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

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/31/1990
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Hereditary Breast and Ovarian Cancer Panel, Sequencing and Deletion/Duplication

ARUP test code 2012026

Breast/Ovarian Cancer Panel Spcm	Whole Blood

Breast/Ovarian Cancer Panel Interp	Positive

INDICATION FOR TESTING
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.211A>G; Heterozygous
Amino Acid Alteration: p.Arg71Gly
Inheritance: Autosomal Dominant

INTERPRETATION
One copy of a pathogenic variant, c.211A>G; p.Arg71Gly, was detected in the BRCA1 gene by massively parallel sequencing and confirmed by Sanger sequencing. This result is consistent with a diagnosis of hereditary breast and ovarian cancer (HBOC) syndrome. Pathogenic variants in the BRCA1 gene increase 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 other targeted genes by massively parallel sequencing or deletion/duplication analysis. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

Evidence for variant classification:
The BRCA1 c.211A>G; p.Arg71Gly variant (rs80357382) has been reported in multiple families with a history of breast and/or ovarian cancers (Diez 1999, Sanz 2010, Vega 2001). Functional characterization of the variant indicates aberrant splicing of

the BRCA1 transcript, resulting in the introduction of a premature termination codon (Houdayer 2012, Sanz 2010, Vega 2001). This variant is reported as pathogenic by multiple laboratories in ClinVar (Variation ID: 17693). It is only observed on one allele in the Genome Aggregation Database, indicating it is not a common polymorphism. This variant is two nucleotides from the canonical splice site, and computational algorithms (Alamut v.2.11) predict the weakening or loss of the splice donor, consistent with observations from functional studies. 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 targeted 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).

LIKELY BENIGN VARIANT
Gene: DICER1 (NM_177438.2) Variant: c.5250A>G; p.Val1750Val - Heterozygous
The DICER1 c.5250A>G; p.Val1750Val variant, to our knowledge, is not reported in the medical literature or gene specific databases. This variant is also absent from general population databases (Exome Variant Server, Genome Aggregation Database). This is a synonymous variant in a weakly conserved nucleotide, and computational analyses (Alamut v.2.11) predict that this variant does not significantly alter splicing. Based on available information, this variant is considered to be likely benign.

COMMENTS
Benign variants are not included in this report.

REFERENCES
Diez O et al. BRCA1 mutation analysis in 83 Spanish breast and breast/ovarian cancer families. Int J Cancer. 1999; 83(4):465-9.
Houdayer C et al. Guidelines for splicing analysis in molecular diagnosis derived from a set of 327 combined in silico/in vitro studies on BRCA1 and BRCA2 variants. Hum Mutat. 2012; 33(8):1228-38.
National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian (3.2019): https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. (Accessed February 2019).
Sanz DJ et al. A high proportion of DNA variants of BRCA1 and BRCA2 is associated with aberrant splicing in breast/ovarian cancer patients. Clin Cancer Res. 2010; 16(6):1957-67.
Sawyer S et al. Biallelic Mutations in BRCA1 Cause a New Fanconi Anemia Subtype Cancer Discov. 2015 February; 5(2): 135-142.
Vega A et al. The R71G BRCA1 is a founder Spanish mutation and leads to aberrant splicing of the transcript. Hum Mutat. 2001; 17(6):520-1.

This result has been reviewed and approved by Weimin Sun, Ph.D.

BACKGROUND INFORMATION: Hereditary Breast and Ovarian Cancer Panel, Sequencing and Deletion/ Duplication

CHARACTERISTICS: Pathogenic variants in multiple genes have been implicated in hereditary breast and/or ovarian cancer, often characterized by early-onset breast and/or ovarian cancer (before 50 years of age) in multiple closely related family members. Pathogenic germline variants in the BRCA1 and BRCA2 genes are associated with hereditary breast and ovarian cancer (HBOC) syndrome. Individuals with a pathogenic BRCA1 or BRCA2 variant are at an increased risk for breast, ovarian, fallopian, peritoneal, pancreatic, prostate, melanoma, and other cancers.

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

Germline variants in other genes causing hereditary breast and/or ovarian cancer have variable expression and are often associated with increased risk for other non-breast/ovarian cancers.

EPIDEMIOLOGY: Approximately 268,000 new cases of breast cancer and 22,000 new cases of ovarian cancer are diagnosed in the U.S. per year. 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.

CAUSE: At least 5-10 percent of all breast cancers and 10-15 percent of all ovarian cancers are associated with a hereditary cause.

INHERITANCE: Autosomal dominant, with the exception of the MUTYH gene which is autosomal recessive but may also have autosomal dominant cancer risks that are not well-defined. Additionally, some genes are also associated with autosomal recessive childhood cancer predisposition or other syndromes.

PENETRANCE: Varies, depending on the gene and specific variant.

GENES TESTED: ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2*, DICER1, EPCAM****, MLH1, MRE11, MSH2, MSH6, MUTYH, NBN, NF1**, PALB2, PMS2, PTEN, RAD51C, RAD51D, RECQL***, STK11, TP53

* - One or more exons are not covered by sequencing for the indicated gene; see limitations section below.
** - Deletion/duplication detection is not available for this gene.
*** - One or more exons are not covered by sequencing, and deletion/duplication detection is not available for this gene; see limitations section below.
**** - Deletion/duplication only; sequencing is not available for this gene.

METHODOLOGY: Targeted capture of all coding exons and exon-intron junctions of the targeted genes, including the PTEN promoter region, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants. A custom tiled comparative genomic hybridization array (aCGH) was used to detect large deletions or duplications in the indicated subset of genes. Human genome build 19 (Hg 19) was used for data analysis. Analysis of the PMS2 gene was performed by bidirectional Sanger sequencing of coding regions and their respective exon intron boundaries as well as multiplex ligation-dependent probe amplification (MLPA). Targeted sequencing was performed for the CHEK2 c.1100delC variant.

ANALYTICAL SENSITIVITY: 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 targeted genes. Regulatory region variants and deep intronic variants will not be identified and breakpoints of large deletions/duplications will not be determined. Single exon deletions/duplications or deletions/duplications less than 1kb may not be detected. Deletions/duplications/insertions of any size may not be detected by massive 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 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.

The following regions are not sequenced due to technical limitations of the assay:
CHEK2(NM_001349956) exon(s) 4
CHEK2(NM_001005735) exon(s) 3
CHEK2(NM_007194) exon(s) 10,12,13,14,15
RECQL(NM_002907) exon(s) 14,15

Single exon deletions/duplications will not be called for the following exons:
BARD1(NM_000465) 1;BRCA1(NM_007300) 13;CDH1(NM_004360) 1;CHEK2(NM_001005735) 3;CHEK2(NM_007194) 11,12,14,15;MRE11(NM_005591) 2;MSH2(NM_000251) 1;MSH2(NM_001258281) 2;MSH6(NM_000179) 10;MUTYH(NM_001128425) 1;PALB2(NM_024675) 1;PTEN(NM_000314) 8,9;PTEN(NM_001304717) 1;RAD51D(NM_002878) 1;TP53(NM_001126113) 10;TP53(NM_001126114) 10

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Breast/Ovarian Cancer Panel Spcm	19-012-400581	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Breast/Ovarian Cancer Panel Interp	19-012-400581	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