ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

August 20, 2018

The Honorable Larry Bucshon
1005 Longworth House Office Building
Washington, DC 20515

The Honorable Michael Bennet
261 Russell Senate Office Building
Washington, DC 20510

The Honorable Diana DeGette
2111 Rayburn House Office Building
Washington, DC 20515

The Honorable Orrin Hatch
104 Hart Senate Office Building
Washington, DC 20510

Sent electronically to: Sarah.Killeen@mail.house.gov; Michelle.Greenhalgh@mail.house.gov; lauren_paulos@hatch.senate.gov; Rita_Habib@bennet.senate.gov

Re: FDA Technical Assistance for the Diagnostic Accuracy and Innovation Act

Dear Representatives Bucshon and DeGette, and Senators Bennet and Hatch:

The American College of Medical Genetics and Genomics (ACMG) appreciates the opportunity to provide comments on the Food and Drug Administration's (FDA) technical assistance on the Diagnostic Accuracy and Innovation Act (DAIA) discussion draft. ACMG is the only nationally recognized professional membership organization dedicated to improving health through the practice of medical genetics and genomics. Our membership includes over 2000 genetics professionals, nearly 80% of whom are board certified clinical and laboratory geneticists and genetic counselors.

There are important aspects of ensuring safe and accurate genetic testing that include both FDA and Clinical Laboratory Improvement Amendments (CLIA) oversight programs. In genetic and genomic testing, examples of these include legislative authority for the oversight of clinical laboratory practices, laboratory personnel qualifications, the evolving separation of analytical components of genomic testing from the clinical interpretive components, and allowances required for rare diseases and conditions. We focus our comments below only on the FDA's technical assistance to the DAIA discussion draft.

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ACMG appreciates FDA's interest in exploring modernized regulatory approaches for the oversight of in vitro clinical tests (IVCTs). Unlike the product-by-product approach proposed in the current DAIA discussion draft, FDA's proposal explores a more flexible regulatory approach aimed at addressing rapid development of technology and advancement of precision medicine. We agree with FDA's statement that patients and health care providers need accurate, reliable, and clinically valid tests to make good healthcare decisions. However, accessibility to appropriate tests should also be considered as well as the critical role that licensed physicians play in interpreting results in the context of other available medical information. Failure to recognize this intersection with medicine risks stifling patient-centered precision medicine by treating medical decisions made by highly trained and qualified physicians as steps in a manufacturing process.

There are several aspects of FDA's proposal that would need clarification in order to understand the overall impact to genetic testing laboratories and the patients that rely on their services. For example, the current proposal describes precertification of a developer for specific test groups rather than premarket review of every IVCT. One of the criteria FDA uses to define a test group is that all IVCTs are intended for use for the same disease or condition. While some genetic tests may target a specific disease, such as a panel that tests for the most common disease-causing variants within a single gene, others may test for a variety of diseases that could be the cause of a specific clinical symptom. Our understanding of the human genome is rapidly evolving with new genetic implications in diseases being reported almost weekly. In order to provide patients with the fastest and most accurate diagnosis or treatment plan, board-certified clinical geneticists need to be able to incorporate our rapidly evolving understanding of the human genome into medical evaluation. Denying a patient access to standard technology just because the target is implicated in a new disease or condition not covered under an existing precertification would only cause unnecessary harm to the patient. It is also important to consider that the result of such a test does not independently inform medical decisions, but rather it is a piece of the medical evaluation that the physician will consider when identifying the best plan of treatment for that individual.

There are also open tests that examine an entire exome or genome and require highly trained professionals to use their medical judgement, based on knowledge of genetic science and pathology, to inform the test interpretation as to whether a change is likely to be pathogenic, benign, or uncertain. Like interpreting the results of an x-ray or other imaging, the interpretation of variations in an exome or genome involve the practice of medicine which FDA does not regulate. There are numerous situations in which a medical geneticist may recommend whole exome or whole genome sequencing, and the intended use of this type of sequencing is not limited to a specific disease or condition. It is unclear how FDA would approach genomic tests that are not specific to a certain disease or condition.

In addition, FDA's precertification proposal is based on precertification of a test developer for a specific group of tests. FDA also defines a developer as being a person rather than an establishment. However, registration and notification requirements are centered around the establishment or facility. The relationship of a person to an establishment in the context of precertification and authority to develop IVCTs is unclear. For example, if a laboratory director is certified as a test developer for a specific test group, can that developer now develop those tests at multiple facilities under that single precertification?

FDA describes reliance on reference standards developed by non-governmental organizations for determining analytical and clinical validity as well as identifying tests for which clinical investigations involving human subjects are needed. We are pleased that FDA recognizes the potential role of clinical expertise to help inform clinical validity and are interested in better understanding the role of medical professional stakeholders and professional societies in developing such standards.

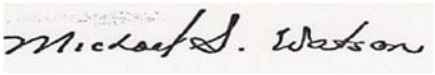
In their proposal, FDA identifies several types of tests that would be exempt from premarket review, such as rare tests (<8,000 tests per year), low risk tests, and grandfathered tests (unless they are modified). While it appears that FDA intends to ease the regulatory burden by exempting these special types of tests, requirements surrounding other proposed regulatory requirements need to be clarified to understand the potential burden on genetics laboratories. For example, these types of tests would still be subject to notification requirements. The FDA notification requirements described in this proposal go beyond that of listing basic information for each test and would require information such as a summary of analytical and clinical performance, lot release criteria, conformance with standards, mitigating measures, and more. The extent of information that FDA would expect to receive is unclear. A single genetic testing laboratory generally offers hundreds of different tests, many of which may be customized at the request of the treating physician following medical evaluation of the unique patient being treated. In order to understand the potential level of burden and related justification, more clarity is needed regarding the amount of information and level of detail that FDA would expect.

In the current proposed approach, the exempted tests described above, as well as those subject to premarket review, would be subject to FDA's quality system requirements. However, FDA notes that if a laboratory develops or modifies IVCTs for use within that laboratory only, and if that laboratory is certified by CLIA for performing high-complexity tests, then the laboratory would only be expected to follow a small subset of FDA's quality system requirements. This appears to be an attempt to leverage systems already required by CLIA and avoid unnecessary duplication. ACMG appreciates this awareness and is interested in exploring other areas of existing CLIA requirements that can be leveraged to ensure that quality tests continue to remain available to the patients who rely on them.

Overall, it has been ACMG's position that modernization of existing CLIA requirements would be an effective means of ensuring that high quality, accurate, and innovate tests remain accessible to the patients who rely on them. However, we are interested in engaging in discussions with your offices and FDA to better understand FDA's intent and identify appropriate solutions. By including clinical testing laboratories and the organizations that represent them in the discussion, we believe we are more likely to reach a solution that supports patient access to high quality, accurate, and clinically valid tests without interfering with the practice of medicine, hindering innovative test development necessary for advancement of precision medicine, or limiting patient access to medically necessary tests.

ACMG is happy to provide more detailed comments on FDA's technical assistance, and we look forward to engaging in further discussions with your offices, FDA, and CMS. We thank you for sharing FDA's technical assistance and providing us with the opportunity to share some initial comments. For additional questions, please contact Michelle McClure at mmcclure@acmg.net.

Sincerely,



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