Helix Comprehensive Cardiomyopathy and Arrhythmias Panel

Item	Description
Test Name	Helix Comprehensive Cardiomyopathy and Arrhythmias Panel
Test Type	Cardio
Catalog Number	CCMA1
Procedure Code	H00724-2 (Helix)
Test Description	This panel evaluates 103 genes associated with cardiomyopathy and arrhythmia, and several syndromic conditions associated with cardiomyopathy and arrhythmia.
Genes Tested	*ABCC9, ACAD9, ACADVL, ACTC1, ACTN2, AGL, ALMS1, ALPK3, ANK2, BAG3, BMP10, BRAF, CACNA1C, CACNA1D, CALM1, CALM2, CALM3, CASQ2, CAV3, CDH2, CPT2, CRYAB, CSRP3, DES, DMD, DNAJC19, DOLK, DSC2, DSG2, DSP, DTNA, ELAC2, EMD, FHL1, FKRP, FKTN, FLNC, GAA, GLA, HCN4, HRAS, JPH2, JUP, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, KRAS, LAMP2, LMNA, LZTR1, MAP2K1, MAP2K2, MRAS, MTO1, MYBPC3, MYH7, MYL2, MYL3, MYL4, MYLK3, MYPN, NEXN, NKX2-5, NRAS, PCCA, PCCB, PKP2, PLN, PPA2, PPCS, PRDM16, PRKAG2, PTPN11, RAF1, RBM20, RIT1, RYR2, SCN5A, SGCD, SHOC2, SLC22A5, SLC4A3, SOS1, SOS2, SYNE2, TAFAZZIN, TBX20, TCAP, TECRL, TMEM43, TMEM70, TNNC1, TNNI3, TNNI3K, TNNT2, TPM1, TRDN, TRIM63, TTN, TTR, VCL*
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 hereditary forms of cardiomyopathies or arrhythmias.
Indications For Testing	A personal or family history suggestive of a hereditary form of cardiomyopathy and/or arrhythmia.
Clinical Descriptions	Cardiomyopathies and channelopathies are broad spectrums of cardiovascular diseases with both overlapping and distinct characteristics. Cardiomyopathies are structural and functional disorders of the heart musculature, and channelopathies are electrophysiological disorders affecting heart ion channels. There are many different causes of these disorders, which range from environmental exposures to inherited genetic risk factors. In cases where an external cause is not identified, or a family history is suspicious of a hereditary risk of either a cardiomyopathy or channelopathy, diagnostic genetic testing may be ordered. Hypertrophic Cardiomyopathy (HCM) is a condition in which the heart muscle becomes abnormally thick. This leads to a decrease in the heart's ability to pump blood effectively. This can cause fatigue, shortness of breath, swelling of the legs, heart rhythm abnormalities and, in severe cases, heart failure or sudden cardiac arrest. Dilated Cardiomyopathy (DCM) is a condition in which the heart chambers become enlarged, weakening the heart muscle. LVNC is characterized by endomyocardial trabeculations which can have variable effects on heart musculature, including ventricular dilation. Individuals with DCM or LVNC may be asymptomatic, or may be symptomatic with arrhythmia, left ventricular dysfunction, thromboembolic disease, and/or life-threatening arrhythmias. Long QT syndrome (LQTS) is an electrophysiologic disorder of the heart that is characterized by prolongation of the QT-interval and T-wave abnormalities, as measured by electrocardiogram (ECG). These may manifest as palpitations, seizures, or arrhythmogenic events such as torsade de pointes (TdP) which may result in syncope or, in rare cases, cardiac arrest or sudden death.

Item	Description
Clinical Descriptions (continued)	Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an electrophysiologic disorder of the heart which predisposes those affected to develop arrhythmias. While patients with CPVT often have normal resting electrocardiograms (ECGs) and normal heart imaging, both exercise and emotional stress can risk development of arrhythmogenic events (commonly ventricular tachycardia) which may result in syncope or, in rare cases, cardiac arrest or sudden death. Short QT syndrome (SQTS) is an electrophysiologic disorder of the heart that is characterized by an abnormally short QT-interval, as measured by electrocardiogram (ECG). This can result in abnormal heart rhythms that can cause palpitations, fainting and an increased risk of sudden cardiac death. Brugada syndrome (BrS) is an electrophysiologic disorder of the heart that is characterized by pathognomonic electrocardiogram (ECG) findings. These findings are associated with increased risk for arrhythmogenic events which may result in syncope or, in rare cases, cardiac arrest or sudden death. Arrhythmogenic cardiomyopathy (ACM) is characterized by fibrofatty infiltration of ventricle musculature which may present as arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC) or arrhythmogenic left ventricular cardiomyopathy/dysplasia (ALVC). These findings are associated with increased risk for ventricular dysfunction, and arrhythmogenic events which may result in syncope or, in rare cases, cardiac arrest or sudden death. Hereditary transthyretin amyloidosis (hATTR) is a slowly progressive, adult-onset neuromuscular condition, characterized by a gradual buildup of amyloid in different organs, tissues, and nerves. This amyloid buildup may gradually cause restrictive cardiomyopathy, autonomic neuropathy, peripheral sensorimotor neuropathy, nephropathy, or in some cases effects to the central nervous system such as seizures, dementia, and psychosis. Individuals with these conditions may be asymptomatic, or may be symptomatic with some/many of the features described above. It is important to note that in some cases these heart conditions may be a feature of a larger syndromic condition. Hereditary forms of HCM, DCM and LVNC may follow autosomal dominant, autosomal recessive, X-linked or mitochondrial inheritance patterns. Hereditary forms of LQTS, CPVT and ACM may follow autosomal dominant or autosomal recessive inheritance patterns. Hereditary forms of BrS, SQTS and ATTR have been seen to follow an autosomal dominant inheritance pattern. This panel does not assess mitochondrial inheritance.
Conditions	Hypertrophic cardiomyopathy (HCM) Dilated cardiomyopathy (DCM) Left ventricular non-compaction (LVNC) Arrhythmogenic cardiomyopathy (ACM) Arrhythmogenic right ventricular cardiomyopathy (ARVC) Arrhythmogenic left ventricular cardiomyopathy (ALVC) Long QT syndrome (LQTS) Short QT syndrome (SQTS) Brugada syndrome (BrS) Catecholaminergic polymorphic ventricular tachycardia (CPVT) Hereditary ATTR amyloidosis (hATTR)

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Item	Description
Conditions (continued)	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: 3-methylglutaconic aciduria type 5 (DNAJC19) Agenesis of corpus callosum, cardiac, ocular, and genital syndrome (ACOGS) (CDH2) Aldosterone-producing adenoma with seizures and neurological abnormalities (CACNA1D) Alstrom syndrome (ALMS1) Atrial fibrillation (KCNQ1, MYL4) Atrial septal defects (ACTC1, NKX2-5) Barth Syndrome (TAFAZZIN) Cantu syndrome (ABCC9) Cardiofaciocutaneous syndrome (BRAF, KRAS, MAP2K1, MAP2K2) Carnitine palmitoyltransferase II deficiency (CPT2) Cataracts (CRYAB) Caveolinopathy (CAV3) Charcot-Marie-Tooth disease (BAG3, LMNA) Combined oxidative phosphorylation defect type 17 (ELAC2) Complex neurodevelopmental disorder (ANK2) Congenital myopathy (ACTN2, LMNA) Conotruncal heart malformations (NKX2-5) Costello syndrome (HRAS) Danon disease (LAMP2) Distal myopathy (FLNC) DK1-congenital disorder of glycosylation (DOLK) Emery-Dreifuss muscular dystrophy (EMD, LMNA) Fabry disease (GLA) Fatal infantile hypertonic myofibrillar myopathy (CRYAB) Glycogen storage disease type III (AGL) Hereditary gingival fibromatosis (SOS1) Hutchinson-Gilford progeria syndrome (LMNA) Hypoplastic left heart (NKX2-5) Intrinsic cardiomyopathy (ACTN2, PLN) Jervell and Lange-Nielsen syndrome (KCNE1, KCNQ1) Limb-girdle muscular dystrophy (SGCD, TCAP) Lipodystrophy (LMNA) Metachondromatosis (PTPN11) Mitochondrial complex I deficiency (ACAD9) Mitochondrial complex V deficiency nuclear type 2 (TMEM70) Mitochondrial hypertrophic cardiomyopathy with lactic acidosis (MTO1) Muscular dystrophy-dystroglycanopathy (FKRP, FKTN) Myofibrillar myopathy (BAG3, CRYAB, DES, FLNC, TTN, MYL2) Myopathy (FHL1, MYPN, TTN) Naxos disease (JUP) Noonan syndrome (BRAF, KRAS, LZTR1, MRAS, NRAS, PTPN11, RAF1, RIT1, SHOC2, SOS1, SOS2) Pompe disease (GAA)

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Item	Description
Conditions (continued)	Primary carnitine deficiency disease (SLC22A5) Progressive muscular dystrophy (DMD) Propionic acidemia (PCCA, PCCB) Restrictive cardiomyopathy (RCM) (FLNC, MYL3, TNNI3, TNNT2) Schwannomatosis (LZTR1) Sinoatrial node dysfunction and deafness (CACNA1D) Sinus node dysfunction or bradycardia (HCN4) Skeletal myopathy (MYH7) Structural heart defects (TBX20) Sudden cardiac failure (PPA2) Tibial muscular dystrophy (TTN) Timothy syndrome (CACNA1C) Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency (ACADVL) Wolff-Parkinson-White syndrome (PRKAG2)
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.
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 Comprehensive Cardiomyopathy and Arrhythmias 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. 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:
AGL: Evaluation of chr1: 99916398 (c.4260-12A>G) will be performed. *ALPK3*: Sensitivity in exon 1 may be reduced. *BRAF*: Sensitivity in exon 1 may be reduced. *CDH2*: Sensitivity in exon 1 may be reduced. *DMD*: Evaluation of chrX:33174335 (c.31+36947G>A), chrX:31261663 (c.9225-647A>G), and chrX:31261301 (c.9225-285A>G) will be performed. *FKTN*: Evaluation of chr9:105606576 (c.648-1243G>T) will be performed. *GAA*: Evaluation of chr17:80104542 (c.-32-13T>G), chr17:80104552 (c.-32-3C>A), chr17:80104554 (c.-32-1G>C), and chr17:80108467 (c.1076-22T>G) will be performed. *GLA*: Evaluation of chrX: 101399747 (c.640-801G>A) will be performed. KCNH2: Evaluation of Chr7:150958048-150958065 (c.910_916+11del) will be performed. *KCNQ1*: Evaluation of Chr11:2461715 (c.386+16231G>A), Chr11:2585210-2585211 (c.1033-1_1117dup) will be performed and sensitivity in *KCNQ1* exon 1 may be reduced. *MAP2K2*: Sensitivity in exon 1 may be reduced. *MYBPC3*: Evaluation of chr11:47332275-47332299 (c.3628-41_2628-17del25), chr11:47347065 (c.906-36G>A), chr11:47346372 (c.927-2A>G), chr11:47343281 (c.1224-19G>A), chr11:47343314 (c.1224-52G>A), chr11:47343158 (c.1227-13G>A), and chr11:47340403 (c.1927+600C>T) will be performed. *PRDM16*: Analysis for exon 1 will not be performed. *PRKAG2*: Sensitivity in exon 5 may be reduced. *SLC22A5*: Evaluation of chr5:132369824 (c.-149G>A), chr5:132378362 (c.394-16T>A), and chr5:132386973 (c.825-52G>A) will be performed. *SOS2*: Sensitivity in exon 1 may be reduced. *TRDN*: Evaluation of Chr6:123636725 (c.22+29A>G) will be performed. *TTN*: Analysis for exons 172 to 197 will not be performed.

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 Comprehensive Cardiomyopathy and Arrhythmias Panel

The following applies to the Helix Comprehensive Cardiomyopathy and Arrhythmias 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: CCMA1

Gene	Transcript	Additional Evaluations	Technical Limitations
ABCC9	NM_020297.4	–	–
ACAD9	NM_014049.5	–	–
ACADVL	NM_000018.4	–	–
ACTC1	NM_005159.5	–	–
ACTN2	NM_001103.4	–	–
AGL	NM_000642.3	Chr1: 99916398 (c.4260-12A>G)	–
ALMS1	NM_001378454.1	–	–
ALPK3	NM_020778.5	–	Sensitivity in ALPK3 exon1 may be reduced
ANK2	NM_001148.6	–	–
BAG3	NM_004281.4	–	–
BMP10	NM_014482.3	–	–
BRAF	NM_004333.6; NM_001374258.1	–	Sensitivity to BRAF exon1 may be reduced
CACNA1C	NM_000719.7; NM_001167623.2	–	–
CACNA1D	NM_001128840.3; NM_000720.4	–	–
CALM1	NM_006888.6	–	–
CALM2	NM_001743.6	–	–
CALM3	NM_005184.4	–	–
CASQ2	NM_001232.4	–	–
CAV3	NM_033337.3	–	–
CDH2	NM_001792.5	–	Sensitivity in CDH2 exon1 may be reduced

Gene	Transcript	Additional Evaluations	Technical Limitations
CPT2	NM_000098.3	–	–
CRYAB	NM_001289808.2	–	–
CSRP3	NM_003476.5	–	–
DES	NM_001927.4	–	–
DMD	NM_004006.3	ChrX:33174335 (c.31+36947G>A) ChrX:31261663 (c.9225-647A>G) ChrX:31261301 (c.9225-285A>G)	–
DNAJC19	NM_145261.4	–	–
DOLK	NM_014908.4	–	–
DSC2	NM_024422.6	–	–
DSG2	NM_001943.5	–	–
DSP	NM_004415.4	–	–
DTNA	NM_001386795.1	–	–
ELAC2	NM_018127.7	–	–
EMD	NM_000117.3	–	–
FHL1	NM_001159699.2; NM_001159702.3	–	–
FKRP	NM_024301.5	–	–
FKTN	NM_001079802.2	Chr9:105606576 (c.648-1243G>T)	–
FLNC	NM_001458.5	–	–
GAA	NM_000152.5	Chr17:80104542 (c.-32-13T>G) Chr17:80104552 (c.-32-3C>A) Chr17:80104554 (c.-32-1G>C) Chr17:80108467 (c.1076-22T>G)	–
GLA	NM_000169.3	ChrX: 101399747 (c.640-801G>A)	–
HCN4	NM_005477.3	–	–
HRAS	NM_005343.4; NM_176795.5	–	–
JPH2	NM_020433.5	–	–
JUP	NM_002230.4	–	–
KCNE1	NM_000219.6	–	–
KCNE2	NM_172201.2	–	–
KCNH2	NM_000238.4	Chr7:150958048-150958065 (c.910_916+11del)	–
KCNJ2	NM_000891.3	–	–

Gene	Transcript	Additional Evaluations	Technical Limitations
KCNQ1	NM_000218.3	Chr11:2461715 (c.386+16231G>A) Chr11:2585210-2585211 (c.1033-1_1117dup)	Sensitivity in KCNQ1 exon 1 may be reduced
KRAS	NM_004985.5; NM_033360.4	–	–
LAMP2	NM_002294.3	–	–
LMNA	NM_170707.4; NM_005572.4	–	–
LZTR1	NM_006767.4	–	–
MAP2K1	NM_002755.4	–	–
MAP2K2	NM_030662.4	–	Sensitivity in MAP2K2 exon 1 may be reduced
MRAS	NM_001085049.3	–	–
MTO1	NM_012123.4	–	–
MYBPC3	NM_000256.3	Chr11:47332275-47332299 (c.3628-41_2628-17del25) Chr11:47347065 (c.906-36G>A) Chr11:47346372 (c.927-2A>G) Chr11:47343281 (c.1224-19G>A) Chr11:47343314 (c.1224-52G>A) Chr11:47343158 (c.1227-13G>A) Chr11:47340403 (c.1927+600C>T)	–
MYH7	NM_000257.4	–	–
MYL2	NM_000432.4	–	–
MYL3	NM_000258.3	–	–
MYL4	NM_002476.2	–	–
MYLK3	NM_182493.3	–	–
MYPN	NM_032578.4	–	–
NEXN	NM_144573.4	–	–
NKX2-5	NM_004387.4	–	–
NRAS	NM_002524.5	–	–
PCCA	NM_000282.4	–	–
PCCB	NM_000532.5	–	–
PKP2	NM_001005242.3	–	–
PLN	NM_002667.5	–	–
PPA2	NM_176869.3	–	–
PPCS	NM_024664.4	–	–

Gene	Transcript	Additional Evaluations	Technical Limitations
PRDM16	NM_022114.4	–	Analysis for exon 1 will not be performed
PRKAG2	NM_016203.4	–	Sensitivity in PRKAG2 exon 5 may be reduced
PTPN11	NM_002834.5	–	–
RAF1	NM_002880.4	–	–
RBM20	NM_001134363.3	–	–
RIT1	NM_006912.6	–	–
RYR2	NM_001035.3	–	–
SCN5A	NM_000335.5; NM_001099404.2	–	–
SGCD	NM_000337.6	–	–
SHOC2	NM_007373.4	–	–
SLC22A5	NM_003060.4	Chr5:132369824 (c.-149G>A) Chr5:132378362 (c.394-16T>A) Chr5:132386973 (c.825-52G>A)	–
SLC4A3	NM_005070.4	–	–
SOS1	NM_005633.4	–	–
SOS2	NM_006939.4	–	Sensitivity in SOS2 exon 1 may be reduced
SYNE2	NM_182914.3	–	–
TAFAZZIN	NM_000116.5	–	–
TBX20	NM_001077653.2	–	–
TCAP	NM_003673.4	–	–
TECRL	NM_001010874.5	–	–
TMEM43	NM_024334.3	–	–
TMEM70	NM_017866.6	–	–
TNNC1	NM_003280.3	–	–
TNNI3	NM_000363.5	–	–
TNNI3K	NM_015978.3	–	–
TNNT2	NM_001276345.2	–	–
TPM1	NM_001018005.2	–	–
TRDN	NM_006073.4	Chr6:123636725 (c.22+29A>G)	–
TRIM63	NM_032588.4	–	–
TTN	NM_001267550.2; NM_133379.5	–	Analysis for exons 172 to 197 will not be performed

Gene	Transcript	Additional Evaluations	Technical Limitations
TTR	NM_000371.4	–	–
VCL	NM_014000.3	–	–