# Next Generation Sequencing Workshops on Standards-Based and Database-Driven Approaches for IVDs

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FDA-Industry IVD Roundtable Meeting
Nov 20, 2015

# The President'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.*

# 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

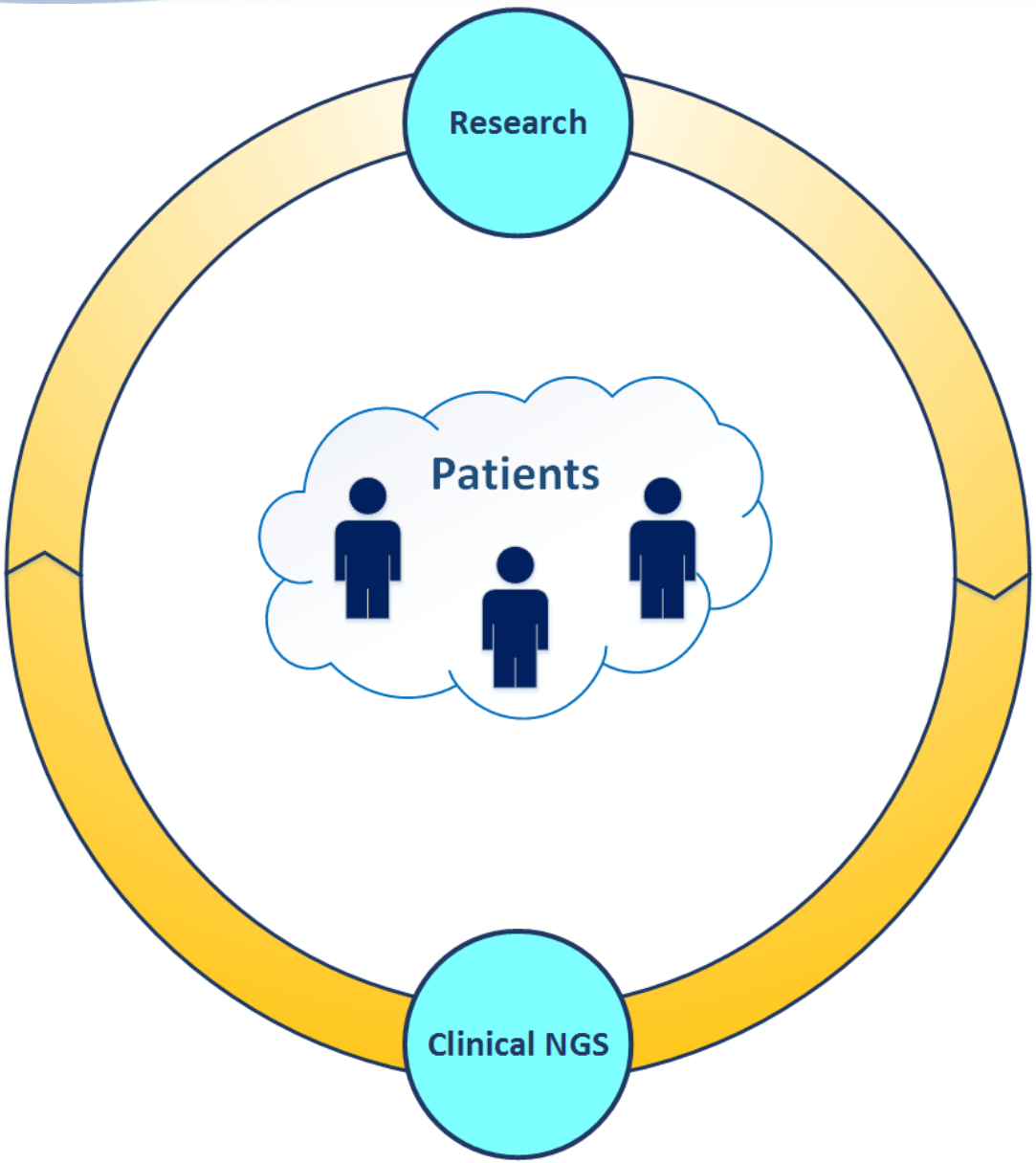
# Precision Medicine Initiative: Modernizing FDA Regulation of Genomic Tests

Traditional testing

Next generation

# 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


Research
Patients
Clinical NGS

# Precision Medicine Initiative - FDA

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

- Near Term: Implement standards and shared resources that will enable the development of knowledge for research and patient decision making
- Longer Term: Implement standards-based regulation of diagnostic tests that will ensure that the tests patients receive provide accurate, reproducible, and meaningful results

# Modernizing FDA Regulation of Genomics

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


**Develop and implement an adaptive standards-based regulatory approach**

# Public Engagement

- FDA workshop on Feb 20, 2015 discussed the overall vision

  http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm427296.htm
- Follow-on workshops to discuss technical details
  - Analytical performance - Nov 12, 2015

    http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm459449.htm
  - Clinical interpretation – Nov 13, 2015

    http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm459450.htm
- Oncopanel workshop - Feb 2016
- Patient/provider perspectives workshop – March 2016

# Public Workshop

# Standards Based Approach to Analytical Performance Evaluation of Next Generation Sequencing In Vitro Diagnostic Tests

# November 12, 2015

# A Spectrum of Approaches for Analytical Validity

***Performance Standards*** — ***Design Concept Standards***

***Intended Use***

Specific metrics and acceptance criteria that the test would have to satisfy

Process for test design and development without specified performance criteria

# Panel 1: Standards-based approaches to analytical validation - a spectrum from design concept standards to performance standards

- **Moderator:** Zivana Tezak, FDA
- **Panelists: Birgit Funke**, Harvard Partners; **Jared Maguire**, Counsyl; **Geoff Otto**, Foundation Medicine; **John Pfeifer**, Washington University School of Medicine; **Arend Sidow**, Stanford; **Erasmus Schneider**, Wadsworth / New York State Dept. of Health

# Panel 1 Conclusions

- Performance and analytical validation concerns
  - Coverage is not the same as accuracy
  - Confirmation bias (confirming only positives and not negatives)
  - Variations between runs due to complexity of system
- Difficult to design performance standards for all possible use cases
- Standards are needed
  - Various considerations: easy regions vs difficult regions, easy variants vs difficult variants, etc.
- Clarity about limitations of the test, transparency about how well the test performs

# Panel 2: Developing analytical standards for NGS-based assays

- **Moderator**: Adam Berger
- FDA **Panelists**: **Gil Alterovitz**, MIT/Global Alliance for Genomics and Health; **Deanna Church**, Personalis; **Lisa Kalman**, CDC; **Girish Putcha**, Palmetto / MolDX; **Catherine Rehder**, Duke/ACMG; **Karl Voelkerding**, ARUP / CAP

# Panel 2 Conclusions

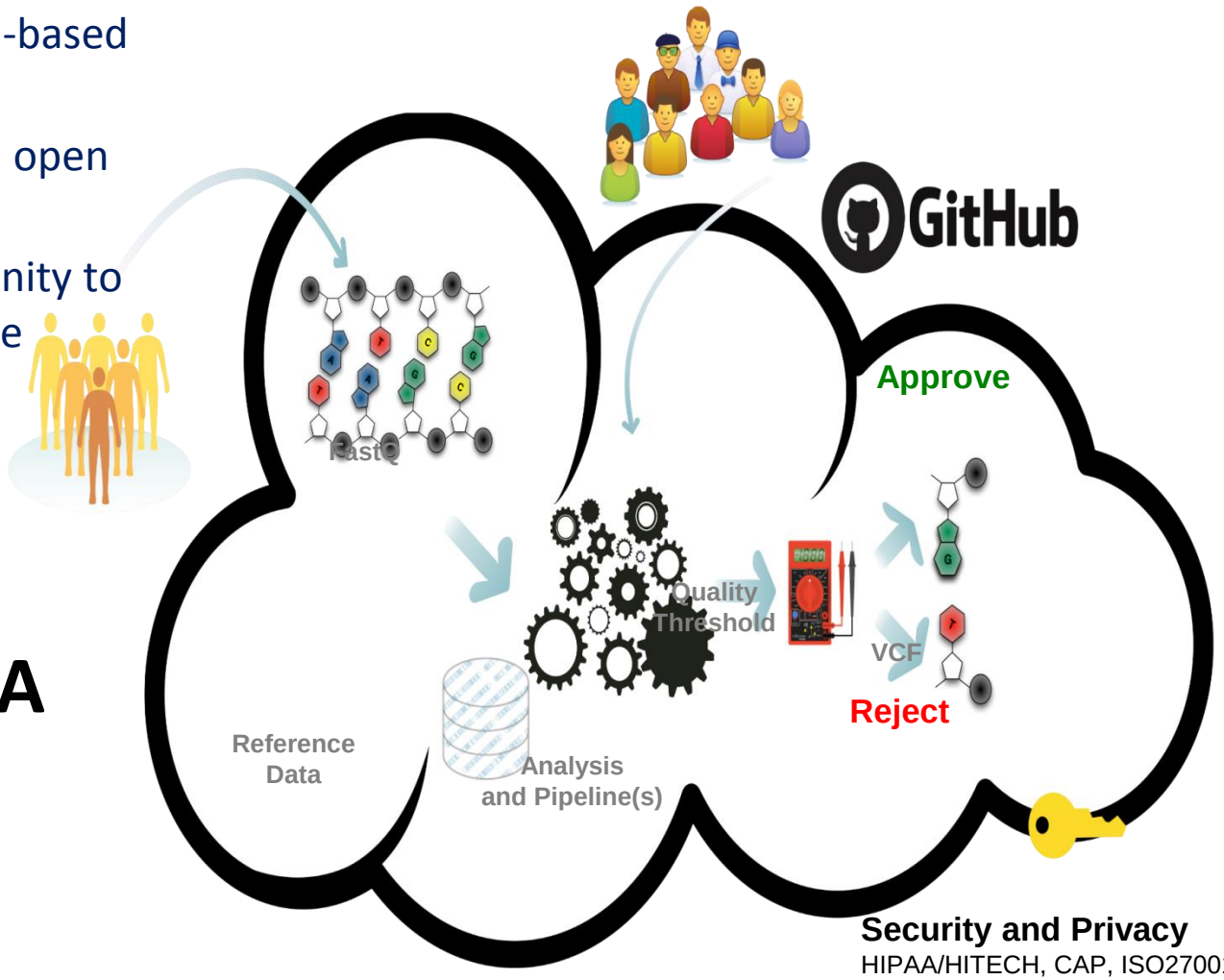
- NGS is already a pretty well-performing technology that may exceed abilities of other technologies.
- Reference materials are needed. Who will pay for this?
- There are many ways to describe the same variant. A common nomenclature or translator is needed.
- Need common nomenclature/standards for reporting test performance and test results.
- Proficiency testing (PT) is difficult given the lack of available materials.
- Questions raised about the role of in silico PT.
- Since research is feeding clinical development, and vice versa, apply standards to both areas.

## Community

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

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




# precisionFDA

## Security and Privacy

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

Courtesy of Taha Kass-Hout, FDA Chief Health Informatics Officer

# Panel 3: Developing bioinformatics strategies and tools for evaluating NGS tests

- **Moderator**: Sharon Liang, FDA
- **Panelists**: **Sean Davis**, NCI; **Tina Hambuch**, Illumina; **Sean Hofherr**, Children's National Medical Center; **Kevin Jacobs**, 23andMe; **Niall Lennon**, Broad Institute; **Narayanan Veeraraghavan**, Baylor College of Medicine

# Panel 3 Conclusions

- Labs have different practices for NGS software and test validation.
- Informatics should be treated as one system, and tuned to upstream input.
- Provenance and versioning of tools should be available.
- Third party bioinformatics companies should not be providing a black box service—should be a partnership with the lab.
- Lots of interest in participating in precisionFDA.

# Public Workshop

# Use of Databases for Establishing the Clinical Relevance of Human Genetic Variants

# November 13, 2015

# Databases as Sources of 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.

# Panel 1: Assessment of Database Quality

- Moderator: Katherine Donigan, FDA
- Panelists
  Jeff Allen (Friends of Cancer Research)
  William Biggs (Human Longevity Inc)
  Melissa Landrum (ClinVar/NIH)
  Saiju Pyarajan (Veterans Association)
  Sophia Yohe (CAP/University of Minnesota)

# Panel 1 Conclusions

- Analytical quality behind variant input is important, but often difficult to understand.
- Many observations may overcome data quality issues
- Need ontologies and nomenclatures for variants, metadata, etc.
- Can patients help with contributing this information about themselves?
- Sharing across databases would be really useful. APIs could be developed for this purpose.
- Need to maintain databases or make sure that data goes somewhere where it can still be accessed. ClinVar may be this place.
- Data sharing is time-consuming – need ways to incentivize this.
- Versioning is important even if labs don't go back and reinform patients.

# Panel 2: Curation of databases: clinical interpretation of genetic test results

- Moderator: Eunice Lee, FDA
- Panelists:
  Michelle Carrillo (PharmGKB/CPIC/Stanford)
  Shashi Kulkarni (ClinGen/Washington University)
  Donna Maglott (Human Variome Project/NIH)
  Erin Ramos (ClinGen/NIH)
  Karen Raraigh (CFTR2)
  Sarah South (23andMe)

# Panel 2 Conclusions

- Data should be looked at by many eyes. Doesn't necessarily require experts at every step, but SOPs and training should be in place. PT or competency assessment is needed.
- Different SOPs may be needed for different types of databases.
- Transparency of SOPs used for databases is important. A clearinghouse of SOPs might allow others to learn from what has already been done.
- Data derived in different ways, e.g. functional, outcomes, etc., may be weighted differently in databases. Levels of evidence can change over time.
- Database curators should try to assure that same data is not over-represented in databases. There are multiple ways to do this.
- Transparency and improving communication between databases is important.

# Panel 3: Communicating clinical interpretations of genetic variants

- Moderator: David Litwack, FDA
- Panelists:
  Ingrid Anderson (My Cancer Genome/Vanderbilt)
  Emily Edelman (Jackson Labs)
  Rachel Erlich (Foundation Medicine)
  Joy Haidle (National Society of Genetic Counselors)
  Heidi Rehm (ClinGen/Partners)
  Sherri Bale (ACMG/GeneDx)

# Panel 3 Conclusions

- Interpreting variants is hard and requires a lot of judgment
- Hard to know when to report VUS; depends on clinical context.
  - More straight-forward with single gene and targeted tests. Harder with exome and WG.
- Patients may be more interested in VUS than physicians; better patient engagement is needed.
- Reporting somatic variants is easier because driver mutations can be identified.
- Keep ClinVar alive!  It's a great resource.
- Need more patient and provider education—how to communicate with lab, and communicate results to patients
- Better communication between doctors and labs would be help interpretation.
- Opt in/opt out for return of results is a good idea..

Thank you

…And stay tuned!