Forum NGS Proficiency Panel Project Meeting

Optimizing FDA’s Regulatory Oversight of Next Generation Sequencing Diagnostic Tests

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<th>MiSeqDx Platform</th>
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|                  | 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 |
currently existing NGS classification

- **Reagents**
  - Class I exempt
    - 21 CFR 862.3800
    - Reagents for molecular diagnostic instrument test systems
    - Must comply with general controls
  - Class II exempt
    - 21 CFR 862.2265
    - Subject to limitations in 862.9
    - High throughput genomic sequence analyzer for clinical use
    - Must comply with general and special controls

- **Platform**
  - Class II exempt
    - 21 CFR 866.5900
    - CFTR gene mutation detection system
    - Must comply with general and special controls
    - New product codes for sequencing assays
    - CFTR variant panel sequencing (clinically significant variants)
    - CFTR gene sequence detection

- **Assays / Whole System**
  - Class II
    - 21 CFR 866.5900
    - CFTR gene mutation detection system
    - Must comply with general and special controls
    - New product codes for sequencing assays
  - Other existing or new classification?
  - Platform
    - (can be cleared or approved as a part of the assay system, or separately)
Registered and Listed Sequencers

• High throughput genomic sequence analyzer for clinical use
  – MiSeqDx - a sequencing instrument that measures fluorescence signals of labeled nucleotides through the use of instrument specific reagents and flow cells, imaging hardware, and data analysis software; intended for targeted sequencing of human genomic DNA from peripheral whole blood samples; not intended for whole genome or de novo sequencing.

• Class 2 exempt
  ✓ Illumina MiSeqDx
  ✓ Life Technologies Ion PGM Dx
  ✓ Vela Sentosa SQ301

Special Controls

• What information should be in the labeling, including:
  – Read depth necessary for claimed sensitivity; limitations
  – Data demonstrating performance characteristics of instrument
Precision Medicine Initiative

- NIH – cohorts and other activities
- FDA – update regulatory framework for NGS
Analytical: Performance Standards as a Regulatory Tool for NGS

- Are performance standards feasible?
- Are performance standards sufficient for all NGS tests and intended uses?
- How should they be implemented?
- **WHO** should develop them?
- How should conformance to standards be verified?

*Answers to these questions will determine where FDA lands.*
Computational 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?
  - Coverage of sample
  - Base error rates and indel error rates
  - Contamination detection
  - Population genetics metrics such as alternate alleles
  - Detection of known variants

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

As part of the PMI - enable the development of this software and make it freely available to the genomics community.
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 evidence on the strength of association between variants and diseases.
- Under one approach, 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 - assess and, if necessary, upgrade existing databases to assure sufficient quality for regulation.
Summary

• NGS tests are unique among existing IVDs because of -
  – the amount of data that can be generated
  – the lack of an a priori definition of what will be detected
  – the number of clinical interpretations that can be made from a single patient sample

• Multiple options under consideration (need efficiency to allow innovation while protecting patients) -
  – computational solutions and standards-based approach to analytical performance of NGS tests
  – mechanisms to assure those standards are met
  – use of centralized curated databases containing up-to-date evidence to support clinical performance

• Public meeting on February 20, 2015 - for FDA to gather information to craft a specific proposal for the regulation of NGS

• Public docket for feedback - Docket FDA-2014-N-2214, open through March 20, 2015
  http://www.regulations.gov/#!docketDetail;rpp=100;so=DESC;sb=docId;po=0;D=FDA-2014-N-2214