OncoGeneDx: Common Cancer Management Panel

Panel Gene List: APC, ATM, AXIN2, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, EPCAM*, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SCG5/GREM1*, SDHB, SDHC, SDHD, SMAD4, STK11, TP53, TSC1, TSC2, VHL

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

Clinical Features:
Cancer is a common disease affecting approximately 1 in 3 individuals in the U.S.\(^1\) 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.

The OncoGeneDx Common Cancer Management Panel includes analysis of 37 cancer-predisposition genes that have expert clinical management guidelines for pathogenic variant carriers. This panel includes genes associated with well-described hereditary syndromes, such as BRCA1, BRCA2 (Hereditary Breast and Ovarian Cancer Syndrome) and MLH1, MSH2, MSH6, PMS2 and EPCAM (Lynch Syndrome), as well as other genes that are less well described, but have overlapping phenotypes.

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-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. 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 or confirm regions with inadequate sequence or copy number data by NGS. 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 37 genes included in the OncoGeneDx Common Cancer Management 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.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Inheritance</th>
<th>Disease Associations</th>
</tr>
</thead>
<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 periangillary, gastric, thyroid, pancreatic, brain (medulloblastoma) &amp; liver (hepatoblastoma) cancers, desmoid tumors, gastrointestinal polyps</td>
</tr>
<tr>
<td>ATM^{6-11}</td>
<td>SERINE-PROTEIN KINASE ATM</td>
<td>AD</td>
<td>Breast, colon &amp; pancreatic cancers</td>
</tr>
<tr>
<td>ATM^{6-11}</td>
<td>ATM</td>
<td>AR</td>
<td>Ataxia telangiectasia</td>
</tr>
<tr>
<td>AXIN2^{12,13}</td>
<td>AXIN-2</td>
<td>AD</td>
<td>Colon cancer, colon polyps</td>
</tr>
<tr>
<td>BMPR1A^{4,14-16}</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>
</tr>
<tr>
<td>BRCA1^{17-27}</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^{17-25,27}</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>BRIP1^{17,28-30}</td>
<td>FANCONI ANEMIA GROUP J PROTEIN</td>
<td>AD</td>
<td>Breast &amp; ovarian cancer</td>
</tr>
<tr>
<td>BRIP1^{17,28-30}</td>
<td>FANCONI ANEMIA GROUP J PROTEIN</td>
<td>AR</td>
<td>Fanconi anemia</td>
</tr>
<tr>
<td>CDH1^{31-37}</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>Protein</td>
<td>Inheritance</td>
<td>Disease Associations</td>
</tr>
<tr>
<td>-------</td>
<td>-------------------------------------------------------------------------</td>
<td>-------------</td>
<td>--------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>CDKN2A</strong>&lt;sup&gt;38–43&lt;/sup&gt;</td>
<td>CYCLIN-DEPENDENT KINASE INHIBITOR 2A, TUMOR SUPPRESSOR ARF</td>
<td>AD</td>
<td>Familial atypical multiple mole melanoma (FAMMM) syndrome: melanoma, pancreatic cancer &amp; astrocytoma</td>
</tr>
<tr>
<td><strong>CHEK2</strong>&lt;sup&gt;7,8,26,44–50&lt;/sup&gt;</td>
<td>SERINE/THREONINE-PROTEIN KINASE CHK2</td>
<td>AD</td>
<td>Breast, colon, prostate, gastric &amp; thyroid cancer</td>
</tr>
<tr>
<td><strong>EPCAM</strong>&lt;sup&gt;51,51–56&lt;/sup&gt;</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; brain cancer, sebaceous neoplasms</td>
</tr>
<tr>
<td><strong>FH</strong>&lt;sup&gt;57–61&lt;/sup&gt;</td>
<td>FUMARATE HYDRATASE, MITOCHONDRIAL</td>
<td>AD</td>
<td>Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer (type II papillary), leiomyomas, pheochromocytoma, paraganglioma</td>
</tr>
<tr>
<td><strong>FLCN</strong>&lt;sup&gt;62–66&lt;/sup&gt;</td>
<td>FOLLICULIN</td>
<td>AD</td>
<td>Birt-Hogg-Dubé syndrome (BHD): renal cancer</td>
</tr>
<tr>
<td><strong>MLH1</strong>&lt;sup&gt;51–55,67,68&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>
</tr>
<tr>
<td><strong>MSH2</strong>&lt;sup&gt;51–56,67,68&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,</td>
</tr>
<tr>
<td>Gene</td>
<td>Protein</td>
<td>Inheritance</td>
<td>Disease Associations</td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>MSH6&lt;sup&gt;51–55,67,69&lt;/sup&gt;</td>
<td>DNA MISMATCH REPAIR PROTEIN MSH6</td>
<td>AR</td>
<td>Constitutional mismatch repair deficiency syndrome</td>
</tr>
<tr>
<td>MUTYH&lt;sup&gt;4,5,70–80&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>
</tr>
<tr>
<td>NBN&lt;sup&gt;61–87&lt;/sup&gt;</td>
<td>NIBRIN</td>
<td>AD</td>
<td>Breast &amp; prostate cancer, non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>NBN&lt;sup&gt;61–87&lt;/sup&gt;</td>
<td>NIBRIN</td>
<td>AR</td>
<td>Nijmegen breakage syndrome</td>
</tr>
<tr>
<td>NF1&lt;sup&gt;88–90&lt;/sup&gt;</td>
<td>NEUROFIBROMIN</td>
<td>AD</td>
<td>Neurofibromatosis type 1 (NF1) syndrome: breast cancer, GIST, optic nerve gliomas, pheochromocytoma, MPNST, neurofibromas, brain tumors</td>
</tr>
<tr>
<td>NTHL&lt;sup&gt;191–94&lt;/sup&gt;</td>
<td>ENDONUCLEASE III-LIKE 1</td>
<td>AR</td>
<td>Colon cancer, colon polyps</td>
</tr>
<tr>
<td>PALB2&lt;sup&gt;7,95–100&lt;/sup&gt;</td>
<td>PARTNER AND LOCALIZER OF BRCA2</td>
<td>AD</td>
<td>Breast, pancreatic &amp; ovarian cancer</td>
</tr>
<tr>
<td>PALB2&lt;sup&gt;7,95–100&lt;/sup&gt;</td>
<td>PARTNER AND LOCALIZER OF BRCA2</td>
<td>AR</td>
<td>Fanconi anemia</td>
</tr>
<tr>
<td>PMS2&lt;sup&gt;51–55,101,102&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>
</tr>
<tr>
<td>Gene</td>
<td>Protein</td>
<td>Inheritance</td>
<td>Disease Associations</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------------------------------------------</td>
<td>-------------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>prostate &amp; brain cancer, sebaceous neoplasms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AR</td>
<td>Constitutional mismatch repair deficiency syndrome</td>
</tr>
<tr>
<td><strong>POLD1</strong>&lt;sup&gt;103,104&lt;/sup&gt;</td>
<td>DNA POLYMERASE DELTA CATALYTIC SUBUNIT</td>
<td>AD</td>
<td>Colon, endometrial cancer, colon polyps</td>
</tr>
<tr>
<td><strong>POLE</strong>&lt;sup&gt;103,105–107&lt;/sup&gt;</td>
<td>DNA POLYMERASE EPSILON CATALYTIC SUBUNIT A</td>
<td>AD</td>
<td>Colon cancer, gastrointestinal polyps</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AR</td>
<td>Facial dysmorphism, immunodeficiency, livedo, and short stature (FILS)</td>
</tr>
<tr>
<td><strong>PTEN</strong>&lt;sup&gt;4,108–111&lt;/sup&gt;</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>RAD51C</strong>&lt;sup&gt;112–115&lt;/sup&gt;</td>
<td>DNA REPAIR PROTEIN RAD51 HOMOLOG 3</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><strong>RAD51D</strong>&lt;sup&gt;112,113,116,117&lt;/sup&gt;</td>
<td>DNA REPAIR PROTEIN RAD51 HOMOLOG 4</td>
<td>AD</td>
<td>Breast &amp; ovarian cancer</td>
</tr>
<tr>
<td><strong>SCG5/GREM1</strong>&lt;sup&gt;118–120&lt;/sup&gt;</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>SDHB</strong>&lt;sup&gt;121–124&lt;/sup&gt;</td>
<td>SUCCINATE DEHYDROGENASE [UBIQUINONE] IRON-SULFUR SUBUNIT, MITOCHONDRIAL</td>
<td>AD</td>
<td>Hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome: paraganglioma, pheochromocytoma, renal cancer, GIST</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AR</td>
<td>Isolated complex II deficiency</td>
</tr>
<tr>
<td><strong>SDHC</strong>&lt;sup&gt;121,122,125–127&lt;/sup&gt;</td>
<td>SUCCINATE DEHYDROGENASE CYTOCHROME B560 SUBUNIT, MITOCHONDRIAL</td>
<td>AD</td>
<td>Hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome: paraganglioma, pheochromocytoma,</td>
</tr>
<tr>
<td>Gene</td>
<td>Protein</td>
<td>Inheritance</td>
<td>Disease Associations</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------</td>
<td>-------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>SDHD</td>
<td>SUCCINATE DEHYDROGENASE [UBIQUINONE] CYTOCHROME B SMALL SUBUNIT, MITOCHONDRIAL</td>
<td>AD</td>
<td>Hereditary paraganglioma/ pheochromocytoma (PGL/PCC) syndrome: paraganglioma, pheochromocytoma, renal cancer, GIST, thyroid cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AR</td>
<td>Isolated complex II deficiency</td>
</tr>
<tr>
<td>SMAD4</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>STK11</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>TP53</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>TSC1</td>
<td>HAMARTIN</td>
<td>AD</td>
<td>Tuberous sclerosis complex (TSC): renal cancer/tumors, CNS tumors (subependymal nodules and subependymal giant cell astrocytomas), hamartomatous tumors (cardiac rhabdomyomas and angiomyolipomas)</td>
</tr>
<tr>
<td>Gene</td>
<td>Protein</td>
<td>Inheritance</td>
<td>Disease Associations</td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
<td>-------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>TSC2&lt;sup&gt;140–142&lt;/sup&gt;</td>
<td>TUBERIN</td>
<td>AD</td>
<td>Tuberous sclerosis complex (TSC); renal cancer/tumors, CNS tumors (subependymal nodules and subependymal giant cell astrocytomas), hamartomatous tumors (cardiac rhabdomyomas and angiomyolipomas)</td>
</tr>
<tr>
<td>VHL&lt;sup&gt;143–146&lt;/sup&gt;</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
- GIST – Gastrointestinal stromal tumor
- LCCSCT - Large cell-calcifying Sertoli cell tumor
- MLPA – Multiplex ligation-dependent probe amplification
- MPNST - Malignant peripheral nerve sheath tumors

References:


86. Buslov, K. G. et al. NBS1 657del5 mutation may contribute only to a limited fraction of breast cancer cases in Russia. Int. J. Cancer 114, 585–589 (2005).

www.genedx.com     Page 10 of 12, Updated: Jan-2020