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

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/31/1752
Sex:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Rapid Genome Sequencing, Familial Comparator

ARUP test code 3019953

RWGS FM Interp **Positive** *

TEST PERFORMED
Rapid Genome Sequencing, Familial Comparator

RESULT
One pathogenic variant was detected in the BRCA1 gene.

PATHOGENIC VARIANT
Gene (Transcript): BRCA1 (NM_007294.4)
OMIM(R) disease: Familial breast-ovarian cancer (MIM: 604370; (1))
Mode of Inheritance: Autosomal Dominant
Zygosity: Heterozygous
Variant: c.68_69del; p.Glu23ValfsTer17
[GRCh37]Chr17:g.41276047_41276048del

INTERPRETATION
One pathogenic variant, c.68_69del; p.Glu23ValfsTer17, was detected in the BRCA1 gene by massively parallel sequencing. Heterozygous pathogenic BRCA1 variants are associated with hereditary breast and ovarian cancer (HBOC) syndrome, a hereditary cancer predisposition syndrome that confers an increased risk for female and male breast, ovarian, prostate, and pancreatic cancer. Lifetime risk varies by cancer type. National Comprehensive Cancer Network (NCCN) guidelines are available for cancer risk management in heterozygous individuals (2). This result is consistent with a diagnosis of HBOC syndrome. Individuals with this variant have a 50 percent chance of transmitting it to offspring.

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 (MIM: 617883; OMIM(R))(3); thus, this individual is predicted to be at least a carrier of this disorder.

The American College of Medical Genetics and Genomics (ACMG) recommends analysis of specific medically actionable secondary findings (SF) genes, including BRCA1, in all consented individuals undergoing genome sequencing even though these genes may not be related to the indication for testing (4).

Evidence for variant classification: The BRCA1 c.68_69del; p.Glu23ValfsTer17 variant (rs386833395, ClinVar Variation ID: 17662), also known as 185delAG, is a well-known founder variant

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

associated with breast, ovarian, and pancreatic cancer in the Ashkenazi Jewish and other ethnic populations (5-9). This variant is found in the general population with an overall allele frequency of 0.02% (58/282,442 alleles) in the Genome Aggregation Database (v2.1.1). 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, the p.Glu23ValfsTer17 variant is considered to be pathogenic.

No additional secondary findings variants involving the ACMG SF v3.3 gene list (10) were detected. This result does not exclude the possibility this individual may carry another pathogenic variant involving one of these genes, or another gene that is not included on this list. If there is clinical suspicion or family history of a genetic condition associated with one of the ACMG SF genes, additional targeted testing should be considered, as genome sequencing will not identify all pathogenic variants involving these genes. Note that single pathogenic variants in autosomal recessive ACMG SF genes are not reported. Please refer to the background information below for the methodology and limitations of this test.

RECOMMENDATIONS
- Genetic consultation is indicated, including a discussion of medical screening and management. - If this individual is of Ashkenazi Jewish ancestry, at-risk adult family members should be offered testing for the detected pathogenic variant as well as two other common pathogenic Ashkenazi Jewish variants (which can be detected by BRCA1 and BRCA2-Associated HBOC Syndrome Panel, ARUP test code 3001855), as some Ashkenazi Jewish families have been reported to harbor more than one pathogenic variant (11). Family members with no Ashkenazi Jewish ancestry should be offered targeted testing for the detected pathogenic variant (Familial Targeted Sequencing, ARUP test code 3005867).
- Counseling for potential reproductive risk associated with Fanconi anemia is recommended (2).

References
1: OMIM(R): Copyright (C) 1996 - Present year, Johns Hopkins University All rights reserved.
2: National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf)
3: Sawyer S et al. Biallelic Mutations in BRCA1 Cause a New Fanconi Anemia Subtype Cancer Discov. 2015. PMID: 25472942.
4: Miller DT, Lee K, Gordon AS, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021. PMID: 34012069.
5: Abeliovich D, Kaduri L, Lerer I et al. The founder mutations 185delAG and 5382insC in BRCA1 and 6174delT in BRCA2 appear in 60% of ovarian cancer and 30% of early-onset breast cancer patients among Ashkenazi women. Am J Hum Genet 1997. PMID:9042909.
6: Antoniou AC, Pharoah PD, Narod S et al. Breast and ovarian cancer risks to carriers of the BRCA1 5382insC and 185delAG and BRCA2 6174delT mutations: a combined analysis of 22 population based studies. J Med Genet 2005. PMID:15994883.
7: King MC, Marks JH, Mandell JB et al. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 2003. PMID:14576434.
8: Laitman Y, Friebel TM, Yannoukakos D et al. The spectrum of BRCA1 and BRCA2 pathogenic sequence variants in Middle Eastern, North African, and South European countries. Hum Mutat 2019. PMID:31209999.
9: Lucas AL, Frado LE, Hwang C et al. BRCA1 and BRCA2 germline mutations are frequently demonstrated in both high-risk pancreatic cancer screening and pancreatic cancer cohorts.

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Cancer 2014. PMID:24737347.
10: Lee K, Abul-Husn NS, Amendola LM et al. ACMG SF v3.3 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med 2025. PMID:40568962.
11: Ramus SJ, Friedman LS, Gayther SA et al. A breast/ovarian cancer patient with germline mutations in both BRCA1 and BRCA2. Nat Genet. 1997; 15(1):14-5. PMID: 8988162.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Rapid Genome Sequencing, Familial Comparator
CHARACTERISTICS: Rapid whole genome sequencing (RWGS) of familial comparator(s) is used to help determine the cause(s) of a disorder in the family proband. RWGS utilizes next generation sequencing (NGS) to interrogate more than 92 percent of the genome (excluding telomeric and centromeric regions), including the mitochondrial genome.

The American College of Medical Genetics and Genomics (ACMG) recommends analysis of certain genes for secondary findings in all individuals undergoing genome sequencing. Please refer to ACMG Secondary Findings Gene List (http://ltd.aruplab.com/Tests/Pub/3019953) for a list of genes analyzed. Note that this gene list is updated periodically and is only accurate for this sample at the time of reporting.

INHERITANCE: Varies by gene and/or variant.

CLINICAL SENSITIVITY: Varies by gene.

METHODOLOGY: Genomic DNA is extracted from whole blood or saliva, prepared into libraries, then sequenced by NGS. Variant calling is performed using the Illumina DRAGEN Bio-IT Platform incorporated with a custom bioinformatics pipeline. Human genome build 19 (Hg 19) is used for data analysis. The analytical procedure identifies single nucleotide variants (SNVs), small insertions/deletions, and copy number variants (CNVs) known, or suspected to be, disease-causing.

LIMITATIONS OF ANALYSIS: Due to technical limitations, some regions of the genome cannot be sequenced or interpreted. SNVs in intergenic or deep intronic regions will only be evaluated if an effect on gene expression is predicted based on annotation software. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations related to pseudogenes or repetitive or homologous regions. This assay is not designed to detect somatic variants, mosaic variants, trinucleotide repeats, uniparental disomy, absence of heterozygosity (AOH), or mitochondrial CNVs. This assay is not designed to detect CNVs greater than 50 bp but less than 1 kb in size. See Additional Technical Information located at http://ltd.aruplab.com/Tests/Pub/3019951 for more information on whole genome sequencing.

REPORTING CONSIDERATIONS: Secondary findings, including disease-associated variants identified in genes on the ACMG-recommended list, or other medically actionable variants at ARUP's discretion, are reported when elected. Interpretation of test results may be impacted if any of the tested individuals have undergone allogeneic stem cell transplantation.

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.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
RWGS FM Interp	25-307-106636	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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