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Regulatory Perspectives on NGS-based CDx

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Outline

- Evolution of Nucleic Acid-Based CDx
- Regulatory Framework of NGS-based IVD
- Evaluation of NGS-based CDx
- NGS-based Oncology Panel
### CDx approved in Japan: Nucleic Acid-Based CDx

<table>
<thead>
<tr>
<th>CDx Trade Name</th>
<th>Drug Trade Name (INN)</th>
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<tbody>
<tr>
<td>POTELIGEO TEST IHC</td>
<td>POTELIGEO (Mogamulizumab)</td>
</tr>
<tr>
<td>POTELIGEO TEST FCM</td>
<td>POTELIGEO (Mogamulizumab)</td>
</tr>
<tr>
<td><strong>Vysis ALK Break Apart FISH probe kit</strong></td>
<td>Xalkori (crizotinib) ALECENSA (alectinib)</td>
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<tr>
<td>Histofine ALK iAEP kit</td>
<td>ALECENSA (alectinib)</td>
</tr>
<tr>
<td><strong>Cobas BRAF V600 mutation test</strong></td>
<td>Zelboraf (vemurafenib)</td>
</tr>
<tr>
<td><strong>THxID BRAF kit</strong></td>
<td>Tafinlar (dabrafenib) Mekinist (trametinib)</td>
</tr>
<tr>
<td><strong>Cobas EGFR mutation test v2.0</strong></td>
<td>TAGRISSO (osimertinib)</td>
</tr>
<tr>
<td><strong>OncoGuide AmoyDx ROS1 Gene Fusions Detection Kit</strong></td>
<td>Xalkori (crizotinib)</td>
</tr>
<tr>
<td>PD-L1 IHC 22C3 pharmDx [Dako]</td>
<td>KEYTRUDA (pembrolizumab)</td>
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IVDs to detect RAS mutation, HER2 gene amplification and EGFR mutation are also used to guide therapies with a corresponding therapeutic product.
Next Generation Sequencing-based CDx

Case 1
In case where various variants of a gene should be analyzed for treatment with the targeted therapy (e.g. \textit{BRCA1/2} gene variants)

Case 2
In case where several genes should be analyzed to choose the suitable therapeutic product for a specific indication

- **gene A variant** → Approved Drug A
- **gene B variant** → Approved Drug B
- **gene C variant** → Approved Drug C
Regulatory Status of NGS-based CDx in US

- **2015**: Use of public DB Use of Stds
- **2016**: Draft Guidance
- **2017**: FoundationFocus CDx <br> <NGS-based CDx> BRCA
- <NGS-based CDx> Oncomine Dx Target Test
- <NGS-based CDx> Praxis Extended RAS panel

Multiple analyt by single test <br> NOT by NGS<br><br>BRACAnalysis CDx
August 2, 2016

FoundationOne® Accepted by FDA and CMS for Parallel Review and FDA Expedited Access Pathway

--Parallel Review of FoundationOne, if Successful, Could Result in FDA Approval of the First Pan-Cancer Comprehensive Genomic Profiling Assay Incorporating a Range of Companion Diagnostics, Concurrently with a CMS National Coverage Determination--

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Foundation Medicine, Inc. (NASDAQ: FMI) today announced that the U.S. Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services (CMS) have accepted FoundationOne for Parallel Review as an innovative technology most likely to benefit from the efficiencies of this program. The FDA also accepted Foundation Medicine's request for review as part of its Expedited Access Pathway (EAP) for breakthrough devices.
Next Generation Sequencing-based CDx

Case 3
CDx for multiple therapeutic products and comprehensive gene profiling

- **gene A variant** → Approved Drug A
- **gene B variant** → Approved Drug B
- **gene C variant** → Approved Drug C
- Comprehensive Genomic Profiling → Reporting of variants to guide therapies?
Evolution of Nucleic Acid Based-CDx

- **1 Drug multiple-variant testing**
  - (e.g. BRCA test)
  - Non-CDx
    - Multiple Drug 1 CDx system
      - (e.g. Oncology panel)
  - 1 Drug multiple CDx
    - (e.g. EGFR-TKI and EGFR mutation test)
  - 1 Drug 1 CDx
    - (e.g. trastuzumab and HER2 test)

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Outline

- NGS-based IVD
- Regulatory Framework of NGS-based IVD
- Evaluation of NGS-based CDx
- NGS-based Oncology Panel
Notification and Administrative Notice on Nucleic Acid Based Test using DNA sequencer

<table>
<thead>
<tr>
<th>Issue date</th>
<th>title</th>
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<tbody>
<tr>
<td>Apr 28, 2016</td>
<td>Legislation Notice to Applicants for Marketing Authorization of DNA Sequencers and Related Products Utilized for Genetic Testing Systems</td>
</tr>
<tr>
<td>Jan 26, 2017</td>
<td>Questions and Answers on Marketing Authorization of DNA Sequencers and Related Products Utilized for Genetic Testing Systems</td>
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</table>
Regulatory framework of DNA sequencer-based IVD

Nucleic acid extraction

Class III IVD
Reagents for library construction

DNA sequencer

Class II MD
Reagents for sequencing sample prep.

Class II or III MD
Software

DNA sequencer-based IVD system (combination MD)

Database

Reference
Questions related to Administrative Notice issued on Jan 26, 2017

- **Combination MD**
  - DNA seq should be specified.
  - Performance characteristics and spec of DNA seq should be described.

- **DNA sequencer**
  - As Class II MD, MAA is required.

- **Software**
  - Reference

- **Database**

- **Reagents for library construction**

- **DNA sequencer**
  - Reagents for sequencing sample prep.
Outline

NGS-based IVD
Regulatory Framework of NGS-based IVD
Evaluation of NGS-based CDx
NGS-based Oncology Panel
Evaluation of NGS-based CDx

- Basic principles are the same as conventional CDx.
  - CDx should provide accurate and reproducible results.
  - CDx should be able to identify a population expected to benefit from the therapeutic.

- Validation approach considering the characteristic feature of NGS-based system could be possible.
Analytical Validation

- Clinical specimen should be used in principle.

- Use of contrived sample
  - For rare variants, use of contrived sample could be acceptable.
  - Appropriateness of the contrived sample should be shown based on the commutability study.

- Pan-tumor claim
  - A range of specimens should be evaluated.
  - Effect of variations in sample preparation and pre-analytical methods should be evaluated.

- Quality metrics
  - Depth of coverage
  - Quality Score, etc.
Representative validation approach

- It is acceptable to validate representative subset of variants including contrived sample if scientific rationale is appropriately provided.
- Representative subset of variants should cover the range of variants to be detected by the system.
  - Variant types (SNV, indels, fusions, etc.)
  - Variant sizes (e.g. indels)
  - Genomic context (GC-rich regions, homopolymeric regions, etc.)
Analytical Validation: Observed issues

- Insufficient consideration on pre-analytical metrics
  - Acquisition methods (e.g. fine needle biopsy, surgical biopsy)
  - Fixation condition for FFPE tumor tissue specimens

- Insufficient quality control of DNA or RNA specimen
  - No acceptance criteria for DNA or RNA quality
Clinical Performance of NGS-based CDx

In cases where the variant classification is crucial for the eligibility of the therapy

- Validity of classification criteria and classification process should be demonstrated.

Variant classification will be evaluated taking into consideration the following aspects:

- Genotype-pathogenesis correlation and the mechanism of action of the therapeutic product
- Rationale for the classification criteria based on scientific evidence
- Robustness of the classification process
CDx with the same intended use as the approved CDx

CDx with the same intended use and the specimen type as the approved CDx

Principles:
- Clinical performance of the proposed CDx should be comparable to the approved CDx.
- Concordance between the approved CDx and the proposed CDx should be reasonably high.
- If clinical performance of the proposed CDx cannot be ensured by the concordance study, clinical performance should be evaluated as a stand-alone CDx.
Outline

- NGS-based IVD
- Regulatory Framework of NGS-based IVD
- Evaluation of NGS-based CDx
- NGS-based Oncology Panel
Example 1: Analytical flow using Oncology Panel

- **DNA sequencing**
- **Oncology Panel**
- **DNA sequencer**

**Raw data**
AGAAGCACCTGG
AGAATACTCAGTGG
CAGCAATTGACT
TACCCACTAAGC
AAAAATCCAGCC
CATCAC......

**Variant call**
Reference seq

**Software**
SNV, indel, CNV, fusion/translocation

- **Pathogenic**
- **Benign**
- **Uncertain significance**

**Output:** List of annotated variants

**Evaluation of Clinical Utility** in Japanese medical setting

**Criteria for clinical evidence?**

**Intended Use**
Clinical validity of each gene
Genotype-pathogenesis correlation based on:
- guideline/guidance
- Public DB, etc.

**Report**
Patient ID: XXXXX
variants XXX
Interpretation XXX

**Approved as IVD?**

**External DB**
Additional info on possible therapy

**Physician**
Further Analysis by Expert Panel?

**Proprietary DB**
Example 2: Analytical flow using Oncology Panel

**DNA sequencing**

**Oncology Panel**

**DNA sequencer**

- **Raw data**
  - AGAAGCACCTGG
  - AGAACTCAGTGG
  - CAGCAATTGACT
  - TACCCACTAAGC
  - AAAAAATCCAGCC
  - CATCAC

- **Variant call**
- **Reference seq**

- **Software**
  - SNV, indel, CNV, fusion/translocation
  - **pathogenic**
  - **Benign**
  - **Uncertain significance**

- **Output:** List of annotated variants

- **Report**
  - Patient ID: 
  - Variants
  - Interpretation

- **Evaluation of Clinical Utility**
  - in Japanese medical setting

- **Intended Use**
  - Clinical validity of each gene
  - Genotype-pathogenesis correlation based on:
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    - Public DB, etc.

- **Approved as IVD?**

- **External DB**

- **Criteria for clinical evidence?**

- **Additional info on possible therapy**

- **Further Analysis by Expert Panel?**

- **Physician**

- **External DB**
Challenges for PMDA: Genes/variants for non-CDx use

- Intended use
- Clinical validity of genes on a panel
  - Coverage of genes/variants
  - Criteria for clinical validity
  - As a measure of tumor mutational burden
    - How many genes are enough?
- Analytical validation
- Interpretation of gene variants detected
  - Should DB be specified?
  - What levels of evidence should be considered?
- Implementation into medical setting
  - Correct use and interpretation of an panel by end-users
Representative researcher:
Dr. Kenjiro Kosaki, Keio University School of Medicine

Research Goal:
Guidance development on:
- Analytical validation of NGS-based IVD
- Points to consider on the use of public DB for NGS-based IVD development
Challenges for PMDA: Genes/variants for non-CDx use

- Intended use
- Clinical validity of genes on a panel
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  - Correct use and interpretation of an panel by end-users
Members of CDx WG and Office of IVD in PMDA
Ask