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Clinical significance of comprehensive genomic profiling tests covered by public insurance in patients with advanced solid cancers in Hokkaido, Japan

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Abstract

Background: Comprehensive cancer genomic profiling has been used recently for patients with advanced solid cancers. Two cancer genomic profiling tests for patients with no standard treatment are covered by Japanese public health insurance since June 2019.

Methods: We prospectively analyzed data of 189 patients with solid cancers who underwent either of the two-cancer genomic profiling tests at Hokkaido University Hospital and its liaison hospitals and whose results were discussed in molecular tumor board at Hokkaido University Hospital between August 2019 and July 2020.

Results: All 189 patients had appropriate results. Actionable gene alterations were identified in 93 patients (49%). Frequent mutations included *PIK3CA* (12%) mutation, *BRCA1/2* alteration (7%), *ERBB2* amplification (6%) and tumor mutation burden-High (4%). The median turnaround time

from sample shipping to acquisition by the expert panel was 26 days. Although 115 patients (61%) were provided with information for genotype-matched therapies, only 21 (11%) received them. Notably, four of eight patients below the age of 20 years were provided information for genotype-matched therapies, and three received them. Their response rates and disease control rates were 29% and 67%, respectively. Most patients who did not undergo the genotype-matched therapies were provided information for only investigational drugs in phases I and II at distant clinical trial sites in central Japan. Twenty-six patients were informed of suspected germline findings, while 11 patients (42%) received genetic counseling.

Conclusions: The publicly reimbursed cancer genomic profilings may lead to the modest but favorable therapeutic efficacy of genotype-matched therapy for solid cancer patients with no standard therapy. However, poor access to genotype-matched therapy needs to be resolved.

Key words: next-generation sequencing, cancer, insurance

Introduction

Next-generation sequencing (NGS)-based comprehensive cancer genome profiling (CGP) to identify genotype-directed therapy has increasingly become a routine practice for patients with solid cancers worldwide. In the USA, several NGS-based CGP tests have been approved by the U.S. Food and Drug Administration (FDA), and patients routinely undergo molecular testing. Although randomized phase II trials in patients with metastatic solid tumors refractory to standard treatments did not show the efficacy of CGP (1,2), retrospective studies that were conducted among patients including those who had not completed standard treatment indicated efficacy (3–6).

In Japan, the National Cancer Center (NCC) began the TOP-GEAR project in 2013 to develop CGP, NCC Oncopanel (7). NCC Oncopanel is an NGS-based analysis of 114 cancer-associated genes. In the second stage of the TOP-GEAR project, 230 cases of advanced solid tumors were examined, and gene profiling data were obtained for 187 cases (81.3%). In these 187 cases, 111 cases (59.4%) harbored actionable gene aberrations, and 25 cases (13.3%) received molecular-targeted therapies according to their gene alterations (7), indicating the utility of CGP in clinical settings.

The Ministry of Health, Labor, and Welfare designated 11 core hospitals and 100 liaison hospitals in February 2018 and expanded designation to 12 core, 33 hub and 161 liaison hospitals by April 2020 (8) to promote cancer genomic medicine. The Center for Cancer Genomics and Advanced Therapeutics (C-CAT) has also been established in the NCC to collect genomic information and clinical characteristics of patients who underwent CGP since 2018 (9). C-CAT functions as the central database for cancer genomic medicine and assists in decision-making by providing reports with information about clinical trials matching patients' genomic data (8).

Since June 2019, two CGP tests—the OncoGuide™ NCC Oncopanel System (NCC Oncopanel) and FoundationOne® CDx cancer genome profiling (F1CDx)—have been reimbursed by the national health insurance system, but only for patients with advanced solid tumors who fail to respond to standard therapies or who do not have any appropriate standard treatments. The use of the publicly reimbursed CGPs is limited to the designated hospitals for cancer genomic medicine. Core and hub hospitals are required to have molecular tumor boards called 'expert panels,' wherein specialists from multiple disciplines interpret genomic information in CGP results clinically.

At the Hokkaido University Hospital (HUH), we have started an in-house CGP (CLHURC) (10) and an outsource CGP (Oncoprime), both of which have not been covered by insurance. The HUH has been a core hospital since February 2018 and has publicly reimbursed CGPs since August 2019.

Although the CLHURC study (10) in addition to the above retrospective studies (3–6) indicated the efficacy of CGP in patients including those who had not completed standard treatments, outcome of CGP in patients with no standard treatment, which has been covered by Japanese public health insurance, is not clear. In this study, we prospectively analyzed data of 189 patients who had undergone the public insurance-covered CGP tests in HUH and its liaison hospitals and whose results were discussed by the expert panel of HUH between August 2019 and July 2020.

Patients and methods

Study design and patients

We conducted a prospective observational study of CGP in patients with histologically confirmed solid tumors at HUH and its liaison hospitals [NHO Hokkaido Cancer Center (core hospital since January 2020), Sapporo Medical University Hospital, Asahikawa Medical University Hospital and Hakodate Municipal Hospital]. The primary objective of the study was the detection of actionable and potentially actionable gene alterations. Secondary objectives included the percentage of patients treated with genotype-matched therapy, therapeutic outcome of the genotype-matched therapy and detection rate of germline findings and presumed germline pathogenic variants (PGPVs). This study was approved by the Ethics Committee of the HUH and other liaison hospitals (No. 016-0260). Written informed consent was obtained from all patients for using genomic and clinical data for this study. Additionally, the patients were asked if they wished to know the results of the possible germline gene alterations before the test.

NGS-based CGP tests

FoundationOne® CDx genome profiling (F1CDx, Chugai Pharmaceutical) and OncoGuide™ NCC Oncopanel System (NCC Oncopanel, Sysmex Corporation) are CGPs covered by Japanese public health insurance for patients with solid tumors for which there is no standard treatment and for patients with locally advanced or

metastatic cancers who have completed standard treatments (including patients expected to complete the treatments).

F1CDx carries 324 genes and determines nucleotide substitutions, insertion/deletion mutations, gene amplification of 309 genes, fusions of 36 genes, microsatellite instability (MSI) and tumor mutation burden (TMB) (11,12). The NCC Oncopanel carries 114 genes and determines base substitutions, insertion/deletion mutations, gene amplification of 114 genes, fusions of 12 genes and TMB (7,13). Non-tumor cell (peripheral blood)-derived DNA is used as the control. Thus, the NCC Oncopanel can distinguish between somatic and germline genetic mutations.

Flow of the clinical sequencing

After explaining the test and confirming the patient's willingness during the first outpatient visit to the physician in charge of genomic medicine, the availability of archival formalin-fixed paraffin-embedded (FFPE) tumor tissue was checked. Pathologists determined if the tissue volume or tumor percentage was sufficient. A biopsy was performed in case it was insufficient. If the tissue was appropriate for CGP, consent for testing was obtained on the second visit. The specimen was subsequently sent to the testing company. After the analysis, the test result was sent to the hospital. After registering the patient's information and CGP results at C-CAT, a C-CAT report with the information including evidence levels for therapeutic efficacy of agents against genomic alterations, the availability of the therapeutic agents and the patient's genotype-matched clinical trial was sent to HUH. Next, an expert panel (via videoconference) was held at HUH once every week with liaison hospitals through a virtual private network connection. The expert panel included medical oncologists, pathologists, bioinformaticians, medical geneticists, certified genetic counselors, cancer genome medical coordinators, specialists in cancer genomic medicine and attending physicians. The panel discussed evidence levels presented in C-CAT report, which were categorized from A to F based on the clinical practice guidance for NGS in cancer diagnosis and treatment (Edition 2.0) issued by the Joint Consensus of Japanese Society of Medical Oncology (JSMO), Japan Society of Clinical Oncology (JSCO), and Japanese Cancer Association (JCA) (14). If required, the panel revised the evidence levels presented in the C-CAT report. The levels of evidence for gene alterations were defined as follows: Level A, genetic abnormality that predicts response to FDA or PMDA-approved therapies for a specific type of tumor, and biomarkers included in professional guidelines as predicting factors for a specific type of tumor; Level B, biomarkers that predict responses to therapies for a specific type of tumor based on well-powered studies with consensus from experts in the field; Level C, biomarkers that predict responses to therapies approved by the PMDA or FDA for a different type of tumor, biomarkers of therapeutic significance based on the results of small studies, biomarkers that predict responses to therapies for a different type of tumor based on well-powered studies with consensus from experts in the field; Level D, biomarkers associated with efficacy in a few case reports; Level E, biomarkers that have plausible therapeutic significance based on preclinical studies; Level E, biomarkers that have plausible therapeutic significance based on preclinical studies and Level F, gene abnormality involved in cancer.

The panel discussed the accessibility of the therapeutic agents presented by C-CAT report, based on the guidance (14). If required, the panel revised the accessibility level. The levels were defined as follows: Level 1, PMDA approved for this cancer type; Level 2, there are domestic clinical trials for this cancer type; Level 3, PMDA approved only for different cancer type; Level 4, there are foreign clinical trials for this cancer type; Level 5, FDA approved regardless of cancer type; Level 6, others.

In our previous report (10) and a report from others (7), actionable gene alterations were defined as gene alterations with evidence level 1A–3A in 'Clinical Practice Guidance for Next-generation Sequencing in Cancer Diagnosis and Treatment (Edition 1.0)' (15). When the NGS guidance changed from version 1 to 2, the names of evidence levels have also changed. We used the same criteria as before for actionable gene alterations, which were defined as alterations at or above evidence level D (biomarker associated with efficacy in a few case reports). Potentially actionable gene alterations were defined as alterations at or above evidence level F (gene abnormality known to be involved in cancer) because they include gene alterations that are candidates for investigational drugs. Based on the patient's treatment history, the patient's background, the level and details of the evidence, and accessibility of drugs, the recommendation of genotype-matched therapy was determined by the expert panel.

If germline variants and PGPVs were detected in genes listed in the American College of Medical Genetics and Genomics (ACMG) recommendations of secondary findings (16), clinical geneticists and certified genetic counselors determined whether the variants should be disclosed based on pathogenicity, allele frequency, phenotype, and family history as per recommendations of the Agency for Medical Research and Development (AMED) Kosugi group (principal investigator: Shinji Kosugi, Kyoto University) (16–19). The expert panel discussed the possibility of germline variants based on the judgments of the clinical geneticist and genetic counselor.

Then, the expert panel generated the final reports of the patients. The results were explained to the patient during the third visit, and the final report was sent to the attending physician.

We conducted a survey (using a questionnaire made by C-CAT) involving attending physicians whether genotype-matched therapy was conducted or not. In case that genotype-matched therapy was conducted; the best response was evaluated based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. In case that genotype-matched therapy was not conducted, we ask attending physicians the reason why patients did not receive genotype-matched therapies.

In order to determine the human resources required to maintain this system, we surveyed the staff involving CGP test about the number of staff and the average time spent by each member in each task for one patient at HUH.

Results

Between August 2019 and July 2020, we obtained results of the public insurance-covered CGP tests for 189 patients (131 patients from HUH and 58 patients from liaison hospitals), all of whom were enrolled in this prospective observational study. Although 216 patients attended the first outpatient visits in charge of genomic medicine, 27 patients were unsuitable for testing due to lack of specimens or poor general conditions. Subsequently, 189 patients submitted specimens for CGP tests on second visits. F1CDx was employed for 171 patients, while NCC Oncopanel was used for the remaining 18 patients.

Characteristics of the 189 patients are summarized in Table 1. The median age was 61 (range 0–79) years. Most patients ($n = 184$, 97%) had Eastern Cooperative Oncology Group (ECOG) performance status scores of 0 or 1. Almost all patients ($n = 184$, 97%) received previous chemotherapy. Characteristics of the 189 FFPE

Table 1. Characteristics of the 189 patients

Characteristics	Value
Age	
Median (range) (years)	61 (0–79)
Sex, *n* (%)	
Male	78 (41%)
Female	111 (59%)
ECOG performance status, *n* (%)	
0	68 (36%)
1	116 (61%)
2	5 (3%)
UICC stage, *n* (%)[a]	
Non-stage IV or recurrence	27 (14%)
Stage IV or recurrence	162 (86%)
Prior treatment, *n* (%)	
Yes	184 (97%)
No	5 (3%)

[a]UICC TNM classification of malignant tumors, 8th edition.
ECOG, Eastern Cooperative Oncology Group.

Table 2. Characteristics of the 189 formalin-fixed paraffin-embedded samples

Characteristics	*n* (%)
Site of specimen	
Primary site	110 (58%)
Metastatic site	79 (42%)
Storage period	
<6 months	70 (37%)
6 months to 3 years	103 (55%)
≧ 3 years (maximum 3.9 years)	16 (8%)

Table 3. Tumor types of the 189 patients

Tumor type	*n* (%)
(A) Tumor types	
Soft-tissue sarcoma	27 (14%)
Colorectal Ca.	24 (13%)
Pancreas Ca.	21 (11%)
Ovarian Ca.	15 (8%)
Head and neck Ca.	13 (7%)
Breast Ca.	10 (5%)
Endometrial Ca.	8 (4%)
Lung Ca.	8 (4%)
Stomach Ca.	8 (4%)
Neuroendocrine Ca.	7 (4%)
Biliary Ca.	7 (4%)
Urologic Ca.	7 (4%)
Melanoma	6 (3%)
Cervical Ca.	5 (3%)
Carcinoma of unknown primary site	3 (2%)
Thymic Ca.	3 (2%)
Others	17 (9%)
Tumor type	*n*
(B) Details of other tumors in (A) ($n = 17$)	
Duodenal Ca.	2
Esophageal Ca.	2
Liver Ca.	2
Mesothelioma	2
Carcinosarcoma	1
Appendiceal Ca.	1
GIST	1
Chordoma	1
Small intestine Ca.	1
Anaplastic oligodendroglioma	1
Adrenocortical Ca.	1
Malignant transformation of a mature cystic teratoma	1
Anal canal Ca.	1

Ca., cancer; GIST, gastrointestinal stromal tumor.

samples are summarized in Table 2. In total, 110 specimens (58%) were collected from primary sites, and 79 specimens (42%) were collected from metastatic sites. Ninety-two percent of the specimens had been stored for less than 3 years in accordance with the recommendations on handling histopathological specimens for genomic diagnosis published by the Japanese Society of Pathology. Eight percent of the specimens had been stored for over 3 years but less than 4 years. In our system, the availability of appropriate tumor specimens was checked before the second visit, and re-biopsy was performed for patients whose samples were not appropriate for genomic profiling test. All 189 patients had appropriate results. The common tumor types were soft-tissue sarcoma (14%) and colorectal (13%), pancreatic (11%), ovarian (8%) and head and neck (7%) cancers (Table 3).

The median turnaround time (TAT) from the first outpatient visit to the expert panel, shipping samples to receiving test results, and shipping samples to the expert panel was 43 days (range 21–118), 14 (range 9–29) days and 26 (range 16–43) days, respectively. Four patients (3%) were not informed about the test results due to the deterioration of their respective diseases.

Potentially actionable genomic alterations were identified in 97% (183/189) of the patients. Frequent ones included *TP53*, 54% (103/189); *KRAS*, 26% (49/189); *CDKN2A*, 19% (35/189); *PIK3CA*, 13% (25/189); and *ARID1A*, 11% (20/189) (Table 4A). Actionable genomic alterations were identified in 93 patients (49%). Frequent mutations included *PIK3CA* mutation, 12% (22/189); *BRCA1/2* mutation, 7% (13/189); *ERBB2* amplification, 6% (11/189); and TMB high, 4% (8/189) (Table 4B). Distribution of the maximum evidence level for therapeutic efficacy and maximum drug accessibility per case, based on the criteria of JSMO, JSCO and JCA guidance (14), is shown in Table 5A. Sixty-five percent of patients had drug accessibilities of 1 and 2, which are equivalent to having a domestically approved drug for the same cancer type and having a domestic clinical trial, respectively (Table 5B).

Thirty-three patients (17%) were provided information for genotype-matched therapies recommended by the expert panel. Eighty-two patients (43%) were provided information for genotype-matched therapies other than the recommended therapies, which typically included phase I and phase II trials based on low-level evidence. In addition to patients with actionable gene alterations at evidence level D or higher, a part of patients with potentially actionable gene alterations at evidence level E or F were also provided with information on genotype-matched therapies, such as phase I trials for *TP53* and *KRAS* mutations. Among a total of 115 patients (60%) who were provided information for genotype-matched therapies, only 21 patients (11%) underwent the therapies before August 2020. Of note, eight patients under the age of 20 years

Table 4. Lists of potentially actionable/actionable gene alterations

Top 10 genes	*n* (%)	
(A) Potentially actionable gene alterations		
TP53	103 (54%)	
KRAS	49 (26%)	
CDKN2A	35 (19%)	
PIK3CA	25 (13%)	
ARID1A	20 (11%)	
APC	19 (10%)	
PTEN	17 (9%)	
SMAD4	17 (9%)	
MTAP	16 (8%)	
BRCA1/2	13 (7%)	
Top 11 genes	**Agents**	***n* (%)**
(B) Actionable gene alterations		
PIK3CA	PIK3/AKT/MTOR inhibitor	22 (12%)
BRCA1/2	PARP inhibitor, platinum	13 (7%)
ERBB2 amplification	HER2 inhibitor/anti-HER2 ADC	11 (6%)
TMB high	PD-1/PD-L1 inhibitor	8 (4%)
PTEN	PIK3/AKT/MTOR inhibitor	6 (3%)
BRAF V600E	BRAF inhibitor	6 (3%)
MDM2 amplification	MDM2 inhibitor	6 (3%)
CDK4 amplification	CDK4/6 inhibitor	4 (2%)
LOH score high	PARP inhibitor, platinum	4 (2%)
MET amplification	MET inhibitor	4 (2%)
TSC1	MEK inhibitor	4 (2%)

ADC, antibody drug conjugate.

were investigated; four (50%) of them were suggested genotype-matched therapies and three had undergone genotype-matched therapies. Detailed information regarding genotype-matched therapy is shown in Table 6. The best overall response rate was analyzed based on the RECIST, version 1.1. The response and disease control rates of the genotype-matched treatments in our cohort were 29% (6/21) and 67% (14/21), respectively.

We conducted a survey (using a questionnaire made by C-CAT) involving attending physicians to understand why patients did not receive genotype-matched therapies (Table 7). We obtained answers for 90 patients who were provided with information for genotype-matched therapy but did not receive therapy. Inability to participate in clinical trials due to non-fulfillment of detailed eligibility criteria or outside of the registration period, deterioration of the general condition of patients, deaths and usage of therapies other than the proposed therapy were some common answers. In the 'other' category, many attending physicians described the reasons for low evidence levels of investigated drugs and for non-participation in clinical trials due to the long distance to clinical trial sites. While examining the 90 patients, we found that 53 patients (59%) were only provided information for investigational drugs in phases I and II at clinical trial sites in central Japan (over 500 miles away from patients' homes).

If germline variants and PGPVs were detected in genes listed in the ACMG recommendations of secondary findings (16), clinical geneticists and certified genetic counselors in our expert panel determined the disclosure of variants based on pathogenicity, allele frequency, phenotype and family history in accordance with the recommendations of the AMED Kosugi group (16–19). Twenty-six patients were found to have PGPVs by tumor-only testing using F1CDx, while three patients showed germline findings using NCC Oncopanel. The PGPVs were detected in *APC* ($n = 3$), *BRCA1* ($n = 6$), *BRCA2* ($n = 2$), *MEN1* ($n = 2$), *MLH1* ($n = 1$), *MSH6* ($n = 2$), *MUTYH* ($n = 2$), *NF2* ($n = 1$), *PTEN* ($n = 3$) and *TP53* ($n = 5$), and the germline findings were detected in *BRCA1* ($n = 1$), *BRCA2* ($n = 1$) and *TP53* ($n = 1$). Twenty-six of the 29 patients with PGPV or germline findings opted for disclosure, and all of them were informed of the findings. Among these 26 patients, only 11 patients (41%) had received genetic counseling. Only 6 of 21 patients in HUH had received the genetic counseling; however, all the five patients in its liaison hospitals received it. Detailed information regarding the 11 patients is shown in Table 8. Out of 10, five patients with PGPVs had germline tests, and two of them received positive results. Reasons for not having the germline test for the five patients included death immediately after disclosure ($n = 2$), the high cost of the germline test ($n = 1$), opposition from other family members ($n = 1$) and priority for treatment ($n = 1$).

In order to determine the human resources required to maintain this system, we surveyed the staff involving CGP test about the number of staff and the average time spent by each member in each task for one patient at HUH (Table 9). A large number of human resources were spent on organizing expert panels and other tasks such as registration of clinical data to C-CAT, maintenance of the C-CAT system, and follow-up surveyrance.

Discussion

Herein, we described the clinical data of a prospective cohort with publicly reimbursed CGPs in the Hokkaido area in Japan. Although some patients benefited from this test, there are several issues that need to be resolved.

In this study, actionable and potentially actionable gene alterations were identified in 49% (93/189) and 97% (183/189) of the patients, which was consistent with previous reports (7,10,20). In our previous report, actionable and potentially actionable gene alterations were detected using in-house clinical sequencing system in 46% (73/160) and 91% (145/160) of the patients, respectively (10). In the Japanese TOP-GEAR project, 59.4% harbored actionable gene aberrations using NCC Oncopanel (7). In a large cohort study from MSK-IMPACT, 37% of patients harbored clinically relevant alterations (20). Although potentially actionable gene alterations were detected in most cases, the detection rate of actionable gene alterations is generally not high enough, which is considered a limitation of the current CGP tests. Incorporation of whole-exome sequence, whole genome sequence, transcriptome and immunological gene profiling in decision-making processes may improve detection of actionable genes or actionable genomic profiles for individual patients.

In total, 115 patients (61%) were provided information for genotype-matched therapies but only 21 patients (11%) actually underwent the therapies; this observation was consistent with previous reports (7,10,20,21). A cohort study from MSK-IMPACT, which included over 10 000 people, reported that patients were enrolled in genotype-matched clinical trials at a rate of 11% (20). Japanese TOP-GEAR project second stage, which was a hospital-based prospective study involving 230 cancer patients, reported that patients received genotype-matched therapies at a rate of 13.3% (7).

Although child and adolescent patients are assumed to be less accessible for treatment based on the results of CGP, four of eight

Table 5. Distribution of maximum evidence level (A) and maximum accessibility of drug (B) for gene alterations detected in patients

Evidence levels	Evidence level classifications	*n* (%)
(A) Evidence levels based on 'clinical practice guidance for NGS in cancer diagnosis and treatment (Edition 2.0)' issued by the Joint Consensus of Japanese Society of Medical Oncology, Japan Society of Clinical Oncology, and Japanese Cancer Association		
A	Genetic abnormality that predicts response to FDA or PMDA-approved therapies for a specific type of tumor	19 (10%)
	Biomarkers included in professional guidelines as predicting factors for a specific type of tumor	
B	Biomarkers that predict responses to therapies for a specific type of tumor based on well-powered studies with consensus from experts in the field	10 (5%)
C	Biomarkers that predict responses to therapies approved by the PMDA or FDA for a different type of tumor	36 (19%)
	Biomarkers of therapeutic significance based on the results of small studies	
	Biomarkers that predict responses to therapies for a different type of tumor based on well-powered studies with consensus from experts in the field	
D	Biomarkers associated with efficacy in a few case reports	28 (15%)
E	Biomarkers that have plausible therapeutic significance based on preclinical studies	27 (14%)
F	Gene abnormality known to be involved in cancer	63 (34%)
None		6 (3%)
Levels	Accessibility classifications	*n* (%)
(B) Accessibility to drug based on 'clinical practice guidance for NGS in cancer diagnosis and treatment (Edition 2.0)' issued by Joint Consensus of Japanese Society of Medical Oncology (JSMO), Japan Society of Clinical Oncology (JSCO), and Japanese Cancer Association (JCA)		
1	PMDA approved for this cancer type	20 (10%)
2	There are domestic clinical trials for this cancer type	102 (54%)
3	PMDA approved only for different cancer type	5 (3%)
4	There are foreign clinical trials for this cancer type	6 (3%)
5	FDA approved regardless of cancer type	3 (2%)
6	Others	1 (1%)
None		52 (27%)

FDA, Food and Drug Administration; PMDA, Pharmaceuticals and Medical Devices Agency.

such patients were provided information for genotype-matched therapies, and three received these treatments in this study. The utility of CGP in child and adolescent patients' needs to be further investigated in a larger cohort.

Although the number of patients who underwent the genotype-matched therapies was small, the response and disease control rates were 29% and 67%, respectively. These are modest but favorable rates for patients without standard drug therapies. Confirmatory, prospective, and genotype-matched trials are required to validate the clinical outcomes of CGP for patients without standard therapies.

The main reasons why patients did not undergo the genotype-matched therapies for which the information was provided were the usage of alternative therapies, the patient's unwillingness, low evidence level of investigated drugs and the inability to participate in clinical trials due to the long distance from patients' homes to clinical trial sites. These reasons exist mainly because most of these patients were only provided information for investigational drugs in phases I and II at distant clinical trial sites in central Japan. There are currently regional disparities in clinical trial information and distance to clinical trial sites. To increase the accessibility of genotype-matched therapy, sharing clinical trial information among the designated core and hub hospitals and expanding clinical trial sites across Japan are necessary.

Another reason was the difficulty in using off-label drugs under Japanese regulations. To access off-label drugs easily, the NCC hospital and other designated core hospitals have launched a phase II basket trial of multiple targeted agents based on the results of gene profiling by multigene panel test (BELIEVE study). Japanese patient-proposed health care services were used for this, wherein three patients from this study were enrolled. Currently, there are only 13 eligible drugs, which are restricted to patients who are older than 15 years. However, the number of eligible drugs is supposed to increase, and the inclusion of pediatric patients is underway to improve drug accessibility.

In total, 22 patients could not participate in clinical trials due to the deterioration of their general conditions and even demise. Four patients were not informed about the test results because of disease deterioration. CGP covered by public insurance is currently only for patients who have completed or were supposed to complete standard chemotherapy. Thus, the patient's general condition tends to worsen by the day. Retrospective studies involving patients with metastatic solid tumors who had not completed standard treatments indicated the efficacy of genotype-matched therapy (3–6). Thus, CGP tests before standard chemotherapy might be more effective. Practically, hospitals must cover most of the cost of CGP in cases where patients cannot be informed of CGP results due to disease deterioration. From June 2020, the NCC hospital launched a prospective study to evaluate the feasibility and utility of a comprehensive genomic profiling test before initial systemic treatment within the Advance Medical Care system. The results are awaited (UMIN000040743).

In this study, of the 26 patients who were informed of PGPVs or germline findings, only 11 patients (42%) had undergone genetic counseling, which reflected the low counseling rate in HUH. Genetic counseling was not reimbursed by public insurance during the first two-thirds of this study period, during which many patients were enrolled at HUH. Because mixed medical care covered partially

Table 6. Detailed information regarding genotype-matched treatments (21 patients)

Tumor type	Targeted gene alteration	Drug type	Treatments	Treatment lines	Best responses
Rhabdomyosarcoma[a]	*ATIC-ALK* fusion	ALK inhibitor	others	3	PR
NSCLC	*EZR-ROS1* fusion	ROS1 inhibitor	PHI	3	PR
Colon Ca.	*NTRK1-LMNA* fusion	NTRK inhibitor	CIT	4	*
Infantile fibrosarcoma[a]	*NTRK1-LMNA* fusion	NTRK inhibitor	PHI	2	SD
Endometrial Ca.	*ERRB2* amplification	HER2 inhibitor (2 drugs)	IIT	4	*
Biliary tract Ca.	*ERRB2* amplification	anti-HER2 ADC	IIT	6	*
Bladder Ca.	*FGFR3* Y373C	FGFR inhibitor	IIT	3	*
GIST	*KIT* D820G	KIT inhibitor	PRMCS pII	4	*
Breast Ca.	*PIK3CA* C420R	mTOR/aromatase inhibitor	PHI	10	PD
Breast Ca.	*PIK3CA* E542K	mTOR/aromatase inhibitor	PHI	3	SD
Breast Ca.	*PIK3CA* H1047R	mTOR/aromatase inhibitor	PHI	6	PD
Soft-tissue sarcoma	*mTOR* amplification	mTOR inhibitor	PRMCS pII	8	*
Ovarian Ca	*BRCA1* H692fs*19	PARP inhibitor	PHI	7	ND
Peritoneal Ca.	*BRCA1* L63*	PARP inhibitor	PHI	6	ND
Breast Ca.	*BRCA2* R2318*	PARP inhibitor	PHI	10	SD
Malignant transformation of ovarian mature teratoma (glioblastma)[a]	LOH score high	Platinum	PHI	1	CR
CUP	MSI high	ICI	PHI	2	CR
Salivary gland Ca.	MSI high	ICI	PHI	5	SD
Gastric Ca.	MSI high	ICI	PHI	3	PR
Esophageal Ca.	TMB high	ICI	PHI	3	PD
Peritoneal Ca.	TMB high	ICI	PRMCS pII	7	*

[a]These are child and adolescent patients, ages 0, 4 and 16 years old, respectively, from the top.
GIST, Gastrointestinal Stromal Tumor; PHI, public health insurance; CIT, company-initiated trial; IIT, investigator-initiated trials; PRMCS pII, patient requested medical care system phase II; ND, not determined. *We cannot disclose response of individual data for CIT, IIT or PRMCS PII. There is one PR in patients treated in CIT, IIT or PRMCS PII.

Table 7. The reasons why patients did not undergo genotype-matched therapy[a]

Questionnaire to the attending physician (overlapped)	*n* (%)
1. The use of alternative therapies	17 (19%)
2. The inability to participate in clinical trials due to non-fulfillment of detailed eligibility criteria or outside of the registration period	24 (27%)
3. Financial situation of the patient	1 (1%)
4. Deterioration of general condition of the patient	22 (24%)
5. The patient's unwillingness to undergo the therapy	9 (10%)
6. Death of the patient	5 (6%)
7. Others (Specify)	16 (18%)
Low evidence level of investigated drugs	12 (13%)
Inability to participate in clinical trials due to the long distance to clinical trial sites	5 (6%)
No system for off-label drug use	5 (6%)
Stable disease	5 (6%)

[a]We obtained answers for 90 patients who were provided with information for genotype-matched therapy but did not receive therapy. Numbers in parentheses denote percentages of the 90 patients.

by public health insurance was prohibited in Japan, patients had to return for genetic counseling on a different day, which made it difficult for patients to receive counseling. Since genetic counseling following the genomic profiling test has been reimbursed since April 2020, all patients receive genetic counseling on the same day as the test results. As a result, the number of patients receiving genetic counseling is now increasing.

Our results and previous reports (8) showed that a large amount of human resources is required to maintain this system, including registering information into C-CAT, and holding weekly expert panels with other liaison hospitals. It is challenging to maintain this system at its current level. The designated core hospitals are now sharing their situations and working together to discuss ways to improve this system.

The limitation of this study is that the outcomes were analyzed in a relatively small number of patients of limited facilities in Hokkaido. Large-scale observational studies in facilities across the country will help to determine the outcome of CGP and elucidate the regional disparities.

In conclusion, the publicly reimbursed CGP leads to modest but favorable therapeutic efficacy in patients with solid cancers without standard drug therapies. However, there are several issues, such as limited access to genotype-matched therapy and the requirement for human resources to maintain the system, that need to be addressed.

Table 8. Detailed information on patients who had genetic counseling

Patients	Primary sites	Age	Test	Genes	AA changes	VAF	Phenotypes	Family history	Genetic testing
1	Colon	60s	F1	*TP53* *APC*	R273H S280*	39 31	Li-Fraumeni syndrome Familial Adenomatous Polyposis	Lymphoma: grandmother Colorectal: sister Small Intestinal: sister	Negative
2	Breast	60s	F1	*TP53*	E286K	29	Li-Fraumeni syndrome	Stomach: father, sister Cervix: mother	Untested
3	Head and Neck	70s	F1	*MUTYH*	splice site 892-2A > G	49	MUTYH-Associated Polyposis	Colorectal: father	Positive
4	Uterus	50s	F1	*PTEN*	C136R, R130Q	39/40	PTEN hamartoma tumor syndrome	Biliary: mother; Lung: grandmother Breast: aunt	Untested
5	Esophagus	60s	F1	*BRCA1*	Q934*	91	Hereditary breast and ovarian cancer	Ovary: mother, sister Stomach: grandfather	Untested
6	Stomach	40s	F1	*MLH1*	R487*	62	Lynch syndrome	Colorectal: father, brother Stomach: grandfather, uncle	Positive
7	Thyroid	70s	F1	*MEN1*	P69fs*44	36	Multiple endocrine neoplasia type1	Stomach: grandfather Breast: sister	Negative
8	Sarcoma	10s	F1	*NF2*	T93fs*26	31	Neurofibromatosis	Colorectal: father, grandfather	Negative
9	Colon	30s	F1	*APC*	E1353fs*62	49	Familial Adenomatous Polyposis	Colorectal: mother, aunt Esophagus: grandfather	Untested
10	Ovary	40s	NCC	*BRCA1*	H692fs*19	38	Hereditary breast and ovarian cancer	Lung: mother Colorectal: grandmother	(NCC)
11	Ovary	10s	F1	*TP53*	R248Q	64	Li-Fraumeni syndrome	Biliary: mother Stomach: grandfather Leukemia: grandfather	Untested

AA, amino acids; VAF, variant allele frequency; F1, FoundationOne CDx; NCC, NCC Oncopanel.

Table 9. The number of staffs and the average time spent by each staff in each task for one patient

Task	Doctor	Cancer genomic medical coordinators	Genetic counseler	Pathology technician	Administrative assistance
Patient care	1 (1.25 h)	1 (1.75 h)			1 (1.0 h)
Specimen preparation	3 (0.25 h)	1 (0.5 h)		1 (2 h)	2 (1.0 h)
Expert panel preparation	10 (0.15 h)		2 (0.25 h)		1 (1 h)
Expert panel	10[a] (0.1 h)	1 (0.1 h)	2 (0.1 h)		2 (1 h)
Other	1 (1 h)	1 (0.5 h)			6 (0.5 h)

[a]The number was counted only for essential staffs.

Other: document management, administration list management, C-CAT system maintenance, registering information into C-CAT, and follow-up surveyrance, etc. Numbers in parentheses denote the average time spent by each member for one patient.

Development of novel molecular-targeted drugs, promotion of clinical trials, the discovery of new therapeutic targets, improvement of regional disparities and human resource development are warranted to promote cancer genomic medicine in clinical settings.

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Conflict of interest statement

None declared.

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