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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	9/5/1942
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	Negative

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

INDICATION FOR TESTING
Personal history of pancreatic cancer and a family history of breast cancer and melanoma.

RESULT
No pathogenic variants were detected in any of the genes tested.

INTERPRETATION
According to information provided to ARUP, this individual has a personal history of pancreatic cancer and a family history of breast cancer and melanoma. No pathogenic variants were identified by massively parallel sequencing of the coding regions and exon-intron boundaries of the genes tested. No large exonic deletions and duplications were identified in the genes tested. This result decreases but does not exclude, a diagnosis of hereditary breast and ovarian cancer (HBOC). Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

RECOMMENDATIONS
Medical screening and management should rely on clinical findings and family history. Genetic consultation is recommended.

LIKELY BENIGN VARIANT
Gene: STK11 (NM_000455.4) Variant: c.1211C>T; p.Ser404Phe - Heterozygous
The STK11 c.1211C>T; p.Ser404Phe variant (rs200078204) is reported in the literature in an individual with breast cancer who also carried a pathogenic BRCA1 variant (Jalkh 2017), and in an individual with colorectal cancer who also carried a pathogenic MLH1 variant (Yurgelun 2017). This variant is reported as likely benign by multiple laboratories in ClinVar (Variation ID: 127700). It is found in the general population with an overall allele frequency of 0.05% (118/250190 alleles) in the Genome Aggregation Database. The serine at codon 404 is moderately conserved, but computational analyses (SIFT: Damaging, PolyPhen-2: Benign) predict conflicting effects of this variant on protein structure/function. Based on available information, this variant is considered to be likely benign.

COMMENTS
Benign variants are not included in this report.

REFERENCES
Jalkh N et al. Next-generation sequencing in familial breast cancer patients from Lebanon. BMC Med Genomics. 2017 Feb 15;10(1):8.
Yurgelun MB et al. Cancer Susceptibility Gene Mutations in Individuals With Colorectal Cancer. J Clin Oncol. 2017 Apr 1;35(10):1086-1095.

This result has been reviewed and approved by Yuan Ji, 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. 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.

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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	19-021-401521	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Breast/Ovarian Cancer Panel Interp	19-021-401521	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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