ACMG
American College of Medical Genetics and Genomics
Translating Genetics into Health

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RE: **Docket No. FDA-2011-D-0360: Framework for Regulatory Oversight of Laboratory Developed Tests; Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; Availability**

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 FDA has such authority, the overwhelming weight of legal precedent establishes that the proposed FDA requirements must be issued through formal notice and comment rulemaking pursuant to the Administrative Procedures Act. Finally, given that the proposed new 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;

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- The unnecessary duplication and potential inconsistency of the new FDA regulatory requirements with those already established 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 becoming available in 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 FDA against assuming that clinical laboratories will be prepared to deliver these services. Moreover, we believe that the proposed FDA policy will result in unintended consequences of compromising access to these critical tests 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 regulatory burden 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.

1. Laboratory Registration, Test Menu Notification, and Adverse Event Reporting

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 clinician access to rare disease diagnostics.

B. Adverse Event Reporting. 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 encountered, 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.

2. Continued Enforcement Discretion for Rare Diseases and Unmet Needs

The ACMG is concerned about the impact that increased regulatory oversight of genetic and genomic LDTs would have on patients with rare diseases and on tests that meet otherwise unmet needs.

As a general rule, the ACMG agrees that concerns about genetic testing vary with the potential volume of testing, the complexity of the test and on how an incorrect result might have an impact on patients. For these and other reasons, the ACMG has proposed a three-tiered risk-based system for the classification and oversight of laboratory developed tests for inherited conditions (see Attachment 1 "ACMG risk classification scheme"). Particular concerns arise, however, with respect to genetic tests for rare diseases and tests that meet unmet needs.

A. **Rare Diseases**. The ACMG has serious concerns about the impact that increased regulatory oversight of genetic and genomic LDTs would have on patients with rare diseases. We are already in a vicious cycle in which rare disease diagnostics are being held to unreasonable standards for determining their regulatory approval and their coverage by payers—these constraints seriously limit the acquisition of knowledge about the relationship of the disease to genetic variation. Not only do these factors limit access to clinically important diagnostic information, they deny families information that can guide their family planning strategies. ACMG is increasingly

concerned that constraining the establishment of an etiological diagnosis to confirm or refute a clinical diagnosis for a patient by either regulatory or coverage policy denies families of many of their options. If work towards diagnostic accuracy in independent laboratories is constrained access to clinical trials of the next generation of personalized therapeutics will be limited and the responsibility for patient diagnostics will be shifted into the clinical trials environment of the drug development process – with the inherent strong profit motives associated with that process.

We also remain concerned that inadequate consideration has been given to ensuring access to rare disease diagnostics. The Humanitarian Device Exemption (HDE) has failed to provide an incentive to device manufacturers to develop products in the area of genetic testing. Transferring this problem to clinical laboratories would have a significant impact on clinical laboratory services. Most genetic and genomic testing laboratories offer hundreds of diagnostic tests for rare diseases that would meet the HDE designation. However, HDE recognition precludes profiting on the test and, if applied to the great majority of a laboratory's test volume, would dramatically stifle innovation in these clinical laboratories.

The HDE also fits poorly with genetic testing. The incidence of disease provides one view of the potential volume of diagnostic testing, but this must be adjusted by the degree of specificity of the phenotype. The less specific the phenotype and the more common the nonspecific finding, the higher the testing volume. Further, clinical validity calculations about test performance are directly related to the likelihood of someone testing positively which is in turn related to how far into a differential diagnostic list one is when consideration of a test arises. This points towards the need for significant latitude in test ordering by physicians and, thus, for particular deference to the practice of medicine exemption.

We concur that traditional LDTs which, for the most part are tests directed at rare genetic diseases, need special considerations. Our ability to get beyond expert-based evidence has been severely constrained by lack of investment in organized data collection at a population level until recently as in the ClinGen Resource Project. However, even in the best of circumstances, evidence will always be weaker for these conditions and even weaker with regard to the pathogenicity of intragenic variation.

B. Unmet needs. LDTs have been developed for many 'unmet needs' when FDA-cleared tests are either not available or are considered inferior to the cleared test. However, cleared tests tend to remain in their cleared state --without further innovation and improvement --for longer periods of time due to the hesitancy of test device manufacturers to resubmit modified devices for re-clearance. In these circumstances, genetic testing laboratories have been able to develop improved and competing LDTs to ensure that their patients receive the best clinical service possible based on contemporary knowledge.

Rare disease tests have been the obvious unmet need in genetics for the past 20-30 years and continue to be. Unmet needs necessitating use of LDTs are also apparent when the health care system has to rapidly respond to infectious disease threats as occurred with the recent Ebola crisis. If laboratories capable of meeting these needs are to be placed under the same constraints that led to the need being unmet by manufacturers, the likely outcome would be for those clinical laboratories and for the patients who depend on their services would be lack of innovation and a slow response to the pressing needs.

In addition, some state legislatures have required FDA clearance of products used in their public health newborn screening (NBS) programs. Because so few products are FDA cleared, it has become an impediment to the expansion of newborn screening for conditions that have been recommended for inclusion by the Discretionary (HHS Secretary's) Advisory Committee on Heritable Disorders of Newborns and Children. The committee outsources evidence reviews and ultimately makes recommendations based on analytical and clinical validity and clinical utility. *There is no need for FDA to duplicate these efforts.* Public health laboratories provide a unique screening service that identifies diseases in our newborns. It is important that they be allowed to fulfill their missions in as timely a way as possible, whether with well validated LDTs or manufactured products.

3. Companion Diagnostics

ACMG recommends that the companion diagnostic linked to a therapeutic be based on the target(s) of testing rather than on the platform on which the test performance characteristics are initially established.

FDA has presented its initial view of which LDTs raise the highest concerns for them. These include:

- Companion diagnostics and products that behave like companion diagnostics.
- LDTs with the same intended use as an FDA cleared device and
- LDTs used to assess safety and effectiveness of blood or blood products.

Of particular concern to the ACMG is the FDA's view of companion diagnostics. FDA suggests that the performance of a therapeutic is directly associated with its companion diagnostic rather than with the scientific or medical information which is detected by the companion diagnostic. ACMG strongly disagrees with this construct. Linkage of tests with therapeutics merely provides yet another means by which FDA seeks to interfere with and regulate the practice of medicine. However, this false construct has driven cost escalation when pharmaceutical companies force a laboratory to acquire an entire testing platform that they otherwise do not need for their laboratories. For genetics, the companion diagnostic linked to a therapeutic should be the target of the test rather than the platform on which that target is detected. Clinical laboratories should be able to rapidly adapt the tests to new knowledge and provide the most precise and efficient results to physicians and patients. Manufacturers of companion diagnostics

have been slow in modifying the tests that were originally cleared by FDA, thereby limiting access to the best testing possible. FDA's requirements for resubmission for new clearance of already approved devices to which an additional variant has been added does not seem to be working well if manufacturers are allowing their previously cleared product to languish without improvements in the marketplace.

4. **Clinical Investigations and Evaluation of Clinical Validity**

ACMG recommends that clinical investigational studies, excluding those aimed at the safety and effectiveness of testing platforms, and evaluations of the clinical validity of a genetic test be recognized as falling within the practice of medicine. Clinical investigation should remain under the purview of the Office of Human Research Protections (OHRP) and local Institutional Review Boards (IRBS).

ACMG questions whether Investigative Device Exemption is appropriate for genetic testing services. It appears that the OHRP and local IRBs have the authority to oversee clinical research unless it involves questions of the safety and effectiveness of manufactured devices. Clinical questions that are answered with LDTs and devices are more appropriately overseen by physicians as the practice of medicine, and OHRP, and IRBs.

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. Improved iterations of this test continued over the next decade with over a thousand such variants being described and catalogued in organized data systems. It was critical that standards existed by which pathogenicity of variants could be predicted as it would be an onerous demand on laboratories to seek regulatory approval for the addition of new clinically significant variants as they are identified over time in patient populations. There has been little other than anecdotal evidence presented to justify this proposed policy. FDA oversight will delay improvements to service delivery access and add unnecessary expense to laboratory budgets which can only be passed on to consumers.

5. **Third party review**

ACMG recommends that a third party review system that is jointly administered by FDA and CLIA be developed--after the roles of FDA, CLIA, and OHRP are clarified. Medical specialists across germ-line and somatic testing and conditions should be well represented to ensure that there are no gaps between regulatory oversight and medical practice in ensuring access to high quality services.

ACMG awaits sufficient clarity in proposals of oversight of LDTs to be able to consider the role of a third party review system. Our prior comments would be consistent with a non-traditional approach: a hybrid model involving FDA, CLIA, and OHRP with significant deference to practice of medicine exemptions. The complexity of genetic and genomic medicine will require

that those with specific expertise in this area be actively involved and is therefore consistent with a third party review system. However, such a system can only be successful if it allweviates the burden on clinical laboratories that results from them having to individually interact with oversight bodies. Moreover, some data required by FDA, and more recently by payers, has been shown to be far more robust when aggregated from laboratories across the country than when provided by individual laboratories. Validation studies in unaffected and affected individuals will have much more statistical power than anything a single clinical laboratory can contribute and will be of much greater value to the individual laboratories and those who refer testing to them.

6. Premarket Review Requirements

ACMG recommends that FDA ensure the safety and effectiveness of testing platforms and that information on the limitations of those platforms be available to users. We strongly recommend against regulatory premarket review of the intended uses of genetic and genomic tests.

The premarket review requirements of this proposed rule are perhaps the most concerning as they appear to drive FDAs impetus to oversee this area of clinical service. They will dramatically slow the pace at which new innovation is introduced into clinical laboratory practice. ACMG favors a coordinated approach to improvement of genetic and genomic testing services predicated on capturing data from testing laboratories that informs everyone's use of the services. This type of 'special control' can easily include data acquired in the initial clinical validation studies from laboratories with ongoing data collection to continuously improve the quality of the services. Genetic variation is vast, requiring new oversight paradigms. Rare diseases and rarer variants in the those gene(s) fits poorly with a regulatory focus on robust statistical power. Rare event evidence bases are often weak and require significant expert involvement in their uses. Medical genetics was established as the 24th primary specialty of medicine if 1992 due to its unique base of medical information and practice. Medical geneticists need sufficient independence to practice that in which they are trained and board certified.

7. Quality System Regulation Requirements

ACMG recommends that FDA better define how it intends to regulate locally developed genetic and genomic testing services before seeking regulatory authority for oversight of this area of medical service.

The quality systems regulation (QSR) proposal for genetic and genomic testing is nearly impossible to react to due to lack of specifics. One thing, however, is clear--clinical laboratories offering LDT services are sufficiently different from traditional device manufacturers that alternative approaches to good manufacturing practice and other features of QSR must be tailored to their environments. Clinical laboratories develop extensive documentation of their premarket test validation and actively monitor their testing systems as required under the CLIA regulations. The potential financial impact on clinical laboratories of being treated like traditional device manufacturers, along with the other proposed requirements, would be lethal to the small innovative laboratories that offer these services.

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.

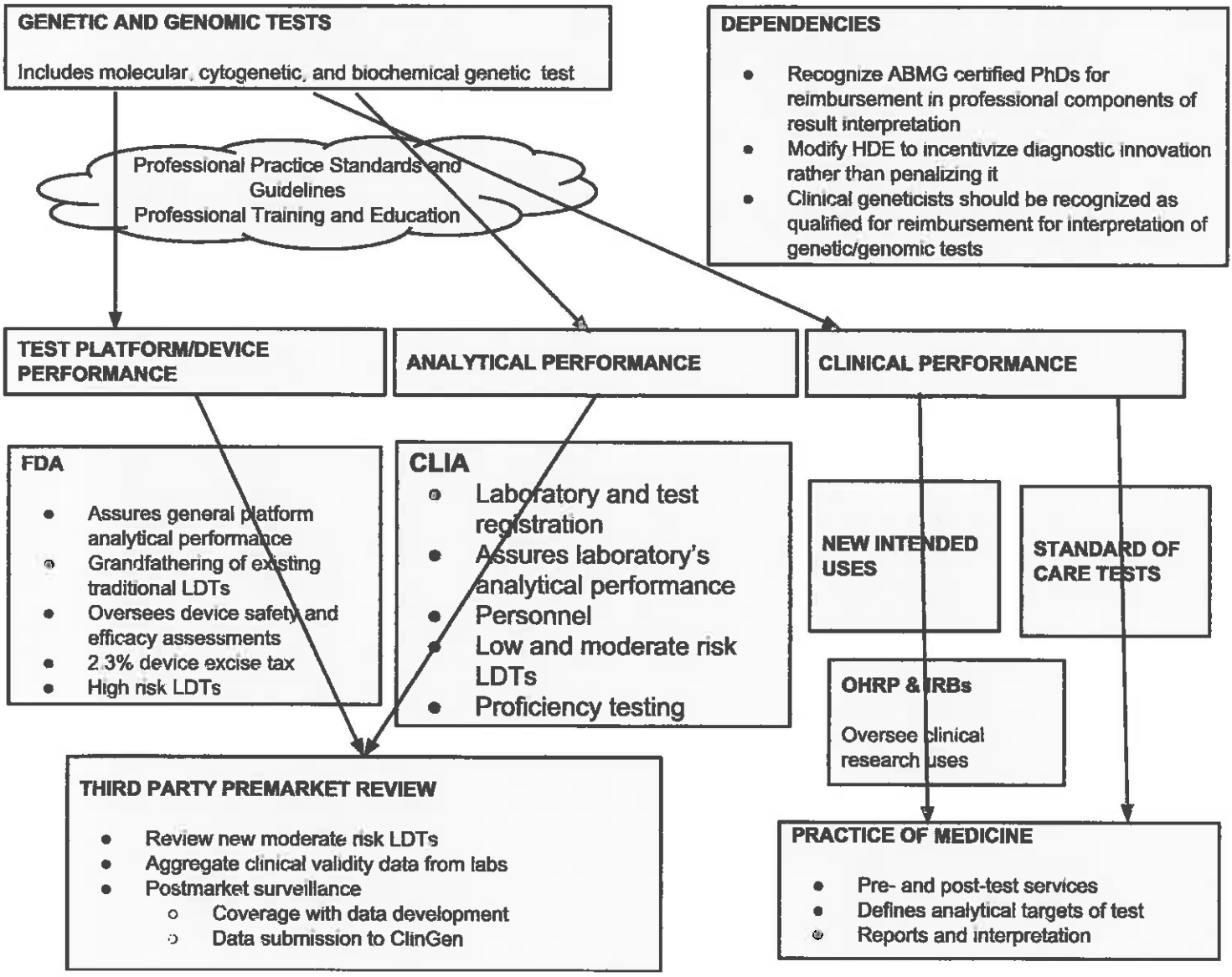
Sincerely,

Michael S. Watson, PhD, FACMG

Executive Director

Gail Herman, MD, PhD

President


GENETIC AND GENOMIC TESTS
Includes molecular, cytogenetic, and biochemical genetic test
Professional Practice Standards and Guidelines
Professional Training and Education
DEPENDENCIES
Recognize ABMG certified PhDs for reimbursement in professional components of result interpretation
Modify HDE to incentivize diagnostic innovation rather than penalizing it
Clinical geneticists should be recognized as qualified for reimbursement for interpretation of genetic/genomic tests
TEST PLATFORM/DEVICE PERFORMANCE
ANALYTICAL PERFORMANCE
CLINICAL PERFORMANCE
FDA
Assures general platform analytical performance
Grandfathering of existing traditional LDTs
Oversees device safety and efficacy assessments
2.3% device excise tax
High risk LDTs
CLIA
Laboratory and test registration
Assures laboratory's analytical performance
Personnel
Low and moderate risk LDTs
Proficiency testing
NEW INTENDED USES
STANDARD OF CARE TESTS
OHRP & IRBs
Oversee clinical research uses
THIRD PARTY PREMARKET REVIEW
Review new moderate risk LDTs
Aggregate clinical validity data from labs
Postmarket surveillance
Coverage with data development
Data submission to ClinGen
PRACTICE OF MEDICINE
Pre- and post-test services
Defines analytical targets of test
Reports and interpretation

Genetics inMedicine | ACMG POLICY STATEMENT

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

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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 Pathologists[1] 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.