistent focus on effective work processes (e.g., lean process improvement), cohesive administrative oversight of all facets of laboratory operations (e.g., quality assurance, instrument selection, training oversight), timely deployment of demonstrably effective technological enhancements (e.g., automation, robust information technology), systematic "make-buy" analyses of test offerings with rational "new test" additions and "old test" discontinuations, and aggressive pursuit of best pricing for expensive

commodities (e.g., blood products, vendor services, reference tests).

While the focus of this chapter is governance of utilization management, optimal alignment of governance and management structure is critical to all facets of an effective laboratory operation.

Utilization Management: Two Layers of Context

Ultimately, “perfect …or optimal” utilization management encapsulates the ideal that presently available or attainable resources can be applied to the care of individual patients without waste or misdirection. It is useful to consider utilization management of pathology and laboratory resources in two contexts, as a component of overall health-care delivery (e.g., nationwide or regional) as well as within the specific institution-wide practice of pathology and laboratory medicine . The decades-long runaway growth in expenditures for health care in the United States has been well chronicled [1–5]. Excessive spending for health care threatens American competitiveness in the global economy [4, 5]. Accordingly, this issue has been the focal point of intense political debate and resulting—albeit embryonic or not yet fully implemented—policy changes centered around mechanisms of funding, reimbursement for services, and a desired shift in orientation toward value-based care [6–9]. Early returns reveal that recent reforms have expanded patient access and, coupled with recent general economic conditions, may have begun to “flatten the cost curve ” [2, 3, 6]. The durability of this downtick in the growth rate of cost and its impact on quality of care remain to be definitively demonstrated. Because pathology and laboratory data drive many critical patient care decisions, the impact on downstream clinical outcomes and cost is multiplied.

Direct expenditures (and reimbursements) for pathology and laboratory services presently constitute a relatively small proportion of the overall direct cost of health care. Current estimates indicate that the direct cost of pathology and laboratory testing account for 3–4 % of health-care cost ($70 billion per year) [10–12]. That pathology and laboratory services account for “only” 3–4 % of the total belie the broader importance of utilization management within this domain. Physicians “trigger” the bulk of direct health-care costs, medical decisions are frequently influenced by the consideration of laboratory data, and the overwhelming majority of electronic medical record transactions include views of laboratory results [13–16]. While these studies do not all

provide insight into the “appropriateness” of laboratory utilization, other data suggest that there is little correlation between numbers of tests ordered and patient care outcomes [13]. Similarly, although there are substantial geographic variations in test usage, there are no clear-cut cross-regional differences in patient care outcomes [13]. Finally, a recent analysis suggests that perhaps “30 % of laboratory testing is likely wasteful” [17]. Single-gene, limited-panel, and microbiology-related molecular diagnostics testing has already had a major impact on medical practice. Multiparameter and whole-genome sequence-based testing are fundamental to the emerging practice of “personalized” or the more recently framed “precision” medicine [18, 19]. There is great hope and expectation that precision medicine will revolutionize patient care [20]. One can predict that even with faster, less expensive testing technology and more efficient and cost-effective downstream patient care, widespread application of precision medicine will increase the proportional and absolute direct expense attributed to pathology and laboratory services. This prediction does not argue against the thoughtful and evidence-based application of multiparameter and whole-genome sequence-based testing, but implies that comprehensive, understandable, quantitative, or semiquantitative assessments of both patient care outcomes and economic impact will be important tools for future policy decisions. One can predict that the high absolute costs of multiparameter and whole-genome sequence-based testing will magnify the financial impact of suboptimal laboratory utilization. Stated in a more provocative manner, the cost of suboptimal utilization of whole-genome sequence-based testing and large molecular diagnostics panels will quickly outstrip the cost of suboptimal utilization of even high volumes of relatively inexpensive blood glucose, serum sodium, and liver function tests. Finally, the rapid commercialization of some new primary molecular diagnostic testing as well as companion diagnostics attached to oncology therapies has led to heightened concern regarding aggressive marketing practices and the potential for widespread misapplication of these very expensive tests [21]. While an accurate estimate of potential financial impact is unclear, these concerns have created an additional mandate for effective utilization management of pathology and laboratory services. Effective governance is absolutely critical to effective utilization management.

Why the Laboratory as Focal Point ?

In recent decades there has been a pronounced trend toward administrative, operational, and spatial migration of laboratory services into the domain of pathology and laboratory medicine. A by-product of this trend has been “the laboratory as focal point” for administrative oversight and fiscal accountability for these services. Such intra-institutional consolidations were initially triggered by the transition of reimbursement mechanisms from cost-based to prospective payment beginning in the early 1980s [22]. Since the 1980s, clinical laboratories have often been characterized as “cost centers” rather than “revenue generators.” This intra-institutional laboratory consolidation trend—as well as that of institution-to-institution mergers and consolidations—has been sustained by the demand for improved cost-effectiveness in health care at large. The trend toward internal consolidation has been particularly evident in larger hospitals where many testing areas evolved in a fragmented but discipline-specific manner. For example, within the University of Michigan Health System (UMHS), a tissue typing-histocompatibility laboratory was created during the 1970s by the Department of Surgery in support of the nascent kidney transplantation program. During the 1970s and 1980s, a virology laboratory was established by the Pediatrics-Infectious Disease Service, a coagulation laboratory by Internal Medicine-Hematology and Immunology by the Internal Medicine-Rheumatology Service. Two separate cytogenetics laboratories were established, one by the Department of Human Genetics and one by Pathology. The former performed karyotyping analyses of prenatal tissue, while the latter performed karyotypes of hematologic neoplasms. The UMHS had no discipline-specific molecular diagnostics laboratory until 1996. While there are differences among laboratory testing menus and primary missions, there are now at least five UMHS laboratories that perform molecular diagnostic testing. Several of these molecular diagnostics laboratories, as well as other “nonmolecular” laboratories, now reside within the Department of Pathology. In turn, the leadership of the Department of Pathology and its cognate associate hospital director is now solely accountable for managerial oversight, a step toward alignment of governance.

Currently, most hospitals house a full-service laboratory that includes pre-analytical, analytical, and post-analytical components of testing. While there are significant variations in ownership, leadership structure, payment schemes, as well as scope and size of services and operations, the fundamental activities of clinical laboratory and pathology fit logically and

operationally under a single umbrella. These activities include logistics, information technology (including order entry, specimen management, and result reporting), billing, regulatory compliance, technology evaluation and implementation (including information technology development and instrument acquisition), quality assurance, and medically informed consultative activities that are neither billed nor reimbursed on a case-by-case basis. Reimbursement for these and other services fall under the aegis of so-called “Professional Component for Clinical Pathology” (PCCP) or “Part A” activity [23]. Sendout-reference laboratory testing is a burgeoning area in nearly every hospital or clinic-based laboratory [24]. There is a vast array of complex, esoteric, and often very expensive tests available via small numbers of large commercial as well as via many smaller “boutique” specialty laboratories. Some available new testing does not add incremental value-based improvements in patient care [21, 24]. While demand for such marginally useful testing will characteristically decay because of lack of utility, untold waste occurs in the interim. Medically informed access to testing performed in such outside (and in-house) laboratories has become an important focal point for utilization management [24, 25]. (More than 60,000 individual tests, at a mean cost of more than $70/test, were sent out from the UMHS in 2014. Some esoteric tests cost more than $5000!) Given the increasingly consolidated nature and breadth of in-house testing and the explosive growth in esoteric outside testing, it is appropriate that the laboratory has become the focal point for utilization management [21, 24]. Despite natural linkage to the laboratory per se, utilization management and its governance are most effectively structured as an institution-wide, medical evidence-driven effort.

Institutional Versus Institution-Wide Goals : Governance Structure Matters

It is imperative that overarching institutional goals mesh with the many—and often disparate—domain-specific activities and goals that exist across an institution. Understandably, “pursuit of alignment” is an oft-repeated mantra of leadership and management training. Unfortunately, alignment of institutional and institution-wide goals is extraordinarily difficult to achieve within complex health-care organizations. Clearly, health-care organizations and laboratories vary widely in terms of scope, organizational structure, and

size. Barriers to alignment within health-care institutions are in large measure attributable to their complexity. It can also be argued that the lag in application of this sentinel principle has also been attributable at least in part to incongruous leadership perspectives and perhaps because of the heretofore lesser degree of true market-based competition seen in health-care delivery than in many other industries.

A comprehensive discourse on the complexity of health care is beyond the scope of this chapter but can be viewed from the perspectives of both medical/scientific and organizational/operational complexity. The first edition of *Primary Immunodeficiency Disease. A Molecular and Genetic Approach*, published in 1998, contained approximately 70 descriptions of primary immunodeficiency disorders defined at the genetic-molecular level; the second edition, published in 2006, contained 120 entities; and the most recent (third) edition, published in 2014, contained 250 entities [26]. Perhaps a more striking example of rapid growth in medical complexity is reflected in the recently implemented ICD-10, the tenth revision of the International Statistical Classification of Diseases and Related Health Problems, a medical classification list created under the auspices of the World Health Organization [27]. ICD-10 lists 14,400 “entities,” more than 16,000 when subclassifications are included [27]. While there can be no doubt that the actual breadth of medical problems (e.g., emerging infectious diseases, complications of new therapies, more finely parsed subcategories of “old” diseases) has increased, much of the increase in complexity is a product of our understanding and perspective. Health-care organizations—and laboratories—have seen a corresponding increase in complexity. (Acute care hospitals once were organized into medical and surgical wards, specimens collected directly by providers, and only a handful of laboratory tests were routinely available.) It is no wonder that maximally effective application of leadership and management principles to health care, and specifically to pathology and laboratory medicine, has been a challenge.

The traditional management model employed in many pathology and clinical laboratory organizations is a partnership between medical leadership and business—administrative leadership. Such partnerships exist in several permutations, the business administrator may report to the medical director or vice versa, and the business administrator may be primarily aligned with the greater institutional hierarchy or with the pathology-laboratory unit per se. Many medicine-business partnerships are very effective. While each realm

encompasses clear-cut domain-specific areas of expertise, continuous dialogue that leads to mutual understanding can increase effectiveness. The past two decades have seen the addition of more formalized leadership and management training exercises to pathology residency educational curricula. Clearly, alignment between medical and business administrative leadership is necessary for effective pathology and laboratory utilization management.

It can be argued that the relatively modest degree of unfettered market-based competition seen in health-care delivery has blunted the development of maximally efficient delivery of health care within geographic domains—as well as within individual hospitals or in large, but single, integrated health-care systems. While it is clearly necessary to balance patient access, scope of service, local-regional competition, and antitrust considerations attendant to mergers and consolidations, our historical system of reimbursement has not fostered full-fledged market-based competition. One of the major objectives of the Affordable Care Act, facilitated by the CMS Innovation Center, is to hasten a shift from volume-based to value-based reimbursement [9]. Part of the strategy is to provide incentives in support of better systems-based delivery. While accurate projections of patient care and cost impact are difficult, as are the substantial political challenges, it is thought provoking to consider examples like the existence of two-tissue typing laboratories within one community (Ann Arbor, Michigan) of 120,000 people, three liver transplantation programs within 150 miles of one another (Michigan), or the parallel nationwide health-care system that operates under the aegis of the Veterans Administration. Clearly, this realm of health-care delivery and financing is a major public policy issue.

Governance Structure: Alignment and Misalignment

The 30-year evolution of laboratory utilization management at the UMHS is an instructive case study of the fundamental importance of effective governance structure. While there is much progress to be made, a governance structure that encompasses the interests of both the institution at large as well as multiple constituencies across the institution has proven to be critical to the degree of success that has been achieved [24]. The “evolutionary history” of UMHS laboratory utilization management has occurred in four distinct phases: an early era of virtually no utilization management, a period in which there was a desire by hospital administration and pathology leadership to

control laboratory test utilization but inadequate tools, a short-lived failed effort to control cost within selected high-cost diagnosis-related groups (DRGs) and, finally, a more successful effort to control laboratory utilization through an institutional Laboratory Formulary Task Group. The latter two periods are notable because the “high-cost DRG effort” suffered from the absence of aligned governance, and the formulary project has been relatively successful in large part due to well-aligned governance [24].

As alluded to above, prior to the nationwide transition in the early 1980s from cost-based reimbursement to a prospective payment system , clinical laboratory testing in the UMHS was distributed among numerous laboratories administered by several different departments. While management of these areas certainly encompassed attention to labor and commodity costs and quality of both service and testing per se, there was little concerted or systematic attention given to utilization management. In some domains, it can be argued that “medically appropriate” testing was fostered by the fact that some specialized testing was conducted in laboratories directed by medical specialists in the relevant field and that most, or at least many, test orders were requested by the specialists themselves. A particularly cogent example is the coagulation laboratory which was operated by Internal Medicine-Hematology and directed by a medical hematologist with subspecialty training in coagulation medicine. Many specialized coagulation tests were not widely understood and, because there was no widespread easily accessible (electronic) ordering capability, it is possible that a relatively high percentage of test requests were medically indicted. Data that explicitly confirm this assertion are not available. There was, however, no clear-cut systematic effort to manage utilization.

In 1996, UMHS leadership mandated a system-wide cost-cutting and productivity-improvement program. This initiative was triggered by the advent of managed care and third-party payer demands. By this time, more than 10 years since the adoption of prospective payment , many smaller specialty-specific clinical laboratories had migrated to the Department of Pathology. In addition to laboratory consolidations, aggressive focus on labor and commodity costs, and careful selective reductions in service levels, pathology leadership embarked on a new utilization management program. The primary focus was on expensive, typically labor-intensive laboratory studies (such as cytogenetic karyotypes and flow cytometry studies) where individual “tests” cost more than $50. The operation of this utilization

management effort was labor intensive as laboratory directors and supervisors triaged cases by calling ordering providers on a case-by-case basis. Ultimately, the impetus for this case-by-case piecemeal utilization management program waned. Significant proportions of expensive testing came from outside institutions. There was logistical difficulty in reaching outside providers and reluctance to challenge their test requests. Within the UMHS, both for inpatients and outpatients, tests were still ordered by paper requisition. The impact of unavailability of electronic order entry was nowhere better illustrated than by an analysis known colloquially as the “11 cent sodium conundrum.” Specifically, the idea of managing utilization of high-volume, low-cost tests was studied. As an example, it was found that the aggregate cost of a serum sodium was approximately $3.00, $2.89 for the test order process, transport, entry into the laboratory work queue, quality control and proficiency testing, etc. The cost of the sodium analysis per se was $0.11! Clearly, it made no sense to intervene on a case-by-case basis—after the expenditure of $2.89—in order to save the “last $0.11.” This is a prototypic example of inadequate tools for a particular facet of system-wide utilization management.

In 2004–2005, the UMHS reframed the relationship between more than 90 clinical services and the Office of Clinical Affairs. Care was taken to explicitly identify clinical service chiefs who would continue to report to their academic department chairperson (medical school) but also with “dotted line accountability” to the chief of clinical affairs for “operational matters related to clinical service.” Every clinical service within the UMHS had a clearly specified service chief. Within this reporting framework, a dozen DRGs in which detailed financial analyses had revealed particularly high expenditures compared to reimbursement rates were presented to the Department of Pathology—with the mandate that pathology leadership work with respective service chiefs to carefully address laboratory utilization practices that might be contributory to the excessive DRG-specific costs. An example was repeat karyotypes and frequent blood cultures ordered in afebrile patients following allogeneic bone marrow transplantation. Access to a UMHS financial analytics group, the “Clinical Information Decision Support Service (CIDSS)” was made available in support of this utilization management initiative. While modest progress was made through the application of several new clinical guidelines regarding frequency of karyotype analysis, blood cultures, serum fungal antigen measurements, etc.,

the overall initiative failed because it was viewed by some service chiefs as a burdensome, low-priority task. In several instances, clinical service chiefs had “not been made aware” of the initiative and diplomatically avoided participation with pathology leadership to examine selected DRGs. Ultimately, the selected high-cost DRG-based utilization management initiative failed as the result of misaligned governance.

In 2008, a new Laboratory Test Utilization Program was launched at the UMHS [24]. Particular attention was paid to the alignment of governance structure. Leadership in the Department of Pathology requested that UMHS leadership charge the Faculty Group Practice (FGP) and the Office of Clinical Affairs (OCA) to form a Laboratory Formulary Task Group that would be granted authority to regulate the availability of laboratory tests to UMHS providers (Fig. 3.1). The UMHS FGP is a nearly 2000-member faculty physician organization that is led by physicians and represents medical practice across the institution. The OCA, led by an elected chief of clinical affairs, includes several elected associate chiefs, a permanent administrative staff group, and members of an elected committee of clinicians from many disciplines. The latter is the Executive Committee for Clinical Affairs (ECCA). In order to foster this aligned governance structure, leadership from UMHS, Pathology, the FGP, and the OCA also agreed that the Laboratory Formulary Task Group should be chaired by an actively practicing clinician (who also happened to be an associate chief of clinical affairs). The membership and key functions of the task group are summarized in Table 3.1. In operation for 7 years, the aligned Laboratory Formulary Task Group has made significant impact on expensive laboratory test utilization through its shaping of the UMHS Laboratory Test Formulary [24].

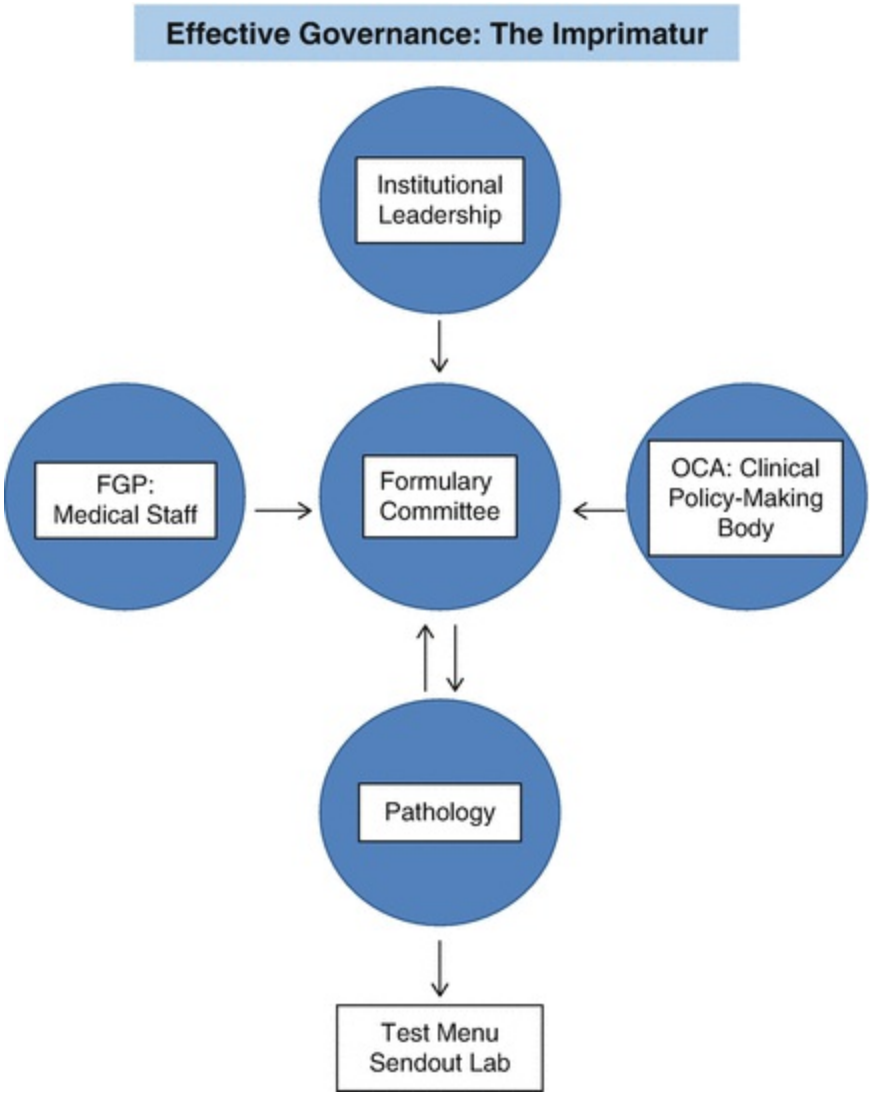


Fig. 3.1 Effective governance depends on the alignment with both institutional and institution-wide goals. *FGP* Faculty Group Practice, *OCA* Office of Clinical Affairs

Table 3.1 UMHS formulary committee

Committee composition	
Chairperson	Actively practicing clinician-leader
Pathology	Laboratory director
	Administrative support
	Information technology
	Data collection
	Sendout Laboratory director
Medical representation	Subspecialists from internal medicine, pediatrics
UMHS administration	Senior associate hospital director

Critical resources	
Order entry	
Menu (the formulary)	
Operation	
Meeting schedule (monthly)	
Agenda	Candidate tests
Evidence-based practice	Medical literature
Content experts	Invitations
Test data	Volume, cost, ordering patterns

Management of Utilization Management

As emphasized in the preceding section, the operation of an effective utilization management program requires the alignment of governance structure with both institutional and institution-wide goals . Communication, clarity of purpose, and tone are also critical to success. In addition to a lack of alignment of governance, the failed UMHS high-cost DRG initiative suffered from shortcomings in these three areas. Some service chiefs, when approached by Pathology, had not been previously briefed on the initiative. The purpose was not clearly articulated and the tone was in several cases perceived as “hospital administration wants us to reduce “their” expense created by “indiscriminant” physician test ordering.”

The more recently implemented Laboratory Test Utilization Program, in addition to a clear-cut mandate from the UMHS, Pathology, the FGP, and the OCA, has been carefully and consistently presented as a “medical evidence-based effort to optimize expensive laboratory testing .” This charge is articulated in every meeting and communication. Clinical content experts are invited to discuss relevant literature, typically selected by them, and to discuss their use of laboratory testing in patient management. Formal communication between the Task Group and relevant service chiefs occurs in the form of a memo that describes the Task Group, its imprimatur, its charge, and its membership (Table 3.2). Service chief memos emphasize the fact that a content expert (by name) has helped shape the particular discussion and decision. A benefit of access to very narrowly focused subspecialists is that content experts hold particular influence among their clinical colleagues. For example, “Dr. X, a neurologist who specializes in cerebellar diseases, recommends…” Frequently, the content expert will engage in back-channel

communications with colleagues who also practice in the area. It's made clear through test vetting exercises that decisions can be appealed that unusual clinical situations will allow for overrides upon consultation and that the Task Group will "err on the side of permissiveness." Test usage data, ordering patterns, and cost data are collected by a pathology administrator who serves with the Task Group (Table 3.1). Follow-up assessments, on a test-by-test basis , are conducted 6–12 months after the implementation of policy changes. A robust change process triggers communication with the Sendout Laboratory where appropriate, specimen processing, relevant clinical laboratories, the Laboratory Handbook curator, and both the order entry and pathology information technology administrators.

Table 3.2 Formulary committee communication

Service chief memos
Back-channel communication (via content experts)
Order entry
Pop-ups
Restrictions/recommendations
Pathology test change control
Sendout Laboratory
"Appeal" process
Tone of communication
Administrative actions by pathology

The Laboratory Formulary Task Group meets monthly. As noted, the group is chaired by an active clinical leader. The agenda is developed by a pathologist who is a standing member of the group and directs the Pathology Sendout Laboratory. Tests to be vetted are selected on the basis of annual cost or because they have been advocated by a particular clinical group. Since the inception of the program in 2008, there has been a distinct shift from focus on high cost already available in sendout tests to recently marketed commercially available multiparameter molecular diagnostics test panels. The importance of consistent communication, clarity of purpose, and tone—that is, "medical evidence-based optimal test usage "—cannot be overemphasized. Despite progress, challenges remain.

Final Notes, Challenges, and the Future

The decades-long steep rise in health-care costs, coupled with the prospect of increasingly advanced but expensive pathology and laboratory testing capabilities, has heightened the need to more effectively manage laboratory utilization. A critical facet of effective utilization management is a governance structure that fosters both institutional and institution-wide goals and activities. This chapter makes the case that aligned governance structure is fundamental to effective utilization management. The assertion that as much as 30 % of laboratory testing is "inappropriate" or "wasteful" is alarming [17]. Well-conceived, expertly operated utilization management programs are, and will continue to be, critical to the achievement of the ideal of "perfect…or optimal" application of pathology and laboratory resources in patient care. Advanced decision support, applied behavioral economic theory, and large clinical data-scanning algorithms hold tremendous promise in the area of utilization management [28]. Clearly, advanced tools and practices will be necessary to eliminate such wastage. The remaining chapters of this text outline many of the strategies and tools as well as laboratory discipline-specific approaches that will help achieve the full realization of value-based medical care.

References

1. Appleby J, Kaiser Health News. Seven factors driving up your health care costs. 2012. http://www.pbs.org/newshour/rundown/seven-factors-driving-your-health-care-costs/.

2. Leonard K. U.S. News Health Care Index shows massive increase in consumer costs. 2015. http://www.usnews.com/news/health-care-index/articles/2015/07/us-news-health-care-index/.

3. Patton M. Health care costs rise faster than inflation. 2015. http://www.forbes.com/sites/mikepatton/2015/06/29/u-s-health-care-costs-rise-faster-than-inflation/.

4. Sisko A, Truffer C, Smith S, et al. Health spending projections through 2018: recession effects add uncertainty to the outlook. Health Aff (Millwood). 2009;28:w346–57. [CrossRef]

5. International monetary fund: world economic outlook database. Figures for the April 2012 update. 2013. http://www.imf.org/external/pubs/ft/weo/2012/01/weodata/index.aspx.

6. Aron HJ. Three cheers for logrolling—the demise of the SGR. N Engl J Med. 2015;372:1977–9. [CrossRef]

7. Rajkumar R, Press MJ, Conway PH. The CMS Innovation Center—a five-year self-assessment. N Engl J Med. 2015;372:1981–3.
[CrossRef][PubMed]

8. Casalino LP, Bishop TF. Symbol of health system transformation? Assessing the CMS Innovation Center. N Engl J Med. 2015;372:1984–5.
[CrossRef][PubMed][PubMedCentral]

9. Blumenthal D, Abrams M, Nuzum R. The affordable care act at 5 years. N Engl J Med. 2015;372:2451–8.
[CrossRef][PubMed]

10. Hanson C, Plumhoff E. Test utilization in the clinical laboratory. Mayo Med Lab Commun. 2012;37:1–4.

11. Baird G. The laboratory test utilization management toolbox. Biochem Med. 2014;24:223–34.
[CrossRef]

12. Wilson ML. Decreasing inappropriate laboratory test utilization. Controlling costs and improving quality of care. Am J Clin Pathol. 2015;143:614–6.
[CrossRef][PubMed]

13. Kim JK, Dzik WH, Dighe AS, et al. Utilization management in a large urban academic medical center: a 10-year experience. Am J Clin Pathol. 2011;135:108–18.
[CrossRef][PubMed]

14. Berndtson K. Managers and physicians come head to head over cost control. Healthc Financ Manage. 1986;40:23–4.
[PubMed]

15. Becich MJ. Information management: moving from test results to clinical information. Clin Leadersh Manag Rev. 2000;14:296–300.
[PubMed]

16. Forsman R. The electronic medical record: implications for the laboratory. Clin Leadersh Manag Rev. 2000;14:292–5.
[PubMed]

17. Zhi M et al. The landscape of inappropriate laboratory testing: a 15-year meta-analysis. PLoS One. 2013;8(11), 8e78962. doi:10.1371/journal.pane.0078962.

18. Ashley EA. The precision medicine initiative: a new national effort. JAMA. 2015;313(21):2119–20.
[CrossRef][PubMed]

19. Jameson JL, Longo DL. Precision medicine-personalized, problematic, and promising. N Engl J Med. 2015;372:2229–34.
[CrossRef][PubMed]

20. 2015 State of the Union. Whitehouse.gov. http://www.whitehouse.gov/SOTU. Retrieved 21 July

2015.

21. Abelson R, Creswell J. Pursuit of cash taints promise of gene tests. 2015 June 24. http://www.nytimes.com/2015/06/25/technology/genetic-testing-case-highlights-thefields-hope/.

22. Brown S, Tyler L. Guide to medical billing: a reimbursement approach. 3rd ed. Saddle River, NJ: Pearson; 2013.

23. Professional component of clinical pathology; Part A. 2012. http://www.cap.org/apps/docs/statline/pdf/palmettocase results.pdf.

24. Warren JS. Laboratory test utilization program. Structure and impact in a large academic medical center. Am J Clin Pathol. 2013;139:289–97.
[CrossRef][PubMed]

25. Zhao JJ, Liberman A. Pathologists' roles in clinical utilization management: a financing model for managed care. Am J Clin Pathol. 2000;113:336–42.
[CrossRef][PubMed]

26. Ochs HD, Edvard Smith CI, Puck JM, editors. Primary immunodeficiency diseases: a molecular and genetic approach. Oxford, UK: Oxford University Press; 2014.

27. International statistical classification of diseases and related health problems 10th revision. 2015. http://apps.who.ht/classifications/ied10/browse/2015/eu/.

28. Khullar D et al. Behavioral economics and physician compensation—promise and challenges. N Engl J Med. 2015;372:2281–3.
[CrossRef][PubMed]

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_4

4. Informatics, Analytics, and Decision Support in Utilization Management

Jason Baron[1, 2]

(1) Department of Pathology, Massachusetts General Hospital, Gray 2, 55 Fruit Street, Boston, MA 02114, USA
(2) Harvard Medical School, Massachusetts General Hospital, Gray 2, 55 Fruit Street, Boston, MA 02114, USA

Jason Baron
Email: jmbaron@partners.org

Keywords Utilization management – Laboratory utilization – Analytics – Decision support – Computerized provider order entry – Ordering alert

Introduction

Informatics underlies some of the most effective laboratory utilization management tools and approaches. This chapter will focus on two domains of utilization management, clinical decision support and data analytics, and the applications of two areas to utilization management. This chapter will also include discussion of the information systems that form the infrastructure to collect data, perform analytics, and provide clinical decision support.

Applications of Clinical Decision Support and Health Information Technology to Utilization Management

Definitions of clinician decision support (CDS) vary, but in its broadest form, CDS may include any electronic or algorithmic process designed to help clinicians select appropriate measures of care including optimal laboratory test selection. Most types of clinician decision support currently used are designed to make clinical knowledge more accessible to clinicians or to help clinicians synthesize and apply clinical knowledge to specific patients. However, in addition to knowledge application, some evolving forms of decision support may incorporate artificial intelligence to enable more precise or efficient clinical diagnosis and patient management. Subsequent subsections will discuss specific types of clinical decision support and strategies to optimize them for utilization management.

Guidelines

Among the simplest though also most commonly used forms of clinical decision support are practice guidelines . Practice guidelines integrate relevant clinical evidence to provide “expert” recommendations regarding patient management. Guidelines generally rely on high-quality clinical evidence (e.g., randomized controlled trials) when available, but often incorporate observational studies, case reports, and expert opinions, particularly in the absence of relevant randomized controlled trials. Many of the most widely applied and authoritative guidelines are produced by consensus panels and are sponsored by well-established and respected organizations such as the American College of Physicians or the US Preventative Task Force. Guidelines are available for a variety of diagnostic and clinical situations. For example, the American Diabetes Association provides recommendations for when physicians should consider screening asymptomatic patients for diabetes using hemoglobin A1c, fasting glucose, or oral glucose tolerance testing [1].

Unfortunately, many laboratory test-ordering questions are not addressed by clear guidelines. For example, few authoritative guidelines describe the appropriate frequency with which to repeat routine lab tests on typical inpatients. Likewise, some laboratory test-ordering questions have conflicting guidelines. For example, the US Preventative Task Force recommends against routine use of the prostate specific antigen test (PSA) in screening healthy men for prostate cancer [2]. However, the American College of Urologists disagrees with this guideline and recommends “shared decision-making for men 55 to 69 years…” [3] Presumably, one of the reasons why

laboratory test-ordering guidelines not infrequently provide conflicting recommendations is that few randomized controlled trials specifically address laboratory test ordering. Thus, laboratory testing guidelines must often rely on lower-quality evidence that leaves greater room varying interpretations or expert opinions that can easily vary between experts. Likewise, clinicians often disregard guidelines. Clinicians may disregard guidelines when they disagree with their recommendations, are unaware of their existence, or feel that the guidelines do not apply to their particular patient, perhaps because the guideline addresses too broad and heterogeneous a patient population. Incorporating guidelines into computerized provider order entry templates (see below for additional information on templates) may optimize care [4].

One source of guidelines relevant to laboratory test utilization is the "Choosing Wisely" initiative [5]. Choosing Wisely is sponsored by the American Board of Internal Medicine and includes lists by over 70 organizations representing a wide range of specialties and describing frequently used test, procedures, or practices that should be questioned. For example, the American Society of Clinical Pathology (ASCP) Choosing Wisely list recommends that physicians "Don't test for myoglobin or CK-MB in the diagnosis of acute myocardial infarction (AMI)…" among other recommendations [6]. Finally, the US Agency for Healthcare Research and Quality (AHRQ) offers a clearinghouse of guidelines [7].

Testing Algorithms

Test algorithms represent a type of guideline that can be represented in a step-by-step flow chart leading from a presenting symptom or abnormality through a series of tests intended to help establish a diagnosis. Importantly, algorithms may call for subsequent test orders depending on the results of earlier tests. For example, a laboratory may establish a "prolonged PTT" algorithm that identifies the cause of a prolonged PTT. Such an algorithm may include mixing studies to distinguish a factor deficiency from an inhibitor; subsequent testing will then depend on whether the mixing study suggests an inhibitor or factor deficiency. Likewise, algorithms can be used within the lab to provide a specific result requested. Guidelines can either be designed to be followed manually by a clinician or can be implemented as reflex protocols (see subsequent sections). Many reference laboratories and other clinical laboratories offer a variety of testing algorithms. Figure 4.1 represents a thyroid evaluation algorithm used by the MGH Clinical

Laboratories; in this case, the algorithm is implemented as a reflex protocol.

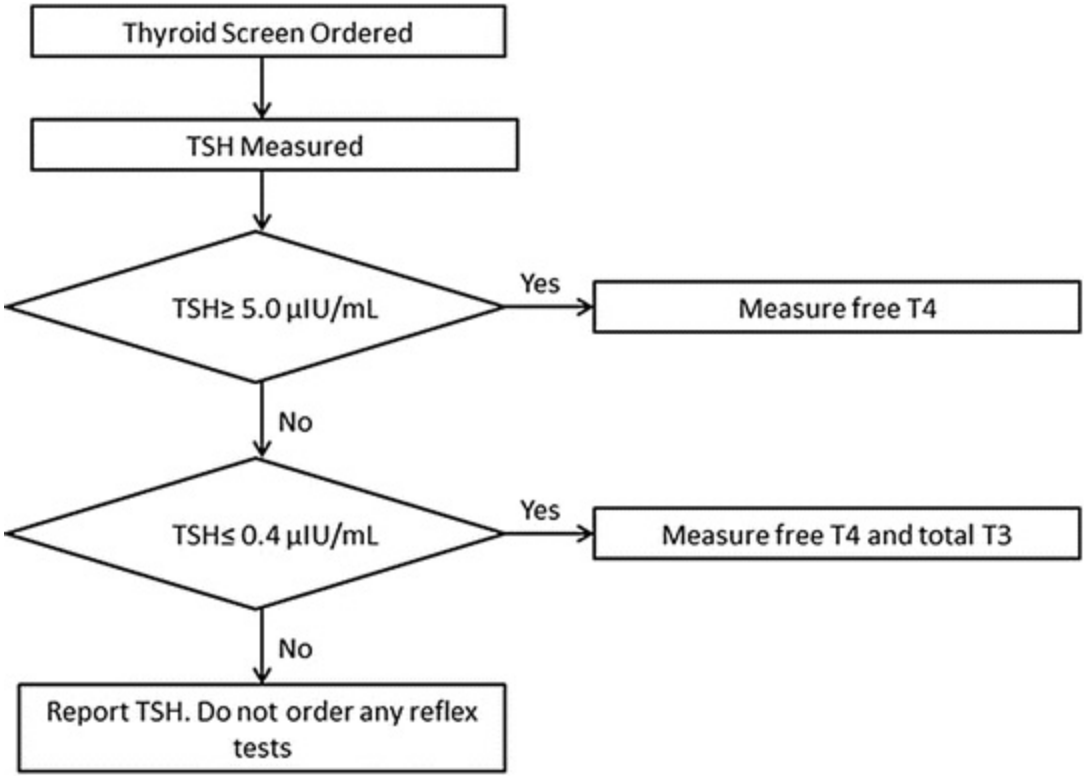


Fig. 4.1 Reflex algorithm example. The Massachusetts General Hospital Core Lab "Thyroid Screen" reflex testing algorithm. *TSH* thyroid stimulating hormone, *T3* triiodothyronine, *T4* thyroxine

Knowledge Links and Laboratory Handbooks

While guidelines, quick references, and testing algorithms often exist in electronic forms, these can exist on paper and the fundamental content is not electronic in nature. Thus, by some definitions, guidelines and testing algorithms would not be considered clinical decision support. This distinction is not just semantic in that guidelines or quick references that are not integrated within an electronic information system or clinical workflow will be less accessible and less often used.

One straightforward strategy to integrate guidelines and quick references within the clinical workflow is to link to them from the electronic health record. Knowledge links go by a variety of names in different information systems, such as "info buttons," and allow clinicians to directly link out to a reference relevant to the information they are viewing. For example, laboratory test results may be displayed with a knowledge link that allows the

clinician to pull up information about that test (e.g., a “quick ref” page) in a single click.

Many computerized provider order systems can display test-specific hyperlinks on test-ordering screens. These can be used to link to corresponding pages in an institutional laboratory handbook. A laboratory handbook can in turn provide decision support, serving not only as a quick reference but also as a source of trusted and institution-specific knowledge. Kim et al. [8] and Blechner et al. [9] offer strategies for developing an effective institutional laboratory handbook.

Passive vs. Active Decision Support

Guidelines, knowledge links, and testing algorithms (unless implemented as a reflex testing protocol) all represent a comparatively passive form of decision support in that the clinician must know they need additional information and then seek the relevant resource. While these passive forms of decision support are quite useful in many contexts, an alternative strategy is to anticipate the information that a clinician might need and actively provide that to him or her at the time it will be most useful. This alternative strategy is termed here “active decision support” and offers several advantages over passive decision support. Active decision support can be more convenient since it provides information automatically. Moreover, clinicians may not always know their information needs and thus might not know when to access more passive decision support. Similarly, active decision support can provide reminders to busy clinicians regarding information which they may know, but overlooked. Many forms of active decision support are delivered through computerized provider order entry and other information systems, and these are reviewed in the subsequent sections.

Provider Order Entry

Computerized provider order entry (CPOE) systems allow clinicians to electronically place orders for diagnostic and therapeutic measures including laboratory tests. Many US hospitals have implemented CPOE systems to meet federal “Meaningful Use” incentives [10], and these systems are becoming quite commonplace. Benefits of CPOE not directly related to utilization management include improved test turnaround time, reduced transcription errors, and improved operational efficiency [11, 12]. However,

many of the most important benefits of CPOE relate to these system's ability to support optimal test selection and decision support for utilization management.

Laboratory CPOE systems vary in functionality [13, 14] but will typically offer a variety of mechanisms for clinicians to input orders. In particular, systems will generally allow clinicians to search for tests by test names and synonyms [12]. Likewise, many CPOE systems allow clinicians to order laboratory tests using clinical templates [12, 15–17]. Templates are usually designed around common clinical conditions, procedures or visit types and include orders for many aspects of care including laboratory testing, nursing, radiology, and medication. For example, a CPOE system may include a congestive heart failure (CHF) admission template, with laboratory tests commonly used to monitor CHF and medications needed to manage CHF exacerbations. Clinicians can then select the specific measures of care needed from the template by checking or unchecking click boxes. Finally, many CPOE system offer facility, practice, or clinician-specific "favorite" lists that clinicians or hospitals can use to list and easily select commonly ordered tests [12]. As described below, each of these test-ordering mechanisms offers strategies to influence test ordering and improve test utilization. Likewise, CPOE systems can provide a critical conduit to provide clinical decision support and interact with clinicians at the time of decision-making and test ordering in ways that can greatly improve utilization. Nonetheless, CPOE will generally not in itself improve utilization; strategic configuration and deployment are needed [12, 14, 15]. The following sections describe utilization strategies that can be implemented through CPOE and aspects of CPOE that can be optimized to enhance utilization.

CPOE Strategies and Optimization Points

Display of Test Cost

Providing clinicians information regarding test costs via CPOE system on can reduce test utilization [18, 19]. Because test costs can be difficult to quantify and accurately express in the case of in-house tests (e.g., should average or marginal cost be used?) and may be difficult to maintain in the case of sendouts, one strategy is to display qualitative costs. For example, tests may be grouped from one to five dollars signs. In some cases, actual quantitative costs can be displayed.

Unbundling Panels

In some cases, requiring clinicians to order test panel components separately (e.g., requiring individual electrolytes to be ordered rather than offering an electrolytes panel) may reduce utilization [20]. Nonetheless, removing single automated tests from an existing collection often provides limited benefit in terms of in-lab cost savings [21], and thus, in some cases, the disadvantages of unbundling may outweigh benefits. Disadvantages of unbundling might include increased clinician time required to enter orders, greater order complexity, and additional risk of needed tests being overlooked.

Quick Picks and Favorite Configurations

As noted above, many CPOE systems allow clinicians to store commonly used orders on a favorites list and/or offer a list of commonly used orders on some form of quick pick screen. These favorites lists will often guide clinician test ordering in much the same way as templates. Thus, when possible, tests to include on quick picks and favorites list should be considered carefully, as including less commonly needed tests may encourage overutilization. For example, Kim et al. [8] removed LDH from a general hospital inpatient "quick pick screen," requiring clinicians wanting to order an LDH to search for it. Following removal of LDH from the quick pick screen, they observed a more than 50 % decrease in inpatient LDH utilization. This presumably was due largely to eliminating the "impulse buy" phenomenon that may accompany seeing a less frequently needed test on a quick pick list. In some systems, clinicians may be able to add any tests they want to a favorites list; nonetheless, the laboratory may attempt to work with clinicians in select cases to customize their favorites lists in ways that drive optimal test utilization.

Display of Prior Test Results

Display of prior tests results may reduce repeat test ordering [15, 22]. For example, a clinician seeing normal CBC results for the past 3 days on an inpatient may decide that the day 4 morning CBC is not needed. The functionality to display prior test results is supported in some commonly used CPOE systems.

Test Frequency Restrictions

Most CPOE systems permit recurrent laboratory test orders, such as “CBC with differential every morning until discontinued” or “plasma electrolytes q 4 h × 12.” Recurrent test orders are sometimes popular among clinicians because they allow them to place some laboratory test ordering on “autopilot” without needing to evaluate and order tests on a daily or more frequent basis. While recurrent orders may be appropriate in some circumstances, they can also encourage overutilization, as orders may not be discontinued when no longer needed. Many clinicians and pathologists as well as authoritative guidelines discourage the use of recurrent daily orders and instead suggest that test orders be considered in the context of the patient and to test specific clinical hypotheses [23]. Many CPOE systems can be configured to restrict or limit recurrent orders.

Redundant Test Checking

Redundant testing occurs when a clinician orders a test identical or similar to the one recently performed on the same patient without realizing the prior testing had been ordered or performed. For example, a physician may order a hemoglobin A1c on a patient, not realizing that another physician had ordered a hemoglobin A1c on the same patient earlier in the day. Redundant testing is a significant problem, estimated to waste at least 5 billion dollars per year in the USA [24].

Many CPOE systems support redundant or duplicate test alerting . For example, since hemoglobin A1c should not change much in the course of a few days and changes in this time period would not be clinically relevant, a redundant test alert may flag as redundant multiple hgbA1c orders within a short period of time (excluding the first order). It is of course important to provide clinicians a mechanism to override redundant test alerts since there may be good reason in some cases to order a test more frequently than generally expected; for example, a clinician may be repeating a test after suspecting a spurious result. One challenge to setting up these types of alerts is determining the acceptable time frequency between repeat tests; as in many utilization questions, the minimum time between repeat tests in some cases can be quite controversial.

Reflex Testing Protocols

Reflex testing protocols are used to automatically order second-line tests depending on the results of initial testing. For example, many hospitals have a thyroid screening reflex protocol whereby the laboratory initially performs a serum TSH assay, and then if the TSH result is abnormal, the laboratory automatically adds on free T4 and T3 testing as needed (see Fig. 4.1). Laboratories can typically automate reflex testing protocols using laboratory information systems (LIS) or laboratory middleware.

Without reflex testing protocols , clinicians face a dilemma in deciding whether to order second-line tests alongside first-line ones, potentially leading to unneeded testing or to delay testing until after the results of the first-line tests become available, potentially leading to diagnostic delays or patient inconvenience. Increased time to diagnosis can be particularly problematic in the inpatient setting or in patients with acute illnesses. Likewise, in the outpatient setting, requiring a patient to return to a clinic for a subsequent blood draw may be inconvenient. Although second-line tests could sometimes be ordered as "add-ons," this is not always feasible due to specimen stability requirements or retention times and even when possible may pose logistically difficulties for the clinician and the laboratory. Reflex testing protocols can streamline utilization by solving this dilemma [25]. With reflex testing, clinicians will be less tempted to order second-line tests upfront, and patients will not face inconvenience or delayed diagnosis due to a decision to order testing sequentially.

Although CPOE is not necessarily needed to implement reflex testing protocols, it can greatly expand the laboratory's ability to offer a much larger menu of customized reflex protocols. For example, a paper requisition might be able to include several commonly used reflex testing protocols but could not practically describe hundreds of highly customized protocols. Likewise, the limited ability to make updates to paper requisitions would constrain the number of reflex protocols that could be practically managed. An electronic system in contrast can support a large menu of reflex test protocols with sufficient guidance regarding how to use them. Care must be taken when establishing reflex protocols to ensure proper billing compliance as described by MacMillan et al. [26].

Alerts

Among the most important utilization management tools involving CPOE are test-ordering alerts. Test-ordering alerts provide clinicians information

relevant to the test selection at the time of test ordering. CPOE alerts can be either interruptive or non-interruptive. The following section will describe alerting strategies and consideration in greater detail.

Alerting Strategies

Non-interruptive Alerts

Non-interruptive alerts by definition do not directly interrupt the workflow and generally take the form of an informational message displayed on a test-ordering screen [12]. For example, users may be shown a non-interruptive alert when trying to order 1,25 OH vitamin D, advising that this test is usually not the test of choice for vitamin D-deficiency screening and that instead 25-OH vitamin D should be ordered (Fig. 4.2).

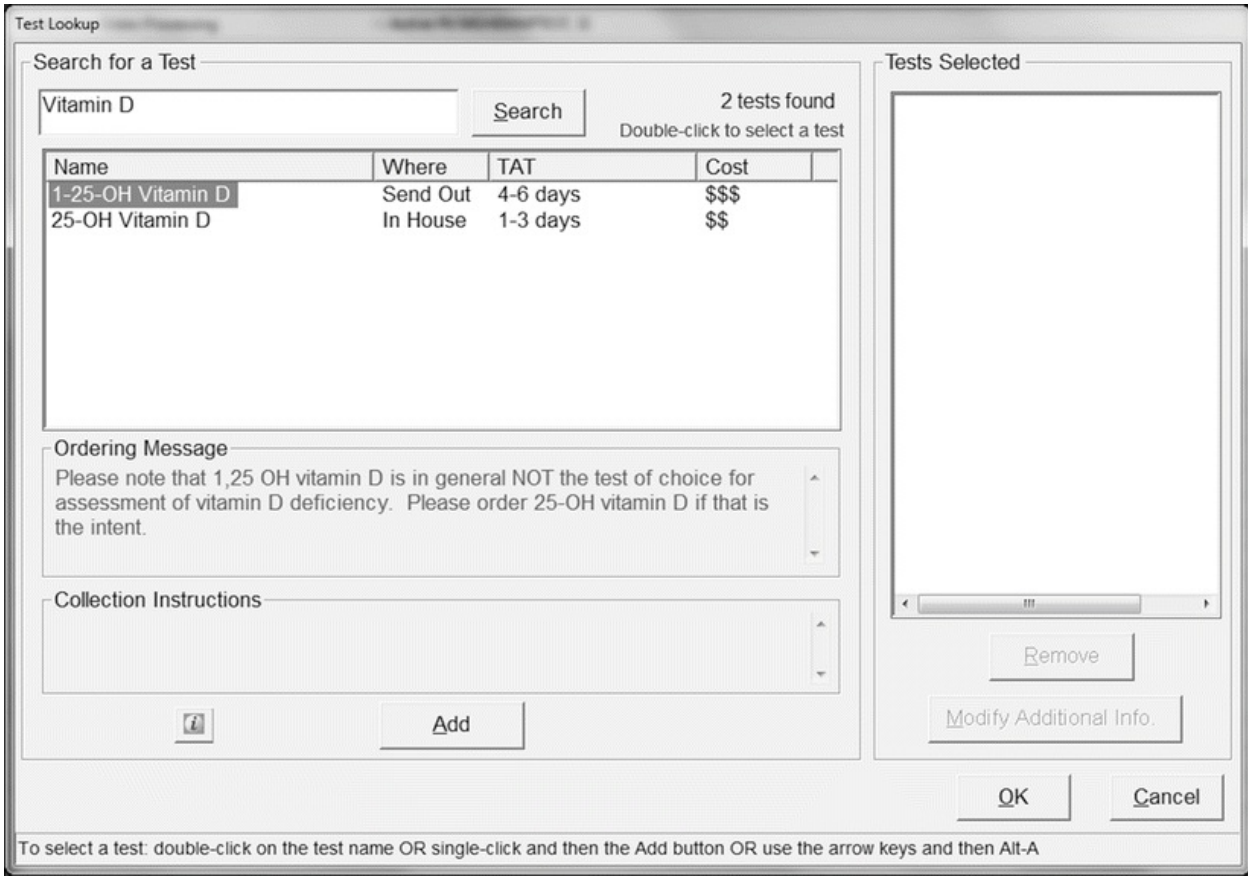


Fig. 4.2 Example of an alert message. Shown is a screenshot from the Massachusetts General Hospital CPOE system displaying a non-interruptive alert related to vitamin D testing

Interruptive Alerts

Interruptive alerts in contrast interrupt the workflow and often take the form of “pop-ups” that display information and require acknowledgment. In place of a simple acknowledgment, interruptive alerts can also ask the user questions intended to ensure that the user has seen and considered the alert. For example, an alert may display appropriate indications for ordering D-dimer on inpatients and then ask ordering clinicians to pick one of the approved indications and/or enter an alternative indication. In this case, the clinicians will be forced to view the appropriate indications for d-dimer and consider whether the patient meets one of these prior to ordering the test.

Alert Fatigue

Another important consideration when designing alerts is the concept of “alert fatigue” [27]. Alert fatigue occurs when clinicians become so inundated with alerts (particularly irrelevant ones) that they begin to ignore all alerts. Even interruptive alerts can be cognitively ignored if clinicians become accustomed to “going through the motions” of clicking the appropriate boxes without really thinking about the alert. To combat alert fatigue, alerts, and particularly interruptive alerts, should be used sparingly and should be made most relevant. Bates et al. provide ten strategies for making decision support alerts most effective [28].

Computational Pathology, Smart Alerts , and Statistical Diagnosis

Presumably making alerts “smarter” so that they are only displayed in cases where they are most likely to be relevant would help to combat alert fatigue. For example, an interruptive alert designed to advise clinicians that 1,25 OH vitamin D is not the test of choice for routine vitamin D-deficiency screening might be less likely to contribute to alert fatigue if it were suppressed on patients with evidence of chronic kidney disease, who may actually need the 1,25 OH vitamin D test. CPOE systems vary in their capacity to incorporate patient data into whether to display alerts. Some commonly used commercial EHR systems include functionality to build rule-based alerts. For example, an alert may be built that only displays in patients with creatinine results greater than a specified threshold or only in pediatric patients. Even in systems that

support patient-specific alerts, building these is often a complex and time-consuming process, and so resource availability may limit their use.

The growing field of “computational pathology ” seeks to integrate patient data from clinical laboratory, pathology, and genomic testing with other diagnostic and clinical data using computational and predictive analytic techniques [29–31]. Moreover, a key goal of computational pathology is to generate more precise diagnostic, prognostic, and prescriptive information than traditional approaches to clinical decision-making [23–25]. One component of this effort may be better customized clinical decision support for test-ordering and test result interpretation. Likewise, advanced statistical approaches have been applied to the discovery of new knowledge and insights regarding test result integration and test ordering that can in turn support better test utilization. For example, Baron et al. describe an algorithm to identify spuriously elevated glucose results and use this algorithm to drive a test-reporting alert [32]. Likewise, Houser et al. describe a Bayesian approach that can help to identify patient populations where tests may be overused [33].

Alert Strategy Selection

Interruptive and non-interruptive alerts have their advantages and disadvantages. The passive nature of non-interruptive alerts allows them to be used quite generously without annoying clinicians. Clinicians who are familiar with the information contained in the alert can simply ignore it. Nonetheless, the passive nature and ability for clinicians to easily ignore alerts can also represent a drawback as important information may be overlooked. Interruptive alerts are much less likely to be overlooked since they require acknowledgment. However, overuse of interruptive alerts can potentially lead to political backlash from annoyed clinicians. Thus, it is usually best to reserve interruptive alerts for particularly important information or cases where the alert is most likely to be relevant. For example, an interruptive alert may be implemented following a new policy related to ordering a certain test to ensure clinicians know about the policy. Of course, as clinicians become more aware of the policy, it may sometimes be appropriate to replace the interruptive alert with a non-interruptive one. Indeed, alerts can impact clinician test-ordering practices both by providing “just-in-time” test-ordering advice and longer-term education [34].

Knowledge Management

As noted, many strategies used to optimize laboratory test ordering involve providing clinicians with key information about tests including test-ordering recommendations and decision support alerts. Whether this information is communicated via laboratory handbooks, CPOE decision support, or other means, a key challenge often remains tracking and synchronizing this test information and implementing updates. In particular, test knowledge may derive from multiple sources including the laboratory information system, laboratory director or staff input, clinician recommendations, reference lab guidelines, and utilization management initiatives. Likewise, some traditional repositories of test-specific information are often not equipped to store all key information; for example, LIS dictionaries are traditionally unable to accommodate provider order entry alert messages [12].

Thus, while not widely commercially available, knowledge management software may prove highly useful in collating, managing, and tracking this test knowledge [35]. Furthermore, updating CPOE systems may require substantial technical resources that may be in short supply, leading to delays in important updates. Grisson et al. developed knowledge management middleware that directly interacts with a CPOE system, allowing the laboratory to make direct updates and helping to overcome these traditional resource constraints [35]. Given the lack of widely used commercial solutions, institutions may consider developing their own “home-grown” knowledge management solutions if the technical resources are available; this also highlights the need for a commercial solution.

Electronic Health Records

Electronic health records (EHRs) can provide a variety of functions, including the generation and retrieval of physician, nursing, procedure and other notes, documentation and tracking of patient visits, vital signs, medication administrations, problem lists, diagnoses and other patient characteristics, and patient billing and revenue management. Likewise, EHR systems often serve as the primary viewer for physicians to review laboratory results, pathology reports, and radiology and other diagnostic studies. Finally, CPOE systems are generally provided as module within the EHR. EHR systems are gaining increasing prevalence in large part due to the Federal “Meaningful Use” program that financially incentivizes eligible providers

and hospitals to use “certified” EHR technology to accomplish specific goals. Specific EHR functions vary by system, although specific functionality is required for systems to meet “Meaningful Use” certification requirements [10, 36].

The role of the EHR in the display of laboratory results makes it of great importance to utilization management. In particular, suboptimal display of test results can negatively impact test utilization. For example, test results that are difficult to find in the electronic medical record would presumably be more likely overlooked. This in turn presents several utilization problems, including that an overlooked test result cannot be properly utilized and may subject a patient to harm. Likewise, a physician unaware of a prior, difficult-to-find test result may be more likely to unnecessarily reorder the test. Tests may be difficult to find if they are named using less commonly known synonyms or abbreviations or if their placement within the EHR is suboptimal (e.g., a test for an infectious organism is listed in the chemistry “bucket”). Similarly, identifying pending test results in the EHR can presumably help to deter unintentional duplicate test orders. Furthermore, optimal electronic result reporting requires clear display of interpretive comments or other information (such as high/low flags as appropriate). Proper deployment and thorough validation of the LIS to EHR interface are essential as an improperly functioning interface can cause test result messages to be mistranslated when sent from the LIS to the EHR and in turn cause results to be incorrectly or suboptimally displayed to clinicians [36]. Finally, the EHR serves as a key source of data that can be used to generate new knowledge as well as to drive clinical decision support.

Other Information Systems

Many other information systems also contribute to utilization management. While an exhaustive list is outside the scope of this chapter, key examples include laboratory middleware and the instruments themselves. For example, instruments and middleware can help to implement rules to facilitate automated processing of reflex testing protocols, which can enable a laboratory to offer a wider menu of reflex testing options and can in turn offer the benefits of reflex testing to a wider array of clinical tests and circumstances [37].

Targeting, Implementing, and Monitoring Utilization Improvement Initiatives Using Data Analytics

In the following subsections, we discuss the application of data analytics to utilization management including strategies to develop utilization metrics, monitor utilization management initiatives, and guide utilization management interventions.

Utilization Monitoring

An important component of a utilization management program is a strategy to evaluate the effectiveness of individual utilization management initiatives and of the utilization management program as a whole. In particular, when monitoring effectiveness, it is important to:

- Determine whether a utilization management initiative is achieving the intended effect; if not, alterations to the initiative might be needed.
- Demonstrate the clinical and economic value of individual initiatives and of the utilization management program as a whole.
- Justify and obtain the resources needed for future utilization management work.

Performance Metrics

Monitoring the effectiveness of a utilization management initiative requires designing one or more metrics. Utilization metrics consist of defined and measurable characteristics that will potentially be impacted by the utilization management initiative. For example, “the number of inpatient vitamin D test orders per month” would be a metric that might be appropriate in monitoring a utilization management initiative designed to reduce inpatient vitamin D testing. While the characteristic of interest might be “inpatient vitamin D ordering,” this in itself is not sufficient since it lacks a specific definition regarding what to measure. Thus, one aspect to developing metrics is translating characteristics of interest into defined metrics. While metrics are generally quantitative, in some cases qualitative assessments may supplement quantitative metrics in assessing utilization management performance.

Ideally, the metrics used to monitor a utilization management initiative

would capture *all* effects caused by the utilization management initiative and *only* those effects caused by the utilization management. However, this ideal is in practice nearly impossible to attain. In particular, given the complexities of health care, impacts to one aspect of care such as laboratory test ordering can have far-reaching effects on other aspects of care such as treatments offered and corresponding patient outcomes. This may be particularly true in the setting of laboratory and other diagnostic testing likely to impact a wide range of clinical decisions. Thus, it is nearly impossible to predict, let alone measure, all of the effects that might be caused by a utilization management initiative. Likewise, with aspects of care far downstream from a utilization management initiative, the impact of the initiative will most likely be small relative to other factors and thus may be difficult to detect. Considering the aforementioned inpatient vitamin D testing example, the utilization management initiative could conceivably impact the rate of hip fractures. However, the effects of the initiative on hip fractures might be expected to be so small relatively to the baseline variability in rates of hip fractures ("noise") that any effects would be nearly impossible to detect.

Likewise, most aspects of care will be impacted by more than just the utilization management initiative. For example, rates of inpatient vitamin D testing might vary with the season, patient mix, clinicians on service, and so forth, and thus, changes in the rate of inpatient vitamin D testing might not be solely attributable to the initiative. This situation represents *confounding*, a concept that will be described in greater detail in subsequent sections. Statistical and other strategies can help to control for confounding as discussed in subsequent sections.

Finally, utilization metrics should be as simple and interpretable as possible and utilize data that is easy to capture and analyze [38].

Approaches to Evaluating Utilization Management Initiatives

Several approaches exist to monitor utilization initiatives. Utilization initiatives are commonly evaluated using "quasi-experimental" approaches; in rare cases, randomized controlled trials have been used. These approaches are reviewed in the following sections.

Randomized Controlled Trials

Randomized controlled trials have occasionally been used in utilization management studies, particularly in the evaluation of decision support interventions. Randomized controlled trials will randomly assign different providers, patients, teams, locations, or other randomization units to receive or not receive the intervention. Researchers will then compare selected outcomes including selected utilization metrics between groups receiving and not receiving the intervention.

In theory, randomized controlled trials can demonstrate better than other trial types that the intervention *caused* utilization outcomes, since the only differences between the control and intervention cases not occurring just by chance will be the intervention. Thus, a well-designed randomized controlled trial will generally provide the most experimentally rigorous and internally valid evidence of the impact of a utilization management initiative.

However, in practice, randomized controlled trials are used rarely to evaluate utilization management initiatives. These studies tend to be much more costly than other methods of monitoring a utilization management initiative, and technical limitations make randomizing certain interventions infeasible; for example, many CPOE systems lack established functionality to display alerts only in randomly selected cases. Likewise, spillover, whereby the intervention impacts control cases, may substantially limit randomized controlled trials occurring in a single center. For example, consider a trial of a CPOE alert that is displayed to providers on randomly assigned patients. Since a provider may see both intervention and control patients, the education effects of the alert will "spillover." Even studies including randomization at the provider level may be limited by spillover, particularly since many patients are cared for in teams. Similarly, randomized controlled trials designed in a highly controlled fashion may lack external validity in that the trial conditions may significantly differ from more routine clinical practice.

Quasi-Experimentation

Much more commonly, utilization management teams use "quasi-experimental " approaches to evaluate utilization management initiatives. Like randomized controlled trials, quasi-experimental evaluations compare utilization metrics or other outcomes in the presence and absence of the initiative. However, quasi-experimental approaches do not randomly assign providers, patients, or units to the control or intervention groups.

"Before-after" comparisons are probably the most common quasi-

experimental framework used to evaluate utilization management initiatives. These comparisons simply compare utilization metrics before and after the implementation of the utilization management initiative. Another approach involves only implementing the utilization initiative in certain settings (e.g., some practices receive an educational seminar while others do not) and comparing utilization metrics between the practices. Similar to quasi-experimentation, the term “natural experiment” is often used to describe comparisons between groups where the researchers are strictly observers and had no direct role in the intervention or assignment of groups to receive it.

Confounding represents a key limitation of quasi-experimental approaches. Confounding occurs when the intervention and control groups differ by factors besides just the intervention, and these differences impact utilization outcomes. For example, consider a before-after comparison of a utilization management initiative designed to reduce vitamin D test utilization. If the initiative was implemented during the fall, test utilization may appear to increase following the initiative due to seasonal variation even if utilization is lower than it would have been in the absence of the initiative. Likewise, one might suspect that a practice that voluntarily signs up to participate in a utilization management initiative may be more interested in utilization management than the one that resists. The following section describes approaches to limit confounding biases in evaluating utilization management initiatives.

Strategies to Control Confounding

Normalization

One important factor that can frequently confound utilization metrics is the volume of underlying clinical activity. For example, we might expect the number of orders each day for many inpatient labs to vary roughly in proportion to the daily inpatient census. Likewise, we would expect a busy primary care physician with a large outpatient practice to order more hgA1c tests than one working part time and with a smaller patient population. Thus, comparisons of “raw” (unadjusted) rates of test utilization over time or between different facilities, physicians, or practices will often not be very meaningful and may be misleading.

Dividing the raw utilization rates by underlying clinical activity can help to normalize them to clinical activity. For example, we could divide the

number of inpatient CBCs that a particular clinical team ordered over a given time period by the number of inpatient admissions attributed to that team to derive a metric of “CBCs per admission.” More generally, the development of normalized metrics will require identifying a relevant utilization measure (the “numerator”) and underlying activity measure (the “denominator”) and will generate a metric with derived units in the form of utilization per activity unit.

When normalizing laboratory utilization metrics , obtaining and expressing the denominator is often more complex than the numerator. For example, using the aforementioned example of utilization of hgbA1c tests by PCPs, we may wish to develop a metric of hgbA1cs per patient-year (by PCP) by dividing the number of hgbA1c tests each PCP ordered (and were performed) in a year by the number of unique patients for whom the physician served as a PCP during the year. In this case, the laboratory will most likely be able to identify the number of hgbA1c tests performed during the year from the laboratory information system. However, determining the number of patients each PCP cared for during the year will most likely require access to data sources outside the laboratory including clinical or billing records, which may be more difficult for laboratory utilization management teams to access. More significantly, generating a relevant denominator will require addressing some difficult “attribution” questions; for example, if a patient sees multiple PCPs during the year, we would need to decide what criteria would determine which PCP “owns” the patient. Likewise, we would need to decide how to attribute a patient who is administratively assigned to a given PCP for insurance purposes, but did not see the PCP during the year.

Because denominator data can be difficult to obtain or calculate, it is sometimes reasonable to develop unnormalized metrics, particularly when there is good justification to believe that underlying clinical activity is relatively constant or will not significantly impact the metric. Alternatively, we may sometimes assess a utilization trend or effect of a utilization initiative by implicitly or explicitly making “what-if” assumptions regarding the relevant denominator. For example, suppose that the rate of serologic testing for babesiosis fell by 90 % in an outpatient clinic following an educational effort encouraging use of smear review in place of serology. In this case, even if we don’t know the exact underlying patient volumes at the clinic, we may know that they have changed by at most 10 % which is much smaller

than the change in the utilization rate. Thus we may be able to confidently conclude that changes in underlying patient volume could not account for most of the change in utilization of babesiosis serology and that the initiative had been effective (assuming other confounders such as seasonal variation were likewise addressed).

An important caveat when developing normalized utilization metrics is that sometimes relevant denominators are themselves measures of health-care utilization. For example, monitoring CBCs per patient-visit for a specialist physician may be appropriate; however this metric could be misleading. For example, suppose we compare a clinician who appropriately sees patients less frequently (fewer visits per patient and a smaller denominator) to one who inappropriately sees patients for follow-up visits more frequently than needed. The physician seeing patients less frequently may appear to have a higher rate of CBC utilization even if the number of CBCs per unique patient is constant. Indeed, since many care models encourage judicious scheduling of follow-up appointments, the clinician who looks like a more judicious utilizer in our example might in fact be just the opposite in terms of overall health-care resource utilization.

Subgrouping

In cases where a utilization management initiative is hypothesized to impact one subgroup of patients or providers more than others, comparing utilization management metrics within that subgroup alone may help control confounding or at least better distinguish signal from noise. For example, suppose that an initiative is intended to increase hgbA1c testing in diabetic patients and is monitored in a before-after comparison looking at the number of hgbA1c tests per patients in all patients (diabetic and nondiabetic). Because diabetic patients are more frequently tested for hgbA1c than the general population, this metric, if calculated for all patients, would vary with the ratio of diabetic to nondiabetic patients. Thus, if this ratio were to change between the before and after periods, the rate of hgbA1c tests per patient could also change, independent of the utilization initiative. In this case, hgbA1c test per patient in diabetic patients only would likely be the better metric.

Accounting for Seasonal Variation

Some tests, including many microbiology tests, follow a seasonal distribution that can easily confound before-after comparisons. Utilization patterns may also exhibit some seasonality for nonbiological reasons, including house staff often starting over the summer, seasonal vacation schedules, and local “busy seasons” (e.g., winter in much of Florida). For tests that vary seasonally, comparisons across an entire year before and after may be helpful as may a year over year comparison (e.g., June 2015 compared to June 2014).

Statistical Adjustment

Statistical techniques can help to adjust utilization metrics for possible confounders to isolate the effects of the initiative. The techniques will often treat possible confounders as well as the presence (or absence) of the utilization initiative as independent variables and the utilization metric of interest as the dependent variable. Fitting these models can help to isolate the impact of the initiative on the metric. These approaches are often unnecessary to gauge the impact of a utilization management initiative, but can be quite helpful in certain situations.

Additional Considerations in Utilization Monitoring

Rare Events

Changes in the rates of rare events can be difficult to detect and may require monitoring for a long period of time to achieve a sufficient sample size to statistically distinguish trends from chance. Nonetheless, certain rare events, such as patient errors attributable to a utilization management initiative or rare outcomes (e.g., deaths from a particular cause), can be important to monitor in the context of certain utilization management initiatives.

In particular, the number of rare events occurring during a given time period will often generally follow the Poisson distribution [39], which has a variance equal to its mean. That means, for example, if a clinician orders three whole exome sequencing tests per month on average (and his or her orders for this test follow the Poisson distribution), there is a 5 % chance that clinician will order none of these in a given month and 8 % chance he or she will order five or more. Thus, tracking orders for only 1–2 months for this test for this physician before and after a utilization initiative could fail to distinguish true changes in underlying rates of test ordering from chance.

Accordingly, it is import to monitor rates of rare of events for a sufficient period of time to assess true underlying trends. Likewise, it is important to avoid being misled by apparent changes that cannot statistically be distinguished from chance.

Difficult to Assess Measures

Many aspects of care that may be impacted by a utilization management initiative are difficult to measure . For example, care and outcomes downstream from the laboratory can be substantially impacted by a utilization initiative and may represent most of the benefit of a utilization management initiative, but are nonetheless difficult to capture. In particular, capturing outcomes downstream from the laboratory often requires the use of non-laboratory clinical data that may be less readily available than laboratory data to a laboratory utilization management team. Even if available, such data may not be in a structured form amenable to analysis. Most significantly, downstream outcomes are often dependent on many factors, and so isolating the effects of a laboratory utilization management initiative can prove difficult . Qualitative approaches, including the development of well-grounded hypotheses based on surveys or discussions with impacted clinicians, may prove highly informative. Developing better infrastructure and methods to capture outcomes downstream from the laboratory represents an important area for future research.

Multiple Hypothesis Correction

The optimal monitoring of utilization management initiatives often requires tracking multiple metrics. However, assessing the impact of an initiative by comparing multiple metrics can introduce statistical complexities related to multiple hypothesis testing. In particular, a utilization management team will often develop statistics around the change in each metric before vs. after the initiative or the difference in each metric between groups receiving vs. not receiving the intervention. These statistics will typically include p-values or confidence intervals that by convention incorporate a 5 % type I error rate; in other words, when the initiative has had no impact on the metric, the utilization management team will only falsely conclude that it has 1 out of 20 times. However, if multiple metrics are considered for each initiative and no adjustment to the p-values is made, the utilization management team will

conclude that at least one metric shows a change more than 1 of 20 times even when the initiative has had no impact whatsoever (assuming statistical independence of the metrics). For example, if the team evaluates ten independent metrics that are wholly unaffected by the initiative, the team will nonetheless find a significant effect in at least one of the metrics nearly 40 % of the time.

While in practice, formal adjustment may not be needed; utilization management teams should at least be aware of this issue when designing and evaluating metrics. Designing metrics in advance of an initiative may help to alleviate this multiple hypothesis challenge. Utilization management teams designing metrics after the initiative may be tempted to look at multiple metrics or variations of metrics to "find the ones that work best." However, this approach can often lead to the subtle and sometimes unintended testing of multiple hypotheses. Likewise, various statistical strategies including familywise error rate correction and false discovery rate correction are available to adjust p-values in the setting of multiple hypothesis testing [40]. However, the appropriate application of these approaches remains controversial.

Sampling

In some cases, data may be costly or challenging to capture. For example, an initiative might seek to limit testing for a non-endemic parasite to patients with a travel history that would put them at risk. A good metric to evaluate this initiative might be rates of orders for this test in patients with and without appropriate travel histories. However, determining appropriate travel history may require a chart review, making it resource intensive to capture this metric on all patients. In such cases, it may be appropriate to base metrics on a sampling of patients. While sampling may be superficially simple, optimal sampling to minimize biases and optimize study power can be complex and can require careful planning [41].

Business Intelligence

Commercially available laboratory "business intelligence" (BI) software is available and can enable laboratories to track productivity, quality, and utilization metrics. This software could serve as a role in a utilization management programs by offering ready access to key metrics. Nonetheless,

at the time of this writing, some commercially available products have limited ability to customize the metrics and reporting and thus can serve as supplement to, but not a replacement for, informaticians or other individuals with informatics capabilities. Presumably, moving forward, the functionality of these products will expand to better meet the needs of a robust and customized utilization management program.

Analytics to Identify Utilization Management Opportunities and Optimize Utilization

One highly valuable application of data analytics in laboratory utilization is in the identification of utilization improvement opportunities and in the selection of optimal utilization management strategies. The following sections describe selected strategies for applying analytics to utilization management target and strategy selection.

Variation Analysis

Variation analysis seeks to identify practice variation between physicians that cannot be explained by clinical factors [42]. For example, a variation analysis could compare CBCs per patient across a group of physicians. Variation analyses often start with the assumption that the "average" clinician and those practicing near the average are providing appropriate care, while outliers may be practicing suboptimally and under- or overutilizing resources. For example, if the average PCP in a practice was found to order 0.4 CBCs per patient per year, a PCP ordering two CBCs per patient per year might warrant further investigation into the reasons for the outlier status and potential utilization improvement opportunities. However, the notion that the average is necessarily clinically optimal is of course not always true. As variation analysis data and methods advance, variation analyses may increasingly incorporate clinical outcomes data to help assess optimal utilization.

In practice, one of the most challenging aspects of variation analysis is controlling for variation that is due to clinical factors. For example, a PCP caring for a large population of diabetic patients might be expected to order more hgbA1c tests per patient than one with fewer diabetic patients. Statistical regression and other statistical approaches are often used to clinically adjust utilization data for use in variation analyses. One strategy is to use models to "predict" an expected level of utilization (e.g., sendout test

costs for a physician) and then compare actual utilization to expected utilization. In practice, the statistical modeling can be quite complex and may require subjective decisions, requiring personnel with expertise in statistics and data science as well as clinical intuition. While utilization management teams may have difficulty finding qualified personnel, a growing cohort of investigators from economics, health service research, and informatics are increasingly developing expertise in variation modeling, and so hopefully these resources will become more widely available moving forward (see Practical Considerations).

After identifying interphysician variation in test ordering, laboratory utilization management teams must decide the best approach to address the variation and apply the data toward improving utilization. Generally, the first step is to confirm that apparent variation identified statistically represents true variation in clinical practice and not in underlying clinical circumstances. Although adequate statistical adjustment will help isolate the variation attributable to physician-dependent practice patterns, statistical adjustment may fail to capture or adjust for all relevant clinical factors. Chart review of selected cases, particularly by a physician within the specialty being analyzed, may help to identify possible clinical factors that might account for apparent variation. Next steps may include presenting variation data to department leadership and to individual physicians. Provider feedback may itself be a valuable utilization management tool [43]. The utilization management team should use judgment in deciding the degree to which to anonymize data; one option is to provide variation reports with physicians identified by a code where individual physicians know their code but do not know which code corresponds to which of their colleagues. Physicians may be encouraged to discuss test-ordering practices among one another to develop more standard practices. In this context, much of the value of variation analysis may lie in its role as catalyst to initiate discussions among physicians and encourage them to be more thoughtful in their test-ordering practices.

Variation analyses can also be used by utilization management teams to identify utilization improvement opportunities. Since suboptimal or wasteful test utilization will often lead to variation, utilization management teams may examine tests, physicians, or practices exhibiting wide interphysician variation to uncover utilization improvement opportunities. Geographic variation in health-care utilization has been clearly demonstrated and reported

[44], and analysis of inter-practice or inter-intuitional variation analysis could presumably also help to target utilization efforts. See other chapter on physician profiling for additional information.

Yield Analysis and Appropriateness Analysis

Another metric that utilization management teams can use to identify utilization improvement opportunities is the proportion of results for a test that are abnormal (the “yield”). Although negative test results certainly have value in many circumstances, utilization management teams may identify tests where nearly 100 % of results are normal. While for most tests, an optimal yield is not defined, a very low yield might suggest clinicians are too frequently ordering the test in patients with a low pretest likelihood of a positive result. Furthermore, utilization management teams can sometimes examine subgroups of patients in yield analyses to identify “pretest” patient characteristics that increase the likelihood of a positive result that may in turn prove useful in guiding test-ordering decisions. Yield analysis can also be combined with variation analysis to overlay variation in utilization with variation in yield. Like with variation analysis, yield analysis can be useful to clinicians as an education tool or catalyst for discussions and to utilization management teams as a tool for identifying utilization improvement opportunities.

Guideline Conformance

In cases where clear clinical guidelines prescribe certain test-ordering patterns, utilization management teams can look to see the rates that various physicians or practices are ordering testing in conformance with the guidelines. One challenge to this type of analysis is that many guidelines rely on clinical data that might not be available to utilization management teams in a structured form suitable for analysis. Guideline nonconformance is likely to represent a utilization improvement opportunity. Radiology utilization initiatives have made fairly extensive use of appropriateness in imaging orders [44] and may provide a template for wider expansion of these approaches to laboratory utilization management.

Benchmarking

Benchmarking involves comparison of performance or utilization data to standards ("benchmarks") [38]. For example, benchmarks may be used to compare hospitals on test utilization with metrics such as tests per patient-admission. Likewise benchmarks might compare laboratories on technologist productivity with metrics such as tests per full-time equivalent (FTE). While benchmarks may have value in certain cases, they need to be used with caution [38]. "External benchmarks" are generally based on performance of theoretically comparable "peer" institutions. Accordingly, the value benchmarks will offer to an institution will depend in part on how comparable the peer institutions are. For example, a comparison across tertiary care academic hospitals and small community hospitals is likely to offer little value. Likewise, even within hospital category, patient mix and clinical needs may vary significantly. Furthermore, metrics are often ill defined. For example, without clear definitions, some institutions may count and report a CBC as single test, where another may count it as many tests, representing each of the different CBC components. Such variability would of course render many count-based utilization or performance metrics mostly meaningless. "Internal" benchmarks likewise look at metrics within an institution, generally comparing performance over time [38].

Unexpected Changes in Practice Patterns

Evaluating trends in utilization data can serve as a very valuable tool in identifying utilization improvement opportunities. A substantial, particularly sudden, increase in utilization of a test may indicate misutilization. For example, a test may have been inappropriately added to a test-ordering template, driving inappropriate orders. Alternatively, a new physician on staff may be responsible for the increase. Another possibility is an appropriate increase in orders, as may occur in the face of new clinical evidence or guidelines. Sudden increases in ordering volume for a test will generally at least deserve investigation to identify the underlying cause.

Data-Driven Targeting of Utilization Management

When a utilization management team identifies misutilization, analysis of data can help to design an appropriate utilization improvement strategy. Key questions that utilization data can address include:

- Who is placing the orders? How many physicians account for most of

the orders? Are most of the orders from a single specialty or small set of specialties?

- Is utilization highly varied between physicians seeing similar patients?
- How are physicians ordering the tests (e.g., using a particular template)?

With answers to these questions, an ideal utilization strategy will often become obvious. For example, if most orders for a test are placed by a single inexperienced clinician and other more experienced clinicians seeing similar patients are infrequently using the test, an optimal utilization strategy may be to arrange a meeting including the inexperienced clinician, one of his or her more experienced colleagues, and members of the utilization management team to discuss appropriate ordering. Utilization of a test ordered within a single small clinical division may be addressed with the division head or a quality assurance chair. If a test is ordered primarily using a particular template, adding decision support to that template may improve utilization. In contrast a test that is very widely used might require a more broadly applied decision support alert.

Challenges and Practical Considerations

Several challenges exist to the application of analytics and informatics to utilization management. One sometimes limiting challenge is data access. Utilization management teams may not be able to extract needed laboratory and clinical data in a form amenable to analysis. Developing a utilization management “data mart” allowing the laboratory and utilization management team to directly access needed data may greatly facilitate data access needs and the pace of utilization management work. A related concern is data quality. While laboratory data is often high quality and well structured, other clinical data may be of varying quality. Data quality is often limited by completeness, accuracy, and structure. Data analysis efforts must develop strategies to check for data quality and resolve it to the extent feasible. For example, checking that the number of CBC tests captured during some time period matches the general “ballpark” expectation could help to serve as a check of completeness. Likewise, natural language processing may help to structure free text.

Another factor that sometimes limits the use of data analytics and informatics is a lack of sufficiently knowledgeable and skilled personnel and,

more generally, analytics and informatics resources. People skilled in data analytics are currently in high demand with demand exceeding supply [45]. Moreover, many utilization analytics projects require personnel with both analytic skills as well as at least some domain knowledge in health care. Such individuals may not be available to a utilization management team or project. Similarly, IT personnel and resources to implement decision support may be a limiting factor in many initiatives. Solutions include hiring outside consultants or collaborating with hospital or health systems departments (e.g., "population health management groups") that might have such personnel available.

With regard to metrics, sometimes simplifying can help economize on resources. More straightforward metrics will sometimes be as good if not better than complex metrics. Furthermore, utilization management teams must decide how much to invest in analytics which often requires deciding whether to make the investment to take a measure from "good enough" but with a few limitations to "perfect." "Perfect" often requires many times the resources that "good enough" does. Likewise, utilization management teams must be careful to avoid "analysis paralysis." Data can often be analyzed ad infinitum, but it is important to balance the effort spent analyzing data against the effort implementing quality and utilization improvements using the data.

Conclusions

As described, informatics and analytics provide key tools in utilization management. Well-designed electronic clinical decision support integrated into the clinical workflow through computerized provider order entry and other systems can substantially improve test utilization. Likewise, data analytics can help to leverage available data to identify utilization improvement opportunities, guide the selection of optimal utilization management strategies, and monitor the impacts of utilization management initiatives. Moving forward, it is likely that analytics systems will increasingly integrate with decision support systems to guide patient-specific testing strategies and drive "smart" alerts.

References

1. American Diabetes Association. Classification and diagnosis of diabetes. Diabetes Care. 2015;38(Suppl):S8–16.
[CrossRef]

2. Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012;157:120–34.
[CrossRef][PubMed]

3. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA Guideline. J Urol. 2013;190:419–26.
[CrossRef][PubMed][PubMedCentral]

4. Wang TJ, Mort EA, Nordberg P, et al. A utilization management intervention to reduce unnecessary testing in the coronary care unit. Arch Intern Med. 2002;162:1885–90.
[CrossRef][PubMed]

5. Choosing Wisely. http://www.choosingwisely.org/. Accessed 11 Nov 2015.

6. Hilborne LH. When less is more for patients in laboratory testing. Am J Clin Pathol. 2013;139:271–2.
[CrossRef][PubMed]

7. National Guideline Clearinghouse. http://www.guideline.gov/. Accessed 11 Nov 2015.

8. Kim JY, Dzik WH, Dighe AS, et al. Utilization management in a large urban academic medical center: a 10-year experience. Am J Clin Pathol. 2011;135:108–18.
[CrossRef][PubMed]

9. Blechner M, Kish J, Chadaga V, et al. Analysis of search in an online clinical laboratory manual. Am J Clin Pathol. 2006;126:208–14.
[CrossRef][PubMed]

10. Henricks WH. “Meaningful use” of electronic health records and its relevance to laboratories and pathologists. J Pathol Inform. 2011;2:7.
[CrossRef][PubMed][PubMedCentral]

11. Thompson W, Dodek PM, Norena M, et al. Computerized physician order entry of diagnostic tests in an intensive care unit is associated with improved timeliness of service. Crit Care Med. 2004;32:1306–9.
[CrossRef][PubMed]

12. Baron JM, Dighe AS. Computerized provider order entry in the clinical laboratory. J Pathol Inform. 2011;2:35.
[CrossRef][PubMed][PubMedCentral]

13. Wright A, Sittig DF, Ash JS, et al. Clinical decision support capabilities of commercially-available clinical information systems. J Am Med Inform Assoc. 2009;16:637–44.
[CrossRef][PubMed][PubMedCentral]

14. Sepulveda JL, Young DS. The ideal laboratory information system. Arch Pathol Lab Med. 2012;137(8):1129–40.
[CrossRef][PubMed]

15. Baron JM, Dighe AS. The role of informatics and decision support in utilization management. Clin Chim Acta. 2014;427:196–201.
[CrossRef][PubMed]

16. Westbrook JI, Georgiou A, Lam M. Does computerised provider order entry reduce test turnaround times? A before-and-after study at four hospitals. Stud Health Technol Inform. 2009;150:527–31.
[PubMed]

17. Westbrook JI, Georgiou A, Rob MI. Test turnaround times and mortality rates 12 and 24 months after the introduction of a computerised provider order entry system. Methods Inf Med. 2009;48:211–5.
[PubMed]

18. Tierney WM, Miller ME, McDonald CJ. The effect on test ordering of informing physicians of the charges for outpatient diagnostic tests. N Engl J Med. 1990;322:1499–504.
[CrossRef][PubMed]

19. Feldman LS, Shihab HM, Thiemann D, et al. Impact of providing fee data on laboratory test ordering: a controlled clinical trial. JAMA Intern Med. 2013;173:903–8.
[CrossRef][PubMed]

20. Neilson EG, Johnson KB, Rosenbloom ST, et al. The impact of peer management on test-ordering behavior. Ann Intern Med. 2004;141:196–204.
[CrossRef][PubMed]

21. MacMillan D. Calculating cost savings in utilization management. Clin Chim Acta. 2014;427:123–6.
[CrossRef][PubMed]

22. Tierney WM, McDonald CJ, Martin DK, et al. Computerized display of past test results. Effect on outpatient testing. Ann Intern Med. 1987;107:569–74.
[CrossRef][PubMed]

23. Angus DC, Deutschman CS, Hall JB, et al. Choosing wisely® in critical care: maximizing value in the intensive care unit. Am J Crit Care. 2014;23:444–6.
[CrossRef][PubMed]

24. Jha AK, Chan DC, Ridgway AB, et al. Improving safety and eliminating redundant tests: cutting costs in U.S. hospitals. Health Aff (Millwood). 2009;28:1475–84.
[CrossRef]

25. Fryer AA, Smellie WS. Managing demand for laboratory tests: a laboratory toolkit. J Clin Pathol. 2013;66:62–72.
[CrossRef][PubMed]

26. MacMillan DH, Soderberg BL, Laposata M. Regulations regarding reflexive testing and narrative interpretations in laboratory medicine. Am J Clin Pathol. 2001;116(Suppl):S129–32.
[PubMed]

27. Ash JS, Sittig DF, Campbell EM, et al. Some unintended consequences of clinical decision support

systems. AMIA Annu Symp Proc. 2007;200:26–30.

28. Bates DW, Kuperman GJ, Wang S, et al. Ten commandments for effective clinical decision support: making the practice of evidence-based medicine a reality. J Am Med Inform Assoc. 2003;10:523–30.
[CrossRef][PubMed][PubMedCentral]

29. Baron JM, Dighe AS, Arnaout R, et al. The 2013 symposium on pathology data integration and clinical decision support and the current state of field. J Pathol Inform. 2014;5(1):2.
[CrossRef][PubMed][PubMedCentral]

30. Louis DN, Feldman M, Carter AB, et al. Computational pathology: a path ahead. Arch Pathol Lab Med. 2016;140(1):41–50.
[CrossRef][PubMed]

31. Louis DN, Gerber GK, Baron JM, et al. Computational pathology: an emerging definition. Arch Pathol Lab Med. 2014;138:1133–8.
[CrossRef][PubMed]

32. Baron JM, Mermel CH, Lewandrowski KB, et al. Detection of preanalytic laboratory testing errors using a statistically guided protocol. Am J Clin Pathol. 2012;138:406–13.
[CrossRef][PubMed]

33. Hauser RG, Jackson BR, Shirts BH. A bayesian approach to laboratory utilization management. J Pathol Inform. 2015;6:10.
[CrossRef][PubMed][PubMedCentral]

34. Baron JM, Lewandrowski KB, Kamis IK, et al. A novel strategy for evaluating the effects of an electronic test ordering alert message: optimizing cardiac marker use. J Pathol Inform. 2012;3:3.
[CrossRef][PubMed][PubMedCentral]

35. Grisson R, Kim JY, Brodsky V, et al. A novel class of laboratory middleware. Promoting information flow and improving computerized provider order entry. Am J Clin Pathol. 2010;133:860–9.
[CrossRef][PubMed]

36. Henricks WH, Wilkerson ML, Castellani WJ, et al. Pathologists' place in the electronic health record landscape. Arch Pathol Lab Med. 2015;139:307–10.
[CrossRef][PubMed]

37. Sunheimer RL, Threatte GA. Analysis: clinical laboratory automation. In: McPherson RA, Pincus MR, Henry JB, editors. Henry's clinical diagnosis and management by laboratory methods. 21st ed. Philadelphia, PA: Saunders Elsevier; 2007. p. 56–63.

38. Melanson SE. Establishing benchmarks and metrics for utilization management. Clin Chim Acta. 2014;427:127–30.
[CrossRef][PubMed]

39. Nitta H, Yamazaki S, Omori T, et al. An introduction to epidemiologic and statistical methods useful in environmental epidemiology. J Epidemiol. 2010;20:177–84.
[CrossRef][PubMed][PubMedCentral]

40. Glickman ME, Rao SR, Schultz MR. False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. J Clin Epidemiol. 2014;67:850–7.
[CrossRef][PubMed]

41. Ash A. The design and analysis of hospital utilization studies. Int J Qual Health Care. 1995;7:245–52.
[PubMed]

42. Cook JA, Collins GS. The rise of big clinical databases. Br J Surg. 2015;102:e93–101.
[CrossRef][PubMed]

43. Janssens PM. Managing the demand for laboratory testing: options and opportunities. Clin Chim Acta. 2010;411:1596–602.
[CrossRef][PubMed]

44. Sistrom CL. The appropriateness of imaging: a comprehensive conceptual framework. Radiology. 2009;251:637–49.
[CrossRef][PubMed]

45. Ovide S. Big Data, Big Blunders: five mistakes companies make—and how they can avoid them. Wall Street J. 2013.

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_5

5. Utilization Management Employing Test Interpretations and Algorithms

Elizabeth M. Van Cott[1]

(1) Massachusetts General Hospital, GRJ235, 55 Fruit Street, Boston, MA 02114, USA

Keywords Utilization management – Pathology interpretation – Diagnostic algorithm – Special coagulation

Introduction

Pathologists and clinicians are increasingly expected to provide care in a cost-effective and expedient manner, limiting unnecessary use of medical resources. Furthermore, maintaining sufficient medical knowledge to manage patients is increasingly challenging for clinicians , as diagnostic and therapeutic options as well as laboratory test menus continue to expand. Pathologists, as directors of clinical laboratories , can facilitate overcoming both of these obstacles, by providing customized interpretations of laboratory data for the patient's medical record and test algorithms. Benefits of interpretations (and algorithms) include avoidance of misdiagnoses; reducing the number of laboratory tests needed; reducing the number of procedures, transfusions, and admissions; shortening the amount of time needed to reach a diagnosis; reducing errors in test ordering; and providing additional information about how the laboratory results might affect other aspects of a patient's care, collectively also reducing costs.

Generating accurate interpretations can be a challenge for many pathologists , given the growing complexity of medical care. Approaches that

facilitate the successful implementation of an interpretation service include algorithm-based testing and interpretation, optimizing laboratory requisitions and/or order-entry systems, proficiency testing programs that assess interpretations and provide constructive feedback, utilization of a collection of interpretive sentences or paragraphs that can be building blocks (“coded comments ”) for constructing preliminary interpretations, middleware for interpretations, and pathology resident participation and education.

The Benefits of Laboratory Interpretations

Laboratory results substantially influence patient care and costs. Laboratory testing represents only 3–5 % of a hospital’s budget , but it impacts 60–70 % of major medical decisions including admissions, discharges, and medications [1, 2]. In one study, only 61.7 % of 6721 adults received appropriate laboratory tests or radiography , suggesting that clinicians need guidance in laboratory test utilization [3]. A cost analysis performed in our hospital found that the coagulation laboratory interpretation service could be saving our hospital 1 million dollars annually [2].

Interpretations of laboratory tests, provided by a laboratory pathologist or other qualified expert, can be very valuable for clinicians. Without an accompanying interpretation, laboratory tests can often be misinterpreted. For example, we encountered a patient who had been misdiagnosed with protein S deficiency during pregnancy, which had led her to abort her pregnancy because she was concerned she would develop recurrent venous thromboembolism . However, neither she nor her physician realized that protein S typically decreases during normal pregnancy. In another case, the diagnosis of von Willebrand disease was missed in a newborn, because the clinicians did not know that the diagnosis can be masked in neonates for the reason that von Willebrand factor is typically elevated above a patient’s baseline at birth. In addition, the newborn was ill from infection and internal bleeding at the time of testing, and acute illness also elevates von Willebrand factor above a patient’s baseline. The missed diagnosis led to the baby’s father being charged with child abuse for her bleeding episodes, and he was imprisoned. These two cases occurred at hospitals outside of our network where pathologists do not provide interpretations. In a third case, an experienced hematologist thought that a slightly elevated hemoglobin A2 in a patient with sickle cell trait indicated coexisting beta thalassemia.

Fortunately, this third case example occurred at our institution, which has been providing interpretations by pathologists for hemoglobin electrophoresis and other complex laboratory tests for the past 20 years. The interpretation for this patient stated that the results are consistent with sickle cell trait and concomitant alpha thalassemia trait, based on the relatively low percentage of hemoglobin S and the low MCV. Hemoglobin S can falsely elevate hemoglobin A2 due to co-elution, without beta thalassemia. Thus, a misdiagnosis was avoided.

At the Massachusetts General Hospital , surveys of physicians receiving pathologist interpretations with their specialized coagulation test results showed that 98 % find the interpretations “useful or informative.” In addition, responses indicated that 72 % of interpretations reduced the number of tests needed to make a diagnosis, 72 % helped avoid a misdiagnosis, and 59 % shortened the time to diagnosis [4]. In a subsequent, larger survey, also at the Massachusetts General Hospital, 77 % of responding clinicians indicated that the interpretations saved them time, and 78 % indicated that the interpretations impacted their differential diagnosis . Responses also indicated that overall the interpretations reduced the number of admissions, the number of procedures and laboratory tests performed, and the number blood products used [4]. More recently, a similar coagulation interpretation service was initiated at Cleveland Clinic , and a survey among clinicians using this service found similar results: the majority of respondents reported that the interpretations impacted the differential diagnosis, shortened the time to diagnosis, prevented misdiagnosis, reduced the number of laboratory tests performed, reduced the number of procedures performed, and led to a change in medications or blood product usage. A minority of respondents indicated that the interpretations avoided a hospital admission or reduced length of hospital stay [5].

Interpretations can also improve physicians’ test ordering practices. We implemented a coagulation interpretation service for a group of outside hospitals and studied the effect of this service on the physician’s laboratory test ordering patterns. Laboratory test ordering patterns were studied immediately after we implemented the interpretation service, and the results were compared to ordering patterns after the interpretation service had been in place for 2.5 years. The number of coagulation test ordering errors decreased by nearly two errors per requisition during the study period ($P < 0.05$) [4]. Furthermore, initially, over 63 % of requisitions had four errors, but

at the end of the study period, only 10 % of equisitions had four errors. For example, clinicians had frequently ordered antigen assays (immunoassays) to assess for protein C, protein S, or antithrombin deficiency , but after receiving interpretations for 2.5 years, they more frequently ordered functional assays, which are the appropriate tests to order. The interpretations include mention that antigen assays are inadequate because they are not able to detect type II (qualitative) deficiencies , as they do not assess protein function. In contrast, functional assays are able to detect both type I (quantitative) and type II deficiencies. The results of this study provided evidence that interpretations can successfully modify physicians' ability to order tests appropriately.

Patient-specific , customized interpretations are more valuable than generic interpretations. Thus, an interpretation has maximum benefit if all the relevant results for a specimen are interpreted together, while also taking into account the patient's medical history. For example, if a patient has low protein C , low protein S , and normal antithrombin , it is most useful for the interpretation to indicate that the most likely explanation for this combination of findings is warfarin or vitamin K deficiency , rather than list all the possible causes of low protein C and then separately list all the possible causes of low protein S. Incorporating the normal antithrombin result into the interpretation allows the exclusion of some other possible causes of low protein C and low protein S or at least rendering them much less likely. The interpretation can also give suggestions for follow-up testing, if appropriate. In the current example, the interpretation would indicate that testing can be repeated any time when the patient has not had warfarin for at least 20 days, because it can take that long for protein S to recover to normal after warfarin discontinuation (protein C recovers more quickly, usually within 10 days).

In another example of a customized interpretation that incorporates relevant information from the medical record, for a patient with low antithrombin and 3+ proteinuria on a urinalysis, the interpretation can note that proteinuria can cause an acquired loss of antithrombin. Other possible causes of low antithrombin can also be included for completeness.

Interpretations can also be an opportunity for the pathologist to improve patient safety and alert the clinician that the laboratory findings can significantly impact other aspects of the patient's care. For example, if a patient on warfarin tests positive for a lupus anticoagulant , the interpretation can notify clinicians that lupus anticoagulants are capable of artifactually

prolonging the prothrombin time (PT) and international normalized ratio (INR) , potentially overestimating the patient's level of warfarin anticoagulation . The interpretation can note that a chromogenic factor X assay can be performed on this specimen if requested, to help determine whether or not the lupus anticoagulant is artifactually prolonging the PT/INR [6].

Challenges for the Pathologist

The fund of knowledge required to care for patients is rapidly expanding not only for clinicians but also for pathologists. This can be a barrier to the successful implementation of a laboratory interpretation service. In one study conducted in the Netherlands and Norway, laboratory specialist recommendations to general practitioners regarding two hypothetical patients agreed with guidelines as infrequently as 23 % of the time, regarding renal function tests (e.g., creatinine or estimated glomerular filtration rate [eGFR]) [7].

In another study, a survey of 81 specialized coagulation laboratories in the United States and Canada (38 % responded) found inconsistent approaches to interpreting von Willebrand test results [8]. Five components, deemed important to include in an adequate interpretation, were appropriately addressed in interpretations performed by the following percentage of laboratories: von Willebrand factor increases with age (13 %), pre-analytical variables can cause falsely low levels (38 %), low levels can be congenital or acquired (58 %), low levels should be confirmed by repeat testing (54 %), blood type O individuals have lower levels (63 %), and low levels can be due to other factors (e.g., illness, injury, pregnancy, stress, estrogen use (63 %)). Thus, many laboratories do not include one or more of these elements in their interpretations , leaving room for improvement among North American laboratories . In addition, the cutoff used to define normal was variable [8].

In another study, pathologists and laboratory scientists in Asia and Africa were asked to interpret a series of laboratory results representing common problems encountered in clinical chemistry. The response rate was 50 %. The authors reported variable quality of interpretations, with some providing incorrect or misleading information [9].

Mechanisms to Facilitate Successful Interpretations

Given the difficulties for pathologists in providing interpretations as well as the challenges for clinicians in ordering the correct tests, the following section describes mechanisms that increase the likelihood of success for an interpretation service. These approaches include algorithm-based testing and interpretation, optimizing laboratory requisitions and/or order-entry systems, proficiency testing programs that assess interpretations and provide constructive feedback, the development of "coded comments ," and pathology resident participation and education.

Algorithms and Laboratory Test Requisitions

An interpretation service is more efficient when combined with strategic testing algorithms that simplify the diagnostic process for clinicians. Reflex test algorithms provide a faster route to reach a diagnosis at lower cost, by avoiding unnecessary tests and blood sample collections [10]. Over 100 reflex testing algorithms are in use at our hospital , which have been approved by our hospital's medical policy committee [10]. Example test algorithms are shown in Fig. 5.1 (protein C) and Fig. 5.2 (celiac disease) [11, 12]. Note that the algorithm for protein C testing incorporates information that is also useful for providing an interpretation, such as the various acquired conditions that can cause low protein C, the falsely normal results that can occur if patients are receiving novel anticoagulants that recently emerged on the market, and how long to wait after warfarin discontinuation before testing. A similar algorithm has also been published for antithrombin testing [13]. Note that the algorithm for celiac disease is also beneficial in controlling costs for sendout testing , by ensuring that the sendout test (antigliadin antibody) is performed only when indicated.

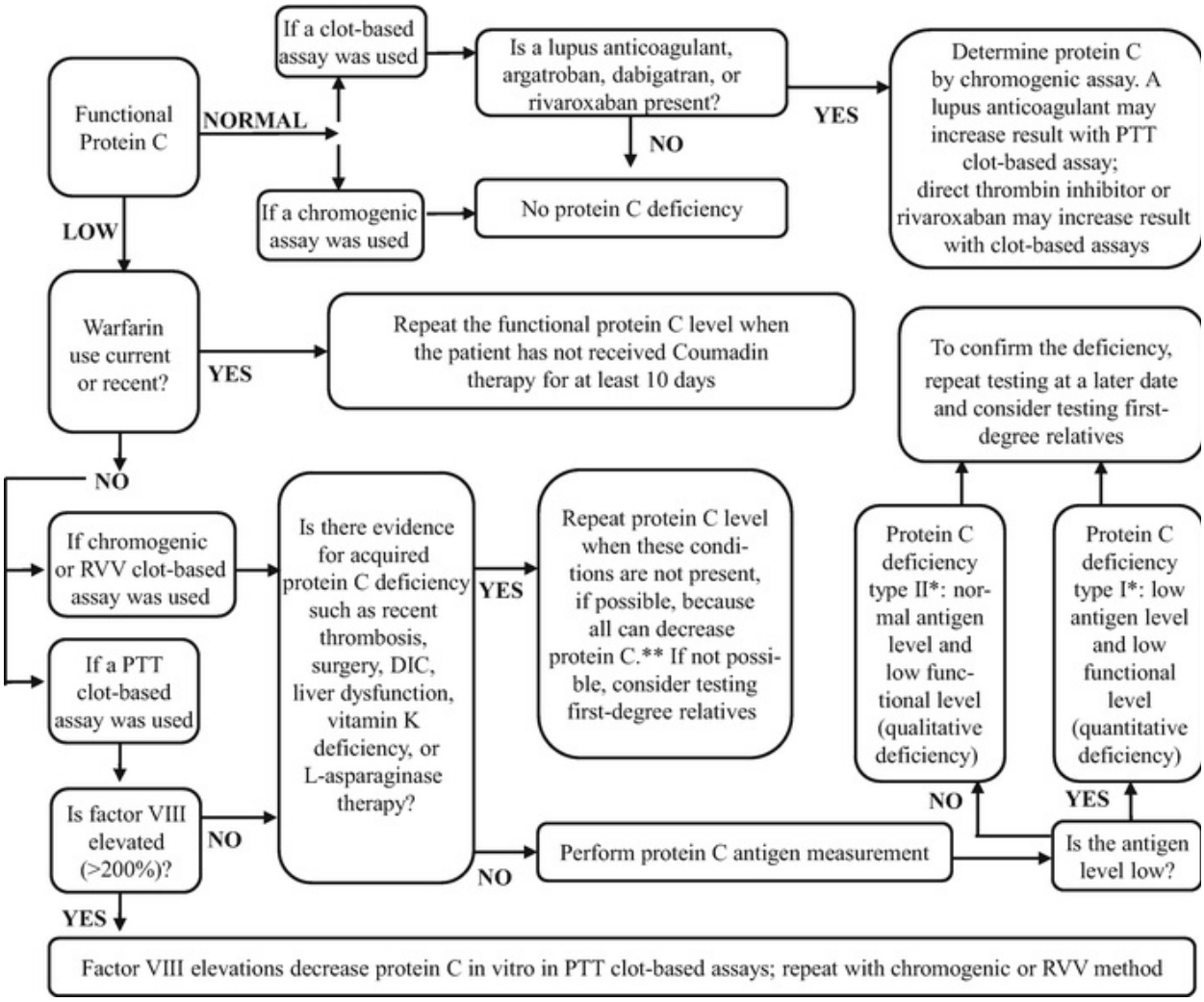


Fig. 5.1 A diagnostic algorithm for hereditary protein C deficiency , using functional assays and, if needed, antigen assays. Functional assays can be either clot-based or chromogenic, and both types of functional assays are included in the algorithm for completeness. Laboratories may chose to use the chromogenic assay and not the clot-based assay, because it has fewer interferences. Testing while on warfarin is not recommended, but this question is included in the figure so that results can be interpreted if testing was inadvertently performed while on warfarin. *If protein S is decreased to a similar extent, an acquired etiology is likely to at least partially account for the decreases, for example, vitamin K deficiency or warfarin. If antithrombin and/or protein S is decreased to a similar extent, then an acquired etiology is likely to account at least partially for the decreases, such as liver dysfunction, thrombosis, disseminated intravascular coagulation (DIC), or surgery. Repeat testing at a later date would be recommended. **A protein C antigen measurement also may be considered, particularly if protein S and antithrombin are normal. Updated from [11]

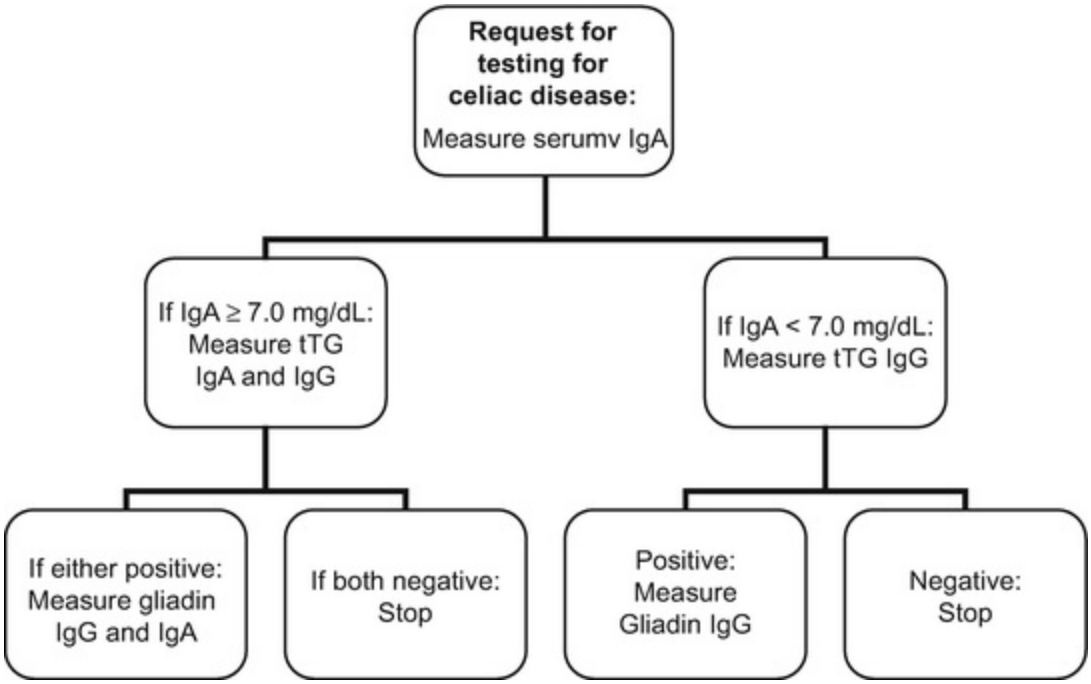


Fig. 5.2 Reflex screening algorithm for celiac disease at the Massachusetts General Hospital. *tTG* tissue transglutaminase. Modified from [12]

Test requisitions or order-entry systems can be simplified to offer the appropriate algorithms. For example, for a patient undergoing evaluation because of a bleeding history, the clinician can order a “prolonged PT and/or aPTT evaluation ,” and the laboratory will follow an algorithm to reach the diagnosis on one specimen, without performing any unnecessary tests. The alternative is cumbersome and inefficient, as well as inconvenient for the patient: the clinician waits for the PT or aPTT results to come back abnormal, collects another specimen, tries to remember which coagulation factors to order for which prolongation, and subsequently would need to collect yet another specimen if it turns out that lupus anticoagulant or inhibitor tests are indicated. The clinicians can also order all of these tests up front, but this wastes health-care resources if the tests turn out to be unnecessary. This approach can also be dangerous if it delays surgery that is urgently needed.

As another, true case example demonstrating the benefits of algorithm-based testing , a 24-year-old woman needing tonsillectomy was incidentally found to have a prolonged preoperative aPTT with a normal PT, at an outside hospital. Surgery was postponed and, since reflex algorithm testing was not available at the outside laboratory, her hematologist appropriately ordered a PTT mix, lupus anticoagulant testing, and aPTT factor assays (factors VIII,

IX, XI, and XII). Results were normal, although a footnote was attached to the factor XII result indicating that “non-parallelism” was seen, which can occur with lupus anticoagulants, heparin, factor inhibitors, or other conditions. Since the prolonged aPTT persisted and no explanation was identified in the laboratory report, surgery was further postponed and the patient was sent to us for a tertiary care referral. Upon review of the outside laboratory’s results, it was evident that the patient was not at risk for aPTT-related bleeding , because all her aPTT factors were normal (VIII, IX, XI, and XII). The most likely explanation was a lupus anticoagulant that was not detected by the laboratory testing, because the performed test involved a mixing step that was corrected, and thus a confirmatory test was not performed. It is now known that the mixing step frequently falsely corrects to normal with lupus anticoagulants, and a confirmatory step was needed in this case to prove the suspected lupus anticoagulant is present. If a “prolonged aPTT” algorithm had been available at the outside laboratory, the laboratory could have pursued further testing (in this case, additional lupus anticoagulant testing), so that the prolonged aPTT could have been explained. In addition, if customized interpretations were available at the outside laboratory, the pathologist could have stated that the non-parallelism in factor XII most likely indicates a lupus anticoagulant in this case. In our laboratory, lupus anticoagulant testing was positive, and the patient’s prolonged aPTT was officially explained in our interpretation. At this point, the patient’s surgery had been delayed for more than 2 months by the time her aPTT was explained. Repeat blood tests , specialist consultation appointments, and time delays could have been avoided if the initial laboratory offered algorithms and customized interpretation.

Algorithms need to be kept current, and as a result, they may change significantly over time. For example, syphilis testing algorithms traditionally begin with either rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) tests , with subsequent confirmation by treponemal tests such as the *T. pallidum* particle agglutination assay (TPPA) , fluorescent treponemal antibody absorption (FTA-Abs) , or the microhemagglutination assay (MHA-TP) . Currently, as certain confirmatory tests have become more readily available, the algorithm is often reversed. Although the original algorithm can still be used, most laboratories in Canada now screen for syphilis using treponemal enzyme immunoassays and then, if positive, confirm whether the infection is past or present using RPR or VDRL tests

(treponemal tests remain positive for life, whereas RPR or VDRL eventually become negative within approximately 3 years of treatment) [14].

Updated algorithms can also reduce costs and increase automation. One academic hospital tests the urine on virtually every newly admitted patient, generating 33,000 urine cultures per year. The urine cultures have a 72 % negative rate, which the pathologists saw as an opportunity to intervene and reduce costs by reducing the number of labor-intensive , expensive urine cultures being performed. Instead, they did a microscopic analysis using an automated urine particle analyzer (Sysmex UF-1000i), which they studied and found it has a 99.3 % negative predictive value. By changing the algorithm to start with an automated microscopic analysis , they reduced the number of cultures being performed by 30 % (10,000) with virtually no false negatives [15].

Test requisitions and/or order-entry systems can be designed to encourage appropriate test ordering of complex tests by offering these as test algorithms or panels, rather than simply listing all test names individually. For example, most clinicians do not realize that “ristocetin cofactor ” is the name of the test for von Willebrand factor activity, so they order “von Willebrand factor antigen” when they see it listed on the requisition or order-entry system. By ordering the antigen test without the activity test, type 2 von Willebrand disease could be misdiagnosed as normal. In contrast, if a von Willebrand panel is offered on the requisition or order-entry system , the appropriate laboratory tests can be ordered. If panels or algorithms are offered, the requisition or order-entry system should explain what tests are or may be included (e.g., on the back of the requisition). For hospital laboratories , it is recommended to initially obtain approval from the hospital’s medical policy committee for the algorithm (reflex test) protocols that the laboratory would like to use. Clinicians still should have the ability to order a test individually. These billing requirements for reflex testing and interpretation are further described in MacMillan et al. [16].

Kahan et al. reported a decrease in test ordering by up to 50 % after they restructured their laboratory requisition for vitamin B12, folate, and ferritin [17]. In our hospital, when the hematology and chemistry labs merged to form a core laboratory, adding aPTT to the core stat lab requisition increased the number of stat aPTT requests by 1.7-fold. These and other analyses demonstrate that changes in laboratory requisitions can substantially influence test ordering patterns [12].

Interpretation algorithms have been published to help clinicians and laboratories with interpretation. For example, an arterial blood gas algorithm that automatically interprets results compared favorably to interpretations generated by two web-based algorithms as well as interpretations written by two experienced clinicians [18]. Guidelines on the interpretation of platelet aggregation studies have also been published [19], as further discussed below.

Lastly, the choice of methodology offered by the clinical laboratory can of course have great impact on the interpretation of the results, as well as a financial impact. For example, switching to an IgG-only heparin-induced thrombocytopenia antibody ELISA format (instead of a polyvalent IgG, IgM, and IgA ELISA) improved the specificity of our testing, eliminating approximately half of the “false positives .” This, in conjunction with requiring a hematology-oncology consult to continue anticoagulation with argatroban (instead of heparin), had the synergistic benefit of dramatically reducing our hospital’s argatroban expenses by almost 90 %, saving several million dollars annually since argatroban is very expensive.

External Quality Assessment (EQA) Proficiency Testing

External quality assessment (EQA) proficiency testing programs that analyze interpretations are another mechanism that improves pathologist interpretation skills. For example, laboratory interpretations on cystic fibrosis laboratory reports improved over a 6-year time period among laboratories participating in an EQA proficiency program that assessed interpretation as well as genotyping results [20]. The improvement was attributed to education achieved by participation in the EQA proficiency program. In another study, a porphyria EQA program reported that their participants improved their diagnostic testing strategies over the course of their participation, attributed to education attained through the EQA program [21]. For example, urine porphobilinogen, plasma fluorescence scanning, and fecal coproporphyrin isomer III:I ratio are needed to diagnose or exclude certain types of porphyria. The number of laboratories performing this correct set of analyses doubled during the 3-year course of the study (initially eight laboratories, increasing to 16, out of 21). Interpretations of the results were found to be accurate in this study. Similarly, laboratory performance improved over time

among participants participating in a platelet aggregation interpretation EQA proficiency program [22, 23]. The percentage of correct interpretations increased with participation in the proficiency program, which provided participants with guidelines for platelet aggregation interpretation [16] and expert feedback on incorrect or not optimal interpretations.

Coded Comments

The pathologist can save material written into interpretations to serve as a resource for future interpretations, rather than rewriting the interpretation "from scratch" every time. The material can be stored broken down into individual sentences or paragraphs that can be cut and pasted into a new interpretation as appropriate. Multiple different stored segments can be mixed and matched for each new interpretation. Each stored segment is given a name, or a "code," to facilitate locating the comment when it is needed. We call these "coded comments." The resulting new interpretation can be edited to customize it for the patient, as appropriate. These coded comments also serve as a resource for training residents and training new pathologists who join the service.

Middleware is commercially available that further facilitates the incorporation of these coded comments into new interpretations and interfaces with the laboratory information system so that interpretations can be automatically entered into the medical record. Some middleware vendors also offer coded comments that can be used.

Pathology Residents

Incorporating pathology residents, if available, into the interpretation service is a mutually beneficial interaction. Residents can prepare a preliminary interpretation, by choosing among the various coded comments and editing as necessary. Residents learn a great deal through this process. This represents a case-based, "hands-on" activity that residents typically find to be a more interesting and effective way to learn than reading a book. The preliminary interpretations and medical history obtained by the resident are very valuable for the pathologist, who modifies the resident's interpretations as needed, before entering them into the medical record.

Conclusions

Utilization management of laboratory tests is strengthened, and incorporation of laboratory test results into patient care is enhanced when pathologist interpretations of the laboratory tests are provided for clinicians and when reflex algorithm testing is utilized. There are multiple benefits from algorithm-based laboratory testing and pathologist interpretations of laboratory tests. Multiple different mechanisms can be applied to assist the pathologist overcome the barriers to successful implementation of an interpretation service.

References

1. Forsman RW. Why is the laboratory an afterthought for managed care organizations? Clin Chem. 1996;42:813–6.
[PubMed]

2. Kratz A, Laposata M. Enhanced clinical consulting—moving toward the core competencies of laboratory professionals. Clin Chim Acta. 2002;319:117–25.
[CrossRef][PubMed]

3. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. N Eng J Med. 2003;348:2635–45.
[CrossRef]

4. Laposata ME, Laposata M, Van Cott EM, Buchner DS, Kashalo MS, Dighe AS. Physician survey of a laboratory medicine interpretive service and evaluation of the influence of interpretations on laboratory test ordering. Arch Pathol Lab Med. 2004;128:1424–7.
[PubMed]

5. Kottke-Marchant K, Yerian L, Rogers J. Challenges and strategies for implementing an interpretive hemostasis service. Oral presentation, International Society for Laboratory Hematology (ILSH) XXVIth international symposium on technological innovations in laboratory hematology, Toronto, Canada, May 12, 2013. http://www.islh.org/online/Presentation_Upload/public.php

6. Arpino P, Demirjian Z, Van Cott EM. Use of the chromogenic factor X assay to predict the international normalized ratio in patients transitioning from argatroban to warfarin. Pharmacotherapy. 2005;25:157–64.
[CrossRef][PubMed]

7. Aekre KM, Oosterhuis WP, Sandberg S. How do laboratory specialists advise clinicians concerning the use and interpretation of renal tests? Scand J Clin Lab Invest. 2012;72:143–51.
[CrossRef]

8. Hayward CPM, Moffat KA, Plumhoff E, Van Cott EM. Approaches to investigating common

bleeding disorders: an evaluation of North American coagulation laboratory practices. Am J Hematol. 2012;87 Suppl 1:S45–50.
[CrossRef][PubMed]

9. Vasikaran SD, Lai LC, Sethi S, Lopez JB, Sikaris KA. Quality of interpretative commenting on common clinical chemistry results in the Asia-Pacific region and Africa. Clin Chem Lab Med. 2009;47:963–70.
[CrossRef][PubMed]

10. Laposata M, Dighe AS. "Pre-pre" and "post-post" analytical error: high-incidence patient safety hazards involving the clinical laboratory. Clin Chem Lab Med. 2007;45:712–9.
[CrossRef][PubMed]

11. Khor B, Van Cott EM. Laboratory tests for protein C deficiency. Am J Hematol. 2010;85:440–2.
[CrossRef][PubMed]

12. Kim JY, Van Cott EM, Lewandrowski KB. The use of decision analysis tools for the selection of clinical laboratory tests: developing diagnostic and forecasting models using laboratory evidence. In: Marchevsky AM, Wick M, editors. Evidence-based pathology and laboratory medicine. 1st ed. New York, NY: Springer/Humana Publishers; 2011. p. 305–22.
[CrossRef]

13. Khor B, Van Cott EM. Laboratory tests for antithrombin deficiency. Am J Hematol. 2010;85:947–50.
[CrossRef][PubMed]

14. Levett PN, Fonseca K, Tsang RSW, Kadkhoda K, Serhir B, Radons SM, Morshed M. Canadian Public Health Laboratory Network laboratory guidelines for the use of serological tests (excluding point-of-care tests) for the diagnosis of syphilis in Canada. Can J Infect Dis Med Microbiol. 2015;26(Suppl A):6A–12.
[PubMed][PubMedCentral]

15. O'Reilly KB. Lab studies new steps in urine and anemia screening. CAP Today. 2015;8:78–9.

16. MacMillan DH, Soderberg BL, Laposata M. Regulations regarding reflexive testing and narrative interpretations in laboratory medicine. Am J Clin Pathol. 2001;116 Suppl 1:S129–32.
[PubMed]

17. Kahan NR, Waitman DA, Vardy DA. Curtailing laboratory test ordering in a managed care setting through redesign of a computerized order form. Am J Manag Care. 2009;15:173–6.
[PubMed]

18. Park SH, Chang YJ, Kim HJ, et al. Development and validation of an arterial blood gas analysis interpretation algorithm for application in clinical laboratory services. Ann Clin Biochem. 2011;48:130–5.
[CrossRef][PubMed]

19. Hayward CM, Moffat KA, Raby A, Israels S, Plumhoff E, Flynn G, Zehnder JL. Development of North American consensus for medical laboratories that perform and interpret platelet function testing using light transmission aggregometry. Am J Clin Pathol. 2010;134:955–63.
[CrossRef][PubMed]

20. Berwouts S, Girodon E, Schwarz M, Stuhrmann M, Morris MA, Dequeker E. Improvement of interpretation in cystic fibrosis clinical laboratory reports: longitudinal analysis of external quality assessment data. Eur J Hum Genet. 2012;20:1209–15.
[CrossRef][PubMed][PubMedCentral]

21. Aarsand AK, Villanger JH, Stole E, et al. European specialist porphyria laboratories: diagnostic strategies, analytical quality, clinical interpretation, and reporting as assessed by an external quality assurance program. Clin Chem. 2011;57:1514–23.
[CrossRef][PubMed]

22. Hayward CPM, Moffat KA, Plumhoff E, Timleck M, Hoffman S, Spitzer E, Van Cott E, Meijer P. External quality assessment of platelet disorder investigations: results of international surveys on diagnostic tests for dense granule deficiency and platelet aggregometry interpretation. Semin Thromb Hemost. 2012;38:622–31.
[CrossRef][PubMed]

23. Moffat K, Plumhoff E, Hoffman S, Van Cott E, Meijer P, Hayward C. International proficiency challenges for platelet light transmittance aggregation—performance and adherence to published guidelines in diagnostic laboratories. International society for laboratory hematology (ILSH) XXIVth international symposium on technological innovations in laboratory hematology, New Orleans Louisiana, May 2011, poster 811.

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_6

6. Calculating Costs and Savings in Utilization Management

Patrick M. Sluss[1]

(1) Pathology Service Core Laboratories, Massachusetts General Hospital, Gray Bldg., Room 554, 55 Fruit St., Boston, MA 02114, USA

Patrick M. Sluss
Email: sluss.patrick@mgh.harvard.edu

Keywords Clinical laboratories – Process accounting – Cost accounting – Job order accounting – Utilization costs – Utilizations savings – Utilization impact

Introduction

Managing the utilization of laboratory tests is a high priority because of the large impact of testing on healthcare operations and because of the steadily increasing cost of testing. It has been estimated that >70 % of medical decisions (and therefore their associated costs) are based on, or heavily influenced by, laboratory tests. Currently there are over 200,000 clinical laboratories providing testing services in the United States. Approximately 11 billion dollars were spent on laboratory testing in 1985 and costs have been increasing approximately 10 % annually. These numbers, especially in the context of much lower rates of improvement in overall population health [1], are serious drivers of national priorities to reduce laboratory costs. Currently about 2 % (1.7 % or 9.7 billion dollars in 2012) of the entire Medicare budget is spent on laboratory testing. Rising laboratory testing costs (5–6 % annually

for most clinical laboratories) are also a target for reducing the cost of care at the local level.

One of the tools laboratory directors have for the rational management of laboratory resources is an assessment of the impact of utilization management . In recent years there has been an effort to define appropriate test utilization based on medical definitions (e.g., standards of care) of which patients require what tests and how often. Associated with this has been the introduction of software tools to determine if testing is being used appropriately and to determine the cost of over or under "utilization." Utilization management is now an activity that requires significant effort and time for most clinical laboratory directors [2]. Ultimately the goal of utilization management is to reduce the cost of care ("cost savings") without reducing the quality of that care. The impact of utilization management is based on evaluating the answers to two questions:

(1) What are the cost savings of changing test utilization with respect to performing the testing (laboratory) budget?

(2) What are the cost savings of the change with respect to delivering effective care and the overall cost to the institution and/or the healthcare system?

It should be noted that the most economical approach to performance of testing (i.e., testing at the lowest expense) is not always associated with the most economical (or effective) delivery of care. Furthermore in today's American healthcare system , reducing testing may result in reduced institutional revenues. For example, reducing the volume of an outpatient test , which is reimbursed based on test volume, can actually result in a net loss of institutional funds if the cost of performing the test is low relative to the reimbursement. In contrast, reducing the volume of inpatient tests, which are usually not reimbursed on a volume basis [3], reduces laboratory costs and results in a net gain for the institution which is paying for the laboratory's expenses. This paradigm is likely to change in the future as outpatient care becomes reimbursed in a fashion similar to what is done currently for inpatient care (e.g., bundled payments for episodes of care). Laboratory directors need to assess more than simple expense impacts in order to effectively communicate to hospital administration the business case for

utilization initiates. It is also important to document the link between utilization optimization and improved or more cost-effective clinical outcomes [4].

A full assessment of cost savings associated with utilization optimization should be based not only on laboratory expenses per se but also on the implications of changing test volumes on institutional reimbursement and on the overall cost of delivering care (i.e., health impact). This creates a serious challenge for the laboratory director. Not only is it necessary to calculate the expense of performing the testing using accessible laboratory data, but it is also necessary to at least estimate institutional reimbursements (e.g., revenues) and to assess the impact of changing test utilization on health outcomes, both of which require data that is not so easily acquired. Hospital reimbursements are usually managed at an institutional level in separate fund centers. It is often very difficult to obtain actual reimbursement information for a given test, which often varies based on different payer contracts. Determining the impact of laboratory testing on clinical care requires institutional and often extra-institutional data not immediately available to laboratory directors. The requisite information is increasingly becoming integrated into electronic medical records which will aid in assessing the impact of testing on clinical care.

This chapter is focused on calculating costs and savings associated with utilization management of laboratory testing in academic hospitals. However, most of the principles discussed also apply to nonacademic settings . As a starting point, a number of useful, and often confusing, definitions as they are used in this chapter are described below.

Capital Budget

Capital budget is the money specifically used to pay for institutional assets including equipment purchases, information systems, or other physical assets (such as space renovations). The fund center for capital expenses is generally managed at the institutional level on an annualized basis (capital equipment cycle). Laboratory-specific capital expenses must compete with requests from other departments for the funds allocated to the institutional budget.

Operating Budget

The operating budget is used to pay for ongoing laboratory operating

expenses including salaries, reagents, disposables, and other expenses. The operating budget is established at the beginning of the organization's fiscal year based on predicted expenses for the coming year. The budget is then adjusted during the year based on the actual expenses incurred over time.

Cost

The cost of a test is the total expense associated with performing the test. This encompasses labor (including specimen acquisition), reagents and consumables, service contracts, utilities, and other expenses [5].

Direct Cost

Direct costs are those that are directly associated with the production of a test. This includes labor, reagents, and other consumables. Direct costs may be classified as variable, fixed, and semi-variable (see below).

Indirect Cost

Indirect costs are those that are not directly related to the production of a test but are necessary to create the environment for testing. Such expenses are not associated directly with the testing performed in the laboratory. This includes such costs as administration, supervision, building maintenance, and utilities. For example, a supervisor salary is an indirect expense as the entire laboratory is served regardless of the mix of tests/systems. Thus, in contrast to direct expenses, indirect expenses are those associated with maintaining the laboratory regardless of the mix of tests or technologies involved.

Other indirect expenses, often referred to as "institutional overhead," also exist but are usually not included in the laboratory operating budget . For example, hospital-wide costs, such as utilities, human resource administration, or legal services, are incurred throughout the hospital and cannot be allocated to individual departments (Table 6.1). Institutions typically recover these expenses, using a formula based on a fixed percentage of each department's operating budget (e.g., 28 %). These expenses are excluded from consideration in this chapter as utilization management changes typically do not impact them.

Table 6.1 Examples of indirect (overhead) costs not in the laboratory operating budget

Cost description

Utilities
Hospital administrative support and oversight
Building maintenance
Insurance (loss and liability)
Building depreciation
Materials management
Safety and local regulatory compliance
Human resource support
Purchasing contracts and agreements

Adapted from [6]

Fixed Costs

A fixed cost is one that is independent of the number (volume) of tests performed. For example, service contract expenses are the same no matter how many tests are performed on a particular instrument. Laboratory director and administrative salaries are also examples of fixed costs.

Variable Cost

Variable costs are directly related to the number (volume) of tests performed. This includes reagents, consumables, and, to a certain extent, technologist labor (see below).

Semi-variable Cost

Semi-variable costs (sometimes called step variable costs) are those that incrementally change as a function of test volume. For example, technologist salaries (labor) or transportation expenses vary in discrete increments based on capacity. For example, adding 1000 new tests to a preexisting laboratory may not require hiring an additional technologist. However, adding 100,000 additional tests may reach a threshold where a new technologist is required.

Job Order Accounting

Job order accounting is a process for assigning expenses to a given test (e.g., sodium, troponin, alkaline phosphatase). Each test has its own unique costs which vary based on the type of test (e.g., reagents, consumables, technical

labor). Job order accounting is used to determine the cost of a test when the costs of different tests in the laboratory are significantly different from each other.

Process Accounting

Process accounting is a system for assigning expenses to tests in which it is assumed that the expenses associated with each test are not significantly different from each other (e.g., alkaline phosphatase, alanine aminotransferase). Expenses are calculated over a given length of time (typically annually) and then allocated to all the tests performed during that time. Process accounting is much easier to perform than job order accounting but it is only valid if the costs of the different tests are roughly the same.

Reimbursement

Reimbursements are monies paid to the institution for services provided. The amount of reimbursement for a given test is usually based on a negotiated percentage of the laboratory list price (charge) which varies depending on the payer (Medicare, Medicaid, private insurance). Thus a laboratory may charge $100 for a test but the payer only reimburses a percentage of the charge.

Test Utilization

Utilization encompasses how and under what circumstances a test is ordered. Assessments of test utilization are based on test volumes ordered for specific types of patients or clinical circumstances. Optimization of test utilization may be based on clinical guidelines and/or standards of care or by local consensus of what testing is appropriate for a given population of patients.

Calculating the Costs of Laboratory Testing

Calculating the cost of laboratory testing has long been a laboratory-based activity. Approaches to cost accounting have previously been reported in detail [6–9]. There are two basic steps involved in calculating the cost associated with a single test: (1) define the individual expenses and sources of data and (2) define the allocation formula for each expense.

Define Expenses and Sources of Data

It is best initially to define all the expenses associated with the testing process as illustrated in Figs. 6.1 and 6.2. The testing process can be divided into pre-analytical, analytical, and post-analytical phases. This approach is particularly efficient in settings where multiple fund centers are used to manage the various components. While analytical and post-analytical expenses are almost always managed in the laboratory operating budget, pre-analytical expenses are often managed in other fund centers (e.g., hospital transport, centralized phlebotomy, nursing, etc.). While the laboratory director may be responsible only for the laboratory operating budget, it is essential for him/her to assess all components of cost in evaluating the impact of the laboratory's utilization management program. Changing the number of tests ordered and/or the settings in which they are ordered potentially impacts all phases of the process, all of which ultimately impact the hospital's overall budget.

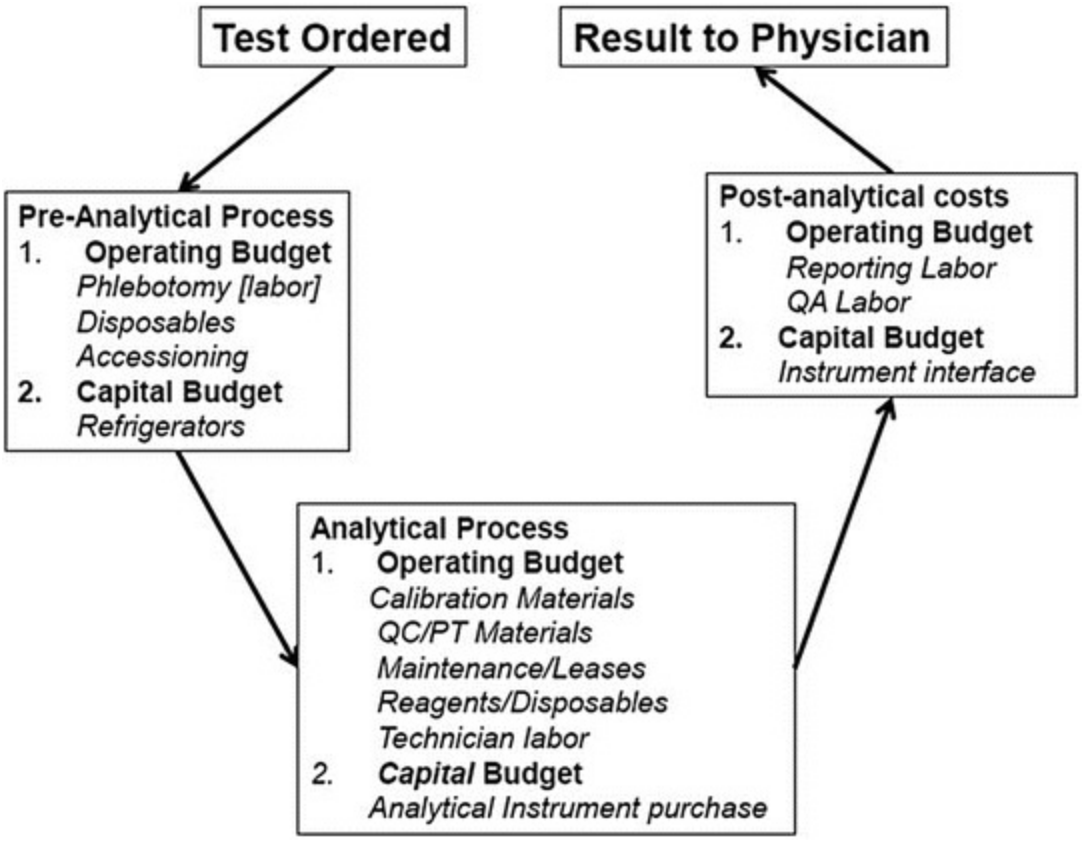


Fig. 6.1 Direct expenses associated with testing

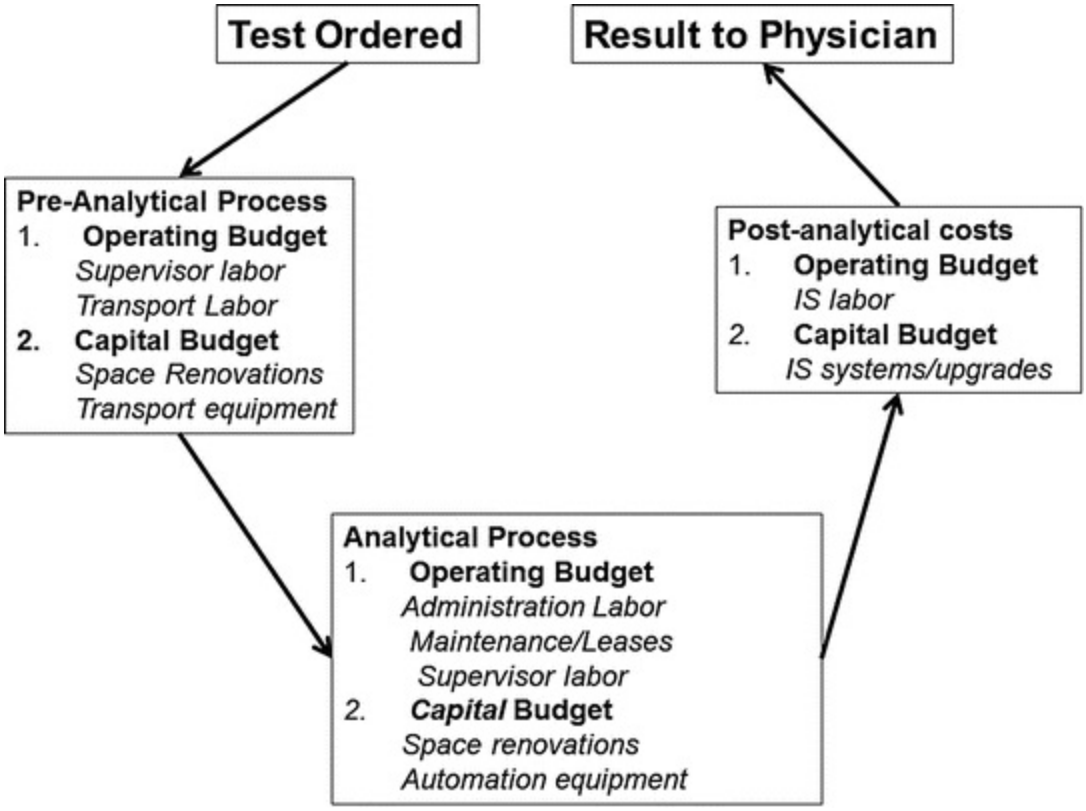


Fig. 6.2 Indirect laboratory expenses

At this stage, direct and indirect expenses should be differentiated because each is allocated to a specific test using different formulas as discussed in the following section. Figure 6.1 illustrates the major direct expenses associated with the various phases of the testing process. All of these expenses, by definition, can be associated with a specific test or group of tests.

Pre-analytical expenses are most often driven by the labor to perform phlebotomy and the individual specimen requirements . For example, expenses associated with gray-top blood tubes are typically associated only with glucose testing, while lavender-top tube expenses are associated with many different tests. It is relatively easy to determine the mix of blood tubes drawn and the tests that can be associated with each tube type from phlebotomy policies and procedures. However, assigning phlebotomy expenses to a particular test or group of tests requires knowing the frequency of draws for a given tube type and the frequency of tests performed from the same tube type. Frequency data is much more difficult to obtain as operating fund summaries list only the monthly or annual costs for labor and tube

types. Generally these expenses are estimated based on test volume reports that can be generated by the LIMS. Note that for a test which is part of a panel, it is necessary to distinguish the number of tests within a panel from the number of tests ordered singly. For example, the same costs of phlebotomy, transport, and sample processing will be incurred when either a test panel (e.g., Na, K, Cl, TCO_2, glucose, creatinine, and calcium) is performed or a single test within that panel (e.g., K). The difference in cost between the panel and the single test will be limited to the analytical costs. For panels with a large number of tests, such as the comprehensive metabolic panel, it is important to determine if the number of single orders for individual tests is insignificant relative to the number of panel orders. If so reports can be filtered on panel orders only, ignoring the small number of single-order tests. The labor associated with phlebotomy also requires a consideration beyond the number of tubes consumed over a given period of time. Consideration must also be given to the number of different tubes drawn per patient which can vary significantly. It is especially complicated to capture phlebotomy expenses for inpatients where labor for blood drawing may be mixed in with labor for non-test-related activities . For example, nursing practice assistants who draw blood often perform other duties. In this case it is often best to determine a reasonable estimate of the cost rather than trying to source actual data.

Direct expenses during the analytical phase are relatively easy to assign. Expenses such as those for reagents or disposables can usually be associated uniquely with each test. However, the expenses associated with the purchase, lease, or service contract of an analyzer will usually be associated with a number of different tests (rarely is a single test performed on a dedicated analyzer). Analytical phase expenses should be readily available to the laboratory director as they are almost always managed by the director using the operating and capital budgets. Even when capital funds are managed centrally, the laboratory-specific items are easily identified.

Post-analytical phase expenses must not be overlooked. These expenses, especially for labor, can vary significantly on a test-by-test basis. For example, there is little post-analytical expense when electronic auto-release reporting rules are employed. On the other hand, labor for test reporting can be a significant expense when it is associated with tests that are reported manually or must be called directly to the physician. For fully automated laboratories with electronic auto-release of test results, post-analytical

expenses are often simply considered an indirect expense.

Figure 6.2 illustrates the major indirect expenses for each phase of the testing process. Pre-analytical processes are an important part of the consideration in calculating costs and savings associated with utilization management because they are complexity driven. For example, utilization changes that reduce the number locations where a test is being ordered or reduce complexity (e.g., mix of blood tubes required from a given patient or storage requirements) can significantly reduce indirect expenses associated with transportation, supervision, or equipment needs.

Indirect expenses associated with analytical and post-analytical processes generally fall into one of two categories: (1) indirect costs associated with multiple tests performed on a specific instrument or area of the laboratory or (2) indirect expenses associated with all tests performed regardless of the mix of instruments or areas involved. As will be discussed in the next section, these considerations underlie decisions regarding the most appropriate accounting method to use in allocating expenses to a particular test whose utilization is being optimized.

Define the Allocation Formula

Once all of the various types of expenses associated with a given test are identified, it is necessary to determine how each of those expenses should be allocated to the test. This process is referred to as cost accounting . Because many of the sources of data are annual fund center reports, cost accounting is usually based on a fiscal year.

There are many approaches to cost accounting. In the simplest case, one can divide the total annual laboratory operating budget by the annual volume of tests to generate an average cost/test. However, the average cost/test fails to distinguish variable, semi-variable, and fixed expenses. It also does not evaluate the marginal cost of a test, i.e., the incremental expense associated with adding (or subtracting) a specific test from an established laboratory operation. Understanding marginal costs is important when trying to calculate the cost savings associated with utilization management . For example, if a laboratory performs one million tests/year, the fixed costs will hardly change if additional 1000 tests are added (or removed). Only the variable costs will increase (or decrease). In most cases utilization management removes tests from an existing laboratory operation. The savings will therefore be limited to the marginal cost of the tests. For example, eliminating 1000 basic metabolic

panels from a laboratory performing 100,000 panels per year will not save 1 % of the operating budget. The actual savings will be much less than the expected because only the variable cost of the 1000 panels will be eliminated. Thus, more complicated accounting formulas than the average cost/test are usually required. The degree of complexity, which is basically the number of expense variables to be considered in the formula, will be driven by a consideration of the workflow associated with a specific test and the magnitude of the subtraction of tests performed annually. Tests that are transported, processed, and/or performed individually must be evaluated using a different formula than tests performed on multi-test instruments where changing the volume of one test in a panel has little impact on the total number of tests still being processed and tested on a specific instrument or area of the laboratory. Furthermore, the largest expense component is usually the labor associated with a given test. A decrease of sufficient volume to affect labor costs (semi-variable cost) has a much bigger impact than one in which the marginal expenses are limited to consumable variable costs alone.

The choice of accounting system can also be determined by the availability and/or reliability of the data sources used to identify expenses [6]. It is important to keep in mind that only costs impacted by the utilization management initiative need be considered. For example, it is rare that changing the utilization of a test or even multiple tests will impact the amount of space occupied by the laboratory. Thus, overhead costs , which are not in the laboratory operating budget , can be ignored. Similarly for a single test whose overall volume has little impact on total revenues (e.g., inpatient testing), it is most efficient to simply ignore revenue and focus only on cost. In contrast making simplifications for tests that significantly impact revenue or overall labor or equipment (e.g., space) can result in significant inaccuracies when estimating the costs/savings of a utilization management initiative. Therefore decisions affecting whether or not a utilization initiative is implement depend on cost/benefit considerations. Underestimating the impact on revenues can result in undesirable outcomes for the laboratory. Likewise, overestimating cost savings can be equally problematic. Thus, getting it right is the key, and this depends on accurate, reliable data as well as the application of appropriate cost accounting formulas.

The most basic and common formulas for cost accounting in calculating savings from utilization management are job order accounting and process accounting or, very often, a hybrid of the two. Job order and process

accounting formulas have their origins in manufacturing where process accounting was useful for items produced by mass production, whereas job order accounting was used to address the nuances of customized manufacturing. In the context of laboratory operations, tests that all have a uniform cost per unit are analogous to mass manufacturing and process accounting is preferred. In contrast, tests with unique expense profiles require job order accounting despite the greater effort required to more accurately calculate the expenses associated with a given test.

Job Order Accounting

The first step in developing an accounting system is to identify all of the expenses associated with performing a given test. This is a labor-intensive process and can be challenging as the sources of data available to the laboratory director are often limited depending on how well purchasing, accounting, and laboratory information systems are integrated. Keeping in mind that the goal is to assess the impact of utilization management changes in test volume, the most significant expenses will be found in the laboratory operating budget . Developing and regularly updating a database for all expenses assignable to specific tests, to groups of tests, or across the entire laboratory operation are a valuable investment of time not only for determining the impact of utilization management but also for informing basic laboratory management decisions such as prioritizing budget reduction opportunities. Once the expense data is obtained, more than one accounting approach can be used and a judgment made as to which most accurately captures the impact of utilization management initiatives.

Once all relevant expenses, both direct and indirect, have been identified, the first step is to determine which allocation method applies to each test. Job order accounting is used for those expenses that vary significantly from test to test or, in the context of multi-test analyzers, across groups of tests. These are sometimes referred to as “heterogeneous” expenses as opposed to expenses which are similar regardless of which test is considered [6]. Expenses that are similar regardless of the test per se are allocated using process accounting procedures as discussed below.

Job order accounting involves allocating to each test expenses that apply specifically to that test. Typically the largest contributors to total expense for individual tests are (1) test-specific reagents and (2) labor.

Reagents used to perform a given test are assigned to the test simply by

dividing the annual expense by the annual volume to generate the average reagent expense (i.e., $/test). However, for accurate assessments it is necessary to consider waste, which may vary considerably from test to test. The goal is to determine the expense per reportable (i.e., billable) test result. Thus, the $/test is adjusted by modifying the number of tests a given unit of reagent can perform to allow for reagents consumed for retesting or testing that does not generate a billable result. For example, the percent of results out of range requiring retesting for quantitative results or confirmation of undetectable levels will vary greatly across tests. Similarly the number of "tests" required for quality control, proficiency testing, and calibration verification will add to expense by consuming reagents and can vary significantly from test to test. Because there is no revenue associated with this testing, it is considered as "waste" for the purpose of calculating expense, which is required to determine savings (or loss) associated with test volume changes.

The most significant contributor to test-specific expense is usually technical labor . Total labor expense is based on the rate of pay ($/hour) which is best calculated from annual expenditures for base salary, fringe benefits, earned time, and any off-shift or overtime adjustments that apply with respect to the service requirements of the test. For example, tests performed continuously 24/7 will usually have significantly more labor expense than those performed in batches on weekdays on the day shift only. Note that utilization management that changes when or how often a test is performed can have a significant impact on technical labor expenses.

Once the total technical labor expense for a test is calculated, allocating technical labor expenses at a test level depends on the testing method. Calculating the technical labor expense per test is fairly straightforward for manual methods . As discussed with respect to test-specific reagent expenses, the average technical expense for a given test must be determined based on the volume of reportable (billable) tests performed:

$$\$/\text{test} = \text{laborrate}\,(\$/\text{hour}) \times \text{amountoflabor}\,(\text{hours}/\text{billabletest})$$

Calculating the technical labor expense /test for automated systems is more appropriately done by hybrid accounting which assigns labor expenses to all tests performed on a given analyzer. As discussed below, this approach also requires an assessment of labor capacity when determining the impact of the volume changes.

Process Accounting

When a group of tests have similar costs, process accounting is a more efficient approach than job order accounting [6]. Because the expenses associated with all tests are similar, often referred to as "homogeneous," process accounting is performed by calculating average expenses based on total expenses and volumes associated with total billable tests. Total expenses include direct and indirect costs, and it is reasonable because all the individual tests have the same expense profiles, e.g., reagent costs, ratio of billable tests to total tests performed, similar fixed expenses, etc. Calculating per test costs and thus the impact of test utilization changes is straightforward and based on easily accessible data.

It is unlikely that utilization changes will significantly impact overhead expenses, but if this needs to be considered, it is done by assigning a percentage of overhead expenses to the tests involved because each test is assumed to have equal impact on overhead or a subset of overhead expenses.

Hybrid Accounting Formulas

In large laboratories the range of test complexity varies from manually performed single test methods to fully automated analytic systems composed of many instruments with nonoverlapping multi-test menus. Furthermore, different hospital laboratories range in complexity. For example, some hospital networks have centralized laboratory-based phlebotomy and transport departments serving several institutions and operated under dedicated fund centers. In these settings most tests represent hybrids with uniform and customized cost components and hybrid cost accounting formulas represent the most accurate approach.

Examples of Cost Accounting

To illustrate the basic concepts of cost accounting in utilization management, four different scenarios are described below. These include:

1. Eliminating one test from a panel

2. Eliminating an entire panel of tests

3. Eliminating a reference laboratory test

4. Eliminating an expensive test (e.g., genetic)

Eliminating One Test from a Panel

An example of hybrid cost accounting to determine the costs of a five-test panel is shown in Table 6.2. In this example the goal is to calculate the cost of each of the five tests that are ordered as a panel (i.e., one billable order for all five tests). Three assumptions are shown in Table 6.2. These assumptions are made to simplify the calculation without significantly altering the accuracy of the cost assigned to each test. Generally a laboratory information management system (LIMS) is configured to separately identify test names and order codes. Thus, it is possible to determine how often a test is ordered in a panel versus individually or in other panels. Expense summaries provide test-specific data (such as reagent costs), instrument-specific data (applicable to all tests done on a given instrument type), and general laboratory expenditures (applicable to all the tests performed within the laboratory or a specific section of the laboratory).

Table 6.2 Example of expense accounting for a five-test panel

Expense category	Description	Unit cost	Subtotal	Source budget	General formula
Assumptions					
	1 blood tube drawn for panel; transported same day without storage				
	5 tests per panel; expense to perform each test is similar				
	10,000 panels (50,000 tests) per year				
Pre-analytical costs					
Direct, variable	Supplies	$0.50		Operating	1 tube; phlebotomy supplies
Direct, semi-variable	Phlebotomy labor	$3.00		Operating	10 min at $0.30/min
Direct, semi-variable	Accessioning labor	$0.90		Operating	3 min at $0.30/min
Indirect, Fixed	Transport labor	$2.50	$6.90	Operating	10 min at $0.25/min
Analytical costs					
Direct,	Reagents	$0.75		Operating	$75/100 test kit

variable					
Direct, semi-variable	Quality control	$1.40		Operating	3 levels/day; $70,000/year; 50,000 tests/year
Direct, semi-variable	Proficiency Testing	$0.02		Operating	15 tests/year; $800/year; 50,000 tests/year
Direct, semi-variable	Technician labor	$0.42		Operating	5 min at $ 0.42/min per specimen (e.g., per panel)
Direct, fixed	Instrument service	$0.02		Operating	$6000 per year/250,000 tests per year
Direct-fixed	Instrument depreciation	$0.04		Capital	$150,000 purchase/15 year lifetime/250,000 tests per year
Indirect, fixed	Supervisor labor	$0.04	$2.69	Operating	$104,000/year; 2,500,000 tests total/year
Post-analytical costs					
Direct, semi-variable	Requisition storage labor	$0.60		Operating	2 min at $ 0.30/min per specimen (e.g., per panel)
Indirect, fixed	IS labor	$0.05		Operating	$125,000/year; 2,500,000 tests total/year
Indirect, fixed	Interface depreciation	$0.01	$0.66	Capital	$10,000 install cost/7-year lifetime/250,000 tests per year
	Total unit cost	$10.25			

Adapted from [6]

Direct and indirect costs are calculated for each phase of the testing process (i.e., pre-analytical, analytical, and post-analytical costs). The source of data and accounting formula is shown in the table for each expense. The outcome is a value for the laboratory expenditure associated with each test, in this example $10.25. However while this level of detail is valuable for budgeting and necessary to fully understand test costs, the calculated cost is not necessarily directly reduced if a given test is eliminated by utilization management because eliminating tests usually only impacts marginal costs. The next step is to determine which expenses are impacted by utilization changes.

The pre-analytical expense is independent of the number of test types in the panel. The expense is driven by the phlebotomy and transport of the tube which is required even if only one of the five tests is performed. The same is true for post-analytical expenses . In this example pre- and post-analytical expenses together represent over 70 % of the total per test cost. Similarly, many of the analytical expenses are relatively insensitive to elimination of a

test. For example, the quality control and proficiency testing costs would be the same even if one test was eliminated when using multi-analyte controls and proficiency challenges. Instrument service and depreciation expenses would not be significantly affected by eliminating one test from the panel. Thus when only one test is eliminated from a panel, the only true savings are the variable costs of that one test. All other costs are unaffected.

Analytical labor costs are also insensitive to the elimination of a single test. Commonly used units for determining technical labor costs are (1) tests per paid full-time equivalent (FTE, 2080 h/year) and (2) productivity ratio (paid hours per billed test). Tests per paid FTE are usually calculated across the laboratory. For example, for a labor with 67 paid FTEs performing 1,000,000 tests annually, the tests per paid FTE are 14,925. Productivity ratio provides insight into the cost at a test level. In the laboratory with 67 paid FTEs performing 1,000,000 tests annually, the productivity ratio is 0.14 (139,360 paid hours for 67 FTEs annually/1,000,000 billed tests annually).

In this example only the reagent expense (about 7 % of the total unit expense) would be meaningfully reduced by eliminating one test from the panel (i.e., only the variable costs of the test are eliminated). Likewise adding a test to the panel could potentially be much cheaper than performing a test ordered and drawn separately. Assuming similar reagent costs, a test added would contribute at most an additional 7 % to the unit cost.

Another important aspect with respect to the context in which tests are ordered is the use of physician order sets. A physician order set is a group of tests that are automatically ordered as a group. Physician order sets are usually established at the request of physicians to save time and reduce omission errors by ordering the set rather than having to order individual tests that are always ordered in a given clinical situation. Usually the tests in the ordering set are performed on the same blood draw and thus the ordering set is effectively a “panel.” Utilization management may identify tests within the ordering set which are not necessary. In this setting the approach to assessing cost savings from eliminating one test from the set is identical to that described in the example of a five-test panel .

Eliminating an Entire Panel of Tests

Consider the cost per test analysis in Table 6.2 for a five-test panel in which the cost of performing each test in the panel is not significantly different than for the other tests. As discussed above eliminating only one test saves only

the per test reagent costs because the other tests must still be performed. However eliminating the entire panel of tests generates additional saving, as summarized in Table 6.3, in addition to saving the expenses associated with the reagents for all five tests. The blood draw is also eliminated saving all of the pre-analytical costs. If the panel is ordered separately, post-analytical savings are realized by eliminating the filing of results and storing the laboratory requisitions.

Table 6.3 Eliminating an entire panel versus a single test in the panel

Expense category	**Description**	**Unit cost**	**Panel cost**	**Savings one test eliminated**	**Savings panel eliminated**
Pre-analytical costs					
Direct, variable	Supplies	$0.50	$0.50		$0.50
Direct, semi-variable	Phlebotomy labor	$3.00	$3.00		$3.00
Direct, semi-variable	Accessioning labor	$0.90	$0.90		$0.90
Indirect, fixed	Transport labor	$2.50	$2.50		$2.50
Analytical costs					
Direct, variable	Reagents	$0.75	$3.75	$0.75	$3.75
Direct, semi-variable	Quality control	$1.40	$1.40		$1.40
Direct, semi-variable	Proficiency testing	$0.02	$0.02		$0.02
Direct, semi-variable	Technician labor	$0.42	$0.42		
Direct, fixed	Instrument service	$0.02	$0.02		
Direct-fixed	Instrument depreciation	$0.04	$0.04		
Indirect, fixed	Supervisor labor	$0.04	$0.04		
Post-analytical costs					
Direct, semi-variable	Requisition storage labor	$0.60	$0.60		$0.60
Indirect, fixed	IS labor	$0.05	$0.05		
Indirect, fixed	Interface depreciation	$0.01	$0.01		
	Totals	$10.25	$13.25	$0.75	$12.67

These two illustrations indicate that greater savings can be achieved by

reducing the frequency of ordering an entire panel rather than eliminating a single test from a test panel. Inpatient testing in academic hospitals is one example of where opportunities can exist to reduce the number of test panels and generate significant savings [10].

It is also important to consider the clinical implications of eliminating a test. Eliminating a single test from a panel may not generate large savings in the laboratory. However, if the test results drive expensive and unnecessary additional medical or diagnostic procedures, eliminating the test may generate significant saving in other areas of the hospital. For example, eliminating a magnesium test might generate only minor savings but can lead to a significant reduction in the number of unnecessary magnesium replacement protocols.

Eliminating a Reference Laboratory Test

Calculating the savings associated with eliminating a test performed by a reference laboratory is usually a job order accounting process as the cost factors vary widely from test to test. Specimens are typically processed in a section of the hospital laboratory. Pre-analytical costs include phlebotomy, transport, and processing specimens to the specifications of the reference laboratory and often involve materials and equipment used primarily, if not exclusively, for sending out specimens for testing. For example, freezers are necessary as many reference laboratory testsTest require that the specimen be frozen on-site and shipped on dry ice. The reference laboratory usually picks up the specimens so pre-analytic specimen acquisition and accessioning costs are similar to those required for in-house testing. The reference laboratory charge to the hospital represents the full cost of the test (e.g., for each test the laboratory is billed). Finally, post-analytical costs are similar to those associated with in-house testing. If there is no electronic interface between the reference laboratory and the laboratory information system (LIMS), additional labor will be required post-analytically for manually entering test results into the LIMS.

An example of the calculation of cost savings by eliminating a reference laboratory test is shown in Table 6.4. Eliminating this test completely would save the laboratory $65,352 annually. Eliminating some, but not all, of the tests will still result in significant savings because the hospital is charged $47.50 for each test performed. Considering the reimbursement of $38.40 per test, the institutional saving is less, $19,272. If the reimbursement rate had

been higher than the reference laboratory charge, the institution would have actually lost rather than saved fund by eliminating the test.

Table 6.4 Saving achieved by eliminating a reference laboratory test

Expense category	Description	Unit cost	Savings $/test eliminated	Note
Assumptions				
	1 blood tube drawn for panel; transported same day without storage			
	Plasma separated and shipped frozen to reference laboratory			
	Reference laboratory accessioning is done on-site electronically			
	Test rests are reported electronically to the LIMS			
	The laboratory billing patient or payer; test is reimbursed at $38.40			
	1200 tests are performed annually			
Pre-analytical costs				
Direct, variable	Supplies	$0.50	$0.50	
Direct, semi-variable	Phlebotomy labor	$3.00	$3.00	
Direct, semi-variable	Accessioning labor	$0.90	$0.90	
Indirect, fixed	Transport labor	$2.50	$2.50	
Direct, fixed	Instrument (e.g., freezer) service	$0.02		$500 annually for service contract and preventative maintenance; supports 25,000 tests total annually
Direct-fixed	Instrument depreciation	$0.03		$9000 purchase; 12-year lifetime; supports 25,000 tests total annually
Analytical costs				
Direct, variable	Reference lab charge to laboratory	$47.50	$47.50	
Indirect, fixed	QA labor	$0.02		
Post-analytical costs				
Direct, semi-variable	Requisition storage labor	$0.60		
Indirect, fixed	IS labor	$0.05	$0.05	

Indirect, fixed	Interface depreciation	$0.01	$0.01	
	Totals	$55.13	$54.46	

Sometimes a reference laboratory test that cannot be eliminated can be performed cheaper in-house to achieve savings. Usually this is true of relatively high-volume tests and depends on leveraging existing equipment and labor. In any case, the approach to calculating potential savings is to determine the unit cost of testing as shown in Table 6.4 for both when performed by the reference laboratory and when performed in-house (make-or-buy analysis). If in this example, the test can be performed in-house for less than $55.13/test, there is a net savings to the laboratory . If the test can be performed in-house for less than $38.40 (the reimbursement rate), the laboratory achieves a savings and the institutional loss is eliminated .

Eliminating an Expensive Test (e.g., Genetic)

Very expensive tests often represent an opportunity to achieve savings even when the test volume is relatively small. For example, eliminating even a modest percentage of tests, such as a genetic test or a high-complexity biomarker test that requires dedicated instrumentation and expensive labor, can result in substantial savings. Such tests are often priority targets for utilization initiatives because not only are they very expensive but they are often poorly reimbursed and/or complex enough to be associated with relatively high ordering errors that can be eliminated.

Calculating cost savings for expensive tests is almost always a job order accounting procedure. Table 6.5 illustrates the calculations for savings associated with reducing the number a whole-exome sequencing (WES) tests . In this example the cost of WES is compared to the cost of a single-gene test; the laboratory cost is three times higher for WES compared to the single-gene test. In some cases utilization management of WES can result in changing 10–20 % of WES order to a single-gene test [11]. In this example a 10 % change from WES to single-gene testing would result in an annual savings of $98,640. Typically most of this savings would be realized institutionally because WES is currently considered investigational for the diagnosis of genetic disorders and/or often does not alter medical treatment. In some cases the WES is poorly reimbursed or not reimbursed at all by

certain payers.

Table 6.5 Calculating savings associated with eliminating and expensive whole-exome sequencing test

Expense category	Description	Unit cost	Unit cost if test eliminated
Assumptions			
	4 blood tube drawn for WES; transported same day without storage		
	Testing performed in a dedicated instrument		
	All orders reviewed by specialized laboratory personnel (genetic counselors)		
	The laboratory billing patient or payer—requires pre-approval		
	600 tests are performed annually		
Pre-analytical costs			
Direct, variable	Supplies	$2.00	$2.00
Direct, semi-variable	Phlebotomy labor	$3.00	$3.00
Direct, semi-variable	Accessioning labor	$0.90	$0.90
Indirect, fixed	Transport labor	$2.50	
Direct, variable	Order review	$208.33	$208.33
Analytical costs			
Direct-variable	Sample preparation	$70.00	$70.00
Direct-variable	Reagents	$800.00	$800.00
Direct-variable	Quality control	$375.00	$375.00
Direct-variable	Proficiency testing	$35.00	$35.00
Direct-variable	Technician labor	$149.17	$149.17
Direct-fixed	Instrument service	$100.00	
Direct-fixed	Instrument depreciation	$147.00	
Direct-fixed	Supervisor labor	$173.33	
Direct-fixed	Director	$566.67	
Post-analytical costs			
Direct-fixed	Manual reporting	$0.00	
Direct, semi-variable	Requisition storage labor	$0.60	$0.60
	Totals	$2633.50	$1644.00

Calculating Revenues

While calculating costs is relatively easy, especially when reasonable assumptions are made, calculating revenue can be quite challenging. This is because the data required are typically difficult to obtain, and reimbursement systems are complex and are different for inpatients versus outpatients and

vary depending on the payer. Given the challenges involved, laboratory directors have historically focused only on cost which is easily determined from laboratory fund centers that are operated as “cost centers.” However as the laboratory takes a leadership role in utilization management, it is necessary to understand and communicate to administrators and ordering physicians the full picture in order to effectively and economically alter test utilization practices. It is critical to obtain “buy-in” and cooperation from key stakeholders outside the laboratory as early as possible given the complexity of the issues. Especially important key stakeholders are the pathology service, hospital administrators, key ordering physicians, and hospital medical advisory committees. “Cost” can no longer be viewed simply as the expense of performing a test within the laboratory as revenues must also be taken into consideration. In general testing performed on inpatients generates no revenue directly as the charges are included in a single, bundled payment for the admission’s diagnosis-related group (DRG) . In contrast most testing on outpatients is reimbursed directly albeit at a negotiated discount to charges depending on the payer.

Once the clinical context(s) in which a test is ordered has been identified, an assessment of the revenue (if any) associated with the test can be undertaken. Revenues vary depending on the contracted payer rates; different payers have different reimbursement agreements. Perhaps the best approach is to use the reimbursement schedule for Medicare which demands the lowest rate the hospital offers to its various payers. It is important for laboratories to be managed within this broader context rather than as an isolated cost center as is the case in most institutions today [1, 12].

Calculating Savings

Savings are calculated based on cost. Optimal utilization is typically based on standards of care, guidelines, and/or local medical consensus. The laboratory then can calculate expenses, revenues, and costs for the testing under optimal conditions using the same data required to determine current expenses and revenues. Currently utilization management by hospital-based laboratories is usually done at a test level. Even when managing a panel of tests, it is usually necessary to assess costs at the test level.

The cost of performing a given test requires calculating the various expense components. Indeed, sometimes the laboratory will only consider

expenses because of the relative complexity of determining reimbursement revenues which are managed in institutional revenue centers. Once expense and revenue data is available for both current and optimal test utilization, calculating savings is straightforward as illustrated in Fig. 6.3. If only the more easily acquired laboratory expense data is considered when assessing the impact of utilization management (e.g., current versus optimized test utilization), the calculated result cost savings is associated just with the laboratory operations (blue box in Fig. 6.3). The more important calculation however is the institutional impact which does take into account the revenues associated with the change in testing. This is the "institutional savings" as calculated in Fig. 6.3 (red box). It is not unusual for a test that is inexpensive to perform but well reimbursed to actually cost the institution (i.e., negative institutional savings) while reducing laboratory expenses following utilization optimization .

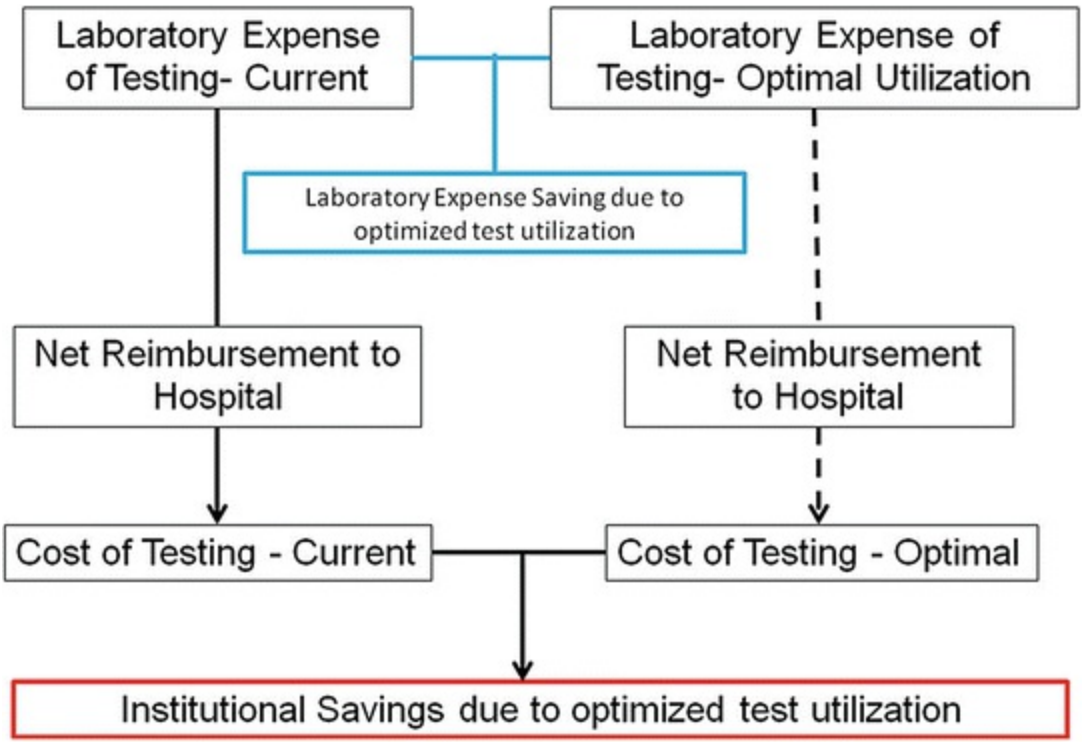


Fig. 6.3 Calculating savings due to test utilization optimization

Assessing the Impact of Utilization Changes

Calculating savings as described above is based solely on the cost associated with a test(s) in the context of the care provided. This has been, and is

currently, the classical approach to laboratory management and assessing the impact of changes made to test utilization. However, there are several limitations associated with this approach. First, utilization management based on standard of care guidelines is a population parameter. It must be recognized that testing optimal for a patient population with a certain condition is not necessary optimal for an individual. Ordering physicians determine appropriate testing at the level of the individual. Increasingly, as precision or personalized medicine becomes a driver of healthcare delivery, it will be challenging to achieve savings based on population management. Second, laboratory medicine currently lacks adequate outcome-based data on which to manage testing. A current perception is that over testing is common and contributes to high health care costs not associated with healthcare improvement. While this is undoubtedly true in specific settings, outcome studies are needed to assess the value of and to manage testing which contributes significantly to about 70 % of delivered healthcare services. These limitations contribute to an increasing recognition that reimbursement needs to be based on “value” rather than cost or complexity [1, 4, 13]. Thus, the ultimate goal of utilization management (reducing the cost of care without reducing quality) should be assessed based on healthcare impact (e.g., “value”).

As illustrated in Fig. 6.4, assessing the impact is basically adding a layer to the process already required to assess the savings associated with utilization management . Impact assessment is based on health outcomes, ultimately mortality/morbidity (e.g., quality-adjusted life-years) [13–16]. Currently such data is virtually impossible to obtain from hospital information systems. While future information systems are likely to integrate laboratory and hospital information systems sufficiently to be able to access external outcome databases, presently this is not possible. Commercial databases , such as Optun One/Humedica [17], can be used to determine the generic relationship between a test and its impact if the specific clinical conditions are represented in the database. This approach is, of course, limited in that it does not necessarily reflect the reality of testing in a given institution. A more realistic approach with respect to available data is to use surrogate indices of healthcare impact . These could include:

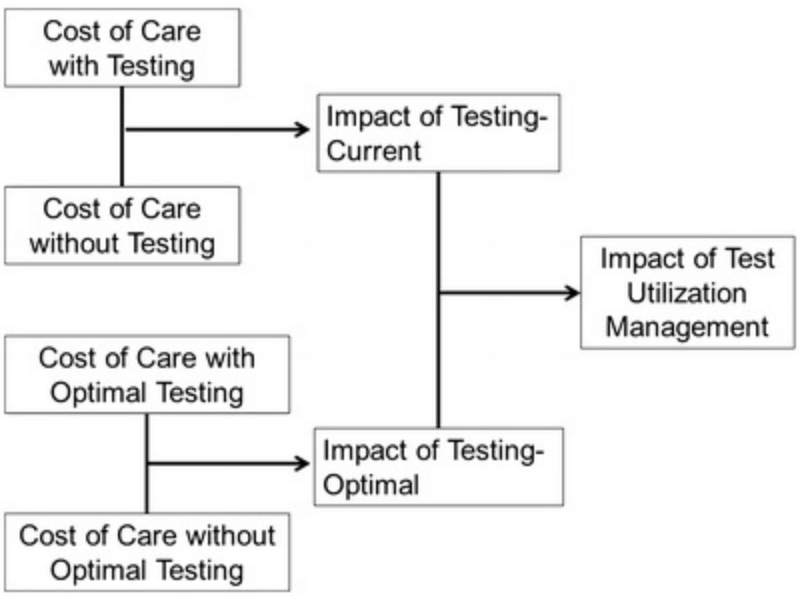


Fig. 6.4 Calculating financial impact of test utilization optimization

- Readmission rate or number of diagnoses of conditions based primarily on blood tests [18]
- Length of stay [19–21]
- Complexity of clinic visit [22]
- Test-related therapy changes [23]

Summary

Simple expense-based calculation methods have long been employed by laboratory directors to manage laboratory operations and to assess the impact of changes to testing operations. These methods are well established but will not be sufficient to fully support utilization optimization in the future. It will be essential to assess in impact of utilization changes on healthcare outcomes. This will require a paradigm shift from the laboratory as an isolated cost center to a fully integrated component of hospital operations. New data information systems will be required to obtain the necessary information to support assessing the impact of utilization management. Such systems are currently being developed. Laboratory directors must take these changes into account and become key players in the process. Ultimately laboratory directors must have access to outcome data and revenues as well as

laboratory cost center data to fully understand and communicate the impact of test utilization optimization.

References

1. Gass Kandilov AM, Pope GC, Kautter J, Healy D. The national market for Medicare clinical laboratory testing: implications for payment reform. Medicare Medicaid Res Rev. 2012;2:1–21.

2. Branda JA, Dighe AS, Dzik W, et al. The practice of clinical pathology: a quantitative description of laboratory director activities at a large academic medical center. Am J Clin Pathol. 2014;142:144–9.
[CrossRef][PubMed]

3. Young DS, Bekeris LG. The inordinate complexity of delivering laboratory services in the USA. Ann Clin Biochem. 1999;36(Pt 2):123–32.
[CrossRef][PubMed]

4. Price CP, St John A. Innovation in healthcare. The challenge for laboratory medicine. Clin Chim Acta. 2014;427:71–8.
[CrossRef][PubMed]

5. Travers EM, McClatchey KD. Basic laboratory management. In: McClatchey KD, editor. Clinical laboratory medicine. 2nd ed. Philadelphia, PA: Lippincott Williams & Williams; 2015. p. 3–49.

6. MacMillan D. Calculating cost savings in utilization management. Clin Chim Acta. 2014;427:123–6.
[CrossRef][PubMed]

7. Buchner DS, Hynes WM. Cost accounting in the clinical laboratory. In: Lewandrowski K, editor. Clinical chemistry: laboratory management and clinical correlations. 1st ed. Philadelphia, PA: Lippincott, Williams & Williams; 2002. p. 70–80.

8. NCCLS. Basic cost accounting for clinical services: approved guideline. Wayne, PA: NCCLS; 1998.

9. Travers EM. Laboratory manager's financial handbook. Cost accounting: the road map to financial success. Clin Lab Manage Rev. 1996;10:265–85.
[PubMed]

10. Lewandrowski K. Managing utilization of new diagnostic tests. Clin Leadersh Manag Rev. 2003;17:318–24.
[PubMed]

11. Miller CE, Krautscheid P, Baldwin EE, et al. Genetic counselor review of genetic test orders in a reference laboratory reduces unnecessary testing. Am J Med Genet A. 2014;164A:1094–101.
[CrossRef][PubMed]

12. Shirts BH, Jackson BR, Baird GS, et al. Clinical laboratory analytics: challenges and promise for

an emerging discipline. J Pathol Inform. 2015;6:9.
[CrossRef][PubMed][PubMedCentral]

13. Zhong Y, Lin PJ, Cohen JT, Winn AN, Neumann PJ. Cost-utility analyses in diabetes: a systematic review and implications from real-world evidence. Value Health. 2015;18:308–14.
[CrossRef][PubMed]

14. Komenda P, Ferguson TW, Macdonald K, et al. Cost-effectiveness of primary screening for CKD: a systematic review. Am J Kidney Dis. 2014;63:789–97.
[CrossRef][PubMed]

15. Fang C, Otero HJ, Greenberg D, Neumann PJ. Cost-utility analyses of diagnostic laboratory tests: a systematic review. Value Health. 2011;14:1010–8.
[CrossRef][PubMed]

16. Westwood M, van Asselt T, Ramaekers B, et al. KRAS mutation testing of tumours in adults with metastatic colorectal cancer: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2014;18:1–132.
[CrossRef]

17. https://www.optum.com/solutions/data-analytics.html. Downloaded 13 Sept 2016.

18. Attali M, Barel Y, Somin M, et al. A cost-effective method for reducing the volume of laboratory tests in a university-associated teaching hospital. Mt Sinai J Med. 2006;73:787–94.
[PubMed]

19. Baron JM, Lewandrowski E, Januzzi JL, Bajwa EK, Thompson BT, Lewandrowski KB. Measurement of high-sensitivity troponin T in noncardiac medical intensive care unit patients. Correlation to mortality and length of stay. Am J Clin Pathol. 2014;141:488–93.
[CrossRef][PubMed]

20. Lamy A, Tong WR, Bainey K, Gafni A, Rao-Melacini P, Mehta SR. Cost implication of an early invasive strategy on weekdays and weekends in patients with acute coronary syndromes. Can J Cardiol. 2015;31:314–9.
[CrossRef][PubMed]

21. Ishak KJ, Stolar M, Hu MY, et al. Accounting for the relationship between per diem cost and LOS when estimating hospitalization costs. BMC Health Serv Res. 2012;12:439.
[CrossRef][PubMed][PubMedCentral]

22. Snider M, Carnes C, Grover J, Davis R, Kalbfleisch S. Cost-benefit and cost-savings analyses of antiarrhythmic medication monitoring. Am J Health Syst Pharm. 2012;69:1569–73.
[CrossRef][PubMed]

23. Szczepura, A. Routine low-cost pathology tests: measuring the value in use of bacteriology tests in hospital and primary care. Health Serv Manage Res. 1992;5:225–237.

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_7

7. Benchmarking and Management Metrics in Utilization Management

Ida Bixho[1] and Stacy E. F. Melanson[2]

(1) Department of Pathology and General Internal Medicine/Primary Care, Brigham and Women's Hospital, 1620 Tremont Street, Suite BC-03-002, Boston, MA 02120, USA
(2) Department of Pathology, Brigham and Women's Hospital, 75 Francis Street, Amory 2, Boston, MA 02115, USA

Ida Bixho
Email: ibixho@partners.org

Stacy E. F. Melanson (Corresponding author)
Email: semelanson@partners.org

Keywords Laboratory utilization – Benchmarking – Utilization management – Clinical laboratory – Benchmarking tools – Utilization metrics – Literature review – Effectiveness – Efficiency – Pathology

Introduction

There is an increasing demand for performance in healthcare including controlling cost, reducing risk, increasing quality, and improving patient satisfaction. This demand has spurred numerous continuous quality improvement initiatives; a popular one in the clinical laboratory is optimizing test utilization. Effective and appropriate test utilization improves the value of healthcare and laboratory medicine [1]. While overutilization of

unnecessary tests or misuse of tests is certainly a concern, current literature suggests underutilization of appropriate tests may be even more frequent [1–5].

There are multiple factors to consider when evaluating laboratory testing utilization , such as the clinical necessity and utility of testing, testing alternatives, cost to a laboratory, and revenue to the hospital [2]. Previous literature has described successful tools to control test utilization [1–9]. Those tools are described in detail in other chapters, but include imposing limits on test ordering, provider education, electronic decision support, clinical pathology consultative services, displaying laboratory test charges, introduction of lab formulary committees, and auditing test utilization [1–9]. Some authors have also advocated to remove obsolete tests such as LDH isoenzymes and bleeding time, from the test menu altogether [4, 10].

Benchmarking is a powerful tool that can be utilized to measure and assess laboratory test utilization at your institution [1, 11]. It is a management approach for implementing best practices and engaging in continuous quality improvement. As a tool, it can create a spirit of competition between organizations that voluntarily and actively collaborate and share information to achieve best practices [11]. Critical to successful benchmarking is choosing an appropriate benchmark, or point of comparison, as well as selection of metrics to monitor progress. The benchmark may vary depending on the goal. This chapter will describe different benchmarks for laboratory test utilization and their advantages and disadvantages. The need for, and selection of appropriate, achievable and attainable metrics will also be discussed.

Benchmarking Tools

Benchmarking is important for successful utilization management. Although many hospital clinical laboratories utilize benchmarking [12], it is typically not related to utilization management. There are several internal and external benchmarking tools available; these tools will be reviewed and their advantages and disadvantages are summarized in Table 7.1. Before participating in benchmarking and determining which tool(s) to employ, laboratories should determine what they hope to gain and how they will utilize the results [13].

Table 7.1 Summary of benchmarking tools and their advantages and limitations

Benchmarking tool(s)	Advantages	Limitations
External tools		
Consulting or paid subscription services	− Allows laboratories to compare their data to national standards and learn best practices − Data analysis is performed by others reducing time commitment from laboratory directors − May provide a breakdown of performances by individual specialty laboratory	− Can be costly − Selection of peers may not be ideal and well defined; standardized metrics may not be utilized, making data difficult to interpret − Time consuming for the laboratory managers to provide the necessary data
Pathology or healthcare organizations	− Data is usually easily accessible and provided by peers − If participation is high, a large volume of data may be available for comparison	− Benchmarking related to laboratory utilization has lagged behind other areas of healthcare − Only general trends may be available, not absolute numbers
Published guidelines and literature	− Provides data that can be utilized to establish internal guidelines and encourage correct diagnostic testing − Allows labs to determine if their test utilization is significantly different than most other laboratories − Provides expert interpretations and suggestions	− Relevant data may not be available and/or not applicable to your patient population − Usually does not allow laboratories to quantitatively compare their test utilization to other laboratories
Internal tools		
Comparing test utilization within service lines	− Removes the bias of peer group selection − Simplifies definition of metrics used − Allows clinical leaders to collaborate with laboratory directors/pathologists to develop institution-specific test algorithms	− Can be challenging to take into account differences in patient acuity and clinical conditions across the institution
Physician profiling	− Targets specific physicians therefore effective at increasing compliance with test utilization guidelines − Effective for educating new residents	− Requires commitment of laboratory director to contact individual physicians
Trend analysis	− Good starting point for benchmarking in utilization management − Can be done relatively rapidly and easily with minimal resource commitment	− Data needs to be interpreted in context of national guidelines so laboratories do not overestimate their success

External Tool No. 1: Consulting or Paid Subscription Services

Services, such as consulting or paid services (e.g., Chi Solutions, Intertek, Dark Daily, Applied Management Systems, or Clinical Lab Consulting), are available for laboratory institutions as benchmarking tools. Although these services are not specific to test utilization, they may be included. Once a laboratory enrolls, the service requests specific and detailed metric data (e.g., STAT test turnaround time (TAT), critical result reporting, or reagent cost per test) as well as laboratory demographics, such as size, affiliations, for-profit status, budget, test complexity, and the range of supported clinical services. Using the demographics provided, the consulting service then places each laboratory into the most suitable peer group. After peer metrics have been analyzed, each laboratory receives a detailed report of how they compare to their peers in relation to the metrics provided.

Paid or consulting services allow laboratories to compare their data to national standards, set realistic goals, and learn best practices (Table 7.1). They offer the advantages of performing all the data analysis for the laboratory and providing detailed and formal reports that are often well received by leadership. They can also provide a breakdown of performance by individual specialty laboratory (e.g., chemistry, hematology). However, there are also disadvantages to paid or consulting services, such as the cost, the suitability of the peer group, the time it may take laboratory managers to provide the necessary data, and the lack of control over the metrics utilized. Data may be challenging to interpret depending on how the company defines a test. The company may use a CPT code to define a test. In that case a basic metabolic panel would be considered one test although it consists of eight separate tests. Alternatively, a test could be defined as a reportable test, but then calculated parameters such as anion gap will be included as a separate test. Laboratories should be aware of how the paid or consulting service defines a test when reviewing the findings (Table 7.1).

External Tool No. 2: Pathology or Healthcare Organizations

Pathology or healthcare organizations [e.g., College of American Pathologists (CAP) or the University Health Consortium (UHC)] offer benchmarking

services. CAP performs Q-Probes studies [14–17]. In Q-Probes studies, a specific question is posed and laboratories are requested to submit data to address that question over a specific length of time. CAP analyzes the data and publishes the study [18]. For example, in a study performed by Howanitz et al. [14], a patient satisfaction survey was performed rating the satisfaction with phlebotomy procedures. The study concluded that the median time for phlebotomy procedures was 6 min and the average number of phlebotomy attempts per patient was 1.03 [14]. CAP also performs Q-Tracks , a program that provides laboratories with periodic reports of their performance on important laboratory initiatives, such as critical values and contamination of blood culture results, compared to their peers [19, 20]. In contrast to Q-Probes, the Q-Tracks program requires the laboratory to continually submit data , similar to consulting services [18–20]. However, to date, Q-Probes and Q-Tracks have not investigated benchmarking for utilization management [6].

Another program offered by CAP is the Laboratory Management Index Program (LMIP) , a paid subscription service that allows laboratory managers and directors to track and compare their performance to other groups on various metrics [6, 13]. One of the studies performed by the LMIP investigated the trends in the expense, productivity, and test utilization of 73 clinical laboratories in the United States that had participated in the program from 1994 to 1999 [13]. The study observed that the reference laboratory charge per test did not change significantly during the study period, even though the amount of tests sent to a reference laboratory increased [6, 13]. The study also found that laboratories sent less than 2 % of their test orders to the reference facility and that an increase in test activity was observed nationwide, particularly for outpatient tests [13]. An annual decline of 4.60 inpatient tests per discharge and an annual decline of 3.36 inpatient tests per hospital day were reported [13]. The authors postulated that the decrease was due to more judicious use of laboratory tests, since the acuity of patients had increased. Two strengths of this study were that one, only laboratories that continuously participated in the program were compared so that the data would not be skewed, and, two, strict standards on how tests were counted were employed. Recent LMIP studies have not reported on benchmarking or metrics for laboratory test utilization.

CAP proficiency testing surveys are a valuable resource as the surveys can identify tests which are decreasing in volume and may be targets for

utilization management. However, laboratories must analyze the data on their own. Melanson et al. [21] made recommendations on the use of urine drug testing and obsolete screening tests based on CAP survey data. To date, CAP has not systematically presented data in proficiency testing, as a benchmarking tool.

The benchmarking programs offered by the UHC (more recently renamed VHA-UHC Alliance NewCo, Inc.) are aimed toward both healthcare and clinical laboratories . The programs facilitate benchmarking by allowing UHC members to pose questions via email to their colleagues, who then in turn respond with data or experience(s). Typically the professional who posed the question summarizes the responses of all UHC participants. A recent correspondence from the UHC demonstrated that tests per discharge ranged from 34.8 tests/discharge to 94.1 tests/discharge, a useful benchmark for other institutions [6]. Participation is free of charge and any questions can be posted; however, the extent and amount of analysis are typically less than other online resources. In addition, many questions are related to laboratory operations as opposed to test utilization.

Choosingwisely.org can be a useful electronic resource as it offers evidenced-based recommendations on which tests are appropriate or inappropriate for patient care based on the patients' diagnosis. The foundation encourages conversations between clinicians and patients to choose care that is "supported by evidence," "not duplicative of any other test procedures already received," "free from harm," and "truly necessary" [22]. Video resources for clinicians and patients are posted on the website. While the website may help laboratories select target(s) for test utilization and provides educational links to send to providers, it does not currently offer benchmarking statistics for utilization among institutions.

An advantage of pathology or healthcare organizations is the potential for a high participation rate and therefore the availability of a large volume of data for comparison. Data is also easily accessible (Table 7.1). On the other hand, pathology organizations have lagged behind other areas of healthcare in the publication of benchmarking data, particularly related to utilization management and metrics. When benchmarking data is available, it can only be used to monitor trends and does not translate into absolute numbers for institutions utilizing the data. Participation in pathology organizations is also voluntary which can bias the data and/or increase the risk that institutions will stop participating and providing comparison metrics (Table 7.1).

External Tool No. 3: Published Guidelines and Literature

Published guidelines or peer-reviewed texts on diagnostic testing algorithms , practice standards, or interpretative guidelines can be extremely helpful as benchmarking tools for laboratory leadership to utilize to guide clinical colleagues [1, 2, 6, 23]. For example, some recent publications [2, 10] described the lack of clinical utility of several laboratory tests (e.g., LDH isoenzymes and CK-MB) and encouraged clinical laboratories to discontinue these tests [2, 10, 24]. Laboratories can use the guidelines as evidence to remove testing from their menus completely. Le et al. [24] built upon previous studies and demonstrated that removal of an obsolete test, CK-MB, in the emergency room did not adversely affect patient care and saved the hospital approximately $47,000 in reagent costs.

Several other published studies provide benchmarks and guidance on test utilization [1–6, 10, 13, 18, 25]. One study by the LabTrends Hospital Laboratory Comparative Program concluded that inpatient tests/discharge was higher in academic teaching hospitals, where residents ordered tests vs. nonteaching hospitals, where medical staff ordered tests [25]. Based on this publication, academic and nonacademic laboratories can compare their median inpatient tests/discharge to 33.5 inpatient tests/discharge and 18.4 inpatient tests/discharge, respectively. The study also acknowledged that patient acuity, hospital size, and length of stay were important factors to take into account when studying test utilization [25]. In another study by Huck et al. [2], an order entry intervention was responsible for decreasing orders for 1,25 OHD (an expensive sendout test) by 70 % and CK-MB by 80 % [2]. They concluded that electronic educational guidelines at the time of test ordering were important in impeding the physicians from ordering inappropriate tests [2].

As mentioned previously, one of the important advantages of published guidelines is that laboratory directors can use them as evidence to guide appropriate testing in their institution (Table 7.1). Not only are the results published, but expert interpretations and suggestions are provided. Published guidelines can also alert laboratories to the fact that their utilization may be significantly different than most other laboratories and provide an impetus to change. Furthermore, factors for appropriate selection and comparison of peers may be demonstrated or suggested in the literature and utilized to

improve other benchmarking tools . However, relevant data may not be available in the literature and/or applicable to one's institution. The literature also does not always allow laboratories to quantitatively compare their test utilization to other laboratories (Table 7.1).

Internal Tool No. 1: Comparing Test Utilization Within Service Lines

This type of benchmarking strategy involves comparing clinical laboratory 's utilization patterns to its own past or present performance. More specifically, test utilization between or within departments, such as the inpatient medical services (e.g., general medicine A to general medicine B), is compared [6]. This tool can help laboratories identify outliers in test volume per department and find targets for educational intervention [6]. For example, location A may be ordering 10 times more amylase tests, a test with limited clinical utility [10]. Thereby a target for intervention has been identified. Based on this information, the laboratory director may decide to contact clinicians who provide care in location A and conduct an in-service educational presentation on the clinical utility of amylase versus alternative assays, such as lipase.

Internal benchmarking offers the distinct advantage of clinical leaders collaborating with laboratory directors/pathologists to develop institution-specific test algorithms (Table 7.1). In addition, this type of benchmarking removes bias of peer group selection and simplifies the definition of metrics . However, comparing within service lines can pose a challenge because of the need to take into account the differences in patient acuity and clinical conditions across the institution (Table 7.1).

Internal Tool No. 2: Physician Profiling

Physician profiling is an effective educational benchmarking tool. It helps identify physicians who are not complying with hospital or other guidelines for test utilization by comparing the total number of laboratory tests ordered per patient per day (or other selected metrics) against their peers. A pathologist can then contact them directly, provide education on test utilization, and occasionally illustrate graphically their test utilization compared to their de-identified peers [6]. In an article by Kim et al. [26], "pop-up" reminders were added to the order entry system to guide test utilization (e.g., performing daily labs for the duration of a hospital stay in

stable patients has limited clinical utility). If the reminder was bypassed, it required an explanation from the physician. Override explanations were reviewed by the laboratory directors and directors followed up with clinicians as appropriate [26].

This strategy has been mainly effective at academic medical centers , where physicians in training are ordering tests, since this particular group does not routinely receive feedback on their resource utilization or ways to improve efficiency [6, 27]. In a study by Dine et al. [27], it was demonstrated that only approximately one-third of residents received feedback on their resource utilization, while the rest had no knowledge of commonly ordered tests [27]. They concluded that when resident-physician utilization of laboratory resources was benchmarked against their peers, it resulted in a long-lasting reduction in test utilization. Furthermore, they warned that for the educational feedback to be effective, physicians must be aware of their own habits and must be willing to modify their behaviors [27].

Physician profiling is very effective at educating and increasing compliance in a targeted group of physicians, including new residents (Table 7.1). The primary disadvantage is that it requires a commitment from pathologists or laboratory directors to select the appropriate target(s) and contact the individuals who ordered the testing inappropriately, which can be time consuming (Table 7.1).

Internal Tool No. 3: Trend Analysis

Trend analysis allows the laboratory to choose a few important test utilization initiatives, monitor patterns within their institution over time, and share results with leadership. An institution may decide to introduce charge display, make changes to a test requisition, implement clinical decision support, remove an obsolete test or implement an educational intervention, and then monitor corresponding test volumes over time [6]. In a recent study, there was a 37 % decrease in the number of laboratory tests ordered, after laboratory test guidelines in their surgical intensive care unit were implemented [28]. The authors reported a sustained decrease for at least a year [28].

An advantage of trend analysis is that data is easy to gather and can be limited in scope if resources are scarce, making it a good starting point for laboratories beginning the process of utilization benchmarking (Table 7.1) [11]. However, one of the areas that laboratories should pay attention to,

while using this benchmarking tool, is the fact that the data should be interpreted in the context of national guidelines or literature so that labs do not get lulled into a false sense of accomplishment. Laboratories may declare success when they have reduced their volume by 80 % only to find that most other laboratories have removed the testing completely (Table 7.1).

Management Metrics

Whichever benchmarking tool(s) is chosen, baseline and continuous metrics must be incorporated. Laboratories should consider the potential difficulty of the data collection. If metrics are too complex or time consuming to gather, they will not be measured consistently and laboratories will not see the benefits of benchmarking [29]. A team member with a strong informatics background is very helpful to determine which metrics can be accurately measured and used to monitor progress [2, 3]. Ideally an automated process can be implemented. While a manual process may be utilized, it can be time consuming and the long-term viability is questionable.

Total test volume, test-specific (e.g., potassium) volume, location-specific (e.g., inpatient) volume, and laboratory-specific (e.g., reference laboratory) volume are usually needed to calculate metrics for test utilization. Some of the most frequent internal test utilization metrics are the number of tests/outpatient encounter, number of tests/inpatient discharge, inpatient tests/hospital day, tests/requisition, volume of overutilized or underutilized tests , number of tests per patient diagnosis, and volume of obsolete tests (Table 7.2) [6]. The number of inpatient tests/discharge should be normalized to test volume as hospital admissions change over time. In addition, reference testing utilization metrics can be useful and include reference testing volume per total number of tests, reference laboratory expense per test, and charges for genetic tests sent to reference labs. It is also very important to consider the number of tests sent to reference laboratory per year (Table 7.2).

Table 7.2 Possible metrics for benchmarking in utilization management

Metric	Description
Internal metrics	
1	Number of tests per outpatient encounter
2	Number of tests per inpatient discharge
3	Inpatient tests per hospital day

4	Volume of over-, underutilized, or obsolete tests
5	Number of tests per patient diagnosis
6	Tests per requisition
Reference laboratory metrics	
1	Reference testing volume per total number of tests
2	Reference laboratory expense per test
3	Charges for genetic tests sent to reference labs
4	Number of tests sent to reference laboratory per year
Patient outcome metrics	
1	Faster and more accurate diagnosis
2	Improved treatment selection
3	Avoidance of misdiagnosis or adverse treatment consequences
5	Improved patient satisfaction and quality of life

To establish the value of test utilization in laboratory medicine, laboratories should also consider how changes in test utilization improve patient outcomes and how to effectively measure these improvements [24]. Improved patient outcomes and associated metrics could be faster or have more accurate diagnosis, improved treatment selection, avoidance of misdiagnosis or adverse treatment consequences, improved patient flow, improved patient satisfaction, or improved quality of life (Table 7.2) [1].

Meaningful use and comparative effectiveness , both tied to financial reimbursement, will ultimately facilitate or drive the development of metrics for utilization . Laboratories should be involved in discussions related to meaningful use and actively participate in metrics utilized at their institution.

Establishing Benchmarking for Test Utilization

Figure 7.1 outlines the overall process for both establishing benchmarking for test utilization in the clinical laboratory and monitoring progress. First, a laboratory must select their target(s) (e.g., obsolete tests, overutilized tests, high-cost tests). Once their targets have been decided, the laboratory should determine their benchmark or point of comparison; internal and/or external options are available as described earlier in this chapter. As mentioned previously, the availability of resources to analyze the data and ease at which internal data can be obtained are critical. It is likely the laboratory will need to partner with their information technology colleagues. If external

benchmarking data can be gathered, the laboratory should compare to internal data and identify any gaps.

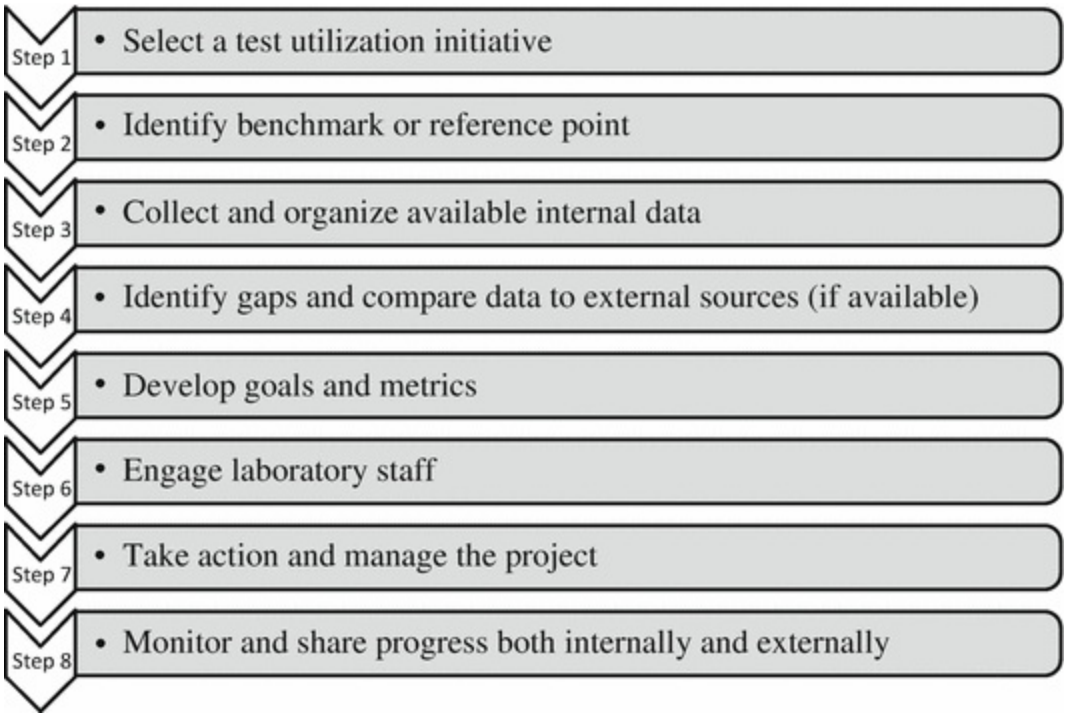


Fig. 7.1 Process of establishing and monitoring benchmarking in utilization management. A step-by-step summary of the process is depicted

Once baseline data is established, the clinical laboratory should set performance targets and appropriate metrics. For successful benchmarking, frontline laboratory staff should be engaged in the project and aware of the goals consistent with Lean principles [30–32]. Leadership should then manage the project and monitor and display progress. Ultimately laboratories need to develop testing algorithms to guide test utilization, demonstrate how clinical outcomes are improved, and publish these findings so they can be utilized as benchmarking tools for other laboratories .

Conclusions

In the changing landscape of healthcare which focuses on quality and patient satisfaction at lower costs, benchmarking can be a valuable strategy for clinical laboratories. Internal and/or external benchmarking tools can be utilized to guide test utilization, and appropriate metrics can be utilized to

monitor progress. Benchmarking related to test utilization has lagged behind other areas; therefore laboratory directors need to advocate for additional resources to generate more data and additional studies examining not only test utilization but also improved patient outcomes.

References

1. Hallworth MJ, Epner PL, Ebert C, Fantz CR, Faye SA, Higgins TN, et al. Current evidence and future perspectives on the effective practice of patient-centered laboratory medicine. Clin Chem. 2015;61(4):589–99.
[CrossRef][PubMed]

2. Huck A, Lewandrowski K. Utilization management in the clinical laboratory: an introduction and overview of the literature. Clin Chim Acta. 2014;427:111–7.
[CrossRef][PubMed]

3. Snozek C, Kaleta E, Hernandez JS. Management structure: establishing a laboratory utilization program and tools for utilization management. Clin Chim Acta. 2014;427:118–22.
[CrossRef][PubMed]

4. Kiechle FL, Arcenas RC, Rogers LC. Establishing benchmarks and metrics for disruptive technologies, inappropriate and obsolete tests in the clinical laboratory. Clin Chim Acta. 2014;427:131–6.
[CrossRef][PubMed]

5. Jackson BR. Managing laboratory test use: principles and tools. Clin Lab Med. 2007;27(4):733–48, v.

6. Melanson SE. Establishing benchmarks and metrics for utilization management. Clin Chim Acta. 2014;427:127–30.
[CrossRef][PubMed]

7. Hernandez JS, Aderton J, Eidem L. The role of project managers who assist physician leaders at Mayo Clinic. Physician Exec. 2011;37(4):62–5.
[PubMed]

8. Warren JS. Laboratory test utilization program: structure and impact in a large academic medical center. Am J Clin Pathol. 2013;139(3):289–97.
[CrossRef][PubMed]

9. Horn DM, Koplan KE, Senese MD, Orav EJ, Sequist TD. The impact of cost displays on primary care physician laboratory test ordering. J Gen Intern Med. 2014;29(5):708–14.
[CrossRef][PubMed]

10. Wu AH, Lewandrowski K, Gronowski AM, Grenache DG, Sokoll LJ, Magnani B. Antiquated tests within the clinical pathology laboratory. Am J Manag Care. 2010;16(9):e220–7.
[PubMed]

11. Ettorchi-Tardy A, Levif M, Michel P. Benchmarking: a method for continuous quality improvement in health. Healthc Policy. 2012;7(4):e101–19.
[PubMed][PubMedCentral]

12. Steiner JW, Murphy KA, Buck EC, Rajkovich DE. How to utilize benchmarking in the clinical laboratory. Clin Leadersh Manag Rev. 2006;20(6):E4.
[PubMed]

13. Valenstein PN, Praestgaard AH, Lepoff RB. Six-year trends in productivity and utilization of 73 clinical laboratories: a College of American Pathologists Laboratory Management Index Program study. Arch Pathol Lab Med. 2001;125(9):1153–61.
[PubMed]

14. Howanitz PJ, Cembrowski GS, Bachner P. Laboratory phlebotomy. College of American Pathologists Q-Probe study of patient satisfaction and complications in 23,783 patients. Arch Pathol Lab Med. 1991;115(9):867–72.
[PubMed]

15. Howanitz PJ, Schifman RB. Phlebotomists' safety practices. A College of American Pathologists Q-Probes study of 683 institutions. Arch Pathol Lab Med. 1994;118(10):957–62.
[PubMed]

16. Steindel SJ. Timeliness of clinical laboratory tests. A discussion based on five College of American Pathologists Q-Probe studies. Arch Pathol Lab Med. 1995;119(10):918–23.
[PubMed]

17. Steindel SJ, Jones BA, Howanitz PJ. Timeliness of automated routine laboratory tests: a College of American Pathologists Q-Probes study of 653 institutions. Clin Chim Acta. 1996;251(1):25–40.
[CrossRef][PubMed]

18. Galloway M, Nadin L. Benchmarking and the laboratory. J Clin Pathol. 2001;54(8):590–7.
[CrossRef][PubMed][PubMedCentral]

19. Bekeris LG, Tworek JA, Walsh MK, Valenstein PN. Trends in blood culture contamination: a College of American Pathologists Q-Tracks study of 356 institutions. Arch Pathol Lab Med. 2005;129(10):1222–5.
[PubMed]

20. Wagar EA, Stankovic AK, Wilkinson DS, Walsh M, Souers RJ. Assessment monitoring of laboratory critical values: a College of American Pathologists Q-Tracks study of 180 institutions. Arch Pathol Lab Med. 2007;131(1):44–9.
[PubMed]

21. Melanson SE, Baskin L, Magnani B, Kwong TC, Dizon A, Wu AH. Interpretation and utility of drug of abuse immunoassays: lessons from laboratory drug testing surveys. Arch Pathol Lab Med. 2010;134(5):735–9.
[PubMed]

22. ABIM Foundation. *Choosing wisely.* 2015. http://www.choosingwisely.org/about-us/. Accessed 22 July 2015.

23. Walker PL, Crook M. Tumour marker requesting in primary care and the role of the laboratory. J Clin Pathol. 2011;64(5):443–6.
[CrossRef][PubMed]

24. Le RD, Kosowsky JM, Landman AB, Bixho I, Melanson SE, Tanasijevic MJ. Clinical and financial impact of removing creatine kinase-MB from the routine testing menu in the emergency setting. Am J Emerg Med. 2015;33(1):72–5.
[CrossRef][PubMed]

25. Portugal B. Benchmarking hospital laboratory financial and operational performance. Hosp Technol Ser. 1993;12(17):1–21.
[PubMed]

26. Kim JY, Dzik WH, Dighe AS, Lewandrowski KB. Utilization management in a large urban academic medical center: a 10-year experience. Am J Clin Pathol. 2011;135(1):108–18.
[CrossRef][PubMed]

27. Dine CJ, Miller J, Fuld A, Bellini LM, Iwashyna TJ. Educating physicians-in-training about resource utilization and their own outcomes of care in the inpatient setting. J Grad Med Educ. 2010;2(2):175–80.
[CrossRef][PubMed][PubMedCentral]

28. Kumwilaisak K, Noto A, Schmidt UH, Beck CI, Crimi C, Lewandrowski K, et al. Effect of laboratory testing guidelines on the utilization of tests and order entries in a surgical intensive care unit. Crit Care Med. 2008;36(11):2993–9.
[CrossRef][PubMed]

29. Reynolds D. Con: current laboratory benchmarking options are not good enough. Clin Leadersh Manag Rev. 2006;20(6):E3.
[PubMed]

30. Morrison AP, Tanasijevic MJ, Goonan EM, Lobo MM, Bates MM, Lipsitz SR, et al. Reduction in specimen labeling errors after implementation of a positive patient identification system in phlebotomy. Am J Clin Pathol. 2010;133(6):870–7.
[CrossRef][PubMed]

31. Ohno T, editor. Toyota production system: beyond large scale production. New York: Productivity Press; 1988.

32. Womack J. Going lean in healthcare. Cambridge, MA: Institute for Healthcare Improvement; 2005.

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_8

8. Laboratory Formularies

Petr Jarolim[1]

(1) Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Petr Jarolim
Email: Pjarolim@partners.org

Keywords Laboratory formulary – Laboratory test utilization – Utilization management – Reference testing – Hospital laboratory – Reference laboratory – Test request – Approval process

What Are Laboratory Formularies ?

The basic meaning of the word formulary has, for a long time, been a list of medicines with varying levels of detail for each medication. Nowadays, when speaking about a hospital formulary , we usually mean the list of medications that have been approved for use in the hospital or have been approved by insurers for prescribing. The development of such formularies is typically driven by considerations around safety and efficacy of the medications and, last but not least, their cost-effectiveness.

The same is true for the laboratory formularies, a relatively recent concept that is quickly increasing in popularity. While taking into account the medical necessity of a test and its diagnostic and therapeutic value, the cost-effectiveness of a diagnostic procedure, in this case of a laboratory test, again plays an essential role.

In addition to improving care, laboratory formularies, as with drug formularies , are gaining popularity as tools to control costs—an imperative

in today's healthcare environment. Laboratory formularies can be distinguished as two very different types : (1) those that describe laboratory testing performed locally in the clinical laboratory and (2) those that capture and regulate reference laboratory testing. These two types of formularies vary widely in multiple ways.

The concept of laboratory formularies is tightly linked to the management of test utilization. There is a substantial and quickly growing body of literature dedicated to utilization management including special issues of laboratory journals (for a review, see paper by Huck and Lewandrowski [1] which was itself published as a part of special issue dedicated to laboratory utilization), while the description of laboratory formularies is largely limited to a few paragraphs in articles about utilization management and a chapter on laboratory formularies [2]. In addition, utilization management is addressed in multiple chapters of this book. This chapter will therefore be limited to the description of a laboratory formulary, the principal differences between hospital and reference laboratory formularies , and to the description of the process of adding a test to, or deleting one from, an existing formulary.

Hospital Laboratory Formularies

Hospital laboratory formularies are considerably more rigid than those regulating reference testing . The test menu is mostly dictated by medical necessity of the individual laboratory tests and turnaround time requirements. While the cost of the testing is always important, economic consideration is overshadowed by the medical necessity of an assay.

Consequently, opportunities to manage or significantly change hospital laboratory formularies are limited, as the core tests have to be performed, sometimes at a financial loss. Nevertheless, even on the side of in-house testing, opportunities may present themselves after a careful periodic review of the laboratory formulary.

Annual review of the laboratory formulary may identify tests that have substantially decreased in volume. Unless these tests are indispensable for timely patient management, they can be phased out from the in-house menu and may be transferred to a reference laboratory or, in other words, moved to the reference testing formulary.

Decreasing test volume is not the only reason for eliminating an assay from a formulary—another reason for abandoning an assay is its clinical

obsolescence and its replacement by a newer, more informative test. One example from the clinical chemistry laboratory is one of the most popular biomarkers of acute myocardial infarction until recently, the MB isoform of creatine kinase (CK-MB) that has outlived its usefulness and has been replaced by the cardiac troponins I and T. Some hospitals have eliminated CK-MB testing altogether; some have implemented physician education or other measures to decrease CK-MB ordering [3]. It is to be expected that within a few years, CK-MB will disappear from most laboratory formularies.

Another example that may be considered in the clinical chemistry laboratory is testing for alanine and aspartate aminotransferases, ALT and AST. While a high De Ritis ratio, i.e., high AST/ALT ratio, may help to detect alcohol abuse, in most cases the two enzymes track each other very closely and thus testing for both is superfluous. Since changes in ALT are usually more prominent than those in AST, it was recently suggested by Xu and coworkers that the elimination of AST from the laboratory formulary , or rather limiting its use, may be associated with a significant cost savings to the hospital laboratory without affecting patient care [4].

In the area of pain management , mass spectrometry assays are gaining ground at the expense of screening immunoassays . Here again, it is expected that many immunoassays that detect pain medications and drugs of abuse will gradually be eliminated from laboratory formularies .

Similar opportunities exist in other parts of the hospital laboratories or at the interface of two or more subspecialty laboratories. Erythrocyte sedimentation rate may not survive in hospital formularies together with the CRP assay that can be performed both inexpensively and expeditiously. Enough has been written about the bleeding time test that does not have a place in today’s busy clinical laboratory. In virology laboratories , qualitative PCR assays for virus detection are being gradually replaced by quantitative assays.

At the other end of the spectrum, periodic review of reference lab testing identifies tests that are quickly increasing in volume and encourages the laboratory to add these tests to the in-house formulary. Recent examples at Brigham and Women’s Hospital are galactomannan and beta-D-glucan testing for early detection and management of fungal infections, numerous molecular assays in the virology laboratory for quick detection of viruses in an immunocompromised host, and multiplexed mass spectrometry assays for opioids and benzodiazepines.

Finally, another essential part of the maintenance of the laboratory formulary is active communication with clinicians. Such frequent conversations within our hospital led to the implementation of fetal fibronectin testing , pain management testing, and current consideration of procalcitonin testing.

Reference Laboratory Formularies

The situation is considerably more complex in the area of sendout testing. There, the number of tests offered by a multitude of reference laboratories keeps growing by the minute. While the number of tests sent to a reference laboratory by a hospital laboratory with an extensive in-house test formulary represents only a small fraction of the total volume of tests ordered, the reference test menu is typically considerably larger than the in-house menu, and the cost of reference testing represents a significant portion of the overall laboratory budget.

The number of genetic variants and biomarkers of diagnostic and prognostic significance has been increasing with an astounding speed. Consequently, the volume, complexity, and cost of reference laboratory testing have also increased at the same rate and, in many instances, even faster. One of the biggest challenges that laboratory directors face is dealing with the sheer number of diagnostic tests that is available to choose from so as to properly evaluate, organize, and triage the hundreds of requests for reference laboratory testing. The technical aspects and clinical benefits of these assays, including their sensitivities, specificities, and positive and negative predictive values in a particular patient population, pose an additional challenge for clinicians to keep abreast given this variety of diagnostic testing. Similar or identical tests bundled into panels of varying sizes may be offered by various reference laboratories. Testing for the same genetic condition may be offered as sequential single-gene testing, performed according to a predetermined reflex algorithm or a large, expensive multiplexed panel.

More and more, as clinical laboratories are expected to oversee sendout reference laboratory testing, this increasing complexity in ordering reference laboratory testing poses a substantial financial and organizational challenge to the hospitals and clinics. While there are many reported decision support strategies to control laboratory test utilization for in-house testing, these

strategies are often not systematically applicable to reference lab testing due to the large number and complexity of indications. Utilization management of reference laboratory testing will be described in detail in the Chap. 19 of this book. In this chapter, we therefore focus on the very first step in the utilization process, the creation of a reference testing formulary . The following discussion is based mainly on the process that was implemented at Brigham and Women's Hospital between 2010 and 2011.

To meet the challenges of the ever-increasing cost of reference laboratory testing at Brigham and Women's Hospital , we implemented a program to review for approval in real-time selected requests for reference laboratory testing, evaluating them for clinical and technical appropriateness. A committee comprised of clinical pathologists , experts from clinical departments, and hospital leadership was convened to oversee and evaluate our reference testing program. This committee's initial responsibility was to generate a formulary, or database, of reference laboratory tests that had been approved for use in our institution. For this purpose, the reference testing committee initially reviewed all reference tests ordered over a 1-year period. Sample type, volume, and sample storage conditions prior to shipping and the preferred reference laboratory for that assay were included in the information in the formulary for each test. Assays were also classified as "active " or "inactive " for those tests that were no longer offered or had been supplanted by another assay.

As a result of this inventory process , we found that the existing test menu contained approximately 2000 active and 700 inactive entries. Each test was then reviewed individually and was categorized as "unrestricted , "restricted ," and "unauthorized ." Additionally, a fourth category of "undefined " tests is used to refer to tests not yet included in the formulary.

The "unrestricted" tests represent frequently ordered tests with clear clinical utility. They are sent to a predetermined CLIA-certified laboratory without a review. Examples of such assays are various serologies or PCR assays . They also include relatively infrequent assays, such as therapeutic drug monitoring for various esoteric drugs . The decision to include such tests on the formulary is based on an assumption that clinicians ordering such assays suspect toxicity or low efficacy of a drug and that there is therefore no reason to review such sendout requests. In addition, most of these tests are relatively inexpensive.

The category of "restricted " tests includes, among others, complex

genetic tests, sequencing of multiple genes, and paraneoplastic antibody panels. These tests are also sent to a predetermined CLIA-certified reference laboratory, but the test request requires a review. All effort is made to perform the test review prior to specimen collection. However, this is not always successful, and, at times, the request review starts after the specimen is collected and arrives in the lab .

The third category, the “unauthorized ” tests, includes tests that are categorically denied or replaced with the appropriate restricted or unrestricted test. This category includes all research use only or investigational use only tests, as well as tests whose utility has not been sufficiently documented by available studies and publications. An example of such tests is a panel that combines multiple tests and calculates various indices or risk scores based on proprietary algorithms.

The final category of tests is called “undefined .” This category includes new tests that have not been previously ordered or defined tests that have been requested to be sent to a different reference laboratory than to the predefined CLIA laboratory. In this case, there is either no predetermined CLIA-certified reference laboratory or the clinician feels that there are sufficiently good reasons for which the testing should be performed in a different laboratory . All undefined test requests require review.

Real-Time Review of Requests for Restricted Reference Testing

Requests for restricted reference laboratory tests proceed according to a formalized protocol. In an ideal situation, clinicians should notify the laboratory about their intention to order such a test. Despite all effort to enforce prior authorization by the clinical pathology residents, a specimen is often collected and sent to the laboratory together with an order for a restricted test. In either case, the reference testing coordinator notifies clinical pathology residents who review the request and contact the ordering clinicians for additional information. They discuss the test request with the laboratory medical director on call and either approve the sendout request or suggest test cancellation.

The role of the Advanced Laboratory Diagnostics Review Committee at Brigham and Women’s Hospital was not only to develop a reference laboratory formulary but also to continuously monitor sendout test utilization

as described above and in an article by Greenblatt et al. [5]. A similar committee named the “Laboratory Formulary Committee” was established at the University of Michigan. The work of this committee on the laboratory formulary, both for the in-hospital laboratory and for reference testing, was described by Warren who also presented examples of reviewed tests and the outcomes of such a review, ranging from “appropriately utilized, no change in formulary” to “removed from formulary” with a number of interim interventions such as limiting ordering of a test to subsets of patients or groups of clinicians, limiting frequency of orders, and additional restrictions. The author also describes the process of vetting proposed new tests by the committee and gives examples of its outcomes [6]. Similarly, a report of a 10-year experience with utilization management in a large urban academic medical center describes discontinuation of tests due to their limited clinical usefulness, emphasizing again the importance of a close involvement of clinicians in this process [7].

Review of an Undefined Test : New Test Proposal

The process of vetting of a new test proposal can be relatively simple, based on a limited review of the literature and cost comparisons, or can be complex and take advantage of relatively complicated statistical concepts of net reclassification improvement, net benefit [8], integrated discrimination improvement [9], or c-statistic. Countless publications on the incremental value of diagnostic and prognostic markers are available, since its assessment is the quintessential outcome of clinical trials of a novel biomarker. The establishment of test benchmarks and examples of obsolete and inappropriate tests were contrasted with novel, disruptive technologies by Kiechle et al. [10]. However their benchmarks were based on a review of the literature, not on the above-mentioned statistical methods .

At Brigham and Women’s Hospital , the vetting process starts with the filling out of a “new test request form” by the clinician requesting availability of a new assay (Fig. 8.1). The requesting clinician typically completes the clinical benefit portion, at times with tentative achievable savings at the clinical end, while the laboratory fills out the technical, logistical, and fiscal information.

BWH Department of Laboratory Control
Reference Testing Services
New Test Request Form

Date: _____ Requesting MD: _____

Clinician ID: _____ Page #: _____ Service: _____

TEST NAME: _____

Suggested Reference Lab: _____

Fax completed form to …….. Attn.: Reference Testing Coordinator

Supporting Documentation – To be completed by the requesting clinician (attach relevant information where applicable)

1. Clinical Justification (i.e. disease of interest, clinical relevance vs. research, why preferred over test available in house).

2. How will treatment be altered based on the test?

3. What is the best alternative to this new assay?

4. Anticipated volume:
   - o Number of patients per year
   - o Frequency per patient
   - o Inpatient vs. Outpatient mix

5. Turnaround time requirements

6. Notes/Comments:

Fig. 8.1 Abbreviated new test request form used at Brigham and Women's Hospital

Clinicians are prompted to submit a brief form describing the expected clinical utility and annual number of requests for any requests for testing that fall into the undefined category. This form is required for the purposes of updating the formulary and initiating a discussion between clinicians and laboratory staff regarding the future utilization of a reference laboratory test. These forms are then reviewed by a selected group of members of the Advanced Laboratory Diagnostics Review Committee . The test request is discussed during the monthly meetings of the Advanced Laboratory Diagnostics Review Committee and either added to the reference testing formulary and classified as either restricted or unrestricted, or the test request is rejected. It should be noted that the reference test formulary is a dynamic

list of sendout tests with associated instructions and interpretive comments and is continually updated as new tests are requested.

Summary

The establishment of a laboratory formulary and management of laboratory utilization are two closely intertwined processes. This means that the future of laboratory formularies depends, to a great extent, on the future of clinical process management.

The laboratory formulary should be created only after a thorough review of the true and perceived clinical value of a test to the patients and of the existing and potential future test utilization. Once the medical need for a test is confirmed and the decision to add it to the formulary is made, the rules for its utilization should become part of the formulary.

The laboratory formulary should be created and maintained in close communication with clinicians whose input is critical for the success of utilization management.

The laboratory formulary is not a rigid list of tests; it should be reviewed on a regular basis and changed as needed. We recommend reviewing the hospital laboratory formularies at least once a year and the reference test formularies more frequently, in particular, those tests in the rapidly developing diagnostic areas.

References

1. Huck A, Lewandrowski K. Utilization management in the clinical laboratory: an introduction and overview of the literature. Clin Chim Acta [Internet]. Elsevier B.V. 2014;427:111–7. doi:10.1016/j.cca.2013.09.021.

2. Jackson BR. Laboratory formularies. Clin Chim Acta [Internet]. Elsevier B.V. 2014;427:151–3. doi:10.1016/j.cca.2013.09.040.

3. Saenger AK, Jaffe AS. Requiem for a heavyweight: the demise of creatine kinase-MB. Circulation [Internet]. 2008;118(21):2200–6. http://www.ncbi.nlm.nih.gov/pubmed/19015414. Accessed 4 Oct 2013.

4. Xu Q, Higgins T, Cembrowski GS. Limiting the testing of AST: a diagnostically nonspecific enzyme. Am J Clin Pathol [Internet]. 2015;144(3):423–6. http://ajcp.ascpjournals.org/cgi/doi/10.1309/AJCPO47VAWYRIDHG

5.

Greenblatt MB, Nowak JA, Quade CC, Tanasijevic M, Lindeman N, Jarolim P. Impact of a prospective review program for reference laboratory testing requests. Am J Clin Pathol. 2015;143(5):627–34.
[CrossRef][PubMed]

6. Warren JS. Laboratory test utilization program: structure and impact in a large academic medical center. Am J Clin Pathol [Internet]. 2013;139(3):289–97. http://www.ncbi.nlm.nih.gov/pubmed/23429364.

7. Kim JY, Dzik WH, Dighe AS, Lewandrowski KB. Utilization management in a large urban academic medical center: a 10-year experience. Am J Clin Pathol [Internet]. 2011;135(1):108–18. http://ajcp.ascpjournals.org/cgi/doi/10.1309/AJCP4GS7KSBDBACF.

8. Steyerberg EW, Pencina MJ, Lingsma HF, Kattan MW, Vickers AJ, Van Calster B. Assessing the incremental value of diagnostic and prognostic markers: a review and illustration. Eur J Clin Invest [Internet]. 2012;42(2):216–28. doi:10.1111/j.1365-2362.2011.02562.x.

9. Kerr KF, McClelland RL, Brown ER, Lumley T. Evaluating the incremental value of new biomarkers with integrated discrimination improvement. Am J Epidemiol [Internet]. 2011;174(3):364–74. http://aje.oxfordjournals.org/cgi/doi/10.1093/aje/kwr086.

10. Kiechle FL, Arcenas RC, Rogers LC. Establishing benchmarks and metrics for disruptive technologies, inappropriate and obsolete tests in the clinical laboratory. Clin Chim Acta [Internet]. Elsevier B.V. 2014;427:131–6. doi:10.1016/j.cca.2013.05.024.

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_9

9. Utilization and Other Resource Management in Clinical Chemistry

Alan H. B. Wu[1, 2]

(1) Department of Laboratory Medicine, University of California, San Francisco, CA, USA
(2) Clinical Laboratories, San Francisco General Hospital, 1001 Potrero Ave., San Francisco, CA 94110, USA

Alan H. B. Wu
Email: wualan@labmed2.ucsf.edu

Introduction

The clinical chemistry laboratory within a hospital typically has the largest volume of testing, the most analytical equipment, highest budget for expenses, and largest numbers of personnel performing tests . Therefore, a program for the effective management of laboratory resources from within the chemistry laboratory division has the potential to have more of a significant impact on the clinical laboratory with regard to costs for delivering services than in other divisions. The chemistry laboratory was also the first to deliver completely automated testing services from sample processing such as labeling and centrifugation, automated analysis, and post-analytical manipulations such as repeat testing, dilutions, and tests that have been “added on” after results reporting. Automated analysis with computerized tracking permits implementation of systematic changes that can have a significant impact on resource utilization .

Utilization management can take one of two forms, both of which will

have the effect of reducing cost:

1. Elimination of unnecessary tests

2. Reducing the unit cost of tests that are performed

Ideally the most effective strategy for a successful utilization management program will incorporate both of these approaches.

Among the specific approaches that can be taken toward improving resource utilization in the clinical chemistry laboratory includes (1) the systematic removal of antiquated tests, (2) elimination of chemistry panels and the introduction of reflex testing, (3) graphical displays of multiple related test results, (4) altering quality control schemes from ones based strictly on statistics toward metrics based on human biological variation of laboratory tests, (5) the use of “middleware” (information technology programs) for autoverification and alerts for unnecessary tests or duplicate requests, (6) incorporating redundancy and overcapacity of testing so that batch testing can be eliminated, (7) switching to plasma as the specimen of choice for testing clinical chemistry analytes, and (8) screening populations for germ line genetic variances .

Removal of Antiquated Tests

The in vitro diagnostics (IVD) industry represents manufacturers who produce instruments and reagents for clinical laboratory tests. In the USA, approval of clinical laboratory tests is under the oversight of the Food and Drug Administration (FDA) . Like many fields that are highly driven by technology, the IVD industry is highly dynamic. New biomarkers for disease diagnosis and management are discovered and implemented each year. In some cases, the new tests do not replace any existing ones but are used in conjunction with other clinical and non-biomarker laboratory information. B-type natriuretic peptide and procalcitonin are new biomarkers for heart failure and sepsis, respectively, that had no preexisting counterpart. In other examples, newer tests such as cardiac troponin T or I have replaced the older tests including creatine kinase (CK)-MB isoenzyme and myoglobin [1]. Given the high volume of requests for cardiac markers , a clinical laboratory that can eliminate testing for CK-MB and myoglobin can reap significant

economic benefits. C-reactive protein is more specific than the erythrocyte sedimentation rate as a marker of inflammation precluding the need for the latter test. In other examples, improvement in analytical technology has led to the redundancy of other laboratory assays. The incorporation of co-lipase and bile salts to the lipase reagent made testing for amylase obsolete, albeit most hospital laboratories continue to offer the test.

Removing tests from a clinical laboratory's formulary is not a trivial procedure. Many physicians may have difficulty in adopting to newer tests. A professional rapport between the clinical laboratory and the medical staff is necessary for a test to be removed without resistance. Arguments based on economic savings by the laboratory are generally not effective. If it can be shown that the institution can save money, e.g., reduced length of stay, some justification can be made. However, such studies are usually difficult to perform within a hospital. Therefore, studies conducted at other institutions or expert opinion through clinical practice guidelines may provide the evidence needed to make a change.

Elimination of Chemistry Panels

The chemistry panel should have been abandoned because of the statistical expectation of producing abnormal results in the absence of disease. The strategy for establishing the reference range induces this type of statistical aberration. A normal range is computed from the mean ±2 standard deviation of results that demonstrate a parametric distribution or the central 95 percentile of results that do not exhibit a parametric distribution. By statistical definition, about 5 % of results will be outside of the reference range. For a chemistry profile of 20 tests, one test per panel on average will be abnormal. If the pretest likelihood is low for the disease indicated by the laboratory test, the finding is most likely to be a false-positive result. Physicians reviewing this report may be obligated to work up this patient for the presence of the indicated disease, thereby unnecessarily increasing medical care costs. The laboratory should discourage panels or clusters where the test analytes are unrelated to each other. Elimination of panels can have a significant impact on test utilization. In a study conducted by Pysher et al., the elimination of predefined multi-test chemistry panels within a pediatric hospital resulted in a 32.7 % reduction in the number of chemistry tests ordered [2]. A greater than 50 % decline was observed for eight of the 23 tests. Other combinations of

tests, e.g., free T4 and thyroid-stimulating hormone, provide differential information and are appropriate as a group of commonly ordered tests .

Table 9.1 shows the result of a hypothetical 21-test chemistry profile for a 63-year-old male patient who is seen for a general medical checkup. He presents with no significant medical history and no medical complaint. The profile shows a marginally high result for total calcium. The other relevant tests including phosphorus, alkaline phosphatase, magnesium, total protein, albumin, and the A/G ratio were normal. The doctor felt obligated to do some follow-up analysis including ordering a parathyroid hormone level which was normal at 25 (15–65 pg/mL). Not satisfied, the doctor ordered a bone density scan, which revealed no osteoporosis, osteolytic lesions, or any bone abnormality. Had this patient developed a calcium-related disease , he would have exposed himself to some medical legal liability. With negative results for the other tests ordered, the attending physician is satisfied that the high calcium result was anomalous. In the absence of a pretest likelihood for bone disease, this physician should not have ordered a general “chemistry panel.” Likewise, to better serve the clinical need, the clinical laboratory should not have made this panel available.

Table 9.1 Chemistry profile results on a hypothetical patient

Test	Result	Reference range
Sodium	142	134–145 mmol/L
Potassium	3.9	3.5–5.0 mmol/L
Chloride	99	96–108 mmol/L
Total CO_2	25	22–30 mmol/L
Glucose	85	70–105 mg/dL
Creatinine	1.02	0.75–1.2 mg/dL
BUN	15	5–26 mg/dL
Total calcium	10.7 H	8.5–10.5 mg/dL
Magnesium	2.2	1.8–2.4 mg/dL
Phosphorus	3.2	2.5–4.5 mg/dL
Iron	43	35–155 μg/dL
Aspartate aminotransferase	32	0–55 U/L
Alanine aminotransferase	25	0–55 U/L
Alkaline phosphatase	73	25–130 U/L
Lactate dehydrogenase	174	100–250 U/L
Uric acid	6.3	2.4–8.2 mg/dL

Cholesterol	198	100–199 mg/dL
Triglycerides	102	0–149 mg/dL
Total bilirubin	0.4	0.1–1.1 mg/dL
Total protein	7.3	6.0–8.0 mg/dL
Albumin	4.3	3.5–5.5 mg/dL
A/G ratio	1.4	1.1–2.5

In contrast to the elimination of panels, “reflex testing ,” where the result of one test triggers the need and performance of another test, is a worthwhile cost-savings measure. This is a superior approach than for a physician ordering all conceivable laboratory tests. For example, if the serum protein electrophoresis (SPE) result shows a monoclonal protein band , the laboratory could reflex the test to the confirmatory procedure, i.e., immunofixation electrophoresis (IFE) . If the SPE is negative, the IFE test would not be necessary in most cases. Reflex testing and test cancellation provide the best utilization of clinical laboratory resources. Table 9.2 lists some other examples of reflexed tests . The establishment of reflex testing/cancellation must be preestablished in writing with the medical staff. A laboratory that submits an invoice for testing reimbursement that was not ordered by the attending doctor could be held responsible or liable for inappropriate reimbursement practices.

Table 9.2 Examples of reflex test

Test	Condition	Reflexed test
Total bilirubin	Increased	Direct bilirubin
Protein electrophoresis	Monoclonal band	Immunofixation electrophoresis
HIV antibody test	Positive	Western blot
Urine drug screen	Positive	Confirmatory by mass spectrometry
Arsenic in urine	Positive	Fractionation into organic vs inorganic
Autoantibody tests	Positive	Titer determination

Graphical Display of Clinical Chemistry Results

When a combination of tests is used for the diagnosis of disease, the clinical laboratory can assist in the interpretation of routine clinical chemistry tests by providing graphical displays of test results. Figure 9.1 illustrates a few examples of this concept. Figure 9.1a shows the interpretation of the IgG

index , a ratio of the CSF/serum IgG over the CSF/serum albumin . Healthy subjects have values that fall within the reference intervals for both indices along the slope of the line. A patient with multiple sclerosis has a disproportionate increase in the CSF/serum IgG over the corresponding ratio for albumin, indicating local synthesis of IgG within the central nervous system (CNS) . A proportionate increase in both indices, i.e., a continuation along the slope of the line, indicates the presence of a disorder characterized by the breakdown of the blood–brain barrier. These include CNS infections, infarctions, and tumors. Results plotted in the other areas may indicate a combination of diseases (top middle) or analytic error (bottom right). Figure 9.1b shows the relationship between ionized calcium and parathyroid hormone concentrations. Primary hyperparathyroidism is readily distinguishable from secondary hyperparathyroidism and primary hypoparathyroidism. High calcium concentrations due to the presence of cancer are characterized by a low parathyroid hormone level. Figure 9.1c shows the inverse relationship between log thyroid-stimulating hormone and free T4. Values that fall outside of this range could be due to thyroid tumors or diseases associated with thyroid resistance. A disproportionate level of one marker over the other may indicate the presence of an interfering antibody, such as human anti-mouse antibody (HAMA) , which produces false-positive results [3]. All dual-site “sandwich”-type immunoassays can exhibit an interference with HAMA. Mitchell et al. developed a rule-based detection algorithm whereby samples that fell outside of expected ratios of TSH and free T4 were flagged [4]. Out of nearly 8000 samples tested, 18 had atypical results, many of which were explained by the presence of an interferent, random error or blood from neonates .

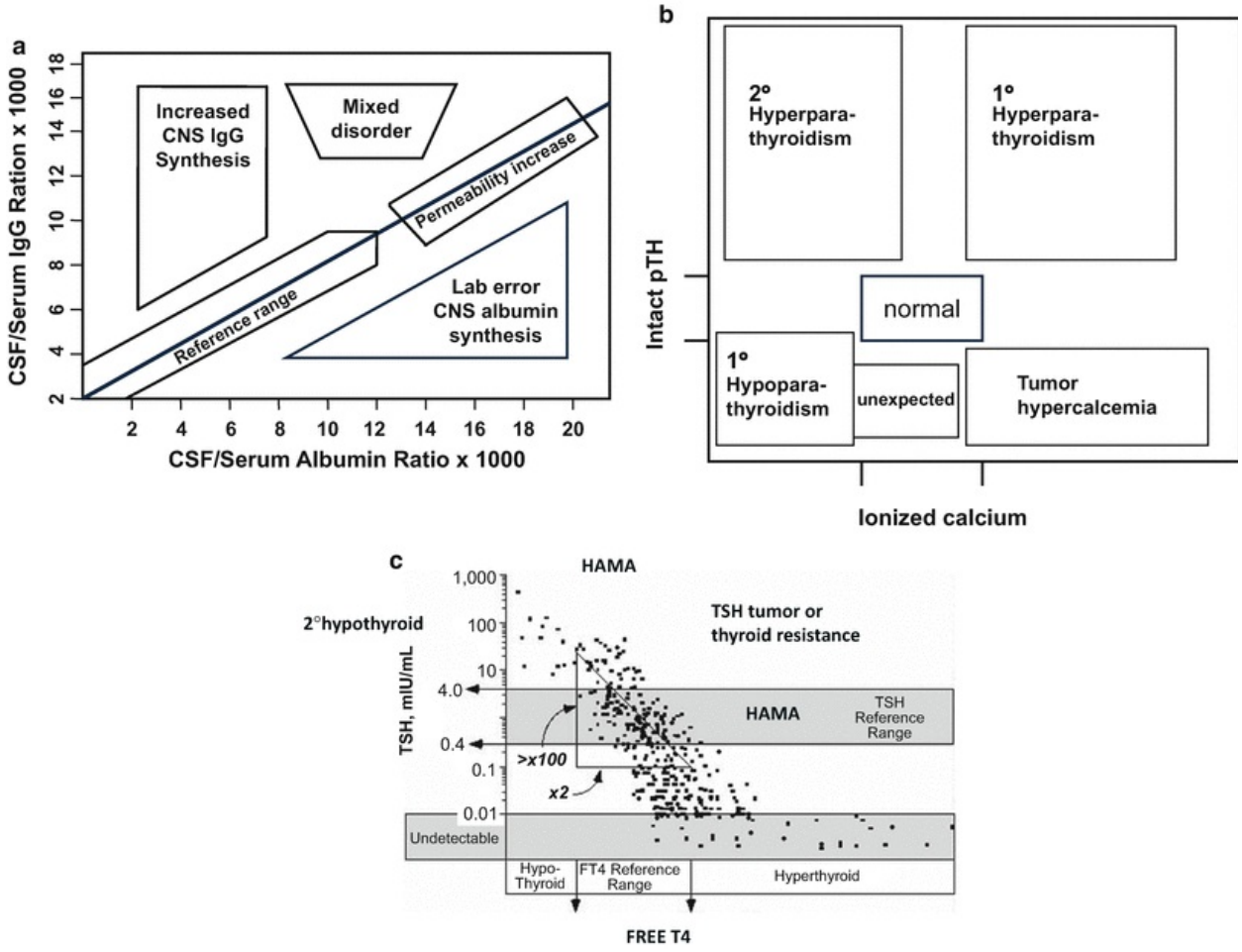


Fig. 9.1 Graphical displays of clinical chemistry test with interpretation of results (see text for description). (**a**) The IgG index for multiple sclerosis and central nervous system disorders associated with a breakdown of the blood–brain barrier. (**b**) The relationship of ionized calcium with parathyroid hormones. (**c**) The relationship of free T4 with thyroid-stimulating hormone (TSH). *HAMA* human anti-mouse antibody (Adapted and used with permission from the American Association for Clinical Chemistry)

Quality Control (QC) Schemes Based on Biological Variation

Quality control procedures are required for all clinical testing under the Clinical Laboratory Improvement Amendment and have been a basic tenet within the clinical laboratory for many decades. The traditional approach has been the use of statistical rules to determine the presence of outliers. Levey-Jennings control charts are used to track results of data on a daily basis. These charts plot mean results and provide limits for 1SD, 2SD, and 3SD.

For results that are parametrically distributed, 68.27 %, 95.45 %, and 99.73 % of results fall within these limits, respectively. Decisions and potential corrective actions are taken by the clinical laboratory staff when results exceed or are below 2SD. Accordingly, 4.54 % of QC results are statistically expected to be outside the 2SD range without any probable cause. Since the laboratory cannot determine if a result is due to a failure or is part of the expected statistics, such a result may trigger an investigation. Many laboratories have adopted Westgard rules, whereby the finding of one result outside the 2SD limits is a warning and not a violation. Multiple QC results must be outside the 2SD limits before testing must be suspended and a root cause analysis is needed.

Given the large number of tests performed by the clinical chemistry laboratory, performing quality controls is a major unavoidable expense to the clinical laboratory. Methods to reduce the rate of false rejections would improve the efficiency of the laboratory. False rejections are becoming an increasing important with improvement in the precision of automated clinical analyzers. Highly precise assays are characterized by a reduced SD, resulting in the setting of lower cutoff limits for an outlier.

One approach to achieve this goal of reducing false QC rejections is to examine the biological variation of clinical laboratory tests [5]. This is an assessment of how clinical laboratory tests change within an individual over time. Biological variation studies are conducted in healthy subjects. Results are used to determine what is an abnormal lab result and how much change in a serial test is considered clinically relevant. There are several tests that have a narrow intra-individual variation. Serum sodium has a reference range of 135–145 mmol/L. A 5 % imprecision can produce normal result into a hypo- or hypernatremic domain. Treatment for an abnormal condition that does not exist could be damaging to the patient; therefore, tight QC rules are needed to minimize testing errors.

There are other tests that have a wide intra-individual variation. Serum enzymes such as creatine kinase and alanine aminotransferase and metabolites such as bilirubin, iron, and lactate have variations that exceed 20 %. In clinical practice, a 20 % change in results would not affect the interpretation of the result. Therefore, acceptable QC limits could be relaxed to limits of 2.5SD or even up to 3SD and would reduce the frequency of false rejections without compromise of the clinical quality of the laboratory test.

Implementation of Middleware

Routine clinical chemistry analyzers are interfaced to a laboratory information system (LIS) for the efficient transfer of clinical laboratory data linked to patient identifiers and then on to hospital information system (HIS) [6]. It is difficult for many of these LIS systems to perform additional procedures that can improve workload efficiency. Because of this, many clinical laboratories have acquired “middleware” a link between clinical laboratory instruments and the LIS system. An important procedure where middleware is particularly helpful is “autoverification .” This is a user-defined set of limits by which clinical laboratory data can be reviewed by a program and alert the staff for unusual or unexpected findings. Results that appear to have a typical pattern can be released to the LIS and HIS. Middleware can also be used to track changes between results from the same patient, even if testing is conducted on different instruments. This will become increasingly important for the diagnosis and rule out of acute myocardial infarction as a change in cardiac troponin results will be important. Middleware can be used to calculate delta changes in test results and flag testing that is abnormal as defined by the user (clinical laboratory).

Overcapacity of Analytical Testing Capabilities

Most laboratories offer “STAT” testing services , i.e., a request from the medical team that the test be assayed immediately. There are medical situations whereby the results of laboratory tests can have a significant impact on important decisions made regarding the management of the patient. Results of stat tests can also facilitate triaging decisions, such as for patients seen in the emergency department. Unfortunately, the labeling of samples as requiring stat attention has been abused by caregivers with the labeling of all samples as stat, irrespective of whether or not the clinical need justifies such a designation. If the clinical laboratory prioritizes stat over those sent for routine analysis, the disruption of workflow reduces clinical laboratory efficiency and increases costs.

An alternative to this problem is to treat all samples as STAT. In this way, there is no effort in the segregation of samples as being emergent or routine. In order to maintain the turnaround time needed for stat testing, the laboratory must have instruments that have excess capacity. This means that

there is sufficient amount of equipment so that there are no significant specimen “bottlenecks” during peak times of the day where most clinical samples are delivered. In a typical laboratory, a high volume of routine samples is sent during the early morning hours from inpatients and near the end of the day shift from outpatient deliveries. If the lab cannot efficiently handle all specimens during the peak periods, the turnaround time for reporting STAT tests may be unacceptably delayed. Under these conditions, additional testing instruments may be necessary.

Plasma-Based Specimens for Testing

Testing of serum requires centrifugation of blood samples after there is a sufficient amount of time to allow for the sample to coagulate. This usually requires 5–10 min, adding to the turnaround time for reporting test results. For testing of samples sent from a clinic, the use of serum and waiting for full clot retraction are not a problem. For patients seen in the hospital where there is rapid delivery of samples to the laboratory , the clotting time can have an effect on the turnaround time for reporting a result. This is especially true if the patient is being treated with an in vivo anticoagulant, e.g., heparin, as the clotting time is prolonged. If a clinical laboratory centrifuges a blood sample without anticoagulants before there is complete clot retraction, the resulting sample will continue to form fibrin strands. This has the potential to clog probes used in automated clinical chemistry analyzers requiring maintenance. The use of plasma with an appropriate anticoagulant, e.g., heparin, can eliminate this problem of clotting. So long as the sample is thoroughly mixed with the anticoagulant present in the tube, samples can be centrifuged as soon as they are received in the laboratory with little possibility of forming strands. Results for most clinical laboratory tests show no difference when serum is used instead of plasma. A notable exception is potassium whereby values are lower in plasma. It is thought that potassium is released from platelets during the clotting process [7], and a separate reference interval may be needed. There may be differences in some other analytes, e.g., lactate dehydrogenase, and bilirubin, but this has not been consistently observed.

Pretesting for Germ Line Mutations of Relevance to

Pharmacogenomics

Pharmacogenomics testing involves genotyping for variances in the genes that participate in the pharmacokinetics and pharmacodynamics of therapeutics. There are a few enzymes such as the cytochrome p450 isoenzymes that participate in the metabolism of dozens of medications relevant to medical practice. Variants in these genes are present within the germ line. Therefore, an individual's pharmacogenomic genotype can be performed at any time. The current pharmacogenomics practice today is to perform "targeted" genotyping when a specific medication is prescribed, e.g., CYP 2C19 for clopidogrel or CYP2D6 for tricyclic antidepressants. A more efficient approach would be to profile the genotype for all of the relevant pharmacogenomics markers simultaneously and ahead of the clinical need for the information. Months or even years later, when a particular patient is in need of a medication for which pharmacogenomic testing is important for drug selection or dosing, the patient's genotype results would already be available in their medical record. Broad genomic screening of a population is more cost-efficient than individual testing of one gene "on demand." There are ethical issues for conducting broad spectrum molecular testing. Testing and disclosure of an individual's risk for development of cancer, for example, can have significant societal issues. The ethical issues for pharmacogenomics testing are not as great because the test results do not predispose an individual to acquiring any disease. Properly used pharmacogenomics testing enables a physician to improve therapeutics and avoid medications that can have significant toxicity. In this regard, determining a genetic variant has no more societal or medical consequences than identifying an individual as having a "peanut allergy."

Molecular diagnostic methods are becoming available today for genetic screening. Large DNA microarrays are used to simultaneously identify the presence of millions of single nucleotide polymorphisms . The "DMET" chip enables detection of thousands of mutations present within hundreds of relevant pharmacogenomics gene targets [8]. The recent introduction of next-generation sequencing enables detection of all genetic variants within a gene's sequence. Access to pharmacogenomics data may be a challenge for an individual who is seen in different hospitals or medical centers. Implementation of this approach would be facilitated in healthcare environments where there is electronic access to medical information. The Veterans Administration Hospital is a system that makes use of an integrated

inpatient and outpatient electronic medical records system (VistA) [9].

Summary

Improvements in resource management for the clinical chemistry laboratory are highly dependent on the existing facility, infrastructure, and management strategy. The gain in implementing a novel program may be significant in one institution and minimal in another. The most successful approaches will require a multidisciplinary effort. A change in one section of the clinical laboratory won't necessarily be applicable to another section. It is especially important to obtain input from bench level technologists who must implement changes. Gradual changes are more tolerated by the laboratory staff than large sweeping mandates. After every step, an assessment must be made to determine the effectiveness of the change. At the Massachusetts General Hospital, process improvements took over a decade to implement [10]. The end result, however, was a 26 % reduction in inpatient tests ordered per discharged patient. There is room for improvement in resource management in every hospital or medical center's laboratory medicine practices.

References

1. Wu AHB, Lewandrowski KB, Gronowski A, Grenache D, Sokoll S, Magnani B. Antiquated tests within the clinical laboratory. Am J Manag Care. 2010;16:e220–7.
[PubMed]

2. Pysher TJ, Bach PR, Lowichik A, Petersen MD, Shields LH. Chemistry test ordering patterns after elimination of predefined multitest chemistry panels in a children's hospital. Pediatr Dev Pathol. 1999;2:446–53.
[CrossRef][PubMed]

3. Kaplan IV, Levinson SS. When is a heterophile antibody not a heterophile antibody? When it is an antibody against a specific immunogen. Clin Chem. 1999;45:616–8.
[PubMed]

4. Mitchell DR, Parvin CA, Gronowski AM. Rules-based detection of discrepancies between TSH and free T4 results. Clin Chim Acta. 2003;332:89–94.
[CrossRef][PubMed]

5. Petersen PH, Fraser CG, Jorgensen L, Brandslung I, Stahl M, Gowans E, Libeer JC, Ricos C. Combination of analytical quality specifications based on biological within- and between-subject

variation. Ann Clin Biochem. 2002;38:543–50.
[CrossRef]

6. Pantanowitz L, Henricks WH, Beckwith BA. Medical laboratory informatics. Clin Lab Med. 2007;27:823–43.
[CrossRef][PubMed]

7. Miles RR, Boberts RF, Putnam AR, Roberts WL. Comparison of serum and plasma samples for measuring chemistry analytes. Clin Chem. 2004;50:1704–5.
[CrossRef][PubMed]

8. Burmester JK, Sedova M, Shapero MH, Mansfield E. DMET microarray technology for pharmacogenomics-based personalized medicine. Methods Mol Biol. 2010;632:99–124.
[CrossRef][PubMed]

9. Brown SH, Lincoln MJ, Groen PJ, Kolodner RM. VistA-US Department of Veterans Affairs national-scale HIS. Int J Med Inform. 2003;69:135–6.
[CrossRef][PubMed]

10. Kim JY, Dzik WH, Dighe AS, Lewandrowski KB. Utilization management in a large urban academic medical center. Am J Clin Pathol. 2011;135:108–18.
[CrossRef][PubMed]

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_10

10. Utilization Management in the Routine Hematology Laboratory

Joseph Rudolf[1] and Kent Lewandrowski[1]

(1) Division of Laboratory Medicine, Department of Pathology, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street, Boston, MA 02114-2696, USA

Joseph Rudolf
Email: jrudolf1@partners.org

Kent Lewandrowski (Corresponding author)
Email: KLEWANDROWSKI@mgh.harvard.edu
Email: klewandrowski@partners.org

Keywords Utilization management – Hematology – Urinalysis – Daily lab orders – Preoperative testing

Introduction

The hematology laboratory traditionally performs testing for blood and fluid cell counts, coagulation, and often urinalysis. Many hematology laboratories have been consolidated with chemistry to form centralized core laboratories. The modern hematology laboratory has undergone a major and continued transition to increasing automation over the past 50 years. Though nearing a state of total automation, there are still a select number of highly manual and skilled tasks to be performed in the hematology laboratory, especially those pertaining to microscopy. Thus, there is a divide in the hematology laboratory

menu characterized by some of the most automated tests (e.g., hemoglobin/hematocrit) and the least automated tests (e.g., manual microscopic review of leukocyte differential).

This dichotomy has a significant effect on the approach to utilization management as the hematology laboratory shares features in common with other highly automated components of the core laboratory, especially chemistry, but also more manual sections of the laboratory such as special coagulation testing. Optimizing utilization of the automated and manual components of hematology testing requires distinct approaches. As such, this chapter is divided into two sections to address the management of each component separately. Key examples of utilization management in hematology are shown in Table 10.1. Utilization management in the special coagulation laboratory is discussed in more detail in the chapter by Van Cott.

Table 10.1 Utilization management strategies for the routine hematology laboratory

Placing limits on daily orders
Discouraging preoperative orders in healthy patients
Banning obsolete laboratory tests
Institute rules for flagging abnormal CBCs to reduce manual microscopic review rates
Institute rules for flagging abnormal urinalysis findings for manual review
Use automated morphological analysis tools to improve efficiency of manual microscopic review

Utilization Management of Automated Testing

Automated complete blood count (CBC) tests comprise a significant fraction of the total requests received in the clinical laboratories. This includes CBC tests on both inpatients and outpatients. Although performed in high volume, routine hematology testing has not been as high a profile a target for utilization management as some other categories of testing. Advances in automation, which lowers the unit cost of the tests, have compensated in part for the increasing volume of requests. The complete blood count is a relatively inexpensive automated test; thus, as long as volume does not exceed the capacity of the instruments, the savings achieved by eliminating these tests is limited to the marginal variable cost of the tests (reagents and consumables) [1].

There are, however, a number of other reasons to optimize utilization of routine hematology tests. It is estimated that as much as 30 % of test requests

are of questionable indication or are unnecessary [2, 3]. This phenomenon is especially true in the hematology laboratory. For example, an estimated 56 % of patients 18 years or older receive a complete blood count at their annual general medical examination, a practice deemed unnecessary in most cases [4]. This practice has been categorized as a top five “useless” activity in general medical practice and accounts for a projected 33 million in wasted costs per year in the United States alone [4]. Among other practices, this contributes to the estimated six billion dollars in unnecessary tests and procedures performed in the United States each year [5]. Even at a low unit cost, such practices are clearly wasteful. Additionally, the instrumentation for routine hematology testing takes up valuable real estate in the core laboratory and unnecessarily clutters patient charts providing further evidence for the need to reduce unnecessary routine hematology testing [6].

In addition to the wasted costs for the health system, unnecessary hematology testing has a negative impact on patients and the way they experience care. Pain associated with phlebotomy , increased risk for hospital acquired anemia, and increased risk of transfusion due to repeated blood draws are all associated with unnecessary hematology orders [6–9]. False-positive or clinically insignificant aberrant results invariably drive additional downstream costs including follow-up testing and unnecessary diagnostic evaluations. These downstream costs also create an unpleasant experience for patients , albeit the true scope of these costs is difficult to quantify and has been poorly documented in the literature.

The key to optimizing appropriate utilization of automated hematology testing is to manage test requests prior to specimen receipt in the laboratory [1, 3]. In doing so the in-laboratory costs are eliminated, as are the costs of specimen collection and transport. Canceling such tests after they have been received in the laboratory produces proportionately less in savings and does nothing to eliminate unnecessary phlebotomy or iatrogenic anemia. Potentially divertible orders comprise four main categories—unnecessary outpatient tests, orders for daily testing on inpatients, preoperative orders, and outmoded tests (1). There is good evidence for undertaking utilization initiatives in each of these cases. Eliminating these tests can be accomplished using a variety of strategies including physician education , establishing practice guidelines, and implantation of alerts or hard stops in a provider order entry system. These strategies have been described in detail in the introductpry chapter of this book.

Daily Orders on Inpatients

Daily orders, those orders set to recur over multiple days or until discontinued, present a major opportunity for utilization management in the hematology laboratory. Daily orders impact the hematology laboratory significantly, as CBC s and coagulation tests are some of the most frequent daily orders [7]. In academic medical centers , house staff may place daily orders for routine tests on all of their patients to save time, obviating the need to consider on each day what tests are actually needed for their patients. However, they may not review the results daily or remember to discontinue orders when they are no longer needed. The most common tests that are typically ordered “daily until discontinued” are the CBC , basic metabolic panel, and calcium/magnesium/phosphate.

A number of decision support strategies have been applied to reduce the use of daily laboratory testing with marked reductions in test usage. Some well-studied interventions for impacting daily order rates include physician education and the collaborative establishment of laboratory test guidelines and formularies with clinical services [2, 3, 10–14]. These strategies are often coupled with initiatives to change the test ordering culture toward mindful ordering of laboratory tests on a daily basis, emphasizing those which will impact the patients trajectory of care, instead of a “set it and forget it” model [7, 13, 15]. Education alone often has a fleeting effect on reducing daily orders [14]. Building hard stops or alerts into an order entry system is much more effective. An important part of any educational initiative regarding test order behavior is provider auditing and feedback (physician profiling) as this increases the durability of the response (Fig. 10.1) [2, 3, 16–18].

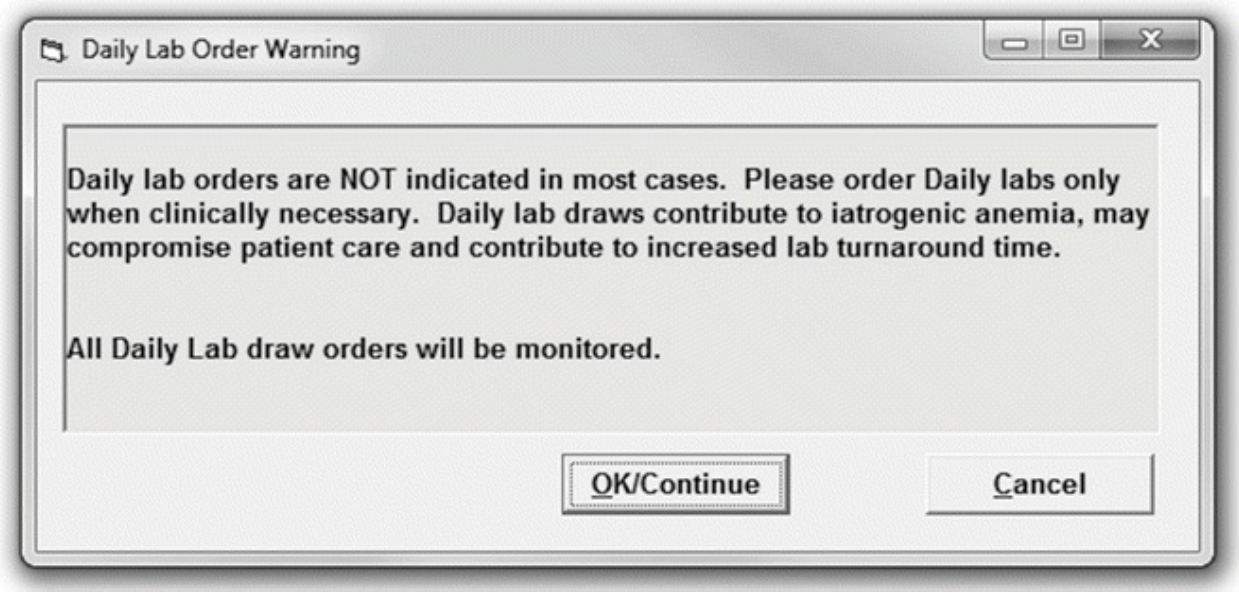


Fig. 10.1 Electronic decision support pop-up message discouraging routine daily orders

For institutions where eliminating daily orders may not be achievable, the simple act of restricting order frequency to once daily in patients who are not actively bleeding can have significant effects on hematology test volumes [1, 14, 19]. Interruptive alerts where providers must call the laboratory to override duplicate orders within a given day (hard stops) have been shown to be more effective than soft stops, or order message alerts, at reducing duplicate orders [5]. However, simple activities that make test ordering more cumbersome through prompts, alerts, or test unbundling have been shown to be effective deterrents against frequent orders [5, 11]. Displaying fee data is another gentle but moderately effective technique for bending the order volume curve [20, 21].

Some institutions have established mechanisms to eliminate daily orders using provider order entry systems to block or eliminate the option to prospectively order tests on a daily basis [14, 22]. At many institutions with policies limiting daily orders, the intensive care unit is a special exception. In critically ill unstable patients, daily laboratory tests may be appropriate [10, 13, 23]. However, which tests should be ordered daily or more frequently depends on the patient. It has previously been demonstrated that practice guidelines concerning daily orders in an intensive care unit can significantly reduce daily orders without impacting morbidity, mortality, or length of stay [13, 22].

Guidelines are emerging that support significantly limiting daily orders.

The American Association of Blood Banks and the Critical Care Societies Collaborative advocate against daily lab orders through the American Board of Internal Medicine Foundation's Choosing Wisely campaign [24]. Putting these guidelines into practice requires a significant culture change among physicians , especially house staff in academic medical centers. However, consensus is starting to emerge for the need to reduce daily laboratory test orders, and this has significant implications for hematology test volumes.

Preoperative Orders

The routine use of preoperative laboratory screening tests directly paralleled the development of automated hematology instruments in the 1960s [25]. At that time it was believed that having more laboratory data on patients would improve patient safety and outcomes [25]. However, in many cases, especially those involving presumptively healthy routine surgery patients, the opposite is true.

It is estimated that 18 billion dollars is spent annually on preoperative testing in the United States [26, 27]. The CBC and routine coagulation testing are among the most frequently ordered preoperative tests. The majority of patients undergoing outpatient surgery, even those with no indication for testing, receive some preoperative laboratory testing [26, 28–30]. Eighty percent of preoperative laboratory tests are ordered by surgeons [26]. When abnormal test results are discovered, they change patient management in only a small minority of cases [28]. The implied goal of preoperative testing is to identify abnormalities that could affect anesthesia or surgical outcomes [26, 27]. It is then reasonable to ask should physicians perform preoperative laboratory screening if the results are not used to change management.

Nonselective preoperative testing invariably leads to many borderline and false-positive results [25]. For screening tests to be beneficial, the prevalence of a disease needs to be at least 1–5 % [31]. In practice the rate of abnormal hematology tests in low-risk surgical patients does not meet this threshold. For example, a retrospective study of low-risk, outpatient, surgical candidates demonstrated a rate of anemia (≤9 mg/dL hemoglobin) of 0.8 %. A prevalence rate of <1 % is not sufficient to yield significant screening benefit and is more likely to produce false-positive results than reveal true disease [26].

Approximately 60 % of surgical procedures performed in North America are outpatient procedures, those lasting less than 2 h with low rates of

complications [26, 27]. These procedures are by definition low risk and have pretest probabilities of disease which do not warrant screening [27]. Studies of preoperative testing in cerebral angiography, tonsillectomy/adenoidectomy, pediatric and adult neurosurgery, and plastic surgery have further confirmed this conclusion [29, 32–37]. For this reason a number of institutions have developed guidelines for preoperative testing.

The realization of the low value of screening preoperative tests led the American Society of Anesthesiologists (ASA) to recommend against preoperative laboratory screening tests in most patients, advocating instead for selective screening based on a patient's medical history [38, 39]. This recommendation was put forth in 2002 and reaffirmed by the group in 2012 [38, 39]. In addition to the ASA, the American Society of Clinical Pathology and the Society of Thoracic Surgeons have supported the proposal in the recent Choosing Wisely campaign [24].

There are a number of cases in which preoperative laboratory testing may be indicated. Common indications include patients who are at increased risk of complications due to a personal history of anemia/bleeding/bruising; are on anticoagulation; have liver disease, metastatic tumors; or are expected to experience blood loss greater than 500 mL [26, 27, 40]. When selective criteria are applied to preoperative laboratory testing, the rate of test abnormalities increases to approximately 30 %, a sufficient pretest probability to warrant their use [27].

Though there is a clear consensus that preoperative laboratory screening is unnecessary in most patients and guidelines have been issued, no study has been done to date on the effectiveness of utilization management strategies to encourage/enforce these guidelines. To the extent that routine hematology tests are among the most common preoperative tests, this is an area that should be a focus of utilization management activities.

Unnecessary/Obsolete Tests

Reducing the utilization of outmoded tests in the clinical laboratory is challenging as order practices can be entrenched, especially in more senior staff [2]. There are two tests in the hematology laboratory that consensus has determined to be outmoded, iron-binding capacity (IBC) and bleeding time [1, 19, 41, 42]. Guidelines and policy changes regarding the ordering of iron-binding capacity, recommending ferritin as a first-line test followed by discontinuation of the IBC order, have been shown to be effective [43].

Restricting IBC test ordering to specific provider groups has also been shown to be an effective strategy [19]. There is no published literature on interventions for reducing bleeding time orders. However, this is widely considered to be an obsolete test that should be removed from test menus [1, 24, 42]. In our institution, we discontinued the bleeding time test over 15 years ago. This was accomplished by working collaboratively with the leadership in cardiac surgery to develop an evidence-based presentation to surgical specialties that had previously utilized the test.

Those tests which are near obsolescence and thus overutilized are another category of tests amenable to utilization management initiatives. One such example in the hematology laboratory is the assessment of serum folate in patients with anemia. Folate is required for the synthesis and maintenance of deoxyribonucleic acids (DNA) , and folate deficiency is a known cause of megaloblastic, macrocytic anemia [44, 45].

While a historically important cause of macrocytic anemia , the prevalence of folate deficiency has decreased substantially in many countries with the implementation of mandatory folic acid food fortification [44, 46]. For example, mandatory folic acid fortification of flour in the United States in the 1990s resulted in decrease in the prevalence of folate deficiency from an estimated 3–16 % to approximately 0.5 % [46]. Despite this reduction in prevalence, recommendations for folate testing have remained in clinical algorithms for the workup of anemia [46]. This despite substantial evidence of low yield in a variety of patients [41, 46]. For example, a search of 2014 folate test data for inpatients and outpatients at the Massachusetts General Hospital revealed only one folate-deficient patient and four patients with borderline folate deficiency among more than 11,000 ordered folate tests. It has also been shown that folate is frequently repeated, even in cases where it is determined to be in the normal range [47]. Given its low yield in folic acid-fortified populations, utilization management strategies to decrease folate testing should be considered. Reduction in folate assessment by as much as 60 % has previously been shown through an electronic test order unbundling strategy [48].

Utilization Management of Manual Testing

The most labor-intensive tasks in the hematology laboratory involve the microscopic review of pathologic elements in the blood, body fluids, and

urine. Manual review is costly in terms of both time and money [49]. Unnecessary manual review increases the workload of technologists, thereby decreasing productivity [50]. Despite being the gold standard for blood differential analysis , manual review also suffers from high inter- and intra-observer variation [51]. Automated analyzers play an important role in screening fluids for pathologic elements meriting review [52]. There are significant utilization management gains to be realized by decreasing the numbers of specimens requiring manual review through the use of instrument flagging criteria. The biggest challenge in implementing flagging criteria is ensuring that the reduction of manual review does not result in the laboratory missing significant clinical findings [50]. This is especially challenging in tertiary care medical centers where the pretest probability of disease and therefore the rates of abnormal findings are high [50].

Rules for Decreasing Hematology Review

Significant advancements have been made in automated hematology analyzers allowing for both high throughputs while maintaining consistent analytical performance [50]. However, up until the most recent generation of analyzers, instrument flagging resulted in around 30 % of CBC differentials requiring manual review [51]. Of these approximately half required a full manual differential, while the other half were released upon review, indicating a high rate of false-positive flagging [50, 51].

The Clinical Laboratory Standards Institute (CLSI) and the International Society for Laboratory Hematology (ISLH) have established criteria for the verification of flagging claims supplied by manufacturers and recommended flagging criteria [53–55]. The ISLH recommends manual review when the following are identified by an automated instrument: any blasts, >1 % immature granulocytes, >5 % atypical lymphocytes, or at least 1 % nucleated red blood cells [53].

Instruments vary in their flagging accuracy for each of these criteria [49]. The newest automated hematology instruments have made significant gains in reducing false-positive flags, including those generated by monocytes mis-categorized as blasts, a common issue with older analyzers [50, 56]. These advancements have driven manual review rates to as low as 9 % in some institutions [56]. Individual rule sets should be validated by each laboratory due to the variation in the prevalence of disease in different populations (Fig. 10.2) [55].

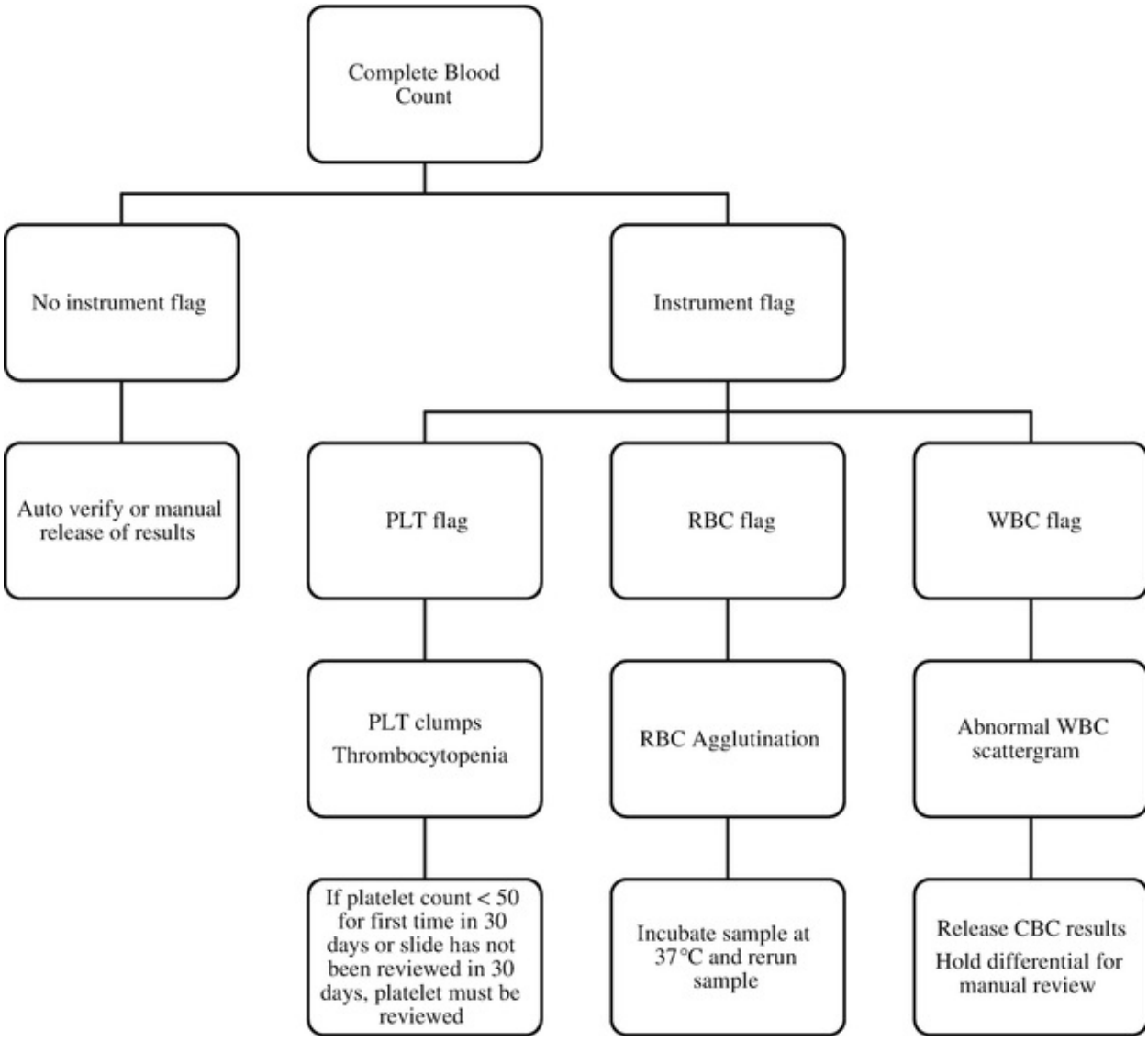


Fig. 10.2 Simplified sample flow chart of instrument flagging criteria used at the Massachusetts General Hospital . *CBC* complete blood count, *PLT* platelet, *RBC* red blood cell, *WBC* white blood cell

Manual reviews can also be reduced by intervening with the clinician at the time the test is ordered. Many patients have known but relatively stable abnormalities on their CBC that do not need to be rereviewed when repetitive blood counts are requested over relatively short time periods (e.g., hours or days). Providing clinicians with an option to order “CBC with auto diff” only followed by an effort at physician education may reduce the number of unnecessary manual differentials. Also, in some cases, the clinician orders a CBC when all they really need is a hemoglobin, hematocrit, or platelet count. Providing an option for selective ordering will facilitate this effort and

eliminate repetitive manual reviews in patients being monitored for potentially clinically significant bleeding.

In cases where manual microscopic review is required, the emergence of automated slide maker-stainers and blood smear analysis by imaging technology have significantly decreased costs associated with technologist labor. These systems rapidly scan slides and then sort cellular findings by cell class, allowing for rapid review and release of results by technologists (Fig. 10.3). Previous studies have shown increases in speed, efficiency, and turnaround time for manual differentials with the use of automated morphological analysis with result review [51, 57]. These systems provide added benefits in terms of the ability to easily review the previous work, identify small numbers of abnormal cells which may be missed by technologists , and decrease interobserver variability [57]. As such, they provide improvements in quality and safety of care in addition to reducing technologist labor.

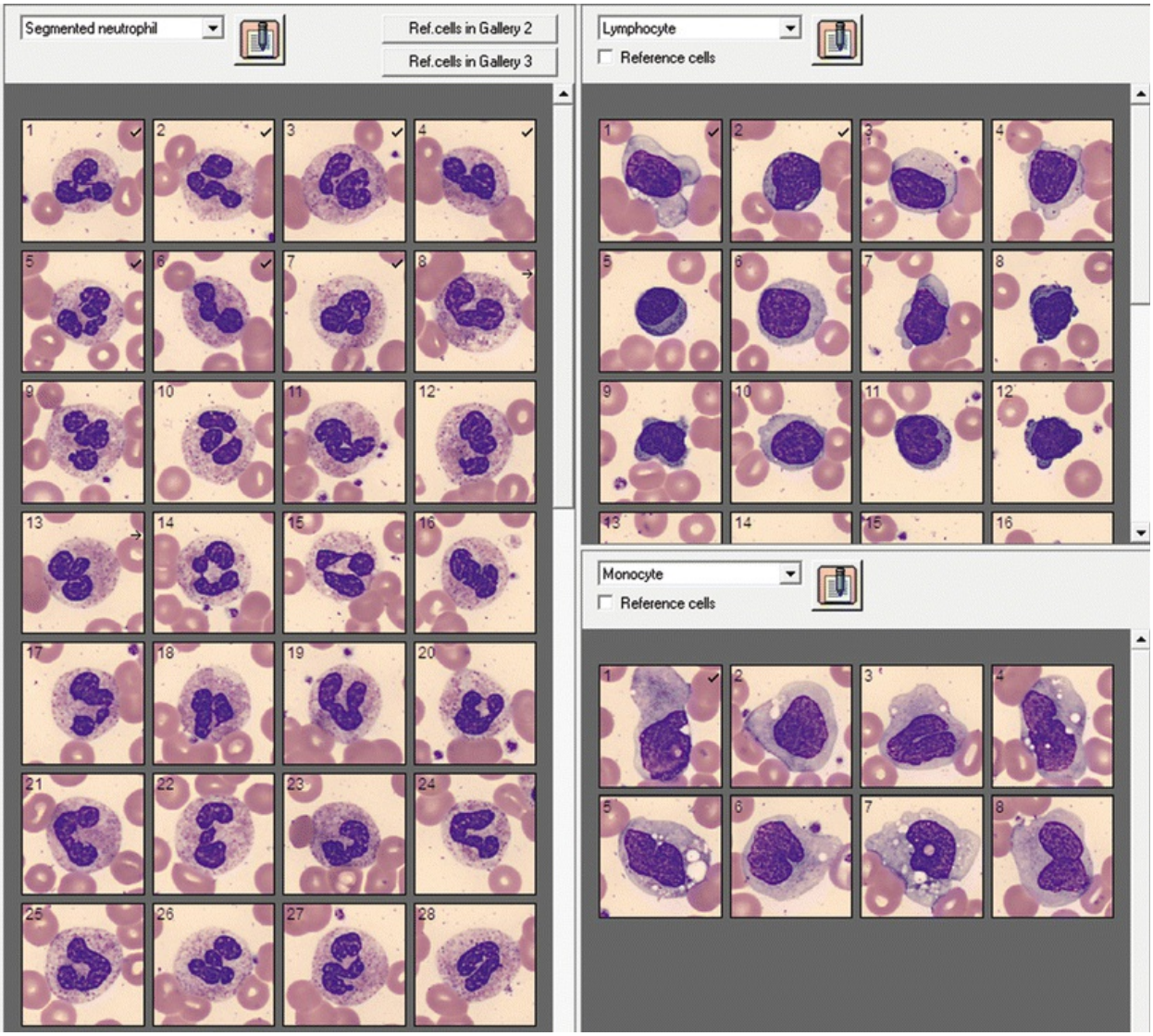


Fig. 10.3 Screen shot of an automated complete blood count image-based morphological analysis platform

Rules for Decreasing Urinalysis Review

Though not strictly a hematology test, urinalysis often falls under the purview of the hematology laboratory. Urinalysis consists of dipstick chemical analysis and visual microscopy in a subset of cases [58]. It is an analogous system to the process of automated hematology testing with reflex to manual microscopy in the case of screening abnormalities. Like automated hematology, urinalysis is a high volume test, with high labor costs associated with manual review [58, 59].

Like automated hematology, modern urinalysis platforms also offer

decision support software for the entry of flagging rules [59]. Examples of urinalysis flags include the presence of red blood cells, white blood cells, hyaline casts, bacteria, and epithelial cells [59]. As with hematology flags, urinalysis flags need to be validated in each individual laboratory [59, 60]. Optimization of flagging protocols can result in review rates of 40–55 % with false-negative rates in the 2–5 % range [59, 60].

One of the largest opportunities for utilization management in urinalysis is the workup of urinary tract infections (UTI) . As many as 80 % of urinalyses will ultimately be determined to be culture negative [61]. Of the positive results, contamination occurs in approximately 30 % of cases [62]. Much recent work has focused on the optimization of urinalysis to rule out UTI [62–64]. Deferring some of these culture workups will result in significant savings for both the hematology and microbiology laboratories (see chapter on utilization management in microbiology). It would also prevent patients from needless antibiotic exposure while awaiting culture results, a process which takes at least 18 h but can often take 24–48 h [64]. Screening algorithms have been developed that achieve negative predictive values of approximately 90 % [63, 64]. This has generally been considered not sufficiently high for use in all patients, particularly those with the potential for a complicated UTI, but may be suitable for those under close clinical supervision or who are asymptomatic or have possible uncomplicated UTI, the most common clinical situation [63, 64].

Current systems are limited in their ability to accurately identify some pathologic elements including renal tubular epithelial cells, transitional epithelial cells, lipids, and some casts [58]. As such, automated urinalysis alone is not a sufficient screening mechanism for patients with suspected kidney injury though it may be suitable for use in asymptomatic patients [65]. Concordance for other cellular elements including red and white blood cells is quite good [65, 66]. Technologies for automated urinalysis technology are quickly maturing, but further development will be required for these devices to be sufficiently analytically proficient to have a substantial impact on culture rates and some types of manual review.

Utilization Management of Routine Specialized Tests : The Anemia Algorithm

The automation and consolidation of hematology platforms with chemistry

instruments on automated track lines are providing new opportunities for utilization management through the use of automated diagnostic reflex algorithms. One notable example is the routine laboratory workup of anemia. The evaluation of anemia is based in large part on laboratory results including hematocrit and mean corpuscular volume, and this directs the need for subsequent tests.

Multiple algorithms have been proposed for the evaluation of anemia in both adults and children [67–70]. However, historically the decision of which tests to order for the evaluation of anemia and when to order them has been left to individual physicians [71]. This results in significant variation in practice and the ordering of unnecessary batteries of tests [71].

In recent years, proposals have emerged to automate the laboratory workup of anemia using diagnostic reflex protocols based on laboratory results [71, 72]. Using such algorithms, the results of preliminary CBC data are used to drive further laboratory evaluation while eliminating tests that are unnecessary as shown in Fig. 10.4. For example, patients with a microcytic anemia may subsequently be tested for ferritin, while those with a macrocytic anemia might be preferentially tested for vitamin B12 deficiency. Without an algorithm, physicians often end up ordering all possible tests up front.

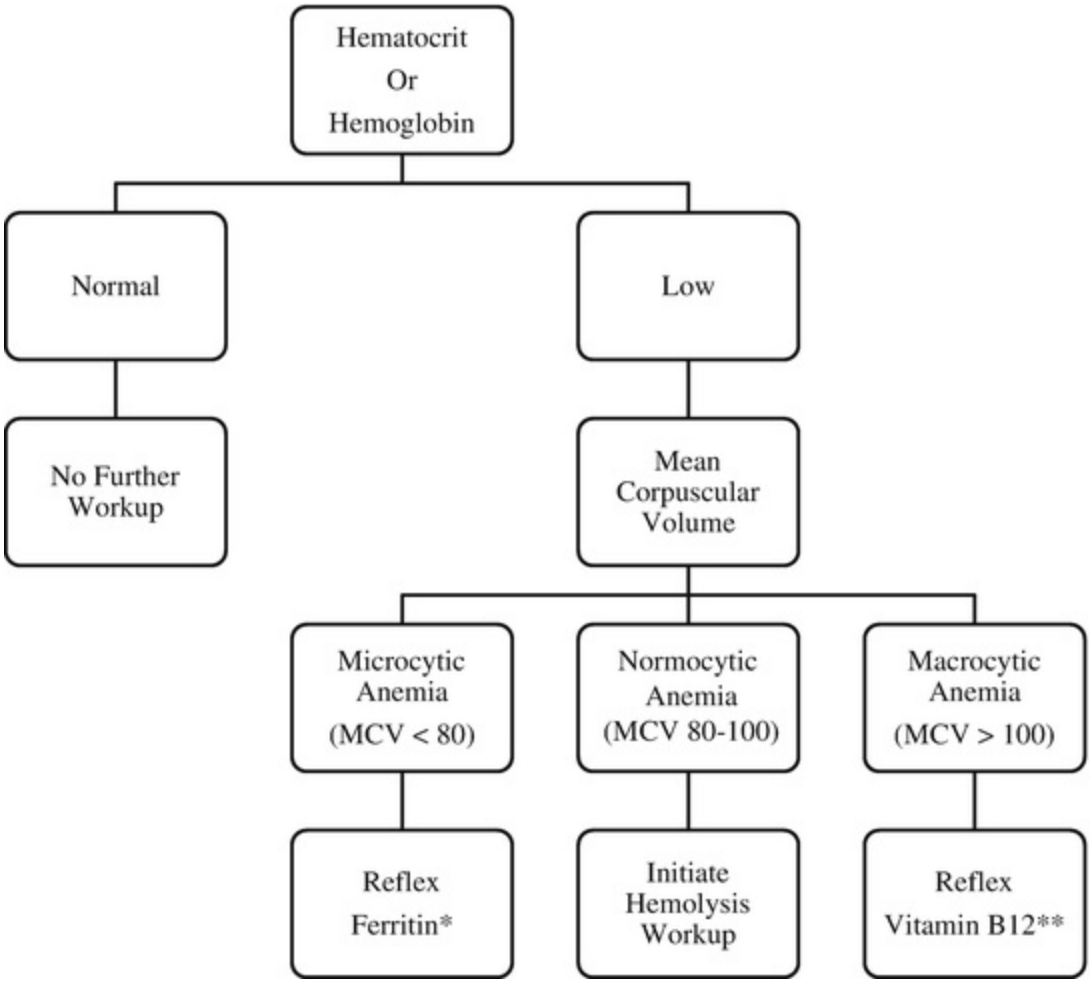


Fig. 10.4 Sample algorithm for anemia workup based on laboratory-driven parameters. Algorithms such as this could be easily automated in the hematology laboratory to increase the efficiency of laboratory anemia evaluations. *MCV* mean corpuscular volume. *Many published algorithms include total iron-binding capacity (TIBC) and iron (Fe). **Many published algorithms include folate testing

Prior to the automation and consolidation of core laboratory test platforms, reflex algorithms such as the anemia algorithm would not have been operationally practical as different tests were often performed on separate instruments. Finding and reloading specimens on multiple instruments would have required significant manual labor. In the modern consolidated hematology laboratory, reflex algorithms can be implemented through instrument-level rule sets , and subsequent add-on testing can occur automatically. As such, automated reflex algorithms for anemia assessment are likely to enter the clinical workflow in the coming years.

Future Technologies Impacting Utilization in the Hematology Laboratory

The last decade has seen the introduction of new image analysis technologies for the automation of morphological analysis in the hematology laboratory [51]. While currently used to improve the efficiency of manual microscopic review of hematology smears, research is underway which suggests that these systems may be capable of autonomously classifying more pathologic elements than previously recognized [73, 74]. Similar image analysis technologies are also available for urinalysis. These advances among others will no doubt continue the trend toward total automation in the hematology laboratory . When achieved, total automation will help to solve some of the utilization management issues associated with manual labor-intensive tests , by significantly reducing the unit cost of these tests. Savings can therefore be achieved by two different approaches: eliminating unnecessary tests altogether or decreasing the unit cost of the tests that are performed, or both.

References

1. Ng VL. Utilization management in the core laboratory. Clin Chim Acta. 2014;427:154–7. [CrossRef][PubMed]

2. Janssens PM. Managing the demand for laboratory testing: options and opportunities. Clin Chim Acta. 2010;411(21–22):1596–602. [CrossRef][PubMed]

3. Fryer AA, Smellie WS. Managing demand for laboratory tests: a laboratory toolkit. J Clin Pathol. 2013;66(1):62–72. [CrossRef][PubMed]

4. Kale MS, Bishop TF, Federman AD, Keyhani S. “Top 5” lists top $5 billion. Arch Intern Med. 2011;171(20):1856–8. [CrossRef][PubMed]

5. Procop GW, Keating C, Stagno P, Kottke-Marchant K, Partin M, Tuttle R, et al. Reducing duplicate testing: a comparison of two clinical decision support tools. Am J Clin Pathol. 2015;143(5):623–6. [CrossRef][PubMed]

6. Malone B. How can labs tackle utilization of high-volume, low-cost tests? AACC; 2013 [cited 12 July 2015]. https://www.aacc.org/publications/cln/articles/2013/september/daily-blood.

7. Thakkar RN, Kim D, Knight AM, Riedel S, Vaidya D, Wright SM. Impact of an educational intervention on the frequency of daily blood test orders for hospitalized patients. Am J Clin Pathol. 2015;143(3):393–7.
[CrossRef][PubMed]

8. Lyon AW, Chin AC, Slotsve GA, Lyon ME. Simulation of repetitive diagnostic blood loss and onset of iatrogenic anemia in critical care patients with a mathematical model. Comput Biol Med. 2013;43(2):84–90.
[CrossRef][PubMed]

9. Thavendiranathan P, Bagai A, Ebidia A, Detsky AS, Choudhry NK. Do blood tests cause anemia in hospitalized patients? The effect of diagnostic phlebotomy on hemoglobin and hematocrit levels. J Gen Intern Med. 2005;20(6):520–4.
[CrossRef][PubMed][PubMedCentral]

10. Wang TJ, Mort EA, Nordberg P, Chang Y, Cadigan ME, Mylott L, et al. A utilization management intervention to reduce unnecessary testing in the coronary care unit. Arch Intern Med. 2002;162(16):1885–90.
[CrossRef][PubMed]

11. Neilson EG, Johnson KB, Rosenbloom ST, Dupont WD, Talbert D, Giuse DA, et al. The impact of peer management on test-ordering behavior. Ann Intern Med. 2004;141(3):196–204.
[CrossRef][PubMed]

12. Wilson ML. Decreasing inappropriate laboratory test utilization: controlling costs and improving quality of care. Am J Clin Pathol. 2015;143(5):614–6.
[CrossRef][PubMed]

13. Kumwilaisak K, Noto A, Schmidt UH, Beck CI, Crimi C, Lewandrowski K, et al. Effect of laboratory testing guidelines on the utilization of tests and order entries in a surgical intensive care unit. Crit Care Med. 2008;36(11):2993–9.
[CrossRef][PubMed]

14. May TA, Clancy M, Critchfield J, Ebeling F, Enriquez A, Gallagher C, et al. Reducing unnecessary inpatient laboratory testing in a teaching hospital. Am J Clin Pathol. 2006;126(2):200–6.
[CrossRef][PubMed]

15. Sponsler KC, Keriwala DV, Flemmons KD, Szentirmai E, Kapp ME, Iams WT, et al. Reduction of daily lab testing among general medicine services is associated with significant cost savings and lab free days. 2015. http://www.shmabstracts.com/abstract/reduction-of-daily-lab-testing-among-general-medicine-services-is-associated-with-significant-cost-savings-and-lab-free-days/.

16. Gama R, Nightingale PG, Broughton PM, Peters M, Ratcliffe JG, Bradby GV, et al. Modifying the request behaviour of clinicians. J Clin Pathol. 1992;45(3):248–9.
[CrossRef][PubMed][PubMedCentral]

17. Bareford D, Hayling A. Inappropriate use of laboratory services: long term combined approach to modify request patterns. BMJ. 1990;301(6764):1305–7.
[CrossRef][PubMed][PubMedCentral]

18. Miyakis S, Karamanof G, Liontos M, Mountokalakis TD. Factors contributing to inappropriate ordering of tests in an academic medical department and the effect of an educational feedback

strategy. Postgrad Med J. 2006;82(974):823–9.
[CrossRef][PubMed][PubMedCentral]

19. Calderon-Margalit R, Mor-Yosef S, Mayer M, Adler B, Shapira SC. An administrative intervention to improve the utilization of laboratory tests within a university hospital. Int J Qual Health Care. 2005;17(3):243–8.
[CrossRef][PubMed]

20. Feldman LS, Shihab HM, Thiemann D, Yeh HC, Ardolino M, Mandell S, et al. Impact of providing fee data on laboratory test ordering: a controlled clinical trial. JAMA Intern Med. 2013;173(10):903–8.
[CrossRef][PubMed]

21. Stuebing EA, Miner TJ. Surgical vampires and rising health care expenditure: reducing the cost of daily phlebotomy. Arch Surg (Chicago, IL: 1960). 2011;146(5):524–7.

22. Pageler NM, Franzon D, Longhurst CA, Wood M, Shin AY, Adams ES, et al. Embedding time-limited laboratory orders within computerized provider order entry reduces laboratory utilization. Pediatr Crit Care Med. 2013;14(4):413–9.
[CrossRef][PubMed]

23. Ioulia I, Hayley M, Tara C, Georgia G, Neda A, Nazli B, et al. Implementation of an on-demand strategy for routine blood testing in ICU patients. D23 QUALITY IMPROVEMENT IN CRITICAL CARE. American Thoracic Society International Conference Abstracts: American Thoracic Society. 2013; A5322–A.

24. American Board of Internal Medicine. Choosing wisely campaign. http://www.choosingwisely.org/.

25. Kumar A, Srivastava U. Role of routine laboratory investigations in preoperative evaluation. J Anaesthesiol Clin Pharmacol. 2011;27(2):174–9.
[CrossRef][PubMed][PubMedCentral]

26. Benarroch-Gampel J, Riall TS. What laboratory tests are required for ambulatory surgery? Adv Surg. 2013;47:81–98.
[CrossRef][PubMed]

27. Richman DC. Ambulatory surgery: how much testing do we need? Anesthesiol Clin. 2010;28(2):185–97.
[CrossRef][PubMed]

28. Soares Dde S, Brandao RR, Mourao MR, Azevedo VL, Figueiredo AV, Trindade ES. Relevance of routine testing in low-risk patients undergoing minor and medium surgical procedures. Braz J Anesthesiol. 2013;63(2):197–201.
[CrossRef][PubMed]

29. Seicean A, Schiltz NK, Seicean S, Alan N, Neuhauser D, Weil RJ. Use and utility of preoperative hemostatic screening and patient history in adult neurosurgical patients. J Neurosurg. 2012;116(5):1097–105.
[CrossRef][PubMed]

30.

Benarroch-Gampel J, Sheffield KM, Duncan CB, Brown KM, Han Y, Townsend Jr CM, et al. Preoperative laboratory testing in patients undergoing elective, low-risk ambulatory surgery. Ann Surg. 2012;256(3):518–28.
[CrossRef][PubMed][PubMedCentral]

31. Olson RP, Stone A, Lubarsky D. The prevalence and significance of low preoperative hemoglobin in ASA 1 or 2 outpatient surgery candidates. Anesth Analg. 2005;101(5):1337–40.
[CrossRef][PubMed]

32. Rai AT, Domico J. Routine pre-procedure laboratory testing for patients undergoing outpatient cerebral angiography is not indicated. J Neurointerv Surg. 2013;5(2):172–6.
[CrossRef][PubMed]

33. Almesbah F, Mandiwanza T, Kaliaperumal C, Caird J, Crimmins D. Routine preoperative blood testing in pediatric neurosurgery. J Neurosurg Pediatr. 2013;12(6):615–21.
[CrossRef][PubMed]

34. Bhasin N, Parker RI. Diagnostic outcome of preoperative coagulation testing in children. Pediatr Hematol Oncol. 2014;31(5):458–66.
[CrossRef][PubMed]

35. Fowler A, Perry DJ. Laboratory monitoring of haemostasis. Anaesthesia. 2015;70 Suppl 1:68–72, e24.

36. Fischer JP, Shang EK, Nelson JA, Wu LC, Serletti JM, Kovach SJ. Patterns of preoperative laboratory testing in patients undergoing outpatient plastic surgery procedures. Aesthet Surg J. 2014;34(1):133–41.
[CrossRef][PubMed]

37. Samkova A, Blatny J, Fiamoli V, Dulicek P, Parizkova E. Significance and causes of abnormal preoperative coagulation test results in children. Haemophilia. 2012;18(3):e297–301.
[CrossRef][PubMed]

38. American Society of Anesthesiologists Task Force on Preanesthesia Evaluation. Practice advisory for preanesthesia evaluation: a report by the American Society of Anesthesiologists Task Force on Preanesthesia Evaluation. Anesthesiology. 2002;96(2):485–96.
[CrossRef]

39. Apfelbaum JL, Connis RT, Nickinovich DG, Pasternak LR, Arens JF, Caplan RA, et al. Practice advisory for preanesthesia evaluation: an updated report by the American Society of Anesthesiologists Task Force on Preanesthesia Evaluation. Anesthesiology. 2012;116(3):522–38.
[CrossRef][PubMed]

40. Feely MA, Collins CS, Daniels PR, Kebede EB, Jatoi A, Mauck KF. Preoperative testing before noncardiac surgery: guidelines and recommendations. Am Fam Physician. 2013;87(6):414–8.
[PubMed]

41. Salinas M, Lopez-Garrigos M, Flores E, Uris J, Leiva-Salinas C. Potential over request in anemia laboratory tests in primary care in Spain. Hematology. 2015;20(6):368–73.
[CrossRef][PubMed]

42. Kiechle FL, Arcenas RC, Rogers LC. Establishing benchmarks and metrics for disruptive

technologies, inappropriate and obsolete tests in the clinical laboratory. Clin Chim Acta. 2014;427:131–6.
[CrossRef][PubMed]

43. van Walraven C, Goel V, Chan B. Effect of population-based interventions on laboratory utilization: a time-series analysis. JAMA. 1998;280(23):2028–33.
[CrossRef][PubMed]

44. Crider KS, Bailey LB, Berry RJ. Folic acid food fortification-its history, effect, concerns, and future directions. Nutrients. 2011;3(3):370–84.
[CrossRef][PubMed][PubMedCentral]

45. Carmel R. Megaloblastic anemias: disorders of impaired DNA synthesis. In: Greer J, Arber D, Bertil G, List A, Means R, Paraskevas F, et al., editors. Wintrobe's clinical hematology. Philadelphia: Lippincott Williams & Wilkins; 2014. p. 927–53.

46. Theisen-Toupal J, Horowitz GL, Breu AC. Utility, charge, and cost of inpatient and emergency department serum folate testing. J Hosp Med. 2013;8(2):91–5.
[CrossRef][PubMed]

47. Ganiyu-Dada Z, Bowcock S. Repeat haematinic requests in patients with previous normal results: the scale of the problem in elderly patients at a district general hospital. Int J Lab Hematol. 2011;33(6):610–3.
[CrossRef][PubMed]

48. Kahan NR, Waitman DA, Vardy DA. Curtailing laboratory test ordering in a managed care setting through redesign of a computerized order form. Am J Manag Care. 2009;15(3):173–6.
[PubMed]

49. Depoorter M, Goletti S, Latinne D, Defour J. Optimal flagging combinations for best performance of five blood cell analyzers. Int J Lab Hematol. 2015;37(1):63–70.
[CrossRef][PubMed]

50. Seo JY, Lee ST, Kim SH. Performance evaluation of the new hematology analyzer Sysmex XN-series. Int J Lab Hematol. 2015;37(2):155–64.
[CrossRef][PubMed]

51. Kratz A, Bengtsson HI, Casey JE, Keefe JM, Beatrice GH, Grzybek DY, et al. Performance evaluation of the CellaVision DM96 system: WBC differentials by automated digital image analysis supported by an artificial neural network. Am J Clin Pathol. 2005;124(5):770–81.
[CrossRef][PubMed]

52. Bruegel M, Nagel D, Funk M, Fuhrmann P, Zander J, Teupser D. Comparison of five automated hematology analyzers in a university hospital setting: Abbott Cell-Dyn Sapphire, Beckman Coulter DxH 800, Siemens Advia 2120i, Sysmex XE-5000, and Sysmex XN-2000. Clin Chem Lab Med. 2015;53(7):1057–71.
[CrossRef][PubMed]

53. Barnes PW, McFadden SL, Machin SJ, Simson E. The international consensus group for hematology review: suggested criteria for action following automated CBC and WBC differential analysis. Lab Hematol. 2005;11(2):83–90.

[CrossRef][PubMed]

54. Koepke JA, Assendelft OWV, Brindza LJ, Davis BH, Fernandes BJ, Gewirtz AS, et al. H20-A2. Reference leukocyte (WBC) differential count (proportional) and evaluation of instrumental methods; approved standard—second edition, vol. 27(4). Clinical and Laboratory Standards Institute; 2007.

55. Rabinovitch A, Barnes P, Curcio KM, Dorman J, Huisman A, Nguyen L, et al. H26-A2. Validation, verification, and quality assurance of automated hematology analyzers; approved standard—second edition, vol. 30(14). Clinical and Laboratory Standards Institute; 2010.

56. Hotton J, Broothaers J, Swaelens C, Cantinieaux B. Performance and abnormal cell flagging comparisons of three automated blood cell counters: Cell-Dyn Sapphire, DxH-800, and XN-2000. Am J Clin Pathol. 2013;140(6):845–52.
[CrossRef][PubMed]

57. VanVranken SJ, Patterson ES, Rudmann SV, Waller KV. A survey study of benefits and limitations of using CellaVision DM96 for peripheral blood differentials. Clin Lab Sci. 2014;27(1):32–9.
[PubMed]

58. Zaman Z. Automated urine screening devices make urine sediment microscopy in diagnostic laboratories economically viable. Clin Chem Lab Med. 2015;53 Suppl 2:s1509–11.
[PubMed]

59. Khejonnit V, Pratumvinit B, Reesukumal K, Meepanya S, Pattanavin C, Wongkrajang P. Optimal criteria for microscopic review of urinalysis following use of automated urine analyzer. Clin Chim Acta. 2015;439:1–4.
[CrossRef][PubMed]

60. Du J, Xu J, Wang F, Guo Y, Zhang F, Wu W, et al. Establishment and development of the personalized criteria for microscopic review following multiple automated routine urinalysis systems. Clin Chim Acta. 2015;444:221–8.
[CrossRef][PubMed]

61. Okada H, Sakai Y, Miyazaki S, Arakawa S, Hamaguchi Y, Kamidono S. Detection of significant bacteriuria by automated urinalysis using flow cytometry. J Clin Microbiol. 2000;38(8):2870–2.
[PubMed][PubMedCentral]

62. Kayalp D, Dogan K, Ceylan G, Senes M, Yucel D. Can routine automated urinalysis reduce culture requests? Clin Biochem. 2013;46(13–14):1285–9.
[CrossRef][PubMed]

63. Sterry-Blunt RE, Randall K, Doughton M, Aliyu S, Enoch D. Screening urine samples for the absence of urinary tract infection using the sediMAX automated microscopy analyser. J Med Microbiol. 2015;64(6):605–9.
[CrossRef][PubMed]

64. Luciano R, Piga S, Federico L, Argentieri M, Fina F, Cuttini M, et al. Development of a score based on urinalysis to improve the management of urinary tract infection in children. Clin Chim Acta. 2012;413(3–4):478–82.

[CrossRef][PubMed]

65. Sharda N, Bakhtar O, Thajudeen B, Meister E, Szerlip H. Manual urine microscopy versus automated urine analyzer microscopy in patients with acute kidney injury. Lab Med. 2014;45(4):e152–5.
[CrossRef][PubMed]

66. Lamchiagdhase P, Preechaborisutkul K, Lomsomboon P, Srisuchart P, Tantiniti P, Khan-u-Ra N, et al. Urine sediment examination: a comparison between the manual method and the iQ200 automated urine microscopy analyzer. Clin Chim Acta. 2005;358(1–2):167–74.
[CrossRef][PubMed]

67. Djulbegovic B, Hadley T, Pasic R. A new algorithm for diagnosis of anemia. Postgrad Med. 1989;85(5):119–22, 127–30.

68. Killip S, Bennett JM, Chambers MD. Iron deficiency anemia. Am Fam Physician. 2007;75(5):671–8.
[PubMed]

69. Kline NE. A practical approach to the child with anemia. J Pediatr Health Care. 1996;10(3):99–105.
[CrossRef][PubMed]

70. Means R, Glader B. Anemia: general considerations. In: Greer J, Arber D, Bertil G, List A, Means R, Paraskevas F, et al., editors. Wintrobe's clinical hematology. Philadelphia: Lippincott Williams & Wilkins; 2014. p. 587–616.

71. Haq SM. Anemia analyzer: algorithm and reflex testing in clinical practice leading to efficiency and cost savings. Stud Health Technol Inform. 2009;143:14–6.
[PubMed]

72. Wu AH. Reflex testing III: efficient use of laboratory markers for anemia. Clin Chim Acta. 2004;343(1–2):241–3.
[CrossRef][PubMed]

73. Mahe ER, Higa D, Naugler C, Mansoor A, Shabani-Rad MT. Accuracy of the CellaVision DM96 platform for reticulocyte counting. J Pathol Inform. 2014;5:17.
[CrossRef][PubMed][PubMedCentral]

74. Horn CL, Mansoor A, Wood B, Nelson H, Higa D, Lee LH, et al. Performance of the CellaVision(®) DM96 system for detecting red blood cell morphologic abnormalities. J Pathol Inform. 2015;6:11.
[CrossRef][PubMed][PubMedCentral]

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_11

11. Patient Blood Management

Cyril Jacquot[1] and Evan M. Bloch[2]

(1) Departments of Laboratory Medicine and Hematology, Children's National Medical Center, Washington, DC, USA
(2) Department of Pathology Transfusion Medicine Division, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Cyril Jacquot
Email: cjacquot@childrensnational.org

Keywords Patient blood management – Bloodless medical and surgical procedures – Utilization – Cost – Blood component transfusion – Transfusion committee – Clinical decision support

Introduction

The past 5 years have witnessed a growing focus on patient blood management (PBM) as defined as "the appropriate use of blood and blood components, with a goal of minimizing their use" [1]. Evidence of comparable or even superior outcomes with conservative blood management predated the development of PBM programs by as much as a decade [2]. However, it was arguably the advent of economic recession and the need for cost containment that provided the impetus for renewed efforts toward rational blood use. However, blood management is not simply about cost ; rather, it is standardization of care through evidence-based practice with a goal to improve patient outcomes. When applied effectively, it saves costs and benefits patients.

Despite serving as a lifesaving therapy for an array of medical conditions,

blood transfusion is certainly not without risk. Transfusion-transmitted infections (TTI) have assumed foremost concern following the appearance of transfusion-transmitted human immunodeficiency virus (HIV) in the 1980s. Ironically, the tragedy of HIV spurred three decades of overhaul of the blood-banking industry with vast improvements in donor selection, quality assurance, and laboratory testing. Consequently, blood transfusion today is relatively safe, at least in high-resource countries. As one example, the risk of HIV transmission from a unit of transfused blood in 1982 was as high as 1 in 100 [3]; today, that risk in the United States is less than 1 in a million, which is similar to that of transfusion-associated hepatitis C virus (HCV) and hepatitis B virus (HBV) [4, 5]. However, continued emergence and reemergence of infectious diseases (e.g., babesia, hepatitis E virus [HEV], chikungunya, and dengue) attest to the need for ongoing hemovigilance and informed decision making surrounding blood transfusion. Furthermore, with the successful mitigation of infectious risk, there has been increasing attention to the noninfectious hazards of transfusion (e.g., transfusion-associated circulatory overload [TACO], transfusion-related acute lung injury [TRALI], and transfusion-related immunomodulation [TRIM]) [6]. Many of these complications are far more common than TTIs and incur significant morbidity and mortality, lending further support to considered blood use.

Overview of Blood Use : Cost , Products, and Evidence-Based Practice

Overview of PBM and Its Implementation (Figs. 11.1 and 11.2)

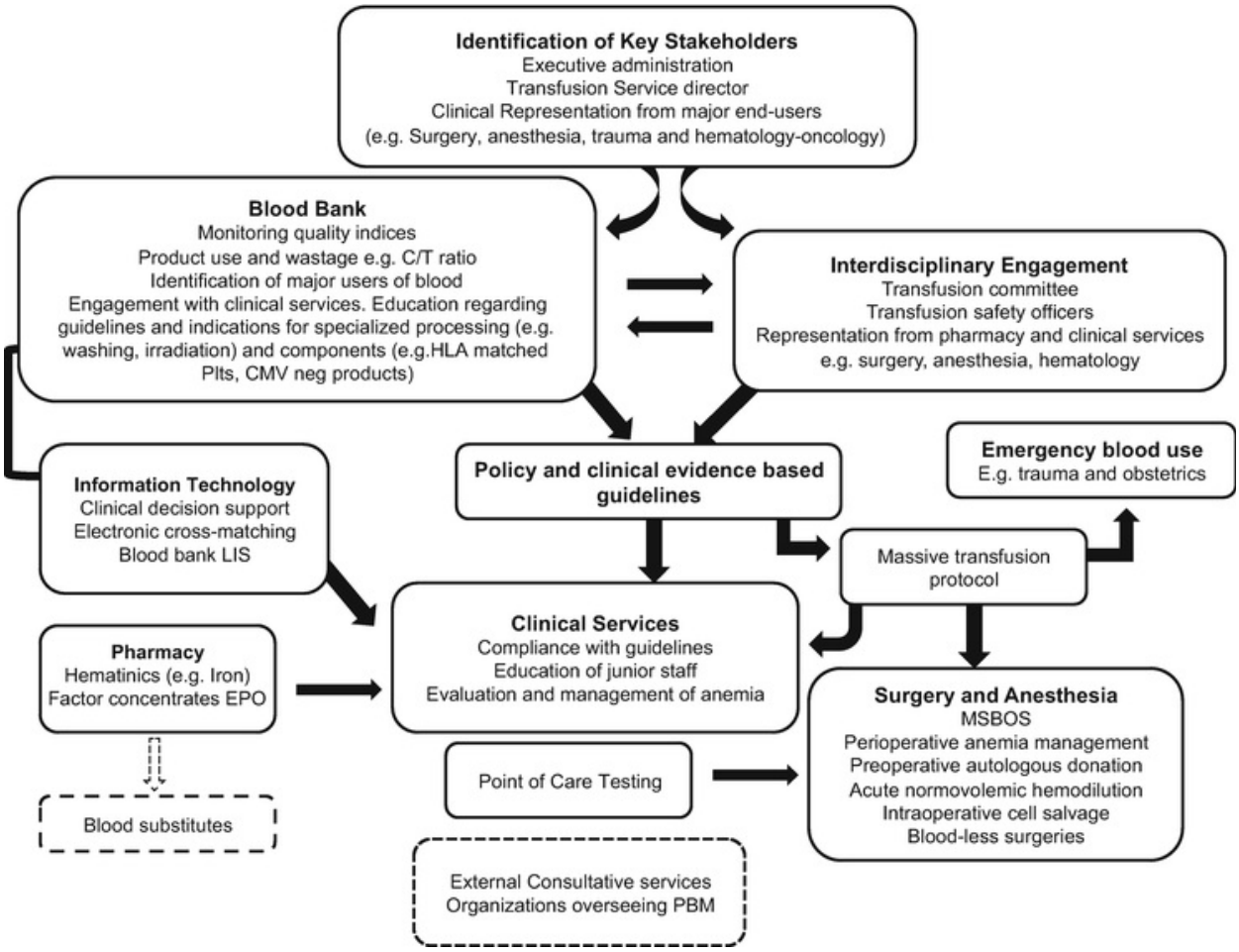


Fig. 11.1 Components of patient blood management program

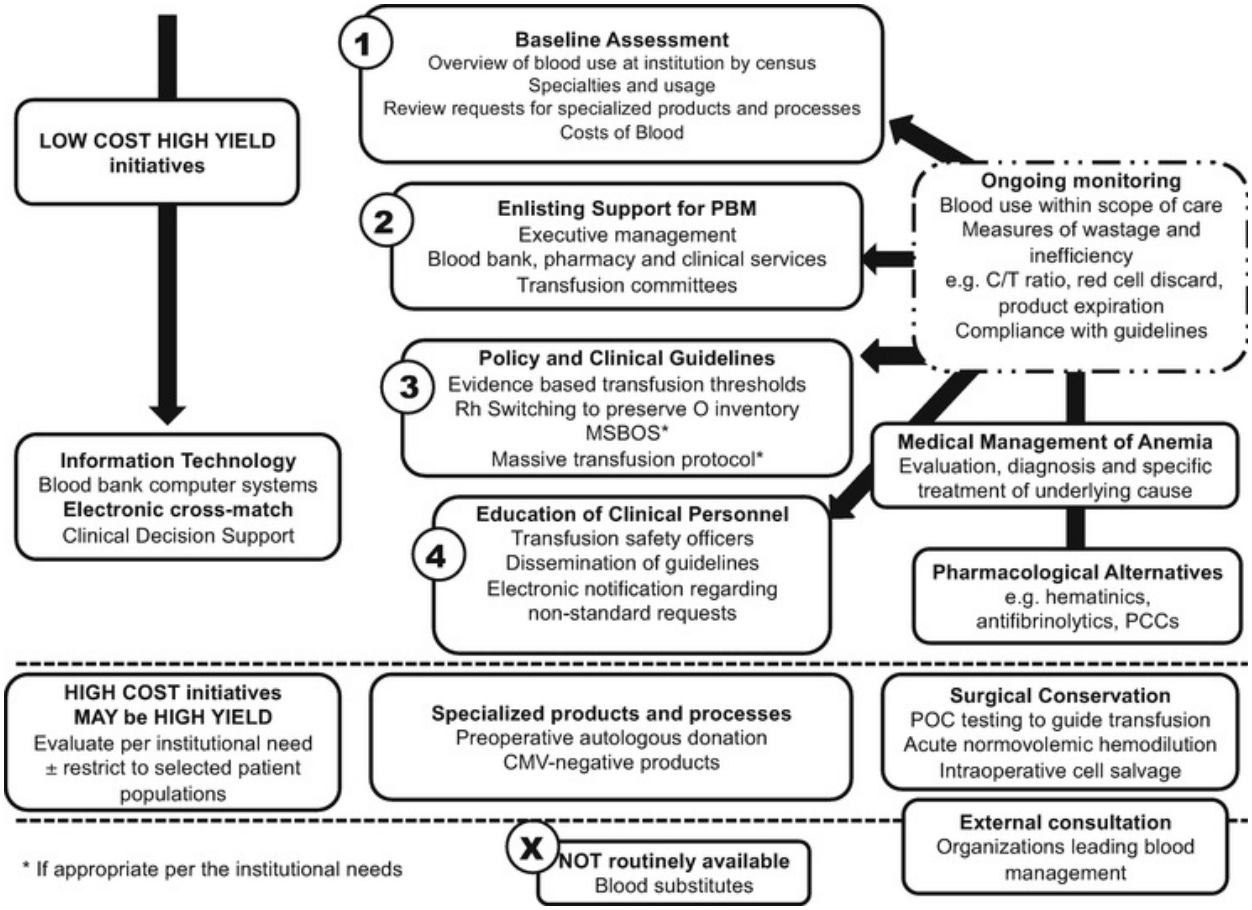


Fig. 11.2 Stepwise implementation of PBM

Blood transfusions are administered in diverse settings spanning small outpatient clinics to large tertiary academic referral centers. Therefore, while certain general principles apply, there isn't a universally applicable model of PBM because not all constituents of PBM are necessarily available or even appropriate at every institution. In this case "One size does not fit all," and the individual needs, resources, and constraints should inform development of a PBM program, ideally favoring those measures with the highest yield and lowest cost for that particular setting. That said, there are still general guidelines.

Foremost, executive support and interdisciplinary coordination with clinical partners are critical; therefore, identification and engagement of key stakeholders are foundational steps. In parallel, a baseline needs assessment serves to identify areas of deficiency, scope for improvement, and appropriate triage of interventions. Baseline data can also help to benchmark performance, set goals, monitor progress, and importantly convince

stakeholders of the need for intervention and the benefits in doing so. There are numerous examples to measure blood utilization , which—at a minimum —should address product use and wastage. Blood utilization in turn needs to be interpreted using the patient census (bed occupancy), extant transfusion practices, scope of specialties (thus reflecting transfusion needs of the patient population), and institutional transfusion guidelines.

The development and implementation of policies and clinical guidelines (if deficient or absent) should follow, ideally having enlisted the support of the key stakeholders using the transfusion committee as a central platform. Broad support from the clinical stakeholders optimizes the probability of successful dissemination and adherence to guidelines, given representation from those individuals who actually prescribe blood. There are also education and outreach measures to support adoption of guidelines such as the use of designated personnel (e.g., transfusion safety officers or transfusion service personnel) to deliver seminars and/or distribute hard copies of guidelines and information technology (e.g., clinical decision support, display on a departmental website).

Additional measures include specific protocols, policies, and procedures to improve efficiency. While there are many examples, those cited in this chapter are the massive transfusion protocol (MTP) , RhD class switching to preserve universal donor (group O RhD-negative) blood , and maximal surgical blood-ordering schedule (MSBOS) . Importantly, with the exception of clinical decision support, most of the above interventions are based on human capacity and are low cost, high yield, and nontechnologically intensive.

There are a host of other more targeted interventions, specifically listed within “perioperative interventions” (e.g., point-of-care testing to guide transfusion, preoperative autologous donation , and cell salvage) and “specialized products and processes.” These are addressed individually and may prove of benefit in certain circumstances.

Costs of Blood

In most developed countries, the proportion of gross domestic product that is spent on healthcare has been increasing for many years and is forecasted to be unsustainable in the long term [7]. Importantly, a substantial proportion of spending is categorized as wasteful [8]. Germane to PBM, blood transfusions represent one of the most frequently performed medical procedures, with an

estimated $14 billion spent on red blood cell (RBC) transfusions in the United States in 2009 alone [7]. Therefore, reduction of unnecessary transfusions is expected to have a beneficial effect on overall healthcare costs, particularly at a time when reimbursement favors quality rather than quantity [9].

The costs of blood products can be categorized into those that are incurred prior to transfusion (i.e., recruitment donation, processing, testing, storage, and transportation), those associated with the actual transfusion (i.e., repeated testing and crossmatching in the transfusion service, the nursing time to oversee transfusion and to monitor the patient), and those following the transfusion (i.e., posttransfusion surveillance, patient follow-up, investigation, and management of adverse events) [10]. Importantly, the purchase price as was reported in the 2011 National Blood Collection and Utilization Survey (NBCUS) (e.g., $225.42 per RBC unit) only reflects charges related to pre-transfusion processes [10, 11]. Thus, pricing alone masks the broader expense to the hospital. The total costs, which are incurred during—as well as after the transfusion, are estimated to be 3.2- to 4.8-fold higher [12].

Furthermore, expanded and improved infectious disease testing, adoption of universal leukoreduction, and more frequent use of specialized blood products (e.g., phenotype-matched units for sickle cell anemia patients, volume-reduced products to mitigate risk of cardiac overload) all add cost. For example, the use of human leukocyte antigen (HLA)-matched platelets is not uncommon in platelet transfusion refractory hematology/oncology patients and can cost upwards of $800 per unit. Therefore, it is important to have policies in place to ensure these higher-priced items are ordered appropriately and that they are not wasted due to improper storage, handling, or expiration.

Focus on a selected number of diagnoses may have a disproportionate effect on cost. Overall, the costs of blood transfusion account for <1 % of total hospital costs for the vast majority of conditions, and many common diagnosis-related groups (DRGs) have no associated blood costs [13]. In contrast, a small number of DRGs are associated with higher frequency of transfusions and therefore incur disproportionate costs for the transfusion service. For example, in one study three DRGs—bone marrow transplantation , liver transplantation , and acute leukemia —accounted for 52 % of overall blood transfusion costs given their high usage of blood products

coupled with the frequent need for specialized—and expensive—blood products (e.g., irradiation, CMV-negative units) [13]. Therefore, although the principles of PBM apply to the whole hospital, a focus on reducing costs in a small number of DRGs can have a significant beneficial effect on overall expenditure.

Specialties and Usage

Data on usage are essential to ensure that the transfusion inventory is appropriately matched to the needs of a given patient population. Mismatched inventories risk excessive blood product expiration as is exemplified by platelet inventory management. Platelets are a high-cost product, with a short shelf life (5 days), and—importantly—their use can vary dramatically depending on the scope of practice at a given institution. For example, a referral hospital with an active hematology/oncology service has very different requirements from that of a small rural hospital; the latter might only transfuse platelets in the rare case of severe trauma. Prospective tracking of product requests and the corresponding transfusion indications can be used to determine institutional blood use, thus informing appropriate ordering [14].

Institutional blood needs will depend both on what specialties are at the institution as well as the scope of practice within a given specialty. Broadly speaking, the major users of blood are unsurprising. According to the 2011 NBCUS survey , the services responsible for the highest use of RBCs were general medicine (31 %), surgery (20 %; general, orthopedic, and cardiac surgery combined) , and hematology/oncology (15 %) [11]. The highest platelet product use was reported in hematology/oncology (34 %), surgery (18 %, combined), general medicine (17 %), and the intensive care unit (12 %). In a breakdown of surgical use, cardiac surgery accounted for 50 % of the platelet transfusions [11].

Blood use varies considerably by discipline, both by the number of units transfused as well as by component type. Even within the same specialty, there may be marked variation between physicians [15–17], which may not necessarily reflect inappropriate use, given the multitude of factors that affect blood use. Those factors include the spectrum of diagnoses in a given specialty, the patient acuity, outpatient vs. inpatient setting, as well as the patient complexity (e.g., presence or absence of comorbid disease). Collectively, this can account for significant differences between institutions, even when matched for scope of practice and application of transfusion

guidelines. For example, two institutions that perform the same procedure may encounter different transfusion rates should one select for higher-risk patients. As one example, four neonatal intensive care units (NICU) within the same healthcare system showed differences of units transfused (from 4.6 transfusions/1000 NICU days up to 21.7 transfusions/1000 NICU days) despite strict adherence (98.9 %) to a shared set of guidelines. In this case, promulgation of policies to prevent anemia (e.g., use of fetal blood in cord/placenta for initial testing, limiting phlebotomy losses, supplemental iron administration) in certain NICUs correlated with lower rates of transfusion [18]. Therefore, while a benchmark determination of inappropriate blood use is appealing, comparison of practices between institutions, or between individual providers, is both difficult and potentially misleading.

Available Blood Products

The earliest attempts at transfusion were confined to whole blood transfusion. With advances in blood separation (centrifugation, closed sterile systems) and storage (plastic bags for platelets), it became possible to address specific patient needs using selected component(s). Not only is this advantageous to patients directly (i.e., addressing specific need such as anemia , coagulopathy), it has increased efficiency whereby multiple patients are able to benefit from a single donation. However, this versatility comes with the challenge of managing a diverse inventory with components that have different shelf lives, clinical indications, and processing and storage requirements.

There are six broad categories of blood component , of which the three most widely used are RBCs , plasma , and platelets . In contrast, the other three—cryoprecipitated antihemophilic factor (cryoprecipitate) , granulocytes , and whole blood —are much less commonly administered. Blood products are typically prepared in standard adult doses but can also be aliquoted into smaller doses for pediatric patients, thus allowing for appropriate weight-based transfusion, minimizing risk of fluid overload while reducing wastage of components .

Blood utilization has changed significantly over the past 5 years at least in part due to PBM initiatives. In 2011, the NBCUS that was performed in the USA showed that the number of transfusions for RBCs , plasma , and platelets were 13,785,000, 3,882,000, and 2,169,000, respectively [11]. More recent regional data reflect a marked decline in transfusion, which has

predominantly affected RBCs and plasma. Regional examples include greater than 20 % reduction in RBC use in a hospital system in Northern California over a 3-year period [19] and decreased plasma use at Massachusetts General Hospital [20].

The clinical indications for each of the products reflect the functions of their major constituents. RBCs regulate tissue oxygenation through hemoglobin and are indicated for treatment of decompensated, symptomatic anemia. Plasma is primarily used to reverse coagulopathy or to treat combined factor deficiencies as in chronic liver disease . Rarely, it is also used as volume replacement during plasma exchange for selected indications. Platelets are used to prevent or minimize bleeding in thrombocytopenic patients. Cryoprecipitate , which is rich in fibrinogen, factor VIII, von Willebrand factor, factor XIII, and fibronectin [21] is primarily indicated for a low fibrinogen level. Older uses in patients with hemophilia A and von Willebrand disease have been superseded by recombinant factor VIII and von Willebrand factor , respectively. Finally, granulocytes are infrequently transfused given the uncertainty surrounding their efficacy; their use is generally reserved for disseminated bacterial/fungal infections in patients with severe neutropenia that fails to respond to antimicrobial therapy .

Interestingly, there has been recent interest in whole blood transfusion , which is challenging the decades-old dogma surrounding exclusive component use (whole blood is only rarely transfused in the US and other high income countries). The findings from research that was conducted in the military (notably in Iraq and Afghanistan) [22] to optimize resuscitation outcomes on the battlefield support component transfusion (i.e., RBCs, platelets, and plasma) in a similar ratio to that of whole blood [23]. However, if one is transfusing components in ratios that resemble reconstituted whole blood, it raises the question as to whether whole blood transfusion (still a licensed product by the Food and Drug Administration [FDA]) might be more appropriate. Not only would whole blood bypass the logistical hassle (processing, storage, and inventory management) of component separation, it may indeed be clinically preferable. A calculation based on a 1:1:1 RBC/plasma/platelet ratio reconstituted unit predicted that the reconstituted product would have lower hematocrit, platelet count, and coagulation factor activity than a unit of whole blood [24]. However, the clinical benefits are still uncertain: for example, two studies in pediatric cardiac surgery patients to compare the effectiveness of whole blood with reconstituted blood showed

mixed results [25, 26]. Additional research is still needed, but favorable or even equivocal outcomes could have major implications for low-resource settings where infrastructure for component preparation is lacking.

Transfusion Thresholds, Clinical Guidelines, and the Decision to Transfuse

Implementation of evidence-based transfusion thresholds (i.e., triggers) is a foundational step in PBM , serving to minimize transfusions and standardize clinical practice [27]. Transfusion triggers are available for each of the three major components (RBCs, plasma, and platelets). Minor variation in transfusion thresholds for selected patient populations (e.g., cardiac or intracranial pathology) is the exception and should not discourage implementation of general transfusion guidelines. Threshold implementation has wide-ranging value. First, it ensures evidence-based practice that optimizes patient outcomes. Second, documentation of transfusion indications and thresholds enables auditing of practice (e.g., by the transfusion committee): one can't evaluate aberrant practice without a standard for measure of comparison. This in turn serves a broader educational purpose (particularly for junior physicians), thus propagating desirable transfusion practices.

The decision to transfuse should be based on both clinical (e.g., history, comorbidity, chronicity, symptoms and signs, evidence of bleeding, and vital sign changes) and laboratory (e.g., hemoglobin, platelet count, and coagulation studies) evaluation. Ideally, patients should undergo repeat clinical and laboratory evaluation after each transfusion to determine whether further transfusion is warranted. The application of a single-unit transfusion policy in stable patients helps restrict transfusion to that which is absolutely necessary. In one hospital , implementation of a single-unit transfusion policy in hematology/oncology patients resulted in a 25 % reduction in RBC transfusions ($2853 cost savings per patient) (Table 11.1) [28].

Table 11.1 Cost savings of patient blood management programs

Process	Investment	Cost reduction/outcome	Reference
Multihospital initiatives			
Implementation of blood conservation initiative at 17 cardiac surgery centers in	Not provided	$49 million statewide over a 2-year study period with a median reduction of $4000 per patient	[228]

Virginia		hospitalization	
Multihospital provincial program in Ontario, Canada—ONTraC	CAD$21 million to implement the program in 23 hospitals; CAD$1.8 million annual cost	CAD$8.64 million annual savings in transfusion costs	[229]
Single hospital initiatives			
CDS (hospital-wide implementation)	Not provided	$1,616,750 savings	[81]
Hospital implementation of single RBC unit policy	Not provided	25 % reduction ($2853 savings per patient) in hematology/oncology patients	[28]
Platelet inventory tracking through computer dashboard system in transfusion service	Not provided	Mean monthly PLT outdate rate decreased from 24.5 to 15.1 %. PLT age at time of transfusion reduced from 3.60 days to 3.46 days	[73]
Updated institution-specific MSBOS/remote electronic blood release system implementation	Not provided	Savings of $137,223 ($6.08 per patient) for surgical patients and $298,966 ($6.20 per patient) for all hospitalized patients	[76]
Clinician education regarding proper blood storage conditions to minimize product wastage	$310 initial investment; small additional amount to replace tote bags/posters and other relevant materials as needed	$131,520, excluding intervention costs	[208]
Hospital unit initiatives			
CDS (implementation within one medical care unit)	$600	$59,616 savings	[82]
Bleeding management protocol in cardiac surgery incorporating point-of-care coagulation testing (ROTEM and multiplate)	POC coagulation testing consumable cost of $44,411	$1,029,118 decrease in the acquisition cost of blood products	[230]
ROTEM/antifibrinolytics in pediatric craniosynostosis surgery	Not provided	17.1 % reduction in transfusion costs, from €1071.82 down to €888.93 per patient	[231]

While it is tempting to rely on laboratory values alone to guide transfusion (i.e., hemoglobin/hematocrit for RBCs, platelet count for platelets, prothrombin time [PT]/international normalized ratio [INR] for plasma, and fibrinogen level for cryoprecipitate), strict adherence to laboratory-based transfusion triggers without attention to clinical status is

flawed. A patient with chronic anemia may meet a transfusion threshold based on the hemoglobin alone; however, the anemia may be well tolerated clinically and best managed by addressing the underlying cause rather than resorting to transfusion. In contrast, a symptomatic cardiac patient with a hemoglobin of 9.5 g/dL may benefit from transfusion independent of guidelines. Unfortunately, the ultimate decision to transfuse requires a measure of clinical acumen, thus accounting for both over- and undertransfusion.

Historically, RBC transfusions were administered liberally to maintain hemoglobin levels above 10 g/dL [29]. In contrast, a major driver for PBM and the concomitant decline in RBC transfusion were evident from studies that demonstrated comparable or even favorable clinical outcomes with restrictive RBC transfusion thresholds (i.e., hemoglobin of 7–8 g/dL) [30, 31]. Consequently, the AABB (formerly the American Association of Blood Banks) recommends a restrictive hemoglobin threshold of 7–8 g/dL in stable hospitalized patients and a threshold of 8 g/dL in patients with preexisting cardiovascular disease. There is still lack of consensus regarding thresholds in patients with acute coronary syndrome, highlighting the need for careful clinical evaluation [31].

Liberal transfusion practice is not unique to RBCs: hospital audits show that a high proportion of plasma transfusion is inappropriate [32]. Inappropriate plasma transfusion exposes patients unnecessarily to infectious and noninfectious risks, particularly TRALI , which remains a leading cause of transfusion-associated mortality in the USA [33]. Examples of improper use include transfusion to correct borderline abnormal INR values and volume replacement. Borderline elevated INR values that are detected during preoperative testing are a frequent, incidental finding; importantly, they have a very poor correlation with bleeding risk. Furthermore, the volume of plasma necessary to correct borderline INR values confers greater risk (e.g., TRALI, TACO) than the finding itself [34]. Similarly, plasma should not be used for routine volume replacement nor should it be used for correction of single-factor deficiencies where safer recombinant factors are available. Instead, the following transfusion indications for plasma are well accepted: active bleeding in the setting of multiple coagulation factor deficiencies; emergency reversal of warfarin in a bleeding patient when prothrombin complex concentrate is not available; and for use as replacement fluid for plasma exchange in selected indications (e.g., thrombotic thrombocytopenic

purpura) [35]. Although not designed as such, the INR is frequently used to guide plasma transfusion. The exact threshold may also vary among hospitals, but an INR between 1.5 and 2 is typical [35, 36].

Similarly, platelets should be prescribed judiciously given transfusion-associated risks, notably those of septic transfusion reactions. The majority of platelets are transfused prophylactically rather than therapeutically. Studies have shown that most patients can tolerate platelet counts much lower than the normal range. While selected patient populations may require a higher nadir given the risk of spontaneous bleeding (e.g., intraocular or neurosurgery), the majority of patients tolerate platelet counts less than 10×10^9 cells/L in the absence of active bleeding, fever, or sepsis [37]. Studies have shown that spontaneous bleeding is unlikely in stable patients with platelet counts greater than 6×10^9 cells/L [38–41]. The AABB recommendation is to transfuse for platelet count $<10 \times 10^9$ cells/L in stable hospitalized patients, $<20 \times 10^9$ cells/L prior to elective central venous catheter placement, and $<50 \times 10^9$ cells/L prior to lumbar puncture or major elective nonneuraxial surgery [37].

Finally, transfusion thresholds for cryoprecipitate and granulocytes are less well defined. Cryoprecipitate is generally transfused when fibrinogen falls below 100 mg/dL although this threshold is empiric [42]. Granulocytes may be used in combination with antimicrobial therapy to treat sepsis in patients with neutropenia (absolute neutrophil count <500 cells/mm^3) or granulocyte dysfunction [43]. Currently, there is insufficient evidence to determine whether granulocytes reduce infectious or all-cause mortality rates [44]. A recently completed randomized clinical trial found no significant benefit in those patients who received granulocyte transfusions. However, the study was constrained by low recruitment and may have lacked the power to detect a significant effect [45].

Oversight and Personnel in PBM

Organizational Oversight of PBM

For the most part, blood is readily available in high- to middle-income countries. However, a recent study from Germany identified a concerning trend in blood supply. As the average age of the population is increasing, a higher proportion of patients are expected to require transfusions; however,

the proportion of eligible young blood donors is expected to decrease, which could lead to a blood shortage in the next decade [46]. A similar analysis was performed using data from the United States . Over the next decade, the disparate rates of increase between the general US population (10 %) and that of the donor population (specifically those aged 16–64 [5.2 %]) could lead to a shortfall in available blood to meet the demand [47]. Therefore, another sound reason for PBM is management of a limited blood supply.

An expanding number of organizations (governments, health care systems, blood centers, physician professional societies) have adopted a proactive approach to lead PBM research, policy, and implementation of programs. Early efforts began in Canada and Australia. In 2002, the Ontario Transfusion Coordinators (ONTraC) program was implemented in Canada to facilitate adoption of PBM in hospitals, to improve cooperation between the transfusion and clinical services, and to monitor subsequent changes in transfusion practices (Table 11.1) [48]. Similarly, in Western Australia (WA) , the Department of Health launched a statewide PBM program in 2008 [49]. The 5-year program received wide executive support from the WA State Health Executive Forum and the Australian Red Cross Blood Service [50], and successfully decreased blood use in a region that already had low use at the outset. Subsequently, Australia became the first country to adopt national PBM guidelines [51]. Both the Canadian and Australian examples underscore the need for high-level (ideally at a national or governmental level) and multidisciplinary (clinical and laboratory services, blood suppliers, and hospital executives) support for effective implementation of PBM [52]. Unfortunately, the lack of support accounts for the sporadic implementation and variable success of PBM around the world [53].

Nonetheless, there is momentum toward wider acceptance of PBM. In 2010, under resolution WHA63.12 , the World Health Organization (WHO) formally acknowledged the importance of PBM and advocated for its implementation [52]. This contributed to greater support in the United States; in 2011, the United States Advisory Committee on Blood Safety and Availability (ACBSA) recommended data collection on blood utilization and patient outcomes, expanded education for medical students and clinicians, and allocation of funding for PBM research. The same year, the Joint Commission (TJC) , which is the leading accrediting organization in health care, announced “transfusion appropriateness” as a key safety focus [54]. TJC has also developed a PBM Certification for accredited hospitals in

recognition of organization-wide implementation of PBM [55]. Similarly, The Accreditation Council for Graduate Medical Education (ACGME) , which oversees residency and fellowship training programs in the USA, has integrated PBM into its requirement for transfusion medicine fellowships [56].

Several other organizations have also come out in support of PBM, in many cases with either guidance or the offer to assist institutions with implementation. The AABB , which offers webinars on various aspects of PBM, recently published a white paper on how to help establish a PBM program [57]. Other focused initiatives include the *Choosing Wisely* initiative between The American Board of Internal Medicine (ABIM) and AABB that advocates for key blood conservation initiatives. The latter include restrictive red blood cell transfusion thresholds and the use of alternatives to blood products such as iron supplementation in stable anemia and vitamin K administration for warfarin reversal [58]. Other professional medical societies have also revised their guidelines to reflect the growing evidence that PBM decreases blood use and reduces cost, while improving patient outcomes [59].

Consultation services for PBM have become available from a variety of organizations (e.g., AABB, blood collection centers, academic medical centers, private corporations). The extent and breadth of PBM implementation can be tailored to the goals and budget of a given center. These services often use proprietary metrics and can benchmark an institution's blood utilization to regional or national data. Consultation costs may either be a fixed amount or a percentage of anticipated or actual cost savings after implementation .

Hospital Transfusion Committee

The transfusion committee's goals are to promote safe and appropriate transfusion, set policies and guidelines, review and revise guidelines as new evidence comes to light, monitor clinical practice, and investigate/adjudicate exceptional events that fall outside of the guidelines [60]. The transfusion committee also plays a crucial role in the evaluation of new biologics such as plasma concentrates or recombinant factors [61]. Although plasma derivatives may fall under the purview of pharmacy in medical centers, they are often used in conjunction with blood products to correct coagulopathies (see separate section). While not something new (TJC has required monitoring of blood utilization since 1961), the transfusion committee has a

critical regulatory function: the AABB calls for review of blood utilization within its quality assurance framework, and the Code of Federal Regulations (CFR) requires review of blood use to qualify for Medicare reimbursement [62].

The practical details differ by institution . A physician who is knowledgeable in transfusion medicine (e.g., the transfusion service medical director) typically chairs the transfusion committee , and the committee members should be selected based on their ability to represent the major clinical services that transfuse (Medicine, Surgery, Orthopedics, Obstetrics and Gynecology, Anesthesia, and Nursing) [62]. Likewise, a representative from pharmacy services may be beneficial given the similarities between transfusion and drug administration, in addition to the growing use of plasma derivatives [61]. Other possible attendees include directors of the institution's main blood supplier(s), representatives from biomedical engineering (e.g., maintenance of refrigerators), and rotating pathology residents/fellows [62]. Committee meetings should be on a fixed schedule and accrediting associations recommend meeting at least quarterly [62–64].

Importantly, transfusion committees have been very effective at changing transfusion practices and reducing RBC use [65]. In one hospital, a marked decrease in the crossmatch-to-transfusion (C/T) ratio from 2.48 to 1.50 occurred after one of the cardiac surgeons established a new Blood Utilization Committee [66]. The ability to compare transfusion metrics between specialties may also inspire competition thus incentivizing improved blood use [52].

Transfusion Safety Officer (TSO)

Another effectively used personnel in PBM are the transfusion safety officers (TSOs). While already well established in Canada, England, and France, the role of the TSO is a recent introduction to the United States [61]. The TSO, who typically has training as a laboratory technologist or nurse , plays an analogous role in blood safety and hemovigilance to that of the pharmacist who rotates on the wards to ensure that medications are used appropriately or the infection control officer who monitors antibiotic resistance and makes recommendations regarding patient isolation [61]. TSOs partner with nursing and ward staff to ensure accurate and complete documentation of transfusions including the final disposition of issued blood (i.e., whether the unit was transfused as intended or discarded). Cooperation between the laboratory and

clinical staff also ensures transfusion reactions are appropriately reported and investigated as part of hemovigilance efforts. This interdisciplinary function provides an intermediary between the blood bank and the clinical ward staff, thus improving cooperation between the services. Similar to the transfusion committees, investment in TSOs is expected to improve transfusion practice through quality oversight and compliance with institutional guidelines [64]. The majority of errors related to blood transfusion actually occur outside of the laboratory/blood bank [67, 68]; in this regard, the TSOs, as representatives of the transfusion service, fulfill a vital role by circulating on the wards where they can interdict or report aberrant practices.

The Use of Information Technology in PBM

Blood Bank Computer Systems

The administrative and logistical challenges inherent to the management of a blood inventory are formidable, particularly given stringent regulatory oversight. The high demands placed on modern transfusion services may be justified where deficient processes risk adverse or even fatal outcomes (e.g., when blood is transfused to the wrong patient). In this regard, laboratory information systems (LIS) have revolutionized blood-banking practices.

The FDA mandates that electronic data systems be able to track every donation from collection to final component disposition and similarly to be able to track blood products back to the donor. These audit trails allow for biovigilance efforts [69]. In this regard, the LIS offers advantages to the blood center and transfusion service alike by storing data pertaining to donors, patients, and individual blood units while also providing search capability.

The LIS also accomplishes many other functions. In blood centers , the LIS stores donor information, donation testing results, and deferral registries. In the hospital transfusion service, the LIS is used to monitor the transfusion inventory, which is critical for blood management (i.e., planning and purchase). The LIS is also able to track modification of blood products (e.g., irradiation, washing) and store patient testing results (e.g., ABO/Rh type, antibody screen). New automated analyzers for blood grouping and antibody screening can even interface with the LIS, whereby automatic uploading of results helps to reduce human error, alleviate workload, and improve

turnaround time (TAT) . In so doing, the LIS frees up the technologists to perform higher skilled tests [70]. The LIS can also generate reports pertaining to blood use, which are invaluable to both the transfusion service and transfusion committee [69]. Importantly, the LIS is necessary to conduct electronic crossmatching, which has repeatedly been shown to enhance efficiency and workflow [71]. Finally, the LIS improves patient safety by maintaining strict algorithms to ensure that only correct or compatible blood products are selected. The latter can be problematic in emergency situations where the system should incorporate a bypass mechanism to allow for faster blood product issue.

Efforts are ongoing to optimize transfusion service performance through computer systems. One area of interest is management of the platelet inventory. Platelets are prone to shortages and wastage (outdate rates are as high as 20 %) [72], in large part due to the short shelf life. Many transfusion services rely on historical data to determine how many platelet units to order —a so-called “order-up-to” approach. In contrast, the LIS can be used effectively to conduct real-time tracking of inventories, enabling laboratory staff to prioritize the use of soon-to-expire platelet units. Specifically, the LIS can display both the platelet inventory with expiration dates and pending patient orders. Application of this function decreased platelets outdate rates from 24.5 to 15.1 % in one tertiary hospital network [73].

Despite the advantages of the LIS, it has not been adopted at all hospitals . As with any test in the clinical laboratory, validation of the LIS is mandatory and must cover all the functions used by the blood bank. Implementation of an LIS thus requires significant investment, given the cost, staff time, and logistical challenges inherent to change. Any blood bank computer system in use for clinical care must also be licensed by the FDA , introducing regulatory considerations [21]. Some laboratory staff may not fully trust computerized systems, instead preferring a manual system where every step and process can be directly checked [74]. While not unique to LIS in the transfusion service , these systems require maintenance and routine; regular backup is imperative after installation. Indeed, disaster planning and a procedure to recover data are regulatory requirements to ensure that the transfusion service has access to critical information at all times [75].

Electronic Crossmatch (EXM)

The electronic crossmatch (EXM) refers to virtual compatibility testing in

which blood products are issued based on the patient's prior ABO testing, antibody screening, and medical history alone. The EXM bypasses the need to perform in vitro formal crossmatching. If used correctly, the EXM confers multiple benefits to blood bank and patient alike: it reduces TAT , improves work flow by avoiding unnecessary testing, reduces reagent costs , and—most importantly—improves safety by minimizing human error and preventing the release of ABO-incompatible products [71]. Electronic crossmatch also enables remote electronic blood release systems. In the latter, blood is stored in a secure "vending machine" near the operating rooms whereby units are released remotely through the blood bank LIS once an order is received (Table 11.1) [76].

The EXM does not apply to all patients: its use is contingent on the absence of clinically significant antibodies (present or historical) and/or evidence of an ABO discrepancy [77]. The computer system needs to be validated to accommodate the EXM with specific attention to prevention of ABO discrepancies. However, despite availability of this high-yield, low-cost intervention , blood banks still fail to implement the EXM even when they demonstrate the capacity to do so [78]. The EXM is a high-yield, low-cost intervention and should be strongly considered if not already in use at a given institution.

Clinical Decision Support

Clinical decision support (CDS) refers to the use of information technology (i.e., software) to integrate clinical and laboratory data with that of institutional guidelines so as to provide a recommendation to the prescribing physician [79]. Although prospective review of blood product requests (i.e., by designated personnel) serves to decrease inappropriate transfusions, it requires considerable staff time and can delay release of blood products. CDS can facilitate or even replace prospective review by alerting the ordering physician when a transfusion request falls outside of institutional guidelines (i.e., "best practices alert"). The system can also display transfusion thresholds /indications for various patient scenarios and offer to cancel or suspend orders. Collectively, the interface offers dual positive effect by interdicting inappropriate requests as well as educating clinicians regarding standard practice. The physician may still be able to override the alert by providing a reason for the transfusion but can't claim not to have been informed when later audited by the transfusion committee. CDS has other

benefits. Specifically, when integrated with electronic health records (EHR) , CDS can identify patients at risk (e.g., of transfusion) using key variables such as admission diagnosis, past medical history, and current laboratory values, which can serve to improve clinical management [9].

Importantly, implementation of CDS has consistently shown improvement both in provider adherence to RBC transfusion guidelines as well as cost savings [80]. As one example, the hospital-wide CDS at Stanford Medical Center led to an estimated annual net savings of $1.6 million and accumulated net savings of $6.4 million (Table 11.1) over a 4-year study period (2010–2013) [81]. The authors do note that some of the savings may have arisen from other concurrent hospital policy changes. Other studies also report modest cost savings of $20,000–60,000 per hospital [80, 82]. Even passive guidance provision of transfusion guidelines at time of ordering of platelets and plasma (rather than a best practices alert requiring physician acknowledgement) is effective and at one hospital was met with a 10 and 12 % respective decrease in platelet and plasma use as compared to a 24 % reduction for RBCs during the same timeframe [9].

Like other facets of PBM, CDS is best accompanied by clinical education/outreach efforts prior to implementation coupled with collective "buy-in" from the clinical services and senior management [9]. Finally, although CDS has wide-ranging benefits, it is by no means a panacea for inappropriate transfusions. If the system is poorly designed with too frequent alerts, providers may become frustrated and begin ignoring the CDS (so-called alert/click fatigue) [9]. The latter may be addressed through limitation of low-impact alerts, which can disrupt workflow or simply evaluating the reasons for overriding alerts to modify the system to changes in clinical practice [9].

Protocols and Policy That Improve Efficiency

Maximal Surgical Blood-Ordering Schedule (MSBOS)

The maximal surgical blood-ordering schedule (MSBOS) refers to the pre-allocation of a defined number of blood products for a given surgical procedure. If used correctly, it improves efficiency by anticipating the intraoperative transfusion needs, thereby bypassing intraoperative requests that can introduce delays, prolong surgery, and risk adverse outcomes. The

benefits of MSBOS are not confined to a specific procedure: preparation ahead of surgery regulates the workflow, thus freeing up staff to work on other patient requests. However, for a MSBOS to prove successful, it needs to be drafted in consultation with the clinical team that is directly involved in the surgery (e.g., surgeon and anesthesiologist), such that it is tailored to the individual needs at the hospital. Likewise the MSBOS must be updated with changes in practice, personnel, and/or the patient complexity [83, 84]. In so doing, it can be very effective. As one example, implementation of a MSBOS and electronic blood release system in a large academic center resulted in a 38 % reduction in the percentage of procedures with preoperative blood orders and a 27 % decrease in the crossmatch-to-transfusion ratio among all hospitalized patients [76]. Together, this represented an annual cost savings of $137,223.

In contrast, implementation of a generic MSBOS (i.e., one that has is not adapted to the individual needs at an institution) can lead to unnecessary wastage of blood products while continuing to place unnecessary demands on the blood bank.

Massive Transfusion Protocol (MTP)

The MTP refers to rapid deployment of blood components in a fixed, predefined ratio to the massively hemorrhaging patient. In general, “massive transfusion” is defined as a transfusion of greater than 10 units in a 24-h period. While typically associated with trauma patients (it has become standard of care in Level I trauma centers) [85, 86], it has shown benefit in a variety of settings including aortic rupture, obstetric hemorrhage, and gastrointestinal bleeding [87]. Similar to the MSBOS, the MTP uses pre-allocation of blood products, in this case in times of emergency to alleviate the burden on the blood bank to procure products urgently. In this manner, the protocol assures rapid access to products during the acute stabilization phase when they are needed most. To this end, the MTP reduces the TAT , promotes efficiency, and reduces both mortality [88, 89] and blood utilization [89].

Much of the support for MTP use is based on studies that have been conducted in trauma patients and specifically investigation of trauma-associated coagulopathy . The latter correlates with poor clinical outcomes, independent of the extent of injury [90], and is exacerbated by large volume transfusion of RBCs in the absence of accompanying plasma and platelet

repletion . This became evident during the US campaigns in Iraq and Afghanistan and led to *damage control resuscitation* , which strives toward balanced blood component therapy to counteract coagulopathy. In contrast to older approaches that favored crystalloid infusions, *damage control resuscitation* introduces fresh frozen plasma (FFP) , platelets , and cryoprecipitate early in patients who undergo massive transfusion and has been shown to improve outcomes, including a reduced mortality in the first 6 h following admission [91].

The optimal component ratio within a trauma pack has long been debated. Early studies that favored a high ratio of plasma and platelet to RBCs were later criticized for observational design, failure to control for survivor bias, and type of injury [92]. However, a recent large multicenter randomized clinical trial showed no difference in mortality between those patients who received plasma, platelets, and red blood cells in a 1:1:1 versus a 1:1:2 ratio [23]. Other practical concerns surrounding MTPs include decisions regarding when to trigger the protocol and what products to include. There is an expanding array of blood products that include platelets in additive solution, liquid plasma, and low-titer plasma, which may be advantageous during resuscitation [93]. For example, liquid plasma (plasma that has never been frozen) is not subject to delays from thawing (as compared to FFP), and group A plasma has been proposed as an alternative to group AB plasma (universal donor plasma) given that it is much more readily available and carries low hemolytic risk [93]. Platelets in additive solution may also reduce risk associated with high-volume plasma transfusion. However, availability of products varies by institution, which in turn is determined by the patient population. Finally, not dissimilar to the MSBOS , despite enthusiasm for the MTP, evidence of favorable outcomes is not always clear [94, 95].

Group O Rh D-Negative Blood and Rh D Switching

One may ask why the RhD switching falls within the scope of blood management. It is a good example of how real-time proactive evaluation and communication can impact practice without compromising patient outcomes. In contrast, a single case of massive hemorrhage can rapidly deplete an inventory of O RhD-negative blood, thus imposing risk to other patients where transfusion of RhD-negative blood is essential.

In blood banking , the RhD antigen is second only to the ABO system in its clinical importance. In RhD-negative individuals, exposure to the RhD

antigen during pregnancy or blood transfusion risks development of an IgG alloantibody against the RhD antigen . Those anti-RhD IgG antibodies can cross the placenta where they can induce immune-mediated destruction of the fetal red cells. In severe cases, the associated fetal anemia may be severe or even fatal (hydrops fetalis). Historically, most severe cases of hemolytic disease of the fetus and newborn (HDFN) were ascribed to RhD alloimmunization [96]. However, owing to clinical vigilance, RhD immunoglobulin prophylaxis, and advances in clinical management (particularly noninvasive monitoring of pregnancies), other alloantibodies (anti-c and anti-Kell) are now more frequently implicated in severe HDFN [97].

The Rh D antigen is highly immunogenic. The earliest studies that were conducted using healthy RhD-negative volunteers demonstrated rates of alloimmunization in excess of 60–80 % [98, 99] following low-dose exposure to RhD-positive red blood cells. Consequently, the practice of transfusing RhD-negative blood to patients who are either RhD negative or unknown (e.g., in emergency) appears sound. However, patients are fundamentally different from healthy volunteers as evidenced by later studies that showed much lower (~20 %) rates of alloimmunization following RhD mismatched RBC transfusion [100, 101]. Rates of alloimmunization are even lower (~10 %) following RhD incompatible platelet transfusions [102, 103]. Indeed the rates of RhD alloimmunization are actually highly variable. Importantly, only 9 % of US blood donors are group O RhD negative [104], yet group O RhD-negative blood remains a mainstay of emergency transfusion stocks; this mismatch in supply vs. demand has led to an unsustainable model for blood centers. Collectively, these data have motivated for triage of group O RhD-negative blood in favor of those patients who most need it, notably women of child-bearing age (e.g., ≤age 50).

With the exception of women of reproductive potential, early switching to O RhD positive is recommended if high-volume transfusion is anticipated (e.g., activation of an MTP) and preservation of group O RhD-negative blood by transitioning to ABO Group specific blood as soon as ABO status is known [105]. The timing of when to switch is informed both by the available inventory as well as the anticipated transfusion needs. For example, if a patient is expected to need only a few units of O RhD-negative blood prior to stabilization, RhD switching is less likely to be necessary. However, an actively bleeding patient with high-expected blood use is more likely to

prompt early RhD switching.

Perioperative Interventions

Preadmission Testing

There are measures that can help to optimize workflow thereby preventing unnecessary delays to planned surgical procedures. Foremost, preadmission testing (e.g., collection of a blood sample for ABO typing and antibody screening) enables the blood bank to evaluate a given patient completely prior to their admission. In the event of identification of a new antibody or antibodies, it allows for procurement of blood prior to surgery or communication to the team to plan accordingly (e.g., postponement or modification of the procedure). Depending on the prevalence of the cognate antigen(s) or immunohematology problem , there may be significant complexity (time and logistics) involved in finding compatible blood. Importantly, without preadmission testing, that work-up and concomitant delay occurs while the patient is already hospitalized, where they incur cost and delay surgery. Worse, if the patient is already in the operating theater, this transitions from a predominantly logistical to a clinical problem with possible serious effect, particularly if compatible blood is not onsite. Preadmission testing is not confined to routine blood bank evaluation, and there are ancillary studies that may also be useful prior to surgery (e.g., coagulation studies, hemoglobin). However, a balanced approach to testing is important given that excessive testing can uncover clinically insignificant abnormal laboratory values, delay surgery, and pose risk of overtreatment. One frequent example is preadmission INR/PT studies prompting requests for plasma transfusion to correct borderline values.

Preoperative Management of Anemia

Preoperative anemia is common. In one large study conducted in Europe, 31.1 % of men and 26.5 % of women who underwent noncardiac surgical procedures were shown to have preoperative anemia. Importantly, preoperative anemia is an independent risk factor for adverse clinical outcomes that include prolonged duration of hospital stay, higher incidence of major postoperative complications (as compared to non-anemic patients), more frequent admission to intensive care and a high incidence of 30-day

mortality [106–108]. Germane to PBM, preoperative anemia is also associated with increased risk of perioperative blood transfusion [106, 109, 110]. Accurate diagnosis and treatment of anemia is critical—particularly in the stable patient—to prevent delay in surgery, downstream bleeding, and transfusion risk. The benefits of treatment are not restricted to red cell transfusion; while the hematocrit is important for tissue oxygenation, it is also important for coagulation [111]. Therefore, baseline anemia renders patients less likely to tolerate intraoperative blood loss (i.e., given a lower functional reserve) or hemorrhage (e.g., trauma or peripartum hemorrhage)) and more likely to bleed given the rheological effects of low hematocrit on coagulation [112].

Given that anemia is readily detectable, it is a preventable risk factor for adverse surgical outcomes [108]. Therefore, hemoglobin should be determined no less than 28 days prior to the planned surgery with formal evaluation of anemia if low [113]. Some advocate that management should target normal hemoglobin reference ranges with possible postponement of surgery if patients are anemic. However, this needs to be evaluated on an individual basis weighing the risks and benefits of delaying surgery.

Point-of-Care Testing to Guide Transfusion Practice

There are a number of point-of-care (POC) technologies in use that may improve transfusion practice through refined evaluation of hemostasis . Coagulation is a dynamic process and formal (as opposed to POC) laboratory testing with traditional coagulation tests (e.g., activated partial thromboplastin time [APTT] and PT/INR) is not optimal for the evaluation of actively bleeding patients. Specifically, comparatively slow TAT with traditional coagulation tests can lead to results that do not adequately reflect the patient’s status. Furthermore, traditional tests of coagulation were never intended to predict bleeding risk [114] or for use in management of the acutely bleeding patient [115]. Instead, their intended uses were that of monitoring anticoagulant therapy and to aid in the diagnosis of abnormalities of the coagulation cascade. This recognition has motivated for the use of tests that impart a real-time evaluation of coagulation in order to guide transfusion.

The most commonly used POC technologies are thromboelastography (TEG , Hemoscope Corporation, Niles, IL, USA) and rotational thromboelastometry (ROTEM , TEM International GmbH, Munich, Germany) [116]. While TEG was initially described in 1948 [116], licensing

of TEG and ROTEM did not occur until 1996 and 2000, respectively [115]. As a result, their adoption in clinical practice has been relatively recent. The principles of TEG and ROTEM are similar and both provide information about clot initiation, formation, and lysis. Since the assays are performed on citrated whole blood, the clotting characteristics are affected by platelet number and function, fibrinogen level and activity, and factors within the coagulation cascade [115]. However, differences in the test methodologies preclude direct comparison [117]. One key advantage of both TEG and ROTEM over formal testing is a rapid turnaround time (~15–20 min), thus improving on the 30–60 min that is typical of formal testing with conventional coagulation tests.

TEG and ROTEM have similar mechanisms. In TEG, the patient's blood sample is placed in a heated cup (37 °C) and a wire and pin are inserted into the blood. As the cup rotates around the pin, torsion on the wire increases as the clot forms. The dynamics and strength of clot formation are traced, thereby imparting a visual representation of clot formation from activation to attainment of maximal clot stability. TEG also captures information on clot breakdown, thus offering a global assessment of the clotting process. In ROTEM, one key distinction from TEG is that the cup remains stationary while the pin rotates. In this case, impedance of the pin's rotation during clot formation is measured [115]. ROTEM may also be modified through the use of different reagents to evaluate the contribution of fibrinogen and platelets to clot formation [118]. For example, the addition of tissue factor to the assay enables evaluation of the extrinsic clotting pathway similar to the PT , while addition of a platelet inhibitor, cytochalasin, allows for differentiation between platelet dysfunction and fibrinogen deficiency [118, 119].

There has been continued improvement on the original designs of both TEG and ROTEM, which has enabled automation and expanded application to diverse settings such as trauma, cardiac surgery, obstetric hemorrhage, and liver transplantation [118]. The assays are typically operated by an anesthesiologist, who uses the information to evaluate the patient. Characteristic findings (e.g., bleeding associated with thrombocytopenia vs. fibrinogen deficiency) are used to guide optimal blood product use accordingly [118]. In this way, implementation of POC-based algorithms has been shown to reduced blood use in several studies (largely conducted in cardiac patients) [120–123].

Other POC coagulation assays include the activated clotting time (ACT)

and PFA-100 . The ACT is used primarily in the intraoperative setting to monitor the effects of heparin. It is performed by activating the intrinsic pathway of the coagulation cascade through the mixing of a fresh whole blood sample (from the patient) with a contact activator (e.g., kaolin, celite); the time taken to form a fibrin clot is then measured. The assay is analogous to the APTT , although the APTT is performed on plasma rather than whole blood [124]. ACT devices vary with respect to the specific activators that they use, the required blood volume, the operating temperatures, and even by their measurement techniques. Thus, ACT standardization and establishment of multi-institutional guidelines for anticoagulation management using ACT during surgery have not been possible [124, 125]. Finally, The PFA-110 assay (Siemens Healthcare, Malvern, PA, USA) measures platelet adhesion. The test is performed using cartridges with either collagen/epinephrine or collagen/adenosine diphosphate; whole blood is pushed through a membrane with a small opening, simulating arterial high shear stress. The instrument measures the time until closure. While POC evaluation of platelet function has potential utility in PBM, the use of PFA-100 in bleeding and coagulopathic patients is—as yet—not well characterized [115].

Intuitively, real-time evaluation of coagulation should impact clinical outcomes favorably. However, the data are less clear. One systematic review of nine randomized clinical trials failed to show a significant difference in morbidity or mortality in severely bleeding patients when TEG or ROTEM was used [126]. Even when blood use is shown to decrease, this does not necessarily correlate with significantly improved patient outcomes [127]. Similarly, while use of POC TEG and ROTEM for the diagnosis of trauma-induced coagulopathy has expanded, a recent review suggests insufficient evidence to support their use as routine in this setting [128].

Preoperative Autologous Blood Donation

Preoperative autologous blood donation (PAD) refers to collection and storage of the patient’s blood in preparation for certain elective surgeries. The rationale for PAD is that if a transfusion is needed either during or after surgery, the patient’s own blood is available for transfusion, thus reducing the exposure and associated risk of allogeneic transfusion (notably transfusion-transmitted infection and incompatibility). Other cited benefits include supplementation of a limited allogeneic blood supply and a decrease in delays to elective surgical procedures due to blood shortages [129]. PAD gained

popularity in the 1980s and 1990s when the incidence of transfusion-transmitted infections was highest. However, the collective improvement in blood screening, decreased rates of perioperative transfusion (introduction of minimally invasive surgery, intraoperative blood salvage), and concomitant reduction in cost-effectiveness have led to a decline in PAD [129]. In 2011, only 0.7 % of RBC units originated from PAD [11], which represents a marked decline from the peak of 8.5 % in 1992 [130, 131].

PAD is not without risk: bacterial contamination and mistransfusion can still occur [129]. PAD is also associated with an increased frequency of perioperative anemia , particularly if the collection occurs close to the surgery. Paradoxically, PAD actually increases transfusion, the reasons for which are twofold. First, the associated perioperative anemia renders patients more likely to need transfusion, and second, there is perceived safety of autologous blood prompting liberal transfusion practice [132]. PAD has other limitations: given that autologous donors are more likely to have comorbid illness (e.g., cardiorespiratory disease) than allogeneic donors [133], PAD is associated with higher rates and increased severity of donor reactions. In contrast, allogeneic donors need to be healthy to donate. Furthermore, given low reimbursement, not all blood centers are willing to collect autologous donations [134], thus imposing logistical challenges for the patient (i.e., finding a suitable blood center). Furthermore, autologous units are subject to the same risks of product loss as allogeneic units (i.e., due to processing failures and administrative deficiencies); however, in contrast to allogeneic units, autologous units are not easily replaced thus incurring unnecessary delays [129]. Finally, another disadvantage of PAD is cost. The majority of PAD is collected as whole blood, but only the RBC component is used. Therefore, this results in a higher cost per unit of blood than that of allogeneic transfusions [135].

In theory, autologous blood that is not transfused could supplement the allogeneic blood supply . However, in practice, this is not the case since autologous donors do not need to satisfy the same stringent criteria as allogeneic donors. For example, autologous donors can donate with a lower hemoglobin than that necessary for allogeneic donation (greater than 11 g/dL rather than greater than 12.5 g/dL) and are not deferred for positive infectious disease screening. Consequently, some institutions even refuse to store autologous units due to the potential consequences of mistransfusion [129].

Transfusion guidelines in the United Kingdom and Spain suggest

restricting PAD to patients where either allogeneic blood is impractical (e.g., situations where there are rare alloantibodies or alloimmunization with multiple alloantibodies) or in settings where the patients refuse to consent to allogeneic transfusion. The guidelines also indicate that surgical procedures with at least a 50 % risk of requiring three or more units of RBCs could benefit from PAD. If PAD is undertaken, supplementation with iron and erythropoietin is recommended to minimize perioperative anemia. In addition, the donation should be timed to allow sufficient time for recovery (at least 3–4 weeks) prior to surgery while still avoiding expiration of the stored autologous blood [136, 137].

Finally, the cost-effectiveness of PAD has decreased. This follows improved infectious testing of allogeneic blood as well as lower rates of transfusion consequent to PBM. It is estimated that the cost of autologous donation now exceeds $160,000 per quality-adjusted life year (QALY) , which is above what is considered sufficiently cost-effective to justify a medical intervention in the United States [129]. In summary, allogeneic rather than autologous transfusion is recommended for the vast majority of patients with an anticipated transfusion need. However, it may still have a place in settings where blood availability is lacking (e.g., parts of Africa). Furthermore, PAD may be the only available option for patients with rare blood types and/or severe alloimmunization.

Acute Normovolemic Hemodilution

Acute normovolemic hemodilution (ANH) is a preemptive blood conservation technique that addresses some of the deficiencies of PAD. In contrast to PAD where autologous blood is collected and stored days or weeks prior to surgery, in ANH, autologous whole blood is collected immediately prior to the procedure with infusion of crystalloid or colloid to maintain normovolemia. When the surgery is near completion, the anticoagulated, autologous whole blood is reinfused. Unlike PAD, where stored blood lacks functional platelets and clotting factors due to refrigerated storage and separation of components, ANH enables transfusion of functional, whole blood. Importantly, the autologous blood might otherwise have been lost during the surgery. ANH also ensures that blood lost during surgery is of a low hematocrit (hemodiluted), in contrast to that which is re-transfused into the patient.

Assuming that the pre-collection hemoglobin is high, ANH is well

tolerated and safe, providing a cost-saving blood conservation technique , which has been used successfully in a variety of surgical settings (notably cardiac and orthopedic surgery) in adults and pediatric patients alike [138]. Since ANH is performed in association with surgery in the operating room, it not only avoids the inconvenience, cost, and administrative hassle of PAD but also avoids the risk of clerical error or mistransfusion [139].

The use of ANH is optimal in patients with a high-anticipated blood loss (>1500 mL) and high preoperative hemoglobin (12 g/dL). Contraindications to ANH include evidence of ischemia, restrictive or obstructive lung disease, renal disease, untreated hypertension, cirrhosis, coagulopathy, and active infection [140]. Multiple studies have reported on the safety of ANH with no significant increase in myocardial ischemia, infection, or mortality [141]. Germane to blood conservation, ANH has been shown to reduce allogeneic blood transfusion significantly by an average of 1.9 units per patient [141]. It can also be used to compliment other blood conservation techniques. For example, one study reported on the combined use of hemodilution and recombinant activated factor VII (rFVIIa) in pediatric cardiac patients to achieve reduction in allogeneic blood use without compromising safety [142].

Nonetheless, while ANH appears safe, the evidence to support its use is mixed and has largely been gleaned from small studies, many of which have been criticized for methodological flaws [141]. The few studies that have evaluated broader outcomes, such as length of hospital stay, suggest lack of effect . In summary, while ANH has been shown to be a safe, cost-saving blood conservation measure, it requires careful coordination with the anesthesiologist and may not impact long-term outcomes.

Intraoperative Blood Conservation: Cell Salvage

Blood salvage during surgery (syn. cell salvage [CS]) involves intraoperative collection and re-transfusion of the patient's own (autologous) blood. A number of RBC processors are available for this purpose and use centrifugation of the salvaged blood to separate the cellular and plasma component. The RBCs subsequently undergo a washing step to remove cytokines, plasma proteins, and contaminating debris prior to reinfusion into the patient.

Intraoperative blood salvage is safe and effective and importantly reduces allogeneic transfusion [143, 144], having been successfully used in a wide

range of settings that include cardiac, spinal, thoracic, and abdominal surgery. CS has even been used safely in obstetric-related hemorrhage (cesarean section, related hysterectomy, and management of obstetric hemorrhage) despite earlier concerns surrounding amniotic fluid contamination [145–147]. Similar to PAD and ANH , cited benefits of CS are inherent to reduced exposure to allogeneic blood and therefore include avoidance of RBC alloimmunization, selected transfusion reactions, and infectious complications [145].

CS is not without limitations. Foremost, while it does reduce allogeneic blood transfusion, it does not necessarily impact clinical outcomes. In one randomized clinical trial comparing intraoperative blood salvage versus allogeneic transfusion in the context of thoracic or abdominal trauma surgery, the investigators reported reduced allogeneic blood use albeit with no benefit to either survival or rates of postoperative infection [148]. CS also has the potential to produce or exacerbate coagulopathy in part due to the dilutional effect following removal of platelets and plasma prior to reinfusion of the salvaged product. To some extent, this can be addressed through proactive concurrent platelet and/or plasma transfusion; the volume of CS blood loss has been shown to be an independent—albeit poor—predictor of platelet and plasma transfusion [149].

In addition, CS is not necessarily cost-effective. There are fixed costs associated with running the cell processor coupled with a minimum volume of blood loss to maintain the circuit. Therefore, the cost-effectiveness of cell salvage depends on several factors that include the type of surgery, the presence of comorbid disease, and importantly, the extent of bleeding [150]. Geography also impacts the cost-effectiveness and is more likely to prove cost-effective if used in a high-resource country when high-volume blood loss is anticipated given the high cost of allogeneic blood [143]. Finally, similar to PAD , the reasons that have motivated for use of CS (e.g., infectious risk of allogeneic blood transfusion) are less relevant than they were two decades ago.

Pharmacological Alternatives to Blood Transfusion

There is an expanding array of pharmacological agents that may be used to supplement and—in some cases—even replace blood transfusion. Selection depends on the patient’s chronicity and bleeding status. Hematinics are well established for use in the stable non-bleeding patient, while single

recombinant coagulation factors, prothrombin complex concentrates (PCCs) , fibrinogen, antifibrinolytics, and desmopressin have all shown benefit in the acutely bleeding or coagulopathic patient. In certain settings, these interventions may replace multicomponent transfusion therapy (i.e., plasma and RBCs). While an exhaustive review of all pharmacological measures falls beyond the scope of this chapter, this section provides a brief introduction to some of the available options. Importantly, the following information does not address treatment of hypotension that in selected patients can be managed with crystalloids, colloids, and vasopressors as guided by the underlying condition.

The Stable Non-bleeding Patient

Hematinics

Hematinics (e.g., iron, folate, and vitamin B12) are used in the management of anemia. Importantly, since anemia is a group of heterogeneous disorders rather than a discrete entity, this requires comprehensive evaluation (history, physical examination, and laboratory testing) to be effective. Iron deficiency is one common example, where the appropriate treatment varies depending on the pathophysiology of disease. Causes can include low intake (malnutrition), increased demand (pregnancy), absolute loss (bleeding), sequestration (anemia of chronic disease/inflammation), or even a combination of causes. While iron supplementation would benefit patients with malnutrition and obviate the need for downstream transfusion [151–153], it may not be effective in anemia of chronic disease. Interestingly, hepcidin (a peptide hormone secreted by hepatocytes) has been implicated in anemia of chronic disease leading to decreased iron absorption and availability; hepcidin blockade could hold promise for future therapy in this regard.

Oral iron is frequently prescribed for iron deficiency; however, even when indicated, it is poorly tolerated accounting for its notoriously low compliance. Specifically, gastrointestinal side effects (e.g., nausea, constipation, diarrhea) are common [151–153]. Parenteral (i.e., intravenous) iron therapy is an alternative and has been shown to reduce the requirement for red blood cell transfusion (risk ratio 0.74, 95 % confidence interval 0.62–0.88), particularly when administered in combination with erythropoiesis-stimulating agents (ESAs) [154]. Specific advantages of intravenous iron

include improved efficacy in iron deficiency due to malabsorption (e.g., inflammatory bowel disease) and chemotherapy-induced anemia [155]. However, there are risks of reactions to parenteral iron therapy, which vary by the preparation used. For example, high-molecular-weight iron dextran has been shown to confer the highest risk of severe reactions [156] including dose-dependent gastrointestinal and vasoactive reactions [157].

Erythropoiesis-Stimulating Agents (ESAs)

Erythropoiesis-stimulating agents (ESAs) have been used successfully to reduce blood transfusion , most notably in patients with chronic renal disease. One meta-analysis of 57 studies in which recombinant human erythropoietins (epoetin and darbepoetin) were used reported a reduced risk of RBC transfusion (relative risk [RR] = 0.64, 95 % CI = 0.60–0.68) and an improved hematologic response [158]. ESAs have also shown favorable benefit to transfusion risk in elective surgery and in oncology practice (e.g., chemotherapy-induced anemia) [156]. However, the risks of ESAs include increased risk of thrombosis and mortality, particularly when used in oncology patients [159] at hemoglobin values above 10 g/dL [156]. There is also concern that ESAs could affect tumor progression through activation of erythropoietin receptors in tumor cells. Finally, similar to other PBM measures, ESAs have been approved based on their reduction in blood use rather than patient benefit [156].

The Acutely Bleeding Patient

Increased recognition of the adverse effect of coagulopathy on clinical outcomes in the acutely bleeding patient (e.g., surgical, trauma, and obstetric resuscitation) has spurred use of an expanding repertoire of therapeutic alternatives to blood transfusion. These options include antifibrinolytics, rFVIIa, desmopressin, fibrinogen, and PCCs.

Antifibrinolytics and Factor XIII Concentrates

Tranexamic acid (TXA) is a lysine analog that irreversibly blocks binding of plasminogen to plasminogen activator and fibrinogen thereby preventing the degradation of fibrin clots . Factor XIII is necessary for cross-linking of fibrinogen and clot stabilization. Both compounds help decrease clot breakdown. TXA use is well established and has been shown to be safe with a low incidence of side effects and reduced blood use in diverse surgical

settings [160, 161]. In a meta-analysis of 11 randomized controlled trials where TXA was compared with placebo in spine surgery, TXA administration was associated with a reduction in the proportion of patients who received transfusion (risk ratio 0.67 [0.54–0.83]) relative to placebo [162]. Interestingly, topical use of TXA has been shown to have comparable benefit to intravenous administration [163]. Factor XIII concentrates are indicated for prophylactic perioperative management of patients with congenital deficiency of factor XIII.

Desmopressin

Desmopressin is primarily indicated in type I von Willebrand disease and hemophilia A given its ability to increase endothelial cell release of von Willebrand factor and factor VIII. It also promotes coagulation through other less well-understood mechanisms that could account for beneficial effects even in individuals without antecedent coagulopathy. Specifically, desmopressin has been shown to reduce perioperative blood loss (almost 80 mL per patient) and transfusion requirement (0.3 units per patient) albeit without affecting the proportion of patients who receive transfusion [164]. While desmopressin is not recommended for routine use, selected patients may benefit from its administration.

PCCs

Single-factor concentrates have long been used for patients with inherited factor deficiencies (e.g., factors VIII and IX in hemophilia A and B, respectively). PCCs contain variable combinations of the vitamin K-dependent proteins (factors II, VII, IX, and X; proteins C, S, and Z), antithrombin III, and heparin [165]. PCCs are classified as either activated or nonactivated preparations. Factor VIII Bypass Inhibitor Activity (FEIBA) is one example of an activated PCC . In contrast, there are many examples of inactivated PCCs, all of which contain variable levels of the vitamin K-dependent clotting factors and are subclassified into 4 or 3 factor PCCs based on their respective inclusion or exclusion of factor VII [156]. PCCs serve as an alternative to FFP to replenish vitamin K-dependent clotting factors rapidly, which can be used for acute warfarin reversal (particularly the 4-factor PCCs), for bypass of strong factor inhibitors (e.g., factor VIII) and for reversal of therapeutic factor antagonists (e.g., factor Xa or thrombin inhibitors). Compared to plasma, these products replenish factors with a lower risk of volume overload. They can also be used in conjunction with

plasma, where they have shown more effective reversal of warfarin overdose than plasma use alone [166]. Given the benefits of PCCs, they are increasingly being incorporated into transfusion guidelines. For example, the Australasian Society of Thrombosis and Haemostasis recommends the use of plasma concentrates as first line for warfarin overdose reversal [167].

However, while PCCs offer promise as alternatives to standard component therapy, their use is constrained by limited availability and lack of experience outside of specialty care settings. PCCs , in particular activated formulations, also carry risk of thrombosis. However, thrombotic risk, particularly in the case of warfarin reversal, may also be ascribed to underlying disease that required treatment (i.e., antecedent thrombotic risk). Furthermore, the risk can be attenuated through incorporation of antithrombotic factors into some preparations or concurrent administration of low-dose anticoagulant (e.g., heparin). In general, PCCs appear safe with one review reporting low rates of adverse effects at least in patients undergoing reversal of warfarin-induced intracranial hemorrhage [165]. Nonetheless, the recommended use of PCC is limited to bleeding patients with (1) inhibitors to a clotting factor or multiple clotting factors and (2) life-threatening, rapid warfarin reversal when 4-factor PCCs are not available. Finally, as plasma derivatives, there remains risk of transfusion-transmissible infections; however, similar to other plasma derivatives, that risk is extraordinarily low owing to pathogen inactivation during preparation.

Fibrinogen

Although fibrinogen is indicated for the treatment of coagulopathy associated with primary a-, hypo-, and dysfibrinogenemia, there are increased reports of its use in acquired coagulopathy (e.g., trauma, postpartum hemorrhage, and surgery) where it has been shown to decrease the requirement for allogeneic blood products [168, 169]. While fibrinogen may be obtained from either plasma or cryoprecipitate, fibrinogen concentrate preparations have the advantages of standardized dosage, low volume, and a very good safety profile. Preparation includes pasteurization and lyophilization thereby mitigating viral risk in the product. Furthermore, the product has a lower risk of immune or allergic reactions as compared to plasma [169]. Importantly, fibrinogen may be reconstituted and administered rapidly in an emergency, thus bypassing the need for thawing blood products. This is a major advantage over plasma and cryoprecipitate during management of an acutely

bleeding patient.

rFVIIa

rFVIIa acts by binding tissue factor at the site of vascular injury and activates the common coagulation cascade through binding of factor X. It has a second mechanism of action whereby it binds to activated platelets and hones to sites of injury [156]. Despite narrow approved indications (i.e., hemophilia A or B with inhibitors, congenital factor VII deficiency, and acquired hemophilia), off-label use has accounted for the overwhelming majority (97 %) of prescriptions [170]. Recently, the use has diminished both due to cost as well as concerns surrounding thromboembolic complications.

Topical Hemostatic Agents, Sealants, and Adhesives

Topical hemostatic agents are a rapidly expanding and diverse group of therapies that vary by design, mode of application, and mechanism of action. Broadly, they are categorized into hemostats , which promote clot formation; sealants, which stall release of body fluids (e.g., blood, lymph, cerebrospinal fluid); and adhesives , which offer rapid tissue fixation [171]. This classification is somewhat arbitrary as there is overlap between the agents. For example, tissue stabilization will also promote clot formation and enhance tissue repair. The mode of action of the different agents relates to development of a clotting matrix (synthetic or semisynthetic scaffold) and/or promotion of clot formation by virtue of their procoagulant constituents (e.g., fibrin or thrombin). While applied to diverse surgical disciplines, their use and concomitant benefits has most widely shown in orthopedic surgery. Collectively, they can contribute to significant reduction in blood use. For example, fibrin sealants have been shown to reduce perioperative blood loss (average of 161 mL per patient) and rate of exposure to allogeneic transfusion (7 % absolute and 37 % relative) [172].

Adverse effects are few and depend on the product used. First, there may be compression effects with certain agents that swell following administration, and this may contribute to tissue injury. Second, animal derivatives (e.g., bovine or porcine thrombin) can result in antibody formation, which cross-react with native proteins, thus resulting in coagulopathy and bleeding. Animal proteins (e.g., equine collagen) may also cause allergies and anaphylaxis upon exposure. However, antibody formation using recombinant preparations is low (less than 1 %) [173] and has also been shown to be safe on reexposure to the agents [174]. Third, human plasma

derivatives still carry risk of infection, although this is extraordinarily low given extant donor screening and pathogen inactivation and importantly is lower than that of blood component therapy.

Specialized Products and Processes (Table 11.2)

Table 11.2 Specialized components and processing

Specialized product	Components	Major indication(s)	Disadvantages
Irradiation	RBC, platelets	TA-GvHD prevention	− Shorter shelf life (28 days or less) − Processing time (especially if irradiator not onsite) − Potassium leakage − Strict security and regulation considerations if using radioactive materials
Washing	RBC, platelets	− Reduce exposure to plasma proteins in patients with recurrent, severe allergic reactions − Reduce isoagglutinins (e.g., ABO-incompatible platelet) − Reduce potassium for high-risk patients (e.g., neonates, renal failure)	− Cell loss, which, if high, may lead to product loss − Preparation time − Shorter shelf life (24 h for washed RBCs, 4 h for washed platelets)
Volume-reduction/drying	RBC, platelets	− Reduce plasma exposure − Reduce risk of volume overload	− Cell loss, which, if high, may lead to product loss − Preparation time
HLA-match/crossmatch	Platelets	Immune-mediated platelet refractoriness	− Additional testing time for crossmatching and increased cost − HLA-matching requires donor/recipient testing, logistics to coordinate platelet collection and transportation within 5 days
CMV negative	RBC, platelets	Subset of CMV-negative patients with immunosuppression	− Availability may be difficult in donor pools where seroprevalence is high − Challenge of maintaining inventory of CMV-“safe” and CMV-negative products − Low incremental benefit if

			concomitant leukoreduction
Leukoreduction	RBC, platelets	Reduced risk of febrile reactions HLA alloimmunization, CMV transmission, TRIM	Increased cost

Blood products may be considered specialized by virtue of their nonroutine clinical indications, coupled with requirements for additional testing (e.g., HLA-matched platelets or cytomegalovirus [CMV]-seronegative blood) or processing (e.g., cell washing). The relationship to PBM becomes evident whereby uninformed requests for these products can burden blood bank staff, unnecessarily increasing cost and delaying issuing of blood (see Table 11.2). The following are three examples.

CMV-Seronegative Products

Cytomegalovirus (CMV) is unusual in that it is the only transfusion-transmissible pathogen where donor seropositivity does not incur donor deferral. This complicates management of blood bank inventories since CMV-untested, CMV-seropositive, and CMV-seronegative products are all available and CMV transfusion requirements are patient specific . Although infection in immunocompetent adults is usually asymptomatic or characterized by a mild mononucleosis-like illness, infection in immunocompromised hosts and fetuses can result in severe morbidity and mortality. Infection is life long, whereby latent infection is established within mononuclear white blood cells and their precursors, and reactivation is possible with immunosenescence [175].

Transfusion-transmitted CMV (TT-CMV) typically occurs following transfusion of a CMV-naïve recipient with latently infected mononuclear cells and/or circulating CMV DNA from a seropositive donor [176, 177]. Although CMV-seronegative blood markedly reduces this risk, universal provision of CMV-seronegative blood is not feasible given that many older donors are seropositive [178]. Furthermore, even when blood is collected from CMV-seronegative donors, there is residual risk—albeit low—of transmission during the pre-seroconversion “window period” (i.e., acute infection) given CMV viremia in the absence of detectable antibodies [179]. CMV DNA testing has been considered but is unlikely to be implemented given the high cost for marginal incremental reduction in risk owing to

widespread use of leukoreduction [180].

Leukoreduction mitigates risk of TT-CMV given that white blood cells harbor the latent virus [181, 182]. Studies have compared the risk of TT-CMV following leukoreduction versus that with CMV-seronegative units. One meta-analysis showed that the risk of TT-CMV following leukoreduced (CMV-“safe”) and CMV-seronegative blood transfusion was reduced by 93.1 % and 92.3 %, respectively [183]. Therefore, leukoreduced products are considered to have similar risk to TT-CMV as CMV-negative products for most patients [184]. In addition, close CMV surveillance of susceptible patients by viral load testing and aggressive preemptive therapy before symptom onset have increased acceptance of CMV-“safe” blood [185]. However, the ideal approach to TT-CMV mitigation remains controversial [186, 187], and recommendations vary between countries and professional societies [188, 189]. The AABB simply recommends that hospital transfusion services establish internal guidelines regarding prevention of TT-CMV to “at-risk” patients [190]. One important practical point is to use pre-transfusion CMV serology testing to determine patients at risk thus helping to conserve limited inventory of CMV-seronegative blood , i.e., seronegative patients are at higher risk for primary CMV infection.

As an example, the current transfusion guidelines at the University of California, San Francisco, recommend provision of CMV-seronegative blood products to all infants less than 4 months of age, transplant patients, and immunocompromised patients on the neonatal and pediatric services; the majority of adult patients receive leukoreduced CMV-untested blood with only a subset of adult immunocompetent patients (e.g., CMV-seronegative pregnant women) qualifying for CMV-seronegative blood products [191]. In summary, to manage the availability of CMV-seronegative blood effectively, it is important to remember that (a) leukoreduced CMV-“safe” blood is equivalent to CMV-negative blood in most patients and that (b) CMV serology should be obtained to aid in clinical decision making.

Irradiation and Cell Washing

Both irradiation and cell washing have explicit indications. Irradiation is performed to prevent transfusion-associated graft-versus-host disease (TA-GvHD) , while cell washing is used in the setting of recurrent, severe allergic reactions, transfusion of IgA-deficient patients with demonstrable anti-IgA antibodies, and hyperkalemia in selected patients (e.g., neonates and pediatric

cardiac patients) [21].

TA-GvHD is almost uniformly fatal once established; therefore, effective management relies on prevention and identification of recipients at risk [192]. TA-GvHD occurs due to engraftment of donor lymphocytes, the underlying mechanism being one of failed recognition of donor cells as foreign or insufficient immune reserve to contend with those cells (i.e., immunocompromise). Failed recognition occurs in the setting of HLA sharing (e.g., a directed donation from a family member or populations with high genetic homogeneity) and may affect immunocompetent recipients. Immunocompromise, the more common risk group , is harder to define, encompassing diverse illnesses and treatment regimens. Therefore, while some indications for irradiation are well established and should be included in transfusion guidelines (e.g., directed donations from relatives, patients with lymphoproliferative disorders, high-dose chemotherapy, history of fludarabine), requests outside of guidelines may still be justified and merit reevaluation on an individual basis.

Requests for irradiation and/or cell washing outside of guidelines can delay blood product issue and compromise blood products. Both procedures require additional procedural and logistical time, which may be significant if an irradiator and/or cell washer is not present in the transfusion service, whereby the blood needs to be transported to a facility with the necessary equipment (i.e., irradiator and cell washer, respectively). Another disadvantage is significant cell loss and platelet activation with cell washing and potassium leakage with irradiation. Finally, both irradiation and cell washing shorten product shelf lives (in the case of washed RBCs, down to 24 h only), which can contribute to wastage. In short, specialized blood products are important but should be reserved for cases where indeed clinically indicated.

Other

Selected Populations Where Transfusion Is Not an Option

There are situations where blood transfusion is not a viable option either due to lack of efficacy (e.g., severe alloimmunization, autoimmune hemolytic anemia) or refusal for religious (e.g., Jehovah’s witnesses) or cultural

reasons. While rare, these situations serve as a test—albeit extreme—of conservation transfusion practice, drawing on the complete repertoire of available alternatives to blood use. Ironically, this has spurred more widespread application of bloodless surgical programs, affording access to a wider patient population with good effect [193].

Management in these cases reverts to management of anemia, which depends on both timing and severity. In the patient with chronic anemia, there is more opportunity for investigation and management of the underlying cause using pharmacological alternatives to transfusion (e.g., high-dose erythropoietin, supplemental iron, and other hematinics) so as to tide deterioration. Surgical and acutely bleeding patients pose a greater problem. Studies have shown that while the risk of death in patients with a hemoglobin of 7–8 g/dL is low, there is a high risk of death at lower nadirs [194, 195]. To some extent, effective management depends on early recognition of risk with aggressive measures to optimize the patient's status ahead of any surgical intervention. Beyond prevention, recommendations that apply to the acutely bleeding patient include conservative surgical practices (endoscopy, interventional radiology where possible), crystalloids or colloids to maintain intravascular blood volume, vasopressors, and local or topical hemostasis (e.g., fibrin glue) to achieve hemostasis [196]. Surgical procedures should be carefully planned with broad engagement of senior members of the surgical team. Modification of both the surgery (e.g., staged procedures) and anesthesiology support (e.g., perioperative blood salvage) can optimize the patient's chances of a positive outcome [197]. Ironically, triage of high-risk cases toward more experienced surgeons may improve outcomes and—ironically—bias support in favor of bloodless medicine. Ancillary measures that can minimize blood loss include consolidation of laboratory tests, low-volume sampling, and general avoidance of "routine" testing . The need for limited phlebotomy is not unique to the transfusion setting and should be routinely implemented.

For Jehovah's witnesses , both blood donation and blood transfusion are prohibited. This follows an interpretation of selected Biblical passages that suggest that transfusion precludes access to the eternal life [196]. The policy prohibiting blood transfusion is relatively recent (since 1945) and historically has supported excommunication of members who have knowingly received blood transfusion. Blood transfusion is well defined within the faith and includes "red cells, white cells, platelets, and plasma ," which are classified

as primary products . However, a change in 2000 has provided for some interpretation of what might be permissible within “secondary blood products” [198], which are generated through fractionation and processing of primary blood products. Albumin and immunoglobulin are examples of secondary blood products that are generally left to personal decision. However, there is divergence of opinion regarding other products . A liberal interpretation might bar whole blood transfusion yet allow for transfusion of components. In contrast, the more stringent view is that the very act of donation is contrary to the faith, thus barring even pre-stored autologous blood . This underscores the need to discuss options directly with the patient so as to ensure that the medical management is optimal given a narrow ethical and legal framework. Beyond the scope of this chapter, it also emphasizes the need for careful documentation and scrutiny of advanced directives.

Monitoring

Quality Indices to Monitor Blood Use

General Metrics of Transfusion Practice

Quality indices offer invaluable insight into the functioning of the transfusion service. Selection of quality indices should be based on the health care domains that have been outlined by the Institute of Medicine, i.e., effectiveness, delivery of evidence-based care, efficiency, timeliness, safety, patient-centeredness, and equity [199]. Within the context of blood banking, high-yield indices are focused on patient identification, operational effectiveness, blood utilization , and product wastage. These indices are monitored by the transfusion committee to evaluate the blood bank performance, detect changes in clinical practice, and assess the impact of policy and procedure modifications [60].

Both TJC and the College of American Pathologists (CAP) have identified quality measures specific to blood banking. The former has long established both patient identification and specimen labeling as priority patient safety goals [200] given high rates of errors related to specimen identification errors (0.1–5 %) [201]. Germane to PBM, mislabeled specimens with the dreaded “wrong blood in tube” can lead to severe (even fatal) transfusion reactions. Consequently, transfusion services often track

errors in patient identification, the numbers of unsuitable specimens, and the number/type of transfusion reactions. Specimen relabeling is controversial and associated policy varies among institutions [201]. Those indices identified by CAP include the timely review of transfusion reactions, RBC antibody identification, apheresis consultations, and standard operating procedures by appropriate staff and supervising pathologists [202]. TAT is another frequently used measure, which enables assessment of the response time following physician ordering. Surveys of TAT enable laboratories to compare performance against peer groups [203]. In addition to identification of deficiencies in work flow, the monitoring of TAT helps to determine whether interventions improve workflow [204].

Appropriateness of blood use (i.e., clinical practice) can also be monitored with attention to transfusion requests that fall outside of institutional guidelines. This can be performed prospectively or retrospectively. Prospective evaluation is typically undertaken by a representative of the transfusion service (e.g., laboratory medicine resident, fellow or faculty member) and confers the advantages of real-time consultation with the ordering physician. While this proactive response to practice can decrease blood use, it risks delayed release of blood products and invites an antagonistic atmosphere between the transfusion service and clinical staff for a perceived gatekeeping role. In contrast, retrospective review involves auditing of a sample of past transfusion requests for evidence of appropriateness. While less intrusive than prospective review, it lacks effectiveness given that the event has already transpired and the information that is necessary to determine whether the request was appropriate is more difficult to obtain [205, 206].

The Crossmatch-to-Transfusion (C/T) Ratio

The C/T ratio is another commonly used quality measure and provides an objective measure of transfusion service effectiveness, institutional blood utilization, and product wastage. It is important to understand the C/T ratio in the context of blood bank process. When a physician orders a type and crossmatch, the blood bank proceeds to perform testing to determine both the blood type (ABO and Rh) and presence of antibodies (screening), unless a specimen from the past 3 days has already been tested. The requested number of RBC units is crossmatched with the patient sample, and compatible units are allocated for the patient, thus removing those units from the general

inventory pending issue.

A C/T ratio of 1 indicates that every crossmatched unit is being transfused, which is ideal and demonstrates that no unnecessary blood bank testing has taken place (all allocated blood has been issued). On the other hand, a high level of crossmatch requests can strain the blood bank inventory unnecessarily; despite the units' physical presence in the blood bank, the inventory is functionally low given that the blood is designated for use by specific patients. This prompts additional ordering (i.e., outside purchase) of blood. If crossmatched units are not used (either the blood is not issued or it is returned to the blood bank), the allocated units are placed back into the general inventory if not yet expired or out of compliance. This can result in an inventory surplus, with associated wastage. A newly described index, the crossmatch-to-issue ratio (C/I) is similar to the C/T ratio but focuses specifically on the blood bank workflow since blood product issue is the last step occurring in the laboratory [204].

In general, a C/T ratio of less than 2 is desirable, but high-performing institutions can attain C/T ratios of less than 1.5 [207]. Several strategies to minimize the C/T ratio have been proposed. Examples include policy to ensure that clinicians ensure that a current (less than 3 days old) type and screen sample is available if there is anticipated blood use; this allows for rapid issue (within 15–20 min of the request) since typing and screening do not need to be repeated. Similarly, both a well-designed MSBOS and the EXM (see separate sections) can also reduce mismatch between requests vs. transfusion [76, 204].

Wastage

Finally, blood wastage should be quantified and monitored by product type, associated costs, and underlying mechanism, e.g., whether wastage occurs due to product expiration (i.e., outdating) vs. disposal following delayed return of non-transfused from the ward, theater, or clinic. Determining reasons for high product wastage can uncover systemic deficiencies. For example, high rates of product expiration ("outdating") in the laboratory may be due to inventory that is poorly matched to the clinical need (e.g., excessive platelet units in a smaller hospital). Root cause analysis is important to guide appropriate interventions. In one large medical center, blood product wastage in the operating room suites was found to be due to improper storage of components. Using a low-cost initiative (i.e., clinical education and issuing of

simple cards to explain how each product should be stored), wastage declined saving an estimated $131,520 (Table 11.1) [208].

However, like other PBM benchmarking, there is no consensus on the "ideal" wastage. By definition, wastage is undesirable but some level is unavoidable given the unpredictability and high-acuity need for blood, e.g., in the trauma and perioperative settings [209]. Minimization of wastage to levels that are acceptable for a given institution is the goal. If a hospital is part of a larger health care system, there may be strategies to reduce wastage by redistribution of blood products (e.g., platelets) as they approach expiration to busier transfusion services so as to prevent outdating [73].

Blood Substitutes

"Blood substitute" refers specifically to manufactured RBC or artificial oxygen-carrying compounds. Although there are no platelet substitutes, plasma substitutes are already well established through routine use of PCCs and recombinant coagulation factors. The ideal blood substitute would improve upon (or at least match) the function of RBCs. Specifically, it would have an oxygen-carrying capacity that is similar to native hemoglobin; have less antigenicity, longer shelf life (preferably at room temperature), long intravascular half-life, and absent risk of toxicity or infection; and be inert with respect to other cellular and plasma components (e.g., complement cascade) [210]. Suffice to say that there is—as yet—no ideal blood substitute. Nonetheless, RBC substitutes have long garnered interest given their potential advantages of bypassing the need for compatibility testing and of mitigating if not eliminating the risks of alloimmunization and transfusion-transmitted infections. As a result, these products would greatly simplify transfusion inventories and product issue. To date, several classes of RBC substitutes have been described of which the perfluorocarbons (PFCs) and hemoglobin-based oxygen carriers (HBOCs) have been most extensively studied [211, 212].

PFCs, originally developed during the Manhattan project, are inert and stable synthetic fluorine-substituted hydrocarbons. Their application to blood substitutes resides with liquid PFCs being excellent solvents that readily dissolve gases (including oxygen and carbon dioxide), therefore obviating the need for oxygen carrier molecules. Early evidence of their utility was shown in a series of animal submersion experiments demonstrating survival for variable periods of time [212]. PFCs have several deficiencies: the

requirement for high ambient doses of oxygen, which is expensive, and extreme hydrophobicity that requires emulsion with a co-administered surfactant such as lecithin to obtain a reasonable solubility in aqueous solutions [213]. Despite early optimism, widespread use of PFCs has been curtailed by reported adverse effects such as stroke, thrombocytopenia, and flu-like symptoms [214]. Despite a PFC product being the only RBC substitute to ever obtain FDA licensure in humans (Fluosol), the product was short-lived with withdrawal in 1994 given the complexity of use, high cost, and frequency of side effects.

Outside of the PFCs , most research on blood substitutes has focused on hemoglobin. Purified hemoglobin was first used—albeit unsuccessfully—in the 1940s given the propensity for renal failure and hypertension. Although hemoglobin has a critical role as an oxygen carrier for RBCs, free extracellular hemoglobin has several detrimental effects [215]. The globin subunits of the protein are filtered through the glomerulus, causing nephrotoxicity. Hemoglobin also scavenges nitric oxide (NO) , a potent vasodilator and inhibitor of platelet activation; the depletion of NO leads to vasoconstriction and increased systemic and pulmonary artery pressures, which can precipitate cardiac ischemia and thrombosis [215]. Finally, free circulating hemoglobin is more readily oxidized to methemoglobin than hemoglobin protected within RBCs [215]; unlike cell-associated hemoglobin, methemoglobin is unable to bind oxygen. Research and development of HBOCs have focused on modifying hemoglobin to mitigate these adverse effects. The first-generation HBOCs used protein cross-linking to prevent degradation into subunits, thus minimizing harmful kidney filtration . Second-generation HBOCs contained modified hemoglobin and RBC antioxidant enzymes to minimize conversion to the ineffective methemoglobin. The third-generation compounds mimic RBCs using lipid vesicles or polymers as protective shells [216].

Despite progress, HBOCs still demonstrate safety concerns. A meta-analysis published in 2008 analyzed 16 trials involving five different HBOCs and 3711 patients. The study concluded that use of HBOCs is associated with a statistically significant increased risk of death (relative risk 1.30; 95 % confidence interval, 1.05–1.61) and myocardial infarction (relative risk, 2.71; 95 % confidence interval, 1.67–4.40) as compared to controls. The latter varied (e.g., saline, packed RBCs, plasma expanders) but each represented the standard of care for the specific patient population that was being

evaluated [217]. By the end of 2009, all of the original companies who were involved in the development of blood substitutes had ceased operations [215].

However, while HBOCs exhibit risk, their use might still be considered in exceptional circumstances when allogeneic transfusion is not viable (e.g., severe anemia in sickle cell anemia patient with multiple alloantibodies or Jehovah's Witness patient) [218–220]. Although none of the HBOCs have attained FDA approval, Hemopure (purified, cross-linked acellular bovine hemoglobin in modified lactated Ringer's solution) has been approved for human use in South Africa and Russia and has also been permitted in the United States under the compassionate-use FDA guidelines [220]. A case series in 2014 reported on six severely anemic Jehovah's Witness patients, who were given Hemopure as a bridge until ESA and iron therapy began to take effect. Hemopure was infused slowly over 4 h (60 mL/h) to minimize potential vasoconstrictive effects [220], and no direct complications were reported.

Ongoing efforts to develop blood substitutes are very limited. There are new third-generation PEGylated hemoglobin compounds, which appear to have better safety profile than their predecessors given that they promote formation of NO and have less interaction with endothelial cells due to steric hindrance [215]. Sanguinate or bovine PEGylated carboxyhemoglobin has undergone a phase I safety study with no serious adverse events reported [220]. A phase 1 trial in end-stage renal disease patients and a phase 2 trial in sickle cell patients with vaso-occlusive crisis are underway [221–223]. In regard to PBM, blood substitutes are a last resort that is rarely available and should only be entertained where all other options have been exhausted.

Patient Blood Management in Low-Resource Countries

The need for conservative blood management is not confined to high-resource settings. Strained transfusion inventories coupled with high demand for blood are a pervasive problem in much of the so-called developing world. As one example, it is estimated that only 40 % of transfusion demand in Africa is currently being met [224]. Transfusion is a lifesaving therapy for a diverse array of medical conditions such as obstetric hemorrhage, traumatic injury, and malaria, all of which are endemic in resource-poor settings . In part, shortfall in provision in blood is ascribed to deficiencies in donor recruitment and limited infrastructure necessary for collections, processing, and distribution [224]. Nonetheless, the enduring irony is such that despite a

transfusion deficit, blood is being wasted. The latter is multifactorial and encompasses limited national oversight, transfusion policy, and failure to develop and/or implement clinical transfusion guidelines, which collectively contribute to variability in transfusion practice. Furthermore, limited capacity to produce blood components precludes diversification of whole blood.

Many of the described measures that optimize blood conservation are neither high cost nor technologically intensive. Rather than stepwise implementation, many of these initiatives should be adopted in parallel. Foremost, policy and dissemination of evidence-based clinical guidelines are paramount. Second, establishment of a transfusion committee is important to monitor compliance with guidelines and to intervene where practices are nonstandard. Early engagement with the clinical teams is imperative in this regard. Clinical involvement should focus broadly on measures that reduce blood use such as early management of anemia (e.g., in the antenatal anemia clinic), while the blood bank should focus on inventory management with attention to wastage and quality indices. Definition of “resource poor” and “developing” is highly variable; therefore, additional PBM measures should be informed by local capacity and need.

Importantly, the benefits of PBM are even clearer in a resource-limited setting: considered transfusion practice serves to preserve a lifesaving resource, reducing wastage and associated cost where—by definition—resources are limited. Furthermore, infectious risk remains a formidable problem in resource-limited settings. As one example, Africa has a high background prevalence of the major TTIs (e.g., HIV, HBV, and HCV) allied with variability in transfusion screening practices [225, 226], quality assurance , and hemovigilance [224], all of which contribute to high risk of TTIs and bacterial contamination [227]. Collectively, this underscores the need for conservative transfusion practice.

Abbreviations

ABIM American Board of Internal Medicine

ACBSA United States Advisory Committee on Blood Safety and Availability

ACGME Accreditation Council for Graduate Medical Education

ACT Activated clotting time

ANH Acute normovolemic hemodilution
APTT Activated partial thromboplastin time
C/I Crossmatch to issue
C/T Crossmatch to transfusion
CAP College of American Pathologists
CDS Clinical decision support
CFR Code of Federal Regulations
CMV Cytomegalovirus
CS Cell salvage
DRG Diagnosis-related group
EHR Electronic health records
EPO Erythropoietin
ESA Erythropoiesis-stimulating agents
EXM Electronic crossmatch
FDA Food and Drug Administration
FEIBA Factor VIII bypass inhibitor activity
FFP Fresh frozen plasma
HBOC Hemoglobin-based oxygen carriers
HBV Hepatitis B virus
HCV Hepatitis C virus
HDFN Hemolytic disease of the fetus and newborn
HEV Hepatitis E virus
HIV Human immunodeficiency virus
HLA Human leukocyte antigen
INR International normalized ratio
LIS Laboratory information system
MSBOS Maximal surgical blood-ordering schedule
MTP Massive transfusion protocol
NBCUS National Blood Collection and Utilization Survey
NICU Neonatal intensive care units

NICU Neonatal intensive care unit
NO Nitric oxide
ONTraC Ontario transfusion coordinators
PAD Preoperative autologous blood donation
PBM Patient blood management
PCC Prothrombin complex concentrates
PEG Polyethylene glycol
PFC Perfluorocarbons
POC Point-of-care
PT Prothrombin time
QALY Quality-adjusted life year
RBC Red blood cell
rFVIIa Recombinant activated factor VII
RhD Rhesus D red blood cell antigen
ROTEM Rotational thromboelastometry
TACO Transfusion-associated circulatory overload
TA-GvHD Transfusion-associated graft-versus-host disease
TAT Turnaround times
TEG Thromboelastography
TJC The Joint Commission
TRALI Transfusion-related acute lung injury
TRIM Transfusion-related immunomodulation
TSO Transfusion safety officer
TT-CMV Transfusion-transmitted cytomegalovirus
TTI Transfusion-transmitted infections
TXA Tranexamic acid
WA Western Australia
WHO World Health Organization

References

1. Goodnough LT, Shander A. Patient blood management. Anesthesiology. 2012;116(6):1367–76. [PubMed]

2. Hebert PC, Transfusion Requirements in Critical Care Investigators and the Canadian Critical Care Trials Group. Transfusion requirements in critical care (TRICC): a multicentre, randomized, controlled clinical study. Br J Anaesth. 1998;81 Suppl 1:25–33. [PubMed]

3. Perkins HA, Busch MP. Transfusion-associated infections: 50 years of relentless challenges and remarkable progress. Transfusion. 2010;50(10):2080–99. [PubMed]

4. Zou S, Dorsey KA, Notari EP, Foster GA, Krysztof DE, Musavi F, et al. Prevalence, incidence, and residual risk of human immunodeficiency virus and hepatitis C virus infections among United States blood donors since the introduction of nucleic acid testing. Transfusion. 2010;50(7):1495–504. [PubMed]

5. Zou S, Stramer SL, Dodd RY. Donor testing and risk: current prevalence, incidence, and residual risk of transfusion-transmissible agents in US allogeneic donations. Transfus Med Rev. 2012;26(2):119–28. [PubMed]

6. Hendrickson JE, Hillyer CD. Noninfectious serious hazards of transfusion. Anesth Analg. 2009;108(3):759–69. [PubMed]

7. Hofmann A, Ozawa S, Farrugia A, Farmer SL, Shander A. Economic considerations on transfusion medicine and patient blood management. Best Pract Res Clin Anaesthesiol. 2013;27(1):59–68. [PubMed]

8. Berwick DM, Hackbarth AD. Eliminating waste in US health care. JAMA. 2012;307(14):1513–6. [PubMed]

9. Goodnough LT, Shah N. The next chapter in patient blood management: real-time clinical decision support. Am J Clin Pathol. 2014;142(6):741–7. [PubMed]

10. Kacker S, Frick KD, Tobian AA. The costs of transfusion: economic evaluations in transfusion medicine, Part 1. Transfusion. 2013;53(7):1383–5. [PubMed]

11. HHS. The 2011 National Blood Collection and Utilization Survey report. Washington, DC: U.S. Department of Health & Human Services; 2011.

12. Shander A, Hofmann A, Ozawa S, Theusinger OM, Gombotz H, Spahn DR. Activity-based costs of blood transfusions in surgical patients at four hospitals. Transfusion. 2010;50(4):753–65. [PubMed]

13. Jefferies LC, Sachais BS, Young DS. Blood transfusion costs by diagnosis-related groups in 60 university hospitals in 1995. Transfusion. 2001;41(4):522–9.
[PubMed]

14. Shortt J, Polizzotto MN, Waters N, Borosak M, Moran M, Comande M, et al. Assessment of the urgency and deferability of transfusion to inform emergency blood planning and triage: the bloodhound prospective audit of red blood cell use. Transfusion. 2009;49(11):2296–303.
[PubMed]

15. Frank SM, Savage WJ, Rothschild JA, Rivers RJ, Ness PM, Paul SL, et al. Variability in blood and blood component utilization as assessed by an anesthesia information management system. Anesthesiology. 2012;117(1):99–106.
[PubMed]

16. Frank SM, Resar LM, Rothschild JA, Dackiw EA, Savage WJ, Ness PM. A novel method of data analysis for utilization of red blood cell transfusion. Transfusion. 2013;53(12):3052–9.
[PubMed]

17. Ejaz A, Spolverato G, Kim Y, Frank SM, Pawlik TM. Variation in triggers and use of perioperative blood transfusion in major gastrointestinal surgery. Br J Surg. 2014;101(11):1424–33.
[PubMed]

18. Henry E, Christensen RD, Sheffield MJ, Eggert LD, Carroll PD, Minton SD, et al. Why do four NICUs using identical RBC transfusion guidelines have different gestational age-adjusted RBC transfusion rates? J Perinatol. 2015;35(2):132–6.
[PubMed]

19. Roubinian NH, Escobar GJ, Liu V, Gardner MN, Carson JL, Kleinman SH, et al. Decreased red blood cell use and mortality in hospitalized patients. JAMA Intern Med. 2014;174(8):1405–7.
[PubMed][PubMedCentral]

20. Pena JR, Dzik WS. Utilization management in the blood transfusion service. Clin Chim Acta. 2014;427:178–82.
[PubMed]

21. Fung MK, Grossman BJ, Hillyer C, Westhoff CM, editors. AABB technical manual. 18th ed. Bethesda, MD: AABB; 2014.

22. Hess JR, Lelkens CC, Holcomb JB, Scalea TM. Advances in military, field, and austere transfusion medicine in the last decade. Transfus Apher Sci. 2013;49(3):380–6.
[PubMed]

23. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA. 2015;313(5):471–82.
[PubMed][PubMedCentral]

24. Murdock AD, Berseus O, Hervig T, Strandenes G, Lunde TH. Whole blood: the future of traumatic hemorrhagic shock resuscitation. Shock. 2014;41 Suppl 1:62–9.
[PubMed]

25. Jobes DR, Sesok-Pizzini D, Friedman D. Reduced transfusion requirement with use of fresh whole blood in pediatric cardiac surgical procedures. Ann Thorac Surg. 2015;99(5):1706–11. [PubMed]

26. Mou SS, Giroir BP, Molitor-Kirsch EA, Leonard SR, Nikaidoh H, Nizzi F, et al. Fresh whole blood versus reconstituted blood for pump priming in heart surgery in infants. N Engl J Med. 2004;351(16):1635–44. [PubMed]

27. Wiegmann TL, Mintz PD. The growing role of AABB clinical practice guidelines in improving patient care. Transfusion. 2015;55(5):935–6. [PubMed]

28. Berger MD, Gerber B, Arn K, Senn O, Schanz U, Stussi G. Significant reduction of red blood cell transfusion requirements by changing from a double-unit to a single-unit transfusion policy in patients receiving intensive chemotherapy or stem cell transplantation. Haematologica. 2012;97(1):116–22. [PubMed][PubMedCentral]

29. Hardy JF. Current status of transfusion triggers for red blood cell concentrates. Transfus Apher Sci. 2004;31(1):55–66. [PubMed]

30. Hogshire L, Carson JL. Red blood cell transfusion: what is the evidence when to transfuse? Curr Opin Hematol. 2013;20(6):546–51. [PubMed]

31. Carson JL, Grossman BJ, Kleinman S, Tinmouth AT, Marques MB, Fung MK, et al. Red blood cell transfusion: a clinical practice guideline from the AABB. Ann Intern Med. 2012;157(1):49–58. [PubMed]

32. Tinmouth A, Thompson T, Arnold DM, Callum JL, Gagliardi K, Lauzon D, et al. Utilization of frozen plasma in Ontario: a provincewide audit reveals a high rate of inappropriate transfusions. Transfusion. 2013;53(10):2222–9. [PubMed]

33. Food and Drug Administration. Fatalities Reported to FDA Following Blood Collection and Transfusion: Annual Summary for Fiscal Year 2012. Rockville, MD: CBER Office of Communication, Training, and Manufacturers Assistance, 2014.

34. Abdel-Wahab OI, Healy B, Dzik WH. Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. Transfusion. 2006;46(8):1279–85. [PubMed]

35. Szczepiorkowski ZM, Dunbar NM. Transfusion guidelines: when to transfuse. Hematology Am Soc Hematol Educ Program. 2013;2013:638–44. [PubMed]

36. UCSF. Fresh frozen plasma (FFP). 2015. http://labmed.ucsf.edu/labmanual/mftlng-mtzn/test/info/

4bb.html - FFP. Accessed 17 Aug 2015.

37. Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, et al. Platelet transfusion: a clinical practice guideline from the AABB. Ann Intern Med. 2015;162(3):205–13.
[PubMed]

38. Slichter SJ. Relationship between platelet count and bleeding risk in thrombocytopenic patients. Transfus Med Rev. 2004;18(3):153–67.
[PubMed]

39. Gaydos LA, Freireich EJ, Mantel N. The quantitative relation between platelet count and hemorrhage in patients with acute leukemia. N Engl J Med. 1962;266:905–9.
[PubMed]

40. Rebulla P, Finazzi G, Marangoni F, Avvisati G, Gugliotta L, Tognoni G, Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto, et al. The threshold for prophylactic platelet transfusions in adults with acute myeloid leukemia. N Engl J Med. 1997;337(26):1870–5.
[PubMed]

41. Heddle NM, Cook RJ, Sigouin C, Slichter SJ, Murphy M, Rebulla P. A descriptive analysis of international transfusion practice and bleeding outcomes in patients with acute leukemia. Transfusion. 2006;46(6):903–11.
[PubMed]

42. Nascimento B, Goodnough LT, Levy JH. Cryoprecipitate therapy. Br J Anaesth. 2014;113(6):922–34.
[PubMed][PubMedCentral]

43. Diaz R, Soundar E, Hartman SK, Dreyer Z, Teruya J, Hui SK. Granulocyte transfusions for children with infection and neutropenia or granulocyte dysfunction. Pediatr Hematol Oncol. 2014;31(5):425–34.
[PubMed]

44. Estcourt LJ, Stanworth S, Doree C, Blanco P, Hopewell S, Trivella M, et al. Granulocyte transfusions for preventing infections in people with neutropenia or neutrophil dysfunction. Cochrane Database Syst Rev. 2015;6:CD005341.

45. Price T. SCI-16 the RING study: a randomized controlled trial of GCSF-stimulated granulocytes in granulocytopenic patients. 56th ASH annual meeting and exposition, San Francisco, CA, 6 Dec 2014.

46. Greinacher A, Fendrich K, Brzenska R, Kiefel V, Hoffmann W. Implications of demographics on future blood supply: a population-based cross-sectional study. Transfusion. 2011;51(4):702–9.
[PubMed]

47. Benjamin RJ, Whitaker BI. Boom or bust? Estimating blood demand and supply as the baby boomers age. Transfusion. 2011;51(4):670–3.
[PubMed]

48. Freedman J. The ONTraC Ontario program in blood conservation. Transfus Apher Sci. 2014;50(1):32–6.

[PubMed]

49. Farmer SL, Towler SC, Leahy MF, Hofmann A. Drivers for change: Western Australia Patient Blood Management Program (WA PBMP), World Health Assembly (WHA) and Advisory Committee on Blood Safety and Availability (ACBSA). Best Pract Res Clin Anaesthesiol. 2013;27(1):43–58.
[PubMed]

50. Leahy MF, Roberts H, Mukhtar SA, Farmer S, Tovey J, Jewlachow V, et al. A pragmatic approach to embedding patient blood management in a tertiary hospital. Transfusion. 2014;54(4):1133–45.
[PubMed]

51. Spahn DR, Shander A, Hofmann A. The chiasm: transfusion practice versus patient blood management. Best Pract Res Clin Anaesthesiol. 2013;27(1):37–42.
[PubMed]

52. Fischer DP, Zacharowski KD, Muller MM, Geisen C, Seifried E, Muller H, et al. Patient blood management implementation strategies and their effect on physicians' risk perception, clinical knowledge and perioperative practice—the Frankfurt experience. Transfus Med Hemother. 2015;42(2):91–7.
[PubMed][PubMedCentral]

53. Shander A, Van Aken H, Colomina MJ, Gombotz H, Hofmann A, Krauspe R, et al. Patient blood management in Europe. Br J Anaesth. 2012;109(1):55–68.
[PubMed][PubMedCentral]

54. JCHO. Patient Blood Management Performance Measures Project. 2011. http://www.jointcommission.org/patient_blood_management_performance_measures_project/default.aspx. Accessed 4 June 2015.

55. JCHO. Coming soon: Patient Blood Management Certification option. The Joint Commission Lab Focus [Internet]. 2013; 2015(3):1. http://www.jointcommission.org/assets/1/18/lab_focus_3_2013.pdf. Accessed 4 June 2015.

56. ACGME. ACGME program requirements for graduate medical education in blood banking/transfusion medicine. 2015. https://www.acgme.org/acgmeweb/Portals/0/PFAssets/ProgramRequirements/305_blood_banking_path_07012015_1-YR.pdf. Accessed 11 Aug 2015.

57. AABB. Building a better patient blood management program: identifying tools, solving problems and promoting patient safety. 2015. http://www.aabb.org/pbm/Documents/pbm-whitepaper-form-direct.html. Accessed 4 June 2015.

58. ABIM. Choosing wisely: five things physicians and patients should question. 2014. http://www.aabb.org/pbm/Documents/Choosing-Wisely-Five-Things-Physicians-and-Patients-Should-Question.PDF. 4 June 2015.

59. Society of Thoracic Surgeons Blood Conservation Guideline Task F, Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg. 2011;91(3):944–82.

60. Kaur G, Kaur P. Hospital transfusion committee: role and responsibilities. Indian J Pathol Microbiol. 2014;57(2):352–4.
[PubMed]

61. Dzik WH, Corwin H, Goodnough LT, Higgins M, Kaplan H, Murphy M, et al. Patient safety and blood transfusion: new solutions. Transfus Med Rev. 2003;17(3):169–80.
[PubMed]

62. Saxena S, Shulman IA. Resurgence of the blood utilization committee. Transfusion. 2003;43(8):998–1006.
[PubMed]

63. AuBuchon JP, Puca K, Saxena S, Shulman IA, Waters JH. Getting started in patient blood management. Bethesda, MD: AABB, 2011.

64. Zijlker-Jansen PY, Janssen MP, van Tilborgh-de Jong AJ, Schipperus MR, Wiersum-Osselton JC. Quality indicators for the hospital transfusion chain: a national survey conducted in 100 Dutch hospitals. Vox Sang. 2015;109(3):287–95.
[PubMed]

65. Boral LI, Bernard A, Hjorth T, Davenport D, Zhang D, MacIvor DC. How do I implement a more restrictive transfusion trigger of hemoglobin level of 7 g/dL at my hospital? Transfusion. 2015;55(5):937–45.
[PubMed]

66. Vrotsos E, Gonzalez B, Goldszer RC, Rosen G, La Pietra A, Howard L. Improving blood transfusion practice by educational emphasis of the Blood Utilization Committee: experience of one hospital. Transfus Clin Biol. 2015;22(1):1–4.
[PubMed]

67. Linden JV, Wagner K, Voytovich AE, Sheehan J. Transfusion errors in New York State: an analysis of 10 years' experience. Transfusion. 2000;40(10):1207–13.
[PubMed]

68. Sazama K. Reports of 355 transfusion-associated deaths: 1976 through 1985. Transfusion. 1990;30(7):583–90.
[PubMed]

69. Sharma G, Parwani AV, Raval JS, Triulzi DJ, Benjamin RJ, Pantanowitz L. Contemporary issues in transfusion medicine informatics. J Pathol Inform. 2011;2:3.
[PubMed][PubMedCentral]

70. Cheng YW, Wilkinson JM. An experience of the introduction of a blood bank automation system (Ortho AutoVue Innova) in a regional acute hospital. Transfus Apher Sci. 2015;53:58–63.
[PubMed]

71. Chapman JF, Milkins C, Voak D. The computer crossmatch: a safe alternative to the serological crossmatch. Transfus Med. 2000;10(4):251–6.
[PubMed]

72. Veihola M, Aroviita P, Linna M, Sintonen H, Kekomaki R. Variation of platelet production and

discard rates in 17 blood centers representing 10 European countries from 2000 to 2002. Transfusion. 2006;46(6):991–5.
[PubMed]

73. Gomez AT, Quinn JG, Doiron DJ, Watson S, Crocker BD, Cheng CK. Implementation of a novel real-time platelet inventory management system at a multi-site transfusion service. Transfusion. 2015;55:2070–5.
[PubMed]

74. Butch SH. Computerization in the transfusion service. Vox Sang. 2002;83 Suppl 1:105–10.
[PubMed]

75. AABB, editor. AABB standards for blood bank and transfusion services, 29th ed. Bethesda, MD: AABB; 2014.

76. Frank SM, Oleyar MJ, Ness PM, Tobian AA. Reducing unnecessary preoperative blood orders and costs by implementing an updated institution-specific maximum surgical blood order schedule and a remote electronic blood release system. Anesthesiology. 2014;121(3):501–9.
[PubMed][PubMedCentral]

77. Mazepa MA, Raval JS, Park YA, Education Committee of the Academy of Clinical Laboratory P, Scientists. Pathology consultation on electronic crossmatch. Am J Clin Pathol. 2014;141(5):618–24.
[PubMed]

78. Bloch EM, Cohn C, Bruhn R, Hirschler N, Nguyen KA. A cross-sectional pilot study of blood utilization in 27 hospitals in Northern California. Am J Clin Pathol. 2014;142(4):498–505.
[PubMed]

79. Hunt DL, Haynes RB, Hanna SE, Smith K. Effects of computer-based clinical decision support systems on physician performance and patient outcomes: a systematic review. JAMA. 1998;280(15):1339–46.
[PubMed]

80. Hibbs SP, Nielsen ND, Brunskill S, Doree C, Yazer MH, Kaufman RM, et al. The impact of electronic decision support on transfusion practice: a systematic review. Transfus Med Rev. 2015;29(1):14–23.
[PubMed]

81. Goodnough LT, Shieh L, Hadhazy E, Cheng N, Khari P, Maggio P. Improved blood utilization using real-time clinical decision support. Transfusion. 2014;54(5):1358–65.
[PubMed]

82. Fernandez Perez ER, Winters JL, Gajic O. The addition of decision support into computerized physician order entry reduces red blood cell transfusion resource utilization in the intensive care unit. Am J Hematol. 2007;82(7):631–3.
[PubMed]

83. Richardson NG, Bradley WN, Donaldson DR, O'Shaughnessy DF. Maximum surgical blood ordering schedule in a district general hospital saves money and resources. Ann R Coll Surg Engl. 1998;80(4):262–5.

[PubMed][PubMedCentral]

84. Cheng G. Experiences with “self service” electronic blood banking. Vox Sang. 1998;74 Suppl 2:427–9.
[PubMed]

85. Shaz BH, Dente CJ, Harris RS, MacLeod JB, Hillyer CD. Transfusion management of trauma patients. Anesth Analg. 2009;108(6):1760–8.
[PubMed][PubMedCentral]

86. Dente CJ, Shaz BH, Nicholas JM, Harris RS, Wyrzykowski AD, Patel S, et al. Improvements in early mortality and coagulopathy are sustained better in patients with blunt trauma after institution of a massive transfusion protocol in a civilian level I trauma center. J Trauma. 2009;66(6):1616–24.
[PubMed]

87. Baumann Kreuziger LM, Morton CT, Subramanian AT, Anderson CP, Dries DJ. Not only in trauma patients: hospital-wide implementation of a massive transfusion protocol. Transfus Med. 2014;24(3):162–8.
[PubMed]

88. Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma. 2007;63(4):805–13.
[PubMed]

89. Cotton BA, Gunter OL, Isbell J, Au BK, Robertson AM, Morris Jr JA, et al. Damage control hematology: the impact of a trauma exsanguination protocol on survival and blood product utilization. J Trauma. 2008;64(5):1177–82. Discussion 82–3.
[PubMed]

90. Pham HP, Shaz BH. Update on massive transfusion. Br J Anaesth. 2013;111 Suppl 1:i71–82.
[PubMed]

91. Holcomb JB, del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, et al. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg. 2013;148(2):127–36.
[PubMed][PubMedCentral]

92. Waters JH. Role of the massive transfusion protocol in the management of haemorrhagic shock. Br J Anaesth. 2014;113 Suppl 2:ii3–8.

93. Dudaryk R, Hess AS, Varon AJ, Hess JR. What is new in the blood bank for trauma resuscitation. Curr Opin Anaesthesiol. 2015;28(2):206–9.
[PubMed]

94. Hendrickson JE, Shaz BH, Pereira G, Parker PM, Jessup P, Atwell F, et al. Implementation of a pediatric trauma massive transfusion protocol: one institution’s experience. Transfusion. 2012;52(6):1228–36.
[PubMed]

95. Mitra B, O'Reilly G, Cameron PA, Zatta A, Gruen RL. Effectiveness of massive transfusion protocols on mortality in trauma: a systematic review and meta-analysis. ANZ J Surg. 2013;83(12):918–23.
[PubMed]

96. de Haas M, Thurik FF, Koelewijn JM, van der Schoot CE. Haemolytic disease of the fetus and newborn. Vox Sang. 2015;109:99–113.
[PubMed]

97. Egbor M, Knott P, Bhide A. Red-cell and platelet alloimmunisation in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2012;26(1):119–32.
[PubMed]

98. Wiener AS, Gordon EB. Simple method of preparing anti-Rh serum in normal male donors. Am J Clin Pathol. 1947;17(1):67–70.
[PubMed]

99. Gunson HH, Stratton F, Cooper DG, Rawlinson VI. Primary immunization of Rh-negative volunteers. Br Med J. 1970;1(5696):593–5.
[PubMed][PubMedCentral]

100. Tchakarov A, Hobbs R, Bai Y. Transfusion of D+ red blood cells to D- individuals in trauma situations. Immunohematology. 2014;30(4):149–52.
[PubMed]

101. Yazer MH, Triulzi DJ. Detection of anti-D in D- recipients transfused with D+ red blood cells. Transfusion. 2007;47(12):2197–201.
[PubMed]

102. Schonewille H, Haak HL, van Zijl AM. Alloimmunization after blood transfusion in patients with hematologic and oncologic diseases. Transfusion. 1999;39(7):763–71.
[PubMed]

103. Baldwin ML, Ness PM, Scott D, Braine H, Kickler TS. Alloimmunization to D antigen and HLA in D-negative immunosuppressed oncology patients. Transfusion. 1988;28(4):330–3.
[PubMed]

104. AABB. Blood FAQ. http://www.aabb.org/tm/Pages/bloodfaq.aspx - a8.

105. UBS. A new standard of transfusion care: appropriate use of O-negative red blood cells. 2015. http://hospitals.unitedbloodservices.org/optimumtx/index.html. Accessed 18 May 2015.

106. Tee MC, Shubert CR, Ubl DS, Habermann EB, Nagorney DM, Que FG. Preoperative anemia is associated with increased use of hospital resources in patients undergoing elective hepatectomy. Surgery. 2015;158:1027–36.
[PubMed]

107. Baron DM, Hochrieser H, Posch M, Metnitz B, Rhodes A, Moreno RP, et al. Preoperative anaemia is associated with poor clinical outcome in non-cardiac surgery patients. Br J Anaesth. 2014;113(3):416–23.
[PubMed]

108. Richards T, Musallam KM, Nassif J, Ghazeeri G, Seoud M, Gurusamy KS, et al. Impact of preoperative anaemia and blood transfusion on postoperative outcomes in gynaecological surgery. PLoS One. 2015;10(7):e0130861.

109. Jans O, Jorgensen C, Kehlet H, Johansson PI, Lundbeck Foundation Centre for Fast-track H, Knee Replacement Collaborative G. Role of preoperative anemia for risk of transfusion and postoperative morbidity in fast-track hip and knee arthroplasty. Transfusion. 2014;54(3):717–26. [PubMed]

110. Khanna MP, Hebert PC, Fergusson DA. Review of the clinical practice literature on patient characteristics associated with perioperative allogeneic red blood cell transfusion. Transfus Med Rev. 2003;17(2):110–9. [PubMed]

111. Sorensen B, Fries D. Emerging treatment strategies for trauma-induced coagulopathy. Br J Surg. 2012;99 Suppl 1:40–50. [PubMed]

112. Darlington DN, Delgado AV, Kheirabadi BS, Fedyk CG, Scherer MR, Pusateri AE, et al. Effect of hemodilution on coagulation and recombinant factor VIIa efficacy in human blood in vitro. J Trauma. 2011;71(5):1152–63. [PubMed]

113. Goodnough LT, Maniatis A, Earnshaw P, Benoni G, Beris P, Bisbe E, et al. Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. Br J Anaesth. 2011;106(1):13–22. [PubMed][PubMedCentral]

114. Segal JB, Dzik WH, Transfusion Medicine/Hemostasis Clinical Trials N. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. Transfusion. 2005;45(9):1413–25. [PubMed]

115. Theusinger OM, Stein P, Levy JH. Point of care and factor concentrate-based coagulation algorithms. Transfus Med Hemother. 2015;42(2):115–21. [PubMed][PubMedCentral]

116. Lance MD. A general review of major global coagulation assays: thrombelastography, thrombin generation test and clot waveform analysis. Thromb J. 2015;13:1. [PubMed][PubMedCentral]

117. Sankarankutty A, Nascimento B, Teodoro da Luz L, Rizoli S. TEG(R) and ROTEM(R) in trauma: similar test but different results? World J Emerg Surg. 2012;7 Suppl 1:S3.

118. Whiting D, DiNardo JA. TEG and ROTEM: technology and clinical applications. Am J Hematol. 2014;89(2):228–32. [PubMed]

119. Butwick AJ, Goodnough LT. Transfusion and coagulation management in major obstetric hemorrhage. Curr Opin Anaesthesiol. 2015;28(3):275–84. [PubMed][PubMedCentral]

120. Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vela-Cantos F, Ergin MA. Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. Anesth Analg. 1999;88(2):312–9.
[PubMed]

121. Nuttall GA, Oliver WC, Santrach PJ, Bryant S, Dearani JA, Schaff HV, et al. Efficacy of a simple intraoperative transfusion algorithm for nonerythrocyte component utilization after cardiopulmonary bypass. Anesthesiology. 2001;94(5):773–81. Discussion 5A–6A.

122. Ak K, Isbir CS, Tetik S, Atalan N, Tekeli A, Aljodi M, et al. Thromboelastography-based transfusion algorithm reduces blood product use after elective CABG: a prospective randomized study. J Card Surg. 2009;24(4):404–10.
[PubMed]

123. Gorlinger K, Dirkmann D, Hanke AA, Kamler M, Kottenberg E, Thielmann M, et al. First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. Anesthesiology. 2011;115(6):1179–91.
[PubMed]

124. Finley A, Greenberg C. Review article: heparin sensitivity and resistance: management during cardiopulmonary bypass. Anesth Analg. 2013;116(6):1210–22.
[PubMed]

125. Galli A, Palatnik A. What is the proper activated clotting time (ACT) at which to remove a femoral sheath after PCI? What are the best “protocols” for sheath removal? Crit Care Nurse. 2005;25(2):88–92, 94–5.

126. Afshari A, Wikkelso A, Brok J, Moller AM, Wetterslev J. Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. Cochrane Database Syst Rev. 2011;(3):CD007871.

127. Wang SC, Shieh JF, Chang KY, Chu YC, Liu CS, Loong CC, et al. Thromboelastography-guided transfusion decreases intraoperative blood transfusion during orthotopic liver transplantation: randomized clinical trial. Transplant Proc. 2010;42(7):2590–3.
[PubMed]

128. Hunt H, Stanworth S, Curry N, Woolley T, Cooper C, Ukoumunne O, et al. Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) for trauma induced coagulopathy in adult trauma patients with bleeding. Cochrane Database Syst Rev. 2015;2:CD010438.

129. Vassallo R, Goldman M, Germain M, Lozano M, BEST Collaborative. Preoperative autologous blood donation: waning indications in an era of improved blood safety. Transfus Med Rev. 2015;29:268–75.

130. Brecher ME, Goodnough LT. The rise and fall of preoperative autologous blood donation (editorial). Transfusion. 2001;41:1459–62; Transfusion. 2002;42(12):1618–22.

131. Brecher ME, Goodnough LT. The rise and fall of preoperative autologous blood donation. Transfusion. 2001;41(12):1459–62.
[PubMed]

132. Henry DA, Carless PA, Moxey AJ, O'Connell D, Forgie MA, Wells PS, et al. Pre-operative autologous donation for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2002;(2):CD003602.

133. Popovsky MA, Whitaker B, Arnold NL. Severe outcomes of allogeneic and autologous blood donation: frequency and characterization. Transfusion. 1995;35(9):734–7.
[PubMed]

134. Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine. Second of two parts—blood conservation. N Engl J Med. 1999;340(7):525–33.
[PubMed]

135. Etchason J, Petz L, Keeler E, Calhoun L, Kleinman S, Snider C, et al. The cost effectiveness of preoperative autologous blood donations. N Engl J Med. 1995;332(11):719–24.
[PubMed]

136. Leal-Noval SR, Munoz M, Asuero M, Contreras E, Garcia-Erce JA, Llau JV, et al. Spanish Consensus Statement on alternatives to allogeneic blood transfusion: the 2013 update of the "Seville Document". Blood Transfus. 2013;11(4):585–610.
[PubMed][PubMedCentral]

137. British Committee for Standards in Haematology TTF, Boulton FE, James V. Guidelines for policies on alternatives to allogeneic blood transfusion. 1. Predeposit autologous blood donation and transfusion. Transfus Med. 2007;17(5):354–65.

138. Habler O, Schwenzer K, Zimmer K, Prager M, Konig U, Oppenrieder K, et al. Effects of standardized acute normovolemic hemodilution on intraoperative allogeneic blood transfusion in patients undergoing major maxillofacial surgery. Int J Oral Maxillofac Surg. 2004;33(5):467–75.
[PubMed]

139. Shander A, Perelman S. The long and winding road of acute normovolemic hemodilution. Transfusion. 2006;46(7):1075–9.
[PubMed]

140. Shander A, Rijhwani TS. Acute normovolemic hemodilution. Transfusion. 2004;44 Suppl 12:26S–34.
[PubMed]

141. Carless P, Moxey A, O'Connell D, Henry D. Autologous transfusion techniques: a systematic review of their efficacy. Transfus Med. 2004;14(2):123–44.
[PubMed]

142. Winch PD, Naguib AN, Bradshaw JR, Galantowicz M, Tobias JD. Decreasing the need for transfusion: infant cardiac surgery using hemodilution and recombinant factor VIIa. Pediatr Cardiol. 2013;34(1):119–24.
[PubMed]

143. Xie Y, Shen S, Zhang J, Wang W, Zheng J. The efficacy, safety and cost-effectiveness of intra-operative cell salvage in high-bleeding-risk cardiac surgery with cardiopulmonary bypass: a prospective randomized and controlled trial. Int J Med Sci. 2015;12(4):322–8.
[PubMed][PubMedCentral]

144. Carless PA, Henry DA, Moxey AJ, O'Connell D, Brown T, Fergusson DA. Cell salvage for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2010; (4):CD001888.

145. Milne ME, Yazer MH, Waters JH. Red blood cell salvage during obstetric hemorrhage. Obstet Gynecol. 2015;125(4):919–23.
[PubMed]

146. Morikawa M, Kuramoto A, Nakayama M, Oguchi H, Hasegawa M, Funakoshi T, et al. Intraoperative red cell salvage during obstetric surgery in 50 Japanese women. Int J Gynaecol Obstet. 2015;128(3):256–9.
[PubMed]

147. Liumbruno GM, Liumbruno C, Rafanelli D. Intraoperative cell salvage in obstetrics: is it a real therapeutic option? Transfusion. 2011;51(10):2244–56.
[PubMed]

148. Li J, Sun SL, Tian JH, Yang K, Liu R, Li J. Cell salvage in emergency trauma surgery. Cochrane Database Syst Rev. 2015;1:CD007379.

149. Al-Khabori M, Al-Riyami AZ, Baskaran B, Siddiqi M, Al-Sabti H. Discriminatory power of the intraoperative cell salvage use in the prediction of platelet and plasma transfusion in patients undergoing cardiac surgery. Transfus Apher Sci. 2015;53:208–12.
[PubMed]

150. Kelly PD, Parker SL, Mendenhall SK, Bible JE, Sivasubramaniam P, Shau DN, et al. Cost-effectiveness of cell saver in short-segment lumbar laminectomy and fusion (</=3 levels). Spine (Phila Pa 1976). 2015;40:E978–85.

151. Bonnar J, Goldberg A, Smith JA. Do pregnant women take their iron? Lancet. 1969;1(7592):457–8.
[PubMed]

152. Habib F, Alabdin EH, Alenazy M, Nooh R. Compliance to iron supplementation during pregnancy. J Obstet Gynaecol. 2009;29(6):487–92.
[PubMed]

153. Tolkien Z, Stecher L, Mander AP, Pereira DI, Powell JJ. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. PLoS One. 2015;10(2):e0117383.

154. Litton E, Xiao J, Ho KM. Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials. BMJ. 2013;347:f4822.
[PubMed][PubMedCentral]

155. Auerbach M, Ballard H, Trout JR, McIlwain M, Ackerman A, Bahrain H, et al. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. J Clin Oncol. 2004;22(7):1301–7.

[PubMed]

156. Goodnough LT, Shander A. Current status of pharmacologic therapies in patient blood management. Anesth Analg. 2013;116(1):15–34.
[PubMed]

157. Chandler G, Harchowal J, Macdougall IC. Intravenous iron sucrose: establishing a safe dose. Am J Kidney Dis. 2001;38(5):988–91.
[PubMed]

158. Bohlius J, Wilson J, Seidenfeld J, Piper M, Schwarzer G, Sandercock J, et al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. J Natl Cancer Inst. 2006;98(10):708–14.
[PubMed]

159. Bennett CL, Silver SM, Djulbegovic B, Samaras AT, Blau CA, Gleason KJ, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. JAMA. 2008;299(8):914–24.
[PubMed]

160. Wingerter SA, Keith AD, Schoenecker PL, Baca GR, Clohisy JC. Does tranexamic acid reduce blood loss and transfusion requirements associated with the periacetabular osteotomy? Clin Orthop Relat Res. 2015;473(8):2639–43.

161. Konig G, Hamlin BR, Waters JH. Topical tranexamic acid reduces blood loss and transfusion rates in total hip and total knee arthroplasty. J Arthroplasty. 2013;28(9):1473–6.
[PubMed]

162. Cheriyan T, Maier 2nd SP, Bianco K, Slobodyanyuk K, Rattenni RN, Lafage V, et al. Efficacy of tranexamic acid on surgical bleeding in spine surgery: a meta-analysis. Spine J. 2015;15(4):752–61.
[PubMed]

163. Wei W, Wei B. Comparison of topical and intravenous tranexamic acid on blood loss and transfusion rates in total hip arthroplasty. J Arthroplasty. 2014;29(11):2113–6.
[PubMed]

164. Crescenzi G, Landoni G, Biondi-Zoccai G, Pappalardo F, Nuzzi M, Bignami E, et al. Desmopressin reduces transfusion needs after surgery: a meta-analysis of randomized clinical trials. Anesthesiology. 2008;109(6):1063–76.
[PubMed]

165. Bershad EM, Suarez JI. Prothrombin complex concentrates for oral anticoagulant therapy-related intracranial hemorrhage: a review of the literature. Neurocrit Care. 2010;12(3):403–13.
[PubMed]

166. Joseph B, Aziz H, Pandit V, Hays D, Kulvatunyou N, Yousuf Z, et al. Prothrombin complex concentrate versus fresh-frozen plasma for reversal of coagulopathy of trauma: is there a difference? World J Surg. 2014;38(8):1875–81.
[PubMed]

167.

Tran HA, Chunilal SD, Harper PL, Tran H, Wood EM, Gallus AS, et al. An update of consensus guidelines for warfarin reversal. Med J Aust. 2013;198(4):198–9.
[PubMed]

168. Ranucci M, Baryshnikova E, Crapelli GB, Rahe-Meyer N, Menicanti L, Frigiola A, et al. Randomized, double-blinded, placebo-controlled trial of fibrinogen concentrate supplementation after complex cardiac surgery. J Am Heart Assoc. 2015;4(6), e002066.

169. Levy JH, Welsby I, Goodnough LT. Fibrinogen as a therapeutic target for bleeding: a review of critical levels and replacement therapy. Transfusion. 2014;54(5):1389–405. Quiz 8.
[PubMed]

170. Logan AC, Yank V, Stafford RS. Off-label use of recombinant factor VIIa in U.S. hospitals: analysis of hospital records. Ann Intern Med. 2011;154(8):516–22.
[PubMed][PubMedCentral]

171. Spotnitz WD, Burks S. Hemostats, sealants, and adhesives III: a new update as well as cost and regulatory considerations for components of the surgical toolbox. Transfusion. 2012;52(10):2243–55.
[PubMed]

172. Carless PA, Henry DA, Anthony DM. Fibrin sealant use for minimising peri-operative allogeneic blood transfusion. Cochrane Database Syst Rev. 2003;(2):CD004171.

173. Ballard JL, Weaver FA, Singla NK, Chapman WC, Alexander WA. Safety and immunogenicity observations pooled from eight clinical trials of recombinant human thrombin. J Am Coll Surg. 2010;210(2):199–204.
[PubMed]

174. Singla NK, Gasparis AP, Ballard JL, Baron JM, Butine MD, Pribble JP, et al. Immunogenicity and safety of re-exposure to recombinant human thrombin in surgical hemostasis. J Am Coll Surg. 2011;213(6):722–7.
[PubMed]

175. Pass R. Cytomegalovirus. In: Knipe DM et al., editors. Fields virology, vol. 2, 4th ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2001. p. 2675–705.

176. Adler SP. Transfusion-associated cytomegalovirus infections. Rev Infect Dis. 1983;5(6):977–93.
[PubMed]

177. Ziemann M, Krueger S, Maier AB, Unmack A, Goerg S, Hennig H. High prevalence of cytomegalovirus DNA in plasma samples of blood donors in connection with seroconversion. Transfusion. 2007;47(11):1972–83.
[PubMed]

178. Staras SA, Dollard SC, Radford KW, Flanders WD, Pass RF, Cannon MJ. Seroprevalence of cytomegalovirus infection in the United States, 1988–1994. Clin Infect Dis. 2006;43(9):1143–51.
[PubMed]

179. Ziemann M, Hennig H. Prevention of transfusion-transmitted cytomegalovirus infections: which is the optimal strategy? Transfus Med Hemother. 2014;41(1):40–4.

[PubMed]

180. Seed CR, Wong J, Polizzotto MN, Faddy H, Keller AJ, Pink J. The residual risk of transfusion-transmitted cytomegalovirus infection associated with leucodepleted blood components. Vox Sang. 2015;109:11–7.
[PubMed]

181. Thiele T, Kruger W, Zimmermann K, Ittermann T, Wessel A, Steinmetz I, et al. Transmission of cytomegalovirus (CMV) infection by leukoreduced blood products not tested for CMV antibodies: a single-center prospective study in high-risk patients undergoing allogeneic hematopoietic stem cell transplantation (CME). Transfusion. 2011;51(12):2620–6.
[PubMed]

182. Wu Y, Zou S, Cable R, Dorsey K, Tang Y, Hapip CA, et al. Direct assessment of cytomegalovirus transfusion-transmitted risks after universal leukoreduction. Transfusion. 2010;50(4):776–86.
[PubMed]

183. Vamvakas EC. Is white blood cell reduction equivalent to antibody screening in preventing transmission of cytomegalovirus by transfusion? A review of the literature and meta-analysis. Transfus Med Rev. 2005;19(3):181–99.
[PubMed]

184. Preiksaitis JK. The cytomegalovirus-"safe" blood product: is leukoreduction equivalent to antibody screening? Transfus Med Rev. 2000;14(2):112–36.
[PubMed]

185. Narvios AB, Przepiorka D, Tarrand J, Chan KW, Champlin R, Lichtiger B. Transfusion support using filtered unscreened blood products for cytomegalovirus-negative allogeneic marrow transplant recipients. Bone Marrow Transplant. 1998;22(6):575–7.
[PubMed]

186. Bowden RA, Slichter SJ, Sayers M, Weisdorf D, Cays M, Schoch G, et al. A comparison of filtered leukocyte-reduced and cytomegalovirus (CMV) seronegative blood products for the prevention of transfusion-associated CMV infection after marrow transplant. Blood. 1995;86(9):3598–603.
[PubMed]

187. Landaw EM, Kanter M, Petz LD. Safety of filtered leukocyte-reduced blood products for prevention of transfusion-associated cytomegalovirus infection. Blood. 1996;87(11):4910.
[PubMed]

188. DOH UK. SaBTO report of the Cytomegalovirus Steering Group. 2012. https://www.gov.uk/government/publications/sabto-report-of-the-cytomegalovirus-steering-group. Accessed 18 May 2015.

189. Ratko TA, Cummings JP, Oberman HA, Crookston KP, DeChristopher PJ, Eastlund DT, et al. Evidence-based recommendations for the use of WBC-reduced cellular blood components. Transfusion. 2001;41(10):1310–9.
[PubMed]

190. Malloy DaL, KS. Update on provision of CMV-reduced-risk cellular blood components. Bethesda, MD: American Association of Blood Banks; 2002. Contract No.: Association Bulletin #02-4.

191. UCSF. CMV-seronegative blood products. 2015. http://labmed.ucsf.edu/labmanual/mftlng-mtzn/test/info/4bb.html - CMVnegBloodProducts. Accessed 6 July 2015.

192. Dwyre DM, Holland PV. Transfusion-associated graft-versus-host disease. Vox Sang. 2008;95(2):85–93.
[PubMed]

193. Frank SM, Wick EC, Dezern AE, Ness PM, Wasey JO, Pippa AC, et al. Risk-adjusted clinical outcomes in patients enrolled in a bloodless program. Transfusion. 2014;54(10 Pt 2):2668–77.
[PubMed][PubMedCentral]

194. Carson JL, Noveck H, Berlin JA, Gould SA. Mortality and morbidity in patients with very low postoperative Hb levels who decline blood transfusion. Transfusion. 2002;42(7):812–8.
[PubMed]

195. Shander A, Javidroozi M, Naqvi S, Aregbeyen O, Caylan M, Demir S, et al. An update on mortality and morbidity in patients with very low postoperative hemoglobin levels who decline blood transfusion (CME). Transfusion. 2014;54(10 Pt 2):2688–95. Quiz 7.
[PubMed]

196. Berend K, Levi M. Management of adult Jehovah's Witness patients with acute bleeding. Am J Med. 2009;122(12):1071–6.
[PubMed]

197. Gohel MS, Bulbulia RA, Slim FJ, Poskitt KR, Whyman MR. How to approach major surgery where patients refuse blood transfusion (including Jehovah's Witnesses). Ann R Coll Surg Engl. 2005;87(1):3–14.
[PubMed][PubMedCentral]

198. Muramoto O. Bioethical aspects of the recent changes in the policy of refusal of blood by Jehovah's witnesses. BMJ. 2001;322(7277):37–9.
[PubMed][PubMedCentral]

199. Shahangian S, Snyder SR. Laboratory medicine quality indicators: a review of the literature. Am J Clin Pathol. 2009;131(3):418–31.
[PubMed]

200. TJC. Improving America's Hospitals—The Joint Commission's Annual Report on quality and safety. Joint Commission; 2008.

201. Wagar EA, Stankovic AK, Raab S, Nakhleh RE, Walsh MK. Specimen labeling errors: a Q-probes analysis of 147 clinical laboratories. Arch Pathol Lab Med. 2008;132(10):1617–22.
[PubMed]

202. CAP. http://www.cap.org/apps/docs/reference/metrics_summary.pdf. Accessed 15 May 2015.

203. Novis DA, Friedberg RC, Renner SW, Meier FA, Walsh MK. Operating room blood delivery

turnaround time: a College of American Pathologists Q-Probe Study of 12647 units of blood components in 466 institutions. Arch Pathol Lab Med. 2002;126(8):909–14.
[PubMed]

204. Lin DM, Goldfinger D, Lu Q, Wallace B, Kosaka-Nguyen D, Wood A, et al. Measuring trade-offs that matter: assessing the impact of a new electronic cross-match policy on the turnaround time and the cross-match workload efficiency. Transfusion. 2014;54(12):3075–9.
[PubMed]

205. Tuckfield A, Haeusler MN, Grigg AP, Metz J. Reduction of inappropriate use of blood products by prospective monitoring of transfusion request forms. Med J Aust. 1997;167(9):473–6.
[PubMed]

206. Silver H, Tahhan HR, Anderson J, Lachman M. A non-computer-dependent prospective review of blood and blood component utilization. Transfusion. 1992;32(3):260–5.
[PubMed]

207. Novis DA, Renner S, Friedberg R, Walsh MK, Saladino AJ. Quality indicators of blood utilization: three College of American Pathologists Q-Probes studies of 12,288,404 red blood cell units in 1639 hospitals. Arch Pathol Lab Med. 2002;126(2):150–6.
[PubMed]

208. Collins RA, Wisniewski MK, Waters JH, Triulzi DJ, Yazer MH. Effectiveness of multiple initiatives to reduce blood component wastage. Am J Clin Pathol. 2015;143(3):329–35.
[PubMed]

209. Whitney GM, Woods MC, France DJ, Austin TM, Deegan RJ, Paroskie A, et al. Reducing intraoperative red blood cell unit wastage in a large academic medical center. Transfusion. 2015;55(11):2752–8.

210. Mali SB. Blood substitutes: the need of hour. J Craniofac Surg. 2015;26(4):1006–8.
[PubMed]

211. Chen JY, Scerbo M, Kramer G. A review of blood substitutes: examining the history, clinical trial results, and ethics of hemoglobin-based oxygen carriers. Clinics (Sao Paulo). 2009;64(8):803–13.

212. Clark Jr LC, Gollan F. Survival of mammals breathing organic liquids equilibrated with oxygen at atmospheric pressure. Science. 1966;152(730):1755–6.
[PubMed]

213. Palmer AF, Intaglietta M. Blood substitutes. Annu Rev Biomed Eng. 2014;16:77–101.
[PubMed]

214. Winslow RM. Current status of blood substitute research: towards a new paradigm. J Intern Med. 2003;253(5):508–17.
[PubMed]

215. Kluger R. Red cell substitutes from hemoglobin—do we start all over again? Curr Opin Chem Biol. 2010;14(4):538–43.
[PubMed]

216. Chang TM. Blood replacement with nanobiotechnologically engineered hemoglobin and

hemoglobin nanocapsules. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2010;2(4):418–30. [PubMed][PubMedCentral]

217. Natanson C, Kern SJ, Lurie P, Banks SM, Wolfe SM. Cell-free hemoglobin-based blood substitutes and risk of myocardial infarction and death: a meta-analysis. JAMA. 2008;299(19):2304–12. [PubMed]

218. Weiskopf RB, Silverman TA. Balancing potential risks and benefits of hemoglobin-based oxygen carriers. Transfusion. 2013;53(10):2327–33. [PubMed]

219. Raff JP, Dobson CE, Tsai HM. Transfusion of polymerised human haemoglobin in a patient with severe sickle-cell anaemia. Lancet. 2002;360(9331):464–5. [PubMed]

220. Posluszny Jr JA, Napolitano LM. How do we treat life-threatening anemia in a Jehovah's Witness patient? Transfusion. 2014;54(12):3026–34. [PubMed]

221. ClinicalTrials.gov. Safety and pharmacokinetics of SANGUINATE™ in sickle cell disease (SCD) patients. 2015. https://clinicaltrials.gov/ct2/show/NCT01374165. Accessed 24 June 2015.

222. ClinicalTrials.gov. Study to assess the safety and impact on humoral sensitization of SANGUINATE in patients with end stage renal disease. 2015. https://clinicaltrials.gov/ct2/show/NCT02437422. Accessed 23 July 2015.

223. ClinicalTrials.gov. Study of SANGUINATE™ in the treatment of sickle cell disease patients with vaso-occlusive crisis. 2015. https://clinicaltrials.gov/ct2/show/NCT02411708. Accessed 23 July 2015.

224. Bloch EM, Vermeulen M, Murphy E. Blood transfusion safety in Africa: a literature review of infectious disease and organizational challenges. Transfus Med Rev. 2012;26(2):164–80. [PubMed]

225. Bloch EM, Shah A, Kaidarova Z, Laperche S, Lefrere JJ, van Hasselt J, et al. A pilot external quality assurance study of transfusion screening for HIV, HCV and HBsAG in 12 African countries. Vox Sang. 2014;107(4):333–42. [PubMed][PubMedCentral]

226. Laperche S, Francophone African Group for Research in Blood Transfusion. Multinational assessment of blood-borne virus testing and transfusion safety on the African continent. Transfusion. 2012;53(4):816–26.

227. Hassall O, Maitland K, Pole L, Mwarumba S, Denje D, Wambua K, et al. Bacterial contamination of pediatric whole blood transfusions in a Kenyan hospital. Transfusion. 2009;49(12):2594–8.

228. LaPar DJ, Crosby IK, Ailawadi G, Ad N, Choi E, Spiess BD, et al. Blood product conservation is associated with improved outcomes and reduced costs after cardiac surgery. J Thorac Cardiovasc Surg. 2013;145(3):796–803. Discussion 4.

229. Freedman J, Luke K, Escobar M, Vernich L, Chiavetta JA. Experience of a network of

transfusion coordinators for blood conservation (Ontario Transfusion Coordinators [ONTraC]). Transfusion. 2008;48(2):237–50.
[PubMed]

230. Pearse BL, Smith I, Faulke D, Wall D, Fraser JF, Ryan EG, et al. Protocol guided bleeding management improves cardiac surgery patient outcomes. Vox Sang. 2015;109(3):267–79.

231. Haas T, Goobie S, Spielmann N, Weiss M, Schmugge M. Improvements in patient blood management for pediatric craniosynostosis surgery using a ROTEM(®)-assisted strategy—feasibility and costs. Paediatr Anaesth. 2014;24(7):774–80.
[PubMed][PubMedCentral]

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_12

12. Utilization Management of Blood Derivatives

Stephan Kadauke[1]

(1) Department of Pathology, Massachusetts General Hospital, Boston, MA 02114, USA

Stephan Kadauke
Email: skadauke@partners.org

Keywords Utilization – Gatekeeping – Blood bank – Transfusion service – Derivatives – Plasma derivatives – IVIg – Albumin – Prothrombin complex concentrate – PCC – Kcentra – rVIIa – NovoSeven

Introduction

Unlike other laboratory medicine services, which primarily perform diagnostic tests, the transfusion service is largely concerned with dispensing therapeutic products. From the perspective of utilization management, a distinguishing feature of transfusion medicine is that the products it dispenses pose tangible direct risks due to their sometimes narrow therapeutic indices, and inappropriate use may therefore not only increase cost (including downstream testing) but also directly cause harm to patients. While utilization management is concerned with both over- and underutilization, there is a perception that blood products are generally overutilized, a view that has been substantiated for red blood cells by multiple randomized controlled trials [1]. The present discussion is limited to strategies aiming to reduce inappropriate use of transfusion products other than the traditional

blood components.

Therapeutic blood products are often divided into two distinct categories (Table 12.1). On the one hand, there are traditional blood components, comprising red blood cells, platelets, plasma, and cryoprecipitate. On the other, there are plasma derivatives which include intravenous immunoglobulin (IVIg) , albumin , and clotting factors . There are a few notable distinctions between components and derivatives. Components tend to be dispensed as high-volume, low-cost units, while blood derivatives are typically low-volume, high-cost products. In addition, while indications for regular components are commonly expressed primarily in terms of one specific laboratory value, the structure of indications for derivatives is often more complex. For example, a restrictive transfusion strategy for hemodynamically stable asymptomatic patients is often guided by a "trigger" hemoglobin level of 7–8 g/dL, below which a red blood cell transfusion is indicated [2]. In contrast, there are numerous distinct clinical scenarios for which IVIg can be considered, as discussed below. These differences in volume and decision complexity are important for the purposes of utilization management , as each situation necessitates different strategies. The scope of this chapter is limited to blood derivatives.

Table 12.1 Comparison of different blood products

	Regular blood components	**Blood derivatives**
Examples	Red blood cells, platelets, plasma, cryoprecipitate	IVIg, albumin, clotting factors
Procurement	In-house (donor center) and purchased from regional blood suppliers	Purchased from manufacturers
Volume	High	Low
Price per unit	Lower	Higher
Rate of inappropriate ordering	High	High
Complexity of indications	Lower	Higher

The term "components" traditionally refers to therapeutics made from whole blood by centrifugation. The term "derivatives" refers to therapeutics purified from plasma and, although not technically precise, artificial plasma proteins manufactured by recombinant DNA engineering. "Products" is a general term referring to both components and derivatives. *IVIg* intravenous

immunoglobulin

Blood derivatives are dispensed in an inpatient as well as outpatient setting. In the United States, inpatient services are currently reimbursed as a blanket payment determined by “disease-related groups” (DRGs) , while outpatient services are paid for on a fee-for-service schedule. For this reason, utilization interventions have generally focused on the inpatient setting (please refer to Chap. 2 for a discussion of reimbursement for medical services). In addition to cost, the risks associated with inappropriate utilization play a major role in the decision whether a utilization intervention is undertaken. Several examples of such interventions, primarily from our experience at the Massachusetts General Hospital (MGH) , are discussed below.

Blood Derivatives Dispensed by the Transfusion Service

The MGH transfusion service spends about 75 % of its operating budget to purchase blood products from outside vendors. About half of this cost is devoted to regular components, and the other half to blood derivatives. As can be seen in Table 12.2, the majority of this cost is driven by IVIg and, to a lesser extent, albumin. Since it is the major driver of cost among derivatives, IVIg has been subject to gatekeeping interventions at the MGH beginning in 2000 (see discussion below).

Table 12.2 Acquisition cost for special blood products purchased by the MGH Blood and Transfusion Service in financial year 2015

Product	Use at the MGH	Estimated cost per ordered dose	Total cost in FY15
IVIg	Hypogammaglobulinemia and others (see Table 12.3)	$2500 or $10,000[a]	$3,850,000
Albumin	Volume replacement in the setting of nonhemorrhagic shock, burns, large-volume paracentesis, plasma exchange, and severe necrotizing pancreatitis	$80–$3500	$1,200,000
Factor VIII	Hemophilia A, von Willebrand disease	$3000	$400,000
4-Factor prothrombin complex	Emergency reversal of warfarin with intracranial hemorrhage	$3000	$250,000

concentrate			
Factor IX	Hemophilia B	$3000	$75,000
Rabies Ig	Rabies postexposure prophylaxis	$2500	$75,000
RhD Ig	Prevention of Rh allosensitization, immune thrombocytopenic purpura	$75	$60,000
CMV Ig	Solid organ transplant recipients who are CMV− and receive a CMV+ organ	$4000	$50,000
Immune serum globulin	Hepatitis A, rubeola, varicella, or rubella postexposure prophylaxis	$60	$2000

Numbers are approximate and do not include fixed or semivariable costs due to storage, inventory management, or infusion

[a]A replacement dose of IVIg costs typically $2500, while an immunosuppressive dose costs $10,000 Ig, immune globulin. CMV, cytomegalovirus

Clotting factors (factor VIIa, VIII, IX, and 4-factor prothrombin complex concentrate) consume a smaller fraction of the MGH blood bank budget , in part due to their narrower range of indications and to successful utilization interventions . Clotting factors can cause potentially fatal thrombotic events, and thus a major reason for review of requests for clotting factor concentrates is to reduce harm to patients.

Albumin has unclear benefit in a high proportion of the clinical scenarios in which it is used. Even though the cumulative cost of albumin is second only to IVIg, no gatekeeping interventions are in place at the MGH, owing in part to the relative safety of albumin administration.

Additional derivatives , including factor IX and specific enriched immune sera such as anti-rabies , anti-RhD , anti-cytomegalovirus (CMV) , and immune serum globulin , have fairly straightforward indications and occupy a much smaller fraction of the blood bank budget . They are therefore not discussed further.

Utilization Interventions

In Chap. 11, point-of-order entry interventions were presented as an efficient mechanism for reducing inappropriate ordering of red blood cells and platelets. Computerized decision support is appropriate in situations in which decision rules are quantitative and the relevant information (such as most

recent hemoglobin level or platelet count) is easily extracted from the medical record or laboratory information system. Compared to regular blood components, decision rules for determining the appropriateness of blood derivatives tend to be more complex. A common theme among derivatives, therefore, is the implementation of routine review of requests (i.e., gatekeeping), a process that is well suited to deal with complex clinical scenarios as long as the ordering volume is low.

An important consideration to ensure the success of implementing a gatekeeping strategy is to minimize the chance that the ordering physician will perceive the intervention as an infringement on his or her autonomy. At the MGH, a three-pronged approach is used to this end: authority through leadership, interdepartmental consensus, and formal guidelines for hospital-wide practice.

To add legitimacy and authority to utilization programs, the Medical Policy Committee (MPC) at the MGH coordinates utilization management activities. The MPC is organized at the highest levels of hospital governance, reporting directly to the General Executive Committee. The Transfusion Committee, a subgroup of the Medical Policy Committee that is responsible for blood transfusion management, is an interdisciplinary group consisting of transfusion medicine representatives as well as leaders of services that use large amounts of blood products, including hematology/oncology, emergency medicine, pediatrics, nursing, surgery, and anesthesiology.

The Transfusion Committee is responsible for developing guidelines for the use of blood derivatives. These documents create a formal hospital-wide standard based on interdepartmental consensus. The guidelines are distributed both to gatekeepers and the ordering providers. At the MGH, transfusion guideline documents are available for the most commonly ordered derivatives , including IVIg, albumin, 4-factor prothrombin concentrate, and recombinant factor VIIa. Each document includes the following sections: (1) a rationale for restriction of use, (2) a detailed list of approved uses with dosing instructions, (3) a list of commonly requested conditions that are *not* approved, (4) a mechanism to request an exception for non-approved conditions, (5) and a list of the authors that have collaborated on the document, who are typically representatives of clinical departments that are large users of the product in question. In this manner, the appropriate uses for derivatives can be readily discerned in most cases, and disagreements can be quickly resolved by consulting the clinical leaders who authored the

guideline .

Intravenous Immunoglobulin (IVIg)

Since Bruton first demonstrated the utility of supplying exogenous human gamma globulin for the treatment of a boy with agammaglobulinemia in 1952 [3], immunoglobulin formulations (first subcutaneous, then intramuscular, and finally intravenous) have been used to treat humoral immunodeficiency. Successful treatment of autoimmune disease with IVIg was first shown in 1981 by Paul Imbach and colleagues, who found that high-dose IVIg therapy led to a dramatic recovery of the platelet count in children with immune thrombocytopenic purpura (ITP) [4]. Since then, there have been reports of success with IVIg therapy for a myriad of autoimmune disorders, although very few of them are substantiated by high-quality randomized controlled trials [5]. As a result, indications for IVIg are steadily increasing, which has not only led to increased cost pressure on health systems but also to IVIg shortages. In addition, IVIg dosing is complex in that it depends not only on the patient's body weight, but it is also given either as low-dose replacement (typically 0.5 g/kg) or as high-dose immunosuppressive therapy (typically 2 g/kg; reviewed in [6]). The typical acquisition cost for a replacement dose is about $2500, while a single immunosuppressive dose costs $10,000 to purchase (see Table 12.2). Therefore, utilization management of IVIg should focus not only on the appropriateness of the clinical scenario but also on correct dosing.

There are quite a few distinct routine uses for IVIg, but for some of these, IVIg should not be used as first-line therapy (Table 12.3). In addition to routine indications, there are clinical situations in which IVIg therapy may be reasonably tried, often as a last resort after standard therapies have failed. A computerized approach that alerts the ordering provider of a possibly inappropriate order would be counterproductive in these cases. A consultative gatekeeping strategy, in which an order for IVIg is released only after review by a blood bank representative, is more sensible.

Table 12.3 Uses of intravenous immunoglobulin (IVIg) at the MGH

Hematology	• Immune thrombocytopenic purpura (ITP) with bleeding[a] • Neonatal alloimmune thrombocytopenia • Posttransfusion purpura

	• Chronic lymphocytic leukemia[a] • Autoimmune hemolytic anemia • Hemolytic disease of the newborn[b]
Infectious disease	• Hypogammaglobulinemia in the setting of recurrent bacterial infections[a] • Toxic shock syndrome or necrotizing fasciitis due to group A streptococcus • Kawasaki's syndrome[a]
Neurology	• Chronic idiopathic demyelinating polyneuropathy[a] • Myasthenia gravis • Guillain-Barré syndrome • Stiff-person syndrome • Multiple sclerosis[b]
Rheumatology	• Pemphigus vulgaris • Dermatomyositis[b] • Systemic vasculitis[b]
Transplant	• Hypogammaglobulinemia in the setting of bone marrow or solid organ transplant • Solid organ transplant antibody-mediated rejection
Other	• Pediatric autoimmune cardiomyopathy

FDA-approved indications for IVIg are marked with a superscript alphabet "a"
In conditions marked with a superscript alphabet "b," IVIg should not be used as first-line therapy

The proportion of IVIg use that is inappropriate has been estimated to be around 50 % [7, 8]. Interestingly, a retrospective review of all IVIg infusions administered at the MGH in 2004 showed that the vast majority matched published guidelines [5], owing to a request review strategy that was initiated in the late 1990s. At the MGH, residents on rotation in the blood transfusion service (with backup by fellows and the blood bank director) act as initial reviewers for special blood products including IVIg, and it is their responsibility to decide whether a request is filled and what dose will be released by the blood bank . This is handled primarily by consulting guideline documents which include a list of positive and negative indications, along with dosing instructions. As discussed above, these documents are authored and maintained by the Transfusion Committee . In questionable cases, a consensus is sought regarding whether the request is rational and consistent

with the pathophysiology of the disease process and whether there exist published data demonstrating benefit .

Albumin

The inception of human serum albumin therapy dates back to World War II. A case report on a patient with traumatic shock after multiple compound fractures showed normalization of systemic blood pressure after intravenous administration of 50 g of albumin. In addition, a case series was published in which albumin was given intravenously to seven patients who were severely burned during the Pearl Harbor attack [9].

Due to its theoretical benefits, albumin was used liberally to treat hypotension as well as hypoalbuminemia until the late 1990s. This practice was challenged when a series of meta-analyses appeared starting in 1998, which suggested that the benefit (if any) of albumin therapy to supplement normal saline for volume resuscitation was marginal and that there may be potential for harm [10–12]. The SAFE study, a large randomized controlled trial performed in critically ill patients, found that while albumin is as safe as normal saline for volume resuscitation, there is no overall therapeutic benefit in using albumin [13]. While the SAFE trial identified trends toward increased mortality in some and toward decreased mortality in other clinical scenarios, further research into the clinical benefit of albumin has been hampered by the difficulty of carrying out sufficiently large randomized studies in the critically ill patient population that receives most of it.

Utilization management of albumin is hindered by the fact that the appropriate use for albumin is difficult to define. In contrast to other derivatives , albumin is a low-unit cost, high-volume product, which makes a generalized gatekeeping intervention impractical. One possibility would be to focus reviews of requests on large users. Inpatients typically receive albumin on multiple consecutive days during their hospitalization. An automatic large-user alert could be implemented to make it possible to initiate a dialogue with the treating team about the goals for albumin therapy. For example, out of 3703 patients who received albumin at the MGH in 2014, 152 (4.1 %) received at least one cumulative daily dose exceeding 125 g (ten bottles), up to a maximum dose of 525 g (42 bottles), in a single day. Together, these few patients received more than a quarter (26.7 %) of all albumin dispensed at the MGH in that year. Thus, by focusing on extreme

users, there is an opportunity for the transfusion service to influence a large portion of albumin use through targeting a limited number of cases .

Recombinant Factor VIIa (rVIIa)

Recombinant activated factor VII (rVIIa) is an activated procoagulant with FDA-approved indications for the treatment of hemophilia A or B with antibody inhibitors to factors VIII or IX, congenital factor VII deficiency, and acquired hemophilia. In Europe, rVIIa is additionally licensed for the treatment of Glanzmann's thrombasthenia . After a case report in 1999 showed a dramatic response to rVIIa in a patient with life-threatening bleeding and coagulopathy after a gunshot wound (who had none of the FDA-approved conditions) [14], off-label use of rVIIa as a general hemostatic agent became rampant despite little evidence of efficacy. A multicenter retrospective analysis of more than 12,000 hospital discharge documents found that between 2000 and 2008, off-label use of rVIIa increased more than 140-fold, such that in 2008, 97 % of rVIIa use was off-label [15]. This trend reversed recently, when several meta-analyses revealed a lack of efficacy of this practice and evidence of potential harm [16, 17].

The MGH implemented a strict review policy for requests for rVIIa. A comparison between the MGH and a peer institution with a similar patient population examined the expenditures for rVIIa in financial year 2011 (Table 12.4). Compared to the peer institution, the MGH utilized 95 % less rVIIa .

Table 12.4 Comparison of expenditures for recombinant factor VIIa at Massachusetts General Hospital and a peer institution in financial year 2011

Hospital	Number of patients treated	Total number of doses given	Total cost
MGH	12	26	$31,000
Peer	43	569	$628,000

Prothrombin Complex Concentrate

Four-factor prothrombin complex concentrate (4-PCC) is a preparation of the vitamin K-dependent clotting factors II, VII, IX, X, as well as proteins C and S, derived from human plasma. PCC is used to replace the coagulation factors depleted by warfarin anticoagulation therapy [18]. Although the use of 4-PCC results in more rapid correction of the INR for patients taking

vitamin K antagonists, it remains controversial whether 4-PCC results in better clinical outcomes compared with FFP. In addition, 4-PCC poses a low but real risk for thromboembolic events [19].

At the MGH, 4-PCC is currently subject to request review by transfusion medicine. The primary indication for 4-PCC use is emergency reversal of warfarin in patients with CNS or pulmonary bleeding. In addition to deciding whether PCC is appropriate, the review process speeds the selection of an appropriate dose and ensures that intravenous vitamin K is given concurrently.

Historically, four-factor PCC was preceded by three-factor PCC (3-PCC), containing factors II, IX, and X with only trace amounts of factor VII. In 2011, an initiative implemented by three major hospitals in the Boston area (MGH, Brigham and Women's Hospital, and North Shore Medical Center) aimed to identify targets of utilization interventions by analyzing practice differences in cardiac surgery between the three sites. The working group was composed of a multi-institutional multidisciplinary team with representatives from cardiac surgery, perfusion, cardiac surgical intensive care unit, cardiac anesthesiology, transfusion medicine, and surgical nursing. The group found that the MGH was the only site that had used 3-PCC for hemostasis during cardiac surgery in the post-pump period as well as albumin for volume replacement. After discussion, it was determined that 3-PCC and albumin were not necessary in cardiac surgery. A change in practice guidelines eliminated routine use of 3-PCC and albumin in cardiac surgery. As a result, the acquisition cost for procurement of 3-PCC dropped by 94 % from $350,000 in financial year 2011 to $20,000 in 2012. This example illustrates how benchmarking against other institutions can identify practice variation and lead to significant cost savings using an interdisciplinary utilization intervention .

References

1. Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev. 2012;4:CD002042.

2. Carson JL, Grossman BJ, Kleinman S, Tinmouth AT, Marques MB, Fung MK, et al. Red blood cell transfusion: a clinical practice guideline from the AABB. Ann Intern Med. 2012;157:49–58. [CrossRef][PubMed]

3.

Bruton OC. Agammaglobulinemia. Pediatrics. 1952;9:722–8.
[PubMed]

4. Imbach P, Barandun S, d'Apuzzo V, Baumgartner C, Hirt A, Morell A, et al. High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. Lancet. 1981;1:1228–31.
[CrossRef][PubMed]

5. Darabi K, Abdel-Wahab O, Dzik WH. Current usage of intravenous immune globulin and the rationale behind it: the Massachusetts General Hospital data and a review of the literature. Transfusion. 2006;46:741–53.
[CrossRef][PubMed]

6. Kerr J, Quinti I, Eibl M, Chapel H, Späth PJ, Sewell WAC, et al. Is dosing of therapeutic immunoglobulins optimal? A review of a three-decade long debate in Europe. Front Immunol. 2014;5:629.
[CrossRef][PubMed][PubMedCentral]

7. Chen C, Danekas LH, Ratko TA, Vlasses PH, Matuszewski KA. A multicenter drug use surveillance of intravenous immunoglobulin utilization in US academic health centers. Ann Pharmacother. 2000;34:295–9.
[CrossRef][PubMed]

8. Feasby TE, Quan H, Tubman M, Pi D, Tinmouth A, So L, et al. Appropriateness of the use of intravenous immune globulin before and after the introduction of a utilization control program. Open Med. 2012;6:e28–34.
[PubMed][PubMedCentral]

9. Caironi P, Gattinoni L. The clinical use of albumin: the point of view of a specialist in intensive care. Blood Transfus. 2009;7:259–67.
[PubMed][PubMedCentral]

10. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. BMJ. 1998;317:235–40.
[CrossRef]

11. Wilkes MM, Navickis RJ. Patient survival after human albumin administration. A meta-analysis of randomized, controlled trials. Ann Intern Med. 2001;135:149–64.
[CrossRef][PubMed]

12. Vincent J-L, Dubois M-J, Navickis RJ, Wilkes MM. Hypoalbuminemia in acute illness: is there a rationale for intervention? A meta-analysis of cohort studies and controlled trials. Ann Surg. 2003;237:319–34.
[PubMed][PubMedCentral]

13. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350:2247–56.
[CrossRef][PubMed]

14. Kenet G, Walden R, Eldad A, Martinowitz U. Treatment of traumatic bleeding with recombinant factor VIIa. Lancet. 1999;354:1879.
[CrossRef][PubMed]

15. Logan AC, Yank V, Stafford RS. Off-label use of recombinant factor VIIa in U.S. hospitals: analysis of hospital records. Ann Intern Med. 2011;154:516–22.
[CrossRef][PubMed][PubMedCentral]

16. Yank V, Tuohy CV, Logan AC, Bravata DM, Staudenmayer K, Eisenhut R, et al. Systematic review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. Ann Intern Med. 2011;154:529–40.
[CrossRef][PubMed][PubMedCentral]

17. Simpson E, Lin Y, Stanworth S, Birchall J, Doree C, Hyde C. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. Cochrane Database Syst Rev. 2012;3:CD005011.

18. Sarode R, Milling TJ, Refaai MA, Mangione A, Schneider A, Durn BL, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation. 2013;128:1234–43.
[PubMed]

19. Dentali F, Marchesi C, Giorgi Pierfranceschi M, Crowther M, Garcia D, Hylek E, et al. Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. A meta-analysis. Thromb Haemost. 2011;106:429–38.
[CrossRef][PubMed]

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_13

13. Utilization Management in the Clinical Microbiology Laboratory

Kent Lewandrowski[1] ✉, Eric S. Rosenberg[2] and John A. Branda[2]

(1) Division of Laboratory Medicine, Department of Pathology, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street, Boston, MA 02114, USA
(2) Department of Pathology, Gray 5 Chemistry, Massachusetts General Hospital, Fruit Street, Boston, MA 02114, USA

✉ **Kent Lewandrowski**
Email: KLEWANDROWSKI@mgh.harvard.edu
Email: klewandrowski@partners.org

Keywords Utilization management – Laboratory utilization – Microbiology – Antimicrobial stewardship – Gatekeeping

Portions of this chapter were abstracted from Branda J, Lewandrowski K. Utilization management in microbiology. Clin Chim Acta. 2014;427:173–7 with permission.

Introduction

The clinical microbiology laboratory encompasses many disciplines including bacteriology, antimicrobial susceptibility testing, virology, parasitology, mycology, mycobacteriology, infectious diseases serology, and

molecular diagnostics. The literature on utilization management in microbiology is relatively limited [1]. Most reports have focused on efforts to minimize unnecessary routine cultures and stool examinations. These tend to be more expensive on a unit cost basis than many of the tests offered in chemistry and hematology, because they are labor intensive and require highly skilled technologists for proper interpretation. However, in recent years the menu of available tests has expanded rapidly, especially in the area of molecular microbiology, and this trend will continue. These assays are associated with very high reagent costs and in some cases are laborious and highly complex. Many are ordered in relatively low volume and are therefore sent out to reference laboratories, often at a high unit cost. They are also frequently unfamiliar to ordering providers, who may have only a limited understanding of the indications for these tests, and their performance characteristics, resulting in excessive utilization and/or inappropriate test selection. As the test menu continues to expand, this “knowledge gap ” will only increase. Collectively, these developments have created a wealth of opportunities to implement utilization management initiatives in microbiology and to provide decision support to guide test selection. The latter can have a significant impact on the downstream costs of medical care, including the use and selection of antimicrobial therapy , specialist consultations, and the assignment of beds for patients requiring isolation/precaution procedures.

A well-managed microbiology laboratory should maintain high quality, while controlling costs and facilitating medical care by offering appropriate and timely services. In developing a utilization management plan for microbiology, first, it is important to be familiar with what is considered the standard of care in this context. To summarize this, the Infectious Diseases Society of America (ISDA) and the American Society for Microbiology have published guidelines for the laboratory diagnosis of infectious diseases [2]. This document describes the most appropriate tests for the diagnosis of a wide range of infections. The second step is to perform a literature search, to identify previously reported articles describing utilization management initiatives. Next, laboratory leadership should review an audit of the microbiology test menu, test volumes, and a list of providers that are ordering specific tests. The degree of detail that can be included in the audit will depend on the capabilities of the laboratory information system and on the ability to access expertise in informatics. Data from the audit should be

analyzed by the laboratory director in collaboration with key stakeholders, particularly Infectious Diseases subspecialist physicians. This collaboration will facilitate the identification of opportunities for utilization management and assist in the design of strategies for successful implementation.

In the pages that follow, we describe a number of utilization management initiatives in microbiology (listed in Table 13.1). Many of these come from published sources. Others are unpublished activities that were implemented in our hospital as part of our internal laboratory utilization management program. Some of the initiatives target costs incurred by the microbiology laboratory directly, while others are directed at downstream costs, such as the use and selection of antimicrobial therapy .

Table 13.1 Utilization management strategies in clinical microbiology

1. Provider education
a. Decision support tools
b. Clinical practice guidelines
c. Internal practice guidelines
d. Diagnostic algorithms
2. Reflex testing algorithms
3. Gatekeeping (stewardship)
4. Banning tests that have no accepted clinical utility

Examples of Utilization Management Initiatives in Microbiology

Provider Education

Provider education can be effective, but must be tailored as much as possible to the individual. Although convenient, it is rarely useful to broadcast educational missives via email, particularly when the subject is irrelevant to many or most recipients. Didactic lectures and other live presentations are often helpful, inasmuch as the contact can be tailored to the audience and the attendees' questions can be answered, but it can be challenging to reach all intended recipients. It may be necessary to repeat the presentation at intervals if there is frequent turnover among the relevant providers (e.g., house officers). As described in this subchapter, an excellent alternative is to provide targeted education at the time tests are ordered, using tools available

within the electronic order entry system. This method, termed “decision support ,” is effective because it provides timely education to the relevant individual, and the information is delivered repetitively so that all users can be reached. In addition, clinical practice guidelines and diagnostic algorithms can be provided to targeted provider groups and endorsed by their leadership, to guide appropriate test utilization.

Decision Support

In many instances, physicians are unsure how to choose the most appropriate test for a given clinical question or presentation. This is especially true when there are multiple different tests for a particular microorganism [e.g., culture-based tests , antigen assays , serologic tests , or nucleic acid amplification tests (NAATs)]. For example, a number of tests are available for the detection of cytomegalovirus (CMV) , including serology (IgM and IgG antibody testing, plus IgG avidity testing), PCR performed on blood and numerous other tissue or fluid specimens, CMV genotyping, and shell vial culture. To make matters more complicated, the test of choice for the detection of CMV viremia has recently changed from a microscope-based test (CMV antigenemia) to a NAAT (CMV PCR). These confusing situations provide opportunities to implement decision support, which is most effective when it can be provided at the time that the test is being ordered.

In our institution, we employ three approaches to accomplish timely decision support. These include electronic provider order entry, an electronic web-based laboratory handbook, and personal consultations with laboratory directors or trainees. Our online laboratory handbook allows the clinician to use the search function. If the clinician types “CMV” into the search function box, the available tests for CMV with specific recommendations are then displayed as shown in Fig. 13.1. Esoteric tests, such as CMV IgG antibody avidity testing —which is only indicated in highly selected situations—are intentionally left out of the handbook . Clinical experts who need them are familiar with how to order them, and their inclusion in the online handbook might drive overutilization . Among those listed, the comments section guides the physician to the most appropriate test. To be effective, the online handbook must be readily available and convenient to access. Our handbook is listed among the standard options in our hospital online “clinical references ” drop-down menu and is also available via links provided in the electronic provider order entry system . The handbook can be accessed from any

workstation in our hospital or outpatient practices .

Test Name	Lab	Comment
CMV antibody (IgG)	Microbiology	Single serum samples are for immunity status only. CMV IgM requests are sent out via Chemistry Lab.
CMV antibody (IgM)	Chemistry (Sendouts)	
CMV genotyping	Chemistry (Sendouts)	This test involves sequence of the phosphotransferase (UL 97) gene and the polymerase (UL 54) gene of CMV. These genes are involved in resistance to Ganciclovir, Foscarnet and Cidofovir.
CMV PCR (blood)	Core Lab	CMV blood PCR is a quantitative PCR-based assay. The assay offers sensitivity and specificity comparable to the CMV antigenemia test. The CMV antigenemia test is no longer available.
CMV PCR (CSF)	Chemistry (Sendouts)	
CMV shell vial culture	Microbiology	

Fig. 13.1 Online laboratory handbook display for query on cytomegalovirus testing (CMV) at the Massachusetts General Hospital. *Key*: *IgG* immunoglobulin G, *IgM* immunoglobulin M, *PCR* polymerase chain reaction, *CSF* cerebrospinal fluid

Clinical Practice Guidelines

Many guidelines relating to diagnostic testing are available from professional societies. In the case of microbiology, the Infectious Diseases Society of America provides a number of practice guidelines on its website (http://www.idsociety.org/Index.aspx). An example of one guideline for the diagnosis and management of diarrheal illnesses is shown in Fig. 13.2. The guideline specifies which tests are appropriate for patients with different clinical presentations and risk factors. Of note, stool examinations for ova and parasites (O&P) are only recommended for patients with persistent diarrhea, especially those with compromised immune systems. It is well known that stool O&P examinations are significantly overutilized, and in our hospital, we will soon begin actively managing utilization of the stool O&P examination by adopting a reflex testing algorithm (see subchapter 2). Similar to other institutions Lab epub ahead of print), we have established a diagnostic testing algorithm that begins with a sensitive antigen test for giardia and cryptosporidium , because these are among the most common pathogenic parasites detected in our patient population. A complete O&P exam will be performed in persistently symptomatic patients as a second step, after review of a required history form to assess risk factors.

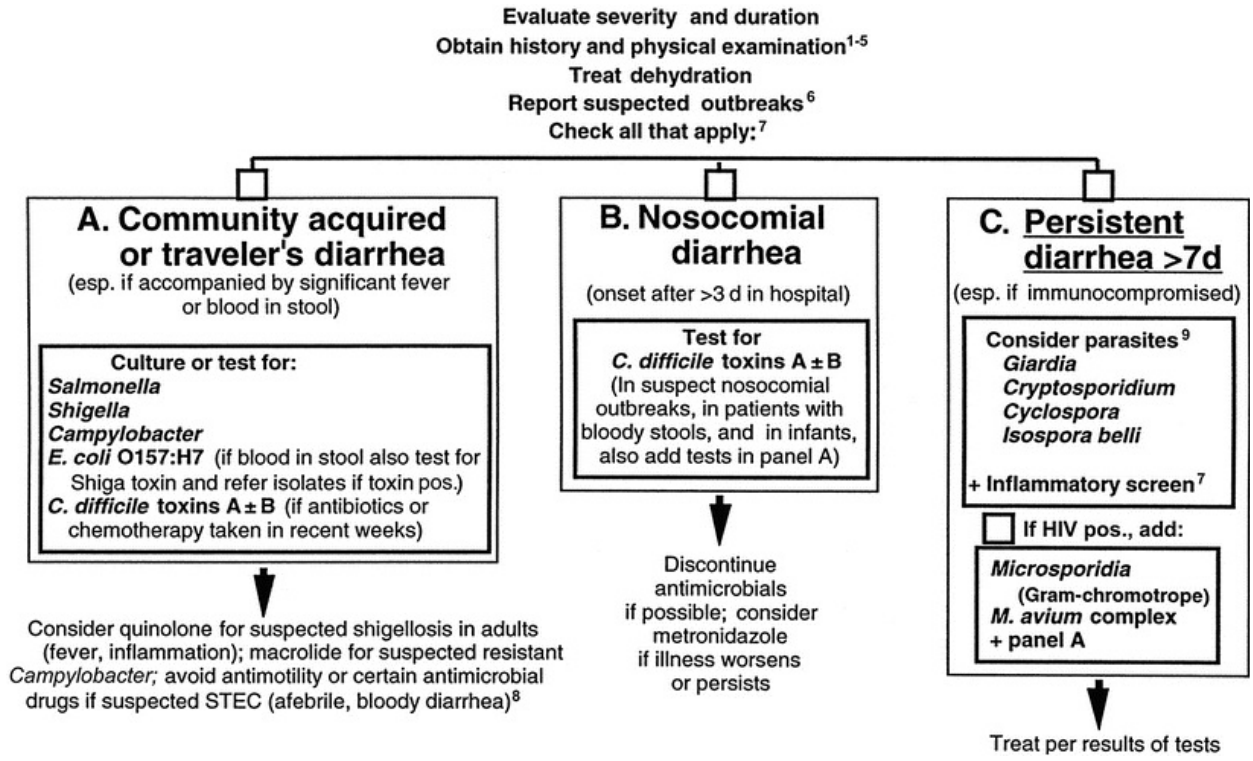


Fig. 13.2 Recommendations for the diagnosis and management of diarrheal illnesses . *Key*: *STEC* shigella toxin-producing *Escherichia coli*, *Numbers* 1–9 refer to footnotes in the text. See original source article for explanations. *From*: Guerrant R, et al. Clin Infect Dis. 2011;32:331–51, with permission

A related effort concerns restricting stool culture and O&P examination in patients with hospital-acquired diarrheal illnesses. A number of studies have shown that stool culture and stool O&P examination is usually not indicated when diarrhea develops more than 3 days after admission to the hospital [3–5], because these tests are designed to detect agents of community-acquired gastrointestinal infection. This recommendation is included in the guideline shown in Fig. 13.2. In contrast, testing for *C. difficile* should be considered in such patients, as this is a major cause of nosocomial diarrheal illness .

In some cases, adherence to clinical practice guidelines that address tangential topics (not directly related to appropriate test utilization) can also help to reduce overutilization. An example is the use of best practices to minimize blood culture contamination during specimen collection . Contamination of blood cultures resulting from improper or careless specimen collection technique has long been recognized as a source of error in clinical care and a significant waste of resources, including unnecessary

diagnostic workups involving laboratory testing. In one study it was estimated that up to 5 % of positive blood cultures are falsely positive due to contamination [6]. Many hospitals have undertaken efforts to reduce the rate of blood culture contamination, by improving staff training or by allowing only certain staff members (e.g., phlebotomists) to collect blood culture specimens. For example, in one study it was reported that blood cultures collected by medical residents had a significantly higher rate of contamination than those collected by phlebotomists [7]. In another study, Bates et al. evaluated the impact of blood culture contamination on hospital length of stay and hospital charges [8]. On average, patients with falsely positive blood cultures had a 4.5-day increase in median hospital length of stay and an increase in hospital charges of 33.4 %, including increased pharmacy charges for intravenous antibiotics (39 % increase) and laboratory charges (20 % increase). Segal and Chamberlain reported a study on falsely positive blood cultures in a pediatric emergency department [9]. Falsely positive cultures resulted in an increase in phone calls, return visits to the emergency department, unnecessary laboratory tests, inappropriate antibiotic administration, and hospital admissions. Microbiology laboratories should periodically measure their blood culture contamination rate and should consider intervention at the enterprise level if the rate approaches or exceeds the benchmark rate of 3 % [10].

ABIM Foundation's "Choosing Wisely" Guidelines

Chapter 2 described the ABIM Foundation's Choosing Wisely campaign [11], an effort modeled on the National Physicians Alliance's "Good Stewardship Project " to address overutilization of laboratory tests. Several of these recommendations relate to microbiology and can form the basis of utilization management initiatives, centered on provider education, restriction of test frequency, or the development of diagnostic algorithms :

1. Don't perform urinalysis, urine culture, blood culture, or *C. difficile* testing unless patients have signs or symptoms of infection.

2. Don't obtain a urine culture unless there are clear signs and symptoms that localize to the urinary tract.

3. Avoid the use of surveillance cultures for the screening and treatment of asymptomatic bacteriuria.

4. Don’t routinely use microbiologic testing in the evaluation and management of acne.

5. Don’t obtain a *C. difficile* toxin test to confirm “cure” if symptoms have resolved.

6. Avoid testing for a *Clostridium difficile* infection in the absence of diarrhea.

7. Don’t repeat hepatitis C viral load testing outside of antiviral therapy.

8. Don’t test for Lyme disease as a cause for musculoskeletal symptoms without an exposure history and appropriate exam findings.

9. Avoid antibiotics and wound cultures in emergency department patients with uncomplicated skin and soft tissue abscesses after successful incision and drainage and with adequate medical follow-up.

The recommendations of the NPA will continue to evolve, and new guidelines will emerge. For this reason it is helpful to remain up-to-date with the NPA program to identify new opportunities for utilization management .

Internal Practice Guidelines

To address local instances of test overutilization, hospitals can develop their own internal consensus guidelines. The clinical microbiologist can spearhead these efforts by bringing together groups of clinicians to work on selected utilization management initiatives. In recent years we have worked on a number of guidelines in the area of infectious disease diagnostics. For example, we noticed a surprising number of test orders for human herpesvirus 6 (HHV6) viral load testing, considering the very limited clinical indications for this test. An audit showed that the vast majority of test orders were coming from the bone marrow transplantation service , including testing

on both inpatients and outpatients. Certain individual physicians were ordering far more tests than their peers. In addition, our audit showed that the presence of low-grade HHV6 viremia was frequently prompting an unnecessary Infectious Diseases consultation . We discussed the findings with representatives from the Infectious Diseases division and with the chief of the bone marrow transplantation service. It was decided that the bone marrow transplantation service would self-police the test, restricting it to patients who have received cord blood stem cell transplantation and are on a clinical or investigative protocol that requires the testing. Figure 13.3 shows the impact on the volume of test orders before and after the internal guideline was ratified in October 2014.

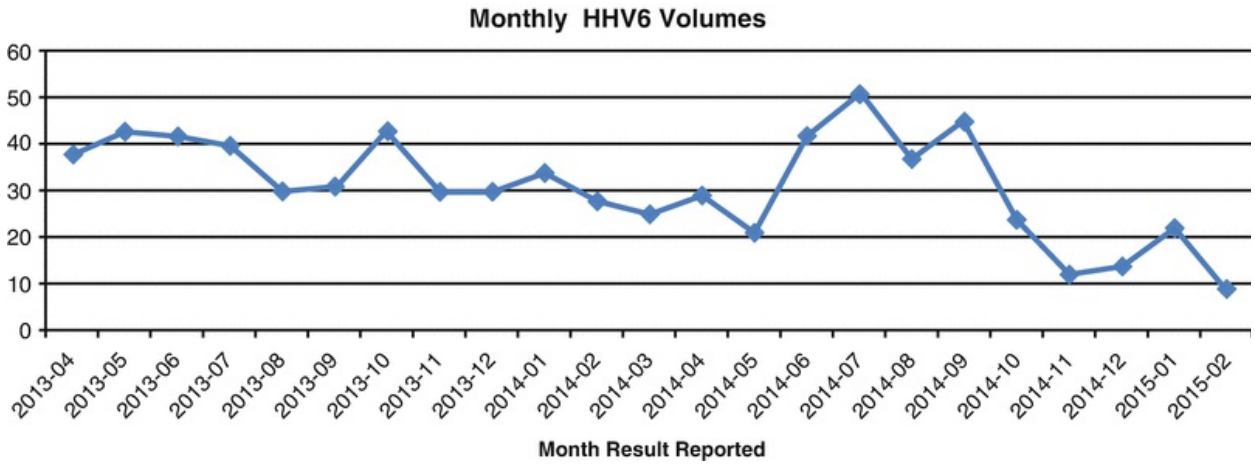


Fig. 13.3 Impact of establishing internal practice guidelines for human herpesvirus 6 (HHV6) testing on cord blood bone marrow transplantation recipients

Diagnostic Algorithms

Many areas involving microbiology testing are complex. In some cases the test menu is rapidly evolving, due to improvements in diagnostic technologies or to changes in the epidemiology of infectious diseases. A case in point is laboratory testing for tick-borne infections . The type of tests that should be considered depends on many factors including the clinical presentation, geographic region and travel history of the patient, and a variety of other factors. Figure 13.4 shows an acute tick-borne disease testing algorithm offered by the Mayo Medical Laboratories reference laboratory. This algorithm was designed for a national client base and, if adopted locally, would require some modifications to account for differences in the

geographic distribution of the individual organisms. Of note, multiple different infectious organisms might be considered, and a variety of different tests are available, including screening and confirmatory serologic tests and polymerase chain reaction (PCR) . Some of the tests target the same organism, which can be very confusing for providers (e.g., anaplasmosis PCR and serology). The algorithm provides a logical, evidence-based approach to the available laboratory tests, including some guidance related to geographic distribution of the infectious agents. Subsequent to the publication of the algorithm, a new tick-borne infectious agent was described called *Borrelia miyamotoi* , which requires an entirely different test for detection. This highlights the need to perform regular audits of laboratory-based algorithms ,and to update them accordingly.

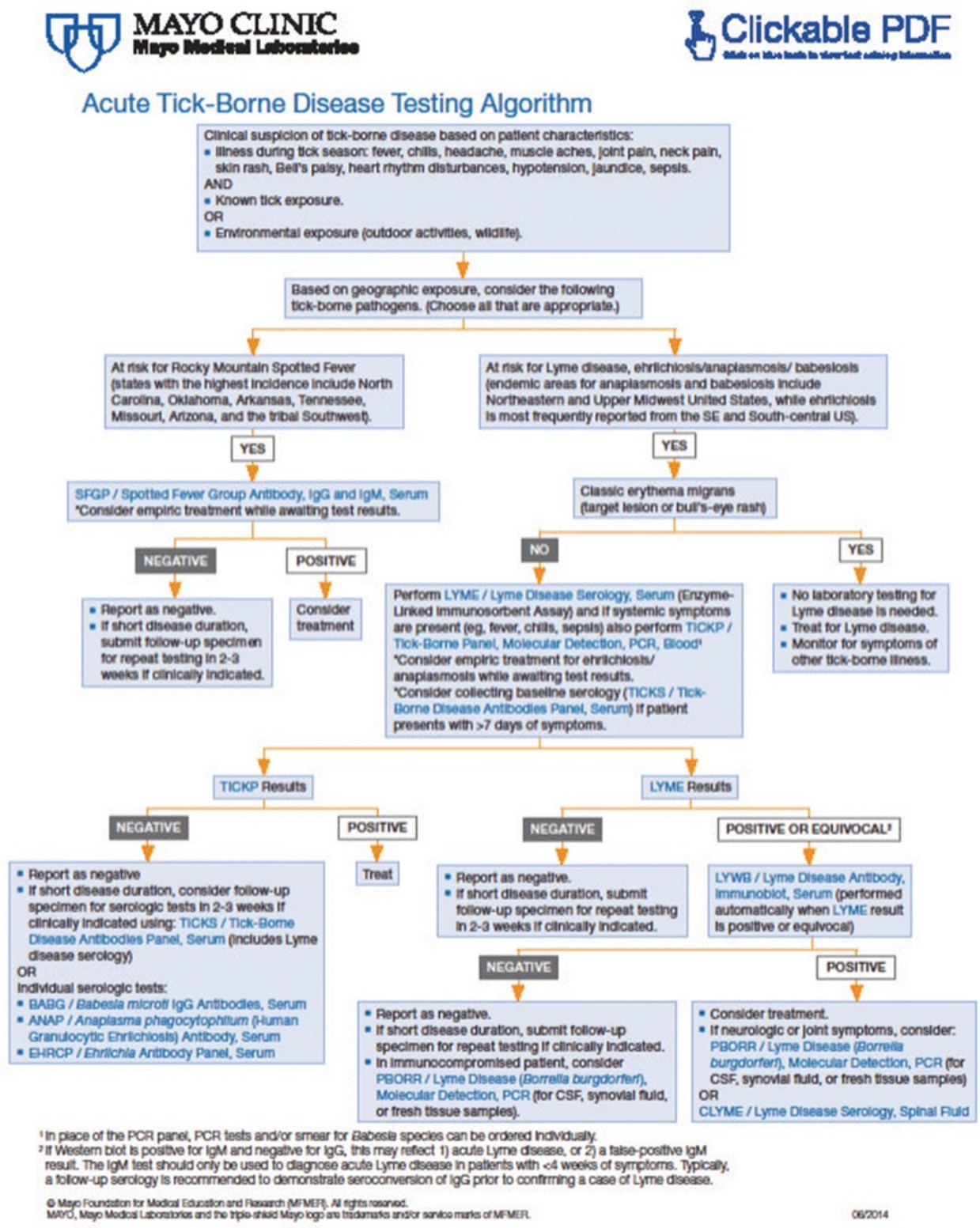


Fig. 13.4 Acute tick-borne disease testing algorithm at the Mayo Medical Laboratories (reprinted with permission)

In our hospital we are developing internal guidelines for the diagnosis of tick-borne infections. Our guidelines are similar to those outlined in the Mayo Medical Laboratories algorithm, with some local modifications and adaptations. For example, in our hospital the test of choice for babesiosis is examination of Giemsa-stained thick and thin blood smears, rather than serology or PCR (see Chap. 2). We also discourage the use of ehrlichia and anaplasma serology , in favor of PCR tests.

It is important to recognize that algorithms will not be of much value if the clinicians who order tests are not aware of them or if they are not readily available at the time that the physician is seeing the patient. One solution to the latter problem is to incorporate the algorithms into an online laboratory handbook, as described in the introductory chapter of this book. The former problem is one of marketing. Physicians must be alerted to the existence of the algorithms and where to find them.

Reflex Testing Algorithms

Unlike clinical practice guidelines or diagnostic algorithms , which rely on the ordering clinician to follow them, reflex testing algorithms can be mandated by laboratory leadership. Reflex testing algorithms involve the rejection of orders for a particular test unless certain conditions are met—typically, a positive result from an initial screening test. Generally speaking, the initial screening test is inexpensive and requires minimal labor to perform, whereas the test performed reflexively is often more expensive and/or labor intensive. Because reflex testing algorithms do not take other factors into consideration, beyond the result of the screening test, one must allow for exceptions when they are medically justified. However, the relative rigidity of this approach also makes it a very effective way to manage test utilization. Certainly, before implementing such an approach, it is important to get the assent of leaders who can speak for the relevant providers. Several examples of reflex testing algorithms adopted at our institution are described below.

HCV Confirmatory Testing (PCR or RIBA)

The laboratory diagnosis of HCV infection usually starts with a screening ELISA, which is highly sensitive. Because the ELISA is poorly specific, however, a positive or equivocal/indeterminate result should be confirmed by

a more specific assay (see www.cdc.gov/hepatitis/hcv.labtesting.htm), either viral RNA detection or (if RNA is not detected) a different serologic test such as a recombinant immunoblot assay (RIBA) . Oethinger et al. reported on the clinical significance of specimens with a low signal-to-cutoff (S/Co) ratio in the Ortho Diagnostics screening ELISA for hepatitis C (HCV) . Of 482 HCV reactive samples, none of the 83 samples with a low S/Co ratio was confirmed by HCV RNA testing. In a second study of 163 reactive samples with a low S/Co ratio, none of the results was confirmed by the confirmatory immunoblot (RIBA) assay. The authors concluded that over 99 % of samples with an S/Co ratio of ≤5 were falsely positive and that the antibody testing algorithm could be modified to eliminate additional testing of samples with low S/Co ratios [12]. Based on these and other reports, it is acceptable to modify the standard reflex testing algorithm to incorporate the screening test S/Co ratio. Specifically, under some circumstances an S/Co ratio exceeding a certain threshold obviates the need for supplemental testing, because the positive predictive value is so high (see www.cdc.gov/hepatitis/hcv. labtesting.htm).

Pre-culture Screening Urinalysis

Urinary tract infections may be classified as either uncomplicated or complicated. Uncomplicated urinary tract infections are very common and occur in nonpregnant female outpatients. Complicated urinary tract infections are associated with structural or functional urinary tract abnormalities [13]. In many settings, the diagnosis of uncomplicated UTI starts with a screening urinalysis, with or without microscopic examination. Urine culture and susceptibility testing are only allowed when urinalysis reveals certain abnormalities, such as leukocyte esterase or nitrites, or when microscopic examination reveals an elevated concentration of white blood cells or bacteria. This strategy reserves culture and susceptibility testing , which are labor intensive and require highly trained technologists for reliable interpretation, for cases with a higher pretest probability of true UTI. Several reports have described approaches to the diagnosis of uncomplicated UTI in adult women using screening urinalysis alone, without the need for confirmatory culture [14, 15]. For example, Stam [14] and Wilson [15] reported that most uncomplicated UTIs in the outpatient setting can be diagnosed without culture. In another report, Wright described a strategy of managing suspected UTI in women over the telephone [16], eliminating both

the office visit and laboratory testing. Other studies have suggested that urine can be screened for significant bacteriuria using either an automated urine sediment examination [17] or flow cytometry [18]. In our hospital we have considered looking at screening strategies such as described in these reports, but have not as yet reached a conclusion .

Sequential Testing

Sequential testing is a variation of the reflex testing approach , in which routine tests for common entities are performed before tests for less common entities. The initial evaluation of a patient will often result in the delineation of a differential diagnosis that may include of number of different possibilities, some of which may be common, and others more rare. Resolution of the differential diagnosis may be dependent on a variety of laboratory tests and other studies. Frequently, the results of one test will determine whether subsequent tests are necessary. For example, in a patient with suspected meningitis, if the cerebrospinal fluid (CSF) Gram stain shows lancet-shaped Gram-positive cocci in pairs, and the CSF culture yields *S. pneumoniae*, the diagnosis of bacterial meningitis has been made, and other entities on the differential diagnosis (for example, viral meningitis) can be excluded. However, at the time an initial CSF sample is collected, it is common for providers to order a battery of tests targeting both bacterial and non-bacterial agents. Thus, in addition to the routine Gram stain and culture, expensive molecular assays for common and uncommon viral agents (e.g., HSV, West Nile virus, etc.) may be performed, along with cultures for mycobacteria and fungi, even though the yield for uncommon agents is low. Ideally, tests for common agents should be performed first, and tests for uncommon agents should be performed only if common agents are not identified by routine tests. However, this approach is often impractical, as the pace of clinical care will not allow for significant delays while tests are performed sequentially rather than simultaneously. On the other hand, if the clinical laboratory is able to perform the key initial test(s) in a timely fashion, it may be possible to process and hold specimens for the secondary tests and cancel some of them based on the results of the initial test. In principle this approach would appear straightforward, but it can create significant logistical problems, because canceling the secondary tests will require approval by the ordering provider. For this reason, the strategy is only practical when the cost of the secondary test(s) is sufficiently high to justify the effort of monitoring

the results of preliminary testing and obtaining permission to cancel secondary tests. Although it does not relate to clinical microbiology, an example is provided by Hanson and Plumhoff, who describe a strategy wherein samples submitted for flow cytometry , molecular diagnostic tests, and cytogenetics could be held pending the results of a bone marrow biopsy examination [19]. We are currently exploring opportunities in microbiology to employ a similar strategy .

Gatekeeping (Stewardship)

Gatekeeping has long been recognized as an effective strategy to reduce test overutilization . Historically, gatekeeping has been used extensively in radiology and pharmacy to control the cost of high-priced imaging and drugs, often through the use of prior approval mechanisms . In the laboratory, the best targets for gatekeeping are those tests with the following characteristics:

1. They are useful only in select clinical presentations and do not address common illnesses , so test volume is low to moderate. It is not practical to gatekeep high-volume tests.

2. They have legitimate indications and therefore cannot be banned entirely.

3. They carry a relatively high unit cost. Gatekeeping can consume considerable time for the gatekeepers; gatekeeping low-cost tests produces little yield, and the savings are minimal.

4. Their performance characteristics (sensitivity/specificity), appropriate clinical indications, or alternatives are not well understood by most providers.

In our hospital we have eliminated many of the tests that have no reasonable clinical indication. For this reason, gatekeeping is becoming an increasingly important component of our utilization management strategy. Many microbiology tests are ordered in low volume and are therefore sent out to reference laboratories. Over time, the cumulative cost of these tests can be substantial. For example, Aesif and colleagues reported an average unit cost of $177 for microbiology reference laboratory tests [20]. In our hospital,

microbiology-related reference laboratory testing accounts for approximately $800,000 in annual expenditures . In the study by Aesif et al., the authors reported the establishment of a gatekeeping intervention for microbiology send-out tests. All requests for reference laboratory microbiology tests were screened by clinical pathology residents prior to final dispensation. The residents then discussed the rationale for the test request during interdisciplinary rounds, or by direct consultation with the ordering physician, resulting in the cancellation of 38 % of the tests. Molecular assays represented most of the screened tests [20]. In our institution, we currently steward several specific microbiology reference laboratory tests by a similar mechanism, including fungal antigen tests (galactomannan and 1,3-beta-D-glucan), and direct PCR detection of microorganisms using universal primers.

Identifying a suitable target for gatekeeping starts with an analysis of the test's clinical indications and an audit of annual test volume, including who is ordering the test and for what indication. For example, we performed an audit of PCR testing for anaplasma , knowing that anaplasmosis is relatively uncommon in Massachusetts. The audit revealed that in 2014, there were 424 requests for anaplasma PCR testing , but only eight of these tests were positive. One clinician in particular, a general internal medicine physician, ordered 62 of these tests—of which none were positive. After reviewing the medical records of the eight patients in whom anaplasmosis was detected, we noticed that in all cases there was an elevation in hepatic transaminases and either a normal or low total white blood cell count (analysis performed by Vikram Pattanak, MD, PhD). Considering that the test is low volume (1.2 tests per day), expensive, rarely positive and that true positive cases have particular routine laboratory abnormalities, we concluded that the anaplasma PCR test is an excellent candidate for gatekeeping . We are developing a plan to begin gatekeeping this test in the near future.

As another example, we have become interested in gatekeeping urine antigen tests for *Legionella pneumophila* and *Streptococcus pneumoniae* , two agents of community-acquired pneumonia (CAP) . CAP has been defined by Musher as a diagnosis based on characteristic clinical, radiologic , and laboratory findings [21]. Recent guidelines provided by the Infectious Diseases Society of America (ISDA) recommend testing for *S. pneumoniae* and *L. pneumophila* urinary antigen in critically ill patients with severe CAP. However, these tests are often ordered routinely on all patients with CAP [22], making them ripe for a gatekeeping effort. The ISDA guidelines do not

recommend urinary antigen testing in patients who are not severely ill or in those who are not failing empiric therapy. The appropriate use of these urinary antigen tests in different clinical scenarios was recently reviewed by Galen et al. [22].

Interventions That Influence Non-laboratory Resource Utilization

Sometimes, the clinical laboratory is in a position to help reduce resource overutilization , even when the resources in question are centered in the clinical sphere rather than the laboratory sphere. For example, microbiologists can effectively participate in antimicrobial stewardship efforts, because much of the data relevant to those efforts are generated in the laboratory. Alternatively, the laboratory may be able to provide testing capabilities that can improve patient outcomes and conserve resources in the form of antimicrobials, hospital beds, and many other services. Specific examples are provided in the paragraphs below.

Establishing an Antimicrobial Stewardship Program for High-Cost Broad-Spectrum Antimicrobial Agents

Many hospitals have established formularies to assist in the management of antimicrobial agents. Often this involves requiring approval from an Infectious Diseases specialist for the use of high-cost, broad-spectrum antibiotics. These efforts are intended both to control costs in the pharmacy and to reduce the incidence of antimicrobial resistance. For example, White et al. reported the results of a prior authorization program for selected antimicrobials [23]. Overall, expenses for parenteral antimicrobial agents decreased by 32 %, with a significant increase in drug susceptibility among bacterial isolates from intensive care unit patients. However, in many cases the initial use of one of these agents is appropriate and is therefore approved, but subsequent culture and susceptibility data reveals that the patient could be treated effectively with a lower cost, narrow-spectrum agent. In this setting, there is no formal mechanism to encourage making the switch once actionable microbiologic data has become available. To address this, an antimicrobial stewardship program can be developed, in which laboratory data and clinical records are reviewed to identify patients whose

antimicrobial coverage could be narrowed. In one study of a rapid pathogen detection strategy combined with antimicrobial stewardship, Perez et al. demonstrated a significant improvement in the time to optimal therapy, a decrease hospital length of stay, and a reduced cost following implementation of the program [24]. In this study, rapid identification of the pathogens was accomplished using a relatively new technology called matrix-assisted laser desorption ionization-time of flight mass spectroscopy (MALDI-TOF MS) . It is known that rapid bacterial identification and susceptibility testing leads to more appropriate use of antibiotics and a decrease in antimicrobial utilization [25]. In the traditional microbiology laboratory, improved turnaround time has historically been accomplished by employing automated versions of manually performed tests, such as automated blood culture systems. The development of commercially available MALDI-TOF MS allows for even faster identification of bacteria and fungi [26], which will facilitate interventions to control the utilization of antimicrobial agents and improve patient outcomes. Although MALDI-TOF MS does not provide antimicrobial susceptibility data, rapid organism identification can nevertheless guide antimicrobial therapy [27].

In our hospital we have begun an antimicrobial stewardship program based in our microbiology laboratory. The laboratory receives a daily report from the pharmacy listing all of the patients currently receiving targeted antimicrobials (e.g., carbapenems , daptomycin , linezolid). The laboratory then reviews the available culture and susceptibility data for these patients. If the laboratory data indicate that the patient can be adequately treated with a less expensive, less broad-spectrum antimicrobial agent, the laboratory sends an email to alert the clinician. An example of an email is shown below [1]:

Dear Dr._____

Your patient _____ is currently receiving a restricted antibiotic : Ertapenem. The use of this restricted drug is being monitored by the MGH Antimicrobial Stewardship Program.

Recent culture and antimicrobial susceptibility data from your patient reveal that the organism(s) is/are susceptible to other, non-restricted antibiotics (see sensitivity report below). Given these data, if clinically appropriate, please consider discontinuing the restricted carbapenem and/or changing to a non-restricted antimicrobial option. This may help reduce both the development of future resistance to these

broad-spectrum drugs and costs of therapy. If you have not already done so, you may request an infectious disease consult in order to obtain assistance on the choice of antimicrobial agents .

Following implementation of the stewardship program, we observed a significant decrease in the use and cost of the targeted antimicrobial agents. Subsequently we have added additional agents to the stewardship program .

Use of Rapid Molecular Diagnostic Tests to Screen for Methicillin-Resistant *Staphylococcus aureus* (MRSA) in Previously Colonized Patients and for *Staphylococcus aureus* (SA) Prior to Orthopedic and Cardiac Surgery

Rapid, simple to perform, automated molecular diagnostic assays for MRSA and SA are now commercially available. These new assays create opportunities to substantially improve clinical care in different settings. For example, hospital patients who are colonized with MRSA require contact precautions and must either be placed in a private room or be cohorted with other MRSA-colonized patients. In hospitals that are at or near capacity, these requirements complicate the management of inpatient beds. Once a patient has been designated as a carrier of MRSA, there are protocols that can be used to identify those who are no longer colonized. This is especially important when a patient is readmitted to the hospital, as those who have not been cleared must continue on contact precautions and be isolated to a private room or cohorted. In our hospital, the criteria for establishing clearance of MRSA colonization stipulate that the last documentation of MRSA colonization must be greater than 90 days prior, and the patient must have either three negative nasal swab MRSA cultures performed at least 24 h apart or a single negative nasal swab MSRA polymerase chain reaction test.

The criteria further stipulate that nasal swabs for MRSA testing (whether by culture or PCR) must be collected when the patient has not received antibiotics for at least 48 h. Clearly, the use of the MRSA PCR test is infinitely more practical, because it can be performed at the time of readmission on a single specimen. To be effective, the MRSA PCR test must

be available 24 h a day, highlighting the need for an easy-to-perform automated test. Cultures would need to be performed on an outpatient basis or would require many days to accomplish once the patient has been admitted. Furthermore, it is difficult to complete the full series of MRSA cultures in many patients, because they are often administered antibiotics during their hospital stay.

Another situation in which rapid PCR testing has proven beneficial is in screening patients for SA colonization before cardiac surgery or major orthopedic surgical procedures (e.g., hip and knee replacement). Patients who are colonized with SA are at increased risk of postoperative infection. These patients can be decolonized using nasal mupirocin and preoperative bathing with chlorhexidine soap. In a study by Bode et al., the use of the decolonization procedure reduced postoperative SA infections from 7.7 to 3.4 % [28]. Postoperative infections following cardiac surgery and major orthopedic procedures can be quite serious and difficult to treat, especially deep surgical site infections with osteomyelitis. Prevention of such infections results in improved outcomes and cost benefits .

Rapid Point-of-Care Testing to Reduce Resource Utilization

Rapid point-of-care testing (POCT) can provide near real-time test results, facilitating clinical decision-making and improving operational efficiency [29]. A number of rapid, point-of-care tests are available for the diagnosis of infectious diseases, including tests for Group A streptococcal pharyngitis, influenza A and B, and other microorganisms [30]. In a randomized, prospective study by Bodner et al., the authors evaluated the use of a POCT for influenza in a pediatric emergency department. Implementation of the test was associated with a significant reduction in additional laboratory tests ordered, a decrease in chest radiographs ordered, and a reduction in emergency department length of stay [31]. In another study of pediatric patients presenting with acute pharyngitis , the use of a rapid Strep A test (compared to culture alone) was associated with a 50 % decrease in prescription antibiotic use [32]. Rapid tests for respiratory viral pathogens have also been used in some hospitals to aid in bed placement decisions, because the presence of specific pathogens may necessitate contact and droplet precautions and private rooms or cohorting [1].

References

1. Branda J, Lewandrowski K. Utilization management in microbiology. Clin Chim Acta. 2014;427:173–7.
[CrossRef][PubMed]

2. Baron E, Miller M, Weinstein M, Richter S, Gillian P, et al. A guide to the utilization of the microbiology laboratory for the diagnosis of infectious diseases: 2013 recommendations of the Infectious Disease Society of America and the American Society for Microbiology. Clin Infect Dis. 2013;57:e22–121.
[CrossRef][PubMed][PubMedCentral]

3. Decre D, Barbut F, Petit J. Role of the microbiology laboratory in the diagnosis of nosocomial diarrhea. Pathol Biol. 2000;48:733–44.
[PubMed]

4. Rao G, Ozerek A, Jeans A. Rational testing for faeces in the investigation of sporadic hospital-acquired diarrhoea. J Hosp Infect. 2001;47:79–83.
[CrossRef]

5. Mathieu A, Tachet A, Pariente A. When should a stool culture be done in adults with nosocomial infections. Presse Med. 2005;34:81–4.
[CrossRef][PubMed]

6. Zwang O, Albert R. Analysis of strategies to improve cost effectiveness of blood cultures. J Hosp Med. 2006;1:272–6.
[CrossRef][PubMed]

7. Rao G, Crook M, Tillyer M. Pathology tests: is the time for demand management ripe at last. J Clin Pathol. 2003;56:243–8.
[CrossRef][PubMed]

8. Bates D, Goldman L, Lee T. Contaminant blood cultures and resource utilization: the true consequences of false positive results. JAMA. 1991;265:365–9.
[CrossRef][PubMed]

9. Segal G, Chamberlain J. Resource utilization and contaminated blood cultures in children at risk for occult bacteremia. Arch Pediatr Adolesc Med. 2000;154:469–73.
[CrossRef][PubMed]

10. Clinical and Laboratory Standards Institute. Principles and procedures for blood cultures: approved guideline. Wayne, PA: Clinical and Laboratory Standards Institute; 2007. CLSI document M47-A.

11. National Physicians Alliance Promoting Good Stewardship in Medicine. http://www.choosingwisely.org/clinician-lists/. Accessed 3 Jan 2016.

12. Oethinger M, Mayo D, Falcone J, Barua P, Griffth B. Efficiency of the Ortho VITROS assay for the detection of hepatitis C virus-specific antibodies increased by elimination of supplemental testing of samples with very low sample to cutoff levels. J Clin Microbiol. 2005;42:2477–80.

[CrossRef]

13. Pallet A, Hand K. Complicated urinary tract infections: practical solutions for the treatment of multiresistant Gram-negative bacteria. J Antimicrob Ther. 2010;65 Suppl 3:iii25–33.

14. Stamm WE, Hooten TM. Management of urinary tract infections in adults. N Engl J Med. 1993;329:1328–34.
[CrossRef][PubMed]

15. Wilson ML, Gaido L. Laboratory diagnosis of urinary tract infections in adult patients. Clin Infect Dis. 2004;38:1150–8.
[CrossRef][PubMed]

16. Wright O, Safranek S. Urine dipstick for diagnosing urinary tract infection. Am Fam Physician. 2006;73:129–32.
[PubMed]

17. Falbo R, Sala MR, Signorelli S, Venturi N, Signorini S, Brambilla P. Bacteriuria screening by automated whole-field-image-based microscopy reduces the number of necessary urine culture. J Clin Microbiol. 2012;50(4):1427–9.
[CrossRef][PubMed][PubMedCentral]

18. Kim S, Kim Y, Lee S, Hwang S, Kim H, Son H, Lee E. Evaluation of the Sysmex UF-100 urine cell analyzer as a screening test to reduce the need for cultures for community-acquired urinary tract infection. Am J Clin Pathol. 2007;128:922–5.
[CrossRef][PubMed]

19. Hanson C, Plumhoff E. Communique, test utilization and the clinical laboratory. MayoMedicalLaboratories.com.

20. Aesif S, Parenti D, Lesky L, Keiser J. A cost effective interdisciplinary approach to microbiologic send-out test use. Arch Pathol Lab Med. 2015;139:194–19821.
[CrossRef][PubMed]

21. Muscher D, Thorner A. Community acquired pneumonia. N Engl J Med. 2014;371:1619–28.
[CrossRef]

22. Galen B, Fogerty R, Manisha J. Don't order a test just because you can. South Med J. 2015;108:251–3.
[CrossRef][PubMed]

23. White C, Atmar R, Wilson J, Cate T, Stager C, Greenberg S. Effects of requiring prior authorization for selected antimicrobials: expenditures, susceptibilities and clinical outcomes. Clin Infect Dis. 1997;25:230–9.
[CrossRef][PubMed]

24. Perez K, Olsen R, Musiak W, Cernoch P, Davis J, Land G, Peterson L, Musser J. Integrating rapid pathogen identification and antimicrobial stewardship significantly decreases hospital costs. Arch Pathol Lab Med. 2013;137:1247–54.
[CrossRef][PubMed]

25. Kerremans J, Verboom P, Hallart-van-Roijen L, Goessens W, Verbrugh H, Vos M. Rapid identification and antimicrobial susceptibility testing reduce antibiotic use and accelerate pathogen-directed antibiotic use. J Antimicrob Chemother. 2008;61:428–35.
[CrossRef][PubMed]

26. Patel R. MALDI-TOF mass spectroscopy: transformative proteomics for clinical microbiology. Clin Chem. 2013;59:340–2.
[CrossRef][PubMed]

27. Clerc O, Prod'hom G, Vogne C, Bizzini A, Calandra T, Greub G. Impact of matrix-assisted laser desorption ionization time-of-flight mass spectrometry on the clinical management of patients with Gram-negative bacteremia: a prospective observational study. Clin Infect Dis. 2013;56(8):1101–7.
[CrossRef][PubMed]

28. Bode L, Kluytmans J, Wertheim H, Bogaers D, Vandenbroucke C, et al. Preventing surgical site infections in nasal carriers of *Staphylococcus aureus*. N Engl J Med. 2010;362:9–17.
[CrossRef][PubMed]

29. Lee-lewandrowski E, Lewandrowski K. Implementing point-of-care testing to improve outcomes. J Hosp Admin. 2013;2:125–32.

30. Dekker J. Infectious disease testing at the point-of-care. Point of Care. 2012;11:85–9.

31. Bonner A, Monroe K, Talley L, Klasner A, Kimberlin D. Impact of the rapid diagnosis of influenza on physician decision making and patient management in the pediatric emergency: results of a randomized, prospective controlled study. Pediatrics. 2003;112:363–7.
[CrossRef][PubMed]

32. Ayanroug S, Waseem M, Quee F, Humphrey A, Reynolds T. Impact of rapid streptococcal test on antibiotic use in a pediatric emergency department. Pediatr Emerg Care. 2009;11:748–50.

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_14

14. Utilization Management in a Large Community Hospital

Frederick L. Kiechle[1] and Rodney C. Arcenas[2]

(1) Department of Clinical Pathology, Memorial Regional Hospital, Pathology Consultants of South Broward, LLP, Hollywood, FL 33021, USA
(2) Microbiology, Molecular Microbiology Laboratory, Department of Clinical Pathology, Memorial Regional Hospital, Pathology Consultants of South Broward, LLP, Hollywood, FL 33021, USA

Frederick L. Kiechle (Corresponding author)
Email: fkiechle@mhs.net

Rodney C. Arcenas
Email: rarcenas@mhs.net

Keywords Community hospital – Laboratory utilization – Physician practices – Hospitalists – Hospital consolidation – CLIA'88 – Cost savings – Economies of scale – Outreach program – POCT – Provider-performed microscopy – Disruptive innovations – Blood cultures – Respiratory pathogens – Gastrointestinal pathogens – MALDI-TOF – Obsolete tests

Introduction

This chapter will review the numerous factors that influence laboratory test utilization in a large community hospital (Table 14.1). Assessment of laboratory test utilization usually relies on data compiled after a utilization

review or analysis of the necessity, appropriateness, and efficiency of laboratory tests on a concurrent and/or retrospective basis. Most laboratory utilization studies have been reported from academic medical centers [1–8], however, there are often common findings in large community hospital settings [9–13]. The major difference between an academic center and community healthcare system is usually the number of hospital-employed physicians versus independent physicians with their own office practices. Some large community hospitals have only employed physicians on their medical staff like Kaiser Permanente, Henry Ford Hospital, and others. Generally, it will be easier to assemble a group of specialists to convene a laboratory utilization committee meeting, if the physicians are accustomed to leaving their practice responsibilities and going to a hospital-oriented committee meeting in the middle of the day. Since the focus of this committee is to review the evidence-based evaluation of a new or old laboratory test to rule in or out a specific disease, attendance and the quality of participation will vary depending on the physician's commitment to the project. In a large community hospital, it may "save time" during these meetings if homework is assigned beforehand. "This includes what do people need to read, think about, bring with them, or come prepared to discuss so the meeting will be more productive" [14].

Table 14.1 Factors that influence laboratory utilization in a large community hospital

Factor
1. Current trends
a. Hospitals buy physician practices
b. Hospitalists
c. Hospital consolidation
2. Regulations
a. CLIA'88 (laboratory test categories)
b. How laboratory tests are counted
3. Economics
a. Calculation of cost savings
b. Economies of scale
4. Technology
a. Disruptive innovations—Resource Table 14.4
b. Microbiology Laboratory: Shifting sands
Positive blood cultures

Respiratory pathogen testing
Infectious gastrointestinal illness testing
Matrix-Assisted Laser Desorption Ionization—Time of Flight (MALDI-TOF)
New methodologies
c. In vitro diagnostic companies
New equipment
Obsolete tests—Table 14.8

One of the authors (FLK) has worked for 23 years directing the clinical laboratory and outreach laboratory at a large community hospital (William Beaumont Hospital) in Royal Oak, MI and for the past 9 years at a six hospital county healthcare system (Memorial Healthcare System) in Hollywood, FL with the co-author (RCA). We will review several of the issues listed in Table 14.1.

Current Trends

In preparation for the shift from fee-for-service to a value-based payment system [15] large community hospitals have been actively engaged in three enterprises which will impact laboratory test utilization: buying physician practices, increasing the use of hospitalists and consolidation of hospitals.

Buying Physician Practices

In the early 1990s during the initiation of health maintenance organizations (HMOs) , hospitals purchased physician practices. In general, at that time, hospitals had a difficult time managing the physicians and their practices. During this second more recent phase of buying, contracts are designed to enhance physician productivity [16–19]. The “key motivation for hospital acquisition of physician practices is the ability to gain market share for inpatient admissions and outpatient services by capturing referrals from physicians employed by the owned practices” [16]. Carlin et al. [16] documented a shift in inpatient admissions, outpatient CT scans and MRI procedures from three large multispecialty clinic systems to a two hospital-owned integrated delivery system (IDS) after the IDS purchased them. This same shift of referral patterns to the new hospital owner will also be true for laboratory tests ordered by newly acquired physician practices. In the USA 57 % of physicians were independent in 2000 compared to 39 % in 2012 [19]

and 36 % of male and 23 % of female physicians in 2015 [17]. In 2004, 11 % of physicians were employed by hospitals compared to 64 % in 2014 [18]. A downside of this trend is the finding that hospitals charge more when the doctors work for them attributing the cause to higher overall costs [19]. This current trend should drive more laboratory testing from new hospital-based physicians to the hospital central laboratory with the consequence of potential utilization issues.

Hospitalists

The hospitalist model of inpatient care is one of the most rapidly growing forms of medical practice in the USA since its introduction in the mid-1990s [20, 21]. In 2006, there were more than 12,000 hospitalists in the USA [20] which has increased to 34,000 in 2014 [21]. Most hospitalists practice in hospitals with greater than 200 beds [20, 21]. Their average starting salary was greater than that for internal medicine or family practice physicians in 2014 [18]. Hospitalists work strictly in the hospital and oversee the care of complex patients with the goal of reducing the need of transferring patients from one physician to another [22]. Most large community hospitals use a voluntary hospitalist system in which primary care physicians can choose to admit to a hospitalist service or attend to their own patients [23]. Large community hospitals are more likely to adopt a hospitalist model if their case mix complexity was greater than the national average for Medicare's diagnosis rated group index, while high health maintenance organization market share resulted in lower interest in this model [22]. The hypothesis that the hospitalist model will lead to a reduction in the patient's length of stay and total hospital costs has been demonstrated [20, 22–24]. Hospitalists may order excessive diagnostic tests secondary to their lack of previous knowledge of the patient [20]. The Choosing Wisely campaign sponsored by the American Board of Internal Medicine Foundation, Consumer Reports, and more than 60 specialty societies have recommended reduction or elimination of inappropriate use of radiologic, laboratory, and therapeutic procedures [12, 25–27]. The first 25 societies provided five selections each, of which 12 % were related to laboratory tests or pathology [27]. One of these lists from the Society of Hospital Medicine recommended reducing the use of repetitive common laboratory testing when the patient is clinically stable [26]. In a quality improvement project focused on hospitalists, an effort was made through education to reduce the repetitive use of complete blood

counts and basic metabolic panels [25]. These panels are often embedded in order sets established for specific diseases or for specific physicians to simplify computerized physician order entry [28]. There was a 10-month baseline period before the intervention followed by a 7-month intervention period [25]. The intervention resulted in a 10 % reduction of these two panels ordered per patient day associated with decreased direct costs of $16.19 per patient and annualized savings of $151,682 [25]. This study illustrates how a small segment of laboratory test ordering physicians can impact expenses through overutilization and by analogy underutilization of laboratory tests.

Hospital Consolidation

Like the first round of hospitals buying physician practices started in the early 1990s, so did the consolidation or mergers of hospitals [29]. There has been a recent increase in both horizontal and vertical consolidation [29, 30]. Horizontal consolidation involves hospitals merging with other hospitals that supply similar services in geographic proximity [29, 30]. These mergers are most likely to be investigated for antitrust violations [29]. Vertical consolidations involve hospitals consolidating with other health care provider entities [16, 29]. From 2007 to 2012, 432 hospital mergers and acquisitions were announced involving 835 hospitals [30]. Sixty percent of hospitals are now part of health systems. The downside to these mergers has been a 10–40 % increase in prices secondary to increased market share [30]. Strategies have been suggested for avoiding this market disequilibrium [30, 31]. No US hospital markets were rated highly competitive [30] while the German market is competitive and the number of hospital systems decreased by 18 % from 2000 to 2007 [32]. There are myths associated with the latest hospital merger activity. The first myth is that consolidation is equivalent to integration [33]. The second is that higher quality is associated with size rather than leadership and competition [33, 34]. Evidence supports the suggestion that hospitals in competitive markets tend to have better administrative management [33]. The combination of hospital mergers and increased hospital-employed physicians [35] will lead to increase in laboratory test volumes and the need for robust utilization management practices.

Regulations

CLIA’88

The Clinical Laboratory Improvement Amendment of 1988 (CLIA’88) went into effect September 1, 1992. The regulations categorize laboratory procedures based on test complexity using well-defined criteria: waived, moderately complex, and highly complex or provider-performed microscopy . These regulations define the universe of tests that a large community hospital laboratory is directly or indirectly responsible for their utilization management. There are a variety of CLIA-tests that have been classified as waived by the FDA and a list of them from 2000 to present can be found at www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfclia/testswaived.cfm. The implementation of point-of-care testing (POCT) usually involves a desire to decrease the total turn-around time for an analytical test and improve patient outcome [36]. However, decreased turn-around time does not always equal improved patient outcome [37, 38]. Two prospective studies analyzed the effect of the POCT i-STAT device (Abbott, Abbott Park, IL) on length of stay in the emergency department after a control period when the central laboratory was used. The i-STAT cartridge that analyzed sodium, potassium, chloride, urea, glucose and calculated hemoglobin was used. Neither study revealed any change in the length of stay or clinical outcome for emergency department patients, although both showed a decrease in time required to obtain laboratory results for the six tests on the cartridge when the iSTAT was used. The blood test was not the rate-limiting step in the patient’s length of stay [38]. In a similar study using five different testing cartridges for the iSTAT (INR, lactate, brain natriuretic peptide, troponin T and chemistry with hemoglobin and hematocrit), Singer et al. [39] reported a reduced turn-around time for POCT compared to the central laboratory which translated into a reduction in time to completion of IV contrast CT and the length of stay of those specific patients.

It is not clear whether relocating POCT tests to the patient’s bedside increases [40, 41] or decreases [42] the test volume of that test in the central laboratory. It has been reported in both adult and newborn intensive-care units that patients with indwelling arterial lines have more blood drawn for laboratory studies than patients without arterial lines [43, 44]. The blood loss may be great enough to require a transfusion [43]. Certainly, utilization management of POCT programs will require investigations to determine the relationship between total laboratory turn-around time for results, patient outcome and hospital costs using cost effectiveness analyses [36].

There are at least 17 different sources of body fluids in a human [45]. Some of these are laboratory specimens that are examined under the bright-field or phase contrast microscope and are classified as provider-performed microscopy (PPM) by CLIA'88 [46, 47]. A separate CMS license is available for sites performing these assays which include KOH preparation, pinworm detection, fern test, microscope urinalysis, semen analysis for presence of sperm and motility, and eosinophils in nasal smears [46, 47]. It is wise for the laboratory POCT administrative committee to assist in the initiation of a PPM testing program in collaboration with the PPM license holder for that clinically defined program, like fern testing in the labor and delivery area under the direction of a staff OB/GYN physician. In this model, training and utilization management is not under the direction of the hospital POCT administrative committee [46, 47].

How Laboratory Tests Are Counted

In order to audit laboratory test utilization year to year it is "essential to understand how test volumes are actually counted" [1]. Are test panels bundled and counted as one test or are the test panels unbundled and each test in the panel counted separately. In an evaluation of the total inpatient test volumes from 1978 to 2000 for the Department of Clinical Pathology at William Beaumont Hospital, Royal Oak, MI, it was determined that the method for counting inpatient tests changed in 1992 and 1996 [36, Table 14.1]. These changes in counting methodology made it impossible to compare data from year to year. How it is done is not as important as it is done the same way year after year.

Economics

Calculation of Cost Savings

There are two categories for cost reductions : "hard" cost savings and "soft" cost avoidance. Tangible "hard" cost savings are often achieved by bringing reference laboratory tests in-house to the clinical laboratory (or eliminating the reference laboratory test altogether) [4, 11]. The more intangible "soft" cost avoidance includes such things as decreases costs associated with the introduction of a new laboratory test with the intent to decrease costs in the future. It also can occur when a cost is lower than the original expense that

would have otherwise been required if the cost avoidance exercise had not been undertaken. Since processes consume overhead and overheard costs money, any significant process improvement could represent significant cost avoidance for an organization. Total cost includes direct and indirect costs [48]. Direct cost includes personnel time to prepare and perform the test, reagents, quality control, proficiency testing, and equipment depreciation. Indirect costs including reporting costs (computer) and hospital overhead. Incremental or marginal costs include only variable direct costs and not the indirect costs [48–50]. Therefore, incremental costs demonstrate what it would cost to perform one more laboratory test, assuming the equipment and facility are already available. Neither total cost analysis nor incremental cost analysis includes an analysis of the defect rate or failure to achieve established goals, like turn-around time [50]. They are defined as internal or external failure rates. Internal failure costs are incurred by the testing center as a consequence of a defect in the testing system. The receiver of the test results incurs the external failure costs. Over utilization of laboratory tests incurs both internal and external failure costs in the excess time spent in the laboratory to generate the result and then excess insurance charges to the patient and nursing/physician time to evaluate the results.

To illustrate cost avoidance , consider the presentation of potential Enterovirus meningitis in the emergency department. Children and adults with detectable Enterovirus in the cerebrospinal fluid (CSF) may exhibit symptoms of meningitis including photophobia, stiff neck, acousticophobia , severe headache with vomiting, confusion, difficulty concentrating, seizure and sleepiness. A molecular test for Enterovirus detection will alter the patient's length of stay in the emergency department. If the patient is positive for Enterovirus in the CSF specimen, the patient will be discharged for home care until the viral meningitis resolves (Table 14.2). If the patient does not have Enterovirus in the CSF, they will need further hospitalization to rule out a bacterial source for the meningitis with culture and sensitivity studies (Table 14.2). Romero [51] has demonstrated the cost range for hospitalization related to Enterovirus testing/care of infection to be $4476–4921 with an average length of stay of 3–4 days. We used $4476 for the calculation in Table 14.2, which illustrates a cost avoidance of $187,992 for 20 patients with or without enteroviral detection by molecular methods.

Table 14.2 Enterovirus (EV) cost avoidance for 20 patients from May 2008 to May 2009

Population	EV positive	EV negative
Total patients	20	20
Total LOS days	26	68
Average LOS days for one patient	1.3	3.4
Literature-based cost for admission due to EV status	$116,376	$304,368

Estimated savings for cost avoidance $187,992 for 20 EV positive patients ($304,368 − $116,376 = $187,992). *LOS* length of stay

Economies of Scale

“Cost per unit went down if you could make longer and longer runs of identical products. This gave rise to the theory of economies of scale ” [52]. The laboratory achieves economies of scale and lower unit costs per test by expanding the volume of laboratory tests it analyzes. In the early 1990s, the number of inpatient laboratory tests at William Beaumont Hospital began to decrease. To fill the gap, after a 3-year preparation period, we initiated an outreach program (Beaumont Reference Laboratory) expanding our laboratory testing services to non-patients from physician offices, nursing homes, and other hospitals [53, 54]. Several years later (1992) Beaumont Reference Laboratory joined a regional laboratory network of other hospital-based laboratory outreach programs in Michigan, Joint Venture Hospital Laboratories , to accommodate the wide geographic coverage required by third party payers [53, 54]. The participating laboratories are independently owned and operated. A central network administrator coordinates negotiations for managed care contracts. The volume of BRL specimens grew to half of the total volume of clinical pathology procedures of six million tests in 2004. This increased volume permitted an expansion of the test menu in each laboratory section. In 2002, we reviewed 2,976,494 procedures ordered by 2806 physicians in nine subspecialty areas (family practice, pediatrics , internal medicine, cardiology, endocrinology, gastroenterology, nursing home, OB/GYN, and urology). The requisitions for physician, procedures per requisition and procedures/physician were calculated for each of the nine groups of physicians [54]. Family practice (464 physicians) and internal medicine (831) ordered the greatest number of total procedures as well as procedures/physician while urology (126) ordered the least of these two categories [54]. The tests ordered by each of the nine groups were counted in seven laboratory sections. All nine groups ordered more chemistry

tests than any other category but the percent varied from 34.5 % for OB/GYN to 90.2 % for internal medicine. The most popular individual tests in five laboratory sections (chemistry, hematology, immunology, microbiology, and molecular diagnostics) were calculated as an average number of a specific test ordered per physician per month. Using this data, a laboratory section could prepare themselves for the increased utilization from a six-member internal medicine group that the Beaumont Reference Laboratory sales force just signed up as a new client. This type of deep dive into specific physician specialty ordering patterns is an invaluable resource for managing a growing outreach business [54]. The 20 million requests for chemistry, hematology, and microbiology tests were included for all physicians in Calgary, Canada who ordered a test in fiscal year 2013–2014 [55]. The physicians were divided into 30 subspecialties and the average yearly cost per group and average yearly cost per physician in each of the 30 groups was calculated. Family practice and internal medicine had the greatest average yearly cost per group while hematology and nephrology had the highest average yearly cost per physician per group secondary to utilization of more expensive laboratory tests [55]. This cost-based approach to utilization review requires the calculation of an average median cost for each test which in the USA would be much less than the price listed on the hospital's charge master.

There was a synergistic relationship between the growth of Beaumont Reference Laboratory and test mix complexity in each laboratory section. In the molecular diagnostics laboratory started in 1992, *Chlamydia trachomatis* (CT) *Nisseria gonorrhoeae* (NG) were performed in urine using the ligase chain reaction in 1996 and PCR in 2002 [56, 57]. More than 75 % of the requests for these two assays are from BRL clients (Table 14.3). The increased volume of these two assays helped turn the molecular diagnostic section into a profit center in 4 years. Annual utilization review revealed that the outreach program contributed 33,019/43,814 = 75 % of the volume, Hospital A (8624/43,814 = 20 %) and Hospital B (2181/43,814 = 5 %). The multiplex assay using primarily urine specimens made a margin of $72.00 per assay billed (at that time) based on an average Medicare reimbursement ($83.00) and cost/test of $11.00. Why was there an exceptionally low NG volume from Hospital B? After an investigation it was learned that Hospital B chose to do the less sensitive NG culture assay [56] to retain laboratory test volume which was encouraged by their hospital administration. Also, a myth existed at hospital B that NG would not survive the transport time (40–60

min) to hospital A. The ordering physicians at hospital B prevailed and the request for molecular detection of NG at hospital B was followed. This case illustrates just how complex problem solving in utilization management issues can be in a large community hospital.

Table 14.3 CT/NG annual test volumes by site

Site	CT volume	NG volume	Total volume
Hospital A	1881	1613	8624
Hospital B	709	184	2181
Outreach clients	13,514	13,226	33,019
		Total	43,844

CT *Chlamydia trachomatis*, NG *Neisseria gonorrhoeae*

Technology

Disruptive Innovations

Some new technologies are defined as disruptive innovations , when they offer new paradigms in diagnostics (Table 14.4) [12, 83, 84]. All seven of the technologies listed in Table 14.4 share similar issues including clarification of the best applications for routine clinical use, paucity of evidence-based outcome literature to review, education of practitioners and physician users of the clinical information generated and software to convert big databases the method generates into useful information. The references in Table 14.4 will direct attention to these issues for the seven disruptive innovations [58–82]. As the paradigm shifts and these strategies become incorporated into daily clinical practice, the debate about appropriate utilization will diminish.

Table 14.4 Current disruptive innovations for the laboratory

Technology	Reference
Next gen sequencing Whole genome sequence	[12, 58–60]
Targeted genome panels	[12, 61, 62]
Cell free DNA	
Fetal DNA	[63–65]
Tumor DNA	[66, 67]
Mass spectrometry in microbiology	[12, 68, 69]

Smartphone apps	
Laboratory tests	[70–72]
Physiologic parameters	[73, 74]
Wearable sensors	[75–77]
Bioinformatics	[78–80]
Digital pathology	[81, 82]

Microbiology Laboratory : Shifting Sands

This next section will devote time to describing the impact of current changes in microbiology (mass spectrometry for bacterial identification [12, 68, 69] and multiplex molecular panels for infectious agent detection for respiratory viral panels and gastric pathogen panels) and future changes (microscopy for antibacterial drug sensitivity).

Traditionally, the laboratory diagnosis of most infectious disease pathogens has relied on culturing and in vitro growth of the causative agent. Once culture growth has been achieved, then automated and/or manual biochemical tests can be performed to identify the microbial organism(s). These methodologies are dependent on skilled medical technologists to perform the manual tasks required to determine the bacterial identification (ID). The approach to ID and antimicrobial susceptibility testing (AST) has been dependent on testing a single pathogen at a time, regardless if the culture growth yielded multiple, significant pathogens. Although automated ID and AST systems can run multiple isolates to help streamline the workflow and maximize throughput, the basic testing is still individually performed for each isolate being analyzed. Another limiting factor for culture based detection methods is that some bacteria do not grow well or at all in vitro adding to the potential of missing a significant organism(s).

Viral cultures are time-consuming because cytopathic effects (CPE) must be observed before other methods can be used to determine the viral identification [85–87]. The development of viral antigen based testing [direct fluorescence antigen (DFA) and other rapid antigen testing devices] directly from the sample shortened the culture time to obtain a faster diagnosis. However, the reliable performance of the viral antigen based testing is highly dependent on the quality of the sample collected and is less sensitive than viral cultures [85]. A suboptimal specimen could lead to a false negative antigen/DFA result. Are viral cultures and antigen based testing truly needed in a clinical microbiology/virology laboratory since molecular methods are

becoming the new gold standard? [85–87]. Many routine clinical microbiology/virology laboratories do not have the capabilities to perform viral cultures lacking the physical space and expertise to interpret the CPE [88].

As technology advances, the traditionally “agrarian society ” of the laboratory is becoming more industrialized with the implementation of automation, molecular based testing, and use of mass spectrometry (MALDI-TOF —Matrix-Assisted Laser Desorption Ionization—Time of Flight). Many of these advances are revolutionizing how microbiology testing is performed and disrupting how traditional clinical microbiology workflows and processes are set up. However, all of these technological advances are shortening the time for a laboratory diagnosis and ultimately maximizing the impact to patient care and how physicians at a large community hospital will utilize the more rapid microbiology laboratory services.

Positive Blood Cultures

There is a trend in clinical microbiology to develop syndromic panels using molecular techniques. For example, positive blood culture panels have been developed to reduce time to start the most appropriate antibiotics in the patient. Once a blood culture bottle is flagged as positive, a Gram stained smear is prepared to determine the presence of bacteria (and potentially yeast) in the patient’s blood sample. If any organism(s) are seen, a call is made to the patient’s healthcare provider so that broad-spectrum antimicrobial therapy can be initiated until the confirmed microbiological ID is resulted. A caveat for the clinician is that s/he must make their best educated guess for determining which antibiotic treatment to use. Clinical microbiology laboratories typically publish an antibiogram so that clinicians and hospital pharmacists know the prevalence of susceptible and resistant phenotypes for their most common bacteria isolated. Although this provides a good start and useful reference, there is a heavy emphasis on antimicrobial stewardship and tailoring therapy as soon as possible so that there is less pressure for the development of antimicrobial resistance . Many institutions have developed or are in the process of developing formal antibiotic stewardship programs/committees in an effort to improve the utilization of antimicrobial treatments.

Molecular methods have been developed that will, within one test,

identify a number of pathogens from a positive blood culture sample. These methods have decreased the amount of time to provide a more definitive ID and an abbreviated antimicrobial resistance genetic profile. AdvanDx/bioMerieux, Inc. utilizes PNA-FISH (peptide nucleic acid—fluorescent in situ hybridization) and detection of a positive fluorescent signal directly from a positive blood culture . Gram stained smear findings typically are resulted as “Gram Positive cocci in clusters” or “Gram Negative rods” (Table 14.5). This information is useful in deciding broad-spectrum therapy, but a more focused therapy is the ultimate goal to ensure that the pathogen is adequately treated. The PNA-FISH assays offer four basic assays [*Staphylococcus* (Gram Positive), *Enterococcus* (Gram Positive), Gram Negative, and *Candida*] that complements the Gram stain result so that clinicians at least have a presumptive genus identification. Additional PNA-FISH probes do have the ability to separate *S. aureus*/coagulase-negative *Staphylococcus* and a *mecA* probe for the identification of MRSA. Use of these PNA-FISH assays requires a fluorescent microscope to visualize the results. A number of studies have shown the clinical benefits of PNA-FISH implementation as part of the blood culture workup before the confirmatory culture growth and potentially identifying methicillin resistance genotype, in the example of *S. aureus*, before the full antibiotic susceptibilities can be performed [89–93]. Antibiotic therapy can, therefore, be tailored or deescalated as appropriate.

Table 14.5 FDA-approved molecular assays for positive blood cultures

Vendor	Assay name	Method	Panel composition
AdvanDx, Inc.	*Quick*FISH, PNA FISH	FISH[a]	*S. aureus*/CNS, *E. faecalis*/*Enterococcus* spp, Gram Negatives, *Candida* species
Cepheid	Xpert MRSA/SA blood culture	Multiplex real-time PCR	Methicillin resistant *S. aureus*/Methicillin sensitive *S. aureus*
Nanosphere, Inc.	Verigene Gram Positive blood culture test	Multiplex real-time PCR	*Staphylococcus* spp[b], *Streptococcus* spp[c], *Enterococcus* spp[d], *Micrococcus* species, *mecA* (methicillin), *vanA* and *vanB* (vancomycin)
	Verigene Gram Negative blood culture test		*E. coli*, *K. pneumonia*, *K. oxytoca*, *P. aeruginosa*, *S. marcescens*, *Acinetobacter* spp., *Citrobacter* spp., *Enterobacter* spp., *Proteus* spp., CTX-M (ESBL), Carbapenemases (IMP, KPC, NDM, VIM)

	Verigene Yeast blood culture test		*Candida* spp[e]., *C. gattii, C. neoformans*
BioFire Diagnostics, Inc.	Blood Culture Identification Panel	Multiplex real-time PCR	Gram positive[f], Gram negative[g], Yeast[h], and Antibiotic Resistance genes[i]

www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm330711.htm (web page accessed July 13, 2015)

[a]Fluorescent in-situ hybridization

[b] *Staphylococcus* species identified (*S. aureus*, *epidermidis*, *lugdunensis*). Other species are identified as *S.* spp.

[c] *Streptococcus* species identified (*S. anginosus* Group, *agalactiae*, *pneumoniae*, *pyogenes*). Other species are identified as *S.* spp.

[d] *Enterococcus* species identified (*E. faecalis*, *faeceium*)

[e] *Candida* species identified (*C. albicans*, *dubliniensis*, *glabrata*, *krusei*, *parapsilosis*, *tropicalis*)

[f] *Enterococcus* spp., *L. monocytogenes*, *Staphylococcus* spp., *S. aureus*, *Streptococcus* spp., *S. agalactiae*, *S. pyogenes*, *S. pneumoniae*

[g] *A. baumanii*, *H. influenza*, *N. meningitides*, *P. aeruginosa*, *Enterobacteriacae* (*E. cloacae complex*, *E. coli*, *K. oxytoca*, *K. pneumonia*, *Proteus* spp., *S. marcescens*)

[h] *C. albicans* , *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*

[i] *mecA*, *vanA*/*B*, KPC

Similar to the PNA-FISH scenario, when utilizing Cepheid's Xpert MRSA/SA Blood Culture test the Gram stained smear prepared from the positive blood culture smear will determine whether Cepheid's assay should be run. Cepheid's methodology is real-time PCR based and does not require any subjective interpretation of the results by the laboratory staff. The cartridge for the Xpert MRSA/SA test houses all the reagents and is compartmentalized to accommodate the nucleic acid extraction, PCR amplification, and detection in one device. The testing is automated once the sample is loaded into the test cartridge and the software analyzes the PCR amplification curves to determine if a patient's blood sample is positive or negative for MRSA or MSSA [94–97]. The Cepheid and AdvanDx tests must be added to the already existing workflow, and serves as another laboratory

tool to more quickly determine the pathogen identification and a preliminary AST profile.

Nanosphere, Inc. and BioFire Diagnostics, Inc. approach testing from positive blood culture bottles by targeting the most common pathogens (bacteria or yeast) that can cause sepsis. This is a unique approach due to the overlap in patient symptoms for a specific syndrome or condition. When the symptoms overlap, clinicians have difficulty defining the causative pathogen(s) infecting their patient solely from the clinical picture, and delaying specific pathogen-based therapy. Use of these syndromic multiplex molecular panels streamlines the testing process to more of a “one-and-done” approach.

Nanosphere offers different panels: (1) Gram positive (BC-GP panel); (2) Gram negative (BC-GN panel); and (3) Yeast (BC-Y panel) and the organism(s) observed from the Gram stained smear will determine which panel(s) to run. Additional testing with the Gram Positive and Gram Negative panels also includes testing for certain antibiotic resistance genes encoding for methicillin (*mecA*) and vancomycin (*vanA* and *vanB*) resistance (Table 14.5). There are many studies showing overall good performance for the BC-GP panel [98–104], Gram negative species and *Candida* spp. panels [105, 106].

There are limitations with molecular testing as observed by Buchan et al. [101]. A positive *mecA* target was not able to be assigned due to the presence of a mixed infection. In this case the full antibiotic sensitivity testing is still recommended because the traditional methods test each bacterial pathogen individually. Beal et al. [102] noted that when blood culture infections were caused by one pathogen, there was good performance of the multiplex molecular assays. When polymicrobial blood culture infections were noted, there was only 33 % agreement with the routine cultures. Mestas et al. [103] also noticed a lower percentage agreement for polymicrobial infections when compared to monomicrobial infections. Polymicrobial bacteremia is relatively rare, but can potentially be severe [107]. Again, cultures are still required to identify the full antibiotic susceptibility profile, and to identify pathogens that are not included in the multiplex molecular panels.

The FilmArray Blood Culture Identification Panel (BCID) is another comprehensive panel that covers Gram positive, Gram negative, and yeast pathogens (Table 14.5) and a Gram stain is not required. However, it is still good routine practice to perform the Gram stain to correlate results with the

molecular panel results and the eventual culture testing and antibiotic susceptibility testing. Altum et al. [105] observed that certain pathogens were detected in routine cultures that were not detected in the FilmArray panel because those pathogens were not in the molecular panel. So although the comprehensive panel covers the most common pathogens, clinical intuition is still ultimately needed especially when clinical symptoms and other laboratory data point to a bacteremic process in the setting of a negative FilmArray panel. Overall, these assays show the potential for a decreased TAT and a preliminary susceptibility profile based on the antibiotic resistance genes tested [104, 105, 108, 109].

The ability to have a more rapid answer that is technically more sensitive and specific will have positive downstream effects on patient care and antibiotic stewardship. The impact of these rapid PCR blood culture assays on the clinical end users (infection control, pharmacy, length of stay, and overall hospital costs) is not well defined. One study by Bauer et al. [95] demonstrated clinical benefit after implementing the Cepheid Xpert MRSA/SA assay for positive blood cultures. A 4-month pre-PCR period was evaluated followed by a 4-month post-PCR period. There was an overall shorter length of stay (6.2 days shorter) and mean hospital costs were $21,387 less than what was observed in the pre-PCR period. Infectious disease pharmacists were more effective in deescalating or changing to more specific antibiotic therapies compared to the pre-PCR period. Benefits were gained by having a more rapid and sensitive test. When adopting newer molecular methods, the laboratory must work with their clinical counterparts to determine the clinical utility of a more rapid test. The cost and potential benefits of the newer tests may not be warranted if the clinical staff is not able to effectively utilize this information in their workflow.

Even though the downstream benefits have been documented and are almost inarguable from a clinical perspective, there are financial and workflow impacts to the microbiology/molecular laboratories that implement these assays. As mentioned prior, the Gram stain results from the positive blood cultures will help drive the culture workup. Thus, there is the time required for a blood culture bottle to alarm as positive, and then the culture time waiting for growth on the culture plates. The use of these molecular methods must be introduced into the workflow and will add additional work because culture ID and AST methods still must be performed. In the setting of having a continual decrease of incoming medical technologist graduates

and an increasing number of laboratorians retiring, this puts the burden of additional testing on the existing staff.

Respiratory Pathogen Testing

Another example of a clinically beneficial, but disruptive test within the laboratory is the development of respiratory pathogen panels. Molecular multiplex panels have been developed to target the general syndrome of a respiratory illness. Table 14.6 shows that there are a variety of FDA-approved assays available with a varying number of pathogens offered within their respective multiplex assay. Each assay also requires varying levels of hands-on-involvement and molecular expertise required by the medical technologist.

Table 14.6 FDA-approved multiplex molecular assays for respiratory pathogens

Vendor	Assay name	Method	Panel composition
Cepheid	Xpert Flu/RSV XC	Multiplex real-time PCR	Influenza A (no subtyping), Influenza B, RSV (no subtyping)
Verigene	Respiratory Virus *Plus*	Multiplex real-time PCR	Influenza A[a], Influenza B, RSV A, RSV B
GenProbe Prodesse, Inc.	Prodesse ProFAST Prodesse ProParaflu	Multiplex real-time PCR	Influenza A[a] Parainfluenza[b]
Quidel Corp	Quidel Molecular Influenza A + B	Multiplex real-time PCR	Influenza A (no subtyping), Influenza B
Abbott Molecular Diagnostics, Inc.	IMDx FluA/B and RSV	Multiplex real-time PCR	Influenza A (no subtyping), Influenza B, RSV (no subtyping)
Focus Diagnostics, Inc.	Simplexa Flu A/B and RSV Direct	Multiplex real-time PCR	Influenza A (no subtyping), Influenza B, RSV (no subtyping)
Quiagen GmbH	Artus Infl A/BRGRT-PCR kit	Multiplex real-time PCR	Influenza A (no subtyping, Influenza B
Iquum/Roche	Liat Influenza A/B	Multiplex real-time PCR	Influenza A (no subtyping, Influenza B
Luminex	xTAG Respiratory	Multiplex PCR, Bead	RSV A, RSV B, Influenza A[c], Influenza B, Parainfluenza[b], Human Metapneumovirus,

	Virus Panel (RVP)	Hybridization	Adenovirus, Enterovirus/Rhinovirus
	xTAG Respiratory Virus Panel (RVP Fast)		RSV (no subtyping), Influenza A[c], Influenza B, Human Metapneumovirus, Adenovirus, Enterovirus/Rhinovirus
GenMark Dx	Respiratory Virus Panel	Multiplex PCR, Electrochemical detection	Influenza A[a], Influenza B, RSV A, RSV B, Parainfluenza, Human Metapneumovirus, Rhinovirus, Adenovirus B/E, Adenovirus C
BioFire Diagnostics, LLC	FilmArray Respiratory Panel	Multiplex real-time PCR	Adenovirus, Coronavirus[d], Human Metapneumovirus, Rhinovirus/Enterovirus, Influenza A[a], Influenza B, Parainfluenza[e]

www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm330711.htm (webpage accessed on July 13, 2015)

[a]Influenza A and further subtyping (H1, H3, and H1-2009)

[b]Parainfluenza 1, 2, and 3

[c]Influenza A and further subtyping (H1 and H3)

[d]Coronavirus species (HKU1, NL63, 229E, OC43)

[e]Parainfluenza 1, 2, 3 and 4

Prior to the implementation of a Respiratory Virus Panel (RVP) in our institution, the only viral testing offered were the rapid antigen immunochromatographic devices for Influenza A/B and Respiratory Syncytial Virus (RSV). With the addition of offering RVP testing, we are now able to provide our clinicians with a more comprehensive answer of which virus(es) are occurring in their patient. This benefits transplant, immunocompromised, and oncology patients who have more frequent respiratory viral infections [110–112]. We had serendipitously brought in the RVP before the 2009 H1N1-Influenza A outbreak which demonstrated the poor performance of the rapid antigen testing [113]. Because of this observation, many laboratories have discontinued their rapid antigen test offerings and now only offer molecular tests. In our laboratory, we have observed a decline in rapid influenza and RSA antigen testing (Fig. 14.1). The spike in volumes in 2008–2009 was related to the 2009 H1N1 Influenza A outbreak. We will eliminate these rapid antigen tests in favor of a rapid molecular test for Influenza and RSV. An algorithm will reflex a negative rapid molecular Influenza A/B and RSV test to a more comprehensive viral

and/or bacterial panel.

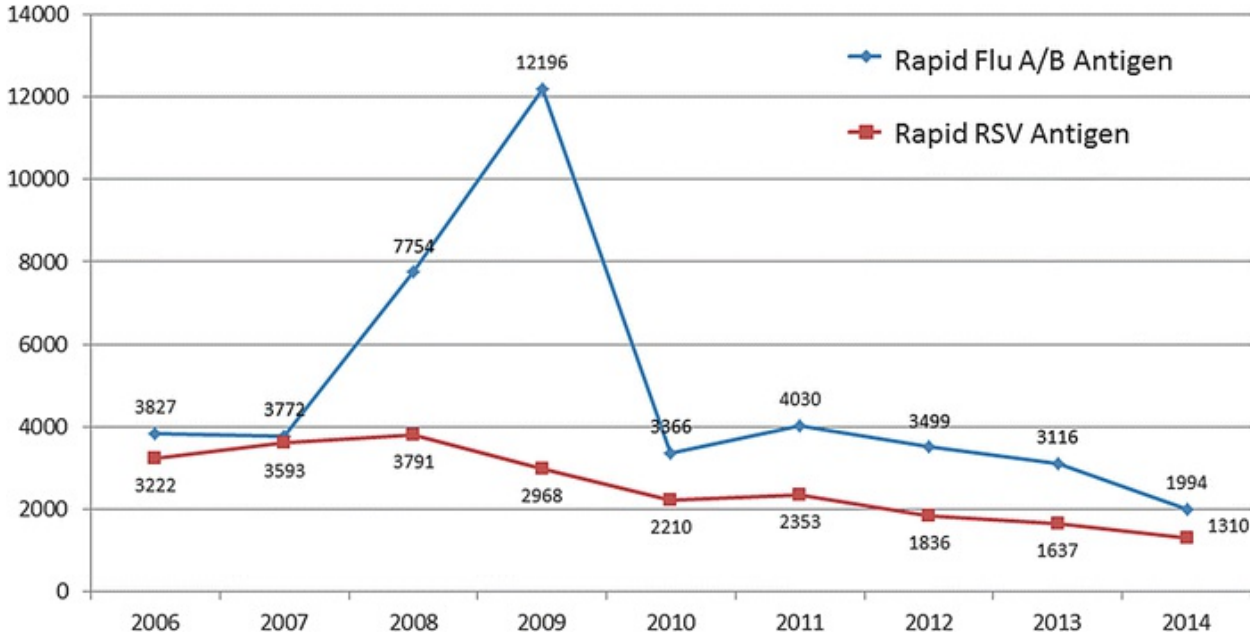


Fig. 14.1 The decline in the rapid antigen influenza and RSV testing volumes in response to the introduction of RVP testing in conjunction with the 2009 H1N1/Influenza A outbreak

When compared to the DFA and/or shell vial culture, a molecular multiplex respiratory virus panel saved time and lowered costs to the patient [114, 115]. Despite the clinical benefits observed, a limitation of molecular based methodologies is that they are batched and can take hours to perform in the laboratory. For example, in our laboratory the testing time is 6–7 h as compared to the 20-min it takes to run the rapid antigen testing. That trade off in time to result is offset by the increase in sensitivity, specificity, and breadth of viral pathogens discovered. This can be a challenge for clinicians because many times they will want a fast answer for the purposes of triaging or taking action on a patient. However, the question that should be asked of them is whether they want a bad quality, rapid answer or a good quality, not-so-fast answer.

BioFire Diagnostics, Inc. has attempted to solve the testing time problem by offering a comprehensive respiratory pathogen panel that tests directly from the respiratory specimen. Only one patient can be run on one instrument and the assay time is approximately 1 h. There will be certain institutional settings where this technology will have benefits such as an urgent care clinic, smaller community hospital, or within a laboratory that has minimal

molecular testing experience. However, for those institutions with a higher volume where batch testing is more optimal, the BioFire may not be the best solution. There are other commercial panels that differ in the number of pathogens offered as well as various levels of medical technologist involvement (Table 14.6). The decision to implement one of these panels is driven by a myriad of factors such as cost, workflow, physician demand, and the technical capabilities of the laboratory staff. Whatever respiratory pathogen panel is introduced, remember that the sample testing volume is highly dependent on seasonal variations. Figure 14.2 shows a graph of our volumes over two respiratory virus seasons (August 2013 through April 2015) with our peak volumes occurring over the winter months. This variability can have a significant impact to how microbiology/molecular laboratories are staffed. Physician demand, coupled with an increase in testing volumes, may be high enough to warrant increasing the number of runs per day as the staffing levels allow, potentially leading to an increase in employee overtime hours. Interestingly during the 2014 respiratory virus season, amidst reports of the Influenza vaccine having suboptimal efficacy [116], we observed a large increase in RVP testing volumes compared to the prior season. Thus, one factor that is virtually impossible to control is the antigenic drift/shift of the Influenza A virus affecting the effectiveness of the current vaccine in use. Assay performance may also be affected due to genetic mutations being introduced into the PCR targeted gene regions.

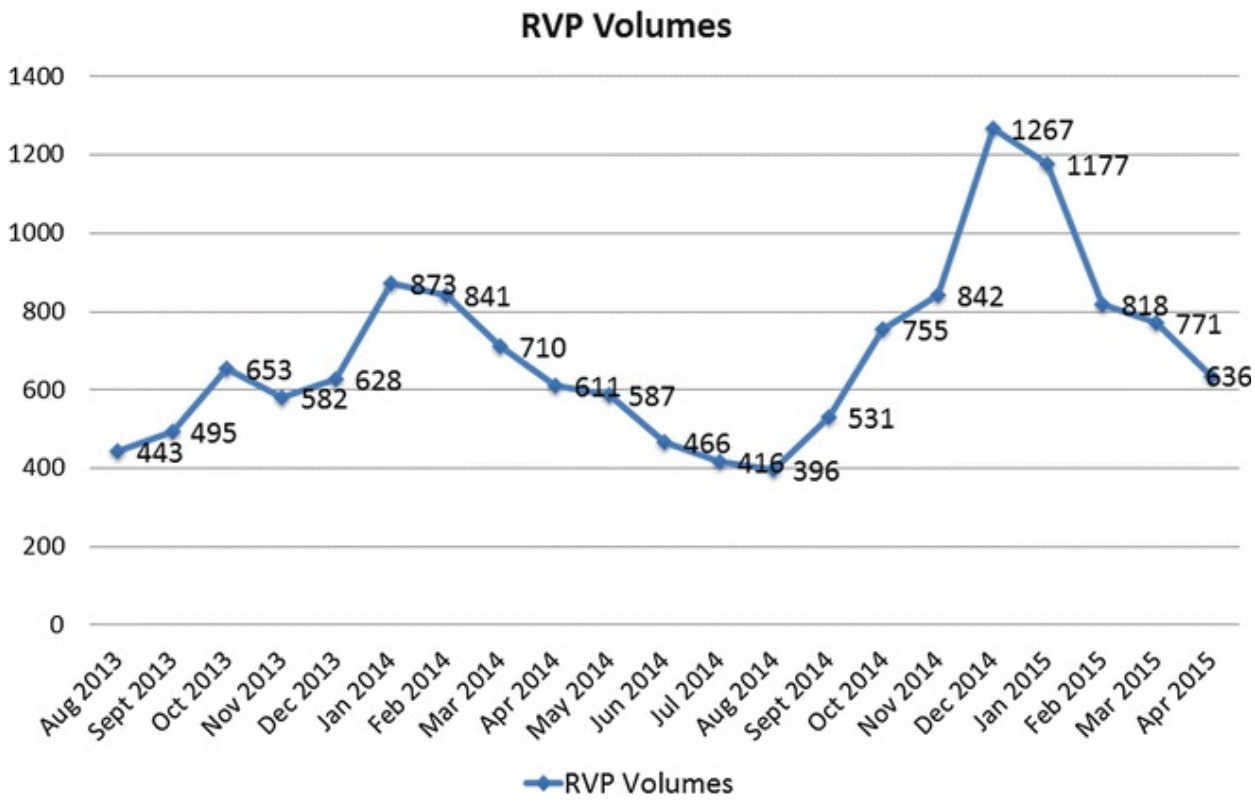


Fig. 14.2 Respiratory virus panel (RVP) testing volumes at Memorial Healthcare System. This figure shows the impact of seasonal variations on the testing volumes experiences by our molecular laboratory

With the limitations of culture and antigen based testing , co-infections were greatly under-appreciated for respiratory viral infections. One can expect an increased incidence of co-infections with multiplex molecular panels. Figures 14.3 and 14.4 show our experiences with co-infections among pediatric and adult patients. The clinical significance of these co-infections is not completely understood in relationship to modulation of disease severity [117–119]. Research is needed to fully understand virus–virus and bacteria–virus co-infections and their interactions with the other pathogens present as well as the pathogen–host interactions . Every respiratory virus season, our laboratory publishes a “Virogram ” that shows the prevalence of viruses currently circulating among the patient population (Fig. 14.5a, b).

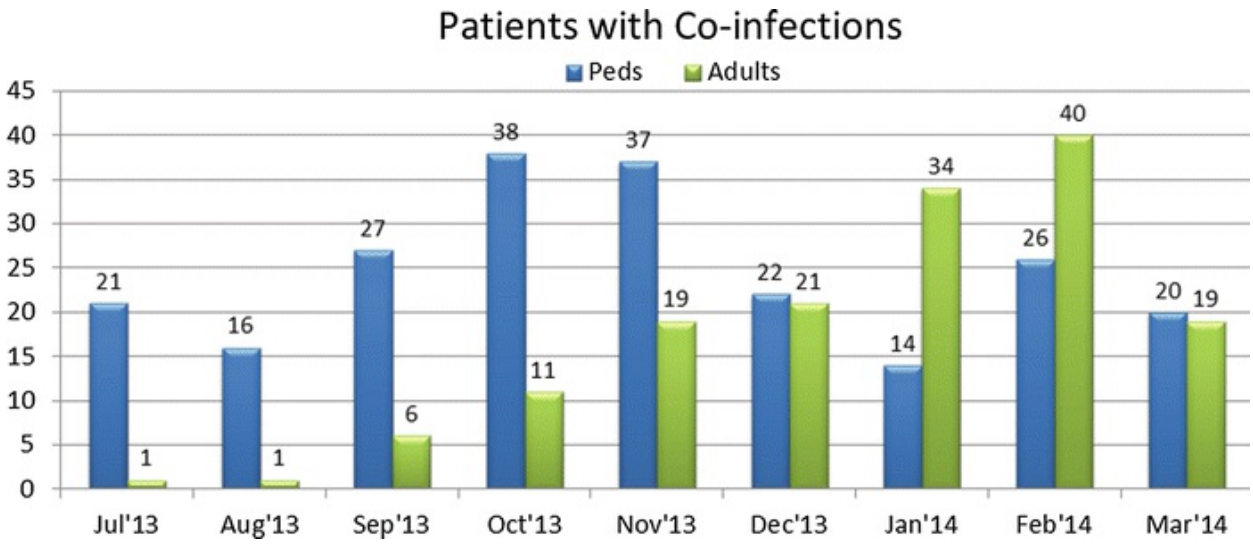


Fig. 14.3 Numbers of co-infections observed for RVP testing for pediatric and adult patients

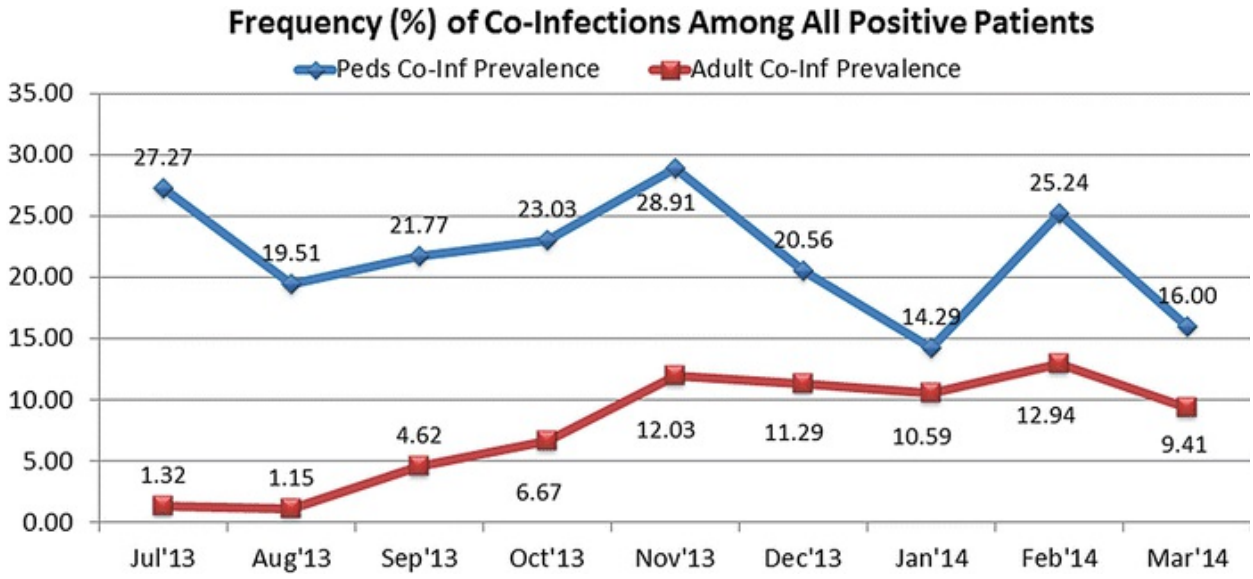


Fig. 14.4 Percent of co-infections observed among pediatric and adult patients. This figure shows that pediatric patients are more likely to have co-infection when compared to adult patients

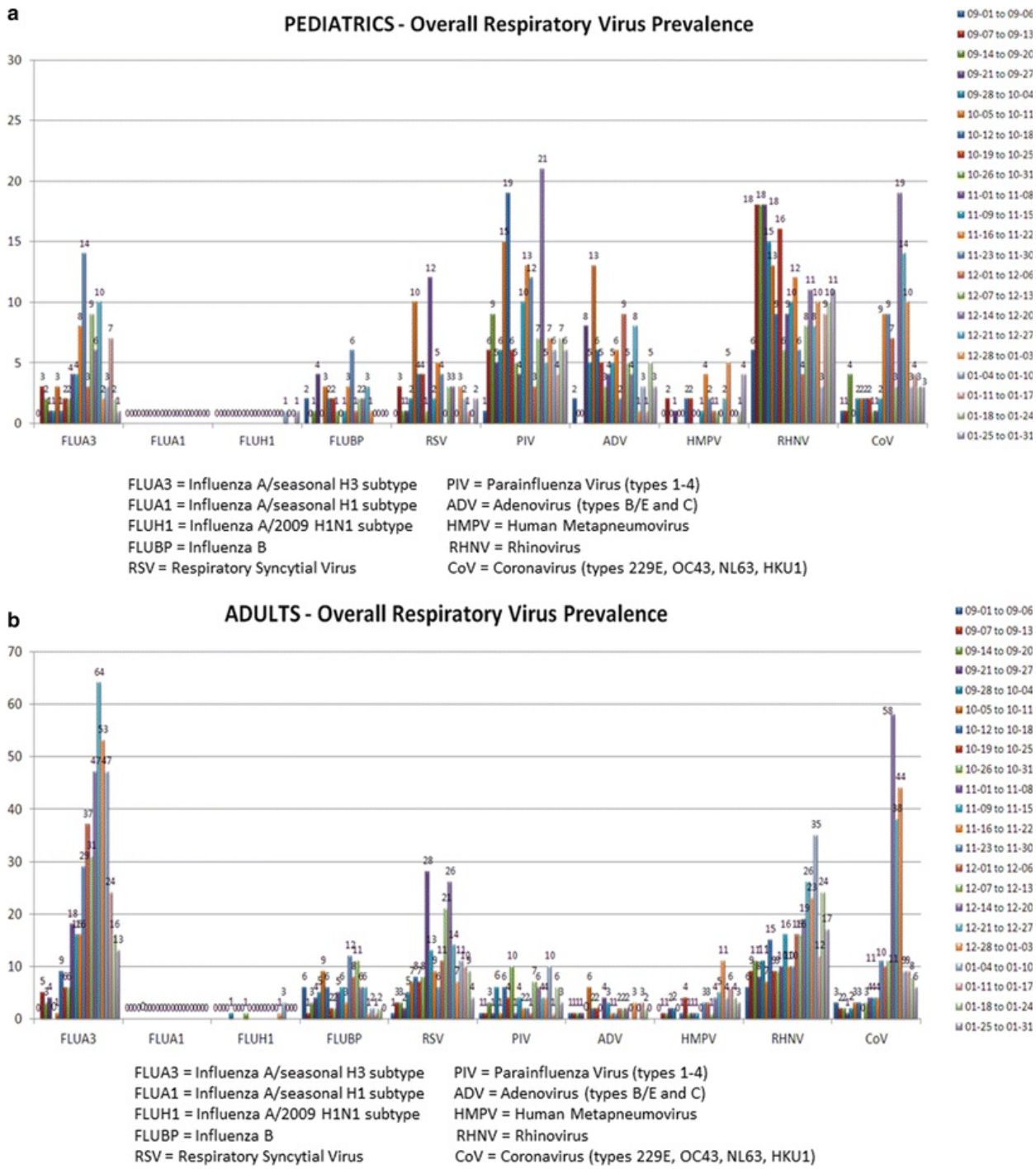


Fig. 14.5 (**a**) Pediatric Virogram showing the overall prevalence of the viruses tested within the RVP assay by week (September 2014 through January 2015). (**b**) Adult Virogram showing the overall prevalence of the viruses tested within the RVP assay by week (September 2014 through January 2015)

Infectious Gastrointestinal Illness Testing

Infectious gastrointestinal illness is another syndrome targeted by commercial vendors. As of this writing, there are a number of FDA-approved assays from Luminex, Inc. , BioFire Diagnostics, Inc. , Becton Dickinson Diagnostics, Inc. , Nanosphere, Inc. , and GenProbe-Prodesse (Table 14.7). Clinicians are often unaware of what pathogens are actually included when they order a stool culture and Ova & Parasite (O&P) testing [120]. Similar to respiratory illness symptoms, the symptoms of an infectious gastrointestinal (GI) illness overlap also making it difficult to ascertain the true pathogen(s) causing the disease.

Table 14.7 FDA-approved molecular assays for gastrointestinal pathogens

Vendor	Assay name	Method	Panel composition
Gen-Probe Prodesse, Inc.	ProGastro SSCS	Multiplex real-time RT-PCR	*Salmonella*, *Shigella*/EIEC1 *Campylobacter* [a], Shiga Toxins 1/2, Shiga Toxin *E. coli*
Nanosphere	Enteric Pathogens Test	Multiplex real-time RT-PCR	*Campylobacter*, *Salmonella*, *Shigella*/EIEC[b], *Vibrio*, *Y. enterocolitica*, Shiga Toxins 1/2 (*stx*1/*stx*2), Norovirus, Rotavirus
BD Diagnostics	BD Max Enteric Panel	Multiplex real-time RT-PCR	*Salmonella*, *Shigella*/EIEC[b], *Campylobacter* [a], Shiga Toxins 1/2 (*stx*1/*stx*2), Shiga Toxin *E. coli*
Luminex Molecular Diagnostics	GastroPathogen Panel	Multiplex PCR, Bead Hybridization	*Campylobacter*, *C. difficile*, *E. coli* O157, ETEC[c], Shiga Toxin 1/2 (*stx*1/*stx*2), *Salmonella*, *Shigella*/EIEC[a], *V. cholerae*, Adenovirus 40/41, Norovirus GI/GII, Rotavirus, *Cryptosporidium*, *E. histolytica*, *G. lamblia*
Biofire Diagnostics	Gastrointestinal Panel	Multiplex real-time RT-PCR	*Campylobacter*, *C. difficile*, *P. shigelloides*, *Y. enterocolitica*, *Vibrio* spp., *V. cholerae*, EAEC[d]EPEC[e], ETEC[c], STEC[f] *Shigella*/EIEC[a], *Cryptosporidium*, *Cyclospora*, *E. histolytica*, *G. lamblia*, Adenovirus 40/41, Astrovirus, Norovirus GI/GII, Rotavirus, Sapovirus

www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm330711.htm (web page accessed July 13, 2015)

[a]Only *C. jejuni* and *C. coli* are detected

[b] *EIEC* enteroinvasive *E. coli*. Assay cannot differentiate due to cross reactivity

[c] *ETEC* enterotoxigenic *E. coli*

[d] *EAEC* enteraggregative *E. coli*

[e] *EPEC* enteropathogenic *E. coli*

[f] *STEC* Shiga toxin *E. coli*

The development of an infectious GI panel that targets bacterial , viral , and parasitic pathogens , provides a more efficient approach to diagnosis compared to standard practices. The appeal to the clinical microbiology laboratory is the consolidation of culture, antigen, biochemical, and single-molecular analyte testing into one comprehensive panel. The implications to the state and public health laboratories that rely on culture isolates for epidemiological typing and characterization may not be immediately recognized when considering these molecular stool panel tests. Because of the improved ability to detect a pathogen(s) with molecular methods as compared to culture, there will be scenarios when the molecular test is positive and the culture growth is negative. It is imperative that clinical laboratories communicate with their state/public health laboratory counterparts to come up with an amenable solution given that there will be discordant molecular and culture results if an isolate is required to be sent to the state/public health laboratory.

Similar to respiratory co-infections , GI co-infections are also an under-appreciated aspect of disease and pathogenicity. What potentially makes GI co-infections more confusing and would require some additional clinical scrutiny is that some bacteria can be colonizers (i.e., *C. difficile*) and so the burden of determining clinical significance is left to the clinician.

Matrix-Assisted Laser Desorption Ionization: Time of Flight

MALDI-TOF is another technology that shortens the time to result for determining the microbial identification of clinically significant pathogens. The reader is referred to a number of reference review articles on the technology itself [121–126]. Recently, MALDI-TOF systems have been made commercially available for use in the clinical microbiology laboratory. How this technology compares with the currently available testing (culture/biochemical and DNA sequencing) is outside the scope of this chapter [127–132]. MALDI-TOF does outperform the conventional methods in overall accuracy and time to result.

Our laboratory has implemented MALDI-TOF as an identification tool. Results are available in approximately 1 day earlier when compared to our

traditional culture based testing. Branda et al. [88] found that MALDI-TOF reduced turn-around time by 1.45 days compared with their traditional testing. A side effect that we have observed is an increased number of calls from clinicians asking for the antimicrobial susceptibility results. These results are available the next day from our automated AST system. In addition laboratories will need to adapt their workflow processes when MALDI-TOF testing is implemented.

The upfront cost of instrumentation is high (approximately $200,000), resulting in delayed implementation in some clinical microbiology laboratories. The financial savings are realized in the cost per isolate of running the MALDI-TOF compared to the cost per isolate for a traditional work-up [127, 133, 134]. There can be reductions in the reagent and laboratory costs when compared to culture/biochemical methodologies [134, 135]. Despite the initial capital expenditure to obtain the instrumentation, there are cost-savings after MALDI-TOF is implemented.

If the organism is not in the MALDI-TOF database, it will need to be confirmed by traditional methods and/or DNA sequencing . Another potential limitation is that the definitive speciation by MALDI-TOF can confuse clinician end users when they see a new bacterial genus/species name that they do not readily recognize and may pose challenges in deciding what antibiotics to prescribe. This new definitive identification is a result of technological advancements that have a greater ability to further speciate bacteria when only a genus answer may have been given with traditional techniques (i.e., coagulase-negative *Staphylococcus* or *Enterobacter cloacae* complexes). From the laboratory perspective, changes in nomenclature must be updated in the Laboratory Information System as appropriate when microorganisms undergo taxonomic reclassifications.

Future advancements with MALDI-TOF technology also will affect the clinical microbiology laboratory workflow. Studies have preliminarily shown the ability to detect the pathogen directly from a patient sample (i.e., positive blood cultures [92, 135, 136] and urines [137–139]), bypassing the current requirement for testing on a culture isolate. However, it should be stressed that direct sample testing is in the very early stages of development. Antibiotic susceptibility testing has also been examined and Hrabak et al. [140] provide an in-depth review of using MALDI-TOF for these purposes. Interestingly, this technology has also been described in identifying the species of ticks potentially minimizing the ectoparasite experience normally

required [141].

Newer Methodologies

Technological advancements are focused on shortening the time of pathogen detection so that clinical action can be taken much more quickly. Two relatively new companies have been working on methodologies that will further disrupt clinical microbiology practices. T2 Biosystems, Inc. has recently received FDA approval for the detection of five *Candida* species (*C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, and *C. glaboratoryrata*) direct from the patient's blood sample without prior incubation within a blood culture bottle. The T2 Biosystems assay claims to detect these *Candida* species within 5 h. This technology shortens start time for appropriate Candidemia treatment. Patient mortality is decreased, the earlier treatment is started [142]. Having the ability to identify the particular *Candida* species is critical since *C. glaboratoryrata* and *C. krusei* have significant rates of azole resistance [143, 144]. Similar to the other blood culture tests mentioned above, this technology will not eliminate the need for culture/PCR and antimicrobial susceptibility testing after a blood culture bottle becomes positive. The technology allows for processing of the whole blood sample, since a thermostable mutated DNA polymerase that is not affected by inhibitors in whole blood detection is used to amplify DNA. Detection of any PCR product is done via T2 Magnetic Resonance technology. (www.t2biosystems.com). Clinical trials data show an overall sensitivity of 91.1 % with a mean time of 4.4 h for detection and species identification [144]. The limit of detection was between 1–3 CFU/ml. Knowing a patient's blood sample is positive can be just as important as knowing the sample is negative and the T2 Candida assay was observed to have a 99–99.5 % negative predictive value. Other studies have demonstrated earlier detection and its effect on antimicrobial stewardship [145, 146]. Because this is a relatively new technology, hospitals and other healthcare institutions are currently determining the most optimal and cost effective way to utilize this technology. This test is not intended as a screening tool, but should be used in a more targeted patient population where Candidemia is more significant and more likely to occur.

Accelerate Diagnostics, Inc. has developed a methodology for both rapid pathogen identification and antimicrobial susceptibility testing that can

purportedly be performed within 5 h (www.accerlatediagnostics.com). The company is conducting clinical trials on blood culture pathogen panel at the time of this writing. The technology utilizes FISH DNA probes to identify the panel pathogens that may be present. The antimicrobial susceptibility testing results are determined by single-cell microbiological analysis via time-lapse computerized images of the pathogen's growth characteristics in the presence of a particular antibiotic. The blood culture pathogen panel assay is intended to be the company's first FDA-approved assay with other sample type panels in their assay pipeline.

Automation in the microbiology laboratory has been a slow to make an impact unlike the other laboratory sections (i.e., chemistry, urinalysis, etc.) attributable to the inherent manual process of specimen preparation required. Vendors are developing automated plate streakers for more consistent yields with culture plating. Also, companies are developing automated specimen processors that can be programmed to inoculate a battery of plates. One can imagine the advantages to be gained with high volume sections of the laboratory such as urine cultures [147–153]. The implementation of microbiology automation is in its infancy and there is debate on the utility of automation and its widespread adoption. The potential is there for a large impact on the manual workflow and disruption of how clinical microbiology laboratories function. Obviously, there is a financial aspect to the implementation of automation and the estimated total cost of a total automated microbiology solution can be in the millions of dollars [149]. It is not out of the realm of possibilities for further advancements for a total microbiology laboratory automated technological solution where clinical microbiologists may be able to function from a "virtual" bench able to work up cultures and set-ups for other downstream tests from a computer touchscreen/tablet eliminating the potential hazard of being exposed to pathogenic and/or bioterrorism organisms.

In Vitro Diagnostic Companies

New Equipment

The arrival of new equipment in a large community hospital laboratory, chemistry automation [154] for example, creates a lot of stress on the staff to complete the performance verification of the new quantitative analytical

systems [155, 156]. The practicing physician and healthcare system depend on this equipment to perform well. The assays will require verification of calibration , linearity , analytic measurement ranges, accuracy, precision, appropriateness of the reference range and quality control requirements [155–157]. A variety of POCT and main chemistry laboratory methods for HbA1C have been evaluated to see if that meets the total allowable error goal set by the CAP proficiency testing program and the National Glycohemoglobin Standardization Program (NGSP) [158–160]. “Clearly, many methods, including a few POC methods, do perform well in laboratories, as seen by data from the CAP proficiency surveys” [160], our new system was not one of those good performers. We replaced immunoassays for HbA1C (Roche Diagnostics method, Siemens Medical Solutions Diagnostics—potential new method) with a capillary electrophoresis method (Sebia) [161–163]. During the evaluation of these three HbA1C methods, the Roche immunoassay reported HbA1C values (3.7–4.8 %) for four patients with no HbA but had HbSC. During the screening of 231 random patients, 13 % had homozygous or heterozygous variants [163]. Hb N-Baltimore comigrates with HbA1C on capillary electrophoresis while Hb Silver Spring and 17 other Hb variants did not [162]. In this case, a method for HbA1C had to be quickly evaluated to replace the immunoassay originally planned for implementation to prevent repeated proficiency testing failures and potential discontinuation of the HbA1C assay.

Obsolete Tests

An obsolete test is a test that is no longer in use or no longer useful (Table 14.8) [12, 164–171]. An effective way to evaluate whether a test has become obsolete is to review it at the Laboratory Utilization Committee that is responsible for the laboratory formulary [172]. The formulary concept comes from the play book of the Pharmacy and Therapeutics Committee that approve medication for use by medical providers and under what circumstances. When a newer more effective drug is FDA approved it may replace an older less effective drug in the formulary. In the laboratory, the perfect obsolete test cannot be ordered by a medical provider because the reagents are no longer provided by the in vitro diagnostics industry. For example, protein bound iodine (PBI) [169] is no longer available at any reference laboratory because the test reagents are no longer manufactured.

However, T3 uptake is just as obsolete and useless; however, its reagents are still manufactured by many vendors and still offered by reference laboratories [12]. In a utilization review of our hospital's send out test volume, it was asked by the reference laboratory why physicians ordered so many T3 uptake assays from them. I said it is not on our formulary just like CK MB [164–166], but both of these obsolete tests and others are still ordered and performed by your reference laboratory. The response was "we offer the test because physicians order the test," however, if the reagents were not available from the manufacturer, it is unlikely the reference laboratory would develop a laboratory developed test to support obsolescence. The workaround for removal of the obsolete tests from the hospital laboratory formulary usually involves the use of an EMR that has reference laboratory test ordering built for the convenience of the medical providers. If this feature is not inactivated for inpatients the hospital laboratory formulary develops a leak from which a flood of abuse can originate. Until locally defined obsolete tests are universally accepted and eliminated from the test lists of hospitals, manufacturers, and reference laboratories, the discovery of ingenious work-arounds will occupy the time of the medical providers who by habit are accustomed to having the obsolete test results by their side.

Table 14.8 Partial list of obsolete tests

Test	Reference
Creatine kinase MB	[164–166]
Amylase isoenzymes	[164]
Lactate dehydrogenase isoenzyme	[12]
Myoglobin	[164]
Prostatic acid phosphatase	[164]
Qualitative serum human chorionic gonadotropin	[164, 167]
Chromium, blood	[168]
T3 uptake	[12]
Free Thyroxine index	[12]
Protein bound iodine	[169]
Myelin basic protein, CSF	[170]
Lecithin/Sphingomyelin ratio, amniotic fluid	[164]
C1Q binding	[168]
Bleeding time	[164]
Most viral cultures	[12]

Group B *Streptococcus* antigen	[12]
Bacterial antigen detection	[12]
HIV-1 Western blot	[12]
Gliadin antibodies, IgA and IgG	[171]

Conclusion

The utilization management of laboratory tests in a large community hospital is similar to academic and smaller community hospitals. There are numerous factors that influence laboratory utilization (Table 14.1). Outside influences like hospitals buying physician practices, increase in the placement of hospitalists and hospital consolidation will influence the number and complexity of test menu that will need to be monitored for over and under utilization in the central laboratory and reference laboratory. The Laboratory Utilization Committee and laboratory formulary stewardship are key to a successful beginning. There are numerous excellent suggestions and reports of the successful implementation of remedies that have been reviewed and arranged in generic toolkits or tool boxes [1, 173, 174] or with solutions for specific laboratory sections like microbiology [12, 88], toxicology [5], chemistry [175], transfusion medicine [176], and molecular diagnostics [177–180]. This useful approach provides a resource for the exploration of laboratory test utilization management issues and their potential resolution using a method that is successful in your local geographical environment.

References

1. Huck A, Lewandrowski K. Utilization management in the clinical laboratory: an introduction and overview of the literature. Clin Chim Acta. 2014;427:111–7.
[PubMed]

2. Warren JS. Laboratory test utilization program. Structure and impact in a large academic medical center. Am J Clin Pathol. 2013;139:289–97.
[PubMed]

3. Kim JY, Dzik WH, Dighe AS, Lewandrowski KB. Utilization management in a large urban academic medical center: a 10-year experience. Am J Clin Pathol. 2011;135:108–18.
[PubMed]

4. MacMillan D, Lewandrowski E, Lewandrowski K. An analysis of reference laboratory (send out) testing: an 8-year experience in a large academic medical center. Clin Leadersh Manag Rev.

2004;18:216–9.
[PubMed]

5. Zhang Y, Kwong TC. Utilization management in toxicology. Clin Chim Acta. 2014;427:158–66.
[PubMed]

6. Calderon-Margalit R, Mor-Yosef S, Mayer M, Adler B, Shapira SC. An administrative intervention to improve utilization of laboratory tests within a university hospital. Int J Qual Health Care. 2005;17:243–8.
[PubMed]

7. Mindemark M, Larsson A. Longitudinal trends in laboratory test utilization at a large tertiary care university hospital in Sweden. Ups J Med Sci. 2011;116:34–8.
[PubMed][PubMedCentral]

8. Krasowski MD, Chudzik D, Dolezal A, Steussy B, Galley MP, Koch B, et al. Promoting improved utilization of laboratory testing through changes in an electronic medical record: experience at an academic medical center. BMC Med Inform Decis Mak. 2015;15:11. doi:10.1186/s12911-015-0137-7.
[PubMed][PubMedCentral]

9. Bunting PS, van Walraven C. Effect of a controlled feedback intervention on laboratory test ordering by community physicians. Clin Chem. 2004;50:321–6.
[PubMed]

10. Procop GW, Yerian LM, Wyleie R, Harroson AM, Kottke-Marchant K. Duplicate laboratory test reduction using a clinical decision support tool. Am J Clin Pathol. 2014;141:718–23.
[PubMed]

11. Kiechle FL, Collins L. Clinical laboratory tests not performed in a central hospital laboratory. J Clin Ligand Assay. 2005;28:198–201.

12. Kiechle FL, Arcenas RC, Rogers LC. Establishing benchmarks and metrics for disruptive technologies, inappropriate and obsolete tests in the clinical laboratory. Clin Chim Acta. 2014;427:131–6.
[PubMed]

13. Janssens PMW. Managing the demand for laboratory testing: options and opportunities. Clin Chim Acta. 2010;411:1596–602.
[PubMed]

14. Martin CA, Tulgan B. Managing the generation mix: from collision to collaboratoryoration. Amherst, MA: HRD Press; 2002. p. 82.

15. Rao SK. Utilization management in the changing health-care environment. Clin Chim Acta. 2014;427:109–10.
[PubMed]

16. Carlin CS, Feddman R, Dowd B. The impact of hospital acquisition of physician practices on referral patterns. Health Econ. 2015. doi:10.1002/hec.3160.

17.

Peckham C. Medical physician compensation report 2015. Medscape. 2015.

18. Florence T. Trends in physician and advanced practitioner employment. 2014. Merritt Hawkins. http://www.meritthawkins.com/candidates/blogposdetail.asqx?posted=40604. Accessed 30 June 2015.

19. Creswell J, Abelson R. Business day: a hospital war reflects a bind for doctors in the U.S. The New York Times. 30 November 2012.

20. Lindenauer PK, Rothberg MB, Pekaw PS, Kenwood C, Benjamin EM, Auerbach AD. Outcomes of care by hospitalists, general internists, and family physicians. N Engl J Med. 2007;357:2589–600.
[PubMed]

21. Weaver SP, Hill J. Academician attitudes and beliefs regarding the rise of hospitalists: a CERA study. Fam Med. 2015;47:357–61.
[PubMed]

22. Depuccio MJ. Managed care and organized influences in hospitalist program adoption. Hosp Top. 2014;92:105–11.
[PubMed]

23. Kociol RD, Hammill BG, Fonarow GC, Heidenreich PA, Go AS, Peterson ED, et al. Associations between use of the hospitalist model and quality of care and outcomes of older patients hospitalized for heart failure. J Am Coll Cardiol HF. 2013;1:445–53.

24. White HL, Geazier RH. Do hospitalist physicians improve quality of inpatient care delivery? A systematic review of process, efficiency and outcome measures. BMC Med. 2011;9:58.
[PubMed][PubMedCentral]

25. Corson AH, Fan VS, White T, Sullivan SD, Asakura K, Myint M, et al. A multifaceted hospitalist quality improvement intervention: decreased frequency of common labs. J Hosp Med. 2015;10:390–5.
[PubMed]

26. Belger J, Nickel W, Messler J, Goldstein J, O'Callaghan J, Auron M, et al. Choosing wisely in adult hospital medicine: five opportunities for improved healthcare value. J Hosp Med. 2013;8:486–92.

27. Morden NE, Calla CH, Sequist TD, Rosenthal MB. Choosing wisely—the politics and economics of laboratoryeling low value services. N Engl J Med. 2014;370:589–92.
[PubMed][PubMedCentral]

28. Olson J, Hollenbreak C, Donald SM, Abendroth T, Castellani W. Default settings on computerized physician order entry system order sets drive ordering habits. J Pathol Inform. 2015;6:16. doi:10.4103/2153-3539.153916.
[PubMed][PubMedCentral]

29. Dafney L. Hospital industry consolidation—still more to come? N Engl J Med. 2014;370:198–9.

30. Cutler DM, Morton FS. Hospitals, market share, and consolidation. JAMA. 2013;310:1964–70.

[PubMed]

31. Ginsburg PB, Pawlson LG. Seeking lower prices where providers are consolidated: an examination of market and policy strategies. Health Aff. 2014;33:1067–75.

32. Schmid A, Ulrich V. Consolidation and concentration in the German hospital market: the two sides of the coin. Health Policy. 2013;109:301–10.
[PubMed]

33. Tsai TC, Jha AK. Hospital consolidation, competition, and quality. Is bigger necessarily better? JAMA. 2014;312:29–30.
[PubMed]

34. Frakt AB. Hospital consolidation isn't the key to lowering costs and raising quality. JAMA. 2015;313:345. doi:10.1001/jama.2014.17412.
[PubMed]

35. Kane CK. Updated data on physician practice arrangements: inching toward hospital ownership. Policy research perspectives. AMA; 2015. p. 1–14.

36. Kiechle FL, Main RI. The Hitchhiker's guide to improving efficiency in the clinical laboratory. Washington, DC: AACC Press; 2002.

37. Parvin CA, Lo SF, Deuser SM, Weaver LG, Lewis LM, Scott MG. Impact of point-of-care testing on patient's length of stay in a large emergency department. Clin Chem. 1996;42:711–7.
[PubMed]

38. Kendall J, Reeves B, Claney M. Point of care testing: randomized controlled trial of clinical outcomes. BMJ. 1998;316:1052–7.
[PubMed][PubMedCentral]

39. Singer AJ, Williams J, Taylor M, LeBlanc D, Thode HC. Comprehensive bedside point of care testing in critical ED patients: a before and after study. Am J Emerg Med. 2015;33:776–80.
[PubMed]

40. Lee Lewandrowski E, Laposta M, Eschenbach K, Camooso C, Nathan DM, et al. Utilization and cost analysis of bedside capillary glucose testing in a large teaching hospital: implications for managing point of care testing. Am J Med. 1994;97:222–30.
[PubMed]

41. Lum G. Assessment of a critical limit protocol for point-of-care glucose testing. Am J Clin Pathol. 1996;106:390–5.
[PubMed]

42. Kiechle FL, Cembrowski G. Quality improvement in critical care laboratory. Crit Care Rep. 1991;2:282–94.

43. Sindler BR, Kruskall MS. Phlebotomy for diagnostic laboratory tests in adults. N Engl J Med. 1986;314:1233–5.

44. Lin JC, Strauss RG, Kulhavy JC, Johnson KJ, Zimmerman BBM, Cress GA, et al. Phlebotomy overdraw in the neonatal intensive care nursery. Pediatrics. 2000;106:e19.

[PubMed]

45. Kiechle FL. Principles and point-of-care testing for body fluids. In: Kost GJ, editor. Practice of point-of-care testing. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 267–83.

46. Kiechle FL, Gauss I, Robinson-Dunn B. Provider-performed microscopy. Point of Care. 2003;2:20–32.

47. Kiechle FL, Gauss I. Provider-performed microscopy. Clin Lab Med. 2009;29:573–82. [PubMed]

48. MacMillan D. Calculating cost savings in utilization management. Clin Chim Acta. 2014;427:123–6. [PubMed]

49. Kiechle FL. Cost-benefit analysis for blood gas POCT. In: Kost GJ, editor. Principles and practice of point-of-care testing. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 601–2.

50. Kiechle FL. Cost analysis of point-of-care glucose testing. In: Kost GJ, editor. Principles and practice of point-of-care testing. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 603–4.

51. Romero JR. Reverse-transcription polymerase chain reaction detection of the enteroviruses. Overview and clinical utility in pediatric enteroviral infections. Arch Pathol Lab Med. 1999;123:1161–9. [PubMed]

52. Toffler A, Toffer H. Creating a new civilization: the politics of the third wave. Atlanta, GA: Turner Publishing; 1994.

53. Skrisson JE, Shaw J, Kiechle FL. Hospital laboratory outreach program builds success through affiliation with a laboratory network. J Clin Ligand Assay. 2001;24:253–6.

54. Kiechle FL, Shaw J, Skrisson JE. Outreach implementation requirement: a case study. In: Garcia LS, editor. Clinical laboratory management. 2nd ed. Washington, DC: American Society for Microbiology; 2014. p. 740–58.

55. Naugler C, Thomas R, Turin TC, Guo M, Vasha M. Yearly clinical laboratory tests expenditures for different medical specialties in a major Canadian city. Am J Clin Pathol. 2015;144:97–102. [PubMed]

56. Papp JR, Schachter J, Gaydos CA, van der Pol B. Recommendations for the laboratory-based detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*—2014. MMWR Recomm Rep. 2014;14:1–19.

57. Castriciano S, Luinstra K, Jang D, Patel J, Mahoney J, Katapala J, et al. Accuracy of results obtained by performing a second ligase chain reaction assay and PCR analysis on urine samples with positive or near-cutoff results in the LCX test for *Chlamydia trachomatis*. J Clin Microbiol. 2002;40:2632–4. [PubMed][PubMedCentral]

58. Meade C, Bonhomme XF. Newborn screening: adapting to advancements in whole-genome

sequencing. Genet Test Mol Biomarkers. 2014;18:597–8.
[PubMed][PubMedCentral]

59. Laudadio J, McNeal JL, Boyd SD, Phi L, Lockwood C, McCloskey CB, et al. Design of a genomics curriculum. Competencies for practicing pathologists. Arch Pathol Lab Med. 2015;139:894–900.
[PubMed]

60. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24.
[PubMed][PubMedCentral]

61. Endris V, Penzel R, Warth A, Muckenhuber A, Schirmacher P, Stenzinger A, et al. Molecular diagnostic profiling of lung cancer specimens with a semiconductor-based massive parallel sequencing approach. Feasibility, costs, and performance compared with conventional sequencing. J Mol Diagn. 2013;15:765–75.
[PubMed]

62. Olliverira TGM, Mitne-Neto M, Cerdeira LT, Marsiglia JDC, Arteaga-Fernandez E, Krieger JE. A variant detection pipeline for inherited cardiomyopathy-associated genes using next-generation sequencing. J Mol Diagn. 2015;17:420–30.

63. Picchiassi E, di Renzo GC, Tarquini F, Bini V, Centra M, Pennacchi F, et al. Non-invasive prenatal RHD genotyping using cell-free fetal DNA from maternal plasma: an Italian experience. Transfus Med Hemother. 2015;42:22–8.
[PubMed]

64. Committee on Genetics, Society for Maternal-Fetal Medicine. Cell—free DNA for fetal aneuploidy. Committee Opinion Number 640. 2015.

65. Bianchi DW, Parker L, Wentworth J, Madan Kurnar R, Saffer C, Das AF, et al. DNA sequencing versus standard prenatal aneuploidy screening. N Engl J Med. 2014;370:799–808.
[PubMed]

66. Bianchi DW, Chudova D, Sehnert AJ, Bhatt S, Murray K, Prosen TL, et al. Noninvasive prenatal testing and incidental detection of occult maternal malignancies. JAMA. 2015;314:162–9.
[PubMed]

67. Francis G, Stein S. Circulating cell-free tumour DNA in the management of cancer. Int J Mol Sci. 2015;16:14122–42.
[PubMed][PubMedCentral]

68. Dingle TC, Bulter-Wu SM. MALDI-TOF mass spectrometry for microorganism identification. Clin Lab Med. 2013;33:589–609.
[PubMed]

69. DeMarco ML, Ford BA. Beyond identification. Emerging and future uses for MALDI-TOF mass spectrometry in the clinical microbiology laboratory. Clin Lab Med. 2013;33:611–28.
[PubMed]

70. Tyburski EA, Gillespie SE, Stoy WA, Manino RG, Weiss AJ, Siu F, et al. Disposable platform provides visual and color-based point-of-care anemia self testing. J Clin Invest. 2014;124:4387–94.
[PubMed][PubMedCentral]

71. Laksanasopin T, Guo TW, Nayak S, Sridhara AA, Xie S, Olowookere OO, et al. A smartphone dongle for diagnosis of infectious disease at the point of care. Sci Transl Med. 2015;7:273re1.

72. Nainggolen L. New quick and cheap bedside test for cortisol uses smartphone. Medscape. 2014.

73. Khan HA, Wineinger NE, Uddin PQ, Mehta HS, Rubernson DS, Topol EA. Can hospital rounds with pocket ultrasound by cardiologists reduce standard echocardiology? Am J Med. 2014;127:669.e1–7.

74. Solomon SD, Saldana F. Point-of-care ultrasound in medical education—stop listening and look. JAMA. 2014;370:1083–5.

75. Elenko E, Underwood K, Zohar D. Defining digital medicine. Nat Biotechnol. 2015;33:456–61.
[PubMed]

76. Bandodkar AJ, Jia W, Yardmici C, Wang X, Ramirez J, Wang J. Tattoo-bases non-invasive glucose monitoring: a proof-of-concept study. Anal Chem. 2015;87:394–8.
[PubMed]

77. Lochner CM, Khan Y, Pierre A, Arias AC. All-organic optoelectronic sensor for pulse oximetry. Nat Commun. 2014;5:5745. doi:10.1038/ncomms6745.
[PubMed]

78. Choudhuri S. Bioinformatics for beginners. Genes, genomes, molecular evolution, databases and analytical tools. London: Academic; 2014.

79. Berger B, Peng J, Singh M. Computational solutions for omics data. Nat Rev Genet. 2013;14:333–46.
[PubMed][PubMedCentral]

80. Baudhuin LM, Lagerstedt SA, Klee EW, Fadra N, Oglesbee D, Ferber MJ. Confirming variants in next-generation sequencing panel testing by Sanger sequencing. J Mol Diagn. 2015;17:456–61.
[PubMed]

81. Park S, Pantanowitz L, Parwani AV. Digital imaging in pathology. Clin Lab Med. 2012;32:557–84.
[PubMed]

82. Pantanowitz L, Sinard GH, Henricks WH, Fatherce LA, Carter AB, Contis L, et al. Validating whole slide imaging for diagnostic purposes in pathology. Guideline from the College of American Pathologists Pathology and Laboratory Quality Center. Arch Pathol Lab Med. 2013;137:1710–22.
[PubMed]

83. Nam SH. Why disruptive innovations matter in laboratory diagnostics. Clin Chem. 2015;61:935–7.

[PubMed]

84. Ziai JM, Smith BR. Pathology resident and fellow education in a time of disruptive technologies. Clin Lab Med. 2012;32:623–38.
[PubMed]

85. Leland DS, Ginocchio CC. Role of cell culture for virus detection in the age of technology. Clin Microbiol Rev. 2007;20:49–78.
[PubMed][PubMedCentral]

86. Doerr HW. Replacement of biologic by molecular techniques in diagnostic virology: thirty years after the advent of PCR technology—do we still need conventional methods? Med Microbiol Immunol. 2013;202:391–2.
[PubMed]

87. Mahony JB. Detection of respiratory viruses by molecular methods. Clin Microbiol Rev. 2008;21:716–47.
[PubMed][PubMedCentral]

88. Branda JA, Lewandrowski K. Utilization management in microbiology. Clin Chim Acta. 2014;427:173–7.
[PubMed]

89. Ly T, Gulia J, Pyrgos V, Waga M, Shogan S. Impact upon clinical outcomes of translation of PNA FISH-generated laboratory data from the clinical microbiology bench to bedside in real time. Ther Clin Risk Manag. 2008;4:637–40.
[PubMed][PubMedCentral]

90. González V, Padilla E, Gimenez M, Vilaplana C, Perez A, Fernandez G, et al. Rapid diagnosis of *Staphylococcus aureus* bacteremia using *S. aureus* PNA FISH. Eur J Clin Mibrobiol Infect Dis. 2004;23:396–8.

91. Hensley D, Tapia R, Encina Y. An evaluation of the AdvanDx *Staphylococcus aureus*/CNS PNA FISH assay. Clin Lab Sci. 2009;22:30–3.
[PubMed]

92. Kothari A, Morgan M, Haake DA. Emerging technologies for rapid identification of bloodstream pathogens. Clin Infect Dis. 2014;59:272–8.
[PubMed][PubMedCentral]

93. Laub R, Knudsen J. Clinical consequences of using PNA-FISH in Staphylococcal bacteraemia. Eur J Clin Microbiol Infect Dis. 2014;33:599–601.
[PubMed]

94. Parta M, Goebel M, Thomas J, Matloobi M, Stager C, Musher DM. Impact of an assay that enables rapid determination of *Staphylococcus* species and their drug susceptibility on the treatment of patients with positive blood culture results. Infect Control Hosp Epidemiol. 2010;31:1043–8.
[PubMed]

95. Bauer K, West JE, Pancholi P, Stevenson KB, Goff D. An antimicrobial stewardship program impact with rapid polymerase chain reaction methicillin-resistant *Staphylococcus aureus*/*S.*

aureus blood culture test in patients with S. aureus bacteremia. Clin Infect Dis. 2010;51:1074–80. [PubMed]

96. Brown J, Paladino JA. Impact of rapid methicillin resistant *Staphylococcus aureus* polymerase chain reaction testing on mortality and cost effectiveness in hospitalized patients with bacteraemia: a decision model. Pharmacoeconomics. 2010;28:567–75. [PubMed]

97. Scanvic A, Coudavault L, Sollet J, Turdu F. Le interest of real-time PCR Xpert MRSA/SA on GeneXpert(®) DX system in the investigation of Staphylococcal bacteremia. Pathol Biol (Paris). 2011;59:67–72.

98. Wojewoda CM, Sercia L, Navas M, Tuohy M, Wilson D, Hall GS, et al. Evaluation of the Verigene Gram-positive blood culture nucleic acid test for rapid detection of bacteria and resistance determinants. J Clin Microbiol. 2013;51:2072–6. [PubMed][PubMedCentral]

99. Sullivan KV, Turner NN, Roundtree SS, Young S, Brock-Haag CA, Lacey D, et al. Rapid detection of Gram-positive organisms by use of the Verigene Gram-positive blood culture nucleic acid test and the BacT/Alert Pediatric FAN System in a multicenter pediatric evaluation. J Clin Microbiol. 2013;51:3579–84. [PubMed][PubMedCentral]

100. Samuel LP, Tibbetts RJ, Agotesku A, Fey M, Hensley R, Meier FA. Evaluation of a microarray-based assay for rapid identification of Gram-positive organisms and resistance markers in positive blood cultures. J Clin Microbiol. 2013;51:1188–92. [PubMed][PubMedCentral]

101. Buchan BW, Ginocchio CC, Manii R, Cavagnolo R, Pancholi P, Swyers L, et al. Multiplex identification of Gram-positive bacteria and resistance determinants directly from positive blood culture broths: evaluation of an automated microarray-based nucleic acid test. PLoS Med. 2013;10:1–13.

102. Beal SG, Ciurca J, Smith G, John J, Lee F, Doern CD, et al. Evaluation of the Nanosphere Verigene Gram-positive blood culture assay with the VersaTREK blood culture system and assessment of possible impact on selected patients. J Clin Microbiol. 2013;51:3988–92. [PubMed][PubMedCentral]

103. Mestas J, Polanco CM, Felsenstein S, Bard D. Performance of the Verigene Gram-positive blood culture assay for direct detection of Gram-positive organisms and resistance markers in a pediatric hospital. J Clin Microbiol. 2014;52:283–7. [PubMed][PubMedCentral]

104. Bhatti MM, Boonlayangoor S, Beavis KG, Tesic V. Evaluation of FilmArray and Verigene systems for rapid identification of positive blood cultures. J Clin Microbiol. 2014;52:3433–6. [PubMed][PubMedCentral]

105. Altun O, Almuhayawi M, Ullberg M, Ozenci V. Clinical evaluation of the FilmArray blood culture identification panel in identification of bacteria and yeasts from positive blood culture bottles. J Clin Microbiol. 2013;51:4130–6. [PubMed][PubMedCentral]

106. Southern TR, Alelew A, Iwen C. Discrimination of *Candida albicans* from *Candida dubliniensis* by use of the BioFire FilmArray blood culture identification panel. J Clin Microbiol. 2015;53:1999–2000.
[PubMed][PubMedCentral]

107. Park S, Park K, Bang K, Chong Y, Kim S, Lee S, et al. Clinical significance and outcomes of polymicrobial *Staphylococcus aureus*. J Infect. 2012;65:119–27.
[PubMed]

108. Desoubeaux G, Bailly E, C LB, Gyan E, Goudeau A, Chandenier J, et al. Prospective assessment of FilmArray technology for the rapid identification of yeasts isolated from blood cultures. J Microbiol Methods. 2014;106:119–22.

109. Blaschke AJ, Heyrend C, Byington CL, Fisher MA, Barker E, Garrone NF, et al. Rapid identification of pathogens from positive blood cultures by multiplex polymerase chain reaction using the FilmArray system. Diagn Microbiol Infect Dis. 2012;74:349–55.
[PubMed][PubMedCentral]

110. Kim Y-J, Boeckh M, Englulnd JA. Community respiratory virus infections in immunocomprised patients: hematopoietic stem cell and solid organ transplant recipients, and individuals with human immunodeficiency virus infection. Semin Respir Crit Care Med. 2007;28:222–42.
[PubMed]

111. Anderson EJ. Viral diagnostics and antiviral therapy in hematopoietic stem cell transplantation. Curr Pharm Des. 2008;14:1997–2010.
[PubMed]

112. Ison MG. Respiratory viral infections in transplant recipients. Antivir Ther. 2007;12:627–38.
[PubMed]

113. Ginocchio CC, Zhang F, Manji R, Arora S, Bornfreund M, Falk L, et al. Evaluation of multiple test methods for the detection of the novel 2009 influenza A (H1N1) during the New York City outbreak. J Clin Virol. 2009;45:191–5.
[PubMed]

114. Mahony JB, Blackhouse G, Babwah J, Smieja M, Buracond S, Chong S, et al. Cost analysis of multiplex PCR testing for diagnosing respiratory virus infections. J Clin Microbiol. 2009;47:2812–7.
[PubMed][PubMedCentral]

115. Xu M, Qin X, Astion ML, Rutledge JC, Simpson J, Jerome KR, et al. Implementation of FilmArray respiratory viral panel in a core laboratory improves testing turnaround time and patient care. Am J Clin Pathol. 2013;139:118–23.
[PubMed]

116. Flannery B, Clippard J, Zimmerman RK, Norwalk MP, Jackson ML, Jackson LA, et al. MMWR. Early estimates of seasonal influenza vaccine effectiveness. United States, January 2015. Morbidity and Mortality Weekly Reports. 2015. http://www.cdc.gov/mmwr/pdf/wk/mm6401.pdf.

117. Stefanska I, Romanowska M, Donevski S, Gawyluk D, Brydak LB. Co-infections with influenza and other respiratory viruses. Adv Exp Med Biol. 2013;756:291–301.
[PubMed]

118. Kristoffersen AW, Nordbo SA, Rognlien A-GW, Christensen A, Dollner H. Coronavirus causes lower respiratory infections less frequently than RSV in hospitalized Norwegian children. Pediatr Infect Dis J. 2011;30:279–83.
[PubMed]

119. Sung RYT, Chan PKS, Tsen T, Li AM, Lam WY, Yeung ACM, et al. Identification of viral and atypical bacterial pathogens in children hospitalized with acute respiratory infections in Hong Kong by multiplex PCR assays. J Med Virol. 2009;81:153–9.
[PubMed]

120. Hennessy TW, Marcus R, Deneen V, Reddy S, Vugia D, Townes J, et al. Survey of physician diagnostic practices for patients with acute diarrhea: clinical and public health implications. Clin Infect Dis. 2004;99508:203–12.

121. Murray PR. What is new in clinical microbiology: microbial identification by MALDI-TOF mass spectrometry. J Mol Diagn. 2012;14:1–5.

122. De Carolis E, Vella A, Vaccaro L, Torelli R, Spanu T, Fiori B, et al. Application of MALDI-TOF mass spectrometry in clinical diagnostic microbiology. J Infect Dev Ctries. 2014;8:1081–8.
[PubMed]

123. Croxatto A, Prod'hom G, Greub G. Applications of MALDI-TOF mass spectrometry in clinical diagnostic microbiology. FEMS Microbiol Rev. 2012;36:380–407.
[PubMed]

124. Seng P, Rolain J-M, Fournier PE, La Scola B, Drancourt M, Raoult D. MALDI-TOF mass spectrometry applications in clinical microbiology. Future Microbiol. 2010;5:1733–54.
[PubMed]

125. Clark AE, Kaleta EJ, Arora A, Wolk M. Matrix-assisted laser desorption ionization—time of flight mass spectrometry: a fundamental shift in the routine practice of clinical microbiology. Clin Microbiol Rev. 2013;26:547–603.
[PubMed][PubMedCentral]

126. Dingle TC, Bulter-Wu SM, Maldi-tofmass spectrometry for microorganism identification. Clin Lab Med. 2013;589–609.

127. Cherkaoui A, Hibbss J, Tangomo M, Girard M, Francois P, Schrenzel J. Comparison of two matrix-assisted laser desorption ionization-time of flight mass spectrometry methods with conventional phenotypic identification of bacteria to the species level. J Clin Microbiol. 2010;48:1169–75.
[PubMed][PubMedCentral]

128. Dubois D, Grare M, Prere MF, Seqands C, Marty N, Oswald E. Performance of the Vitek MS matrix-assisted laser desorption ionization-time of flight mass spectrometry system for rapid identification of bacteria in routine clinical microbiology. J Clin Microbiol. 2012;50:2568–76.
[PubMed][PubMedCentral]

129. Van Veen SQ, Claas ECJ, Kuijper EJ. High-throughput identification of bacteria and yeast by matrix-assisted laser desorption ionization-time of flight mass spectrometry in conventional medical microbiology laboratories. J Clin Microbiol. 2010;48:900–7.

[PubMed][PubMedCentral]

130. Bizzini A, Durussel C, Billie J, Greub G, Prod G. Performance of matrix-assisted laser desorption ionization-time of flight mass spectrometry of identification of bacterial strains routinely isolated in a clinical microbiology laboratory. J Clin Microbiol. 2010;48:1549–54. [PubMed][PubMedCentral]

131. Tan KE, Ellis BC, Lee R, Stamper PD, Zhang SX, Carroll KC. Prospective evaluation of a matrix-assisted laser desorption ionization-time of flight mass spectrometry system in a hospital clinical microbiology laboratory for identification of bacteria and yeasts: a bench-by-bench study of assessing the impact on time to identification and cost-effectiveness. J Clin Microbiol. 2012;50:3301–8. [PubMed][PubMedCentral]

132. Lau SKP, Tang BSF, Teng JLL, Chan T-M, Curreem SOT, Fan RYY, et al. Matrix-assisted laser desorption ionization-time of flight mass spectrometry for identification of clinically significant bacteria that are difficult to identify in clinical laboratories. J Clin Pathol. 2014;67:361–6. [PubMed]

133. Dhiman N, Hall L, Wohlfiel SL, Buckwalter SP, Wengenack NL. Performance and cost analysis of matrix-assisted laser desorption ionization-time of flight mass spectrometry for routine identification of yeasts. J Clin Microbiol. 2011;49:1614–6. [PubMed][PubMedCentral]

134. Patel R. MALDI-TOF MS, for the diagnosis of infectious diseases. Clin Chem. 2015;61:100–11. [PubMed]

135. Rand K, Delano J. Direct identification of bacteria in positive blood cultures: comparison of two rapid methods, FilmArray and mass spectrometry. Diagn Microbiol Infect Dis. 2014;79:293–7. [PubMed]

136. Martinez RM, Bauerie ER, Fang FC, Butler-wu SM. Evaluation of three rapid diagnostic methods for direct identification of microorganisms in positive blood cultures. J Clin Microbiol. 2014;52:2521–9. [PubMed][PubMedCentral]

137. Wang XH, Zhang G, Fan YY, Yang X, Sui WJ, Lu XX. Direct identification of bacteria causing urinary tract infections by combining matrix-assisted laser desorption ionization-time of flight mass spectrometry with UF-1000i urine flow cytometry. J Microbiol Methods. 2013;92:231–5. [PubMed]

138. Rossello GAM, Rodriguez MPG, Leonardo RO de L, Domingo AO, Perez MAB. Procedure for microbial identification based on matrix-assisted laser desorption ionization-time of flight mass spectrometry from screening-positive urine samples. APMIS. 2014;122:790–5.

139. Ferreira L, Sanchez-Juanes F, Gonzaelz-Avila M, Cembrero-Fucinos D, Herrero-Hernandez A, Gonzalez-Buitrago JM, et al. Direct identification of urinary tract pathogens from urine samples by matrix-assisted laser desorption ionization—time of flight. J Clin Microbiol. 2010;48:2110–5. [PubMed][PubMedCentral]

140. Hrabák J, Chudác E, Walková R. Matrix-assisted laser desorption ionization—time of flight

(MALDI-TOF) mass spectrometry for detection of antibiotic resistance mechanisms: from research to routine diagnosis. Clin Microbiol Rev. 2013;26:103–14.
[PubMed][PubMedCentral]

141. Yssouf A, Flaudrops C, Drali R, Socolovschi C, Berenger J, Parola P, et al. Matrix-assisted laser desorption ionization—time of flight mass spectrometry for rapid identification of tick vectors. J Clin Microbiol. 2013;51:522–8.
[PubMed][PubMedCentral]

142. Orozco AS, Higginbotham LM, Hitchock CA, Parkinson T, Falconer D, Ibrahim AS, et al. Mechanism of fluconazole resistance in *Candida krusei*. Antimicrob Agents Chemother. 1998;42:2645–9.
[PubMed][PubMedCentral]

143. Pappas PG, Kauffman CA, Andes D, Banjamin DK, Calandra TF, Edwards JE, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;48:503–35.
[PubMed]

144. Mylonakis E, Clancy CJ, Ostrosky-Zeichner L, Garey KW, Alangaden GJ, Vazquez JA, et al. T2 magnetic resonance assay for the rapid diagnosis of candidemia in whole blood: a clinical trial. Clin Infect Dis. 2015;60:892–9.
[PubMed]

145. Skewis LR, Lebedeva T, Papkov V, Thayer EC, Massefski W, Cuker A, et al. T2 magnetic resonance: a diagnostic platform for studying integrated hemostasis in whole blood—proof of concept. Clin Chem. 2014;60:1174–82.
[PubMed]

146. Beyda ND, Alam MJ, Garey KW. Comparison of the T2Dx instrument with T2Candida assay and automated blood culture in the detection of candida species using seeded blood samples. Diagn Microbiol Infect Dis. 2013;77:324–6.
[PubMed]

147. Bourbeau PP, Ledeboer NA. Automation in clinical microbiology. J Clin Microbiol. 2013;51:1658–65.
[PubMed][PubMedCentral]

148. Ledeboer NA, Dallas SD. Point-counterpoint: the automated clinical microbiology laboratory: fact of fantasy? J Clin Microbiol. 2014;52:1–26.

149. Novak SM, Marlowe EM. Automation in the clinical microbiology laboratory. Clin Lab Med. 2013;33:567–88.
[PubMed]

150. Buchan BW, Ledeboer NA. Emerging technologies for the clinical microbiology laboratory. Clin Microbiol Rev. 2014;27:783–822.
[PubMed][PubMedCentral]

151. Mutters NT. Laboratory automation in clinical microbiology: a quiet revolution. Austin J Infect Dis. 2014;1:2–3.

152. Greub G, Prod'hom G. Automation in clinical bacteriology: what system to choose? Clin Microbiol Infect. 2011;17:655–60.
[PubMed]

153. Matthews S, Deutekom J. The future of diagnostic bacteriology. Clin Microbiol Infect. 2011;17:651–4.
[PubMed]

154. Kiechle FL. The William Beaumont Hospital experience with total laboratory automation. Arab J Lab Med. 1999;2:163–70.

155. Nichols JH. Verification of method performance for clinical laboratories. Adv Clin Chem. 2009;47:121–37.
[PubMed]

156. Killeen AA, Long T, Souers R, Styer P, Ventura CB, Klee GC. Verifying performance characteristics of quantitative analytical systems. Arch Pathol Lab Med. 2014;13:1173–81.

157. Ehrmeyer SS. Satisfying regulatory and accreditation requirements for quality control. Clin Lab Med. 2013;33:27–40.
[PubMed]

158. Lenters-Westra E, Slingerland RJ. Three of 7 hemoglobin A1C point-of-care instruments do not meet generally accepted analytical performance criteria. Clin Chem. 2014;60:1062–72.
[PubMed]

159. Woodworth A, Karpi-Sterner N, Mille JJ, Rao LV, Yundt-Pacheco J, Kuchipudi L. Utilization of assay performance characteristics to estimate hemoglobin A1C result reliability. Clin Chem. 2014;60:1073–9.
[PubMed]

160. Little RR. Performance of hemoglobin A1C assay methods: good enough? Clin Chem. 2014;60:1031–3.
[PubMed][PubMedCentral]

161. Heylen O, van Neyghem S, Exerbille S, Wehlou C, Gorus F, Weets I. Evaluation of the Sebia CAPILLARYS 2 flex piercing for the measurement of Hb A1C on venous and capillary blood samples. Am J Clin Pathol. 2014;141:867–77.
[PubMed]

162. Little RR, La'ulu SC, Hanson SE, Rohlfing CL, Schmidt RL. Effects of 49 rare Hb variants on Hb A1C measurements in eight methods. J Diabetes Sci Technol. 2015;208. doi:10.1177/1932296815572367.

163. Kiechle FL, Woolaver P, Roger LC. Hemoglobin A1C: evaluation of 4 methods. Am Clin Lab Sci. 2015;45:472 (Abstract # 35).

164. Wu AHB, Lewandrowski K, Gromoski AM, Grenache DG, Sokull LJ, Magnani B. Antiquated tests within the clinical pathology laboratory. Am J Manag Care. 2010;16:e220–7.
[PubMed]

165.

Saenjer AK, Jaffe AS. Requiem for a heavyweight: the demise of creatine kinase-MB. Circulation. 2008;118:2200–6.

166. Singh G, Baweja PS. Creatine kinase-MG. The journey to obsolescence. Am J Clin Pathol. 2014;141:415–9.
[PubMed]

167. Furtado LV, Lehman CM, Thompson C, Grenache DG. Should the qualitative serum pregnancy test be considered obsolete? Am J Clin Pathol. 2012;137:194–202.
[PubMed]

168. Aetna clinical policy bulletin: obsolete and unreliable tests and procedures. 2012. http://www.aetna.com/cpd/medical/data/400.499/0438.html.

169. Acland JD. The interpretation of the serum protein-bound iodine: a review. J Clin Pathol. 1971;24:187–218.
[PubMed][PubMedCentral]

170. Greene DN, Schmidt RL, Wilson AR, Freedman MS, Grenache DG. Cerebrospinal fluid myelin basic protein is frequently ordered but has little value. A test utilization study. Am J Clin Pathol. 2012;138:262–72.
[PubMed]

171. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol. 2013;108:656–76.
[PubMed][PubMedCentral]

172. Jackson BR. Laboratory formularies. Clin Chim Acta. 2014;427:151–3.
[PubMed]

173. Baird G. The laboratory test utilization management toolbox. Biochem Med. 2014;24:223–34.

174. Khalifa M, Khalid P. Reducing unnecessary laboratory testing using health informatics applications. A case study in a tertiary care hospital. Procedia Computer Science. 2014;37:253–60.

175. Van Walraven C, Goel V, Chan B. Effect of population-based interventions on laboratory utilization. A time series analysis. JAMA. 1998;280:2028–33.
[PubMed]

176. Pena JRA, Dzik WS. Utilization management in the blood transfusion service. Clin Chim Acta. 2014;427:178–82.
[PubMed]

177. Carter AB. Clinical requests for molecular tests. The 3-step evidence check. Arch Pathol Lab Med. 2012;136:1585–92.
[PubMed]

178. Riley JD, Procop GW, Kottke-Marchant R, Wylie R, Lacbawan FL. Improving molecular genetic test utilization through order restriction, test review, and guidance. J Mol Diagn. 2015;17:225–9.
[PubMed]

179. Miller CE, Krayt-scheid P, Baldwin EE, Tvrdik T, Openshaw AS, Hart K, et al. Genetic counselor review of genetic test orders in a reference laboratory reduces unnecessary testing. Am J Med Genet A. 2014;164A:1094–101.
[PubMed]

180. Cragun D, Camperlengo L, Robinson E, Caldwell M, Kim J, Phelan C, et al. Differences in BRCA counseling and testing practices based on ordering provider type. Genet Med. 2015;17:51–7.
[PubMed]

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_15

15. Utilization Management: The Role of Reference Laboratories

Brian Jackson[1]

(1) ARUP Laboratories, University of Utah, 500 Chipeta Way, Salt Lake City, UT 84108, USA

Brian Jackson
Email: brian.jackson@aruplab.com

Keywords Laboratory management – Informatics – Reference laboratories – Utilization management – Clinical practice variation

Introduction and Discussion

Changing doctors' test ordering behavior is a complex management problem. It involves many different use cases spread across the full spectrum of medical care and medical specialties. As readers of this book have no doubt already noted, no single technique or tool will solve the problem completely. Rather, there are a number of different principles, techniques, and tools that can be applied in complementary fashion depending on the setting. Some can best (or only) be applied by the organization where the care is directly delivered. Others can best be provided by centralized organizations such as reference laboratories.

What Is a Reference Laboratory ?

The simplest definition is a laboratory that performs testing on behalf of other

laboratories. This is in contrast to the laboratories operated on a local level by hospitals and large clinics in order to serve the day-to-day clinical operational needs. Local laboratories typically perform high volume tests themselves while sending complex and uncommon esoteric tests to outside reference laboratories. For simplicity, this chapter will use the terms “local laboratory” and “reference laboratory” to distinguish the two roles. It must be acknowledged, however, that many hospital as well as commercial laboratories have components of both of these roles.

Which Types of Organizations Are Best Positioned for Which Roles in Influencing Doctors’ Behavior?

From an organizational perspective, effective oversight activities require authority, power, resources, credibility, and sensitivity to local nuance. No one individual or entity within the healthcare ecosystem can claim to simultaneously optimize everything on this list. Any given organization will be stronger in some of these aspects than others (See Fig. 15.1). Local leaders , such as clinical section chiefs, are highly tuned to clinical nuance through close relationships with frontline clinicians and care processes. On the other hand, higher-level entities such as insurance companies and regulatory agencies have resources for developing and enforcing oversight structures, along with the power to impose them on clinicians.

Fig. 15.1 Clinical care oversight hierarchy

Many readers will be familiar with the quality management principles developed at Toyota, which are variously referred to as “lean” or the Toyota Production System . A key element of Toyota’s system is pushing many

detailed decisions to the frontline personnel and their supervisors, under the theory that they are the ones best equipped to assess the effect of changes on the overall quality and efficiency of the process [1]. This has the added advantage of engaging the creativity of frontline personnel. If this general approach works well in a highly standardized environment such as automobile assembly, then it ought to make even more sense in medicine. Physicians and other clinicians are among the most educated and trained individuals in the modern economy, and the patients they see have enormous heterogeneity in their presentations, comorbidities, and preferences. These are key reasons why healthcare organizations have historically chosen not to extensively manage physician behavior, thus contributing to some of the major cost and quality problems that our healthcare system sees today. Toyota's management system, then, suggests a way to respect physicians' knowledge and cognitive skills, within a context of active management, to standardize processes in ways that are responsive to the heterogeneous situations that physicians encounter day to day.

Does this mean, however, that there is no useful role to play in utilization management for other entities more distant from the front line of care? Not at all. The roles are simply different. Within a large healthcare organization such as a hospital or healthcare system, higher-level decision makers play a key role in coordinating and promulgating efforts across the organization. This includes goal setting, infrastructure, facilitating, measurement, etc. Beyond the organizational boundaries lie additional resources and capabilities, e.g., those provided by reference laboratories, that can complement and extend the resources available within the organization .

How Can Reference Laboratories Use Their Unique Resources to Provide Practical Benefits to Assist in Utilization Management?

On the surface it might appear that reference laboratories have little incentive to assist their clients in utilization management. Reducing the number of tests that are sent to the laboratory will have a corresponding negative impact on revenues. However, if all that a reference laboratory does is to simply perform and report test results to their clients, then significant parts of their business will be commoditized and customers will send their samples to the

lowest bidder. For this reason many reference laboratories make a significant effort to bring added value to their customers such as by setting up local specimen collection centers, establishing timely and reliable specimen pickup and logistics, implementing electronic order entry and results reporting in physician practices, and providing consultative services and assistance with utilization management. There are a number of areas where reference laboratories can assist their clients in utilization management activities as shown in Table 15.1. These depend on the unique knowledge, data, and relationships available at reference laboratories and will be described in the pages that follow.

Table 15.1 Reference laboratory approaches to assist in utilization management

1. Provide expert consultative services across multiple specialties in laboratory medicine
2. Develop and disseminate testing algorithms
3. Provide continuing education webinars and print publications
4. Develop online laboratory handbooks with built-in decision support
5. Provide hospital-specific utilization management reports
6. Provide peer-to-peer benchmarking reports

Reference laboratories who engage extensively in esoteric test development have scientific and medical staff with deep scientific and medical expertise in the tests and associated diseases. This knowledge obviously comes in handy when interpretive questions arise. A generally underutilized benefit, on the other hand, is the potential to tap this knowledge for utilization management. This does require a particular mindset on the part of the medical directors and scientists developing the tests: They need to not fall prey to the “new technology” bias that tends to overestimate the benefits and underestimate the limitations of emerging tests. Ideally, experts at reference laboratories should understand the diseases as well as the associated diagnostic and therapeutic approaches in sufficient detail in order to suggest which test ordering patterns would be associated with high-quality care and which ones might suggest waste or misuse. Such experts can author scientific and clinical summaries of the indications for tests, such as literature reviews, which can be used in utilization management educational efforts.

Provide Real-Time Professional Consultation Across

Multiple Specialties in Laboratory Medicine

Most community hospitals have only minimal in-house expertise in the selection and interpretation of laboratory test results. Even large academic medical centers who employ full-time clinical pathologists are not sufficiently staffed to provide expert consultation in many areas of specialty practice such as genetics, endocrinology, coagulation, and infectious disease. In contrast, some large reference laboratories, especially those that serve hospital-based clients, often have many experts on staff who cover most of the major disciplines in laboratory medicine. Traditionally these expert consultations are offered free of charge to the reference laboratory clients. The consultants can be accessed through a centralized customer service center. In one study by Miller et al., the genetics division of ARUP Laboratories reported on the value of genetic counselors in assisting physicians in appropriate test selection [2]. Genetic counselors in the laboratory reviewed orders for complex genetic tests including the clinical and family history and, where necessary, contacted the ordering institution for additional information. They reported that the genetic counselors changed the test orders in 26 % of cases and saved the referring institutions on average $48,000 per month. Very few hospitals have the resources to hire an in-house genetic counselor to provide oversight of genetic testing being sent out to a reference laboratory. Reference laboratories that provide this function offer significant value to their clients who otherwise would have to make do without this expertise .

Develop and Disseminate Testing Algorithms

Algorithms have proven helpful in guiding the selection and interpretation of diagnostic tests. In addition, algorithms can be very effective in reducing the volume of testing required to resolve a number of common clinical problems. Most algorithms are based on initial screening tests, the result of which determines what subsequent tests are required. An example of a diagnostic algorithm for porphyria is shown in Fig. 15.2. Instead of ordering a multitude of tests up front, the clinician using the algorithm can select a more limited number of the most appropriate up-front tests based on the clinical findings, while avoiding those that are not yet necessary. In many cases laboratories can automate the algorithmic cascade such that the differential diagnosis is resolved in a logical stepwise fashion while eliminating many tests along the

way. This process works most effectively when the clinician can order the algorithm itself rather than individual tests such that the laboratory can perform the diagnostic workup without the need for further interaction by the physician. Some hospitals such as the Massachusetts General Hospital (MGH) have published a number of diagnostic algorithms in their “online” laboratory handbooks. However, most hospitals, especially community hospitals, have not. Even in the case of a large academic medical center such as the MGH, the list of available algorithms is by no means complete and is limited by the available in-house expertise in laboratory medicine and by time constraints due to the myriad other duties that must be performed by the laboratory directors. Developing and disseminating diagnostic algorithms is one area of utilization management where reference laboratories have a unique opportunity to offer added value to their clients. First, large reference laboratories have extensive online websites with the required informatics resources to build comprehensive decision support capabilities. Second, these laboratories employ directors and consultants from a large number of laboratory medicine specialties. They therefore have the necessary in-house expertise to develop decision support functions across a wide range of diagnostic problems. Finally, reference laboratories have large test menus and are therefore capable of performing all of the required testing in-house efficiently without the need to send specimens to outside laboratories. For example, in the porphyria algorithm shown in Fig. 15.2, most or all of the tests are not even performed by the majority of hospital laboratories. These hospitals would not have the ability to offer such an algorithm without access to a reference laboratory that had developed the algorithm and could perform all of the tests .

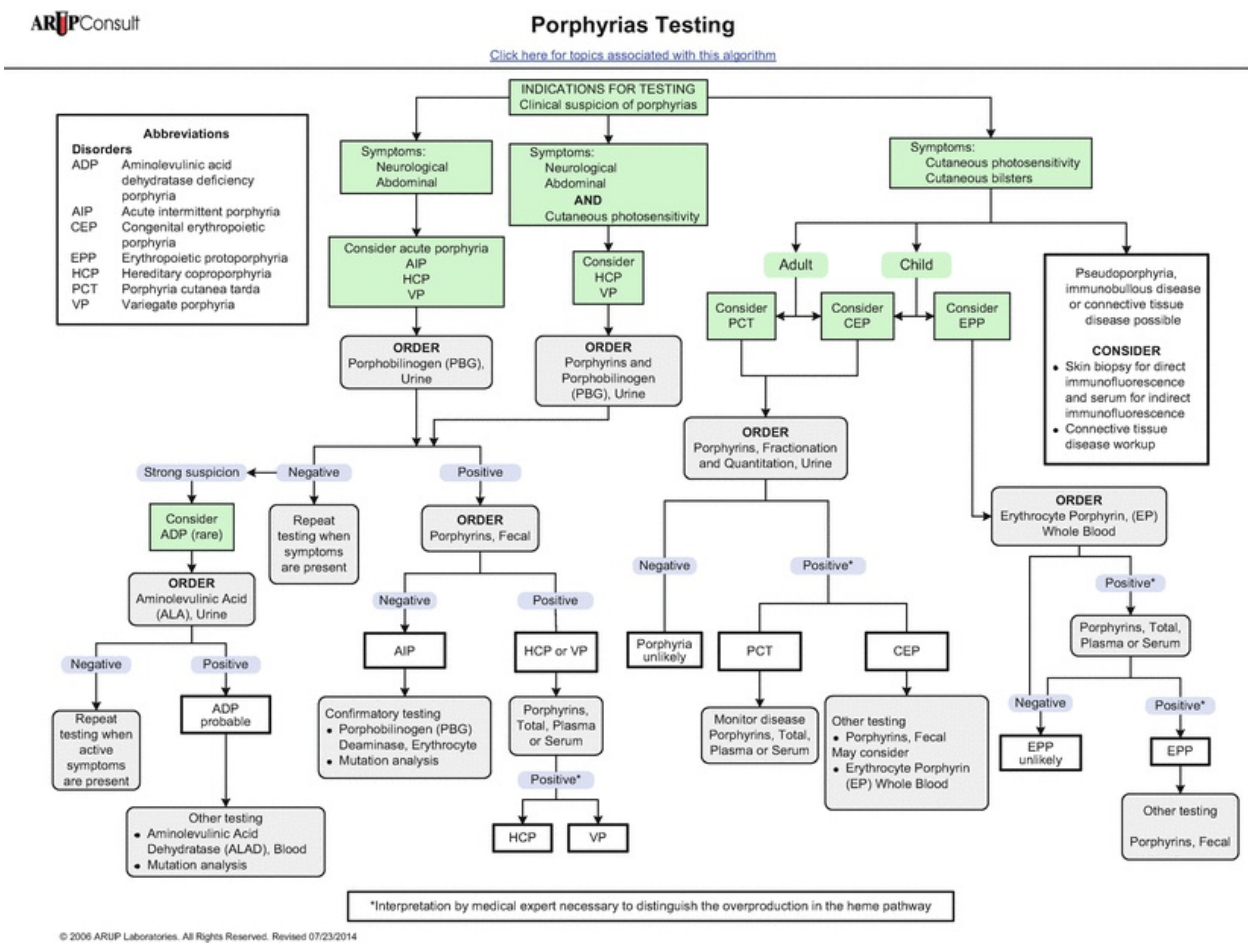


Fig. 15.2 Example of a diagnostic testing algorithm for porphyria published by a reference laboratory. From ARUP Consult (www.arupconsult.com). Used with permission

Develop Online Laboratory Handbooks with Built-In Decision Support

The value of developing an online laboratory handbook with a built-in decision support functions was described in Chap. 1. In contrast to print versions of laboratory handbooks which rapidly become obsolete, the online handbook can continually be updated as test menus, reference ranges, and specimen requirement change. In addition these online handbooks can have built-in decision support functions including diagnostic algorithms, advice on test selection and interpretation, “contact” functions wherein consultations can be requested electronically, and other functions. As the number of available laboratory tests continues to expand and new or updated clinical guidelines come into mainstream practice, it is virtually impossible for the

typical clinician to keep up with the current practice of laboratory medicine. Some hospitals have developed in-house electronic online laboratory handbooks including some elements of decision support. Usually this takes the form of a search function that then displays the available tests along with indications for the most appropriate test in different clinical situations. Other features may include a library of diagnostic algorithms and access to literature and white papers covering different topics relevant to laboratory test selection. For most hospitals, building a robust electronic laboratory handbook can be extremely challenging due to a variety of factors including:

1. Insufficient informatics resources to build and maintain the handbook

2. Insufficient expertise across the various specialties of laboratory medicine

3. Insufficient time available for pathologists due to multiple competing duties

As described above, large reference laboratories usually have far more resources and much greater in-house expertise than even the largest hospital laboratories. For this reason reference laboratories have the ability to offer a much more robust and comprehensive online handbook than hospital-based laboratories covering a larger number of tests and diagnostic challenges. However, as yet, this opportunity is only just beginning to be realized. Those reference laboratories that excel in developing their online handbook with extensive decision support will therefore be at a competitive advantage. The main problem with reference laboratory handbooks is that many practicing physicians are unaware of them and therefore will not access the information when it is needed. The local hospital laboratory can assist in solving this problem by alerting physicians to the existence of the handbook and by providing a convenient link to the handbook in their order entry system or electronic medical record.

One emerging area is the collaboration between reference laboratories and their hospital-based clients to develop client-specific laboratory handbooks. These handbooks contain information about tests performed in the hospital laboratory with a parallel reference laboratory section that includes testing information and decision support. The reference laboratory

provides the basic template for the handbook and then assists the hospital in building their own local laboratory handbook.

One of the most useful tools in utilization management is data on physician variation (see chapter on physician profiling and variation analysis). When physicians see that they use a resource such as a test, drug, or procedure much more frequently than their peers do, this awareness can in many cases become a powerful influence toward self-regulation. A major benefit of this type of data is its high level of face validity. A doctor might argue with the laboratory about the appropriateness of using a particular test at a particular frequency, but it's much harder to argue about whether the data shows that they use that test at a higher or lower rate than other physicians. In principle, variation in use of laboratory tests can be measured across physicians within a single hospital or clinical setting. However, in many cases, physicians practice in ways that are similar to their local peers, which makes it even more valuable to measure variation across hospitals and across larger geographic regions [3]. Such data is often not readily available at a local level. Some comparative physician data may be available through insurance companies and group purchasing organizations. These entities commonly rely on aggregated insurance claims data, however, which severely limits its interpretability. Insurance claims code laboratory orders at the Current Procedural Terminology (CPT) level, which fails to identify many genetic and other expensive tests of interest. Reference laboratories, on the other hand, because they serve multiple hospitals across regions or even nationally, can be an excellent source of comparative test volume data .

Provide Hospital-Specific Utilization Management Reports and Peer-to-Peer Benchmarking Reports

Many reference laboratories supply their clients with utilization reports that list the tests performed, test volumes, and total costs. These reports help the hospital laboratory to track their reference laboratory activity over time and to identify potential targets for in-sourcing or utilization management . This concept could be easily extended to providing clients with peer-to-peer utilization reports that compare testing across different hospitals. Such data can be extremely valuable for identifying outliers in the hospital reference laboratory budget assuming the hospital can be assigned to an appropriate peer group . For example, if a test is being regularly ordered by only one

hospital in the peer group, this often identifies a potential target for utilization management. In addition the reference laboratory could function as a "clearing house" for sharing utilization management initiatives among their hospital clients.

The art and science of managing physicians' clinical activities is a very young one. Any healthcare organization embarking on this journey would do well to keep a close eye on what others across the laboratory industry are doing. Reference laboratories, as a result of extensive client relationships, are well positioned to provide their customers with networking with laboratory peers. This might take several forms, e.g., conferences, real-time collaboration, and social media .

What's the Best Business Model for Reference Laboratories to Deliver Utilization Management Services?

Clayton Christenson in his book *The Innovator's Prescription* [4] lays out three different patterns of business models. The simplest and most common is the "value-added process" consisting of taking inputs, adding or creating some form of additional value, and charging typically on a per-item basis. Most manufacturing and retail business follow this pattern. Reference laboratories do as well: receive an order with an accompanying specimen, perform the test, issue the result, and charge for each performed test. In theory, some utilization management services could be offered under this type of fee for service model. In many cases, though, reference labs should entertain the other two patterns described by Christenson, namely, "solution shops" and "facilitated networks ."

Solution shops include high-end consulting firms and law firms, which provide highly customized solutions to relatively unstructured problems. When reference laboratories assist their customers with establishing formulary committees or other types of organizational engineering, they are essentially offering management consulting. As such, they should look to established management consulting firms to find examples of how to organize, deliver, and scale their services. Such projects are typically scoped at the level of a lengthy engagement rather than a single interaction at a time.

Facilitated networks include membership organizations such as clubs and

professional societies. In many cases annual membership fees provide access to the network's resources. The most important feature of this model is that the main value of the network derives from the membership itself, rather than being directly created by the company that administers the program. Many commercial ride sharing services and room sharing services are set up as facilitated networks. They do not directly employ drivers, nor do they purchase or lease rooms to provide to customers. Rather, they connect individuals providing the services with individuals consuming the services and charge a transaction fee for each event. The value of these companies is directly related to how many people are participating in these two roles. From a reference laboratory perspective, some utilization management services can take the form of networking among healthcare organizations and their leaders, sharing their best practices and related artifacts (data, written procedures, etc.). To the extent that reference laboratories organize services along this type of model, they can learn from observing how professional societies and other membership organizations operate and grow .

What Is the Relationship of Utilization Management to the Research and Development of New Tests?

Many though not all reference laboratories engage in research and development of new diagnostic tests. This presents both challenges and opportunities with respect to utilization management. Typical steps in new test development are shown in Table 15.2. Current US regulation (notably the Clinical Laboratory Improvement Amendments or CLIA) emphasizes that laboratories assess analytic performance, i.e., that tests accurately and reproducibly measure what they purport to measure. For this reason, analytic performance studies form the core of reference laboratory research and development (R&D) efforts. Demonstrating clinical benefit is a much harder challenge, though. As a simple example, consider a hypothetical test that accurately measures a diagnostically relevant analyte. Such a test might nonetheless be of no benefit if there is an existing alternative way for doctors to acquire the same information. There might be an alternative diagnostic test, such as an imaging study or other laboratory analyte; there might be a functional study such as a therapeutic trial of a medication; or there might be a relevant physical finding on examination or during surgery. Diagnostic value is also critically dependent on the (implicit or explicit) therapeutic

decision-making process, e.g., where a doctor's therapeutic actions are determined before the test is even ordered [5]. Any of these issues might in some cases result in an accurate and precise test being of little or no practical value.

Table 15.2 Typical steps in development of a new diagnostic test

1. Identify opportunity based on plausible link between a measurable analyte and diagnostic decision making
2. Engineer the assay for practical performance
3. Assess analytic performance, especially precision and accuracy
4. Make the assay available for clinical use
5. Assess clinical performance and patient benefit (ideally formally through clinical research, but more often informally through clinical experience)

Despite the challenges to studying clinical benefit, reference laboratories can and should consider how they could use their R&D activities to study clinical impact. For example, laboratories should be open to participating in or even underwriting clinical trials. At a minimum, it should be considered an ethical obligation to cooperate with organizations conducting independent trials of a new diagnostic test. This obligation is particularly strong in the special case where a laboratory owns exclusive intellectual property to the test in question. Finally, in the future, there may be opportunities for postmarketing surveillance of new diagnostic tests, e.g., in the form of diagnostic registries .

How Do Reference Laboratory Sales and Marketing Efforts Relate to Utilization Management?

When laboratories market their services to customers, this typically takes the form of promoting individual tests and/or their full package of services. Some laboratories focus on the former, some on the latter, and some have a mixed approach.

Promotion of individual tests can be problematic with respect to utilization management. In many cases, the tests being promoted are newer tests that have not yet developed significant clinical demand, and the goal of promotion is to create awareness and demand across a broader clinical audience. There are two problems here. One is that many new tests do not yet

have strong evidence for patient benefit. This evidence may eventually emerge in the course of gaining broader clinical experience (informal evidence) and/or incorporation of the test in the context of clinical research of therapeutic interventions (formal evidence). In the mean time, though, the responsible approach of utilization management efforts is to encourage doctors to limit the use of the diagnostic test to settings where the benefit is most plausible based on first-principle reasoning. Active marketing of a test can easily come in conflict with this approach. The second problem is that even for a test with strong evidence of clinical utility, marketing of the test's benefits can potentially lead to overuse in terms of frequency and/or application in diseases or settings where evidence for benefit is lacking.

For laboratories who primarily market their overall package of services rather than individual tests, utilization management represents a significant opportunity to expand their value message to customers. Many business-to-business (B2B) vendors , including reference laboratories, sell to decision makers at senior levels within large organizations where the primary interest may be economic value as opposed to product quality or service quality. In that setting, emphasizing "total cost of ownership" (TCO) is common and provides a way for vendors to redirect emphasis away from price per unit and onto larger discussions of value. One of the biggest detractors from diagnostic value in a healthcare organization is overuse and misuse of tests; thus, a convincingly effective utilization management program can be a strong marketing tool for reference laboratories .

References

1. Womack JP, Jones DT, Roos D. The machine that changed the world: how lean production revolutionized the car wars. New York: Simon & Schuster; 2007.

2. Miller C, Krautscheid P, Baldwin E, Tvrdik T, Opensaw A, Hart K, et al. Genetic counselor review of genetic orders in a reference laboratory reduces unnecessary testing. Am J Genet Part A. 2014;164A:1094–101.

3. Fisher ES, Wennberg DE, Stukel TA, et al. The implications of regional variations in Medicare spending. Part 1: The content, quality and accessibility of care. Ann Intern Med. 2003;138:273–87. [CrossRef][PubMed]

4. Christensen CM, Grossman JH, Hwang J. The innovator's prescription. New York: McGraw-Hill; 2009.

5.

Holmes KP, Fang JC, Jackson BR. Cost-effectiveness of six strategies for *Helicobacter pylori* diagnosis and management in uninvestigated dyspepsia assuming a high resource practice pattern. BMC Health Serv Res. 2010;10:344.
[CrossRef][PubMed][PubMedCentral]

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_16

16. Utilization Management in Anatomic Pathology

Kent Lewandrowski[1]

(1) Division of Laboratory Medicine, Department of Pathology, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street, Boston, MA 02114, USA

Kent Lewandrowski
Email: klewandrowski@partners.org
Email: KLEWANDROWSKI@mgh.harvard.edu

Keywords Utilization management – Anatomic pathology – Surgical pathology – Cytopathology – Reimbursement

Portions of this chapter were derived from a recent review by the author published in Clin Chim Acta. 2014;427:183–7.

Introduction

Anatomic pathology (AP) includes surgical pathology , cytopathology , autopsy pathology , and special studies such as immunohistochemistry and molecular pathology .

In many areas of medical practice, there is an abundant literature on utilization management . The literature is probably most extensive for clinical laboratory testing, radiology, and pharmacy. Most large hospitals are making significant efforts at utilization management in these areas. In the case of anatomic pathology, the literature and cumulative experience on utilization

management is extremely limited. There are several reasons for this:

1. Compared to clinical laboratory testing and blood transfusion services , the overall hospital budget for anatomic pathology technical services is relatively modest. In our hospital anatomic pathology comprises only about 20 % of the hospital budget for pathology and laboratory services. Utilization management efforts typically target areas of high overall cost particularly where there is significant variation in the practice of individual physicians. Neither of these are the case with anatomic pathology.

2. Physicians and hospital administrators have little understanding of the practice of anatomic pathology and the costs of its individual components. A typical clinician has no knowledge of whether a particular special stain is actually needed or not and would not know how many tissue blocks or levels should be examined for a particular tissue specimen. The majority of clinicians other than surgeons and some specialties (e.g., endoscopists) only occasionally review pathology reports. Anatomic pathology is essentially off the radar of most leaders in utilization management.

3. Pathologists themselves have limited incentive to control utilization in anatomic pathology [1]. In anatomic pathology there is both a professional (part B) and a technical (part A) billing component. Most pathology practices derive the majority of their practice support from billing for professional services related to the evaluation and diagnosis of tissue specimens and special studies. Reducing these services could have impact the revenues of the practice. The technical component (part A) also generates revenue. In some cases this goes to the hospital that manages and operates the pathology laboratory. In other cases the revenues go to the practice if they have their own histopathology laboratory. A variant of this arrangement may occur with certain medical and surgical specialty practices that generate a large volume of biopsies (e.g., urology, gastroenterology, dermatology). Some of these practices manage their own pathology laboratories. These laboratories typically hire pathologists on contract and do their own histopathology allowing

them to bill for the technical and professional component directly.

As with many areas in medicine, there is a misalignment of incentives for pathology services between the major stakeholders including the hospital, the physician (pathologist), and third-party payers. To illustrate this point, consider the situation of a tissue biopsy in which there is an initial hematoxylin and eosin (H and E) stained slide and two additional H and E levels of the block and an immunohistochemical (IHC) stain . From the perspective of the hospital that pays the costs of making the slides, the levels and the IHC are all costs which can be offset by technical component billing. The initial H and E slide and the IHC stain can be billed but the additional levels cannot. The levels become pure cost. The pathologist does not incur any costs for the technical components. The pathologist bills for the professional component of the biopsy and the IHC stain (but not for the two levels). Reviewing the levels will take the pathologists time but will not incur a cost beyond that. The third-party payer will receive a bill for both the professional and technical components. Based on current reimbursement systems, they will not pay more for the two levels. Third-party payers are not concerned with the costs to the hospital or the pathologist's time, only the bill that they actually receive. In short, neither incentives to control costs or revenues are aligned.

As another example, consider a utilization initiative in which a decision is made not to have a pathologist examine certain types of tissue specimens. In this case the hospital eliminates the cost of processing the tissue and making the slides. The third-party payer never receives a bill for the technical or professional component. However, the pathologist loses the professional payment for examining the tissue. Unlike clinical laboratory testing where there is usually no professional component, the situation in anatomic pathology is more complex because the physician is a major determinant in the overall cost/revenue equation. Pathologists have a significant impact on the cost of pathology services because they use their professional judgment to determine how and in what manner a tissue specimen will be evaluated. This includes how many tissue blocks will be examined, the number of levels taken of each block, and what additional studies such as special stains and IHC are required. However, the pathologist is rarely held accountable for the cost of these decisions.

Another factor that will tend to discourage pathologists from actively participating in utilization management in anatomic pathology is that this

activity is not reimbursed either by third-party payers or the hospital. Unlike clinical pathologists who are usually salaried employees, for the anatomic pathologist, hours spent developing and implementing utilization management initiatives take time away from generating revenue in their practice. In many group practices, the pathologist's salary is based significantly on the number of relative value units generated for the practice. Other activities are either not factored in to the existing salary model or may receive relatively low compensation in comparison to signing out anatomic pathology specimens. In the private practice environment, many pathology groups contract with hospitals to provide clinical laboratory directors as required by regulatory agencies. The practice is usually paid a fixed amount for this service. This arrangement usually allows the practice to capture all of the surgical pathology generated in the hospital and its affiliated outpatient clinics. In this setting the pathologist has little incentive to engage in utilization management in either the clinical laboratory or surgical pathology as this only adds uncompensated time to the laboratory contract while reducing revenue-generating surgical pathology activities.

The above-described situation evolved in the era of the pure fee-for-service model of physician compensation. The more surgical pathology that was performed, the more income the practice would generate. However, the landscape for physician compensation in the United States is starting to change. New models of compensation based on global payments to healthcare organizations for episodes of care or entire populations of patients are starting to be introduced, along with financial risk sharing where physicians share with the payer part of the financial risk or benefit for meeting a budget goal for healthcare spending. There are many potential variants in these new models but in its most simple form, a multispecialty physician organization (such as the Massachusetts General Physicians Organization) would get a global budget to provide all of the care for a fixed population of patients. If the cost of care exceeded the global budget, the physician organization would incur financial penalties. If the cost was less than the budget, they would share in the savings. This is the basic concept behind Accountable Care Organizations (ACOs) currently being established under "Obamacare ." In this model there is no incentive to provide more care than is medically necessary creating a motivation for physicians to manage the utilization of clinical services. This arrangement has the potential to place all physicians at risk. The income or "value" of the physician will not be

determined by billable units but rather by their role or perceived value within the system. Pathologists will be forced to compete with other specialties for their share of the global payment. In this arrangement there is no incentive to perform any more services than is absolutely needed for clinical care. Pathologists who are successful at managing the utilization of their service (and thus reducing its cost) will have a corresponding increase in their perceived value. Equally important, pathologists will have a significant opportunity to lead utilization management efforts relating to clinical laboratory services and to participate in clinical care redesign teams. One trend that will support this realignment of the role of the pathologist is that many pathologists are currently, or will become, salaried physicians as part of a group practice or physician organization. This model is now common among academic medical centers and integrated health networks [1]. As salaried physicians the income of the individual pathologist will be based less on aggregate billed units and more on the overall role they serve within the organization. Utilization management will become a recognized activity that is compensated either directly or as part of a fixed salary package. The College of American Pathologists has been working at the state level to ensure that pathologists have a key role in promoting quality and lowering costs within ACOs. For example, Illinois has passed legislation (Public Act 098-0708) that requires ACOs to form clinical laboratory advisory boards in which pathologists will play a key role [2].

This chapter will describe a number of approaches for utilization management in anatomic pathology that are either currently in practice or that have been described in the literature. The focus will be on general themes for utilization management with specific examples rather than a comprehensive review of the many individual initiatives that have been implemented.

Utilization Management Initiatives in Anatomic Pathology

Compared to clinical laboratory utilization management, there is comparatively little published literature on the subject in anatomic pathology although the number of reported initiatives has been increasing. Table 16.1 illustrates the general categories of utilization management in anatomic pathology along with some specific examples. Many of these are described in the text that follows.

Table 16.1 Potential areas for utilization management in anatomic pathology

1. Implement evidence-based guidelines (e.g., evidence-based guidelines for cytogenetics and molecular testing in hematopathology
2. Implement established national guidelines (e.g., frequency of PAP smears)
3. Develop guidelines for specimens that do not need pathological examination
4. Classify selected pathology specimens as “gross-only” examination eliminating histopathological examination
5. Develop protocols to limit the number of standard paraffin blocks taken from specific specimens
6. Eliminate up-front automatic special stains for types of specimens where rapid turnaround time is not required (e.g., automatic *H. pylori* stains on gastric biopsies)
7. Develop protocols to specify how many levels are required for specific specimen types
8. Pathologist review of cases to be sent for expensive multiplex molecular testing to ensure appropriateness
9. Develop protocols that eliminate unnecessary sections from selected specimens (e.g., tumor margins remote from the primary tumor)
10. Develop protocols to specify how many tissue specimens can be included in one block (e.g., prostate needle biopsies)
11. Develop guidelines for when frozen sections are unnecessary
12. Develop guidelines to specify appropriate special stains and immunohistochemistry studies for specific diagnoses
13. Restrict cerebrospinal fluid flow cytometry in patients with neurological indications but without a hematologic malignancy or elevated white blood cell count
14. Develop protocols to specify what molecular pathology studies are appropriate for specific tumors
15. Review the necessity for internal review of outside pathology reports from institutions within a single healthcare network
16. Develop a standardized evidence base for when cytopathology specimen acquisition may be more cost effective than surgical biopsy
17. Develop a standardized evidence base for when a rapid on-site evaluation of cytopathology specimens is cost effective

Reprinted from Clin Chim Acta. 2014;427:183–7 with permission

Implement Practice Guidelines for High-Cost Ancillary and Special Studies

The pathological examination of bone marrow biopsies for neoplastic hematological disease may involve a number of special studies including flow cytometry , cytogenetics fluorescent in-situ hybridization , and molecular diagnostic testing . Biopsies may be obtained for initial diagnosis,

staging and monitoring, and pre- and post-stem cell transplant. In a study by Seegmiller et al. [3], a team of pathologists and clinicians developed evidence-based protocols for cytogenetic and molecular testing on various bone marrow specimens. These included acute lymphoblastic leukemia , acute myelogenous leukemia , myelodysplastic syndrome , bone marrow failure , and cytopenias of unknown etiology. The pathologist reviewed the patient's history, initial microscopy, and flow cytometric testing. Based on this review, follow-up tests were ordered according to the practice guidelines. After implementation they observed a significant decrease in test orders that were discordant with the guidelines, omitted tests, and reduced the cost to payers. Based on a financial analysis, they estimated an average cost saving of $442 per specimen and a savings to payers of between $522,000 and $1,069,200.

In our hospital we are currently reviewing the use of cerebrospinal fluid flow cytometry in patients with neurological indications but without a known hematologic malignancy or an elevated white cell count. This initiative follows a study by Kovach et al. in which the authors reviewed the utility of performing flow cytometry in this subset of patients [4]. They concluded that restricting the use of flow cytometry in these cases would eliminate testing in 23 % of requested cases without a negative impact on clinical care.

Implement Established National Guidelines

Current guidelines for use and frequency of Papanicolaou smears (PAP) to screen for cervical cancer have been established by the US Preventive Services Task Force in conjunction with the American Cancer Society/American Society for Colposcopy and Cervical Pathology and the American Society for Clinical Pathology . An example of a screening guideline is shown in Table 16.2 (note that newer guidelines utilizing co-testing have been introduced). These guidelines would be expected to significantly reduce the number of PAP tests performed when compared to the traditional approach that utilized PAP smears for all adult patients at regular intervals [5]. Specifically the guidelines specify groups of patients where screening is either no longer required or where the interval between screening tests may be extended. Although not all of the practices in our hospital are currently following the guidelines, an analysis of our PAP smear volumes over time showed a significant 29 % decrease over 5 years in PAP smear volume and the trend is continuing. Recently we began a population

health initiative to convince practices to follow the guidelines . One problem with the guidelines is that they are somewhat complex and are difficult to remember. For this reason ongoing clinician education is key to achieving consistent adherence to the guidelines. Recently the US Food and Drug Administration approved a human papillomavirus (HPV) DNA test that can be used to screen women without the need for a PAP smear. The test detects DNA from 14 high-risk HPV types with specific identification of HPV 16 and 18. If the test detects HPV 16 or 18, then a colposcopic examination is recommended, whereas if one of the other types is detected, then a follow-up PAP smear is required. The long-term impact of this new test on PAP smear volumes is yet to be determined. Potentially the test could replace the majority of labor-intensive PAP smears that require specialized training to interpret with an automated instrumented test that any competent medical technologist could perform. However, the relative cost of the new test versus the alternative of a conventional PAP smear with a reflex to HPV testing in selected cases is yet to be determined. In general HPV tests cost about twice as much as a PAP smear alone but this does not take into account the rate of reflex HPV testing in different patient populations or the relative impact of the two different strategies on downstream costs including colposcopy and cervical biopsies .

Table 16.2 Example of guidelines for cervical cancer screening [a]

Age or group	Screening interval	Comment
<21	No screening	
21–29	PAP every 3 years	
30–65	PAP and HPV every 5 years or PAP every 3 years	
History of CIN2-3 within last 20 years	Routine screening as above after a period of more intensive surveillance	May extend screening after age 65 or after complete hysterectomy
High-risk patients 1. DES exposure 2. Immunocompromised (e.g., HIV positive 3. History of cervical cancer	PAP annually	

Patient with complete hysterectomy	Screening may stop	If no history of CIN2-3 within last 20 years
Over 65	Screening may stop	Assuming three normal PAPs or two negative HPV tests in the last 10 years; screen older women with inadequate history of PAP smears. For patients with a history of CIN2-3 continue screening for 20 years

Source: Modified from: Shana Birnbaum, MD, Raymond Liu, MD. Massachusetts General Hospital Primary Care Operations Improvement (PCOI) Website. Reprinted from Clin Chim Acta. 2014;427:183–7 with permission

PAP papanicolaou smear, *HPV* human papilloma virus testing, *HIV* human immunodeficiency virus, *CIN* cervical intraepithelial hyperplasia

[a]Newer guidelines based on co-testing have been developed

Establishing Guidelines for Specimens That Do Not Require Pathologic Examination

Pathologic examination of some tissue specimens provides essentially no useful clinical information and is not cost effective. Selected examples include normal placentas from uncomplicated child birth, finger and toenail resections, and cosmetic plastic surgery specimens. Table 16.3 shows the list of specimens that do not need to be submitted for pathological examination in our institution. In addition to specimens that clearly do not require pathological examination, there are other types of specimens that are submitted to pathology primarily for the purpose of documentation of tissues or hardware removed during surgery (e.g., loose bodies from joints, ribs removed during thoracotomy, skin tags). Beyond documenting what was removed in the medical record, pathological examination of these specimens provides essentially no useful clinical information (e.g., loose bodies from joints, bunion repair specimens, skin tags, and tendon/soft tissue repair specimens). Cumulatively these types of specimens represent a not insignificant volume in general surgical pathology . As pressure to control costs grows, the pathological examination of low diagnostic yield specimens submitted for documentation will be increasingly scrutinized. In the extreme case, many other tissue specimens could probably be safely submitted as gross examination only as described below including such common specimens as grossly normal appendectomies and gallbladders with no gross

evidence of malignancy. In the past the counterargument to this approach was generally based on rare anecdotes about the discovery of unsuspected tumors or other significant pathology typically verbalized in the form of “I once saw an appendix that turned out to have a mesothelioma that was clinically unknown.” In the vast majority of cases, a gross examination by the pathologist would detect such unsuspected conditions.

Table 16.3 List of specimens not submitted for pathology examination and gross-only examination at the Massachusetts General Hospital

Specimens that need not be submitted
Foreign bodies
Hardware
Nail pairings
Normal infant foreskin
Normal tissue removed for exposure of nonmalignant organs (includes adipose tissue Cardiac atrial appendages
Scars excised during operation for nonmalignant disease
Teeth
Therapeutic radioactive sources
Uncomplicated pediatric hernia sacs
Unused portions of veins removed for bypass operations
Gross-only specimens
Bilateral adenoids
Bilateral tonsils
Amputations for vascular disease
Breast implants, testicular implants, chin implants
Cutaneous scars removed during exploration for nonmalignant disease
Excised skin from plastic surgery procedures
Nasal septal cartilage
Normal ribs removed to expose non-tumorous organs
Stones
Teeth
Foreign bodies
Hardware from orthopedic procedures

Reprinted from Clin Chim Acta. 2014;427:183–7 with permission

Most hospitals have a tissue committee that reviews what specimens must

be sent for pathological examination. The list of specimens that do not require pathology varies widely between different organizations. A study by Zarbo and Nakhleh surveyed the “exempt for submission” policies of 413 institutions [6]. They reported that most institutions had a written policy for gross only and exempt from submission specimens with a range of 2–40 specimens in the exempt category and 6–57 in the gross-only category. In many cases the gross-only examinations are performed by pathology assistants , residents, and histotechnologists eliminating the need for a staff pathologist. Included among the specimens on the list were incidental appendices, debridement for recent trauma, inguinal hernia sacs, ribs removed for surgical exposure, fallopian tubes for voluntary sterilization, placentas from normal deliveries, and a number of other specimens from general surgery, gynecology, ophthalmology, oral surgery, orthopedics, otolaryngology, urology, pediatrics, and vascular surgery. At present there is little incentive for pathologists to aggressively advocate the conversion of specimens to exempt or gross-only categories. These specimens bring income into the practice with essentially no medical risk. However, as reimbursements systems change, this situation will also change. Pathologists should work actively with their respective tissue committees to review the list of specimens that require no pathological examination or can be safely reviewed as gross-only specimens. This analysis should take into consideration the likely yield of useful diagnostic information relative to the cost to the healthcare system. Also the approach should, where possible, be evidence based taking into account published literature or using searches of large computerized databases to determine the risk of failing to diagnose significant pathology. There is also an opportunity for pathology professional societies such as the College of American Pathologists to develop national guidelines for these types of specimens to standardize practice and to ensure safe practice in an era of cost containment .

Developing a List of Specimens That Can Be Submitted for “Gross-Only” Examination

As described above there are a number of pathology specimens that can be submitted as gross-only examination thus eliminating the need for histopathology and microscopic examination by the pathologist as determined by the hospital tissue committee working in conjunction with a

pathologist. Joint Commission accreditation standards require that hospital clinical staff and a pathologist jointly determine and document which surgical pathology specimens require only a gross description. As a general guide, the College of American Pathologists has published a policy and list of examples of specimen types that can be submitted for gross examination only [7]. Typically these specimens are submitted to pathology for the purpose of documenting what tissues or hardware was removed during a procedure. The list of "gross-only" specimens in our institution is shown in Table 16.3. As one example from our institution, we recently changed our protocol for pathologic examination of bilateral tonsil and adenoid specimens to "gross only" unless histopathological examination was specifically requested by the surgeon (e.g., suspected lymphoma).

Reduce the Number of Standard Blocks Submitted for Common Pathology Specimens

General guidelines for the processing and/or reporting of common and important surgical pathology specimens have been published by several authoritative sources including the College of American Pathologists Cancer Protocol Templates and the textbook Rosai and Ackerman's *Surgical Pathology* . The guidelines specify recommended final pathology reporting formats or recommend specific tissue sites to be sectioned (e.g., margins). Some sources recommend the number of tissue blocks that should be examined for certain tumors or other types of specimens. These guidelines are voluntary, and each pathology practice must determine its own individual protocols. Despite these general guidelines, there is limited peer-reviewed literature on the appropriate number of tissue paraffin blocks that should be submitted for many routine surgical pathology specimens. As a consequence there is considerable variation in how many tissue blocks are submitted for microscopic examination depending on many factors including variation in protocols among different pathology practices and the practice patterns of individual pathologists. In general pathology residents and inexperienced junior pathologists submit many more tissue blocks for microscopic examination than more experienced senior pathologists. In academic medical centers, over-submission of tissue blocks is widespread owing to the inexperience of the prosector and the desire to archive tissues for future teaching and research. The existence of significant variation in practice

among different physicians is usually an indicator of an opportunity for utilization management. In our institution we have revisited our approach across the various pathology subspecialties and have made changes to some of our previous protocols as illustrated in Table 16.4. For example, in bone and soft tissue pathology , we reduced the number of blocks for total knee replacement specimens from 4 to 3 and for femoral head resections from 3 to 2. In an article by Goss from the Cleveland Clinic , a number of cost-reducing strategies were described including efforts to reduce the number of tissue blocks on selected cases [8]. These included:

Table 16.4 Examples of some recent utilization management initiatives in anatomic pathology at the Massachusetts General Hospital

A. Ear, nose, and throat 1. All tonsils and adenoids from adult patients submitted for tonsillitis or other benign indications will be processed as gross only. Tonsils and adenoids submitted for a mass lesion, or for suspected lymphoma will still be processed for microscopic examination and a lymphoma work-up 2. Middle ear ossicles will be processed as gross only unless a microscopic exam is specifically requested by the clinician
B. Pulmonary For lobectomy or pneumonectomy performed for nonneoplastic disease, three blocks of any lesional tissue (such as abscess or bronchiectasis, two blocks of seemingly normal lung, and one block of lymph node. No sections of any resection margins
C. Cardiac 1. On transplant endomyocardial biopsies with low-grade (1R) cellular rejection do not automatically obtain a CD4 immunohistochemical stain 2. On explanted hearts process no more than ten blocks of ventricular myocardium
D. Hematopathology 1. Eliminate automatic reticulin stain on bone marrow biopsies 2. Eliminate Giemsa stain on lymph nodes for lymphoma work-up
E. Gastrointestinal pathology Do not take sections of mesenteric and axial margins on colon cancers when the grossly evaluated margin is greater than 5 cm from the tumor
F. Bone and soft tissue Reduce the number of blocks for total knee replacement from 4 to 3 and for femoral heads from 3 to 2
G. Neuropathology Focus use of immunohistochemistry in the evaluation of pituitary adenomas: Nonfunctioning tumors (from clinical data), all pituitary hormones (LH, FSH, TSH, alpha-subunit, GH, ACTH, prolactin) as well as p53 and Ki-67; prolactinomas, prolactin, GH, p53, Ki-67; Cushing's syndrome, ACTH, alpha-subunit, p53, Ki-67; acromegaly, GH, prolactin, Cam5.2, alpha-subunit, p53, Ki-67
H. Urologic pathology

1. Testis tumor cases: reduce requirement of three sections of cord down to one proximal margin 2. Deletion of requirement for normal epididymis to be sampled. Delete requirement for section of tumor to uninvolved parenchyma 3. Bladder cancer cases: delete requirement of tumor to trigone. Modification of current requirement of two sections of each uninvolved wall to two random sections of uninvolved wall. Delete requirement for section of grossly negative vas deferens and seminal vesicles
I. Gynecologic pathology 1. For benign ovarian tumors, reduce requirement of one section per cm to one per 2 cm 2. For borderline ovarian tumors, decrease requirement of two blocks per cm to one per cm
J. Renal pathology Reduce blocks taken for nonneoplastic nephrectomies to four (ureter with artery, two cortex-medulla, plus any gross lesion)
K. Breast pathology Previous requirement for submission of ten cassettes for mammoplasty reduction specimens (one tissue section/cassette and ten cassettes per breast) in women >50 or those women <50 with a family history of breast cancer. Going forward submit two sections of tissue in five cassettes for each mammoplasty specimen (five cassettes per breast)
L. Dermatopathology For the immunohistochemical evaluation of atypical lymphoid infiltrates discontinue use of CD7. This stain is routinely included in the panel for evaluating T cell infiltrates in the skin because it may be abnormally absent in atypical lymphocytes. It is now known that reactive infiltrates may also show loss of this marker, its clinical utility in this setting is limited
M. Obstetric pathology Implement protocol specifying three blocks on placentas

Reprinted from Clin Chim Acta. 2014;427:183–7 with permission

1. Not taking sections of colon cancer resection margins when the margins are grossly free of tumor.

2. Not sampling mucosal polyps or diverticuli from colon cancer resection specimens.

3. Submitting only one section of the cervix (instead of anterior and posterior sections) on uteri removed for prolapse.

4. Placing four sections from loop electrosurgical excision pocedures (LEEP) of the cervix into each cassette instead of 12 sections placed each into a separate cassette. They perform roughly 500 LEEP procedures per

year and therefore eliminated 4000 blocks per year.

5. Specimens for nodular prostatic hyperplasia are often submitted by pathology laboratories in their entirety. The new protocol was changed and only 12 g of prostate chips were required to be submitted unless cancer was found in the slides in which case the entire specimen is submitted.

These changes were not derived from any established base of evidence but rather reflected the informed opinion of experienced anatomic pathologists. The guidelines reduce the cost of processing tissue blocks in histopathology and reduce the number of slides that must be reviewed by the pathologist. However the reimbursement from third-party payers is the same regardless of how many tissue blocks are submitted. This illustrates another example of the disconnect between reducing costs in the pathology practice and the perspective of the payers .

Eliminate “Up-Front” Special Stains on Non-turnaround Time-Dependant Surgical Pathology Specimens

In many cases pathologists establish protocols for automatically ordering special stains or immunohistochemistry up front at the time of tissue processing. This practice is very helpful when an urgent diagnosis is required or only a small piece of tissue is available. For routine specimens ordering studies up front offers convenience for the pathologist since all potentially needed stains are available at the time of initial histopathological examination. However, for specimens where the turnaround time is not urgent, this practice can be quite wasteful particularly when the probability of the stain contributing important diagnostic information is low. In a recent study by Chikara [9], the author evaluated the cost effectiveness of up-front stains for *Helicobacter pylori* in gastric biopsy specimens. *Helicobacter pylori* was not detected in any of the biopsy specimens with normal or near normal histology or mild inactive gastritis. The authors concluded that up-front staining for *H. pylori* is not cost effective. In another study by Owens, the authors reviewed the relationship between a clinical request to rule out *H. pylori* on the requisition and the presence of *H. pylori* on biospy. They

concluded that a request on the requisition should have no role in deciding to use *H. pylori* special stains [10].

The issue of ordering up-front immunohistochemical stains has also come under the scrutiny of Medicare and other regulators particularly as it relates to in-office laboratories utilizing self-referral arrangements. One Medicare administrative contractor released guidance on special stains in gastric pathology that stated that ordering of special stains or immunostains prior to review of the H and E slide is not necessary and that special stains and immunostains requests should not exceed 20 % of biospies. They further stated that pathologists who exceeded the 20 % guideline would face further action .

Establish Guidelines for the Number of Separate Specimen Jars Submitted for Multi-biopsy Specimens: The Case of Prostate Biopsies and the Challenges of Self-Referral

When performing a prostate biopsy, the urologist often obtains 12 specimens representing different areas of the prostate gland. Unlike payment for the biopsy itself, Medicare will reimburse a provider for the number of individual specimens containing tissue that are submitted for separate diagnosis. In 2010 the Medicare national global payment for one jar was approximately $140. If six jars are submitted with two tissue cores in each, the reimbursement would be six times the one specimen rate. If all 12 cores are submitted as individual specimens, the reimbursement would be roughly $1248 [11]. Billing for the pathological examination of the tissues contains two components, the technical component for processing the tissues and making the slides and the professional component for interpreting the diagnosis . There are no clear guidelines to determine how many tissue core specimens should be submitted in any one jar, and so this decision is largely at the discretion of the urologist who may tailor the approach to meet the needs of the individual patient. Placing too many cores in a jar may make tissue processing and getting complete sections of all of the tissue cores very challenging. Placing only one core in each jar results in a significant increase in the cost of processing and in the charges submitted to third-party payers . So long as the urologist does not directly benefit from decisions concerning how many cores to submit in a

jar, then there is no incentive to drive up costs by submitting more jars than is clinically required. In most situations federal law prohibits physicians from referring Medicare patients for studies or procedures to facilities in which they have a financial interest. However, anatomic pathology has been allowed an exception to the self-referral guidelines that permits some medical specialties such as urologists, gastroenterologists, and dermatologists to establish their own pathology laboratories or contract with a pathology practice. This results in two different potential self-referral scenarios :

1. The urology practice owns the laboratory and hires a pathologist to interpret the slides. The practice then bills for both the technical and the professional component and pays the pathologist a salary.

2. The urology practice owns the laboratory and processes the tissue and makes the slides. They then contract with a pathology practice to interpret the biopsies. The urology practice bills for the technical component and the pathology practice bills for the professional component .

A study by Mitchell reported on the impact of self-referral by urology practices on the rate of utilization of pathology services, specifically the number of jars submitted on average for patients undergoing a prostate biopsy [11]. In locations where self-referral accounted for more than 50 % of the total utilization, the rate of prostate biopsy specimens obtained per 1000 male patients was 41.5 units higher than in locations where there was no self-referral. The author stated that self-referral of prostate biopsies offered the urologist a significant opportunity to increase practice revenues and increased the overall rate of prostate biopsies. Eliminating self-referral would result in significant savings for Medicare . The problem of self-referral of pathology services has become visible at the national level. President Obama in his fiscal year 2016 budget has asked congress to approve his proposal to exclude anatomic pathology from the In-Office Ancillary Services Exception to the Stark Law . This proposal has the support of the College of American Pathologists who have stated that “self-referral for these services does not benefit patient care and leads to higher Medicare costs.”

A related issue concerns the current controversy surrounding recent guidelines by the US Preventative Services Task Force concerning the

routine screening for prostate cancer using prostate-specific antigen. Specifically the USPSTF “recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.” The American Urological Association (AUA) has also released guidelines based on patient age, risk factors, and patient preference that are less absolute [12]. Specifically the AUA recommends against PSA screening in men under age 40, against routine screening in men 40–54 unless there are risk factors for prostate cancer, and for men 55–69 the decision to screen should be based on shared informed decision making between the physician and the patient.

From the perspective of the overall cost of our medical care system , decisions as to which guidelines to follow or not have significant ramifications. Since screening with PSA results in a significant number of men undergoing prostate biopsies for an elevated PSA level who, in the absence of screening , would not have a biopsy, the implications for the overall cost of care for clinical laboratories that perform the PSA test and for urologists and pathologists incomes are considerable. For a practice that self refers their biospies to a laboratory in which they have a financial interest, there is a clear conflict concerning the value of screening men with PSA testing. The author of this chapter does not have the expertise to support one set of guidelines or the other. The intent is to show the potential impact of guidelines in one area of medicine (in this case the clinical laboratory) on costs and physician incomes in other areas .

Develop Guidelines for When Frozen Sections Are Unnecessary

Frozen section pathological examination is essential for guiding intraoperative decisions during surgery. However, according to Taxy, frivolous requests with no direct consequences for clinical care should not be honored [13]. It is well known by pathologists that in some cases frozen sections are unnecessary or do not influence the surgical approach to the patient. There are relatively few peer-reviewed studies that evaluate the medical necessity of frozen sections in different clinical scenarios. In one study, Prey et al. reported on guidelines for practical utilization of frozen section specimens. They recommended that lymph nodes for lymphoproliferative disorders and breast tissue for which a malignant

diagnosis would not result in an immediate mastectomy not be submitted for frozen section diagnosis [14]. In another report evaluating the value of frozen section analysis of re-excision specimens in preventing reoperation in breast-conserving therapy , the authors reported that the use of frozen sections of margins did not impact patient outcomes as there was no difference in further excisions, total operations, or conversion to mastectomy in patients with and without frozen sections [15, 16].

In some cases the use of frozen sections is more a matter of local practice patterns. In others frozen sections are performed according to the preferences of individual clinicians. For example, surgery for patients with hyperparathyroidism due to parathyroid adenoma or hyperplasia may be guided by one of four different approaches:

1. The surgeon relies on clinical experience to determine if the surgery has been successfully completed.

2. The surgeon utilizes intraoperative frozen sections to guide the surgery.

3. The surgeon utilizes intraoperative parathyroid hormone (IO-PTH) testing to guide the surgery.

4. The surgeon utilizes both frozen sections and IO-PTH to guide the surgery.

One of the authors (KBL) recently attended a meeting where surgeons were discussing their various approaches to parathyroid surgery. Within the group there were surgeons who used each of the above four strategies. The opportunity to standardize care and reduce utilization of frozen sections or IO-PTH was clearly apparent. No consensus was obtained. In situations such as this, the pathologist has the opportunity to engage clinicians and potentially to bring them to a consensus on a practice guideline . In most cases such an initiative will take many meetings and attempts at persuasion without any guarantee of success. However, persistence on the part of the pathologist and attempts to build a collaborative evidence-based approach to utilization management initiatives often pays off .

Establish Guidelines for Special Studies Including Immunohistochemistry

Immunohistochemistry has become an essential component of diagnostic surgical pathology . Over the years there has been a continued expansion in the number of immunohistochemical markers that are available for assisting in the diagnosis of tumors and other disorders. Some of these markers are essential to make an accurate diagnosis, whereas others only support what is essentially a diagnosis made on hematoxylin and eosin stained slides. In our histology laboratory, we currently perform over 181 different immunohistochemical tests. Under current reimbursement systems, there is an incentive for pathologists to order more immunohistochemical stains. Although reimbursement rules vary, typically the pathologist gets more reimbursement for each stain ordered (sometimes with a cap on the total number: typically 10). The issue of ordering up-front immunohistochemical studies was described previously. This discussion concerns what stains are normally required to make a diagnosis on different types of tissues. We have observed considerable variation in the utilization of immunohistochemical stains among different pathologists in our department. In general more experienced pathologists order fewer stains than junior faculty and fellows. While some immunohistochemical stains are considered the standard of practice, many stains are optional and are requested at the discretion of the pathologist. Pathologists who are less confident of their diagnostic skills will tend to order more stains than are necessary. This highlights an excellent opportunity for physician profiling and for developing standards of practice in the utilization of immunohistochemistry. As pressures to reduce costs increase, pathologists will need to reassess their utilization of all special studies including immunohistochemistry.

With some exceptions there are no accepted standards for which immunohistochemical studies are appropriate for different types of pathologic diagnoses. The decision is largely left up to the individual pathologist. Developing standards for optimal use of immunohistochemistry across different specimen types represents a significant opportunity for utilization management. Such standards would reduce costs in histology, save pathologists time, and reduce charges to third-party payers .

Molecular Diagnostics

Molecular diagnostics is rapidly becoming an essential component of anatomic pathology and will significantly increase the overall cost of diagnostic services although their impact on patient care may, in some cases, not be well documented. Molecular tests may cost hundreds or even thousands of dollars per specimen. New molecular diagnostic tests and multigene panels are rapidly proliferating and are becoming an integral part of the evaluation of patients with cancer. Developing strategies to manage the appropriate utilization of these new molecular tests will be an important function of the surgical pathologist.

Role of Pathology Professional Societies

Many pathology practices have designed local utilization management initiatives. In the majority of cases, these are not published in medical journals and are therefore not readily available to other practices. Although pathology professional societies such as the College of American Pathologists will occasionally publish general guidelines, these are few in number and are generally well known. For many areas of pathology (e.g., breast, genitourinary, dermatopathology), the best individuals to recommend utilization related guidelines are physicians who subspecialize in these areas of practice. It would be very valuable for pathology professional societies to establish subspecialty practice utilization management committees to develop guidelines in their area of expertise which could then be made available nationally. Further, guidelines that are endorsed by national physician organizations would also afford some degree of protection from medical-legal issues when implemented in individual practices. The US Congress is currently considering legislation under which professional societies can submit practice guidelines for review and approval by the Secretary of Health and Human Services. These guidelines would offer protection for physicians in cases of alleged malpractice [15, 16]. As new technologies and testing modalities are developed, these societies could provide guidance on appropriate utilization. This will become even more important in the near future as a number of companies are starting to offer multigene panels to be used for prognosis or to guide treatment of various neoplasms. As the number of available gene panels proliferates, the utilization and aggregate cost of

these services will increase accordingly though next-generation sequencing may in the future lower the overall cost of care. Lacking national consensus guidelines, many practitioners will find themselves in a very disadvantaged position to control physician requests for testing. Pathology professional organizations should also work actively with third-party payers to develop guidelines for reimbursement of these new genetic tests. A role for pathologists should be developed wherein the local pathologist offers prior approval for these tests and can function as a guide to appropriate utilization .

Developing the Role of the Pathologist in Clinical Care Redesign

Traditionally the role of the anatomic pathologist was to provide a diagnosis on tissue specimens submitted to the laboratory. As described above the changing landscape of reimbursement for professional services will require pathologists to adapt to new roles in which they can provide value to the healthcare system. In many cases the provision of a final pathology report sets off a chain of clinical events in which additional tests are required (such as radiological scans), specialty consultations are obtained, and treatment plans developed. The structure of the information contained in the pathology report should be developed in collaboration with the clinicians who will act on the report. The report should contain all of the necessary information required by the clinician in a concise easy to understand format.

Many clinical services are facing significant capacity constraints due to rising patient volumes and the increasing complexity of care. Unlike the clinical laboratory which can offer STAT services for a large number of tests, most traditional pathology services with the exception of frozen sections are not provided on the same day as the procedure. This necessitates follow-up appointments after the pathology report is available and delays treatment. The practice of histopathology has recently advanced to the point that many small tissue biopsies can be processed and evaluated within hours of the procedure. In practice this capability would permit the clinician to perform the biopsy in the morning and meet the patient for a follow-up visit on the same day streamlining the overall process for both the patient and the physician. Specialty consultations or follow-up studies could also be arranged as necessary on the same day. The Mayo Clinic in Rochester Minnesota has developed a unique approach to same day diagnosis using frozen sections. In

contrast to most pathology practices that provide frozen sections for diagnosis, the Mayo Clinic offers a much more extensive frozen section service in which entire specimens including margins are assessed while the patient is still in the operating room. As one benefit they have reported that re-excision rates for breast lumpectomy cases were reduced to only 4 % of cases. This provides an example of where a pathology service can redesign its workflow to expedite care and reduce utilization of other clinical services. Presumably the service also facilitates planning for future treatment since the process can begin on the same day as the procedure. Pathology practices that take the initiative in promoting efficient care at a reduced cost will be considered valued members of the medical team and will not be easily commoditized or relegated to vendor status when global reimbursement systems become the norm .

Conclusion

In the past anatomic pathologists had little incentive to take a leadership role in utilization management. Reducing the number of specimens examined or eliminating special studies such as immunohistochemistry would have a negative impact on reimbursement for both the technical and professional components. Consequently there have been very few studies on utilization management in anatomic pathology reported in the peer-reviewed literature. As reimbursement systems move away from fee for service toward global payments for care, the incentive structure will begin to change. As this chapter illustrates, there are many well-established examples of utilization management initiatives in anatomic pathology. Planning such initiatives requires an understanding of where the savings will occur and the incentive structure of the various stakeholders including the pathologists themselves, the laboratory, the healthcare network, and the payers. Many of the examples described will reduce costs in the laboratory but could have a negative impact on revenues which currently support the practice. On the other hand, payers do not care about costs incurred in the laboratory. They are only concerned with what they pay. It will be important for pathologists to take visible leadership roles in these efforts as this will strengthen the understanding of clinicians of the value of pathologist s to the overall physician organization. If pathologists are viewed as key leaders in utilization management, their value and income will be insulated from commoditization. Pathologists who

perform a strictly technical role in the review and diagnosis of histopathology specimens may be commoditized and risk losing their practice to a lower priced outside entity. To protect pathologists from placing themselves at risk of medical-legal liabilities , it will be important for pathology professional organizations to develop standards of care around common utilization management activities. These organizations should develop subspecialty expert panels to set standards that are legally defensible while at the same time ensuring that the quality of care is not sacrificed.

References

1. Wilson M, Storfa A. Physician productivity: issues and controversies. Am J Clin Pathol. 2015;143:6–9.
[CrossRef][PubMed]

2. Volk E. College of American Pathologists Advocacy: the effort to preserve fair payment. Arch Pathol Lab Med. 2015;139:161–2.
[CrossRef][PubMed]

3. Seegmiller A, Kim A, Mosse C, Levy M, Thompson M, et al. Optimizing personalized bone marrow testing using an evidence-based, interdisciplinary team approach. Am J Clin Pathol. 2013;140:643–50.
[CrossRef][PubMed][PubMedCentral]

4. Kovach A, DeLelys M, Kelliher A, Dillon L, Hasserjian R, Ferry J, Preffer F, Sohani A. Diagnostic utility of cerebrospinal fluid flow cytometry in patients with and without prior hematologic malignancy. Am J Hematol. 2014;81:978–84.
[CrossRef]

5. Eltoum I, Robertson J. Impact of expected changes in national Papanicolaou test volume on the cytotechnology labor market. Am J Clin Pathol. 2007;128:665–70.
[CrossRef][PubMed]

6. Zarbo R, Nakhleh R. Surgical pathology specimens for gross examination only and exempt from submission. Arch Pathol Lab Med. 1999;123:133–9.
[PubMed]

7. Fitzgibbons P, Clearly K. CAP offers recommendations on selecting surgical specimens for examination. CAP Today. 1996;40.

8. Goss G. Money saving tips for anatomic pathology. Advance for Laboratory Administrators. 2001.

9. Chitkara Y. Upfront special staining for Helicobacter pylori in gastric biopsy specimens is not indicated. Am J Clin Pathol. 2015;143:84–8.
[CrossRef][PubMed]

10. Hartman D, Owens S. Are routine ancillary stains required to diagnose Helicobacter infection in gastric biopsy specimens. An institutional quality assurance review. Am J Clin Pathol. 2012;137:255–60.
[CrossRef][PubMed]

11. Mitchell J. Linkages between utilization of prostate surgical pathology services and physician self-referral. Medicare Medicaid Res Rev. 2012;2:E1–18.
[CrossRef]

12. Ballentine C, Albertsen P, Barry M, Etzioni R, Freedland S. Early detection of prostate cancer: AUA guideline. https://www.auanet.org/education/guidelines/prostate-cancer-detection.cfm. Accessed 3 Feb 2015.

13. Taxy J. Frozen section and the pathologist. Arch Pathol Lab Med. 2009;133:1135–8.
[PubMed]

14. Prey M, Martin S. Guidelines for practical utilization of frozen sections. Arch Surg. 1989;124:331–5.
[CrossRef][PubMed]

15. Jorns J, Daignault S, Sabel M, Wu A. Is intraoperative frozen section analysis of reexcision specimens of value in preventing reoperation in breast-conserving therapy. Am J Clin Pathol. 2014;142:601–8.
[CrossRef][PubMed]

16. Sullivan W. Why “choosing wisely” wont protect you in a lawsuit. Medscape, http://www.medscape.com/viewarticle/837399.

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_17

17. Utilization Analysis in Hematopathology

Annette S. Kim[1] ✉, Claudio A. Mosse[2], Aaron C. Shaver[2] ✉ and Adam C. Seegmiller[2]

(1) Department of Pathology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA
(2) Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, TN 37232-2561, USA

✉ **Annette S. Kim (Corresponding author)**
Email: ASKIM@partners.org

✉ **Aaron C. Shaver**
Email: aaron.shaver@vanderbilt.edu

Unique Challenges in Hematopathology

Utilization management in pathology requires the physician to consider whether a test is necessary and appropriate for the current condition of the patient. This has both medical care implications—how best to detect disease with the highest sensitivity and specificity—and fiscal implications. In an era where reimbursement is tied increasingly to bundled incidents of care or to particular quality measures, unnecessary lab costs must be avoided while adhering to the physician imperative to do no harm.

The field of neoplastic hematopathology has unique characteristics that provide fertile ground for utilization management. This field was one of the

earliest to practice precision medicine, with landmark discoveries such as the BCR-ABL1 rearrangements in chronic myelogenous leukemia in 1960 by Nowell [1] and the FDA approval of imatinib in 2001 [2]. The field has remained at the forefront of precision medicine, and currently many classification categories and treatments are determined either entirely or in part by their underlying genetic lesions [3]. However, with advances in molecular techniques, the number of molecular lesions in all fields of pathology has been burgeoning, and neoplastic hematopathology has remained one of the most highly examined. As the number of molecular aberrations in hematopathology has increased, so too has the number of available tests, including now highly multiplexed assays such as next-generation sequencing panels for somatic mutations in myeloid and lymphoid neoplasms. Moreover, older tests and methodologies remain an ordering option, further complicating test selection. Therefore, testing menus have evolved over time to become increasingly diverse, using ever-more sophisticated technologies whose results require specialized training to interpret.

The wealth of testing options magnifies the risk of ordering inappropriate tests, a type of pre-analytic error, for all possible diagnoses that a clinician may be considering for a given clinical presentation. Since most testing is traditionally ordered by the direct care providers (DCPs, such as clinical hematologists or nurse practitioners), the breadth of the differential based entirely upon clinical factors at the time of ordering may be quite broad, with a correspondingly broad set of potential tests to interrogate each entity.

Hematopathology has always spanned multiple traditional specialties. This is exemplified by the historical and practical complexities of the workflow surrounding the evaluation of bone marrow specimens, which this chapter will use as a case study for utilization management . Historically in some centers, hematologists have assessed peripheral smears and aspirates (fresh cytology fluids), while pathologists reviewed bone marrow biopsies (paraffin-embedded tissues). Over time additional modalities were incorporated into the diagnosis, such as immunohistochemistry and flow cytometry . Today, cytogenetic, molecular, and genomic pathology are also utilized in diagnosis and monitoring of hematolymphoid malignancies . Since these results are produced from various laboratories within a single institution or even from several different institutions (e.g., send-out testing), multiple separate reports are generated and may be found in multiple different

locations in the medical record. The turnaround times for these assays are also quite variable , ranging from hours to days or even weeks. Given this disjointed reporting, clinicians may misinterpret results or the reports may provide conflicting results on the same specimen, both examples of post-analytic errors.

The explosion of test options available to the clinician and the technical intricacies of differing testing methodologies for the same analyte have increased the challenge in selecting and interpreting the proper test for each clinical scenario. To address these pre-analytic and post-analytic testing errors, pathologists have become increasingly integral to test selection and interpretation [4]. However, while pathologists may be the natural advocates of laboratory utilization management, they cannot succeed without strong support and collaboration from clinicians. This chapter will demonstrate one method to implement a hematopathology utilization management system for the evaluation of bone marrow biopsies .

Rules to Redesign Health Care

The fields of medicine and health care delivery have increasingly focused on systems thinking to address the issues of rising health-care costs. In 2001, the Institute of Medicine (IOM) convened a multidisciplinary group, drawing upon expertise in health care and engineering, to optimize the delivery of quality health care [5]. These quality issues focused on the misuse, overuse, and underuse of health-care resources. The goals of applied systems thinking were to improve the safety, effectiveness, efficiency, timeliness, patient-centeredness, and equity of health-care delivery.

Ten rules for the redesign of the health-care system were outlined (Table 17.1) [5]. The rules were based on some common principles, including the appropriate utilization of information technology and the optimization of human-instrument interactions , the use of standardized procedures to minimize the human factors, and the improved communications between health-care teams. This model for the reexamination of health-care processes can be applied specifically to the workflow in hematopathology. Hematopathology presents unique challenges to the ten rules of redesign.

Table 17.1 The ten rules of redesign of health-care systems [5] and the unique challenges presented in hematopathology

Ten rules for redesign	Hematopathology-specific issues
1. Care is based on continuous healing relationships	• Patients cycle between inpatient and outpatient encounters • Patients cycle between multiple direct care providers • Patients specimens are handled by multiple different laboratories within pathology
2. Care is customized according to patient needs and values	• Typical testing panels do not take into account the unique molecular features of the patient's disease • Typical testing panels do not take into account the stage of the disease course
3. The patient is the source of control	• Testing decisions should be with full endorsement and confidence of the patient and the patient's proxy (typically the direct care provider)
4. Knowledge is shared and information flows freely	• Communication is required between the laboratory and the direct care providers • Communication is also required between the different laboratories within pathology, since diagnostic criteria in hematopathology include integration of multiple testing modalities
5. Decision-making is evidence based	• Evidence-based data is lacking for many stages if disease (particularly at times of routine follow-up), relying upon expert opinion in many cases
6. Safety is a system property	• Without uniform testing practices, tests may be overutilized or underutilized • Without uniform reporting, incomplete reports may jeopardize care
7. Transparency is necessary	• It is difficult to track what testing has been performed, especially when the list of tests ordered may vary from care provider to care provider and from patient encounter to encounter • Results of testing may appear in a multitude of different reports which may be found in various locations in the medical record
8. Needs are anticipated	• Unexpected findings in the marrow study that the direct care provider could not have anticipated may be identified that could affect testing decisions
9. Waste is continuously decreased	• Without tracking testing practices, there is no way to continuously improve the quality of care
10. Cooperation among clinicians is a priority	• In order for consensus practice decisions to be made, the direct care providers and all laboratorians/pathologists need to be working with a common harmonious goal of patient care, with complete understanding of what tests need to be performed and which portions of the decision-making process lie with which parties

1. *Care is based on continuous healing relationships*. In practice , there is discontinuity of patient care for patients with hematologic malignancies. Patients are often seen by a series of DCPs as they cycle

between inpatient and outpatient services as per the requirements of their disease care. The pathologists that evaluate the patient specimens, particularly in larger centers, cycle between different services as well, and a single individual may not see the same patient's material over time. In addition, due to the complex physical and logistical organization of the many individuals and laboratories involved in evaluating a bone marrow, a number of different physicians may see one bone marrow specimen for separate aspirate cytology , biopsy histology , flow cytometry , karyotype , fluorescence in situ hybridization (FISH) , and various molecular pathology testing platforms ranging from single target allele-specific assays to broad next-generation sequencing panels. Thus, in both direct patient care and in the laboratory, the number of individuals responsible for the care of the patient varies over time and health-care function .

2. *Care is customized according to patient needs and values*. At many institutions , a set panel of tests are ordered for a given disease type. This ignores the unique characteristics of the patient's neoplasm and disease course. For instance, certain molecular markers may be seen in a given disease, but an individual patient's neoplasm may only demonstrate a few of those variants. This is further complicated by the fact that some of these variants may be seen in only a subset of the neoplastic cells and that the techniques for following these markers to monitor residual disease may be quite varied in their analytical sensitivities. In addition, different stages of a patient's disease course may require different types of testing, such as differences in testing at diagnosis versus follow-up or pre- versus post-stem cell transplantation (SCT) .

3. *The patient is the source of control*. Ideally, this is a tenet followed throughout medicine. However, when it comes to the determination of which laboratory tests are most appropriate for the patient, typically the ordering clinician acts as the patient's proxy. Therefore all testing decisions, especially if determined after the sample reaches the laboratory for reflex testing, must be with full endorsement and confidence by the patient's primary health-care provider .

4. *Knowledge is shared and information flows freely*. Since the diagnosis of numerous hematolymphoid neoplasms requires the incorporation of not only histologic findings but also clinical, molecular, genetic, and immunophenotypic data, a complete diagnosis cannot be rendered until all the data is aggregated and interpreted as a group . Data from the clinic as well as numerous laboratories within the pathology must be collectively interpreted. Making sure all the data is available for integration is paramount in hematopathology. Moreover, sharing knowledge requires assuring that the results from various tests are easily and quickly available for review by anyone on the health-care team. Collating that data in one site that is easily found and reviewed meets that expectation .

5. *Decision-making is evidence based*. If certain tests are appropriate for only a particular disease and disease state, the pathologist must ascertain the disease state with the most pretesting information possible. In addition, the clinical utility of each test for its stated purpose should also be considered. The pathologist should use published evidence where it is available. However, in many facets of hematopathology, evidence-based testing recommendations are lacking. The vast majority of the hematopathology literature is focused on diagnostic recommendations, rather than disease monitoring, limiting the base of evidence for many testing practices to “best practices .”

6. *Safety is a system property*. Safety concerns that may arise even with quality pathology review lie in the “human factor.” These include both the underutilization of necessary testing and the overutilization of unnecessary testing. In addition, pathology reports may provide an avenue for omitted or misrepresented data. These latter issues may be especially true with pathologists who do not routinely see hematopathology cases .

7. *Transparency is necessary*. In practice , it is often a challenge both for pathologists and DCPs to know what tests have been ordered and what the status of those tests may be. Further complicating this issue, testing

that impacts hematopathology may be the product of multiple different laboratories with different turnaround times and different reporting locations within the medical record .

8. *Needs are anticipated*. Although DCPs know in detail the clinical status of their patients, it is impossible for them to know the cellular content of their patients' bone marrows, necessitating a microscopic analysis of the tissue. Therefore, it is correspondingly difficult for a DCP to anticipate the appropriate testing prior to the morphologic review of the marrow. DCPs therefore either cast a broad net through testing, some of which may not be relevant to the patient's disease state, or run the risk of omitting the critical test appropriate for the marrow findings. Both impact the quality of cost-effective medicine .

9. *Waste is continuously decreased*. Without tracking testing practice , there is no way to identify potential areas for waste elimination. In most hematopathology practices, there is no ongoing record of testing activities, precluding iterative quality improvement. In addition, hematopathology is a rapidly evolving field, with increasing emphasis upon new molecular markers of disease and a concomitant rapid evolution of testing practices. This scenario is ripe for potentially wasteful testing if too much flexibility is allowed in ordering practices and for the omission of new clinically validated markers if ordering restrictions are too strict.

10. *Cooperation among clinicians is a priority*. The clinicians on the front line of direct patient care as well as the clinicians in the laboratories must make a cohesive team for optimal patient care. There must be a harmonious understanding of the clinical value of each test. In addition, there must be agreement on which practitioner is best positioned to provide the various facets of patient information required to make educated testing decisions. In addition, informaticians need to work closely with both groups to ensure that the information technologies meet the needs of each individual group and provide the communication tools required for the groups to work together .

Diagnostic Management Team Approach to Hematopathology

At Vanderbilt University Medical Center (VUMC) , three groups—pathologists/laboratorians (including those involved in hematopathology, immunopathology, cytogenetics, and molecular diagnostics), DCPs (hematologists and hematology nurse practitioners), and biomedical informaticians—comprise the core of the diagnostic management team (DMT) in hematopathology. The DMT was developed as a way to incorporate all ten of the IOM rules of health-care system redesign to create a cohesive and transparent team approach to patient care.

A key mission of the DMT is to maximize the pretesting information available to guide appropriate testing practices. In conventional practice, the primary patient care team (hematologists and hematology nurse practitioners) typically orders tests prior to morphologic review of the specimen. However, since morphologic data can markedly modify the differential diagnosis and thereby significantly influence test selection, a pathologist-driven testing model may refine the selection of tests in many cases. The DMT combines information about the clinical scenario with the morphologic and immunophenotypic findings of the marrow study prior to making testing decisions. The combination of all this information determines the assignment of a clinicomorphologic decision point (CMDP) for testing. A CMDP is essentially the patient's disease, and the point in therapy (new diagnosis, relapse, remission, etc.) at which the current patient encounters occurs. In all clinical testing, the positive predictive value of a test is maximized by increasing the prevalence of disease. In the case of bone marrow-associated testing, knowing the true clinical and morphologic disease status prior to testing increases the value of any appropriate testing.

This DMT approach involved creating teams of DCPs and laboratorians that together decided upon the appropriate testing practices surrounding each disease category at each CMDP within the neoplastic hematopathology. The development and maintenance of these mutually agreed-upon standard ordering protocols (SOPs) represent one of the main activities of the DMT (Fig. 17.1). This allows the pathologist to order agreed-upon sets of tests after integrating both the clinical information provided by the electronic medical record and the DCP with the actual marrow findings, whether those findings

be diagnostic/overt or for residual disease testing.

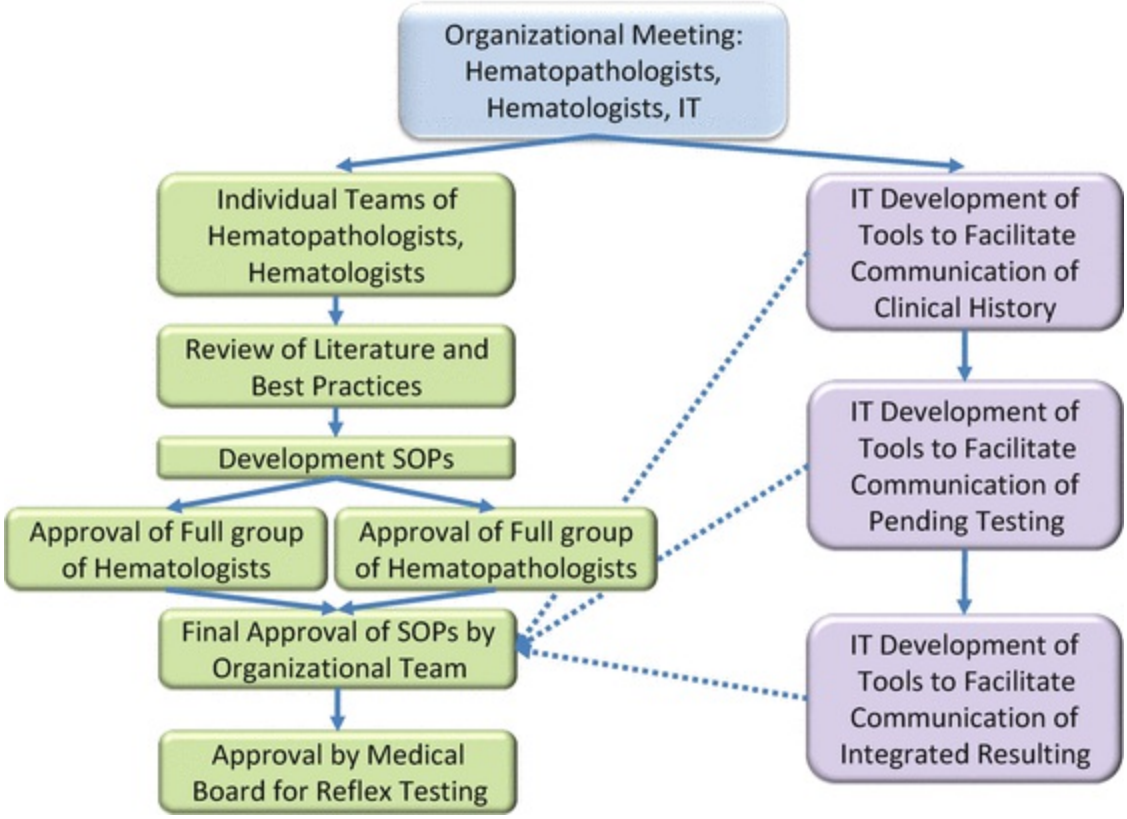


Fig. 17.1 Schematic of the parallel development of the standard ordering protocols (SOPs) and information technology (IT) tools for the DMT

In order to enhance the communication between the patients, the DCPs, and the pathologists and pathology laboratories, the DMT developed a number of informatics tools (see Sect. 3.2 below). These included online ordering forms and clinical history flow sheets to facilitate communication of the clinical history to the laboratories. To enable communication on which tests were ordered on a given bone marrow specimen as well as the status of those tests, dashboards displaying testing status were created in the electronic medical record (EMR) rather than the laboratory information system (LIS) so that it would be accessible to all parties. Finally, the DMT group designed new synoptic or structured morphologic reports, as well as comprehensive reports. The latter compile in a single place all the results associated with a single bone marrow specimen and synthesize an overarching interpretation. These informatics tools represent the second activity of the DMT (Fig. 17.1). Through these means, all members of the clinical care teams can be reassured

that the testing appropriate for the patient is being performed while minimizing unnecessary testing .

Development of the SOPs

The development of disease-specific SOPs is a fundamental building block for the DMT. These SOPs are applied to each disease , taking into account both the stage of therapy and the pathologist's initial morphologic review of the bone marrow specimens. The implementation of the SOPs allows for an agreed-upon set of tests to be ordered by the pathologist rather than the DCP using the shared knowledge of the patient's disease, the patient's stage of therapy, and the pathologist's initial review of morphology (CMDPs). Ancillary testing practices for each disease category must be extensively researched by teams of collaborating hematologists and pathologists.

At VUMC , the DMT focused initially on optimizing the testing for bone marrow biopsies , since the operational workflow for these specimens was the most uniform. In the first iteration, seven teams were formed, each dedicated to one of seven most common disease categories for which bone marrow biopsies are ordered. SOPs were generated for acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) together, bone marrow failure syndromes , myeloproliferative neoplasms , lymphoma , plasma cell neoplasms , and acute lymphoblastic leukemia/lymphoma (B and T, considered separately). These disease entities represent approximately 95 % of all adult bone marrow cases at VUMC . Subsequent iterations of this process have redefined these categories, as some disease entities proved to be best handled by the SOPs in their own specialized categories. However, it should be noted that each institution should examine its own case distribution and testing practices to form these teams in an institution-appropriate manner.

The teams identified all relevant evidence-based recommendations for the utilization of any given test at given stages of a disease course. Published literature and guidelines for testing in certain disease categories formed the basis of these SOPs. Recommendations are available through the National Comprehensive Cancer Network (NCCN), bone marrow transplantation or clinical trial requirements, and various professional societies with dedicated educational missions such as the College of American Pathologists (CAP) , the Association for Molecular Pathology (AMP) , and the American Society for Clinical Pathology (ASCP) . In addition, validation documentation on the clinical utility of tests is required for accreditation agencies such as the

College of American Pathologists (CAP) , Clinical Laboratory Improvement Amendments (CLIA) , Joint Commission in Accreditation of Healthcare Organizations (JCAHO) , individual state accreditation programs, and potentially the US Food and Drug Administration (FDA) . These recommendations are considered level 1 and level 2 evidence, considered the best forms of evidence in the hierarchy of evidence-based medicine (see Fig. 17.2), and formed a minimal base for testing standardization.

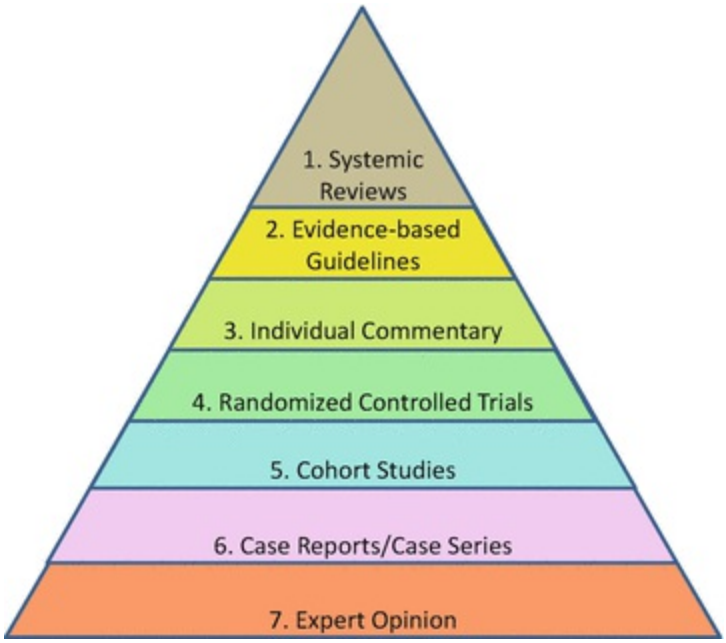


Fig. 17.2 Levels of evidence . Levels 1–3 contain compiled data, while levels 4–6 represent primary data. Level 7 represents expert opinion that may be based on best clinical practice and experience, but does not rely upon validated data (adapted from the EBM Pyramid and EBM page Generator, © 2006 Trustees of Dartmouth College and Yale University)

However, there is a paucity of medical literature with strong evidence-based data or published guidelines for many lab tests at particular CMDPs . While much of the literature is devoted to appropriate studies to be performed at diagnosis or relapse, the literature on testing when there is no morphologic evidence of disease, including bone marrow biopsies for therapy monitoring and pre- and post-stem cell transplantation (SCT) , is often less clear. Moreover, much of the literature is focused on proving that a particular test shows clinical validity, rather than demonstrating superior clinical utility over alternative tests (as an extreme example, leukocyte alkaline phosphatase staining score does detect chronic myeloid leukemia, but qPCR is preferred). The SOP teams, therefore, also included recommendations based upon best

clinical practice and mutually agreed upon community standards. However, these latter represent simply expert opinion , considered the lowest level of evidence (Fig. 17.2, level 7).

Interestingly, every SOP team at VUMC independently came to very similar conclusions about how to define relevant CMDPs. Since there were relatively well-defined recommendations on testing at initial diagnosis and moderately defined support for testing practices at relapse, these two CMDPs were created. In later iterations, persistent disease (i.e., multiple encounters with continued disease) became a CMDP as well. All of these were collectively grouped together as “overt disease” categories. A “no overt disease” CMDP might include multiple encounters during routine follow-up of the treated patient with testing focused on minimal residual disease detection with possible inclusion of specific testing required related to the pre- or post-SCT setting. Within this basic framework, individual adaptations were required for certain disease types with additional distinct CMDPs . For instance, negative staging bone marrows for lymphoma were separated from bone marrows with overt involvement by lymphoma . In addition, the other CMDPs were then segregated by whether or not lymphomatous involvement was ever present in the marrow.

There are two general paradigms that have been explored for these SOPs (Fig. 17.3). The first creates a two-dimensional array of diseases by CMDPs with the appropriate testing panel designated for each point in the array (Fig. 17.3a). While this array is quite intuitive, it does not take into account the elements of data that contribute to the decision of which CMDP is relevant, and testing options within each point of the array may vary depending upon the patient’s prior testing results . Therefore, for clarity and ease of automation, a decision tree model may be more helpful, with branching logic for each key question in the assignment of the correct CMDP (Fig. 17.3b). While some of the questions require clinical and historical input, others require morphologic assessment, and these contributions are clearly discriminated in the decision tree model.

a

Disease	Diagnosis	Staging	Follow-up (Overt Disease)		Follow-up (No Overt Disease)		Post-SCT
			Persistent Disease	Relapse	New Patient	Routine (MRD)	
1. AML							
2. MDS							
3. BM Failure							
4. MPN							
5. B-ALL							
6. T-ALL							
7. Lymphoma							
8. Myeloma							

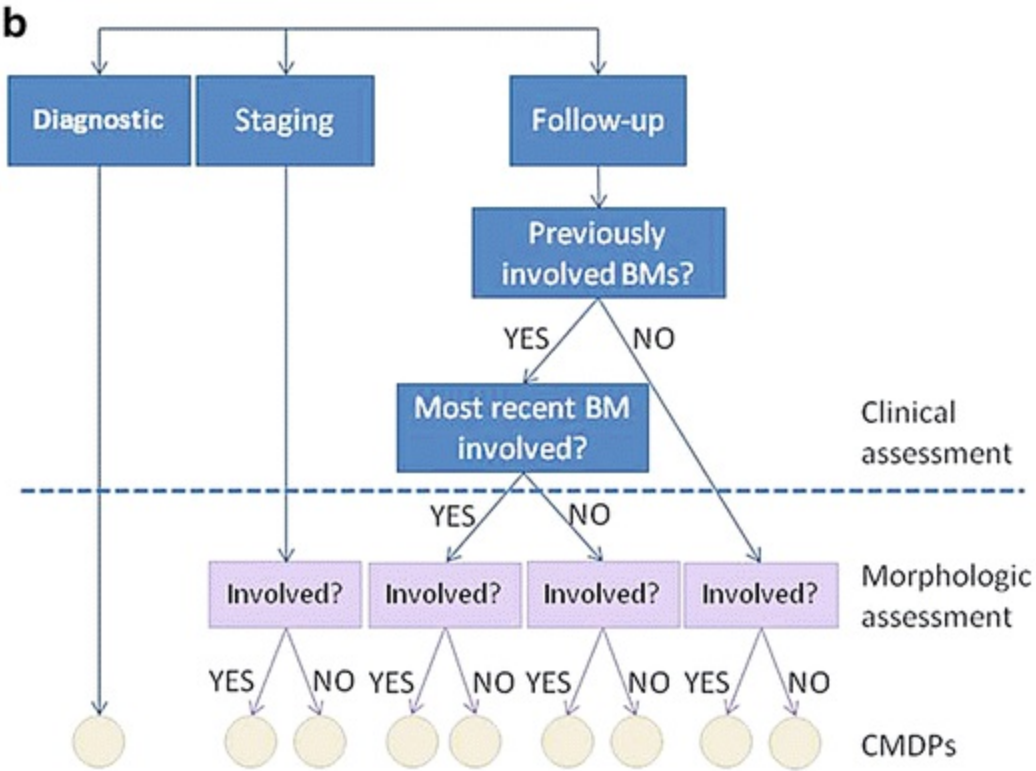


Fig. 17.3 (**a**) Example of a two-dimensional array of hematopoietic malignancies and clinicomorphologic decision points (CMDPs in *gold*). (**b**) Example of a decision tree for the determination of clinicomorphologic decision points (CMDPs in *gold*) with clearer separation of the pre-procedure input information (clinical assessment, *blue*) and the morphologic assessment (*lavender*)

Several guiding principles were applied to the determination of appropriate testing for any given disease at any given CMDP (Table 17.2). Within the overt disease category, tests should be ordered at initial diagnosis if they demonstrate clinical utility for diagnosis, prognosis, therapy, or future disease monitoring. At relapse, however, only therapeutic or future disease monitoring concerns are most salient, as diagnosis is already established, and most disease is already considered poor prognosis at that time. Although some additional prognostic information may still be helpful moving forward, these are most relevant in the context of informing future therapy from the time of relapse (such as acquisition of a mutation that would indicate a need for transplantation or refractoriness to certain therapies). Finally, in cases of morphologically persistent disease, testing should be ordered only if there is some clinical reason to suspect a change in mutational status that would affect therapy decisions. Tests at follow-up time points with no overt disease should be ordered only if they (1) were positive in the most recent marrow with overt disease, (2) are sufficiently sensitive for residual disease detection (i.e., better analytical sensitivity than morphologic and routine immunophenotypic studies), and (3) represent the most analytically sensitive testing modality (if there is more than one modality of testing).

Table 17.2 Purpose of testing for key clinicomorphologic decision points

		Purpose of testing				
	Time point	Diagnosis	Prognosis	Therapy	Routine residual disease monitoring	Chimerism monitoring
Overt disease	Diagnosis	+	+	+	+	
	Relapse			+	+	If applicable[a]
	Persistent Dz			±		If applicable[a]
No overt disease	Routine follow-up				+	If applicable[a]

[a]If applicable = after allogeneic stem cell transplantation

At VUMC, the full committee of hematologists and pathologists, including representatives from molecular pathology and cytogenetics laboratories, reviewed and approved the recommendations from each disease-specific team prior to implementation. Each of the seven disease categories underwent a similar development process with multiple rounds of evidence-

based discussion, group presentations , and revisions. Because the implementation of SOPs also easily allows for iterative refinement of the SOPs themselves, the DMT chose to implement initially an overly inclusive set of tests with the promise of subsequent improvement by recursive data analysis (see section Iterative Rapid Learning System (Quality Improvement)).

The utility of SOPs is multifactorial, directly addressing many of the IOM rules (Table 17.1). The assignment of CMDPs is critical to customizing care to the true clinical stage of the patient's disease course (rule #2)—truly personalized medicine . In addition, the CMDPs are designed to take into account the individual molecular features of the patient's neoplasm as well (rule #2). The use of SOPs effectively extends empowerment to the pathologists to act directly on the patient's behalf, becoming the surrogate for patient-centered control of their clinical care (rule #3). This can only be achieved through the mutual agreement and collaboration of patients with their DCPs and the DCPs with the laboratorians (rule #10). The testing decisions of each CMDP are evidence based wherever possible (rule #5). Safety is addressed by the uniformity of the testing algorithms to minimize overutilization and minimize underutilization (rule #6). Finally, the ability of the SOPs to readily adapt to unexpected findings the marrow addresses also addressed rule #8. Therefore, the use of SOPs remakes clinical hematopathology practice according to IOM recommended standards .

Development of Informatics Tools

Informatics tools, although not essential to the DMT , can greatly optimize the workflow and information transfer processes while simultaneously minimizing error. These tools facilitate and document the initial communication of clinical history from the clinician to the pathologist (online ordering forms), the interrogation of the patient medical record by the pathologist (clinical flow sheets), the communication from the pathologist to the clinical team of which ancillary tests are being ordered for the patient and the tracking of the status of those studies (dashboards of pending tests), the standardization of the report output (synoptic or structured reporting), and the communication of different laboratory findings to the clinical team as individual reports as well as in an aggregated form with a comprehensive interpretation (comprehensive reports). In the process of implementing the DMT, development of these tools ideally may proceed in parallel to the

development of the SOPs , as the precise requirements and structure of these tools will often be informed by the needs of the DMT participants (Fig. 17.1).

Online Ordering Forms

The utilization of electronic ordering forms provides a measure of quality control to the ordering process by mandating the type of patient information required to provide adequate clinical context to the pathologist, addressing IOM rules on knowledge sharing and cooperation (rules #4 and 10, respectively). The benefit of specialized ordering forms is that the DMT process may depend on different information than is usually provided in the context of a pathology interpretation. Because the SOP depends on both determining the current state of disease and a detailed knowledge of the patient's diagnostic and testing history, required data should include information about the diagnosis and the previous genetic and molecular aberrations that characterize the patient's disease. In addition, critical information about the state of the patient's disease , including current treatment (particularly those modalities that may affect the results or interpretation of ancillary testing, such as cytotoxic chemotherapy , targeted inhibitors, or growth factors), and relevant details of any SCT, such as type (reduced intensity or myeloablative) and date of transplant, should be included. Finally, the form should include mention of any clinical concerns about the status of the patient, e.g., whether this is a routine follow-up marrow, or if the patient has recently dropping counts or displays failure of count recovery after chemotherapy. Including this data ensures that the pathologist customizes test ordering for that particular patient (rule #2). The form also allows the clinical team to mandate specific tests regardless of the morphologic findings, based upon their clinical concern or clinical trial requirements. This encourages continued empowerment of the DCPs to represent their patients where certain testing needs are not clear from the clinical history (rule #3). For the pathologist, this context allows them to understand the context of specific testing ordered outside of the confines of the SOP and perhaps guide or suggest additional or more appropriate testing once the CMDP has been determined.

Clinical Flow Sheets

Clinical flow sheets in the EMR may be used as a way to visualize the important longitudinal information about a patient's entire hematopathologic

history quickly and succinctly, rather than in multiple documents in multiple locations. Given the frequent discontinuity of clinical care in hematology (*vide supra*), a shared timeline display can provide continuity to the entire team (rule #1). By tying the flow sheet to the EMR rather than to a disconnected database, the information displayed is guaranteed to remain up to date as relevant clinical information is added, and pathologists and DCPs have access to the same pool of information. Moreover, at the time of the morphologic review of the current specimen, the pathology team can easily supplement the clinical data from the electronic ordering form as needed, which is particularly important in complicated cases or patients with a history of multiple previous tests. By its very design, this system promotes transparency of clinical care (rules #4 and 7) (Fig. 17.4).

	2/1/2015	2/15/2015	2/29/2015	5/1/2015	8/1/2015	11/1/2015	12/1/2015
Comprehensive Diagnosis	Acute myeloid leukemia (47% blasts) with NPM1 and FLT3-ITD mutations	Low level involvement by acute myeloid leukemia by cytogenetic and molecular studies	1) Complete remission marrow 2) No morphologic, immunophenotypic, cytogenetic or molecular evidence of leukemia 3) ANC = 3.89, PLT = 390	1) Complete remission marrow 2) No morphologic, immunophenotypic, cytogenetic or molecular evidence of leukemia 3) ANC = 4.21, PLT = 415	1) Complete remission marrow 2) No morphologic, immunophenotypic, cytogenetic or molecular evidence of leukemia 3) ANC = 3.59, PLT = 387	1) Complete remission marrow 2) No morphologic, immunophenotypic, cytogenetic or molecular evidence of leukemia 3) Fully engrafted marrow (0% Recipient DNA) 4) ANC = 5.32, PLT = 323	1) Recurrent acute myeloid leukemia (24% blasts), NPM1+, FLT3-ITD+ 2) Incompletely engrafted marrow (12% Recipient DNA)
Cytogenetics	46,XY,del(9)(q13q22)[12]/46,XY[8]	46,XY,del(9)(q13q22)[2]/46,XY[7]	46,XY[20]	46,XY[20]	46,XY[20]	//46,XX[20]	46,XY,del(9)(q13q22)[5]//46,XX[15]
FISH	Normal for the tested MDS and AML panels						
NPM	Detected	Detected	Not Detected	Not Detected	Not Detected	Not Detected	Detected
NPM Allelic Ratio	0.73	0.07					0.18
FLT3-ITD	Detected	Detected	Not Detected	Not Detected	Not Detected	Not Detected	Detected
FLT3-ITD Allelic Ratio	0.12	0.03					0.19
CEBPA	Not Detected						
C-KIT	Not Detected						
Chimerism						0% Recipient	12% Recipient
WBC	24.3	0.1	10.6	8.6	8.2	9.5	10.2
ANC	0.4	0	3.89	4.21	3.59	5.32	1.2
Hgb	10.5	8.4	11.2	12.4	11.9	11.7	6.8
PLT	46	20	390	415	387	323	107

Fig. 17.4 Example of a patient flow sheet . Clinical pathology encounters are listed in chronological order across the top, while different testing results are listed along the Y axis. Of note, the list of tests included on the flow sheet is flexible and may change as testing modalities evolve

Synoptic or Structured Reporting

Structured reporting, most often implemented in the context of pathologic

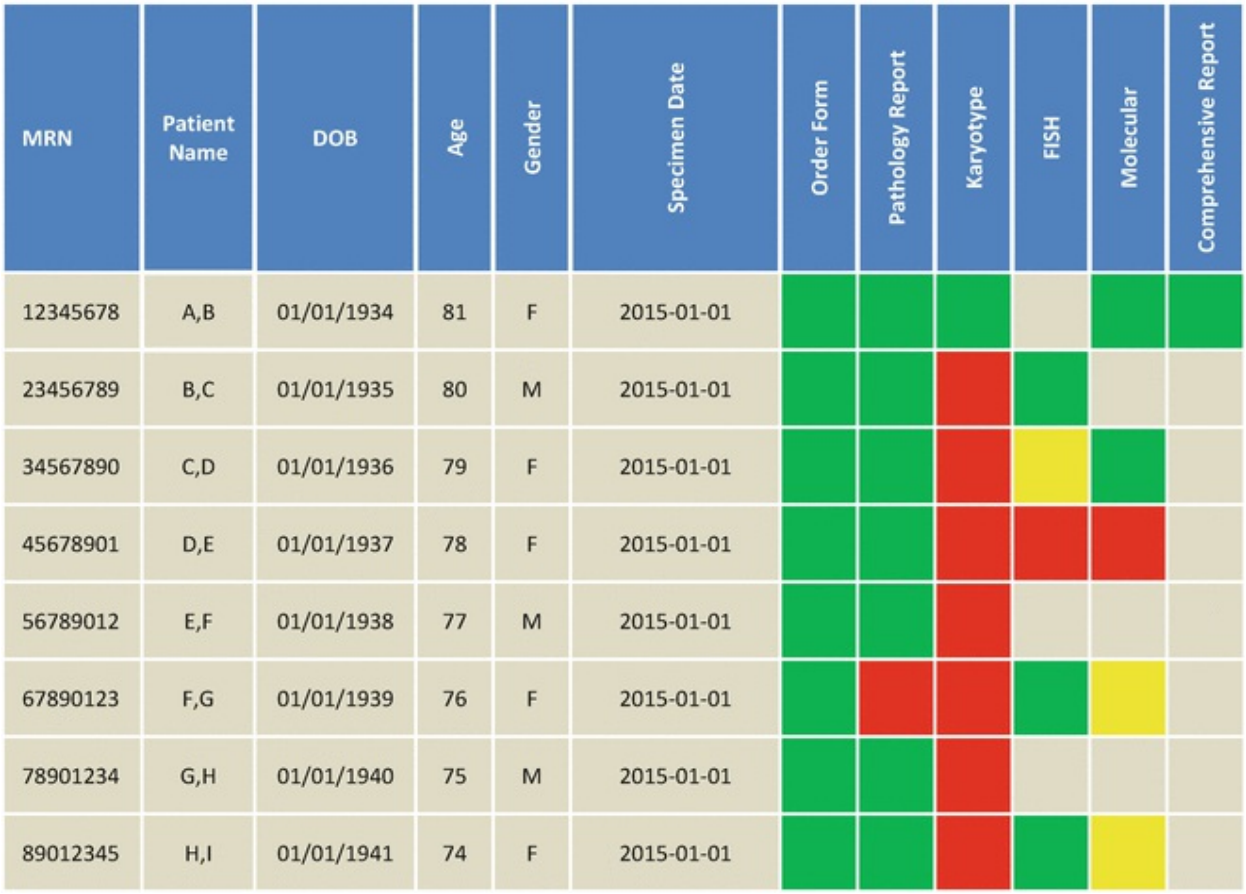
reports in the style of the CAP-recommended synoptic reports, is a vital part of the DMT process for at least two distinct reasons. First, it enforces uniformity in the information that is included in the report. This ensures that the report meets not only the quality requirements mandated by external accrediting agencies such as JCAHO or the CAP but also the needs of the DMT process, by documenting the determination of the CMDP at the level of detail necessary for proper implementation of the SOP. With a properly designed structured report, a wide variety of pathologists can create reports without jeopardizing the ability of any given report to feed into the DMT process for future encounters with that patient. Because information is provided in the same location every time, structured reporting promotes communication between clinical care teams (rule #4) and provides structure to minimize the risk of inadvertent omission of critical information (rule #6). Structured reporting may also be designed to ensure transparent documentation of any pending ancillary testing, an important element of communication with the clinical care teams as well as within the laboratory (rule #7). A beneficial by-product of this uniformity, particularly in academic medical institutions, is that the structured report can serve as a useful didactic model for teaching trainees or practicing pathologists unfamiliar with the DMT system .

Second, structured reporting greatly simplifies the process of parsing the report into discrete data elements for storage in a database, which is a vital part of the iterative nature of optimizing the DMT (rule #9). This is an area where traditional synoptic reporting in the style encouraged by the CAP falls short and where more specialized tools provide a powerful opportunity. Rather than a “fill-in-the-blank” style synoptic report, where the contents of the data fields can be recorded but do not necessarily conform to predefined values, custom data structures can be developed that allow very detailed parsing and storage of data elements , with minimal user input necessary.

Pending Lists

These electronic tools allow clinicians and laboratorians alike to have real-time access to the status of all pending testing, another important element in communication between health-care teams (rule #4) (Fig. 17.5). While pending tests may be readily identifiable within the laboratory information systems (LIS) of most laboratories , the DCPs typically do not have access to

the LIS. By embedding the pending lists in the EMR, it is accessible to all participants in the DMT process (rule #7). Additionally, by collecting the pending lists for a set of patients in one place (Fig. 17.5), it is easier for the pathologist to manage the process of creating and updating comprehensive reports in a timely manner. Pending lists may also be useful to the laboratories as an additional quality control measure of turnaround times, a CAP requirement .



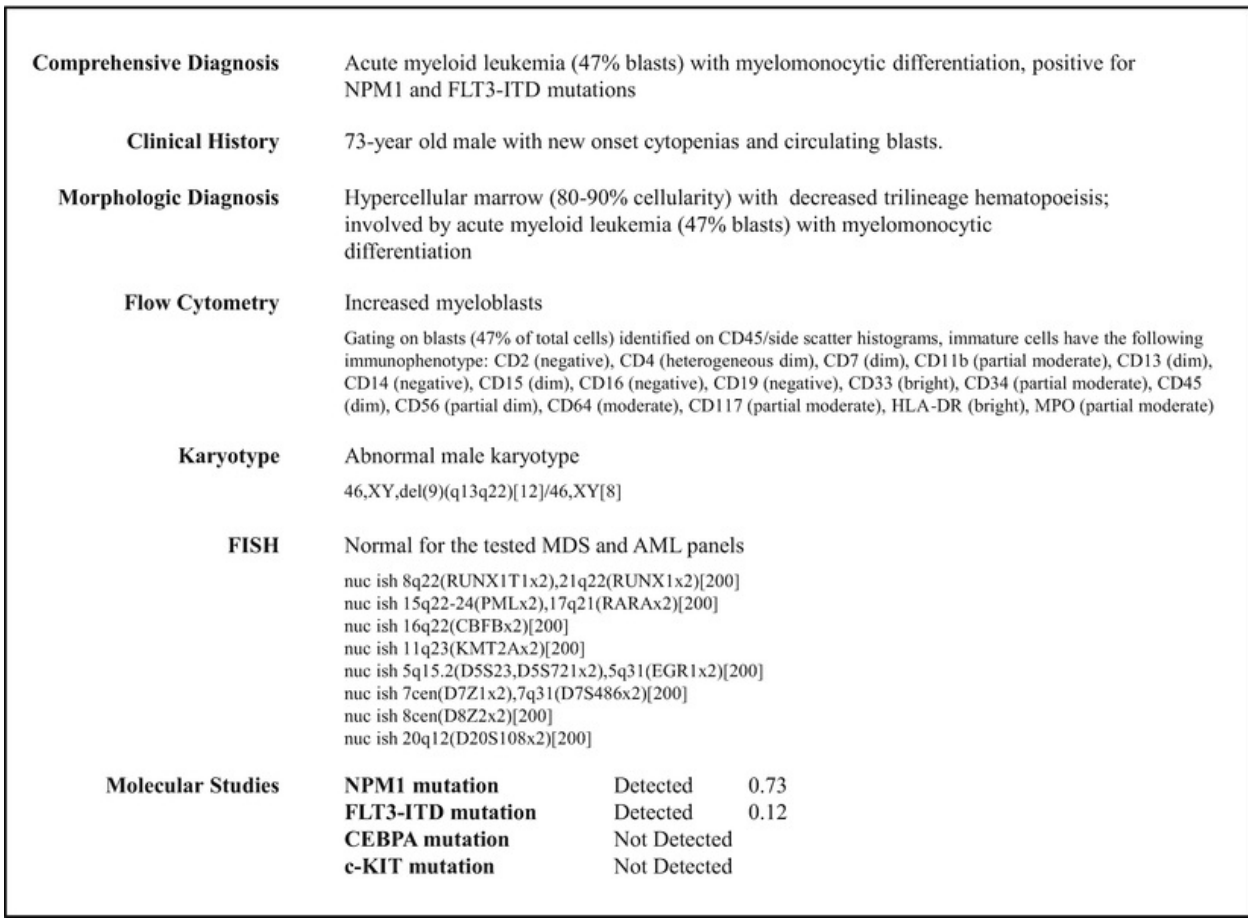
MRN	Patient Name	DOB	Age	Gender	Specimen Date	Order Form	Pathology Report	Karyotype	FISH	Molecular	Comprehensive Report
12345678	A,B	01/01/1934	81	F	2015-01-01						
23456789	B,C	01/01/1935	80	M	2015-01-01						
34567890	C,D	01/01/1936	79	F	2015-01-01						
45678901	D,E	01/01/1937	78	F	2015-01-01						
56789012	E,F	01/01/1938	77	M	2015-01-01						
67890123	F,G	01/01/1939	76	F	2015-01-01						
78901234	G,H	01/01/1940	75	M	2015-01-01						
89012345	H,I	01/01/1941	74	F	2015-01-01						

Fig. 17.5 Example of a pending list which reflects the status of testing. The *green* color indicates that a final report is available. *Red* indicates that a result or report is pending. *Yellow* indicates that some tests within that category have been resulted and some are still pending (e.g., multiple molecular tests have been requested and only some are complete). Panels can be created on demand, according to the needs of the creator; for a pathologist, it might represent all the bone marrows reviewed on any given period of time on service. For a direct care provider, it might represent their clinic or inpatient team list

Comprehensive Interpretation

Finally, informatics tools can be designed to facilitate the creation of comprehensive reports that bring all the available data—clinical,

morphologic, immunohistochemical, flow cytometric, cytogenetic, FISH, and molecular—in one place to create a final summative diagnosis (Fig. 17.6), enabling clear communication of all the data to all clinical teams (rule #4). A final diagnosis at all stages of disease in hematopathology is dependent upon the incorporation of critical ancillary testing data, in particular molecular genetic diagnostic or prognostic categories and various molecular and flow cytometric measures of residual disease. To serve this purpose, the comprehensive diagnosis tool is created to be flexible and incorporate multiple modalities of clinical and laboratory evidence, as indicated by the CMDP of the patient (rules 2 and 5).



Comprehensive Diagnosis	Acute myeloid leukemia (47% blasts) with myelomonocytic differentiation, positive for NPM1 and FLT3-ITD mutations		
Clinical History	73-year old male with new onset cytopenias and circulating blasts.		
Morphologic Diagnosis	Hypercellular marrow (80-90% cellularity) with decreased trilineage hematopoeisis; involved by acute myeloid leukemia (47% blasts) with myelomonocytic differentiation		
Flow Cytometry	Increased myeloblasts Gating on blasts (47% of total cells) identified on CD45/side scatter histograms, immature cells have the following immunophenotype: CD2 (negative), CD4 (heterogeneous dim), CD7 (dim), CD11b (partial moderate), CD13 (dim), CD14 (negative), CD15 (dim), CD16 (negative), CD19 (negative), CD33 (bright), CD34 (partial moderate), CD45 (dim), CD56 (partial dim), CD64 (moderate), CD117 (partial moderate), HLA-DR (bright), MPO (partial moderate)		
Karyotype	Abnormal male karyotype 46,XY,del(9)(q13q22)[12]/46,XY[8]		
FISH	Normal for the tested MDS and AML panels nuc ish 8q22(RUNX1T1x2),21q22(RUNX1x2)[200] nuc ish 15q22-24(PMLx2),17q21(RARAx2)[200] nuc ish 16q22(CBFBx2)[200] nuc ish 11q23(KMT2Ax2)[200] nuc ish 5q15.2(D5S23,D5S721x2),5q31(EGR1x2)[200] nuc ish 7cen(D7Z1x2),7q31(D7S486x2)[200] nuc ish 8cen(D8Z2x2)[200] nuc ish 20q12(D20S108x2)[200]		
Molecular Studies	**NPM1 mutation**	Detected	0.73
	FLT3-ITD mutation	Detected	0.12
	CEBPA mutation	Not Detected	
	c-KIT mutation	Not Detected	

Fig. 17.6 Example of a comprehensive report that incorporates in one place a summary of all the results obtained on a single bone marrow study, tied together by an interpretive summary that includes all the data. Ideally the results from all other reports would be automatically merged (autopopulated) into the comprehensive report to minimize transcription error and time. The type of data included can range from binary values (detected/not detected) to complex text strings like flow immunophenotype to panels of testing such as the results of next-generation sequencing

Iterative Rapid Learning System (Quality Improvement)

An important feature of the DMT is the ability to utilize accumulated data through the DMT process to guide further refinements of the SOPs such that waste is continuously decreased (rule #9). In many ways, this follows the PDSA (plan-do-study-act) model of quality improvement that allows rapid cycle improvement for improving processes or implementing changes (Fig. 17.7) [6]. After implementation of the DMT, test utilization and results are monitored carefully and studied, so that further actions may be taken. In the case of the hematopathology DMT, data on the clinical utility of the results of certain tests are monitored to determine if their utilization is warranted. This is particularly critical when published data regarding the clinical validity of certain tests at specific CMDPs are lacking. This iterative process enables each institution to study the efficacy of their own testing practices in their clinical/institutional environment and, based upon that data, to determine if tests may be removed from the SOPs . In essence, each institution can create its own cohort studies in support of their testing practices (Fig. 17.2, level 5 evidence). In addition, the continuously evolving nature of the SOPs also easily permits the addition of tests as literature provides evidence for their utility or as new molecular genetic aberrations become known.

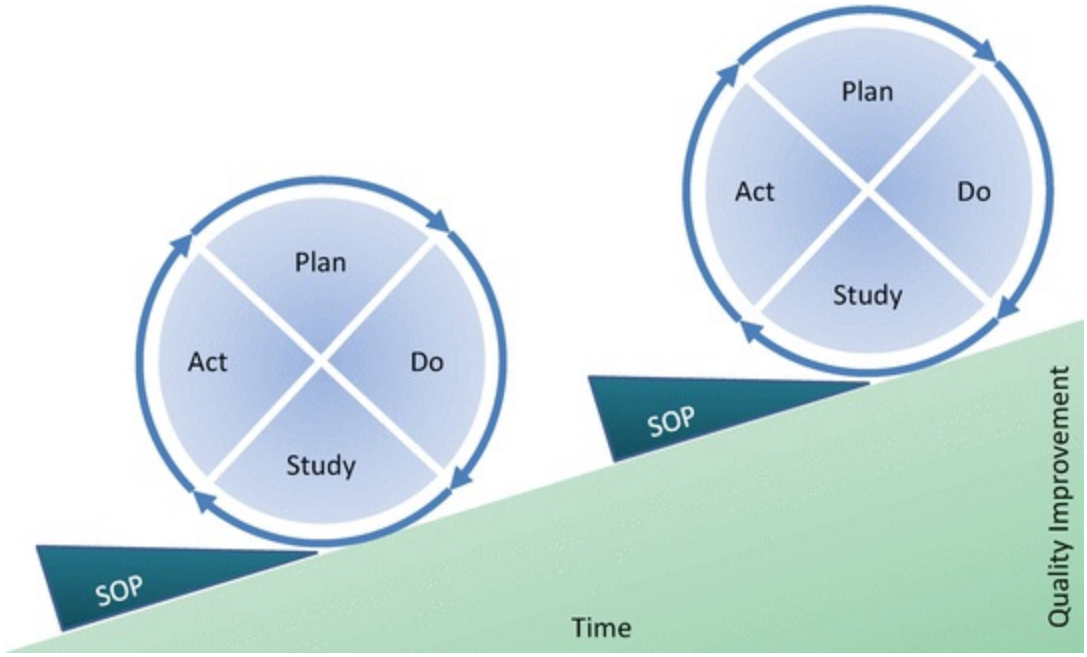


Fig. 17.7 Long-term quality improvement with the DMT. With each iteration of the SOPs, new data is acquired about testing practices and results. This data is in turn used to plan and implement the next iteration with successive improvement in the quality of testing practices over time. In addition, this iterative process enables the flexible incorporation over time of additional biomarkers as they are demonstrated to have clinical utility (adapted from https://en.wikipedia.org/wiki/PDCA#/media/File:PDCA_Process.png)

Test Utilization Analysis: Outcomes and Impact of the DMT

To measure the outcome of the DMT implementation, our group established four criteria of success. If successful, (1) our clinician colleagues would express confidence in the system, (2) the system would be more efficient, (3) there would be improved test utilization and performance, and (4) the testing guidelines would evolve as evidence for best practices accumulates. These outcomes were detailed by Seegmiller et al. [7].

Clinician confidence was measured in two ways. First, the 34 DCPs that interacted with the DMT service were surveyed 11 months after the initiation of the DMT to evaluate their experience. This survey showed that a majority (73 %) of the clinicians were aware of the option to have pathologists order the tests and were familiar with the SOPs on which these decisions were made. In addition, most DCPs expressed trust that the pathologists (81 %) and the SOPs (86 %) would make correct testing decisions for their patients. One of the major concerns expressed during DMT development was that clinicians might be hesitant to cede decision-making authority over test selection for their patients. However, after experiencing the DMT approach, the vast majority of DCPs (91 %) indicated that they preferred this approach to one in which they had primary responsibility for testing decisions .

Perhaps the best indicator of clinician confidence is their voluntary utilization of the DMT. There is an opt-out provision in the DMT that allows clinicians to order tests themselves outside of the SOPs. During the first few weeks of DMT implementation, a majority of clinicians continued to order tests in this manner. However, as familiarity and experience with the DMT increased, that percentage rapidly fell. Ten weeks post-implementation, the DMT process was utilized voluntarily in greater than 80 % of bone marrow biopsies .

Efficiency was also measured in the clinician survey. When asked, a vast majority of clinicians indicated that both the DMT reflex testing system (86

%) and the comprehensive reports (63 %) reduced the time spent in ordering bone marrow tests and reviewing the results. Clinicians estimated that with these two activities, the DMT saved approximately 10 min each time a patient had a bone marrow biopsy .

Test utilization was clearly improved as a result of DMT implementation (Fig. 17.8). To measure utilization, bone marrow cytogenetic and molecular tests were categorized as concordant (i.e., recommended by the SOPs for a patient with a specific hematologic neoplasm , at a particular stage of therapy), discordant (i.e., not recommended by the SOPs), or omitted (i.e., recommended by the SOP, but not ordered). A retrospective analysis showed that prior to the DMT, more than one-third of tests were discordant and that there were frequent test omissions (Fig. 17.8a). Improved test utilization would be reflected by a decrease in discordant and omitted tests. Indeed, in the first 12 months following implementation of the DMT, there was a 69 % decrease in discordant tests (Fig. 17.8b) and an 88 % decrease in omitted tests (Fig. 17.8c), leading to an overall 15 % decrease in total tests. These combined effects reduced by 18 % ($442 per marrow) the average cost of bone marrow testing to payers. This reduction in waste is an important component of IOM rule #9.

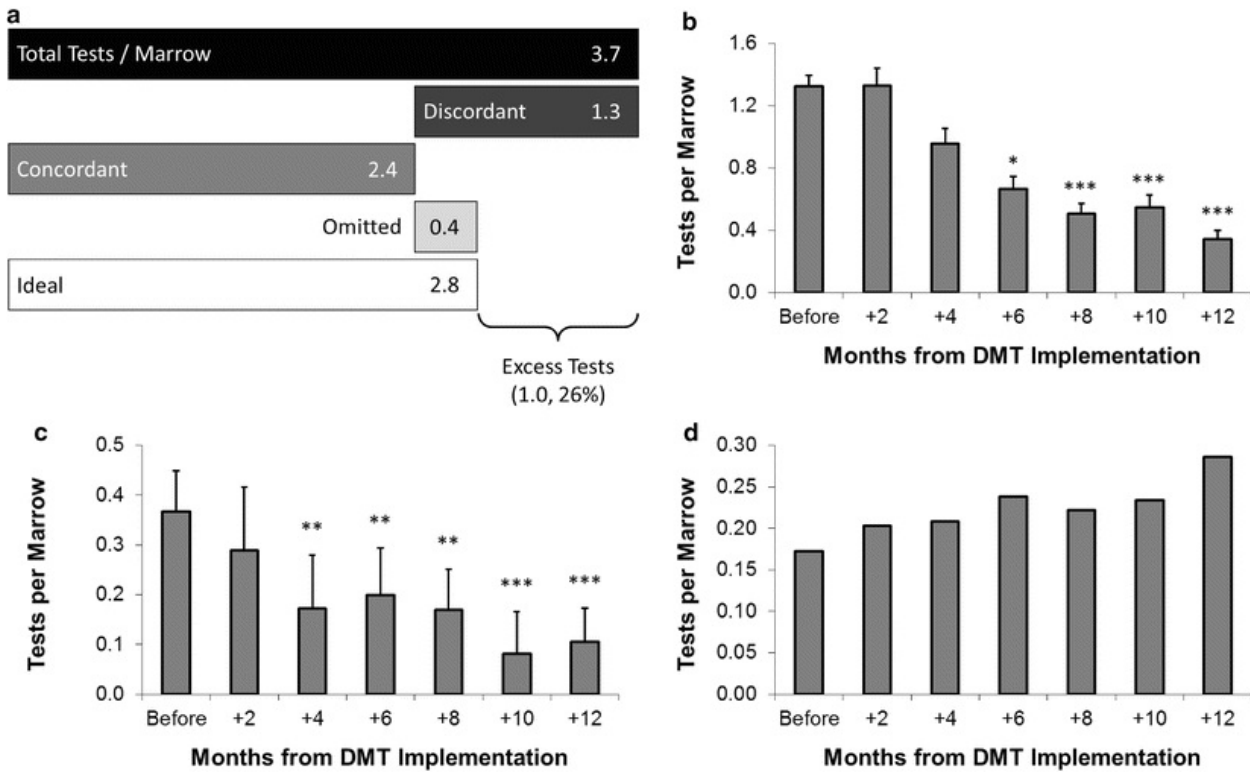


Fig. 17.8 Change in testing practices after institution of the DMT . (**a**) Summary of the average number of tests per marrow study (3.7) prior to the institution of the DMT with the number of tests that would have been deemed discordant to the SOP (overutilization, 1.3), the number of tests that would have been concordant to the SOP (2.4), and the number of tests that should have been ordered according to the SOP but were not (underutilization, 0.4). (**b**) Longitudinal graph of the number of discordant tests before and after the implementation of the DMT in bimonthly increments. (**c**) Longitudinal graph of the number of omitted tests before and after the implementation of the DMT in bimonthly increments. (**d**) The fraction of tests that were determined to be positive on the bone marrow studies as a surrogate for the increased positive predictive value of the testing

Accompanying any reduction in utilization is the concern that the changes go too far and that at least some of the reduction comes at the cost of essential laboratory information that may impact patient care. To address this concern, we used test results (positive or negative) as a rough surrogate measure of test utility, with the assumption that positive test results provide more important clinical information than negative test results. While it is recognized that some negative test results are highly significant, this measure is still a valid first approximation for test utility. Reviewing 18 months of test results from before and after DMT implementation, we found that a significantly higher fraction of concordant tests generated positive results compared with discordant tests (27 vs. 4 %). Furthermore, the majority of positive discordant tests were unlikely to have clinical impact (i.e., they were redundant with other recommended testing or they were transient changes/false-positive results). Accordingly, there was a significant increase in the fraction of positive results after DMT implementation (Fig. 17.8d). As the DMT changes the pretest probability of a positive test, one can surmise that these improvements would improve test performance, particularly positive predictive value.

The last measure of success is the ability of the DMT system to evolve over time. This is important for two reasons. First, the initial SOPs were constructed using incomplete information. As discussed above, for many testing decisions, there was little or no published evidence, no practice guidelines, nor other consensus documents available to guide decisions. Second, with technological advances, there is a continual increase in the list of possible testing options, and a decision support tool must always stay current with test menus. In the DMT, we addressed this through continual data collection and analysis, allowing us to generate evidence that could be used to regularly refine the SOPs. Through this cycle of SOP creation, data collection, analysis, and refinement, the DMT acted as a rapid learning system, a recognized approach to successful health-care innovation [8, 9].

One example of this rapid-cycle revision is fluorescence in situ hybridization (FISH) testing for myelodysplastic syndrome (MDS). The original SOP recommended a complete MDS FISH panel be performed on every bone marrow from patients with suspected MDS. The subsequent study indicated that routine karyotype testing was adequate to assess the cytogenetic status of patients, and the results of FISH testing were redundant and no more sensitive in most cases [10]. Subsequent elimination of FISH testing in patients with an adequate quality karyotype (i.e., 20 metaphases) resulted in further decreases in total testing with improved test performance. This evidence-based revision of SOPs based upon internally collected data on our testing practices allowed us to replace decisions that were based on expert opinion alone (level 7 evidence in Fig. 17.2 above) with more reliable cohort study data (level 5 evidence).

Generating data such as these, the DMT groups revised the SOPs to reflect experience using the DMT protocol over the first year and to take into account new evidence obtained by observing test result and utilization patterns. In most cases, these revisions reduced tests in particular diseases and at particular CMDPs where results were rarely if ever positive. There were, however, occasional situations for which the data indicated that application of the SOPs excluded tests that may sometimes generate clinically important data. These tests were added back to the new SOPs. Data analysis over the subsequent year indicated a further decrease in total tests and associated costs and additional increase in rate of positive tests (unpublished data).

These outcomes illustrate the impact of the DMT process on bone marrow testing at Vanderbilt. Through this program, we were able to reduce wasteful testing with its associated costs, while improving test performance, with the full support of the ordering clinicians. We improved communication of ongoing cases and provided a more comprehensive diagnosis for each patient biopsy. We think that this process can serve as a template for utilization management in other areas of complex pathology testing. Importantly, while what we present here is a solution for Vanderbilt hematopathology , each site must customize its approach to development and implementation of a utilization management system .

References

1. Nowell PC, Hungerford DA. Chromosome studies in human leukemia. II. Chronic granulocytic leukemia. J Natl Cancer Inst. 1961;27:1013–35.
[PubMed]

2. Kantarjian HM, Talpaz M. Imatinib mesylate: clinical results in Philadelphia chromosome-positive leukemias. Semin Oncol. 2001;28:9–18.
[CrossRef][PubMed]

3. Swerdlow SH, Campo E, Harris NL, et al., editors. World Health Organization classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: IARC Press; 2008.

4. Laposata M. Putting the patient first—using the expertise of laboratory professionals to produce rapid and accurate diagnoses. Lab Med. 2014;45:4–5.
[CrossRef][PubMed]

5. America CoQoHCi. Crossing the quality chasm: a new health system for the 21st century. Washington, DC: National Academy Press; 2001.

6. Langley G, Nolan K, Nolan T, Norman C, Provost L. The improvement guide: a practical approach to enhancing organizational performance. 2nd ed. San Francisco, CA: Jossey Bass; 2009.

7. Seegmiller AC, Kim AS, Mosse CA, et al. Optimizing personalized bone marrow testing using an evidence-based, interdisciplinary team approach. Am J Clin Pathol. 2013;140:643–50.
[CrossRef][PubMed][PubMedCentral]

8. Abernethy AP, Etheredge LM, Ganz PA, et al. Rapid-learning system for cancer care. J Clin Oncol. 2010;28:4268–74.
[CrossRef][PubMed][PubMedCentral]

9. Etheredge LM. A rapid-learning health system. Health Aff (Millwood). 2007;26:w107–18.
[CrossRef]

10. Seegmiller AC, Wasserman A, Kim AS, et al. Limited utility of fluorescence in situ hybridization for common abnormalities of myelodysplastic syndrome at first presentation and follow-up of myeloid neoplasms. Leuk Lymphoma. 2014;55:601–5.
[CrossRef][PubMed]

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_18

18. Laboratory Utilization

Daniel Dante Yeh[1]

(1) Trauma Emergency Surgery Surgical Critical Care, Harvard Medical School, Massachusetts General Hospital, 165 Cambridge St. #810, Boston, MA 02114, USA

Daniel Dante Yeh
Email: dyeh2@partners.org

Keywords Utilization – Bundling – Screening – Homeostatic – Administrative – Ordering – Monitoring

Introduction

Diagnostic testing is an important component of patient care in inpatient medical care. While it is indisputable that labs are sometimes indispensible, it is also increasingly recognized that a significant proportion of labs ordered by clinicians may be redundant or unnecessary (up to 50 %) [1–4]. While systems-based practice is already considered a core competency by the Accreditation Council for Graduate Medical Education and the American Board of Medical Specialties , some have suggested adding a seventh general competency: “cost-consciousness and stewardship of resources ” [5]. In this era of intense scrutiny of healthcare expenditures, most attention is directed at decreasing high visibility line items such as hospital length of stay (LOS) , intensive care unit (ICU) utilization , and invasive procedures, with little serious attention focused on reducing wasteful laboratory expenditures, even though it has been estimated that diagnostic testing can comprise up to 25 % of healthcare expenditures [6–9]. Within laboratory testing , more attention is

focused on “big ticket ” items, which are costly, but infrequently utilized. However, the more commonly ordered “little ticket ” items usually account for a larger proportion of hospital charges [10]. While relatively inexpensive, the financial weight of “little ticket” items is derived from the frequency with which they are ordered. Interestingly, for the same diagnosis, there is evidence of wide variability (almost 20-fold difference) in laboratory-testing behavior between nations, regions within the same country, hospitals, and individual physicians [11–17]. Without convincing evidence that more testing leads to better outcomes [11, 18], such practice variation is amenable to improvement, and standardization of indications and utilization may help streamline wasteful practices without compromising care. Indeed, some authors have reported negative correlations between testing volume and patient outcomes [19]. The focus of this paper will be to examine the uses of “little ticket ” (common and inexpensive) laboratory investigations in hospitalized patients and explore various strategies for eliminating excessive utilization.

Reasons for Ordering a Lab

Broadly speaking, there are five reasons for ordering a lab (Table 18.1): screening, homeostatic, case finding, diagnostic, and therapeutic [8]. Within this conceptual framework, the first step in thoughtful, conscientious laboratory investigation is to estimate the pretest probability of the diagnostic yield based on the patient and presentation. As an absurdly extreme example, ordering a prostate-specific antigen screening test in a 5-year-old boy presenting to the emergency department (ED) with elbow pain after a fall would result in a very low-yield investigation. However, ordering a troponin level in a 55-year-old diabetic, hyperlipidemic smoker complaining of nausea, shortness of breath, and crushing left-sided chest pain would be a relatively high-yield investigation. Thus, between the two extremes of never ordering any labs and ordering every single possible lab in every single patient, all clinicians perform such mental calculations every time they encounter a patient. More mental effort should be devoted to explicitly and intentionally performing such calculations within all encounters. As a general rule, diagnostic and therapeutic testing tend to be higher yield while screening and especially homeostatic testing are usually very low yield.

Table 18.1 A framework of indications for laboratory testing

Indication for laboratory testing	Description	Example(s)
Screening	Testing to detect asymptomatic abnormalities	Hemoglobin concentration in patient with sepsis; liver function tests in patient with status asthmaticus
Homeostatic	Testing performed on recurring basis to ensure prior "normal" test results remain within reference interval	Daily hemoglobin concentration in patients who are not bleeding; daily coagulation panel in patients not receiving anticoagulants
Case finding	Testing to detect abnormalities associated with a documented disease or syndrome	Creatinine in patient with septic shock; phosphate in a patient failing spontaneous breathing trials
Diagnostic	Testing to confirm or refute a suspected clinical syndrome or disease	Toxicology analyses in patient with suicidal overdose; sodium in patient with delirium
Therapeutic	Testing to determine response to specific therapy, including adverse events and monitoring of therapeutic drug levels	Platelet counts in patient being treated for heparin-induced thrombocytopenia; creatinine in patient receiving aminoglycosides; aPTT in patient on intravenous heparin

Reprinted with permission from: Ezzie ME, Aberegg SK, O'Brien JM, Jr. Laboratory testing in the intensive care unit. Crit Care Clin. 2007 Jul;23(3):435–65

Screening

Screening tests must be considered within the context of disease prevalence, which determines the positive predictive value (PPV) or negative predictive value (NPV) of a positive or negative result, respectively. For example, ordering a screening HIV test in a low-risk patient is inappropriate because the likelihood of a false positive result (leading to additional testing and patient anxiety) is much higher than the likelihood of a true positive. Unfortunately, physicians often lack understanding of basic principles of diagnostic test interpretation and value [20]. Additionally, in order to provide value, earlier diagnosis through screening must allow for earlier treatment and improved patient outcome, not just lead time bias. One common example of a low-yield screening test is the routine trauma screening panel (complete blood count, chemistry panel, liver enzymes, amylase/lipase, troponin ,

toxicology screen, type and cross) obtained in the ED for almost all injured patients regardless of injury severity, physiologic acuity, or patient demographic. Several factors contribute to the low utility of the “routine” trauma panel . Firstly, the sensitivity and specificity of lab abnormalities are too poor such that derangements are more likely to be non-diagnostic than truly helpful. False positive tests (e.g., an elevated amylase or transaminase) may lead to unnecessary ionizing radiation or hospital admission for follow-up of spuriously elevated values. In a 3-year review of pediatric trauma screening tests using computed tomography (CT) as the gold standard for intra-abdominal injury , Capraro et al. reported that no routine laboratory test had adequate sensitivity, specificity, PPV, or NPV [21]. Secondly, in order to be valuable, a lab abnormality must be actionable. In two separate studies, Tortella et al. and Tasse et al. reported that while abnormalities of screening chemistry panels and complete blood counts (CBC) were very common (almost 90 % incidence), <1 % of derangements were clinically significant and resulted in treatment changes [22, 23]. Thirdly, the time required to obtain test results must be considered. In acutely unstable trauma patients, clinical decisions are driven mainly by clinical signs (such as hypotension , visible bleeding , or obtundation) or imaging findings (such as hemoperitoneum, fractures on radiographs , or contrast extravasation). Labs contribute minimally to the diagnosis and decision-making in these situations, and results are often not available until after clinical decisions have been made [24–26]. One group of investigators estimated that selective lab ordering can potentially save >$1.5 million per year at their single institution without compromising patient care. Another common “little ticket” lab ordered routinely in injured patients is a type and screen or crossmatch, despite the fact that <5 % of trauma patients actually receive a blood transfusion within the first 24 h [22]. Thoughtful and directed lab utilization can lead to significant savings without negatively affecting patient outcomes [24, 27, 28].

Homeostatic

Homeostatic (i.e., repetitive) laboratory monitoring in stable, hospitalized patients in the absence of clinical change is responsible for a large proportion of unnecessary lab utilization. This practice is not evidence-based and questionable at best yet can account for up to 75 % of inpatient labs [1]. Furthermore, in the majority (>90 %) of repeated labs, no clinical indication

is apparent [29]. As such, “routine” homeostatic labs which are drawn purely to reassure the nervous or inexperienced clinician represent an easy target to reduce wasteful utilization .

Case Finding and Diagnostic

In the initial stages of the workup of an unspecified symptom (e.g., dizziness or abdominal pain), it is common to order multiple concomitant laboratory investigations in parallel. With a broad differential, this “carpet-bomb” approach to diagnosis is probably justified by the more rapid diagnosis, especially when considering patient acuity of illness and other factors such as ED crowding and hospital LOS. Additionally, initiating multiple lines of investigation mitigates the risk of premature closure or anchoring bias, which may have serious consequences if the team is led astray chasing an incorrect diagnosis. As in all investigations , the diagnostic accuracy of the lab must be considered in the context of the particular patient and presentation. For example, a “fever workup” is useful in an immunosuppressed patient with altered mental status but is practically useless in the first few days after a major operation or trauma. Similarly, ordering a D-dimer test in the ED or outpatient clinic to rule out pulmonary embolism in a patient presenting with shortness of breath and chest pain is justified, but the same lab hasvery poor accuracy in other settings, such as after surgery or in the ICU [30, 31]. Laboratory investigation should never supplant careful history taking and physical examination .

Therapeutic Monitoring

Once a diagnosis has been made or an abnormality uncovered, labs may be repeated at intervals in order to monitor response to therapy or to trigger new interventions. For example, in a dehydrated patient with severe hypernatremia receiving fluid replenishment, serial measurements of sodium are monitored to ensure that correction does not occur too rapidly. In a patient being treated nonoperatively for a splenic laceration, a declining hemoglobin value (even with hemodynamic stability) will alert the astute clinician about an ongoing hemorrhage and prompt interventions such as splenectomy or angioembolization prior to clinical deterioration. It must be emphasized, however, that serial monitoring is only valuable when changes are correlated with prognosis or will result in change in treatment. For

example, daily measurements of amylase/lipase in established acute pancreatitis are considered unnecessary because the degree of derangement and slope of change do not often correlate with clinical symptoms and do not usually drive clinical decisions. Monitoring of therapeutic drug levels or to assess the response to therapy (e.g., correction of hypernatremia) is very rarely excessive and is usually clinically justified. As this form of testing does not contribute much to waste and is of high usefulness, there is not much reason to decrease the frequency of therapeutic lab testing .

Factors Contributing to Unnecessary Laboratory Utilization

Laboratory utilization is the result of a complex interplay of predisposing, enabling, and reinforcing factors, including pre-existing attitudes, ease of ordering, knowledge of test characteristics, peer pressure for thoroughness, fear of medicolegal consequences, desire for diagnostic closure, financial incentives, and patient requests [1, 32]. Unfortunately, increasing experience (and confidence) has not been correlated with decreased rates of excessive laboratory utilization [13].

Ease of Order Entry

Perhaps the strongest factor influencing laboratory utilization is the ease with which the lab result can be obtained. Imagine how many daily CBCs would be requested if the ordering clinician had to personally draw the blood, mix the reagents, run the test, and log the results! The computerized care provider order entry (CPOE) thus represents a double-edged sword. It allows for efficient use of clinician time and resources, can provide clinical decision support at the time of ordering, and can decrease variability through the use of standardized treatment algorithms. Some authors have also translated this into improved outcomes such as decreased hospital LOS and decreased transfusions [33, 34].

However, CPOE has also resulted in a proliferation of “little ticket” laboratory utilization through two factors: bundling and automated repetition. Commonly used bundles, such as a CBC, chemistry panel, coagulation panel, and liver function tests (LFTs) co-locate similar and related labs, allowing the ordering clinician to order the entire panel with a single keystroke.

Unfortunately, the use of bundles can result in profound wasteful excess when only one lab in that panel is required. For example, in a patient being monitored for bleeding, the complete blood count includes information irrelevant to the case such as WBC and cell differential. Similarly, therapeutic monitoring of heparin or warfarin should include only the aPTT or INR coagulation test of interest, rather than the standard “coagulation panel” which includes both. Generations of clinicians have become accustomed to the standard “little ticket” lab bundles which can, at times, act as a mental crutch, preventing conscientious and thoughtful investigation.

The second great enabler of wasteful lab utilization is automated repetition, as exemplified by the “daily until discontinued” orders . It is the author’s opinion that this option should be removed completely from all CPOE , as it discourages the clinician from reviewing medical necessity and therefore contributes to mental laziness. These repeated labs are often ordered for homeostatic monitoring and usually outlive their utility. The impact of automated repetition should not be underestimated; studies have demonstrated that elimination of “routine daily labs ” resulted in a 65–71 % decrease in lab utilization per patient-ICU-day without compromise in patient care [35, 36]. Another strategy is to place boundaries on the frequency of repetition. For example, tests are commonly repeated when transferring the patient from one hospital location to another (such as from the ED to the ICU) without any clinical justification. In the absence of clinical changes, it has been shown to be feasible and safe to lengthen the intervals , assuming previously normal values [37]. In one audit of an academic hospital , 28 % of targeted laboratory tests were considered “early repeats” (e.g., chemistry panel more than once every 12 h), with about one-half of these early repeats following normal values. Of these, deeper chart review revealed that in only 8 % there was a clinical change justifying this early repetition. By eliminating redundant testing of ten common “little ticket” items, the authors estimated annual savings of almost $1 million [29]. In a follow-up study, the authors designed a computer-based intervention requiring manual override (and justification input) for tests identified as redundant. When prompted, clinicians canceled redundant orders 69 % of the time. Of the non-canceled redundant orders, chart review revealed that the override was indeed clinically justified in a large percentage of cases. While the intervention was successful in reducing redundant testing based on lab ordering, the overall impact on cost savings was only modest because the investigators discovered

that more than half of all redundant orders were being performed without corresponding computer orders [38]! This practice thus represents an additional target for reducing utilization in stable patients. Nonemergency labs should *never* be drawn without an order .

Fear of Litigation

One commonly cited reason for excessive laboratory utilization is the fear of medical malpractice lawsuits. It is widely acknowledged that some aspects of modern healthcare (labs, imaging, procedures, hospital admission , consultations, etc.) are ordered purely to maintain the appearance of being a dedicated and diligent clinician, a practice called “defensive medicine .” In one study of trauma patients, over 1/3 of CT scans were ordered purely for defensive purposes [39]. While diagnostic errors are indeed a leading cause of malpractice claims, it is not commonly appreciated that the overwhelming majority of these errors are due to faulty reasoning [40]. Furthermore, failure to follow-up on an abnormal lab value or misinterpretation of existing information is more common than deficient data gathering. Thus, excessive lab utilization may actually expose oneself to higher risk of litigation because of the increased risk of misinterpreting the additional data or forgetting to follow up on a battery of unnecessary tests .

Inexperience

Excessive test ordering is particularly rampant in training institutions, where the task of lab ordering is usually delegated to junior trainees with minimal formal instruction in lab utilization [10, 41, 42]. Inexperience , fear of reprimand by peers or supervisors, discomfort with uncertainty, and cost unawareness are common factors contributing to this phenomenon [4]. One study of ICU patients demonstrated that teaching institutions ordered twice as many lab tests as did nonteaching institutions [43]. Teaching institutions often promulgate a hidden curriculum of exhaustive thoroughness while rarely criticizing the accompanying consequence of data overload and low signal-to-noise ratio. It is more common to hear, “Why didn’t you order that test?” and uncommon to hear, “Why did you order this and what am I going to do with the results now?” Unfortunately, overreliance on laboratory investigations may hamper the development of other important skills such as history taking and physical examination [44]. To accomplish lasting practice

change, educators and role models must place greater importance on value through conscientious investigation and should chastise wasteful behavior [45].

Reasons for Decreasing Unnecessary Laboratory Investigations

In any discussion about healthcare economics, it is important to distinguish between hospital charges and costs. It is nearly impossible to accurately estimate actual costs in terms of reagents, electricity, labor, etc., and therefore, most studies have reported savings in terms of patient charges. Because charges are sometimes wildly inflated, and fixed costs (salary, etc.) are immutable, decreases in lab utilization usually result in far less dramatic costs savings [46]. However, beyond laboratory costs and patient charges, other reasons for eliminating unnecessary labs include reductions in patient discomfort, anxiety, and blood loss.

Unbeknownst to most clinicians, the “normal” reference range for many clinical laboratories excludes the upper and lower 2.5 % of results, and therefore 5 % of normal individuals will obtain an “abnormal” result. With increasing labs ordered, the likelihood of an abnormal result increases such that if a healthy patient undergoes ten unrelated tests, there is a 40 % chance of at least one abnormal result [10, 47]. While these “abnormal” results may be appropriately ignored, sometimes they are not and result in additional unnecessary investigations, a phenomenon termed the *Ulysses Syndrome* [48]. Ulysses (Odysseus), the Greek hero of Homer’s Odyssey, endured 20 years of trials and tribulations to return home to his original point of departure. Likewise, a healthy patient may be subjected to costly, anxiety-provoking, and sometimes dangerous investigations to ultimately conclude that nothing was ever wrong in the first place. While true Ulysses Syndrome is relatively uncommon, a more tangible negative consequence of excessive testing is the phlebotomy required to obtain blood tests. This negative effect is usually imperceptible to both the clinician and patient, but its repetition over time becomes significant. It is estimated that daily phlebotomy is up to 40 mL per day in the ICU and can total more than 1000 mL during an extended ICU stay [49, 50]. Of ICU patients receiving blood transfusions, almost half had large losses attributable to phlebotomy that contributed to the transfusion requirements [51]. Decreasing laboratory utilization has been

correlated with decreasing blood transfusion [52]. Even seemingly trivial decreases are impactful, as it has been reported that every 3.5 ml increase in daily phlebotomy *doubles* the odds of being transfused [53].

Potential Interventions

Physician behavior , like patient behavior, is very difficult to modify [54]. Many continue to practice according to patterns and habits learned in residency or medical school, and there is little incentive to change, especially regarding “little ticket” items. The desire to avoid missing something is a powerful motivator, and clinicians must be confident that decreasing excessive lab utilization will not compromise quality of care [55]. A valueless lab result, no matter how inexpensive, represents poor quality care. End-user stakeholder buy-in and support are critical, as physicians will naturally oppose any changes which are perceived as restricting autonomy [56]. Three categories of interventions are considered: education, peer review/feedback, and administrative [10, 57].

Education

Education may be passive (as in simple distribution of guidelines) or active (as in interactive lecture or one-on-one instruction). Since clinicians are commonly ignorant about laboratory charges [42, 58], one form of passive education which has produced mixed results is displaying the charges on the screen when attempting to order a lab [7, 59, 60]. While this has not been consistently shown to be effective, it has not been shown to be harmful. If cost-awareness strategies are easy to implement, they should be considered. Active education is very time and labor intensive, especially at training institutions where trainee turnover is high [4]. Not surprisingly, educational interventions alone rarely result in long-lasting practice change. This is not to say that educational efforts are not worthwhile. Physicians usually ingrain their career-long practice patterns during training, and therefore, targeted education and role modeling or junior trainees are crucial for long-lasting culture change. However, it is readily apparent that education, while necessary, is insufficient alone and must be combined with other modalities to be effective [61–64].

Peer Review and Audit

One of the most powerful methods to influence physician behavior is comparison with peers. Clinicians who realize that their practice patterns are widely different from those of their colleagues are likely to change their behavior in order to conform to their peers [2, 15, 65]. Anonymous peer rankings are especially effective [17]. Chart review and feedback about practice have been shown to be effective in reducing lab utilization, reducing unnecessary blood transfusions, decreasing hospital LOS, and improving compliance with cancer-screening guidelines [32, 56, 66–68]. This form of intervention can also be time and labor intensive, and one must tread carefully, lest the physician feels targeted or ostracized. Thankfully, no studies have reported evidence of backlash , and, when examined, decreases in unnecessary labs have not been accompanied by decreases in clinically indicated appropriate testing [64].

Administrative Changes

Interventions involving the clinician-laboratory interface (i.e., order requisition forms can be very effective and efficient [69, 70]). Subtle redesign of default settings or work flow may go unnoticed or provide gentle “nudges” without being perceived as restricting access [71]. For example, Hindmarsh et al. demonstrated that substituting “amylase” for “calcium” on a STAT order form led to increased amylase ordering and decreased calcium ordering [72]. In a similar study, Emerson also demonstrated differential ordering behavior after simply reshuffling test panels [73]. Taking this one step further, removing a test order from a standard order set for “quick-pick” order screen is very effective and can result in immediate request reduction of up to 50 % without reductions in *appropriate* test requests [33, 74]. Obsolete tests should be removed altogether from the ordering system.

Gentle roadblocks can be used to educate and to provoke reflection. Pop-up windows alerting ordering physicians of redundant tests or showing prior normal values lead to cancelation in a significant proportion of cases [38]. Requiring a clinical justification will force clinicians to seriously ponder the actual *need* for the test. Mozes et al. reported that while an educational intervention did not change test-ordering behavior regarding routine preoperative coagulation panel screening, the threat of administrative restriction and additional paperwork (written justification for each order)

were extremely successful [75]. When implementing such administrative changes , one must be careful to use them sparingly, as excessive roadblocks causing significant workflow interruption will likely be interpreted as harassment and ultimately prove counterproductive.

Unbundling of test panels may also be considered to allow clinicians to order only those components that are required. In one study, unbundling common panels (as one component of a multifaceted approach) resulted in cost savings of $1.9 million via decreasing test ordering without adversely affecting patient outcomes [76]. Others have reported similar decreases in excess lab ordering without obvious negative patient consequences [73].

Restriction of automated repetition of future orders has been demonstrated to significantly decrease recurrent testing without compromising patient care [77]. Visual prompts , such as a line graph displaying the past week history of the ordered test, can aid clinicians in recognizing when labs have been normal and decrease homeostatic monitoring [77]. Clinical decision support (CDS) at the time of order entry has been shown to be effective in improving compliance with evidence-based guidelines in other domains such as cervical spine injury imaging, ankle fracture imaging, and venous thromboembolism prophylaxis [78–80]. It is worthwhile to consider development of similar prediction rules and decision support to decrease unnecessary laboratory investigations.

One interesting strategy is to require authorization by a trainee's supervisor for labs with limited utility which are commonly overused [81]. Fear of harassing one's supervisor may have equal potency in limiting low-yield investigations as fear of reprimand for incomplete investigations.

From several decades of laboratory utilization research, several common themes have emerged. First, education is necessary but not sufficient alone to produce long-lasting change. The most successful interventions combine education with peer review, feedback, and administrative (order entry) changes [32, 33, 54, 56, 69, 82–84]. Interventions should begin with an initial "gap analysis" to identify locally unique barriers and develop targeted interventions to address those gaps [62], progressing in an orderly manner: education should precede administrative changes, which should then be followed by peer audit and timely feedback. Leadership level support is absolutely essential, as initial effort and costs are likely to go high. Involvement of all stakeholders (including the ultimate end users) from the outset is especially effecting in ensuring buy-in [85–88].

Conclusion

In conclusion, excessive “little ticket” laboratory testing is an insidious problem which contributes to exorbitant healthcare charges, excess phlebotomy, and low-value healthcare. Incentives to order more labs are numerous and include peer pressure, “defensive medicine ,” clinician inexperience , practice inertia, and ignorance of test accuracy. Decades of efforts have been largely unsuccessful in curbing the overuse of common labs, which are extremely easy to order due to modern conveniences such as bundling and automated repetition. Beyond economics, the costs borne by the patient include the discomfort of needle sticks, blood loss from repeated phlebotomy, and additional unnecessary workup of spurious results. Multiple strategies for limiting use have been described, but no single method is universally successful in all situations. Education alone (especially passive distribution) is rarely sufficient, and multifaceted strategies are required to combine education with other strategies such as computer ordering system changes , peer review, and audit. Top-down administrative support is mandatory, and involvement of local end users and respected local champions will greatly enhance efforts. At teaching institutions, educators must place greater emphasis on conscientious, value-based lab ordering, as practice patterns learned during training tend to persist for a physician’s entire career. While autonomy is required during training, increased senior physician oversight and reassurance can help decrease the amount of labs ordered out of fear, ignorance, or laziness. No matter how trivial the task may seem, it is incumbent upon us to strive for high value and high quality care through thoughtful investigation and critical reasoning.

References

1. Martin AR, Wolf MA, Thibodeau LA, Dzau V, Braunwald E. A trial of two strategies to modify the test-ordering behavior of medical residents. N Engl J Med. 1980;303(23):1330–6. [CrossRef][PubMed]

2. Gortmaker SL, Bickford AF, Mathewson HO, Dumbaugh K, Tirrell PC. A successful experiment to reduce unnecessary laboratory use in a community hospital. Med Care. 1988;26(6):631–42. [CrossRef][PubMed]

3. Eisenberg JM. An educational program to modify laboratory use by house staff. J Med Educ. 1977;52(7):578–81.

[PubMed]

4. Miyakis S, Karamanof G, Liontos M, Mountokalakis TD. Factors contributing to inappropriate ordering of tests in an academic medical department and the effect of an educational feedback strategy. Postgrad Med J. 2006;82(974):823–9.
[CrossRef][PubMed][PubMedCentral]

5. Weinberger SE. Providing high-value, cost-conscious care: a critical seventh general competency for physicians. Ann Intern Med. 2011;155(6):386–8.
[CrossRef][PubMed]

6. Robinson A. Rationale for cost-effective laboratory medicine. Clin Microbiol Rev. 1994;7(2):185–99.
[CrossRef][PubMed][PubMedCentral]

7. Tierney WM, Miller ME, McDonald CJ. The effect on test ordering of informing physicians of the charges for outpatient diagnostic tests. N Engl J Med. 1990;322(21):1499–504.
[CrossRef][PubMed]

8. Ezzie ME, Aberegg SK, O'Brien Jr JM. Laboratory testing in the intensive care unit. Crit Care Clin. 2007;23(3):435–65.
[CrossRef][PubMed]

9. Griner PF, Liptzin B. Use of the laboratory in a teaching hospital. Implications for patient care, education, and hospital costs. Ann Intern Med. 1971;75(2):157–63.
[CrossRef][PubMed]

10. Grossman RM. A review of physician cost-containment strategies for laboratory testing. Med Care. 1983;21(8):783–802.
[CrossRef][PubMed]

11. Daniels M, Schroeder SA. Variation among physicians in use of laboratory tests. II. Relation to clinical productivity and outcomes of care. Med Care. 1977;15(6):482–7.
[CrossRef][PubMed]

12. Schroeder SA, Kenders K, Cooper JK, Piemme TE. Use of laboratory tests and pharmaceuticals. Variation among physicians and effect of cost audit on subsequent use. JAMA. 1973;225(8):969–73.
[CrossRef][PubMed]

13. Sood R, Sood A, Ghosh AK. Non-evidence-based variables affecting physicians' test-ordering tendencies: a systematic review. Neth J Med. 2007;65(5):167–77.
[PubMed]

14. Epstein AM, McNeil BJ. Physician characteristics and organizational factors influencing use of ambulatory tests. Med Decis Making. 1985;5(4):401–15.
[CrossRef][PubMed]

15. Epstein AM, McNeil BJ. Relationship of beliefs and behavior in test ordering. Am J Med. 1986;80(5):865–70.
[CrossRef][PubMed]

16. Williams SV, Eisenberg JM. A controlled trial to decrease the unnecessary use of diagnostic tests. J Gen Intern Med. 1986;1(1):8–13.
[CrossRef][PubMed]

17. Berwick DM, Coltin KL. Feedback reduces test use in a health maintenance organization. JAMA. 1986;255(11):1450–4.
[CrossRef][PubMed]

18. Schroeder SA, Schliftman A, Piemme TE. Variation among physicians in use of laboratory tests: relation to quality of care. Med Care. 1974;12(8):709–13.
[CrossRef][PubMed]

19. Garland A, Shaman Z, Baron J, Connors Jr AF. Physician-attributable differences in intensive care unit costs: a single-center study. Am J Respir Crit Care Med. 2006;174(11):1206–10.
[CrossRef][PubMed]

20. Parker VL, Ritchie JE, Drake TM, Hookham J, Balasubramanian SP. A randomised assessment of trainee doctors' understanding and interpretation of diagnostic test results. World J Surg. 2016;40(1):21–8.
[CrossRef][PubMed]

21. Capraro AJ, Mooney D, Waltzman ML. The use of routine laboratory studies as screening tools in pediatric abdominal trauma. Pediatr Emerg Care. 2006;22(7):480–4.
[CrossRef][PubMed]

22. Tasse JL, Janzen ML, Ahmed NA, Chung RS. Screening laboratory and radiology panels for trauma patients have low utility and are not cost effective. J Trauma. 2008;65(5):1114–6.
[CrossRef][PubMed]

23. Tortella BJ, Lavery RF, Rekant M. Utility of routine admission serum chemistry panels in adult trauma patients. Acad Emerg Med. 1995;2(3):190–4.
[CrossRef][PubMed]

24. Fenton SJ, Peterson DN, Connors RC, Hansen KW, Metzger RR, Scaife ER. A standard pediatric trauma laboratory panel: a plea for a minimalist approach. J Trauma. 2009;66(3):703–6.
[CrossRef][PubMed]

25. Namias N, McKenney MG, Martin LC. Utility of admission chemistry and coagulation profiles in trauma patients: a reappraisal of traditional practice. J Trauma. 1996;41(1):21–5.
[CrossRef][PubMed]

26. Keller MS, Coln CE, Trimble JA, Green MC, Weber TR. The utility of routine trauma laboratories in pediatric trauma resuscitations. Am J Surg. 2004;188(6):671–8.
[CrossRef][PubMed]

27. Chu UB, Clevenger FW, Imami ER, Lampard SD, Frykberg ER, Tepas 3rd JJ. The impact of selective laboratory evaluation on utilization of laboratory resources and patient care in a level-I trauma center. Am J Surg. 1996;172(5):558–62. Discussion 62–3.
[CrossRef][PubMed]

28. Jacobs IA, Kelly K, Valenziano C, Chevinsky AH, Pawar J, Jones C. Cost savings associated with changes in routine laboratory tests ordered for victims of trauma. Am Surg. 2000;66(6):579–84.

[PubMed]

29. Bates DW, Boyle DL, Rittenberg E, Kuperman GJ, Ma'Luf N, Menkin V, et al. What proportion of common diagnostic tests appear redundant? Am J Med. 1998;104(4):361–8.
[CrossRef][PubMed]

30. Bounameaux H, Cirafici P, de Moerloose P, Schneider PA, Slosman D, Reber G, et al. Measurement of D-dimer in plasma as diagnostic aid in suspected pulmonary embolism. Lancet. 1991;337(8735):196–200.
[CrossRef][PubMed]

31. Crowther MA, Cook DJ, Griffith LE, Meade M, Hanna S, Rabbat C, et al. Neither baseline tests of molecular hypercoagulability nor D-dimer levels predict deep venous thrombosis in critically ill medical-surgical patients. Intensive Care Med. 2005;31(1):48–55.
[CrossRef][PubMed]

32. Solomon DH, Hashimoto H, Daltroy L, Liang MH. Techniques to improve physicians' use of diagnostic tests: a new conceptual framework. JAMA. 1998;280(23):2020–7.
[CrossRef][PubMed]

33. Kim JY, Dzik WH, Dighe AS, Lewandrowski KB. Utilization management in a large urban academic medical center: a 10-year experience. Am J Clin Pathol. 2011;135(1):108–18.
[CrossRef][PubMed]

34. Miller RA, Waitman LR, Chen S, Rosenbloom ST. The anatomy of decision support during inpatient care provider order entry (CPOE): empirical observations from a decade of CPOE experience at Vanderbilt. J Biomed Inform. 2005;38(6):469–85.
[CrossRef][PubMed][PubMedCentral]

35. Prat G, Lefevre M, Nowak E, Tonnelier JM, Renault A, L'Her E, et al. Impact of clinical guidelines to improve appropriateness of laboratory tests and chest radiographs. Intensive Care Med. 2009;35(6):1047–53.
[CrossRef][PubMed]

36. Marx WH, DeMaintenon NL, Mooney KF, Mascia ML, Medicis J, Franklin PD, et al. Cost reduction and outcome improvement in the intensive care unit. J Trauma. 1999;46(4):625–9. Discussion 9–30.
[CrossRef][PubMed]

37. Schubart JR, Fowler CE, Donowitz GR, Connors Jr AF. Algorithm-based decision rules to safely reduce laboratory test ordering. Stud Health Technol Inform. 2001;84(Pt 1):523–7.
[PubMed]

38. Bates DW, Kuperman GJ, Rittenberg E, Teich JM, Fiskio J, Ma'luf N, et al. A randomized trial of a computer-based intervention to reduce utilization of redundant laboratory tests. Am J Med. 1999;106(2):144–50.
[CrossRef][PubMed]

39. Chen J, Majercik S, Bledsoe J, Connor K, Morris B, Gardner S, et al. The prevalence and impact of defensive medicine in the radiographic workup of the trauma patient: a pilot study. Am J Surg. 2015;210(3):462–7.

[CrossRef][PubMed]

40. Graber ML, Franklin N, Gordon R. Diagnostic error in internal medicine. Arch Intern Med. 2005;165(13):1493–9.
[CrossRef][PubMed]

41. Greene HL, Goldberg RJ, Beattie H, Russo AR, Ellison RC, Dalen JE. Physician attitudes toward cost containment. The missing piece of the puzzle. Arch Intern Med. 1989;149(9):1966–8.
[CrossRef][PubMed]

42. Post J, Reed D, Halvorsen AJ, Huddleston J, McDonald F. Teaching high-value, cost-conscious care: improving residents' knowledge and attitudes. Am J Med. 2013;126(9):838–42.
[CrossRef][PubMed]

43. Zimmerman JE, Seneff MG, Sun X, Wagner DP, Knaus WA. Evaluating laboratory usage in the intensive care unit: patient and institutional characteristics that influence frequency of blood sampling. Crit Care Med. 1997;25(5):737–48.
[CrossRef][PubMed]

44. Griner PF, Glaser RJ. Sounding boards. Misuse of laboratory tests and diagnostic procedures. N Engl J Med. 1982;307(21):1336–9.
[CrossRef][PubMed]

45. Stammen LA, Stalmeijer RE, Paternotte E, Oudkerk Pool A, Driessen EW, Scheele F, et al. Training physicians to provide high-value. Cost-conscious care: a systematic review. JAMA. 2015;314(22):2384–400.
[CrossRef][PubMed]

46. Winkelman JW. Less utilization of the clinical laboratory produces disproportionately small true cost reductions. Hum Pathol. 1984;15(6):499–501.
[CrossRef][PubMed]

47. Axt-Adam P, van der Wouden JC, van der Does E. Influencing behavior of physicians ordering laboratory tests: a literature study. Med Care. 1993;31(9):784–94.
[CrossRef][PubMed]

48. Rang M. The Ulysses syndrome. Can Med Assoc J. 1972;106(2):122–3.
[PubMed][PubMedCentral]

49. Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, et al. Anemia and blood transfusion in critically ill patients. JAMA. 2002;288(12):1499–507.
[CrossRef][PubMed]

50. Shaffer C. Diagnostic blood loss in mechanically ventilated patients. Heart Lung. 2007;36(3):217–22.
[CrossRef][PubMed]

51. Smoller BR, Kruskall MS. Phlebotomy for diagnostic laboratory tests in adults. Pattern of use and effect on transfusion requirements. N Engl J Med. 1986;314(19):1233–5.
[CrossRef][PubMed]

52.

Kumwilaisak K, Noto A, Schmidt UH, Beck CI, Crimi C, Lewandrowski K, et al. Effect of laboratory testing guidelines on the utilization of tests and order entries in a surgical intensive care unit. Crit Care Med. 2008;36(11):2993–9.
[CrossRef][PubMed]

53. Chant C, Wilson G, Friedrich JO. Anemia, transfusion, and phlebotomy practices in critically ill patients with prolonged ICU length of stay: a cohort study. Crit Care. 2006;10(5):R140.
[CrossRef][PubMed][PubMedCentral]

54. Smith WR. Evidence for the effectiveness of techniques to change physician behavior. Chest. 2000;118(2 Suppl):8S–17.
[CrossRef][PubMed]

55. Kassirer JP. Our stubborn quest for diagnostic certainty. A cause of excessive testing. N Engl J Med. 1989;320(22):1489–91.
[CrossRef][PubMed]

56. Greco PJ, Eisenberg JM. Changing physicians' practices. N Engl J Med. 1993;329(17):1271–3.
[CrossRef][PubMed]

57. Eisenberg JM, Williams SV. Cost containment and changing physicians' practice behavior. Can the fox learn to guard the chicken coop? JAMA. 1981;246(19):2195–201.
[CrossRef][PubMed]

58. Allan GM, Lexchin J. Physician awareness of diagnostic and nondrug therapeutic costs: a systematic review. Int J Technol Assess Health Care. 2008;24(2):158–65.
[CrossRef][PubMed]

59. Feldman LS, Shihab HM, Thiemann D, Yeh HC, Ardolino M, Mandell S, et al. Impact of providing fee data on laboratory test ordering: a controlled clinical trial. JAMA Intern Med. 2013;173(10):903–8.
[CrossRef][PubMed]

60. Bates DW, Kuperman GJ, Jha A, Teich JM, Orav EJ, Ma'luf N, et al. Does the computerized display of charges affect inpatient ancillary test utilization? Arch Intern Med. 1997;157(21):2501–8.
[CrossRef][PubMed]

61. Davis DA, Thomson MA, Oxman AD, Haynes RB. Changing physician performance. A systematic review of the effect of continuing medical education strategies. JAMA. 1995;274(9):700–5.
[CrossRef][PubMed]

62. Grimshaw JM, Shirran L, Thomas R, Mowatt G, Fraser C, Bero L, et al. Changing provider behavior: an overview of systematic reviews of interventions. Med Care. 2001;39(8 Suppl 2):II2–45.
[PubMed]

63. Bunting PS, Van Walraven C. Effect of a controlled feedback intervention on laboratory test ordering by community physicians. Clin Chem. 2004;50(2):321–6.
[CrossRef][PubMed]

64.

Kroenke K, Hanley JF, Copley JB, Matthews JI, Davis CE, Foulks CJ, et al. Improving house staff ordering of three common laboratory tests. Reductions in test ordering need not result in underutilization. Med Care. 1987;25(10):928–35.
[CrossRef][PubMed]

65. Bareford D, Hayling A. Inappropriate use of laboratory services: long term combined approach to modify request patterns. BMJ. 1990;301(6764):1305–7.
[CrossRef][PubMed][PubMedCentral]

66. Yeh DD, Naraghi L, Larentzakis A, Nielsen N, Dzik W, Bittner EA, et al. Peer-to-peer physician feedback improves adherence to blood transfusion guidelines in the surgical intensive care unit. J Trauma Acute Care Surg. 2015;79(1):65–70.
[CrossRef][PubMed]

67. Winkens RA, Pop P, Grol RP, Kester AD, Knottnerus JA. Effect of feedback on test ordering behaviour of general practitioners. BMJ. 1992;304(6834):1093–6.
[CrossRef][PubMed][PubMedCentral]

68. Winkens RA, Pop P, Bugter-Maessen AM, Grol RP, Kester AD, Beusmans GH, et al. Randomised controlled trial of routine individual feedback to improve rationality and reduce numbers of test requests. Lancet. 1995;345(8948):498–502.
[CrossRef][PubMed]

69. Lundberg GD. Changing physician behavior in ordering diagnostic tests. JAMA. 1998;280(23):2036.
[CrossRef][PubMed]

70. May TA, Clancy M, Critchfield J, Ebeling F, Enriquez A, Gallagher C, et al. Reducing unnecessary inpatient laboratory testing in a teaching hospital. Am J Clin Pathol. 2006;126(2):200–6.
[CrossRef][PubMed]

71. Thaler RH, Sunstein CR. Nudge: improving decisions about health, wealth, and happiness. New York, NY: Penguin; 2009. Rev. and expanded ed.

72. Hindmarsh JT, Lyon AW. Strategies to promote rational clinical chemistry test utilization. Clin Biochem. 1996;29(4):291–9.
[CrossRef][PubMed]

73. Emerson JF, Emerson SS. The impact of requisition design on laboratory utilization. Am J Clin Pathol. 2001;116(6):879–84.
[CrossRef][PubMed]

74. Groopman DS, Powers RD. Effect of “standard order” deletion on emergency department coagulation profile use. Ann Emerg Med. 1992;21(5):524–7.
[CrossRef][PubMed]

75. Mozes B, Lubin D, Modan B, Ben-Bassat I, Gitel SN, Halkin H. Evaluation of an intervention aimed at reducing inappropriate use of preoperative blood coagulation tests. Arch Intern Med. 1989;149(8):1836–8.
[CrossRef][PubMed]

76.

Attali M, Barel Y, Somin M, Beilinson N, Shankman M, Ackerman A, et al. A cost-effective method for reducing the volume of laboratory tests in a university-associated teaching hospital. Mt Sinai J Med. 2006;73(5):787–94.
[PubMed]

77. Neilson EG, Johnson KB, Rosenbloom ST, Dupont WD, Talbert D, Giuse DA, et al. The impact of peer management on test-ordering behavior. Ann Intern Med. 2004;141(3):196–204.
[CrossRef][PubMed]

78. Stiell IG, McKnight RD, Greenberg GH, McDowell I, Nair RC, Wells GA, et al. Implementation of the Ottawa ankle rules. JAMA. 1994;271(11):827–32.
[CrossRef][PubMed]

79. Haut ER, Lau BD, Kraenzlin FS, Hobson DB, Kraus PS, Carolan HT, et al. Improved prophylaxis and decreased rates of preventable harm with the use of a mandatory computerized clinical decision support tool for prophylaxis for venous thromboembolism in trauma. Arch Surg. 2012;147(10):901–7.
[CrossRef][PubMed]

80. Hoffman JR, Mower WR, Wolfson AB, Todd KH, Zucker MI. Validity of a set of clinical criteria to rule out injury to the cervical spine in patients with blunt trauma. National Emergency X-Radiography Utilization Study Group. N Engl J Med. 2000;343(2):94–9.
[CrossRef][PubMed]

81. Stuart PJ, Crooks S, Porton M. An interventional program for diagnostic testing in the emergency department. Med J Aust. 2002;177(3):131–4.
[PubMed]

82. Barie PS, Hydo LJ. Lessons learned: durability and progress of a program for ancillary cost reduction in surgical critical care. J Trauma. 1997;43(4):590–4. Discussion 4–6.
[CrossRef][PubMed]

83. Fowkes FG, Hall R, Jones JH, Scanlon MF, Elder GH, Hobbs DR, et al. Trial of strategy for reducing the use of laboratory tests. Br Med J (Clin Res Ed). 1986;292(6524):883–5.
[CrossRef]

84. Barie PS, Hydo LJ. Learning to not know: results of a program for ancillary cost reduction in surgical critical care. J Trauma. 1996;41(4):714–20.
[CrossRef][PubMed]

85. Buntinx F, Winkens R, Grol R, Knottnerus JA. Influencing diagnostic and preventive performance in ambulatory care by feedback and reminders. A review. Fam Pract. 1993;10(2):219–28.
[CrossRef][PubMed]

86. Spiegel JS, Shapiro MF, Berman B, Greenfield S. Changing physician test ordering in a university hospital. An intervention of physician participation, explicit criteria, and feedback. Arch Intern Med. 1989;149(3):549–53.
[CrossRef][PubMed]

87. Merkeley HL, Hemmett J, Cessford TA, Amiri N, Geller GS, Baradaran N, et al. Multipronged strategy to reduce routine-priority blood testing in intensive care unit patients. J Crit Care.

2015;1(1):212–6.

88. Han SJ, Saigal R, Rolston JD, Cheng JS, Lau CY, Mistry RI, et al. Targeted reduction in neurosurgical laboratory utilization: resident-led effort at a single academic institution. J Neurosurg. 2014;120(1):173–7.
[CrossRef][PubMed]

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_19

19. Test Utilization: Controlling Costs in Reference Laboratory Testing

Valerie L. Ng[1, 2]

(1) Department of Laboratory Medicine, School of Medicine, University of California San Francisco, San Francisco, CA 94143, USA
(2) Department of Laboratory Medicine and Pathology, Alameda Health System/Highland Hospital, 1411 E. 31st Street, Oakland, CA 94602, USA

Valerie L. Ng
Email: vang@alamedahealthsystem.org

Keywords Reference laboratory selection – Reference laboratory utilization – Medicare – Cost – Make versus buy – Clinical justification – Clinical consultation – Laboratory formulary – Prior authorization

Introduction

A “Reference Laboratory” is defined as “A Medicare -enrolled laboratory that receives a specimen from another, referring laboratory for testing and that actually performs the test” [1]. By definition, Medicare-enrolled reference laboratories meet minimal federal laboratory regulations [2] or more stringent clinical laboratory accreditation requirements (e.g., College of American Pathologists, The Joint Commission, etc.). Most commonly used reference laboratories are large national or international corporations offering a wide array of clinical laboratory tests.

Given its essential role for clinical laboratories, surprisingly little peer-

reviewed literature or systematic analyses exist for reference laboratory utilization management.

The Magnitude of Reference Laboratory Testing

Reference Laboratories

Reference laboratories are typically for profit entities under intense scrutiny by payers. While Medicare Part B clinical laboratory expenditures comprise only 2.4–3 % of the total Medicare Parts A and B fee-for-service expenses [3, 4], “laboratory tests also influence health care expenditures far beyond their proportion of actual costs because decisions about the provision of other medical services often hinge on the results of laboratory tests ” [3].

One study reviewed a 5 % national random sample of payments for Medicare fee-for-service beneficiaries in calendar year 2006 to assess the clinical laboratory market [4]. $6.7 billion was paid to physicians and facilities billing on behalf of fee-for-service Medicare beneficiaries. Of this $6.7 billion, payments to independent laboratories represented 2.54 billion or 38.1 % of all Medicare Part B laboratory test payments.

Independent laboratories were ranked in order of Medicare Part B payments received (Fig. 19.1). Payments to the top two ranked national-independent laboratories comprised 29.5 % (~$749 million) and 18.8 % (~$479 million), respectively, of the total payments to independent laboratories.

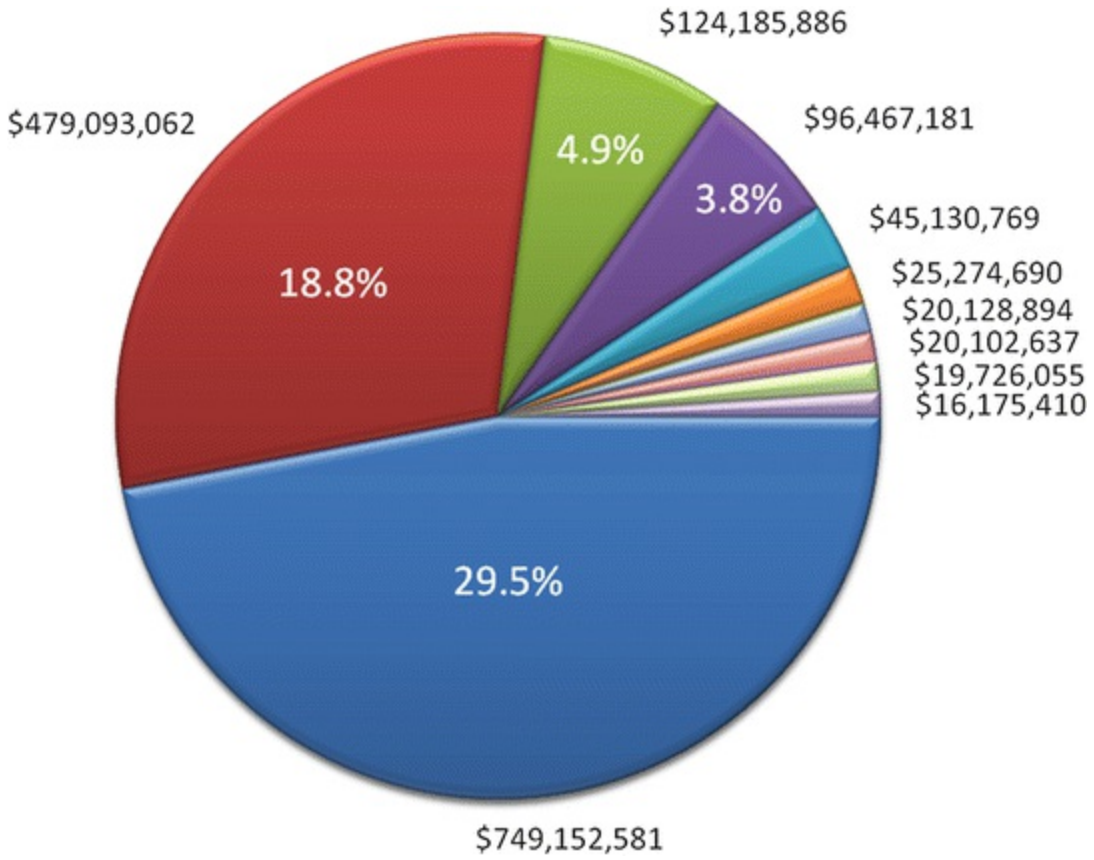


Fig. 19.1 Calendar year 2006 Medicare Part B Payments (dollar, % of total) to the top ten independent laboratories ranked by payment received; adapted from Kandilov et al. [4]

The coverage areas of these top two reference laboratories is considerable, as judged by the number of separate facilities [defined by unique Clinical Laboratory Improvement Amendments (CLIA) numbers] and counties served. The top-ranked independent laboratory had 206 separate facilities and served 3114 counties; the second 228 separate facilities and 3014 counties. Together these two laboratories received $1.23 billion, roughly half of the total Medicare Part B payments to independent laboratories and almost 20 % of the total $6.7 billion paid for all laboratory testing. Payments to the next three independent laboratories comprised 4.9 % ($124 million), 3.8 % (~$96 million), and 1.8 % (~$45 million) of the total payments, each having only 3, 2, or 6 CLIA numbers and serving 1360, 938, and 773 counties, respectively. Two of these three laboratories focused primarily on testing for patients with end-stage renal disease (ESRD) . The final five independent laboratories comprised only 4 % of the total payments, of which one offered testing primarily for ESRD patients and the other for

heart disease assessment. The authors cautioned the representation of market share and counties served was likely an underestimate given the review of only 5 % of the dataset.

The authors concluded that only two major independent laboratories have a significant share of Medicare laboratory testing . They suggested competitive bidding to be designated a “national Medicare laboratory” would have the advantage of soliciting “aggressive” bids and the potential of achieving “substantial economies in the bidding and contracting process .” This suggestion was based on the economic theory in which the underlying premise is the “product” (i.e., laboratory test result) is “homogeneous” and firms therefore compete on price. They further postulated implementation of competitive bidding would lower Medicare expenditures and would alter the clinical laboratory market, e.g., if competitive bidding reduced prices paid by Medicare to the marginal testing costs of large national laboratories capable of achieving high economies of scale, smaller laboratories might minimize losses by outsourcing their own testing.

In 2003 CMS was charged with conducting a “demonstration project” for competitive acquisition of clinical laboratory services , with the goal of determining whether competitive bidding could continue the provision of quality and accessible Part B clinical laboratory services at fees below current Medicare rates [5]. A competitive bidding demonstration was initiated October 2007 for the San Diego metropolitan area. This demonstration was halted in April 2008 and ultimately repealed in summer 2008 by both the US House of Representatives and the Senate.

The top two major independent clinical laboratories continue to demonstrate significant profits, fueling continued governmental efforts to reduce reimbursement with components stipulated within balanced budget acts reminiscent of the CMS demonstration project. Since reduction in clinical laboratory payments would affect all clinical laboratories, not just the top two reference laboratories, substantial unintended and unfortunate consequences for the majority of clinical laboratories would be expected [6].

Clinical Laboratories and Reference Laboratory Use

Thousands of clinical laboratory tests are available today. Obviously no single laboratory could offer the entire test menu. The decision of which tests to send to a reference laboratory for testing is a complex decision influenced by laboratory staffing, expertise, instrumentation, cost , informatics,

turnaround time (TAT) requirements linked to clinical care decisions and treatment and other issues. Each clinical laboratory is substantially unique in the patient population served and clinical demands for laboratory testing, influencing whether testing should be performed “in-house” versus at a reference laboratory. For truly esoteric testing, reference laboratories have the requisite test volume and expertise to maximally achieve cost-effectiveness since the low volume of such esoteric testing for any individual clinical laboratory, even if the infrastructure was present, would be cost prohibitive.

Choosing a Reference Laboratory

Choosing a reference laboratory involves many considerations including quality, cost-effectiveness, and efficiency [7]. Quality assessment involves personnel qualifications, instrumentation, acceptable performance with external quality assessment specimens, and ongoing performance improvement activities. Client satisfaction is often revealing of a laboratory’s perceived quality and can be readily assessed by networking with colleagues. Cost-effectiveness is self-explanatory. Efficiency considerations include scope of available testing and related issues of specimen collection, processing, transportation, timely return of results, ease and assistance with electronic interfacing, and availability of professional interpretations.

The performance of the reference laboratory should be continuously evaluated to assure it continues to meet the needs of the referring laboratory .

Reference Laboratory Use by Clinical Laboratories

What percent of the typical testing offered by a hospital clinical laboratory is sent for reference lab testing? In one study and of 94 hospital laboratories surveyed, the median % of all requested testing referred for reference laboratory testing was 5 % (tenth percentile, 2 %; 90 % percentile, 20 %) [8].

While reference laboratory testing represents only a small percentage of overall testing, it has a disproportionately higher cost . In one study reference laboratory testing comprised only 1.06 % of total laboratory testing volume yet accounted for 12.4 % of the total laboratory budget [9]. The average cost of a reference laboratory test was approximately 13 times greater than the average unit cost of a test performed in the clinical laboratory.

The overall cost of reference laboratory testing to the individual clinical

laboratory is significant. Reductions in reference laboratory test volumes therefore can result in considerable savings. The University of Michigan Health System (UMHS) , through their Laboratory Test Utilization Program , held reference laboratory testing for UMHS patients' cost constant at ~$5 million/year for fiscal years 2008–2012 [10]. Since there was a concomitant increase in laboratory testing growth, this dollar amount actually represented normalized annual decreases in total clinical laboratory expense from 18 % in FY 2008 to 13.1 % in FY 2012. A laboratory utilization initiative at the University of Iowa Hospitals and Clinics focused on using the electronic medical record for sendout test utilization control realized a 2-year post-interventional savings of ~$600,000 [11]. The laboratory leadership at the Brigham and Women's Hospital , by prospective review of reference laboratory testing allowed within their formulary , deflected the upward trend of their reference laboratory testing budget and saved 54 % ($3.7 million) of projected costs and 25 % ($1.1 million) in actual expenditures for fiscal year 2013 [12].

Make Versus Buy

Referring Testing Out ("Buy")

The decision of when to refer testing to a reference laboratory often relies on a "make versus buy" analysis [13, 14]. The decision will depend on many factors unique to each clinical laboratory, minimally including specimen acquisition and transport, informatics, the complexity of testing currently offered in the individual clinical laboratory, anticipated volume of requested testing, relative costs , staffing, staff expertise, and instrumentation.

Additional Costs

Reference laboratory testing brings additional costs to a clinical laboratory [8]. This often includes a dedicated sendout area for packaging and shipping specimens, specially trained personnel to assure correct specimen handling, and often dedicated personnel spending more than 50 % of effort in the sendout area. Under certain circumstances, the reference laboratory may provide the necessary staffing to assure test ordering and handling accuracy.

The number of reference laboratory tests used by a single referring laboratory can vary from 200 (10th percentile) to 492 (50th percentile, or median) to

1000 (90th percentile). Reference laboratory tests usually require unique test definitions/mnemonics/builds in the LISs and always exceed the number of tests offered by the individual clinical laboratory. The informatics costs is significant and necessary to assure correct interfacing of clinical laboratory information systems (LIS) with those of reference laboratories to assure correct outbound orders and inbound results transmission.

Paying for Reference Laboratory Testing Costs

Clinical laboratories have been tasked with maximizing productivity as measured by cost-efficiency. Cost-efficiency can be affected adversely if the direct costs of reference laboratory testing are included within the clinical laboratory's overall budget. Two predominant methods are used to pay for reference laboratory testing. The "institutional billing" ("direct client bill") method is preferred by reference laboratories since it simply involves billing the referring laboratory directly for all expenses. The referring laboratory pays the bill directly and the full cost of reference laboratory testing is included within the overall budget of the referring clinical laboratory. Another option is to work with reference laboratories to directly bill the patient's insurance carrier, effectively shifting the cost and removing it from the referring clinical laboratory's budget. This method requires the clinical laboratory to provide accurate demographic and billing information to the reference laboratory, however, a nontrivial effort with additional management costs. Finally a "balanced billing" method is often negotiated in which insurance carriers are directly billed, and the referring laboratory is responsible for costs rejected or only partially covered by the insurance carrier.

Reference Laboratory Ordering Accuracy

Given the higher costs of reference laboratory testing, a desired goal is 100 % accuracy of ordered tests. One study assessed the accuracy of reference laboratory testing by laboratory personnel, many specially trained and or dedicated to sendout testing, and demonstrated approximately 98 % of ordered reference laboratory tests were correctly ordered [8]. Conversely 2 % were not, however, an error rate double that reported for inpatient and outpatient tests [15, 16]. Given the higher per unit costs of reference laboratory tests, the costs associated with these errors was speculated to be significant. It was also speculated this 2 % order error rate occurring with

trained laboratory personnel familiar with reference laboratory test names and clinical indications would increase when providers were allowed to directly order reference laboratory testing through electronic ordering systems. This is because providers would be less experienced in navigating the plethora of available reference laboratory tests, many with similar ("look alike, sound alike") or related names , linked to the accuracy of test menus in electronic ordering systems .

Examples of "look alike, sound alike" tests mistakenly ordered included manganese orders when magnesium was desired and beta-2-microglobulin orders when beta-2-glycoprotein was desired [16]. Implementation of warning "prompts" was highly effective resulting in a total of only one or three incorrect orders for manganese or beta-2-microglobulin post-intervention.

Another example of the incorrect "look alike, sound alike" test inclusion in test order sets was the inclusion and therefore misordering of 1,25-OH vitamin D instead of 25-OH vitamin D, the preferred screening test for vitamin D deficiency [11]. Educational efforts coupled with revising the order sets to contain the correct test (25-OH vitamin D) resulted in a sustained 75 % reduction in 1,25-OH vitamin D test orders.

Bringing Reference Laboratory Testing In-House ("Make")

Reference laboratory test utilization should be regularly reviewed. Through this review tests of significant test volume can be identified and considered for performing in-house. If the correct instrumentation, staffing, and staff expertise is available, it may be more cost-effective to perform testing in-house.

An example in my laboratory was the use of reference laboratory testing for an "acute viral hepatitis panel ." The panel included hepatitis A IgM, hepatitis B surface antibody, hepatitis B surface antigen, and hepatitis C antibody . The clinical laboratory was sending a ~1000–3000 specimens annually to the reference laboratory for testing (Fig. 19.2). Until 2010 the laboratory did not have the staffing or instrumentation to perform these tests.

a

Test	# Tests	Cost
Lead, Blood	523	$4,912.02
O&P Concentrate & Strain	523	$4,562.01
HIV-1 RNA, QT bDNA 3.0	594	$55,377.00
HCV RNA, PCR, Quant	601	$67,312.00
Hemoglobinopathy Eval	641	$8,083.01
HIV-1 RNA, QT bDNA	642	$60,385.50
PTH, Intact and Calcium	645	$21,193.28
Rheumatoid Factor	674	$3,702.72
VZV Ab IgG	828	$9,499.00
Hepatitis Panel	869	$57,623.39
Rubella Immune Status	1044	$5,012.02
ANA,IFA w/rfl Titr,Pattrn	1095	$6,635.70
Iron and TIBC	1553	$17,407.96
C-Reactive Protein	1681	$8,073.50
Hep B Core Ab (IgM)	1863	$27,075.06
Hepatitis A IgM	1870	$24,401.69
HBV Surface Ag w/rfl	3346	$75,014.46
Subtotal		*$456,270.32*

b

Test	# Tests	Cost
Resp Allergy Prof Reg XIV	58	$10,030.52
JAK2 Mutation,QN,Leumeta	21	$10,500.00
HSV 1,2 DNA, PCR	66	$11,880.00
von Willebrand Comp Panel	18	$12,276.00
HCV RNA, QUAL TMA	112	$12,880.00
T3, Free	469	$13,192.46
StoneRisk Diagnostic Prof	37	$13,440.00
MaterniT21 (TM) Plus	25	$13,685.00
Lymphocyte Subset Panel 5	346	$14,054.52
Cryptococcal Ag Scr w/rfl	140	$15,066.11
HCV RNA, PCR, Quant	142	$15,904.00
AFP, Tumor Marker	480	$16,060.80
Iron and TIBC	1553	$17,407.96
CCP Antibody (IgG)	263	$20,043.00
TPMT Activity	56	$20,130.00
ANCA scr,MPO,PR3 w/rfl	135	$20,790.00
PTH, Intact and Calcium	645	$21,193.28
Methylmalonic Acid,GCMSMS	420	$23,045.00
Hepatitis A IgM	1870	$24,401.69
HCV RNA GENOTYPE, LIPA	254	$25,300.00
Hep B Core Ab (IgM)	1863	$27,075.06
HBV Virus DNA, Quant, PCR	269	$30,411.30
HIV-1 Genotype	109	$35,425.00
H. pylori Ab(IgG,IgA,IgM)	415	$39,674.00
Testosterone,F&B&T,LCMSMS	319	$40,481.10
HIV-1 RNA, QT bDNA 3.0	594	$55,377.00
Hepatitis Panel	869	$57,623.39
HIV-1 RNA, QT bDNA	642	$60,385.50
HCV RNA, PCR, Quant	601	$67,312.00
HBV Surface Ag w/rfl	3346	$75,014.46
Subtotal		*$820,059.15*

Fig. 19.2 Review of one referring laboratory's reference laboratory testing ranked ordered by (**a**) test volume exceeding 500 tests/year and (**b**) individual tests each cumulatively costing more than $10,000/year

The first step was bringing hepatitis C antibody (HCVAb) testing in-house . This move was triggered in 2012 by the recommendations from the Centers for Disease Control and Prevention (CDC) to identify those with chronic HCV infection by screening persons born between 1945 and 1965 [17]. The screening test algorithm consisted of testing for HCVAb, and if positive, to reflexively perform quantitative HCV viral load testing. Our Emergency Department initiated an HCV screening program and requested a 1 h HCV antibody test TAT. This rapid TAT was to assure that the patient was still in the Emergency Department to obtain a new specimen for HCV load quantification in case HCV antibodies were detected. The desired 1 h TAT was much faster than the 3–5 days routine TAT for the reference laboratory HCV antibody testing and required the laboratory to bring this test in-house and to offer it "stat." In-house HCVAb testing was successfully implemented in early 2013 and preceded establishment of the other necessary

components of this screening program (i.e., referral and timely access to a clinic dedicated to treatment of chronic hepatitis C infection, effective pharmaceutical therapy, and to gastroenterologists for specialized evaluation for cirrhosis or hepatocellular carcinoma when necessary).

As a related matter, the physicians had been requesting a faster TAT for hepatitis B surface antigen (HbSAg) results than the 3–5 day TAT provided by reference laboratory. HbSAg results were essential for assigning a newly diagnosed adult ESRD inpatient to the appropriate hemodialysis center and speeding discharge or hastening the decision of whether to administer hepatitis B immunoglobulin to a neonate when the mother's hepatitis B infection status was not known. The 3–5 day reference laboratory HbSAg TAT resulted in prolonged and unnecessary hospitalizations for both groups of patients.

In 2010 the laboratory switched immunology testing platforms to one capable of random access testing for each of these hepatitis tests. Until in-house HCVAb testing was implemented, we had not taken advantage of offering the other hepatitis tests as in-house testing. Analysis of our reference laboratory testing costs indicated we had been spending a total of ~$180,000/year on these tests , representing 22 % of all reference lab tests performed and 22 % of the total cost for reference laboratory testing (Fig. 19.2).

Labor was our major consideration for bringing all other hepatitis tests in-house. We determined in-house testing would not require additional staff because the testing platforms were fully automated. Laboratory staff intervention was further minimized by implementing automatic electronic release ("autoverification") for all negative results. Following configuration of the LIS and all relevant inbound and outbound information systems, and successful participation in external proficiency testing, in-house testing was implemented. This new rapid TAT was noticed quickly by the physicians, with appreciation enthusiastically expressed for decreasing hospital lengths of stay for adults with ESRD and mother–baby pairs.

Examples of in-sourcing reference laboratory testing at other institutions abound [12]. Regular review of reference laboratory tests and test volumes is essential in managing costs and determining when it makes sense to bring testing in-house. Further review of our current reference laboratory testing indicates our next big gain will be to bring molecular testing, especially viral load quantification, in-house (Fig. 19.2). Currently we lack instrumentation

and personnel to develop this new line of testing .

Strategies for Controlling the Use of Reference Laboratories

An individual clinical laboratory either lacks the necessary infrastructure or the low volume of individual esoteric tests is too costly to perform in-house, resulting in obtaining testing services from reference laboratories. A myriad of methods have been described for effective management of reference laboratory testing [18].

Requiring Clinical Justification

Liu et al. performed a simple intervention—requiring documentation of clinical justification—for any chemistry sendout test costing more than $20 Canadian (CDN) [19]. Over a 12-month period, 910 requests were received. Of these 428 (47 %) were approved and 482 (52.9 %) canceled. The reasons for cancelation varied from lack of ordering provider response to the request for clinical documentation (367, or 74.1 %) to cancelation by the ordering physician (120, or 24.9 %) to cancelation by the reviewing pathologist (5, or 1.0 %). There was no significant difference in reasons for cancelation for primary care physicians versus specialists .

The largest group of cancelations was due to lack of response from the ordering physicians. While not systematically monitored, many of the canceled tests were not subsequently reordered suggesting lack of clinical need for the original request.

A graded difference in test cancelation was observed. 238 (61 %) of 390 requests from primary care practitioners were canceled, compared with 182 (42.5 %) of 428 requests from specialists, followed by 23 (92 %) of the 25 tests ordered by medical residents. Based on this differential cancelation rate, the authors suggested limiting the ability of medical residents from ordering sendout tests .

The total cost of all requested testing (~$134,000 CDN) was reduced by 47 % (~$71,000 CDN). This savings vastly exceeded the $5820 CDN administrative costs incurred by the laboratory for providing the administrative intervention.

Clinical Consultation

The University of Washington group at Seattle Children's Hospital developed an active utilization management program to manage expensive genetic testing [20]. Tests scrutinized included those costing more than $1000, multiple genetic test requests on a single requisition, requests to send testing to non-preferred or international laboratories, or tests performed in-house but requested to be sent to a reference laboratory. The review team comprised a total of 0.7 full-time equivalents (FTE) , consisting of three doctoral-level scientists (0.1 FTE each) and one genetic counselor (0.4 FTE). Of 199 genetic tests from a total of 251 cases meeting review criteria, 24 % were either downgraded to sequential testing (21 cases, or 11 %) or canceled (25 cases, 13 %). The consultative service was used more frequently by non-geneticists (i.e., hematology/oncology, neurology, cardiology, endocrinology, rheumatology, or other practitioners). From a total test request cost of ~$610,000, ~$119,000 in savings was achieved. This represented 19.5 % of original total test costs or an average savings of $463 per test request. Cumulative the savings exceeded the personnel costs of providing the consultative service and was cost justified.

Formularies

A few organizations have promulgated the use of laboratory formularies, analogous to the common use of pharmaceutical formularies and their restrictions on pharmaceutical use.

At the University of Michigan Health System (UMHS) and after a decade of laboratory-initiated ineffective test utilization attempts, a multidisciplinary Laboratory Test Utilization Program was formed in July 2008 [10]. A standing "Laboratory Formulary Committee" was created, led by a practicing clinician with "strong" representation by Pathology. "Content experts" were invited for specific test discussions as necessary. The laboratory's role was to provide test volume, cost , reimbursement, and utilization data. Evidence-based peer-reviewed literature was used to guide decisions. Decisions were publicized to all providers and encoded into the appropriate information systems. Follow-up surveys were conducted every 6 months, whenever there is a change in medical practice or by "appeal."

Given UMHS clinical laboratories are full service and comprehensive, UMHS reference laboratory tests by default were of low or moderate test

volume, expensive, and extraordinarily esoteric. Since its inception, the committee has evaluated and vetted 43 reference laboratory tests. The work of this committee has allowed the UMHS to hold reference laboratory test costs relatively stable (actually decreasing if adjusted for inflation) at ~$5 million/year [10].

The University of Iowa Hospitals and Clinics implemented restrictions on 170 sendout tests in July 2012 [11]. Of these 170 tests, pathologist approval was required for 164, infectious disease attending for four and neurology attending for two. Post-implementation, orders decreased by 23 % with direct cost savings of $600,000.

The Laboratory Medicine leadership at the Brigham and Women's Hospital implemented a reference laboratory test formulary [12]. Residents and their respective attending were tasked with prospective review and approval of the requested reference laboratory tests, seeking consultation from specialists (e.g., neurology, medical genetics) as needed. They identified 32 % of tests were not clinically indicated, 26 % not needed for inpatient management, 4 % redundant with existing data, 6 % order entry error, and 4 % each for testing inappropriate for the clinical question or for research purposes. 24 % of reference laboratory tests were substituted with an alternative test. Through this process and compared with the baseline utilization determined from fiscal years 2005–2009, the upward trend of reference laboratory tests was deflected resulting in a 54 % ($3.7 million) reduction in projected costs and 25 % ($1.1 million) in actual costs.

Prior Authorization

Prior authorization allows selected individuals to order esoteric testing without requiring approval or having the test order scrutinized. Reference laboratory test formulary development has used the concept of prior authorization by delegating approval of specialty-specific tests to certain subspecialists (e.g., neurology, medical genetics, infectious diseases, endocrinology) [11, 12]. Others have incorporated the prior authorization principle into color-coded test ordering schemes [21].

If reliable data exists, another option is to allocate or jointly share budget responsibility for specific reference laboratory tests that are used primarily by a single specialty. The specialty service vets and has the authority to approve all requests for the specific reference laboratory test(s).

Limiting Reference Laboratory Testing for Inpatients

One group has set a general criterion that reference laboratory testing for inpatients should influence management during the current admission. Real-time review of reference laboratory testing determined 26 % of reference laboratory testing did not meet these criteria and was therefore canceled [12].

Electronic Orders and Decision Support

Electronic medical or health record systems or configuration of such to improve test utilization are still in their infancy regarding providing useful real-time decision support. Rudimentary interventions include “pop-up” alerts when a particular ordered test has attached conditions (e.g., requires approval, automatic cancelation for particular patient settings, etc.) and their effectiveness suffers from user “pop-up” alert fatigue. More effective is the use of “hard stops,”i.e., programming which halts the user from further action [11]. Other tactics to minimize overuse of reference lab testing include warnings about high cost and very high cost warnings, long TATs, required genetic counseling, and reflex warning (when appropriate) [11]. Acknowledging tests as “sendouts” and having a prolonged TAT can dramatically reduce duplicate orders placed with the assumption the test was not performed because a result was not available within the customary in-house laboratory test TAT .

Reference Laboratory Utilization Review

At a very rudimentary level, test utilization reports should be regularly obtained and reviewed by the referring laboratory. From these reports high-volume tests can be identified and considered for in-house testing (Fig. 19.2). Regular monitoring of tests with low volume and/or of high complexity can quickly identify unexpected increased test volumes, triggering utilization review for appropriateness of testing and implementation of real-time processes to allow only clinically justifiable tests to be performed.

The reference laboratory may assist the referring laboratory with additional analyses regarding whether referred testing patterns align with evidence-based testing recommendations [22].

References

1. US Government Printing Office. Medicare claims processing manual. 2015. https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/clm104c16.pdf (cited 14 Sept 2015).

2. CLIA Law & Regulations: Centers for Disease Control and Prevention. http://wwwn.cdc.gov/clia/Regulatory/default.aspx (cited 14 Sept 2015).

3. Institute of Medicine. Medicare laboratory payment policy. Now and in the future. http://iom.nationalacademies.org/Reports/2000/Medicare-Laboratory-Payment-Policy-Now-and-in-the-Future.aspx (cited 14 Aug 2015).

4. Gass Kandilov AM, Pope GC, Kautter J, Healy D. The national market for medicare clinical laboratory testing: implications for payment reform. Medicare Medicaid Res Rev. 2012;2(2):1–21.

5. Medicare Prescription Drug, Improvement, and Modernization Act of 2003. 2003. http://www.gpo.gov/fdsys/pkg/PLAW-108publ173/pdf/PLAW-108publ173.pdf (cited 14 Aug 2015).

6. Wilson ML. Decreasing inappropriate laboratory test utilization: controlling costs and improving quality of care. Am J Clin Pathol. 2015;143(5):614–6.
[CrossRef][PubMed]

7. Rickert R, Blank C, Brase S, Crystal R, Hausler Jr W, Hollander I, et al. Selecting and evaluating a referral laboratory; approved guideline. Wayne, PA: NCCLS; 1998. 1-56238-357-4 Contract No.: GP9-A.

8. Valenstein PN, Walsh MK, Stankovic AK. Accuracy of send-out test ordering: a College of American Pathologists Q-Probes study of ordering accuracy in 97 clinical laboratories. Arch Pathol Lab Med. 2008;132(2):206–10.
[PubMed]

9. MacMillan D, Lewandrowski E, Lewandrowski K. An analysis of reference laboratory (send out) testing: an 8-year experience in a large academic medical center. Clin Leadersh Manag Rev. 2004;18(4):216–9.
[PubMed]

10. Warren JS. Laboratory test utilization program: structure and impact in a large academic medical center. Am J Clin Pathol. 2013;139(3):289–97.
[CrossRef][PubMed]

11. Krasowski MD, Chudzik D, Dolezal A, Steussy B, Gailey MP, Koch B, et al. Promoting improved utilization of laboratory testing through changes in an electronic medical record: experience at an academic medical center. BMC Med Inform Decis Mak. 2015;15:11.
[CrossRef][PubMed][PubMedCentral]

12. Greenblatt MB, Nowak JA, Quade CC, Tanasijevic M, Lindeman N, Jarolim P. Impact of a prospective review program for reference laboratory testing requests. Am J Clin Pathol. 2015;143(5):627–34.
[CrossRef][PubMed]

13. MacMillan D. Calculating cost savings in utilization management. Clin Chim Acta. 2014;427:123–6.
[CrossRef][PubMed]

14. Wilkinson D, Dilts T, Woolf W, Lifshitz M. Financial Management. In: McPherson R, Pincus M, editors. Henry's clinical diagnosis and management by laboratory methods. 22nd ed. Philadelphia, PA: Elsevier Saunders; 2011. p. 141–54.

15. Valenstein P, Meier F. Outpatient order accuracy. A College of American Pathologists Q-Probes study of requisition order entry accuracy in 660 institutions. Arch Pathol Lab Med. 1999;123(12):1145–50.
[PubMed]

16. Valenstein PN, Howanitz PJ. Ordering accuracy. A college of American pathologists Q-Probes study of 577 institutions. Arch Pathol Lab Med. 1995;119(2):117–22.
[PubMed]

17. Centers for Disease Control and Prevention. Testing for HCV infection: an update of guidance for clinicians and laboratorians. MMWR. 2013;62(18):362–5.

18. Baird G. The laboratory test utilization management toolbox. Biochem Med (Zagreb). 2014;24(2):223–34.
[CrossRef]

19. Liu Z, Abdullah A, Baskin L, Lewis G, Kelter G, Naugler C. An intervention to reduce laboratory utilization of referred-out tests. Lab Med. 2012;43(5):164–7.
[CrossRef]

20. Dickerson JA, Cole B, Conta JH, Wellner M, Wallace SE, Jack RM, et al. Improving the value of costly genetic reference laboratory testing with active utilization management. Arch Pathol Lab Med. 2014;138(1):110–3.
[CrossRef][PubMed]

21. Sluss PM. Reference laboratory utilization management. Clin Chim Acta. 2014;427:167–72.
[CrossRef][PubMed]

22. Analyzing Test Ordering Patterns Helps Labs Cut Costs. 2007. http://www.aruplab.com/AboutARUP/resources/articles_interviews/g2dttr.arupatop2007.06.pdf (cited 15 Aug 2015).

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_20

20. Utilization Management of Genetic Testing

Jane A. Dickerson[1], Jessie H. Conta[1] and Christina M. Lockwood[2]

(1) Department of Laboratories, Seattle Children's Hospital, 4800 Sand Point Way NE, OC.8.720, Seattle, WA 98105, USA
(2) Laboratory Medicine, University of Washington, 1959 NE Pacific St, NW120, Box 357110, Seattle, WA 98195, USA

Jane A. Dickerson (Corresponding author)
Email: jane.dickerson@seattlechildrens.org

Jessie H. Conta
Email: Jessie.conta@seattlechildrens.org

Christina M. Lockwood
Email: tinalock@uw.edu

Keywords Molecular testing – Utilization management – Genetic testing – Provider report cards – Privileging – Intervention – Next-generation sequencing – Newborn screening – Exome testing – Inherited disorders

Introduction

The motivation for monitoring and improving the utilization of genetic tests is similar to other domains in the laboratory—maximizing the value for the

patient by emphasizing the quality and clinical utility of the test and minimizing cost to the patient and health system. However, unlike other fields in laboratory medicine, genetic testing can elicit dread from laboratory leadership because of its rate of rapid growth, complex and constantly changing methodologies, and disproportionate expense relative to test volumes.

Genetic testing is increasing at an annual rate of 15 % whereas non-molecular tests are experiencing less than 5 % annual growth [1]. The national spend on genetic testing is similarly trending upwards and is estimated to reach $15–25 billion by 2021 [2]. For many labs, this can represent a large portion of their annual spend on referral lab services [3]. In one example from a retrospective review of reference testing at Brigham and Women's Hospital, they reported that 51 % of their annual reference lab spend is for molecular testing [4]. Technology and prices evolve rapidly, requiring continuous review to evaluate the costs and benefits of any particular genetic test [5].

There is a need for guidance around test selection and result interpretation of molecular tests. Nongeneticists are incorporating more genetic and genomic testing in their practices while reporting a lack of confidence in their fundamental understanding of molecular biology [6, 7]. Selecting the right test is confounded by inconsistencies in naming (i.e., gene name, syndrome name, protein target). One such example is confusion surrounding ordering of the *RET* gene (applicable to MEN type 2) instead of the intended test for Rett syndrome (the *MECP2* gene). Even medical geneticists and laboratory professionals struggle to keep abreast of the thousands of clinical testing options that are performed and marketed in different ways by hundreds of commercial and academic laboratories. It has been estimated that several new tests are validated and released each month, and the recent introduction of clinical next-generation sequencing assays has only increased the rate of growth of available genetic tests.

Traditional approaches to genetic testing have interrogated a single gene or a few genes relevant to a specific clinical indication. The methods historically used include Southern blots, restriction enzyme digests, and PCR amplification with products visualized on agarose gels or more recently capillary electrophoresis and sequencing. Chain-terminating dideoxynucleotide sequencing , more commonly referred to as Sanger sequencing , was published in the mid-1970s and remained the mainstay of

sequencing through completion of the Human Genome Project [8]. Sanger sequencing is highly accurate and relatively quick from setup to data analysis but is also laborious and quite expensive. Although the method was automated in the 1990s, which facilitated the faster than projected completion of the Human Genome Project, sequencing technology did not significantly change until the widespread adoption of massively parallel sequencing. The NHGRI monitors the cost of sequencing based on centers the Institute funds; the cost per genome has decreased from $100M in 2001 to less than $4500 in 2015 [9, 10]. Two notable advantages of next-generation sequencing (NGS) when compared to Sanger sequencing are the base output per sequencing "run" and the cost per megabase of sequence. The quantity of bases produced varies by platform, but a conservative estimate for NGS is 35M bases *more* than an automated Sanger sequencing run. The cost per megabase is also approximately 8000-fold higher for Sanger sequencing. However, many clinical tests continue to effectively utilize Sanger sequencing, which is the most appropriate assay for a targeted region such as a few sites in a gene or even an entire gene. Depending on the specific platform, NGS tends to be most efficient when sequencing greater than 10,000 bases, typically in the setting of a multigene assay. The exome refers to the portion of the genome that codes for proteins, which is approximately 1 % of the entire human genome. Exome sequencing is advantageous when the clinical question is broad, such as determining all variants in a tumor specimen or searching for an unknown causative gene in an apparently Mendelian condition.

Next-generation sequencing has allowed the precipitous development of massive gene panels without the incremental cost. Whole exome, whole genome, and 50+ gene panels are clinically available and, at the time of this publication, cost at least several thousand dollars. However, clinical availability does not necessarily mean that NGS can or should completely replace traditional single and sequential gene testing approaches. There are many factors to consider when deciding the best testing approach, such as the differential diagnosis, previously performed testing, clinical context, laboratory expertise, and numerous logistical factors. When considering the differential diagnosis, for example, a single-gene assay is an appropriate test for neurofibromatosis type 1, while a panel approach is recommended when searching for the molecular etiology underlying a clinical diagnosis of Noonan syndrome . The context of a patient's previous testing is also relevant; for example, pursuing multiple single-gene assays may be less

efficient and more expensive than opting for a targeted panel or whole exome sequencing. Clinical influences include the clinical acuity, availability of actionable treatment options, and family factors such as a current pregnancy. Another aspect that may not be immediately apparent to the ordering provider is the experience of the lab offering the assay, including the director's experience with result interpretation. Finally, there are myriad logistical issues of the analysis such as cost, turnaround time, and sample type; for example, *RB1* analysis for retinoblastoma has a higher diagnostic yield in tumor tissue but, if unavailable, can be completed using a blood sample.

It has been said that utilization management is best practiced locally. Utilization management is not a one-size-fits-all process because institutions each have unique provider and administrative culture(s), as well as distinct challenges and strategic goals. Furthermore, the goals of utilization management programs are not solely focused on financial improvements but also on quality improvement to demonstrate that the UM strategy neither results in patient harm nor hinders clinical utility [11]. Cost savings is a beneficial by-product of test utilization management; however, the greatest benefit of UM programs is improved patient care.

This chapter outlines principles of successful utilization management of genetic testing using a combination of gentle, medium, and strong interventions , each of which can be customized to best fit an institution. The strength of the intervention refers to its overall success at stopping an unwanted behavior. Gentle interventions are usually educational in nature and do not require systematic changes or hard stops. Medium interventions include systematic changes, but allow for navigation around them. For example, removing tests from the requisition or hiding tests in CPOE , but allowing the same test to be ordered if specifically requested. Finally, strong interventions employ different mechanisms to produce hard stops. It should be emphasized that these interventions are not mutually exclusive; using more than one intervention increases the impact on behavior. Examples for each intervention type are outlined in Table 20.1 [12, 13].

Table 20.1 Examples of gentle, medium, and strong interventions

Gentle	Medium	Strong
Posting guidelines on the requisition	Utilization report cards	Utilization report cards with peer or leadership review
Computerized reminders regarding utilization guidelines	Changes to manual requisitions	Privileging specific tests to specialty providers

Educational lectures	Hiding tests in computerized provider order entry systems	Send-outs formulary
Consensus reference lab preselection for specialized testing		Requirement for high-level approval or consultation
		Rules requirement

Because the field of genetic testing is rapidly evolving, this chapter would be quickly obsolete if it attempted to provide an exhaustive discussion of all types and appropriate uses of genetic testing. Instead, by using case vignettes illustrating commonly encountered challenges in different patient populations, the genetic test utilization strategies proposed here will remain relevant despite the changing landscape of genetic testing. Note that a clinical exome vignette is shown with gentle, medium, and strong interventions to demonstrate the effectiveness of each in the specific context of this test that is a utilization challenge for many institutions.

Patient Populations

Genetic testing patterns and utilization management considerations can differ among populations due to their variable testing considerations. These variables include clinical urgency, specimen type, specimen collection, specimen stability, and medical rationale (Fig. 20.1). Different types of interventions will have more or less impact because of these variables. Populations to consider include maternal-fetal medicine (MFM) , pediatric, and adult. Within these populations, testing can be directed at determining inherited conditions, present in the germline, or those found in somatic tissue that are acquired over time. In addition, it is important to consider the timing of test coordination, as there are additional variables to address between the inpatient and outpatient setting .

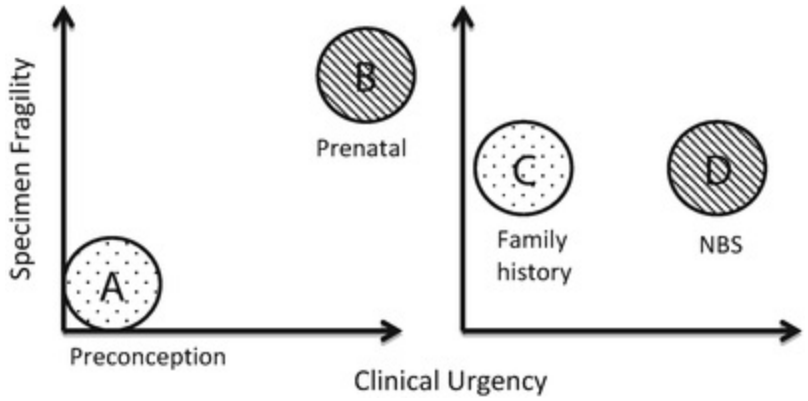


Fig. 20.1 Cystic fibrosis as an example of the variables to consider when performing genetic testing in different patient populations. The overall degree of shading reflects the strength of the medical rationale for testing with increased shading corresponding to higher clinical utility. Specimen fragility indicates the overall difficulty of obtaining a specimen. (**a**) A couple with family history of cystic fibrosis; interested in testing prior to starting a family. (**b**) A couple with family history of cystic fibrosis and currently 12 weeks pregnant; interested in prenatal testing. (**c**) An asymptomatic infant with family history of cystic fibrosis; parents interested in testing. (**d**) An asymptomatic infant with abnormal newborn screen result for cystic fibrosis and referred for clinical follow-up

Maternal-Fetal Medicine Screening

Maternal-fetal medicine screening can broadly be divided into carrier screening, which is directed at the parent(s) or fetal screening. Each of these is briefly discussed below.

Carrier screening for genetic disease in preconception and prenatal medicine has been an established practice for decades. The intent of carrier screening is to assist with reproductive planning by identifying individuals at increased risk of having a child with a serious medical disorder. Two broad approaches to carrier screening include applying testing to an unselected, general population and testing a narrowly focused, at-risk population. Professional organizations provide guidance through consensus recommendations and position statements. For example, the American College of Medical Genetics and Genomics (ACMG) , the American College of Obstetricians and Gynecologists (ACOG) , and the National Society of Genetic Counselors all recommend general population screening for cystic fibrosis [14–16]. For select conditions , the ACMG and the ACOG recommend ancestry-based screening, such as screening individuals at higher risk for Tay-Sachs disease [17, 18]. However, recommendations may be discordant for other conditions, such as spinal muscular atrophy (SMA) . The

ACOG recommends SMA testing in the setting of a positive family history, whereas the ACMG recommends general population screening [19, 20]. Advances in contemporary genomic sequencing have made it technologically feasible to expand carrier screening to the general population, though important limitations remain. The number of conditions screened varies between tests; expanded screening has increased from a handful of disorders recommended in the current guidelines to the simultaneous detection of upwards of 100 conditions [21]. A joint statement from five professional organizations examined several of the relevant factors for expanded carrier screening without making specific recommendations, which highlights the controversy of this issue [22]. Many advocate that expanded carrier screening be performed prior to conception, which has the substantial benefit of alleviating the clinical urgency that accompanies prenatal screening. Although expanded carrier screening is at least theoretically efficient and can be more economical than several single-gene tests, universal expanded carrier screening awaits consensus among professional societies as well as the resolution of numerous ethical and social considerations [23].

Prenatal screening for chromosomal aneuploidies has also been offered to pregnant women for decades. There are many testing options, though traditional screening has involved a combination of maternal serum screening plus ultrasound. A recent development in prenatal screening has been noninvasive prenatal testing (NIPT) , which uses cell-free fetal DNA detectable in the maternal bloodstream combined with NGS. Since the fetal fraction of maternal plasma increases with gestational age, NIPT is currently not technologically feasible until a gestational age of 10 weeks. NIPT has been commercially offered since 2011 with assays minimally able to detect trisomy 21, 18, and 13 and sex chromosome aneuploidies [24]. The clinical implementation in only a few years has been extremely rapid with one recent survey of maternal-fetal medicine specialists reporting that 94 % of respondents offer NIPT to at least a portion of their patients [25]. It must be emphasized that NIPT is similar to previous serum screening assays in that it is a *screening* test and NIPT-positive women should be offered confirmatory diagnostic testing. A recent joint committee opinion from multiple professional organizations, including the ACOG, ACMG, and Society for Maternal-Fetal Medicine recommends NIPT as a screening method in patients at increased risk of fetal aneuploidies [26]. Expanding NIPT to a universal population has not been recommended for several reasons,

including a lower positive predictive value due to the decreased prevalence of aneuploidies in a low-risk population and an inferior cost-effectiveness relative to traditional prenatal screening modalities [26]. There have also been several reports of discrepancy between the NIPT-determined aneuploidy and the actual fetal karyotype. An important biological factor that contributes to these discrepancies is that the circulating DNA termed “fetal” is actually derived from the placenta; therefore, fetal or placental mosaicism can cause either false-positive or false-negative results [27, 28]. Another significant cause of increased circulating DNA is maternal malignancy, which may be undiagnosed at the time of NIPT [29]. The rapid maturation and evolution of NIPT are a challenge for both professional organization guidelines and utilization management policies, which should therefore be reviewed and updated frequently.

Both expanded carrier screening and NIPT are currently available as commercial direct-to-consumer tests. Given the inherent limitations of both tests, it is particularly important to involve expert health professionals who can provide essential test information and counseling. Fetal sex determination and paternity testing early in pregnancy are the most commonly marketed indications for DTC testing, and both have generated numerous controversies and ethical concerns .

Pediatric

In the pediatric setting, genetic testing ranges from routine screening in neonates to diagnostic testing for rare diseases to somatic testing in malignancy across the entire age spectrum. Newborn screening typically occurs within the first 2 days of life and involves sample collection from a heel stick transferred to a newborn blood spot card. The disorders screened for vary between states but must include 21 specific disorders and can include up to 50 others [30]. The disorders screened for must meet certain criteria, which stipulate that the disease causes serious medical complications and there is potential for successful treatment. In many instances, testing involves a screening test with additional confirmatory genetic testing coordinated as needed. However, there are also conditions where molecular testing is performed directly from DNA obtained from the newborn blood spot. For example, in some states, cystic fibrosis screening involves *CFTR* mutation analysis for the most common 23 mutations typically included in

cystic fibrosis carrier screening [31]. Challenges to consider for utilization management in this population include the need for timely family follow-up; high rate of false positives; sample integrity issues including improper labeling, timing and quality of the blood spot collection; and delays in mailing/processing specimens.

Beyond newborn screening , genetic testing in the pediatric population involves testing for inherited rare diseases. Genetic testing is a powerful diagnostic tool in this setting because of the rarity of conditions, broad and overlapping phenotypic spectrums that are constantly evolving, and lack of consensus clinical diagnostic criteria for most conditions. Results of genetic testing may provide genotype-phenotype correlations that guide medical management and provide valuable prognostic information for clinicians and families. Many conditions have a high morbidity and mortality rate, and it is therefore essential to consider the urgency of testing and the potential impact of results. The pattern of testing in this population typically includes a high total volume of tests that are relatively expensive and may only be ordered once or twice a year, with novel tests encountered frequently. Genetic testing in pediatric populations is further complicated by the different and potentially conflicting motivations of different stakeholders, including the provider, the payer, the patient, and the parents/family. While a provider is motivated to provide the best care possible to the patient, secondary motivations of scientific advancement and rare disease discovery can confound a rational approach to testing. Payers are often reluctant to provide coverage for novel tests and slow to create rational coverage policies in comparison to the rapid evolution of genetic testing. Parents or other family members may be motivated to end the diagnostic odyssey and/or identify a molecular etiology to guide reproductive counseling and testing options for future pregnancies, even if the testing will not directly impact the care of the patient undergoing the testing. Each of these factors is an important consideration when undertaking efforts to guide appropriate utilization of genetic testing in the pediatric population .

Adult

In the adult setting, genetic testing can be broadly classified as diagnostic, predictive or presymptomatic, carrier (see MFM population above), or pharmacogenomic testing.

As is implied by the name, diagnostic testing is used to confirm or rule out a known or suspected genetic disorder in a symptomatic individual. As of August 31, 2015, there are greater than 4500 genetic disorders with a known molecular basis cataloged in the NCBI Online Mendelian Inheritance in Man (OMIM) database [32]. Prior to the implementation of clinical exome and genome testing, testing for exceedingly rare disorders was often performed on a research basis before a clinically validated assay was offered in a clinical lab. Initial testing may still occur as part of a research study, but clinical confirmation typically does not lag far behind. Diagnostic testing is almost invariably performed on peripheral blood, though buccal cells or normal tissue may also be appropriate depending on the clinical indication. For example, if testing for an inherited disorder is appropriate in a patient who has received an allogeneic bone marrow transplant, buccal cells are most commonly used.

Predictive testing of an asymptomatic individual may be indicated in the setting of a family history of an inherited disorder . There are numerous important considerations that specifically apply to predictive testing, including whether early diagnosis changes medical interventions , how life-planning decisions can be affected, whether and how family members will be informed, and several additional psychological issues. The penetrance of a disorder is another key factor to contemplate prior to pursuing presymptomatic testing . In order to adequately address all of these issues, the value of thorough pre- and posttest genetic counseling cannot be emphasized enough. One of the first presymptomatic genetic tests offered was for Huntington disease , which is an autosomal dominant triplet repeat expansion disease with nearly complete penetrance. Recent advances in our understanding of cancer predisposition have also led to sharply increased testing for familial cancer syndromes and genes.

Pharmacogenomic testing can guide the most beneficial or effective medication and dosage that a patient receives. There are numerous examples of clinical indications for pharmacogenomic testing that range from anticoagulant therapy to chemotherapeutic dosage adjustment. Since this testing is aimed at determining a patient’s inherited genotype, peripheral blood is the most common specimen type .

Somatic Testing

Genetic testing can also be performed on somatic tissue in either a maternal-fetal, pediatric, or adult population and has unique considerations. Most somatic testing is performed in the context of cancer where the molecular profile of many genes or a single important mutation is determined in a tumor biopsy. A critical consideration that can cause false-negative results is the extent of tumor DNA in the sample tested. For example, a Sanger-based *EGFR* sequencing assay with an analytical sensitivity of 20 % would *not* be appropriate for a lung cancer biopsy specimen with only 10 % tumor nuclei. It is therefore imperative that a systematic approach is applied to quantifying tumor nuclei prior to molecular cancer testing. Tumor heterogeneity, timing of molecular testing , specimen suitability (fixed vs fresh tissue), and the utility of genetic testing are several additional factors that should be considered prior to somatic molecular testing .

Inpatient Testing

Genetic testing in each of these populations (MFM, pediatric, and adult) can be requested in the outpatient or inpatient setting. Additional caution should be paid for genetic test requests in the inpatient setting. The number of providers and their rate of turnover, especially at sites with resident training programs, confound appropriate coordination of inpatient testing. The consulting specialist is generally not the person entering the order, and frequently there are several specialties involved that request concurrent testing. While these factors may be less of an issue for tests with rapid turnaround times, the average turnaround time for genetic tests is several weeks to months, which is often longer than the inpatient stay. Risks to the patient include the potential for the wrong test to be ordered and risk for failure to retrieve and act on the result. Appropriate utilization review of testing in the inpatient setting can help to mitigate these risks .

Gentle Interventions

Gentle interventions are often a good place to start with new utilization management programs. While their ultimate impact is typically lower compared to medium and strong interventions, starting with gentle, low-technology interventions can be a good litmus test for the institution’s cultural readiness to improve laboratory test utilization. Institutional culture

includes both the administrative and provider culture. Provider cultures range from limited management with no or limited ordering restrictions (everything is on the test menu) to extensive management, where providers are incentivized or required to limit their test ordering practices. Teaching institutions and the availability of resources are also components of an institution's culture that influence prioritization and success of laboratory utilization interventions.

Gentle interventions include both passive, such as posting of guidelines or cost of tests, and active educational efforts, such as targeted presentations and communications [11]. In order to sustain the impact of an educational intervention, repeat educational efforts are almost always required [33]. With that in mind, a strategic start to engaging in genetic test utilization can be providing educational tools targeted at defined genetic tests that are either appropriate in a specific population or have no or unknown evidence-based clinical utility. The following vignettes illustrate the use of educational interventions through several commonly encountered clinical examples .

Vignette 1: Whole Exome Sequencing Educational Intervention

Background

Whole exome sequencing (WES) specifically targets the protein-coding regions of the genome, though it is important to note that current methods actually include approximately 90 % of the protein-coding regions of the human genome [34]. While WES is typically not an appropriate first-tier test, it can be appropriate if initial testing is unrevealing and a clear genetic condition is not evident to guide more targeted testing. Secondary findings must be considered with WES, and pretest counseling is a critical element of test coordination, though secondary findings overall are a controversial aspect of WES [35]. Given these concerns, laboratories should consider implementing policies and procedures to ensure that the testing is used and coordinated appropriately.

A low-technology, gentle intervention could involve creation of a best-practice recommendation that outlines a standard approach to WES testing, such as requiring evaluation by a medical genetics provider, obtaining insurance pre-authorization, and pretest genetic counseling. This type of recommendation has the highest likelihood of success if it is created with the

input from the experts (e.g., genetics providers) who will be most impacted. Once created, the recommendations can be posted on the lab test catalog and presented to providers during educational department meetings to guide clinicians toward optimal ordering practices .

Case Example

A 5-year-old boy was evaluated in the neurology clinic because of his history of severe encephalopathy, developmental delay, and seizures. The neurologist was interested in identifying an underlying etiology of his features in order to improve his treatment and to provide recurrence information for a future pregnancy. Rather than proceed with a single-gene approach, the neurologist decided that exome sequencing offered the best diagnostic yield. The previous month, a laboratory genetic counselor visited their department and presented the utility, complicating factors, and best-practice recommendations of using WES in the clinical setting. Since the neurologist planned to collect the sample that day, he consulted the lab test guide to find the best reference lab, and in doing so, he reviewed the best-practice recommendations listed in the online test guide. Based on the recommended approach, the provider collected the specimen and concurrently requested insurance pre-authorization. Although the recommendation was to refer for pretest counseling to a genetic counselor, the provider recently finished a genetics rotation and felt confident that he could adequately counsel the family regarding the benefits, risks, and limitations of whole exome sequencing.

Six months later, the results are returned with several variants of uncertain significance that will not impact management. The family was also alarmed to receive a $7000 bill in the mail. When they called their insurance provider, it was explained that the test was considered investigational and would not be covered.

Comments

This outcome can feel all-too-familiar to the well-meaning laboratorian. Patient complaints about cost are often directed to the laboratory, with the feedback rarely reaching the ordering provider. However, having led a discussion at the Neurology Department meeting, a relationship was built, providing a foundation for a follow-up conversation. This is an excellent

opportunity to explain the family's disappointment and offer constructive advice for future testing. As this example demonstrates, the gentle intervention of posting a best-practice recommendation can only achieve minimal impact because the provider can elect to override the recommendation .

Vignette 2: Fabry Testing with Pop-Up Reminder

Background

Fabry disease is caused by deficient activity of the enzyme alpha-galactosidase. It is an X-linked condition, and carrier females can variably be symptomatic or asymptomatic. Classic symptoms include periodic crises of severe pain in the extremities, vascular cutaneous lesions, sweating abnormalities, characteristic corneal and lenticular opacities, and proteinuria. Progressive renal and cardiac diseases are the main causes for morbidity and mortality in affected individuals. Diagnostic testing helps guide management including early routine heart and kidney function screening, treatment for pain and proteinuria, and enzyme replacement therapy. Choosing the right test is confounded by the confusing array of enzyme and gene tests, and the approach should be specific to the sex of the individual. In symptomatic males, enzyme activity testing of isolated leukocytes, plasma, or dried blood spots is the best first step. In females, however, enzyme activity testing is unreliable because females have both an affected and also an unaffected X chromosome, making full gene sequencing of the GLA gene the recommended approach.

A simple educational pop-up reminder in CPOE, or guideline printed on the requisition, can improve selection of the most appropriate test. This type of recommendation is not controversial; it does not require committee meetings or obtaining consensus from the expert users. The lab can implement the reminder without fear of reprisal beyond "pop-up fatigue ." Even with its simplicity, it can still have an impact on appropriate test utilization because the appropriate gender-specific testing approach can be easily forgotten.

Case Example

A 54-year-old female was referred to a pediatric biochemical geneticist to

assess her symptoms of weight loss, fatigue, neuropathy, and low free carnitine levels. Included in the differential was Fabry disease, late-onset Charcot-Marie-tooth disease , and mitochondrial disease. The provider chose to start with Fabry disease testing because it is a potentially treatable disorder. While searching for the alpha-galactosidase test in the computer ordering system, the pop-up below appeared (Fig. 20.2).

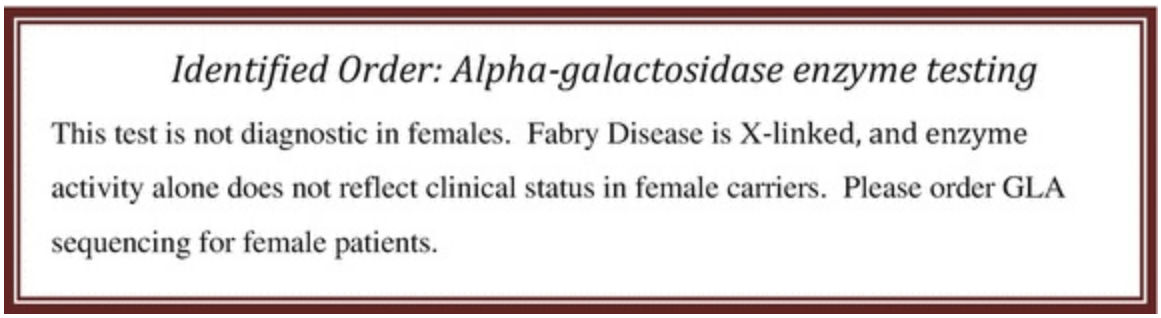


Fig. 20.2 Pop-up message with Fabry testing recommendations for females

The provider read the pop-up message and ordered GLA sequencing for her patient. Both the sequencing and deletion/duplication were negative for mutations, ruling out Fabry as a cause for this patient's clinical features.

Comments

In this example, a simple, relatively low-technology solution provided real-time, meaningful feedback to the provider and ultimately guided the appropriate testing choice. While not applicable for every case, pop-ups can be powerful tools when implemented thoughtfully. It is important to recognize that overutilizing this tool can result in "pop-up fatigue ," and, thus, lose its effectiveness .

Vignette 3: Thoracic Aortic Aneurysm Testing with Multidisciplinary Reference Lab Selection

Background

Aortic aneurysm complications are a significant cause of morbidity and mortality in Western countries and account for 1–2 % of all deaths [36]. Thoracic aortic aneurysm/TAA is caused by multiple disorders that can be acquired or inherited. Current estimates are that inherited or familial TAA

comprises at least 20 % of all TAA, though this is likely an underestimate [37]. Examples of heritable TAA include Marfan syndrome , Loeys-Dietz syndrome , vascular Ehlers-Danlos syndrome , and others. More than a dozen genes are associated with familial TAA disease, and inheritance can be autosomal dominant or recessive. Although the clinical history, family history, and physical exam can facilitate diagnosis, there is considerable phenotypic overlap between syndromes that may necessitate mutation testing. Determining the underlying genetic defect has implications for patient management, surveillance, and therapeutic treatments. For example, consensus guidelines from ten professional organizations recommend surgical aortic repair at a smaller aortic diameter for patients with mutations in *TGFBR1* and *TGFBR2* as compared to a patient with a mutation in *FBN1* [38]. Since affected family members can be asymptomatic, determining the underlying mutation is also critical as these individuals could be at risk for a life-threatening complication.

Selecting an appropriate genetic test is challenging both from a clinical and laboratory perspective because the genes involved in familial TAA are rapidly evolving. This has led to some clinicians relying on large panel tests that interrogate all relevant genes instead of specifically tailoring a test request based on the clinical findings. Alternatively, some laboratories have required that testing for a common gene be sent to a preferred reference lab without appreciating that reflex testing unavailable at the preferred reference lab may be indicated. Creating a multidisciplinary team to discuss utilization management and collaboratively determine an appropriate reference lab and testing strategy can dramatically improve clinical care.

Case Example

A 35-year-old pregnant woman (G1P0) in the 20th week of pregnancy was referred to the genetics clinic with no apparent relevant family history and a clinical diagnosis of Marfan syndrome based on the 1996 Ghent nosology. The cardiovascular clinic followed the patient, who had a stable aorta with sinuses dilated to 33 mm at her most recent clinic visit prior to pregnancy. No genetic testing had been performed on the patient. In consultation with the genetics clinic, it was decided that her mutation status would help guide risk assessment of aortic dissection and *FBN1* testing (Marfan syndrome) was ordered. Rather than sending to the primary reference lab, which offered *FBN1* sequencing, the decision was made to instead send *FBN1* testing to a

specialty cardiovascular lab based on a gene-specific, predefined reference lab list.

When no mutation was identified in *FBN1*, the genetics provider was able to add on additional testing of *TGFBR1* and *TGFBR2* (Loeys-Dietz syndrome) at the specialty cardiovascular lab . If the original specimen had been sent to the primary reference lab, a new specimen would have been required. A pathogenic mutation was identified in *TGFBR1*, which significantly increased the risk of pregnancy-related arterial dissection and impacted the woman's treatment. The High-risk obstetrics, genetics, and cardiovascular clinical teams jointly elected to perform a cesarean section in the 35th week of pregnancy without complication.

Comments

This example illustrates the effectiveness of engaging clinical stakeholders in utilization management . Consolidating rare genetic testing at a single laboratory can be particularly important when multiple disorders are on the differential diagnosis or there is an overlapping phenotype between disorders. In this example, the initial use of the nonprimary reference lab ultimately saved the patient from an additional clinical visit and unnecessary phlebotomy draw, thereby increasing patient safety and improving customer service to both the clinical teams and patient. Although privileging was not required in this example (Fig. 20.3), privileging can be another UM strategy that may be employed in conjunction with esoteric testing .

Recommendation: Depends on the clinical context and assessment of the information below. Assessment: Testing has historically been sent to Lab A. More recently, the availability of panels for these conditions has expanded. An available panel option at Lab B is listed below which was recommended by a multi-disciplinary team.		
	Lab A	**Lab B**
Test name/ code	Marfan syndrome testing	Vascular Aneurysm Panel + FBN1, MYLK, MYH11, PRKG1, SLC2A10
List Price (excludes sendout mark-up)	FBN1 sequencing: $1600	Sequencing panel: $3000
Turn-around Time	2 weeks	4-6 weeks
CPT code(s)	81408	81410
For panel testing, list of genes included on panel	FBN1 full gene sequencing	20 gene panel: ACTA2, CBS, COL3A1, COL5A1, COL5A2, FBN1, FBN2, FLNA, MED12, MYH11, MYLK, NOTCH1, PRKG1, SKI, SLC2A10, SMAD3, SMAD4, TGFB2, TGFBR1, TGFBR2
Methodology	Sanger sequencing	NGS

Fig. 20.3 Reference laboratory comparison spreadsheet

Medium Interventions

Medium interventions involve system changes without hard stops. System changes should be designed to make it easy for the provider to do the "right thing." It has been shown that removing tests from manual requisitions decreases the majority of inappropriate use [12]. In the age of computerized provider order entry (CPOE) systems , it is even more crucial to consider provider behaviors since there is automatic access to thousands of laboratory tests, the ability to customize order frequency, and the potential for confusion among similarly or misnamed tests [39]. For example, when considering naming of genetic tests , it is important to be consistent with naming conventions. Well-intentioned providers have ordered the wrong test by searching for the syndrome or protein target rather than the name of the gene. Simply renaming or hiding a test name can have significant impact on appropriate ordering patterns [40].

Providing feedback regarding provider ordering patterns in a collegial, non-blaming environment is another method used to influence appropriate testing behavior. The ability to fairly compare ordering patterns between peers is a powerful tool to standardize test utilization [41]. Another approach

to reduce inappropriate testing is implementing testing cascades, algorithms, and best-practice recommendations in CPOE. The following cases illustrate specific scenarios where these approaches can have positive impact on ordering behavior of genetic tests.

Vignette 4: Clinical Exome Sequencing: Extract and Hold Policy

Background

The current cost of WES is 3–4 times the cost of a single-gene test or targeted panel. Furthermore, WES is generally considered a novel "investigational" technology by insurance payers, who consequently provide limited or no coverage at present. Given the cost and restrictive coverage policies, insurance pre-authorization is necessary to reduce financial liability for patients and institutions. Providers can be educated about this background information and the need for pre-authorization, but it can be difficult to enforce restricting WES in the absence of pre-authorization without an institution-wide policy.

Case Example

Recall the case example in Vignette 1 in which the neurologist evaluated the 5-year-old boy with a history of severe encephalopathy, developmental delay, and seizures and was eager to identify an underlying etiology for the child's clinical constellation. The family context in this case was relevant in that the child's mother was pregnant and concerned about the chance of having another child with significant medical issues. The child's features did not fit a specific genetic syndrome, and the clinical urgency was increased because of the mother's pregnancy. The neurologist recommended rapid exome sequencing as the most efficient and cost-effective testing approach and sent the family to the lab for sample collection. When the order was received, it was flagged for case review by the utilization management consultant because of the cost of the test and complicated nature of the test. The consultant determined that the provider did not follow the established process for coordination of exome sequencing, which included pre-authorization and pretest counseling. After explaining the concern for avoidable financial liability and the hospital policy requiring genetic testing insurance pre-

authorization before a sample can be sent, the consultant offered to extract DNA from the blood sample and hold the DNA while pre-authorization was requested.

Comments

If the consultant merely suggested that the family might receive a considerable bill without having pre-authorization in place, but didn't have a policy to enforce the practice, the provider may have maintained that the testing was emergent and that he didn't have time to pursue authorization. An established policy with interdepartmental endorsement that requires pre-authorization before testing can be sent demonstrates the positive impact of a medium-strength intervention. Pairing the policy with a procedure to stabilize the sample adds strength to the intervention. By offering to preserve the sample, it will be easier to guide the provider to the appropriate procedure, and this practice importantly avoids an unnecessary recollection from the patient .

Vignette 5: Charcot-Marie-Tooth: Algorithm Intervention

Background

Charcot-Marie-Tooth (CMT) hereditary neuropathy refers to a group of disorders characterized by a chronic motor and sensory polyneuropathy. Clinical presentation typically includes distal muscle weakness and atrophy often associated with mild to moderate sensory loss , depressed tendon reflexes, and high-arched feet. Distinguishing the genetic neuropathies from the many causes of acquired (nongenetic) neuropathies is important for prognosis and medical management. Identification of the genetic cause of CMT can support recurrence risk counseling, natural history studies, and participation in clinical trials . Clinical diagnosis is based on family history and characteristic findings on physical examination, electrophysiologic studies (EMG/NCV testing), and occasionally sural nerve biopsy. There are more than 40 genes associated with CMT phenotypes and the identification of a genetic etiology is not possible for all cases. Building on the low-technology intervention of a best-practice recommendation, CMT lends itself to guideline-based sequential testing strategies. Through the creation of a

logical evaluation and testing strategy for CMT, including input from experts in neurology, the laboratory can implement an effective UM intervention using an algorithmic approach.

Case Example

A 10-year-old male was referred to the neurology clinic for evaluation of bilateral pes cavus foot deformity and weakness. Based on a detailed medical evaluation and discussion of family history, the neurologist suggested a possible diagnosis of hereditary sensory motor neuropathy. The patient's mother and maternal grandmother also had weakness, by report. The results of an EMG (electromyogram) and nerve conduction study were consistent with demyelinating neuropathy. Based on the family history , the neurologist raised the possibility of an X-linked form of hereditary neuropathy and attempted to order a Charcot-Marie-Tooth (CMT) demyelinating panel. Although the family history could have been consistent with an X-linked form of CMT, the most common genetic etiology for demyelinating CMT is a *PMP22* duplication. Based on the CMT algorithm , the recommendation is to start with *PMP22* duplication analysis, followed by a broader gene panel. The neurologist saw the CPOE pop-up explaining that CMT demyelinating panel was not available as a first-line test and redirected the provider to order *PMP22* duplication analysis.

One month later, the results indicated a heterozygous duplication involving *PMP22*, confirming the diagnosis of CMT1A. The order modification resulted in a timelier molecular diagnosis (2–3 week turnaround for the single-gene test compared to 4–6 weeks for the panel) and cost savings of approximately $5300.

Comments

This example highlights a case where a sequential testing strategy can be defined in CPOE when evidence-based testing recommendations exist. With the continued growth of next-generation sequencing , single-gene tests, and multigene panels, this type of intervention may decline. It is important to establish a post-implementation process to review and audit interventions to ensure that the rationale behind the testing approach is still relevant .

Vignette 6: Using Provider Report Cards to Influence

Testing Patterns for Cystic Fibrosis

Background

Cystic fibrosis (CF) is an autosomal recessive condition caused by mutations in the *CFTR* (cystic fibrosis transmembrane conductance regulator) gene that ultimately impacts ion transport across cellular membranes in the pancreas, lung, and sweat glands. There is a broad range of phenotypes that complicate diagnosis. Furthermore, over 1500 variants have been reported in the *CFTR* gene, most of which are not pathogenic. The most common mutation, deltaF508 (HGVS nomenclature p.F508del), accounts for approximately two-thirds of all mutations worldwide. Guidelines for patient diagnosis and management by the Cystic Fibrosis Foundation rely on a combination of newborn screening results, clinical features, sweat chloride testing, and gene analysis [42]. Specifically, diagnosis is established by the presence of one or more characteristic phenotypic features of CF *and* one of the following laboratory confirmations: (1) two identified pathogenic mutations in the *CFTR* gene, (2) two abnormal sweat chloride values (>60 meq/L), or (3) transepithelial nasal potential difference measurements. In the prenatal and neonatal populations, diagnosis can readily be made with laboratory analysis alone (two pathogenic mutations or sweat chloride analysis).

There are several clinically available genetic testing options for CF, including targeted gene panels of the most common mutations, mutation testing of a previously identified familial mutation, and full gene sequencing. Molecular diagnosis is recommended when sweat testing is unable to be performed or uninformative. Full gene sequencing is recommended with caution because of the expense and potential for the identification of variants of unknown significance. Laboratory leaders and clinicians from a CF clinic decided to provide monthly feedback to providers on their actual use of the testing strategies compared to predetermined benchmarks. The non-blinded report cards were presented and discussed collegially at CF division meetings. The laboratory audited volumes of full gene sequencing over time as a metric of the impact of the intervention.

Case Example

A female Caucasian newborn was referred to the CF clinic at 2 weeks of age after her newborn screening sample was abnormal for cystic fibrosis. The

state NBS laboratory uses immunoreactive trypsinogen (IRT) as the screening biomarker, which is prone to false positives. The specialist examined her and noted that the baby did not have any visible symptoms and appeared healthy. The patient's history was significant for a traumatic birth that required emergency C-section, which can cause elevated IRT levels. The family was very anxious as this was their first child, and the mother had a cousin who died from the disease in childhood. The provider counseled the family on the inheritance pattern of CF as well as the need for confirmatory testing. The provider initially planned to order *CFTR* full gene sequencing because of the compelling family history and the belief that this would yield a definitive diagnosis in one step that would relieve the family's anxiety. Coincidentally, the division had just discussed the practice's ordering patterns earlier in the week, and it was noted that this provider (B) utilized full gene sequencing more than any other provider (Fig. 20.4). Based on this feedback, the provider opted against ordering *CFTR* full gene sequencing as the initial testing and instead referred the family to the laboratory to schedule the sweat chloride test procedure.

Targets		75%	50%	5%
Provider	# patients	% sweat Cl	% targeted panel	% Full gene sequencing
Provider A	27	59%	37%	4%
Provider B	10	30%	20%	50%
Provider C	22	68%	27%	5%

Fig. 20.4 Example Quarterly Report Card illustrating provider ordering patterns in the clinic's follow-up newborn screening population. This clinic sees all referrals for potential cystic fibrosis patients in the state

The sweat chloride was not elevated (23 mEq/L), but given the family history, the provider decided to proceed with targeted mutation panel. One mutation was detected (*CFTR* p.F508del), identifying the patient as a carrier of CF. The family was counseled appropriately regarding the implications of knowing her carrier status, and they were relieved to learn that she was not affected with the condition .

Comments

As shown in this example, provider report cards can impact test utilization when strategically employed. Implementation requires identifying an area of

improvement and thorough design of the report and review process. In this CF clinic, the data collected was targeted to referrals for follow-up testing in the newborn screening population and normalized using the number of patients each provider encountered for a fair comparison between providers. The clinic and laboratory collaboratively designed the content and frequency of the report. Their target goal was defined by using a distribution of all testing based on a joint consensus of what seemed reasonable. A target goal could also be designed toward test reduction over time. This intervention's success could largely be attributed to the clinic's consistent leadership review and discussion of the report at their quarterly meetings .

Strong Interventions

Strong interventions are designed to eliminate unnecessary and unintended laboratory testing. Removal of obsolete/antiquated tests from the laboratory formula is one effective approach that is frequently implemented for nongenetic tests. However, genetic tests are often so new that their clinical validity has not yet been carefully scrutinized. Other forms of strong interventions include privileging to specialty providers, implementing hard stops in CPOE (e.g., duplicate testing rules), and using diagnostic management teams to guide a provider to the most effective testing plan [12].

In cases where algorithms and rules either don't exist or are hard to implement, interventions will require a more nuanced, case-by-case approach. Examples of cases that could benefit from additional review and approval include questionable or brand-new tests, requests to send to a non-vetted genetic testing laboratory, genetic tests ordered on inpatients, tests ordered for "academic interest" whose results will not change patient care, and tests that are part of a research protocol. The literature describes many examples of the impact of mandatory high-level review and critique of genetic test orders. Both national reference laboratories [43, 44] and health care institutions [45, 46] have successfully utilized these approaches. Studies have consistently demonstrated that review of genetic test orders results in either modification or cancellation of up to 30 % of tests. Although this results in significant cost savings, it should be emphasized that alternative advantages include improved turnaround time (e.g., more narrowly focused testing) and reduced, unnecessary downstream follow-up (e.g., incidental or secondary findings) [43, 45]. The vignettes below illustrate the power that

strong interventions can have in improving genetic test utilization.

Vignette 7: Clinical Exome Sequencing : Subcommittee Review

Background

A strong intervention related to management of WES requests is the creation of a subcommittee whose primary responsibility is to determine whether the test is appropriate and reasonable based on predefined criteria or whether alternate testing should be considered first. In addition to case adjudication, the committee could serve in an advisory capacity to vet reference laboratories and provide recommendations for efficient coordination of testing logistics. Committee members could include the following stakeholders: genetics providers and other specialists on an ad hoc basis (e.g., neurologists, cardiologists, hematology-oncologists, and dermatologists), laboratory leadership such as a molecular laboratory director, and genetic counselors.

Case Example

Returning to the case illustrated in vignettes 1 and 4, the neurologist reviewed the hospital lab test catalog to determine the best reference lab to facilitate collecting and sending the sample that same day . In this example, he would instead encounter information detailing the subcommittee review process. The neurologist completed the request form that required documentation of the child's features and the provider's rationale for exome sequencing and submitted the request for review. The subcommittee case review revealed that the child did not yet have chromosomal microarray analysis (CMA) performed. Due to the child's features, the subcommittee denied the request for exome sequencing and recommended an initial evaluation by CMA. A few weeks later, the neurologist was notified that CMA identified an abnormal copy number variant, microdeletion of 5q31.3. This finding provided an established explanation for the child's features, and exome sequencing was no longer indicated.

Comments

By engaging experts in the review process, the requesting provider received helpful guidance to order the most appropriate test. In this example, the ordering provider was not familiar with the current recommendation that this constellation of findings should use CMA as a first-tier test [47]. As genetic and genomic tests continue to rapidly evolve and increase in complexity, the continued development and refinement of professional organization recommendations will be essential. The incorporation of a subcommittee review process prevents “curiosity” testing or testing precipitously ordered by a provider who may be unfamiliar with the necessary process to ensure that testing is coordinated responsibly. It must be noted that this intervention requires commitment from providers to serve on the subcommittee, and the institution leadership must support the entire process as a point person must coordinate the case review process in order to ensure efficient management of requests (Fig. 20.5).

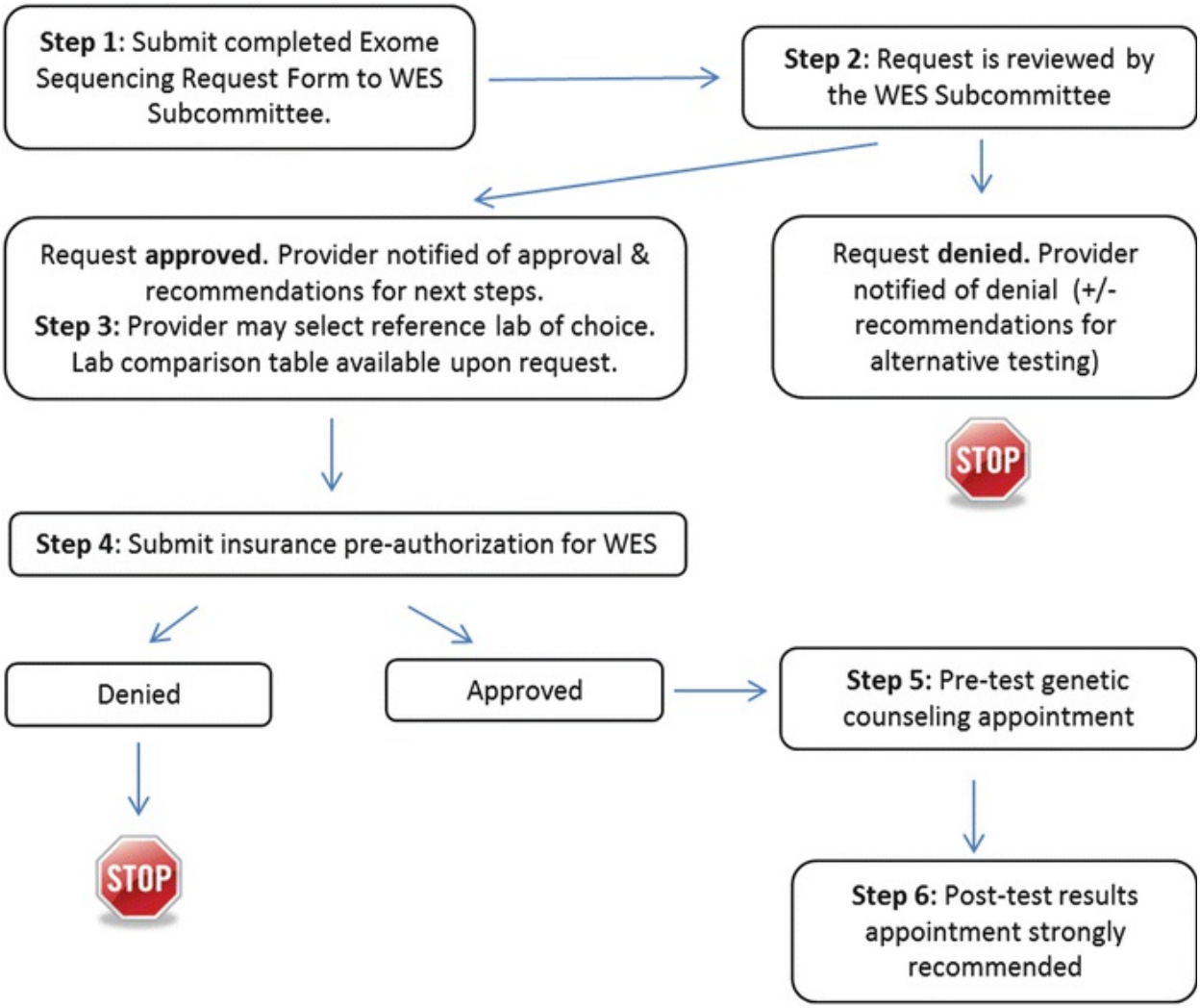


Fig. 20.5 Sample flow diagram for WES requests

Vignette 8: Algorithmic Approach to Cancer Testing

Background

Acute myeloid leukemia /AML is a relatively rare malignancy with over 20,000 new cases estimated in the United States in 2015 [10]. Since the first morphological classification schemes, it has been recognized that AML is heterogeneous with highly variable survival rates from 15 to 70 %. In the past decade, guidelines from the European Leukemia Network and the National Comprehensive Cancer Network have incorporated cytogenetic and molecular findings into broad categories of favorable risk, intermediate risk, and poor risk [48, 49]. A select few findings are diagnostic, most notably the

PML-RARA translocation between chromosomes 15 and 17 that defines acute promyelocytic leukemia; however, most of the risk stratification defines prognosis. Combining the morphologic, cytogenetic, and molecular profile has the highest utility in stratifying the intensity of AML therapy. The initial induction treatment is virtually unchanged for all AML patients except for those with acute promyelocytic leukemia . Following remission, determination of whether to pursue high-dose consolidation treatment, allogeneic stem cell transplantation, or an investigational therapy is heavily guided by cytogenetic and molecular results.

One of the most challenging aspects of AML risk stratification is that some aberrations “trump” others and the combinations are different in each patient. For example, an AML patient with normal cytogenetics results and an *NPM1* mutation is at favorable risk ; however, the same *NPM1* mutation in combination with complex cytogenetics results (greater than three clonal chromosomal alterations) or a *FLT3-ITD* mutation is classified as poor risk. This has led to the increasing popularity of comprehensive genomic profiling, either in isolation or in combination with traditional cytogenetics. Since testing is often performed at a reference lab, integrating multiple results from different modalities frequently rests on the busy hematologist-oncologist. Another approach is to employ a testing algorithm where histopathologic diagnosis and cytogenetic results direct the appropriate molecular test(s). A multidisciplinary UM committee is ideally suited to designing an effective testing algorithm based on histopathologic diagnosis and cytogenetics results.

Case Example

A 58-year-old man presented to the emergency department with a 1-week history of high fever with chills (38.8 °C), epistaxis, shortness of breath, and fatigue. The CBC and peripheral blood smear revealed leukocytosis with the presence of numerous myeloblast cells. Flow cytometry showed 60 % blasts in a subsequent bone marrow aspirate, and the histopathologic diagnosis was AML , specifically acute monoblastic leukemia. The patient was initiated on the standard (7 + 3) induction therapy and achieved complete remission. Analysis of the patient’s bone marrow by fluorescent in situ hybridization showed a favorable core-binding factor translocation of chromosomes 8 and 21 [t(8;21)]. Molecular testing for *KIT* mutation was positive, which changed the risk category for the patient from favorable risk to intermediate risk. The hematologist-oncologist treating the patient advised allogeneic stem cell

transplantation since the patient's sister was willing to donate and was a good HLA match.

Comments

Prior to implementation of the comprehensive cancer center's hematologic malignancy testing algorithm, the patient in this example likely would not have had genetic testing after determination that he had core-binding factor AML . In the worst-case scenario, it could have resulted in the patient remaining classified as favorable risk and receiving high-dose consolidation treatment instead of progressing immediately to allogeneic stem cell transplantation. A significant obstacle in this utilization strategy is that results from multiple laboratory and pathology specialists must be consolidated to guide molecular testing . In this example, the strategy resulted in the additional *KIT1* testing which increased rather than decreased cost but ultimately improved overall clinical utility .

Vignette 9: Genetic Testing on Inpatients : Restricted and Privileged Testing

Background

Genetic testing is typically coordinated in the outpatient setting because it is not typically used to influence real-time medical decisions during an acute crisis. Although genetic testing is urgent in very rare cases involving inherited disorders , it may be requested during an inpatient admission for convenience rather than medical necessity. From a system perspective, it can be easier for providers to order all testing that might be relevant for a patient's care while they are an inpatient. Providers worry that patients may be lost to follow-up after discharge, and there is a belief that families won't be billed separately for expensive testing performed during a hospital admission. Despite these motivations for genetic testing on inpatients , there are risks to the both the patient and the hospital system that need to be considered.

The biggest risk for the patient is failure to retrieve the result. This is the third highest cause for lab-related litigation in the United States [50]. In a teaching hospital, residents or a rotating medical unit attending for that week may order laboratory testing instead of the specialists recommending the

tests. In addition, the turnaround time for genetic tests is on the order of weeks to months, which is often longer than the inpatient stay. For both of these reasons, when a genetic test result is returned, there is an increased risk that the result will not be retrieved by the appropriate provider or communicated to the patient.

The financial liability to the family and the hospital is another factor to consider. Inpatient billing is nontransparent, institution dependent, and likely to be reimbursed by payer plans using a value-based model . However, the billing of the genetic test is comparatively simple; the laboratory sending the test pays the reference laboratory. Laboratory budgets are forced to consider these financial implications in order to provide necessary and routine services for all the patients. Therefore, it is reasonable to implement strong interventions to prevent or reduce these high-risk, high financial liability genetic tests in the inpatient setting. One method described in the following case is to restrict genetic testing to the outpatient setting. A necessary corollary is the creation of a method for review and approval in the inpatient setting in order to escalate the rare, urgent request.

Case Example

A 7-month-old female with a recent diagnosis of gallstones was admitted for vomiting, jaundice, and elevated gamma-glutamyltransferase (GGT) and lipase . The care team was concerned about biliary obstruction and needed to identify the underlying cause for her condition. Mutations in the *ABCB4* gene are associated with progressive familial intrahepatic cholestasis 3 , which is characterized by elevated GGT and liver dysfunction. The clinical team discussed *ABCB4* sequencing during inpatient rounds. The resident charged with ordering the test was unable to do so in CPOE because the hospital had a policy restricting genetic testing to the outpatient setting. The resident called the laboratory for guidance on how to order the test. The laboratory genetic counselor explained the policy and the process for escalation if the attending wanted to appeal the decision. The escalation process involved filling out a form that clearly outlined how the testing would change patient care during the inpatient admission. Within the laboratory, the form required approval from the laboratory medical director . In the past 3 years, only two exceptions to this inpatient restriction policy were made. The resident and attending agreed to consider deferring testing until after the patient was discharged home.

The patient stabilized and was discharged within a week. At her 1-month follow-up visit, her symptoms had completely resolved and genetic testing was no longer indicated.

Comments

More often than not, genetic testing is not needed for the immediate management of inpatients. Through the use of strong interventions, testing in this patient population can be dramatically reduced. It is important to consider exceptions to this policy. Such exceptions include the rare inherited conditions where management truly can be modified with genetic testing results (e.g., atypical hemolytic uremic syndrome testing for eculizumab treatment) as well as treatment of somatic conditions and pharmacogenetic testing that may not be able to be deferred to an outpatient setting. Facilitation of DNA banking, or a sample hold process, can be valuable to prevent the need for recollection as well as provide the option for recurrence testing after a patient expires during their admission. This example highlights an escalation or appeals process to allow for these rare exceptions. This strategy can help foster a positive relationship between the lab and clinical providers by giving the clinical team a platform by which to be heard.

Conclusions

Genetic testing does not easily lend itself to standard UM interventions/strategies, such as a hard-wired CPOE intervention or a limited formulary. Rapid gene discovery and an increasing array of advanced technologies for testing have resulted in important improvements to genetic diagnosis and ultimately to patient care. Genetic testing has expanded beyond the sole domain of the medical geneticist and spans the population age continuum. The complexities of appropriate genetic test coordination and potential patient harm from misorders warrant a thoughtful and thorough utilization management approach. As demonstrated in the vignettes, this is further nuanced by the population being testing. Monitoring and ensuring the appropriate utilization of genetic testing is an issue that affects all institutions and should not be ignored or deferred because of minimal resources or expertise. Creating a gentle intervention requires minimal resources and can have positive impact. It is true of all issues in utilization management that

doing something small, even if it has minimal impact, is better than doing nothing. A successful strategy will incorporate multiple gentle, medium, and strong interventions along with a process for periodic review to ensure the interventions are still appropriate and effective. Utilization management for genetic testing will also need to adapt to changes in best-practice recommendations. It has been predicted that the cost of genomic testing will decrease such that everyone will have their exome interrogated as part of the wave of precision or personalized medicine. For that future vision to be realized, a plethora of advances in bioinformatics, testing infrastructure, result interpretation and re-interpretation, billing practices, reimbursement models, and ethical considerations are needed. In the interim, there is a clear shift from single-gene analysis to next-generation sequencing panels. During this transition, nimble utilization management strategies are critical to continue to ensure that right patients get the right and best genetic test at the right time.

References

1. Gomah ME, Turley JP, Lu H, Jones D. Modeling complex workflow in molecular diagnostics: design specifications of laboratory software for support of personalized medicine. J Mol Diagn. 2010;12(1):51–7.
[CrossRef][PubMed][PubMedCentral]

2. United Health, Center for Health Reform and Modernization. Personalized medicine: trends and prospects for the new science of genetic testing and molecular diagnostics. Working Paper 7. 2012.

3. Sluss PM. Reference laboratory utilization management. Clin Chim Acta. 2014;427:167–72.
[CrossRef][PubMed]

4. Greenblatt MB, Nowak JA, Quade CC, Tanasijevic M, Lindeman N, Jarolim P. Impact of a prospective review program for reference laboratory testing requests. Am J Clin Pathol. 2015;143(5):627–34.
[CrossRef][PubMed]

5. Beaudet AL. Which way for genetic-test regulation? Leave test interpretation to specialists. Nature. 2010;466(7308):816–7.
[CrossRef][PubMed]

6. Mainous 3rd AG, Johnson SP, Chirina S, Baker R. Academic family physicians' perception of genetic testing and integration into practice: a CERA study. Fam Med. 2013;45(4):257–62.
[PubMed]

7. Shields AE, Burke W, Levy DE. Differential use of available genetic tests among primary care

physicians in the United States: results of a national survey. Genet Med. 2008;10(6):404–14. [CrossRef][PubMed][PubMedCentral]

8. Sanger F, Nicklen S, Coulson AR. DNA sequencing with chain-terminating inhibitors. Proc Natl Acad Sci U S A. 1977;74(12):5463–7. [CrossRef][PubMed][PubMedCentral]

9. Wetterstrand K. DNA sequencing costs: data from the NHGRI Genome Sequencing Program (GSP). 2015. http://www.genome.gov/sequencingcosts/. Accessed 5 Sept 2015.

10. Surveillance, Epidemiology, and End Results Program. 2015. http://seer.cancer.gov/statfacts/html/amyl.html.

11. Huck A, Lewandrowski K. Utilization management in the clinical laboratory: an introduction and overview of the literature. Clin Chim Acta. 2014;427:111–7. [CrossRef][PubMed]

12. Baird G. The laboratory test utilization management toolbox. Biochem Med (Zagreb). 2014;24(2):223–34. [CrossRef]

13. Solomon DH, Hashimoto H, Daltroy L, Liang MH. Techniques to improve physicians' use of diagnostic tests: a new conceptual framework. JAMA. 1998;280(23):2020–7. [CrossRef][PubMed]

14. Watson MS, Cutting GR, Desnick RJ, Driscoll DA, Klinger K, Mennuti M, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. Genet Med. 2004;6(5):387–91. [CrossRef][PubMed][PubMedCentral]

15. American College of Obstetricians and Gynecologists Committee on Genetics. ACOG Committee Opinion No. 486: update on carrier screening for cystic fibrosis. Obstet Gynecol. 2011;117(4):1028–31. [CrossRef]

16. Langfelder-Schwind E, Karczeski B, Strecker MN, Redman J, Sugarman EA, Zaleski C, et al. Molecular testing for cystic fibrosis carrier status practice guidelines: recommendations of the National Society of Genetic Counselors. J Genet Couns. 2014;23(1):5–15. [CrossRef][PubMed]

17. Gross SJ, Pletcher BA, Monaghan KG, Professional Practice Guidelines Committee. Carrier screening in individuals of Ashkenazi Jewish descent. Genet Med. 2008;10(1):54–6. [CrossRef][PubMed][PubMedCentral]

18. ACOG Committee on Genetics. ACOG Committee Opinion No. 442: preconception and prenatal carrier screening for genetic diseases in individuals of Eastern European Jewish descent. Obstet Gynecol. 2009;114(4):950–3. [CrossRef]

19. ACOG Committee on Genetics. ACOG Committee Opinion No. 432: spinal muscular atrophy. Obstet Gynecol. 2009;113(5):1194–6. [CrossRef]

20. Prior TW, Professional Practice Guidelines Committee. Carrier screening for spinal muscular atrophy. Genet Med. 2008;10(11):840–2.
[CrossRef][PubMed][PubMedCentral]

21. Nazareth SB, Lazarin GA, Goldberg JD. Changing trends in carrier screening for genetic disease in the United States. Prenat Diagn. 2015;35:931–5.
[CrossRef][PubMed][PubMedCentral]

22. Edwards JG, Feldman G, Goldberg J, Gregg AR, Norton ME, Rose NC, et al. Expanded carrier screening in reproductive medicine-points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. Obstet Gynecol. 2015;125(3):653–62.
[CrossRef][PubMed]

23. Lindheim SR, Jaeger AS. Expanded preconception carrier screening in clinical practice: cutting the Gordian Knot. Fertil Steril. 2015;104(2):281–2.
[CrossRef][PubMed]

24. McCullough RM, Almasri EA, Guan X, Geis JA, Hicks SC, Mazloom AR, et al. Non-invasive prenatal chromosomal aneuploidy testing—clinical experience: 100,000 clinical samples. PLoS One. 2014;9(10), e109173.
[CrossRef][PubMed][PubMedCentral]

25. Haymon L, Simi E, Moyer K, Aufox S, Ouyang DW. Clinical implementation of noninvasive prenatal testing among maternal fetal medicine specialists. Prenat Diagn. 2014;34(5):416–23.
[CrossRef][PubMed]

26. Committee Opinion No. 640: cell-free DNA screening for fetal aneuploidy. Obstet Gynecol. 2015;126:e31–7.

27. Wang Y, Chen Y, Tian F, Zhang J, Song Z, Wu Y, et al. Maternal mosaicism is a significant contributor to discordant sex chromosomal aneuploidies associated with noninvasive prenatal testing. Clin Chem. 2014;60(1):251–9.
[CrossRef][PubMed]

28. Lebo RV, Novak RW, Wolfe K, Michelson M, Robinson H, Mancuso MS. Discordant circulating fetal DNA and subsequent cytogenetics reveal false negative, placental mosaic, and fetal mosaic cfDNA genotypes. J Transl Med. 2015;13:260-015-0569-y.

29. Bianchi DW, Chudova D, Sehnert AJ, Bhatt S, Murray K, Prosen TL, et al. Noninvasive prenatal testing and incidental detection of occult maternal malignancies. JAMA. 2015;314(2):162–9.
[CrossRef][PubMed]

30. Newborn Screening, Genetics Home Reference. 2015. http://ghr.nlm.nih.gov/nbs. Accessed 6 Aug 2015.

31. Wagener JS, Zemanick ET, Sontag MK. Newborn screening for cystic fibrosis. Curr Opin Pediatr. 2012;24(3):329–35.
[CrossRef][PubMed]

32.

OMIM Entry Statistics. 2015. http://www.omim.org/statistics/entry. Accessed 5 Sept 2015.

33. Miyakis S, Karamanof G, Liontos M, Mountokalakis TD. Factors contributing to inappropriate ordering of tests in an academic medical department and the effect of an educational feedback strategy. Postgrad Med J. 2006;82(974):823–9.
[CrossRef][PubMed][PubMedCentral]

34. Xue Y, Ankala A, Wilcox WR, Hegde MR. Solving the molecular diagnostic testing conundrum for Mendelian disorders in the era of next-generation sequencing: single-gene, gene panel, or exome/genome sequencing. Genet Med. 2015;17(6):444–51.
[CrossRef][PubMed]

35. Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med. 2013;15(7):565–74.
[CrossRef][PubMed][PubMedCentral]

36. Lindsay ME, Dietz HC. Lessons on the pathogenesis of aneurysm from heritable conditions. Nature. 2011;473(7347):308–16.
[CrossRef][PubMed][PubMedCentral]

37. Gillis E, Van Laer L, Loeys BL. Genetics of thoracic aortic aneurysm: at the crossroad of transforming growth factor-beta signaling and vascular smooth muscle cell contractility. Circ Res. 2013;113(3):327–40.
[CrossRef][PubMed]

38. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey Jr DE, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation. 2010;121(13):e266–369.

39. Krasowski MD, Chudzik D, Dolezal A, Steussy B, Gailey MP, Koch B, et al. Promoting improved utilization of laboratory testing through changes in an electronic medical record: experience at an academic medical center. BMC Med Inform Decis Mak. 2015;15:11-015-0137-7.

40. Dickerson JA, Jack RM, Astion ML, Cole B. Another laboratory test utilization program: our approach to reducing unnecessary 1,25-dihydroxyvitamin D orders with a simple intervention. Am J Clin Pathol. 2013;140(3):446–7.
[CrossRef][PubMed]

41. Staff L. Improving laboratory test utilization through physician report cards: an interview with Dr. Kim Riddell. Lab Errors Patient Safety. 2005;2:2–4.

42. Farrell PM, Rosenstein BJ, White TB, Accurso FJ, Castellani C, Cutting GR, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. J Pediatr. 2008;153(2):S4–14.
[CrossRef][PubMed][PubMedCentral]

43. Kotzer KE, Riley JD, Conta JH, Anderson CM, Schahl KA, Goodenberger ML. Genetic testing utilization and the role of the laboratory genetic counselor. Clin Chim Acta. 2014;427:193–5. [CrossRef][PubMed]

44. Miller CE, Krautscheid P, Baldwin EE, Tvrdik T, Openshaw AS, Hart K, et al. Genetic counselor review of genetic test orders in a reference laboratory reduces unnecessary testing. Am J Med Genet A. 2014;164A(5):1094–101. [CrossRef][PubMed]

45. Dickerson JA, Cole B, Conta JH, Wellner M, Wallace SE, Jack RM, et al. Improving the value of costly genetic reference laboratory testing with active utilization management. Arch Pathol Lab Med. 2014;138(1):110–3. [CrossRef][PubMed]

46. Riley JD, Procop GW, Kottke-Marchant K, Wyllie R, Lacbawan FL. Improving molecular genetic test utilization through order restriction, test review, and guidance. J Mol Diagn. 2015;17(3):225–9. [CrossRef][PubMed]

47. Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet. 2010;86(5):749–64. [CrossRef][PubMed][PubMedCentral]

48. Dohner H, Estey EH, Amadori S, Appelbaum FR, Buchner T, Burnett AK, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. 2010;115(3):453–74. [CrossRef][PubMed]

49. O'Donnell MR. Risk stratification and emerging treatment strategies in acute myeloid leukemia. J Natl Compr Canc Netw. 2013;11 Suppl 5:667–9. [PubMed]

50. Gandhi TK, Kachalia A, Thomas EJ, Puopolo AL, Yoon C, Brennan TA, et al. Missed and delayed diagnoses in the ambulatory setting: a study of closed malpractice claims. Ann Intern Med. 2006;145(7):488–96. [CrossRef][PubMed]

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_21

21. The Use of Physician Profiling and Prior Approval (Gatekeeping) in Utilization Management in the Clinical Laboratory

Kent Lewandrowski[1] and Jason Baron[2]

(1) Division of Laboratory Medicine, Department of Pathology, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street, Boston, MA 02114, USA
(2) Department of Pathology, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street, Boston, MA 02114, USA

Kent Lewandrowski (Corresponding author)
Email: KLEWANDROWSKI@mgh.harvard.edu
Email: klewandrowski@partners.org

Jason Baron
Email: jmbaron@partners.org

Keywords Utilization management – Physician profiling – Laboratory utilization

Physician Profiling

In recent years it has become clear that there are significant opportunities to improve the quality and cost-effectiveness of medical care . The use of

physician profiling is increasingly being used for this purpose to identify variations in clinical practice and to assess adherence to clinical guidelines. For over four decades there has been recognition that there exist wide differences in clinical practice among groups of physicians. In the 1970s, Wennburg reported that communities in the state of Vermont showed significant variation in the amount of health care utilization that could not be explained by the overall health of the populations within the individual communities. Rather the variation was attributed to differences in physician practices [1]. In another study, Welch et al. reported an analysis of inpatient practice patterns in Florida and Oregon. They found that physicians in Florida used significantly more physician relative value units (35 %) than physicians in Oregon [2]. These and many other studies demonstrating large variations in clinical practice and outcomes among physicians highlight the opportunity to improve quality and cost by analyzing physician behavior and standardizing care according to evidence-based guidelines.

One approach to address variation in clinical practice is the use of physician profiling to compare performance on various measures across groups of physicians. However, previous studies have demonstrated that physician profiling has only a modest but still statistically significant impact on the utilization of clinical procedures [3]. According to Lewis, the overall track record of physician profiling is not impressive and, when it is effective, this usually is observed only for simple interventions [4].

The American Academy of Family Physicians (AAFP) has defined physician profiling as an analytic tool that uses epidemiological methods to compare physician practice patterns across various quality of care dimensions (process and outcomes). According to the AAFP, “cost, service, and resource utilization data are dimensions of measuring quality but should not be used as independent measures of quality” [5]. Physician profiling can be undertaken with a variety of objectives in mind including:

1. Improving the quality of care.

2. To assess metrics for performance of preventative and other services.

3. To establish metrics for pay-for-performance physician compensation.

4. To control costs or to reduce utilization of procedures, referrals to

specialists, laboratory tests, high cost drugs, and radiological scans.

5. To permit patients to make informed choices regarding their providers and clinical care.

Physician profiling may be performed by a variety of organizations with different objectives in mind. This includes hospitals and physician's organizations (to improve quality and standardize care), individual departments within hospital systems (e.g., pharmacy, radiology, and the clinical laboratory to control cost and reduce unnecessary services) and government and other third party payers (to reduce costs or to evaluate pay-for-performance metrics).

Many organizations believe that the primary goal of physician profiling should be to improve quality [5, 6] as opposed to its use to evaluate physician competency or as a tool to restrict or limit patient access to care. However, the majority of physician profiling efforts have targeted reducing costs or the overutilization of health care services and procedures [6]. The value of any physician profiling effort, regardless of its intended use, ultimately rests on the quality and statistical reliability of the data. According to Charvet, major concerns with physician profiling include the data itself and the interpretation of the data [7]. These issues have impaired the use of profiling data as an acceptable tool for quality improvement and controlling cost [7]. For example, physician profiles that utilize insurance claims lack validity and may be based on small sample sizes. Claims-based data cannot accurately represent an episode of care or a patient's baseline status [7]. Additional problems with data quality were described by Charvet and include the fact that more than one physician may be involved in a patients care, lack of reliable case mix adjustment, and failure of the profiling system to account for differences in practice characteristics. Many models for risk adjustment used by health plans are of questionable reliability [8]. Interpreting physician profiling data can be equally problematic. Without a clear understanding of how the data is generated and the unique circumstances of the individual physicians practice, erroneous conclusions can be drawn that are not based on reliable data comparing physician performance. Hofer et al. reported a study on the reliability of physician profiling for diabetes care including hospitalization rates, visit rates, laboratory utilization , and glycemic control.

They observed that only 4 % or less of the overall variance between physicians could be attributed to differences in practice and that the reliability of the physician's median case mix adjusted profile was very poor. They concluded that for diabetes , one of the most common clinical conditions in general medical practice, the physician report cards were unable to detect true practice differences [9]. They also cautioned that the misuse of physician profiling data could result in physicians avoiding patients with high costs, poor compliance, or a poor response to treatments. In a study by Adams et al., only 59 % of physician profiles had a "reliability score" above suboptimal. They concluded that current methods for profiling physician costs and services may lead to erroneous results and conclusions [10].

The historical development of physician profiling systems has been described by Sandy et al. [11]. Early "first generation " quality profiles were initially derived from population health and preventative service metrics such as the Healthplan Effectiveness Data and Information Set (HEDIS) . According to Sandy, these systems typically used a defined population as the unit for analysis as, for example, reporting on the rate of eye examinations for diabetic patients. Thus for a physician caring for 100 diabetic patients the rate of screening could be determined from the total number of patients and the number of eye examinations performed. A newer "second generation" of systems for physician profiling was developed using an episode-based approach to profiling. These systems aggregate data from a variety of sources such as claims, pharmacy, laboratory, and administrative data sources [6]. These data are then used to construct episodes of care for the purpose of improving quality and reducing costs. The authors stated that episode-based profiling has a number of advantages but cautioned that it also suffers from significant opportunities to misidentify high and low performing physicians. For example, a limited number of unusual or high cost patients could easily distort an individual physician's profile.

Physician Profiling in Clinical Laboratory Utilization Management

Data derived from clinical laboratory testing has been commonly employed for physician profiling. Usually this data is available electronically and can be matched with ordering providers, test results, patient demographics, and specific clinical encounters. In principle obtaining this data and

benchmarking it across a group of physicians should be relatively straightforward. However, there are many factors that may confound the data or make its interpretation challenging (or in some cases meaningless). These include but are not limited to:

1. Differences in patient populations that are cared for by seemingly homogeneous groups of physicians.

2. Differences in the patient case load among physicians.

3. Differences between specialists versus general practitioners.

4. Differences in patient types seen by subspecialists within a medical specialty (e.g., a stroke specialist within neurology).

5. Differences in community practice versus academic medical centers.

For these reasons physician profiling data should be interpreted with caution until a thorough understanding of the profiled physicians and the unique aspects of their practice is well understood. This is often best accomplished by reviewing the data directly with physicians and making any necessary adjustments after obtaining their input. The use of a collegial team-oriented approach is more likely to be successful than a strategy of confrontation or embarrassment of one's peers.

To date most of the literature concerning physician profiling in laboratory medicine has come from academic medical centers [12]. According to Bunting, interventions with the most impact are ones that use multiple approaches, are repeated regularly over time, include peer comparisons, and have a personal approach. Using this strategy they performed an intervention in a community practice setting and demonstrated a significant 7.9 % reduction in the number of tests ordered per visit [12]. In a similar study Ramoska evaluated laboratory utilization before and after implementation of a physician profiling intervention. He demonstrated a 17.8 % decrease in laboratory utilization with a corresponding decrease in total cost [13].

In our hospital laboratory utilization management program we are coming to rely more and more on profiling data to identify utilization management

opportunities, to evaluate which physicians are ordering certain tests, to establish institutional practice guidelines, and to eliminate unnecessary testing. These activities require a robust laboratory informatics capability to obtain and manipulate data into a form that permits reliable interpretations and conclusions. Raw utilization data is of little value unless it can be viewed in the appropriate context taking into account factors such as general versus specialist practices, patient case loads, rate of test results that produce clinically actionable information and other factors. To illustrate these concepts specific examples where we have used physician profiling are described below.

Case Example 1: Profiling to Identify Which Physicians Are Ordering Certain Tests

Testing patients for Babesiosis infection is relatively common in certain parts of the USA. This may include a thick and thin blood smear, serologic testing for Babesia antibodies or polymerase chain reaction (PCR) testing. In most cases the thin and thick smear is the preferred test. We observed that we were receiving over 470 tests a year for Babesia serology testing at an annual cost of approximately $33,000. The first question we asked was who was ordering the tests and how often the test results were positive (a positive test is not diagnostic of Babesiosis due to false positive serologic tests and prior infection). As shown in Fig. 21.1 the majority of the tests were being requested by a limited number of doctors and only a small percentage were positive. The intervention included multiple steps. First we met with clinical leaders in infectious disease to develop a practice guideline for testing for Babesiosis. Next we presented the data and guideline to the hospital Medical Policy Committee to get approval of the guideline and to set up a gatekeeper function in the clinical laboratory. Next we met directly with the highest volume users to explain the data and the logic behind the policy. Finally an email (shown below) was sent to all physicians who had ordered two or more tests in the previous year based on the audit. There were no negative responses from the physicians as most were thankful for the guidance on appropriate Babesia test ordering. Finally the laboratory included Babesia serology in our gate-keeping activities. Very few tests are now sent out to our reference laboratory.

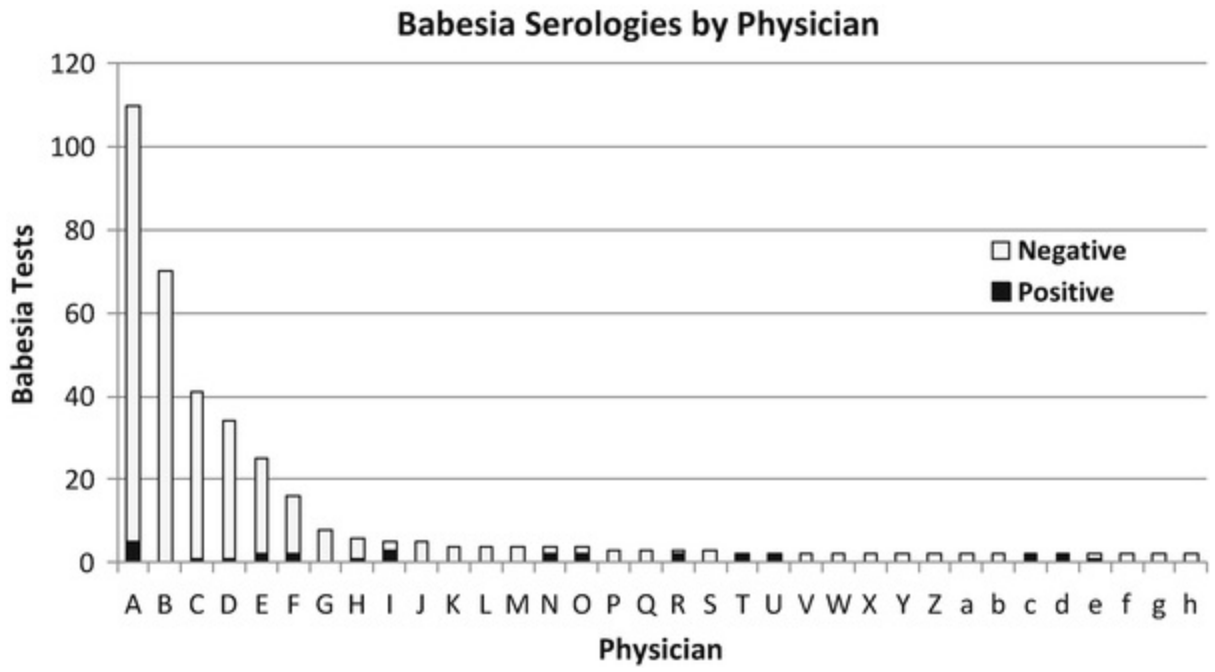


Fig. 21.1 Physician profiling for Babesia antibody testing at the Massachusetts General Hospital . The letters *A–h* indicate individual physicians and the volume of tests ordered per year is indicated on the Y-axis. *Shaded area* at the top of each physician bar indicates the number of tests with a positive result

Email to Providers Concerning Babesia Serology Testing

Good day. You are probably aware that the hospital is facing significant budget challenges. The clinical laboratories have been working with a number of medical services to identify tests of low or marginal clinical utility that can be eliminated from the test menu. One such test is serology IgG and IgM for Babesiosis. You are receiving this email because you have ordered two or more Babesia serologies based on a recent audit. Infectious disease specialists have concluded that the most appropriate test to detect active infection with Babesia is the thick and thin blood smear. Serologic tests cannot differentiate current from past infection and suffer from false negative and positive results. For this reason Babesia serology will no longer be offered by the clinical laboratory as the blood smear is the preferred approach. The MGH Medical Policy Committee has approved this change to the testing menu . We recognize that there may be occasional situations where the serologic test offers clinical value. The Pathology Core Laboratory

resident on-call is available to approve these requests. The MGH Core Lab resident on call can be reached by paging 2-1827.

Case Example 2: Profiling Including the Integration of Multiple Tests with Decision Support

Testing for Ehrlichosis and Anaplasmosis may include blood smears, polymerase chain reaction (PCR) , and immunoglobulin IgG/IgM serologies. In Massachusetts Ehrlichosis is only rarely seen, yet we receive a number of test requests for both serology and PCR testing. Anaplasmosis may occur in our region although the majority of tests are negative. For example, only 1.9 % of Anaplasma PCR tests are positive in our hospital. Again the first step was to determine who was ordering the tests and how many of the tests were positive. In the case of Ehrlichia we received 276 requests for Ehrlichia PCR in 2012. Of those not a single test was positive. Profiling data showed that most of the testing was ordered sporadically by a number of providers albeit one provider ordered 60 (22 %) of the tests. This provider left the institution shortly after the analysis hence no individual meeting was required. Figure 21.2 shows an analysis of Ehrlichia and Anaplasma serological testing. These tests are usually ordered together. The large majority of serological tests were negative. In addition, many physicians requested both PCR and serological testing. Given the relatively high cost of testing for Ehrlichia and Anaplasma and the very low yield, we began to search for a strategy to manage utilization. After consultation with infectious disease, we obtained approval from our medical policy committee to discontinue serological testing and only accept testing by PCR . The cost of the PCR testing was less than the serological assays and discontinuing serology eliminated a significant amount of redundant testing. In addition, given the low rate of positive tests we are also planning to set up a gatekeeper function to screen PCR test requests for clinical appropriateness. As shown in Fig. 21.3 patients who tested positive for Anaplasmosis by PCR always had an elevated aspartate aminotransferase (AST) level. Likewise we also found that in patients with a positive PCR test for Anaplasmosis, the white blood cell count (WBC) was always either normal or low. We concluded that an elevated AST and a normal or low WBC could be used to aid decision support when the gatekeeper in the laboratory spoke with individual clinicians (much of this analysis was performed by Vikram Pattanayak, MD).

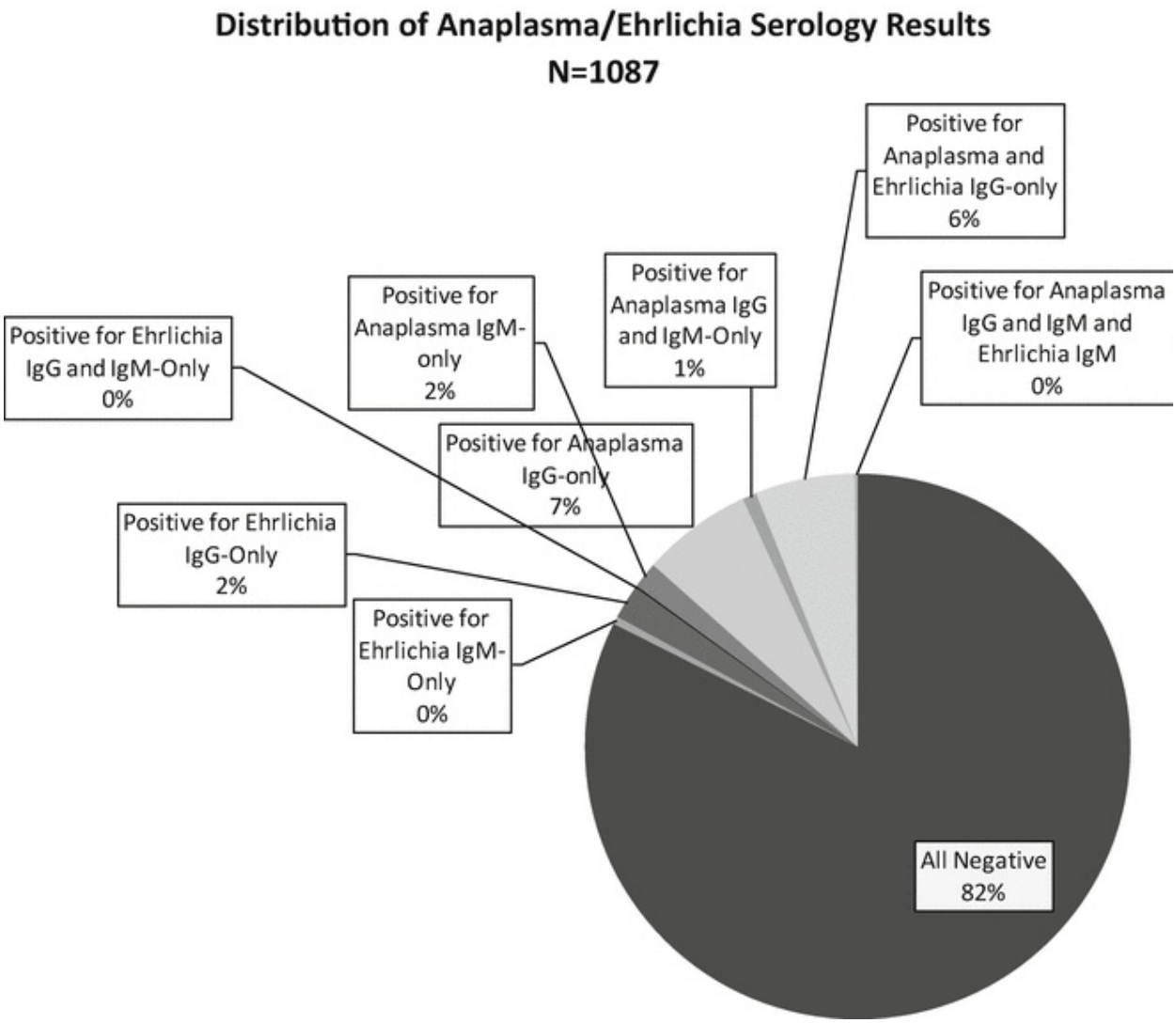


Fig. 21.2 Analysis of Ehrlichia and Anaplasma serological testing showing the number and percent of orders for testing in each category

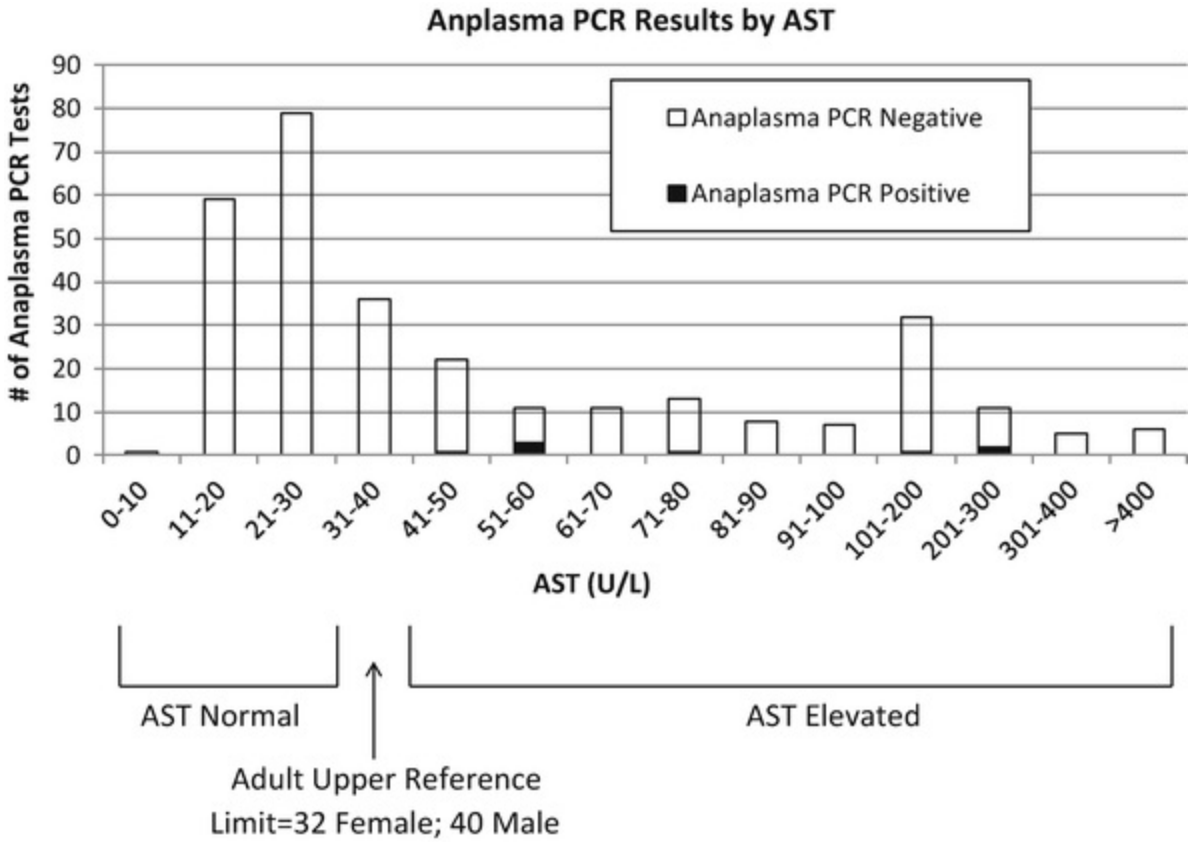


Fig. 21.3 Anaplasma polymerase chain reaction (PCR) testing compared to the aspartate aminotransferase (AST) value. Shaded areas of bars show the number of PCR tests that were positive. Note that no positive PCR results were observed in patients with normal concentrations of AST

Case Example 3: Using Physician Profiling to Establish Practice Guidelines

The number of available tests for genetic disorders has undergone rapid and continuous expansion. These tests are usually very expensive resulting in large costs to our hospital from reference laboratories. To evaluate opportunities to standardize practice for genetics testing we performed an electronic audit to establish a physician profile across medical specialties. Figure 21.4 shows physician profiling data for genetic testing by specialty (data supplied by Anand Dighe, MD, PhD). Not surprisingly the pediatric genetics group accounted for a large percentage of the total testing expenditures followed by neurology. Of the top five physicians ordering genetic tests, four were from the pediatric genetics service. Of note one physician ordered approximately $550,000 of testing in a single year. This suggested that there might be significant variation in practice. Therefore this

group was selected for a targeted intervention. One of our directors (Anand Dighe, MD, PhD) met with the pediatric genetics group to review the profiling data and assess the opportunity for establishing practice standards. Several guidelines were recommended by the pediatric genetics group . Post intervention monitoring indicated that the guidelines saved the institution approximately $6000 per month.

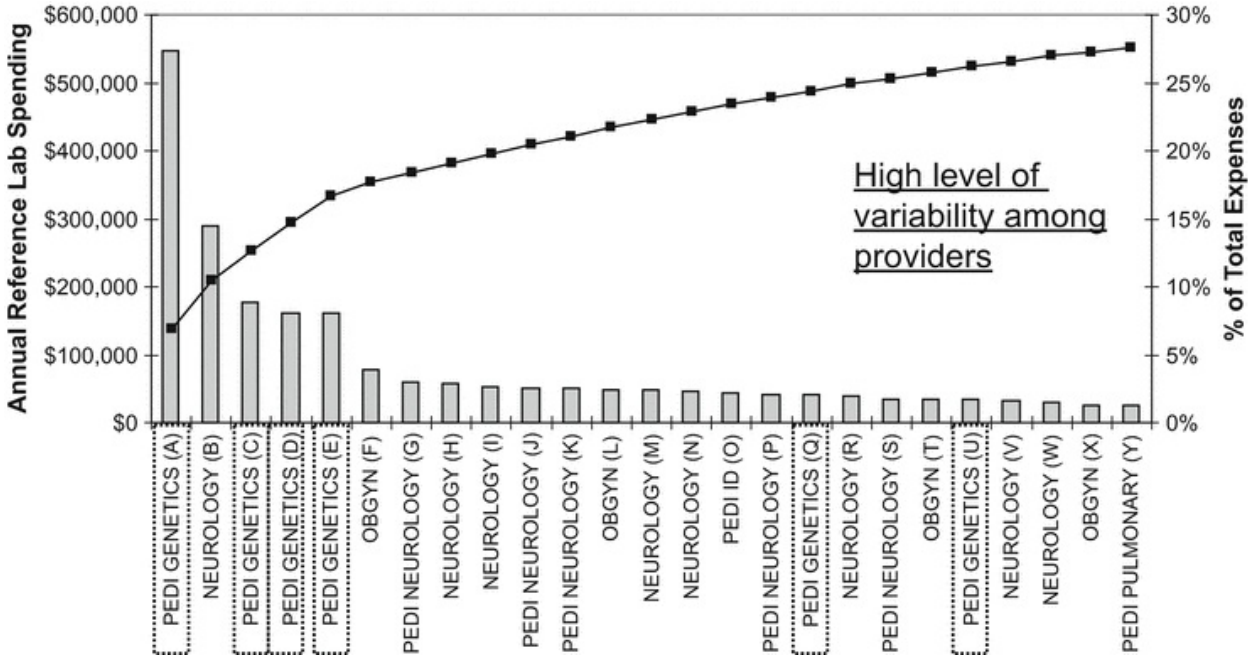


Fig. 21.4 Reference laboratory testing for genetic disorders. The letters *A–Y* indicate individual physicians and their practice specialty. The Y-axis designates the annual cost of genetic testing for each physician

Case Example 4: Using Profiling Data to Eliminate Inappropriate Testing

Patients who receive bone marrow stem cell transplantations are at risk for reactivation of Human Herpesvirus 6 (HHV6) and may develop encephalitis. This is particularly true for patients who receive cord blood stem cell transplants (as opposed to conventional stem cell transplants). In our laboratory we were receiving approximately 420 requests per year for HHV6 quantitative PCR. Many of these tests appeared to have been ordered on outpatients without apparent symptoms and were invariably negative. Physician profiling data revealed that two physicians on the bone marrow transplant service ordered 58 % of the tests whereas other physicians ordered

far fewer tests. Of those in the latter group, most requests were on inpatients with symptoms suggestive of HHV6 reactivation. The profiling data was shared with the director of the Bone Marrow Transplant service (BMT) . The Director of the BMT service concluded that the test should be primarily ordered in the setting of meningoencephalitis in cord blood stem cell transplant recipients. The director met with the bone marrow transplant clinicians to announce the new practice standard. The intervention resulted in a 51 % reduction in the HHV6 test volume saving approximately $35,000 per year.

Case Example 5: Profiling of Medical Residents by Inpatient Service: Reducing Unnecessary Ordering of Daily Routine Laboratory Testing

Medical residents frequently order routine laboratory tests on a daily basis. Typically this includes chemistry panels, complete blood counts, and calcium/magnesium/phosphate. A number of manual order sets and electronic order entry systems allow these laboratory tests to be ordered “daily until discontinued” at the time of the patients admission. While in some cases this may be necessary, in the majority of instances the practice relates more to convenience than to a conscious decision regarding what tests are required each day for medical care. Over the years we have made a number of efforts to curtail this practice. Ultimately our new order entry system will be constructed to block the automatic ordering of daily laboratories altogether. In the meantime we tried educational initiatives and various pilot projects which had a temporary impact but ultimately the practice of daily laboratory testing returned to its original baseline. In our latest effort we began using resident physician profiling. First we received Medical Policy Committee approval to formally discourage “daily labs” to a limited number of indications including:

1. Patients on chemotherapy

2. Patients receiving Coumadin

3. Patients receiving heparin

4. Patients on immunosuppressive therapy

Our first intervention involved an order entry pop-up display that was intended to educate house staff about the policy as shown in Fig. 21.5. The pop-up had only a minor impact on the test ordering volumes but did alert the residents that “daily labs” would be monitored. Next we began a “profiling” intervention in which residents who ordered more than four daily until discontinued labs per week without an approved indication received an email from the laboratory director indicating that they were ordering non-approved “daily labs” and had been identified by electronic audit. Figure 21.6 shows the impact on “daily labs” orders over time. For our next intervention we are working directly with the medical senior residents and attendings to implement a Department of Medicine laboratory testing dashboard showing the numbers of tests and “daily labs” ordered by each of our medical teams along with the number of patients on each service. A portion of this dashboard is shown in Fig. 21.7. This dashboard profiles each of the resident medical teams collectively (as opposed to individual residents) and allows comparisons in performance across different teams. We believe this team-profiling approach has merit because the residents on each team change over time as they move from one service to another or leave the program after the completion of their training.

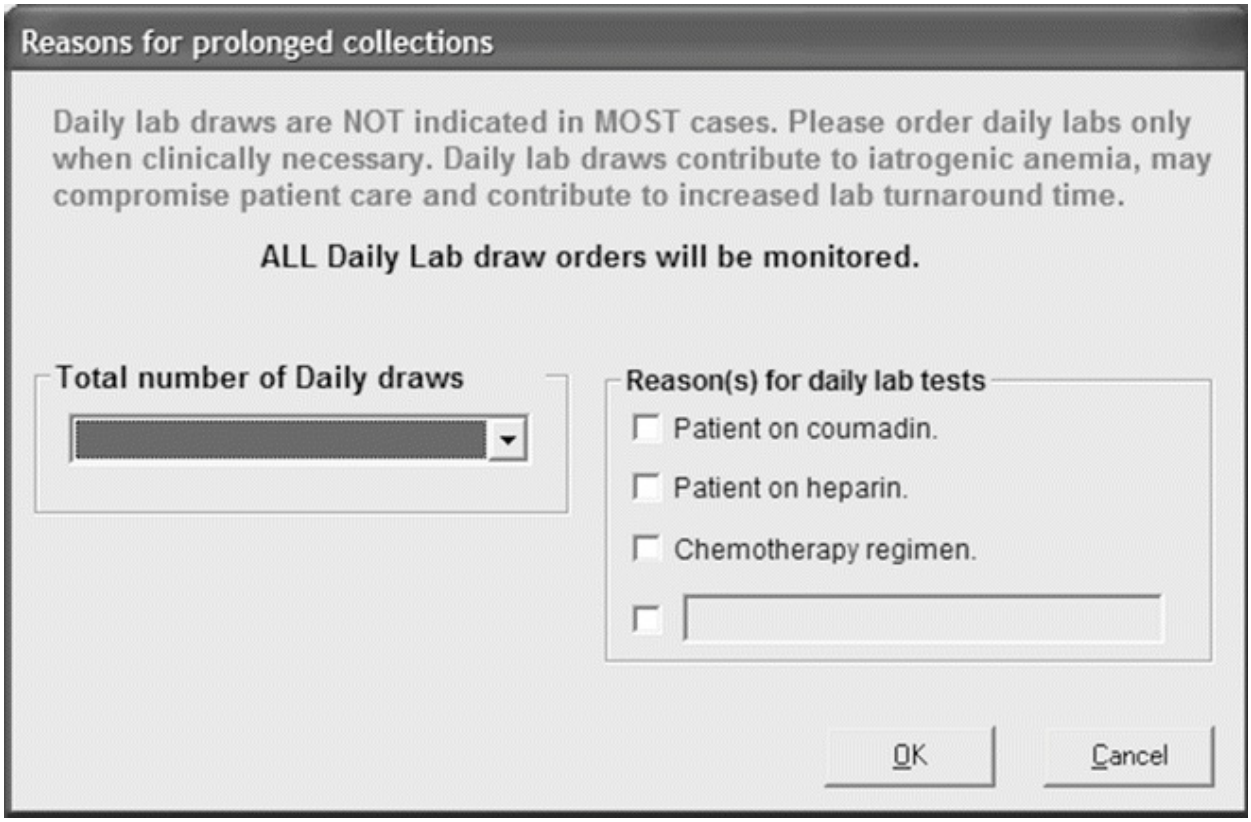


Fig. 21.5 Order entry pop-up screen shot used to discourage "daily until discontinued" laboratory test ordering

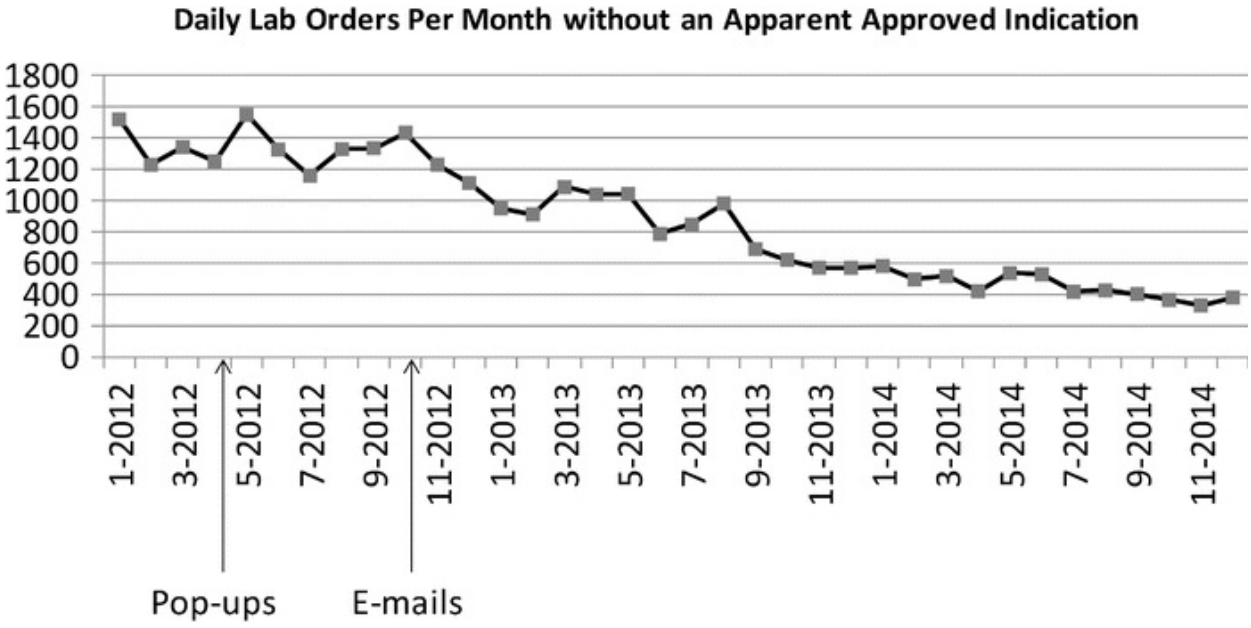


Fig. 21.6 Shown are the monthly volumes of daily orders (for three or more collections) without an apparent approved indication (tests orders using templates excluded). The decline in volumes over

several years is attributed to a cultural shift

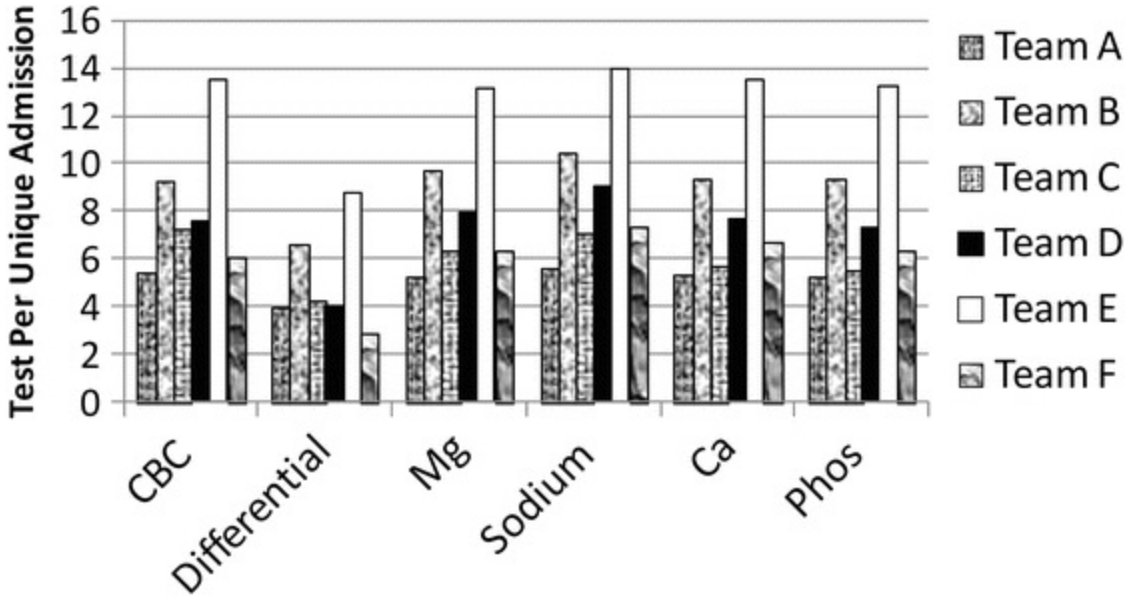


Fig. 21.7 Selected screenshot of our Department of Medicine House-Staff Team Service Profile

Case 6: Profiling to Establish a Standard of Care

It has long been recognized that ordering pre-operative screening tests in presumptively healthy outpatient day surgery patients is not cost effective. Yet many physicians continue this practice even when it has been discouraged by guidelines established within an individual institution. In our hospital we have a pre-admission testing service (PATA) that has developed guidelines for pre-operative testing based on the risk of the procedure (low, moderate, or high) and the patients acuity. According to this guideline, low risk, low acuity patients should receive an electrocardiogram but no laboratory testing. However, in practice, this guideline is not always followed. As shown in Fig. 21.8 , a review of one specialty surgical service showed significant variation in the number of pre-operative orders for routine tests. This information will be reviewed by the chief of the service working with the laboratory utilization group.

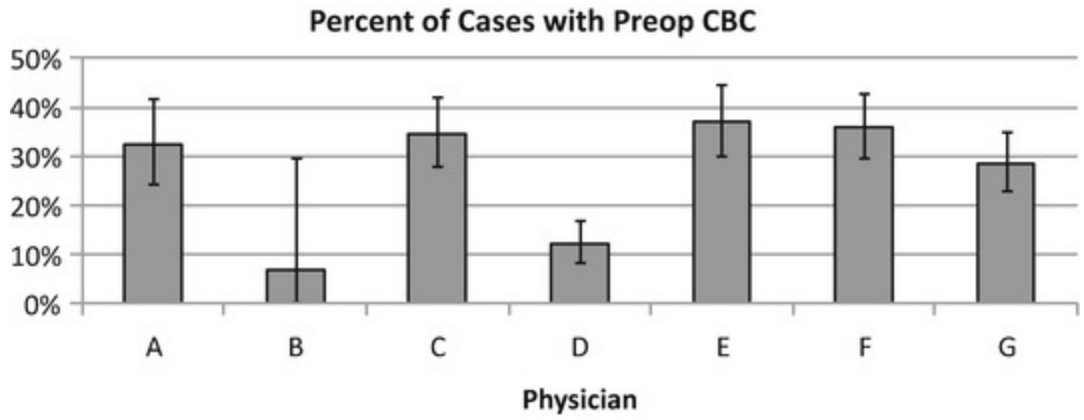


Fig. 21.8 Analysis of pre-operative complete blood count (CBC) test orders on a surgical specialty practice. The letters *A–G* represent individual physicians and the y-axis shows the percentage of that physician's patient-cases who had a pre-op order for a CBC. Significant variation in practice is observed from <10 % of patients for some physicians to over 30 % for others. *Error bars* indicate 95 % confidence intervals

Case 7: Normalizing Physician Profiling Data to Account for Different Case Loads and Subspecialty Practices

One high cost area of laboratory testing in our institution is neurogenetics which is sent out to reference laboratories. Many of these tests are highly specialized and are expensive. We profiled our neurologists to evaluate variations in practice among providers in our department of neurology. As expected there were significant differences in the types and volumes of tests requested by different neurologists. We presented this data to our neurology leadership and, in their opinion, the data was essentially worthless. The reason they gave was that neurology practice in our hospital is highly sub-specialized: there are specialists in stroke, epilepsy, movement disorders, neurodegenerative disorders and a variety of other areas. Also many neurologists spend a significant portion of their time on research, whereas others are predominantly clinical. Therefore case loads within each specialty varied considerably. Working with a medical economist (Michael Hidrue, PhD) we began developing a model to predict, based on specialty and case load, what types and volume of testing would be expected for each specialty area versus what was observed for each individual clinician. In this way we could assess which physicians were above or below the "expected" volume of testing as shown in Fig. 21.9. We observed significant outliers in a number of

specialties. Since then we have been meeting with individual clinicians to better understand the unique aspects of their practices and to develop strategies to control the overall cost of the testing. The clinicians have been receptive and have recommended a number of useful follow-up initiatives. Over time we have observed a significant decrease in the total annual cost of neurogenetics testing . Also our neurology department decided to use standardization and reductions in reference laboratory expenses as one of their bonus-eligible quality improvement initiatives.

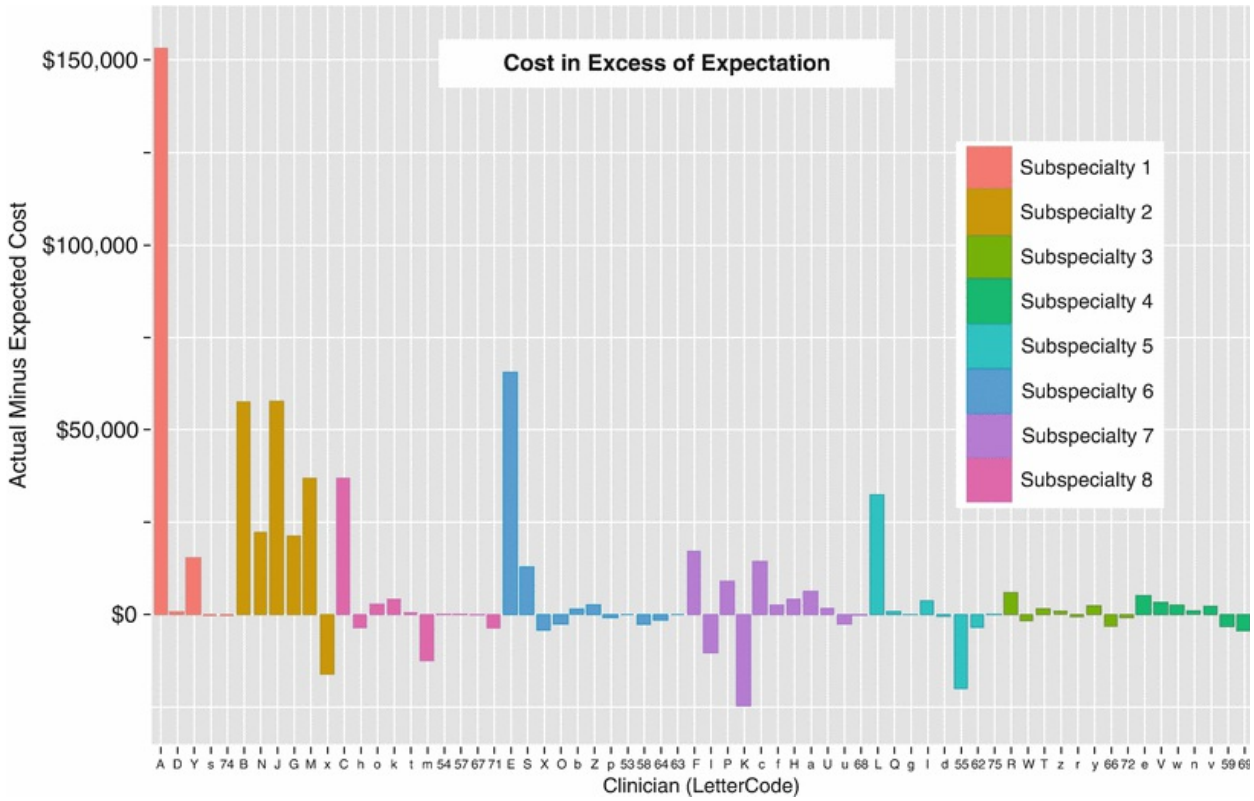


Fig. 21.9 Shown is the variation in sendout costs across physicians within a single speciality. Physicians are grouped by subspecialty (expressed by the color of the bars). The height of each bar represents the actual spending of each physician in excess of expected spending. Expected spending was based on physician subspecialty and patient volume and patient characteristics (including diagnoses). Data for this figure was compiled by Michael Hidrue, PhD

Conclusions

Physician profiling is widely employed to improve quality, reduce costs and to standardize physician practice in clinical care. However, profiling data may not be reliable leading to misinterpretation of potential opportunities indentified through analysis of the data. In this chapter we have presented

case examples of where we have used physician profiling in our laboratory utilization management program. Profiling allows us to identify which clinicians are ordering different tests, the rate of clinically actionable results, and the ability to link the data to specific patient encounters. To be successful the laboratory must have a robust informatics capability and a willingness to work with clinicians in a collegial team-oriented environment.

Prior Approval (Gate-keeping)

According to Mackinnon and Kumar, “prior approval is an administrative tool that requires the prescriber to get pre-approval for prescribing (a drug) in order to qualify for reimbursement” [14]. Traditionally prior approval was used by third party payers to restrict access to high cost procedures (such as radiology scans) and pharmaceuticals. In concept prior approval systems are intended to ensure that the patient gets the most appropriate procedure or treatment and that cost-effective alternatives such as generic drugs in place of brand names are utilized whenever possible. However, in practice, prior approval requirements by third party payers usually result in time-consuming paperwork for physicians and have frequently taken on more of an obstructive rather than restrictive approach. An article by Grumet published as far back as 1989 highlighted the onerous strategy often employed by third party payers with the quote “But another feature has crept into the managed care formula that has been largely overlooked: that of slowing and controlling the use of services and payment for services by impeding, inconveniencing and confusing providers and consumers alike” [15]. In the article he described eight of these approaches including:

1. Procedural complexity: requirements for multiple forms and procedure codes

2. Exotic terms: The use of unique or exotic procedures, codes and terms (e.g., corridor deductibles)

3. Slowdowns: Slowing authorization for procedures and claims

4. Shifting of procedures: Frequent changes to codes, forms, and policies

5. Fail-safe payment systems: Protocols designed to inhibit approving claims where any negative condition will stop fulfilling the claim

6. Overlapping coverage: Systems designed to shift coverage to other payors

7. Fragmentation of transactions: Systems requiring the provider to interact with multiple offices within the insurance carrier

8. Uncertainty of coverage: Ambiguity about whether certain services will be covered.

Some studies on prior approval systems have also documented a number of unintended effects resulting from restrictions to access for medical services . For example, a study by Bloom and Jacobs evaluated the impact of a pharmacy formulary program and reported a significant reduction in drug expenses but with a corresponding increase in physician visits and inpatient hospital costs [16].

The recent introduction of high cost molecular and genetic tests has prompted many payers to initiate prior approval mechanisms into clinical laboratory testing [17]. Genetic tests can cost from $500 to $10,000 or more [17] and studies have shown that these tests are frequently ordered inappropriately. In a study by Dickerson et al., the authors reviewed genetic test requests using a team of laboratory directors and a genetic counselor. They reported that 25 % of requests were “modified in a downward direction … saving 19 % of the test requests under management” [18]. While such a high error rate in genetic test orders would seem to justify initiating a prior approval strategy, there is a significant difference between the approaches used by Dickerson et al. and those being utilized by many third party payers. In the case of Dickerson et al., the authors used a collaborative approach and provided the ordering physician with expert consultation before modifying the test order. In contrast, most third party payers require the physician to engage with a complex bureaucracy that provides little or no decision support. The former approach is usually appreciated by the ordering physician and is educational whereas the latter is largely obstructive (albeit

effective).

Hospital laboratories are also beginning to employ prior approval strategies to control the utilization of expensive tests using laboratory directors and residents to screen and approve test requests. Usually these activities are referred to as “gate-keeping” rather than prior approval.

Hospital-based gate-keeping originally began with the establishment of pharmacy formularies. For example, many large hospitals require physicians to get approval from infectious disease specialists before being allowed to prescribe restricted (and expensive) antimicrobial agents. More recently gate-keeping initiatives have become more common in clinical pathology. In our hospital we have utilized gate-keeping strategies in our blood transfusion service for many years in an effort to control the use of high cost blood components as described in reference [19]. For further details, see the chapter “Utilization management of special blood bank components.”

Our earliest experience with gate-keeping dates back to the 1980s. In 1987 our laboratory set up a mandatory laboratory approval for requests for lactic dehydrogenase isoenzyme analysis (LDH isoenzymes), a marker for myocardial infarction that was being supplanted by assays for creatine kinase MB isoenzyme. At the time most physicians ordered both tests simultaneously. The gate-keeping effort reduced requests for LDH isoenzymes from approximately 2000 per month to 7 per month (>99 %) [20]. As described in Chap. 1, a number of studies have reported on similar successes. For example, Fryer et al. reported an 83 % decrease following a gate-keeping initiative for toxicology screens [21] and Hutton et al. an 85 % reduction in C-reactive protein testing [22]. In another study Liu et al. reported on a gate-keeping initiative to reduce tests sent out to a reference laboratory. For every test costing more than $20 (Canadian) a letter was sent to the ordering provider requesting a clinical justification for the test. This intervention reduced reference laboratory testing by approximately 50 % [23].

Gate-keeping is an effective approach to utilization management on two fronts: first it imposes a barrier to ordering the test, and, second it creates an opportunity for physician education.

Gate-keeping activities can be quite labor intensive as it requires multiple steps to bring the test request to a resolution including:

1. Identification of the test request in the laboratory

2. Review of the request by the laboratory director

3. Telephone or email discussion with the ordering physician

4. Cancellation or approval of the test request

For this reason it is generally only practical to gate-keep low volume-high cost tests. However, if the gate-keeping function provides physician education, over time the number of tests that need to be reviewed should decline. This is particularly true for tests that are being overutilized but have only rare clinical indications. In some cases a significant percentage of the test requests are appropriate. In this case the gate-keeping function would be expected to continue over an extended period of time. Here physician education is equally important: the goal being to eliminate the overutilized tests such that the gate-keeping function can be discontinued once the unnecessary testing has been eliminated. Before beginning a gate-keeping initiative we have found it helpful to identify which physicians are ordering the majority of the tests and to communicate with them before stating the initiative. This helps to eliminate many of the unnecessary orders in the first place, obviating the need for further intervention. Despite this, realistically, laboratory directors are only able to gate-keep a limited number of tests any one time. For example, we are currently targeting Babesia serology testing, Anaplasma and Ehrlichia serology, and two tests for invasive fungal infections (galactomannan and Beta-D-glucan). Gate-keeping a test once the sample has already arrived in the laboratory is problematic for obvious reasons. As we expand our gate-keeping efforts we will therefore rely more on electronic provider order entry using decision support to screen out unnecessary tests before the physician has placed the order.

Conclusions

Prior approval (gate-keeping) has long been employed by both third party payers and hospitals to control the utilization of medical services. In the clinical laboratory, gate-keeping is being increasingly used to reduce expensive tests in genetics and other specialties. The best gate-keeping initiatives include an educational component such that the time required to

maintain the function decreases over time. Ideally, unnecessary laboratory tests will be eliminated before the physician has placed the order obviating the need for phlebotomy and subsequent interaction between the gatekeeper and the physician provider. This is best accomplished through the use of electronic provider order entry systems that are embedded with decision support to guide the most optimal utilization of laboratory services.

References

1. Gittelson A, Wennberg J. Small area variations in health care delivery. Science. 1973;182:1102–8. [CrossRef]

2. Welsh G, Miller M, Welch P. Physician profiling: an analysis of inpatient practice patterns in Florida and Oregon. NEJM. 1994;330:607–12. [CrossRef]

3. Balis A, Boren S, Brown G, Ewigman B, Mitchell J, Perkoff G. Effect of physician profiling on utilization: meta analysis of randomized clinical trials. J Gen Intern Med. 1996;11:584–90. [CrossRef]

4. Lewis S. The future of physician profiling. J Ambul Care Manage. 1999;22:11–6. [CrossRef]

5. Physician profiling, guiding principles. American Academy of Family Physicians; 2015. http://www.aafp.org/about/policies/all/physician-profiling.html. Accessed 14 Feb 2014.

6. Principles for profiling physician performance. The health report. Massachusetts Medical Society; 1999. http://www.massmed.org/Advocacy/Key-Issues/Tiering-and-Pay-for-Performance/Principles-for-Physician-Profiling-(1998)/#.VOC8wDtOXcc. Accessed 14 Feb 2015.

7. Charvet H. The problems with physician profiling: what have we learned? N Y Med Cent Stud Med J. 2009;2:43–7.

8. Thomas J, Grazier K, Ward K. Economic profiling of primary care physicians: consistency among risk-adjusted measures. Health Serv Res. 2004;39:985–1003. [CrossRef][PubMed][PubMedCentral]

9. Hofer T, Hayward R, Greenfield S, Wagner E, Kaplan S, Manning W. The unreliability of individual physician “report cards” for assessing the costs and quality of care in chronic disease. JAMA. 1999;281:2098–105. [CrossRef][PubMed]

10. Adams J, Mehrotra A, Thomas W, McGlynn E. Physician cost profiling: reliability and risk misclassification. NEJM. 2010;362:1014–21. [CrossRef][PubMed][PubMedCentral]

11. Sandy L, Rattray M, Thomas W. Episode-based physician profiling: a guide to the perplexing. J

Gen Intern Med. 2008;23:1521–4.
[CrossRef][PubMed][PubMedCentral]

12. Bunting P, van Walraven C. Effect of a controlled feedback intervention on laboratory test ordering by community physicians. Clin Chem. 2004;50:321–6.
[CrossRef][PubMed]

13. Ramoska E. Information sharing can reduce laboratory use by emergency physicians. Am J Emerg Med. 1998;16:34–6.
[CrossRef][PubMed]

14. MacKinnon N, Kumar R. Prior authorization programs: a critical review of the literature. J Manag Care Pharm. 2001;7:297–302.

15. Grumet G. Health care rationing through inconvenience. NEJM. 1989;321:607–11.
[CrossRef][PubMed]

16. Bloom B, Jacobs J. Cost effects of restricting cost-effective therapy. Med Care. 1985;23:872–80.
[CrossRef][PubMed]

17. Connole P. Insurers clamp down on genetic testing via counseling, prior authorization. Health Business Daily. 2014;24(37). http://aishealth.com/archive/nhpw102714-02.

18. Dickerson J, Cole B, Conta J, Wellner M, Wallace S, et al. Improving the value of costly genetic reference laboratory testing with active utilization management. Arch Pathol Lab Med. 2014;138:110–3.
[CrossRef][PubMed]

19. Kim J, Dzik W, Dighe A, Lewandrowski K. Utilization management in a large urban academic medical center: a 10-year experience. Am J Clin Pathol. 2011;135:108–18.
[CrossRef][PubMed]

20. Fryer A, Smellie W. Managing demand for laboratory tests: a laboratory toolkit. J Clin Pathol. 2013;66:62–72.
[CrossRef][PubMed]

21. Lewandrowski K, Bailey E, Dhanak E, Laposata M, Flood J. Mandatory laboratory consultation as a method to aid appropriate test utilization: the case of lactate dehydrogenase isoenzyme analysis. Lab Med. 1994;27:460–3.
[CrossRef]

22. Hutton H, Drummond H, Fryer A. The rise and fall of C-reactive protein: managing demand within clinical biochemistry. Ann Clin Biochem. 2009;45:155–8.
[CrossRef]

23. Liu Z, Abdullah A, Baskin L, Lewis G, Kelter G. An intervention to reduce laboratory utilization of referred-out tests. Lab Med. 2012;43:164–7.
[CrossRef]

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_22

22. Test Utilization: The Essential Role of the Clinical Consultant

Elizabeth Stewart[1] and Valerie L. Ng[2, 3]

(1) Department of Medicine, Alameda Health System/Highland Hospital, Oakland, CA, USA
(2) Department of Laboratory Medicine, School of Medicine, University of California, San Francisco, San Francisco, CA, USA
(3) Department of Laboratory Medicine and Pathology, Alameda Health System/Highland Hospital, Oakland, CA, USA

Valerie L. Ng
Email: vang@alamedahealthsystem.org

Keywords Laboratory medicine – Clinical consultation – Clinical consultant – Laboratory test lifecycle – Appropriate test utilization – Requisition design – Blood component use – Coagulation testing – Targeted feedback

Introduction

The explosive growth of clinical laboratory tests in the last century has resulted in the availability of at least 4000 tests [1, 2]. Observed regional variation in laboratory testing without differences in clinical outcome coupled with the ever rising costs of healthcare has logically focused attention on "appropriate" test utilization [3]. The definition of "appropriate" testing is still evolving and an outcomes-based definition of "appropriate laboratory utilization" in its infancy [3–7]. Historical attention (including this chapter) has focused on inappropriate test overutilization; it has been much more

difficult to accurately assess inappropriate test underutilization [7–9].

Appropriate laboratory testing education in medical school has been minimal and continues to decline [5, 10, 11]. One study compared the perceptions of students versus their supervisors regarding the readiness of the students for post-graduate residency training [12]. Approximately 18–19 % of the students rated themselves as “less than quite well prepared” while their supervisors placed 22–25 % in this same category. Notably 49 % of students considered themselves “quite well prepared” and 29 % “more than quite well prepared” for “making the best use of laboratory & other diagnostic services” [12].

Residency training regarding appropriate laboratory testing has substantial variability. Traditionally it is integrated with patient care and centered within individual patient care teams and [5, 13–15]. It is widely recognized that part of the expense of graduate medical education is due to increased testing by “clinically inexperienced trainees” [14]. Studies on the laboratory ordering practices of interns, residents, and attendings have consistently demonstrated fewer laboratory tests are ordered with increasing experience. In one study assessing test ordering variation, interns not only ordered more tests but were also responsible for 45 % of the laboratory test ordering variation. Resident and attendings ordered progressively fewer tests and contributed only 27 % and 10 %, respectively, to the observed test ordering variation [14]. Interns and residents had distorted perceptions of who really “controlled” test ordering—only 20 % of interns and 52 % of residents believed they had “much” or “total” control when in fact the majority of test variation was attributable to them [14]. Attendings had surprisingly little impact on laboratory test ordering even on a “hospitalist-run teaching-intensive service at an academic medical center” where attendings would be expected to have the most influence. This study concluded residents and interns are almost entirely responsible for variation in laboratory test use, with residents and interns unaware of their own control and relative performance. A commentary noted excessive laboratory testing by interns is attributable to the inexperience and uncertainty of the novice with “no easy shortcut to the attainment of expertise” [16].

The ever increasing volume of laboratory testing has unfortunately refocused Laboratory Medicine internally to maximize clinical testing efficiency while maintaining quality standards. There is little time for laboratorians to interact with clinicians, let alone to have dedicated time to

assist with developing guidelines for appropriate testing. Adding to these competing priorities is the well-recognized clinical laboratory workforce shortage with a continued decline in trainees in Laboratory Medicine (e.g., doctoral level laboratory directors, medical scientists/technologists) [5]. These factors have converged to result in Laboratory Medicine having little representation for clinical collaboration in the larger healthcare organization, and clinical laboratories becoming autonomous factory-like "production" facilities. Laboratory Medicine's traditional Clinical Consultant role of improving patient care by delivering accurate and timely laboratory information (not just data) is vanishing [5].

Ironically a Laboratory Medicine specialist has become even more essential in these times of explosive growth of new laboratory tests. Laboratory Medicine has well-recognized the lifecycle of a new laboratory test, beginning with extreme enthusiasm based on a few studies, muted over time by subsequent studies narrowly defining the clinical utility of the test, and ending with "right-sizing" test utilization to typically only a few clinical conditions. This "lifecycle of a new test" is entirely congruent with the well-known Information Technology "Hype cycle" (Fig. 22.1a) [17].

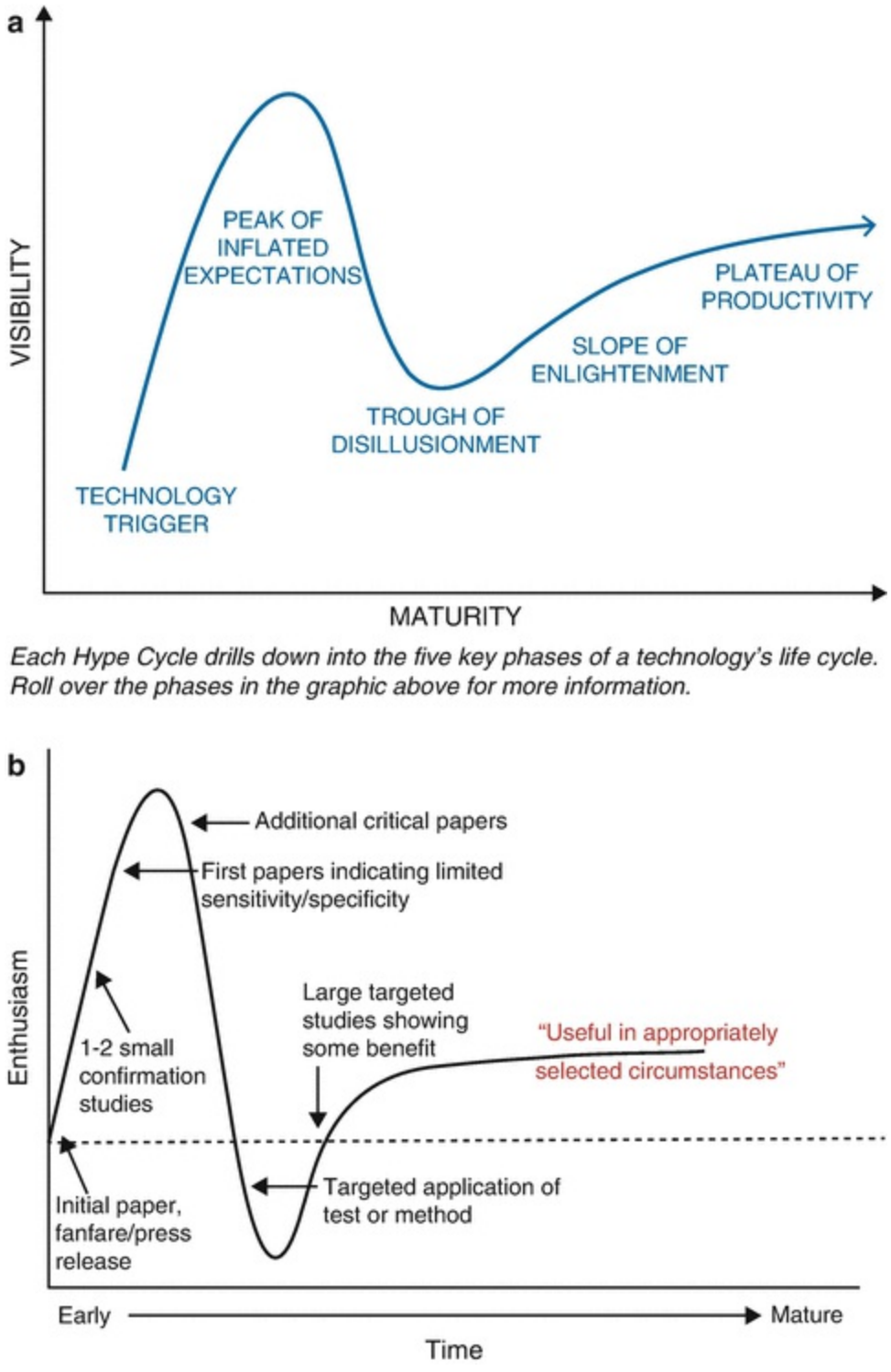


Fig. 22.1 The "hype" cycle (panel **a**) [17], modified to represent the lifecycle of a "new" test (panel **b**)

An example of the "hype cycle" as applied to laboratory testing is the evolution of prostate specific antigen (PSA) testing to screen for prostate

cancer—from the development of an assay to quantify PSA ("new technology"), to the initial widespread enthusiasm of its use to identify prostate cancer early in the course of disease ("peak of inflated expectations"), to the recognition of concurrent benign prostatic hypertrophy (BPH) having elevated PSA levels and confounding interpretation ("trough of disillusionment") to the current state when evidence-based practice ("slope of enlightenment") has identified the limited settings in which PSA testing adds value to clinical care ("plateau of productivity"). The generic features of a new test can thus be applied to the "hype cycle" (Fig. 22.1b).

Academic medical centers are particularly prone to inappropriate testing related to new tests. Often these new tests are developed by research laboratories within the institution and "translated" prematurely to clinical care. Academic colleagues are keen to assess the clinical utility of the new test in new clinical settings, often applied to a single patient and outside the rigor of a structured clinical study. Likewise trainees at Academic medical centers are particularly prone to new lab test hype from their attendings that might be involved in related research or have learned about new tests but lack the experience to determine how the test will really change management or improve outcome.

One strategy to manage this process has been to create a multidisciplinary committee to achieve consensus on appropriate laboratory utilization [3, 4]. From the laboratory perspective, however, the time needed for effective participation is considerable, often non-existent and often not possible. Since each new test or use usually presents unique issues, Laboratory Medicine participation must be continuous. There is no "one size fits all" solution. One study documented a minimum weekly physician time commitment of 36 physician hours—19 h weekly for Clinical Pathologists involved with the bone marrow transplant service, 12 h weekly for the core laboratory director, and five hours weekly for the "director of clinical services." An additional 8 h weekly of administrative support was required [3].

The role of the Laboratory Medicine specialist who interfaces with the clinical services ("Clinical Consultant") is to understand the patient population being treated in his/her own setting, and from this knowledge develop in partnership with colleagues the optimal use of the clinical laboratory. The desirable characteristics of a Laboratory Medicine Clinical Consultant have not changed [18]. In short, requirements include excellent interpersonal and communication skills, firm grasp of laboratory testing

methodology and Laboratory Medicine evidence-based practice, keen analytical skills, comfort with uncertainty and open mindedness and willingness to change. The practice of Medicine is continuously evolving [19] and so must Laboratory Medicine.

The Value of Partnership

While the Laboratory Medicine specialist ("Clinical Consultant") may be the expert on laboratory aspects of testing, it is the clinical counterpart ("Clinician") who is often the expert on how a particular test influences patient care. It is the close collaboration of both to plan the path forward in optimizing appropriate use of the Clinical Laboratory.

The Clinician should be recognized and respected as a "thought leader" and influential in implementing change [18]. Clinicians are usually not department heads but instead "middle-level active clinicians." The Clinician and Clinical Consultant synergy facilitates rational (and ideally evidence-based) laboratory testing algorithms best meeting patient care needs and appropriate laboratory utilization. Key in their effectiveness is "partnership"—i.e., equal participation, influence, responsibility, accountability, and respect.

Academic settings have the benefit of an abundance of clinical subject matter Clinician experts to assist with optimal laboratory utilization. Non-academic settings have, however, variable expertise, interest, or protected time for either the Clinician or Clinical Consultant to assume this responsibility. Knowledge gaps can be bridged by professional society recommendations or independent authoritative guidelines (e.g., Cochrane reviews, United States Preventive Task Force, or USPTF). The Clinical Consultant or Clinician must identify the correct counterpart to influence implementation and practice change.

There will be situations when the Clinical Consultant and Clinician fundamentally disagree. A compromise must be made, sometimes with the final conclusion of "agreeing to disagree." This means there must be respectful agreement on the decision for the identified issue with acknowledgement of the underlying controversy. Common to controversial issues, there would be agreement to revisit it over time as new evidence becomes available [19]. There are many situations where the Laboratory Medicine literature disagrees with the relevant clinical literature, and it is the

effective partnership of the Clinical Consultant with the Clinician to determine the optimal practice in their clinical setting.

The skills for either person in this partnership are typically considered "soft" skills—i.e., effective communication, ability to discuss controversial topics objectively and neutrally without inflammation, willingness to engage in "crucial conversations," and other non-quantifiable skills linked to core physician competencies of professionalism and interpersonal and communication skills.

The effective Clinician and Clinical Consultant partnership can prepare the organization for agreed upon change with education, feedback, and incentives. These traditional approaches are well-documented weak interventions, however, with minimal sustained impact. Effective and sustained change relies on strong interventions such as basic fundamental system level changes (i.e., "process changes" or "administrative changes") to standardize and optimize laboratory utilization [20].

Requisition Design

The conventional laboratory requisition is simply a listing of commonly requested tests. The earliest Laboratory Medicine foray into clinical consultation involved intelligent requisition design.

The first experiment arose when "considerable misuse" and over ordering of "thyroid testing" was recognized, in particular inappropriate ordering of T4, T3, T3 uptake, and thyroid stimulating hormone, or TSH [21]. One study redesigned the test requisition to list individual test panels of "hypothyroid panel," "hyperthyroid panel," and "thyroid screen," noting the individual tests within each panel, instead of listing the individual tests and allowing individual clinicians to select which to order. A final option of "other thyroid test" was included to allow clinicians to order testing not conveniently configured into panels. Creatine kinase (CK) and lactate dehydrogenase (LDH) test orders for diagnosis of acute myocardial infarction were not altered and served as experimental controls for the effectiveness of thyroid testing requisition design. Education on appropriate use of all thyroid tests, CK, and LDH occurred through presentations at departmental meetings. Laboratory-produced educational bulletins were published and widely circulated. Following these changes a 38–62 % decrease in thyroid testing was observed while CK and LDH test utilization did not change. This study

demonstrated the sustained value of requisition redesign in improving test utilization for thyroid testing. It also reproduced the well-recognized time-limited effectiveness of other methods (education, feedback).

The Emersons had similar findings from a study assessing outpatients and laboratory utilization by different specialty groups [22]. The impetus for the study was increased regulatory and institutional burdens for assuring medical necessity of laboratory testing. They redesigned requisitions with tests grouped by organ, disease or specialty with specific “cascades” of testing. The “cascades” ensured medical necessity while minimizing time to diagnosis and maximizing convenience to both physicians and patients (e.g., thyroid “cascade,” urine screen for culture, “anemia cascade”). They demonstrated a significant decrease in the overall number of tests ordered per outpatient visit.

Today these requisition design interventions are facilitated by information technology with controls for “appropriate” testing built into electronic orders [6, 23].

Blood Bank and the Transfusion Service

The significant cost of blood components, recognition transfusion is not always “safe” [24] and the well-understood downsides to overtransfusion automatically focus attention on appropriate utilization.

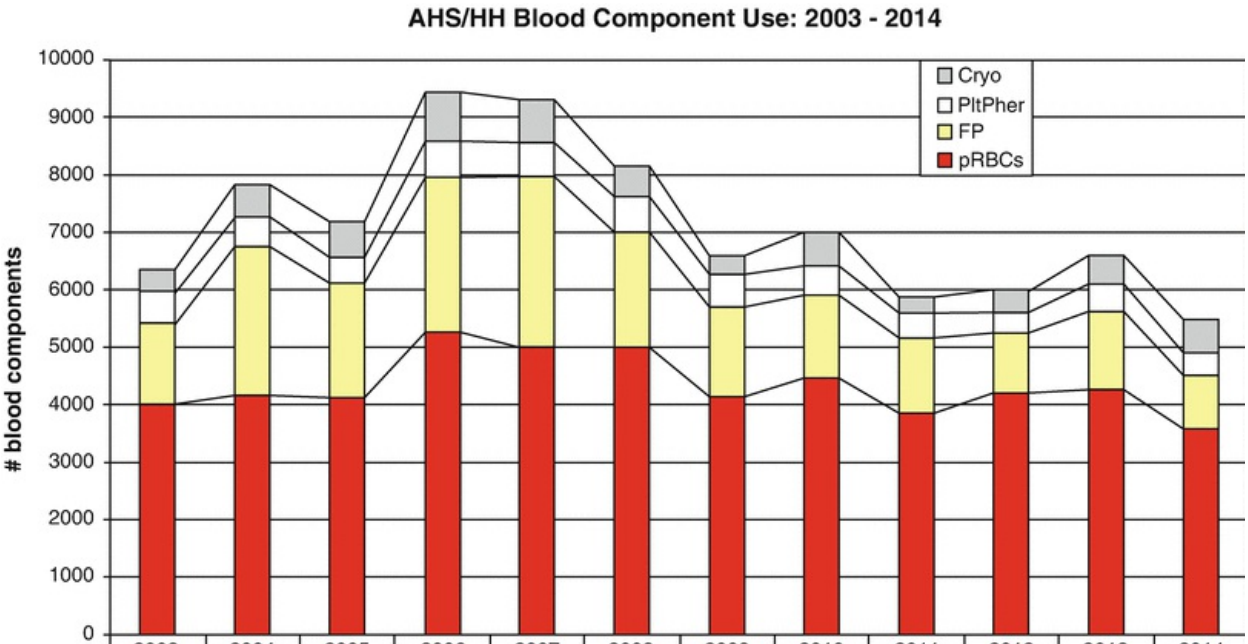
What added value is contributed by the Blood Bank Clinical Consultant (i.e., Transfusion Service Director)? Various evidence-based clinical guidelines have been promulgated regarding appropriate blood component use [25–27]. Within our organization, accepted indications for transfusion are listed with orders for each component, prompting the provider to select the indication justifying the transfusion before the order can be completed. In the list of possible indications is an “other” category. This category is intended to provide flexibility in permitting transfusion when the transfusion indication is not standard. The physician must complete the order by documenting the non-standard reason for transfusion. These orders are an obvious target for utilization review and targeted feedback on appropriate usage to individual physicians.

Aside from reviewing individual non-standard transfusion orders, Blood Bank and Transfusion service activity is regularly reviewed as part of an overarching quality management system. Blood component use over time can

be evaluated to identify opportunities for improvement.

Blood Component Use

Figure 22.2 depicts blood component use in our organization from 2003 to 2014. This utilization would be typical of a community based general hospital without tertiary care and need for specialized components or specialized uses for existing components (e.g., bone marrow or solid organ transplant program).



	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Cryo	387	545	653	841	735	534	345	558	294	388	507	587
PltPher	542	516	435	630	630	599	564	520	420	329	457	390
FP	1433	2606	1999	2710	2969	2044	1567	1438	1315	1058	1346	908
pRBCs	3981	4138	4091	5239	4963	4964	4119	4459	3837	4204	4261	3585

Fig. 22.2 Overall blood component use from 2003 through 2014

There was a significant increase in blood component use in 2006 and 2007, primarily in packed Red Blood Cells (pRBCs) and frozen plasma (FP) . This was a practice variation identified by relatively simple monitoring. Investigations into the increased FP use uncovered indiscriminate diagnoses of thrombotic thrombocytopenic purpura (TTP) . A TTP diagnosis automatically triggered multiple cycles of plasmapheresis requiring FP, explaining the increased FP use. An educational effort ensued regarding the correct diagnostic criteria for TTP as well as feedback to individual

physicians who had been less exacting in diagnosing TTP. FP use declined by approximately 1000 units annually shortly thereafter, and this lower rate of FP use has since been sustained. The FP cost at this time was $55/unit, and this intervention resulted in $55,000 deferred annual costs.

rFVIIa Use

Another example of practice variation identified by simple monitoring was the use of clotting factor concentrates, in particular recombinant activated FVII (rFVIIa) . This concentrate was originally approved by the United States Food and Drug Administration (US FDA) in 1999 to treat patients with hemophilia and factor inhibitors who were experiencing significant bleeding. Its broadly applicable mechanism of action as an “all purpose hemostatic clamp” quickly caught the attention of trauma surgeons to treat massively bleeding patients who had incurred blunt or penetrating trauma. Others also quickly resorted to “off label” use when faced with seemingly intractable bleeding.

This concentrate was extraordinarily expensive at $1000/mg with the average dose 4 or 5 mg. It had a half-life of only 2 h so frequent redosing was necessary if hemostasis had not yet been achieved.

In our organization rFVIIa quickly caught the attention of our trauma surgeons, our critical care intensivists and our Emergency Room physicians. Utilization review for each use was instigated and performed by the Transfusion Service Director (Fig. 22.3). The dramatic usages in calendar year 2004 and 2005 were for each of two critically ill patients on the Medicine service each year. rFVIIa was used “off label” and attributable to a single intensivist. Targeted feedback and education occurred with the agreement rFVIIa would no longer used “off label” by this physician. The Trauma surgeons meanwhile became enamored of its use with massively injured patients, especially those for whom massive transfusion had occurred. The Emergency Medicine physicians became interested in its use for early treatment of life-threatening hemorrhagic strokes. True to the “hype curve,” our organization “peak of expectations” for rFVIIa use had been reached circa 2005. Evidence began mounting shortly thereafter of increased adverse thrombotic events associated with rFVIIa use, and increasingly publications were describing no apparent outcome benefit. Finally a seminal 2010 publication definitively demonstrated an increased thrombotic risk with rFVIIa use [9, 28]. Furthermore the thrombotic risk increased with increasing

age, the range of which included most of our patients with hemorrhage strokes for whom rFVIIa administration was being considered.

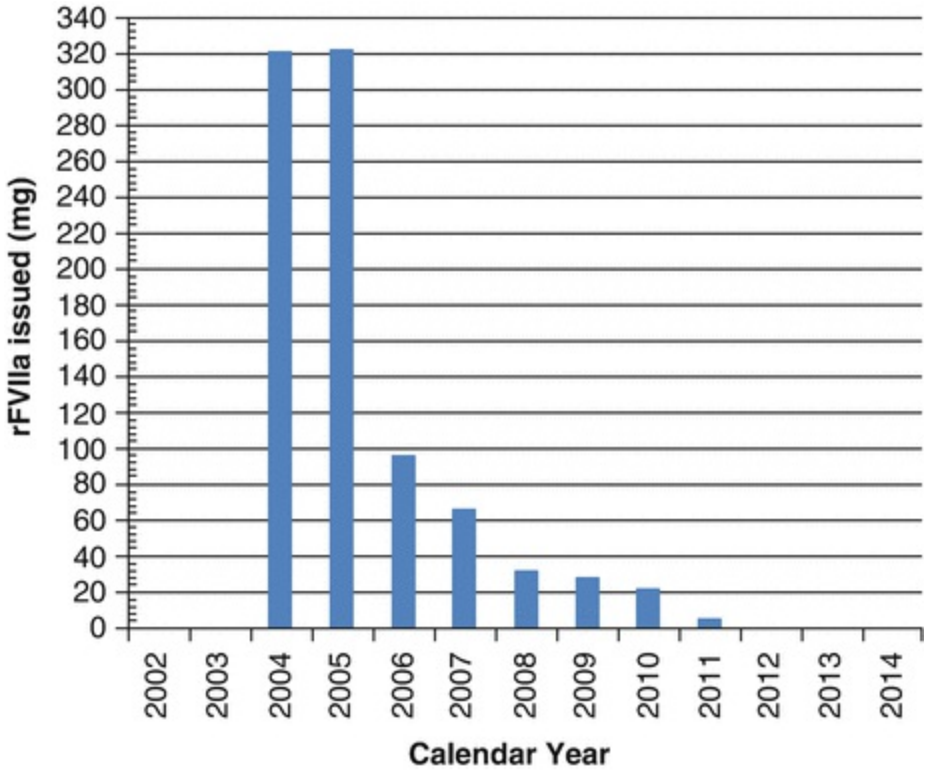


Fig. 22.3 Overall use of activated recombinant Factor VII

Continued education and targeted feedback on the accepted use of rFVIIa to ordering physicians by the Transfusion Service Director minimized “off label” use. Over time its use in the organization has dramatically declined. When compared to the $320,000 expenditure in each of calendar years 2004 and 2005, the reduction in use has been consistent and sustained with annual deferred cost of $320,000.

Massive Transfusion and Blood Wastage

Massive transfusion protocols can be associated with significant blood wastage. Within our organization one explanation for the wastage was patients died before the components could be transfused. Untimely storage or return to the Blood Bank compounded the wastage. The Transfusion Service Director investigated and categorized massive transfusion associated wastage relative to patient survival (Fig. 22.4). Approximately 2/3 of patients for who

massive transfusion had been activated and blood wastage occurred died before transfusion could be completed. This identified 1/3 for which either transfusion could be completed or unused blood components returned timely to reduce wastage. Targeted feedback was provided to the involved surgical teams. With no other interventions, reduction in massive transfusion related blood wastage was observed within 1 year.

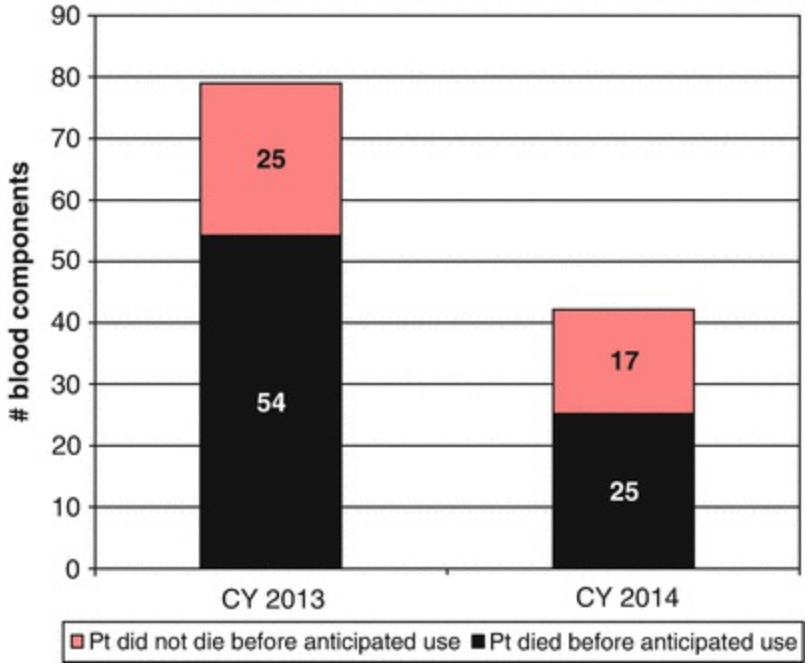


Fig. 22.4 Massive transfusion protocol related blood component wastage for calendar years 2013 and 2014

Thawed Frozen Plasma

The manufacturing of blood components is regulated by the Centers for Biologics Evaluation and Research (CBER) within the US FDA. Frozen plasma thawed for patient use has 6 h stability when refrigerated (stipulated in the US Code of Federal Regulations 21 CFR 600.120). Meanwhile acceptable clotting factor activity was demonstrable in thawed refrigerated FP for up to 5 days after thawing [29]. Blood Banks were interested in maximizing the use of thawed and refrigerated FP by extending the expiration period from 6 h to 5 days. The FDA required a variance to extend the stability from 6 to 24 h. After 24 h the FDA considered thawed plasma an unlicensed and therefore unregulated product so no further governmental approval was needed to extend the stability from 24 h to 5 days.

This change provided an opportunity for Blood Banks to “repurpose” plasma which had been thawed for a specific patient but had not been transfused. This was a significant advantage for organizations with massive transfusion protocols in which thawed plasma was not used and wastage significant. The first step was presenting evidence to the surgeons that clotting factor activity was sufficient for hemostasis in thawed and refrigerated FP. Once the surgeons were convinced of its efficacy, we obtained the necessary FDA variance to extend the expiration of thawed plasma from 6 to 24 h. We then continued the continued storage for a total of 5 days and actively “repurposed” thawed plasma. We were able to achieve and sustain significant savings and reduced wastage (Fig. 22.5).

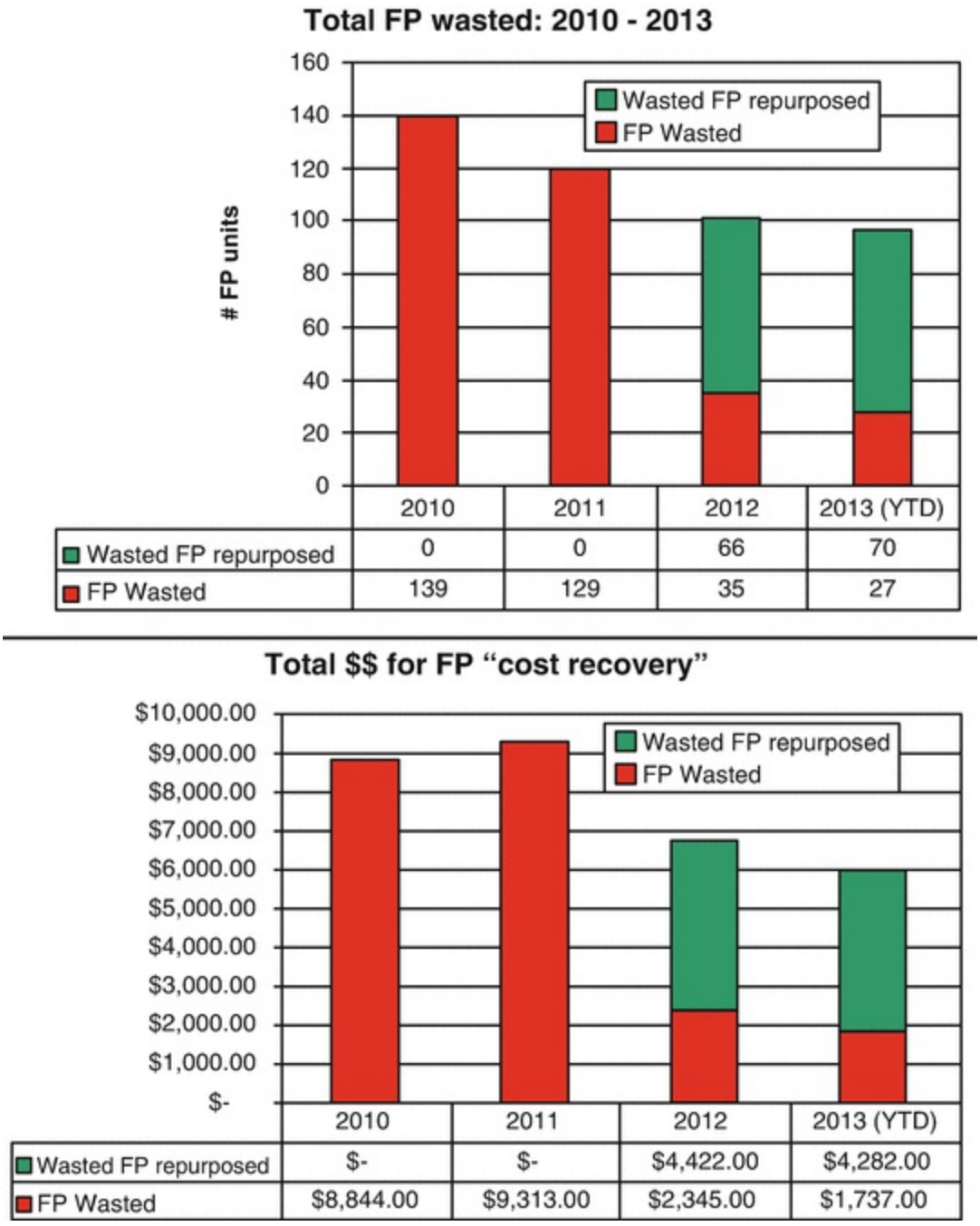


Fig. 22.5 Thawed frozen plasma (FP) wastage before (2010–2011) and after (2012–2013) obtaining the necessary approvals and implementing the necessary processes to use 5 days after thawing

Contract Negotiations

This is an essential function of the Transfusion Service Director, but is not an activity commonly shared with many outside of the laboratory. Often the organization's Transfusion Committee serves as the "Clinician" partner with

the Clinical Consultant (Transfusion Service Director) in assuring contract terms meet organizational needs.

Typically a single organization does not have sufficient leverage (i.e., blood component use) to negotiate best price. As part of a larger consortium, however, the combined blood component use can be substantial, providing significant leverage for effective negotiations. Our organization belongs to a regional network of hospitals with a considerable combined usage of blood components, giving us sufficient leverage for effective contract negotiations.

Three successive rounds of blood component price negotiations with our blood supplier occurred in 2012, 2013, and 2015, resulting in substantial price reductions (Fig. 22.6). The 2015 negotiations had a new surcharge for "universal donor" Type O Rh-negative packed RBCs and Type AB plasma, plus additional new fee charges for reference laboratory testing. The Transfusion Service Directors of the various hospitals had to assess the impact of these new fees on clinical practice.

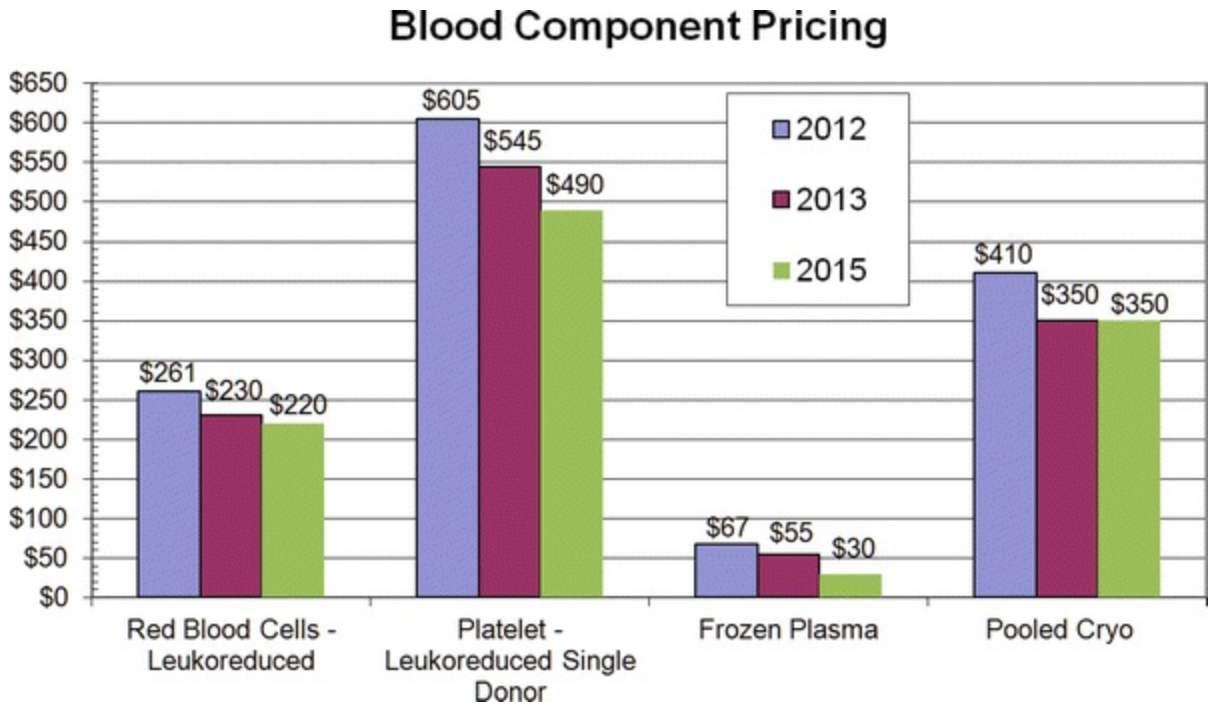


Fig. 22.6 Blood component pricing (price per unit) over time

We did not expect a negative impact of these new charges because of existing utilization controls for these "universal donor" blood components. Specifically and aside from patients with these specific blood types, Type O Rh-negative RBCs were restricted to emergency use only with a four unit

maximum limit, and AB plasma was used only for patients with blood type AB. Other hospitals were concerned about the new surcharges for the universal donor RBCs and FP because significant use of these components can be associated with massive transfusion protocols, especially when the patient's own blood type is unknown. We were fortunate in that our existing massive transfusion protocol required a pre-transfusion specimen, allowing us to determine the patient's own blood type. This is turn allowed us to release type specific components and avoid excessive use of universal donor RBCs or plasma.

Similarly we did not expect a significant increase in costs for reference lab testing. This is because our Blood Bank has substantive expertise such that reference lab testing is used infrequently. In contrast, smaller hospitals in our network with less experienced or fewer staff rely considerably on the reference laboratory for complex testing and had to consider the impact of increased costs.

In discussion with our Transfusion Committee, the group concluded the proposed contract should be favorable to our organization. Similar discussions occurred at the other organizations. The hospital network also ultimately concluded the terms of the proposed contract were acceptable.

The contract negotiations resulted in a savings in blood component costs of $140,923 in 2013 solely from lowered pricing. In 2014 an additional savings of $253,522 was achieved because of decreased blood component utilization. Combined this represented an annual savings of $400,000.

Coagulation

Clinical Consultation

The coagulation test menu consists of at least 60 different tests, and aside from the PT/INR and PTT, most are unfamiliar to the typical clinician. A Laboratory Medicine Clinical Coagulation Consultant has been demonstrated to add value to patient care [30]. Benefits included shortening the time to diagnosis, reduction of the number of laboratory tests required for diagnosis, avoiding misdiagnosis and reduction in length of stay. Given the increasing complexity of today's clinical coagulation laboratory, the Clinical Coagulation consultant is best positioned to optimize laboratory evaluation.

New Technology and Partnership

Occasionally new laboratory testing technology requires everyone to adjust. The Laboratory Clinical Consultant is essential in coordinating organizational adjustment as Clinicians must be educated on the correct use of the new technology. Success is directly related to the effective partnership between the Clinical Consultant and the Clinicians. Below are a few examples of successful partnership in effecting change in response to new technology.

Elimination of Inpatient D-Dimer Testing and the "DIC Panel"

The Clinical Consultant is frequently brokering compromises between different medical disciplines, with a particular test having different applications for different populations. D-dimer testing is such an example. D-dimer assays were in evolution in the early 2000s, with sensitive D-dimer assays becoming commercially available and replacing historically less sensitive assays. The sensitive D-dimer assay was clinically useful in excluding pulmonary embolism (PE) in a low risk population [31]. The co-existence of sensitive and less sensitive D-dimer assays and relative non-comparability between assays was and remains still confusing even today to both clinicians and laboratorians [32, 33].

In May 2005 our laboratory switched from a manually performed insensitive D-dimer assay to the newer automated sensitive D-dimer assay. This method change was necessary to adapt to a laboratory workforce shortage and inability to offer a manual D-dimer test 24 h daily.

At this time our Emergency Medicine practitioners had adopted a "PE exclusion" algorithm using a low D-dimer value from our sensitive D-dimer assay (i.e., <500 ng/mL fibrinogen equivalent units, or FEU) [31]. Our Internal Medicine hospitalist service had been using elevated D-dimer values with the insensitive assay to support a clinical diagnosis of disseminated intravascular coagulation (DIC).

As a related matter, the laboratory had been offering a "DIC panel" consisting of D-dimer, PT/PTT, platelet count, and fibrinogen. Review of ordering patterns identified 96 % of inpatient D-dimer orders were part of a "DIC panel," contrasted with only 9 % of D-dimer orders originating from the Emergency Department (ED) . Previous studies had demonstrated

elevated sensitive D-dimer values for 95 % of inpatients, calling into question the use of inpatient D-dimer testing [34–37]. Review of our internal D-dimer data verified this finding in our inpatient population. There had also been an increase in D-dimer requests for inpatients with an incorrect assumption and clinical justification that a low value (<500 ng/mL FEU) could be used to exclude PE. This practice highlighted a fundamental lack of understanding of the clinical scenario for when a sensitive D-dimer test added clinical value [34–37].

Common practice at this time was to obtain a D-dimer value only once daily. DIC panels were repeatedly ordered within a single day for convenience, however, since it was simpler to order the panel of five tests than ordering the five tests individually. The multiple orders within a 24 h period were needed to assess treatment efficacy for individual abnormal "DIC" laboratory values (i.e., correction of prolonged PT or PTT following frozen plasma administration, platelet count increase following platelet transfusion, and/or fibrinogen level increase following cryoprecipitate administration). It was universally agreed multiple D-dimer values within a 24 h period did not alter patient care.

The laboratory verified that multiple D-dimer tests were being ordered for inpatients within 24 h. The laboratory also identified unnecessary platelet counts whenever a DIC panel was ordered, since the patient usually had a Complete Blood Count (CBC) , including a platelet count, obtained at the same time. These "duplicate" orders created additional work to cancel and credit the order to avoid a duplicate charge.

This information was shared with the medical staff. The hospitalists readily acknowledged their practice of ordering a D-dimer test was to support a clinical diagnosis of DIC. They were aware D-dimer values were included in most DIC scoring systems as evidence of fibrinolysis [38], and fibrinolysis was not specific for DIC and occurred in a variety of settings. The non-standardization of D-dimer assays and the recommendation individual laboratories determine the clinical validity of the D-dimer assay in use for DIC diagnoses [39] was bewildering to all. The hospitalists concluded D-dimer results offered only minimal incremental clinical value and instead opted to eliminate D-dimer testing for inpatients. A clinical diagnosis of DIC could be supported by trending fibrinogen levels, PT/PTT values, and platelet counts.

The hospitalists also agreed to the elimination of the DIC panel to

minimize duplicate, inappropriate and unnecessary testing. The proposal was submitted and approved by the Medical Executive Committee November 2005. Electronic orders were configured to block D-dimer orders for inpatients. Implementation started January 2006. Inpatient D-dimer orders remained available but only by pathologist approval.

Communication was distributed to all medical staff. Physicians were notified the DIC panel was discontinued, encouraged to order only those individual tests needed for patient management and educated that 96 % of inpatients would have "positive" D-dimer values (>500 ng/mL FEU). D-dimer orders were restricted to the ED and outpatient clinics. Organizationwide test volumes declined immediately by 70 % (D-dimer), 60 % (PT/PTT), 50 % (fibrinogen), and 95 % (platelet count) and have been sustained (Fig. 22.7).

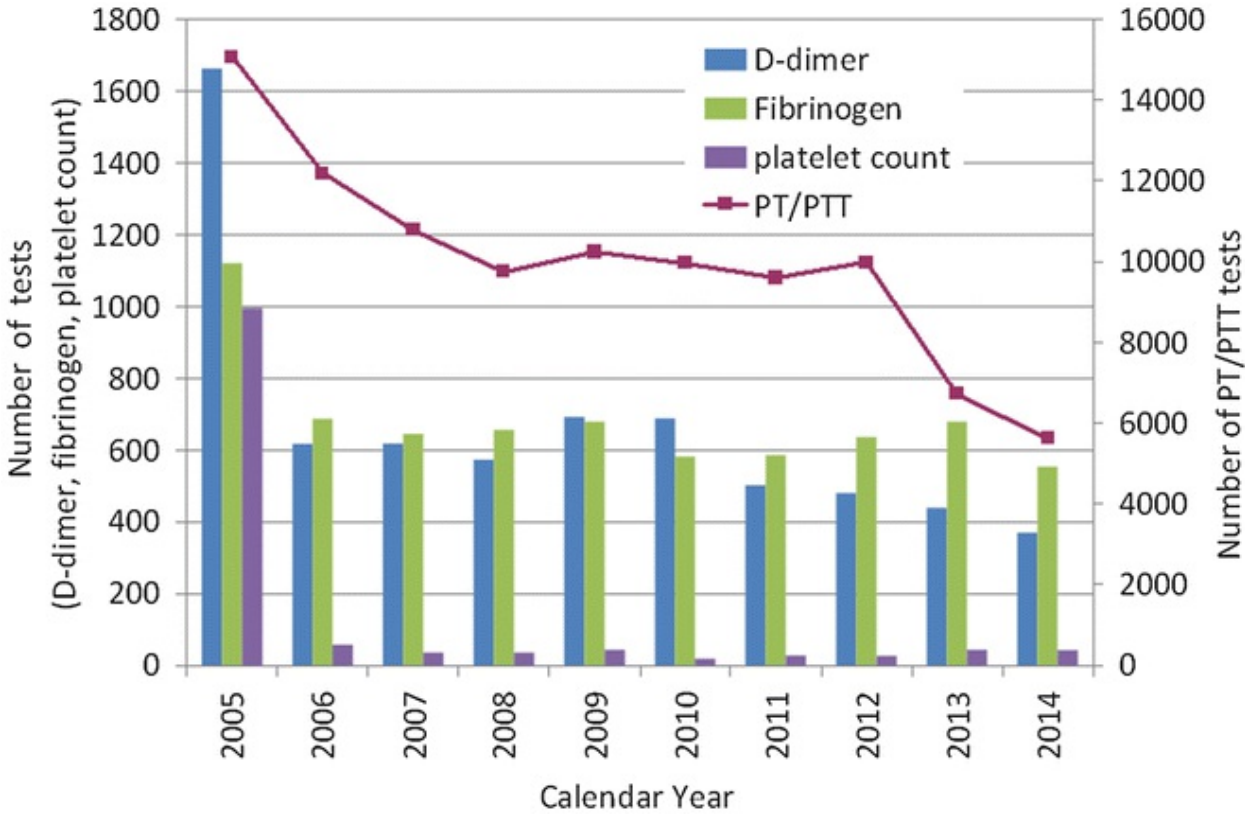


Fig. 22.7 Overall use of D-dimer, fibrinogen, platelet count, and PT/PTT tests before (2005) and after the "DIC" panel was eliminated (2006–on)

Four requests for inpatient D-dimer tests were received within the first few months after implementation of this new process. In each case the testing

was requested for an inpatient with the clinical justification of excluding PE. All four D-dimer values were above 2000 ng/mL FEU and did not advance the clinical diagnosis or management. Targeted feedback and education was given to the ordering physicians.

This experience also highlights the overutilization of tests when only one or a few are needed yet more are ordered because they are grouped together in and is quicker and easier to order as a “panel.”

Automated Urinalysis and Inaccurate Bacteriuria Reporting

In May 2008, confronted with severe labor workforce shortages, the Clinical Laboratory introduced fully automated urinalysis. The instrumentation involved automated dipstick urinalysis and reflex flow cytometry-based “microscopic” analysis when certain dipstick parameters were abnormal (e.g., blood or leukocyte esterase—trace or greater, nitrite—positive, pH greater than 8.0, protein 30 mg/dL or greater). The automated microscopy would quantify RBCs, WBCs, epithelial cells, hyaline casts, and bacteria. A manual microscopic examination of urine sediment was performed only if the automatic microscopy detected urinary formed elements suggestive of pathological casts, crystals, “small round cells,” yeast, and/or sperm. The labor savings of this automation were considerable—historically at least 40–50 % of urine specimens had one or more dipstick abnormalities requiring microscopic review of the urine sediment. The automated microscopy replaced at least 80 % of manual microscopy, freeing one full time equivalent (FTE) Clinical Laboratory Scientist on each shift to be reassigned to other duties.

Soon after its implementation questions arose regarding the disproportionate unreliability of squamous epithelial cell and urine bacteria quantification, especially in voided urine specimens collected from pre-menopausal females being evaluated for urinary tract infection (UTI) . These had serious downstream implications for incorrect clinical treatment. For example, a specimen containing more than a “few” squamous epithelial cells would be considered “contaminated” and any of the other results unreliable and ignored. As another example any degree of bacteriuria was interpreted as supportive evidence for UTI and antibiotics incorrectly prescribed; urine cultures were not always performed. Despite these mounting concerns, many

providers were asking the laboratory to implement “reflex urine culture” of the same specimen if abnormalities were detected by routine urinalysis.

Emergency Medicine colleagues at our institution conducted a study to determine whether automated microscopic urinalysis results differed by method of specimen collection. Healthy asymptomatic pre-menopausal female staff collected urine specimens by two different methods (i.e., no special collection method versus instructions to collect clean catch midstream urine). All specimens were subjected to urinalysis (dipstick and automated microscopy) and urine culture.

The study findings were surprising. Collection method did not matter. Except for nitrite, abnormal urinalyses were common for all measured parameters regardless of collection method [40]. Increased squamous cells detected by urinalysis and suggestive of “contamination” did not correlate with culture results expected for “contaminated” specimens (i.e., growth of normal urogenital flora). Urinalysis of specimens obtained from pre-menopausal females was concluded to have very limited clinical value in general [40]. These findings were reproduced in a population of adult women presenting to the Emergency Department with complaints suggestive of UTI [41].

How did these findings affect test utilization? This collaborative study demonstrated the lack of correlation between automated urinalysis and urine culture results, and highlighted the inability of urinalysis to predict UTI. Emergency Medicine colleagues became the laboratory’s strongest allies in fending off requests to the Clinical Laboratory to implement “reflex” urine cultures based on abnormal urinalysis results. As a related issue the Clinical Laboratory was requested to stop reporting “bacteria” from automated microscopy to avoid misinterpretation as supportive evidence for UTI, assignment of UTI diagnosis, and subsequent inappropriate treatment. This was an example of a clinical study yielding useful guidance for clinical laboratory testing and results reporting.

Myoglobin, CK-MB, and Troponin

The past decade has witnessed a shift in tests for myocardial infarction (myoglobin, CK-MB) to troponin testing. Troponin testing is more specific for myocardial ischemia and acute coronary syndromes (ACS) , with particular value for diagnosing or excluding non-ST-segment-elevation myocardial infarction (NSTEMI) . During our transition period from primary

use of myoglobin and CK-MB testing to troponin testing, myoglobin was retained because of the time advantage of elevation up to 3 h before troponin elevations would be detected. Theoretically this should have translated into practice as ordering a myoglobin for only the first testing event. Depending on the practice of using two or three sequential troponin values over time to exclude NSTEMI , only 50 or 33 % of troponin tests should be accompanied by a myoglobin test. Review of our internal testing practice demonstrated both tests were ordered together 80–85 % of the time, indicating excessive myoglobin testing.

The diagnostic time advantage of myoglobin disappeared with the introduction of high sensitivity (hs) troponin assays. We introduced a hs troponin I assay in 2010. Despite widespread lobbying of our clinical counterparts, the laboratory was unsuccessful in eliminating myoglobin testing. The major issue was the medical culture was entrenched in the historical practice of ordering both tests simultaneously (“myotrop”), reinforced by the Emergency Department’s electronic ordering system containing a single “myotrop” panel for ease of ordering both tests with a single click, and the laboratory’s inability to reach agreement with our Cardiology colleagues.

The Clinical Laboratory realized we were an outlier in continuing to provide myoglobin testing. This became very obvious when we encountered a shortage in myoglobin reagents. There was no one in the local area from which we could “borrow” reagents because no one else was offering this test.

A multidisciplinary “high value care committee” including representatives from Internal Medicine, Pediatrics, OB-GYN, and Emergency Medicine had just been initiated, and when asked what would be a high priority test utilization project, the laboratory volunteered elimination of myoglobin testing for ACS. Coincidentally the American College of Cardiology and the American Heart Association had just released guidelines definitively stating myoglobin testing was not necessary in the evaluation of ACS when a hs troponin assay was in use [42]. The group agreed to implement reduced myoglobin testing.

A seemingly small operational change was to remove the “myotrop ” panel order from the Emergency Department’s electronic ordering system. This would force physicians to order both tests individually if both were needed.

The “myotrop” panel was removed 02/19/15. The change was dramatic

and virtually overnight (Fig. 22.8). While troponin test volumes remained unchanged, myoglobin testing decreased by 90–95 %, and the percentage of troponin tests for which a myoglobin test was concurrently ordered dropped from 85 to 10 %. The decrease in test utilization has been sustained.

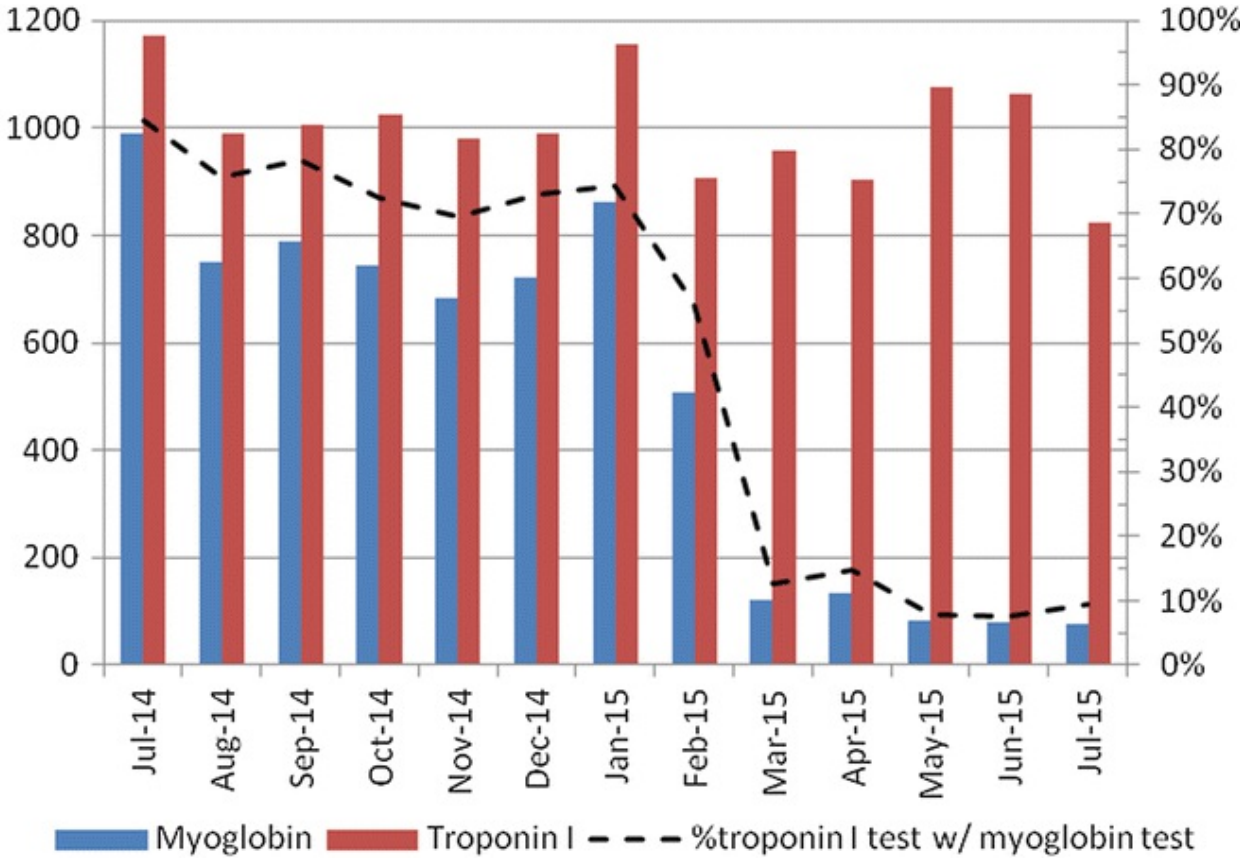


Fig. 22.8 Overall decline in myoglobin testing and percentage of all troponin I tests with a concurrent myoglobin test once the "myotrop" test panel was eliminated from the emergency department's electronic test menu effective 02/19/2015

Cost Savings

A frequent misconception is that decreased laboratory testing will result in significant cost savings. The typical budget of a clinical laboratory, however, is only 3–5 % of the overall organizational budget. A substantial savings in the laboratory budget is only achievable through drastic reduction in overall testing (e.g., 50 %) [43] expected to adversely impact patient care.

The responsibility of "appropriate laboratory testing" is often disproportionately placed on the Clinical Laboratory and typically imposed

by mandated budget reductions. Ironically those “in control” of testing are not held accountable. For teaching programs, post-graduate teaching programs “accept” an increased rate of “less discriminate” laboratory testing as a “rite of passage along the road to expertise,” even though clinical and economical “downsides” are well recognized [16]. Relatively little attention has been focused on teaching appropriate laboratory utilization in post-graduating teaching programs because it is perceived as a “low profile, low risk feature of clinical behavior” with the ultimate benefit of attaining expertise in clinical decision-making [7, 14, 16].

The majority of publications regarding “appropriate test utilization” have focused on cost savings within the laboratory due to decreasing test overutilization. What cannot be easily quantified, however, are the unnecessary extra downstream costs of prescriptions, imaging studies, procedures, surgeries, hospital lengths of stay due to test overutilization. Similarly the costs of missed diagnoses, treatments, or loss of quality of life are not easily quantifiable when tests are underutilized.

Conclusions

An effective partnership between the Clinical Laboratory and the clinicians optimizes the benefit and appropriateness of laboratory testing. Evidence-based ideas and patient-centered algorithms for “right-sizing” laboratory testing can originate from the laboratory, clinician, or jointly. The Laboratory Clinical Consultant has an essential role in this process.

References

1. King LS. XII. Clinical laboratories become important, 1870–1900. JAMA. 1983;249(22):3025–9. [CrossRef][PubMed]

2. Laboratory medicine: a national status report [Internet]. 2008. http://wwwn.cdc.gov/futurelabmedicine/pdfs/2007%20status%20report%20laboratory_medicine_-_a_national_status_report_from_the_lewin_group_updated_2008-9.pdf.

3. Kim JY, Dzik WH, Dighe AS, Lewandrowski KB. Utilization management in a large urban academic medical center: a 10-year experience. Am J Clin Pathol. 2011;135(1):108–18. [CrossRef][PubMed]

4. Hauser RG, Shirts BH. Do we now know what inappropriate laboratory utilization is? An expanded systematic review of laboratory clinical audits. Am J Clin Pathol. 2014;141(6):774–83.

[CrossRef][PubMed]

5. Plebani M, Laposata M, Lundberg GD. The brain-to-brain loop concept for laboratory testing 40 years after its introduction. Am J Clin Pathol. 2011;136(6):829–33.
[CrossRef][PubMed]

6. Wilson ML. Decreasing inappropriate laboratory test utilization: controlling costs and improving quality of care. Am J Clin Pathol. 2015;143(5):614–6.
[CrossRef][PubMed]

7. Zhi M, Ding EL, Theisen-Toupal J, Whelan J, Arnaout R. The landscape of inappropriate laboratory testing: a 15-year meta-analysis. PLoS One. 2013;8(11), e78962.
[CrossRef][PubMed][PubMedCentral]

8. McGlynn EA, Asch SM, Adams J, Keesey J, Hicks J, DeCristofaro A, et al. The quality of health care delivered to adults in the United States. N Engl J Med. 2003;348(26):2635–45.
[CrossRef][PubMed]

9. Aledort LM. Off-label use of recombinant activated factor VII—safe or not safe? N Engl J Med. 2010;363(19):1853–4.
[CrossRef][PubMed]

10. Gottfried EL, Kamoun M, Burke MD. Laboratory medicine education in United States medical schools. Am J Clin Pathol. 1993;100(6):594–8.
[CrossRef][PubMed]

11. Smith BR, Kamoun M, Hickner J. Laboratory medicine education at U.S. medical schools: a 2014 status report. Acad Med. 2015;91:107–12.
[CrossRef]

12. Jones A, McArdle PJ, O'Neill PA. Perceptions of how well graduates are prepared for the role of pre-registration house officer: a comparison of outcomes from a traditional and an integrated PBL curriculum. Med Educ. 2002;36(1):16–25.
[CrossRef][PubMed]

13. Eisenberg JM, Williams SV. Cost containment and changing physicians' practice behavior. Can the fox learn to guard the chicken coop? JAMA. 1981;246(19):2195–201.
[CrossRef][PubMed]

14. Iwashyna TJ, Fuld A, Asch DA, Bellini LM. The impact of residents, interns, and attendings on inpatient laboratory ordering patterns: a report from one university's hospitalist service. Acad Med. 2011;86(1):139–45.
[CrossRef][PubMed]

15. Vidyarthi AR, Hamill T, Green AL, Rosenbluth G, Baron RB. Changing resident test ordering behavior: a multilevel intervention to decrease laboratory utilization at an academic medical center. Am J Med Qual. 2015;30(1):81–7.
[CrossRef][PubMed]

16. Croskerry P. Commentary: lowly interns, more is merrier, and the Casablanca Strategy. Acad Med. 2011;86(1):8–10.
[CrossRef][PubMed]

17. Gartner I. Gartner hype cycle. http://www.gartner.com/technology/research/methodologies/hype-cycle.jsp. Accessed 17 Aug 2015.

18. Lundberg GD. Changing physician behavior in ordering diagnostic tests. JAMA. 1998;280(23):2036.
[CrossRef][PubMed]

19. Prasad V, Cifu A. Medical reversal: why we must raise the bar before adopting new technologies. Yale J Biol Med. 2011;84(4):471–8.
[PubMed][PubMedCentral]

20. Baird G. The laboratory test utilization management toolbox. Biochem Med (Zagreb). 2014;24(2):223–34.
[CrossRef]

21. Wong ET, McCarron MM, Shaw Jr ST. Ordering of laboratory tests in a teaching hospital. Can it be improved? JAMA. 1983;249(22):3076–80.
[CrossRef][PubMed]

22. Emerson JF, Emerson SS. The impact of requisition design on laboratory utilization. Am J Clin Pathol. 2001;116(6):879–84.
[CrossRef][PubMed]

23. Procop GW, Keating C, Stagno P, Kottke-Marchant K, Partin M, Tuttle R, et al. Reducing duplicate testing: a comparison of two clinical decision support tools. Am J Clin Pathol. 2015;143(5):623–6.
[CrossRef][PubMed]

24. Refaai MA, Blumberg N. The transfusion dilemma—weighing the known and newly proposed risks of blood transfusions against the uncertain benefits. Best Pract Res Clin Anaesthesiol. 2013;27(1):17–35.
[CrossRef][PubMed]

25. Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev. 2012;4, CD002042.
[PubMedCentral]

26. Roback JD, Caldwell S, Carson J, Davenport R, Drew MJ, Eder A, et al. Evidence-based practice guidelines for plasma transfusion. Transfusion. 2010;50(6):1227–39.
[CrossRef][PubMed]

27. Slichter SJ. Evidence-based platelet transfusion guidelines. Hematology Am Soc Hematol Educ Program. 2007;172–8.

28. Levi M, Levy JH, Andersen HF, Truloff D. Safety of recombinant activated factor VII in randomized clinical trials. N Engl J Med. 2010;363(19):1791–800.
[CrossRef][PubMed]

29. Yazer MH, Cortese-Hassett A, Triulzi DJ. Coagulation factor levels in plasma frozen within 24 hours of phlebotomy over 5 days of storage at 1 to 6 degrees C. Transfusion. 2008;48(12):2525–30.
[CrossRef][PubMed]

30. Laposata ME, Laposata M, Van Cott EM, Buchner DS, Kashalo MS, Dighe AS. Physician survey of a laboratory medicine interpretive service and evaluation of the influence of interpretations on laboratory test ordering. Arch Pathol Lab Med. 2004;128(12):1424–7.
[PubMed]

31. Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med. 2003;349(13):1227–35.
[CrossRef][PubMed]

32. Michiels JJ, Gadisseur A, van der Planken M, Schroyens W, De Maeseneer M, Hermsen JT, et al. Different accuracies of rapid enzyme-linked immunosorbent, turbidimetric, and agglutination D-dimer assays for thrombosis exclusion: impact on diagnostic work-ups of outpatients with suspected deep vein thrombosis and pulmonary embolism. Semin Thromb Hemost. 2006;32(7):678–93.
[CrossRef][PubMed]

33. Olson JD, Cunningham MT, Higgins RA, Eby CS, Brandt JT. D-dimer: simple test, tough problems. Arch Pathol Lab Med. 2013;137(8):1030–8.
[CrossRef][PubMed]

34. Brotman DJ, Segal JB, Jani JT, Petty BG, Kickler TS. Limitations of D-dimer testing in unselected inpatients with suspected venous thromboembolism. Am J Med. 2003;114(4):276–82.
[CrossRef][PubMed]

35. Perrier A. D-dimer for suspected pulmonary embolism: whom should we test? Chest. 2004;125(3):807–9.
[CrossRef][PubMed]

36. Rathbun SW, Whitsett TL, Vesely SK, Raskob GE. Clinical utility of D-dimer in patients with suspected pulmonary embolism and nondiagnostic lung scans or negative CT findings. Chest. 2004;125(3):851–5.
[CrossRef][PubMed][PubMedCentral]

37. Schrecengost JE, LeGallo RD, Boyd JC, Moons KG, Gonias SL, Rose Jr CE, et al. Comparison of diagnostic accuracies in outpatients and hospitalized patients of D-dimer testing for the evaluation of suspected pulmonary embolism. Clin Chem. 2003;49(9):1483–90.
[CrossRef][PubMed]

38. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. Br J Haematol. 2009;145(1):24–33.
[CrossRef][PubMed]

39. Lehman CM, Wilson LW, Rodgers GM. Analytic validation and clinical evaluation of the STA LIATEST immunoturbidimetric D-dimer assay for the diagnosis of disseminated intravascular coagulation. Am J Clin Pathol. 2004;122(2):178–84.
[CrossRef][PubMed]

40. Frazee BW, Enriquez K, Ng V, Alter H. Abnormal urinalysis results are common, regardless of specimen collection technique, in women without urinary tract infections. J Emerg Med. 2015;48(6):706–11.

[CrossRef][PubMed]

41. Tomas ME, Getman D,Donskey CJ, Hecker MT.Over-diagnosis of Urinary Tract Infection of Sexually Transmitted Infection in Adult Women Presenting to an Emergency Department.J Clin Microbiol 2015;53:2686–92.

42. Amsterdam EA, Wenger NK, Brindis RG, Casey Jr DE, Ganiats TG, Holmes Jr DR, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;64(24):e139–228.
[CrossRef][PubMed]

43. Winkelman JW. Less utilization of the clinical laboratory produces disproportionately small true cost reductions. Hum Pathol. 1984;15(6):499–501.
[CrossRef][PubMed]

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_23

23. The Role of the Genetic Counselor in Utilization Management of Genetic Testing

Kelly Branda[1]

(1) Informed DNA, St. Petersburg, FL, USA

Kelly Branda
Email: jbranda@partners.org

Keywords Utilization management – Genetic counselor – Genetic test – Molecular pathology

There has been unprecedented growth in genetic testing within the last decade, due in part to increased public awareness of testing, optimism about the potential benefits of testing and the possibility of using results of testing to improve health [1, 2]. There has also been a dramatic decrease in the costs of genetic analyses [3].

At the same time that public interest in genetic testing has increased, the technology available for genetic analyses has also changed dramatically with the relatively recent clinical introduction of next-generation sequencing methods such as multi-gene panels, whole-exome sequencing and whole-genome sequencing. This has led to a dramatic increase in the number of genetic tests available: several hundred were listed in 2003 [4] and over 50,000 were reported more than a decade later in 2016 [5]; current estimates are that a new genetic test is introduced almost daily [5]. A 2008 study by the

Department of Health and Human Services Secretary's Advisory Committee on Genetics, Health, and Society projected that over 60 % of the population within the USA may eventually benefit from the results of genetic analysis [6]. Although genetic tests may be helpful in improving patient care, they are also among the most expensive tests ordered in medicine: a study of United Healthcare members found that spending on genetic testing increased at a rate of 14 % per year between 2008 and 2010 [7]. Spending on genetic testing was estimated at about $5 billion in 2010 within the USA and projected to increase to $15 billion to $25 billion by the year 2021 [7].

To cope with this demand, physicians, particularly primary care physicians and family practitioners, are increasingly called upon to review family histories, to discuss genetic information with patients and to order genetic tests. A survey of 190 family physicians performed in 2001 revealed that all had discussed at least one genetic condition with a patient within the last year and the majority had discussed the genetics of common diseases (such as cancer or cardiovascular disease) with two or more patients during the same time frame [8]. Approximately 60 % of primary care physicians within the USA reported that they had ordered at least one genetic test during their time in practice [9], and primary care and other physicians with specialties outside the area of genetics such as neurology and cardiology are ordering an ever increasing percentage of genetic tests.

However, there is growing evidence to indicate that physicians may not feel entirely comfortable with this role. For example, more than half of primary care physicians surveyed within the USA and Canada felt that they lacked sufficient knowledge of genetic testing [10]. In a similar study of 220 internists, the majority rated their knowledge of genetics (73.7 %) or genetic testing (87.1 %) as very or somewhat poor [11]. Interestingly, this number has not changed much over time, as a study performed more than a decade earlier found that 71 % of physicians similarly rated their knowledge of genetics and genetic testing as fair to poor [12].

This perceived lack of knowledge may be due to the minimal amount of formal training that most physicians receive during medical school [13, 14]. A curriculum study of medical schools in the USA and Canada found that slightly less than half (46 %) of medical students were taught genetics as a stand-alone course; instead, genetics concepts were typically integrated into other courses [15]. Furthermore, in most programs, medical genetics instruction was limited to an average of 20–40 h, although in nearly one-fifth

of programs, the courses encompassed less than 20 h. In addition, the vast majority of this time focused on general concepts within genetics as compared to the application of these concepts in medical practice [15].

In addition to limited training, genetic testing can be complex, especially with the time constraints imposed upon many physicians today [16, 17]. The technology continues to evolve rapidly, making it difficult for professionals outside the field to stay current. In addition, there are various technical, ethical, and emotional concerns that are unique to genetic tests with which professionals outside of genetics may not be familiar [18].

These complexities have caused many genetic tests to be ordered inappropriately. An analysis by ARUP Laboratories [19] looked at modifications made to orders for complex genetic tests within their laboratory over a 21-month period and found that approximately one-quarter of all molecular tests were ordered incorrectly. The most common reason for a test order to be modified was because the original genetic test ordered was inappropriate. For example, in 20 % of cases, the wrong test was ordered: in these cases, the test was cancelled and a more appropriate test was added instead. In a smaller percentage of cases (13 %), the wrong test was ordered but no additional testing was recommended. In other cases, a genetic sequencing test was ordered when a more targeted panel was more appropriate (10 %) or when a more targeted test for a known familial mutation was recommended instead (8 %). Other reasons cited for misorders included a test that was performed previously or a duplicate order (3 %), the sample that was sent was compromised or insufficient (0.1 %) or a test was cancelled because the results of previous testing indicated that it was no longer necessary (0.5 %).

Even when a genetic test is ordered appropriately, there may be an incorrect interpretation of genetic test results. For example, in a study by Giardiello et al. [20], 83 % of patients at risk for familial adenomatous polyposis (FAP) underwent genetic testing of the *APC* gene based upon appropriate indications. However, in nearly one third of these cases (31.6 %), the result was interpreted incorrectly by the ordering provider and would have led to misinformation being passed on to a patient, particularly related to the misinterpretation of negative results in the absence of a known familial mutation. This type of mistaken interpretation can dramatically alter the follow-up screening that is recommended and can have devastating effects on the health of individual patients.

Lastly, the results from many genetic tests have long turnaround times, typically weeks to months. This may increase the likelihood that test results are not returned to the patient promptly, which could also lead to delayed or missed diagnoses and suboptimal medical care. In addition to decreasing the quality of patient care , the inappropriate ordering and misinterpretation of genetic test results also adds to unnecessary costs within the health care system overall.

In response to the increase in the number of tests offered by clinical genetics laboratories within the last two decades as well as to improve the appropriate utilization of genetic testing, many laboratories have hired genetic counselors to provide various services related to the utilization of genetic tests [21, 22], resulting in a corresponding increase in the number of genetic counselors who identify themselves as laboratory-based genetic counselors . This includes genetic counselors who work directly for clinical genetic testing laboratories as well as a smaller (albeit growing) group who work for internal hospital laboratories.

Genetic counseling is a relatively new field involving the study of genetics as well as counseling skills, the interpretation of personal and family history, and risk assessment. It first developed approximately 50 years ago, partially in response to a mandate for newborn screening for inherited disorders, which created the need for a specialist who could interpret these results for patients and families. During the 1970s, the emphasis of genetic counseling changed from public health education more toward the communication of genetic risk and non-directive counseling on an individual basis [23]. As the genetic basis of more disorders was identified, another shift was seen, in which genetic counseling focused more on aiding pre-symptomatic genetic testing and now toward genetic predisposition for common complex diseases, such as heart disease and diabetes.

Genetic counselors are trained through masters' degree training programs. As the demand for trained genetic counselors has increased, so too have the number of training programs, which have now expanded to include 32 programs at colleges and universities throughout the USA as well as multiple programs internationally. The National Society of Genetic Counselors (NSGC) was formed in 1979 in order to "promote the professional interests of genetic counselors," as well as provide opportunities for collaboration, continuing education and networking (NSGC website).

In 1983, the NSGC developed a formal definition of a genetic counselor

as a professional who works as part of a health care team to provide "information and support to families who have members with birth defects or genetic disorders and to families who may be at risk for a variety of inherited conditions. They identify families at risk, investigate the problem present in the family, interpret information about the disorder, analyze inheritance patterns and risks of recurrence and review available options with the family" [24]. Genetic counselors are certified through The American Board of Genetic Counseling , which conducts a qualifying examination to evaluate competency and re-certifies genetic counselors every 5 years.

Many genetic counselors work primarily in clinical roles in which they provide care to individual patients and families with genetic disorders. This includes work in prenatal, pediatric, and adult clinics, as well as specialty clinics, such as oncology, neurology, and cardiology. Clinical genetic counselors typically record and interpret an individual's medical and family history to try and determine the inheritance pattern and/or recurrence risk, provide education about inheritance, testing and management, review options available to the patient and family, help to coordinate genetic testing if applicable, help to interpret results of genetic testing, aid in follow-up care for the patient and family, and provide ongoing supportive counseling and resources (NSGC website).

Although the majority of genetic counselors still work in clinical positions, since the onset of the profession, there have also been counselors in "non-traditional" roles. These included genetic counselors working within laboratories, both commercial and academic, as well as genetic counselors working in the fields of public health, education, administration, and research [18].

The number of genetic counselors working in "non-traditional" roles continues to increase, in part due to the increased demand for and availability of genetic testing. The NSGC conducts a professional status survey (PSS) every 2 years in which they survey members about various aspects of their work, including their work setting, job responsibilities, and salary. In results from the PSS in 2000, 5 % of respondents listed a diagnostic laboratory as their primary job setting, which was the first year in which this data was recorded [25]; by 2014, this number had risen to16.8 % [26]. More specifically, 49 % of non-clinical genetic counselors indicated that they worked primarily in a diagnostic commercial laboratory and 26 % of non-clinical counselors worked within a university medical center or public or

private hospital or medical facility [26]. Other work settings include cytogenetic laboratories, maternal serum screening laboratories, biochemical laboratories, and public laboratories [18, 26].

Genetic counselors working within molecular testing laboratories have various roles [18, 19, 27, 28]. As pointed out in Zetzsche et al. [29], "laboratories differ in business models, marketing styles, and internal resources … and these factors can influence the types of opportunities available to genetic counselors and what needs they may be asked to fill." Most often, the responsibilities of genetic counselors working within a laboratory setting include serving as a liaison for providers and (less frequently) for patients. They may field questions regarding the technical aspects of testing and methodology , review various testing options that are available, discuss the risks, benefits, and limitations of testing, and/or help with the logistics of testing. They may also provide more patient-specific information, such as reviewing the appropriateness of testing for a specific patient, recommending a testing strategy based upon a patient's individual medical and family histories or interpreting an individual patient's test results within the context of the personal and family history.

Laboratory-based genetic counselors also regularly assist in the interpretation of the results of testing within the laboratory. This role is expected to grow further as additional results are generated from next-generation sequencing [28]. Particularly with the advent of testing that involves large panels of multiple genes or the whole exome or whole genome, the volume of incidental findings and uncertain or variant results for individual patients is also expected to rise dramatically [30, 31]. With additional data, many of these variants will ultimately be reclassified as normal polymorphisms or, less frequently, as deleterious mutations. In the interim, however, genetic counselors will need to be involved in trying to provide as much information as is available about the variant—such as the predicted impact on the function of the protein and the degree of conservation of the impacted amino acids throughout evolution—to help guide the medical management of the patient until the variant can be more definitively reclassified.

Other responsibilities of laboratory-based genetic counselors includes calling out and discussing test results with health care providers, and providing recommendations for appropriate follow-up testing and patient resources as needed. Another common responsibility for genetic counselors

working within a laboratory setting involves screening test requests to determine the appropriateness of testing. Other laboratory-based counselors may have administrative duties, be involved in teaching and/or supervision of students, coordinate research or clinical studies, develop and maintain genetic databases, management responsibilities and even involvement in graphic design, website and database development, the development of education or marketing materials for patients and providers, and sales and marketing [18, 19, 28].

Laboratory genetic counselors, whether working within a clinical testing laboratory or an internal hospital laboratory, may serve as a "gatekeeper" to review the genetic test(s) ordered and determine whether it most appropriately provides relevant clinical information that can be used to benefit the patient and/or family members. This helps to improve patient care and to reduce medical costs.

It should be noted that although the majority of laboratory-based genetic counselors do not have direct contact with patients, some are contracted by clinical practices to provide counseling directly to their patients [28, 32]. Such relationships typically developed because it is not cost effective for most clinical practices to employ their own individual genetic counselor, but they recognize the need for their patients to have access to genetic counseling services. However, concerns have been raised about a potential conflict of interest for these counselors, in which they encourage their patients to undergo genetic tests offered by their employer over other available options. Indeed, one major national health insurance company (Cigna) drafted a policy requiring patients to undergo genetic counseling by a non-laboratory employed genetic counselor before genetic testing for various conditions [33]. Although the author is not aware of any reports of a genetic counselor employed by a laboratory acting unethically in this way, others have suggested that genetic counselors who are employed by a laboratory and who also counsel patients directly should be paid on salary rather than on commission to minimize this potential [28].

It can be difficult to quantify improvements in patient care or the avoidance of negative outcomes. However, inappropriate genetic testing or misinterpretation of results can negatively influence screening and treatment, including regarding irreversible medical decisions such as prophylactic surgery or pregnancy termination. Ordering a genetic test with a high probability of generating a false positive result can lead to a cascade of

further medical tests and screening, creating further medical costs and undue anxiety for the family [34]. Ordering an inappropriate genetic test and getting a negative result can be falsely reassuring and prevent appropriate continuation of medical care and screening, which can further lead to negative patient outcomes [34].

Although quantifying improvements in patient care can be difficult, there are several examples within the literature which illustrate the effect that genetic counselors may have on patient care. One example cited in Kotzer et al. [22] reveals that a genetic counselor working within an internal hospital laboratory received a request for a patient sample to be sent out for sequencing of the *MLH1* mismatch repair gene involved in Lynch syndrome . She reviewed the patient's medical record and found that a familial mutation had previously been identified within the *MSH2* gene. Without this intervention, the patient would likely have received falsely reassuring results from the *MLH1* genetic analysis, which would have resulted in medical decisions to forego additional screening for the cancers associated with Lynch syndrome and could have had significant impact of the patient's health. In addition to dramatically altering the patient's medical care, the decision by the genetic counselor saved thousands of health care dollars by performing site-specific analysis rather than the more costly full sequencing testing.

Another example of improvements to patient care involves a review of a test order for evaluation of the *CFTR* gene involved in cystic fibrosis [22]. A genetic counselor working within an internal hospital laboratory was reviewing send-out tests and realized that samples from the same patient were being sent to two different reference labs: one for single gene testing of the *CFTR* gene and another for a multi-gene panel that included the *CFTR* gene. She was able to cancel the multi-gene panel, focusing only on the *CFTR* gene. This not only saved the cost of running duplicate tests, but prevented testing of genes that are less likely to be implicated in the disease and may have prevented variant results.

Genetic counselors, particularly those within a clinical testing laboratory, are also well suited to save money by reviewing samples as they are received by the laboratory and screening them to ensure that prior genetic testing has not been performed. For example, if a patient begins seeing a new physician or if a patient is followed by multiple specialists, it is possible that a genetic test that was ordered previously could be recommended and sent again. If the

sample was sent to the original testing laboratory, a genetic counselor within the laboratory would recognize that a duplicate order had been generated and could help to facilitate the process of sharing previous results with the new physician or other members of the health care team.

Genetic counselors employed within a clinical testing laboratory may also recognize when multiple genetic tests are ordered that may yield duplicate results [22]. For example, a physician caring for a child with a congenital heart defect may want to test for DiGeorge syndrome by sending a sample for analysis of the 22q11.2 chromosomal region with fluorescence in situ hybridization (FISH). The physician may also order a congenital microarray to look at other disorders which may be associated with congenital heart defects. This type of microarray would also detect DiGeorge syndrome, rendering the FISH analysis unnecessary. If samples for both tests were sent to the same laboratory, a genetic counselor reviewing the case would likely recognize the duplication and could contact the ordering physician to cancel the additional analysis [35].

Lastly, genetic counselors working with a testing laboratory may help to identify orders that are incorrectly sent as a result of similarity or overlap in the names of genetic conditions [22]. For example, acute intermittent porphyria (AIP) and congenital erythropoietic porphyria (CEP) are frequently confused in testing despite very different clinical presentations and genetic causes. By reviewing samples when they are received, genetic counselors can also review and (if needed) confirm the clinical information that is sent with the sample to ensure that the appropriate analysis was ordered.

Several recent publications have documented the financial impact of genetic counselors within a laboratory setting. For example, seven laboratory-based genetic counselors at ARUP Laboratories reviewed genetic test requests sent to the laboratory for most sequencing or large duplication/deletion analysis before testing was performed over a 21-month period [19]. Based upon the clinical information that was provided with the test sample, genetic counselors considered the clinical utility and cost-effectiveness of the tests that were requested. They then contacted the ordering physician or institution to obtain additional clinical information, to confirm testing, or to suggest alternative testing options based upon the available clinical information and/or family history. Using this strategy, genetic counselors cancelled or changed an average of almost 100 complex genetic test orders per month, representing approximately 26 % of all tests

ordered. This translated to approximately $48,000 in savings per month or over one half million dollars per year.

Similarly, a genetic counselor, two clinical pathologists or a clinical chemist at Seattle Children's Hospital reviewed a subset of approximately 250 genetic tests that were being sent to external reference laboratories over an 8-month period, accounting for approximately 250 cases [34]. These included tests costing over $1000, multiple genetic tests on the same requisition, tests sent to non-preferred or international laboratories, or tests that are normally performed in house. Nearly a quarter were modified in some manner, with 13 % being cancelled and 11 % being altered to sequential testing instead. This was estimated to represent an annual savings of $178,428.

Lastly, a group at The Cleveland Clinic sought to improve the utilization of molecular genetic testing through several initiatives, including the use of a laboratory-based genetic counselor to review daily orders for genetic and genomic testing [36]. After comparing the test ordered with the indication and clinical findings as well as reviewing the medical record and consulting with the ordering physician as needed, tests were approved, modified or cancelled. These efforts resulted in the modification of over 250 genetic test orders as well as a gross cost savings of over $1.5 million in a 28-month period.

Laboratory genetic counselors are also uniquely suited to serve as a resource for professionals in other areas [22]. For example, they may be able to provide updates about newly available tests, such as information about the technical details as well as issues surrounding interpretation of test results. They are also able to share updates about practice-based guidelines for genetic testing.

The American Board of Genetic Counselors (ABGC) has defined the "establishment and maintenance of inter- and intradisciplinary professional relationships as part of a healthcare delivery team" as one of the six core competencies of genetic counselors [37]. Genetic counselors are encouraged to foster relationships with health care professionals in a variety of other fields and to serve as a resource to improve utilization of genetic testing. As an example of this, a laboratory genetic counselor and the chief of neurology at Seattle Children's Hospital worked together to develop a guideline for evaluation and genetic testing for children who are suspected of having Charcot-Marie-Tooth hereditary neuropathy [22].

Lastly, laboratory-based genetic counselors have also worked to develop educational seminars for other genetics professionals as well as for those outside of the specialty [28]. For example, genetic counselors working at Verinata Health developed an educational course for prenatal genetic counselors to learn more about non-invasive prenatal testing (NIPT) . It included an analysis of clinical validation studies related to NIPT, as well as the clinical implementation and ethical challenges associated with NIPT. Another such example comes from genetic counselors with Illumina, who helped to develop the "Understand Your Genome" symposium focusing on the clinical application of whole-genome sequencing.

As stated in Kotzer et al. [22], "laboratory genetic counselors are well-suited to provide utilization management of genetic testing, both within the hospital laboratory and the genetic testing laboratory." Although the number of genetic tests available continues to grow dramatically, so too does the complexity of this testing. Given the escalating costs of medical care, the utilization management of genetic testing by laboratory-based genetic counselors may provide a much-needed service to help contain some of these costs and improve patient care.

References

1. Facio FM, Brooks S, Loewenstein J, Green S, Biesecker LG, Biesecker BB. Motivators for participation in a whole-genome sequencing study: implications for translational genomics research. Eur J Hum Genet. 2011;19(12):1213–7.
[CrossRef][PubMed][PubMedCentral]

2. Henneman L, Vermeulen E, van El CG, Claassen L, Timmermans DR, Cornel MC. Public attitudes towards genetic testing revisited: comparing opinions between 2002 and 2012. Eur J Hum Genet. 2013;21(8):793–9.
[CrossRef][PubMed]

3. Wetterstrand KA. DNA sequencing costs: data from the NHGRI genome sequencing program (GSP). 2013. www.genome.gov/sequencingcosts. Accessed 24 Nov 2015.

4. Nagy R, Sturm AC. Personalized medicine: impact on patient care in Genetic Counseling. Curr Genet Med Rep. 2013;1(2):129–34.
[CrossRef]

5. GeneTests medical genetics information resource (database online). Copyright: Seattle: University of Washington; 1993–2013. http://www.genetests.org. Accessed 14 Feb 2016.

6. Department of Health and Human Services Secretary's Advisory Committee on Genetics, Health,

and Society. U.S. system of oversight of genetic testing: a response to the charge of the Secretary of Health and Human Services. 2008. http://osp.od.nih.gov/sites/default/files/SACGHS_oversight_report.pdf. Accessed 14 Feb 2016.

7. UnitedHealth Center for Health Reform & Modernization. Personalized medicine: trends and prospects for the new science of genetic testing and molecular diagnostics. Minnetonka, MN: United Health Group; 2012. http://www.unitedhealthgroup.com/~/media/uhg/pdf/2012/unh-working-paper-7.ashx. Accessed 20 Nov 2015.

8. Acheson LS, Stange KC, Zyzanksi S. Clinical genetics issues encountered by family physicians. Genet Med. 2005;7(7):501–8.
[CrossRef][PubMed]

9. Shields AE, Burke W, Levy DE. Differential use of available genetic tests among primary care physicians in the United States: results of a national survey. Genet Med. 2008;10(6):404–14.
[CrossRef][PubMed][PubMedCentral]

10. Mainous III AG, Johnson SP, Chirina S, Baker R. Academic family physicians' perception of genetic testing and integration into practice: a CERA study. Fam Med. 2013;45(4):257–62.
[PubMed]

11. Klitzman R, Chung W, Marder K, Shanmugham A, Chin LJ, Stark M, Leu CS, Appelbaum PS. Attitudes and practices among internists concerning genetic testing. J Genet Couns. 2013;22(1):90–100.
[CrossRef][PubMed]

12. Menasha JD, Schecter C, Willner J. Genetic testing: a physician's perspective. Mt Sinai J Med. 2000;67(2):144–51.
[PubMed]

13. Burke W, Emery J. Genetics education for primary-care providers. Nat Rev Genet. 2002;3(7):561–6.
[CrossRef][PubMed]

14. Greendale K, Pyeritz RE. Empowering primary care health professionals in medical genetics: how soon? How fast? How far? Am J Med Genet. 2001;106(3):223–32.
[CrossRef][PubMed]

15. Thurston VC, Wales PS, Bell MA, Torbeck L, Brokaw JJ. The current status of medical genetics instruction in U.S. and Canadian medical schools. Acad Med. 2007;82(5):441–5.
[CrossRef][PubMed]

16. Blumenthal D, Causino N, Chang YC, Culpepper L, Marder W, Saglan D, Stafford R, Starfield B. The duration of ambulatory visits to physicians. J Fam Pract. 1999;48(4):264–71.
[PubMed]

17. Rich EC, Burke W, Heaton CJ, Haga S, Pinsky L, Short MP, Acheson L. Reconsidering the family history in primary care. J Gen Intern Med. 2004;19(3):273–80.
[CrossRef][PubMed][PubMedCentral]

18. Christian S, Lilley M, Hume S, Scott P, Somerville M. Defining the role of laboratory genetic

counselor. J Genet Couns. 2012;21(4):605–11.
[CrossRef][PubMed]

19. Miller CE, Krautscheid P, Baldwin EE, Tvrdik T, Openshaw AS, Hart K, Lagrave D. Genetic counselor review of genetic test orders in a reference laboratory reduces unnecessary testing. Am J Med Genet A. 2014;164A(5):1094–101.
[CrossRef][PubMed]

20. Giardiello FM, Brensinger JD, Petersen GM, Luce MC, Hylind LM, Bacon JA, Booker SV, Parker RD, Hamilton SR. The use and interpretation of commercial *APC* gene testing for familial adenomatous polyposis. N Engl J Med. 1997;336(12):823–7.
[CrossRef][PubMed]

21. Amos R, Gold B. Testing environment for single-gene disorders in U.S. reference laboratories. Hum Mutat. 1998;12(5):293–300.
[CrossRef][PubMed]

22. Kotzer KE, Riley JD, Conta JH, Anderson CM, Schahl KA, Goodenberger ML. Genetic testing utilization and the role of the laboratory genetic counselor. Clin Chim Acta. 2014;427:193–5.
[CrossRef][PubMed]

23. Harris A, Kelly SE, Wyatt S. Counseling customers: emerging roles for genetic counselors in the direct-to-consumer genetic testing market. J Genet Couns. 2013;22(2):277–88.
[CrossRef][PubMed]

24. National Society of Genetic Counselors. FAQs about genetic counselors and the NSGC. http://nsgc.org/p/cm/ld/fid=43. Accessed 24 Nov 2015.

25. National Society of Genetic Counselors. 2000 Professional status survey. 2000. http://www.nsgc.org/MemberCenter/LeadershipCenter/tabid/190/Default.aspx?EntryId=269. Accessed 18 Nov 2015.

26. National Society of Genetic Counselors. 2014 Professional status survey: work environment. 2014. http://nsgc.org/p/do/sd/sid=2478&type=0. Accessed 18 Nov 2015.

27. Scacheri C, Redman JB, Pike-Buchanan L, Steenblock K. Molecular testing: improving patient care through partnering with laboratory genetic counselors. Genet Med. 2008;10(5):337–42.
[CrossRef][PubMed]

28. Swanson A, Ramos E, Snyder H. Next generation sequencing is the impetus for the next generation of laboratory-based genetic counselors. J Genet Couns. 2014;23(4):647–54.
[CrossRef][PubMed]

29. Zetzsche LH, Kotzer KE, Wain KE. Looking back and moving forward: an historical perspective from laboratory genetic counselors. J Genet Couns. 2014;23(3):363–70.
[CrossRef][PubMed]

30. American College of Medical Genetics and Genomics. American College of Medical Genetics and Genomics policy statement: points to consider in the clinical application of genomic sequencing. Genet Med. 2012;14(8):759–61.
[CrossRef]

31. Ormond KE, Wheeler MT, Hudgins L, Klein TE, Butte AJ, Altman RB, Ashley EA, Greely HT. Challenges in the clinical application of whole-genome sequencing. Lancet. 2010;375(9727):1749–51.
[CrossRef][PubMed]

32. Pollack A. Conflict potential seen in genetic counselors. The New York Times. 2012.

33. Cigna. (2013). Genetic testing and counseling program. http://www.cigna.com/healthcare-professionals/resources-for-health-care-professionals/genetic-testing-and-counseling-program. Accessed 24 Nov 2015.

34. Dickerson JA, Cole B, Conta JH, Wellner M, Wallace SE, Jack RM, Rutledge J, Astion ML. Improving the value of costly genetic reference laboratory testing with active utilization management. Arch Pathol Lab Med. 2014;138(1):110–3.
[CrossRef][PubMed]

35. Anderson C, Goodenberger M, Kotzer K, Schahl K. Test utilization and appropriate test orders: the role of the genetic counselor. Communique. Rochester: Mayo Medical Laboratories; 2012. http://www.mayomedicallaboratories.com/articles/communique/2012/05utiliz.html. Accessed 14 Feb 2016.

36. Riley JD, Procop GW, Kottke-Marchant K, Wyllie R, Lacbawan FL. Improving molecular genetic test utilization through order restriction, test review, and guidance. J Mol Diagn. 2015;17(3):225–9.
[CrossRef][PubMed]

37. American Board of Genetic Counselors. Practice-based competencies. http://www.abgc.net/docs/Practice%20Based%20Competencies_Aug%202006%2010-29-09.pdf. Accessed 22 Nov 2015.

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_24

24. Utilization Management in Radiology

Garry Choy[1] and Alexander Ryu[1]

(1) Department of Radiology, Massachusetts General Hospital, Boston, MA, USA

Garry Choy
Email: gchoy@partners.org

Keywords

Introduction

Medical imaging is a tremendous diagnostic tool within medicine. The ability to non-invasively detect and screen for disease holds significant impact for medical or surgical treatment decisions. Monitoring of disease progression, whether infectious, inflammatory, or neoplastic is possible due to medical imaging. Over the years, access to medical imaging modalities such as X-ray, ultrasound, magnetic resonance (MR), computed tomography (CT), and positron-emission tomography (PET) has dramatically increased. In addition to expenditures related to pharmaceuticals, imaging is the next largest segment of costs for health plans, both private and public. As a result, significant growth of imaging utilization is a growing concern for healthcare. Appropriate utilization of imaging is a very important topic within healthcare utilization and optimization of decisions support systems, guidelines, and value-based imaging is critical to the future.

Medical Imaging Utilization Trends

Radiologist vs. Non-radiologists

Not all the imaging increase has been due to radiologist performed and interpreted imaging studies. Significant numbers of imaging studies have been performed by non-radiologists. For instance, between 2009 and 2013, relative growth in imaging by cardiologists and vascular surgeons for vascular imaging has outpaced that of imaging by radiologists. Radiologists have also studied the effect of reader experience and recommendation rate on effect on self-referral and increased subsequent advanced utilization. As such, younger radiologists and those in a higher liability subspecialty may be more likely to recommend a follow-up examination leading to increased advanced imaging utilization.

Causes of overutilization of imaging
• Fear of malpractice risk by clinicians
• Recommendations in interpretation by radiologist or non-radiologist issuing report
• Follow-up imaging for unclear or indeterminate diagnostic findings
• Patient driven requests and anxiety
• Access related to availability and ease of scheduling of imaging
• Access related to shorter wait times due to increasing numbers of scanners (i.e., MR and CT)
• Medical practice patterns changing to more data driven—(i.e., diagnostic work-ups and practice patterns by current generation of physicians rely less on physical exams for instance and more on data, driven by technology)

Technology and Strategies for Utilization Management

Technology and strategies for utilization management
• Health Information Exchanges
• Imaging Sharing Platforms
• Electronic Medical Record Interoperability
• Radiology Benefit Management (RBMs)
• Radiology Decision Support

Health Information Exchanges and Image Sharing

Technologies to improve sharing of imaging studies between studies have been shown to decrease duplicate studies, particularly at tertiary care centers

and in the most medically complex patients. The Center for Information Technology Leadership at Harvard University (CITL) has determined that up to 20 % of hospital-based imaging are duplicates resulting in approximately $20 billion per year of unnecessary cost (Mullaney, Timothy: This Man Wants To Heal Health Care, BusinessWeek, October 31, 2005). Image sharing platforms such as those created by commercial vendors (PowerShare, LifeImage are examples) can be leveraged by health systems and clinicians to share DICOM/medical images. Electronic medical record interoperability will also lead to the ability to share cases and raw imaging data to decrease the need for unnecessary imaging. Secure sharing of clinical data as well as actual images between clinical terms, especially in patients who are transferred between healthcare facilities and those that may seek imaging at private outpatient centers that are otherwise not linked to where they may receive most of their care.

Radiology Benefit Management (RBM) Organizations

Radiology benefit managers (RBMs) are corporations, generally comprised of radiologists and sometimes other clinical staff, who are responsible for managing the utilization of radiological services. RBMs are hired by private insurance companies to issue prior authorizations for imaging studies and to review the appropriateness of claims filed for radiological services [1]. These determinations are made using algorithms that consider a patient's state of health, demographics, previous imaging, and the type of imaging study ordered, among other things. RBMs may also have an effect of deterring the use of imaging simply by creating another piece of bureaucracy for the ordering provider to navigate. In these ways, RBMs serve as "gatekeepers" for radiological services [2]. Of note, Congress prohibits the use of prior authorizations among Medicare beneficiaries. This model was predated by Pharmacy Benefit Managers (PBMs) , which achieved prominence in the mid-1990s to serve a similar function in limiting the utilization of expensive medications, although PBMs' functions have expanded significantly since [3].

The need for radiology benefit managers can be attributed to several factors. First, many radiological services are relatively expensive, thus increased utilization of radiological services generally contributes significantly to greater costs for healthcare payors, private and public.

Spending on radiological services also experienced rapid growth in the early 2000s, which then drew regulatory scrutiny [4]. Second, there are several incentives and trends that can encourage overuse of radiological services. Healthcare providers may overuse imaging if they are up-to-date on changing imaging recommendations [5]. Providers also have an incentive to defensively order imaging as a diagnostic catchall to avoid litigation relating to missed or uncertain diagnoses. In some cases, radiologists' income has historically been tied directly to imaging volumes through direct ownership of imaging facilities, although this practice has been largely abolished. Finally, providers may, at times, acquiesce to patients' expectations for imaging, some of which may not be medically appropriate [6, 7]. These issues, of course, are not unique to radiology. Concerns regarding the overuse of expensive treatments for similar reasons have been raised with respect to certain pharmaceuticals, cardiac surgeries, and intensity-modulated radiation therapy, among others [3, 8, 9].

With respect to their overall goal of containing imaging costs, RBMs seem to have been successful [4, 10]. Studies have a demonstrated a 10–15 % reduction in imaging utilization attributable to RBMs [11]. Some concerning findings have emerged as well, with one study noting that over 90 % of overturned authorization denials were in fact supposed to be covered, and these required, on average, 15.4 patient emails, calls, or faxes to overturn [12]. Still, the RBM market has grown to provide services for an estimated half of all privately insured patients [10]. One corporate sale dated 2007 suggests that the RBM industry was valued at $1-3B at that time. Since that time, however, the growth in imaging expenditures has grown more slowly, and industry consolidation has occurred. As of 2015, it is estimated that the four largest RBMs control utilization for 85 % of all patients under RBM review [13]. Extrapolating from this and another corporate merger in 2014 suggests that the RBM industry may be valued at $3-6B at present [1, 14].

Moving forward, the RBM industry will continue to come under pressure, not only due to slowing growth of radiology expenditures, but also due to the rise of software packages that are replacing RBMs' function. This change has been enabled by both advances in radiological information technology infrastructure and the broad adoption of a standardized set of imaging appropriateness criteria, in contrast to the proprietary algorithms used in the past [15].

Radiology Order Entry

Radiology Order Entry (ROE) is a class of software that enables the computerized entry of radiological orders and may provide decision support to help clinicians order radiological studies more appropriately. In this chapter, ROE will refer exclusively to systems that include decision support. The factors that dictate the need for decision support are described in the previous section on Radiology Benefit Managers (RBM). Modern ROE systems guide the appropriate use of radiological studies by using computerized algorithms to generate an appropriateness score. Over time, these algorithms have become more standardized as the American College of Radiology (ACR) Appropriateness Criteria [1] have gained national acceptance. As with RBM algorithms, the patient's demographics, health state, previous imaging, and proposed imaging study are considered in determining overall study appropriateness. However, unlike RBM algorithms which required data to be submitted to a third party for manual review, ROE systems score a study's appropriateness at the time of ordering by requiring responses to a limited list of questions that are integrated into existing information technology (IT) systems.

The origins of ROE systems can be traced back to Provider Order Entry (POE) systems, which are decision support tools designed to help providers prescribe in accordance with current guidelines and avoid medication errors. Early POE systems emerged in the 1970s [2] but gained traction in the mid-1990s [3, 4], and their functions have expanded since then. Most data indicate that POE systems were indeed successful at reducing medication errors, hospital length of stay and costs while improving the auditability of physician orders and compliance with best practices [5–13]. Other studies suggested that POE systems can also save time by streamlining workflows [14–17]. Achieving positive results, however, seems dependent on the quality of the system's user interface, integration with existing IT systems, and a willingness to make iterative modifications to the system as needed [18–20]. Data showing a direct relationship between POE adoption and patient outcomes has been less clear, however [7, 8, 12, 13, 21]. Over their lifetime, POE systems initially faced some skepticism and unintended consequences in their implementation [22–25], but over time, have improved and enjoyed swifter uptake. Still, they are far from ubiquitous and controversies regarding the generalizability and ease of implementation of decision support remain [26, 27]. A 2009 study estimated that just 15 % of US hospitals use a POE

system [18], while a 2011 study found that roughly 30 % of US emergency departments had a POE system in place [28].

Roughly one decade after the first POE systems were conceived, two early ROE systems were created. *PHOENIX* was a system that provided imaging workup flowcharts for a limited set of diagnoses [29, 30], while *CASPER* was a database of imaging appropriateness and diagnostic data that could be searched by its complement application, *Explorer* [30, 31]. The algorithms in these early applications appear to have been based on the authors' synthesis of existing literature and both were developed by academic institutions. Opportunities to input patient-specific factors were minimal [29–31]. Over the subsequent decade, ROE systems continued to evolve by development of more powerful algorithms, better integration with existing IT and addition of other useful functions, such as study scheduling [32]. Studies on ROE systems show that they can decrease the ordering of inappropriate studies [33–35], improve efficiency [36], and improve the quality of patient histories provided to radiologists [37]. Additionally, ROE systems have been shown to slow growth in outpatient imaging volumes [38], although another study found that ROE suggestions to ordering providers were often ignored, negating the utility of decision support [39].

In recent years, adoption of ROE systems has been incentivized by key policy developments. In 2009, as part of the national stimulus bill, Congress approved the Health Information Technology for Economic and Clinical Health (HITECH) Act which offered incentives for "meaningful use" of various pieces of information technology in hospitals; ROE was one of these technologies [40]. Then in 2013, the American College of Radiology, in collaboration with National Decision Support Company, began offering ACR Select, a web-based, widely integrable ROE system based on ACR's Appropriateness Criteria [41]. ACR Select represents the first ACR-endorsed ROE offering, which promises to bring greater standardization to ROE systems nationally. This standardization offers promise to reduce or eliminate the need for radiology benefit managers; at least one hospital has negotiated a plan with its payors to use ROE in lieu of a radiology benefit manager [42]. At present, the literature lacks a current estimate of ROE adoption, but this likely parallels POE adoption, given the need of an electronic health records system as a foundation for both POE and ROE.

In the near future, adoption of ROE systems will likely accelerate, given the recent improvements in standardization and top-down promotion from

ACR . Given the history of POE and ROE adoption, any single ROE solution will likely still require some customization to meet a given practice's needs. Similar decision support tools will also help to reshape information technology in other medical fields, given the many benefits that computerized order entry systems can provide. Historically, decision support applications have been created for many fields, from psychiatry to dental medicine [43]. More recently, there has been interest in greater use of decision support for pathology, dermatology, and various high-cost procedures [44–48]. The range of opportunities for decision support continues to expand.

References

1. American College of Radiology of ACR Appropriateness Criteria. 2015. http://www.acr.org/quality-safety/appropreatness

2. Stürzlinger H, Hiebinger C, Pertl D, Traurig P. Computerized physician order entry—effectiveness and efficiency of electronic medication ordering with decision support systems. GMS Health Technol Assess. 2009;5:Doc07. doi:10.3205/hta000069.
[PubMed][PubMedCentral]

3. Bates DW, O'Neil AC, Boyle D, et al. Potential identifiability and preventability of adverse events using information systems. J Am Med Inform Assoc. 1994;1(5):404–11. https://pallas2.tcl.sc.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=mnh&AN=7850564&site=ehost-live.
[CrossRef][PubMed][PubMedCentral]

4. Tierney WM, Miller ME, Overhage JM, McDonald CJ. Physician inpatient order writing on microcomputer workstations. Effects on resource utilization. JAMA. 1993;269:379–83. doi:10.1001/jama.269.3.379.
[CrossRef][PubMed]

5. Hwang JI, Park HA, Bakken S. Impact of a physician's order entry (POE) system on physicians' ordering patterns and patient length of stay. Int J Med Inform. 2002;65:213–23. doi:10.1016/S1386-5056(02)00044-8.
[CrossRef][PubMed]

6. Bates DW, Leape LL, Cullen DJ, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. JAMA. 1998;280(15):1311–6. doi:10.1001/jama.280.15.1311.
[CrossRef][PubMed]

7. Van Rosse F, Maat B, Rademaker CM, van Vught AJ, Egberts AC, Bollen CW. The effect of computerized physician order entry on medication prescription errors and clinical outcome in pediatric and intensive care: a systematic review. Pediatrics. 2009;123:1184–90. doi:10.1542/peds.2008-1494.

[CrossRef][PubMed]

8. Holdsworth MT, Fichtl RE, Raisch DW, et al. Impact of computerized prescriber order entry on the incidence of adverse drug events in pediatric inpatients. Pediatrics. 2007;120:1058–66. doi:10.1542/peds.2006-3160.
[CrossRef][PubMed]

9. Kaushal R, Jha AK, Franz C, et al. Return on investment for a computerized physician order entry system. J Am Med Inform Assoc. 2006;13(3):261–6. doi:10.1197/jamia.M1984.
[CrossRef][PubMed][PubMedCentral]

10. Ammenwerth E, Schnell-Inderst P, Machan C, Siebert U. The effect of electronic prescribing on medication errors and adverse drug events: a systematic review. J Am Med Inform Assoc. 2008;15(5):585–600. doi:10.1197/jamia.M2667.
[CrossRef][PubMed][PubMedCentral]

11. Lobach DF, Hammond WE. Computerized decision support based on a clinical practice guideline improves compliance with care standards. Am J Med. 1997;102(1):89–98. doi:10.1016/S0002-9343(96)00382-8.
[CrossRef][PubMed]

12. Garg AX, Adhikari NKJ, McDonald H, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. JAMA. 2005;293(10):1223–38. doi:10.1001/jama.293.10.1223.
[CrossRef][PubMed]

13. Hunt DL, Haynes RB, Hanna SE, Smith K. Effects of computer-based clinical decision support systems on physician performance and patient outcomes. JAMA. 1998;280(15):1339. doi:10.1001/jama.280.15.1339.
[CrossRef][PubMed]

14. Coleman RW. Translation and interpretation: the hidden processes and problems revealed by computerized physician order entry systems. J Crit Care. 2004;19(4):279–82. doi:10.1016/j.jcrc.2004.09.001.
[CrossRef][PubMed]

15. Wright A, Feblowitz JC, Pang JE, et al. Use of order sets in inpatient computerized provider order entry systems: a comparative analysis of usage patterns at seven sites. Int J Med Inform. 2012;81(11):733–45. doi:10.1016/j.ijmedinf.2012.04.003.
[CrossRef][PubMed][PubMedCentral]

16. Teich JM, Spurr CD, Schmiz JL, O'Connell EM, Thomas D. Enhancement of clinician workflow with computer order entry. Proc Annu Symp Comput Appl Med Care. 1995;459–463.

17. Overhage JM, Perkins S, Tierney WM, McDonald CJ. Controlled trial of direct physician order entry: effects on physicians' time utilization in ambulatory primary care internal medicine practices. J Am Med Inform Assoc. 2001;8(4):361–71. doi:10.1136/jamia.2001.0080361.
[CrossRef][PubMed][PubMedCentral]

18. Aarts J, Koppel R. Implementation of computerized physician order entry in seven countries. Health Aff (Millwood). 2009;28(2):404–14. doi:10.1377/hlthaff.28.2.404.

[CrossRef]

19. Niazkhani Z, Pirnejad H, Berg M, Aarts J. The impact of computerized provider order entry systems on inpatient clinical workflow: a literature review. J Am Med Inform Assoc. 2009;16(4):539–49. doi:10.1197/jamia.M2419.
[CrossRef][PubMed][PubMedCentral]

20. Campbell EM, Guappone KP, Sittig DF, Dykstra RH, Ash JS. Computerized provider order entry adoption: implications for clinical workflow. J Gen Intern Med. 2009;24(1):21–6. doi:10.1007/s11606-008-0857-9.
[CrossRef][PubMed]

21. Berger RG, Kichak JP. Computerized physician order entry: helpful or harmful? J Am Med Inform Assoc. 2004;11(2):100–3. doi:10.1197/jamia.M1411.
[CrossRef][PubMed][PubMedCentral]

22. Bates DW, Kuperman GJ, Teich JM. Computerized physician order entry and quality of care. Qual Manag Health Care. 1994;2(4):18–27.
[CrossRef][PubMed]

23. Weiner M, Gress T, Thiemann DR, et al. Contrasting views of physicians and nurses about an inpatient computer-based provider order-entry system. J Am Med Inform Assoc. 1999;6(3):234–44. doi:10.1136/jamia.1999.0060234.
[CrossRef][PubMed][PubMedCentral]

24. Massaro TA. Introducing physician order entry at a major academic medical center: I. Impact on organizational culture and behavior. Acad Med. 1993;68(1):20–5.
[CrossRef][PubMed]

25. Ash JS, Sittig DF, Poon EG, Guappone K, Campbell E, Dykstra RH. The extent and importance of unintended consequences related to computerized provider order entry. J Am Med Inform Assoc. 2007;14(4):415–23. doi:10.1197/jamia.M2373.
[CrossRef][PubMed][PubMedCentral]

26. Bobb AM, Payne TH, Gross PA. Viewpoint: controversies surrounding use of order sets for clinical decision support in computerized provider order entry. J Am Med Inform Assoc. 2007;14(1):41–7. doi:10.1197/jamia.M2184.
[CrossRef][PubMed][PubMedCentral]

27. Campbell EM, Sittig DF, Ash JS, Guappone KP, Dykstra RH. Types of unintended consequences related to computerized provider order entry. J Am Med Inform Assoc. 2006;13(5):547–56. doi:10.1197/jamia.M2042.
[CrossRef][PubMed][PubMedCentral]

28. Pallin DJ, Sullivan AF, Espinola JA, Landman AB, Camargo CA. Increasing adoption of computerized provider order entry, and persistent regional disparities, in US emergency departments. Ann Emerg Med. 2011;58(6):543–50. doi:10.1016/j.annemergmed.2011.05.015. e3.
[CrossRef][PubMed]

29. Kahn Jr CE, Messersmith RN, Jokich MD. PHOENIX: an expert system for selecting diagnostic imaging procedures. Invest Radiol. 1987;22(12):978–80.

[CrossRef][PubMed]

30. Kahn Jr CE. Artificial intelligence in radiology: decision support systems. Radiographics. 1994;14:849–61. doi:10.1148/radiographics.14.4.7938772.
[CrossRef][PubMed]

31. Greenes RA, Tarabar DB, Krauss M, et al. Knowledge management as a decision support method: a diagnostic workup strategy application. Comput Biomed Res. 1989;22(2):113–35. doi:10.1016/0010-4809(89)90021-9.
[CrossRef][PubMed]

32. Khorasani R. Computerized physician order entry and decision support: improving the quality of care. Radiographics. 2001;21(4):1015–8. doi:10.1148/radiographics.21.4.g01jl371015.
[CrossRef][PubMed]

33. Rosenthal DI, Weilburg JB, Schultz T, et al. Radiology order entry with decision support: initial clinical experience. J Am Coll Radiol. 2006;3(10):799–806. doi:10.1016/j.jacr.2006.05.006.
[CrossRef][PubMed]

34. Raja AS, Ip IK, Prevedello LM, et al. Effect of computerized clinical decision support on the use and yield of CT pulmonary angiography in the emergency department. Radiology. 2012;262(2):468–74. doi:10.1148/radiol.11110951.
[CrossRef][PubMed][PubMedCentral]

35. Vartanians VM, Sistrom CL, Weilburg JB, Rosenthal DI, Thrall JH. Increasing the appropriateness of outpatient imaging: effects of a barrier to ordering low-yield examinations. Radiology. 2010;255(3):842–9. doi:10.1148/radiol.10091228.
[CrossRef][PubMed]

36. Juluru K, Eng J. Internet-based radiology order-entry, reporting, and workflow management system for coordinating urgent study requests during off-hours. AJR Am J Roentgenol. 2012;7:2127–34. http://www.ajronline.org.ezp-prod1.hul.harvard.edu. Accessed 19 Oct 2015.

37. Alkasab TK, Alkasab JR, Abujudeh HH. Effects of a computerized provider order entry system on clinical histories provided in emergency department radiology requisitions. J Am Coll Radiol. 2009;6(3):194–200. doi:10.1016/j.jacr.2008.11.013.
[CrossRef][PubMed]

38. Sistrom CL, Dang PA, Weilburg JB, Dreyer KJ, Rosenthal DI, Thrall JH. Effect of computerized order entry with integrated decision support on the growth of outpatient procedure volumes: seven-year time series analysis. Radiology. 2009;251(1):147–55. doi:10.1148/radiol.2511081174.
[CrossRef][PubMed]

39. Bowen S, Johnson K, Reed MH, Zhang L, Curry L. The effect of incorporating guidelines into a computerized order entry system for diagnostic imaging. J Am Coll Radiol. 2011;8(4):251–8. doi:10.1016/j.jacr.2010.11.020.
[CrossRef][PubMed]

40. Blumenthal D. Launching HITECH. N Engl J Med. 2010;362(5):382–5. doi:10.1056/NEJMp0912825.
[CrossRef][PubMed]

41. AC Radiology. ACR Select puts ACR appropriateness criteria at physicians' fingertips. ACR Qual Saf eNews. 2013. http://www.acr.org/Quality-Safety/eNews/Issue-04-December-2013/ACR-Select. Accessed 19 Oct 2015.

42. Lau L, Ng K-H, editors. Radiological safety and quality. Dordrecht: Springer Netherlands; 2014. doi:10.1007/978-94-007-7256-4.

43. Miller RA. Medical diagnostic decision support systems–past, present, and future: a threaded bibliography and brief commentary. J Am Med Inform Assoc. 1994;1(1):8–27. /pmc/articles/PMC116181/?report=abstract. Accessed 19 Oct 2015. [CrossRef][PubMed][PubMedCentral]

44. Georgiou A, Westbrook JI. Computerised order entry systems and pathology services--a synthesis of the evidence. Clin Biochem Rev. 2006;27(2):79–87. /pmc/articles/PMC1579412/?report = abstract. Accessed 19 Oct 2015. [PubMed][PubMedCentral]

45. Georgiou A, Williamson M, Westbrook J, Ray S. The impact of computerised physician order entry systems on pathology services: a systematic review. Int J Med Inform. 2007;76(7):514–29. doi:10.1016/j.ijmedinf.2006.02.004. [CrossRef][PubMed]

46. Mazzola L, Cavazzina A, Pinciroli F, et al. Towards a decision support system for hand dermatology. Stud Health Technol Inform. 2014;205:58–62. http://www.ncbi.nlm.nih.gov/pubmed/25160145. Accessed 19 Oct 2015. [PubMed]

47. Papier A. Decision support in dermatology and medicine: history and recent developments. Semin Cutan Med Surg. 2012;31(3):153–9. doi:10.1016/j.sder.2012.06.005. [CrossRef][PubMed]

48. Fonseca E. On the cutting edge: using decision support tools to assess procedural appropriate use and increase healthcare value. HBS Open Forum 2014. Harvard Business School

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_25

25. Strategies for the Clinical and Financial Management of Drug Utilization

Christopher Fortier[1] ✉, Prabashni Reddy[2], Nathan Thompson[3] and Andy Pulvemacher[4]

(1) Department of Pharmacy, Massachusetts General Hospital, 55 Fruit Street, GRB-005, Boston, MA 02114, USA
(2) Center for Drug Policy, Partners Healthcare, Boston, MA, USA
(3) Department of Pharmacy, John Hopkins Medicine, Baltimore, MD, USA
(4) University of Wisconsin Hospital and Clinics, Madison, WI, USA

✉ **Christopher Fortier**
Email: Fortier@partners.org

Keywords Drug – Managed care – Specialty pharmacy – Pharmacist – Generic – Fee-for-service – Cost containment – Reimbursement – Third-party payors – Medical benefit – Prescription benefit

Introduction

Recent data shows a 12.2 % increase in US pharmaceutical spending at the end of 2014 (Fig. 25.1) [1]—Originally published in [full citation of article] © [2015], American Society of Health-System Pharmacists, Inc. All rights reserved. Reprinted with permission. (R1509). This significant spending

increase compared to previous years (2012 and 2013, 2.1 % and 3.3 %, respectively) is a result of a variety of factors changing within the healthcare environment and pharmaceutical industry [1]. Healthcare reform has resulted in expanded coverage and the increase of medications within the aging population. Additionally, we have seen an influx of new and extremely expensive medications, significantly higher costs for age-old generic medications, and continue to battle drug shortages. These increases in drug expenditures, reimbursement margins continue to drop.

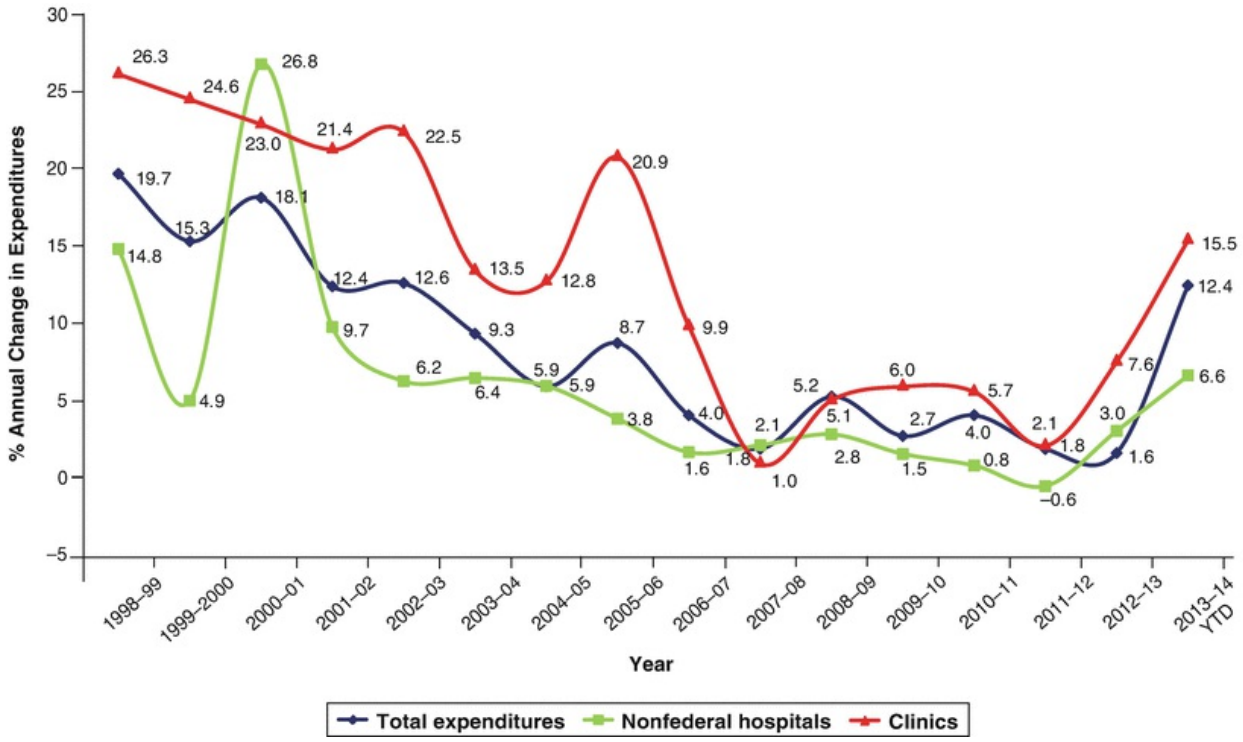


Fig. 25.1 Pharmaceutical spending in the United States showing the percent annual change over time

Combining the increases in drug costs, the goal for improved patient outcomes, and the need to manage total medical expense the clinical and financial aspects of drug utilization are becoming an increased priority across the healthcare sector and for hospital leadership . Pharmacists , especially in the hospital, clinic, and specialty pharmacy settings, will need to play an increased direct patient care role through a multidisciplinary collaboration with providers to achieve definite outcomes that improve a patient's quality of life. Numerous published studies have shown the positive impact that pharmacists, in a variety of settings, have had on utilization management, medication safety, readmissions, population health management, and

transitions of care.

In this chapter we will discuss how medications are utilized across various settings (inpatient, ambulatory clinics, specialty, retail, and managed care pharmacy), strategies to manage the clinical and financial aspects, and to create awareness of new practice limitation trends.

Inpatient Drug Utilization Strategies

Drug expenditures in the inpatient setting have continued to rise at a rate of 3–7 % in the past 5 years [1]. Given that drugs are not typically separately reimbursed but are rather included in the overall diagnosis-related group (DRG) payment for a specific admission, there will likely be an ongoing incentive to reduce inappropriate drug utilization and its associated costs [2]. Key drivers of cost growth in the inpatient area have been specialty drugs, unexpected price spikes of generic drugs, changes in distribution channels leading to loss of previous discounts, and drug shortages [1]. Utilization management is one tool to address rising costs.

Limiting the population who may use a medication is at the core of utilization management. This may typically be achieved by developing criteria for drug use or more comprehensive clinical pathways that outline the role of specific agents [3]. A critical evaluation of the literature, citing national guidelines, meta-analyses, randomized controlled trials, and economic analyses, as available, should be undertaken [3]. It is recommended that local expert consensus be obtained using clinical multidisciplinary groups to ensure that recommendations are relevant and can be implemented at the institution [4]. In addition to the clinical review , it is also helpful to assess the budget impact under various scenarios, as that will facilitate decision making by understanding the economic implications of different recommendations.

Other tools to manage drug utilization (and ultimately costs) include generic substitution, intravenous (IV) to oral conversion, as well as therapeutic drug interchange [3]. Except for generic substitution of drugs that have been deemed bioequivalent by the Food and Drug Administration (FDA) , providers will need to agree with these proposed changes and this may best be achieved through review and approval by the hospital’s Pharmacy and Therapeutics (P&T) committee . A detailed review of clinical and economic data followed by presentation to the P&T committee is

recommended.

Generic substitution has long been a medication utilization strategy and data now show that some 80 % of prescriptions in the USA are filled with generic medications [5]. IV to oral conversion promotes the use of a lower cost and safer route of administration of a particular drug. Therapeutic interchange entails using a drug with similar efficacy and safety, often in the same pharmacological class [3]. In general, standardization to fewer products and reducing utilization of non-formulary medications can lead to savings for the organization. A special form of therapeutic interchange in the future will involve biosimilars. The Biologics Price Competition and Innovation Act of 2009 , enacted as part of the Affordable Care Act of 2010 , created an abbreviated pathway for biological products to demonstrate biosimilarity or interchangeability with a reference product. The first of these was approved by the FDA in March 2015 [6]. These have the potential to moderate the growth in drug spending given their lower cost relative to the innovator agent.

Once guidelines, clinical pathways, generic/therapeutic substitution, IV to oral conversion or other approaches to drug utilization have been approved by the P&T committee, an assessment will need to be made of the best method to implement the utilization effort [3]. Available options include education, pre-authorization approval by a clinician, development of order sets, use of decision support in computerized physician ordering to direct prescribing, as well as post-authorization intervention to discontinue inappropriate use.

Printed educational materials (e.g., inservices, newsletters, email communication) have been shown to provide a small beneficial effect on professional practice outcomes [7]. A more advanced approach is academic detailing with prescriber-feedback where data on utilization are shared with the clinician. Pre-authorization approval via a specialist consult and approval can be an effective tool to ensure that patient meets criteria for use [8]. This is a resource intensive activity and the P&T committee will need to ensure that there are sufficient personnel resources to address requests in a timely manner without delaying patient care. An alternative approach is to direct prescribing to particular agents through order sets, which list the medications that may be used, as well as their recommended doses. As providers would have to make a separate request to use a medication not listed in the order set, this will serve as a deterrent from using a non-preferred drug. The use of

order sets and other decision support in computerized physician order entry systems (CPOE) has been shown to reduce inappropriate utilization [9].

Post approval review of medications can be undertaken by a pharmacist with communication to providers if patients do not meet the criteria for use. This has been well studied and shown to reduce inappropriate utilization [10]. However, this approach is resource intensive and sufficient pharmacists need to be available to use this approach.

Including quality measures within utilization management may garner additional interest in and adherence by providers. For example, a project that focused on achieving lower hemoglobin targets with erythropoietin as a safety issue also resulted in a reduction in drug utilization and associated costs [11]. Another approach may be the use of financial incentives to manage utilization but data in the hospital setting are limited and therefore this warrants further exploration [12].

In recent years, comprehensive stewardship programs have emerged, primarily in the infectious disease area [6]. These encompass a wide range of utilization management strategies listed above and are multidisciplinary in nature (e.g., pre-authorization, guidelines, computerized decision support, etc.). Such programs have focused on optimizing antimicrobial use and have been shown to decrease antimicrobial costs and utilization, and improve microbial outcomes. While most data are in the infectious disease area, this appears to be an approach that has the potential for widespread adoption (i.e., oncology, anticoagulation).

External benchmarking (i.e., comparison to use at other similar hospitals) has been shown to reduce drug utilization and is associated with cost savings [13]. Appropriate data sets need to be available. One issue is timeliness as there may be a data lag. Nevertheless, this is an additional tool that may be used to manage drug utilization.

Ambulatory Clinic Drug Management

Drug expenditures in the hospital clinic setting are rising at a faster rate than in the inpatient setting and are projected to be some 12–14 % higher in 2015 [1]. This setting is dominated by specialty drugs, especially IV oncology and inflammatory condition medications. One difference compared to the inpatient setting is the payment structure. As this is typically paid by a fee-for-service, there is a financial incentive to increase utilization as revenue for

the hospital will increase alongside the increase in use [2]. However, in systems with at-risk financial contracts, there will be some incentive to reduce utilization, as this will decrease total medical expenses.

In addition, trends to shift the site of care and for changing medications from the medical to a pharmacy benefit should be kept in mind . Much of the toolkit and implementation described above in the inpatient setting applies to the clinic setting, however, implementation will be more challenging due to the influence of various health plans. Specifically, health plans may have their own utilization criteria that may differ from those of the hospital. In general, hospital's utilization criteria should be at least as restrictive as those of the major health plans; otherwise, the hospital will be at risk for payment denials and a loss of revenue. In addition, health plans may have different preferred products and may be receiving rebates if they achieve target market share. This in turn may impact the ability of a hospital to standardize products.

Specialty Pharmacy Services

The significant advancements in developing complex and protein-based products have created a new class of therapies commonly referred to as "specialty medications." These medications often have special handling requirements, unique drug delivery devices, require additional patient monitoring, are used in niche patient populations, or are high-cost [14]. They are designated as "specialty" products by payers and are commonly used to treat conditions such as rheumatoid arthritis, cystic fibrosis, and solid organ transplants (Table 25.1).

Table 25.1 Top specialty pharmacy drug disease states

Oncology	**Multiple sclerosis**
HIV/AIDS	Rheumatoid arthritis
Hemophilia	Intravenous immunoglobulin
Irritable Bowel Syndrome	Hepatitis C
Growth Hormone	Transplant
Cardiovascular	End Stage Renal Disease

Due to the small patient populations and limited patient research, some medications are mandated by the Food and Drug Administration to provide

medication-specific Risk Evaluation and Mitigation Strategies (REMS) to evaluate the population-based risks associated with rare or severe side effects of medication therapies, in relation to their benefits [15]. Due to compliance with REMS requirements and narrow patient populations, pharmaceutical manufacturers may restrict the access of pharmacies to specialty medications. Through the expansion of these limited distribution networks and rapid development of complex medications, “Specialty Pharmacies” which specialize in the management of high-cost and complex therapies have become common in the pharmacy marketplace.

Due to the significant costs associated with these therapies, payers control the utilization of these agents through the traditional tools of reimbursement pressure, narrow networks, and formulary management. Third party payer networks may also require reporting of data to demonstrate the quality of care provided by the specialty pharmacy for specialty patients. Common reporting metrics include customer service measures such as call center reporting, patient satisfaction, and medication compliance rates. However, payers have an increased focus on documenting patient outcomes and pharmacist interventions in the care of specialty patients. These medications may be paid for through the medical or prescription benefit .

Outpatient Pharmacy Services

Traditional outpatient pharmacy services (retail chain, independent, hospital) continue to provide the greatest access for patients to pharmacy services. Retail pharmacy services include: medication dispensing, patient counseling, and insurance billing. The customer-base of a retail pharmacy typically coincides with the population surrounding the pharmacy. Medications are typically paid for through the prescription benefit.

Core services of a mail-order pharmacy are similar to those of a retail pharmacy, with patient counseling typically occurring telephonically. Prescription volume is typically much higher than a retail pharmacy, and can originate from a wide geographic area (e.g., a state, a region). Pharmaceutical manufacturers or wholesalers negotiate or contract directly with a mail-order facility. All medications are shipped to the facility for dispensing to patients who have chosen to use this alternative for medication delivery. This can reduce the cost and financial risk to the supplier, which can lead to a price reduction for the Managed Care Organization (MCO) [16]. Medications are

typically paid for through the prescription benefit .

Home infusion therapy typically involves administration of medication through a needle or catheter. “Traditional” prescription drug therapies administered via home infusion include antibiotics, antifungals, pain management, and parenteral nutrition . Technological advances have enabled safe and effective administration of infusion therapies in the home. The desire of patients to resume a normal lifestyle has evolved home infusion therapies into a comprehensive medical therapy that is a much less costly alternative to inpatient treatment in a hospital or skilled nursing facility [17]. Medications are typically paid for through the medical benefit . However, the prescription benefit may be used in some instances.

Managed Care Pharmacy

As the overall cost of medical care is managed, several mechanisms of cost containment have arisen. The first and most prominent is the restriction of care networks and management of reimbursement.

Health Maintenance Organizations (HMOs) and other types of MCOs such as Preferred Provider Organizations (PPOs) and insurance plans finance and either directly provide health care to members through their own facilities and staff, or indirectly by negotiating with providers to accept lower reimbursement for services rendered in order to capitalize on larger patient volumes or scope of services [16]. Typically, an MCO receives payment for services from plan sponsors, also referred to as payors (e.g., employers, unions, government agencies), and patients who pay a portion of costs through co-payments, co-insurances, and deductibles [16]. Pharmacy Benefit Manager (PBM) companies may manage pharmaceutical benefits for MCOs, other medical providers, or employers [16].

Restricted provider network agreements may be structured under a fee-for-service model in which health care providers are paid for each service individually, or through a bundled payment arrangement for services provided to patients [18]. The “bundling” of services, and provider’s acceptance of risk for expenses for cost of care that could be greater than reimbursement, is a means of cost management for medical and medication related services.

With the creation of at-risk contracts, payers and providers are increasingly focused on delivering care in the most cost-effective setting

(e.g., the hospital, the medical office, the home). Reimbursement for medications administered within the home represents the lowest overall cost for third-party payers , while hospital administration is commonly considered the most expensive. Identifying the most appropriate site of care represents an opportunity to leverage differential reimbursement and contract rates.

The decision of site of care must be balanced with the patient's readiness to comply with therapy, overcoming perceived barriers to therapy, identifying and resolving third-party payer-related coverage, and mitigating financial barriers for patients. By prospectively managing these barriers to patient therapy acceptance, site of care may be a useful tool in reducing overall healthcare costs related to medication therapy.

With the implementation of payment reform, Pay for Performance (PFP) reimbursement arrangements are being created where providers assume financial risk for the quality and cost of care being provided to patients. In these models, the payment can be recouped or sequestered based on specific defined quality metrics [18]. The provider's performance with regard to the assigned metrics may lead to full payment of contracted services, loss of sequestered funds, or potentially lack of reimbursement for readmissions or iatrogenic-based sequelae of care.

A hallmark of the management of pharmaceutical benefits is the development and maintenance of a formulary, or a preferred list of medications, which helps to guide utilization and control costs [19]. Medications covered under a formulary are determined based on clinical evidence supporting use, risks of use, and net cost of the medication compared to alternative agents. The formulary provides a framework for product selection by medical and pharmacy providers as well as reimbursement for services rendered for medication delivery to patients. In collaboration with a formulary, restricted networks of pharmacies may be identified to reduce prescription-based reimbursement.

Many strategies can be utilized to manage pharmaceutical benefits. For example, rebate agreements for specific medications may be executed with pharmaceutical manufacturers in which monies are returned based upon utilization factors such as formulary placement or market share [16]. For some high-cost medications, prior authorizations must be completed to ensure appropriate use. Step edits can be utilized to ensure lower cost medication options are utilized as the first options for treatment. Medications may also be placed in higher-level formulary "tiers" that necessitate higher

patient cost sharing (i.e., co-payments, co-insurances).

The administration of medications can occur across a myriad of practice settings, but can be loosely bundled according to billing process. Medications administered by a healthcare provider within a medical office or home are traditionally billed via Healthcare Common Procedure Coding System (HCPCS) units, which are commonly referred to as J-Codes. HCPCS or J-Code billing is typically indicative of medical benefit billing processes. HCPCS codes are unique for a specific drug product and corresponding billing unit of administration; billing is completed using multiples of HCPCS code units to correspond to the administered dose. Payment for services rendered under medical benefit billing are reimbursed under negotiated agreements that may be inclusive of non-medication related, negotiated reimbursement contracts.

Medications reimbursed under a prescription benefit are typically patient self-administered within the home and billed via National Drug Code (NDC) -based reimbursement (Table 25.2). NDCs are standardized 11-digit codes, which correspond to the manufacturer, drug product, and package size of the specific drug product. Claims are often processed electronically in "real-time" (i.e., electronic adjudication). Reimbursement contracts for prescription-benefit billing are often negotiated by PBMs and other pharmacy payers independently of medical benefits.

Table 25.2 Differences in medical and prescription-based billing for medications

Medical benefit	Prescription benefit
Typically for medications administered by a healthcare provider	Typically for patient-administered medications
Typically billed via Healthcare Common Procedure Coding System (HCPCS) otherwise known as J-Codes	Typically billed by National Drug Code (NDC)
Billing may be inclusive of non-medication related negotiated reimbursement contracts	Billing typically electronic, in real-time, and specific to the medication

Conclusion

Due to the significant increases in drug expenditures, compounded with accountable care goals and total medical expense limits, focus and collaboration is critical to manage the clinical and financial aspects around the use of medications across the continuum.

References

1. Schumock GT, Li EC, Suda KJ, et al. National trends in prescription drug expenditures and projections for 2015. Am J Health Syst Pharm. 2015;72:e19–38. [CrossRef]

2. American Academy of Managed Care Pharmacy. AMCP guide to pharmaceutical payment methods. Executive summary. Version 3. http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=16476. Accessed 21 Aug 2015.

3. American Society of Health-System Pharmacists. ASHP guidelines on the pharmacy and therapeutics committee and formulary system. Am J Health-Syst Pharm. 2008;43:1272–83.

4. Weant KA, Bowers RC, Reed J, et al. Safety and cost-effectiveness of a clinical protocol implemented to standardize the use of crotalidae polyvalent immune fab antivenom at an academic medical center. Pharmacotherapy. 2012;32:433–40. [CrossRef][PubMed]

5. Food and Drug Administration. Facts about generic drugs. http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/understandinggenericdrugs/ucm167991.htm. Accessed 21 Aug 2015.

6. Food and Drug Administration. FDA approves first biosimilar product Zarxio. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm Accessed 21 Aug 2015.

7. Giguere A, Legare F, Grimshaw J. Printed educational materials: effects on professional practice and healthcare outcomes. Cochrane Database Syst Rev. 2015;3. doi:10.1002/14651858.CD004398.pub3.

8. Delory T, De Pontfarcy A, Emirian A, et al. Impact of a program combining pre-authorization requirement and post-prescription review of carbapenems: an interrupted time-series analysis. Eur J Clin Microbiol Infect Dis. 2013;32:1599–604. [CrossRef][PubMed]

9. Sonstein L, Clark C, Seidensticker S, et al. Improving adherence for management of acute exacerbation of chronic obstructive pulmonary disease. Am J Med. 2014;127:1097–104. [CrossRef][PubMed][PubMedCentral]

10. Flood KL, Carroll MB, Le CV, et al. Polypharmacy in hospitalized older adult cancer patients: experience from a prospective, observational study of an oncology-acute care for elders unit. Am J Geriatr Pharmacother. 2009;7:151–8. [CrossRef][PubMed]

11. Selvan MS, Sittig DF, Thomas EJ, et al. Improving erythropoietin-stimulating agent administration in a multihospital system through quality improvement initiatives: a pre-post comparison study. J Patient Saf. 2011;7:127–32. [CrossRef][PubMed]

12. Sturm H, AustvollDahlgren A, Aaserud M, et al. Pharmaceutical policies: effects of financial incentives for prescribers. Cochrane Database Syst Rev. 2011;10:CD006731.

13. O'Neal BC, Couldry RJ, Wilkinson ST, et al. Leveraging drug-utilization and external benchmarking data to drive change in prescribing behaviors. Am J Health Syst Pharm. 2012;69:1916–22.
[CrossRef][PubMed]

14. American Pharmacists Association. Specialty pharmacy: a unique and growing industry. 2013. Retrieved from American Pharmacists Association http://www.pharmacist.com/specialty-pharmacy-unique-and-growing-industry.

15. U.S. Food and Drug Administration. A brief overview of risk evaluation and mitigation strategies. n.d. Retrieved from U. S. Food and Drug Administration: http://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM328784.pdf.

16. Academy of Managed Care Pharmacy. Maintaining the affordability of the prescription drug benefit: how managed care organizations secure price concessions from pharmaceutical manufacturers. n.d. Retrieved from Academy of Managed Care Pharmacy: http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=9299.

17. National Home Infusion Association. Infusion FAQs. n.d. Retrieved from National Home Infusion Association. http://www.nhia.org/faqs.cfm.

18. Centers for Medicare and Medicaid Services. Linking quality to payment. n.d. Retrieved from Medicare.gov. https://www.medicare.gov/hospitalcompare/linking-quality-to-payment.html.

19. U.S. Office of Personnel Management. OPM.gov. n.d. Retrieved from Frequently Asked Questions. https://www.opm.gov/faqs/QA.aspx?fid=fd635746-de0a-4dd7-997d-b5706a0fd8d2&pid=162b86b1-5da8-45dc-ab32-3385f17e3460.

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_26

26. Laboratory Utilization Management in Canada

Christopher Naugler[1]

(1) Departments of Pathology and Laboratory Medicine and Family Medicine, Cumming School of Medicine, University of Calgary, C414, Diagnostic and Scientific Centre, 9, 3535 Research Road NW, Calgary, AB, Canada, T2L 2K8

Christopher Naugler
Email: Christopher.Naugler@cls.ab.ca

Keywords Clinical pathology – Clinical biochemistry – Hematology – Health economics – Utilization management – Clinical practice guidelines – Laboratory funding – Value in health care

Introduction

Canada has a long history of interest in the overuse of laboratory tests, dating back to at least 1965 when Dr. H.E. Emson drew attention to unsustainable increases in laboratory test volumes in Saskatoon, Saskatchewan [1]. A few years later, Korvin and Pearce [2] pointed out the potential waste associated with indiscriminate laboratory screening and argued that screening tests were generally unnecessary if the chance of a positive result was either very high or very low. The following year, Dr. M. Rang coined “The Ulysses Syndrome ” to refer to the overuse of medical testing and the associated medical misdirection [3]. The eponym refers to Homer’s *Odyssey*, where Ulysses undergoes a series of pointless misadventures only to arrive back 20

years later to where he started. The Ulysses Syndrome has since become an apt metaphor to describe the pointless and sometimes harmful practice of over ordering of laboratory tests. “The etiology of the syndrome ,” Rang argued, “is attributable to a meritorious desire to investigate the patient fully, the pathogenesis [is attributable] to gullibility” [3]. These authors and others have raised the important issue of false positive results in healthy patients receiving tests with a low-pre-test probability. False positive test results are an important harm to over-testing as they may lead to further unnecessary testing, diagnostic procedures, and patient distress.

It is often stated that 80 % of the costs of health care are driven by decisions made by health care providers. Although lacking in empirical evidence, this axiom is in line with the shared experiences of health care leaders. Taken in this context, the interest in utilization management in Canada is perhaps not surprising given that laboratory testing in Canada is publically funded. Despite the level of interest in utilization management, however, the public nature of health delivery has opened the door for political interference in utilization management decisions in Canada. The politicized nature of health delivery along with the siloed nature of health care funding has further reduced the potential value of utilization management initiatives. To understand the opportunities and challenges for utilization management in Canada it is therefore important to first understand how laboratories are funded in Canada. In this chapter I first provide an overview of laboratory funding in Canada and information on current test ordering practices in Canada. I then briefly discuss the history of utilization management as well as current initiatives in Canada. Finally, I discuss potential future directions for utilization management.

Laboratory Funding Models in Canada

Canadian health care systems have a number of important differences compared to their US counterparts. Therefore a brief review of Canadian laboratory funding models will be useful in putting utilization management efforts in context. The most important of these differences is the lack of private insurance involvement in Canadian laboratory testing. Although there is considerable private payer and insurance paid involvement in Canada, physician fees and medically necessary diagnostic testing are not within the scope of private insurance and are essentially all publically funded. Another

important difference is the lack of integrated accountable care-type organizations in Canada. The lack of accountability among different delivery arms of health care in Canada means that in practice funding exists in “silos” that resist the efficient redistribution of health care dollars.

The overarching health legislation in Canada is the *Canada Health Act* , which states that medically necessary services must be publically insured. This includes medically necessary laboratory testing. Although the *Canada Health Act* is a piece of federal legislation, the actual delivery of healthcare in Canada is a provincial/territorial responsibility. This means that there are actually 13 different laboratory funding systems in place, a different one for each province and territory.

This has created is a patchwork of laboratory testing delivery models across Canada with some provinces offering testing only through hospital laboratories while others have a mixture of hospital laboratories and community laboratories. Likewise some provinces have only publically owned laboratories while others have a mixture of public and private laboratories. Regardless of the service delivery model, the vast majority of laboratory testing in Canada is ultimately publically funded. Laboratories may augment their incomes with non-insured or so-called third party work (for example, research testing, employer-sponsored testing, etc.) but this typically makes up only a small portion of laboratory budgets. A summary of current provincial funding models for laboratories is given in Table 26.1.

Table 26.1 Overview of laboratory funding models in Canada (after Ndegwa [4] and Bayne [5])

Jurisdiction	Summary of funding model
Newfoundland and Labrador	Testing available only at publically funded hospital laboratories
Nunavut	Testing available only at publically funded hospital laboratories
Northwest Territories	Testing available only at publically funded hospital laboratories
Yukon Territory	Testing available only at publically funded hospital laboratories
Prince Edward Island	Testing available only at publically funded hospital laboratories
Nova Scotia	Testing available only at publically funded hospital laboratories
New Brunswick	Testing available only at publically funded hospital laboratories
Quebec	Testing available only at publically funded hospital laboratories
Ontario	Mix of public and private laboratories. Reimbursement to private laboratories is capped
Manitoba	Mix of public and private laboratories. Reimbursement to private laboratories is capped

Saskatchewan	Mix of public and private laboratories. Reimbursement to private laboratories is capped
Alberta	Mix of public and private laboratories. Reimbursement to private laboratories is capped
British Columbia	Mix of public and private laboratories. Reimbursement to private laboratories is capped

The salient point from this comparison is that essentially all laboratory testing in Canada is publically funded. In fact, even private laboratories are funded ultimately by provincial departments of health. This model has resulted in often weak incentives to develop utilization management programs as the savings are generally not realized by the laboratories themselves but rather by the provincial funding agencies that provide funding to the laboratories. In the situation of private laboratories in Canada, their ongoing funding levels are often tied to testing volumes meaning that a reduction in testing would also result in a reduction in future government payments.

Direct government funding of laboratories has also resulted in the opportunity for utilization management initiatives to be met with public complaints of disenfranchisement directed toward provincial governments. The resulting political pressure has at times resulted in laboratories to not following through on planned utilization management initiatives. This is illustrative of a common dynamic in Canadian health care where there is simultaneous pressure to mitigate rising costs as well as pressure to maintain all current services, even when certain ones are not evidence-based or cost-effective. Laboratory testing has certainly not been spared from this problem.

Historical and Current Landscape of Utilization Management in Canada

As noted earlier, the issue of unsustainable increases in laboratory testing volumes was first raised almost 50 years ago by Dr. H. E. Emson [1] who wrote that the “present systems of hospital financing are not designed to cope adequately with such a rapidly expanding part of the hospital service.” The public nature of laboratory funding in Canada has both encouraged utilization management by removing profit-driven incentives to over-order tests and at the same time has politicized the delivery of health care, which has

discouraged initiatives that may be publically unpopular.

The summation of these factors appears to have resulted in laboratory utilization rates that are roughly on par with the USA [6]. That is to say that inappropriate laboratory test utilization is widespread in Canada, as it is in the USA [7–14]. Many attempts at utilization management in Canada have gone undocumented but a modest literature exists on a variety of prior utilization management programs [15]. For example, audit and feedback has been shown in several studies to have decreased laboratory utilization [16, 17]. However Canadian data suggests that administrative interventions such as removal of tests from requisitions [12], test requisition redesign [11], removal of funding for the test in question [12], and pathologist vetting of esoteric tests [18] are far more effective. An environmental scan of current Canadian utilization management initiatives, most of them unpublished, has recently been completed by the Canadian Agency for Drugs and Technologies in Health [18].

Since its launch in April 2014, the Canadian discussion surrounding unnecessary medical tests and procedures has largely centered on the recommendations of Choosing Wisely Canada (CWC) . CWC is loosely based on the Choosing Wisely campaign in the USA. The Canadian iteration, organized by Dr. Wendy Levinson in partnership with the Canadian Medical Association, asks Canadian National Specialty Societies to develop lists of "Five Things Physicians and Patients Should Question." According to CWC, "These lists identify tests, treatments or procedures commonly used in each specialty, but are not supported by evidence, and/or could expose patients to unnecessary harm" (www.choosingwiselycanada.org, accessed 15 Aug 2015). Because healthcare in Canada is a provincial/territorial responsibility, each province is developing its own implementation strategies for the Choosing Wisely Canada recommendations. These are supported nationally through a website and smartphone app. At the time of writing, more than 150 recommendations have been released. The initial CWC laboratory testing recommendations were provided by the Canadian Association of Pathologists and are listed in Table 26.2.

Table 26.2 Laboratorily-related Choosing Wisely Canada recommendations (current to August 2015)

Don't perform population-based screening for 25-OH-Vitamin D deficiency
Don't screen women with Pap smears if under 21 years of age or over 69 years of age
Avoid routine preoperative laboratory testing for low risk surgeries without a clinical indication

Avoid standing orders for repeat complete blood count (CBC) on inpatients who are clinically/laboratorily stable
Don’t send urine specimens for culture on asymptomatic patients including the elderly, diabetics, or as a follow-up to confirm effective treatment

A common problem with many CWC recommendations is that there is not readily accessible data with which to monitor the effectiveness of management interventions. CWC has recognized the need to improve data on utilization rates and in 2015 partnered with the *Canada Health Infoway* to challenge health care researchers across Canada to contribute data on health care (including laboratory) utilization. Canada Health Infoway is an independent, federally funded, not-for-profit organization tasked with accelerating the development of electronic health records (EHR) across Canada (www.infoway-inforoute.ca/en/, accessed 15 Aug 2015).

Current Canadian Laboratory Testing Ordering Practices

Similar to laboratories in other developed countries, Canadian laboratories have seen annual increases in the range of 6–8 % resulting in a predicted doubling or tripling of laboratory test volumes by 2036. Chemistry tests have seen the biggest increases both in absolute terms and in per capita test volumes. The estimated current and future Canadian test volumes were modelled by Rockey et al. [19]. Their projections are given in Fig. 26.1.

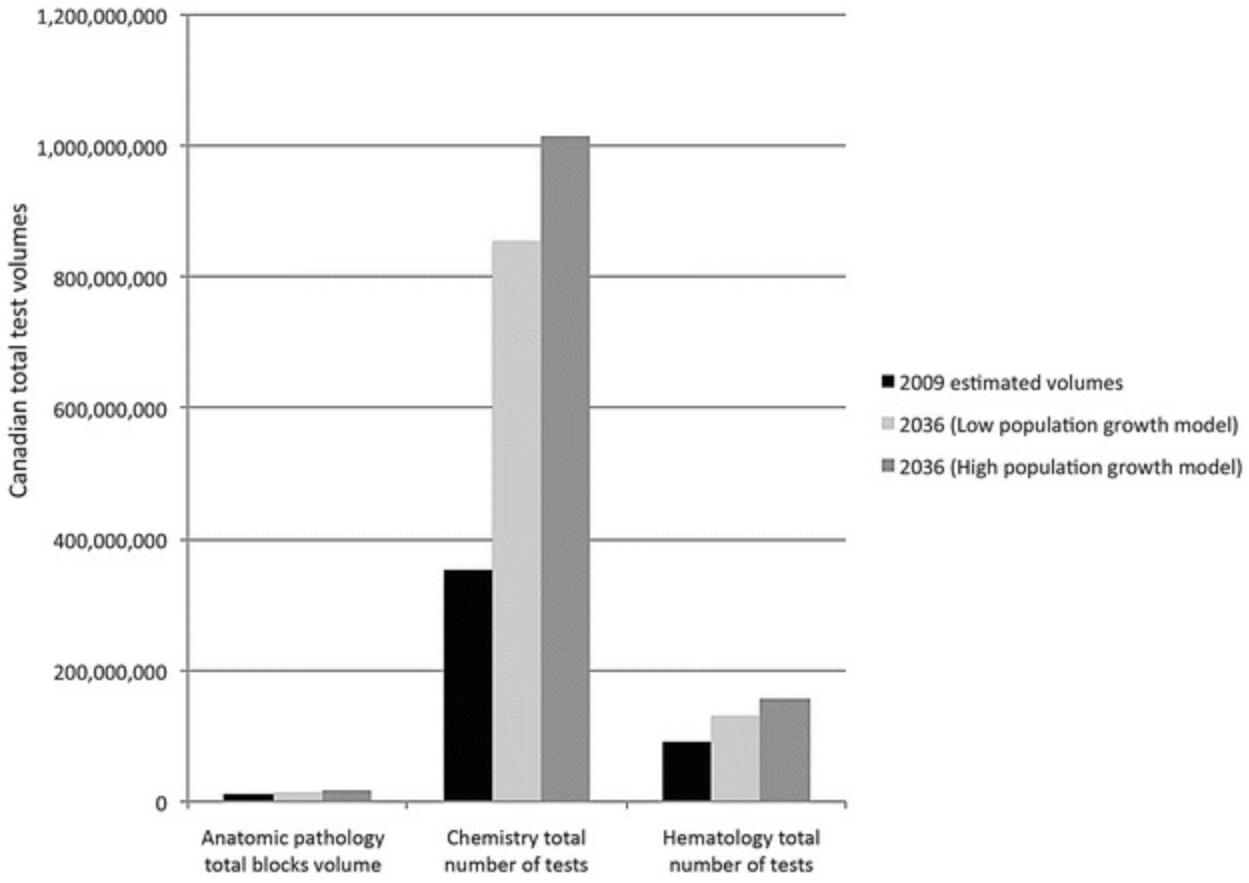


Fig. 26.1 Estimated current and future Canadian test volumes for anatomic pathology, chemistry, and hematology . Future growth is modelled under both low population growth and high population growth scenarios based on Census Canada predictions (see Rockey et al. [19] for more details)

Utilization of laboratory testing by individual physician specialty groups was further modelled for the City of Calgary Alberta by Naugler et al. [20]. They examined all tests ordered in their laboratory information system for the 2013/14 fiscal year (April 1, 2013 to March 31, 2014). Because their laboratory (Calgary Laboratory Services) is the sole provider of clinical laboratory tests for the entire City of Calgary , this information represented the complete testing picture for this population. Genetic testing was not included in this analysis as this testing was partially completed by Calgary Laboratory Services and partly by other provincial laboratories. Therefore the study included only chemistry, hematology , and microbiology tests. These tests were attributed to the 3499 individual physicians in the city who ordered at least one test during the study year. These physicians were then divided into 30 medical specialty groups. Finally, costs of laboratory testing per physician and per physician group were calculated based on median test costs

obtained from data from 10 Canadian laboratories. Based on this analysis, the average cost attributed to all physicians was 27,945 $CAD per year. Numerically, family physicians (often referred to as primary care physicians in Canada) accounted for 44 % of physicians who ordered laboratory tests during the study period but accounted for well over half of the costs of laboratory tests. The yearly percentage of laboratory costs for the top 10 specialties by cost is listed in Table 26.3.

Table 26.3 Utilization of laboratory tests by cost for the top 10 specialty groups in Calgary, Alberta, Canada [19]

Specialty group	Proportion of total laboratory testing expenditures (%)
Primary care (family medicine)	58.5
Internal Medicine	8.9
Emergency Medicine	4.5
Hematology	3.8
Pediatrics	3.4
Obstetrics and gynecology	3.3
Cardiology	2.8
Nephrology	2.4
Gastroenterology	2.2
General surgery	2.0

The most striking finding from this study was that laboratory testing decisions made by family physicians are far more important than any other specialty group, and indeed more important than all other specialty groups combined. Therefore any utilization management initiatives intended to have a major impact on overall laboratory costs must consider family physicians and preferably should have family physicians involved in the planning stages.

Few attempts have been made to quantify inappropriate laboratory test ordering rates in Canada. In particular, little direct evidence exists on rates of test ordering in variance with clinical practice guidelines in Canada. There is, however, some data on rates of repeat test orders. Van Walraven and Raymond [21] reported an overall repeat testing rate of 30 % within 1 month using laboratory data from Eastern Ontario. Morgen and Naugler [22] reported similar retesting rates in a population-based study in Calgary, Alberta. In this study, the authors further examined six tests (cholesterol, HbA1c, TSH, vitamin B12, vitamin D, ferritin) where either consensus-based or easily justified criteria could be used to define inappropriately repeated

tests. They reported that 16 % of repeats for these tests within a 1-year period were inappropriate. This translated to a population-scaled yearly cost for Canada of up to CDN $160 million.

Future of Utilization Management in Canada

Given the identified challenges to utilization management in Canada combined with the importance of family physicians as the primary utilizers of laboratory testing, a working group meeting sponsored by the Canadian Agency for Drugs and Technologies in Health (CADTH) was held in 2015 to discuss strategies for engaging family doctors in laboratory utilization management [23]. The workshop addressed two main questions: (1) what is the best way to engage primary care physicians in utilization management initiatives, and (2) which initiatives are most likely to succeed?

The working group produced a summary of the barriers and suggested potential solutions to engaging primary care physicians in utilization management , which is given in Table 26.4. Three strategies emerged by consensus as clearly having the highest acceptability to primary care physicians. First, a multi-pronged education approach customized to each stakeholder group; second, physician laboratory test audit and feedback; and third, a shared savings program for re-investment of utilization management savings (Table 26.5) . In a shared savings model, the physicians themselves would be primarily responsible for carrying out the utilization interventions and an independent third party would audit the effectiveness of the interventions. A proportion of any realized savings would be retained by the laboratory and a portion would be given to the participating primary care groups for use in their own defined health system priorities. It is recognized that this last recommendation would necessarily involve a coordinated effort among health system payers, clinical laboratories, and primary care clinical practice groups.

Table 26.4 Summary of barriers and potential solutions to engaging primary care physicians in laboratory testing issues as identified by the participant workshop

Identified barrier	Suggested solutions
Primary care generally not involved in planning interventions	Laboratories should ensure that primary care representatives are involved in all aspects of planning and evaluating utilization management interventions
Lack of positive incentives	Laboratories and health system payers should explore models of sharing

for physicians to participate	savings with primary care groups
Ordering a lab test is often a time-saver	Adequate IT supports must be in place to allow physicians to easily check previous results instead of re-ordering tests. Significant support needed to educate both physicians and patients on tests appropriate for a given clinical scenario
There are many other quality improvement initiatives competing for primary care engagement	Laboratory utilization initiatives need to be critically examined in the context of competing priorities by primary care groups
There is a perceived lack of support from government	Health system payers and leaders need to be educated and engaged in utilization management strategies. There needs to be support from elected officials when unpopular strategies are implemented
Patients do not understand the risks inherent in testing	Patient-focused education campaigns are needed
Limited access to data on laboratory testing practices	Laboratories and health funders must make investments in providing individual and group level data on ordering practices
Lack of testing guidelines in many areas of clinical practice	Specialty groups, primary care physicians, and laboratories should all contribute to guidelines for optimal laboratory test use
Lack of understanding as to why lab tests are ordered in individual circumstances	Research must be directed to better understand the drivers of laboratory test ordering
There is a lack of established mechanisms to communicate directly with the public at large	System-wide communication strategies are needed to communicate optimal laboratory test use directly to the public
Lack of knowledge among physicians on optimal use of laboratory testing	Undergraduate training for students and CME for practising physicians

Table 26.5 Recommendations from the Canadian working group on engaging primary care physicians in laboratory utilization management

A multi-pronged education approach customized to each stakeholder group should form part of any utilization management initiative
Laboratory test audit and feedback to individual physicians is both relatively effective and highly acceptable to family physicians and should be one of the first utilization management initiatives considered
Health system payers should consider entering into shared savings agreements with family physician practice groups for re-investment of any realized savings into defined health system priorities
These recommendations could serve as a framework for laboratories to begin discussions on this important topic with family physician groups
Gaps in our current knowledge should be addressed through collaborative research between primary care and laboratory researchers

A number of gaps still exist in both our knowledge of the definition of optimal laboratory utilization and in our ability to initiate and sustain meaningful utilization management initiatives. Verbrugghe [24] identified four important barriers to laboratory utilization optimization initiatives in Canada: (1) lack of infrastructure to deal with laboratory big data, (2) lack of interoperability of existing data systems, (3) logistic and regulatory difficulties, and (4) a lack of engagement from physicians and other key stakeholders. Some progress is being made on these issues in various jurisdictions in Canada. For example, a number of Canadian provinces have undertaken the construction of integrated laboratory test databases. These will provide a rich source of data on current laboratory testing practices and will serve as baseline comparisons against which to measure the effectiveness of future initiatives. Several initiatives are also underway, particularly in Ontario and Alberta, to develop capacity to perform big data analytics on laboratory data (see Mohammed et al. [25]).

While the technical and regulatory hurdles appear to be solvable, challenges remain with regard to stakeholder engagement. It was clear from the working group meeting described earlier that family physician engagement remains one of the key challenges. This physician group, perhaps more than any other is feeling pressure from multiple sources to do more with less, while simultaneously facing challenges of keeping up to date with new guidelines and recommendations in different areas of practice. Given the competing demands on family physicians' time it is not surprising that there has often been less than enthusiastic uptake of utilization management initiatives that will inevitably interfere with the established practice patterns of family physicians.

Another important knowledge gap is in regard to the identification of suboptimal laboratory test ordering practices. Prior reviews have suggested that compliance with clinical practice guidelines is the most objective criteria by which to judge appropriateness [10, 26]. However, this approach suffers from the limitations that clinical practice guidelines don't exist for most laboratory tests, often vary by jurisdiction, or require clinical information generally not available to laboratories. Morgen and Naugler [22] argue that tests with definable criteria for inappropriate repeat testing provide an alternative objective measure of repeat testing. Apart from these examples, there is a further need to define other potential markers of suboptimal ordering practices. One promising approach is to look for test ordering

practices with a wide variance among practitioners, as these are considered in other areas of medicine to represent opportunities for standardization of practice [27–34]. Despite the previous demonstration of unexplained variation in laboratory test ordering practices [29, 35], the idea of identifying practice variation in laboratory test ordering as a quality measure is only beginning to be explored in laboratory medicine. Mohammed et al. [36] present a method for converting individual test volumes from physicians into z-scores and then using these to compare the laboratory test utilization of individuals to a defined peer group. While such a metric would not definitively identify inappropriate ordering practices, it would allow individual benchmarking of physician practices against their peer group and could form part of an audit and feedback program.

Finally, there is a general lack of evidence regarding the effectiveness of specific utilization management initiatives in Canada. Indeed, very little guidance exists as to which types of utilization management initiatives should be employed in specific circumstances. There is a great need in Canada for research to address these knowledge gaps. There is also a need for leadership from academia, provincial departments of health and physician leadership groups to create the necessary environment and supports to enable the optimization of laboratory testing in Canada.

References

1. Emson HE. The growth of a laboratory. Can Med Assoc J. 1965;93:211–8. [PubMed][PubMedCentral]

2. Korvin CC, Pearce RH. Laboratory screening. A critical survey. Can Med Assoc J. 1971;105:1053–5. [PubMed][PubMedCentral]

3. Rang M. The Ulysses syndrome. Can Med Assoc J. 1972;106:122–3. [PubMed][PubMedCentral]

4. Ndegwa S. Funding of laboratory testing in Canada [environmental scan, issue 19]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2011.

5. Bayne L. BC laboratory services review [Internet]. In: Victoria (BC): British Columbia. Ministry of Health Services; 2003 July [cited 2011 Feb 17]. Available from http://www.health.gov.bc.ca/library/publications/year/2003/lab_review.pdf

6. Katz SJ, McMahon LF, Manning WG. Comparing the use of diagnostic tests in Canadian and US

hospitals. Med Care. 1996;34:117–25.
[CrossRef][PubMed]

7. McNeely MD. The use of ordering protocols and other maneuvers: the Canadian experience. Clin Lab Med. 2002;22:505–14.
[CrossRef][PubMed]

8. Lyon AW, Greenway DC, Hindmarsh JT. A strategy to promote rational clinical chemistry test utilization. Am J Clin Pathol. 1995;103:718–24.
[CrossRef][PubMed]

9. van Walraven C, Goel V, Austin P. Why are investigations not recommended by practice guidelines ordered at the periodic health examination? J Eval Clin Pract. 2000;6:215–24.
[CrossRef][PubMed]

10. van Walraven C, Naylor CD. Do we know what inappropriate laboratory utilization is? A systematic review of laboratory clinical audits. JAMA. 1998;280(6):550–8.
[CrossRef][PubMed]

11. Hindmarsh JT, Lyon AW. Strategies to promote rational clinical chemistry test utilization. Clin Biochem. 1996;29:291–9.
[CrossRef][PubMed]

12. van Walraven C, Goel V, Chan B. Effect of population-based interventions on laboratory utilization: a time-series analysis. JAMA. 1998;280:2028–33.
[CrossRef][PubMed]

13. Laupland KB, Church DL, Gregson DB. Blood cultures in ambulatory outpatients. BMC Infect Dis. 2005;5:35.
[CrossRef][PubMed][PubMedCentral]

14. Huang SJ, McMahon LF, Manning WG. Comparing the use of diagnostic tests in Canadian and US hospitals. Med Care. 1996;34:117–257.
[CrossRef]

15. Naugler C. A perspective on laboratory utilization management from Canada. Clin Chim Acta. 2014;427:142–4.
[CrossRef][PubMed]

16. Huang Y, Don-Wauchope AC, Grey VL, Mansour M, Brill H, Armstrong D. Improving serological test ordering patterns for the diagnosis of celiac disease through clinical laboratory audit of practice. Clin Biochem. 2012;45:455–9.
[CrossRef][PubMed]

17. Bunting PS, Van Walraven C. Effect of a controlled feedback intervention on laboratory test ordering by community physicians. Clin Chem. 2004;50:321–6.
[CrossRef][PubMed]

18. Liu Z, Abdullah A, Baskin L, Lewis G, Kelter G, Naugler C. An intervention to reduce laboratory utilization of referred out tests. Lab Med. 2012;43:9–12.
[CrossRef]

19. Rockey MJ, Naugler C, SIdhu D. Laboratory test utilization trends: past and future. Can J Pathol. 2013;5:65–71.

20. Naugler C, Thomas R, Turin TC, Guo M, Vaska M. Yearly clinical laboratory test expenditures for different medical specialties in a Canadian city. Am J Clin Pathol. 2015;144:1–6. [CrossRef]

21. van Walraven C, Raymond M. Population-based study of repeat laboratory testing. Clin Chem. 2003;49:1997–2005. [CrossRef][PubMed]

22. Morgen E, Naugler C. Inappropriate repeats of six common laboratory tests in a Canadian City. Am J Clin Pathol 2015;144:704–712.

23. Thommason A, Clement F, Kinniburgh DW, Lau CK, Guo M, Viczko J Kelly Guggisberg K, Thomas RE, Turin TC, Wesenberg JC, Abdullah A, Hnydyk WS, Crain J, Zimmerman G, Naugler C. How do we engage family physicians in laboratory utilization management? Report from a working group meeting, 20 Feb 2015. Report available from the author.

24. Verbrugghe S. Initiatives to optimize the utilization of laboratory tests. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2014 (Environmental Scan; issue 44).

25. Mohammed EA, Far BH, Naugler C. Applications of the MapReduce programming framework to clinical big data analysis: current landscape and future trends. BioData Min. 2014;7:22. [CrossRef][PubMed][PubMedCentral]

26. Hauser RG, Shirts BH. Do we now know what inappropriate laboratory utilization is? An expanded systematic review of laboratory clinical audits. Am J Clin Pathol. 2014;141:774–83. [CrossRef][PubMed]

27. Wennberg JE. Understanding geographic variations in health care delivery. N Engl J Med. 1999;40:52. [CrossRef]

28. Wells RD, Dahl B, Nilson B. Comparison of the levels of quality of inpatient care delivered by pediatrics residents and by private, community pediatricians at one hospital. Acad Med. 1998;73:192–7. [CrossRef][PubMed]

29. Welch WP, Miller ME, Welch HG, et al. Geographic variation in expenditures for physicians' services in the United States. N Engl J Med. 1993;328:621–7. [CrossRef][PubMed]

30. Wahlström R, Hummers-Pradier E, et al. Variations in asthma treatment in five European countries —judgement analysis of case simulations. Fam Pract. 2002;19:452–60. [CrossRef][PubMed]

31. Ashton CM, Petersen NJ, Souchek J, et al. Geographic variations in utilization rates in Veterans Affairs hospitals and clinics. N Engl J Med. 1999;340:32–9. [CrossRef][PubMed]

32. Meade MO, Jacka MJ, Cook DJ, et al. Survey of interventions for the prevention and treatment of

acute respiratory distress syndrome. Crit Care Med. 2004;32:946–54.
[CrossRef][PubMed]

33. Christakis DA, Cowan CA, Garrison MM, et al. Variation in inpatient diagnostic testing and management of bronchiolitis. Pediatrics. 2005;115:878–84.
[CrossRef][PubMed]

34. Luft HS, Bunker JP, Enthoven AC. Should operations be regionalized? The empirical relation between surgical volume and mortality. N Engl J Med. 1979;301:1364–9.
[CrossRef][PubMed]

35. Busby J, Schroeder K, Woltersdorf W, et al. Growth and geographic variation in the use of laboratory tests by NHS general practices: using routine data to identify research priorities. Br J Gen Pract. 2013;63:e256–66.
[CrossRef][PubMed][PubMedCentral]

36. Mohammed AA, Naugler C, Far BH. Emerging business intelligence framework for a clinical laboratory through big data analytics. In: Tran QN, Arabnia H, editors. Emerging trends in computational biology, bioinformatics, and systems biology: algorithms and software tools. New York: Elsevier/MK; 2015. p. 577–602.
[CrossRef]

Kent Lewandrowski and Patrick M. Sluss (eds.), Utilization Management in the Clinical Laboratory and Other Ancillary Services, DOI 10.1007/978-3-319-34199-6_27

27. Utilization Management Initiatives That Can Be Imported into Healthcare Systems

Patrick M. Sluss[1]

(1) Pathology Service Core Laboratories, Massachusetts GeneralHospital, Gray Bldg., Room 554, 55 Fruit St., Boston, MA 02114, USA

Patrick M. Sluss
Email: sluss.patrick@mgh.harvard.edu

The purpose of this chapter is to provide a roadmap of utilization management content so that the reader can identify the location of recommendations for utilization topics that are described in this book. These recommendations and discussions provide guidance to the reader in developing specific utilization initiatives in their institutions. Topics have been arranged alphabetically. The list of recommendations described below supplements other lists of utilization management initiatives referenced in the individual chapters such as the National Physicians Alliance Promoting Good Stewardship in Medicine Choosing Wisely Campaign.

- 25 Hydroxy-Vitamin D testing; not recommended for population based screening in Canada: Chap. 26
- Accountable care organizations in Canada: Chap. 26
- Albumin therapy ; utilization management: Chap. 12

- Drug utilization management; in-patients: Chap. 25
- Drug utilization management ; managed care pharmacies: Chap. 25
- Drug utilization management; out-patient pharmacy services: Chap. 25
- Drug utilization; strategies for clinical and financial management: Chap. 25
- Ehrlichia and Anaplasma serology; physician profiling with decision support: Chap. 13
- Eliminating a panel of tests: Chap. 6
- Eliminating a reference laboratory test: Chap. 6
- Eliminating an expensive test (e.g., genetic test): Chap. 6
- Eliminating bleeding time testing: Chap. 10
- Eliminating iron binding capacity testing: Chap. 10
- Eliminating one test for a panel of tests: Chap. 6
- Eliminating same-day duplicate tests: Chap. 2
- Eliminating unnecessary tests: Chap. 9
- Email to Individual Providers: Chap. 2
- Establishing a diagnostic management team in hematopathology: Chap. 17
- Establishing a diagnostic management team reduced total tests/marrow by 26 % annually: Chap. 17
- Establishing clinical guidelines to support the decision to transfuse: Chap. 11
- Establishing guidelines for infectious disease diagnostic testing: Chap. 13
- Establishing guidelines for special studies including immunohistochemistry: Chap. 16
- Exome sequencing (Clinical); extract and hold policy: Chap. 20
- Exome sequencing (Clinical); use of sub-committee review of orders:

Index

A

B

C

D

E

Electronic data systems
Electronic health records (EHRs)
Electronic laboratory handbook
Electronic medical records (EMR) system
Electronic ordering systems
Electronic orders and decision support
ELISA
Emergency department (ED)
Emergency Medicine
End-stage renal disease (ESRD)
Enterobacter cloacae
Enterococcus
Enterovirus
Entry screen design
Enzymes
Erythrocyte sedimentation rate
Erythropoiesis-stimulating agents (ESAs)
Esoteric drugs
Estimated glomerular filtration rate (eGFR)
Evidence-based peer-reviewed literature
Evidence-based transfusion thresholds
Exempt for submission policies
Exome sequencing
Expenses and source of data
External benchmarking tool
External quality assessment (EQA) proficiency testing

F

Fabry disease
Fabry testing with pop-up reminder
Facilitated networks
Factor VIII Bypass Inhibitor Activity (FEIBA)
False positive tests
Familial adenomatous polyposis (FAP)
Fear of harassing
Fear of litigation
Fee-for-service system

G

H

I

J

K

L

M

N

Nanosphere, Inc.
Nasal mupirocin
National Blood Collection and Utilization Survey (NBCUS)
National Drug Code (NDC)
National Glycohemoglobin Standardization Program (NGSP)
National Medicare laboratory
National pathologist professional organizations
National Society of Genetic Counselors (NSGC)
NBCUS survey
NCBI Online Mendelian Inheritance in Man (OMIM) database
Negative institutional savings
Negative predictive value (NPV)
Neonatal intensive care units (NICU)
Neoplastic hematopathology
Neutropenia
New test proposal
Newborn genetic screening
Next-generation sequencing
Nisseria gonorrhoeae (NG)
Nitric oxide (NO)
No overt disease
Nonacademic laboratories
Non-blinded report cards
Nongeneticists
Noninvasive prenatal testing (NIPT)
Non-laboratory resource utilization
Nonselective preoperative testing
Non-ST-segment-elevation myocardial infarction (NSTEMI)
Non-test-related activities
Non-turnaround time-dependant surgical pathology specimens
Noonan syndrome
Normal antithrombin
North American laboratories
Nosocomial diarrheal illness
Novel anticoagulants

O

P

Q

R

S

T

U

V

W