October 6, 2016

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

Re: Docket No. FDA-2016-D-1270-0001: 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Regulatory Oversight of Next Generation Sequencing-Based In Vitro Diagnostics Used for Diagnosing Germline Diseases; Draft Guidance for Stakeholders and Food and Drug Administration Staff

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Docket No. FDA-2016-D-1233-0001: 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Human Genetic Variant Databases To Support Clinical Validity for Next Generation Sequencing-Based In Vitro Diagnostics; Draft Guidance for Stakeholders and Food and Drug Administration Staff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 Sir or Madam:

On behalf of the 30 million Americans with one of the nearly 7,000 known rare diseases, NORD thanks the Food and Drug Administration (FDA) for the opportunity to provide comments on the Agency's Draft Guidances 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" and "Use of Public Human Genetic Variant Databases To Support Clinical Validity for Next Generation Sequencing-Based In Vitro Diagnostics". The following comments encompass our thoughts on both draft guidances, and will be submitted to both online dockets.

NORD is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services.

Rare disease patients often face a diagnostic odyssey that averages seven years from identification of symptoms to achieving an accurate diagnosis. This is due to various factors, including a lack of understanding and attention to their disease within the medical community, complex and heterogeneous symptoms that do not always map easily to particular diagnoses, and a dearth of accurate and accessible diagnostic tests.

Next generation sequencing (NGS) proves particularly promising in the identification of genetic disorders within our rare disease patient population. Over 80% of rare diseases are genetic, and are often inaccessibly locked away in the genetic code. NGS gives patients hope that their particular disease can be identified and understood using NGS technologies.

For these reasons, we are pleased that the FDA has put forth these draft guidances with the intent to "provide a flexible and streamlined approach to the oversight" of NGS technologies.

The following are our comments on each specific draft guidance:

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:

NORD thanks the FDA for the careful construction and considerations contained within this draft guidance, as well as the thorough and collaborative process undertaken to support its creation.

This draft guidance is a culmination of several public workshops and open forums and is intended to provide a structure to regulating a field that has not historically been seen as a part of the FDAs regulatory environment. Historically, diagnostic laboratories in the US are regulated by the Centers for Medicare and Medicaid Services (CMS) and are governed by the Clinical Laboratory Improvement Act (CLIA). Accreditation is typically performed through several accrediting bodies (College of American Pathologists- CAP, Joint Commission) and through the state or territories Department of Health.

While several clinical diagnostic molecular assays have been cleared by the FDA as an In Vitro Diagnostic (IVD), these have historically been low complexity targeted assays that fall mostly within the infectious disease space and the molecular pathology space (cancer) and are intended to detect a limited number of predefined analytes. Currently, all high complexity molecular sequencing tests are lab developed tests and are not cleared by the FDA as IVD assays. This clearance by the FDA and classification as an IVD assay has exclusively been the responsibility of the commercial vendor which is developing the assay for commercial purposes by selling kits/equipment to clinical laboratories.

This process of clearing a test as an IVD product is lengthy, expensive, and complex, but most of all it is not scalable to complex genomic sequencing assays like whole exome sequencing, whole genome sequencing, or large sequencing panels. These complex assays can have thousands to millions of "analytes" being tested, and in this document it is recognized that the current processes in place for FDA clearance are not suitable for these extremely complex genomic assays.

As part of the Precision Medicine Initiative (PMI), this draft guidance establishes recommendations for designing, developing, and validating next generation sequencing (NGS) tests. The draft guidance also proposes a process for premarket submission of NGS based tests and considerations for the possible classification of certain NGS based tests in class II and potentially exempting them from premarket notification requirements. This exemption would be contingent on the test being safe and effective based on the guidelines outlined in the document. These include assurances that the assay conforms with FDA recognized standard for analytical validity and the public availability of and access to performance data.

It is NORD's understanding that this draft guidance is regarded favorably by the clinical molecular diagnostics field. This document demonstrates that the FDA recognizes the unique nature of NGS based testing, and how this makes the standard framework for IVD clearance by the FDA nearly impossible, especially for testing labs as opposed to commercial assay vendors.

The detailed breakdown in the guidance of the different components of the assay and the general recommendations for design, development, and validation of each component are clear, concise, and easy to understand. These recommendations should already be part of any clinical laboratories validation of a new lab developed NGS assay and should not be burdensome for laboratories to comply.

In addition to this draft guidance, these recommendations coupled to the recently available PrecisionFDA bioinformatics platform (https://precision.fda.gov/), there is little holding laboratories back from incorporating these recommendations into their regular processes.

After consulting with our scientific and medical advisors, NORD supports this draft guidance as it appears to facilitate the development and dissemination of NGS tests for our rare disease patients. The FDA is supporting and streamlining, not hindering, the development and usage of NGS, and we are thankful for the FDA's attention to this burgeoning field.

Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing-Based In Vitro Diagnostics:

NORD has long believed that in order to successfully diagnose and treat patients with rare diseases, the medical and scientific community must collaborate and work together without silos or barriers to collaboration. We have routinely encouraged such environments through participation in the Common Rule update, as well as the NIH's Undiagnosed Diseases Network.

The establishment of publicly accessible human genetic variant databases appears to be fit well within our overall priority of facilitating earlier and more accurate diagnoses for rare disease patients with genetic diseases. Since these diseases can often be incredibly rare, it is critical to facilitate collaboration across researchers and medical professionals.

In regards to the solicitation of comments on "Other Issues for Consideration", it appears these questions would be best answered by professionals in the NGS and diagnostic fields, and thus we do not have any additional comments to make.

We thank FDA for the opportunity to comment, and we look forward to working with FDA to ensure the continued growth in diagnostic development for rare diseases. For questions regarding NORD or the above comments, please contact me at mrinker@rarediseases.org or (202) 588-5700, ext. 102.

Thank you in advance for your consideration.

Sincerely,

Martha Rinker, J.D.
Vice President, Public Policy