

## 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.<sup>1</sup> 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.<sup>2,3</sup>

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.<sup>4</sup> 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.<sup>4-10</sup> This risk depends on the age at which the first breast cancer was detected.<sup>9</sup> 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.<sup>11,12</sup>

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 pathogenic *BRCA1* variant carriers and 11-27% for pathogenic *BRCA2* variant carriers.<sup>4-6,8,10</sup> Other associated cancers in women include fallopian tube carcinoma, primary peritoneal carcinoma, and uterine serous carcinoma.<sup>13-15</sup>

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.<sup>16,17</sup> Male pathogenic *BRCA1* variant carriers have been shown to have a slightly increased risk for prostate cancer before age 65 while pancreatic cancer has been suggested to also be slightly increased in both men and women.<sup>11, 18-20</sup>

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 is extracted from the submitted specimen. For skin punch biopsies, fibroblasts are cultured and used for DNA extraction. This DNA is 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.

## TEST SENSITIVITY

Regarding clinical sensitivity, these three variants account for approximately 95% of pathogenic variants in the *BRCA1* and *BRCA2* genes in Ashkenazi Jewish individuals.<sup>21,22</sup> 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 *BRCA1* or *BRCA2* genes.<sup>23-26</sup> The methods used by GeneDx are expected to be greater than 99% sensitive in detecting identifiable pathogenic variants by sequencing.

Genetic testing using the methods applied at GeneDx is expected to be highly accurate. Normal findings do not rule out the diagnosis of a genetic disorder since some genetic abnormalities may be undetectable by this test. False negatives may also occur in the setting of bone marrow transplantation, recent blood transfusion, or suboptimal DNA quality. In individuals with active or chronic hematologic neoplasms or conditions, there is a possibility that testing may detect an acquired somatic variant, resulting in a false positive result. As the ability to detect genetic variants and naming conventions can differ among laboratories, rare false negative results may occur when no positive control is provided for testing of a specific variant identified at another laboratory. The chance of a false positive or false negative result due to laboratory errors incurred during any phase of testing cannot be completely excluded. Interpretations are made with the assumption that any clinical information provided, including family relationships, are accurate. Consultation with a genetics professional is recommended for interpretation of results.

Gene	Protein	Inheritance	Disease Associations
<i>BRCA1</i>	Breast cancer type 1 susceptibility protein	AD	Hereditary Breast and Ovarian Cancer (HBOC) syndrome: Breast, ovarian, pancreatic, prostate & endometrial serous cancer
<i>BRCA2</i>	Breast cancer type 2 susceptibility protein	AD	Hereditary Breast and Ovarian Cancer (HBOC) syndrome: breast, ovarian, pancreatic, prostate, melanoma & endometrial serous cancer
		AR	Fanconi anemia

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

CGH – Comparative genomic hybridization

AR – Autosomal Recessive

MLPA – Multiplex ligation-dependent probe amplification

**REFERENCES:**

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