The Precision Medicine Initiative and a Research Roadmap for Next Generation Sequencing Informatics

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Disclaimer

- NGS is raising new policy and regulatory issues; thoughts presented here are preliminary and do not represent finalized FDA policy.

Overview

- Precision medicine and NGS tests
- The Precision Medicine Initiative
  - Regulatory tools and approaches
  - Analytical validation
  - Clinical validation
  - precisionFDA
  - Recent FDA activities
- A Research Roadmap for Next Generation Sequencing Informatics
  - 9 research areas

Success of Precision Medicine Requires:

- ***Safe and accurate diagnostic tests*** that reliably identify individual variation
- ***Learning health systems*** that enable researchers and clinicians to learn from and inform the patient experience
- ***Development of targeted therapies*** that are more efficacious or have less deleterious side effects for specific individuals
- ***Updated research and regulatory policies*** that catalyze the development of new treatments while protecting patients

FDA – A Long History of Enabling Precision Medicine

- 23 companion diagnostics cleared or approved
- 50 biomarkers used in targeting 147 approved drugs*
  - Cystic Fibrosis, Cancer, Cholesterol, Psychiatric, Pulmonary, Infectious Diseases, etc.
- More than 60 approved/cleared human nucleic acid based tests**
- More than 24 Guidances issued since 2005

* http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
** http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm and http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm330711.htm

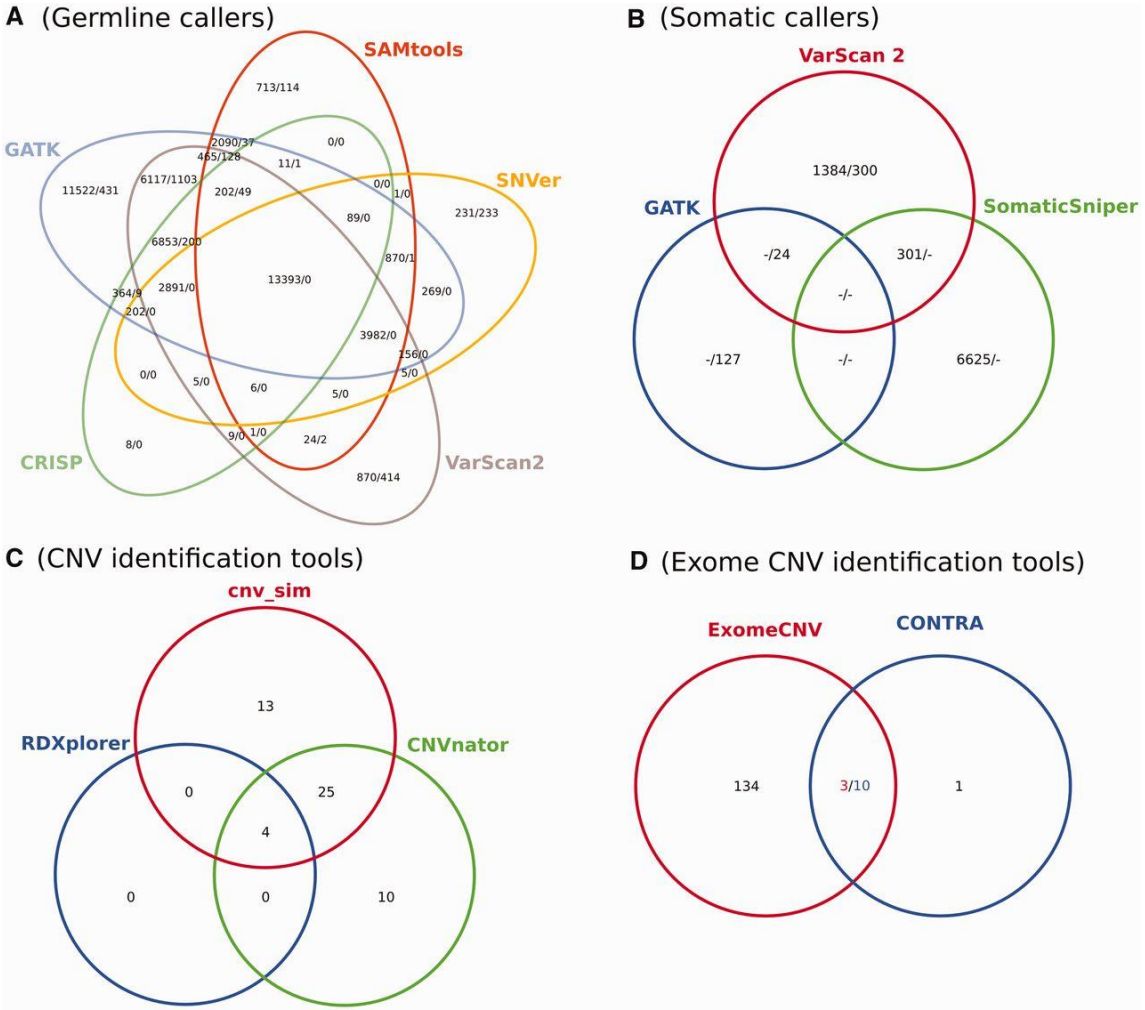
In Vitro Diagnostics in the Age of Precision Medicine

Conventional Diagnostics	Precision Medicine
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 randomized controlled trials – research separate from practice	Clinical evidence from learning health systems – merging of research and practice

Barriers to Precision Medicine

- **NGS tests – a moving target**
  - NGS tests exist in many configurations
  - Frequent modifications to NGS tests
  - Rapidly evolving technology
  - Different labs may obtain different results
- **Potential results are unlimited**
  - Even a single gene test could detect previously unobserved variants
  - It is not possible to validate every possible result
- **Unprecedented ability to detect rare variants**
  - Difficult to gather clinical evidence to understand data
  - Discovery outpacing understanding

Analytical Challenges in Genomics



Pabinger et al., 2013, doi:10.1093/bib/bbs086

Barriers to Evidence Generation

Traditional clinical studies not possible because the number of patients with a given variant is usually too small.

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
- Is there a more efficient way to oversee NGS tests than "one analyte-one claim"?

President Obama's Precision Medicine Initiative (PMI)

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

Developing New Regulatory Approaches for Genomic Tests

Vision: Implement new regulatory policies to promote research and accelerate the translation of precision medicine technologies into treatments that *benefit patients*.

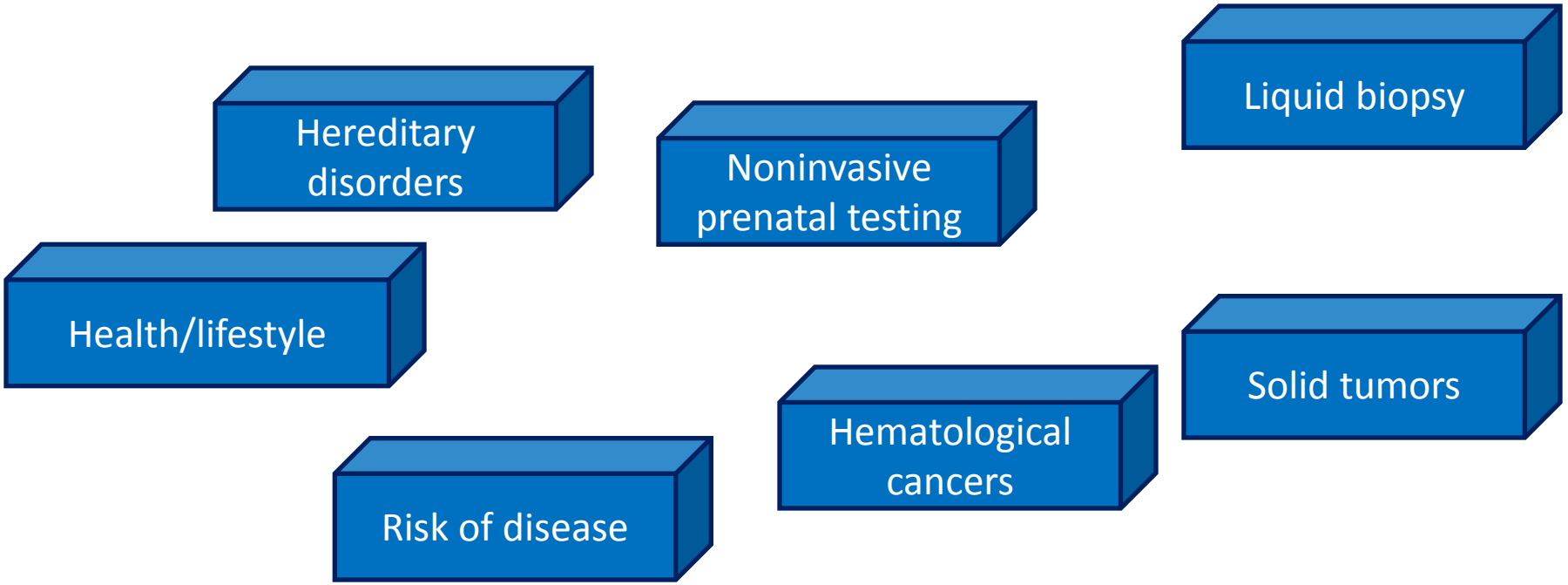
Goal: Develop and implement an adaptive standards-based regulatory approach.

- Develop and implement ***standards*** to assure quality
- Develop ***open-source tools*** to help test developers meet standards
- Support the development of a ***data commons*** for evidence on the clinical relevance of genetic variation

Available Tools

Binning Uses of NGS

Risk depends on use



FDA's Concepts for NGS Regulation

1. Technical standards for NGS.

- Test developers that meet these standards would not have to submit an application to FDA.
- Standards would be developed with the scientific community, and can be updated as science and technology advance.
- FDA would develop and provide open-source software to enable test developers to meet standards.

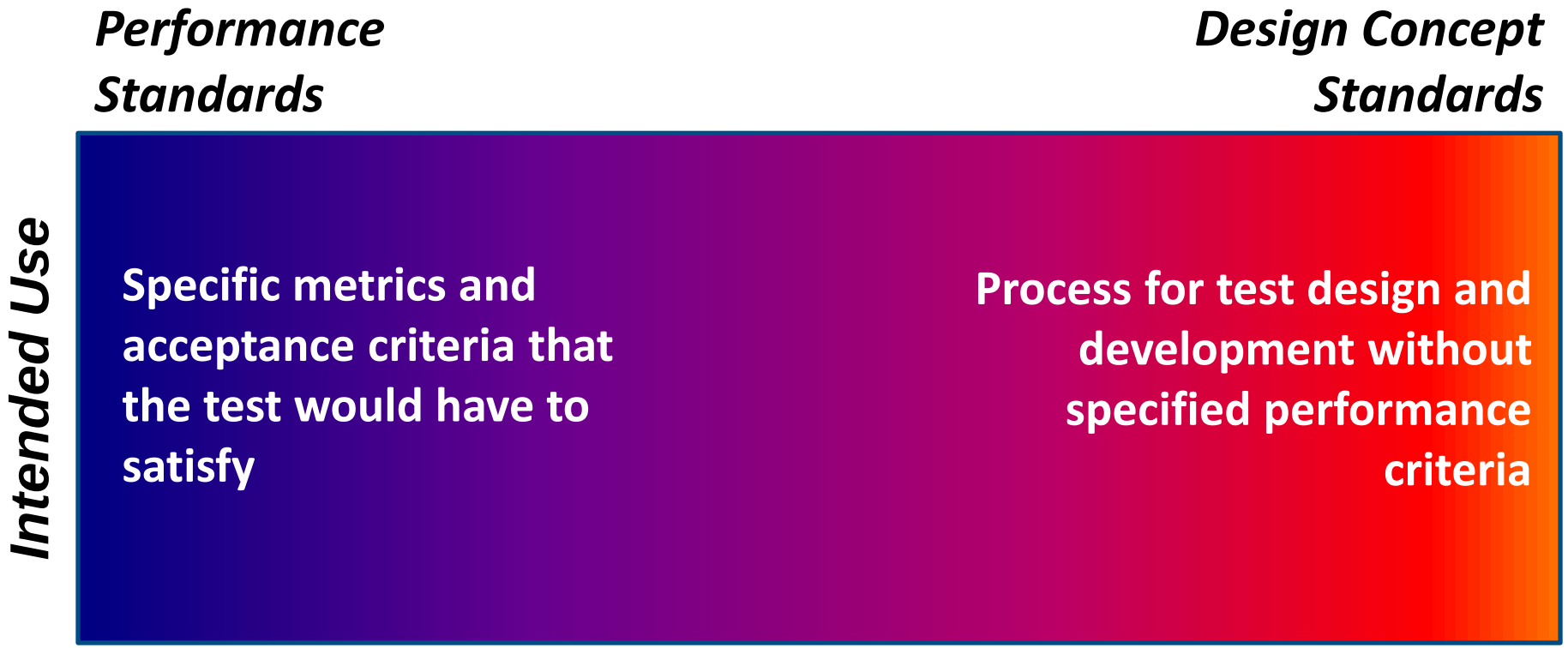
2. Use of curated databases to provide clinical evidence.

- Use "regulatory grade" databases as information sources to support the link between genetic variation and health/disease.
- Test developers can use such databases in lieu of traditional clinical studies.
- Such databases could also be used by laboratories and physicians as part of a genomic test.

In Vitro Diagnostics in the Age of Precision Medicine

Conventional Diagnostics	NGS-Based Diagnostics
Number of analytes: usually one, maybe a few	*Number of analytes:* undefined (millions?)
Analytical validation : Review of each analyte for each test in premarket submissions	*Analytical validation in premarket submissions:* Process-based approach to assure adequate performance over all possible analytes

A Spectrum of Approaches for Analytical Validity



In Vitro Diagnostics in the Age of Precision Medicine

Conventional Diagnostics	NGS-Based Diagnostics
Number of analytes: usually one, maybe a few	*Number of analytes:* undefined (millions?)
Evidence source used for premarket submissions: Sponsor-led clinical studies	*Evidence source used for premarket submissions:* Need for crowd-sourced data

Databases as Sources of Clinical Evidence for NGS Tests

- Promote the development of "regulatory grade" databases containing evidence linking genetic information to disease
- Quality concepts
  - Curation practices
  - Annotation (patient, diagnostic, etc.)
  - Versioning
  - Data quality/Source of testing results
  - Sustainability
  - Other
- Define language that can be used to report clinical evidence found in databases
- Through PMI, FDA will assess and, if necessary, upgrade existing databases to assure sufficient quality for regulation.

precisionFDA

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

Log in | Request Access →

precisionFDA demonstrates FDA's commitment to innovating the regulatory science needed to advance the growing era of precision medicine

ROBERT CALIFF

FDA

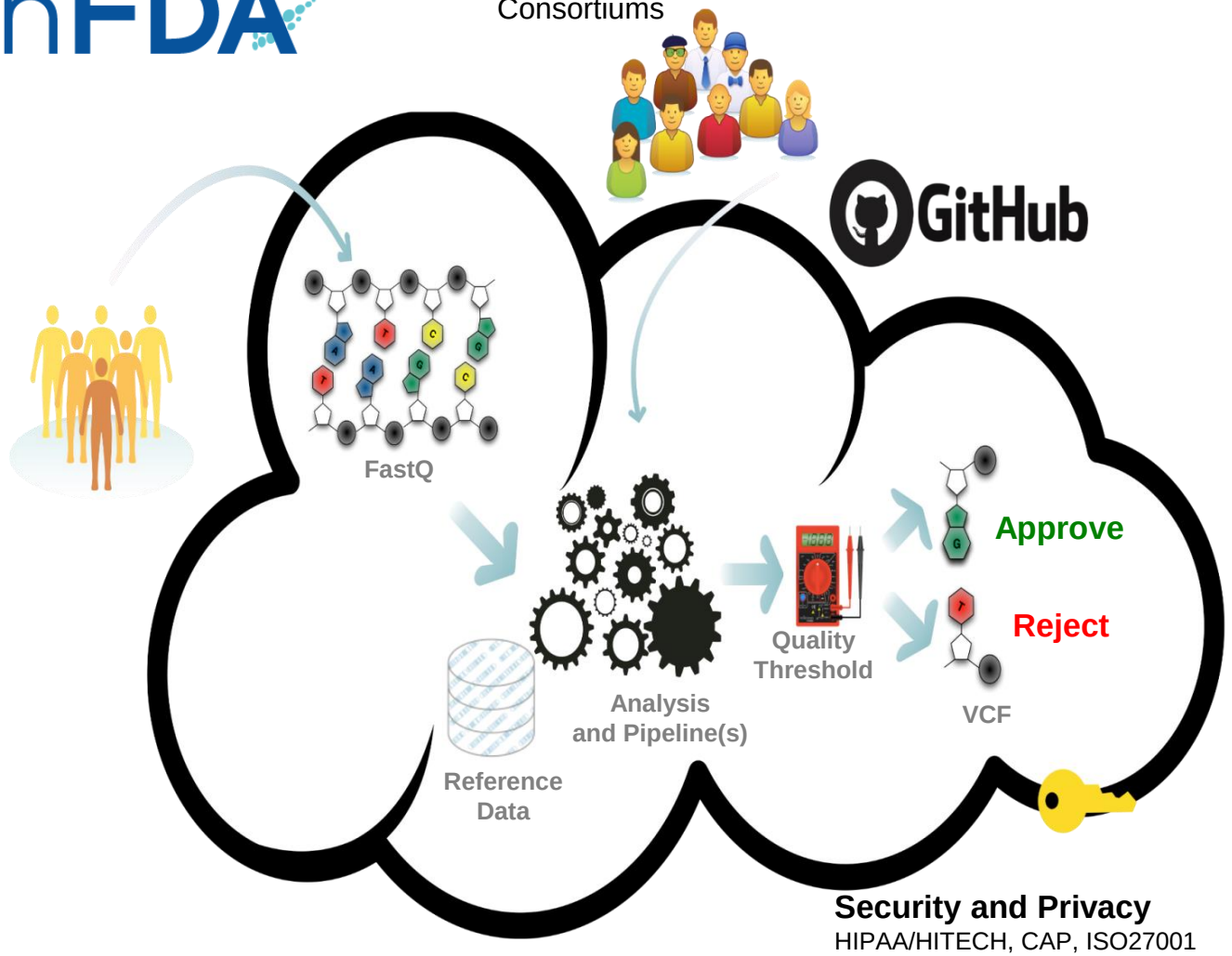
precisionFDA

Advancing the accuracy and reproducibility of NGS

- Crowd-sourced, cloud-based platform
- Will provide tools and open access resources
- Will allow the community to test, pilot, and validate approaches to NGS

Community

NGS-Based Test Developers (large and small), NIST, FDA Scientists, Standards Bodies, Academic Centers, Patient-Facing Providers, Consortiums



Security and Privacy

HIPAA/HITECH, CAP, ISO27001
Uniquely identified and immutable data
Version-controlled applications

Slide courtesy of Taha Kass-Hout, FDA's Chief Health Informatics Officer

WELCOME to precisionFDA

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

Create a Note
Write and publish rich notes describing your thoughts and your work

Learn **Create note**

Upload a File
Upload files to your private space to use as inputs for apps or comparisons

Learn **Upload file**

Run a Comparison
Look at the differences between a test set and a benchmark set of genomic variants

Learn **Run comparison**

Launch an App
Run bioinformatics or other Linux-based software on the cloud

Learn **Launch app**

Add an Asset
Contribute a tarball with software that can be used by apps

Learn **Add asset**

Create your own app
Combine assets with a shell script, and achieve just about anything

Learn **Create app**

Ready to learn more?

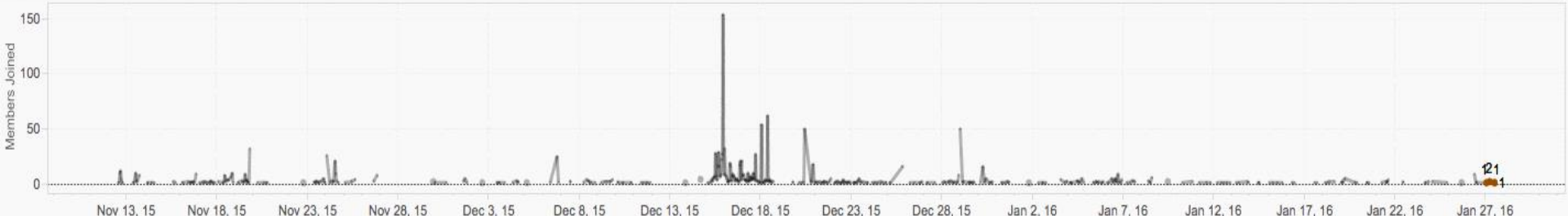
Read our Docs

Understand our

Community Guidelines

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

>1100 members from >647 organizations around the world



U.S. Food and Drug Administration
Protecting and Promoting Public Health

www.fda.gov

precision.fda.gov

Request Access to precisionFDA

Thank you for your interest!
To request access, please leave your information below.

ABOUT ME

First name

Last name

Email address

Organization

☐ I do not represent any organization

Address

Phone #

DUNS # Optional

MY INTEREST IN PRECISIONFDA

Tell us a bit more about your goals / reasons why are requesting access:

precisionFDA Overview Discussions Notes Files Comparisons Apps Feedback Guidelines Docs

Over 20 Organizations Participated in precisionFDA Challenge…

PrecisionFDA Consistency Challenge

Engage and improve DNA test results with our first community challenge

CHALLENGE JOINED!
26 DAYS REMAINING

The **Food and Drug Administration (FDA)** calls on the genomics community to further assess, compare, and improve techniques used in DNA testing by launching the first precisionFDA challenge.

President Obama's Precision Medicine Initiative envisions a day when an individual's medical care will be tailored in part based on their unique characteristics and genetic make-up.

The goal of the FDA's first precisionFDA challenge is to engage the genomics community in advancing the quality standards in order to achieve more consistent results in the context of genetic tests (related to whole human genome sequencing), advancing the goal of better personalized care.

PrecisionFDA invites all innovators to take the challenge and assess their software on the supplied reference human datasets. Participation is voluntary, but instrumental in helping the community prepare for the coming genomic data revolution.

PrecisionFDA Consistency Challenge

COMMUNITY CHALLENGE AWARDS

TOP OVERALL
PERFORMANCE

AWARDED TO
Sentieon team

Rafael Aldana Hanying Feng
Brendan Gallagher Jun Ye

HIGHEST
REPRODUCIBILITY

AWARDED TO
Sentieon team

Rafael Aldana Hanying Feng
Brendan Gallagher Jun Ye

HIGHEST
ACCURACY

AWARDED TO
Sanofi-Genzyme

Deepak Grover

Overview of Results

We received a total of 21 entries to the challenge, summarized in the following table. **The entries are sorted in order of date of submission.**

We would like to acknowledge and thank all of those who participated in the precisionFDA Consistency Challenge, for their engagement and contributions. We hope that everyone will feel like a winner. After considering the performance in reproducibility and accuracy comparisons, as well as other parameters, we have decided to hand out awards and recognitions, as illustrated in the table.

PrecisionFDA Truth Challenge

Engage and improve DNA test results with our community challenges

CHALLENGE CLOSED
VIEW RESPONSES

The **Food and Drug Administration (FDA)** calls on the genomics community to further assess, compare, and improve techniques used in DNA testing by launching the second precisionFDA challenge.

President Obama's Precision Medicine Initiative envisions a day when an individual's medical care will be tailored in part based on their unique characteristics and genetic make-up.

The goal of the FDA's second precisionFDA challenge, similarly to the first challenge, is to continue engaging the genomics community in advancing the quality standards in order to achieve more accurate and consistent results in the context of genetic tests (related to whole human genome sequencing), advancing the goal of better personalized care.

PrecisionFDA invites all innovators to take the challenge and assess their (or their favorite!) software on the supplied human datasets. Participation is voluntary, but instrumental in helping the community prepare for the coming genomic data revolution.

FDA's PMI Efforts - Update

- Organization of technical efforts - ongoing
  - Analytical standards (e.g., GIAB)
  - Clinical performance
  - Informatics, including open-source computational solutions for validating NGS test performance
- Engagement with external stakeholders - ongoing
- Public workshops
  - Optimizing FDA's Regulatory Oversight of Next Generation Sequencing Diagnostic Tests (Feb 20, 2015)
  - Standards Based Approach to Analytical Performance Evaluation of Next Generation Sequencing IVDs (Nov 12, 2015)
  - Use of Databases for Establishing the Clinical Relevance of Human Genetic Variants (Nov 13, 2015)
  - Patient and Medical Professional Perspectives on the Return of Genetic Test Results (Mar 2, 2016)
- Development of draft policy (2016)

Public Workshops - Summary

- **Standards Based Approach to Analytical Performance Evaluation of NGS Tests**
  - Broad support for the development of standards and enhanced transparency to ensure quality of NGS testing
  - Standards should include a blend of design concept standards and performance standards
  - Need for development of more reference materials
- **Use of Genetic Databases for Establishing Clinical Relevance of Human Genetic Variants**
  - Need for common data formats and nomenclature
  - Broad support for enhanced transparency about how genetic variants are evaluated, use of standard operating procedures for data evaluation
  - Need for standardized reporting formats
- **Patient and Medical Professional Perspectives on Return of Genetic Test Results**
  - Broad support for providing patients and their healthcare providers with genetic test reports that are readily understandable
  - Need for different ways of representing results – color coding, graphical explanations, lifetime risk vs. relative risk
  - Need to update patient's medical record as new information becomes available about genetic variants

PERSPECTIVE

REGULATORY SCIENCE

A research roadmap for next-generation sequencing informatics

Russ B. Altman,[1]* Snehit Prabhu,[2] Arend Sidow,[3] Justin M. Zook,[4,11] Rachel Goldfeder,[5] David Litwack,[6] Euan Ashley,[7] George Asimenos,[8] Carlos D. Bustamante,[2] Katherine Donigan,[6] Kathleen M. Giacomini,[9] Elaine Johansen,[6] Natalia Khuri,[10] Eunice Lee,[6] Xueying Sharon Liang,[6] Marc Salit,[4,10,11] Omar Serang,[8] Zivana Tezak,[6] Dennis P. Wall,[12] Elizabeth Mansfield,[6] Taha Kass-Hout[6]

Next-generation sequencing technologies are fueling a wave of new diagnostic tests. Progress on a key set of nine research challenge areas will help generate the knowledge required to advance effectively these diagnostics to the clinic.

The Precision Medicine Initiative (PMI) is a U.S. national effort "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" (*1*). One goal is to bring about the routine use of next-generation precision diagnostics to benefit individuals and public health. Central to the introduction of safe and effective new precision diagnostic technologies is an adequate understanding of how well they perform. Through the PMI, the U.S. Food and Drug Administration (FDA) is seeking to address this issue by providing dynamic, flexible, and well-balanced regulation of precision diagnostics. Because these complex technologies pose new challenges in understanding their likely benefits and their limits in terms of accuracy, precision, and clinical validity, FDA is advancing a robust research agenda in regulatory science. New knowledge gained from this agenda will inform the next generation of regulation for precision medicine

that included a public workshop and discussions on identifying key activities needed to evaluate the clinical implications of next-generation nucleic acid sequencing (NGS). Here we summarize the ideas and directions that were proposed and put forth a working "roadmap"

Eventually, these developments are likely to culminate in the routine sequencing of patients' genomes. In the meantime, there will be several years during which the process of DNA sequence determination remains challenging and in which cost-, quality-, and goal-driven tradeoffs result in a large diversity of testing strategies. In this Perspective, we lay out the technological challenges that are slowing the routine clinical use of a new generation of genetic tests and propose questions that regulatory science should address to arrive at a flexible yet robust regulatory framework that results in maximum benefit for patients.

As part of its PMI effort, FDA seeks to undertake and support regulatory science research that will enhance our understanding of NGS test products and their development and validation, as well as how the results of such tests are best communicated in an evolving health care environment.

A centerpiece of this effort is precisionFDA, a research and development portal that

Research Roadmap: 9 regulatory science areas

1. Secure storage of genomic data and software

- Methods for storing and accessing large numbers of genomes
- Methods to ensure security and confidentiality of information and access controls tied to specifics of the informed consent obtained from those who provide samples
- Robust systems for version control of software and data are also needed, so that experimental results can be effectively tracked and audited

2. Reference data sets covering expected uses

- A large suite of data sets to provide assurance that different types of variants in different contexts are adequately represented in pipeline testing
- Some data sets may be generated from sequencing human samples and other could be created using genome “synthesizers”
- FDA’s regulatory science effort will benefit from community sharing of new synthesizer tools to aid in generating suitable data sets for evaluation of bioinformatics pipelines

8. Develop methods for using non-FDA databases for regulatory decision making

- The field of genetics is fortunate to have a number of public databases that catalog functionally critical variants alongside the evidence supporting each, providing focus on regions that are important for clinical applications of NGS
- The value in these third-party resources could be leveraged in FDA regulatory science, which could seek to develop ways to evaluate their content and recognize them (and their standard operating procedures) as resources for test developers and clinicians to use in many of the activities described in the previous sections

9. Understand how to communicate genetic test results to providers/patients

- The ability to understand the implications of genetic test results for health care decisions without always requiring the involvement of a genetics expert is critical if genetic testing is to become widely and effectively used in current and future health care settings
- Regulatory science research could work with a broadly drawn cross section of both health care providers and the public to understand provider and patient preferences for test labeling and how test risks, benefits, and limitations are adequately communicated within the label

Future Directions

- **Working with the community to develop analytical standards for NGS tests (e.g., germline, tumor sequencing panels, etc.) and address regulatory science needs**
- **Issuance of draft guidances and open dockets for public comment**
- **More community challenges through precisionFDA**

Questions?

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3. Error models of technologies, and strategies for combining technologies

- The various existing sequencing platforms demonstrate different biases and errors; these differences will only increase as new platforms emerge
- Developing an error profile for each technology will help guide decisions surrounding the types of interrogated genomic regions for which the technology is best suited and, by extension, the range of expected uses for which it might be deployed
- Additional research into representative error models for each platform will need to be pursued
- The availability of gold-standard genome sequence data sequenced by multiple vendors on the precisionFDA portal could encourage experimentation with such combinatorial tests

4. Systematic comparison methods for NGS pipelines

- A comprehensive suite of metrics to evaluate how well different NGS platforms perform in the context of a variety of expected uses is an important goal for FDA regulatory science
- A series of precisionFDA competitions could be organized to build communal knowledge of high-quality pipelines and best practices
- Competition success metrics could reflect performance focused around specific uses as well as overall performance of candidate platforms in the contexts of the type of variation

5. Best methods for creating test data sets (benchmarks)

- **Benchmarking methods are likely to vary in their ability to evaluate the different wet-lab and informatics stages of a pipeline**
- **An important research goal is to compare natural data with different strategies for creating synthetic test sequences to understand the utility of various synthetic strategies**

6. Understand population genetic effects on detection & interpretation

- **A critical challenge for clinical NGS is to accurately identify medically relevant variation in the context of an ethnically and geographically diverse and admixed target population**
- **Collection of high-quality samples representing many population groups through the PMI and other efforts will enable their characterization and contribute to the creation of gold standard reference data sets for specific ethnicities and geographically defined groups**
- **The precisionFDA community might help in determining the proper role of population-specific reference genomes in benchmarking clinical tests**

7. Understand technology performance in particular contexts

- **PrecisionFDA may play a role in catalyzing research into methods for recognizing medically important genomic regions and promoting the performance assessment of single and combinatorial technologies at effectively interrogating variants of known and unknown significance**
- **These regions may be identified collaboratively with genetic data resources that focus on particular genes, diseases, or drug responses, while the overall characterization of NGS platforms for clinical use would emphasize performance in these critical areas**