Welcome to Today's FDA/CDRH Webinar

Thank you for your patience while we register all of today's participants.

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Conference Number: PW9346229

Next Generation Sequencing (NGS) Draft Guidances: Technical and Regulatory Aspects

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Agenda

- Background
- Technical and regulatory aspects of the draft guidances
  - Analytical standards draft guidance
  - Genetic databases draft guidance
- Summary and implications
- Next steps
- Questions and answers

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White House Precision Medicine Initiative

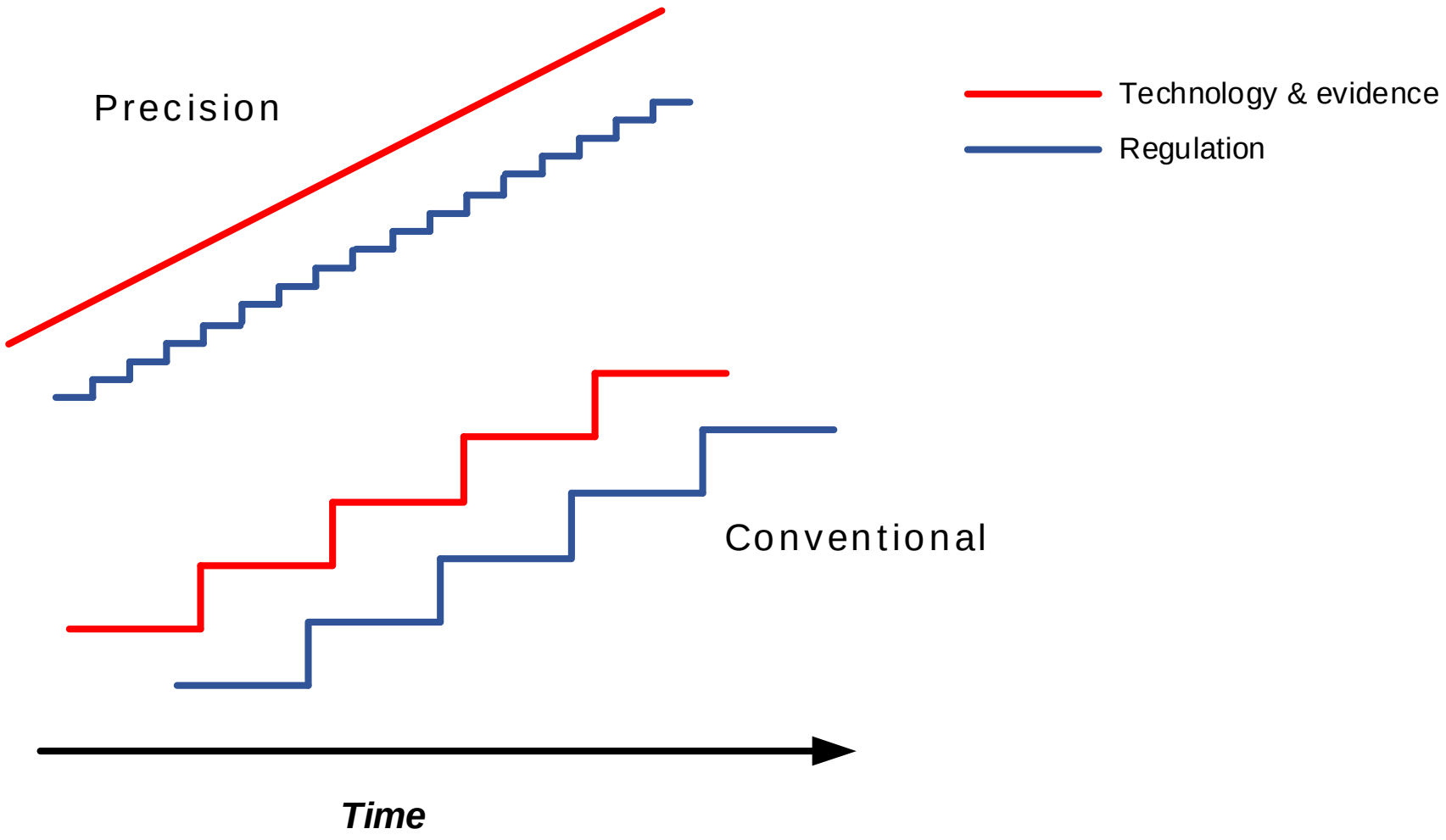
To enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized care.

FDA's Role in PMI

Optimize regulatory oversight of Next Generation Sequencing tests

- 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

Precision Medicine: Need for Optimized Regulatory Approach



Elements of FDA Premarket Review

- Analytical validity
  - Does the test correctly detect the analyte(s)?
  - How precise is the test?
  - What are limits of detection/measurement?
- Clinical validity
  - Does the test correctly identify the disease/condition?
  - What are the clinical sensitivity, specificity and predictive values?
  - Evidence must be scientifically valid
- Labeling
  - Are the directions clear? Is what you say about the test truthful and not misleading?
- Based on intended use of the test

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Purpose of the Draft Guidances

- Anticipate and support the needs of rapidly-evolving NGS technologies
- Support reliable, accurate and understandable test 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 upon open processes and accessibility

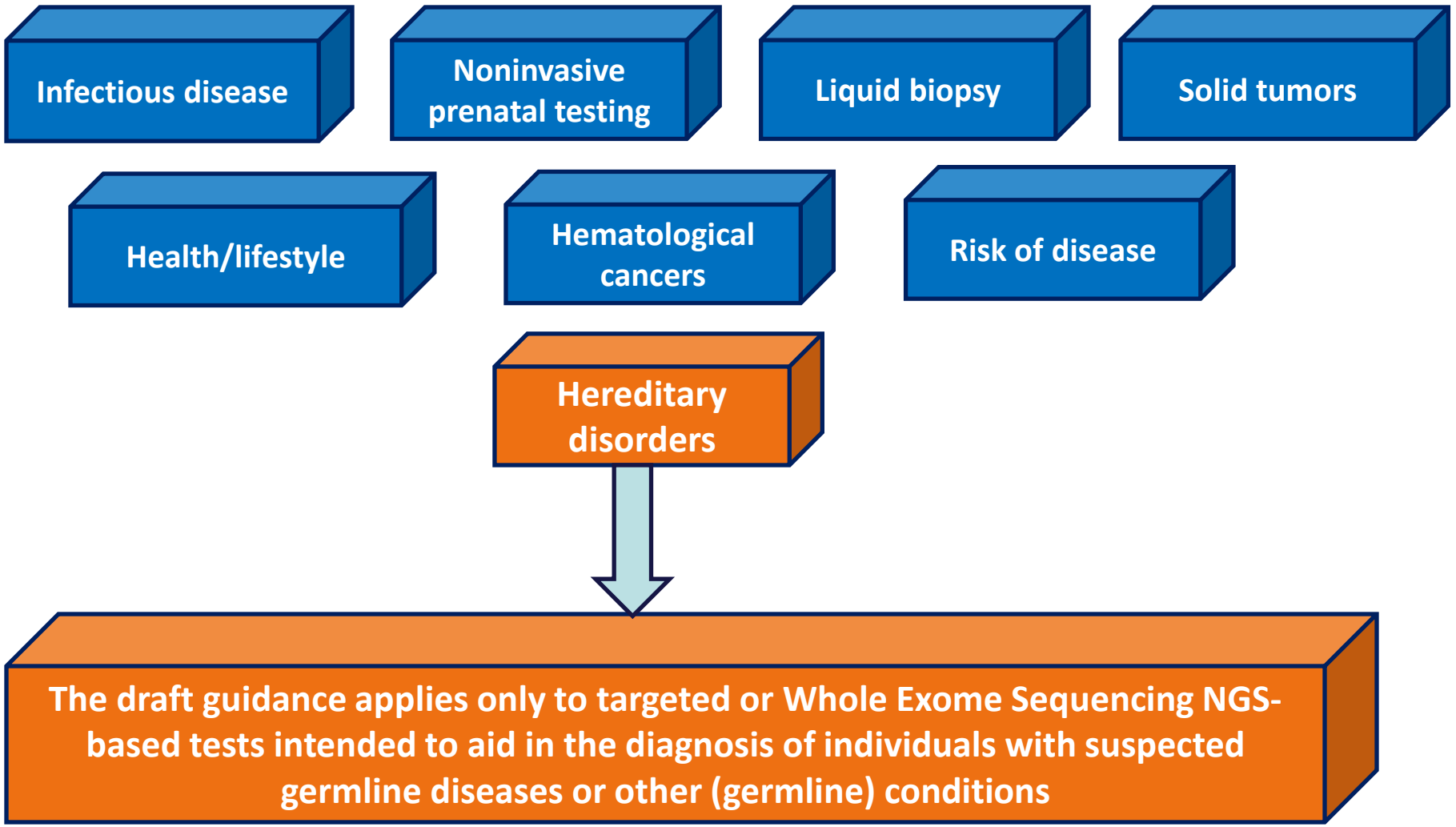
IMPORTANT

These draft guidances are proposals released for public comment and have *not* been finalized

Draft Guidance:

Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based *In Vitro* Diagnostics (IVDs) Used for Diagnosing Germline Diseases

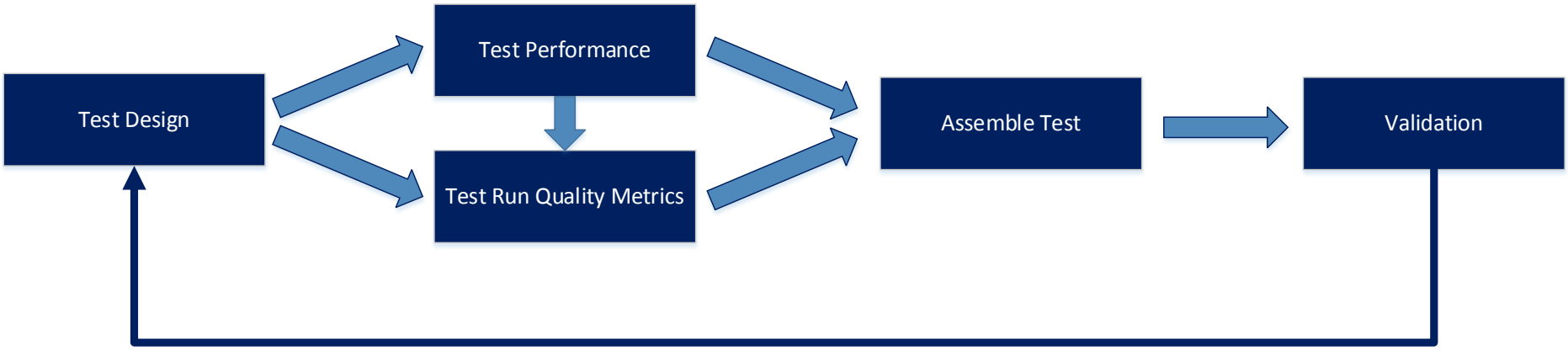
Scope of the Analytical Standards Draft Guidance



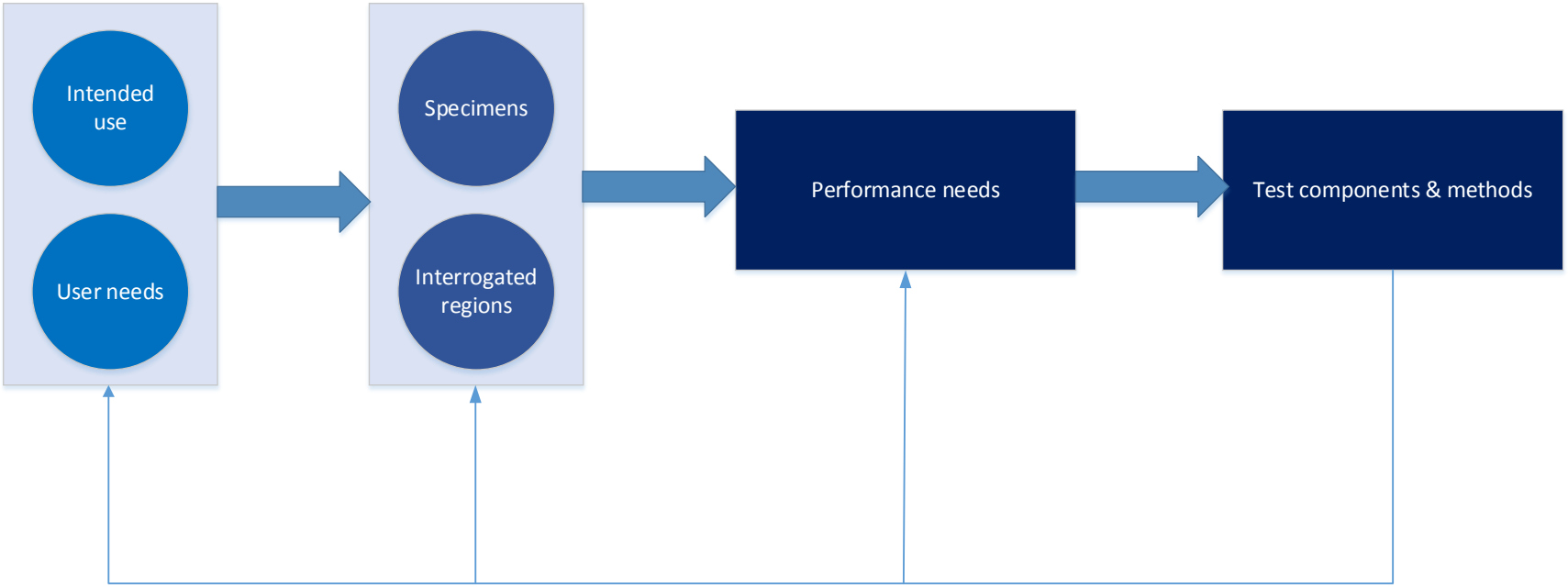
Technical Recommendations

- Describes approach to test design
- Accommodates different test designs, components, indications, etc.
- Can form the basis for future FDA-recognized standard(s) and/or special controls

Design Standards



Test Design


Intended use
User needs
Specimens
Interrogated regions
Performance needs
Test components & methods

Test Performance Characteristics

- Identify performance metrics and set minimally acceptable values
- The guidance specifies four overall performance *metrics* that should always be assessed
  - Accuracy
  - Precision (reproducibility and repeatability)
  - Limit of detection
  - Analytical specificity
    - Includes cross-reactivity (e.g., pseudogenes) and cross-contamination

Minimum Performance Thresholds

- In some cases, the guidance recommends minimum performance thresholds
  - Accuracy: 99.9%
  - Precision: 95.0% (lower bound of 95% CI)

Test Run Quality Metrics

- These metrics assess whether a test run or variant call should be accepted
- FDA recognizes that different test developers use different metrics, or use the same metrics for different purposes
- The guidance specifies coverage as the only metric that developers should always use
- The test developer should select other metrics for various steps of the end-to-end test, such as:
  - Specimen quality
  - DNA quality and processing
  - Sequence generation and base-calling

General Recommendations for Performance Evaluation Studies

- The guidance defines elements that should always be included in validation experiments
- Points to stress
  - Evaluate end-to-end performance
  - Include representative genomic regions, variant types, sequence contexts relevant to indication
  - Identify the types of sequence variants test cannot detect with adequate accuracy and precision
  - Use appropriate specimen types, and conduct commutability studies if inferring performance based on validation using plasmids or other synthetic constructs
- Test developers should determine the number of specimens required for validation experiments

Accuracy Studies

- Comparator method, and/or,
- Comparison of test-generated sequence to consensus sequence of agreed-upon well-characterized samples, if appropriate

Documenting Results of Validation Studies

- Report the confidence interval, not just the point estimate
- Break down results by variant, sequence context, specimen type, etc.
- Other recommendations listed in guidance

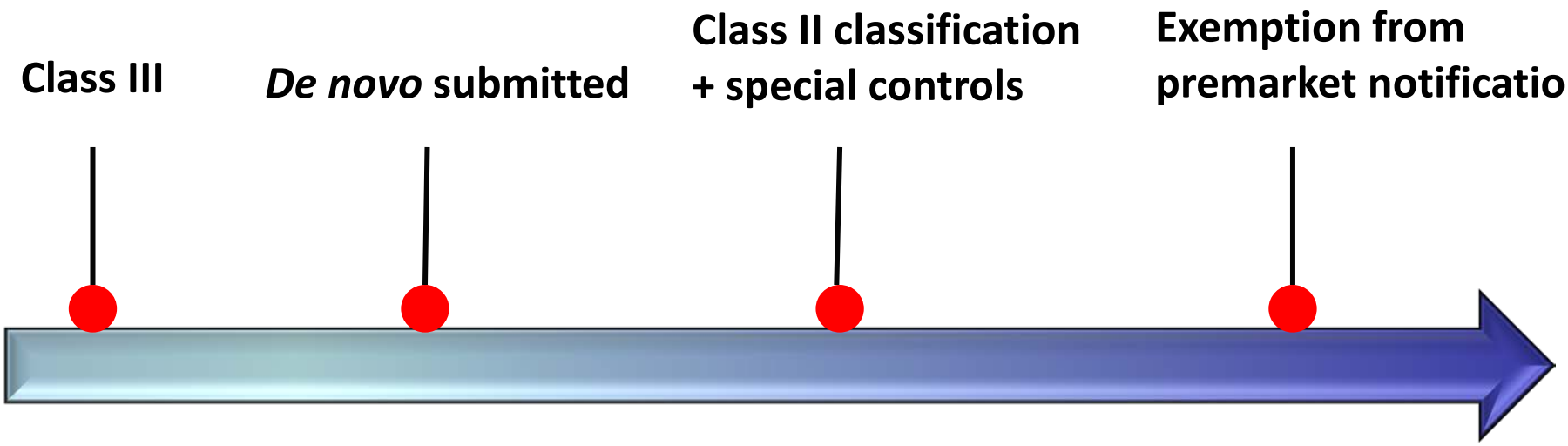
Other Recommendations

- Supplemental procedures (e.g., Sanger confirmation)
  - Not part of the core process for generating variant calls from input specimens or DNA
  - May affect how validation is conducted
- Variant annotation and filtering
- Presentation of test performance and test reports
- Modifications

Regulatory Considerations

- NGS-based tests for the use described in the draft guidance are currently Class III *by default*
- FDA believes it may be possible to classify these tests as Class II devices; the draft guidance outlines what FDA believes is needed to support this classification
- Discussion of the possibility that in the future these tests could be exempted from premarket review

Potential Future Class II Classification and Exemption



Draft Guidance:

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

Benefits of Using 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

Genetic Databases Draft Guidance

- Publicly accessible databases only
- 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

Proposed FDA Recognition of a Database

- Voluntary request for database recognition
- FDA evaluation of policies and procedures
  - Transparency
  - Statement of the types of variants the genetic variant database assertions address (e.g., germline, somatic)
  - SOPs, policies, or other documents
  - Documentation of personnel qualifications
  - Data preservation plan
  - Conflict of interest policies and disclosures of conflicts of interest
  - Validation studies for interpretation SOPs
- Maintenance of FDA recognition
  - Periodic review to maintain recognition

Use of FDA-Recognized Genetic Databases

- Data and assertions from databases that follow the recommendations would generally constitute valid scientific evidence to support clinical validity claims
  - Assertions include a variety of variant types and descriptive language (including VUS)
  - Assertions should be appropriate to the level of certainty and the nature of the genotype-phenotype relationship and be adequately supported
  - Assertions that a particular genotype-phenotype association is clinically valid should generally involve multiple lines of evidence and should identify a primary source of scientific evidence
  - Assertions should not be false or misleading

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Summary

- These guidances are intended to encourage innovation, 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 would have an efficient path to market and possibly even an exemption from premarket review in the future

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Next Steps

- Public comment
  - 90 day open comment period
  - Upcoming public workshop
- Expansion to other indications/intended uses
- Implementation

Please Submit Comments

- Analytical standards draft guidance
  - https://www.regulations.gov/docket?D=FDA-2016-D-1270
- Federal Register notice
  - https://www.federalregister.gov/articles/2016/07/08/2016-16201/guidance-for-industry-use-of-standards-in-the-food-and-drug-administrations-regulatory-oversight-of
- Databases draft guidance
  - https://www.regulations.gov/docket?D=FDA-2016-D-1233
- Federal Register notice
  - https://www.federalregister.gov/articles/2016/07/08/2016-16200/use-of-public-human-genetic-variant-databases-to-support-clinical-validity-for-next-generation

We Need Your Help

- Standards
- Reference materials
- Data sharing
- Sustainable, high quality databases
- Curation

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Questions?

Email us at: PMI@fda.hhs.gov
FDA Precision Medicine Web site:
http://www.fda.gov/precisionmedicine/

Slide Presentation, Transcript and
Webinar Recording will be available at:

http://www.fda.gov/training/cdrhlearn

Under the heading “In Vitro Diagnostics (IVD)"