Panel Gene List: ALK, APC, ATM, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN2A, CHEK2, DICER1, EPCAM*, FANCC, FH, FLCN, HOXB13, MAX, MEN1, MET, MITF, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, NF2, NTHL1, PALB2, PHOX2B*, PMS2, POLD1, POLE, POT1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RECQL, RET*, SCG5/GREM1*, SDHA*, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL, WT1

*Testing includes sequencing and deletion/duplication analysis for all genes except EPCAM (del/dup only), PHOX2B (seq only), RET (seq only), SCG5/GREM1 (del/dup only) and SDHA (seq 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. Features 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.

GeneDx offers a variety of hereditary cancer panels to facilitate testing of the genes related to certain types of cancer, such as the OncoGeneDx Breast/Gyn Cancer Panel or OncoGeneDx Colorectal Cancer Panel. However, GeneDx also offers the option of ordering single-gene testing and/or a customized cancer panel from a list of 64 cancer susceptibility genes. The option of ordering each gene individually or in any combination allows the provider the flexibility to choose the most appropriate testing approach for their patient when an available OncoGeneDx panel is not desired.

Many of the cancer genes offered at GeneDx are involved in the mismatch repair pathway, the Fanconi anemia pathway and/or DNA damage repair. Specifically, they are associated with common cancer syndromes such as Hereditary Breast and Ovarian Cancer Syndrome (BRCA1, BRCA2), Lynch Syndrome (MLH1, MSH2, MSH6, PMS2, EPCAM) or are newly described cancer genes such as AXIN2, NTHL1, or RECQL. While the risks associated with the BRCA and Lynch genes have been well characterized, accurate risk assessment for pathogenic variants in more recently described genes may be complicated by factors which include small numbers of patients studied, potential ascertainment bias in the available studies, patients from only certain ethnic cohorts, low penetrance of pathogenic variants, wide confidence intervals in the results, and/or studies based on only one variant. Since the cancer risks are not yet well defined, no consensus guidelines for medical management may be available for these newer genes.
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. The DNA is enriched for the complete coding regions and splice 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; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Concurrent MSH2 Exons 1-7 Inversion analysis from NGS data is also performed. For PHOX2B, RET and SDHA, only sequencing is performed. In addition, polyalanine repeats for the commonly expanded region in exon 3 of PHOX2B are not resolved. 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 NGS. Reported clinically significant variants are confirmed by an appropriate method. Sequence variants are reported according to the Human Genome Variation Society (HGVS) guidelines. Copy number variants are reported based on the probe coordinates, the coordinates of the exons involved, or precise breakpoints when known. 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 64 genes included in the OncoGeneDx Custom 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. Sensitivity for NF2 is limited by somatic mosaicism; therefore, testing of tumor tissue may be considered after a negative result in an apparently de novo patient with a high clinical suspicion of NF2 syndrome.

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>ALK²</td>
<td>ALK TYROSINE KINASE RECEPTOR</td>
<td>AD</td>
<td>Neuroblastic tumors</td>
</tr>
<tr>
<td>APC³–⁶</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 (medulloblastoma) &amp; liver (hepatoblastoma) cancers, desmoid tumors, gastrointestinal polyps</td>
</tr>
<tr>
<td>ATM⁷–¹²</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>AXIN²¹³,¹⁴</td>
<td>AXIN-2</td>
<td>AD</td>
<td>Colon cancer, colon polyps</td>
</tr>
<tr>
<td>BAP¹⁵,¹⁶</td>
<td>UBIQUITIN</td>
<td>AD</td>
<td>Uveal/cutaneous melanoma</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
<th>Mode of Inheritance</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CARBOXYL-TERMINAL HYDROLASE BAP1</strong></td>
<td></td>
<td></td>
<td>mesothelioma, renal cancer</td>
</tr>
<tr>
<td><strong>BARD1^17–20</strong></td>
<td>BRCA1-ASSOCIATED RING DOMAIN PROTEIN 1</td>
<td>AD</td>
<td>Breast &amp; ovarian cancer</td>
</tr>
<tr>
<td><strong>BMPR1A^3,21–23</strong></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><strong>BRCA1^24–34</strong></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><strong>BRCA2^24–31,33,34</strong></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, endometrial serous cancer</td>
</tr>
<tr>
<td><strong>BRIP1^7,35–37</strong></td>
<td>FANCONI ANEMIA GROUP J PROTEIN</td>
<td>AD, AR</td>
<td>Fanconi anemia</td>
</tr>
<tr>
<td><strong>CDC73^38</strong></td>
<td>PARAFIBROMIN</td>
<td>AD</td>
<td>Parathyroid cancer, jaw fibromas, renal tumors, uterine tumors, hyperparathyroidism</td>
</tr>
<tr>
<td><strong>CDH1^39–45</strong></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><strong>CDK4^46–48</strong></td>
<td>CYCLIN-DEPENDENT KINASE 4</td>
<td>AD</td>
<td>Melanoma, non-melanoma skin &amp; pancreatic cancer</td>
</tr>
<tr>
<td><strong>CDKN2A^46,49–53</strong></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>CHEK2^7,8,32,54–60</strong></td>
<td>SERINE/THREONINE-PROTEIN KINASE CHK2</td>
<td>AD</td>
<td>Breast, colon, prostate, gastric &amp; thyroid cancer</td>
</tr>
<tr>
<td><strong>DICER^61,62</strong></td>
<td>ENDORIBONUCLEASE DICER</td>
<td>AD</td>
<td>Pleuropulmonary blastoma, multinodular thyroid goiter and thyroid cancer, pineal and pituitary gland tumors/cancers,</td>
</tr>
<tr>
<td>Gene</td>
<td>Description</td>
<td>Inheritance</td>
<td>Cancer Types</td>
</tr>
<tr>
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</tr>
<tr>
<td><strong>EPCAM</strong>&lt;sup&gt;63–68&lt;/sup&gt;</td>
<td><strong>EPITHELIAL CELL ADHESION MOLECULE</strong></td>
<td><strong>AD</strong></td>
<td>Cystic nephroma, ovarian cancer (SLCT), cervical embryonal rhabdomyosarcoma, among others</td>
</tr>
<tr>
<td><strong>FANCC</strong>&lt;sup&gt;69,70&lt;/sup&gt;</td>
<td><strong>FANCONI ANEMIA GROUP C PROTEIN</strong></td>
<td><strong>AD</strong></td>
<td>Breast cancer</td>
</tr>
<tr>
<td><strong>FH</strong>&lt;sup&gt;71–75&lt;/sup&gt;</td>
<td><strong>FUMARATE HYDRATASE, MITOCHONDRIAL</strong></td>
<td><strong>AD</strong></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;76–80&lt;/sup&gt;</td>
<td><strong>FOLLICULIN</strong></td>
<td><strong>AD</strong></td>
<td>Birt-Hogg-Dubé syndrome (BHD): renal cancer</td>
</tr>
<tr>
<td><strong>HOXB13</strong>&lt;sup&gt;81–83&lt;/sup&gt;</td>
<td><strong>HOMEBOX PROTEIN HOX-B13</strong></td>
<td><strong>AD</strong></td>
<td>Prostate cancer</td>
</tr>
<tr>
<td><strong>MAX</strong>&lt;sup&gt;84–88&lt;/sup&gt;</td>
<td><strong>PROTEIN MAX</strong></td>
<td><strong>AD</strong></td>
<td>Paraganglioma, pheochromocytoma</td>
</tr>
<tr>
<td><strong>MEN1</strong>&lt;sup&gt;89–93&lt;/sup&gt;</td>
<td><strong>MENIN</strong></td>
<td><strong>AD</strong></td>
<td>Multiple endocrine neoplasia type 1 (MEN1): parathyroid tumors, pancreatic neuroendocrine tumors, anterior pituitary tumors, pheochromocytoma, meningioma, ependymoma, hyperparathyroidism</td>
</tr>
<tr>
<td><strong>MET</strong>&lt;sup&gt;94–97&lt;/sup&gt;</td>
<td><strong>HEPATOMECYTE GROWTH FACTOR RECEPTOR</strong></td>
<td><strong>AD</strong></td>
<td>Hereditary papillary renal carcinoma (HPRC): renal cancer (type I papillary)</td>
</tr>
<tr>
<td><strong>MITF</strong>&lt;sup&gt;98–100&lt;/sup&gt;</td>
<td><strong>MICROPHTHALMIA-ASSOCIATED TRANSCRIPTION FACTOR</strong></td>
<td><strong>AD</strong></td>
<td>Renal cancer, melanoma</td>
</tr>
<tr>
<td><strong>MLH1</strong>&lt;sup&gt;63,65–68,101,102&lt;/sup&gt;</td>
<td><strong>DNA MISMATCH REPAIR PROTEIN MLH1</strong></td>
<td><strong>AD</strong></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>MLH1</strong>&lt;sup&gt;63,65–68,101,102&lt;/sup&gt;</td>
<td><strong>CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY SYNDROME</strong></td>
<td><strong>AR</strong></td>
<td>Constitutional mismatch repair deficiency syndrome</td>
</tr>
</tbody>
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<th>Inheritance</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MSH2</strong>&lt;sup&gt;63–68,101,102&lt;/sup&gt;</td>
<td>DNA MISMATCH REPAIR PROTEIN MSH2</td>
<td>AD</td>
<td>urinary tract, small bowel, prostate &amp; brain cancer, sebaceous neoplasms</td>
</tr>
<tr>
<td><strong>MSH6</strong>&lt;sup&gt;63,65–68,101,103&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>
</tr>
<tr>
<td><strong>MUTYH</strong>&lt;sup&gt;3,4,104–114&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><strong>NBN</strong>&lt;sup&gt;115–121&lt;/sup&gt;</td>
<td>NIBRIN</td>
<td>AD</td>
<td>Breast &amp; prostate cancer, non-Hodgkin lymphoma</td>
</tr>
<tr>
<td><strong>NF1</strong>&lt;sup&gt;122–124&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><strong>NF2</strong>&lt;sup&gt;125–128&lt;/sup&gt;</td>
<td>MERLIN</td>
<td>AD</td>
<td>Neurofibromatosis type 2 (NF2) syndrome: schwannomas - vestibular and other, spinal tumors, meningiomas</td>
</tr>
<tr>
<td><strong>NTHL1</strong>&lt;sup&gt;129–132&lt;/sup&gt;</td>
<td>ENDONUCLEASE III-LIKE 1</td>
<td>AR</td>
<td>Colon cancer, colon polyps</td>
</tr>
<tr>
<td><strong>PALB2</strong>&lt;sup&gt;7,133–138&lt;/sup&gt;</td>
<td>PARTNER AND LOCALIZER OF BRCA2</td>
<td>AD</td>
<td>Breast, pancreatic, &amp; ovarian cancer</td>
</tr>
<tr>
<td><strong>AR</strong></td>
<td>Constitutional mismatch repair deficiency syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description</td>
<td>Inheritance</td>
<td>Associated Conditions</td>
</tr>
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</tr>
<tr>
<td><strong>PHOX2B</strong></td>
<td>Paired Mesoderm Homeobox Protein 2B</td>
<td>AD</td>
<td>Neuroblastic tumors</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, 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></td>
<td>DNA Polymerase Delta Catalytic Subunit</td>
<td>AD</td>
<td>Colon, endometrial cancer, colon polyps</td>
</tr>
<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></td>
<td></td>
<td>AR</td>
<td>Facial dysmorphism, immunodeficiency, livedo, and short stature (FILS)</td>
</tr>
<tr>
<td><strong>POT1</strong></td>
<td>Protection of Telomeres 1</td>
<td>AD</td>
<td>Melanoma &amp; brain glial tumors</td>
</tr>
<tr>
<td><strong>PRKAR1A</strong></td>
<td>Camp-Dependent Protein Kinase Type 1-Alpha Regulatory Subunit</td>
<td>AD</td>
<td>Thyroid cancer, testicular tumors (LCCSCT), myxomas, psammomatous melanotic schwannomas (PMSs), primary pigmented nodular adrenocortical disease, pituitary adenomas, among others</td>
</tr>
<tr>
<td><strong>PTCH1</strong></td>
<td>Protein Patched Homolog 1</td>
<td>AD</td>
<td>Gorlin syndrome: basal cell carcinoma, medulloblastoma, meningioma, fibromas, jaw tumors (ontogenic keratocysts)</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>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></td>
<td></td>
<td>AR</td>
<td>Fanconi anemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Description</th>
<th>Inheritance</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RB1</strong></td>
<td>RETINOBLASTOMA-ASSOCIATED PROTEIN</td>
<td>AD</td>
<td>Hereditary retinoblastoma: retinoblastoma, sarcoma, leukemia, melanoma, pineoblastoma</td>
</tr>
<tr>
<td><strong>RECQL</strong></td>
<td>RECQ PROTEIN-LIKE</td>
<td>AD</td>
<td>Breast cancer</td>
</tr>
<tr>
<td><strong>RET</strong></td>
<td>PROTO-ONCOGENE TYROSINE-PROTEIN KINASE RECEPTOR RET</td>
<td>AD</td>
<td>Multiple endocrine neoplasmia type 2 (MEN2): medullary thyroid cancer, pheochromocytoma, hyperparathyroidism</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>SDHA</strong></td>
<td>SUCCINATE DEHYDROGENASE [UBIQUINONE] FLAVOPROTEIN SUBUNIT, MITOCHONDRIAL</td>
<td>AD</td>
<td>Hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome: paraganglioma, pheochromocytoma, GIST</td>
</tr>
<tr>
<td><strong>SDHAF2</strong></td>
<td>SUCCINATE DEHYDROGENASE ASSEMBLY FACTOR 2, MITOCHONDRIAL</td>
<td>AD</td>
<td>Hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome: paraganglioma</td>
</tr>
<tr>
<td><strong>SDHB</strong></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><strong>SDHC</strong></td>
<td>SUCCINATE DEHYDROGENASE CYTOCHROME B560 SUBUNIT, MITOCHONDRIAL</td>
<td>AD</td>
<td>Hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome: paraganglioma, pheochromocytoma, renal cancer, GIST</td>
</tr>
<tr>
<td><strong>SDHD</strong></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>
</tbody>
</table>
| **SMAD4** | MOTHERS AGAINST DECAPENTAPLEGIC | AD | Juvenile polyposis syndrome (JPS): colorectal, gastric (if
<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
<th>Mutations</th>
<th>Phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HOMOLOG 4</strong></td>
<td>gastric polyps, small bowel &amp; pancreatic cancer, gastrointestinal polyps</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SMARCA4</strong>&lt;sup&gt;202–206&lt;/sup&gt;</td>
<td>TRANSCRIPTION ACTIVATOR BRG1</td>
<td>AD</td>
<td>Ovarian (SCCOHT) cancer, Malignant rhabdoid tumors-atypical teratoid/rhabdoid tumor of the brain and malignant rhabdoid tumors of the kidney</td>
</tr>
<tr>
<td><strong>SMARCB1</strong>&lt;sup&gt;207–210&lt;/sup&gt;</td>
<td>SWI/SNF-RELATED MATRIX-ASSOCIATED ACTIN-DEPENDENT REGULATOR OF CHROMATIN SUBFAMILY B MEMBER 1</td>
<td>AD</td>
<td>Malignant rhabdoid tumors-atypical teratoid/rhabdoid tumor of the brain and malignant rhabdoid tumors of the kidney, schwannomas, meningiomas</td>
</tr>
<tr>
<td><strong>STK11</strong>&lt;sup&gt;3,211–213&lt;/sup&gt;</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>SUFU</strong>&lt;sup&gt;160,161,214,215&lt;/sup&gt;</td>
<td>SUPPRESSOR OF FUSED HOMOLOG</td>
<td>AD</td>
<td>Medulloblastoma, basal cell carcinoma, meningioma</td>
</tr>
<tr>
<td><strong>TMEM127</strong>&lt;sup&gt;84,216,217&lt;/sup&gt;</td>
<td>TRANSMEMBRANE PROTEIN 127</td>
<td>AD</td>
<td>Hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome: pheochromocytoma</td>
</tr>
<tr>
<td><strong>TP53</strong>&lt;sup&gt;32,218–222&lt;/sup&gt;</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>TSC1</strong>&lt;sup&gt;223–225&lt;/sup&gt;</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><strong>TSC2</strong>&lt;sup&gt;223–225&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),</td>
</tr>
<tr>
<td>Gene Symbol</td>
<td>Tumor Type</td>
<td>Inheritance</td>
<td>Disease Type</td>
</tr>
<tr>
<td>------------</td>
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</tr>
<tr>
<td><strong>VHL</strong>226–229</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>
<tr>
<td><strong>WT1</strong>230–232</td>
<td>WILMS TUMOR PROTEIN</td>
<td>AD</td>
<td>Wilms tumor</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 tumors
- MLPA – Multiplex ligation-dependent probe amplification
- MPNST - Malignant peripheral nerve sheath tumors
- SCCOHT - Small cell carcinoma of the ovary, hypercalcaemic type
- SLCT - Sertoli-Leydig cell tumor

**References:**


119. 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).


