ORIGINAL

Clinical Outcomes of Comprehensive Genomic Profiling Tests for Gastrointestinal Cancers: Experience from Tokushima University Hospital

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Abstract : In Japan, cancer genome profiling (CGP) for cancer patients without standard treatment has been covered by public insurance since June 2019. This study analyzed data of 122 patients with gastrointestinal tumors who underwent CGP to clarify cancer genome medicine's current status and possible problems at the Tokushima University Hospital. The major types of cancer included pancreatic (n=30), colorectal (n=25), biliary tract (n=15), gastric (n=11), and hepatocellular carcinoma (n=8). CGP tests included F1CDx in 70 patients (57%), F1LCDx in 36 (30%), TSO500 in 14 (11%), and NCC Oncopanel in 2 (2%). Actionable gene alterations were identified in 72 patients (59%), but only 5 patients (4%) were treated for pancreatic (n=1), colorectal (n=3), and small bowel cancers (n=1). The main reasons for not receiving genotype-matched therapy included the lack of appropriate drugs or clinical trials that matched the actionable gene alterations (n=40) and the inability to participate in clinical trials (n=10). There is still not a sufficient number of patients receiving genotype-matched treatment for gastrointestinal cancers. To promote cancer genome medicine in regional areas, attempts to improve access to genotype-matched therapies are required, as well as to promote the development of new molecular-targeted drugs and clinical trials for these drugs. J. Med. Invest. 70 : 154-159, February, 2023

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INTRODUCTION

Recently, next-generation sequencing (NGS)-based comprehensive cancer genome profiling (CGP) has been introduced in clinical practice and is increasingly integrated into the routine care of patients with solid tumors. Although randomized phase II trials of patients with metastatic solid tumors refractory to standard therapy did not show efficacy of CGP (1), retrospective studies of patients who had not completed standard therapy showed efficacy of CGP (2, 3). In the United States, several NGS-based CGP tests have been approved by the United States Food and Drug Administration, and patients can routinely undergo CGP. In Japan, the National Cancer Center (NCC) launched the TOP-GEAR project in 2013 and developed the NCC Oncopanel, which uses NGS to analyze 114 cancer-related genes (4). In the study of the NCC Oncopanel with 230 advanced solid tumors, genetic profiling data were available for 187 (81.3%) patients, and 111 (59.4%) had actionable genetic alterations. Of these, 25 (13.3%) patients received molecularly targeted therapy based on their genetic alterations (4), suggesting the usefulness of CGP in clinical settings. Additionally, the Center for Cancer Genomics and Advanced Therapeutics (C-CAT) was established at the NCC in 2018 to collect genomic information and clinical characteristics of patients undergoing CGP. The C-CAT serves as a central database for cancer genomic medicine and assists the attending physician in decision making by providing a report of clinical trial information that matches patients' genomic data (5).

Starting in June 2019, two CGP tests, FoundationOne® CDx cancer genome profiling (F1CDx) and OncoGuide™ NCC Oncopanel System (NCC Oncopanel) were reimbursed by the National Health Insurance System. F1CDx has also been approved as a companion diagnostic agent. For example, if the *FGFR2* fusion gene is found using this test in biliary tract cancer cases, the use of pemigatinib can be covered by insurance. In addition, pemprolizumab can be used when microsatellite instability-high (MSI-H) or tumor mutation burden-high (TMB-H ; ≥10 Muts/Mb) is detected, and entrectinib and larotrectinib are available as reimbursable treatments when the *NTRK* fusion gene is detected. The NCC Oncopanel is a matched-pair test comparing DNA obtained from tumor cells with DNA derived from normal tissue (peripheral blood). Some germline pathological variants can be detected using DNA derived from normal tissue. Although it is not approved as a companion diagnostic agent, if approved by an expert panel, certain drugs can be used in the same way as a companion diagnostic for F1CDx under the insurance reimbursement. In August 2021, the FoundationOne® Liquid CDx cancer genome profiling (F1LCDx) was also approved for reimbursement, expanding the range of testing options. F1LCDx is a liquid biopsy test that does not require tissue collection, allows easy specimen collection, and provides profiling information based on cancer heterogeneity. However, it is possible that accurate results may not be obtained if the amount of circulating tumor DNA in the blood is insufficient due to the effects of anticancer drugs or other factors. Furthermore, it should be noted that the companion diagnostic framework of this test differs significantly from that of F1CDx. Currently, the companion diagnoses of MSI-H and TMB-H approved for F1CDx are not permitted for F1LCDx, and only entrectinib is approved for *NTRK*. For the *FGFR2* fusion

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gene, there is still no consensus on the use of pemigatinib based on F1LCDx. Thus, the hurdle in using F1LCDx in the clinical setting is high from the drug use aspect. Yet, TSO500, which was introduced at Okayama University Hospital on December 1, 2020, was implemented within the framework of the Advanced Medical Care (Advanced Medical Care B) System. Compared to the conventional cancer gene panel test, the TSO500 can examine 523 genes, and is expected to increase the possibility of finding a therapeutic drug. Moreover, these applications have been restricted to patients with advanced solid tumors that do not respond to standard therapy or patients for whom there is no appropriate standard therapy. These regulations for CGP testing indicate that many issues need to be resolved to promote the use of CGP testing in Japan.

Currently, there are 12 core hospitals, 33 hub hospitals, and 188 liaison hospitals for cancer genome medicine in Japan (6). Core and hub hospitals are required to set up "expert panels" where multidisciplinary experts clinically interpret the genomic information from the CGP test results. Under this system, cancer genome testing is now being conducted in general clinical practice.

In the Chugoku and Shikoku block, the core hospital for cancer genome medicine is Okayama University Hospital. The three hub hospitals are Hiroshima University Hospital, Kagawa University Hospital, and Shikoku Cancer Center. Tokushima University Hospital is currently a liaison institution with Okayama University Hospital (as of November 1, 2022). However, there are only a few cases in the Tokushima Prefecture that can benefit from clinical trials and studies based on cancer genome test results since it is located far away from the metropolitan area. Furthermore, the spread of coronavirus disease (COVID-19) makes it difficult for patients to visit distant medical institutions, making it an urgent issue to develop a treatment strategy that considers these factors. Therefore, this study was conducted to clarify the current status of cancer genome medicine in the Department of Gastroenterology at Tokushima University Hospital, where the number of cancer gene panel tests is the highest.

PATIENTS AND METHODS

Ethics statements

This study was approved by the Ethics Committee of the Tokushima University (number : 4223), and the need for informed consent was waived. The patient records were anonymized and deidentified before analysis. All procedures in studies involving human participants were conducted in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Patients

In this observational study, the medical records of 122 patients with histopathologically confirmed gastrointestinal tumors, who underwent NGS-based multiplex gene assays between December 2019 and September 2022 at the Department of Gastroenterology, Tokushima University Hospital, were analyzed retrospectively. The primary objectives of the study were to detect actionable gene alterations in CGP tests, the percentage of patients who received genotype-matched therapy, and the detection rate of germline findings.

NGS-based CGP tests

The following Japanese publicly insured CGP tests were used for patients with solid tumors without standard treatment and patients with locally advanced or metastatic cancer who completed standard treatment (including those expected to complete treatment). F1CDx (Chugai) 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) (7). F1LCDx (Chugai) obtains genetic mutation information similar to F1CDx from free DNA obtained from plasma isolated from the whole blood of patients with solid tumors (8). The NCC Oncopanel (NCC Oncopanel, Sysmex Corporation) carries 114 genes and determines base substitution, insertion/deletion mutations, gene amplification of 114 genes, fusion of 12 genes, and TMB. DNA derived from non-tumor cells (peripheral blood) is used as the control. Thus, the NCC Oncopanel can distinguish between genetic mutations of somatic and germline origin (9). In addition, some patients received Illumina's TruSight Oncology 500 (TSO500) test, which employs a hybrid-capture approach for target enrichment of 523 clinically-relevant cancer genes with unique molecular indices to enable detection of low frequency variants, copy number variants, DNA fusions, and TMB and MSI analyses (10) through the Advance Medical Care B system.

Flow of the clinical sequencing

At the first outpatient visit with the genomic medicine physician, the outline of the CGP test was explained, and patient consent was obtained. Then, a pathologist determined whether stored formalin-fixed paraffin-embedded tumor tissue was available and whether the amount of tissue and percentage of tumor were sufficient. If the tissue is suitable for the CGP test, the testing company performs the analysis, and the CGP test results and patient information are registered in C-CAT. Next, the C-CAT report, which includes information on the level of evidence of therapeutic efficacy of drugs for genomic abnormalities, availability of therapeutic drugs, and clinical trials suitable for the patient's genotype, is sent to the core base hospital, Okayama University Hospital, where an expert panel is held. The expert panel included oncologists, pathologists, bioinformaticians, medical geneticists, certified genetic counselors, cancer genomic medicine coordinators, cancer genomic medicine specialists, and attending physicians. The accessibility of therapeutics presented in the C-CAT report was discussed by the panel based on guidance (11). Actionable gene alteration was defined as an alteration at evidence level D (biomarkers are associated with efficacy in a few case reports) or higher. The expert panel decided to recommend genotype-matched therapy considering the patient's treatment history, background, the level and details of the evidence, and the accessibility of the drug. Additionally, some patients with gene alterations with an evidence level E (biomarkers have plausible therapeutic significance based on preclinical studies) or F (gene abnormality involved in cancer) were also provided with information on genotype-matched treatments, including phase I trials for *TP53* and *KRAS* mutations.

RESULTS

Patient and tumor samples

From August 2019 to July 2022, 122 patients with gastrointestinal cancer refractory to standard chemotherapy underwent CGP at Tokushima University Hospital. Patient characteristics are summarized in Table 1. Patients' median age was 65 years (range, 33–68 years). Common tumor types included pancreatic cancer (30 cases, 25%), colorectal cancer (26 cases, 21%), biliary tract cancer (15 cases, 12%), gastric cancer (11 cases, 9%), and hepatocellular carcinoma (8 cases, 7%). Seventy-seven samples (63%) were collected from the primary site, and nine samples (7%) were collected from metastatic sites using biopsy (34%),

surgical resection (29%), endoscopic ultrasound-fine needle aspiration (EUS-FNA) (8%), and cell block from ascites (1%). Specimens were collected from peripheral blood in 30% of all patients. CGP tests included F1CDx in 70 (57%), F1LCDx in 36 (30%), TSO500 in 14 (11%), and NCC Oncopanel in 2 (2%) (Table 2). According to F1LCDx using blood samples, 14 cases (14/36, 39%) were pancreatic cancer, and 9 cases (9/36, 25%) were biliary tract cancer, with biliopancreatic cancer accounting for most cancers. However, according to CGP (F1CDx, NCC Oncopanel, and TSO500) using tissue samples, 17 cases (17/86, 20%) were pancreatic cancer, and 1 case (1/86, 1%) was biliary tract cancer, indicating that F1LCDx was more frequently used in biliopancreatic cancer than other cancers.

Identification of actionable gene alterations

Overall, actionable gene alterations were identified in 72 patients (59.0%) (Figure 1). The most frequent alterations were *TP53* mutations in 55% (67/122), *KRAS* mutations in 35% (43/122), and *APC* mutations in 22% (27/122).

The frequency of *TP53* by tumor was as follows : neuroendocrine cancer (NEC), 4/4 cases (100%) ; colorectal cancer, 20/25 cases (80%) ; gastric cancer, 8/11 cases (73%) ; pancreatic cancer, 14/30 cases (47%) ; biliary system cancer, 6/15 cases (40%) ; and hepatocellular carcinoma, 2/8 cases (25%). The frequency of *KRAS* by tumor was as follows : pancreatic cancer, 17/30 (56.7%) ; colorectal cancer, 10/25 (40%) ; biliary tract cancer, 5/15 (33.3%) ; gastric cancer, 3/11 (27.3%) ; NEC, 1/4 (25%) ; and hepatocellular carcinoma, 0/8 (0%). The frequency of *APC* by tumor was as follows : colorectal cancer, 19/25 (76%) ; NEC, 1/4 (25%) ; biliary tract cancer, 2/15 (13.3%) ; pancreatic cancer, 2/30 (6.7%) ; gastric cancer, 0/11 (0%) ; and hepatocellular carcinoma, 0/8 (0%).

Therapeutic implications of actionable gene alterations

Sixty-nine patients (56.6%) were provided with information on genotype-matched therapy as recommended by the expert panel. By cancer type, these included pancreatic cancer (20/69, 66.7%), colorectal cancer (18/69, 72%), biliary tract cancer (7/69, 46.7%), gastric cancer (5/69, 45.5%), NEC (2/69, 50%), and others (17/69, 47.2%). Of the 69 patients who were provided with information on genotype-matched treatments, only 5 (5/122, 4.1%) received treatment by November 2022. Treatment was provided by public health insurance (2 cases) and by the patient-requested medical care system (3 cases). By cancer type, pancreatic cancer (1 case), colorectal cancer (3 cases), and small bowel cancer (1 case) were treated (Table 3). The treatment effect of these patients was progressive disease in 1 patient and partial response in 1 patient. Three patients used patient-requested medical care system, and their progress is not available yet.

The main reasons for not receiving genotype-matched treatment were a lack of appropriate drugs or clinical trials that matched the actionable genetic alteration (40 patients), inability to participate in clinical trials due to the distant location of the trial site (10 patients), deterioration of the patient's general condition (10 patients), failure to meet clinical trial eligibility criteria, or end of the enrollment period of the clinical trials (4 patients).

Incidental findings

Presumed germline pathogenic variant (PGPV) or germline variants were found in 10 patients, all of whom chose to disclose and were informed of the findings. Of these 10 patients, 2 (2/10,20%) received genetic counseling. Two patients with PGPV underwent germline testing, which was negative ; PGPVs were *ATM* (n=4), *BRCA2* (n=3), *KIT* (n=1), and *MEN1* (n=2).

Table 1. Characteristics of the 122 patients

Characteristic	Number of patients (%)
Age	
Median, years	65
Range	33–68
Sex	
Male	70 (57)
Female	52 (43)
Tumor type	
Pancreatic cancer	30 (25)
Colorectal cancer	26 (21)
Biliary tract cancer	15 (12)
Stomach cancer	11 (9)
Hepatocellular carcinoma	8 (7)
Neuroendocrine tumor	7 (6)
Neuroendocrine cancer	4 (3)
Carcinoma of unknown primary site	4 (3)
Duodenal cancer	4 (3)
Esophageal cancer	4 (3)
Small intestine cancer	3 (2)
Sarcoma (small intestine)	3 (2)
Melanoma (rectum)	1 (1)
Peritoneal Mesothelioma	1 (1)
GIST (stomach)	1 (1)
Gastric sarcomatoid carcinoma	1 (1)

GIST, gastrointestinal stromal tumor.

Table 2. Samples

Characteristic	Number of patients (%)
Site of the specimen	
Primary site	77 (63)
Metastatic site	9 (7)
Peripheral blood	36 (30)
Specimen type	
Biopsy	42 (34)
Peripheral blood	36 (30)
Surgical resection	35 (29)
EUS-FNA (pancreas)	8 (7)
Cytological specimen	1 (1)
Cancer gene panel	
FoundationOne CDx	70 (57)
FoundationOne Liquid CDx	36 (30)
Sight Oncology 500 (TSO500)	14 (11)
NCC Oncopanel	2 (2)

EUS-FNA, endoscopic ultrasound-fine needle aspiration.

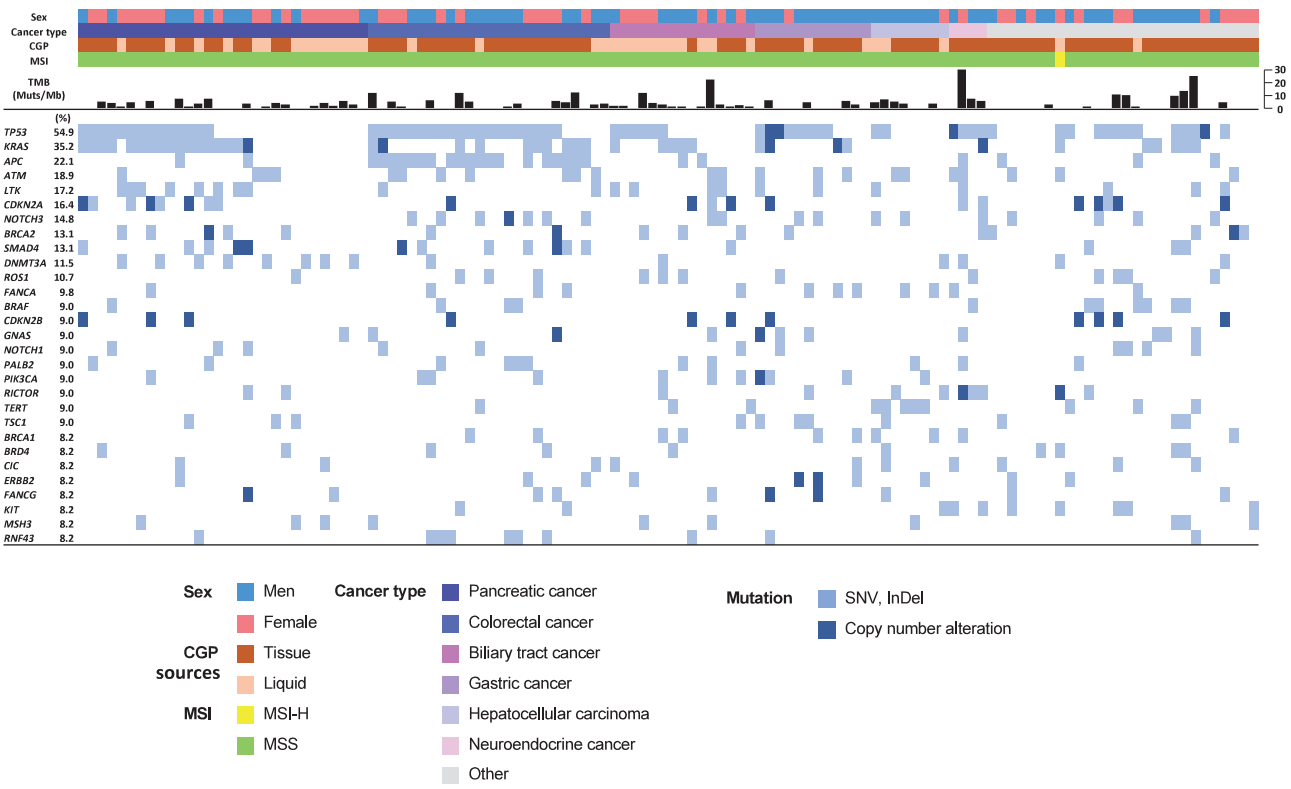

Figure 1. Heatmap describing the potentially actionable mutations identified in each patient by cancer type. Each column represents 1 patient, and each row represents 1 gene. SNV, single nucleotide variant ; CGP, cancer genome profiling ; MSI-H, microsatellite-instability-high ; MSS, microsatellite-stable.

Table 3. Detailed information of the genotype-matched treatments (5 patients)

Tumor type	Targeted gene alteration	Drug	Treatment	Number of treatment lines	Best response
Small intestine	TMB-high	Atezolizumab	Patient-requested medical care system	3	#
Colon	TMB-high	Pembrolizumab	Public health insurance	5	PD
Colon	*MET*	Capmatinib	Patient-requested medical care system	5	#
Colon	TMB-high	Pembrolizumab	Public health insurance	3	PR
Pancreatic	*ROS1*	Crizotinib	Patient-requested medical care system	4	#

TMB, tumor mutational burden ; PD, progressive disease ; PR, partial response.
We could not access the patients' responses from the patient-requested medical care system.

DISCUSSION

The ability of patients with gastrointestinal cancer to undergo tumor molecular profiling and receive appropriate targeted therapy remains a major challenge. In this study, we analyzed the clinical data of patients with gastrointestinal cancer who underwent CGP at Tokushima University Hospital to clarify the status of using CGP for patients with gastrointestinal cancer in the Tokushima prefecture. We found that only 4% of patients received targeted therapies, although 59% had actionable alterations, mainly because of either the aggressiveness of the disease or poor access to genotype-matched therapy.

Pancreatic cancer, which accounted for the highest number of our CGP cases, is one of the cancers with the poorest prognosis and, therefore, was the most common candidate for CGP ; yet, the number of cases in which CGP could be performed was limited because of the difficulty in obtaining sufficient tumor specimens. Recently, however, with the increase in the number of cases collected by EUS-FNA (8/30, 27%) and the introduction of F1LCDx in 2021, the number of CGP cases has increased and accounts for 47% (14/30) of the total GCP cases, nearly half of all cases. Similarly, the number of F1LCDx cases for biliary tract tumors, for which specimen collection is difficult, also increased, accounting for 60% (9/15) of all cases. Thus, biliary tract and pancreatic cancers accounted for more than half (64%, 23/36) of the cancer cases in which F1LCDx was performed, and we expect that future accumulation of cases will validate the usefulness of liquid biopsy. It should be noted, however, that the risk of false negatives in liquid biopsy should be considered in pancreatic cancer because of the low amount of circulating

tumor DNA (12).

Herein, actionable gene alterations were identified in 72 patients (59.0%), which is consistent with findings of previous CGP reports (4, 13, 14). For example, the TOP-GEAR project in Japan, using the NCC Oncopanel, reported that 59.4% of patients had actionable gene aberrations (4). In a large cohort study of MSK-IMPACT in the United States, 37% of patients had clinically relevant alterations (13). Thus, the current detection rate of actionable genetic abnormalities is not sufficient, and this is considered a limitation of current CGP testing. To address this issue, incorporating whole-exome sequencing, whole genome sequencing, transcriptome, and immunological gene profiling into the decision-making process in the future may improve the detection of actionable genes for individual patients with cancer (15).

In the MSK-IMPACT cohort study of > 10,000 patients, the proportion of patients enrolled in genotype-matched clinical trials was 11% (13), and previous Japanese studies (4, 14, 16) reported that 13.3% to 15.2% of patients received genotype-matched therapies. Yet, in the present study, among 122 patients who underwent the CGP, only 5 patients (5/122, 4%) received treatment, a relatively small population compared to that in the previous reports. Among them, TMB-H was the most common (3/5, 60%) in 3 patients, 2 of whom were treated with pembrolizumab under the insurance scheme. Thus, genotype-matched therapies will be facilitated if more drugs can be reimbursed by national health insurance.

To promote genotype-matched therapies, it is imperative to develop new molecular-targeted drugs that target actionable genetic alterations. However, a problem in regional areas is that patients cannot participate in clinical trials because of the long distance between their homes and the clinical trial sites, which was the case in as many as 10 patients in the present study. In general, patients who can benefit from clinical trials based on cancer genome test results are concentrated in the Tokyo metropolitan area, and participation from local areas is often difficult due to economic and social factors. In addition, the COVID-19 pandemic has made it difficult for patients to visit medical facilities in other regions. In particular, for patients who are physically weak after standard treatment, it is extremely difficult for patients from the Shikoku regions to participate in a clinical trial in a metropolitan area. To improve access to genotype-matched treatment, it is necessary to share clinical trial information among core, hub, and liaison hospitals, expand the number of facilities conducting clinical trials, and develop nationwide access.

In addition, a total of 10 patients were unable to participate in the clinical trials due to deterioration of their general condition or even death. In Japan, CGP is currently covered by public insurance only for patients who have completed or are scheduled to complete standard chemotherapy. Gastrointestinal cancer is a disease that can easily lead to systemic deterioration due to gastrointestinal obstruction, cholangitis, jaundice, peritoneal dissemination, and malignant ascites during tumor progression, and performance status often deteriorates rapidly over a few weeks. In patients who applied for cancer genome testing after all standard treatments had failed, the disease had already worsened by the time the results were returned, and even if actionable mutations were detected, they often did not meet the criteria for inclusion in a clinical trial. In particular, the application timing for cancer genome testing should be carefully considered, particularly for rapidly progressing cancers, such as biliary tract and pancreatic cancers.

In other countries, retrospective studies in patients with metastatic solid tumors who have not completed standard treatment have shown the efficacy of genotype-matched therapy (3, 17), suggesting that CGP testing is likely to be beneficial. In Japan, since June 2020, the NCC Hospital has been conducting a prospective study to evaluate the feasibility and usefulness of comprehensive genomic profiling testing before the first systemic treatment under the advanced medical care system (clinical trial registration number : UMIN000040743) (18).

Moreover, Japanese regulations make it difficult to use off-label drugs. Therefore, the availability of off-label drugs depends on the patient's economic status. To facilitate access to off-label drugs, designated core hospitals are conducting a phase II basket study (the NCCH1901/BELIEVE study) using multiple targeted drugs based on the results of genetic profiling using a multi-gene panel test. The Japanese patient-proposed health care services were used for this study, and 3 patients have been enrolled in our study. In the future, it is desirable to enhance the support system for the implementation of cancer genome medicine, such as the establishment of a permanent system for the provision of these drugs and the prompt approval by insurance of drugs that have been proven to be effective.

A limitation of this study is that the outcomes were analyzed for a limited and small number of patients at a single institution, but analysis of the status of CGP in the region may help to elucidate regional disparities in cancer genomic medicine.

In conclusion, clinical sequencing of 122 gastrointestinal cancer cases at Tokushima University Hospital revealed that 69 patients (56.6%) were provided with information on genotype-matched therapy, but only 5 (4%) received treatment. To promote cancer genome medicine in local areas, it is expected not only to develop and implement effective new molecular-targeted drugs but also to improve regional disparities by promoting clinical trials and access to treatments in the region.

CONFLICTS OF INTEREST

There is no conflict of interest to declare.

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