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FDA Streamlines Reviews Of Next Generation Sequencing Tests

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The U.S. Food and Drug Administration issued two draft guidance documents on July 8 for next generation sequencing (NGS)-based tests as part of the White House's Precision Medicine Initiative, which was launched to encourage the development of health care treatment and prevention strategies that are tailored to people's unique characteristics, including genome sequence, microbiome composition, health history, lifestyle and diet. A critical component of the initiative is to promote development of tests designed to analyze a person's genetic sequence, to aid in the diagnosis of individuals with certain suspected diseases or conditions. These efforts have become even more pressing with the president's announcement of the National Cancer Moonshot initiative.


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The two new draft guidances address the Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases and Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics. In these guidance documents, the FDA describes regulatory pathways intended to streamline the development of NGS-based tests. While these proposals may lead to more efficient premarket reviews in the long run, there could be long ramp-up times and challenges for early adopters. Further, the immediate impact of these draft guidances may be limited, as most NGS-based tests are laboratory-developed tests (LDTs), currently subject to enforcement discretion. This will change, however, if and when FDA moves forward with its plans to classify and require premarket review for LDTs.[1]


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These two new guidances are the latest in a string of FDA efforts to shape and outline its policies for NGS-based tests. So far this year, the FDA has held public workshops in February and March on NGS-based tests and it issued another draft guidance in May for infection disease NGS-based tests.

Use of Standards to Support Analytical Validity of NGS-Based Tests

The first guidance on use of standards addresses analytical validity of NGS-based tests. The FDA proposes that, through use of standards, there may be a pathway for NGS-based tests for germline disease to be exempt from FDA premarket review requirements. Importantly, the FDA clarified in a stakeholder telephone conference that the draft guidance limits this opportunity to tests for germline diseases, indicating that other tests may be added at a later point.

Initially, the process to obtain exemption from premarket review may require several steps. The FDA states that it believes that most NGS-based tests for germline diseases will be Class II. However, an applicant first would need to submit a de novo request for classification, because there currently are no legally marketed predicates for these types of tests that would enable submission of a 510(k) premarket notification. After the FDA classifies a germline test as Class II, the agency would consider the ability to rely on conformity with an FDA-recognized standard for supporting or assuring the analytical validity of the test, in deciding whether to exempt such device from 510(k) premarket notification requirements. The draft guidance describes the elements that would need to be included in a design and development standard, in order for the standard to attain FDA recognition. The FDA also recommends that applicants consider discussing their tests early in the development process via a presubmission.

One important strategic consideration for companies considering submission of a de novo request for a novel NGS-based test is whether submission of a premarket approval application (PMA) would provide greater business advantages. Approval of a PMA will present a greater barrier to entry for competitors, and this should be weighed against the current unpredictability of data requirements and FDA review times for de novo requests, particularly if an applicable standard does not exist.

Use of Public Human Genetic Variant Databases

The second draft guidance describes how publicly accessible databases of human genetic variants can be a source of valid scientific evidence to support the validity of NGS-based tests. The FDA notes the importance of genetic variant data aggregation, and encourages database administrators to consider the opportunities that may be associated with obtaining FDA recognition. The draft guidance describes the recognition process and the database policies and procedures that would be required to achieve and maintain FDA recognition.

This new draft guidance could create significant opportunities for entities that maintain genetic variant databases. Companies that seek FDA-recognition for their databases will be able to market them to developers of NGS-based tests to help establish the clinical validity of such tests. The use of FDA-recognized genetic variant databases could help streamline the FDA's premarket review for NGS-based tests. The FDA suggests that, in some cases, submission of additional valid scientific evidence to support variant assertions (i.e, the linkage between a variant and a disease or condition) found in these databases may not be necessary.

Laboratory-Developed Tests

Significantly, FDA officials have clarified that the agency's issuance of these two draft guidances is completely independent of its efforts to establish a regulatory framework for oversight of LDTs. The draft guidances are intended for those test developers that determine they want to seek FDA review and clearance or approval of their NGS-based tests. Most NGS-based tests, however, are LDTs subject to FDA enforcement discretion and do not require premarket review. If, however, the FDA moves forward with its plan subject LDTs to active regulation and issues a final guidance for LDT oversight, the above-referenced guidance documents would apply. The FDA, therefore, may be offering these potential pathways to a more streamlined review in anticipation of receiving a large number of submissions for NGS-based tests in the future.

In federal register notices accompanying the two draft guidance documents, the FDA requests comments from industry on specific issues related to its proposed approach for the use of standards and

public genetic variant databases.[2] Comments on the draft guidances must be submitted by Oct. 6, 2016 to ensure they will be considered before the final version of the guidance issues.

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[1] FDA, Draft Guidance, Framework for Regulatory Oversight of Laboratory Developed Tests (Oct. 3, 2014).

[2] 81 Fed. Reg. 44614 (July 8, 2016); 81 Fed. Reg. 44611 (July 8, 2016).
