Helix THIS IS A SCREENING TEST

Helix Hereditary Cancer Screen

Patient Name: Client Client	**Patient ID:** 0123456	**Collection Date:** 02-01-2024
Date of Birth: 01-01-1990	**Helix ID:** TEST12345	**Order Date:** 02-01-2024
Sex Assigned at Birth: MALE	**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	LDLR	c.1747C>T	p.His583Tyr	Heterozygous	AD

One Pathogenic variant was detected in the LDLR gene.
These results indicate a predisposition to, or diagnosis of, familial hypercholesterolemia.

The LDLR gene is associated with the following condition(s):
- familial hypercholesterolemia (FH) (MedGen UID: 152875)

FH is an adult-onset condition characterized by elevated cholesterol in the blood, which may form blockages (plaques) that increase the risks of chest pain (angina), heart attack, and stroke. Affected individuals may have deposits of cholesterol in the tendons (xanthomas), around the eyelids (xanthelasmas) and colored part of the eyes (irides). Having two pathogenic variants in LDLR, one in each copy of the gene, is also associated with FH, but symptoms are much more severe and present at an earlier age.

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

MEDICAL MANAGEMENT recommendations and/or guidelines are available for LDLR-related conditions: PMID: 31838973, 35466160

Biological family members may be at risk for developing familial hypercholesterolemia.

Genetic test results should be interpreted in the context of an individual's personal medical and family history. Genetic counseling is recommended. Clinical correlation is advised.

Additional Considerations
- This is a screening test; individuals may still carry pathogenic or likely pathogenic variant(s) in the tested genes that are not detected by this test.
- For individuals at risk for these or other related conditions based on factors including personal or family history, diagnostic testing is recommended.
- The Variant Interpretation section below may provide additional details regarding the reported variant(s).
- The absence of pathogenic or likely pathogenic variant(s) in any of the other 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.

Test Description

Helix Hereditary Cancer Screen is a screening test that analyzes 48 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), prostate, and those in the gastrointestinal system. This test only reports clinically significant pathogenic and likely pathogenic variants but does not report variants of uncertain significance (VUS).

Helix THIS IS A SCREENING TEST

Helix Hereditary Cancer Screen

Patient Name: Client Client	**Patient ID:** 0123456	**Collection Date:** 02-01-2024
Date of Birth: 01-01-1990	**Helix ID:** TEST12345	**Order Date:** 02-01-2024
Sex Assigned at Birth: MALE	**Provider Name:** Client Client	**Report Date:** 02-17-2024
Specimen Type: WHOLE BLOOD	**Provider Address:** -	

Genes Tested

APC, ATM, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, CTNNA1, DICER1, EPCAM, FH, GREM1, HOXB13, KIT, MBD4, MEN1, MLH1, MSH2, MSH3, MSH6, MUTYH, NF1, NTHL1, PALB2, PDGFRA, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SDHA, SDHB, SDHC, SDHD, SMAD4, SMARCA4, STK11, TP53, TSC1, TSC2, VHL

Classific tion	Gene	DNA Change	Protein Change	Zygosity	Inheritance
PATHOGENIC	LDLR	c.1747C>T	p.His583Tyr	Heterozygous	AD

Transcript:	Genomic Change:
NM_000527.5	NC_000019.10:g.11116900C>T

Variant Interpretation

This variant (NM_000527.5:c.1747C>T p.His583Tyr, NC_000019.10:g.11116900C>T) results in the substitution of histidine with tyrosine at codon 583 in the LDLR protein. This variant is also known as His562Tyr. It is present in the gnomAD population database (PMID: 32461654) at the highest allele frequency in the East Asian subpopulation (24/19952 alleles, 0.12%). It is a founder variant in the East Asian subpopulation (PMID: 22353362, 26608663, 33746137). This variant has been observed in numerous individuals affec ed with clinical features of familial hypercholesterolemia (PMID: 7903864, 22353362, 23155708, 26608663, 27206935, 33746137, 35741760). Functional studies suggest that this variant may affect protein function (PMID: 7903864, 15741231, 21511053, 32695144). 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: 200921). In conclusion, this variant has been classified as Pathogenic.

Patient Name: Client Client
Date of Birth: 01-01-1990
Sex Assigned at Birth: MALE
Specimen Type: WHOLE BLOOD

Patient ID: 0123456
Helix ID: TEST12345
Provider Name: Client Client
Provider Address: -

Collection Date: 02-01-2024
Order Date: 02-01-2024
Report Date: 02-17-2024

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. Interpretation is based upon guidelines published by the American College of Medical Genetics and Genomics (ACMG), the Association for Molecular Pathology (AMP) or their modification by ClinGen Variant Curation Expert Panels when available and/or review of previous clinical assertions available in the ClinVar database. 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:

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; 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 c.251G>A (p.Gly84Glu) variant; MLH1: analysis includes CNV of the promoter; MSH2: analysis includes detection of the Boland inversion (inversion of exons 1-7) and detection of c.942+3A>T; MSH3: analysis excludes sequencing of exon 1 repeat region (chr5:80654878-80654946); PMS2: analysis is limited to exons 1-10;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); 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)

Helix Hereditary Cancer Screen

Patient Name: Client Client	**Patient ID:** 0123456	**Collection Date:** 02-01-2024
Date of Birth: 01-01-1990	**Helix ID:** TEST12345	**Order Date:** 02-01-2024
Sex Assigned at Birth: MALE	**Provider Name:** Client Client	**Report Date:** 02-17-2024
Specimen Type: WHOLE BLOOD	**Provider Address:** -	

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 certifie 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 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 elated 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