Blueprint Genetics

Hereditary Pediatric Cancer Panel

Test code: ON0801

Is ideal for patients with a clinical suspicion of an inherited or a sporadic pediatric cancer syndrome due to *de novo* mutation. This panel is designed to detect heritable germline mutations and should not be used for the detection of somatic mutations in tumor tissue. The genes on this panel are included in the Comprehensive Hereditary Cancer Panel.

This Panel covers genes associated with a broad spectrum of hereditary cancer syndromes that may affect children. It has been estimated that around 1-10% of pediatric cancers are accounted for by these syndromes that have predominantly autosomal dominant inheritance pattern. The Hereditary Pediatric Cancer Panel is suited for detecting heritable germline mutations and may not be used for the detection of somatic mutations in tumor tissue. This Panel is part of the Comprehensive Hereditary Cancer Panel.

About Hereditary Pediatric Cancer

Childhood leukemia is the most common pediatric cancer and accounts for more than a third of all new cancer diagnoses in children and adolescents. Most cancers occurring in children are thought to be sporadic and a genetic predisposition is rarely implicated. However, a small proportion of childhood leukemia and solid tumors are caused by hereditary cancer syndromes. The hereditary cancers that occur commonly in children include Wilms tumor (*WT1*) and medulloblastoma (*SUFU*). The main forms of hereditary cancer syndromes affecting children, adolescents, and young adults are Li-Fraumeni syndrome (*TP53*), hereditary pheochromocytoma-paraganglioma (*SDH* genes), pleuropulmonaryblastoma tumor predisposition syndrome (*DICER1*), rhabdoid tumor of the kidney (*SMARCB1*) and multiple endocrine neoplasia (*MEN1* and *RET*). In particular, when children present with adult type cancers, such as skin or gastrointestinal tract cancer, an underlying genetic predisposition should be suspected. The risk of developing cancer in individuals carrying pathogenic germline mutations varies but can be as high as 80% for *SDH* and 100% for *RET* mutation carriers. Genetic testing for pediatric cancer patients has important implications for screening, prevention and treatment.

Availability

Results in 3-4 weeks

Gene set description

Genes in the Hereditary Pediatric Cancer Panel and their clinical significance

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
ALK	Neuroblastoma	AD	31	15
APC	Gardner syndrome, Desmoid disease, hereditary, Familial adenomatous polyposis	AD	773	1926
AXIN2	Oligodontia-colorectal cancer syndrome, Oligondontia, isolated	AD	19	18
BAP1	Tumor predisposition syndrome	AD	74	113
BLM	Bloom syndrome	AR	152	119
BMPR1A*	Polyposis, juvenile intestinal	AD	110	140
BRAF*	LEOPARD syndrome, Noonan syndrome, Cardiofaciocutaneous syndrome	AD	134	65
BUB1B	Mosaic variegated aneuploidy syndrome, Premature chromatid separation trait	AD/AR	14	28

CBL	Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia	AD	24	43
CDC73	Carcinoma, parathyroid, Hyperparathyroidism, Hyperparathyroidism-jaw tumor syndrome	AD	50	101
CDKN1C	Beckwith-Wiedemann syndrome, IMAGE syndrome	AD	35	81
CEBPA	Acute myeloid leukemia, familial	AD	15	13
DICER1*	DICER1 syndrome	AD	197	137
DIS3L2*	Perlman syndrome	AR	12	14
EPCAM	Diarrhea 5, with tufting enteropathy, congenital, Colorectal cancer, hereditary nonpolyposis	AD/AR	38	80
EZH2	Weaver syndrome	AD	29	41
FH	Hereditary leiomyomatosis and renal cell cancer	AD/AR	178	207
GATA2	Myelodysplastic syndrome, Chronic neutropenia associated with monocytopenia, evolving to myelodysplasia and acute myeloid leukemia, Acute myeloid leukemia, Emberger syndrome, Immunodeficiency	AD	30	142
GPC3	Simpson-Golabi-Behmel syndrome	XL	33	75
HRAS	Costello syndrome, Congenital myopathy with excess of muscle spindles	AD	43	31
KRAS*	Noonan syndrome, Cardiofaciocutaneous syndrome	AD	63	35
LZTR1	Schwannomatosis, Noonan syndrome	AD/AR	34	71
MAP2K1	Cardiofaciocutaneous syndrome	AD	45	23
MAP2K2	Cardiofaciocutaneous syndrome	AD	21	35
MAX	Pheochromocytoma	AD	13	31
MEN1	Hyperparathyroidism, familial primary, Multiple endocrine neoplasia	AD	263	730
MLH1	Muir-Torre syndrome, Endometrial cancer, Mismatch repair cancer syndrome, Colorectal cancer, hereditary nonpolyposis	AD/AR	873	1191
MSH2	Muir-Torre syndrome, Endometrial cancer, Colorectal cancer, hereditary nonpolyposis,, Mismatch repair cancer syndrome	AD/AR	933	1249
MSH6	Endometrial cancer, Mismatch repair cancer syndrome, Colorectal cancer, hereditary nonpolyposis	AD/AR	672	586
NBN	Breast cancer, Nijmegen breakage syndrome	AD/AR	188	97
NF1*	Watson syndrome, Neurofibromatosis, Neurofibromatosis-Noonan syndrome	AD	1157	2901
NF2	Schwannomatosis, Neurofibromatosis	AD	66	433
NRAS	Noonan syndrome	AD	31	14
NSD1	Sotos syndrome, Weaver syndrome, Beckwith-Wiedemann syndrome	AD	329	517

NSUN2	Dubowitz syndrome, Non-syndromic intellectual disability	AD/AR	8	7
PAX5	Pre-B cell acute lymphoblastic leukemia	AD		7
PHOX2B	Central hypoventilation syndrome, congenital, Neuroblastoma, susceptiblity to, Neuroblastoma with Hirschsprung disease	AD	11	86
PMS2*	Mismatch repair cancer syndrome, Colorectal cancer, hereditary nonpolyposis	AD/AR	319	342
PRF1	Lymphoma, non-Hodgkin, Aplastic anemia, adult-onset, Hemophagocytic lymphohistiocytosis	AR	24	183
PRKAR1A	Myxoma, intracardiac, Acrodysostosis, Pigmented nodular adrenocortical disease, Carney complex	AD	75	183
PTCH1	Basal cell nevus syndrome	AD	193	522
PTEN*	Bannayan-Riley-Ruvalcaba syndrome, Lhermitte-Duclos syndrome, Cowden syndrome	AD	435	638
PTPN11	Noonan syndrome, Metachondromatosis	AD	135	140
RAF1	LEOPARD syndrome, Noonan syndrome, Dilated cardiomyopathy (DCM)	AD	45	53
RASA2#	Noonan syndrome	AD	1	3
RECQL4	Baller-Gerold syndrome, RAPADILINO syndrome, Rothmund-Thomson syndrome	AR	82	114
REST	Fibromatosis, gingival, 5	AD	3	16
RET	Hirschsprung disease, Central hypoventilation syndrome, congenital, Pheochromocytoma, Medullary thyroid carcinoma, Multiple endocrine neoplasia	AD/AR	122	407
RIT1	Noonan syndrome	AD	23	26
RRAS	Noonan-syndrome like phenotype	AD/AR		2
RUNX1	Platelet disorder, familial, with associated myeloid malignancy	AD	47	101
SDHA*	Leigh syndrome/Mitochondrial respiratory chain complex II deficiency, Gastrointestinal stromal tumor, Paragangliomas, Dilated cardiomyopathy (DCM), Cardiomyopathy, dilated, 1GG	AD/AR	54	87
SDHAF2	Paragangliomas	AD	4	5
SDHB	Paraganglioma and gastric stromal sarcoma, Pheochromocytoma, Gastrointestinal stromal tumor, Paragangliomas, Cowden-like syndrome	AD	151	272
SDHC	Paraganglioma and gastric stromal sarcoma, Gastrointestinal stromal tumor, Paragangliomas	AD	29	60
SDHD	Paraganglioma and gastric stromal sarcoma, Pheochromocytoma, Paragangliomas, Carcinoid tumors, intestinal, Cowden syndrome, Mitochondrial complex II deficiency	AD	68	170
SHOC2	Noonan-like syndrome with loose anagen hair	AD	2	4

SMAD4	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome, Polyposis, juvenile intestinal, Myhre dysplasia, Hereditary hemorrhagic telangiectasia	AD	179	143
SMARCA4	Rhabdoid tumor predisposition syndrome	AD	76	57
SMARCB1	Schwannomatosis, Rhabdoid tumor predisposition syndrome, Coffin-Siris syndrome 3	AD	36	118
SOS1	Noonan syndrome	AD	44	71
SOS2	Noonan syndrome 9	AD	4	6
STK11	Peutz-Jeghers syndrome	AD	173	460
SUFU	Medulloblastoma, Basal cell nevus syndrome	AD	22	44
TMEM127	Pheochromocytoma	AD	30	52
TP53	Colorectal cancer, Li-Fraumeni syndrome, Ependymoma, intracranial, Choroid plexus papilloma, Breast cancer, familial, Adrenocortical carcinoma, Osteogenic sarcoma, Hepatoblastoma, Non-Hodgkin lymphoma	AD	393	505
TSC1	Lymphangioleiomyomatosis, Tuberous sclerosis	AD	177	372
TSC2	Lymphangioleiomyomatosis, Tuberous sclerosis	AD	396	1195
VHL	Erythrocytosis, familial, Pheochromocytoma	AD/AR	206	614
WRN*	Werner syndrome	AR	64	107
WT1	Denys-Drash syndrome, Frasier syndrome, Wilms tumor, Nephrotic syndrome, type 4	AD	42	183

*Some regions of the gene are duplicated in the genome. Read more.

The gene has suboptimal coverage (means <90% of the gene's target nucleotides are covered at >20x with mapping quality score (MQ>20) reads), and/or the gene has exons listed under Test limitations section that are not included in the panel as they are not sufficiently covered with high quality sequence reads.

The sensitivity to detect variants may be limited in genes marked with an asterisk (*) or number sign (#)

Gene refers to the HGNC approved gene symbol; Inheritance refers to inheritance patterns such as autosomal dominant (AD), autosomal recessive (AR), mitochondrial (mi), X-linked (XL), X-linked dominant (XLD) and X-linked recessive (XLR); ClinVar refers to the number of variants in the gene classified as pathogenic or likely pathogenic in this database (ClinVar); HGMD refers to the number of variants with possible disease association in the gene listed in Human Gene Mutation Database (HGMD). The list of associated, gene specific phenotypes are generated from CGD or Mitomap databases.

Non-coding disease causing variants covered by the panel

Gene	Genomic location HG19	HGVS	RefSeq	RS-number
APC	Chr5:112043009–112043595			
APC	Chr5:112043220	c.-195A>C	NM_001127511.2	
APC	Chr5:112043223	c.-192A>G/T	NM_001127511.2	
APC	Chr5:112043223	c.-192A>G	NM_001127511.2	rs879253784
APC	Chr5:112043223	c.-192A>T	NM_001127511.2	

APC	Chr5:112043224	c.-191T>C	NM_001127511.2	
APC	Chr5:112043225	c.-190G>A	NM_001127511.2	
APC	Chr5:112043289	c.-125delA	NM_001127511.2	
APC	Chr5:112072710–112073585			
APC	Chr5:112111314	c.423-12A>G	NM_000038.5	
APC	Chr5:112111315	c.423-11A>G	NM_000038.5	
APC	Chr5:112115546	c.532-941G>A	NM_000038.5	rs730881227
APC	Chr5:112151175	c.835-17A>G	NM_000038.5	
APC	Chr5:112158419	c.1408+731C>T	NM_000038.5	
APC	Chr5:112158423	c.1408+735A>T	NM_000038.5	
BAP1	Chr3:52435659	c.*644delG	NM_004656.3	
BUB1B	Chr15:40409289	c.-44133G>A	NM_001211.5	rs576524605
BUB1B	Chr15:40504689	c.2386-11A>G	NM_001211.5	rs751421137
CDKN1C	Chr11:2905209	c.*5+20G>T	NM_000076.2	rs760540648
DICER1	Chr14:95559038	c.5364+1187T>G	NM_177438.2	
EPCAM	Chr2:47606078	c.556-14A>G	NM_002354.2	rs376155665
GATA2	Chr3:128202131	c.1017+572C>T	NM_032638.4	
GATA2	Chr3:128202162	c.1017+513_1017+540delGGAGTTTCCTATCCGGACATCTGCAGCC	NM_032638.4	
GATA2	Chr3:128202171	c.1017+532T>A	NM_032638.4	
LZTR1	Chr22:21336623	c.-38T>A	NM_006767.3	
LZTR1	Chr22:21350968	c.2220-17C>A	NM_006767.3	rs1249726034
MEN1	Chr11:64571394	c.*412G>A	NM_000244.3	
MEN1	Chr11:64575165	c.670-15_670-14delTC	NM_000244.3	
MEN1	Chr11:64577602	c.-23-11_-22delTTGCCTTGCAGGC	NM_000244.3	
MEN1	Chr11:64577603	c.-23_-22insT	NM_000244.3	
MEN1	Chr11:64577626	c.-23-22C>A	NM_000244.3	
MLH1	Chr3:37034619	c.-413_-411delGAG	NM_000249.3	rs953169437
MLH1	Chr3:37034932	c.-107C>G	NM_000249.3	rs587778886
MLH1	Chr3:37034976	c.-63_-58delGTGATTinsCACGAGGCACGAGCACGA	NM_000249.3	
MLH1	Chr3:37034997	c.-42C>T	NM_000249.3	rs41285097
MLH1	Chr3:37035012	c.-27C>A	NM_000249.3	rs587779001
MLH1	Chr3:37035260	c.116+106G>A	NM_000249.3	
MLH1	Chr3:37038099	c.117-11T>A	NM_000249.3	rs267607711
MLH1	Chr3:37050292	c.454-13A>G	NM_000249.3	rs267607749
MLH1	Chr3:37061788	c.885-9_887dupTCCTGACAGTTT	NM_000249.3	rs63751620
MLH1	Chr3:37070436	c.1558+13T>A	NM_000249.3	rs267607834
MSH2	Chr2:47630106	c.-225G>C	NM_000251.2	rs138068023
MSH2	Chr2:47630150	c.-181G>A	NM_000251.2	rs786201698
MSH2	Chr2:47630249	c.-81dupA	NM_000251.2	rs560991330,rs587779187
MSH2	Chr2:47630251	c.-78_-77delTG	NM_000251.2	rs587779182
MSH2	Chr2:47698086	c.1662-17dupG	NM_000251.2	rs587779099

MSH6	Chr2:48018295	c.457+33_457+34insGTGT	NM_000179.2	
MSH6	Chr2:48030536	c.3173-16_3173-5delCCCTCTCTTTTA	NM_000179.2	
MSH6	Chr2:48034014	c.*15A>C	NM_000179.2	
MSH6	Chr2:48034047	c.*49_*68dupTTCAGACAACATTATGATCT	NM_000179.2	rs777409019
NF1	Chr17:29422055	c.-273A>C	NM_001042492.2	
NF1	Chr17:29422056	c.-272G>A	NM_001042492.2	
NF1	Chr17:29431417	c.60+9031_60+9035delAAGTT	NM_001042492.2	
NF1	Chr17:29475515	c.61-7486G>T	NM_001042492.2	
NF1	Chr17:29488136	c.288+2025T>G	NM_001042492.2	
NF1	Chr17:29508426	c.587-14T>A	NM_001042492.2	
NF1	Chr17:29508428	c.587-12T>A	NM_001042492.2	
NF1	Chr17:29510334	c.888+651T>A	NM_001042492.2	
NF1	Chr17:29510427	c.888+744A>G	NM_001042492.2	
NF1	Chr17:29510472	c.888+789A>G	NM_001042492.2	
NF1	Chr17:29527428	c.889-12T>A	NM_001042492.2	
NF1	Chr17:29530107	c.1260+1604A>G	NM_001042492.2	
NF1	Chr17:29533239	c.1261-19G>A	NM_001042492.2	
NF1	Chr17:29534143	c.1392+754T>G	NM_001042492.2	
NF1	Chr17:29540877	c.1393-592A>G	NM_001042492.2	
NF1	Chr17:29542762	c.1527+1159C>T	NM_001042492.2	rs878853868
NF1	Chr17:29548419	c.1642-449A>G	NM_001042492.2	
NF1	Chr17:29549489	c.*481A>G	NM_001128147.2	
NF1	Chr17:29553439	c.2002-14C>G	NM_001042492.2	
NF1	Chr17:29554225	c.2252-11T>G	NM_001042492.2	
NF1	Chr17:29556025	c.2410-18C>G	NM_001042492.2	
NF1	Chr17:29556027	c.2410-16A>G	NM_001042492.2	
NF1	Chr17:29556028	c.2410-15A>G	NM_001042492.2	
NF1	Chr17:29556031	c.2410-12T>G	NM_001042492.2	
NF1	Chr17:29556839	c.2851-14_2851-13insA	NM_001042492.2	
NF1	Chr17:29557267	c.2991-11T>G	NM_001042492.2	
NF1	Chr17:29558777	c.3198-314G>A	NM_001042492.2	
NF1	Chr17:29563299	c.3974+260T>G	NM_001042492.2	
NF1	Chr17:29577082	c.4110+945A>G	NM_001042492.2	
NF1	Chr17:29580296	c.4173+278A>G	NM_001042492.2	
NF1	Chr17:29588708	c.4578-20_4578-18delAAG	NM_001042492.2	
NF1	Chr17:29588715	c.4578-14T>G	NM_001042492.2	
NF1	Chr17:29654479	c.5269-38A>G	NM_001042492.2	
NF1	Chr17:29656858	c.5610-456G>T	NM_001042492.2	
NF1	Chr17:29657848	c.5812+332A>G	NM_001042492.2	rs863224491
NF1	Chr17:29661577	c.5813-279A>G	NM_001042492.2	
NF1	Chr17:29664375	c.6428-11T>G	NM_001042492.2	

NF1	Chr17:29664618	c.6642+18A>G	NM_001042492.2	
NF1	Chr17:29676126	c.7190-12T>A	NM_001042492.2	
NF1	Chr17:29676127	c.7190-11_7190-10insGTTT	NM_001042492.2	
NF1	Chr17:29685177	c.7971-321C>G	NM_001042492.2	
NF1	Chr17:29685481	c.7971-17C>G	NM_001042492.2	
NF1	Chr17:29685665	c.8113+25A>T	NM_001042492.2	
NF2	Chr22:30050946	c.516+232G>A	NM_000268.3	
NSUN2	Chr5:6622224	c.538-11T>G	NM_017755.5	
PMS2	Chr7:6027263	c.1145-31_1145-13delCTGACCCTCTTCTCCGTCC	NM_000535.5	rs751973268
PMS2	Chr7:6048599	c.23+21_23+28delTCCGGTGT	NM_000535.5	
PRKAR1A	Chr17:66508599	c.-97G>A	NM_002734.4	
PRKAR1A	Chr17:66508689	c.-7G>A	NM_002734.4	
PRKAR1A	Chr17:66508690	c.-7+1G>A	NM_002734.4	
PRKAR1A	Chr17:66521878	c.550-17T>A	NM_002734.4	
PRKAR1A	Chr17:66523964	c.709-7_709-2delTTTTTA	NM_002734.4	rs281864801
PTCH1	Chr9:98226337	c.2561-2057A>G	NM_000264.3	
PTEN	Chr10:89622883–89623482			
PTEN	Chr10:89622988	c.-1239A>G	NM_000314.6	
PTEN	Chr10:89623049	c.-1178C>T	NM_000314.6	
PTEN	Chr10:89623056	c.-1171C>T	NM_000314.6	rs587779981
PTEN	Chr10:89623116	c.-1111A>G	NM_000314.6	
PTEN	Chr10:89623226	c.-1001T>C	NM_000314.4	
PTEN	Chr10:89623296	c.-931G>A	NM_000314.4	rs587781959
PTEN	Chr10:89623306	c.-921G>T	NM_000314.4	
PTEN	Chr10:89623331	c.-896T>C	NM_000314.4	
PTEN	Chr10:89623365	c.-862G>T	NM_000314.4	rs587776675
PTEN	Chr10:89623373	c.-854C>G	NM_000314.4	
PTEN	Chr10:89623392	c.-835C>T	NM_000314.4	rs587779994
PTEN	Chr10:89623428	c.-799G>C	NM_000314.4	rs587779992
PTEN	Chr10:89623462	c.-765G>A	NM_000314.4	
PTEN	Chr10:89690791	c.210-8dupT	NM_000314.4	
PTEN	Chr10:89692749	c.254-21G>C	NM_000314.4	
PTEN	Chr10:89725294	c.*65T>A	NM_000314.4	
PTEN	Chr10:89725304	c.*75_*92delTAATGGCAATAGGACATTinsCTATGGCAATAGGACATTG	NM_000314.4	
PTPN11	Chr12:112915602	c.934-59T>A	NM_002834.3	
REST	Chr4:57793760	c.983-2247C>G	NM_005612.4	
RET	Chr10:43572670	c.-37G>C	NM_020975.4	
RET	Chr10:43572680	c.-27C>G	NM_020975.4	
RET	Chr10:43582162	c.73+9385_73+9395delAGCAACTGCCA	NM_020975.4	rs368137511
RET	Chr10:43606948	c.1522+35C>T	NM_020975.4	rs377130948
RET	Chr10:43612192	c.2284+13C>T	NM_020975.4	

RET	Chr10:43612198	c.2284+19C>T	NM_020975.4	
RET	Chr10:43613947	c.2392+19T>C	NM_020975.4	rs778745375
SMARCB1	Chr22:24130008	c.93+559A>G	NM_003073.3	
SMARCB1	Chr22:24176316	c.1119-12C>G	NM_003073.3	
SMARCB1	Chr22:24176437	c.*70C>T	NM_003073.3	
SMARCB1	Chr22:24176449	c.*82C>T	NM_003073.3	
STK11	Chr19:1220520	c.597+16_597+33delGGGGGGCCCTGGGGCGCCinsTG	NM_000455.4	
STK11	Chr19:1220530	c.598-32_597+31delGCCCCCTCCCGGGC	NM_000455.4	
TMEM127	Chr2:96931137	c.-18C>T	NM_017849.3	rs121908813
TP53	Chr17:7571520		NM_000546.5	
TP53	Chr17:7577647	c.673-39G>A	NM_000546.5	
TP53	Chr17:7579601	c.97-11C>G	NM_000546.5	
TP53	Chr17:7590694	c.-29+1G>T	NM_000546.5	
TSC1	Chr9:135800306	c.363+668G>A	NM_000368.4	
TSC2	Chr16:2098067	c.-30+1G>C	NM_000548.3	rs587778004
TSC2	Chr16:2106052	c.600-145C>T	NM_000548.3	
TSC2	Chr16:2107460	c.848+281C>T	NM_000548.3	
TSC2	Chr16:2110656	c.976-15G>A	NM_000548.3	rs45517150
TSC2	Chr16:2127477	c.2838-122G>A	NM_000548.3	
TSC2	Chr16:2138031	c.5069-18A>G	NM_000548.3	rs45484794
VHL	Chr3:10183453	c.-75_-55delCGCACGCAGCTCCGCCCCGCG	NM_000551.3	rs727503744
VHL	Chr3:10183471	c.-54_-44dupTCCGACCCGCG	NM_000551.3	
VHL	Chr3:10191719	c.*70C>A	NM_000551.3	
VHL	Chr3:10191719	c.*70C>T	NM_000551.3	rs552290225
WRN	Chr8:30966107	c.2089-3024A>G	NM_000553.4	rs281865157
WRN	Chr8:30999982	c.3234-160A>G	NM_000553.4	

Test Strengths

The strengths of this test include:

- CAP accredited laboratory
- CLIA-certified personnel performing clinical testing in a CLIA-certified laboratory
- Powerful sequencing technologies, advanced target enrichment methods and precision bioinformatics pipelines ensure superior analytical performance
- Careful construction of clinically effective and scientifically justified gene panels
- Some of the panels include the whole mitochondrial genome (please see the Panel Content section)
- Our Nucleus online portal providing transparent and easy access to quality and performance data at the patient level
- Our publicly available analytic validation demonstrating complete details of test performance
- ~2,000 non-coding disease causing variants in our clinical grade NGS assay for panels (please see 'Non-coding disease causing variants covered by this panel' in the Panel Content section)
- Our rigorous variant classification scheme
- Our systematic clinical interpretation workflow using proprietary software enabling accurate and traceable processing of NGS data
- Our comprehensive clinical statements

Test Limitations

The following exons are not included in the panel as they are not sufficiently covered with high quality sequence reads: *SDHD* (NM_001276506:4). Genes with suboptimal coverage in our assay are marked with number sign (#) and genes with partial, or whole gene, segmental duplications in the human genome are marked with an asterisk (*) if they overlap with the UCSC pseudogene regions. Gene is considered to have suboptimal coverage when >90% of the gene's target nucleotides are not covered at >20x with mapping quality score (MQ>20) reads. The technology may have limited sensitivity to detect variants in genes marked with these symbols (please see the Panel content table above).

This test does not detect the following:

- Complex inversions
- Gene conversions
- Balanced translocations
- Some of the panels include the whole mitochondrial genome but not all (please see the Panel Content section)
- Repeat expansion disorders unless specifically mentioned
- Non-coding variants deeper than ±20 base pairs from exon-intron boundary unless otherwise indicated (please see above Panel Content / non-coding variants covered by the panel).

This test may not reliably detect the following:

- Low level mosaicism in nuclear genes (variant with a minor allele fraction of 14.6% is detected with 90% probability)
- Stretches of mononucleotide repeats
- Low level heteroplasmy in mtDNA (>90% are detected at 5% level)
- Indels larger than 50bp
- Single exon deletions or duplications
- Variants within pseudogene regions/duplicated segments
- Some disease causing variants present in mtDNA are not detectable from blood, thus post-mitotic tissue such as skeletal muscle may be required for establishing molecular diagnosis.

The sensitivity of this test may be reduced if DNA is extracted by a laboratory other than Blueprint Genetics.

For additional information, please refer to the Test performance section and see our Analytic Validation.

Test performance

Our panels are sectioned from our high-quality, clinical grade NGS assay. Please see our sequencing and detection performance table for details regarding our ability to detect different types of alterations (Table).

Assays have been validated for various sample types including EDTA-blood, isolated DNA (excluding from formalin fixed paraffin embedded tissue), saliva and dry blood spots (filter cards). These sample types were selected in order to maximize the likelihood for high-quality DNA yield. The diagnostic yield varies depending on the assay used, referring healthcare professional, hospital and country. Plus analysis increases the likelihood of finding a genetic diagnosis for your patient, as large deletions and duplications cannot be detected using sequence analysis alone. Blueprint Genetics' Plus Analysis is a combination of both sequencing and deletion/duplication (copy number variant (CNV)) analysis.

Performance of Blueprint Genetics high-quality, clinical grade NGS sequencing assay for panels.

	Sensitivity % (TP/(TP+FN)	Specificity %
Single nucleotide variants	99.89% (99,153/99,266)	>99.9999%
Insertions, deletions and indels by sequence analysis		

1-10 bps	99.2% (7,745/7,806)	>99.9999%
11-50 bps	99.13% (2,524/2,546)	>99.9999%
Copy number variants (exon level dels/dups)		
1 exon level deletion (heterozygous)	100% (20/20)	NA
1 exon level deletion (homozygous)	100% (5/5)	NA
1 exon level deletion (het or homo)	100% (25/25)	NA
2-7 exon level deletion (het or homo)	100% (44/44)	NA
1-9 exon level duplication (het or homo)	75% (6/8)	NA
Simulated CNV detection		
5 exons level deletion/duplication	98.7%	100.00%
Size range (0.1-47 Mb)	100% (25/25)	
The performance presented above reached by Blueprint Genetics high-quality, clinical grade NGS sequencing assay with the following coverage metrics		
Mean sequencing depth	143X	
Nucleotides with >20x sequencing coverage (%)	99.86%	

Performance of Blueprint Genetics Mitochondrial Sequencing Assay.

		Specificity
ANALYTIC VALIDATION (NA samples; n=4)		
Single nucleotide variants		
Heteroplasmic (45-100%)	100.0% (50/50)	100.0%
Heteroplasmic (35-45%)	100.0% (87/87)	100.0%
Heteroplasmic (25-35%)	100.0% (73/73)	100.0%
Heteroplasmic (15-25%)	100.0% (77/77)	100.0%
Heteroplasmic (10-15%)	100.0% (74/74)	100.0%
Heteroplasmic (5-10%)	100.0% (3/3)	100.0%
Heteroplasmic (<5%)	50.0% (2/4)	100.0%
CLINICAL VALIDATION (n=76 samples)		
All types		

Single nucleotide variants n=2084 SNVs		
Heteroplasmic (45-100%)	100.0% (1940/1940)	100.0%
Heteroplasmic (35-45%)	100.0% (4/4)	100.0%
Heteroplasmic (25-35%)	100.0% (3/3)	100.0%
Heteroplasmic (15-25%)	100.0% (3/3)	100.0%
Heteroplasmic (10-15%)	100.0% (9/9)	100.0%
Heteroplasmic (5-10%)	92.9%(12/13)	99.98%
Heteroplasmic (<5%)	88.7% (47/53)	99.93%
Insertions and deletions by sequence analysis n=42 indels		
Heteroplasmic (45-100%) 1-10bp	100.0% (32/32)	100.0%
Heteroplasmic (5-45%) 1-10bp	100.0% (3/3)	100.0%
Heteroplasmic (<5%) 1-10bp	100.0% (5/5)	>0.9999
SIMULATION DATA /(mitomap mutations)		
Insertions, and deletions 1-24 bps by sequence analysis; n=17		
Homoplasmic (100%) 1-24bp	100.0% (17/17)	99.98%
Heteroplasmic (50%)	100.0% (17/17)	99.99%
Heteroplasmic (25%)	100.0% (17/17)	100.0%
Heteroplasmic (20%)	100.0% (17/17)	100.0%
Heteroplasmic (15%)	100.0% (17/17)	100.0%
Heteroplasmic (10%)	94.1% (16/17)	100.0%
Heteroplasmic (5%)	94.1% (16/17)	100.0%
Copy number variants (separate artifical mutations; n=1500)		
Homoplasmic (100%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (50%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (30%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (20%) 500 bp, 1kb, 5 kb	99.7%	100.0%
Heteroplasmic (10%) 500 bp, 1kb, 5 kb	99.0%	100.0%
The performance presented above reached by following coverage metrics at assay level (n=66)		
	Mean of medians	Median of medians
Mean sequencing depth MQ0 (clinical)	18224X	17366X

Nucleotides with >1000x MQ0 sequencing coverage (%) (clinical)	100%
rho zero cell line (=no mtDNA), mean sequencing depth	12X

Bioinformatics

The target region for each gene includes coding exons and ±20 base pairs from the exon-intron boundary. In addition, the panel includes non-coding and regulatory variants if listed above (Non-coding variants covered by the panel). Some regions of the gene(s) may be removed from the panel if specifically mentioned in the 'Test limitations" section above. The sequencing data generated in our laboratory is analyzed with our proprietary data analysis and annotation pipeline, integrating state-of-the art algorithms and industry-standard software solutions. Incorporation of rigorous quality control steps throughout the workflow of the pipeline ensures the consistency, validity and accuracy of results. Our pipeline is streamlined to maximize sensitivity without sacrificing specificity. We have incorporated a number of reference population databases and mutation databases including, but not limited, to 1000 Genomes Project, gnomAD, ClinVar and HGMD into our clinical interpretation software to make the process effective and efficient. For missense variants, *in silico* variant prediction tools such as SIFT, PolyPhen, MutationTaster are used to assist with variant classification. Through our online ordering and statement reporting system, Nucleus, ordering providers have access to the details of the analysis, including patient specific sequencing metrics, a gene level coverage plot and a list of regions with <20X sequencing depth if applicable. This reflects our mission to build fully transparent diagnostics where ordering providers can easily visualize the crucial details of the analysis process.

Clinical interpretation

We provide customers with the most comprehensive clinical report available on the market. Clinical interpretation requires a fundamental understanding of clinical genetics and genetic principles. At Blueprint Genetics, our PhD molecular geneticists, medical geneticists and clinical consultants prepare the clinical statement together by evaluating the identified variants in the context of the phenotypic information provided in the requisition form. Our goal is to provide clinically meaningful statements that are understandable for all medical professionals regardless of whether they have formal training in genetics.

Variant classification is the corner stone of clinical interpretation and resulting patient management decisions. Our classifications follow the Blueprint Genetics Variant Classification Schemes based on the ACMG guideline 2015. Minor modifications were made to increase reproducibility of the variant classification and improve the clinical validity of the report. Our experience with tens of thousands of clinical cases analyzed at our laboratory allowed us to further develop the industry standard.

The final step in the analysis is orthogonal confirmation. Sequence variants classified as pathogenic, likely pathogenic and variants of uncertain significance (VUS) are confirmed using bi-directional Sanger sequencing when they do not meet our stringent NGS quality metrics for a true positive call. Reported heterozygous and homo/hemizygous copy number variations with a size <10 and <3 target exons are confirmed by orthogonal methods such as qPCR if the specific CNV has been seen and confirmed less than three times at Blueprint Genetics.

Our clinical statement includes tables for sequencing and copy number variants that include basic variant information (genomic coordinates, HGVS nomenclature, zygosity, allele frequencies, in silico predictions, OMIM phenotypes and classification of the variant). In addition, the statement includes detailed descriptions of the variant, gene and phenotype(s) including the role of the specific gene in human disease, the mutation profile, information about the gene's variation in population cohorts and detailed information about related phenotypes. We also provide links to the references, abstracts and variant databases used to help ordering providers further evaluate the reported findings if desired. The conclusion summarizes all of the existing information and provides our rationale for the classification of the variant.

Identification of pathogenic or likely pathogenic variants in dominant disorders or their combinations in different alleles in recessive disorders are considered molecular confirmation of the clinical diagnosis. In these cases, family member testing can be used for risk stratification. We do not recommend using variants of uncertain significance (VUS) for family member risk stratification or patient management. Genetic counseling is recommended.

Our interpretation team analyzes millions of variants from thousands of individuals with rare diseases. Our internal database and our understanding of variants and related phenotypes increases with every case analyzed. Our laboratory is therefore well-positioned to re-classify previously reported variants as new information becomes available. If a variant previously

reported by Blueprint Genetics is re-classified, our laboratory will issue a follow-up statement to the original ordering health care provider at no additional cost.

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ICD codes

Commonly used ICD-10 codes when ordering the Hereditary Pediatric Cancer Panel

ICD-10	Disease
Q82.2	Bloom syndrome
Q87.3	Beckwith-Wiedemann syndrome
Q87.89	Gorlin syndrome
D48.9	Li-Fraumeni syndrome
Q85.8	Peutz-Jeghers syndrome
Q82.8	Rothmund-Thomson syndrome
Q87.3	Simpson-Golabi-Behmel syndrome
E34.8	Werner syndrome
Q85.8	Von Hippel-Lindau disease
C18.0	Hereditary nonpolyposis colon cancer
D12.6	Juvenile polyposis syndrome
C71.9	Medulloblastoma predisposition
D44.9	Multiple endocrine neoplasia
C64.9	Nephroblastoma
Q85.1	Tuberous sclerosis complex
D12.6	Familial adenomatous polyposis
C75.0	Hereditary paraganglioma-pheochromocytoma
Q85.00	Neurofibromatosis type 1
Q85.00	Neurofibromatosis type 2

Accepted sample types

- EDTA blood, min. 1 ml
- Purified DNA, min. 3µg*
- Saliva (Oragene DNA OG-500 kit)

Label the sample tube with your patient's name, date of birth and the date of sample collection.

Note that we do not accept DNA samples isolated from formalin-fixed paraffin-embedded (FFPE) tissue.

Resources

- American Childhood Cancer Organization
- Association for Multiple Endocrine Neoplasia Disorders
- Basal Cell Carcinoma Nevus Syndrome Life Support Network
- Beckwith-Wiedemann Children's Foundation International
- Bloom's Syndrome Association
- Childhood Eye Cancer Trust
- GeneReviews - Beckwith-Wiedemann Syndrome
- GeneReviews - Bloom Syndrome
- GeneReviews - Bloom's Syndrome.
- GeneReviews - Gorlin Syndrome
- GeneReviews - Hereditary Paraganglioma-Pheochromocytoma Syndromes
- GeneReviews - Juvenile Polyposis Syndrome
- GeneReviews - Li-Fraumeni Syndrome
- GeneReviews - Multiple Endocrine Neoplasia Type 2
- GeneReviews - Nevoid Basal Cell Carcinoma Syndrome
- GeneReviews - Peutz-Jeghers Syndrome
- GeneReviews - Retinoblastoma
- GeneReviews - Rothmund-Thomson Syndrome
- GeneReviews - Simpson-Golabi-Behmel Syndrome Type 1
- GeneReviews - Tuberous Sclerosis
- GeneReviews - Tuberous Sclerosis Complex
- GeneReviews - Von Hippel-Lindau Syndrome
- GeneReviews - Werner Syndrome
- GeneReviews - von Hippel-Lindau Syndrome
- International Registry of Werner Syndrome
- NORD - Beckwith-Wiedemann Syndrome
- NORD - Bloom Syndrome
- NORD - Familial Adenomatous Polyposis
- NORD - Gorlin Syndrome
- NORD - Multiple Endocrine Neoplasia Type 1
- NORD - Multiple Endocrine Neoplasia Type 2
- NORD - Peutz-Jeghers Syndrome
- NORD - Pheochromocytoma
- NORD - Retinoblastoma
- NORD - Rothmund-Thomson Syndrome
- NORD - Simpson-Golabi-Behmel Syndrome
- NORD - Tuberous Sclerosis
- NORD - Von Hippel-Lindau Syndrome
- NORD - Werner Syndrome
- Pediatric Cancer Foundation
- Pheo Para Troopers
- Rothmund-Thomson Syndrome Foundation
- Tuberous Sclerosis Alliance
- Tuberous Sclerosis Complex International
- VHL Alliance
- Zhang, J. et al. Germline Mutations in Predisposition Genes in Pediatric Cancer. N Engl J Med. 2015 Dec 10;373(24):2336-2346.