Blueprint Genetics

Sample report as of July 7, 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

PATIENT

NAME	DOB	AGE	GENDER	ORDER ID

PRIMARY SAMPLE TYPE	SAMPLE COLLECTION DATE	CUSTOMER SAMPLE ID
DNA		

SUMMARY OF RESULTS

PRIMARY FINDINGS

The patient is homozygous for a deletion *PMS2* c.(2445+1_2446-1)_(*1_?)del, which encompasses the last exon (exon 15) of *PMS2*. This alteration is classified as pathogenic.

PRIMARY FINDINGS: COPY NUMBER ABERRATIONS

GENE	EVENT	COPY NUMBER	GENOTYPE	IMPACT	LINKS	CLASSIFICATION
PMS2	COPY NUMBER LOSS	0	HOM	PMS2: Partial gene	UCSC	**Pathogenic**
	OMIM	**PHENOTYPE** Colorectal cancer, hereditary nonpolyposis, Mismatch repair cancer syndrome			**COMMENT** -	

SEQUENCING PERFORMANCE METRICS

PANEL	GENES	EXONS / REGIONS	BASES	BASES > 20X	MEDIAN COVERAGE	PERCENT > 20X
Comprehensive Hereditary Cancer Panel	160	2457	501526	501306	196	99.96

TARGET REGION AND GENE LIST

The Blueprint Genetics Comprehensive Hereditary Cancer Panel 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 5-year-old child complaining of frequent attacks of short duration headache with effort. Eye examination revealed severe decrease visual aquity in left eye and slight decrease in right eye (nasal field). MR examination revealed optic chiasma tumor suggested to be low grade glioma. Hormonal pituitary profile is within normal.

First cousin had malignant brain tumor in the brain stem. NF1 by Sanger for this cousin inconclusive for a pathogenic variant but large rearrangement could not be excluded. Family history of also café au lait spots.

CLINICAL REPORT

Del/Dup (CNV) analysis using the Blueprint Genetics (BpG) Comprehensive Hereditary Cancer Panel identified a homozygous deletion *PMS2* c.(2445+1_2446-1)_(*1_?)del encompassing the last exon, exon 15, of *PMS2*. This deletion is estimated to cover the genomic region 7:6012969-6013233. However, a custom confirmation assay using long range PCR indicates that the deletion also includes exon 1 of the adjacent *RSPH10B* gene and is by this method estimated to be 7-9 kilobase pairs in size. Of note, the exact breakpoints of the deletion cannot be determined using the present methods, and therefore its exact size and genomic position are unknown.

Analysis of the *PMS2* gene exon 15 is complicated by a highly homologous pseudogene *PMS2CL* on chromosome 7. Deletion calling from the NGS data cannot accurately identify or distinguish potential deletion in the pseudogene and the actual *PMS2* gene. Our CNV detection algorithm indicated a deletion in the index patient sample covering the last exon of *PMS2* gene. Additional bioinformatic analysis supported the deletion. Homozygous deletion of exon 15 was confirmed with dPCR and long range PCR using specific assays.

PMS2 c.(2445+1_2446-1)_(*1_?)del

Deletions encompassing the *PMS2* gene exon 15 have been reported in 2 heterozygous individuals in the Exome Aggregation Consortium (ExAC) control cohorts but not in the Genome Aggregation Database control cohorts (gnomAD SVs v2.1, ExAC data available in the gnomAD browser). A homozygous deletion encompassing *PMS2* exon 15 has been reported by Bakry *et al*. in two related individuals (PMID: 24440087). One of them had glioblastoma (GBM) at age 11 and T-cell ALL at age 13. The patient also had cafe-au-lait spots. Immunohistochemistry was negative for PMS2 both in the glioblastoma tumor and normal skin sample. The patient's two cousins were not genetically tested but had GBM and medulloblastoma at ages 8 and 9. Tumor sample immunohistochemistry was PMS2 negative for both individuals. The patient's sister (homozygous for the deletion) developed brain tumor and cafe-au-lait spots; immunohistochemistry of normal skin sample was negative for PMS2. Later, Farah *et al*. published a new paper of apparently the same family (PMID: 31233827). Furthermore, a heterozygous deletion of *PMS2* exon 15 was reported in an additional patient (PMID: 21618646). This patient had glioblastoma at age 8 and an NF1

phenotype. In addition to the deletion, the patient had *PMS2* c.1687C>T, p.(Arg563*) variant. The patient's sibling and mother showed heterozygous deletions of *PMS2* exon 15 (PMID: 21618646).

PMS2

PMS2 encodes a key component of the mismatch repair system that functions to correct DNA mismatches and small insertions and deletions that can occur during DNA replication and homologous recombination. The protein forms heterodimers with MLH1 to form the MutL-alpha heterodimer (GeneCards - PMS2). Pathogenic germline variants in *PMS2* (MIM *600259) have been associated with hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome (MIM # 614337, GeneReviews NBK1211) and constitutional mismatch repair deficiency (CMMRD; MIM #619101).

Lynch syndrome is inherited in an autosomal dominant manner and is characterized by an increased risk for colon cancer and cancers of the endometrium, ovary, stomach, small intestine, hepatobiliary tract, urinary tract, brain, and skin. Lynch syndrome can be caused by germline mutations in four mismatch-repair (MMR) genes: *MLH1, MSH2, PMS2* and *MSH6,* or rarely, by germline deletions in the *EPCAM* gene (PMID: 21309036). *MLH1* and *MSH2* germline pathogenic variants are identified in approximately 90% of the families with Lynch syndrome; *MSH6* pathogenic variants in about 7%-10%; and *PMS2* pathogenic variants in fewer than 5%. The loss of MMR function leads to somatic DNA replication errors in repetitive sequences (microsatellites). Thus, microsatellite instability (MSI) is a hallmark in the Lynch syndrome associated tumors. Traditionally, MSI testing and immunohistochemistry on tumor tissue have been used to identify the probability of Lynch syndrome and to identify which gene is most likely to have a causative germline mutation.

In a large cohort study by Broeke *et al.*, the cumulative risk (CR) of colorectal cancer for male mutation carriers by age 70 years was 19%. The CR among female carriers was 11% for colorectal cancer and 12% for endometrial cancer. The mean age of CRC development was 52 years. (PMID: 25512458) Recommendations for surveillance of mutation positive individuals include colonoscopy with removal of precancerous polyps every one to two years beginning between ages 20 and 25 years or two to five years before the earliest age of diagnosis in the family, whichever is earlier (GeneReviews NBK1211). The efficacy of surveillance for cancer of the endometrium, ovary, stomach, duodenum, and urinary tract is unknown.

The association of breast cancer as a part of Lynch syndrome is still debated (PMID: 23510156, 25737380, 25673086). A recent study by Roberts *et al*. showed that pathogenic variants in *MSH6* and *PMS2* implicated in Lynch syndrome associate with an increased risk for breast cancer (PMID: 29345684). They calculated that approximately 37 percent of women with pathogenic PMS2 variant will develop breast cancer by the age of 60 years, compared to approximately 15 percent of women in the general population. In addition, several studies have also shown that breast tumors in women with Lynch syndrome show microsatellite instability and loss of one or more mismatch repair proteins more frequently compared with sporadic breast tumors (PMID: 8646682, 19123071, 19575290, 22034109, 22691310).

Constitutional mismatch repair deficiency (CMMRD; MIM #276300) syndrome is a severe childhood cancer predisposition syndrome that results from homozygous or compound heterozygous germline mutations in one of the four MMR genes: *MLH1, MSH2, MSH6* or *PMS2.* Due to the constitutional defect in MMR capacity, individuals with biallelic MMR gene mutations have a high risk of developing a diverse spectrum of malignancies already in childhood and adolescence. The spectrum includes mainly hematological malignancies, brain/central nervous system (CNS) tumors and colorectal cancer and other cancers that are typically seen in Lynch Syndrome patients at a later age. Also a variety of other malignancies have been observed in CMMRD patients. Many of the CMMRD patients, but not all, show features reminiscent of NF1, particularly multiple café au lait maculae (PMID: 24737826).

Currently there are more than 380 *PMS2* variants listed in the Disease causing Mutation (DM) category in HGMD Professional (2022.1; last accessed May 2022). These include all kinds of variants: 8% of them are missense variants; 15% nonsense variants; 1% are start lost variants; 13% splicing variants; 28% small deletions, insertions, or indels, 29% gross deletions, 3% gross insertions, and 2% complex rearrangements. Majority (60%) of them are associated with colorectal cancer.

Mutation nomenclature is based on GenBank accession NM_000535.7 (*PMS2*) with nucleotide one being the first nucleotide of the translation initiation codon ATG.

CONCLUSION

We classify the identified deletion *PMS2* c.(2445+1_2446-1)_(*1_?)del, affecting exon 15, as pathogenic, based on established association between the gene and the patient’s phenotype, the variant's rarity in control populations, identification of the variant in other individuals with the same phenotype, moderate proof of segregation, functional assay data, and variant type

(gross deletion). Disease caused by *PMS2* variants can be inherited in an autosomal dominant or recessive manner. The patient is homozygous for the variant, which is consistent with autosomal recessive inheritance. If the patient's parents are each confirmed to be carriers of this variant, any siblings of the patient will have a 25% chance of being homozygous for the variant and thus affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being an unaffected non-carrier. Genetic counseling and family member testing are recommended.

CONFIRMATION

Deletion *PMS2* c.(2445+1_2446-1)_(*1_?)del has been confirmed by digital PCR and long range PCR.

STEP	DATE
Order date	
Sample received	
Sample in analysis	
Reported	

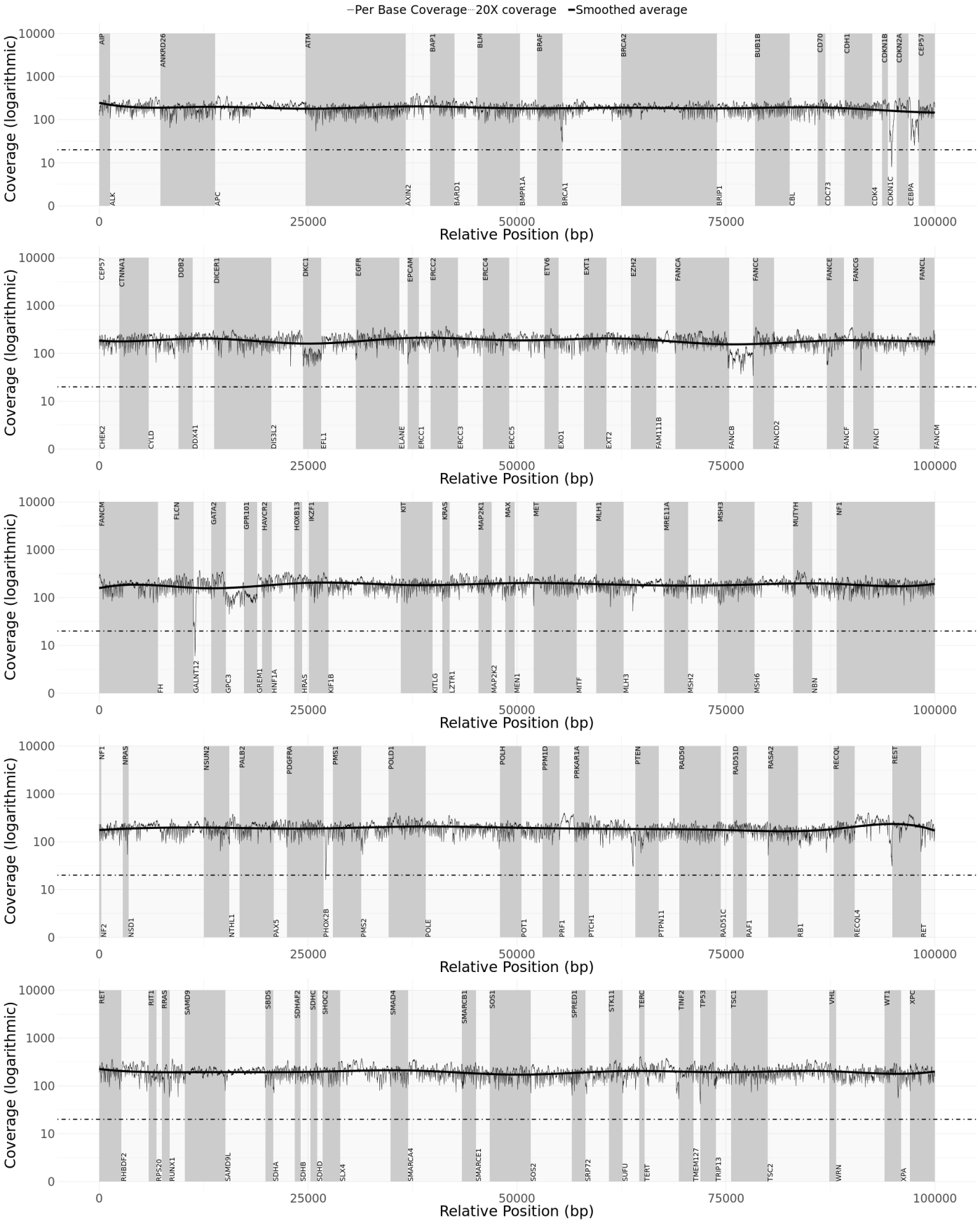
This statement has been prepared by our geneticists and physicians, who have together evaluated the sequencing results:

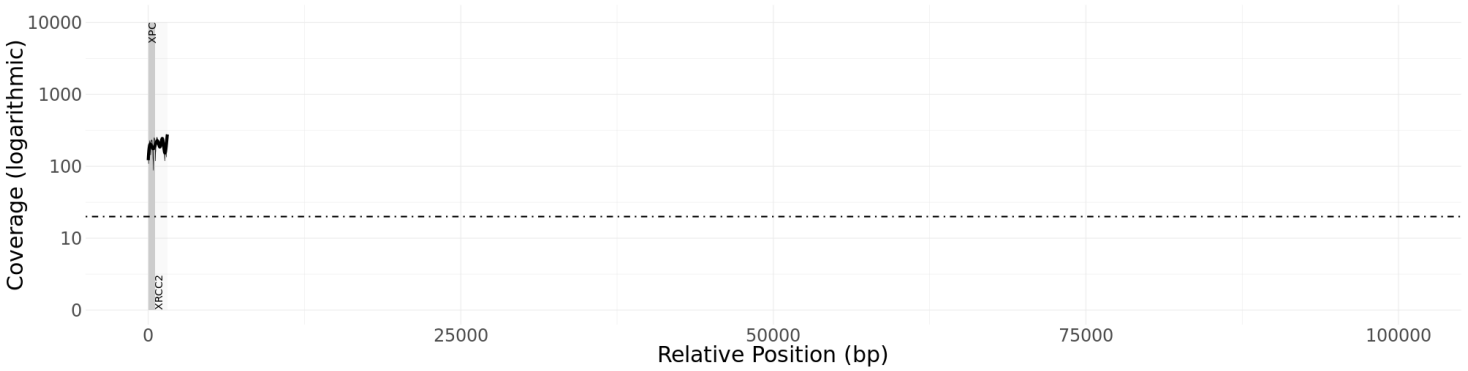
Signature

Name

Title

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.




10000
1000
100
10
0
Coverage (logarithmic)
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. DNA quality and quantity were assessed using electrophoretic methods at Blueprint Genetics. After assessment of DNA quality, 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.These steps were performed at Blueprint Genetics.
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. Bioinformatics and quality control processes were performed by Blueprint Genetics.
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. The interpretation was performed at Blueprint Genetics.
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. Inquiry regarding potential changes to the classification of the variant is strongly recommended prior to making any future clinical decision. For questions regarding variant classification updates, please contact us at support@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.The confirmation of sequence alterations was performed at Blueprint Genetics.

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.The confirmation of copy number variants was performed at Blueprint Genetics.

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 (excluding mtDNA testing).

PERFORMING SITE:

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

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,
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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,
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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,
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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,
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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)
AR = autosomal recessive
CNV = Copy Number Variation e.g. one exon or multiexon deletion or duplication
gnomAD = genome Aggregation Database (reference population database; >138,600 individuals)
gnomAD AC/AN = allele count/allele number in the genome Aggregation Database (gnomAD)
HEM = hemizygous
HET = heterozygous
HOM = homozygous
ID = rsID in dbSNP
MT = Mitochondria
MutationTaster = *in silico* prediction tools used to evaluate the significance of identified amino acid changes.
Nomenclature = HGVS nomenclature for a variant in the nucleotide and the predicted effect of a variant in the protein level

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.