U.S. FOOD & DRUG ADMINISTRATION

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Next Generation Sequencing (NGS) Final Guidances

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May 24, 2018

Agenda

- Background
- Final guidances
  - Design, development and analytical validation of NGS IVDs guidance
  - Use of human genetic variant databases guidance
- Summary
- Questions and answers

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In Vitro Diagnostics in the Age of Precision Medicine

Traditional testing

Next generation sequencing

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**.

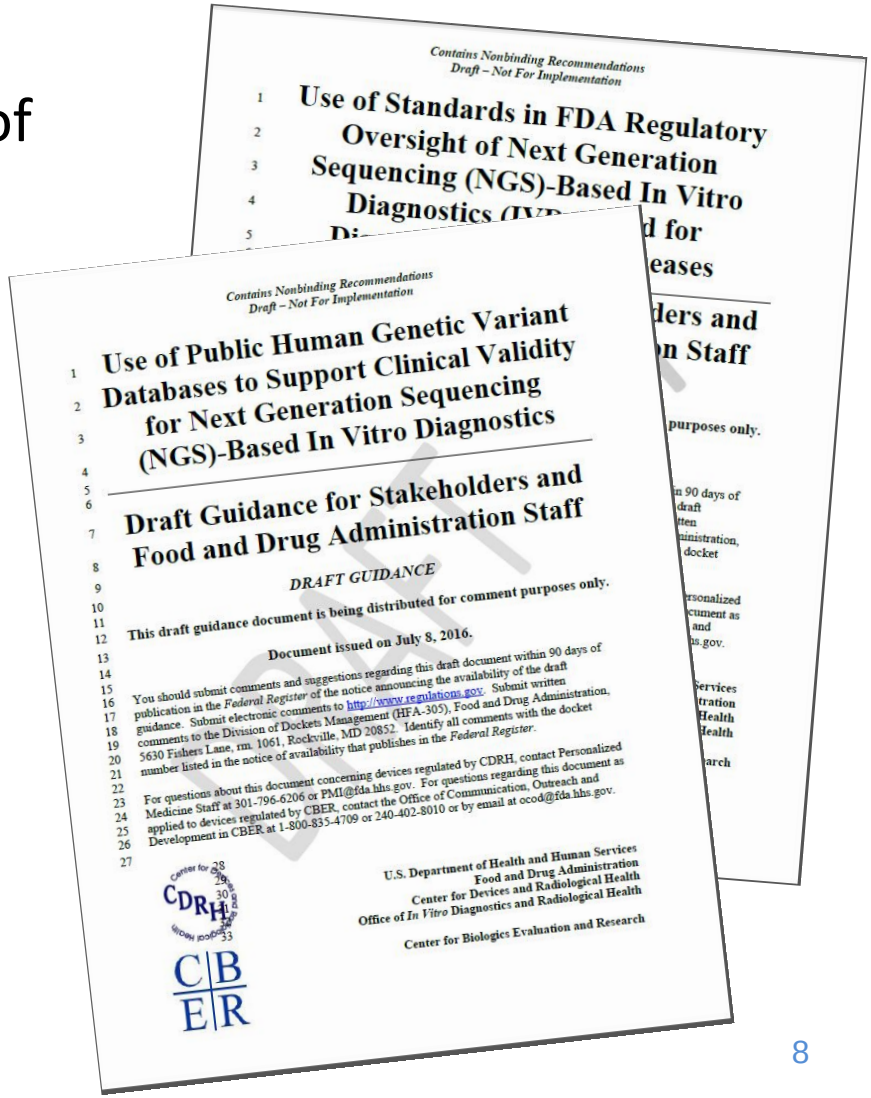
Goal: Improve regulatory efficiency; encourage and speed innovation

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

NGS draft guidances (July 2016)

- Describe a regulatory pathway for NGS-based tests for certain uses
- Anticipate and support the needs of rapidly-evolving NGS technologies
- Intended to **ensure patient safety**, encourage **innovation**, and assure the **quality and reliability** of NGS-based tests and promote adoption of NGS-based tests into clinical practice
- NGS tests developed according to these guidances are anticipated to have an **efficient path to market**



Contains Nonbinding Recommendations
Draft – Not For Implementation

Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics

Draft Guidance for Stakeholders and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on July 8, 2016.

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document concerning devices regulated by CDRH, contact Personalized Medicine Staff at 301-796-6206 or PMI@fda.hhs.gov. For questions regarding this document as applied to devices regulated by CBER, contact the Office of Communication, Outreach and Development in CBER at 1-800-833-4709 or 240-402-8010 or by email at ocod@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of *In Vitro* Diagnostics and Radiological Health

Center for Biologics Evaluation and Research

FDA's Concepts for Regulation of NGS-Based IVDs for Diagnosing Germline Diseases

- **Technical/analytical standards for NGS**
  - Test developers that meet these standards may not have to submit a premarket submission to the FDA.
  - Standards would be developed with the scientific community, and can be updated as science and technology advance.
- **Use of FDA-recognized 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.

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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

2016: Draft Guidance Use of Standards in FDA Regulatory Oversight of NGS-Based IVDs for Diagnosing Germline Diseases

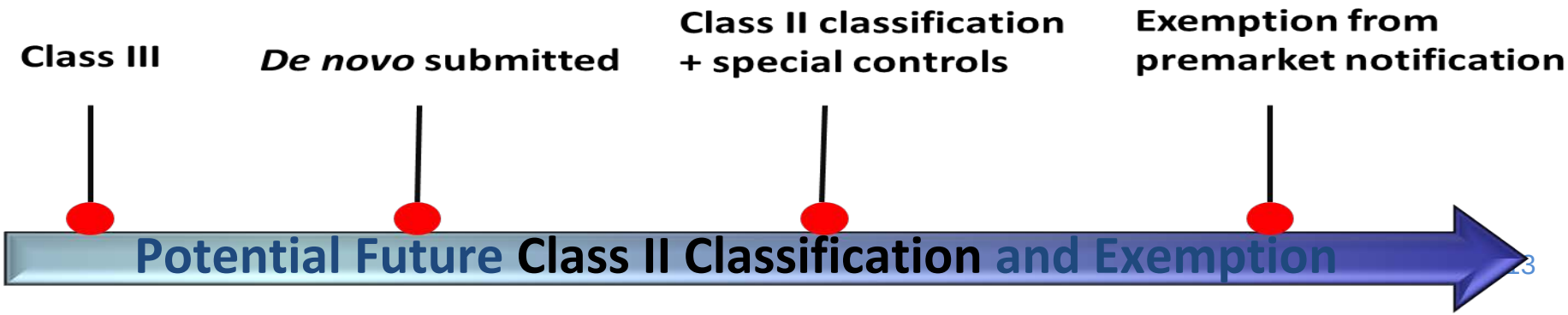
Scope:

The draft guidance applies only to targeted or Whole Exome Sequencing 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

- All novel tests, including those with the intended use described in the guidance, are Class III *by default*
- The FDA believes it may be possible to classify tests that fall within the scope of the guidance as Class II devices; the guidance outlines what FDA believes is needed to support this classification
- As we gain more experience with these devices, the FDA believes that it may be possible, in the future, to develop special controls that could provide a reasonable assurance of the safety and effectiveness of NGS-based tests intended to aid in the diagnosis of suspected germline disease, possibly under certain conditions of exemption, without the need for 510(k) premarket review



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, limit of detection, 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

Highlights

- Thresholds would be defined in upcoming consensus standards or special controls
  - Will depend on the specific tests and indications for use, and variables such as types of variants detected and reported
- Accuracy
  - Definitions of positive percent agreement (PPA), negative percent agreement (NPA), and technical positive predictive value (TPPV)
  - Calculating accuracy

    Appendix with a simplified example of calculations
- Performance evaluation studies
  - Describing types of samples and studies for different indications and variant types
  - Evaluate end-to-end performance
  - Break down accuracy evaluation results by variant, sequence context, specimen type, etc.

Accuracy Evaluation Studies

- Comparator method
  - Appropriate comparator, and/or consensus sequence of agreed-upon well-characterized samples, as appropriate
- Study samples (reflecting test specimen types)
  - Well characterized reference samples
  - Clinical samples relevant for the test
  - Appropriate surrogate samples
- Include what can test detect (what is relevant for indication)
  - Representative genomic regions, variant types, sequence contexts
  - Clinically meaningful regions
  - Appropriately sized increments
- Number of specimens based on test performance, point estimate and statistical confidence intervals

Additionally, guidance includes:

- Discussion on supplemental procedures such as trio testing or orthogonal confirmation
- Variant annotation and filtering considerations
- Recommendations for presentation of test performance / labeling such as:
  - Identify regions of the genome in which sequence **meeting pre-specified performance specifications** can be generated by the NGS-based test
  - Types of sequence **detected and reported** by the test
  - Types of sequence **variants test cannot detect** with adequate accuracy and precision
  - **Performance summary**
  - The relationship between reported variants and the clinical presentation, as applicable
- How to address NGS test modifications

Significance

- Provides **key considerations** for designing, developing, and establishing analytical validity of NGS-based tests for suspected germline diseases
- Informs the development of **consensus standards** by experts in the community
  - Consensus standards developed by accredited consensus standards bodies (SDO) and recognized by FDA could help streamline review process
- Recommendations in this guidance and/or standards that address these recommendations may form the basis of **special controls**, allowing these tests to be candidates for down-classification
  - Could be considered for exemption from premarket notification if they meet certain criteria

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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 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.

Benefits of Using Data from Publicly Accessible Genetic Databases

- Evidence generated by multiple parties
- Aggregated data provide a stronger evidence base (i.e., current state of scientific knowledge)
- As clinical evidence improves, new assertions could be supported

Use of Genetic Variant Databases to Support Regulatory Decisions

- CFTR2 database accepted as valid scientific evidence to demonstrate clinical validity for the Illumina MiSeq CF 139 Variant Assay
  - Data regarding variants sufficient to provide assurance of the clinical validity of the variants reported by the test
  - Acceptance specific to this single intended use

- Myriad proprietary database and interpretation processes accepted as valid scientific evidence for BRACAnalysis CDx
  - Data and evidence evaluation process sufficient to provide assurance of clinical validity of the variants reported by the test
  - Myriad allowed to report novel variants to physicians and patients

July 2016 Draft Guidance

Title: Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics

- 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
Recommendations for Administrators

Outlines recommendations for administrators of publicly accessible genetic variant databases to demonstrate that the database can be considered a source of "valid scientific evidence"

- Transparency of database operations: documentation, versioning, SOPs, standard formats
- Data quality: information about data and its sources (nomenclature and metadata)
- SOPs for the evaluation of variants with validation studies supporting their use
- Relies upon expert curation: training and disclosure of conflicts of interest
- Database hygiene: privacy, security, data preservation

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

Recognition Process

Prior to Submission: Contact FDA

1.Database administrators interested in seeking recognition should contact FDA staff at OIRPMGroup@fda.hhs.gov

Get Advice from FDA Prior to Submission

1.FDA staff will advise database administrators on how to address their recognition request.

Submit your Recognition Application

1.Applications should be submitted as an "informational meeting" Q-submission and demonstrate that all of the recommendations in the final guidance have been met.

FDA Review of Applications

FDA staff will review applications and issue a recognition decision. If additional information is necessary to conduct the review, FDA staff will work interactively with database administrators to obtain it.

Possible FDA Recognition

For more information: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/PrecisionMedicine-MedicalDevices/ucm603675.htm

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Key Take Aways

- 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.

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Questions?

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Under Heading: In Vitro Diagnostics

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immediately following the conclusion of the live webinar.

Accuracy calculations

PPA – TP/TP+FN (number of known variants detected by the test (TP) divided by the number of known variants tested (TP + FN) for each variant type that is being reported)

NPA - TN/TN+FP (number of TN results divided by the number of wild type results for variants tested (TN + FP) for each variant type that is being reported)

TPPV – TP/TP+FP (number of TPs from the test divided by the total number of positive results (TP + FP) obtained by the test)