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SPECIAL ARTICLE

Revisiting Oversight and Regulation of Molecular-Based Laboratory-Developed Tests

A Position Statement of the Association for Molecular Pathology

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Since 2006, the US Food and Drug Administration, Congress, and other policymakers have explored the appropriate way to guarantee the clinical and analytical validity of laboratory-developed tests. In the past, the Association for Molecular Pathology has publicly urged the Food and Drug Administration to exercise caution in implementing regulatory changes that could potentially hinder innovation or interfere with the practice of medicine. In 2012, the Association for Molecular Pathology Professional Relations Committee chose to develop this paper with the goal of outlining the best methods for ensuring appropriate oversight and validation of molecular diagnostic procedures. At the conclusion of this process, the workgroup reaffirmed the Association's previous position that the Centers for Medicare and Medicaid Services Clinical Laboratory Improvement Amendments program can provide the appropriate level of oversight for the vast majority of diagnostic tests. *(J Mol Diagn 2014, 16: 3—6; http://dx.doi.org/10.1016/j.jmoldx.2013.10.003)*

The Association for Molecular Pathology (AMP) believes that clinical laboratory tests are central components essential for medical practice. Pathologists, geneticists, and other laboratory professionals who perform such tests have (and will continue to have) vital roles in working with treating physicians and other health care providers to optimize

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The opinions expressed in this paper are solely those of the AMP and its Professional Relations Committee, and shall in no way be construed as being endorsed by the authors' home institutions.

Standard of practice is not being defined by this article, and there may be alternatives.

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patient management and advance the quality of medical care. In molecular pathology laboratories, the laboratory professionals, which include pathologists and doctoral scientists, have used laboratory-developed tests (LDTs) to enable major advancements in the diagnosis and management of a wide range of infectious, and inherited and oncologic diseases. In addition, laboratory professionals use LDTs to identify suitable bone marrow donors and engage in subsequent monitoring of disease course in transplant recipients. It is difficult to overestimate the key roles that LDTs play in the medical practice. Without LDTs, many of our most celebrated medical advances would likely not have been implemented, to the detriment of our patients.

AMP is a vigorous advocate for the principle that only high-quality, clinically and analytically valid diagnostic tests should be used in clinical practice. All laboratories that perform clinical testing should meet, at a minimum, if not exceed, Clinical Laboratory Improvement Amendments (CLIA) standards; adhere to established professional society and laboratory practice guidelines; and obtain required and optional certifications and accreditations as appropriate for their particular settings. The CLIA program, laboratory accreditation by professional societies such as the College of American Pathologists (CAP), and board certification and licensure of laboratory directors and other laboratory personnel have engendered safe, effective, high quality, accessible, patient-oriented test services. Supporting this premise are the recognized proficiency testing surveys of the Centers for Medicare and Medicaid Services (CMS), which include challenges for the most common tested analytes and have demonstrated excellent performance of LDTs in the area of molecular pathology for a decade or more.[1,2]

Similar to other medical specialties, the pathologists, molecular geneticists, and other clinical laboratory scientists draw on their experience and medical and scientific expertise when they implement a new procedure or diagnostic approach to improve patient care. Nimble innovation in new test development is crucial to our ability to respond to emerging public health challenges. This was evident during the 2009 H1N1 influenza outbreak in which laboratory professionals rapidly developed and validated diagnostic tests to detect the virus and its spread through the population, sometimes in advance of public health laboratories.

The current regulatory oversight system enables pathologists and other laboratory professionals to rapidly incorporate new findings into practice, and to modify existing laboratory tests and their usage in accordance with advances in clinical knowledge. This has allowed timely and appropriate introduction of innovative testing into practice, and it has also helped foster patient access to the most up-to-date treatment options. The AMP has urged the United States (US) Food and Drug Administration (FDA) to recognize the value of the system that has served patients and providers well over the past 25 years, and to preserve the same flexibility in any new or modified approaches to LDT oversight. The Professional Relations Committee and Board of Directors of the AMP have reached a consensus on the following approach to assess the analytical and clinical validity of complex diagnostic tests. This position statement applies only to LDTs performed in high complexity CLIA laboratories.

Defining LDTs

One of the challenges in determining the appropriate level of oversight of diagnostic tests is the variability in how stakeholders define LDTs. The FDA considers LDTs to be a class of *in vitro* diagnostics that are developed, validated, and offered within and by a single CLIA-certified laboratory using components that are regulated individually by the FDA as Analyte Specific Reagents, or other specific or general reagents (*http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm212830.htm*, last accessed June 15, 2013). AdvaMed, the trade association representing medical device manufacturers, concurs that LDTs are medical devices that fall under jurisdiction of the FDA. AdvaMed believes that the FDA should regulate all diagnostic tests, arguing that *in vitro* diagnostic kits and LDTs present the same risks and benefits for patients irrespective of their site of development or manufacture.[3]

By contrast, the American Clinical Laboratory Association endorsed a 2011 bill introduced by Congressman Michael C. Burgess (R-TX26),[3] which was entitled the *Modernizing Laboratory Test Standards for Patients Act of 2011* (H.R. 3207). H.R. 3207 defines LDTs as tests developed and performed by a clinical laboratory "solely to furnish clinical laboratory testing services for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings..." The definition of this bill further distinguishes LDTs by specifying that they are not otherwise introduced into interstate commerce.

The CAP has a more nuanced approach to the FDA regulation of LDTs than the Burgess bill, but shares some common elements. Importantly, the CAP also believes that LDTs are fundamentally different from either traditional medical devices or *in vitro* diagnostic kits. The CAP considers LDTs to be tests that are developed within a CLIA-certified laboratory, used in patient management, and performed by the laboratory in which the test was developed, which is neither FDA cleared nor approved.[4] Further exploring the existence of two regulatory pathways, the US Department of Health and Human Services Office of the Inspector General announced in 2013 that it intends to study the agencies oversight of LDTs and describe the challenges of regulating LDTs. This report is anticipated in 2014.

Finally, Senator Orrin Hatch (R-UT) has proposed legislation that is supported by some diagnostics companies and an umbrella organization known as the Coalition for 21st Century Medicine. The Hatch approach would create a new category of medical products called advanced personalized