Precision Medicine Update

Katherine Donigan, PhD
Personalized Medicine Staff
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Overview

- Next Generation Sequencing (NGS) Final Guidances – released April 12, 2018
  - Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS)–Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases
  - Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics
- PrecisionFDA – a cloud-based portal for research and collaboration
  - Platform overview
  - FDA-issued challenges

Developing a Nimble Regulatory Approach for Genomic Tests

Vision: Implement new regulatory policies to promote research and accelerate the translation of precision medicine technologies into treatments that *benefit patients*.

Goal: improve regulatory efficiency, encourage and speed innovation

- Develop **standards** to support analytical validation (guidance)
- Support use of **curated databases** for clinical validation (guidance)
- precisionFDA (**cloud platform** for NGS bioinformatics)

Collaborative efforts and public engagement

Key Themes from Public Engagement

- Analytical standards should be a combination of design process and performance standards
- Need clarity/transparency about test performance and limitations
- Need to incentivize data sharing
- Need common nomenclature/standards for test results – *essential for providers and patients*
- Need for development of more reference materials

FDA's Concepts for Regulation of NGS-Based IVDs for Diagnosing Germline Diseases – Draft Guidances (2016)

- **Technical/analytical standards for NGS**
  - Test developers that meet these standards may not have to submit an application to FDA.
  - Standards would be developed with the scientific community, and can be updated as science and technology advance.
- **Use of curated databases to provide clinical evidence**
  - Use databases as information sources to support the link between genetic variation and health/disease.
  - Test developers may be able to use such databases in support or in lieu of traditional clinical studies.

Guidance:

Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS)–Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases

Draft Guidance - 2016

- Scope: targeted or WES NGS-based tests intended to aid in the diagnosis of individuals with suspected germline diseases or other germline conditions
- Can form the basis for future FDA-recognized standard(s) and/or special controls.

Regulatory Considerations

Comments on the Draft Guidance

- Public comments received from 38 organizations and individuals
- Commenters were generally supportive of the proposed regulatory approach
- Requests for clarification of the background, scope, and certain technical recommendations

April 2018 Final Guidance: *Changes from Draft to Final*

- Title Revised
  - To better reflect scope and content
  - To acknowledge that currently there are no applicable standards that FDA can recognize
  - To support community engaging in developing standards by SDOs
- Scope Revised
  - Clarify that the document only specifically applies to NGS-based tests intended to aid clinicians in the diagnosis of symptomatic individuals with suspected germline diseases
- Thresholds Removed
  - Guidance recommends that test developers predefine, justify, and report minimum acceptable overall and target threshold metrics such as accuracy, precision, and coverage
- Revised Recommendations for Design, Development, and Validation
  - Clarifications to accuracy metrics, performance evaluation studies, and other technical recommendations

Recommendations for Design, Development, and Validation

- Test design considerations:
  - Approach to test design
  - Recommendations are flexible, to accommodate different test designs, components, indications, etc.
- Test performance characteristics
  - Accuracy, precision, LoD, analytical specificity
- Test run quality metrics
  - Including read depth, completeness
- General recommendations for performance evaluation studies

Can form the basis for future FDA-recognized consensus standard(s) and/or special controls

Additionally, guidance includes:

- Supplemental procedures (e.g., trio testing, orthogonal confirmation)
- Variant annotation and filtering considerations
- Recommendations for presentation of test performance / labeling such as:
  - Identify regions of the genome targeted by the test
  - Types of sequence variants detected and reported by the test
  - Types of sequence variants test cannot reliably detect
  - Performance summary
  - The relationship between reported variants and the clinical presentation, as applicable
- How to address NGS test modifications

Guidance:

Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics

What do we mean by a human genetic variant database?

- For the purpose of this guidance, a human genetic database is:
  - A collection of assertions about a link between a genetic variant and a disease or condition.
  - Publicly accessible – meaning that those assertions, and any underlying data, are transparent and available to all users.

Draft Guidance - 2016

- Outlined recommendations for administrators of publicly accessible genetic variant databases to demonstrate that the database can be considered a source of “valid scientific evidence”
- Evidence from such databases could support the clinical validity of NGS-based tests
- Defined a **voluntary** database recognition pathway (similar to standards recognition)

Comments on the Draft Guidance

- Public comments from 38 organizations and individuals.
- Commenters were generally supportive
- Requests to expand the scope:
  - Somatic Genetic Databases
  - For genetic and genomic based test that use technology other than NGS
- Clarify what is meant by "publicly accessible"
- Discuss how proprietary databases can leverage this guidance document
- Requests for clarity on or technical corrections to other aspects of the draft guidance

April 2018 Final Guidance: *Changes from Draft to Final*

Title: Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics

- Evidence from such databases could support the clinical validity of genetic and genomic-based tests
- Clarified what is meant by publicly accessible
- Noted that aspects of guidance could be useful for proprietary models
- Clarified recommendations are applicable to germline and somatic variant databases
- Expanded details about the voluntary database recognition pathway

April 2018 Final Guidance
Recognition Pathway

- **Voluntary** request for database recognition
  - Cover Letter detailing scope of recognition application
  - Application
    - SOPs, policies or other documents related to the recommendations in the guidance
    - Validation studies for evaluation SOPs
    - Documentation of the qualifications of the individuals evaluating variants and policies for approving those individuals
    - Data preservation plan
    - Conflict of interest policies and disclosures of conflicts of interest
    - A commitment to make all recommended documents publicly accessible via weblinks
- Maintenance of FDA recognition
  - Periodic review to maintain recognition

April 2018 Final Guidance
Use of Recognized Databases

- Assertions in FDA-recognized databases can include a variety of variant types and descriptive language (e.g., clinically significant, pathogenic, variant of uncertain significance), but must be supported by the evidence.
- Assertions from FDA-recognized databases would generally constitute valid scientific evidence
- Can be used to support the clinical validity of genetic and genomic tests

Summary

- These two final guidances represent part of FDA's approach to reviewing innovative and rapidly evolving technologies in a least burdensome manner.
- The analytical guidance arms developers with insight on ways to validate their tests and provides a potential expedited path to market.
- The database guidance enables test developers to harness crowd-sourced data to support the clinical validity of their tests.

precisionFDA

precision.FDA.gov

precisionFDA is a cloud based portal that engages a community of over 2500 users across the world. It allows researchers to experiment, share data and tools, and collaborate to help define standards for evaluating analytical pipelines.

precisionFDA
precision.FDA.gov

FDA

precisionFDA provides…

- Community
- Resources
- Challenges
- A library of Reference Materials, Tools, etc. including community contributions such as:
  - GA4GH VCF comparison tool
  - BWA-MEM mapper
  - GATK 3.5 licensed to precisionFDA
  - VarSim simulator
  - NA12878 NIST, Garvan, and Platinum Genome sequences
- Ability to "dockerize" applications for ease of use, transportability and consistency in performance across platforms

Members include…

- NGS-based test providers
- Standards-making bodies
- Pharmaceutical & Biotechnology Companies
- Healthcare providers
- Academic medical centers
- Research consortia
- Government Agencies

A research roadmap for NGS informatics
Science Translational Medicine, 2016 Apr20, PMID 27099173

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Comparisons, Outputs, Visualization, Variants

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precisionFDA Challenges

Major focus: reliability and accuracy of NGS bioinformatics pipelines

Current Challenge

Questions?

katherine.donigan@fda.hhs.gov
PMI@fda.hhs.gov