American Society of Hematology's Response to FDA on its Request for Comments on the Use of Standards in the FDA Regulatory Oversight of Next Generation Sequencing-Based In Vitro Diagnostics Used for Diagnosing Germline Diseases, p. 1

September 29, 2016

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

RE: Comments to Docket: Docket No. FDA-2016-D-1270: 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Regulatory Oversight of Next Generation Sequencing-Based In Vitro Diagnostics Used for Diagnosing Germline Diseases; Draft Guidance for Stakeholders and Food and Drug Administration Staff; Availability.

Submitted electronically through: http://www.regulations.gov

Dear Sir or Madam,

The American Society of Hematology (ASH) appreciates the opportunity to provide comments to the Food and Drug Administration’s (FDA) on its draft guidance on the Use of Standards in the FDA Regulatory Oversight of Next Generation Sequencing-Based In Vitro Diagnostics Used for Diagnosing Germline Diseases issued on July 8, 2016.

ASH represents over 16,000 clinicians and scientists worldwide who are committed to the study of blood and blood-related diseases. These encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma as well as non-malignant conditions such as sickle cell anemia, thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. ASH membership is comprised of physicians who order Next Generation Sequencing (NGS)-based tests for their patients as well as pathologists and laboratory-based hematologists who develop these tests and interpret the results. The use of NGS-based tests on several familial hematologic disorders like acute leukemia and myelodysplastic syndrome has provided novel insights into disease initiation, progression, diagnosis and response to therapy. As such, the Society’s members have a vested interest in this draft guidance and its potential impact on disease diagnosis as well as overall patient care.

ASH commends the FDA for developing recommendations that will foster the effective design, development and validation of NGS-based tests for hematologic malignancies like familial acute myeloid leukemia and other germline hematologic diseases like sickle cell anemia. These recommendations would facilitate the improvement in overall quality control of testing laboratories, improve the tests’ clinical benefits and, more importantly, advance diagnosis and treatment outcomes.
While the recommendations in this draft guidance explain the FDA’s approach to regulating NGS-based tests for germline diseases, the guidance excludes other types of NGS tests whose application has tremendous potential for advancing precision medicine. Furthermore, the guidance could also benefit from clarity on the Agency’s review and approval process of NGS-based tests as well as its role in regulating variant interpretive services. Below are ASH’s recommendations for additional topics that should be covered in the final guidance:

1. **Clarifying the review process for germline diseases.** The FDA affirms in the draft guidance that NGS-based tests for germline diseases are considered new types of medical devices and hence automatically classified as class III devices. However the Agency fails to explain why NGS-based tests for germline diseases should undergo a different review and approval process from NGS-based tests that are currently being used to diagnose diseases or predict cancer risks. Furthermore, the FDA’s possible reclassification and/or exemption of NGS-based tests for germline diseases from the scientific and regulatory review process (i.e., premarket review) creates ambiguity in the FDA’s review and approval process. ASH recommends that the final guidance contain further clarification on the FDA’s review process of NGS-based tests for germline diseases as well as the impact this process might have on expeditious evaluation of these tests. Providing clear regulations and procedures will foster the development and analysis of these tests and more importantly ensure that these tests are made available to patients in a timely fashion.

2. **Including other NGS-based tests.** One of the major shortcomings of NGS-based tests is their inability to identify structural genetic alterations that could have a great impact on disease diagnosis, especially in hematologic diseases. Tumor genome sequencing and RNA sequencing can help identify multiple types of disease-associated genetic alterations including sequence mutations and chromosomal rearrangements. These tests can also help detect unique variants in germline and somatic mutations in both malignant and non-malignant hematologic diseases, thus making them highly valuable tools for precision medicine. ASH strongly recommends that the FDA address tests that identify genetic alterations in the final guidance.

3. **Addressing variant interpretation.** The Agency’s regulatory approach towards variant interpretive services like standard operating procedures, decision matrices, and software products requires further clarification. ASH recognizes the rapid evolution in this area and wants to ensure that laboratories have the flexibility to interpret NGS-based tests while promoting the integrity of the results and standard of care given to patients. ASH recommends that the FDA address how such interpretive services will be regulated and the impact the Agency’s regulation might have on variant interpretation. Such clarification will provide appropriate guidance to laboratories wishing to devise their own interpretive processes.

4. **Developing guidance for somatic diseases.** Due to the prominent role of NGS in detecting possible disease variants in various somatic hematologic diseases like leukemia and lymphoma, there is a need for a similar or complimentary guidance document focused on addressing the FDA’s regulation and oversight in such disease areas. The lack of guidance for NGS-based tests for somatic diseases means each laboratory implements its own sets of rules which could lead to unfavorable outcomes in clinical practice and difficulty in comparing results between different laboratories. Uniform standards for NGS-based tests focused on somatic diseases would counteract current practices of self-regulation.
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Many aspects already present in the guidance document for germline diseases can be made applicable to somatic screening; however, additional parameters worth considering for such a guidance could include:

- Requiring parallel sequencing of tumor/normal genes to filter out germline and somatic variants;
- Establishing test criteria that account for the detection of low level mutations, especially in disease entities where minimal residual disease occurs;
- Clarifying the use of databases for interpretation of somatic vs. germline variants.

ASH would like to thank the FDA for the opportunity to comment on the draft guidance and appreciates the Agency’s ongoing efforts in ensuring timely access to reliable, accurate, transparent and clinically relevant newly developed tests. As the scientific and medical community continue to look to genotyping platforms like NGS for disease diagnosis and patient care, the establishment of clear and concise regulatory processes will be crucial for the safe and effective translation of such platforms into the clinical setting.

ASH looks forward to working with the FDA on this important scientific priority, to provide further information, and to be a resource for the Agency. Please contact the ASH Scientific Affairs Manager, Alice Kuaban, MS, at akuaban@hematology.org for any additional information.

References:


Sincerely,

Charles S. Abrams, MD
President