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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

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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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The Association for Molecular Pathology's Framework for the Evidence Needed to Demonstrate Clinical Utility Task Force consists of members from the Professional Relations Committee, Economic Affairs Committee, and the Clinical Practice Committee. The 2014 and 2015 Professional Relations Committee consisted of Stephen P. Day, Rajyasree Emmadi, Andrea Ferreira-Gonzalez, Robert F. Klees, Roger D. Klein (Chair), Jordan Laser, Elaine Lyon, Roberta Madej, Shelby Melton, Timothy J. O'Leary, Victoria M. Pratt, and Daniel Sabath. The 2014 and 2015 Economic Affairs Committee consisted of Dara Aisner, Aaron D. Bossler (2014 Co-Chair, 2015 Chair), Samuel Caughron (2015 Vice Chair), Pranil Chandra, Jill Hagenkord (2015 Vice Chair), Elaine Lyon, Jan Nowak (2014 Co-Chair), Richard Press (2015 Vice Chair), Linda Sabatini, Michele Schoonmaker, and Ester Stein. The 2014 and 2015 Clinical Practice Committee consisted of Matthew Bankowski, Milena Cankovic, Christopher Coldren, Linda Cook, Jennifer H. Crow, Jennifer Dunlap, Birgit H. Funke, Larissa V. Furtado, Lawrence Jennings, Loren Joseph (2014 Chair), Arivarasan Karunamurthy, Annette Kim, Bryan Krock, Marilyn M. Li, Melissa B. Miller, Marina N. Nikiforova (2015 Chair), Mary Lowery Nordberg, Carolyn Sue Richards, Paul Rothberg, and Somak Roy.

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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.

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