国立研究開発法人
国立がん研究センター
National Cancer Center Japan

Algorithms for C-CAT Findings

National Cancer Center

Division of Cellular Signaling/Section of Knowledge Integration,
C-CAT, National Cancer Research Center

Shinji Kohsaka

Shinji Kohsaka, M.D., Ph.D.

Division of Cellular Signaling, National Cancer Research Center

EDUCATION/TRAINING

2001–2007	Shinshu University of Medicine, Matsumoto, Japan
2007–2011	Hokkaido University Graduate School of Medicine, Sapporo, Japan

POSITIONS

2011–2012	Fellow, Department of Cancer Pathology, Hokkaido University Graduate School of Medicine
2012–2014	Fellow, Molecular Pathology & Diagnostics, Memorial Sloan-Kettering Cancer Center, NY
2015–2017	Assistant professor, Division of Cellular Signaling, Graduate School of Medicine, The University of Tokyo
2017–2020	Senior Staff Scientist, Division of Cellular Signaling, National Cancer Center Research Institute
2020–Present	Chief, Division of Cellular Signaling, National Cancer Center Research Institute

BOARD CERTIFICATION

Board-Certified Member of Japanese Cancer Association

Board-Certified Member of The Japanese Society of Pathology

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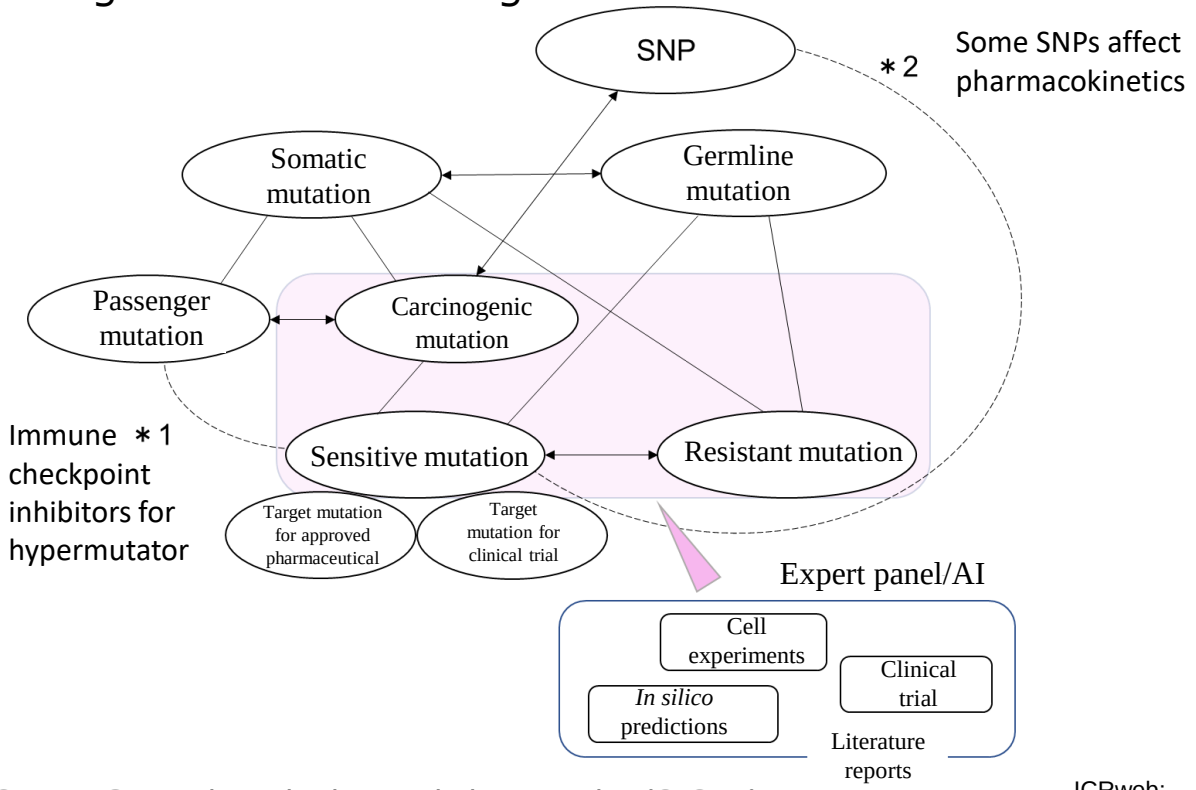
Interpretation and Significance of Mutations

① **Oncogenic markers - Oncogenic**

Essential information for understanding carcinogenesis. Biological significance of the tumor.
Includes biomarkers that enable prediction of the disease type, diagnosis, and prognosis.
It is necessary to check whether any molecular targeted drugs are available.

② **Predictive markers for therapeutic effect - Predictive**

Clinical oncology significance. Whether treatment is accessible is important information for selecting treatment for drug-sensitive mutations.



Interpretation and Significance of Mutations

③ **Disease predisposition marker - Predisposing**

Carcinogenesis-related germline variants belong in this category. For example, hereditary breast and ovarian cancer (HBOC) syndrome is caused by a pathogenic variant of *BRCA1* or *BRCA2* gene. Affected persons have a high risk of developing hereditary breast cancer or ovarian cancer. This type of cancer accounts for 5–10% of the estimated 100,000 cases of breast or ovarian cancer in Japan each year. For patients diagnosed with HBOC, risk-reducing surgery should be considered, and their clinical course should be carefully monitored by screening. These measures can lead to the prevention and early detection of cancer.

④ **Diagnostic markers - Diagnostic**

These markers are related to patient diagnosis. Histopathologic examinations mainly involving evaluation of cell morphology are used in pathology-based diagnosis. Protein expression and localization of markers specific to certain types of cancer is evaluated using immunostaining, in addition to histological imaging of the cancer. Genetic mutations can also assist in diagnosis. For example, the tall cell variant of papillary thyroid cancer, a subtype of papillary thyroid cancer, is associated with a higher incidence of extrathyroid invasion and distant metastasis compared to the highly differentiated type, indicating that the cancer is highly malignant with a poor prognosis. *BRAF V600E* is positive at a high rate in these cancers, making it a useful diagnostic marker.

⑤ **Prognostic markers - Prognostic**

These markers are related to factors such as cancer progression, severity, and survival prognosis, and can specify the biological malignancy of the cancer. For example, the *IDH2 R140K* mutation in acute myeloid leukemia indicates an improved overall prognosis compared to wild-type *IDH2*.

Evidence Level Classification

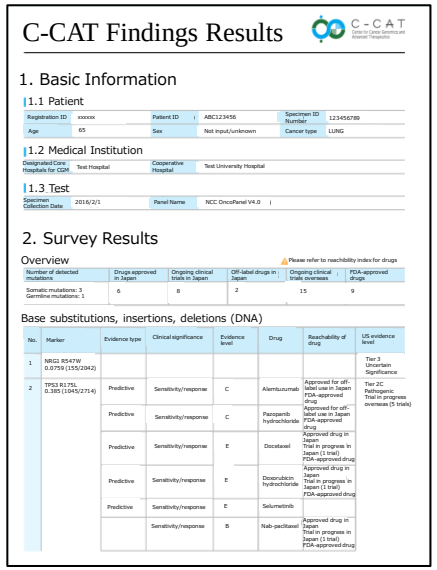
Criteria	3 Japanese Associations	3 US Associations	Hematopoietic malignancy
Biomarkers that predict response to PMDA-approved therapies for a specific type of tumor	A		A
Biomarkers that predict response to FDA-approved therapies for a specific type of tumor	A	A	A
Biomarkers included in professional guidelines that predict response to therapies for a specific type of tumor	A	A	A
Biomarkers that predict response to therapies for a specific type of tumor based on well-powered studies with consensus from experts in the field	B	B	B
Biomarkers that predict response to therapies approved by the PMDA or FDA for another type of tumor	C	C	C
Biomarkers that predict response to therapies for another type of tumor based on well-powered studies with consensus from experts in the field	C		
Biomarkers that predict response to therapies for another type of tumor based on small-scale clinical trials	C	C	D
Used as clinical trial selection criteria	-	C	C
Biomarkers that predict response to therapies for any type of tumor based on case reports	D		D
Biomarkers that show plausible therapeutic significance based on preclinical studies	E	D	D
Biomarkers that is associated with tumorigenesis	F		
Drug-resistant mutation	R		

	Drug accessibility
1	PMDA-approved drug for a specific tumor type
2	Ongoing clinical trials in Japan for a specific tumor type
3	Approved drug in Japan for another tumor type (off-label use)
4	Ongoing clinical trials overseas for a specific tumor type
5	FDA-approved drug for any tumor type
6	None of the above

- Described for each drug
- Evidence level and accessibility are written together (example: C3)
- Generally, evidence levels D or higher are stated (treatments linked to clinical trials in Japan are included as appropriate: E2,F2)
- Listed in order of evidence level, starting from treatments with high accessibility

Japanese Society of Medical Oncology, Japan Society of Clinical Oncology, Japanese Cancer Association Guidance for Cancer Treatment based on Gene Panel Tests using Next-Generation Sequencers Ver. 2.1 (15 May 2020)

Results of C-CAT Findings


C-CAT Findings Results

1. Basic Information

1.1 Patient

1.2 Medical Institution

1.3 Test

2. Survey Results

Overview

Base substitutions, insertions, deletions (DNA)

2. Survey Results

Overview

⚠ Please refer to reachibility index for drugs

Number of detected mutations	Drugs approved in Japan	Ongoing clinical trials in Japan	Off-label drugs in Japan	Ongoing clinical trials overseas	FDA-approved drugs
Somatic mutations: 15 Germline mutations: 5	14	16	0	29	15

Base substitutions, insertions, deletions (DNA)

No.	Marker	Evidence type	Clinical significance	Evidence level	Drug	Accessibility of drug	US evidence level
1	AKT1 E17K 0.59 (3358/5727)	Predictive	Sensitivity/response	B	Capivasertib		Tier 2C Pathogenic Trials in progress overseas (5 trials)
		Oncogenic	Oncogenic	F			
					TAS-117 (drug target match)	Trial in progress in Japan (1 trial)	
					TAS-117 + futibatinib (trial condition match)	Trial in progress in Japan (1 trial)	
2	ESR1 D538G 0.39 (642/1646)	Predictive	Sensitivity/response	B	AZD9496		Tier 1B Pathogenic
		Predictive	Sensitivity/response	B	Fulvestrant	Approved drug in Japan	
		Predictive	Sensitivity/response	E	Tamoxifen citras	Approved drug in Japan FDA-approved drug	
		Oncogenic	Sensitivity/response	F			
3	PIK3CA H1047R 0.81 (1599/1972)	Predictive	Sensitivity/response	B	GDC-0077		Tier 1A Pathogenic Trials in progress overseas (10 trials)
		Predictive	Sensitivity/response	B	Alpelisib		

An expert panel is held to review survey results prepared by C-CAT for the respective patient when examining a patient who has given consent to have his/her data submitted to C-CAT

Excerpt from “Notes on implementation after partial revision of medical fee calculation method”

Overview of C-CAT Findings Results

SECTION		CONTENT
Section 1	Basic information	Describes information on patients, medical institutions, and tests.
Section 2	Survey results	Describes information on the number of markers detected, markers, evidence level, evidence type, and more. I will explain this section in detail later.
Section 3	List of candidate clinical trials	Provides information on clinical trials targeting the detected markers. I will explain this section in detail later.
Section 4	Details on mutant genes	Provides detailed information on the genes associated with the detected markers.
Section 5	Reference literature	Provides information on reference literature such as articles on the detected markers.
Section 6	Software version used	Describes the software version and database version used to generate the annotations and C-CAT Findings results.
Section 7	Evidence level definition	Describes the classification of evidence levels for therapeutic efficacy.
Section 8	US evidence level	Describes information on overseas evidence levels.
Section 9	Points to note/ Disclaimer	Describes points to note and disclaimers regarding the C-CAT Findings results.

Attention

Please note that these survey results are created to be used as reference materials for conferences held by specialists (expert panel) and that **“these results are not created with the expectation that patients will receive either the original or a copy”**.

When providing this information to a patient upon request, please provide the information after understanding and carefully explaining the purpose of these results (the two points below) to the patient.

(1) **Interpretation by experts**, including the patient’s attending physician, **is required** to determine whether the information described herein is applicable to an individual patient. When doing so, a broad range of candidate clinical trials should be considered to determine whether the patient can participate in a clinical trial; however, this does not guarantee that the listed clinical trials are suitable for the patient or that the respective patient can participate in the trials.

* Considering the C-CAT Findings results alone may be misleading, and these results may suggest that there are a large number of clinical trials in which the patient can participate. **Therefore, please explain to the patient that the expert panel or attending physician will contact the clinical trial authorities to confirm whether registration is possible based on factors such as the eligibility conditions and implementation status of the clinical trial.**

(2) The contact details for each clinical trial are listed so that medical personnel can contact the authorities conducting the clinical trial as needed, as stated in (1); please note that these contact details are not for inquiries from patients”.

1. Basic Information

1.1 Patient

Registration ID	5123456789	Patient ID	00NOA18073105	Specimen ID number	1616006918073100
Age	62	Sex	F		
Cancer type	Breast, Invasive Breast Carcinoma				

1.2 Medical Institution

Designated Core Hospitals for CGM	University Hospital E
Cooperative Hospital	Test Hospital E1

1.3 Test

Specimen collection Date	2020/05/11	Panel name	OncoGuide™ NCC OncoPanel System ver.2.01-00
Test specimen	Tumor and matched-normal		

1.4 Sequencing Sample Information Using a Next-Generation Sequencer

No.	By specimen type	DNA-seq/ RNA-seq	Duplication rate	Mapping rate	Mean read depth	Median read depth	Sample condition
1	Tumor	DNA-seq	40.12	92.34	1612.00	1582.00	
2	Normal	DNA-seq	26.00	92.38	765.20	682.00	

The following information is included under the heading “2 Survey Results”.

(1) Overview
(2) Biomarkers other than genetic mutations
(3) Base substitutions, insertions, deletions (DNA)
(4) Gene rearrangement (DNA), structural variations (DNA)
(5) Copy number variation
(6) Germline mutation (only T/N tests)
(7) Composite marker table

2. Survey Results

Overview

⚠ Please refer to reachibility index for drugs

Number of detected mutations	Drugs approved in Japan	Ongoing clinical trials in Japan	Off-label drugs in Japan	Ongoing clinical trials overseas	FDA-approved drugs
Somatic mutations: 10 Germline mutations: 2	5	32	9	37	17

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Biomarkers other than genetic mutations

■ Number is a link to reference literature,
● Number is the number of clinical trials in Japan,
▲ Number is a link to detailed information on overseas clinical trials.

No.	Marker	Branch No.	Evidence type	Clinical significance	Evidence level	Drug	Reachability of drug
1	MSI high 57.89%	1	Predictive	Sensitivity/response	A	Pembrolizumab ■1	Approved drug in Japan FDA-approved drug Trials in progress in Japan (7 trials) ●1–7
		2	Predictive	Sensitivity/response	C	Ipilimumab + nivolumab ■1	Off-label drug in Japan FDA approved drug
		3	Predictive	Sensitivity/response	C	Nivolumab ■1	Off-label drug in Japan FDA-approved drug Trials in progress in Japan (14 trials) ●6, 8–20
		4	Oncogenic	Oncogenic	F ■3, 4		
2	TMB 34.56 Muts/Mb	1	Predictive	Sensitivity/response	A	Pembrolizumab ■2	FDA-approved drug Trials in progress in Japan (6 trials) ●2–7

Base substitutions, insertions, deletions (DNA)

■ Number is a link to reference literature,
● Number is the number of clinical trials in Japan,
▲ Number is a link to detailed information on overseas clinical trials.

No.	Marker	Branch No.	Evidence type	Clinical significance	Evidence level	Drug	Reachability of drug	US evidence level
3	ABL1 p.F336L 0.26 (548/2141)	1	Oncogenic	Likely oncogenic	F ■5			Tier 2C Pathogenic Trials in progress overseas (9 trials) ▲ 1–9
		2				Nilotinib (drug target match) ■27	Off-label drug in Japan Trial in progress in Japan (1 trial) ●21	
		3	Predictive	Resistance	R2*	Dasatinib ■6	Off-label drug in Japan	
		4	Predictive	Resistance	R2*	Imatinib mesylate ■7	Off-label drug in Japan FDA-approved drug	
4	TP53 p.A268V 0.80 (376/469)	1				AMG 650 (trial condition match) ■25	Trial in progress in Japan (1 trial) ●22	Tier 2C Likely pathogenic Trials in progress overseas (2 trials) ▲ 10–11
5	ATM p.E2444K 0.39 (165/421)							Tier 2C Likely pathogenic Trials in progress overseas (9 trials) ▲ 12–20
6	BRCA2 p.V2109I 0.51 (387/755) *ToMMo Allele							Tier 3 Uncertain significance

Gene rearrangement (DNA), Structural variations (DNA)

■ Number is a link to reference literature,
● Number is the number of clinical trials in Japan,
▲ Number is a link to detailed information on overseas clinical trials.

No.	Marker	Branch No.	Evidence type	Clinical significance	Evidence level	Drug	Reachability of drug	US evidence level
7	GBA-NTRK1 gene fusion Q22-q23.1	1	Predictive	Sensitivity/ response	A	Entrectinib ■1	Approved drug in Japan FDA-approved drug Trials in progress in Japan (2 trials) ●21, 23	Tier 1A Pathogenic Trials in progress overseas (8 trials) ▲2, 8, 21–26
		2	Predictive	Sensitivity/ response	A	Larotrectinib ■1	Approved drug in Japan FDA-approved drug	
		3	Oncogenic	Likely oncogenic	F ■8			
		4				Repotrectinib (trial condition match) ■26	Trial in progress in Japan (1 trial) ●24	

Copy number variations

■ Number is a link to reference literature,
● Number is the number of clinical trials in Japan,
▲ Number is a link to detailed information on overseas clinical trials.

No.	Marker	Branch No.	Evidence type	Clinical significance	Evidence level	Drug	Reachability of drug	US evidence level
9	CDK4 Amplification log2 fold-change: 2.13 chr12: 58,141,510-58,146,093	1	Predictive	Sensitivity/ response	C	Palbociclib ■12, 13	Trials in progress in Japan (5 trials) ●25–29	Tier 2C Pathogenic Trials in progress overseas (10 trials) ▲ 20,26, 30–37
		2	Oncogenic	Oncogenic	F ■14–16			
		3				Abemaciclib (drug target match) ■28	Approved drug in Japan FDA approved drug Trials in progress in Japan (3 trials) ●30–32	

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Germline mutation (only T/N tests)

■ Number is a link to reference literature,
● Number is the number of clinical trials in Japan,
▲ Number is a link to detailed information on overseas clinical trials.
⚠ Displays analysis results of DNA derived from non-cancer tissue.

No.	Marker	Branch No.	Evidence type	Clinical significance	Evidence level	Drug	Reachability of drug	US evidence level
11	BRCA2 p.R2318* 0.51 (102/200) *ToMMO Allele frequency = 0.03%	1	Predictive	Sensitivity/ response	A	Olaparib ■1	Approved drug in Japan FDA-approved drug Trial in progress in Japan (1 trial) ●3	-
		2	Predictive	Sensitivity/ response	A	Talazoparib ■2	FDA approved drug	
		3	Predictive	Sensitivity/ response	C	Bevacizumab + Olaparib ■1	Approved drug in Japan FDA-approved drug	
		4	Predictive	Sensitivity/ response	C	Niraparib ■1	Approved drug in Japan FDA-approved drug	
		5	Predictive	Sensitivity/ response	C	Platinum compound ■20		
		6	Predictive	Sensitivity/ response	C	Rucaparib ■2	FDA-approved drug	
		7	Predisposing	Pathogenic breast-ovarian cancer, familial 2	F ■21			

2 Survey Results (7) Composite Marker Table

Composite marker table

■ Number is a link to reference literature,
● Number is the number of clinical trials in Japan,
▲ Number is a link to detailed information on overseas clinical trials.

No.	Marker	Branch No.	Evidence type	Clinical significance	Evidence level	Drug	Reachability of drug
13	ABL1 p.F336L BCR-ABL1 gene fusion	1	Predictive	Sensitivity/ Response	C	Ponatinib hydrochloride ■22	Off-label drug in Japan FDA-approved drug Trial in progress in Japan (1 trial) ●21
		2	Predictive	Resistance	R2*	Dasatinib ■23	Off-label drug in Japan
		3	Predictive	Resistance	R2*	Imatinib mesylate ■24	Off-label drug in Japan FDA-approved drug

Testing company comments

Mutation of interest	Comment
Entire mutation	The total mutation expression rate reported from the OncoGuide NCC Oncopanel system is listed as a TMB value. The method for determining the TMB from the total mutation expression rate has not been clinically established.
Entire mutation	The method for determining MSI reported from the OncoGuide NCC Oncopanel system has not been clinically established.
Entire mutation	This test is a comprehensive genome profiling test of tumor tissue for patients with solid tumors and is not intended for the diagnosis of hereditary diseases. Please base decisions about disclosing to patients results related to germline variant information detected in this test on the medical insititution's expert panel and regulations clearly stipulated by the medical insititution.

3 List Of Candidate Clinical Trials

3 List of candidate clinical trials

* It is necessary to confirm with the Medical Institution (contact details) whether the patient meets the detailed eligibility criteria/exclusion criteria of the following clinical trial and whether the trial is currently recruiting patients.

List of clinical trials in Japan

●1

Marker No.	1-1	Trial Name (trial ID, date of data update, date additional information was provided by the pharmaceutical company).
Phase	Phase 2	Study of Pembrolizumab (MK-3475) in Participants with Advanced Solid Tumors (MK-3475-158/KEYNOTE-158) (NCT02628067, 2021/06/24, no additional information provided)
Drug Name	Biological: Pembrolizumab	
Cancer Types	Advanced Cancer|Anal Carcinoma|Anal Cancer|Biliary Cancer|Cholagiocarcinoma|Bile Duct Cancer|Neuroendocrine Tumor|Carcinoid Tumor|Endometrial Carcinoma|Endometrial Cancer|Cervical Carcinoma| Cercival Cancer|Vulva Carcinoma|Vulva Cancer|Small Cell Lung Carcinoma|Small Cell Lung Cancer (SCLC)| Mesothelioma|Thyroid Carcinoma|Thyroid Cancer|Salivary Gland Cancer|Salivary Cancer|Parotid Gland Cancer| Advanced Solid Tumors|Colorectal Carcinoma	
Implementing Institution	Merck Sharp & Dohme Corp.	
Contact Details	1-888-577-8839,	

List of clinical trials overseas

▲1

Marker No.	3	Trial Name (trial ID, date of data update, date additional information was provided by the pharmaceutical company).
Phase	Phase 1	A Phase Ib/II Study of the Safety and Pharmacology of Nilotinib to Prevent Paclitaxel-Induced Peripheral Neuropathy in Patients with Breast Cancer (NCT04205903)
Drug Name	Nilotinib, paclitaxel	
Cancer Types	Breast Cancer	
Implementing Institution	The Ohio State University Comprehensive Cancer Center	
Contact Details	OSUCCCClinicaltrials@osumc.edu, 1-800-293-5066	

4 Details On Mutant Genes

4 Detailed description of mutant gene

Marker	ABL1	Outline
		ABL1 encodes the Abelson tyrosine-protein kinase 1 protein, c-Abl, which is involved in cell growth and survival [PMID:20841568]. Activation of c-Abl has been reported in several tumor types, ascribed to either ABL1 activating mutations or overexpression [PMID:22307624, PMID:22521882, PMID:3856862, PMID:7665185]. The chromosomal translocation t(9;22)(q34;q11), resulting in the BCR-ABL1 fusion, has been reported as the hallmark of chronic myeloid leukemia (CML) [PMID:15719031, PMID:27069254, PMID:9808572].

5 References

Japan

Reference No.	Reference	Marker No.
■ 1	PMDA	No.1-1, 1-2, 1-3, 7-1, 7-2, 8-3, 8-4, 8-6, 11-1, 11-3, 11-4
■ 2	FDA	No.2-1, 8-1, 8-5, 10-1, 11-2, 11-6
■ 3	Cancer Genome Atlas Network "Comprehensive molecular characterization of human colon and rectal cancer." Nature(2012) PMID:22810696	No.1-4
■ 4	Cyriac Kandoth et al. "Integrated genomic characterization of endometrial carcinoma." Nature(2013) PMID:23636398	No.1-4
■ 5	Simona Soverini et al. "BCR-ABL kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European LeukemiaNet." Blood(2011) PMID:21562040	No.3-1

Overseas

Reference No.	Reference	Marker No.
■ 29	ABL tyrosine kinases: evolution of function, regulation, and specificity.	No.3, 8
■ 30	Cell lines and clinical isolates derived from Ph1-positive chronic myelogenous leukemia patients express c-abl proteins with a common structural alteration.	No.3, 8
■ 31	Efficient and rapid induction of a chronic myelogenous leukemia-like myeloproliferative disease in mice receiving P210 bcr/abl-transduced bone marrow.	No.3, 8
■ 32	Global tyrosine kinome profiling of human thyroid tumors identifies Src as a promising target for invasive cancers.	No.3, 8

6 Used software version

C-CAT CKDB	4.2.0
refGene	20191020
ensGene	v32(20191028)
1000 Genomes	Phase_3(20170504)
ESP6500	V2-SSA137
ExAC	r0.3
HGVD	v2.30(20170807)
ToMMo	3.5kjpnv2-20181105
COSMIC	v87(20181113)
ClinVar	20190114
Report Software Version	1.00
Layout Version	2.12

7 Evidence level definition

Criteria	Classification
There are approved drugs in Japan/FDA-approved drugs for the respective cancer, and treatment is described in the guidelines	A
Consensus among clinical trials, meta-analysis and experts, with a high statistical credibility regarding the respective cancer type	B
There are approved drugs in Japan/FDA-approved drugs for a different type of cancer/consensus among clinical trials, meta-analysis and experts, with a high statistical credibility regarding a different cancer type/efficacy has been demonstrated in small-scale clinical trials, iirrespective of the cancer type	C
Efficacy has been demonstrated in case reports, irrespective of cancer type	D
There are reports on efficacy in pre-clinical trials (*in vitro* and *in vivo*)	E
Known to be associated with cancer	F
In terms of involvement in drug resistance, statistical tests in clinical trials have demonstrated with a high degree of reliability that there is a drug-resistant variant	R1
In terms of involvement in drug resistance, there are reports of secondary resistant variants, which have been verified in cell experiments and structural analysis	R2
In terms of involvement in drug resistance, resistant variants have been evaluated in pre-clinical trials	R3

R1, R2, and R3 indicate evidence of resistance for drugs approved in Japan or by the FDA. Evidence on drug resistance in other types of cancer is marked with an asterisk (*).

[Drug Reachability Index]

1. There are approved drugs in Japan for the respective cancer.
2. There are clinical trials in Japan for the respective cancer.
3. There are approved drugs in Japan for other types of cancer (off-label use).
4. There are clinical trials overseas for the respective cancer.
5. There are FDA-approved drugs, irrespective of the type of cancer
6. Other.

8 US Evidence Level (AMP/ASCO/CAP Guidelines)

Strong Significance	Tier 1A	Biomarker predicts response or resistance to an FDA or EMA approved therapy,according to drug label or professional guidelines for this diagnosis Biomarker included in professional guidelines is prognostic or diagnostic for this diagnosis
	Tier 1B	Biomarker predicts response or resistance to a therapy for this diagnosis based on well-powered studies Biomarker is prognostic or diagnostic for this diagnosis based on well-powered studies
Potential Significance	Tier 2C	Biomarker is associated with response or resistance to an FDA or EMA approved therapy,according to drug label or professional guidelines but only for different diagnosis Biomarker is an inclusion criterion for an active clinical trial Biomarker is prognostic or diagnostic based on multiple small studies
	Tier 2D	Biomarker shows plausible response or resistance based on case or preclinical studies Biomarker may assist in disease diagnosis or prognosis based on small studies
Uncertain Significance	Tier 3	Biomarker has uncertain clinical significance and not known to be likely benign or benign

https://jmd.amjpathol.org/article/S1525-1578(16)30223-9/fulltext

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

9 Points To Note / Disclaimer

9注意事項・免責事項

○ C-CAT調査結果（以下「本調査結果」という。）は、エキスパートパネルにおいて臨床情報等と併せて衛生検査所等が発行する遺伝子パネル検査結果報告書の解釈と活用を検討するための参考資料として提供されるものです。

○ 本調査結果は、エキスパートパネルにおける検討に資するよう、がんゲノム情報管理センターが構築した知識データベースと商用データベース（QIAGEN Clinical Insight*1）を基に患者毎にゲノム解析結果に対して解釈・臨床的意義づけを行ったものですが、その活用に際しては、次の点に十分に注意をお願いします。

①本調査結果については、本国内において臨床検査として承認されたものではなく、現時点では臨床検査としての正確性が保証されたものではありません。その内容については、エキスパートパネルにおいて、適応性、妥当性、適時性などを判断の上で、活用する必要があります。

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③臨床試験に関して公開されている情報はゲノム医療を前提として記述されていないため、必ずしも遺伝子に紐付けされておらず、本調査結果において患者さんが参加可能な臨床試験を網羅的に掲載できていない可能性があります。また、掲載されている臨床試験が各患者さんに適応しているとは限りません。

⑭遺伝子パネル検査のパネル種別がFoundationOne Liquid CDxの場合、FoundationOne Liquid CDx解析結果レポートのOTHER ALTERATIONS & BIOMARKERS IDENTIFIEDに「# Variants in this gene may be derived from a nontumor source such as clonal hematopoiesis (CH).」と記載されている変異情報は、本調査結果で腫瘍由来の体細胞変異とみなして調査し、調査結果作成しております。

⑮本調査結果は、遺伝子パネル検査が生殖細胞系列変異を検査対象外としている場合は、変異情報を体細胞変異とみなして調査し、調査結果作成しております。

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⑰個々の治療は、患者に対する十分な説明を行った上で、個々の治療を直接担当する医師の責任及び判断に基づいて行うものであり、C-CATが治療に関する判断と結果、患者への説明について責任を負うものではありません。

*1 QIAGEN Clinical Insight (QCI™) is a variant analysis, interpretation and decision support tool for research and clinical labs analyzing human genetics data and is not intended to be used for diagnostic purposes.
米国エビデンスレベル、臨床試験および参考文献のうち海外と記載のあるもの、海外臨床試験中の数、変異遺伝子の詳細はQIAGEN Clinical Insight - Interpret 由来となります。

以上

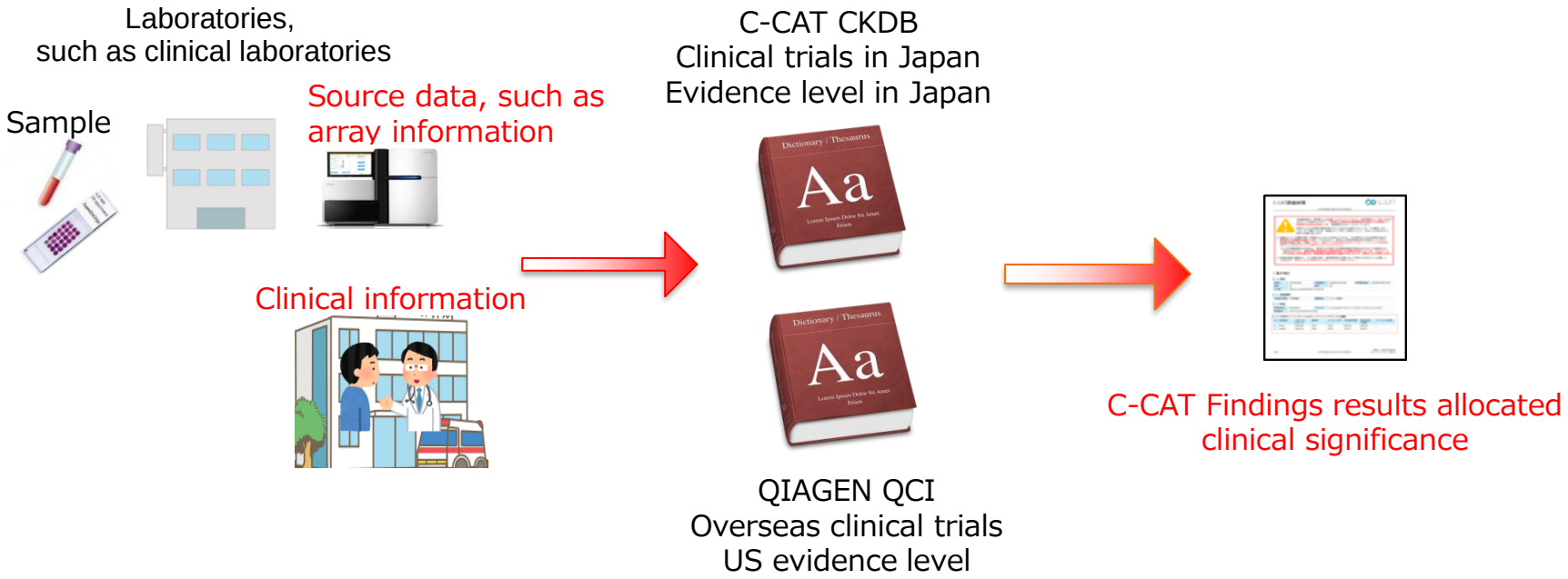
ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Knowledge Database

Knowledge database (Cancer Knowledge DataBase)

Generated image of the C-CAT Findings results (general overview)

The C-CAT Findings results are created for each patient after interpretation and allocation of clinical significance to the genome analysis results sent from laboratories, such as clinical laboratories, or Designated Core Hospitals for CGM, based on the knowledge database (Cancer Knowledge DataBase: hereinafter referred to as C-CAT CKDB) built by C-CAT and QIAGEN Clinical Insight (hereinafter referred to as QCI), a commercial service.

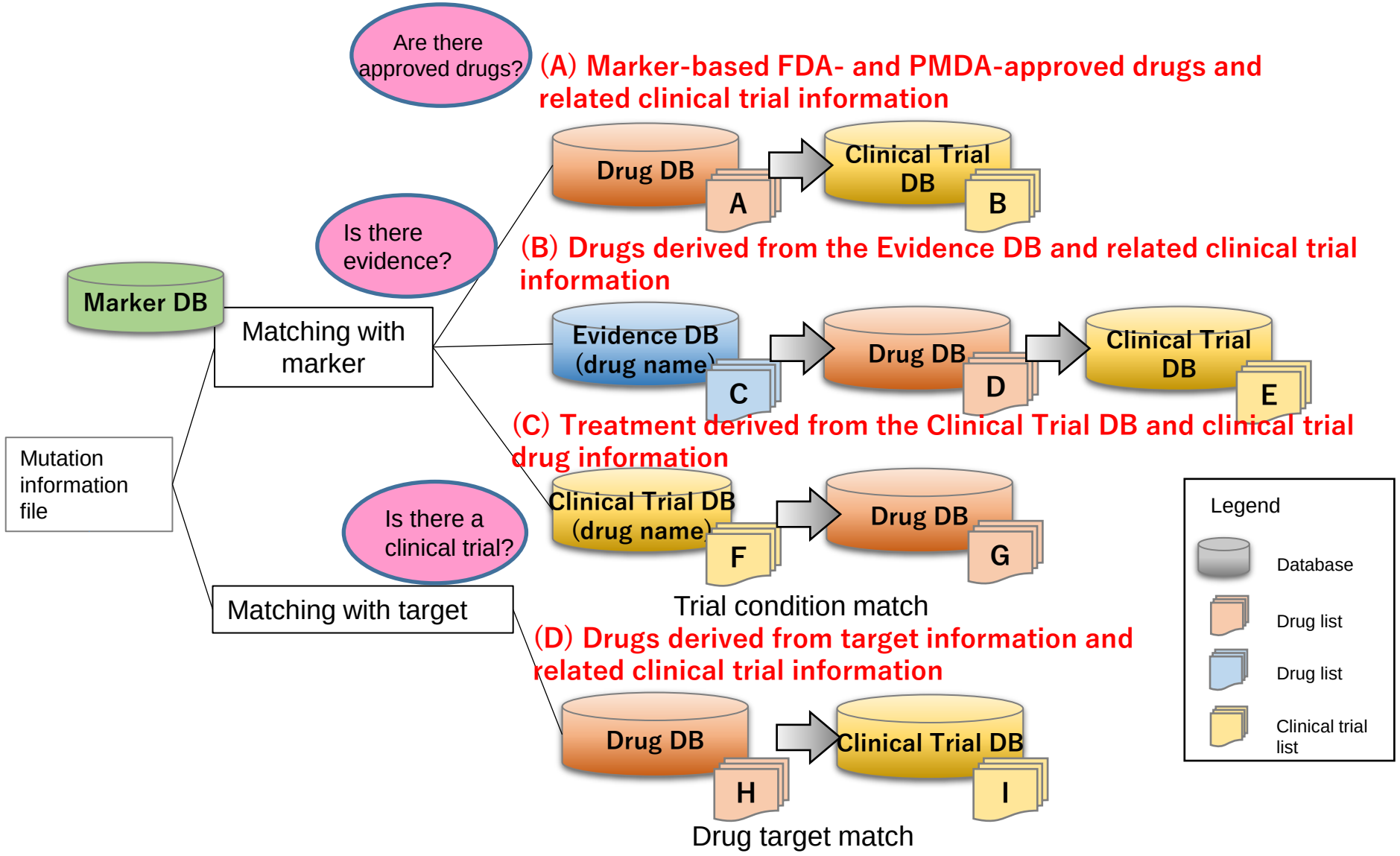


CKDB Database Structure

➢ C-CAT CKDB is comprised of the four databases shown in the table below.

Name of database	
Marker DB	List of cancer-related gene markers Example) EGFR T790M Example) BRCA1 germline mutation * In addition to single genetic mutations, some markers are a combination of two or more markers.
Drug DB	List of cancer-related drugs. Lists mainly cancer-related drugs that are approved in Japan, FDA-approved drugs, or drugs under development in Japan, arranged by approved target disease, markers, and target molecules
Evidence DB	Arranges predictive, prognostic, diagnostic, predisposing, and oncogenic evidence obtained from public databases (ClViC, BRCAExchange, ClinVar, COSMIC) and the NCC database * Diagnostic and prognostic evidence are not used in survey results
Clinical DB	List of cancer-related clinical trials in Japan. Lists cancer-related clinical trials from JAPIC, UMIN, JMACCT, jRCT, and ClinicalTrials.gov, arranged by drugs, diseases, and markers of interest.

C-CAT Findings Results Report Logic



Copy number variations

No.	Marker	Evidence type	Clinical significance	Evidence level	Drug	Reachability of drug	US evidence level
9	ERBB2 amplification	Predictive	Sensitivity/ response	A	Lapatinib	Approved drug in Japan Trial in progress in Japan (1 trial) FDA-approved drug	Tier 1A Pathogenic Trials in progress overseas (10 trials)

Copy number variations

No.	Marker	Evidence type	Clinical significance	Evidence level	Drug	Reachability of drug	US evidence level
14	ERBB2 amplification	Predictive	Sensitivity/ response	B	Trastuzumab emtansine	Off-label drug in Japan FDA-approved drug	Tier 2C Pathogenic Trials in progress overseas (10 trials)
		Predictive	Sensitivity/ response	C	Capecitabine + lapatinib	Off-label drug in Japan FDA-approved drug	
		Predictive	Sensitivity/ response	C	Capecitabine + trastuzumab	Off-label drug in Japan FDA-approved drug	

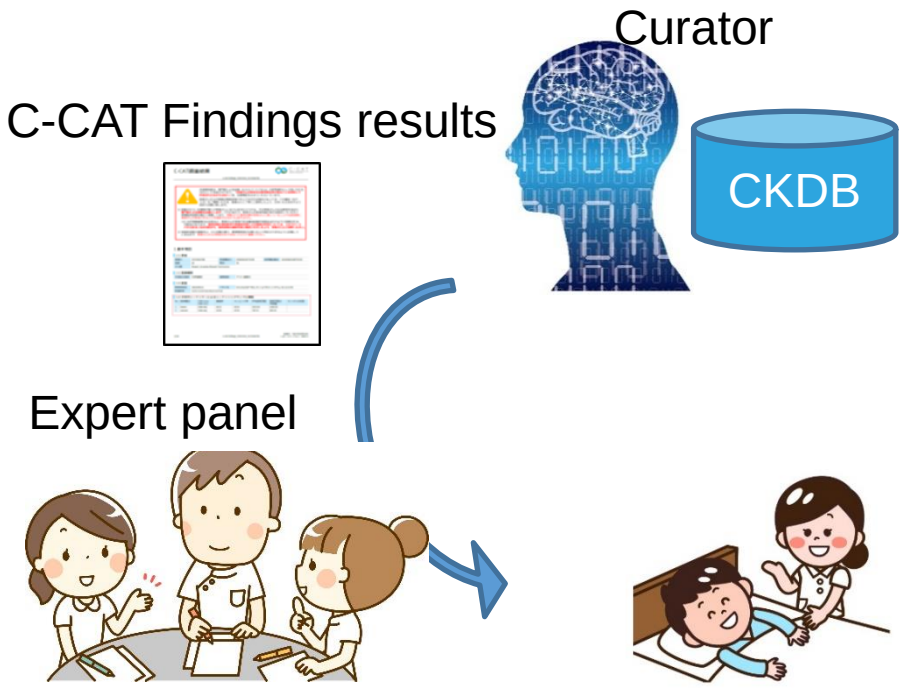
No.	Marker	Evidence type	Clinical significance	Evidence level	Drug	Reachability of drug	US evidence level
					NJH395 (trial condition match)	Trial in progress in Japan (1 trial)	

Marker no.	14-13	Trial Name (trial ID, date of data update)
Marker of interest	Her2-positive	An Open-Label Multicenter Collaborative Phase I Dose Setting Study on Intravenous Administration of NJH395 in Patients with HER2 Positive Advanced Malignancies Other Than Breast Cancer
In Japan/overseas	In Japan	
Phase	Phase 1	
Drug name	NJH395	
Cancer types	HER2-positive advanced malignancies other than breast cancer	
Implementing institution (contact details)	Novartis Japan (0120-003-293)	

No.	Marker	Evidence type	Clinical significance	Evidence level	Drug	Reachability of drug	US evidence level
14	ERBB2 amplification				Pertuzumab (drug target match)	Off-label drug in Japan Trial in progress in Japan (1 trial) FDA-approved drug	

CKDB Curation

- Established CKDB (Cancer Knowledge Database), refines creation of C-CAT Findings results
- Started in February 2019
- Promotes clinical trials in Japan
- Ultimately gives back to patients



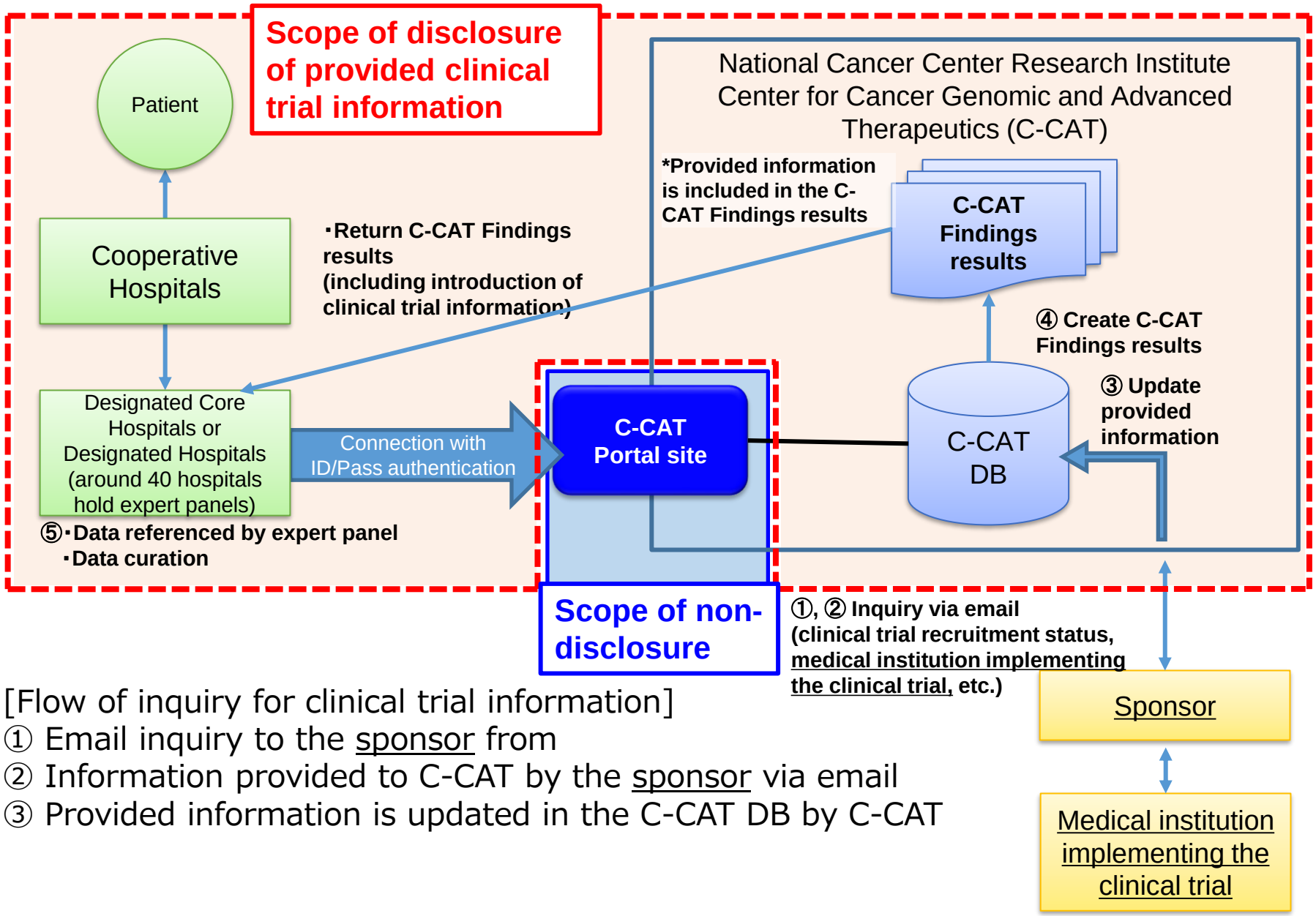
- Literature information (150,000 evidence examples)
- Clinical trial information (752 clinical trials in Japan)
- Drug information (1208 drugs)
- Cancer disease information

Drug trials targeting cancer that have not published details on marker conditions

→ **Unique interpretation of specific gene mutations for each marker**

Title of the study	
Item	Japanese
Scientific title	Phase II Study on Olaparib Monotherapy for Treated Homologous Recombination Repair Gene Mutations (HRRm) or Homologous Repair Deficiency (HRD) Positive Advanced Cancer
Public title	Olaparib monotherapy for HRRm or HRD-positive cancer
Investigative drug	
Item	Japanese
Investigational material	Medicine
Investigational materials	
Generic name, etc.	Olaparib
INN of investigational material	Olaparib Olaparib monotherapy for HRRm or HRD-positive cancer
Investigational material: medicine: therapeutic category code	429/other antitumor agents
Dosage and administration for investigational material	Administer olaparib 300 mg twice per day (BID)

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

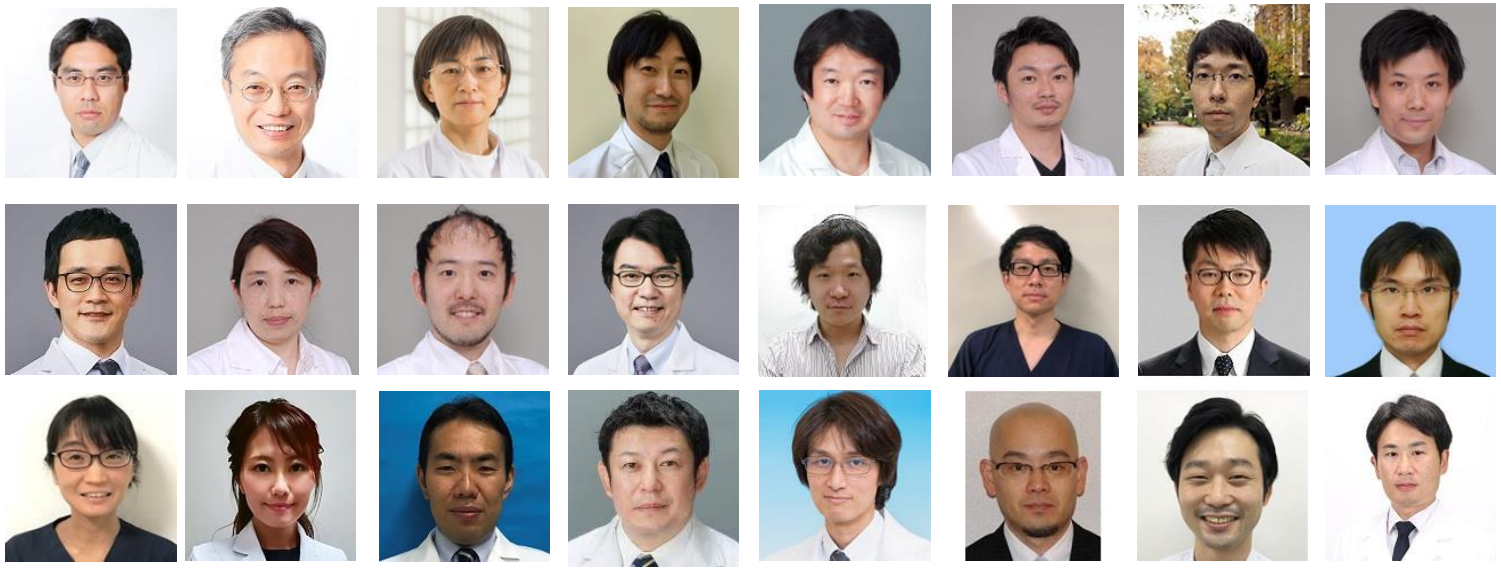


[Flow of inquiry for clinical trial information]
① Email inquiry to the sponsor from
② Information provided to C-CAT by the sponsor via email
③ Provided information is updated in the C-CAT DB by C-CAT

2021 Curators

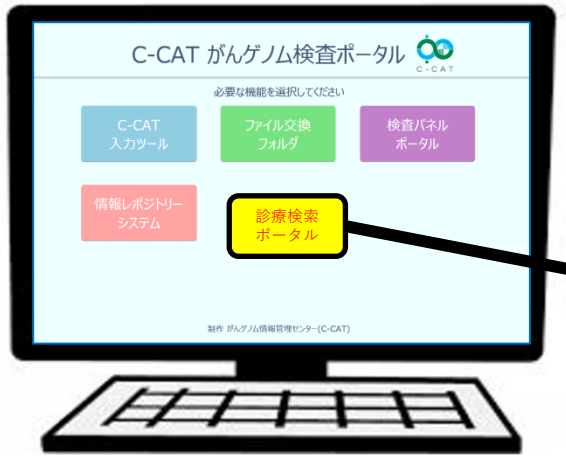
2021 Curators 31 people

Hokkaido University Hospital Clinical Research and Medical Innovation Center	Toraji Amano
Division of Clinical Cancer Genomics, Hokkaido University Hospital	Ichiro Kinoshita
Division of Clinical Cancer Genomics, Hokkaido University Hospital	Junko Kikuchi
Department of Medical Oncology, Tohoku University Hospital	Keigo Komine
National Cancer Center Hospital East	Yoichi Naito
Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital	Akihiro Oba
Department of Diagnostic Pathology, National Cancer Center Hospital	Junpei Kashima
Department of Medical Oncology, National Cancer Center Hospital	Yuki Kojima
Department of Thoracic Oncology, National Cancer Center Hospital	Yuki Shinno
Department of Pediatric Oncology, National Cancer Center Hospital	Kayoko Tao
Department of Gastrointestinal Medical Oncology, National Cancer Center Hospital	Hidekazu Hirano
Department of Hematology, National Cancer Center Hospital	Suguru Fukuhara
Department of Thoracic Oncology, National Cancer Center Hospital	Hidehito Horinouchi
Division of Cancer Genomics, National Cancer Center Research Institute	Akihiko Fukagawa
Division of Cancer Genomics, National Cancer Center Research Institute	Yuya Kobayashi
Division of Cellular Signaling, National Cancer Center Research Institute	Tsuyoshi Hirose
Division of Cellular Signaling, National Cancer Center Research Institute	Yosuke Tanaka
Division of Cellular Signaling, National Cancer Center Research Institute	Mitsuru Yanagaki
Division of Cellular Signaling, National Cancer Center Research Institute	Hiroshi Hirose
Department of Clinical Laboratory, The University of Tokyo Hospital	Kousuke Watanabe
Department of Respiratory Medicine, The University of Tokyo Hospital	Yosuke Amano
Department of Pediatrics, The University of Tokyo Hospital	Yoshiko Nakano
Genomics Unit, Keio Cancer Center, Keio University School of Medicine	Mitsuho Imai
Genomics Unit, Keio Cancer Center, Keio University School of Medicine	Hideyuki Hayashi
Advanced Medical Development Center, Cancer Institute Hospital of JFCR	Takahiro Kogawa
Division of Integrated Facilities, Center for Innovative Cancer Treatment, Tokyo Medical and Dental University Hospital	Sadakatsu Ikeda
Gastroenterological Surgery 1, Nagoya University Hospital	Toshio Kokuryo
Osaka University, Graduate School of Medicine, Department of Gastroenterological Surgery	Norikatsu Miyoshi
Department of Otorhinolaryngology, Okayama University Hospital	Mizuo Ando
Department of Hematology, Oncology & Cardiovascular medicine, Kyushu University Hospital	Mamoru Ito
Department of Respirology, Kyushu University Hospital	Eiji Iwama



Medical Search Portal

Mechanism of using information collected by C-CAT for medical care by hospitals conducting cancer genomic medicine



New functions will be added to the C-CAT cancer genome test portal

Medical search portal
(The data cannot be used for academic conferences or dissertation presentations)

Medical information **C-CAT integrated data**

Classification	Item*
Basic patient information	Hospital code, sex, age, cancer type classification, etc.
Specimen information	Test type, tumor cell ratio, collection site, etc.
Patient background	Pathology diagnosis name, smoking history, ECOG-PS, family history, etc.
Cancer type information	Where there is metastasis, genetic test results, etc.
Drug therapy Before and after panel	Drug name, start/end date Best overall effect, adverse events, etc.
Outcome	Outcome, last confirmed survival date, date of death, cause of death

Mutation information **Genetic mutations reported by tests covered by insurance**

Medical search portal (β version scheduled to start by end of September 2020)

Free search using a combination of medical care and genetic information
⇒ Display/download results

No charge

Ethical review not needed

⇒ Consider treatment strategy, medical cooperation/patient transfer support

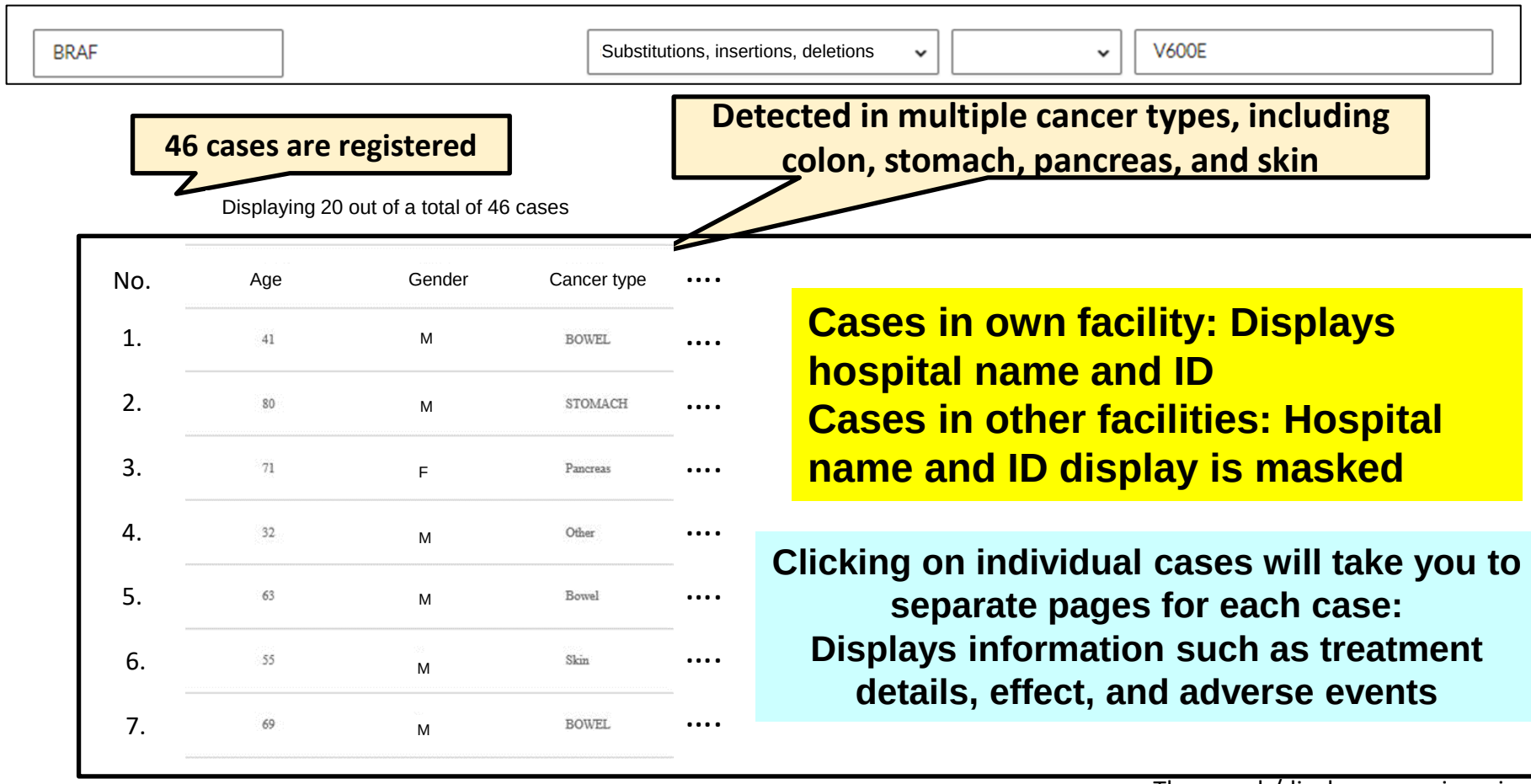
Data from patients who did not provide consent for secondary use of data are also included
→Cannot be used for academic conferences or dissertation presentations

Example) The BRAF_V600E mutation is detected in your patient with cancer

→ Is the mutation common in this type of cancer?

→ What type of treatment is used?

Nationwide search of all cancer types with BRAF_V600E mutation



The search/display screen is an image

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Clinical Trial Update Function

Clinical trial update results (number of clinical trials)

Update number	CKDB updates	Number of clinical trials	Number of new clinical trials
First	First update of 2021	774	70
Second	First update of FY2021	790	64
Third	Second update of FY2021	786	54
Fourth	Third update of FY2021	792	39
Fifth	Fourth update of FY2021	804	45

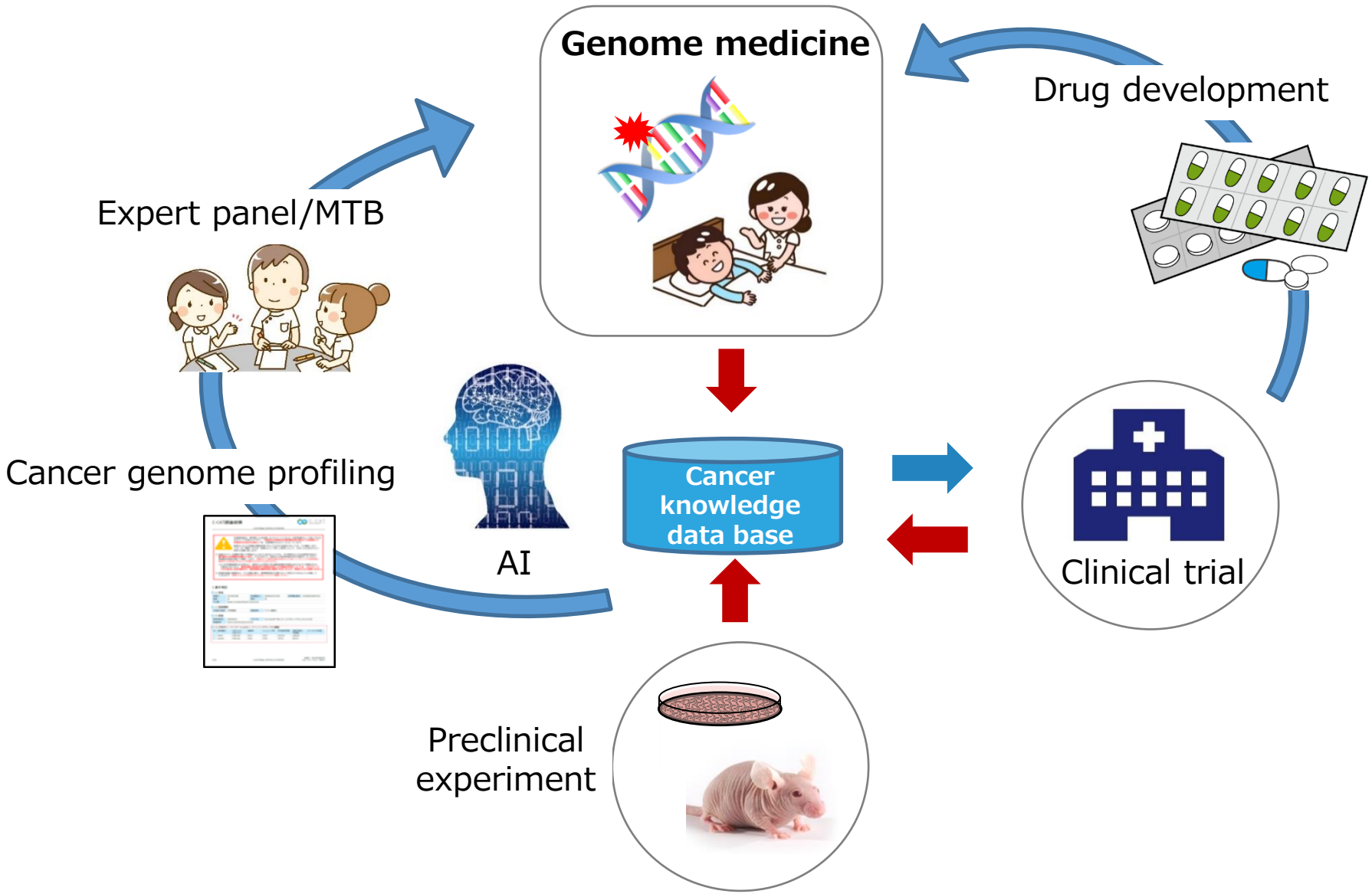
ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Clinical Trial Update Function Actual Example

A clinical trial related to the drug sotorasib was newly registered in the third CKDB update in 2021. Updating information on clinical trials using CKDB newly matched sotorasib to 151 of 11,951 cases.

Reference study ID	jRCT2031210121
Title of trial	Study on Sotorasib Activity in Patients with Advanced Solid Tumors with KRAS p.G12C Mutation (CodeBreaK101)
Sponsor	Amgen K.K.
Study outline	Evaluation of Safety and Tolerance when Sotorasib is Administered in Combination with Various Regimens in Patients with Advanced Solid Tumors with KRAS p.G12C Mutation
Phase	Phase 1/2
Name of disease	Advanced solid tumors with KRASp.G12C mutation
Investigational drug	Sotorasib
Eligibility criteria	• Male or female patients aged 18 years and older • Patients with pathologically confirmed or recorded locally advanced or metastatic malignant tumor, confirmed to be positive for the KRAS p.G12C mutation through molecular testing
Exclusion criteria	• Primary brain tumor • Patients with spinal cord compression, untreated, symptomatic or active brain metastasis, or carcinomatous meningitis brain metastasis caused by tumors other than a brain tumor • Myocardial infarction within 6 months before day 1 • Digestive disease that would make it difficult to take oral medication
Study progression status	Recruiting
Implementing medical institution	Amgen K.K., National Cancer Center Hospital East
Study classification	Clinical trial

Future Of Genome Medicine



Thank You!