

February 2, 2015

Margaret Hamburg, M.D.
Commissioner
Food and Drug Administration
Dept. of Health and Human Services
Hubert H. Humphrey Bldg.
200 Independence Ave., SW
Washington, DC 20201

Submitted electronically via <http://www.regulations.gov>

**RE: Docket No. FDA-2011-D-0357: FDA Notification and Medical
Device Reporting for Laboratory Developed Tests (LDTs)**

Dear Dr. Hamburg:

The American College of Medical Genetics and Genomics (ACMG) welcomes the opportunity to comment on the proposed guidance for oversight of Laboratory Developed Tests (LDTs) ("proposed LDT guidance"). Initially, we believe that the Food and Drug Administration (FDA) lacks the statutory authority to regulate genetic testing services developed and offered by laboratories as medical devices under the 1976 Medical Device Amendments (MDA) to the Food Drug & Cosmetic (FD&C) Act. Moreover, even if it is decided that FDA did have such authority, the overwhelming weight of legal precedent establishes that the proposed new FDA requirements must be issued through formal notice and comment rulemaking pursuant to the Administrative Procedures Act. Finally, given that the proposed requirements conflict with existing regulations and would impose substantial new regulatory and financial burdens on clinical laboratories, physicians and their patients, the ACMG hereby reserves the right to challenge the proposed guidance in a proper forum.

In addition to the statutory and procedural objections stated above, our primary substantive concerns relate to the following:

- The impact of the costs of complying with the proposed LDT requirements, particularly on smaller, innovative clinical laboratories;
- The unnecessary duplication and potential inconsistency of the new FDA regulatory requirements with those already established

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- in the Clinical Laboratory Improvement Amendments of 1988 (CLIA); and
- The stifling of innovation that has historically come from the small academic clinical laboratories that develop and provide the testing services needed within their institution.

These concerns will be discussed below in connection with the components of the proposed LDT guidance

About ACMG

ACMG is the only nationally recognized medical organization dedicated to improving health through the practice of medical genetics and genomics. ACMG has over 1750 members, nearly 80% of whom are board certified clinical and laboratory geneticists and genetic counselors. The College's mission includes the following major goals: 1) to define and promote excellence in the practice of medical genetics and genomics and to facilitate the integration of new research discoveries into medical practice; 2) to provide medical genetics and genomics education to fellow professionals, other healthcare providers, and the public; 3) to improve access to medical genetics and genomics services and to promote their integration into all of medicine; and 4) to serve as advocates for providers of medical genetics and genomics services and their patients.

Background

Since the 1970s, genetic testing has been developed and delivered as a clinical service, most often beginning in academic medical centers before reaching large reference laboratories. Only a very small number of genetic tests have been made available as products by classical device manufacturers in the past 30+ years, though some of these manufacturers also have chosen to develop their test as a service rather than as a product to be sold to clinical laboratories. The rarity of most genetic conditions is poorly aligned with the typical needs to obtain sufficient statistical power to minimize the influence of expert opinion-based evidence.

Unlike the success of the Orphan Drug Act in aligning incentives for product development that led the pharmaceutical industry to innovate in this space, the incentives in the device industry have never been adequate to support a viable business model. As a result, the research and development related to genetic and genomic testing has been taken up by clinical laboratory service providers without which availability of and access to genetic testing would have stagnated.

The first iterations of a genetic or genomic test develop as diagnostics that are targeted at individuals with rare diseases. Of the roughly 7,000 described rare genetic diseases, over 5,000 have been associated with particular genes and many have related biochemical genetic tests. The types of abnormalities that can be associated with genetic diseases distribute their etiological testing between cytogenetics, molecular cytogenetics, and molecular genetics. The great majority of cytogenetic testing was grandfathered into use with the advent of the MDA while the great majority of molecular and molecular cytogenetic tests were developed as clinical services locally. The remaining 2,000 clinically defined genetic conditions are rapidly being tied to specific genes known to be associated with a disease or to genes not previously known to have disease associations. Most have strong effects on disease development. Diagnostic testing is now available in thousands of the disease-associated genes.

However, device manufacturers cannot justify the investment in clinical trials and product development until a genetic test can be offered to broader populations through carrier screening or newborn screening, or to those presenting with either common nonspecific phenotypes. Recognizing this regulatory and business model, we caution the FDA against assuming that clinical laboratories will be prepared to deliver these services. Moreover, we believe that FDA policy will result in the unintended consequence of compromising access to these critical tests by putting them at significant risk. ACMGs view of the appropriate balance between regulation of traditional genetic testing and the emerging genetic and genomic technologies is based on the complexity of the tests at issue. It can be summarized as follows:

- Most traditional genetic tests, including high-complexity tests, have been in use for many years and should be grandfathered into LDT use without the unnecessary burdens of FDA medical device-like registration; current CLIA requirements for laboratory licensing provide sufficient registration/listing for clinical laboratory tests. Expanding standardization of practice guidelines on determining the validity of genes and the pathogenicity of variants in those genes has guided the use of LDTs for decades without evidence of anything more than rare anecdotal reports of errors. Even designating genetic and genomic testing laboratories as manufacturers is more likely to result in limiting access to these innovative diagnostic tests than it is to ensure their safe and effective use.
- For emerging genome-scale testing, FDA should ensure the general analytical performance of manufactured devices used in genetic and genomic testing. The general capabilities and limitations of different testing platforms/technologies for different types of genetic changes should be clear. Their use analytically in clinical laboratories, however, should remain under the oversight of CLIA, and should be subject to the practice of medicine exception to FDA regulation. The Office of Human Resource Protections (OHRP) should maintain its role in patient protection in connection with translational clinical research.
- ACMG acknowledges that there are tests that may properly be classified as high risk (see Attachment 1 “ACMG risk classification scheme”) and, as such, may require appropriate regulatory oversight. However, contrary to the proposed burdensome requirements set forth in the proposed LDT guidance, modifications of current regulatory authorities that result in a hybrid oversight model involving both FDA and CLIA for high-risk tests seem more appropriate, at least for genetic tests.. A graphical representation of how the various components of an oversight scheme can be assigned to different agencies is included as Attachment 2.
- As the use of new genome-scale technologies with integrated bioinformatic filtering expands, decisions about which information from the genome is appropriate for visualization and communication to patients must remain within the practice of medicine.

We will now address individual components of the proposed LDT guidance.

Notification to FDA and Registration of all LDTs Manufactured by a Laboratory

The ACMG recommends that traditional laboratory-developed genetic testing, which currently is regulated under CLIA, should be exempt from additional regulation by the FDA. These tests should not be required to meet FDA registration or test menu notification requirements or be subject to adverse event reporting.

A. Registration and test menu notification requirements. Genetic testing laboratories currently register with CLIA in the course of acquiring their license to perform high-complexity testing. CLIA criteria include notification of all tests being done in the laboratory; specific requirements for facilities, equipment, materials, records, documentation of compliance, and personnel; and periodic proficiency testing. Since the implementation of CLIA in the late 1990's, requirements for keeping test lists current have been modified to focus on notification of tests using new technologies rather than all new tests. Reverting back to the original requirements would enable notification of CLIA all new tests being offered. The amount of information to support such notification can then be managed to avoid negative impact on laboratory financial stability.

Most high-complexity genetic testing laboratories offer hundreds of rare disease tests. Estimates from laboratories are that rare disease test registrations with the level of detail proposed by FDA would require significant investment in new laboratory staff to ensure compliance. Even FDA's low estimate of a 0.3 – 0.5 full time staff equivalents per laboratory for compliance with just the registration process would negatively impact an already compromised financial balance in genetic testing laboratories, since genetic testing labs typically offer hundreds of individual tests. The confluence of significant changes in coverage and reimbursement for genetic testing with increased regulatory requirements argues strongly for the need for an economic impact analysis to better understand the implications of these new rules on clinical laboratory economics and patient and physician access to rare disease diagnostics.

2. Notification to FDA Regarding Significant Changes to LDTs

We believe that much can be learned from prior experiences in genetic test evolution. Genetic testing for cystic fibrosis began well before the implication of the CFTR gene in its cause. Testing services began when only six mutations had been described in the CFTR gene and were of great value to those whose disease was caused by one of these more common variations. Within three years, laboratories were testing 30 variants found to be disease associated and in the next three years up to 82 mutations were included in testing. Improved iterations of this test continued over the next decade with over a thousand such variants being described and catalogued in organized data systems with the more common and phenotypically consistent being part of carrier screening.

The magnitude of this problem is apparent from review of the NIH/NCBI's ClinVar database. As of January 18, 2015, ClinVar contained 149,354 submissions across 19,778 genes (129,595 unique sequence and structural variants) from 270 submitters including clinical and research laboratories, locus-specific databases, aggregate databases (OMIM, GeneReviews), expert consortia, professional organizations, healthcare providers. When molecular tests are used in population level testing, only the most common and phenotypically consistent variants are included. However, such constraints are impractical and potentially

dangerous in a diagnostic setting. Rare and private variation not seen previously must be managed by trained providers and interpreted in the context of professional standards and guidelines that establish their pathogenicity. It was critical that standards existed by which pathogenicity of variants could be predicted as it would be an onerous demand for laboratories to seek regulatory approval for the addition of new clinically significant variants as they are identified over time in patient populations. These guidelines have evolved from specificity to sequencing in single genes to use in genome-scale sequencing.

3. Medical Device and Adverse Event Reporting

FDA proposes a program for clinical laboratories that significantly departs from reality. Clinical laboratories lack the legal, administrative, and regulatory expertise required for compliance with manufacturers rules for devices. Further, training programs for laboratory staff do not train people in this area. Proposals such as this significantly favor corporate laboratories over the small innovative laboratories that deliver a significant proportion of genetic and genomic testing in the U.S..

Two types of adverse testing events have been experienced in genetic testing; some have been caused by defects in materials or devices—devices manufactured by FDA-regulated device manufacturers—used in the testing procedure, while others were due to previously unreported rare population variability that led to DNA amplification failure. However, only those related to devices manufactured by classical manufacturers are assumed to fit this requirement. The events we have experienced to date have resulted from manufacturing changes to things as seemingly innocuous as how collection tubes are sterilized, overlaid with variables such as time in storage prior to initiation of testing. In the two individual events in which we have been involved, *both were identified in the laboratory testing community through their own system monitoring* as broad test system failures. Their resolution required identification of inter-laboratory practice variables that pushed test systems over thresholds of tolerance of the manufacturer's change FDA was not directly involved in their identification or correction, aside from being notified that there was a problem.

Test failures resulting from very rare variations in DNA sequences to be recognized by PCR primers also have been experienced. The rarity of these sorts of sequence variants require enormous population studies for their elucidation. Rare and private variation in both clinically validated genes and in reaction targets in the genome (e.g., amplification primer target) often require that millions of people to be tested to identify and characterize the variant sequences. This has led to the creation of data repositories such as those of the Clinical Genomics (ClinGen) Resource Project that is funded by the National Institutes of Health (NIH) to collect data from laboratories across the country and to subsequently curate variants in validated genes which are better sources of data related to rare population variation than is available within a single laboratory. These databases can provide a valuable shared resource for clinical laboratories and those utilizing genetic and genomic testing. Contribution of data from numerous laboratories performing testing is critical to the development of this resource. When combined with practice guidelines that provide laboratories with the means by which variation can be

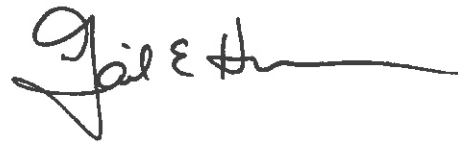
interpreted across the spectrum from benign to pathogenic, without the variation having been previously identified which act as a set of tools that can minimize interpretive inconsistency in result reporting can be developed. ACMG will continue to make such standards available to the testing community.

The ACMG appreciates the opportunity to comment on the proposed rules and welcomes the opportunity to continue to work with practitioners and regulatory bodies to find appropriate and effective means of ensuring high quality genetic and genomic testing services. Please feel free to call on us for any assistance we can provide..

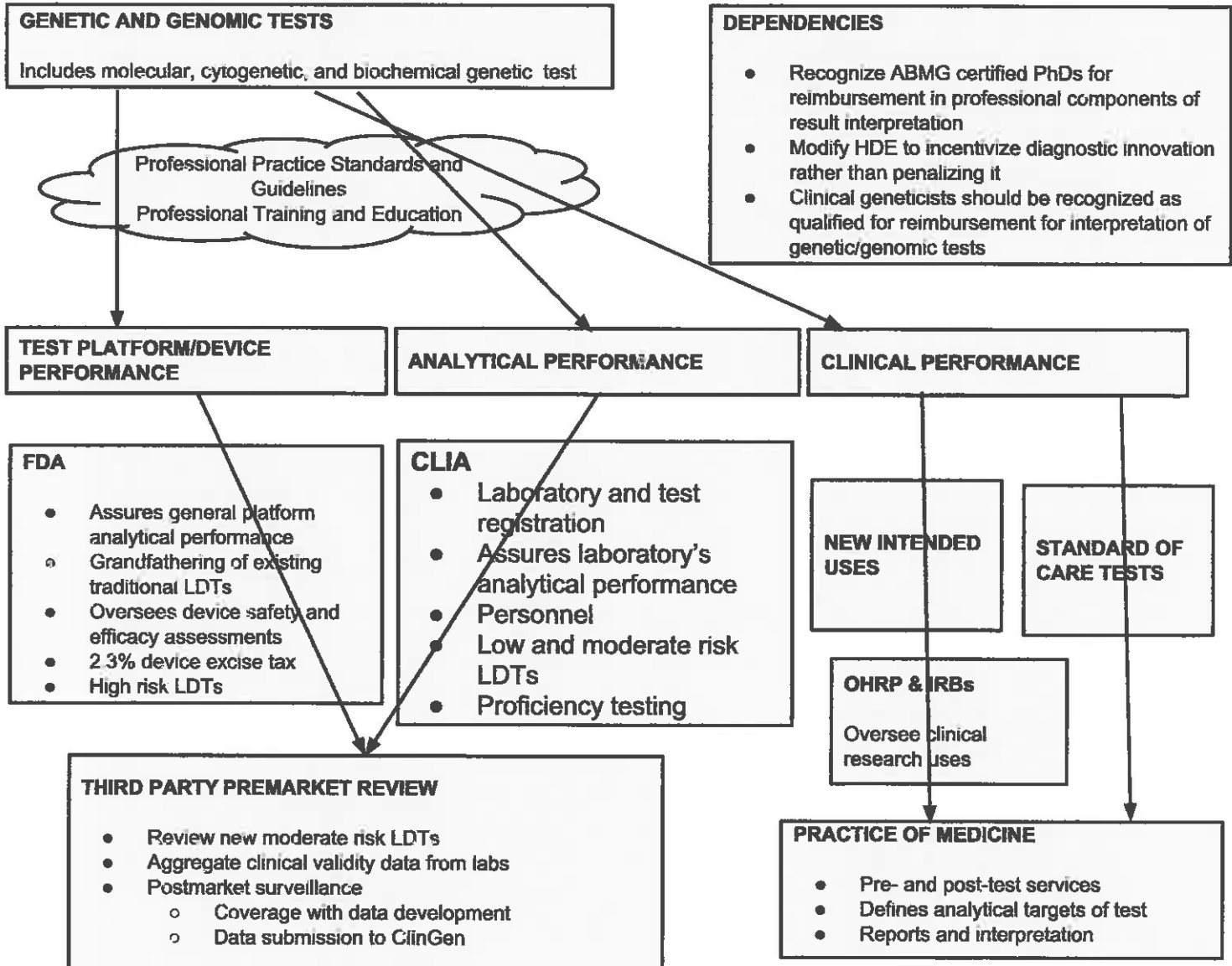
Sincerely,

A handwritten signature in cursive script that reads "Michael S. Watson".

Michael S. Watson, PhD, FACMG
Executive Director

A handwritten signature in cursive script that reads "Gail E. Herman".

Gail Herman, MD, PhD
President



Risk categorization for oversight of laboratory-developed tests for inherited conditions

Kristin G. Monaghan, PhD¹, Judith Benkendorf, MS², Athena M. Cherry, PhD³, Susan J. Gross, MD⁴, C. Sue Richards, PhD⁵, Vernon Reid Sutton, MD⁶ and Michael S. Watson, PhD²; a joint working group of the Laboratory Quality Assurance and the Professional Practice and Guidelines Committees of the American College of Medical Genetics and Genomics

This document represents the proposed approach of the American College of Medical Genetics and Genomics (ACMG) to classify laboratory-developed tests for inherited conditions. Risk classification has been the determinant of whether or not medical tests are overseen and regulated by the US Food and Drug Administration (FDA). Therefore, because laboratory-developed tests for germline mutations continue to proliferate without sound regulatory frameworks in place, an

ACMG-appointed workgroup of laboratorians and clinicians considered the medical risks and implications resulting from germline mutation analysis in a variety of contexts to develop the proposed approach. It is expected that the expert opinion represented in this proposed classification system will be used to guide federal agencies, policymakers, and other stakeholders.

The ACMG has categorized testing for inherited conditions by utilizing the three-tiered risk-based system (Table 1), as

Table 1 ACMGs proposed approach to risk classification and oversight of laboratory developed tests for inherited conditions

Classification	Determining factors	Oversight recommendations
Low risk: the consequence of an incorrect result or interpretation is unlikely to lead to serious morbidity or mortality for patients or their offspring	The test result is typically used in conjunction with other clinical findings to establish or confirm diagnosis, no claim that the test result alone determines prognosis or direction of therapy	The laboratory internally performs analytical validation and determines adequacy of clinical validation before offering for clinical testing; the accreditor during the normally scheduled inspections will verify that the laboratory performed appropriate validation studies
Moderate risk: the consequence of an incorrect result or interpretation may lead to serious morbidity or mortality for patients or their blood relatives; the test methodology is well understood and independently verifiable; and interlaboratory comparisons can be performed or external proficiency testing is available.	The test result may be used for predicting disease progression or identifying whether a patient is eligible for a specific therapy. It includes diagnostic, presymptomatic, and predisposition genetic testing; carrier screening; preimplantation genetic diagnosis and prenatal testing, in which the confirmatory procedure may incur significant morbidity or mortality to the patient or fetus (including but not limited to invasive prenatal diagnostic procedures that may directly affect pregnancy management, outcome, and reproductive decision making).	Test results require expert interpretation by an appropriately trained board-certified (ABPath/ABMG or ABMG) MD or PhD. The laboratory must submit validation studies to the CMS-deemed accreditor for review, and the accreditor must make a determination that there is adequate evidence of analytical and clinical validity before the laboratory may offer the test clinically. A system needs to be developed by the American College of Medical Genetics and Genomics in conjunction with a CMS-deemed accreditor to create an algorithm for the test validation review process. The laboratory should submit validation studies demonstrating analytical and clinical validity to the CMS-deemed accreditor. Because of rapidly expanding knowledge and new techniques that improve clinical molecular testing, a rapid turnaround time for the accreditor review is necessary.
High risk: the consequence of an incorrect result or interpretation could lead to serious morbidity or mortality, and the test methodology is based on a unique algorithm or proprietary method or is not independently verifiable	The test is used to predict risk of, progression of, or patient eligibility for a specific therapy to treat a disease associated with significant morbidity or mortality, and/or the test result cannot be tied to the methods used or interlaboratory comparisons cannot be performed	Test results require expert interpretation by an appropriately trained, board-certified (ABPath/ABMG or ABMG) MD or PhD. The laboratory must submit test to the FDA for review before offering the test clinically. The CMS and accreditor determine compliance

ABMG, American Board of Medical Genetics; ABPath, American Board of Pathology; FDA, US Food and Drug Administration; CMS, Centers for Medicare and Medicaid Services.

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recommended by the College of American Pathologists¹ and consistent with the usual FDA determination of testing-associated risk, whereby the FDA aligns risk with the medical decision made on the test results. The proposed risk categorization model of the ACMG is based on how an incorrect result might have an impact on patients and their blood relatives (including offspring). The risk model specifies determining factors for categorization and oversight recommendations for each level of risk. It should be recognized that genetic testing is a process including not only the analytical phase addressed in this document, but also preanalytical and postanalytical components, which are beyond the scope of this document. Patient harms can occur in the preanalytical phase (e.g., lack of education/counseling, disregard for the informed consent process, wrong test ordered) as well as postanalytically in the delivery of results and subsequent clinical follow-up.

Although the ACMG is in agreement with the features that the College of American Pathologists recommends to be included in the oversight framework for laboratory-developed tests, we recommend additional considerations for germline genetic testing. We recommend that all clinical molecular genetic tests fall into either the moderate-risk or high-risk category. Tests that (i) do not utilize proprietary methods or algorithms, (ii) are amenable to interlaboratory comparisons, and (iii) are evaluated by external proficiency testing should be categorized as moderate risk.

Due to the potentially serious implications of an incorrect result or interpretation for the patient and the patient's blood relatives, we recommend that all clinical molecular genetic test results be reviewed and interpreted by an individual certified in either Clinical Molecular Genetics (American Board of Medical Genetics, ABMG) or Molecular Genetic Pathology (American Board of Pathology/ABMG). The professional interpretation of test results should be provided by an individual certified in clinical genetics (ABMG), clinical cytogenetics (ABMG), clinical molecular genetics (ABMG), or molecular genetic pathology (American Board of Pathology/ABMG). In addition, we recommend that an ABMG-certified clinical geneticist and/or American Board of Genetic Counseling/ABMG-certified genetic counselor provide pre- and posttest counseling to patients, as necessary.

DISCLOSURE

The authors declare no conflict of interest. However, please note that all authors (except J.B. and M.S.W.) direct clinical testing laboratories.

REFERENCE

1. College of American Pathologists. Proposed Approach to Oversight of Laboratory Developed Tests draft proposal (4/28/2010). http://www.cap.org/apps/docs/advocacy/ldt/oversight_model.pdf Accessed 25 July 2012.