Blueprint Genetics

Hereditary Leukemia Panel

Test code: ON0101

Is a 42 gene panel that includes assessment of non-coding variants.

Is ideal for patients with a personal history of a syndrome that confers an increased risk of leukemia or patients with a family history of a syndrome that confers an increased risk of leukemia.

About Hereditary Leukemia

An inherited predisposition to hematological malignancies, namely acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and bone marrow myelodysplastic syndrome (MDS) may be associated with syndromic features or occur as the principal clinical feature. MDSs and AMLs can occur in the context of syndromic bone marrow failure (eg. dyskeratosis congenita, Fanconi anemia). Other hereditary syndromes with an increased risk of leukemia include Li-Fraumeni syndrome (*TP53*), ataxia telangiectasia (*ATM*), Bloom syndrome (*BLM*), neurofibromatosis type 1 (*NF1*) and less frequently Noonan syndrome (*PTPN11, CBL*). Some reports have also shown an association of biallelic germline mutations in constitutional mismatch repair-deficiency syndrome genes, *MLH1, MSH2, MSH6*, and *PMS2* with the development of ALL. Isolated hematological malignancies are associated with germline mutations in *RUNX1* (familial platelet syndrome with predisposition to acute myelogenous leukemia), *CEBPA* (familial AML), *GATA2* (*GATA2*-associated syndromes) and *DDX41*(*DDX41* -related myeloid neoplasms). There is a rapidly expanding list of germline mutations associated with increased risks for myeloid malignancies and inherited predisposition to hematologic malignancies may be more common than has been thought. Many different genetic defects associated with the development of leukemia have been described but the common underlying mechanism is a dysfunctional DNA damage response. Recognition of an inherited cause provides a specific molecular diagnosis and helps to guide treatment, understand unique disease features, prognosis and other organ systems that may be involved, and identify others in the family who may be at risk.

Availability

4 weeks

Gene Set Description

Genes in the Hereditary Leukemia Panel and their clinical significance

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
ANKRD26	Thrombocytopenia	AD	6	21
ATM	Breast cancer, Ataxia-Telangiectasia	AD/AR	1047	1109
BLM	Bloom syndrome	AR	152	119
BRAF*	LEOPARD syndrome, Noonan syndrome, Cardiofaciocutaneous syndrome	AD	134	65
BRCA1*	Pancreatic cancer, Breast-ovarian cancer, familial	AD	2997	2631
BRCA2	Fanconi anemia, Medulloblastoma, Glioma susceptibility, Pancreatic cancer, Wilms tumor, Breast-ovarian cancer, familial	AD/AR	3369	2659
CBL	Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia	AD	24	43
CDKN2A	Melanoma, familial, Melanoma-pancreatic cancer syndrome	AD	87	232
CEBPA	Acute myeloid leukemia, familial	AD	15	13

DDX41	Familial myeloproliferative/lymphoproliferative neoplasms, multiple types, susceptibility to	AD	9	21
DKC1	Hoyeraal-Hreidarsson syndrome, Dyskeratosis congenita	XL	48	74
EFL1	Shwachman-Diamond syndrome		3	2
EPCAM	Diarrhea 5, with tufting enteropathy, congenital, Colorectal cancer, hereditary nonpolyposis	AD/AR	38	80
ETV6	Thrombocytopenia 5	AD	10	38
FANCA	Fanconi anemia	AR	191	677
GATA2	Myelodysplastic syndrome, Chronic neutropenia associated with monocytopenia, evolving to myelodysplasia and acute myeloid leukemia, Acute myeloid leukemia, Emberger syndrome, Immunodeficiency	AD	30	142
HAVCR2				
HRAS	Costello syndrome, Congenital myopathy with excess of muscle spindles	AD	43	31
IKZF1#	Immunodeficiency, common variable, 13	AD	10	35
KRAS*	Noonan syndrome, Cardiofaciocutaneous syndrome	AD	63	35
MAP2K1	Cardiofaciocutaneous syndrome	AD	45	23
MAP2K2	Cardiofaciocutaneous syndrome	AD	21	35
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
NRAS	Noonan syndrome	AD	31	14
PAX5	Pre-B cell acute lymphoblastic leukemia	AD		7
PMS2*	Mismatch repair cancer syndrome, Colorectal cancer, hereditary nonpolyposis	AD/AR	319	342
PTPN11	Noonan syndrome, Metachondromatosis	AD	135	140
RIT1	Noonan syndrome	AD	23	26
RUNX1	Platelet disorder, familial, with associated myeloid malignancy	AD	47	101
SAMD9	Mirage syndrome, Tumoral calcinosis, normophosphatemic	AD/AR	10	27
SAMD9L	Ataxia-pancytopenia syndrome	AD	4	16

SBDS*	Aplastic anemia, Shwachman-Diamond syndrome, Severe spondylometaphyseal dysplasia	AR	19	90
SOS1	Noonan syndrome	AD	44	71
SRP72*	Bone marrow failure syndrome 1	AD	2	5
TERC	Aplastic anemia, Pulmonary fibrosis and/or bone marrow failure, telomere-related, Dyskeratosis congenita	AD	42	73
TERT	Aplastic anemia, Pulmonary fibrosis and/or bone marrow failure, telomere-related, Dyskeratosis congenita	AD/AR	48	156
TINF2	Revesz syndrome, Dyskeratosis congenita	AD	25	42
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

*

Some, or all, of the gene is duplicated in the genome. Read more.

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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 (#). Due to possible limitations these genes may not be available as single gene tests.

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
ANKRD26	Chr10:27389371	c.-116C>G	NM_014915.2	
ANKRD26	Chr10:27389373	c.-118C>A	NM_014915.2	
ANKRD26	Chr10:27389374	c.-119C>A	NM_014915.2	
ANKRD26	Chr10:27389374	c.-119C>A/G	NM_014915.2	
ANKRD26	Chr10:27389376	c.-121A>C	NM_014915.2	
ANKRD26	Chr10:27389380	c.-127_-126delAT	NM_014915.2	
ANKRD26	Chr10:27389381	c.-126T>C	NM_014915.2	

ANKRD26	Chr10:27389381	c.-126T>G	NM_014915.2	
ANKRD26	Chr10:27389382	c.-127A>G	NM_014915.2	
ANKRD26	Chr10:27389382	c.-127A>T	NM_014915.2	
ANKRD26	Chr10:27389383	c.-128G>T	NM_014915.2	
ANKRD26	Chr10:27389383	c.-128G>A	NM_014915.2	
ANKRD26	Chr10:27389383	c.-128G>C	NM_014915.2	
ANKRD26	Chr10:27389389	c.-134G>A	NM_014915.2	rs863223318
ATM	Chr11:108093770	c.-174A>G	NM_000051.3	
ATM	Chr11:108094508	c.-31+595G>A	NM_000051.3	
ATM	Chr11:108098321	c.-30-1G>T	NM_000051.3	rs869312754
ATM	Chr11:108138753	c.2639-384A>G	NM_000051.3	
ATM	Chr11:108141209	c.2839-579_2839-576delAAGT	NM_000051.3	
ATM	Chr11:108151710	c.3403-12T>A	NM_000051.3	rs201370733
ATM	Chr11:108158168	c.3994-159A>G	NM_000051.3	rs864622543
ATM	Chr11:108164028	c.4612-12A>G	NM_000051.3	
ATM	Chr11:108179837	c.5763-1050A>G	NM_000051.3	rs774925473
ATM	Chr11:108214779	c.8418+681A>G	NM_000051.3	rs748635985
BRCA1	Chr17:41196352	c.*1340_*1342delTGT	NM_007294.3	rs1281551853
BRCA1	Chr17:41196424	c.*1271T>C	NM_007294.3	
BRCA1	Chr17:41197167	c.*528G>C	NM_007294.3	rs1060504556
BRCA1	Chr17:41197588	c.*103_*106delTGTC	NM_007294.3	rs431825382
BRCA1	Chr17:41197637	c.*58C>T	NM_007294.3	rs137892861
BRCA1	Chr17:41197859	c.5468-40T>A	NM_007294.3	rs80358151
BRCA1	Chr17:41199745	c.5407-25T>A	NM_007294.3	rs758780152
BRCA1	Chr17:41201232	c.5333-36_5333-22delTACTGCAGTGATTTT	NM_007294.3	
BRCA1	Chr17:41206122	c.5277+2916_5277+2946delAAATTCTAGTGCTTTGGATTTTTTCCTCCATinsGG	NM_007294.3	
BRCA1	Chr17:41209164	c.5194-12G>A	NM_007294.3	rs80358079
BRCA1	Chr17:41215994	c.5075-27delA	NM_007294.3	
BRCA1	Chr17:41251909	c.442-22_442-13delTGTTCTTTAC	NM_007294.3	rs879254224
BRCA1	Chr17:41256984	c.213-11T>G	NM_007294.3	rs80358061
BRCA1	Chr17:41256985	c.213-12A>G	NM_007294.3	rs80358163
BRCA1	Chr17:41256988	c.213-15A>G	NM_007294.3	
BRCA1	Chr17:41276134	c.-19-2A>G	NM_007294.3	
BRCA2	Chr13:32889805	c.-40+1G>A	NM_000059.3	
BRCA2	Chr13:32890469	c.-39-89delC	NM_000059.3	
BRCA2	Chr13:32890556	c.-39-1_-39delGA	NM_000059.3	rs758732038
BRCA2	Chr13:32890558	c.-39-1G>A	NM_000059.3	rs1060499566
BRCA2	Chr13:32900222	c.426-12_426-8delGTTTT	NM_000059.3	rs276174844
BRCA2	Chr13:32945079	c.8488-14A>G	NM_000059.3	
BRCA2	Chr13:32953872	c.8954-15T>G	NM_000059.3	

BRCA2	Chr13:32971007	c.9502-28A>G	NM_000059.3	rs397508059
BRCA2	Chr13:32971023	c.9502-12T>G	NM_000059.3	rs81002803
CDKN2A	Chr9:21968346	c.458-105A>G	NM_000077.4	
CDKN2A	Chr9:21972311	c.151-1104C>G	NM_000077.4	
CDKN2A	Chr9:21973573	c.150+1104C>A	NM_000077.4	rs756102261
CDKN2A	Chr9:21974401	c.*73+2T>G	NM_058197.4	
CDKN2A	Chr9:21974847	c.-21C>T	NM_000077.4	
CDKN2A	Chr9:21974875	c.-49C>A	NM_000077.4	rs1064797383
CDKN2A	Chr9:21974882	c.-56G>T	NM_000077.4	
CDKN2A	Chr9:21974916	c.-93_-91delAGG	NM_000077.4	
DKC1	ChrX:153991099	c.-142C>G	NM_001363.3	rs199422241
DKC1	ChrX:153991100	c.-141C>G	NM_001363.3	
DKC1	ChrX:153993704	c.85-15T>C	NM_001363.3	
EPCAM	Chr2:47606078	c.556-14A>G	NM_002354.2	rs376155665
FANCA	Chr16:89805127	c.4261-19_4261-12delACCTGCTC	NM_000135.3	
FANCA	Chr16:89816056	c.3239+82T>G	NM_000135.2	
FANCA	Chr16:89818822	c.2982-192A>G	NM_000135.2	
FANCA	Chr16:89831215	c.2778+83C>G	NM_000135.2	rs750997715
FANCA	Chr16:89836111	c.2504+134A>G	NM_000135.2	
FANCA	Chr16:89836805	c.2223-138A>G	NM_000135.2	
FANCA	Chr16:89849346	c.1567-20A>G	NM_000135.2	rs775154397
FANCA	Chr16:89864654	c.893+920C>A	NM_000135.2	
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	
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	
NF1	Chr17:29548419	c.1642-449A>G	NM_001042492.2	rs863224655
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	
PMS2	Chr7:6027263	c.1145-31_1145-13delCTGACCCTCTTCTCCGTCC	NM_000535.5	rs751973268
PMS2	Chr7:6048599	c.23+21_23+28delTCCGGTGT	NM_000535.5	
PTPN11	Chr12:112915602	c.934-59T>A	NM_002834.3	
TERC	Chr3:169482870	n.-22C>T	NR_001566.1	
TERC	Chr3:169482906		NR_001566.1	
TERC	Chr3:169482948	n.-100C>G	NR_001566.1	rs199422256
TERC	Chr3:169483086		NR_001566.1	rs199422255
TERT	Chr5:1271334	c.2383-15C>T	NM_198253.2	rs574645600
TERT	Chr5:1295161	c.-57A>C	NM_198253.2	
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	

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

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. 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

The genes on the panel have been carefully selected based on scientific literature, mutation databases and our experience.

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.

The performance metrics listed below are from an initial validation performed at our main laboratory in Finland. The performance metrics of our laboratory in Seattle, WA, are equivalent.

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%
Microdeletion/-duplication sdrs (large CNVs, n=37))		
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.

	Sensitivity %	**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=2026 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%)	92.3% (12/13)	99.98%
Heteroplasmic (<5%)	88.9% (48/54)	99.93%
Insertions and deletions by sequence analysis n=40 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)	99,997%
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. If the test includes the mitochondrial genome the target region gene list contains the mitochondrial genes. 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 suboptimal coverage (<20X for nuclear genes and <1000X for mtDNA) 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 ACMG guideline 2015.

The final step in the analysis is orthogonal confirmation. Sequence and copy number variants classified as pathogenic, likely pathogenic and variants of uncertain significance (VUS) are confirmed using bi-directional Sanger sequencing or by orthogonal methods such as qPCR/ddPCR when they do not meet our stringent NGS quality metrics for a true positive call.

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.

CPT code(s) *

81162, 81218, 81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81351, 81403, 81404 x2, 81405, 81406 x5, 81408 x2, 81479

* The CPT codes provided are based on AMA guidelines and are for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payer being billed.

ICD Codes

Refer to the most current version of ICD-10-CM manual for a complete list of ICD-10 codes.

Sample Requirements

- Blood (min. 1ml) in an EDTA tube
- Extracted DNA, min. 2 µg in TE buffer or equivalent
- Saliva (Please see Sample Requirements for accepted saliva kits)

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

We do not accept DNA samples isolated from formalin-fixed paraffin-embedded (FFPE) tissue. In addition, if the patient is affected with a hematological malignancy, DNA extracted from a non-hematological source (e.g. skin fibroblasts) is strongly recommended.

Please note that, in rare cases, mitochondrial genome (mtDNA) variants may not be detectable in blood or saliva in which case DNA extracted from post-mitotic tissue such as skeletal muscle may be a better option.

Read more about our sample requirements here.

For Patients

Other

- American Cancer Society - Acute Myeloid Leukemia
- Ataxia Telangiectasia Children's Project
- Ataxia-Telangiectasia Society
- Bloom's Syndrome Association
- Canadian Fanconi Anemia Research Fund
- Children's Leukemia Research Association
- Churpek, J. Familial myelodysplastic syndrome/acute myeloid leukemia. Best Pract Res Clin Haematol. 2017 Dec;30(4):287-289.
- Costello Kids
- Dyskeratosis Congenita Outreach
- Fanconi Anemia Research Fund
- Fanconi Hope
- GeneReviews - Ataxia Telangiectasia
- GeneReviews - Bloom Syndrome
- GeneReviews - CEBPA-Associated Familial Acute Myeloid Leukemia (AML)
- GeneReviews - Costello Syndrome
- GeneReviews - Dyskeratosis Congenita
- GeneReviews - Dyskeratosis Congenita
- GeneReviews - ELANE-Related Neutropenia
- GeneReviews - Familial Acute Myeloid Leukemia
- GeneReviews - Fanconi Anemia
- GeneReviews - Li-Fraumeni Syndrome
- GeneReviews - Lynch Syndrome
- GeneReviews - Neurofibromatosis
- GeneReviews - Neurofibromatosis 1
- GeneReviews - Noonan Syndrome
- GeneReviews - Shwachman-Diamond Syndrome
- Leukaemia CARE
- Leukaemia Foundation
- Leukemia & Lymphoma Society

- Lynch Syndrome International
- NORD - Ataxia Telangiectasia
- NORD - Bloom Syndrome
- NORD - Costello Syndrome
- NORD - Dyskeratosis Congenita
- NORD - Fanconi Anemia
- NORD - Lynch Syndrome
- NORD - Neurofibromatosis
- NORD - Noonan Syndrome
- NORD - Severe Chronic Neutropenia
- NORD - Shwachman-Diamond Syndrome
- NORD-Acute Myeloid Leukemia
- National Ataxia Foundation
- National Neutropenia Network
- Neurofibromatosis Network
- Neutropenia Support Association
- Noonan Syndrome Association
- Noonan Syndrome Foundation
- RASopathies Network USA
- Shwachman-Diamond Syndrome Foundation