U.S. FOOD & DRUG ADMINISTRATION

Next Generation Sequencing Guidances

E. David Litwack, Ph.D.

October 14, 2016

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.

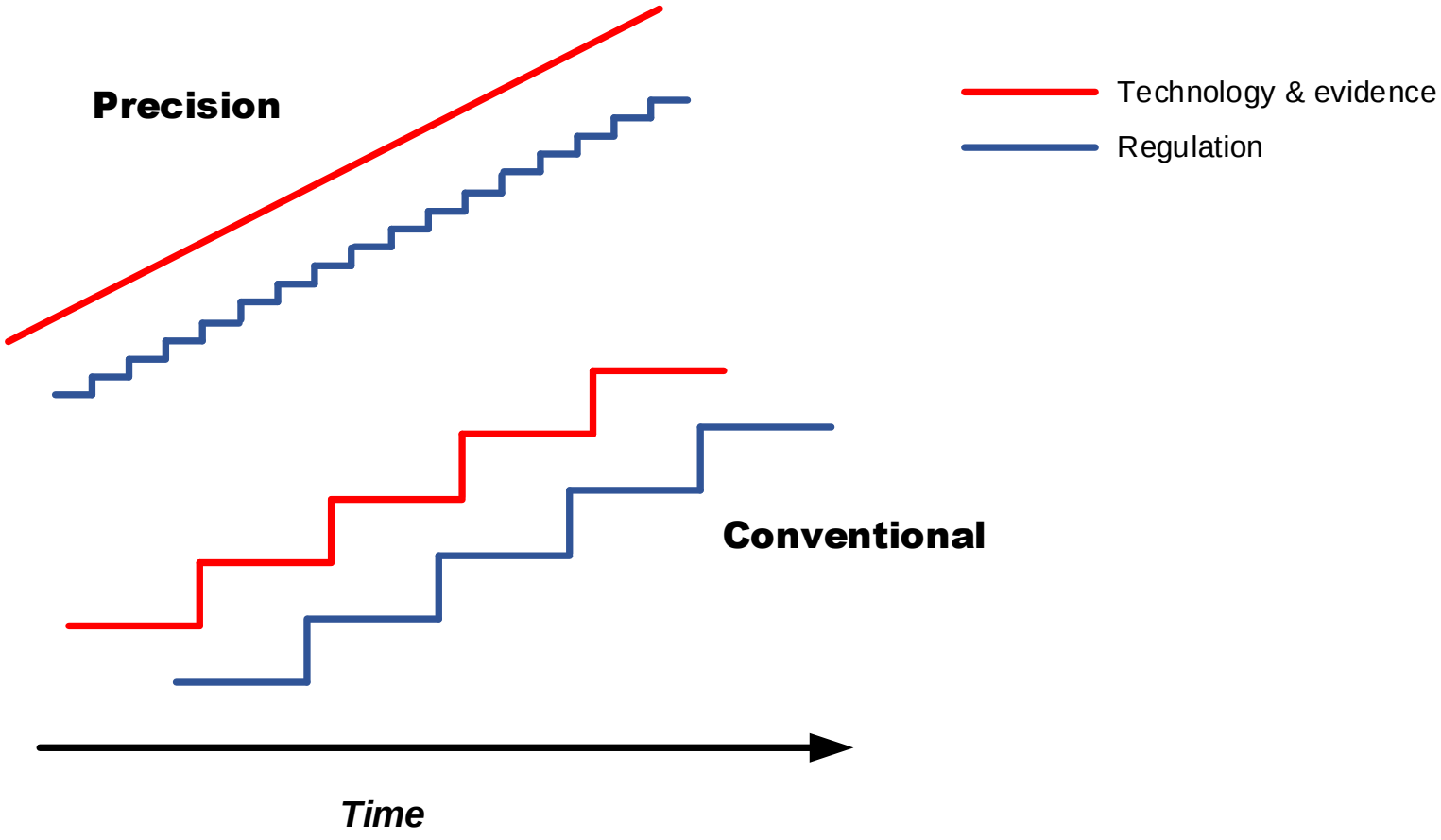
In Vitro Diagnostics in the Age of Precision Medicine

Conventional Diagnostics	Precision Diagnostics
Low/medium resolution technology	High resolution technology (“omics”)
Detect a finite number of analytes (usually one)	Undefined (millions?)
One test – one disease	One test – many diseases
Clinical evidence from clinical studies – research separate from practice	Clinical evidence from learning health systems – merging of research and practice

The Special Challenges of NGS

- Rapidly evolving technology
  - ✓ Frequent modifications to NGS tests.
  - ✓ Different labs may obtain different results.
- Unprecedented ability to detect rare variants
  - ✓ Difficult to gather clinical evidence to understand data.
  - ✓ Gradual accumulation of clinical evidence.
  - ✓ Discovery outpacing understanding.
- Potential results are unlimited – broad intended uses
  - ✓ Can't predefine the results that will be obtained. Even a single gene test could detect previously unobserved variants.
  - ✓ Often don't know the disease that will be diagnosed until the test is performed.
  - ✓ Incidental findings.

Precision Medicine & the Need for New Regulatory Approaches



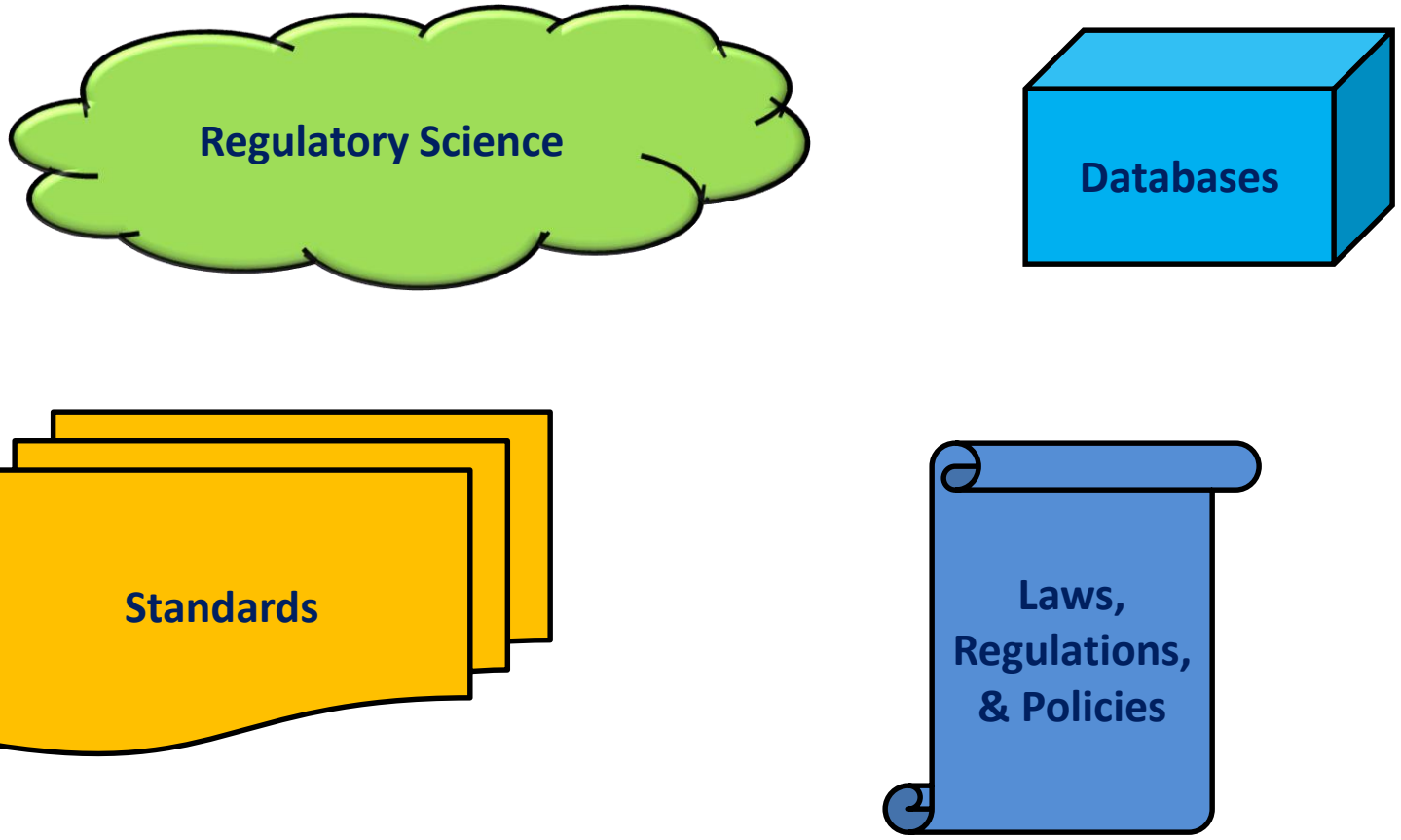
Goals of the Approach

- 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
  - Recognize genetic databases for evidence on the clinical relevance of genetic variations
  - Describe a regulatory pathway for NGS-based tests for certain uses
  - Based upon open processes and accessibility

FDA's PMI plan

- Implement a regulatory framework optimized for next generation sequencing
- What does this mean? How is FDA developing this framework?
- How can FDA use its existing regulatory authorities, regulations, and policies to create a new approach?

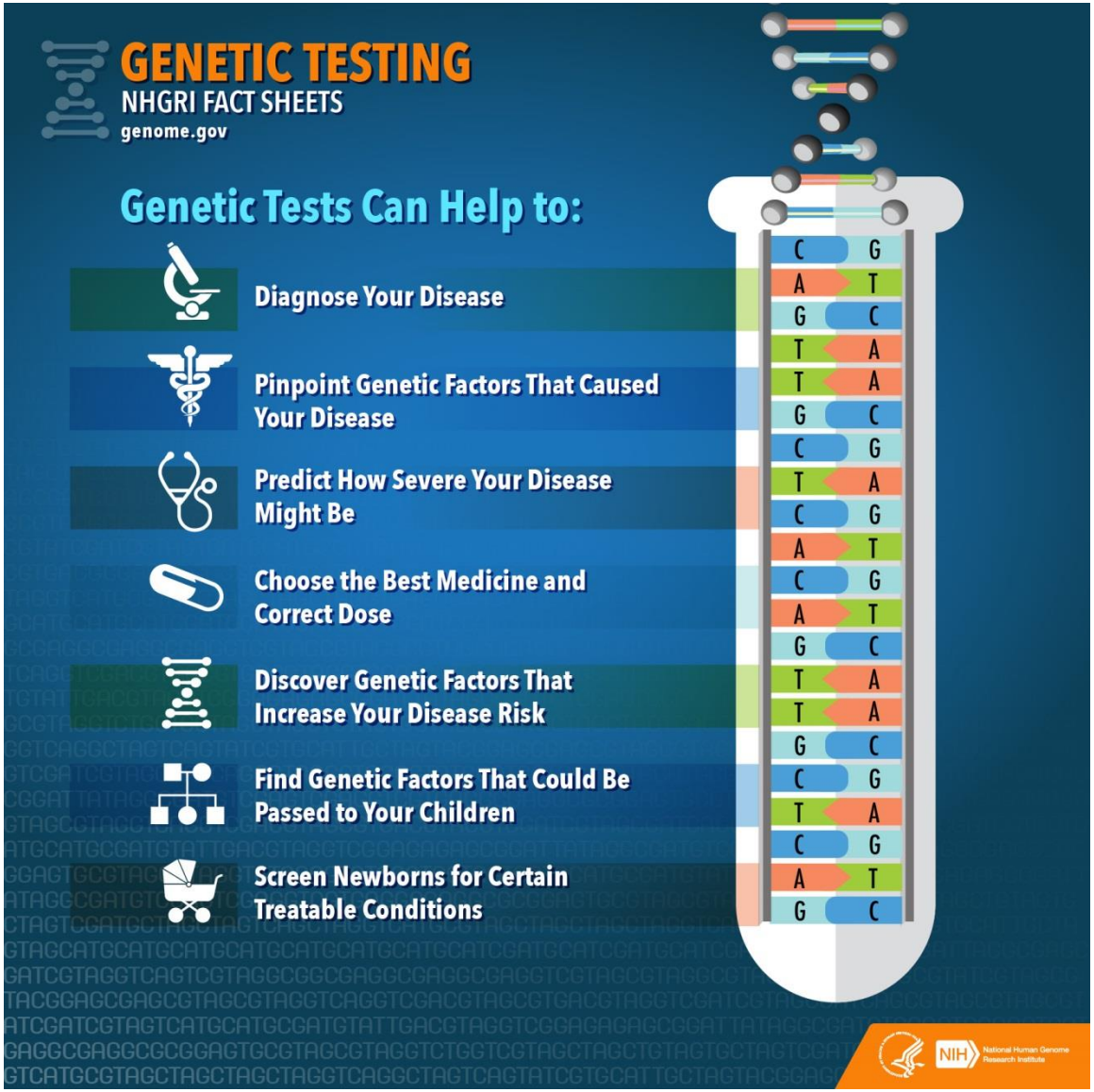
Components of FDA's Approach



Concept Development

- Optimizing FDA's Regulatory Oversight of Next Generation Sequencing Diagnostic Tests Public Workshop, February 20, 2015
  - http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm427296.htm
- Standards Based Approach to Analytical Performance Evaluation of Next Generation Sequencing In Vitro Diagnostic Tests, November 12, 2015
  - http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm459449.htm
- Use of Databases for Establishing the Clinical Relevance of Human Genetic Variants, November 13, 2015
  - http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm459450.htm
- Patient and Medical Professional Perspectives on the Return of Genetic Test Results, March 2, 2016
  - http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm478841.htm

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



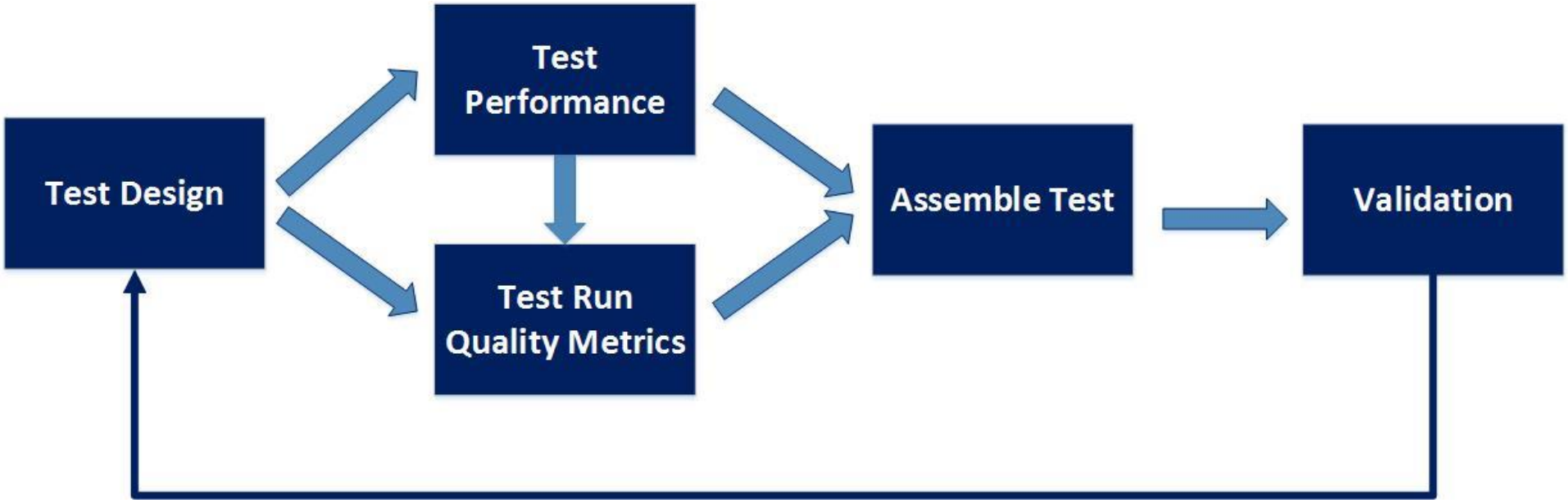
https://www.genome.gov/19516567/faq-about-genetic-testing/

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

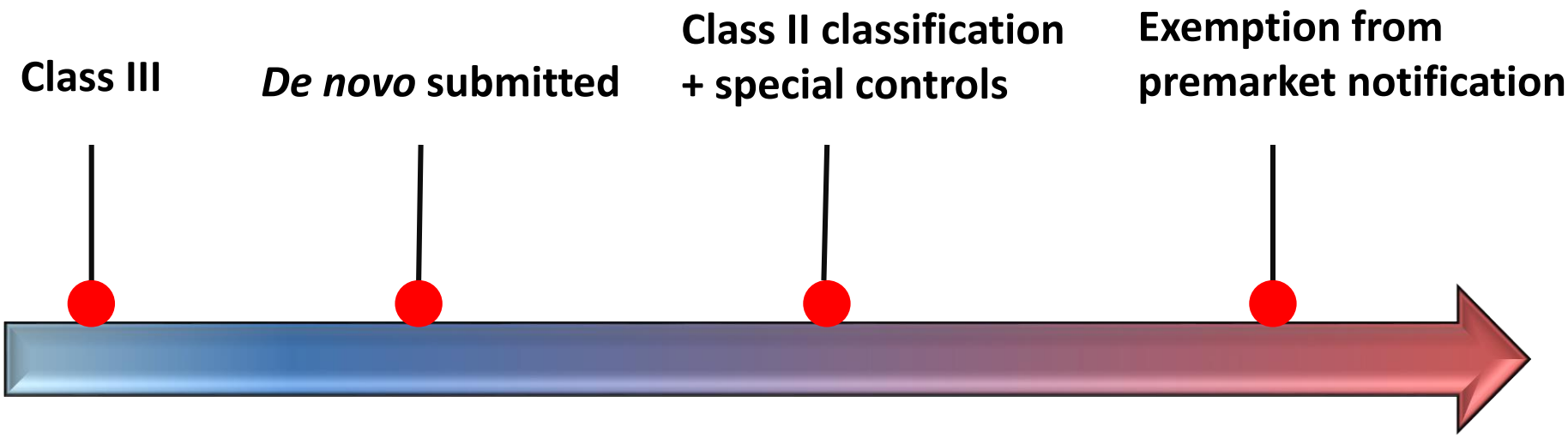
Technical Recommendations

- 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



Regulatory Considerations



The technical recommendations in the draft guidance can serve as:

- General recommendations
- Special controls
- Standards

How does the draft guidance accommodate NGS tests?

Conventional	PMI Framework
Test developers submit data for each new test.	Test developers conform to standards.
Special controls cannot be updated easily.	Standards are reviewed regularly by FDA, and can be updated as technology and knowledge advance.
Modifications can require FDA review.	Modifications can be included in conformance to standards.

USE OF PUBLIC HUMAN GENETIC VARIANT DATABASES TO SUPPORT CLINICAL VALIDITY FOR NGS-BASED IN VITRO DIAGNOSTICS

Harnessing the Power of Publicly Accessible Genetic Variant Databases

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

FDA review of IVDs relies upon valid scientific evidence

21 CFR 860.7(c)(2). - Valid scientific evidence is defined as evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, **well-documented case histories conducted by qualified experts**, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is a reasonable assurance of safety and effectiveness.

Scope

Only applicable to publicly accessible databases of human genetic variants that use expert human interpretation.

Does not apply to:

- databases used for microbial genome identification and detection of antimicrobial resistance and virulence markers
- software used to classify and interpret genetic variants
- proprietary databases

Databases as Sources of VSE

- The evidence residing in many genetic variant databases has been collected from multiple sources that can meet the valid scientific evidence definition
- Parallels between the standards set forth by well-recognized professional guidelines for variant interpretation and FDA review of clinical validity
- If databases adhere to the recommendations in the draft guidance and obtain FDA recognition, the data and assertions within would generally constitute valid scientific evidence that can be used to support clinical validity.

Recommendations

- Transparency of database operations: documentation, versioning, SOPs, standard formats
- Data quality: information about data and its sources (nomenclature and metadata)
- SOPs for curation, aggregation, and interpretation; use of validated decision matrices to make assertions
- Relies upon expert personnel: training and disclosure of COI
- Database hygiene: privacy, security, data preservation

Database Recognition

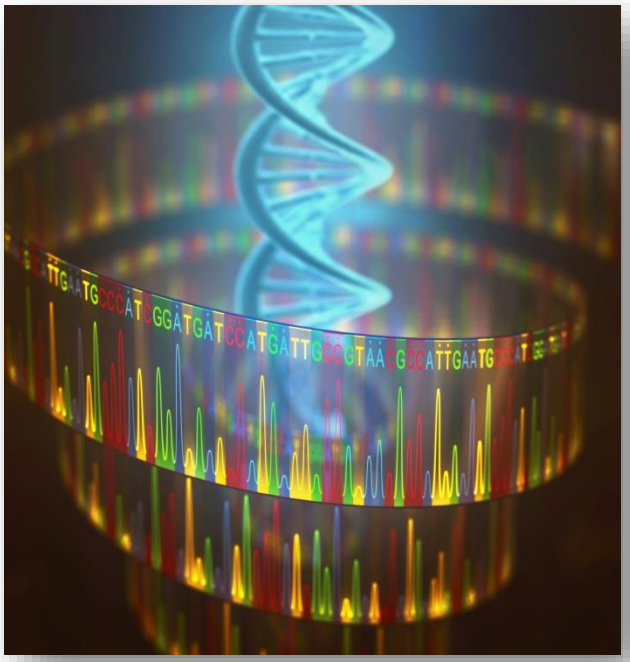
- Voluntary Request for Recognition by Database
- FDA Evaluation of Genetic Variant Database Policies and Procedures
  - Statement of the types of variants the genetic variant database assertions address (e.g., germline, somatic)
  - SOPs, policies, or other documents related to recommendations
  - Documentation 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 of Policies and Procedures

Clinical Interpretation

- Data from FDA-recognized genetic variant databases are likely to constitute valid scientific evidence that would strongly support the clinical validity of the genotype-phenotype relationships.
  - Assertions about a variant can include descriptive language such as responder, non-responder, pathogenic, benign, likely pathogenic, likely benign, variant of unknown significance, etc.
  - Language describing a variant assertion should be supported by adequate evidence detailed within the genetic variant database.
  - Assertions should be an accurate reflection of the current state of scientific knowledge and generally involve multiple lines of evidence.
  - Assertions must not be false or misleading.

Summary

- Streamlined evidence generation that leverages what the genomics community is already doing.
- Reduces barriers for evidence generation for test developers – incentivizing innovation and speeding tests to market.
- Helps enable patients and providers to receive results about a variety of genetic variants.



Next Step

- Expand approach to other intended uses of NGS-based tests

ernest.litwack@fda.hhs.gov
PMI@fda.hhs.gov