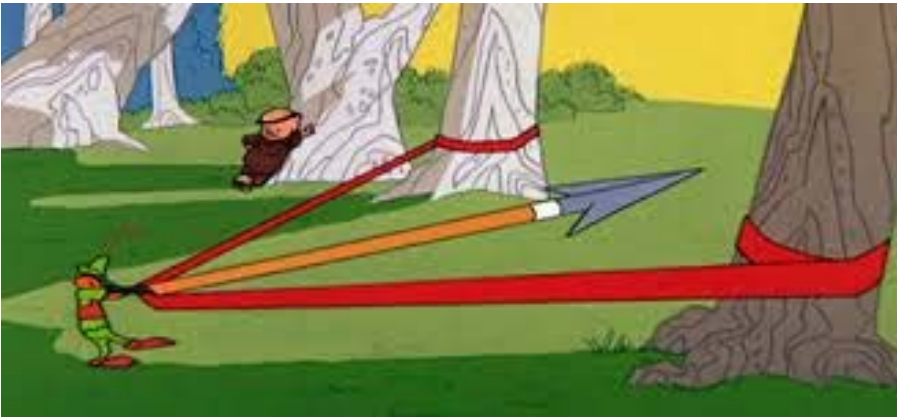


Personalized Medicine Update





Agenda

- DTC and Pharmacogenetics
- Guidance and Policy Development
 - Codevelopment of IVDs with Therapeutics
 - Investigational Device Exemptions
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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

www.fda.gov

The screenshot shows the FDA's website for Direct-to-Consumer Tests. The header includes the FDA logo, "U.S. FOOD & DRUG ADMINISTRATION", and navigation links for "A to Z Index", "Follow FDA", and "En Español". A search bar is also present. The main navigation bar lists various categories: Home, Food, Drugs, Medical Devices, Radiation-Emitting Products, Vaccines, Blood & Biologics, Animal & Veterinary, Cosmetics, and Tobacco Products. The "Medical Devices" section is active, showing a breadcrumb trail: Home > Medical Devices > Products and Medical Procedures > In Vitro Diagnostics. On the left, a sidebar menu for "In Vitro Diagnostics" includes links to Companion Diagnostics, Direct-to-Consumer Tests (which is highlighted), Nucleic Acid Based Tests, Precision Medicine, Laboratory Developed Tests, Tests Used In Clinical Care, Home Use Tests, Blood Glucose Monitoring Devices, Warfarin INR Test Meters, and Drugs of Abuse Tests. The main content area is titled "Direct-to-Consumer Tests" and features social media sharing options (Share, Tweet, LinkedIn, Pin It, Email, Print). Below this, a "More Information:" section lists two links: "Lists of Direct-To-Consumer Tests with Marketing Authorization" and "Frequently Asked Questions About Direct-To-Consumer Tests". The text explains that in vitro diagnostics (IVDs) are marketed directly to consumers without a health care provider's involvement. It defines direct-to-consumer tests as those that collect a specimen (like saliva or urine) and send it to a company for testing and analysis. The text further elaborates that direct-to-consumer testing is expanding the number of people who can get genetic testing of their DNA (or genome). It notes that a person's genome is made up of thousands of genes that carry hereditary information about traits like eye color or height. This information is based on the arrangement of distinct molecules (also known as "bases") that make up genes. Some of these arrangements, or variants, can be used to diagnose a rare disease, provide information about a person's risk of developing disease, or other types of information. Some variants have clinical significance and may give consumers insight into monitoring their own health, or about potential disease or conditions. The text also states that not all direct-to-consumer tests are genetic tests; some measure other things like levels of proteins in the body, levels of toxins in urine, or levels and types of bacterial flora (referred to as a "microbiome"). Finally, it mentions that direct-to-consumer tests have varying levels of evidence supporting their claims, and that there can be disagreements in the clinical community about the role that different genetic variants have in contributing to disease, with new information being learned every day. There are tens of thousands of variants and varying information available to determine whether those variants are relevant to whether a person may get a disease or condition. Not all variants that contribute to a person's risk of getting a

<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.



**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

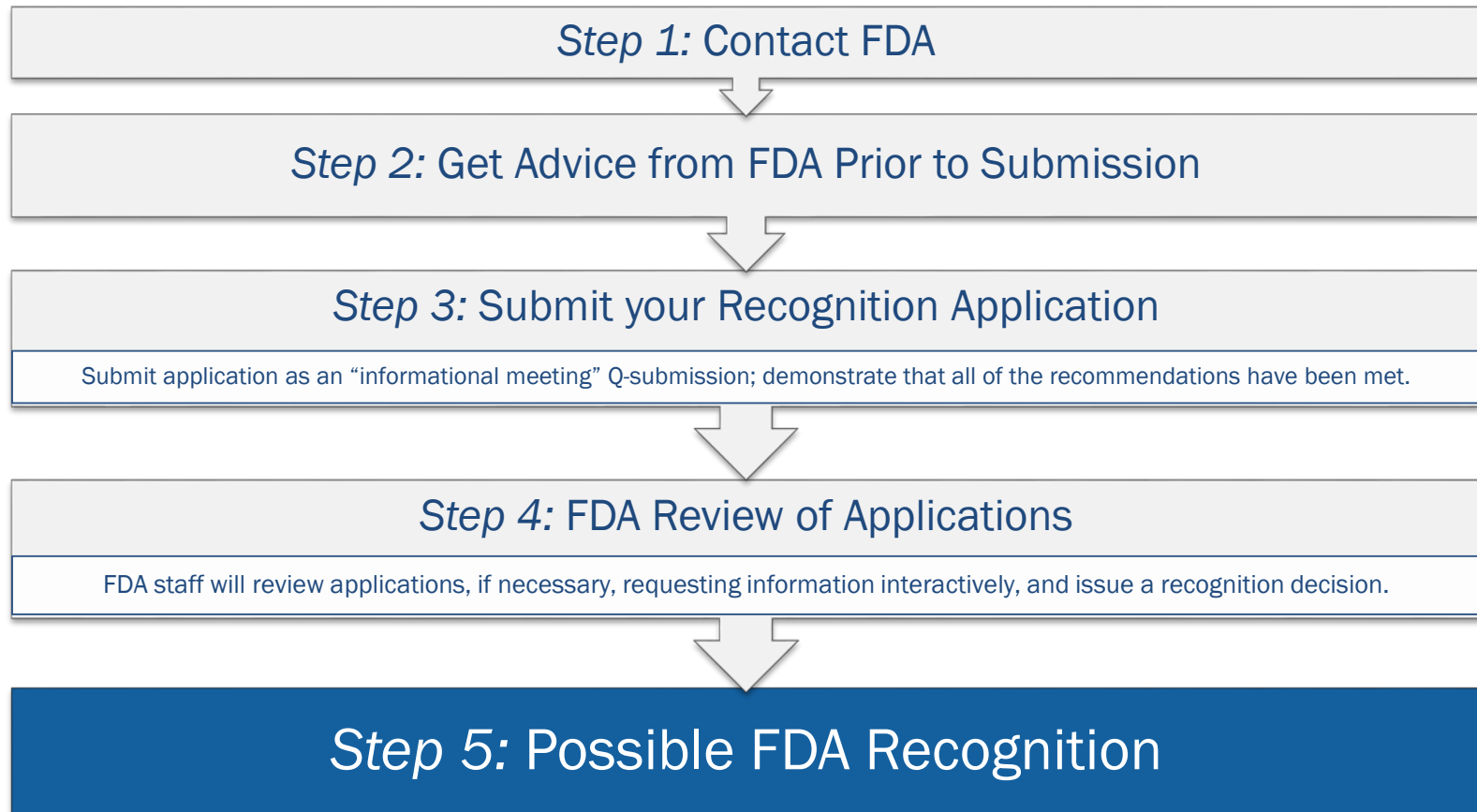
How can sponsors use recognized databases?



- 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



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

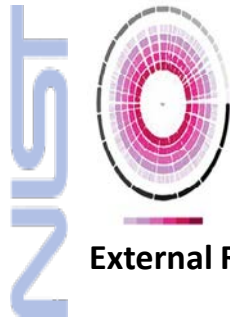


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Reference Sample Projects

Ongoing efforts - differences and similarities



Genome in a Bottle

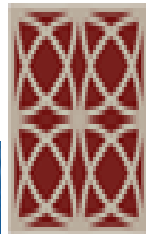
External RNA Controls Consortium



Registry of Standard Biologic Parts



MAQC/SEQC2



SPOT/Dx



GeT-RM



ABRF-NGS



WHO KRAS Reference Panel

precisionFDA



ctDNA standards

AACR

American Association
for Cancer Research



Align. Achieve. Accelerate.

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



Commercial interest



www.fda.gov

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



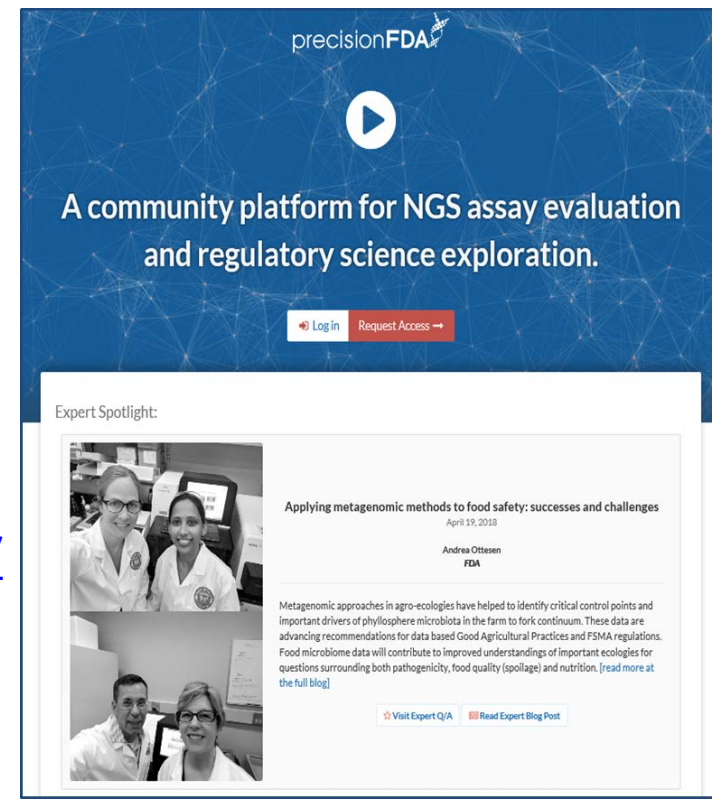
Genome in a Bottle

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/>



precisionFDA

A community platform for NGS assay evaluation and regulatory science exploration.

Log in Request Access

Expert Spotlight:

Applying metagenomic methods to food safety: successes and challenges
April 19, 2018
Andrea Ottosen
FDA

Metagenomic approaches in agro-ecologies have helped to identify critical control points and important drivers of phyllosphere microbiota in the farm to fork continuum. These data are advancing recommendations for data based Good Agricultural Practices and FSMA regulations. Food microbiome data will contribute to improved understandings of important ecologies for questions surrounding both pathogenicity, food quality (spoilage) and nutrition. [read more at the full blog]

Visit Expert Q/A Read Expert Blog Post

FOCUSING EXPERTS AROUND THE WORLD ON ADDRESSING COMMON PROBLEMS

FDA

🏆 App-a-thon in a Box

28 responses • 79 followers

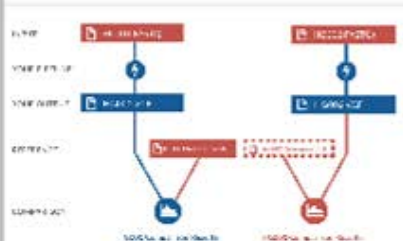
- ✓ Challenge started 31 Aug 2016 12:00 UTC
- ✓ Submissions closed 31 Dec 2016 23:59 UTC
- ✓ Results announced 04 Jan 2017 22:10 UTC



🏆 Truth Challenge

25 responses • 59 followers

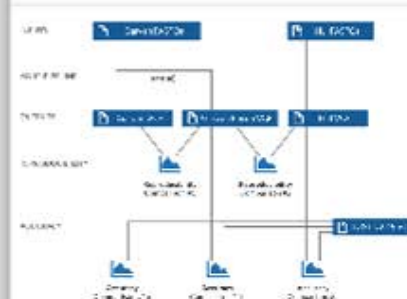
- ✓ Challenge started 27 Apr 2016 03:59 UTC
- ✓ Submissions closed 27 May 2016 03:59 UTC
- ✓ Results announced 29 Jun 2016 13:30 UTC



🏆 Consistency Challenge

17 responses • 55 followers

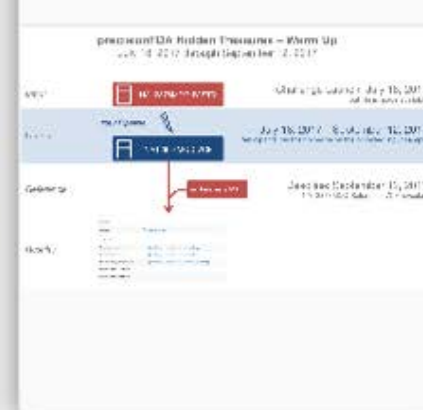
- ✓ Challenge started 26 Feb 2016 03:59 UTC
- ✓ Submissions closed 26 Apr 2016 03:59 UTC
- ✓ Results announced 26 May 2016 00:50 UTC



🏆 Hidden Treasures - Warm Up

157 responses • 0 followers

- ✓ Challenge started 18 Jul 2017 00:00 UTC
- ✓ Submissions closed 13 Sep 2017 06:59 UTC
- ✓ Results announced TBD



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.

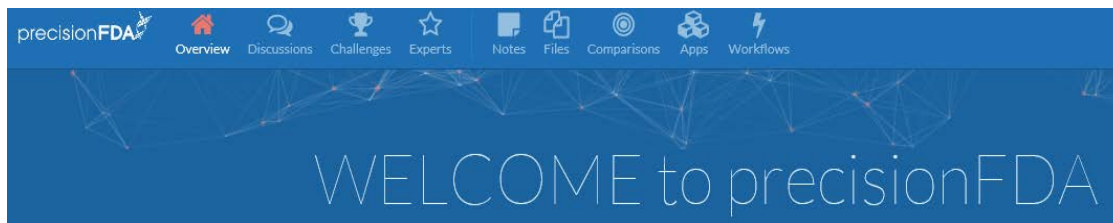
www.fda.gov



It's a Challenge!

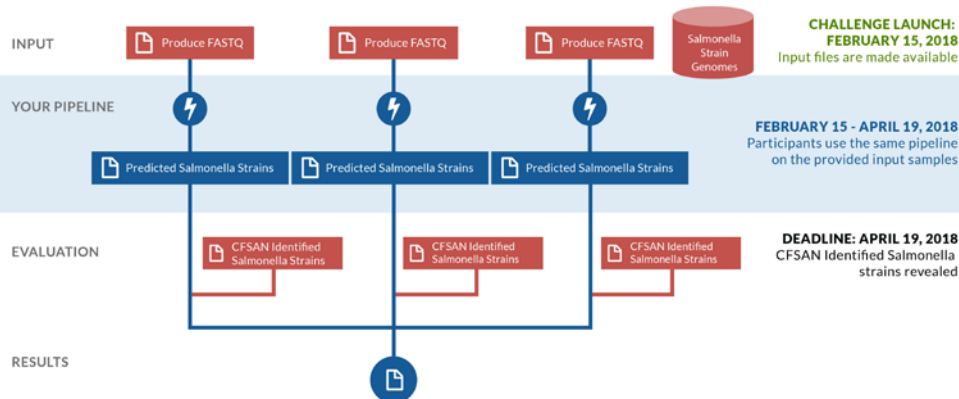
precisionFDA: FDA's Collaborative Omics Platform

FDA



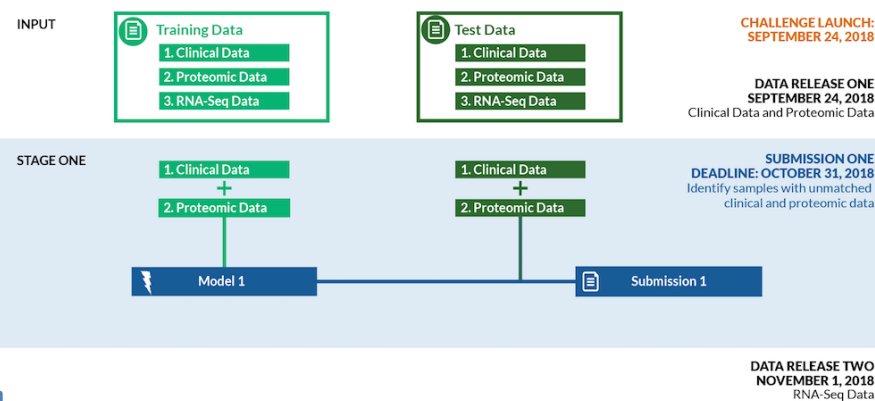
precisionFDA CFSAN Pathogen Detection Challenge

February 15 through April 19



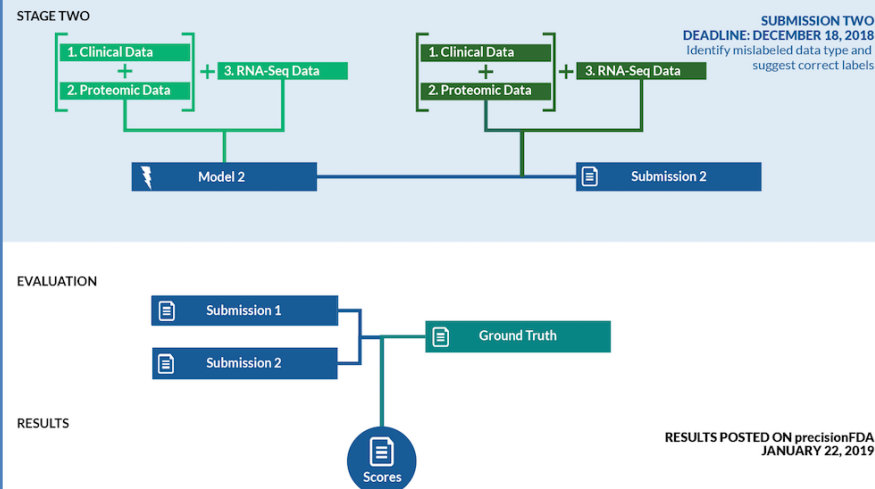
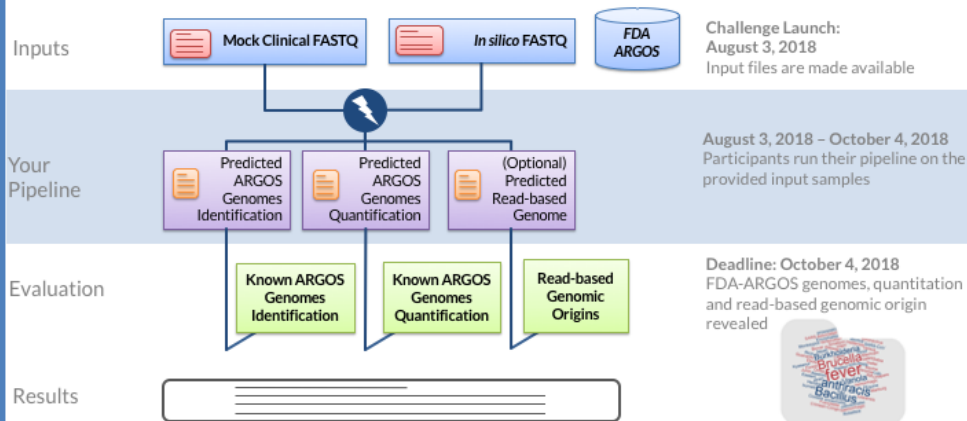
precisionFDA NCI-CPTAC Multi-omics Enabled Sample Mislabeling Correction Challenge

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**