U.S. FOOD & DRUG ADMINISTRATION

NIST-FDA Genome Editing Workshop

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Gaithersburg, MD
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Overview

- Personalized Medicine Efforts
- Next Generation Sequencing Based Tests
  - Final Guidances
  - Recent Approvals (Oncopanels)
- CDRH Strategic Priorities
  - Collaborative Communities

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

FDA Personalized Medicine Efforts

- Targeted Therapeutic Development
  - Pharmacogenetics
    - 192 drugs with PGx in label (as of 7/29/17) across 18 therapeutic areas
  - Immunotherapies
- Personalized Biologics
  - 3D printed organs
  - Genome editing
- Food Safety
  - Outbreak tracking
- Genetic Testing
  - Oncopanels
  - Next-Generation Sequencing (NGS)
  - Liquid Biopsy

Scientific Review : IVD Performance

- Analytical Performance Characteristics
  - Reliability and accuracy of analyte measurements
  - Studies specific to the assay technology such as accuracy for molecular assays

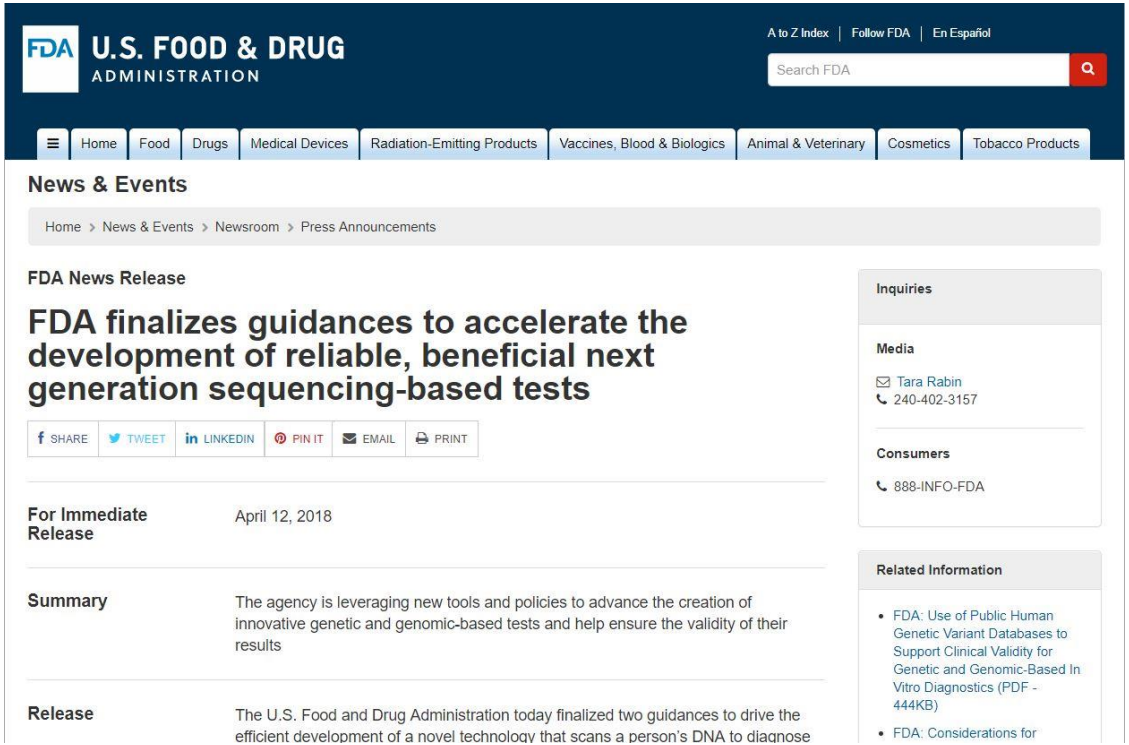
- Clinical Performance Characteristics
  - Clinical sensitivity and specificity
  - Positive and negative predictive values

- Labeling
  - Intended use, device design, directions for use, warnings/limitations, result interpretation, performance

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

- **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.

Final Guidances Issued (04/12/2018)



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FDA News Release

FDA finalizes guidances to accelerate the development of reliable, beneficial next generation sequencing-based tests

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For Immediate Release April 12, 2018

Summary The agency is leveraging new tools and policies to advance the creation of innovative genetic and genomic-based tests and help ensure the validity of their results

Release The U.S. Food and Drug Administration today finalized two guidances to drive the efficient development of a novel technology that scans a person's DNA to diagnose

Inquiries

Media

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Consumers

888-INFO-FDA

Related Information

- FDA: Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics (PDF - 444KB)
- FDA: Considerations for

https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM509837.pdf

https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM509838.pdf

2018: Finalization of NGS Guidances

Analytical Guidance overview:

- 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.
- 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

Recommendations for Design, Development, and Validation

- Test **design** considerations:
  - Approach to test design
  - Recommendations are flexible, to accommodate different test designs, components, indications, etc.
- Test **performance characteristics**
  - Accuracy, precision, LoD, analytical specificity
- Test **run quality** metrics
  - Including read depth, completeness
- General recommendations for performance **evaluation studies**

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

Additionally, guidance includes:

- Discussion on supplemental procedures such as trio testing or orthogonal confirmation
- Variant annotation and filtering considerations
- Recommendations for presentation of test performance / labeling such as:
  - Identify regions of the genome in which sequence **meeting pre-specified performance specifications** can be generated by the NGS-based test
  - Types of sequence **detected and reported** by the test
  - Types of sequence **variants test cannot detect** with adequate accuracy and precision
  - **Performance summary**
  - The relationship between reported variants and the clinical presentation, as applicable
- How to address NGS test modifications

Significance of NGS Standards Guidance

- Provides **key considerations** for designing, developing, and establishing analytical validity of NGS-based tests for suspected germline diseases
- Informs the development of **consensus standards** by experts in the community
- Recommendations in this guidance and/or standards that address these recommendations may form the basis of **special controls**, allowing these tests to be candidates for down-classification
  - Could be considered for exemption from premarket notification if they meet certain criteria

2018: Finalization of NGS Guidances

Database Guidance overview:

- 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"
- Evidence from databases could support the clinical validity of NGS-based tests

- **Voluntary database recognition pathway** (similar to standards recognition)

Benefits of Using Data from Publicly Accessible 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

Webinar

- On Thursday, May 24 from 2:00 – 3:30PM ET, we will have a webinar about these final guidances. You can find more information about the webinar at http://www.fda.gov/CDRHwebinar.

First FDA Authorizations of NGS Platform and Assays

	Intended Use	Analytical Performance	Clinical Performance
MiSeqDx Platform	targeted sequencing of human genomic DNA.	• Clinical and cell line samples • Well-standardized panel with known variants • Performance demonstrated on a representative set of variants	NA
Universal Kit 1.0	use with the MiSeqDx instrument.	See above	NA
Cystic Fibrosis Clinical Sequencing Assay	re-sequences the protein coding regions and intron/exon boundaries of the CFTR gene; reports *any variant* in the cystic fibrosis gene	Validation of both specific variants and CFTR normal sequence	Well-established association of CFTR and CF; expert interpretation
Cystic Fibrosis 139 Variant Assay	simultaneously detect 139 clinically relevant cystic fibrosis disease-causing mutations and variants of the CFTR gene; reports only a *discrete number of variants* with established clinical significance	Specific validation of 139 variants	Use of the CFTR2 database (JHU) for evidence

Approvals of NGS-based Companion Diagnostics

CDx test provides **essential** information for the safe and effective use of the therapeutic product.

- **FoundationFocus CDxBRCA Assay** (Foundation Medicine, Dec 2016): **First NGS CDx**
- **Oncomine Dx Target Test** (Thermo Fisher, June 2017): First CDx to **simultaneously evaluate multiple biomarker/therapy** for NSCLC) - 3 CDx claims, 23 genes
- **Praxis Extended RAS Panel** (Illumina, June 2017): First NGS CDx **based on "negative" mutation** finding

Summary of Safety and Effectiveness Data (SSED) for each device approval:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P160018
https://www.accessdata.fda.gov/cdrh_docs/pdf16/p160045b.pdf
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160038

Recent NGS-based test approvals

- **MSK-IMPACT**
  - Solid tumor panel
  - 468 genes + MSI
  - De Novo set up Class II pathway, potential 3rd party review

- FDA authorized the first **NGS Tumor Profiling Oncopanel** (MSK-IMPACT) on November 15, 2017.
- The *De Novo* authorization established a **new class II regulatory pathway** for NGS tumor profiling tests. Future NGS tumor profiling tests are **eligible for 510(k)** clearance process, either by applying directly **to FDA or** through an accredited **third-party reviewer** (such as NYSDOH).

- **Foundation Medicine's F1CDx**
  - Solid tumor panel
  - 15 CDx claims in 5 cancer types
  - 324 genes + MSI, TMB

1st Breakthrough-Designated Test to Detect Extensive Number of Cancer Biomarkers

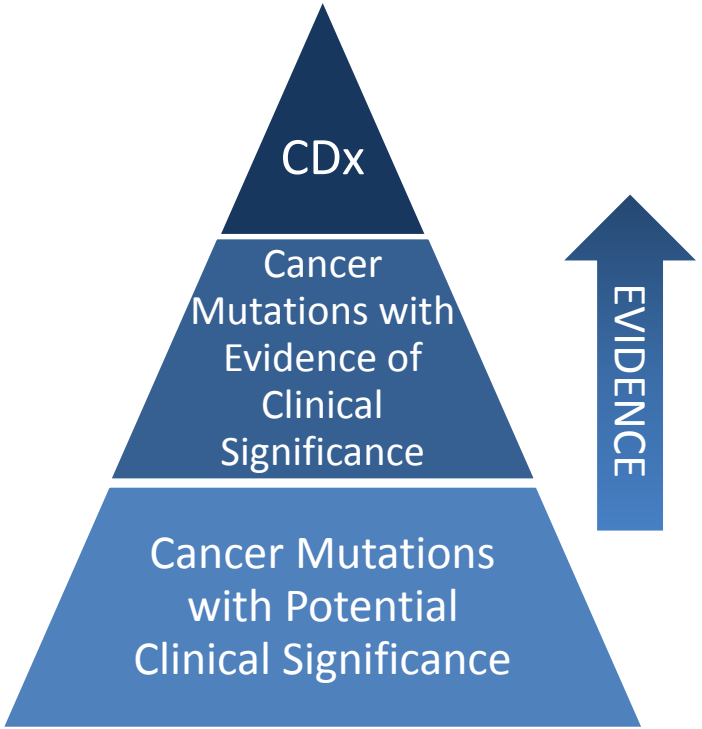
- Parallel review – received a NCD from CMS

Three Tiered Approach for Reporting Biomarkers in Cancer Panels

Level 1 companion diagnostics: AV for each biomarker; CV established by clinical study or clinical concordance with a previous CDx

Level 2 biomarkers: AV either per biomarker or representative; CV established in professional guidelines, but **NOT** demonstrated with the test.

Level 3 biomarkers: AV by representative approach; CV validity not demonstrated either in professional guidelines or with the test, but suggestive based on clinical/biological evidence.

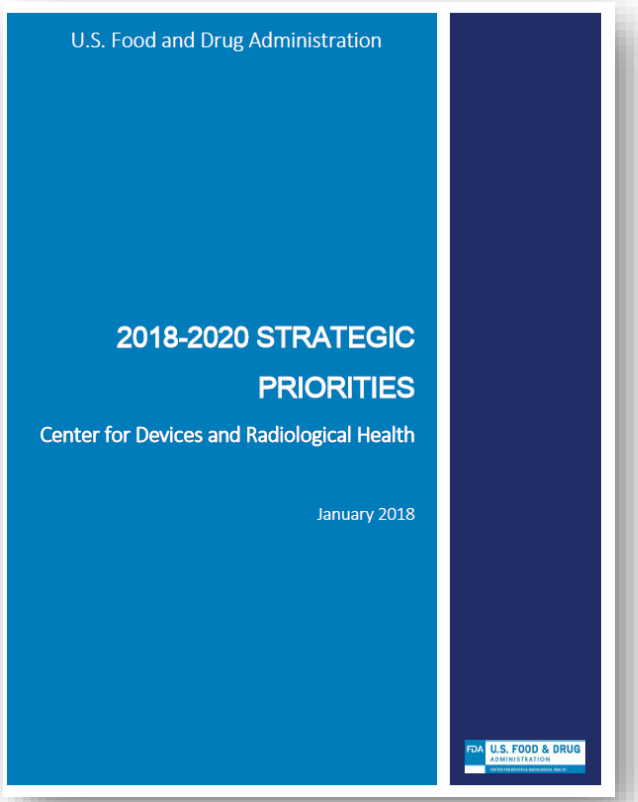


CDRH Strategic Priorities

Collaborative Communities

The hallmark of a Collaborative Community is a continuing forum where public and private sector members proactively work together to solve both shared problems and problems unique to other members in an environment of trust and openness, where participants feel safe and respected to communicate their concerns.

- Goal to create 10 new Collaborative Communities by 2020.



https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHVisionandMission/UCM592693.pdf

Questions?

- **Gene editing – methodologies for detection of mutations that were created?**
  - Potential of using NGS for evaluating “off-target” editing effects such as insertions or deletions at unintended genetic loci?

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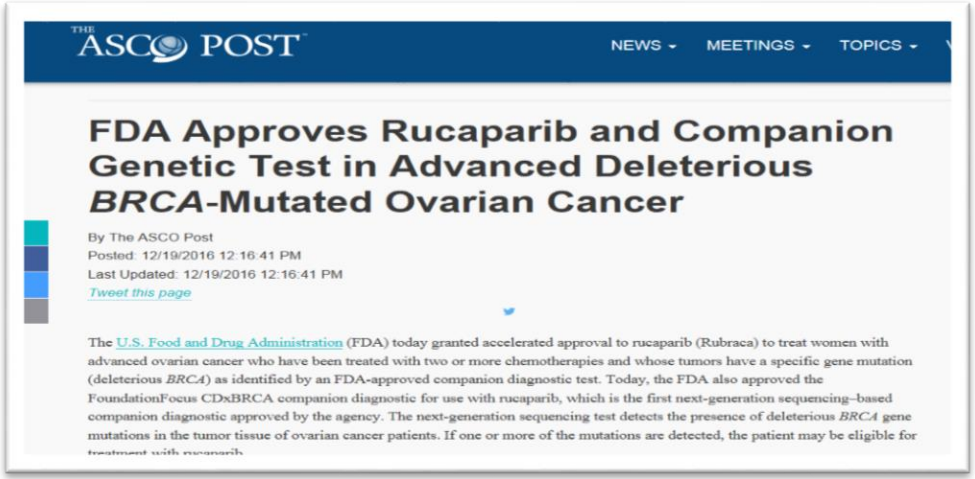
FOUNDATIONFOCUS™ CDx BRCA

FDA

- **First NGS-based CDx approved by FDA**
- CDx that detects *BRCA1/2* variants in tumor tissue – Rubraca (rucaparib)
- NGS-based assay performed on DNA (200ng) from FFPE biopsy or surgical resection specimens
- Uses the Illumina HiSeq 4000 platform, hybrid-capture-selected libraries sequenced to median 500X with >99% of exons at coverage >100
- Custom-developed analysis pipeline identifies *BRCA1/2* SNVs, short indels up to 13 bp, large rearrangements and homozygous deletions



THE ASCO POST

NEWS MEETINGS TOPICS

FDA Approves Rucaparib and Companion Genetic Test in Advanced Deleterious *BRCA*-Mutated Ovarian Cancer

By The ASCO Post
Posted: 12/19/2016 12:16:41 PM
Last Updated: 12/19/2016 12:16:41 PM
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The U.S. Food and Drug Administration (FDA) today granted accelerated approval to rucaparib (Rubraca) to treat women with advanced ovarian cancer who have been treated with two or more chemotherapies and whose tumors have a specific gene mutation (deleterious *BRCA*) as identified by an FDA-approved companion diagnostic test. Today, the FDA also approved the FoundationFocus CDxBRCA companion diagnostic for use with rucaparib, which is the first next-generation sequencing–based companion diagnostic approved by the agency. The next-generation sequencing test detects the presence of deleterious *BRCA* gene mutations in the tumor tissue of ovarian cancer patients. If one or more of the mutations are detected, the patient may be eligible for

Praxis Extended RAS Panel

- **First single NGS test to detect multiple RAS mutations approved by FDA**
- The Praxis™ Extended RAS Panel is a qualitative in vitro diagnostic test using targeted high throughput parallel sequencing for the detection of 56 specific mutations in RAS genes [KRAS (exons 2, 3, and 4) and NRAS (exons 2, 3, and 4)] in DNA extracted from formalin-fixed, paraffin-embedded (FFPE) colorectal cancer (CRC) tissue samples.
- The Praxis™ Extended RAS Panel is indicated to aid in the identification of patients with colorectal cancer for treatment with Vectibix® (panitumumab) based on a **no mutation detected** test result. The test is intended to be used on the Illumina MiSeqDx® instrument.

June 2017