Cost-effectiveness analysis of germline/somatic BRCA testing in patients with advanced ovarian cancer

Jaehyeok Jang

Department of Medicine

The Graduate School, Yonsei University

Cost-effectiveness analysis of germline/somatic BRCA testing in patients with advanced ovarian cancer

Directed by Professor Kyung-A Lee

The Master's Thesis
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for
the degree of Master of Medical Science

Jaehyeok Jang

December 2021

This certifies that the Master's Thesis of

Jaehyeok Jang is approved.

Thesis Supervisor : Kyung-A Lee

Thesis Committee Member#1 : Jae-Hoon Kim

Thesis Committee Member#2 : Yoonjung Kim

The Graduate School
Yonsei University

December 2021

ACKNOWLEDGEMENTS

I would like to thank all of those who have guided and helped me throughout the course of completing my Master's degree thesis and research.

I wish to express special thanks to my thesis supervisor, Professor Kyung-A Lee for providing direction in this research, as well as giving detailed advice in every step of the way. All of this was possible because of the attention and support she has given, not to mention being allowed the chance to develop a greater scope in the field of research.

In addition, I would also like to thank Professor Yoonjung Kim, Professor Jae-Hoon Kim, and Professor Sun-Mi Cho for providing advices and feedbacks in all the points necessary to finishing my thesis.

Lastly, I would like to thank my family for the love and support they have shown me throughout my life.

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Cost-effectiveness analysis of germline/somatic BRCA testing in patients with advanced ovarian cancer

Jaehyeok Jang

Department of Medicine

The Graduate School, Yonsei University

(Directed by Professor Kyung-A Lee)

Background: BRCA testing for ovarian cancer is necessary to establish a management plan, especially for the use of maintenance therapy with PARP inhibitors. Although genetic testing strategy for BRCA testing among patients with advanced ovarian cancer is recommended, several different strategies with various configurations, including germline and somatic testing are implemented in real clinical practice in South Korea. The aim of this study was to evaluate and compare the cost-effectiveness of the strategies.

Method: A decision model was developed consisting of five BRCA testing strategies which are generally implemented in South Korea: (1) Germline testing first, followed by somatic tumor testing for patients without germline mutation, (2) somatic testing first, followed by germline testing for patients with mutation detected by somatic testing, (3) both germline and somatic testing, (4) germline testing alone, and (5) somatic testing alone. Participants of clinical trials of PARP inhibitors, SOLO-1 and PRIMA, were used for simulated

population. Health outcome was calculated in progression-free life-year gain (PF-LYG) using the primary outcome of the clinical trials. Costs were estimated from the fee schedule of the National Health Insurance Service in South Korea. Costs were calculated in Korean won (KRW). The incremental cost and incremental effectiveness of each strategy were calculated by subtracting cost and effectiveness of no testing strategy from those of each strategy. The incremental cost-effectiveness ratio (ICER) was obtained as a representation of the cost-effectiveness of the strategy. One-way sensitivity analysis was conducted to test uncertainty of key parameters. This analysis was conducted from the patient's perspective.

Result: Assuming a willingness-to-pay (WTP) of 20,000,000 KRW/PF-LYG, the ICERs of all five strategies were far lower than willingness-to-pay threshold, therefore all five strategies were considered cost-effective. Although strategy 4 (germline testing alone) gained the least PF-LYG of 0.33, it was the most cost-effective option with an ICER of 3,017,290 KRW per PF-LYG because of the least cost. The other strategies gained a higher PF-LYG of 0.49. Strategy1 (germline testing first, followed by somatic testing) was the second most cost-effective strategy with an ICER of 4,417,570 KRW per PF-LYG, followed by strategy 5 (somatic testing alone), strategy 2 (somatic testing first, followed by germline testing) and strategy 3 (both germline and somatic testing) with respective ICERs of 4,492,440 KRW; 4,533,730 KRW; and 4,680,120 KRW per PF-LYG. Even when parameters were varied within possible range, the ICERs of all strategies did not exceed willingness-to-pay threshold.

Conclusion: All five BRCA testing strategies were cost-effective compared to

no testing strategy. Considering not only cost-effectiveness but also the impact of knowledge of a patient's BRCA genes status for the management of advanced ovarian cancer, BRCA testing strategy of germline testing first, followed by somatic testing for patients without germline mutation may be a reasonable option for patients with advanced ovarian cancer.

Key words : cost-effectiveness analysis, BRCA testing, advanced ovarian cancer

Cost-effectiveness analysis of germline/somatic BRCA testing in patients with advanced ovarian cancer

Jaehyeok Jang

Department of Medicine

The Graduate School, Yonsei University

(Directed by Professor Kyung-A Lee)

I. INTRODUCTION

Genetic testing to identify BRCA genes (BRCA1 and BRCA2) status is recommended to ovarian cancer patients for its clinical implications by guidelines from National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO).[1, 2] Genetic testing should be conducted at the time of diagnosis, as it can help clinicians to establish management strategies based on the patient's genetic status.[2] Risk assessment of other BRCA-related cancers for patients and genetic counseling for their family members could be considered if a BRCA germline mutation is found.[1-3]

Under the concept of synthetic lethality, olaparib, the first poly (ADP-ribose) polymerase (PARP) inhibitor, was introduced as a therapeutic agent for BRCA mutated cancer.[4] SOLO-1 and PRIMA are multinational, randomized, phase III

clinical trials of PARP inhibitors (olaparib and niraparib, respectively) maintenance monotherapy in patients with advanced ovarian cancer. An efficacy of olaparib first-line maintenance therapy in patients who were newly diagnosed with BRCA mutated ovarian cancer and responded to platinum-based chemotherapy was proven by significantly improving progression-free survival (PFS) compared to placebo in the SOLO-1 trial.[5, 6] In the PRIMA trial, the use of niraparib as a first-line maintenance therapy was also shown to prolong PFS in patients with platinum-sensitive advanced ovarian cancer compared to placebo, regardless of BRCA status. Efficacy was greatest in participants with BRCA mutation.[7] Olaparib and niraparib were approved by the US Food and Drug Administration as maintenance therapy for patients with advanced ovarian cancer.

National Health Insurance (NHI) as single payer system in South Korea is implemented by the Ministry of Health and Welfare, covering 97% of population with uniform benefit coverage. The Ministry of Health and Welfare determines which health services are included in the NHI benefit package,[8] which largely influences clinician decision making. Both germline BRCA testing and somatic testing in patients with ovarian cancer are included in the NHI benefit package. The use of PARP inhibitors for patients with platinum-sensitive BRCA-mutated advanced ovarian cancer is included in the NHI benefit package as maintenance therapy. In addition, PARP inhibitor monotherapy for patients with platinum-sensitive BRCA mutated advanced ovarian cancer is the only maintenance therapy included in the NHI benefit package. Maintenance therapy including bevacizumab is not included in the

NHI benefit package. And other practices for patients with BRCA mutated ovarian cancer such as genetic counseling, preventive surgeries and genetic testing for unaffected family members of patients are also not included in the NHI benefit package.

Decision making about healthcare interventions should take the cost of interventions into consideration as well as the effectiveness given the limited resources. In South Korea, 2,898 patients were newly diagnosed with ovarian cancer in 2018, and the incidence of ovarian cancer gradually increased by an annual percentage change of 2.0% between 1999-2018.[9] The frequency of BRCA mutation in advanced ovarian cancer has been reported to be 14-18% for germline mutations and 4-7% for somatic mutations.[10-13] Therefore it is important to consider the cost-effectiveness of BRCA testing as the number of patients who need to receive BRCA testing increases.

The cost-effectiveness of BRCA testing and the use of PARP inhibitors has been evaluated in many countries. Germline BRCA testing in women with high-grade epithelial ovarian cancer and cascading testing for their relatives have been shown to be cost-effective from the aspect of cancer risk management.[14-17] Although the use of PARP inhibitors against ovarian cancer increases both the cost and effectiveness of treatment compared with observation, PARP inhibitor maintenance therapy was not considered cost-effective because of the high price of PARP inhibitor.[18-20] However the cost-effectiveness of PARP inhibitor maintenance therapy varies under different conditions.[18-22]

Healthcare systems differ from country to country, thus cost-effectiveness

should be evaluated according to each country's health care system. To our knowledge, the cost-effectiveness of BRCA testing for ovarian cancer in South Korea has not yet been evaluated. In this study, we evaluated the cost-effectiveness of BRCA testing strategies undertaken in South Korea based on the NHI system from the patient's perspective.

II. MATERIALS AND METHODS

1. Decision model

The population used in the current analysis was participants of SOLO-1 and PRIMA trials. Participants were 18 years old or older and newly diagnosed with advanced ovarian cancer, with complete or partial response to platinum-based chemotherapy.

For all patients with epithelial ovarian cancer, the guideline recommend BRCA testing strategy of germline testing first, followed by somatic testing for those in whom germline BRCA mutation was not detected.[2] BRCA testing strategies implemented in real clinical setting varies according to configurations of germline and somatic testing. The decision model composed of five BRCA testing strategies which are generally implemented in South Korea was developed (**Figure 1)**.

Strategy 1 was germline testing first, followed by somatic testing if germline testing revealed no BRCA mutation. Strategy 2 was somatic testing first, followed by germline testing if somatic testing revealed BRCA mutation, to determine if the mutation is germline or somatic. Strategy 3 was germline testing in tandem with somatic testing. Strategy 4 was only germline testing. Strategy 5 was only somatic testing. The comparator was no testing strategy.

In every strategy, except for the no testing strategy, two cases were possible according to the result of BRCA testing: BRCA mutation detected or not. The probability of the cases depended on the type of BRCA testing conducted (germline and/or somatic testing) and the frequency of germline or somatic mutation of BRCA genes in advanced ovarian cancer. Then the cost and

effectiveness of both of the cases for each strategy were obtained. If BRCA mutation was detected, it was assumed that patients received PARP inhibitor maintenance monotherapy. Because olaparib and niraparib are the only PARP inhibitors included in the NHI benefit package, they are only two options for PARP inhibitor maintenance therapy in South Korea. In base case, it was assumed that a half of patients received olaparib and the rest received niraparib in South Korea, and therefore it was assumed that the probability of the patient with BRCA mutation receiving olaparib was 50% and the probability of receiving niraparib was 50%. If BRCA mutation was not detected, it was assumed that no maintenance therapy was considered. The treatments preceding PARP inhibitors maintenance therapy such as cytoreductive surgery and platinum-based chemotherapy were not considered in this model, because there was no difference between strategies. In the no testing strategy, it was assumed that BRCA mutation was not detected. Finally, the cost and effectiveness of each strategy were calculated by combining the values obtained by multiplying each cost and effectiveness by the probability of each case.

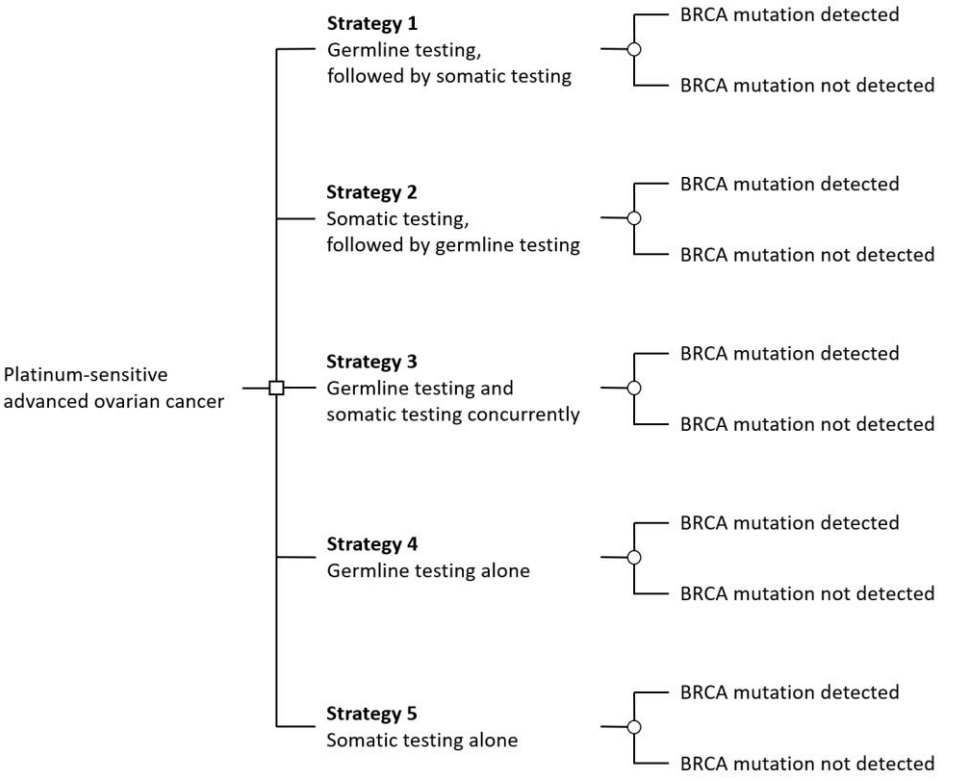

Figure 1. Model schematic

2. Cost

Costs were estimated based on the fee schedule of the Korea Health Insurance Review and Assessment Service,[23] which is responsible for the management of the NHI benefit package and the reimbursement price of the services therein.[8] Costs were calculated as co-payment which is obtained by multiplying insurance fee schedule and the co-payment rate. We estimated direct medical costs including costs of genetic testing, PARP inhibitors and monitoring. Costs were calculated in Korean won (KRW).

In base case analysis, the patient who had BRCA mutation was assumed to receive 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 an office visit weekly for the first month, followed by once monthly visits for two years. The patient without BRCA mutation was assumed to have an office visit every three months for two years. Monitoring costs included costs of laboratory testing such as cancer antigen 125 and complete blood count, computed tomography scans, and office visit.

3. Health utility

In the NHI benefit package, the impact of BRCA testing for patients with advanced ovarian cancer is to find out whether the patient is eligible to PARP inhibitors, because other managements for BRCA mutated ovarian cancer such as genetic counseling and risk-reducing surgeries are not included in the NHI benefit package. In this study, therefore, effectiveness of PARP inhibitor maintenance monotherapy was only considered, and health utility was assessed

with the gain in PFS of PARP inhibitors use in clinical trials. PF-LYG was calculated as the difference in median PFS between patients who received PARP inhibitor and those who received placebo.

4. Cost-effectiveness analysis

The incremental cost and incremental effectiveness of each strategy were calculated as the difference in cost and effectiveness between the strategy and no testing strategy. The ICER was obtained by dividing the incremental cost by the incremental effectiveness. The cost-effectiveness of the strategies in base case were compared with the ICER. Base case values are shown in **Table 1.**

5. Sensitivity analysis

A one-way sensitivity analysis was conducted to test uncertainty and the impact of key parameters on the ICER.[24] Key parameters included the frequency of germline and somatic mutations in patients with advanced ovarian cancer, costs of PARP inhibitors, the gain in PFS of PARP inhibitor use, and the proportion of olaparib use among the two available PARP inhibitors, olaparib or niraparib. Parameters were varied within possible range. Probability values varied by ± 50%, and the costs and the gain in PFS of PARP inhibitor use varied by ± 30%. The cost of BRCA testing was considered constant, because the cost of BRCA testing varies within about 2% in a real clinical environment and it was assumed that germline and/or somatic testing were performed once according to each strategy.

Table 1. Model input

Parameters	Base case values
Cost (KRW)	
Germline testing	91,880
Somatic testing	856,840
Olaparib (30 days)	291,900
Niraparib (30 days)	209,800
Monitoring in treatment (24 months)	131,310
Monitoring in observation (24 months)	50,760
The gain in PFS (months)	
Olaparib maintenance monotherapy	42.2
Niraparib maintenance monotherapy	11.2
Probability (%)	
Frequency of germline BRCA mutation in OC	15
Frequency of somatic BRCA mutation in OC	7
Proportion of olaparib use (niraparib use)	50 (50)

Abbreviations: KRW, Korean won; PFS, progression-free survival; OC, ovarian cancer

III. RESULTS

1. Cost-effectiveness analysis

Estimated cost and PF-LYG of each strategy are summarized in **Table 2**. Assuming a WTP of 20,000,000 KRW per PF-LYG, all five strategies were considered cost-effective. Strategy 4 (germline testing alone), was the most cost-effective strategy showing an ICER of 3,017,290 KRW per PF-LYG. The co-payment of germline BRCA testing is remarkably cheaper than that of somatic testing, therefore strategy 4 produced the lowest cost. It is not possible to detect somatic mutations by germline testing alone, therefore the patient with somatic mutation cannot receive PARP inhibitor therapy under strategy 4. Consequently strategy 4 showed the lowest PF-LYG. On the other hand, strategy 5 (somatic testing alone) could detect both germline and somatic mutations, as could be three other strategies composed of both germline and somatic testing. Therefore the probability of detecting BRCA mutation was estimated to be the same for strategies 1, 2, 3 and 5. When a mutation is detected by somatic testing, it is impossible to distinguish between germline and somatic mutations. However, the distinction is not necessary since PARP inhibitors can be used regardless of whether the mutation is germline or somatic. Thus, these four strategies have the same PF-LYG. In strategy 1 (germline testing first, followed by somatic testing in patients without germline BRCA mutation), the patient who received germline testing had about 85% chance of receiving somatic testing, assuming that the frequency of germline BRCA mutation in ovarian cancer was 15%. Due to the high co-payment of somatic testing, strategy 1 was less costly than strategy 5 and strategy 2 (for both of

which patients always receives somatic testing). Strategy 3 was the most costly option in the model, because patients receive both germline and somatic testing. Strategy 1 was the second most cost-effective strategy with ICER of 4,417,570 KRW per PF-LYG. This was followed by strategy 5 (ICER of 4,492,440 KRW per PF-LYG), strategy 2 (4,533,730 KRW per PF-LYG), and strategy 3 (4,680,120 KRW per PF-LYG).

Table 2. Results of cost-effectiveness analysis

Testing Strategy	Cost (KRW)	PF-LYG (year)	ICER (KRW/PF-LYG)
Strategy 1	2,213,160	0.49	4,417,570
Strategy 2	2,270,020	0.49	4,533,730
Strategy 3	2,341,680	0.49	4,680,120
Strategy 4	1,057,780	0.33	3,017,290
Strategy 5	2,249,810	0.49	4,492,440
No testing (Comparator)	50,760	referent	-

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

2. Sensitivity analysis

One-way sensitivity analysis was conducted for the key parameters, and costs and effectiveness were estimated (**Table 3**). Even when the parameters were varied, the ICERs of five strategies were below WTP threshold of 20,000,000 KRW/PF-LYG (**Figure 2**). Therefore, all five strategies remained cost-effective. Changes in the proportion of olaparib use and the gain in PFS of olaparib use had significant influences on the cost-effectiveness of the strategies. The strategies became more cost-effective if the proportion of olaparib use compared to niraparib use increased. It indicates that BRCA testing is more cost-effective with olaparib than niraparib. Changes in the frequency of somatic mutation and the gain in PFS of niraparib use had little influences on the cost-effectiveness of the strategies. Somatic mutations could not be detected by conducting germline testing alone, therefore the frequency of somatic mutation had no influence on the cost-effectiveness of strategy 4. When parameters were varied, strategy 1 was estimated more cost-effective than strategy 5 as in the base case. However, when the frequency of germline BRCA mutation decreased from 15% to 7.5%, strategy 5 (ICER of 5,397,850 KRW per PF-LYG) was estimated more cost-effective than strategy 1 (ICER of 5,483,460 KRW per PF-LYG).

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 (KRW)	Lo: 204,300	1,931,210	0.49	1,988,080	0.49	2,059,740	0.49	849,390	0.33	1,967,870	0.49
	Up: 379,470	2,393,580	0.49	2,450,450	0.49	2,522,110	0.49	1,164,640	0.33	2,430,240	0.49
Cost of niraparib (KRW)	Lo: 146,860	1,996,240	0.49	2,053,100	0.49	2,124,760	0.49	893,730	0.33	2,032,890	0.49
	Up: 272,740	2,328,560	0.49	2,385,430	0.49	2,457,090	0.49	1,120,310	0.33	2,365,210	0.49
Olaparib PFS gain (months)	Lo: 29.5	2,162,400	0.37	2,219,260	0.37	2,290,920	0.37	1,007,020	0.25	2,199,050	0.37
	Up: 54.9	2,162,400	0.61	2,219,260	0.61	2,290,920	0.61	1,007,020	0.41	2,199,050	0.61
Niraparib PFS gain (months)	Lo: 7.8	2,162,400	0.46	2,219,260	0.46	2,290,920	0.46	1,007,020	0.31	2,199,050	0.46
	Up: 14.6	2,162,400	0.52	2,219,260	0.52	2,290,920	0.52	1,007,020	0.35	2,199,050	0.52
Freq of germline BRCAm (%)	Lo: 7.5	1,769,100	0.32	1,754,800	0.32	1,833,360	0.32	549,450	0.17	1,741,480	0.32
	Up: 22.5	2,555,710	0.66	2,683,730	0.66	2,748,500	0.66	1,464,600	0.50	2,656,620	0.66
Freq of somatic BRCAm (%)	Lo: 3.5	1,948,880	0.41	2,002,510	0.41	2,077,400	0.41	1,007,020	0.33	1,985,510	0.41
	Up: 10.5	2,375,940	0.57	2,436,010	0.57	2,504,460	0.57	1,007,020	0.33	2,412,580	0.57
Proportion of olaparib use (%)	Lo: 25	2,054,030	0.35	2,110,890	0.35	2,182,550	0.35	933,130	0.24	2,090,680	0.35
	Up: 75	2,270,770	0.63	2,327,640	0.63	2,399,300	0.63	1,080,910	0.43	2,307,420	0.63

Abbreviations: Inc cost, incremental cost (KRW); Inc eff, incremental effectiveness (year); KRW, Korean won; PFS, progression-free survival; Lo, lower limit; Up, upper limit; Freq, frequency; BRCAm, BRCA mutation

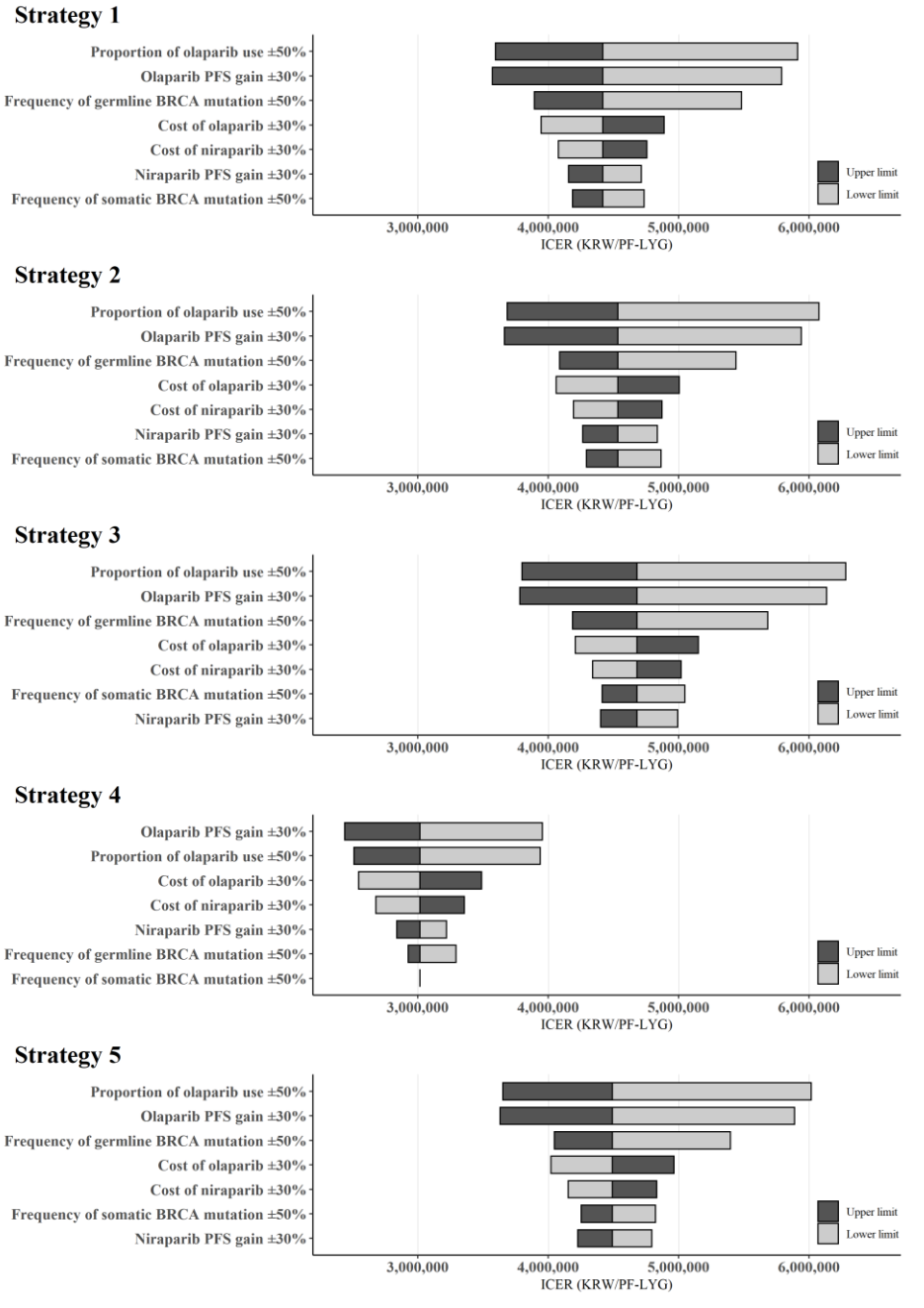

Figure 2. Results of one-way sensitivity analysis, incremental cost-effectiveness ratio

Abbreviations: PFS, progression-free survival; ICER, incremental cost-effectiveness ratio; KRW, Korean won; PF-LYG, progression-free life-year gain

IV. DISCUSSION

We evaluated the cost and effectiveness of five BRCA testing strategies which are implemented in real clinical settings in South Korea, and demonstrated that all five strategies were cost-effective under an assumed WTP of 20,000,000 KRW/PF-LYG. The overall insurance fee schedule is strictly supervised by the Korea government. 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 tablet of olaparib is about 2,430 KRW and the co-payment of a 100 mg capsule of niraparib is about 3,490 KRW. Many medical services for patients with ovarian cancer included in the NHI benefit package are covered by 'Health care benefits'. However somatic testing for BRCA genes is performed using Next-generation sequencing (NGS) which is covered by 'Selective benefits' where medical services have uncertain economic feasibility or efficacy, and the co-payment rate is higher compared to 'Health care benefits'. In most cases, the costs charged to patients with ovarian cancer are only 5% of insurance fee schedule. Therefore, it may be natural for all strategies to be cost-effective from the patient's perspective.

NGS is a widely used technique for BRCA testing.[25] It has a high throughput performance and is cost-effective compared to Sanger sequencing which is considered as gold standard of BRCA sequencing.[26] Recently, BRCA status has been assessed in tumor tissue samples of ovarian cancer using NGS platform.[27-31] Tumor tissue consists of normal cells and one or more subtypes of tumor cells.[32, 33] Thus, it is therefore theoretically possible to detect both

germline mutation and somatic mutation simultaneously by only performing somatic testing of tumor tissue. However somatic testing has technical and clinical drawbacks. Tumor tissue samples processed in formalin-fixed paraffin-embedded (FFPE) are routinely used for testing. Formalin fixation may cause artifacts such as crosslinking and DNA fragmentation. DNA extracted from FFPE can be affected by the extraction method and the condition of the specimen.[34] Amplification of DNA extracted from FFPE results in sequence artifact that is a change of DNA sequence C to T and G to A due to deamination of cytosine to uracil.[35-37] A previous study showed that BRCA testing using NGS in FFPE samples had higher false positive calls than in buffy coat samples which had no false positive call, mainly due to the sequence artifact change of C to T and G to A. NGS using tumor samples including FFPE and fresh frozen showed disproportionate variant allele frequency (VAF) compared with using matched buffy coat samples. Furthermore, the analytical performance of NGS using tumor tissues can be affected by sequencing artifacts and VAF shifted variant.[38] In previous studies, Tumor BRCA testing in ovarian cancer was unsuccessful in about 1-3% of cases.[29-31] Germline mutation and somatic mutation cannot be distinguished by somatic testing. Although, except for the use of PARP inhibitors, no other medical interventions required to the patient with germline BRCA mutation are included in the NHI benefit package, clinicians generally consider other management plans which are not included in the NHI benefit package in real clinical practice, therefore they need to know the germline BRCA status of the patient. In terms of clinical benefit, performing germline testing alone as well as somatic testing alone are not optimal options.

This study has several limitations. First, the full costs and effectiveness of BRCA testing incurred by the patient were not considered in this analysis. The use of PARP inhibitors has some adverse events which may affect the treatment plan[5, 7], and may result in further medical intervention with related costs. The SOLO-1 and PRIMA trials reported that about 10% of participant had adverse events related to treatment which required dose change or, in rare cases, discontinuation[5, 7]. Nausea and anemia were frequently observed in both trials and further costs may be incurred in relation to these events. However, a lack of data, the cost of adverse events were not considered, and also nonmedical costs related to treatment were not included in this analysis. And several other managements considered for patients with BRCA mutated ovarian cancer in real clinical practice such as genetic counseling, preventive surgeries and genetic testing for unaffected family members of patients were not included in this analysis, because it is hard to estimate the cost of medical services which are not included in the NHI benefit package and besides risk reducing mastectomy is rarely performed in patients without breast cancer in South Korea.[39]

Second limitation concerns health utility from different clinical trials. Two distinct populations that received different PARP inhibitors were included in this analysis. Participants between SOLO-1 and PRIMA trials were similar but not identical. There was a difference in PF-LYG between the two included studies. This may be contributable to the fact that they used two different PARP inhibitors and that the populations must have had variable demographic characteristics.

V. CONCLUSION

This study was conducted to evaluate cost-effectiveness of five BRCA testing strategies which are implemented in real clinical practice in South Korea. Results demonstrated that all five BRCA testing strategies were cost-effective compared to no testing strategy under assumed WTP of 20,000,000 KRW per PF-LYG. Considering clinical implications as well as the cost-effectiveness, the strategy of germline testing first, followed by somatic testing if germline mutation is not detected may be a reasonable option for patients with advanced ovarian cancer.

REFERENCES

1. M. B. Daly, et al., *Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology.* J Natl Compr Canc Netw, 2021. **19**(1): p. 77-102.

2. P. A. Konstantinopoulos, et al., *Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline.* J Clin Oncol, 2020. **38**(11): p. 1222-1245.

3. US Preventive Services Task Force, *Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer: US Preventive Services Task Force Recommendation Statement.* JAMA, 2019. **322**(7): p. 652-665.

4. P. C. Fong, et al., *Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers.* N Engl J Med, 2009. **361**(2): p. 123-34.

5. K. Moore, et al., *Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer.* N Engl J Med, 2018. **379**(26): p. 2495-2505.

6. S. Banerjee, et al., *811MO Maintenance olaparib for patients (pts) with newly diagnosed, advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): 5-year (y) follow-up (f/u) from SOLO1*. Annals of Oncology, 2020. **31**: p. S613.

7. A. González-Martín, et al., *Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer.* N Engl J Med, 2019. **381**(25): p. 2391-2402.

8. World Health Organization. Regional Office for the Western Pacific,

Republic of Korea health system review. Health systems in transition vol.5, no.4. 2015: Manila : WHO Regional Office for the Western Pacific.

9. Korea Central Cancer Registry, National Cancer Center, *Annual report of cancer statistics in Korea in 2018*. 2020: Ministry of Health and Welfare.

10. K. Alsop, et al., *BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group.* J Clin Oncol, 2012. **30**(21): p. 2654-63.

11. B. M. Norquist, et al., *Inherited Mutations in Women With Ovarian Carcinoma.* JAMA Oncol, 2016. **2**(4): p. 482-90.

12. K. P. Pennington, et al., *Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas.* Clin Cancer Res, 2014. **20**(3): p. 764-75.

13. J. M. Cunningham, et al., *Clinical characteristics of ovarian cancer classified by BRCA1, BRCA2, and RAD51C status.* Sci Rep, 2014. **4**: p. 4026.

14. J. S. Kwon, et al., *BRCA mutation testing for first-degree relatives of women with high-grade serous ovarian cancer.* Gynecol Oncol, 2019. **152**(3): p. 459-464.

15. C. Moya-Alarcón, et al., *Cost-utility analysis of germline BRCA1/2 testing in women with high-grade epithelial ovarian cancer in Spain.* Clin Transl Oncol, 2019. **21**(8): p. 1076-1084.

16. R. Manchanda, et al., *Cost-effectiveness of population screening for BRCA mutations in Ashkenazi jewish women compared with family*

history-based testing. J Natl Cancer Inst, 2015. **107**(1): p. 380.

17. A. Eccleston, et al., *A Cost-Effectiveness Evaluation of Germline BRCA1 and BRCA2 Testing in UK Women with Ovarian Cancer.* Value Health, 2017. **20**(4): p. 567-576.

18. R. Gonzalez, et al., *Cost-effectiveness analysis comparing "PARP inhibitors-for-all" to the biomarker-directed use of PARP inhibitor maintenance therapy for newly diagnosed advanced stage ovarian cancer.* Gynecol Oncol, 2020. **159**(2): p. 483-490.

19. C. A. Penn, M. S. Wong, and C. S. Walsh, *Cost-effectiveness of Maintenance Therapy Based on Molecular Classification Following Treatment of Primary Epithelial Ovarian Cancer in the United States.* JAMA Netw Open, 2020. **3**(12): p. e2028620.

20. L. Zhong, et al., *Cost-Effectiveness of Niraparib and Olaparib as Maintenance Therapy for Patients with Platinum-Sensitive Recurrent Ovarian Cancer.* J Manag Care Spec Pharm, 2018. **24**(12): p. 1219-1228.

21. D. Muston, et al., *Cost-effectiveness of olaparib as a maintenance treatment for women with newly diagnosed advanced ovarian cancer and BRCA1/2 mutations in the United States.* Gynecol Oncol, 2020. **159**(2): p. 491-497.

22. D. S. Tan, et al., *Cost-effectiveness of olaparib versus routine surveillance in the maintenance setting for patients with BRCA-mutated advanced ovarian cancer after response to first-line platinum-based chemotherapy in Singapore.* J Gynecol Oncol, 2021. **32**(2): p. e27.

23. Health Insurance Review and Assessment Service, *Health insurance*

benefit cost (2021.02). 2021: Health Insurance Review and Assessment Service.

24. Peter Muennig, Mark Bounthavong, *Cost-effectiveness analysis in health: a practical approach*. Third ed. 2016: Jossey-Bass.

25. A. E. Toland, et al., *Clinical testing of BRCA1 and BRCA2: a worldwide snapshot of technological practices.* NPJ Genom Med, 2018. **3**: p. 7.

26. A. J. Wallace, *New challenges for BRCA testing: a view from the diagnostic laboratory.* Eur J Hum Genet, 2016. **24 Suppl 1**(Suppl 1): p. S10-8.

27. A. Mafficini, et al., *BRCA somatic and germline mutation detection in paraffin embedded ovarian cancers by next-generation sequencing.* Oncotarget, 2016. **7**(2): p. 1076-83.

28. M. M. de Jonge, et al., *Validation and Implementation of BRCA1/2 Variant Screening in Ovarian Tumor Tissue.* J Mol Diagn, 2018. **20**(5): p. 600-611.

29. Caterina Fumagalli, et al., *Tumor BRCA Test for Patients with Epithelial Ovarian Cancer: The Role of Molecular Pathology in the Era of PARP Inhibitor Therapy.* Cancers, 2019. **11**(11): p. 1641.

30. J. R. Vos, et al., *Universal Tumor DNA BRCA1/2 Testing of Ovarian Cancer: Prescreening PARPi Treatment and Genetic Predisposition.* J Natl Cancer Inst, 2020. **112**(2): p. 161-169.

31. D. Rivera, et al., *Implementing NGS-based BRCA tumour tissue testing in FFPE ovarian carcinoma specimens: hints from a real-life experience within the framework of expert recommendations.* J Clin Pathol, 2021. **74**(9): p. 596-603.

32. V. W. Chen, et al., *Pathology and classification of ovarian tumors.*

Cancer, 2003. **97**(10 Suppl): p. 2631-42.

33. A. A. Alizadeh, et al., *Toward understanding and exploiting tumor heterogeneity.* Nat Med, 2015. **21**(8): p. 846-53.

34. Olga Kofanova, et al., *Standardization of the preanalytical phase of DNA extraction from fixed tissue for next-generation sequencing analyses.* New Biotechnology, 2020. **54**: p. 52-61.

35. M. Hofreiter, et al., *DNA sequences from multiple amplifications reveal artifacts induced by cytosine deamination in ancient DNA.* Nucleic acids research, 2001. **29**(23): p. 4793-4799.

36. H. Do, A. Dobrovic, *Dramatic reduction of sequence artefacts from DNA isolated from formalin-fixed cancer biopsies by treatment with uracil-DNA glycosylase.* Oncotarget, 2012. **3**(5): p. 546-58.

37. S. Q. Wong, et al., *Sequence artefacts in a prospective series of formalin-fixed tumours tested for mutations in hotspot regions by massively parallel sequencing.* BMC Med Genomics, 2014. **7**: p. 23.

38. Yoonjung Kim, et al., *An optimized BRCA1/2 next-generation sequencing for different clinical sample types.* Journal of gynecologic oncology, 2020. **31**(1): p. e9-e9.

39. Sung Mi Jung, et al., *Trends in Risk-Reducing Mastectomy and Risk-Reducing Salpingo-Oophorectomy in Korean Carriers of the BRCA1/2 Mutation.* J Breast Cancer, 2020. **23**(6): p. 647-655.

ABSTRACT(IN KOREAN)

진행성 난소암 환자에서 생식세포성/체세포성 BRCA 유전자 검사의 비용효과분석

<지도교수 이경아>

연세대학교 대학원 의학과

장 재 혁

연구배경: 난소암 환자에게 BRCA 유전자를 포함한 유전자 검사는 PARP 억제제의 사용을 포함한 치료계획의 수립에 있어 필수적이다. 유전자 검사의 전략에 대해 권고된 바가 있지만, 현재 한국에서는 생식세포성 검사와 체세포성 검사의 구성에 따라서 여러 검사 전략들이 시행되고 있다. 이번 연구에서는 한국에서 시행되는 여러 BRCA 검사 전략들에 대해서 전략에 따라 발생하는 비용과 효과를 계산해보고 각 전략들 간의 비용-효과성을 평가하고 비교해보았다.

연구방법: 한국의 실제 임상에서 시행되고 있는 다음과 같은 다섯 가지 검사 전략으로 구성된 결정모델을 설정하였다. (1) 생식세포성 유전자 검사를 먼저 시행 후, 생식세포 돌연변이가 발견되지 않은 환자들에게 체세포성 유전자 검사를 시행, (2) 체세포성 유전자 검사를

시행 후, 돌연변이가 발견된 환자들에게 생식세포성 유전자 검사를 시행, (3) 생식세포성 유전자 검사와 체세포성 유전자 검사를 동시에 시행, (4) 생식세포성 유전자 검사만 단독으로 시행, (5) 체세포성 유전자 검사만 단독으로 시행. 모델에 사용된 인구 집단은 PARP 억제제의 무작위 대조군 임상연구인 SOLO-1과 PRIMA의 참가자들을 사용하였다. 효과는 임상연구의 결과를 이용하여 무진행생존연수증가(Progression-free life-year gain, PF-LYG)로 산출하였다. 비용은 건강보험심사평가원의 건강보험요양급여비 자료를 이용하여 계산하였다. 각 전략들의 비용과 효과를 검사를 시행하지 않는 전략의 비용과 효과와 비교하여 점증적 비용과 점증적 효과를 계산하였다. 이를 통해 비용효과성을 나타내는 점증적 비용효과비를 계산하여 전략들 간의 비용효과성을 비교하였다. 변수들의 불확실성을 확인하기 위하여 일원 민감도 분석을 시행하였다. 분석은 환자 관점에서 시행되었다.

연구결과: 지불의사 한계값을 20,000,000원/PF-LYG로 가정하면, 분석에 포함된 다섯가지 전략들이 모두 비용효과적이라고 볼 수 있었다. 전략4(생식세포성 유전자 검사만 시행)의 경우 0.33 PF-LYG로 가장 적은 효과를 보였지만, 비용도 가장 적게 발생하였고, 점증적 비용효과비는 3,017,290원/PF-LYG로 가장 비용효과적인 전략이었다. 전략4를 제외한 나머지 전략들의 효과는 0.49 PF-LYG로 계산되었다. 전략1(생식세포성 유전자 검사 후 생식세포 돌연변이가 발견되지 않은 환자에게 체세포성 유전자 검사를 시행)의 점증적 비용효과비는

4,417,570원/PF-LYG으로 두번째 비용효과적인 전략으로 볼 수 있었다. 이후로는 전략5, 전략2, 전략3 순서로 비용효과적이었으며 점증적 비용효과비는 각각 4,492,440원/PF-LYG; 4,533,730원/PF-LYG; 4,680,120원/PF-LYG였다. 변수들의 변화에도 각 전략들의 점증적 비용효과비는 지불의사 한계값인 20,000,000원/PF-LYG를 넘지 않았다.

결론: 다섯가지 전략은 모두 비용효과적인 전략으로 볼 수 있었다. 비용효과성 뿐만 아니라 BRCA 유전자 상태에 대한 임상적인 효과를 고려한다면, 가이드라인에서 권고되는 바와 같이 생식세포성 유전자 검사를 시행 후 생식세포 돌연변이가 발견되지 않은 환자에게 체세포성 유전자 검사를 시행하는 전략을 합리적인 선택으로 볼 수 있을 것이다.

핵심되는 말 : 비용효과분석, BRCA 유전자 검사, 진행성 난소암