EDITORIAL

Genomic medicine in clinical practice: national genomic medicine program in Japan

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Cancer statistics in Japan

Cancer is the most common cause of death in Japan based on Statistics 20211. Since statistics were first gathered, infectious diseases, such as tuberculosis, and cerebrovascular disease have been the main causes of death in Japan. Cancer surpassed cerebrovascular disease as the main cause of death in 1981, and the number of cancer deaths has increased. Approximately 38,000 people died of cancer in 2021. The National Cancer Center (NCC) reported that the 5-year survival rate for patients with cancer was improving (62% for males and 66.9% for females) in a population-based cancer registry.

Basic plan to promote the cancer control program

The Cancer Control Act was established in 2006 and was amended in 2016 by the National Diet of Japan to promote cancer control measures comprehensively and systematically2. Based on this act, the 1st term of the Basic Plan to Promote the Cancer Control Program was formulated in 20063. In 2017, the 3rd term of the Basic Plan to Promote the Cancer Control Program2 was formulated to enable Japanese to understand and overcome cancer. The overall goals of the 3rd term of the Basic Plan to Promote the Cancer Control Program were improvement of cancer prevention and screening based on scientific evidence, realization of patient-oriented cancer medicine, and establishment of a society where patients can live with cancer. The concrete strategies are cancer prevention, improvement of cancer treatment, living with cancer, and development of a foundation to support the first three parts. Cancer genomic medicine (CGM) was set at the top of the list for improvement of cancer treatments. In this review, we summarize how CGM has been established and developed in Japan.

The Ministry of Health, Labour, and Welfare (MHLW) addressed six elements to promote CGM, as follows:
1. Establish a system for providing CGM
Core hospitals for CGM should be established to provide and lead CGM.
2. Establish a system to aggregate and use genomic information
A Center for Cancer Genomics and Advanced Therapeutics (C-CAT) should be established as a hub for CGM, and Japanese genomic information should be aggregated in this center.
3. Consider insurance coverage of genomic tests and related pharmaceuticals
Comprehensive Genomic Profiling (CGP) tests should be covered by the national health system, as well as related pharmaceuticals.
4. Develop human resources in CGM
Human resources required for CGM are important to implement and support CGM.
5. Promote research in cancer genomics
Promoting research using genomic information is essential to develop CGM.

6. Build up a consortium with experts, patients, and citizens
A Cancer Genomic Medicine Promotion Consortium should be established to construct a system that examines the promotion of CGM with the participation of not only medical professionals, but also patients and the public.

Cancer Genomic Medicine Promotion Consortium

The Council of Cancer Genomic Medicine Promotion Consortium was established in 2018. An overview of this Council is shown in Figure 1.

Patients, the general public, pharmaceutical companies, and research organizations (universities and medical hospitals) participated in this consortium. CGM was discussed from each participant’s perspective, and the consortium collaborated with regulatory authorities as needed.

CGP tests

Two gene panel tests were covered by the national health insurance in Japan in June 2019 [the OncoGuide™ NCC Oncopanel System (Sysmex Corporation) and the FoundationOne® CDx Cancer Genomic Profile (Chugai Pharmaceutical)]. The FoundationOne® Liquid CDx Cancer Genomic Profile (Chugai Pharmaceutical) was also covered in September 2021. These tests have been approved for all solid tumors as CGP tests and are covered under national health insurance for patients who have completed the standard treatments or for patients for whom no standard treatment exists.

Genetic counseling is one of the most important issues during the development of the CGP test. In cases in which germline pathogenic variants in a hereditary cancer syndrome
are found, patients can undergo genetic counseling and counselors should help the patients decide their therapy regarding hereditary cancer syndrome.

**CGP tests for hematologic malignancies**

To date, patients with hematologic malignancies cannot undergo CGP tests under national health insurance coverage in Japan. Recently, the CGP test for hematologic malignancies has been developed by the National Cancer Center Hospital (NCCH) and is expected to be covered by national health insurance in a few years. The Japanese Society of Hematology discussed how to use the panel for hematologic malignancies and in August 2022, supported by an MHLW Sciences Research Grant, guidance was prepared that followed the *Guideline for Genomic Examination for Hematologic Malignancies*, which was published in 2018. The utility of the genomic examination was described in terms of the diagnosis, prognosis, and treatment choice for hematologic malignancies in this guideline, and the recommendation levels were shown for each hematologic malignancy or gene abnormality.

**Hospitals for CGM**

Three types of medical hospitals are the driving force behind CGM [designated core hospitals (DCHs), designated hospitals (DHs), and cooperative hospitals (CHs)].

The MHLW designated DCHs and DHs to determine whether the hospitals satisfied the designation requirements (mentioned hereafter). To establish the body to provide CGM, the MHLW issued the *Guideline for Maintenance of Designated Core Hospitals for CGM*, which described the key requirements for CGM in Japan hospitals (Table 1). Thus far, there are 12 DCHs that have had the most important role in this collaborative system. The guideline is revised every 4 years depending on the development of CGM, and DCHs are re-evaluated accompanied with a revision of the guideline.

There are currently 12 DCHs nationwides. DCHs discuss treatment strategies based on the results of CGP tests in the Molecular Tumor Board (MTB). CHs do not conduct the MTB at their own facility, thus the MTB is entrusted to an affiliated DCH. Because CGM has been extended to include cancer patients, an increased capacity of MTB is needed. Therefore, in September 2019 the MHLW designated 34 hospitals as DHs from the CHs to expand the capacity of the MTB. CHs can cooperate with DCH or CH when patients need a MTB. There are currently 32 DHs and 188 CHs in Japan. Patients can receive CGP tests at any of these hospitals. Adopting this collaborative system ensures that patients with cancer can receive CGM anywhere in Japan.

**MTB**

The MTB is a multidisciplinary team that reviews the molecular profiles of patients with cancer from CGP tests to

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**Table 1**  Key elements of hospitals for CGM and key issues to be considered by the MTB

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<tr>
<th>Elements of hospitals for CGM</th>
<th>Key issues to be considered by MTB</th>
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<tr>
<td>•  A system for providing the CGP tests and a group of experts who are able to medically interpret the results of the CGP tests</td>
<td>•  Specimen and data quality</td>
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<tr>
<td>•  Provide expert genetic counseling to patients, including those with hereditary tumors</td>
<td>•  Biological significance and evidence levels of genomic mutations detected</td>
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<tr>
<td>•  Collect, manage, and register the results of the CGP tests and clinical information</td>
<td>•  Presence or absence of secondary findings and their related evidence levels</td>
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<td>•  Store biological samples with fresh cryopreservation, including surgical specimens</td>
<td>•  Recommendation of subsequent actions to take and the expected risks</td>
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<td>•  Conduct clinical trials, advanced medicine, patient-proposed health services, and other clinical studies</td>
<td>•  Approval status of therapeutic drugs</td>
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<tr>
<td>•  Provide information to patients and their families</td>
<td>•  Presence or absence of clinical trial information of related therapeutic drugs</td>
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<td>•  Develop human resources and education in CGM</td>
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<tr>
<td>•  Cooperate with DHs and CHs</td>
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<tr>
<td>•  Deal with pediatric patients</td>
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<td>•  DCHs are designated not to be confined to specific areas</td>
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CGP: comprehensive genomic profiling; CGM: cancer genomic medicine; DHs: designated hospitals; CHs: cooperative hospitals; DCHs: designated core hospitals
provide personalized treatment recommendations, including targeted therapies, chemotherapy, and clinical trial enrollment, thus enhancing patient care and advancing cancer research.

According to the Guideline for Maintenance of Designated Core Hospitals for CGM, the MTB members include the following:

- Medical doctors who administer cancer chemotherapy
- Medical doctors specializing in medical genetics
- Individuals with genetic counseling skills
- Pathologists
- Experts in molecular genetics and CGM
- Experts in bioinformatics
- Pediatricians who discuss pediatric patients in their own facilities
- The patient’s attending physician

The results of the CGP tests are discussed from each member’s perspective. Because it is not always possible to discuss rare cases, such as pediatric cases in their own facilities, another MTB with experience in the case should be consulted.

To guide next-generation sequencing-based cancer tests, the Consensus Clinical Practice Guidelines for Next Generation Sequencing in Cancer Diagnosis and Treatment edition 1.0 was prepared by three cancer-related societies (Japanese Society of Medical Oncology, Japan Society of Clinical Oncology, and Japanese Cancer Association) in October 2017. These guidelines describe how to use CGP tests according to cancer type and provides information on evidence classification in the use of CGP tests. The guidelines also stipulate the matters that should be considered by MTBs.

**C-CAT**

To aggregate and use genomic information, C-CAT was built in the NCC with national government funds in June 2018. Genomic information includes original base sequence data (FASTQ or BAM) and a list of genetic mutations (VCF or XML). C-CAT constructs the Cancer Knowledge Data Base (CKDB). The CKDB reports annotate the clinical significance of the CGP tests, which describe information about a list of matching clinical trials. The CKDB reports are sent back to the MTB, and the MTB discusses the treatment strategies based on the results of CGP tests and the CKDB reports.

The C-CAT is also required to manage the information and promote research using the information. Japan has a unique health system in which almost all Japanese are covered by national health insurance, so C-CAT has a uniform and high-quality national database containing data.

**CGP test achievements**

Information from nearly 45,000 patients is included in C-CAT, which is almost equal to the number of patients who underwent CGP testing under national health insurance. In January 2022, C-CAT reported the registered data of the first 25,991 patients. The data showed that the most common cancer performed CGP tests was colon cancer. Based on the background of patients who underwent CGP testing, rare cancers, such as ovarian/fallopian tube cancer, were overrepresented in the C-CAT database.

DCHs, DHs, and CHs offer annual reports about the CGM achievements to the MHLW. This report includes the number of CGP tests to be performed and information on patient background and outcome. The MHLW recently summarized these annual reports and showed CGM progress in Japan. According to the report, an estimated 1,500 individuals in Japan received CGP tests monthly. DCHs held the MTB for the patients of affiliated hospitals as well as for their own patients, but DHs tended to hold the MTB for their own patients, with fewer patients from other hospitals. Additionally, there seemed to be a difference in MTB capacity between DCHs and DHs.

Genetic counseling is recognized as one of the most important factors when CGP tests are administered to patients with cancer and variability in the quality of genetic counseling are apparent from the annual reports.

**Molecular-matched therapy based on the results of CGP tests**

*Access to non-approved drugs under national health insurance in Japan*

There has been a limitation of approaching non-approved drugs in Japan compared to other countries. A limited compassionate use program for investigational drugs was introduced in January 2016. This program includes drugs that are not approved or are used off-label and are in the final stage of development, and is applicable when the pivotal trial has ended or enrollment is completed. The Patient Proposed Healthcare Service (PPHS) took effect in 2016. This framework was intended to expedite access to non-approved drugs, devices,
regenerative medical products, and gene therapy regardless of the regulatory status worldwide. Following the patients’ proposal to use off-label drugs, hospitals which are either Medical Service Act-certified clinical research core hospitals or Medical Service Act-certified advanced treatment hospitals prepare the application documents, including the protocol and informed consent form. The Institutional Review Board then evaluates the scientific and safety applications.

**Basket trials**

Drug access represents a universal issue for patients and various efforts have been made in each country to resolve this issue. In general, it is difficult to conduct large-scale, randomized, controlled phase III trials for cancers with a small number of patients. In the United States, the Targeted Agent and Profiling Utilization Registry (TAPUR) study was initiated in 2016. The TAPUR study aimed to provide patients with genomically-matched therapies that are approved for different cancers by the Food and Drug Administration.

A similar cross-organ/biomarker-based clinical trial was initiated in October 2019 under the PPHS and led by NCCH [the BELIEVE study (jRCTs031190104)]. It is a clinical trial under the Japanese Clinical Trial Act, not an investigator-initiated registration-directed trial, and it has a platform trial design in which several drug cohorts are pre-established, allowing patients to participate in molecular-targeted treatments. All DCHs participated in this trial, and drugs were provided at no charge from 7 pharmaceutical companies with 20 drug cohorts as of January 2023.

The MHLW reported the achievements of CGP tests. Of the patients who received CGP tests between September 2020 and August 2021, 7% \((n = 830)\) received the treatments recommended by the MTB. Of the 830 patients, 59% received treatments that were covered by national health insurance, 15% participated in company-sponsored registration-directed trials (RDTs), and 5% participated in investigator-initiated RDTs. Additionally, 14% were treated under the PPHS. From these data, it was suggested that not only clinical trials, but also PPHS plays an important role for patients to access genomically-matched therapies.

**Figure 2** Center for Cancer Genomics and Advanced Therapeutics (C-CAT). This is the flow of information around C-CAT. When clinical information and genomic information for each patient are registered in the C-CAT CKDB, a level of clinical significance is allocated to the results of the CGP tests, and C-CAT survey results are generated that describe information in clinical studies and clinical trials conducted in Japan. These C-CAT survey results are returned to the MTB, and the MTB considers treatment strategies based on the CGP test results using the C-CAT survey results.
Future prospects

Sunami et al.\textsuperscript{13} recently reported that more and more patients could receive molecular-targeted therapies. Additionally, there was a positive correlation between the number of patients enrolled in clinical trials and the proportion receiving molecular-targeted therapies. The clinical trials in the report included investigator-initiated and company-driven clinical trials, and PPHS. PPHS is one of the important ways to access the molecular-targeted treatments.

Moreover, genomic-matched therapy has been shown to improve the survival of patients with cancer\textsuperscript{14}. When the same study also compared the proportion of patients receiving genomic-matched therapy between common cancers (top 10 most frequent cancers in terms of mortality defined by the World Health Organization) and uncommon cancers and showed that patients with common cancers received genomic-matched therapy more often than those with uncommon cancers (16.2% vs. 9.4%, respectively). This finding may be because patients with uncommon cancer had fewer chances to participate in clinical trials than patients with common cancers. Furthermore, uncommon cancers, such as sarcomas and pediatric cancers, often display gene rearrangements or gene fusion\textsuperscript{15}, which makes the cancers difficult to detect using the current CGP tests that mainly involve DNA sequencing. As a result, both DNA and RNA sequencing may be helpful for CGM for uncommon cancers.

Patients cannot undergo CGP testing at the time of first-line chemotherapy under national health insurance in Japan at this time. Indeed, it has been reported that CGP tests are useful for chemotherapy-naïve patients\textsuperscript{16}. Reimbursement for CGP testing of chemotherapy-naïve patients may be discussed in the near future. Furthermore, some new CGP tests have been developed. For example, the Todai OncoPanel (TOP) is a dual DNA-RNA panel, so gene fusion and rearrangements can be detected, and patients can have more therapeutic or diagnostic recommendations\textsuperscript{17}.

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

All authors contributed equally to this work.

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