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Chronological improvement in precision oncology implementation in Japan

Kuniko Sunami[1] | Yoichi Naito[2] | Keigo Komine[3] | Toraji Amano[4] |
Daisuke Ennishi[5] | Mitsuho Imai[6] | Hidenori Kage[7] | Masashi Kanai[8] |
Hirotsugu Kenmotsu[9] | Takafumi Koyama[10] | Takahiro Maeda[11] | Sachi Morita[12] |
Daisuke Sakai[13] | Shinji Kohsaka[14] | Katsuya Tsuchihara[15] | Yusuke Saigusa[16] |
Takayuki Yoshino[17]

[1]Department of Laboratory Medicine, National Cancer Center Hospital, Tokyo, Japan

[2]Department of Breast and Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan

[3]Department of Medical Oncology, Tohoku University Hospital, Sendai, Japan

[4]Clinical Research and Medical Innovation Center, Hokkaido University Hospital, Sapporo, Japan

[5]Department of Hematology and Oncology, Okayama University Hospital, Okayama, Japan

[6]Genomics Unit, Keio University School of Medicine, Tokyo, Japan

[7]Department of Next-Generation Precision Medicine Development Laboratory, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[8]Department of Therapeutic Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

[9]Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan

[10]Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan

[11]Department of Hematology, Oncology and Cardiovascular Medicine, Kyushu University Hospital, Fukuoka, Japan

[12]Department of Clinical Oncology and Chemotherapy, Nagoya University Hospital, Nagoya, Japan

[13]Center for Cancer Genomics and Personalized Medicine, Osaka University, Suita, Japan

[14]Section of Knowledge Integration, Center for Cancer Genomics and Advanced Therapeutics, National Cancer Center, Tokyo, Japan

[15]Division of Translational Informatics, National Cancer Center Exploratory Oncology Research and Clinical Trial Center, Tokyo, Japan

[16]Department of Biostatistics, Yokohama City University Graduate School of Medicine, Yokohama, Japan

[17]Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Correspondence
Takayuki Yoshino, Department of Gastrointestinal Oncology, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa-shi, Chiba 277-8577, Japan,
Email: tyoshino@east.ncc.go.jp

Abstract

In Japan, comprehensive genomic profiling (CGP) tests for refractory cancer patients have been approved since June 2019, under the requirement that all cases undergoing CGP tests are annotated by the molecular tumor board (MTB) at each government-designated hospital. To investigate improvement in precision oncology, we evaluated and compared the proportion of cases receiving matched treatments according to CGP results and those recommended to receive genetic counseling at all core hospitals between the first period (11 hospitals, June 2019 to January 2020) and second

period (12 hospitals, February 2020 to January 2021). A total of 754 and 2294 cases underwent CGP tests at core hospitals in the first and second periods, respectively; 28 (3.7%) and 176 (7.7%) patients received matched treatments ($p < 0.001$). Additionally, 25 (3.3%) and 237 (10.3%) cases were recommended to receive genetic counseling in the first and second periods, respectively ($p < 0.001$). The proportion was associated with the type of CGP test: tumor-only ($N = 2391$) vs. tumor-normal paired ($N = 657$) analysis (10.0% vs. 3.5%). These results suggest that recommendations regarding available clinical trials in networked MTBs might contribute to increasing the numbers of matched treatments, and that tumor-normal paired rather than tumor-only tests can increase the efficiency of patient referrals for genetic counseling.

KEYWORDS
comprehension genomic profiling test, genetic counseling, genomically matched therapy, molecular tumor board, precision oncology

1 | INTRODUCTION

Comprehensive genomic profiling (CGP) tests have been covered by the Japanese Public Health Insurance System since June 2019 (https://www.mhlw.go.jp/content/12400000/000514782.pdf). To assure the quality of precision oncology based on the result of CGP tests, the Ministry of Health, Labour and Welfare (MHLW) restricted reimbursement for CGP tests to those performed at designated hospitals (https://www.mhlw.go.jp/content/12400000/000514782. pdf),[1] which numbered 226 as of September 2019 (Core: 12, Hub: 33, Cooperative: 181; https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/gan/gan_byoin.html).

The current challenge in precision oncology is the accessibility to genomically matched therapies. We previously reported that 3.7% of tested cases received genomically matched treatment in the first 8 months after reimbursement for CGP tests at 11 Cores.[2] To provide patients with opportunities to receive genomically matched therapies, the National Cancer Center Hospital (NCCH) launched a prospective, patient-proposed platform trial of targeted agents (NCCH1901; jRCTs031190104) in October 2019. As of June 2021, 15 molecular-targeted agents, including two immune checkpoint inhibitors, were available in this trial (https://jrct.niph. go.jp/latest-detail/jRCTs031190104). In addition, since June 2019, the molecular tumor boards (MTBs) across all Cores and Hubs have been systematically networked to enhance sharing of information of available clinical trials for investigational new drugs (INDs) and to increase the proportion of patients who receive genomically matched treatments.

Genetic counseling plays an important role in dealing with germline findings detected by the CGP tests. In our previous report, 3.3% of tested cases were referred for genetic counseling among the 11 Cores.[2]

Here, we investigated the proportion of patients receiving genomically matched therapies and referral for genetic counseling.

Moreover, we explored factors affecting the accessibility of genomically matched drugs by focusing on the drug therapy type, such as INDs, NCCH1901, off-label use, and approved drugs, and the factors associated with differences in the proportion of patients referred for genetic counseling.

2 | METHODS

2.1 | Data collection

We collected data on cases that underwent CGP tests at all Cores between June 2019 and January 2020 (first period) and between February 2020 and January 2021 (second period). As one hospital was newly designated as Core in April 2020, the data were collected from 11 Cores in the first period and 12 Cores in the second period. We evaluated the number of cases that received genomically matched treatments and the number of patients who were recommended to be referred for genetic counseling in both periods. To investigate the factors affecting drug accessibility and frequency of genetic counseling references, information on the types of CGP tests (i.e., tumor-only test or tumor-normal paired test) and drug types in matched therapies were also collected. The NCC Institutional Review Board (IRB) officially confirmed that the present study did not require IRB approval or patient consent.

2.2 | Evaluation of improvement

To assess improvements in drug accessibility and frequency of genetic counseling references, the proportions of patients receiving matched treatments and referrals to genetic counseling between the first and second periods were compared using Fisher's exact test. The degree of association between the proportion of patients

receiving matched therapies and the number enrolled in clinical trials was assessed using Spearman's rank correlation.

All statistical analyses were performed with R version 3.5.1 (R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Increase in patients receiving genomically matched therapies

A total of 754 (range; 5-172) and 2294 (range; 83-450) cases underwent CGP tests at Cores in the first and second periods, respectively. The proportion of patients receiving genomically matched therapies increased at 10 hospitals (except hospital E). Among all Cores, a total of 28 and 176 cases received matched treatments in the first and second periods, respectively ($p < 0.001$, 3.7% vs. 7.7%) (Table 1).

In the second period, 107 of the 176 cases who received matched treatments (4.7% of the 2295 cases) participated in clinical trials including INDs ($n = 60$) and NCCH1901 ($n = 47$), and 17 cases (0.7% of the 2295 cases) received genomically matched drugs as off-label use. The remaining 52 cases (2.3% of the 2295 cases) received approved drugs (Table 2). In terms of INDs, the most common treatments were FGFR inhibitors for *FGFR/FGF* alterations ($n = 13$), followed by PARP inhibitors for *BRCA1/2* alterations ($n = 7$) and immune checkpoint inhibitors for high tumor mutation burden (TMB-high) ($n = 7$). Regarding approved drugs, pembrolizumab for microsatellite instability-high (MSI-high) tumors was the most common ($n = 12$) (Table S1). Compared with the first period, cases enrolled in clinical trials (2.1% vs. 4.7%, $p = 0.002$) and receiving approved drugs (1.1% vs. 2.3%, $p = 0.048$) were significantly higher in the second period (Table 2).

For the entire period, the proportion of patients receiving matched therapies was 6.7%, and there was variability in the proportion of therapy types among the 12 Cores (range; 2.4-10.4%) (Figure S1). The proportion of patients receiving matched therapies at each hospital correlated positively with the number of cases enrolled in clinical trials (Spearman's rank correlation coefficient, $R = 0.73$) (Figure S2).

3.2 | Increase in referrals for genetic counseling

While 25 cases (3.3%, range 0%-15.4%) were referred for genetic counseling in the first period, 237 cases (10.3%, range 2.9%-20.3%) were recommended to receive genetic counseling in the second period, indicating a significantly higher proportion in the second study period ($p < 0.001$) (Table 3).

For the entire period, 2391 cases and 657 cases were assessed by tumor-only analysis and tumor-normal paired analysis, respectively. While the proportion of cases recommended to receive genetic counseling was higher among those who underwent tumor-only analysis versus tumor-normal paired analysis (10.0 vs. 3.5%), the actual consultation rate for recommended cases was higher in cases of paired analysis (82.6 vs. 51.5%) (Table 4). Among cases recommended for genetic counseling by tumor-only analysis, 25.5% of cases received genetic tests to confirm pathogenic germline variants (PGVs), and 14.6% of cases had PGVs. On the other hand, no additional genetic tests were performed in any except two of the patients who underwent tumor-normal paired analysis.

TABLE 1 Proportion of patients who received genomically matched therapies in the first and second periods

| Core hospital | 1st period | | 2nd period | | P value |
	No. of patients who underwent CGP testing	No. of patients who received "matched" therapies (%)	No. of patients who underwent CGP testing (%)	No. of patients who received "matched" therapies	
A	75	3 (4.0%)	138	18 (13.0%)	
B	73	2 (2.7%)	201	12 (6.0%)	
C	5	0 (0.0%)	102	3 (2.9%)	
D	41	0 (0.0%)	158	6 (3.8%)	
E	160	16 (10.0%)	251	23 (9.2%)	
F	172	4 (2.3%)	450	47 (10.4%)	
G	13	1 (7.7%)	83	9 (10.8%)	
H	85	0 (0.0%)	218	15 (6.9%)	
I	13	0 (0.0%)	142	16 (11.3%)	
J	24	0 (0.0%)	221	6 (2.7%)	
K	93	2 (2.2%)	179	9 (5.0%)	
L	-	-	151	12 (7.9%)	
Total	754	28 (3.7%)	2294	176 (7.7%)	<0.001

Abbreviation: CGP, comprehensive genomic profiling.

TABLE 2 Proportion of patients who received genomically matched therapies by drug and therapy type

Core hospital	1st Period					2nd Period				
	All	Clinical trials		Off-label use	Approved drugs	All	Clinical trials		Off-label use	Approved drugs
		Investigational drugs	NCCH1901				Investigational drugs	NCCH1901		
A	75	3 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	138	1 (0.7%)	7 (5.1%)	2 (1.4%)	8 (5.8%)
B	73	2 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	201	1 (0.5%)	3 (1.5%)	0 (0.0%)	8 (4.0%)
C	5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	102	1 (1.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)
D	41	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	158	1 (0.6%)	0 (0.0%)	0 (0.0%)	5 (3.2%)
E	160	7 (4.4%)	0 (0.0%)	2 (1.3%)	7 (4.4%)	251	9 (3.6%)	9 (3.6%)	1 (0.4%)	4 (1.6%)
F	172	2 (1.2%)	0 (0.0%)	1 (0.6%)	1 (0.6%)	450	28 (6.2%)	4 (0.9%)	7 (1.6%)	8 (1.8%)
G	13	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	83	0 (0.0%)	7 (8.4%)	0 (0.0%)	2 (2.4%)
H	85	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	218	2 (0.9%)	7 (3.2%)	1 (0.5%)	5 (2.3%)
I	13	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	142	6 (4.2%)	4 (2.8%)	4 (2.8%)	2 (1.4%)
J	24	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	221	1 (0.5%)	1 (0.5%)	1 (0.5%)	3 (1.4%)
K	93	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	179	0 (0.0%)	4 (2.2%)	0 (0.0%)	5 (2.8%)
L	-	- (-)	- (0.0%)	- (-)	- (-)	151	10 (6.6%)	0 (0.0%)	0 (0.0%)	2 (1.3%)
Total	754	16 (2.1%)	0 (0.0%)	3 (0.4%)	8 (1.1%)	2294	60 (2.6%)	47 (2.0%)	17 (0.7%)	52 (2.3%)

TABLE 3 Proportion of patients referred for genetic counseling in the first and second periods

	1st period		2nd period		
Core hospital	No. of patients who underwent CGP testing	No. of patients referred for genetic counseling (%)	No. of patients who underwent CGP testing	No. of patients referred for genetic counseling (%)	P value
A	75	3 (4.0%)	138	28 (20.3%)	
B	73	0 (0.0%)	201	21 (10.4%)	
C	5	0 (0.0%)	102	3 (2.9%)	
D	41	1 (2.4%)	158	15 (9.5%)	
E	160	5 (3.1%)	251	22 (8.8%)	
F	172	2 (1.2%)	450	25 (5.6%)	
G	13	2 (15.4%)	83	7 (8.4%)	
H	85	0 (0.0%)	218	37 (17.0%)	
I	13	0 (0.0%)	142	25 (17.6%)	
J	24	2 (8.3%)	221	18 (8.1%)	
K	93	10 (10.8%)	179	13 (7.3%)	
L	-	-	151	23 (15.2%)	
Total	754	25 (3.3%)	2294	237 (10.3%)	<0.001

Abbreviation: CGP, comprehensive genomic profiling.

TABLE 4 Proportion of patients referred for genetic counseling by test type

	No. of patients who underwent CGP test		No. of patients recommended for genetic counseling		No. of patients who received genetic counseling	
	T-only analysis	T/N paired analysis	T-only analysis (%)	T/N paired analysis (%)	T-only analysis (%)	T/N paired analysis (%)
A	195	18	28 (14.4%)	3 (16.7%)	13 (46.4%)	3 (100%)
B	264	10	21 (8.0%)	0 (0.0%)	21 (100%)	0 (-)
C	59	48	1 (1.7%)	2 (4.2%)	1 (100%)	1 (50.0%)
D	141	58	13 (9.2%)	3 (5.2%)	13 (100%)	3 (100%)
E	383	28	27 (7.0%)	0 (0.0%)	14 (51.9%)	0 (-)
F	255	367	17 (6.7%)	10 (2.7%)	5 (29.4%)	7 (70.0%)
G	48	48	6 (12.5%)	3 (6.3%)	6 (100%)	3 (100%)
H	293	10	37 (12.6%)	0 (0.0%)	9 (24.3%)	0 (-)
I	138	17	25 (18.1%)	0 (0.0%)	7 (28.0%)	0 (-)
J	226	19	20 (8.8%)	0 (0.0%)	10 (50.0%)	0 (-)
K	246	26	21 (8.5%)	2 (7.7%)	12 (57.1%)	2 (100%)
L	143	8	23 (16.1%)	0 (0.0%)	12 (52.2%)	0 (-)
Total	2391	657	239 (10.0%)	23 (3.5%)	123 (51.5%)	19 (82.6%)

Note: T-only analysis: only tumor samples evaluated; T/N paired analysis: paired tumor/normal samples evaluated.

Abbreviation: CGP, comprehensive genomic profiling.

4 | DISCUSSION

Our results indicate a chronological improvement in the proportion of matched treatments and genetic counseling for cancers over the study period. A total of 754 and 2294 cases underwent CGP testing at core hospitals in the first and second periods, respectively, of whom 28 (3.7%) and 176 (7.7%) received matched treatments ($p < 0.001$). The proportion of patients referred for genetic counseling also increased from 3.3% to 10.3% ($p < 0.001$) during this period.

Evaluation of the improvement of drug accessibility by treatment type showed that cases enrolled in clinical trials (2.1% vs. 4.7%, $p = 0.002$) and those who received approved drugs (1.1% vs. 2.3%, $p = 0.048$) increased significantly over time. Moreover, we showed a positive correlation between the number of cases enrolled in clinical trials and the proportion receiving matched treatments at each

hospital ($R = 0.73$). These results suggest that improvement of enrollment in clinical trials might contribute to an increase in the number of matched treatments.

In the framework of Japanese precision oncology, CGP test results of each patient are required to be discussed in an MTB.[1] As the MTB makes recommendations for genomically matched treatments, including new investigational drugs, sharing the information of available clinical trials across all MTBs is important to improve accessibility to matched drugs.

The MTB also evaluates whether referral for genetic counseling is warranted based on the CGP test result. While tumor-only analyses only identify presumed germline pathogenic variants, tumor-normal paired analysis can confirm PGVs. Therefore, paired analysis can lead to more efficient referral of patients for genetic counseling in the MTB as compared with tumor-only analysis.

In conclusion, we achieved chronological improvement in the proportion of matched therapies and referrals for genetic counseling. For further improvement of precision oncology in Japan, it might be necessary to establish a systematically networked framework to share the latest information on clinical trials across all MTBs.

ORCID

Kuniko Sunami https://orcid.org/0000-0002-7137-5649
Yoichi Naito https://orcid.org/0000-0002-8490-9064
Mitsuho Imai https://orcid.org/0000-0001-8736-0399
Masashi Kanai https://orcid.org/0000-0002-6954-4474
Hirotsugu Kenmotsu https://orcid.org/0000-0003-0590-9259
Takafumi Koyama https://orcid.org/0000-0001-5807-8458
Sachi Morita https://orcid.org/0000-0002-3115-2336
Shinji Kohsaka https://orcid.org/0000-0001-8651-6136
Katsuya Tsuchihara https://orcid.org/0000-0001-7507-2349
Takayuki Yoshino https://orcid.org/0000-0002-0489-4756

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.