



October 6, 2016

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

Comments on “Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases”

Docket No. FDA-2016-D-1270

Dear Sir or Madam:

The American Society of Human Genetics (ASHG) welcomes the opportunity to provide comments to the Food and Drug Administration (FDA) on the use of standards to assure the analytical validity of next-generation sequencing (NGS)-based tests. Founded in 1948, ASHG is the world’s largest genetics professional society, with some 8,000 members representing all areas of research and the clinical application of genetics. Members of the Society are using NGS to deepen our knowledge of the human genome and the relationship between genomic variation and health, and are at the forefront of developing new clinical applications of DNA sequencing technologies.

In previous comments submitted to the FDA (see letter submitted on 12/24/15 to docket: FDA-2015-N-3015), the Society expressed support for the agency exploring innovative ways of establishing the oversight of NGS-based tests. With the issuance of this draft guidance and the companion draft guidance describing how databases of genomic variants could inform the clinical validity of tests, ASHG would like to reaffirm the Society’s support for the FDA’s pursuit of a novel approach. NGS-based multi-gene panels and genome-wide tests represent a paradigm shift from traditional genetic tests used to detect the presence or absence of variants in a single well-characterized gene associated with a specific disease. The complexity of results from multi-gene panel or genome-wide tests, and the variety of possible intended uses of such tests, warrants a different approach.

General Comments

The Society is supportive of the overall approach laid out in the draft guidance. Many of the recommendations reflect the standard practices of clinical laboratories performing NGS-based testing. In addition, ASHG recognizes that FDA is attempting to minimize the regulatory burden for testing laboratories by seeking to declare a category of NGS tests for diagnosing germline diseases as class II-exempt. This would mean that tests meeting FDA standards could come to market without undergoing pre-market review, with the FDA instead establishing special controls to assure test quality. Declaring tests as class II-exempt would greatly reduce the burden to testing laboratories launching new tests.

The Society also appreciates that the regulatory framework proposed by the FDA enables test developers to report not only on variants known to be pathogenic, but also variants of unknown significance (VUSes). This is an important feature of the draft guidance that should be retained when the guidance is finalized.



This enables a clinician to conduct an independent assessment of the clinical significance of a variant, to discuss the result with the testing laboratory, and to conduct follow-up co-segregation studies. Similarly, Genes of Unknown Significance or minimal evidence should also be captured in test reports since these can be included in multi-gene panels and genome wide tests.

Performance characteristics and quality metrics

In the draft guidance, the FDA has proposed a number of metrics to measure test performance and test run quality. Currently, while there are standard metrics used to assess test quality for NGS-based testing, the quality thresholds that laboratories use typically vary by test. The challenge for FDA in establishing specific performance benchmarks for the tests covered by the draft guidance is that it is difficult to determine what metric thresholds are appropriate for all these tests. For instance, a higher level of stringency is appropriate for targeted panels compared with exome sequencing tests. Also, if a laboratory confirms all positive test results with a second DNA sequencing methodology such as Sanger sequencing, it may be appropriate to use a test with a relatively low specificity in order to reduce the number of false negatives.

The Society recognizes that performance specifications provide clarity to test developers seeking to bring tests to market. However, there is insufficient evidence to ascertain what those thresholds should be. Therefore, if the agency retains specific performance specifications in the final guidance, the Society urges the agency to also clarify that test developers may propose alternative specifications for ensuring the veracity of a given test. In addition, the Society urges the FDA to add tools in PrecisionFDA (precision.fda.gov) that allow testing laboratories to assess whether their test performance is meeting the FDA's recommendations.

The Society further requests that the final guidance clarifies how the test performance characteristics and test run quality metrics would apply to the bioinformatics pipeline, since the assay performance is tied to the bioinformatics pipeline used by the laboratory. Some testing laboratories routinely sequence several thousand genes but only report out a much smaller *in silico* panel, dependent upon the clinical assessment of the ordering healthcare professional.

The Society also recommends that the final guidance addresses how the performance characteristics apply to analysis of trios where, rather than establishing the presence or absence of an individual variant in an individual's genome, the test identifies *de novo*, segregating recessive, inherited dominant, X-linked variants present in a child's genome compared with the parents' genomes. The filtering and analysis pipeline is different for this type of test.

The draft guidance proposes that testing laboratories assess test accuracy by measuring Positive Percent Agreement (PPA), Negative Percent Agreement (NPA), and Technical Positive Predictive Value (TPPV). The Society considers it sufficient to calculate the PPA and NPA, as described in the draft guidance, in order to assess test accuracy, and believes that there is little additional value to be gained from calculating the TPPV. The Society therefore recommends that the TPPV recommendation be removed in the final guidance.



Lastly, the FDA is interested in whether the same metrics could be used for addressing analytical validation of genome sequencing. ASHG believes these same metrics are appropriate, but that the performance thresholds should be different, such as a lower level of coverage.

Other comments

The FDA is interested in how to minimize bias and over-fitting. Currently, although there are several efforts underway to develop reference materials, there is only one genome reference material currently available from the National Institutes of Standards and Technology (RM 8389; also called NA12878). In the event that more reference materials become available, FDA could require that testing laboratories use more than one reference sample.

Finally, the Society believes that the term 'next generation sequencing' will soon be outdated. Anticipating the final guidance will be used to guide the genetics community for many years, the Society recommends that the FDA instead refer to 'massively parallel sequencing'. Similarly, the Society believes that the terms 'whole exome sequencing' and 'whole genome sequencing' are inaccurate and misleading, and that it is more accurate to simply refer to 'exome sequencing' and 'genome sequencing'.

The Society appreciates how the FDA has engaged the genetics community in the development of this guidance, and stands ready to assist as the FDA finalizes the guidance.

Sincerely,

Harry C. Dietz, MD
President