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Next Generation Sequencing Regulatory Update

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October 8, 2015
AMDM's 2015 IVD Focus Meeting
Los Gatos, California

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Risk-Based Regulation

Non-investigational clinical use

3 classification levels:

- **Class I**: low risk –usually no premarket submission
- **Class II**: moderate risk – usually 510(k), de novo
- **Class III**: high risk – usually PMA

Risk is based on consequences of a false result in the context of clinical care

Elements of FDA Premarket Review

- Analytical performance
  - Correctly detects analyte
  - Accuracy, precision, limits of detection/measurement
- Clinical performance
  - Correctly identifies disease/condition
  - Clinical sensitivity, clinical specificity, predictive values
- Labeling

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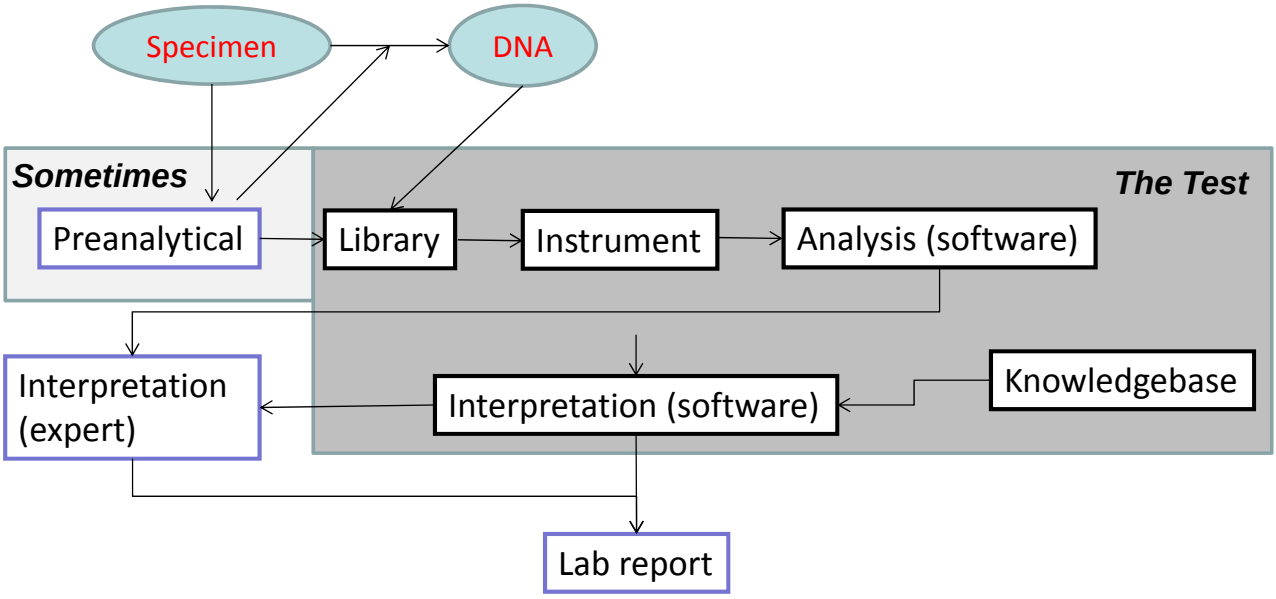
What is an "NGS test"?



Special issues with NGS

- Lack of specific intended use
  - Can simultaneously diagnose multiple conditions
  - Incidental findings
- Can't predefine what the test will detect
  - Even a single gene test could detect previously unobserved variation
- Unprecedented ability to detect rare variants
- Difficulty in communicating results to physicians and patients
- Rapidly evolving technology
- High throughput allows discovery to outpace understanding

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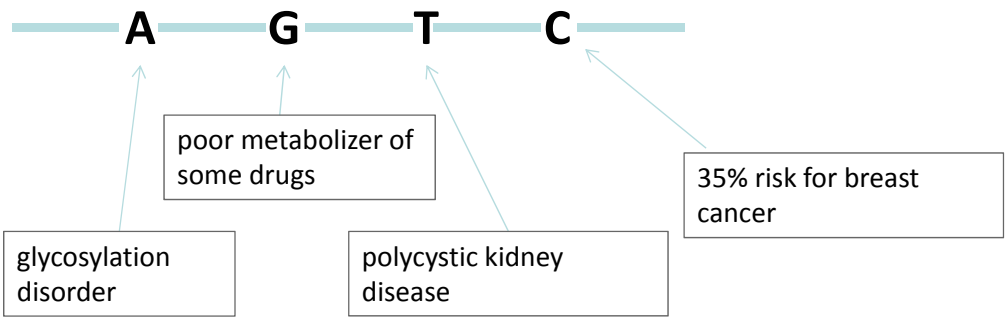
The problem of incidental findings

Rare disease testing



- Performance requirements may vary depending on results
- Results aren't known until test is run
- How will FDA apply risk-based regulation to NGS?

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Clearance 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	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	Specific validation of 139 variants	Use of the CFTR2 database (JHU) for evidence

Analytical evaluation strategies

- Accuracy - approach - select and validate adequate subset of genetic markers → inference that **platform** as a whole analytically valid -
  - Enrich with analytically challenging markers, classes of variations
  - Include clinically relevant markers
  - Homopolymeric regions, indels, repeats, CNVs, redundant sequences, samples across the genome / chromosomes, etc
- Comparator / reference method; orthogonal methods? Standards or well characterized samples
- Hereditary diseases; mixed populations (cancer, infectious diseases)?
- Easy-to-call vs difficult regions – different performance expectations

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Analytical evaluation strategies (assays)

- Accuracy – for sequencing assay, genes, panels:
  - Sequence **clinical samples** from the intended use population and compare to reference method results (e.g., Sanger)
  - Sequence procured samples that span the classes of variations the assay is testing and compare to reference method results
  - Sequence well-characterized reference samples to determine error rates across amplicons in the assay and compare to reference sequence
  - Absence of variations

510(k) Decision Summary for 2 cleared sequencing assays –
http://www.accessdata.fda.gov/cdrh_docs/reviews/K124006.pdf
http://www.accessdata.fda.gov/cdrh_docs/reviews/K132750.pdf

CFTR2 Database (http://www.cftr2.org/)

Datatype	Information Captured
Mutation Name/Associated Nomenclature	Provides a standardized mutation name and mutation by amino acid and nucleotide number (relative to the CFTR gene)
Associated Clinical Characteristics	Provides the following relevant clinical characteristics: •Average sweat chloride value at time of diagnosis •Range of FEV1 percent predicted value based on age group •Percentage of patients with positive Pseudomonas aeruginosa culture •Percentage of pancreatic insufficient individuals
Functional Testing	Notes the results in vitro laboratory tests performed for applicable mutations. Specifically, assesses protein processing and maturation, CFTR dependent chloride current, and gene splicing.
Literature Review	Notes research previously completed on this particular mutation.
Annotation History	Provides a history of changes and timestamps of any revisions to the annotation.

Illumina Special Controls

- Specify the information that should be in the label
- Includes:
  - Read depth necessary for claimed sensitivity
  - Data demonstrating performance characteristics of instrument

Registered and Listed Sequencers

- High Throughput DNA Sequence Analyzer: A high throughput sequencing technology performing targeted DNA sequencing of amplicons from a defined genetic region or a subset of genes in human genomic DNA from a clinical sample.
- Class 2 exempt
- Illumina MiSeqDx
- Life Technologies Ion PGM Dx
- Vela Sentosa SQ301

Building on this approach: Why Now?

- Data has been accumulated in multiple centers that makes new approaches possible
- Current efforts by the community to create technical and performance standards are progressing
- Efforts at improving database quality and curating evidence have advances
- Rapid translation into clinic

Goals for FDA Regulatory Oversight of NGS

- Efficiency to allow innovation while protecting patients
  - Compress the time between discovery and clinical use
- Take into account the state of the technology and current practices
- Anticipate future developments in technology and practice

Desired Features of a Regulatory Framework

- Accommodate multiple test configurations on a single instrument.
  - Variations in library, informatics, etc. depending on use and what is being detected (e.g., CNVs, SNVs)
  - Users can select the right configuration if they have proper controls in place.
- Enable improvements by incorporating the ability to easily modify a test
  - Users can modify if they have proper controls in place
- Recognize that evidence supporting the clinical relevance of results will come from the community, not from the test developer.
  - Need to take advantage of high quality sources of evidence and community efforts
- Enable physicians and patients to access and understand genomic test results to advance clinical decision-making
- FDA oversight to ensure analytical and clinical performance

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Analytical: Performance Standards as a Regulatory Tool for NGS

Premarket Review
- Analytical performance for each test reviewed by FDA

Performance Standards
- FDA recognizes standards that guarantee analytical performance
- accredited inspections

- Are performance standards feasible?
- How should they be implemented?
- How should develop them?
- How should conformance to standards be verified, and by who?

Answers to these questions will determine where FDA lands.

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Should Analytical Standards Apply Only to Laboratories?

Premarket Review
- Manufacturers of assays and components
- Laboratories that purchase kits for use

Performance Standards
Laboratories that:
- assemble tests from components
- develop software
- perform interpretation

FDA Oversight of NGS Tests Using Performance Standards

- Regular review and acceptance of standards
- Regular review and acceptance of databases and/or clinical assertions about variants
- Regular accreditation of inspectors
- Adverse event reporting
- Premarket review of components and kits

Informatic solutions to analytical performance

Use vast genomic datasets now in existence to create new tools to assess the analytical performance of NGS tests

Is software possible that will verify the quality of an individual NGS run?

As part of its effort in the PMI, FDA will enable the development of this software and make it freely available to the genomics community.

Additional concepts include the establishment of systems to validate NGS software.

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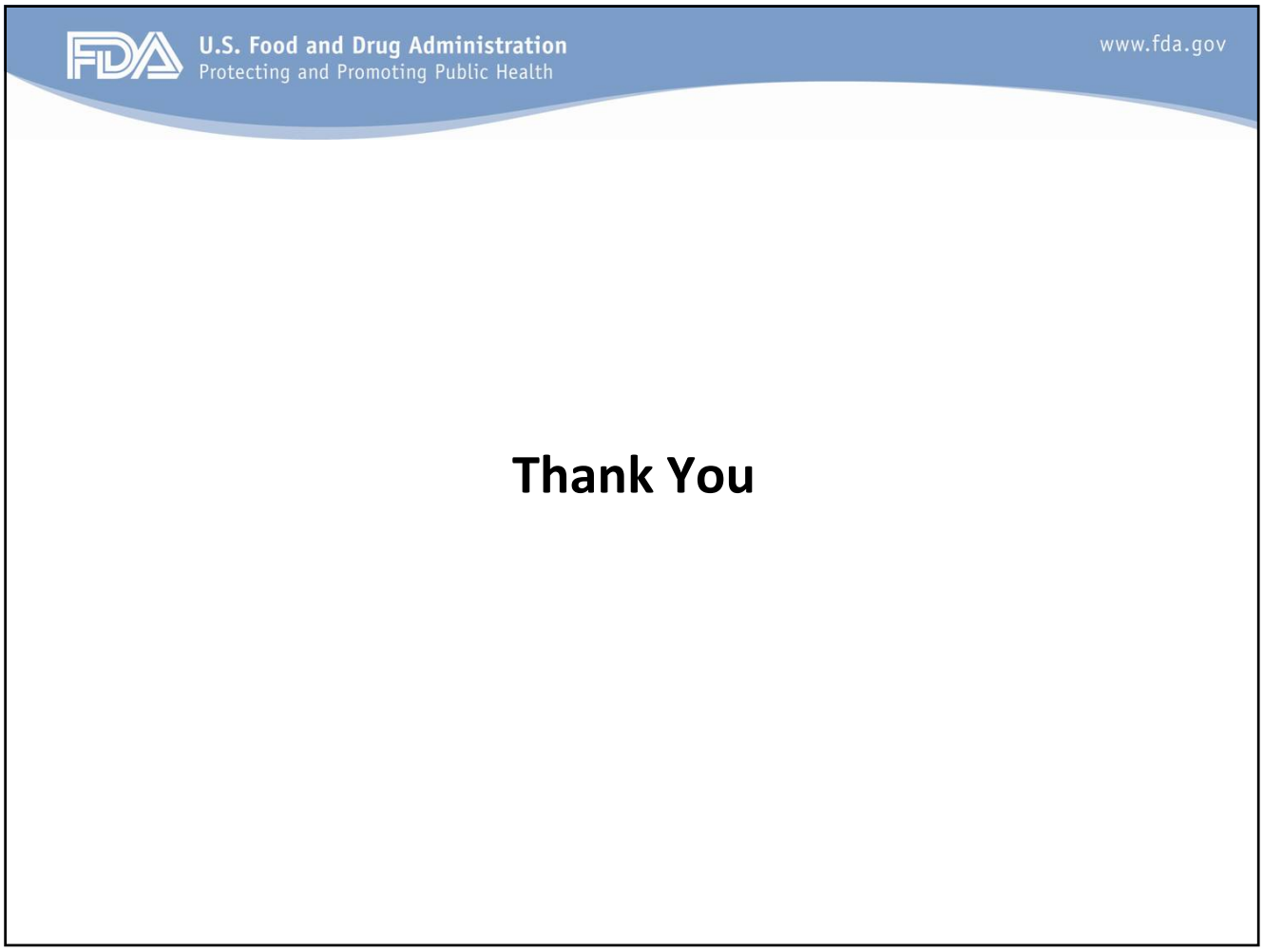
Using Databases to Assess the Clinical Performance of NGS Tests

- Replicate experience with CFTR2 on a large scale
- Concept of a "regulatory grade" curated database that provides evidenced on the strength of association between variants and diseases.
- If accepted by FDA, any test developer (manufacturer or laboratory) could use assertions supported by a predefined level of evidence to support clinical claims without any further requirements.
- Quality concepts
  - Annotation (patient, diagnostic, etc.
  - Versioning
  - Source of testing results
  - Procedures and practices
  - Sustainability
- Through PMI, FDA will assess and, if necessary, upgrading existing databases to assure sufficient quality for regulation.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Thank You