Molecular diagnostic tests continue to expand outside of the esoteric genetic laboratory into primary care, oncology, neurology, and for any provider of prescribed medications. Some of the newer molecular tests represent an advance in technology enabling more refined and comprehensive analysis, such as the evolution from standard G-banded karyotyping to chromosomal microarrays to gene panels based on massively parallel (“next gen”) sequencing. These technical innovations promise to deliver more accurate and complete information at progressively lower costs to laboratories and ultimately the health care system. Yet patients will not have access to these tests without adequate coverage and reimbursement by payers, since most patients cannot afford to pay for the tests out of pocket. Recently, there have been significant changes to the coding for molecular diagnostics in an effort to increase transparency and specificity in billing (1), with the net effect that reimbursed prices for many molecular diagnostic tests have actually decreased. Nevertheless, due to increased utilization of tests by clinicians and continued introduction of new tests, payers remain concerned that in the aggregate, molecular diagnostic tests represent a technology category with considerable potential for cost growth that merits additional scrutiny.

For example, in a recent report focused on the topic of personalized medicine, UnitedHealthcare found that their expenditures on molecular diagnostic tests increased 14% annually between 2008 and 2010, a rate significantly higher than that of clinical laboratory services overall (2). Approximately 70% of this increase was due to increased test use; the remainder was due to higher prices and test complexity and intensity. Projections of the rate of growth of the molecular diagnostics market over the next 5–10 years are dependent on assumptions about test adoption rates, pricing trends, and technical innovations, but most analysts predict continued rapid expansion.

This same study surveyed a statistically representative sample of primary and specialty-based US physicians (n = 1254) regarding their use of molecular diagnostic testing and found that although current utilization was relatively low, the number one reason reported by the majority of respondents (77%) was concern over the cost and reimbursement of the test for their patients. Equally worrisome was the finding that three-fourths of physicians were somewhat or very concerned about the quality of evidence supporting the use of genetic testing.

Clinical utility is defined as the assessment of the effects of testing on net patient health outcomes and is the evidentiary standard applied by most payers when evaluating tests for coverage decision-making. Research has demonstrated that the access to evidence of clinical utility drives payers’ coverage and reimbursement policies for molecular diagnostic testing in general (3). Clinical utility, as well as information regarding analytic validity, clinical validity, the target condition, and the affected population provides payers with the evidence base for making an informed coverage determination. In a recent study of the publicly available genetic testing coverage policies of private payers, 50% of insurers specifically referenced the need for evidence of clinical utility; tests that were uniformly covered tended to be those supported by clear evidence and recommended by professional and governmental guidelines (4). For example, most payers will cover a US Food and Drug Administration-approved companion diagnostic test that is codeveloped with a drug, although questions about clinical utility may remain when the test and drug are developed independently.

With no regulatory demand for clinical utility information, payers have placed this burden on the test developers to prove the value of their products (5). The evaluation of clinical utility of a molecular diagnostic test is inherently a comparative effectiveness question, as the assessment requires a comparison of the effects of testing vs not testing (or new test vs standard test) on clinical decision-making and patient outcomes. What is not often appreciated is that this assessment does not always require that the study be a randomized controlled trial but may include other methodologies, such as observa-
tional studies, depending on the state of the evidence and the clinical context (6).

While the field of comparative effectiveness research has garnered increased attention to inform evidence-based medical practice, it has not appeared to have had as substantial an impact on the fields of pathology and genetics, thereby contributing to the slow implementation of molecular diagnostic testing in clinical settings (7). The role of clinical laboratories in comparative effectiveness research has not been considered in detail, either as the beneficiary of comparative effectiveness research or as a contributor to comparative effectiveness research. This is no longer the case because there is growing appreciation that analytic validity, clinical validity, and clinical utility are not independent properties and that the technical features of the test need to be confirmed before proceeding to studies to evaluate clinical utility.

It will be particularly important to involve molecular diagnostic researchers, pathologists, and genetics professionals when designing studies to demonstrate the clinical utility of next generation sequencing–based tests, given the complexity of information produced and the potential for variation in the results generated across different testing platforms. What is also needed is the ability to conduct comparative effectiveness studies using data collected as part of routine clinical care delivery to reduce the costs of research and increase the quality and quantity of evidence available to decision-makers such as payers.

Development of the research infrastructure to efficiently conduct comparative effectiveness research is one important strategy to address the barriers to generating better evidence of clinical utility. For example, the Patient Centered Outcomes Research Institute has funded the creation of a national comparative effectiveness research network comprising 29 centers across the country linked by a common data platform that is intended to facilitate both randomized controlled trials and observational studies that reflect the priorities of patients and frontline clinicians (8). Another hurdle has been the lack of methodological standards to guide the design of studies that would meet the information needs of decision-makers such as payers and professional societies. A multistakeholder group met recently to review the various methods used and to evaluate the quality of studies underpinning evidence-based recommendations or treatment guidelines (9). While many organizations appraise the robustness of the scientific evidence on the basis factors such as clinical topic, study design, consistency of estimated effect, and sample size, the approaches to evidence evaluation vary, as do the criteria for setting evidentiary thresholds for decision-making.

The reasons for the lack of clinical utility data are multifactorial and solutions will require the participation of all stakeholder groups, including laboratory professionals. Although there is widespread agreement about the need for information about clinical utility, there is also recognition that requiring randomized clinical trials for all tests before introduction into clinical practice is not feasible and may stifle innovation. Groups such as the Institute of Medicine’s Roundtable on Translating Genomic-Based Research for Health has identified comparative effectiveness research as an important strategy to facilitate clinical utility studies by promoting both a wider range of valid study designs and stakeholder-informed priorities and outcome measures (10).

Comparative effectiveness studies are characterized by their emphasis on providing results that are informative to decision-makers. Typically they include study populations and settings that are representative of clinical practice and data elements that are reflective of the priorities of a broader range of stakeholders such as patients, clinicians, and payers. The study designs may be retrospective or prospective and the funding may include public–private partnerships or novel reimbursement mechanisms such as “coverage with evidence development” for which provisional coverage is granted by a payer under the condition that additional evidence is collected as part of a study. A number of studies in pharmacogenetics have compared genotype-guided treatments to standard of care. For example, the longstanding debate regarding the use of testing to guide warfarin dosing remains unsettled according to the results of 2 recent randomized clinical trials (11, 12). These findings were attributed in part to protocol-driven careful monitoring of anticoagulation status, as well as the selection of an intermediate endpoint (differences in international normalized ratio values) rather than clinical endpoints (13). The results of the coverage with evidence development study supported by the Centers for Medicare and Medicaid Services are still pending, but this trial focuses on warfarin-related clinical events, including major hemorrhage and thromboembolic events as the primary endpoints. Nevertheless, until the results of this trial are available, many payers will continue to not provide coverage for pharmacogenetic testing for warfarin due to lack of evidence of clinical utility.

In contrast, evidence supporting the clinical utility of genetic testing for Lynch syndrome in first-degree relatives of patients newly diagnosed with colorectal cancer was determined on the basis of modeling, constructing a chain of evidence using data from various sources (14). Testing for Lynch syndrome is frequently covered by payers, based on the positive evidence review conducted by EGAPP (Evaluation of Genomic Applications in Practice and Prevention). Payers also routinely cover Kirsten rat sarcoma viral oncogene homolog (KRA5) testing prior to prescribing panitumumab and cetuximab in the setting of metastatic colorectal cancer, for which the association between KRA5 mutation status and treatment response was established by prospective–retrospective
analyses using archived tissue samples from the drug efficacy trials (15, 16).

Evidence-based coverage policies for molecular diagnostics are intended to promote the adoption of testing that provides a net benefit to patients while limiting access to costly testing that does not. On the basis of numerous examples of tests with demonstrated utility, particularly in the area of companion diagnostics and tests for hereditary cancers, payers are cautiously optimistic about the potential for molecular diagnostics to make health care more cost-effective but require objective evidence to support these claims. Investments in comparative effectiveness research infrastructure and methods are critical enablers of current and future clinical utility studies that require participation from all stakeholders to ensure their relevance for decision-making.

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References