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Comparative Analysis of a Dual DNA–RNA Panel and a DNA-Only Panel for Sarcoma: Real-World Data From a Nationwide Genomic Database

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ABSTRACT

Next-generation sequencing-based comprehensive cancer genomic profiling is promising in cancer management; however, most studies rely on tumor-only DNA panels from single institutions. In 2023, Japan introduced an insurance-covered cancer genomic profiling test—the GenMine TOP Cancer Genome Profiling System—a dual DNA–RNA panel with matched tumor–normal testing. This study evaluated its utility compared to a conventional DNA-only test (FoundationOne CDx) in managing sarcoma patients using a nationwide genetic profiling database provided by the Center for Cancer Genomics and Advanced Therapeutics. This study included 1046 patients registered between August 2023 and October 2024. The dual DNA–RNA test identified significantly more fusion genes (20.3% vs. 7.4%, $p < 0.001$) and therapeutically targetable kinase fusions (3.5% vs. 1.2%, $p = 0.019$) than the DNA-only test. Among patients with translocation-related sarcomas, histology-specific fusion genes were identified in 77.5% using the dual panel, compared to 40.0% with the DNA-only panel ($p < 0.001$). In non-gastrointestinal stromal tumor sarcomas, the dual test showed a trend toward higher rates of genotype-matched therapy (4.3% vs. 2.6%, $p = 0.25$) and a significantly higher rate of molecular targeted therapy (4.3% vs. 1.5%, $p = 0.03$). Additionally, 5.7% of patients had pathogenic germline variants identified through tumor–normal matched analysis. These findings suggest that a dual DNA–RNA panel with matched tumor–normal testing may improve diagnostic accuracy and inform treatment decisions in the routine clinical management of sarcoma.

Abbreviations: ACMG/AMP, American College of Medical Genetics and Genomics and the Association for Molecular Pathology; C-CAT, center for cancer genomics and advanced therapeutics; CGP, cancer genomic profiling; CNV, copy number variations; COSMIC, catalogue of somatic mutations in cancer; CPS, cancer predisposition syndromes; DDLS, dedifferentiated liposarcoma; DFSP, dermatofibrosarcoma protuberans; ES, ewing sarcoma; GenMine TOP, GenMine Top cancer genome profiling system; GPVs, germline pathogenic variants; LMS, leiomyosarcoma; MSI, microsatellite instability; MSS, microsatellite-stable; MTB, molecular tumor boards; NCC, National Cancer Center; NGS, next-generation sequencing; OS, overall survival; SNV, single nucleotide variants; STS, soft tissue sarcoma; SYNS, synovial sarcoma; TMB, tumor mutation burden; TRS, translocation-related sarcomas; ULMS, uterine leiomyosarcoma; VUS, variants of unknown significance.

1 | Introduction

The development of next-generation sequencing (NGS) has revealed various genetic mutations and functional pathways in different cancers [1, 2]. Large-scale databases such as the Catalogue of Somatic Mutations in Cancer (COSMIC) and the AACR Project GENIE have revealed the genomic landscape and novel therapeutic targets in sarcoma [3, 4]. NGS-based comprehensive cancer genomic profiling (CGP) tests are now widely implemented in clinical practice [1, 2]. In Japan, CGP testing was introduced in 2019, and the Center for Cancer Genomics and Advanced Therapeutics (C-CAT) was established as a national initiative to collect real-world genomic and clinical data from cancer patients, providing valuable resources for cancer genome research [5–10]. Currently, the Japanese public health insurance system reimburses five types of CGP tests. The first four are DNA-based, capable of detecting 124–309 gene alterations and 13–36 gene rearrangements: FoundationOne CDx cancer genome profiling (F1CDx, Chugai Pharmaceutical) and OncoGuide NCC Oncopanel System (NCC Onco-panel, Sysmex Corporation, Hyogo, Japan), FoundationOne Liquid CDx cancer genome profiling (F1LCDx; Chugai Pharmaceutical, Tokyo, Japan), and Guardant360 CDx (Guardant Health, Guardant Health Inc., Redwood City, CA, USA) [11]. Although the identification of fusion genes is essential in certain malignancies, such as sarcomas, these panels have limitations in detecting them effectively. Recently, cancer predisposition syndromes (CPS) have gained increased recognition due to the broader use of CGP tests [12, 13]. CGP tests reportedly play a crucial role in identifying germline alterations, which are detected in 3.3%–16.7% of patients with various malignancies undergoing CGP tests in clinical settings [12, 13]. However, most CGP tests utilize tumor-only sequencing, which cannot distinguish between somatic and germline variants. This limitation may lead to either a failure to confirm pathogenic germline variants or the misclassification of germline variants as somatic, thereby missing a CPS diagnosis. To resolve the limitations of the ordinary CGP test, its development was warranted.

In 2023, an insurance-covered CGP test called the GenMine TOP Cancer Genome Profiling System (GenMineTOP) was introduced in Japan [12, 14, 15]. GenMineTOP is a novel dual DNA–RNA panel that functions as a paired tumor–normal matched test. It simultaneously integrates and analyzes DNA and RNA data, detecting 737 gene alterations through its DNA panel and identifying 455 fusion transcripts, exon-skipping events in five genes, and expression levels of 27 genes via its RNA panel [10–14]. GenMineTOP offers several advantages over DNA-only panels. These include improved detection of gene fusions using the RNA panel, enhanced identification of potential therapeutic targets, and the ability to detect potential germline variants (PGVs), which are critical for identifying hereditary cancer predispositions. These features contribute to a more accurate diagnosis, better selection of targeted therapies, and assessment of hereditary cancer risk. The utility of GenMineTOP has been demonstrated in studies conducted under the Advanced Medical Care B program in various cancer types [12, 14, 15]. However, data on the utility of this panel in clinical settings after the implementation of insurance coverage is lacking.

Sarcomas are rare cancers, accounting for approximately 1%–2% of all malignancies [16]. Most sarcomas are treated with cytotoxic drugs, which show limited efficacy. Some sarcomas exhibit distinct molecular characteristics that are critical for accurate diagnosis and treatment planning. These include the *EWSR1::FLI1* fusion in Ewing sarcoma (ES), *SYT::SSX* fusion in synovial sarcoma (SYNS), and *MDM2* amplification in dedifferentiated liposarcoma (DDLS) [17]. Due to their rarity and heterogeneity of sarcomas, diagnostic errors are relatively common, with reported rates of up to 10.5% [18]. Several studies have examined the use of CGP in sarcoma [18–24], reporting that 32%–62% of patients harbor potentially actionable alterations, and 8%–16% receive therapies targeting these alterations. However, these studies primarily utilized DNA-only panels. The clinical performance of dual DNA–RNA panels, particularly in routine settings, has not yet been evaluated in patients with sarcoma. Therefore, we evaluated the clinical impact of GenMineTOP in the management of patients with sarcomas using real-world genomic data from Japan's nationwide C-CAT database.

2 | Material and Methods

2.1 | Study Population From the C-CAT Database

Genomic and clinical information of patients diagnosed with sarcoma was retrieved from the C-CAT on December 27, 2024, via the C-CAT portal (https://www.ncc.go.jp/en/c_cat/use/index.html). The study included patients registered between August 2023 and October 2024, which corresponds to the initial period of GenMineTOP data entry into the C-CAT database. Patients with benign bone and soft tissue tumors were excluded. The information includes genetic alterations, sex, age, Eastern Cooperative Oncology Group performance status, histology, specimen type, site and collection method, treatment before and after the oncogene panel test, date of last known alive, and date of death. Histological classifications were based on the World Health Organization (WHO) classification [16]. Histologic subtypes were grouped into three categories according to their known genetic features: translocation-related sarcomas (TRS), which are characterized by specific reciprocal translocations resulting in oncogenic fusion transcripts; genomically complex sarcomas, which exhibit multiple, complex karyotypic abnormalities without a recurrent pattern; and other sarcomas, defined by the presence of specific oncogenic mutations or recurrent amplifications (Table S1) [18].

2.2 | Comprehensive Genomic Profiling Tests

Two CGP tests reimbursed by the Japanese public health insurance system were used in this study: FoundationOne CDx (F1CDx, Chugai Pharmaceutical) and GenMineTOP (GenMine, Konica Minolta REALM Inc. Tokyo, Japan) (Table S2). The gene lists analyzed by each CGP test are shown in Table S3. F1CDx evaluates 324 genes and identifies single nucleotide variants (SNV), insertions/deletions (indels), and copy number variations (CNV, including amplifications and gains) in 309 genes. It also detects fusions involving 36 genes,

as well as microsatellite instability (MSI) and tumor mutation burden (TMB) [13]. F1CDx is a tumor-only panel and therefore cannot distinguish between germline and somatic mutations. In contrast, GenMineTOP is a dual-panel test that integrates DNA and RNA analysis. Its DNA panel detects 737 gene alterations, including SNV, indels, and CNV (amplifications), while its RNA panel identifies 455 fusion transcripts, exon skipping events in five genes, and expression profiles of 27 genes [10–13, 15]. The RNA panel targets RNA isolated from formalin-fixed paraffin-embedded tumor samples, converts it into cDNA, and uses targeted probes to capture specific regions of interest. GenMineTOP reports CNVs limited to amplifications but does not detect copy number losses. Additionally, MSI status is not assessed by this panel. GenMineTOP operates as a paired tumor-normal matched test; genomic DNA is also extracted from peripheral blood samples to serve as a normal reference, allowing for the discrimination between somatic and germline variants. Among the 40 genes analyzed for germline variants are *TP53*, *RB1*, *NF1*, and *BRCA1* (Table S3). Germline alterations were reported as pathogenic or likely pathogenic variants if classified accordingly in the ClinVar or Ambry Genetics databases [25, 26]. In addition, null variants in tumor suppressor genes were also considered germline pathogenic variants. Further technical details regarding the CGP assays and the associated bioinformatics pipelines can be found in previously published studies [10–13, 15].

2.3 | Annotation of the NGS Results

The C-CAT was established at the National Cancer Center (NCC) to centralize genomic and clinical data from patients undergoing CGP reimbursed by public health insurance in Japan [6–9]. C-CAT constructs and maintains the Cancer Knowledge Database, a national resource that supports the interpretation of genomic data and provides clinical annotations to inform cancer treatment decisions [6, 7]. For each patient, clinical information and CGP results were collected in C-CAT. The pathogenicity of each identified variant was annotated according to the C-CAT guidelines, developed through a joint consensus by the Japanese Society of Medical Oncology, the Japan Society of Clinical Oncology, and the Japanese Cancer Association [9]. These annotations were based on a database of genomic profiles from over 90,000 patients. Reports were generated to provide personalized treatment recommendations, tailored to each patient's genomic profile [5–8]. Genomic alterations were classified into seven evidence levels (A–F and R), as defined by the C-CAT evidence-tier system (Table S4) [13]. C-CAT reports included details such as the evidence level for therapeutic efficacy, the availability of therapeutic agents, and relevant genotype-matched clinical trials. These reports were sent to the corresponding hospitals. All CGP test results were reviewed by institutional molecular tumor boards (MTB), also referred to as "expert panels." These panels consisted of multidisciplinary teams including organ-specific oncologists, clinical geneticists, certified genetic counselors, pathologists, bioinformaticians, and pharmacists [6–8]. As described previously, potentially oncogenic and druggable gene alterations were defined as those classified at or above evidence level F and level D [13]. Based on each patient's treatment history, clinical background, the strength and nature of the supporting evidence, and the accessibility of therapeutic agents, the expert panel determined recommendations for genotype-matched therapies. The corresponding data were then aggregated within the C-CAT system [6–8].

2.4 | Profiling of Genomic Alterations

SNVs, indels, CNV, and gene fusions were analyzed. Variants of unknown significance (VUS) were excluded from the analysis. Identified fusion genes were confirmed through cross-referencing with five publicly available fusion gene databases: FusionGDB2, TCGA Fusion Gene Database, Fusion Profiling Interactive Analysis, the Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer, and the COSMIC Fusions database [27–31]. Additionally, relevant published literature was searched in PubMed to validate fusion events [32]. A fusion was defined as recurrent if it had been previously reported in at least one case of the same morphological STT subtype. If the fusion had not been previously reported in that same morphological soft tissue sarcoma (STS) subtype, it was defined as novel [17]. All fusion genes identified in the study were visualized using a Circos plot generated with the R package "circlize" (version 0.4.16 [RStudio, Boston, MA, USA]).

2.5 | Oncoplot of Reported Oncogenic Mutations

To visualize the overall landscape of identified genetic alterations, an Oncoplot was generated using the Julia package "CairoMakie" (version 0.10.4 [GitHub, San Francisco, CA, USA]). The visualization included single nucleotide variations (SNVs) and indels.

2.6 | Tumor Mutation Burden (TMB)

TMB was assessed, and a high TMB (TMB-H) was defined as ≥ 10 mut/Mb [33]. MSI scores were also evaluated and classified as either MSI-high (MSI-H) or microsatellite-stable (MSS).

2.7 | Evaluation of Germline Pathogenic Variants

Germline pathogenic variants (GPVs) were identified from genes assessed by the GenMine TOP panel [34, 35]. The clinical significance of the detected germline variants was interpreted according to the classification guidelines of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) [36].

2.8 | Assessment of Study Outcomes

2.8.1 | Statistical Analysis

We compared the detection rates of oncogenic gene alterations, including SNV, indels, CNV, and gene fusions, as well as druggable gene alterations, histology-specific fusion genes, and potentially therapeutically targetable kinase fusions between the F1CDx and GenMineTOP. Categorical variables were analyzed using Fisher's exact test. Overall survival (OS) was defined

as the time from the date of CGP testing to the date of death from any cause or the last follow-up visit. Patients who were alive at the time of analysis were censored on the date of their most recent disease assessment. We evaluated the association between OS and the type of CGP panel used, as well as the receipt of genotype-matched therapy in patients who underwent CGP testing without a history of chemotherapy or during first or second-line chemotherapy. Survival curves were generated using the Kaplan–Meier method. Differences in survival were assessed using Cox proportional hazards regression analysis. A $p < 0.05$ was considered statistically significant. All statistical analyses were conducted using BellCurve for Excel (Social Survey Research Information Co. Ltd., Tokyo, Japan).

3 | Results

3.1 | Patient Characteristics

A total of 1046 patients were included in this study, comprising 915 STS cases and 131 bone sarcoma cases (Table S5). F1CDx and GenMineTOP were used in 677 (64.7%) and 369 (35.3%) patients, respectively. Among the STS patients, uterine leiomyosarcoma (ULMS) was the most common subtype, diagnosed in 142 patients, followed by dedifferentiated liposarcoma (DDLS) in 118 patients and leiomyosarcoma (LMS) in 103 patients (Table S6). Osteosarcoma was the most commonly diagnosed bone sarcoma, accounting for 77 patients, followed by chondrosarcoma in 18 patients. TRS accounted for 160 patients, while 886 patients had genomically complex or other sarcomas. The median follow-up duration was 131 days (range: 6–407 days).

3.2 | Re-Classification

Based on the detection of highly histology-specific fusion genes from sequencing results, 16 (1.5%) patients were reclassified (Table 1). Reclassification occurred in seven patients (1.0%) in the F1CDx group and nine patients (2.4%) in the GenMineTOP group ($p = 0.11$). Two patients initially diagnosed with fibrosarcoma were reclassified as dermatofibrosarcoma protuberans (DFSP) based on the presence of the *COL1A1-PDGFB* fusion. Cases initially diagnosed as small round cell sarcoma and desmoplastic small round cell tumor were reclassified as *CIC*-rearranged sarcoma (CIC) and extraskeletal myxoid chondrosarcoma based on the detection of the *CIC::DUX4* and *NR4A3::EWSR1* fusions, respectively. Four patients originally diagnosed as sarcoma NOS were reclassified as *NTRK*-rearranged spindle cell neoplasm (NTRK), *CIC*-rearranged sarcoma, sarcoma with *BCOR* genetic alterations (BCOR), and SYNS, based on the fusion genes *EML4::NTRK3*, *CIC::DUX4*, *BCOR::CCNB3*, and *EWSR1::SSX1*, respectively.

3.3 | Profiling of Genomic Alterations

Oncogenic gene alterations (SNVs/indels, CNV, and fusions) were detected in 650 (96.0%) patients using F1CDx and 275 (74.5%) patients using GenMineTOP ($p < 0.001$) (Table 2). SNVs/indels were observed in 493 (72.8%) patients in the F1CDx group and 203 (55.0%) patients in the GenMineTOP group ($p < 0.001$) (Table 2). These alterations are shown in the Oncoplot (Figure 1). The most frequently mutated gene was *TP53*, followed by *KIT*, *RB1*, *TERT*, *NF1*, and *PIK3CA* (Table S7). The most common SNVs/indels in the F1CDx group were *TP53* (35.2%), *KIT* (14.6%), and *RB1* (7.5%). In the GenMineTOP group, the most common were *TP53* (24.7%), *TERT* (6.8%), and *RB1* (5.7%) (Figures S1A–C). CNVs were observed in 488 (72.1%) and 105 (28.5%) patients with F1CDx and GenMineTOP, respectively ($p < 0.001$) (Table 2). In the GenMineTOP, the most frequently amplified genes were cyclin-dependent kinase 4 (*CDK4*) (14.4%), *MDM2* (13.3%), and *CCND3* (3.5%). In the F1CDx group, cyclin-dependent kinase inhibitor 2A (*CDKN2A*) (23.8%), *CDKN2B*, and *MDM2*

TABLE 1 | Reclassification based on genomic data.

Initial diagnosis	Reclassified diagnosis	Genomic specificity	Patients, number
Desmoplastic small round cell tumor	Extraskeletal myxoid chondrosarcoma	*NR4A3::EWSR1*	1 (F)
Ewing sarcoma (soft tissue)	*CIC*-rearranged sarcoma	*CIC::DUX4*	1 (F)
Fibrosarcoma	Dermatofibrosarcoma protuberans	*COL1A1::PDGFB*	2 (G)
Sarcoma, NOS	Sarcoma with *BCOR* genetic alterations	*BCOR::CCNB3*	1 (G)
	CIC-rearranged sarcoma	*CIC::DUX4*	4 (G;2, F2)
	Epithelioid hemangioendothelioma	*WWTR1::CAMTA1*	1 (G)
	Extraskeletal myxoid chondrosarcoma	*EWSR1::NR4A3*	1 (F)
	NTRK-rearranged spindle cell neoplasm	*EML4::NTRK3*	1 (G)
	Synovial sarcoma	*ETV6::NTRK3*	1 (G)
		LMNA::NTRK1	1 (F)
		EWSR1::SSX1	1 (F)
Spindle cell/sclerosing rhabdomyosarcoma	Alveolar rhabdomyosarcoma	*PAX3::FOXO1*	1 (G)

Abbreviations: F, FoundationOne CDx cancer genome profiling; G, GenMine TOP Cancer Genome Profiling System.

TABLE 2 | Oncogenic and druggable gene alteration.

Characteristics	F1CDx ($n=677$)	GenMineTOP ($n=369$)	p
Oncogenic gene alteration	650 (96.0%)	275 (74.5%)	$p<0.001$
Single nucleotide variants	493 (72.8%)	203 (55.0%)	$p<0.001$
Copy-number variation	488 (72.1%)	105 (28.5%)	$p<0.001$
Evidence-level classifications for druggable gene alterations			
A	96 (14.2%)	13 (3.5%)	
B	0 (0%)	1 (0.3%)	
C	139 (20.5%)	169 (45.8%)	
D	7 (1.0%)	1 (0.3%)	
Total	242 (35.7%)	176 (47.7%)	$p<0.001$

Abbreviations: F1CDx, FoundationOne CDx cancer genome profiling; GenMineTOP; GenMine TOP Cancer Genome Profiling System.

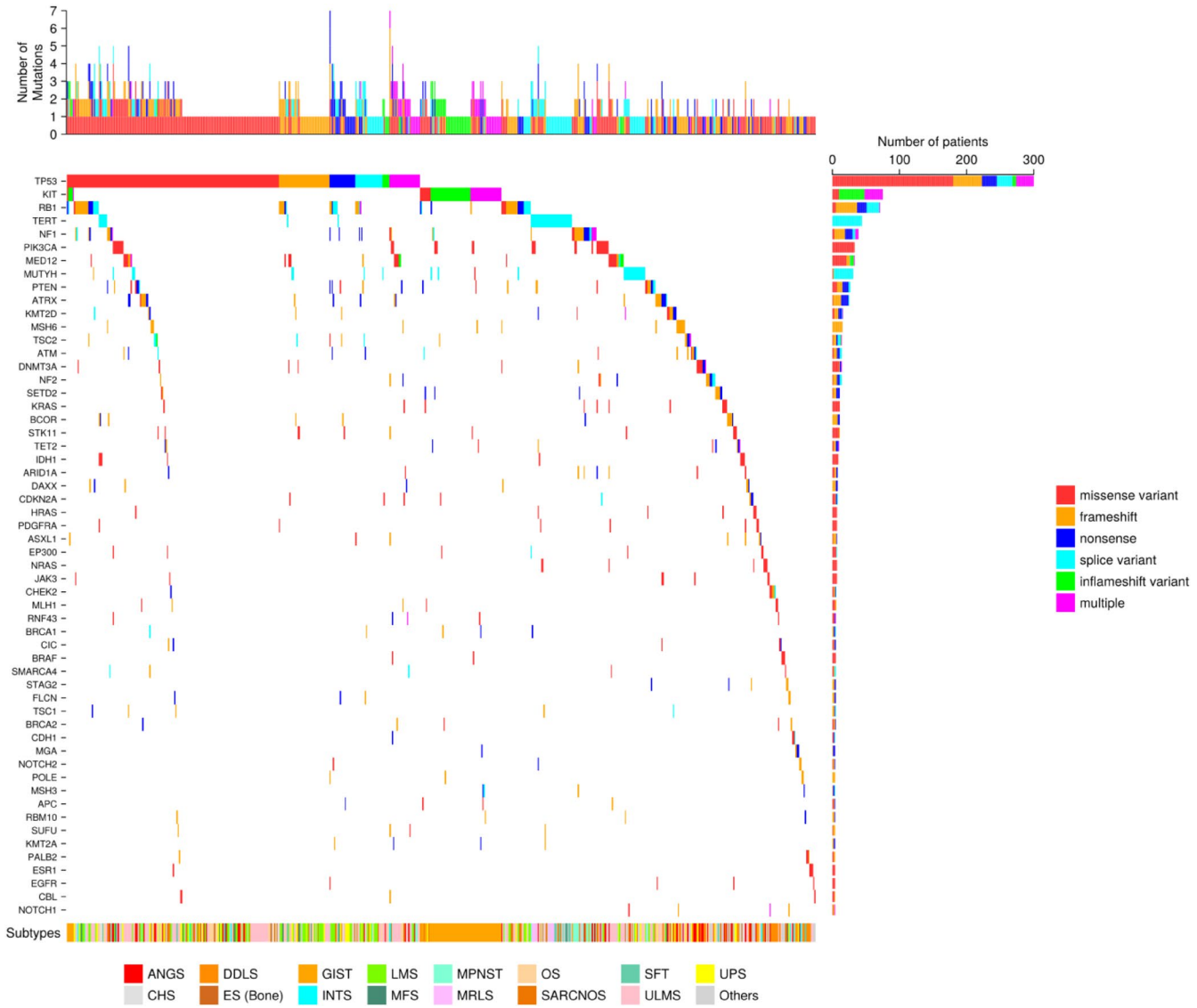

FIGURE 1 | Oncogenic gene alteration by subtype. Oncoplot of oncogenic genomic alterations (SNV/Indels) identified in the study population. Oncogenic genomic alterations in specific genes detected at a frequency > 0.3% and tumor subtypes at a frequency > 10 cases are shown. Tumor subtypes are represented in colored text below Oncoplot. The histogram on top of the mutation Oncoplot represents the number of mutations per patient.

(16.2%) were the most commonly altered (Figures S1D–F). The highest evidence-level classifications of druggable gene alterations, as defined in the C-CAT system, are shown in Table 2. Druggable alterations were identified in 418 patients (40.0%). GenMineTOP identified a significantly higher proportion of druggable gene alterations compared to F1CDx (47.7% vs. 35.7%, $p < 0.001$).

3.4 | Gene Fusions

A total of 127 fusion genes were identified in 125 patients (12.0%), with two patients harboring two distinct fusion genes. Fusion genes were detected in 50 patients using F1CDx (7.4%) and in 75 patients (20.3%) using the RNA panel of GenMineTOP ($p < 0.001$). These results are visualized in the Circos plot (Figure 2A,B). Among the patients with TRS, histology-specific fusion genes were detected in 94 cases. These included *SYT::SSX* in SYNS, *EWSR1::FLI1* in ES, *PAX3::FOXO1* in alveolar rhabdomyosarcoma, *BCOR::CCNB3* in sarcoma with *BCOR* genetic alterations, and *ASPSCR1::TFE3* in alveolar soft tissue sarcoma. Histology-specific fusion genes were identified in 32 of 80 TRS cases (40.0%) using F1CDx and in 62 of 80 TRS cases (77.5%) using GenMineTOP ($p < 0.001$) (Table 3). Potentially therapeutically targetable kinase fusions were found in 21 patients (2.0%). These included six cases each of *NTRK* and *FGFR* fusions, two cases each of *BRAF, RAF1*, and *ALK* fusions, and one case each of *RET*, *ROS1*, and *EGFR* fusions. These fusions were detected in eight patients (1.2%) using F1CDx and in 13 patients (3.5%) using GenMineTOP ($p = 0.019$). Additionally, 25 novel fusion events were identified in 24 patients (Table 4), including 16 patients (2.4%) using F1CDx and nine patients (2.4%) using GenMineTOP.

3.5 | TMB

TMB data were available for all patients except two. The median TMB was 1.6 mutations per megabase (range: 0–152). TMB-H was observed in 22 patients (2.1%). These included five patients with ULMS (3.5%), four with ANGS (5.6%), and two each with LMS (1.9%), UPS (3.2%), OS (2.6%), and SARCNOS (2.7%). TMB-H was identified in 19 patients (2.8%) using F1CDx and in three patients (0.8%) using GenMineTOP ($p = 0.04$). Microsatellite instability status was observed in six cases, all of whom underwent F1CDx testing. All six cases were also classified as TMB-high.

3.6 | Targetable Genomic Alterations in STS and the Clinical Impact of Genotype-Matched Therapy

In non-Gastrointestinal Stromal Tumor (GIST) sarcomas, clinical information regarding the recommendation for genotype-matched therapy was available for 695 patients (206 with therapy recommendations, 489 without). Genotype-matched therapy was administered to 22 patients (3.2%), including 12 of 464 patients (2.6%) in the F1CDx group and 10 of 231 patients (4.3%) in the GenMineTOP group ($p = 0.25$) (Table 2). Therapies administered included 13 approved drugs, such as targeted small-molecule inhibitors ($n = 8$; e.g., pazopanib, Larotrectinib) and immune checkpoint inhibitors ($n = 5$; e.g., pembrolizumab). Additionally, nine off-label drugs were used, comprising two targeted small-molecule inhibitors and seven clinical trials. Molecular targeted therapy was administered more frequently in the GenMineTOP group (10 of 231 patients, 4.3%) than in the F1CDx group (7 of 464 patients, 1.5%) ($p = 0.03$).

3.7 | GPVs

GPVs were detected in 21 patients (5.7%) using the tumor–normal matched GenMineTOP panel (Table S8). The affected genes included *TP53* (two cases of DDLS and one case each of OS, LMS, and UPS); *NF1* (three cases of MPNST and two cases of GIST); *BRCA2* (one case each of ULMS, WDLS, and SARCNOS); and *PMS2* (one case each of OS and SARCNOS). Allele frequencies ranged from 21.9% to 55.2%. Fifteen patients had a family

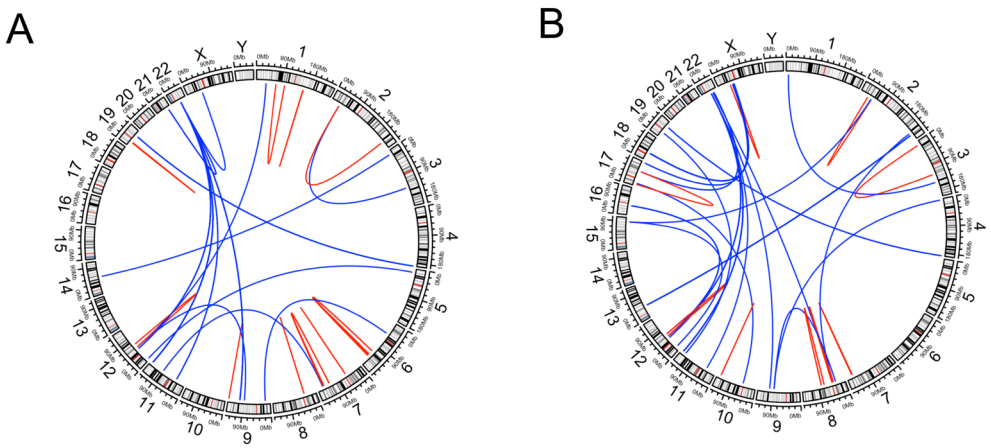

FIGURE 2 | Circos plot of identified fusion genes. The identified fusion genes were visually represented in the Circos plot. (A) FoundationOne CDx cancer genome profiling. (B) GenMine TOP Cancer Genome Profiling System.

TABLE 3 | The difference of the detection of common recurrent fusion.

Histology of translocation-related sarcomas	Common recurrent fusion	Patients, number	
		GenMineTOP	F1CDx
Alveolar rhabdomyosarcoma	*PAX3::FOXO1*	8 (9)	0 (2)
Alveolar soft part sarcoma	*ASPSCR1::TFE3*	6 (7)	0 (3)
Clear cell sarcoma	*EWSR1::ATF1*	5 (7)	3 (4)
CIC-rearranged sarcoma	*CIC::DUX4*	2 (2)	3 (3)
Dermatofibrosarcoma protuberans	*COL1A1::PDGFB*	2 (2)	0 (1)
Desmoplastic small round cell tumor	*EWSR1::WT1*	1 (1)	2 (2)
Epithelioid hemangioendothelioma	*WWTR1::CAMTA1*	1 (4)	0 (7)
Extraskeletal myxoid chondrosarcoma	*EWSR1::NR4A3*	1 (1)	4 (4)
	NR4A3::EWSR1		1 (1)
Ewing sarcoma	*EWSR1::FLI1*	9 (13)	15 (16)
	EWSR1::ERG		1 (1)
	ERG::EWSR1		1 (1)
Sarcoma with *BCOR* genetic alterations	*BCOR::CCNB3*	1 (1)	—
Infantile fibrosarcoma		0 (1)	
Myxoid/round cell liposarcoma	*FUS::DDIT3*	3 (8)	0 (4)
NTRK-rearranged spindle cell neoplasm	*EML4::NTRK3*	1 (1)	1 (1)
	ETV6::NTRK3	1 (1)	
	LMNA::NTRK1		
Solitary fibrous tumor	*NAB2::STAT6*	7 (8)	0 (12)
Synovial sarcoma	*SS18::SSX1, 2*	15 (17)	0 (15)
	EWSR1::SSX1	1 (1)	
Mesenchymal chondrosarcoma	*HEY1::NCOA2*	1 (1)	0 (2)

Abbreviations: F1CDx, FoundationOne CDx cancer genome profiling; GenMineTOP, GenMine TOP Cancer Genome Profiling System.

history of cancer. According to the ACMG/AMP classification guidelines, 20 variants were classified as pathogenic and one as likely pathogenic.

3.8 | Association Between OS, CGP Test Type, and Receipt of Genotype-Matched Therapy

The 1-year OS rates of patients tested with F1CDx and GenMineTOP were 62.6% and 63.9%, respectively ($p=0.80$) (Figure S2). Among all patients, the 6-month OS rates were 100% for those who received genotype-matched therapy, 81.0% for patients with druggable alterations who did not receive genomically matched therapy, and 81.5% for patients without druggable alterations ($p=0.38$) (Figure S3A). In the F1CDx cohort, the corresponding 6-month OS rates were 100%, 82.6%, and 81.5%, respectively ($p=0.98$) (Figure S3B). In the GenMineTOP cohort, the 6-month OS rates were 100% for patients who received genotype-matched therapy, 72.8% for those with druggable alterations who did not receive genomically matched therapy, and 83.6% for patients without druggable alterations ($p=0.076$) (Figure S3C).

4 | Discussion

This study suggests that a dual DNA–RNA panel covered by public health insurance may improve diagnostic accuracy and therapeutic decision-making for sarcoma in clinical practice. Compared to conventional DNA-only panels like F1CDx, GenMineTOP demonstrated superior performance in detecting fusion genes and therapeutically targetable kinase fusions, particularly in TRS. Moreover, its integrated tumor–normal matched analysis identified GPVs, highlighting its potential for personalized surveillance and preventive strategies for patients and their at-risk relatives.

Boddu et al. reported that *TP53* (36.8%), *CDKN2A/B* (20.2%), *CDK4/MDM2* (19.3%), *ATRX* (13.2%), and *RB1* (13.2%) were among the most frequent oncogenic mutations detected using CGP in patients with advanced or metastatic sarcoma [19]. Consistent with previous findings, this study found *TP53*, *KIT*, and *RB1* to be the most frequently altered genes in the SNV category. The most frequently mutated genes were nearly identical between the F1CDx and GenMineTOP cohorts. While F1CDx

TABLE 4 | Novel Gene Fusions in sarcoma subtypes.

Rearrangement-1-MARKER	Gender	Age	Diagnosis	Panel	Rearrangement-1-METHOD	Rearrangement-1-TRANSCRIPT_ID	Previously reported malignancy
KMT2A::ELL	Woman	11	Sarcoma, NOS	GenMineTOP	RNA-seq	ENST00000389506-NM_006532	Acute myeloid leukemia, acute lymphoblastic leukemia/ lymphoblastic lymphoma, Acute monoblastic leukemia
HMGA2::MSRB3	Man	41	Undifferentiated pleomorphic sarcoma	GenMineTOP	RNA-seq	NM_003483-NM_198080	Bladder urothelial carcinoma, head and neck squamous cell carcinomas, thyroid cancer
GOLGB1::RAF1	Woman	66	Clear cell sarcoma	GenMineTOP	RNA-seq	NM_004487-NM_002880	—
FGFR1::RBFOX2	Woman	75	Dedifferentiated liposarcoma	GenMineTOP	RNA-seq	NM_023110-NM_001349998	—
FGFR1::DDHD2	Woman	80	Dedifferentiated liposarcoma	GenMineTOP	RNA-seq	NM_001174067-NM_015214	—
RBPMS::NTRK2	Man	50	Malignant peripheral nerve sheath tumor	GenMineTOP	RNA-seq	NM_006867-NM_006180	Astrocytoma, glioblastoma
FGFR1::HOOK3	Woman	56	Uterine leiomyosarcoma	GenMineTOP	RNA-seq	NM_023110-NM_032410	—
HTT::NTRK2	Man	72	Chondrosarcoma	GenMineTOP	RNA-seq	NM_002111-NM_006180	—
FGFR2::ATE1	Man	18	Osteosarcoma	GenMineTOP	RNA-seq	NM_023029-NM_007041	Bladder urothelial carcinoma, breast invasive carcinoma, lung adenocarcinoma, uterine corpus endometrial carcinoma
KTN1::RAF1	Man	57	Undifferentiated pleomorphic sarcoma	F1CDx	DNA-seq	—	—
CDK4::NTRK2	Woman	50	Leiomyosarcoma	F1CDx	DNA-seq	—	—
CCDC171::CCND3	Man	73	Gastrointestinal Stromal Tumor	F1CDx	DNA-seq	—	—
HAUS8::NOTCH3	Woman	55	Myxofibrosarcoma	F1CDx	DNA-seq	—	—
MET::LUZP6	Man	65	Leiomyosarcoma	F1CDx	DNA-seq	—	—

(Continues)

TABLE 4 | (Continued)

Rearrangement-1-MARKER	Gender	Age	Diagnosis	Panel	Rearrangement-1-METHOD	Rearrangement-1-TRANSCRIPT_ID	Previously reported malignancy
EGFR::VOPP1	Woman	73	Undifferentiated pleomorphic sarcoma	F1CDx	DNA-seq	—	—
KIAA1244::ROS1	Woman	68	Dedifferentiated liposarcoma	F1CDx	DNA-seq	—	—
ROS1::HBS1L	Woman	68	Dedifferentiated liposarcoma	F1CDx	DNA-seq	—	—
ENPP1::MYB	Woman	57	Dedifferentiated liposarcoma	F1CDx	DNA-seq	—	—
CDK4::ZCCHC17	Man	65	Sarcoma, NOS	F1CDx	DNA-seq	—	—
NOTCH1::SEC16A	Man	47	Angiosarcoma	F1CDx	DNA-seq	—	Lung squamous cell carcinoma, head and neck squamous cell carcinomas, thyroid cancer, breast cancer
CCND2::CTNND2	Man	66	Dedifferentiated liposarcoma	F1CDx	DNA-seq	—	—
BRAF::DLG2	Woman	26	Malignant peripheral nerve sheath tumor	F1CDx	DNA-seq	—	—
JAK1::FNBP1L	Man	73	Malignant peripheral nerve sheath tumor	F1CDx	DNA-seq	—	—
MET::KIAA1549	Woman	44	Malignant peripheral nerve sheath tumor	F1CDx	DNA-seq	—	—
ALK::PPP2R3A	Woman	55	Uterine leiomyosarcoma	F1CDx	DNA-seq	—	—

Abbreviations: F1CDx, FoundationOne CDx cancer genome profiling; GenMineTOP, GenMine TOP Cancer Genome Profiling System.

demonstrated a higher overall detection rate of oncogenic gene alterations, GenMineTOP identified a significantly greater proportion of druggable gene alterations, suggesting its clinical utility in identifying actionable mutations.

A key advantage of GenMineTOP over DNA-only panels lies in its ability to accurately detect gene fusions through RNA-based analysis. DNA fusion panels may fail to identify functional fusions due to factors such as transcriptional silencing, epigenetic modifications, structural rearrangements, or post-transcriptional regulation [17]. GenMineTOP addresses these limitations by using an RNA-based approach, resulting in a significantly higher detection rate of fusion genes than F1CDx (20.3% vs. 7.4%, $p < 0.001$). The histopathological diagnosis of sarcomas remains challenging, and CGP reportedly contributes to diagnostic reclassification in approximately 4%–10% of cases [19, 21]. In this study, GenMineTOP enabled reclassification in 2.4% of patients, compared with 1.0% using F1CDx. For example, the identification of the *COL1A1::PDGFB* fusion by GenMineTOP led to the reclassification of two cases initially diagnosed as fibrosarcoma to the fibrosarcomatous variant of dermatofibrosarcoma protuberans (FS-DFSP). This is a clinically meaningful distinction, as FS-DFSP is classified as an intermediate tumor under the WHO classification and is typically treated with imatinib as first-line therapy per NCCN guidelines, whereas fibrosarcoma is considered malignant and generally treated with doxorubicin [37, 38]. Therefore, the accurate classification of these two entities, given their differing prognoses and therapeutic approaches, is of significant clinical importance. In this study, sarcoma NOS cases were reclassified as *NTRK*-rearranged spindle cell neoplasm, *CIC*-rearranged sarcoma, sarcoma with *BCOR* genetic alterations, or SYNS based on the detection of histology-specific fusion genes such as *EML4::NTRK3*, *CIC::DUX4*, *BCOR::CCNB3*, and *EWSR1::SSX1*. The identification of histology-specific fusion genes is particularly crucial in TRS, where molecular characterization informs diagnosis and therapeutic strategy [39, 40]. However, most DNA-only panels detect a limited spectrum of fusion genes. For example, histology-specific fusion genes were detected in only 40.0% of patients with TRS using F1CDx. In contrast, GenMineTOP identified 455 fusion genes, encompassing the majority of histology-specific fusions reported in bone and soft tissue tumors, and enabled their detection in 77.5% of patients with TRS.

In sarcoma, the proportion of patients with potentially druggable alterations and those who actually receive genotype-matched therapy in real-world settings reportedly range from 47% to 61%, and from 7.3% to 8.8%, respectively [19–21]. In our cohort, 40.0% of patients harbored at least one druggable alteration. Genotype-matched therapies, including targeted small-molecule inhibitors, immune checkpoint inhibitors, and clinical trials, were administered in 3.2% of patients: 2.6% in the F1CDx group and 4.3% in the GenMineTOP group. Although this overall rate is lower than those reported in earlier studies, this may reflect limitations such as the unavailability of approved therapies or ongoing clinical trials, restricted access to specialized treatment centers, or disease progression prior to therapy initiation [19, 20, 41]. Targeted therapies and immunotherapies represent promising treatment options for sarcomas identified through CGP, which have the potential to improve outcomes. Tyrosine kinase inhibitors (TKIs), for instance, have demonstrated strong efficacy in tumors harboring oncogenic fusion genes involving kinase activity [42]. These include ALK inhibitors such as crizotinib and alectinib for *ALK* fusion-positive sarcomas, and TRK inhibitors such as larotrectinib and entrectinib for *NTRK* fusion-positive sarcomas [43]. In our study, potentially actionable kinase fusions, including *ALK*, *PDGFRA*, *NTRK1,2*, and *ROS1*, were identified more frequently by GenMineTOP (3.5%) than by F1CDx (1.2%). Moreover, molecular targeted therapy, including the use of TRK inhibitors, was more frequently administered in patients analyzed by GenMineTOP than by F1CDx for non-GIST sarcomas (4.3% vs. 2.6%, $p = 0.03$). These findings suggest that the combined DNA and RNA profiling approach used in GenMineTOP enhances the detection of fusion genes, which may expand therapeutic opportunities in sarcoma management.

Tumor sequencing data contain a mixture of somatic mutations and variants of germline origin. Matched tumor–normal testing provides a more accurate distinction between these two categories and is an efficient approach for both somatic and germline analysis [44]. This approach enables timely personalized cancer management, facilitates appropriate surveillance and preventative interventions for patients and at-risk relatives, and supports the selection of targeted molecular therapies. Kikuchi et al. identified PGPVs in 15.2% of patients using F1CDx, a tumor-only panel, whereas GPVs were detected in 16.7% of patients using the NCC Onco-panel, a paired tumor–normal matched test [13]. The hereditary contribution to sarcoma has long been recognized, and several cancer predisposition genes have been implicated, including *TP53*, *BRCA1/2*, *RB1*, and *NF1* [13]. However, reports on the detection rates of germline pathogenic variants using CGP in real-world sarcoma cases remain limited. This is largely due to the widespread use of tumor-only CGP panels, which cannot reliably distinguish germline from somatic mutations. In contrast, GenMineTOP incorporates tumor–normal matching design and identified GPVs in 5.7% of patients in our study. Most of these mutations occurred in genes associated with homologous recombination repair or known hereditary cancer syndromes, including *BRCA2*, *TP53*, and *NF1*. It is likely that some of these patients carried underlying hereditary cancer syndromes such as neurofibromatosis type 1 (NF1) or Li-Fraumeni syndrome [45]. An additional advantage of detecting germline mutations is their relevance to targeted therapies. Germline defects in homologous recombination repair genes, such as *BRCA1* and *BRCA2*, are predictive biomarkers for response to PARP inhibitors [44]. Therefore, integrating germline testing into clinical cancer management is increasingly necessary to guide both therapeutic strategies and genetic counseling.

The effectiveness of genotype-matched therapies guided by CGP in improving survival outcomes across cancer types remains controversial [46, 47]. While several studies showed promising results, others report limited clinical benefits. For example, Ida et al. reported that 12.2% of patients received genotype-matched therapy following CGP, and those who had significantly longer overall survival compared to those who did not ($p = 0.032$) [46]. However, the type of CGP panel used was not significantly associated with OS, suggesting that the specific panel employed may not be the decisive factor influencing prognosis.

In our study, among patients tested with GenMineTOP, those who received genotype-matched therapy demonstrated a trend

toward improved 6-month overall survival compared to patients with druggable alterations who did not receive matched therapy and patients without druggable alterations. These findings suggest a potential clinical benefit of genotype-matched therapy. Future studies with larger patient cohorts and longer follow-up durations are needed to better assess the survival benefits of genomically matched therapies in sarcoma.

This study had some limitations. First, the C-CAT database lacks detailed clinical information on surgical procedures, radiation therapy, referral for genetic testing and/or genetic counseling, and treatment response, making it difficult to correlate genomic alterations with clinical outcomes in a comprehensive manner. Second, due to the retrospective nature, there is a risk of selection bias in determining which patients underwent CGP testing. To better assess the utility of CGP panels in sarcoma care, a prospective study including all patients over a defined period would provide more robust evidence. Third, the clinical response to genotype-matched therapies could not be evaluated due to insufficient data on treatment efficacy for the drugs recommended. Fourth, GeneMineTOP was introduced relatively recently, resulting in a short follow-up period. This limited observation window restricted our ability to evaluate its long-term clinical impact and effectiveness.

In conclusion, GenMineTOP identified more druggable gene alterations than F1CDx in patients with sarcoma. The superiority of GenMineTOP over other DNA panels is its ability to accurately identify histology-specific fusion genes in TRS and potentially therapeutically targetable kinase fusions using an RNA panel. Additionally, its use of tumor–normal matched testing enabled the detection of germline pathogenic variants. Results suggest that GenMineTOP may be a valuable tool for guiding precision oncology in sarcoma. Its potential to improve prognosis through genomically matched therapy should be further validated in a large-scale, prospective study.

Author Contributions

Eiji Nakata: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, writing – original draft, writing – review and editing. **Kiichiro Ninomiya:** conceptualization, investigation, writing – original draft. **Tatsunori Osone:** investigation, writing – review and editing. **Daisuke Ennishi:** conceptualization, investigation, writing – original draft. **Shuta Tomida:** conceptualization, investigation, writing – original draft. **Tomohiro Fujiwara:** conceptualization, investigation, writing – original draft. **Toshiyuki Kunisada:** conceptualization, investigation, writing – original draft. **Mashu Futagawa:** conceptualization, investigation, writing – original draft. **Akira Hirasawa:** conceptualization, investigation, writing – original draft. **Shinichi Toyooka:** conceptualization, project administration, writing – original draft. **Toshifumi Ozaki:** conceptualization, investigation, writing – original draft.

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Ethics Statement

Approval of the research protocol by an Institutional Reviewer Board. This study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of Okayama University Hospital approved this study (approval number K2111-047).

Consent

All informed consent was obtained from the patients.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** The types and number of oncogenic gene alteration. (A) In total, the most frequently mutated genes were *TP53*, following *KIT*, and *RB1* in SNVs/Indels. (B) The most common SNV/Indels being *TP53*, *KIT*, and *RB1* in FoundationOne CDx cancer genome profiling. (C) The most common SNV/Indels being *TP53*, *TERT*,

and *RB1* in GenMine TOP Cancer Genome Profiling System. (D) In total, the most common CNV being cyclin-dependent kinase inhibitor 2A, *MDM2*, and *CDK4*. (E) The most common CNV being cyclin-dependent kinase inhibitor 2A, cyclin-dependent kinase inhibitor 2B, and *MDM2* in FoundationOne CDx cancer genome profiling. (F) The most common CNV being *CDK4* and *MDM2* in GenMine TOP Cancer Genome Profiling System. **Figure S2:** Association between overall survival and kind of comprehensive cancer genomic profiling tests. The kind of panel had no association with overall survival. F1CDx; FoundationOne CDx cancer genome profiling. GenMineTOP; GenMine TOP Cancer Genome Profiling System. **Figure S3:** Association between overall survival and the receivement of genomically matched therapy. (A) Overall survival of patients who received genotype-matched therapy, patients with druggable alteration not receiving genomically matched therapy, and patients without druggable alteration. (B) Overall survival of patients who received genotype-matched therapy, patients with druggable alteration not receiving genomically matched therapy, and patients without druggable alteration in FoundationOne CDx cancer genome profiling. (C) Overall survival of patients who received genotype-matched therapy, patients with druggable alteration not receiving genomically matched therapy, and patients without druggable alteration in GenMine TOP Cancer Genome Profiling System. **Table S1:** Categorization of sarcoma types. **Table S2:** Comprehensive cancer genomic profiling tests. **Table S3:** Gene list tested in each comprehensive genomic profiling test. **Table S4:** Evidence levels based on clinical practice guidance for next-generation sequencing in cancer diagnosis and treatment (Edition 2.0). **Table S5:** Patient characteristics. **Table S6:** Histology of the patients. **Table S7:** Profiling of genomic alterations. **Table S8:** Germline findings.