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; 1 in 8 women will develop the disease. In contrast, men have a lifetime risk of 0.13%, or about 1 in 1,000.

Ovarian cancer is a malignancy in the ovaries caused by uncontrolled division of abnormal cells. The lifetime risk of developing ovarian cancer in the general population is 1.4%, or about 1 in 71.

Hereditary Breast and Ovarian Cancer (HBOC)
DNA changes (mutations) in the BRCA1 and BRCA2 genes can lead to significantly increased lifetime risks for breast and ovarian cancer (Figure 1). Mutations in BRCA1 and BRCA2 lead to a condition known as “hereditary breast and ovarian cancer” syndrome or HBOC. HBOC accounts for 5-7% of breast cancer cases and 8–13% of epithelial ovarian cancer cases; however, BRCA1 and BRCA2 mutations account for up to 80% of breast and ovarian cancer in families with multiple cases of either disease. Schematic representations of family pedigrees diagnosed with HBOC are depicted in figure 2. Importantly, mutations in either BRCA1 or BRCA2 can be inherited from the maternal as well as the paternal side of the family. HBOC syndrome is also associated with increased risk of other types of cancer, including but not limited to fallopian tube, peritoneal, pancreatic, prostate, and male breast cancers.

Lifetime Risk of Cancer (%)
Figure 2: Schematic representations of family pedigrees diagnosed with pathogenic mutations in either the *BRCA1* or *BRCA2* gene. Interpretation guide: (1) ovals represent females while squares represent males, (2) shading indicates an affected individual, (3) a diagonal line indicates the individual is deceased and (4) each level indicates a generation. Age of diagnosis is indicated as “dx”.

**BRCA1/2 and Ethnicity**

Prevalence of *BRCA1*/2 in the general population has been reported to be approximately 1/400. Large population studies of breast cancer survivors under the age of 65 revealed strong ethnic differences in the prevalence of pathogenic mutations in *BRCA1* or *BRCA2* gene (Table 1).

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazi Jewish</td>
<td>8.3-10.2%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3.5%</td>
<td>Data not available</td>
</tr>
<tr>
<td>Caucasian (non-Ashkenazi Jewish)</td>
<td>2.2-2.9%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Asian-American</td>
<td>0.5%</td>
<td>Data not available</td>
</tr>
</tbody>
</table>

**Table 1:** Prevalence of *BRCA1* and *BRCA2* mutations in women with breast cancer by ethnic groups within U.S. 

**Potential Indications for BRCATrue®**

The BRCATrue® test is best suited for individuals with either a history of early onset breast or ovarian cancer or a strong family history of breast and/or ovarian cancer. Individuals with the following medical or family history factors should consider testing for mutations in *BRCA1*/2:

- Early onset breast cancer (especially if under 50 years of age)
- Bilateral or multiple breast cancers
- Diagnosed with both breast and ovarian cancer
- Family history of breast and/or ovarian cancer
- Two or more *BRCA1* or *BRCA2*-related cancers in a single family member
- Male breast cancer within family
- Ashkenazi Jewish ethnic background
**BRCATrue® Test Technology**

Pathway Genomics uses Next Generation Sequencing (NGS) technology to search for mutations in the coding regions of BRCA1 and BRCA2; regions of insufficient coverage by NGS are sequenced using Sanger chemistry. Mutations found by NGS are confirmed using Sanger chemistry sequencing technology. Large deletions and duplications within BRCA1 and BRCA2 genes are detected using sensitive qPCR assays and confirmed by array comparative genomic hybridization (aCGH).

**Possible Outcomes**

Pathway Genomics classifies variants using a 5-tier system based on the American College of Medical Genetics (ACMG) guidelines. According to this system, variants are classified as either “Pathogenic”, “Likely Pathogenic”, “Uncertain Pathogenicity (VUS)”, “Likely Benign” or “Benign”. Pathogenic, Likely Pathogenic and Uncertain Pathogenicity (VUS) are always reported in the BRCATrue® test. Likely Benign and Benign variants are not reported.

- **Pathogenic**: Mutations with known clinical significance and demonstrated to increase the risk of cancer pathogenesis.
- **Likely Pathogenic**: Genetic changes that have some preliminary clinical data suggesting an association with cancer but not sufficient to make a definitive determination of pathogenicity and associated cancer risk.
- **Uncertain Pathogenicity (VUS)**: Genetic changes with either no supporting data or the data are conflicting, thus a determination of pathogenicity cannot be made.
- **Likely Benign**: Likely benign variants are genetic changes with strong but limited evidence to be classified as benign and are not likely to increase the risk for cancer.
- **Benign**: Benign variants are genetic changes that are previously reported and have sufficient evidence to be classified as benign with no clinical relevance.
References


