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The Current Status of Comprehensive Genomic Profiling in the Management of Metastatic Castration-Resistant Prostate Cancer: A Study from a Cooperative Hospital for Cancer Genomic Medicine in Japan

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Background: Several effective treatment modalities against metastatic castration-resistant prostate cancer (mCRPC) are available; however, an unmet clinical need persists for mCRPC treatment because resistance to these therapies is inevitable. This study aimed to evaluate the status of comprehensive genomic profiling (CGP) and its impact on subsequent treatments for patients with mCRPC at our hospital.

Methods: Between December 2020 and August 2023, we assessed 41 patients with mCRPC who underwent CGP testing at the Nippon Medical School Hospital. The testing comprised FoundationOne® CDx for 30 patients and FoundationOne® Liquid CDx for 11 patients, following the procedures outlined by the Japanese Urological Association.

Results: CGP testing was successfully conducted in 40 out of 41 patients (97.6%), which resulted in the identification of 140 actionable genomic alterations. The most common alteration was *TP53* in 12 patients (30.0%). Twenty-three patients (57.5%) with druggable gene alterations were identified; 21 were recommended for clinical trials, four for patient-proposed healthcare services, and six for insurance-covered drugs. Consequently, genotype-matched therapy with insurance-covered drugs was administered to five patients (12.5%) with a *BRCA2* mutation. Notably, none of the patients underwent clinical or prospective trials based on patient-suggested medical services.

Conclusions: Our results offer insights into the real-world application of CGP testing for patients with mCRPC at a cooperative hospital for cancer genomic medicine in Japan. Thus, urologists require a comprehensive understanding of the current status of CGP testing to enhance mCRPC management.

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Key words: prostate cancer, next-generation sequencing, metastatic castration-resistant prostate cancer

Introduction

Metastatic castration-resistant prostate cancer (mCRPC) is a heterogeneous disease associated with poor prognosis[1,2]. In recent years, several effective treatment modalities for mCRPC have been made available, including androgen receptor pathway inhibitors[3–5], taxane-based chemotherapy[6], radiopharmaceutical agents[7], and immunotherapy[8]. Despite the availability of these modalities, an unmet clinical need exists for mCRPC treatment due to inevitable resistance to these therapies.

Next-generation sequencing has enabled comprehensive genomic profiling (CGP), which allows the identifi-

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cation of gene alterations associated with carcinogenesis in each patient[9,10]. CGP testing has been covered by insurance for patients with mCRPC in Japan since 2020[9,10]. Based on CGP results, clinicians can administer poly (ADP-ribose) polymerase inhibitors (PARPi) to patients with mCRPC who are *BRCA1/2* mutation-positive[11] and programmed death receptor-1 (PD-1) monoclonal antibodies to those with microsatellite instability (MSI-high) and/or high tumor mutation burden (high-TMB)[12]. However, as medical professionals, we must recognize that there may be differences between Japanese and Western populations in the genomic landscape associated with prostate cancer[13]. Therefore, the extent to which CGP testing in Japanese patients can contribute to the implementation of genotype-based treatments requires further evaluation in actual clinical settings.

In Japan, cancer genome medicine is offered through three types of medical facilities, each operating under a distinct system, following the national order[14]. Designated Core Hospitals for Cancer Genomic Medicine (DCH) play a key role in providing medical treatment based on cancer genome information, conducting clinical research and trials on new drugs, and fostering human resources related to cancer genomics. Designated Hospitals for Cancer Genomic Medicine interpret genomic information at their own facilities and conduct research, development, and human resource development in the field of cancer genomics, in cooperation with DCH. In contrast, Cooperative Hospitals for Cancer Genomic Medicine (CH) perform medical treatments for cancer genome medicine, but collaborate with other facilities when participating in clinical trials or patient-directed therapy systems for genome-matched therapy. To date, there is a notable lack of decisive evidence from CH in Japan regarding genome-matched therapy. Therefore, we aimed to evaluate the initial experience of CGP testing for mCRPC and assess the impact of the results on the treatment options at a CH in Japan.

Patients and Methods

Patient Population

We included patients with mCRPC who underwent CGP testing between December 2020 and August 2023 at the Nippon Medical School Hospital (NMSH) (Tokyo, Japan), which is a government approved CH[14,15]. This study initially included 41 patients previously treated for mCRPC with androgen receptor pathway inhibition and/or taxane-based chemotherapy. We retrospectively reviewed electronic medical records, pathological findings, and results of CGP testing. The study was approved by the Human Ethics Committee of the NMSH (approval number: B-2022-619) and was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective nature of the study and absence of intervention. Participants had the option to decline involvement through the NMSH Ethics Committee website in an opt-out manner.

Genome Analysis

Attending doctors recommended that patients with mCRPC undergo CGP testing using either of the two cancer multi-gene panels, the FoundationOne® CDx or The FoundationOne® Liquid CDx, which is covered by Japan's health insurance system in accordance with the procedures outlined by the Japanese Urological Association[16]. FoundationOne® CDx only analyzes tumor DNA for genetic alterations in 324 cancer-related genes (exonic regions of 309 genes and intronic and promoter regions of 36 genes), MSI, and TMB. The FoundationOne® Liquid CDx analyzes the same panel of genes as the FoundationOne® CDx using circulating tumor DNA in the blood. Tumor tissues were collected at the NMSH based on our institution's pathological methods and were prepared according to the manufacturer's instructions. Based on the results of CGP testing, discussions were conducted at the cancer genomic board with the DCH, consisting of medical geneticists, pathologists, and medical oncologists, to identify cancer gene alterations and their corresponding treatment options. Before conducting CGP testing, clinical geneticists and genetic counselors specializing in hereditary tumors explained to the patients the possibility that germline pathogenic variants would be detected. When testing indicated such variants, additional counseling was provided by the same specialists. In this study, druggable gene alterations were defined as alterations for which our study recommended genome-matched treatment. We prescribed drugs covered by insurance, such as a PARPi (olaparib) for *BRCA*-positive patients and PD-1 monoclonal antibodies (pembrolizumab) for patients with MSI and/or high-TMB.

Evaluation

We collected the demographic and clinical data of patients who underwent CGP testing. Additionally, we assessed the clinical course of patients who received genotype-matched therapy following CGP testing. Categorical data are expressed as frequencies and percentages, while continuous data are presented as medians and ranges. Adverse events associated with genotype-matched therapy were assessed using the Common Ter-

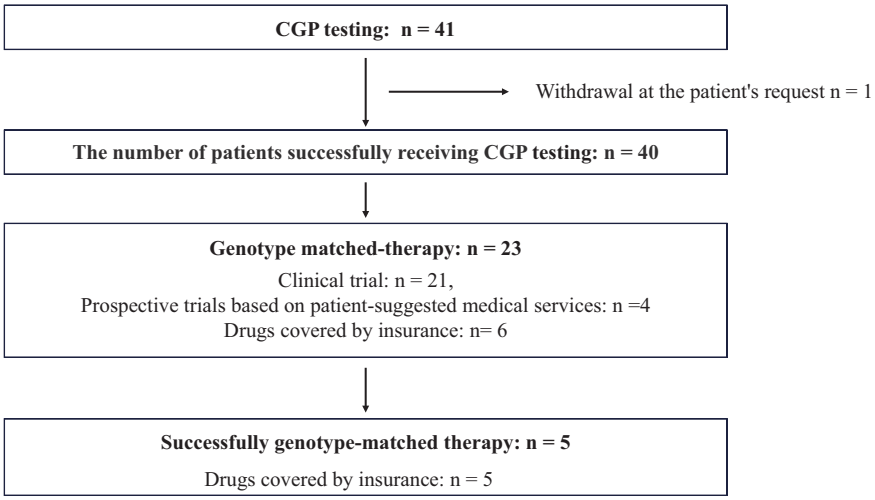


Fig. 1 Summary of the patient flow after the CGP testing.
CGP, comprehensive genomic profiling.

Table 1 Characteristics of the enrolled patients

Characteristics	
Median age (years), range	73.5 (57-86)
Median PSA at PCa diagnosis (ng/mL), range	129.3 (1.5-13,000)
Median PSA at CGP testing (ng/mL), range	10.1 (0.02-2,152)
Gleason score	
≤ 7	7
≥ 8	32
Unknown	1
Site of metastasis	
Bone	30
Lung	5
Liver	1
Lymph node	12
Time to CRPC (months)	13.1 (0.6-136.9)
Number of treatment types after CRPC	2 (1-5)

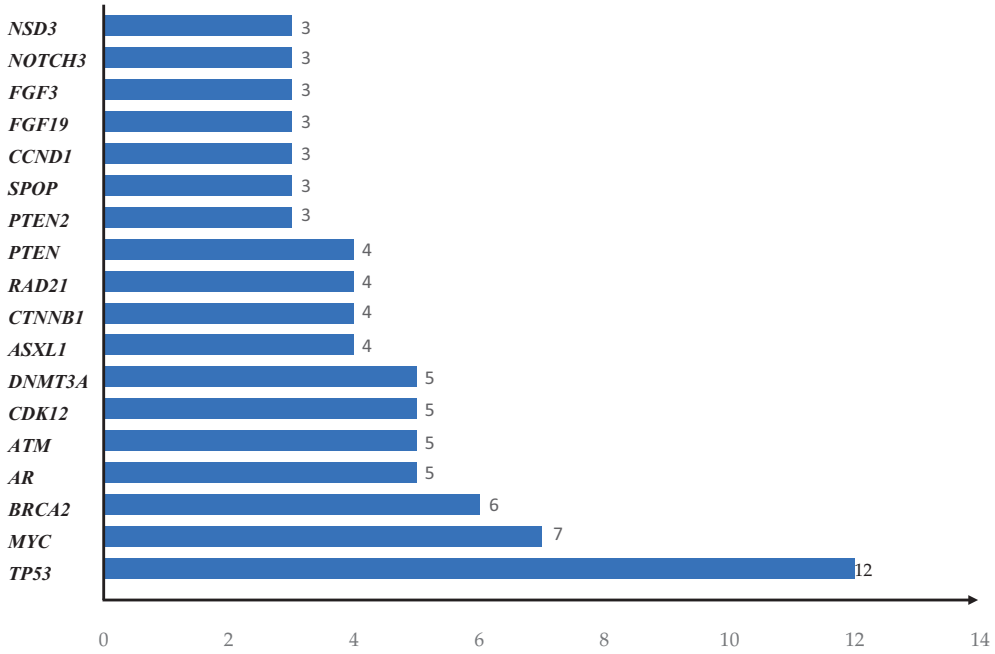
PSA: prostate-specific antigen, PCa: prostate cancer, CGP: comprehensive genome profile, CRPC: castration-resistant prostate cancer

minology Criteria for Adverse Events version 5.0[17].

Results

Patient Characteristics and the Results of CGP Testing for mCRPC

Figure 1 shows a summary of the patient flow after CGP testing at our hospital. During the study period, 40 of 41 patients diagnosed with mCRPC successfully underwent CGP testing, representing a completion rate of 97.6%. Patient characteristics are summarized in **Table 1**. The median age was 73.5 years (range: 57-86 years). At our hospital, the normal range for prostate-specific antigen (PSA) levels is defined as below 4.0 ng/mL, with higher levels suggesting disease progression. A majority of the patients presented with aggressive disease features characterized by elevated PSA levels at diagnosis (median: 129.3 ng/mL; range: 1.5-13,000 ng/mL). Thirty-two patients (80.0%) had Gleason scores (GS) of ≥ 8, indicating aggressive pathological features of prostate cancer. Analysis of metastatic sites during CGP testing revealed bone metastasis in 30 (75.0%) patients, lung metastasis in 5 (12.5%) patients, and distant lymph node metastasis in 12 (30.0%) patients. The median time to CRPC was 13.1 months (range: 0.6-136.9 months), and the number of treatment types after CRPC prior to the CGP testing was 2 (range: 1-5).



The X-axis represents the number of patients with each genetic alternations.

Fig. 2 Genetic alternations present in three or more individuals.

Among the patients who successfully underwent CGP testing, 27 patients opted for FoundationOne® CDx, while 13 patients selected FoundationOne Liquid® CDx. Among the patients who opted for FoundationOne Liquid® CDx, three patients had previously experienced FoundationOne® CDx failures due to suboptimal specimen conditions. Of the 40 patients, 38 (95.0%) had at least one actionable genetic alteration, and the total number of actionable genetic alterations was 140. The average number of actionable genetic alterations per patient was 3.5 (range, 0-10). The median TMB was 2.9 (range, 0-11), and one patient had a high TMB. The most common actionable genetic alterations were in the *TP53* (n=12, 30.0%), *MYC* (n=7, 17.5%), *BRCA2* (n=6, 15.0%), *AR* (n=5, 12.5%), *ATM* (n=5, 12.5%), *CDK12* (n=5, 12.5%), and *DNMT3A* (n=5, 12.5%) genes (**Fig. 2**). Other actionable genetic alterations were observed in four or fewer cases. A total of 23 patients (57.5%) exhibiting druggable genetic alterations were identified; 21 patients were recommended for participation in clinical trials, four patients for participation in patient-proposed healthcare services allowing them to access novel treatments before approval by the Japanese insurance system, and six patients for medication with insurance-covered drugs. Among the 23 patients, five (12.5%) received genotype-matched therapy (PARPi covered by insurance). None were qualified for either clinical trials or patient-proposed healthcare services, and unfortunately, one patient with a high TMB died before receiving pembrolizumab treatment. Based on the results of the CGP testing, six cases were considered secondary findings. Specialists in hereditary tumors explained the possibility of germline pathogenic variants to the patients. Additional evaluation for germline pathogenic variants was conducted in one case, but no germline pathogenic variants were detected.

Patients Undergoing Successful Genotyped-Matched Therapy

The clinical details of the five patients who underwent genotype-matched therapy with PARPi (olaparib) are listed in **Table 2**.

Case 1

A 67-year-old male underwent radical prostatectomy for localized PCa {GS (4+5) 9, pT3b, RM1}. The patient developed biochemical recurrence 41 months after surgery and underwent salvage radiotherapy. After 62 months of combined androgen blockade (CAB) therapy, the disease progressed to mCRPC with lymph node metastases, which was treated with enzalutamide and docetaxel. CGP testing revealed *BRCA2* positivity 147 months after the initial diagnosis, with PSA elevated to 2.0 ng/mL. Treatment with olaparib (600 mg) reduced the PSA to 0.7 ng/mL; however, the disease progressed 13 months later. A subsequent biopsy confirmed the presence of a neuroendocrine tumor, which was treated with etoposide and carboplatin. Currently, 20 months after the discontinuation of olaparib, the patient remains alive.

Table 2 Clinical profile of the patients treated with genome-matched therapy using olaparib

No	Gene	Age Initial diagnosis (years)	Age CGP (years)	CGP	GS	PSA at diagnosis (ng/mL)	Time to CRPC	PSA pretreatment (ng/mL)	PSA nadir (ng/mL)	AE	AE grade ≥ 3	Time to PD (months)	Site of metastasis	Current status
1	*BRCA2*	67	79	F1Cdx	9 (4+5)	12.6	62	2.0	0.7	-	-	13.0	lymph node	alive
2	*BRCA2*	70	72	F1Cdx	9 (4+5)	63	15	2.1	1.2	appetite loss anemia	-	7.6	bone liver	alive
3	*BRCA2*	77	79	F1Cdx	9 (4+5)	103	17	4.1	0.5	appetite loss anemia	-	8.0	bone lung	alive
4	*BRCA2*	80	81	F1Cdx	9 (5+4)	142	18	6.2	1.3	anemia	-	9.2	bone	alive
5	*BRCA2*	73	76	liquid	8 (4+4)	357	25	2,152	-	-	-	1.3	bone lymph node	cancer death

CGP: comprehensive genome profile, GS: Gleason score, PSA: prostate-specific antigen, PCa: prostate cancer, CRPC: castration-resistant prostate cancer, AE: adverse event, PD: progression disease

Case 2

A 70-year-old male was diagnosed with PCa with a GS of (4+5) 9, staged as cT3aN1M1b, and a PSA level of 63.0 ng/mL. Despite initiation of CAB therapy, mCRPC developed 15 months after treatment initiation. Enzalutamide was administered; however, lung metastasis occurred. CGP testing revealed *BRCA2* positivity. Treatment with olaparib (600 mg) resulted in transient appetite loss and anemia (both grade 1). After 1.7 months of treatment, the olaparib dose was reduced to 500 mg. Furthermore, despite a PSA nadir of 1.2 ng/mL, PSA elevation was observed 7.6 months after treatment. The patient is currently receiving docetaxel therapy.

Case 3

A 77-year-old male with PCa {GS (4+5) 9, cT3a+ bN1M0, PSA level 103 ng/mL} was undergoing CAB therapy. Seventeen months after treatment initiation, PSA levels recurred, which led to the administration of enzalutamide. Subsequently, liver metastasis was identified, and *BRCA2* positivity was confirmed by CGP testing. Although olaparib (600 mg) treatment was initiated, it was subsequently discontinued due to appetite loss (grade 2) and anemia (grade 1). Olaparib treatment (300 mg) was resumed later on; however, the patient experienced an elevated PSA level and progression of liver metastasis after eight months. Despite our recommendations for treatment changes, the patient opted for a transition to end-of-life care.

Case 4

An 80-year-old male was diagnosed with PCa {GS (5+4) 9, with neuroendocrine differentiation, initial PSA 142 ng/mL, cT3aN0M1b} 27 months ago. The patient received CAB therapy and four courses of etoposide and cisplatin chemotherapy, followed by enzalutamide administration; however, the disease progressed. Subsequent CGP testing revealed *BRCA2* positivity, leading to the initiation of treatment with olaparib (600 mg). However, the patients experienced anemia (grade 1) as a side effect of the treatment. After 9.2 months on the regimen, a rising PSA level was noted, prompting consideration of switching to the next regimen.

Case 5

A 73-year-old male was diagnosed with PCa with a PSA level of 357 ng/mL, GS (4+4) 8, and stage cT3bN0M 1b. The patient had participated in a clinical trial involving androgen deprivation therapy and enzalutamide. Disease progression was confirmed. Despite receiving palliative radiation therapy for bone metastases and three courses of docetaxel therapy, the patient experienced an

Table 3 Reported studies on CGP for mCRPC in Japan

Author	Time	Study designs	CGP	Actionable genomic alterations	The most frequency alternation	*BRCA* mutations	Genotype-matched therapy	The details of Genotype-matched therapy
Uemura et al.[19]	2022	a multicenter, noninterventional cohort study	143 cases	-	*CDK12* 19 cases (13.3%) in homologous recombination repair pathway genes	*BRCA1/2* 19 cases (13.3%)	-	-
Fukushima et al. [20]	2023	a single-center (DCH), retrospective cohort study	60 cases	216	*AR* 17 cases (28.3%)	*BRCA2* 5 cases (8.3%)	13 cases (21.7%)	Olaparib was used in five cases, cisplatin monotherapy was used in four cases, ceritinib and atezolizumab were used as clinical trials (jRCTs031190104) in two cases and as another clinical trial in one case and pembrolizumab was used in one case.
Koguchi et al. [21]	2023	a single-center (CH), retrospective cohort study	45 cases	23 cases	*BRCA2* 7 cases (15.6%)	*BRCA1/2* 8 cases (17.8%)	10 cases (22.2%)	Drugs covered by public insurance (17.8%, n=8) Patient-proposed healthcare services (4.4%, n=2)
Our study	2024	a single-center (CH), retrospective cohort study	41 cases	140	*TP53* 12 cases (30.0%)	*BRCA2* 6 cases (15.0%)	5 cases (12.5%)	Drugs covered by public insurance (12.5%, n=5)

mCRPC: metastatic castration-resistant prostate cancer, CGP: comprehensive genome profile, DCH: Designated Core Hospitals for Cancer Genomic Medicine, CH: Cooperative Hospitals for Cancer Genomic Medicine

increase in PSA level to 2,152 ng/mL. CGP testing revealed *BRCA2* positivity; however, disease progression occurred after approximately 1.3 month of olaparib treatment, eventually leading to cancer-related death.

Discussion

We assessed the results of CGP testing and their impact on the subsequent treatment of patients with mCRPC at a CH in Japan. Our results revealed that out of 41 patients, wherein 40 (97.6%) successfully underwent testing, 23 patients (57.5%) had druggable genetic alterations and 5 (12.5%) were administered genotype-matched therapy.

CGP testing provides a wealth of sequence information, leading to significant advancements in the clinical and research fields[18]. However, only a small number of reports on genotype-matched therapy for mCRPC are available, where CGP testing was employed, in Japan (**Table 3**)[19,20]. The ZENSHIN study, a multicenter noninterventional cohort study conducted at 24 Japanese institutions, focused on CGP testing for mCRPC[19]. Among the 143 patients analyzed, homologous recombination repair-related mutations were detected in 51 patients (35.7%). Among them, *CDK12* was the most prevalent (n =19; 13.3%), followed by *BRCA2* (n=18; 12.6%), *ATM* (n= 8; 5.6%), and *CHEK2* (n=3; 2.1%). Additionally, according to a single-center, retrospective cohort study in Japan, CGP testing performed on mCRPC showed that among all genetic alterations, the most frequently detected was *AR* alteration, found in 17 patients (28.3%), followed by *TP53* in 15 patients (25.0%), *CDK12* in 14 patients (23.3%), *PTEN* in 10 patients (16.7%), and *ATM* in 9 patients (15.0%)[20]. In our study, we were able to properly evaluate 40 patients (97.6%). The most common genetic alteration was in *TP53* (n=12, 30.0%), followed by *MYC, BRCA2, AR, ATM, CDK12*, and *DNMT3A*. We confirmed *BRCA2* mutations in 6 patients (15.0%) through CGP testing conducted at a CH in Japan, a result that was in line with those of previous Japanese studies[19–21]. To advance genomic medicine for mCRPC in Japan, urologists must better understand the characteristics and challenges of CGP testing.

The PROfound trial is a randomized phase III study that investigated the effectiveness of olaparib in patients with mCRPC harboring homologous recombination re-

pair mutations[11]. According to this study, the median overall survival for patients receiving olaparib was 17.3 months, compared to 14.0 months (hazard ratio: 0.79) for those receiving other AR-targeted agents, while maintaining a high level of tolerability[22]. Based on the analysis of the Asian subset in the PROfound trial, 25 patients with *BRCA1/2* alterations were randomly assigned to receive olaparib[23]. The results showed a median radiological progression free survival of 9.3 months, overall survival of 26.8 months, and an objective response rate of 50.0% (7/14 patients), all of which were superior to the outcomes observed in the control group. Our study identified five patients (12.5%) in whom olaparib was administered as a genome-matched therapy, demonstrating both acceptable efficacy and tolerability for clinical use within Japan. Thus, olaparib may emerge as a pivotal drug with expanding indications. Urologists should carefully monitor their role in the management of mCRPC.

Based on our experience at a CH in Japan, identified several significant issues regarding genomic medicine for mCRPC. We identified 23 patients (57.5%) with druggable genetic alterations; however, 18 patients (78.3%) were unable to receive genome-matched therapy. These individuals, being older and in poor health, found it difficult to visit the DCH and did not meet the eligibility criteria for clinical trials or patient-directed therapy systems for genome-matched therapy. The primary goal of CGP testing is to guide genome-matched therapies towards more effective treatments. Given that mCRPC patients are typically older with poor health conditions, it is advisable to undergo CGP testing at an earlier stage when overall health is better, especially when managing patients with mCRPC in a CH. Second, we had five cases that were *ATM*-positive but *BRCA*-negative, thus precluding the administration of PARPi. To date, PARPi is covered by insurance for *ATM*-positive cases by the FDA, but not by insurance in Japan. Therefore, it is essential to ensure appropriate utilization of treatment opportunities for this genetic alteration through clinical trials and patient-directed therapy systems for genome-matched therapy in Japan. Thirdly, there is a possibility that the evaluation of germline pathogenic variants in patients was insufficient. Our team, consisting of the attending physician, a clinical genetic specialist, and a genetic counselor, explained to the patients in advance of CGP testing that there was a possibility germline pathogenic variants would be detected. When such variants were susupected, we ensured that the patients received further genetic counseling. However, it is possible that the patients did not fully understand the significance or necessity of additional testing. In managing patients with mCRPC, a system is needed to provide more detailed explanation of germline pathogenic variants. To promote genomic medicine in the treatment of mCRPC, it will be important in the future to emphasize the significance of CGP testing and the necessity of additional testing.

Nonetheless, our study had some limitations. This was a retrospective study conducted at a single institution with a limited number of patients. In the field of prostate cancer, genome medicine based on CGP testing is still in its nascent stages. Consequently, the findings of our research should be interpreted with careful consideration. By examining data from various institutions, we will be able to obtain a more accurate view of the current state of genome medicine for prostate cancer in Japan. Furthermore, a longer follow-up period is required to provide a clearer understanding of the impact of CGP testing, thereby increasing the reliability and robustness of our findings. Addressing these limitations is crucial to ensure that our results lead to comprehensive and widely applicable conclusions.

We assessed the status of CGP testing in patients with mCRPC and its effect on subsequent treatment at our hospital. Our findings may reflect the current state of CGP testing for patients with mCRPC. Therefore, urologists should gain a more comprehensive understanding of the current characteristics and challenges of CGP testing in Japan to enhance the quality of mCRPC management via CGP testing.

Availability of data and materials: The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Authors' contributions: Conceptualization: J.A. and G.K.; Methodology: J.A.; Formal Analysis: J.A.; Investigation: J.A., S.H., M.T., T.S., T.I., H.H., H.M., K.O., H.T., Y.E., and Y.T.; Resources: T.Y. and Y.K.; Data Curation: J.A. and S.H.; Writing: J.A. and G.K.; Supervision: G.K., T.Y., and Y.K.; Project Administration: J.A.; Funding Acquisition: J.A., Y.Y., and Y.K. All authors have read and approved of the final manuscript.

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Conflict of Interest: The authors declare that they have no competing interests.

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