本邦における遺伝子検査パネル等の承認に向けた動き

Regulatory Trends toward Approval of Oncology panels and Relevant IVDs in Japan

医薬品医療機器総合機構
体外診断薬審査室
矢花直幸
Naoyuki Yabana　Office of IVD, PMDA
Disclaimer

The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA.
From CDx Era to Oncology Panel Era

The first time approval of oncology panel in Japan?

- Approval of Trastuzumab
- Approval of Gefitinib for EGFR- TK positive NSCLC
- Notification on CDx & relevant drugs

Report of Cancer Genome medical consortium

- Nature 2014 507: 294
Commercialization of NGS is making the following changes:

- Enabling to obtain a lot of genome information on driver genes including SNV, Ins/Dels, CNA and structural variants.
- Enabling precision medicine based on therapeutic response factors and prognostic factors in addition to CDx.
Clinical implementation of NGS is making the following changes:

- Drastic increase of information for annotation and interpretation of variants requisites the reference databases.
- Establishment of clinical field for the genome precision medicine which interprets the genome profile and selects optimal medication.
- Emergence of various type of diagnostic system, i.e. single-site assay performed at marketing authorization holder’s lab.
Case1: BRACAnalysis CDx™ (BRACAnalysis診断システム)

- This assay identifies breast cancer patients with deleterious or suspected deleterious germline BRCA mutation from more than 19,000 variants.

- Approved as CDx system for Olaparib in 2018 in the category of software as a medical device.

- Annual post-marketing report on summary of newly variant classification is requested.
Case2: Oncomine™ Dx Target Test
(オンコマイン Dx Target Test CDxシステム)

- This assay is indicated to CDx on 3 genes (BRAF, ROS1, EGFR). Also indicated to qualitative diagnostic tests of 23 genes for patients who have already been considered for all appropriate therapies in US SSED.

- Approved as CDx system for Tafinlar/Mekinist in Japan in 2018. The test result of other genes on the panel could be provided for clinical research use only.

- First NGS-based CDx in Japan.
Case3: NCC Oncopanel

- This NGS-based IVD system is developed mainly by the National Cancer Center, and has received designation under the Sakigake Designation System in 2017.
- This assay detects SNV, Ins/Dels, CNA and gene rearrangements of 114 driver genes.

<table>
<thead>
<tr>
<th>114 mutation amplification (whole exon)</th>
<th>13 fusion genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABL1</td>
<td>CRKL</td>
</tr>
<tr>
<td>ACTN4</td>
<td>CREBBP</td>
</tr>
<tr>
<td>AKT1</td>
<td>COTNBN1/b-catenin</td>
</tr>
<tr>
<td>AKT2</td>
<td>CUL3</td>
</tr>
<tr>
<td>AKT3</td>
<td>DDR2</td>
</tr>
<tr>
<td>ALK</td>
<td>EGFR</td>
</tr>
<tr>
<td>APC</td>
<td>ENO1</td>
</tr>
<tr>
<td>BRAF</td>
<td>EPHB3</td>
</tr>
<tr>
<td>ARID1A</td>
<td>ERBB2/HER2</td>
</tr>
<tr>
<td>ARID2</td>
<td>ERBB3</td>
</tr>
<tr>
<td>ATM</td>
<td>ERBB4</td>
</tr>
<tr>
<td>AXIN1</td>
<td>ESR1/ER</td>
</tr>
<tr>
<td>AXL</td>
<td>EZH2</td>
</tr>
<tr>
<td>BAP1</td>
<td>FBXW7</td>
</tr>
<tr>
<td>BARD1</td>
<td>FGFR1</td>
</tr>
<tr>
<td>BCL2L11/BIM</td>
<td>FGFR2</td>
</tr>
<tr>
<td>BRAF</td>
<td>FGFR3</td>
</tr>
<tr>
<td>BRCACA1</td>
<td>FGFR4</td>
</tr>
<tr>
<td>BRCACA2</td>
<td>FLT3</td>
</tr>
<tr>
<td>CCND1</td>
<td>GNA11</td>
</tr>
<tr>
<td>CD274/PD-L1</td>
<td>GNAQ</td>
</tr>
<tr>
<td>CDK4</td>
<td>GNAS</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>HRAS</td>
</tr>
<tr>
<td>CHEK2</td>
<td>IDH1</td>
</tr>
</tbody>
</table>

2017.10.4 厚生労働省 がん診療連携拠点病院等の指定要件に関するWG資料
Case 4: FoundationOne CDx™

- This assay is NGS-based IVD test that can detect genetic mutations in 324 genes and two genomic signatures i.e. MSI and TMB in any solid tumor type.

- This assay provides the information of 6 CDx genes and can identify which patients with any of five tumor types may benefit from 17 different FDA-approved targeted treatment options.

- Submitted to MHLW in March 2018 and under the review of PMDA.
Framework of cancer genome precision medicine in Japan

11 core hospitals for cancer genome precision medicine

Approx. 100 associate hospitals for cancer genome precision medicine

- Obtain the genome variants data using the oncology panel
- Annotation of variants using databases and report the comprehensive genome profile
- Finalizing the report of the evidence-based categorization of variants by expert panel
### CDx vs Comprehensive Gene Profile (CGP)

<table>
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<tr>
<th>Indication for use</th>
<th>CDx</th>
<th>CGP</th>
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<tr>
<td>Assumed Medication</td>
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<td>Output of the diagnostics system</td>
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<td>Major Regulatory evaluation points</td>
<td>Positive and negative predictive values</td>
<td>Analytical performance based on validated accuracy, reproducibility, repeatability etc.</td>
</tr>
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</table>
Typical Schematic Flow of Medication using Oncology Panels

DNA sequencing
Oncology Panel
DNA sequencer

Variant call
GeneX: c.2611C>T
GeneY: c.1652A>G
GeneZ: ..........

Annotation

Software
SNV, Ins/Del, CNV, Rearrangements

Report
GeneA: SNV: xxxx
GeneB: Indel: xxxx

Knowledge Database

Mutation Database

Approved as IVD Device

Bioinformatics Pipeline

Patient #:
Tier1:xxxxxxxx
Tier2:xxxx....

Report

Interpretation by Expert Panel
Points to Consider in Reviewing Oncology Panels

Evaluation of Analytical Performance
How to evaluate the analytical performance on multiple types of mutations in hundreds of genes?

Evaluation of Software
How to evaluate the quality of the annotation report?

Evaluation of Database
Does PMDA evaluate the integrity of the database?

Evaluation of Clinical Performance
How to evaluate the clinical performance of oncology panels?

Evaluation of Clinical Utility
Need to establish the clinical utility of oncology panels in Japan?
Clinical Utility is already established by the report of Cancer Genome Medical Consortium, and also demonstrated in the medication under advanced medical care.

Clinical Performance = Analytical Performance

Recognized but not evaluated: Public Database
Evaluated in the review and Recognized: In-house database
Evaluated in the review and Approved: Bioinformatics Pipeline

Evaluation of Software
Quality of the annotation report is evaluated based on the design and the validation reports of NGS test and bioinformatics pipeline.
Analytical Validity

- Accuracy should be stated in terms of Positive Percentage Agreement and Positive Predictive Value using reference samples or reference methods for each mutation type (e.g. SNVs, Ins/Dels, CNAs, structural variants).

- How to select the reference method (orthogonal method) in Japan?

Example: FoundationOne CDx SSED Table 6

<table>
<thead>
<tr>
<th>Variant Type</th>
<th>F1CDx+/evNGS+</th>
<th>F1CDx-/evNGS+</th>
<th>F1CDx+/evNGS-</th>
<th>F1CDx-/evNGS-</th>
<th>PPA*(95%CI)</th>
<th>NPA*(95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All short variants</td>
<td>1282</td>
<td>73</td>
<td>375</td>
<td>284218</td>
<td>94.6%</td>
<td>99.9%</td>
</tr>
<tr>
<td></td>
<td>(93.3%-95.8%)</td>
<td>(99.9%-99.9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substitutions</td>
<td>1111</td>
<td>39</td>
<td>334</td>
<td>242540</td>
<td>96.6%</td>
<td>99.9%</td>
</tr>
<tr>
<td></td>
<td>(95.4%-97.6%)</td>
<td>(99.8%-99.9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indels</td>
<td>171</td>
<td>34</td>
<td>41</td>
<td>41678</td>
<td>83.4%</td>
<td>99.9%</td>
</tr>
<tr>
<td></td>
<td>(77.6%-88.2%)</td>
<td>(99.9%-99.9%)</td>
<td></td>
<td></td>
<td></td>
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</tr>
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</table>
What would happen after the clinical implementation of Oncology Panels?

Marker X-positive patients were selected for the phase 3 study in the development of new drug. Marker X has already been measured using approved oncology panel to obtain the comprehensive gene profile (CGP). Is it required to apply new CDx for marker X for approval application of the new drug?

New CDx for marker X is approved to identify the patients for the new drug. Marker X has already been measured using approved oncology panel to obtain the CGP. Is it possible to identify the patients for the new drug based on the result report of the CGP without using CDx for marker X?
# CDx vs Comprehensive Gene Profile (CGP)

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What is the essence of CDx?

Clinical trial of Drug

Lab test1

Lab test2

Lab test3

Lab test4

Clinical validation via a concordance study

Post Market of Drug

Reference standard Dx system in Japan

Reimbursement
What is the essence of CDx?

Clinical trial of Drug
- Lab test1
- Lab test2
- Lab test3
- Lab test4

Post Market of Drug
- Follow-on CDx
- Clinical validation via a concordance study
- Reference standard Dx system in Japan
- Reimbursement
After the clinical implementation of Oncology Panels

The concept of CDx never changes

Clinical trial of Drug

Lab test1

Lab test2

Lab test3

Lab test4

Clinical validation via a concordance study

Reference standard Dx system in Japan

Reimbursement

Post Market of Drug
CDx in the Oncology Panel Era?

Clinical trial of Drug

NGS 1
NGS 2
NGS 3
NGS 4

Post Market of Drug

Clinical validation via a concordance study

Additional Reimbursement?
Near Future World With No More CDx
Conclusion

- Along with the promotion of the cancer genome precision medicine, movement to provide the approved oncology panel in medical practice is progressing.
- Review policies for evaluation of the oncology panel in PMDA are being established.
- The emergence of oncology panels does not change the regulatory need for CDx system in Japan, however the standardization of panels in the future could lead to the equivalence of NGS-based tests and possibly the shift in CDx-based regulatory framework.