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***

Comprehensive Cancer Screen

POSITIVE

REFERRING HEALTHCARE PROFESSIONAL

NAME **HOSPITAL**

INDIVIDUAL

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

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

SUMMARY OF RESULTS

PERSONAL RISKS

The individual is heterozygous for *TP53* c.586C>T, p.(Arg196*), which is pathogenic.

CARRIERSHIP(S) OF AUTOSOMAL RECESSIVE DISEASE(S)

Negative for pathogenic or likely pathogenic variants.

SEQUENCING PERFORMANCE METRICS

PANEL	GENES	EXONS / REGIONS	BASES	BASES > 20X	MEDIAN COVERAGE	PERCENT > 20X
Comprehensive Cancer Screen	83	1373	274898	274898	290	100

TARGET REGION AND GENE LIST

The Blueprint Genetics Comprehensive Cancer Screen (version 1, Jun 10, 2023) Plus Analysis includes sequence analysis and copy number variation analysis of the following genes: *AIP*, *ANKRD26*, *APC*, *ATM*, *AXIN2*, *BAP1*, *BARD1*, *BMPR1A**, *BRCA1**, *BRCA2*, *BRIP1*, *CDC73*, *CDH1*, *CDK4*, *CDKN1B*, *CDKN2A*, *CEBPA*, *CHEK2**, *CTNNA1*, *CYLD*, *DDX41*, *DICER1**, *EGFR*, *EPCAM*, *ERCC6L2*, *ETV6*, *EXT1*, *EXT2*, *FH*, *FLCN*, *GATA2*, *GREM1*, *HOXB13*, *KIT*, *LZTR1*, *MAX*, *MEN1*, *MET*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *NF1**, *NF2*, *NTHL1*, *PALB2*, *PDGFRA*[#], *PHOX2B*, *PMS2**, *POLD1*, *POLE*, *POT1*, *PRKAR1A*, *PTCH1*, *PTEN**, *RAD50*, *RAD51C*, *RAD51D*, *RB1*, *RECQL**, *RET*, *RHBDF2*, *RUNX1*, *SDHA**, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*[#], *SMAD4*, *SMARCA4*, *SMARCB1*, *STK11*, *SUFU*, *TERC*, *TERT*, *TINF2*, *TMEM127*, *TP53*, *TSC1*, *TSC2*, *VHL* and *WT1*. The following exons are not included in the panel as they are not covered with sufficient high quality sequence reads: PDGFRA (NM_001347828:2) 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

TEST INDICATION

This individual is a 29-year-old. Genetic testing with the Comprehensive Cancer Screen Panel has been requested.

PERSONAL RISKS: SEQUENCE ALTERATIONS

GENE	TRANSCRIPT	NOMENCLATURE	GENOTYPE	CONSEQUENCE	INHERITANCE	CLASSIFICATION
TP53	NM_000546.5	c.586C>T, p.(Arg196*)	HET	stop_gained	AD	Pathogenic
	ID	**ASSEMBLY**	**POS**	**REF/ALT**		
		GRCh37/hg19	17:7578263	G/A		
	gnomAD AC/AN	**POLYPHEN**	**SIFT**	**MUTTASTER**	**PHENOTYPE**	
	1/251474	N/A	N/A	disease_causing	Adrenocortical carcinoma, Breast cancer, familial, Choroid plexus papilloma, Colorectal cancer, Ependymoma, intracranial, Hepatoblastoma, Li-Fraumeni syndrome, Non-Hodgkin lymphoma, Osteogenic sarcoma	

CLINICAL REPORT

Sequence analysis using the Blueprint Genetics (BpG) Comprehensive Cancer Screen identified a heterozygous missense variant TP53 c.586C>T, p.(Arg196*).

TP53 c.586C>T, p.(Arg196*)

The variant generates a premature stop codon in exon 6 (of 11 total exons) and is predicted to lead to loss of normal protein function, either through protein truncation or nonsense-mediated mRNA decay. The TP53 c.586C>T, p.(Arg196*) variant has been reported in several individuals and families affected with Li-Fraumeni or Li-Fraumeni-like syndrome (including PMID: 7978053, 21552135, 21761402, 23894400, 27501770, 28177947, 30268473, 30709875, 11479205, 15381368, 19468865). The DNA binding activity of the p.(Arg196*) mutant was shown to be decreased compared to wild type p53 (PMID: 20128691). The TP53 c.586C>T, p.(Arg196*) variant has also been detected by other laboratories in the context of clinical testing and submitted to ClinVar (variation ID 43589). Loss of TP53 is an established disease mechanism, and other truncating variants in the gene have been described in patients with phenotypes consistent with TP53-related disease (HGMD).

TP53

The *TP53* (MIM *191170) gene encodes a tumor suppressor protein p53 that contains transcriptional activation, DNA binding, and oligomerization domains. It responds to diverse cellular stresses to regulate expression of target genes, thereby inducing cell cycle arrest, apoptosis, senescence, DNA repair, or changes in metabolism (PMID: 17380161). Although p53 has been shown to be involved in diverse regulatory pathways, its best characterized role is in protecting against cancer development. The loss of p53 function decreases the likelihood that cells with genetic errors will be flagged for DNA repair or apoptosis, enabling these cells to further proliferate resulting in a colony of abnormal cells and eventually a malignant tumor. Mutations in *TP53* have been associated with an increased susceptibility to a variety of cancers, including hereditary cancers such as Li-Fraumeni syndrome (LFS; MIM #151623). LFS is a cancer predisposition syndrome characterized by an autosomal dominant inheritance and early onset of tumors, multiple tumors within an individual, and multiple affected family members (GeneReviews NBK1311). The most common types of tumors are soft tissue sarcoma, osteosarcoma, pre-menopausal breast cancer, brain tumors, leukemia, and adrenocortical carcinoma. In addition, renal cell carcinomas, as well as endometrial, ovarian, prostate and gonadal germ cell tumors have been reported in families with LFS (GeneReviews NBK1311). *TP53* variants may also affect response to anticancer and also other treatments and medication (PMID 25981898, 17613549). The penetrance of LFS is high: the lifetime risk for cancer is estimated to be nearly 100% for females and about 70% for males by the age of 70 years (PMID: 10864200; 16912210). Around 80% of families with LFS have an identifiable *TP53* pathogenic

variant (PMID: 21779515), while it has been estimated that the prevalence of these mutations ranges from 1/10,000 to 1/25,000 (ORPHA524). To date, ClinVar reports over 400 pathogenic or likely pathogenic TP53 variants observed in clinical testing (April 2020). The majority of these variants are missense (around 60%) and truncating (around 40%) variants. Most TP53 pathogenic variants are located within exons 5-8, which encode the core DNA-binding region of the gene.
Currently, there is evidence of early tumor detection through surveillance to be associated with improved long-term survival in children and adults with germline TP53 pathogenic variants (PMID: 27501770). Currently, it is recommended that: (1) children and adults undergo comprehensive regular physical examination; (2) children and adults be encouraged see a physician promptly for evaluation of lingering symptoms and illnesses; (3) women undergo breast cancer monitoring, with annual breast MRI and twice annual clinical breast examination beginning at age 20-25 years (GeneReviews NBK1311). The use of mammograms has been controversial because of radiation exposure and limited sensitivity. When included, annual mammograms should alternate with breast MRI, with one modality every six months; (4) adults consider routine screening for colorectal cancer with colonoscopy every 2-3 years beginning no later than age 25 years; (5) individuals consider organ-targeted surveillance based on the pattern of cancer observed in their family. Intensified surveillance with whole-body MRI protocols for adults and children who carry a germline TP53 pathogenic variant are being evaluated in investigational settings.

A pathogenic heterozygous TP53 variant may be inherited in an autosomal dominant manner (cancer predisposition syndrome called as Li-Fraumeni syndrome) and the second variant or loss of heterozygosity (LOH) may occur as somatic mutation in smaller cell population and act as a "driver mutation" during the tumorigenesis (PMID: 9047394).

Somatic mutations in the TP53 gene are one of the most frequent alterations in human cancers.

Loss-of-function is a disease-causing mechanism for the TP53 gene and currently HGMD Professional 2020.1 lists more than 500 disease-causing variants. These include 7% nonsense, 51% missense, 9% splicing, 19% small deletions, 5% insertions, 2% small indels, 6% gross deletions, 0.4% gross insertions and 0.6% complex rearrangements.

Mutation nomenclature is based on GenBank accession NM_000546.5 (TP53) with nucleotide one being the first nucleotide of the translation initiation codon ATG.

CONCLUSION

TP53 c.586C>T, p.(Arg196*) is classified as pathogenic, based on currently available evidence supporting its disease-causing role. Disease caused by this variant is inherited in an autosomal dominant manner. Therefore, this individual is at risk of developing TP53-related disease. Any offspring of this individual are at 50% risk of inheriting the variant. TP53-related disease may be caused by a de novo variant. Genetic counseling and family member testing are recommended.

STEP	DATE
Order date	
Sample received	
Sample in analysis	

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

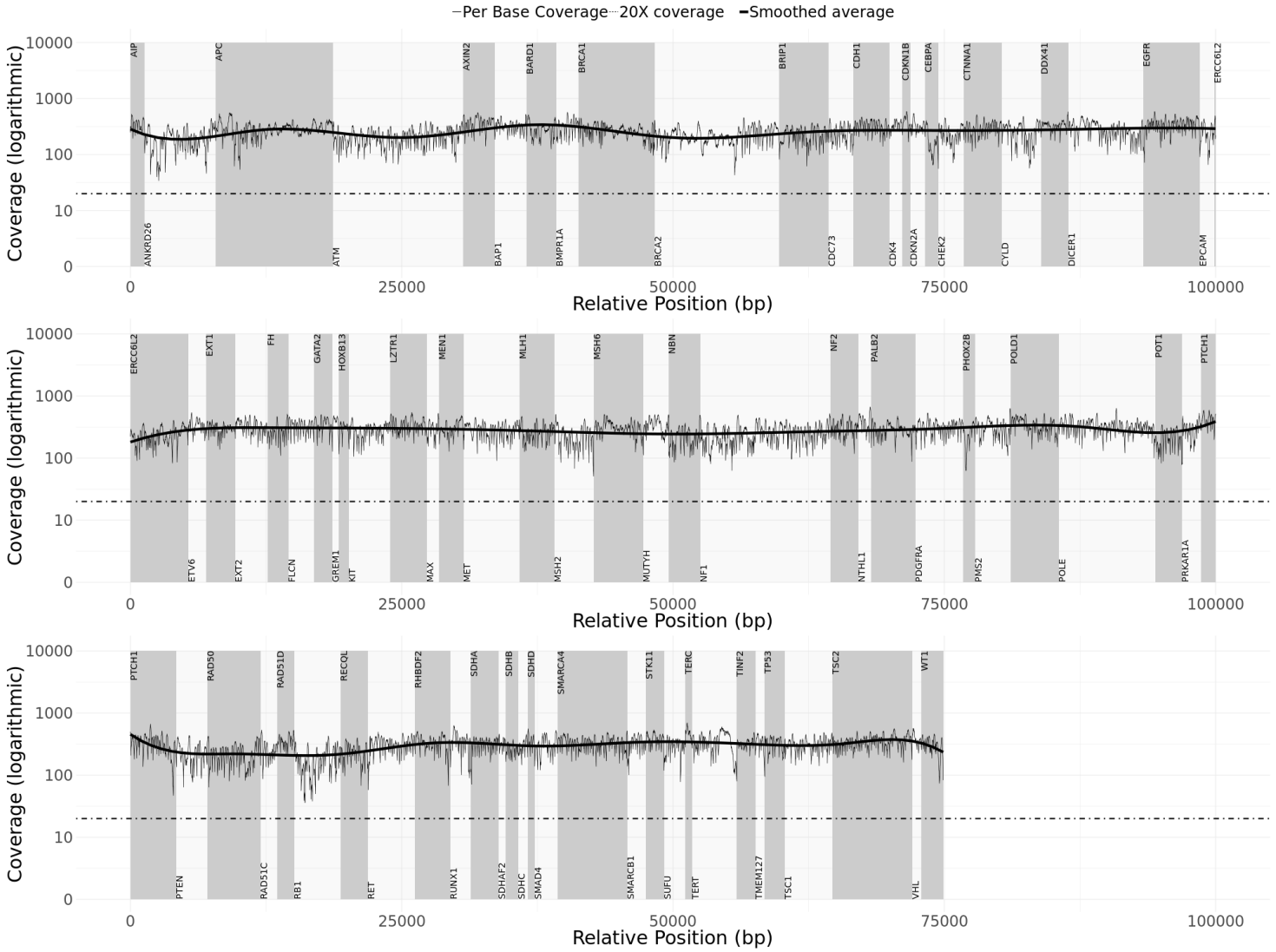
Signature

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.



SUMMARY OF THE TEST

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 CBC files as the final output.

Bioinformatics and quality control: Base called raw sequencing data was transformed into FAST format using Illumina's software (bcl2fastq). Sequence reads of each sample were mapped to the human reference genome (GRCh37/hq19). 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 DNA. Variant data for was annotated using a collection of tools (VcfAnno and VP) 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 samples) 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 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. Benign variants, Likely benign variants, and Variants of uncertain significance (VUS) were not reported. Information about estimated residual risks after negative test result using Blueprint Genetics Reproductive Screen Panels is available on our website: https://blueprintgenetics.com/residual-risk-table/

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 variants) 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. 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 variant, the degree of evolutionary conservation as well as a 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 mDNA variants specific databases including e.g. Mitomap, HmtVar and 1000G were used.

Confirmation of variants: Reporting focuses on high-quality variants that meet our stringent NGS quality metrics for a true

positive call but they were not confirmed with alternative methods. Ordering health care professional should consider further confirmation of the reported variants using a diagnostic test.

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 a pathogenic or likely pathogenic variant in the tested genes 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.

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/G
NM_014915.2(*ANKRD26*):c.-119C>A
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_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_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_177438.2(*DICER1*):c.5364+1187T>G
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
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_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_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_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_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_198253.2(*TERT*):c.2383-15C>T
NM_198253.2(*TERT*):c.-57A>C
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_000535.5(*PMS2*):c.1145-31_1145-13delCTGACCCTCTTCTCCGTCC
NM_000535.5(*PMS2*):c.23+21_23+28delTCCGGTGT
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_000264.3(*PTCH1*):c.2561-2057A>G
NM_000368.4(*TSC1*):c.363+668G>A

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.