The Cutting Edge of in vitro Diagnostics: Regulation on 21st Century Therapies

Office of In Vitro Diagnostics
Pharmaceuticals and Medical Devices Agency
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IVD Regulation in Japan
Schematic Representation of Regulation of IVD in Japan

Certification/ approval system (GHTF classification)

Establishment of review requirements (GHTF guidance)

Quality control and QMS inspection (ISO-compliant)

Application form & Contents of Application Dossier

Establishment of domestic guidance on approval standards, etc.

Rules for concrete operations

Implementation of the regulatory system in Japan

GHTF

Global concepts

Classification, Basic Principles, Quality Management, Clinical Evidence etc.
IVD reagents are regulated under the rules based on the medical devices.

- Risk based classification
- QMS requirements
- Essential principle
- Generic name etc.
## Classification and Regulation of IVD

### Risk

<table>
<thead>
<tr>
<th>Class1</th>
<th>Class2</th>
<th>Class3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relatively Low diagnostic information risk</strong>&lt;br&gt;<strong>Have minor impacts</strong>&lt;br&gt;<strong>Have certified calibration standards</strong>&lt;br&gt;<strong>Easy self-checking</strong>&lt;br&gt;(Examples) Amino acids, hormones, enzyme activities, minerals, etc.</td>
<td><strong>Relatively Low diagnostic information risk</strong>&lt;br&gt;<strong>Have minor impacts</strong>&lt;br&gt;<strong>OTC tests</strong>&lt;br&gt;(Examples) Hormones, enzyme activities, allergy-related substances (IgE), autoantibody assays, etc.&lt;br&gt;<strong>Ovulation test kits, pregnancy test kits, etc.</strong></td>
<td><strong>Relatively High diagnostic information risk</strong>&lt;br&gt;<strong>Have major impacts</strong>&lt;br&gt;(Examples) Hormones, enzyme activities, allergy-related substances (IgE), autoantibody assays, etc.&lt;br&gt;Ovulation test kits, pregnancy test kits, etc.&lt;br&gt;<strong>Antigens, DNA, RNA, antibody titers associated with microbial infection</strong>&lt;br&gt;<strong>Human genetic tests</strong>&lt;br&gt;<strong>Cancer-related biomarkers, companion diagnostics etc.</strong></td>
</tr>
</tbody>
</table>

### PMD Act

<table>
<thead>
<tr>
<th>Conform to notified standards</th>
<th>Not conform to notified standards</th>
<th>Conform to notified standards</th>
<th>Not conform to notified standards</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novel products&lt;br&gt;Products in category without notified standards&lt;br&gt;Not conform to standards</td>
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### Self-certification<br>Approval (reviewed by PMDA)<br>Third-party certification<br>Approval (reviewed by PMDA)<br>Approval (reviewed by PMDA)
1. Emerging Advances in IVDs
1. **Quantitative diagnostic markers** based on molecular-level elucidation of pathology and accumulation of genomic data are expected.

2. **Precision medicine** based on the accumulation of genomic data is expected.

3. **Faster and simultaneous multiple** sample measurements based on technical advance are implemented.

4. **Non-invasive diagnostics** based on measurement of small amounts of sample with high sensitivity and accuracy are widely expected.

5. **Algorithms** based on huge amount of clinical information are being introduced to clinical tests.
Clinical Implementation of Biomarkers for non-invasive diagnosis: example

- E Test “TOSOH” II (autotaxin)
  - The test measures serum free-autotaxin due to liver injury to support a diagnosis of progressive liver fibrosis.
  - Supported by AMED Project of Translational and Clinical Research Core Centers
  - Approved in 2017
Clinical Implementation of Technology for infectious diagnosis: example

- **Genelyzer KIT FGNK-0003A for ZIKA virus**
  - The test is intended to be used to support a diagnosis of Zika virus infection.
  - Supported by AMED Project of Translational and Clinical Research Core Centers
  - Approved in 2018.

<table>
<thead>
<tr>
<th>Control method</th>
<th>Whole blood</th>
<th>Serum</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pos.</td>
<td>0</td>
<td>1</td>
<td>45</td>
</tr>
<tr>
<td>Neg.</td>
<td>0</td>
<td>104</td>
<td>4</td>
</tr>
<tr>
<td>TBD</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>
2. Precision Medicine based on Genome Profiling
Framework of cancer genome precision medicine in Japan

11 core hospitals for cancer genome precision medicine

obtain the genome variants data using approved oncology panel (OncoGuide NCC Oncopanel System, FoundationOne CDx)

annotation of variants using databases and report the comprehensive genome profile

156 associate hospitals for cancer genome precision medicine

Finalizing the report of the evidence-based categorization of variants by expert panel
## CDx vs Comprehensive Genome Profiling

<table>
<thead>
<tr>
<th>Indication for use</th>
<th>Companion Dx</th>
<th>Comprehensive Genome Profiling (CGP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication based on the diagnostics</td>
<td>Established medication</td>
<td>Medication with potential evidence</td>
</tr>
<tr>
<td>Output of the diagnostics system</td>
<td>Interpretation is not acceptable</td>
<td>Interpreted by the expert panel for the clinical significance</td>
</tr>
<tr>
<td>Major regulatory evaluation points</td>
<td>Positive and negative predictive values</td>
<td>Analytical performance</td>
</tr>
<tr>
<td>medical institutes of implementation</td>
<td>-</td>
<td>Core hospitals for cancer genome precision medicine</td>
</tr>
</tbody>
</table>
Framework of cancer genome repository and Knowledge DB medicine in Japan

Certified Labs for genomic testing
- Analysis using approved oncology panel
- Specimens
- Report

Center for Cancer Genomics and Advanced Therapeutics: C-CAT
- Cancer genomics info repository
- Development of new drugs, biomarkers and diagnostics systems
- Maximize treatment opportunity in collaboration with core and associated hospitals

11 core hospitals for cancer genome precision medicine
156 associate hospitals for cancer genome precision medicine

Clinical info
- Sequence Data
- CKDB report
What we have implemented

- DNA sequencing
  - Oncology Panel
  - DNA sequencer
- Variant call
- Annotation
- Software
- Mutation Database
  - SNV, Ins/Del, CNV, Rearrangements
- Report
  - GeneA: SNV: xxxx
  - GeneB: Indel: xxxx...
  - GeneX: c.2611C>T
  - GeneY: c.1652A>G
  - GeneZ: ............

- OncoGuide NCC Oncopanel
- FoundationOne CDx

Approved
3. Innovation of IVD using AI
Concept of i

Concept of IVD

Clinical data
+ Reagents
+ Algorithm
+ Quality Control

Clinical data
= Database

IVD products
+ Quality Control

Algorithm

Concept of i (= IVD + ICT)
Case 1: BRACAnalysis CDx™

- 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.

Case2: FoundationOne CDx

- This analysis program annotate the variants of DNA sequences of tumor tissue samples sent to FMI in the United States, based on the reference to the database, and output as a clinical report, using the analysis results.

Modified from the Review Report (http://www.pmda.go.jp/medical_devices/2019/M20190123001/450045000_23000BZX00403_A100_1.pdf)
4. Absolute Early Diagnosis
Innovation in IVD

- Genome & post-Genome
- Database
- Micro-analysis technology

Precision Medicine
Early Diagnoses
## IVD products of SAKIGAKE Designation

<table>
<thead>
<tr>
<th>Designation date</th>
<th>Brand Name</th>
<th>Applicant Company</th>
<th>Indication or performance for marketing</th>
<th>Approval date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feb. 10, 2017</td>
<td>OncoGuide NCC Oncopanel System</td>
<td>Sysmex Corporation</td>
<td>The system targets all solid tumors and is intended for use in obtaining comprehensive genomic profiles from patients’ tumor</td>
<td>Dec. 25, 2018</td>
</tr>
<tr>
<td>April 9, 2019</td>
<td>MI-004</td>
<td>Toray Corporation</td>
<td>The system analyses the expression pattern of microRNA in blood samples for diagnosis of pancreatic and biliary tract cancer</td>
<td></td>
</tr>
</tbody>
</table>
### Expectation and Concern to Early Diagnoses

<table>
<thead>
<tr>
<th>item</th>
<th>category</th>
<th>Evidence required</th>
</tr>
</thead>
<tbody>
<tr>
<td>● diagnosis of cancer with one drop of blood</td>
<td>diagnostics</td>
<td>Sensitivity and specificity of diagnosis</td>
</tr>
<tr>
<td>● diagnosis of influenza within 12 hours from onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Blood tests which correlate with accumulation of β-amyloid in brain</td>
<td>Risk factor or diagnostics?</td>
<td>Long-term events-based evaluation?</td>
</tr>
<tr>
<td>● Blood biomarker for microcarcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Blood tests which predict the onset of cerebral infarction</td>
<td>Risk factor</td>
<td>Long-term events-based evaluation</td>
</tr>
<tr>
<td>● Blood markers which predict the onset of cardiovascular events</td>
<td></td>
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</table>
Absolute vs Relative Early Diagnosis

Chronic disease

Improvement of living habits?

Risk factors

Absolute Early Diagnosis = identification of the candidate of patients

Prevention = Established Risk Management and surveillance

Malignant tumor

Absolute Early Diagnosis

Definite diagnosis = Relative Early Diagnosis

Established surveillance? Early Treatment?

Onset

Treatment

Treatment

Diagnosis

Diagnosis
5. 21st Century Therapies
21st Century Therapies

20th Century

21st Century

Database

Genome & Biomarkers

Precision Medicine targeting disease cause

Absolute Early Diagnosis

Established Risk Management, Surveillance, and Treatments

Profiling of disease risk

Onset

Diagnosis

Treatment

Onset

Onset

Treatment
Regulatory issues on 21st Century Therapies

20th Century

Onset

Diagnosis

Treatment

21st Century

= A Century of Real World Data

Regulation on the diagnostic systems using DB and AI

Establishment of the absolute early diagnosis and risk management therapies

Establishment of the personalized therapies

21st Century Therapies

Regulation on the diagnostic systems using DB and AI

Establishment of the absolute early diagnosis and risk management therapies

Establishment of the personalized therapies

21st Century Therapies
In Japan, in-vitro diagnostics are classified according to GHTF rules, and PMDA conducts approval review for high-risk products.

Technological advances have made it possible to collect significantly more information from less invasive clinical samples. The development of information technology is rapidly promoting the analysis and clinical application of these multivariate information.

The 21st century therapies would be based on absolute early diagnosis, profiling of each patient, and established risk management before onset of disease.