Use of standards in FDA regulatory Oversight of Next Generation Sequencing-Based In Vitro Diagnostics used for diagnosing Germline Diseases (Draft Guidance)

Provides recommendations for designing, developing and validating NGS-based tests for rare hereditary diseases and addresses the potential for using FDA-recognized standards to demonstrate analytical validity.

Updated last August 8, 2016 for the 07/08/2016 draft guidance.

WHAT IT DOES

“In support of the President’s Precision Medicine Initiative, the U.S. Food and Drug Administration [FDA]” ... issued a draft guidance that “will provide a flexible and streamlined approach to the oversight of tests that detect medically important differences in a person’s genomic makeup. The powerful new technology, known as next generation sequencing (NGS), can scan a person’s DNA to detect genomic variations that may determine whether a person has or is at risk of disease or may help to inform treatment decisions. While current regulatory approaches are appropriate for conventional diagnostics that measure a limited number of substances associated with a disease or condition”... “new sequencing technologies can examine millions of DNA variants at a time, and thus require a flexible approach to oversight that is adapted to the novel nature of these tests” (FDA Press Release).

Due to NGS-based test’s large variability and huge potential in providing clinical information, appropriate regulatory oversight targeting NGS-based test has been an important topic for FDA regulation. The draft guidance (noticed via 81 Federal Register 44614) addresses Next Generation Sequencing (NGS)-based In Vitro Diagnostic (IVD) tests for germline diseases, by providing “recommendations for designing, developing and validating NGS-based tests for rare hereditary diseases, and addresses the potential for using FDA-recognized standards to demonstrate analytical validity, which is how well a test predicts the presence or absence of a particular genomic change” (FDA Press Release). The suggestions aim to provide a reasonable assurance of the analytical validity of targeted and whole exome human DNA sequencing (WES) NGS-based tests to ensure accuracy and safety. The document:

- Outlines considerations for possibly classifying certain NGS-based tests for germline diseases into a lower class of medical device (instead of class III, accomplished through a de novo application) and potentially exempting such a test from a premarket notification requirement, so long as the FDA is reasonably sure that the device is safe and effective.
- Indicates that an FDA-recognized NGS-based test should include standards addressing at least the following design, development and validation activities:
  - **Test Design:** Determine and document (1) the specific clinical need driving test development, (2) detailed test features necessary to meet user needs, (3) acceptable specimen types, (4) interrogated regions of the genome, (5) performance needs, such as metrics and associated thresholds, as well as (6) components and methods for running the test;
  - **Test Performance:** Establish and document (1) accuracy, (2) precision, in terms of reproducibility and repeatability, (3) limit of detection, which is the smallest amount of a substance that an analytical method can reliably distinguish from zero, and (4) analytical specificity, to determine interfering or contaminating substances;
  - **Test Run Quality:** Establish and note minimum acceptable thresholds for (1) coverage, in terms of depth and completeness, and (2) performance of each step in the testing process; and
  - Documentation related to test performance evaluation, supplemental procedures, genetic variant filtering, public presentation of test performance, and test reports, which should be compliant with labeling standards for in vitro diagnostic products (21 CFR 809.10).
- Clarifies that modifications to approved NGS tests will require follow-up analytical validation and may also require a new submission for FDA approval.
- Provides additional resources for stakeholders navigating the process of obtaining FDA approval.
DNA is the template for all biological information and is made up of different bases. Much like letters create words, individual DNA bases create long strands of DNA that are the genetic code for life. We can determine the precise order of DNA molecules by a process called sequencing. The first generation of sequencing techniques, such as Chan-termination methods (Sanger sequencing), relied on the difference between fluorescence of bases. The critical difference between Sanger Sequencing and NGS technologies is that instead of sequencing a single DNA fragment, NGS extends this process across millions of fragments in a massively parallel fashion. Multiple fragmented sequence reads are then assembled together on the basis of their overlapping areas. The use of NGS-based tests in both research and clinical practice allows identification of more genetic variants, including rare variants of unknown significance. NGS-based tests also reduce the time needed for sequencing the genome of a large population. By comparing the genome aggregates, researchers can reveal rare disease-related genetic variants.

A germline mutation is any detectable and inheritable variation in the genome of germ cells, which give rise to gametes of an organism that reproduces sexually. Mutations in these cells are transmitted to the offspring. A germline mutation will give rise to a constitutional mutation in the offspring, which is present in virtually every cell.

An in vitro diagnostic (IVD) device is a device that is intended for the examination of specimens derived from the human body solely or principally to provide information for diagnostics, monitoring or compatibility purposes. In vitro experiments are conducted in a laboratory or controlled environment, as opposed to in vivo tests that are done in the native context. These diagnostics are in vitro because the sample is taken from the body of the patient and thus outside of the native context. IVDs are somewhat limited as the diagnostic capabilities rely on prior knowledge. A specific condition and the cause must already be known to make use of IVD. By contrast, NGS-based tests can reveal new information because millions of DNA bases are sequenced and may be related to numerous conditions that have the potential to identify previous unidentified variants. It is often the case that the variants and the nature of the clinical information remain unknown until after the test has been run. IVD can only be utilized if the user knows what they are looking for, whereas NGS tests can be exploratory in nature.

**ENDORSEMENTS & OPPOSITION**

Endorsements:

- At this time, there are no publicly reported endorsements for the draft guidance.

More broadly, there has been wide endorsement for the development of NGS-based tests for disease diagnosis. For example, a paper entitled “Next-Generation Sequencing for Cancer Diagnostics: a Practical Perspective” published in November, 2011 stated that “Next-generation sequencing (NGS) is arguably one of the most significant technological advances in the biological sciences of the last 30 years. The second generation sequencing platforms have advanced rapidly to the point that several genomes can now be sequenced simultaneously in a single instrument run in under two weeks. Targeted DNA enrichment methods allow even higher genome throughput at a reduced cost per sample. Medical research has embraced the technology and the cancer field is at the forefront of these efforts given the genetic aspects of the disease.”

Opposition:

- At this time, there is no publicly reported opposition to the draft guidance.

In more general context, there has been wide concern about the quality of NGS-based tests. The European Journal of Human Genetics expresses such concern in “Guidelines for next-generation sequencing” published on October 28, 2015: “The available NGS platforms are not stable yet in a sense that the technology and applications change constantly and rapidly.” “The one thing that should prevent people from prematurely offering NGS diagnostics is poor quality. Insufficiently validated tests do present a threat to patients, and their use in a clinical diagnostic setting is unacceptable.” The article further stated that “NGS should not be transferred to clinical practice without an acceptable validation of the tests according to the emerging guidelines.”
The FDA is also concerned with the quality of NGS-based tests. The discussion paper “Optimizing FDA’s Regulatory Oversight of Next Generation Sequencing Diagnostic Tests,” issued in December, 2014, proposed “implementing analytical standards that would ensure that NGS tests produce accurate and reliable results.”

**STATUS**

The document was issued by the FDA’s Center for Devices and Radiological Health (CDRH) on July 8, 2016. Opportunity for public comment closes October 6, 2016.

**RELATED POLICIES**

On January 20, 2015, President Obama announced the Precision Medicine Initiative (PMI). PMI aims to encourage research in precision medicine to enable health care providers to tailor treatment and prevention strategies to people’s unique characteristics, including their genome sequence, microbiome composition, health history and diet. NGS’s huge potential in detecting genetic variability among individuals makes it one of the key players in the project.

“Infectious Disease Next Generation Sequencing Based Diagnostic Devices: Microbial Identification and Detection of Antimicrobial Resistance and Virulence Marker” introduces FDA guidance for studies to establish the analytical and clinical performance characteristics of Infectious Disease NGS-based Diagnostic Devices for Microbial Identification and Detection of Antimicrobial Resistance and Virulence Markers. The draft targets the large variability of human infectious disease, whose diagnosis requires accurate, rapid and actionable results. The draft also provides detailed information on the types of data FDA recommends be submitted in support of a Class II premarket submission. It was issued by the Center for Devices and Radiological Health (CDRH) on May 13, 2016 and is being distributed for comment purposes. Comment closing date is August 11, 2016.

Another FDA draft guidance, “Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics” describes how publicly accessible databases of human genetic variants can serve as sources of valid scientific evidence to support the clinical validity of genotype-phenotype relationships in the FDA’s regulatory review of NGS-based tests. The draft outlines the process by which administrators of publicly accessible genetic variant databases could voluntarily apply to FDA for recognition and how FDA would review applications and reevaluate recognized databases. The draft was issued by the Center for Devices and Radiological Health (CDRH) on July 8, 2016 and is currently being distributed for comment purposes. Comment closing date is October 6, 2016.

Various panels have also been held by the FDA to discuss possible regulatory approaches. On February 20, 2015, FDA held a public workshop entitled, “Optimizing FDA regulatory Oversight of Next Generation Sequencing Diagnostic Tests” to discuss and receive feedback from community stakeholders on possible regulatory approaches for tests for human genetics or genomics using NGS technology. To build on the feedback received, FDA held a second public workshop on November 12, 2015 entitled, “Standards Based Approach to Analytical Performance Evaluation of Next Generation Sequencing In Vitro Diagnostic Tests.” A number of stakeholders suggested the need for standards covering test design and performance evaluation for NGS-based tests to prevent false diagnosis. The FDA is unaware of any existing, comprehensive standards for NGS-based tests in germline disease diagnosis and the need for a standard to ensure safety and accuracy is eminent.

**POLICY HISTORY**

There is no previous related regulation.

**PRIMARY AUTHOR**

Nancy Zhang
EDITOR(S)

Jacqueline Robinson-Hamm, PhD Candidate & Aubrey Incorvaia, MPP

RECOMMENDED CITATION