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

Physician: Doctor, Example

Patient: Patient, Example

DOB	9/16/2020
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

BRCA1 and BRCA2-Associated HBOC Syndrome Panel, Sequencing and Deletion/Duplication

ARUP test code 3001855

BRCA Specimen: Whole Blood

BRCA Interp: Positive

INDICATION FOR TESTING
Personal and family history of breast cancer.

RESULT
One pathogenic variant was detected in the BRCA1 gene.

PATHOGENIC VARIANT
Gene: BRCA1 (NM_007294.3)
Nucleic Acid Change: c.4574_4575delAA Heterozygous
Amino Acid Alteration: p.Gln1525ArgfsTer5
Inheritance: Autosomal Dominant

INTERPRETATION
One pathogenic variant, c.4574_4575delAA; p.Gln1525ArgfsTer5, was detected in the BRCA1 gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic BRCA1 variants are inherited in an autosomal dominant manner, and are associated with hereditary breast and ovarian cancer (HBOC) syndrome. HBOC syndrome increases the 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.

No additional pathogenic variants were identified in the BRCA1 or BRCA2 genes by massively parallel sequencing or deletion/duplication analysis. Please refer to the background information included in this report for the clinical sensitivity and limitations of this test.

Evidence for variant classification: The BRCA1 c.4574_4575delAA; p.Gln1525ArgfsTer5 variant (rs80357813), also known as 4693delAA, is reported in the literature in individuals with

breast or ovarian cancer (Ellis 2000, Greenman 1998, Morgan 2010, Robertson 2012, Song 2014) and is classified as pathogenic by an expert review panel in ClinVar (Variation ID: 55229). This variant is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. This variant causes a frameshift by deleting two nucleotides, so it 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 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 variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). Counseling for potential reproductive risk associated with Fanconi anemia is recommended (NCCN Guidelines).

COMMENTS
Likely benign and benign variants are not included in this report.

REFERENCES
Ellis D et al. Low prevalence of germline BRCA1 mutations in early onset breast cancer without a family history. J Med Genet. 2000 Oct;37(10):792-4.

Greenman J et al. Identification of missense and truncating mutations in the BRCA1 gene in sporadic and familial breast and ovarian cancer. Genes Chromosomes Cancer. 1998 Mar;21(3):244-9.

Morgan JE et al. Genetic diagnosis of familial breast cancer using clonal sequencing. Hum Mutat. 2010 Apr;31(4):484-91.

National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (1.2020): https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. (Accessed May 2020).

Robertson L et al. BRCA1 testing should be offered to individuals with triple-negative breast cancer diagnosed below 50 years. Br J Cancer. 2012 Mar 13;106(6):1234-8.

Sawyer S et al. Biallelic Mutations in BRCA1 Cause a New Fanconi Anemia Subtype Cancer Discov. 2015 February; 5(2): 135-142.

Song H et al. The contribution of deleterious germline mutations in BRCA1, BRCA2 and the mismatch repair genes to ovarian cancer in the population. Hum Mol Genet. 2014 Sep 1;23(17):4703-9.

This result has been reviewed and approved by [redacted]

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

BACKGROUND INFORMATION: BRCA1 and BRCA2-Associated HBOC Syndrome Panel, Sequencing and Deletion/Duplication
CHARACTERISTICS: Individuals with a single germline BRCA1 or BRCA2 pathogenic variant have an increased risk for breast (female and male), ovarian, fallopian tube, peritoneal,pancreatic, and prostate cancers. Additionally, BRCA2 carriers may be at increased risk for melanoma.
EPIDEMIOLOGY: 1 in 40 individuals of Ashkenazi Jewish decent or 1 in 400 individuals in the general population have a germline BRCA1 or BRCA2 pathogenic variant; 5-10 percent of breast cancers and 10-15 percent of ovarian cancers are associated with a hereditary cause.
CAUSE: Pathogenic germline variants in the tumor suppressor genes BRCA1 and BRCA2 cause hereditary breast and ovarian cancer (HBOC) syndrome. Approximately 20-60 percent of inherited breast and/or ovarian cancers are due to pathogenic germline variants in BRCA1 and BRCA2.
INHERITANCE: Autosomal dominant
CLINICAL SENSITIVITY: Greater than 90 percent of BRCA1 and BRCA2 pathogenic variants.
GENES TESTED: BRCA1 (NM_007294), BRCA2 (NM_000059)
METHODOLOGY: Multiplex ligation-dependent probe amplification (MLPA) of the BRCA1 and BRCA2 genes. Capture of all coding exons and exon-intron junctions of the BRCA1 and BRCA2 genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants.
ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity for MLPA is 99 percent. The analytical sensitivity of this test is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.
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 BRCA1 and BRCA2 genes. Regulatory region variants and deep intronic variants will not be identified and breakpoints of large deletions/duplications will not be determined. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level mosaic or somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Non-coding transcripts were not analyzed.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

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VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
BRCA Specimen	20-262-111164	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
BRCA Interp	20-262-111164	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