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 Cancer High-Risk Panel, Sequencing and Deletion/Duplication

ARUP test code 3005632

BCHR Specimen: Whole Blood

BCHR Interp: Positive

RESULT
One pathogenic variant was detected in the PALB2 gene.

PATHOGENIC VARIANT
Gene: PALB2 (NM_024675.4)
Nucleic Acid Change: c.1684+1G>A; Heterozygous
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.1684+1G>A, was detected in the PALB2 gene by massively parallel sequencing. Pathogenic germline variants in PALB2 are associated with autosomal dominant susceptibility to breast cancer (MIM: 620442), ovarian cancer, and pancreatic cancer. 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 PALB2 pathogenic variants is associated with Fanconi anemia complementation group N, a condition characterized by congenital anomalies, bone marrow failure, and a predisposition to malignancies (MIM: 610832); 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 PALB2 c.1684+1G>A variant (rs1555461148), also known as 1559+1G>A, is reported in the literature in individuals with breast cancer (Yang 2017, Zhou 2020). This variant is also reported in ClinVar (Variation ID: 482029). It is absent from the Genome Aggregation Database (v2.1.1), indicating it is not a common polymorphism. This variant disrupts the canonical splice donor site of intron 4, and minigene assays have shown it to cause skipping of exons 4 and 5 which is predicted to result in a frameshift leading to nonsense mediated decay (Lopez-Perolio 2019). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS

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

Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic PALB2 variant (Familial Targeted Sequencing, ARUP test code 3005867).

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
Lopez-Perolio I et al. Alternative splicing and ACMG-AMP-2015-based classification of PALB2 genetic variants: an ENIGMA report. J Med Genet. 2019 Jul;56(7):453-460. PMID: 30890586.

National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (2.2024): https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

Yang XR et al. Prevalence and spectrum of germline rare variants in BRCA1/2 and PALB2 among breast cancer cases in Sarawak, Malaysia. Breast Cancer Res Treat. 2017 Oct;165(3):687-697. PMID: 28664506.

Zhou J et al. Spectrum of PALB2 germline mutations and characteristics of PALB2-related breast cancer: Screening of 16,501 unselected patients with breast cancer and 5890 controls by next-generation sequencing. Cancer. 2020 Jul 15;126(14):3202-3208. PMID: 32339256.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Hereditary Breast Cancer High-Risk Panel, Sequencing and Deletion/Duplication
CHARACTERISTICS: Pathogenic germline variants in multiple genes have been implicated in hereditary breast cancer. Risk-reducing options have been recommended for high-risk hereditary breast cancer genes. These genes include: BRCA1, BRCA2, CDH1, PALB2, PTEN, and TP53.

EPIDEMIOLOGY: Approximately 5-10 percent of breast cancer is associated with a hereditary cause.

CAUSE: Pathogenic germline variants in genes associated with a high lifetime risk of hereditary breast cancer.

INHERITANCE: Autosomal dominant. Additionally, some genes are also associated with autosomal recessive childhood cancer predisposition or other syndromes.

GENES TESTED: BRCA1*; BRCA2; CDH1*; PALB2; PTEN*; TP53

*One or more exons are not covered by sequencing and/or deletion/duplication analysis for the indicated gene; see limitations section below.

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 PTEN was performed by bidirectional Sanger sequencing.

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. 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.

LIMITATIONS: A negative result does not exclude a heritable form of breast 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

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; PTEN (NM_000314, NM_001304718) 9; PTEN (NM_001304717) 1,10

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
BCHR Specimen	23-310-401466	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
BCHR Interp	23-310-401466	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