



October 6, 2016

ATTN: Robert M. Califf, M.D.
U.S. Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket Nos. FDA-2016-D-1270 and FDA-2016-D-1233

Use of Standards in the Food and Drug Administration's Regulatory Oversight of Next Generation Sequencing-Based In Vitro Diagnostics Used for Diagnosing Germline Diseases: Draft Guidance for Stakeholders and Food and Drug Administration Staff

AND

Use of Public Human Genetic Variant Databases To Support Clinical Validity for Next Generation Sequencing-Based In Vitro Diagnostics; Draft Guidance for Stakeholders and Food and Drug Administration Staff

Dear Dr. Califf:

The Personalized Medicine Coalition (PMC) appreciates the opportunity to submit comments regarding the U.S. Food and Drug Administration (FDA)'s draft guidance documents, *Use of Standards in the Food and Drug Administration's Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases* and *Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics*. The draft guidance documents raise considerations and policy recommendations for the oversight of certain applications of next generation sequencing (NGS) diagnostic tests.

PMC, representing innovators, scientists, patients, providers, and payers, promotes the understanding and adoption of personalized medicine concepts, services, and products to benefit patients and the health system.

Personalized medicine is an emerging field that uses diagnostic tools to identify specific biological markers, often genetic, that help determine which medical treatments and procedures will work best for each patient. By combining this information with an individual's medical records and circumstances, and values, personalized medicine allows doctors and patients to develop targeted prevention and treatment plans.

Our interest in the draft guidance documents pertains to how the concepts therein can support this emerging field. NGS technologies hold great promise for advancing personalized

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medicine. The ability to know one's genomic data can and will change the way that physicians and patients evaluate personal health. NGS will allow for the identification of many genetic variants at once. This information can be used to make health care decisions based on the genetic makeup of each individual patient, thus truly personalizing health care.

While NGS holds great promise for the future of health care, appropriate regulatory oversight of these innovations will be needed to protect patients while maintaining a strong environment for innovation. Providing optimal access to high-quality validated diagnostic tests will help deliver on the promise of personalized medicine while protecting patients and public health.

Scope and Statement of Neutrality

PMC is focusing these comments on the use of standards for the oversight of NGS-based IVDs and the use of public human genetic variant databases as they relate to personalized medicine diagnostic tests. These comments do not pertain to the use of NGS technologies for ancestry testing and other direct-to consumer, non-medical applications.

Many of PMC's members will present their own responses to the agency and will actively advocate for those positions. PMC's comments are designed to provide feedback so that the general concept of personalized medicine can advance, and are not intended to impact adversely the ability of individual PMC members, alone or in combination, to pursue separate comments with respect to the guidance documents or related issues. PMC's response is focused exclusively on personalized medicine issues related to all genomic diagnostic tests, including NGS and all accompanying technologies (the combination of these is referred to herein as NGS).

Since our comments are focused on how NGS technologies can advance personalized medicine, and because there are some differences of opinion within our membership, PMC will not take a position on whether FDA has the statutory authority to regulate laboratory developed tests (LDTs) as medical devices or on the processes by which FDA may regulate them, even though many NGS-based diagnostic tests are developed and performed in single laboratory enterprises.

Acknowledgement of FDA's Efforts on Genomic Technologies

These draft guidance documents represent new concepts and processes for the regulation of diagnostic tests with consideration of the impracticality of applying some traditional processes to NGS tests. They demonstrate FDA's creativity and progressive approach to policy development.

PMC appreciates that FDA is engaging diverse stakeholders at the earliest stages of development in order to promote thought and incorporate various perspectives. We encourage FDA to continue that engagement, and look forward to working with the agency on this topic.

Modifications to Existing Tests

While an NGS test itself might not functionally change, the clinical application of the information provided by the test may change over time with additional knowledge about genomic variants and their clinical significance. While we cannot assume that the detection of additional mutations provides new or improved clinically actionable information, FDA should be willing to accept a reasonable level of evidence to analytically validate additional or expanded endpoints.

Requiring revalidation of tests end-to-end for each additional modification, including aggregate validation of previous modifications, is impractical for many NGS-based diagnostic tests, and could have a significant chilling effect on innovation. The agency should devise new processes for reporting and validating modifications that do not impair performance of existing NGS-based tests.

Recommendations and Requests for Clarification Regarding Use of Standards in FDA Regulatory Oversight of NGS-Based IVDs (Docket No. FDA-2016-D-1270)

Many of the issues described within the draft guidance document titled *Use of Standards in the Food and Drug Administration's Regulatory Oversight of Next Generation Sequencing-Based In Vitro Diagnostics Used for Diagnosing Germline Diseases* are best evaluated by experts within the clinical genetics and laboratory testing fields. However, we offer these comments about the scope of the draft guidance and how it could affect the field of personalized medicine in general.

Limitations

The draft guidance document provides “non-binding” recommendations for the use of standards and databases for FDA oversight of NGS-based IVDs. The document describes, however, a class II, de novo process for classification of germline tests, thereby potentially providing a less onerous pathway regarding pre-market requirements. Additional clarification is needed regarding the FDA’s decision requirements for de novo requests for NGS tests, and the binding versus non-binding implications of the subsequent classification.

PMC appreciates that this first foray into a new process for regulatory oversight addresses only one discrete subcategory of uses for NGS-based testing, but we note that the majority of uses for NGS tests are thereby not covered. Uses that are not addressed include screening, microbial genome testing, risk prediction, tumor genome sequencing, and use as companion diagnostics. The processes developed here should be considered when developing policies for regulatory oversight of these other applications and contexts, and if possible, the FDA should develop, and share with the public, a timeline for expanding these policies to other uses of NGS-based tests.

Analytical Validity Determination

FDA's oversight of NGS must facilitate safe, accurate, and reliable determination of clinically relevant information without being overly burdensome. Policies and processes for the regulatory oversight of NGS-based tests should provide access to novel technologies and promote innovation.

In this context, the analytical validity determination recommendations outlined in the draft guidance may in some ways be too specific for this stage of policy development. The specificity of the document is particularly notable when one considers its application for technological areas in which there is not yet a clear path for the use of standards. The FDA should remain flexible in consideration of revising initial benchmarks and policies as NGS technologies continue to develop. We suggest that FDA develop a process for regular review of relevant policies as well as validity assertions of database endpoints. The agency should establish processes in coordination with database administrators and test developers and allow for necessary adjustments that assure safety, accuracy, and appropriate access to novel tests.

Performance Characteristics

The standards for accuracy described in the draft guidance document are, in many cases, difficult to achieve, and may be overly stringent.

NGS performance characteristics are often dependent on a test's intended use and the characteristics of the applicable population. The agency should adjust performance thresholds to take into account the genes being interrogated, risks to the tested population of false-negative or false-positive results, and potential uses of information. Minimum performance thresholds may not be necessary in all contexts. The guidance document acknowledges this in section VI-A-5: "Performance Needs," which states that performance thresholds should consider metrics based on a test's indication and predefined user needs.

Performance characteristic expectations can vary widely depending on the target enrichment platform, the genome region of interest, and the type of variant being interrogated. The suggested thresholds for positive and negative percent agreement (PPA and NPA), technical positive predictive value (TPPV), and some test run quality metrics are high and may not be attainable for certain variant types including but not limited to whole genome sequencing, some difficult to sequence regions of the genome, and heterozygous variants. Thus, the agency should not apply a single performance threshold metric to all variants. The agency should instead calibrate the threshold levels and metrics when possible, based on variant type, genome region, and target enrichment, as well as the intended use of the NGS based test.

Consideration of Existing Standards

While establishing analytic validation characteristics for germline NGS-based tests, FDA should take into consideration established guidelines for germline and related diagnostic tests that have been developed by professional organizations including the American College of Medical Genetics (ACMG), the New York State Department of Health (NYSDH), and the College of American Pathologists (CAP). While these guidelines may

not apply strictly to NGS-based platforms, many of the concepts within may be applicable across testing platforms and intended uses.

Recommendations and Requests for Clarification Regarding Use of Public Human Genetic Variant Databases to Support Clinical Validity for NGS-Based IVDs (Docket No. FDA-2016-D-1233)

We commend FDA for developing policies applicable to the use of publicly accessible databases of genetic variants to establish clinical validity for NGS-based diagnostic tests. We offer these comments pertaining to how it could affect the field of personalized medicine in general.

Regulatory Grade

It is unclear what constitutes “regulatory grade” with respect to public databases. Further clarity is needed on what parameters (evidentiary classifications, adherence to defined standards, curation methods, accessibility requirements, etc.) are considered to classify a database as regulatory grade.

Differentiating Responsibilities

The responsibilities of FDA, database administrators, and test data submitters are not clearly delineated, especially as they pertain to curation, variant interpretation, and tracking. Further clarification is necessary regarding who is responsible for specific elements and processes for achieving regulatory grade compliance, and who is responsible for tracking approved submissions in the database to make sure that they accurately depict known versus unknown clinical significance, as this may change over time, and otherwise keep up with the state of the science.

The agency has stipulated that variant calls require a minimum of two experts to agree. While that standard may be largely acceptable, in the case of rare variants, it may not always be feasible. We suggest that the agency consider recognized professional guidelines, such as the National Comprehensive Cancer Network (NCCN) guidelines, and recently established and curated databases, such as the Genomic Data Commons (GDC), to keep pace with current research and to potentially limit time and resource constraints. The recognition of guidelines and quality databases may ensure an efficient process that expedites access to meaningful information that can inform care.

Accessibility

PMC supports process-driven transparency and public accessibility of variant databases. The agency should consider, however, limiting the ability to report emerging information when defining accessibility requirements.

Where possible, there should be an effort to incorporate real-time observational data obtained through learning health systems with appropriate classification of the quality of information such as investigational use only, disputed significance, and other data quality indicators. How often a database incorporates new data will be important for reporting variant interpretations.

Conclusions/Recommendations

PMC recognizes and appreciates that the processes described in the draft guidance documents could represent a paradigm shift in how diagnostic tests are conducted, interpreted, and regulated.

Some elements of the innovative approaches to the regulatory oversight of NGS-based tests that the FDA has described in these draft guidance documents have many elements that could be applied to other diagnostic platforms and technologies in personalized medicine. We recommend that FDA consider applying these oversight elements to other diagnostic technologies regulated under the FDCA, such as Sanger sequencing, mass spectrometry-based tests, multiplex genetic panels, and other PCR-based assays, as appropriate.

As the agency continues to consider these concepts, there are four key overarching principles that should be recognized:

1. Information from NGS-based diagnostic tests must be validated, accurate, and reliable.
2. Patients should be assured access to state-of-the art technologies.
3. Oversight policies must provide a process for easily reporting and validating modifications of NGS-based tests.
4. FDA must continue to engage all stakeholders to develop important details on how such an oversight system would be resourced, standardized, and administered.

PMC appreciates the opportunity to provide these comments. PMC and FDA are united by a shared goal to provide patients and health care providers with safe and effective technologies that will best serve the needs of patients and the health care system. If you have any questions about the content of this letter, please contact me at dpritchard@personalizedmedicinecoalition.org or (202) 787-5912. We look forward to further opportunities to provide feedback.

Sincerely yours,



Daryl Pritchard, Ph.D.
Vice President, Science Policy