

Hereditary Melanoma and Skin Cancer Panel

Test code: ON0501

Is a 19 gene panel that includes assessment of non-coding variants.

Is ideal for patients with a clinical suspicion of an inherited susceptibility to melanoma and skin cancer. This panel is designed to detect heritable germline mutations and should not be used for the detection of somatic mutations in tumor tissue.

About Hereditary Melanoma and Skin Cancer

Cancers arising in the skin include basal-cell cancer, squamous cell cancer, and melanoma. Melanomas may rarely also occur in the mouth, intestines or eye. Ultraviolet radiation from exposure to sun light or tanning beds is the main cause for skin cancer. A subset of skin cancers is associated with various hereditary cancer syndromes. Familial atypical multiple mole melanoma syndrome is caused by mutations in the *CDKN2A* gene that may be present in up to 40% of the familial cases of melanoma. Mutations in the *CDK4* gene also cause familial melanoma predisposition. Gorlin syndrome is associated with pathogenic mutations in the *PTCH1* and *SUFU* genes and increases the risk of developing basal cell carcinomas. Other cancer susceptibility syndromes/genes that increase the risk of developing skin cancers, either as a primary or secondary disease, include *BAP1*-related tumor predisposition syndrome (*BAP1*), hereditary breast and ovarian cancer syndrome (*BRCA1* and *BRCA2*), xeroderma pigmentosum (several genes), *MITF*-related melanoma and renal cell carcinoma predisposition syndrome (*MITF*), Li-Fraumeni syndrome (*TP53*), Cowden syndrome (*PTEN*), and Werner syndrome (*WRN*).

Availability

4 weeks

Gene Set Description

Genes in the Hereditary Melanoma and Skin Cancer Panel and their clinical significance

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
BAP1	Tumor predisposition syndrome	AD	74	113
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
CDK4	Melanoma, cutaneous malignant	AD	4	14
CDKN2A	Melanoma, familial, Melanoma-pancreatic cancer syndrome	AD	87	232
DDB2	Xeroderma pigmentosum	AR	4	17
ERCC2	Xeroderma pigmentosum, Trichothiodystrophy, photosensitive, Cerebrooculofacioskeletal syndrome 2	AR	26	98
ERCC3	Xeroderma pigmentosum, Trichothiodystrophy, photosensitive	AR	10	19
ERCC4	Fanconi anemia, Xeroderma pigmentosum, XFE progeroid syndrome	AR	13	70
ERCC5	Xeroderma pigmentosum, Xeroderma pigmentosum/Cockayne syndrome	AR	21	54

MITF	Tietz albinism-deafness syndrome, Waardenburg syndrome, Coloboma, osteopetrosis, microphthalmia, macrocephaly, albinism, and deafness (COMMD)	AD/AR	32	58
POT1	Glioma susceptibility 9, Melanoma, cutaneous malignant, susceptibility to 10	AD	2	34
PTCH1	Basal cell nevus syndrome	AD	193	522
<u>PTEN</u> *	Bannayan-Riley-Ruvalcaba syndrome, Lhermitte-Duclos syndrome, Cowden syndrome	AD	435	638
SUFU	Medulloblastoma, Basal cell nevus syndrome	AD	22	44
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
<u>WRN</u> *	Werner syndrome	AR	64	107
XPA	Xeroderma pigmentosum	AR	49	47
XPC	Xeroderma pigmentosum	AR	67	91

*

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
BAP1	Chr3:52435659	c.*644delG	NM_004656.3	
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

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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+2946delAAATTCTAGTGCTTTGGATTTTTCTCCATinsGG	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	
ERCC5	Chr13:103514354	c.881-26T>G	NM_000123.3	
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	

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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	
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	
WRN	Chr8:30966107	c.2089-3024A>G	NM_000553.4	rs281865157
WRN	Chr8:30999982	c.3234-160A>G	NM_000553.4	
XPA	Chr9:100449555	c.390-12A>G	NM_000380.3	
XPC	Chr3:14187285	c.*156G>A	NM_004628.4	rs121965092
XPC	Chr3:14209904	c.413-24A>G	NM_004628.4	rs794729657

Test Strengths

Assesses for non-coding disease causing variants in one or more genes, including promoter variants in *PTEN*.

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
- ~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.

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)		

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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%



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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 artificial 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 cornerstone 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 healthcare provider at no additional cost, according to our latest follow-up reporting policy.

CPT code(s) *

81162, 81321, 81323, 81351, 81404, 81479

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* 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 Melanoma Foundation](#)
- [Bright Pink](#)
- [Cancer.Net - Cowden Syndrome](#)
- [Cancer.net - Gorlin Syndrome](#)
- [Fighting Hereditary Breast and Ovarian Cancer](#)
- [Forgotten Diseases Research Foundation](#)
- [GeneReviews - *BAP1* Tumor Predisposition Syndrome](#)
- [GeneReviews - Gorlin Syndrome](#)
- [GeneReviews - Li-Fraumeni Syndrome](#)
- [GeneReviews - Nevoid Basal Cell Carcinoma Syndrome](#)
- [GeneReviews - Retinoblastoma](#)
- [GeneReviews - Werner Syndrome](#)
- [GeneReviews - Xeroderma Pigmentosum](#)
- [HBOC Society](#)
- [International Registry of Werner Syndrome](#)
- [Li-Fraumeni Syndrome Association](#)
- [NORD - Atypical Mole Syndrome](#)
- [NORD - Gorlin Syndrome](#)
- [NORD - Melanoma, Malignant](#)
- [NORD - Retinoblastoma](#)
- [NORD - Werner Syndrome](#)
- [NORD - Xeroderma Pigmentosum](#)
- [Skin Cancer Foundation](#)
- [The Eye Cancer Foundation](#)