

OncoGeneDx: Breast/Gyn Cancer Panel

PANEL GENE LIST

ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, FANCC, FANCM, MLH1, MSH2, MSH6, MUTYH, NF1, PALB2, PMS2, POLD1, PTEN, RAD51C, RAD51D, RECQL, STK11, TP53*

*Testing includes sequencing and deletion/duplication analysis for all genes except *EPCAM* (del/dup only).

CLINICAL FEATURES

In the general population, approximately 1 in 8 women (12%) will develop breast cancer in their lifetime, 1 in 75 women (1.4%) will be diagnosed with ovarian cancer in their lifetime, and 1 in 36 women (2.8%) will develop endometrial cancer, also known as uterine cancer.¹ Most cases of breast, ovarian, and endometrial cancer develop sporadically with no family history of the cancer. However, 5-10% of breast and endometrial cancer cases and 15-20% of ovarian cancer cases are due to a hereditary predisposition. The features of a personal and/or family history of cancer that are 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.

Approximately 20-25% of familial breast cancer risk is thought to be attributed to pathogenic variants in the *BRCA1* and *BRCA2* genes.²⁻⁴ The additional 22 genes on this panel may also account for a substantial proportion of hereditary breast, ovarian, and endometrial cancer cases. Many of these genes are involved in the Fanconi anemia pathway and/or play a role in DNA damage repair similar to the *BRCA1* and *BRCA2* genes. Newer genes, such as *FANCC* and *RECQL*, have been identified in families with breast and/or ovarian cancer and have been included in the panel to make it as comprehensive as possible. The evidence available to date may be derived from a small number of patients with wide confidence intervals or is based upon an ethnic cohort with one specific variant. Accurate risk assessment may be complicated by the low penetrance of pathogenic variants in these genes and/or ascertainment bias. Since the cancer risks are not yet well defined, no consensus guidelines for medical management are available for these genes.

INHERITANCE PATTERN

Most genes on this panel are associated with an autosomal dominant cancer risk with the exception of *MUTYH*, which is associated with an autosomal recessive cancer risk. Some of the genes on this panel are also associated with extremely rare conditions when inherited in an autosomal recessive fashion. The specifics of this inheritance are outlined in the table below.

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). For *PTEN* nucleotides c.-700 through c.-1300 in the promoter region are also captured. 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; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Concurrent *MSH2* Exons 1-7 Inversion analysis from NGS data is also performed. For *EPCAM*, deletion/duplication analysis, but not sequencing, is performed. 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.

CLINICAL SENSITIVITY

The clinical sensitivity of sequencing and deletion/duplication analysis of the 24 genes included in the OncoGeneDx Breast/Gyn Cancer 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
<i>ATM</i> ⁵⁻⁹	SERINE-PROTEIN KINASE ATM	AD	Breast, pancreatic, prostate & colon cancer
		AR	Ataxia telangiectasia
<i>BARD1</i> ¹⁰⁻¹²	BRCA1-ASSOCIATED RING DOMAIN PROTEIN 1	AD	Breast cancer
<i>BRCA1</i> ^{13,14}	BREAST CANCER TYPE 1 SUSCEPTIBILITY PROTEIN	AD	Hereditary Breast and Ovarian Cancer (HBOC) syndrome: breast, ovarian, pancreatic, & prostate cancer
<i>BRCA2</i> ^{13,15}	BREAST CANCER TYPE 2 SUSCEPTIBILITY PROTEIN	AD	Hereditary Breast and Ovarian Cancer (HBOC) syndrome: breast, ovarian, pancreatic, prostate cancer & melanoma
		AR	Fanconi anemia
<i>BRIP1</i> ^{10,12,12,15-18}	FANCONI ANEMIA GROUP J PROTEIN	AD	Breast, ovarian & prostate cancer
		AR	Fanconi anemia
<i>CDH1</i> ¹⁹⁻²²	CADHERIN 1	AD	Hereditary Diffuse Gastric Cancer (HDGC) syndrome:

			gastric (diffuse), breast & colon (signet ring) cancer
<i>CHEK2</i> ^{12,23-26}	SERINE/THREONINE-PROTEIN KINASE CHK2	AD	Breast, colon, prostate, gastric & thyroid cancer
<i>EPCAM</i> ²⁷⁻²⁹	EPITHELIAL CELL ADHESION MOLECULE	AD	Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate & brain cancer, sebaceous neoplasms
		AR	Constitutional mismatch repair deficiency syndrome
<i>FANCC</i> ^{12,15,30,31}	FANCONI ANEMIA GROUP C PROTEIN	AD	Breast cancer
		AR	Fanconi anemia
<i>FANCM</i> ^{12,32}	FANCONI ANEMIA GROUP M PROTEIN	AD	Breast cancer
		AR	Fanconi anemia-like cancer susceptibility
<i>MLH1</i> ^{33,34}	DNA MISMATCH REPAIR PROTEIN MLH1	AD	Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate & brain cancer, sebaceous neoplasms
		AR	Constitutional mismatch repair deficiency syndrome
<i>MSH2</i> ^{33,34}	DNA MISMATCH REPAIR PROTEIN MSH2	AD	Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate & brain cancer, sebaceous neoplasms
		AR	Constitutional mismatch repair deficiency syndrome
<i>MSH6</i> ^{33,34}	DNA MISMATCH REPAIR PROTEIN MSH6	AD	Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate & brain cancer, sebaceous neoplasms
		AR	Constitutional mismatch repair deficiency syndrome
<i>MUTYH</i> ^{35,36}	ADENINE DNA GLYCOSYLASE	AR	<i>MUTYH</i> -associated polyposis (MAP): colorectal, small bowel & endometrial serous cancer, gastrointestinal polyps
<i>NF1</i> ^{37,38}	NEUROFIBROMIN	AD	Neurofibromatosis type 1 (NF1) syndrome: breast cancer, GIST, optic nerve gliomas,

			pheochromocytoma, MPNST, neurofibromas, brain tumors
<i>PALB2</i> ^{10,39,40}	PARTNER AND LOCALIZER OF BRCA2	AD	Breast, ovarian, pancreatic & prostate cancer
		AR	Fanconi anemia
<i>PMS2</i> ^{33,34}	MISMATCH REPAIR ENDONUCLEASE PMS2	AD	Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate & brain cancer, sebaceous neoplasms
		AR	Constitutional mismatch repair deficiency syndrome
<i>POLD1</i> ^{41,42}	DNA POLYMERASE DELTA CATALYTIC SUBUNIT	AD	Colon & endometrial cancer, colon polyps
<i>PTEN</i> ⁴³	PHOSPHATIDYLINOSITOL 3,4,5-TRISPHOSPHATE 3-PHOSPHATASE AND DUAL-SPECIFICITY PROTEIN PHOSPHATASE PTEN	AD	<i>PTEN</i> hamartoma tumor syndrome (PHTS): breast, thyroid, endometrial, colon, melanoma & renal cancer, gastrointestinal polyps, Lhermitte-Duclos disease
<i>RAD51C</i> ^{12,18,44}	DNA REPAIR PROTEIN RAD51 HOMOLOG 3	AD	Breast, ovarian & prostate cancer
		AR	Fanconi anemia
<i>RAD51D</i> ^{12,18,44}	DNA REPAIR PROTEIN RAD51 HOMOLOG 4	AD	Breast, ovarian & prostate cancer
<i>RECQL</i> ^{12,45}	RECQ PROTEIN-LIKE	AD	Breast cancer
<i>STK11</i> ⁴⁶⁻⁴⁸	SERINE/THREONINE-PROTEIN KINASE STK11	AD	Peutz-Jeghers syndrome (PJS): breast, colorectal, pancreatic, gastric, small bowel, ovarian, lung, cervical & endometrial cancer, testicular tumors (LCCSCT), gastrointestinal polyps
<i>TP53</i> ⁴⁹	CELLULAR TUMOR ANTIGEN P53	AD	Li-Fraumeni syndrome (LFS): breast cancer, sarcoma, brain cancer, hematologic malignancies, adrenocortical carcinoma, among others**

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.

** High overall risk of cancer: 75% lifetime risk for males to develop cancer, nearly 100% risk for females.

Abbreviations:

AD – Autosomal Dominant

AR – Autosomal Recessive

CGH – Comparative genomic hybridization

MLPA – Multiplex ligation-dependent probe amplification

MPNST – Malignant peripheral nerve sheath tumor

GIST – Gastrointestinal stromal tumor

REFERENCES:

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