Helix

THIS IS A DIAGNOSTIC TEST

Helix Hereditary Breast and Gynecologic Cancers Panel

Patient Name: Jane Doe	Patient ID: 96138	Provider Name: Client Client	Order Date: 06-05-2024
Date of Birth: 01-01-1990	Helix ID: THelixId705	Collection Date: 06-05-2024	Report Date: 11-10-2025

Results POSITIVE

Classification	Gene	DNA Change	Protein Change	Zygosity	Inheritance
PATHOGENIC	BRCA1	c.3598C>T	p.Gln1200Ter	Heterozygous	AD

One Pathogenic variant was detected in the BRCA1 gene.

These results indicate a predisposition to, or diagnosis of, autosomal dominant hereditary breast and ovarian cancer syndrome. These results also indicate carrier status for autosomal recessive Fanconi anemia.

The BRCA1 gene is associated with the following condition(s):
- autosomal dominant hereditary breast and ovarian cancer (HBOC) syndrome (HBOC) (MedGen UID: 382914)
- autosomal recessive Fanconi anemia, type S (FA) (MedGen UID: 1632414)

Having one pathogenic variant in the BRCA1 gene is associated with autosomal dominant HBOC, an adult-onset condition that causes an increased risk of certain cancers, particularly breast and ovarian in females, although affected males have cancer risks as well.
- BRCA1-associated cancer risks include: breast cancer, 53-72% lifetime risk in biological females; contralateral breast cancer (the chance of later developing breast cancer in their other breast) within 10 years after the first diagnosis, 21-43% risk; male breast cancer, 0.4-1% lifetime risk; ovarian or fallopian tube cancer, 39-59% lifetime risk in biological females; pancreatic cancer, 3% lifetime risk; there may be an increased risk for other cancers including prostate and uterine; however, these associations are unclear.

Having two pathogenic variants in BRCA1, one in each copy of the gene, is associated with autosomal recessive FA. FA is a rare, childhood-onset condition that affects various parts of the body with symptoms including short stature, a small head size (microcephaly), developmental delay, abnormal skin pigmentation, scoliosis, abnormally formed bones, and frequent infections due to a weakened immune system. There is also significant impact to the bone marrow's ability to form blood cells including platelets leading to fatigue and easy bruising and bleeding in addition to an increased risk of blood cancer (acute myeloid leukemia) and malignant solid tumors of the head and neck, skin, and genitourinary tract.

The age of onset, severity, and types of symptoms associated with BRCA1-associated conditions can vary widely, even among affected individuals from the same family.

MEDICAL MANAGEMENT recommendations and/or guidelines are available for BRCA1-related condition(s): https://www.nccn.org/ , PMID: 36485157, https://www.fanconi.org/images/uploads/other/Fanconi_Anemia_Clinical_Care_Guidelines_5thEdition_web.pdf
REFERENCES: PMID: 33471974, 33471991, 28632866, 26700119, 15197194, 20204502, 32676552, 18042939, 35077220, 12677558, 23628597, 31495749, 28954295, 25224030

Biological family members may be at risk for developing autosomal dominant hereditary breast and ovarian cancer syndrome and are at risk for, or may be carriers of, autosomal recessive Fanconi anemia.

The Variant Interpretation section below may provide additional details regarding the reported variant(s). Genetic test results should be interpreted in the context of an individual's personal medical and family history. It is important to note that this assay cannot detect all variants known to increase disease risk. Genetic counseling is recommended. Clinical correlation is advised.

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Test Description

This panel evaluates 21 genes that have an established, primary association with hereditary breast and/or gynecologic cancers (ovarian and uterine).

Genes Tested

ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, DICER1, EPCAM, MLH1, MSH2, MSH6, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, SMARCA4, STK11, TP53

Classification	Gene	DNA Change	Protein Change	Zygosity	Inheritance
PATHOGENIC	BRCA1	c.3598C>T	p.Gln1200Ter	Heterozygous	AD

Transcript:	Genomic Change:
NM_007294.4	NC_000017.11:g.43091933G>A

Variant Interpretation

This variant (NM_007294.4:c.3598C>T p.Gln1200Ter) results in the creation of a premature stop codon in the BRCA1 gene. It is predicted to result in nonsense-mediated mRNA decay or in the production of a truncated protein, leading to loss-of-function (LOF). LOF variants in this gene are known to be deleterious (PMID: 20104584, 20301575). It is present in the gnomAD population database (v4.1, https://gnomad.broadinstitute.org) at the highest allele frequency in the South Asian subpopulation among non-founder subpopulations (1/91078 alleles, 0.0011%). This variant has been observed in individual(s) with a personal and/or family history of BRCA1-related conditions (PMID: 9452076, 12181777, 15955237, 16162645, 18159056, 22006311, 22711857, 25371446, 25682074, 33606809). An analysis of the personal and family history of cancer of 6 probands supports that this variant is deleterious (PMID: 31853058). This variant is present in ClinVar (Variation ID: 54929). In conclusion, this variant has been classified as Pathogenic.

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Methods & Limitations

Extracted DNA is enriched for targeted regions and then sequenced using the Helix Exome+ (R) assay on an Illumina DNA sequencing system. Data is then aligned to a modified version of GRCh38 and all genes are analyzed using the MANE transcript and MANE Plus Clinical transcript, when available. Small variant calling is completed using a customized version of Sentieon's DNAseq software, augmented by a proprietary small variant caller for difficult variants. Copy number variants (CNVs) are then called using a proprietary bioinformatics pipeline based on depth analysis with a comparison to similarly sequenced samples. Reportable variants in PMS2 exons 11-15 are confirmed by PacBio long reads. Both the MSH2 Boland inversion (exons 1-7) and the BRCA2 Alu insertion are detected by identifying discordant read-pairs spanning the breakpoints. Interpretation is based upon guidelines published by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) or their modification by ClinGen Variant Curation Expert Panels when available. Interpretation is limited to the transcripts indicated on the report, +/- 10 bp into intronic regions, except as noted below. Helix variant classifications include pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign. Variants classified as pathogenic, likely pathogenic, or VUS are included in the report. All reported variants (except for VUSs with limited evidence of pathogenicity) are confirmed through secondary manual inspection of DNA sequence data or orthogonal testing. Benign and likely benign variants are not reported but are available upon request. Risk estimations and management guidelines included in this report are based on analysis of primary literature and recommendations of applicable professional societies, and should be regarded as approximations.

Based on validation studies, this assay delivers > 99% sensitivity and specificity for single nucleotide variants and insertions and deletions (indels) up to 20 bp. Larger indels and complex variants are also reported but sensitivity may be reduced. Based on validation studies, this assay delivers > 99% sensitivity to multi-exon CNVs and > 90% sensitivity to single-exon CNVs. This test may not detect variants in challenging regions (such as short tandem repeats, homopolymer runs, and segment duplications), sub-exonic CNVs, chromosomal aneuploidy, or variants in the presence of mosaicism. Phasing will be attempted and reported, when possible. Structural rearrangements such as inversions, translocations, complex rearrangements, and gene conversions are not tested in this assay unless explicitly indicated. Additionally, deep intronic, promoter, and enhancer regions may not be covered. It is important to note that this assay cannot detect all variants known to increase disease risk, and that a negative result does not guarantee that the tested individual does not carry a rare, undetectable variant in genes analyzed. Any potential incidental findings outside of these genes and conditions will not be identified, nor reported. The results of a genetic test may be influenced by various factors, including bone marrow transplantation, blood transfusions, or in rare cases, hematolymphoid neoplasms.

Gene Specific Notes:
BRCA1: sequencing analysis extends to CDS +/-20 bp; BRCA2: analysis includes detection of c.156_157insAlu and sequencing analysis extends to CDS +/-20 bp; EPCAM: analysis is limited to CNV of exons 8-9; MLH1: analysis includes CNV of the promoter; MSH2: analysis includes detection of the Boland inversion (inversion of exons 1-7) and detection of NM_000251.3(MSH2):c.942+3A>T; PTEN: analysis includes CNV of the promoter; STK11: sensitivity of exon 3 analysis may be reduced; TP53: analysis includes CNV of the promoter.

Disclaimer

This test was developed and validated by Helix, Inc. This test has not been cleared or approved by the United States Food and Drug Administration (FDA). The Helix laboratory is accredited by the College of American Pathologists (CAP) and certified under the Clinical Laboratory Improvement Amendments (CLIA #: 05D2117342) to perform high-complexity clinical tests. This test is used for clinical purposes. It should not be regarded as investigational use only or for research use only.

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Reports Signed By

Matt Ferber, Ph.D. FACMGG

Helix's Sequence Once, Query Often® Model

When your provider orders a genetic test through Helix, we use our proprietary Sequence Once, Query Often®model to perform whole exome sequencing and analyze the specific genes related to the test. Helix securely stores your whole exome for future clinical use. With your permission, this allows your health care providers to order future medically necessary genetic tests from Helix without needing another sample. Instead, these tests are conducted through digital analysis of your stored genetic information.

To learn more about how Helix protects the privacy and security of your genetic information and learn more about your rights, please visit https://www.helix.com/privacy-and-policy-highlights

SAMPLE