

October 6, 2016

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

Re: Docket No. FDA-2016-D-1270 for Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases

To Whom It May Concern:

On behalf of the American Association for Cancer Research (AACR), the oldest and largest scientific organization in the world dedicated to the prevention and cure of cancer through research, education, communication, and collaboration, we sincerely thank the U.S. Food and Drug Administration (FDA) for the opportunity to provide comments in response to the July 2016 draft guidance, “Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases.”

NGS technologies, which allow for the rapid sequencing of whole genomes and exomes, have revolutionized the field of oncology from basic research to clinical treatment. The AACR is pleased to see that the FDA is committed to *“implementing a flexible and adaptive regulatory oversight approach that fosters innovation and simultaneously assures that patient test results are accurate and meaningful.”* We commend the FDA’s efforts to obtain community input to help shape this guidance, most notable in two public workshops on this issue: “Optimizing FDA’s Regulatory Oversight of Next Generation Sequencing Diagnostic Tests” held on February 20, 2015, and “Standards Based Approach to Analytical Performance Evaluation of Next Generation Sequencing In Vitro Diagnostic Tests” held on November 12, 2015.

The AACR believes that in order for NGS-based tests to be safe and reliable, there should be a common set of performance characteristics with minimum requirements that would be consistently applied across different labs and NGS-based testing platforms. This guidance reflects a concerted effort by the FDA to streamline the regulatory process for NGS-based tests for germline diseases and conditions, and the AACR applauds the FDA for outlining the Agency’s approach for the use of standards in providing oversight of these tests. There are a few areas in which we believe additional guidance and clarification would be beneficial. Most notably, given that this draft guidance is specific for germline diseases, the AACR strongly encourages the FDA to expedite guidance for establishing standards for NGS-based IVDs used for detecting somatic mutations.

There are a number of areas in which additional clarity would be beneficial, and the AACR respectfully asks the FDA to provide further guidance in the following sections:

In **Section IV.A: Possible Classification of NGS-Based Tests for Germline Diseases in Class II**, the guidance states, “*The applicant should provide information in the premarket submission to demonstrate that general controls or general controls and special controls are sufficient to provide a reasonable assurance of safety and effectiveness for that test.*” The AACR asks the FDA to provide further clarity on the nature of these general and/or special controls and, if possible, provide specific examples.

In **Section IV.B: Possible Exemption of NGS-based Tests for Germline Diseases from Premarket Notification Requirements**, the guidance discusses how “*conformity with such recognized standards may be appropriate to support or provide a reasonable assurance of analytical validity*” but has not clarified how sponsors could demonstrate such conformity. The AACR looks forward to hearing how the FDA will determine how this conformity should be demonstrated in future guidance documents.

In **Section V: Elements of an NGS-Based Test for Germline Diseases**, the Agency demonstrates their flexibility in regards to regulation of NGS-based tests and acknowledges that “*any two NGS-based tests may differ in their design and workflows.*” The guidance recognizes that each NGS-based test may contain different elements including “*reagents, consumables, instruments, and software*”, and may encompass different steps such as (a) *specimen collection, processing, and storage*, (b) *DNA extraction*, (c) *DNA processing and library preparation*, (d) *generation of sequence reads and base calling*, (e) *sequence alignment/mapping*, (f) *variant calling*, (g) *variant annotation and filtering*, (h) *variant classification/interpretation*, and (i) *generation of test report*. The AACR supports this flexible approach for determining design and workflow of NGS-based tests for clinical use.

An important distinction that is stated in the guidance is that “*Manual variant interpretation, performed by healthcare providers and laboratory professionals, is not considered part of the test.*” This distinction is important to the AACR as we believe that the practice of medicine should **NOT** be regulated or overseen by the Agency. The AACR’s primary concern is patient safety and we want to ensure that all NGS-based tests offered for patient care continue to meet high standards and have high-quality performance characteristics. The interpretation of NGS-based test results must rely on the judgment of qualified medical and laboratory personnel, should continue to be considered as the practice of medicine, and should **NOT** be regulated or overseen by the Agency.

In **Section VI: Recommendations for Design, Development, and Validation of NGS-based Tests for Germline Diseases**, the FDA describes one approach to supporting the analytical validation of NGS-based tests, which is through “*conformity with one or more FDA-recognized standards (if available) or special controls.*” For a standard to be recognized by the FDA, it should include a description of the design activities that should be carried out, the performance characteristics that should be validated, and the specific methodologies, materials, and performance thresholds. The AACR supports the idea of

careful documentation of accuracy, specificity, and sensitivity for these tests and believes that adherence to high-quality standards will ensure that these tests are safe and reliable.

In **Section VI.A: Test Design Considerations**, the FDA outlines recommendations that, if test developers follow, will increase the analytical validity of the test. The guidance states that “*during the test design phase, developers should establish and justify minimum acceptable and target values for each performance metric appropriate for the indications for use of the test.*” The FDA believes that test developers should identify the clinical need and target population of the test, identify the users’ needs, and specify the acceptable specimen type and interrogated regions of the genome. The AACR appreciates that the FDA provides several examples for common clinical uses and target populations, specific user needs for the test, specimen types, and interrogated regions of the genome. The guidance goes on to outline how test developers should demonstrate performance needs, document all test components, and develop and document procedures and methods for running the test. The AACR agrees that there should be careful documentation of all test design considerations to ensure that the minimum sensitivity and specificity of the test has been met.

In **Section VI.A.6.b: Methods**, the guidance discusses a list of recommendations for select components of an NGS-based test including “*sample preparation and input.*” The AACR supports the establishment of specific methods for specimen handling and input; however, the FDA should allow for flexibility in the establishment of these methods to allow for professional judgment and expertise in the day-to-day handling of specimens.

In **Section VI.B: Test Performance Characteristics**, the FDA stresses the importance of validating the individual steps of an NGS-based test and that the complete NGS-based test should be analytically validated in its entirety prior to initiating its clinical use. The FDA recommends that the positive percent 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.*” Additionally, they recommend “*thresholds for reproducibility and repeatability that meet or exceed 95.0% for the lower bound of the 95% CI.*” How did the FDA determine these values? Does the Agency intend to be flexible with these values? Ultimately, the AACR’s primary concern is patient safety, and the AACR supports the development of high-quality NGS tests with high analytic performance characteristics.

In **Section VI.C.1: Coverage (Read Depth and Completeness)**, the FDA states that they “*do not intend to recommend specific thresholds for coverage metrics in most instances*”, yet the draft guidance proposes specific threshold values within this section. For example, earlier in this section, the guidance states, “*for detecting germline heterozygous variants using a targeted panel, set a threshold of 20X or greater for minimum coverage depth and 300x for average coverage depth at 100% of the bases for targeted panels and at least 97% of the bases for WES.*” The AACR would like to confirm that “300x for average coverage depth” is a typographical error. Additionally, does the Agency intend to be flexible with these

values? The AACR strongly advocates for high-quality NGS-based tests that demonstrate high analytic performance characteristics which will have a positive impact on patient care.

In **Section VI.H: Test Reports**, the draft guidance recommends that sponsors “*Report variants using a widely accepted nomenclature.*” The AACR supports the use of established, widely accepted nomenclature, such as the sequence variant nomenclature authorized by the Human Genome Variant Society (HGVS), the Human Variome Project (HVP), and the Human Genome Organization (HUGO). The AACR agrees that the use of established, widely accepted nomenclature will reduce confusion and misrepresentation of reporting, and asks the FDA to cite specific examples of widely accepted nomenclature in the guidance such as those authorized by HGVS, HVP, and HUGO.

In conclusion, this guidance reflects a dedicated effort by the FDA to provide recommendations for designing and developing NGS-based tests to ensure analytical validity. The AACR applauds the FDA for its commitment to incorporating scientific advances into its regulatory framework and is pleased to extend its resources and broad expertise to the FDA as the Agency further refines its guidance for use of standards in regulatory oversight of NGS-based IVDs used for diagnosing germline diseases and drafts initial guidance for this topic in relation to non-germline diseases.

If you have any further questions, please contact Anna Sadusky, PhD, Director, Regulatory Science and Policy, at 267-765-1028 or anna.sadusky@aacr.org.

Sincerely,



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