Blueprint Genetics

*Sample report as of June 14, 2022. Regional differences may apply. For complete and up-to-date test methodology description, please see your report in Nucleus online portal. Accreditation and certification information available at **blueprintgenetics.com/certifications***

Comprehensive Hereditary Cancer Panel Plus

REFERRING HEALTHCARE PROFESSIONAL

NAME **HOSPITAL**

PATIENT

NAME **DOB** **AGE** **GENDER** **ORDER ID**
Female

PRIMARY SAMPLE TYPE **SAMPLE COLLECTION DATE** **CUSTOMER SAMPLE ID**

SUMMARY OF RESULTS

PRIMARY FINDINGS

The patient is heterozygous for *BRCA2* c.5073dup, p.(Trp1692Metfs*3), which is pathogenic.

PRIMARY FINDINGS: SEQUENCE ALTERATIONS

GENE	TRANSCRIPT	NOMENCLATURE	GENOTYPE	CONSEQUENCE	INHERITANCE	CLASSIFICATION
BRCA2	NM_000059.3	c.5073dup, p.(Trp1692Metfs*3)	HET	frameshift_variant	AD,AR	Pathogenic
	ID	**ASSEMBLY**	**POS**	**REF/ALT**		
	rs80359480	GRCh37/hg19	13:32913558	C/CA		
	gnomAD AC/AN	**POLYPHEN**	**SIFT**	**MUTTASTER**	**PHENOTYPE**	
	4/230778	N/A	N/A	N/A	Breast-ovarian cancer, familial, Fanconi anemia, Glioma susceptibility, Medulloblastoma, Pancreatic cancer, Wilms tumor	

SEQUENCING PERFORMANCE METRICS - NUCLEAR GENOME

PANEL	GENES	EXONS / REGIONS	BASES	BASES > 20X	MEDIAN COVERAGE	PERCENT > 20X
Comprehensive Hereditary Cancer Panel	160	2457	501526	500963	217	99.89

TARGET REGION AND GENE LIST

The Blueprint Genetics Comprehensive Hereditary Cancer Panel (version 5, Oct 30, 2021) Plus Analysis includes sequence analysis and copy number variation analysis of the following genes: *AIP*, *ALK*, *ANKRD26*, *APC*, *ATM*, *AXIN2*, *BAP1*, *BARD1*, *BLM*, *BMPR1A**, *BRAF**, *BRCA1**, *BRCA2*, *BRIP1*, *BUB1B*, *CBL*, *CD70*, *CDC73*, *CDH1*, *CDK4*, *CDKN1B*, *CDKN1C*, *CDKN2A*, *CEBPA*, *CEP57*, *CHEK2**, *CTNNA1*, *CYLD*, *DDB2*, *DDX41*, *DICER1**, *DIS3L2**, *DKC1*, *EFL1**, *EGFR*, *ELANE*, *EPCAM*, *ERCC1*, *ERCC2*, *ERCC3*, *ERCC4*, *ERCC5*, *ETV6*, *EXO1*, *EXT1*, *EXT2*, *EZH2*, *FAM111B**, *FANCA*, *FANCB*, *FANCC*, *FANCD2**, *FANCE*, *FANCF*, *FANCG*, *FANCI*, *FANCL*, *FANCM*, *FH*, *FLCN*, *GALNT12*, *GATA2*, *GPC3*, *GPR101*, *GREM1*, *HAVCR2*, *HNF1A*, *HOXB13*, *HRAS*, *IKZF1*, *KIF1B*, *KIT*, *KITLG*, *KRAS**, *LZTR1*, *MAP2K1*, *MAP2K2*, *MAX*, *MEN1*, *MET*, *MITF*, *MLH1*, *MLH3*, *MRE11A*, *MSH2*, *MSH3*, *MSH6*, *MUTYH*, *NBN*, *NF1**, *NF2*, *NRAS*, *NSD1*, *NSUN2*, *NTHL1*, *PALB2*, *PAX5*, *PDGFRA*[#], *PHOX2B*, *PMS1*[#], *PMS2**, *POLD1*, *POLE*, *POLH**, *POT1*, *PPM1D*, *PRF1*, *PRKAR1A*, *PTCH1*, *PTEN**, *PTPN11*, *RAD50*, *RAD51C*, *RAD51D*, *RAF1*, *RASA2*, *RB1*, *RECQL**, *RECQL4*, *REST*, *RET*, *RHBDF2*, *RIT1*, *RPS20*, *RRAS*, *RUNX1*, *SAMD9*, *SAMD9L*, *SBDS**, *SDHA**, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*[#], *SHOC2*, *SLX4*, *SMAD4*, *SMARCA4*, *SMARCB1*, *SMARCE1*, *SOS1*, *SOS2*, *SPRED1*, *SRP72**, *STK11*, *SUFU*, *TERC*, *TERT*, *TINF2*, *TMEM127*, *TP53*, *TRIP13*, *TSC1*, *TSC2*, *VHL*, *WRN**, *WT1*, *XPA*, *XPC* and *XRCC2*. The following exons are not included in the panel as they are not covered with sufficient high quality sequence reads: PDGFRA (NM_001347828:2), PMS1 (NM_001321049:4) and SDHD

(NM_001276506:4). This panel targets protein coding exons, exon-intron boundaries (± 20 bps) and selected non-coding, deep intronic variants (listed in the SUMMARY OF THE TEST section). This panel should be used to detect single nucleotide variants and small insertions deletions (INDELs) and copy number variations defined as single exon or larger deletions and duplications. This panel should not be used for the detection of repeat expansion disorders or diseases caused by mitochondrial DNA (mtDNA) mutations. The test does not detect balanced translocations or complex rearrangements, and it may not detect low-level mosaicism.

*Some, or all, of the gene is duplicated in the genome. Read more: https://blueprintgenetics.com/pseudogene/

#The gene has suboptimal coverage when >90% of the gene's target nucleotides are not covered at >20x with a mapping quality score of MQ>20 reads.

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

STATEMENT

CLINICAL HISTORY

Patient is a female with breast cancer and a family history of cancer.

CLINICAL REPORT

Sequence analysis using the Blueprint Genetics (BpG) Comprehensive Hereditary Cancer Panel identified a heterozygous frameshift variant *BRCA2* c.5073dup, p.(Trp1692Metfs*3).

BRCA2 c.5073dup, p.(Trp1692Metfs*3)

There are 4 individuals heterozygous for this variant in gnomAD, a large reference population database (n>120,000 exomes and >15,000 genomes) which aims to exclude individuals with severe pediatric disease. Of note, the variant lies in a genomic region which is well covered by exome sequencing but poorly covered by genome sequencing in the gnomAD dataset, and therefore estimations of its population frequency based on the gnomAD data may be unreliable. This variant generates a frameshift in exon 11 (of a total of 27 exons) resulting in a premature stop codon. This is predicted to lead to a loss of normal protein function, either through protein truncation or nonsense-mediated mRNA decay. Loss of function is an established disease-mechanism in this gene (HGMD). *BRCA2* c.5073dup, p.(Trp1692Metfs*3) has been reported in multiple individuals with breast and/or ovarian cancer, pancreatic cancer, colon cancer and Fanconi anemia (PMID: 11179017, 32918181, 25479140, 28176296, 26026974, 14559878, 28486781, BpG unpublished observations). The variant has been submitted to ClinVar by other clinical testing laboratories (variation ID 37943).

BRCA2

BRCA2 (MIM *600185) gene encodes breast cancer type 2 susceptibility protein involved in double-strand break repair and homologous recombination. BRCA2 acts as a tumor suppressor. Germline pathogenic variants in *BRCA2* cause hereditary breast and ovarian cancer syndrome (HBOC; GeneReviews: *NBK1247*). HBOC is an autosomal dominant cancer predisposition syndrome caused by germline variants in *BRCA1* or *BRCA2*. HBOC is associated with an increased risk for female and male breast cancer, ovarian cancer, and to a lesser extent other cancers such as prostate cancer, pancreatic cancer, and melanoma primarily in individuals with a *BRCA2* pathogenic variant (GeneReviews: NBK1247). In males with *BRCA2* pathogenic variants, the estimated risk for breast cancer by age 80 years is up to 8.9%, while the general population risk is at 0.1% (PMID *20587410*; GeneReviews: NBK1247). Male breast cancer is more commonly associated with variant of *BRCA2* than *BRCA1*. Males with *BRCA2* pathogenic variants have also increased risk for prostate cancer, with an estimated 15% risk by age 65, while the general population risk to prostate cancer through age 69 is at 6% (GeneReviews: NBK1247).

The probability of cancer development in carriers of *BRCA2* variants seems variable, even within families with the same variant (PMID: 9150153). The BRCA1 and BRCA2 proteins play important role in maintaining genomic stability by promoting efficient and precise repair of double strand breaks (PMID: 16998501). Most pathogenic variants in *BRCA2* are truncating (frameshift, nonsense, splice site variants; altogether >95% of those reported in the ClinVar as pathogenic). The clinical significance of rare missense variants remain often uncertain, especially without family segregation data. Recessive variants of *BRCA2* cause Fanconi anemia (FA) complementation group D1 (MIM #605724). Some 3% of all FA cases are attributed to pathogenic variants in *BRCA2* (GeneReviews NBK1401).

For carriers of pathogenic and likely pathogenic *BRCA2* variants surveillance should be organized to detect possible cancers at an as early stage as possible and in female carriers, prophylactic surgery (mastectomy and oophorectomy) can be considered. Genetic counseling and family member testing should be organized.

Mutation nomenclature is based on GenBank accession NM_000059.3 (*BRCA2*) with nucleotide one being the first nucleotide of the translation initiation codon ATG.

CONCLUSION

BRCA2 c.5073dup, p.(Trp1692Metfs*3) is classified as pathogenic, based on currently available evidence supporting its disease-causing role. Disease caused by *BRCA2* c.5073dup, p.(Trp1692Metfs*3) is expected to be inherited in an autosomal dominant manner. Any offspring of the patient are at 50% risk of inheriting the variant and of being affected with increased risk for *BRCA2*-related cancers. Genetic counseling and family member testing are recommended.

STEP	DATE
Order date	
Sample received	
Sample in analysis	
Reported	

(This statement has been prepared by our geneticists and physicians, who have together evaluated the sequencing results.)

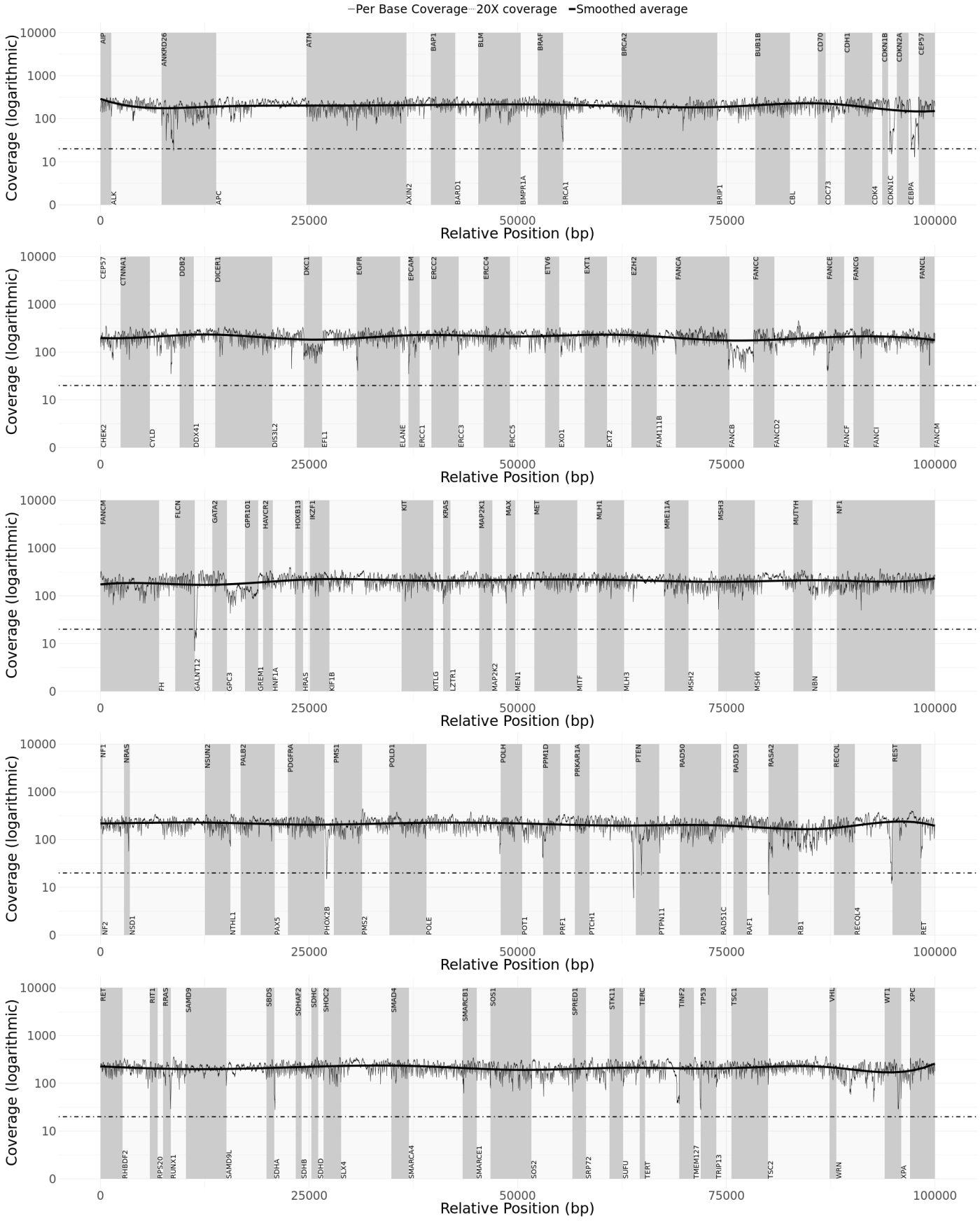
Signature

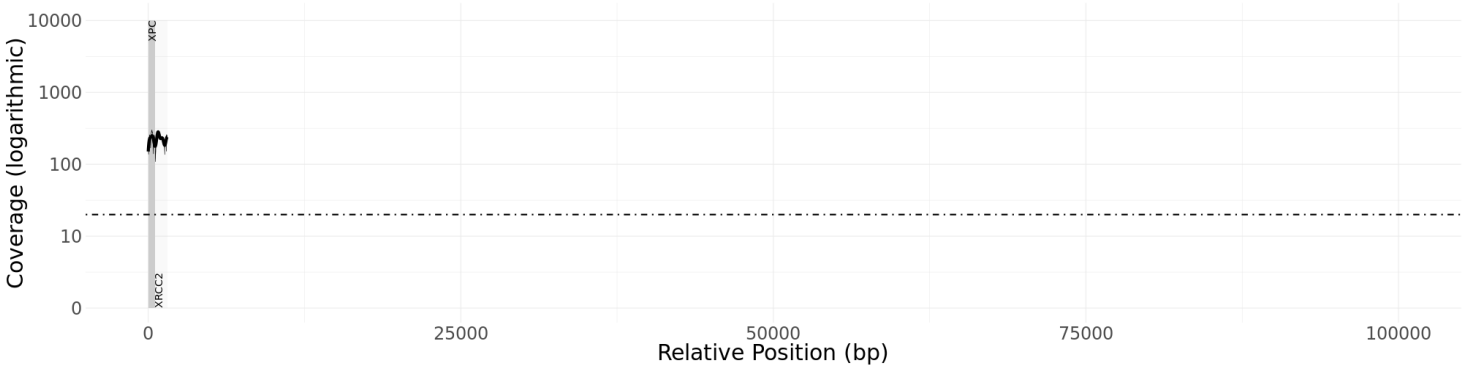
Name

Title

COVERAGE PLOT - NUCLEAR GENES

Readability of the coverage plot may be hindered by faxing. A high quality coverage plot can be found with the full report on nucleus.blueprintgenetics.com.




Coverage (logarithmic)
10000
1000
100
10
0
XPC
XRCC2
0
25000
50000
75000
100000
Relative Position (bp)

APPENDIX 5: SUMMARY OF THE TEST

PLUS ANALYSIS

Laboratory process: When required, the total genomic DNA was extracted from the biological sample using bead-based method. Quantity of DNA was assessed using fluorometric method. After assessment of DNA quantity, qualified genomic DNA sample was randomly fragmented using non-contact, isothermal sonochemistry processing. Sequencing library was prepared by ligating sequencing adapters to both ends of DNA fragments. Sequencing libraries were size-selected with bead-based method to ensure optimal template size and amplified by polymerase chain reaction (PCR). Regions of interest (exons and intronic targets) were targeted using hybridization-based target capture method. The quality of the completed sequencing library was controlled by ensuring the correct template size and quantity and to eliminate the presence of leftover primers and adapter-adapter dimers. Ready sequencing libraries that passed the quality control were sequenced using the Illumina's sequencing-by-synthesis method using paired-end sequencing (150 by 150 bases). Primary data analysis converting images into base calls and associated quality scores was carried out by the sequencing instrument using Illumina's proprietary software, generating CBCL files as the final output.
Bioinformatics and quality control: Base called raw sequencing data was transformed into FASTQ format using Illumina's software (bcl2fastq). Sequence reads of each sample were mapped to the human reference genome (GRCh37/hg19). Burrows-Wheeler Aligner (BWA-MEM) software was used for read alignment. Duplicate read marking, local realignment around indels, base quality score recalibration and variant calling were performed using GATK algorithms (Sentieon) for nDNA. Variant data for was annotated using a collection of tools (VcfAnno and VEP) with a variety of public variant databases including but not limited to gnomAD, ClinVar and HGMD. The median sequencing depth and coverage across the target regions for the tested sample were calculated based on MQ0 aligned reads. The sequencing run included in-process reference sample(s) for quality control, which passed our thresholds for sensitivity and specificity. The patient's sample was subjected to thorough quality control measures including assessments for contamination and sample mix-up. Copy number variations (CNVs), defined as single exon or larger deletions or duplications (Del/Dups), were detected from the sequence analysis data using a proprietary bioinformatics pipeline. The difference between observed and expected sequencing depth at the targeted genomic regions was calculated and regions were divided into segments with variable DNA copy number. The expected sequencing depth was obtained by using other samples processed in the same sequence analysis as a guiding reference. The sequence data was adjusted to account for the effects of varying guanine and cytosine content.
Interpretation: The clinical interpretation team assessed the pathogenicity of the identified variants by evaluating the information in the patient requisition, reviewing the relevant scientific literature and manually inspecting the sequencing data if needed. All available evidence of the identified variants was compared to classification criteria. Reporting was carried out using HGNC-approved gene nomenclature and mutation nomenclature following the HGVS guidelines. Likely benign and benign variants were not reported.
Variant classification: Our variant classification follows the Blueprint Genetics Variant Classification Schemes modified from the ACMG guideline 2015. Minor modifications were made to increase reproducibility of the variant classification and improve the clinical validity of the report. The classification and interpretation of the variant(s) identified reflect the current state of Blueprint Genetics' understanding at the time of this report. Variant classification and interpretation are subject to professional judgment, and may change for a variety of reasons, including but not limited to, updates in classification guidelines and availability of additional scientific and clinical information. This test result should be used in conjunction with the health care provider's clinical evaluation. Inquiries regarding potential changes to the classification of the variant is strongly recommended prior to making any future clinical decisions. For questions regarding variant classification updates, please contact our customer support (Global: support@blueprintgenetics.com, US: support.us@blueprintgenetics.com, Canada: support.ca@blueprintgenetics.com).
Databases: The pathogenicity potential of the identified variants were assessed by considering the predicted consequence of the change, the degree of evolutionary conservation as well as the number of reference population databases and mutation databases such as, but not limited to, the gnomAD, ClinVar, HGMD Professional and Alamut Visual. In addition, the clinical relevance of any identified CNVs was evaluated by reviewing the relevant literature and databases such as Database of Genomic Variants and DECIPHER. For interpretation of mtDNA variants specific databases including e.g. Mitomap, HmtVar and 1000G were used.
Confirmation of sequence alterations: Sequence variants classified as pathogenic, likely pathogenic and variants of uncertain significance (VUS) were confirmed using bi-directional Sanger sequencing when they did not meet our stringent NGS quality metrics for a true positive call. In addition, prenatal case with diagnostic findings were confirmed.

Confirmation of copy number variants: CNVs (Deletions/Duplications) were confirmed using a digital PCR assay if they covered less than 10 exons (heterozygous), less than 3 exons (homo/hemizygous) or were not confirmed at least three times previously at our laboratory. Furthermore, CNVs of any size were not confirmed when the breakpoints of the call could be determined.
Analytic validation: The detection performance of this panel is expected to be in the same range as our high-quality, clinical grade NGS sequencing assay used to generate the panel data (nuclear DNA: sensitivity for SNVs 99.89%, indels 1-50 bps 99.2%, one-exon deletion 100% and five exons CNV 98.7%, and specificity >99.9% for most variant types). It does not detect very low level mosaicism as a variant with minor allele fraction of 14.6% can be detected in 90% of the cases. Detection performance for mtDNA variants (analytic and clinical validation): sensitivity for SNVs and INDELs 100.0% (10-100% heteroplasmy level), 94.7% (5-10% heteroplasmy level), 87.3% (<5% heteroplasmy level) and for gross deletions 100.0%. Specificity is >99.9% for all.
Test restrictions: A normal result does not rule out the diagnosis of a genetic disorder since some DNA abnormalities may be undetectable by the applied technology. Test results should always be interpreted in the context of clinical findings, family history, and other relevant data. Inaccurate, or incomplete information may lead to misinterpretation of the results.
Technical limitations: This test does not detect the following: complex inversions, gene conversions, balanced translocations, repeat expansion disorders unless specifically mentioned, non-coding variants deeper than ±20 base pairs from exon-intron boundary unless otherwise indicated (please see the list of non-coding variants covered by the test). Additionally, this test may not reliably detect the following: low level mosaicism, stretches of mononucleotide repeats, indels larger than 50bp, single exon deletions or duplications, and variants within pseudogene regions/duplicated segments. The sensitivity of this test may be reduced if DNA is extracted by a laboratory other than Blueprint Genetics. Laboratory error is also possible. Please see the Analytic validation above.
Regulation and accreditations: This test was developed and its performance characteristics determined by Blueprint Genetics (see Analytic validation). It has not been cleared or approved by the US Food and Drug Administration. This analysis has been performed in a CLIA-certified laboratory (#99D2092375), accredited by the College of American Pathologists (CAP #9257331) and by FINAS Finnish Accreditation Service, (laboratory no. T292), accreditation requirement SFS-EN ISO 15189:2013. All the tests are under the scope of the ISO 15189 accreditation.

PERFORMING SITE:

BLUEPRINT GENETICS OY, KEILARANTA 16 A-B, 02150 ESPOO, FINLAND Laboratory Director: JUHA KOSKENVUO, MD, PHD, CLIA: 99D2092375

- DNA extraction and QC
- Next-generation sequencing
- Bioinformatic analysis
- Confirmation of sequence alterations
- Confirmation of copy number variants
- Interpretation

NON-CODING VARIANTS COVERED BY THE PANEL:

NM_001128425.1(*MUTYH*):c.998-13T>G
NM_001128425.1(*MUTYH*):c.504+19_504+31delTAGGGGAAATAGG
NM_014915.2(*ANKRD26*):c.-116C>G
NM_014915.2(*ANKRD26*):c.-118C>A
NM_014915.2(*ANKRD26*):c.-119C>A
NM_014915.2(*ANKRD26*):c.-119C>A/G
NM_014915.2(*ANKRD26*):c.-121A>C
NM_014915.2(*ANKRD26*):c.-127_-126delAT
NM_014915.2(*ANKRD26*):c.-126T>C
NM_014915.2(*ANKRD26*):c.-126T>G
NM_014915.2(*ANKRD26*):c.-127A>G
NM_014915.2(*ANKRD26*):c.-127A>T
NM_014915.2(*ANKRD26*):c.-128G>T
NM_014915.2(*ANKRD26*):c.-128G>A

NM_014915.2(*ANKRD26*):c.-128G>C
NM_014915.2(*ANKRD26*):c.-134G>A
NM_020975.4(*RET*):c.-37G>C
NM_020975.4(*RET*):c.-27C>G
NM_020975.4(*RET*):c.73+9385_73+9395delAGCAACTGCCA
NM_020975.4(*RET*):c.1522+35C>T
NM_020975.4(*RET*):c.2284+13C>T
NM_020975.4(*RET*):c.2284+19C>T
NM_020975.4(*RET*):c.2392+19T>C
chr10:g.89622883-89623482
NM_000314.6(*PTEN*):c.-1239A>G
NM_000314.6(*PTEN*):c.-1178C>T
NM_000314.6(*PTEN*):c.-1171C>T
NM_000314.6(*PTEN*):c.-1111A>G
NM_000314.4(*PTEN*):c.-1001T>C
NM_000314.4(*PTEN*):c.-931G>A
NM_000314.4(*PTEN*):c.-921G>T
NM_000314.4(*PTEN*):c.-896T>C
NM_000314.4(*PTEN*):c.-862G>T
NM_000314.4(*PTEN*):c.-854C>G
NM_000314.4(*PTEN*):c.-835C>T
NM_000314.4(*PTEN*):c.-799G>C
NM_000314.4(*PTEN*):c.-765G>A
NM_000314.4(*PTEN*):c.210-8dupT
NM_000314.4(*PTEN*):c.254-21G>C
NM_000314.4(*PTEN*):c.*65T>A
NM_000314.4(*PTEN*):c.*75_*92delTAATGGCAATAGGACATTinsCTATGGCAATAGGACATTG
NM_000076.2(*CDKN1C*):c.*5+20G>T
NM_000244.3(*MEN1*):c.*412G>A
NM_000244.3(*MEN1*):c.670-15_670-14delTC
NM_000244.3(*MEN1*):c.-23-11_-22delTTGCCTTGCAGGC
NM_000244.3(*MEN1*):c.-23_-22insT
NM_000244.3(*MEN1*):c.-23-22C>A
chr11:g.67250360-67250360
NM_003977.2(*AIP*):c.-220G>A
NM_000051.3(*ATM*):c.-174A>G
NM_000051.3(*ATM*):c.-31+595G>A
NM_000051.3(*ATM*):c.-30-1G>T
NM_000051.3(*ATM*):c.2639-384A>G
NM_000051.3(*ATM*):c.2839-579_2839-576delAAGT
NM_000051.3(*ATM*):c.3403-12T>A
NM_000051.3(*ATM*):c.3994-159A>G
NM_000051.3(*ATM*):c.4612-12A>G
NM_000051.3(*ATM*):c.5763-1050A>G
NM_000051.3(*ATM*):c.8418+681A>G
NM_004064.3(*CDKN1B*):c.-454_-451delTTCC
NM_002834.3(*PTPN11*):c.934-59T>A
NM_000545.5(*HNF1A*):c.-538G>C
NM_000545.5(*HNF1A*):c.-462G>A
NM_000545.5(*HNF1A*):c.-291T>C
NM_000545.5(*HNF1A*):c.-287G>A
chr12:g.121416285-121416285
NM_000545.5(*HNF1A*):c.-283A>C
NM_000545.5(*HNF1A*):c.-258A>G
NM_000545.5(*HNF1A*):c.-218T>C

NM_000545.5(*HNF1A*):c.-187C>A/T
chr12:g.121416385-121416385
chr12:g.121416385-121416385
chr12:g.121416391-121416391
chr12:g.121416437-121416437
chr12:g.121416446-121416446
NM_000545.5(*HNF1A*):c.-119G>A
NM_000545.5(*HNF1A*):c.-97T>G
chr12:g.121416508-121416508
NM_006231.2(*POLE*):c.1686+32C>G
NM_000059.3(*BRCA2*):c.-40+1G>A
NM_000059.3(*BRCA2*):c.-39-89delC
NM_000059.3(*BRCA2*):c.-39-1_-39delGA
NM_000059.3(*BRCA2*):c.-39-1G>A
NM_000059.3(*BRCA2*):c.426-12_426-8delGTTTT
NM_000059.3(*BRCA2*):c.8488-14A>G
NM_000059.3(*BRCA2*):c.8954-15T>G
NM_000059.3(*BRCA2*):c.9502-28A>G
NM_000059.3(*BRCA2*):c.9502-12T>G
chr13:g.48877814-48877814
chr13:g.48877836-48877836
NM_000321.2(*RB1*):c.-212G>A
NM_000321.2(*RB1*):c.-198G>A
NM_000321.2(*RB1*):c.-198G>T
NM_000321.2(*RB1*):c.-197G>A
chr13:g.48877853-48877853
NM_000321.2(*RB1*):c.-193T>A/G
chr13:g.48877856-48877856
chr13:g.48877856-48877856
NM_000321.2(*RB1*):c.-192G>A
NM_000321.2(*RB1*):c.-189G>T
NM_000321.2(*RB1*):c.-150G>C
NM_000321.2(*RB1*):c.-149G>T
NM_000321.2(*RB1*):c.501-15T>G
NM_000321.2(*RB1*):c.608-3418A>G
NM_000321.2(*RB1*):c.861+828T>G
NM_000321.2(*RB1*):c.1215+63T>G
NM_000321.2(*RB1*):c.1390-14A>G
NM_000321.2(*RB1*):c.1421+20_1421+33delTAAAAAATTTTTTT
NM_000321.2(*RB1*):c.1696-14C>T
NM_000321.2(*RB1*):c.1696-12T>G
NM_000321.2(*RB1*):c.1815-11A>G
NM_000321.2(*RB1*):c.2212-13T>A
NM_000321.2(*RB1*):c.2326-14T>C
NM_000321.2(*RB1*):c.2490-1398A>G
NM_000321.2(*RB1*):c.2490-28T>C
NM_000321.2(*RB1*):c.2490-26A>C/G/T
NM_000321.2(*RB1*):c.2490-26A>C
NM_000321.2(*RB1*):c.2490-26A>T
NM_000321.2(*RB1*):c.2490-26A>G
NM_000123.3(*ERCC5*):c.881-26T>G
NM_177438.2(*DICER1*):c.5364+1187T>G
NM_001211.5(*BUB1B*):c.-44133G>A
NM_001211.5(*BUB1B*):c.2386-11A>G
NM_001113378.1(*FANCI*):c.1583+142C>T

NM_000548.3(*TSC2*):c.-30+1G>C
NM_000548.3(*TSC2*):c.600-145C>T
NM_000548.3(*TSC2*):c.848+281C>T
NM_000548.3(*TSC2*):c.976-15G>A
NM_000548.3(*TSC2*):c.2838-122G>A
NM_000548.3(*TSC2*):c.5069-18A>G
NM_024675.3(*PALB2*):c.109-12T>A
NM_015247.2(*CYLD*):c.1139-148A>G
NM_004360.3(*CDH1*):c.687+92T>A
NM_000135.3(*FANCA*):c.4261-19_4261-12delACCTGCTC
NM_000135.2(*FANCA*):c.3239+82T>G
NM_000135.2(*FANCA*):c.2982-192A>G
NM_000135.2(*FANCA*):c.2778+83C>G
NM_000135.2(*FANCA*):c.2504+134A>G
NM_000135.2(*FANCA*):c.2223-138A>G
NM_000135.2(*FANCA*):c.1567-20A>G
NM_000135.2(*FANCA*):c.893+920C>A
chr17:g.7571520-7571520
NM_000546.5(*TP53*):c.673-39G>A
NM_000546.5(*TP53*):c.97-11C>G
NM_000546.5(*TP53*):c.-29+1G>T
NM_001042492.2(*NF1*):c.-273A>C
NM_001042492.2(*NF1*):c.-272G>A
NM_001042492.2(*NF1*):c.60+9031_60+9035delAAGTT
NM_001042492.2(*NF1*):c.61-7486G>T
NM_001042492.2(*NF1*):c.288+2025T>G
NM_001042492.2(*NF1*):c.587-14T>A
NM_001042492.2(*NF1*):c.587-12T>A
NM_001042492.2(*NF1*):c.888+651T>A
NM_001042492.2(*NF1*):c.888+744A>G
NM_001042492.2(*NF1*):c.888+789A>G
NM_001042492.2(*NF1*):c.889-12T>A
NM_001042492.2(*NF1*):c.1260+1604A>G
NM_001042492.2(*NF1*):c.1261-19G>A
NM_001042492.2(*NF1*):c.1392+754T>G
NM_001042492.2(*NF1*):c.1393-592A>G
NM_001042492.2(*NF1*):c.1527+1159C>T
NM_001042492.2(*NF1*):c.1642-449A>G
NM_001128147.2(*NF1*):c.*481A>G
NM_001042492.2(*NF1*):c.2002-14C>G
NM_001042492.2(*NF1*):c.2252-11T>G
NM_001042492.2(*NF1*):c.2410-18C>G
NM_001042492.2(*NF1*):c.2410-16A>G
NM_001042492.2(*NF1*):c.2410-15A>G
NM_001042492.2(*NF1*):c.2410-12T>G
NM_001042492.2(*NF1*):c.2851-14_2851-13insA
NM_001042492.2(*NF1*):c.2991-11T>G
NM_001042492.2(*NF1*):c.3198-314G>A
NM_001042492.2(*NF1*):c.3974+260T>G
NM_001042492.2(*NF1*):c.4110+945A>G
NM_001042492.2(*NF1*):c.4173+278A>G
NM_001042492.2(*NF1*):c.4578-20_4578-18delAAG
NM_001042492.2(*NF1*):c.4578-14T>G
NM_001042492.2(*NF1*):c.5269-38A>G
NM_001042492.2(*NF1*):c.5610-456G>T

NM_001042492.2(*NF1*):c.5812+332A>G
NM_001042492.2(*NF1*):c.5813-279A>G
NM_001042492.2(*NF1*):c.6428-11T>G
NM_001042492.2(*NF1*):c.6642+18A>G
NM_001042492.2(*NF1*):c.7190-12T>A
NM_001042492.2(*NF1*):c.7190-11_7190-10insGTTT
NM_001042492.2(*NF1*):c.7971-321C>G
NM_001042492.2(*NF1*):c.7971-17C>G
NM_001042492.2(*NF1*):c.8113+25A>T
NM_007294.3(*BRCA1*):c.*1340_*1342delTGT
NM_007294.3(*BRCA1*):c.*1271T>C
NM_007294.3(*BRCA1*):c.*528G>C
NM_007294.3(*BRCA1*):c.*103_*106delTGTC
NM_007294.3(*BRCA1*):c.*58C>T
NM_007294.3(*BRCA1*):c.5468-40T>A
NM_007294.3(*BRCA1*):c.5407-25T>A
NM_007294.3(*BRCA1*):c.5333-36_5333-22delTACTGCAGTGATTTT
NM_007294.3(*BRCA1*):c.5277+2916_5277+2946delAAATTCTAGTGCTTTGGATTTTTTCCTCCATinsGG
NM_007294.3(*BRCA1*):c.5194-12G>A
NM_007294.3(*BRCA1*):c.5075-27delA
NM_007294.3(*BRCA1*):c.442-22_442-13delTGTTCTTTAC
NM_007294.3(*BRCA1*):c.213-11T>G
NM_007294.3(*BRCA1*):c.213-12A>G
NM_007294.3(*BRCA1*):c.213-15A>G
NM_007294.3(*BRCA1*):c.-19-2A>G
NM_032043.2(*BRIP1*):c.1629-498A>T
NM_002734.4(*PRKAR1A*):c.-97G>A
NM_002734.4(*PRKAR1A*):c.-7G>A
NM_002734.4(*PRKAR1A*):c.-7+1G>A
NM_002734.4(*PRKAR1A*):c.550-17T>A
NM_002734.4(*PRKAR1A*):c.709-7_709-2delTTTTTA
NM_000455.4(*STK11*):c.597+16_597+33delGGGGGGCCCTGGGGCGCCinsTG
NM_000455.4(*STK11*):c.598-32_597+31delGCCCCCTCCCGGGC
NM_202001.2(*ERCC1*):c.603-26G>A
NM_002354.2(*EPCAM*):c.556-14A>G
NM_000251.2(*MSH2*):c.-225G>C
NM_000251.2(*MSH2*):c.-181G>A
NM_000251.2(*MSH2*):c.-81dupA
NM_000251.2(*MSH2*):c.-78_-77delTG
NM_000251.2(*MSH2*):c.1662-17dupG
NM_000179.2(*MSH6*):c.457+33_457+34insGTGT
NM_000179.2(*MSH6*):c.3173-16_3173-5delCCCTCTCTTTTA
NM_000179.2(*MSH6*):c.*15A>C
NM_000179.2(*MSH6*):c.*49_*68dupTTCAGACAACATTATGATCT
NM_001114636.1(*FANCL*):c.375-2033C>G
NM_017849.3(*TMEM127*):c.-18C>T
NM_006767.3(*LZTR1*):c.-38T>A
NM_006767.3(*LZTR1*):c.2220-17C>A
NM_003073.3(*SMARCB1*):c.93+559A>G
NM_003073.3(*SMARCB1*):c.1119-12C>G
NM_003073.3(*SMARCB1*):c.*70C>T
NM_003073.3(*SMARCB1*):c.*82C>T
NM_000268.3(*NF2*):c.516+232G>A
NM_033084.3(*FANCD2*):c.696-121C>G
NM_033084.3(*FANCD2*):c.1766+40T>G

NM_033084.3(*FANCD2*):c.1948-16T>G
NM_000551.3(*VHL*):c.-75_-55delCGCACGCAGCTCCGCCCCGCG
NM_000551.3(*VHL*):c.-54_-44dupTCCGACCCGCG
NM_000551.3(*VHL*):c.*70C>A
NM_000551.3(*VHL*):c.*70C>T
NM_004628.4(*XPC*):c.*156G>A
NM_004628.4(*XPC*):c.413-24A>G
NM_000249.3(*MLH1*):c.-413_-411delGAG
NM_000249.3(*MLH1*):c.-107C>G
NM_000249.3(*MLH1*):c.-63_-58delGTGATTinsCACGAGGCACGAGCACGA
NM_000249.3(*MLH1*):c.-42C>T
NM_000249.3(*MLH1*):c.-27C>A
NM_000249.3(*MLH1*):c.116+106G>A
NM_000249.3(*MLH1*):c.117-11T>A
NM_000249.3(*MLH1*):c.454-13A>G
NM_000249.3(*MLH1*):c.885-9_887dupTCCTGACAGTTT
NM_000249.3(*MLH1*):c.1558+13T>A
NM_004656.3(*BAP1*):c.*644delG
NM_032638.4(*GATA2*):c.1017+572C>T
NM_032638.4(*GATA2*):c.1017+513_1017+540delGGAGTTTCCTATCCGGACATCTGCAGCC
NM_032638.4(*GATA2*):c.1017+532T>A
NR_001566.1(*TERC*):n.-22C>T
chr3:g.169482906-169482906
NR_001566.1(*TERC*):n.-100C>G
chr3:g.169483086-169483086
NM_006206.4(*PDGFRA*):c.*34G>A
NM_005612.4(*REST*):c.983-2247C>G
NM_198253.2(*TERT*):c.2383-15C>T
NM_198253.2(*TERT*):c.-57A>C
NM_017755.5(*NSUN2*):c.538-11T>G
chr5:g.112043009-112043595
NM_001127511.2(*APC*):c.-195A>C
NM_001127511.2(*APC*):c.-192A>G/T
NM_001127511.2(*APC*):c.-192A>G
NM_001127511.2(*APC*):c.-192A>T
NM_001127511.2(*APC*):c.-191T>C
NM_001127511.2(*APC*):c.-190G>A
NM_001127511.2(*APC*):c.-125delA
chr5:g.112072710-112073585
NM_000038.5(*APC*):c.423-12A>G
NM_000038.5(*APC*):c.423-11A>G
NM_000038.5(*APC*):c.532-941G>A
NM_000038.5(*APC*):c.835-17A>G
NM_000038.5(*APC*):c.1408+731C>T
NM_000038.5(*APC*):c.1408+735A>T
NM_006502.2(*POLH*):c.-5+1G>C
NM_000535.5(*PMS2*):c.1145-31_1145-13delCTGACCCTCTTCTCCGTCC
NM_000535.5(*PMS2*):c.23+21_23+28delTCCGGTGT
NM_000553.4(*WRN*):c.2089-3024A>G
NM_000553.4(*WRN*):c.3234-160A>G
NM_000077.4(*CDKN2A*):c.458-105A>G
NM_000077.4(*CDKN2A*):c.151-1104C>G
NM_000077.4(*CDKN2A*):c.150+1104C>A
NM_058197.4(*CDKN2A*):c.*73+2T>G
NM_000077.4(*CDKN2A*):c.-21C>T

NM_000077.4(*CDKN2A*):c.-49C>A
NM_000077.4(*CDKN2A*):c.-56G>T
NM_000077.4(*CDKN2A*):c.-93_-91delAGG
NM_000136.2(*FANCC*):c.-78-2A>G
NM_000136.2(*FANCC*):c.-79+1G>A
NM_000264.3(*PTCH1*):c.2561-2057A>G
NM_000380.3(*XPA*):c.390-12A>G
NM_000368.4(*TSC1*):c.363+668G>A
NM_001363.3(*DKC1*):c.-142C>G
NM_001363.3(*DKC1*):c.-141C>G
NM_001363.3(*DKC1*):c.85-15T>C

GLOSSARY OF USED ABBREVIATIONS:

AD = autosomal dominant
AF = allele fraction (proportion of reads with mutated DNA / all reads)
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CNV = Copy Number Variation e.g. one exon or multiexon deletion or duplication
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OMIM = Online Mendelian Inheritance in Man®
PolyPhen = *in silico* prediction tool used to evaluate the significance of amino acid changes.
POS = genomic position of the variant in the format of chromosome:position
SIFT = *in silico* prediction tool used to evaluate the significance of amino acid changes.

Blueprint Genetics

Sample report as of June 14th, 2022. Regional differences may apply. For complete and up-to-date test methodology description, please see your report in Nucleus online portal. Accreditation and certification information available at ***blueprintgenetics.com/certifications***

Hereditary Breast Cancer High Risk Panel Plus

REFERRING HEALTHCARE PROFESSIONAL

NAME **HOSPITAL**

PATIENT

NAME **DOB** **AGE** **GENDER** **ORDER ID**

Female

PRIMARY SAMPLE TYPE **SAMPLE COLLECTION DATE** **CUSTOMER SAMPLE ID**

SUMMARY OF RESULTS

PRIMARY FINDINGS

Negative

SEQUENCING PERFORMANCE METRICS - NUCLEAR GENOME

PANEL	GENES	EXONS / REGIONS	BASES	BASES > 20X	MEDIAN COVERAGE	PERCENT > 20X
Hereditary Breast Cancer High Risk Panel	8	134	34801	34801	313	100

TARGET REGION AND GENE LIST

The Blueprint Genetics Hereditary Breast Cancer High Risk Panel (version 3, Oct 19, 2019) Plus Analysis includes sequence analysis and copy number variation analysis of the following genes: *BRCA1**, *BRCA2*, *CDH1*, *PALB2*, *PTEN**, *RECQL**, *STK11* and *TP53*. This panel targets protein coding exons, exon-intron boundaries (± 20 bps) and selected non-coding, deep intronic variants (listed in the SUMMARY OF THE TEST section). This panel should be used to detect single nucleotide variants and small insertions deletions (INDELs) and copy number variations defined as single exon or larger deletions and duplications. This panel should not be used for the detection of repeat expansion disorders or diseases caused by mitochondrial DNA (mtDNA) mutations. The test does not detect balanced translocations or complex rearrangements, and it may not detect low-level mosaicism.

*Some, or all, of the gene is duplicated in the genome. Read more: https://blueprintgenetics.com/pseudogene/
The sensitivity to detect variants may be limited in genes marked with an asterisk (*).

STATEMENT

CLINICAL HISTORY

Patient is a female with breast cancer.

CLINICAL REPORT

Sequence and Del/Dup (CNV) analysis using the Blueprint Genetics (BpG) Hereditary Breast Cancer High Risk Panel did not detect any known disease-causing or rare variants that could explain the patient's phenotype as described to the laboratory at the time of interpretation.

STEP	DATE
Order date	
Sample received	
Sample in analysis	
Reported	

(This statement has been prepared by our geneticists and physicians, who have together evaluated the sequencing results.)

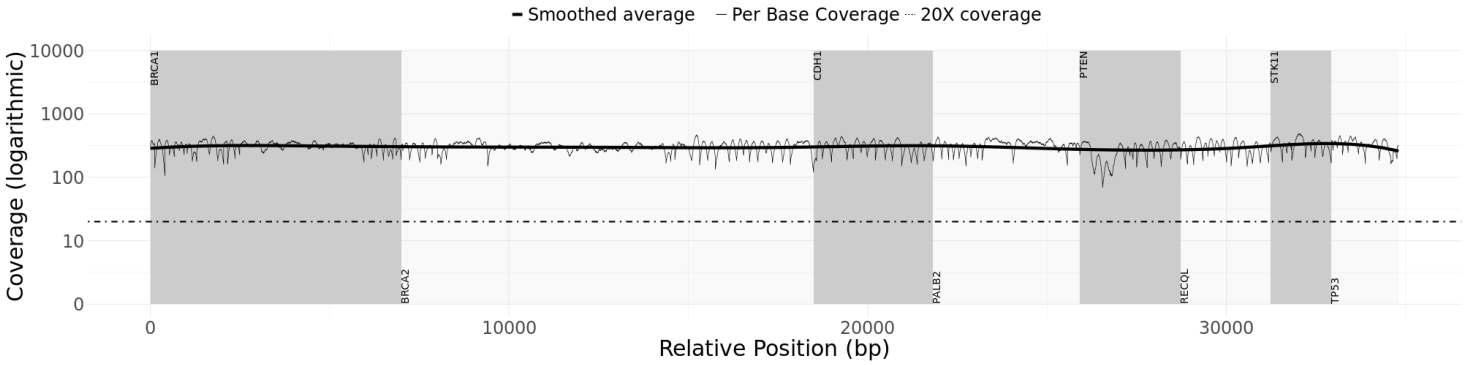
Signature

Name

Title

COVERAGE PLOT - NUCLEAR GENES

Readability of the coverage plot may be hindered by faxing. A high quality coverage plot can be found with the full report on nucleus.blueprintgenetics.com.



APPENDIX 5: SUMMARY OF THE TEST

PLUS ANALYSIS

Laboratory process: When required, the total genomic DNA was extracted from the biological sample using bead-based method. Quantity of DNA was assessed using fluorometric method. After assessment of DNA quantity, qualified genomic DNA sample was randomly fragmented using non-contact, isothermal sonochemistry processing. Sequencing library was prepared by ligating sequencing adapters to both ends of DNA fragments. Sequencing libraries were size-selected with bead-based method to ensure optimal template size and amplified by polymerase chain reaction (PCR). Regions of interest (exons and intronic targets) were targeted using hybridization-based target capture method. The quality of the completed sequencing library was controlled by ensuring the correct template size and quantity and to eliminate the presence of leftover primers and adapter-adapter dimers. Ready sequencing libraries that passed the quality control were sequenced using the Illumina's sequencing-by-synthesis method using paired-end sequencing (150 by 150 bases). Primary data analysis converting images into base calls and associated quality scores was carried out by the sequencing instrument using Illumina's proprietary software, generating CBCL files as the final output.
Bioinformatics and quality control: Base called raw sequencing data was transformed into FASTQ format using Illumina's software (bcl2fastq). Sequence reads of each sample were mapped to the human reference genome (GRCh37/hg19). Burrows-Wheeler Aligner (BWA-MEM) software was used for read alignment. Duplicate read marking, local realignment around indels, base quality score recalibration and variant calling were performed using GATK algorithms (Sentieon) for nDNA. Variant data for was annotated using a collection of tools (VcfAnno and VEP) with a variety of public variant databases including but not limited to gnomAD, ClinVar and HGMD. The median sequencing depth and coverage across the target regions for the tested sample were calculated based on MQ0 aligned reads. The sequencing run included in-process reference sample(s) for quality control, which passed our thresholds for sensitivity and specificity. The patient's sample was subjected to thorough quality control measures including assessments for contamination and sample mix-up. Copy number variations (CNVs), defined as single exon or larger deletions or duplications (Del/Dups), were detected from the sequence analysis data using a proprietary bioinformatics pipeline. The difference between observed and expected sequencing depth at the targeted genomic regions was calculated and regions were divided into segments with variable DNA copy number. The expected sequencing depth was obtained by using other samples processed in the same sequence analysis as a guiding reference. The sequence data was adjusted to account for the effects of varying guanine and cytosine content.
Interpretation: The clinical interpretation team assessed the pathogenicity of the identified variants by evaluating the information in the patient requisition, reviewing the relevant scientific literature and manually inspecting the sequencing data if needed. All available evidence of the identified variants was compared to classification criteria. Reporting was carried out using HGNC-approved gene nomenclature and mutation nomenclature following the HGVS guidelines. Likely benign and benign variants were not reported.
Variant classification: Our variant classification follows the Blueprint Genetics Variant Classification Schemes modified from the ACMG guideline 2015. Minor modifications were made to increase reproducibility of the variant classification and improve the clinical validity of the report. The classification and interpretation of the variant(s) identified reflect the current state of Blueprint Genetics' understanding at the time of this report. Variant classification and interpretation are subject to professional judgment, and may change for a variety of reasons, including but not limited to, updates in classification guidelines and availability of additional scientific and clinical information. This test result should be used in conjunction with the health care provider's clinical evaluation. Inquiries regarding potential changes to the classification of the variant is strongly recommended prior to making any future clinical decisions. For questions regarding variant classification updates, please contact our customer support (Global: support@blueprintgenetics.com, US: support.us@blueprintgenetics.com, Canada: support.ca@blueprintgenetics.com).
Databases: The pathogenicity potential of the identified variants were assessed by considering the predicted consequence of the change, the degree of evolutionary conservation as well as the number of reference population databases and mutation databases such as, but not limited to, the gnomAD, ClinVar, HGMD Professional and Alamut Visual. In addition, the clinical relevance of any identified CNVs was evaluated by reviewing the relevant literature and databases such as Database of Genomic Variants and DECIPHER. For interpretation of mtDNA variants specific databases including e.g. Mitomap, HmtVar and 1000G were used.
Confirmation of sequence alterations: Sequence variants classified as pathogenic, likely pathogenic and variants of uncertain significance (VUS) were confirmed using bi-directional Sanger sequencing when they did not meet our stringent NGS quality metrics for a true positive call. In addition, prenatal case with diagnostic findings were confirmed.

Confirmation of copy number variants: CNVs (Deletions/Duplications) were confirmed using a digital PCR assay if they covered less than 10 exons (heterozygous), less than 3 exons (homo/hemizygous) or were not confirmed at least three times previously at our laboratory. Furthermore, CNVs of any size were not confirmed when the breakpoints of the call could be determined.
Analytic validation: The detection performance of this panel is expected to be in the same range as our high-quality, clinical grade NGS sequencing assay used to generate the panel data (nuclear DNA: sensitivity for SNVs 99.89%, indels 1-50 bps 99.2%, one-exon deletion 100% and five exons CNV 98.7%, and specificity >99.9% for most variant types). It does not detect very low level mosaicism as a variant with minor allele fraction of 14.6% can be detected in 90% of the cases. Detection performance for mtDNA variants (analytic and clinical validation): sensitivity for SNVs and INDELs 100.0% (10-100% heteroplasmy level), 94.7% (5-10% heteroplasmy level), 87.3% (<5% heteroplasmy level) and for gross deletions 100.0%. Specificity is >99.9% for all.
Test restrictions: A normal result does not rule out the diagnosis of a genetic disorder since some DNA abnormalities may be undetectable by the applied technology. Test results should always be interpreted in the context of clinical findings, family history, and other relevant data. Inaccurate, or incomplete information may lead to misinterpretation of the results.
Technical limitations: This test does not detect the following: complex inversions, gene conversions, balanced translocations, repeat expansion disorders unless specifically mentioned, non-coding variants deeper than ±20 base pairs from exon-intron boundary unless otherwise indicated (please see the list of non-coding variants covered by the test). Additionally, this test may not reliably detect the following: low level mosaicism, stretches of mononucleotide repeats, indels larger than 50bp, single exon deletions or duplications, and variants within pseudogene regions/duplicated segments. The sensitivity of this test may be reduced if DNA is extracted by a laboratory other than Blueprint Genetics. Laboratory error is also possible. Please see the Analytic validation above.
Regulation and accreditations: This test was developed and its performance characteristics determined by Blueprint Genetics (see Analytic validation). It has not been cleared or approved by the US Food and Drug Administration. This analysis has been performed in a CLIA-certified laboratory (#99D2092375), accredited by the College of American Pathologists (CAP #9257331) and by FINAS Finnish Accreditation Service, (laboratory no. T292), accreditation requirement SFS-EN ISO 15189:2013. All the tests are under the scope of the ISO 15189 accreditation.

PERFORMING SITE:

BLUEPRINT GENETICS OY, KEILARANTA 16 A-B, 02150 ESPOO, FINLAND Laboratory Director: JUHA KOSKENVUO, MD, PHD, CLIA: 99D2092375

- DNA extraction and QC
- Next-generation sequencing
- Bioinformatic analysis
- Confirmation of sequence alterations
- Confirmation of copy number variants
- Interpretation

NON-CODING VARIANTS COVERED BY THE PANEL:

chr10:g.89622883-89623482
NM_000314.6(*PTEN*):c.-1239A>G
NM_000314.6(*PTEN*):c.-1178C>T
NM_000314.6(*PTEN*):c.-1171C>T
NM_000314.6(*PTEN*):c.-1111A>G
NM_000314.4(*PTEN*):c.-1001T>C
NM_000314.4(*PTEN*):c.-931G>A
NM_000314.4(*PTEN*):c.-921G>T
NM_000314.4(*PTEN*):c.-896T>C
NM_000314.4(*PTEN*):c.-862G>T
NM_000314.4(*PTEN*):c.-854C>G
NM_000314.4(*PTEN*):c.-835C>T
NM_000314.4(*PTEN*):c.-799G>C
NM_000314.4(*PTEN*):c.-765G>A

NM_000314.4(*PTEN*):c.210-8dupT
NM_000314.4(*PTEN*):c.254-21G>C
NM_000314.4(*PTEN*):c.*65T>A
NM_000314.4(*PTEN*):c.*75_*92delTAATGGCAATAGGACATTinsCTATGGCAATAGGACATTG
NM_000059.3(*BRCA2*):c.-40+1G>A
NM_000059.3(*BRCA2*):c.-39-89delC
NM_000059.3(*BRCA2*):c.-39-1_-39delGA
NM_000059.3(*BRCA2*):c.-39-1G>A
NM_000059.3(*BRCA2*):c.426-12_426-8delGTTTT
NM_000059.3(*BRCA2*):c.8488-14A>G
NM_000059.3(*BRCA2*):c.8954-15T>G
NM_000059.3(*BRCA2*):c.9502-28A>G
NM_000059.3(*BRCA2*):c.9502-12T>G
NM_024675.3(*PALB2*):c.109-12T>A
NM_004360.3(*CDH1*):c.687+92T>A
chr17:g.7571520-7571520
NM_000546.5(*TP53*):c.673-39G>A
NM_000546.5(*TP53*):c.97-11C>G
NM_000546.5(*TP53*):c.-29+1G>T
NM_007294.3(*BRCA1*):c.*1340_*1342delTGT
NM_007294.3(*BRCA1*):c.*1271T>C
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NM_007294.3(*BRCA1*):c.5407-25T>A
NM_007294.3(*BRCA1*):c.5333-36_5333-22delTACTGCAGTGATTTT
NM_007294.3(*BRCA1*):c.5277+2916_5277+2946delAAATTCTAGTGCTTTGGATTTTTTCCTCCATinsGG
NM_007294.3(*BRCA1*):c.5194-12G>A
NM_007294.3(*BRCA1*):c.5075-27delA
NM_007294.3(*BRCA1*):c.442-22_442-13delTGTTCTTTAC
NM_007294.3(*BRCA1*):c.213-11T>G
NM_007294.3(*BRCA1*):c.213-12A>G
NM_007294.3(*BRCA1*):c.213-15A>G
NM_007294.3(*BRCA1*):c.-19-2A>G
NM_000455.4(*STK11*):c.597+16_597+33delGGGGGGCCCTGGGGCGCCinsTG
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