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Evaluating the Clinical Utility and Policy Impact of Next-Generation Sequencing Panel Testing under Japan's Universal Health-Care System: A Retrospective Study from a University Hospital

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ABSTRACT

Next-generation sequencing (NGS) has been integrated into routine cancer care in Japan, supported by coverage from the national universal health-care system. However, this reimbursement currently applies only to patients who have completed standard therapeutic options. In this retrospective analysis, we reviewed data from 221 individuals who received the Foundation One CDx (F1CDx) test at our university hospital. Each patient's sequencing results were evaluated by a molecular tumor board (MTB) to determine possible targeted treatment strategies. When patients consented, the MTB also reviewed potential germline variants, which were later disclosed during follow-up consultations. Among the total cases, 204 patients successfully underwent testing, and 195 results were analyzed. Due to disease progression, 13.8% of patients were unable to receive their reports. Of the 168 individuals who reviewed their results, 41.6% showed at least one actionable genomic alteration, and 3.6% received therapies matched to their genetic profiles. Presumed germline variants were identified in 24 patients, with 16.7% choosing to consult a genetics counselor.

Our findings indicate that performing NGS earlier in a patient's treatment timeline could enhance its clinical value. Broader insurance coverage for NGS testing would likely improve access to precision oncology and increase opportunities for matched therapies. Moreover, incorporating the disclosure of suspected germline variants appears to be a practical approach in daily clinical settings.

Keywords: Next-generation sequencing, Solid malignancies, National health insurance, Precision oncology, Germline variant disclosure

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Introduction

Over the past decade, advancements in molecular biology have deepened our understanding of cancer pathogenesis, leading to remarkable progress in diagnosis and treatment. The development of next-generation sequencing (NGS) has enabled rapid, large-scale genetic analysis at a reasonable cost, allowing clinicians to identify clinically significant mutations and apply precision oncology in routine care. Multiple studies have demonstrated that NGS-guided molecular profiling can enhance treatment response and survival outcomes in selected cancer populations [1–5].

For instance, the MOSCATO 01 trial showed that patients who received targeted therapies aligned with their genomic profiles experienced improved survival outcomes, with 33% (63 of 193) benefiting from matched treatments [4]. Similarly, the TAPUR study reported favorable clinical responses in several patient subgroups, such as those treated with pertuzumab plus trastuzumab for *ERBB2*-amplified or overexpressed colorectal cancer [6], vemurafenib plus cobimetinib for *BRAF V600E/D/K/-* mutated colorectal cancer [7], and pembrolizumab for metastatic breast and colorectal cancers characterized by high tumor mutational burden [8–10].

NGS testing has now become a standard component of cancer care in many countries, supported by reimbursement systems in both Western and Asian regions [11]. In Japan, national health insurance began covering two NGS-based panel tests—Foundation One CDx (F1CDx) and OncoGuide NCC Oncopanel System—in June 2019. These tests are available for patients with advanced malignancies who have completed all standard therapeutic options [12–14]. Although this represents a major milestone in implementing precision oncology nationwide, several practical challenges remain, including the interpretation of complex genomic data and the integration of personalized therapies into existing clinical workflows.

To evaluate the real-world applicability and clinical benefit of NGS in Japan's universal health-care setting, we retrospectively analyzed patients who underwent the F1CDx assay at our university hospital. This study reports detailed patient characteristics, detected genetic alterations—including presumed germline variants reviewed by the molecular tumor board (MTB)—and subsequent clinical interventions.

Results and Discussion

Feasibility of next-generation sequencing (NGS) and patient characteristics

Of the 221 patients initially enrolled, tumor samples from 213 were submitted for analysis, while nine were excluded due to insufficient tumor volume, as assessed by a pathologist. Ultimately, 204 patients underwent F1CDx testing, and successful sequencing results were obtained for 195 cases (95.6%). Test failures occurred due to inadequate tumor material (n = 4), poor DNA quality (n = 4), or sample contamination (n = 1).

Among the 195 successfully analyzed cases, 168 patients (86.6%) received their F1CDx results and corresponding MTB-reviewed reports in clinical consultations. However, 27 patients (13.8%) were unable to obtain results because of rapid disease progression—10 due to death and 17 due to declining health. The median turnaround time, defined as the interval from sample receipt to MTB review, was 43 days (range: 35–51 days).

Clinical and demographic data for the 168 patients are summarized in **Table 1**. The median patient age was 62 years (range: 3–92 years). Most patients (97%) had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1, and only five patients (3%) had a PS of 2. The majority had received multiple prior systemic therapies, with a median of three previous chemotherapy regimens (range: 1–11). Nearly half (44.6%, n = 75) were referred for NGS testing from smaller regional hospitals affiliated with our institution. The most prevalent tumor types were colorectal cancer (26.8%), sarcoma (13.1%), and pancreatic cancer (10.7%). The median overall survival following testing was 217 days (95% confidence interval: 185–262 days).

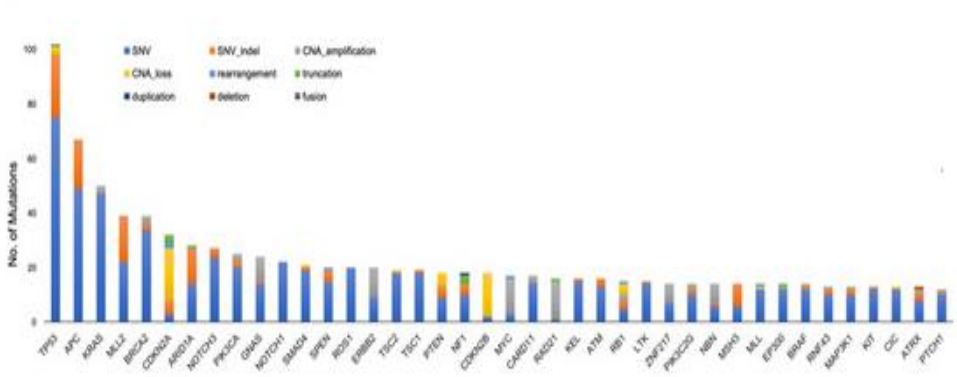
Table 1. Patient demographics and characteristics.

Total		**168**
Sex	Male (n, %)	87 (51.8)
	Female (n, %)	81 (48.2)
Age	Median (min/max)	62 (3/92)
ECOG PS	0 (n, %)	131 (78.0)
	1 (n, %)	32 (19.0)
	2 (n, %)	5 (3.0)
No. of previous chemotherapy lines	Median (min/max)	3 (1/11)
Referral to our hospital for NGS assay	Yes, n (%)	75(44.6)
	No, n (%)	93(55.4)
Tissue of Origin	Primary site (n, %)	111 (66.0)
	Metastatic site (n, %)	57 (34.0)
Turnaround Time	Average (min/max)	43 (35/51)
Cancer Type	Colorectal	45 (26.8)
	Sarcoma	22 (13.0)
	Pancreatic	18 (10.7)
	Gastric	13 (7.7)
	Ovarian	11 (6.5)
	Bile duct	9 (5.4)

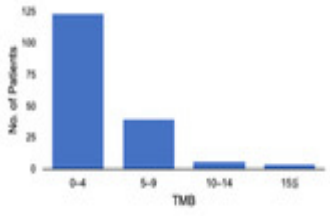
Esophageal	8 (4.8)
Breast	7 (4.2)
Cervical	6 (3.6)
Small Intestinal	5 (3.0)
Hepatocellular	3 (1.8)
Unknown Primary	3 (1.8)
Endometrial	3 (1.8)
Non-Small Cell Lung	3 (1.8)
Brain	3 (1.8)
Neuroblastoma	3 (1.8)
Melanoma	3 (1.8)
Kidney	1 (0.6)
Prostate	1 (0.6)
Urinary tract	1 (0.6)

NGS: next-generation sequencing; ECOG PS: Eastern Cooperative Oncology Group performance status.

An overview of the genomic alterations identified in this cohort is illustrated in **Figure 1a**. On average, each tumor harbored approximately 4.7 mutations, with values ranging from none to 14 per sample. The tumor mutational burden (TMB) had a median value of 2.52 mutations per megabase, spanning a range of 0 to 21.42, and eight patients were classified as having high TMB (TMB-H) **(Figure 1b)**.



a)



b)

Figure 1. (a) Top 40 genomic alterations and (b) distribution of tumor mutational burden (TMB) in 168 patients who completed analysis. CAN: copy number alteration; SNV: single nucleotide variant.

Implementation of targeted therapies based on genetic findings

Of the 168 patients who were provided with their sequencing results, 70 individuals (42%) exhibited at least one mutation considered actionable, amounting to 107 mutations overall **(Figure 2)**. Patients carried between one and five actionable alterations, with a median of 1.53 per patient. Classification according to OncoKB evidence levels

revealed that 9 mutations were level 1A, 6 were level 2, 6 were level 3A, 44 were level 3B, and 17 fell under level 4.

The genes most commonly implicated included PIK3CA (18 patients), TP53 (11 patients), ERBB2 (9 patients), MDM2 (6 patients), and FGFR3 (3 patients). Based on recommendations from the molecular tumor board (MTB), patients were directed toward different therapeutic options: one patient received advice solely for off-label drug use, 13 patients were guided to pursue both off-label therapies and clinical trials, and 56 patients were referred exclusively to clinical trials. Notably, 14 patients qualified for mutation-specific trials conducted at our hospital. Ultimately, six patients (3.6%) received treatments tailored to their genetic profile **(Figure 2)**. Four participated in a total of five clinical trials, four of which were hosted by our institution. Two patients received off-label targeted therapy, with one showing a significant clinical response. This patient, a 75-year-old woman with advanced cholangiocarcinoma, carried a high-copy ERBB2 amplification (CN = 114). She initially underwent dual HER2 blockade (trastuzumab and pertuzumab), achieving tumor control for nine months until pleural effusion developed. Subsequent therapy with trastuzumab deruxtecan led to tumor reduction within six weeks, but treatment was discontinued upon patient request due to grade 3 fatigue, which resolved over several weeks.

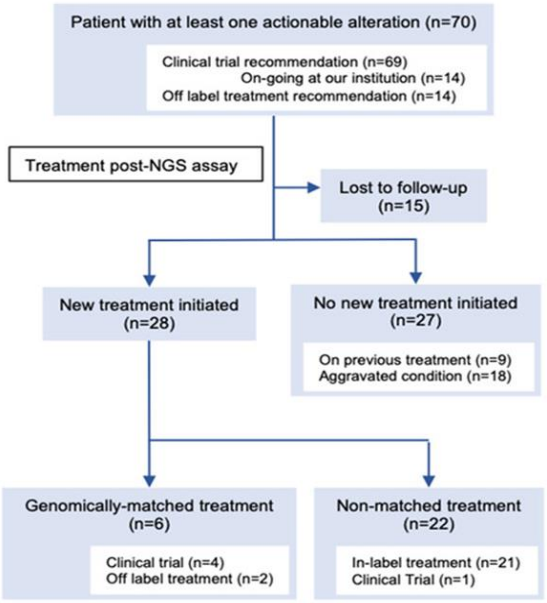
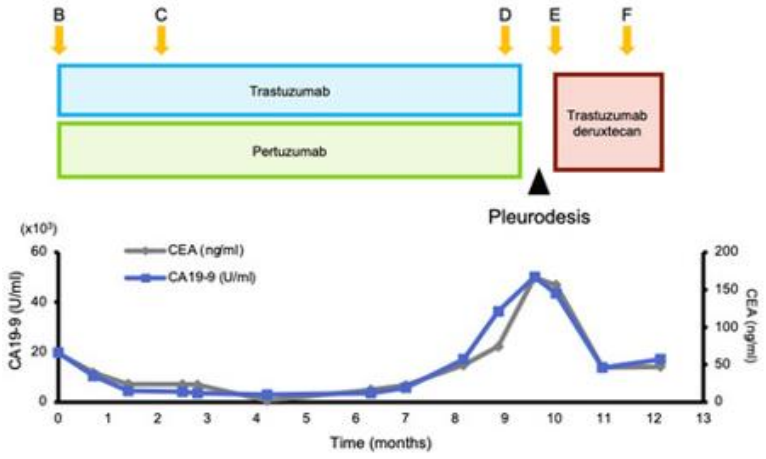


Figure 2. Flow diagram illustrating the post-NGS treatment outcomes for patients with one or more actionable mutations identified in the molecular tumor board (MTB) report. Some patients appear in multiple categories (e.g., receiving recommendations for both clinical trials and off-label therapy), so totals do not sum to the full cohort.



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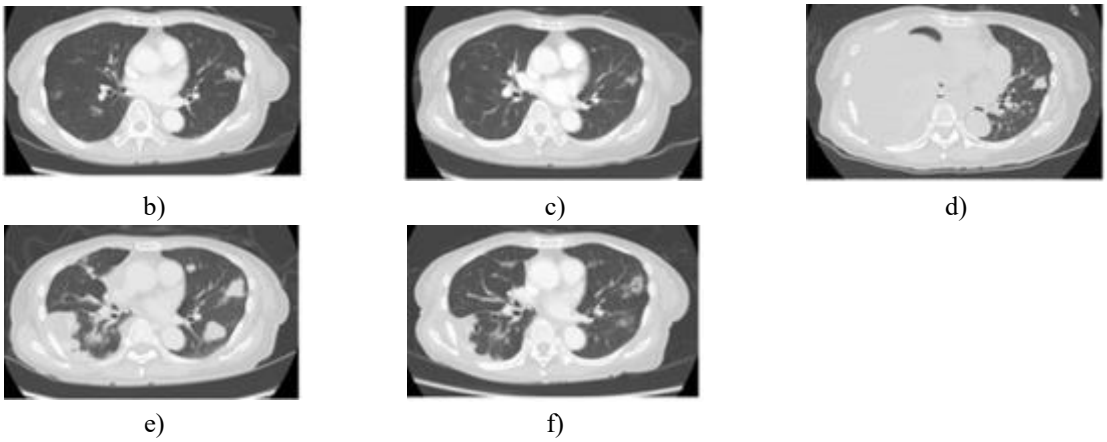

Figure 3. Treatment trajectory and imaging of a patient undergoing HER2-targeted therapy. (a) Changes in tumor markers, including CEA and CA 19-9, over the course of therapy. (b–f) Contrast-enhanced CT images documenting treatment response. At the initiation of trastuzumab/pertuzumab, multiple metastatic lesions were present in the lungs and liver (liver lesions not shown) (b). After two months, a notable partial response was observed (c). By nine months, disease progression manifested as a large right pleural effusion (d). Following pleurodesis (e), therapy was switched to trastuzumab deruxtecan, resulting in tumor reduction within six weeks (f).

Analysis of presumed germline variants

Most patients were interested in germline information, with 166 out of 168 (98.8%) opting to receive these results and 156 adult patients (95.1%) choosing to share the findings with relatives. A germline-focused analysis identified 26 potential pathogenic variants in 24 patients (14.3%) across multiple genes: SMAD4 (6 cases), BRCA2 (4), PTEN (3), BRCA1 (3), RB1 (2), STK11 (2), ATM, BRIP1, MSH6, RAD51, TP53, and TSC2 (1 case each) **(Table 2)**.

All presumed germline findings were documented in MTB reports and communicated directly to patients. Following disclosure, five patients (21%) sought genetic counseling, and one patient underwent confirmatory germline testing.

Table 2. Presumed germline findings nominated on MTB reports.

Gene	Cancer Type	SNV Function	SNV Nucleotide Change	SNV Amino Acid Change	RefSNP Number	CNA Number of Exons	CNA Position
ATM	Small intestinal	frameshift	c.6710dup	p.E2238fs*11	-	-	-
BRCA1	**Ovarian**	**nonsense**	**c.2800C > T**	**p.Q934 ***	**rs80357223**	-	-
	Small intestinal	missense	c.236T > G	p.F79C	-	-	-
	Ovarian	missense	c.5557T > A	p.Y1853N	-	-	-
BRCA2	Ovarian	nonsense	c.6952C > T	p.R2318*	rs80358920	-	-
	HCC	**frameshift**	**c.5110_5113delAGAA**	**p.R1704fs*1**	-	-	-
	Small intestinal	**missense**	**c.8524C > T**	**p.R2842C**	**rs80359104**	-	-
	Pancreatic	**nonsense**	**c.7969A > T**	**p.K2657 ***	-	-	-
BRIP1	Ovarian	nonsense	c.1741C > T	p.R581 *	rs780020495	-	-
MSH6	Esophageal	missense	c.1082G > A	p.R361H	rs63750440	-	-
PTEN	Uterine	nonsense	c.733C > T	p.Q245 *	rs786202918	-	-
	Ovarian	missense	c.376G > A	p.A126T	rs1554898129	-	-
	Breast	nonsense	c.295G > T	p.E99 *	-	-	-
RAD51	Gastric	frameshift	c.1dup	p.M1fs	rs55714242	-	-

RB1	Sarcoma	frameshift	c.869delA	p.N290fs*11	rs1131690901	-	-
	Colorectal (CNA_loss)	-	-	-	-	16 of 27	chr13:48881414-49010994
SMAD4	**Colorectal**	**missense**	**c.1487G > A**	**p.R496H**	**rs876660045**	-	-
	Colorectal	missense	c.1081C > T	p.R361C	rs80338963	-	-
	Colorectal	missense	c.290G > A	p.R97H	rs1555685159	-	-
	Colorectal	frameshift	c.282delC	p.Y95fs*15	-	-	-
	Pancreatic	nonsense	c.346C > T	p.Q116 *	-	-	-
	Bile duct	missense	c.1058A > G	p.Y353C	rs377767346	-	-
STK11	Gastric (CNA_loss)	-	-	-	-	8 of 9	chr19:1152647-1223171
	NSCLC	missense	c.580G > A	p.D194N	rs121913315	-	-
TP53	Ovarian	splice	c.672 + 1G > A	-	rs863224499	-	-
TSC2	Colorectal	nonsense	c.3412C > T	p.R1138 *	rs45451497	-	-

This study provides real-world insights into the use of NGS for patients with advanced cancers who had exhausted standard treatment options at our institution. Overall, the NGS assay demonstrated high feasibility in clinical practice, with a high success rate and typical turnaround time [15]. We also report how MTB recommendations, genomically matched therapies, and the management of presumed germline findings were integrated into routine care. The recurrently altered genes and the proportion of patients receiving MTB recommendations were consistent with other studies, but the proportion of patients who ultimately received targeted therapy based on NGS was lower in our cohort compared to previous reports [16–19]. Several factors likely contributed to this low treatment rate.

Firstly, the timing of NGS testing may have limited its utility. In Japan, NGS reimbursement is restricted to patients who have completed standard therapy and are eligible only for palliative care. Consequently, **27 patients (13.2%)** experienced disease progression or death while awaiting NGS results, making the findings unusable for treatment decisions. Disease progression is a well-known barrier to initiating therapy after NGS, as reported previously [19]. Although the optimal timing for NGS testing is still unclear, our data suggest that performing NGS earlier in the disease course could maximize its therapeutic benefit. Prospective studies are ongoing to evaluate the feasibility of performing large-panel NGS prior to first-line systemic therapy, with the goal of enabling reimbursement for frontline use in metastatic cancer patients in Japan [20]. Additionally, nearly half of the patients were referred from smaller community hospitals that lack MTB infrastructure, highlighting the need for early referral and education among clinicians to optimize NGS utilization.

Secondly, limited availability of early-phase clinical trials restricted opportunities for enrollment in genomically matched studies, consistent with prior reports [17, 21]. For comparison, a study from the National Cancer Center Hospital (NCCH) showed that 13.3% of patients (25/230) received matched targeted therapy after completing standard chemotherapy, which is approximately four times higher than the 3.6% (6/168) observed in our cohort [16]. NCCH has extensive early-phase trial programs, providing more opportunities for genomic-driven enrollment. To address this gap, our institution launched a basket/umbrella trial in July 2019, similar to the TAPUR study, offering 15 targeted agents for patients with actionable mutations [22]. In addition, virtual consultations and telemedicine platforms are gradually being integrated to enhance access to clinical trials [23, 24].

Thirdly, access to off-label targeted agents is limited under Japan's health-care system. Unlike in the United States and Europe, no formal expanded access programs exist, and the costs of off-label treatments are largely out-of-pocket. Each case also requires institutional review committee approval, making off-label prescribing restrictive [25]. In our study, the MTB recommended off-label therapy for 14 patients (8.3%), but only two received treatment, with one demonstrating clinical benefit. The MTB focused off-label recommendations on genetic alterations with evidence from prior trials, such as *ERBB2*, *BRCA1*, *BRCA2*, and *BRAF V600E*. While off-label

use can be beneficial, it also carries potential risks, and our conservative approach appears reasonable given the current system [26, 27].

The management of presumed germline findings is increasingly relevant. Both ESMO and ACMG recommend reporting such findings even from tumor-only sequencing. In our cohort, most patients consented to receive this information and share it with family members, reflecting similar preferences as reported in Western populations [28, 29]. A total of 26 presumed germline variants were identified in 24 patients; five consulted a genetic counselor, and one underwent confirmatory testing. While a genetic specialist is not strictly required for returning these results, the low uptake of genetic counseling suggests that closer collaboration with genetics professionals may improve patient follow-up [30].

This study has limitations. It is a single-center, retrospective analysis with a heterogeneous patient population, including individuals with advanced disease awaiting NGS approval. The short follow-up period (six months), patient attrition, and the small number of patients receiving targeted therapy limit the reliability of survival analyses, which are therefore not presented. Furthermore, presumed germline variants were inferred from tumor-only sequencing, making it difficult to definitively distinguish somatic from germline alterations. Careful interpretation is required.

Despite these limitations, this study provides the first real-world dataset of patients with various cancers undergoing NGS under Japan's universal health-care system, highlighting both feasibility and areas for improvement in precision oncology implementation.

Materials and Methods

Patients

We retrospectively reviewed the records of 221 consecutive patients treated at Osaka University who consented to undergo the Foundation One CDx assay, which is covered under Japan's public health insurance, between September 2019 and July 2020. The median follow-up for this cohort was 179 days, with a range of 48 to 439 days. Clinical and demographic data were obtained from medical charts.

NGS assay under national health insurance coverage

The process of performing NGS under Japan's universal health-care system has been described previously. In brief, patients were eligible if they had a confirmed diagnosis of a solid tumor and had completed or were completing standard chemotherapy. For patients under 20 years old, consent was obtained from a parent or guardian, along with patient assent. At the time of consent, patients and guardians were also asked whether they wished to be informed about potential germline findings.

Tumor specimens, either archival formalin-fixed paraffin-embedded blocks or 20 serial unstained slides, were reviewed by certified pathologists to assess tumor content and suitability for sequencing. Samples were then sent to Foundation Medicine for the F1CDx assay, which examines 324 genes. This includes all coding exons of 309 cancer-related genes, one promoter region, one noncoding RNA, and selected intronic regions of 34 genes frequently involved in rearrangements. The assay also measures tumor mutational burden and microsatellite instability.

After pathology review, DNA was extracted and libraries were prepared for sequencing. Libraries meeting quality standards were hybridized and sequenced. The resulting sequences were aligned to the human reference genome hg19, PCR duplicates were removed, and quality metrics were calculated. Local realignment was conducted, and variant calling was restricted to targeted regions. Tumor mutational burden was calculated by counting all coding synonymous and nonsynonymous single nucleotide variants and small insertions or deletions present at a frequency of 5% or higher, while excluding likely germline variants based on reference databases. Microsatellite instability was assessed across 95 intronic homopolymer loci, with an overall score generated using principal component analysis.

Following sequencing, the variant reports were reviewed by the molecular tumor board, which included clinicians, oncologists, pathologists, genetic counselors, and clinical geneticists. Each alteration was evaluated for clinical relevance using public databases and information on available genomically matched treatments or clinical trials in Japan. The MTB-approved report, containing recommended therapies, was then communicated to patients and, if appropriate, their families through the treating clinician.

Definition and classification of actionable mutations

Actionable mutations were defined as those for which the MTB recommended a matched therapeutic approach. Previously identified oncogenic variants were only considered actionable if they indicated treatment beyond standard care. Variants predicting resistance to therapy were excluded. Recommendations regarding tumor mutational burden were updated during the study period in line with the FDA approval of pembrolizumab for patients with TMB-high solid tumors.

Actionable variants were classified according to levels of clinical evidence. The highest level indicated FDA-approved biomarkers predictive of response to approved drugs for a specific cancer type. Other levels reflected standard-of-care biomarkers, clinical evidence within the same or other tumor types for investigational therapies, or biologically plausible targets without formal regulatory approval.

Presumed germline findings

After obtaining informed consent, a germline-focused analysis of tumor sequencing data was conducted. This process followed the recommendations of the Japan Agency for Medical Research and Development regarding genomic medicine information sharing [31]. A clinical geneticist reviewed 43 genes recommended for germline assessment using variant call files, with variant classification verified through databases including ClinVar and COSMIC.

The clinical relevance of each variant was then evaluated by a certified genetic counselor and the clinical geneticist, taking into account allele frequency, patient and family history, and clinical presentation. For BRCA1 and BRCA2, pathogenic and likely pathogenic variants were disclosed as presumed germline findings regardless of allele frequency. For other genes, pathogenic and likely pathogenic variants were typically reported if the allele frequency was 30% or higher for single nucleotide substitutions and 20% or higher for small insertions or deletions. For genes such as APC, RB1, TP53, or variants with allele frequencies below these thresholds, patient phenotypes were carefully reviewed prior to disclosure. All assessments were discussed and confirmed at the molecular tumor board before reporting.

Presumed germline findings were documented in the MTB-approved report and communicated to patients or their families through the primary clinician. Patients were offered genetic counseling and the option of confirmatory germline testing when relevant findings were identified.

Statistical analysis

Data analysis was performed using EZR, a graphical interface for R (The R Foundation for Statistical Computing). Descriptive statistics were used to summarize the majority of the data. Overall survival was estimated using the Kaplan–Meier method. The study was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice. Ethical approval was obtained from the Osaka University Institutional Review Board, and all participants provided written informed consent for the use of their clinical and genomic data in research.

Conclusion

This study provides insights into the practical use of NGS under Japan's universal health-care system at a single university hospital. Although precision oncology aims to match patients with appropriate therapies or clinical trials, only a small proportion of patients in this cohort received genomically guided treatments. Restricting NGS reimbursement to patients who have completed standard therapies results in delays, during which some patients experience disease progression, limiting the clinical utility of the test. Performing NGS earlier in the treatment course could enhance the opportunities for targeted therapy and improve patient outcomes.

Regional availability of clinical trials remains a barrier to implementing matched therapies. Our findings also indicate that the management of presumed germline findings is feasible in routine practice, demonstrating that NGS can be integrated into standard care. For precision medicine to be effectively implemented, NGS must be more fully integrated into the health-care system, allowing timely testing and optimized use of genomic data to guide treatment decisions.

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