Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108
UNITED STATES

Physician: TEST,

Patient: PROCAN NGS, POS

DOB
Sex: Male
Patient Identifiers: 44253
Visit Number (FIN): 44580
Collection Date: 11/15/2022 08:12

Hereditary Prostate Cancer Panel, Sequencing and Deletion/Duplication

ARUP test code 3005686

PROCAN Specimen	Whole Blood
PROCAN Interp	Positive

RESULT
One pathogenic variant was detected in the BRCA1 gene.

PATHOGENIC VARIANT
Gene: BRCA1 (NM_007294.4)
Nucleic Acid Change: c.5510G>A; Heterozygous
Amino Acid Alteration: p.Trp1837Ter
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.5510G>A; p.Trp1837Ter, was detected in the BRCA1 gene by massively parallel sequencing. This result is consistent with a diagnosis of hereditary breast and ovarian cancer (HBOC) syndrome. Pathogenic germline variants in BRCA1 are associated with an increased risk for several types of hereditary cancers including female/male breast, ovarian, prostate, and pancreatic; lifetime risks for different cancers vary. National Comprehensive Cancer Network (NCCN) guidelines are available for cancer risk management in heterozygous individuals. Other genetic/environmental factors may influence an individual's risk of developing cancer. This individual's offspring have a 50 percent chance of inheriting the pathogenic variant.

In addition, autosomal recessive inheritance of two BRCA1 pathogenic variants may be associated with Fanconi anemia, a condition characterized by congenital anomalies, bone marrow failure, and a predisposition to malignancies (Sawyer, 2015; MIM: 617883); thus, this individual is at least a carrier of this disorder.

Please refer to the background information included in this report for a list of the genes analyzed, methodology, and limitations of this test.

Evidence for variant classification:
The BRCA1 c.5510G>A; p.Trp1837Ter variant (rs80357307), also known as 5629C>A for traditional nomenclature, is reported in the literature in multiple individuals and families with hereditary breast and ovarian cancer syndrome and shown to cosegregate disease (Couch, 1996; George, 2021; Rebbeck, 2018; Vallon-Christersson, 2001). This variant is classified as pathogenic by an expert review panel in ClinVar (Variation ID: 55608). It is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. This variant results in a premature termination codon in the last exon of the BRCA1

gene, resulting in a truncated protein which removes a portion of the BRCT domain. Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At risk family members should be offered testing for the identified pathogenic BRCA1 variant (Familial Targeted Sequencing, ARUP test code 3005867). Counseling for potential reproductive risk associated with Fanconi anemia is recommended (NCCN Guidelines).

COMMENTS
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations:
NONE

REFERENCES
Couch FJ, et al. Mutations and polymorphisms in the familial early-onset breast cancer (BRCA1) gene. Breast Cancer Information Core. Hum Mutat. 1996;8(1):8-18. PMID: 8807330

George SHL, et al. Gene sequencing for pathogenic variants among adults with breast and ovarian cancer in the Caribbean. JAMA Netw Open. 2021;4(3):e210307. PMID: 33646313

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: genetic/familial high-risk assessment: breast, ovarian, and pancreatic (2.2022): https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

Rebbeck TR, et al. Mutational spectrum in a worldwide study of 29,700 families with BRCA1 or BRCA2 mutations. Hum Mutat. 2018;39(5):593-620. PMID: 29446198

Sawyer S, et al. Biallelic mutations in BRCA1 cause a new Fanconi anemia subtype. Cancer Discov. 2015;5(2): 135-142. PMID: 25472942

Vallon-Christersson J, et al. Functional analysis of BRCA1 C-terminal missense mutations identified in breast and ovarian cancer families. Hum Mol Genet. 2001;10(4):353-360. PMID: 11157798

BACKGROUND INFORMATION: Hereditary Prostate Cancer Panel, Sequencing and Deletion/Duplication
CHARACTERISTICS: Pathogenic germline variants in multiple genes have been implicated in hereditary prostate cancer. Hereditary cancer syndromes are often characterized by early age of cancer onset (typically before 50 years of age) and multiple, multifocal, and/or similar cancers in a single individual or in a closely related family member(s).

EPIDEMIOLOGY: Approximately 10% of prostate cancers are associated with a hereditary cause.

CAUSE: Pathogenic germline variants in genes associated with hereditary prostate cancer

INHERITANCE: Autosomal dominant. Additionally, some genes are also associated with autosomal recessive childhood cancer predisposition or other syndromes.

GENES TESTED: ATM; BRCA1*; BRCA2; CHEK2*; EPCAM**; HOXB13; MLH1; MSH2; MSH6; NBN; PALB2; PMS2; RAD51D; TP53

* One or more exons are not covered by sequencing and/or

deletion/duplication analysis for the indicated gene; see limitations section below.
**Deletion/duplication analysis of EPCAM (NM_002354) exon 9 only, sequencing is not available for this gene.

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and to confirm reported variants that do not meet acceptable quality metrics. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large deletions/duplications confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis. Testing of selected exons (and exon/intron boundaries) of PMS2 and MSH2 was performed by bidirectional Sanger sequencing. Deletion/duplication testing of PMS2 was performed by multiplex ligation-dependent probe amplification (MLPA).

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. Deletions of 2 exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of 3 exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes. The analytical sensitivity for MLPA is greater than 99 percent.

LIMITATIONS: A negative result does not exclude a heritable form of cancer. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants will not be identified. Precise breakpoints for large deletions or duplications are not determined in this assay and single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement. The actual breakpoints for the deletion or duplication may extend beyond or be within the exon(s) reported. This test is not intended to detect duplications of two or fewer exons in size, though these may be identified. Single exon deletions are reported but called at a lower sensitivity. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) variants, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
BRCA1 (NM_007300) exon 13
CHEK2 (NM_001005735) exon 3
CHEK2 (NM_001349956) exon 4

Deletions/duplications will not be called for the following exons:
BRCA1 (NM_007294, NM_007299, NM_007300) 2; BRCA1 (NM_007298) 1; CHEK2 (NM_007194) 11-15; CHEK2 (NM_001005735) 3,12-16; CHEK2 (NM_001257387) 12-16; CHEK2 (NM_001349956) 4,10-14; CHEK2 (NM_145862) 10-14

H=High, L=Low, *=Abnormal, C=Critical

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. This test was performed in a CLIA-certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
PROCAN Specimen	22-319-101132	11/15/2022 8:12:00 AM	11/15/2022 8:12:37 AM	11/15/2022 8:15:00 AM
PROCAN Interp	22-319-101132	11/15/2022 8:12:00 AM	11/15/2022 8:12:37 AM	11/15/2022 8:15:00 AM

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical