Helix Hereditary Multi-Cancer Panel

Item	Description
Test Name	Helix Hereditary Multi-Cancer Panel
Test Type	Hereditary Cancer
Catalog Number	CCAN1
Procedure Code	H00124-3 (Helix)
Test Description	This panel evaluates 70 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), colorectal, pancreatic, prostate, kidney, skin, brain and nervous system, and endocrine glands (adrenal, pituitary, parathyroid, thyroid).
Genes Tested	*AIP, ALK, APC, ATM, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN1B, CDKN2A, CHEK2, CTNNA1, DICER1, EGFR, EPCAM, FH, FLCN, GREM1, HOXB13, KIT, LZTR1, MAX, MBD4, MEN1, MET, MITF, MLH1, MSH2, MSH3, MSH6, MUTYH, NF1, NF2, NTHL1, PALB2, PDGFRA, PMS2, POLD1, POLE, POT1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TMEM127, 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), colorectal, pancreatic, prostate, kidney, skin, brain and nervous system, and endocrine glands (adrenal, pituitary, parathyroid, thyroid).
Indications For Testing	A relevant personal and/or family history suggestive of a hereditary form of cancer.
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), 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 increased cancer screening and preventative surgery for early-detection and prevention. 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. Analyzing a wide range of genes in a single test can provide an efficient, cost-effective method of testing for several hereditary cancer conditions. This approach increases the chance of identifying the underlying diagnosis responsible for an individual's or family's cancer predisposition.

Conditions	Familial adenomatous polyposis (APC) ALK-related neuroblastic tumor susceptibility (ALK) Attenuated FAP (APC) ATM-related cancer susceptibility (ATM) BAP1 tumor predisposition syndrome (BAP1) BARD1-related cancer susceptibility (BARD1) Birt-Hogg-Dube syndrome (FLCN) Bloom syndrome (BLM) BRIP1-related cancer susceptibility (BRIP1) Carney complex (PRKAR1A) CDC73-related conditions (CDC73) 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) Familial isolated pituitary adenoma (AIP) Familial meningioma (SMARCE1) gastric adenocarcinoma and proximal polyposis of the stomach (APC) Gastrointestinal stromal tumors predisposition (KIT) GIST-plus syndrome (PDGFRA) Gorlin syndrome, also known as basal cell nevus syndrome (PTCH1 and SUFU) 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 papillary renal cell carcinoma (MET) Hereditary paraganglioma-pheochromocytoma syndrome (MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD and TMEM127) Hereditary predisposition to lung cancer (EGFR) Hereditary predisposition to melanoma (MITF) Hereditary predisposition to prostate cancer (HOXB13) Hereditary retinoblastoma (RB1) Juvenile polyposis syndrome (BMPR1A and SMAD4) Li-Fraumeni syndrome (TP53) Lynch syndrome (MLH1, MSH2, MSH6, PMS2 and EPCAM) LZTR1-related schwannomatosis (LZTR1) 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) Multiple endocrine neoplasia type 2 (RET) Multiple endocrine neoplasia type 4 (CDKN1B) MUTYH-associated polyposis (MUTYH) Neurofibromatosis (NF1) NF2-related schwannomatosis (NF2) NTHL1-associated polyposis (NTHL1)

Item	Description
Conditions (continued)	Oligodontia-cancer predisposition syndrome (AXIN2) PALB2-related cancer susceptibility (PALB2) Peutz-Jeghers syndrome (STK11) Polymerase proofreading associated polyposis (POLD1 and POLE) POT1 tumor predisposition syndrome (POT1) PTEN hamartoma tumor syndrome (PTEN) RAD51C-related cancer susceptibility (RAD51C) RAD51D-related cancer susceptibility (RAD51D) Rhabdoid tumor predisposition syndrome (SMARCA4 and SMARCB1) SMARCB1-related schwannomatosis (SMARCB1) 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: Autosomal dominant acrodysostosis (PRKAR1A) Autosomal dominant butterfly-shaped pigmentary macular dystrophy (CTNNA1) Autosomal dominant Coffin-Siris syndrome (SMARCA4, SMARCB1 and SMARCE1) Autosomal dominant and autosomal recessive mitochondrial complex II deficiency (SDHA and SDHB) Autosomal dominant and autosomal recessive Noonan syndrome (LZTR1) Autosomal dominant Hirschsprung's disease (RET) 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) Autosomal recessive Joubert syndrome (SUFU) Autosomal recessive nonsyndromic deafness (MET)
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 and reported with interpretive comments detailing their potential or known significance.
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.

Item	Description
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	7 to 24 days
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 (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 Multi-Cancer Panel

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. Reportable variants in *PMS2* exons 12-15 are confirmed by PacBio long reads. The *MSH2* Boland inversion (exons 1-7) is detected by identifying discordant read-pairs spanning the presumed breakpoint. 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, +/- 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. Variants classified as pathogenic, likely pathogenic, or VUS are included in the report. All reported variants (except for VUSs with limited evidence of pathogenicity) are confirmed through secondary manual inspection of DNA sequence data or orthogonal testing. Benign and likely benign variants are not reported but are available upon request. 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 assay cannot detect all variants known to increase disease risk, and that a negative result does not guarantee that the tested individual does not carry a rare, undetectable variant in genes analyzed. 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; *EGFR:* analysis is limited to the NM_005228(EGFR):c.2369C>T (p.Thr790Met) variant; *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 NM_006361.6(HOXB13):c.251G>A (p.Gly84Glu) variant; *MITF:* analysis is limited to the NM_000248.4(MITF):c.952G>A (p.Glu318Lys) variant; *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; *MSH3:* analysis excludes sequencing of exon 1 repeat region (chr5:80654878-80654946); *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); *PTCH1:* sensitivity of exon 1 analysis may be reduced; 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 Helix Hereditary Multi-Cancer Panel

The following applies to the Helix Hereditary Multi-Cancer 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 March 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: CCAN1

Gene	Transcript	Additional Evaluations	Technical Limitations
AIP	NM_003977.4	–	–
ALK	NM_004304.5	–	–
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	–	–
BLM	NM_000057.4	–	–
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	–	–
CDC73	NM_024529.5	–	–
CDH1	NM_004360.5	–	–
CDK4	NM_000075.4	–	–
CDKN1B	NM_004064.5	–	–
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	–	–

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Gene	Transcript	Additional Evaluations	Technical Limitations
EGFR	NM_005228.5	–	Results limited to NM_005228(EGFR): c.2369C>T (p.Thr790Met)
EPCAM	NM_002354.3	–	Results limited to CNV and limited to exons 8 and 9
FH	NM_000143.4	–	–
FLCN	NM_144997.7	–	–
GREM1	NM_013372.7	–	Results limited to CNV of promoter region
HOXB13	NM_006361.6	–	Results limited to NM_006361.6(HOXB13): c.251G>A (p.Gly84Glu)
KIT	NM_000222.3	–	–
LZTR1	NM_006767.4	–	–
MAX	NM_002382.5	–	–
MBD4	NM_001276270.2	–	–
MEN1	NM_001370259.2	–	–
MET	NM_000245.4	–	–
MITF	NM_000248.4	–	Results limited to NM_000248.4(MITF): c.952G>A (p.Glu318Lys)
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	–	–
NF2	NM_000268.4	–	–
NTHL1	NM_002528.7	–	–
PALB2	NM_024675.4	–	–
PDGFRA	NM_006206.6	–	–
PMS2	NM_000535.7	–	–
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

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Gene	Transcript	Additional Evaluations	Technical Limitations
POT1	NM_015450.3	–	–
PRKAR1A	NM_002734.5	–	–
PTCH1	NM_000264.5; NM_001083603.3	–	Sensitivity in PTCH1 exon 1 may be reduced
PTEN	NM_000314.8	Includes CNV detection in the promoter	–
RAD51C	NM_058216.3	–	–
RAD51D	NM_002878.4	–	–
RB1	NM_000321.3	–	–
RET	NM_020975.6	–	–
SDHA	NM_004168.4	–	CNVs not reported
SDHAF2	NM_017841.4	–	–
SDHB	NM_003000.3	–	–
SDHC	NM_003001.5	–	–
SDHD	NM_003002.4	–	–
SMAD4	NM_005359.6	–	–
SMARCA4	NM_003072.5; NM_001387283.1	–	–
SMARCB1	NM_003073.5	–	–
SMARCE1	NM_003079.5	–	–
STK11	NM_000455.5	–	Sensitivity in STK11 exon 3 may be reduced
SUFU	NM_016169.4	–	–
TMEM127	NM_017849.4	–	–
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)