OncoGeneDx: Pediatric Tumor Panel

Panel Gene List: *ALK, APC, CDC73, DICER1, EPCAM*, MEN1, MLH1, MSH2, MSH6, NF1, NF2, PHOX2B*, PMS2, PRKAR1A, PTCH1, PTEN, RB1, RET*, SMARCA4, SMARCB1, STK11, SUFU, TP53, TSC1, TSC2, VHL, WT1*

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

Clinical Features:

Approximately 1 in 285 children and adolescents will be diagnosed with cancer before age 20 which represents 1% of all new cancer diagnoses in the United States.[1] While the majority of pediatric cancers and other neoplasms are sporadic in nature, 5-10% of pediatric cancer cases are thought to be due to a hereditary predisposition.[2] The proportion of cases due to hereditary predisposition varies considerably between cancer types.[2,3] In addition, certain benign tumors or other clinical features may also be suggestive of hereditary cancer predisposition. The features of a personal and/or family history of cancer that are suggestive of a hereditary cancer predisposition include: early age at diagnosis, multiple primary cancers in a single individual, rare cancers or tumors, and multiple 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 Pediatric Tumor Panel offered at GeneDx includes analysis of 27 genes associated with hereditary predisposition syndromes including Carney complex (*PRKAR1A*) and other *PRKAR1A*-related disorders, constitutional mismatch repair deficiency syndrome (*EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*), familial adenomatous polyposis (*APC*), Gorlin syndrome (*PTCH1*), hereditary retinoblastoma (*RB1*), hereditary neuroblastic tumor susceptibility (*ALK*, *PHOX2B*), hyperparathyroidism-jaw tumor syndrome (HPT-JT) and other *CDC73*-related disorders (*CDC73*), Li-Fraumeni syndrome (*TP53*), multiple endocrine neoplasia types 1 (*MEN1*) and 2A/2B (*RET*), neurofibromatosis types 1 (*NF1*) and 2 (*NF2*), Peutz-Jeghers syndrome (*STK11*), *PTEN* hamartoma tumor syndrome (*PTEN*), tuberous sclerosis complex (*TSC1*, *TSC2*), von Hippel-Lindau disease (*VHL*), and *WT1*-related disorders (*WT1*).

Newer genes that have been identified in association with pediatric onset neoplasms have also been included in the panel. These genes include *DICER1*, *SMARCA4*, *SMARCB1* and *SUFU*. Accurate risk assessment may be complicated by small numbers of patients, low penetrance of pathogenic variants in these genes and/or ascertainment bias. Since the cancer risks are

not yet well defined, no consensus guidelines for medical management are available for these genes.

Inheritance Pattern:
All of the genes on this panel are associated with autosomal dominant inheritance with the exception of constitutional mismatch repair deficiency syndrome (CMMR-D) which is inherited in an autosomal recessive manner.

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 *PHOX2B* and *RET*, only sequencing is performed. In addition, polyalanine repeats for the commonly expanded region in exon 3 of *PHOX2B* are not resolved. 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 27 genes included in the OncoGeneDx Pediatric 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. 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.

Gene	Protein	Inheritance	Disease Associations
ALK[4]	ALK TYROSINE KINASE RECEPTOR	AD	Neuroblastic tumors
APC[5–8]	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
CDC73[9]	PARAFIBROMIN	AD	Parathyroid cancer, jaw fibromas, renal tumors, uterine tumors, hyperparathyroidism
DICER1[10,11]	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
EPCAM[12–17]	EPITHELIAL CELL ADHESION MOLECULE	AD	Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric,

Gene	Protein	Inheritance	Disease Associations
			pancreatic, biliary tract, urinary tract, small bowel, prostate & brain cancer, sebaceous neoplasms
		AR	Constitutional mismatch repair deficiency syndrome
MEN1[18–22]	MENIN	AD	Multiple endocrine neoplasia type 1 (MEN1): parathyroid tumors, pancreatic neuroendocrine tumors, anterior pituitary tumors, pheochromocytoma, meningioma, ependymoma, hyperparathyroidism
MLH1[13–17,23,24]	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
MSH2[12–17,23,24]	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
MSH6[13–17,23,25]	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
NF1[26–28]	NEUROFIBROMIN	AD	Neurofibromatosis type 1 (NF1) syndrome: breast cancer, GIST, optic nerve gliomas, pheochromocytoma, MPNST, neurofibromas, brain tumors
NF2[29–32]	MERLIN	AD	Neurofibromatosis type 2 (NF2) syndrome: schwannomas - vestibular and other, spinal tumors, meningiomas
PHOX2B[33–36]	PAIRED MESODERM HOMEOBOX PROTEIN 2B	AD	Neuroblastic tumors
PMS2[13–17,37,38]	MISMATCH REPAIR ENDONUCLEASE PMS2	AD	Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract,

Gene	Protein	Inheritance	Disease Associations
			small bowel, prostate & brain cancer, sebaceous neoplasms
		AR	Constitutional mismatch repair deficiency syndrome
PRKAR1A[39–42]	CAMP-DEPENDENT PROTEIN KINASE TYPE 1-ALPHA REGULATORY SUBUNIT	AD	Thyroid cancer, testicular tumors (LCCSCT), myxomas, psammomatous melanotic schwannomas (PMSs), primary pigmented nodular adrenocortical disease, pituitary adenomas, among others
PTCH1[43–45]	PROTEIN PATCHED HOMOLOG 1	AD	Gorlin syndrome: Basal cell carcinoma, medulloblastoma, fibromas, jaw tumors (ontogenic keratocysts)
PTEN[5,46–49]	PHOSPHATIDYLINOSITOL 3,4,5-TRISPHOSPHATE 3-PHOSPHATASE AND DUAL-SPECIFICITY PROTEIN PHOSPHATASE PTEN	AD	*PTEN* hamartoma tumor syndrome (PHTS): breast, thyroid, endometrial, colon, melanoma & renal cancer, gastrointestinal polyps, Lhermitte-Duclos disease
RB1[50–54]	RETINOBLASTOMA-ASSOCIATED PROTEIN	AD	Hereditary retinoblastoma: retinoblastoma, sarcoma, leukemia, melanoma, pineoblastoma
RET[20,55–57]	PROTO-ONCOGENE TYROSINE-PROTEIN KINASE RECEPTOR RET	AD	Multiple endocrine neoplasia type 2 (MEN2): medullary thyroid cancer, pheochromocytoma, hyperparathyroidism
SMARCA4[58–62]	TRANSCRIPTION ACTIVATOR BRG1	AD	Ovarian (SCCOHT) cancer, malignant rhabdoid tumors-atypical teratoid/rhabdoid tumor of the brain and malignant rhabdoid tumors of the kidney
SMARCB1[63–66]	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, schwannomas, meningiomas
STK11[5,67–69]	SERINE/THREONINE-PROTEIN KINASE STK11	AD	Peutz-Jeghers syndrome (PJS): breast, colorectal, pancreatic, gastric, small bowel, ovarian, lung, cervical & endometrial cancer, testicular tumors (LCCSCT), gastrointestinal polyps
SUFU[43,45,70,71]	SUPPRESSOR OF FUSED	AD	Medulloblastoma, basal cell carcinoma,

Gene	Protein	Inheritance	Disease Associations
	HOMOLOG		meningioma
TP53[72–77]	CELLULAR TUMOR ANTIGEN P53	AD	Li-Fraumeni syndrome (LFS): breast cancer, sarcoma, brain cancer, hematologic malignancies, adrenocortical carcinoma, among others**
TSC1[78–80]	HAMARTIN	AD	Tuberous sclerosis complex (TSC): renal cancer/tumors, CNS tumors (subependymal nodules and subependymal giant cell astrocytomas), hamartomatous tumors (cardiac rhabdomyomas and angiomyolipomas)
TSC2[78–80]	TUBERIN	AD	Tuberous sclerosis complex (TSC): renal cancer/tumors, CNS tumors (subependymal nodules and subependymal giant cell astrocytomas), hamartomatous tumors (cardiac rhabdomyomas and angiomyolipomas)
VHL[81–84]	VON HIPPEL-LINDAU DISEASE TUMOR SUPPRESSOR	AD	von Hippel-Lindau (VHL) disease: Renal cancer (clear cell), pancreatic neuroendocrine tumors, hemangioblastoma, pheochromocytoma, endolymphatic sac tumors
WT1[85–87]	WILMS TUMOR PROTEIN	AD	Wilms tumor

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

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