OncoGeneDx: Comprehensive Common Cancer Panel

PANEL GENE LIST

APC, ATM, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, CTNNA1, EPCAM, FANCC, FANCM, FH, FLCN, HOXB13, MET, MITF, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PMS2, POLD1, POLE, POT1, PTEN, RAD51C, RAD51D, RECQL, SCG5/GREM1*, SDHB, SDHC, SDHD, SMAD4, STK11, TP53, TSC1, TSC2, VHL*

*Testing includes sequencing and deletion/duplication analysis for all genes except *EPCAM* 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.

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 Comprehensive Common Cancer Panel offered at GeneDx includes analysis of 49 genes associated with hereditary predisposition to various cancers including the most common hereditary cancer syndromes such as Hereditary Breast and Ovarian Cancer syndrome (*BRCA1, BRCA2*) and Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*), as well as newly described genes.

Many of the genes on this panel are involved in the mismatch repair pathway, the Fanconi anemia pathway and/or play a role in DNA damage repair. Newer genes that have been identified in families with cancer have been included in the panel to make it as comprehensive as possible. These genes include, but are not limited to, *AXIN2, CTNNA1, MSH3, NTHL1,* and *RECQL*. The evidence available to date may be derived from a small number of patients with wide confidence intervals or is based upon an ethnic cohort with one specific variant. Accurate risk assessment may be complicated by the low penetrance of pathogenic variants in these genes and/or ascertainment bias.

INHERITANCE PATTERN

Most genes on this panel are associated with an autosomal dominant cancer risk with the exception of *MSH3*, *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 *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 49 genes included in the OncoGeneDx Comprehensive Common 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.

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[2,3]	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[4–8]	SERINE-PROTEIN KINASE ATM	AD	Breast, pancreatic, prostate & colon cancer
		AR	Ataxia telangiectasia

Gene	Protein	Inheritance	Disease Associations
AXIN2[9,10]	AXIN-2	AD	Colon cancer, colon polyps
BAP1[11,12]	UBIQUITIN CARBOXYL-TERMINAL HYDROLASE BAP1	AD	Uveal/cutaneous melanoma, basal cell carcinoma, mesothelioma, renal cancer
BARD1[13–15]	BRCA1-ASSOCIATED RING DOMAIN PROTEIN 1	AD	Breast cancer
BMPR1A[16,17]	BONE MORPHOGENETIC PROTEIN RECEPTOR TYPE-1A	AD	Juvenile Polyposis syndrome (JPS): colorectal, gastric (if gastric polyps), small bowel & pancreatic cancer, gastrointestinal polyps
BRCA1[18,19]	BREAST CANCER TYPE 1 SUSCEPTIBILITY PROTEIN	AD	Hereditary breast and ovarian cancer (HBOC) syndrome: breast, ovarian, pancreatic & prostate cancer
BRCA2[18,20]	BREAST CANCER TYPE 2 SUSCEPTIBILITY PROTEIN	AD	Hereditary breast and ovarian cancer (HBOC) syndrome: breast, ovarian, pancreatic, prostate cancer & melanoma
		AR	Fanconi anemia
BRIP1[13,20–22]	FANCONI ANEMIA GROUP J PROTEIN	AD	Breast, ovarian & prostate cancer
		AR	Fanconi anemia
CDH1[23–25]	CADHERIN 1	AD	Hereditary diffuse gastric cancer (HDGC) syndrome: gastric (diffuse), breast & colon (signet ring) cancer
CDK4[26–28]	CYCLIN-DEPENDENT KINASE 4	AD	Melanoma, non-melanoma skin & pancreatic cancer
CDKN2A[28–33]	CYCLIN-DEPENDENT KINASE INHIBITOR 2A, TUMOR SUPPRESSOR ARF	AD	Familial atypical multiple mole melanoma (FAMMM) syndrome: melanoma, pancreatic cancer & astrocytoma
CHEK2[15,34–37]	SERINE/THREONINE-PROTEIN KINASE CHK2	AD	Breast, colon, prostate, gastric & thyroid cancer
CTNNA1[25,38]	CATENIN ALPHA-1	AD	Diffuse gastric cancer
EPCAM[39–41]	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
FANCC[20,42,43]	FANCONI ANEMIA GROUP C PROTEIN	AD	Breast cancer
		AR	Fanconi anemia
FANCM[15,44]	FANCONI ANEMIA GROUP M PROTEIN	AD	Breast cancer
		AR	Fanconi anemia-like cancer susceptibility
FH[45,46]	FUMARATE HYDRATASE, MITOCHONDRIAL	AD	Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer, leiomyomas, pheochromocytoma, paraganglioma
		AR	Fumarate hydratase deficiency

Gene	Protein	Inheritance	Disease Associations
FLCN[47]	FOLLICULIN	AD	Birt-Hogg-Dubé syndrome (BHD): renal cancer
HOXB13[48,49]	HOMEOBOX PROTEIN HOX-B13	AD	Prostate cancer
MET[50,51]	HEPATOCYTE GROWTH FACTOR RECEPTOR	AD	Hereditary papillary renal carcinoma (HPRC): renal cancer (type I papillary)
MITF[52,53]	MICROPHTHALMIA-ASSOCIATED TRANSCRIPTION FACTOR	AD	Renal cancer, melanoma
MLH1[54,55]	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[54,55]	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
MSH3[56,57]	DNA MISMATCH REPAIR PROTEIN MSH3	AR	Colorectal cancer, colonic polyposis
MSH6[54,55]	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[58,59]	ADENINE DNA GLYCOSYLASE	AR	*MUTYH*-associated polyposis (MAP): colorectal, small bowel & endometrial serous cancer, gastrointestinal polyps
NBN[60–62]	NIBRIN	AD	Prostate cancer
		AR	Nijmegen breakage syndrome
NF1[63,64]	NEUROFIBROMIN	AD	Neurofibromatosis type 1 (NF1) syndrome: breast cancer, GIST, optic nerve gliomas, pheochromocytoma, MPNST, neurofibromas, brain tumors
NTHL1[57,65]	ENDONUCLEASE III-LIKE 1	AR	Colon cancer, colon polyps
PALB2[13,20,66,67]	PARTNER AND LOCALIZER OF BRCA2	AD	Breast, pancreatic, ovarian & prostate cancer
		AR	Fanconi anemia
PMS2[54,55]	MISMATCH REPAIR ENDONUCLEASE PMS2	AD	Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic,

Gene	Protein	Inheritance	Disease Associations
			biliary tract, urinary tract, small bowel, prostate & brain cancer, sebaceous neoplasms
		AR	Constitutional mismatch repair deficiency syndrome
POLD1[68,69]	DNA POLYPMERASE DELTA CATALYTIC SUBUNIT	AD	Colon & endometrial cancer, colon polyps
POLE[70,71]	DNA POLYPMERASE EPSILON CATALYTIC SUBUNIT A	AD	Colon cancer, gastrointestinal polyps
		AR	Intrauterine growth restriction, metaphyseal dysplasia, congenital adrenal hypoplasia, and genitourinary anomalies in males (IMAGe) with variable immunodeficiency
POT1[72,73]	PROTECTION OF TELOMERES 1	AD	Melanoma, hematologic malignancy, brain glial tumors
PTEN[74]	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[15,21,75]	DNA REPAIR PROTEIN RAD51 HOMOLOG 3	AD	Breast, ovarian & prostate cancer
		AR	Fanconi anemia
RAD51D[15,21,75]	DNA REPAIR PROTEIN RAD51 HOMOLOG 4	AD	Breast, ovarian & prostate cancer
RECQL[15,76]	RECQ PROTEIN-LIKE	AD	Breast cancer
SCG5/ GREM1[77–79]	NEUROENDOCRINE PROTEIN 7B2/GREMLIN-1	AD	Hereditary mixed polyposis syndrome (HMPS): colon cancer, colon polyps
SDHB[80,81]	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[80]	SUCCINATE DEHYDROGENASE CYTOCHROME B560 SUBUNIT, MITOCHONDRIAL	AD	Hereditary paraganglioma/ pheochromocytoma (PGL/PCC) syndrome: paraganglioma, pheochromocytoma, renal cancer, GIST
SDHD[80,82]	SUCCINATE DEHYDROGENASE [UBIQUINONE] CYTOCHROME B SMALL SUBUNIT, MITOCHONDRIAL	AD	Hereditary paraganglioma/ pheochromocytoma (PGL/PCC) syndrome: paraganglioma, pheochromocytoma, renal cancer, GIST
		AR	Isolated complex II deficiency
SMAD4[83,84]	MOTHERS AGAINST DECAPENTAPLEGIC HOMOLOG 4	AD	Juvenile polyposis syndrome (JPS): colorectal, gastric (if gastric polyps), small bowel & pancreatic cancer, gastrointestinal polyps

Gene	Protein	Inheritance	Disease Associations
STK11[85–87]	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[88]	CELLULAR TUMOR ANTIGEN P53	AD	Li-Fraumeni syndrome (LFS): breast cancer, sarcoma, brain cancer, hematologic malignancies, adrenocortical carcinoma, among others**
TSC1[89–91]	HAMARTIN	AD	Tuberous sclerosis complex (TSC): renal cancer/tumors, central nervous system tumors, cardiac rhabdomyomas, angiomyolipomas
TSC2[89–91]	TUBERIN	AD	Tuberous sclerosis complex (TSC): renal cancer/tumors, central nervous system tumors, cardiac rhabdomyomas, angiomyolipomas
VHL[92,93]	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 tumors
MLPA – Multiplex ligation-dependent probe amplification
MPNST - Malignant peripheral nerve sheath tumors

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