Helix Hereditary Actionable Disorders Panel

Item	Description
Test Name	Helix Hereditary Actionable Disorders Panel
Test Type	Screening
Catalog Number	HADP1
Procedure Code	H00224-4
Test Description	Helix Hereditary Actionable Disorders Panel is a screening test that analyzes genes related to hereditary predisposition to oncology, cardiology, metabolic, muscular and blood clottting disorders. This test only reports clinically significant pathogenic and likely pathogenic variants but does not report variants of uncertain significance (VUS).
Genes Tested	ACTC1 APC APOB BAG3 BMPR1A BRCA1 BRCA2 CALM1 CALM2 CALM3 CASQ2 DES DSC2 DSG2 DSP EPCAM F2 F5 FLNC GAA GLA HFE KCNH2 KCNQ1 LDLR LDLRAP1 LMNA MAX MEN1 MLH1 MSH2 MSH6 MUTYH MYBPC3 MYH7 MYL2 MYL3 NF2 PALB2 PCSK9 PKP2 PMS2 PRKAG2 PTEN RB1 RBM20 RET RYR2 SCN5A SDHAF2 SDHB SDHC SDHD SERPINA1 SMAD4 STK11 TMEM127 TMEM43 TNNC1 TNNI3 TNNT2 TP53 TPM1 TRDN TSC1 TSC2 TTN TTR VHL
Genetics Information	This test utilizes next-generation sequencing to detect single nucleotide variants, insertions and deletions up to 20 bp, and copy number variants for most genes on this panel; 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, unlike diagnostic testing, which also reports variants of uncertain significance (VUS).
Clinical Use	The genes included in this screening test have established medical management interventions that may prevent disease and/or significantly reduce morbidity and mortality. This is a screening test and therefore is not recommended for individuals with a personal and/or family history suggestive of one of the associated conditions; in such instances, a diagnostic test is appropriate and should be discussed with a healthcare provider.
Clinical Descriptions	Hereditary Actionable Disorders Panel Screen analyzes 69 genes related to hereditary predisposition to oncology, cardiology, metabolic, muscular and blood clottting disorders. See condition list below.
Conditions	HEREDITARY ONCOLOGY CONDITIONS Familial adenomatous polyposis (APC) Lynch syndrome (EPCAM, MLH1, MSH2, MSH6, PMS2) Juvenile polyposis syndrome (BMPR1A, SMAD4) Hereditary breast and ovarian cancer syndrome (BRCA1, BRCA2) Tuberous sclerosis complex (TSC1, TSC2) Hereditary paraganglioma-pheochromocytoma syndrome (MAX, SDHAF2, SDHB, SDHC, SDHD, TMEM127) Multiple endocrine neoplasia type 1 (MEN1) MUTYH-assoc. polyposis (MUTYH) NF2-related schwannomatosis (NF2) PTEN hamartoma tumor syndrome (PTEN) Retinoblastoma (RB1) Familial medullary thyroid carcinoma (RET) Multiple endocrine neoplasia type 2 (RET) Peutz-Jeghers syndrome (STK11) Li-Fraumeni syndrome (TP53) PALB2-related cancer susceptibility (PALB2) von Hippel-Lindau syndrome (VHL) HEREDITARY CARDIOLOGY CONDITIONS Familial hypercholesterolemia (APOB, LDLR, LDLRAP1, PCSK9) Long QT syndrome (CALM1, CALM2, CALM3, KCNH2, KCNQ1, SCN5A, TRDN) Short QT syndrome (KCNH2, KCNQ1) Catecholaminergic polymorphic ventricular tachycardia (CASQ2, TRDN, RYR2) Arrhythmogenic right ventricular cardiomyopathy (DES, DSC2, DSG2, DSP, PKP2, TMEM43) Arrhythmogenic right ventricular cardiomyopathy with woolly hair (DSP) Brugada syndrome (SCN5A) Dilated cardiomyopathy (BAG3, DES, DSP, FLNC, LMNA, TPM1, TNNT2, TNNI3, TNNC1, TTN, SCN5A, RBM20, MYH7) Hypertrophic cardiomyopathy (ACTC1, FLNC, TPM1, TNNT2, TNNI3, TNNC1, MYL2, MYL3, MYBPC3, MYH7) Left ventricular noncompaction (TNNT2, TPM1, MYBPC3, MYH7) Restrictive cardiomyopathy (TNNT2, TNNI3, MYL3, FLNC) Atrial fibrillation (KCNQ1) Jervell and Lange-Nielsen syndrome (KCNQ1)

Item	Description
Conditions	BLOOD CLOTTING CONDITIONS Prothrombin-related thrombophilia/prothrombin deficiency (F2) Thrombophilia due to activated protein C resistance/short factor V Leiden bleeding disorder/Factor V deficiency (F5) DISORDERS OF METABOLISM Glycogen storage-related Wolff-Parkinson-White with or without hypertrophic cardiomyopathy (PRKAG2) Pompe disease (GAA) Fabry disease (GLA) Hereditary hemochromatosis (HFE) Hereditary transthyretin-related amyloidosis (TTR) Alpha-1-antitrypsin deficiency (SERPINA1) In addition, one or more of the genes on this panel are associated with other conditions for which a predisposition to, or carrier status of, may incidentally be identified: Autosomal recessive mitochondrial complex II deficiency (SDHB) Autosomal dominant Hirschsprung's disease (RET) Autosomal dominant Myhre syndrome (SMAD4) Autosomal dominant hereditary hemorrhagic telangiectasia (SMAD4) Autosomal recessive Fanconi anemia (BRCA1, BRCA2, PALB2) Constitutional mismatch repair deficiency (MLH1, MSH2, MSH6, PMS2 and EPCAM)
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) 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: 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. EPCAM: analysis is limited to CNV of exons 8-9; F2: analysis is limited to NM_000506.5:c.*97G>A; F5: analysis is limited to NM_000130.5:c.1601G>A (p.Arg534Gln); HFE: Analysis is limited to NM_000410.4:c.845G>A (p.Cys282Tyr) and NM_000410.4:c.187C>G (p.His63Asp); 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; PMS2: analysis is limited to exons 1-10; PTEN: analysis includes CNV of the promoter; SERPINA1: analysis is limited to NM_000295.5:c.1096G>A, NM_000295.5:c.863A>T; TP53: analysis includes CNV of the promoter; VHL: analysis excludes coverage of the cryptic E1' exon (chr3:10142758-10143009)
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.
Interpretation	All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity; however, this test only reports pathogenic and likely pathogenic variants along with interpretive comments detailing the evidence applied towards classification. Variants of uncertain significance are not reported.
Reclassification of Variants	Helix does not systematically review their variant database looking for classification changes. Helix will review the classification of previously reported variants upon request of the ordering physician/provider. Ordering physicians/providers may contact Helix Customer Support or their Dedicated Advisor and request a review of the variant classification to be performed. At the discretion of the laboratory director, the frequency of reclassification requests may be limited to once per year, no earlier than 12 months after initial variant interpretation has been performed.

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Variant Evaluation	Variant classification is performed using the guidelines set forth by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, with modifications as suggested by domain specific Expert Panels of the Clinical genome Resource (ClinGen) when available. Variant pathogenicity is categorized into a 5 tier system that ranges from benign, or not disease causing, to pathogenic, or disease causing.
Turnaround Time	3 to 6 weeks
Available in NY State	No
Test Classification	This test was developed, and its performance characteristics determined, by Helix, Inc. in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.
Performing Laboratory Information	CLIA Laboratory Number: 05D2117342 Laboratory Hours of Operation: Monday-Saturday (6AM-10PM PST) Address: 10170 Sorrento Valley Road, Suite 100, San Diego, CA 92121 Helix Customer Service: (844) 211-2070 Email: support@helix.com
Regulatory Information	CLIA Complexity: High Test Classification: Non-Waived/ Laboratory Developed Test
CLIA Category	Chemistry / Routine Chemistry

Targeted Genes & Methodology Details for Hereditary Actionable Disorders Panel

The following applies to the Helix Hereditary Actionable Disorders Panel. Testing is performed to evaluate for the presence of variants in coding regions and extending to +/- 10 base pairs of adjacent intronic sequences on either side of the coding exons of the genes analyzed. In addition, the analysis will cover select non-coding variants, as listed below. Next-generation sequencing is performed to test for the presence of small variants and copy number variants in the genes analyzed. Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

This list is current from September 2024 to the present. This document is intended to highlight additional evaluations for variants of high clinical interest as well as technical limitations. For questions regarding genes, reference transcripts, or specific regions covered, contact Helix Customer Service at (844) 211-2070.

Genomic Build: GRCh38
Catalog Number: HADP1

Gene	Transcript	Additional Evaluations	Technical Limitations
ACTC1	NM_005159.5		
APC	NM_000038.6	Includes CNV detection of Promoters 1A and 1B and sequencing of Promoter 1B	
APOB	NM_000384.3		
BAG3	NM_004281.4		
BMPR1A	NM_004329.3	Includes CNV detection in the promoter	
BRCA1	NM_007294.4	Sequencing analysis extends to CDS +/-20 bp	
BRCA2	NM_000059.4	Sequencing analysis extends to CDS +/-20 bp	
CALM1	NM_006888.6		
CALM2	NM_001743.6		
CALM3	NM_005184.4		
CASQ2	NM_001232.4		
DES	NM_001927.4		
DSC2	NM_024422.6		
DSG2	NM_001943.5		
DSP	NM_004415.4		
EPCAM	NM_002354.3		Results limited to CNV and limited to exons 8 and 9
F2	NM_000506.5		Results limited to c.*97G>A

Gene	Transcript	Additional Evaluations	Technical Limitations
F5	NM_000130.5		Results limited to c.1601G>A (p.Arg534Gln)
FLNC	NM_001458.5		
GAA	NM_000152.5		
GLA	NM_000169.3		
HFE	NM_000410.4		Results limited to c.845G>A (p.Cys282Tyr) and c.187C>G (p.His63Asp)
KCNH2	NM_000238.4		
KCNQ1	NM_000218.3		Sensitivity in KCNQ1 exon 1 may be reduced
LDLR	NM_000527.5		
LDLRAP1	NM_015627.3		
LMNA	NM_170707.4		
MAX	NM_002382.5		
MEN1	NM_001370259.2		
MLH1	NM_000249.4	Includes CNV detection in the promoter	
MSH2	NM_000251.3	Includes detection of the exon 1-7 rearrangement known as the Boland Inversion and of c.942+3A>T	
MSH6	NM_000179.3		
MUTYH	NM_001048174.2		
MYBPC3	NM_000256.3		
MYH7	NM_000257.4		
MYL2	NM_000432.4		
MYL3	NM_000258.3		
NF2	NM_000268.4		
PALB2	NM_024675.4		
PCSK9	NM_174936.4		
PKP2	NM_001005242.3		
PMS2	NM_000535.7		Analysis for exons 11 to 15 will not be performed
PRKAG2	NM_016203.4		

Gene	Transcript	Additional Evaluations	Technical Limitations
PTEN	NM_000314.8	Includes CNV detection in the promoter	
RB1	NM_000321.3		
RBM20	NM_001134363.3		
RET	NM_020975.6		
RYR2	NM_001035.3		
SCN5A	NM_000335.5, NM_001099404.2		
SDHAF2	NM_017841.4		
SDHB	NM_003000.3		
SDHC	NM_003001.5		
SDHD	NM_003002.4		
SERPINA1	NM_000295.5, NM_001127701.1		Results limited to c.1096G>A (Z allele), c.863A>T (S allele)
SMAD4	NM_005359.6		
STK11	NM_000455.5		
TMEM127	NM_017849.4		
TMEM43	NM_024334.3		
TNNC1	NM_003280.3		
TNNI3	NM_000363.5		
TNNT2	NM_001276345.2		
TP53	NM_000546.6	Includes CNV detection in the promoter	
TPM1	NM_001018005.2		
TRDN	NM_006073.4		
TSC1	NM_000368.5		Sensitivity in TSC1 exon 21 may be reduced
TSC2	NM_000548.5		
TTN	NM_001267550.2, NM_133379.5		Analysis for exons 172 to 197 will not be performed
TTR	NM_000371.4		
VHL	NM_000551.4		Excludes coverage of cryptic exon E1' (chr3:10142758-10143009)