Helix THIS IS A DIAGNOSTIC TEST

Helix Hereditary Multi-Cancer Panel

Patient Name: Jane Doe	**Patient ID:** 0123456	**Collection Date:** 12-20-2024
Date of Birth: 02-20-1975	**Helix ID:** TST12345	**Order Date:** 12-20-2024
Sex Assigned at Birth: FEMALE	**Provider Name:** Client Client	**Report Date:** 01-03-2025
Specimen Type: WHOLE BLOOD	**Provider Address:** -	

Results POSITIVE

Classific tion	Gene	DNA Change	Protein Change	Zygosity	Inheritance
PATHOGENIC	BRCA2	c.5303_5304del	p.Leu1768ArgfsTer5	Heterozygous	AD

One Pathogenic variant was detected in the BRCA2 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 BRCA2 gene is associated with the following condition(s):
- autosomal dominant hereditary breast and ovarian cancer syndrome (HBOC) (MedGen UID: 382625)
- autosomal recessive Fanconi anemia, type D1 (FA) (MedGen UID: 325420)

Having one pathogenic variant in the BRCA2 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 affec ed males have cancer risks as well.
- BRCA2-associated cancer risks include: breast cancer, 44-61% 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, 11 35%; male breast cancer, 4-7% risk; ovarian or fallopian tube cancer, 11-20% lifetime risk in biological females; pancreatic cancer, 4-6% lifetime risk; prostate cancer, 28% lifetime risk in biological males; it is unclear whether lifetime risk is significantly increased above the general population for skin cancer (melanoma).

Having two pathogenic variants in BRCA2, 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 BRCA2-associated conditions can vary widely, even among affected individuals from the same family.

MEDICAL MANAGEMENT recommendations and/or guidelines are available for BRCA2-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: 32676552, 33471974, 33471991, 26700119, 20204502, 15197194, 18042939, 35077220, 25849179, 28632866, 23099806, 30900310, 31495749, 25524463

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 70 genes associated with hereditary cancer conditions that predispose to a variety of primarily adult-onset solid tumors across many organ systems including: breast, gynecologic (ovarian and uterine), colorectal, pancreatic, prostate, kidney, skin, brain and nervous system, and endocrine glands (adrenal, pituitary, parathyroid, thyroid).

Genes Tested

AIP, ALK, APC, ATM, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN1B, CDKN2A, CHEK2, CTNNA1, DICER1, EGFR, EPCAM, FH, FLCN, GREM1, HOXB13, KIT, LZTR1, MAX, MBD4, MEN1, MET, MITF, MLH1, MSH2, MSH3, MSH6, MUTYH, NF1, NF2, NTHL1, PALB2, PDGFRA, PMS2, POLD1, POLE, POT1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL

Classific tion	Gene	DNA Change	Protein Change	Zygosity	Inheritance
PATHOGENIC	**BRCA2**	**c.5303_5304del**	**p.Leu1768ArgfsTer5**	**Heterozygous**	**AD**

Transcript:	Genomic Change:
NM_000059.4	**NC_000013.11:g.32339658_32339659del**

Variant Interpretation

This variant (NM_000059.4:c.5303_5304del p.Leu1768ArgfsTer5) results in a frameshift, which creates a premature stop codon in the BRCA2 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). This variant is also known as 5531delTT. It is a rare variant that is absent from the non-cancer cohort of the large gnomAD population database (PMID: 32461654). This variant has been observed in individual(s) with BRCA2-related cancers (PMID: 21895635, 34399810, 36169650, 35264596). Clinical laboratory interpretations available in ClinVar are in broad agreement that this variant is pathogenic (ClinVar Variation ID: 37957). The most relevant articles have been cited but the list is not exhaustive. 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 difficul 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 12-15 are confirmed b PacBio long reads. The MSH2 Boland inversion (exons 1-7) is detected by identifying discordant read-pairs spanning the presumed breakpoint. 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 modific tion 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 classific tions include pathogenic, likely pathogenic, variant of uncertain significan e (VUS), likely benign, and benign. Variants classifie as pathogenic, likely pathogenic, or VUS are included in the report. All reported variants (except for VUSs with limited evidence of pathogenicity) are confirmed th ough 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 specifici y 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 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 onditions will not be identified, no 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 No es:
APC: analysis includes CNV of promoters 1A and 1B and sequencing of promoter 1B; BMPR1A: analysis includes CNV of promoter; BRCA1: sequencing analysis extends to CDS +/-20 bp; BRCA2: sequencing analysis extends to CDS +/-20 bp. CDKN2A: analysis includes sequencing of the p16 (p16INK4a) and p14 (p14ARF) transcripts; EGFR: analysis is limited to the NM_005228(EGFR):c.2369C>T (p.Thr790Met) variant; EPCAM: analysis is limited to CNV of exons 8-9; GREM1: analysis is limited to CNV of the promoter; HOXB13: analysis is limited to the NM_006361.6(HOXB13):c.251G>A (p.Gly84Glu) variant; MITF: analysis is limited to the NM_000248.4(MITF):c.952G>A (p.Glu318Lys) variant; 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; MSH3: analysis excludes sequencing of exon 1 repeat region (chr5:80654878-80654946); POLD1: CNV analysis is not performed and sequencing is limited to the 3'-5' exonuclease domain (chr19:50402681-50407039); POLE: CNV analysis is not performed and sequencing is limited to the 3'-5' exonuclease domain (chr12:132676653-132672296); PTCH1: sensitivity of exon 1 analysis may be reduced; PTEN: analysis includes CNV of the promoter; SDHA: analysis excludes CNV; STK11: sensitivity of exon 3 analysis may be reduced; TP53: analysis includes CNV of the promoter; TSC1: sensitivity of exon 21 analysis may be reduced; VHL: analysis excludes coverage of the cryptic E1' exon (chr3:10142758-10143009)

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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)

Helix's Sequence Once, Query Often ® Model

When your provider rst 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 elated 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.