Helix THIS IS A SCREENING TEST

Helix Tier One Population Screen

Patient Name: Jane Doe	**Patient ID:** 0123456	**Collection Date:** 02-01-2024
Date of Birth: 02-20-1985	**Helix ID:** TST12345	**Order Date:** 02-01-2024
Sex Assigned at Birth: FEMALE	**Provider Name:** Client Client	**Report Date:** 02-17-2024
Specimen Type: WHOLE BLOOD	**Provider Address:** -	

Results POSITIVE

Classification	Gene	DNA Change	Protein Change	Zygosity	Inheritance
PATHOGENIC	BRCA1	c.5266dupC	p.Gln1756ProfsTer74	Heterozygous	AD, AR

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; contralteral 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.

Genetic test results should be interpreted in the context of an individual's personal medical and family history. Genetic counseling is recommended. It is important to note that this assay cannot detect all variants known to increase disease risk. Clinical correlation is advised.

Additional Considerations

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- This is a screening test; it is not intended to diagnose a condition, determine medical treatment, or provide information regarding an individual's current health status.
- The absence of pathogenic or likely pathogenic variant(s) in the analyzed genes, while reassuring, does not eliminate the possibility of a hereditary condition; there are other variants and genes associated with heart disease and hereditary cancer that are not included in this test.
- For individuals at significant risk for carrying a pathogenic variant(s) associated with these or other related conditions, diagnostic testing is recommended.

Test Description

Helix Tier One Population Screen is a screening test that analyzes 11 genes related to hereditary breast and ovarian cancer (HBOC) syndrome, Lynch syndrome, and familial hypercholesterolemia. This test only reports clinically significant pathogenic and likely pathogenic variants, unlike diagnostic testing, which also reports variants of uncertain significance (VUS). In addition, analysis of the PMS2 gene excludes exons 11-15, which overlap with a known pseudogene (PMS2CL).

Genes Tested

BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, EPCAM, APOB, LDLR, LDLRAP1, PCSK9

Classification	Gene	DNA Change	Protein Change	Zygosity	Inheritance
PATHOGENIC	BRCA1	c.5266dupC	p.Gln1756ProfsTer74	Heterozygous	AD, AR

Transcript: NM_007294.4 Genomic Change: NC_000017.11:g.43057065dup

Variant Interpretation

This variant (NM_007294.4:c.5266dupC, NC_000017.11:g.43057065dup) results in a frameshift (p.Gln1756ProfsTer74), which creates a premature stop codon in the *BRCA1* gene.
This variant is not expected to cause mRNA nonsense-mediated decay, but it is expected to result in the production of a truncated protein.
It is also known as 5382insC and 5385insC.
It is present in the non-cancer cohort of the gnomAD population database (PMID: 32461654) at the highest allele frequency in the European (non-Finnish) subpopulation among non-founder subpopulations (12/102752 alleles, 0.0117%).
This variant has been observed in numerous individuals affected with hereditary breast and ovarian cancer (HBOC) syndrome (PMID: 22430266, 24312913, 29446198, 33471991). In a large, multi-ethnic, case-control cohort, this variant was found in 97/60466 breast cancer cases and 11/53461 unaffected controls (PMID:33471991). It is one of the most frequently reported pathogenic variants in BRCA1 and a founder variant in the Ashkenazi Jewish population and other European populations (PMID: 20301425, 24312913, 29446198).
Functional studies suggest that this variant may affect protein function (PMID: 32546644).
The most relevant articles have been cited but this list is not exhaustive.
Clinical laboratory interpretations available in ClinVar are in broad agreement that this variant is pathogenic (Variation ID: 17677).
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. Analysis of the PMS2 gene is limited to exons 1-10; exons 11-15. The interpretation and reporting of variants in APOB, PCSK9, and LDLR is specific to familial hypercholesterolemia; variants associated with hypobetalipoproteinemia are not included. 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 and +/- 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. Only variants classified as pathogenic and likely pathogenic are included in the report. All reported variants are confirmed through secondary manual inspection of DNA sequence data or orthogonal testing. 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, 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 is a screening test and cannot detect all disease-causing variants. A negative result does not guarantee the absence of a rare, undetectable variant in the genes analyzed; consider using a diagnostic test if there is significant personal and/or family history of one of the conditions analyzed by this test. 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: sequencing analysis extends to CDS +/-20 bp. EPCAM: analysis is limited to CNV of exons 8-9; MLH1: 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 or for research.

Reports Signed By

Philip D Cotter, PhD, FACMG, FFSC (RCPA)

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Helix's Sequence Once, Query Often® Model

When your provider first orders a genetic test through Helix, Helix leverages its proprietary Sequence Once, Query Often® model to perform whole exome sequencing and interpret the specific genes related to the test being ordered. Helix will then continue to store your genetic information for future clinical use. This means that, with your permission, your health care providers can order future medically necessary genetic tests from Helix without the need for you to submit another sample in most cases. Instead, future tests will be performed through digital analysis of your genetic information that is stored by Helix.

When you receive a genetic test performed by Helix, you are in control of how and when your genetic information is used. To manage your genetic information and understand your rights, please visit https://www.helix.com/privacy-and-policy-highlights.