OncoGeneDx: Colorectal Cancer Panel

Panel Gene List: APC, ATM, AXIN2, BMPR1A, CDH1, CHEK2, EPCAM*, MLH1, MSH2, MSH6, MUTYH, NTHL1, PMS2, POLD1, POLE, PTEN, SCG5/GREM1*, SMAD4, STK11, TP53

*Testing includes sequencing and deletion/duplication analysis for all genes except EPCAM (del/dup only) and SCG5/GREM1 (del/dup only).

Clinical Features:
Individuals in the general population have an approximately 4.3% lifetime risk of developing colorectal cancer. Most cases of colorectal cancer develop sporadically. Approximately 5-10% of colorectal cancers are due to a hereditary predisposition. Individuals with hereditary colorectal cancer syndromes often have a high risk of developing gastrointestinal cancers and require increased screening and surveillance to reduce their cancer risk. The features suggestive of a hereditary colorectal cancer predisposition include: young age at diagnosis, history of colorectal cancer or multiple polyps in one or more close relatives, multiple primary cancers in a single individual, and several relatives affected with cancer spanning multiple generations.

Of the cases that are suspected of having a hereditary predisposition to colorectal cancer, the most common causes are Lynch syndrome, due to pathogenic MLH1, MSH2, MSH6, PMS2 variants and EPCAM deletions, as well as Familial Adenomatous Polyposis (FAP) and Attenuated FAP (AFAP) due to pathogenic APC variants. The other 14 genes on this panel account for an additional proportion of hereditary colorectal cancer cases.

The genes included on this panel have been shown to cause an increased risk for colorectal cancer and, in many cases, other cancers as well. Newer genes, such as AXIN2 and NTHL1, have been identified in families with colorectal 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.

Inheritance Pattern:
Most genes on this panel are associated with an autosomal dominant cancer risk with the exception of MUTYH and NTHL1, which are 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-CNВ). 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. Concurrent MSH2 Exons 1-7 Inversion analysis from NGS data is also performed. For EPCAM and SCG5, 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 20 genes included in the OncoGeneDx Colorectal 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-CNВ 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.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Inheritance</th>
<th>Disease Associations</th>
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<tbody>
<tr>
<td>APC(^{2-5})</td>
<td>ADENOMATOUS POLYPOSIS COLI PROTEIN</td>
<td>AD</td>
<td>Familial Adenomatous Polyposis (FAP)-associated condition: colorectal, duodenal or peripancreatic, gastric, thyroid, pancreatic, brain (medulloblastoma) &amp; liver (hepatoblastoma) cancers, desmoid tumors, gastrointestinal polyps</td>
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<td>ATM(^{6-11})</td>
<td>SERINE-PROTEIN KINASE ATM</td>
<td>AD</td>
<td>Breast, colon &amp; pancreatic cancers</td>
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<td></td>
<td></td>
<td>AR</td>
<td>Ataxia telangiectasia</td>
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<tr>
<td>AXIN2(^{12,13})</td>
<td>AXIN-2</td>
<td>AD</td>
<td>Colon cancer, colon polyps</td>
</tr>
<tr>
<td>BMPR1A(^{2,14-16})</td>
<td>BONE MORPHOGENETIC PROTEIN RECEPTOR TYPE-1A</td>
<td>AD</td>
<td>Juvenile Polyposis syndrome (JPS): colorectal, gastric (if gastric polyps), small bowel &amp; pancreatic cancer, gastrointestinal polyps</td>
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<tr>
<td>CDH1(^{17-23})</td>
<td>CADHERIN 1</td>
<td>AD</td>
<td>Hereditary Diffuse Gastric Cancer (HDGC) syndrome: gastric (diffuse), breast &amp; colon (signet ring) cancer</td>
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<tr>
<td>CHEK2(^{2,7,24-31})</td>
<td>SERINE/THREONINE-PROTEIN KINASE CHK2</td>
<td>AD</td>
<td>Breast, colon, prostate, gastric &amp; thyroid cancer</td>
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<tr>
<td>EPCAM(^{32-37})</td>
<td>EPITHELIAL CELL ADHESION MOLECULE</td>
<td>AD</td>
<td>Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate &amp;</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
<th>AD/AR</th>
<th>Phenotypic features</th>
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<tbody>
<tr>
<td><strong>MLH1</strong>&lt;sup&gt;32,34–39&lt;/sup&gt;</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, prostate &amp; brain cancer, sebaceous neoplasms</td>
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<td><strong>MSH2</strong>&lt;sup&gt;32–39&lt;/sup&gt;</td>
<td>DNA MISMATCH REPAIR PROTEIN MSH2</td>
<td>AD</td>
<td>Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate &amp; brain cancer, sebaceous neoplasms</td>
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<tr>
<td><strong>MSH6</strong>&lt;sup&gt;32,34–38,40&lt;/sup&gt;</td>
<td>DNA MISMATCH REPAIR PROTEIN MSH6</td>
<td>AD</td>
<td>Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate &amp; brain cancer, sebaceous neoplasms</td>
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<tr>
<td><strong>MUTYH</strong>&lt;sup&gt;2,3,41–51&lt;/sup&gt;</td>
<td>ADENINE DNA GLYCOSYLASE</td>
<td>AR</td>
<td>MUTYH-associated polyposis (MAP): colorectal, small bowel &amp; endometrial serous cancer, gastrointestinal polyps</td>
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<tr>
<td><strong>NTHL1</strong>&lt;sup&gt;52–55&lt;/sup&gt;</td>
<td>ENDONUCLEASE III-LIKE 1</td>
<td>AR</td>
<td>Colon cancer, colon polyps</td>
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<tr>
<td><strong>PMS2</strong>&lt;sup&gt;32,34–37,56,57&lt;/sup&gt;</td>
<td>MISMATCH REPAIR ENDONUCLEASE PMS2</td>
<td>AD</td>
<td>Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate &amp; brain cancer, sebaceous neoplasms</td>
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<tr>
<td>Gene</td>
<td>Description</td>
<td>Inheritance</td>
<td>Cancer/Tumor Types</td>
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<tr>
<td><strong>POLD1</strong>⁵⁸,⁵⁹</td>
<td>DNA POLYMPERASE DELTA CATALYTIC SUBUNIT</td>
<td>AR</td>
<td>Constitutional mismatch repair deficiency syndrome</td>
</tr>
<tr>
<td><strong>POLE</strong>⁵⁸,⁶⁰–⁶²</td>
<td>DNA POLYMPERASE EPSILON CATALYTIC SUBUNIT A</td>
<td>AD</td>
<td>Colon &amp; endometrial cancer, colon polyps</td>
</tr>
<tr>
<td><strong>PTEN</strong>²,⁶³–⁶⁶</td>
<td>PHOSPHATIDYLINOSITOL 3,4,5-TRISPHOSPHATE 3-PHOSPHATASE AND DUAL-SPECIFICITY PROTEIN PHOSPHATASE PTEN</td>
<td>AD</td>
<td>PTEN hamartoma tumor syndrome (PHTS): breast, thyroid, endometrial, colon, melanoma &amp; renal cancer, gastrointestinal polyps, Lhermitte-Duclos disease</td>
</tr>
<tr>
<td><strong>SCG5/GREM1</strong>¹⁵,⁶⁷,⁶⁸</td>
<td>NEUROENDOCRINE PROTEIN 7B2/GREMLIN-1</td>
<td>AD</td>
<td>Hereditary Mixed Polyposis syndrome (HMPS): colon cancer, colon polyps</td>
</tr>
<tr>
<td><strong>SMAD4</strong>²,¹⁴,¹⁶,⁶⁹,⁷⁰</td>
<td>MOTHERS AGAINST DECAPENTAPLEGIC HOMOLOG 4</td>
<td>AD</td>
<td>Juvenile Polyposis syndrome (JPS): colorectal, gastric (if gastric polyps), small bowel &amp; pancreatic cancer, gastrointestinal polyps</td>
</tr>
<tr>
<td><strong>STK11</strong>²,⁷¹–⁷³</td>
<td>SERINE/THREONINE-PROTEIN KINASE STK11</td>
<td>AD</td>
<td>Peutz-Jeghers syndrome (PJS): breast, colorectal, pancreatic, gastric, small bowel, ovarian, lung, cervical &amp; endometrial cancer, testicular tumors (LCCSCT), gastrointestinal polyps</td>
</tr>
<tr>
<td><strong>TP53</strong>²⁴,⁷⁴–⁷⁸</td>
<td>CELLULAR TUMOR ANTIGEN P53</td>
<td>AD</td>
<td>Li-Fraumeni syndrome (LFS): breast cancer, sarcoma, brain cancer, hematologic malignancies, adrenocortical carcinoma, among others**</td>
</tr>
</tbody>
</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.
References:


