Personalized Medicine Update

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AMDM Annual Meeting
April 27, 2017

Disclaimer: Thoughts on new regulatory issues and policies are preliminary and do not represent finalized FDA policy

Overview

- Codevelopment of Companion Diagnostics
- Emerging Complexities: Complementary Diagnostics and Liquid Biopsy
- Precision Medicine Initiative
  - Next-Generation Sequencing (NGS)
  - precisionFDA

Personalized Medicine

- The success of personalized medicine depends on having accurate, reproducible and clinically useful companion diagnostic tests to identify patients who can benefit from targeted therapies.
- Companion Diagnostics are those tests that provides information that is essential for the safe and effective use of a corresponding drug or biological product.

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FDA expectations for Companion Diagnostics

- Guidance finalized August 6, 2014 – Guidance for Industry and FDA Staff: In Vitro Companion Diagnostic Devices
- Defines companion diagnostic (CoDx) as being essential for the safe and effective use of a corresponding therapeutic product
- Describes FDA policies for approval and labeling
- Goal is contemporaneous regulatory approvals of the device and drug

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Many successful CoDx examples

	Companion Diagnostics in Oncology
36	Approved IVD Companion Diagnostic-Therapeutic Product Pairs
26	Approved IVD Companion Diagnostics
17	Approved Cancer Therapeutic Products
11	Molecular markers ALK, BRCA, BRAF, C-KIT, EGFR, HER-2/NEU, KIT, KRAS, PDGFRB, PD-L1, 17p deletion

- Plus 1 imaging device
- www.fda.gov/companiondiagnostics

(#'s as of 2/24/2017)

Draft Guidance: Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product

- Intended to provide the “how to” –- the practical aspects of codevelopment to support the design and implementation of successful codevelopment programs
- Published on July 15, 2016
- Webinar: http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm511178.htm

Codevelopment Draft Guidance in Brief (I)

- Interact with FDA early and often
- Use clinical trials strategy that provides evidence for both the therapeutic product and IVD (see also Enrichment Draft Guidance)
- Plan ahead for the IVD – collect specimens (annotate and store well) for AV studies, bridging studies
- Engage IVD partner as soon as possible

Codevelopment Draft Guidance in Brief (II)

- Determine what IDE requirements apply to the investigational IVD
- Complete analytical validation studies before using IVD in trial
- Use test with “market-ready” performance in pivotal trials
- Relevant beyond companion diagnostics

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“Complementary” IVDs

- Many different definitions
- No formal regulatory definition
- New concept (?)

Companion or “Complementary”?

- A **companion diagnostic** is an IVD that provides information that is essential for the safe and effective use of a corresponding therapeutic product
- A **complementary diagnostic** is an IVD that identifies a biomarker-defined subset of patients with a different benefit-risk profile than the broader population for which a therapeutic product is indicated, but that is not a prerequisite for receiving the therapeutic product

THIS IS NOT AN OFFICIAL DEFINITION

Companion vs. “Complementary”

pembrolizumab

- Studied only in PD-L1-positive NSCLC pts
- Companion Dx required/part of drug indication
- PD-L1 IHC 22C3 pharmDX
  - IU (excerpt): indicated as an aid in identifying NSCLC patients for treatment with KEYTRUDA® (pembrolizumab).
  - Tps ≥ 50% of viable tumor cells have membrane staining

nivolumab

- No specific PD-L1 eligibility requirement; Prespecified analysis suggests better response when PD-L1 present
- No companion Dx/not in drug indication
- PD-L1 IHC 28-8 pharmDx
  - IU (excerpt): PD-L1 expression as detected by PD-L1 IHC 28-8 pharmDx in non-squamous NSCLC may be associated with enhanced survival from OPDIVO ® (nivolumab).
  - ≥1% staining

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“Complementary” IVD Approvals

	Intended Use (excerpts)
PD-L1 IHC 28-8 pharmDx	PD-L1 expression as detected by PD-L1 IHC 28-8 pharmDx in non-squamous NSCLC may be associated with enhanced survival from OPDIVO ® (nivolumab).
PD-L1 IHC 28-8 pharmDx	Positive PD-L1 status as determined by PD-L1 IHC 28-8 pharmDx in melanoma is correlated with the magnitude of the treatment effect on progression-free survival from OPDIVO®.
Ventana PD-L1(SP142) CDX ASSAY	PD-L1 expression in ≥ 5% IC determined by VENTANA PD-L1 (SP142) Assay in urothelial carcinoma tissue is associated with increased objective response rate (ORR) in a non-randomized study of TECENTRIQ™ (atezolizumab).

Complementary Diagnostics

- Questions:
  - How are they identified?
  - What goes into the drug label?
  - What goes into the IVD label?
  - What evidence is required?
  - Will contemporaneous approval be required?
- Developing guidance to answer some of these questions

Liquid Biopsies

- FDA-AACR Workshop: Liquid Biopsies in Oncology Drug and Device Development (July 2016)
  - Initiate broader dialogue; understand expectations
  - Focused on non-small cell lung cancer and circulating tumor DNA technologies
  - http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/pages/fda-aacr-liquid-biopsies-in-oncology-drug-and-device-development.aspx#bypslides

FDA Approval of a Liquid Biopsy Test

cobas EGFR Mutation Test v2 (using plasma specimens)

Roche Molecular Systems, Inc.

- First “liquid biopsy test” approved for NSCLC
- Approved on June 1, 2016, as a companion diagnostic to identify patients eligible for treatment with Tarceva (erlotinib).
- Approved on September 28, 2016, as a companion diagnostic to identify patients eligible for treatment with Tagrisso (osimertinib).
- Test was previously approved for same indication using FFPE tissue specimens.

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Analytical Performance

- Test = [Specimen to Result] (validate all steps)
- Pre-analytic steps are part of assay
  - e.g., plasma processing, ctDNA isolation
  - Every step from blood draw, plasma processing, to storage can greatly affect sample quality and ctDNA yield
- Validation with the intended specimen type, using clinical specimens from the intended population
  - May be limiting
- All studies should follow protocol in labeling
- Studies should demonstrate robustness at clinical cut-off, as needed
- Analytical validation precedes clinical validation

Lots of Promise but Lots of Work Remains

- Biology – many outstanding questions…
  - Plasma sampling, etc.
  - LB to Tissue concordance: Relevance to clinical outcomes, not just analytical status, should be demonstrated
- Lack of reference method / standards
- Points to need for validation with specimens with clinical information

Resources

FDA website on companion diagnostics: http://www.fda.gov/companiondiagnostics

FDA companion diagnostic guidance:
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf

FDA-AACR: Liquid Biopsies in Oncology Drug and Device Development (7/19/2016):
http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/pages/fda-aacr-liquid-biopsies-in-oncology-drug-and-device-development.aspx#bypslides

cobas EGFR Mutation Test v2 – SSEDs:
http://www.accessdata.fda.gov/cdrh_docs/pdf15/P150047B.pdf
http://www.accessdata.fda.gov/cdrh_docs/pdf15/P150044B.pdf

FDA Draft guidance on Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product:
http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm510824.pdf

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Precision Medicine - Tailoring Health Care

- The right treatment
- The right patient
- The right time

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

In Vitro Diagnostics in the Age of Precision Medicine

Traditional testing

Next generation

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

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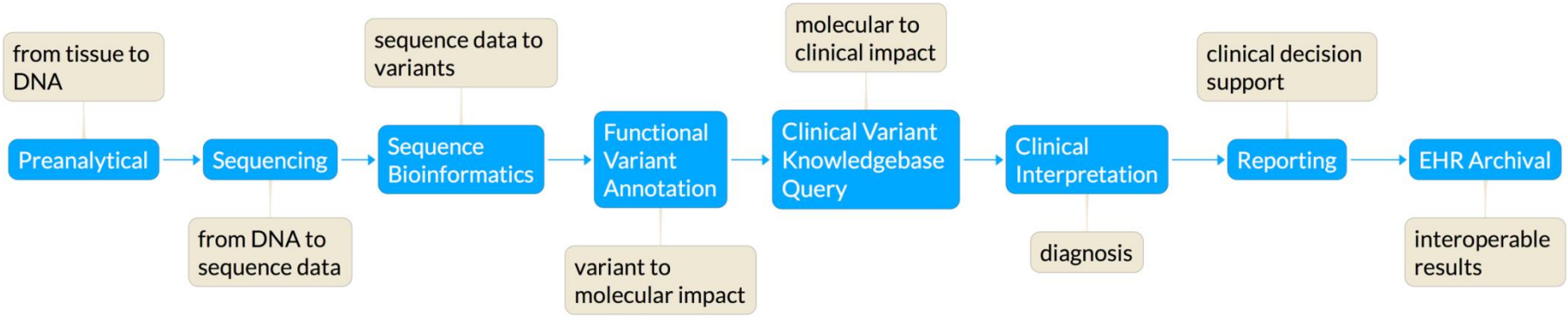
NGS workflow



Regulatory Issues

- NGS tests can have broad intended uses
  - Can't predefine the results that will be obtained
  - Often don't know the disease that will be diagnosed until the test is performed
- Validation of NGS tests at each variant is not feasible
- Conventional requirements for review
  - Review each claim
  - Review modifications that affect the safety and effectiveness of a test

Regulation of Genomic Laboratory Tests

- Need to ensure that the information that patients receive from NGS tests is accurate and relevant to their condition (analytically and clinically valid)
- ***Differences in data volume and interpretation may warrant a new regulatory approach*** that will ensure that patients and providers are able to make treatment decisions based on accurate test results (clinical utility).

Developing New Regulatory Approaches for Genomic Tests

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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.
- Support the development of ***databases*** for evidence on the clinical relevance of genetic variation.
- Advance regulatory science for NGS.

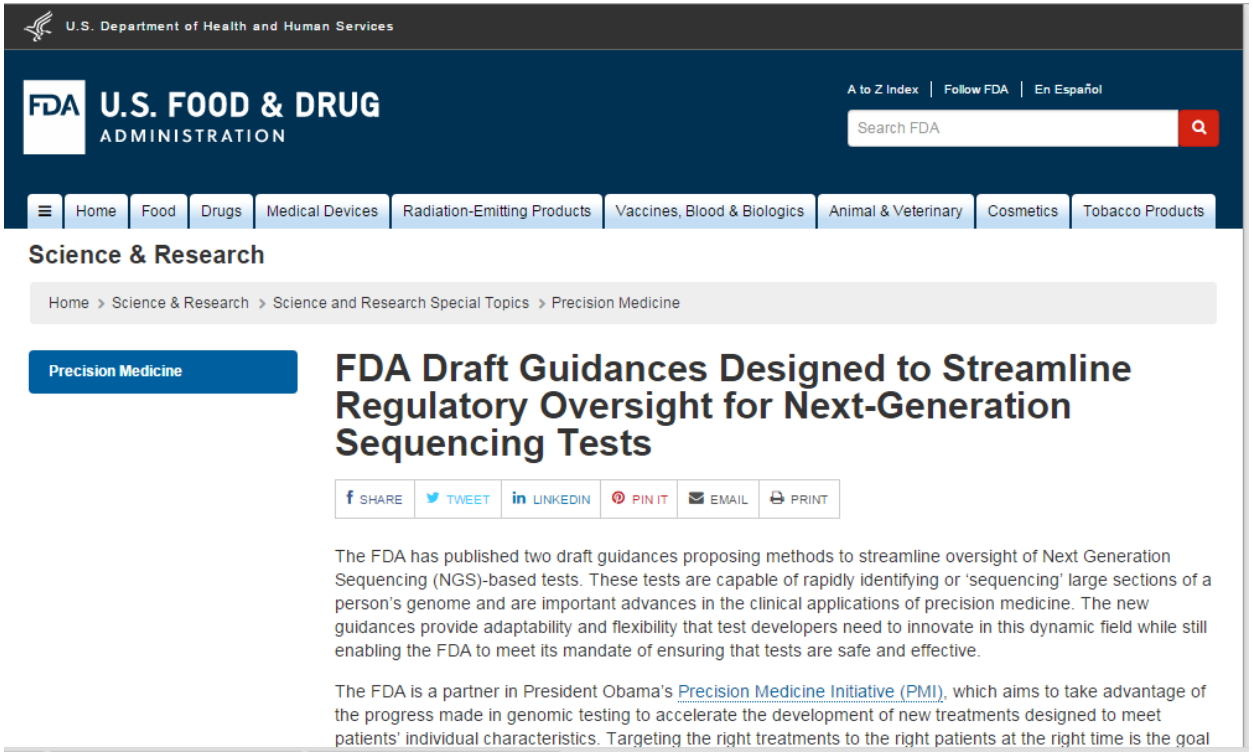
Public Input: Five Workshops

- FDA workshop to discuss the overall vision (February 2015)
  http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm427296.htm
- Follow-on workshops to develop technical details
  - Analytical performance (November 2015)
    http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm459449.htm
  - Clinical interpretation (November 2015)
    http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm459450.htm
- Patient/provider perspectives workshop (March 2016)
  http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm478841.htm
- Adapting Regulatory Oversight of Next Generation Sequencing-Based Tests (September 2016)
  http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm514720.htm

Key Themes from Public Engagement

- Analytical standards should be a combination of design process and performance standards
- Lots of interest in participating in precisionFDA
- Need clarity/transparency about test performance and limitations
- Need to incentivize data sharing
- Need common nomenclature/standards for test results – *essential for providers and patients*
- Need for development of more reference materials

FDA NGS Guidances



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Precision Medicine

FDA Draft Guidances Designed to Streamline Regulatory Oversight for Next-Generation Sequencing Tests

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The FDA has published two draft guidances proposing methods to streamline oversight of Next Generation Sequencing (NGS)-based tests. These tests are capable of rapidly identifying or 'sequencing' large sections of a person's genome and are important advances in the clinical applications of precision medicine. The new guidances provide adaptability and flexibility that test developers need to innovate in this dynamic field while still enabling the FDA to meet its mandate of ensuring that tests are safe and effective.

The FDA is a partner in President Obama's Precision Medicine Initiative (PMI), which aims to take advantage of the progress made in genomic testing to accelerate the development of new treatments designed to meet patients' individual characteristics. Targeting the right treatments to the right patients at the right time is the goal

Use of Standards in FDA Regulatory Oversight of NGS-Based IVDs for Diagnosing Germline Diseases

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- The draft guidance presents recommendations for the design, development, and validation of NGS-based tests to aid in diagnosis of genetic diseases or conditions:
  - Describes approach to test design (accommodates different test designs, indications for use, user needs, components, methods)
  - Test performance characteristics (including accuracy, precision)
  - Test run quality metrics (including read depth, completeness, performance thresholds)
  - Additional recommendations

- **Can form the basis for future FDA-recognized standard(s) and/or special controls**.

Scope:

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

Benefits of Using Genetic Databases

- Evidence generated by multiple parties; aggregated data provide a stronger evidence base (i.e., current state of scientific knowledge)
- As clinical evidence improves, new assertions could be supported
- Draft guidance applies to publicly accessible databases only
- 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

Draft Guidance - Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics

https://www.federalregister.gov/articles/2016/07/08/2016-16200/use-of-public-human-genetic-variant-databases-to-support-clinical-validity-for-next-generation

Use of FDA-Recognized Genetic Databases

- FDA evaluation of **policies and procedures**
  - Transparency
  - Types of variants the genetic variant database assertions address (e.g., germline, somatic)
  - SOPs, policies, or other documents; validation studies for interpretation SOPs
  - Documentation of personnel qualifications
  - Data preservation plan
  - Conflict of interest policies and disclosures of conflicts of interest
- Data and assertions from databases that follow the recommendations would generally constitute valid scientific evidence to support clinical validity claims
  - Assertions include a variety of variant types and descriptive language (including VUS)
  - Assertions should be appropriate to the level of certainty and the nature of the genotype-phenotype relationship and be adequately supported
  - Assertions that a particular genotype-phenotype association is clinically valid should generally involve multiple lines of evidence and should identify a primary source of scientific evidence
  - Assertions should not be false or misleading

FDA's Concepts for NGS Regulation

- **Technical/analytical standards for NGS**
  - Test developers that meet these standards may 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.
- **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 may be able to use such databases in lieu of traditional clinical studies.

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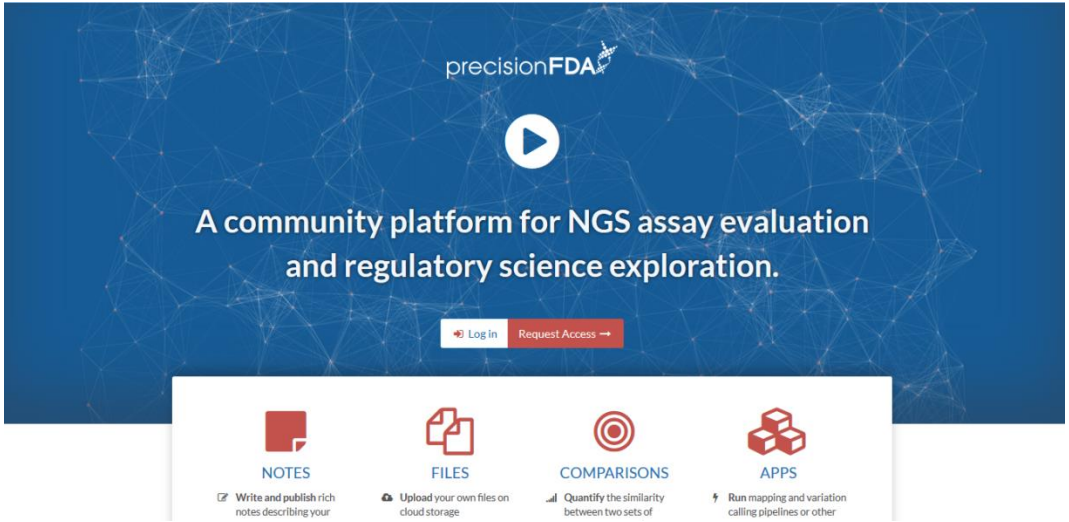

precisionFDA is a cloud based portal that engages a community of over 2500 users across the world. It allows researchers to experiment, share data and tools, and collaborate to help define standards for evaluating analytical pipelines.

precisionFDA and the Community

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precisionFDA provides…

- Resources
- Challenges
- A library of Reference Material, Tools, etc. including community contributions such as:
  - GA4GH VCF comparison tool
  - BWA-MEM mapper
  - GATK 3.5 licensed to precisionFDA
  - VarSim simulator
  - NA12878 NIST, Garvan, and Platinum Genome sequences
- Ability to “dockerize” applications for ease of use, transportability and consistency in performance across platforms

Members include…

- NGS-based test providers
- Standards-making bodies
- Pharmaceutical & Biotechnology Companies
- Healthcare providers
- Academic medical centers
- Research consortia
- Government Agencies

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

Participate in the

Consistency Challenge

Understand our

Community Guidelines

Test Set

VCF	NA12878-Garvan-Vial1.hc.vqsr.vcf.gz
TBI	NA12878-Garvan-Vial1.hc.vqsr.vcf.gz.tbi
BED OPTIONAL	Not set

with

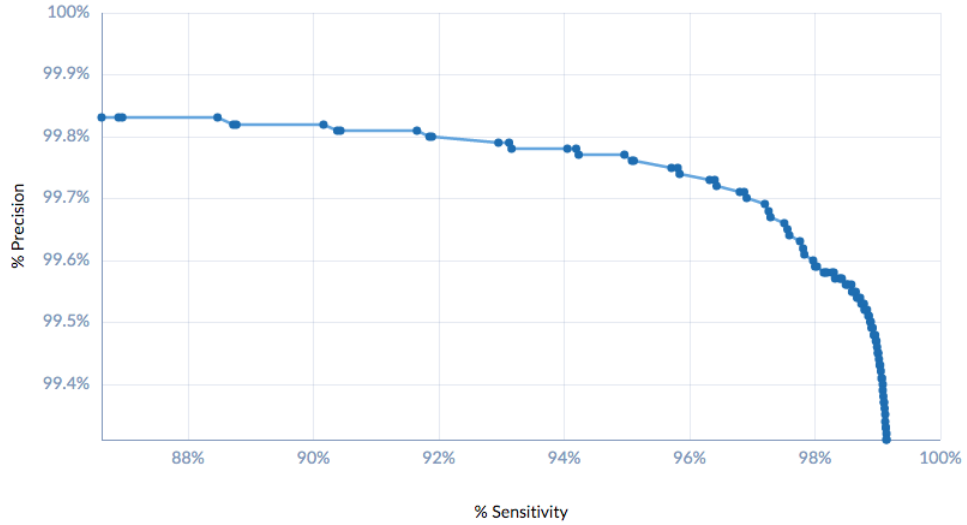
Benchmark Set

VCF	NA12878-NISTv2.19.vcf.gz
TBI	NA12878-NISTv2.19.vcf.gz.tbi
BED OPTIONAL	NA12878-NISTv2.19.bed

PRECISION	99.31%
RECALL	99.14%
F-MEASURE	99.22%

TRUE-POSITIVES	3,123,990
FALSE-POSITIVES	21,846
FALSE-NEGATIVES	27,029

CURVE FOR PRECISION VS SENSITIVITY PER GQ SCORE



Fork Coverage of Key Genes

APP NAME key_gene_coverage TITLE Coverage of Key Genes

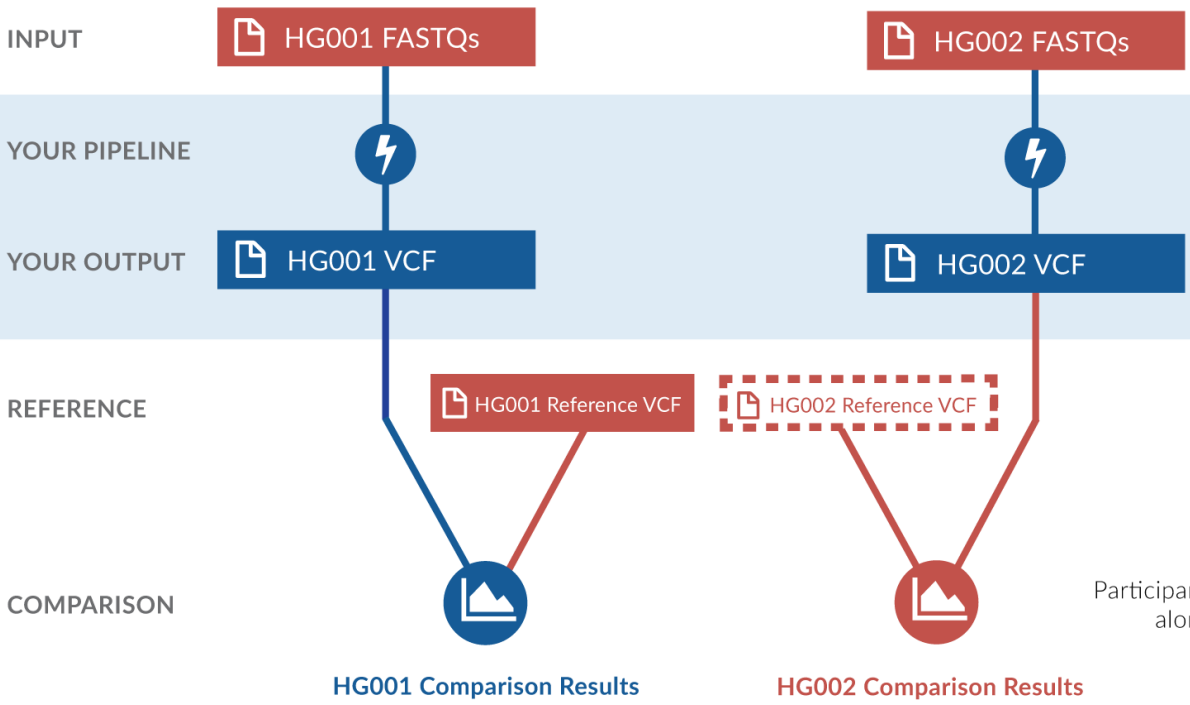
I/O SPEC Configure Input & Output Fields | VM ENVIRONMENT Configure your resources | SCRIPT Write your shell script | README Describe your app

Need help? Learn more about the app script

```
##############################################
# 1. Run GATK Depth of Coverage
##############################################

mkdir coverage
mv $bai_path /work/in/bam/

java -Xmx"$mem"G -jar "$gatk_path" \
  -T DepthOfCoverage \
  -mbq "$bq" \
  -mmq "$mq" \
  -L "$gene_list_path" \
  -I "$bam_path" \
  --summaryCoverageThreshold 0 \
  -R "$ref_genome" \
  -o coverage/"$bam_prefix"."$bq"bq."$mq"mq.txt

head coverage/"$bam_prefix"."$bq"bq."$mq"mq.txt
##############################################
# 2. Turn GATK output text file into a bed file
##############################################

awk -v OFS="\t" -v c="$cov" 'NR>1{if($2 >= c){split($1, a, ":"); print a[1],a[2]-1,a[2]}}' coverage/"$bam_prefix"."$bq"bq."$mq"mq.txt  \
  >  coverage/"$bam_prefix"."$bq"bq."$mq"mq.bed

head coverage/"$bam_prefix"."$bq"bq."$mq"mq.bed

##############################################
# 3. Intersect output bed with orig gene list
##############################################
words=$(wc -l < coverage/"$bam_prefix"."$bq"bq."$mq"mq.bed)
```

PrecisionFDA Truth Challenge

April 26, 2016 through May 26, 2016



CHALLENGE LAUNCH: APRIL 26th, 2016
Input files are made available

APRIL 26th - MAY 26th, 2016
Participants use the same pipeline on both input samples

DEADLINE: MAY 26th, 2016
HG002 Reference VCF revealed

Participants run the HG001 comparison and submit it along with their HG001 and HG002 output VCFs

PrecisionFDA runs the HG002 comparison after the challenge deadline

Summary of HG002 results | Datasets

Label	Submitter	Organization	SNP-Fscore	SNP-recall	SNP-precision	INDEL-Fscore	INDEL-recall	INDEL-precision
anovak-vg	Adam Novak et al.	vgteam	98.4545 %	98.3357 %	98.5736 %	70.4960 %	69.7491 %	71.2591 %
astatham-gatk	Aaron Statham et al.	KCCG	99.5934 %	99.2091 %	99.9807 %	★ 99.3424 %	★ 99.2404 %	★ 99.4446 %
asubramanian-gatk	Ayshwarya Subramanian et al.	Broad Institute	98.9379 %	97.9985 %	99.8954 %	98.8418 %	98.5404 %	99.1451 %
bgallagher-sentieon	Brendan Gallagher et al.	Sentieon	★ 99.9296 %	99.9673 %	99.8919 %	99.2678 %	★ 99.2143 %	99.3213 %
cchapple-custom	Charles Chapple et al.	Saphetor	99.8448 %	99.8832 %	99.8063 %	99.1388 %	98.8448 %	★ 99.4346 %
ccogle-snppet*	Christopher Cogle et al.	CancerPOP						
ciseli-custom	Christian Iseli et al.	SIB	97.7648 %	98.8356 %	96.7169 %	83.5453 %	82.5314 %	84.5844 %
ckim-dragen	Changhoon Kim	Macrogen	99.8268 %	★ 99.9524 %	99.7015 %	99.1359 %	★ 99.1574 %	99.1143 %
ckim-gatk	Changhoon Kim	Macrogen	99.6466 %	99.4788 %	99.8150 %	99.2271 %	★ 99.1551 %	99.2992 %
ckim-isaac	Changhoon Kim	Macrogen	98.5357 %	97.1616 %	★ 99.9494 %	95.8099 %	93.7006 %	98.0163 %
ckim-vqsr	Changhoon Kim	Macrogen	99.2866 %	98.6511 %	★ 99.9303 %	99.2541 %	99.0614 %	★ 99.4476 %
dgrover-gatk	Deepak Grover	Sanofi-Genzyme	★ 99.9456 %	★ 99.9631 %	★ 99.9282 %	99.4009 %	99.3458 %	★ 99.4561 %
egarrison-hhga	Erik Garrison et al.	-	99.8985 %	99.8365 %	★ 99.9607 %	97.4253 %	97.1646 %	97.6874 %
eyeh-varpipe	ErhChan Yeh et al.	Academia Sinica	99.4670 %	★ 99.9638 %	98.9751 %	92.5779 %	91.3854 %	93.8021 %
gduggal-bwafb	Geet Duggal et al.	DNAnexus Science	99.7820 %	99.8619 %	99.7021 %	96.9474 %	95.5004 %	98.4390 %
gduggal-bwaplat	Geet Duggal et al.	DNAnexus Science	98.8646 %	98.0471 %	99.6958 %	92.6621 %	87.0843 %	99.0034 %
gduggal-bwavard	Geet Duggal et al.	DNAnexus Science	99.3249 %	99.0431 %	99.6083 %	87.3464 %	87.1769 %	87.5166 %
gduggal-snapfb	Geet Duggal et al.	DNAnexus Science	99.2501 %	99.8026 %	98.7037 %	92.2602 %	90.5733 %	94.0112 %
gduggal-snapplat	Geet Duggal et al.	DNAnexus Science	99.0030 %	98.6815 %	99.3266 %	76.4210 %	69.0418 %	85.5664 %
gduggal-snapvard	Geet Duggal et al.	DNAnexus Science	99.0871 %	98.9341 %	99.2406 %	83.0264 %	83.4429 %	82.6139 %
ghariani-varprowl	Gunjan Hariani et al.	Quintiles	99.3496 %	99.8685 %	98.8361 %	87.2025 %	87.3272 %	87.0781 %
hfeng-pmm1	Hanying Feng et al.	Sentieon	★ 99.9496 %	★ 99.9227 %	★ 99.9766 %	★ 99.3397 %	99.0289 %	★ 99.6526 %
hfeng-pmm2	Hanying Feng et al.	Sentieon	★ 99.9416 %	★ 99.9254 %	★ 99.9579 %	★ 99.3119 %	99.0152 %	★ 99.6103 %
hfeng-pmm3	Hanying Feng et al.	Sentieon	★ 99.9548 %	★ 99.9339 %	★ 99.9756 %	★ 99.3628 %	99.0161 %	99.7120 %
jlack-gatk	Justin Lack	NIH	99.7200 %	★ 99.9393 %	99.5016 %	98.6899 %	98.8138 %	98.5664 %
jli-custom	Jian Li et al.	Roche	★ 99.9382 %	★ 99.9603 %	99.9160 %	★ 99.3675 %	99.0788 %	★ 99.6580 %
jmaeng-gatk	Ju Heon Maeng	Yonsei University	99.6144 %	99.4608 %	99.7686 %	99.1098 %	99.0216 %	99.1981 %

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April 2017 Expert Spotlight:

My Challenge to the PrecisionFDA Community

April 3, 2017

Adam Resnick, PhD
Children's Hospital of Philadelphia

1. How might the pediatric cancer and rare disease community best engage the precisionFDA NGS assay development community and sponsor the further development of a sustainable compete-to-share ecosystem for collaborative discovery on behalf children?

2. How can the precisionFDA bioinformatics community be better empowered to partner with the pediatric cancer and rare disease community through a shared economy of accessible data and a shared interest in new models of attribution and/or reproducibility of results?

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Overview

- Codevelopment of Companion Diagnostics
- Emerging Complexities: Complementary Diagnostics and Liquid Biopsy
- Precision Medicine Initiative
  - Next-Generation Sequencing (NGS)
  - precisionFDA

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