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 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 PTEN, nucleotides c.-700 through c.-1300 in the promoter region, and 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 and SCG5 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.

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-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 and CHEK2, 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>
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</thead>
<tbody>
<tr>
<td>APC</td>
<td>ADENOMATOUS POLYPOSIOS 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>AR</td>
<td>Ataxia telangiectasia</td>
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</tr>
<tr>
<td>AXIN2</td>
<td>AXIN-2</td>
<td>AD</td>
<td>Colon cancer, colon polyps</td>
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<td>BMPR1A</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>
</tr>
<tr>
<td>CDH1</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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<td>CHEK2</td>
<td>SERINE/THREONINE-PROTEIN KINASE CHK2</td>
<td>AD</td>
<td>Breast, colon, prostate, thyroid, endometrial &amp; ovarian 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</td>
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<tr>
<td>Genes</td>
<td>Proteins</td>
<td>Inheritance</td>
<td>Description</td>
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<tr>
<td><strong>MLH1</strong></td>
<td>DNA MISMATCH REPAIR PROTEIN MLH1</td>
<td><em>AD</em></td>
<td>Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel &amp; brain cancer, sebaceous neoplasms</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>AR</em></td>
<td>Constitutional mismatch repair deficiency syndrome</td>
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<tr>
<td><strong>MSH2</strong></td>
<td>DNA MISMATCH REPAIR PROTEIN MSH2</td>
<td><em>AD</em></td>
<td>Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, urinary tract, pancreatic, biliary tract, small bowel &amp; brain cancer, sebaceous neoplasms</td>
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<tr>
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<td></td>
<td><em>AR</em></td>
<td>Constitutional mismatch repair deficiency syndrome</td>
</tr>
<tr>
<td><strong>MSH6</strong></td>
<td>DNA MISMATCH REPAIR PROTEIN MSH6</td>
<td><em>AD</em></td>
<td>Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, small bowel &amp; brain cancer, sebaceous neoplasms</td>
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<tr>
<td></td>
<td></td>
<td><em>AR</em></td>
<td>Constitutional mismatch repair deficiency syndrome</td>
</tr>
<tr>
<td><strong>MUTYH</strong></td>
<td>ADENINE DNA GLYCOSYLASE</td>
<td><em>AR</em></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></td>
<td>ENDONUCLEASE III-LIKE 1</td>
<td><em>AR</em></td>
<td>Colon cancer, colon polyps</td>
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<tr>
<td><strong>PMS2</strong></td>
<td>MISMATCH REPAIR ENDONUCLEASE PMS2</td>
<td><em>AD</em></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><em>AR</em></td>
<td>Constitutional mismatch repair deficiency syndrome</td>
</tr>
<tr>
<td><strong>POLD1</strong></td>
<td>DNA POLYMERASE DELTA CATALYTIC SUBUNIT</td>
<td><em>AD</em></td>
<td>Colon &amp; endometrial cancer, colon polyps</td>
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<tr>
<td>Gene</td>
<td>Description</td>
<td>Inheritance</td>
<td>Cancer Risk</td>
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<tr>
<td><strong>POLE</strong></td>
<td>DNA POLYMERASE EPSILON CATALYTIC SUBUNIT A</td>
<td>AD</td>
<td>Colon cancer, gastrointestinal polyps</td>
</tr>
<tr>
<td><strong>PTEN</strong></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></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></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></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></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.

Abbreviations:
AD – Autosomal Dominant
AR – Autosomal Recessive
CGH – Comparative genomic hybridization
LCCSCT – Large cell-calcifying Sertoli cell tumors
MLPA - Multiplex ligation-dependent probe amplification

References:


