

## 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.<sup>1</sup> 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.<sup>2,3</sup> 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 *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*, 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.

Gene	Protein	Inheritance	Disease Associations
<i>APC</i> <sup>4-7</sup>	ADENOMATOUS POLYPOSIS COLI PROTEIN	AD	Familial Adenomatous Polyposis (FAP)-associated condition: colorectal, duodenal or periampullary, gastric, thyroid, pancreatic, brain (medulloblastoma) & liver (hepatoblastoma) cancers, desmoid tumors, gastrointestinal polyps
<i>CDKN1B</i> <sup>8,9</sup>	CYCLIN-DEPENDENT KINASE INHIBITOR 1B	AD	Multiple endocrine neoplasia type 4 (MEN4): primary hyperparathyroidism, pituitary adenomas, gastro-entero-pancreatic neuroendocrine tumors, parathyroid adenomas
<i>CDKN2A</i> <sup>10-15</sup>	CYCLIN-DEPENDENT KINASE INHIBITOR 2A, TUMOR SUPPRESSOR ARF	AD	Familial atypical multiple mole melanoma (FAMMM) syndrome: melanoma, pancreatic cancer & astrocytoma
<i>DICER1</i> <sup>16,17</sup>	ENDORIBONUCLEASE DICER	AD	Pleuropulmonary blastoma, multinodular thyroid goiter and thyroid cancer, pineal and pituitary gland tumors/cancers, cystic nephroma, ovarian cancer (SLCT), cervical embryonal rhabdomyosarcoma, among others
<i>EPCAM</i> <sup>18-23</sup>	EPITHELIAL CELL ADHESION MOLECULE	AD	Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic,

			biliary tract, urinary tract, small bowel, prostate & brain cancer, sebaceous neoplasms
		AR	Constitutional mismatch repair deficiency syndrome
<i>MEN1</i> <sup>24-28</sup>	MENIN	AD	Multiple endocrine neoplasia type 1 (MEN1): parathyroid tumors, pancreatic neuroendocrine tumors, anterior pituitary tumors, pheochromocytoma, meningioma, ependymoma, hyperparathyroidism
<i>MLH1</i> <sup>18,20-23,29,30</sup>	DNA MISMATCH REPAIR PROTEIN MLH1	AD	Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate & brain cancer, sebaceous neoplasms
		AR	Constitutional mismatch repair deficiency syndrome
<i>MSH2</i> <sup>18-23,29,30</sup>	DNA MISMATCH REPAIR PROTEIN MSH2	AD	Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate & brain cancer, sebaceous neoplasms
		AR	Constitutional mismatch repair deficiency syndrome
<i>MSH6</i> <sup>18,20-23,29,31</sup>	DNA MISMATCH REPAIR PROTEIN MSH6	AD	Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate & brain cancer, sebaceous neoplasms
		AR	Constitutional mismatch repair deficiency syndrome
<i>NF1</i> <sup>32-34</sup>	NEUROFIBROMIN	AD	Neurofibromatosis type 1 (NF1) syndrome: breast cancer, GIST, optic nerve

			gliomas, pheochromocytoma, MPNST, neurofibromas, brain tumors
<i>NF2</i> <sup>35–38</sup>	MERLIN	AD	Neurofibromatosis type 2 (NF2) syndrome: schwannomas - vestibular and other, spinal tumors, meningiomas
<i>PMS2</i> <sup>18,20–23,39,40</sup>	MISMATCH REPAIR ENDONUCLEASE PMS2	AD	Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate & brain cancer, sebaceous neoplasms
		AR	Constitutional mismatch repair deficiency syndrome
<i>POT1</i> <sup>41–45</sup>	PROTECTION OF TELOMERES 1	AD	Melanoma & brain glial tumors
<i>PTCH1</i> <sup>46–48</sup>	PROTEIN PATCHED HOMOLOG 1	AD	Gorlin syndrome: basal cell carcinoma, medulloblastoma, meningioma, fibromas, jaw tumors (ontogenic keratocysts)
<i>PTEN</i> <sup>4,49–52</sup>	PHOSPHATIDYLINOSITOL 3,4,5-TRISPHOSPHATE 3-PHOSPHATASE AND DUAL-SPECIFICITY PROTEIN PHOSPHATASE PTEN	AD	<i>PTEN</i> hamartoma tumor syndrome (PHTS): breast, thyroid, endometrial, colon, melanoma & renal cancer, gastrointestinal polyps, Lhermitte-Duclos disease
<i>SMARCA4</i> <sup>53–57</sup>	TRANSCRIPTION ACTIVATOR BRG1	AD	Ovarian (SCCOHT) cancer, Malignant rhabdoid tumors-atypical teratoid/rhabdoid tumor of the brain and malignant rhabdoid tumors of the kidney
<i>SMARCB1</i> <sup>58–61</sup>	SWI/SNF-RELATED MATRIX-ASSOCIATED ACTIN-DEPENDENT REGULATOR OF CHROMATIN SUBFAMILY B MEMBER 1	AD	Malignant rhabdoid tumors-atypical teratoid/rhabdoid tumor of the brain and malignant rhabdoid tumors of the kidney, schwannoma, meningioma

<i>SMARCE1</i> <sup>53,62-65</sup>	SWI/SNF-RELATED, MATRIX-ASSOCIATED, ACTIN-DEPENDENT REGULATOR OF CHROMATIN, SUBFAMILY E, MEMBER 1	AD	Coffin-Siris syndrome, cranial and spinal meningiomas (clear cell)
<i>SUFU</i> <sup>46,47,66,67</sup>	SUPPRESSOR OF FUSED HOMOLOG	AD	Medulloblastoma, basal cell carcinoma, meningioma
<i>TP53</i> <sup>68-73</sup>	CELLULAR TUMOR ANTIGEN P53	AD	Li-Fraumeni syndrome (LFS): breast cancer, sarcoma, brain cancer, hematologic malignancies, adrenocortical carcinoma, among others**
<i>TSC1</i> <sup>74-76</sup>	HAMARTIN	AD	Tuberous sclerosis complex (TSC): renal cancer/tumors, CNS tumors (subependymal nodules and subependymal giant cell astrocytomas), hamartomatous tumors (cardiac rhabdomyomas and angiomyolipomas)
<i>TSC2</i> <sup>74-76</sup>	TUBERIN	AD	Tuberous sclerosis complex (TSC): renal cancer/tumors, CNS tumors (subependymal nodules and subependymal giant cell astrocytomas), hamartomatous tumors (cardiac rhabdomyomas and angiomyolipomas)
<i>VHL</i> <sup>77-80</sup>	VON HIPPEL-LINDAU DISEASE TUMOR SUPPRESSOR	AD	von Hippel-Lindau (VHL) disease: renal cancer (clear cell), pancreatic neuroendocrine tumors, hemangioblastoma, pheochromocytoma, endolymphatic sac tumors

**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

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