Information Meeting on FoundationOne® Liquid CDx Cancer Genomic Profile

Agenda

Moderator: Toshiya Sasai, Head of Corporate Communcations Dept., Chugai Pharmaceutical Co., Ltd.

1. **Product Overview of FoundationOne Liquid CDx Cancer Genomic Profile**

   Satoru Ito, Lifecycle Leader, Foundation Medicine Unit, Chugai Pharmaceutical Co., Ltd.

2. **Current Status of Cancer Genomic Medicine in Japan and Expectations for FoundationOne Liquid CDx Cancer Genomic Profile**

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

3. **Q&A Session**

Innovation all for the patients

CHUGAI PHARMACEUTICAL CO., LTD.

Roche Group

Product Overview

FoundationOne® Liquid CDx

Cancer genomic profile

Software for gene variants analysis (for cancer genome profiling),
Software for analysis of somatic cell gene variants (for eligibility identification of antineoplastic agents)

Specially controlled medical device

Approval number: 30300BZX00074000

Satoru, Ito
Foundation Medicine Lifecycle Leader
Chugai Pharmaceutical Co., Ltd.

September 9, 2021

Significance of FoundationOne Liquid CDx

- FoundationOne Liquid CDx Cancer Genomic Profile (F1LCDx) is the only* blood-based cancer genomic profiling (CGP) test which has obtained regulatory approval and been covered by National Health Insurance (NHI) system in Japan.
- With the new blood-based CGP test F1LCDx becoming available in addition to the tissue-based FoundationOne CDx Cancer Genomic Profile (F1CDx) , support for clinical decision-making on therapeutic strategies, according to patient's condition and treatment status, can be provided to more patients, which is expected to advance personalized healthcare based on alterations status in patients.

* As of September 9, 2021.

FoundationOne CDx Cancer Genomic Profile (F1CDx)

FOUNDATIONONE® CDx
Cancer genomic profile

Approval: December 28, 2018
NHI coverage: June 2019 (start of laboratory testing service)

FoundationOne Liquid CDx Cancer Genomic Profile (F1LCDx)

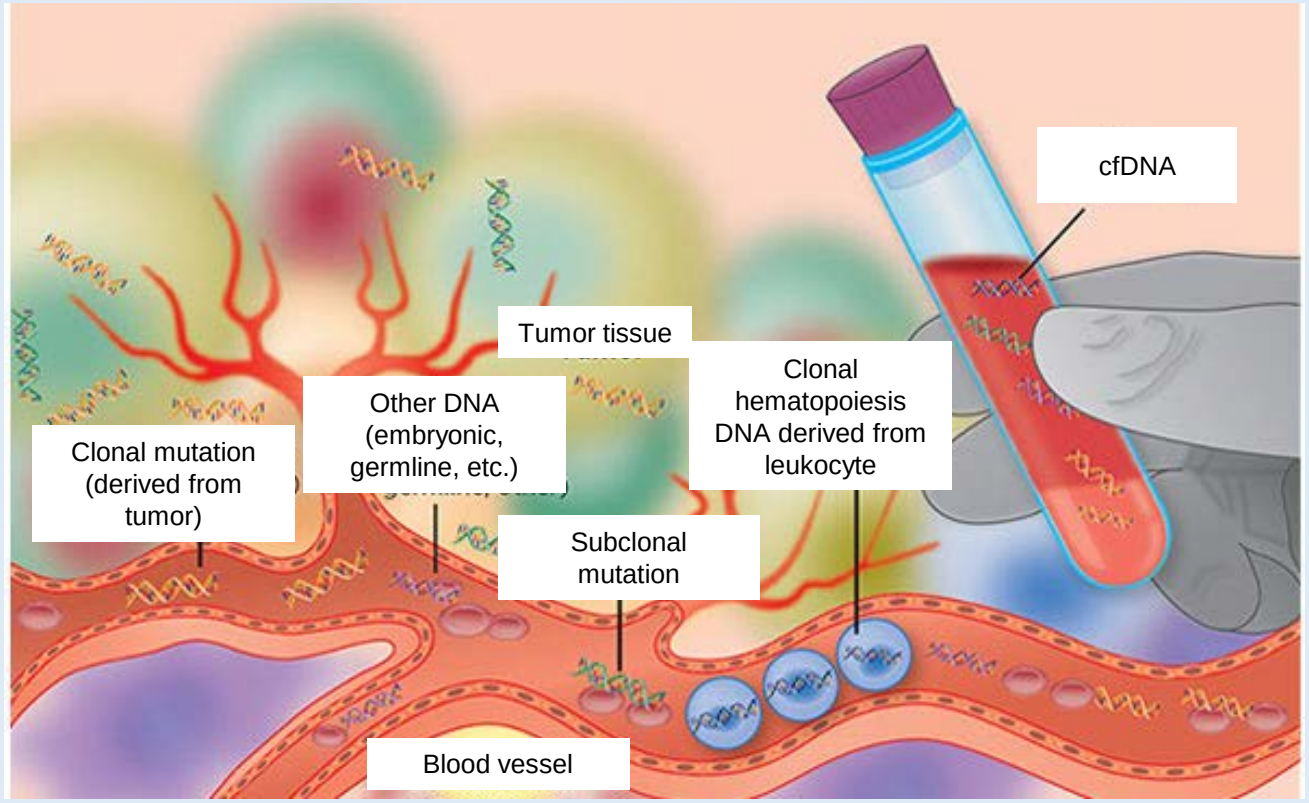
FOUNDATIONONE® LIQUID CDx
Cancer genomic profile

Approval: March 22, 2021
NHI coverage: August 2021 (start of laboratory testing service)

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

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

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"
Joint task force for cancer genome medicine among Japanese Society of Medical Oncology/Japan Society of Clinical Oncology/Japanese Cancer Association, January 20, 2021

Approval Summary of FoundationOne Liquid CDx

FOUNDATIONONE® LIQUID CDx Cancer genomic profile

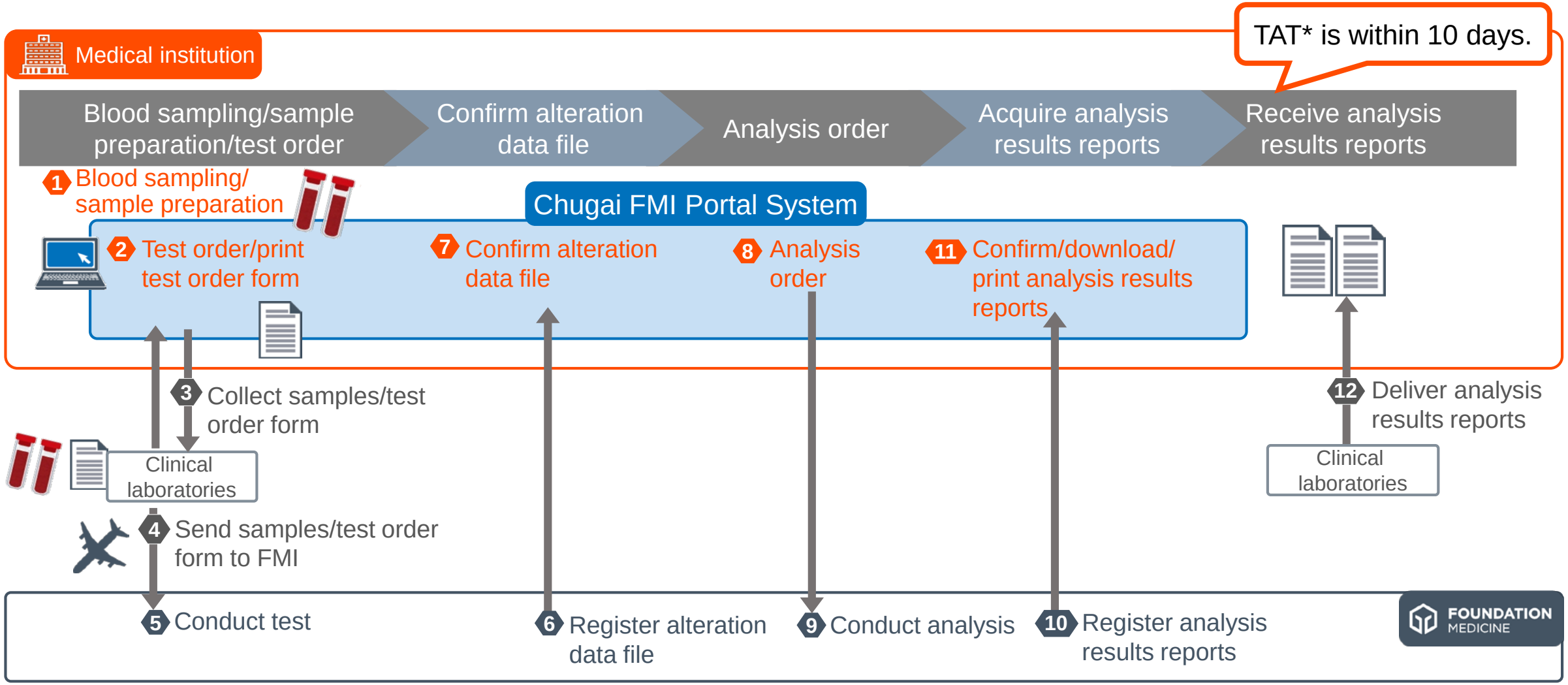
- Application date: March 2020, approval date: March 2021
- Generic name: Alteration Analysis Program (for cancer genomic profiling tests)
  Somatic Alteration Analysis Program (for assessing eligibility for anticancer drugs)
- Intended use:
  - To obtain comprehensive genomic profiles of tumor tissues 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

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.

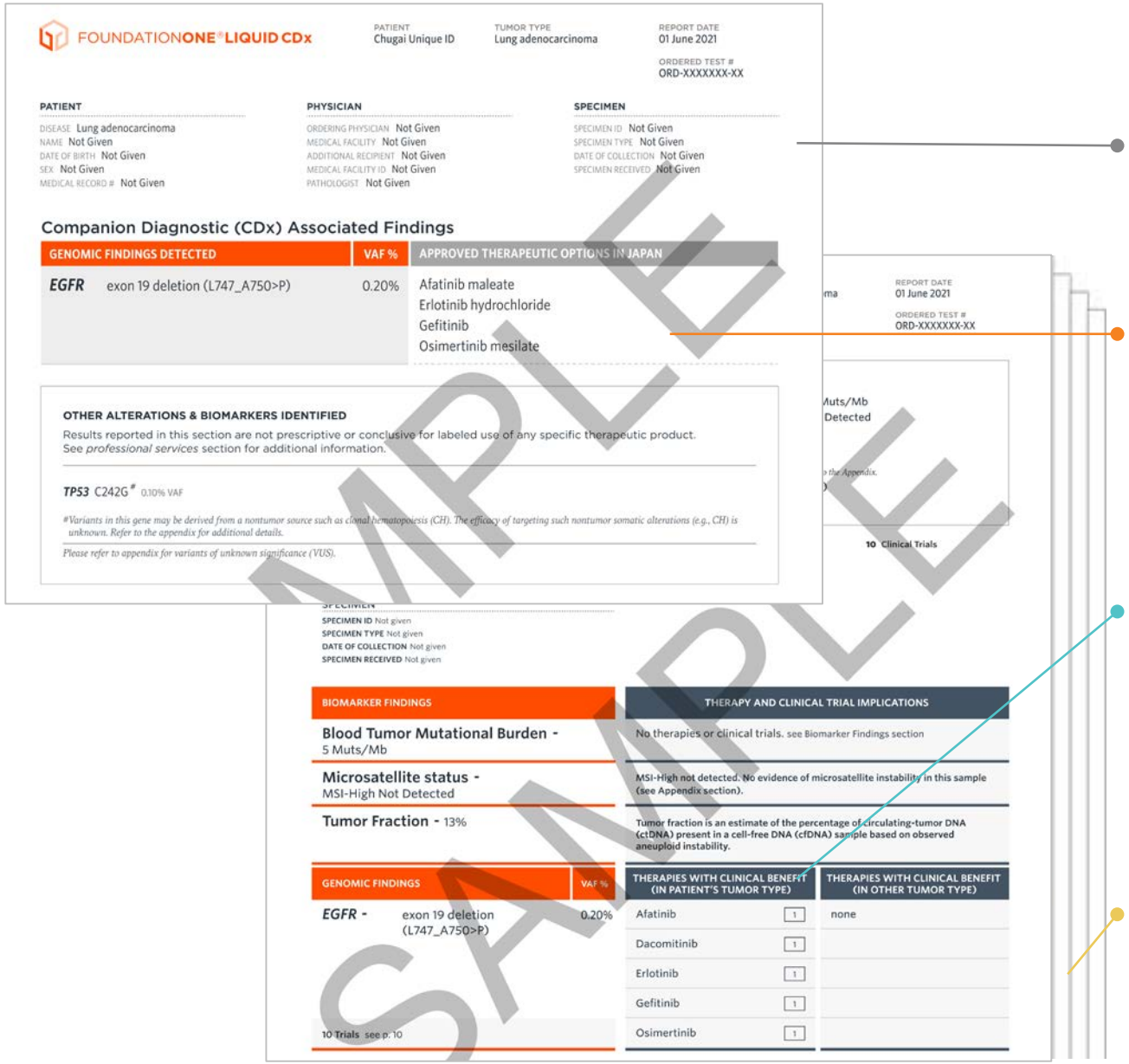
Process Flow in Testing

- FoundationOne Liquid CDx and FoundationOne CDx are conducted under a same test flow through “Chugai FMI Portal System,” etc., except for sample preparation process.



* TAT: turnaround time (from sample reception at FMI to report return)

F1LCDx: Overview of Analysis Results Reports



Background information of patient / medical institution, etc.

Summary of detected alterations

- Approval status of corresponding targeted therapies (indicated cancer type, other cancer type)
- Ongoing clinical trials targeting detected alterations

Summary of references on detected alterations and potential therapies

Conclusion

- FoundationOne Liquid CDx Cancer Genomic Profile (F1LCDx) is the only* blood-based cancer genomic profiling (CGP) test which has obtained regulatory approval and been covered by National Health Insurance (NHI) system in Japan.

- With the new blood-based CGP test F1LCDx becoming available in addition to the tissue-based FoundationOne CDx Cancer Genomic Profile (F1CDx) , support for clinical decision-making on therapeutic strategies, according to patient's condition and treatment status, can be provided to more patients, which is expected to advance personalized healthcare based on alterations status in patients.

* As of September 9, 2021.

Current Status of Cancer Genomic Medicine in Japan and Expectations for FoundationOne Liquid CDx Cancer Genomic Profile

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

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.

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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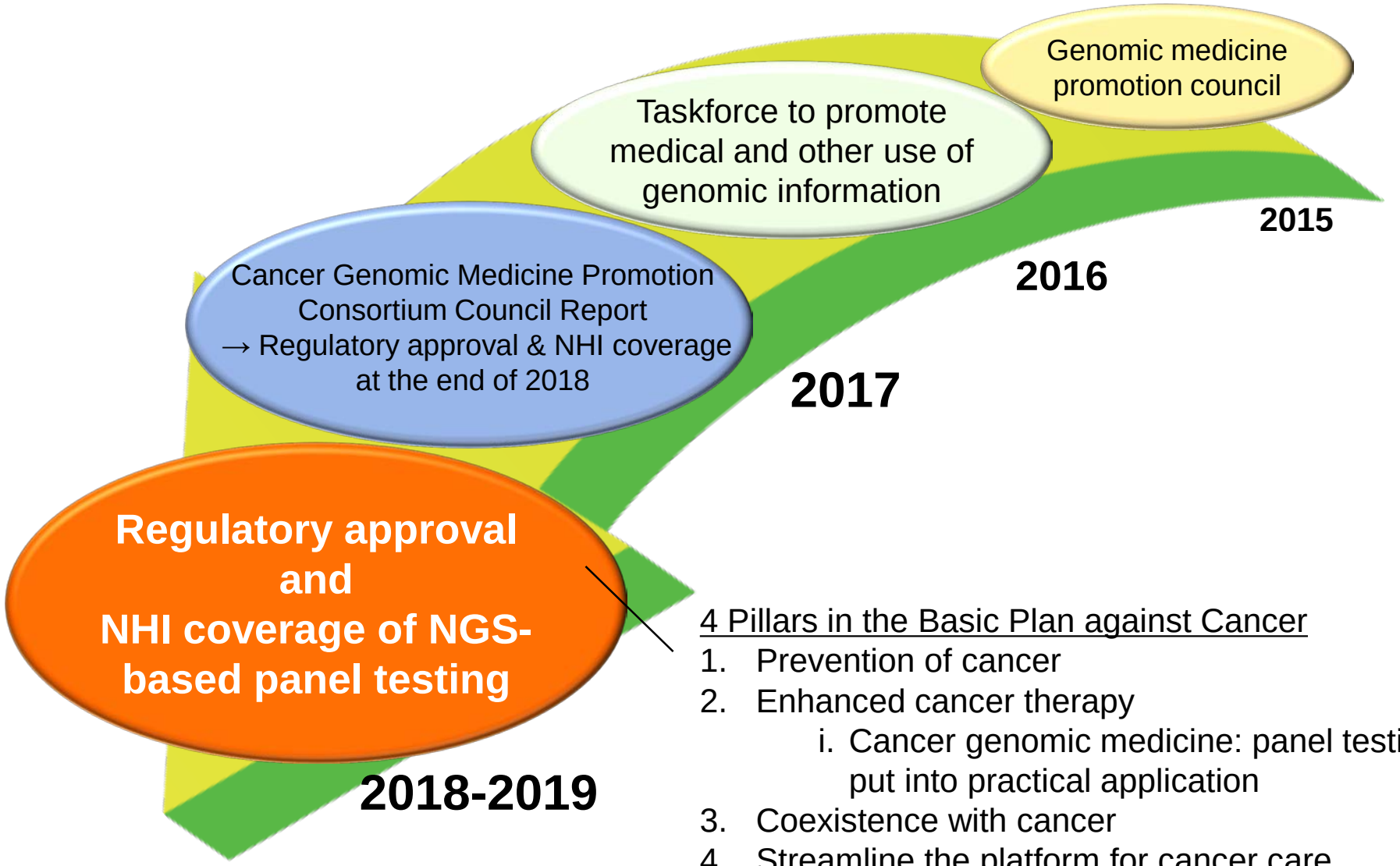
Governmental Activities for Genomic Medicine



4 Pillars in the Basic Plan against Cancer

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

NGS: Next-generation sequencer
NHI: National health insurance

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.

C-CAT registration Cumulative registered number

From the start of NHI coverage of the tests on June 1, 2019, to the end of June, 2021.

18,239 patients

* “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

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

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.

Designated core hospital for cancer genomic medicine

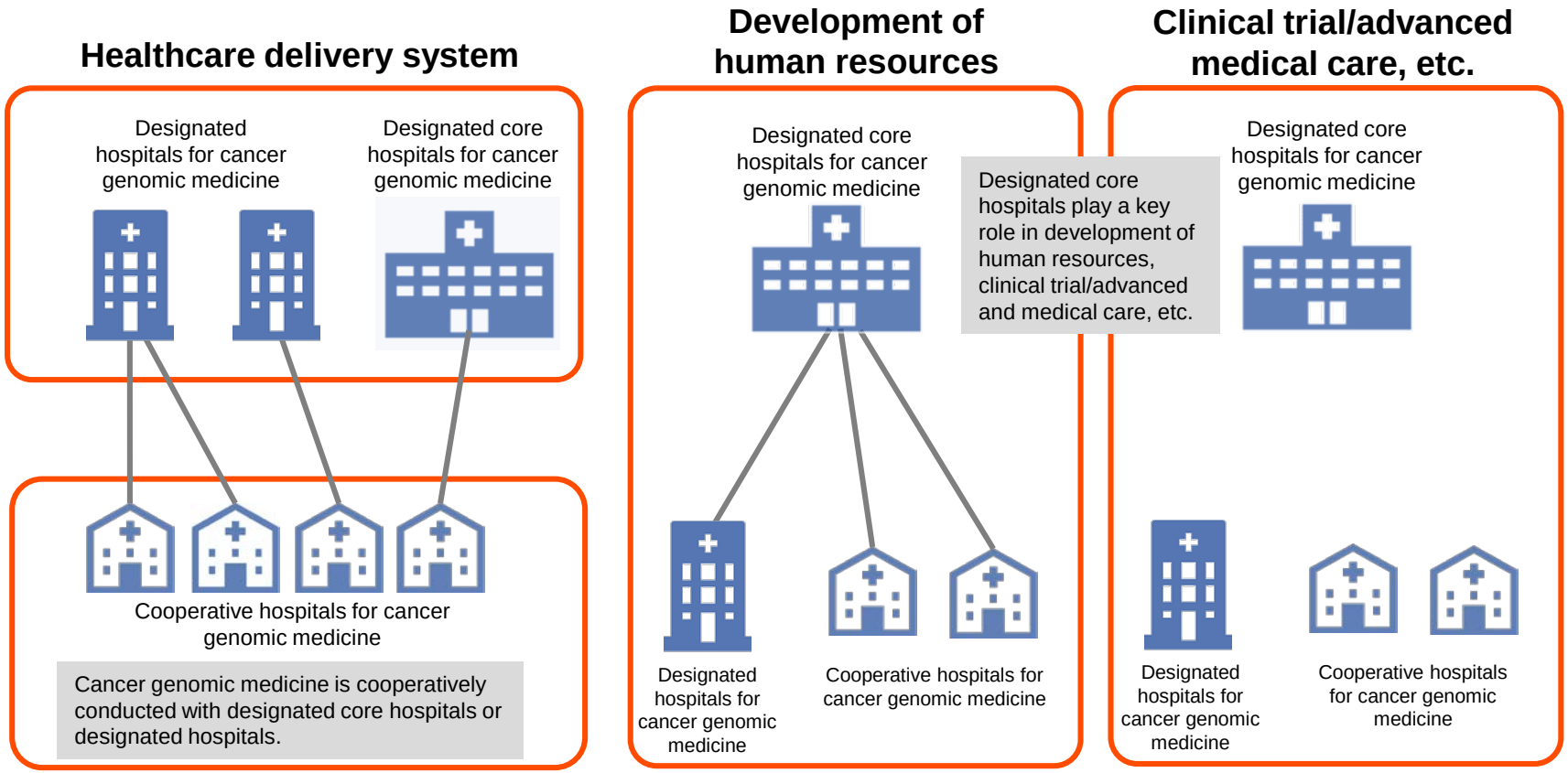
- Function for development of human resources
- Medical care support
- Leading clinical trial/advanced medical care
- Research and development
- Complete medical interpretation for gene panel test in its own facility

Designated hospital for cancer genomic medicine

- Complete medical interpretation for gene panel test in its own facility

Cooperative hospital for cancer genomic medicine

- Medical care using gene panel test is cooperatively conducted with designated core hospitals for cancer genomic medicine or designated hospitals for cancer genomic medicine.



- Cooperative hospitals should convene Expert Panel and cooperate with one designated core hospital or designated hospital * in principle.
  *: in some specific areas, cooperation with other designated core hospitals is expected
- Personnel training is conducted by designated core hospitals in cooperation with designated hospitals and cooperative hospitals.
- For clinical trial/advanced medical care, etc, no restrictions are placed on designated core hospitals to cooperate

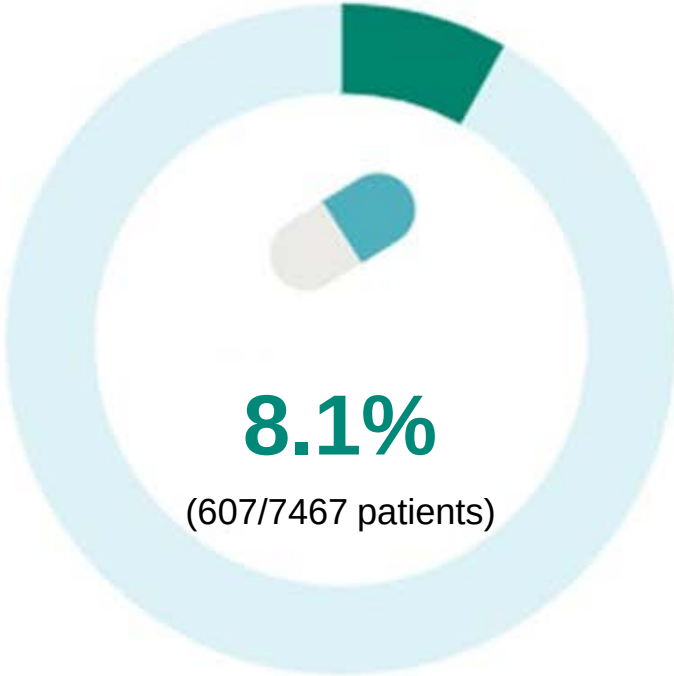
[1] Cancer and Disease Control Division, Health Service Bureau, Ministry of Health, Labour, and Welfare: modified from Preparation of Designated Cancer Hospitals (https://www.mhlw.go.jp/content/10901000/000526091.pdf) (as of March 2021) Accessed August 2021

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

Number of patients who received a new treatment after cancer gene panel test*

607 patients

Percentage of patients who received a new treatment after cancer gene panel test*



- 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

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%).

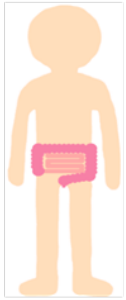
Designated core hospitals for cancer genomic medicine	Number of patients received cancer gene panel test based on health insurance	Number of patients received treatment based on gene alterations
A	75	3 (4%)
B	60	2 (3.3%)
C	5	0 (0%)
D	41	0 (0%)
E	160	16 (10%)
F	172	4 (2.3%)
G	13	1 (7.7%)
H	13	0 (0%)
I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

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

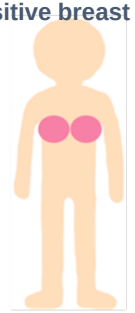
Analyzed by **NCC oncopanel**

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	alpelislb, 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

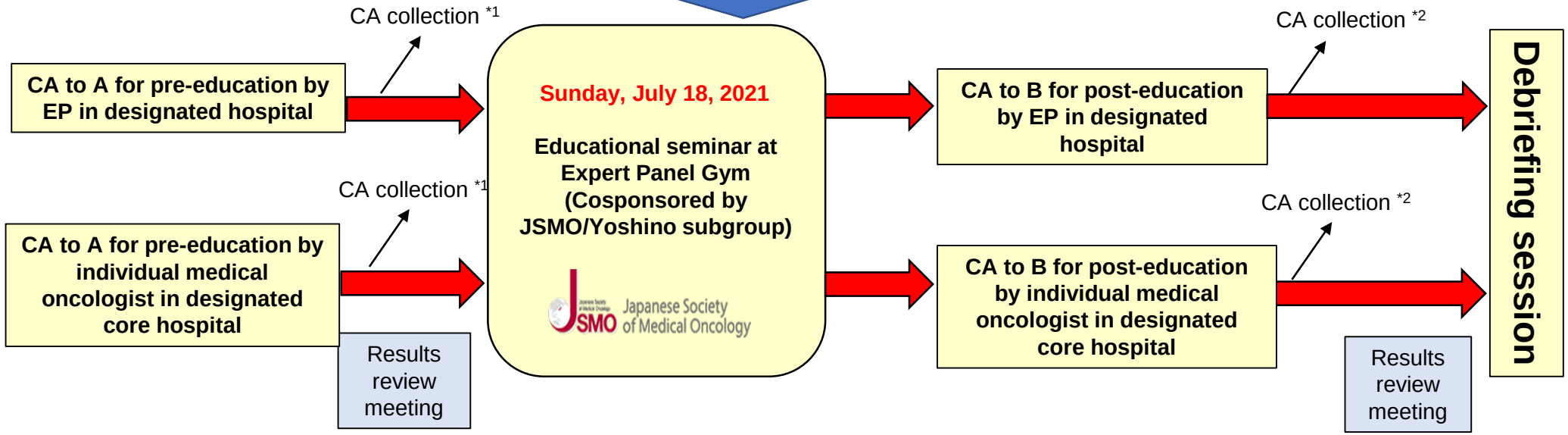
“Expert Panel Program” (Yoshino Subgroup, Health and Labor Sciences Research Grants)

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

Prerequisite work

50 simulated cases are divided into 2 groups by biostatisticians (25 cases each; A for pre-education, B for post-education).

Assign into 2 groups without disproportionation of factors affecting the match rate with consensus annotation, based on the data from 12 designated core hospitals.



[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)**

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

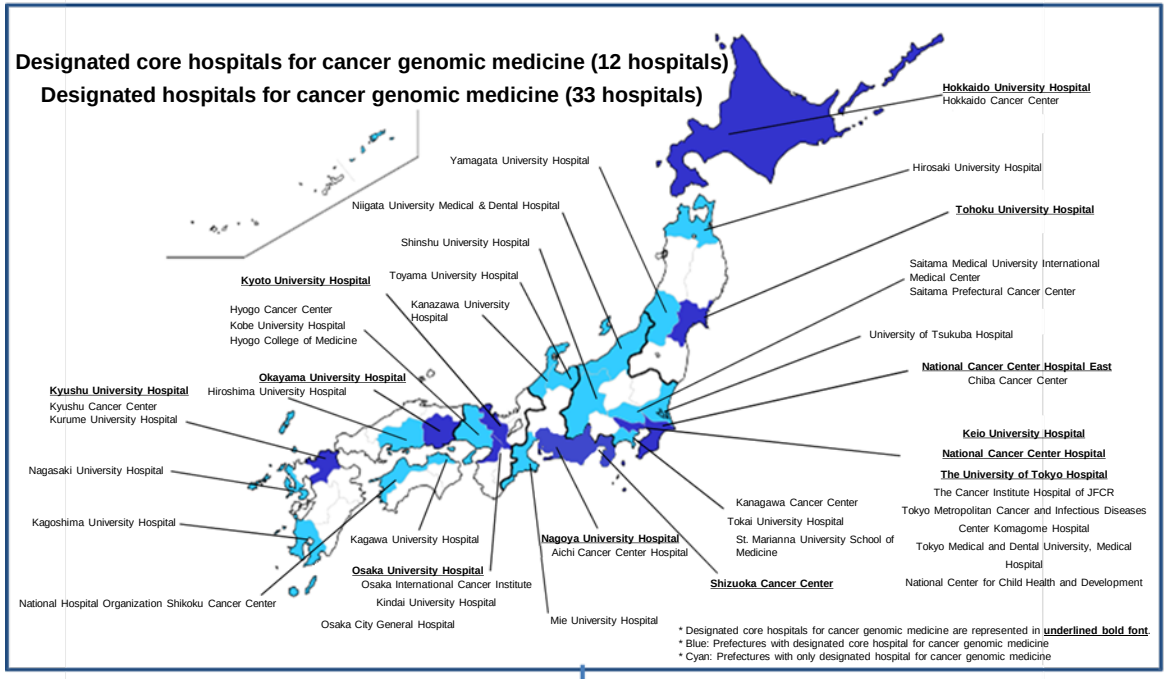
[Contact]
Expert Panel Gym Management Office (in Peak 1 Co., Ltd.)
expert_panel@event-info.jp

[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.

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

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?

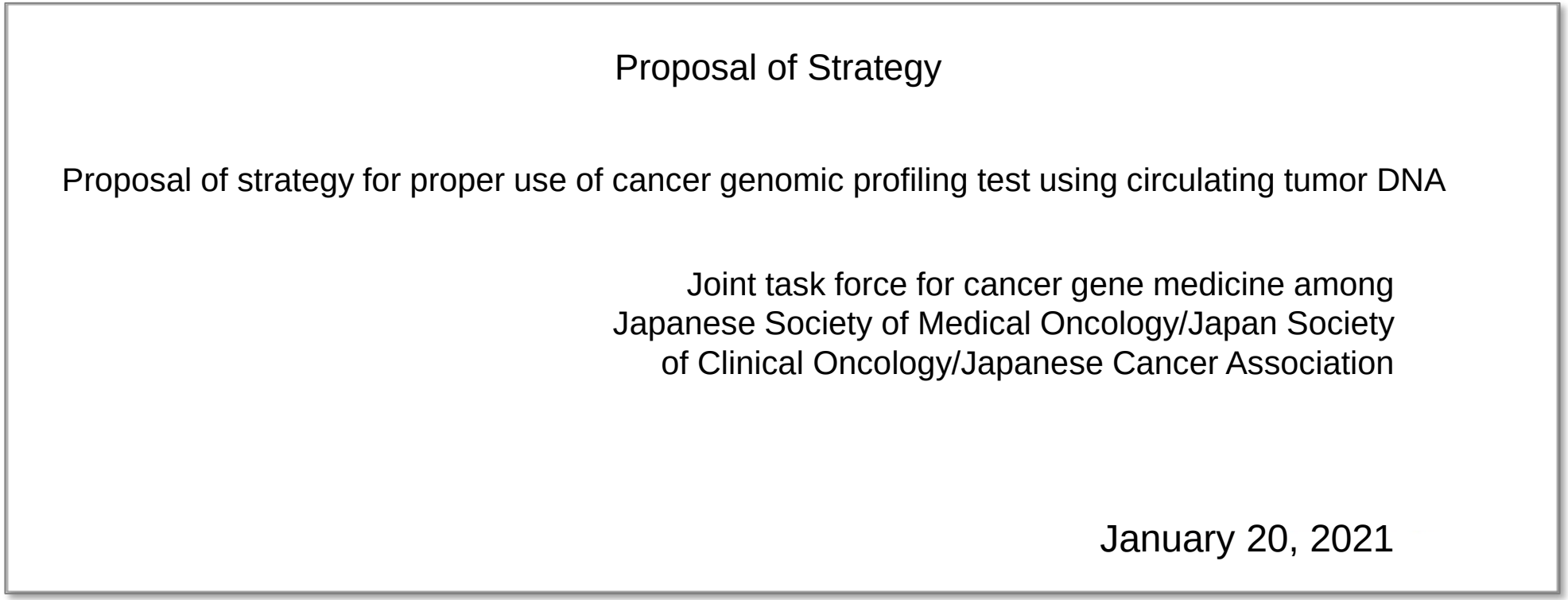
- **It is recommended to consider optimal timing** to conduct cancer genomic profiling test, **considering not only therapeutic line** but also subsequent treatment plan.

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.

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

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

What is Liquid Biopsy? [1]

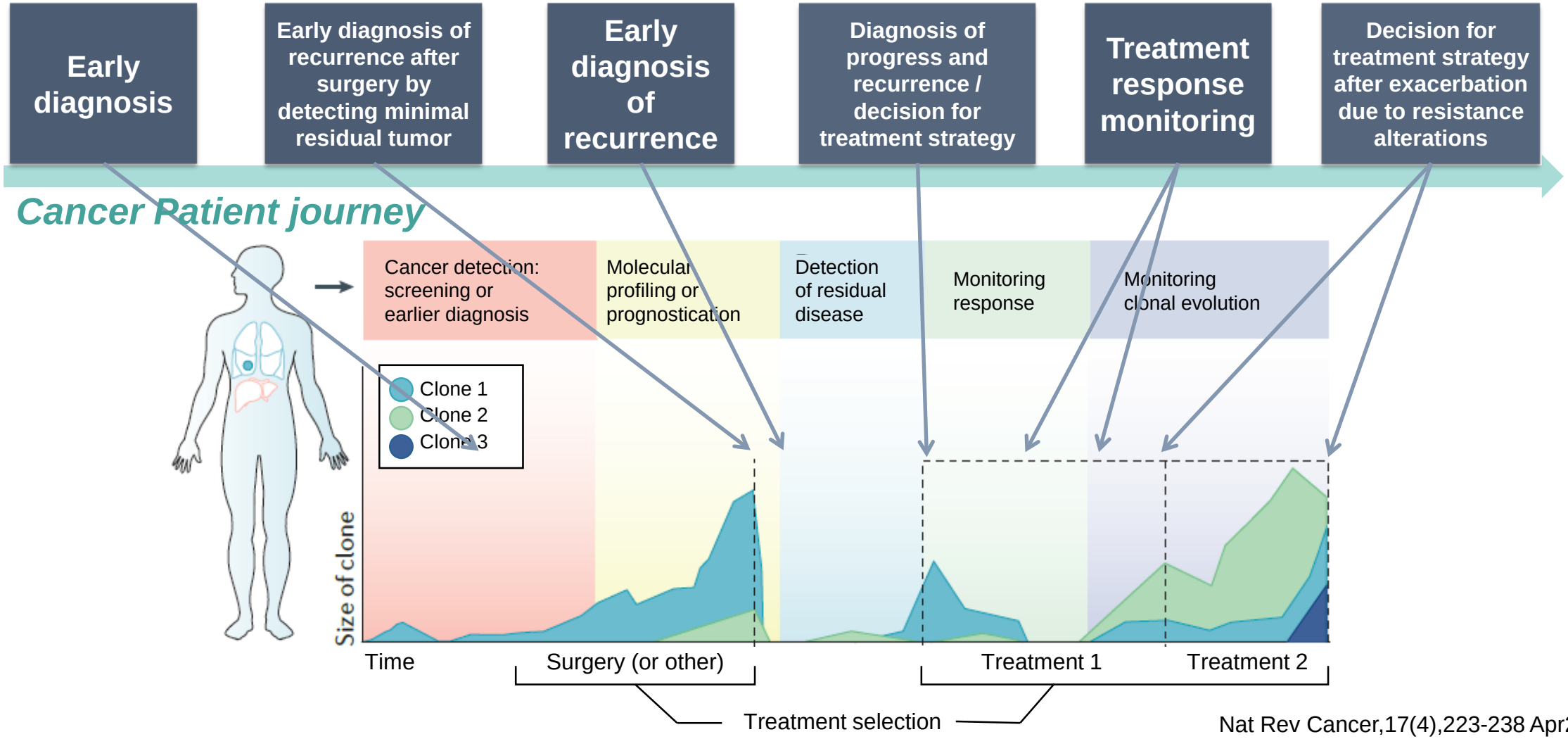
- Liquid biopsy is expected as less-invasive or noninvasive gene testing. Liquid biopsy means an analysis using tumor-derived samples (cells, nucleic acids, etc.) obtained from blood and body fluid. Especially, part of circulating tumor DNA (ctDNA) analysis has been already applied in clinical.

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)

Positioning of Liquid Biopsy (LBx)

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



Nat Rev Cancer,17(4),223-238 Apr2017

Tumor-Derived Components in Blood

ctRNA (circulating tumor RNA) [1]

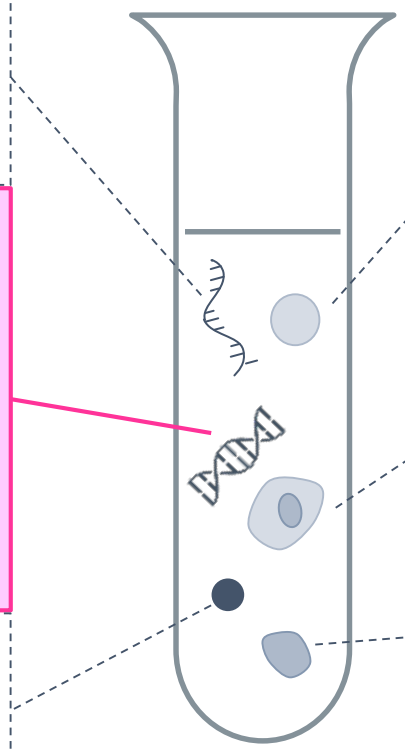
Various RNAs including miRNA, mRNA and lncRNA are contained in ctRNA.

ctDNA (circulating tumor DNA) [1–3]

- ctDNA may represent the genomic profile of tumor.
- ctDNA is suitable for detection of alteration, insertion/deletion, amplification, translocation, and methylation.

Tumor proteins [1]

Tumor proteins are suitable for clinical protein assay.



Exosome [1]

- The surface and lumen of exosomes deliver protein biomarkers.
- DNA and RNA profiling can be conducted using nucleic acids delivered by exosomes.

CTC (circulating tumor cells) [1,4,5]

- CTC provides information source for genome, proteomics, transcriptome, and cytogenetics.
- The clinical usefulness is limited by its scarcity and technical issues.

TEPs (tumor-educated platelets) [1]

TEPs are suitable for RNA profiling to clarify tumor-related RNA signature.

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

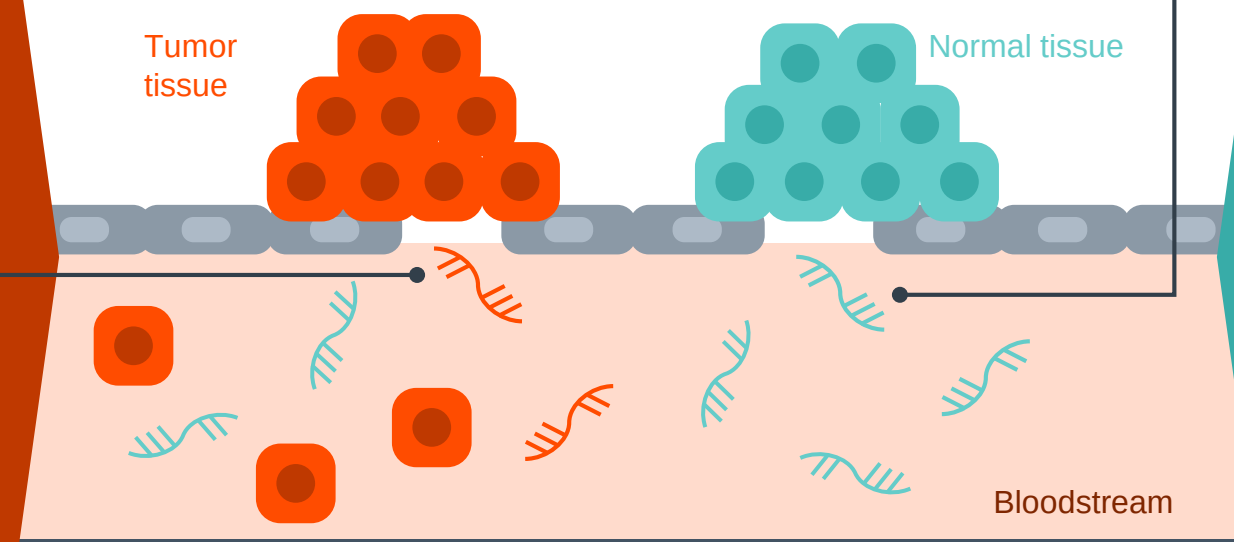
What is Circulating Tumor DNA (ctDNA)?

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

ctDNA is tumor-derived, fragmented DNA released by cell death (apoptosis/necrosis) that circulates in the bloodstream[1,3]

>75% of advanced cancer cases have ctDNA[3,4]

In metastatic cancer, ctDNA can potentially capture genomic alterations found at more than one tumor site[3]



ctDNA usually represents a small fraction of the cell-free DNA found in the bloodstream[2]

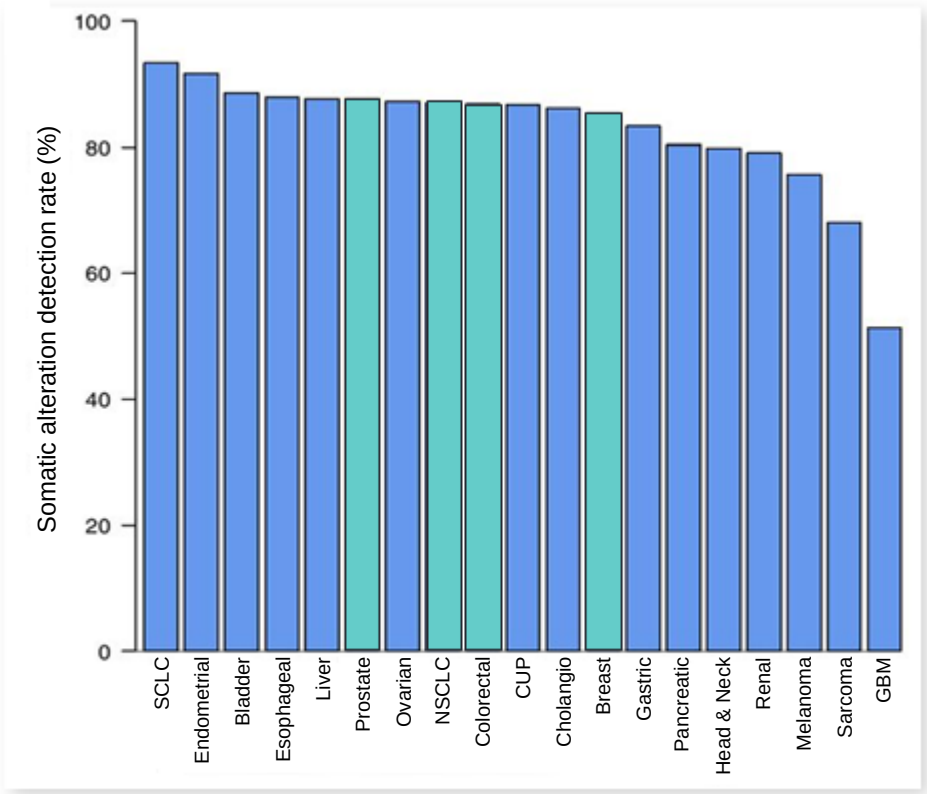
Factors impacting the amount of ctDNA include:[1]

- Tumor burden (amount and location)
- Cancer type
- Timing and type of last therapy

Tumor-derived DNA in blood may be less than 1% of total cell free DNA in plasma, compared to ~20-40% tumor DNA in a biopsy specimen[2]

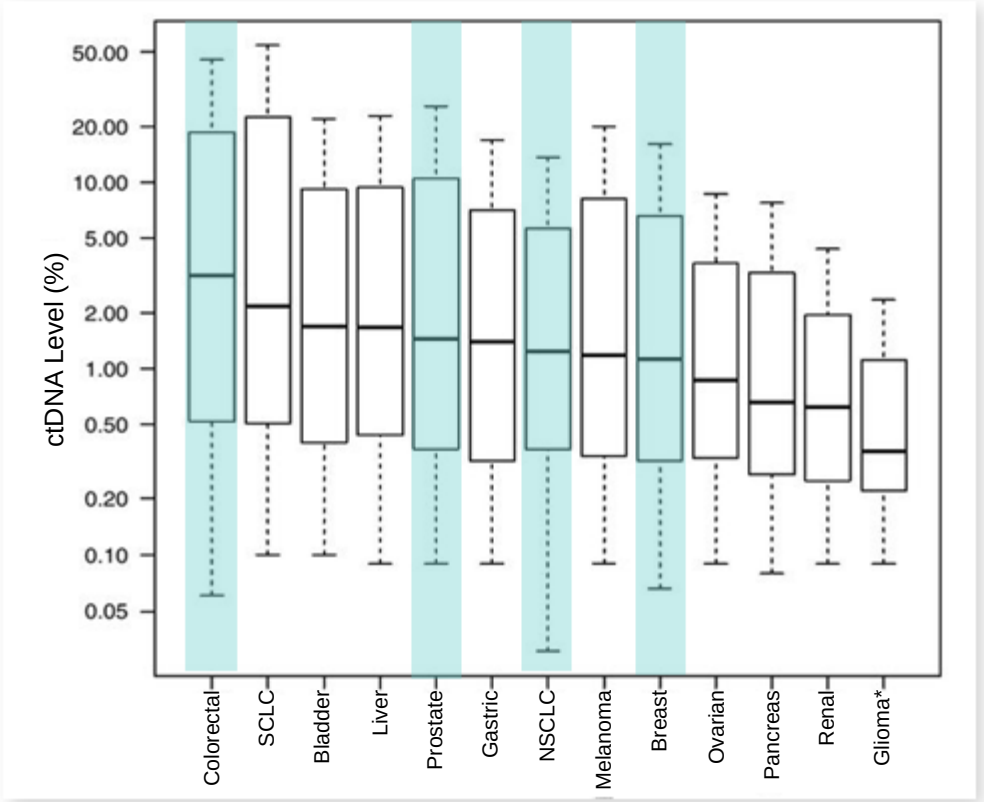
1. Corcoran RB, et al. *N Engl J Med*. 2018;379(18):1754-1765.
2. Heitzer E, et al. *Genome Med*. 2013;5(8):73.
3. Hench IB, et al. *Front Med (Lausanne)*. 2018;5-9.
4. Zill OA, et al. *Clin Cancer Res*. 2018;24(15):3528-3538.

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.

Percentage of Patients with Detectable ctDNA by Disease Stage

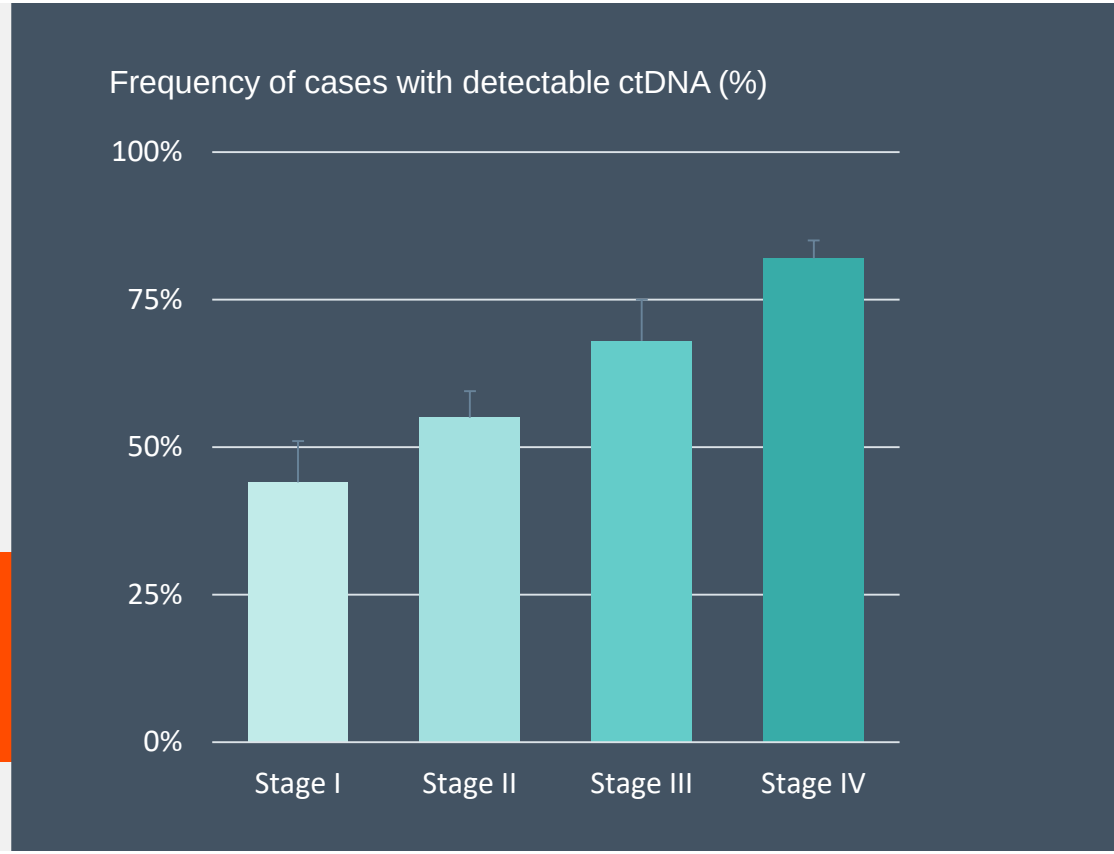
➢ ctDNA level increases as disease stage progresses (Stages I to III: 55%⇒Stage IV: >80%).

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

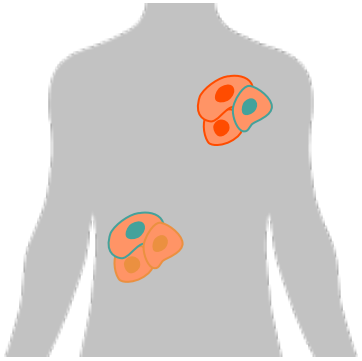
What is Heterogeneity? [1]

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.

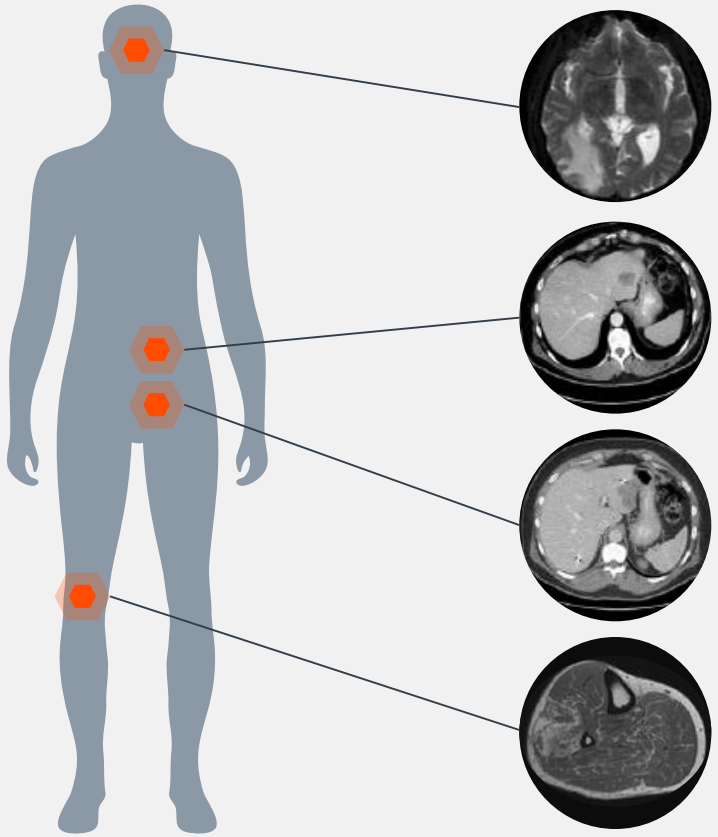
Tissue samples from single lesion may miss any specific alteration at other location.

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

Intratumor Heterogeneity: Case with Metastatic Colorectal Cancer (mCRC)

- All 4 resistance genes were detected via liquid biopsy.



Brain lesion
BRAF V600E, AF 54.7%
EGFR amp
KRAS G12S not detected
NRAS Q61R not detected

Liver biopsy 1
BRAF V600E, AF 36.4%
EGFR amp, not detected
KRAS G12S, AF 6.4%
NRAS Q61R, AF 3.1%

Liver biopsy 2
BRAF V600E, AF 61.6%
EGFR amp, not detected
KRAS G12S, AF 22.4%
NRAS Q61R, not detected

Subcutaneous lesion
BRAF V600E, *EGFR* amp, not detected
AF 45.4%
KRAS G12S, AF 0.2%
NRAS Q61R, not detected

Diverse resistance mechanisms were identified through tissue biopsies from different lesions in a patient with *BRAF* V600E positive metastatic CRC

Liquid biopsy captured all 4 resistance mechanisms

cfDNA

BRAF V600E, AF 24%
EGFR amp
KRAS G12S, AF 2.1%
NRAS Q61R AF 0.6%

AF = allelic fraction, cfDNA = cell-free DNA

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.

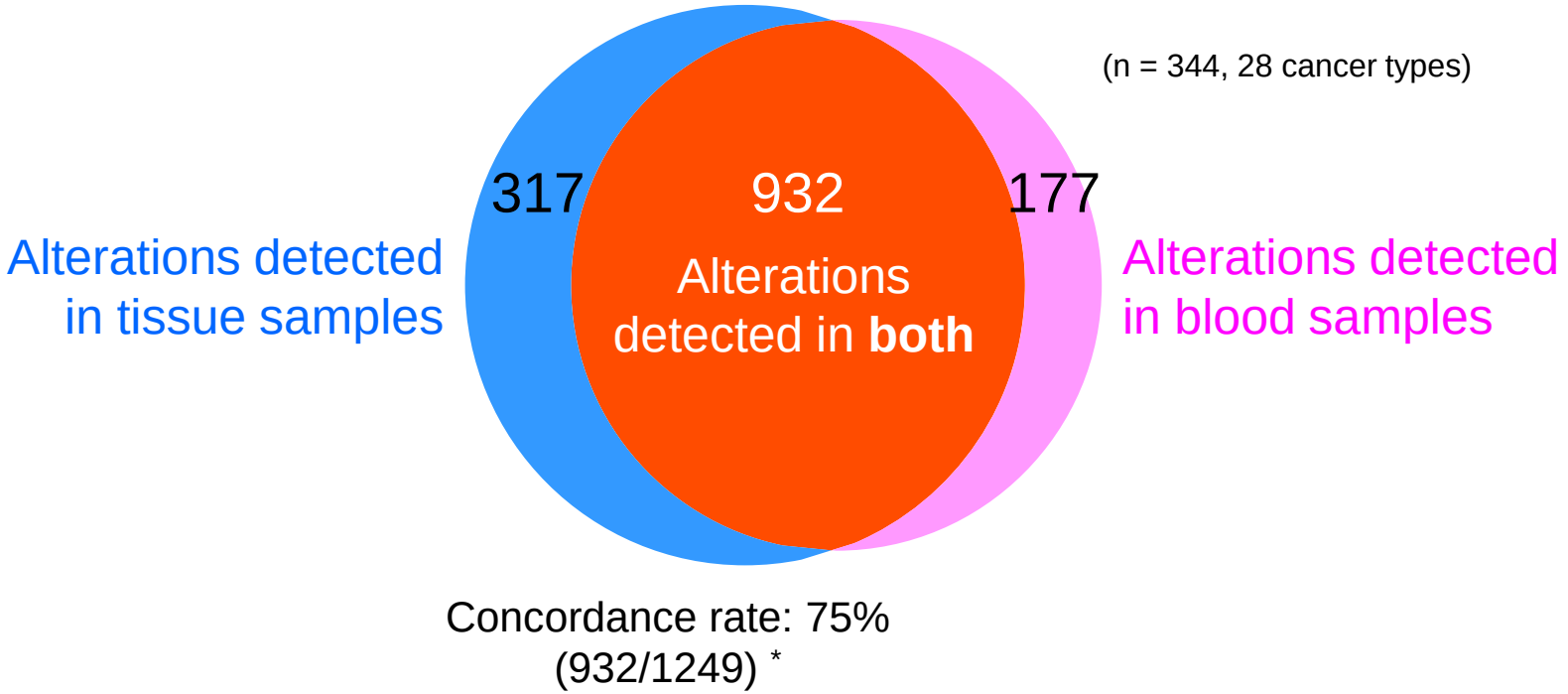
Joint task force for cancer gene medicine among Japanese Society of Medical Oncology/Japan Society of Clinical Oncology/Japanese Cancer Association
Excerpted from “Proposal of strategy for proper use of cancer genomic profiling test using circulating tumor DNA” (January 20, 2021)
https://www.jsmo.or.jp/file/dl/newsj/2765.pdf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

CGP: comprehensive genomic profiling, CHIP: clonal hematopoiesis of indeterminate potential.

Concordance Rate between Blood Samples and Tissue Samples

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

Analysis across cancer types (overseas data) [1]

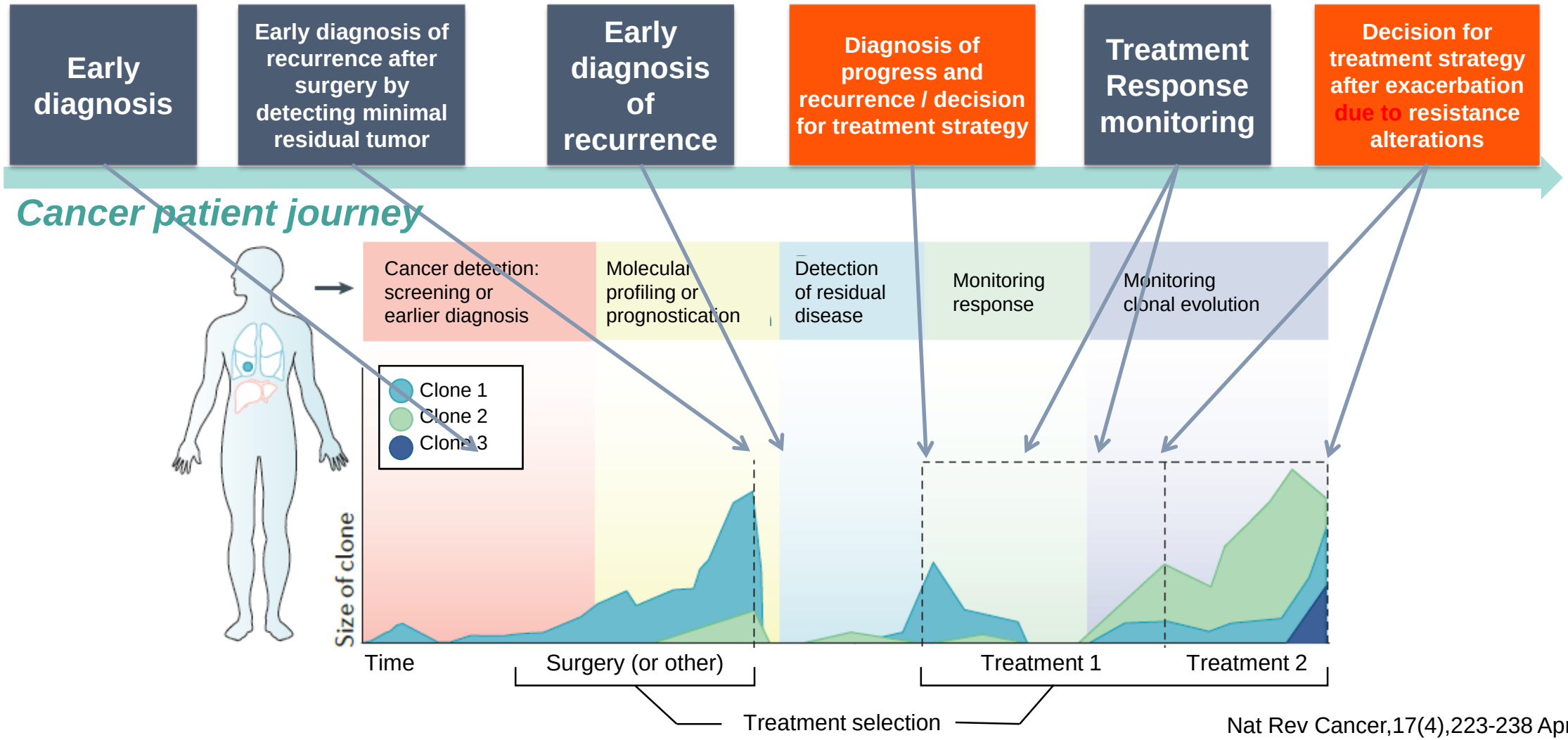


[Method] In 344 patients with 28 cancer types, CGP was conducted using tissue and blood samples collected from same patients, and the concordance rate of detected gene alteration was examined.
*: Percentage of detectable gene alterations both in blood and tissue samples to total detectable alterations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

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

Positioning of Plasma-based CGP Test

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



Nat Rev Cancer,17(4),223-238 Apr2017

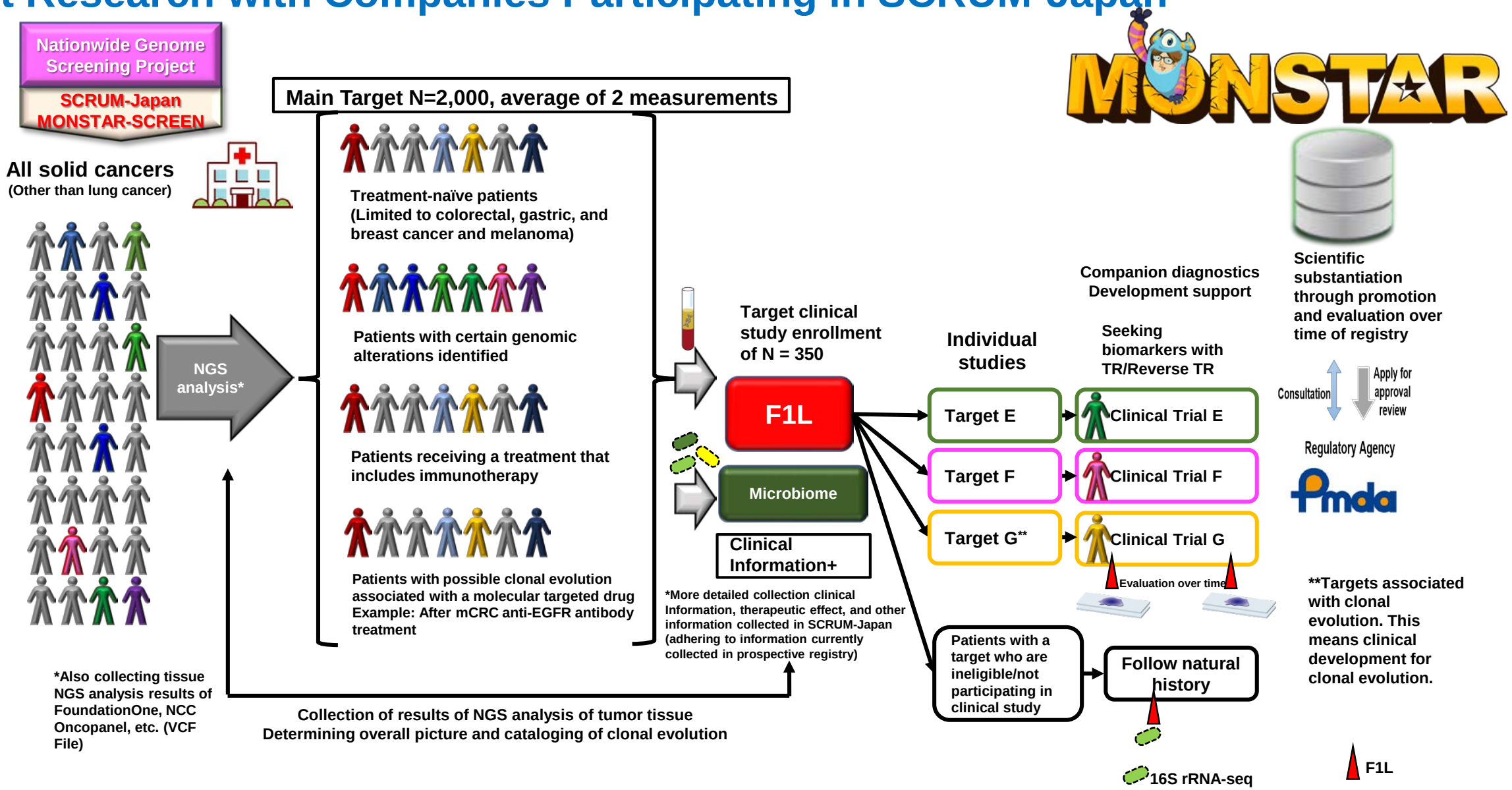
Conclusion: Characteristics of Liquid Biopsy

- *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.*

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

Joint Research with Companies Participating in SCRUM-Japan



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

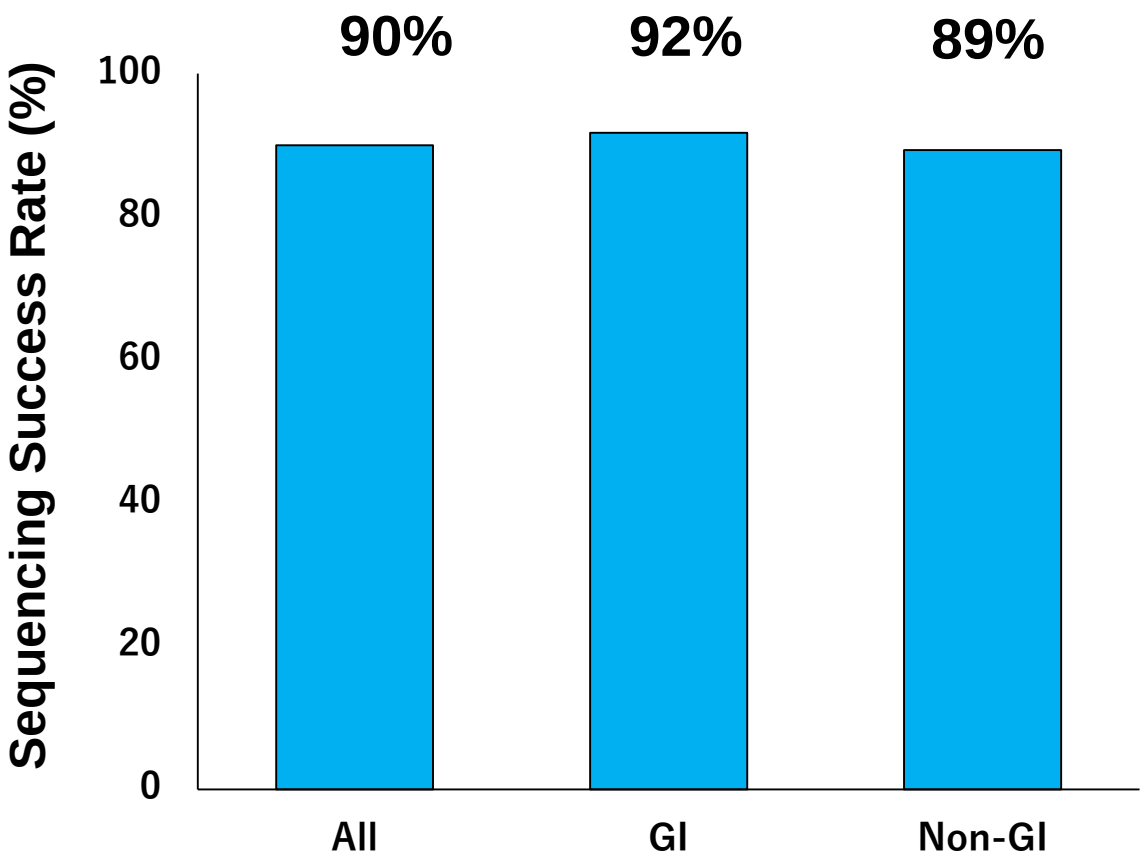
Fujisawa T, et al. JSMO2021

Sequencing Success Rate

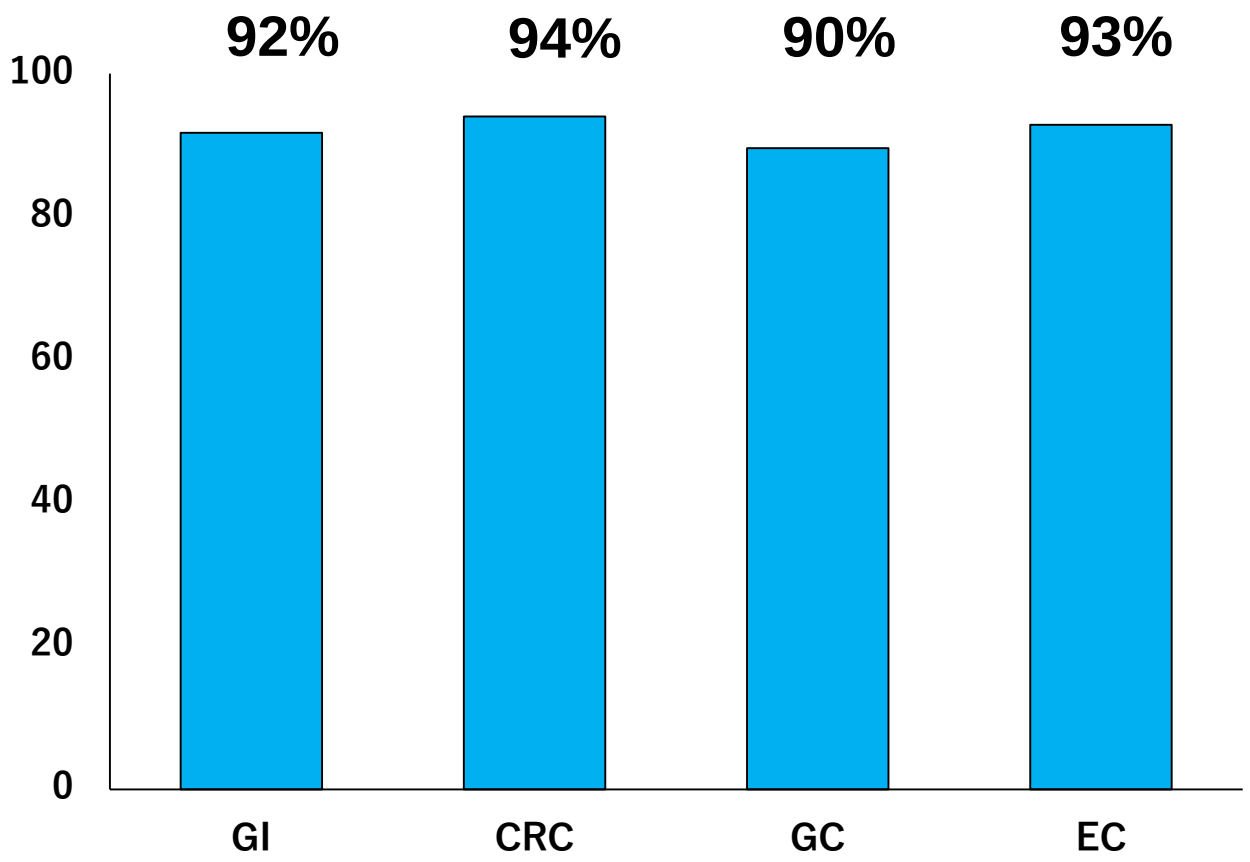
100% = 470 patients with an available ctDNA result

GI: gastroenterological cancer, CRC: colorectal cancer
GC: gastric cancer, EC: esophageal cancer

GI vs. Non-GI



CRC vs. GC vs. EC

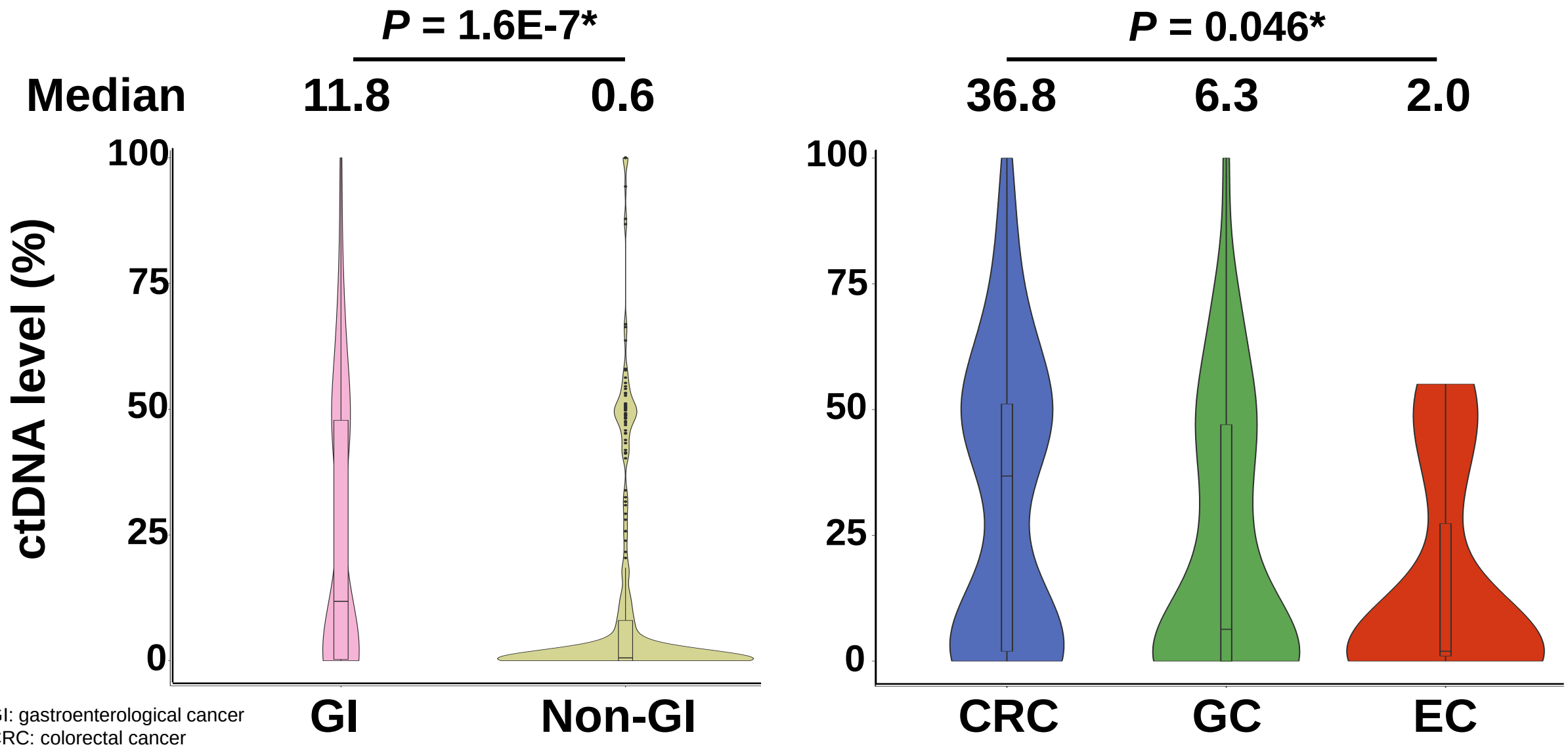


Data under examination at our own facilities. Not peer reviewed. Not necessarily the latest data.

Fujisawa T, et al. JSMO2021

ctDNA Level according to Cancer Type

*Mann-Whitney test

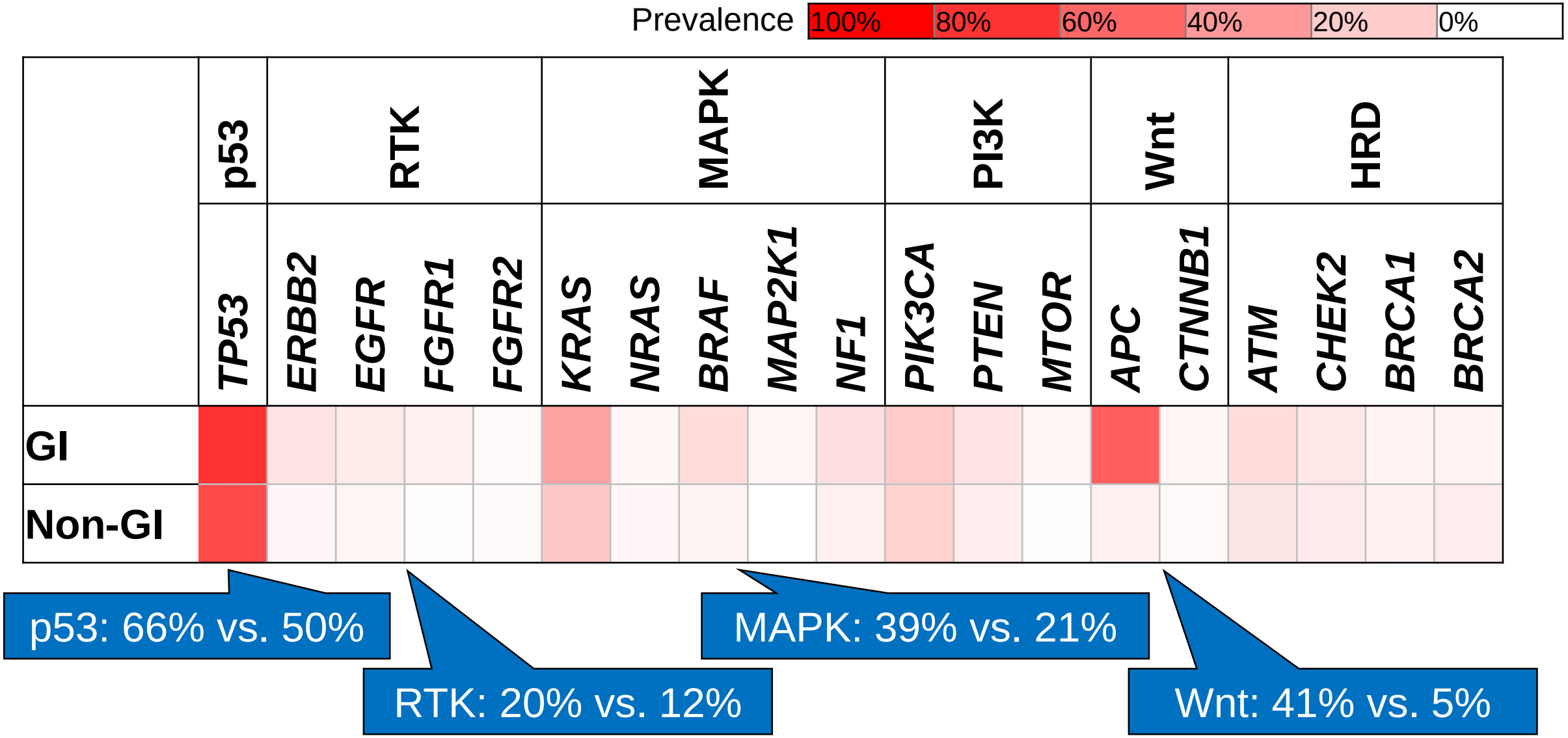


GI: gastroenterological cancer
CRC: colorectal cancer
GC: gastric cancer
EC: esophageal cancer

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

Fujisawa T, et al. JSMO2021

Prevalence of ctDNA Alterations



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

Fujisawa T, et al. JSMO2021

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

Characteristics of FoundationOne Liquid CDx Cancer Genomic Profile

- Comprehensive detection/analysis of alterations*1 in 324 oncogenes

*1: substitutions, insertion/deletion alterations, and rearrangements

- Companion diagnostics
- Analysis result report provides expert review and assignment of clinical significance (annotations)
- Users have a choice between blood-based FoundationOne Liquid CDx Cancer Genomic Profile and tissue-based FoundationOne CDx Cancer Genomic Profile
- Tested and analyzed with abundant experience *2 in FMI

*2: Owned a unique bioinformatics system consisting of over 0.4 million patient profiles in the US (as of Jan, 2021).[1)]

1）Foundation Medicine, Inc. https://www.foundationmedicine.com/service/genomic-data-solutions (As of Jan., 2021)

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)

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)

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

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)

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.

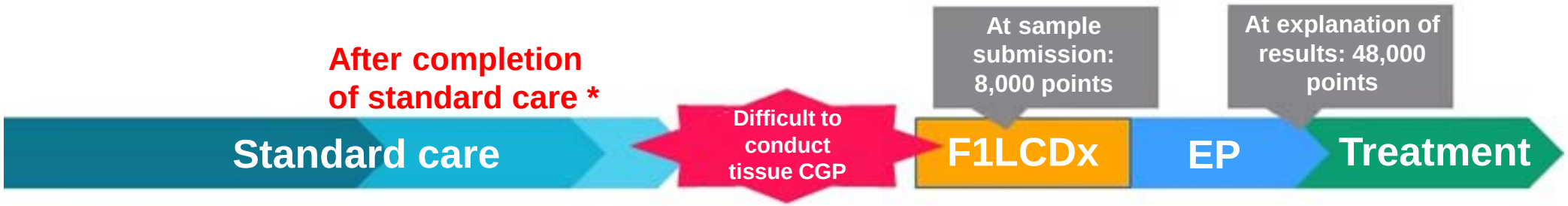
b **In the case when the results of comprehensive cancer genomic profiling cannot be obtained from cancer genomic profiling test using tumor cells from solid tumor.** In this case, the fact should be written in the abstract field of a breakdown of medical expenses.

(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）

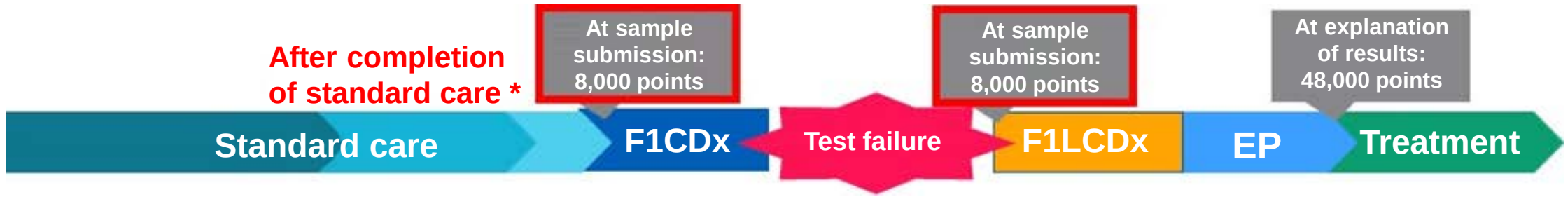
Insurance Calculation for FoundationOne Liquid CDx (in the case that standard of care therapy can be provided)

(1) In case of “a”: FoundationOne Liquid CDx can be used for patients who could not obtain proper tissue samples and could not receive CGP test up to now.
(1) Amount of tissue sample is insufficient, (2) Tissue sample is available but less tumor content,
(3) Since long time has passed from the initial diagnosis, tissue sample is deteriorated over time.
(4) Since gene alteration profile may be changed due to the treatment with molecular targeted drugs, the tissue sample used at the initial diagnosis is not suitable.



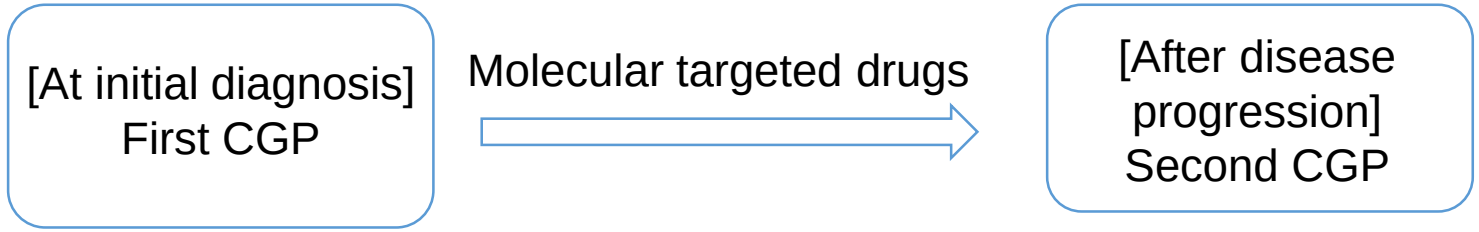
(2) In case of “b”: In the case of test failure in tissue CGP, a re-examination with FoundationOne Liquid CDx will be available.

Since preparation/submission/testing of samples can cost at a certain level, test can be calculated twice.



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

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.

Prospective Foresight

- Toward further utilization of cancer genomic profiling test
  - Revision of insurance reimbursement system (multiple tests regardless of the presence or absence of standard care)
  - Improvement of Expert Panel operation (consider necessity for all cases, increase in eligible hospitals)

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.

Forward-Looking Statements

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the “Company”). These statements reflect the Company’s current analysis of existing information and trends.
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