ARUP LABORATORIES
800-522-2787 | aruplab.com
500 Chipeta Way, Salt Lake City, UT 84108-1221
Jonathan R. Genzen, MD, PhD, Chief Medical Officer

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

Physician: ARUP, ARUP

Patient: FAM NGS, POSITIVE EXAMPLE

DOB	
Sex:	Female
Patient Identifiers:	44375
Visit Number (FIN):	44702
Collection Date:	11/16/2022 13:43

Familial Targeted Sequencing

ARUP test code 3005867

FAM Interp

Positive

RESULT
Positive for the requested pathogenic variant in the BRCA1 gene.

PATHOGENIC VARIANT
Gene: BRCA1 (NM_007294.4)
Nucleic Acid Change: c.1960A>T; heterozygous
Amino Acid Alteration: p.Lys654Ter
Inheritance: Autosomal dominant

INTERPRETATION
The familial BRCA1 variant, c.1960A>T; p.Lys654Ter, was detected in the BRCA1 gene by massively parallel sequencing. This variant was previously reported to be associated with hereditary breast and ovarian cancer (HBOC) syndrome in the family. This individual is predicted to have the predisposition to hereditary cancers associated with this variant. Pathogenic BRCA1 variants are inherited in an autosomal dominant manner and are associated with 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 individuals 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.

Evidence for variant classification: The BRCA1 c.1960A>T; p.Lys654Ter variant (rs80357355) is reported in the literature in multiple individuals with breast and/or ovarian cancer, particularly in individuals of Hispanic origin (John, 2007; Judkins, 2005; Weitzel 2005; Weitzel 2013). This variant is reported as pathogenic by several sources in the ClinVar database, including an expert panel (Variation ID: 37436). This variant is found on a single chromosome in the Genome Aggregation Database, indicating it is not a common polymorphism. This variant induces an early termination codon in exon 11b (of 24) 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 pathogenic.

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

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

COMMENTS
Reference Sequence: BRCA1 (NM_007294.4)

REFERENCES
John EM, et al. Prevalence of pathogenic BRCA1 mutation carriers in 5 US racial/ethnic groups. JAMA. 2007;298(24):2869-76. PMID: 18159056.

Judkins T, et al. Application of embryonic lethal or other obvious phenotypes to characterize the clinical significance of genetic variants found in trans with known deleterious mutations. Cancer Res. 2005;65(21):10096-103. PMID: 16267036.

National Comprehensive Cancer Network. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic (2.2022): https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

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

Weitzel JN et al. Prevalence of BRCA mutations and founder effect in high-risk Hispanic families. Cancer Epidemiol Biomarkers Prev. 2005;14(7):1666-71. PMID: 16030099.

Weitzel JN et al. Prevalence and type of BRCA mutations in Hispanics undergoing genetic cancer risk assessment in the southwestern United States: a report from the Clinical Cancer Genetics Community Research Network. J Clin Oncol. 2013;31(2):210-6. PMID: 23233716.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Familial Targeted Sequencing

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted gene(s) region(s), followed by massively parallel sequencing. Variants in genes, other than the gene(s) region(s) specifically requested, were not evaluated. Human genome build 19 (Hg 19) was used for data analysis.

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. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude all genetic diagnoses in this individual. This test only evaluates the specified familial variant(s) of interest and other pathogenic or likely pathogenic variants by massively parallel sequencing related to the condition of interest within the targeted gene(s) region(s). Refer to Targeted Sequencing Gene List for complete list of genes available for this test and any gene-specific technical limitations. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants, deep intronic variants, and large

deletions/duplications will not be identified. 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) mutations, aneuploidies, 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.

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
FAM Interp	22-320-112500	11/16/2022 1:43:00 PM	11/16/2022 1:43:29 PM	11/16/2022 1:46:00 PM

END OF CHART

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