OncoGeneDx: BRCA1/2 Ashkenazi Founder Panel in Hereditary Breast and Ovarian Cancer (HBOC)

**Gene List:** BRCA1, BRCA2

**Clinical Features:**
In the general population, approximately 1 in 8 women (12%) will develop breast cancer in their lifetime, and 1 in 75 women (1.4%) will be diagnosed with ovarian cancer in their lifetime (SEER). Most cases of breast or ovarian cancers develop sporadically with no family history of the cancer. Individual risk factors and exposures, such as age, pregnancy history, menstrual history, benign breast disease, radiation exposure, and alcohol intake, are known to modify a woman’s chance of developing these types of cancers. However, 5-10% of breast cancer cases and 15-20% of ovarian cancer cases are thought to be due to a hereditary predisposition. The features suggestive of a hereditary cancer predisposition include: young age at diagnosis, multiple primary cancers in a single individual, diagnosis of a cancer type that is not common in general population (such as ovarian cancer, male breast cancer, or pancreatic cancer), and several relatives affected with related cancers spanning multiple generations.

The OncoGeneDx BRCA1/2 Ashkenazi Founder Panel includes analysis of two pathogenic founder variants in the BRCA1 gene (c.68_69delAG and c.5266dupC) and one in the BRCA2 gene (c.5946delT). Of note, these variants are listed according to the current Human Genome Variation Society (HGVS) guidelines, but are well-known by their previous nomenclature (185delAG or 187delAG, 5382insC or 5385insC, and 6174delT, respectively). Approximately 2.5% of individuals of Ashkenazi Jewish descent carry one of these three pathogenic BRCA1/2 variants (Roa 1996, Struwing 1997).

Pathogenic BRCA1 and BRCA2 variants increase the lifetime risk for breast and ovarian cancer significantly over the general population risk. The chances to develop breast cancer begin increasing when a woman is in her mid 20s (King 2003). Women with pathogenic BRCA1 or BRCA2 variants have between a 41-87% lifetime risk to develop breast cancer and up to a 63% risk for a contralateral breast cancer (Antoniou 2003, Chen 2007, Claus 1996, Ford 1998, Graeser 2009, King 2003, Risch 2006). This risk depends on the age at which the first breast cancer was detected (Graeser 2009). The lifetime risk for breast cancer in males with a pathogenic BRCA2 variant is approximately 7%, and slightly increased for those with a pathogenic BRCA1 variant (Liede 2004, Tai 2007).

The risk of ovarian cancer begins to increase in the mid-30s, but becomes most significant in the 50s and beyond. The lifetime risk to develop ovarian cancer is between 24-54% for

The risk for other malignancies has been reported in families with pathogenic variants in BRCA1 or BRCA2 including prostate cancer in men as well as pancreatic cancer and melanoma in both men and women. Male and female pathogenic BRCA2 variant carriers are estimated to have up to a 7% risk for pancreatic cancer while male carriers are estimated to have up to a 34% risk for prostate cancer (Ozelik 1997, The Breast Cancer Linkage Consortium 1999). Male pathogenic BRCA1 variant carriers have been shown to have a slightly increased risk for prostate cancer before age 65 while pancreatic cancer have been suggested to also be slightly increased in both men and women (Brose 2002, Leongamornlert 2012, Liede 2004, Thompson 2002).

Two pathogenic variants in the BRCA2 gene, one in each copy of the gene (biallelic pathogenic variants), are associated with an extremely rare autosomal recessive syndrome called Fanconi anemia. This condition is characterized by an increased risk for malignancy in children including leukemia and certain solid tumors as well as physical abnormalities and bone marrow failure. Therefore, if both mother and father are carriers of a pathogenic BRCA2 variant, each of their children would have a 25% chance to inherit both variants, a 50% chance to inherit one of the variants, and a 25% chance to inherit neither variant.

**Inheritance Pattern:**
BRCA1 and BRCA2 are associated with an autosomal dominant cancer risk. BRCA2 is also associated with Fanconi Anemia when inherited in an autosomal recessive fashion. The specifics of this inheritance are outlined above.

**Test Methods:**
Genomic DNA from the submitted specimen was PCR-amplified for targeted DNA sequence analysis of specific portions of exons 2 and 19 in the BRCA1 gene and exon 11 in the BRCA2 gene to detect the three pathogenic founder variants in the Ashkenazi Jewish population: BRCA1 c.68_69delAG, also known as 185delAG or 187delAG; c.5266dupC, also known as 5382insC or 5385insC; and BRCA2 c.5946delT, also known as 6174delT. All sequence alterations are described according to the Human Genome Variation Society (HGVS) nomenclature guidelines. Benign and likely benign variants, if present, are not reported but are available upon request.
Test Sensitivity:
Regarding clinical sensitivity, these three variants account for approximately 95% of pathogenic variants in the \textit{BRCA1} and \textit{BRCA2} genes in Ashkenazi Jewish individuals (Frank 2002, Kauff 2002). Overall, approximately 20-25% of familial breast cancer risk and 75% of hereditary ovarian cancer risk are thought to be attributed to pathogenic variants in the \textit{BRCA1} or \textit{BRCA2} genes (Easton 1999, Pharoah 2002, van der Groep 2011, Walsh 2011). The methods used by GeneDx are expected to be greater than 99% sensitive in detecting identifiable pathogenic variants by sequencing. The likelihood of a false positive result is expected to be <1%.

Technical Limitations: False negatives may also occur in the setting of bone marrow transplantation, recent blood transfusion, or suboptimal DNA quality. In individuals with active leukemia or lymphoma or with known chronic myeloid or lymphoid neoplasms (such as low grade MDS, CML, ET, P. vera, PMF, CLL), there is a possibility that testing of specimens containing leukocytes may detect an acquired somatic variant, resulting in a false positive result. In this situation, please contact one of our genetic counselors to discuss the utility of submitting an alternate specimen. Additionally, rare false negatives may occur when testing for a specific variant identified at a laboratory other than GeneDx if a positive control is not provided. The ability to detect genetic variants and naming conventions can differ among laboratories.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Inheritance</th>
<th>Disease Associations</th>
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</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>BREAST CANCER TYPE 1 SUSCEPTIBILITY PROTEIN</td>
<td>AD</td>
<td>Hereditary Breast and Ovarian Cancer (HBOC) syndrome: Breast, Ovarian, Pancreatic, Prostate &amp; Endometrial serous cancer</td>
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<tr>
<td>BRCA2</td>
<td>BREAST CANCER TYPE 2 SUSCEPTIBILITY PROTEIN</td>
<td>AD</td>
<td>Hereditary Breast and Ovarian Cancer (HBOC) syndrome: Breast, Ovarian, Pancreatic, Prostate, Melanoma &amp; Endometrial serous cancer</td>
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<tr>
<td></td>
<td></td>
<td>AR</td>
<td>Fanconi Anemia</td>
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</tbody>
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Because of evolving and expanding phenotypes, this list of cancer/tumor types is not exhaustive. Gene-specific risk for some of the cancers and other features listed are not well-defined.

Abbreviations:
AD – Autosomal Dominant
AR – Autosomal Recessive
CGH – Comparative genomic hybridization
MLPA – Multiplex ligation-dependent probe amplification

References: