Cost-Effectiveness of Laboratory Testing

James S. Hernandez, MD, MS

Objective.—To illustrate how laboratorians and pathologists must demonstrate accountability for efficiency (how well something is done), effectiveness (what is done), and cost-effectiveness (a proxy for value, in which value equals quality per cost).

Data Sources.—A literature search was conducted, including documents in the National Library of Medicine.

Study Selection.—The literature on cost-effectiveness of laboratory testing was reviewed.

The costs of caring for an increasingly older population of patients with chronic illnesses are stressing the US health care system. Many of these patients require laboratory tests to detect and to monitor diseases. In addition, the demand for medical technology is largely driven by an insatiable quest to detect diseases earlier. The genomic revolution will undoubtedly fuel the demand for sophisticated medical technology. A savvy, health-conscious population will want access to the emerging technologies at an earlier stage. Payers, including Medicare, commercial insurers, and employers, want more accountability for both safety and quality. The demand for proving the value of medical interventions, including laboratory testing, will soar.

Much of the demand for medical care begins with diagnoses that depend on laboratory testing. Along with expenditures for imaging studies, laboratory testing accounts for a significant percentage of health care expenses, despite efforts by Medicare and commercial insurers to limit payments for laboratory testing. It is no longer sufficient for laboratories to provide efficient testing. Increasingly, payers demand to know the value of the tests, with value equaling quality per unit of cost. Payers want laboratories to prove that tests are cost-effective. Physicians are asked to eliminate overuse and misuse of laboratory tests.

This article includes an in-depth review of the literature on cost-effectiveness of laboratory testing and an expository model for assessing the value of newer laboratory tests. The analysis asks the basic question, “Who determines the value of laboratory testing?”

REVIEW OF THE LITERATURE ON COST-EFFECTIVENESS

Relatively few studies address the cost-effectiveness of laboratory testing. Unlike the literature of cardiology, general internal medicine, family practice, and radiology, laboratory medicine and pathology literature is a difficult source in which to find articles that address both clinical efficacy and cost-effectiveness. In the past, laboratorians and pathologists believed that striving for maximal sensitivity, specificity, accuracy, and reliability was sufficient and that clinicians would not want anything more from the laboratory. Few articles in the laboratory medicine literature address broader issues, such as cost-effectiveness, especially cost-effectiveness beyond dealing with direct and indirect costs in the laboratory.

It is critical for physicians to think broadly and strategically. Thinking about how laboratory tests affect the practice of medicine should be based on sound principles delineated in the medical and medical decision-making literature. Three previous articles have addressed the efficacy and cost consequences of laboratory testing: “The Efficacy of Diagnostic Imaging,” by Fryback and Thornbury; “Use of Methodological Standards in Diagnostic Test Research: Getting Better but Still Not Good,” by Reid et al; and “Estimating Diagnostic Accuracy From Multiple Conflicting Reports: A New Meta-analytic Method,” by Littenberg and Moses. These articles give physicians new tools with which to think more broadly about the effect of laboratory tests on the practice of medicine. The first and the third articles are from the medical decision-making literature, and the second article is from the general medical literature.

The first article, by Fryback and Thornbury, deals with efficacy in testing. Although diagnostic imaging is addressed, the principles are pertinent to laboratory medicine and testing. Fryback and Thornbury lay out sound principles for assessing the contribution of testing in patient care. The article provides an analytic infrastructure of 6 levels to assess the efficacy of testing. Demonstration of efficacy at each lower level in this hierarchy is logically necessary, but not sufficient, to assure efficacy at higher levels (Table 1).

The second article is a scholarly treatise on what constitutes a methodologically sound study. Reid et al ad-
Table 1. Levels Used to Assess Efficacy of Testing in Patient Care

<table>
<thead>
<tr>
<th>Level No.</th>
<th>Variable Evaluated</th>
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<tr>
<td>1</td>
<td>Technical quality</td>
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<tr>
<td>2</td>
<td>Accuracy, sensitivity, specificity</td>
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<tr>
<td>3</td>
<td>Whether test changes referring physician’s diagnostic thinking</td>
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<tr>
<td>4</td>
<td>Effect on patient management</td>
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<tr>
<td>5</td>
<td>Effect on patient outcomes</td>
</tr>
<tr>
<td>6</td>
<td>Effect on societal costs and benefits</td>
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Table 2. Methodologic Standards for Evaluation of Tests

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<th>Standard</th>
<th>How Standard Is Met</th>
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<tr>
<td>1. Spectrum composition</td>
<td>At least 3 of 4 descriptors are provided: age distribution, sex distribution, summary of presenting symptoms or disease stage, or eligibility criteria</td>
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<tr>
<td>2. Analysis of pertinent subgroups</td>
<td>Results of indexes of accuracy are cited for pertinent demographic or clinical subgroup of population</td>
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<tr>
<td>3. Avoidance of workup bias</td>
<td>All subjects in cohort studies are assigned to receive both diagnostic and “best method” verification</td>
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<tr>
<td>4. Avoidance of review bias</td>
<td>For prospective cohort studies in which patients always receive diagnostic test first, credit is given if best available procedures are evaluated independently</td>
</tr>
<tr>
<td>5. Precision of results for test accuracy</td>
<td>Standard errors or confidence intervals are reported for test sensitivity and specificity or likelihood ratios</td>
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<tr>
<td>6. Presentation of indeterminate test results</td>
<td>Study reports all the appropriate positive, negative, and indeterminate results, and whether indeterminate results are included or excluded when indexes of accuracy are calculated</td>
</tr>
<tr>
<td>7. Test reproducibility</td>
<td>For tests requiring observer interpretation, at least some of the test subjects are evaluated for a summary measure of observer variability</td>
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dress the 7 accepted methodologic standards for the evaluation of tests (Table 2). Following their guidelines would eliminate poor or useless tests before they become widely accepted, improve the quality of diagnostic test information, reduce health care costs, and improve patient care.

The third article, by Littenberg and Moses, is also from the medical decision-making literature. Physicians should not get lost in the mathematics. The basic message is a description of the so-called summary receiver operator curve. It is a way to summarize and understand the variety of published reports on diagnostic accuracy. Receiver operator characteristic curves are in common use in laboratories. The article describes case studies and provides guidelines on the use of summary curves. The summary receiver operator curve can be used to understand different tests in the literature that report different accuracy rates.

A search of the laboratory medicine and pathology literature showed that very few articles incorporate the rigor and high standards outlined by these 3 articles to qualify as cost-effectiveness studies. A few examples of articles that represent sound cost-effectiveness studies follow.

In 1999, Boelaert et al described a good cost-effectiveness analysis that included a tree diagram, sensitivity analysis, and plausible ranges for the probability values used in the decision analysis. The analysis included different values for sensitivity and specificity of the proposed test, a serologic direct agglutination test. The proposed test was compared to the standard test, fine-needle aspirate of internal organs, in order to determine the proposed test’s ability to identify the parasite.

Another article, published in 1994 by Phatak et al, used a decision analysis to determine whether screening the population at large for hereditary hemochromatosis would be cost-effective. The study was based on a model that compared the cost and outcome of a strategy of either performing screening transferrin saturation tests on groups of 30-year-old men or waiting for symptoms to appear. Baseline estimates of the prevalence and complication rates for the disease were derived from the literature. Sensitivity analysis showed that 4 variables had the greatest impact on the decision to screen: prevalence of hereditary hemochromatosis, probability of developing the disease manifestations, cost of the screening test, and discount rate.

In this study, screening was a dominant strategy for asymptomatic men, provided that the prevalence of hereditary hemochromatosis was at least 3 per 1000, the probability of developing disease manifestations was greater than .4, the test cost was less than US$12, and the discount rate was less than 3%. The authors recommended screening under these conditions.

One of the best studies on cost-effectiveness was from the Johns Hopkins University Departments of Epidemiology and Health Policy and Management. The goal of the study was to estimate the cost-effectiveness of periodic screening for mild thyroid failure by measurement of the concentration in serum of thyroid-stimulating hormone. The design of the study was a cost-utility analysis with a state-transition computer decision model that accounted for case finding, medical consequences of mild thyroid failure, and costs of care during 40 years of simulated follow-up. The main outcome measures were discounted quality-adjusted life years (QALYs) and direct medical costs from a societal perspective. The results of the model showed that the cost-effectiveness of screening 35-year-old patients with a serum thyroid-stimulating hormone assay every 5 years was $9223 per QALY for women and $22,595 per QALY for men. The cost of the assay and the importance to patients of symptoms associated with thyroid failure were the most influential factors in the sensitivity analysis. The authors concluded that the cost-effectiveness of screening for mild thyroid failure compared favorably with other generally accepted preventive medical practices. The cost-effectiveness of screening is most favorable in elderly women. The analysis included model estimates for base-case and sensitivity analyses that were fairly extensive and thoroughly researched. The study included tables that presented the cost per QALY, the length of time horizon, and the incremental cost and QALY. Interestingly, laboratory testing for mild thyroid failure (subclinical hypothyroidism) in women compared quite favorably with...
breast cancer screening every 2 years between ages 50 and 70 years, and with hypertension screening at age 40 years.

Some other studies in the literature, although not formal cost-effectiveness studies, contribute to how we think about laboratory testing and its impact on patient care. For example, O’Kane et al1 at the Mayo Clinic stated that new test assays should allow the clinician to interact with and treat a patient more effectively. Furthermore, the “new assays should facilitate recapture of system resources, enabling cost savings or reinvestment of resources.” The authors stated,

assays [could] be prioritized for up-grading to newer cost-effective technologies, provided the changes maintain or improve analytical and clinical performance. Predicting which research assay will have future value is difficult when clinical performance is not fully validated.

Wilkinson,6 of the Pathology and Health Administration of the Virginia Commonwealth University, recognized that

the collision of explosive growth in biomedical technology and pressure to contain cost requires that managers of health-care services base decisions to introduce new technology on hard evidence that the benefits outweigh the costs of the new technology. Outcomes research measures the impact of new technology and changes in clinical practice on patient well-being or financial performance.

Wilkinson stated that the systematic collection of data was best done in conjunction with a broader health services research effort that included a multidisciplinary team of laboratorians, clinicians, administrators, and statisticians.

Finally, the literature from the American College of Physicians and the American Society of Internal Medicine offered solutions for thinking about how to resolve the tension between evidence-based medicine and cost-effectiveness. There are similarities between evidence-based medicine and cost-effectiveness. If a treatment is not efficacious (ie, it does more harm than good), it cannot be cost-effective and cost-effectiveness. If a treatment is not efficacious (ie, it does not represent good use of resources).

First, ineffective procedures should be eliminated because they are wasteful of resources. Here, estimates of the extent of the cost consequences may galvanise clinicians and managers to bring about changes in practice.

Second, high-cost treatments should be replaced by others that are equally effective but consume fewer resources. Here, the contribution of evidence-based medicine would be to ensure that the appropriate literature was considered and that spurious claims by manufacturers of expensive health technologies are rebutted.

Third, more debate should occur, probably through discussion of clinical practice guidelines, of the trade-offs between effectiveness and cost. The challenge will be to identify situations where a substantial amount of resources can be saved without seriously compromising the individual clinical ethic. For example, it may be possible to develop protocols that suggest the use of inexpensive technologies as first-line therapy. The evidence on the relative effectiveness and cost-effectiveness of alternative treatments is central to guidelines development. Therefore, it is important that more practitioners of evidence-based medicine accept the social ethic as well as the individual clinical ethic in the interest of providing effective care to more patients.

An article available on the Web site sponsored by the American College of Physicians and the American Society of Internal Medicine addresses the importance of physicians joining the evidence-based movement in medicine by including \( \kappa \) scores. \( \kappa \) scores quantify reproducibility of physicians’ interobserver diagnoses. For example, a \( \kappa \) score of 0 corresponds to agreement no better than chance, whereas 1 is perfect interobserver agreement. In practice, a score above 0.6 is considered “good agreement.” Another important question for physicians to ask themselves is, “How relevant are these features to diagnosis, management, or outcome?”

AN EXPOSITORY MODEL FOR ASSESSING LABORATORY TESTS

One of the most insightful articles in the laboratory medicine literature on the role of assessing the impact of costs is entitled “Public Health Applications of New Laboratory Technologies for Communicable Diseases,” by John Pfister, MS, (AAM), serving as the director of the Wisconsin State Laboratory of Hygiene (WSLH), Public Health Research and Epidemiology Division.

The desire to achieve maximum sensitivity and specificity must be balanced against practical considerations. Not surprisingly, public health department laboratories have run into budget restraints sooner than the laboratories in the private sector. Pfister proposed the following schematic model for weighing the major factors of test assay performance, epidemiology, and costs. He envisioned 3 partly overlapping circles representing assay performance, epidemiology, and costs (Figure).

Assay performance includes the factors that traditionally have been of most importance to laboratorians and pathologists. These are sensitivity, specificity, reproducibility, supplemental testing, quality assurance, and turnaround time. Most laboratories would be quite satisfied if they thought that they were doing their best to maximize these factors. Sometimes laboratorians are tempted to concentrate only on these factors to the exclusion of more practical considerations. This policy was considered sufficient in the past. Nowadays, budget restraints have forced a broader, more global view. Medical directors have been forced to look beyond the walls of the laboratory and examine how the laboratory affects the hospital and the integrated health care system. Many laboratories have
been quite successful in examining the efficiency of their operations. Few have gone further in scrutinizing the effectiveness, especially the cost-effectiveness, of their operations. In other words, many laboratories are doing things as well as can be expected. However, are they doing the right things? Are they offering the tests and algorithms that provide the best value (quality per dollar of cost)?

The second major factor is the epidemiology of the disease or condition. Epidemiology consists of prevalence, clinical setting, and risk indicators, including demographic, behavioral, and clinical variables. These factors can affect how useful the test is in ruling in or ruling out a disease or condition. Where the 2 circles that represent assay performance and epidemiology overlap, Pfister places specimen collection, predictive values, specimen type, symptoms, and gender.

The third major factor is the cost of the test, including both testing costs and nontesting costs. Where cost overlaps with epidemiology, Pfister places selective screening and presumptive treatment. Where cost overlaps with assay performance, he puts instrumentation, throughput, facilities, and personnel.

At the place all 3 circles—assay performance, epidemiology, and cost—overlap, Pfister envisions cost-effectiveness, cost benefit, and cost utility.

This model for assessing newer laboratory tests is particularly germane with the advent of newer technologies that allow timely and accurate identification of organisms. The newer technologic procedures include polymerase chain reaction (PCR), ligase chain reaction, and transcription-mediated amplification. All these newer tests are expensive. How will we assess their value?

Pfister devised 2 new testing strategies for assessing new tests to detect the sexually transmitted disease caused by Chlamydia trachomatis, an increasingly burdensome public health problem. These testing strategies take into account all the factors of assay performance, epidemiology, and costs to make the most judicious use of these newer, expensive tests.

For men, the first testing strategy is to use 3 tests for detecting Chlamydia: urethral swab enzyme immunoassay (EIA), urine EIA, and urine PCR assay. The first 2 tests are less expensive but have lower sensitivity. The PCR test is more expensive but has a higher sensitivity. Since Chlamydia infections are readily curable with currently available antibiotics, maximum sensitivity is desirable. A fourth inexpensive test, urinary leukocyte esterase test, which is not specific for Chlamydia but can assess the acute inflammation expected with Chlamydia, is also used in the testing strategy for Chlamydia in men.

The testing strategy is as follows: selective testing of urine specimens by an amplified molecular assay (urine EIA) replaces WSLH’s current procedure of urethral swab EIA. However, men attending sexually transmitted disease clinics or family planning clinics are tested by PCR or ligase chain reaction (the more expensive, newer tests) if they are at high risk for infection because of symptoms and sexual history. These clinical factors increase the probability of obtaining a true-positive test result. In other words, they increase the positive predictive value of the test because it is used in a population with a higher prevalence of Chlamydia determined by pretest clinical assessment. Men at lower risk are prescreened by the inexpensive urinary leukocyte esterase test, with only leukocyte esterase test—positive urine samples tested for Chlamydia.

For women, the second testing strategy involves continuing WSLH’s current procedure of testing endocervical swabs by EIA. However, the sensitivity of the EIA is increased by PCR or ligase chain reaction testing of residual EIA specimens, because the EIA has many high-negative “gray zone” results, or false-negative results.
Table 3. Questions to Ask for Cost-Effectiveness Analysis

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<thead>
<tr>
<th>Question</th>
<th>Answer</th>
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<tr>
<td>1. Was a well-defined question posed in answerable form?</td>
<td>Did the study examine both costs and effects of services? Did the study involve a comparison of alternatives? Was a viewpoint for the analysis stated, and was the study placed in any particular decision-making context?</td>
</tr>
<tr>
<td>2. Was a comprehensive description of the competing alternatives given?</td>
<td></td>
</tr>
<tr>
<td>3. Was the effectiveness of the program or services established?</td>
<td></td>
</tr>
<tr>
<td>4. Were all the important and relevant costs and consequences for each alternative identified?</td>
<td></td>
</tr>
<tr>
<td>5. Were costs and consequences measured accurately in appropriate physical units?</td>
<td></td>
</tr>
<tr>
<td>6. Were costs and consequences valued credibly?</td>
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<tr>
<td>7. Were the costs and consequences adjusted for differential timing (discounted to present value)?</td>
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</tr>
<tr>
<td>8. Was an incremental analysis of costs and consequences of alternatives performed?</td>
<td></td>
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<tr>
<td>9. Was allowance made for uncertainty in the estimates of costs and consequences?</td>
<td></td>
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<tr>
<td>10. Did the presentation and discussion of study results include all issues of concern to users?</td>
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For both testing strategies, the sensitivity of detecting persons with *Chlamydia* infection is weighed against the cost considerations of the types of tests for identifying *Chlamydia*. For both strategies, sensitivity is plotted against the cost per infection detected. Graphs of this testing can be accessed via the Internet at the WSLH Web site (www.slh.wisc.edu/results/results_old/97.spring/pfister.html).

In my opinion, Pfister’s model is both simple and elegant. It does not discount the traditional procedures that pathologists and laboratory professionals view as good tests. Most laboratories have viewed epidemiology in the purview of the clinicians. With increasing constraints on revenue, laboratories are being asked to help guide the clinicians’ choice of which test to use in which clinical situation. In the public health laboratories, scientists like Pfister can bridge the gap between laboratory science and economics. Seeking the common ground where costs intersect with sound laboratory science and epidemiology, Pfister has demonstrated that laboratories can help clinicians find the laboratory test or pathway that provides the best value.

Formal cost-effectiveness analyses are complex and expensive. The model that Pfister has demonstrated is especially useful for physicians to think about in the era of revenue constraints. In addition, it offers one of the best models synthesizing what we traditionally think of as excellent laboratory medicine ( assay performance) with the practical considerations of costs. It also encourages laboratories to consider the epidemiology of the disease or condition when designing tests and algorithms. Although not a formal cost-effectiveness analysis, the approach by Pfister is easy for any laboratory to incorporate into its design infrastructure. Ultimately, thinking about the importance of cost-effectiveness is the first step toward including cost-effectiveness in the flow of laboratory work.

Table 3 addresses questions that are typically posed in a cost-effectiveness analysis.

Physicians need to think beyond the traditional definitions of cost, which have historically included only the direct and indirect costs incurred in the laboratory. Costs include the downstream costs typically not measured by laboratories. Users of the laboratory and key decision makers need to take a longer and broader view of the costs of laboratory testing. The studies by Pfister demonstrate how this can be done.

Physician executives and decision makers who decide which laboratory should perform the tests should consider the value of the tests being offered. For example, if a laboratory offered sophisticated assay performance in addition to cost-effective testing algorithms, what would that be worth to the users of the laboratory? Despite attempts to make laboratory tests a commodity, are all tests equally valuable?

Laboratory testing can be viewed as a rocket launch to the moon. On earth, our calculations may seem to make perfect sense. But if we are off in our calculations, we find that we can miss the moon, sometimes by quite a bit. Is it the same for laboratory testing? What is the true value of lower sensitivity, lower specificity, poor precision, or poor accuracy? What are the actual downstream costs of false-positive or false-negative test results? What is the value of a laboratory that uses sophisticated testing algorithms to guide clinicians in their judicious use of tests? What is the value of dedicated pathologists who can guide and suggest proper testing strategies? Who benefits ultimately from these efforts?

WHO DETERMINES THE VALUE OF LABORATORY TESTS?

Examination of the cost-effectiveness of laboratory tests raises the following question: “Who determines the value of laboratory tests?” In the past, the value of laboratory tests was likely to be judged by the end-users of the tests, the physicians themselves. Now the payers are more influential in determining where the laboratory tests should be sent. Payers ultimately decide the value of laboratory tests, and until recently, many said that the tests were commodities. All Papanicolaou tests or thyroid tests or immunology tests were equal, at least in the eyes of the payers.

Some of that thinking may be changing. Recent Institute of Medicine (IOM) reports on patient safety and quality show that large employers are becoming more assertive in demanding accountability for quality and safety. Employers were stirred by the IOM report chronicled in the book *To Err Is Human: Building a Safer Health System.* The 1999 IOM study showed that more people die from medical mistakes each year than from highway accidents, breast cancer, or acquired immunodeficiency syndrome. The newest IOM report, *Crossing the Quality Chasm: A New Health System for the 21st Century,* makes specific suggestions for decreasing medical errors. The IOM says public and private purchasers should develop payment policies that reward quality, because current methods provide little financial reward for improvements in the quality of health care delivery.

Employers are showing that they are increasingly concerned with the quality of health care, and that they are willing to exert their financial muscle to steer their employees to health care systems that demonstrate quality and safety. Recently, the Washington (DC) Business Group on Health conducted a study with the consulting firm Watson Wyatt Worldwide and the Healthcare Financial Management Association. They surveyed 360 employers of 4.7 million full-time workers. Employers ranked quality higher than cost. Only one fourth of the employers would consider cost more than quality. In addition, 41%
of employers surveyed said cost pressures are hurting the
quality of care health plans provide.

Janet Corrigan, director of the Board of Health of the
IOM, stated, "We think that all the stakeholders in the
health care system need to be concerned not only about
cost and resource use but also about quality, because that's
what determines the value." Increased employer involve-
ment, she continued, is "a positive development for phy-
sicians and other clinicians because the activities of the
purchasing community are getting better aligned with
where physicians have been trying to move the system,
[which is] to satisfaction and quality for patients." 14

The Leapfrog Group, a consortium of large employers,
was formed in November 2000 with support from the
Business Roundtable to support the IOM recommenda-
tions on patient safety and quality. The Leapfrog Group
represents 66 of the largest employers in the country and
is growing in numbers and influence. Suzanne Delbanco,
the executive director of the Leapfrog Group, says it will
take at least 2 years to assess Leapfrog's impact, but she
hopes that in the future more patients will be going to
safer hospitals because of Leapfrog's work.

CONCLUSION

Many factors are stressing the American health care
system, including an increasingly older population of pa-
tients with chronic illnesses and increasing demands for
more sophisticated medical technologies. Laboratories are
no exception. Pathologists and laboratorians must demon-
strate clinical significance, efficiency, and effectiveness,
including cost-effectiveness, of laboratory testing strate-
gies. Purchasers of health care are demanding that labo-
raries provide an accounting for the value of the dollars
spent for health care on behalf of their employees. In an
article in the New England Journal of Medicine, Arnold Rel-
man16 called this the "third revolution in health care." With
increasing emphasis on safety and quality, labora-
tories that are poised to prove that they provide high-quality
laboratory tests at reasonable cost are likely to be the
winners in the quest for value.

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