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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	Unknown
Gender:	Unknown
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 pathogenic variant was detected in the BRCA1 gene.

PATHOGENIC VARIANT
Gene: BRCA1 (NM_007294.4)
Nucleic Acid Change: c.211A>G; Heterozygous
Amino Acid Alteration: p.Arg71Gly
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.211A>G; p.Arg71Gly, was detected in the BRCA1 gene by massively parallel sequencing. This result is consistent with a diagnosis of hereditary breast and ovarian cancer (HBOC) syndrome. Pathogenic germline variants in BRCA1 are associated with an increased 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.

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 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,

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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 testing for the identified pathogenic BRCA1 variant (Familial Targeted Sequencing, ARUP test code 3005867). Counseling for potential reproductive risk associated with Fanconi anemia is recommended (NCCN Guidelines).

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
Diez O et al. BRCA1 mutation analysis in 83 Spanish breast and breast/ovarian cancer families. Int J Cancer. 1999; 83(4):465-9. PMID: 10508480.
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. PMID: 22505045.
National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (1.2023): https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf
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. PMID: 20215541.
Sawyer S et al. Biallelic Mutations in BRCA1 Cause a New Fanconi Anemia Subtype. Cancer Discov. 2015 February; 5(2): 135-142. PMID: 25472942.
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. PMID: 11385711.

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

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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	22-294-117968	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Breast/Ovarian Cancer Panel Interp	22-294-117968	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