

OncoGeneDx: Pancreatic Cancer Panel

Panel Gene List: *APC, ATM, BRCA1, BRCA2, CDK4, CDKN2A, EPCAM*, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, TP53, VHL*

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

Clinical Features:

In the general population, approximately 1.5% individuals will develop pancreatic cancer in their lifetime.¹ Most cases of pancreatic cancers develop sporadically. Up to 10% of pancreatic cases are thought to be due to a hereditary predisposition.^{2,3} The features of a personal and/or family history of cancer that are suggestive of a hereditary cancer predisposition include: young ages at diagnosis, multiple primary cancers in a single individual, diagnosis of a cancer type that is not common in general population (such as pancreatic cancer), and several relatives affected with cancer spanning multiple generations.

Germline *BRCA2* gene pathogenic variants account for approximately 5-17% of familial pancreatic cancer families, making up the highest percentage of known causes of inherited pancreatic cancer.⁴ Pathogenic variants in *PALB2, CDKN2A, STK11*, and the Lynch syndrome genes (*MLH1, MSH2, MSH6, PMS2*, and *EPCAM*) are also associated with significantly increased risk of pancreatic cancer.⁴ The other six genes on this panel account for additional causes of hereditary pancreatic cancer cases, and may increase the risk for other cancers as well.

Inheritance Pattern:

All of genes on this panel are associated with an autosomal dominant 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, and for *APC*, promoters 1A and 1B 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. For *EPCAM*, deletion/duplication analysis, but not sequencing, is performed. 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 15 genes included in the OncoGeneDx Pancreatic 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>APC</i> ⁵⁻⁸	ADENOMATOUS POLYPOSIS COLI PROTEIN	AD	Familial Adenomatous Polyposis (FAP)-associated condition: colorectal, duodenal or periampullary, gastric, thyroid, pancreatic, brain (medulloblastoma) & liver (hepatoblastoma) cancers, desmoid tumors, gastrointestinal polyps
<i>ATM</i> ⁹⁻¹⁴	SERINE-PROTEIN KINASE ATM	AD	Breast, colon & pancreatic cancers
		AR	Ataxia telangiectasia
<i>BRCA1</i> ¹⁵⁻²⁵	BREAST CANCER TYPE 1 SUSCEPTIBILITY PROTEIN	AD	Hereditary Breast and Ovarian Cancer (HBOC) syndrome: breast, ovarian, pancreatic, prostate & endometrial serous cancer
<i>BRCA2</i> ^{15-23,25}	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
<i>CDK4</i> ²⁶⁻²⁸	CYCLIN-DEPENDENT KINASE 4	AD	Melanoma, non-melanoma skin & pancreatic cancer
<i>CDKN2A</i> ^{4,26,29-32}	CYCLIN-DEPENDENT KINASE INHIBITOR 2A, TUMOR SUPPRESSOR ARF	AD	Familial atypical multiple mole melanoma (FAMMM) syndrome: melanoma, pancreatic cancer & astrocytoma
<i>EPCAM</i> ³³⁻³⁸	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>MLH1</i> ^{33-37,39,40}	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> ³³⁻⁴⁰	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> ^{33-37,39,41}	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>PALB2</i> ^{10,42-47}	PARTNER AND LOCALIZER OF BRCA2	AD	Breast, pancreatic & ovarian cancer
		AR	Fanconi anemia
<i>PMS2</i> ^{33-37,48,49}	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>STK11</i> ^{15,50-52}	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> ^{24,53-57}	CELLULAR TUMOR ANTIGEN P53	AD	Li-Fraumeni syndrome (LFS): breast cancer, sarcoma, brain cancer, hematologic malignancies, adrenocortical carcinoma, among others**
<i>VHL</i> ⁵⁸⁻⁶¹	VON HIPPEL-LINDAU DISEASE TUMOR SUPPRESSOR	AD	von Hippel-Lindau (VHL) disease: renal cancer (clear cell), pancreatic neuroendocrine tumors, hemangioblastoma, pheochromocytoma, endolymphatic sac tumors

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

LCCSCT - Large cell-calcifying Sertoli cell tumors

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