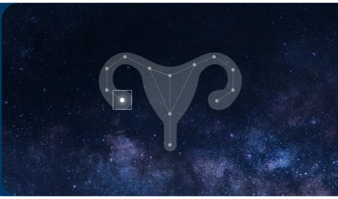
HRD in Advanced Ovarian Cancer

Ensure eligible patients with ovarian cancer are tested for HRD.



Reading time: **13 min**

Jump to: Guidelines · Prevalence · Sample Types · Diagnostic Tests · Results Interpretation · Considerations for Your Practice · Helpful Resources

Clinical Relevance of Homologous Recombination Deficiency

Homologous recombination deficiency (HRD) is defined by having *BRCA1/2* mutations and/or measures of genomic instability, including loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transitions (LST).[1] In patients with HRD, tumor cells cannot accurately repair double-strand breaks (DSBs) in DNA. Patients with HRD may benefit from PARPi treatments that target the deficiency via synthetic lethality. To help inform maintenance therapy decisions, collaborate with your multidisciplinary team (MDT) to ensure HRD testing for eligible patients in the upfront setting.[1,2]

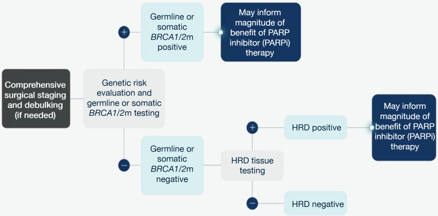
BRCA1/2, BReast CAncer susceptibility gene 1/2; DNA, deoxyribonucleic acid; DSB, double-stranded break; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; LST, large-scale state transitions; MDT, multidisciplinary team; PARPi, poly-ADP ribose polymerase inhibitor; TAI, telomeric allelic imbalance.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Ovarian Cancer Recommend Testing for HRD at Diagnosis

NCCN Guidelines® recommend germline and somatic testing, including considering testing for HRD status in the absence of a *BRCA1/2* mutation, for patients with newly diagnosed advanced ovarian cancer[3]

Test all patients for actionable germline and somatic biomarkers. Ensure somatic testing includes, at a minimum, *BRCA1/2* mutations, and LOH or HRD, in the absence of a germline *BRCA1/2* mutation.[3,4]

NCCN Guidelines recommendations[3]:


Comprehensive surgical staging and debulking (if needed)
Genetic risk evaluation and germline or somatic *BRCA1/2*m testing
+
Germline or somatic *BRCA1/2*m positive
May inform magnitude of benefit of PARP inhibitor (PARPi) therapy
−
Germline or somatic *BRCA1/2*m negative
HRD tissue testing
+
HRD positive
May inform magnitude of benefit of PARP inhibitor (PARPi) therapy
−
HRD negative

Footnotes

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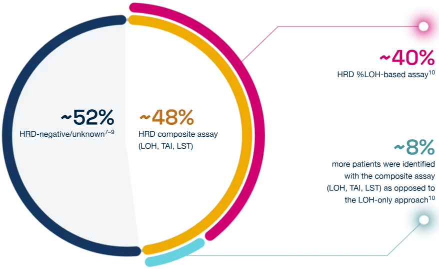
SGO recommends concurrent germline and somatic testing, including HRD, at diagnosis for optimal treatment for patients with advanced ovarian cancer[5]

Somatic tumor testing is recommended for patients undergoing upfront ovarian cancer treatment and should, at minimum, include *BRCA1/2* variants, LOH, and HRD status.

BRCA1/2, BReast CAncer susceptibility gene 1/2; *BRCA1/2*m, BReast CAncer susceptibility gene 1/2 mutation; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; NCCN, National Comprehensive Cancer Network; PARP, poly-ADP polymerase inhibitor; SGO, Society of Gynecologic Oncology.

~1 in 2 Patients With Advanced Ovarian Cancer Are HRD-Positive[6–10]

Test for HRD in patients with aOC using an assay that includes all measures of genomic instability (LOH, TAI, and LST) instead of an LOH-only approach, which can miss up to 8% of patients[10,a]



Footnotes

[a] Myriad MyChoice® (composite score of LOH, TAI, and LST) was compared to a %LOH-based assay to assess HRD status in archival tumor samples from patients with platinum-sensitive, relapsed advanced ovarian cancer (N=148). Patients with germline *BRCA*m were excluded from this analysis. The study concluded that the %LOH-based assay identified 8% less HRD-positive tumor samples than the Myriad MyChoice® CDx.[10]

aOC, advanced ovarian cancer; *BRCA*m, BReast CAncer susceptibility gene mutation; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; LST, large-scale state transitions; TAI, telomeric allelic imbalance.

Understanding the Molecular Components of HRD

HRD is assessed by two types of biomarkers in ovarian cancer: *BRCA1/2* mutations, as well as genomic instability.[8,11]

Genomic instability, or large-scale structural rearrangements to chromosomes, results in specific measurable genomic aberrations and serves as collateral damage that can occur to the genome as a result of HRD.[8,11]

FOR HCPS

Homologous recombination deficiency and cancer care

Watch how homologous recombination deficiency (HRD) testing can help with tumor characterization and the development of a personalized treatment plan.

4:51 MIN

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HRD, homologous recombination deficiency; *BRCA1/2*, BReast CAncer susceptibility gene 1/2.

Consider Testing Tumor Tissue for HRD[3]

Use saliva or blood for g*BRCA1/2* and tumor tissue for somatic *BRCA1/2* and GIS testing[2,5]

HRD testing may include germline *BRCA1/2*, somatic *BRCA1/2*, and genomic instability.[5] Germline testing provides familial, prognostic and predictive insights, whereas somatic testing for *BRCA1/2* along with a measure of GIS provides insight into the magnitude of benefit from targeted therapy.[8]

Sample type	Clinical relevance	Limitations
Germline (blood or saliva)	May have familial implications[11]	Do not report somatic variants[4]
Plasma ctDNA	May be used for molecular analysis when tissue-based analysis not clinically feasible[3]	Depends on adequate levels of ctDNA[12]
Somatic (tumor tissue)	Determines total mutation status (somatic and germline)[5]	• Samples can be heterogeneous, containing malignant and normal cells[13] • Testing somatic tissue cannot discriminate between somatic and germline variants[14]

BRCA1/2, BReast CAncer susceptibility gene 1/2; ctDNA, circulating tumor deoxyribonucleic acid; g*BRCA1/2*, germline BReast CAncer susceptibility gene 1/2; GIS, genomic instability; HRD, homologous recombination deficiency; LGR, large genomic rearrangement; NGS, next-generation sequencing.

Test for HRD With an Assay That Includes a Measure of Genomic Instability

Commercial assays can assess HRD as well as genomic instability supporting HRD determination.[4,15–26] Provided below is a list of commercial labs that offer testing for patients with aOC that includes measures of genomic instability. Testing typically takes up to 2 weeks to turnaround[15–26]

Laboratory	Assay name	Biomarkers assessed				Minimum sample requirement	Turnaround time	FDA-approved test
		BRCA1/2	Large-scale structural rearrangements					
Caris[15–18]	Molecular Intelligence® Comprehensive Tumor Profiling	✓	✓ LOH	✓ LST		FFPE tissue (block or 10 unstained slides; 4–6 needle biopsies preferred)	<14 days	
Foundation Medicine[19–21]	FoundationOne® CDx	✓	✓ LOH			FFPE tissue (block + 1 H&E slide or 10 unstained slides + 1 H&E slide)	~9 days	✓
Myriad[4,22,23]	MyChoice® CDx	✓	✓ LOH	✓ LST	✓ TAI	FFPE tissue (block or 8–20 unstained slides + 1 H&E slide)	~14 days or less[a]	✓
Tempus[24–26]	Tempus® HRD	✓	✓ LOH			FFPE tissue (block + 10–20 unstained slides for NGS + 1 optional H&E stained slide)	~7–10 days	

This information is intended as educational and is not intended as a complete list of available testing options. AstraZeneca is not responsible for any test provider and does not endorse any particular diagnostic test. The accuracy and results of diagnostic tests vary, and AstraZeneca shall have no liability arising from such testing. Information provided herein should in no way be considered a guarantee of coverage, reimbursement, or patient assistance. Providers should contact third-party laboratories for information on their patient assistance programs. While diagnostic testing may assist providers in identifying appropriate treatment for patients, the decision and action should be decided by a provider in consultation with the patient. All products are trademarks of their respective holders, all rights reserved.

Footnotes

[a] Turnaround time measured from the day the sample arrives at Myriad labs.

aOC, advanced ovarian cancer; *BRCA1/2*, BReast CAncer susceptibility gene 1/2; CDx, companion diagnostic; FDA, US Food and Drug Administration; FFPE, formalin-fixed paraffin-embedded; H&E, hematoxylin and eosin; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; LST, large–scale state transitions; TAI, telomeric allelic imbalance.

Interpreting and Reporting Biomarker Test Results

What HRD is[6,27]

HRD status can be determined by testing for:

- *BRCA1/2* mutations
- Genomic instability markers, including LOH, LST, and TAI

As LOH-only approaches can miss up to 8% of patients when compared to an LOH, TAI, and LST approach,[10,a] consider reflexive testing of negative LOH-only results as a more comprehensive approach to maximize identification of eligible patients.

What HRD is not[28–30]

Genomic instability used to determine HRD status is distinct from

- **TMB**
- **PD-1/PD-L1 expression**
- **MSI/MMR**

Genomic instability results in specific measurable genomic aberrations and serves as the "collateral damage" that can occur to the genome because of HRD.[8,11]

Footnotes

[a] Myriad MyChoice® (composite score of LOH, TAI, and LST) was compared to a %LOH-based assay to assess HRD status in archival tumor samples from patients with platinum-sensitive, relapsed advanced ovarian cancer (N=148). Patients with germline *BRCA*m were excluded from this analysis.[10]

BRCA1/2, BReast CAncer susceptibility gene 1/2; *BRCA*m, BReast CAncer susceptibility gene mutation; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; LST, large-scale state transitions; MMR, mismatch repair; MSI, microsatellite instability; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TAI, telomeric allelic imbalance; TMB, tumor mutational burden.

Considerations for Your Practice

Ensure all eligible patients with ovarian cancer receive a biomarker test as recommended by NCCN Guidelines and the 2024 SGO clinical practice statement[3,5]

- Discuss establishing a testing protocol with the multidisciplinary team at your institution[31]
- Consider performing somatic HRD testing in the absence of germline *BRCA1/2* mutations[3]
- Increase *BRCA* awareness; direct patients to online resources explaining the link between *BRCA* and ovarian cancer risk, and how *BRCA* status can help them make the most out of targeted treatment at beBRCAware
- Find major testing labs in your area which can perform biomarker testing
- Test reflexively and comprehensively for LOH, TAI, and LST[6,27]

Use the results from biomarker testing in clinical practice for:

- Predictive insights: HRD status can be used to drive treatment choice and develop a comprehensive treatment plan[8,32]
- Prognostic insights: *BRCA1/2* status can provide insights on the course of the disease[8,32]
- Hereditary risk insights: Germline mutations in *BRCA1/2* aid in familial risk assessment[33]

Explore Solutions

Find out how to address common challenges you may face by visiting our Testing Solutions page.

Find testing solutions →

BRCA1/2, BReast CAncer susceptibility gene 1/2; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; LST, large-scale state transitions; NCCN, National Comprehensive Cancer Network; SGO, Society of Gynecologic Oncology; TAI, telomeric allelic imbalance.

Helpful Resources

Check out these featured resources on biomarker testing in ovarian cancer.

Add your preferred resources to **My Favorites**—a personalized list of resources to download and share with your peers or patients.

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3:45 MIN

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The role of molecular testing in advanced ovarian cancer

Watch Dr. ElNaggar discuss the clinical utility of homologous recombination deficiency (HRD) and how testing for HRD at diagnosis can help identify appropriate treatment options in advanced ovarian cancer.

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12:45 MIN

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Leading the way: Approaches in biomarker testing for cancer

Watch Dana Clark, a genetic counselor, share her experience in standardizing biomarker testing in advanced ovarian cancer, involving pilot efforts, negotiating responsibilities, and implementing a user-friendly tracking

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