Regulatory Updates, Options and Challenges for NGS

Cathy Craft, RAC
Senior Director, Regulatory

October 17, 2014

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Illumina FDA Down-Classifications and Clearances for NGS

U.S. Department of Health and Human Services

U.S. Food and Drug Administration
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FDA NEWS RELEASE

For Immediate Release: Nov. 19, 2013
Media Inquiries: Susan Laine, 301-796-5349, susan.laine@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA allows marketing of four "next generation" gene sequencing devices

Two devices aid in screening and diagnosis of cystic fibrosis

Today the U.S. Food and Drug Administration allowed marketing of four diagnostic devices that can be used for high throughput gene sequencing, often referred to as "next generation sequencing" (NGS). These instruments, reagents, and test systems allow labs to sequence a patient's DNA (deoxyribonucleic acid).

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Perspective

First FDA Authorization for Next-Generation Sequencer

Francis S. Collins, M.D., Ph.D., and Margaret A. Hamburg, M.D.

N Engl J Med 2013; 369:2369-2371 | December 19, 2013 | DOI: 10.1056/NEJMp1314561

http://www.nejm.org/doi/full/10.1056/NEJMp1314561#t=article

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NGS Down-classifications and Clearances
Instrument Platform - MiSeqDx

- Product Code: PFF
- Device Type: High throughput genomic sequence analyzer for clinical use
- Class: II (special controls), exempt from the premarket notification requirement subject to the limitations in 21 CFR 862.9
- Regulation: 21 CFR 862.2265

NGS Down-classifications and Clearances
Instrument Platform - MiSeqDx

- Intended Use:
- The MiSeqDx Platform is a sequencing instrument that measures fluorescence signals of labeled nucleotides through the use of instrument specific reagents and flow cells (MiSeqDx Universal Kit 1.0), imaging hardware, and data analysis software. The MiSeqDx Platform is intended for targeted sequencing of human genomic DNA from peripheral whole blood samples. The MiSeqDx Platform is not intended for whole genome or de novo sequencing.

NGS Down-classifications and Clearances
Instrument Platform - MiSeqDx

- Unique regulatory pathway
  - Previous multiplex instruments (micro-arrays) were Class II requiring new 510(k)
    - Required assays and instruments to enter the market together
  - This approach allows new sequencers to enter the market with no 510(k)
    - Thermo Fischer recently registered Ion Torrent instrument without having to bring an assay through along with it

Additional NGS Down- classifications and Clearances

- Reagents – Universal Reagent Kit 1.0
- Device Type: Reagents for the creation of a library specimen from a sample of human genomic; reagents for preparation of a library specimen for use with high-throughput genomic sequence analyzer
- Class: I, 21 CFR 862.3800
- Intended Use: ….a set of reagents and consumables used in the processing of human genomic DNA samples derived from peripheral whole blood, and in the subsequent targeted re-sequencing of the resulting sample libraries. **User-supplied analyte specific reagents are required for the preparation of libraries targeting specific genomic regions of interest.** The MiSeqDx Universal Kit 1.0 is intended for use with the MiSeqDx instrument.

Additional NGS Clearances

- Illumina MiSeqDx™ Cystic Fibrosis 139-Variant Assay
- DeviceType: CFTR (cystic fibrosis transmembrane conductance regulator) gene from human peripheral whole blood specimens
- Class: 2, 21 CFR 866.5900, CFTR (cystic fibrosis transmembrane conductance regulatory) gene mutation detection system

Additional NGS Clearances
Illumina MiSeqDx™ Cystic Fibrosis 139-Variant Assay

- Intended Use: ….a qualitative in vitro diagnostic system used to simultaneously detect 139 clinically relevant cystic fibrosis disease-causing mutations and variants of the cystic fibrosis transmembrane conductance regulator (CFTR) gene in genomic DNA isolated from human peripheral whole blood specimens. The variants include those recommended in 2004 by the American College of Medical Genetics (ACMG) and in 2011 by the American College of Obstetricians and Gynecologists (ACOG). The test is intended for carrier screening in adults of reproductive age, in confirmatory diagnostic testing of newborns and children, and as an initial test to aid in the diagnosis of individuals with suspected cystic fibrosis. The results of this test are intended to be interpreted by a board-certified clinical molecular geneticist or equivalent and should be used in conjunctions with other available laboratory and clinical information.
- This test is not indicated for use for newborn screening, fetal diagnostic testing, pre-implantation testing, or for stand-alone diagnosis.
- This test is to be used on the Illumina MiSeqDx instrument

NGS Clearances
Challenges with Validation of Large Panel

- Difficult to find actual samples for rare variants
- Solution for 139 Variant Assay
- Due to the rarity of many of the variants included in the assay (frequency of ≤0.001% observed from the data based on the CFTR2 database published in Sosnay et al, 2013), it was not possible to obtain clinical specimens for all variants detected by the assay. Therefore, the accuracy of the assay to detect these variants was established using synthetic heterozygous constructs created by blending linearized synthetic plasmids with CFTR wild type gDNA.

Additional NGS Clearances

- Illumina MiSeqDx™ Cystic Fibrosis Clinical Sequencing
- DeviceType: Protein coding regions and intron/exon boundaries of the cystic fibrosis transmembrane conductance gene regulator (CFTR) gene
- Class: 2, 21 CFR 866.5900 - CFTR gene mutation detection system

Additional NGS Clearances

Illumina MiSeqDx™ Cystic Fibrosis Clinical Sequencing Assay

- Intended Use: …. a targeted sequencing in vitro diagnostic system that re-sequences the protein coding regions and intron/exon boundaries of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene in genomic DNA isolated from human peripheral whole blood specimens collected in K2EDTA. The test detects single nucleotide variants, and small InDels within the region sequenced, and additionally reports on two deep intronic mutations and two large deletions. The test is intended to be used on the Illumina MiSeqDx Instrument. The test is intended to be used as an aid in the diagnosis of individuals with suspected cystic fibrosis (CF). The test is most appropriate when the patient has an atypical or non-classic presentation of CF or when other mutation panels have failed to identify both causative mutations. The results of the test are intended to be interpreted by a board-certified clinical molecular geneticist or equivalent and should be used in conjunction with other available information including clinical symptoms, other diagnostic tests, and family history. This test is not indicated for use for stand-alone diagnostic purposes, fetal diagnostic testing, for pre-implantation testing, carrier screening, newborn screening, or population screening.

Options/Considerations and What's Next for NGS

Where NGS is Moving?

- Open platform availability leverages future assay development, clearances/approvals
  - Work to be performed to include new sample types
  - Faster market access
- Observations of FDA perspective
  - Illumina clearances represent FDA support for moving NGS from research to a clinical setting
  - Clear recognition that NGS is becoming more commonplace for patients with cancer
  - Consistent with approach that Pharma and NGS companies are recommending
  - Recognition that the current model of one test/one drug is limited

Moving Towards a Cancer Panel Approach

genomeweb

August 21, 2014

Illumina to Develop NGS-based Oncology Companion Dx with AstraZeneca, Janssen Biotech, Sanofi

By a GenomeWeb staff reporter

NEW YORK (GenomeWeb) — Illumina has partnered with AstraZeneca, Janssen Biotech, and Sanofi to develop a universal next-generation sequencing-based oncology test system for multi-analyte companion diagnostics, the company said today.

The goal of the partnership is to transition from single-analyte companion diagnostics to panel-based assays to select cancer therapies for patients.

The new system, which will run assays that detect several variants in parallel, will be used as part of the partners' clinical trials of targeted cancer therapies. Illumina plans to develop, commercialize, and gain regulatory approval for multi-gene panels for therapy selection, which it previously referred to as Onco Panels.

Illumina also said it is working with "key thought leaders" to set standards for NGS-based assays in routine clinical oncology and to define regulatory frameworks for these types of tests.

September 25, 2014

Thermo Fisher Scientific to Develop NGS-based Oncology Companion Dx with Pfizer, GSK

NEW YORK (GenomeWeb) – Thermo Fisher Scientific, GlaxoSmithKline, and Pfizer are collaborating to develop a universal next-generation sequencing-based oncology test for solid tumors that will serve as a companion diagnostic for several drug programs, Thermo said today.

Following development and validation, Thermo Fisher plans to submit the test to the US Food and Drug Administration for premarket approval, as well as to other regulatory agencies.

The test will be developed on the Ion PGM Dx platform, which the company recently listed as a class II medical device with the FDA, and will use the Ion AmpliSeq amplification technology.

NGS- Applications for Cancer Panels

- Companion Diagnostic
  - Panel screen includes actionable targets as an approved companion diagnostic for selection of an approved drug
  - Specific pre-defined genes can be analyzed for their mutational status as a CDx
  - The sequencing data for remaining genes in the panel can be managed via software and not be reported for clinical use
- Clinical Trial Selection
  - NGS Panel identifies patients with specific variants as potential candidates for enrollment in drug clinical trials
  - Enables opportunity for optimal treatment for each subject
- Exploratory
  - Biomarkers/variants intended for studies to establish clinical utility and labeled as RUO

Ongoing Issues and Challenges for NGS

Ongoing Challenges for NGS From FOCR Public Meeting

- Standardization
  - Little or no standardization of markers
  - No standardization of performance and bioinformatics analysis between the tests
- Reference method
  - Different orthogonal reference methods for validation
  - New technologies have greater sensitive than bi-directional Sanger sequencing, the gold standard
- Validation
  - Unpublished validation data
  - Different orthogonal reference methods making comparisons difficult
  - Lack of proficiency test guidance for NGS panels
  - Different underlying platform technologies that have individual strengths and weakness

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Ongoing Challenges for NGS
From FOCR Public Meeting

- Bio-specimen issues
  - Quality and quantity of biopsy material available to support the one-test/one-drug model
  - Accurate determination of the fraction of neoplastic cells in input DNA over the total of neoplastic + normal cells
- Regulatory consideration and reimbursement challenges
  - All are assumed to need a PMA when used in the context of determining treatment (applies to predictive and prognostic markers)
  - Reimbursement based on payment for select biomarkers on a panel linked to levels of clinical utility

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Summary Report 9.30.14

FRIENDS of CANCER RESEARCH

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A Blueprint for Drug/Diagnostic Co-Development: Next-Generation Sequencing (NGS) in Oncology

- Proposals
  - Proposal #1: Define a regulatory pathway for cancer panels intended to identify actionable oncogenic alterations that allows flexibility in the appropriate FDA medical device pathway
  - Proposal #2: Approaches for performing validation studies should be based on the types of alterations measured by the assay, rather than every alteration individually
  - Proposal #3: Determine the contents of a cancer panel by classifying potential markers based on current utility in clinical care and clinical trials
  - Proposal #4: Promote the standardization of cancer panels through the use of a common set of samples to ensure reproducibility on each platform
  - Proposal #5: Establish a framework for determining the appropriate reference method rather than relying on any single reference method for all studies

Thank You

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