Towards High-quality Clinical Trials And
Implementation Of Genomic Medicine

ATLAS Training Program

Course : Administrative perspectives and staffing to conduct genomic medicine

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EDUCATION

Osaka University, Japan (1991 - 1997)

WORK EXPERIENCE

Resident/Staff, Department of Gastroenterology and Hepatology, Osaka University and affiliated hospital (1997-2005)

Chief Resident, Department of Gastrointestinal Oncology, National Cancer Center Hospital (2005 - 2008)

Reviewer, Office of New Drug V, Pharmaceuticals and Medical Devices Agency (2009 - 2013)

Medical Staff, Division of Gastrointestinal Oncology, National Cancer Center Hospital (2013 - 2015)

Deputy Director, Health Service Division, Ministry of Health and Labour and Welfare (2015-2017)

Section Chief, Clinical Research Support Office, National Cancer Center Hospital (2017-2021)

Division Chief, Clinical Research Support Office, National Cancer Center Hospital (2021-)

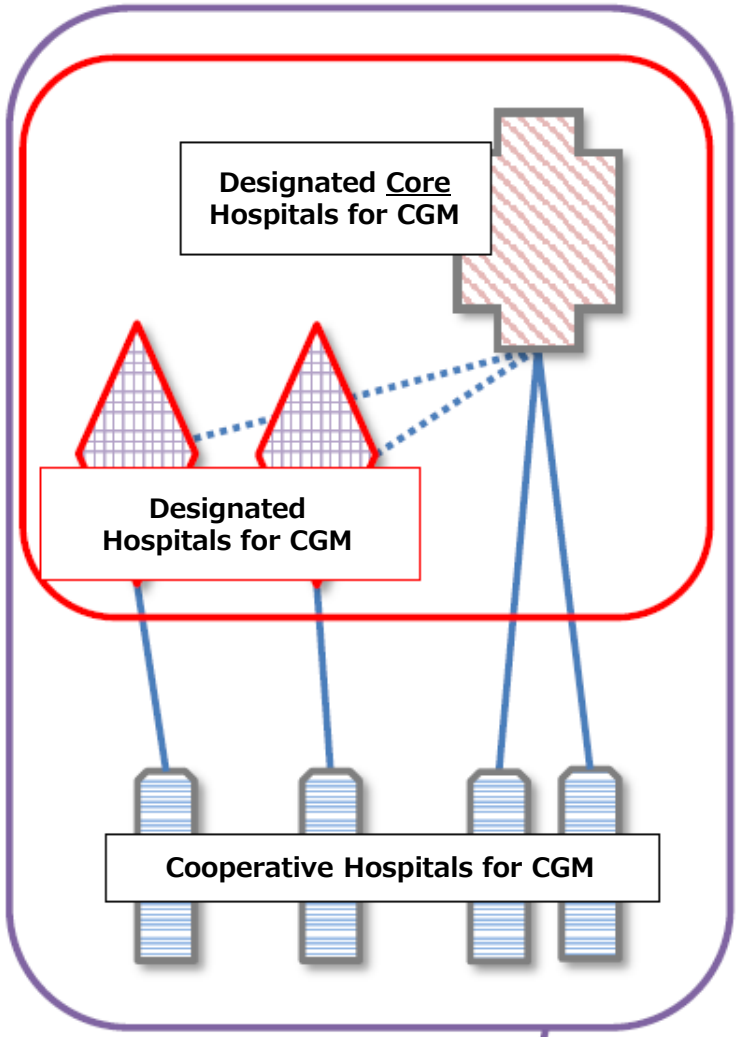
Goals

- To understand the facilities and personnel required to implement genomic medicine.
- To understand the structure of medical care systems involving genomic medicine.
- To understand treatment options based on genomic testing.

Content

- Japan's system for providing cancer genomic medicine
- Flow of oncogene panel testing and required system and personnel
  - ✓ Informed consent
  - ✓ Sample selection and preparation
  - ✓ Specimen submission and receipt of reports
  - ✓ Expert panel
  - ✓ Explanation of results and selection of treatment
  - ✓ Genetic counseling
- Building a collaborative system, such as establishment of supervising departments and committees
- Genomic testing and treatment based on results

Japan's System For Providing Cancer Genomic Medicine



Informed consent, testing → Specimen preparation → Sequencing → Expert panel → Report preparation → Explanation of treatment → Medical care ⇢ Clinical trials, advanced medical care, R&D

Employee development

	Informed consent, testing, specimen preparation	Sequencing	Expert panel	Report preparation	Informed consent	Medical care	R&D	Employee development
Core	Essential	May be outsourced	Essential		Essential	Essential	Essential	Essential
Hospital	Essential	May be outsourced	Essential		Essential	Essential	CH	CH
CH	Essential	May be outsourced	Participate in expert panels held at Designated Core Hospitals or Designated Hospitals for CGM		Essential	Essential	CH	CH

Designated Core Hospitals for CGM or Designated Hospitals for CGM apply for Cooperative Hospitals for CGM *

CH: Cooperative hospital

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

Main Qualifying Requirements For Designated Core Hospitals For CGM (Facility)

The facility should have:

- A pathology laboratory with third-party certification.
- An established department that conducts genetic counseling and has a collaborative system with other clinical departments.
- An established department that manages information related to cancer genomic medicine.
- A system for providing information to the Center for Cancer Genomics and Advanced Therapeutics (C-CAT).
- A system for appropriate storage and management of biological samples, including surgical specimens of different organs.
- An established department to oversee cancer genomic medicine.
- A system able to provide information to patients.
- An established department for medical safety management.

Main Qualifying Requirements For Designated Core Hospitals For CGM (Personnel)

The personnel should include

- Doctors with specialized knowledge and skills in pathology.
- Clinical laboratory technicians with advanced expertise in handling pathology specimens.
- Doctors with specialized knowledge and skills in genetics.
- Staff with specialized genetic counseling skills related to genetic medicine.
- Staff to provide supplementary explanations on gene panel tests and collaborate with departments that provide genetic counselling.
- Staff to manage clinical information and genomic information related to cancer genomic medicine.
- Specialists with sufficient knowledge on molecular genetics and cancer genomic medicine.
- Specialists with sufficient knowledge on bioinformatics when sequencing is performed in-hospital.

Flow Of Oncogene Panel Testing And Required System And Personnel

Informed consent and testing

Doctor/nurse (provision of supplementary explanation)
Administrators (medical accounting/medical information)

Sample selection and preparation

Pathologist/clinical laboratory technician

Specimen submission and receipt of report

Clinical laboratory technician and administrators (information management)

Outsourced tests

Analysis

Reference/judgement using suitable DB

Test report

Expert panel

Pathologist, molecular geneticist, oncologist, medical geneticist, genetic counselor, and administrators

Explaining results and selecting treatment

Doctor/nurse (assist explanation)
Medical geneticist, genetic counselor
Administrators (medical accounting)

Establish an overseeing department; Build a collaborative system; Establish committees

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

Oncogene Panel Testing Explanatory Document And Consent Form

- Creating explanatory documents and consent forms: A template* is created and prepared for electronic medical records

* In Japan, there is a model document that has been examined by the national council

[Content of explanatory documents]

- ✓ Purpose of the test, advantages and limitations (including potential treatment)
- ✓ Test methods
- ✓ Possibility of detecting a hereditary tumor
- ✓ Number of days required to explain the results and whether the informationあ can be explained to the patient's family
- ✓ Handling genomic data (collection and use of information, use in the testing company)

[Content of consent forms]

- ✓ Consent related to the test
- ✓ Whether the information can be explained to the patient's family
- ✓ Whether information on hereditary tumors should be provided
- ✓ Whether the data will be provided to and used by third parties
- ✓ Whether the data can be used by the testing company

(Procedures for changing decision)

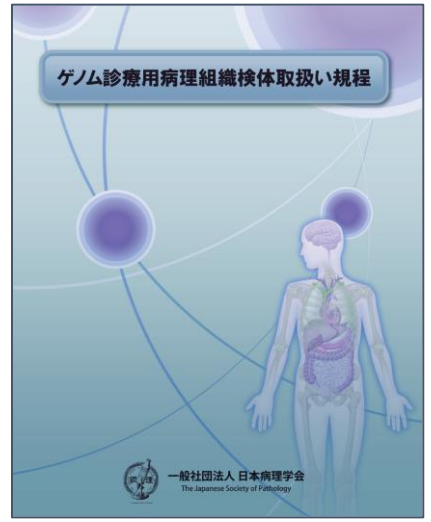
- Explaining the test and obtaining consent: Doctor
- Providing supplementary explanation about the test: Nurse, CRC, etc. (for research)
- Storage of consent forms

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

Establishing A System For Ordering Tests

- Organize the content required for gene panel test inspection; consider whether orders for testing should be created using an online database or paper forms, and determine details (who, what, when) of order placement.
- When using pathology specimens, there are two separate procedures: ① checking the suitability of the specimen (for e.g., tumor cell ratio measurement) and ② conducting the gene panel test, and these may be ordered together or separately.
- Appropriately link both specimens for TN paired tests, which require both pathology and blood specimens.
- Establish a system that links with the accounting system.
- Required personnel
  - ➢ Clinical laboratory technician: Organizes the content required for test orders
  - ➢ Medical information department: Establishes the ordering system.

Selection And Preparation Of Histopathologic Specimens



- Required procedures
  - Appropriate fixing and storage during sampling
  - Sample selection (considering how long the sample has been stored so far, etc.)
  - Tumor cell ratio measurements
  - Sample preparation for specimen submission (compliance with procedures to avoid contamination)
- Required personnel
  - Pathologist: Diagnosis of suitability of pathology specimens
  - Clinical laboratory technician: Collection and processing of blood specimens; preparation of pathology specimens

Specimen Submission And Receipt Of Report

- The specimen and request form are submitted in accordance with the regulations of the testing company.
- The test data is returned from the testing company's portal site and is then appropriately received and stored.
- Necessary information, such as genomic information and clinical information, is collated for each patient to enable consideration by the expert panel.

- Required personnel
  - Clinical laboratory technicians: Submission of specimen and request form, receiving test data
  - Medical information department staff: Establishes a system to manage data safely

C-CAT Survey Results


C-CAT調査結果

c-cat-findings_20211119_5123456789

本調査結果は、専門家による会議（エキスパートパネル）の参考資料として用いられるものとして作成されており、「患者さんが原本又は複写物を受け取ることを想定して作成されたものではない」旨、注意喚起をさせていただいています。

患者さんからの情報公開請求等に応じて交付する場合にあっては、この趣旨（以下2.6）をご理解いただき、患者さんに丁寧にご説明した上で、交付いただきますよう改めてお願い致します。

① 記載されている情報が個々の患者さんに当てはまるかどうかは、その患者さんの主治医等を含めた専門家による解釈を必要とします。これにあたり、患者さんが参加可能か否かを検討していただく候補臨床試験を幅広く掲載しており、掲載された臨床試験が患者さんに適しているここや当該臨床試験に患者さんが参加できることを保証するものではありません。

※C-CAT調査結果のみを見ると、患者さんが参加できる臨床試験が多数あるかのように誤解される可能性があります。臨床試験の適格条件や実施状況等による登録の可否については、エキスパートパネルあるいは主治医から、臨床試験の連絡先等に確認いただいた上で、患者さんにご説明ください。

② 各臨床試験の連絡先は、①に記載の通り、医療関係者が必要に応じて照合せできるように記載しているもので、患者さんからの問合せ先ではないことにご留意ください。

1 基本項目

1-1 患者

登録ID	5123456789	患者識別ID	00NOA18073105	検体識別番号	1616006918073100
年齢	62	性別	女		
がん種	Breast, Invasive Breast Carcinoma				

1-2 医療機関

中核拠点病院	大学病院E
連携病院	テスト病院E1

1-3 検査

検体採取日	2020/05/11	パネル名	OncoGuide™ NCC オンコパネル システム ver.2.01-00
検査検体	tumor and matched-normal		

1-4 次世代シーケンサーによるシーケンシングサンプル情報

No.	検体種別	DNA-seq/RNA-seq	重複率	マッピング率	平均読取深度	読取深度の中央値	サンプルの状態
1	tumor	DNA-seq	40.12	92.34	1612.00	1582.00	
2	normal	DNA-seq	26.00	92.38	765.20	682.00	

- In Japan, the Center for Cancer Genomics and Advanced Therapeutics (C-CAT) publishes the results of C-CAT surveys as reference data for gene panel test results, using information from patients who consented to collection of genomic information.
- The C-CAT survey results include the evidence level of the genetic mutation and information on related clinical trials. This information must be referred to during consideration by the expert panel.
- Required personnel
  - Clinical laboratory technicians: Receives and stores C-CAT survey results
  - Medical information department staff: Establishes a system to manage data safely

System Required To Conduct Expert Panels

- Clinical information and reports are checked in advance by the core members (for e.g., doctors and researchers well-versed in molecular genetics, clinicians involved in early clinical studies, and clinical geneticists), the results are interpreted, and an evidence level is allocated using various genome databases and clinical trial databases, as needed.
  - Genome databases: COSMIC, gnomAD, etc.
  - Clinical trial databases: ClinicalTrials.gov, NIPH Clinical Trials Search, etc.
- When conducting an expert panel via a Web conference with a Cooperative hospital, it is necessary to use a web conference system and data sharing system that satisfies security standards.
- Contracts are signed with Cooperative hospitals to agree on matters such as handling of personal information and cost burden.

Expert panel

- The expert panel considers the following to appropriately interpret the results of the gene panel test:
  - The quality of the specimen and analysis data
  - The patient's clinical information
  - The significance of genetic anomalies
  - Corresponding therapeutic drug and level of evidence
  - Candidate drugs (including investigational drugs)
  - How to deal with secondary findings, if detected
- Members
  - Clinician (attending physician)
  - Clinician involved in early clinical trials
  - Pathologist
  - Genomic researchers and doctors familiar with molecular genetics
  - Clinical geneticists
  - Certified genetic counselor
  - Bioinformatician; When conducting sequencing in-hospital

Held once a week.
In each session, 25 to 40 cases are examined in 1 to 1.5 hours.
Discussions are held via web conferences with Cooperative hospitals.

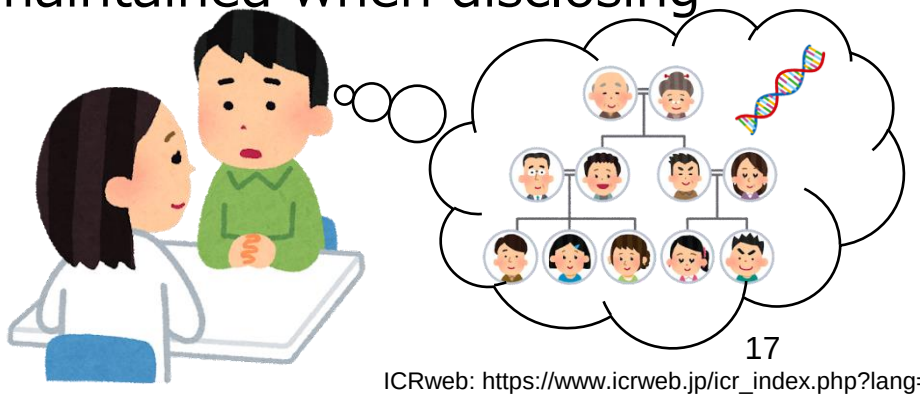
***In the National Cancer Center Hospital**

Explaining Test Results, Selecting Treatment

- Treatment strategies are decided by the attending physician depending on the patient's condition, test results, and expert panel report.
- The test results* are handed to the patient, and the doctor explains their interpretation of the results and the recommended treatment.
  * The expert panel report and C-CAT survey results are subject to medical record disclosure, so they are not given directly to the patient.
- The patient is referred to departments that provide genetic counseling, if necessary.
- Required staff organization
  - Clinician: Confirms test results, decides and explains treatment strategies to patients
  - Nurse/cancer genomic medicine coordinator: Supplementary explanation, collaboration with other departments

Genetic Counseling

- Using the explanatory document and other information, it is essential to explain in advance about the possibility of discovering secondary findings related to germline mutations, such as hereditary tumors.
- It is also vital that personnel with specialized knowledge in the interpretation of germline genetic mutations participate in the expert panel.
- If secondary findings are suspected based on the results of the gene panel test, a system should be established whereby the patient can receive specialized genetic counseling if they desire.
- A system that enables definitive testing and support for relatives should be established, if needed.
- It is necessary to secure a place where privacy is maintained when disclosing the results.
- Required personnel
  - Clinical geneticist
  - Genetic counselor

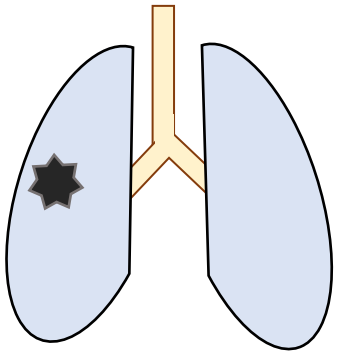


Establishing Departments And Committees To Oversee CGM

- Various departments and personnel are involved in the implementation of cancer genomic medicine
- Various issues arise in each department and linked system; therefore, a committee comprising all involved personnel should be established to identify and resolve issues faced by the members.
- A department should be established to oversee the processes and personnel involved in genomic medicine.
- Committee members
  - Doctor (molecular genetics, clinical geneticists, pathologists, oncologists, clinical researchers)
  - Clinical laboratory technician (clinical laboratory department, pathology department)
  - Nurse
  - Pharmacist
  - Genetic counselor
  - Medical information department staff
  - Social worker
  - Administrators

Current State Of Genomic Testing And Result-based Treatment In Japan

Oncogene panel testing



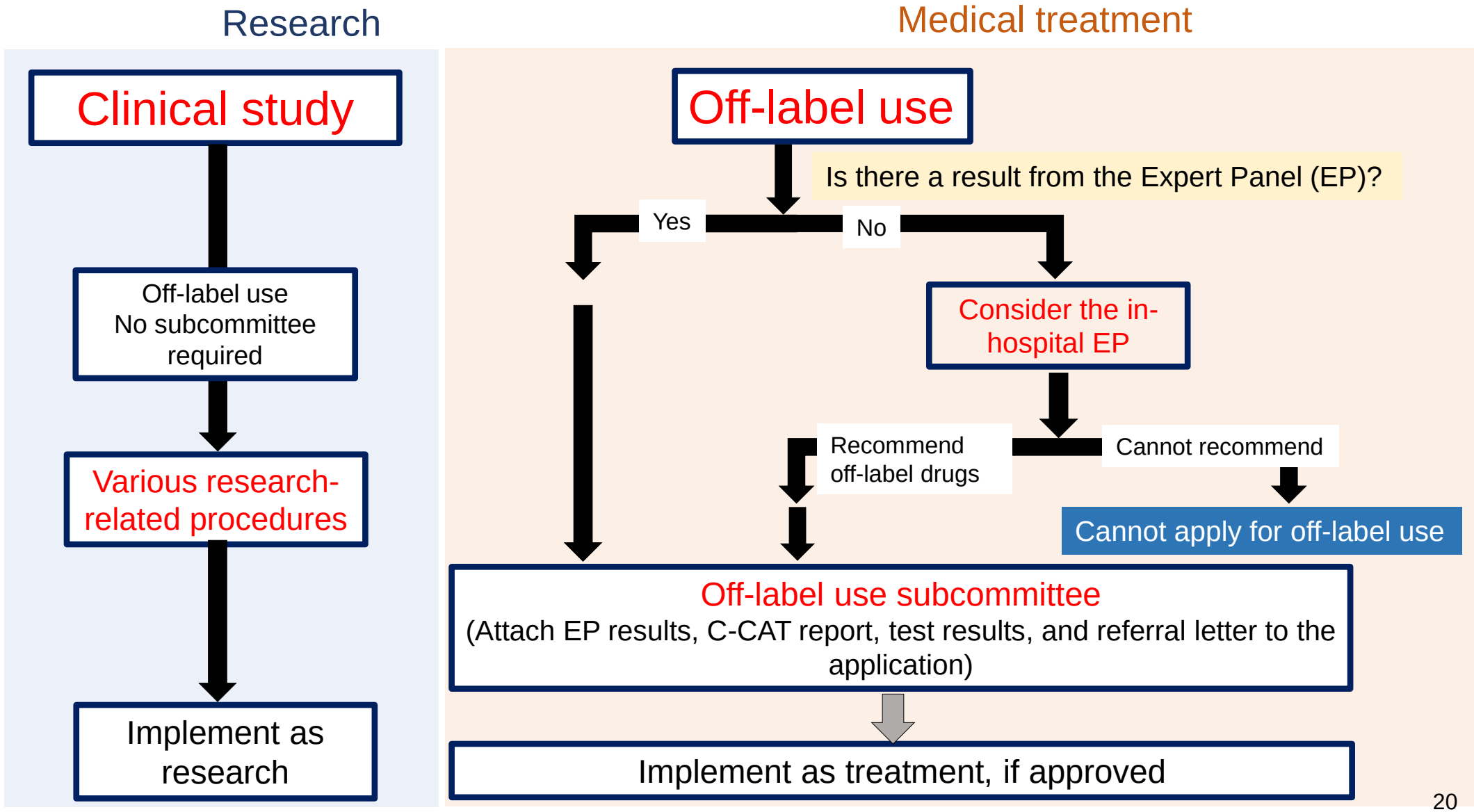
Report

Patient ID: xxx

Genetic aberrations: **XX gene abnormality**

- Implement medical treatment covered by insurance
- Participate in clinical trials, clinical studies (advanced medical care)
- Patient-proposed healthcare services
- Off-label use (application to institutional review board)

In-hospital System For Consideration Of Off-label Use



Promoting Registration In Clinical Trials After Gene Panel Testing

- Utilize list of clinical trials for C-CAT survey results
- Distribute list of clinical trials conducted at this hospital to affiliated Cooperative Hospitals for CGM
- Utilize clinical trial information sites
  - ClinicalTrials.gov (https://clinicaltrials.gov/)
  - NIPH Clinical Trials Search (https://rctportal.niph.go.jp/en)

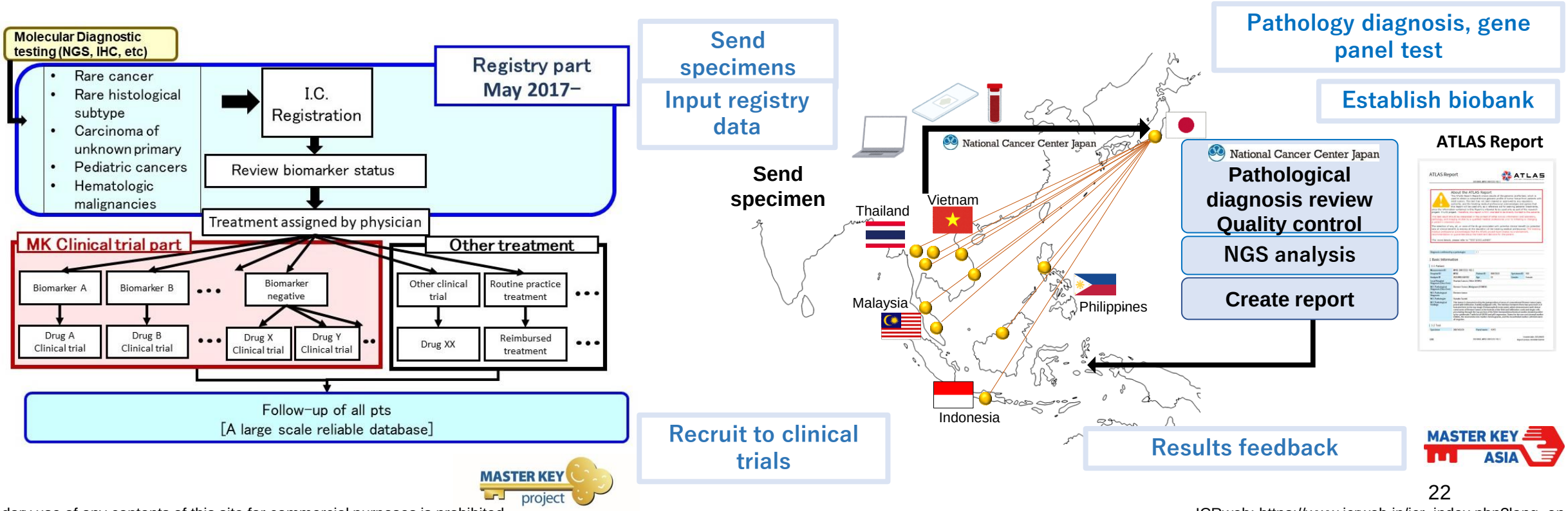
→ Connect more patients to treatment by sharing the necessary information among affiliated hospitals

- Plan and implement physician-led clinical trials based on genomic information
  - MASTER KEY Project
  - BELIEVE (NCCH1901) study (patient-proposed healthcare services)

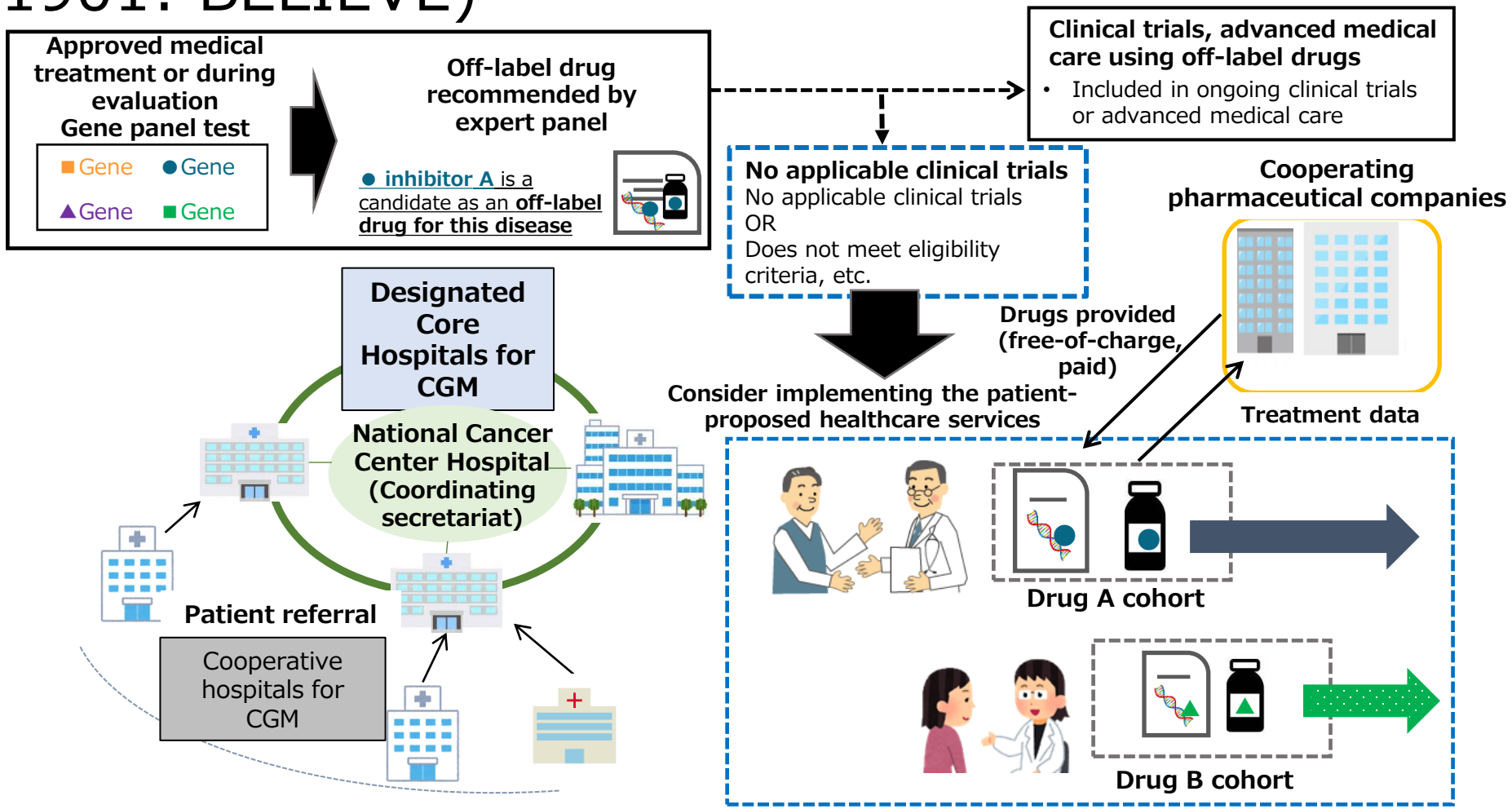
→ It is essential for academia to also formulate and implement clinical trials to develop new therapies

MASTER KEY Project

- A quality-controlled rare cancer registry and multiple clinical trials aiming for regulatory approval will operate in parallel to promote development of therapeutic drugs for rare cancers.
- Expanding to five Asian countries as MASTER KEY ASIA.



Patient-proposed healthcare services: Using multiplex gene panel tests
Molecular-targeted treatment based on genetic profiling (NCCH1901: BELIEVE)



Summary

- The genomic medicine provision system in Japan stipulates several facility requirements, including the need for quality-controlled pathology laboratories and proper data management, and personnel requirements, including having experts in various fields such as pathology, genetic medicine, and molecular genetics.
- A department must be established to oversee management, build a collaborative system with related departments, maintain function, and assign the personnel required for the smooth flow of genomic medical care.
- Treatment options based on genomic information are limited; thus, it is essential to actively promote registration in clinical trials and promote planning and implementation of new clinical trials.