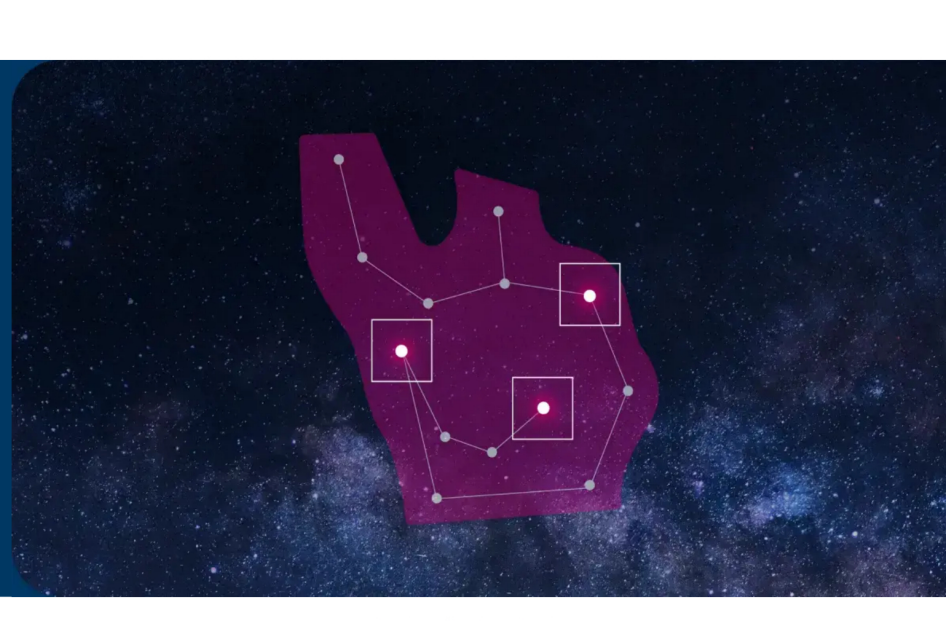


BRCA1/2 Mutations in Breast Cancer

Explore *BRCA1/2* mutation testing in breast cancer with guideline recommendations and actionable best practices.

Reading time: **20 min**

Jump to: Clinical Relevance · Testing Recommendations · Prevalence · Role of *BRCA1/2* · Sample Type Considerations · Diagnostic Assays · Interpreting & Reporting · Testing

Testing for Germline *BRCA1* and *BRCA2* Mutations Can Guide Treatment[1–3]

Mutations in *BRCA1* and *BRCA2* are associated with a high lifetime risk of developing breast cancer.[1] Testing for these mutations in eligible patients with breast cancer can inform preventative, prognostic and therapeutic decisions.[2,3]

BRCA1/2, BReast CAncer susceptibility gene 1/2.

BRCA1 and *BRCA2* Testing Recommendations Aim to Identify the Risk of Developing Breast Cancer and Inform Treatment[1]

Find additional recommendations in the NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate.[1]

Non-metastatic invasive breast cancer | Metastatic breast cancer

Why test

- To aid in systemic treatment decisions[2–4]
- To assess risk of recurrence[4]
- To assess familial risk for breast, ovarian, pancreatic and prostate cancer[1]

Whom to test

- All patients with TNBC upon diagnostic work-up[4]
- Certain patients[a] with HR+/HER2-negative invasive breast cancer upon diagnostic work-up[2,3]

How to test

- Commercial assays, including multigene panels, are available for germline testing of *BRCA1* and *BRCA2* mutations[5,b]
- Perform germline testing on blood or saliva/buccal swabs[5]
- Use the FDA-approved BRACAnalysis CDx®[6]

American Society of Clinical Oncology and the Society for Surgical Oncology (ASCO-SSO) joint germline testing guidelines recommend *BRCA1/2* testing in anyone[7]:

- With breast cancer ≤65 years of age
- Who may be eligible for a PARP inhibitor (regardless of family history)
- With a personal history of breast cancer who are without active disease if the result will inform personal risk management or family risk assessment

The American Society of Breast Surgeons (ASBrS) recommend testing anyone with a personal history of breast cancer as well as patients who don't have a history of disease but meet NCCN Guidelines® criteria[8]

Footnotes

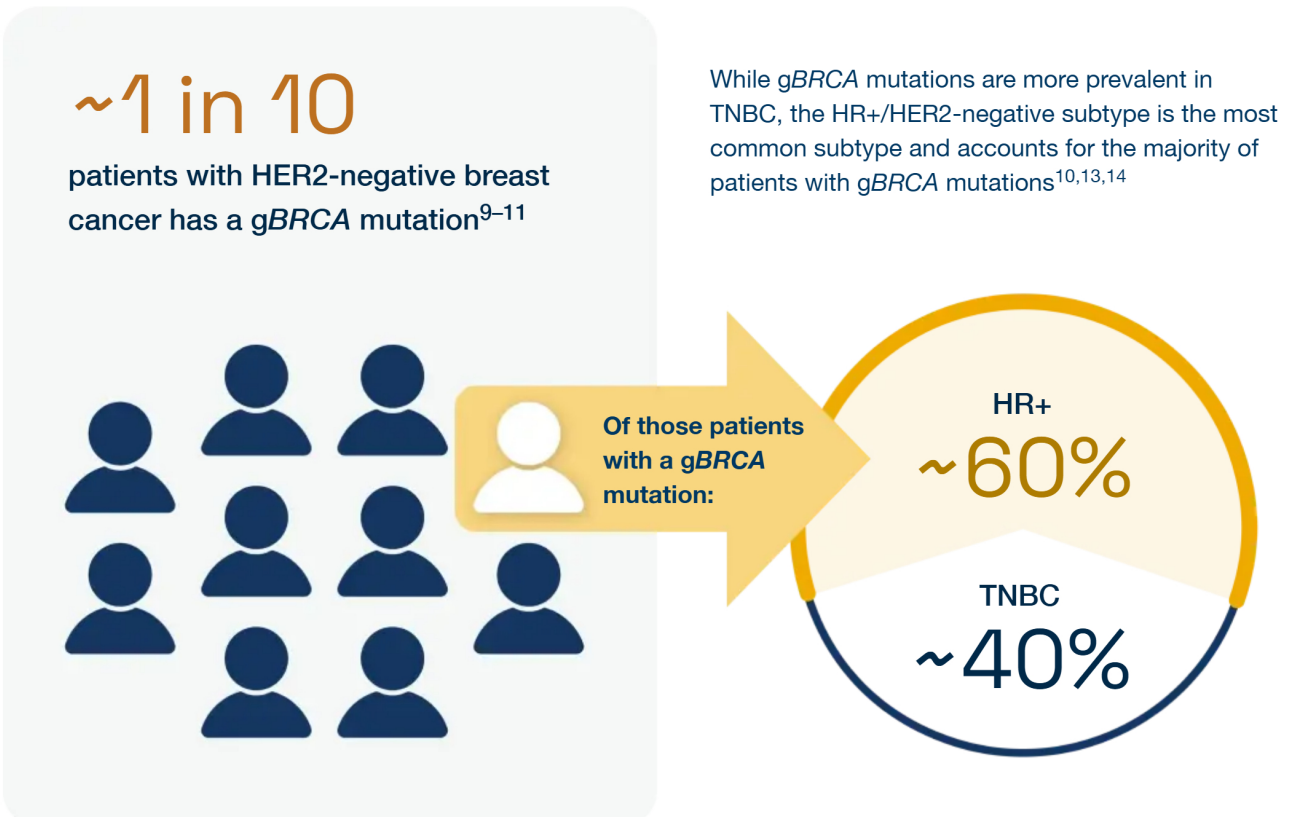
[a] Four or more positive pathologically confirmed lymph nodes if treated with adjuvant chemotherapy; clinical and pathologic stage (CPS) + estrogen receptor status and histologic grade (EG) score of 3 or higher and absence of complete pathologic response following treatment with neoadjuvant chemotherapy.[1] [b] If using a commercial assay for testing, check the manufacturer's sample requirements.

ASCO, American Society of Clinical Oncology; ASBrS, American Society of Breast Surgeons; *BRCA1/2*, BReast CAncer susceptibility gene 1/2; CDx, companion diagnostic; CPS, clinical and pathologic stage; EG, histologic grade; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NCCN, National Comprehensive Cancer Network; PARP, poly-ADP ribose polymerase; SSO, Society for Surgical Oncology; TNBC, triple-negative breast cancer.

Around 1 in 10 Patients With HER2-Negative Breast Cancer Have a g*BRCA* Mutation, Highlighting Implications for Treatment and Genetic Counseling[9–11]

HR+/HER2-negative breast cancer accounts for around 60% of patients with g*BRCA* mutations[9–11]

BRCA2 mutations are more common than *BRCA1* mutations in HR+/HER2-negative breast cancer[12]



~1 in 10

patients with HER2-negative breast cancer has a g*BRCA* mutation[9–11]

While g*BRCA* mutations are more prevalent in TNBC, the HR+/HER2-negative subtype is the most common subtype and accounts for the majority of patients with g*BRCA* mutations[10,13,14]

BRCA1/2, BReast CAncer susceptibility gene 1/2; g*BRCA*, germline BReast CAncer susceptibility gene; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; TNBC, triple-negative breast cancer.

BRCA1/2 Mutations Can Eventually Lead to Breast Cancer Development[15]

Both BRCA and PARP proteins are important for repairing DNA. Mutations in *BRCA* prevent the proper repair of DNA and may eventually lead to breast cancer development.[15]

FOR HCPS

Role of *BRCA1/2* mutations in breast cancer

Learn how BReast CAncer susceptibility gene (*BRCA*) mutations may play a role in breast cancer development and understand the role of poly (ADP-ribose) polymerase (PARP).

1:22 MIN

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BRCA1/2, BReast CAncer susceptibility gene 1/2; DNA, deoxyribonucleic acid; PARP, poly (ADP-ribose) polymerase.

Consider Sample Type and *BRCA* Mutation Type to Inform Outcomes[16]

Germline testing can be performed on blood or saliva/buccal swabs

BRCA mutation type	Sample type	Clinical relevance	Limitations
Germline	Blood, saliva, or buccal swab	May inform familial risk, prognosis, and treatment	Saliva and buccal swab samples do not identify patients with somatic mutations[16,17]

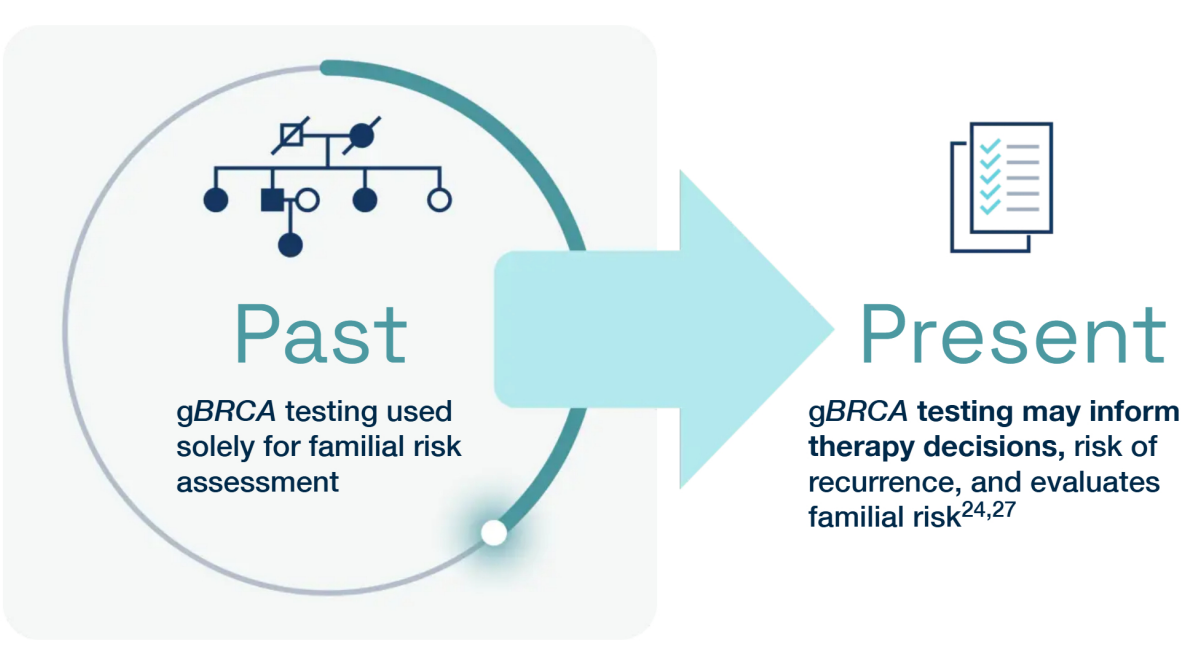
Testing tumor tissue and ctDNA does not currently distinguish between somatic and germline mutations

BRCA mutation type	Sample type	Clinical relevance	Limitations
Somatic	Tumor tissue	Determines total mutation status (somatic and germline)[18]	• Samples can be heterogeneous, containing both malignant and normal cells[18] • Does not distinguish between somatic and germline mutations without analyzing non-tumor samples[19]
	Blood (plasma ctDNA)	Use to support tissue testing or when tumor tissue is unavailable[20]	• Mutation profiling is dependent on tumor shedding[21] • Does not distinguish between somatic and germline mutations without confirmatory testing[22,23]

Find best practice to address sample limitations.

Browse Testing Solutions

g*BRCA1/2* testing may aid your clinical approach: It is no longer just for familial risk assessment[24–27]



Past
g*BRCA* testing used solely for familial risk assessment
Present
g*BRCA* testing may inform therapy decisions, risk of recurrence, and evaluates familial risk[24,27]

BRCA1/2, BReast CAncer susceptibility gene 1/2; ctDNA, circulating tumor DNA; g*BRCA1/2*, germline BReast CAncer susceptibility gene 1/2.

Diagnostic Assays Screen for and Identify *BRCA1/2* Mutations

Testing should include full gene sequencing, deletion/duplication analysis, and detection of known pathogenic/likely pathogenic variants in a Clinical Laboratory Improvement Amendments (CLIA)-certified and/or College of American Pathologists (CAP)-accredited genetic testing laboratory.[28] Sanger sequencing is considered the gold standard for detection of genetic mutations.[29]

Labs offering g*BRCA1/2* testing have turnaround times of around 2 weeks[a]

FDA-approved tests[30]

Laboratory	Test name	Sample requirements	Turnaround time (days)
Myriad Genetics	BRACAnalysis CDx®[31,32]	Blood: ~7 mL	≤14
Invitae	Common Hereditary Cancers Panel[33–35]	Blood (preferred) 3 mL, saliva, buccal swabs, or DNA (5 μg)	10–21

Non-FDA-approved tests

Laboratory	Test name	Sample requirements	Turnaround time (days)
Ambry Genetics	*BRCA1* and *BRCA2*[36,37]	Blood: 3–4 cc, Saliva: 1 mL, 2 buccal swabs, 5 μg DNA	6–10
	CancerNext®[36,38]		14–21
GeneDx	*BRCA1/2* Sequencing and Del/ Dup Analysis[39]	Blood: 2–5 mL, buccal swabs	8–10
	Comprehensive Common Cancer Panel[40]		14
Invitae	*BRCA1* and *BRCA2* STAT Panel[41]	Blood (preferred) 3 mL, saliva	5–12
Myriad Genetics	MyRisk®[42–44]	Blood, saliva	7–14

[a] 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.

BRCA1/2, BReast CAncer susceptibility gene 1/2; CAP, College of American Pathologists; CDx, companion diagnostic; CLIA, Clinical Laboratory Improvement Amendments; DNA, deoxyribonucleic acid; FDA, US Food and Drug Administration.

Comprehensive Interpretation and Reporting of Germline *BRCA1/2* Test Results is Critical for Informing Treatment Decisions[18]

Detecting *BRCA1/2* sequence variations may require more than one method

Sequence variations in *BRCA1* and *BRCA2* fall into three broad categories[18]:

- Single-nucleotide changes
- Small insertion or deletion events (indels)
- Large genomic rearrangements (LGRs)

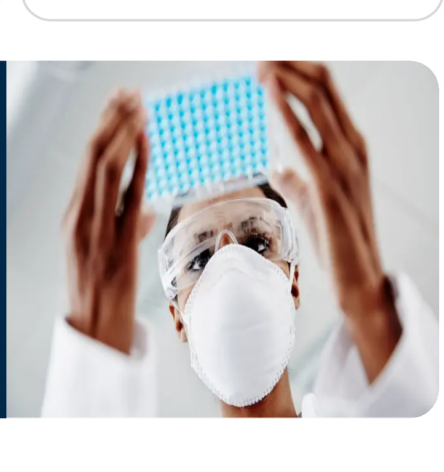
Single-nucleotide changes and indels can be detected by direct Sanger sequencing or NGS[18]

LGRs cannot be detected by direct Sanger sequencing

- Instead, alternative polymerase chain reaction (PCR)-based techniques (e.g. quantitative PCR, multiplex ligation-dependent probe amplification) are required[18]

Whether performing in-house testing or sending to a testing lab, ensure the methodology is comprehensive and includes LGRs and indels.[18]

Find a Testing Lab



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***BRCA* genes can harbor many different types of mutation; therefore, test results may not be a straightforward positive or negative[18,45]**

Positive

Indicates:

- A known actionable mutation has been identified, and the patient is *BRCA* mutation-positive[45]

May also be called:

- Pathogenic, likely pathogenic, deleterious, suspected deleterious[46,47]

Negative

Indicates:

- No mutation was detected by the testing methodology[48]

Variant of unknown significance (VUS)

Indicates:

- A *BRCA* variant was detected, but the specific variant has not been previously classified as harmful or harmless; the variant has an unknown effect on protein function and risk of disease.[18,45,49] While not clinically actionable at the time of the test, the reporting laboratory may follow up on the clinical relevance of VUS if more information becomes available over time[47]

Treatment decisions should not be made based on a VUS result.

May also be called:

- Inconclusive or variant of uncertain significance[45,46,50]

Benign variant

Indicates:

- A *BRCA* sequence variant was detected, but the variant is nonpathogenic; treat as *BRCA* mutation-negative[7,47]

May also be called:

- Benign variant, likely benign, favor polymorphism[46,47]

BRCA1/2, BReast CAncer susceptibility gene 1/2; indels, small insertion or deletion events; LGR, large genomic rearrangement; NGS, next-generation sequencing; PCR, polymerase chain reaction; VUS, variant of unknown significance.

Solutions to *BRCA1/2* Testing Challenges Focus on Tissue Sample Quality and Standardization[51,52]

Knowing which biomarkers to test for is valuable, but it's equally important to anticipate common challenges that providers may experience during the testing phase, including:

- **Tissue sample quality and handling[51,52]**
  - Factors to consider include age of the sample, new vs. archival tissue, DNA yield, tumor content, and primary vs. metastatic site[53]
- **The need for a standardized testing workflow[52]**
- **The need for leadership in the management of the testing program[51,54]**

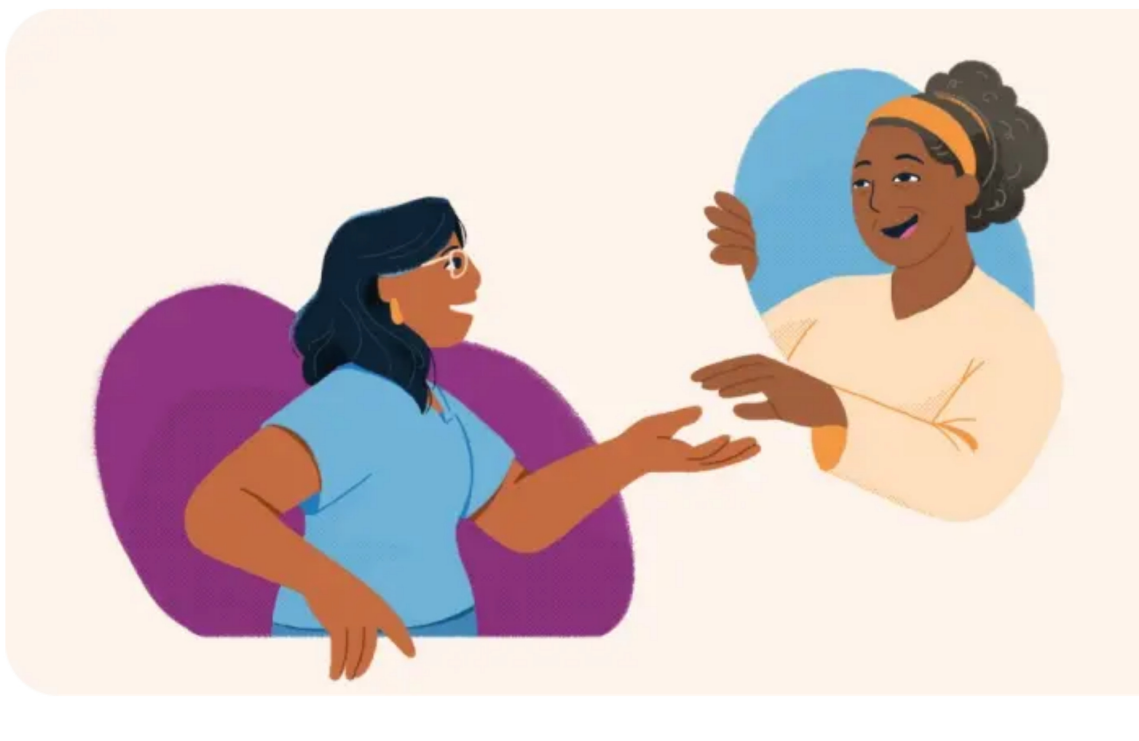
Find solutions to common challenges you may face during biomarker testing.

Browse Testing Solutions

Gene&i

Many eligible patients with breast cancer may be missing out on genetic testing. Gene&i.com has been developed in collaboration with experts to break through testing barriers, with educational resources in English and Spanish.

Connect with a Precision Medicine team member or view clinical conversation aids to help cover essential information about genetic testing with your patients, alongside video animations to bring your discussions to life.



FOR PATIENTS

Gene&i: What is genetic testing?

Share this video with patients with breast cancer covering how genetic mutations can play a pivotal role in breast cancer care and what they may mean for patients.

2:15 MIN

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FOR PATIENTS

Gene&i: Why is genetic testing important in breast

Share this video with patients with breast cancer to increase understanding of what genetic testing involves and how they may benefit from the results.

1:54 MIN

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FOR PATIENTS

Gene&i: Making sense of risk in breast cancer

Share this video with patients with breast cancer to help make sense of risk in the context of genetic testing in breast cancer and how best to manage risk status.

1:46 MIN

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FOR PATIENTS

Gene&i: Genetic testing in the breast cancer journey

Share this video with patients with breast cancer to inform them of the laws surrounding their genetic data and turnaround times (TAT) for genetic testing results.

2:39 MIN

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Considerations for Your Practice

Implement germline *BRCA1/2* testing for appropriate patients with breast cancer, considering guidance from NCCN®, ASCO-SSO and ASBrS.

- View a suite of educational resources that facilitate genetic testing conversations between you and patients with breast cancer at Gene&i.com

Looking for a genetic counselor?

Find a genetic counselor

Learn how genetic counseling can be integrated into clinical practice

ASCO, American Society of Clinical Oncology; ASBrS, American Society of Breast Surgeons; *BRCA1/2*, BReast CAncer susceptibility gene 1/2; NCCN, National Comprehensive Cancer Network; SSO, Society for Surgical Oncology.

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Helpful Resources

Check out these featured resources on *BRCA* biomarker testing in breast cancer.

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

View My Favorites

beBRCAware

FOR PATIENTS

Be *BRCA*-aware patient website

Share this website with your patients to help them understand how BReast CAncer susceptibility gene (*BRCA*) status can help them make the most out of their treatment.

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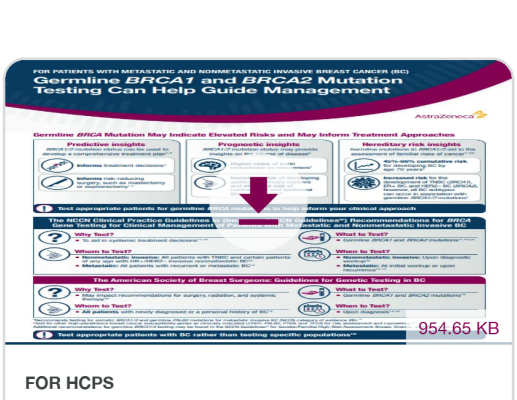

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FOR HCPS

Testing for germline *BRCA* mutations in metastatic BReast

Learn how germline BReast CAncer susceptibility gene (*BRCA*) mutation testing for all patients with recurrent or metastatic breast cancer can help inform treatment decisions.

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Connect with the Precision Medicine Team for actionable support with *BRCA1/2* testing in breast cancer.

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BRCA1/2, BReast CAncer susceptibility gene 1/2.

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