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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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...
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
diagnostics (APDx). Under the Hatch proposal, APDx would be defined as laboratory tests that analyze DNA, RNA, chromosomes, proteins, or metabolites, or otherwise are chemosensitivity assays, and are intended to be used for the diagnosis, prevention, cure, mitigation, or treatment of any disease or impairment, including the prognosis or prediction of a treatment or assessment of health. Although all other types of laboratory tests would also be considered medical devices, regulators would address APDx differently. The AMP LDT Working Group considered the preceding definitions of LDTs together with other possible approaches. Along with some of the other stakeholders previously mentioned, the working group recognized that unlike the FDA-regulated medical devices, laboratory tests have a professional interpretive component that offers additional opportunities to enhance patient care through professional interpretive judgment. This professional judgment and test performance intersect at the points of design, development, validation, and continued improvement of LDTs. Thus, a surgeon purchases a medical device, such as a stent off-the-shelf for implantation during surgery. The surgeon trusts that the product was correctly manufactured for its intended use. By contrast, a pathologist is involved in designing LDTs, setting their analytic parameters, and subsequently in consulting with the ordering physician in determining the appropriate test(s) to perform for a given patient based on his/her clinical presentation. The pathologist then interprets the results of the testing in the context of other medical information. Consequently, LDTs require a regulatory pathway that acknowledges these differences from medical devices and preserves the role of the laboratory professional.

**Defining LDPs**

To clearly distinguish LDTs from traditional medical devices, the AMP has proposed the new appellation Laboratory-Developed Procedure (LDP), formerly referred to as LDTs. We define an LDP as follows:

*An LDP is a professional service that encompasses and integrates the design, development, validation, verification, and quality systems used in laboratory testing and interpretive reporting in the context of clinical care.*

The professionals who provide these procedures possess education, training, and national certifications that enable them to safely and effectively provide LDPs to patients for clinical care. Such professionals provide continuous supervision and have ongoing involvement in every aspect of the procedures, which are developed or validated independently in each CLIA-certified facility. This new term, LDP, better represents the nature of complex laboratory testing, which is very much a medical service provided by appropriately trained and qualified professionals. These laboratory professionals include pathologists, geneticists, and other doctoral scientists, and they constantly address clinical and biological variability that heretofore was not previously considered or perhaps even imagined. Molecular testing continues to rapidly increase in complexity, generating ever-increasing amounts of potentially useful data. In turn, this enhances the complexity and value of the interpretive component, which is concomitantly becoming the most professional time-consuming aspect for many tests. This professional service yields the final information that can be applied by direct caregivers to establish a patient’s diagnosis, estimate his/her prognosis, and identify optimal, appropriate, and/or potential treatment options, and more.

**Position Statement and Specific Recommendations: Current CLIA Regulations Provide Sufficient Oversight for LDPs**

The AMP believes that the CLIA program at the CMS is the appropriate vehicle through which to conduct oversight of the LDPs. Providers of LDPs are knowledgeable about the CLIA regulations and understand the CLIA requirements for demonstrating that analytical validity has been established. Essentially all molecular LDPs are categorized as high complexity tests, which are subject to the most stringent CLIA regulations. These regulations set forth parameters such as personnel qualifications, quality control, and quality assessment systems and procedures, and reporting responsibilities.

Under the CLIA regulations, clinical laboratories are permitted to develop their own tests or LDPs, and can offer these services as long as the laboratory establishes the following for each test system: the performance specifications for accuracy, precision, analytical sensitivity, analytical specificity, reportable range of test results, reference intervals, and any other performance characteristics deemed to be required for proper test performance. Furthermore, the CLIA regulations incorporate a quality systems approach that addresses the total test process to ensure accurate, reliable, and timely procedure results. LDP design, development, and validation are documented, and importantly the performance is closely monitored. In addition to these determinations, the laboratory professionals performing the LDPs are required to set and document the type and frequency of calibration and requisite quality control for the entire test system. The documentation required by CLIA and its deemed entities for quality systems have proved to be successful for troubleshooting actual, suspected, or potential LDP-related performance issues. Although the CLIA regulations do not explicitly require laboratories to verify clinical validity of the LDPs, the regulations can be read to mandate this. High complexity laboratories must have a clinical consultant who should be responsible for consultation regarding the appropriateness of testing ordered and interpretation of test results. This individual must:

“(b) Be available to assist the laboratory’s clients in ensuring that appropriate tests are ordered to meet the clinical expectations; (c) Ensure that reports of test results
include pertinent information required for specific patient interpretation; and (d) Ensure that consultation is available and communicated to the laboratory’s clients on matters related to the quality of the test results reported and their interpretation concerning specific patient conditions.”

The CLIA program maintains a registry of laboratories and their test offerings. However, these data are not publicly available. To increase transparency in its regulatory process, the CMS should update its information technology infrastructure to make this database easily and readily available to the general public and other stakeholders. Moreover, the registry should make public information about adverse events and other significant problems that have occurred within a particular laboratory.

The working group also reaffirmed the AMP’s prior position that some very high-risk tests do require pre-introduction review by a third party reviewer. The Working Group defined risk itself as:

The potential for harm to patients due to an incorrect or misinterpreted result when the test is ordered in a manner consistent with the laboratory’s claims.

Based on this definition, the members further defined LDPs that may require pre-introduction review to be:

Those LDPs for which the consequences of an incorrect result or incorrect interpretation could lead to serious morbidity/mortality to the patient or otherwise burden public health AND which use a methodology that is not well understood or the results from which are not independently verifiable. Such LDPs would be used to predict risk of or risk of progression of disease, or patient eligibility for a specific therapy to treat a disease that is associated with significant morbidity or mortality, AND: use test methodologies that involve proprietary algorithms or computations such that the test results cannot be tied to the methods used and/or do not allow for interlaboratory comparisons to be performed.

The preceding, exceptionally high-risk LDPs include those for which methods or other determinants of results lack transparency, or assays for which a skilled laboratory professional cannot independently interpret or assess the validation of the test or its results. Assays that contain hidden, or black box algorithms, or use proprietary software are examples of the types of tests that lack sufficient transparency for laboratory professionals and ordering physicians to apply without independent third-party review. Typically, such LDPs will be offered by a single provider and there are no proficiency tests available. It is essential that third party reviewers, whether from the FDA or entities external to it, have sufficient knowledge, familiarity with the relevant technology, statistical expertise, and access to the needed data to enable them to adequately evaluate an assay and ensure both its analytic and clinical validity.

References