WOMEN'S HEALTH & GENETICS

Hereditary Breast and Ovarian Cancer

Clinical guide: Genes, cancers and testing options

labcorp

About hereditary breast and ovarian cancer syndrome

Hereditary cancer syndromes are inherited disorders in which the risk to develop cancer is higher than the general population, and where cancer usually occurs at an earlier age than expected. Hereditary cancer syndromes are caused by inherited mutations (pathogenic variants) in certain genes and account for approximately 5% to 10% of all cancers.[1] In hereditary breast and ovarian cancer syndrome (HBOC), there is a higher risk of developing breast and ovarian cancer, as well as other cancers such as pancreatic cancer and melanoma.[2]

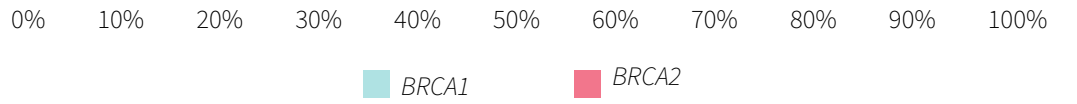
What is a pathogenic variant?

Pathogenic variant is defined as a genetic change that increases an individual's susceptibility or predisposition to a certain disease or disorder.[4]

- Pathogenic variants or mutations in the *BRCA1* and *BRCA2* genes account for the majority of families with HBOC[2]
- Although mutations in *BRCA1* and *BRCA2* are the most common cause for HBOC, other genes have been associated with HBOC[2,3]

Estimated lifetime cancer risk for individuals with *BRCA1* and *BRCA2* mutations[5]

Cancer type (General population risk %)	Range of risk
Female breast cancer (12%)	
Ovarian cancer (1-2%)	
Male breast cancer (0.1%)	
Prostate cancer (6% through age 69)	
Pancreatic cancer (0.5%)	



Adapted from Petrucelli N, Daly MB, Pal T, et al. *BRCA1*- and *BRCA2*-Associated Hereditary breast and Ovarian Cancer. *Gene Reviews.*

Genetic testing to identify mutations can be beneficial to patients and their familes[2,3]

- Confirms that a patient has a predisposition to cancer
- Allows for personalized medical management related to a patient's risks for cancer
- Promotes targeted genetic testing in family members

According to guidelines, which patients should be considered for genetic assessment?

Current guidelines from the National Comprehensive Cancer Network (NCCN) and the American College of Obstetricians and Gynecologists (ACOG)* state that HBOC should be suspected and genetic testing considered in patients with a personal and/or family history of cancer and who meet certain criteria.[2,3] While most cancers are sporadic, there are clues to look for in the patient's personal and family histories that may indicate your patient is at risk.

Young	• Earlier age of cancer diagnosis than is typical • Breast at ≤50 years of age
Rare	• Examples include ovarian cancer, male breast cancer and pancreatic cancer in blood relatives
Bilateral	• Same cancer occurring in both of a pair of organs such as the breasts
Multiple	• More than one type of cancer or multiple primary cancers in a single person • Same or related cancer in two or more family members related by blood • Multiple generations affected
Familial Mutation	• A known mutation in a relative
Ethnic Predisposition	• Ashkenazi Jewish heritage

*Complete guidelines may be found at www.nccn.org and www.ACOG.org

Genetic counseling and the patient

Obtaining the patient's personal and family history is important to identify patients who meet testing criteria as outlined by NCCN and ACOG. Utilizing genetic counseling services can aid in determining who should be tested as well as provide patients with information to help them determine if testing is right for them.

Additionally, genetic counseling is a key component of a coordinated patient care program. The genetic counseling services provided by Labcorp support patients and healthcare providers in many ways:

- Identifying hereditary cancer risks
- Explaining appropriate genetic testing options
- Discussing the implications of test results
- Helping patients make thoughtful genetic healthcare decisions

To learn more about the genetic counseling services offered by Labcorp, please call **855-GC CALLS (855-422-2557)** or visit **womenshealth.labcorp.com/genetic-counseling.**

Choosing the type of testing that is most appropriate

When determining which test is best for a particular patient, there are some things to consider for both the patient and your practice.

The patient's personal and family history

Patient and provider's comfort with uncertain results

Availability of screening and management guidelines for gene mutation carriers

Need assistance with testing?

Laboratory-focused genetic counselors are available to offer healthcare providers support in test selection and ordering at **800-345-GENE (4363).**

Testing options

BRCAssure *BRCA1* and *BRCA2* Comprehensive Analysis	VistaSeq Multi-gene Panels	Ashkenazi Jewish Profile for *BRCA1* and *BRCA2*	Targeted Analysis
A single test that consists of full gene sequencing along with deletion and duplication analysis of both the *BRCA1* and *BRCA2* genes. Patients with a personal or family history suggestive of HBOC may benefit from comprehensive analysis.	Multi-gene testing is often recommended when the personal and family history is not specific to a single inherited cancer syndrome or when more than one gene can explain a hereditary cancer syndrome. Testing includes full gene sequencing and deletion and duplication analysis for most genes.	Assesses three known pathogenic variants that occur in high frequency in persons of Ashkenazi Jewish ancestry: *BRCA1* (c.68_69delAG and c.5266dupC) and *BRCA2* (c.5946delT).	Testing that assesses the patient only for the presence of a known familial variant. Patients with a family member that has tested positive for a pathogenic variant may benefit from this testing. A lab report identifying the familial variant is required to perform this testing.

Gene penetrance, cancer risk and medical management

Penetrance refers to the likelihood that a clinical condition will occur when a particular genotype is present.[4] With hereditary cancer, penetrance refers to the risk for developing cancer. While BRCAssure tests for two high-penetrance (high-risk) genes (*BRCA1* and *BRCA2*), the VistaSeq Hereditary Cancer panels include genes with high, moderate, and low-penetrance.

- **High-penetrance (high-risk)** genes are associated with a greater than five-fold increased risk of developing cancer relative to someone in the general population.[6] NCCN guidelines recommend more frequent screening and other medical management strategies for individuals with pathogenic variants in high-penetrance breast cancer genes such as *BRCA1*, *BRCA2* and *TP53*[3]
- **Moderate-penetrance (moderate-risk)** genes are associated with a two- to five-fold increased risk of developing cancer relative to someone in the general population.[6] NCCN guidelines recommend more frequent screening for patients with pathogenic variants in a moderate-risk gene. Other medical management strategies may or may not be recommended depending on the patient's family history. Examples of moderate-penetrance breast cancer genes include *ATM* and *CHEK2*[6]
- **Low-penetrance (low-risk)** breast cancer genes such as *MRE11A* and *RAD50* currently have insufficient evidence for NCCN to make any recommendations for screening or medical management[3]

Please note: Gene penetrance will vary by cancer type. A gene that may be highly penetrant for one cancer may have a lower penetrance for another cancer. As current knowledge evolves, the penetrance for genes which have limited data about risk for cancer may change

Genetic testing results

Genetic testing results are reported as negative, variant of uncertain significance (VUS), or positive.

Negative	VUS	Positive
No genetic variant was found A negative result means that the patient did not inherit a mutation in the genes tested. It is possible that a mutation in a different gene may explain the cancer seen in the patient and/or her family. Additionally, the genetic reason for a predisposition to cancer may not be identifiable using current testing methods. A negative result must be interpreted in the context of the patient's personal and family history.	**A variant of uncertain significance (VUS) was found** A VUS means that a variant has been found but it is uncertain if that change is associated with increased risk for cancer. Because the impact of these variants is currently unknown, clinical management decisions (e.g., surgical intervention or chemoprevention) should not be made based on the VUS result.	**A pathogenic or likely pathogenic variant was found** A pathogenic or likely pathogenic mutation was found in a gene that causes increased risk to develop cancers. Based on a positive result in a gene associated with HBOC, the NCCN recommends increased breast cancer screening, patient discussions regarding medical management options (e.g., risk-reducing surgeries), and genetic testing of at-risk adult relatives.[3,5]

Genetic counseling is recommended to help patients understand the implications of genetic test results.[1]

Variant classification and data sharing

Variant classification for hereditary cancer testing at Labcorp follows the guidelines set forth by the American College of Medical Genetics and Genomics (ACMG)[7] in conjunction with our in-house developed method of assessment to assure a systematic, traceable and thorough review of all available evidence supporting classification outcome. All variants, including pathogenic variants and VUS, are classified by our team of variant scientists using many lines of weighted evidence, including:

- Type of variant and genetic mechanism of disease
- Variant frequencies in population databases
- Published, peer-reviewed literature
- Functional prediction algorithms
- Collaboration with other genetic testing institutions, including variant databases such as ClinVar

As part of our commitment to the highest quality in variant classification, Labcorp participates in data sharing through ClinVar, a public database of DNA variants identified in human samples. ClinGen[8], a public genomic resource that has the goal of defining the clinical relevance of genes and variants for clinical use, is partnered with ClinVar. Labcorp meets ClinGen's Minimum Requirements for Data Sharing to Support Quality Assurance. In fact, in the majority of our submissions, Labcorp exceeds the minimum by including evidence submitted to support our interpretation, and we actively participate in an interlaboratory discrepancy resolution process.[9]

All variants undergo rigorous classification using both new and emerging data. All variants, regardless of classification, are reevaluated on a scheduled time frame following the last assessment. In addition, variant reevaluations are also undertaken upon client request.

Your partner for HBOC genetic testing

Providing medical care can be challenging in today's healthcare environment. Labcorp can be your partner in predisposition genetic testing for HBOC by providing quality services and patient-centric testing options supported by over 30 years of experience.

For additional information on genetic testing and services, please visit **womenshealth.labcorp.com** call client services at **800-345-GENE (4363).**

References
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We provide the scientific expertise you need and the customer experience patients want.

Rapid results
Samples have a typical turnaround time of three weeks after arrival at our lab.

Extensive managed care contracts
Help patients maximize their benefits. Where applicable, Labcorp can initiate prior authorization for hereditary cancer testing with or without a specimen.

Convenient blood draws
We have a nationwide network of patient service centers, allowing for convenient access to sample collection. Visit labcorp.com to find your nearest location.

Confirmatory testing for direct to consumer results
Our hereditary cancer portfolio provides the testing options needed to confirm patient results from direct to consumer genetics laboratories as appropriate.

Women's health and wellness
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