BRCATrue®

Technical Bulletin
Hereditary Breast and Ovarian Cancer (HBOC) Syndrome

1. Breast and Ovarian Cancer

Breast cancer is defined as a malignant tumor in the breast caused by uncontrolled division of abnormal cells. The disease occurs in men and in women, though male breast cancer is rare. Women in the general population have a 12.3% lifetime risk of breast cancer; that is about 1 in 8 women will develop the disease.\(^1\) In contrast, men have a lifetime risk of 0.13%, or about 1 in 1000.\(^1\) The most common type of breast cancer is ductal carcinoma, occurring in about 7 of 10 women with the disease.\(^2\) Approximately 1 in 10 women with breast cancer has lobular cancer.\(^2\) A mixture between ductal and lobular, and other less common types account for the remainder of breast cancer cases.\(^2\)

Ovarian cancer is a malignancy in the ovaries caused by uncontrolled division of abnormal cells. The lifetime risk of developing ovarian cancer is 1.4%, or about 1 in 72.\(^1\) The most common types of ovarian cancer are ovarian epithelial carcinoma and malignant germ cell tumors.\(^3\)

2. HBOC Syndrome

Increased incidence of breast and ovarian cancer is observed among women with a family history of the disease.\(^4\) Studies have demonstrated that highly penetrant genetic variations in a small number of genes are responsible for the increased risk of breast and ovarian cancer in families.\(^1\) In the early 1990s, \textit{BRCA1} and \textit{BRCA2} were identified as the two, predominant genes harboring these highly penetrant mutations (Table 1). Mutations in either \textit{BRCA1} or \textit{BRCA2} result in an up to 85% life-time risk of breast and ovarian cancer in high-risk families.\(^5,6,7\) Cases of familial breast and ovarian cancer not related to \textit{BRCA1} or \textit{BRCA2} are thought to be caused by other genes, each one accounting for a small fraction of the total.\(^8\) Some of these additional susceptibility genes include, \textit{ATM, CDH1, CHEK2, MLH1, MSH2, MSH6, PTEN, STK11}, and \textit{TP53}.\(^7\)
Table 1: Proportion of cancer attributable to BRCA1, BRCA2, or other loci in high-risk families.\(^6\)

<table>
<thead>
<tr>
<th>Family Type</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>Other Loci</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Families with female breast cancer only</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Four or five breast cancers</td>
<td>0.36</td>
<td>0.08</td>
<td>0.56</td>
</tr>
<tr>
<td>Six or more breast cancers</td>
<td>0.29</td>
<td>0.66</td>
<td>0.05</td>
</tr>
<tr>
<td>Overall</td>
<td>0.35</td>
<td>0.36</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>Families with breast and ovarian cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One ovarian cancer</td>
<td>0.67</td>
<td>0.16</td>
<td>0.17</td>
</tr>
<tr>
<td>Two or more ovarian cancers</td>
<td>0.80</td>
<td>0.18</td>
<td>0.02</td>
</tr>
<tr>
<td>Overall</td>
<td>0.74</td>
<td>0.16</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>All families (female breast cancer only families + breast-ovarian cancer families)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Four or five breast cancers</td>
<td>0.56</td>
<td>0.05</td>
<td>0.39</td>
</tr>
<tr>
<td>Six or more breast cancers</td>
<td>0.50</td>
<td>0.42</td>
<td>0.08</td>
</tr>
<tr>
<td>Overall</td>
<td>0.54</td>
<td>0.27</td>
<td>0.19</td>
</tr>
</tbody>
</table>

HBOC syndrome is an autosomal dominant disorder primarily caused by germline mutations in the BRCA1 and BRCA2 genes. Inheritance of one mutation in either gene is sufficient to cause the syndrome. HBOC syndrome accounts for 5-7% of breast cancer cases\(^9\) and 8–13% of epithelial ovarian cancer cases;\(^10\) however, germline BRCA1 and BRCA2 mutations account for 80% of breast and ovarian cancer in families with multiple cases of either disease.\(^5,6,7\) The primary risks associated with HBOC syndrome are early-onset, female breast cancer and ovarian cancer (Table 2). Mutations in BRCA1 and BRCA2 are uncommon in sporadic breast cancer\(^9\).

HBOC syndrome is also associated with increased risk of other types of cancer, including but not limited to fallopian tube,\(^11,12,13\) peritoneal,\(^14,15,16\) pancreatic,\(^17,18,19\) prostate,\(^17,20,21,22\) and male breast cancers.\(^23,24\)

Table 2: HBOC syndrome cancer risk associated with BRCA1 and BRCA2 mutations.\(^6,12,25,26,27,28\)

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female breast cancer</td>
<td>Cumulative risk up to 57-70% by age 70 years.</td>
<td>Cumulative risk up to 45-55% by age 70 years.</td>
</tr>
<tr>
<td>Female breast cancer in high-risk families</td>
<td>Cumulative risk up to 85% by age 70 years.</td>
<td>Cumulative risk up to 84% by age 70 years.</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>Cumulative risk up to 40% by age 70 years.</td>
<td>Cumulative risk up to 11-18% by age 70 years.</td>
</tr>
<tr>
<td>Ovarian cancer in high-risk families</td>
<td>Cumulative risk up to 60% by age 70 years.</td>
<td>Cumulative risk up to 27% by age 70 years.</td>
</tr>
</tbody>
</table>
3. Reported Genes

3.1. **BRCA1**

The *BRCA1* (breast cancer 1, early onset) gene encodes a multifunctional protein that interacts with tumor suppressors, DNA repair proteins, cell cycle regulators, RNA polymerase II holoenzyme, transcription factors, corepressors, chromatin remodeling enzymes, and RNA processing factors. *BRCA1*, therefore, has a critical role in maintaining genomic stability and is involved in many cellular processes important in tumor biology, including DNA repair, cell cycle progression, and transcriptional regulation. Loss or inactivation of one copy of *BRCA1* is thought to result in accumulation of mutations and structural changes in the genome, thereby increasing risk of cancer.

3.2. **BRCA2**

The *BRCA2* (breast cancer 2, early onset) gene encodes a protein with important roles in the DNA damage response and DNA repair pathways. The BRCA2 is a tumor suppressor protein that mediates recruitment of the RAD51 recombinase protein to DNA double-strand breaks. The primary function of the BRCA2 protein is to facilitate homologous recombination, an important DNA repair mechanism in maintenance of genomic integrity. Loss or inactivation of one copy of *BRCA2* is thought to result in accumulation of mutations and structural changes in the genome, thereby increasing risk of cancer.

4. Possible Outcomes

The classification and interpretation of variants identified in this test reflects the current state of scientific understanding. In some instances, the classification and interpretation of variants may change as new scientific information becomes available.

4.1. **Pathogenic Mutations** are genetic changes that have sufficient evidence to be classified as capable of causing disease thus increasing the risk for cancer.

Consultation with a health care professional who has training and experience in cancer genetics is strongly recommended for patients with a pathogenic mutation in order to discuss risk for cancer and other associated diseases with this genetic test result. The type and frequency of cancer surveillance and cancer prevention options and strategies, and the impact of this result on the cancer risk for members of the patient’s family are recommended topics of discussion with a health care professional.

4.2. **Likely Pathogenic** variants are genetic changes with strong but limited evidence to be classified as pathogenic and are likely to increase the risk for cancer.

Consultation with a health care professional who has training and experience in cancer genetics is strongly recommended for patients with a likely pathogenic variant in order to discuss the potential cancer risk and other associated diseases with this genetic test result. The type and frequency of cancer surveillance and cancer prevention options and strategies, and the impact of this result on the potential cancer risk for members of the patient’s family are recommended topics of discussion with a health care professional.

4.3. **Uncertain Pathogenicity Variants (VUS)** are genetic changes that are either previously not reported or have inadequate/conflicting evidence to determine clinical relevance and cancer risk.
The most effective way to help understand the uncertain cancer risk for patients with VUS(s) is through Pathway Genomics' Familial Studies Program. By testing additional family members for the same variant and tracking whether or not the variant co-occurs in family members with cancer, the information about clinical relevance of the variant may improve.

Consultation with a health care professional who has training and experience in cancer genetics is recommended for a patient with VUS(s) in order to discuss if appropriate cancer surveillance and prevention options that take into account the patient’s age, personal risk factors and health history and their family history of cancer are required.

5. Limitations and Warnings

_BRCATrue®_ DNA sequencing test is clinically useful to detect mutations, variants, small insertions and deletions as well as large gene rearrangements occurring within the _BRCA1_ and _BRCA2_ genes. Pathogenic mutations, likely pathogenic variants and VUS(s) are always reported. Genetic changes that are not likely to contribute to cancer pathogenesis, such as likely benign and benign variants are not reported.

The etiology of cancer is multifactorial and can occur as a result of various factors, including both inherited and acquired genetic mutations, diet, lifestyle choices and age. Pathway Genomics’ genetic test evaluates only inherited genetic mutations. It is possible that mutations in genes and genetic regions not tested in Pathway Genomics’ _BRCATrue®_ test may contribute to an individual’s risk for cancer. Therefore, a negative test result, where no mutations are detected, does not eliminate the individual’s cancer risk.

6. References


35. Petrucelli N, Daly MB, Feldman GL. *BRCA1 and BRCA2 Hereditary Breast and Ovarian Cancer* 1993;