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 (SEER). Most cases of pancreatic cancers develop sporadically. Up to 10% of pancreatic cases are thought to be 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 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. 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. 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 from the submitted specimen is enriched for the complete coding region and splice site junctions of the genes on the panel using a proprietary targeted capture system developed by GeneDx. (For APC, promoters 1A and 1B are also captured.) The products are sequenced on an Illumina HiSeq instrument with 2x100 paired-end reads. The sequence is aligned to reference sequences based on human genome build GRCh37/UCSC hg19. Capillary sequencing is used to confirm all variants with clinical or uncertain significance and to analyze regions with inadequate coverage by Next Generation sequencing (NGS). If present, apparently homozygous variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. All sequence alterations are described according to the Human Genome Variation Society (HGVS) nomenclature guidelines. Concurrent deletion/duplication analysis from NGS data is performed for all relevant genes on the panel to
detect multi-exonic and most single-exon deletions and duplications. For specimens with insufficient copy number data and for confirmation of identified copy number changes, exon-level array CGH, MLPA or other appropriate methods are used. Concurrent MSH2 Exons 1-7 Inversion analysis from NGS data is also performed. For EPCAM, deletion/duplication analysis, but not sequencing, is performed. Copy-number alterations are reported according to the International System for Human Cytogenetic Nomenclature (ISCN) guidelines. Benign and likely benign variants, if present, are not 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 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. The likelihood of a false positive result is expected to be <1%.

Technical Limitations: Neither sequencing, exon-level array CGH nor MLPA can reliably detect mosaicism, and cannot detect chromosomal aberrations. Deletions involving more than 20bp and insertions involving more than 10bp are not reliably detected by the sequencing methodology, and deletions or duplications of less than 250bp are not reliably detected by NGS-CNV analysis or array CGH. Regions of certain genes have inherent sequence properties that yield suboptimal data, potentially impairing accuracy of the results. For instance, sequence and deletion/duplication analysis of PMS2, among others, is complicated by the presence of pseudogenes or homologous sequences that involve multiple exons of these genes. In the absence of mRNA/cDNA studies, we cannot completely exclude the possibility of undetectable clinically significant variants in certain regions of these genes. False negatives may also occur in the setting of bone marrow transplantation, recent blood transfusion, or suboptimal DNA quality. In individuals with active leukemia or lymphoma or with known chronic myeloid or lymphoid neoplasms (such as low grade MDS, CML, ET, P. vera, PMF, CLL), there is a possibility that testing of specimens containing leukocytes may detect an acquired somatic variant, resulting in a false positive result. In this situation, please contact one of our genetic counselors to discuss the utility of submitting an alternate specimen. The ability to detect genetic variants and naming conventions can differ among laboratories. Rare false negatives, therefore, may occur when testing for a specific variant identified at a laboratory other than GeneDx, if a positive control is not provided. Based on the specific array design and technology used, the reported coordinates of duplications and deletions at the exon
or gene level can slightly differ among family members tested but, in general, relatives are expected to have the same copy number variant.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Inheritance</th>
<th>Disease Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>ADENOMATOUS POLYPOSIS COLI PROTEIN</td>
<td>AD</td>
<td>Familial Adenomatous Polyposis (FAP)-associated condition: colorectal, duodenal or periampullary, gastric, thyroid, pancreatic, brain &amp; liver (Hepatoblastoma) cancers, desmoid tumors, gastrointestinal polyps</td>
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<tr>
<td>ATM</td>
<td>SERINE-PROTEIN KINASE ATM</td>
<td>AD</td>
<td>Breast, colon &amp; pancreatic cancers</td>
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<tr>
<td>ATM</td>
<td>AD</td>
<td>AR</td>
<td>Ataxia telangiectasia</td>
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<td>BRCA1</td>
<td>BREAST CANCER TYPE 1 SUSCEPTIBILITY PROTEIN</td>
<td>AD</td>
<td>Hereditary Breast and Ovarian Cancer (HBOC) syndrome: breast, ovarian, pancreatic, prostate &amp; endometrial serous cancer</td>
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<tr>
<td>BRCA2</td>
<td>BREAST CANCER TYPE 2 SUSCEPTIBILITY PROTEIN</td>
<td>AD</td>
<td>Hereditary Breast and Ovarian Cancer (HBOC) syndrome: breast, ovarian, pancreatic, prostate, melanoma &amp; endometrial serous cancer</td>
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<tr>
<td></td>
<td></td>
<td>AR</td>
<td>Fanconi Anemia</td>
</tr>
<tr>
<td>CDK4</td>
<td>CYCLIN-DEPENDENT KINASE 4</td>
<td>AD</td>
<td>Melanoma, non-melanoma skin &amp; pancreatic cancer</td>
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<tr>
<td>CDKN2A</td>
<td>CYCLIN-DEPENDENT KINASE INHIBITOR 2A, TUMOR SUPPRESSOR ARF</td>
<td>AD</td>
<td>Familial atypical multiple mole melanoma (FAMMM) syndrome: melanoma &amp; pancreatic cancer</td>
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<tr>
<td>EPCAM</td>
<td>EPITHELIAL CELL ADHESION MOLECULE</td>
<td>AD</td>
<td>Lynch syndrome: colorectal, endometrial, ovarian, gastric pancreatic, biliary tract, urinary tract, small bowel &amp; brain cancer, sebaceous neoplasms</td>
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<td></td>
<td></td>
<td>AR</td>
<td>Constitutional mismatch repair deficiency syndrome</td>
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<tr>
<td>MLH1</td>
<td>DNA MISMATCH REPAIR PROTEIN MLH1</td>
<td>AD</td>
<td>Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel &amp; brain cancer, sebaceous neoplasms</td>
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<tr>
<td></td>
<td></td>
<td>AR</td>
<td>Constitutional mismatch repair deficiency syndrome</td>
</tr>
<tr>
<td>MSH2</td>
<td>DNA MISMATCH REPAIR PROTEIN MSH2</td>
<td>AD</td>
<td>Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, urinary</td>
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<tr>
<td>Gene</td>
<td>Description</td>
<td>AD</td>
<td>AR</td>
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<tr>
<td>MSH6</td>
<td>DNA MISMATCH REPAIR PROTEIN MSH6</td>
<td>Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, small bowel &amp; brain cancer, sebaceous neoplasms</td>
<td>Constitutional mismatch repair deficiency syndrome</td>
</tr>
<tr>
<td>PALB2</td>
<td>PARTNER AND LOCALIZER OF BRCA2</td>
<td>Breast, pancreatic &amp; ovarian cancer</td>
<td>Fanconi anemia</td>
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<td>PMS2</td>
<td>MISMATCH REPAIR ENDONUCLEASE PMS2</td>
<td>Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel &amp; brain cancer, sebaceous neoplasms</td>
<td>Constitutional mismatch repair deficiency syndrome</td>
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<tr>
<td>STK11</td>
<td>SERINE/THREONINE-PROTEIN KINASE STK11</td>
<td>Peutz-Jeghers Syndrome (PJS): breast, colorectal, pancreatic, gastric, small bowel, ovarian, lung, cervical &amp; endometrial cancer, testicular tumors (LCCSCT), gastrointestinal polyps</td>
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<tr>
<td>TP53</td>
<td>CELLULAR TUMOR ANTIGEN P53</td>
<td>Li-Fraumeni syndrome (LFS): breast cancer, sarcoma, brain cancer, hematologic malignancies, adrenocortical carcinoma, among others**</td>
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<td>VHL</td>
<td>VON HIPPEL-LINDAU DISEASE TUMOR SUPPRESSOR</td>
<td>von Hippel-Lindau (VHL) disease: renal cancer (clear cell), pancreatic neuroendocrine tumors, hemangioblastoma, pheochromocytoma, endolymphatic sac tumors</td>
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</table>

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
References: