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Information Meeting on FoundationOne Liquid CDx

September 9, 2021

Event Summary

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[Venue Size]	
[Participants]	
[Number of Speakers]	3

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Dr. Takayuki Yoshino	Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East (NCCE), Japan

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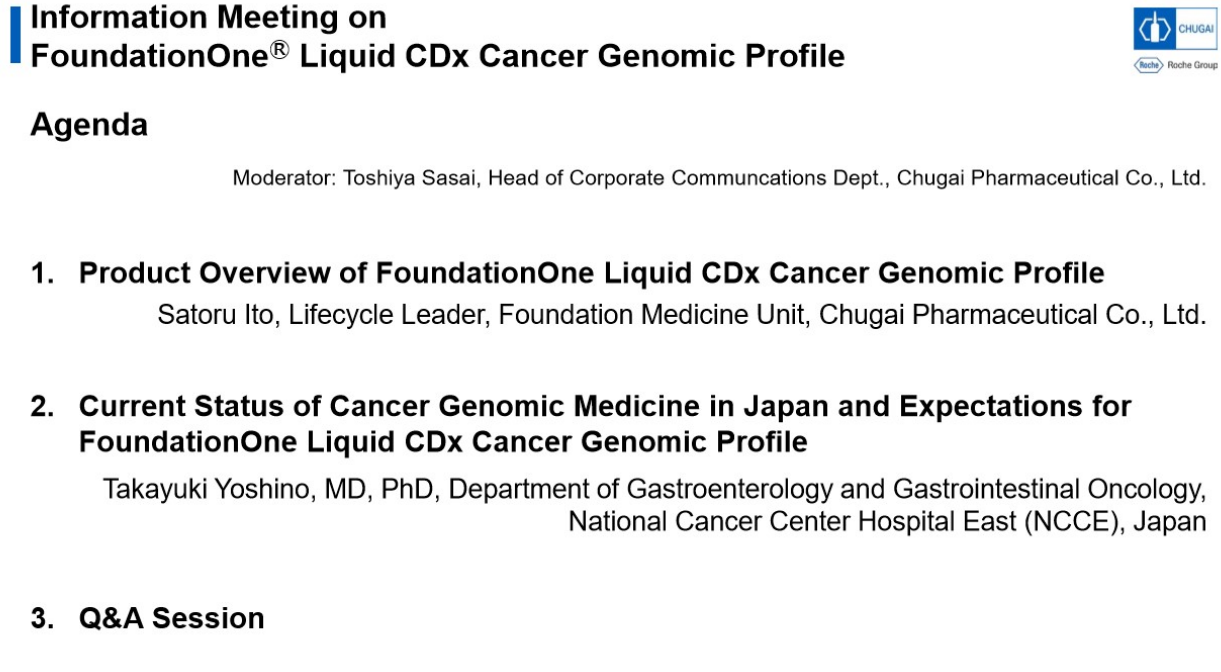
*Analysts that SCRIPTS Asia was able to identify from the audio who spoke during Q&A.

Presentation

Sasai: Thank you for joining us for today's presentation on the FoundationOne Liquid CDx Cancer Genome Profile.

I'm Sasai from the Corporate Communications Department of Chugai Pharmaceutical, and I'll be moderating today's session. Thank you.

In light of the ongoing coronavirus pandemic, today's session will be conducted in the form of a conference call.

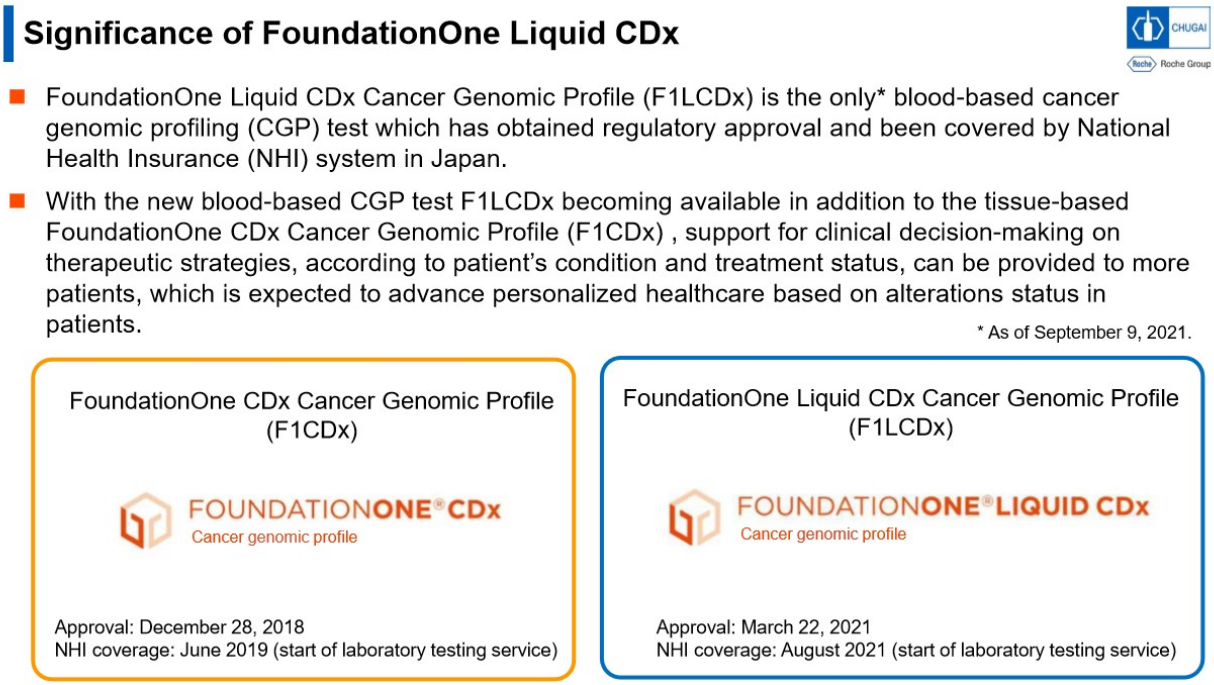


The agenda for today's meeting is shown on the screen, and also on the second page of the presentation materials. This is the format our presentation will follow.

Today, we have invited special lecturer Dr. Takayuki Yoshino, Director, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East (NCCE), Japan. I would like to skip the introduction of Dr. Yoshino's background here, as it has been sent to you along with the presentation materials for today.

Q&A session will be taken after all presentations have been completed.

Mr. Ito, Lifecyle Leader at Chugai's Foundation Medicine Unit, will now provide an overview of the FoundationOne Liquid CDx Cancer Genome Profile.



Ito: Hello, everyone. This is Ito of Chugai Pharmaceutical.

First, I would like to give an overview of the FoundationOne Liquid CDx Cancer Genome Profile product.

First, I would like to explain the significance of the launch of the FoundationOne Liquid CDx Cancer Genome Profile. As you know, the FoundationOne CDx Cancer Genome Profile is a comprehensive cancer genome profile test. It uses tumor cells and tumor tissues as specimens and was approved in Japan at the end of December 2018. It launched in June 2019, followed by the start of contract testing. It has been 2 years since then.

On March 22 of this year, FoundationOne Liquid CDx Cancer Genome Profile became the first comprehensive cancer genome profiling test, or CGP test, to be approved for testing blood samples in Japan. It became eligible for national health insurance coverage on August 1, and we started contract testing the following day.

The launch of the CGP test for blood specimens is significant. Until then, the FoundationOne CDx test could only be used for tumor tissue specimens. This means that the test could not be used on patients in whom a tumor cell specimen could not be obtained, or on an old tumor specimen.

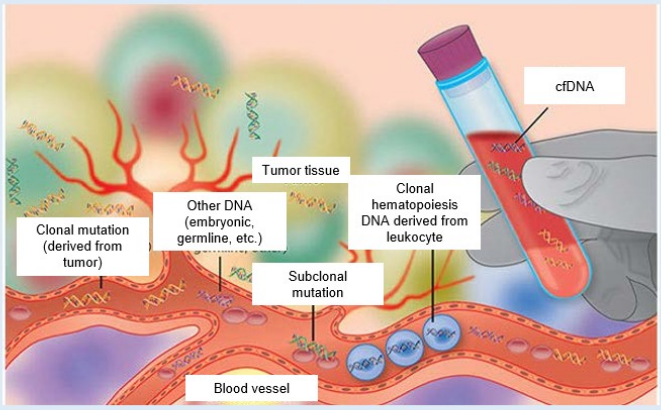
In addition, there are some patients for whom the test was submitted, but the final results were not obtained due to issues such as the quality of the specimen. For these patients, the addition of a new option for cancer genome profiling test is very significant in cancer treatment. This is a very significant step for cancer treatment.

With these 2 products, we are now able to provide support to more patients with solid cancers. These products allow more detailed treatment plans to be made, according to the patient's situation and stage of treatment. This is expected to lead to the advancement of personalized healthcare, a long-held goal of our company.

Summary of CGP Using cfDNA

➢ **In liquid biopsy test, cell-free DNA (cfDNA) including circulating tumor DNA (ctDNA) is analyzed.**

Overview of cfDNA (conceptual illustration) [1]



- The liquid biopsy test uses cfDNA for NGS analysis for genomic profiling.
- The amount of tumor cell-derived ctDNA in cfDNA as well as detected alterations suggested a possibility to provide useful information for treatment selection.
- cfDNA includes not only ctDNA but other DNAs with gene alterations. It was considered that clonal hematopoiesis of indeterminate potential (CHIP) derived from leukocyte would become an issue in cancer genomic profiling.

cfDNA: cell-free DNA, CGP: comprehensive genomic profiling,
CHIP: clonal hematopoiesis of indeterminate potential, ctDNA: circulating tumor DNA,
NGS: next generation sequencer

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[1] Bauml J, et al. Clin Cancer Res. 2018; 24(18): 4352-4354

Let me give you a brief overview of the test.

A liquid biopsy, FoundationOne Liquid CDx, analyzes cell-free DNA floating in the blood to identify circulating tumor DNA (cfDNA).

It has been suggested in previous papers that the analysis of this data may provide useful information for selecting treatments based on the detected alterations in cancer-related genes. This product has been commercialized and was the first to be approved and covered by national health insurance in Japan.

Proposal of Strategy for Proper Use of Cancer Genomic Profiling Test Using Circulating Tumor DNA

	Benefits	Reminders
Plasma CGP	• Easy to collect samples and possible to obtain information on gene abnormality in tumor at each sampling point. • Shorter time until obtaining results.	• May not be detectable when tumor burden is not sufficient. • Considered to show higher false-negative rate, compared with tissue samples. • False-positive rate increases with aging due to CHIP. • Evaluation of copy number alteration and gene fusion is difficult in some cases.
Tissue CGP	• Able to directly evaluate gene abnormality in tumor cells.	• Patient's burden for sampling and risk for complication. • Longer time until obtaining results. • False-negative may occur when the percentage of tumor cells is low. • Past samples may not reflect the present gene abnormality in tumor cells. • Samples may deteriorate at 3–5 years or more after sampling.

Partially modified from "Proposal of Strategy for Proper Use of Cancer Genomic Profiling Test Using Circulating Tumor DNA" 5
Joint task force for cancer genome medicine among Japanese Society of Medical Oncology/Japan Society of Clinical Oncology/Japanese Cancer Association, January 20, 2021

In January this year, the Task Force for the promotion of genomic medicine, a joint effort of the Japanese Society of Medical Oncology, the Japan Society of Clinical Oncology, and the Japanese Cancer Association, issued a proposal of strategy for proper use of cancer genomic profiling test using circulating tumor DNA.

FoundationOne Liquid CDx, which is a plasma CGP test using blood samples, and FoundationOne CDx, which is a tissue CGP test using tumor tissue samples, are shown here, along with benefits and points of note for each.

We believe that FoundationOne Liquid CDx and FoundationOne CDx each have their own strengths and will be positioned as complementary tests.

We believe that clinical practitioners should consider the characteristics of each test and decide which test is more appropriate based on the patient's individual situation and the course of treatment.

Dr. Yoshino will introduce the details later.

Approval Summary of FoundationOne Liquid CDx

FOUNDATIONONE® LIQUID CDx Cancer genomic profile

- Application date: March 2020, approval date: March 2021
- Generic name: Alteration Analysis Program (for cancer genomic profiling tests)
  Somatic Alteration Analysis Program (for assessing eligibility for anticancer drugs)
- Intended use:
  - To obtain comprehensive genomic profiles of tumor tissues in patients with solid cancers using whole blood samples.
  - To detect gene alterations to support the assessment of drug indications listed in the table below.

Alterations	Cancer type	Relevant drugs
Activated *EGFR* alterations	Non-small cell lung cancer (NSCLC)	Afatinib maleate, erlotinib hydrochloride, gefitinib, osimertinib mesilate
EGFR exon 20 T790M alterations		Osimertinib mesilate
ALK fusion genes		Alectinib hydrochloride, crizotinib, ceritinib
ROS1 fusion genes		Entrectinib
NTRK1/2/3 fusion gene	Solid tumors	Entrectinib
BRCA1/2 alteration	Prostate cancer	Olaparib

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Prepared based on the package insert of F1LCDx revised in May 2021 (Version 2). For the latest information about the product, please refer to the full version of package insert.

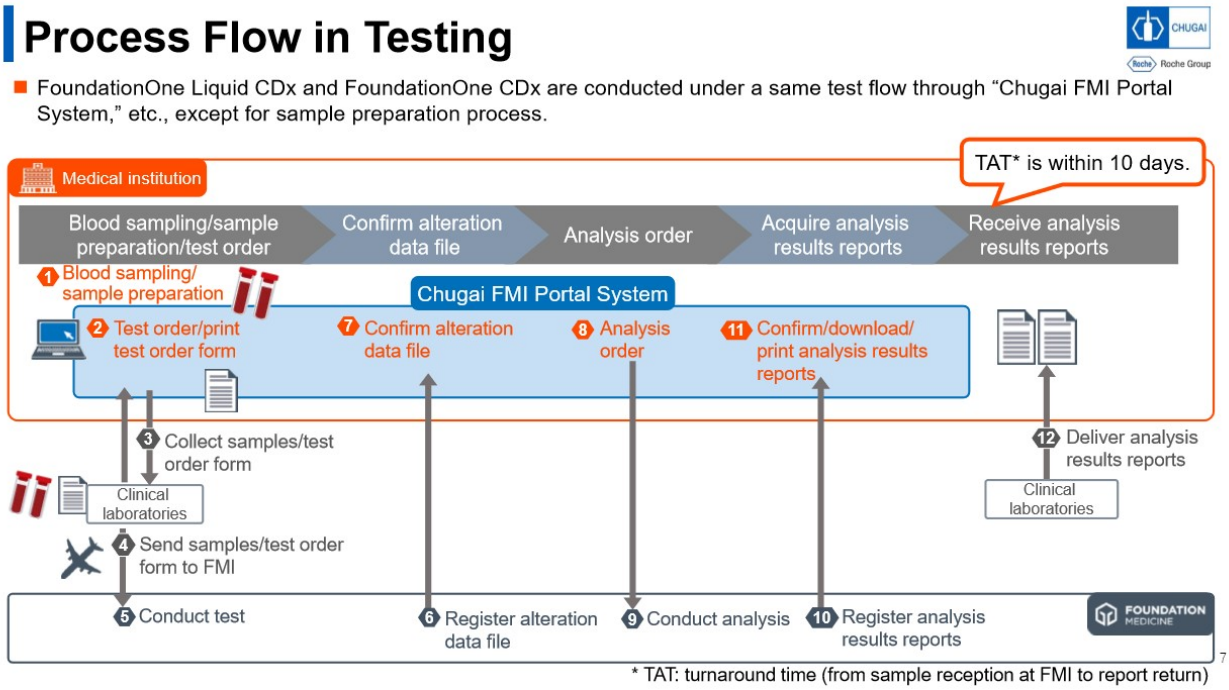
The next item is the approval summary.

As I mentioned earlier, the FoundationOne Liquid CDx Cancer Genome Profile was approved in March of this year, and the generic name is the same as that for FoundationOne CDx.

These are the 2 intended uses. The first is to obtain a comprehensive genomic profile of a tumor using whole blood samples for patients with solid tumors. The second is to detect gene alterations to assist in the determination of drug indications, as shown in the table here. Except for the difference in specimen type, this description is the same as for the other FoundationOne CDx product.

However, the table is different for the 2 products. FoundationOne Liquid CDx can be used to identify appropriate treatments for non-small cell lung cancer based on gene alterations in *EGFR*, *ALK*, and *ROS1*. Another example is the use of Entrectinib for *NTRK1/2/3* fusion gene alterations. This applies for solid tumors in general. There is also an Olaparib treatment for *BRCA1/2* mutation-positive prostate cancer and the companion diagnostic function.

As you can see from this table, FoundationOne CDx has more companion diagnostic functions. Overall, the 2 tests provide different benefits. Therefore, we believe that the appropriate test will be selected on a per-patient basis by the attending physician.



The next slide is the test flow.

The test flow is almost the same for FoundationOne CDx and FoundationOne Liquid CDx. Before ordering a FoundationOne Liquid CDx test, medical institutions should prepare 2 tubes of whole blood; 2 8.5ml tubes, 17ml altogether. After that, the Chugai FMI Portal System, which is also used by FoundationOne CDx, is also used by Liquid to receive inspection requests.

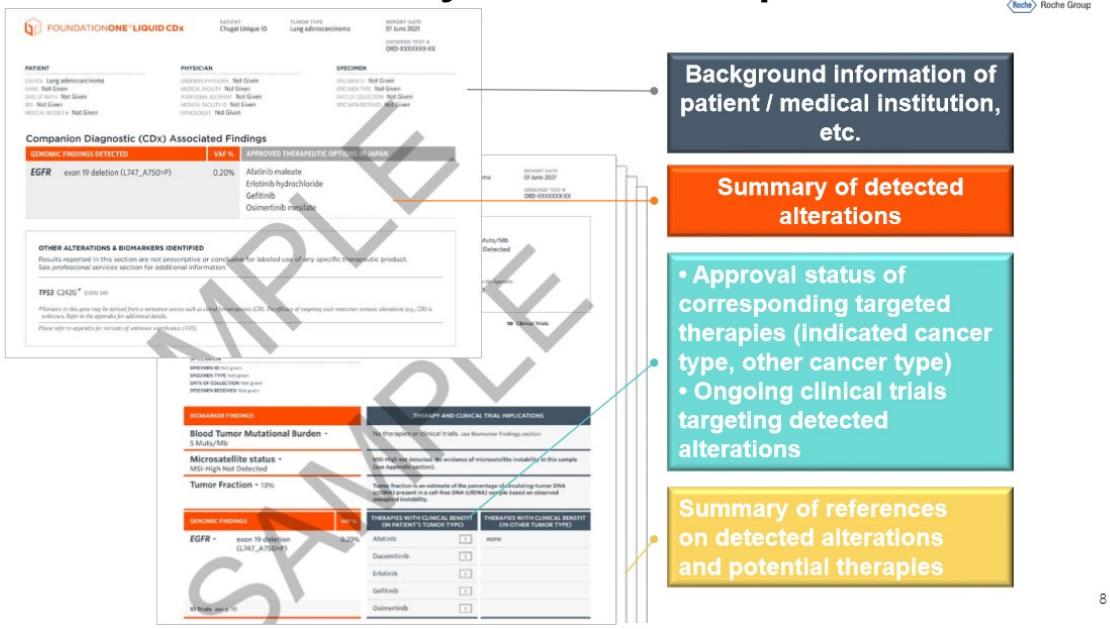
After receiving a request for testing, the specimens are sent to FMI through SRL, a laboratory.

The turnaround time is defined as the time between the arrival of the specimen at the FMI and the return of the report. A result is available for FoundationOne Liquid CDx a few days earlier than for FoundationOne CDx.

The reason for this is that some of the inspection processes are different, so we can return these results quickly.

After FMI receives the specimen, gene alterations analysis is conducted. The analysis report is registered in the Chugai FMI portal system and can be downloaded by the attending physician. After an expert panel, the final results are fed back to the patient.

F1LCDx: Overview of Analysis Results Reports



The content of the analysis report is broadly the same for FoundationOne CDx and FoundationOne Liquid CDx.

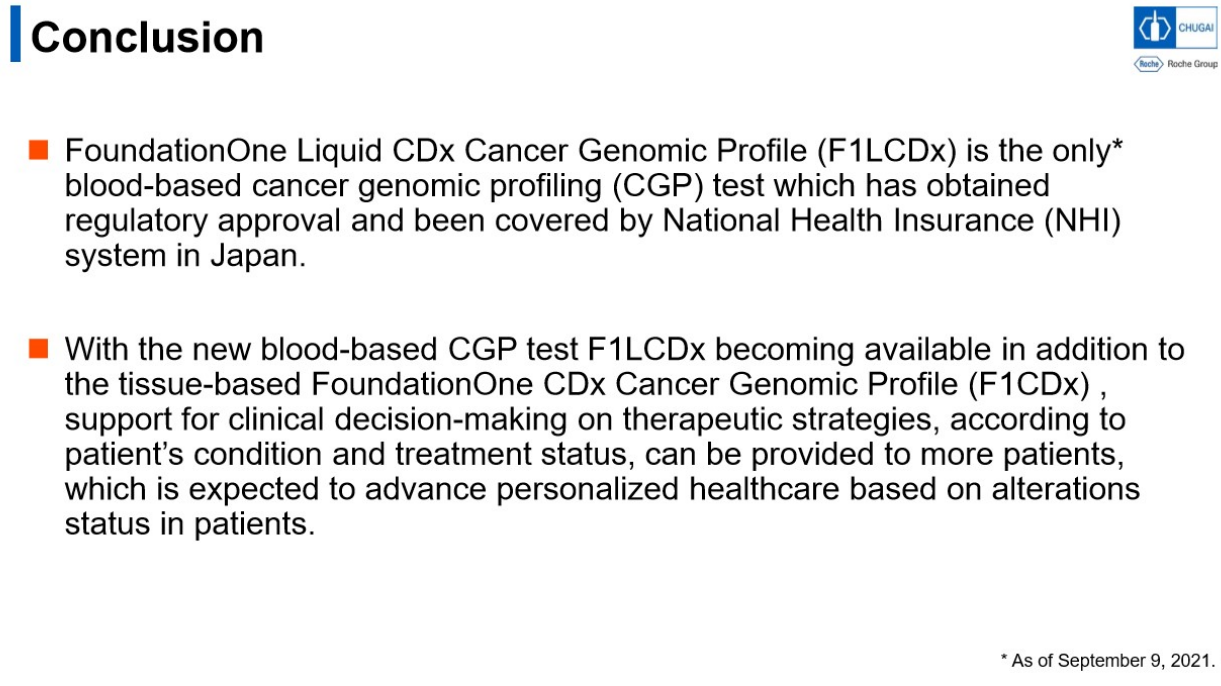
The first page contains background information about the patient and the medical institution, and after that there is a summary of the cancer-related gene alterations detected in the test. If a genetic alteration related to the accompanying diagnosis is found, the result of the alteration will be listed in the orange area on the upper left of this page, and the appropriate drugs will be listed on the right side.

Genetic alterations unrelated to the accompanying diagnosis are listed in the Other Alterations section.

The second and subsequent pages are for reference only. They are called Professional Services, and they contain information on molecular targeted therapies that correspond to the detected cancer gene alteration, and their approval status. In addition to the cancer type in question, there will also be information on the status of other cancer types.

A summary of ongoing clinical trials for the alteration will also be added here. Then, a summary based on the literature will be included to explain the clinical significance of the detected genetic alterations, cancer-related genetic alterations, and the evidence-based therapeutic agents that have been proposed as candidates.

So, all in all, the report will be about 10 pages to 20 pages long. The FoundationOne Liquid CDx report will be returned in the same way as that of FoundationOne CDx. To date, these reports have been highly rated by specialists in Japan, so we will continue to send out this type of report.



That was my brief introduction to the FoundationOne Liquid CDx Cancer Genome Profile.

This is a new CGP test using on blood samples. Based on these 2 products, we will continue our efforts to contribute to the treatment of solid tumors. We hope to provide this cancer genome profile test to as many solid cancer patients in Japan as possible. Thank you, very much, for your attention.

Sasai: Next, Dr. Yoshino will discuss the current status of cancer genome medicine, as well as expectations for the FoundationOne Liquid CDx cancer genome profile.

Please go ahead, Doctor.

Yoshino: Hello everyone. I am Dr. Yoshino, Director, the Department of Gastroenterology and Gastrointestinal Oncology at the National Cancer Center Hospital East, Kashiwa-city.

I am very grateful to have the time to speak to you today, and I apologize if speaking by webcast like this feels somewhat distant. There will be a Q&A session afterwards, and I would appreciate your frank opinions and questions. I would also like to thank Chugai for giving me the opportunity to talk today.

Today, I would like to talk about the current status of cancer genomic medicine and expectations for the newly approved FoundationOne Liquid CDx cancer genome profile from the viewpoint of an oncologist.

Disclosure of Conflict of Interests

Name: Takayuki Yoshino

Lecture Fee:

Sanofi K.K., TAIHO PHARMACEUTICAL CO., LTD., Takeda Pharmaceutical Company Ltd., Chugai Pharmaceutical Co., Ltd., Bayer Yakuhin K.K., Merck Biopharma K.K.

Research Funding:

Amgen Astellas BioPharma K.K., Ono Pharmaceutical Co., Ltd., Sanofi K.K., TAIHO PHARMACEUTICAL CO., LTD., DAIICHI SANKYO COMPANY, LTD., Sumitomo Dainippon Pharma Co., Ltd., Chugai Pharmaceutical Co., Ltd., PAREXEL International Inc., MSD K.K.

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This slide shows conflicts of interest.

Topics

- Current status of cancer genomic medicine in Japan
- What is liquid biopsy?
- Clinical research data using liquid biopsy
- Expectation and issues around FoundationOne Liquid CDx Cancer Genomic Profile

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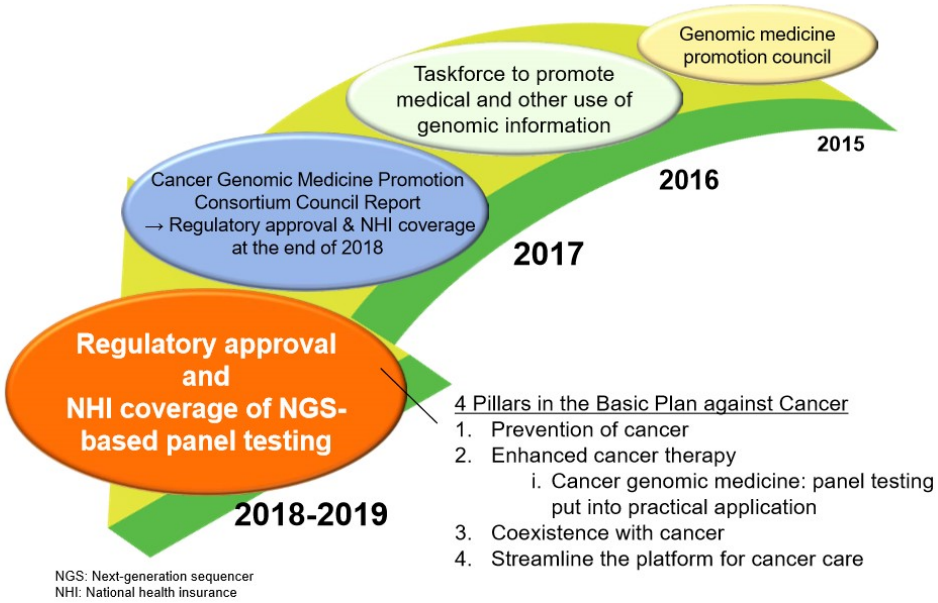
Today, I would like to spend some time discussing these 4 topics. This should cover about 50 minutes.

First of all, let me start with the current status of cancer genome medicine in Japan.

Governmental Activities for Genomic Medicine

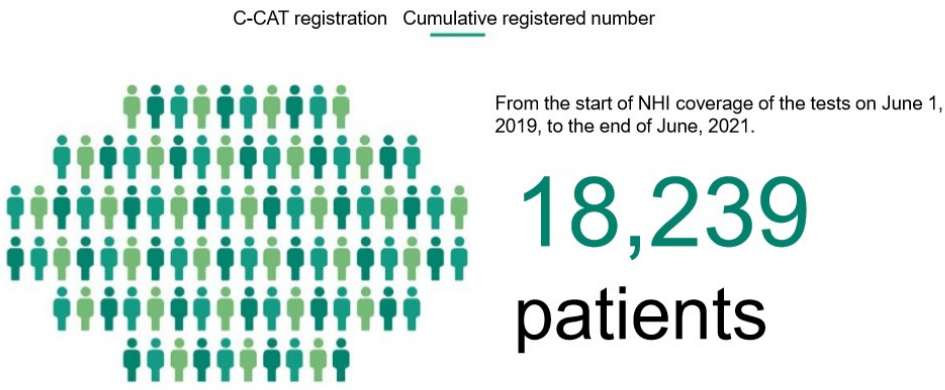


From the outset, cancer genome medicine has been the subject of many governmental councils and task forces. Recently, a big topic has been in the second of the 4 pillars of the Basic Plan against Cancer: the practical application of cancer genome medicine panel tests.

From June 2019, a cancer tissue NGS-based panel from FoundationOne was included in coverage for national health insurance. This marked the first year of cancer genomic medicine. Cancer genomic medicine had started in Japan. This next-generation sequencer panel is necessary for the practice of cancer genome medicine. With the approval of this panel, cancer genome medicine entered practice in Japan in June 2019.

Implementation Status of Cancer Gene Panel Test in Japan

- The cumulative number of patients who received cancer gene panel test and were registered in C-CAT is 18,239.
- The number of patients who died from cancer in 2019 is 376,425#.
- The percentage of patients who received cancer gene panel test is less than 5% among the annual number of patients who died from cancer.



* "Cancer Registry and Statistics" Cancer Information Service, National Cancer Center (https://for-patients.c-cat.ncc.go.jp/registration_status/) Accessed on Aug., 2021
# Cancer Statistics Update, Cancer Information Service (https://ganjoho.jp/reg_stat/statistics/stat/summary.html) Accessed on Aug., 2021

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So, how many patients have actually received cancer gene panel test in the past 2 years? As of June 2021, a total of 18,239 people has undergone this panel test using the next-generation sequencer.

However, the number of patients who died of cancer in 2019 was 370,000. So, if we use this as the denominator for the number of people who received the treatment, it is about 4.8% so less than 5%.

Currently, this panel test is approved for patients for whom there is no standard of care. This means all the established treatments have been tried, and they are no longer effective. Basically, it is approved in cases where no other options are available.

This means that typically, the patient's disease is in a very advanced state. These patients have only a short time left to live, and they are usually quite desperate to undergo this test. However, in reality only 5% of patients who died from cancer actually underwent this test.

Implementation System of Cancer Genomic Medicine in Japan [1]

	Patient explanation (testing)	Sample preparation	Sequencing	Expert Panel (expert meeting)	Preparation of reports	Patient explanation (results)	Treatment	Clinical trials/research and development of advanced medical care	Development of human resources
Designated core hospitals for cancer genomic medicine	Essential		Outsourcing available	Essential		Essential	Essential	Essential	Essential
Designated hospitals for cancer genomic medicine	Essential		Outsourcing available	Essential		Essential	Essential	Cooperation	Cooperation
Cooperative hospitals for cancer genomic medicine	Essential		Outsourcing available	Participation in meeting, etc. in designated core hospitals for cancer genomic medicine or designated hospitals for cancer genomic medicine		Essential	Essential	Cooperation	Cooperation

Application of cooperative hospitals for cancer genomic medicine by designated core hospitals for cancer genomic medicine or designated hospitals for cancer genomic medicine. *

*: A designated core hospital for cancer genomic medicine or a designated hospital for cancer genomic medicine should apply own cooperative hospitals institution candidates to the Minister of Health, Labour and Welfare, after the confirmation of fulfilling the requirements for preparation guidelines. Thereafter, the designated core hospital for cancer genomic medicine or designated hospital for cancer genomic medicine should apply the addition of cooperative hospitals for cancer genomic medicine around every 1 year.

[1] Cancer and Disease Control Division, Health Service Bureau, Ministry of Health, Labour, and Welfare: modified from Progress of Approach on Cancer Genomic Medicine (https://www.mhlw.go.jp/content/10901000/000573711.pdf) (as of March 2021) Accessed August 2021 16

In fact, the implementation system for cancer genome medicine in Japan is led by the Ministry of Health, Labor and Welfare. Hospitals are rated in 3 categories: core hospitals for cancer genome medicine, which are generally referred to as designated core hospitals; then designated hospitals for cancer genomic medicine; and finally, cooperative hospitals for cancer genomic medicine.

The most important difference is whether or not an expert panel takes place at the hospital. These are only held at designated hospitals and designated core hospitals. The cooperative hospitals below will be studying in a way that is tied to a designated hospital or designated core hospital.

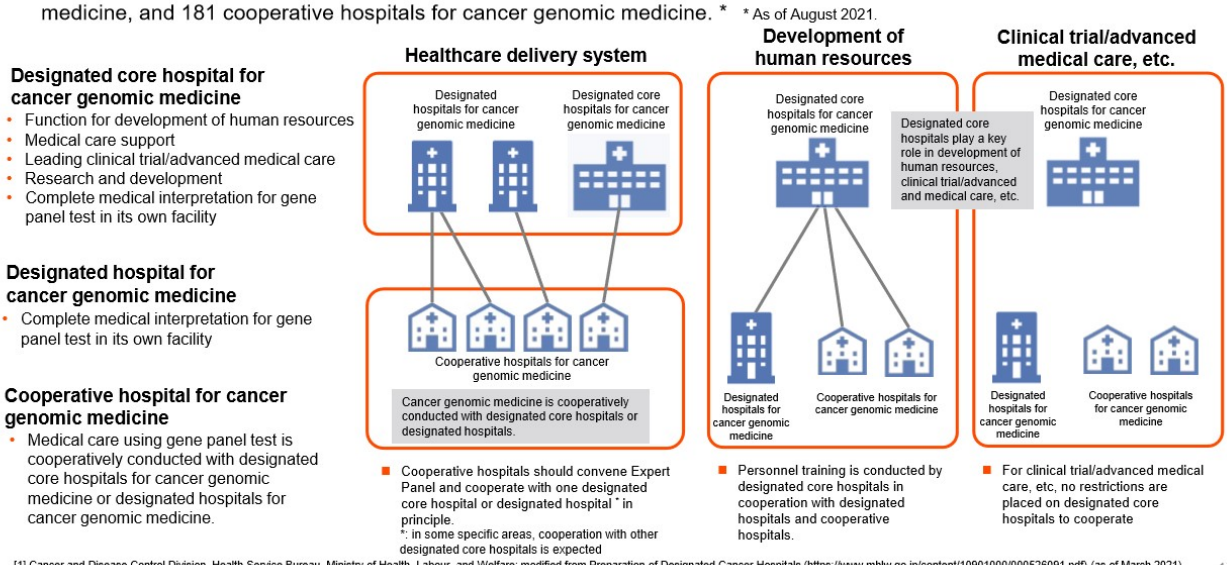
Patients can be tested at any of these 3 types of hospitals. However, the results of these tests, which I will show you later, must be discussed at a meeting of experts called an expert panel, and a report must be prepared before we can move on to explaining the results to the patient. This system means we can return correctly interpreted results to patients.

What is the difference between designated core hospitals and designated hospitals?

At the designated core centers, clinical trials, advanced medical treatment, research and development, and human resource development, all take place. The other hospitals are tied to them. This is the difference.

Cooperative System between Designated Core Hospitals for Cancer Genomic Medicine, etc. [1]

- There are 12 designated core hospitals for cancer genomic medicine, 33 designated hospitals for cancer genomic medicine, and 181 cooperative hospitals for cancer genomic medicine. * * As of August 2021.



[1] Cancer and Disease Control Division, Health Service Bureau, Ministry of Health, Labour, and Welfare: modified from Preparation of Designated Cancer Hospitals (https://www.mhlw.go.jp/content/10901000/000526091.pdf) (as of March 2021) Accessed August 2021

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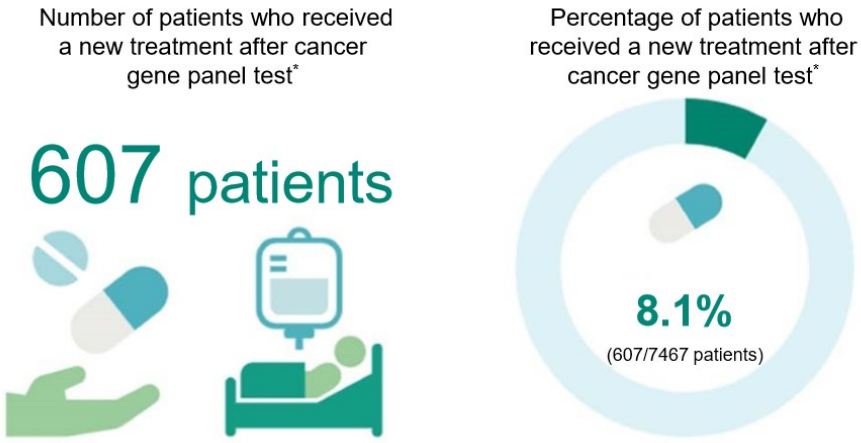
The data shows how many such hospitals there actually are. As of August 2021, there are 12 designated core hospitals, 33 designated hospitals, and 181 cooperative hospitals. This is how the hospitals are arranged.

As shown here, hospitals are not necessarily connected to each other in terms of medical care delivery systems, human resource development, clinical trials, and advanced medical care.

In terms of the medical care delivery system, the designated core and designated hospitals will naturally take the lead in providing medical care in collaboration with the cooperative hospitals.

In terms of human resource development also, the designated core hospitals will take the lead. In the case of clinical trials and advanced medical care, 3 hospitals are defined as core centers.

Percentage of Patients Received Genomically Matched Treatment (Reported by C-CAT)



- Patients represent persons who received any drug proposed at Expert Panel. Performance from September 1, 2019, to August 31, 2020 (based on survey by Ministry of Health, Labour, and Welfare)

https://for-patients.c-cat.ncc.go.jp/registration_status/ Accessed August 2021

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In fact, from September 2019 to August 2020, an MHLW survey showed that the number of people who actually received drugs after a cancer gene panel test, including new clinical trials and so-called approved drugs, was 607. The results showed that it was 8.1% of the 7,467 people tested by that time.

A quick look at this may lead you to believe that it is a very inefficient test, as not even 1 in 10 people receive the medicine, but this is also the case in other countries.

Percentage of Patients Who Received New Treatment Based on Cancer Gene Panel Test in Designated Core Hospitals for Cancer Genomic Medicine (11 Hospitals)

- Under the current health insurance reimbursement system, 3.7% of patients received treatment following cancer gene panel test after completion (or before potential completion) of standard of care. (Research conducted at 11 Designated core hospitals for cancer genomic medicine from Jun, 2019 to Jan, 2021)
- It was also confirmed that the percentage of patients, who received treatment following the panel test, differed between designated core hospitals for cancer genomic medicine (0 to 10%).

Designated core hospitals for cancer genomic medicine	Number of patients received cancer gene panel test based on health insurance	Number of patients received treatment based on gene alterations
A	75	3 (4%)
B	60	2 (3.3%)
C	5	0 (0%)
D	41	0 (0%)
E	160	16 (10%)
F	172	4 (2.3%)
G	13	1 (7.7%)
H	13	0 (0%)
I	98	0 (0%)
J	24	0 (0%)
K	86	2 (2.3%)
Total	**747**	**28 (3.7%)**

Sunami K, et al. Int J Clin Oncol 2021; 26(3): 443-449. 19

However, at that time, when there were 11 core hospitals, of which there are now 12, there was a MHLW team that I am working with and the MHLW C-CAT survey included standard of care other than clinical trials. The MHLW's C-CAT survey includes standard of care other than clinical trials, but if we look at the results when we focus only on clinical trials and new drugs the figure is 3.7%.

However, as you can see, there are quite a few regional differences, ranging from no hospitals at all to hospitals that receive up to 10%. As for this update, we are planning to report at a European conference in 2 weeks that cancer genome medicine has become quite popular in Japan.

Recommended Treatment by Expert Panel: Difference between Hospitals

(Yoshino subgroup, Health and Labor Sciences Research Grants)

Simulated case 1: colorectal cancer

Somatic variants
BRAF V600E
ATM R35*
NF1 Y1521*
TP53 R273H
APC c.1312+1G>A
ARAF R326*
NTRK2 L138P
Germline variant
BRCA2 V208G

Analyzed by **NCC oncopanel**

Colon cancer

FOLFOX+bevacizumab
FOLFIRI+cetuximab
Investigational drug
regorafeinib
-
-
Mother: Breast cancer (40's)
Sister: Breast cancer (50's)
Hypertension
OncoGuide™ NCC oncopanel

Site	Recommended therapy	Considered therapy
A	dabrafenib+trametinib	LXH254, TP0903. olaparib, talazoparib+avelumab, BAY1895344, TAK-931
B	dabrafenib+trametinib	-
C	binimetinib+cetuximab +encorafenib	-
D	dabrafenib+trametinib	-
E	binimetinib+cetuximab+encorafenib, dabrafenib+trametinib, talazoparib+avelumab, BAY1895344	-
F	dabrafenib+trametinib, TP0903, BAY1895344	-
G	-	dabrafenib+trametinib
H	dabrafenib+trametinib	-
I	binimetinib+cetuximab+encorafenib, dabrafenib+trametinib, TP0903	-
J	dabrafenib+trametinib	-
K	binimetinib+cetuximab+encorafenib, dabrafenib+trametinib, PARP inhibitor	-

-: no therapies recommended / considered

Simulated case 2: Hormone receptor-positive breast cancer

Somatic variants
PIK3CA H1047R
ERBB2 S310Y
CCND1 amplification

Analyzed by **F1CDx**

Breast cancer (ER+, PgR+, HER2 1+)

anastrozole
fulvestrant+palbociclib
paclitaxel+bevacizumab
eribulin
capecitabine
doxorubicin+cyclophosphamide
FoundationOne CDx Cancer Genomic Profile

Site	Recommended therapy	Considered therapy
A	-	everolimus+exemestane
B	-	-
C	trastuzumab deruxtecan	-
D	everolimus+exemestane, trastuzumab deruxtecan	-
E	trastuzumab deruxtecan	-
F	-	everolimus+exemestane
G	-	-
H	alpelisib	afatinib
I	alpelisIb, neratinib	-
J	-	everolimus+exemestane
K	PI3K inhibitor	-

-: no therapies recommended / considered

ER: Estrogen receptor, PgR: Progesterone receptor

Sunami K, Naito Y, et al. Int J Cln Oncol 2021;26:443-449

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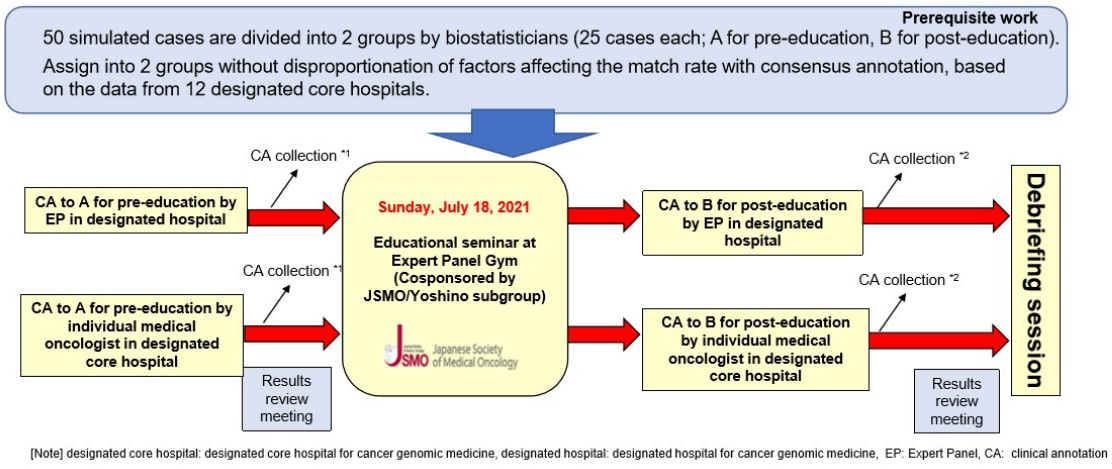
There are high expectations for the so-called expert panels, which consists of expert doctors as well as some non-doctors.

We created 2 fictitious cases, which experts thought might actually exist, and asked the expert panels at the 11 core hospitals to recommend treatment.

The conclusion was that the recommended treatment varies greatly from facility to facility. In other words, we found that there are large differences among facilities. We believe that this is due to the information gap between what clinical trials are running and what is currently underway in Japan.

"Expert Panel Program" (Yoshino Subgroup, Health and Labor Sciences Research Grants)

Entire Picture of Training Program for Expert Panel and Doctors Involved in Cancer Genomic Medicine



[Note] designated core hospital: designated core hospital for cancer genomic medicine, designated hospital: designated hospital for cancer genomic medicine, EP: Expert Panel, CA: clinical annotation

- **Evidence creation from Japan where Expert Panel is conducted throughout the country**
- **Exploratory evaluation on effectiveness of AI, etc. can be conducted (industry–government–university: participation of AI companies)**

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Last year, we held frequent group meetings with doctors from the 12 core hospitals that currently exist, and we have been trying to network such clinical trial information. In other words, to share it and to deliver clinical trials to patients by sharing information on restrictions.

In the process, a group of experts created 50 simulated cases, 50 more advanced cases than the 2 I mentioned earlier, and created a consensus annotation of the answers to these cases. We will distribute it to the 12 core hospitals, and we will present the results of how many correct answers we get at the ESMO in 2 weeks. This will be announced.

Recently, we have been conducting a program called the [Expert Panel] Program, in which 25 questions are given to expert panels at designated hospitals and individuals from designated core hospitals. They are asked to solve the questions.

We are now in the second half of the 25 cases. We have been teaching information about the drugs that are available when cancer abnormalities are detected at the educational seminars here.

We expect that if this program leads to improved interpretation and annotation among expert panels at designated hospitals, then it will contribute to the standardization of care.

However, as I mentioned earlier, even if the number of patients is only 5% of the total number of patients in the country, the expert panels nationwide already have quite a heavy workload. There is a limit to how much we can do by ourselves. Perhaps, in the future, companies will need to enter the market. I believe that the introduction of AI in this area is necessary.

Overview of Expert Panel Gym

[Sponsor/planner]
Cosponsored by Japanese Society of Medical Oncology/Yoshino subgroup (integrated research project on accelerated measures for cancer; Health and Labor Sciences Research Grants)

[Supporter]
Japanese Cancer Association, Japan Society of Clinical Oncology, Hokkaido University Hospital, Tohoku University Hospital, National Cancer Center Hospital East, National Cancer Center Hospital, Keio University Hospital, The University of Tokyo Hospital, Shizuoka Cancer Center, Nagoya University Hospital, Kyoto University Hospital, Osaka University Hospital, Okayama University Hospital, Kyushu University Hospital

[Contact]
Expert Panel Gym Management Office (in Peak 1 Co., Ltd.)
expert_panel@event-info.jp

[Remarks]
- The analysis results for the effectiveness of this education will be published at any medical conference in Japan and overseas or in any literature.
- Also, it will be reported in integrated research project on accelerated measures for cancer of the Minister of Health, Labour and Welfare, JSMO administrative board, and education results in designated core hospitals for cancer genomic medicine.

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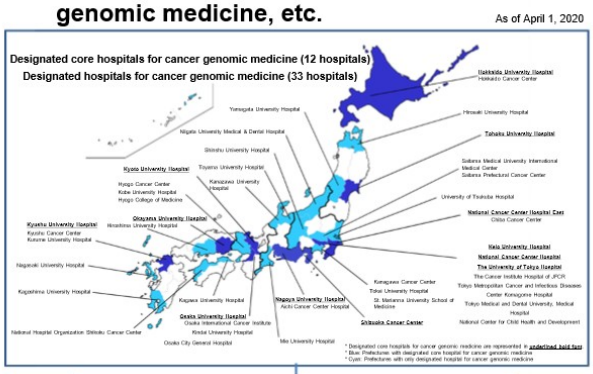
As shown here, the 3 major cancer societies, the Japanese Association for Cancer Research and the Japanese Association for Cancer Therapy, are firmly committed to this event. And all of the 12 core cancer genome hospitals are also supporting it. This is currently in progress, and we hope to present the results next year.

Current Situation and Issues of Expert Panel Operation

Designated core hospitals for cancer genomic medicine, etc.

As of April 1, 2020



Cooperative hospitals for cancer genomic medicine

- There are only 45 hospitals (designated core hospitals and designated hospitals for cancer genomic medicine) throughout the country which can conduct Expert Panel.
- Some prefectures do not have any facility for Expert Panel.

Modified from the 2nd meeting of the working group on analysis of entire genome in cancer, Ministry of Health, Labour, and Welfare (November 19, 2019)
https://www.mhlw.go.jp/stf/newpage_07955.html (Accessed Aug., 2021)

Preparation before Expert Panel

- Time and effort required for preliminary preparation (around 30 min per case)
- There are some Expert Panels which request preliminary preparation to cooperative hospitals.
- Participation of AI companies

Convening of Expert Panel

- Increase in cases: 10 to 30 cases per panel (according to EPWG)
- Required time per case: 3 to 15 min (according to EPWG)
- Securement of necessary personnel for convening, and education
- Missing calculation: 177 of 4404 events (4.0%) in designated core hospitals

Consideration by EPWG

- Share the current situation of each facility.
- Cases in cooperative hospitals are increasing → Bringing burden
- Sorting into cases with focused examination and else cases
- Shortening time by not conducting case presentation by attending physicians

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This is the expert panel. I mentioned earlier that it is quite overworked but let me show you how much energy is needed for annotation.

We don't suddenly have a discussion at the meeting where we do the expert panel, but preparations are made in advance. This takes about 30 minutes per case. The meeting time spent per case is about 3 minutes to 15 minutes because of the advance preparation. This is a result of the coronavirus pandemic.

The truth is that it is quite difficult to have a conference with that many different experts in 1 place. However, due to the fact that this is tied to national health insurance points, we have no choice but to do it. There is also the securing and training of the human resources necessary for the event.

However, on top of that, I mentioned earlier that the patients are those who have completed all the standard of care, so their condition is likely to worsen. The cost cannot be calculated without explaining it to the patient, which means that 4% of the cost is actually omitted from the calculation. The amount of money involved in 1 missed calculation is JPY480,000, so even at 4%, this is a considerable amount of money.

In fact, there is a working group of experts called C-CAT that is sharing information, but the number of cases is increasing rapidly, and the field is becoming overwhelmed. In addition, due to the effects of the coronavirus pandemic, the burden on the expert panel is becoming so great that it is becoming practically impossible to treat all cases.

Clinical Practice Guidance Based on Gene Panel Test Using Next Generation Sequencer, Etc. (Guidance from 3 Societies *)

* Japanese Society of Medical Oncology/Japan Society of Clinical Oncology/Japanese Cancer Association

Version 1.0 Published: October 11, 2017

3. Utilization of gene panel test according to cancer type
3-1 Attitude to common target case and timing for test
(1) Before starting pharmacotherapy
To consider elaborate therapeutic strategy for patients with solid cancer who have no standard of care, based on cancer genome information, the test will be conducted before starting pharmacotherapy in principle to obtain information on genomic alteration related to drug selection using gene panel test.

(2) Exploration of new treatment for progressed disease after standard of care
For the selection of treatment, the standard of care specified in the guidelines of each society will have priority, and diagnosis related to drug application, etc. will be conducted using companion drugs, if necessary. **Gene panel tests will be conducted for patients with recurrent or progressed disease after standard of care in order to determine drugs expected to be effective.**

Version 2.1 Published: May 15, 2020 Excerpt

CQ6: When should cancer genomic profiling test be conducted?

- **It is recommended to consider optimal timing** to conduct cancer genomic profiling test, **considering not only therapeutic line** but also subsequent treatment plan.

CQ12: When should the consideration at Expert Panel be conducted?

- Regarding cancer genomic profiling test, in the case when "cancer genomic profiling test is conducted for patients with solid cancer who have no standard of care or completed (or will complete) standard of care due to local progression or metastasis, and were determined to be likely subjected to chemotherapy after implementation of this test **by attending physician**, based on their general conditions, organ functions, etc., according to the guidelines on chemotherapy from any relevant society," **the test results should be discussed at Expert Panel as soon as possible and explained to patients.**
- When cancer genomic profiling test results are obtained in any case excluding the above, the results should be also discussed at Expert Panel as soon as possible. **Individual action is recommended** after the timing to explain the results is considered at Expert Panel.
- For patients who have already have the results of cancer genomic profiling test due to any reason, **the postponement of consideration at Expert Panel until completion of standard of care as well as the queuing of results return are not acceptable in terms of science and ethics, because they may limit the patient's therapeutic option or have risk for delayed action or delayed or insufficient information provision for matters to be addressed including secondary finding.** The test results as well as the timing to return the results should be considered at Expert Panel as soon as possible, thereafter, individual action is preferred to be taken after determination of the matters requiring prompt return and the matters requiring continual appropriate discussion.

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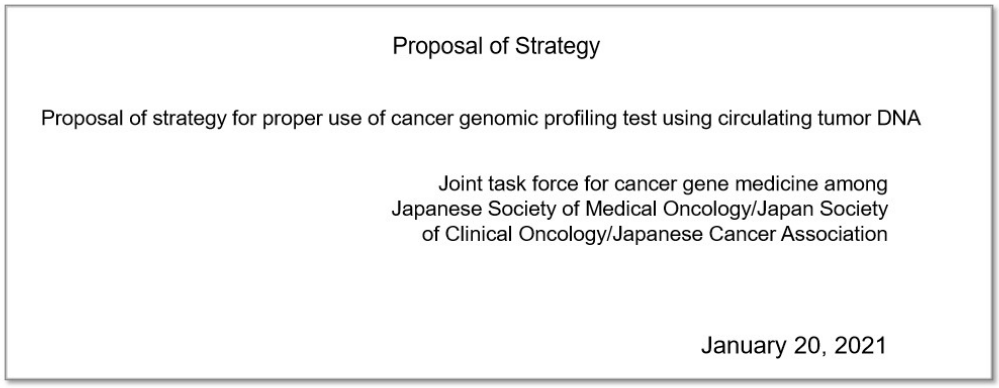
The reason for this positioning of the panel test, where it is offered after all standards of care are exhausted, is that guidance recommending it from the 3 societies was produced in 2017. At that time, there was still little evidence.

However, recent guidance suggests that it should be done at an appropriate time, and that the expert panel should discuss the results and explain them to the patient as soon as possible. It has been suggested that it is important to perform this NGS gene panel test at a much earlier stage.

However, the current national health insurance coverage is only for later treatment, which means that the results are not easily utilized.

Proposal of Strategy for Proper Use of CGP Test Using Circulating Tumor DNA

- To implement plasma CGP test without delay in Japan, the proposal of strategy for proper use of cancer genomic profiling test using circulating tumor DNA (ctDNA) was issued by the Joint task force for cancer genome medicine among 3 societies in January of this year.


Proposal of Strategy

Proposal of strategy for proper use of cancer genomic profiling test using circulating tumor DNA

Joint task force for cancer gene medicine among
Japanese Society of Medical Oncology/Japan Society
of Clinical Oncology/Japanese Cancer Association

January 20, 2021

CGP: Comprehensive genomic profiling 25

As Mr. Ito of Chugai Pharmaceutical mentioned earlier, this blood-based CGP test was welcomed by the 3 academic societies, and the 3 societies made a joint policy proposal.

What is Liquid Biopsy? [1]

- Liquid biopsy is expected as less-invasive or noninvasive gene testing. Liquid biopsy means an analysis using tumor-derived samples (cells, nucleic acids, etc.) obtained from blood and body fluid. Especially, part of circulating tumor DNA (ctDNA) analysis has been already applied in clinical.

Excerpted from Section 3.2 “New technology” (p. 73–75), Clinical practice guidance based on gene panel test using next generation sequencer, etc. (revision, version 2.1) edited by Japanese Society of Medical Oncology/Japan Society of Clinical Oncology/Japanese Cancer Association.

[1] Clinical practice guidance based on gene panel test using next generation sequencer, etc. (revision, version 2.1), 2020, p. 73–75 edited by Japanese Society of Medical Oncology/Japan Society of Clinical Oncology/Japanese Cancer Association.
Japanese Society of Medical Oncology (https://www.jsmo.or.jp/about/doc/20200310.pdf, as of November 2020)
Japan Society of Clinical Oncology (http://www.jca.gr.jp/researcher/topics/2020/files/20200518.pdf, as of November 2020)
Japanese Cancer Association (http://www.jsco.or.jp/jpn/user_data/upload/File/20200519.pdf, as of November 2020)

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In this context, liquid biopsy has attracted a lot of attention. But first of all, what is liquid biopsy?

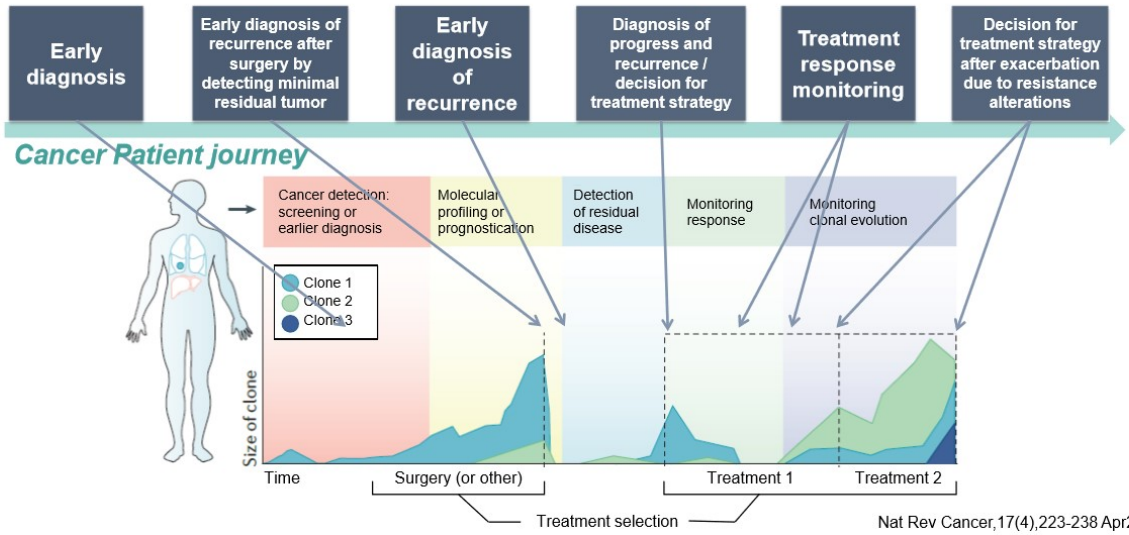
There are many different kinds of human body fluids. For example, human tears and saliva are also body fluids. And then there's urine. And blood, too. Also, you can include feces. The term "liquid" is used to describe all of these things.

All of these things are applicable. It can be anything, anything derived from the blood, body fluids, or anything like this in the body, and this is called a liquid biopsy. That is the name of the analysis. That's why we don't call it liquid biopsy analysis.

If there is a circulating tumor or cancer in the blood, cancer cells are spilling out into the body and into the bloodstream. This results in circulating tumor DNA, or ctDNA, in the blood.

Positioning of Liquid Biopsy (LBx)

- Liquid biopsy is used for a variety of purposes, from diagnosis to treatment policy decisions



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In fact, there are various timings for the positioning of this liquid biopsy test.

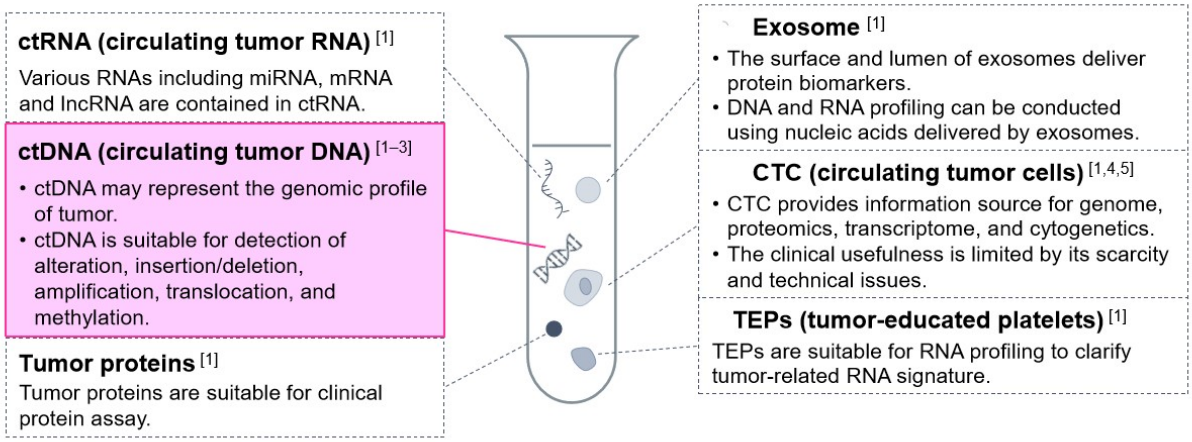
First of all, there is the so-called patient journey, which includes early diagnosis to find cancer in people who are not aware that they have cancer, detection of recurrence of cancer after treatment, and early detection of recurrence. Then, in the advanced stage of the disease, it is used to determine the treatment plan and to monitor the effectiveness of treatment.

As I will talk about later, cancer is changing rapidly. So, if we capture the changes, we can see these various processes in the patient journey of cancer. There is evidence for all of this as well.

The recently approved FoundationOne Liquid CDx is used here in this progressive phase. In the area of advanced and recurrent disease, there are actually applications in areas such as recurrence after surgery, early diagnosis, and detection of cancer, which is now being done in medical checkups.

The potential of the test system is that it has the potential to expand to all cancer patients and to screening.

Tumor-Derived Components in Blood



CTC: circulating tumor cells, lncRNA: long noncoding RNA, miRNA: micro RNA, mRNA: messenger RNA, TEPs: tumor-educated platelets.

[1] De Rubis G, et al.: Trends Pharmacol Sci 2019; 40(3): 172-86 [2] Francis G, et al.: Int J Mol Sci 2015; 16(6): 14122-42 [3] Cheng F, et al.: Oncotarget 2016; 7(30): 48832-41
[4] Kulkarni RP: Sci Transl Med 2019; 11(489): eaax1730 [5] Ciurte A, et al.: PLoS One 2018; 137(12): e0208385

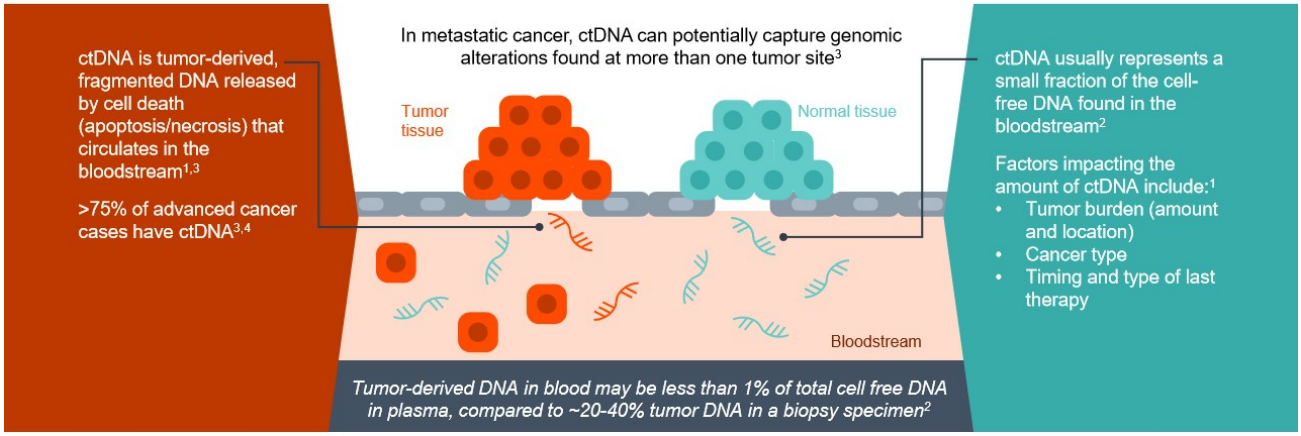
There are various kinds of tumor-derived components floating in the blood to begin with.

The development of testing for circulating tumor DNA, or ctDNA, in the blood, shown here in pink, has made remarkable progress. And now we have reached clinical implementation.

In the future, Exosome-based liquid biopsy and CTC-based liquid biopsy may be put to practical use. The top runner was a test for this ctDNA.

What is Circulating Tumor DNA (ctDNA)?

➢ ctDNA is tumor derived, fragmented DNA released from dead cells that circulate in the bloodstream.

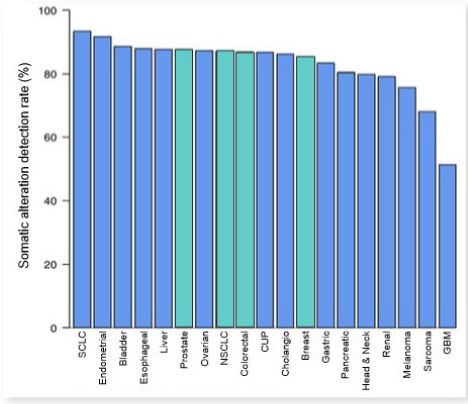


1. Corcoran RB, et al. *N Engl J Med*. 2018;379(18):1754-1765.
2. Heitzer E, et al. *Genome Med*. 2013;5(8):73.
3. Hench IB, et al. *Front Med (Lausanne)*. 2018;5-9.
4. Zill OA, et al. *Clin Cancer Res*. 2018;24(15):3528-3538.

30

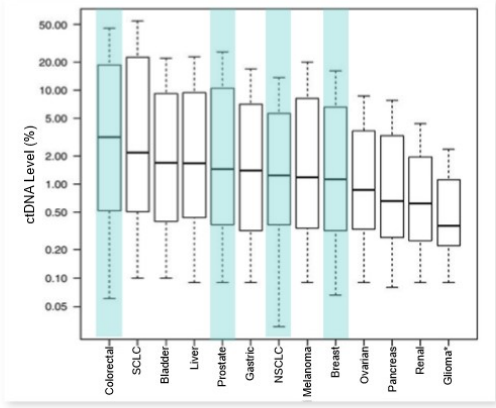
What is ctDNA? It is fragmented tumor-derived DNA, or pieces of DNA, released from dead cells in the bloodstream. It represents cancer-derived DNA. Of course, fragments of DNA from normal cells also flow in the blood, but more so from tumor cells. The ability to capture and test these fragments derived from tumor cells is truly an advancement in technology.

Percentage of Patients with Detectable Somatic Alterations and ctDNA Level by Cancer Type (Overseas data)



Somatic ctDNA alterations were detected in 85% of patients (n=21,807) across all cancer types

Alteration-positive samples had average of 3-4 alterations including copy number amplifications



CRC had the highest average ctDNA fraction while pancreas, renal cancers and glioblastoma had the lowest

Cholangio = cholangiocarcinoma, CRC = colorectal cancer, ctDNA = circulating tumor DNA, CUP = carcinoma of unknown primary, GBM = glioblastoma, NSCLC = non-small cell lung cancer, SCLC = small cell lung cancer. *Glioblastoma.

Zill OA, et al. *Clin Cancer Res*. 2018;24(15):3528-3538.

31

In fact, the question is, how much can we detect? This is a summary of data from 21,000 cancer patients, where DNA derived from cancer cells was found in 85% of cases. The amount of ctDNA flowing into the bloodstream differs depending on the type of cancer, as shown by the fact that the amount was very high in colorectal cancer and low in pancreatic cancer, renal cancer, and glioblastoma.

Percentage of Patients with Detectable ctDNA by Disease Stage

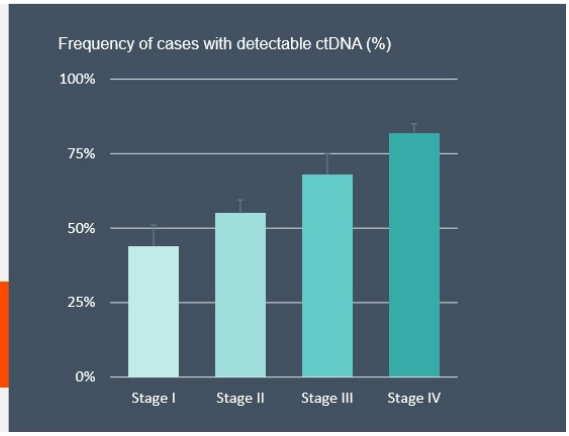
➢ ctDNA level increases as disease stage progresses (Stages I to III: 55%⇒Stage IV: >80%).

ctDNA was analyzed in 640 patients with solid tumors

ctDNA levels increased in accordance with the stage of cancer and tumor burden

- ctDNA was detectable in 55% of patients with localized disease (stages I-III)
- ctDNA was detectable in >80% of patients with metastatic disease (stage IV)

ctDNA may be particularly useful in prostate, breast and other tumors that tend to metastasize to bone and be difficult for biopsy



Bettegowda C, et al. *Sci Transl Med*. 2014;6(224):224ra224.
ctDNA = circulating tumor DNA

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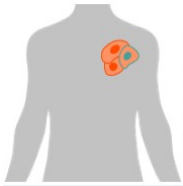
In fact, if we look at the progress of the disease from the youngest stage where the cancer is easily cured to stage IV, where the cancer is difficult to cure, we can see that the detection of ctDNA is insufficient at the earliest stage. But in the stage IV, it can be detected in a large number of patients. This means that as the disease progresses, more and more tumor-derived DNA is flowing out into the bloodstream. This means that it gets easier to test for.

In addition, there are recent data that show that the results of these tests are about 80% in stage I, and 99% in stage IV. However, for patients with prostate cancer that has metastasized only to the bone, or breast cancer that has metastasized only to the bone, it is not necessary to insert a needle into the bone if the test is done with blood.

What is Heterogeneity? [1]

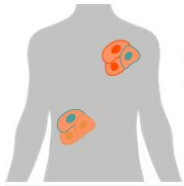
Intratumor heterogeneity



Cancer genome information may not be homogenous even in single tumor.

Tissue samples may not capture subclone populations in tumor cells with different alterations.

Heterogeneity in body



Cancer genome information may not be homogenous, depending on tumor location in the body.

Tissue samples from single lesion may miss any specific alteration at other location.

Also, cancer genome information can change over time; thus, there is time-dependent heterogeneity.

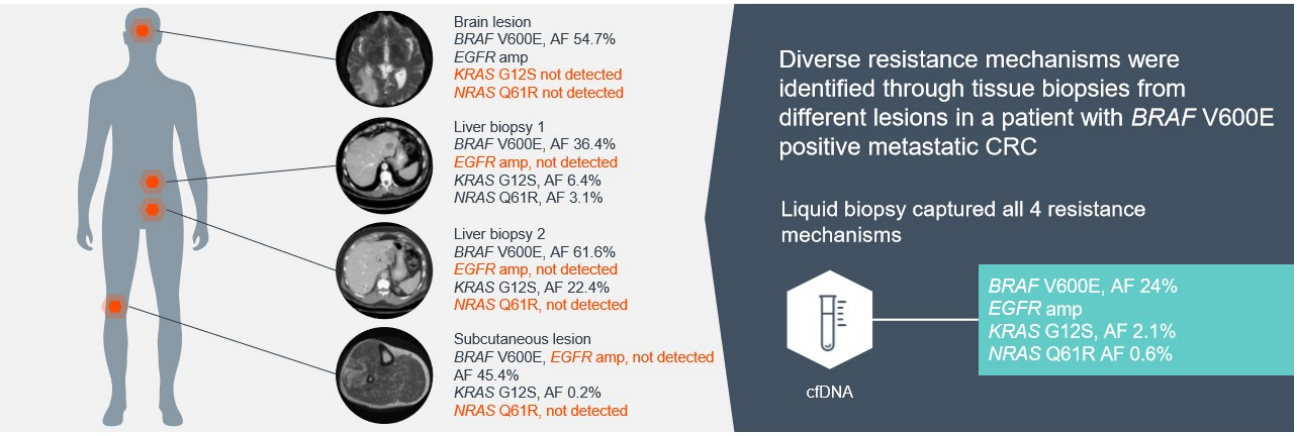
[1] Scherer F: Recent Results Cancer Res 2020; 215: 213-30 33

Also, and this is very important, liquid biopsy can look at heterogeneity, which we call tumor heterogeneity. In other words, cancer is a process of progression, and the consequence of this is that cancer may grow or spread to other parts of the body. It can also spread to several different places.

Such cancers are not necessarily homogeneous tissues. For example, a cancer that starts in the left shoulder and metastasizes to the right stomach will gradually change in nature. This means that not all cancers are uniform. In other words, the heterogeneity within the tumor and the heterogeneity within the body occurs because of changes in the cancer over time.

Intratumor Heterogeneity: Case with Metastatic Colorectal Cancer (mCRC)

- All 4 resistance genes were detected via liquid biopsy.



AF = allelic fraction, cfDNA = cell-free DNA

Parikh AR, et al. *Nat Med*. 2019;25(9):1415-1421. 34

In this case, this patient had a lesion in the brain, another 2 in the liver, and also a lesion under the skin. If we examine the foci of each of these 4 diseases separately using a next-generation sequencer, we can see that the various mutations and changes are different.

This means that cancer can change from place to place. However, when tested with liquid biopsy, the test captured all the changes seen here. In other words, liquid biopsy can capture all the changes occurring in the cancer because cancer cells are flowing out of various places into the blood. This is called spatial heterogeneity, and it is possible to capture such heterogeneity.

Characteristics of "CGP Using Plasma Sample" and "CGP Using Tissue Sample"

Benefits and reminders of CGP tests using plasma and tissue samples

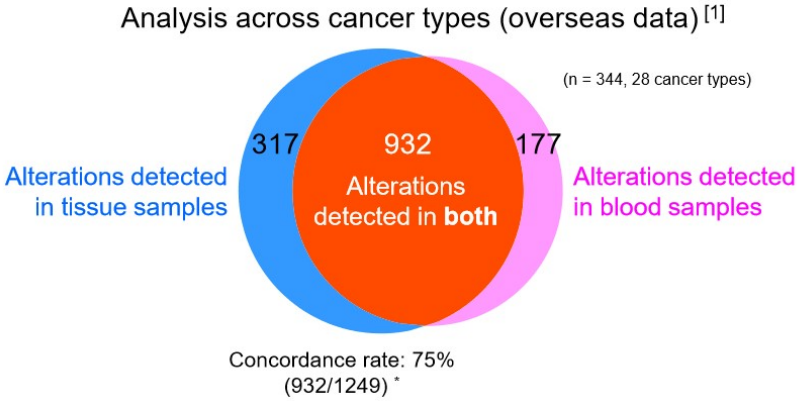
	Benefits	Reminders
Plasma CGP	• Easy to collect samples and possible to obtain information on gene abnormality in tumor at each sampling point. • Shorter time until obtaining results.	• May not be detectable when tumor burden is not sufficient. • Considered to show higher false-negative rate, compared with tissue samples. • False-positive rate increases with aging due to CHIP. • Evaluation of copy number alteration and gene fusion is difficult in some cases.
Tissue CGP	• Direct evaluation of gene abnormality in tumor cells is possible.	• Patient's burden and complication risk for sampling. • Longer time until obtaining results. • False-negative may occur when the percentage of tumor cells is low. • Past samples may not reflect the present gene abnormality in tumor cells. • Samples may deteriorate at 3–5 years or more after sampling.

Joint task force for cancer gene medicine among Japanese Society of Medical Oncology/Japan Society of Clinical Oncology/Japanese Cancer Association
Excerpted from "Proposal of strategy for proper use of cancer genomic profiling test using circulating tumor DNA" (January 20, 2021)
https://www.jsmo.or.jp/file/dl/newsj/2765.pdf (accessed on April 28, 2021)
CGP: comprehensive genomic profiling, CHIP: clonal hematopoiesis of indeterminate potential. 35

As mentioned by Mr. Ito of Chugai, there are advantages and disadvantages to tests using blood or tumor tissue. We believe that they are complementary to each other.

Concordance Rate between Blood Samples and Tissue Samples

- The test results from tissue samples are not biologically (scientifically) consistent with those from blood samples.



[Method] In 344 patients with 28 cancer types, CGP was conducted using tissue and blood samples collected from same patients, and the concordance rate of detected gene alteration was examined.
*: Percentage of detectable gene alterations both in blood and tissue samples to total detectable alterations in tissue samples.

[1] Shu Y, et al.: Sci Rep 2017; 7(1): 583

In fact, neither test completely captures the genes in the cancer. If you do both tests, they will match roughly 75% of the time, but there will be cases where alterations are only detected in one or the other.

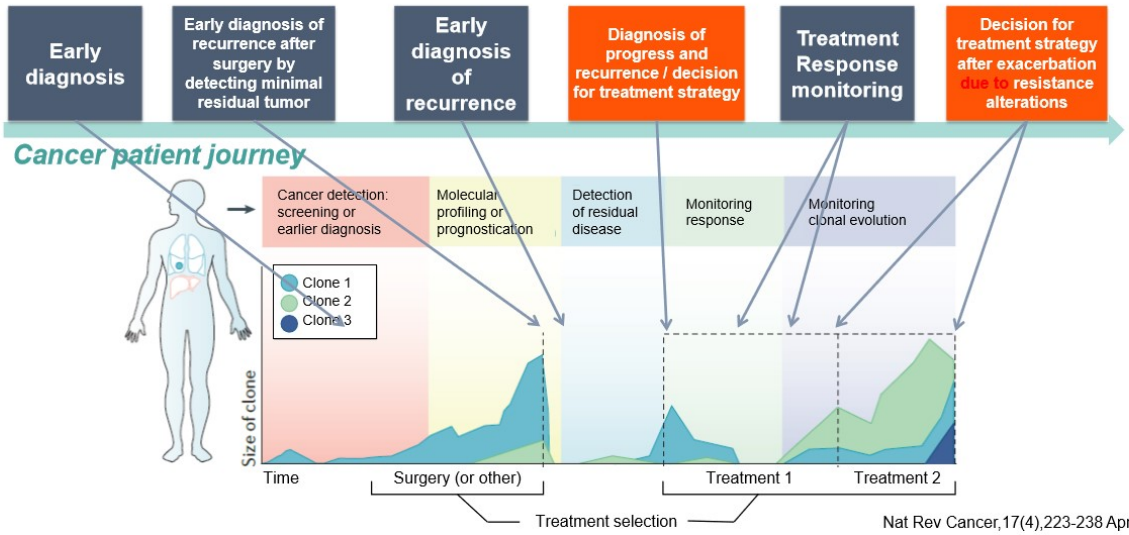
There is also the question of whether or not there are drugs for all the genes found, so it is difficult to say scientifically whether it is better if the gene is found only in the tissue or only in the blood.

Though the disease progresses, the tissues showed the condition when it was taken and become older and older. On the other hand, blood is liquid, which means it can be taken frequently. It is estimated that the number of mutations detectable in blood will increase rapidly.

In other words, the blood test is more reflective of the cancer patient's condition at a given time.

Positioning of Plasma-based CGP Test

- Plasma-based CGP is used to support treatment decision-making for patients with advanced or recurrent solid tumors.



Therefore, these blood-based CGP tests and panel tests can be used in a variety of ways, such as determining the treatment strategy, monitoring treatment response, and determining the treatment strategy based on the emergence of resistant genes.

In other words, if we can collect blood frequently, instead of just once, we can check the status of cancer by collecting blood over and over again because each blood sample is only 17 mL.

Conclusion: Characteristics of Liquid Biopsy

- *Enables less-invasive access to less accessible tumors and multiple metastatic lesions.*
- *Enables to resolve heterogeneity of cancer genome information in tissue samples and capture entire picture of disease.*
- *Enables to obtain information on therapeutic effect prediction, prognosis prediction, drug resistance, etc.*
- *Attention should also be paid to the precautions described in the policy recommendations, such as the possibility that tumor burden may not be detected if the tumor burden is insufficient.*

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This slide shows the features of this liquid biopsy.

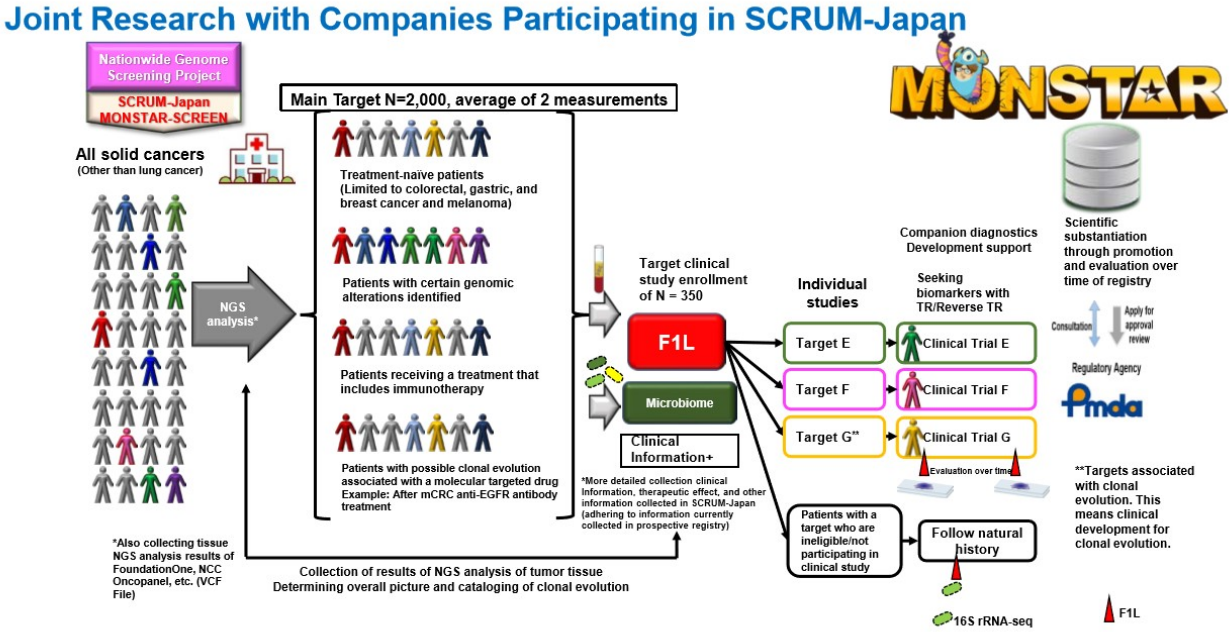
For example, if we cannot collect tissue then we have no choice but to use liquid. And even in this case, only 17 mL of blood is required, which is almost the same as the amount of blood normally collected in a clinic visit.

In tissue tests, a sample from a very small part of a tumor is taken. In contrast, liquid biopsy is a collection of leaked tissue from the whole body. As a result, with liquid biopsy, it is possible to capture the whole picture of heterogeneity.

In addition, it is possible to obtain information related to prediction of therapeutic effects, prognosis, drug resistance, and so on. We will look at the most recent genetic information of the cancer at that time, and since cancer changes, we will be able to capture the changes that are important at that time.

There are situations where the amount of tumor leaking into the bloodstream is small. For example, suppose there's a case where a cancer is treated, and the treatment is very effective. In such a case, the amount of cancer cells will decrease, so if liquid biopsy is performed, it may not detect any trace of cancer.

While considering the patient's condition or treatment, I think it is important to perform the test by taking advantage of the characteristics of the test, paying attention to situations where liquid biopsy may not be able to detect cancer, or may give false negative results.

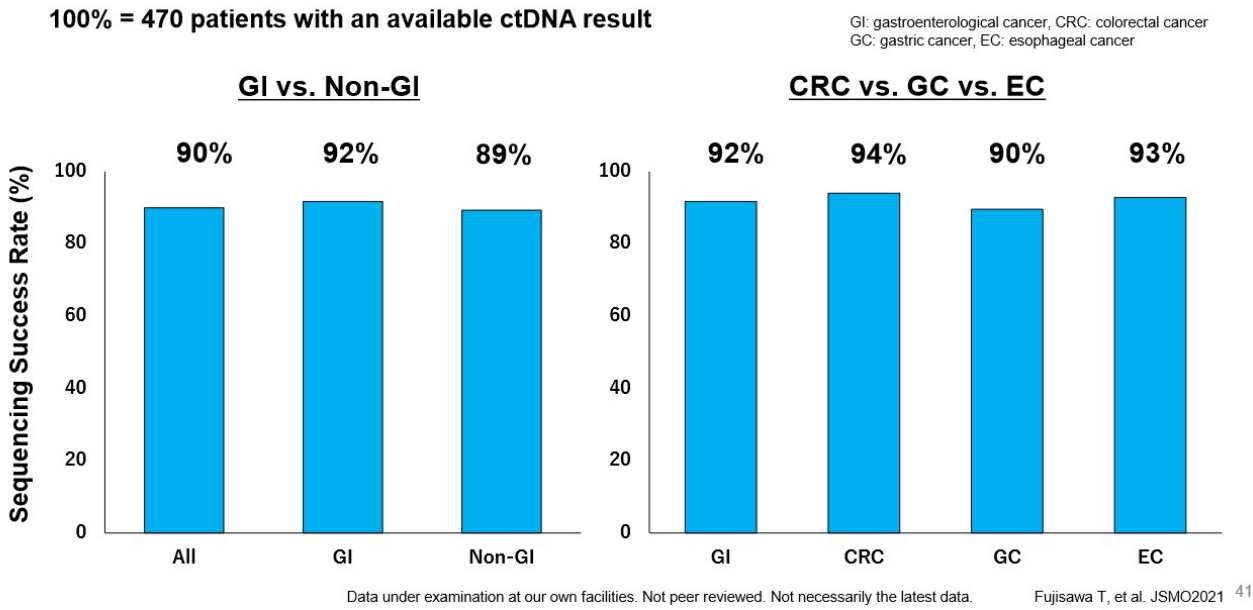


Data under examination at our own facilities. Not peer reviewed Not necessarily the latest data. Fujisawa T, et al. JSMO2021 40

I would like to continue with our own data from here.

We formed something called SCRUM-Japan in 2015, and we are still going. This was done as part of the third phase of SCRUM-Japan, called MONSTAR-SCREEN. For solid cancers, which are cancers other than hematological cancers, we have had 2,000 patients participate in the test using the same technology as the currently approved FoundationOne Liquid CDx.

Sequencing Success Rate

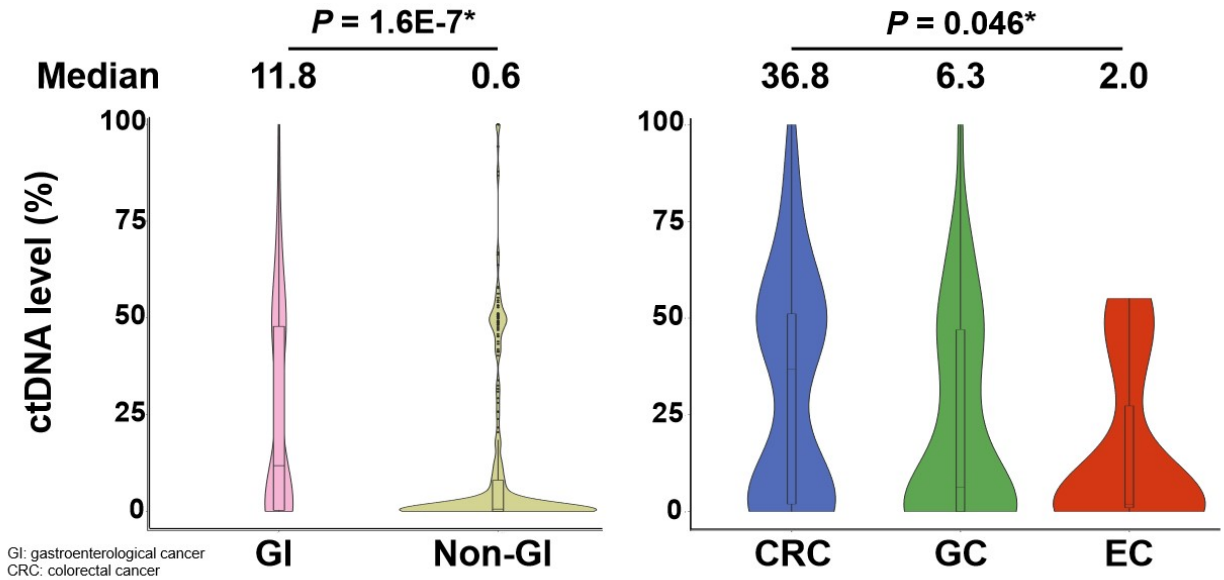


The result is the probability of success of the test itself. This was reported at the Japan Society of Clinical Oncology in February this year, and the success rate of the test itself is 90%.

This result is equivalent to or higher than that of the current tissue-based sequencing, indicating that the test has a success rate equivalent to or higher than that of tissue-based sequencing. Whether it is gastrointestinal cancers or other solid cancers, or any cancer such as colorectal cancer, gastric cancer or esophageal cancer within the gastrointestinal category, the success rate is the same.

ctDNA Level according to Cancer Type

*Mann-Whitney test



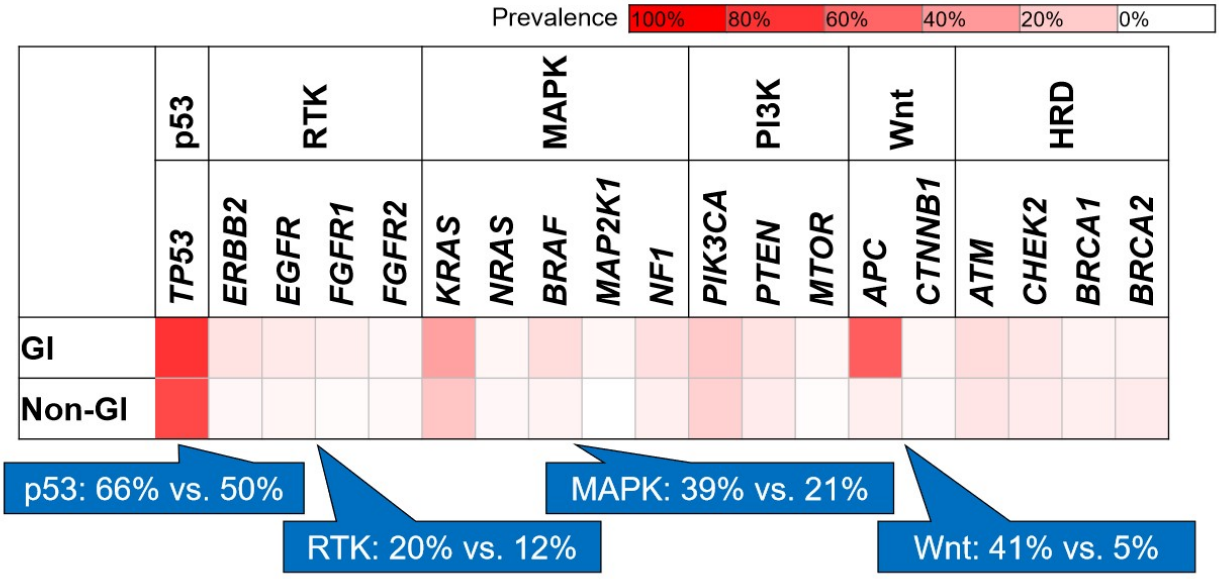
Data under examination at our own facilities. Not peer reviewed. Not necessarily the latest data.

Fujisawa T, et al. JSMO2021 42

However, the amount of this ctDNA is important for ease of testing, gastrointestinal cancers tend to have very high levels of ctDNA in the blood. Other cancers, such as breast cancer and skin cancer, are slightly lower, but gastrointestinal cancers release a lot of ctDNA into the blood.

Among them, we also found that colorectal cancer releases the most, followed by gastric cancer, and then esophageal cancer.

Prevalence of ctDNA Alterations



Data under examination at our own facilities. Not peer reviewed. Not necessarily the latest data. Fujisawa T, et al. JSMO2021 43

In fact, when we look at various mutations, we find that, for example, the p53 gene abnormality is high in gastrointestinal cancers. The RTK here is quite specialized, but I heard that gastrointestinal cancers are also high in terms of RTK. Gastrointestinal cancers are also high for MAPK. Wnt is clearly high in gastrointestinal cancers, so we can also compare the genetic abnormalities that are high in gastrointestinal cancers.

There are clinically very important 3 cases with negative results by NGS using tissue, even though positive results were given by liquid biopsy using ctDNA. For example, this is *BRAF*, a gene with a very poor prognosis. This is an examination of the tissue, and when done in our study, there were no abnormalities. However, liquid biopsy revealed that there was an abnormality in a gene called *BRAF*. This is a patient with colorectal cancer, and here is a metastasis of the liver. So, when we give BRAF inhibitors to those patients, they work very well.

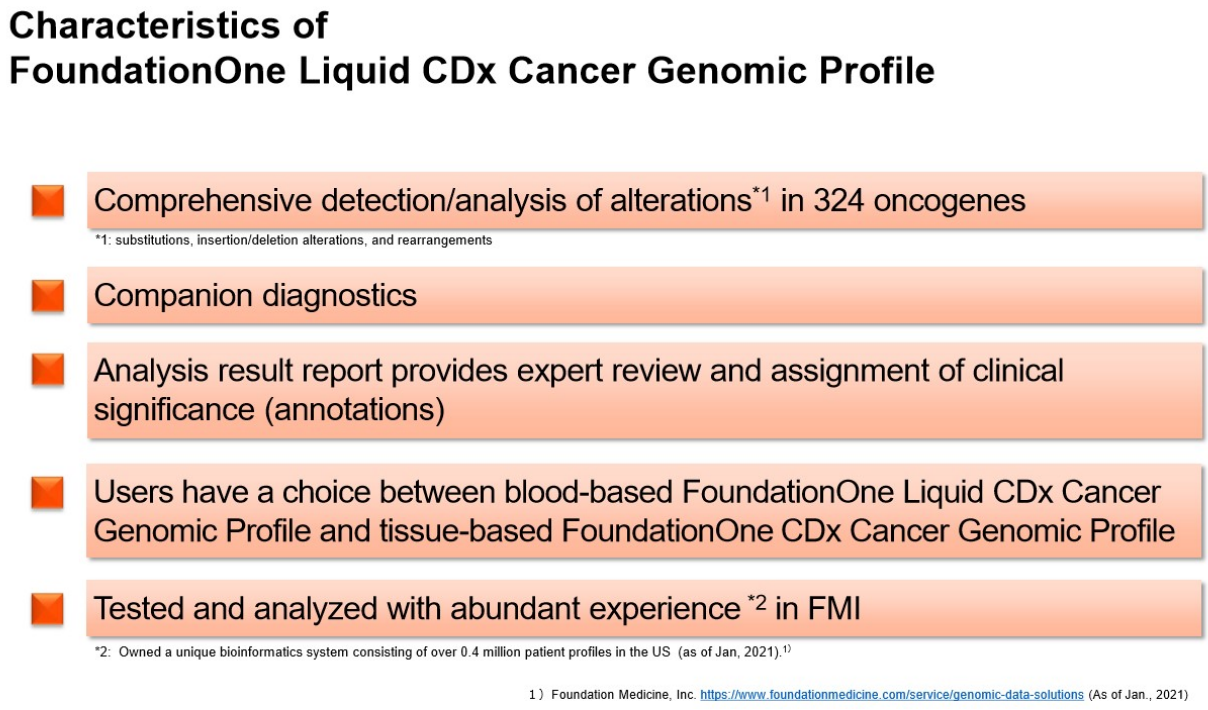
In other words, if this patient had only received a tissue test, there would have been no reason to administer this drug to this patient.

Next, another patient with colon cancer, this time MSI-High, whose tissue test also tested negative. Testing for ctDNA gave a positive result. In the case of patients with MSI-High, so-called immune checkpoint inhibitors are very effective. So, we administered them to the patients, and they responded very well.

In other words, if we had only examined the tissue, we would not have been able to identify the MSI-High status, so we would not have been able to put this patient on an immune checkpoint inhibitor.

This time, *FGFR2* amplification in gastric cancer was negative in the tissue. This is an example of a case where the liquid biopsy was positive. And when we specially added a FGFR inhibitor, it worked very well.

In this way, there are things that cannot be detected in tissue tests but can be detected with liquid biopsy. There have been many cases where patients have been lucky because they received NGS blood tests.



Lastly, I would like to show the expectations and challenges for FoundationOne Liquid CDx Cancer Genomic Profile.

FoundationOne Liquid CDx can analyze as many as 324 genes simultaneously. This is the exact same number as the tissue test, FoundationOne CDx.

Then, as I will tell you later, it has a companion diagnostic function. In other words, it contains a large number of genes that have been proven to be reliable for some drugs and its efficacy.

The results of this expert review and clinically meaningful analysis are included in the report, which will be very helpful for the expert panel at each hospital.

There are 2 products to choose from: the newly approved FoundationOne Liquid CDx, which uses blood, and FoundationOne CDx, which uses tissue. Using one test alone exposes the weaknesses of that test, suggesting complementary use.

In addition, Foundation Medicine, which has tested over 400,000 people, is conducting the tests and analyzing the results.

Companion diagnostics[1)]

Genomic alterations	Cancer type	Relevant drugs
Activated *EGFR* alterations	Non-small cell lung cancer (NSCLC)	afatinib maleate, erlotinib hydrochloride, gefitinib, osimertinib mesilate
EGFR exon 20 T790M alterations		osimertinib mesilate
ALK fusion genes		alectinib hydrochloride, crizotinib, ceritinib
ROS1 fusion genes		entrectinib
NTRK1/2/3 fusion gene	Solid tumors	entrectinib
BRCA1/2 alteration	Prostate cancer	olaparib

1) Prepared based on the package insert of FoundationOne Liquid CDx revised in May 2021 (Version 2)

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Regarding companion diagnostics, for the genes shown here, it has already been clinically proven that a certain drug has a definite clinical effect. This means that we can say with some confidence that if a patient has a specific genetic abnormality, we can give a concrete answer.

Clinical Study Results: Overview of Pivotal Studies Used for Regulatory Approval

- **Efficacy of each drug was confirmed in patients who tested positive for gene alteration with FoundationOne Liquid CDx (including previous versions of the test).**

Overview of pivotal studies that formed the basis of the drugs' regulatory approval[1)]

Genomic alterations	Overview of clinical studies
ALK fusion genes (NSCLC)	In Cohort A of phase II/III B-FAST study in patients with previously untreated ALK-fusion-positive*1 advanced NSCLC, 87 patients received alectinib orally, showing the investigator-assessed response rate of 87.4% (95%CI:78.5-93.5%).
ROS1 fusion genes (NSCLC)	In STARTRK-2 study, 33 patients with ROS1 fusion-positive*2 locally advanced or metastatic NSCLC received 600 mg of entrectinib orally once daily, showing an independent assessment response rate of 75.8% (95% CI:57.7-88.9%) based on RECIST ver 1.1. The response rate was 72.2% (95% CI:49.1-87.5%) in the 18 patients with confirmed positive with the product*3.
NTRK fusion gene (solid tumor)	In STARTRK-2 study, 51 patients with advanced or recurrent NTRK fusion-positive*4 solid tumors received 600 mg entrectinib orally once daily, showing an independent assessment response rate of 56.9% (95% CI:42.3-70.7%) based on RECIST ver 1.1. The response rate was 72.2% (95% CI:49.1-87.5%) in the 18 patients confirmed positive with the product*3.

*1: The ALK-fusion gene was confirmed positive using a test with cfDNA of the previous generation of product*3 as the specimen.
*2: ROS1-fusion was confirmed positive using a nucleic acid-based diagnostic method.
*3: FoundationOne Liquid CDx Cancer Genomic Profile
*4: NTRK-fusion was confirmed positive using a nucleic acid-based diagnostic method.
95% CI: 95% confidence interval

1) Prepared based on the package insert of FoundationOne Liquid CDx revised in May 2021 (Version 2)

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Here is a detailed description of the test results of *ALK*, *ROS1*, and *NTRK*, which I think you will find in the slides. These are the clinical trial results on which the approval of the drug was based.

Comparison between FoundationOne Liquid CDx and FoundationOne CDx

- **Although FoundationOne Liquid CDx and FoundationOne CDx differ in their CDx-functions and sample species, the numbers and regions of genes included in the analysis are identical.**

	FoundationOne Liquid CDx Cancer Genomic Profile	FoundationOne CDx Cancer Genomic Profile
Japanese medical device nomenclature (JMDN)	•Software for gene variants analysis (for cancer genome profiling) •Software for analysis of somatic cell gene variants (for eligibility identification of antineoplastic agents)	•Software for gene variants analysis (for cancer genome profiling) •Software for analysis of somatic cell gene variants (for eligibility identification of antineoplastic agents)
Intended uses or indications	The Product is used for comprehensive genomic profiling of **blood samples** in patients with solid tumors.	The Product is used for comprehensive genomic profiling of **tissue samples** in patients with solid tumors.
	The Product is used for detecting gene mutations and other alterations to support the assessment of drug indications listed in the table below. (table for companion diagnostics indications is omitted)	The Product is used for detecting gene mutations and other alterations to support the assessment of drug indications listed in the table below. (table for companion diagnostics indications is omitted)
Numbers of genes	324 genes	324 genes

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Now, if I put both of these blood-based tests, FoundationOne Liquid CDx and FoundationOne CDx, together here, they have the same number of genes. This is as I mentioned earlier. This is a test that uses tissue and blood, and whole blood means ordinary blood, so the samples are different for both.

Of course, the programs are different, but they are both very well-established tests.

Summary of Health Insurance Coverage of FoundationOne Liquid CDx

[Health insurance coverage]

- The reimbursement price is the same as that of FoundationOne CDx (tissue CGP) and NCC oncopanel
  - ✓D006-19 Cancer genomic profiling test
- CGP testing, either tissue-based or plasma-based, can be covered by the national health insurance only once per case
  - ✓D006-19 Cancer genomic profiling test, (2) At explanation of results: 48,000 points is given once.
- "Test using blood sample" can be calculated in the following case
  - ✓When cancer genomic profiling test using tumor cell as a sample is difficult to conduct due to medical reasons, the reasons should be described in the medical record and the abstract field of the statement of medical expenses. *1

1)Prepared based on Partial revision of "Notes on implementation due to partial revision of medical fee calculation method" (R2.March 0305 No. 1)50

So, the outline of the insurance coverage at this time is that it will be treated in the same way as the tissue CGP, with a total of 56,000 points, 8,000 points and 48,000 points, or JPY560,000.

When for medical reasons, it is difficult to test tumor cells of solid tumors and cancer genome profiling tests using cancer tissues, it is written that tests such as this blood test should be performed.

This is very different from what I have just explained.

Change in Points to Consider Associated with Additional Insurance Coverage of FoundationOne Liquid CDx

- D006-19 Cancer Genomic Profiling Test

The underlined texts will be added for D006-19 “Cancer genomic profiling test.”

(1) (1) At sample submission: When comprehensive genomic profiling is conducted using tumor cells from solid tumor **or blood** as sample and using approved or certificated next generation sequencing as medical device for genomic profiling to obtain 100 or more cancer-related mutations, etc., the calculation can be conducted **only once per case (twice in the case of b below)**. **However, in the case of test using blood sample, the calculation can be conducted only in the case below.**

a **When cancer genomic profiling test using tumor cell as a sample is difficult to conduct due to medical reasons**, the reasons should be described in the medical record and the abstract field of the statement of medical expenses.

b **In the case when the results of comprehensive cancer genomic profiling cannot be obtained from cancer genomic profiling test using tumor cells from solid tumor.** In this case, the fact should be written in the abstract field of a breakdown of medical expenses.

(2) (2)At explanation: When the results of comprehensive genomic profiling obtained (1) at sample submission are provided to patients after consideration at meeting (Expert Panel) to medically interpret the results by persons with multiple job types (doctor with professional knowledge and skill for cancer pharmacotherapy, doctor with professional knowledge and skill for genetic medicine, person with genetic counseling skill) as well as the treatment strategy is explained to patients in written form, the calculation can be conducted only **once per case**.

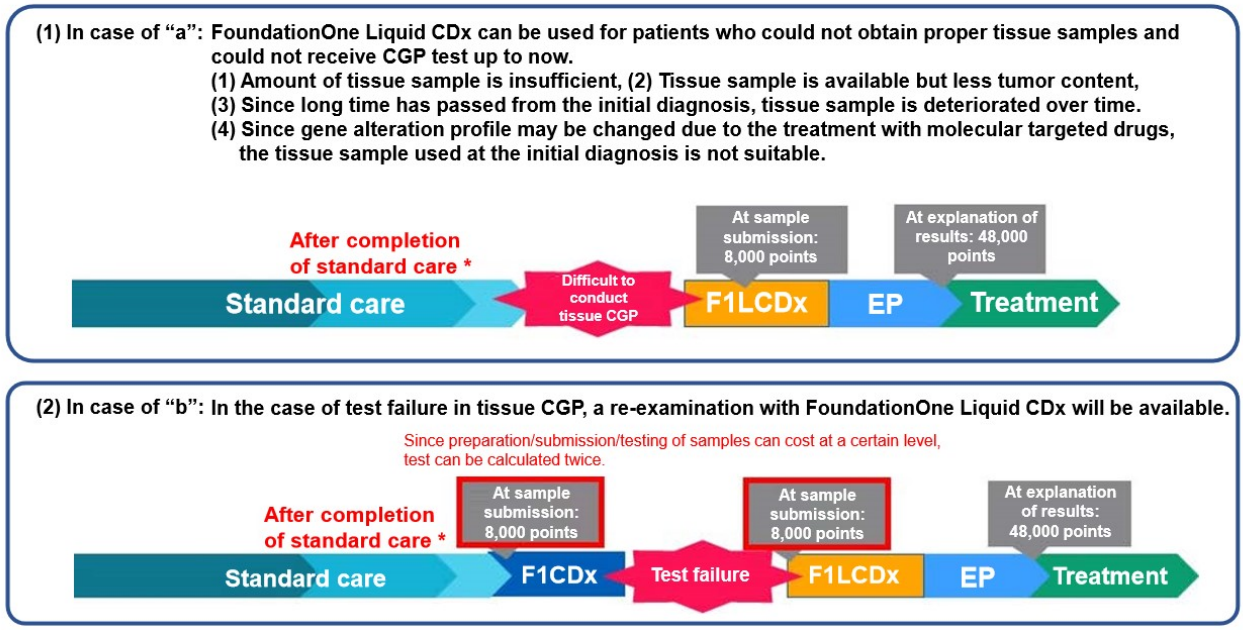
Prepared based on "Notes on implementation due to partial revision of medical fee calculation method" (R2.March 0305 No. 1)
Partial revision of "Notes on implementation due to partial revision of medical fee calculation method" (R2.March 0305 No. 1) 51

As a note to the addition of insurance coverage, simply put, it says that the tissue test is a priority, and the blood test is secondary. It also says that only 1 of these can be performed. Because it costs JPY560,000, it says that you cannot do both.

However, for those in whom a tissue sample cannot be obtained, a blood test should be carried out. Also, where results are not obtained using a tissue test, a blood test can be done. And either of tests is only allowed once in a patient's lifetime.

Earlier, I said that cancer is changeable. It changes, and the information in the genes at any given time changes. We talked about the possibility of therapeutic effects using the changed genetic information, but the indication does not match that.

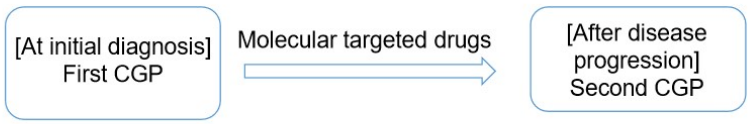
Insurance Calculation for FoundationOne Liquid CDx (in the case that standard of care therapy can be provided)



This is the image of the insurance calculation. I'll spare you the details, but to give a summary, this is an expensive test. The test costs JPY560,000. In the case of the test itself, for example, in the case of "b" if the test is unsuccessful in the tissue CGP, the FoundationOne Liquid CDx can be carried out, and the final amount will be JPY560,000.

Significance of Multiple Tests

- The change in gene alteration profile due to time passage and treatment with molecular targeted drugs can be captured.



(4) For multiple tests

[2] In terms of CDx, using OncoBEAM™ RAS CRC kit, a kit to detect alterations in RAS gene, for multiple tests has been allowed to determine the re-administration of an anti-EGFR antibody, in addition to the case when it is difficult to conduct a test using tissue samples (single testing is allowed in this case). Acquired RAS alteration due to the resistance mechanism against anti-EGFR antibody drugs is a minor allele which is known to decrease over time, and **it has been reported that clinical efficacy could be obtained again via the re-administration of anti-EGFR drugs to patients without detectable alteration in RAS gene test using plasma samples**.

[3] In terms of CDx, it has been reported that **resistance mutation in NSCLC with EGFR alteration and ALK fusion as well as change in RAS alteration through the treatment of large intestine carcinoma could be evaluated by multiple gene tests using plasma samples,** which contributes to the selection of subsequent treatment.

Partially modified from "Proposal of Strategy for Proper Use of Cancer Genomic Profiling Test Using Circulating Tumor DNA"
Joint task force for cancer genome medicine among Japanese Society of Medical Oncology/Japan Society of Clinical Oncology/Japanese Cancer Association, January 20, 2021 53

The truth is the science is clear that multiple tests make sense. And these scientific reports are strewn all through the policy statements.

For example, we are aware of a report of a case in which clinical response was re-established by re-administration of anti-EGFR antibody drugs in a patient whose blood-based *RAS* gene test showed no mutation. For this purpose, the OncoBEAM RAS CRC kit, which is an amazingly inexpensive test that costs less than JPY100,000, has no limit to the number of times it can be tested. In other words, some of us recognize the significance of frequent liquid biopsy covered by insurance.

Also, in non-small cell lung cancer, it is said that appropriate evaluation of *EGFR* mutation, resistance mutation in non-small cell lung cancer with *ALK* fusion gene, *RAS* in colorectal cancer, et cetera, can be achieved by conducting multiple genetic tests using plasma samples.

In other words, it would be best if we could do the test many times because liquid biopsy gives us information about the cancer at that time.

New Issues on the Current Insurance Reimbursement System Associated with the Addition of FoundationOne Liquid CDx

- Only one test per patient is currently available although multiple tests may reportedly lead to optimal treatment when drug resistance or secondary alterations are anticipated during treatment.
- If genome abnormality is not detected by tissue CGP test, plasma CGP test cannot be conducted, and alterations detectable by plasma CGP test may be left unnoticed. This could result with less opportunities to offer right treatment options to patients, causing disadvantage to them.
- In the package insert of FoundationOne Liquid CDx, important precautions there is a description in the important precautions (precautions for handling) that “When the result of companion diagnostics using this product is negative, test using tissue sample should be considered as far as possible.” However, the test can be conducted only once; thus, potentially causing disadvantage to patients as stated above.

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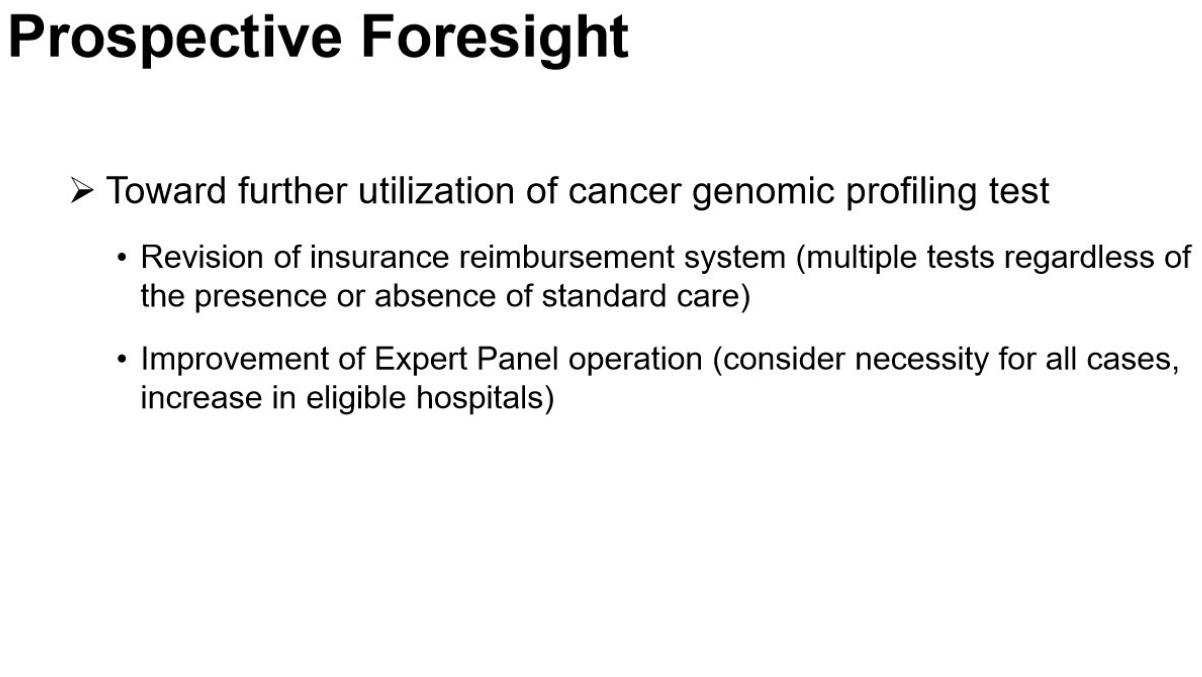
Although reimbursed, the new problem with the current reimbursement system is that it has been reported that multiple tests can lead to optimal treatment in cases where these drugs have stopped working or secondary mutations are expected to appear. However, at present, only 1 test can be conducted per person.

If a genomic abnormality cannot be detected by the tissue CGP test, the plasma CGP test cannot be performed, and mutations that can be detected by the plasma CGP test may be missed. This reduces the opportunity to provide appropriate treatment to patients and may lead to patient disadvantage.

Here is the package insert for FoundationOne Liquid CDx, which states that if the results of companion diagnostics with this product are negative, tissue-based tests, et cetera, should be considered whenever possible. But, since only 1 test can be performed, it may be to the detriment of the patient.

Although scientific progress in this field has been quite rapid, there is a discrepancy between the insurance coverage and the current recommendations of the academic societies.



As for future prospects, in order to make more effective use of cancer genome profiling tests, the current insurance reimbursement system should be revised so that tests can be started earlier. This would help us to detect the abnormalities in patients' cancers at an earlier stage, rather than after all standard treatments have been completed.

Furthermore, I think we should be able to do multiple tests, at least once for tissue and once for liquid, twice combined, though it would be great if we could do more.

In terms of expert panels, even 5% of the total number of patients are now being treated, which puts heavy workloads. And if 1 patient is treated more than once, the number will be enormous. Then it would be difficult to annotate in the expert panel itself. Automation of annotation is necessary.

In addition, the fact that the number of facilities that can do this is limited to about 200 nationwide restricts the geographical accessibility for patients.

In the end, I believe that expanding the availability of such tests at more and more facilities will contribute to the improvement of public health for patients.

Take Home Message

- Since FoundationOne Liquid CDx Cancer Genomic Profile has been approved and covered by health insurance in Japan, the clinical application of cancer genomic profiling test using circulating tumor DNA (ctDNA) has become possible.
- It is important to select appropriate tests according to patient's condition and treatment phase, based on the benefits and reminders of tissue CGP and plasma CGP as mentioned in the Proposal of Strategy.
- For more appropriate medical application of mutually complementary tests, i.e., tissue CGP and plasma CGP, urgent revision of the current insurance reimbursement system will be required in the future.

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As you can see on the last slide, FoundationOne Liquid CDx has been approved and covered by insurance in Japan, and this type of cancer genome profiling test using ctDNA is now available for clinical settings.

It is important to choose the appropriate test according to the patient's condition and the stage of treatment based on the advantages and cautions of tissue and blood testing, as mentioned in the policy recommendations. These tests are complementary to each other, and the current insurance reimbursement system needs to be revised as soon as possible so that they can be used more in the field.

Currently, many stakeholders, including various academic societies, are speaking out against this system, and we should definitely change the system so that both tests can be used.

This concludes my presentation. Thank you very much for your attention.

Sasai: Thank you very much, Dr. Yoshino.

Question & Answer

Sasai: We will now move on to the Q&A session.

Please note that in order to allow as many people as possible to ask questions, we would like to limit questions to 2 per person. If you have any questions, please let us know your company name and your name before asking your question.

Let's start with Mr. Kohtani of Nomura Securities.

Kohtani: I'm Kohtani from Nomura Securities. I would like to ask Dr. Yoshino for his views on 2 topics. First, thank you for your very detailed explanation. It was very easy to understand.

As you said, you feel it should be possible to use this liquid biopsy as many times as necessary, but at JPY560,000, it is probably not possible to use it within insurance. The situation is quite severe for pharmaceuticals as well, but I think that Japan has always been quite reluctant to put points on clinical tests, so unless they are quite cheap, they will not be available for use more than once.

I hope you don't mind me bringing this up here, but I was wondering if all 300 or so genes need to be tested all together. Wouldn't it be better to limit the number of genes to 8 or so, only for drugs of a specific cancer type? That way, the reimbursement points could be lower.

I believe that the National Cancer Center is now using a method called Meets, which uses a next generation sequencer. But since only about 8 tests are performed, the cost of clinical tests can be reduced significantly. Is such a method preferable?

There's also the Onco RAS, although I was a bit surprised and didn't expect to see the Sysmex Onco RAS. The Onco RAS is a flow cytometer, which can measure not only the *RAS* but also *ALK* and about 8 other things, so the price can be kept very low.

What’s the best way to think about this? This is my first question.

Yoshino: Thank you very much. And thank you for posing such a high-level question.

In my personal opinion, the cost of testing is indeed high. Of course, I am aware of the culture in Japan of not wanting to put much of a price on the inspection itself. I think it is important for multiple companies to participate in the market. I think one of the most important things to do is to use market principles to reduce the cost of the tests themselves.

You suggested limiting the number of measured genes to those that are really necessary. However, in current clinical practice, by measuring a large number of genes we can get an overall picture, which is called the signature of a cancer. By measuring the number of mutations, for example, the number of mutations in the signature of cancer, we know that certain drug is effective.

In the past, for example, if there was an abnormality in gene A, an inhibitor for A would work, and if there was a change in gene B, an inhibitor for B would work.

In this sense, there are 22,000 exons in the human gene pool alone, but of these, 324 are still very small, and without more than 300, the counting of drug effects and mutations will be inaccurate. If the number of genes is too small, the significance of a single gene may be overestimated. Rather than reducing the number of

genes, the current trend in the world is to increase the number of genes, which will lead to more therapeutic opportunities.

Therefore, as a physician, I personally would like to oppose, from the standpoint of science, a move toward reducing the number from the current 324 genes, as this would lead to a reduction in the opportunity to provide future medicines to patients.

However, as for how to reduce the cost of the test, 1 point is that other companies coming in will have that effect. Another point is that insurance will be paid following the expert panel. So, if we don't improve this part, we'll never be able to lower the insurance points. This is the point.

Therefore, I personally think it is necessary to revise this part, the part where results cannot be returned to patients without the results of the expert panel. Then, as I just mentioned, relying on new entrants to reduce the costs.

The other thing to consider is the fundamental question of whether testing is that cheap in the first place. In the past, the significance of tests was small, and medicines were more valuable than tests. However, it is also true that the value of testing is becoming greater and greater since we are now in an era where treatment decisions are completely dependent on testing.

In our current situation, no one sees a problem with paying JPY1 million per month for the treatment, but JPY500,000 for testing is a different story. In the past, the cost of testing may have been JPY20,000, but the value gained from these new tests is actually increasing.

If anything, I think it is necessary to give more weight to testing, not only for this product, but also to give a higher allowance for testing as a whole.

I hope I have answered your question.

Kohtani: In that case, if we can come up with a way to make next-generation sequencers cheaper, they can be used more widely. I think it would be quite difficult to change the way we think about clinical laboratories and how we score them for insurance purposes.

Do you understand that it can be used widely if that happens?

Yoshino: Indeed. Yes. If it's cheaper, that's fine with me. The reimbursement points in Japan are much higher than those in Medicare and Medicaid in the United States, for example. I think it's about USD3,000 in the United States and Europe. The price is higher. This is also inexplicable to me. In fact, I think it's an inexplicable price, considering the prices overseas. That's what I think.

Kohtani: My second question is on a slightly different topic.

When it comes to this kind of liquid biopsy, I suppose 1 ultimate goal is to be able to diagnose early-stage cancer, stage I or II. As you mentioned in the presentation, there are many cancers that do not release ctDNA, depending on the type of cancer. I believe Onco RAS also has a warning that if you have lung metastasis, you can't or shouldn't measure it.

In the end, I think it was CCGA, from the company called GRAIL, which showed the specificity was very high, but the sensitivity was 51.5%. Looking at this, it was 16.8% in stage I patients, which means that there is a limit to what ctDNA can do in the first place.

Then, if we really want to use blood for early-stage cancer, what do you think we should add to this, besides ctDNA? I know this is a very difficult question, but besides exosome-derived miRNAs, what else do you think is needed? This is my last question.

Yoshino: Thank you very much. Very high-level question, thank you.

The OncoBEAM RAS, which was mentioned earlier, is a highly sensitive PCR method that uses a technology called BEAMING. In the case of lung metastasis, the shedding of ctDNA is limited to begin with, and as a result, there is little data. Our team has published a paper on this.

As I mentioned earlier about GRAIL, the point is to recover the ctDNA flowing in the body, and there must be an efficient collection limit. We were able to recover quite a bit of ctDNA with the new Streck tubes and other tubes, but I think we are certainly limited from here on out.

The next challenge for us now is probably nucleosomes and exosomes. I think 1 of the key points is how much of the ctDNA, ctRNA, proteins, and so on can be recovered from the exosomes.

Now, worldwide, the term ctNA has already been coined, and we have already started to use whole exome and whole transcriptome with this liquid biopsy and exosome-based technology. We are at the stage where we are starting to experiment to see if it is really clinically practical. If this becomes possible, the amount of DNA and RNA recovered will increase, and this will lead to higher sensitivity and specificity that will in turn lead to earlier diagnosis.

Therefore, I think that the trend will be toward clinical implementation in the direction of increasing sensitivity by combining not only ctDNA but also RNA, protein, and methylation.

Kohtani: Understood. Thank you very much. It was a great learning experience.

Sasai: Next, Mr. Hashiguchi from Daiwa Securities, please go ahead.

Hashiguchi: My name is Hashiguchi from Daiwa Securities. Thank you. I would like to ask Dr. Yoshino for his views on 2 topics**:** the immediate future and the long term.

As for the immediate future, I think you mentioned earlier that in the expert panel, people in the field are quite exhausted. Just from what you said, I had the impression that unless the current system is changed, it would be difficult to spread it much further.

On the other hand, the sales recorded by Chugai for this foundation medicine are currently growing at an annual rate of about 80%. In that sense, I would like to know how the spread of the system is progressing in the field, and how much more room there is for further spread, as long as the current system remains unchanged.

Yoshino: Thank you very much.

I think the first limitation of the expert panel is that we are doing all cases. After all, what we should do is to switch to doing only those cases that are really necessary, not all cases.

However, the reason why we have to do all the cases now is because of the problem I mentioned earlier, namely that the 48,000 reimbursement points will not be generated unless they go through an expert panel. Therefore, when the insurance score and the expert panel are connected, there is no way to move them in the system. We have been complaining to the Ministry of Health, Labor and Welfare about this.

In this regard, we need to increase the number of cases that do not need to be reviewed. We need to change the system from all cases to cases that need to be reviewed.

However, even so, I personally think that the limit is probably double the current level. That is, if the current number of hospitals does not increase. As far as the 45 hospitals are concerned, I think the limit is about double the current level. In other words, the number of cases per year, right now, is said to be roughly 1,200 per month, so if those 1,200 cases become 2,400 I think we're pretty much at the limit.

Where we should allow intervention here is with the entry of AI diagnosis and treatment as a substitute for expert panels, which is very important in a sense. If we can get, for example, pharmaceutical approval or medical device program approval in Class 3 or higher, we can simply apply it, and it will become a substitute for the expert panel.

Hashiguchi: Thank you very much.

Another point is about the future. I think Dr. Yoshino mentioned earlier on page 28 that it would be technically possible not only for patients with advanced recurrence, but also for those with early-stage disease, for example, in medical checkups.

For example, I think it was Dr. Yoshino who conducted research on the possibility of using ctDNA to identify people who require adjuvant therapy.

You mentioned earlier that ctDNA has its limitations and that you are considering various other methods. Also, if someone from Chugai Pharmaceutical can make a comment, could you please say a few words about the business challenges and what hurdles remain to be overcome in the early-stage disease?

Yoshino: I would like to say a few words here.

As for the broader usage of liquid biopsy, including this kind of ctDNA test, I think there are 3 categories. These are early diagnosis, prediction of recurrence, and advanced-stage testing.

With early diagnosis, prediction of recurrence, and progression, the number of such cancer-derived products in the bloodstream increases. In other words, early diagnosis needs higher sensitivity. And in the advanced stage, there are more tumor-derived products that leak so the so-called Limit of Detection, or LOD, of the test can be low. On the contrary, for early diagnosis, there are fewer leaking tumor-derived products, including ctDNA, so higher LOD and detection sensitivity are required.

As for the prediction of recurrence, I am working on a project called CIRCULATE-Japan, which is currently screening 5,000 people to see how recurrence is detected. This technology doesn't necessarily look at a lot of genes, but first of all, it predicts recurrence after surgery, so tissue is taken when a patient has surgery. We took operative samples, and we did a whole exome analysis where we examined all the genes in 22,000 locations.

If you look at 22,000 gene locations, you find mutations that are found in very high frequency in tumor cells. Among the 22,000 sites, cancer causes various numbers of mutations, such as 20 per person or 100 per person, and the top 16 are selected to make a custom panel.

In other words, the idea is that 1 of those 16 genes will be the first to be detected when the disease recurs. It's what we call the PCR method. It's looking at it ultra-deep, with a detection sensitivity of 0.001%. The concept is different because it allows us to identify recurrence faster.

In other words, we select 16 genes of the patients whose cancer recurrence is likely to be recognized first and monitor them by taking their blood every 3 months. Each test costs about only tens of thousands of JPY. However, tests of whole exomes are expensive. However, this type of test would be relatively inexpensive and very useful in predicting recurrence.

In this area, we are already conducting clinical implementation and testing the path toward regulatory approval, and I really think that it will be approved within a few years. This isn't directly related to Chugai Pharmaceutical, but I believe it will be approved.

Early diagnosis may take a little more time. I personally predict that it will take about 3 years to predict recurrence, and that early diagnosis will be implemented clinically within 5 years to 10 years.

Hashiguchi: Thank you very much.

Ito: I'm Ito of Chugai Pharmaceutical. I will answer the second part of your question.

As you can see on slide 37, the FoundationOne Liquid CDx introduced today and the FoundationOne CDx, which has already been introduced, are the tests that are used to determine the treatment plan for advanced recurrence, which is shown here in orange. This is a test that will be useful in determining the treatment plan for advanced recurrence.

As Dr. Yoshino explained earlier, if the test is to be used for early diagnosis, the concept of the test itself will change, and we are aware that new products will need to be developed. In this regard, we and FMI are making efforts to further improve our service provision.

I think it will be important to accumulate a great deal of evidence, as well as work to promote the development of these products.

Hashiguchi: Understood. Thank you very much. That's all from me.

Sasai: Thank you very much. The next speaker is Mr. Sakai from Credit Suisse Securities, please go ahead.

Sakai: My name is Sakai from Credit Suisse Securities. Thank you very much for your time today. I learned a great deal.

I don't mean to ask a backward-looking question, but Chugai Pharmaceutical held a FoundationOne CDx study session in July 2019 with another expert. At that time, the peak sales of FoundationOne CDx were estimated to be JPY7.5 billion, and since this was based on the results of the Central Social Insurance Medical Council, which seemed as if it could change in future, with the assumption it could become commonplace in 2 years to 3 years.

However, this time, Dr. Yoshino talked about various restrictions, and you said that the environment has not changed much from that time to this time, even though liquid biopsy has appeared. I think the same is true for the JPY560,000 reimbursement point issue.

In this context, the first question is how do you think this liquid biopsy, CDx, will be used in the field in the short term?

One more thing, you mentioned the use of AI, but I would like you to be more specific about this. I don't think AI can be used for definitive diagnosis, but I wonder if you could tell us how it would be possible to reduce the burden of testing in all cases.

Yoshino: First of all, could I answer the first question, regarding the ideal image of the test? Is that a fair summary of the question?

Sakai: Yes, thank you.

Yoshino: As for the ideal type, for me personally, it is actually very important to get the results back quickly. For the patient, that is. We published data in October last year in the journal *Nature Medicine* showing that the earlier we start treatment, the more likely we are to make use of the test results.

Essentially, my ideal would be to test all cases before first line treatment for advanced stage cases, or at least for advanced stage panels. My personal opinion is a first line test should be done before starting treatment, and it should be a blood test. However, there is quite a bit of disagreement among researchers here, and some people think that a tissue test should be done first. I, for one, think it would be ideal to do a blood test and then check with the tissue test if no results are obtained.

They call it a reflex test. If there is no abnormality in the blood test, a tissue test would be done. But with the blood results, treatment could be started. In that case, it would take 10 days for the Foundation to test the blood and more than a month for the tissue test. So, if you think about it, you can start the treatment sooner. However, if there is no abnormality in the blood, treatment could be commenced, and if the tissue test yields a result, the treatment could be changed accordingly.

Thereafter, every time a patient is no longer responding to treatment, just before switching to a new treatment, another round of liquid biopsy would be performed. I think that the best image is for patients to undergo liquid biopsy about 3 times in their lifetime. This is my basic idea.

As for how to expand AI diagnosis, we are in the midst of discussions with the MHLW about how to do this, so there are a lot of confidentiality. I have my own ideas about this, and if we use these ideas, we can create a medical device program like this.

Basically, clinical trial data is highly sensitive. It's highly sensitive and changes almost daily. To be honest, even if AI companies use public information, such as information on the Internet, it is impossible to obtain information on whether or not a clinical trial is really available here. The only people who have this information are a company's development headquarters and the sites where the trials are being conducted.

Therefore, from a company's standpoint, the most frightening thing is that the information is leaked to other companies. They are terrified of data being exposed. There are differences in attitude among companies here but sharing among research sites conducting clinical trials is permitted.

Therefore, when information is shared between AI companies and clinical trial sites under a rather strict contract, the information that the clinical trial is being conducted in a hospital is conveyed to patients with NGS results on time. In other words, patients will flow to the site where the clinical trial is being conducted, which will accelerate the clinical trial.

Therefore, what we need to discuss now is how to support academia in the conflicting areas of handling sensitive information versus how to promote clinical trials, and then how to achieve that collaboration between academia and AI companies. I think that will change in the future. I think the question of how that will develop is very important. I think this is tantamount to a national project, and we are still in the midst of such discussions.

Sakai: In that case, your understanding is that the technology for AI has already reached a certain level, but the problem will be to create the framework and infrastructure to utilize it.

Yoshino: That's right. Yes. Good. In the past, when various AI devices were being approved, a certain snapshot of the correct answer was created, and approval was based on the percentage of agreement with that answer. I think we have to prove how the AI is following and tracking correct answers that change every day, which is probably a type of test that no one has ever done before.

This is a difficult area, but if we can reach an agreement with the PMDA and MHLW on this, I think we will be able to move forward quickly.

Sakai: Understood. Thank you very much.

Sasai: Next, Ms. Mitsutake from the NIKKEI, please go ahead.

Mitsutake: My name is Mitsutake from the NIKKEI.

Dr. Yoshino, you mentioned earlier that the percentage of people who underwent cancer gene panel testing was 5% of those who died, and that the number of people where a therapeutic drug was identified and used was 607.

How do you think these numbers will change with the advent of this blood-based test? Of course, this would be under the restrictions that you mentioned today.

Yoshino: Thank you very much.

In fact, we wrote a paper in *Nature Medicine* last November focusing on this very topic. The paper reports the result that if the number of people entering a clinical trial based on the results of histology, for example, the frequency of entering a clinical trial, is set at 1, the number expands by 2.5x.

The reason for this is that the results come back faster. This is the most important point. Many patients' conditions deteriorate within 2 weeks or a month, so making them wait a month is quite critical.

The liquid test takes a week or 2, and the Foundation results are returned in 10 days. But for a tissue test, it can take 2 months. It takes 6 weeks to 2 months. During that time, patients become sick and are not able to enter a clinical trial. That is the current situation.

That can be prevented in the case of the blood test, but the expert panel issue could interfere with that. If the expert panel was held late, the test results would be returned in 2 weeks, but if the results were not communicated to the patients until a month later, the chance of entering a clinical trial would decrease.

I don't have the data for the Foundation yet, but I think there is a possibility of a 2.5-fold increase, at least according to our past studies of the NGS-based blood test.

Mitsutake: Understood. Thank you.

I also have 1 more question. I would like to ask you about the impact of the coronavirus pandemic. For example, as you mentioned earlier, in order to calculate the cost of insurance, you are holding meetings of expert panels in person. How has this affected the frequency of meetings?

Yoshino: We are now networking 12 core base hospitals with our members, and from what I hear, they are definitely doing it once a week. Most places do it twice a week. When this is a designated core hospital, it is taking place. However, if it spreads to designated hospitals, the number of times it is held may be less due to manpower issues, such as once every 2 weeks.

Due to the coronavirus pandemic, the frequency of meetings decreases. However, there are many things that can be discussed without actually meeting face to face. For example, I think it would be more flexible in terms of time if email discussions were allowed. There is also the issue of the coronavirus pandemic, but if we think about it in a normal way, it would be better to change to a more flexible and elastic operation.

Also, there are members who say that an expert panel cannot be formed without this group of members, but if we narrow down the number of members a bit more, I think we could create smaller expert panels with more mobility.

Mitsutake: Is it correct to say that the current situation does not yet allow for such mobility and flexibility in operation?

Yoshino: Indeed. I hear that there is a lot of discussion going on in the Ministry of Health, Labor and Welfare about that.

Mitsutake: Understood. Thank you.

Sasai: Thank you very much. Next, a question from Mr. Osakabe.

Osakabe: My name is Osakabe, and I am a reporter at *Nikkan Yakugyou*.

I would like to ask you a few questions. In your talk today, you mentioned that the cancer gene panel test is actually used in only 5% of cases, and that the percentage of patients who received the cancer gene panel test and found a new treatment was about 8.1%.

With the spread of liquid biopsy as a new option, will there be any change in the percentages here? Thank you.

Yoshino: First of all, with the cancer genome test, there are probably 10% of people who cannot be tested because we cannot obtain tissue samples, so the number of tests will probably increase by 10% or 20%.

However, the penetration of testing has increased anyway over time. So, I think there will be an increase for the reasons I mentioned, as well as a natural increase over time. I think that the number of patients will increase by about 10% or 20%, if we go with the straightforward insurance-based calculation based on testing where tissue samples are not available.

Also, as I mentioned earlier, I think the frequency of 8% is a bit overestimated because it includes drugs that are already approved. I think the 3.7% data I gave earlier is more correct because it is for clinical trials. I think the data from that side will be about 2.5x larger.

I think the slide, this one, is relevant. This 3.7% figure will be 2.5x larger. Therefore, I think that the rate will be over 10%.

Osakabe: Thank you very much.

Sasai: Thank you very much. Due to time constraints, I will conclude with the next question.

Mr. Yamaguchi of Citigroup Global Markets Japan, please go ahead.

Yamaguchi: My name is Yamaguchi from Citi. Thank you for your time today.

I have heard a few times about TAT, or turnaround time, but I understand that at present, there is a difference in turnaround time depending on whether the organization has a domestic laboratory or whether the sample is taken overseas, like with Chugai.

In the case of the blood test, the time in Japan is 10 days or less, but if this is shortened a little more, can we assume that the possibility of saving the patient will be higher, as you mentioned?

Yoshino: Companies refer to turnaround time as the time from the sample arriving at their laboratory to the time the results are returned. However, in the case of tissues in the field, it takes time to first obtain consent from the patient and then to prepare the tissue. Tissue samples already stored in the storage are removed, and the slices will be prepared. The slicing process takes about 1 week or 2 weeks. This is the first step for tissue.

It's fine if the storage is available at your facility, but if it's at another facility you have to order it. Then it easily becomes 3 weeks or more. That's the part that's taking a long time. Furthermore, even if the results are returned to the expert panel, they are still stocked for the expert panel, so you have to wait until the next meeting to produce the result. If it's a weekly Thursday meeting, and the result is delivered to the expert panel on Friday, that adds more time.

That adds almost a week, so in total, an extra 4 weeks can be added. So, a tissue test can take the amount of time that the tester says, plus up to an additional 4 weeks. In the case of the blood test, you can take a patient's blood and send it the same day. If we add 10 days to that, and then we have an expert panel, for example, if we hold it for a week, we can get the results back in about 3 weeks.

However, the sooner you do this, the better. Even 1 week is quite important, so the important thing for the patient is getting the result as quickly as possible so we can administer medication.

Yamaguchi: I understand. So, while there are pros and cons for both tests, you would say that overall, the blood test is likely to be preferable? Would it be correct to assume that even if the total number of tests does not increase much, there is likely to be a shift from tissue tests to blood tests?

Yoshino: Personally, I think that there are still some technological limitations of blood tests. Various technologies, not only ctDNA, but also the nucleosome part mentioned earlier are constantly evolving. I personally believe that the time will eventually come when everything will be blood tests not tissue.

Yamaguchi: Theoretically, as long as the return is clearly faster, if the result is the same, the blood test is better, isn't it?

Yoshino: Indeed. If the results were the same, yes, and I think there will be a time when the results will actually be more accurate.

Yamaguchi: I understand. Also, I think there was a technical reason for testing fewer genes in the blood test?

Yoshino: No, the Foundation test has the same number of genes for both tests, 324 genes.

Yamaguchi: That's right. However, there are specific ones, such as ALK, ROS1, and NTRK. The cancer type and related genes are the ones that the drug is attached to. I have a feeling that these numbers are different, but are they the same?

Yoshino: The issue here is that results aren't available for the new technology. The older ones have a better track record, while the newer ones don't have the same track record. So, I think it's safe to say that the only difference is in the type of cancer.

Yamaguchi: I understand. Thank you very much.

Sasai: Thank you very much. This concludes the presentation on the FoundationOne Liquid CDx Cancer Genome Profile. If you have any questions that we were unable to answer due to time constraints, please contact the Corporate Communications Department. Contact information can be found on the last page of the presentation materials.

Thank you very much for taking time out of your busy schedule to join us today.

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