A positive BRCA1 result is associated with the following cancer risks:

- **Lifetime high risk:** Up to 87% female breast; Up to 63% ovarian; 1-2% male breast
- **Lifetime increased risk:** Pancreatic; prostate

### Variant details

The BRCA1 c.5497G>A (p.Val1833Met) variant is associated with HBOC (Hereditary Breast and Ovarian Cancer Syndrome). This missense variant is predicted to disrupt normal gene function. It has been reported in ClinVar and in the literature. Functional studies suggest this variant may disrupt normal gene function. Based on LabCorp’s in-house variant classification protocol and in accord with the American College of Medical Genetics’ guidelines, this variant has been classified as likely pathogenic and is associated with an increased risk for hereditary breast and ovarian cancer.

### Gene summary

BRCA1 and BRCA2 (OMIM 600185) are tumor suppressor genes that play a critical role in normal DNA repair, cell cycle control, and genomic stability. Pathogenic variants in these genes are associated with familial cancers, including breast, ovarian, pancreatic, prostate, and melanoma.
**ADDITIONAL CLINICAL INFORMATION**

**NCCN Guidelines**

When BRCA1 and BRCA2 results are negative, additional testing may be helpful for some patients with breast, ovarian, and pancreatic cancer. Guidelines from the National Comprehensive Cancer Network® (NCCN®) recommend considering germline genetic testing for high-penetrance breast and/or ovarian cancer genes (including, but not limited to, BRCA1/2, CDH1, PALB2, PTEN, and TP53) in patients with any of the criteria in the table below. To discuss comprehensive genetic testing for breast, ovarian, and pancreatic cancer genes, an Integrated Genetics’ Genetic Coordinator is available at 800-345-4363.

<table>
<thead>
<tr>
<th>Clinical Indication</th>
<th>Variant Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer diagnosed ≤ age 45</td>
<td>Ovarian cancer at any age</td>
</tr>
<tr>
<td>Breast cancer diagnosed age 46-50 with ≥1 close relative with breast, ovarian, pancreatic, or high-grade prostate cancer</td>
<td>Breast cancer diagnosed at any age, with ≥1 close relative with breast cancer ≤ age 50, or ovarian, pancreatic, or metastatic prostate cancer</td>
</tr>
<tr>
<td>Male breast cancer at any age</td>
<td>Pancreatic cancer at any age</td>
</tr>
<tr>
<td>Triple negative breast cancer diagnosed ≤60</td>
<td>Metastatic prostate cancer at any age</td>
</tr>
<tr>
<td>Breast, ovarian, or pancreatic cancer at any age; and Ashkenazi Jewish ancestry</td>
<td>A first or second degree relative meeting any of the criteria in this table</td>
</tr>
</tbody>
</table>

**RECOMMENDATIONS**

NCCN Guidelines provide clinical management recommendations. The most current guidelines may be found at NCCN.org. Modification of surveillance, including initiation of earlier and/or more frequent screening, may be based on guidelines and a patient’s personal and/or family history for specific associated cancers.

Genetic counseling is recommended to discuss the potential clinical and/or reproductive implications of these results, as well as recommendations for testing family members. There is a 50% chance (1 in 2) of a first-degree relative having this variant. To access Integrated Genetics’ Genetic Counselors please visit www.integratedgenetics.com/genetic-counseling or call (855) GC-CALLS (855-422-2557). To discuss targeted analysis for other family members with a Labcorp Genetic Coordinator please call 800-345-4363.

**METHODS AND LIMITATIONS**

Next-generation sequencing: Genomic regions of interest are selected using a custom capture reagent for target enrichment and sequenced via the Illumina(R) next generation sequencing platform. Regions of interest include all exons and intron/exon junctions (+/-20 nucleotides) of the BRCA1 (NM_007294.3) and BRCA2 (NM_000059.3) genes. Sequencing reads are aligned with the human genome reference GRCh37/hg19 build. Minimum mean coverage is 40X. Any segment failing minimum read depth coverage is rescued by bi-directional Sanger sequencing to complete sequence analysis. Variants, including SNVs and CNVs, are identified using a custom bioinformatics pipeline.
**METHODS AND LIMITATIONS**

**Reported variants:** Pathogenic and likely pathogenic variants and variants of uncertain significance (VUS) are reported. Non-deletion variants are specified using the numbering and nomenclature recommended by the Human Genome Variation Society (HGVS, http://www.hgvs.org/). Benign variants are not reported. Variant classification and confirmation are consistent with ACMG standards and guidelines (Richards, PMID:25741868; Rehm, PMID:23887774). Detailed variant classification information is available upon request. A variant of uncertain significance (VUS) should not be used in clinical decision making; a VUS is classified based on inadequate or conflicting evidence regarding its pathogenicity or clinical relevance.

**Limitations:** Technologies used do not detect germline mosaicism and do not rule out the presence of large chromosomal aberrations, including rearrangements, gene fusions, or variants in regions or genes not included in this test, or possible inter/ intragenic interactions between variants. Variant classification and/or interpretation may change over time if more information becomes available. False positive or false negative results may occur for reasons that include: genetic variants, pseudogene interference, technical handling, blood transfusions, bone marrow transplantation, mislabeling of samples, or erroneous representation of family relationships. For heterozygous variants in the same gene the assay cannot determine whether they are on the same or a different chromosomes; to determine phase and clinical significance, rarely, parental testing may be required. Exact breakpoints of exon-level deletions/duplications are not determined. The presence of an inherited cancer syndrome due to a different genetic cause cannot be ruled out. Any interpretation should be clinically correlated with information about the patient’s presentation and relevant family history.

**REFERENCES**


This test was developed and its performance characteristics determined by LabCorp. It has not been cleared or approved by the Food and Drug Administration.