FDA Overview on Next Generation Sequencing (NGS) Testing

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Overview

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- Regulatory Issues
- FDA Goals
- Current Guidance Documents

Regulatory Issues

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- NGS tests often lack a specific intended use
  - Can't predefine the results that will be obtained
  - Often don't know the disease that will be diagnosed until the test is performed
  - Incidental findings
- Traditional requirements for review
  - Review each claim
  - Review modifications that affect the safety and effectiveness of a test
- *Differences in data volume and interpretation may warrant a new regulatory approach* that will ensure that patients and providers are able to make treatment decisions based on accurate test results
- Need to ensure that the information that patients receive from NGS tests is accurate and relevant to their condition (analytically and clinically valid)

FDA's Goals

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Optimize regulatory oversight of NGS tests to:

- Help to ensure the accuracy of genetic tests
- Develop approach suited to unique nature of NGS tests
- Adapt regulatory processes to encourage innovation while helping to ensure safety and effectiveness

Released two draft guidances for public comment in July 2016, finalized in April 2018

Purpose of the Guidances

- Anticipate and support the needs of rapidly-evolving NGS technologies
- Support reliable, accurate and understandable tests results
- Promote an efficient path to market for all test developers
  - Encourage the development and implementation of *standards* to assure test quality
  - Describe a regulatory pathway for NGS-based tests for certain uses
  - Recognize genetic *databases* for evidence on the clinical relevance of genetic variations
  - Based on open processes and accessibility

Guidance #1

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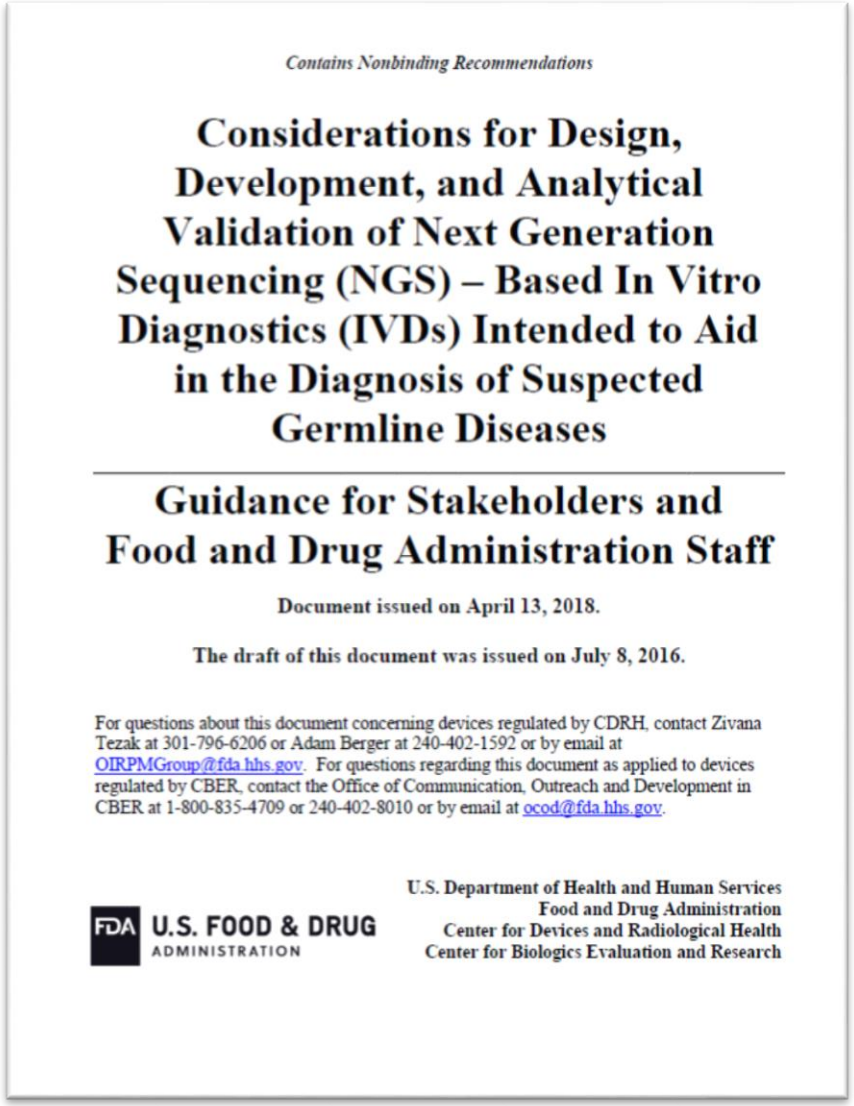
Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS) – Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases



Contains Nonbinding Recommendations

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

Guidance for Stakeholders and Food and Drug Administration Staff

Document issued on April 13, 2018.

The draft of this document was issued on July 8, 2016.

For questions about this document concerning devices regulated by CDRH, contact Zivana Tezak at 301-796-6206 or Adam Berger at 240-402-1592 or by email at OIRPMGroup@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 1-800-835-4709 or 240-402-8010 or by email at ocod@fda.hhs.gov.

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Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM509838.pdf

Analytical Standards Guidance

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Recommendations

- Design
  - Indications for use
  - User needs
  - Components and methods
  - Understand and document technical limitations of NGS-based tests
- Performance characteristics and test quality metrics
  - Accuracy, precision
  - Read depth, completeness, performance thresholds
- Test Reports

Benefits

- Combines design and performance standard approaches
- Accommodates different test designs
- Can form the basis for future FDA-recognized standard(s) and/or special controls

Guidance #2

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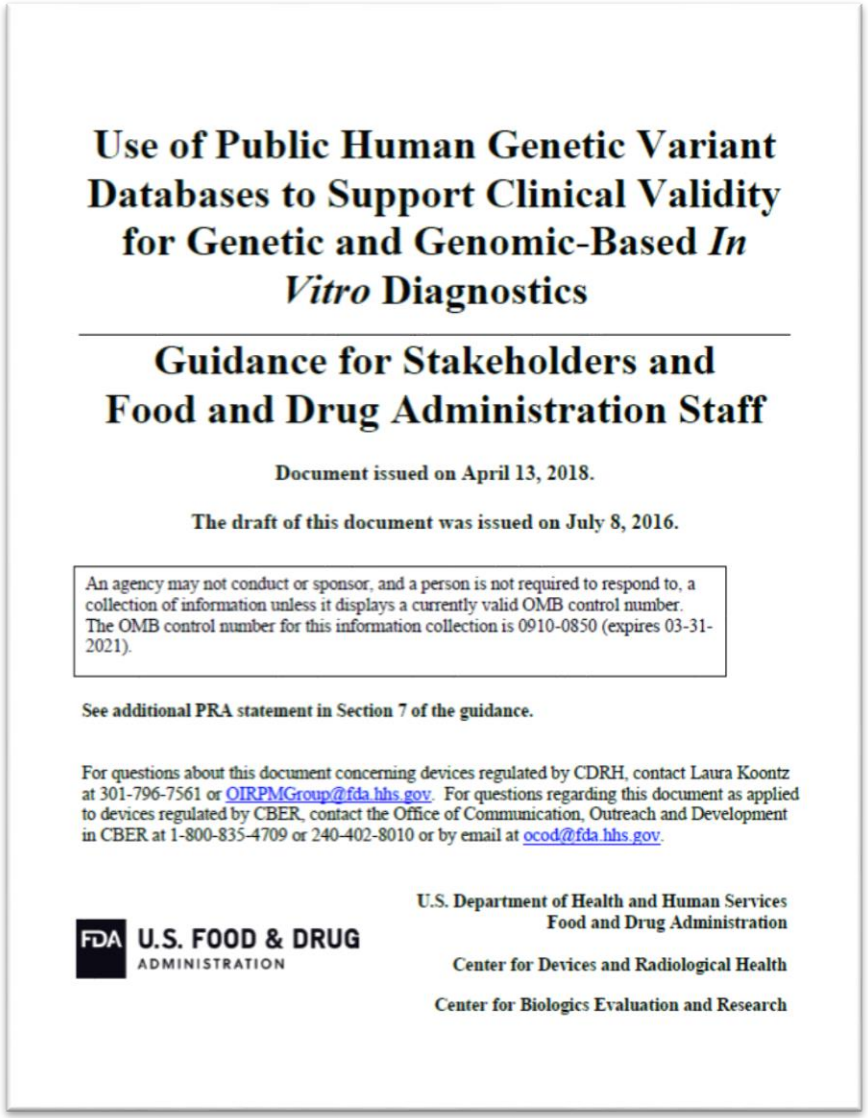
Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics



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

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An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0850 (expires 03-31-2021).

See additional PRA statement in Section 7 of the guidance.

For questions about this document concerning devices regulated by CDRH, contact Laura Koontz at 301-796-7561 or OIRPMGroup@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 1-800-835-4709 or 240-402-8010 or by email at ocod@fda.hhs.gov.

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https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm509837.pdf

Genetic Databases Guidance

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- Recommendations for administrators of databases to demonstrate that the database can be considered a source of “valid scientific evidence”
- **Voluntary** database recognition pathway (similar to standards recognition)
- Evidence from databases could support the clinical validity of NGS-based tests

Benefits of Using Data from Genetic Databases

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

Guidances: Summary

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- The approaches outlined in the FDA guidance documents are intended to:
  - Incentivize innovation
  - Assure the quality and reliability of NGS-based tests
  - Promote their adoption into clinical practice
  - Improve patient care
  - Advance precision medicine

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Thank You