

Hereditary Breast Cancer High Risk Panel

Test code: ON1901

Is ideal for patients with a clinical suspicion of hereditary breast or ovarian cancer who only wish assessment of genes with established management guidelines. This panel is designed to detect heritable germline mutations and should not be used for the detection of somatic mutations in tumor tissue.

Breast cancer is the most common cancer in women. While majority of the breast cancers are sporadic, 5-10% of breast cancer cases are caused by pathogenic germline mutations in cancer susceptibility genes. Inheritance pattern of these genetic cancer susceptibility conditions is predominantly autosomal dominant. The Hereditary Breast Cancer High Risk 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 and Hereditary Breast and Gynecological Cancer panel.

About Hereditary Breast Cancer High Risk

Hereditary breast and ovarian cancer syndrome (HBO) is caused by germline mutations in *BRCA1* or *BRCA2*, and is characterized by an increased risk for breast cancer, ovarian cancer, prostate cancer and pancreatic cancer. The lifetime risk of developing breast cancer is 40-80% in an individual with a pathogenic *BRCA1* or *BRCA2* variant. The risk for ovarian cancer is 11-40 % and lower for the other cancers. Although HBO account for a small number of all breast cancers (less than 5 %) it accounts for a greater proportion of breast cancer in younger women and in women with triple-negative breast cancer. After a cancer predisposing germline mutation in *BRCA1* or *BRCA2* has been identified in a patient, genetic counselling should be offered. Subsequently, genetic counselling and targeted mutation testing of family members can be recommended. Genetic counselling should be offered for high-risk individuals with a cancer predisposing mutation to discuss surveillance and possibilities for reducing the risk of breast and ovarian cancer. Individuals with the following cancer susceptibility syndromes also have increased lifetime risks of breast cancer: Li-Fraumeni syndrome (*TP53*), Cowden syndrome (*PTEN*), hereditary diffuse gastric cancer (*CDH1*), and Peutz-Jeghers syndrome (*STK11*). In addition, women who have cancer predisposing variants in *PALB2* gene have relatively high lifetime risk of breast cancer (PMID 25099575).

Availability

Results in 3-4 weeks

Gene set description

Genes in the Hereditary Breast Cancer High Risk Panel and their clinical significance

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
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
CDH1	CDH1-related cancer, Blepharocheilodontic syndrome 1	AD	178	242
PALB2	Fanconi anemia, Pancreatic cancer, Breast cancer	AD/AR	495	406
PTEN*	Bannayan-Riley-Ruvalcaba syndrome, Lhermitte-Duclos syndrome, Cowden syndrome	AD	435	638
RECQL	Breast cancer	AD	9	27
STK11	Peutz-Jeghers syndrome	AD	173	460

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
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*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
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+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_442-13delITGTTCTTTAC	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	

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BRCA2	Chr13:32971007	c.9502-28A>G	NM_000059.3	rs397508059
BRCA2	Chr13:32971023	c.9502-12T>G	NM_000059.3	rs81002803
CDH1	Chr16:68842843	c.687+92T>A	NM_004360.3	
PALB2	Chr16:23649285	c.109-12T>A	NM_024675.3	rs774949203
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	
STK11	Chr19:1220520	c.597+16_597+33delGGGGGGCCCTGGGGCGCCinsTG	NM_000455.4	
STK11	Chr19:1220530	c.598-32_597+31delGCCCCCTCCCGGGC	NM_000455.4	
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	

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
- Our publicly available analytic validation demonstrating complete details of test performance

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- ~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

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).¹

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 %

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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%



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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 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 MQO (clinical)	18224X	17366X
Nucleotides with >1000x MQO 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.



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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 Breast Cancer High Risk Panel

ICD-10	Disease
D61.09	Fanconi anemia
C50 C56	Hereditary breast and ovarian cancer syndrome
Q85.8	Peutz-Jeghers syndrome
C50	Breast and ovarian cancer
Q85.8	Cowden syndrome
C16.9	Hereditary diffuse gastric cancer

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

- [Bright Pink](#)
- [Cancer.Net - Cowden Syndrome](#)
- [Cancer.Net - Hereditary Breast and Ovarian Cancer](#)
- [Cancer.Net - Hereditary Diffuse Gastric Cancer](#)
- [Cancer.Net - Peutz-Jeghers Syndrome](#)
- [Fighting Hereditary Breast and Ovarian Cancer](#)
- [GeneReviews - *BRCA1*- and *BRCA2*-Associated Hereditary Breast and Ovarian Cancer](#)
- [GeneReviews - *PTEN* Hamartoma Tumor Syndrome](#)
- [GeneReviews - BRCA1 and BRCA2 Hereditary Breast and Ovarian Cancer](#)
- [GeneReviews - Hereditary Diffuse Gastric Cancer](#)
- [GeneReviews - Li-Fraumeni Syndrome](#)
- [GeneReviews - PTEN Hamartoma Tumor Syndrome \(PHTS\)](#)
- [GeneReviews - Peutz-Jeghers Syndrome](#)
- [HBOC Society](#)
- [Li-Fraumeni Syndrome Association](#)
- [NORD - Peutz Jeghers Syndrome](#)
- [No Stomach for Cancer](#)

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- [PALB2Interest Group](#)
- [PTEN Hamartoma Tumor Syndrome Foundation](#)

