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Cost-Effectiveness Analysis of Germline and Somatic *BRCA* Testing in Patients With Advanced Ovarian Cancer

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Background: *BRCA* testing is necessary for establishing a management strategy for ovarian cancer. Several *BRCA* testing strategies, including germline and somatic testing, are implemented in clinical practice in Korea. We aimed to comparatively evaluate their cost-effectiveness from patients' perspective.

Methods: We developed a decision model comprising five *BRCA* testing strategies implemented in Korea: (1) germline testing first, followed by somatic tumor testing for patients without a germline variant; (2) somatic testing first, followed by germline testing for patients with a variant detected by somatic testing; (3) both germline and somatic testing; (4) germline testing alone; and (5) somatic testing alone, with no testing as the comparator. One-way sensitivity analysis was conducted to test the uncertainty of key parameters.

Results: Assuming a willingness-to-pay of $20,000 per progression-free life-year gain (PF-LYG), all five strategies were considered cost-effective. Strategy 4 was the most cost-effective option, with an incremental cost-effectiveness ratio (ICER) of $2,547.7 per PF-LYG, followed by strategy 1, with an ICER of $3,978.4 per PF-LYG. Even when the parameter values were varied within the possible range, the ICERs of all strategies did not exceed the willingness-to-pay threshold.

Conclusions: Considering the importance of knowing a patient's *BRCA* gene status, germline testing first, followed by somatic testing, may be a reasonable option.

Key Words: *BRCA* testing, Cost-effectiveness analysis, Advanced ovarian cancer

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INTRODUCTION

The guidelines of the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) recommend genetic testing to identify the mutation status of *BRCA* genes (*BRCA1* and *BRCA2*) in ovarian cancer patients because of its clinical implications [1, 2]. Genetic testing of the *BRCA* genes should be conducted at the time of diagnosis as this can help clinicians establish management strategies based on the genetic status of a patient after primary treatment [2, 3]. When a germline *BRCA* variant is found in a patient, risk assessment of other *BRCA*-related cancers in the patient and genetic counseling for their family members is considered [1, 2, 4].

Based on the concept of synthetic lethality, olaparib was the first poly (ADP-ribose) polymerase (PARP) inhibitor introduced as a therapeutic agent for *BRCA*-mutated cancers [5]. SOLO-1 and PRIMA are international, randomized, phase III clinical trials of PARP inhibitors (olaparib and niraparib, respectively) for maintenance monotherapy in patients with advanced ovarian cancer. In the SOLO-1 trial, olaparib, as a first-line maintenance

therapy in patients with newly diagnosed *BRCA*-mutated ovarian cancer and responsive to platinum-based chemotherapy, significantly improved the progression-free survival (PFS) when compared with that by the placebo [6, 7]. In the PRIMA trial, niraparib, as a first-line maintenance therapy, prolonged PFS in patients with platinum-sensitive advanced ovarian cancer when compared with the placebo, regardless of *BRCA* status. The highest efficacy was observed in patients with *BRCA* variants [8].

In Korea, 2,898 patients were newly diagnosed with ovarian cancer in 2018, and the incidence of ovarian cancer gradually increased by 2.0% per year between 1999 and 2018 [9]. The prevalence of germline and somatic *BRCA* variants in advanced ovarian cancer are 14%–18% and 4%–7%, respectively [10-13]. Further, prevalence of germline *BRCA* variants in ovarian cancer is reported to be 11.5% in Korea [14]. As *BRCA* testing is required for patients with ovarian cancer, the number of *BRCA* testing will increase as the number of patients increases. Therefore, given the limited resources, an economic evaluation of *BRCA* testing should be considered.

Cost-effectiveness should be evaluated based on the healthcare system of each country. To our knowledge, the cost-effectiveness of *BRCA* testing for ovarian cancer in Korea has not been evaluated to date. We assessed the cost-effectiveness of *BRCA* testing strategies followed by PARP inhibitor maintenance therapy based on the National Health Insurance (NHI) system of Korea, from the patient's perspective.

MATERIALS AND METHODS

Decision model

In Korea, the use of PARP inhibitors as a first-line maintenance therapy for patients with *BRCA*-mutated platinum-sensitive ovarian cancer is included in the NHI benefit package. In the present study, we included patients who were at least 18 years of age, newly diagnosed with advanced ovarian cancer, and had complete or partial response to platinum-based chemotherapy. Study population data were collected from the SOLO-1 and PRIMA trials [6-8].

For patients with epithelial ovarian cancer, the ASCO guidelines recommend germline testing first, followed by somatic testing for those in whom a germline *BRCA* variant was not detected [2]. *BRCA* testing strategies implemented in clinical settings vary according to the germline and somatic testing configurations used. We developed a decision model comprising five *BRCA* testing strategies implemented in Korea (Fig. 1). Strategy 1 entailed germline testing first, followed by somatic testing if no germline *BRCA* variant was revealed. Strategy 2 was somatic testing first, followed by germline testing if somatic testing revealed a *BRCA* variant to determine whether the variant was germline or somatic. Strategy 3 was germline testing in tandem with somatic testing. Strategy 4 was germline testing alone, and strategy 5 was somatic testing alone. The comparator was no testing.

For all strategies except the no-testing strategy, there were two possible outcomes: *BRCA* variant detected or not detected. The frequencies of germline and somatic variants were calculated as average values from four previous studies [10–13]. The probability of each outcome depended on the type of *BRCA* testing conducted (germline and/or somatic) and the prevalence of germline or somatic *BRCA* variants in advanced ovarian cancer. The cost and effectiveness of both outcomes were obtained for each strategy. If a *BRCA* variant was detected, it was assumed that patients only received PARP inhibitor maintenance monotherapy because other maintenance therapies, including bevacizumab, and other practices, such as genetic counseling, preventive surgeries, and genetic testing for unaffected family members of patients, are not included in the NHI benefit package. Olaparib and niraparib are the only PARP inhibitors included in the NHI benefit package and hence are the only two options for PARP inhibitor maintenance therapy. At baseline, we assumed that half of the patients received olaparib and the other half received niraparib (i.e., the probability that a patient with a *BRCA* variant received olaparib was 50% and the probability that a patient received niraparib was 50%). If a *BRCA* variant was not detected, it was assumed that maintenance therapy was not considered. Treatments preceding PARP inhibitor maintenance therapy, such as cytoreductive surgery and platinum-based chemotherapy, were not considered in this model because these do not vary according to the strategy used. Finally, the cost and effectiveness of each strategy were calculated by summing the values obtained by multiplying cost and effectiveness by the probability of each case.

Costs

Costs were estimated based on the fee schedule of the Korea Health Insurance Review and Assessment Service [15], which is responsible for the management of the NHI benefit package and the reimbursement price of the services included therein [16]. Costs were calculated as co-payment, which was obtained by multiplying the insurance fee schedule and co-payment rate. We estimated the direct medical costs, which included the costs

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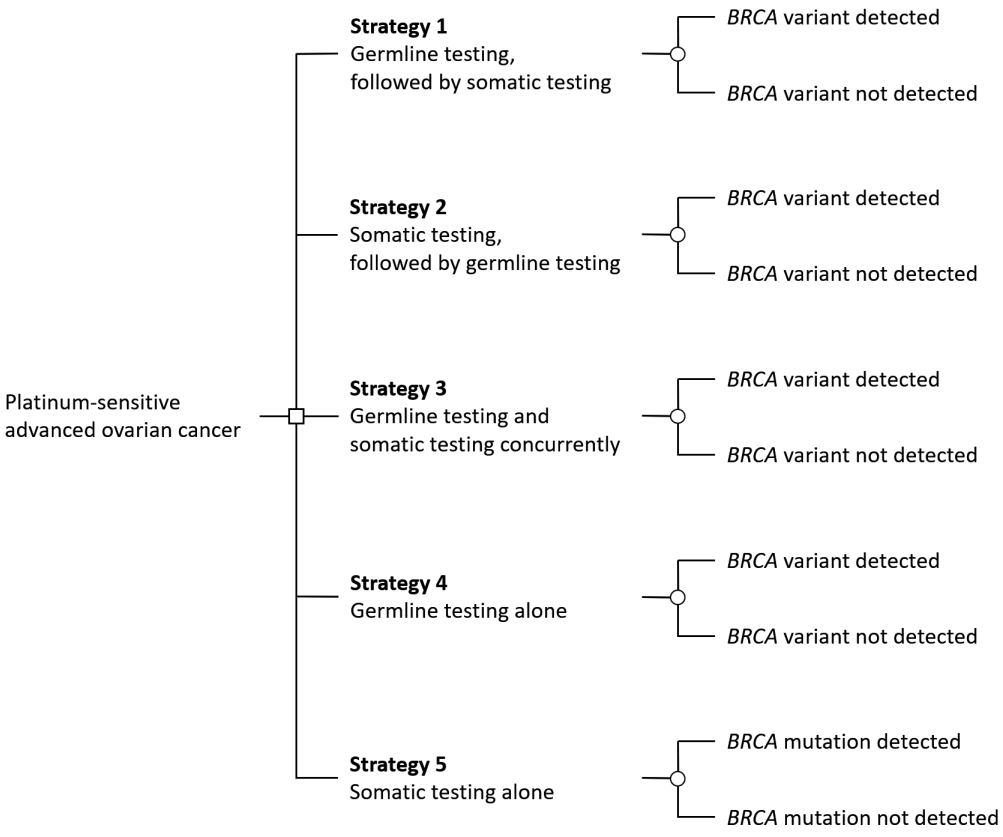

Fig. 1. Schematic representation of the model.

of genetic testing, PARP inhibitors, and monitoring. Costs were calculated in Korean won and converted to US dollar at an exchange rate of 1,200 Korean won = 1 US dollar.

The NHI provides different health insurance services according to the type of *BRCA* testing. In this study, fee schedule codes for germline *BRCA* testing were "Genetic Testing for Germline Variant–Sequencing (C5809 and C5810)," which cover single *BRCA1* and *BRCA2* testing, respectively. The fee schedule code for somatic *BRCA* testing was "Next Generation Sequencing (NGS) Technology-based Genetic Panel Test–Genetic Tests for Somatic Variants (CB004)," which covers NGS-based gene panel testing for multiple genes, including the *BRCA* genes.

We assumed patients with a *BRCA* variant to have received olaparib at a dose of 300 mg twice daily for two years or niraparib at a dose of 200 mg once daily for two years and to have made weekly hospital visits during the first month, followed by monthly visits for two years. The overall costs of drugs were calculated by multiplying the costs of the drugs for 30 days by 24. Patients without a *BRCA* variant were assumed to have made hospital visits every three months for two years. Monitoring costs included the costs of office visits, computed tomography scans, and laboratory testing, including cancer antigen 125 testing and complete blood count.

Health utility

We considered the effectiveness of only PARP inhibitor maintenance monotherapy. Health utility was assessed as the gain in PFS achieved by PARP inhibitor use in clinical trials and was expressed as progression-free life-year gain (PF-LYG), which was calculated as the difference in median PFS between patients who received PARP inhibitors and those who received a placebo based on clinical trial outcomes.

Cost-effectiveness analysis

The incremental cost and effectiveness of each strategy were calculated as the difference in cost and effectiveness between the strategy and no-testing strategy. The incremental cost-effectiveness ratio (ICER) was obtained by dividing the incremental cost by the incremental effectiveness. The cost-effectiveness of each strategy at baseline was compared with the ICER. Baseline values are provided in Table 1.

Sensitivity analysis

A one-way sensitivity analysis was conducted to test the uncertainty and effect of key parameters on the ICER [17]. The key parameters included the frequency of germline and somatic variants in patients with advanced ovarian cancer, costs of PARP inhibitors, PF-LYG with PARP inhibitor use, and the proportion of olaparib use among the two PARP inhibitors available (olaparib and niraparib). We calculated ICER by changing values of the parameters within the possible interval. Probability values varied by ±50%, and the costs and PF-LYG with PARP inhibitor use varied by ±30%. We assumed that germline and/or somatic testing were conducted once for each strategy.

Table 1. Model input

Parameters	Baseline values
Cost ($)	
Germline testing	76.6
Somatic testing	714.0
Olaparib treatment (30 days)	243.3
Niraparib treatment (30 days)	174.8
Monitoring in treatment (24 months)	109.4
Monitoring in observation (24 months)	42.3
PF-LYG (y)	
Olaparib maintenance monotherapy	3.52
Niraparib maintenance monotherapy	0.93
Probability (%)	
Prevalence of germline *BRCA* variant in OC	13.1
Prevalence of somatic *BRCA* variant in OC	5.4
Proportion of olaparib use (niraparib use)	50 (50)

Abbreviations: PF-LYG, progression-free life-year gain; OC, ovarian cancer.

RESULTS

Cost-effectiveness analysis

The estimated cost and PF-LYG of each strategy are summarized in Table 2. With reference to an evaluation of willingness-to-pay (WTP) in Korea, which reports a range of 15-35 million

Table 2. Results of cost-effectiveness analysis

Testing strategy	Cost ($)	PF-LYG (y)	ICER ($/PF-LYG)
Strategy 1	1,680.0	0.41	3,978.4
Strategy 2	1,711.1	0.41	4,054.1
Strategy 3	1,773.5	0.41	4,205.7
Strategy 4	784.9	0.29	2,547.7
Strategy 5	1,696.9	0.41	4,019.7
No testing (comparator)	42.3	referent	–

Abbreviations: PF-LYG, progression-free life-year gain; ICER, incremental cost-effectiveness ratio.

Table 3. Results of one-way sensitivity analysis, costs and effectiveness

Parameters	Values	Strategy 1		Strategy 2		Strategy 3		Strategy 4		Strategy 5	
		Inc cost	Inc eff	Inc cost	Inc eff	Inc cost	Inc eff	Inc cost	Inc eff	Inc cost	Inc eff
Cost of olaparib ($)	Lo: 170.3	1,475.6	0.41	1,506.8	0.41	1,569.2	0.41	627.9	0.29	1,492.6	0.41
	Up: 316.2	1,799.6	0.41	1,830.8	0.41	1,893.2	0.41	857.3	0.29	1,816.6	0.41
Cost of niraparib ($)	Lo: 122.4	1,521.2	0.41	1,552.3	0.41	1,614.7	0.41	660.1	0.29	1,538.2	0.41
	Up: 227.3	1,754.1	0.41	1,785.2	0.41	1,847.6	0.41	825.0	0.29	1,771.0	0.41
Olaparib PF-LYG (y)	Lo: 2.46	1,637.6	0.31	1,668.8	0.31	1,731.2	0.31	742.6	0.22	1,654.6	0.31
	Up: 4.57	1,637.6	0.51	1,668.8	0.51	1,731.2	0.51	742.6	0.36	1,654.6	0.51
Niraparib PF-LYG (y)	Lo: 0.65	1,637.6	0.39	1,668.8	0.39	1,731.2	0.39	742.6	0.27	1,654.6	0.39
	Up: 1.21	1,637.6	0.44	1,668.8	0.44	1,731.2	0.44	742.6	0.31	1,654.6	0.44
Prev of germline *BRCA* variant (%)	Lo: 6.6	1,351.4	0.27	1,330.7	0.27	1,398.2	0.27	409.6	0.15	1,321.6	0.27
	Up: 19.7	1,923.9	0.56	2,006.8	0.56	2,064.2	0.56	1,075.6	0.44	1,987.6	0.56
Prev of somatic *BRCA* variant (%)	Lo: 2.7	1,500.4	0.35	1,529.4	0.35	1,593.9	0.35	742.6	0.29	1,517.3	0.35
	Up: 8.1	1,774.9	0.47	1,808.1	0.47	1,868.4	0.47	742.6	0.29	1,791.9	0.47
Proportion of olaparib use (%)	Lo: 25	1,561.7	0.29	1,592.8	0.29	1,655.2	0.29	688.8	0.21	1,578.7	0.29
	Up: 75	1,713.6	0.53	1,744.7	0.53	1,807.1	0.53	796.4	0.38	1,730.5	0.53

Abbreviations: Inc cost, incremental cost ($); Inc eff, incremental effectiveness (y); PF-LYG, progression-free life-year gain; Lo, lower limit; Up, upper limit; Prev, prevalence.

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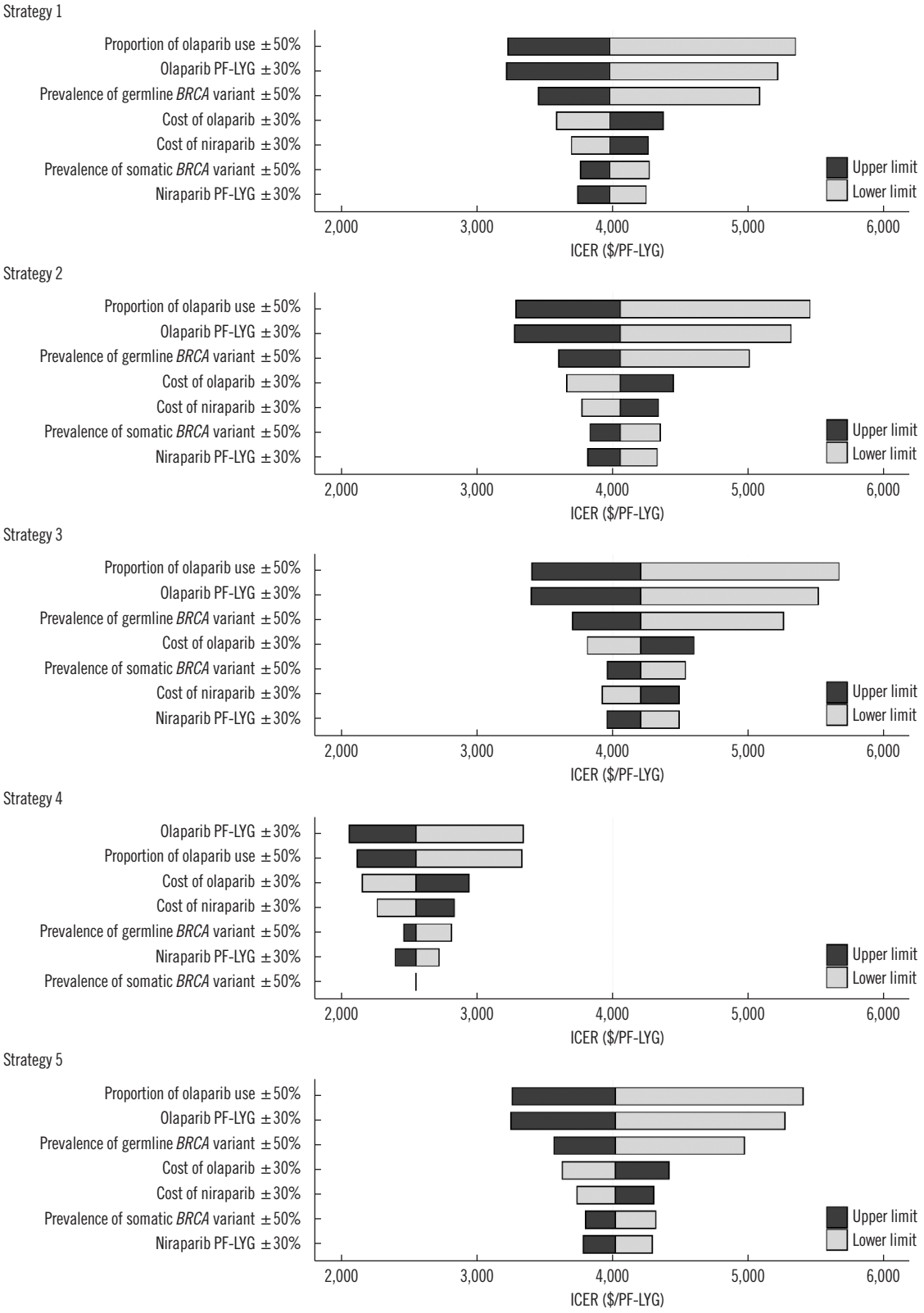

Fig. 2. Results of one-way sensitivity analysis and incremental cost-effectiveness ratio.
Abbreviations: PF-LYG, progression-free life-year gain; ICER, incremental cost-effectiveness ratio.

Korean won [18], we assumed a WTP of $20,000 per PF-LYG. All five strategies were considered cost-effective at a given WTP of $20,000 per PF-LYG. Strategy 4 (germline testing alone) was the most cost-effective, with an ICER of $2,547.7 per PF-LYG. As the co-payment of germline *BRCA* testing is remarkably lower than that of somatic testing, strategy 4 had the lowest cost. As it is impossible to detect somatic variants by germline testing alone, patients with a somatic variant could not receive PARP inhibitor therapy in strategy 4. Consequently, strategy 4 showed the lowest PF-LYG. Strategy 5 (somatic testing alone) and the other three strategies involving both germline and somatic testing can detect both germline and somatic variants. Therefore, the probability of detecting a *BRCA* variant was estimated to be the same for strategies 1, 2, 3, and 5. When a variant is detected by somatic testing, it is impossible to determine whether it is a germline or somatic variant. However, PARP inhibitors can be used regardless of whether the variant is germline or somatic. Thus, these four strategies had the same PF-LYG. In strategy 1, patients who underwent germline testing had an approximately 85% probability of undergoing somatic testing thereafter, assuming that the prevalence of germline *BRCA* variants in ovarian cancer was 15%. Because of the high co-payment of somatic testing, strategy 1 was less costly than strategies 2 and 5 (in which patients receive somatic testing as a standard). Strategy 3 was the costliest option in the model because patients underwent both germline and somatic testing. Strategy 1 was the second most cost-effective strategy, with an ICER of $3,978.4 per PF-LYG, followed by strategy 5 (ICER of $4,019.7 per PF-LYG), strategy 2 ($4,054.1 per PF-LYG), and strategy 3 ($4,205.7 per PF-LYG).

Sensitivity analysis

One-way sensitivity analysis was conducted for the key parameters, and the costs and effectiveness were estimated (Table 3). Even when the parameters were varied, the ICERs of all five strategies were below the WTP threshold of $20,000 per PF-LYG (Fig. 2). Thus, all five strategies remained cost-effective. Changes in the proportion of olaparib use and PF-LYG with olaparib use had significant effects on the cost-effectiveness of the strategies. The strategies became more cost-effective when the proportion of olaparib use increased as compared with that of niraparib use. This indicates that *BRCA* testing is more cost-effective when olaparib is used. Changes in the prevalence of somatic variants and PF-LYG with niraparib use had limited effects on the cost-effectiveness of the strategies. Somatic variants could not be detected by germline testing alone; therefore, the prevalence of somatic variants did not affect the cost-effectiveness of strategy 4. When the parameters were varied, strategy 1 was more cost-effective than strategy 5. However, when the prevalence of germline *BRCA* variants decreased to 6.6%, strategy 5 (ICER of $4,970.5 per PF-LYG) was more cost-effective than strategy 1 (ICER of $5,082.5 per PF-LYG).

DISCUSSION

We evaluated the cost-effectiveness of five *BRCA* testing strategies and demonstrated that all five strategies were cost-effective under an assumed WTP of $20,000 per PF-LYG. The results demonstrated that *BRCA* testing for Korean patients with advanced ovarian cancer is cost-effective when followed by PARP inhibitor maintenance therapy for *BRCA*-mutated ovarian cancer. Studies have shown that germline *BRCA* testing is cost-effective with regard to cancer risk management in patients with epithelial ovarian cancer [19, 20] and first-degree relatives [21]. However, the cost-effectiveness of PARP inhibitor maintenance therapy varied under different conditions in different studies [22–26]. In some studies, olaparib maintenance therapy was considered cost-effective for patients with ovarian cancer when compared with no maintenance therapy [25, 26].

The overall insurance fee schedule is strictly supervised by the Korean government under the single-payer health insurance system. In the NHI, patients diagnosed with ovarian cancer are classified as "Registered cancer patient" and have a uniform co-payment rate of 5% to medical services covered by "Health care benefits." For patients with ovarian cancer, the co-payment of a 150-mg olaparib tablet is approximately $2.0, and the co-payment of a 100-mg niraparib capsule is approximately $2.9. Many medical services for patients with ovarian cancer included in the NHI benefit package are covered by "Health care benefits." However, somatic *BRCA* testing is conducted using NGS, which is covered by "Selective benefits" for cases where medical services have uncertain economic feasibility or efficacy, and the co-payment rate is higher than that of "Health care benefits." In most cases, the cost incurred by patients with ovarian cancer is only 5% of the insurance fee schedule. Therefore, it seems obvious for all strategies to be cost-effective from the patient's perspective.

Both germline and somatic *BRCA* testing are required for the preventive and therapeutic management of patients and their family members. In terms of clinical benefit, conducting germline testing or somatic testing alone is not optimal. However, conducting both tests concurrently is not economical. The ASCO

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guidelines recommend germline testing prior to somatic testing for all patients diagnosed with ovarian cancer because germline testing is more sensitive than somatic testing [2]. Because somatic variants cannot be detected in DNA extracted from blood, *BRCA* testing of tumor tissue prior to peripheral blood testing is considered an effective approach for patients diagnosed with ovarian cancer because germline and somatic variants can theoretically be detected simultaneously, albeit they cannot be distinguished, by tumor tissue testing [27]. Recently, *BRCA* testing of tumor tissue samples in ovarian cancer using NGS has been evaluated [27-31]. However, somatic testing has technical drawbacks. Formalin-fixed paraffin-embedded (FFPE) tumor tissue samples are routinely used for testing. Formalin fixation may cause artifacts because of crosslinking and DNA fragmentation. DNA extracted from FFPE samples can be affected by the extraction method used and the specimen condition [32]. The amplification of DNA extracted from FFPE results in sequence artifacts, e.g., DNA nucleotide substitutions of C with T and G with A, due to the deamination of cytosine to uracil [33–35]. Compared with *BRCA* testing by NGS using buffy coat samples, which yielded no false-positive results, *BRCA* testing by NGS using FFPE samples was associated with a higher rate of false-positive results, mainly due to C-to-T and G-to-A transitions [36]. Moreover, NGS using FFPE and fresh frozen tumor samples resulted in a disproportionate variant allele frequency (VAF) when compared with NGS using matched buffy coat samples; thus, the analytical performance of NGS using tumor tissues can be affected by sequencing artifacts and VAF-shifted variants [36]. In previous studies, tumor *BRCA* testing in ovarian cancer was unsuccessful in 1%–3% of cases [27, 30, 31]. Given these issues, conducting somatic testing prior to germline testing may not be an efficient choice.

This study had several limitations. First, the full cost-effectiveness of *BRCA* testing incurred by the patient was not considered. The use of PARP inhibitors is associated with some adverse events that may affect the treatment strategy and may result in further medical intervention with related costs [6, 8]. The SOLO-1 and PRIMA trials reported that approximately 10% of patients had treatment-related adverse events, which required a dose change or, in rare cases, discontinuation [6, 8]. Nausea and anemia were frequently observed in both trials and further costs may be incurred due to these events. However, because of a lack of data, the costs of adverse events were not considered, and nonmedical costs related to treatment were not included. Moreover, as mentioned before, the costs of several other management practices required for patients with *BRCA*-mutated ovarian cancer in clinical practice, such as genetic counseling, preventive surgeries, and genetic testing for unaffected family members of the patients, were not included because the costs of medical services not included in the NHI benefit package are hard to estimate, and risk-reducing mastectomy is rarely conducted in non-breast cancer patients in Korea [37]. Second, this study involved two distinct populations that received different PARP inhibitors. Moreover, there was a difference in PF-LYG between the two studies, because they used two different PARP inhibitors and the populations had variable demographic characteristics.

In conclusion, *BRCA* testing strategies implemented in clinical settings in Korea are considered cost-effective because of the low co-payment. However, considering the clinical implications as well as the cost-effectiveness, the strategy recommended by the ASCO guidelines (i.e., germline testing first, followed by somatic testing if no germline variant is detected) may be a reasonable option from the standpoints of both patients and clinicians.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Jang J, Kim Y, and Lee KA conceptualized and designed the study. Jang J collected the data, conducted the analyses, and wrote the manuscript. Cho SM helped conduct the analysis with constructive discussions. Kim Y, Kim JH, and Cho SM reviewed and commented the manuscript. Lee KA supervised the study and finalized the manuscript. All authors take responsibility for the intellectual content of this manuscript.

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