Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

**Patient: Patient, Example**

| | |
|---|---|
| **DOB** | 4/16/1951 |
| **Gender:** | Female |
| **Patient Identifiers:** | 01234567890ABCD, 012345 |
| **Visit Number (FIN):** | 01234567890ABCD |
| **Collection Date:** | 00/00/0000 00:00 |

## Hereditary Breast and Gynecological Cancers Panel, Sequencing and Deletion/Duplication

ARUP test code 2012026

| | |
|---|---|
| Breast/Ovarian Cancer Panel Spcm | Whole Blood |
| Breast/Ovarian Cancer Panel Interp | Positive |

RESULT
One likely pathogenic variant was detected in the ATM gene. Two variants of uncertain clinical significance were detected in the PALB2 gene.

LIKELY PATHOGENIC VARIANT
Gene: ATM (NM_000051.4)
Nucleic Acid Change: c.7889T>A; Heterozygous
Amino Acid Alteration: p.Leu2630Ter
Inheritance: Autosomal dominant

VARIANT OF UNCERTAIN SIGNIFICANCE
Gene: PALB2 (NM_024675.4)
Nucleic Acid Change: c.2788A>T; Heterozygous
Amino Acid Alteration: p.Asn930Tyr
Inheritance: Autosomal dominant

VARIANT OF UNCERTAIN SIGNIFICANCE
Gene: PALB2 (NM_024675.4)
Nucleic Acid Change: c.1066A>G; Heterozygous
Amino Acid Alteration: p.Lys356Glu
Inheritance: Autosomal dominant

INTERPRETATION
One likely pathogenic variant, c.7889T>A; p.Leu2630Ter, was detected in the ATM gene by massively parallel sequencing. Pathogenic germline variants in ATM are associated with autosomal dominant increased risk for breast cancer (MIM: 114480), ovarian cancer, pancreatic cancer, and prostate cancer. 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 likely pathogenic variant. In addition, autosomal recessive inheritance of two ATM pathogenic variants is associated with ataxia-telangiectasia (MIM: 208900); thus, this individual is at least a carrier of this disorder.

Two variants of uncertain clinical significance, c.2788A>T; p.Asn930Tyr and c.1066A>G; p.Lys356Glu, were detected in the PALB2 gene by massively parallel sequencing. Pathogenic germline variants in PALB2 are associated with autosomal dominant susceptibility to breast cancer (MIM:620442), ovarian cancer, and pancreatic cancer. However, it is uncertain whether this

variant is disease-associated or benign.

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 ATM c.7889T>A; p.Leu263Ter variant, to our knowledge, is not reported in the medical literature but is reported in ClinVar (Variation ID: 664950). This variant is absent from the Genome Aggregation Database (v2.1.1), indicating it is not a common polymorphism. This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Based on available information, this variant is considered to be likely pathogenic.

The PALB2 c.2788A>T; p.Asn930Tyr variant (rs1227325413), to our knowledge, is not reported in the medical literature but is reported in ClinVar (Variation ID: 460960). This variant is only observed on one allele in the Genome Aggregation Database (v2.1.1), indicating it is not a common polymorphism. Computational analyses are uncertain whether this variant is neutral or deleterious (REVEL: 0.22). Due to limited information, the clinical significance of this variant is uncertain at this time.

The PALB2 c.1066A>G; p.Lys356Glu variant (rs1202130508), to our knowledge, is not reported in the medical literature but is reported in ClinVar (Variation ID: 460875). This variant is only observed on one allele in the Genome Aggregation Database (v2.1.1), indicating it is not a common polymorphism. Computational analyses predict that this variant is neutral (REVEL: 0.02). Due to limited information, the clinical significance of this variant is uncertain at this time.

RECOMMENDATIONS
Medical screening and management should rely on clinical findings and family history. Genetic consultation is recommended. At-risk family members should be offered testing for the identified likely pathogenic ATM variant (Familial Targeted Sequencing, ARUP test code 3005867). Counseling for potential reproductive risk associated with ataxia-telangiectasia is recommended (NCCN Guidelines). Surveillance of the literature for new information concerning the uncertain variants is recommended.

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
National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (3.2024): https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

This result has been reviewed and approved by [redacted]
BACKGROUND INFORMATION: Hereditary Breast and Gynecological Cancers Panel, Sequencing and Deletion/Duplication
CHARACTERISTICS: Pathogenic germline variants in multiple genes have been implicated in hereditary breast, ovarian, and endometrial cancers. Hereditary cancer predisposition is often characterized by early-onset cancer (typically before age 50) and multiple, multifocal, and/or related cancers in a single individual or in a closely related family member(s). This test includes analysis of several genes associated with hereditary breast and/or gynecological cancer(s) that cause variable phenotypes and cancer risks, including non-breast/gynecological cancers.

EPIDEMIOLOGY: Approximately 5-10 percent of breast cancer, 10-15 percent of ovarian cancer, and 5 percent of endometrial cancers are associated with a hereditary cause. Prevalence of pathogenic BRCA1 and BRCA2 variants is estimated at 1 in 40 in the Ashkenazi Jewish population and 1 in 400 in the general population. Lynch syndrome occurs in approximately 1 in 279 individuals in the general population.

CAUSE: Pathogenic germline variants in genes associated with breast, ovarian, and/or endometrial cancer.

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

GENES TESTED: ATM; BARD1; BRCA1*; BRCA2; BRIP1; CDH1*; CHEK2*; DICER1; EPCAM**; MLH1; MSH2; MSH6; NBN; NF1; PALB2; PMS2; PTEN*; RAD51C; RAD51D; RECQL*; SMARCA4; STK11; 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, (including selected PTEN promoter variants), 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, PTEN and MSH2 was performed by bidirectional Sanger sequencing. Deletion/duplication testing of PMS2 was performed by multiplex ligation-dependent probe amplification (MLPA).

ANALYTICAL SENSITIVITY: 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 2 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
RECQL (NM_002907) exons 14,15
RECQL (NM_032941) exons 15,16

Deletions/duplications will not be called for the following exons:
BRCA1 (NM_007294, NM_007299, NM_007300) 2; BRCA1 (NM_007298) 1; CDH1 (NM_001317185) 10; 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; PTEN (NM_000314, NM_001304718) 9; PTEN (NM_001304717) 1,10; RECQL (NM_002907) 14-15; RECQL (NM_032941) 15-16

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 |
|---|---|---|---|---|
| Breast/Ovarian Cancer Panel Spcm | 24-032-116537 | 00/00/0000 00:00 | 00/00/0000 00:00 | 00/00/0000 00:00 |
| Breast/Ovarian Cancer Panel Interp | 24-032-116537 | 00/00/0000 00:00 | 00/00/0000 00:00 | 00/00/0000 00:00 |

END OF CHART

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