CANCER GENETICS

original reports abstract

Germline Testing and Somatic Tumor Testing for *BRCA1/2* Pathogenic Variants in Ovarian Cancer: What Is the Optimal Sequence of Testing?

Janice S. Kwon, MD, MPH[1,2]; Anna V. Tinker, MD[1,2]; Jennifer Santos, RN[1,2]; Katie Compton, MSc, CGC[1,2]; Sophie Sun, MD[1,2]; Kasmintan A. Schrader, MBBS, PhD[1,2]; and Aly Karsan, MD[1,2]

PURPOSE In 2020, ASCO recommended that all women with epithelial ovarian cancer have germline testing for *BRCA1/2* mutations, and those without a germline pathogenic variant (PV) should have somatic tumor testing to determine eligibility for a poly (ADP-ribose) polymerase inhibitor. Consequently, the majority of patients with ovarian cancer will have both germline testing and somatic testing. An alternate strategy is tumor testing first and then germline testing if there is a PV in the tumor and/or significant family history. The objective was to conduct a cost-effectiveness analysis comparing the two testing strategies.

METHODS The Markov model compared the costs (US dollars) and benefits of two testing strategies for newly diagnosed ovarian cancer: (1) ASCO strategy and (2) tumor testing triage for germline testing. Data were applied from SOLO-1, and costs were from wholesale acquisition prices, Medicare, and published sources. Sensitivity analyses accounted for uncertainty around various parameters. Monte Carlo simulation estimated the number tested and identified with germline and somatic *BRCA* PV for olaparib maintenance treatment annually in the US population.

RESULTS The ASCO strategy was more effective but more costly than tumor testing triage in identifying patients for olaparib, with an incremental cost-effectiveness ratio of $281,296 US dollars per progression-free life year gained. Assuming 10,000 eligible patients with ovarian cancer annually, Monte Carlo simulation yielded comparable numbers of patients with *BRCA* PV in the germline and tumor with the ASCO and tumor testing triage strategies (2,080 *v* 2,062, respectively), but substantially higher number of patients tested using the ASCO strategy (8,052 *v* 3,076).

CONCLUSION The ASCO strategy may identify more *BRCA* PVs but is not cost-effective. Tumor testing in epithelial ovarian cancer as triage for germline testing is the favored strategy in this health care system.

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INTRODUCTION

In 2020, ASCO published guidelines on germline and somatic testing for *BRCA1/2* pathogenic variants (PVs) and other ovarian cancer susceptibility genes.[1] The recommendation was to offer germline testing to all patients with epithelial ovarian cancer and to offer somatic testing only if there is no pathogenic/likely PV in the germline to determine which patients could be offered treatments that are US Food and Drug Administration approved in the upfront and the recurrent setting. However, this process translates into the majority of patients having both germline and somatic (tumor) testing for *BRCA1/2* PVs. An alternate strategy is to start with tumor testing first and to offer germline testing only if a PV is identified in the tumor or if there is a significant family history of cancer. This algorithm could reduce the number of tests required as the minority of patients would have both tumor and germline testing done. The objective was to conduct a cost-effectiveness analysis of these two testing strategies.

METHODS

We conducted a Markov model to estimate the lifetime costs (in US dollars [USD]) and benefits of two genetic testing strategies for patients with epithelial ovarian cancer. The two testing strategies were (1) germline testing first for *BRCA1/2* and other ovarian cancer susceptibility genes, followed by tumor testing only in the absence of a germline PV (ASCO strategy); and (2) tumor testing first for *BRCA1/2* and other genes, followed by germline testing only if a PV is identified in the tumor or if there is a significant family history of cancer (tumor testing triage). This project was exempt from Research Ethics Board review as there were no individual level data used in this study.

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CONTEXT

Key Objective

The optimal sequence of germline and somatic testing for *BRCA* pathogenic variants (PVs) in ovarian cancer remains controversial. This study is a cost-effectiveness analysis comparing two different strategies: (1) germline testing first, followed by somatic testing if a germline PV is not identified; and (2) tumor testing first, followed by germline testing only if there is a PV in the tumor and/or significant family history.

Knowledge Generated

Tumor testing first as a triage for germline testing is a cost-effective strategy, assuming high sensitivity of tumor testing for predicting germline PV. When tumor testing is done first, there will be far fewer patients having both germline and tumor testing, yet comparable number of *BRCA* PV identified.

Relevance

Tumor testing for *BRCA* PV could serve as a triage for germline testing because of more efficient use of genetic and laboratory resources and lower cost in the context of this health care system.

We assumed that women entered the model at primary diagnosis of epithelial ovarian cancer (not recurrence) after having completed surgery and first-line chemotherapy. Panel testing was done for both germline testing and tumor testing; however, only those with a PV in *BRCA1/2* were eligible for a poly (ADP-ribose) polymerase (PARP) inhibitor, specifically olaparib, which was used for a median of 2 years. If a PV of one of the moderately penetrant genes (eg, *BRIP1*, *RAD51C/D*) was identified on tumor testing, the patient would be referred for germline testing. The model was populated with data from various sources, including data from SOLO-1 on survival outcomes with olaparib,[2,3] and published data on tumor testing performance.[4,5] For the base case, the proportion of ovarian cancer tissue samples sufficient for tumor testing was estimated at 95%.[4,5] Those with an insufficient tissue sample for testing would automatically have germline testing. The sensitivity of tumor testing to detect germline PVs was estimated to be 97.5%.[3-6] We did not model reversion mutations in *BRCA1/2*, which could yield a false negative tumor test, but these reversion mutations are more likely to influence outcomes in the future as a mechanism of resistance to platinum-based therapy or olaparib[7-9] rather than the initial selection of patients for maintenance therapy. Costs were estimated from Medicare reimbursements (panel testing for tumor, germline, counseling with genetic counselor and/or physician),[10,11] and wholesale acquisition costs of olaparib,[12] in addition to estimated costs of monitoring and management of adverse effects during 24 months of treatment.[13] This costing estimate also accounts for dose reductions documented in 28% of patients in SOLO-1.[3] Data for the base case are summarized in Table 1.

Primary outcomes included the proportion of patients with ovarian cancer identified as candidates for olaparib, and the incremental cost-effectiveness ratio (ICER), defined as the difference in cost divided by the difference in effectiveness between two strategies. A threshold ICER of $100,000 USD was considered cost-effective.[19] According to the recommendations of the Second Panel for Cost-Effectiveness in Health and Medicine, we adopted a societal perspective, and costs and progression-free life years (PFLY) were calculated with an annual discount rate of 3%.[20] A Monte Carlo simulation estimated the number of patients with newly diagnosed epithelial ovarian cancer annually in the US population who would be eligible for germline testing and tumor testing according to each of the two strategies and the total with germline or somatic *BRCA1/2* PV eligible for olaparib. Sensitivity analyses were conducted to account for uncertainty around various parameters, such as tumor testing performance characteristics (proportion of patients with a sufficient tissue sample for tumor testing, sensitivity of tumor testing to detect germline PVs) as well as costs of genetic and tumor testing, and olaparib, along with monitoring and management of adverse effects. The time horizon for the model was 40 years.

RESULTS

The ASCO strategy (germline testing first followed by tumor testing if *BRCA1/2* PV not identified) was more effective but more costly than tumor testing triage for patients with ovarian cancer. Table 2 summarizes the model base case with average lifetime costs, benefits in terms of PFLY gained, and ICER. The average incremental benefit from the ASCO strategy was small (0.022 PFLY) and would be achieved at substantial cost to the health care system, with an ICER of $281,296 USD per PFLY gained relative to the tumor testing triage strategy. Table 3 summarizes the Monte Carlo simulation. It is estimated that 21,000 women will be diagnosed with ovarian cancer in the United States this year.[21] After excluding those with nonepithelial cancers and those with early-stage disease not requiring adjuvant therapy or maintenance therapy after surgery, we assumed that approximately half of them would have epithelial ovarian cancer and would be eligible for genetic testing and maintenance therapy. We therefore simulated a cohort of

TABLE 1. Selected Data for Base Case

Parameter	Expected Value	Range
Cost inputs, USD		
Olaparib at 600 mg/d, annual[12]	204,000	90,000-300,000
Olaparib monitoring per year for 2 years[14]	1,500	1,000-15,000
Olaparib adverse events[13]	8,000	1,000-15,000
Somatic tumor testing[14,15]	3,500	1,950-5,800
Germline testing, including genetic counseling, full sequencing including del/dup[14]	2,288	1,000-3,000
Annual ovarian cancer care, after initial treatment, indexed for inflation[16]	10,021	5,000-20,000
Clinical inputs		
Sensitivity of tumor testing[4,5]	99%	95%-100%
Sufficient sample for tumor testing[4,5]	99%	90%-100%
Germline *BRCA* PV[17,18]	19%	15%-22%
Somatic *BRCA* PV[17]	3%	3%-6%
Moderately penetrant gene PV[5]	5%	3%-6%
Progression-free survival olaparib *v* placebo[2,3]		
1 year	88% *v* 51%	
2 years	74% *v* 35%	
3 years	60% *v* 27%	
4 years	53% *v* 11%	
5 years	48% *v* 21%	(41%-55%) *v* (14%-28%)

Abbreviations: PV, pathogenic variant; USD, US dollars.

10,000 patients with ovarian cancer. With the ASCO strategy, there are 10,000 patients who undergo germline testing first, and 8,052 will be triaged for tumor testing to identify those with somatic *BRCA* mutations. With the tumor testing triage strategy, 9,480 patients will have tumor testing first (while the remaining 520 have germline testing because of insufficient tissue for tumor testing), and 3,076 will be triaged for germline testing. In the end, there are 2,080 and 2,062 patients identified as eligible for olaparib (either germline or somatic *BRCA* PV) at the expense of 8,052 and 3,076 patients having both germline and tumor testing in the ASCO and tumor testing triage strategies, respectively.

Extensive sensitivity analyses were conducted around parameters of uncertainty, including the proportion of patients with ovarian cancer with germline and somatic *BRCA* PV, testing performance, and costs. We found that our results were sensitive to variations in the annual costs of olaparib and sensitivity of tumor testing for *BRCA* PV. Figure 1 illustrates that when the sensitivity of tumor testing falls below 98%, the ASCO strategy becomes increasingly cost-effective, but only at low annual costs of olaparib. For example, if the sensitivity of tumor testing is only 90% and the annual cost of olaparib is $150,000 USD, the ASCO strategy is cost-effective. The threshold annual cost of olaparib beyond which tumor testing triage becomes cost-effective is $105,217 USD ($8,678 USD monthly), as shown in Figure 2. On the other hand, if the sensitivity of tumor testing is > 98%, then tumor testing triage will always be cost-effective over the ASCO strategy, irrespective of the annual cost of olaparib. Figure 3 is a tornado diagram of 10,000 trials representing the changes in ICER after varying specific parameters simultaneously, and it illustrates that the variables that have the greatest impact on ICER are the proportion of patients with ovarian cancer having tumor tissue samples sufficient for testing and the germline *BRCA* PV rate. However, the only variable that has the potential to decrease the ICER to an acceptable level is the cost of olaparib.

DISCUSSION

We have come a long way in improving the identification of *BRCA* mutation carriers in patients with ovarian cancer, from initially relying on traditional risk factors such as early age at diagnosis, family history, and ethnicity, to a histology-based strategy,[22] and now to a combination of germline and tumor testing to maximize therapeutic options using PARP inhibitors. However, testing both germline and tumor requires time, resources, and costs. There is no question about the importance of identifying somatic *BRCA* mutations because of the unprecedented improvement in progression-free survival of over 3 years.[2,3]

The ASCO strategy of germline testing first for all patients with epithelial ovarian cancer is important to identify those with a hereditary predisposition, for whom cascade testing would be recommended in family members. Only about 20% of patients will have a PV, which leaves the remaining 80% who will undergo somatic testing. Of this remaining 80%, a small fraction will have a somatic PV. On the other

TABLE 2. Average Lifetime Costs and Benefits for Base Case

Testing Strategy	Lifetime Costs (USD)	Incremental Cost (USD)	Effectiveness (PFLY)	Incremental Benefit (PFLY)	ICER
Tumor testing triage	$121,330	—	2.6299	—	—
ASCO strategy	$127,508	$6,178	2.6518	0.022	$281,296

NOTE. Tumor testing triage = tumor testing first, followed by germline testing if PV identified in the tumor, or significant family history; ASCO = germline testing first, followed by tumor testing if PV not identified in germline.

Abbreviations: ICER, incremental cost-effectiveness ratio; PFLY, progression-free life years; PV, pathogenic variant; USD, US dollars.

TABLE 3. Monte Carlo Simulation of 10,000 Patients With Advanced Epithelial Cancer Diagnosed in the United States Annually

Testing Strategy and Outcome	ASCO Strategy: No. of Patients	Tumor Testing Triage: No. of Patients
Germline testing	10,000	3,076
Tumor testing	8,052	9,480
Eligible for olaparib	2,080	2,062
Germline *BRCA* PV identified	1,470	1,445
Tested twice (germline and tumor)	8,052	3,076

Abbreviation: PV, pathogenic variant.

hand, when tumor testing is done first, only a minority of patients will have a PV in the tumor, and/or significant family history, who will then be triaged to germline testing. This means that the majority of patients will *not* have to undergo germline testing, which will save costs associated with genetic counseling and testing, and spare these patients distress and anxiety that may be associated with genetic testing.[23-25]

Early experience with tumor testing in SOLO-1 revealed that up to 5% of germline mutations were missed[3]; however, this was attributed to test coverage, variant classification, and large genomic rearrangements. The parallel germline and somatic testing study (SIGNPOST) in the United Kingdom also demonstrated a high miss rate (20% of germline PV were missed by tumor testing first), with a 23% miss rate in diagnostic biopsies.[26] Most of the germline PV missed were large genomic rearrangements. On the other hand, a similar parallel testing study in Korea revealed that somatic testing only missed one patient with a *BRCA* reversion mutation.[6] These studies were conducted before 2020, and with refined testing and bioinformatics algorithms, currently the likelihood of missing a germline mutation by screening the tumor is exceedingly low (essentially 0%).[4,5] Therefore, tumor testing may be almost equivalent to germline testing in identifying those with inherited PVs, with the added benefit of identifying somatic mutations as well. Tumor testing may also identify *NTRK* fusions and tumor mutation burden, which may be actionable targets for treatment.[27-29] On the other hand, tumor testing will likely always be more costly than germline testing, although the cost of tumor testing is expected to decrease over time. Tumor testing does reduce costs and saves resources by reducing the proportion of patients with ovarian cancer referred for germline testing. It can be facilitated quickly and easily if done in a reflex manner after core biopsy or surgery, and the results are available within a few weeks, well in advance of having to make a decision about starting olaparib as a maintenance therapy.

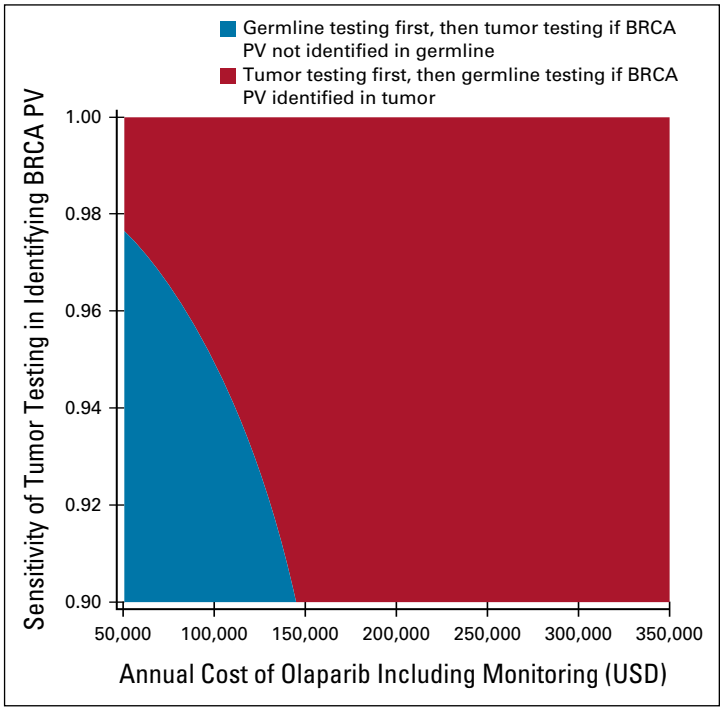

FIG 1. Two-way sensitivity analysis on costs of somatic tumor testing and olaparib (USD). PV, pathogenic variant; USD, US dollars.

In this analysis, we assumed that the sensitivity for detecting a germline *BRCA* PV in tumor tissue was < 100%, and for that reason, it will be less effective than the gold standard of germline testing first. However, when germline testing is done first followed by tumor testing for the remaining majority of patients to identify somatic *BRCA* PV, the incremental benefit of this approach is extremely small and achieved at substantial cost. The ASCO strategy is not cost-effective in the context of our current health care system. On the other hand, the tumor testing triage approach identifies almost the same number of *BRCA* mutation carriers as the ASCO strategy, at less cost, and therefore would be the preferred strategy.

The strength of this study is that it models a comparison that will likely never be feasible in a randomized trial. Although germline testing for all patients with epithelial ovarian cancer is widely recommended,[30,31] the real-life experience is that the majority of these patients with ovarian cancer (up to 90%) are never tested.[32,33] On the other hand, tumor testing rates approaching 90% have been reported when performed systematically.[34] The subsequent germline testing rates for those with a PV in the tumor are also reported to be high. Therefore, in real-world practice, the strategy of tumor testing first may actually yield more *BRCA* PV than germline testing first, particularly if upfront germline testing rates are very low.

This study is limited by the uncertainty of parameters in the model, such as the proportion of patients with ovarian cancer agreeing to have testing, the costs of testing and drugs, and the long-term outcomes associated with olaparib. Although the benefit of olaparib appears to be sustained well beyond the end of treatment as in SOLO-1,[2] long-term survival outcomes remain unknown. There was no stratification according to *BRCA1*, *BRCA2*, or PV within

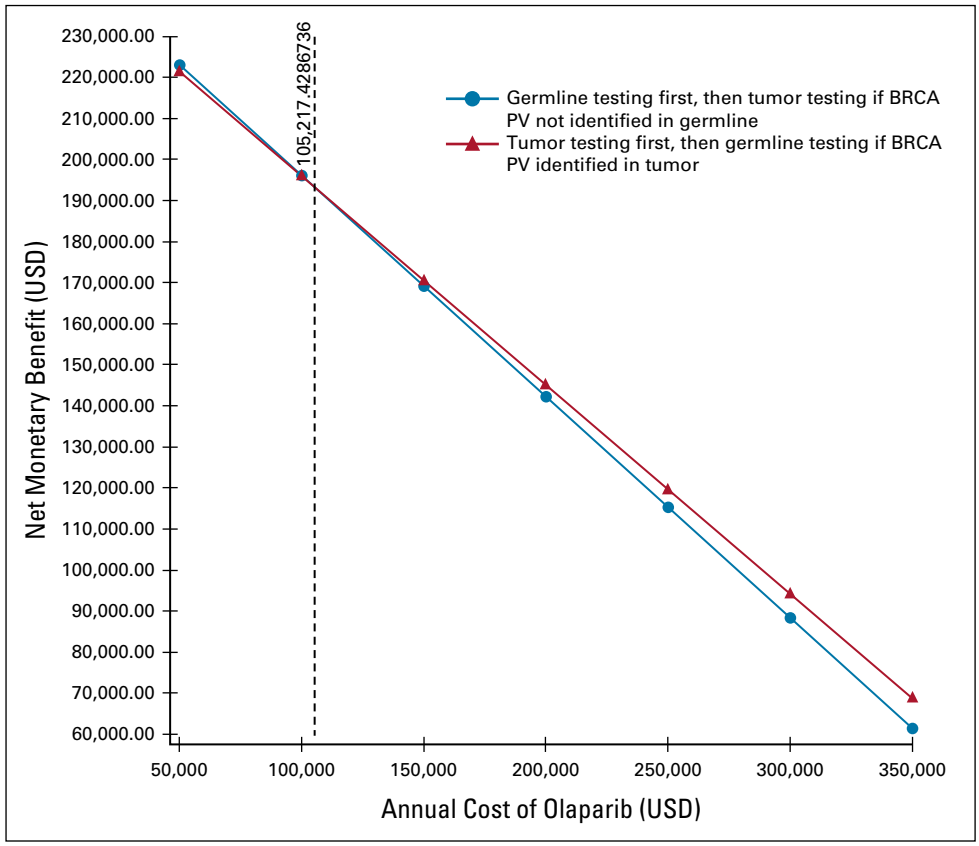

FIG 2. Sensitivity analysis on annual cost of olaparib (USD). USD, US dollars.

ovarian cancer cluster regions,[35] which could have yielded variable outcomes. In addition, we did not have health utilities associated with olaparib and its associated adverse effects, and therefore, we did not model quality of life. We did not include costs associated with treatment of recurrent ovarian cancer as there could be many different scenarios for recurrence and subsequent treatments. As a result, we may have underestimated the costs associated with each of the strategies. On the other hand, we did not estimate the number of ovarian cancers prevented and subsequent health costs saved from cascade testing for those with a germline PV. We did not model downstream risks and costs

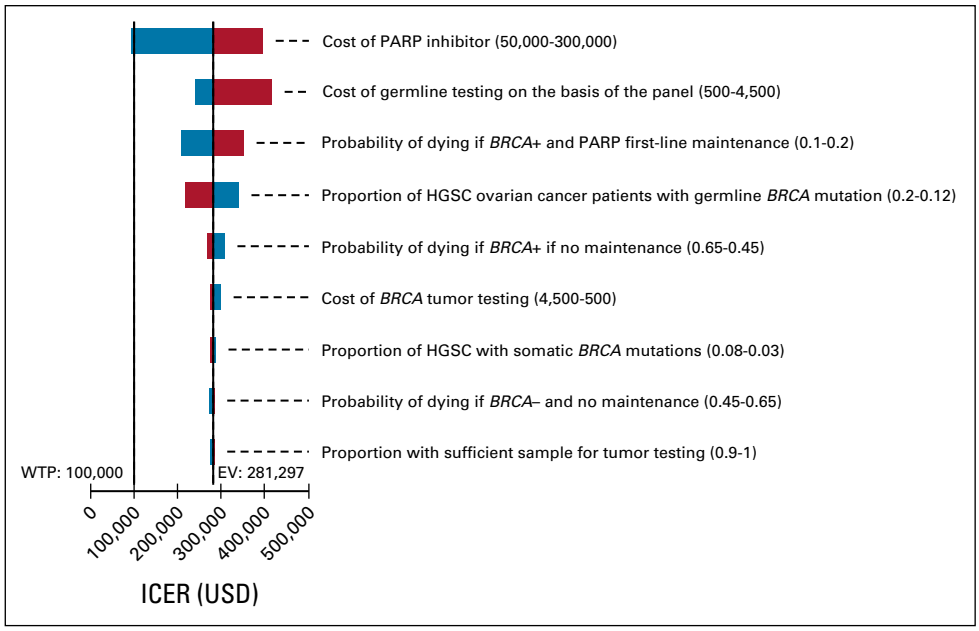

FIG 3. Tornado diagram of model parameters and ICER. EV, expected value; ICER, incremental cost-effectiveness ratio; HGSC, high-grade serous carcinoma; PARP, poly (ADP-ribose) polymerase; USD, US dollars; WTP, willingness to pay.

of olaparib including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). However, the number of patients receiving olaparib should be similar in both testing strategies; therefore, the increase in overall cost and the decrease in overall life expectancy attributed to MDS/AML should be comparable between the two strategies, with minimal impact on the ICER. Furthermore, the absolute risk of MDS and AML is still estimated to be $< 1\%$, on the basis of collective evidence from a meta-analysis,[36] although the long-term incidence rate is still unknown. Finally, we did not model homologous recombination deficiency testing or treatment with other PARP inhibitors such as niraparib, rucaparib, or veliparib, which also prolong progression-free survival, even in those without a *BRCA* mutation,[37-39] or the combination of olaparib with bevacizumab.[40] Homologous recombination deficiency testing is becoming increasingly common in clinical care as it stratifies patients for maintenance therapy.[41,42] However, the intent of this analysis was to compare two different sequences of genetic testing in ovarian cancer, rather than a cost-effectiveness analysis of maintenance therapy options, which has already been published.[43] It is interesting to note that in the aforementioned cost-effectiveness analysis, olaparib must be less than $8,950 USD per month, or $107,400 USD per year, to be considered cost-effective at a willingness-to-pay threshold of $100,000 USD per PFLY. We essentially arrived at the same annual cost threshold for olaparib ($105,217 USD), below which the ASCO strategy would be cost-effective. The lower cost of olaparib would offset the higher costs associated with double testing (germline and tumor testing) in the majority of patients with the ASCO strategy. Recognizing that reducing the annual cost of olaparib (which includes monitoring and management of adverse events) to this threshold may not be feasible in this health care system, tumor testing first as a triage for germline testing will be the favored, fiscally responsible strategy.

In summary, the strategy of germline testing first, followed by tumor testing for those without a PV, has the potential to identify the highest number of individuals with *BRCA* PVs; however, this is not a cost-effective strategy, and it relies on a high proportion of patients with ovarian cancer having germline testing at initial diagnosis. On the other hand, tumor testing first, followed by germline testing only for those with a PV identified in the tumor or family history, is associated with lower cost and appears to be the preferred strategy in the context of this health care system.

AFFILIATIONS

[1]University of British Columbia, Vancouver, British Columbia, Canada
[2]BC Cancer, Vancouver, British Columbia, Canada

CORRESPONDING AUTHOR

Janice S. Kwon, MD, MPH, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of British Columbia, 2775 Laurel St, 6th Floor, Vancouver, BC, Canada V5Z 1M9; e-mail: Janice.kwon@vch.ca

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AUTHOR CONTRIBUTIONS

Conception and design: Janice S. Kwon, Sophie Sun, Kasmintan A. Schrader, Aly Karsan
Financial support: Janice S. Kwon
Administrative support: Janice S. Kwon
Provision of study materials or patients: Janice S. Kwon, Sophie Sun, Kasmintan A. Schrader
Collection and assembly of data: Janice S. Kwon, Jennifer Santos, Katie Compton, Sophie Sun
Data analysis and interpretation: Janice S. Kwon, Anna V. Tinker, Sophie Sun, Kasmintan A. Schrader, Aly Karsan
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Janice S. Kwon
Honoraria: AstraZeneca
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Research Funding: AstraZeneca (Inst)

Anna V. Tinker
Honoraria: AstraZeneca, GlaxoSmithKline Canada, Eisai, Viatris, Merck Serono
Consulting or Advisory Role: AstraZeneca
Research Funding: AstraZeneca/MedImmune (Inst)
Other Relationship: AstraZeneca
Uncompensated Relationships: GlaxoSmithKline

Katie Compton
Consulting or Advisory Role: AstraZeneca
Research Funding: AstraZeneca

Sophie Sun
Consulting or Advisory Role: AstraZeneca, Merck, Novartis

Kasmintan A. Schrader
Consulting or Advisory Role: Pfizer, AstraZeneca, Precision RxDx
Research Funding: AstraZeneca (Inst)

Aly Karsan
Honoraria: Jazz Pharmaceuticals
Research Funding: AstraZeneca, Pfizer

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