



Better health through  
laboratory medicine.

October 6, 2016

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, rom. 1061  
Rockville, Maryland 20852

FDA-2016-D-1270-0002

Dear Sir/Madam:

The American Association for Clinical Chemistry (AACC) appreciates the opportunity to comment on the Food and Drug Administration (FDA) draft guidance entitled, “*Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases*,” which provides recommendations for designing, developing, and validating NGS-based tests for germline diseases and discusses the use of FDA-recognized standards for regulatory oversight of these tests. AACC shares the agency’s goal of ensuring “a flexible and adaptive regulatory oversight approach” for NGS testing. Unfortunately, we are concerned that this document may hinder, rather than promote NGS testing, in light of the FDA’s pending guidance on laboratory developed tests (LDTs).

AACC is a global scientific and medical professional organization dedicated to clinical laboratory science and its application to healthcare. AACC brings together more than 50,000 clinical laboratory professionals, physicians, research scientists, and business leaders from around the world focused on clinical chemistry, molecular diagnostics, mass spectrometry, translational medicine, lab management, and other areas of laboratory science to advance healthcare collaboration, knowledge, expertise, and innovation.

### **Current Oversight Structure**

AACC believes that NGS is an innovative and potentially invaluable technology for improving the abilities of healthcare providers to diagnose patients and improve patient outcomes. These assays are generally LDTs regulated under the Clinical Laboratory Improvement Amendments (CLIA). As high complexity tests, NGS testing is subject to stringent personnel, technical and clinical validation, quality control and proficiency testing requirements as well as regular inspections. Furthermore, a number of professional organizations and state entities already provide laboratories with guidance on how to perform, ensure the quality, and verify the accuracy of NGS tests. AACC supports the continuation of the existing public-private partnership.

### **Technological Advances**

AACC is also concerned that the FDA's proposed guidance could stifle ongoing efforts to expand and improve NGS technology. As the agency acknowledges, NGS testing will play an important role in advancing the President's Precision Medicine Initiative (PMI), which is designed to "accelerate biomedical discoveries and provide clinicians with new tools, knowledge, and therapies to select which treatment will work best for which patients." Creating new regulatory barriers for clinical laboratories (assuming the FDA moves forward with its LDT guidance), such as requiring them to obtain agency approval or clearance before introducing advances in NGS testing, may impede technological improvements and hinder PMI. AACC does not believe additional guidance is needed at this time. We offer some specific comments regarding the FDA draft guidance below.

### **Standards for Analytical Validation**

The FDA states that it's "unaware of any existing, comprehensive standards for analytical validation applicable to NGS-based tests for germline diseases that it believes could be used to help provide a reasonable assurance of the safety and effectiveness of these tests." This is not accurate. There are current guidelines available for both inherited disease and somatic alterations in Oncology. For example, the American College of Medical Genetics and Genomics (ACMG) has published guidelines as well as New York State. In addition, the College of American Pathologists (CAP) Molecular Pathology checklist contains a section on NGS testing. General guidelines for analytical validation of clinical diagnostic assays are also available from the Joint Commission and can be adapted to NGS testing. There is sufficient guidance available to clinical laboratories to analytically validate their NGS-based tests.

### **Test Design Consideration**

FDA states that "examples of common clinical uses under the broad indications for use statement considered here include: aid in diagnosing children with signs and symptoms of developmental delay or intellectual disability, patients with undiagnosed diseases, patients with hereditary cancer syndromes, etc." FDA should clarify that in regards to hereditary cancers, test developers should specify the specific application - either diagnostic or screening - since the quality metrics can be different. The agency also lists examples of target populations. We suggest that ethnic variability be included as one of the one of the considerations for determining the target populations.

The FDA further states that "a test intended to diagnose suspected genetic disorders in newborns may use WES rather than a more restricted panel of genes with well-defined clinical significance. In such a case, the test may be configured to report only a subset of genes from WES that may be related to suspected disease(s) or other condition(s) based on a patient's phenotype, clinical presentation, and previous available test results for the patient." We believe that incidental findings should be discussed with the patient's physician since they need to be interpreted in the context of the patient's disease condition.

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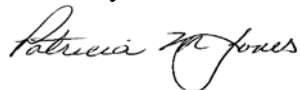
### **Test Performance Characteristics**

AACC is concerned that the accuracy requirements proposed by the FDA are unrealistic in the near term. The agency is recommending that the positive percentage agreement (PPA), negative percent agreement (NPA) and technical positive predictive value (TPPV) “be set at no less than a point estimate of 99.9% with a lower bound of the 95% confidence interval (CI) of 99.0% for all variant types reported by the test.” This is not feasible as NGS technology metrics and pipelines may differ. This is especially true for somatic variants and insertions and deletions in particular. Further, this level of accuracy is impossible to achieve for rare inherited diseases where positive samples for a condition are difficult to obtain. We suggest the FDA reconsider this recommendation or that it release the clinical and scientific evidence that supports this proposal.

AACC has similar concerns with the FDA Precision proposal. The agency “recommends thresholds for reproducibility and repeatability that meet or exceed 95.0% for the lower bound of the 95% CI, calculated by conditions tested and genomic context, separately for each variant type.” Establishing 95% precision will require 20 runs for each variant type. This threshold may be achieved by medical device manufacturers, but it will be cost-prohibitive for academic medical centers performing NGS testing.

AACC looks forward to continuing to a dialogue with the FDA on this important issue. If you have any questions, please email Vince Stine, PhD, AACC Director of Government Affairs, at [vstine@aacc.org](mailto:vstine@aacc.org).

Sincerely,



Patricia M. Jones, PhD, DABCC, FACB  
President, AACC