Helix Hereditary Actionable Disorders Screen

Item	Description
Test Name	Helix Hereditary Actionable Disorders Screen
Test Type	Screening
Catalog Number	HADS1
Procedure Code	H00224-4 (Helix)
Test Description	Helix Hereditary Actionable Disorders Screen is a screening test that analyzes 89 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	*ABCD1, ACTA2, ACTC1, ACVRL1, APC, APOB, ATP7B, BAG3, BMPR1A, BRCA1, BRCA2, BTD, CACNA1S, CALM1, CALM2, CALM3, CASQ2, COL3A1, CYP27A1, 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, PLN, PMS2, PRKAG2, PTEN, RB1, RBM20, RET, RPE65, RYR1, RYR2, SCN5A, SDHAF2, SDHB, SDHC, SDHD, SERPINA1, SMAD3, SMAD4, STK11, TGFBR1, TGFBR2, TMEM127, TMEM43, TNNC1, TNNI3, TNNT2, TP53, TPM1, TRDN, TSC1, TSC2, TTN, TTR, VHL, WT1*
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. This test only reports clinically significant pathogenic and likely pathogenic variants, unlike diagnostic testing, which also reports variants of uncertain significance (VUS).
Indications For Testing	The genes included in this screening test have established medical management interventions that may prevent disease and/or significantly reduce morbidity and mortality.
Clinical Descriptions	Hereditary Actionable Disorders Screen analyzes 89 genes related to hereditary predisposition to cancer, cardiac disease, metabolic disorders, muscular disorders, and blood clotting 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)

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	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)"" 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 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)
Interpretation	All detected variants are evaluated according to American College of Medical Genetics and

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	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 reviews variant classifications annually when they arise in routine processes and upon request from providers. The timing of re-review depends on clinical risk. Providers can request a variant re-review by contacting Helix Customer Support. If a classification by Helix is updated, Helix identifies affected past patients and issues revised reports. Updated results are communicated to providers prior to results being uploaded to the EHR, and patients are notified through the EHR patient portal.
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 as benign, likely benign, variant of uncertain significance (VUS), likely pathogenic, or pathogenic.
Turnaround Time - Standard	Typically 1 to 4 weeks
Turnaround Time - Requery (SOQO®)	Typically ≤ 21 days
Available In NY State	Yes
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 (7AM-10:30PM 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

Methods & Limitations for Helix Hereditary Actionable Disorders Screen

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)

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.

Targeted Genes & Methodology for Helix Hereditary Actionable Disorders Screen

The following applies to the Helix Hereditary Actionable Disorders Screen. 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 July 2025 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: HADS1

Gene	Transcript	Additional Evaluations	Technical Limitations
ABCD1	NM_000033.4	–	–
ACTA2	NM_001613.4	–	–
ACTC1	NM_005159.5	–	–
ACVRL1	NM_000020.3	–	–
APC	NM_000038.6	Includes CNV detection of Promoters 1A and 1B and sequencing of Promoter 1B	–
APOB	NM_000384.3	–	Results limited to c.10580G>A and c.10579C>T
ATP7B	NM_000053.4	–	–
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	–
BTD	NM_001370658.1	–	–
CACNA1S	NM_000069.3	–	–
CALM1	NM_006888.6	–	–
CALM2	NM_001743.6	–	–
CALM3	NM_005184.4	–	–
CASQ2	NM_001232.4	–	–
COL3A1	NM_000090.4	–	–
CYP27A1	NM_000784.4	–	–
DES	NM_001927.4	–	–

Gene	Transcript	Additional Evaluations	Technical Limitations
DSC2	NM_024422.6	–	–
DSG2	NM_001943.5	–	–
DSP	NM_004415.4	–	–
ENG	NM_001114753.3	–	–
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
F5	NM_000130.5	–	Results limited to c.1601G>A (p.Arg534Gln)
FBN1	NM_000138.5	–	–
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)
HNF1A	NM_000545.8	–	–
KCNH2	NM_000238.4	–	–
KCNQ1	NM_000218.3	–	Sensitivity in KCNQ1 exon 1 may be reduced
LDLR	NM_000527.5	Includes CNV detection in the promoter	–
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	–	–
MYH11	NM_002474.3, NM_001040113.2	–	–
MYH7	NM_000257.4	–	–

Gene	Transcript	Additional Evaluations	Technical Limitations
MYL2	NM_000432.4	–	–
MYL3	NM_000258.3	–	–
NF2	NM_000268.4	–	–
OTC	NM_000531.6	–	–
PALB2	NM_024675.4	–	–
PCSK9	NM_174936.4	–	–
PKP2	NM_001005242.3	–	–
PLN	NM_002667.5	–	–
PMS2	NM_000535.7	–	Analysis for exons 11 to 15 will not be performed
PRKAG2	NM_016203.4	–	–
PTEN	NM_000314.8	Includes CNV detection in the promoter	–
RB1	NM_000321.3	–	–
RBM20	NM_001134363.3	–	–
RET	NM_020975.6	–	–
RPE65	NM_000329.3	–	–
RYR1	NM_000540.3	–	–
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)
SMAD3	NM_005902.4	–	–
SMAD4	NM_005359.6	–	–
STK11	NM_000455.5	–	Sensitivity in STL11 exon 3 may be reduced
TGFBR1	NM_004612.4	–	–
TGFBR2	NM_003242.6	–	–
TMEM127	NM_017849.4	–	–
TMEM43	NM_024334.3	–	–

Gene	Transcript	Additional Evaluations	Technical Limitations
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	–	Analysis is limited to exons 1-10, 14-44, 47, 49-50, 101, 104-114, 220-224, 226-242, and 244-363
TTR	NM_000371.4	–	–
VHL	NM_000551.4	–	Excludes coverage of cryptic exon E1' (chr3:10142758-10143009)
WT1	NM_024426.6	–	–