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.

Gene	Protein	Inheritance	Disease Associations
APC[2–5]	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
ATM[6–11]	SERINE-PROTEIN KINASE ATM	AD	Breast, colon & pancreatic cancers
		AR	Ataxia telangiectasia
AXIN2[12,13]	AXIN-2	AD	Colon cancer, colon polyps
BMPR1A[4,14–16]	BONE MORPHOGENETIC PROTEIN RECEPTOR TYPE-1A	AD	Juvenile Polyposis syndrome (JPS): colorectal, gastric (if gastric polyps), small bowel & pancreatic cancer, gastrointestinal polyps
BRCA1[17–27]	BREAST CANCER TYPE 1 SUSCEPTIBILITY PROTEIN	AD	Hereditary Breast and Ovarian Cancer (HBOC) syndrome: breast, ovarian, pancreatic, prostate & endometrial serous cancer
BRCA2[17–25,27]	BREAST CANCER TYPE 2 SUSCEPTIBILITY PROTEIN	AD	Hereditary Breast and Ovarian Cancer (HBOC) syndrome: breast, ovarian, pancreatic, prostate, melanoma & endometrial serous cancer
		AR	Fanconi anemia
BRIP1[7,28–30]	FANCONI ANEMIA GROUP J PROTEIN	AD	Breast & ovarian cancer
		AR	Fanconi anemia
CDH1[31–37]	CADHERIN 1	AD	Hereditary Diffuse Gastric Cancer (HDGC) syndrome: gastric (diffuse), breast & colon (signet ring) cancer

Gene	Protein	Inheritance	Disease Associations
CDKN2A[38–43]	CYCLIN-DEPENDENT KINASE INHIBITOR 2A, TUMOR SUPPRESSOR ARF	AD	Familial atypical multiple mole melanoma (FAMMM) syndrome: melanoma, pancreatic cancer & astrocytoma
CHEK2[7,8,26,44–50]	SERINE/THREONINE-PROTEIN KINASE CHK2	AD	Breast, colon, prostate, gastric & thyroid cancer
EPCAM[51,51–56]	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
FH[57–61]	FUMARATE HYDRATASE, MITOCHONDRIAL	AD	Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer (type II papillary), leiomyomas, pheochromocytoma, paraganglioma
		AR	Fumarate hydratase deficiency
FLCN[62–66]	FOLLICULIN	AD	Birt-Hogg-Dubé syndrome (BHD): renal cancer
MLH1[51–55,67,68]	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[51–56,67,68]	DNA MISMATCH REPAIR PROTEIN MSH2	AD	Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract,

Gene	Protein	Inheritance	Disease Associations
			urinary tract, small bowel, prostate & brain cancer, sebaceous neoplasms
		AR	Constitutional mismatch repair deficiency syndrome
MSH6[51–55,67,69]	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
MUTYH[4,5,70–80]	ADENINE DNA GLYCOSYLASE	AR	*MUTYH*-associated polyposis (MAP): colorectal, small bowel & endometrial serous cancer, gastrointestinal polyps
NBN[81–87]	NIBRIN	AD	Breast & prostate cancer, non-Hodgkin lymphoma
		AR	Nijmegen breakage syndrome
NF1[88–90]	NEUROFIBROMIN	AD	Neurofibromatosis type 1 (NF1) syndrome: breast cancer, GIST, optic nerve gliomas, pheochromocytoma, MPNST, neurofibromas, brain tumors
NTHL1[91–94]	ENDONUCLEASE III-LIKE 1	AR	Colon cancer, colon polyps
PALB2[7,95–100]	PARTNER AND LOCALIZER OF BRCA2	AD	Breast, pancreatic & ovarian cancer
		AR	Fanconi anemia
PMS2[51–55,101,102]	MISMATCH REPAIR ENDONUCLEASE PMS2	AD	Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel,

Gene	Protein	Inheritance	Disease Associations
			prostate & brain cancer, sebaceous neoplasms
		AR	Constitutional mismatch repair deficiency syndrome
POLD1[103,104]	DNA POLYPMERASE DELTA CATALYTIC SUBUNIT	AD	Colon, endometrial cancer, colon polyps
POLE[103,105–107]	DNA POLYPMERASE EPSILON CATALYTIC SUBUNIT A	AD	Colon cancer, gastrointestinal polyps
		AR	Facial dysmorphism, immunodeficiency, livedo, and short stature (FILS)
PTEN[4,108–111]	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
RAD51C[112–115]	DNA REPAIR PROTEIN RAD51 HOMOLOG 3	AD	Breast & ovarian cancer
		AR	Fanconi anemia
RAD51D[112,113,116,117]	DNA REPAIR PROTEIN RAD51 HOMOLOG 4	AD	Breast & ovarian cancer
SCG5/ GREM1[118–120]	NEUROENDOCRINE PROTEIN 7B2/GREMLIN-1	AD	Hereditary mixed polyposis syndrome (HMPS): colon cancer, colon polyps
SDHB[121–124]	SUCCINATE DEHYDROGENASE [UBIQUINONE] IRON-SULFUR SUBUNIT, MITOCHONDRIAL	AD	Hereditary paraganglioma/ pheochromocytoma (PGL/PCC) syndrome: paraganglioma, pheochromocytoma, renal cancer, GIST
		AR	Isolated complex II deficiency
SDHC[121,122,125–127]	SUCCINATE DEHYDROGENASE CYTOCHROME B560 SUBUNIT, MITOCHONDRIAL	AD	Hereditary paraganglioma/ pheochromocytoma (PGL/PCC) syndrome: paraganglioma, pheochromocytoma,

Gene	Protein	Inheritance	Disease Associations
			renal cancer, GIST
SDHD[121–123,128,129]	SUCCINATE DEHYDROGENASE [UBIQUINONE] CYTOCHROME B SMALL SUBUNIT, MITOCHONDRIAL	AD	Hereditary paraganglioma/ pheochromocytoma (PGL/PCC) syndrome: paraganglioma, pheochromocytoma, renal cancer, GIST, thyroid cancer
		AR	Isolated complex II deficiency
SMAD4[4,15,16,130,131]	MOTHERS AGAINST DECAPENTAPLEGIC HOMOLOG 4	AD	Juvenile Polyposis syndrome (JPS): colorectal, gastric (if gastric polyps), small bowel & pancreatic cancer, gastrointestinal polyps
STK11[4,132–134]	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
TP53[26,135–139]	CELLULAR TUMOR ANTIGEN P53	AD	Li-Fraumeni syndrome (LFS): Breast cancer, sarcoma, brain cancer, hematologic malignancies, adrenocortical carcinoma, among others**
TSC1[140–142]	HAMARTIN	AD	Tuberous sclerosis complex (TSC): renal cancer/tumors, CNS tumors (subependymal nodules and subependymal giant cell astrocytomas), hamartomatous tumors (cardiac rhabdomyomas and angiomyolipomas)

Gene	Protein	Inheritance	Disease Associations
TSC2[140–142]	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[143–146]	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
LCCSCT - Large cell-calcifying Sertoli cell tumor
MLPA – Multiplex ligation-dependent probe amplification
MPNST - Malignant peripheral nerve sheath tumors

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