OncoGeneDx: *BRCA1/2* Sequencing and Deletion/Duplication Analysis 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.[1] 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.

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.[2] 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.[2–8] This risk depends on the age at which the first breast cancer was detected.[7] 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.[9,10]

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.[2–4,6,8] Other associated cancers in women include fallopian tube carcinoma, primary peritoneal carcinoma, and uterine serous carcinoma.[11–13]

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.[14,15] 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.[9,16–18]

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.

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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 enriched for the complete coding regions and splice site junctions of the genes on this panel using a proprietary targeted capture system developed by GeneDx for next generation sequencing with CNV calling (NGS-CNV).The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

TEST SENSITIVITY

Regarding clinical sensitivity, 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.[19–22] The test is expected to be greater than 99% sensitive in detecting variants identifiable by sequencing and will detect most single exon deletions and duplications.

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. The methods used cannot reliably detect deletions of 20bp to 250bp in size, or insertions of 10bp to 250 bp in size. Sequencing cannot detect low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect mosaicism and cannot identify balanced chromosome aberrations. Rarely, incidental findings of large chromosomal rearrangements outside the gene of interest may be identified. Regions of certain genes have inherent sequence properties (for example: repeat, homology, or pseudogene regions, high GC content, rare polymorphisms) that yield suboptimal data, potentially impairing accuracy of the results. 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
BRCA1	BREAST CANCER TYPE 1 SUSCEPTIBILITY PROTEIN	AD	Hereditary Breast and Ovarian Cancer (HBOC) syndrome: breast, ovarian, pancreatic, prostate & endometrial serous cancer
BRCA2	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
AR – Autosomal Recessive

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