

Specimen ID: 00000000000

Control ID:

Lab Case ID: 0000000000000000

PATIENT, ANY

Acct #: 00000000

Phone: (000) 000-000

CMBP QA TEST ACCOUNT

CMBP QA DEPT RTP.

RTP

RTP NC 27215-5820

Patient Details

DOB: 00/00/0000

Age(y/m/d): 000/00/00

Gender:

Patient ID:

Specimen Details

Date collected: 00/00/0000 00:00 Local

Date received: 00/00/0000 00:00

Date entered: 00/00/0000 00:00

Date reported: 00/00/0000 00:00 ET

Physician Details

Ordering:

Referring:

ID:

NPI: 0000000000

Specimen Type: Saliva, Oral Fluid

Clinical Indication: Personal and/or family history of Hereditary Breast and Ovarian Cancer (HBOC)

RESULTS

POSITIVE FOR AT LEAST ONE PATHOGENIC VARIANT

At least one clinically significant variant was detected in the *BRCA1* gene.

No variants of uncertain significance were identified.

GENE	VARIANT
<i>BRCA1</i>	POSITIVE Heterozygous for c.68_69delAG (p.Glu23ValfsX17) (Pathogenic)
<i>BRCA2</i>	NEGATIVE No pathogenic variants were identified.

INTERPRETATION

This result increases this individual's risk for cancer.

Variant details

The *BRCA1* c.68_69delAG (p.Glu23ValfsX17) variant is associated with HBOC (Hereditary Breast and Ovarian Cancer Syndrome). This frameshift variant is predicted to result in a downstream premature termination codon. This variant is a known founder variant which has been reported to segregate with disease. It has been reported in ClinVar and in the literature. Based on LabCorp's in-house variant classification protocol and in accord with the American College of Medical Genetics' guidelines, this variant has been classified as pathogenic and is associated with an increased risk for hereditary breast and ovarian cancer.

Gene summary

BRCA1 and *BRCA2* (OMIM 600185) are tumor suppressor genes that play a critical role in normal DNA repair, cell cycle control, and genomic stability. Pathogenic variants in these genes are associated with familial cancers, including breast, ovarian, pancreatic, prostate, and melanoma.

ADDITIONAL CLINICAL INFORMATION

Cancer risks applicable to this individual

A positive *BRCA1* result is associated with the following cancer risks:

Lifetime high risk: Up to 87% female breast; Up to 63% ovarian; 1-2% male breast

Lifetime increased risk: Pancreatic; prostate

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ADDITIONAL CLINICAL INFORMATION

NCCN Guidelines

When *BRCA1* and *BRCA2* results are negative, additional testing may be helpful for some patients with breast, ovarian, and pancreatic cancer. Guidelines from the National Comprehensive Cancer Network® (NCCN®) recommend considering germline genetic testing for high-penetrance breast and/or ovarian cancer genes (including, but not limited to, *BRCA1/2*, *CDH1*, *PALB2*, *PTEN*, and *TP53*) in patients with any of the criteria in the table below. To discuss comprehensive genetic testing for breast, ovarian, and pancreatic cancer genes, an Integrated Genetics' Genetic Coordinator is available at 800-345-4363.

Breast cancer diagnosed \leq age 45	Ovarian cancer at any age
Breast cancer diagnosed age 46-50 with ≥ 1 close relative with breast, ovarian, pancreatic, or high grade prostate cancer	Breast cancer diagnosed at any age, with ≥ 1 close relative with breast cancer \leq age 50, or ovarian, pancreatic, or metastatic prostate cancer
Male breast cancer at any age	Pancreatic cancer at any age
Triple negative breast cancer diagnosed ≤ 60	Metastatic prostate cancer at any age
Breast, ovarian, or pancreatic cancer at any age; and Ashkenazi Jewish ancestry	A first or second degree relative meeting any of the criteria in this table

RECOMMENDATIONS

NCCN Guidelines provide clinical management recommendations. The most current guidelines may be found at NCCN.org. Modification of surveillance, including initiation of earlier and/or more frequent screening, may be based on guidelines and a patient's personal and/or family history for specific associated cancers.

Genetic counseling is recommended to discuss the potential clinical and/or reproductive implications of these results, as well as recommendations for testing family members. There is a 50% chance (1 in 2) of a first-degree relative having this variant. To access Integrated Genetics' Genetic Counselors please visit www.integratedgenetics.com/genetic-counseling or call (855) GC-CALLS (855-422-2557). To discuss targeted analysis for other family members with a Labcorp Genetic Coordinator please call 800-345-4363.

COMMENTS

The three Ashkenazi Jewish founder variants, *BRCA1* c.68_69delAG, *BRCA1* c.5266dupC and *BRCA2* c.5946delT, are also known by their legacy names: *BRCA1* 187delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT, respectively.

METHODS AND LIMITATIONS

Next-generation sequencing: Genomic regions of interest are selected using a custom capture reagent for target enrichment and sequenced via the Illumina(R) next generation sequencing platform. Regions of interest include all exons and intron/exon junctions (+/-20 nucleotides) of the *BRCA1* (NM_007294.3) and *BRCA2* (NM_000059.3) genes. Sequencing reads are aligned with the human genome reference GRCh37/hg19 build. Minimum mean coverage is 40X. Any segment failing minimum read depth coverage is rescued by bi-directional Sanger sequencing to complete sequence analysis. Variants, including SNVs and CNVs, are identified using a custom bioinformatics pipeline.

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METHODS AND LIMITATIONS

Reported variants: Pathogenic and likely pathogenic variants and variants of uncertain significance (VUS) are reported. Non-deletion variants are specified using the numbering and nomenclature recommended by the Human Genome Variation Society (HGVS, <http://www.hgvs.org/>). Benign variants are not reported. Variant classification and confirmation are consistent with ACMG standards and guidelines (Richards, PMID:25741868; Rehm, PMID:23887774). Detailed variant classification information is available upon request. A variant of uncertain significance (VUS) should not be used in clinical decision making; a VUS is classified based on inadequate or conflicting evidence regarding its pathogenicity or clinical relevance.

Limitations: Technologies used do not detect germline mosaicism and do not rule out the presence of large chromosomal aberrations, including rearrangements, gene fusions, or variants in regions or genes not included in this test, or possible inter/ intragenic interactions between variants. Variant classification and/or interpretation may change over time if more information becomes available. False positive or false negative results may occur for reasons that include: genetic variants, pseudogene interference, technical handling, blood transfusions, bone marrow transplantation, mislabeling of samples, or erroneous representation of family relationships. For heterozygous variants in the same gene the assay cannot determine whether they are on the same or a different chromosomes; to determine phase and clinical significance, rarely, parental testing may be required. Exact breakpoints of exon-level deletions/duplications are not determined. The presence of an inherited cancer syndrome due to a different genetic cause cannot be ruled out. Any interpretation should be clinically correlated with information about the patient's presentation and relevant family history.

REFERENCES

1. NCCN Genetic/Familial High Risk Assessment: Breast, Ovarian, and Pancreatic. Version 1.2020.
2. Petrucelli, et al. *BRCA1*- and *BRCA2*-Associated Hereditary Breast and Ovarian Cancer. GeneReviews, updated 2016. PMID: 20301425.

This test was developed and its performance characteristics determined by LabCorp. It has not been cleared or approved by the Food and Drug Administration.

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