Laboratory Medicine and Comparative Effectiveness Research

Prepared for: American Clinical Laboratory Association and Advanced Medical Technology Association (AdvaMed)

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The Lewin Group Center for Comparative Effectiveness Research

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Center for Comparative Effectiveness Research

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Submitted by:
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Executive Summary

Comparative effectiveness research (CER) is reshaping the evaluation of health care technology in the United States, with implications for innovation, regulation, payment, access, quality, and costs. The interest in CER arises from a widely perceived shortfall in evidence to inform decisions by clinicians, patients, health care provider organizations, and payers. The evidence expectations inherent in CER offer distinct challenges to the laboratory sector, as well as opportunities for those that can demonstrate the value of laboratory tests in the CER paradigm.

Demand for CER in the public and private sectors is fueled by multiple factors, including some of particular relevance to laboratory testing. Among these are evidence of large variations in practice and inappropriate use of health technologies. There is insufficient evidence comparing alternative interventions for particular conditions and on benefits and harms of interventions in “real-world” practice. Evidence that meets requirements for market approval or clearance by the Food and Drug Administration (FDA), or requirements for testing subject to the Clinical Laboratory Improvement Amendments (CLIA), may not be sufficient to inform care decisions and policies of clinicians, patients, and payers. Many advocates of CER cite it as one means for helping to improve efficiency of health care spending.

CER calls for evidence in ways that depart from traditional approaches in laboratory medicine. It involves head-to-head comparisons of the effectiveness and safety of alternative technologies. It emphasizes demonstrating impact on patient outcomes such as morbidity, mortality, quality of life, adverse events, and symptoms, rather than intermediate or surrogate outcomes, and usual health care settings rather than ideal settings. CER can draw on a variety of study designs, ranging from randomized clinical trials to analyses of health care claims data to systematic reviews of existing evidence.

The American Recovery and Reinvestment Act of 2009 (ARRA) appropriated $1.1 billion in new federal spending for CER, and called for the Institute of Medicine and the new Federal Coordinating Council for Comparative Effectiveness Research to generate recommendations for national priorities for CER. These recommendations address the full range of interventions, including drugs, biologics, tests, imaging, and medical and surgical procedures, as well as health care delivery system organization, delivery, and financing. Some of these recommended priorities address particular types of clinical laboratory tests, and many other of these priorities involve or depend on laboratory testing.

This report explains the rationale for CER, what CER is, and its significance for laboratory medicine. It describes the types of evidence generated by CER and how it compares with the evidence usually generated for regulatory purposes. The report summarizes current federal activities in CER that are relevant to laboratory medicine. Further, it describes implications of CER for the laboratory testing sector. The main findings of this report are the following.

1. Laboratory testing has multiple roles in CER, including to assess intermediate and long-term outcomes in CER focusing on therapies and other interventions, and as the subject intervention in CER, e.g., in head-to-head comparisons of tests or as part of broader protocols of testing and treatment for managing particular health risks or diseases.
2. CER evidence expectations for head-to-head comparisons, routine practice settings, diverse patient groups, and health outcome measures are adding to, and may otherwise modify, existing evidence requirements for regulation and reimbursement of laboratory testing.

3. The currently available evidence base for most laboratory tests generally does not extend to the types of evidence sought for CER. Evidence presented to FDA for meeting applicable requirements for market approval or clearance of laboratory tests, and provisions for quality requirements pertaining to laboratory-developed tests under CLIA, typically do not address comparative effectiveness, patient outcomes, or other attributes of CER.

4. In contrast to the typically direct relationship between a therapy and health outcomes, the relationship between a laboratory test and health outcomes is usually indirect. It is essential to recognize this difference when planning and conducting CER, including in setting priorities and selection of study design, outcome measures, and other aspects.

5. RCTs should not be the default study design for CER of laboratory tests. The need for an RCT is diminished when the therapeutic decision based on accurate test information is well established and when there is strong evidence pertaining to the impact of the therapy on patient outcomes or on a validated surrogate outcome.

6. New methods and analytical tools are emerging for demonstrating the comparative effectiveness of laboratory testing, including variations in traditional clinical trial designs; “data mining” of claims data, patient registries, and EHRs; retrospective studies of specimen remnants; and analyses of linked data sets of laboratory data and patient outcomes.

7. CER of laboratory testing should draw on the full portfolio of evolving CER methods. For example, certain observational studies can provide useful evidence for clinical validity and clinical utility of laboratory tests. Linking administrative and clinical data has significant potential to contribute to CER, although this will depend on such technical improvements as harmonizing patient identifiers across data sets and greater standardization in EHRs.

8. Innovations in gene-based laboratory testing, including in pharmacogenomics, is focusing greater attention on evidence requirements for these tests. Evidence needs will vary for demonstrating their analytic validity, clinical validity, and clinical utility. Improved coding of these tests, standards for collecting and storing laboratory test data, and other data collection on the availability and adequacy of genetic testing services are needed.

9. Few comparative effectiveness reviews to date have focused on laboratory tests. Those that have been conducted call for more evidence of the impact of testing on health outcomes and for more resources to monitor use and impact of gene-based testing on health outcomes.

10. Laboratory testing has prominent roles in the national agenda for CER that provides opportunities for broad demonstration of value in “real-world” health care. At the same time, many laboratory tests have well-established clinical value, are not associated with high clinical uncertainty, and are unlikely to be priority topics for CER.

11. Along with related evidence requirements of health care decision-makers, CER is influencing innovation in laboratory testing. CER can steer innovation toward greater value; technologies that achieve prevailing evidence requirements and demonstrate superior effectiveness or comparable effectiveness at lower cost will gain market advantages.
I. Introduction

Comparative effectiveness research (CER) is reshaping the evaluation of health care technology in the United States, with implications for innovation, regulation, payment, access, quality, and costs. The interest in CER arises from a widely perceived shortfall in evidence to inform decisions by clinicians, patients, health care provider organizations, and payers. The evidence expectations inherent in CER offer distinct challenges to the laboratory sector, as well as opportunities for those that can demonstrate the value of laboratory tests in the CER paradigm.

Many stakeholders are demanding better evidence about the relative benefits and risks of alternative interventions\(^1\) used to manage particular health problems. A growing body of research on the comparative effectiveness of interventions is being sponsored or conducted by such federal agencies as the Agency for Healthcare Research and Quality (AHRQ), the National Institutes of Health (NIH), and the Veterans Administration, and in the private sector, including payers and health technology makers. Proponents of CER contend that such evidence can contribute to better patient outcomes and more efficient use of health care resources.

In the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), Section 1013 authorized AHRQ to conduct and support research on “comparative clinical effectiveness.” For this purpose, MMA authorized $50 million initially and “such sums as necessary” for later years. However, actual appropriations were lower, ranging from $15 million to $50 million annually for the fiscal years 2005-09. MMA provided impetus for AHRQ to establish internal and external programs to conduct CER and strengthen related methods development and communications of CER.\(^2\) In February 2009, the American Recovery and Reinvestment Act of 2009 (ARRA) greatly increased federal funding for CER, appropriating $1.1 billion to “accelerate the development and dissemination of CER of health care treatments and strategies.” This included allocations of $300 million to AHRQ, $400 million to NIH, and $400 million for the Secretary of HHS.

ARRA mandated the Secretary of HHS to contract with the Institute of Medicine (IOM) to produce and submit a report to the Congress and the Secretary by June 30, 2009, that included recommendations on national priorities for CER to be conducted or supported with the ARRA funds.\(^3,4\) ARRA also established a Federal Coordinating Council for Comparative Effectiveness Research (FCCCER) comprising senior federal officers from HHS and other agencies and called for it to submit a report by June 30, 2009, to the President and the Congress containing

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\(^1\) The term “interventions” refers broadly to screening and diagnostic tests, drugs, biologics, devices, medical and surgical procedures, as well as organizational, delivery, financing, and other systems of care.

\(^2\) These included the Effective Health Care Program, which encompasses CER-related activities of AHRQ Evidence-based Practice Centers (EPCs), Developing Evidence to Inform Decisions About Effectiveness (DEcIDE) network, Centers for Education and Research on Therapeutics (CERTs), and development of methods reference guides.


information describing current federal activities on CER and recommendations for CER to be conducted or supported from ARRA funds.\footnote{5}

Various subsequent bills have sought to increase the role of the federal government in supporting and conducting CER. These include proposals to establish a CER center within AHRQ that would be overseen by a broadly representative commission, supported with a federal CER trust fund.\footnote{6} Others would establish an independent CER institute as a nonprofit corporation that would be funded in part by some combination of ARRA, Medicare, and private payers.\footnote{7,8}

These ongoing efforts to augment the national capacity for CER will increase the interest in such research as it pertains to clinical laboratory testing. As evident in the June 2009 priority setting reports of the IOM and the FCCCER, this research will address the full range of interventions, including drugs, biologics, tests, imaging, and medical and surgical procedures, as well as health care delivery system organization, delivery, and financing. As described elsewhere in this report, certain of these recommended national priorities focus on particular types of clinical laboratory tests, and many others will involve or depend on clinical laboratory testing to, e.g., identify patients with particular health risks or track their response to therapies.

II. Why Comparative Effectiveness Research?

A. Rationale

A diverse group of public and private sector stakeholders continue to call for filling gaps in and otherwise augmenting evidence to support decisions by clinicians, patients, and provider organizations, and to inform policies by payers and policymakers. The widely perceived shortfall in evidence to inform decisions is summarized by the IOM:

\begin{quote}
As ever-increasing options evolve in health care, current gaps in knowledge and practice about which care works best will persist or worsen without the appropriate information on which to base health care decisions. The rate with which new interventions are introduced into the medical marketplace is currently outpacing the rate at which information is generated on their effectiveness and the circumstances of best use. If trends continue, the ability to deliver appropriate care will be strained and may be overwhelmed.\footnote{9}
\end{quote}

By establishing what is the most effective intervention for patients with a given condition, proponents describe CER as having the potential to improve patient outcomes, reduce unnecessary care, and improve efficiency. The primary objective of CER is to generate evidence about which treatments and other health interventions are most effective and to disseminate the findings effectively and efficiently to target users. New technology continues to be identified as one of the main factors contributing to rising health care costs, and some stakeholders explicitly

\footnote{7 ARRA 2009.}
advocate CER as a means for restraining unnecessary cost growth.\textsuperscript{10} While use of CER findings may decrease costs of care for certain conditions or indications, it may increase it for others. Under some circumstances, e.g., with certain changes in one or more of health care delivery, benefit design, incentive structures, and information dissemination, use of CER findings might reduce overall health care spending. However, there is no clear evidence regarding the direction or magnitude of any resulting changes in spending.\textsuperscript{11}

CER is intended to augment evidence that is not directly or consistently generated by federal agencies charged with evaluating health care interventions, or by other research sponsors. The Food and Drug Administration (FDA) regulates pharmaceuticals, biologicals, and medical devices, including certain laboratory test kits and systems, but not most medical and surgical procedures or other types of health care interventions. For products that are regulated by FDA, the types of evidence reviewed are intended to meet established requirements for market approval or clearance, as appropriate for those respective products. However, this evidence usually does not include comparisons of an intervention to standard care (e.g., for pharmaceuticals, the comparator often is placebo) for impact on patient outcomes under usual or routine conditions of care, as intended for CER.

All laboratory testing (except research) performed on humans in the U.S. is regulated by the Centers for Medicare & Medicaid Services (CMS) through the Clinical Laboratory Improvement Amendments (CLIA). For laboratory developed testing subject to CLIA, laboratories are required to assure that test results are accurate, reliable, timely, and confidential. Further, laboratory directors must ensure that “The test methodologies selected have the capability of providing the quality of results required for patient care.”\textsuperscript{12} However, CLIA requirements do not extend into the types of evidence generated by CER, such as effectiveness of testing in terms of patient outcomes.

As the nation’s lead biomedical research agency, NIH supports investigations to understand the causes of disease and to discover ways to prevent, treat, and sometimes cure disease. Although it has sponsored some CER, including certain large, important effectiveness trials,\textsuperscript{13} NIH has not traditionally focused on comparisons of the effectiveness of interventions used in practice. However, given that ARRA included appropriations for $400 billion to NIH for CER, this practice appears to be changing.\textsuperscript{14} The comparative effectiveness work of the far more modestly

\textsuperscript{12} Regarding this requirement of CLIA (42 CFR § 493.1445(e)), the Secretary’s Advisory Committee on Genetics, Health, and Society (SACGHS) states: “Implicit in this regulation is the responsibility of the laboratory director to use medically relevant test methodologies that have an effective clinical purpose—otherwise those methodologies cannot be said to be ‘required for patient care.’” SACGHS goes on to state that “analytical validity is the only performance measure that CLIA fully enforces or has ever enforced. CLIA does not assess laboratory performance in clinical validity or utility, and CMS is not required to enforce any requirements except those related to analytical validity per the CLIA statute.” See: U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services. Report of the Secretary’s Advisory Committee on Genetics, Health, and Society. April 2008. Accessed January 15, 2010. http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf.
\textsuperscript{13} Some examples are the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), and Women’s Health Initiative postmenopausal hormone therapy trials.
\textsuperscript{14} Lauer MS. Comparative effectiveness research: the view from the NHLBI. J Am Coll Cardiol 2009;53(12):1084-6.
funded AHRQ generally has involved systematic reviews of existing evidence and analyses of various data sets, rather than generating evidence in clinical trials of alternative interventions, along with research methods development and certain research translation and dissemination efforts. The $300 million in new CER funds for AHRQ has nearly doubled that agency’s budget, and will substantially increase the volume of CER it produces.

Support for CER has come from organizations in the public and private sectors. Government agencies that have expressed support for CER include the Congressional Budget Office (CBO) and the Medicare Payment Advisory Committee. Private sector support has come from, e.g., American College of Physicians (ACP) and other health professional groups, Blue Cross Blue Shield Association (BCBSA), America’s Health Insurance Plans, and AARP. Others have expressed reservations about further institutionalizing CER. These organizations cite such concerns about CER as involving inappropriate study designs for answering certain questions, bias in interpreting results, disregard of individual differences in treatment outcomes, and delays in access to health care technology that could result from provider and payer reliance on CER findings.

**B. Defining CER**

CER differs from other research on the impact of health care technologies in that it is intended to make head-to-head comparisons of alternative interventions for a given health problem or condition. Although there is no standard definition of CER, most generally share these attributes or emphases:

- Direct comparisons of alternative interventions (as opposed to comparison with placebo or indirect comparisons), including standard care, for a given health problem
- Evaluation of *effectiveness* in realistic/routine health care settings (preferred over evaluation of *efficacy* in ideal circumstances)
- Evaluation of health care outcomes, e.g., morbidity, mortality, quality of life, adverse events, and symptoms (preferred over surrogate or other intermediate endpoints)
- Primary data collection, especially through head-to-head RCTs or other prospective studies that meet requirements for effectiveness research, where feasible
- Use of observational/epidemiological studies, registries, claims data, and other methods to augment or substitute for RCTs and other clinical trials as appropriate
- Systematic reviews (or “comparative effectiveness” reviews) that integrate relevant comparative evidence from available primary studies

Of particular relevance to the evolving national interest in CER are the definitions used in ARRA and by the IOM and the FCCCER (Box 1). Also included are definitions from other groups that support CER and that illustrate certain differences in its desired scope.

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Box 1
Definitions of Comparative Effectiveness Research

American Recovery and Reinvestment Act of 2009: Research assessing the comparative effectiveness of health care treatments and strategies, through efforts that: (1) conduct, support, or synthesize research that compares the clinical outcomes, effectiveness, and appropriateness of items, services, and procedures that are used to prevent, diagnose, or treat diseases, disorders, and other health conditions; and (2) encourage the development and use of clinical registries, clinical data networks, and other forms of electronic health data that can be used to generate or obtain outcomes data.19

Federal Coordinating Council on Comparative Effectiveness Research: The conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in “real world” settings. The purpose of this research is to improve health outcomes by developing and disseminating evidence-based information to patients, clinicians, and other decision-makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances.

- To provide this information, comparative effectiveness research must assess a comprehensive array of health-related outcomes for diverse patient populations and subgroups.
- Defined interventions compared may include medications, procedures, medical and assistive devices and technologies, diagnostic testing, behavioral change, and delivery system strategies.
- This research necessitates the development, expansion, and use of a variety of data sources and methods to assess comparative effectiveness and actively disseminate the results.20

Institute of Medicine: The generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.21

American College of Physicians: The evaluation of the relative (clinical) effectiveness, safety, and cost of 2 or more medical services, drugs, devices, therapies, or procedures used to treat the same condition.22

Blue Cross Blue Shield Association: A variety of research — including clinical trials, cohort studies, literature reviews, and other studies — evaluating the comparative clinical and cost effectiveness of different procedures, drugs, devices, and biologics.23

Congressional Budget Office: A rigorous evaluation of the impact of different options that are available for treating a given medical condition for a particular set of patients. Such a study may compare similar treatments, such as competing drugs, or they may analyze very different approaches such as surgery and drug therapy. The analysis may focus only on the relative medical benefits and risks of each option, or it may go on to weigh both the costs and the benefits of those options.24

These definitions present aspects of particular relevance to laboratory testing. Reflecting, in part, public input to their priority setting processes, the IOM and FCCCER definitions account for evidence pertaining to various patient subgroups that is useful at the level of individual patients, as opposed to only population-based “average” findings. Most of these definitions call for a variety of methods for use in CER. These and other definitions describe CER as applying across health care interventions, including health care organization, delivery, and financing systems, not focused on any particular type of technology.

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19 ARRA 2009.
20 FCCCER 2009.
21 IOM 2009.
22 American College of Physicians 2008.
24 CBO 2008.
Although there is overlap in these selected definitions, there is less agreement concerning a role for economics in CER, including assessments of cost-effectiveness or other clinical and economic tradeoffs. Among the definitions shown in Box 1, those of the ACP, BCBSA, and CBO include references to cost analysis.

III. Main Roles of Laboratory Testing in CER

Two main roles for laboratory testing in CER are: 1) in CER focusing on other interventions, identification of patients eligible for study and as an indicator of intermediate and long-term health outcomes, and 2) as the subject (i.e., index or focal) intervention in a direct comparison with alternatives (Box 2).

<table>
<thead>
<tr>
<th>Box 2</th>
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<tr>
<td><strong>Main Roles of Clinical Laboratory Tests in CER</strong></td>
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<td><strong>Used to support CER of other interventions:</strong> Laboratory tests are used to identify patients eligible for a study, quantify baseline characteristics, assess intermediate outcomes, and conduct subgroup analyses of other interventions. Among these are treatments used for priority health conditions such as diabetes, obesity, heart disease, stroke, kidney disease, HIV/AIDS, mental health/substance abuse, pneumonia, cervical and colon cancer, and pregnancy. For example, hemoglobin A1c (HbA1c) is an indicator to evaluate the effectiveness of alternative oral medication regimens (e.g., sulfonylureas, biguanides, dipeptidyl peptidase IV inhibitors, or combination therapy) to treat type 2 diabetes.</td>
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<td><strong>The subject (i.e., index or focal) intervention(s) in head-to-head comparisons involving alternative laboratory tests or comparisons of a laboratory test to another type of test for a particular health care condition.</strong> For example, a CER study may compare a new molecular test assessing the gene expression profile of RNA from the peripheral blood of heart transplant recipients to the current standard of care assessing RNA from invasive endomyocardial (heart tissue) biopsy procedures. Another CER study might evaluate the effectiveness of HPV testing for cervical cancer compared to conventional Pap smear testing.</td>
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A. Laboratory Testing in Support of CER of Other Interventions

Given its integral role in diagnosis, treatment, and monitoring for a multitude of health conditions, laboratory testing is often an essential element in CER. CER of many health care interventions will involve laboratory testing, for example, to:

- identify patients eligible for particular studies CER for therapeutic interventions
- assess patient baseline characteristics (e.g., risk stratification for prospective subgroups)
- assess biomarkers during the course of interventions (e.g., for therapeutic drug monitoring)
- assess surrogate outcomes where appropriate
- identify patient subgroups retrospectively from clinical trial or observational data that may be associated with different health outcomes, for subsequent trials or other studies.

B. Laboratory Testing as the Subject of CER

Laboratory tests themselves can be the subject or focus of CER, or part of a broader protocol for managing particular health risks or diseases, such as an integrated testing and treatment program to reduce the prevalence of an infectious disease, that is the subject of CER. Comparisons of screening or diagnostic tests may provide clinicians with evidence on how a new test improves patient health outcomes relative to a standard test by describing the relative impact of the tests along a causal pathway between testing and outcome.\(^{28}\) CER indicating comparable or greater effectiveness of laboratory testing versus other diagnostic procedures (e.g., surgical biopsy) may change patterns of use of laboratory testing by clinicians. Increased emphasis on CER may boost those innovations that can demonstrate superiority, or non-inferiority at a lower cost, compared to alternatives in improving medical decisions and patient outcomes in real-world settings.\(^{29}\)

Few comparative effectiveness reviews have focused on laboratory tests, largely because CER priorities to date have included few laboratory tests and due to the lack of primary studies of the comparative effectiveness of laboratory tests. To date, the AHRQ Effective Health Care Program has embarked on eight comparative effectiveness reviews that focus on laboratory testing, at least three of which have been completed, along with a few reports on related methodological issues (Box 3.) In general, these reviews to date have called attention to the need for more evidence of the impact of testing on health outcomes and for more resources to monitor use and impact on outcomes of gene-based testing.

C. National Priorities for CER and Laboratory Testing

As noted above, the IOM and the FCCCER generated recommended national priorities for CER in reports issued in June 2009.\(^{30}\) The IOM priorities report included six topics for which laboratory testing is a focal technology, including two such topics among the top tier of 25 (Box 4). Several of these involve genetic/genomic testing; three involve infectious disease (methicillin resistant \textit{Staphylococcus aureus} infection, HIV, and hepatitis C); and two involve one or more types of cancer. As a group, these six priorities present a very large potential scope of inquiry. One priority addresses genetic and biomarker testing for five types of cancer and “possibly other clinical conditions.” Another priority addresses the impact of new biomarkers in general on motivating behavior change and improving health outcomes. Further, the IOM priorities include many other topics for which laboratory testing is not a focal technology but would be integral to conducting the CER.\(^{31}\)

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\(^{30}\) ARRA 2009.

\(^{31}\) IOM 2009.
Box 3

AHRQ Effective Health Care Program – Studies Focusing on Laboratory Testing

Reports on Testing:

- Testing for Cytochrome P450 Polymorphisms in Adults With Non-Psychotic Depression Treated With Selective Serotonin Reuptake Inhibitors (SSRIs) (2007)
- HER2 Testing to Manage Patients with Breast or Other Solid Tumors (2008)
- Comparative Effectiveness of Core Needle Breast Biopsy and Surgical Excision Biopsy for Diagnosing Breast Lesions (2009)
- A Case Control Study to Assess Association of Variations in OCT Genes with Effectiveness of Metformin in Diabetic Patients (in progress)
- MRSA Reservoirs in Hospitals and Nursing Homes (in progress)
- Effectiveness of Screening and Treatment of C. difficile Infections (in progress)

Methods and Infrastructure:

- Infrastructure to Monitor Utilization and Outcomes of Gene-Based Applications: An Assessment (2008)
- Analytic Validity, Quality Rating and Evaluation Frameworks of Genetic and Other Laboratory Tests (in progress)


The FCCCER priorities report focused less on specific interventions and more on building the national capacity and infrastructure for CER. In describing the need to strengthen the data infrastructure for CER, the FCCCER report cited the need for inventories of various types of data, including laboratory data. Also, diagnostic testing is one of the six broad “cross-cutting” intervention types in which the FCCCER called for investment of CER funding, because they “address large and varied populations, resulting in high potential impact, are areas of high clinical uncertainty, and are not being adequately addressed by other entities.” (Other cross-cutting intervention types are medical and assistive devices, procedures and surgery, behavioral change, delivery system strategies, and prevention.)[^32]

Some of these priorities (e.g., some topics listed in the IOM report) are being addressed by research that was already underway in 2009, and others are starting to be reflected in additional federal spending under ARRA, including in grants and contracts from AHRQ, NIH, and other agencies. Given the considerable breadth of health care interventions, resource limitations, and the need to set priorities for CER, certainly not all laboratory tests will be subject to CER. For example, many existing and new laboratory tests are not associated with areas of high clinical uncertainty or do not otherwise meet priority criteria for CER.

[^32]: FCCCER 2009.
Laboratory testing as subject technology (including as part of a protocol for managing a health risk or disease) in CER:

- Compare the effectiveness of various screening, prophylaxis, and treatment interventions in eradicating methicillin resistant *Staphylococcus aureus* (MRSA) in communities, institutions, and hospitals.
- Compare the effectiveness of genetic and biomarker testing and usual care in preventing and treating breast, colorectal, prostate, lung, and ovarian cancer, and possibly other clinical conditions for which promising biomarkers exist.
- Compare the effectiveness of new screening technologies (such as fecal immunochemical tests and computed tomography [CT] colonography) and usual care (fecal occult blood tests and colonoscopy) in preventing colorectal cancer.
- Compare the effectiveness of adding information about new biomarkers (including genetic information) with standard care in motivating behavior change and improving clinical outcomes.
- Compare the effectiveness of HIV screening strategies based on recent Centers for Disease Control and Prevention recommendations and traditional screening in primary care settings with significant prevention counseling.
- Compare the effectiveness of alternative clinical management strategies for hepatitis C including alternative duration of therapy) for patients based on viral genomic profile and patient risk factors (e.g., behavior-related risk factors).

Examples of other IOM CER priorities that would involve laboratory testing:

- Compare the effectiveness of different treatment strategies (e.g., modifying target levels for glucose, lipid, or blood pressure) in reducing cardiovascular complications in newly diagnosed adolescents and adults with type 2 diabetes.
- Compare the effectiveness and cost-effectiveness of conventional medical management of type 2 diabetes in adolescents and adults, versus conventional therapy plus intensive educational programs or programs incorporating support groups and educational resources.
- Compare the effectiveness of anticoagulant therapies (e.g., low-intensity warfarin, aspirin, injectable anticoagulants) for patients undergoing hip or knee arthroplasty surgery.


IV. Laboratory Testing and Health Outcomes

The relationship between a laboratory test and health outcomes is usually indirect. Typically, there are multiple intervening steps between a test and improved health outcomes. For example, a test must have the ability to detect (or rule out) a target condition (risk or disease). If so, the test results may be used to inform a treatment choice that, in turn, may affect intermediate outcomes (e.g., change in blood lipids or HbA1c), which may affect or be associated with patient outcomes. As such, the impact of the test on patient outcomes can be affected by these and other factors that are not related to the performance of the test. In some instances, it is possible to demonstrate the impact of the test on patient outcomes in a prospective clinical trial that tracks a tested population through these intervening steps to patient outcomes. However, this relationship is more often inferred or presented using a chain of evidence, starting with evidence to demonstrate test accuracy, followed by evidence establishing the relationships between the subsequent steps leading to patient outcomes. Often at issue is whether such chains of evidence provide expert physician panels with sufficient confidence to conclude that a test has an ultimate impact on outcomes and can be recommended for
clinical use. This consideration of direct vs. indirect evidence of the impact of a test is often portrayed in a clinical pathway or analytic framework, such as shown in Figure 1.

Figure 1. Generic Clinical Analytic Framework for Screening and Diagnostic Tests

Questions correspond to numbers above.

1. Is there direct evidence that the test reduces morbidity, mortality, and/or quality of life?
2. What is the prevalence of disease in the target group? Can a high-risk group be reliably identified?
3. Can the test accurately detect the target condition? (a) What are the sensitivity and specificity of the test? (b) Is there significant variation between examiners in how the test is performed? (c) In actual testing programs, how much earlier are patients identified and treated?
4. Does treatment reduce the incidence of the intermediate outcome? (a) Does treatment work under ideal, clinical trial conditions? (b) How do the efficacy and effectiveness of treatments compare in community settings?
5. Is the intermediate outcome reliably associated with reduced morbidity and/or mortality?
6. Does treatment improve health outcomes for people diagnosed clinically? (a) How similar are people diagnosed clinically to those diagnosed by screening? (b) Are there reasons to expect people diagnosed by screening to have even better health outcomes than those diagnosed clinically?
7. Does testing result in adverse effects? (a) Is the test acceptable to patients? (b) What are the potential harms, and how often do they occur?
8. Does treatment result in adverse effects?

The great majority of CER to date has focused on comparisons of the largely direct impacts of alternative therapies on health outcomes. In contrast, when a laboratory test is the subject technology in a head-to-head comparison (e.g., to another laboratory test, diagnostic imaging, or other screening or diagnostic procedure) of effectiveness, the relationship between the test and health outcomes is typically indirect. It is essential to recognize these differences when considering, planning, and conducting CER, including selection of outcomes to be compared, study design, and other aspects. Also, laboratory tests can have further effects on patient outcomes, including cognitive, emotional, social, or behavioral effects, such as in the instances of HIV testing, prenatal testing for fetal abnormalities, and genetic testing for cancer risk. These effects, which can be beneficial or harmful, may have further influences on clinical outcomes.33

A. Validity and Utility of Laboratory Tests

There are various paradigms for evaluating laboratory test performance in clinical settings. A recent systematic review of the published literature over the last three decades cited 19 schemes for phased, stepwise, or hierarchical evaluation of medical tests (including laboratory testing, diagnostic imaging, and others). Despite variation among these schemes, many shared phases or steps of evaluating technical efficacy, diagnostic accuracy, diagnostic thinking efficacy, 

therapeutic efficacy, patient outcome, and societal aspects (including cost-effectiveness). Such phases or steps are not a necessary sequence of test evaluation, as particular phases or earlier ones can suffice, depending on the evidence question or whether other evidence is available, e.g., on the effect of therapies on patient outcomes. Among the more prominent and widely cited hierarchies or other schemes for evaluation of tests include those used by the U.S. Preventive Services Task Force (USPSTF) and the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative. Hierarchies of evidence for testing and their use by such groups as USPSTF and EGAPP are described further elsewhere.

In one paradigm, there are three main orders of performance. The first-order concern is the performance of a given test result in terms of sensitivity and specificity in actual practice, or diagnostic accuracy. The second-order is the predictive value of the test as determined by Bayes’ theorem. The third-order is the actual probability of a change in health status of the patient resulting from any therapeutic interventions either instituted or forgone based on the test result. As described above, CER focuses on patient outcomes, corresponding to the third-order of laboratory test performance. Other paradigms use analytical frameworks.

A related approach to assessing the value of tests involves multiple determinations grouped into three main concepts: analytic validity, clinical validity, and clinical utility, as summarized in Box 5. While this set of concepts is useful in all laboratory testing, it is gaining increased attention and further definition in the realm of genetic and genomic testing.

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34 This addresses whether results of a test changed the pre-test perception of the referring clinician. Diagnostic thinking efficacy is lacking when the information derived from a test does not alter the clinician’s perception of diagnostic probability.


38 See: Lewin Group. The Value of Laboratory Screening and Diagnostic Tests for Prevention and Health Care Improvement. Prepared for the American Clinical Laboratory Association and Advanced Medical Technology Association (AdvaMed), September 2009.

The interpretation of these concepts is relevant for CER, which can involve diverse populations, health conditions, and other factors that can affect test performance. For example, clinical validity of a test can vary with the prevalence of a condition within the population being tested, changes in disease patterns over time, and other factors, e.g., age, race and ethnicity, family history, severity of disease, and comorbidities. For many conditions, patients with severe disease are more likely to have positive tests than those with mild or early-stage disease, and healthy patients are more likely to have negative tests than those with significant comorbidities.44,45

### B. The Challenge of Linking Laboratory Testing to Outcomes

One of the challenges of demonstrating the clinical utility of testing is to show the causal links—whether with direct or indirect evidence—between ordering tests and ultimate changes in patient outcomes. Across many clinical areas, there is only limited direct evidence that conducting a test results in improved outcomes. Even for many therapies, available evidence of effectiveness is limited to their impact on intermediate or surrogate outcomes. When studies are conducted to determine the impact of laboratory tests, the overarching question addressed is “Does the information provided by the test alter a clinical decision and subsequent outcomes compared to not having that information available?” Two major groups of patient outcomes are health outcomes and patient-centered or “humanistic” outcomes (Box 6).

The challenge of assessing many laboratory tests arises because the ability of tests to influence clinical decisions and outcomes is subject to factors that are beyond or independent of the technical attributes of the tests themselves.40 As noted above, in order to influence outcomes, a laboratory test must be ordered, conducted, appropriately interpreted, and affect a decision for further diagnosis or treatment that results in changes in outcomes.41 Clinicians may interpret and act on laboratory test

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results differently and unpredictably, which can confound the evaluation of the impact of tests on patient outcomes.\textsuperscript{42} For various reasons, patients and clinicians might ignore positive results or proceed with a clinical intervention despite a negative test. This includes instances in which laboratory testing is used to monitor intermediate outcomes of treatment in order to guide further treatment toward desirable outcomes. Given the amount of time that must transpire between testing for many conditions and subsequent changes in outcomes that may have been influenced by testing, evidence of the impact of testing on long-term health outcomes is limited. Thus, the ability to establish a cause-and-effect relationship between a test and patient outcomes is limited by the inherent role of testing in the detection and management of diseases and disorders.

<table>
<thead>
<tr>
<th>Box 6</th>
</tr>
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<tbody>
<tr>
<td><strong>Main Types of Patient Outcomes</strong></td>
</tr>
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</table>

- **Health outcomes** include mortality (e.g., infant death rate), morbidity, symptoms (e.g., pain), clinical events (e.g., need for hospitalization, medical error), and biomarkers of physiologic state (e.g., laboratory values for HbA1c). Some biomarkers known to be associated with or predictors of long-term outcomes are used as surrogate outcomes.

- **Patient-centered outcomes** are used to assess quality of life, functioning (e.g., disability), patient-centeredness of care, patient satisfaction, etc. Like many other interventions, laboratory testing can have cognitive, emotional, social, and behavioral effects.

Despite the challenges of generating direct evidence of the impact of testing on outcomes, there are notable instances in which this is clearly demonstrated. As described in Box 7, one example involves fecal occult blood test (FOBT) screening for colorectal cancer, where the USPSTF concluded that there is “convincing evidence” that screening with FOBT or two other tests reduces colorectal cancer mortality in adults age 50 to 75 years.

In many instances, the impact of laboratory practice on health outcomes can be inferred through linkages between the tests and **surrogate outcomes** that have been validated as being strongly associated with subsequent patient outcomes, particularly in routine practice settings.\textsuperscript{43,44} Examples are length of stay for mortality, number of clinical visits for morbidity, and disease markers for quality of life. Because surrogate outcomes are generally measured earlier and more easily than the patient outcomes with which they are associated, they are used more commonly to determine the effects of testing and other health care interventions.\textsuperscript{45} Some surrogate outcomes are better predictors of patient outcomes than others. Other examples of surrogate outcomes assessed by laboratory testing include: HbA1c for diabetes morbidity and CD4 cell counts and viral RNA levels for progression of AIDS, cardiac troponin for identifying and predicting outcome of acute coronary syndrome, INR (International Normalized Ratio)/prothrombin time for predicting thrombolytic events, and HER-2/neu for predicting response to treatment with trastuzumab (Herceptin) in women with breast cancer.


\textsuperscript{43} Price 2003.

\textsuperscript{44} Panteghini 2004.

Box 7
FOBT Screening for Colorectal Cancer

A 2008 systematic review conducted for the U.S. Preventive Services Task Force (USPSTF) examined long-term follow-up of four RCTs of guaiac fecal occult blood tests (FOBTs) and endoscopic follow-up of positive test results. The review found that colorectal cancer mortality was reduced 13-21% after 8-13 years of screening in two trials and that two other trials did not show mortality benefit until after 15-18 years of screening. A 2007 systematic review conducted by the Cochrane Collaboration that identified reports of four RCTs and two other controlled trials involving more than 320,000 participants with follow-up ranging from 8 to 18 years concluded, based on the RCT evidence, that participants allocated to screening had a 16% reduction in the relative risk of colorectal cancer mortality. Among those RCTs was one involving more than 46,000 patients, which found that cumulative mortality over an 18-year period was reduced 33% with annual testing and 21% in biennial testing. In its 2008 recommendation, the USPSTF stated that “There is convincing evidence that screening with any of the 3 recommended tests [fecal occult blood testing, sigmoidoscopy, or colonoscopy] reduces colorectal cancer mortality in adults age 50 to 75 years.” The USPSTF noted the importance of considering the lag time between testing and impact on outcomes: “There is adequate evidence that the benefits of detection and early intervention decline after age 75 years. The lead time between the detection and treatment of colorectal neoplasia and a mortality benefit is substantial, and competing causes of mortality make it progressively less likely that this benefit will be realized with advancing age.”

V. CER Methods and Laboratory Testing

CER can be conducted using one or a mix of study designs that are used to evaluate health care technologies, including primary data collection and secondary studies or syntheses. Primary data collection includes various experimental designs, such as randomized clinical trials, and observational designs using claims data or registries. Secondary studies include systematic reviews, meta-analyses, and other designs that use data from multiple existing studies. The main types of study designs used in CER are summarized below, with discussion about their applications for laboratory testing.

A. Primary Studies

1. Clinical Trials

Randomized clinical trials (RCTs) are regarded as the gold standard of scientific evidence for establishing causality of a given intervention on particular health outcomes. Their strength derives from their ability to minimize sources of bias and other factors that might confound determination of that causal relationship. For new drugs and some medical devices (though typically not for laboratory tests), RCT evidence is used to establish efficacy and safety, often compared to placebo or no treatment rather than a standard of care or other active intervention, for gaining market approval in the U.S. by the FDA. While this is essential evidence for determining whether an intervention works under a particular set of conditions, it may not generate the evidence needed to evaluate real-world effectiveness of an intervention in patient populations with diverse characteristics under different conditions. In contrast to real-world

conditions, RCTs typically involve narrowly defined patient groups (e.g., in a specific age range with a single disease with narrowly defined or no comorbidities), practice settings, and outcomes. Further, they can be too small to discern treatment effects with statistical significance and rare adverse events, or too short in duration to capture certain important longer-term outcomes and delayed adverse events.\(^\text{50,51}\) As such, RCTs may not generate the type of evidence sought in CER. Also, RCTs can be costly to perform.

**Practical (or pragmatic) clinical trials (PCTs),** sometimes known as “effectiveness trials,” address some of the disadvantages inherent in RCTs and other types of studies in CER. PCTs compare alternative interventions that are relevant to clinicians and their patients, focus on more heterogeneous patient populations and practice settings, and collect data on a broad range of health outcomes. PCTs may be randomized; types include large simple trials, cluster-randomized studies, and time-series analyses of planned changes in care. PCTs can be expensive and require large sample sizes and long follow-up periods. While the difference in effectiveness between two treatments may be clinically meaningful, that difference may be considerably smaller than the difference between each active treatment and placebo. As such, detecting clinically meaningful differences with statistical significance between the alternatives in a “head-to-head” PCT can require much larger sample sizes, which can increase the costs and time to complete these trials.\(^\text{52}\) PCTs may be designed for prospective comparison of particular subgroups, or, as is so for RCTs, they may be subject to retrospective analyses for subgroup differences that can be studied in subsequent prospective trials.

**Adaptive clinical trials and other trial designs** offer improved ways of “stratifying” (identifying and testing subgroups of) population response to interventions. Of particular note are adaptive clinical trials, which are “learn-as-you-go” approaches to conducting clinical trials. In adaptive clinical trials, one or more decision points are built into the trial design for analysis of outcomes and associated patient or disease characteristics to identify subgroups who are responding favorably to an investigational treatment. Planning for such mid-course corrections can help to focus trial resources on enrolling more patients with particular biomarkers that are more likely to have favorable results and enrolling fewer patients who are less likely to respond or more likely to experience adverse effects. This can increase the chances of detecting statistically significant treatment effects in a population subgroup that otherwise would have been statistically lost in a broader pool of patients with a higher proportion of non-responders.

### 2. Observational Studies

Observational studies include analyses of various sources, including **insurance claims** and **other administrative data sets,** **patient medical/health records,** **patient registries,** **integrated health system databases,** and **other clinical databases.** Observational studies can be prospective or retrospective, but they are not experimental and cannot demonstrate causality between an intervention and patient outcomes. They are more likely to be subject to certain biases and confounding factors that RCTs and PCTs are designed to diminish. Data that would be available

\(^{50}\) Horn SD, Gassaway J. Practice-based evidence study design for comparative effectiveness research. Medical Care 2007;45 (10 Suppl 2):S50-7.


\(^{52}\) Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. JAMA 2003;290(12):1624-32.
Laboratory Medicine and Comparative Effectiveness Research

In an experimental research design to adjust for factors such as disease severity that can bias findings may be missing from claims and other administrative data sets. Observational studies are limited by whatever data elements are collected for their original purposes, e.g., payment of claims. However, to the extent that they can be linked to other sources, e.g., claims data linked to de-identified electronic health record (EHR) data for corresponding patients, they can provide important data about associations between health interventions and outcomes.

Observational studies often enable including populations and particular subgroups that tend to be underrepresented in clinical trials. In patients with given diseases or conditions, particularly those with stable or steadily progressing courses, these studies can be used to examine relationships among certain interventions, patient characteristics, provider characteristics and differences in biomarkers, outcomes, and adverse events. They can be used to generate hypotheses about these relationships that can be tested in prospective clinical trials. Because they often rely on existing data and non-experimental designs, observational studies typically are less costly than RCT, PCTs, and other clinical trials.

Observational studies can detect associations between interventions and outcomes that can be investigated by clinical trials. Also, certain observational studies (e.g., linked laboratory data and EHRs) can assess associations between test analytes (e.g., genotypes or other biomarkers) and diseases or disorders (phenotypes), which can be used to establish clinical validity of laboratory tests.

**Patient registries** are structured inventories of data on patients who have received particular interventions or exposures (e.g., a particular drug, implanted device, surgical procedure, or diagnostic test). Among the types of evidence gaps that registries can fill are the types and frequency of adverse events that could not be detected in clinical trials, which may have had too few participants to detect rare adverse events or were not long enough to detect delayed adverse events. Some of the nation’s integrated health care systems are using their large clinical and administrative data systems and registries to conduct CER to determine the most effective interventions for subgroups of patients. Registries and other observational studies (including retrospective analyses of patient subgroups in RCTs), can be used to identify subgroups with potentially important differences in response to interventions. Such subgroups can then be enrolled in RCTs or other prospective studies to confirm whether these differences truly exist.

Registries can augment claims-based analyses by providing information to control for differences among patients getting different treatments and allowing a broader set of outcomes to be measured. Data on health status or test results that are captured in registries can support understanding of how treatment choices are made. Incorporating laboratory test result data into the registries can be essential for managing certain diseases. Also, they are of increasing importance in population-based research, e.g., tracking the natural course of disease, treatment


54 For example, Kaiser Permanente, Group Health, and Geisinger Health have initiated programs that use their large databases to complement clinical trial findings for purposes consistent with CER. The Health Maintenance Research Network (HMORN) includes 15 managed care organizations covering more than 15 million individuals and working cooperatively on effectiveness research. See: IOM. Learning What Works Best. September 2007; and HMO Research Network. Research Projects.

55 Research on the Comparative Effectiveness of Medical Treatments. CBO 2008.
effectiveness, costs, and other parameters. Large or comprehensive registries can provide such advantages as large sample sizes (broader patient representation, statistical power), more data elements and long-term follow-up. These registries can be challenging to organize and costly to develop and maintain.

B. Syntheses of Existing Evidence

**Systematic literature reviews** are prospectively designed, comprehensive literature reviews that are focused on well-defined evidence questions. (In the context of CER, systematic reviews are sometimes known as “comparative effectiveness reviews.”) They are intended to identify, appraise, and synthesize all relevant high-quality research evidence. They may incorporate meta-analyses in instances where the available evidence from primary studies is sufficiently homogeneous with respect to the populations, interventions, and outcomes studies. While they can yield more robust findings from existing evidence, systematic reviews do not generate new data, and they are limited by availability, quality, and heterogeneity of available evidence from clinical trials and other primary studies. Given the general lack of clinical trials of head-to-head comparisons of alternative interventions, there are few systematic reviews or meta-analyses of such direct comparisons. In some instances, systematic reviews can generate sufficiently useful findings of comparative effectiveness from available evidence; in others, they may suggest the need for further research. For example, systematic reviews can identify and compile available evidence on subgroups from multiple studies, which can be used to generate hypotheses about treatment effects in these groups that can be tested in new RCTs or PCTs. Systematic literature reviews generally are far less costly to conduct than clinical trials.

**Modeling** refers to quantitative representations or simulations of health care. It may be used when available evidence is insufficient to answer a research question or to project risks, benefits, or costs of alternative care scenarios. In CER, decision-analytic modeling can be used to simulate the linkages between alternative test-and-treat strategies and patient outcomes, using relevant evidence where available and accounting for uncertainties and assumptions. Among the challenges of such modeling are the adequacy of understanding of the physiological pathways or decision processes pertaining to the patients and interventions being modeled, the scarcity of data on key parameters, obtaining summary estimates for test performance data, applying estimates of test performance across studies, and selection of outcomes. Modeling does not generate new primary data. However, supported by new analytical techniques and advances in computing power, modeling can tap findings from clinical trials and other primary research as well as existing data sources to simulate head-to-head comparisons of alternative treatments.

Using large sets of de-identified data from multiple health plans, and drawing on known causal relationships established in clinical trials, modeling can detect varying levels of association

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56 Meta-analysis refers to statistical techniques for combining results from multiple existing studies. This combination may produce a stronger conclusion than can be provided by any singular study. It is generally most appropriate when there are not definitive studies on a topic and non-definitive studies are in some disagreement (e.g., regarding direction or magnitude of a treatment effect).

57 AHRQ 2007.


between interventions and outcomes in stratified patient populations.\textsuperscript{60} Modeling can help inform decisions about using screening and diagnostic tests by estimating their likely benefits and harms when applied to populations and subgroups with particular risk factors or other characteristics, such as in screening for cancer or prediabetes. As more patient-specific (including genomic) information is captured in clinical registries, EHRs, and other databases, modeling is being used to simulate clinical decisions and outcomes for individual patients.

\section*{C. RCTs: Not the Default Design}

The main strength of RCTs is their internal validity—how well a study design and execution diminish the opportunity to introduce bias or inferential error that can affect results regarding the true impact of interventions on outcomes under the particular conditions of the study.\textsuperscript{61} In RCTs, randomization ensures that intervention groups (e.g., one getting a new intervention and one getting standard care) differ only in their exposure to the intervention, so that differences in observed impacts can be attributed to differences in the intervention.

Results of RCTs, typically conducted with carefully selected patients under carefully controlled conditions, may not be generalizable to the broader patient population in real-world clinical practice. RCTs may not be able to account for patient preferences, which may reflect on their relevance for patient-centered care.\textsuperscript{62,63} To the extent that a substantial body of evidence from other study designs has accumulated, it may be strong enough to obviate the need for RCTs. Indeed, enrolling sufficient numbers of patients in RCTs and identifying clinical investigators may be impractical under circumstances where there is a substantial body of evidence from other sources.

There are particular disadvantages to RCTs for laboratory tests. Given the multiple intervening factors between accurate diagnostic results and improved health outcomes, it can be time-consuming, complex, costly, and, in certain instances, not feasible, to conduct RCTs on laboratory tests for direct evidence on patient outcomes.\textsuperscript{64} The time between the use of a laboratory test until the time that patients experience a change in health outcomes that may have been influenced by that test can be years or even decades. Blinding of patients (as well as clinicians and investigators) in an RCT, e.g., as to whether patients received one test vs. another, or a test vs. no test, is impractical in most instances.

An RCT is the most rigorous design to use when the purpose of a study is to establish whether a test has a direct impact on survival, morbidity, or quality of life. However, this can present considerable challenges, and may be impractical in many instances. In conducting RCTs of laboratory tests to determine impact on outcomes, the test is incorporated into a protocol or other patient management involving one or more therapies or other interventions, each of which introduces random variation to patient response. In general, this additional random

\begin{footnotes}
\item Eddy, DM, Linking electronic medical records to large-scale simulation models: can we put rapid learning on turbo? Health Affairs 2007;26(2):w125-36.
\item AHRQ. Methods reference guide. 2007.
\item Ibid.
\end{footnotes}
variation necessitates enrolling larger numbers of patients in the RCT to discern any true difference in patient outcomes with sufficient statistical confidence. Indeed, the independent contribution of the test to patient outcomes may be small compared to the variation in patient response to a therapy, thereby requiring larger sample sizes (and greater costs) to discern any differential impact of the test itself on outcomes.

The need for an RCT is diminished when the therapeutic decision based on accurate test information is well established and when there is strong evidence pertaining to the impact of the therapy on patient outcomes or on a validated surrogate outcome. As such, the impact of a test can be assessed in separate studies providing evidence in support of analytical validity, analytical utility, and clinical utility. For analytical validity, this may involve a cross-sectional study in a representative patient population in which all patients receive both the subject test and gold standard comparator test (in random order) and the sensitivity and specificity of the subject test are assessed versus the gold standard comparator. Separate evidence from epidemiological or other observational studies may be used to determine clinical validity, i.e., whether the test analyte predicts or is associated with the disease or disorder of interest. Whether the test result has an impact on patient management and outcomes, i.e., clinical utility, may be addressed using separate evidence or other analyses. This might involve decision analysis based on available evidence pertaining to clinician decision-making and other evidence (especially from RCTs) of the impact of the relevant therapies on patient outcomes.

D. Selecting Study Designs and Data Sources to Fit the Evidence Question

The appropriate study design for assessing the effectiveness of a laboratory test depends on the evidence question. For example, if the evidence question concerns the impact of a new test on patient outcomes (e.g., survival, morbidity, quality of life), then the best study design may be an RCT that randomizes patients to the new test and to a comparator test (which may be a gold standard) and follows patients through their respective courses of treatment or other management to their outcomes. If a particular biomarker is validated as a surrogate outcome for a health outcome of interest, then it may only be necessary to follow patients to those surrogate outcomes. If available evidence demonstrates that treatment and other management of patients who are accurately identified by a test achieve improved outcomes, it may be inferred indirectly that use of that test in that at-risk patient population can contribute to improved outcomes.

If the evidence question concerns the accuracy of a new test, then it is not necessary to follow patients to their health outcomes. Rather, the best study design for this question may be a

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66 For some tests, there is no gold standard. A reference standard may not be available or validated for all types of patients, an existing one may be imperfect, or there may be no accepted reference standard. In these instances, it may be possible to impute or adjust for missing data on an existing reference standard, correct an imperfect reference standard, construct a reference standard from multiple existing tests, or validate index test results with respect to future clinical events or other clinical characteristics. See, e.g., Rutjes AWS, Reitsma JB, Coomarasamy A, et al. Evaluation of diagnostic tests when there is no gold standard. A review of methods. Health Technol Assess 2007;11(50).
67 A framework for evaluating tests can be modeled on hypothetical long-term RCTs of testing and treatment strategies to guide the selection and interpretation of available evidence, or new evidence as necessary, to assess the indirect impact of testing on outcomes. The evidence required may vary according to whether a new test will be used as a replacement, add-on, or triage test, and its intended benefits. See: Lord SJ, Irwig L, Bossuyt PM. Using the principles of randomized controlled trial design to guide test evaluation. Med Decis Making 2009;29(5):E1-E12.
prospective cross-sectional study that compares sensitivity and specificity and positive and negative predictive values of the new test to that of an acknowledged gold standard in a spectrum of patients at risk for the disease or condition in question.

The method for assessing prognosis of a disease or condition may be a patient cohort study of people with the condition with follow-up at uniform time intervals in the clinical course of the condition. Case control studies can be used to identify risk factors for a condition. As noted above, registries and surveillance studies can be used to monitor patient populations for the incidence of serious or rare adverse effects that may not arise in RCTs that are too small, insufficiently representative of target patient populations, or too short in duration to detect such adverse effects. Although observational studies and clinical trials that are not randomized tend to be less rigorous than RCTs, well-designed studies of these types can provide evidence that is sufficiently strong for making clinical and policy decisions.68, 69

Recent and evolving evidence hierarchies and standards pertaining to testing increasingly are reflecting the need to fit the evidence requirement to the question. For example, as shown in Figure 2, EGAPP recognizes different levels of evidence derived from various study designs and data sources for each of analytic validity, clinical validity, and clinical utility.

Figure 2. EGAPP Hierarchies of Data Sources and Study Designs for Components of Evaluation

<table>
<thead>
<tr>
<th>Level</th>
<th>Analytic Validity</th>
<th>Clinical Validity</th>
<th>Clinical Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (highest)</td>
<td>Collaborative study using a large panel of well-characterized samples</td>
<td>Well-designed longitudinal cohort studies</td>
<td>Meta-analysis of RCTs</td>
</tr>
<tr>
<td></td>
<td>Summary data from well-designed external proficiency testing schemes or interlaboratory comparison programs</td>
<td>Validated clinical decision rule</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Other data from proficiency testing schemes</td>
<td>Well-designed case-control studies</td>
<td>A single RCT</td>
</tr>
<tr>
<td></td>
<td>Well-designed peer-reviewed studies (e.g., method comparisons, validation studies)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Expert panel reviewed FDA summaries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Less well designed peer-reviewed studies</td>
<td>Lower quality case-control and cross-sectional studies</td>
<td>Controlled trial without randomization</td>
</tr>
<tr>
<td></td>
<td>Unpublished and/or non-peer-reviewed research, clinical laboratory, or manufacturer data</td>
<td>Unvalidated clinical decision rule</td>
<td>Cohort or case-control study</td>
</tr>
<tr>
<td>4</td>
<td>Studies on performance of the same basic methodology, but used to test for a different target</td>
<td>Case series</td>
<td>Case series</td>
</tr>
<tr>
<td></td>
<td>Unpublished and/or non-peer-reviewed research, clinical laboratory, or manufacturer data</td>
<td>Unpublished and/or peer-reviewed studies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consensus guidelines</td>
<td>Clinical laboratory or manufacturer data</td>
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<td></td>
<td>Expert opinion</td>
<td>Consensus guidelines</td>
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<td>Expert opinion</td>
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68 Sawaya 2007.
E. Strengthening the Contribution of Laboratory Testing Data to CER

As described above, administrative and clinical data from laboratory testing have significant potential to contribute to CER. Laboratory results provide objective, scientific, patient-specific data for accurate diagnosis, treatment, and management of disease. Laboratory data enable risk-stratification of populations to identify patients at different levels of risk for case management and disease management interventions. They provide the ability to track and improve clinical outcomes that can translate into cost savings through avoided hospital admissions, fewer adverse events, and a reduction in morbidity related to chronic illnesses.\(^{70}\) Laboratory data also support assessments that link clinical interventions to evidence-based guidelines.

Although claims data analyses have a prominent role in CER, there are limitations in the presence and consistency of laboratory data in claims data. Claims usually have data on diagnoses, treatments (medical and surgical procedures, drugs, device implants, etc.), and certain types of events and outcomes. However, claims data typically lack detailed information on laboratory test results and other clinical variables such as lifestyle factors and other physiological measures. As noted above, analyses that can link claims data, registries, and other data sources will be a key element of CER. The ability to do so depends on patient identifiers that enable matching data across these sources. However, as noted in the IOM priorities report, linking of laboratory data this way presents greater challenges:

“Patient identifiers in pharmaceutical dispensing, hospital discharges, and diagnosis and procedure codes are standardized across most systems. However, information from laboratory results, enrollment, and utilization data usually require significant harmonization of patient identifiers to link the information from multiple sources into an analyzable, single patient record.”\(^{71}\)

Greater standardization in EHR systems and expansion of integrated health information networks will contribute to more consistent and reliable use of laboratory data for CER.

Evidence requirements and grading approaches that are applied to laboratory testing are gradually changing and are being affected by trends in generation of primary data and analyses of observational data. While RCTs will remain the preferred study design for generating direct evidence of causal effects of interventions on patient outcomes, strengthening of other study designs and emergence of others are helping to supplement and, in some instances, substitute for RCTs. Included are evolving variations in traditional clinical trial designs (e.g., practical clinical trials and adaptive and Bayesian trial designs) and “mining” and other analyses of clinical data sources (e.g., electronic medical records, patient registries) to evaluate populations, interventions, and outcomes. New methods also may involve studies by clinical laboratories that can link de-identified patient samples gathered for testing purposes to patient outcomes. New methods and tools for developing and evaluating evidence are necessary to adequately address the effectiveness of interventions on risks, the changing disease patterns of comorbidities, and heterogeneity of treatment effects based on individuals’ genetic variations.\(^{72}\)

\(^{70}\) Mennemeyer 2000.
\(^{71}\) IOM 2009.
The importance of the contribution of laboratory medicine to CER has been highlighted with the increased focus on gene-based laboratory testing. AHRQ has recognized that “data are needed for public health surveillance of the utilization of gene-based tests to be able to monitor trends in use, appropriateness of use, and potential disparities in utilization.” AHRQ commissioned one of its Evidence-based Practice Centers to assess existing databases in the U.S. to monitor utilization and outcomes of gene-based applications. AHRQ found limited information on the use of gene-based tests over time, the extent to which patients and families are aware of these tests and their benefits and harms, and longitudinal evidence on the impact of these tests on clinical decisions and patient outcomes (Box 8). Inadequate information on gene-based tests will limit the ability to demonstrate the value of these tests to clinicians, patients, and payers, especially to the extent that these decision-makers seek information about clinical utility of these tests. AHRQ’s recommendations include improving coding of gene-based tests, adopting standards for collecting and storing genetic testing data from laboratories, and other data collection on the availability and adequacy of services related to genetic testing. Clearly, there is an opportunity for the laboratory medicine sector to make contributions to the national capacity for CER and to increase its role in CER priority setting, study design, and conduct of studies by leveraging an improved infrastructure for laboratory data.

**Box 8**

Infrastructure to Monitor Utilization and Outcomes of Gene-Based Applications

**Findings:**
- Only limited, sporadic information is available on the utilization of gene-based tests over time.
- Some research and surveys suggest that knowledge on the part of some providers about the availability and utility of tests may be reasonably widespread and accurate.
- Little or nothing is known about the extent to which patients and their families are aware of tests and knowledgeable about their benefits and harms.
- There are few longitudinal data to indicate the benefits and risks of using genetic tests to guide interventions and medical decisions, such as in the selection of therapies, and their short- or long-term outcomes.

**Recommendations:**
- Improve the coding of gene-based tests in many of the relevant databases so that the test types, reason for test, and test results can be readily determined.
- Develop or adopt standards for the proper collection and storage of data from genetic testing laboratories for archiving the tests performed and facilitating interoperability between databases.
- Explore the possibility of adding questions to ongoing surveys or developing new surveys to monitor the availability of genetic testing centers, adequate counseling, and barriers to accessing counseling services.
- Consider establishing survey of genetic testing laboratories similar to National Ambulatory Medical Care Survey for medical clinics and the National Hospital Discharge Survey for hospitals.
- Develop pilot studies for a small set of diseases and tests.

F. Accounting for Personalized Medicine

The increasing prominence of personalized medicine (PM) presents important considerations for CER of laboratory testing. Among the various definitions of PM is the following:

“Personalized medicine” refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not. — President’s Council of Advisors on Science and Technology

The ability to deliver PM depends in large part on laboratory testing, particularly genetic and genomic testing, to distinguish such patient traits as ability to metabolize certain medications. Examples include genetic/genomic testing for: tamoxifen therapy for early stage breast cancer, selective serotonin-reuptake inhibitors (SSRI) treatment for adult depression, warfarin anticoagulation response, and epidermal growth factor receptor (EGFR) inhibitor (e.g., cetuximab and panitumumab) treatment for metastatic colorectal cancer. The information from test results is incorporated into the tailoring of medical treatments to patients’ individual characteristics and other aspects of their care.

Although the purpose of CER is to determine which health care intervention works best for a given health care problem, the purpose of PM is to ensure that health care delivers ‘the right treatment to the right patient at the right time.’ Like most other forms of evaluation of health care interventions, CER is usually oriented toward evaluating the impact of therapies and other interventions across study populations, while PM focuses on using individuals’ genomic information and other personal traits to inform decisions about their health care. This distinction has implications for applying CER findings to PM. Interventions that have a statistically significant treatment effect across a population on average do not necessarily work for all treated patients; they may be ineffective for some patients and harmful for others. Interventions that do not have a statistically significant treatment effect across a study population—and that may be dismissed as ineffective—may work for certain subgroups.

For CER to contribute to PM, it must account for individual patient and subgroup differences that influence the impact of interventions on health outcomes. These characteristics can include severity of disease, comorbidities and risk factors, genetic characteristics, sociodemographic characteristics, health-related behaviors, environmental factors, and more. The variable impacts on patient outcomes, including health benefits and harmful side effects that can arise from these different characteristics, are sometimes known as “heterogeneity of treatment effects” (HTEs).

CER must draw from its broad methods portfolio to address the needs of PM. Different methods may be required, for example, to assess short- and long-term comparative effectiveness of alternative therapies, identify subgroups with variable treatment responses, identify short-term as well as rare or delayed adverse effects, and compare alternative tests for accuracy and ultimate impact on health outcomes. Of key relevance to PM is the extent to which one or a combination of these methods can generate clinically and statistically significant effects.

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findings at sufficiently discrete levels to inform decisions about using interventions whose outcomes are sensitive to individual differences. Certainly, the need for subgroup-specific CER findings varies for different health care problems and interventions. The strengths and limitations of CER findings and other evidence, including whether it accounts for HTEs as opposed to an average effect across a population, must be accurately reflected in product labeling, guidelines, payment policies, utilization management, and other gatekeeping policies.

There are encouraging signs for the recognition of PM in CER. The IOM and FCCCER priority setting reports, as well as pending health reform legislation, emphasize the need for subgroup analyses. In describing the purpose of CER, the IOM includes “improve health care at both the individual and population level” and “describing results at the subgroup level.” The FCCCER definition states that CER “must assess a comprehensive array of health-related outcomes for diverse patient populations and subgroups.” Recognizing the importance of documenting the extent to which CER accounts for PM and identifying ways to further this capacity, AHRQ is sponsoring an analysis of how well comparative effectiveness studies conducted by CER agencies in the U.S. and abroad have accounted for HTEs.

VI. Main Implications for the Laboratory Testing Sector

The increased focus on CER in the U.S. and related global developments have significant implications for the laboratory testing sector, including makers of laboratory test kits and systems regulated by FDA and clinical laboratories providing laboratory testing subject to CLIA.

CER evidence expectations pertaining to head-to-head comparisons, routine practice settings, diverse patient groups, and health outcome measures are augmenting, and may modify, existing evidence requirements for regulation, reimbursement, and quality assessment of laboratory testing. Evidence requirements are generally increasing, although there are some flexibility and diversity of approaches. In particular, it is difficult to demonstrate causal connections between laboratory tests and health outcomes. Innovators and makers of laboratory tests should anticipate evidence requirements of gatekeepers and other decision-makers throughout technology lifecycle. Who will want what evidence when?

In developing and validating new tests, innovators should plan how to demonstrate to relevant decision-makers the impact of tests, including their comparative effectiveness on patient outcomes, where appropriate. This may entail determining the feasibility and value of demonstrating impact using one or more approaches. One may be indirectly, through chains of existing or new evidence from a test to a therapeutic decision or to surrogate outcomes or to patient outcomes. Another approach may be to generate new evidence that establishes a direct link between a test and patient outcomes. Various types of modeling may be used to simulate these determinations. Whether in the U.S. or abroad, the approach to demonstrating value may

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74 IOM 2009.
75 FCCCER 2009.
be informed by preliminary communications with such groups as health professional organizations, regulatory agencies, government and private payers, health technology assessment organizations, or other entities. Demonstrating one or more of analytic validity, clinical validity, or clinical validity will call for particular data sources and study designs, and related resource requirements.

Drawing upon its considerable scientific and technical expertise, experience, and perspectives, the laboratory medicine sector can make important contributions to CER. This sector should continue to monitor and participate in developments pertaining to building national CER capacity and the conduct of CER. This includes matters of CER priority setting, study design, and data sources, as well as the transparency and accountability of the conduct, reporting, and use of the findings of CER. Given the special scientific, medical, and public emphasis on the emerging field of PM, it will be especially important to ensure that CER study design and data collection account for HTEs.

The laboratory medicine sector should carefully consider, anticipate, and act upon the opportunities and risks that CER poses to innovation. CER is influencing innovation, posing opportunities for development of some new tests and diminishing prospects for others that are less likely to fare well in a market informed by head-to-head comparisons. With that emphasis on head-to-head comparisons as well as impact on patient outcomes and utility in usual or routine practice settings, CER can help to orient innovation toward greater value. Technologies that achieve prevailing evidence requirements and demonstrate superior effectiveness or comparable effectiveness at lower cost will gain market advantages. Federal funding and other support for CER and related analytical tools and methods, databases, and training will augment and complement industry R&D and could reduce development costs of some tests, including those used in PM. As is occurring in the global pharmaceutical and biotechnology sectors, the laboratory testing sector should incorporate these considerations into strategies for R&D.

VII. Key Findings and Conclusions

Overarching conclusion:

CER presents distinct challenges and opportunities to laboratory medicine, which has multiple integral roles in the national CER agenda. CER of laboratory testing requires informed selection of study designs, outcome measures, and other research characteristics that are suitable for assessing the typically indirect, though often substantial, contribution of laboratory testing to patient health.

1. Laboratory testing has multiple roles in CER, including as:

   - An indicator of intermediate and long-term patient outcomes in CER focusing on therapies and other interventions.
   - The subject intervention in CER, e.g., in head-to-head comparisons involving alternative laboratory tests or comparisons of a laboratory test to another type of test for a particular health care condition, or as part of broader protocols (e.g., involving alternative sets of tests and therapies) being compared for managing particular health risks or diseases.

2. CER evidence expectations for head-to-head comparisons, routine practice settings, diverse patient groups, and health outcome measures are adding to, and may otherwise modify, existing evidence requirements for regulation and reimbursement of laboratory testing.
3. The currently available evidence base for most laboratory tests generally does not extend to the types of evidence sought for CER. Evidence presented to FDA for meeting applicable requirements for market approval or clearance of laboratory tests, and provisions for quality requirements for laboratory-developed tests subject to CLIA, typically do not address comparative effectiveness or other attributes of CER, such as head-to-head comparisons versus a standard of care provided to diverse patient populations under routine rather than ideal conditions, and emphasizing the impact on patient outcomes rather than surrogate or other intermediate measures.

4. In contrast to the typically direct relationship between a therapy and health outcomes such as survival, morbidity, and quality of life, the relationship between a laboratory test and health outcomes is usually indirect.

   - It is essential to recognize this difference when planning and conducting CER, including in setting priorities and selection of study design, outcome measures, and other aspects.
   - Where validated surrogate outcomes exist, it may not be necessary to follow patients long enough to detect differences in health outcomes.

5. Although an RCT is the most rigorous study design to use when the object of an investigation is to establish whether a test has a direct impact on health outcomes, RCTs should not be the default study design for CER of laboratory tests.

   - Given the multiple intervening steps between accurate test results and improved health outcomes, conducting RCTs on laboratory tests for direct evidence on patient outcomes can be time-consuming, complex, costly, and, in certain instances, infeasible.
   - The need for an RCT is diminished when the therapeutic decision based on accurate test information is well established and when there is strong evidence pertaining to the impact of the therapy on patient outcomes or on a validated surrogate outcome.
   - Whether the test result has an impact on patient management and outcomes might involve decision analysis based on available evidence pertaining to clinician decision-making and other evidence (especially from RCTs) of the impact of the relevant therapies on patient outcomes.

6. New methods and analytical tools are emerging for demonstrating the comparative effectiveness of laboratory testing. While RCTs remain the preferred study design for establishing causal effects of interventions on patient outcomes, strengthening and emergence of other study designs are helping to supplement and, in some instances, may substitute for traditional RCTs. Included are variations in traditional clinical trial designs; “data mining” of claims data, patient registries, and EHRs; retrospective studies of specimen remnants; and analyses of linked data sets of laboratory data and patient outcomes.

7. CER of laboratory testing should draw on the full portfolio of evolving CER methods in order to answer different types of evidence questions.

   - Certain types of observational studies, particularly linked analyses of claims data, patient registries, and de-identified EHR data, can provide useful evidence for clinical validity and clinical utility of laboratory tests.
The prospect of linking administrative and clinical data from laboratory testing has significant potential to contribute to CER. However, in contrast to other health care services, far more effort is needed to harmonize patient identifiers to enable linking information from laboratory results, enrollment, and utilization into a set of analyzable patient records. Greater standardization in EHRs and expansion of integrated health information networks will contribute to achieving this potential.

8. Innovation in gene-based laboratory testing, including in pharmacogenomic testing to inform targeted use of drugs, is focusing greater attention on evidence requirements for these tests. Currently inadequate information on many gene-based tests limits the ability to demonstrate their value to clinicians, patients, and payers.
   - Evidence needs, and corresponding study designs and data sources, will vary across these tests for demonstrating analytic validity, clinical validity, and clinical utility.
   - Improved coding of gene-based tests, adopting standards for collecting and storing genetic testing data from laboratories, and other data collection on the availability and adequacy of services for genetic testing are needed. Such improvements would improve the contribution of the laboratory medicine sector to the national capacity for CER.

9. Few comparative effectiveness reviews focusing on laboratory tests have been conducted, largely because CER priorities to date have included few laboratory tests and due to the lack of primary studies of the comparative effectiveness of laboratory tests. Those that have been completed to date by AHRQ and other organizations call attention to the need for more evidence of the impact of testing on health outcomes and for more resources to monitor use and impact of gene-based testing on health outcomes.

10. Laboratory testing has prominent roles in the national agenda for CER that provides opportunities for broad demonstration of value in “real-world” health care.
   - National CER priorities recommended by the IOM and FCCCER, along with large CER-related grants of NIH, include those with laboratory testing as the subject technology and many others for which laboratory testing would be integral to conducting the CER.
   - Included among the IOM’s top tier of recommended national CER priorities are screening for methicillin resistant *S. aureus* (MRSA) and genetic and biomarker testing for five major types of cancer and “possibly other clinical conditions.”
   - Many laboratory tests have well-established clinical value, are not associated with high clinical uncertainty, and are unlikely to be priority topics for CER.

11. Along with related evidence requirements of health care decision-makers, CER is influencing innovation in laboratory testing. CER can steer innovation toward greater value; technologies that achieve prevailing evidence requirements and demonstrate superior effectiveness or comparable effectiveness at lower cost will gain market advantages.
   - Federal funding and other support for CER and related methods, infrastructure, and training could reduce development costs of some tests, including those used in PM.
   - As is so for the global pharmaceutical and biotechnology sectors, the laboratory testing sector should incorporate these considerations into strategies for R&D.