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ORIGINAL ARTICLE

Clinical availability and characteristics of multigene panel testing for recurrent/advanced gynecologic cancer

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Abstract

Background Japan's health insurance covers multigene panel testing. This study aimed to determine the potential availability and utility of gene panel testing clinically in gynecologic oncology.

Methods We analyzed the characteristics of patients with gynecologic cancer who underwent gene panel testing using FoundationOne® CDx or OncoGuide™ NCC Oncopanel between November 2019 and October 2022.

Results Out of 102 patients analyzed, 32, 18, 43, 8, and 1 had cervical, endometrial, ovarian cancers, sarcoma, and vaginal cancer, respectively. Druggable gene alteration was found in 70 patients (68.6%; 21 with cervical cancer, 15 with endometrial cancer, 28 with ovarian cancer, 5 with sarcoma, and 1 with other). The most common druggable gene alteration was *PIK3CA* mutation ($n=21$), followed by *PTEN* mutation ($n=12$) and high tumor mutation burden (TMB-H) ($n=11$). TMB-H was detected in 5 patients with cervical cancer, 5 with endometrial cancer, and 1 with endometrial stromal sarcoma. Eleven patients (10.8%) received molecularly targeted therapy according to their gene aberrations. Gene panel testing was mostly performed when the second-line treatment was ineffective. Of all 102 patients, 60 did not have recommended treatment, and 15 died or had worsened conditions before obtaining the test results.

Conclusion Through multigene panel testing, although many patients had druggable gene alterations, 10.8% of them received the recommended treatment. TMB-H was mainly observed in cervical/endometrial cancer, suggesting its potential as a therapeutic biomarker of immune checkpoint inhibitors. Furthermore, patients' prognosis and performance status should be considered before performing the test.

Keywords Cancer genomic profiling · Ovarian cancer · Cervical cancer · Endometrial cancer · Molecular tumor board

Introduction

The incidence of gynecological malignancies in Japan is approximately 42,500, with 11,684 deaths, per year [1]. Systemic chemotherapy is the standard treatment for advanced gynecologic cancer with distant metastasis or recurrence. However, standard chemotherapy has many refractory cases. Although the prognosis varies greatly depending on histological type, progression stage, and patient background, personalized medicine is currently being recommended.

In June 2019, the Pharmaceuticals and Medical Devices Agency launched comprehensive genome profiling (CGP), a multigene panel testing method, for "patients with solid tumors for which no standard treatment is available, or patients with locally advanced or metastatic solid tumors for which standard therapy has been completed (including those expected to complete standard therapy)" in Japan [2]. At the same time, FoundationOne® CDx (Foundation Medicine, Inc.; Cambridge, MA, US; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) and OncoGuide™ NCC Oncopanel (Sysmex Corp., Kobe, Japan) were approved to be covered by Japan's health insurance for all solid tumors. Concurrently, the cancer genome medical system was innovated with the establishment of the Designated Core Hospital for Cancer

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OncoGuide™ NCC Oncopanel has been conducted in Japan, and 124 genes (including 13 fusion genes) have been analyzed, with tumor tissue (formalin-fixed paraffin-embedded [FFPE]) DNA and nontumor tissue (whole blood) DNA as target samples. FoundationOne® CDx analyzes 324 genes (including 36 fusion genes) with tumor tissue (FFPE) DNA as the target sample. FoundationOne® cannot distinguish whether the detected variants are somatic or germline in origin. In both tests, the biomarkers for immune checkpoint inhibitors (ICIs) are microsatellite instability (MSI) and tumor mutation burden (TMB) (Table 1).

Since the health insurance approved to cover CGP, the number of CGP exams performed has been increasing [2–6]; however, the status of multigene panel testing in gynecological malignancies and the clinicopathological characteristics of the patients remain insufficiently reported [7, 8]. Thus, this study aimed to summarize the results of the CGP examination at our hospital (Designated Core Hospital for Cancer Genomic Medicine) to investigate its usefulness as a potential treatment option for advanced and recurrent gynecologic cancers.

Patients and methods

Study design and patients

We enrolled patients who underwent CGP for gynecologic malignancies at our hospital between November 2019 and October 2022 and identified those who received CGP via FoundationOne® CDx and those via OncoGuide™ NCC Oncopanel. FoundationOne® CDx has more target genes compared to OncoGuide™ NCC Oncopanel, enabling loss of heterozygosity (LOH) score can be calculated, and homologous recombination deficiency (HRD) status can be determined. OncoGuide™ NCC Oncopanel may be selected in cases of suspected hereditary tumors. The indication and timing of CGP were determined by the attending physician, but as a principle of health insurance coverage, this study included patients who were refractory to the standard therapy or the current therapy. No restrictions were made in terms of carcinoma or histological type among gynecological malignancies, as well as pre-examination treatment.

Tumor samples were obtained from surgical or biopsy specimens. We did not use cell blocks taken from pleural or ascites fluid.

The clinicopathological characteristics of the 102 patients who underwent CGP were extracted from medical records and characterized after the study protocol was approved by the ethics committee of the hospital (approval No.: 20120243, 20070081, and 20150197).

Results

Patients and characteristics

This study included 102 patients with advanced gynecologic cancer who underwent CGP between November 2019 and October 2022 (Table 2). Among them, 9 underwent OncoGuide™ NCC Oncopanel, whereas 93 underwent FoundationOne® CDx (Table 1). Table 2 summarizes patients' characteristics, test results, and post-test follow-up. All patients were treated at the hospital, and they gave informed consent before multigene panel testing. The median age was 55.5 years. None of them had unsuitable specimens; thus, all could be examined.

The majority of these patients had ovarian cancer (including peritoneal cancer and granulosa cell tumor) ($n=43$), followed by cervical cancer, endometrial cancer (including 2 carcinosarcomas), sarcoma, and vaginal cancer ($n=32$, 18, 8, and 1, respectively). One patient with stage 0 cervical cancer was initially diagnosed with adenocarcinoma in situ pathologically before metastasis.

Table 3 shows the histological types. Of the patients with ovarian cancer, 25 had high-grade serous carcinoma (HGSC) and 1 had low-grade serous carcinoma.

Table 1 Tissue gene panel testing approved in Japan

	OncoGuide™ NCC oncopanel	FoundationOne® CDx
Country of origin	Japan	US
Number of genes	124	324
Required sample	FFPE, blood	FFPE
Proportion of tumor cells needed for analysis	> 20%	> 20%
Biomarkers for immune checkpoint inhibitor	MSI, TMB	MSI, TMB
Number of cases using the test	9	93

FFPE formalin-fixed paraffin-embedded, *MSI* microsatellite instability, *TMB* tumor mutation burden, *US* United States

Table 2 Patients' characteristics and results

	Cervical cancer $n=32$ (%)	Endometrial cancer** $n=18$ (%)	Ovarian cancer*** $n=43$ (%)	Sarcoma $n=8$ (%)	Vaginal cancer $n=1$ (%)	Total 102	% 100
FIGO stage, *n*							
Stage 0	1* (3.1)						
Stage I	14 (43.8)	2 (11.0)	5 (11.6)	4 (50)	0 (0)	25	24.5
Stage II	9 (28.1)	3 (16.7)	0 (0)	4 (50)	0 (0)	16	15.6
Stage III	5 (15.6)	3 (16.7)	27 (62.8)	0 (0)	0 (0)	35	34.3
Stage IV	3 (9.4)	10 (55.6)	11 (25.6)	0 (0)	1 (100)	25	24.5
Gene results, *n*							
Actionable gene (+)	30 (93.8)	18 (100)	42 (97.7)	7 (87.5)	1 (100)	98	96
(–)	2 (6.2)	0 (0)	1 (2.3)	1 (12.5)	0 (0)	4	3.9
Druggable gene (+)	21 (65.6)	15 (83.3)	28 (65.1)	5 (62.5)	1 (100)	70	68.6
(–)	11 (34.4)	3 (16.7)	15 (34.9)	3 (37.5)	0 (0)	32	31.3
Common gene alterations, *n*							
BRCA1	2	0	5	0	0	2	
PIK3CA	9	5	5	0	1	21	
TMB-H	5	5	0	1	0	11	
LOH-high	0	0	9	0	0	9	
ERBB2	4	2	2	0	0	8	
ATM	1	1	1	0	0	3	
PTEN	2	5	3	1	1	12	
CDKN2A	5	1	1	1	0	8	
CCND1	2	1	0	0	0	3	
FGF3	2	1	0	0	0	3	
MSI-H	0	1	0	0	0	1	
Timing of tests, *n*							
After 1st-line	9 (28.1)	2 (11.1)	5 (11.6)	4 (50)	1 (100)	21	20.5
After 2nd-line	17 (53.1)	11 (61.1)	13 (30.2)	4 (50)	0 (0)	45	44.1
After 3rd-line	3 (9.4)	3 (16.7)	12 (27.9)	0 (0)	0 (0)	18	17.6
After 4th-line	3 (9.4)	2 (11.1)	11 (25.6)	0 (0)	0 (0)	16	15.6
More	0 (0)	0 (0)	2 (4.7)	0 (0)	0 (0)	2	1.9
After the results were provided, *n*							
Died before the results were provided	0 (0)	0 (0)	1 (2.3)	0 (0)	1 (100)	2	1.9
Could not be treated because of worsened performance status (PS > 2)	5 (15.6)	4**** (22.2)	4 (9.3)	0 (0)	0 (0)	13	12.7
Denied treatment	2 (6.3)	1 (5.6)	2 (4.7)	1 (12.5)	0 (0)	6	5.8
Did not have the recommended treatment	17 (53.1)	8 (44.4)	29 (67.4)	6 (75)	0 (0)	60	58.8
Not yet administered	3 (9.4)	3 (16.7)	3 (7.0)	1 (12.5)	0 (0)	10	9.8
Received molecularly targeted therapy	5 (15.6)	2 (11.1)	4 (9.3)	0 (0)	0 (0)	11	10.7

LOH loss of heterozygosity, *MSI-H*, high microsatellite instability, *TMB-H* high tumor mutation burden

*Includes a patient with metastasis after an initial diagnosis of adenocarcinoma in situ

**Includes two patients with carcinosarcoma of the uterus

***Includes 6 patients with peritoneal cancers and 1 patient with granular-cell carcinoma

****Includes a patient who could not be treated because of severe medical history

Common druggable gene alterations

Gene results revealed 98 patients with actionable gene alterations and 70 patients with druggable gene alterations. The most common druggable gene alteration was *PIK3CA* mutation, followed by *PTEN* mutation and high TMB (TMB-H) ($n=21$, 12, and 11, respectively).

Table 3 Histological subtypes of gynecologic cancers included in the study

	N (%)	Actionable gene alteration (+)	Druggable gene alteration (+)	Common gene alterations							
				BRCA1	*PIK3CA*	TMB-H	*ERBB2*	*PTEN*	*CDKN2A*	*CCND1*	*FGF3*
Cervical cancer	32 (100)	30	21	2	9	5	4	2	5	2	2
Squamous cell carcinoma	12 (37.5)	12	8	1	4	4	0	1	1	0	0
Adenocarcinoma	12 (37.5)	12	9	1	2	0	2	1	3	2	2
Endocervical adenocarcinoma, usual type	7 (21.9)	7	6	1	1	0	2	1	3	1	1
Mucinous adenocarcinoma	2 (6.3)	2	1	0	0	0	0	0	0	0	0
Adenocarcinoma, gastric type	2 (6.3)	2	2	0	1	0	0	0	0	1	1
Adenocarcinoma admixed with neuroendocrine carcinoma	1 (3.1)	1	0	0	0	0	0	0	0	0	0
Adenosquamous carcinoma	5 (15.6)	3	2	0	2	1	1	0	0	0	0
Neuroendocrine tumors	3 (9.4)	3	2	0	0	0	1	0	1	0	0
Endometrial cancer	18 (100)	18	15	1	5	5	2	5	1	1	1
EMG1/G2	5 (27.8)	5	4	0	1	1	1	2	0	0	0
EMG3	2 (11.1)	2	2	0	1	1	0	2	0	1	1
Serous carcinoma	6 (33.3)	6	5	1	1	1	1	0	0	0	0
Clear cell carcinoma	2 (11.1)	2	2	0	0	1	0	0	1	0	0
Carcinosarcoma	2 (11.1)	2	1	0	1	0	0	0	0	0	0
Others	1 (5.6)	1	1	0	1	1	0	1	0	0	0
Ovarian cancer	43 (100)	42	28	5	5	0	2	3	1	0	0
Serous carcinoma	26 (60.5)	25	17	5	1	0	0	1	0	0	0
HGSC	25 (58.1)	24	17	5	1	0	0	1	0	0	0
LGSC	1 (2.3)	1	0	0	0	0	0	0	0	0	0
Clear cell carcinoma	8 (18.6)	8	6	0	2	0	1	0	0	0	0
EM	5 (11.6)	5	5	0	2	0	1	2	1	0	0
Small cell carcinoma	1 (2.3)	1	0	0	0	0	0	0	0	0	0
Carcinosarcoma	1 (2.3)	1	0	0	0	0	0	0	0	0	0
Mixed carcinoma (serous + clear)	1 (2.3)	1	0	0	0	0	0	0	0	0	0
Granulosa cell tumor	1 (2.3)	1	0	0	0	0	0	0	0	0	0
Sarcoma	8 (100)	7	5	0	0	1	0	1	1	0	0
Leiomyosarcoma	6 (75)	6	4	0	0	0	0	1	1	0	0
Endometrial stromal sarcoma	2 (25)	1	1	0	0	1	0	0	0	0	0
Vaginal cancer	1 (100)	1	1	0	1	0	0	1	0	0	0
Large cell neuroendocrine carcinoma	1 (100)	1	1	0	1	0	0	1	0	0	0

EM endometrioid carcinoma, *G* grade, *HGSC* high-grade serous carcinoma, *LGSC* low-grade serous carcinoma

Patients with cervical cancer, endometrial cancer, and endometrial stromal sarcoma exhibited TMB-H. The histological types of cervical cancer were squamous cell carcinoma in 4 patients and adenosquamous carcinoma in 1 patient. Three of them received the recommended therapy, one was still on current therapy but was being offered pembrolizumab as a treatment option, and one did not receive pembrolizumab at the patient's request. Furthermore, the histological types found in patients with TMB-H endometrial cancer were endometrioid carcinoma (EM) grade (G) 2, EMG3, serous carcinoma, clear cell carcinoma, and adenocarcinoma individually. Only one of them was eligible for the recommended treatment; the others could not receive the recommended treatment because of deterioration of the general condition, regardless of the test results.

Among all the patients, only one had high MSI (MSI-H). This patient had stage IIIC1 endometrial cancer with *MSH2* pathogenic variant. Genetic counseling was recommended, but when the result was obtained, the patient could not receive treatment because of an aggravated general condition. This patient died shortly afterward.

Results and course of CGP

The attending physician conducted CGP when the patient was diagnosed with the progression of disease during or after the first-line treatment ($n=21$), during or after the second line ($n=45$), during or after the third line ($n=18$), during or after the fourth line ($n=16$), and after more than the fourth line ($n=2$) (Table 2).

Unfortunately, two patients (1.9%) died before the test results were available. In addition, 13 (12.7%) could not be treated with chemotherapy because of a very poor general condition when the test results were provided (performance status > 2). One of these patients was ineligible for chemotherapy because of medical history, even though the recommended therapy was offered. Although 70 patients had druggable gene alteration, 10 patients for whom PARP inhibitor was recommended and had already been treated with a PARP inhibitor were classified as having no recommended treatment. In addition, 18 patients who had recommended treatment for which there were no off-label clinical trials were also categorized as "patients who did not have recommended treatment group". As a result, 60 patients (58.8%) had no recommended treatment. Meanwhile, 10 patients (9.8%) had a recommended treatment but did not pursue it because they were responding to their current treatment (Table 2). They were supposed to receive the recommended treatment if the current treatment would not effective.

A total of 11 patients (5 with cervical cancer, 2 with endometrial cancer, and 4 with ovarian cancer) (10.8%) received the recommended treatment (Table 4). Among them, 3 were tested after the initial treatment, 5 after the second-line, 2 after the third-line, and 1 in the fourth-line. Nivolumab was the most commonly administered drug as a recommended therapy.

Patients with cervical cancer received the most frequently recommended treatment among gynecological cancers, with 5 (15.6%) being eligible for the recommended treatment. Among these 5 patients, 4 had squamous cell carcinoma and 1 had endocervical adenocarcinoma, usual type. Conversely, 17 had no recommended treatment. Most of the patients were examined after the second line, and their conditions mainly had progressed or relapsed after systemic chemotherapy for recurrence after concurrent chemoradiation therapy (CCRT).

Table 4 Summary of the 11 patients who received molecularly targeted therapy

	Age	Diagnosis	Histology	Stage	Lines of chemotherapy	Druggable gene alteration	Medicine
1	40	Cervical cancer	Squamous cell carcinoma	IIIB	2	TMB-H, *BRCA1*	Pembrolizumab
2	55	Cervical cancer	Endocervical adenocarcinoma, usual type	IA	2	*PTEN, BRCA1*	Olaparib
3	56	Cervical cancer	Squamous cell carcinoma	IB1	1	TMB-H	Nivolumab
4	57	Cervical cancer	Squamous cell carcinoma	IIIB	2	*PIK3CA*	Everolimus
5	78	Cervical cancer	Squamous cell carcinoma	IIIB	3	TMB-H	Nivolumab
6	59	Ovarian cancer	EMG2	IC1	3	*PIK3CA*	Everolimus
7	66	Ovarian cancer	HGSC	IIIA1	2	LOH-high, *CD274, PDCD1LG2*	Nivolumab
8	66	Ovarian cancer	HGSC	IVB	4	*TSC1, BRIP1*	Platinum drugs
9	79	Ovarian cancer	EMG2	IA	1	*PIK3CA, ERBB2* amplification	Trastuzumab
10	64	Endometrial cancer	Serous carcinoma	IVB	1	TMB-H, *PIK3CA, BRCA1*	Nivolumab
11	63	Endometrial cancer	EMG2	II	2	*PTEN*	Everolimus

EM endometrioid carcinoma grade, *G* grade, *HGSC* high-grade serous carcinoma, *LOH* loss of heterozygosity, *TMB-H* high tumor mutation burden

Regarding endometrial carcinoma, two patients (10.5%) could receive the recommended treatment. The patient with EMG2 had a *PTEN* mutation and received everolimus. The other patient, who was diagnosed with serous carcinoma, had TMB-H and received nivolumab.

In ovarian cancer, four patients (9.3%) were eligible for the recommended treatment (2 with HGSC and 2 with EMG2). One of the patients had *PIK3CA* mutation and *ERBB2* amplification and received trastuzumab, a HER2 inhibitor. While most of the patients who could receive the recommended treatment had been tested after second-line chemotherapy, one was tested after four times of recurrence before receiving the recommended treatment.

Genetic counseling recommendation

Based on the CGP results, genetic counseling was recommended in 19 cases (18.6%) (ovarian cancer: 11, endometrial cancer: 3, cervical cancer: 3, and sarcoma: 2). Target genes included *BRCA1* (8 cases), *BRCA2* (2 cases), *STK11* (1 case), *BRIP1* (1 case), *PALB2* (1 case), *TP53* (2 cases), *MSH2* (2 cases), *MSH6* (1 case), *ATM* (2 cases), *PTEN* (1 case) and *FH* (1 case). Of the 18 patients who requested counseling based on the result of CGP, 11 cases (61.1%) received genetic counseling based on the CGP results; 5 cases (27.8%) died before counseling (Table 5).

Discussion

In Japan, approximately, 22.3% of patients who underwent CGP in all solid tumors were treated with molecularly targeted therapy as the recommended treatment [4], but few were reported with regard to gynecological malignancies [7].

Of all 102 included patients, 32 had no druggable gene alterations, suggesting that these 32 patients did not receive the recommended treatment. In contrast, 11 (10.7%) out of 70 patients who had druggable gene alterations received the recommended treatment, with cervical cancer as the most common case (5 cases). The druggable gene alterations were TMB-H in 4 patients, *PIK3CA* in 4 patients, and *BRCA1* in 3 patients, and nivolumab was the most common drug administered as the recommended treatment. According to KEYNOTE-158 [9], which reported that ICIs are effective for solid tumors with MSI-H, most of the MSI-H tumors have TMB-H (> 20 mut/Mb) [10, 11]. Only one patient was diagnosed with MSI-H by CGP in this study. The result was consistent with the previous report that CGP was performed on 130 patients and MSI-H was found in only one patient (0.8%) with a primary unknown cancer, although the analysis included other cancers [4]. This might be because the MSI test had been performed before the CGP test, and patients with MSI-H were already undergoing treatment. The fact that MSI-H patients have a higher ICI response

Table5 Cases where genetic counseling was recommended by comprehensive genome profiling

Case	Status	Diagnosis	Method	Target genes	%
1	Performed genetic counseling	Cervical cancer	FoundationOne® CDx	*BRCA1, STK11*	Genetic counseling performed: 11/18 (61.1%)
2	Performed genetic counseling	Cervical cancer	FoundationOne® CDx	*BRCA2*	
3	Performed genetic counseling	Endometrial cancer	FoundationOne® CDx	*BRCA1*	
4	Performed genetic counseling	Ovarian cancer	Oncogide™NCC Oncopanel	*BRCA1*	
5	Performed genetic counseling	Ovarian cancer	FoundationOne® CDx	*BRIP1*	
6	Performed genetic counseling	Ovarian cancer	FoundationOne® CDx	*BRCA1*	
7	Performed genetic counseling	Ovarian cancer	FoundationOne® CDx	*BRCA1*	
8	Performed genetic counseling	Ovarian cancer	FoundationOne® CDx	*BRCA1*	
9	Performed genetic counseling	Sarcoma	FoundationOne® CDx	*TP53*	
10	Performed counseling elsewhere	Ovarian cancer	FoundationOne® CDx	*BRCA1*	
11	Performed counseling elsewhere	Sarcoma	FoundationOne® CDx	*BRCA2*	
12	Died before counseling	Endometrial cancer	FoundationOne® CDx	*MSH2*	Died before counseling: 5/18 (27.8%)
13	Died before counseling	Ovarian cancer	FoundationOne® CDx	*ATM*	
14	Died before counseling	Ovarian cancer	FoundationOne® CDx	*BRCA1*	
15	Died before counseling	Ovarian cancer	FoundationOne® CDx	*MSH2, MSH6*	
16	Died before counseling	Ovarian cancer	FoundationOne® CDx	*PALB2*	
17	Not yet announced	Endometrial cancer	FoundationOne® CDx	*ATM*	Not yet announced: 2/18 (11.1%)
18	Not yet announced	Ovarian cancer	FoundationOne® CDx	*PTEN, TP53*	
19	No desire to perform counseling	Cervical cancer	FoundationOne® CDx	*FH*	NA

NA not applicable

rate and a lower relapse rate may also have contributed to the result that only one patient was diagnosed with MSI-H. Considering the fact that only one patient had MSI-H in the present study and roughly 4% of cancers have MSI-H [10], MSI-H alone could not be a helpful biomarker for ICI treatments in a broad spectrum. Nevertheless, microsatellite-stable tumors with TMB-H benefit from ICIs [11].

Treatment options for recurrent gynecologic malignancies have widened these days. However, while the views on the treatment of recurrent tumors have been generalized to some extent, defining a standard treatment remains difficult. Although treatment options that may offer a longer prognosis are increasing in number, prognosis may still be poor because of the severity of diseases. Nonetheless, CGP may help expand treatment options for these patients.

In this study, the most common time for CGP testing in patients with cervical cancer was around the second-line of treatment. Currently, radiotherapy and systemic chemotherapy are the most common treatment options for recurrent cervical cancer [12]; surgery is sometimes performed [13], but its effect on prognosis has not been established [13–15]. Given the current situation, many patients are expected to undergo multigene panel testing for recurrence after standard treatment around second-line. Recently, following the results of KEYNOTE-826 [16], treatment with additional ICIs and cytotoxic chemotherapeutic agents for patients with advanced or relapsed cervical cancer has been covered by insurance in Japan. In addition to pembrolizumab, ICIs such as cemiplimab [17, 18] and dual checkpoint blockades such as balstilimab plus zalifrelimab [19] and the human anti-tissue factor antibody of tisotumab vedotin [20] are gaining attention. Especially cemiplimab has just been covered by insurance in Japan. These new drugs for cervical cancer have shown promising therapeutic efficacy, and depending on the response rate to these drugs, the timing of multigene panel testing after second-line treatment may be acceptable. However, given the risk of mortality or worsening of the general condition at the time when panel test results are already available, panel testing may be conducted after the recurrence of advanced cancer of special histological types.

The treatment of recurrent endometrial cancer has been partly surgery and mainly systemic chemotherapy (paclitaxel plus carboplatin, and docetaxel plus cisplatin [DP]). In KEYNOTE-775, lenvatinib plus pembrolizumab enabled prolonged progression-free survival and overall survival in patients with recurrent endometrial cancer, regardless of being mismatch repair proficient or deficient, compared with the conventional therapy of DP [21]. In Japan, lenvatinib plus pembrolizumab has already been covered by health insurance for the treatment of recurrent advanced endometrial cancer since December 2021. Given that our study period began in November 2019, we were able to include many cases with worsened general conditions after DP therapy. If lenvatinib plus pembrolizumab therapy will be shown to be effective in the future in Japan, the timing and prognosis of multigene panel testing may change.

In January 2018, olaparib was approved as maintenance therapy in platinum-sensitive recurrent ovarian cancer, and in June 2019, it was approved as maintenance therapy after initial chemotherapy in *BRCA1/2* mutation-positive ovarian cancer [22]. The PRIMA trial showed the benefit of niraparib in advanced ovarian cancer with or without HRD [23]. In addition, the PAOLA-1 trial showed that olaparib plus bevacizumab is effective for advanced ovarian cancer with HRD [24], and the efficacy of rucaparib also gained attention [25]. Thus, treatment options with poly (ADP-ribose) polymerase (PARP) inhibitors for ovarian cancer have evolved remarkably over the past few years. However, many challenges are still existing in the treatment of clear cell carcinoma [26], which is relatively common in the Japanese population and refractory to chemotherapy, and mucinous carcinoma, which does not respond well to chemotherapy. While CGP is promising for patients without treatment options, previously administered treatments are recommended by CGP for some cases. For example, PARP inhibitor was recommended for a patient who already received PARP inhibitor before. In such a case, PARP inhibitor may not be given because the patient is already practically refractory to PARP inhibitor. Therefore, the 7 patients were included in the 29 patients for which no treatment was recommended as written in Table 2. Although the treatment options for recurrent ovarian cancer are diversified and difficult to standardize, CGP should be performed in case the standard therapy will no longer be effective, and then linked to the recommended therapy.

Regarding rare gynecologic tumors, we had one patient with vaginal cancer. Generally, vaginal cancer is uncommon and has a poor prognosis. Our patient had a histology of neuroendocrine and had no recommended treatment. Although the patient was already stage IVB of neuroendocrine carcinoma at the time of diagnosis and was submitted for the CGP test immediately after the first-line chemotherapy because it was assumed to be a poor prognosis, unfortunately, she died before the result was obtained. More cases of vaginal cancer should be accumulated in the future.

Although chemotherapy widens the range of treatment options, the patient's general condition should be evaluated. However, in this study, 2 patients died and 13 were in poor general condition when the results were obtained. Considering that the test is performed under the assumption that chemotherapy will be administered, the patient's prognosis should be predicted, and the test should be performed at the appropriate time. The range of prognosis and treatment options for recurrence differs depending on the type of cancer; hence, our study results are impossible to be generalized. At our hospital, the timing of CGP testing was left to the discretion of the attending physician. The prognosis

varies not only by tumor and stage but also by patient background and age; thus, scheduling of tests may be necessary, with the anticipation that the standard treatment may be no longer effective in the future. In principle, testing is performed when a patient is refractory to standard therapy, but at the attending physician's discretion, testing was performed somewhat earlier in some cases. For example, recurrence in the irradiated field immediately after CCRT for cervical cancer was considered to have a poor prognosis, and testing was performed during chemotherapy after resection of the recurrent tumor. Specific histology such as neuroendocrine tumors of cervical cancer was also considered to have a poor prognosis and was examined after initial chemotherapy. In other cases, when a patient's general condition tended to be poor, testing was performed earlier in anticipation of the loss of efficacy of standard therapy. In some cases, testing at an earlier phase has made it possible to administer recommended therapy. In addition, six patients did not receive treatment at their request. Although their exact reasons were not fully examined in this study, they expressed difficulty in traveling to the distant medical institution where the clinical trial was being conducted, or they were resistant to the new treatment. We need to emphasize that the gene panel test is a test for additional treatment and that the patient's living will should be checked again before the test.

Genetic counseling may be recommended based on phenotypes of inherited disease or variant allele frequency of gene mutation based on CGP results. The results of CGP not only lead to new treatments but also to recommendations for genetic counseling. In this study, genetic counseling was provided in 19 cases (18.6%). This is higher than the previously reported 3.2% of hereditary tumors among those who underwent cancer gene panel testing [2]. One possible reason is the high percentage of ovarian cancers in our study, which have a higher percentage of hereditary tumors than other cancer types.

In 4 cases, genetic counseling could not be provided because the patient had already died by the time the counseling was recommended. The timing of CGP testing should be a little earlier to increase the probability of receiving new treatments or to link the patient to genetic counseling.

The limitation of the study was the fact that this study was conducted only in a single center, resulting that the sample size and patients' characteristics being limited. It should be noted that almost all the patients were Asian, and the characteristics of cancer incidence and frequency of occurrence also vary by race.

In conclusion, by CGP, 10.8% of patients received the recommended treatment despite druggable gene alterations being found in many cases. Although there are reports of CGP results, there are still few reports specific to gynecologic cancers. This study is a novel study that was able to identify the utility of CGP in gynecologic cancers and the characteristics of cases for which recommended treatment is possible. TMB-H was observed in various histological subtypes of cervical/endometrial cancer; thus, it can be a therapeutic biomarker of immune therapy. Furthermore, patients' prognosis and personal status should be considered before ordering the test.

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Declarations

Conflict of interest Tatsuyuki Chiyoda reported grants from Takeda Pharmaceutical Company. Daisuke Aoki reported honoraria from Takeda Pharmaceutical Company, Chugai Pharmaceutical Company, AstraZeneca, MSD and Myriad Genetics. The other authors declare no conflicts of interest regarding this study.

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