

Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline

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abstract

PURPOSE To provide recommendations on genetic and tumor testing for women diagnosed with epithelial ovarian cancer based on available evidence and expert consensus.

METHODS A literature search and prospectively defined study selection criteria sought systematic reviews, meta-analyses, randomized controlled trials (RCTs), and comparative observational studies published from 2007 through 2019. Guideline recommendations were based on the review of the evidence.

RESULTS The systematic review identified 19 eligible studies. The evidence consisted of systematic reviews of observational data, consensus guidelines, and RCTs.

RECOMMENDATIONS All women diagnosed with epithelial ovarian cancer should have germline genetic testing for *BRCA1/2* and other ovarian cancer susceptibility genes. In women who do not carry a germline pathogenic or likely pathogenic *BRCA1/2* variant, somatic tumor testing for *BRCA1/2* pathogenic or likely pathogenic variants should be performed. Women with identified germline or somatic pathogenic or likely pathogenic variants in *BRCA1/2* genes should be offered treatments that are US Food and Drug Administration (FDA) approved in the upfront and the recurrent setting. Women diagnosed with clear cell, endometrioid, or mucinous ovarian cancer should be offered somatic tumor testing for mismatch repair deficiency (dMMR). Women with identified dMMR should be offered FDA-approved treatment based on these results. Genetic evaluations should be conducted in conjunction with health care providers familiar with the diagnosis and management of hereditary cancer. First- or second-degree blood relatives of a patient with ovarian cancer with a known germline pathogenic cancer susceptibility gene variant should be offered individualized genetic risk evaluation, counseling, and genetic testing. Clinical decision making should not be made based on a variant of uncertain significance. Women with epithelial ovarian cancer should have testing at the time of diagnosis.

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INTRODUCTION

It is estimated that there will be 22,530 new cases of ovarian cancer diagnosed in 2019 in the United States, and despite advances in treatment, an estimated 13,980 women will die of the disease.¹ Ovarian cancer ranks fifth in cancer deaths among women, accounting for more deaths than any other cancer of the female reproductive system. A woman's risk of getting ovarian cancer during her lifetime is approximately 1 in 78. Her lifetime chance of dying from ovarian cancer is approximately 1 in 108.¹ The strongest risk factor for ovarian cancer is a family history of breast or ovarian cancer, and approximately 25% of all ovarian cancers are caused by a heritable genetic condition.² Of these, mutations in *BRCA1* and *BRCA2* account for almost

40% of ovarian cancers in women with a family history of the disease,¹ and approximately one quarter (6% of all ovarian/fallopian tube/peritoneal cancers) are caused by genes other than *BRCA1* and *BRCA2*, including many genes associated with the Fanconi anemia pathway or otherwise involved with homologous recombination.² Knowledge about underlying molecular alterations in ovarian cancer could allow for more personalized diagnostic, predictive, prognostic, and therapeutic strategies for the patient but also have clinical implications for her family members.^{3,4} Many medical societies recommend genetic testing for all women diagnosed with ovarian cancer, yet only approximately 30% of women undergo any genetic testing.⁵ Moreover, oncology providers often still have

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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THE BOTTOM LINE

Germline And Somatic Tumor Testing In Epithelial Ovarian Cancer: ASCO Guideline

Guideline Questions

1. In which individuals should risk evaluation, counseling, and genomic testing for germline and somatic tumor alterations be performed?
2. Which genomic alterations have demonstrated clinical utility to direct therapy for women with ovarian cancer?
3. What are the most appropriate sequencing and timing of testing?

Target Population

Women diagnosed with ovarian cancer and their families.

Target Audience

Medical, radiation, and surgical oncologists; gynecologic oncologists; gynecologists; geneticists; genetic counsellors; other health professionals; women with ovarian cancer and their families.

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature and on informal consensus.

Recommendations

Recommendation 1.1. All women diagnosed with epithelial ovarian cancer should be offered germline genetic testing for *BRCA1*, *BRCA2*, and other ovarian cancer susceptibility genes, irrespective of their clinical features or family cancer history. Somatic tumor testing for *BRCA1* and *BRCA2* pathogenic or likely pathogenic variants should be performed in women who do not carry a germline pathogenic or likely pathogenic *BRCA1/2* variant (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.2. Women diagnosed with clear cell, endometrioid, or mucinous ovarian cancer should be offered somatic tumor testing for mismatch repair deficiency (dMMR) (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.3. Testing for dMMR may be offered to women diagnosed with other histologic types of epithelial ovarian cancer (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.4. Those genetic evaluations should be conducted in conjunction with health care providers, including genetic counselors, familiar with the diagnosis and management of hereditary cancer syndromes to determine the most appropriate testing strategy and discuss implications of the findings, positive or negative, for first- or second-degree blood relatives (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 1.5. First- or second-degree blood relatives of a patient with ovarian cancer with a known germline pathogenic cancer susceptibility gene mutation or variant should be offered individualized genetic risk evaluation, counseling, and genetic testing (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 2.1. Women diagnosed with epithelial ovarian cancer with identified germline or somatic pathogenic or likely pathogenic variants in *BRCA1* and *BRCA2* genes should be offered treatments that are US Food and Drug Administration (FDA) approved under their labeled indication in the upfront and the recurrent setting. *BRCA1/2* pathogenic or likely pathogenic variants qualify for and have been associated with higher rates of response to FDA-approved treatments such as poly (ADP-ribose) polymerase (PARP) inhibitors (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 2.2. Women diagnosed with recurrent epithelial ovarian cancer with identified dMMR should be offered FDA-approved treatment under their labeled indication based on these results. dMMR qualifies for FDA-approved treatment (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 2.3. No recommendations can be made supporting routine tumor testing using currently available homologous recombination deficiency (HRD) assays. Current assays evaluating HRD have been applied to stratify women with ovarian cancer for treatment (No recommendation; Evidence quality: low; Strength of recommendation: not applicable).

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THE BOTTOM LINE (CONTINUED)

Recommendation 2.4. Clinical decisions should not be based on a variant of uncertain significance (VUS). Care providers and patients and family members tested should be aware that reclassification of VUS is an ongoing process and it may eventually become possible to definitively determine if a variant is deleterious or benign. Until that time, the patient's clinical features and family history should inform clinical decision making (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 3.1. Women with epithelial ovarian cancer should be offered testing, as outlined in recommendation 1.1, at the time of diagnosis. This has implications for therapeutic decision making (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 3.2. Women with epithelial ovarian cancer who have not had germline testing at the time of diagnosis should be offered germline genetic testing as soon as feasibly possible, as outlined in recommendation 1.1. In women who do not carry a germline pathogenic or likely pathogenic *BRCA1/2* variant, somatic tumor testing for *BRCA1* and *BRCA2* pathogenic or likely pathogenic variants should be offered. Somatic tumor testing for *BRCA1* and *BRCA2* pathogenic or likely pathogenic variants may be reserved for time of recurrence for women who have completed upfront therapy and are currently in observation, as presence of these mutations qualifies the patient for FDA-approved treatments (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Additional Resources

More information, including a Data Supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/gynecologic-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

an insufficient understanding and/or a lack of resources and strategies for how to best incorporate genomic testing into their practice.

The purpose of this clinical practice guideline is to provide clinicians (including but not limited to medical oncologists, radiation oncologists, gynecologic oncologists, and gynecologists), other health care practitioners, nurses, social workers, patients, and caregivers with recommendations regarding the role of genomic testing in epithelial ovarian cancer based on the best available evidence. In this document, the term *germline* refers to sequences in the DNA of all cells in the body, and the term *somatic* indicates alterations that occur in the DNA of tumor cells. Because this is a rapidly evolving topic, future directions and updates will also be reported.

GUIDELINE QUESTIONS

This clinical practice guideline addresses 3 overarching clinical questions:

1. In which individuals with ovarian cancer should genomic testing for germline and somatic alterations be performed?
2. Which genomic alterations have demonstrated clinical utility to direct therapy for women with ovarian cancer?
3. What are the most appropriate sequencing and timing of testing?

METHODS

Guideline Development Process

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel, which included medical oncology, gynecologic oncology, molecular biology, and cancer genetics professionals; a patient representative; and an ASCO guidelines staff member with health research methodology expertise. The Expert Panel met via teleconference and/or webinar and corresponded through e-mail. Based on the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks, allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of guideline, which was then circulated for external review and submitted to the *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee prior to publication. All funding for the administration of the project was provided by ASCO.

The evidence review was conducted in a planned 2-staged approach. The first stage included searching for existing guidelines and/or systematic reviews, and this was then followed by a search for primary studies. An electronic search using PubMed was performed to systematically search for systematic reviews evaluating the clinical utility of germline and somatic tumor testing in ovarian cancer. PubMed was searched from January 1, 2007, to March 23, 2018, and the search was updated on March 7, 2019. Relevant trials released at the European Society for Medical Oncology 2019 annual meeting were also identified. In addition, Web sites and databases of specific guideline developers that used systematic review as their evidentiary base, as well as systematic review producers, were also searched for the same time period.

A priori decision rules were established that specified only comprehensive systematic reviews with relevance to at least 1 of the 3 original questions posed would undergo formal quality assessment. Relevant systematic reviews were assessed using the 11-item Assessment of Multiple Systematic Reviews⁶ tool to determine whether they met a minimum threshold for methodologic quality and could be considered for inclusion in the evidence base.

As a second stage, the focus was on locating and evaluating primary literature not already covered in any existing systematic reviews. PubMed was used to systematically search for articles evaluating the clinical utility of germline and somatic tumor testing in ovarian cancer, again between 2007 and March 23, 2018. The search combined disease-specific terms (neoplasm, carcinoma, cancer) along with site-specific terms (ovary, ovarian) and gene-specific terms (*BRCA1/2*, *BRIP1*, *PALB2*, *BARD1*, *RAD51C/D*). The complete literature search strategy can be found in the Data Supplement. In addition to PubMed searches, reference lists of included systematic reviews and primary literature were scanned for potentially useful studies.

Articles were selected for inclusion in the systematic review of the evidence if they prospectively enrolled women with epithelial ovarian cancer or small-cell ovarian carcinoma of hypercalcemic type who underwent germline and/or somatic tumor testing. Articles were excluded from the systematic review if they were editorials, commentaries, letters, news articles, case reports, or narrative reviews or were published in a non-English language. The guideline recommendations were crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software.⁷ In addition, a guideline implementability review was conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation.

Detailed information about the methods used to develop this guideline is available in the Methodology Supplement

at www.asco.org/guideline-methodology, including an overview (eg, panel composition, development process, and revision dates), literature search and data extraction, the recommendation development process (GLIDES and BRIDGE-Wiz), and quality assessment. Appendix Table A1 (online only) lists the guideline Expert Panel members, and Appendix Table A2 (online only) lists terms and definitions.

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc. (ASCO) to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like “must,” “must not,” “should,” and “should not” indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an “as is” basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO’s Conflict of Interest Policy Implementation for Clinical Practice Guidelines (“Policy,” found at <http://www.asco.org/rwc>). All members of the Expert Panel completed ASCO’s disclosure form, which requires

disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Nineteen studies compose the evidence base.⁸⁻³⁰ They include 6 meta-analyses⁸⁻¹³; 11 randomized controlled trials (RCTs),^{14-25,28-30} one of which was available only in abstract form²⁹; and 2 observational studies.^{26,27} Outcomes are listed in Tables 1 and 2. In addition, 12 guidelines were identified and used to support who should be tested³¹⁻⁴² (Table 3).

Study design aspects related to individual study quality, strength of evidence, strength of recommendations, and risk of bias were assessed. In general, the quality of the included studies ranged from intermediate to high. Refer to the Methodology Manual (www.asco.org/guideline-methodology) for more information and for definitions of ratings for overall potential risk of bias.

RECOMMENDATIONS

CLINICAL QUESTION 1

In which individuals should risk evaluation, counseling, and genomic testing for germline and somatic tumor alterations be performed?

Recommendation 1.1

All women diagnosed with epithelial ovarian cancer should be offered germline genetic testing for *BRCA1*, *BRCA2*, and other ovarian cancer susceptibility genes, irrespective of their clinical features or family cancer history. Somatic tumor testing for *BRCA1* and *BRCA2* pathogenic or likely pathogenic variants should be performed in women who do not carry a germline pathogenic or likely pathogenic *BRCA1/2* variant (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.2

Women diagnosed with clear cell, endometrioid, or mucinous ovarian cancer should be offered somatic tumor testing for mismatch repair deficiency (dMMR) (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.3

Testing for dMMR may be offered to women diagnosed with other histologic types of epithelial ovarian cancer (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.4

Those genetic evaluations should be conducted in conjunction with health care providers, including genetics counselors, familiar with the diagnosis and management of hereditary cancer syndromes to determine the most appropriate testing strategy and discuss implications of the findings, positive or negative, for first- or second-degree blood relatives (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 1.5

First- or second-degree blood relatives of a patient with ovarian cancer with a known germline pathogenic cancer susceptibility gene mutation or variant should be offered individualized genetic risk evaluation, counseling, and genetic testing (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Literature review and analysis. The evidentiary base consists of 12 guidelines or position statements from national and international professional medical societies or Expert Panels (Table 3), including the Society of Gynecologic Oncology,⁴¹ the National Comprehensive Cancer Network,^{36,37} and the American College of Medical Genetics and Genomics,³³ among others.^{31,32,34,35,38,40,43,44} Due to a relatively high prevalence of identified genetic mutations, these guidelines consistently recommend routine testing in all women diagnosed with epithelial ovarian cancer for germline *BRCA1* and *BRCA2* mutations and/or consideration be given to testing tumors for a somatic *BRCA1/2* mutation to inform patients' medical and reproductive decisions and those of their relatives.

Evidence exists to suggest that genetic counseling decreases cancer worry, anxiety, and depression; can change the frequency of testing; and can also increase knowledge and the accuracy of perceived risk.^{42,45} A systematic review of RCTs reported that telephone counseling or interactive online platforms are often equivalent or noninferior to in-person genetic counseling, suggesting these alternate delivery modes may be sufficient for teaching key information about test results.⁴⁵ Most of the included trials in the systematic review assessed psychological well-being to ensure that these alternative, cost-effective interventions did not lead to greater distress than in-person counseling.⁴⁵

Meta-analysis data estimate the relative risk for ovarian cancer among women with first-degree relatives with cancer to be 3.1 (95% CI, 2.6 to 3.7), although these analyses did not take inherited mutation status into

TABLE 1. Prognostic Utility Study and Year of Publication

Study and Year of Publication	Study Design	No. of Patients	Included Histologic Subtypes	Genomic Alteration	Survival Results
Huang, ¹⁰ 2018	Systematic review and meta-analysis	7,745 from 33 studies	Vast majority with serous primary or recurrent OC	<i>BRCA1</i> and <i>BRCA2</i> v WT	OS: <i>BRCA1</i> or <i>BRCA2</i> v WT: HR, 0.75 (95% CI, 0.64 to 0.88) <i>BRCA1</i> v WT: HR, 0.75 (95% CI, 0.62 to 0.91) <i>BRCA2</i> v WT: HR, 0.83 (95% CI, 0.58 to 1.19) PFS: <i>BRCA1</i> or <i>BRCA2</i> v WT: HR, 0.80 (95% CI, 0.64 to 0.99) <i>BRCA1</i> v WT: HR, 0.85 (95% CI, 0.67 to 1.07) <i>BRCA2</i> v WT: HR, 0.66 (95% CI, 0.43 to 1.02) Response rate: <i>BRCA1</i> or <i>BRCA2</i> v WT: OR, 2.64 (95% CI, 1.38 to 5.05) <i>BRCA1</i> v WT: OR, 1.30 (95% CI, 0.31 to 5.44) <i>BRCA2</i> v WT: OR, 3.48 (95% CI, 0.94 to 12.9)
Xu et al, ¹² 2017	Systematic review and meta-analysis	18,396 patients from 34 studies	Predominantly serous histologic features	<i>BRCA1</i> and <i>BRCA2</i> mutations	<i>BRCA1/2m</i> v noncarriers: OS: HR, 0.67 (95% CI, 0.57 to 0.78) PFS: HR, 0.62 (95% CI, 0.53 to 0.73) <i>BRCA1m</i> v noncarriers: OS: HR, 0.73 (95% CI, 0.63 to 0.86) PFS: HR, 0.68 (95% CI, 0.52 to 0.89) <i>BRCA2m</i> v noncarriers: OS: HR, 0.57 (95% CI, 0.45 to 0.73) PFS: HR, 0.48 (95% CI, 0.30 to 0.75)
Sun et al, ¹¹ 2014	Systematic review and meta-analysis	7,986 from 34 studies	Predominantly serous histologic features	<i>BRCA1</i> and <i>BRCA2</i> dysfunction ^a	OS: <i>BRCA1/2</i> dysfunction ^a overall: HR, 0.69 (95% CI, 0.61 to 0.79) (v EOC that displayed normal <i>BRCA</i> function) Subgroup analysis: <i>BRCA1/2m</i> , germline or somatic: HR, 0.69 (95% CI, 0.59 to 0.80) <i>BRCA1</i> : HR, 0.78 (95% CI, 0.69 to 0.87) <i>BRCA2</i> : HR, 0.65 (95% CI, 0.50 to 0.86) PFS: <i>BRCA1/2</i> dysfunction ^a overall: HR, 0.69 (95% CI, 0.63 to 0.76) Subgroup analysis: <i>BRCA1/2m</i> , germline or somatic: HR, 0.65 (95% CI, 0.57 to 0.73)
Zhong et al, ¹³ 2015	Systematic review and meta-analysis	9,588 in 27 studies	Predominantly serous primary EOC	<i>BRCA1</i> and <i>BRCA2</i> v noncarriers	OS: <i>BRCA1m</i> : HR, 0.76 (95% CI, 0.70 to 0.83) <i>BRCA2m</i> : HR, 0.58 (95% CI, 0.50 to 0.66) PFS: <i>BRCA1m</i> : HR, 0.65 (95% CI, 0.52 to 0.81) <i>BRCA2m</i> : HR, 0.61 (95% CI, 0.47 to 0.80)

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TABLE 1. Prognostic Utility (continued)

Study and Year of Publication	Study Design	No. of Patients	Included Histologic Subtypes	Genomic Alteration	Survival Results
Alsop et al, ²⁶ 2012	Observational	1,409	Serous EOC	<i>BRCA1</i> and <i>BRCA2</i> v noncarriers	OS: <i>BRCA2</i> v <i>BRCA1m</i> : HR, 1.36 (95% CI, 0.76 to 2.43) Noncarrier v <i>BRCA1mut</i> : HR, 1.73 (95% CI, 1.16 to 2.57) PFS: <i>BRCA2</i> v <i>BRCA1m</i> : HR, 1.07 (95% CI, 0.65 to 1.76) Noncarrier v <i>BRCA1m</i> : HR, 1.57 (95% CI, 1.13 to 2.18)
Bolton et al, ²⁷ 2012	Observational study	3,879 patients with EOC (909 <i>BRCA1</i> and 304 <i>BRCA2</i> mutation carriers and 2,666 noncarriers).	Predominantly serous primary EOC	<i>BRCA1</i> and <i>BRCA2</i> v noncarriers	OS: <i>BRCA1</i> v noncarrier: adjusted HR, 0.73 (95% CI, 0.64 to 0.84) <i>BRCA2</i> v noncarrier: adjusted HR, 0.49 (95% CI, 0.39 to 0.61)
Cai et al, ⁸ 2014	Systematic review and meta-analysis	2,499 in 11 studies	Predominantly serous histologic features	PTEN (expression determined from tumor tissue, mostly by IHC)	OS: HR, 0.99 (95% CI, 0.75 to 1.29)
Heider-Woolderink et al, ⁹ 2016	Systematic review and meta-analysis	2,499 in 12 studies	Mixed type	Women with Lynch syndrome; most frequent mutations were <i>MSH2</i> (47%) and <i>MLH1</i> (38%)	10-year OS: range, 81%-87% v sporadic cancer at < 40%

NOTE. Prognostic utility was established for all studies except Cai et al.⁸

Abbreviations: *BRCAm*, *BRCA* mutation; *BRCA1m*, mutation in *BRCA1* only; *BRCA1/2m*, *BRCA1* and *BRCA2* mutations; *BRCA2m*, mutation in *BRCA2* only; EOC, epithelial ovarian cancer; HR, hazard ratio; IHC, immunohistochemistry; mut, mutation; OC, ovarian cancer; OR, odds ratio; OS, overall survival; PFS, progression-free survival; WT, wild-type.

^a*BRCA* dysfunction statuses include *BRCA1/2* germline/somatic mutations, low *BRCA1* expression tested by IHC or reverse transcriptase polymerase chain reaction, and *BRCA1* promoter methylation in sporadic EOCs.

TABLE 2. Clinical Utility

Study and Year of Publication	Design	No. of Patients	Treatment	Included Histologic Subtypes	Genomic Alteration	Survival Results
First-line therapy and maintenance						
Coleman et al, ²⁸ 2019	Phase III RCT: VELIA	1,140	Veliparib (150 mg twice a day) plus carboplatin/paclitaxel then veliparib (400 mg twice a day) maintenance therapy	HGSOC	All-comers population, with and without a <i>BRCA</i> mutation	PFS overall: HR, 0.68 (95% CI, 0.56 to 0.83) PFS by subgroup: HRD <i>BRCA</i> m: HR, 0.44 (95% CI, 0.28 to 0.68) HRD <i>BRCA</i> wt: HR, 0.74 (95% CI, 0.52 to 1.06) HRP <i>BRCA</i> wt: HR, 0.81 (95% CI, 0.60 to 1.09)
Maintenance after front-line therapy						
Moore et al, ²³ 2018	Phase III RCT: SOLO1	391	Olaparib (300-mg tablet formulation)	HGSOC	Germline and somatic <i>BRCA1</i> and <i>BRCA2</i>	PFS overall: HR, 0.30 (95% CI, 0.23 to 0.41) PFS by subgroup: Germline <i>BRCA1</i> m: HR, 0.4 (95% CI, 0.29 to 0.56) Germline <i>BRCA2</i> m: HR, 0.2 (95% CI, 0.10 to 0.38)
Ray-Coquard et al, ²⁹ 2019 (abstract)	Phase III RCT: PAOLA-1	806	Olaparib (300 mg twice a day) plus bevacizumab	HGS/endometrioid	All-comers population, with and without a <i>BRCA</i> mutation	PFS overall: HR, 0.59 (95% CI, 0.49 to 0.72) PFS by subgroup: Tumor <i>BRCA</i> m: HR, 0.31 (95% CI, 0.20 to 0.47) <i>BRCA</i> wt: HR, 0.71 (95% CI, 0.58 to 0.88) HRD (including tumor <i>BRCA</i> m): HR, 0.33 (95% CI, 0.25 to 0.45) HRD/ <i>BRCA</i> wt: HR, 0.43 (95% CI, 0.28 to 0.66) HRP or unknown/ <i>BRCA</i> wt: HR, 0.92 (95% CI, 0.72 to 1.17)
González-Martín et al, ³⁰ 2019	Phase III RCT: PRIMA	733	Niraparib (300 mg)	HGS/endometrioid	All-comers population, with and without a <i>BRCA</i> mutation	PFS overall: HR, 0.62 (95% CI, 0.50 to 0.76) PFS by subgroup: HRD/ <i>BRCA</i> m: HR, 0.40 (95% CI, 0.27 to 0.62) HRD/ <i>BRCA</i> wt: HR, 0.50 (95% CI, 0.31 to 0.83) HRP: HR, 0.68 (95% CI, 0.49 to 0.94)
Maintenance therapy for recurrent platinum-sensitive disease						

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TABLE 2. Clinical Utility (continued)

Study and Year of Publication	Design	No. of Patients	Treatment	Included Histologic Subtypes	Genomic Alteration	Survival Results
Ledermann et al, 2012, ¹⁸ 2014, ¹⁹ and 2016 ²⁰ ; Matulonis et al, ²¹ 2016, Dougherty et al, ¹⁶ 2017	Phase II RCT: Study 19 (<i>BRCA</i> mutation analyzed retrospectively)	316	Olaparib (400-mg capsule formulation)	HGSOC	Germline and somatic <i>BRCA1</i> and <i>BRCA2</i>	PFS overall (<i>BRCAm</i> subset, n = 136): HR, 0.18 (95% CI, 0.1 to 0.31) PFS: <i>gBRCAm</i> : HR, 0.17 (95% CI, 0.09 to 0.34) <i>sBRCAm</i> : HR, 0.23 (95% CI, 0.04 to 1.12) OS overall (<i>BRCAm</i> subset, n = 136): HR, 0.62 (95% CI, 0.41 to 0.94) OS by subgroup ² : <i>BRCAm</i> : HR, 0.62 (95% CI, 0.41 to 0.94) <i>gBRCAm</i> : HR, 0.64 (95% CI, 0.39 to 1.04) <i>sBRCAm</i> : HR, 0.26 (95% CI, 0.04 to 1.21) <i>BRCA1m</i> : HR, 0.60 (95% CI, 0.36 to 0.99) <i>BRCA2m</i> : HR, 0.62 (95% CI, 0.29 to 1.37)
Pujade-Lauraine et al, ²⁴ 2017	Phase III RCT: SOLO2	295	Olaparib (300-mg tablet formulation)	HGSOC	Germline and somatic <i>BRCA1</i> and <i>BRCA2</i>	PFS overall: HR, 0.30 (95% CI, 0.22 to 0.41) OS overall: HR, 0.80 (95% CI, 0.50 to 1.31)
Coleman 2017 ¹⁴	Phase III RCT: ARIEL3	564	Rucaparib (600-mg capsule formulation)	HGSOC or endometrioid	Germline <i>BRCA1</i> and <i>BRCA2</i> Somatic <i>BRCA1</i> and <i>BRCA2</i> Homologous recombination genes (<i>BRCA1</i> , <i>BRCA2</i> , <i>ATM</i> , <i>ATR</i> , <i>ATRX</i> , <i>BARD1</i> , <i>BLM</i> , <i>BRIP1</i> , <i>CHEK1</i> , <i>CHEK2</i> , <i>FANCA</i> , <i>FANCC</i> , <i>FANCD2</i> , <i>FANCE</i> , <i>FANCF</i> , <i>FANCG</i> , <i>FANCI</i> , <i>FANCL</i> , <i>FANCM</i> , <i>MRE11A</i> , <i>NBN</i> , <i>PALB2</i> , <i>RAD50</i> , <i>RAD51</i> , <i>RAD51B</i> , <i>RAD51C</i> , <i>RAD51D</i> , <i>RAD52</i> , <i>RAD54L</i> , <i>RPA1</i>)	PFS overall: HR, 0.37 (95% CI, 0.30 to 0.45) PFS by subgroup: <i>BRCA1</i> : HR, 0.32 (95% CI, 0.19 to 0.53) <i>BRCA2</i> : HR, 0.12 (95% CI, 0.06 to 0.26) Germline: HR, 0.25 (95% CI, 0.16 to 0.39) Somatic: HR, 0.23 (95% CI, 0.10 to 0.54) <i>BRCAm</i> according to blood or tissue test: HR, 0.23 (95% CI, 0.16 to 0.33) <i>BRCAwt</i> : LOH high: HR, 0.44 (95% CI, 0.29 to 0.66) LOH low: HR, 0.58 (95% CI, 0.40 to 0.85) LOH indeterminate: HR, 0.25 (95% CI, 0.11 to 0.56)
Mirza et al, ²² 2016	Phase III RCT: NOVA	553 (203 with <i>gBRCAm</i>)	Niraparib (300-mg capsule formulation)	Predominantly HGS histologic features	Germline and somatic <i>BRCA1</i> and <i>BRCA2</i> HRD (as determined by myChoice HRD test)	PFS by subgroup: <i>gBRCAm</i> : HR, 0.27 (95% CI, 0.17 to 0.41) No <i>gBRCAm</i> with HRD positivity: HR, 0.38 (95% CI, 0.24 to 0.59) No <i>gBRCAm</i> : HR, 0.45 (95% CI, 0.34 to 0.61)

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TABLE 2. Clinical Utility (continued)

Study and Year of Publication	Design	No. of Patients	Treatment	Included Histologic Subtypes	Genomic Alteration	Survival Results
Later-line treatment						
Dornheck et al, ¹⁵ 2016	Phase II single arm: Study 42	193 ovarian subset (154 with germline <i>BRCA1/2</i> mutation)	Olaparib (400-mg capsules formulation)	HGSOC	Germline <i>BRCA1</i> and <i>BRCA2</i>	PFS rate: 54.6% Median PFS by subgroup: 7 months
Kristleit et al, ¹⁷ 2017	Phase II single arm: Study 10	42	Rucaparib (600 mg twice a day, capsule)	HGSOC or endometrioid	Germline <i>BRCA1</i> and <i>BRCA2</i>	PFS rate: 59.5% Median PFS by subgroup: 7.8 months
Swisher et al, ²⁵ 2017	Phase II single arm: ARIEL2	40	Rucaparib (600 mg twice a day, capsule)	HGSOC or endometrioid	Germline and somatic <i>BRCA1</i> and <i>BRCA2</i>	<i>BRCAm</i> : 50% LOH low: 10% PFS HR, 0.27 (95% CI, 0.16 to 0.44) <i>P</i> < .0001 LOH high: 28% LOH low: 10% PFS HR, 0.62 (95% CI, 0.42 to 0.90) <i>P</i> = .011

NOTE. Clinical utility not established. Demonstrated utility is prognostic for all studies.

Abbreviations: *BRCAm*, *BRCA* mutation; *BRCA1m*, mutation in *BRCA1* only; *BRCA2m*, mutation in *BRCA2* only; *BRCAwt*, *BRCA* wild-type; *gBRCAm*, germline *BRCA* mutation; HGS, high-grade serous; HGSOC, high-grade serous ovarian cancer; HR, hazard ratio; HRD, homologous recombination deficient; HRP, homologous recombination proficient; LOH, loss of heterozygosity; PFS, progression-free survival; RCT, randomized controlled trial; *sBRCAm*, somatic *BRCA* mutation.

^aHomologous recombination gene mutations have been preclinically linked to poly (ADP-ribose) polymerase inhibitor sensitivity. They are mechanistically analogous to *BRCAm* and linked to prolonged survival and platinum sensitivity in ovarian cancer. However, it is difficult to gauge the impact of individual genes due to low prevalence and some evidence of nonmutual exclusivity.¹¹⁴

TABLE 3. Genetic Counseling and Testing Guideline Matrix

Resource	Target Population	Recommendations for Genetic Counseling	Recommendations for Genetic Testing	Timing of Testing	Other Recommendations
SGO Clinical Practice Statement: Genetic Testing for Ovarian Cancer, 2014 ⁴¹ ; and SGO Risk Assessment for Inherited Gynecologic Cancer Predispositions, 2015 ³⁴	Women diagnosed with epithelial ovarian, tubal, and peritoneal cancers	Women diagnosed with epithelial ovarian, tubal, and peritoneal cancers should receive genetic counseling. Patients with an increased likelihood of having an inherited predisposition to breast and ovarian, tubal, or peritoneal cancer should receive genetic counseling.	Patients with an increased likelihood of having an inherited predisposition to breast and ovarian, tubal, or peritoneal cancer should be offered genetic testing. All women diagnosed with epithelial ovarian, tubal, and peritoneal cancers should be offered genetic testing, even in the absence of a family history.	Early referral at the time of cancer diagnosis may allow for use of the genetic information in treatment planning.	Genetic testing for cancer predisposition requires informed consent that should include pretest education and counseling concerning the risks, benefits, and limitations of testing, including the implications of both positive and negative genetic test results.
American Congress of Obstetricians and Gynecologists, 2017 ³⁹	Women with or at risk for hereditary cancer syndromes that include risks of breast cancer, ovarian cancer, and endometrial cancer	Genetic counseling should be offered to all women with epithelial ovarian cancer (including fallopian tube and primary peritoneal cancer). If a hereditary cancer risk assessment suggests an increased risk of a hereditary cancer syndrome, referral to a specialist in cancer genetics or a health care provider with expertise in genetics is recommended for expanded gathering of family history information, risk assessment, education, and counseling, which may lead to genetic testing.	Genetic testing should be offered when counseling indicates an inherited cancer syndrome.	NR	—
NCCN Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer (version 1.2019) ³⁷ ; NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian (version 3.2019) ³⁶	Women diagnosed with ovarian, fallopian tube, or primary peritoneal cancers	Patients with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer should have genetic risk evaluation. Patients with an increased likelihood of having an inherited predisposition to breast and ovarian, tubal, or peritoneal cancer should receive genetic counseling.	Patients with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer should have <i>BRCA1/2</i> testing if not previously done. Patients with an increased likelihood of having an inherited predisposition to breast and ovarian, tubal, or peritoneal cancer should be offered genetic testing. Testing recommended to include at least <i>BRCA1/2</i> and MSI or DNA mismatch repair if not previously done. Evaluation of HRD can be considered.	Primary treatment should not be delayed for a genetic counseling referral. Germline and/or somatic <i>BRCA1/2</i> status may inform maintenance therapy.	Validated molecular testing should be performed in a CLIA-approved facility.

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TABLE 3. Genetic Counseling and Testing Guideline Matrix (continued)

Resource	Target Population	Recommendations for Genetic Counseling	Recommendations for Genetic Testing	Timing of Testing	Other Recommendations
NICE (United Kingdom) Familial Breast Cancer: Classification, Care and Managing Breast Cancer and Related Risks in People With a Family History of Breast Cancer Clinical Guideline (CG164); published 2013, last updated 2015 ³¹	Patients with breast or ovarian cancer or people with a family history of breast, ovarian, or a related (prostate or pancreatic) cancer	Families containing 1 relative with ovarian cancer at any age and on the same side of the family should be offered a referral to a specialist genetic clinic.	Offer genetic testing in specialist genetic clinics to a person with breast or ovarian cancer if the person's combined <i>BRCA1</i> and <i>BRCA2</i> mutation carrier probability is 10% or more.	Offer people eligible for referral to a specialist genetic clinic a choice of accessing genetic testing during initial management or at any time thereafter.	Discuss the potential risks and benefits of genetic testing. Include in the discussion the probability of finding a mutation, the implications for the individual and the family, and the implications of either a variant of uncertain significance or a null result.
American College of Medical Genetics and Genomics and National Society of Genetic Counselors, 2015 ³³	Patients with suspected hereditary breast-ovarian cancer syndrome	Referral should be considered for any individual with a personal history of or first-degree relative with (1) breast cancer diagnosed at or before age 50 years; (2) triple-negative breast cancer diagnosed at age ≤ 60 years; (3) ≥ 2 primary breast cancers in the same person; (4) ovarian, fallopian tube, or primary peritoneal cancer; (5) Ashkenazi Jewish ancestry and breast or pancreatic cancer at any age; or (6) male breast cancer.	Genetic testing should be offered to individuals with a personal or family history suggestive of an inherited cancer syndrome; when the test can be adequately interpreted; if testing will influence medical management of the patient or relatives; when potential benefits outweigh potential risks; if testing is voluntary; and when the individual seeking testing or their legal proxy can provide informed consent.	NR	—
SIGN Management of Epithelial Ovarian Cancer, 2013 ⁴⁰	Women with nonmucinous ovarian or fallopian tube cancer	Women with ovarian cancer who have a family history of breast, ovarian, or colon cancer should have a genetic risk assessment. Women with a family history that appears to place them at high risk of developing ovarian cancer should be offered referral to a clinical genetics service for assessment, confirmation of family history, and consideration of genetic testing of an affected family member.	All women with nonmucinous ovarian or fallopian tube cancer should be offered <i>BRCA1</i> and <i>BRCA2</i> mutation testing. <i>BRCA1</i> and <i>BRCA2</i> mutation analysis should be considered in a family where there is a 10% or greater risk of a mutation being present.	NR	Close collaboration between primary care and specialist cancer genetics services is to be encouraged so that genetic cancer risk assessment in individuals who are at medium or high risk can be carried out efficiently.
ESMO Prevention and Screening in <i>BRCA</i> Mutation Carriers and Other Breast/Ovarian Hereditary Cancer Syndromes, 2016, and Newly Diagnosed and Relapsed Epithelial Ovarian Carcinoma: eUpdate 2016 ³⁸	Patients with high-grade tumors	In all cases in which a patient may be referred for <i>BRCA</i> testing, it is recommended that informed consent and genetic counseling be completed first. Carriers should be encouraged to advise close family members to obtain genetic counseling.	Patients with high-grade tumors should be tested for a germline <i>BRCA</i> mutation. Consideration should be given to testing tumors for a somatic <i>BRCA</i> mutation.	NR	—

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TABLE 3. Genetic Counseling and Testing Guideline Matrix (continued)

Resource	Target Population	Recommendations for Genetic Counseling	Recommendations for Genetic Testing	Timing of Testing	Other Recommendations
Spanish Society of Pathology and Spanish Society of Medical Oncology, 2018 ³⁵	Patients with nonmucinous epithelial ovarian cancer	NR	Germline <i>BRCA1/2</i> mutational analysis first. In patients who test negative for germline mutations, analysis should be completed with somatic testing of tumor tissue.	NR	<i>BRCA</i> mutation tests to be done in accredited laboratories, with internal and external quality control systems.
Multinational guideline ³²	Patients with ovarian cancer	Written information and a discussion on the implications for the patients and their families of the test result, which may either be performed personally or via a host of telemedicine technologies, are highly recommended for patients referred for testing.	Testing from tumor tissue for both germline and somatic <i>BRCA1/2</i> mutations.	Ideally undertaken upon diagnosis	Tumor testing approach could facilitate a focused germline testing effort and overall reduction in genetic testing.
USPSTF, 2019 ⁴²	Women who have family members with breast, ovarian, tubal, or peritoneal cancer	Women who have family members with breast, ovarian, tubal, or peritoneal cancer and have been identified as having a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (<i>BRCA1</i> or <i>BRCA2</i>) should receive genetic counseling and, if indicated after counseling, <i>BRCA</i> testing. The USPSTF recommends against routine genetic counseling for women whose family history is not associated with an increased risk for potentially harmful mutations in the <i>BRCA1/2</i> genes.	Women who have family members with breast, ovarian, tubal, or peritoneal cancer and have been identified as having a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (<i>BRCA1</i> or <i>BRCA2</i>) should receive <i>BRCA</i> testing if indicated after counseling. The USPSTF recommends against routine <i>BRCA</i> testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the <i>BRCA1/2</i> genes.	NR	—

Abbreviations: CLIA, Clinical Laboratory Improvement Amendments; ESMO, European Society for Medical Oncology; HRD, homologous recombination deficient; MSI, microsatellite instability; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Clinical Excellence; NR, not reported; SGO, Society of Gynecologic Oncology; SIGN, Scottish Intercollegiate Guidelines Network; USPSTF, US Preventive Services Task Force.

account.⁴⁶ The US Preventive Services Task Force reported on the accuracy of family cancer history information from studies that validated self-reported family histories with medical records. A report of ovarian cancer in a first-degree relative had a sensitivity of 50%, specificity of 99%, positive likelihood ratio of 34.0 (95% CI, 5.7 to 202.0), and negative likelihood ratio of 0.51 (95% CI, 0.13 to 2.10).⁴⁷

In a recent survey of 94 women with epithelial ovarian cancer referred for genetic testing, test cost was the most important attribute in preference between single-gene and

multigene genetic testing, followed by the ability of a test to detect deleterious mutations or variant of uncertain significance (VUS).⁴⁸ Sample requirements and turnaround time did not significantly drive the choice of genetic testing. At subsequent genetics consultation, 81% of patients chose multigene testing, 12% chose *BRCA1/2* testing only, and 7% declined testing.⁴⁸

Clinical interpretation. Germline mutations in *BRCA1* and *BRCA2* have been identified in 13%-15% of women diagnosed with ovarian cancer, and somatic mutations are

found in an additional 7%.^{26,49-51} The high incidence of these mutations and the advent of therapy targeted toward *BRCA* mutations warrant testing in all individuals diagnosed with ovarian cancer for the purpose of determining treatment recommendations, risk of other cancers, and need for cascade testing of family members. Testing for germline mutations should be done at the time of initial diagnosis. Presence of a germline mutation in a woman with advanced cancer identifies her as eligible for maintenance treatment with a poly (ADP-ribose) polymerase (PARP) inhibitor (olaparib) after response to initial chemotherapy.²³ Presence of a germline mutation in a woman with any stage cancer should trigger discussions with family members to evaluate their cancer risks.

Sequencing of germline DNA is the most sensitive approach. If germline DNA is negative for *BRCA* mutation, then DNA from tumor tissue should be sequenced because an additional 5% of women will have somatic mutations in *BRCA* genes.^{19,20} Conversely, the decision to sequence germline DNA should not depend on finding a mutation in tumor tissue because the somatic testing is less sensitive. Up to 5% of germline mutations will be missed if using tumor somatic mutation results to determine whether to sequence germline DNA.²³ Missing a germline mutation has grave implications for family members who may be falsely reassured that they are not at risk.

This Expert Panel recommends that germline sequencing of *BRCA1* and *BRCA2* be performed in the context of a multigene panel that includes, at minimum, *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *PALB2*. *BRCA1* and *BRCA2* are part of the BRCA-Fanconi anemia pathway, and additional Fanconi genes *BRIP1* (*FANCI*), *RAD51C* (*FANCD1*), and *RAD51D* have each been associated with inherited risk of ovarian cancer,⁵²⁻⁵⁹ leading the National Comprehensive Cancer Network to add guidelines to consider risk-reducing salpingo-oophorectomy in women with mutations in these genes. Mutations in the Fanconi gene *PALB2* (*FANCD2*) lead to significant risks of breast cancer,⁶⁰ and some studies suggest an association with ovarian cancer risk^{52,61,62} and some do not.^{5,53} Mutations in the mismatch repair genes that cause Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) predict cancer risks of ovarian, endometrial, and colon cancer,⁶³⁻⁶⁶ in addition to predicting microsatellite instability. The cost and availability of panel testing are comparable to those of testing *BRCA1* and *BRCA2* alone, making this a practical choice.⁶⁷ Mutations in these genes may suggest cancer susceptibility to chemotherapy (platinum), PARP inhibitors, or experimental agents targeting DNA repair or cell cycle pathways.^{14,50,68,69} Ongoing studies are investigating their utility in predicting response to such agents. Future clinical trials should include companion diagnostics to direct therapy and to facilitate treatment recommendations in the future.

Although high-grade serous ovarian cancer (HGSOC) has the highest mutation frequency of *BRCA* mutations, other histologies have appreciable rates of mutations, and genetic testing should not be restricted to HGSOC.^{50,52} Women with endometrioid, clear cell, low-grade serous, or carcinosarcoma subtypes of ovarian cancer have a risk of carrying germline *BRCA* mutation approaching that of HGSOC (28%).⁵⁰ Women with a diagnosis of mucinous ovarian cancer are the least likely to have germline hereditary mutations in *BRCA*, but up to 20% may have (germline or somatic) mutations conferring dMMR.⁷⁰ Mucinous cancers involving the ovary are rare, composing only 1%-3% of all ovarian cancers, and a comprehensive diagnostic evaluation should be performed to investigate a nonovarian, GI primary source of the cancer.

dMMR is found in approximately 10%-12% of unselected epithelial ovarian cancers and has been reported in all histologic subtypes but with an overrepresentation of nonserous histologies.⁷¹⁻⁷³ Specifically, endometrioid (19.2%), mucinous (16.9%), and clear cell (11.5%) histologic subtypes exhibit the highest proportion of dMMR. Notably, evaluation of a small subset of clear cell ovarian cancers with microsatellite instability (3 of 30 ovarian cancers, 10%) showed that these tumors are immunogenic and may thus be responsive to immune checkpoint blockade.⁷⁴ The incidence of dMMR in serous cancers has been reported to be lower, ranging from 1%-8%, with significant between-study heterogeneity.⁷¹⁻⁷³ All these observations argue for routine testing of dMMR in clear cell, endometrioid, and mucinous ovarian, fallopian, and primary peritoneal cancers, although testing for dMMR may also be offered to women diagnosed with other histologic types. The identification of a dMMR phenotype or genotype presents an opportunity for treatment with pembrolizumab in the setting of recurrent disease, regardless of tissue of origin (https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s014lbl.pdf).

Genetic counseling and shared decision making. Oncologists are increasingly performing pretest consent, ordering their own genetic testing, and discussing genetic test results to facilitate patient management. It is important that oncologists have a working knowledge of several topics related to cancer genetics and testing as well as of current guidelines, and they must consider the responsibilities of ordering, interpreting, and following up with test results.⁷⁵ Nongenetic providers should establish working relationships with genetics professionals, and ideally, results of genomic testing should be delivered in conjunction with a genetic counselor to communicate the complexities and far-reaching implications of the findings.⁴⁵ Indeed, there is legal precedence of physicians being held liable for failing to obtain an adequate family history, recommend appropriate testing, refer to a geneticist or genetic counselor, interpret test results correctly and/or in a timely manner, recommend appropriate risk mitigation strategies, and/or

disclose their patients' test results to at-risk family members.⁷⁶ Furthermore, recent evidence suggests that genetic counseling improves levels of both patient engagement⁷⁷ and empowerment.⁷⁸

Shared decision making is preferred by most patients, can improve both physician and patient understanding of goals of care, and is associated with improved disease-related outcomes⁷⁹ and quality of life.⁸⁰ *BRCA* mutations are inherited in an autosomal dominant pattern. Once an index patient is confirmed to carry a deleterious germline mutation, first-degree relatives have a 50% chance of carrying the same mutation, and second-degree relatives have a 25% risk. Given the high penetrance of cancer in individuals carrying *BRCA* mutations, each adult first- and second-degree relative should be tested.⁴³

CLINICAL QUESTION 2

Which genomic alterations have demonstrated clinical utility to direct therapy for women with ovarian cancer?

Recommendation 2.1

Women diagnosed with epithelial ovarian cancer with identified germline or somatic pathogenic or likely pathogenic variants in *BRCA1* and *BRCA2* genes should be offered treatments that are US Food and Drug Administration (FDA) approved under their labeled indications in the upfront and the recurrent setting. *BRCA1/2* pathogenic or likely pathogenic variants qualify for and have been associated with higher rates of response to FDA-approved treatments such as PARP inhibitors (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 2.2

Women diagnosed with recurrent epithelial ovarian cancer with identified dMMR should be offered FDA-approved treatment under their labeled indications based on these results. dMMR qualifies for FDA-approved treatment (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 2.3

No recommendations can be made supporting routine tumor testing using currently available homologous recombination deficiency (HRD) assays. Current assays evaluating HRD have been applied to stratify women with ovarian cancer for treatment (No recommendation; Evidence quality: low; Strength of recommendation: not applicable).

Recommendation 2.4

Clinical decisions should not be based on a VUS. Care providers and patients and family members tested should be aware that reclassification of VUS is an ongoing process and it may eventually become possible to definitively determine if a variant is deleterious or benign. Until that time,

the patient's clinical features and family history should inform clinical decision making (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Literature review and analysis. Eleven randomized clinical trials were identified that met the eligibility criteria and are included in this systematic review (Table 2). The SOLO1 trial evaluated the efficacy of olaparib as first-line maintenance therapy in patients with newly diagnosed advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer with a mutation in *BRCA1*, *BRCA2*, or both (*BRCA1/2*) who had a complete or partial clinical response after platinum-based chemotherapy. Based on the positive results of SOLO1, the FDA approved olaparib for maintenance in the front-line setting. In PAOLA-1, olaparib plus bevacizumab as first-line maintenance therapy in a broad population of women with advanced ovarian cancer, not restricted by surgical outcome or *BRCA* mutation status, demonstrated a statistically significant improvement in progression-free survival (PFS). Tumor *BRCA* mutation status was used as stratification, whereas HRD testing was exploratory. Prespecified subgroup analyses showed that patients with tumor *BRCA* mutations (hazard ratio [HR], 0.31; 95% CI, 0.20 to 0.47) and patients with positive HRD status (including *BRCA*-mutated tumors; HR, 0.33; 95% CI, 0.25 to 0.45) had the greatest PFS benefits.

The PRIMA trial investigated the efficacy and safety of niraparib maintenance therapy after a response to platinum-based chemotherapy in patients with newly diagnosed advanced ovarian cancer at high risk for relapse. HRD testing, with a more stringent discriminant than used in VELIA, was used as stratification factor. The trial confirmed that the clinical benefit of first-line treatment with niraparib could be extended to all patients with advanced ovarian cancer regardless of HRD status. Niraparib provided a significant clinical benefit over placebo in the patients who had tumors with HRD with respect to the median duration of PFS both in patients with *BRCA* mutations (22.1 v 10.9 months, respectively; HR, 0.40) and in those without *BRCA* mutations (19.6 v 8.2 months, respectively; HR, 0.50). The extended median duration of PFS was also observed in the niraparib group compared with the placebo group (8.1 v 5.4 months, respectively; HR, 0.68) in the subgroup of patients with HR-proficient tumors.

The PFS benefit in the VELIA trial of veliparib in combination with chemotherapy as initial therapy followed by veliparib maintenance was seen across the intent-to-treat cohort (HR, 0.68; $P < .001$) and HRD cohort (HR, 0.57; $P < .001$), although the largest benefit of veliparib is seen in patients with *BRCA* mutation (HR, 0.44; $P < .001$). Stratification was based on germline *BRCA* status and was added 14 months after initiation of the study, at which time the study was more than half accrued. No PFS benefit was

seen in patients with HRD *BRCA* wild-type disease (HR, 0.74; 95% CI, 0.52 to 1.06) or those with homologous recombination–proficient (HRP) disease (HR, 0.81; 95% CI, 0.60 to 1.09).

Two trials evaluated olaparib for maintenance therapy after recurrence. Study 19 evaluated olaparib capsules in patients with advanced platinum-sensitive HGSOC who had received 2 or more previous platinum-containing regimens and had demonstrated an objective response to their last platinum-based chemotherapy regimen.^{16,18-21} SOLO2 evaluated maintenance treatment with olaparib tablets in patients with relapsed HGSOC (including patients with primary peritoneal and/or fallopian tube cancer) or high-grade endometrioid cancer with *BRCA* mutations who had responded to immediate prior platinum-based chemotherapy and led to FDA approval.²⁴ FDA approval of niraparib as maintenance therapy for women with recurrent epithelial ovarian cancer in complete or partial response to platinum-based chemotherapy was based on the NOVA trial.²² For inclusion, patients had to have received ≥ 2 prior platinum-based regimens. The ARIEL3 RCT demonstrated clinical benefits of rucaparib in patients with platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma who had received at least 2 previous platinum-based chemotherapy regimens and had achieved complete or partial response to their last platinum-based regimen.¹⁴ Rucaparib, as later-line treatment, received accelerated FDA approval for the treatment of germline and/or somatic *BRCA*-mutated advanced ovarian cancer in women who have previously received ≥ 2 chemotherapy lines based on results from 2 single-arm studies—ARIEL2 and Study 10.^{17,25} Olaparib also received FDA approval in the later-line treatment setting based on the results of Study 42, a single-arm phase II study.¹⁵ Based on these 11 trials of PARP inhibitors, women with ovarian cancer who carry *BRCA1/2* mutations have been reported to have improved PFS compared with noncarriers, regardless of tumor stage, grade, or histologic subtype.

Clinical interpretation. Three PARP inhibitors (ie, niraparib, olaparib, and rucaparib) are FDA approved for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who exhibit complete or partial response to platinum-based chemotherapy. Importantly, all 3 PARP inhibitors are approved in that setting regardless of *BRCA* mutation status and HRD status. Nonetheless, data from 4 RCTs^{14,16,18-22,24} indicate that the magnitude of the PFS benefit of PARP inhibitors over placebo is most prominent in tumors with germline or somatic *BRCA* mutations (HR, 0.18-0.3), followed by HRD-positive tumors (HR, 0.32-0.38),^{14,22} and is least prominent in *BRCA* wild-type and HRD-negative tumors (HR, 0.58 in both ARIEL3 and NOVA studies).

Olaparib was FDA approved on December 19, 2018, for the maintenance of response in the first-line treatment of patients with deleterious or suspected deleterious germline or

somatic *BRCA*-mutated advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. The approval was based on the SOLO1 phase III trial whereby maintenance olaparib reduced the risk of progression or death compared with placebo by 70% (PFS: HR, 0.30; 95% CI, 0.23 to 0.41; $P < .0001$).

Three additional RCTs have evaluated incorporation of PARP inhibitor therapy in the first-line setting—VELIA, PRIMA, and PAOLA-1 (Table 2). In all 3 studies, tumors with *BRCA* mutations exhibited the most prominent benefit from PARP inhibitor therapy, with an HR of 0.4 (niraparib maintenance v placebo) in PRIMA, HR of 0.31 (olaparib and bevacizumab maintenance v bevacizumab and placebo maintenance) in PAOLA-1, and HR of 0.44 (chemotherapy with veliparib followed by veliparib maintenance v chemotherapy and placebo followed by placebo maintenance) in VELIA. The VELIA and PAOLA-1 studies stratified patients based on *BRCA* mutation status (tumor *BRCA* mutation status in PAOLA-1 and germline *BRCA* mutation status in VELIA [added as stratification 14 months after trial initiation]). In these trials, compared with *BRCA*-mutated tumors, the benefit of addition of PARP inhibitor therapy in patients with *BRCA* wild-type tumors was much less prominent, with an HR of 0.8 (95% CI, 0.64 to 1.00) in VELIA²⁸ and HR of 0.71 (95% CI, 0.58 to 0.88) in PAOLA-1.²⁹

Beyond *BRCA*-mutated tumors, current HRD assays do not provide sufficient differentiation of patient response to PARP inhibitors to routinely recommend their use. In the PRIMA trial, stratification was based on tumor HRD assessed by the myChoice test (Myriad Genetics, Salt Lake City, UT) as deficient or proficient/undetermined. Beyond *BRCA*-mutated tumors (where the HR for niraparib benefit was 0.4), in a preplanned exploratory analysis of subgroups defined by HRD, niraparib exhibited benefit both in patients with HRD/*BRCA* wild-type tumors (HR, 0.5; 95% CI, 0.31 to 0.83) and in HRP tumors (HR, 0.68; 95% CI, 0.49 to 0.94). Although the point estimate of the niraparib HR in HRD/*BRCA* wild-type tumors was lower than that in HRP tumors (0.5 v 0.68, respectively), the CIs exhibited considerable overlap, suggesting that the ability of HRD testing to detect niraparib benefit beyond *BRCA*-mutated tumors is not optimal. Similarly, in an exploratory analysis in VELIA (where HRD testing was not used as a stratification factor) using a cutoff HRD score of ≥ 33 to indicate HRD status (as opposed to a cutoff of 42 used in PRIMA and PAOLA-1), the HR of veliparib was similar in HRD/*BRCA* wild-type tumors (HR, 0.74; 95% CI, 0.52 to 1.06) and HRP tumors (HR, 0.81; 95% CI, 0.6 to 1.09). In PAOLA-1, exploratory analysis of HRD testing showed that the benefit of olaparib plus bevacizumab versus bevacizumab plus placebo was evident only in HRD/*BRCA* wild-type tumors (HR, 0.43; 95% CI, 0.28 to 0.66) and not in HRP/HRD-unknown tumors (HR, 0.92; 95% CI, 0.72 to 1.17). However, caution is needed in interpreting this finding because HRD testing

was not a stratification factor in PAOLA-1, the number of patients with HRD/*BRCA* wild-type tumors was small (97 patients received olaparib plus bevacizumab and only 55 patients received placebo plus bevacizumab), and HRD testing has not been validated for response to combined PARP inhibitor and antiangiogenic therapy.

PARP inhibitors have also been approved for use in the treatment setting. Olaparib is FDA approved for the treatment of patients with deleterious or suspected deleterious germline *BRCA*-mutated ovarian, fallopian, or primary peritoneal cancer who have received 3 or more prior lines of chemotherapy. Rucaparib is also FDA approved for the treatment of patients with deleterious *BRCA* (germline and/or somatic) mutation-associated ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 2 or more chemotherapy regimens. In the ARIEL2 study, rucaparib was also active in a small cohort (n = 5) of ovarian cancers with *RAD51C* or *RAD51D* mutations, with 3 partial responses and 2 patients with prolonged stable disease for 8.3 and 11.0 months. The recently reported single-arm, nonrandomized QUADRA trial of niraparib in recurrent ovarian cancer met its primary end point demonstrating activity in the primary efficacy population of fourth- and fifth-line HRD-positive (which included *BRCA*-mutated cancers) patients who were PARP inhibitor naïve and considered to be platinum sensitive to the last platinum therapy (n = 47), with an overall response rate of 28% and median duration of response of 9.2 months. On October 23, 2019, the FDA approved niraparib for patients with advanced ovarian, fallopian tube, or primary peritoneal cancer treated with 3 or more prior chemotherapy regimens, who are PARP inhibitor naïve and whose cancer is associated with HRD-positive status determined using the Myriad Genetics myChoice CDx as either tumor *BRCA* mutated and/or a genomic instability score ≥ 42 . Patients with HRD-positive cancers but without *BRCA* mutations must have experienced progression at least 6 months after the last dose of platinum-based therapy (ie, must have platinum-sensitive disease). The value of testing for the mismatch repair (MMR) phenotype is the tissue-agnostic FDA approval of pembrolizumab for patients with microsatellite instability-high (MSI-H) or dMMR recurrent solid tumors. This provides another treatment option for patients with recurrent ovarian, fallopian tube, or primary peritoneal cancers that are MSI-H/dMMR. Multiple laboratory tests are available to evaluate the status of the MMR pathway. MSI-H or dMMR status can be determined using polymerase chain reaction (PCR) tests to assess microsatellite instability or immunohistochemistry (IHC) tests for expression status of the key MMR proteins. Next-generation sequencing (NGS) has also been used to predict microsatellite status by focusing on targeted sequencing of known microsatellite loci or analysis of microsatellite regions using novel informatics algorithms.⁸¹⁻⁸⁴ Furthermore, the mutational phenotype (eg, number of total mutations or number

of total mutations per megabase in combination with number of single-base insertion or deletion mutations in repeats per megabase) assessed by targeted NGS using standard informatics pipelines has also been used to infer dMMR, although it was not defined as an acceptable discriminant in the FDA approval.^{85,86} However, none of these assays have been prospectively validated in terms of their ability to detect dMMR in ovarian cancer or to predict response to pembrolizumab or other immune checkpoint inhibitors in this disease.

Several lines of evidence indicate that standard MSI PCR panels used by most clinical laboratories and MSI testing by NGS have decreased sensitivity for detecting dMMR cancers outside the GI tract (ie, in endometrial and prostate cancers).⁸⁷⁻⁹⁰ Of note, in one study of an immune checkpoint inhibitor in endometrial cancer, PCR missed 1 patient with a dMMR tumor who responded to immunotherapy.⁹¹ However, IHC is simple and cost effective and is widely available in most pathology laboratories, although it is important to underscore that IHC may miss dMMR tumors due to mutations that lead to loss of MMR function but retain antigenicity.^{88,92}

Clinical decision making should not be made based on a VUS. Physicians and patients should be aware that reclassification of VUS is an ongoing process and it may eventually become possible to definitively determine if a variant is deleterious or benign. Testing laboratories and commercially available diagnostics should report reclassifications from VUS to either deleterious (pathogenic or likely pathogenic) or not (benign or likely benign) to the ordering clinician, who in turn has the responsibility to discuss the information and offer appropriate recommendations with patients on an ongoing basis.⁷⁵ Physicians should be encouraged to refer patients to clinical research on variant classification if available.

Isolated reports of response to specific targeted agents and/or novel synthetic lethal strategies have been reported for several molecular alterations, including (but not limited to) mutations in the *BRAF*, *KRAS*, *ARID1A*, *PIK3CA*, and *PTEN* genes; amplification of *CCNE1*, *CCND1*, *CCND2*, and *MYC*; and deletion of *RB* and *CDKN2A*. Recently, exploratory analysis from the MILO/ENGOT-ov11 trial suggests that response to the MEK inhibitor binimetinib is greater in *KRAS*-mutated tumors,⁹³ but there are currently no data that *KRAS* mutation status predicts benefit of MEK inhibitor therapy over standard-of-care chemotherapy in this disease. It is important to underscore that the association between presence of specific molecular alterations and response to specific therapies may be context specific (ie, may differ depending on the specific tumor type, histology, and the concomitant presence of other molecular alterations). Therefore, participation in clinical trials, including basket trials such as the NCI-MATCH, NCI-CombiMatch, and TAPUR trials, is encouraged until more definitive data about the potential clinical utility of these alterations are available.

CLINICAL QUESTION 3

What are the most appropriate sequencing and timing of testing?

Recommendation 3.1

Women with epithelial ovarian cancer should be offered testing, as outlined in recommendation 1.1, at the time of diagnosis. This has implications for therapeutic decision making (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 3.2

Women with epithelial ovarian cancer who have not had germline testing at the time of diagnosis should be offered germline genetic testing as soon as feasibly possible, as outlined in recommendation 1.1. In women who do not carry a germline pathogenic or likely pathogenic *BRCA1/2* variant, somatic tumor testing for *BRCA1* and *BRCA2* pathogenic or likely pathogenic variants should be offered. Somatic tumor testing for *BRCA1* and *BRCA2* pathogenic or likely pathogenic variants may be reserved for time of recurrence for women who have completed upfront therapy and are currently in observation, as presence of these mutations qualifies the patient for FDA-approved treatments (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and analysis. Three observational studies were identified and form the evidentiary base for clinical question 3 recommendations.^{16,94,95} In addition to these 3 studies, 2 abstracts were also identified and are discussed as supporting evidence only, because data reported only in abstract form are not used to inform recommendations.^{96,97} Evidence demonstrates that results from testing may have an impact on clinical management in a proportion of patients. Thus, it is important that testing for *BRCA1/2* status be undertaken as soon as possible after diagnosis such that the results are available to direct treatment decisions, factoring in the local testing turnaround times, the potential need for genetic counseling, and other relevant considerations based on the approvals at the time of this guideline publication.³²

Jorge et al⁹⁶ found that results from simultaneous next-generation DNA sequencing performed on paired germline and tumor specimens affected clinical decisions in nearly 25% of patients, 16% of whom carried somatic (*BRCA1*, *BRCA2*, *RAD51B*, *BRIP1*) and 7% germline mutations (*BRCA1*, *BRCA2*, *PMS2*). In 42% of patients with negative or inconclusive germline testing results, information on actionable molecular alterations was provided with paired somatic testing. A retrospective analysis of data from Study 19 found that NGS identified somatic *BRCA1/2* mutations absent from germline testing in 10% of patients.¹⁶

Chen et al⁹⁷ considered the proportion of patients eligible for PARP inhibitor treatment based on testing and found that 7%, 83%, and 10% of patients were eligible based on

germline, somatic, and germline and somatic *BRCA1/2* mutations, respectively. Up to 31% of patients were negative for germline and somatic *BRCA1/2* mutations but tested positive for germline or somatic pathogenic mutations in other homologous recombination genes or for tumor promoter methylation in *BRCA1* or *RAD51C*.

Clinical interpretation. All women with epithelial ovarian cancer who have not had germline testing at the time of diagnosis should have germline genetic testing as soon as possible, as outlined in recommendation 1.1 and discussed in the literature review and analysis. Somatic tumor testing for *BRCA1* and *BRCA2* pathogenic or likely pathogenic variants should be offered to women who do not carry a germline pathogenic *BRCA1/2* variant, as these results could have implications for therapeutic decision making. However, for women who have completed upfront therapy and are currently in observation, somatic tumor testing for *BRCA1* and *BRCA2* pathogenic or likely pathogenic variants may be reserved for the time of recurrence.

Repeat tumor testing has not been shown to be of any utility in terms of therapeutic decision making for patients who have already undergone somatic testing. Although a number of elegant studies have identified secondary *BRCA1/2* mutations⁴⁹ or *RAD51C/RAD51D* mutations⁹⁸ in recurrent tumor samples as well as secondary *BRCA1/2* mutations in circulating cell-free DNA⁹⁹ from patients who developed resistance to platinum and/or PARP inhibitor therapy, at this point, presence of these alterations does not have any direct therapeutic implications for patients who have already experienced progression on prior PARP inhibitor therapy. Furthermore, presence of these alterations cannot be used to deny PARP inhibitor therapy to patients who are PARP inhibitor naïve and are otherwise eligible for such therapy.

As discussed, physicians, other care providers, and patients should be aware that reclassification of VUS is an ongoing process and it may eventually become possible to definitively determine if a variant is deleterious or benign. Testing laboratories and commercially available diagnostics should report reclassifications from VUS to either deleterious (pathogenic or likely pathogenic) or not (benign or likely benign), and physicians should be encouraged to share variant results and refer patients to clinical research on variant classification if available.

PATIENT AND CLINICIAN COMMUNICATION

Clinicians should educate patients, family members, and/or caregivers about the value of genetic testing for those diagnosed with high-grade epithelial ovarian cancer. However, a recent study showed that only one third of all women diagnosed with ovarian cancer had genetic testing.⁵ Patients who undergo genetic testing should be offered both pre- and posttest genetic counseling. All patients should be provided a copy of their genetic test results. A clinician

and/or genetics counselor should discuss the results with the patient and ask if the patient has any questions. The terms used to explain germline and somatic mutations as well as the test results should be at an educational level that the patient can easily understand. Those with germline (hereditary) mutations should be provided information regarding how to share that information with first- and second-degree family members.

It is important that clinicians discuss with patients the role genetic test results may have on their current and future treatment plans. While genetic testing at time of diagnosis can have implications for therapeutic decision making, it can nonetheless be difficult for patients psychosocially. While discussing considerations of genetic testing, such as potential uncertainty with test results, limitations of testing, implications of testing for hereditary cancer risk for family members, and insurance discrimination, clinicians should acknowledge the patient's and family members' feelings of worry, anxiety, guilt, fear, and distress about future financial strain, which can be common.⁷⁵ It is also paramount that clinicians discuss the Genetic Information Non-discrimination Act, a federal law that protects individuals from genetic discrimination in health insurance and employment (<http://www.ginahelp.org/GINAhelp.pdf>).⁷⁵ For recommendations and strategies to optimize patient-clinician communication, see "Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline."¹⁰⁰ In addition, information on health literacy may be found at www.cdc.gov/healthliteracy.

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. A recent large population-based study of multigene testing in patients with breast and ovarian cancer observed disparities in germline testing, particularly among patients with ovarian cancer.⁵ Racial and ethnic disparities in health care contribute significantly to this problem in the United States. While approximately 34% of non-Hispanic white women were tested, only approximately 22% of black women and 24% of Hispanic women received testing. Patients with cancer who are members of racial or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.¹⁰¹⁻¹⁰⁴ As expected, genetic testing is reported to be lower among uninsured patients (21%) compared with those with insurance (35%).⁵ Moreover, racial or ethnic differences in pathogenic variants observed in patients with ovarian cancer include *BRCA1*, which is reported to be 7% in whites and 16% in Hispanics.⁵ Many other patients lack access to care because of their geographic location and

distance from appropriate treatment facilities. Awareness of these disparities should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have 2 or more such conditions—referred to as multiple chronic conditions (MCCs)—is challenging. Patients with MCCs are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCCs. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCCs, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCCs, and this highlights the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of these considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCCs, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCCs.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their medical costs through deductibles and coinsurance.^{105,106} Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer screening and testing.^{107,108}

A recent cost-effectiveness analysis compared universal genetic testing to tumor testing as a companion diagnostic for PARP inhibitor treatment.¹⁰⁹ The primary outcome of interest was average life expectancy gain in HGSOc patients, and costs were estimated from Medicare claims and wholesale acquisition costs for drugs with a time horizon of 50 years. Assuming 10,000 newly diagnosed women with HGSOc every year in the United States, the model predicts that tumor testing

and germline testing will identify 1,908 and 1,808 women eligible for PARP inhibitor treatment, respectively. The average lifetime costs for tumor testing and germline testing were \$43,174 and \$41,353, respectively. The average life expectancy gains for tumor testing and germline testing were 3.64 and 3.63 years, respectively, yielding an incremental cost-effectiveness ratio (ICER) of \$162,740. Ultimately the authors concluded that tumor testing is cost effective (ICER < \$100,000) if tumor testing and annual PARP inhibitor costs are < \$2,000 and \$120,000, respectively.¹⁰⁹

Another cost-utility analysis in a European jurisdiction considered patients with high-grade epithelial ovarian cancer without a family history of ovarian or breast cancer who were germline *BRCA1/2* mutation carriers and their relatives and compared the following 2 scenarios: *BRCA1/2* testing versus no testing. Results suggest that providing this screening test to patients with high-grade epithelial ovarian cancer and their relatives is cost effective and that it improved the quality of life among the patients' relatives by 43.8 quality-adjusted life-years.¹¹⁰

Discussion of cost can be an important part of shared decision making.¹¹¹ Formal cost-effectiveness strategies for germline genetic and somatic tumor testing in ovarian cancer suggest costs have diminished considerably but still can present a barrier to access, especially if not covered by third-party payers. Evidence suggests that review of or involvement in genetic test orders by genetic counselors can increase the appropriateness and clinical utility as well as reduce health care costs to hospitals, insurers, and patients.^{112,113} Yet, given the substantial costs of diagnosis and treatment of ovarian cancer, as well as the lethality of the disease, early diagnosis and appropriate targeted treatment are likely cost beneficial to society. A transparent discussion about potential out-of-pocket costs of testing should be conducted with patients and families.

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from May 2 through May 16, 2019. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation. A total of 15 respondents, who had not previously reviewed the recommendations, either agreed or agreed with slight modifications to the vast majority of the recommendations. The draft was also submitted to 2 external reviewers with content expertise. The draft was rated as high quality, and it was agreed it would be useful in practice. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated prior to Clinical Practice Guidelines Committee review and approval.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in the *Journal of Clinical Oncology* and the *JCO Oncology Practice*.

LIMITATION OF THE RESEARCH AND FUTURE RESEARCH

As discussed, treatment of epithelial ovarian cancer, especially front-line therapy, represents a rapidly changing field. Additionally, several molecular alterations represent areas of active investigation and may eventually emerge as genomic alterations that will demonstrate clinical utility to direct therapy. Finally, although multiple laboratory tests are available to evaluate the status of the MMR pathway, no assay has been prospectively validated in terms of its ability to detect dMMR in ovarian cancer or to predict response to pembrolizumab or other immune checkpoint inhibitors in this disease.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a Data Supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/gynecologic-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Circulating Tumor DNA Analysis in Patients With Cancer (<https://ascopubs.org/doi/pdf/10.1200/JCO.2017.76.8671>)
- Molecular Testing for the Selection of Patients With Lung Cancer for Treatment With Targeted Tyrosine Kinase Inhibitors Guideline Endorsement (<https://ascopubs.org/doi/pdf/10.1200/JCO.2017.76.7293>)
- Molecular Biomarkers for the Evaluation of Colorectal Cancer (<https://ascopubs.org/doi/pdf/10.1200/JCO.2016.71.9807>)

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EDITOR'S NOTE

This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/gynecologic-cancer-guidelines.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI <https://doi.org/10.1200/JCO.19.02960>.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline**

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APPENDIX

TABLE A1. Guideline Expert Panel Membership

Name and designation	Affiliation/Institution	Role/Area of Expertise
Christina M. Annunziata, MD, PhD, co-chair	NCI, Women's Malignancies Branch	Medical oncology, genomics
Panagiotis A. Konstantinopoulos, MD, PhD, co-chair	Dana-Farber Cancer Institute	Gynecologic oncology
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Barbara Norquist, MD	University of Washington Medicine	Gynecologic oncology
Karen H. Lu, MD, ASCO Genetics Subcommittee representative	MD Anderson Cancer Center	Gynecologic oncology
Elise C. Kohn, MD	NCI, Gynecologic Cancer Therapeutics	Medical oncology
Deborah Armstrong, MD	Johns Hopkins	Medical oncology
Tricia L. Kalwar, MD, Practice Guidelines Implementation Network representative	Broward Health Medical Center	Medical oncology
Dorinda Sparacio, patient representative	Hightstown, NJ	Patient advocacy
Christina Lacchetti	ASCO	Staff/health research methodologist

Abbreviations: ASCO, American Society on Clinical Oncology; MSKCC, Memorial Sloan Kettering Cancer Center; NCI, National Cancer Institute; OSUCCC, Ohio State University Comprehensive Cancer Center.

TABLE A2. Definition of Terms

Term	Description
Genetic variant	An alteration in the most common DNA nucleotide sequence. The term <i>variant</i> can be used to describe an alteration that may be benign, pathogenic, or of unknown significance. The term <i>variant</i> is increasingly being used in place of the term <i>mutation</i> .
Germline variant	A gene change in a reproductive cell (egg or sperm) that becomes incorporated into the DNA of every cell in the body of the offspring. A variant contained within the germline can be passed from parent to offspring and is, therefore, hereditary.
Somatic variant	An alteration in DNA that occurs after conception and is not present within the germline. Somatic variants can occur in any of the cells of the body except the germ cells (sperm and egg) and, therefore, are not passed on to children. Somatic variants can (but do not always) cause cancer or other diseases.
Actionable genetic information	The presence or absence of a genetic variant in a tumor or the germline that can be used to inform clinical management. (Adapted from Dancey JE, et al. Cell 148:409-420, 2012).
Pathogenic	Directly contributes to the development of disease. Additional evidence is not expected to alter the classification of this variant. (Note: Not all pathogenic variants are fully penetrant).
Likely pathogenic	Very likely to contribute to the development of disease, but scientific evidence is currently insufficient to prove this conclusively.
Uncertain significance	There is not enough information at this time to support a more definitive classification of this variant.
Likely benign	Not expected to have a major effect on disease, but the scientific evidence is currently insufficient to prove this conclusively.
Benign	Does not cause disease. Additional evidence is not expected to alter classification of this variant.

Adapted from Richards et al.⁴⁴