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

Konstantinopoulos et al.
Introduction

- 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.
- Of these, mutations in \textit{BRCA1} and \textit{BRCA2} account for almost 40% of ovarian cancers in women with a family history of the disease, and approximately one quarter are caused by genes other than \textit{BRCA1} and \textit{BRCA2}.
- 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.
- The purpose of this guideline is to provide recommendations regarding the role of genomic testing in epithelial ovarian cancer based on the best available evidence.
ASCO Guideline Development Methodology

The ASCO Clinical Practice Guidelines Committee guideline process includes:

• a systematic literature review by ASCO guidelines staff
• an expert panel provides critical review and evidence interpretation to inform guideline recommendations
• final guideline approval by ASCO CPGC

The full ASCO Guideline methodology manual can be found at:
www.asco.org/guideline-methodology
Clinical Questions

This clinical practice guideline addresses three 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?
Target Population and Audience

**Target Population**
Women diagnosed with ovarian cancer and their families.

**Target Audience**
Medical, radiation, and surgical oncologists; gynecologic oncologists; gynecologists; geneticists; genetic counselors; other health professionals; women with ovarian cancer and their families.
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)
Summary of Recommendations

**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)
Summary of Recommendations

**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)
Summary of Recommendations

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)
Summary of Recommendations

**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)
Summary of Recommendations

**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)
Summary of Recommendations

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)
Summary of Recommendations

**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)
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.

- 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.

- 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.
Health Disparities

- 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.
  - Approximately 34% of non-Hispanic white women were tested; only approximately 22% of black women and 24% of Hispanic women received testing.

- Genetic testing is reported to be lower among uninsured patients (21%) compared with those with insurance (35%).

- 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.

- Awareness of these disparities should be considered in the context of this guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.
Cost Considerations

- Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer screening and testing.

- 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.
Limitation of the Research and Future Research

- Treatment of epithelial ovarian cancer, especially front-line therapy, represents a rapidly changing field.

- Several molecular alterations represent areas of active investigation and may eventually emerge as genomic alterations that will demonstrate clinical utility to direct therapy.

- 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.
Additional Resources

More information, including a Data Supplement, slide sets, and clinical tools and resources, is available at


Patient information is available at www.cancer.net
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