

American College of Medical Genetics and Genomics

Oversight of Laboratory Developed Tests (LDTs)

The Issue: The US Food and Drug Administration (FDA) is working on a final regulatory framework for laboratory-developed tests (LDTs) and policymakers are considering how best to clarify the rules for LDTs. In doing so, both the FDA and Congress must recognize that not LDTs are used in a wide variety of settings, and that LDTs used for genetic testing and counseling need to be differently treated than other more routine diagnostic tests due to the rarity and genetic variability of genetic diseases. The American College of Medical Genetics and Genomics (ACMG), the nation's most experienced body in genetic testing and interpretation, believes that any oversight framework ensure high quality genetic testing remains available to physicians and patients and that it keeps pace with the rapid innovation that currently characterizes this field.

Genetic Tests Are Different: Genetic and genomic tests are highly complex tests based on recently acquired and rapidly evolving knowledge; they are not tests that produce individualized results on their own but require expert interpretation informed by medical and family histories to ensure their safe and effective use by providers. The single most difficult challenge for these complex tests has resulted from the rarity and genetic variability of genetic diseases. To comply with FDA requirements, a manufacturer would need to pursue enormous clinical trials in order to study sufficient patients to generate adequate statistical power to support claims of clinical validity. Very few genetic test kits and devices have been approved or cleared by FDA; the great majority of guidance for providers and laboratories has been through the promulgation of standards and guidelines for testing and the development of educational programs by professional organizations such as ACMG.

Types of Genetic Tests: There are two different approaches to molecular testing for genetic disease: tests that target specific types of variation known to be associated with a particular condition such as Down syndrome and acute leukemias, to more open test platforms that sequence the entire genome and provide a comprehensive look at known and previously undescribed potential contributors to a disease.

- Targeted testing confines analysis to a variant(s) in a gene, a gene panel, or to specific gene products known to be associated with a condition.
 - Because the target of the test is known, these test are amenable to test validation and direct oversight of laboratory performance in detecting the target.
- Open testing examines the entire genome and requires professional determinations as to the likelihood that a genetic change is the cause of a condition. Cytogenetic technologies, used since the 1970s, provide results that may be exceedingly rare or

private to an individual and not previously reported, such that clinical validity could not have been established prior to offering testing. In such situations, professional judgments based on knowledge of genetic science and pathology inform the test interpretation as to whether a change is likely to be pathogenic, benign, or uncertain. Like cytogenetics that assesses entire genomes at low resolution, entire genome sequencing requires higher levels of geneticist training and expertise to interpret results obtained at high levels of resolution. Both targeted and untargeted or open tests require a unique base of specialized medical knowledge and training to ensure both that the proper test is ordered as well as interpreted in the context of individuals and their families.

- More open forms of testing require higher levels of Medical Geneticist training and expertise to interpret variation than do targeted tests. When platforms are used that offer open results, oversight models such as that for radiologic imaging are more appropriate; the platform or machine is the regulated device while the interpretation of the information provided is a professional service.

Key Features of Any Proposed LDT Oversight System:

As policymakers evaluate approaches to strengthen Clinical Laboratory Improvement Amendments (CLIA) and determine the appropriate role for FDA oversight, we believe that any proposed oversight system will (and can) only be effective if:

1. CLIA (the Clinical Laboratory Improvement Amendments) regulations for oversight of genetic testing laboratory practices are greatly enhanced to include:

- A **tiered and risk-based system** that ensures oversight appropriate to the test and its intended uses (see attached 2013 ACMG Policy Statement: *Risk Categorization for Oversight of Laboratory-Developed Tests for Inherited Conditions*);
 - Protection of rare disease diagnostics and tests used in public health surveillance.
- The development of a **third-party review system** for tests being offered that aligns with the aforementioned risk-based system.
- **Public reporting of test performance** characteristics.
- **Coordination of CMS/CLIA and FDA efforts** to minimize duplication of oversight that focuses on non-high-risk tests in the enhanced CLIA program.
- **Identification of prior assessment system of test clinical validity** to determine existing tests that should be **grandfathered** into the system.
- **Adverse event reporting** similar to that of FDA.

2. Third-party genetic testing laboratory accreditors' roles are enhanced.

- Assessment of analytical validity of new tests being offered to the public.
- Assessment of clinical validity of new tests being offered to the public within a system that does not require each laboratory to provide separate clinical validity details for tests already accepted as clinically valid.

- **FDA would retain a limited role in oversight of high-risk LDTs through a joint CMS/FDA third-party test review process under CLIA authorities.** It is focused on those tests for which validation data is held privately and therefore, is not readily available to user through the clinical commons. Developers of high-risk LDTs could use the third-party reviewer if they were willing to reveal the components of their risk calculating algorithms that are the distinguishing feature of high-risk tests as compared to low or moderate risk tests. Alternatively, if they choose to retain control of the trade secrets that underlie their laboratory test interpretation, more traditional means of regulatory oversight could be used.
 - Moderate risk tests would be pre-certified through a third-party review system.
 - Low risk tests would be overseen during laboratory inspections by third-party accreditation bodies responsible for those inspections.
 - Tests kits and devices manufactured for broad clinical laboratory use would be overseen by FDA.
 - **Standards for third-party laboratory accreditors** including timely response to requests for new LDT assessments.
- 3. For tests in the low and moderate risk genetic testing categories, provide precertification of clinical validity of new tests, to be integrated into CLIA and delivered by the third-party accreditors. For high-risk tests, provide oversight through a new jointly sponsored CLIA/FDA third-party review system under CLIA authority.**
- Utilization of the **Clinical Laboratory Improvement Advisory Committee (CLIAAC)**, the advisory body responsible for recommendations on how to improve CLIA or CLIA staff. Improvements would include:
 - Bringing greater specificity to **how a joint CMS/FDA third-party test review process under CLIA authorities can be developed;**
 - Outlining how the moderate risk category can be structured to ensure that **appropriate expertise** related to the uses of LDTs with similar analytical methods for different specialty uses (e.g., molecular testing in somatic cancer, heritable disease, infectious disease) is represented;
 - Determining how to align the appropriate training and experience of personnel in different areas of genetic testing.
 - **At the same time, reduce availability of non-validated tests** through the continued attention of the Federal Trade Commission and State Attorneys General to the marketing and sales of tests for which clinical validation is inadequate.
- 4. Ongoing development of a public Information Commons with NIH support.**
- Support for the continued development of an **Information Commons** in which clinical laboratories and clinicians share data to continuously improve

everyone's knowledge of the clinical significance of rare genetic variation is needed. The information commons is a key component of the Precision Medicine Initiative and is already in development through the NIH/NHGRI's Clinical Genome (ClinGen) Resource that partners clinical investigators, professional medical associations (e.g., ACMG) and by individual professional medical associations such as the American Society of Clinical Oncology (ASCO) through its CancerLinQ program. The Information Commons can:

- **Inform test validity and postmarket surveillance** of tests that can benefit both laboratories offering LDTs and device manufacturers challenged by the magnitude of clinical trials required for rare genetic diseases.
- **Provide a means for improving the basis for clinical interpretation and ongoing reinterpretation** of results as data accrues in databases.

ACMG believes that a critical step in the continued improvement of genetic and genomic testing is to better balance the roles of the regulatory bodies involved in the oversight of test kit and device manufacturers (FDA) and of the practices of clinical laboratories (CLIA). We welcome the opportunity to work with Congress to ensure that genetic and genomic testing is safe and effective for the public, and that we ensure clinical and academic laboratories can quickly innovate and respond to new medical findings and patient needs to deliver on the promise of personalized medicine.