OncoGeneDx: High/Moderate Risk Panel

Panel Gene List: APC, ATM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, EPCAM*, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53, VHL

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

Clinical Features:
Cancer is a common disease affecting approximately 1 in 3 individuals in the U.S (SEER). While the majority of cancers are sporadic in nature, some families have hereditary forms of cancer that are associated with increased cancer risks compared with the general population. Approximately 5-10% of cancer 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, and several relatives affected with the same type of cancer or related cancers spanning multiple generations.

For some of the well-described hereditary conditions discussed below, clinical diagnostic criteria, based on personal medical history and family history, are available to help identify patients most likely to have a hereditary cancer syndrome. In many cases, however, patients do not meet the clinical diagnostic criteria or the criteria may overlap for multiple conditions, making it difficult to decide which genes should be tested and in what order. The OncoGeneDx High/Moderate Risk Panel offered at GeneDx includes analysis of 23 genes associated with hereditary predisposition to various cancers including the most well-known hereditary cancer syndromes such as Hereditary Breast and Ovarian Cancer Syndrome (BRCA1, BRCA2) and Lynch Syndrome (MLH1, MSH2, MSH6, PMS2 and EPCAM) as well as moderately penetrant genes including ATM, BRIP1, CHEK2, RAD51C and RAD51D. Many of the genes on this panel are involved in the mismatch repair pathway, the Fanconi anemia pathway and/or play a role in DNA damage repair.

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 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 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. 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. Data analysis is performed using gene-specific filtering; the genes evaluated by this test are listed on the first page of the report.

Test Sensitivity:
The clinical sensitivity of sequencing and deletion/duplication analysis of the 23 genes included in the OncoGeneDx High/Moderate Risk 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 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>
</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>
</tr>
<tr>
<td>ATM</td>
<td>SERINE-PROTEIN KINASE ATM</td>
<td>AD</td>
<td>Breast, colon &amp; pancreatic cancers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AR</td>
<td>Ataxia telangiectasia</td>
</tr>
<tr>
<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>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>
</tr>
<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>
</tr>
<tr>
<td></td>
<td></td>
<td>AR</td>
<td>Fanconi Anemia</td>
</tr>
<tr>
<td>BRIP1</td>
<td>FANCONI ANEMIA GROUP J PROTEIN</td>
<td>AD</td>
<td>Breast &amp; ovarian cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AR</td>
<td>Fanconi Anemia</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>
</tr>
<tr>
<td>Gene</td>
<td>Description</td>
<td>Mode</td>
<td>Associated Conditions</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------------------------------------</td>
<td>------</td>
<td>--------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>CDKN2A</strong></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>
</tr>
<tr>
<td><strong>CHEK2</strong></td>
<td>SERINE/THREONINE-PROTEIN KINASE CHK2</td>
<td>AD</td>
<td>Breast, colon, prostate, thyroid, endometrial &amp; ovarian cancer</td>
</tr>
<tr>
<td><strong>EPCAM</strong></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>
</tr>
<tr>
<td><strong>MLH1</strong></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>
</tr>
<tr>
<td><strong>MSH2</strong></td>
<td>DNA MISMATCH REPAIR PROTEIN MSH2</td>
<td>AD</td>
<td>Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, urinary tract, pancreatic, biliary tract, small bowel &amp; brain cancer, sebaceous neoplasms</td>
</tr>
<tr>
<td><strong>MSH6</strong></td>
<td>DNA MISMATCH REPAIR PROTEIN MSH6</td>
<td>AD</td>
<td>Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, small bowel &amp; brain cancer, sebaceous neoplasms</td>
</tr>
<tr>
<td><strong>MUTYH</strong></td>
<td>ADENINE DNA GLYCOSYLASE</td>
<td>AR</td>
<td>MUTYH-associated polyposis (MAP): colorectal, small Bowel &amp; endometrial serous cancer, gastrointestinal polyps</td>
</tr>
<tr>
<td><strong>PALB2</strong></td>
<td>PARTNER AND LOCALIZER OF BRCA2</td>
<td>AD</td>
<td>Breast, pancreatic &amp; ovarian cancer</td>
</tr>
<tr>
<td><strong>PMS2</strong></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 &amp; brain cancer, sebaceous neoplasms</td>
</tr>
<tr>
<td>Gene</td>
<td>Description</td>
<td>Inheritance</td>
<td>Phenotype</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>PTEN</strong></td>
<td>PHOSPHATIDYLINOSITOL 3,4,5-TRISPHOSPHATE 3-PHOSPHATASE AND DUAL-SPECIFICITY PROTEIN PHOSPHATASE PTEN</td>
<td>AR</td>
<td>Constitutional mismatch repair deficiency syndrome</td>
</tr>
<tr>
<td><strong>RAD51C</strong></td>
<td>DNA REPAIR PROTEIN RAD51 HOMOLOG 3</td>
<td>AD</td>
<td>Breast &amp; ovarian cancer</td>
</tr>
<tr>
<td><strong>RAD51D</strong></td>
<td>DNA REPAIR PROTEIN RAD51 HOMOLOG 4</td>
<td>AD</td>
<td>Breast &amp; ovarian cancer</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>
<tr>
<td><strong>VHL</strong></td>
<td>VON HIPPEL-LINDAU DISEASE TUMOR SUPPRESSOR</td>
<td>AD</td>
<td>von Hippel-Lindau (VHL) disease: renal cancer (clear cell), pancreatic neuroendocrine tumors, hemangioblastoma, pheochromocytoma, endolymphatic sac tumors</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
- MLPA – Multiplex ligation-dependent probe amplification
- LCCSCT - Large cell-calcifying Sertoli cell tumor
References:


