OncoGeneDx: Custom Cancer Panel

PANEL GENE LIST

AIP, ALK, ANKRD26, APC, ATM, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN1B, CDKN2A, CEBPA, CHEK2, CTNNA1, DDX41, DICER1, EPCAM*, ETV6, FANCC, FANCM, FH, FLCN, GALNT12, GATA2, HOXB13, IKZF1, KIT, LZTR1, MAX, MEN1, MET, MITF, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, NTHL1, PALB2, PAX5, PDGFRA, PHOX2B*, PMS2, POLD1, POLE, POT1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RECQL, RET*, RNF43, RPS20, RTEL1, RUNX1, SAMD9, SAMD9L, SCG5/GREM1*, SDHA*, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, SRP72, STK11, SUFU, TERC, TERT, TINF2, TMEM127, TP53, TSC1, TSC2, VHL, WT1*

*Testing includes sequencing and deletion/duplication analysis for all genes except *CEBPA* (seq only), *EPCAM* (del/dup only), *PHOX2B* (seq only), *RET* (seq only), *SCG5/GREM1* (del/dup only) and *SDHA* (seq 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. Features 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.

GeneDx offers a variety of hereditary cancer panels to facilitate testing of the genes related to certain types of cancer, such as the OncoGeneDx Breast/Gyn Cancer Panel or OncoGeneDx Colorectal Cancer Panel. However, GeneDx also offers the option of ordering single-gene testing and/or a customized cancer panel from a list of 91 cancer susceptibility genes. The option of ordering each gene individually or in any combination allows the provider the flexibility to choose the most appropriate testing approach for their patient when an available OncoGeneDx panel is not desired.

Many of the cancer genes offered at GeneDx are involved in the mismatch repair pathway, the Fanconi anemia pathway and/or DNA damage repair. Specifically, they are associated with common cancer syndromes such as Hereditary Breast and Ovarian Cancer Syndrome (*BRCA1, BRCA2*), Lynch Syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*) or are newly described cancer genes such as *AXIN2, NTHL1, or RECQL*. While the risks associated with the *BRCA* and Lynch genes have been well characterized, accurate risk assessment for pathogenic variants in more recently described genes may be complicated by factors which include small numbers of patients studied, potential ascertainment bias in the available studies, patients from only certain ethnic cohorts, low penetrance of pathogenic variants, wide confidence intervals in the results, and/or studies based on only one variant. Since the cancer risks are not yet well defined, no consensus guidelines for medical management may be available for these newer genes. In addition, the OncoGeneDx Custom Cancer Panel includes emerging cancer genes, such as *GALNT12, RNF43*, and *RPS20*, for which there is some evidence of an association with cancer risk or a cancer-related phenotype, but the evidence for these genes does not warrant inclusion on other OncoGeneDx Hereditary Cancer panels at this time.

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.

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 *CEBPA, PHOX2B, RET* and *SDHA*, only sequencing is performed. In addition, polyalanine repeats for the commonly expanded region in exon 3 of *PHOX2B* are not resolved. 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.

CLINICAL SENSITIVITY

The clinical sensitivity of sequencing and deletion/duplication analysis of the 91 genes included in the OncoGeneDx Custom 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. 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
AIP[2]	ARYL HYDROCARBON RECEPTOR-INTERACTING PROTEIN	AD	Pituitary adenomas
ALK[3]	ALK TYROSINE KINASE RECEPTOR	AD	Neuroblastic tumors

ANKRD26[4,5]	ANKYRIN REPEAT DOMAIN-CONTAINING PROTEIN 26	AD	Thrombocytopenia-2: Myeloid malignancies (AML, MDS, CML)
APC[6,7]	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[8–12]	SERINE-PROTEIN KINASE ATM	AD	Breast, colon, prostate & pancreatic cancers
		AR	Ataxia telangiectasia
AXIN2[13,14]	AXIN-2	AD	Colon cancer, colon polyps
BAP1[15,16]	UBIQUITIN CARBOXYL-TERMINAL HYDROLASE BAP1	AD	Uveal/cutaneous melanoma, basal cell carcinoma, mesothelioma, renal cancer
BARD1[17–19]	BRCA1-ASSOCIATED RING DOMAIN PROTEIN 1	AD	Breast cancer
BMPR1A[20,21]	BONE MORPHOGENETIC PROTEIN RECEPTOR TYPE-1A	AD	Juvenile polyposis syndrome (JPS): colorectal, gastric (if gastric polyps), small bowel & pancreatic cancer, gastrointestinal polyps
BRCA1[22,23]	BREAST CANCER TYPE 1 SUSCEPTIBILITY PROTEIN	AD	Hereditary breast and ovarian cancer (HBOC) syndrome: breast, ovarian, pancreatic, & prostate cancer
BRCA2[22,24]	BREAST CANCER TYPE 2 SUSCEPTIBILITY PROTEIN	AD	Hereditary breast and ovarian cancer (HBOC) syndrome: breast, ovarian, pancreatic, prostate cancer, & melanoma
		AR	Fanconi anemia
BRIP1[19,24–26]	FANCONI ANEMIA GROUP J PROTEIN	AD	Breast, ovarian & prostate cancer
		AR	Fanconi anemia
CDC73[27]	PARAFIBROMIN	AD	Parathyroid cancer, jaw fibromas, renal tumors, uterine tumors, hyperparathyroidism
CDH1[28–30]	CADHERIN 1	AD	Hereditary diffuse gastric cancer (HDGC) syndrome:

			gastric (diffuse), breast & colon (signet ring) cancer
CDK4[31,32]	CYCLIN-DEPENDENT KINASE 4	AD	Melanoma, non-melanoma skin & pancreatic cancer
CDKN1B[33,34]	CYCLIN-DEPENDENT KINASE INHIBITOR 1B	AD	Multiple endocrine neoplasia type 4 (MEN4): primary hyperparathyroidism, pituitary adenomas, gastroentero-pancreatic neuroendocrine tumors, parathyroid adenomas
CDKN2A[31,35]	CYCLIN-DEPENDENT KINASE INHIBITOR 2A, TUMOR SUPPRESSOR ARF	AD	Familial atypical multiple mole melanoma (FAMMM) syndrome: melanoma, pancreatic cancer & astrocytoma
CEBPA[36,37]	CCAAT/ENHANCER-BINDING PROTEIN, ALPHA	AD	*CEBPA*-associated familial acute myeloid leukemia: AML
CHEK2[19,38–41]	SERINE/THREONINE-PROTEIN KINASE CHK2	AD	Breast, colon, prostate, gastric & thyroid cancer
CTNNA1[28,42]	CATENIN ALPHA-1	AD	Diffuse gastric cancer
DDX41[43,44]	DEAD/H BOX 41	AD	AML, MDS
DICER1[45]	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[46–48]	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
ETV6[49,50]	ETS VARIANT GENE 6	AD	Thrombocytopenia-5: MDS, AML, ALL
FANCC[24,51,52]	FANCONI ANEMIA GROUP C PROTEIN	AD	Breast cancer
		AR	Fanconi anemia
FANCM[19,53]	FANCONI ANEMIA GROUP M PROTEIN	AD	Breast cancer
		AR	Fanconi anemia-like cancer susceptibility

FH[54,55]	FUMARATE HYDRATASE, MITOCHONDRIAL	AD	Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer, leiomyomas, pheochromocytoma, paraganglioma
		AR	Fumarate hydratase deficiency
FLCN[56]	FOLLICULIN	AD	Birt-Hogg-Dubé syndrome (BHD): renal cancer
GALNT12[57–59]	POLYPEPTIDE N-ACETYLGALACTOSAMINYLTRANSFERASE 12	AD	Colon cancer, polyposis
GATA2[60,61]	GATA-BINDING PROTEIN 2	AD	Familial MDS/AML, monocytopenia and mycobacterial infection (MonoMAC) syndrome, Emberger syndrome
HOXB13[62,63]	HOMEOBOX PROTEIN HOX-B13	AD	Prostate cancer
IKZF1[64–66]	DNA-BINDING PROTEIN IKAROS	AD	Immunodeficiency with B-cell deficiency, B-cell ALL
KIT[67]	MAST/STEM CELL GROWTH FACTOR RECEPTOR KIT	AD	Gastrointestinal stromal tumors (GIST)
LZTR1[68–70]	LEUCINE-ZIPPER-LIKE TRANSCRIPTIONAL REGULATOR 1	AD	Schwannomatosis, Noonan syndrome
		AR	Noonan syndrome
MAX[71,72]	PROTEIN MAX	AD	Paraganglioma, pheochromocytoma
MEN1[73]	MENIN	AD	Multiple endocrine neoplasia type 1 (MEN1): parathyroid tumors, pancreatic neuroendocrine tumors, pituitary tumors, pheochromocytoma, meningioma, ependymoma, hyperparathyroidism
MET[74,75]	HEPATOCYTE GROWTH FACTOR RECEPTOR	AD	Hereditary papillary renal carcinoma (HPRC): renal cancer (type I papillary)
MITF[76,77]	MICROPHTHALMIA-ASSOCIATED TRANSCRIPTION FACTOR	AD	Renal cancer, melanoma
MLH1[78,79]	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[78,79]	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[80,81]	DNA MISMATCH REPAIR PROTEIN MSH3	AR	Colorectal cancer, colonic polyposis
MSH6[78,79]	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[82,83]	ADENINE DNA GLYCOSYLASE	AR	*MUTYH*-associated polyposis (MAP): colorectal, small bowel & endometrial cancer, gastrointestinal polyps
NBN[84–86]	NIBRIN	AD	Prostate cancer
		AR	Nijmegen breakage syndrome
NF1[87,88]	NEUROFIBROMIN	AD	Neurofibromatosis type 1 (NF1) syndrome: neurofibromas, GIST, optic nerve gliomas, MPNST, breast cancer, pheochromocytoma, brain tumors
NF2[88,89]	MERLIN	AD	Neurofibromatosis type 2 (NF2) syndrome: schwannomas - vestibular and other, spinal tumors, meningiomas
NTHL1[81,90]	ENDONUCLEASE III-LIKE 1	AR	Colon cancer, colon polyps
PALB2[17,24,91,92]	PARTNER AND LOCALIZER OF BRCA2	AD	Breast, pancreatic, ovarian & prostate cancer

		AR	Fanconi anemia
PAX5[93]	PAIRED BOX PROTEIN PAX-5	AD	B-cell ALL
PDGFRA[94]	PLATELET-DERIVED GROWTH FACTOR RECEPTOR ALPHA	AD	Gastrointestinal stromal tumors (GIST)
PHOX2B[95,96]	PAIRED MESODERM HOMEOBOX PROTEIN 2B	AD	Neuroblastic tumors
PMS2[78,79]	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
POLD1[97,98]	DNA POLYPMERASE DELTA CATALYTIC SUBUNIT	AD	Colon & endometrial cancer, colon polyps
POLE[99,100]	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[101,102]	PROTECTION OF TELOMERES 1	AD	Melanoma, hematologic malignancy, & brain glial tumors
PRKAR1A[103]	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[104]	PROTEIN PATCHED HOMOLOG 1	AD	Gorlin syndrome: basal cell carcinoma, ontogenic keratocysts, meningioma, medulloblastoma, fibromas
PTEN[105]	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[19,26,106]	DNA REPAIR PROTEIN RAD51 HOMOLOG 3	AD	Breast, ovarian & prostate cancer

		AR	Fanconi anemia
RAD51D[19,26,106]	DNA REPAIR PROTEIN RAD51 HOMOLOG 4	AD	Breast, ovarian & prostate cancer
RB1[107]	RETINOBLASTOMA-ASSOCIATED PROTEIN	AD	Hereditary retinoblastoma: retinoblastoma, sarcoma, leukemia, melanoma, pineoblastoma
RECQL[19,108]	RECQ PROTEIN-LIKE	AD	Breast cancer
RET[109,110]	PROTO-ONCOGENE TYROSINE-PROTEIN KINASE RECEPTOR RET	AD	Multiple endocrine neoplasia type 2 (MEN2): medullary thyroid cancer, pheochromocytoma, hyperparathyroidism
RNF43[111,112]	E3 UBIQUITIN-PROTEIN LIGASE RNF43	AD	Serrated polyposis, colon cancer
RPS20[113]	40S RIBOSOMAL PROTEIN S20	AD	Colorectal cancer
RTEL1[114,115]	REGULATOR OF TELOMERE ELONGATION HELICASE 1	AD	Dyskeratosis congenita (DC), AML, MDS, BMF & pulmonary fibrosis
		AR	Hoyeraal-Hreidarsson syndrome
RUNX1[116,117]	RUNT-RELATED TRANSCRIPTION FACTOR 1	AD	Familial platelet disorder with propensity to acute myeloid leukemia (FPD/AML), MDS
SAMD9[118–120]	STERILE ALPHA MOTIF DOMAIN-CONTAINING PROTEIN 9	AD	AML, MDS; Myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy (MIRAGE) syndrome
		AR	Normophosphatemic familial tumoral calcinosis (NFTC)
SAMD9L[119,121]	STERILE ALPHA MOTIF DOMAIN-CONTAINING PROTEIN 9-LIKE	AD	AML, MDS, Ataxia–pancytopenia syndrome (ATXPC)
SCG5/ GREM1[122–124]	NEUROENDOCRINE PROTEIN 7B2/GREMLIN-1	AD	Hereditary mixed polyposis syndrome (HMPS): colon cancer, colon polyps
SDHA[71,125]	SUCCINATE DEHYDROGENASE [UBIQUINONE] FLAVOPROTEIN SUBUNIT, MITOCHONDRIAL	AD	Hereditary paraganglioma/ pheochromocytoma (PGL/PCC) syndrome: paraganglioma, pheochromocytoma, GIST
		AR	Leigh syndrome
SDHAF2[71]	SUCCINATE DEHYDROGENASE ASSEMBLY FACTOR 2, MITOCHONDRIAL	AD	Hereditary paraganglioma/

			pheochromocytoma (PGL/PCC) syndrome: paraganglioma
SDHB[71,126]	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[71]	SUCCINATE DEHYDROGENASE CYTOCHROME B560 SUBUNIT, MITOCHONDRIAL	AD	Hereditary paraganglioma/ pheochromocytoma (PGL/PCC) syndrome: paraganglioma, pheochromocytoma, renal cancer, GIST
SDHD[71,127]	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[128,129]	MOTHERS AGAINST DECAPENTAPLEGIC HOMOLOG 4	AD	Juvenile polyposis syndrome (JPS): colorectal, gastric (if gastric polyps), small bowel & pancreatic cancer, gastrointestinal polyps
SMARCA4[130,131]	TRANSCRIPTION ACTIVATOR BRG1	AD	Ovarian cancer (SCCOHT), atypical teratoid/rhabdoid tumor of the brain, malignant rhabdoid tumors of the kidney & other sites, Coffin-Siris syndrome
SMARCB1[68,130,131]	SWI/SNF-RELATED MATRIX-ASSOCIATED ACTIN-DEPENDENT REGULATOR OF CHROMATIN SUBFAMILY B MEMBER 1	AD	Atypical teratoid/rhabdoid tumor of the brain, malignant rhabdoid tumor of the kidney & other sites, schwannomas, meningiomas, Coffin-Siris syndrome
SMARCE1[131,132]	SWI/SNF-RELATED, MATRIX-ASSOCIATED, ACTIN-DEPENDENT REGULATOR OF CHROMATIN, SUBFAMILY E, MEMBER 1	AD	Cranial & spinal clear cell meningiomas, Coffin-Siris syndrome
SRP72[133]	SIGNAL RECOGNITION PARTICLE, 72-KD	AD	MDS, BMF

STK11[134–136]	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[104]	SUPPRESSOR OF FUSED HOMOLOG	AD	Medulloblastoma, basal cell carcinoma, meningioma
TERC[114,137]	TELOMERASE RNA COMPONENT	AD	Dyskeratosis congenita (DC): AML, MDS, BMF, head and neck squamous cell carcinoma, anogenital cancers, pulmonary fibrosis
TERT[114,137,138]	TELOMERASE REVERSE TRANSCRIPTASE	AD	Dyskeratosis congenita (DC): AML, MDS, BMF, head and neck squamous cell carcinoma, anogenital cancers, pulmonary fibrosis
		AR	Hoyeraal-Hreidarsson syndrome
TINF2[114]	TERF1-INTERACTING NUCLEAR FACTOR 2	AD	Dyskeratosis congenita, Hoyeraal-Hreidarsson syndrome, Revesz syndrome
TMEM127[71]	TRANSMEMBRANE PROTEIN 127	AD	Hereditary paraganglioma/ pheochromocytoma (PGL/PCC) syndrome: pheochromocytoma, paraganglioma
TP53[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, central nervous system tumors, angiomyolipomas, cardiac rhabdomyomas,
TSC2[140–142]	TUBERIN	AD	Tuberous sclerosis complex (TSC): renal cancer/tumors, central nervous system tumors, angiomyolipomas, cardiac rhabdomyomas,
VHL[143,144]	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[145]	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
ALL – Acute lymphocytic leukemia
AML – Acute myeloid leukemia
BMF – Bone marrow failure
CGH – Comparative genomic hybridization
CML – Chronic myeloid leukemia
GIST – Gastrointestinal stromal tumor
LCCSCT – Large cell-calcifying Sertoli cell tumors
MDS – Myelodysplastic syndrome
MLPA – Multiplex ligation-dependent probe amplification
MPNST – Malignant peripheral nerve sheath tumors
SCCOHT - Small cell carcinoma of the ovary-hypercalcemic type
SLCT - Sertoli–Leydig cell tumor

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