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CLIENT ALERT

Next-Generation Sequencing: FDA Issues New Guidance for Genetic Tests

By Kim Tyrrell-Knott and James A. Boiani

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On July 6, 2016, the U.S. Food and Drug Administration ("FDA" or "Agency") released the following two draft guidance documents on the oversight of next-generation sequencing ("NGS") tests:

- "Use of Standards in FDA Regulatory Oversight of Next-Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases" ("NGS Guidance")[1] and

- "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics" ("Genetic Variant Database Guidance").[2]

Taken together, these draft guidances propose a framework that recognizes that certain NGS IVDs may be eligible for a lower regulatory classification and include standards for establishing analytical and clinical validity of NGS-based tests. While these draft guidances are aimed at streamlining the regulatory process and providing certainty about the standards that will be applied to NGS-based tests, they could have significant implications for IVD manufacturers and—given FDA's proposed regulatory framework for laboratory developed tests ("LDTs")[3]—for laboratories as well.

All stakeholders should carefully assess the recommendations in these draft guidances and consider how they could affect the test development process and patients' access to safe and effective diagnostics. Comments are due by October 6, 2016, and can be made electronically through http://www.regulations.gov or in writing to Division of

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[1] The NGS Guidance is available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM509838.pdf.
[2] The Genetic Variant Database Guidance is available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM509837.pdf.
[3] FDA, Laboratory Developed Tests, *available at* http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407296.htm.

Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The docket number for the NGS Guidance is FDA-2016-D-1270 and for the Genetic Variant Database Guidance is FDA-2016-D-1233. If you have any questions about the notice and comment process or about the draft guidances, please feel free to contact your Epstein Becker Green attorney at your convenience.

Background

NGS tests are a key advancement in precision medicine. FDA has committed to optimizing its oversight of NGS-based tests in an effort to support continued innovation and adoption of precision medicine. The draft guidances are some of the Agency's initial steps in its precision medicine initiative. These guidances also address concerns raised by laboratories regarding the lack of standards that would apply to LDTs if FDA's proposed LDT regulatory framework goes into effect.

I. NGS Guidance

The draft NGS Guidance focuses on targeted and whole exome human DNA sequencing NGS-based tests intended to aid in the diagnosis of patients with suspected genetic diseases or other conditions that are inherited or arise from genetic variations (also referred to as "germline diseases"). The NGS Guidance does not apply to stand-alone diagnostic tests or to tests that have other analytical characteristics not addressed by the guidance's recommendations, such as screening, microbial genome testing, risk prediction, cell-free DNA testing, fetal testing, pre-implantation embryo testing, tumor genome sequencing, RNA sequencing, or companion diagnostics.

Nevertheless, this reduction in premarket review requirements and increase in clarity with respect to what design, development, and testing standards apply to these NGS-based tests has the potential to accelerate access to these tests and encourage continued innovation in the precision medicine area. There are two elements of the NGS Guidance: (i) a discussion of a potential reduced classification and pathway for certain NGS-based tests and (ii) a detailed description of the design, development, and validation requirements to demonstrate analytical validity.

Proposed Classification and Premarket Review

Currently, NGS IVDs are generally considered class III devices, subjecting their tests to stringent premarket approval ("PMA") requirements. Similarly, although FDA has not subjected LDTs to these requirements to date, certain LDTs would be subject to PMA under FDA's proposed LDT framework. The NGS Guidance acknowledges the potential opportunity to down-classify certain tests either through the *de novo* process or an independent FDA action. In either event, the guidance opens the door to a premarket notification ("510(k)"), or even 510(k)-exempt, pathway for NGS-based tests, which would reduce the premarket regulatory burden. Given the unique characteristics of NGS

IVDs, FDA proposes that the NGS Guidance serve as the basis for determining whether a 510(k) is required for evaluating NGS-based tests. [4]

Recommendations for Establishing Analytical Validity of NGS-Based Tests

FDA's recommendations for establishing analytical validity apply to the NGS-based test "system" as a whole, as opposed to a single component of the test. This approach is consistent with recent FDA trends and the Agency's apparent preference for a "system-based" approach to regulation, where pre-analytical, analytical, *and* post-analytical (e.g., test report) steps are considered. Specifically, the NGS Guidance applies to following steps:

- Specimen collection, processing, and storage
- DNA extraction
- DNA processing and library preparation
- Generation of sequence reads and base calling
- Sequence alignment or mapping
- Variant calling
- Variant annotation and filtering
- Variant classification or interpretation
- Generation of a test report

The NGS Guidance is intended to serve as a comprehensive standard for analytical validation to be used in providing a reasonable assurance of safety and effectiveness. The guidance outlines FDA's recommendations for the design, development, and validation of NGS-based tests.

Design

As part of the test design, developers are expected to establish and justify minimum acceptable target values for predetermined performance metrics. The following activities are recommended by FDA, with examples for each listed in the draft guidance:

- **Indications for Use Statement(s).** FDA requests a description of the specific clinical need driving the development of the test, including the targeted disease

[4] The NGS Guidance would replace "Procedures for Class II Device Exemptions from Premarket Notification, Guidance for Industry and CDRH Staff," available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm080198.htm, for purposes of NGS-based tests.

or other condition of interest, intended clinical use, and target population. The Agency further suggests providing a description of the clinical setting of the test administration.

- **Specific User Needs for the Test.** FDA recommends the use of consultation, professional experience, guidelines, and other sources to determine and record specific test features needed to assure the development of a test that meets user needs.

- **Specimen Type.** FDA recommends documenting acceptable specimen types in order to help determine the type of collection device required, minimum volume or quantity of the sample, and collection conditions for sample stability. Multiple specimen and collection types may be acceptable.

- **Interrogated Regions of the Genome.** FDA requests that developers identify the regions, including genes and variants that will be tested. The Agency also recommends that developers try to pre-specify what will be reported if only a portion of sequenced targets are requested by an ordering clinician.

- **Performance Needs.** FDA recommends that developers establish a minimum set of performance metrics, performance thresholds, and a degree to which interrogated sequences that do not meet test run quality metrics can be included; identify use of secondary procedures such as familial testing; and provide any possible limits to test performance.

- **Components and Methods.** FDA recommends that developers specify all test components, including procedural and general lab equipment, as well as the technical specifications and limitations for the test components based on identified user needs for each step of the test (i.e., the test system). The Agency provides specific recommendations for select components or steps of NGS-based tests, including the sequencing platform, controls and reference materials, and bioinformatics. FDA also asks that developers provide the procedures and methods of the test, in detail, for each step, including any instructions and limitations for use of instruments, consumables, reagents, and supporting methods. Finally, FDA recommends providing the type of sequencing to be used, and offers specific recommendations for select methods such as sample preparation and input, multiplexing, library preparation and target enrichment, and follow-up procedures.

Development

FDA recommends the following criteria for NGS-based test performance:

- **Accuracy.** Demonstrate accuracy by measuring positive percent agreement ("PPA"), negative percent agreement ("NPA"), technical positive predictive value ("TPPV"), and rate of "no calls" or "invalid calls." FDA recommends that PPA,

NPA, and TPPV be set at no less than a point estimate of 99.9 percent with lower bound of 95 percent confidence interval ("CI") of 99 percent for all variant types.

- **Precision.** Evaluate precision (reproducibility and repeatability) for variant and wild type calls, using a threshold of 95 percent for the lower bound of the 95 percent CI per variant type.

- **Limit of Detection ("LoD").** Establish and document the minimum and maximum amount of DNA that will enable the test to provide expected results in 95 percent of test runs with an acceptable level of invalid or "no calls."

- **Analytical Specificity.** Establish and document analytical specificity to determine whether, using the proposed methods, potential interfering and cross-reacting substances or cross-contamination affects the test performance. If test performance is affected, the developer must revise the methods.

Validation

In general, FDA recommends incorporating the following into performance evaluation studies when evaluating a test design and configuration:

- Perform validation studies on genomic regions and variants representative of the test's intended use and targeted population.

- Assess test limitations.

- Use specimens that reflect the actual specimen type and the identified target population.

- Include diverse genotypes of specimens and samples consistent with a test's indications for use.

- Ensure DNA preparation, specimen and reagent acquisition, handling, and storage for the evaluation of end-to-end test performance.

- Test different allele ratios for DNA samples or specimens with mixed content.

- Show the finalized bioinformatics pipeline for data processing and analysis for the beginning-to-end test validation.

- Validate sample pooling methods to ensure that individual sample identity is maintained (if applicable).

FDA also provides specific recommendations for NGS-based test accuracy evaluation and documenting results on validation studies. Finally, FDA outlines high-level considerations for test run quality metrics, inclusion of supplemental procedures,

filtering algorithms and annotation of variants, presentation of test performance, and test report content.

Modifications to Approved NGS-Based Tests for Germline Diseases

Changes to NGS-based tests will require analytical validation. However, FDA recognizes that the type of studies that will be required depend on the nature and extent of the modification. As a result, FDA provides recommended procedures for developers when making modifications to NGS-based tests for germline diseases and reminds manufacturers to reevaluate test performance whenever modifications are made.

II. Genetic Variant Database Guidance

In addition to demonstrating analytical validity, developers of NGS-based tests must provide valid scientific evidence of the tests' clinical performance. There are a number of non-public databases in existence today that aggregate data regarding genetic variants and the relationship of genotype-phenotype with certain diseases and conditions. FDA acknowledges that such databases have the potential to serve as sources of scientific evidence to support the clinical validity of a test if they meet certain requirements.

The draft Genetic Variant Database Guidance proposes a process by which FDA would recognize such genetic variant databases and outlines the requirements that such databases need to meet in order to be recognized by FDA. The guidance also suggests that, in some instances, data and assertions from FDA recognized that genetic variant databases would be sufficient, in and of themselves, to support clinical validity. The ability to avoid the need to develop and submit additional clinical data about the variant, in certain circumstances, could benefit manufacturers significantly.

Requirements of FDA-Recognized Databases

In order for a genetic variant database to be eligible for FDA recognition, the database must satisfy the following criteria.

Database Procedures and Operations

FDA recommends that genetic variant database administrators make sufficient information regarding data sources and standard operating procedures ("SOPs") for the evaluation and interpretation of evidence publicly available to enable an understanding of the criteria and processes used to collect and interpret evidence about variants. According to the draft guidance, administrators should also implement SOP version control processes as well as controls related to data preservation, security and privacy, and the use of standardized data formats.

Data Quality

In order to assure that the information in the database is of sufficient quality and based on current scientific knowledge, FDA proposes standards based on nomenclature, metadata, and data uniqueness. The nomenclature must be widely accepted by the genomics community and accompanied by a detailed description. The metadata must include, among other things, the number of laboratories and studies reporting the variant relationship, the name of the laboratory that reported the variant, and details of the test used to find the variant. "Data uniqueness" simply refers to databases applying methods to avoid duplicative data points.

Curation, Variant Interpretation, and Assertions

FDA requires written SOPs for curation and variant interpretation; this information must be made available to the public. Any assertions made should be appropriate to the level of certainty and the nature of the genotype-phenotype relationship and be adequately supported, truthful, and not misleading. A key point here is that in order to be FDA-recognized, a genetic variant database should not include any recommendations regarding clinical treatment or diagnosis.

Professional Training and Conflicts of Interest

FDA also requires adequate training and continuous proficiency testing of any personnel interpreting genetic variants within the database. All data must have been collected in compliance with procedures for collecting patient health information and human subject research. Additionally, FDA warns against conflicts of interest that could introduce bias and encourages professionals to minimize and be transparent about any potential conflicts of interest.

FDA Recognition Process

FDA proposes a recognition process for the genetic variant databases. The Agency makes clear that recognition does not subject the database to FDA oversight, other than what is required for maintaining FDA-recognized status. Obtaining FDA recognition is voluntary and involves three steps:

1) **Voluntary Submission for Recognition.** Administrators seeking submission should demonstrate that they have followed the recommendations in the FDA guidance document, and the Agency recommends consultation through the Pre-Submission Program before submission.

2) **FDA Review of Genetic Variant Database Policies and Procedures.** FDA recommends that documentation be included in the application for recognition, such as the types of variants addressed in the database, SOPs followed, personnel qualifications, data preservation plans, conflict-of-interest policies, disclosures of conflicts of interest, and validation studies for interpretation SOPs. The Agency notes that the information included in the recognition application is

generally treated as confidential but that the administrator must make the information publicly available upon recognition.

3) **Maintenance of FDA Recognition.** FDA intends to review recognized databases on a regular schedule to ensure continued compliance with the database's SOPs and the Genetic Variant Database Guidance. The Agency highlights the database's transparency of methods and assertions as critical in maintaining recognition.

Conclusion

The NGS Guidance and the Genetic Variant Database Guidance reflect a concerted effort by FDA to streamline the regulatory process for NGS-based tests for germline diseases and conditions and to clarify the requirements for establishing analytical and clinical validity. While the Agency's proposed frameworks have the potential of enabling innovation and access to NGS-based tests, developers of these tests should assess how these draft guidances may impact their design, development, and validation operations.

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This Client Alert was authored by **Kim Tyrrell-Knott** *and* **James A. Boiani**. **Megan E. Robertson,** *a Summer Associate (not admitted to the practice of law) in Epstein Becker Green's Washington, DC, office, contributed to the preparation of this Client Alert. For additional information about the issues discussed in this Client Alert, please contact one of the authors or the Epstein Becker Green attorney who regularly handles your legal matters.*

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