FoundationOne® CDx Cancer Genomic Profile Product Overview

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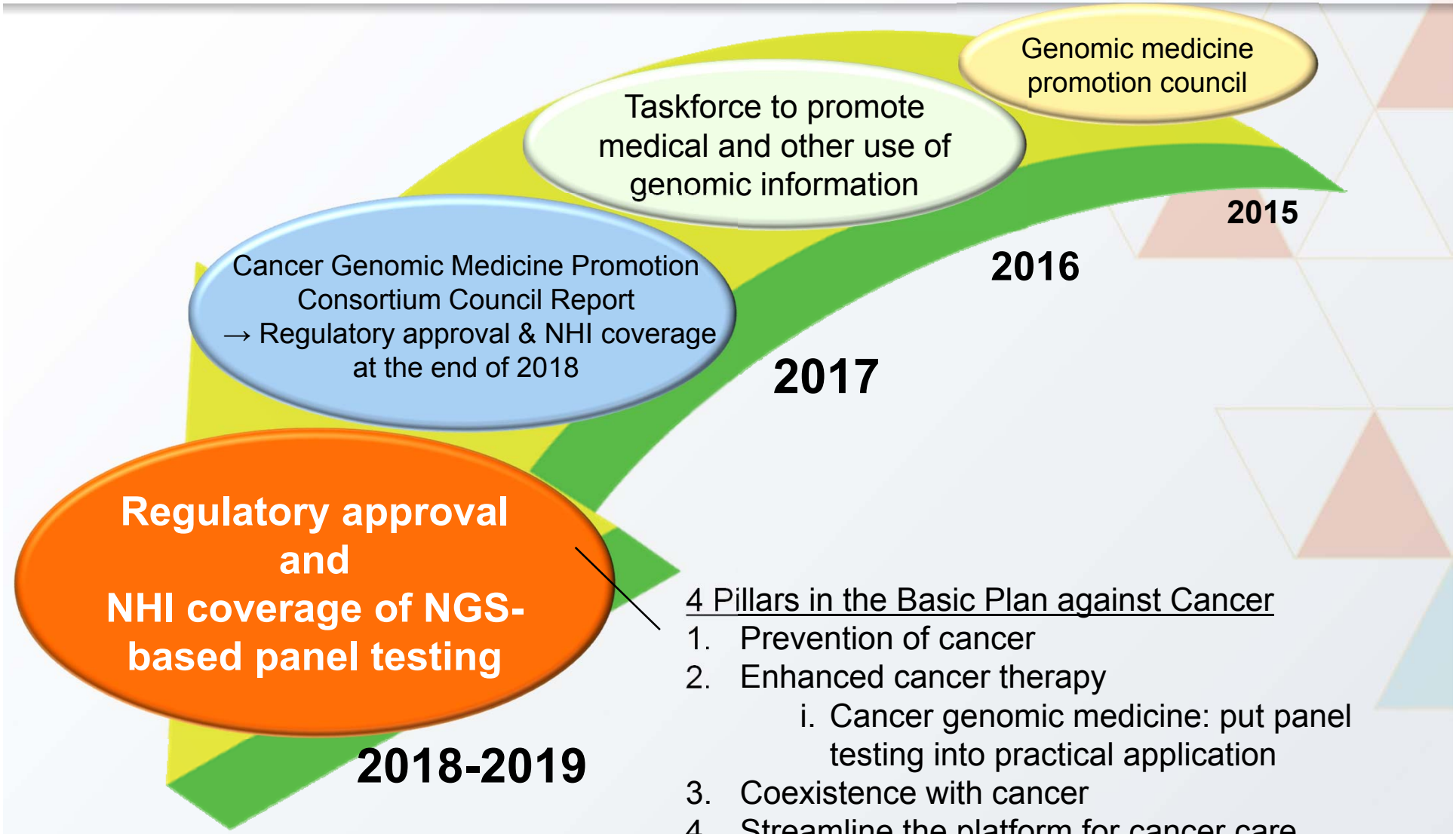
2019/07/04

Transformational Shift in Oncology

2009	2019
Cancer is an anatomical disease	Cancer is a genomic disease
Clinical trials are conducted solely by academia or a pharmaceutical company	Collaborative clinical trials, basket/ umbrella trials
Few targeted therapy trials	> 600 therapies in development, thousands of clinical trials
Significant decrease in use of immunostimulants	Rapid adoption of immunotherapies
Disparate approaches to diagnostic assays	Emergence of comprehensive diagnostic assays

Source: FOUDATION MEDICINE materials, partly modified

Governmental Activities for Genomic Medicine

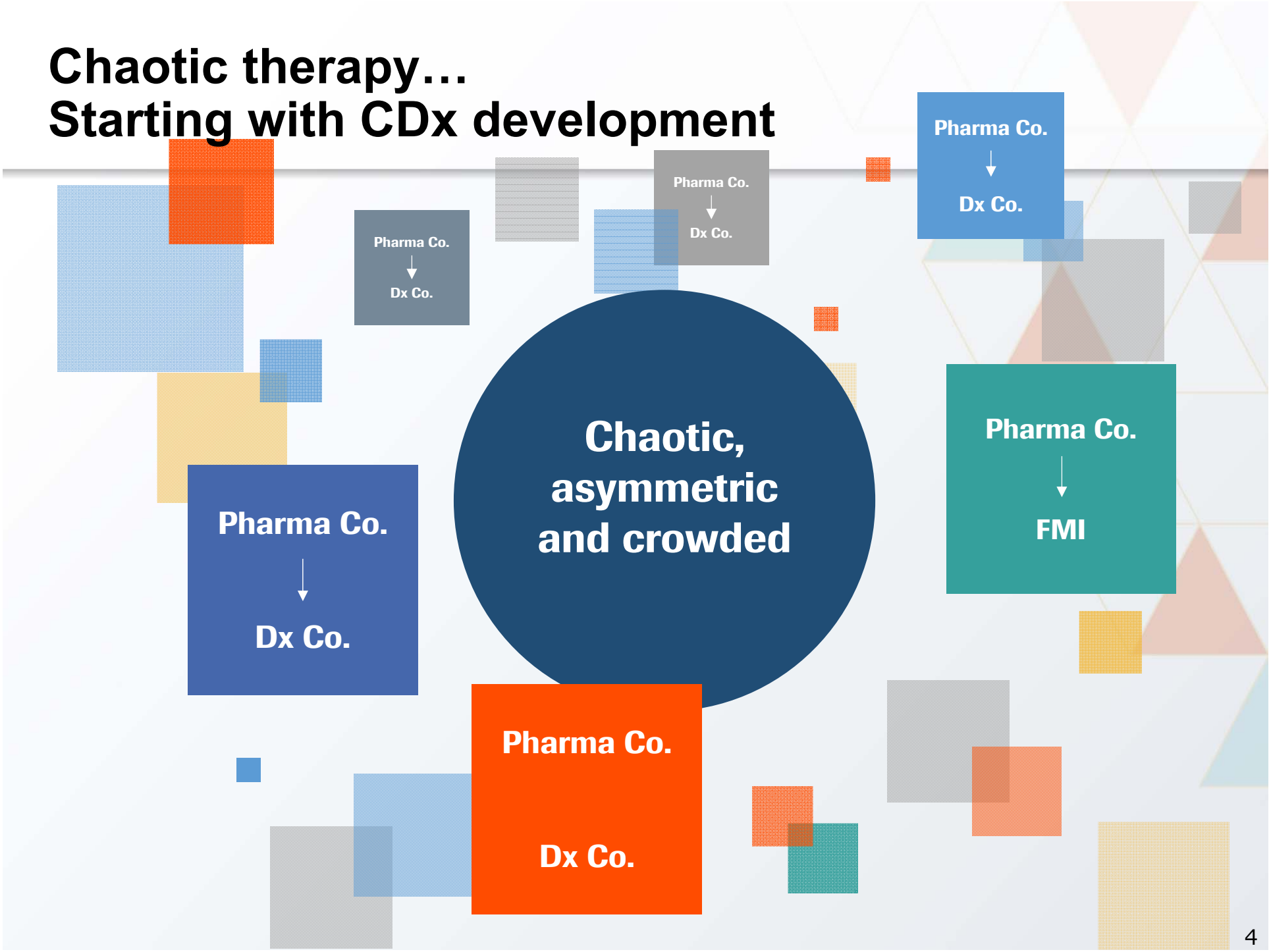


4 Pillars in the Basic Plan against Cancer

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

NGS: Next-generation sequencer
NHI: National health insurance

Chaotic therapy…
Starting with CDx development



Deliver Novel Platform Solution

FoundationOne® CDx
Intended Usage or Indications

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

CGP

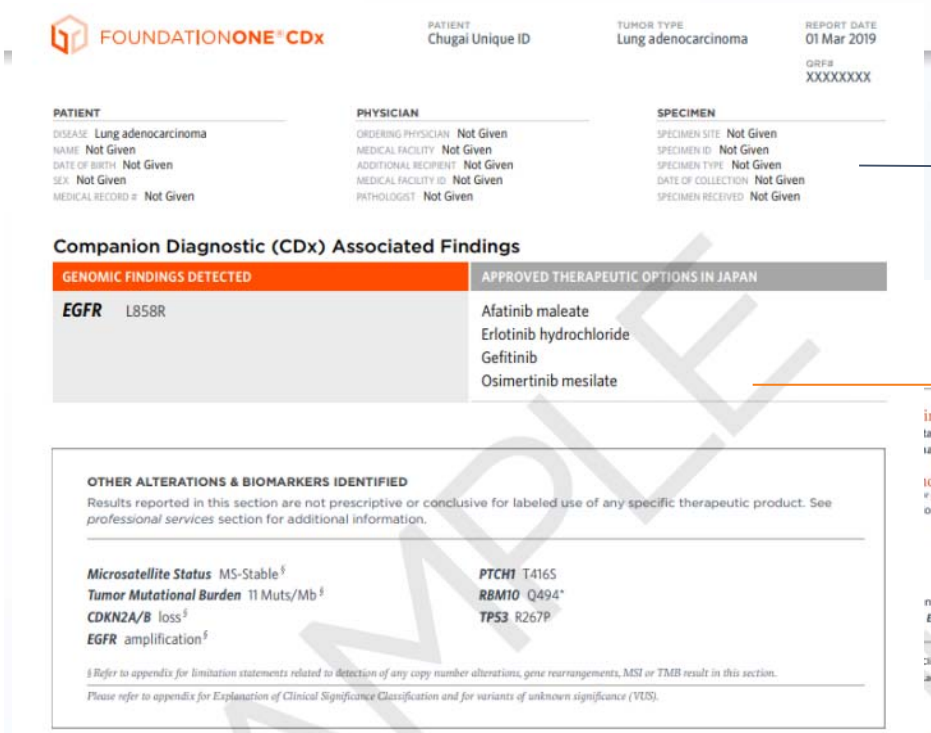
CDx

Alternations	Cancer type	Relevant drugs
EGFR exon 19 deletions and *EGFR* exon 21 L858R alterations	Non-small cell lung cancer (NSCLC)	afatinib dimaleate, erlotinib hydrochloride, gefitinib, osimertinib mesylate
EGFR exon 20 T790M alterations		osimertinib mesylate
ALK fusion genes		alectinib hydrochloride, crizotinib, ceritinib
BRAF V600E and V600K alterations	Malignant melanoma	dabrafenib mesylate, trametinib dimethyl sulfoxide, vemurafenib
ERBB2 copy number alterations (HER2 gene amplification positive)	Breast cancer	trastuzumab (genetical recombination)
KRAS/NRAS wild-type	Colorectal cancer	cetuximab (genetical recombination), panitumumab (genetical recombination)
NTRK1/2/3 fusion gene	Solid tumors	entrectinib

CGP: Comprehensive Genomic Profiling CDx: Companion Diagnostic

Source: Package insert

FoundationOne CDx Cancer Genomic Profiling



FOUNDATIONONE® CDx

PATIENT Chugai Unique ID | TUMOR TYPE Lung adenocarcinoma | REPORT DATE 01 Mar 2019 | ORF# XXXXXXXX

PATIENT
DISEASE Lung adenocarcinoma
NAME Not Given
DATE OF BIRTH Not Given
SEX Not Given
MEDICAL RECORD # Not Given

PHYSICIAN
ORDERING PHYSICIAN Not Given
MEDICAL FACILITY Not Given
ADDITIONAL RECIPIENT Not Given
MEDICAL FACILITY ID Not Given
PATHOLOGIST Not Given

SPECIMEN
SPECIMEN SITE Not Given
SPECIMEN ID Not Given
SPECIMEN TYPE Not Given
DATE OF COLLECTION Not Given
SPECIMEN RECEIVED Not Given

Companion Diagnostic (CDx) Associated Findings

GENOMIC FINDINGS DETECTED	APPROVED THERAPEUTIC OPTIONS IN JAPAN
EGFR L858R	Afatinib maleate Erlotinib hydrochloride Gefitinib Osimertinib mesilate

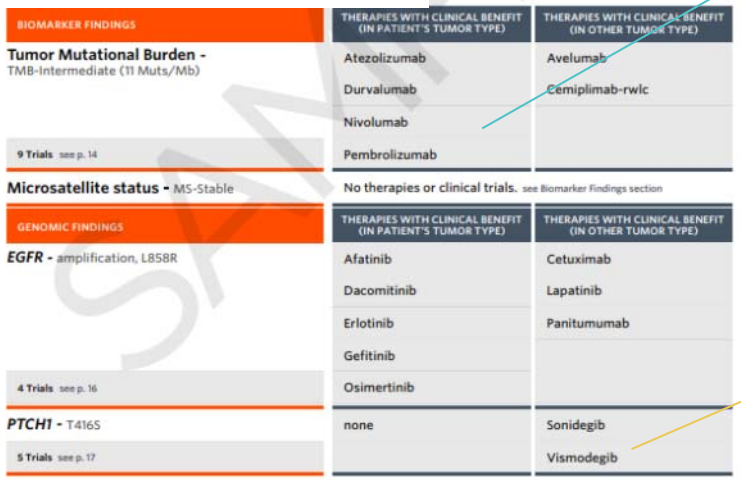
OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for additional information.

Microsatellite Status MS-Stable §
Tumor Mutational Burden 11 Muts/Mb §
CDKN2A/B loss §
EGFR amplification §
PTCH1 T416S
RBM10 Q494*
TP53 R267P

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, MSI or TMB result in this section.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).



BIOMARKER FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Tumor Mutational Burden - TMB-Intermediate (11 Muts/Mb)	Atezolizumab	Avelumab
	Durvalumab	Cemiplimab-rwlc
	Nivolumab	
9 Trials see p. 14	Pembrolizumab	
Microsatellite status - MS-Stable	No therapies or clinical trials. see Biomarker Findings section	

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
EGFR - amplification, L858R	Afatinib	Cetuximab
	Dacomitinib	Lapatinib
	Erlotinib	Panitumumab
	Gefitinib	
4 Trials see p. 16	Osimertinib	
PTCH1 - T416S	none	Sonidegib
5 Trials see p. 17		Vismodegib

Background information on the patient, the medical facility etc.

Summary of detected alterations

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

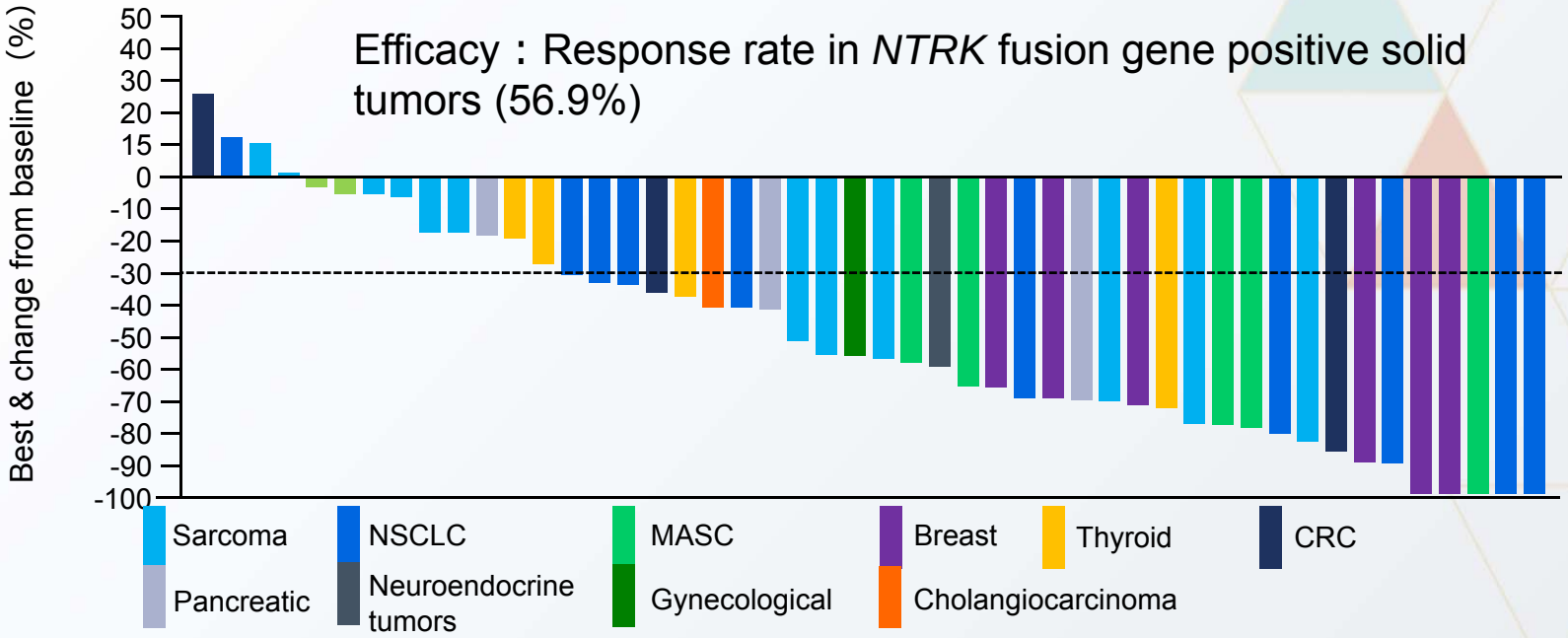
Summary of references on detected alterations and potential therapies

From Organs to Gene Alterations/Biomarkers

Tumor agnostic approval + New histology independent medicines

https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm560040.htm
Annals of Oncology, Volume 29, Issue suppl_8

Rozlytrek: The Second Drug in Japan Approved Across All Solid Tumors



Source：Roche's Virtual Pipeline Event from ESMO 2018

Study design

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

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

Outcomes

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

Clinically Significant Adverse Reactions

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

Source：package insert

CGP: Comprehensive Genomic Profiling

Which position of usage benefits the patient?

- Finding matched therapy and selecting optimal treatment
- Understanding pathogenesis from clonal evolution
- Understanding pathogenesis including passenger alterations, not only searching for driver alterations
- Understanding pathogenesis from multiple genetic alterations
- Comprehensive treatment plan from biomarkers (TMB, MSI, LOH), etc.

ASCO2019 CSS: Targeting Breast Cancer: Breaking the Code

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

FGFR1: Promotes early progression of CDK4/6i

RB1: Possible CDK4/6i resistant mutation

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

PD expected soon after administration of palbociclib

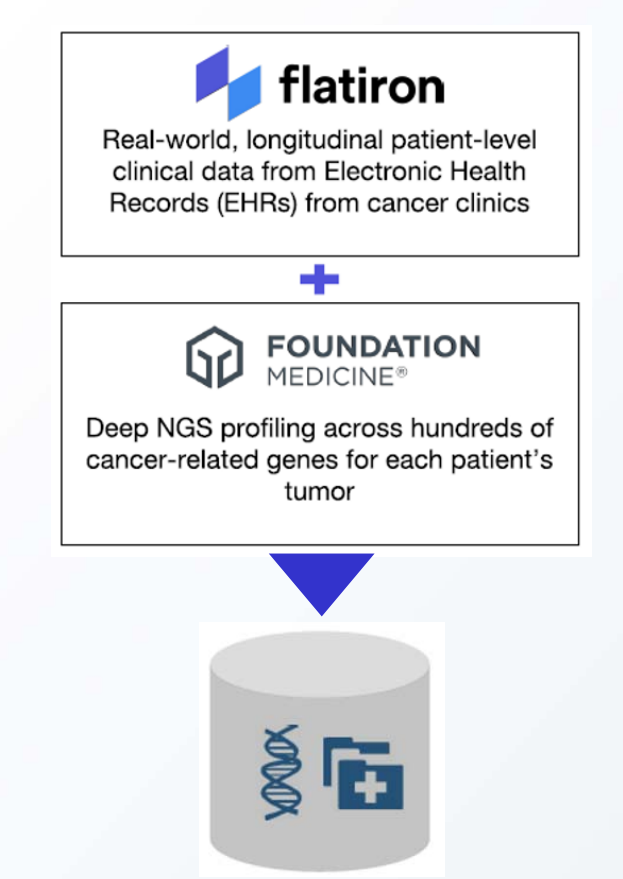
Earlier treatment plan from CGP

Tolerization by enhancement during administration of palbociclib

Monitoring of ctDNA CGP

TMB: Tumor Mutational Burden, MSI: MicroSatellite Instability,
LOH: Loss of Heterozygosity

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



>42,000 patients (as of 2019.2)

■Filing with FDA

- ●U.S. FDA APPROVES IBRANCE® (PALBOCICLIB) FOR THE TREATMENT OF MEN WITH HR+, HER2- METASTATIC BREAST CANCER
  - ✓Approval of expanded indication based predominately on real-world data

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

Access: 28 June, 2019.
https://www.pfizer.com/news/press-release/press-release-detail/u_s_fda_approves_ibrance_palbociclib_for_the_treatment_of_men_with_hr_her2_metastatic_breast_cancer

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

Cancer Precision Medicine

Transform genomic medicine into true precision medicine

Personalized Health Care

Fit one target to One Organ

e.g. Targeted therapies

Genome Medicine

Fit one target to Multiple Organs

e.g. Comprehensive Universal diagnostics

Precision Medicine

Focus on Individual patients

e.g. Insight and Decision for patients based on Mixed genome and clinical info

Cancer Genomic Medicine
— Clinical Implementation and Challenges —

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

COI Disclosure

Presenter: Manabu Muto

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

COI description	Company name, etc.
Directorial/advisory roles:	None
Presentation fees:	None
Manuscript fees:	None
Joint research fees:	Mitsui Knowledge Industry, Sysmex Corporation, Riken Genesis

Agenda

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

Cancer Genomic Medicine

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

Precision Medicine

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

Source: NIH website (as of June 25, 2019)
https://ghr.nlm.nih.gov/primer/precisionmedicine/definition

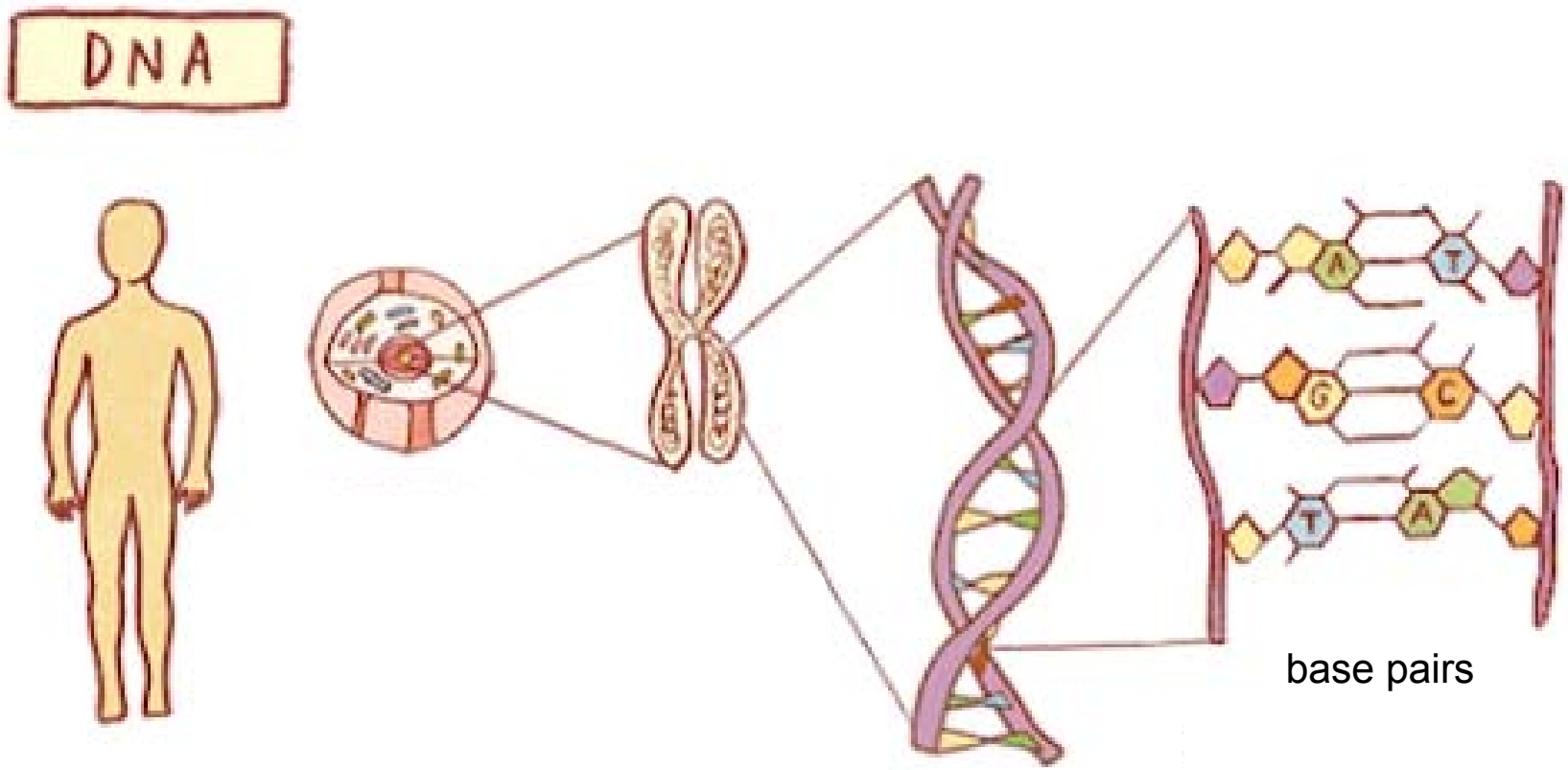
Cancer Genomic Medicine

Precision medicine in the diagnosis and treatment of cancer

Cancer

Cancer is a disease caused by genetic abnormalities

About DNA



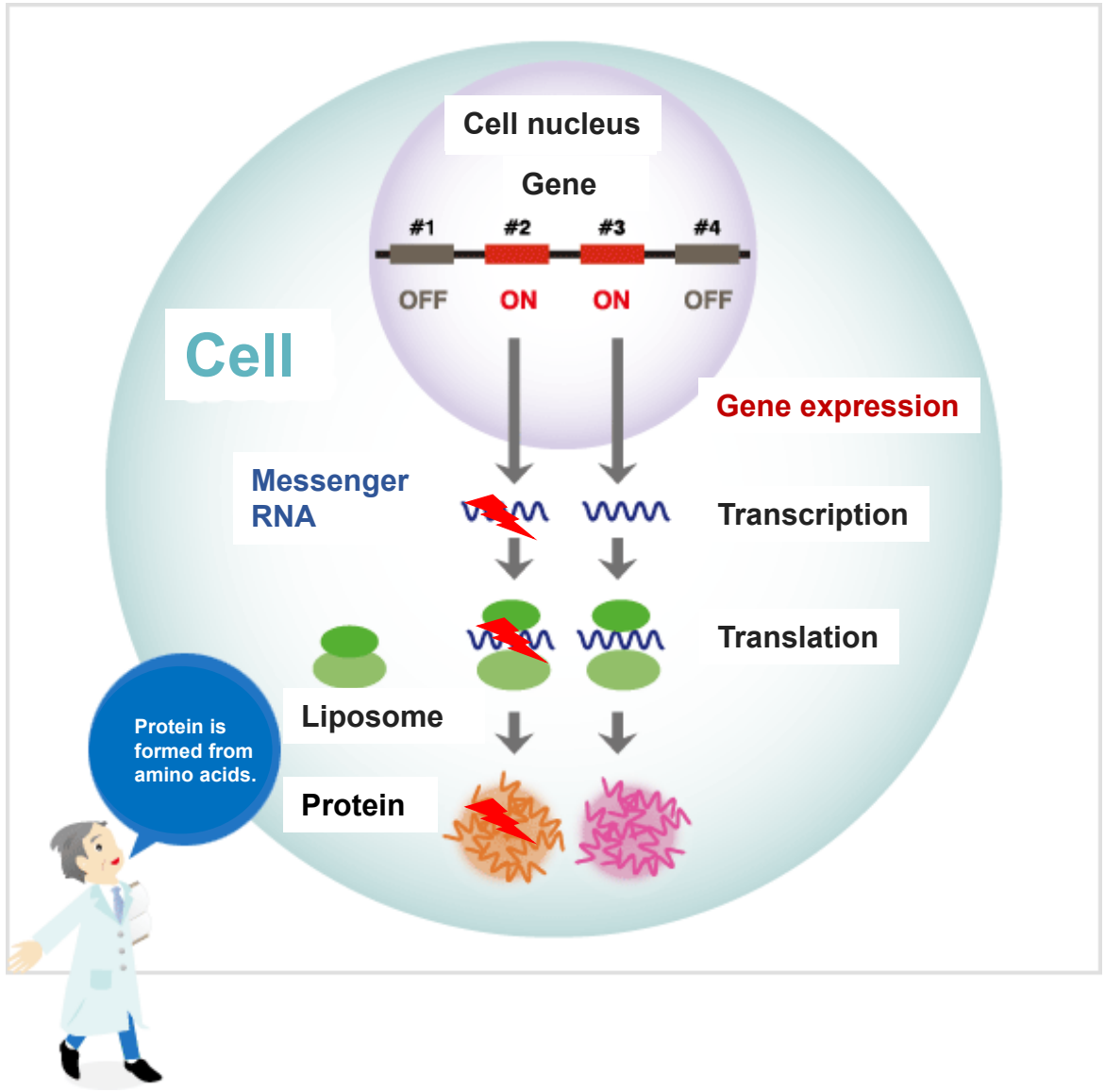
DNA is a biological molecule that regulates expression and transfer of genetic information

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

Structure and base of DNA

source： *Easy biotechnology and genome*, Chugai Pharmaceutical website (Japanese only, as of June 28, 2019)
https://www.chugai-pharm.co.jp/ptn/bio/genome/genomep08.html

Protein Synthesis from Gene Transcription



Disease blog, TAKAHASHI CLINIC https://hatchobori.jp/blog/4854 Accessed: 2019/07/03

Gene Sequence Abnormalities

Baseline sequence

Normal	5’ – CTA GCC CAA TTA CAT -3‘

Gene Sequence Abnormalities

Baseline sequence

Normal	5’ – CTA GCC CAA TTA CAT -3‘
Point mutation	5’ – CTA ACC CAA TTA CAT -3‘

Gene Sequence Abnormalities

Baseline sequence

Normal	5’ – CTA GCC CAA TTA CAT -3‘

Deletion 5’ – CTA --- CAA TTA CAT -3‘

Gene Sequence Abnormalities

Baseline sequence

Normal	5’ – CTA GCC CAA TTA CAT -3‘

Insertion 5’ – CTA GCC GCA ATT ACA T-3‘

Gene Sequence Abnormalities

Baseline sequence

Normal	5’ – CTA GCC CAA TTA CAT -3‘

Amplification	5’ – CTA GCC GCC CAA TTA CAT -3‘

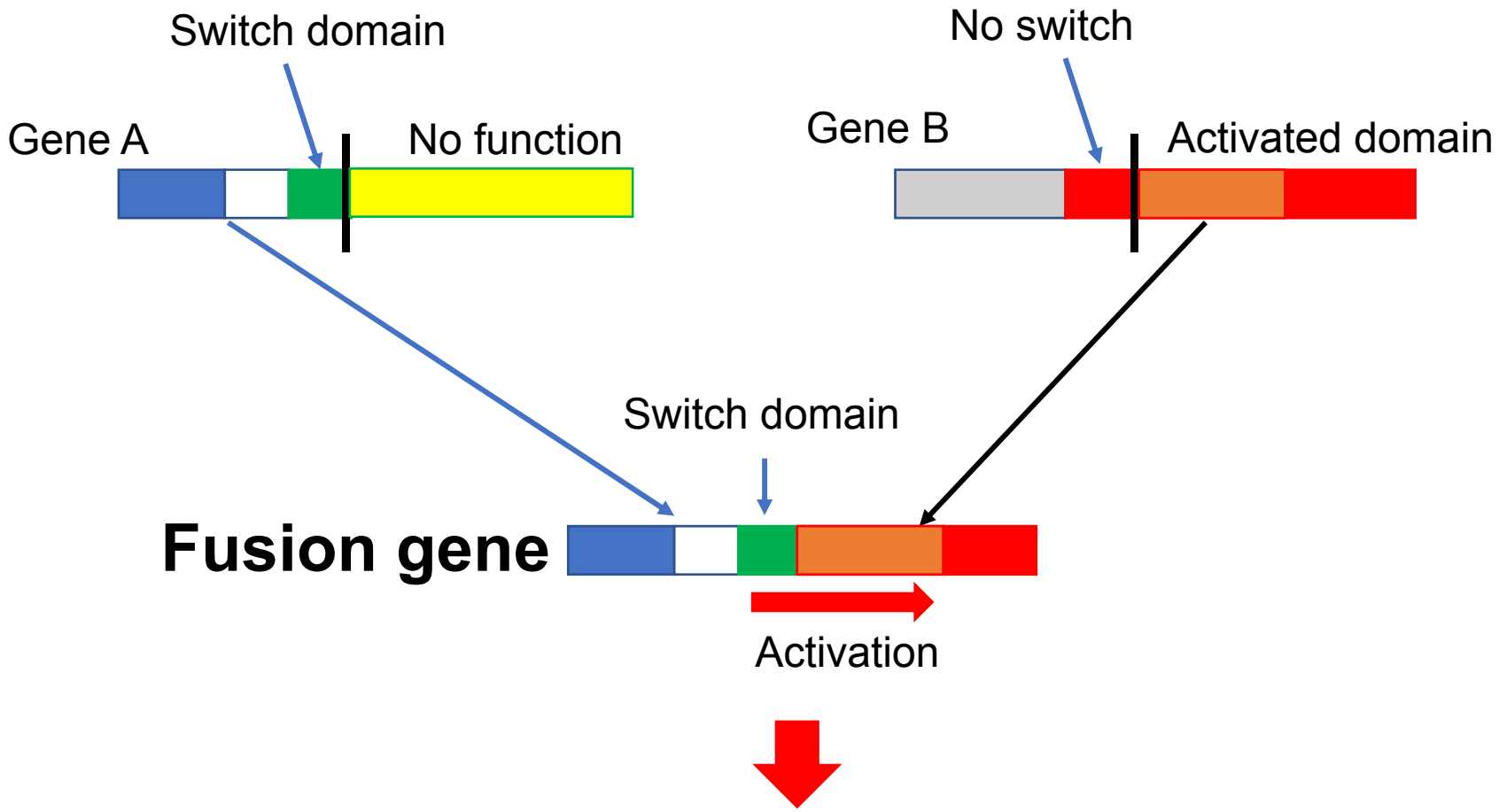
Gene Sequence Abnormalities

Baseline sequence

Normal	5’ – CTA GCC CAA TTA CAT -3‘
Point mutation	5’ – CTA ACC CAA TTA CAT -3‘
Deletion	5’ – CTA --- CAA TTA CAT -3‘
Insertion	5’ – CTA GCC GCA ATT ACA T-3‘
Amplification	5’ – CTA GCC GCC CAA TTA CAT -3‘

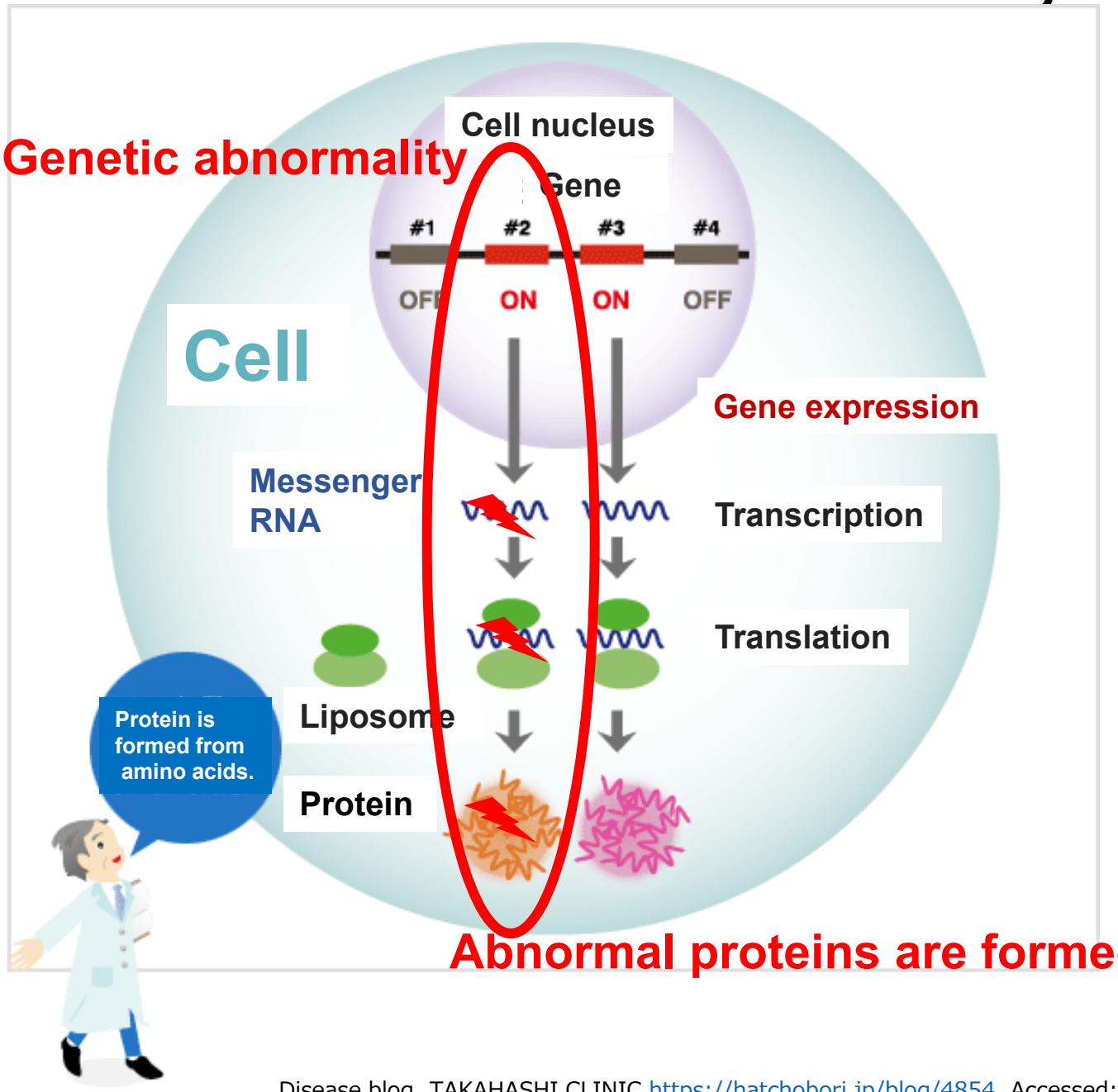
Abnormal Structure of Gene

[Conceptual illustration]



Malignant transformation / Increase in proliferation ability

Genetic Abnormalities Cause Abnormal Protein Synthesis



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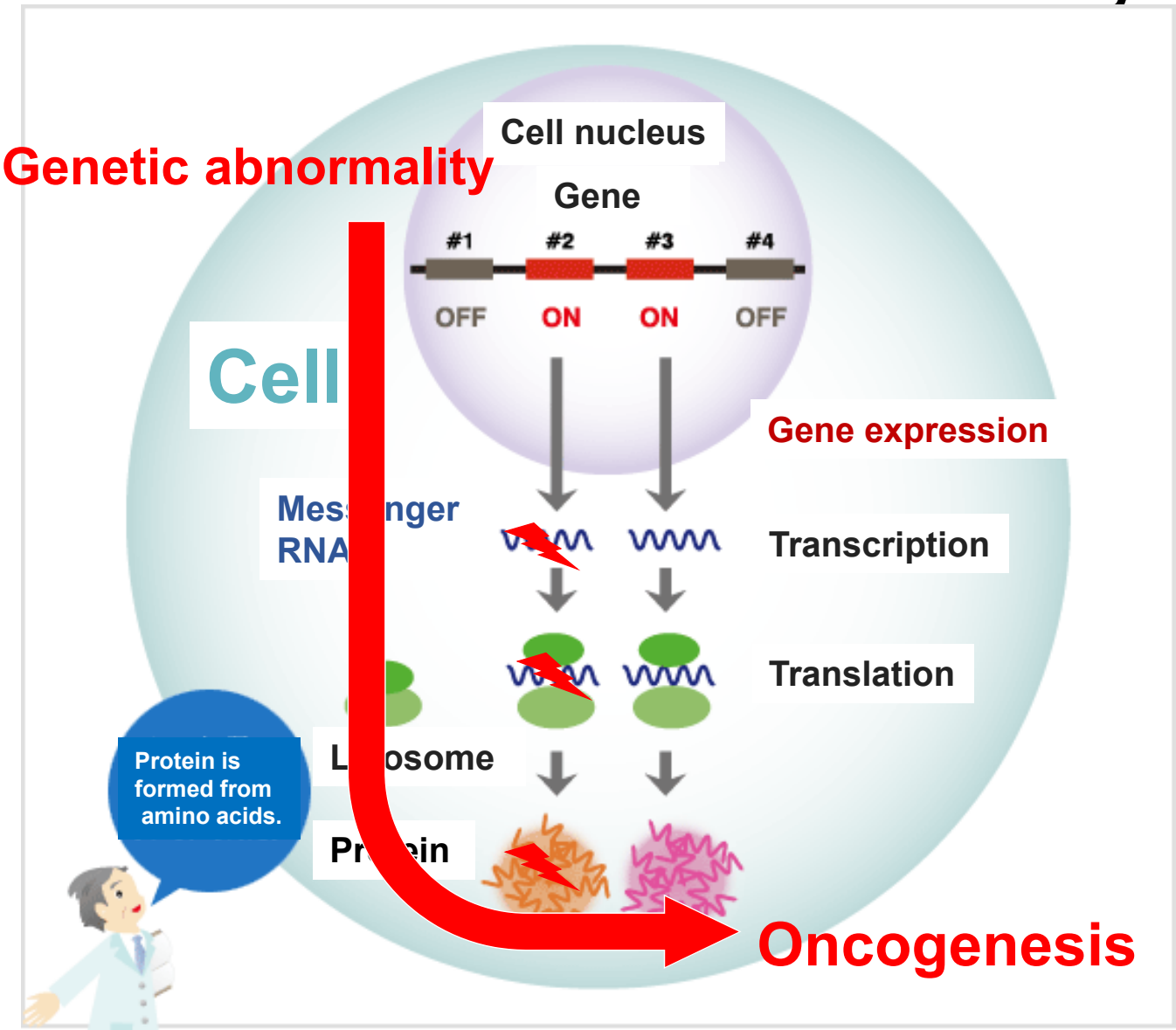
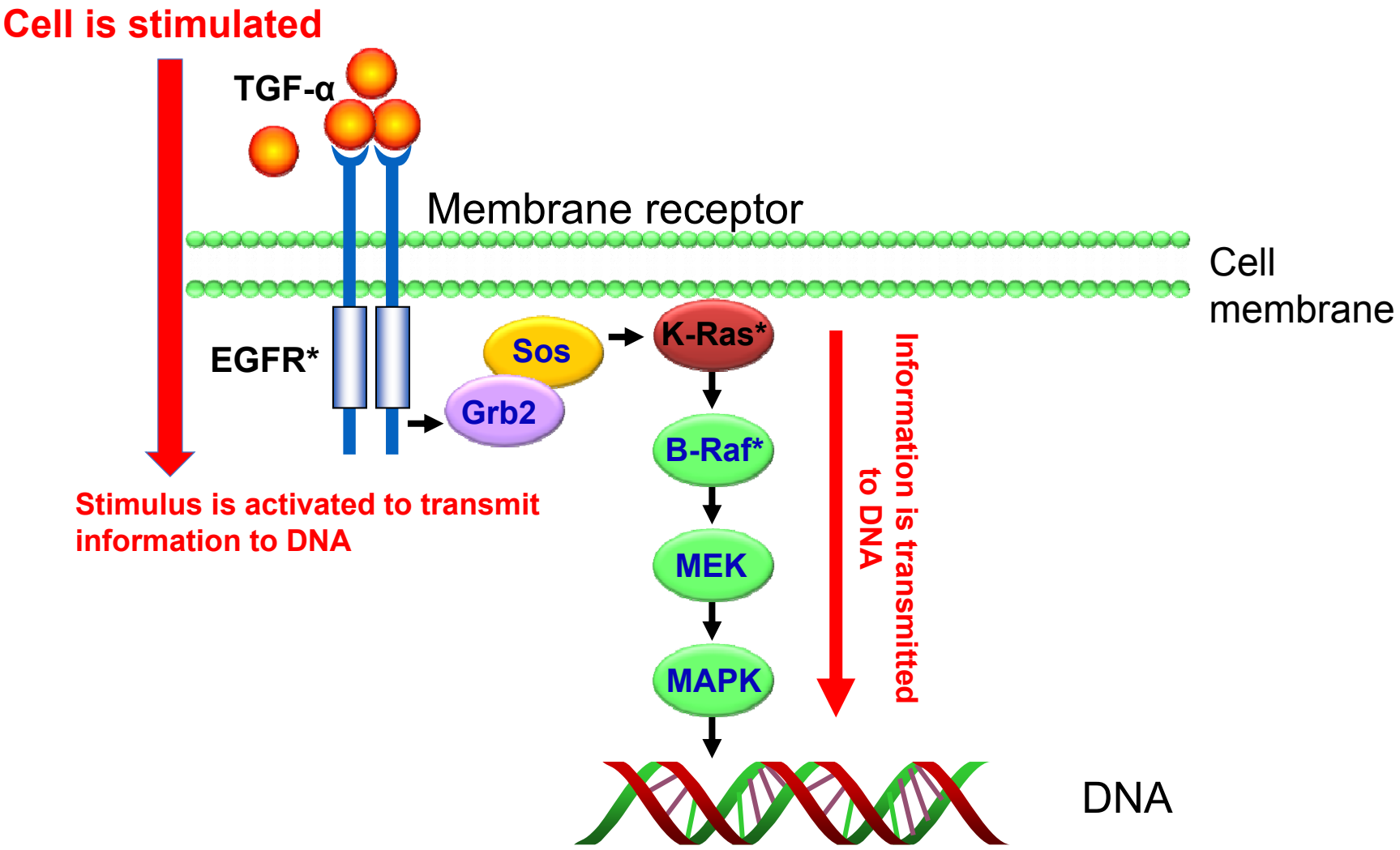
Genetic Abnormalities Cause Abnormal Protein Synthesis



Abnormal proteins may induce oncogenesis

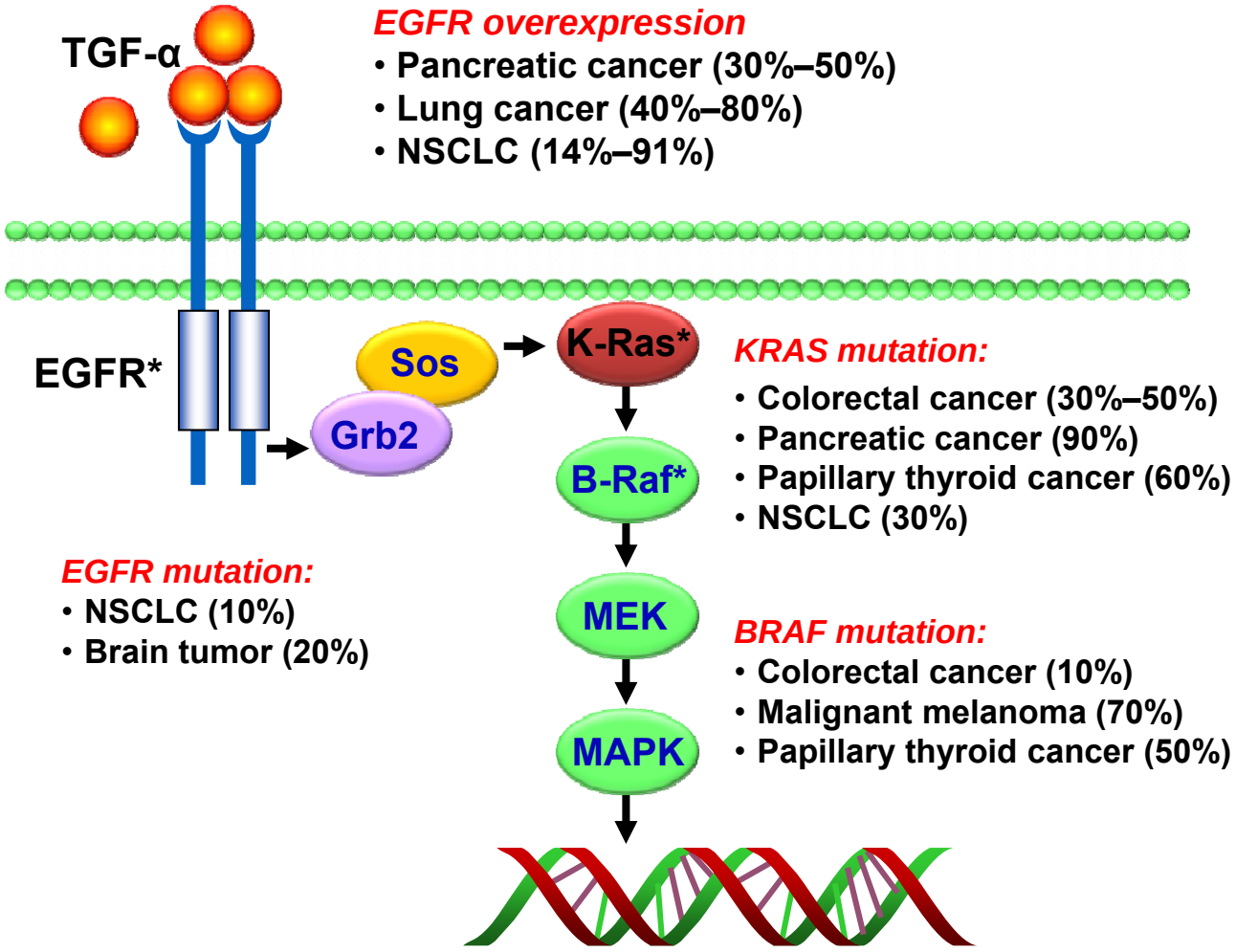
Disease blog, TAKAHASHI CLINIC https://hatchobori.jp/blog/4854 Accessed: 2019/07/03

Example: Cell Signaling



Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer.
Roberts PJ, Der CJ., Oncogene 2007

Genetic Abnormalities
Cause Abnormal Cell Signaling = Oncogenesis



NSCLC: Non-small cell lung cancer

Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer.
Roberts PJ, Der CJ., Oncogene 2007

Gene (genome) abnormalities cause cancer

Gene (genome) abnormalities need to be examined

An Example of Personalized Medicine

Testing of cancer gene abnormalities in individual patients to explore therapeutic options

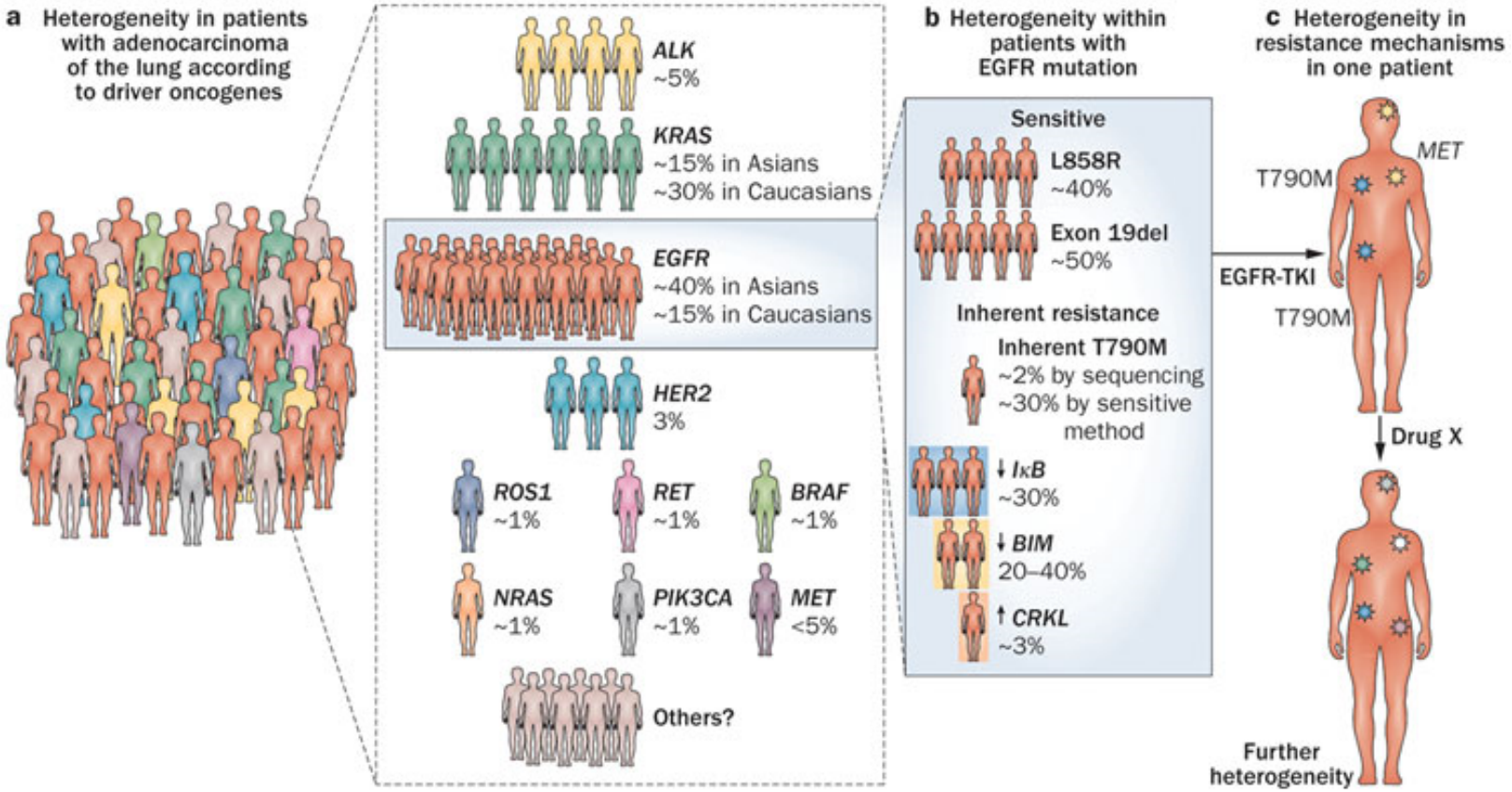
Testing Methods for Genetic Abnormalities

Under conventional approaches, individual genes are examined for abnormalities and drugs are administered to treat diseases caused by these abnormalities.

Molecular targeted drug therapy

Why is Genomic Medicine Necessary in the Field of Oncology?

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



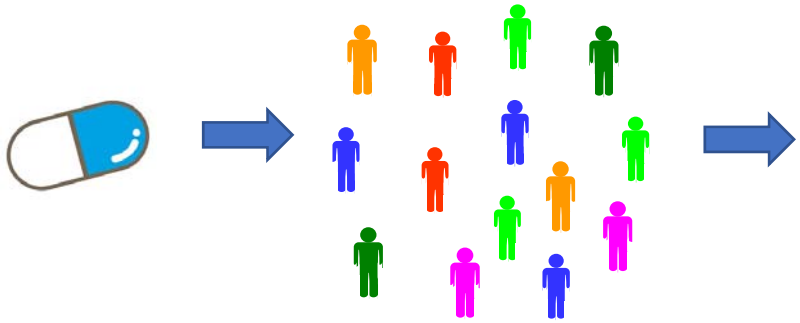
The treatment of cancer has already entered the age of anticancer drug therapy based on genetic testing, and "cancer genomic medicine" will yield even greater therapeutic advancement.

Mitsudomi, T. et al. Nat. Rev. Clin. Oncol. 10, 235–244 (2013)

【Conceptual illustration】

Before

Use one drug for same cancer types

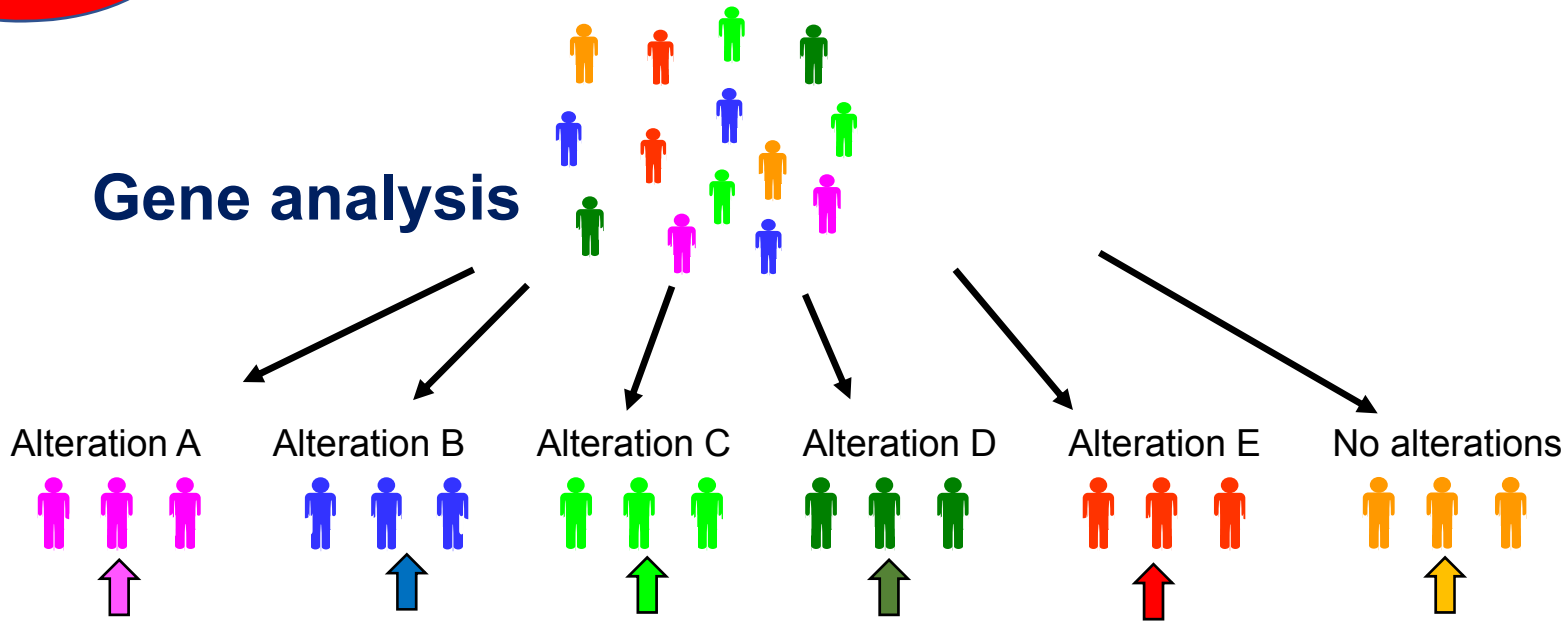


Limited efficacy
(approx. 20% response)

Now

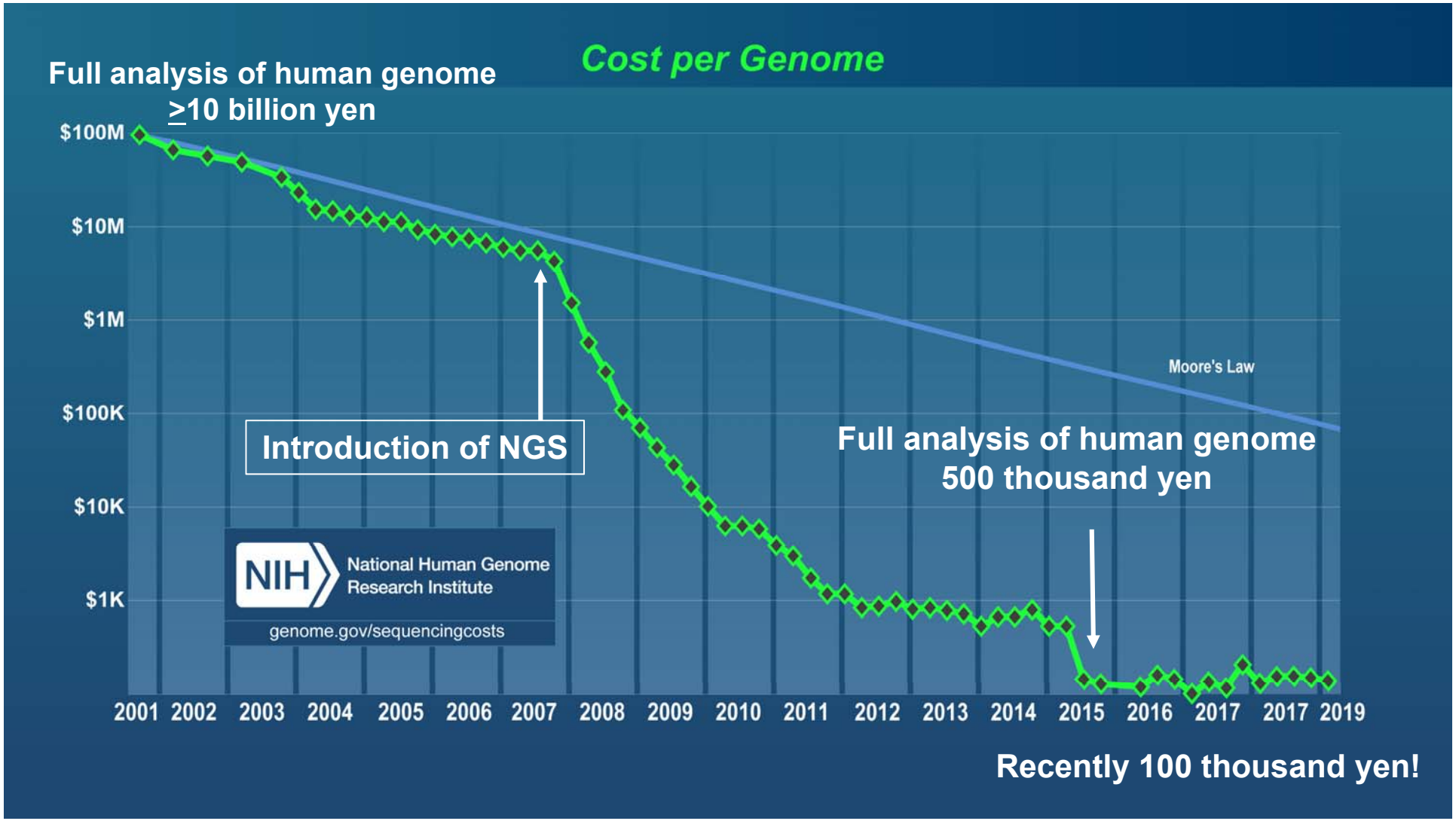
Use drugs that best suit individuals regardless of cancer types based on their genetic features.

Gene analysis



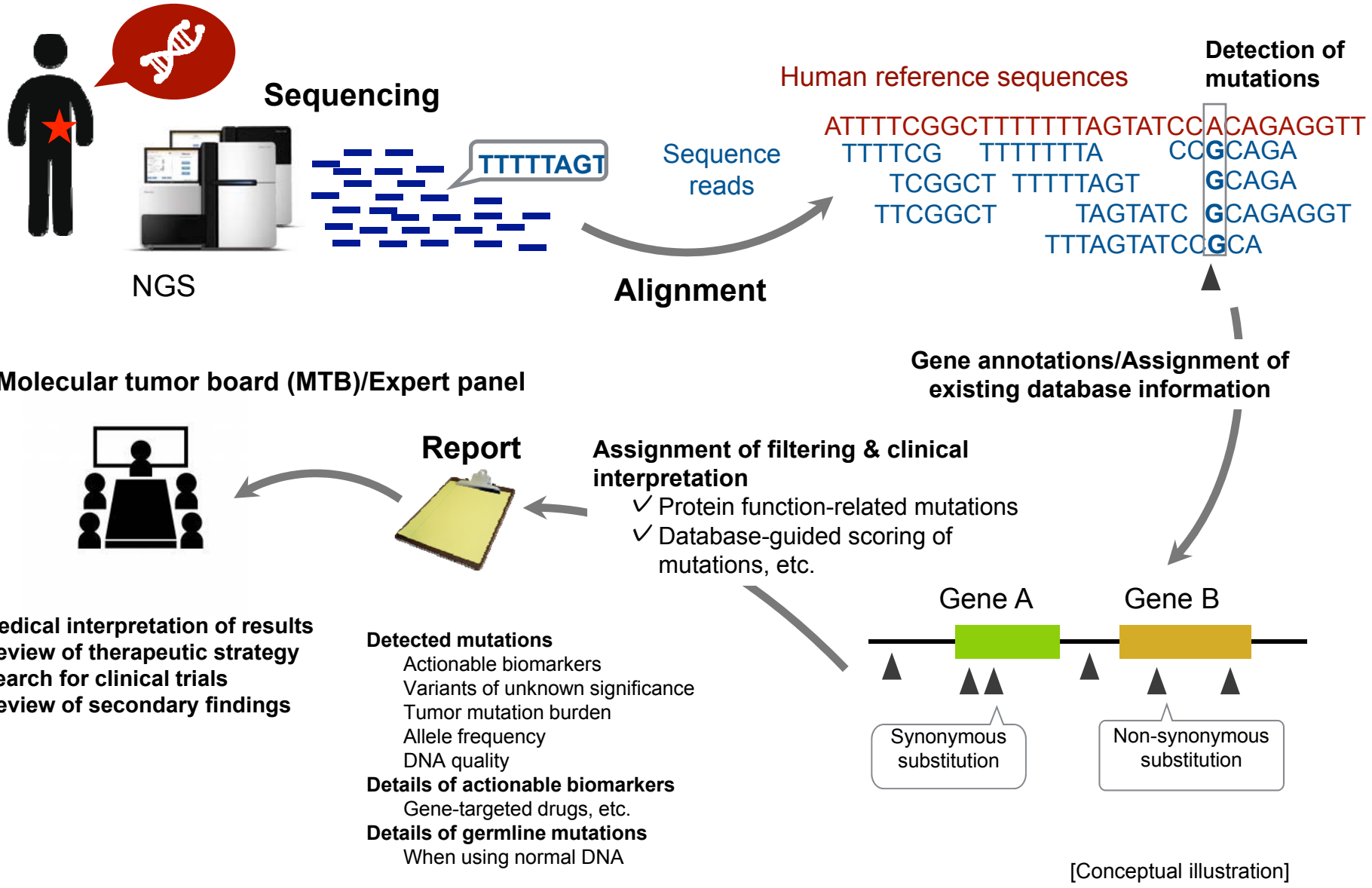
Better efficacy (>50%) can be expected from molecular targeted therapies

Advances in Gene Analysis Technologies



The Cost of Sequencing a Human Genome, National Human Genome Rearch Institute
https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost Accessed: 2019/06/28

Flow of Genomic Medicine Using NGS



[Conceptual illustration]

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

OncoGuide™ NCC Oncopanel System (Sysmex)

FoundationOne® CDx Cancer Genomic Profile (Chugai/Roche)

OncoGuide NCC Oncopanel System

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

FoundationOne CDx Cancer Genomic Profile

FoundationOne CDx Cancer Genomic Profile is an analysis program that outputs data on gene mutations to support the development of treatment strategies and the assessment of drug indications based on comprehensive genomic profiles of 324 cancer-related genes identified in patients with solid cancers.

FoundationOne CDx Cancer Genomic Profile Can Also be Used as a Companion Diagnostic

Alterations	Cancer type	Relevant drugs
EGFR exon 19 deletions and *EGFR* exon 21 L858R alterations	Non-small cell lung cancer	afatinib dimaleate, erlotinib hydrochloride, gefitinib, osimertinib mesylate
EGFR exon 20 T790M alterations		osimertinib mesylate
ALK fusion genes		alectinib hydrochloride, crizotinib, ceritinib
BRAF V600E and V600K alterations	Malignant melanoma	dabrafenib mesylate, trametinib dimethyl sulfoxide, vemurafenib
ERBB2 copy number alterations (*HER2*gene amplification positive)	Breast cancer	trastuzumab (genetical recombination)
KRAS/NRAS wild-type	Colorectal cancer	cetuximab (genetical recombination), panitumumab (genetical recombination)
NTRK1/2/3 fusion gene	Solid tumors	entrectinib

Source: Chugai Obtains Approval of FoundationOne CDx Cancer Genomic Profile as a Companion Diagnostic for Rozlytrek https://www.chugai-pharm.co.jp/english/news/detail/20190627120000_628.html (accessed on June 28, 2019)

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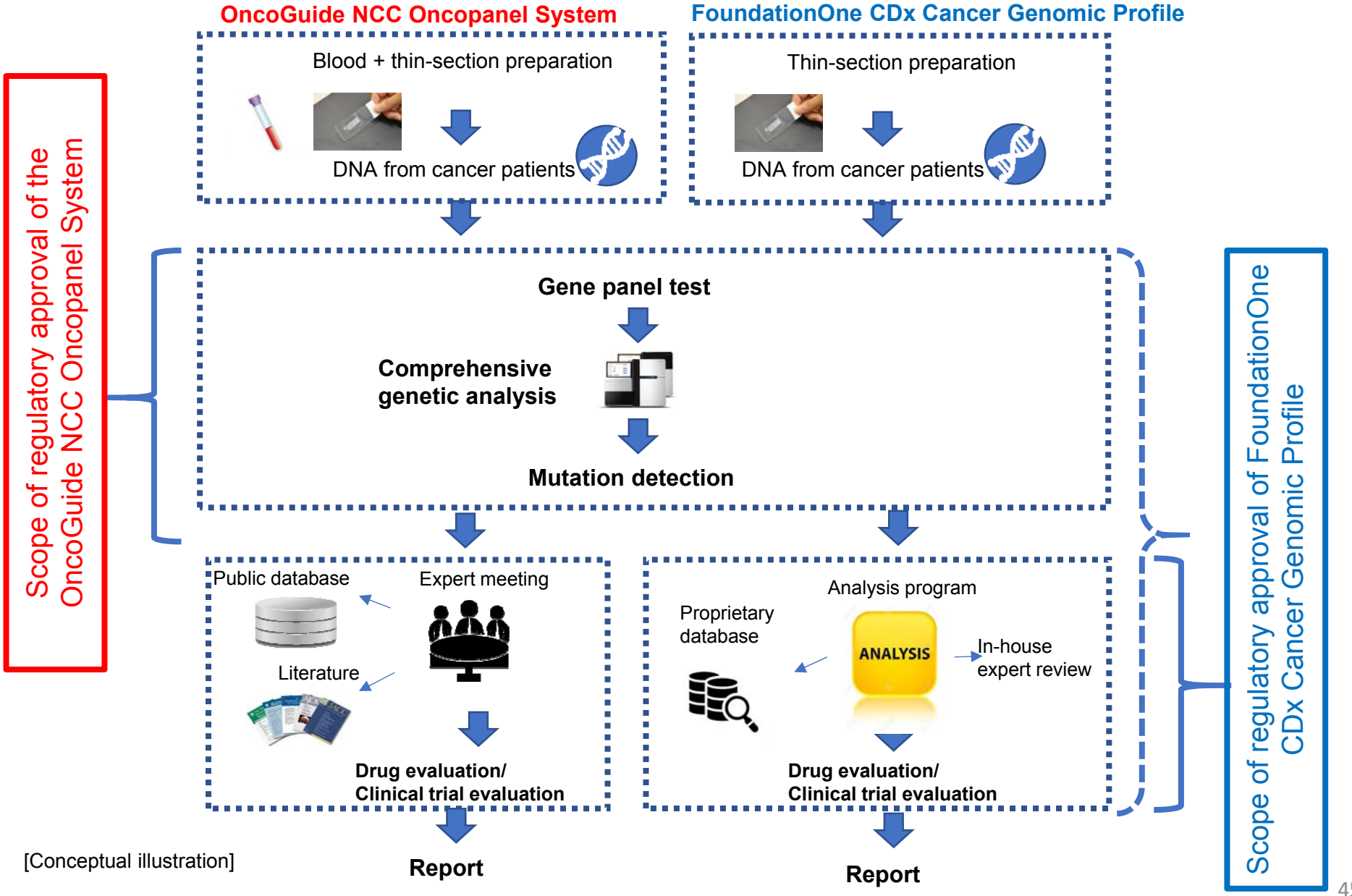
Difference in Scope of Regulatory Approval of Genomic Medicine using NGS



[Conceptual illustration]

An Example of C-CAT Survey Results

作成中

C-CAT調査結果

1 基本項目

1-1 患者

登録ID	xxxxxx	匿名化患者ID	ABC123456	検査ID	123456789
年齢	65	性別	男性	がん種	Breast Cancer

1-2 医療機関

連携病院	テスト大学病院	拠点病院	テスト病院	中核拠点病院	テスト病院

1-3 検査

検体採取日	2016/2/1	腫瘍細胞割合	70%	組織名	肺
パネル名	NCC oncopanel	測定日	2018/4/5		

2 検査結果

概要

▲ 薬剤への到達性の指標をご参照ください。

検出変異数	国内承認薬	国内臨床試験中	国内適用外承認	海外臨床試験中	FDA承認薬
体細胞変異：9 生殖細胞系列変異：3	5	2	2	2	7

塩基置換、挿入、欠失(DNA)

No.	マーカー	変化	アレル頻度	エビデンスタイプ	臨床的意義	エビデンスレベル	薬剤	薬剤への到達性	QCI
1	*EGFR*	p.L858R	0.288 (553/1918)	Predictive	Sensitive	A	Gefitinib	国内承認 FDA承認	Tier 1A Pathogenic
				Predictive	Sensitive	A	Erlotinib	国内承認 FDA承認	
				Predictive	Sensitive	A	Afatinib	国内承認 FDA承認	
				Predictive	Sensitive	A	Osmertinib	国内承認 FDA承認	
				Predictive	Sensitive	A	Dacomitinib	FDA承認	
				Oncogenicity	Likely Oncogenic	F			
2	*MSH2*	p.S900*	0.530 (1459/2752)	Predisposing	Pathogenic	F			Tier 1A Pathogenic
				Oncogenicity	Likely Oncogenic	F			
3	*FGFR3*	N718S	0.474 (832/1754)						
4	*STK11*	F354L	0.502 (722/1437)						
5	*APC*	D900V	0.500 (150/300)						
6	*BRCA1*	Y856H	0.47 (94/200)						

作成日：2018年11月2日
レポートバージョン：1.0

作成中

遺伝子再構成(DNA)、構造異型(DNA)

No.	マーカー	変異種類	サイトバンド	エビデンスタイプ	臨床的意義	エビデンスレベル	薬剤	薬剤ステータス	QCI
7	*CCDC6-RET*	Rearrangement	chr10:61,657,343 chr10:43,611,194	Predictive	Sensitive	C	Vandetanib	国内適応外	Tier 1A Pathogenic
				Predictive	Sensitive	C	Lenvatinib	国内適応外	
				Predictive	Sensitive	D	Nintedanib		
				Oncogenicity	Oncogenic	F			

コピー数変化 (T/N実施検査のみ)

No.	マーカー	コピー数変化	サイトバンド	エビデンスタイプ	臨床的意義	エビデンスレベル	薬剤	薬剤ステータス	QCI
8	*MYC*	19.5	chr8:127,736,069-127,741,434	Oncogenicity	Oncogenic	F			

融合遺伝子(RNA)やエクソンスキッピング(RNA)

No.	マーカー	融合遺伝子	サイトバンド	リード数	エビデンスタイプ	臨床的意義	エビデンスレベル	薬剤	薬剤ステータス	QCI
9	*MYB*	*MYB-NFIB* (15/16 – 11/12)	6q23.3-9q23	540 (98.5%)	Predisposing	Pathogenic	F			

Tumor Mutational Burden (T/N実施検査のみ)

Tumor Mutational Burden
6 (Mut/Mb)

生殖細胞系列変異 (T/N実施検査のみ)

▲ 非がん部組織由来のDNA解析結果を表示しております。

No.	マーカー	変化	アレル頻度	エビデンスタイプ	臨床的意義 ClinVar ID	エビデンスレベル	薬剤	薬剤ステータス	QCI
1	*PTEN*	C136Y	0.500 (150/300)	Predisposing	Pathogenic RCV000169797.1				Pathogenic
2	*BRCA1*	Y856H	0.47 (94/200)	Predisposing	Likely benign RCV000148383.1				Benign
3	*BRCA1*	E1559K	-	Predisposing	Pathogenic				Tier 1A Pathogenic
				Predictive	Sensitive	A	Olaparib	国内承認 FDA承認	
				Predictive	Sensitive	D	Rucaparib	国内試験中 FDA承認国	
				Predictive	Sensitive	B	Talazoparib	国内試験中 FDA承認	
							Niraparib	FDA承認	

3 候補となる臨床試験一覧

※下記の治験・臨床試験については、詳細な適格基準・除外基準に合致しているか否か、患者登録受付中であるか否か、「実施機関（連絡先）」への確認が必要となります。

Rucaparibを用いた国内臨床試験

臨床試験DB	試験ID	試験名称	Phase	対象マーカー	データ更新日	実施機関（連絡先）
Clinicaltrials	NCT03499444	A Study of Rucaparib in Japanese Patients With a Previouslytreated Solid Tumor	P2	*BRCA1* E1559K	2018/4/5	ClovisOncology (clovistrials@emergingmed.com)

作成日：2018年11月2日
レポートバージョン：1.0

from Information meeting for Core hospitals on 2019/02/05

Characteristics of FoundationOne CDx Cancer Genomic Profile

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

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

- Companion diagnostics

- MSI*2 determination/TMB*3 score calculation

＊2：Microsatelite Instability　＊3：Tumor Mutational Burden

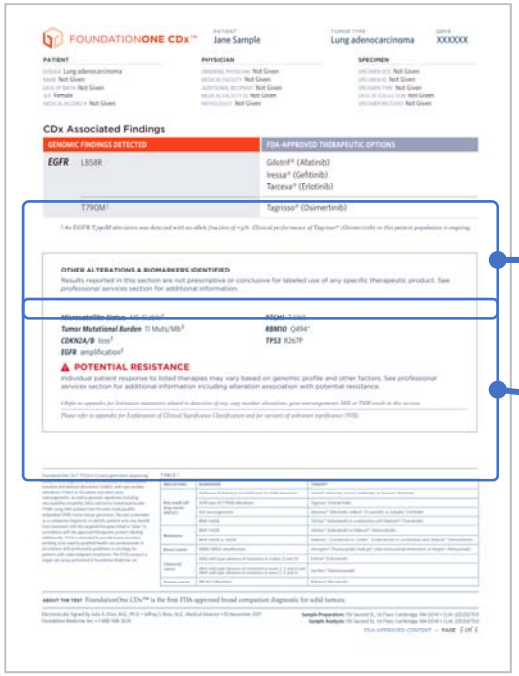
- Analysis result report provides expert review and assignment of clinical significance (annotations)

- Tested and analyzed with abundant experience in FMI

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

Analysis Report of FoundationOne CDx

APPROVED THERAPEUTIC OPTION IN JAPAN



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

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

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

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

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

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

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

Source: Chugai website (accessed on June 28, 2019)
https://chugai-pharm.jp/content/dam/chugai/product/f1t/cdx/report-fullmock/doc/F1CDx-Report-Fullmock.pdf

Analysis Report of FoundationOne CDx Cancer Genomic Profile

PROFESSIONAL SERVICES

(1) Results of gene mutation and biomarker detection

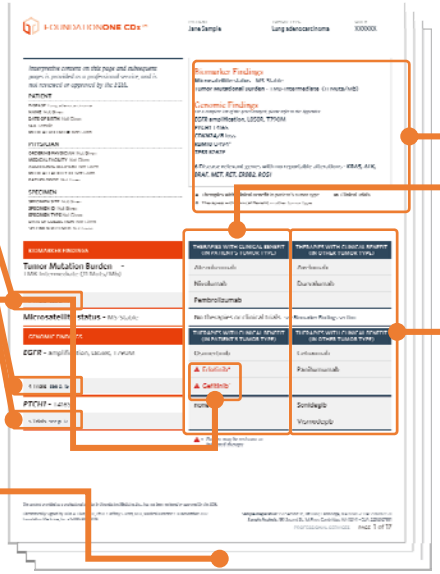
(2) Therapeutic drugs with an indication for the cancer type with detected gene mutations and biomarkers

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

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

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

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



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

[Precautions]
- In case of confirmation of the Analysis result report, please refer to the latest package insert of FoundationOne CDx Cancer Genomic Profile.
- "PROFESSIONAL SERVICES" is not approved by the Ministry of Health, Labour and Welfare.

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

Source: Chugai website (accessed on June 28, 2019)
https://chugai-pharm.jp/content/dam/chugai/product/f1t/cdx/report-fullmock/doc/F1CDx-Report-Fullmock.pdf

Cancer genomic medicine in Japan

Draft Selection Criteria for Core Hospitals for Cancer Genomic Medicine

資料5

がんゲノム医療中核拠点病院（案）等の指定要件（案）

厚生労働省健康局
がん・疾病対策課

Report of Cancer Genomic Medicine Promotion Consortium Council (excerpt)

Requirements for medical institutions to implement cancer genomic medicine:

(1) A system to conduct panel tests (including outsourcing to external organizations)

(2) A group of experts to offer medical interpretation of panel test results (including collaboration with other organizations in some areas of medical care)

(3) Ability to provide expert genetic counseling for patients with hereditary and other cancers

(4) Access to a certain number of patients who are eligible for panel testing, etc.

(5) Ability to collect and manage panel test results and clinical information in a secured manner, and to register necessary information with Center for Cancer Genomics and Advanced Therapeutics.

(6) A system for rapid freezing and storage of surgical specimens and other biological specimens

(7) An appropriate framework for and experiences in conducting clinical studies including those for advanced medical care, investigator-initiated clinical trials, and global clinical trials.

(8) Comprehensive and accessible contact services for patients and other stakeholders regarding use of medical information, clinical trial information and etc.

Document 5, the 2nd Meeting of Sub-Working Group on Designation Criteria for Core Hospitals for Cancer Genomic Medicine (tentative name) (2017/09/11)
https://www.mhlw.go.jp/file/05-Shingikai-10901000-Kenkoukyoku-Soumuka/0000177034.pdf
Accessed: 2019/06/25

Committee on Designation of Core Hospital for Cancer Genomic Medicine (2018/2/14)

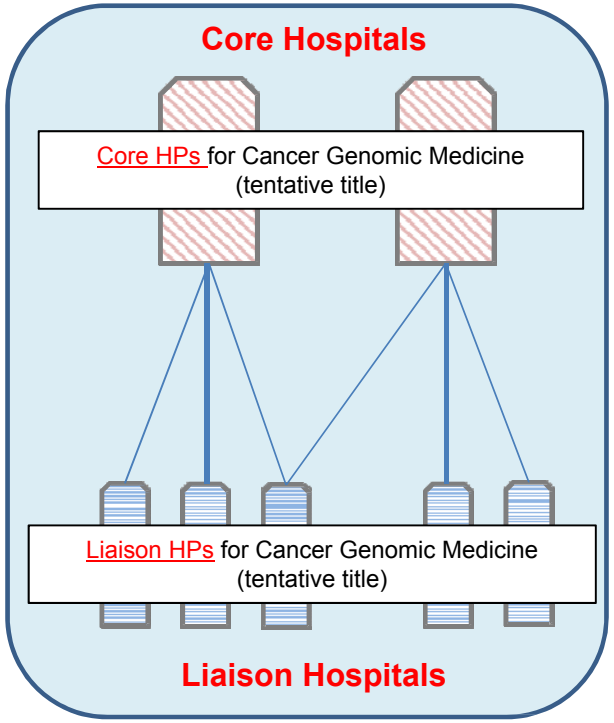
The committee selected the following medical institutions.

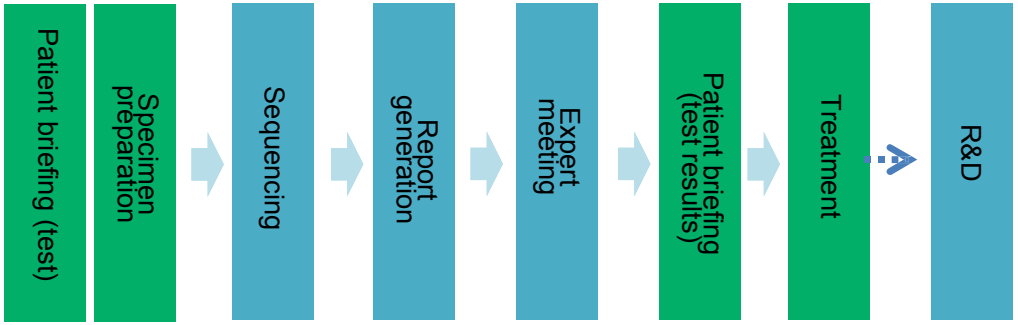
Minister of Health, Labour and Welfare will designate Core Hospital for Cancer Genomic Medicine based on today's discussion.

#	Prefecture	Core hospitals for cancer genomic medicine
1	Hokkaido	Hokkaido University Hospital
2	Miyagi	Tohoku University Hospital
3	Chiba	National Cancer Center (NCC) Hospital East
4	Tokyo	Keio University Hospital
5	Tokyo	University of Tokyo Hospital
6	Tokyo	NCC Hospital
7	Aichi	Nagoya University Hospital
8	Kyoto	Kyoto University Hospital
9	Osaka	Osaka University Hospital
10	Okayama	Okayama University Hospital
11	Fukuoka	Kyushu University Hospital

Committee on designation of Core Hospitals for Cancer Geniomic Medicine (2018/02/14)
https://www.mhlw.go.jp/file/05-Shingikai-10901000-Kenkoukyoku-Soumuka/0000194191.pdf
Accessed: 2019/06/25

Conceptual Illustration of the System for Delivering Cancer Genomic Medicines and Required Functions (draft)





	Patient briefing/ Specimen preparation	Sequencing	Report generation	Expert meeting	Patient briefing	Treatment	R&D
Core HPs	Required	Required (can be outsourced)	Required		Required	Required ※1	Required
Liaison HPs	Required	・Submit request to core HPs ・Participate in core HP meetings etc.			Required	Required ※2	Cooperation

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

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

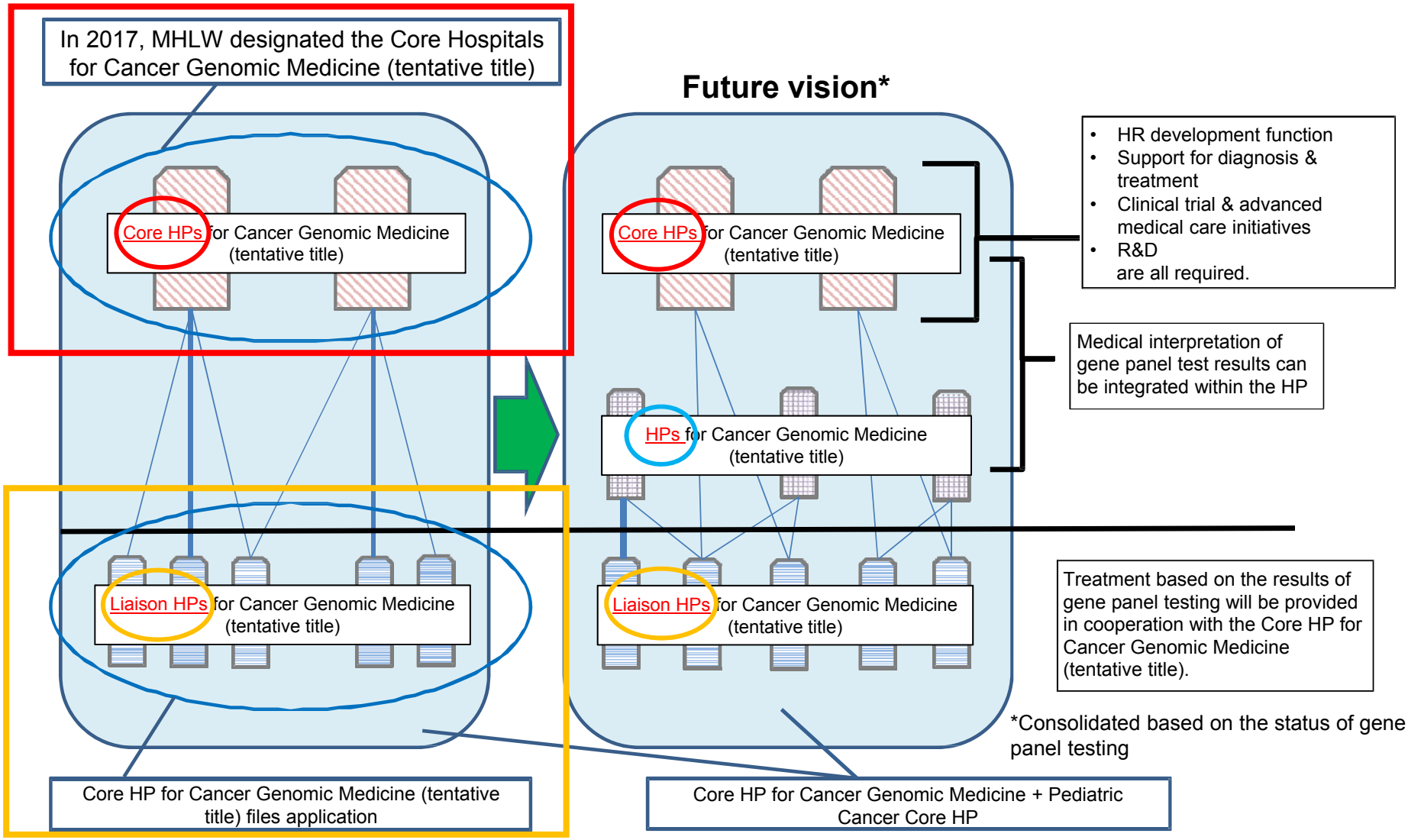
Source: The 2nd Sub-working group meeting on the designated requirements of core HPs for Cancer Genomic Medicine (tentative title), Document #4（2017/09/11）
https://www.mhlw.go.jp/file/05-Shingikai-10901000-Kenkoukyoku-Soumuka/0000177033.pdf
Accessed: 2019/06/25

Number of Liaison Hospitals Affiliated with Each Core Hospital

Core hospitals for cancer genomic medicine	Apr 2018	Oct 2018	Apr 2019
Hokkaido University Hospital	2	4	4
Tohoku University Hospital	6	8	8
National Cancer Center (NCC) Hospital East	6	8	9
Keio University Hospital	24	35	36
National Cancer Center Hospital	9	20	23
University of Tokyo Hospital	14	16	19
Nagoya University Hospital	14	18	21
Kyoto University Hospital	20	23	28
Osaka University Hospital	8	13	15
Okayama University Hospital	16	21	29
Kyushu University Hospital	13	16	19
No. of liaison hospitals *Some liaison hospitals are affiliated with multiple core hospitals.	100	135	156

System for Delivering Cancer Genomic Medicine: Cancer and Disease Control Division, Health Services Bureau, Ministry of Health, Labour and Welfare (MHLW)

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



Source: The 2nd Sub-working group meeting on the designated requirements of core HPs for Cancer Genomic Medicine (tentative title), Document #4 (2017/09/11) https://www.mhlw.go.jp/file/05-Shingikai-10901000-Kenkoukyoku-Soumuka/0000177033.pdf

Accessed: 2019/06/25

Outline of the Working Group Meeting on the Designated Requirements of Core HPs for Cancer Genomic Medicine (Document in Japanese Only)

資料１

「がんゲノム医療中核拠点病院等の指定要件に関するワーキンググループ」
開催要綱

１．　趣旨

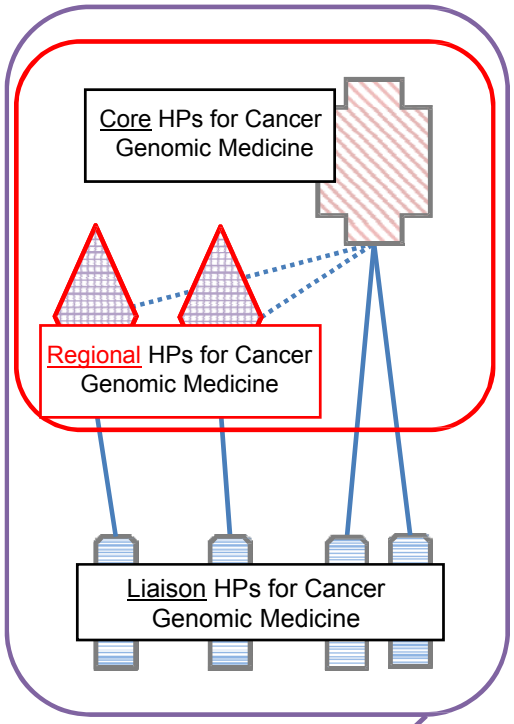
政府としては、平成 30 年（2018）３月に閣議決定された第３期がん対策推進基本計画に基づき、ゲノム医療を必要とするがん患者が、全国どこにいても、がんゲノム医療を受けられる体制整備を進めてきた。

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

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

Source: The 1st working group meeting on the designated requirements of core HPs for Cancer Genomic Medicine, Document #1
https://www.mhlw.go.jp/content/10901000/000505966.pdf
Accessed: 2019/06/28

Future functions of Core, Regional & Liaison Hospitals for Cancer Genomic Medicine (draft)



Patient briefing (test) → Specimen preparation → Sequencing → Expert panel → Report generation → Patient briefing (test results) → Treatment → Advanced medical care, clinical trial, R&D → HR development

	Patient briefing/ Specimen preparation	Sequencing	Expert meeting	Report generation	Patient briefing	Treatment	R&D	HR development
Core HPs	Required	Can be outsourced	Required		Required	Required	Required	Required
Regional HPs (proposed)	Required	Can be outsourced	Required		Required	Required	Work together	Work together
Liaison HPs	Required	Can be outsourced	Participate in Core or Regional HP meetings, etc.		Required	Required	Work together	Work together

The Core HP for Cancer Genomic Medicine submits the application for accreditation of the Liaison HP for Cancer Genomic Medicine*

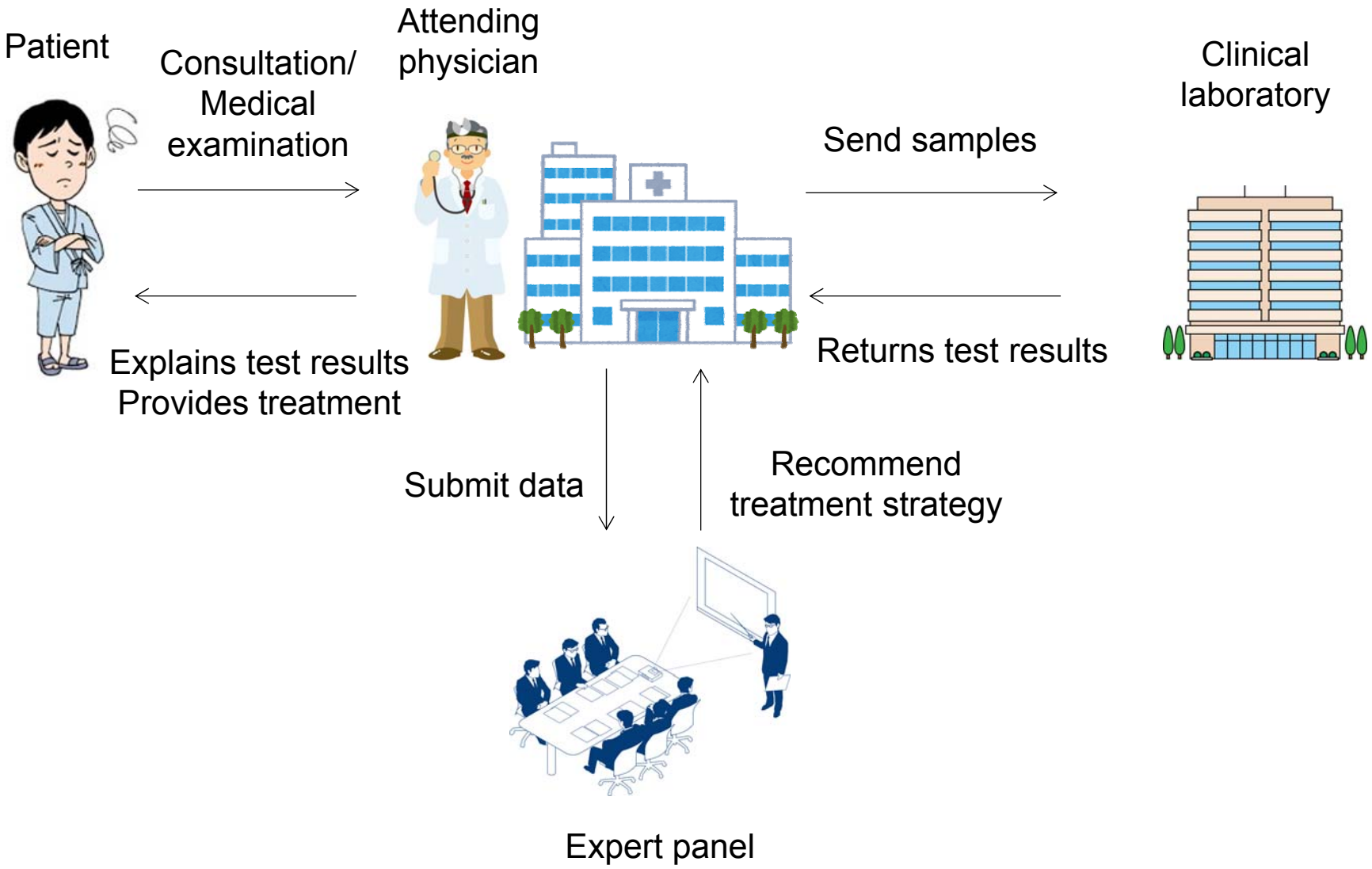
*After confirming that the developmental requirements stipulated in the above-mentioned guidance have been satisfied, the Core HP or Regional HP for Cancer Genomic Medicine will submit an application to the MHLW Minister seeking accreditation of medical institutions with which it collaborates as Liaison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

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

Source: The 1st working group meeting on the designated requirements of core HPs for Cancer Genomic Medicine, Document #3
https://www.mhlw.go.jp/content/10901000/000505968.pdf Accessed: 2019/06/28

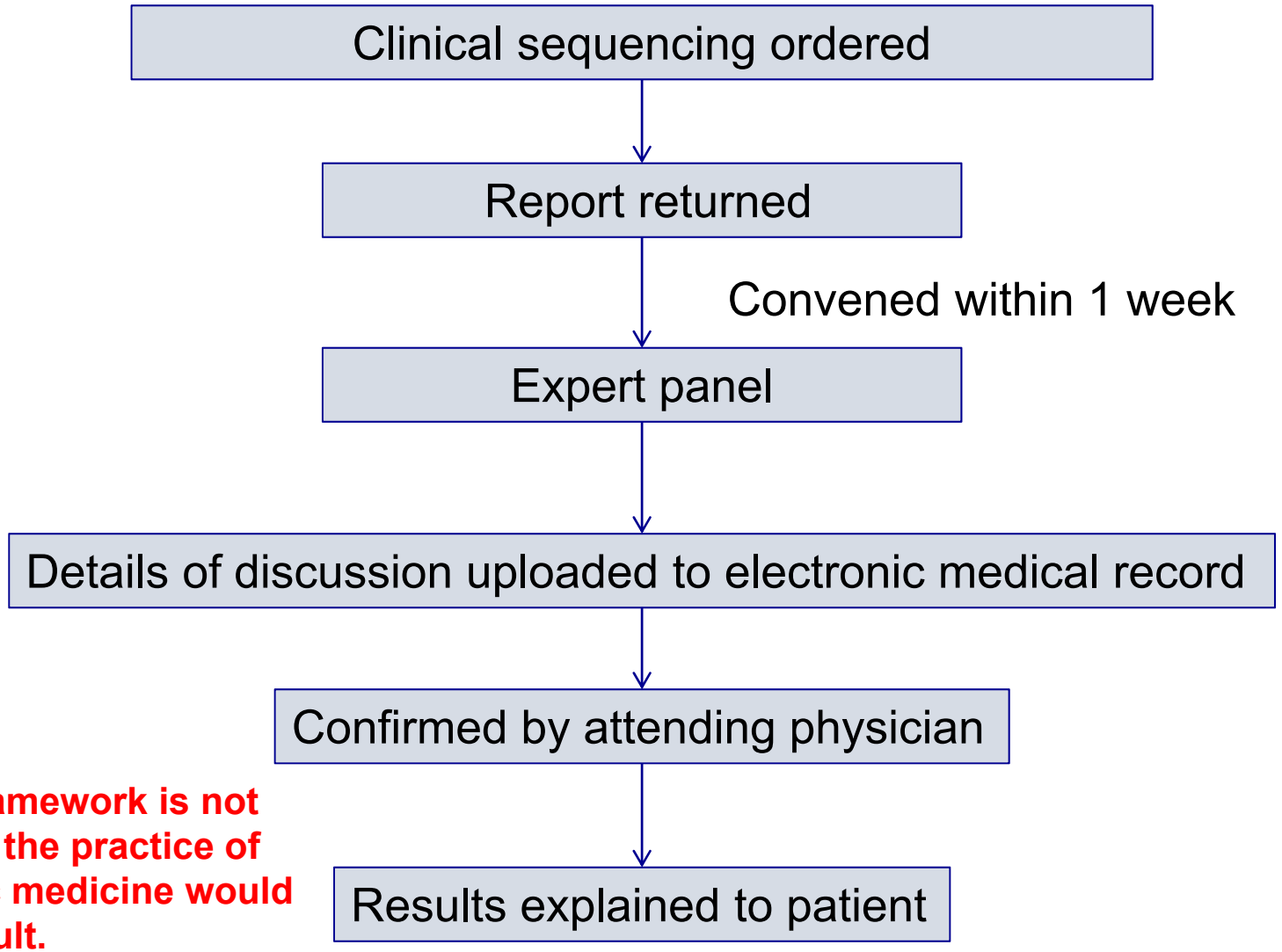
Ideal Concept for Delivering Cancer Genomic Medicine

All aspects should be integrated within a single hospital



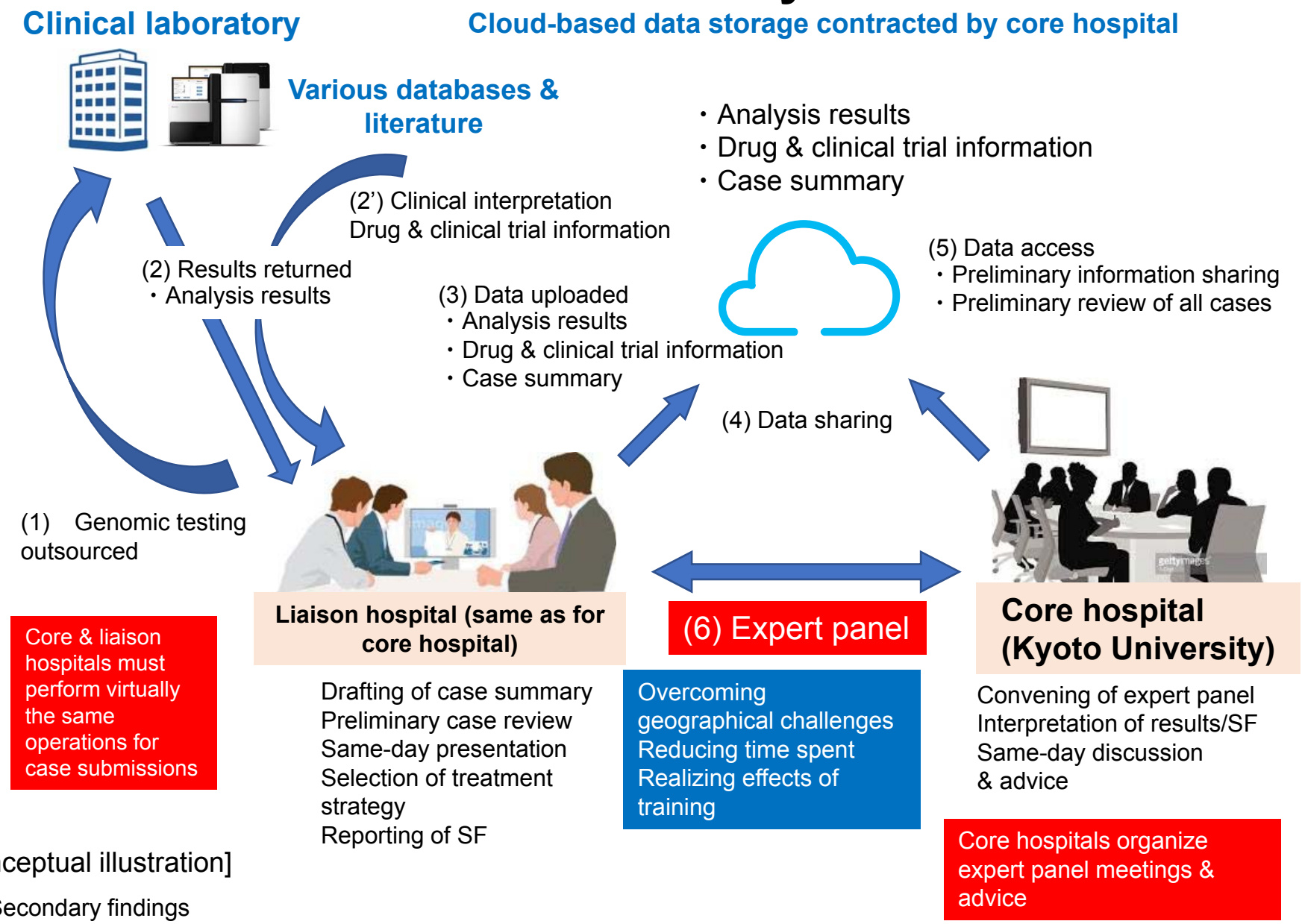
Convening the expert panel

Flowchart for returning reports to attending physicians & explaining results to patients



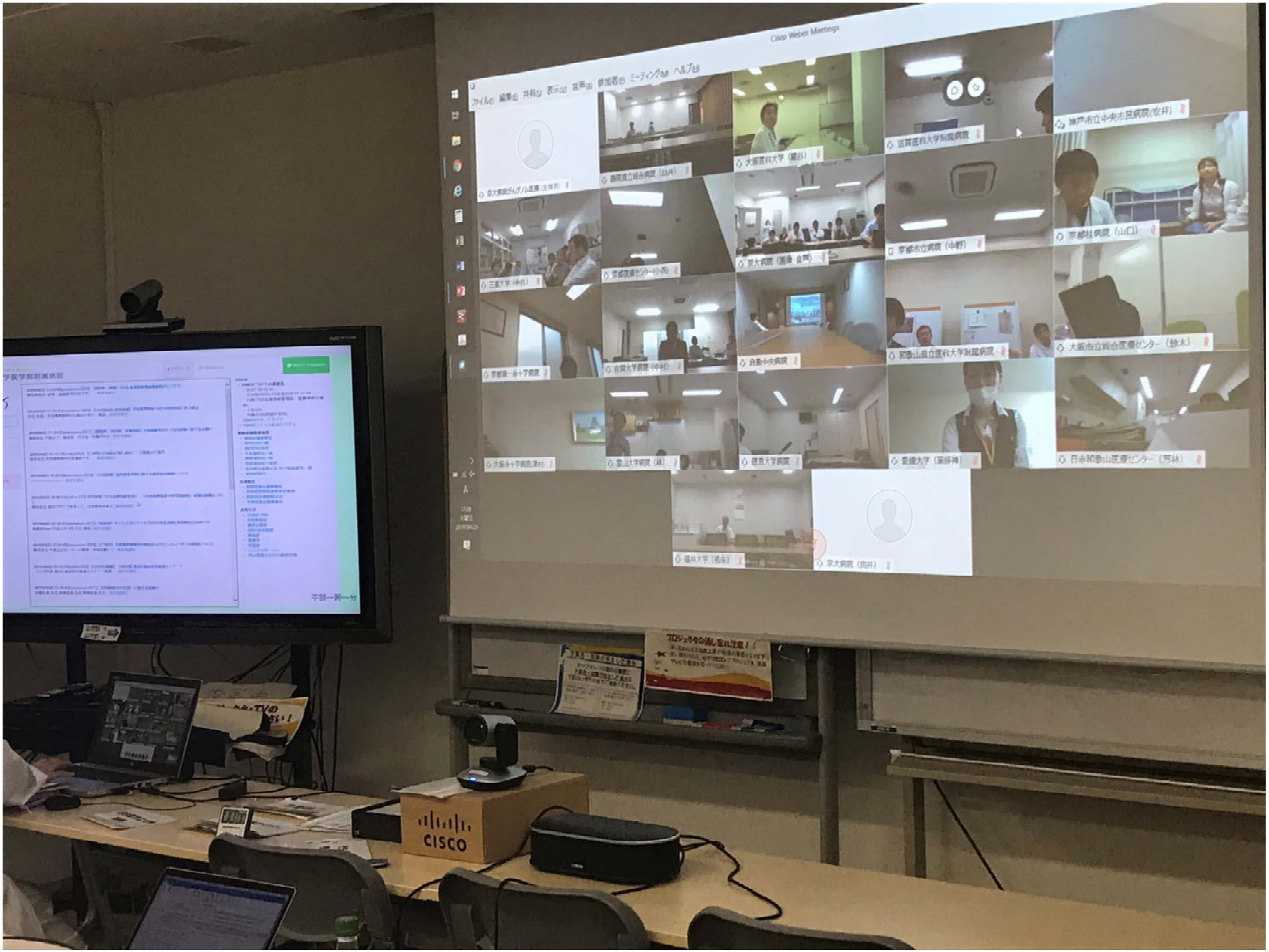
If this framework is not present, the practice of genomic medicine would be difficult.

Practical Example of Expert Panel Operation via Web-based System



[Conceptual illustration]

SF: Secondary findings


Cisco Webex Meetings
CISCO


EPSON

Expert Panel Structure & Performance

- Panel members

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

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

- Time & date of expert panel meetings:

  From 5:30pm every Tuesday @Common Conference Room, 1F, Kyoto University Hospital Cancer Center

- Meeting format:

  Web conference via WebEx: Liaison Hospitals attend (it is allowed to join the conference without cases)

Procedure in Preparation for Expert Panel Meeting

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

Challenges
(1) Burden on web conference supervisor
(2) Burden of drafting summaries
(3) Limit on number of cases that can be reviewed (limit of 7-8 cases)

Standardizing Summaries for Web-based Expert Panel Meetings

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

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

Drug & clinical trial information on positive biomarker

Interpretation of secondary findings

Summary of results

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

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

VUS: Variant of unknown significance

Cancer Clinical Sequencing in Practice

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

KUH: Kyoto University Hospital

Target Patients

- Cancers of unknown primary origin
- Rare cancers
- Recurrent advanced cancers refractory to standard-of-care therapy

List of Genes Sequenced in OncoPrime

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

Genes with FDA-approved drugs

ABL	BLM	CRLF2	ESR1	H3F3A	MAP3K1	NFE2L2	PIK3R2	SETD2	TP53
ABL2	BRAF	CSF1R	EZH2	HNF1A	MAPK1	NOTCH1	PIK3R5	SF3B1	TP63
ACVR1B	BRCA1	CTNNA1	FAM123B	HRAS	MDM2	NOTCH2	PMS1	SMAD2	TP73
AKT1	BRCA2	CTNNB1	FANCA	IDH1	MDM4	NOTCH3	PMS2	SMAD3	TPMT
AKT2	BTK	CYP1A2	FBXW7	IDH2	MED12	NOTCH4	PPP2R1A	SMAD4	TRAF7
AKT3	CARD11	CYP2C19	FGFR1	IGF1R	MEN1	NPM1	PRDM1	SMARCA4	TSC1
ALK	CASP8	CYP2C9	FGFR2	IGF2R	MET	NRAS	PTCH1	SMARCB1	TSC2
APC	CBL	CYP2D6	FGFR3	IKZF1	MITF	NTRK1	PTCH2	SMO	TSHR
AR	CCND1	DAXX	FGFR4	IL7R	MLH1	NTRK2	PTEN	SOCS1	TYMS
ARAF	CCND2	DDR2	FLT1	INSR	MLL	NTRK3	PTPN11	SRC	U2AF1
ARID1A	CCND3	DNMT3A	FLT3	JAK1	MPL	PALB2	RAD50	SRSF2	UGT1A1
ARID1B	CCNE1	DPYD	FLT4	JAK2	MRE11A	PARP1	RAD51	STAG2	VHL
ASXL1	CDC73	EGFR	FOXL2	JAK3	MSH2	PAX5	RAF1	STAT1	VKORC1
ATM	CDH1	EP300	G6PD	KDM6A	MSH6	PBRM1	RB1	STAT3	WRN
ATR	CDK4	ERBB2	GATA1	KDR	MTHFR	PDGFRA	RET	STK11	WT1
ATRX	CDK6	ERBB3	GATA2	KIT	MTOR	PDGFRB	RICTOR	SUFU	XPC
AURKA	CDKN2A	ERBB4	GATA3	KLF4	MYC	PDK1	RNF43	TERT	XRCC1
AURKB	CDKN2B	ERCC1	GLI1	KRAS	MYCN	PGR	ROS1	TET2	
AXIN1	CEBPA	ERCC2	GNA11	MAML1	MYD88	PHF6	RPTOR	TGFBR2	
BAP1	CHEK1	ERCC3	GNAQ	MAP2K1	NBN	PIK3CA	RSPO2	TNFAIP3	
BCL2	CHEK2	ERG	GNAS	MAP2K2	NF1	PIK3CG	RSPO3	TOP1	
BCOR	CREBBP	ERRFI1	GRIN2A	MAP2K4	NF2	PIK3R1	RUNX1	TOP2A	

- Translocations (17 genes)

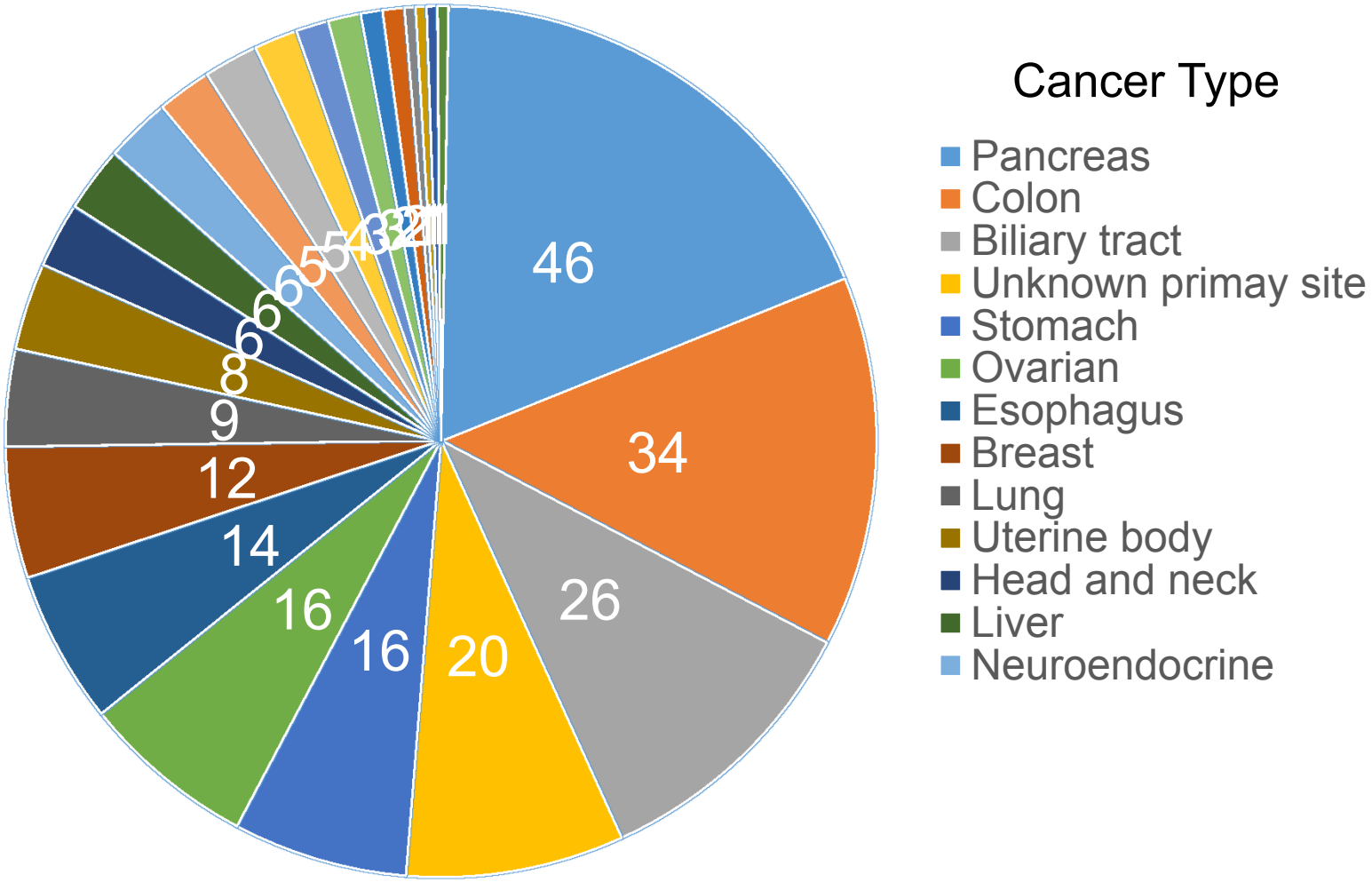
ALK *
BCR
ETV4
MLL *
RARA
BRAF *
EGFR *
ETV6
PDGFRB *
ROS1 *
ETV5
ETV1
EWSR1
RAF1 *
TMPRSS2
PDGFRA *
RET *

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

Kou T, Kanai M, Muto M. et al. JJCO 2015.

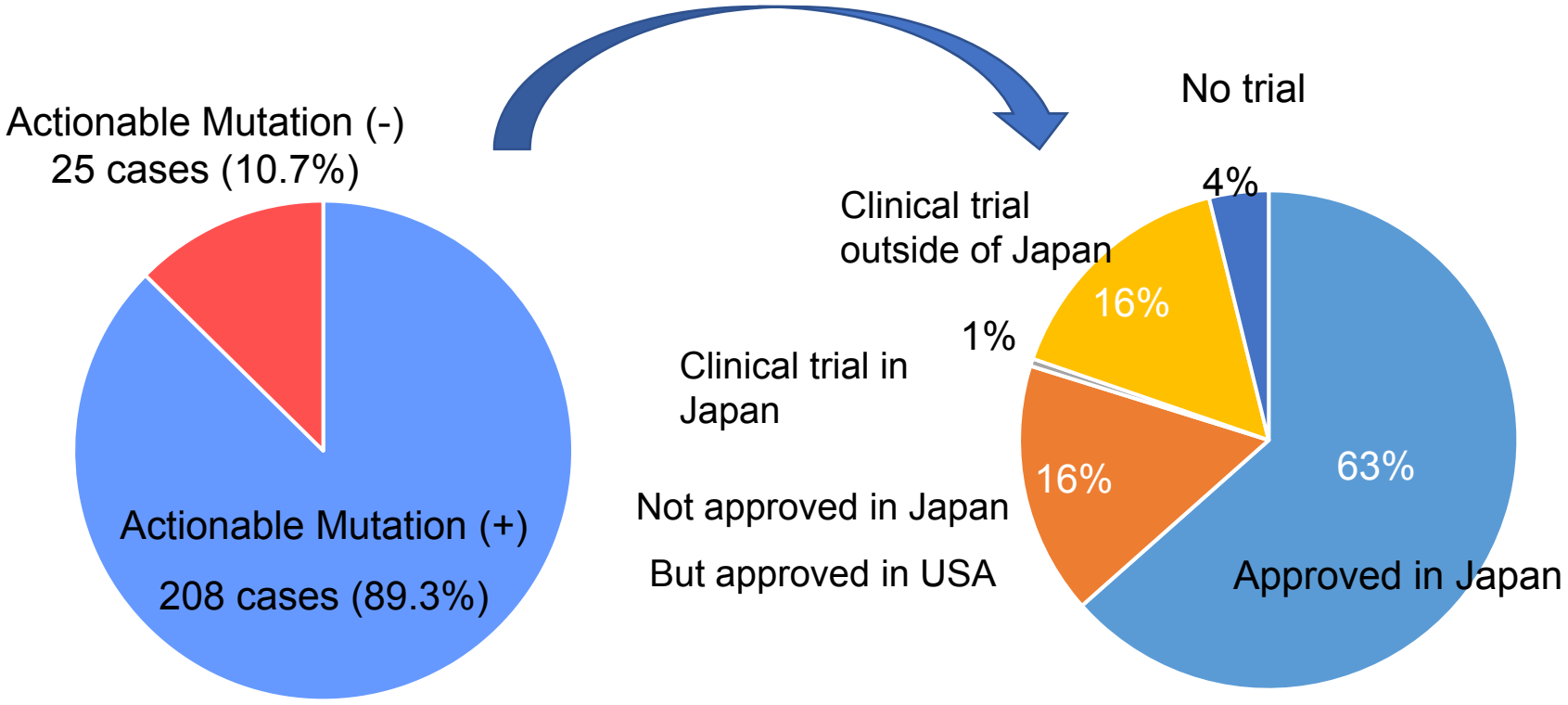
Patients Characteristics

2015 April ~ 2018 September (n=251)



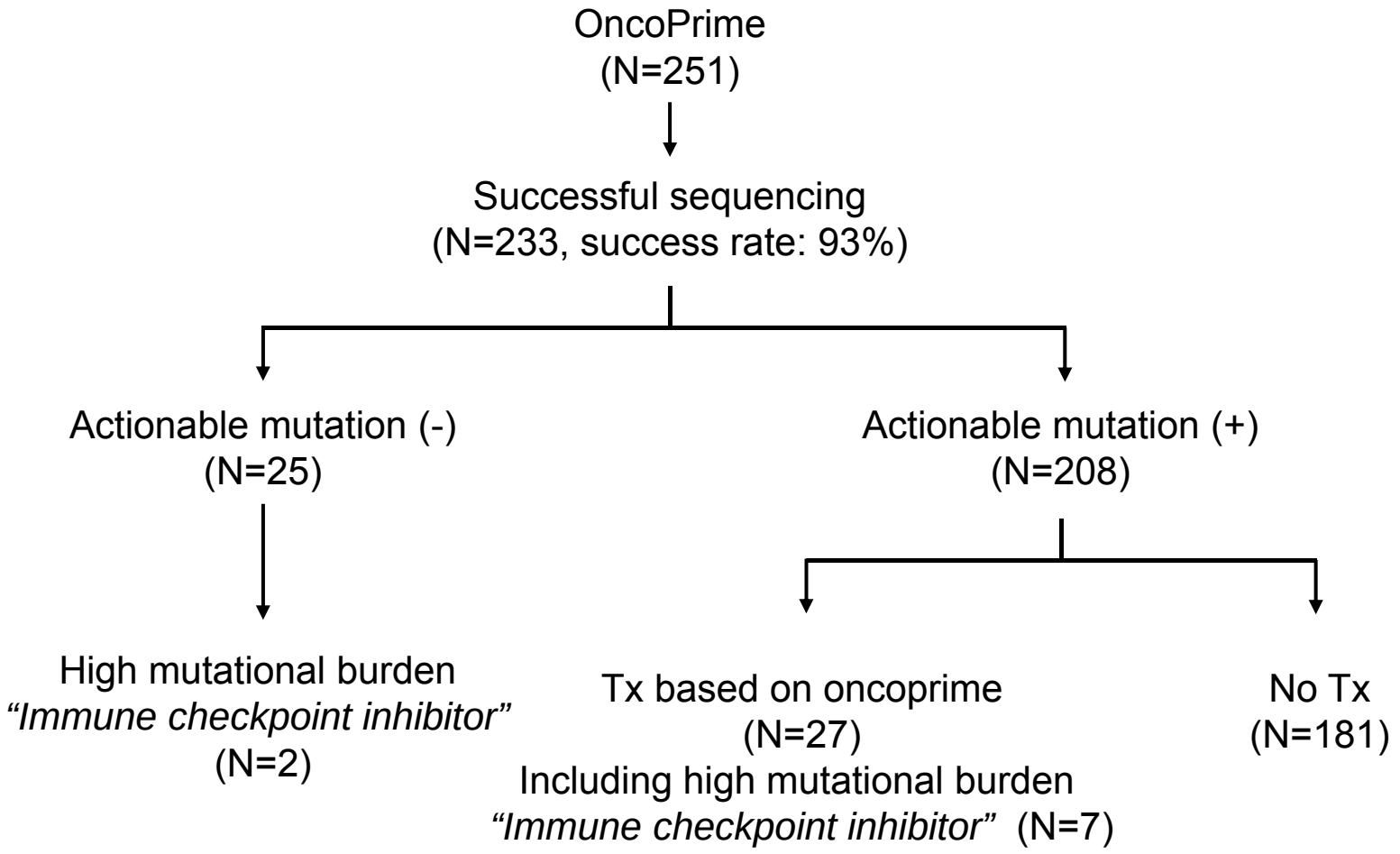
Actionable Mutation and Druggable Mutation

2015 April ~ 2018 September (n=251)



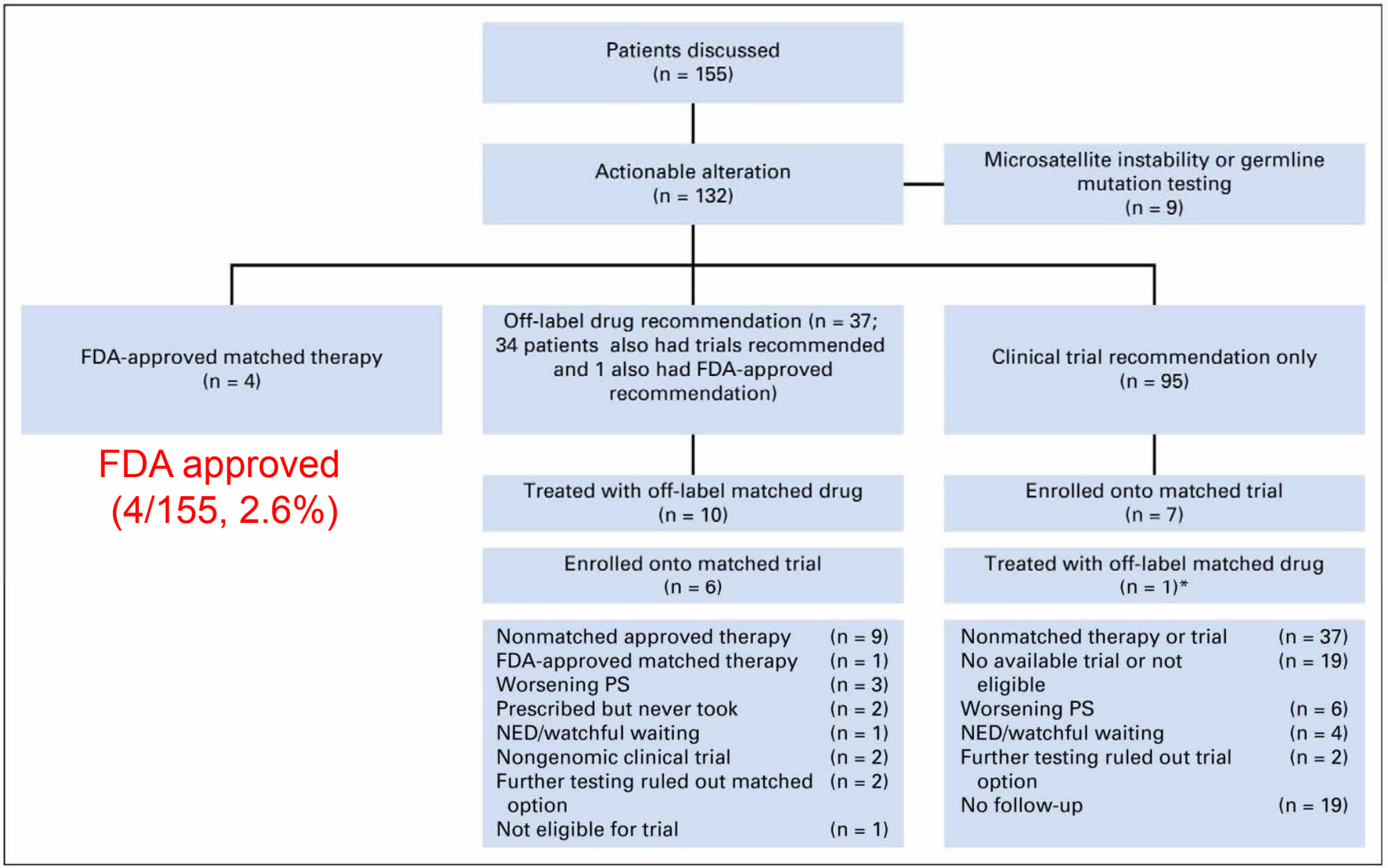
Most of them were OFF-label

Clinical Flow after Sequencing



Pts administered Tx = 12.4% (29/233)

(Reference) Personalized Medicine in the Oncology Clinic: Implementation and Outcomes of the Johns Hopkins Molecular Tumor Board

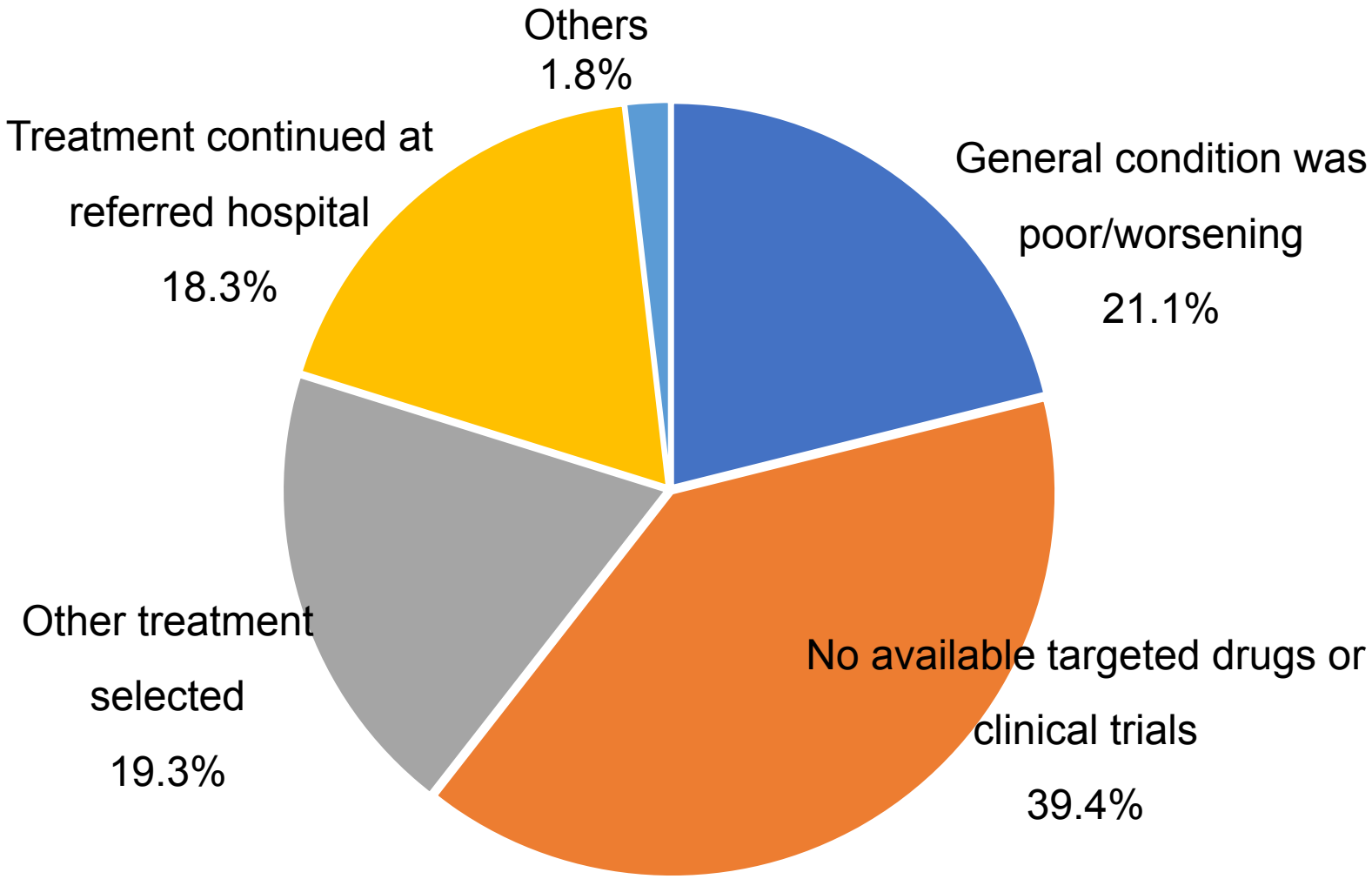


FDA approved (4/155, 2.6%)

Off-label (37/155, 24%)

Dalton WB et al., Personalized Medicine in the Oncology Clinic: Implementation and Outcomes of the Johns Hopkins Molecular Tumor Board. JCO Precis Oncol. 2017;2017. doi: 10.1200/PO.16.00046. Epub 2017 May 31

Reasons why Therapies could not be Selected Based on Test Results



Responders to Treatment

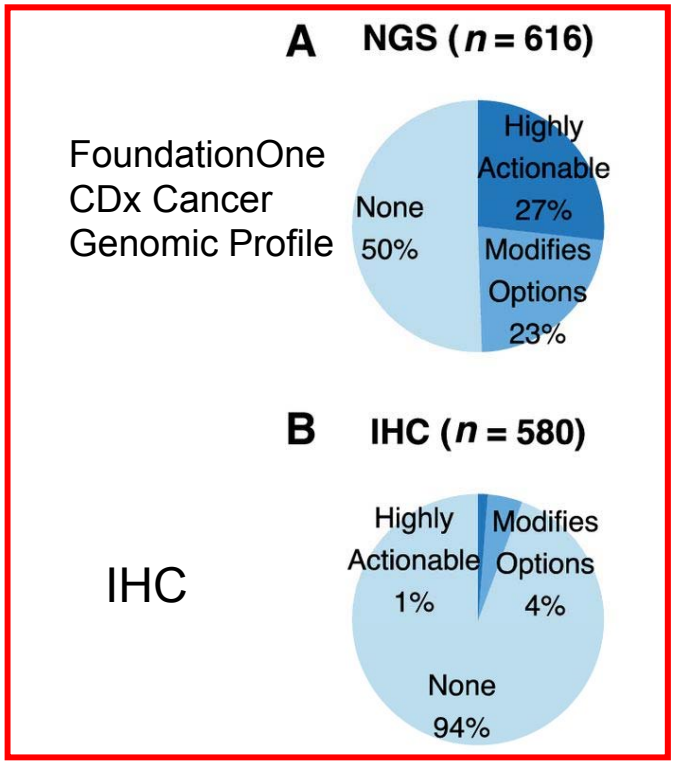
Precision Cancer Medicine in Practice

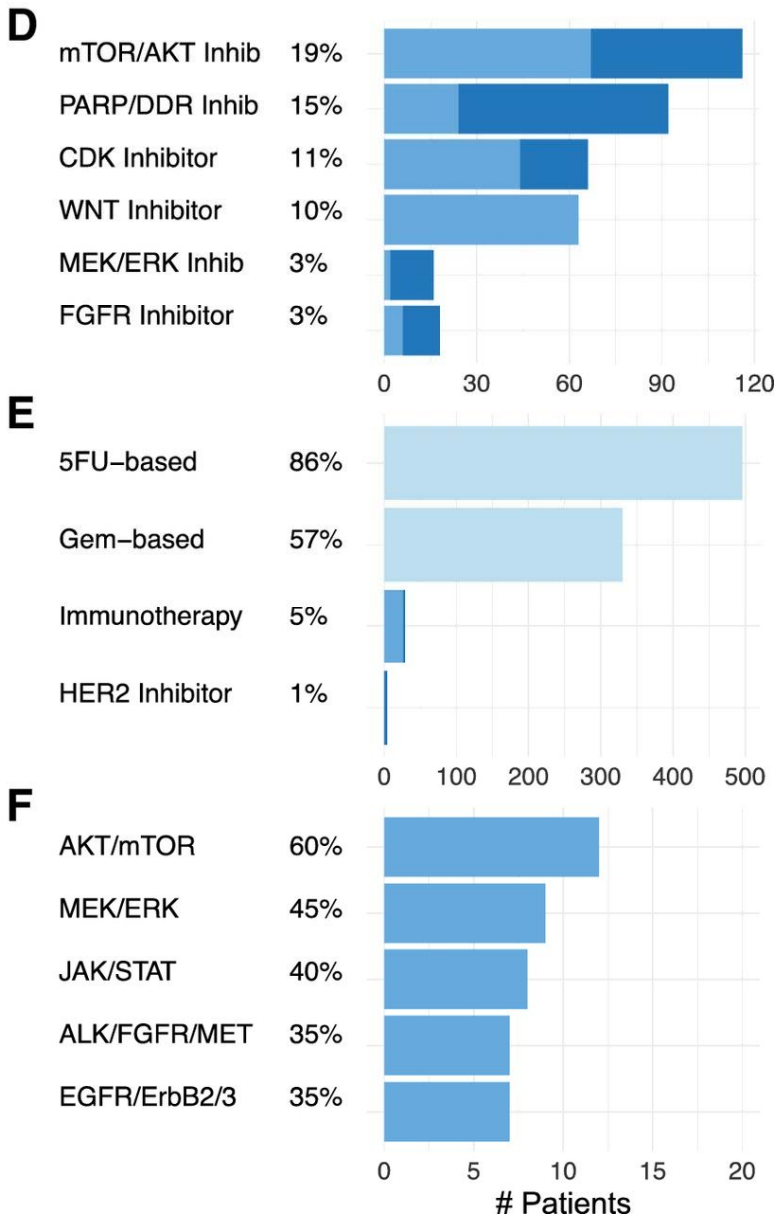
Treatment A won in a randomized clinical trial.
Let's use this drug.

Your cancer was caused by a mutation in gene XX. So, let's start a treatment targeting this mutation.

Comparison of Actionable Biomarkers in Pancreatic Cancer Patients

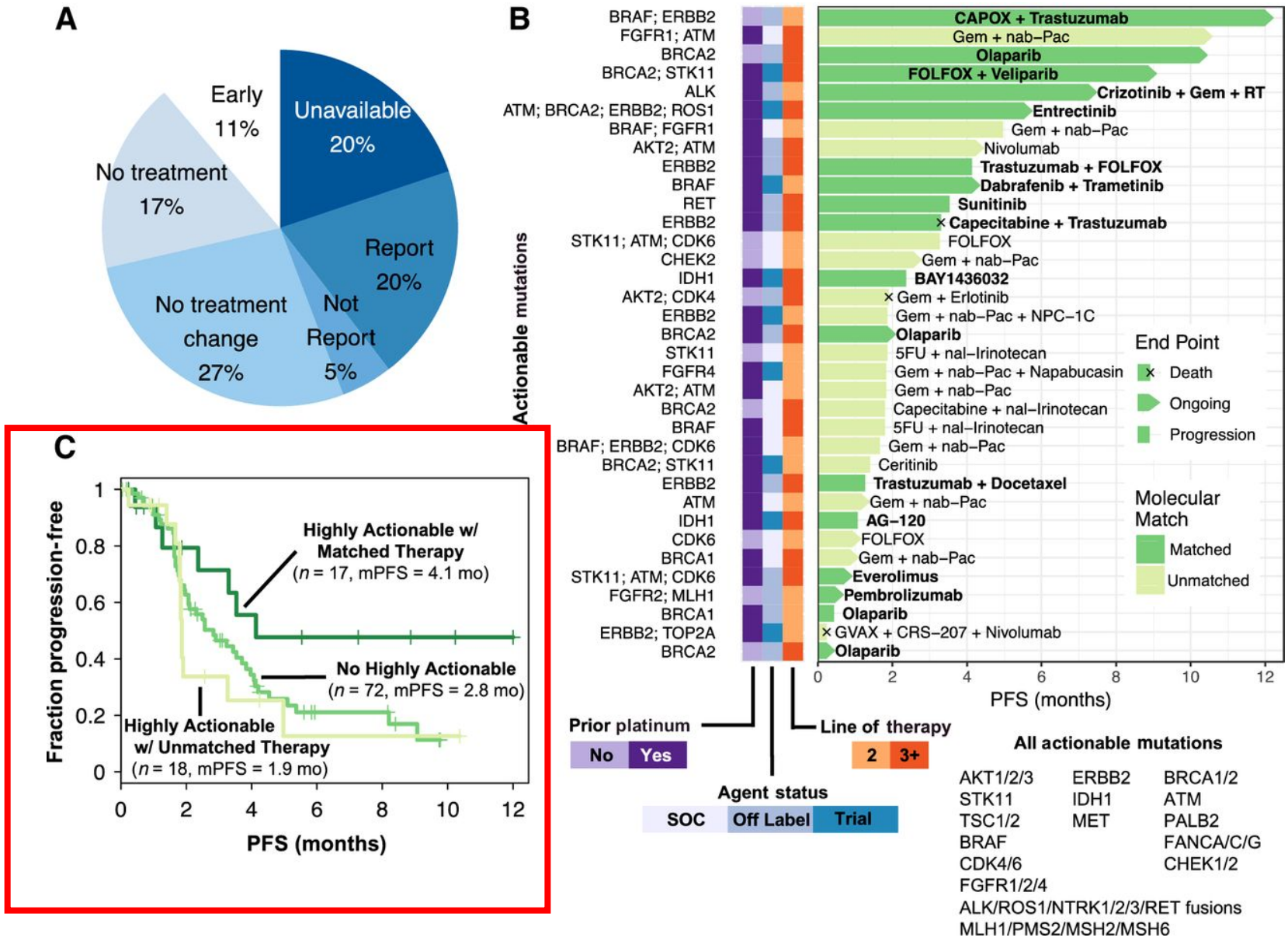
(99 % of results come from FoundationOne CDx Cancer Genomic Profile)





Michael J. Pishvaian et al. Clin Cancer Res 2018;24:5018-5027

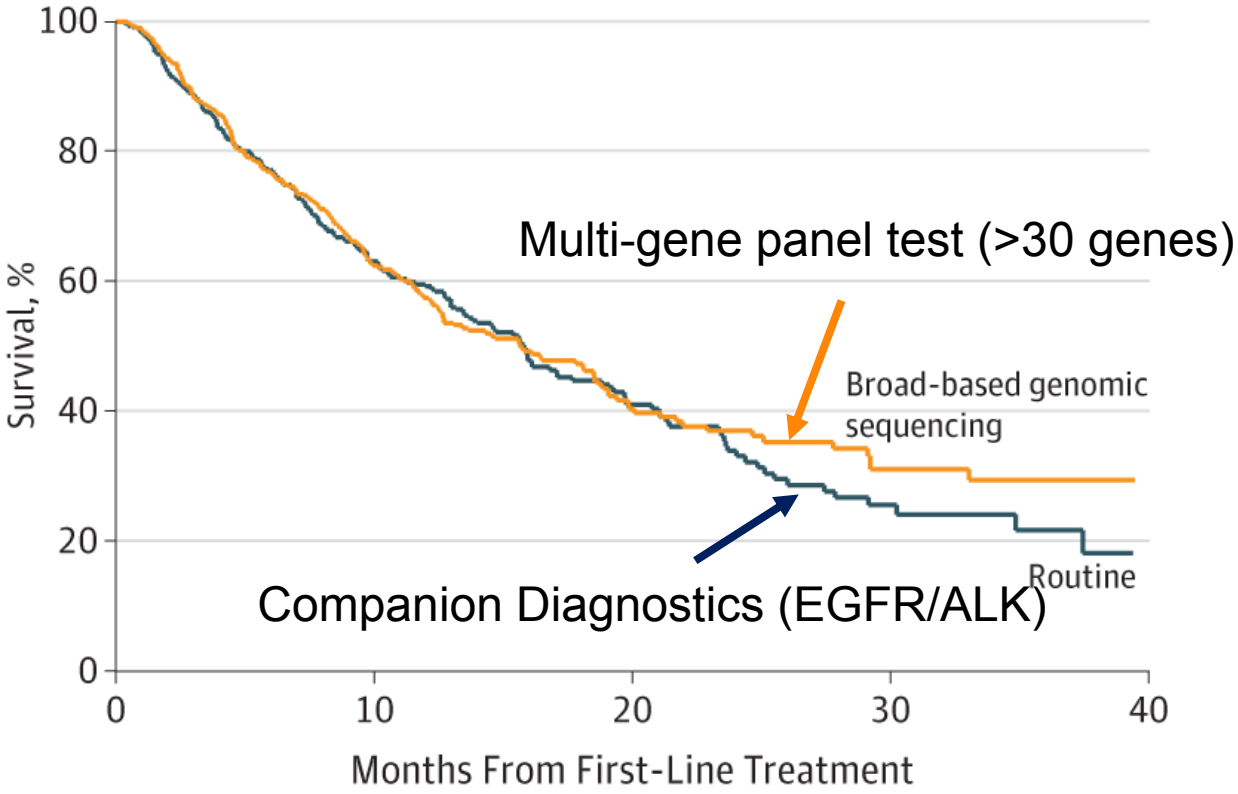
Treatment Effect on Pancreatic Cancer Patients with Actionable Mutations



Michael J. Pishvaian et al. Clin Cancer Res 2018;24:5018-5027

Comprehensive Panel Testing and CDx Shows No Difference in Prognosis in NSCLC

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



No. at risk					
Testing method					
Broad-based genomic sequencing	515	195	64	23	8
Routine	513	192	66	18	<5

JAMA. 2018;320(5):469-477. doi:10.1001/jama.2018.9824

Challenges to Cancer Genomic Medicine in Japan

Patients Who Can Use Genomic Testing under the NHI Scheme

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

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

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

The 415th Central Social Insurance Medical Council (General Meeting)
https://www.mhlw.go.jp/content/12404000/000513115.pdf Accessed: 2019/7/3

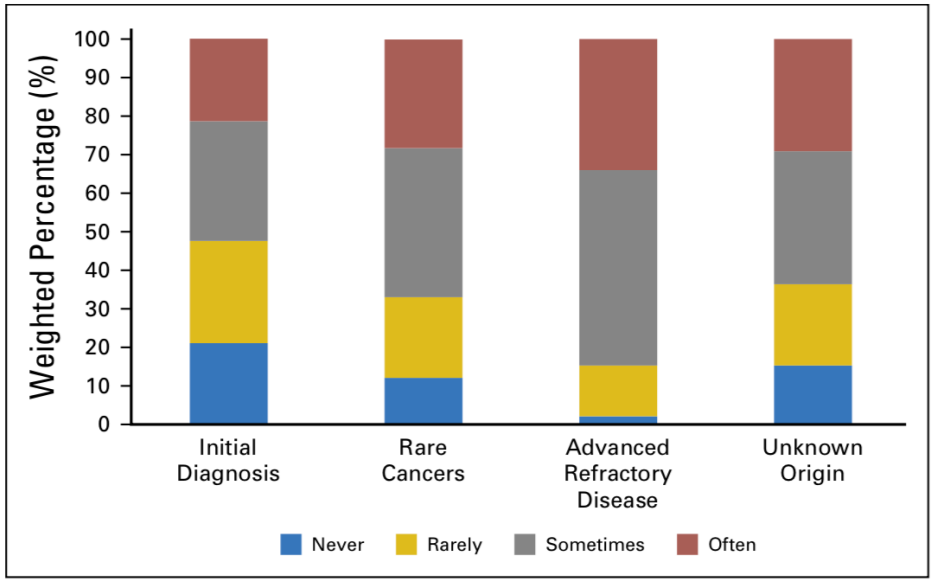
Centers for Medicare & Medicaid Services Press release on March 16, 2018
https://www.cms.gov/newsroom/press-releases/cms-finalizes-coverage-next-generation-sequencing-tests-ensuring-enhanced-access-cancer-patients Accessed: 2019/7/3

Use of Next-Generation Sequencing Tests to Guide Cancer Treatment: Results From a Nationally Representative Survey of Oncologists in the United States

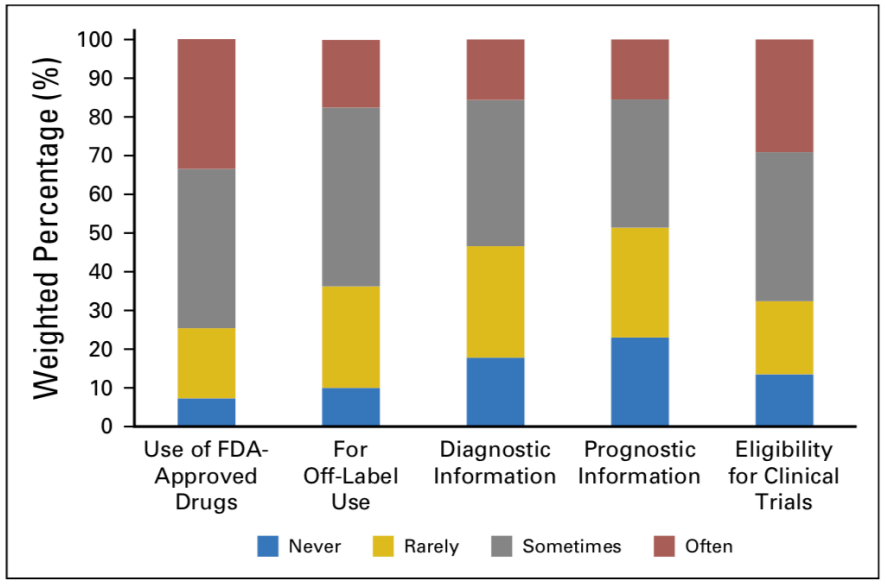
Research period
- one year, 2017
- conducted by email
- N=1,281

(cooperation rate=38%)

When to use NGS?



What to use NGS for？



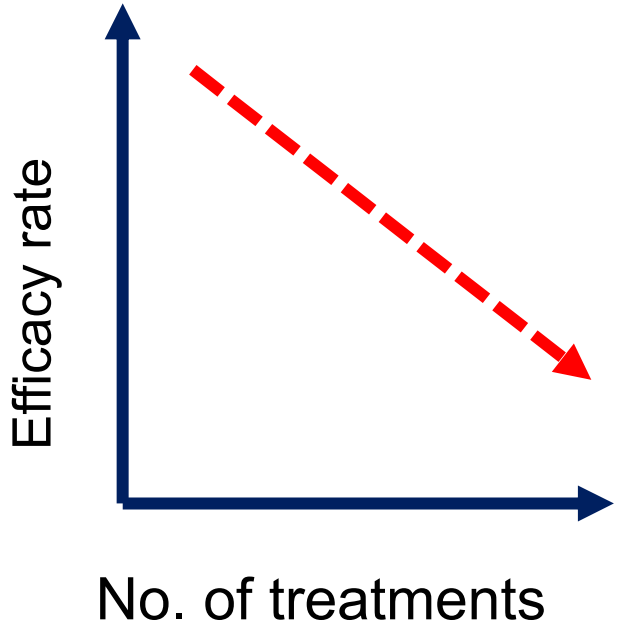
75.6% of oncologists who answered use NGS to determine treatment plan

Andrew NF, et al. JCO Precis Oncol. © 2018
https://ascopubs.org/doi/pdfdirect/10.1200/PO.18.00169

Eligibility for genomic testing in Japan

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

[Conceptual illustration]

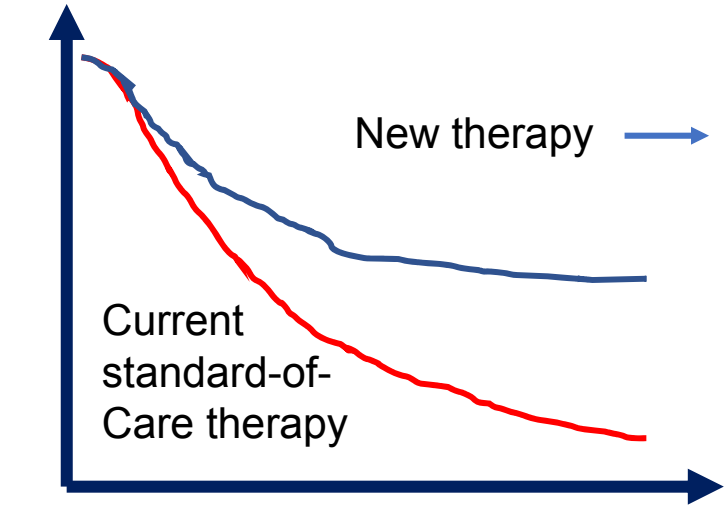


When a treatment is repeated, its effectiveness generally decreases (development of resistance).

The decision to administer a drug that is expected to be effective at the initial stage should therefore be viewed as a logical one.

So is it acceptable to perform genomic testing before initial treatment?

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



[conceptual illustration]

New therapy → New standard-of-care therapy → Regulatory approval

↓

NHI drug price listing
NHI medical fee reimbursement

↓

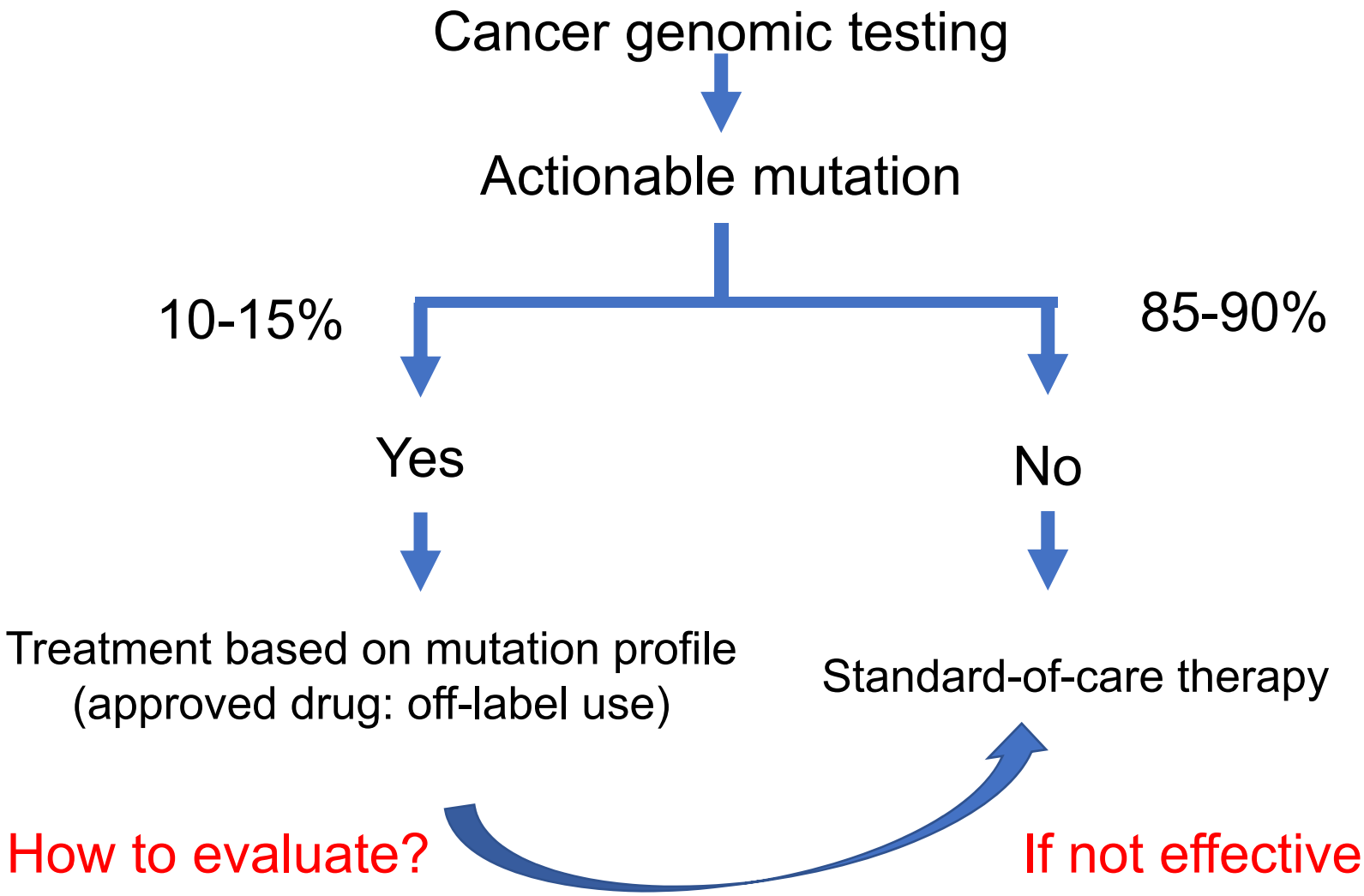
Becomes feasible under NHI system

↓

Adopted as standard-of-care therapy

Even if a drug candidate is identified in genomic testing, there is no guarantee that it will become readily available

Flow of Genomic Testing Used for Initial Treatment



Eligibility for genomic testing in Japan

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

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

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

Self-contradiction in Precision Cancer Medicine

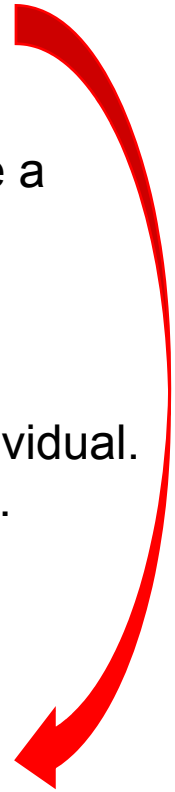
Precision cancer medicine is a treatment tailored to each individual

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

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

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

The question of whether a drug will be effective in a particular individual can only be answered by evaluating the drug in that individual.



Issues on Access to Treatment

Treatment-related Issue: How can Patients be Treated with Off-label Drugs?

	Patient briefing/ Specimen preparation	Sequencing	Expert meeting	Report drafting	Patient briefing	Treatment	R&D
Core hospital	Required	Required (Can be outsourced)	Required		Required	Required ※1	Required
Liaison hospital	Required	• Ask for Core Hospitals • Participate in Core or Regional Hospital meetings, etc			Required	Required ※2	Cooperation

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

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

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

Source: The 1st working group meeting on the designated requirements of core HPs for Cancer Genomic Medicine, Document #3
https://www.mhlw.go.jp/content/10901000/000505966.pdf
Accessed: 2019/06/28

Issue in Treatment: How to Treat?

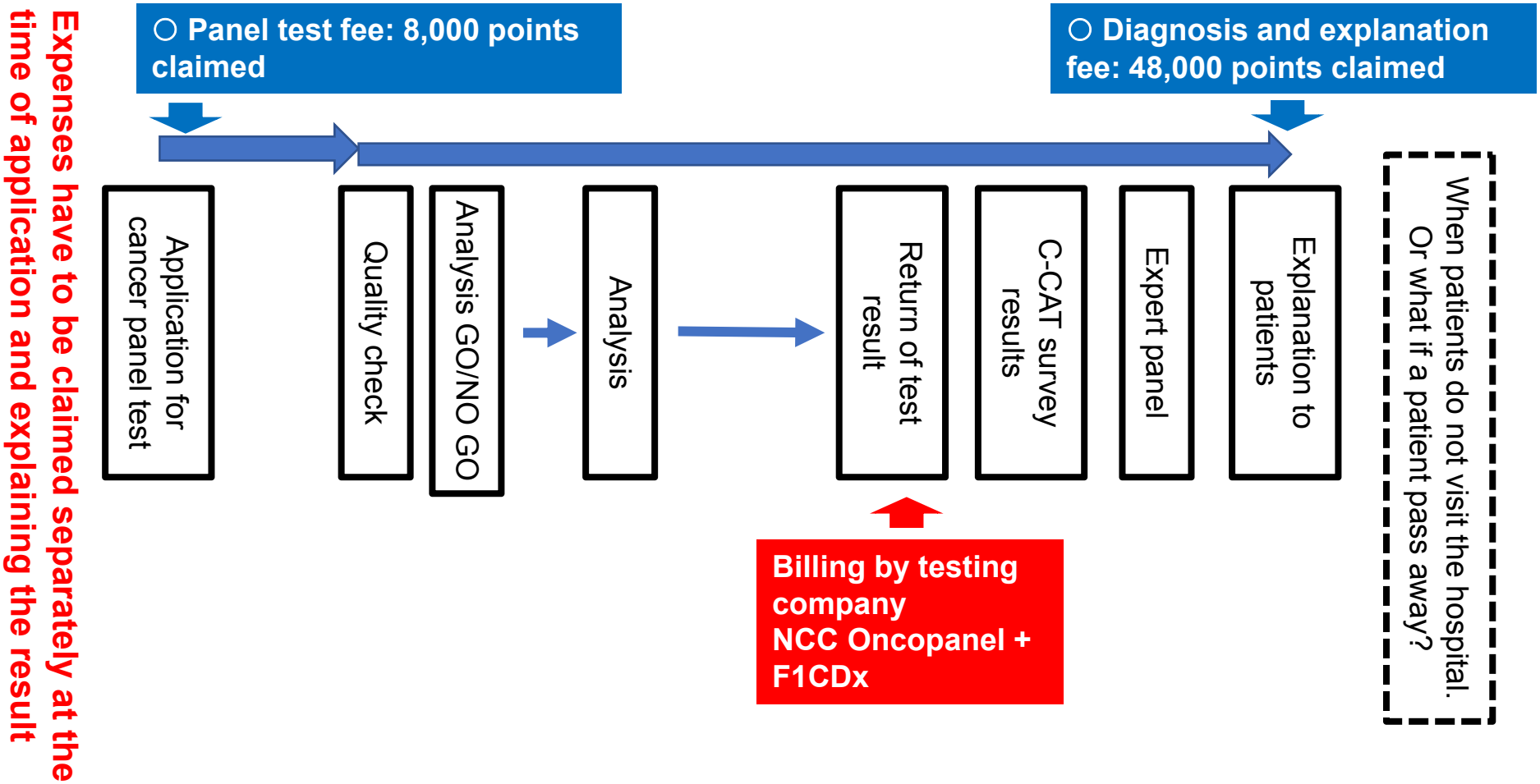
- Dealing with off-label use of drugs
  - ✓ For the time being, apply for off-label use on a case-by-case basis
  - ✓ In the future, it will be necessary to leverage programs such as compassionate use & 'patient-requested medical care' (although there are considerable obstacles because the usage would have to be based on clinical trials)
  - ✓ **Introduction of single patient IND**

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

- Should beneficiaries pay?
  - ✓ Dealing with test and treatment costs involving life insurance companies
  - ✓ Expansion of private insurance including non-covered medical treatments

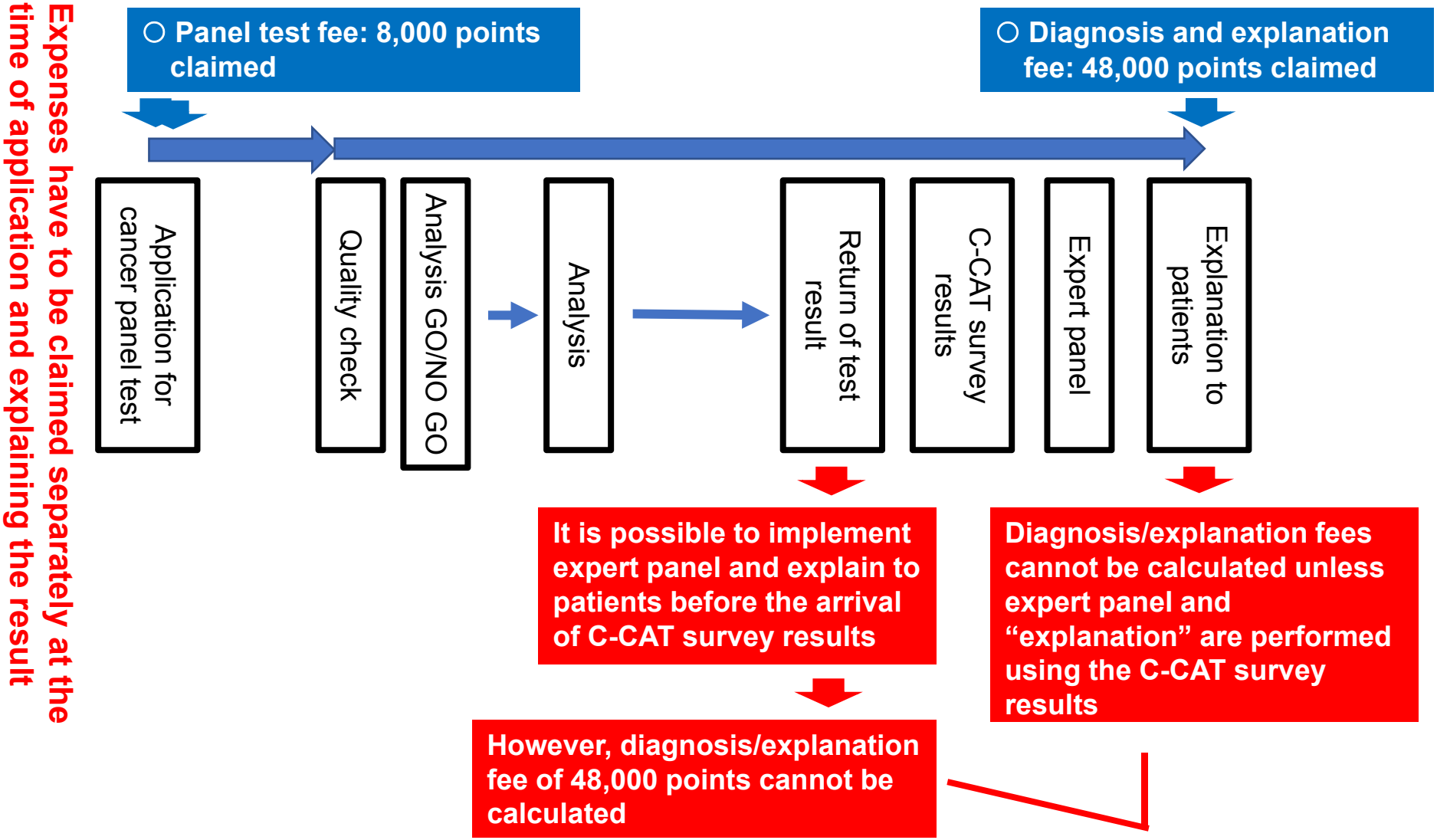
Timing Issues on Calculation of Medical Fees

Timing Issues on Calculation of Medical Fees



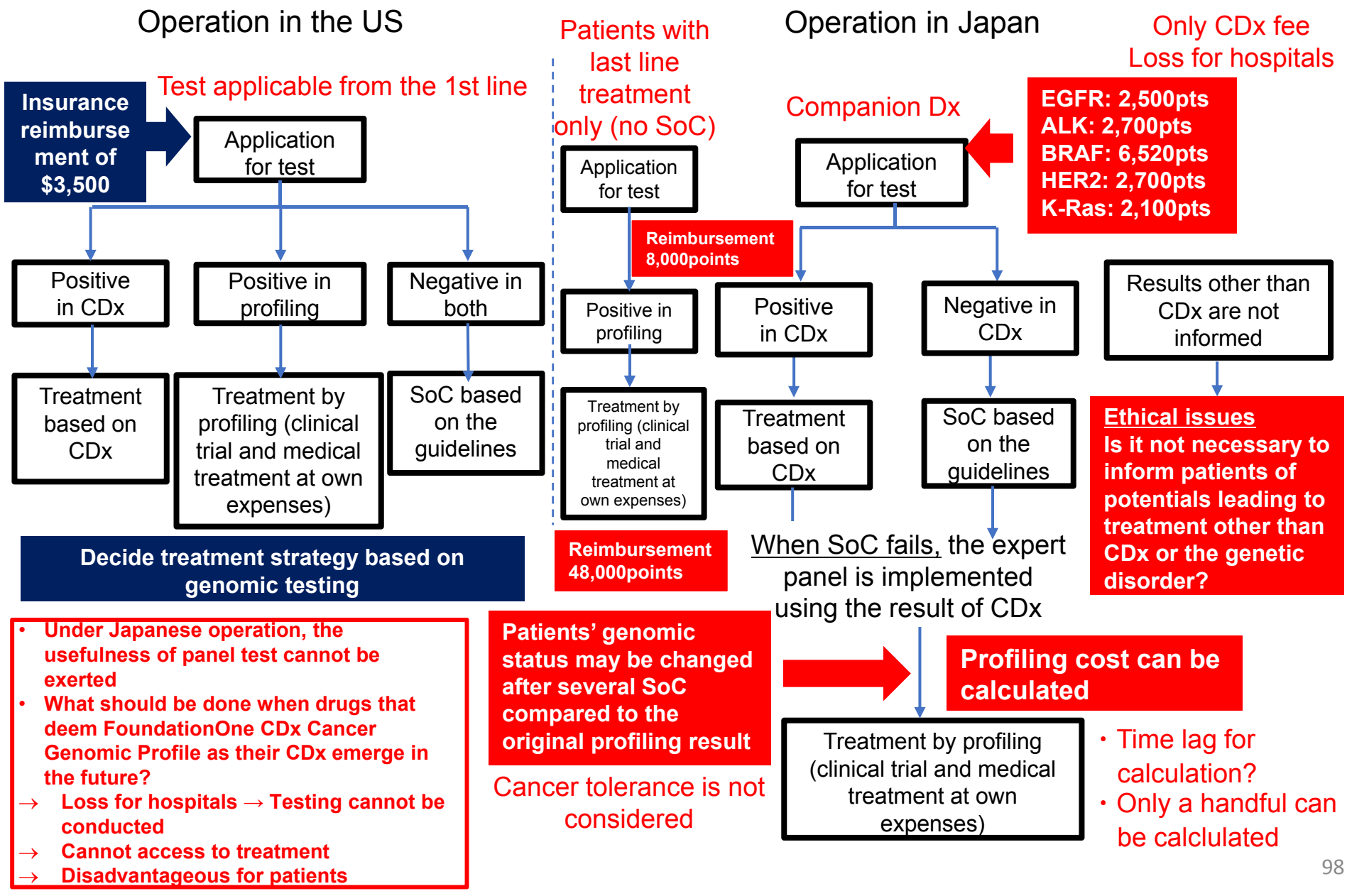
It is important to select patients whose condition is unlikely to worsen after the tests

Timing Issues on Calculation of Medical Fees



Challenges in the Use of FoundationOne CDx Cancer Genomic Profile as Companion Diagnostics

Timing issues with FoundationOne CDx Cancer Genomic Profile as Companion Diagnostics



Take Home Messages

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

2. The time of Precision Medicine has come.

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

Thank you.

Disclaimer

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