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Association for Molecular Pathology's Comments at the FDA/CDRH Public Meeting:
Oversight of Laboratory Developed Tests
July 19-20, 2010

The Association for Molecular Pathology (AMP) is an international professional association representing approximately 1,800 physicians, doctoral scientists, and medical technologists who perform laboratory testing based on knowledge derived from molecular biology, genetics and genomics. Membership includes professionals who work in academic medicine, community hospitals, commercial reference laboratories, government, and the *in vitro* diagnostics industry. In March 2010, AMP requested that the FDA hold a public workshop to discuss the oversight of laboratory-developed tests (LDTs), and AMP commends the FDA for arranging this public forum. We thank the organizers for their efforts, and the opportunity to participate.

AMP believes that LDTs are an essential and central component of medical practice. Anatomic and clinical pathologists, geneticists and other laboratory professionals who perform such tests have, and will continue to have, vital roles in working with clinicians to improve patient management. In molecular pathology laboratories, LDTs have provided major advancements in the diagnosis and management of inherited and infectious diseases, as well as a wide range of cancers. Additionally, LDTs identify suitable bone marrow donors, and allow us to monitor the disease course in transplant recipients. These are but a few of the hundreds of examples of LDTs available from accredited molecular pathology laboratories. Without LDTs, the practice of medicine that we know today would be severely reduced in scope. These tests continue to play essential and formative roles in delivery of preventative care, diagnosis, and disease management.

AMP believes that only high quality, clinically and analytically valid diagnostic tests should be performed in clinical laboratories. All laboratories should meet CLIA standards, adhere to established guidelines, and seek appropriate certifications and accreditations. AMP also believes that for the vast majority of molecular pathology tests, the CLIA program, laboratory accreditation by professional societies such as the College of American Pathologists (CAP), and board certification and licensure of laboratory directors have provided a safe, effective, appropriate, and patient-oriented oversight system for clinical diagnostic laboratories. Moreover, CMS-recognized proficiency testing surveys in which large numbers of laboratories participate have demonstrated excellent performance of LDTs in the area of molecular pathology for a decade or more.

AMP recognizes the increasing discourse surrounding the oversight of LDTs and the FDA's interest in revisiting their longstanding enforcement discretion of LDTs. We previously have communicated our interest in working with the FDA to implement a balanced regulatory system that increases transparency of laboratory tests without hindering innovation and the practice of medicine. We again offer our assistance today.

A regulatory model should not interfere with the practice of medicine:

Similar to other medical specialties, pathologists, molecular pathologists, molecular geneticists and other clinical laboratory scientists draw on their experience and expert scientific and medical judgment when incorporating new procedures or diagnostic approaches 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 clinical laboratories rapidly developed and validated diagnostic tests to detect the virus and its spread through the population, sometimes in advance of the public health laboratories.

It is important to recognize the value of the current oversight system for enabling clinical laboratories to rapidly incorporate new findings into practice and to modify existing laboratory tests and their usage in accordance with advances in our understanding of clinical utility and disease pathogenesis. The current environment which has included focused FDA oversight has ensured rapid implementation of innovative testing and access to the most current treatment options. This mechanism has served us well over the past half century and advanced modern medicine to our current status. AMP strongly urges the FDA to preserve that flexibility within new or modified approaches to LDT oversight.

The New York State Department of Health's Clinical Laboratory Evaluation Program (CLEP) requires submission and approval of laboratory developed tests prior to their implementation. Without empiric data that demonstrates better health outcomes in New York patients than those of patients in other states, it is difficult to assess the value of this oversight approach in protecting public safety. Additionally, many AMP members who direct clinical laboratories have expressed frustration with the long review times encountered in that program for tests that are readily available throughout the rest of the country. Understandably, AMP is concerned about undue delays and reduced patient access to tests that could result from an overly bureaucratic and under-resourced oversight system. AMP encourages the FDA to collect data and assess the effectiveness of existing oversight models prior to implementing new approaches. It will be extremely important to demonstrate that any proposed oversight system would lead to improved health outcomes.

LDTs that may need additional oversight:

AMP believes that LDTs in all disciplines of laboratory medicine should be subject to the same oversight mechanisms, and that molecular or genetic tests should not singled out for heightened scrutiny simply due to the heritable nature of nucleic acids. AMP does agree that some tests may require greater scrutiny and may warrant additional regulatory review. An LDT that may require further regulation is one that:

- Uses a non-transparent algorithm with multiple markers that cannot be elucidated by other test developers, or

- Relies on technology that is not easily replicated by multiple laboratories, and for which
  - a false result would cause significant morbidity or mortality, or
  - a false result could have a widespread adverse effect for public health

AMP understands the potential need for additional oversight for these test categories because the quality of results are difficult to assess in an external review (such as an inspection) even for those knowledgeable in the field

We feel it important to recognize the potential impact of increased oversight on infrequent or low volume tests. Overzealous regulation of such tests could prove to be overly burdensome and cost prohibitive for laboratories developing and offering important but infrequently utilized tests. Acknowledging that the quality of all testing must meet the same high standards, there needs to be a mechanism to allow laboratories to continue providing these critical clinical services.

Any oversight protocol must address barriers to test development:

Reference Materials
Recently, AMP has been collaborating with NIST to develop standard reference materials for molecular based diagnostics. The modern healthcare system offers great potential for personalized and effective medical care. However, the recognition and implementation of advances in medical research may be hindered by a lack of certified reference materials. Molecular assays provide the cutting edge for many individualized therapies in oncology, transplantation, infectious disease and genetics, but the production of certified reference materials has fallen far behind the technical capabilities of these assays. Reference materials are important to ensure the necessary quality indicators of sensitivity, specificity and level of reproducibility of intra- and inter-laboratory test results. The best approach to achieve consistent and comparable quantitative data among laboratories is through the use of internationally established reference reagents.

Additionally, AMP has worked with the Centers for Disease Control and Prevention Genetic Testing Reference Materials Coordination Program (GeT-RM) to validate genotypes by consensus in existing, publicly available human cell lines. Although great strides have been made, laboratories still face difficulties obtaining characterized samples to further validate LDTs and FDA cleared or approved kits.

Reimbursement
A major hurdle for laboratories is securing coverage and reimbursement for the tests they provide. The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) in its document "Coverage and Reimbursement of Genetic Tests and Services" recognized that "from the perspective of the laboratory or manufacturer offering genetic testing services, inadequate payment rates can potentially threaten a laboratory's willingness to develop and offer genetic tests if they are provided at a financial loss, potentially limiting the availability of genetic tests to patients."

Escalating costs for test development, performance, interpretation and reporting, compounded with additional costs to satisfy new regulatory requirements could result in the elimination of important clinical tests. In considering revisions to the current oversight processes, AMP urges FDA to realize the potential ramifications on test availability due to economic considerations.

A Place to Start:

Validation Standards:
Developing validation standards would constitute a first step for ensuring the quality performance of LDT's. Although minimum standards and guidances exist, there is room for improvement. AMP is willing to participate with other professional organizations to develop and promote such standards.

An External Advisory Committee:
As noted previously, AMP agrees that some tests may require greater scrutiny and may warrant additional regulatory review. We recommend that FDA appoint an external advisory committee composed of individuals with expertise in the relevant diagnostic areas to assist in identifying the appropriate risk classifications.

Conclusion:

As the FDA considers its approach to regulating LDTs, AMP encourages the agency to consider the unanticipated effects that significant modifications to the current oversight system could represent for clinical laboratories. These include the possibility that laboratories may be compelled to discontinue services and/or potentially lose flexibility to rapidly introduce and continually improve tests, all of which would adversely impact delivery of effective care to our patients.

Thank you very much for considering AMP's comments on the oversight of LDTs. In holding this two-day meeting, FDA has taken an important step forward. AMP looks forward to partnering with the FDA and continuing to work with the Agency for the benefit of patients.