Helix Hereditary Cancer Screen

Item	Description
Test Name	Helix Hereditary Cancer Screen
Test Type	Screening
Catalog Number	CMCS1
Procedure Code	H01025-3
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).
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*
Genetics Information	This test utilizes next-generation sequencing to detect single nucleotide variants, insertions and deletions up to 20 bp, and copy number variants in genes associated with a variety of hereditary conditions predisposing to a variety of cancers including: breast, gynecologic (ovarian and uterine), prostate, and those in the gastrointestinal system. 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	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. Early detection and/or intervention for the conditions tested here could significantly reduce morbidity and mortality.
Clinical Descriptions	This panel includes genes that have an established association with multiple cancer types including breast, colorectal, uterine, ovarian, prostate, kidney, pancreatic, skin, endocrine glands (thyroid, parathyroid, pituitary, adrenal) gastrointestinal, and nervous system. These genes are primarily associated with adult-onset solid tumors, although some may develop in childhood. The genes on this panel were specifically selected for their established association with hereditary cancer predisposition. Identification of a pathogenic variant may facilitate early and more frequent screening to help detect cancer at a more treatable stage. Certain medications and preventive surgeries can help to reduce the risk of developing cancer. Identification of a pathogenic variant also helps identify at-risk family members, who can pursue genetic testing and preventive measures. The genes on this panel are associated with conditions that have autosomal dominant and/or autosomal recessive inheritance. Note that some of these genes may also be associated with other unrelated conditions; this means that when undergoing this test, there is a possibility of incidentally detecting carrier status for, or predisposition to, one of these conditions.

Item	Description
Conditions	Familial adenomatous polyposis (APC) Attenuated FAP (APC) ATM-related cancer susceptibility (ATM) BAP1 tumor predisposition syndrome (BAP1) BARD1-related cancer susceptibility (BARD1) BRIP1-related cancer susceptibility (BRIP1) CHEK2-related cancer susceptibility (CHEK2) Constitutional mismatch repair deficiency (MLH1, MSH2, MSH6, PMS2 and EPCAM) Cutaneous melanoma predisposition (CDK4) DICER1 pleuropulmonary blastoma tumor predisposition syndrome (DICER1) gastric adenocarcinoma and proximal polyposis of the stomach (APC) Gastrointestinal stromal tumors predisposition (KIT) GIST-plus syndrome (PDGFRA) Hereditary breast and ovarian cancer syndrome (BRCA1 and BRCA2) Hereditary diffuse gastric cancer syndrome (CDH1 and CTNNA1) Hereditary leiomyomatosis and renal cell cancer (FH) Hereditary mixed polyposis syndrome (GREM1) Hereditary paraganglioma-pheochromocytoma syndrome (SDHA, SDHB, SDHC and SDHD) Hereditary predisposition to prostate cancer (HOXB13) Juvenile polyposis syndrome (BMPR1A and SMAD4) Li-Fraumeni syndrome (TP53) Lynch syndrome (MLH1, MSH2, MSH6, PMS2 and EPCAM) MBD4-associated neoplasia syndrome (MBD4) Melanoma-neural system tumors syndrome (CDKN2A) Melanoma-pancreatic cancer syndrome (CDKN2A) MSH3-associated polyposis (MSH3) Multiple endocrine neoplasia type 1 (MEN1) MUTYH-associated polyposis (MUTYH) Neurofibromatosis (NF1) NTHL1-associated polyposis (NTHL1) Oligodontia-cancer predisposition syndrome (AXIN2) PALB2-related cancer susceptibility (PALB2) Peutz-Jeghers syndrome (STK11) Polymerase proofreading associated polyposis (POLD1 and POLE) PTEN hamartoma tumor syndrome (PTEN) RAD51C-related cancer susceptibility (RAD51C) RAD51D-related cancer susceptibility (RAD51D) Rhabdoid tumor predisposition syndrome (SMARCA4) Tuberous sclerosis complex (TSC1 and TSC2) Uveal melanoma predisposition (MBD4) Von Hippel-Lindau syndrome (VHL) 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:

Item	Description
Conditions (continued)	Autosomal dominant butterfly-shaped pigmentary macular dystrophy (CTNNA1) Autosomal dominant Coffin-Siris syndrome (SMARCA4) Autosomal dominant and autosomal recessive mitochondrial complex II deficiency (SDHA and SDHB) Autosomal dominant mastocytosis (KIT) Autosomal dominant Myhre syndrome (SMAD4) Autosomal dominant piebaldism (KIT) Autosomal recessive ataxia-telangiectasia (ATM) Autosomal recessive familial erythrocytosis type 2 (VHL) Autosomal recessive Fanconi anemia (BRCA1, BRCA2, PALB2, BRIP1 and RAD51C) Autosomal recessive fumarate hydratase deficiency (FH)
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.
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	1 to 6 weeks
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 Cancer 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. 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)

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 Cancer Screen

The following applies to the Helix Hereditary Cancer 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 March 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: CMCS1

Gene	Transcript	Additional Evaluations	Technical Limitations
APC	NM_000038.6	Includes CNV detection of Promoters 1A and 1B and sequencing of Promoter 1B	–
ATM	NM_000051.4	–	–
AXIN2	NM_004655.4	–	–
BAP1	NM_004656.4	–	–
BARD1	NM_000465.4	–	–
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	–
BRIP1	NM_032043.3	–	–
CDH1	NM_004360.5	–	–
CDK4	NM_000075.4	–	–
CDKN2A	NM_000077.5; NM_058195.4	Includes analysis of both the p16 (p16INK4a) and p14 (p14ARF) transcripts	–
CHEK2	NM_007194.4	–	–
CTNNA1	NM_001903.5	–	–
DICER1	NM_177438.3	–	–
EPCAM	NM_002354.3	–	Results limited to CNV and limited to exons 8 and 9
FH	NM_000143.4	–	–
GREM1	NM_013372.7	–	Results limited to CNV of promoter region

Gene	Transcript	Additional Evaluations	Technical Limitations
HOXB13	NM_006361.6	–	Results limited to NM_006361.6(HOXB13): c.251G>A (p.Gly84Glu)
KIT	NM_000222.3	–	–
MBD4	NM_001276270.2	–	–
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	–
MSH3	NM_002439.5	–	Excludes known repeat region in MSH3 exon 1
MSH6	NM_000179.3	–	–
MUTYH	NM_001048174.2; NM_001128425.2	–	–
NF1	NM_001042492.3	–	–
NTHL1	NM_002528.7	–	–
PALB2	NM_024675.4	–	–
PDGFRA	NM_006206.6	–	–
PMS2	NM_000535.7	–	Analysis for exons 11 to 15 will not be performed
POLD1	NM_002691.4	–	CNVs not reported, and sequencing isolated to the exonuclease domain
POLE	NM_006231.4	–	CNVs not reported, and sequencing isolated to the exonuclease domain
PTEN	NM_000314.8	Includes CNV detection in the promoter	–
RAD51C	NM_058216.3	–	–
RAD51D	NM_002878.4	–	–
SDHA	NM_004168.4	–	CNVs not reported
SDHB	NM_003000.3	–	–
SDHC	NM_003001.5	–	–
SDHD	NM_003002.4	–	–
SMAD4	NM_005359.6	–	–
SMARCA4	NM_003072.5; NM_001387283.1	–	–

Gene	Transcript	Additional Evaluations	Technical Limitations
STK11	NM_000455.5	–	Sensitivity in STK11 exon 3 may be reduced
TP53	NM_000546.6	Includes CNV detection in the promoter	–
TSC1	NM_000368.5	–	Sensitivity in TSC1 exon 21 may be reduced
TSC2	NM_000548.5	–	–
VHL	NM_000551.4	–	Excludes coverage of cryptic exon E1' (chr3:10142758-10143009)