FDA Issues Guidance for Next Generation Sequencing

by Jennifer K. Wagner

On July 8, 2016, the FDA issued draft guidance on the subject of next generation sequencing (NGS) activities: (1) “Uses of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases” and (2) “Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics.” The first focuses on the FDA’s proposed use of standards to help establish the safety and efficacy of NGS-based tests. The second focuses on the importance of high quality and publicly accessible databases to provide robust scientific evidence for understanding genomic variation, to inform decision-making, and to assess the clinical validity of NGS-based tests. Guidance is not a formal regulation, but rather an agency’s statement about how it will interpret or apply a regulation in the future. Draft guidance is a proposed policy that means the agency is formulating a position, whereas a final guidance is a document that represents what the agency has settled on as its interpretive policy. In theory, guidance is intended to serve as additional instructions for complying with rules and not intended to serve as the rules themselves.

The premise underlying the draft guidance is the controversial and—as yet—legally untested assertion that genomic analyses of all kinds are “medical devices” that Congress has, by statute, authorized the FDA to regulate. If they are, then the FDA would have the power to bring them under its current risk-based classification scheme for medical devices or to create a new scheme for them. If they are not medical devices, then the effort to regulate them might exceed the FDA’s statutory authority and conceivably amount to an unconstitutional regulatory overreach. Both draft guidance documents avoid any mention of the overarching debate, a subject covered extensively on Genomics Law Report, surrounding FDA oversight of all laboratory developed tests (LDTs) and in vitro diagnostic multivariate index assays (IVDMIAs). As others have noted, it is impossible to consider these new pieces of draft guidance outside of that context. Nonetheless, even the FDA asserts (via Twitter and elsewhere) that the two new drafts are intended to facilitate the Precision Medicine Initiative (PMI) and are distinct from the agency’s expressed intention to regulate LDTs. These pieces of draft guidance also give a policy-based reason for pause, as they could be another example of governance by guidance, a highly problematic approach as highlighted recently by John Conley with regard to the HIPAA right to access lab data and results.

Draft Guidance #1: Use of Standards for NGS Oversight

It is important to recognize the limited intended effect of the first draft guidance. The draft #1 underscores that complying with the guidance will not be required. The FDA acknowledges that alternative approaches to those outlined in the guidance on use of standards for NGS analysis could satisfy the existing statutes and regulations and that such alternative approaches would remain permissible. This draft guidance (see Lines 180-191) also contains a lengthy statement of what testing practices are outside of its intended reach. Specifically, the guidance does not apply to NGS-based tests intended for any of the following:

- stand-alone diagnostic purposes
- screening
- microbial genetic testing
- risk prediction
- cell-free DNA testing
- fetal testing
- pre-implantation embryo testing
- tumor genome sequencing
- RNA sequencing, or
- use as companion diagnostics.

The guidance applies solely to “targeted and WES NGS-based tests intended to aid in the diagnosis of individuals with suspected germline diseases or other conditions.” However, the FDA repeats its implication that there is something inherently more dangerous or risky about direct-to-consumer (DTC) access to results as opposed to results obtained in a healthcare setting, noting that for DTC delivery “additional recommendations and controls would be needed.”

Following the FDA’s premise that NGS-based analyses are medical devices, the guidance explains that NGS-based IVDs, as medical devices that have not yet been classified, are by law automatically categorized as Class III devices. The guidance outlines a process by which individuals or entities could make a de novo request for an NGS-based IVD to be classified as Class I or Class II by providing adequate premarket submission information. If classified by the FDA as Class II, the NGS-based IVD could then be marketed and serve as a predicate for future 510(k) submissions. The FDA also indicates that it has the discretion on its own or upon request to exempt NGS-based IVDs from premarket notification requirements, and the factors relevant for such a determination would be those set forth in this guidance (rather than the current guidance for Class II device exemptions issued in 1998).

The FDA conceptualizes NGS-based analyses as “medical devices” consisting of nine separate parts or elements, detailed in the draft guidance as the following: biospecimen collection and processing; DNA extraction; DNA processing and library preparation; generation of sequence reads and base calling; alignment of sequences or mapping; variant calling; variant annotation and filtering; variant classification/interpretation; and generation of a report. Notably, this list excludes any manual variant interpretation done by laboratory personnel or healthcare providers. This omission seems to be an attempt to resolve tensions between FDA-imposed restrictions on manual variant interpretation and the First Amendment (which would circumvent earlier criticisms of FDA restrictions based on genomic information as a form of speech) and avoid interference with state licensing schemes for the practice of medicine.


Demonstrated conformity with the proposed standards is not required but would be evidence to support claims of analytical validity. The guidance provides recommendations for test design, performance characteristics, test run quality metrics, performance evaluation studies, variant annotation and filtering, presentation of test performance, and test reports. The guidance identifies six key aspects of test design: the indications for use statement for the test, specific user needs for the tests, specimen type, interrogated regions of the genome, performance needs, and components and methods. The guidance further identifies four key aspects of test performance (accuracy, precision, limit of detection, and analytical specificity) and six test run quality metrics (coverage, specimen quality, DNA quality and processing, sequence generation and base calling, mapping or assembly metrics, and variant calling metrics). Several minimum standards for test performance and quality metrics are suggested, including the following (we pass these statistical points along essentially verbatim for the benefit of interested readers—for others, they won’t be on the exam):

- a point estimate of 99.9% accuracy (e.g., positive predictive agreement, negative predictive agreement, and technical positive predictive value) with a lower bound of the 95% confidence interval of 99.0% for all variant types reported;
- reproducibility and repeatability of at least 95% of a lower bound of the 95% confidence interval
- for detection of heterozygous variants, a minimum coverage (i.e., depth and completeness) threshold of 20x for targeted panels and 300x average coverage depth at 100% of bases targeted in the panel or 97% of bases for WES; and
- base calling or sequence generation with a base quality score of at least 30.

One threshold has already been identified as having a critical typo: 300x coverage, which many have assumed should be 30x. While a list of resources is provided at the end of the document, the draft guidance contains no explanation of where or how these specific items or thresholds were identified as appropriate for ensuring analytical validity. It also provides no insight about how the standards might be reevaluated and revised over time to ensure they continue to promote acceptable levels of safety and efficacy as science and technologies further develop. In an interview with Turna Ray for GenomeWeb, the FDA’s Director of Personalized Medicine and Molecular Genetics, Elizabeth Mansfield, explained that the agency arrived at a set of “conservative” figures from consulting a number of sources and further stated, “…one of the values of putting out a draft guidance is that people have ample opportunity to let us know that they think we got it wrong and why.” No specific questions were posed to the public for response in the draft guidance itself.

**Legal issues regarding the use of standards**

The use of standards in regulations has been the focus of extensive scrutiny. Section 12(d)(1) of the National Technology Transfer and Advancement Act (P. L. 104-113), now 20 years old, requires agencies to use standards from industry except where contrary to law or otherwise impractical. OMB Circular A-119 (initially issued in 1982, revised in 1998 and revised again on January 27, 2016), emphasized a “strong preference” for agencies to rely upon voluntary consensus standards in the relevant industry rather than creating their own government-unique standards. There remains considerable support for agencies to have the “flexibility to choose among standards developed in the private sector, particularly standards developed for emerging technologies that may or may not precisely follow the traditional voluntary consensus standards development process.”

Within the draft guidance on NGS-based tests, the FDA states that it “is unaware of any existing, comprehensive standards” (Line 158). But within the second draft guidance on database recognition, the FDA acknowledges that standards are emerging from the private sector (Lines 158-161: “Some organizations that are currently developing genetic variant databases have adopted protocols and methodologies (e.g., quality measures) and/or external guidelines (e.g., from professional societies or standards development organizations) for evidence aggregation, curation, and interpretation practices”).

Significant legal questions arise when an agency does choose to use standards from the private sector (or a private standard-developing organization) and then does so by incorporating those standards by reference (i.e., citing the standards but not repeating their details verbatim in the regulation). For example, when standards are incorporated by reference, they must be reasonably accessible to the public or at least the intended parties affected by those standards. “Publicly accessible” does not necessarily mean free of charge, and battles have been fought over whether standards that are incorporated by reference into regulations thereby enter the public domain or can still be protected by copyright. Section 5(f) of the revised OMB Circular A-119 enumerates a non-exhaustive list for agencies to consider regarding “reasonable availability.” The Circular also details that the agency has a responsibility to ensure the standards are reviewed every 3-5 years to keep them updated (Section 5(m)).

For additional reading on the use of standards in regulations, see, e.g., Nina A. Mendelson (2014), Private Control Over Access to the Law: Perplexing Federal Regulatory Use of Private Standards, 112 Mich. L. Rev. 73.

**Draft Guidance #2: Use of Public Human Genetic Variant Databases for Clinical Validity of NGS**

In the second guidance, the FDA explains its planned approach to recognizing databases as containing reliable evidence relevant to clinical validity. Such recognition could help to resolve some of issues that have been at the heart of recent lawsuits involving genetic testing, including the South Carolina case of Williams v. Quest Diagnostics, Inc., et al., discussed previously on Genomics Law Report. FDA recognition would provide, in essence, an example of what a clinically valid variant database looks like and that could be used by litigants to serve as a model against which private databases are evaluated. Accordingly, such FDA-recognized databases will have the potential to set standards of care throughout the nation and help distinguish the complicated practice of medicine (e.g., what to do with a variant classification and how to direct medical care decisions that take that genomic information into account, along with other relevant biomedical information) from the more straightforward process of variant calling and classification according to current biomedical knowledge and the application of published classification criteria.

According to Draft #2, the agency’s recognition of a database is a voluntary process for those entities or individuals providing or maintaining the databases. It would involve three steps: submission, FDA review for recognition, and maintenance of recognized status. The hope is that the establishment of FDA-recognized databases that can be trusted as containing scientifically valid evidence to support clinical validity will streamline FDA premarket reviews of NGS-based tests and help everyone (providers, patients, and regulators alike) make better decisions.
The FDA has identified four key features that it will consider when evaluating a database: (1) the database procedures and operations; (2) data quality; (3) curation and assertions ("assertion" are defined in Draft #2 as a notation made in the database about a particular variant based on current scientific knowledge, such as whether a variant is/is not benign, pathogenic, drug resistant, etc.); and (4) proper training and management of conflicts of interest for personnel. One aspect of the draft guidance is particularly interesting: "In order to be FDA-recognized, a genetic variant database should not include any recommendations regarding clinical treatment or diagnosis." There could be several reasons for that stipulation, such as the FDA not wanting to be perceived as endorsing one treatment option or pharmaceutical company over another and not wanting recognition of a database to usurp the role of licensed medical doctors in determining appropriate health care or disease management.

What's Next?
The public has an opportunity until October 6, 2016 to comment on both draft guidance documents (Docket Numbers [FDA-2016-D-1270-000](https://www.reginfo.gov/public/do/RegDetail?D=20160712-D-000000-1230) and [FDA-2016-D-1233-000](https://www.reginfo.gov/public/do/RegDetail?D=20160712-D-000000-1231)). Now is the time for the industry and other stakeholders to express support or opposition and question whether these standards are appropriate. What the FDA will do next with these guidance documents is speculation. The clock is ticking for the FDA, as the agency is motivated to move quickly to facilitate implementation of the Precision Medicine Initiative before the exit of the current administration.