OncoGeneDx: Breast Cancer Surgical Panel

PANEL GENE LIST
BRCA1, BRCA2, PALB2

CLINICAL FEATURES
In the general population, approximately 1 in 8 women (12%) will develop breast cancer in their lifetime.[1] Most cases of breast cancer develop sporadically with no family history of the cancer; however, 5-10% of cases are thought to be due to a hereditary predisposition. The features suggestive of a hereditary cancer predisposition include: young age at diagnosis (before age 50), multiple primary cancers in a single individual, diagnosis of a cancer type that is not common in the general population (such as ovarian cancer, male breast cancer, or pancreatic cancer), and several relatives affected with related cancers spanning multiple generations.

The OncoGeneDx Breast Cancer Surgical Panel includes three genes associated with an increased level of breast cancer risk that may influence surgical management. These genes include BRCA1 and BRCA2, which are associated with Hereditary Breast and Ovarian Cancer syndrome and PALB2, which is associated with an increased risk for both breast and pancreatic cancer.

It is estimated that 20-25% of familial breast cancer risk can be attributed to pathogenic variants in the BRCA1 and BRCA2 genes.[2–4] The contribution of pathogenic variants in the PALB2 gene to familial breast cancer risk overall is less well-characterized but is likely lower than the contribution of BRCA1 and BRCA2 pathogenic variants.

Hereditary Breast and Ovarian Cancer syndrome (BRCA1 and BRCA2): Women with pathogenic variants in BRCA1 or BRCA2 have a 41-87% lifetime risk to develop breast cancer and an up to 63% risk for contralateral breast cancer.[5–11] Studies have shown that the lifetime risk to develop ovarian cancer is between 24-54% for BRCA1 pathogenic variant carriers and 11-27% for BRCA2 pathogenic variant carriers.[5,6,8,9,11] Other cancers associated with pathogenic variants in BRCA1 and BRCA2 in women include fallopian tube carcinoma, primary peritoneal carcinoma, and uterine serous carcinoma.[12–14] The lifetime risk for breast cancer in male BRCA1/2 pathogenic variant carriers is approximately 7% with a pathogenic variant in BRCA2 and slightly increased with a pathogenic variant in BRCA1.[15,16] Other malignancies reported in families with pathogenic variants in BRCA1 or BRCA2 include prostate cancer in men, as well as pancreatic cancer and melanoma in both men and women.

PALB2: Women with a pathogenic variant in PALB2 have been estimated to have a 2 to 3-fold increased risk of breast cancer over the general population[17,18] resulting in a lifetime risk of approximately 25% to 40%. More recent data have suggested a lifetime risk (up to age 70) ranging from 33% to 58% depending on the individual's family history of breast cancer.[19] Women with a pathogenic variant in PALB2 who have a family history of early-onset breast cancer may have a lifetime risk up to 58%.[19,20] Casadei et al.[21] found that PALB2 pathogenic variant carriers are 6-fold more likely to have a family history of pancreatic cancer, 1.3-fold more likely to have a family history of ovarian cancer and 4-fold more likely to have a family history of male breast cancer. Although the association of pathogenic variants in PALB2 and pancreatic cancer has been established, the exact risks are not yet well-understood.[22,23]

INHERITANCE PATTERN
All of the genes on this panel are associated with an autosomal dominant cancer risk. BRCA2 and PALB2 are also associated with an extremely rare condition when inherited in an autosomal recessive fashion. The specifics of this inheritance are outlined in the table below.

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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 regions with inadequate sequence or copy number data by next generation sequencing (NGS). Reported clinically significant variants are confirmed by an appropriate method. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. 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

The clinical sensitivity of sequencing and deletion/duplication analysis of the 3 genes included in the OncoGeneDx Breast Cancer Surgical Panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with features suggestive of a hereditary predisposition to cancer as outlined above. DNA sequencing will detect nucleotide substitutions and small insertions and deletions, while NGS-CNV analysis, array CGH, or MLPA will detect exon-level deletions and duplications. These methods are expected to be greater than 99% sensitive in detecting pathogenic variants identifiable by sequencing or CNV technology.

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

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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
PALB2	PARTNER AND LOCALIZER OF BRCA2	AD	Breast, pancreatic & ovarian 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
CGH – Comparative genomic hybridization
MLPA – Multiplex ligation-dependent probe amplification

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