Helix THIS IS A DIAGNOSTIC TEST

Helix Hereditary Breast and Gynecologic Cancers Panel

Patient Name: JOHN DOE	**Patient ID:** 0123456	**Collection Date:** 06-03-2024
Date of Birth: 02-20-1992	**Helix ID:** TEST1234	**Order Date:** 06-03-2024
Sex Assigned at Birth: MALE	**Provider Name:** CLIENT CLIENT	**Report Date:** 06-06-2024
Specimen Type: WHOLE BLOOD	**Provider Address:** -	

Results POSITIVE

Classification	Gene	DNA Change	Protein Change	Zygosity	Inheritance
PATHOGENIC	MSH2	c.1165C>T	p.Arg389Ter	Homozygous	AD

These results indicate a predisposition to, or diagnosis of autosomal dominant *MSH2*-related conditions. These results also indicate carrier status for autosomal-recessive *MSH2*-related conditions.

The *MSH2* gene is associated with the following condition(s):
- autosomal dominant Lynch syndrome (MedGen UID: 423615)
- autosomal recessive constitutional mismatch repair defciency syndrome (CMMRD) (MedGen UID: 1750327)

Having one pathogenic variant in the *MSH2* gene is associated with autosomal dominant Lynch syndrome, an adult-onset condition that causes an increased risk of certain cancers, particularly colorectal and other gastrointestinal cancer as well as cancer of the reproductive organs.
- *MSH2*-associated cancer risks include: colorectal cancer, 43-56% risk; stomach cancer, 4-9% risk; small bowel cancer, 3-7% risk; cancer of the biliary tract (including bile duct and gallbladder), 2-5% risk; urinary tract cancer, 16-20% risk; bladder cancer, 9-13% risk; pancreatic cancer, 3-4% risk; brain cancer, 2-7% risk; uterine cancer, 44% risk in biological females; ovarian cancer, 13% risk in biological females; prostate cancer, 24% risk in biological males; it is unclear whether lifetime risk is significantly increased above the general population for certain types of skin findings such as sebaceous adenomas, sebaceous adenocarcinomas, and keratoacanthomas.

Having two pathogenic variants in *MSH2*, one on each copy of the gene, is associated with autosomal recessive CMMRD. This condition is characterized by an increased risk of various cancers including blood cancers, brain and other central nervous system cancers, and Lynch syndrome-associated cancers (colon, stomach, and endometrial cancer) that typically develop in childhood and early adulthood. Individuals with CMMRD often have characteristic patches of coffee-colored skin (cafe-au-lait spots) that are noncancerous.

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

MEDICAL MANAGEMENT recommendations and/or guidelines are available for *MSH2*-related condition(s): https://www.nccn.org/, PMID: 32613597
REFERENCES: PMID: 18398828, 19900449, 37181409

Biological family members may be at risk for developing autosomal dominant *MSH2*-related condition(s) and are at risk for, or may be carriers of, autosomal recessive *MSH2*-related conditions.

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.

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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	MSH2	c.1165C>T	p.Arg389Ter	Homozygous	AD

Transcript: NM_000251.3 Genomic Change: NC_000002.12:g.47429830C>T

Variant Interpretation

This variant (NM_000251.3:c.1165C>T, NC_000002.12:g.47429830C>T) results in the substitution of arginine for a nonsense codon (p.Arg389Ter), which creates a premature stop codon in the *MSH2* gene.

This variant is expected to result in the production of a truncated protein or mRNA nonsense-mediated decay resulting in loss of function, which is an established disease mechanism for the *MSH2* gene (PMID: 15849733, 24362816).

It is a rare variant that is absent from the large gnomAD population database (PMID: 32461654).

This variant has been observed in several individuals affected with clinical features of autosomal dominant *MSH2*-related conditions (PMID: 15235030, 25117503).

The most relevant articles have been cited but the list is not exhaustive.

Clinical laboratory interpretations available in ClinVar are in broad agreement that this variant is Pathogenic (ClinVar Variation ID: 90557).

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 12-15 are confirmed by 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 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, 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: 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 or for research.

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Reports Signed By

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

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.