OncoGeneDx: Brain Tumor Panel

Panel Gene List: APC, CDKN1B, CDKN2A, DICER1, EPCAM*, MEN1, MLH1, MSH2, MSH6, NF1, NF2, PMS2, POT1, PTCH1, PTEN, SMARCA4, SMARCB1, SMARCE1, SUFU, TP53, TSC1, TSC2, VHL
Testing includes sequencing and deletion/duplication analysis for all genes except EPCAM (del/dup only).

Clinical Features:
In the general population, approximately 0.6% of individuals will be diagnosed with a brain or other nervous system cancer during their lifetime. Tumors of the brain and nervous system can be benign or malignant. The majority of these tumors are sporadic; however, approximately 5-12% may be associated with a hereditary predisposition. The features of a personal and/or family history of cancer that are suggestive of a hereditary predisposition include young age at diagnosis, multiple family members affected with brain cancer/tumors, and/or the association of brain cancer with other cancers, such as breast, colon, thyroid, ovarian, skin, or renal.

The OncoGeneDx Brain Tumor Panel includes analysis of 23 genes that have been implicated in a predisposition for the development of brain tumors. All of the genes on this panel also predispose to an increased risk for other cancers and/or tumors, and many are associated with hereditary syndromes that have expert clinical management guidelines for pathogenic variant carriers. These include Lynch syndrome and constitutional mismatch repair deficiency syndrome (EPCAM, MLH1, MSH2, MSH6, PMS2), familial adenomatous polyposis (APC), familial atypical multiple mole melanoma syndrome (CDKN2A), multiple endocrine neoplasia type 1 (MEN1), Gorlin syndrome (PTCH1, SUFU), Li-Fraumeni syndrome (TP53), neurofibromatosis types 1 (NF1) and 2 (NF2), PTEN hamartoma tumor syndrome (PTEN), tuberous sclerosis complex (TSC1, TSC2), and von Hippel-Lindau disease (VHL). Six additional genes, CDKN1B, DICER1, POT1, SMARCA4, SMARCB1, and SMARCE1, have only recently been described in association with an increased cancer risk. Since the cancer risks for these genes are not yet well defined, no consensus medical management guidelines have been published, but management guidelines have been asserted by disease-specific experts.

Inheritance Pattern:
All of the genes on this panel are associated with an autosomal dominant 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 \textit{PTEN} nucleotides c.-700 through c.-1300 in the promoter region, and for \textit{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 \textit{MSH2} Exons 1-7 Inversion analysis from NGS data is also performed. For \textit{EPCAM}, 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 23 genes included in the OncoGeneDx Brain Tumor 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</td>
<td>ADENOMATOUS POLYPOSIS COLI PROTEIN</td>
<td>AD</td>
<td>Familial Adenomatous Polyposis (FAP)-associated condition: colorectal, duodenal, duodenal or perianpillary, gastric, thyroid, pancreatic, brain (medulloblastoma) &amp; liver (hepatoblastoma) cancers, desmoid tumors, gastrointestinal polyps</td>
</tr>
<tr>
<td>CDKN1B</td>
<td>CYCLIN-DEPENDENT KINASE INHIBITOR 1B</td>
<td>AD</td>
<td>Multiple endocrine neoplasia type 4 (MEN4): primary hyperparathyroidism, pituitary adenomas, gastro-entero-pancreatic neuroendocrine tumors, parathyroid adenomas</td>
</tr>
<tr>
<td>CDKN2A</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>DICER</td>
<td>ENDORIBONUCLEASE DICER</td>
<td>AD</td>
<td>Pleuropulmonary blastoma, multinodular thyroid goiter and thyroid cancer, pineal and pituitary gland tumors/cancers, cystic nephroma, ovarian cancer (SLCT), cervical embryonal rhabdomyosarcoma, among others</td>
</tr>
<tr>
<td>EPCAM</td>
<td>EPITHELIAL CELL ADHESION MOLECULE</td>
<td>AD</td>
<td>Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic,</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>MEN1</strong>&lt;sup&gt;24–28&lt;/sup&gt;</td>
<td>MENIN</td>
<td>AD</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>MLH1</strong>&lt;sup&gt;18,20–23,29,30&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;18–23,29,30&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>
</tr>
<tr>
<td><strong>MSH6</strong>&lt;sup&gt;18,20–23,29,31&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>NF1</strong>&lt;sup&gt;32–34&lt;/sup&gt;</td>
<td>NEUROFIBROMIN</td>
<td>AD</td>
<td>Neurofibromatosis type 1 (NF1) syndrome: breast cancer, GIST, optic nerve</td>
</tr>
<tr>
<td>Gene</td>
<td>Description</td>
<td>Inheritance</td>
<td>Associated Conditions</td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td><strong>NF2</strong>&lt;sup&gt;35–38&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>PMS2</strong>&lt;sup&gt;18,20–23,39,40&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><strong>POT1</strong>&lt;sup&gt;41–45&lt;/sup&gt;</td>
<td>PROTECTION OF TELOMERES 1</td>
<td>AD</td>
<td>Constitutional mismatch repair deficiency syndrome</td>
</tr>
<tr>
<td><strong>PTCH1</strong>&lt;sup&gt;46–48&lt;/sup&gt;</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>&lt;sup&gt;4,49–52&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>SMARCA4</strong>&lt;sup&gt;53–57&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;58–61&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, schwannoma, meningioma</td>
</tr>
<tr>
<td>Gene</td>
<td>Description</td>
<td>Autosomal Dominance</td>
<td>Cancer/Tumor Types</td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
<td>---------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>SMARCE1</strong>&lt;sup&gt;53,62–65&lt;/sup&gt;</td>
<td>SWI/SNF-RELATED, MATRIX-ASSOCIATED, ACTIN-DEPENDENT REGULATOR OF CHROMATIN, SUBFAMILY E, MEMBER 1</td>
<td>AD</td>
<td>Coffin-Siris syndrome, cranial and spinal meningiomas (clear cell)</td>
</tr>
<tr>
<td><strong>SUFU</strong>&lt;sup&gt;46,47,66,67&lt;/sup&gt;</td>
<td>SUPPRESSOR OF FUSED HOMOLOG</td>
<td>AD</td>
<td>Medulloblastoma, basal cell carcinoma, meningioma</td>
</tr>
<tr>
<td><strong>TP53</strong>&lt;sup&gt;68–73&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;74–76&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;74–76&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><strong>VHL</strong>&lt;sup&gt;77–80&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
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:
1. Probability of Developing or Dying of Cancer - Surveillance Research Program. Available at: https://surveillance.cancer.gov/devcan/.