

Adaptation to the Progress in Cancer Genomic Medicine by a Japanese Community Hospital

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Abstract: *Background:* Remarkable progress in cancer genomic medicine (CGM) has been made with the advent of next-generation sequencing and advanced computational data analysis approaches. In Japan gene panel testing has been covered by the National Health Insurance System since June 2019. Although Nagoya Memorial Hospital has been designated as a regional medical support hospital, their medical staff are unfamiliar with CGM and generally experience difficulty in explaining the genetic testing to cancer patients.

Methods: A multi-disciplinary CGM team was created in July 2019 to adapt to the clinical application of gene panel testing. Hospital functions were then maintained focusing on the following three aspects: a pathology system for handling genetic information, human resource development related to CGM, and a patient support system, including genetic counseling.

Results: Third party ISO15189 (International Organization for Standardization) certification was acquired for the Department of Pathology to establish a quality-assured laboratory. Here, we report on 21 cancer patients who consulted and received information from the CGM outpatient department of our hospital. Among them 14 patients were introduced into a group of certified hospitals by the Japanese Ministry of Health, Labour, and Welfare and 10 patients underwent gene panel tests.

Conclusions: As a regional medical support hospital dealing with many cancer patients, we will further improve hospital functions to match the progress in CGM.

Keywords: Cancer genomic medicine, gene panel test, third party certification, multi-disciplinary team, pathology system, human resource development, patient support system.

INTRODUCTION

The combination of next-generation sequencing (NGS) and advanced computational data analysis approaches has revolutionized our understanding of cancer development and progression [1, 2]. NGS can reveal sequence mutations, small insertions and deletions, copy number alterations, structural rearrangements, and loss of heterozygosity in tumor DNA samples [3]. Cancer genome analyses have revealed that abnormal growth drivers may be shared among distinct cancer subtypes. Therefore, it has become apparent that the choice of molecularly

targeted drugs should be optimized to the genome profiles, and not to the origin of the tumor for each patient [4, 5]. Cancer genomic medicine (CGM) was realized by NGS-based analysis of more than 100 genes [6] and genomic alterations in tumors can be simultaneously examined for genes with the available matching drugs [7, 8]. More highly effective therapeutic drugs can be selected based on genetic mutations, facilitating personalized medicine, tailored to individual patients. Because there are some reported cases of exceptional and super-responding to the molecularly targeted drugs in the presence of the matching molecular alterations [9, 10], clinical trials to develop precision oncology are now encouraged in the hope of producing long-lasting remission and extending the survival [4, 5, 11]. Since June 1, 2019, Japan has begun the use of CGM by approving cancer gene panel

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tests covered by the National Health Insurance System [12]. Japan is unique in that almost every Japanese person is covered by the National Health Insurance System; therefore, CGM should only be conducted by a group of certified CGM-ready hospitals.

Nagoya Memorial Hospital, which has 416 beds with 43 departments including medical oncology, was designated as a regional medical support hospital in 2009; however, it has not yet been included in certified as a CGM-ready hospital.

METHODS

To adapt to the remarkable CGM progress made in Japan, a multi-disciplinary CGM team was formed in the Nagoya Memorial Hospital in July 2019. The members of the multi-disciplinary CGM team comprised two doctors, one nurse, one pharmacist, one technician, one medical social worker, and two administrative assistants. According to the project team's proposal, our hospital prepared countermeasures for CGM. We began by conducting several study sessions, which comprised basic knowledge of genetics, information on CGM, hereditary cancer, and the Japanese system of CGM, for hospital staff including office clerks. We then maintained hospital functions focusing on three aspects: a pathology system for handling genetic information, human resource development related to CGM, and a patient support system, including genetic counseling.

RESULTS

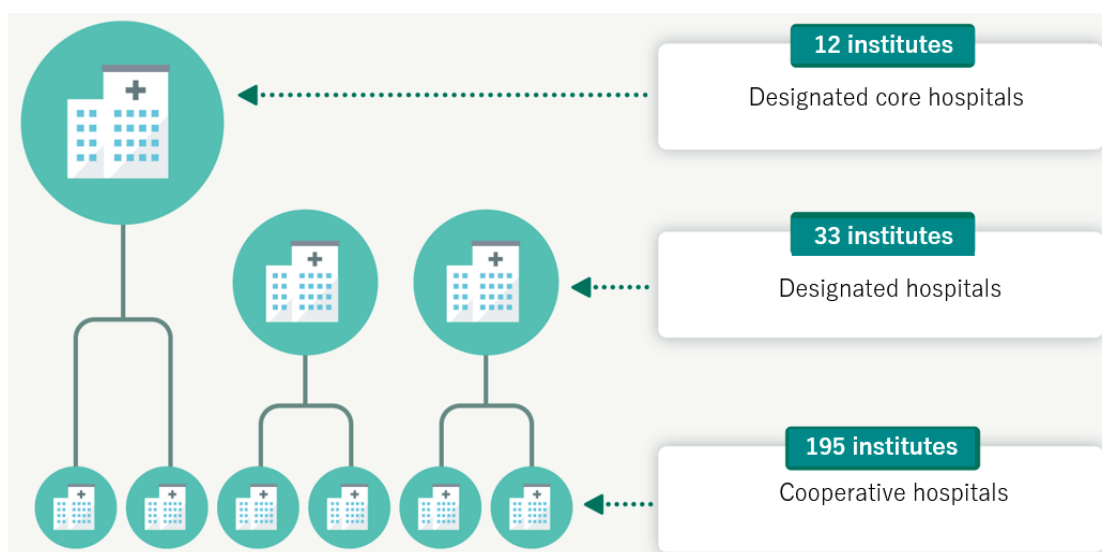
We undertook the ISO15189 (International Organization for Standardization) assessment in December 2022 to acquire a third party certification for the pathology laboratory.

- In January 2020, we signed a contract with the Tsukuba i-Laboratory Support Center for technical advice.
- Following the suggestions made by the above consultants, the area of the pathology laboratory was expanded sufficiently for zoning and a safety cabinet was installed in September 2020.
- Many documents, including 27 on quality management systems, 10 on standard operating procedures, 8 equipment maintenance management standard operation manuals, and several equipment maintenance tables, were prepared.

- Working environments were improved in the pathology laboratory to deal safely with poisonous or deleterious substances, organic solvents such as formalin, and dangerous gases.
- An education system for internal auditor training was established. An internal audit was then performed for quality management, with the aim of continuous improvement.

Additionally, regarding human resource development, two of the project members (KI and YK) received certification as genome medical research coordinators (GMRC) from the Japanese Society of Human Genetics in 2021. Three members (KN, SH, and YS) attended the CGM coordinator workshop, a commissioned project of the Japanese Ministry of Health, Labour and Welfare, in 2022. Since November 2019, each project member has participated in an expert panel held by the designated hospital (Aichi Cancer Center Hospital) for self-improvement.

With regard to the patient support system, the cancer counseling support center (CCSC) has consolidated its position to deal with inquiries concerning CGM from cancer patients and their families. In addition, an outpatient department of CGM was established in December 2019 to identify cancer patients who requested information on genetic examination, such as gene panel testing or BRCA analysis. The medical oncologist (KI; Diplomate, Subspecialty Board of Medical Oncology, JSMO) oversees the CGM outpatient department. Before consulting the CGM outpatient department, patients received an explanation regarding the general concepts of CGM, merits and demerits of undertaking genetic examination, and their costs from GMRC (YK; medical social worker). We examined 21 cancer patients over 2 years: seven for colorectal cancer, six for ovarian cancer, one for pancreatic cancer, one for bile duct cancer, one for osteosarcoma, one for endometrial cancer, one for gastric cancer, one for cancer of the small intestine, and two for unknown primary cancer. After consulting the CGM outpatient department, nine patients were introduced to the designated core hospital and five to the designated hospital for gene panel testing. Among the above 14 patients, 10 undertook gene panel test (NCC Oncopanel Test 5, FoundationOne CDx 5). However, only one patient with mediastinal tumors of unknown primary origin (10%) had a druggable gene mutation (exon23:c.3168+1G>T on *SMARCA4*). BRCA analysis was conducted in two patients; two patients with



As of February 2023, 240 institutes are eligible for cancer genomic medicine under the National Health Insurance System.

Figure 1: Japanese certified hospitals for cancer genomic medicine.

ovarian cancer were not eligible for BRCA analysis. Additionally, two patients did not want genetic testing after receiving an explanation from the CGM outpatient department. The condition of another patient worsened immediately after seeing the CGM outpatient department.

DISCUSSION

Community hospitals face several difficulties in performing gene panel tests for cancer patients. As of February 2023, Japan has 12 designated core hospitals, 33 designated hospitals, and 195 cooperative hospitals (Fig. 1), and a total of 240 institutes are eligible for CGM under the National Health Insurance System. Other hospitals have yet to introduce patients to these certified hospitals for gene panel testing.

Careful laboratory processing of surgical or biopsy specimens is critical for the accurate and robust analysis of tumor DNA. Because NGS tests require large amounts of high-quality DNA in order to achieve a successful test results [3], tumor tissue samples should be reviewed for specimen suitability before testing. Otherwise, clinically actionable or significant variants would not have been identified. Therefore, the pathology laboratory should be reformed into an ISO15189 accredited diagnostic genomics laboratory to minimize sample failure, including that due to poor DNA quality [13]. Doing this is expensive and takes approximately 2 years from the outset to the acquisition of ISO15189 certification.

Additionally, it takes several years to foster staff that are well-versed in CGM. The number of certified genetic counselors (GC) is 304 at present and very limited in Japan. Since there is a shortage of human resources in CGM, the members of the multi-disciplinary CGM team have become GMRC or CGM coordinators in our hospital. On behalf of certified GC, medical oncologist has received genetic counseling training from skilled clinical geneticists since November 2017. In addition, CCSC plays an active role as a consultation counter for the CGM. A staff member of the CCSC (certified GMRC) coordinates an introduction to either a designated core hospital or designated hospital, for patients to undertake gene panel testing along with genetic counseling, as well as consultation at the CGM outpatient department of our hospital.

CONCLUSION

Our initiatives on CGM including the preparation of an ISO15189 accredited laboratory may help the cancer patients, who have never visited certified CGM-ready hospitals, benefit from the precision oncology. We will further improve the quality of hospital functions for CGM and establish a genetic counseling system.

ABBREVIATIONS

CCSC	=	Cancer counseling support center
CGM	=	Cancer genomic medicine
GC	=	Genetic counselor

GMRC = Genome medical research coordinators

ISO = International Organization for Standardization

NGS = Next-generation sequencing

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