Lynparza®
olaparib
tablets 150 mg

What is HRD?

AstraZeneca

Please see below for Important Safety Information and links to complete Prescribing Information, including Medication Guide.

HRD Is the Inability to Accurately Repair Double-Strand DNA Breaks

HRD is the **inability to accurately repair** double-strand DNA breaks.

DNA double-strand breaks

Repair pathway

Defects in the HRR pathway lead to HRD, the inability to accurately repair double-strand DNA breaks

OFF in HRD — HRR — **HIGH FIDELITY:** Homologous recombination repair — *BRCA*

ON in HRD — NHEJ — **LOW FIDELITY:** Nonhomologous end joining

Mutations in *BRCA* and other HRR genes force the cell to rely on NHEJ, a less accurate repair pathway. Over time, DNA double-strand breaks can persist, leading to genomic instability and cell death.

BRCA, BReast CAncer gene; DNA, Deoxyribonucleic Acid; HRD, homologous recombination deficiency; HRR, homologous recombination repair; NHEJ, nonhomologous end joining.

O'Connor MJ. *Mol Cell.* 2015;60:547-560.

Please see below for Important Safety Information and links to complete Prescribing Information, including Medication Guide.

DNA Damage and Repair by the HRR Pathway

DNA damage is a constantly occurring event in **normal cells.**

The HRR pathway repairs **double-strand breaks** in DNA

DNA single-strand breaks

Repair pathway

DNA damage response — BER — Base excision repair

PARP enzymes bind to single-strand breaks

DNA single-strand breaks

Repair pathway

HRR genes include: *BRCA*1, *BRCA*2 — HRR — Homologous recombination repair

Cells rely on *BRCA* and other HRR genes for accurate repair of DNA double-strand breaks

DNA, Deoxyribonucleic Acid; *BRCA*, BReast CAncer gene; PARP, poly (ADP-ribose) polymerase.

O'Connor MJ. *Mol Cell.* 2015;60:547-560.

Please see below for Important Safety Information and links to complete Prescribing Information, including Medication Guide.

Germline and Somatic Mutations

Germline (inheritable) mutations	Somatic (acquired) mutations
Mutations present in germ cells[1]	No mutation in germ cells[1]
All cells in embryo contain mutation[1]	No mutation in embryo[1]
All cells in adult body contain mutation[1]	Mutation in somatic cells; only cells arising from mutated cell affected[1]
Reproductive cells carry mutations that can be passed down to offspring[1]	No reproductive cells carry mutation; cannot be passed down to offspring[1]
Identified by testing blood or tumor cells[2,*]	Identified by testing tumor cells[2]

Testing tumor tissue alone cannot distinguish between germline and somatic mutations.[2]

*Tumor tissue testing can identify germline and somatic mutations but cannot distinguish between them.[2]

1. Vijg J, et al. *Trends Mol Med.* 2023;29:530-540.
2. Capoluongo E, et al. *Semin Oncol.* 2017;44:187-197.

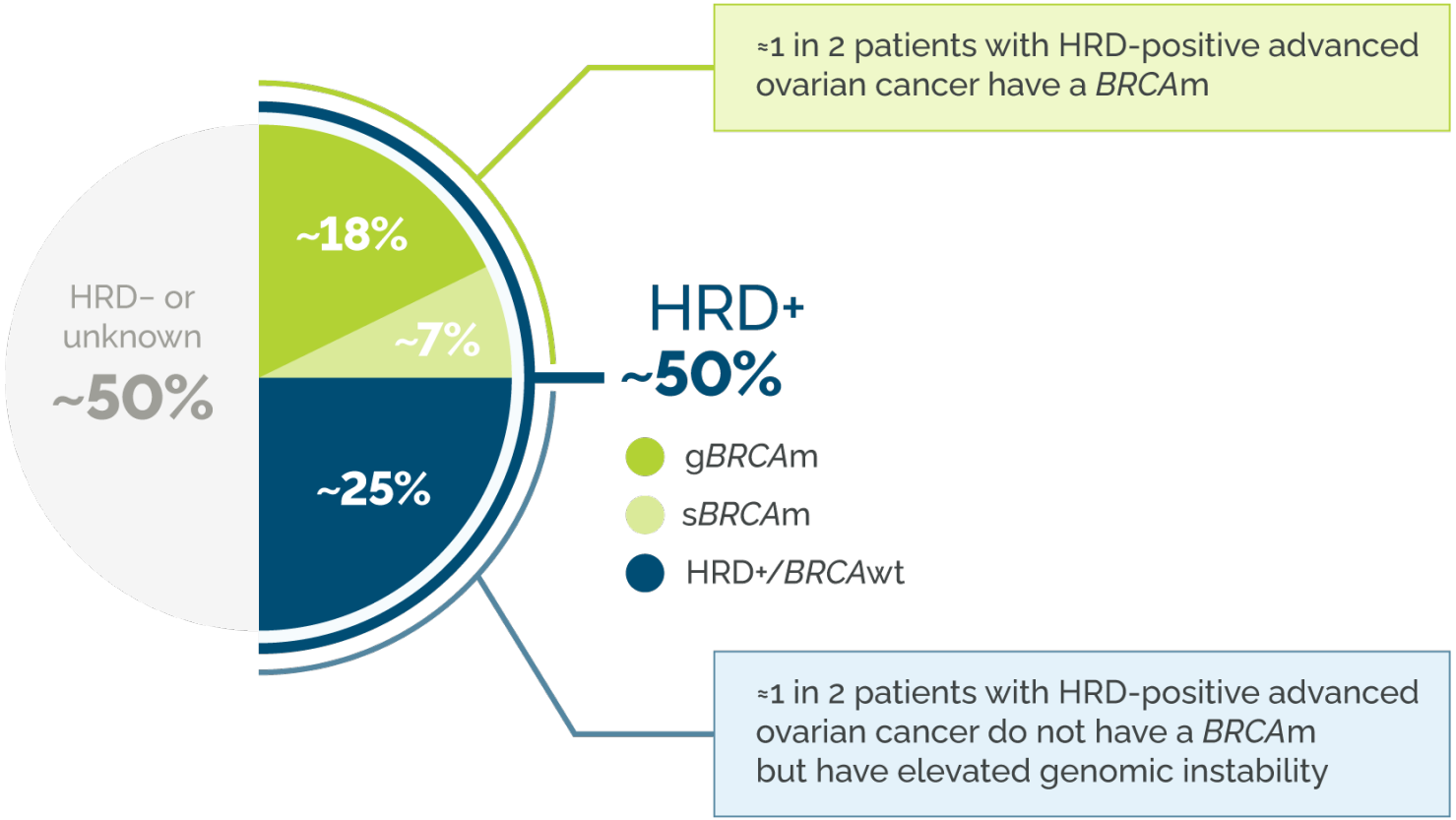
Please see below for Important Safety Information and links to complete Prescribing Information, including Medication Guide.

What Proportion of Advanced Ovarian Cancers Exhibit HRD?

About half of high-grade serous ovarian cancers exhibit HRD; half of these do not have *BRCA*m but have genomic instability.[1,2]

HR status can be characterized as

- ⊕ HRD-positive: HRD or HR deficiency
- ⊖ HRD-negative: HRP or HR proficiency



BRCA, BReast CAncer gene; *BRCA*m, *BRCA* mutation; *BRCA*wt, *BRCA* wild-type; g*BRCA*m, germline *BRCA* mutation; HR, homologous recombination; HRD, homologous recombination deficiency; HRD+, homologous recombination deficiency–positive; HRD–, homologous recombination deficiency–negative; HRP, homologous recombination proficiency; s*BRCA*m, somatic *BRCA* mutation.

1. Konstantinopoulos PA, et al. *Cancer Discov.* 2015;5:1137-1154.
2. Pennington KP, et al. *Clin Cancer Res.* 2014;20:764-775.

Please see below for Important Safety Information and links to complete Prescribing Information, including Medication Guide.

Proportion of Patients With Advanced Ovarian Cancer That Will Test Positive

Tumor sample (germline and somatic)[1-3]

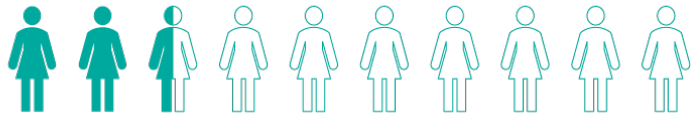
Tumor sample

HRD
(including t*BRCA*1 and t*BRCA*2 and/or genomic instability markers LOH, TAI, and LST)

≈50% of women

t*BRCA*

≈25% of women

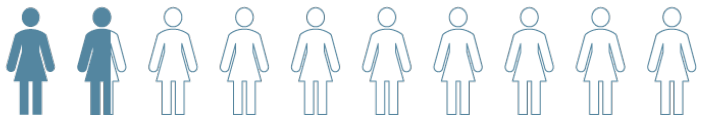


Blood sample (germline)[1-3]

Blood sample

***g*BRCA**

≈18% of women



Testing for HRD including genomic instability tests **identifies more patients** than testing for *BRCA* mutations alone.[1-3]

Testing only for *BRCA*m will **miss half of all patients with HRD**.[1,2]

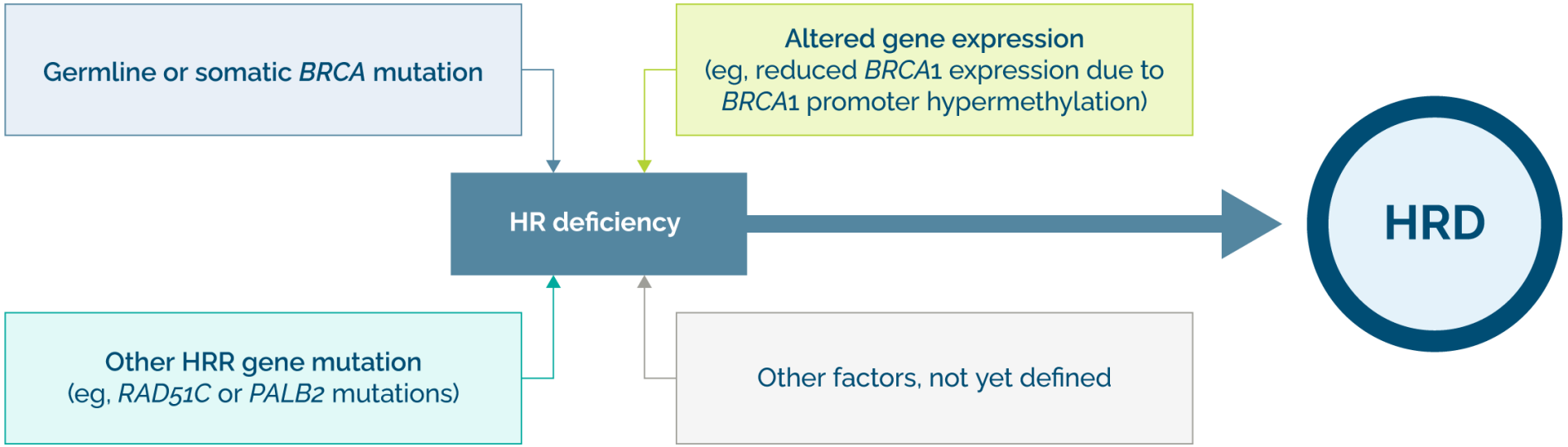
BRCA, BReast CAncer gene; *BRCA*m, *BRCA* mutation; g*BRCA*, germline *BRCA*; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; LST, large-scale transitions; TAI, telomeric allelic imbalance; t*BRCA*, tumor *BRCA*.

1. Konstantinopoulos PA, et al. *Cancer Discov*. 2015;5:1137-1154.
2. Pennington KP, et al. *Clin Cancer Res*. 2014;20:764-775.
3. Capoluongo E, et al. *Semin Oncol*. 2017;44:187-197.

Please see below for Important Safety Information and links to complete Prescribing Information, including Medication Guide.

Causes of HRD

Many different events can **impair the HRR pathway**. This leads to HRD.



***BRCA* mutations** are the archetypal cause of HRD.

***BRCA* mutations, mutations in other HRR genes, and other causes** can lead to **HRD**.

BRCA, BReast CAncer gene; HRD, homologous recombination deficiency; HRR, homologous recombination repair.

Miller RE, et al. *Ann Oncol.* 2020;31:1606-1622.

Please see below for Important Safety Information and links to complete Prescribing Information, including Medication Guide.

Detection of HRD

HRD can be detected by looking for the **causes** or the **effects** of HRD.[1]

HRR gene panel test[1]

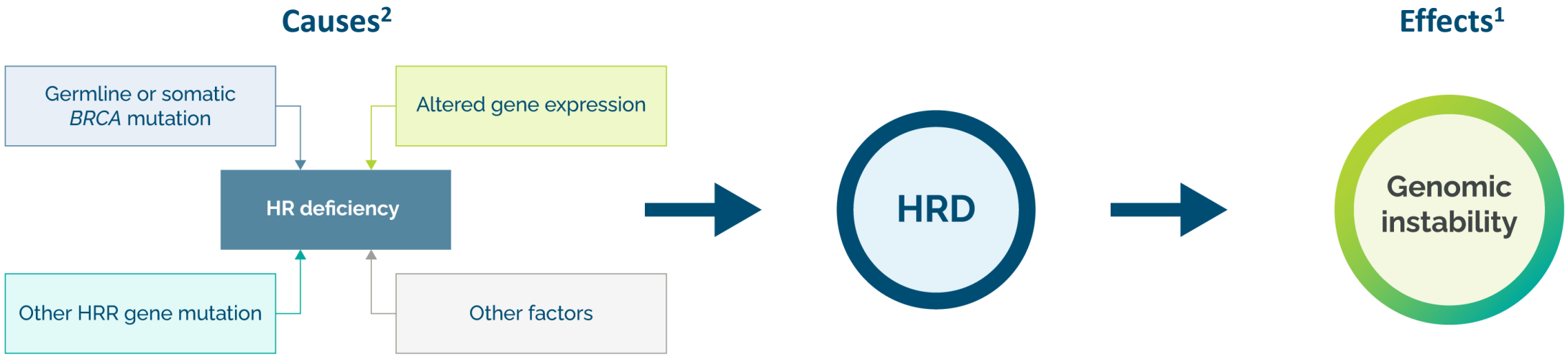
Look for the ***cause*** of HRR deficiency

Identify pathogenic mutations in HRR genes

HRD genomic instability test[1]

Look for the ***effect*** of HRR deficiency

Quantify genomic aberrations that are characteristic of homologous recombination deficiency; sometimes referred to as a genomic scar test

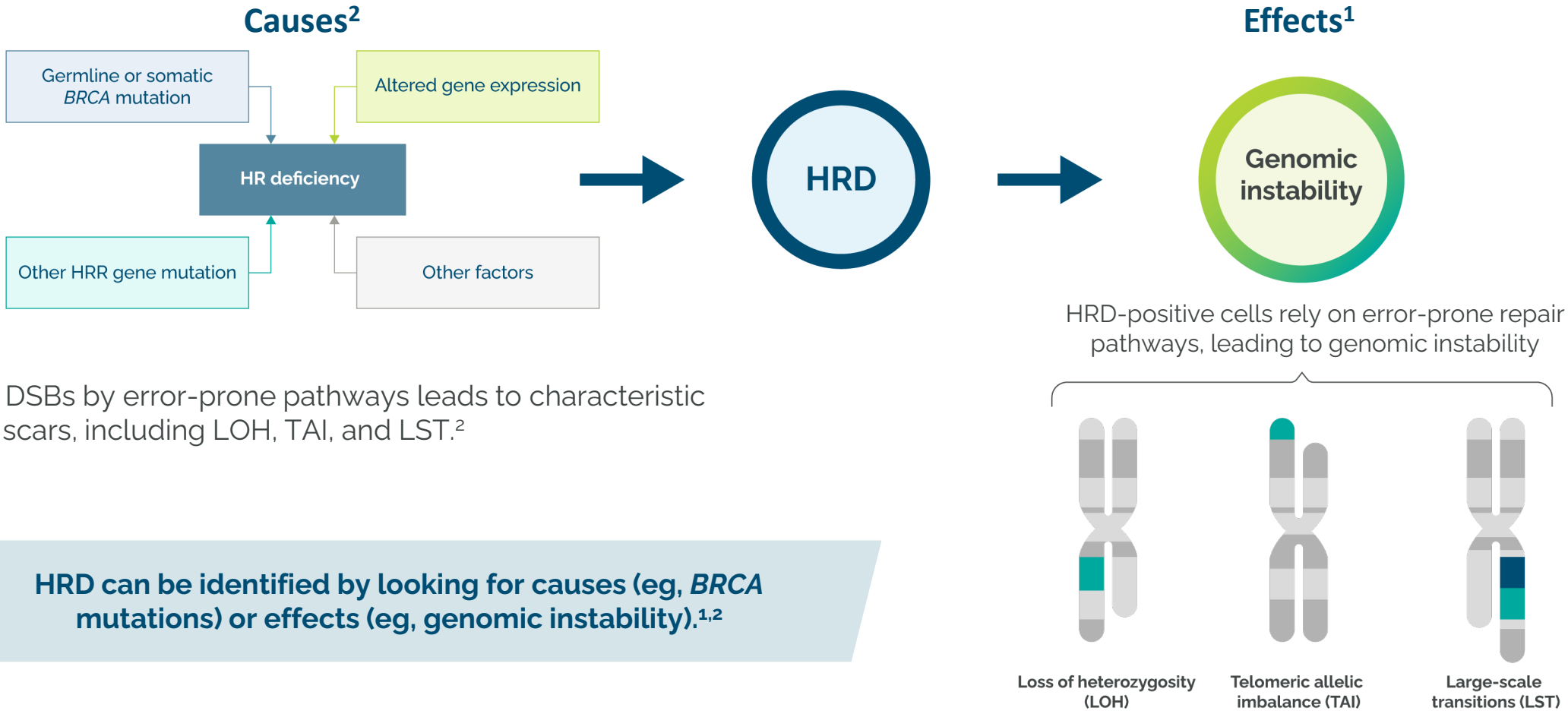


BRCA, BReast CAncer gene; HRD, homologous recombination deficiency; HRR, homologous recombination repair.

1. Stewart MD, et al. *Oncologist.* 2022;27:167-174.
2. Miller RE, et al. *Ann Oncol.* 2020;31:1606-1622.

Please see below for Important Safety Information and links to complete Prescribing Information, including Medication Guide.

Biomarkers of Genomic Instability



Repair of DSBs by error-prone pathways leads to characteristic genomic scars, including LOH, TAI, and LST.[2]

HRD can be identified by looking for causes (eg, *BRCA* mutations) or effects (eg, genomic instability).[1,2]

BRCA, BReast CAncer gene; DSB, double-strand break; HRD, homologous recombination deficiency; HRR, homologous recombination repair; LOH, loss of heterozygosity; LST, large-scale transitions; TAI, telomeric allelic imbalance.

1. Miller RE, et al. *Ann Oncol.* 2020;31:1606-1622.
2. Stewart MD, et al. *Oncologist.* 2022;27:167-174.

Please see below for Important Safety Information and links to complete Prescribing Information, including Medication Guide.

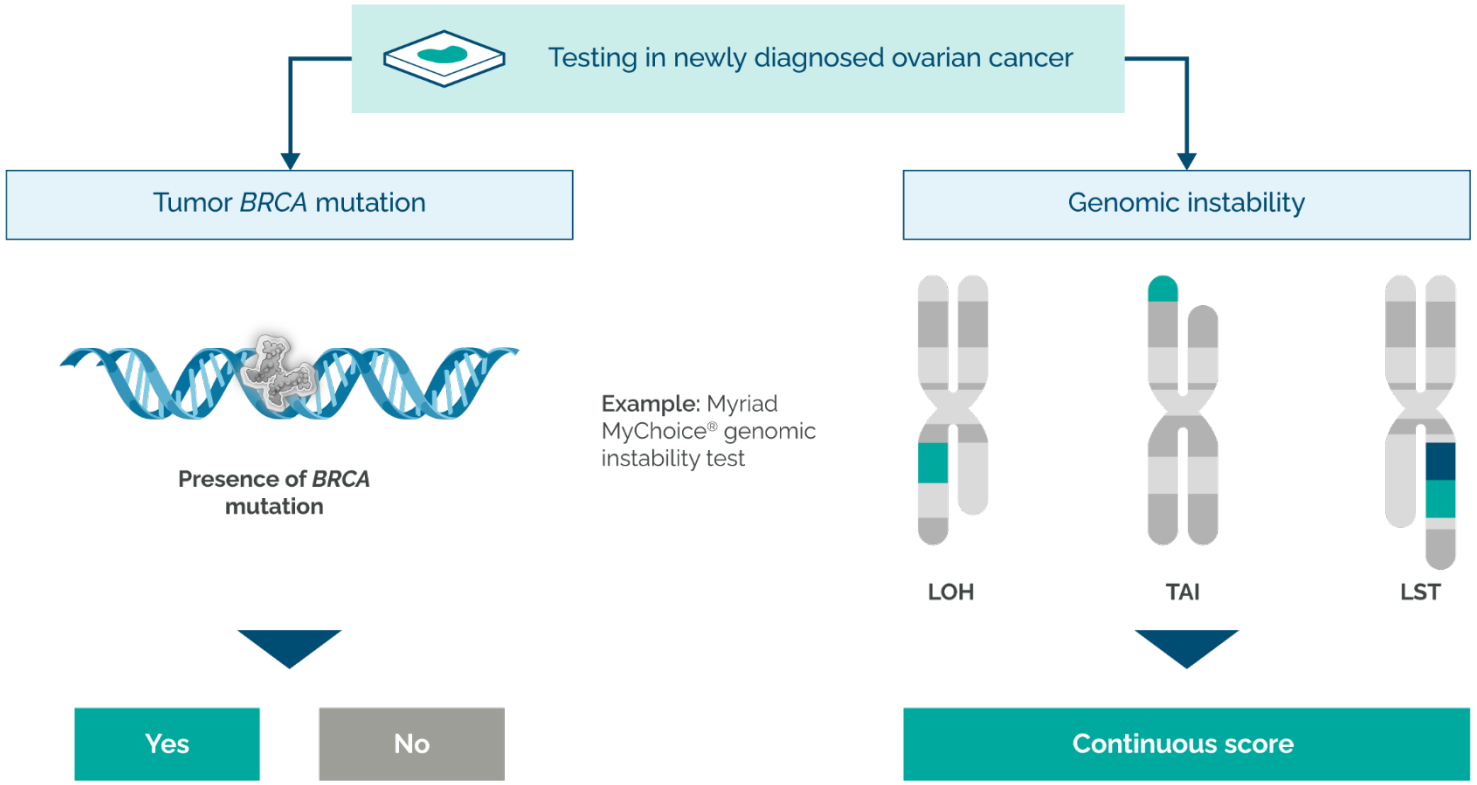
How Is a Positive HRD Test Defined?

Clinically validated methods to detect HRD in newly diagnosed ovarian cancer require ***BRCA*m testing and scoring of genomic instability.**[1]

Analysis is performed on DNA isolated from FFPE tumor tissue and assesses 2 factors to determine HRD status[1,2]:

- Tumor *BRCA* mutation
- Genomic instability

BRCA, BReast CAncer gene; *BRCA*m, *BRCA* mutation; FFPE, formalin-fixed, paraffin-embedded; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; LST, large-scale transitions; TAI, telomeric allelic imbalance.



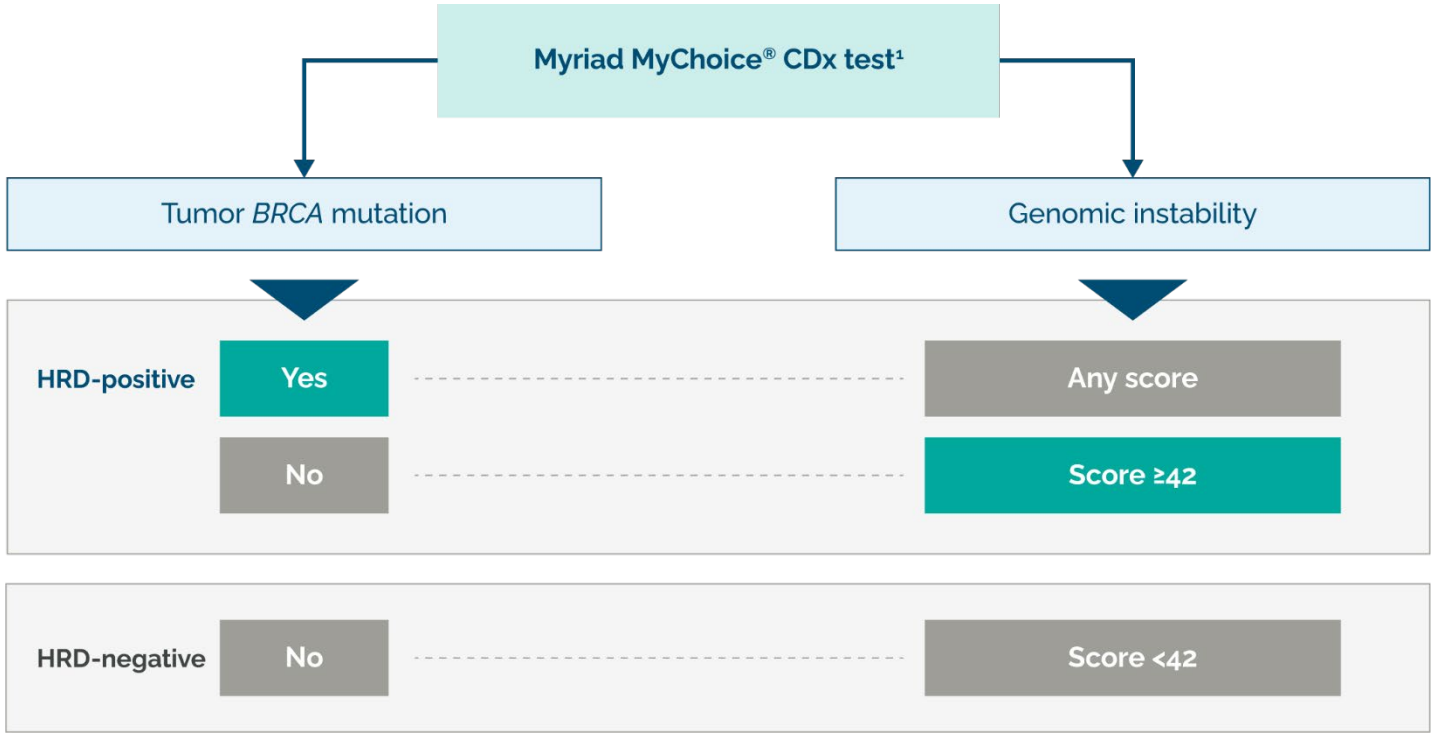
A positive HRD test is defined as either **the presence of a tumor *BRCA* mutation and/or a genomic instability score.**[1,2]

1. Miller RE, et al. *Ann Oncol*. 2020;31:1606-1622.
2. Myriad Genetic Laboratories, Inc. Myriad MyChoice® CDx Technical Information. Accessed June 30, 2025. https://s3.amazonaws.com/myriad-web/myChoiceCDx/downloads/myChoiceCDxTech.pdf

Please see below for Important Safety Information and links to complete Prescribing Information, including Medication Guide.

Example: Myriad MyChoice® CDx Test

For example, the Myriad MyChoice® CDx test defines patients as HRD-positive **if they have a *BRCA* mutation and/or a genomic instability score ≥42**.[1,2]



BRCA, BReast CAncer gene; CDx, companion diagnostic; HRD, homologous recombination deficiency.

The Myriad MyChoice® CDx test is **approved for use with LYNPARZA as a companion diagnostic**.[1]

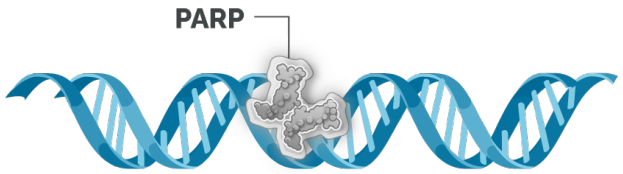
1. Myriad Genetic Laboratories, Inc. Myriad MyChoice® CDx Technical Information. Accessed June 30, 2025. https://s3.amazonaws.com/myriad-web/myChoiceCDx/downloads/myChoiceCDxTech.pdf
2. Ray-Coquard I, et al. *N Engl J Med*. 2019;381:2416-2428.

Please see below for Important Safety Information and links to complete Prescribing Information, including Medication Guide.

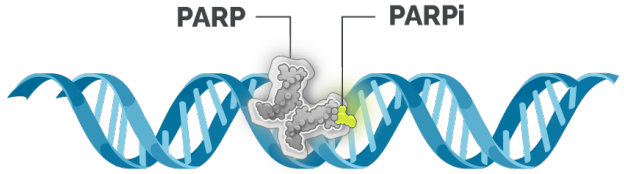
Tumors with HRD Are Sensitive to PARP Inhibition

PARP inhibitors disrupt the DNA repair process and potentially kill tumor cells.[1]

Cells accumulate DNA damage[1]



Tumor cells survive by repairing their damaged DNA via the PARP enzyme, among other cellular processes[1,2]



Disrupting the DNA-repair process with a PARP inhibitor may help drive tumor cell death[1]

HRD is associated with **increased sensitivity to PARPi maintenance therapy.**[3]

PARP inhibitors may drive **tumor cell death in tumors with HRD.**[1]

HRD, homologous recombination deficiency; HRR, homologous recombination repair; PARP, poly (ADP-ribose) polymerase; PARPi, poly (ADP-ribose) polymerase inhibitor.

1. O'Connor MJ. *Mol Cell.* 2015;60:547-560.
2. Murai J, et al. *Cancer Res.* 2012;72:5588-5599.
3. Ngoi NYL, et al. *ESMO Open.* 2021;6:100144.

Please see below for Important Safety Information and links to complete Prescribing Information, including Medication Guide.

Take-Home Messages

- The HRR pathway repairs double-strand breaks in DNA[1]
- Defects in the HRR pathway lead to HRD, the inability to accurately repair double-strand DNA breaks[1]
- About half of high-grade serous ovarian cancers exhibit HRD; half of these do not have *BRCA* mutations but have genomic instability[2,3]
- Testing only for *BRCA* mutations will miss half of all patients with HRD[2-4]
- *BRCA* mutations, mutations in other HRR genes, and other causes can lead to HRD[2]
- HRD can be identified by looking for causes (eg, *BRCA* mutations) or effects (eg, genomic instability)[2,6]
- PARP inhibitors may drive tumor cell death in tumors with HRD; HRD is associated with increased sensitivity to PARPi maintenance therapy[1,7]

BRCA, BReast CAncer gene; DNA, Deoxyribonucleic Acid; HRD, homologous recombination deficiency; HRR, homologous recombination repair; PARP, poly (ADP-ribose) polymerase.

1. O'Connor MJ. *Mol Cell.* 2015;60:547-560.
2. Miller RE, et al. *Ann Oncol.* 2020;31:1606-1622.
3. Konstantinopoulos PA, et al. *Cancer Discov.* 2015;5:1137-1154.
4. Pennington KP, et al. *Clin Cancer Res.* 2014;20:764-775.
5. Capoluongo E, et al. *Semin Oncol.* 2017;44:187-197.
6. Stewart MD, et al. *Oncologist.* 2022;27:167-174.
7. Ngoi NYL, et al. *ESMO Open.* 2021;6:100144.

Please see below for Important Safety Information and links to complete Prescribing Information, including Medication Guide.