

Helix Hereditary Actionable Disorders Screen

Patient Name: Jane Doe	Specimen Type: WHOLE BLOOD	Provider Name: Client Client	Report Date: 06-15-2025
Date of Birth: 01-01-1990	Patient ID: 123456	Collection Date: 06-10-2025	
Sex Assigned at Birth: Female	Helix ID: Test12345	Order Date: 06-15-2025	

Results NEGATIVE

No pathogenic or likely pathogenic variants were detected in the genes analyzed by this test.

Genetic test results should be interpreted in the context of an individual's personal medical and family history. Alteration to medical management is NOT recommended based solely on this result. 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 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.

Test Description

Helix Hereditary Actionable Disorders Screen is a screening test that analyzes 86 genes related to hereditary predisposition to cancer, cardiac disease, metabolic disorders, muscular disorders, and blood clotting disorders; analysis of the PMS2 gene excludes exons 11-15, which overlap with a known pseudogene (PMS2CL) and analysis of the F2, F5, HFE, and SERPINA1 genes is limited to specific targeted variants. This test only reports clinically significant pathogenic and likely pathogenic variants but does not report variants of uncertain significance (VUS).

Genes Tested

ACTA2, ACTC1, ACVRL1, APC, APOB, ATP7B, BAG3, BMPRI1, BRCA1, BRCA2, BTD, CACNA1S, CALM1, CALM2, CALM3, CASQ2, COL3A1, DES, DSC2, DSG2, DSP, ENG, EPCAM, F2, F5, FBN1, FLNC, GAA, GLA, HFE, HNF1A, KCNH2, KCNQ1, LDLR, LDLRAP1, LMNA, MAX, MEN1, MLH1, MSH2, MSH6, MUTYH, MYBPC3, MYH7, MYH11, MYL2, MYL3, NF2, OTC, PALB2, PCSK9, PKP2, PMS2, PRKAG2, PTEN, RB1, RBM20, RET, RPE65, RYR1, RYR2, SCN5A, SDHAF2, SDHB, SDHC, SDHD, SERPINA1, SMAD3, SMAD4, STK11, TGFBRI, TGFBRI2, TMEM127, TMEM43, TNNC1, TNNI3, TNNT2, TP53, TPM1, TRDN, TSC1, TSC2, TTN, TTR, VHL, WT1

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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. 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), 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; APOB: analysis is limited to c.10580G>A and c.10579C>T; BMPR1A: analysis includes CNV of promoter; 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; F2: analysis is limited to c.*97G>A; F5: analysis is limited to c.1601G>A (p.Arg534Gln); HFE: Analysis is limited to c.845G>A (p.Cys282Tyr) and c.187C>G (p.His63Asp); KCNQ1: Sensitivity in KCNQ1 exon 1 may be reduced; LDLR: analysis includes CNV of the promoter; 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; PMS2: analysis is limited to exons 1-10; PTEN: analysis includes CNV of the promoter; SERPINA1: analysis is limited to c.1096G>A and c.863A>T; STK11: Sensitivity in STK11 exon 3 may be reduced; TP53: analysis includes CNV of the promoter; TSC1: Sensitivity in TSC1 exon 21 may be reduced; TTN: analysis is limited to exons 1-10, 14-44, 47, 49-50, 101, 104-114, 220-224, 226-242, and 244-363; 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

Celina Andrade

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>