FoundationOne® CDx Cancer Genomic Profile
Product Overview

Kosuke Iijima
Department Manager of Foundation Medicine Business Department
Chugai Pharmaceutical Co., Ltd.
2019/07/04
Transformational Shift in Oncology

2009

- Cancer is an anatomical disease
- Clinical trials are conducted solely by academia or a pharmaceutical company
- Few targeted therapy trials
- Significant decrease in use of immunostimulants
- Disparate approaches to diagnostic assays

2019

- Cancer is a genomic disease
- Collaborative clinical trials, basket/umbrella trials
- > 600 therapies in development, thousands of clinical trials
- Rapid adoption of immunotherapies
- Emergence of comprehensive diagnostic assays

Source: Foudation Medicine materials, partly modified
Governmental Activities for Genomic Medicine

4 Pillars in the Basic Plan against Cancer
1. Prevention of cancer
2. Enhanced cancer therapy
   i. Cancer genomic medicine: put panel testing into practical application
3. Coexistence with cancer
4. Streamline the platform for cancer care

NGS: Next-generation sequencer
NHI: National health insurance
Chaotic therapy…
Starting with CDx development

Chaotic, asymmetric and crowded
Deliver Novel Platform Solution

- FDA Approval
- CMS Reimbursement
- Regulatory approved
- Covered by NHI

Pharma CDx

FoundationOne® CDx
がんゲノムプロファイル

Pharma CDx
Pharma CDx
Pharma CDx
Pharma CDx
**FoundationOne® CDx**

Intended Usage or Indications

- Obtain comprehensive genome profiling with tumor tissues in patients with solid tumors
- Detect gene alterations to support the assessment of drug indications listed in the table below

<table>
<thead>
<tr>
<th>Alternations</th>
<th>Cancer type</th>
<th>Relevant drugs</th>
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<td><em>NTRK1/2/3</em> fusion gene</td>
<td>Solid tumors</td>
<td>entrectinib</td>
</tr>
</tbody>
</table>

CGP: Comprehensive Genomic Profiling  
CDx: Companion Diagnostic  
Source: Package insert
### FoundationOne CDx Cancer Genomic Profiling

#### Background information on the patient, the medical facility etc.

- Approval status of corresponding targeted therapies
- Ongoing clinical trials targeting detected alterations

#### Summary of detected alterations

<table>
<thead>
<tr>
<th>Genomic Findings Detected</th>
<th>Approved Therapeutic Options in Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>LER899</td>
</tr>
<tr>
<td></td>
<td>Erlotinib hydrochloride</td>
</tr>
<tr>
<td></td>
<td>Gefitinib</td>
</tr>
<tr>
<td></td>
<td>Oxamustine mesilate</td>
</tr>
</tbody>
</table>

#### Summary of references on detected alterations and potential therapies

- Tumor Mutational Burden - TMB: 8 Mutations
- NGS: 12 Mutations
- EGFR: Amplification, LER899
From Organs to Gene Alterations/Biomarkers

Tumor agnostic approval + New histology independent medicines

FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

On May 23, 2017, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co.) for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This is the FDA's first tissue/site-agnostic approval.
Rozlytrek: The Second Drug in Japan Approved Across All Solid Tumors

Study design
- Phase II, global, multicenter, open-label basket study (STARTRK-2)
- Target: People aged 18 older with NTRK fusion-positive* metastatic or relapse solid tumors. N=51 including 1 Japanese.
- Administer oral entrectinib 600 mg/day
- Primary endpoint: objective response rate (Time Frame: approx. 24 months)

*NTRK fusion–positive status was determined with a nucleic acid–based diagnostic test. FoundationOne CDx Cancer Genomic Profile, confirmed to be equivalent to this diagnostic test, is marketed as a companion diagnostic.

Outcomes
- ORR was **56.9%** (95% CI: 42.3%–70.7%) by INV assessment per RECIST v1.1

Clinically Significant Adverse Reactions
- 1 Cardiac disorders (4.8%) Cardiac disorders such as cardiac failure, ventricular extrasystoles, and myocarditis may occur. 2 Prolonged QT interval (frequency unknown) 3 Cognitive disorder, ataxia (28.6%) Cognitive disorder, confusional state, mental status changes, memory impairment, hallucinations, ataxia, dysarthria, etc., may occur. 4 Interstitial lung disease (1.6%)

Source: Roche’s Virtual Pipeline Event from ESMO 2018
Source: package insert
• Finding matched therapy and selecting optimal treatment

• Understanding pathogenesis from clonal evolution

• Understanding pathogenesis including passenger alterations, not only searching for driver alterations

• Understanding pathogenesis from multiple genetic alterations

• Comprehensive treatment plan from biomarkers (TMB, MSI, LOH), etc.

**ASCO2019 CSS: Targeting Breast Cancer: Breaking the Code**

*TP53*: Poor prognostic factor but promotes early progression of CDK4/6i

*FGFR1*: Promotes early progression of CDK4/6i

*RB1*: Possible CDK4/6i resistant mutation

*PTEN loss*: Lowers IC50 of CDK4/6i to promote tolerization

PD expected soon after administration of palbociclib

**Earlier treatment plan from CGP**

Tolerization by enhancement during administration of palbociclib

Monitoring of ctDNA CGP
Positioning of NGS Panel Test Directly Relates to Use and Quality of Clinico-Genomic DB

Filing with FDA

- U.S. FDA APPROVES IBRANCE® (PALBOCICLIB) FOR THE TREATMENT OF MEN WITH HR+, HER2- METASTATIC BREAST CANCER

✓ Approval of expanded indication based predominately on real-world data

“…. The approval is based on data from electronic health records and postmarketing reports of the real-world use of IBRANCE in male patients sourced from three databases: IQVIA Insurance database, Flatiron Health Breast Cancer database and the Pfizer global safety database. ….”

>42,000 patients (as of 2019.2)


Note) IBRANCE for male with HR+, HER2- breast cancer is NOT approved in Japan

Transform genomic medicine into true precision medicine

**Cancer Precision Medicine**

**Personalized Health Care**
Fit one target to One Organ
e.g. Targeted therapies

**Genome Medicine**
Fit one target to Multiple Organs
e.g. Comprehensive Universal diagnostics

**Precision Medicine**
Focus on Individual patients
e.g. Insight and Decision for patients based on Mixed genome and clinical info
Cancer Genomic Medicine
— Clinical Implementation and Challenges —

Manabu Muto, M.D., Ph.D., Professor

Therapeutic Oncology Course, Kyoto University Graduate School of Medicine
Department of Clinical Oncology, Kyoto University Hospital
## COI Disclosure

**Presenter:** Manabu Muto

The presenter has the following conflict of interests relating to this presentation.

<table>
<thead>
<tr>
<th>COI description</th>
<th>Company name, etc.</th>
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<tr>
<td>Directorial/advisory roles:</td>
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<tr>
<td>Presentation fees:</td>
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<td>Manuscript fees:</td>
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<td>Joint research fees:</td>
<td>Mitsui Knowledge Industry,</td>
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<td></td>
<td>Sysmex Corporation, Riken Genesis</td>
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Agenda

1. Cancer and Genetics
2. Cancer Genomic Medicine in Healthcare Settings
3. Cancer Genomic Medicine in Current Clinical Practice
4. Future Challenges in Cancer Genomic Medicine
Cancer Genomic Medicine

Several years from now, cancer genomic medicine will likely become standard practice.
**Precision Medicine**

An emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.

Source: NIH website (as of June 25, 2019)

https://ghr.nlm.nih.gov/primer/precisionmedicine/definition

**Cancer Genomic Medicine**

*Precision medicine in the diagnosis and treatment of cancer*
Cancer

Cancer is a disease caused by genetic abnormalities
About DNA

DNA is a biological molecule that regulates expression and transfer of genetic information.

In almost all living things, DNA is the carrier and is the genetic information encoded by its base sequence.

source: *Easy biotechnology and genome*, Chugai Pharmaceutical website (Japanese only, as of June 28, 2019)

[https://www.chugai-pharm.co.jp/ptn/bio/genome/genomep08.html](https://www.chugai-pharm.co.jp/ptn/bio/genome/genomep08.html)
Protein Synthesis from Gene Transcription

Protein is formed from amino acids.
Gene Sequence Abnormalities

Baseline sequence

Normal 5’ – CTA GCC CAA TTA CAT -3’
Gene Sequence Abnormalities

Baseline sequence

Normal 5’ – CTA GCC CAA TTA CAT -3’

Point mutation 5’ – CTA ACC CAA TTA CAT -3’
Gene Sequence Abnormalities

Baseline sequence

Normal

5' – CTA GCC CAA TTA CAT -3'

Deletion

5' – CTA (---) CAA TTA CAT -3'
Gene Sequence Abnormalities

Baseline sequence

Normal  5’ – CTA GCC CAA TTA CAT -3’

Insertion  5’ – CTA GCC GCA ATT ACA T-3’
Gene Sequence Abnormalities

Baseline sequence

Normal: 5’ – CTA GCC CAA TTA CAT -3’

Amplification: 5’ – CTA GCC GCC CAA TTA CAT -3’
<table>
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<th>Type</th>
<th>Sequence</th>
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<tbody>
<tr>
<td>Normal</td>
<td>5’ – CTA GCC CAA TTA CAT -3’</td>
</tr>
<tr>
<td>Point mutation</td>
<td>5’ – CTA <strong>ACC</strong> CAA TTA CAT -3’</td>
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<tr>
<td>Deletion</td>
<td>5’ – CTA --- CAA TTA CAT -3’</td>
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</table>
Abnormal Structure of Gene

Fusion gene

Gene A

Switch domain

No function

Gene B

Activated domain

No switch

Switch domain

Activation

Malignant transformation / Increase in proliferation ability
Genetic Abnormalities Cause Abnormal Protein Synthesis

- Genetic abnormality
  - Cell
    - Gene
      - Gene expression
      - Transcription
      - Translation
      - Protein is formed from amino acids.
    - Messenger RNA
    - Liposome
    - Protein
  - Abnormal proteins are formed
Genetic Abnormalities Cause Abnormal Protein Synthesis

Genetic abnormality

Abnormal proteins may induce oncogenesis

Protein is formed from amino acids.

Gene expression

Transcription

Translation

Protein

Liposome

 Messenger RNA

Gene

#1 #2 #3 #4

OFF ON ON OFF

Cell nucleus

Cell

Gene

Disease blog, TAKAHASHI CLINIC https://hatchobori.jp/blog/4854 Accessed: 2019/07/03
Roberts PJ, Der CJ., Oncogene 2007
Genetic Abnormalities Cause Abnormal Cell Signaling = Oncogenesis

**EGFR overexpression**
- Pancreatic cancer (30%–50%)
- Lung cancer (40%–80%)
- NSCLC (14%–91%)

**EGFR mutation**
- NSCLC (10%)
- Brain tumor (20%)

**KRAS mutation**
- Colorectal cancer (30%–50%)
- Pancreatic cancer (90%)
- Papillary thyroid cancer (60%)
- NSCLC (30%)

**BRAF mutation**
- Colorectal cancer (10%)
- Malignant melanoma (70%)
- Papillary thyroid cancer (50%)

NSCLC: Non-small cell lung cancer

Gene (genome) abnormalities cause cancer

Gene (genome) abnormalities need to be examined
Testing of cancer gene abnormalities in individual patients to explore therapeutic options
Under conventional approaches, individual genes are examined for abnormalities and drugs are administered to treat diseases caused by these abnormalities.

Molecular targeted drug therapy
Cancers are caused by abnormal gene functions. For instance, lung cancers caused by different genetic abnormalities will be treated with different therapies.

"Why is Genomic Medicine Necessary in the Field of Oncology?"

The treatment of cancer has already entered the age of anticancer drug therapy based on genetic testing, and “cancer genomic medicine” will yield even greater therapeutic advancement.

Before

Use one drug for same cancer types

Limited efficacy
(approx. 20% response)

Now

Use drugs that best suit individuals regardless of cancer types based on their genetic features.

Gene analysis

- Alteration A
- Alteration B
- Alteration C
- Alteration D
- Alteration E
- No alterations

Better efficacy (>50%) can be expected from molecular targeted therapies
Advances in Gene Analysis Technologies

The Cost of Sequencing a Human Genome, National Human Genome Research Institute

https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost
Accessed: 2019/06/28
Flow of Genomic Medicine Using NGS

Sequencing

Human reference sequences

ATTTTCGGCTTTTTTTAGTATCCACAGAGGTT

TTTTTCGG

TAGTATCGAGGTTAAGTATCCACAGAGGTT

Alignment

Sequence reads

Human reference sequences

ACAGAGGGTT

TTTTTCGG

TAGTATCGAGGTTAAGTATCCACAGAGGTT

Gene annotations/Assignment of existing database information

Gene A

Gene B

Detection of mutations

Synonymous substitution

Non-synonymous substitution

Report

Assignment of filtering & clinical interpretation

✓ Protein function-related mutations
✓ Database-guided scoring of mutations, etc.

Detected mutations

Actionable biomarkers
Variants of unknown significance
Tumor mutation burden
Allele frequency
DNA quality

Details of actionable biomarkers
Gene-targeted drugs, etc.

Details of germline mutations
When using normal DNA

Molecular tumor board (MTB)/Expert panel

Medical interpretation of results
Review of therapeutic strategy
Search for clinical trials
Review of secondary findings

Sequencing

TTTTTAGT

NGS
Main NGS-based genomic profiling tests with regulatory approval & national health insurance coverage (NHI) in Japan
(Reviewed by Committee on Medical Devices and in vitro Diagnostics on Dec 13, 2018; Reviewed by Central Social Insurance Medical Council [Chuikyo] on May 30, 2019)

OncoGuide™ NCC Oncopanel System (Sysmex)

FoundationOne® CDx Cancer Genomic Profile (Chugai/Roche)
OncoGuide NCC Oncopanel System

The OncoGuide NCC Oncopanel System is a combination of medical devices comprising a template DNA preparation reagent and analysis program. It is used to output gene mutation data to support the development of therapeutic strategies based on comprehensive genomic profiling of 114-cancer related genes identified in patients with solid cancers.

FoundationOne CDx Cancer Genomic Profile

FoundationOne CDx Cancer Genomic Profile is an analysis program that outputs data on gene mutations to support the development of treatment strategies and the assessment of drug indications based on comprehensive genomic profiles of 324 cancer-related genes identified in patients with solid cancers.
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Source: Chugai Obtains Approval of FoundationOne CDx Cancer Genomic Profile as a Companion Diagnostic for Rozlytrek
OncoGuide NCC Oncopanel System

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Difference in Scope of Regulatory Approval of Genomic Medicine using NGS

OncoGuide NCC Oncopanel System
- Blood + thin-section preparation
- DNA from cancer patients
- Gene panel test
- Comprehensive genetic analysis
- Mutation detection
- Drug evaluation/
  Clinical trial evaluation
- Report

FoundationOne CDx Cancer Genomic Profile
- Thin-section preparation
- DNA from cancer patients
- Gene panel test
- Comprehensive genetic analysis
- Mutation detection
- Drug evaluation/
  Clinical trial evaluation
- Report

Scope of regulatory approval of the OncoGuide NCC Oncopanel System

Scope of regulatory approval of FoundationOne CDx Cancer Genomic Profile

[Conceptual illustration]
An Example of C-CAT Survey Results

from Information meeting for Core hospitals on 2019/02/05
Characteristics of FoundationOne CDx Cancer Genomic Profile

- Comprehensive detection/analysis of mutations*1 in 324 oncogenes
  *1: substitutions, insertion/deletion alterations, copy number alterations, and rearrangements

- Companion diagnostics

- MSI*2 determination/TMB*3 score calculation
  *2 : Microsatellite Instability   *3 : Tumor Mutational Burden

- Analysis result report provides expert review and assignment of clinical significance (annotations)

- Tested and analyzed with abundant experience in FMI

* FoundationOne CDx Cancer Genomic Profile, Chugai Website. Accessed: 2019/06/28
  https://chugai-pharm.jp/pr/npr/f1t/index/
Analysis Report of FoundationOne CDx

APPROVED THERAPEUTIC OPTION IN JAPAN

(1) CDx results with identified gene mutations and corresponding drugs

Results should be used for diagnosis and finding applicable anticancer drugs (companion diagnostics) based on identified gene mutations.

(2) Non-CDx results with identified gene mutations and biomarkers that are not used for companion diagnostics

Identified gene mutations and biomarkers that are not used for companion diagnostics are listed. Results should be used for diagnosis and support for treatment decision.

* You can review mutation data file and download/print the Analysis results reports at Chugai FMI portal site. Printed Analysis result report will be sent to medical institutions from Health inspection stations. Contents of both reports are identical.

[Precautions]
- In case of confirmation of the Analysis results reports, please refer to the latest package insert of FoundationOne CDx Cancer Genomic Profile.
- "APPROVED THERAPEUTIC OPTION IN JAPAN" is prepared based on approved drug information at the time of first approval of FoundationOne CDx Cancer Genomic Profile in Japan. In case of determining therapeutic drugs, please refer to the latest package inserts of the drugs.

APPROVED THERAPEUTIC OPTION IN JAPAN provides CDx results with identified gene mutations and corresponding drugs, Non-CDx results with other identified gene alterations, testing results of microsatellite instability and tumor mutation burden.

Source: Chugai website (accessed on June 28, 2019)
Analysis Report of FoundationOne CDx Cancer Genomic Profile

PROFESSIONAL SERVICES

(1) Results of gene mutation and biomarker detection

(2) Therapeutic drugs with an indication for the cancer type with detected gene mutations and biomarkers

(3) Therapeutic drugs with an indication for other cancer types with detected gene mutations and biomarkers

(4) Ongoing clinical trial information for the treatment of cancers with detected gene mutations and biomarkers

(5) Therapeutic drugs with an indication for the cancer type with detected gene mutations, but with no expected effectiveness due to tolerance etc.

Explanations for detected gene mutations and biomarkers, therapeutic drugs with expected efficacy and clinical trials are described in following pages. Explanations for VUS (Variant of Unknown Significance) and FoundationOne CDx Cancer Genomic Profile are described in Appendices.

PROFESSIONAL SERVICES provide information such as detected gene mutation and MSI/TMB (biomarker), therapeutic drugs with expected clinical efficacy, clinical studies and tolerance etc.

Source: Chugai website (accessed on June 28, 2019)
Cancer genomic medicine in Japan
Draft Selection Criteria for Core Hospitals for Cancer Genomic Medicine

がんゲノム医療中核拠点病院（案）等の指定要件（案）

厚生労働省健康局
がん・疾病対策課
Requirements for medical institutions to implement cancer genomic medicine:

1. A system to conduct panel tests (including outsourcing to external organizations)
2. A group of experts to offer medical interpretation of panel test results (including collaboration with other organizations in some areas of medical care)
3. Ability to provide expert genetic counseling for patients with hereditary and other cancers
4. Access to a certain number of patients who are eligible for panel testing, etc.
5. Ability to collect and manage panel test results and clinical information in a secured manner, and to register necessary information with Center for Cancer Genomics and Advanced Therapeutics.
6. A system for rapid freezing and storage of surgical specimens and other biological specimens
7. An appropriate framework for and experiences in conducting clinical studies including those for advanced medical care, investigator-initiated clinical trials, and global clinical trials.
8. Comprehensive and accessible contact services for patients and other stakeholders regarding use of medical information, clinical trial information and etc.
Committee on Designation of Core Hospital for Cancer Genomic Medicine (2018/2/14)

The committee selected the following medical institutions. Minister of Health, Labour and Welfare will designate Core Hospital for Cancer Genomic Medicine based on today’s discussion.

<table>
<thead>
<tr>
<th>#</th>
<th>Prefecture</th>
<th>Core hospitals for cancer genomic medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hokkaido</td>
<td>Hokkaido University Hospital</td>
</tr>
<tr>
<td>2</td>
<td>Miyagi</td>
<td>Tohoku University Hospital</td>
</tr>
<tr>
<td>3</td>
<td>Chiba</td>
<td>National Cancer Center (NCC) Hospital East</td>
</tr>
<tr>
<td>4</td>
<td>Tokyo</td>
<td>Keio University Hospital</td>
</tr>
<tr>
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<td>NCC Hospital</td>
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<td>Kyushu University Hospital</td>
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Conceptual Illustration of the System for Delivering Cancer Genomic Medicines and Required Functions (draft)

<table>
<thead>
<tr>
<th>Patient briefing/ Specimen preparation</th>
<th>Sequencing</th>
<th>Report generation</th>
<th>Expert meeting</th>
<th>Patient briefing</th>
<th>Treatment</th>
<th>R&amp;D</th>
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<tbody>
<tr>
<td>Core HPs</td>
<td>Required</td>
<td>Required (can be outsourced)</td>
<td>Required</td>
<td>Required</td>
<td>Required ※1</td>
<td>Required</td>
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| Liaison HPs                            | Required   | • Submit request to core HPs  
• Participate in core HP meetings etc. | Required | Required ※2 | Cooperation |

※1 In order to secure access to non-approved & off-label drugs, the Core Hospital for Cancer Genomic Medicine (tentative title) must establish a system capable of taking the initiative in conducting clinical trials (including investigator-initiated trials) and advanced medical care.

※2 The Liaison Hospital for Cancer Genomic Medicine (tentative title) must establish a system to facilitate participation in the above-mentioned clinical trials and advanced medical care.

Source: The 2nd Sub-working group meeting on the designated requirements of core HPs for Cancer Genomic Medicine (tentative title), Document #4 (2017/09/11)
Accessed: 2019/06/25
### Number of Liaison Hospitals Affiliated with Each Core Hospital

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<td>National Cancer Center (NCC) Hospital East</td>
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<tr>
<td>Keio University Hospital</td>
<td>24</td>
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<td>Kyushu University Hospital</td>
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<tr>
<td><strong>No. of liaison hospitals</strong></td>
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</table>

*Some liaison hospitals are affiliated with multiple core hospitals.*
System for Delivering Cancer Genomic Medicine: Cancer and Disease Control Division, Health Services Bureau, Ministry of Health, Labour and Welfare (MHLW)

**Future vision of the system for delivering cancer genomic medicine (draft)**

In 2017, MHLW designated the Core Hospitals for Cancer Genomic Medicine (tentative title)

Medically interpretation of gene panel test results can be integrated within the HP

Future vision*

- HR development function
- Support for diagnosis & treatment
- Clinical trial & advanced medical care initiatives
- R&D are all required.

Treatment based on the results of gene panel testing will be provided in cooperation with the Core HP for Cancer Genomic Medicine (tentative title).

*Consolidated based on the status of gene panel testing

Accessed: 2019/06/25
「がんゲノム医療中核拠点病院等の指定要件に関するワーキンググループ」

開催要綱

1. 趣旨

政府としては、平成 30 年（2018）3 月に閣議決定された第 3 期がん対策推進基本計画に基づき、ゲノム医療を必要とするがん患者が、全国どこにいても、がんゲノム医療を受けられる体制整備を進めてきた。

平成 29（2017）年 12 月に「がんゲノム医療中核拠点病院等の整備に関する指針（平成 29 年 12 月 25 日健発 1225 第 3 号厚生労働省健康局長通達の別添）」を発出し、平成 30（2018）年 2 月に、がんゲノム医療を牽引する高度な機能を有する医療機関として「がんゲノム医療中核拠点病院（以下、中核拠点病院）」を全国に 11 箇所指定し、中核拠点病院と連携して、がんゲノム医療を提供する「がんゲノム医療連携病院」を平成 31（2019）年 4 月までに 156 箇所公表してきた。

今般、がんゲノム医療提供体制をさらに充実させるため、「がんゲノム医療中核拠点病院等の整備に関する指針」を見直すとともに、自施設ががんゲノム医療を完結できる医療機関として「がんゲノム医療拠点病院」の指定要件を策定するため、本ワーキンググループを設置し、検討結果を「がん診療提供体制のあり方にに関する検討会」に報告することとする。
The Core HP for Cancer Genomic Medicine submits the application for accreditation of the Liaison HP for Cancer Genomic Medicine*

*After confirming that the developmental requirements stipulated in the above-mentioned guidance have been satisfied, the Core HP or Regional HP for Cancer Genomic Medicine will submit an application to the MHLW Minister seeking accreditation of medical institutions with which it collaborates as Liaison HPs for Cancer Genomic Medicine.

Thereafter, the Core HP or Regional HP for Cancer Genomic Medicine will submit approximately one application each year to the Minister of MHLW to seek accreditation of additional Liaison HPs.

Source: The 1st working group meeting on the designated requirements of core HPs for Cancer Genomic Medicine, Document #3
Ideal Concept for Delivering Cancer Genomic Medicine

All aspects should be integrated within a single hospital

- Patient
  - Consultation/Medical examination
  - Explains test results
    - Provides treatment

- Attending physician
  - Send samples
  - Returns test results
  - Recommend treatment strategy
  - Submit data

- Expert panel
- Clinical laboratory
Convening the expert panel
Flowchart for returning reports to attending physicians & explaining results to patients

Clinical sequencing ordered

Report returned

Expert panel

Convened within 1 week

Details of discussion uploaded to electronic medical record

Confirmed by attending physician

Results explained to patient

If this framework is not present, the practice of genomic medicine would be difficult.
Practical Example of Expert Panel Operation via Web-based System

Clinical laboratory

Cloud-based data storage contracted by core hospital

Various databases & literature

(2') Clinical interpretation
Drug & clinical trial information

(3) Data uploaded
- Analysis results
- Drug & clinical trial information
- Case summary

(4) Data sharing
- Analysis results
- Drug & clinical trial information
- Case summary

(5) Data access
- Preliminary information sharing
- Preliminary review of all cases

(6) Expert panel

Liaison hospital (same as for core hospital)

Core hospital (Kyoto University)

Core & liaison hospitals must perform virtually the same operations for case submissions

Drafting of case summary
Preliminary case review
Same-day presentation
Selection of treatment strategy
Reporting of SF

Overcoming geographical challenges
Reducing time spent
Realizing effects of training

Convening of expert panel
Interpretation of results/SF
Same-day discussion & advice

Core hospitals organize expert panel meetings & advice

[Conceptual illustration]

SF: Secondary findings
Expert Panel Structure & Performance

- Panel members

<table>
<thead>
<tr>
<th>Specialization</th>
<th>Specialization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical oncologist (clinical department)</td>
<td>Accredited genetic counselor</td>
</tr>
<tr>
<td>Surgical oncologist (surgery department)</td>
<td>Bioinformatician (NGS analyst)</td>
</tr>
<tr>
<td>Pathologist</td>
<td>Biobank personnel</td>
</tr>
<tr>
<td>Radiotherapist</td>
<td>Genomic medicine personnel</td>
</tr>
<tr>
<td>Clinical geneticist</td>
<td>CRC</td>
</tr>
<tr>
<td>Nurse</td>
<td>Postgraduate student in basic medical sciences</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>Postgraduate student in genetic counseling</td>
</tr>
<tr>
<td>Clinical laboratory technician</td>
<td>Participation is also open to interested individuals</td>
</tr>
</tbody>
</table>

Expert panel members are required to sign a confidentiality agreement, and attendance is confirmed.

- Time & date of expert panel meetings:
  From 5:30pm every Tuesday @Common Conference Room, 1F, Kyoto University Hospital Cancer Center

- Meeting format:
  Web conference via WebEx: Liaison Hospitals attend (it is allowed to join the conference without cases)
# Procedure in Preparation for Expert Panel Meeting

<table>
<thead>
<tr>
<th></th>
<th>Fri</th>
<th>Sat</th>
<th>Sun</th>
<th>Mon</th>
<th>Tue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Core hospitals</strong></td>
<td>• Check liaison hospital report(s)</td>
<td></td>
<td></td>
<td>• Distribute case summaries (for preliminary reviews)</td>
<td>• Send web conference invitation</td>
</tr>
<tr>
<td></td>
<td>• Notify liaison hospital coordinating physician and web conference supervisor of scheduled meeting</td>
<td></td>
<td></td>
<td></td>
<td>• Prepare web conference connection (from 3:00 pm)</td>
</tr>
<tr>
<td></td>
<td>• Also notify core hospital participants of scheduled meeting</td>
<td></td>
<td></td>
<td></td>
<td>• Prepare web conference meeting (from 5:00 pm)</td>
</tr>
<tr>
<td></td>
<td>• Report whether any cases will be reviewed (by 9:00 am on the day of meeting)</td>
<td></td>
<td>Draft case summary</td>
<td>• Upload presentation summary to Box by morning of meeting</td>
<td>• Convene web-based expert panel meeting (5:30 pm – around 7:00 pm)</td>
</tr>
<tr>
<td><strong>Liaison hospitals</strong></td>
<td>• Report if any case reviews are scheduled (by 9:00 am on the day of meeting)</td>
<td>Discussion of relevant literature</td>
<td>Report secondary findings</td>
<td>• Participate in meeting via web conferencing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Upload analysis report of case review(s) to Box</td>
<td></td>
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</tbody>
</table>

## Challenges
(1) Burden on web conference supervisor
(2) Burden of drafting summaries
(3) Limit on number of cases that can be reviewed (limit of 7-8 cases)
Standardizing Summaries for Web-based Expert Panel Meetings

Case outline
Age, sex, clinical diagnosis, histopathological diagnosis, family history, past & current medical history, representative images, etc.

Sequencing results
Positive biomarker, VUS, allele frequency, tumor mutational burden (TMB), any secondary findings (Y/N), etc.

Drug & clinical trial information on positive biomarker

Interpretation of secondary findings

Summary of results

Discussion of relevant literature
Drug & clinical trial evidence on positive biomarker, etc.

*Due to data storage limitations, summaries must not exceed 15 PowerPoint slides and/or 5 MB in size.

VUS: Variant of unknown significance
Cancer Clinical Sequencing in Practice

Cancer clinical sequencing at KUH
Data from OncoPrime, a non-covered medical treatment

KUH: Kyoto University Hospital
Target Patients

- Cancers of unknown primary origin
- Rare cancers
- Recurrent advanced cancers refractory to standard-of-care therapy
## List of Genes Sequenced in OncoPrime

- **Gene mutations (SNV, insertion, deletion) (all exons of 210 genes)**
- **Translocations (17 genes)**

<table>
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<tr>
<th>Gene Mutations</th>
<th>Translocations</th>
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</tbody>
</table>

*Genes marked with an asterisk are included in both lists.

Patients Characteristics
2015 April ~ 2018 September (n=251)

Cancer Type
- Pancreas
- Colon
- Biliary tract
- Unknown primary site
- Stomach
- Ovarian
- Esophagus
- Breast
- Lung
- Uterine body
- Head and neck
- Liver
- Neuroendocrine
Actionable Mutation and Druggable Mutation
2015 April ~ 2018 September (n=251)

Actionable Mutation (+)
208 cases (89.3%)

Actionable Mutation (-)
25 cases (10.7%)

Not approved in Japan
16% 4%

But approved in USA
16%

Clinical trial outside of Japan
1%

Clinical trial in Japan
63%

No trial

Most of them were OFF-label
Clinical Flow after Sequencing

OncoPrime (N=251)

↓

Successful sequencing (N=233, success rate: 93%)

↓

Actionable mutation (-) (N=25)

↓

High mutational burden “Immune checkpoint inhibitor” (N=2)

↓

Tx based on oncoprime (N=27)

Including high mutational burden “Immune checkpoint inhibitor” (N=7)

↓

Actionable mutation (+) (N=208)

↓

No Tx (N=181)

Pts administered Tx = 12.4% (29/233)

Successful sequencing (N=233, success rate: 93%)

↓

Actionable mutation (-) (N=25)

↓

High mutational burden “Immune checkpoint inhibitor” (N=2)

↓

Tx based on oncoprime (N=27)

Including high mutational burden “Immune checkpoint inhibitor” (N=7)

↓

Actionable mutation (+) (N=208)

↓

No Tx (N=181)

Pts administered Tx = 12.4% (29/233)
FDA approved (4/155, 2.6%)

Off-label (37/155, 24%)
Reasons why Therapies could not be Selected Based on Test Results

- No available targeted drugs or clinical trials: 39.4%
- General condition was poor/worsening: 21.1%
- Other treatment selected: 19.3%
- Treatment continued at referred hospital: 18.3%
- Others: 1.8%
Responders to Treatment
Treatment A won in a randomized clinical trial. Let’s use this drug.

Your cancer was caused by a mutation in gene XX. So, let’s start a treatment targeting this mutation.
Comparison of Actionable Biomarkers in Pancreatic Cancer Patients
(99 % of results come from FoundationOne CDx Cancer Genomic Profile)

A. NGS (n = 616)

- Highly Actionable: 27%
- Modifies Options: 23%
- None: 50%

B. IHC (n = 580)

- Highly Actionable: 1%
- Modifies Options: 4%
- None: 94%

C. RPPA (n = 20)

- None: 20%
- Actionable: 80%

D. Actionable Biomarkers

- mTOR/AKT Inhib: 19%
- PARP/DDR Inhib: 15%
- CDK Inhibitor: 11%
- WNT Inhibitor: 10%
- MEK/ERK Inhib: 3%
- FGFR Inhibitor: 3%

E. Therapeutic Approaches

- 5FU–based: 86%
- Gem–based: 57%
- Immunotherapy: 5%
- HER2 Inhibitor: 1%

F. Frequency of Biomarkers

- AKT/mTOR: 60%
- MEK/ERK: 45%
- JAK/STAT: 40%
- ALK/FGFR/MET: 35%
- EGFR/ErbB2/3: 35%

Michael J. Pishvaian et al. Clin Cancer Res 2018;24:5018-5027
Treatment Effect on Pancreatic Cancer Patients with Actionable Mutations

A

No treatment: 17%
No treatment change: 27%
Report: 20%
Unavailable: 20%
Early: 11%

B

C

Fraction progression-free

Highly Actionable w/ Matched Therapy
(n = 17, mPFS = 4.1 mo)

No Highly Actionable
(n = 72, mPFS = 2.8 mo)

PFS (months)

Michael J. Pishvaian et al. Clin Cancer Res 2018;24:5018-5027
Comprehensive Panel Testing and CDx Shows No Difference in Prognosis in NSCLC

From: Association of Broad-Based Genomic Sequencing With Survival Among Patients With Advanced Non–Small Cell Lung Cancer in the Community Oncology Setting

No. at risk | Testing method                | Months From First-Line Treatment |  
|------------|------------------------------|---------------------------------|  
|            | Broad-based genomic sequencing | 515                             | 195 64 23 8  
|            | Routine                       | 513                             | 192 66 18 <5  

Challenges to Cancer Genomic Medicine in Japan
Patients who have solid tumors for which there are no standard therapies, and patients with locally advanced or metastatic solid tumors who have completed standard therapies (including those who are expected to complete standard therapies)

Patients for whom their treating physician judges to be suitable for chemotherapy based on the functional status of organs, their overall condition and etc, in accordance with relevant chemotherapy guidelines

In the US, all patients with stage 3 or 4 cancer can use FoundationOne CDx under CMS coverage.
When to use NGS?

75.6% of oncologists who answered use NGS to determine treatment plan.
Eligibility for genomic testing in Japan

1. Cancers of unknown primary origin and Rare cancers
2. Cancers refractory to standard-of-care therapy

When a treatment is repeated, its effectiveness generally decreases (development of resistance).

The decision to administer a drug that is expected to be effective at the initial stage should therefore be viewed as a logical one.
So is it acceptable to perform genomic testing before initial treatment?

Standard-of-care therapy is determined by the results of large-scale Phase III clinical trials.

Even if a drug candidate is identified in genomic testing, there is no guarantee that it will become readily available.
Flow of Genomic Testing Used for Initial Treatment

Cancer genomic testing

Actionable mutation

10-15%

Yes

Treatment based on mutation profile (approved drug: off-label use)

How to evaluate?

85-90%

No

Standard-of-care therapy

If not effective
Eligibility for genomic testing in Japan

1. Cancers of unknown primary origin and Rare cancers
2. Cancers refractory to standard-of-care therapy

Is it possible to treat patients with targeted drugs under NHI coverage if genomic testing identified actionable alterations for patients whose cancers is unknown of its primary origin or for patients with rare cancers?

Eg.) Genomic testing identified ALK gene fusion in patients with cancer of unknown primary. Then, is it possible to treat patients under the diagnosis of ALK positive lung cancer? Answer is NO.
Is it possible to treat such a patient based on MoA with detailed record of his symptoms?
Precision cancer medicine is a treatment tailored to each individual.

The results of our genomic testing have identified drugs that are a potential match for each individual!

But we don’t know if this drug is a good match for this particular individual. And we don’t know if it will be effective in this particular organ.

We’ll evaluate the drug in a clinical trial. It may have different effects on different organs.

The question of whether a drug will be effective in a particular individual can only be answered by evaluating the drug in that individual.
Issues on Access to Treatment
### Treatment-related Issue:
**How can Patients be Treated with Off-label Drugs?**

<table>
<thead>
<tr>
<th></th>
<th>Patient briefing/ Specimen preparation</th>
<th>Sequencing</th>
<th>Expert meeting</th>
<th>Report drafting</th>
<th>Patient briefing</th>
<th>Treatment</th>
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<tr>
<td>Core hospital</td>
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<td>Required</td>
<td>Required</td>
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<td>Required ※1</td>
<td>Required</td>
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<tr>
<td>Liaison hospital</td>
<td>Required</td>
<td>• Ask for Core Hospitals&lt;br&gt;• Participate in Core or Regional Hospital meetings, etc</td>
<td>Required</td>
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<td>Cooperation</td>
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</table>

MHLW guidance states that the use of off-label drugs based on genomic testing is anticipated in clinical trials and advanced medical treatments...

**But do clinical trials & advanced medical treatments constitute precision medicine?**

If such treatment is to be administered in a clinical study, it should be done in a ‘basket trial’ to obtain an additional indication for an approved drug.

Source: The 1st working group meeting on the designated requirements of core HPs for Cancer Genomic Medicine, Document #3
[https://www.mhlw.go.jp/content/10901000/000505966.pdf](https://www.mhlw.go.jp/content/10901000/000505966.pdf)
Accessed: 2019/06/28
Dealing with off-label use of drugs
- For the time being, apply for off-label use on a case-by-case basis
- In the future, it will be necessary to leverage programs such as compassionate use & ‘patient-requested medical care’ (although there are considerable obstacles because the usage would have to be based on clinical trials)
- **Introduction of single patient IND**

What about off-patent drugs or drugs without data protection period?
- Companies would not be willing to conduct clinical trials for these drugs

Should beneficiaries pay?
- Dealing with test and treatment costs involving life insurance companies
- Expansion of private insurance including non-covered medical treatments
Timing Issues on Calculation of Medical Fees
Timing Issues on Calculation of Medical Fees

- Panel test fee: 8,000 points claimed
- Diagnosis and explanation fee: 48,000 points claimed

Expenses have to be claimed separately at the time of application and explaining the result.

Billing by testing company: NCC Oncopanel + F1CDx

It is important to select patients whose condition is unlikely to worsen after the tests.
Expenses have to be claimed separately at the time of application and explaining the result.

It is possible to implement expert panel and explain to patients before the arrival of C-CAT survey results.

However, diagnosis/explanation fee of 48,000 points cannot be calculated.

Should expert panel be implemented twice?

Diagnosis/explanation fees cannot be calculated unless expert panel and “explanation” are performed using the C-CAT survey results.
Challenges in the Use of FoundationOne CDx Cancer Genomic Profile as Companion Diagnostics
Timing issues with FoundationOne CDx Cancer Genomic Profile as Companion Diagnostics

Operation in the US

- Test applicable from the 1st line
- Positive in CDx: Treatment based on CDx
- Positive in profiling: Treatment by profiling (clinical trial and medical treatment at own expenses)
- Negative in both: SoC based on the guidelines

Decide treatment strategy based on genomic testing

- Reimbursement: 8,000 points

Operation in Japan

- Companion Dx
- Application for test
- Positive in CDx: Treatment by profiling (clinical trial and medical treatment at own expenses)
- Negative in CDx: SoC based on the guidelines

When SoC fails, the expert panel is implemented using the result of CDx

Profiling cost can be calculated

- EGFR: 2,500 pts
- ALK: 2,700 pts
- BRAF: 6,520 pts
- HER2: 2,700 pts
- K-Ras: 2,100 pts

Reimbursement: 48,000 points

- Results other than CDx are not informed

Ethical issues
Is it not necessary to inform patients of potentials leading to treatment other than CDx or the genetic disorder?

- Patients’ genomic status may be changed after several SoC compared to the original profiling result
- Cancer tolerance is not considered

- Only CDx fee
Loss for hospitals

- Under Japanese operation, the usefulness of panel test cannot be exerted
- What should be done when drugs that deem FoundationOne CDx Cancer Genomic Profile as their CDx emerge in the future?
  → Loss for hospitals → Testing cannot be conducted
  → Cannot access to treatment
  → Disadvantageous for patients

- Time lag for calculation?
- Only a handful can be calculated

- Patients with last line treatment only (no SoC)
- Application for test
- Positive in profiling: Treatment by profiling
- Negative in both: SoC based on the guidelines

Reimbursement: 8,000 points

- Results other than CDx are not informed

- Only CDx fee
Loss for hospitals

- Under Japanese operation, the usefulness of panel test cannot be exerted
- What should be done when drugs that deem FoundationOne CDx Cancer Genomic Profile as their CDx emerge in the future?
  → Loss for hospitals → Testing cannot be conducted
  → Cannot access to treatment
  → Disadvantageous for patients

- Time lag for calculation?
- Only a handful can be calculated
Take Home Messages

1. FoundationOne CDx is now available under the National Health Insurance scheme in Japan.

2. The time of Precision Medicine has come.

3. Further efforts are needed to bring an optimized treatment to patients faster.
Thank you.
Disclaimer

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