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SPECIAL ARTICLE

The Spectrum of Clinical Utilities in Molecular Pathology Testing Procedures for Inherited Conditions and Cancer

A Report of the Association for Molecular Pathology

Loren Joseph,[*†] Milena Cankovic,[*‡] Samuel Caughron,[*§] Pranil Chandra,[*¶] Rajyasree Emmadi,[*‖] Jill Hagenkord,[*,**] Stephanie Hallam,[*††] Kay E. Jewell,[*‡‡] Roger D. Klein,[*§§] Victoria M. Pratt,[*¶¶] Paul G. Rothberg,[*‖‖] Robyn L. Temple-Smolkin,[***] and Elaine Lyon[*†††]

From the Association for Molecular Pathology's Framework for the Evidence Needed to Demonstrate Clinical Utility Task Force,[*] the Association for Molecular Pathology,[***] Bethesda, Maryland; the Department of Pathology,[†] Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; the Department of Pathology and Laboratory Medicine,[‡] Henry Ford Hospital, Detroit, Michigan; the MAWD Pathology Group, PA,[§] North Kansas City, Missouri; the PathGroup, LLC,[¶] Brentwood, Tennessee; the Department of Pathology,[‖] College of Medicine, University of Illinois at Chicago, Chicago, Illinois; 23andMe, Inc.,[**] Mountain View, California; Good Start Genetics, Inc.,[††] Cambridge, Massachusetts; the Tara Center, LLC,[‡‡] Stevens Point, Wisconsin; the Department of Molecular Pathology,[§§] Cleveland Clinic, Cleveland, Ohio; the Department of Medical and Molecular Genetics,[¶¶] School of Medicine, Indiana University, Indianapolis, Indiana; the Department of Pathology and Laboratory Medicine,[‖‖] School of Medicine and Dentistry, University of Rochester Medical Center, Rochester, New York; and the Department of Pathology,[†††] University of Utah School of Medicine and ARUP Laboratories, Salt Lake City, Utah

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Address correspondence to Elaine Lyon, Ph.D., Department of Pathology, University of Utah School of Medicine and ARUP Laboratories, 15 N Medical Dr E, Salt Lake City, UT 84112. E-mail: lyone@aruplab.com.

Clinical utility describes the benefits of each laboratory test for that patient. Many stakeholders have adopted narrow definitions for the clinical utility of molecular testing as applied to targeted pharmacotherapy in oncology, regardless of the population tested or the purpose of the testing. This definition does not address all of the important applications of molecular diagnostic testing. Definitions consistent with a patient-centered approach emphasize and recognize that a clinical test result's utility depends on the context in which it is used and are particularly relevant to molecular diagnostic testing because of the nature of the information they provide. Debates surrounding levels and types of evidence needed to properly evaluate the clinical value of molecular diagnostics are increasingly important because the growing body of knowledge, stemming from the increase of genomic medicine, provides

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many new opportunities for molecular testing to improve health care. We address the challenges in defining the clinical utility of molecular diagnostics for inherited diseases or cancer and provide assessment recommendations. Starting with a modified analytic validity, clinical validity, clinical utility, and ethical, legal, and social implications model for addressing clinical utility of molecular diagnostics with a variety of testing purposes, we recommend promotion of patient-centered definitions of clinical utility that appropriately recognize the valuable contribution of molecular diagnostic testing to improve patient care. *(J Mol Diagn 2016, 18: 605—619; http://dx.doi.org/10.1016/j.jmoldx.2016.05.007)*

The roles of clinical validity (CV) and clinical utility (CU) in determining the medical usefulness of a molecular pathology testing procedure have been the subject of intensifying discussions since the implementation of new molecular pathology current procedural terminology codes (current procedural terminology is a registered trademark of the American Medical Association). Establishing CV is fundamental to CU (Table 1). Qualitative criteria for CV have historically been the standard for insurance coverage determinations.[1] Title XVIII of the Social Security Act, Section 1862(a)(1)(A) prohibits Medicare payment "…for items or services which are not reasonable and necessary for the diagnosis and treatment of illness or injury…" with certain exceptions.

Increasing costs of targeted therapies for patients whose molecular test results indicate a likelihood of response potentially may lead to unsustainable payments and concomitant premium increases. The IMS Institute for Healthcare Informatics demonstrated the average monthly price of cancer therapy in the United States increased 39% in the 10-year period of 2004 to 2014, from $14,821 to $20,700, when adjusted for inflation, with targeted therapies and medications accounting for almost 50% of the spending (IMS Health Holdings, Inc., *http://www.imshealth.com/en/thought-leadership/ims-institute/reports/global-oncology-trend-2015#ims-form*, last accessed April 9, 2016). Advances in cancer patient care increased the US 5-year relative cancer survival rates between 1990 and 2010 across multiple cancer types. The variety and increasing complexity of molecular testing methods, especially gene expression signatures and next-generation sequencing (NGS) tests, are factors payers cite as reasons for comprehensive scrutiny of the validity, outcomes, and cost-effectiveness.

Recently, several Medicare administrative contractors have associated evaluations of both analytical validity and CV with Medicare's reasonable and necessary requirement and have demanded evidence for both in addition to evidence of CU (Centers for Medicare and Medicaid Services Local Coverage Determination Palmetto L33599; CGS L36021; Noridian L33541, details available at *www.cms.gov*, accessed May 6, 2016). Of most concern are expensive genomic sequencing procedures (GSPs). Although NGS gene panels and even whole exome sequencing (WES) may be cost-effective compared with testing several known relevant genes, a potential indirect cost of large oncology gene panels is the increased likelihood of finding a mutation for which there is an expensive therapy, possibly off-label, or in a clinical trial. For inherited diseases, gene panels or exome testing may identify variants of currently unknown clinical significance potentially triggering a cascade of other medical procedures. This affects discussion of costs in complex ways, but providers find these analyses to have CU, as they are taking action based on the molecular results.

Levels and types of evidence to properly evaluate the clinical value of molecular diagnostics merit discussions to standardize criteria because the growing body of knowledge from genomic medicine provides many new opportunities for molecular testing to improve health care.[2] Practical challenges in demonstrating CU for molecular pathology testing procedures exist under any model. General principles for evaluating CU in molecular diagnostics are the same as for any test in medicine, from imaging to clinical chemistry. However, molecular diagnostics can have unique features that hinder collecting evidence at the same level. For inherited disorders, constraints include low prevalence for specific disorders (although high in aggregate), lack of available targeted therapies, difficulty quantifying the impact of testing on psychological well-being and long-term care, and difficulty obtaining pertinent family information. In oncology, limitations include a low frequency for many mutations in a given type of cancer, even lower frequency for combinations of mutations, prolonged cancer clinical trials because of low levels of patient recruitment, and the paucity of broad molecular profile data in most cancer trials to date. In fact, many neoplasms remain rare and/or contain undefined causative genetic alterations. Despite the challenges, patient-centered clinical molecular diagnostics, including interpretation, conducted by appropriately trained and certified molecular pathologists or clinical medical geneticists can demonstrate compelling CU, as described in examples provided herein. We recommend a definition of CU for molecular diagnostic procedures on the basis of a modified analytic validity, clinical validity, clinical utility, and ethical, legal, and social implications (ACCE) framework (Table 1) (Centers for Disease Control, *http://www.cdc.gov/genomics/gtesting/ACCE/acce_proj.htm*, accessed April 9, 2016) as follows: CU for molecular diagnostics is the ability of a test result to provide information to the patient, physician, and payer related to the care of the patient and his/her family members to diagnose, monitor, prognosticate, or predict disease progression, and to inform treatment and reproductive decisions.

Although the scope of this report is restricted to molecular pathology testing procedures for inherited conditions and cancer, these recommendations can be extended to additional applications of molecular testing.

Clinical Utility Has Many Faces

Molecular diagnostics are used for multiple purposes, ranging from diagnosis of disease in patients, risk assessment of an inherited disease in family members, evaluation of patients whose family history indicates they are at high risk of a disease, prediction of future disease, prognosis, monitoring, disease recurrence, and therapy selection. Some tests can be used for multiple indications; thus, the CU of molecular diagnostics is context dependent (Supplemental Appendix S1).[3–10] The Medical Test Methods Guide presented by the Agency for Healthcare Research and Quality includes the assertion that the value of a medical test must always be linked to the context of use, including molecular diagnostics.[11] Although CU has many aspects, the ultimate goal is to provide information necessary to care for the patient or a family member. Molecular diagnostics can have broad impacts for patient care. Molecular results need to be integrated with additional clinical findings into the medical team's global patient assessment and management, especially in the context of patient-centered care (Supplemental Tables S1[12] and S2 and Supplemental Appendix S1[11,13–20]). The decision to perform molecular testing is made by the treating clinician on the basis of the patient's symptoms, history, and clinical findings, often after pretest consultation with a molecular pathology/medical genetics professional.[21] The reasons for testing are commonly classified as diagnosis, prognosis, and prediction. Of these, diagnosis is the foundation.

Diagnosis

Importance of Molecular Diagnosis in Inherited Diseases

Establishing a diagnosis by molecular genetic testing procedures for a patient with an inherited or de novo genetic germline disorder has inherent CU even in the absence of guided therapy. Historically, inherited conditions were diagnosed on the basis of clinical history and phenotype. This clinical paradigm—a treating physician forms an initial clinical impression, including a differential diagnosis, and orders the appropriate clinical or confirmatory tests—remains applicable to molecular diagnostics.

For many inherited diseases, the phenotype does not always point to a definitive diagnosis. Even classic mendelian single gene disorders can present challenges, such as variable expressivity, locus heterogeneity, allelic heterogeneity, and incomplete (or reduced) penetrance. Basing a diagnosis on phenotype alone can result in incorrect and/or delayed diagnosis. Accurate and timely diagnoses can significantly affect patient, family, and physician decision-making by clarifying the level of risk and prognosis, treatment options, and associated comorbidities. Genetic diagnosis provides recurrence risk for the family and thereby facilitates preconception intervention or prenatal diagnosis for at-risk relatives. Marfan syndrome is a connective tissue disorder with variable clinical expression[22] and is caused by pathogenic variants in *FBN1*, but has overlapping phenotypes with other genetic diseases. Aortic dysfunction is present in some cases of Marfan syndrome and, when detected, can be prophylactically treated with β-blockers; other surveillance can identify early eye or skeletal complications.

In patients with suspected genetic disorders, the standard of practice has been to follow phenotype-driven iterative algorithms, single gene test at a time, including radiographic studies, biopsies, metabolic analysis, and cytogenomic analysis. Despite these efforts, most patients remain without a diagnosis.[23] Consecutive negative results can delay a definitive diagnosis and allow development of adverse consequences (ie, increased morbidity). Termed the diagnostic odyssey, this approach to diagnosis is expensive and causes frustration to the patient, their family, and the clinicians.

When inherited genetic disorders have substantial genotypic and/or phenotypic overlap, testing several candidate genes simultaneously by a multigene panel may be appropriate. Although possible with classic Sanger sequencing, a multigene panel analyzed by NGS can result in a faster time to diagnosis and reduced cost. Continuing the example above, aortic dysfunction or dilation syndromes, which include Marfan syndrome, Loeys Dietz syndrome, Ehlers Danlos syndrome type IV, and arterial tortuosity syndrome, are tested by NGS for currently known causative genes (eg, *FBN1*, *TGFBR1*, *TGFBR2*, *COL3A1*, *MYH11*, *ACTA2*, *SLC2A10*, *SMAD3*, and *MYLK*).[22] Even though symptoms are overlapping, differentiating among these diseases is important because the clinical course of each syndrome differs.

For well-defined clinical phenotypes, an NGS gene panel can show modestly superior performance in gene coverage relative to WES.[24] In developmental delay or neurological disorders that show extensive genotypic and/or phenotypic overlap, WES is appropriate.[25] WES can also reveal incidental pathogenic variants not related to the patient's phenotype but that are associated with treatable genetic diseases (eg, hereditary cancer syndromes). Inherited cardiomyopathies are a genetically and phenotypically heterogeneous group of disorders in which mutations in dozens of different genes can lead to similar, yet different, cardiac phenotypes. These disorders are most familiar for causing sudden cardiac death in otherwise healthy, young athletes, but they also share the symptoms of palpitations and syncope. Mutations in >50 genes are known; identification of the causative variant enables the correct diagnosis and anticipation of disease course in the proband, the opportunity to prevent sudden cardiac death in these individuals,

Table 1 Definitions and Considerations

Term	Definition	Considerations
Molecular pathology testing procedures (molecular diagnostic)	Any clinical laboratory testing performed to find alterations in nucleic acids in the germline (inherited disease) or in somatic tissues (cancer).	Other applications of molecular diagnostics, such as to infectious disease or HLA typing, are beyond the scope of this document.
Clinical validity	Ability of a test to correctly classify a patient with respect to a diagnostic, prognostic, or predictive category. For example, demonstrating that the results of a test method for identifying MSI in colon cancer correlates with Lynch syndrome, or that the presence of pathogenic mutations in a specific gene is strongly associated with the presence of developmental delay.	The clinical validity for a test, even with respect to a particular application, is not a fixed value. The prevalence of the condition of interest in the population tested affects the positive predictive value and negative predictive value. The significance of a positive result in a patient with a high-risk history will be different from that for a positive result obtained from testing (screening) unselected populations. When a genetic variant affects more than one clinical outcome, the clinical end point studied needs to be specified. The clinical validity may be high for one end point and low for another.
Clinical utility	Improved patient management is determined on the basis of the results of the test in question compared to management on the basis of results of a different test or no test at all. It includes a wide range of diagnostic, prognostic, and predictive applications. The test result is necessary for the care of the patient or a family member, who may be either a future or as yet undiagnosed patient and thus is essential information for the health care professional, the patient, the patient's family, and society. We recommend a definition of clinical utility for molecular diagnostics on the basis of a modified ACCE framework as follows: Clinical utility for molecular diagnostics is the ability of a test result to provide information to the patient, physician, and payer related to the care of the patient and his/her family members to diagnose, monitor, prognosticate, or predict disease progression, and to inform treatment and reproductive decisions.	The clinical utility of molecular diagnostic testing is context dependent. A test can show excellent clinical validity but no clinical utility, depending on the context. Patient outcomes measurements are insufficient because they are greatly affected by clinical decisions that occur downstream from the molecular diagnostic test result. For clinical utility to be accurately assessed, test results must be correctly interpreted and acted on. For example, one way to demonstrate the clinical utility of MSI testing would be to show that a specific change in the standard treatment regimen led to better survival for patients with MSI-positive tumors than for patients with MSI-negative tumors. A different end point may show that testing of a proband with an inherited mutation in the MSI pathway led to identification of relatives who are carriers of the mutation and that the identified carriers fared better than unscreened relatives. An accurate diagnosis has inherent clinical utility and is foundational to directing patient care to improve clinical outcomes.
Cost-effectiveness	Impact of a medical test or treatment on the cost of care and/or on patient welfare. The latter is often measured in quality-adjusted life years.	Although numerous methods have been proposed for quantifying quality of life, or even the cost of treatment, this information is difficult to reliably estimate. Cost-effectiveness analysis is not a prerequisite for determining clinical utility, although it often supports evidence for clinical utility when such numbers are available. This type of analysis, although important, is beyond the scope of the present document.

ACCE, analytic validity, clinical validity, clinical utility, and ethical, legal, and social implications; HLA, human leukocyte antigen; MSI, microsatellite instability.

and allows subsequent targeted analysis for at-risk family members. Although gene panels are available for cardiomyopathies, American College of Medical Genetics guidelines for reporting incidental variants include examining and reporting known pathogenic variants for cardiomyopathy genes, even if not related to the patient's phenotype when WES is performed.[26] Detection of such variants provides a preventative medicine opportunity for both the proband and at-risk family members.

Thousands of clinical exomes have been described in the medical literature, demonstrating the feasibility of establishing diagnoses for rare, clinically unrecognizable, or puzzling disorders that are suspected to be genetic in origin, often delineating new genetic disorders.[27–32] Currently, diagnostic yield for WES in this setting is approximately 25%,[25] but can be up to 50% depending on clinical presentation and/or availability of family studies, and expected to increase as many more exomes are sequenced in national surveys.[33–35] A review of molecular diagnostic testing menus in US clinical laboratories reveals >100 inherited disorder-specific multigene panels.[36] Recognizing increased clinical use of NGS, the American Medical Association has established genomic sequencing current procedural terminology codes for several inherited genetic conditions, including gene panels such as aortic dysfunction, exomes, and genomes. Notably, the Blue Cross Blue Shield Association Center for Clinical Effectiveness favorably assessed WES for suspected inherited disorders, defining CU as the attainment of a diagnosis, not the direct effect on health status.[37] Whole genome sequencing is currently more expensive than WES, requires greater analysis, and generates more variants of uncertain significance. WES is a plausible approach when the clinical picture cannot be affirmed using a specific gene panel.[38] As technologies and understanding of variants advance, whole genome sequencing might become the test of choice.

Importance of Molecular Diagnosis in Oncology

Diagnosis of malignancy does not rely on molecular diagnostics to the same degree as inherited disease; however, there are situations in which molecular diagnostic testing serves an important role in distinguishing benign from malignant proliferations. Molecular testing is often the modality of choice to establish a definitive diagnosis, especially in cases that remain unclear after morphologic, immunohistochemical, conventional cytogenetics, or flow cytometric analyses. Molecular studies of the antigen receptor genes can help distinguish lymphoma from benign lymphoproliferations.[39,40] Molecular mutation analyses in cystic neoplasia of the pancreas and of thyroid lesions of indeterminate cytology can be used to help differentiate benign from malignant lesions.[41–50] In suspected myelodysplasia, guidelines recommend testing a panel of genes to establish presence of clonal hematopoiesis.[51]

Stratification of cancer has now become a part of the primary diagnosis. Accurate molecular diagnosis is fundamental to understanding the pathology of the disease process, which, in turn, will inform proper clinical management of the patient. The World Health Organization classification of lymphomas and leukemias requires molecular diagnostic data for many tumor categories.[7,39] In turn, correct molecularly assisted diagnosis is essential to evidence-based management of patients.[52] Until recently, the diagnosis of lung cancer included histological classification only (eg, non–small-cell lung carcinoma and adenocarcinoma). Mutation status has now become a part of the disease name of an increasing number of cancers because they predict recurrence or have implications for targeted therapy, sometimes for multiple mutations (eg, *BRAF*-, *MEK*-, and *RAS*-mutant melanoma[53–55]). NGS can be used to interrogate multiple gene regions that have been characterized as mutational hot spots, providing an efficient method for identifying several somatic mutations known to be important cancer drivers.[42,56–58]

As important as diagnostic efficiency are limitations presented by specimen type, which can affect materials available for analysis. Lung cancer patients benefit from the introduction of minimally invasive procedures (eg, bronchoscopy); however, small specimen size may be an obstacle to successful testing. During initial lung cancer diagnosis, which currently relies on a combination of staining, immunohistochemical, cytogenetic, and molecular diagnostic procedures, it is not uncommon to exhaust the available biopsy tissue. Should additional clinical testing be needed, the patient may be faced with a rebiopsy procedure with inherent risks and impacts, assuming rebiopsy is possible. Using multigenic testing approaches or GSPs, patients can be treated on the basis of their mutational status for multiple genes with fewer tests. This provides an economy of scale—sparing limited biopsy material, avoiding patient risk exposure, and minimizing payer expenses from additional procedures and potential related complications—that cannot be achieved by an iterative, one-gene-at-a-time testing strategy. GSPs may be less expensive than the combination of multiple molecular procedures they replace. Care must be taken to ensure that the technical and professional expertise necessary to perform and interpret this complex clinical information is adequately represented in reimbursement policies to ensure continued availability.[59]

Importance of Molecular Diagnosis in the Absence of Treatment

Accurate diagnosis is essential even when curative interventions are not available.[60] In the absence of a definitive treatment, determination of the optimal supportive care is as important and may be determined by molecular test results. The term supportive at times presupposes that the only purpose of medical care is to cure or significantly alter the natural progression of a condition through medical interventions, such as drugs or surgery. This implies that if interventions cannot cure or alter the progression of a

disorder they are not medically necessary, do not carry the same level of importance, and perhaps are not properly considered part of medical care. Positive patient outcomes in medicine have not historically been narrowly defined as only cure or prevention of disease. Many diseases are chronic conditions that can be effectively and appropriately managed when curative pharmacological therapies are not available. Health care resources are then focused on managing the disorder, associated comorbidities, effects on other medical conditions, impact on life expectancy, and quality of life. Huntington disease is an autosomal dominant disorder that is characterized by behavioral and cognitive decline and chorea with typically adult onset (after the age of 40 years), but without interventions to prevent or slow disease progression. Molecular testing is the only way to determine, presymptomatically, if an at-risk individual has inherited the disorder. Knowing mutation status can be beneficial for family and life planning (eg, reproductive decision-making, documenting advanced directives, end of life preparations).

Prognosis

Beyond making a diagnosis, molecular diagnostics can provide individualized prognostic information (ie, the expected clinical outcome in the absence of treatment or with the application of the standard treatment). For inherited disorders, a prognostic marker assesses the likelihood of development of a disease. For oncology, a prognostic marker assesses the prospect of disease progression or survival without disease specific intervention, other than general supportive care. Two key questions to be addressed are as follows: Does a specific molecular finding have sufficient prognostic evidence to effect a change in management that will improve the clinical outcome? Will the prognosis contribute to personal life management decisions for the patient and the patient's family?

Prognostic Molecular Diagnostics in Inherited Diseases

Many inherited disorders with similar primary phenotypes can later develop distinct associated secondary conditions (eg, hearing loss may be isolated or associated with a syndrome). Definitive molecular diagnosis can assist with monitoring and/or preparation for these secondary conditions. Usher syndrome patients present with hearing loss but develop retinitis pigmentosa (night blindness and tunnel vision) as they age.[61] Neurofibromatosis presentation is variable, and patients with an uncertain diagnosis on the basis of clinical criteria should receive a definitive diagnosis by molecular diagnostic testing. Surveillance is critical for neurofibromatosis patients who may develop plexiform neurofibromas that can obstruct or become entangled around vital organs[62]; thus, early detection of these tumors will facilitate surgical removal before they become life threatening.

Prognostic Molecular Diagnostics in Oncology

Molecular testing can inform prognosis at the time of diagnosis and guide surveillance and intervention. Knowledge of *FLT3—ITD* mutational status in cytogenetically normal acute myeloid leukemia has prognostic impact and affects the selection of appropriate treatment, even though at present it does not point to specific targeted therapy except in clinical trials.[63] Molecular testing to quantify mRNA expression of the *BCR-ABL1* fusion gene in chronic myelogenous leukemia is an example of using molecular diagnostics to monitor response to therapy, monitor minimal residual disease (surveillance), and in some cases indicate specific changes in therapy.[64]

Complex prognostic molecular diagnostics measuring gene expression have been shown to have CU in treatment of early-stage breast cancer. Within the estrogen and progesterone hormone-receptor—positive (ESR1/PGR-positive, or ER/PR-positive) group, demonstrated by immunohistochemistry, chemotherapy is available for those considered at a high risk of recurrence while sparing others considered low-risk for the possible complication of chemotherapy-related second malignancies (leukemia/lymphoma). This treatment stratification currently involves the use of genomic/transcriptomic data obtained from molecular diagnostics. Herein, the meaning of prognosis and prediction overlap because the result can favor chemotherapy (predictive) or favor withholding therapy, a reflection of a good prognosis.

For breast cancers that do not express *ESR1*, *PGR*, or *ERBB2* (*HER2*) (triple-negative tumors), treating physicians must consider molecular testing for inherited *BRCA* mutations, potentially facilitating complete care of the patient and the extended family. *BRCA* mutation-positive patients may elect to have a prophylactic mastectomy of the uninvolved breast as well as bilateral oophorectomy.[65—67] Prognostic molecular diagnostics for colon cancer have also demonstrated CU in predicting the risk of relapse of stage II colorectal cancers, independent of conventional tumor stage and DNA mismatch repair status.[68,69]

Presymptomatic and Predictive Testing

The CU of molecular diagnostics for inherited disease in asymptomatic individuals depends on both the condition and whether the test is being performed on an individual with a family history or testing within the general population. If the condition has high penetrance (eg, Huntington disease), the molecular diagnostic test is used to predict future disease (presymptomatic testing) with high confidence.[70] Presymptomatic testing additionally includes prenatal screening, fetal testing, newborn screening, or preimplantation genetic diagnosis when a familial mutation is known. Molecular testing also can predict an individual's drug response because of germline variants in drug-metabolizing enzymes and transporters. Pharmacogenomic

testing can predict drug efficacy, adjust dose, and identify the potential for drug-related adverse events[71] (PharmGKB, *https://www.pharmgkb.org/view/dosing-guidelines.do?source=CPIC*, accessed April 8, 2016).

A predictive factor in oncology is associated with response or lack of response to a particular therapy (ie, molecular testing for *KRAS* and *EGFR* mutations to determine whether epidermal growth factor receptor–targeted therapy is appropriate).[52,72] Particular mutations in either gene serve as predictive factors for the success of epidermal growth factor receptor–targeted therapy. Molecular testing can address clinically useful issues beyond drug response (eg, whether dosing adjustments are needed, whether treatment should be by a different drug, and the risk of adverse events). One example where identification of therapy resistance and to optimize dosing is illustrated with gastrointestinal stromal tumors: *KIT* exon 9 positive tumors have longer progression-free survival if treated with high dosages of the tyrosine kinase inhibitor (imatinib).[73] In addition, imatinib-resistant chronic myelogenous leukemia is often because of resistance mutations in the *BCR-ABL1* fusion gene; identifying the mutation is useful to predict the optimal alternative drug.[74]

Importance of Molecular Testing to the Healthcare System

Despite the modest cost of testing, an accurate molecular diagnosis can lead to more efficient and appropriate use of health care resources. Most notably, it can stop the repeated office visits and testing associated with the diagnostic odyssey, which can increase costs. Hereditary hemorrhagic telangiectasia is characterized by recurring nosebleeds and cerebral and pulmonary arteriovenous malformations, which are typically present but undetected at birth, and eventually present catastrophically. Such arteriovenous malformations are detectable and treatable with a timely genetic diagnosis. Without molecular assessment, a currently healthy individual with an affected relative is at risk and requires the same monitoring as a diagnosed affected individual.[75] Evaluation by a specialist is recommended every 5 years for affected or at-risk individuals and includes brain magnetic resonance imaging and echocardiogram, with approximately 20% needing follow-up chest computed tomography. With accurate molecular diagnosis, unaffected family members are spared costly procedures and radiation exposure.

Evaluating the impact of molecular diagnostics on the health care system in cancer treatment may be difficult by comparison to inherited disease in which a diagnosis is a discrete end point. Large-scale clinical trials currently underway may provide a systematic evaluation (eg, National Cancer Institute Molecular Analysis for Therapy Choice trial, *http://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match*, last accessed April 3, 2016) (Supplemental Appendix S1[76]). Although the cost of molecular testing is seemingly high, it is negligible compared to the cost of many components of cancer care, from routine imaging to targeted therapy. Significant expenses may arise from molecular results leading to the use of targeted therapies, with associated costs typically two to three orders of magnitude greater than the testing costs. The CV of many mutation-targeted drug associations is well established, especially with respect to dramatic short-term responses in individual cases. It is important to show that precision therapy based on molecular diagnostics leads to improved outcomes. To date, this has required large multiyear studies typically assessing one target and one drug (eg, epidermal growth factor receptor inhibitors for lung and colon cancer). The application of NGS panels or exomes and the development of new clinical trial models promise to make this a more efficient process in which one test can assess suitability for many therapies. In patients in whom traditional therapy has failed, the finding of an actionable mutation using GSPs has been associated, in some cases, with dramatic responses.[77–83]

The field is moving rapidly toward gene panels for patient benefits (eg, avoidance of rebiopsy) and because of the economy of scale that the multigenic analyses provide. In 2015, the Association for Molecular Pathology initiated a microcosting and health economic evaluation of three clinical scenarios using GSPs, including use of targeted gene panels in the diagnosis and management of patients with sensorineural hearing loss, exome analysis in the diagnosis and management of children with neurodevelopmental disorders of unknown genetic etiology, and a targeted gene panel for the purposes of optimizing patients with advanced non–small-cell lung cancer.[84] Each GSP-guided care pathway was compared to traditional care; in all three scenarios, the GSP-guided care models exhibited value by either reducing health care costs or properly identifying appropriate care pathways.

Recommendations

Alternatives to Randomized Controlled Trials

The most appropriate RCT approach for demonstrating CU centers on how a specific genetic mutation affects response to a specific (usually targeted) therapy. The randomized controlled trial (RCT) remains the gold standard to evaluate interventions, but at a practical level not every question of CU can be answered by a traditionally structured RCT.[85] Although traditional RCTs are the preferred method to generate evidence for the CU of molecular diagnostics that provides information regarding potential response to a specific therapy, they are costly, require large cohorts, and take years to reach end points. Even well-designed RCT studies may not provide evidence that identifies all patient populations that would benefit from the treatment, requiring additional studies. The traditional method of selecting and

Table 2 Limitations, Concerns, and Suggested Modifications to the ACCE Model List of Targeted Questions Aimed at a Comprehensive Review of Genetic Testing Clinical Utility

Component	Targeted questions	Limitations/concerns	Suggested expansion of ACCE model
	What is the natural history of the disorder?	Knowledge of underlying genetic variant(s) impact on the natural history of many disorders is still evolving.	Recognize limitations of understanding underlying genetic component impacts on a disorder's natural history, which introduces challenges when defining the clinical utility of molecular diagnostic testing. Remove Intervention as the component.
Intervention	What is the impact of a positive (or negative) test on patient care?	Molecular diagnostic test utilization within the oncology and inherited diseases categories can be diagnostic, prognostic, and/or predictive. Each of these can be useful to different stakeholders: clinician, patient, family, society, regulators, and payors.	Define molecular diagnostic test setting and purpose broadly. Include clinical utility purpose to achieve a balance of outcomes where the expected health benefits exceed the expected negative consequences of testing for the patient.
Intervention	If applicable, are diagnostic tests available?	Interventions are currently narrowly defined as actionability. Many molecular diagnostics will be used for multiple purposes (eg, to guide treatment and affect morbidity of the genetic condition and to provide information that will influence overall management).	Recognize all of therapeutic options are interventions, even when they are not curative. Recognize clinical utility evaluation for molecular diagnostics should be appropriate for the different purposes, in different populations, and for the symptoms and presentation being assessed. Define monitoring and patient management as an appropriate intervention.
Effectiveness	Is there an effective remedy, acceptable action, or other measurable benefit?	Definition of effectiveness often limited to selection of a therapeutic drug (eg, companion diagnostics model) that is not appropriately applied to all types of molecular diagnostic tests.	Define effectiveness as the ability of the molecular diagnostic test and any associated services to bring out the intended purpose (often, but not invariably, improvements in health) when used under the most favorable circumstances (efficacy) and under routine conditions (effectiveness). Recognize clinician utility: diagnostic, therapeutic, prognostic, and predictive management (even in the absence of therapy). Recognize patient utility: disease management, decision-making, family planning, pregnancy management, long-term care decisions. Recognize family utility: impact of molecular diagnostic on family members (presymptomatic or predisposition testing), educational access to caregivers/supportive care. Recognize societal utility: cost of testing and missed diagnosis, economic measures, and health care resource management. Change component from Intervention to Effectiveness.

(*table continues*)

Table 2 (*continued*)

Component	Targeted questions	Limitations/concerns	Suggested expansion of ACCE model
Quality assurance	What quality assurance measures are in place?	Uncertain many potential reviewers have adequate knowledge base to evaluate the quality of complex molecular diagnostic testing.	Recognize that molecular diagnostic testing is regulated by CLIA and subject to proficiency testing and other quality assurance measures as are other clinical laboratory tests with established clinical utility. Support a modernization of CLIA to better incorporate molecular diagnostic testing.
Evidence	What are the results of pilot trials?	Pilot trials are not viewed as being foundational or adequate for reimbursement; RCTs will not exist for many disorders.	Recognize alternates to RCT as appropriate for establishing clinical utility evidence. Change component from Pilot Trials to Evidence.
	What are the financial costs associated with testing? What are the economic benefits associated with actions resulting from testing?	Inadequate data available comparing cost of appropriate molecular diagnostic tests to costs of diagnostic odyssey, unnecessary care, missed diagnosis, health care, and education systems.	Recognize molecular diagnostic tests can be an affordable alternative to costs of diagnostic odyssey, inappropriate/unnecessary utilization of health care, and educational systems. Identify gaps in appropriate economic outcomes data.
Facilities	What facilities/personnel are available or easily put in place?	Molecular diagnostic testing is widely available, but challenges in coverage and payment for professional services remain.	Recognize gaps in coding, coverage, and reimbursement for both molecular diagnostic testing and associated professional medical services.
Education	What educational materials have been developed and validated and which of these are available?	Treating physicians often lack information necessary to choose the appropriate test, particularly those in specialties who don't typically order molecular testing.	Encourage and facilitate collaborative education among relevant professional societies.
	Are there informed consent requirements?	Informed consent does not determine clinical utility of a molecular diagnostic test.	Apply informed consent requirements in the few inherited conditions where it is appropriately used.
	What guidelines have been developed for evaluating program performance?	Guidelines for evaluating test and analytical and clinical validity are available, but guidelines for clinical utility have not reached consensus. Clinical practice guidelines are available for some conditions, but are not available for all disorders/test uses; there is no systematic reasoning for guideline topic selection; requiring guidelines is onerous and limits patient access to testing; guidelines do not keep pace with the evidence base.	Do not limit evaluation of clinical utility (and subsequent lack of reimbursement) to rely on the existence of clinical practice guidelines, as this will result in decreased test availability for patients and negative impacts on patient care. Recognize that many disorders will not have clinical practice guidelines available.

Centers for Disease Control, *http://www.cdc.gov/genomics/gtesting/ACCE/acce_proj.htm*, accessed April 7, 2016.

ACCE, analytic validity, clinical validity, clinical utility, and ethical, legal, and social implications; CLIA, Clinical Laboratory Improvement Amendment; RCT, randomized controlled trial.

grouping patients for clinical trials on the basis of their tumor type and grade, which does not leverage the patient's genomic information, is being re-examined with the introduction of new clinical trial models. This is especially true for rare inherited diseases and for malignancies, common or rare, driven by uncommon combinations of mutations. The difficulty of obtaining an adequate patient cohort drives up the cost of an adequately powered trial; and, the accrual of

Table 3 Recommendations

The following recommendations are made to clinicians, professional organizations, and other stakeholders (to include but not limited to federal and state agencies, insurers, managed care organizations, patient advocacy groups, and others involved in health care policy development):

Promote Patient-Centered Definitions of Clinical Utility

- Recognize that the patient is the ultimate arbiter of clinical utility.
- Incorporate patient-centered outcome measures, such as ethical, legal, and social implications, quality-of-life improvements, functional status, and patient satisfaction, into evaluations of clinical utility.
- Recognize the essential role of an accurate diagnosis in providing patient-centered care.
- Recognize the patient's right to be involved in all aspects of his/her health care and to make fully informed decisions.
- Current clinical utility determination models in genetic testing have limitations and harms:
  - A laboratory test result in isolation is only a portion of the entire professional medical service and needs to be viewed in that context. Meaningful use of a test (the indication for testing and interpretation of that test in the context of the individual patient's management) will affect a test's clinical utility.
  - Defining clinical outcomes depends on a specific disease being diagnosed and/or managed using molecular methods.
  - There are identifiable patient harms to limiting access to genetic testing on the basis of an unrealistic evidentiary level for clinical utility. Insufficient evidence for lack of clinical utility evidence, particularly in emerging technologies, should not be a barrier to reimbursement and patient access to testing. A lack of evidence for clinical utility is not the same as evidence of a lack of clinical utility.

Propose Utilizing a Modified ACCE Model that Incorporates the Aspects of Clinical Utility Beyond Drug Selection

- Recognize that an accurate molecular diagnosis has inherent clinical utility.
- Establish that predictive and prognostic molecular diagnostic testing can also demonstrate clinical utility when evaluated in context.
- Describe three purposes for tests: to reduce morbidity or mortality, to provide information salient to the care of the patient or family members, and/or to assist the patient or family members with reproductive decision-making.
- Do not restrict the definition of clinical utility to selection of a pharmacological intervention.
- Table 2 for suggested modifications to the list of targeted questions aimed at clinical utility.

Support Multiple Modalities for Establishing Evidence to Evaluate Clinical Utility

- Support the development of clinical grade high-quality databases of outcomes together with the related and genetic information for oncology and inherited disease.
- Support retrospective data evaluation from n-of-one trials and compassionate use/off-label use exception uses of approved therapies.
- Support alternative clinical trial modalities, such as bucket and basket trial designs in oncology with molecular marker identification and/or molecular diagnosis–driven selection of treatment arms.
- National database development to develop better RCT, assist in clinical decision making in the absence of RCT data, and, in some cases, open avenues for new therapies:
  - Anecdotal and small case series that involve n-of-one correlations of response to treatment information correlated with genetic information in oncology.
  - Rare diseases correlated with genetic information in inherited diseases to permit further knowledge of the disorders, natural histories, and genotype-phenotype correlations.

Recognize the Critical Role of the Molecular Professional in Disease Management

- Molecular pathologists and clinical molecular geneticists/laboratory professionals are key medical professionals with specialized knowledge needed to guide patient management decisions.[21]
- Molecular diagnostics professionals have the education, training, and board certifications to appropriately guide test selection and utilization and should be relied on by treating clinicians.[88]
- Patient's team of medical providers—molecular pathologists, molecular geneticists/laboratory professionals, pathologists, oncologists, genetic counselors, surgeons, primary care providers, other providers—all have distinct scopes of practice that work in concert to support disease management and improve outcomes.
- Professional teams already have existing quality metrics and oversight mechanisms to guide proper test utilization (laboratory accreditation, practice guidelines, standards of care, tumor boards, medical staff reviews).

Support the Development of Professional Organization–Driven Practice Guidelines

- Professional organization–driven guidelines should be used as part of the chain of evidence to develop clinical utility.
- Encourage efforts to develop collaborative interdisciplinary clinical practice guidelines.
- Support professional organization–driven development of peer-to-peer clinical laboratory practice guidelines to guide best practices, particularly in areas of new/emerging technologies, and to assist clinicians in and stakeholder evaluation of molecular diagnostics and interpretation of results.
- Support professional organization–driven development of interim clinical practice guidelines and expert opinion guidance documents that address aspects of clinical utility where RCT evidence is minimal and/or emergent technologies are used.
  - Support development of appropriate evidence-based medicine tools for evaluation of molecular diagnostics and pathology literature.
  - Increase engagement between professional associations and other stakeholders (eg, FDA, CMS, payers, community service providers, and patient groups).
  - Encourage incorporation of comparative effectiveness research and health economics consideration into professional practice guidelines.
  - Increase available AHRQ/CDC/IOM/PCORI grant funding to support these projects.

ACCE, analytic validity, clinical validity, clinical utility, and ethical, legal, and social implications; AHRQ, Agency for Healthcare Research and Quality; CDC, Centers for Disease Control; CMS, Centers for Medicare and Medicaid Services; FDA, Food and Drug Administration; IOM, Institute of Medicine; PCORI, Patient-Centered Outcomes Research Institute; RCT, randomized controlled trial.

potential benefits to only a few patients discourages funding from private or public sources.

Limiting medical care to what has been validated by RCTs is neither practical nor appropriate. Some situations do not require an RCT because observational data and historical controls may be sufficient to define safe practices where pathophysiological knowledge can support an intervention. A case in point is with the use of prophylactic thyroidectomy for individuals with pathogenic *RET* mutations as family studies have demonstrated previously a high penetrance for these mutations.[86] A recent review indicates that requiring RCTs in conjunction with current evidence-based medicine classification of data quality to assess diagnostic criteria is inadequate, proposing that alternative scales are needed to determine the value of pathology results outside of the limited scope of evaluating RCT drug trial outcomes for prognostic and predictive data.[87]

Although RCTs are meaningful in some contexts (eg, determining if selecting cancer therapy on the basis of molecular test results improves responses), retrospective studies are more suitable for determining if mutations in a particular gene are correlated with a specific clinical presentation. Given these limitations, alternate types of well-designed prospective and retrospective clinical study designs (eg, case control and other observational studies) and data analysis methods (eg, comparative effectiveness and decision analysis) should be recognized as appropriate and sufficient for determining CU for molecular diagnostics (Supplemental Appendix S1). Recent efforts by patient advocacy groups to improve clinical trial enrollment and the development of crowd-sourced data resources may support future evidence development efforts. When taken together, recommendations in this report describe a new approach to identifying and assessing evidence necessary to demonstrate CU (Tables 2 and 3).

Modification of ACCE Framework Application to Molecular Diagnostics

Viewed in the ACCE model (Centers for Disease Control, *http://www.cdc.gov/genomics/gtesting/acce/index.htm*, accessed April 8, 2016), molecular diagnostics provide critical information to the physician, patient, and patient's family, which can be used to reduce morbidity and mortality, or to assist the patient or family members with reproductive decision-making. Like the Agency for Healthcare Research and Quality guide, ACCE links CU of testing with the care provided. Using as an example newborn screening tests, if the purpose of a test is to reduce the morbidity or mortality of rare inborn errors of metabolism, which is not achieved unless the child who tests positive is provided with the appropriate intervention and follow-up care (eg, additional testing and genetic and nutritional counseling). However, the value of molecular diagnostics is not fully captured by the ACCE framework. We propose extensions of the ACCE model and make additional recommendations to better incorporate the value of molecular diagnostic testing into discussions regarding CU (Tables 2 and 3).

Recommendations for a New Approach

The working definition of CU is often narrowed to actionability, meaning that molecular diagnostics with established CV must also mandate or inform therapy selection with an expected improvement in health outcome.[85] This attempts to force all molecular diagnostics into a companion diagnostics model for CU evaluations (Center for Medical Technology Policy, *http://www.cmtpnet.org/docs/resources/MDX_EGD.pdf*, last accessed May 22, 2016). This restriction excludes a wide range of purposes for molecular diagnostics and ignores many aspects of the CU of a test for the clinician, patient, family, or society (Supplemental Tables S1 and S2). Molecular diagnostic testing results are an intermediate outcome, relying on necessary changes in physician and/or patient behavior to directly link the test results to the typically analyzed health outcomes, such as overall and disease-free survival.

A new approach to evaluate CU in molecular pathology testing procedures is required; traditional models are too constrained or impractical. The existence of evidence for CU that is outside of the norm of traditional models is different from evidence against CU. Emerging CU evidence published in highly regarded journals, particularly in emerging technologies, should be considered in determining insurance coverage and patient access to testing. In summary, we recommend the following:

- Promotion of patient-centered definitions of CU;
- Utilization of a modified ACCE model incorporating aspects of CU beyond drug selection;
- Support for multiple modalities of CU evidence generation;
- Development of professional organization–driven practice guidelines; and
- Recognition of the critical role of the molecular professional in patient care.

Our recommendations (Table 3) and the framework presented, based on an expanded ACCE model that includes broader parameters for its assessment, recognize the many applications of molecular diagnostics and the varied impacts on patients, families, and society. In doing so, the capabilities and benefits of molecular diagnostics can be realized while ensuring appropriate access and improved patient outcomes.

Conclusion

The capabilities and applications of molecular diagnostics are rapidly evolving. Although alone, individual inherited genetic diseases may be rare, combined they are common. An estimated 2% to 3% of births have a genetically determined

abnormality. Although alone, individual inherited genetic diseases may be rare, combined they are common. An estimated 2% to 3% of births have a genetically determined abnormality. Seven percent of the population has a rare medical condition with a significant genetic component (Genetic Alliance UK, *https://www.geneticalliance.org.uk/information/learn-about-genetics/rare-diseases*, last accessed August 2, 2016). Regardless of the disease, disorder, or condition—even in the absence of a curative therapy—an accurate diagnosis inherently has CU. Molecular pathology testing procedures provide powerful tools for insight and analysis into various aspects of clinical practice, but to reach the goal of providing precision medicine to every patient, the value of elucidating their individual genetic/molecular diagnosis is fundamental to achieving positive downstream patient care outcomes. Without the foundation of an accurate molecular diagnosis, the treating clinician may have to make decisions on the basis of incomplete or inaccurate information. Although this practice was often unavoidable in the pregenomic medicine era, the post-genomic era enables a higher level of diagnostic precision.

The CU of molecular diagnostics is not limited to diagnosis alone. It also applies to prognosis and prediction. As the CU of an individual molecular diagnostic procedure is often context dependent, specifying the spectrum of CU that can be addressed by the test is essential. The ability of molecular markers to prospectively identify individuals at risk of disease development, evaluate risk of disease recurrence, or assess the prospect of disease progression/survival provides clinically valuable information used by the medical team, patients, and their families to provide proactive patient-centered care. This, in turn, holds societal benefits by focusing medical resources appropriately. As the clinical genomic knowledge base further expands, molecular professionals and the test results they provide and interpret will increasingly be able to classify a patient's disease or disorder and/or guide management. This is the promise of precision medicine.

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