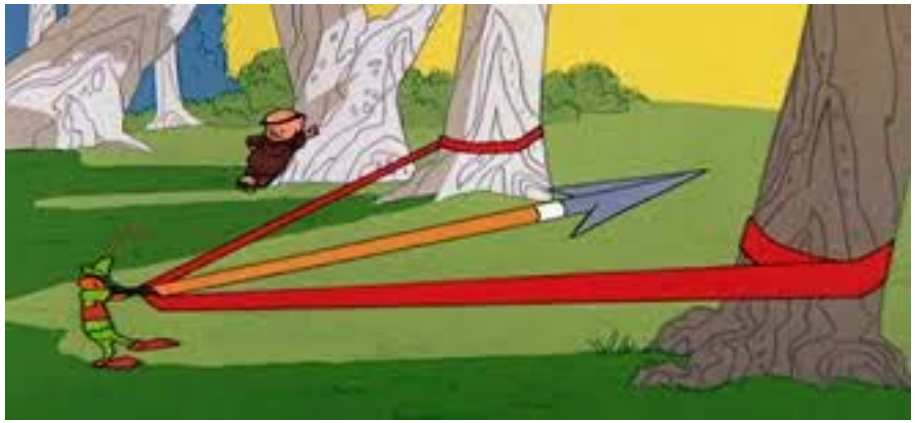
Personalized Medicine Update



www.fda.gov

Agenda

- DTC and Pharmacogenetics
- Guidance and Policy Development
  - Codevelopement of IVDs with Therapeutics
  - Investigational Device Exemptions
  - Database Guidance and the Database Recognition Program
  - Analytical Standards for Next Generation Sequencing
- Reference Materials Projects

23andMe PGx test authorization (DEN180028)

- Allows 23andMe to report 33 variants in 8 genes known to be involved in medication metabolism.
- Can report the impact that variant makes on metabolism rate (e.g., slow metabolizer, rapid metabolizer)
- Can report which therapeutics may be metabolized by each gene
- Can NOT make any claims about how a patient may respond to a medication based on the variants they have.
- Labeling tells consumers they should not make any changes to their medications on their own and should speak with a health care provider.

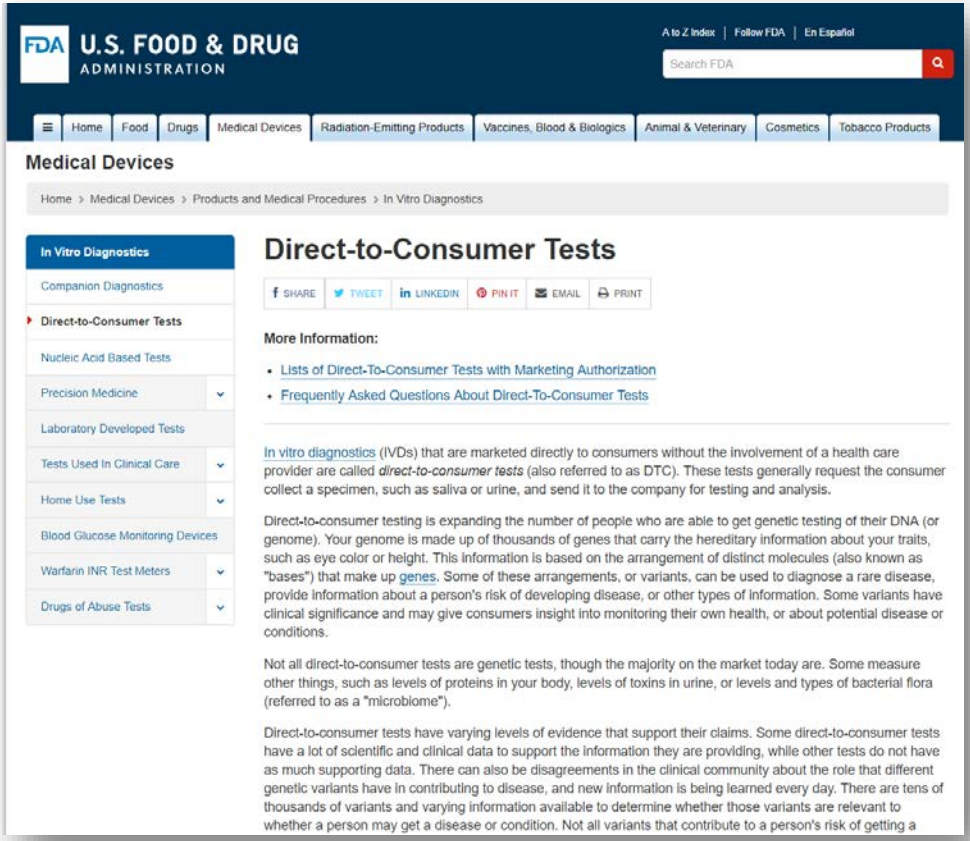
PGx Safety Communication

- Genesis:
  - FDA learned that patients and health care providers are making inappropriate treatment decisions based on PGx test
  - Many tests, software programs are making unsupported claims in variety of disease conditions (e.g., depression, heart conditions)
- Put out alert to tell consumers, health care providers, and laboratories that some claims about PGx testing that is not supported by clinical or scientific evidence
- What is supported? PGx info in therapeutic labels, FDA authorized IVD labeling.

https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm624725.htm

DTC information for consumers

- What are DTC tests and how should consumers approach their use
- FDA and DTC tests:
  - What we review
  - What we don't
  - Regulatory pathways
  - List of FDA approved tests
- FAQs



https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm624726.htm

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Codevelopment Draft Guidance

Published July 2016

- "Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product"
- Intended to be a "How To" for Codevelopment
  - described points to consider in both therapeutic and diagnostic development programs
  - described FDA preferences for certain elements
  - does not prescribe any particular development pathway
- Addressing comments, working on finalizing

Codevelopment Draft Guidance

Draft to Final

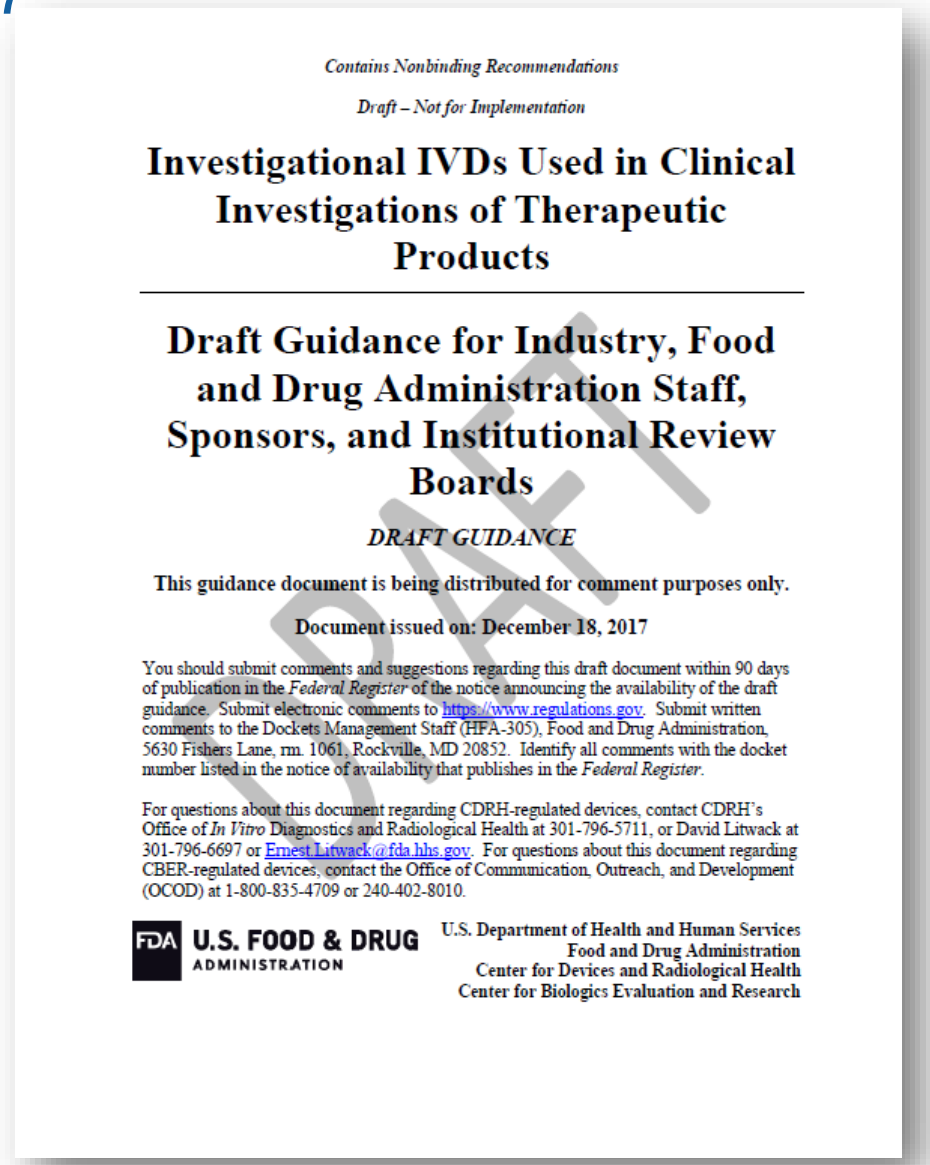
- 290 Comments received from 13 organizations
- Overarching themes:
  - Provide information regarding complementary diagnostics
  - Additional details requested on various validation strategies, trial designs, labeling, follow on CDx, etc.
  - Request for guidance on investigational IVDs
  - Request for better coordination between Centers
  - Requests for clarification on terminology, etc

Investigational IVDs Draft Guidance

Published December 2017

- Clarifies that IVDs used in clinical investigations are subject to the IDE regulation.
- Assists sponsors and IRBs in determining the risks of the use of an investigational IVD.
- Defines the responsibilities of sponsors and IRBs in complying with the IDE regulations
- Provides FDA's recommendations and requirements for submitting an IDE application, when required.

Comment period closed on March 19, 2018 and PM is working on finalizing



Contains Nonbinding Recommendations

Draft – Not for Implementation

Investigational IVDs Used in Clinical Investigations of Therapeutic Products

Draft Guidance for Industry, Food and Drug Administration Staff, Sponsors, and Institutional Review Boards

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Document issued on: December 18, 2017

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 https://www.regulations.gov. Submit written comments to the Dockets Management Staff (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 regarding CDRH-regulated devices, contact CDRH's Office of *In Vitro* Diagnostics and Radiological Health at 301-796-5711, or David Litwack at 301-796-6697 or Ernest.Litwack@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

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

- **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.

- **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.

Genetic Database Guidance

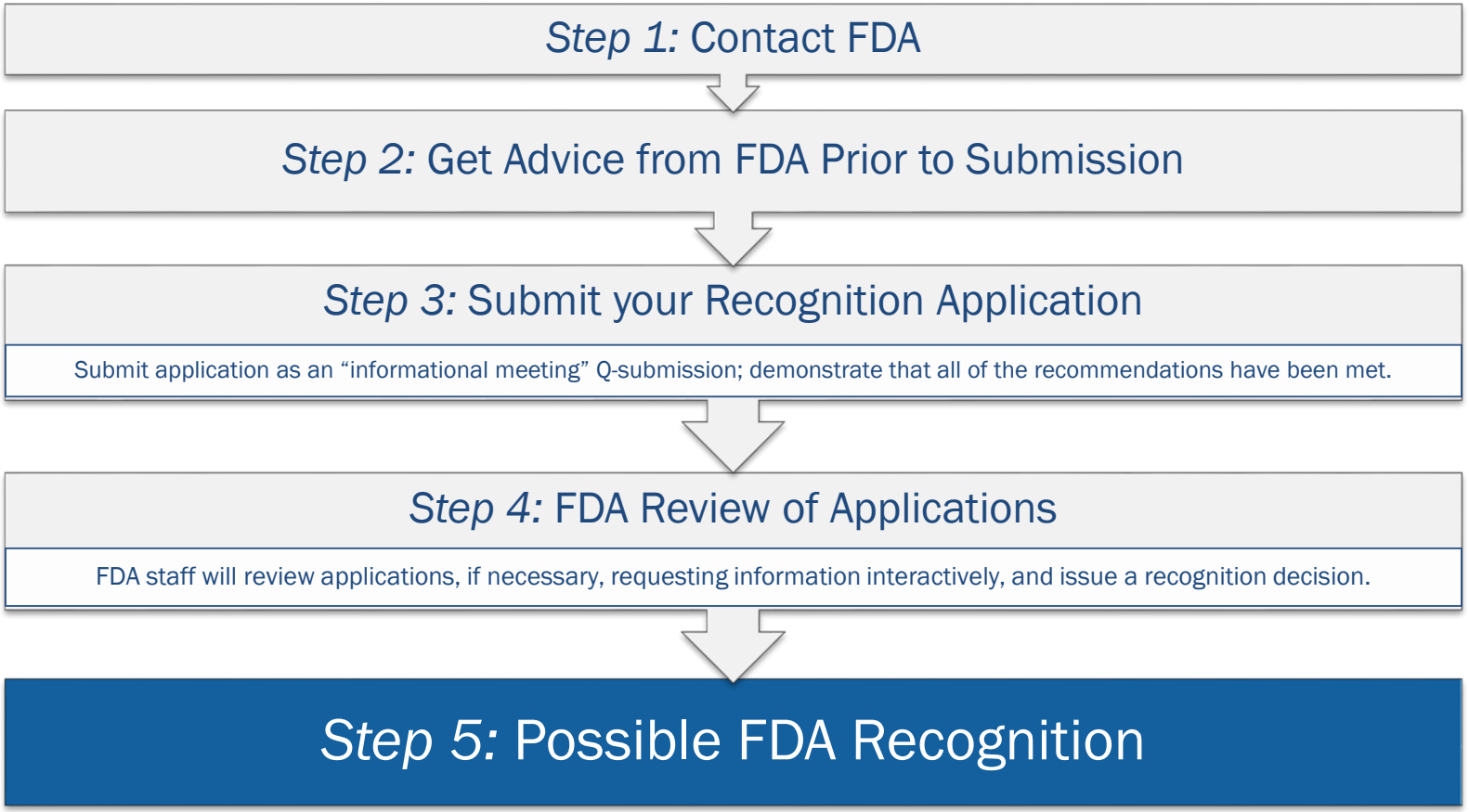
Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics

- Scope: publicly accessible databases of genetic variants
- 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

How can sponsors use recognized databases?

- Can be used to support the clinical validity of genetic and genomic tests.
- 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.
- FDA recognition will not extend to treatment recommendations.

Database Recognition Process



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

Analytical NGS 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

- Scope: germline WES or panels
- Makes a series of technical recommendations for how NGS-test developers can design and validate their tests
- Accommodates different test designs, components, indications, etc.
- Validation – performance characteristics, evaluation studies
- Labeling recommendations
- Can form the basis for future FDA-recognized **standard(s)** and/or **special controls**
- Discusses potential for an **expedited path to market** for tests that meet these standards

Scope:

The 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

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Reference Sample Projects

Ongoing efforts - differences and similarities

Genome in a Bottle

External RNA Controls Consortium

Registry of Standard Biologic Parts

MAQC/SEQC2

SPOT/Dx

GeT-RM

ABRF-NGS

WHO KRAS Reference Panel

ctDNA standards

Commercial interest

http://mdic.org/clinicaldx/somatic-reference-samples/

National Institute of Standards and Technology

- CDRH has supported NIST genome reference material development since 2012
  - IAAs: 2012-2014; 2014-2016; 2016-2018; 2018-2020 (currently in process for award)
  - Medical countermeasures
  - Analytical Materials/Method Standards for Next Generation Sequencing (NGS) as a Clinical Diagnostic
  - Challenging Variants and Regions for NGS

- Materials developed
  - 5 reference genomes
    - NA12878
    - Ashkenazi Jewish son
    - Ashkenazi Jewish trio
    - Son of Chinese Ancestry
    - Microbial Genomic DNA standards MG-001, MG-002, MG-003, MG-004

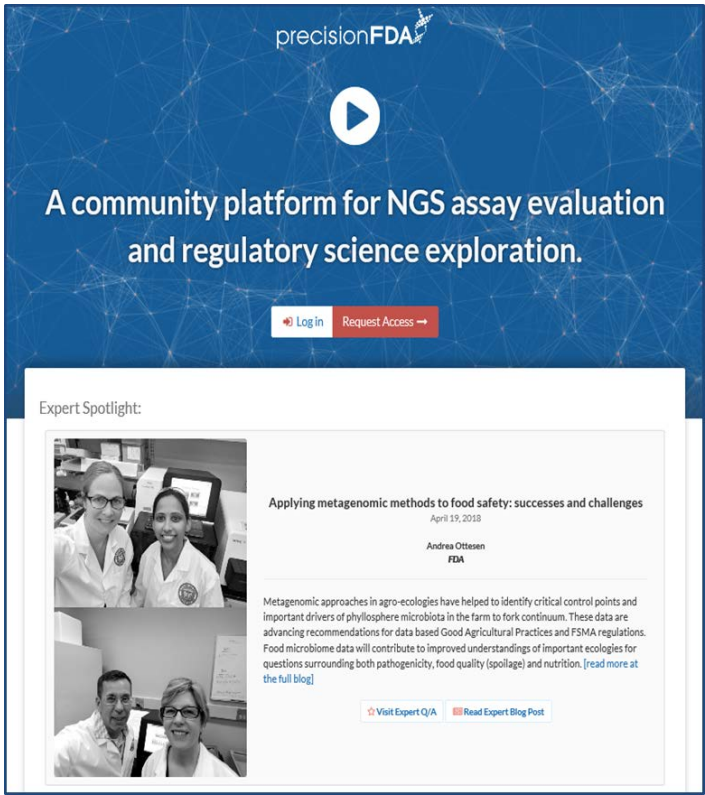
Genome in a Bottle

Reference Samples and Possibilities

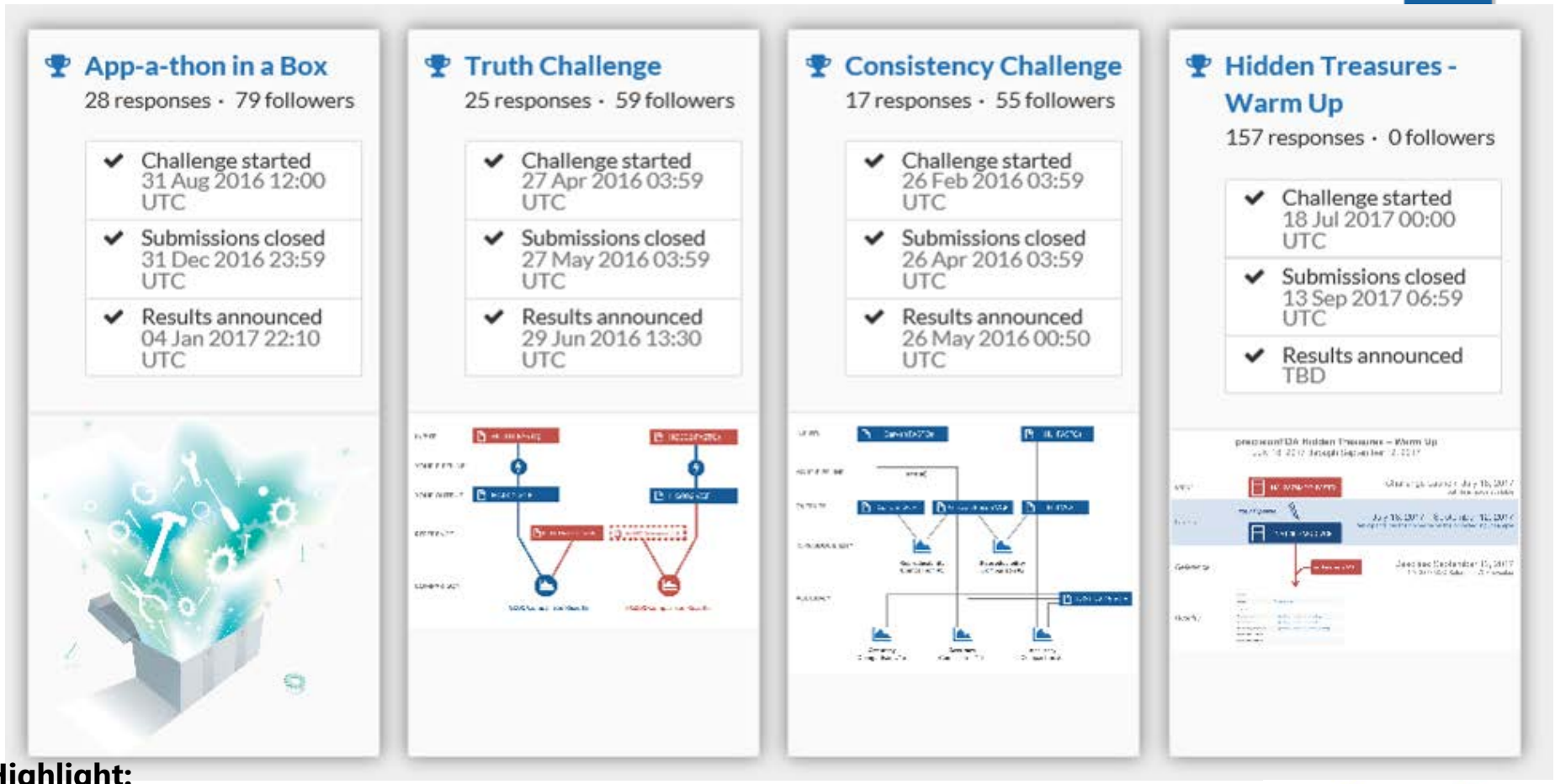
- Develop, characterize, make publicly available NGS **reference sample sets**
  - Characterization efforts; generating "truth sets"
- Community effort – reference sequence
  - Sequence deposition on easily accessible **platform**
    - Integrate calls
    - Develop constantly ***evolving "truth" sequence***
    - Metadata explains technical characteristics
  - Characterized samples available
  - Sequence and metadata available

precisionFDA – platform, can be used to analyze, integrate and compare data sets

https://precision.fda.gov/



FOCUSING EXPERTS AROUND THE WORLD ON ADDRESSING COMMON PROBLEMS



Highlight:

The Truth, Consistency, and Hidden Treasures – Warm Up challenges provided several important takeaways for FDA regulatory science, including: (1) assessing variant calling pipeline accuracy, which differs depending on the type and size of the genetic variants being assessed, and (2) ways *in silico* injected variants can be used to assess variant calling pipeline accuracy.

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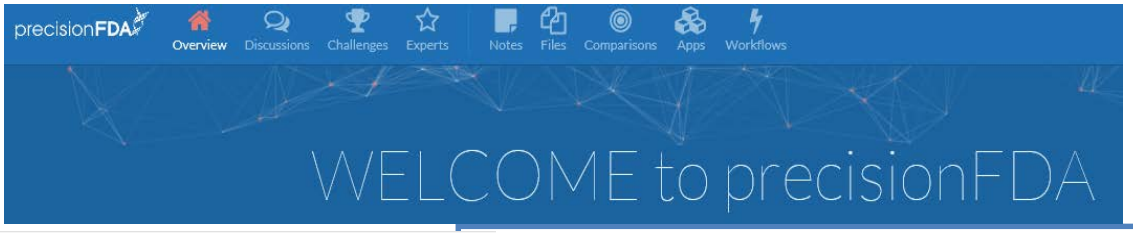
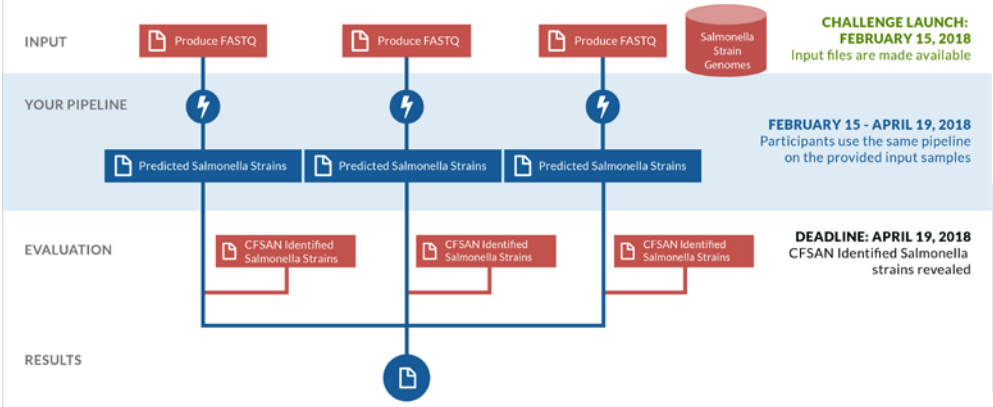
It's a Challenge!

precisionFDA: FDA's Collaborative Omics Platform



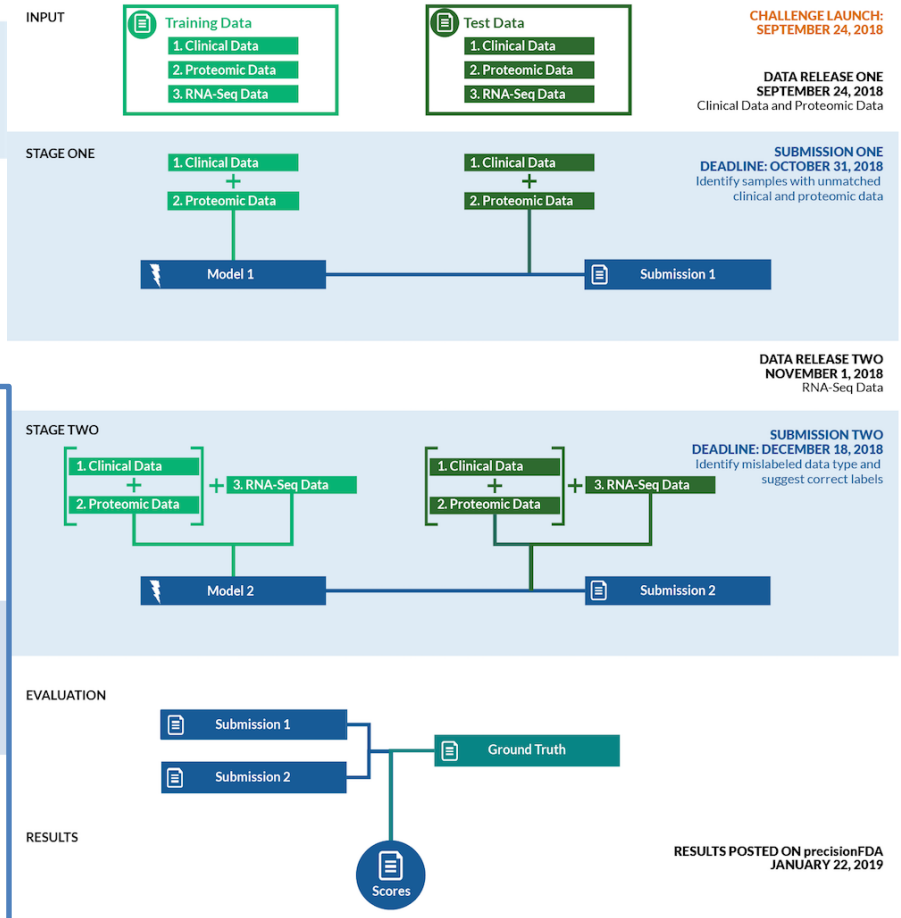
precisionFDA CFSAN Pathogen Detection Challenge

February 15 through April 19



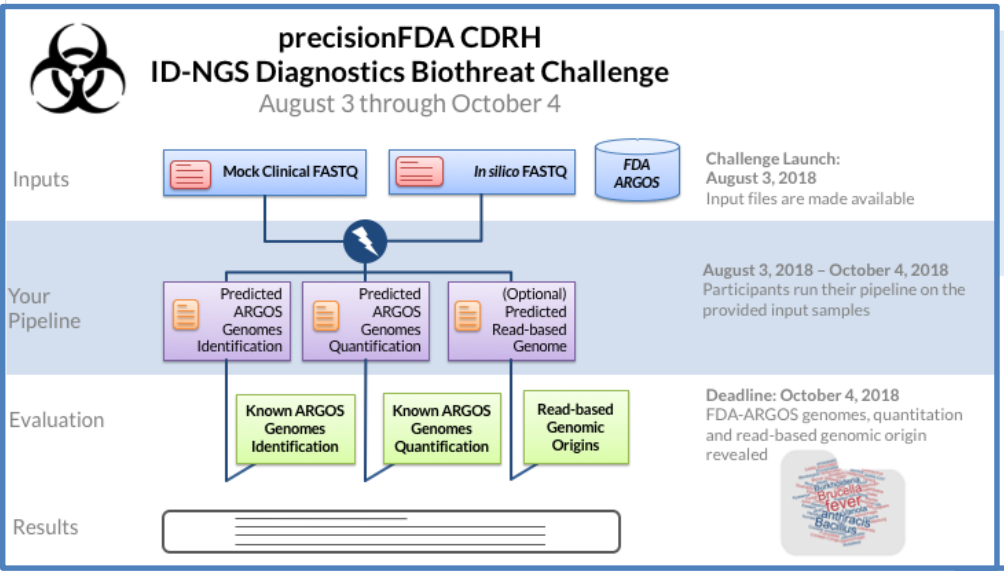
precisionFDA NCI-CPTAC Multi-omics Enabled Sample Mislabeling Correction Challenge

September 24 through December 18



precisionFDA CDRH ID-NGS Diagnostics Biothreat Challenge

August 3 through October 4



Cancer Genomic Somatic Reference Samples

Goal: Improve the efficiency and cost-effectiveness of accurate NGS-based test development and validation by establishing and organizing a collaborative community effort to develop needed reference samples.

Benefits of this work: Availability of reference samples will aid in efficient NGS test development and validation, which will in turn *streamline and possibly obviate steps in the regulatory process for diagnostic companies, provide transparency, and compress development timelines for targeted therapeutics developers.*

Working Group Members:

- **Professional**
- ***Academic Medical Centers***
- ***FDA*** (CDRH, CDER, OCE)
- ***Industry*** (Diagnostics, Pharma)
- ***Biorepositories***
- ***Payors***

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MEDICAL DEVICE INNOVATION CONSORTIUM