Genetic Testing for Cardiac Conditions

Humana®

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Medical Coverage Policy

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Related Medical/Pharmacy Coverage Policies

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Description

Cardiovascular Disease Genetic Markers

Cardiovascular disease (CVD) risk testing is performed to help determine an individual's risk of having a cardiovascular event such as a heart attack or stroke. The most common test used to determine CVD risk is the lipid profile, which measures cholesterol, high density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides.

Panels beyond the basic lipid profile are commercially available and may include analysis of genetic markers for CVD risk including single nucleotide polymorphism (SNPs) genotyping and often pharmacogenomics tests. SNP genotype testing has been proposed to identify an individual at risk for atrial fibrillation (AF), coronary artery disease and early myocardial infarction (MI). Examples include but may not be limited to:

- 4q25 genotype testing (eg, 4q25-AF Risk Genotype Test, Cardio IQ 4q25-AF Risk Genotype Test) **(Refer to Coverage Limitations section)**

- 9p21 genotype testing (eg, Cardio IQ 9p21 Genotype Test) **(Refer to Coverage Limitations section)**

- LPA Intron-25 genotype testing (eg, Cardio IQ LPA Intron-25 Genotype Test, LPA-Intron 25 Genotype Test) **(Refer to Coverage Limitations section)**

- Multianalyte DNA analysis of SNPs reported as a risk score for a CVD event (eg, CardoRisk+, Epi+GenCHD and PrecisionCHD) **(Refer to Coverage Limitations section)**

- ST2 (growth stimulation expressed gene 2) (eg, Cardio IQ ST2) **(Refer to Coverage Limitations section)**

CVD risk panels may also include genetic tests to determine an individual's susceptibility for hypercoagulation or thrombosis, which has been proposed as a risk factor for CVD. Testing may include factor II (*F2* gene), factor V (*F5* gene) or plasminogen activator inhibitor (PAI-1). **(Refer to Coverage Limitations section)**

Health and wellness SNP genotyping tests are also commercially available to analyze genes associated with various wellness factors, such as diet, exercise and metabolism, to purportedly guide an individual to personalized lifestyle choices to improve overall health and wellbeing. These tests may also be marketed to improve CVD risk by choosing a diet or exercise regimen based on an individual's genetic makeup. Examples of these tests include but may not be limited to: Cardiac Healthy Weight DNA Insight, Healthy Woman DNA Insight. **(Refer to Coverage Limitations section)**

Inherited Cardiomyopathies and Channelopathies

Cardiomyopathy is a chronic disease of the myocardium (heart muscle). The heart muscle becomes enlarged, thick or rigid, resulting in a failure to pump blood effectively, which can lead to arrhythmias (irregular heartbeats) and possible heart failure. Cardiomyopathy can be acquired or inherited. Hypertrophic cardiomyopathy (HCM) is one of the main types of cardiomyopathy.

Cardiac ion channelopathies are a group of diseases that develop due to defects in ion channels and can be caused by either genetic or acquired factors. Inherited cardiac channelopathies include, but are not limited to, Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT) and long QT syndrome (LQTS).

Genetic testing may be used to detect variants believed to be linked to inherited cardiomyopathies and channelopathies to assist with diagnosis, determine prognosis and identify susceptibility in at-risk, unaffected family members.

A variety of **multigene panel tests**, with or without next-generation sequencing (NGS) technology, that simultaneously analyze many genes at one time are currently commercially available. **Targeted multigene panels** examine only those genes associated with a given disease.

Multicondition multigene panels are also available to analyze a broader range of genes associated with a group of diseases (eg, inherited channelopathies). In this example, the panel may target genes for all inherited channelopathies including BrS, CPVT and LQTS. **(Refer to Coverage Limitations section)**

Finally, what can be termed as **comprehensive multigene panels** offer analysis of an even broader range of genes and include those associated with both inherited cardiomyopathies and channelopathies. **(Refer to Coverage Limitations section)**

Examples of multicondition and comprehensive multigene panels include, but may not be limited to:

- Arrhythmia Panel
- AtheroGxOne
- Cardiomyopathies Del/Dup Panel
- Cardiomyopathy and Arrhythmia Panel
- Cardiomyopathy Panel
- CardioNext
- CMNext
- Combined Cardiac Panel
- Comprehensive Cardiomyopathy Multi-Gene Panel
- DCMNext
- GeneSeq: Cardio Familial Arrhythmia Panel
- GeneSeq: Cardio Familial Cardiomyopathy Profile
- Genomic Unity Cardiac Ion Channelopathies Analysis (0237U)
- HCMNext
- Invitae Arrhythmia and Cardiomyopathy Comprehensive Panel
- Invitae Arrhythmia Comprehensive Panel
- Invitae Arrhythmogenic Cardiomyopathy Panel
- Invitae Cardiomyopathy Comprehensive Panel
- Invitae Hypertrophic Cardiomyopathy Panel
- LongQTNext
- Pan Cardiomyopathy Panel
- RhythmNext

Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is a genetic (autosomal dominant) disorder. Gene variants can inhibit the liver from metabolizing excess low density lipoprotein cholesterol (LDL-C), resulting in lifelong exposure to elevated LDL-C levels which contributes to premature atherosclerotic cardiovascular disease.

There are two forms of FH including heterozygous FH (HeFH) (single gene variant received from one parent) and homozygous FH (HoFH) (more than one variant received from one or both parents). HeFH is the most common form and is found in approximately 1:250 individuals. HoFH is rare, occurring in approximately 1:350,000 individuals, but can have an earlier onset with more severe outcomes.[60]

Coverage Determination

Any state mandates for genetic testing for cardiac conditions take precedence over this medical coverage policy.

Genetic testing may be excluded by certificate. Please consult the member's individual certificate regarding Plan coverage.

Apply General Criteria for Genetic and Pharmacogenomics Tests when disease- or gene-specific criteria are not available on a medical coverage policy. For information regarding **General Criteria for Genetic and Pharmacogenomics Tests**, please refer to Genetic Testing Medical Coverage Policy.

Catecholaminergic Polymorphic Ventricular Tachycardia (*CALM1, CALM2, CALM3, CASQ2, KCNJ2, RYR2, TECRL and TRDN* Genes)

Humana members may be eligible under the Plan for **genetic testing for catecholaminergic polymorphic ventricular tachycardia (CPVT)** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
    - Individual to be tested exhibits clinical features suggestive of CPVT including unexplained exercise- or catecholamine-induced polymorphic ventricular arrhythmias and syncope during physical activity or acute emotion occurring in a structurally normal heart; **OR**

      CPVT Testing Strategy (Affected): perform single gene testing of *CALM1, CALM2, CALM3, CASQ2, KCNJ2, RYR2, TECRL* or *TRDN* genes or targeted multigene analysis (sequencing and/or deletion/duplication) of *CALM1, CALM2, CALM3, CASQ2, KCNJ2, RYR2, TECRL and TRDN* genes.
    - Individual to be tested is unaffected and has an affected first-degree relative in whom a pathogenic or likely pathogenic CPVT variant has been identified

      Testing Strategy: test for known familial variant (KFV)

Familial Hypercholesterolemia (*APOB, LDLR, LDLRAP1* [*ARH*] and *PCSK9 Genes*)

Humana members may be eligible under the Plan for **genetic testing for familial hypercholesterolemia (FH)** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
    - Acquired and secondary causes of hypercholesterolemia (eg, diet and medication-induced hypercholesterolemia, endocrine, hepatic and renal disease) have been excluded by standard diagnostic evaluation; **AND**
        - Individual to be tested has a persistent LDL-C level***** greater than 190 mg/dL (18 years of age or older) or 160 mg/dL (17 years of age or younger); **OR**

- Individual to be tested has diagnosis of premature atherosclerotic cardiovascular disease (before age 55 in males; before age 60 in females); **OR**

- Individual to be tested has an affected first- or second-degree relative with one of the following:

  - Diagnosis of premature atherosclerotic cardiovascular disease (54 years of age or younger in males, 59 years of age or younger in females); **OR**

  - Diagnosis of FH functional variant(s)

Testing Strategy: perform single gene testing of *APOB*, *LDLR*, *LDLRAP1* or *PCSK9* genes or targeted multigene analysis (sequencing and/or deletion/duplication) of *APOB*, *LDLR*, *LDLRAP1* and *PCSK9* genes. If the individual to be tested has an affected first- or second-degree relative with a diagnosis of FH functional variant(s), test for KFV.

*****Two or more measurements, including assessment after intensive lifestyle modification.[20]

Hypertrophic Cardiomyopathy – Nonsyndromic (*ACTC1*, *MYBPC3*, *MYH7*, *MYL2*, *MYL3*, *TNNI3*, *TNNT2* and *TPMI* Genes)

Humana members may be eligible under the Plan for **genetic testing for hypertrophic cardiomyopathy (HCM)** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**

  - Individual to be tested has an affected first-degree relative in whom a pathogenic or likely pathogenic HCM variant has been identified; **OR**

    Testing Strategy: test for KFV

  - Individual to be tested has been diagnosed with left ventricular hypertrophy (LVH) using noninvasive cardiac imaging (eg, electrocardiogram [ECG], echocardiography and/or cardiac magnetic resonance imaging [MRI]) and no identifiable cause (eg, valvular disease, hypertension, infiltrative or neuromuscular disorder) has been identified

    Testing Strategy: perform targeted multigene analysis for pathogenic variants of *ACTC1, MYBPC3*, *MYH7*, *MYL2*, *MYL3, TNNI3*, *TNNT2* and *TPMI* genes

Long QT Syndrome (*KCNH2, KCNQ1* and *SCN5A* Genes)

Humana members may be eligible under the Plan for **genetic testing for long QT syndrome (LQTS)** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**

- Individual to be tested has prolonged QT interval on ECG in whom an acquired cause of QT interval prolongation has been ruled out (eg, bradycardia, electrolyte imbalances, heart failure or medications); **OR**

  Testing Strategy for LTQS (Affected):

  1. Testing begins with sequence analysis of *KCNH2, KCNQ1 and SCN5A* genes

  2. Deletion/duplication analysis may be performed next if no pathogenic variant is identified

- Individual to be tested has an affected first-degree relative in whom a pathogenic or likely pathogenic LQTS variant has been identified

  Testing Strategy: test for KFV

Coverage Limitations

Humana members may **NOT** be eligible under the Plan for **genetic testing for cardiac conditions** for any indications or tests other than those listed above including, but may not be limited to:

- Cardiovascular disease (CVD) risk markers, alone or within panels including, but may not be limited to:
  - 4q25 genotype testing (eg, 4q25-AF Risk Genotype, Cardio IQ 4q25-AF Risk Genotype)
  - 9p21 genotype testing (eg, 9p21 Genotype)
  - Apolipoprotein E (Apo E) genotype testing
  - CARDIO inCode-Score (0401U)
  - Hypercoagulation, prothrombin or thrombophilia genetic testing including, but not limited to:
    - Factor II (thrombin) (*F2* gene)
    - Factor V Leiden (*F5* gene)
    - Plasminogen activator inhibitor (PAI-1)
  - LPA Intron-25 genotype testing (eg, Cardio IQ Intron-25 Genotype, LPA Intron-25 Genotype
  - Multianalyte DNA analysis of SNPs reported as a risk score for a CVD event (eg, CardioRisk+ [0466U], Epi+GenCHD [0439U] and PrecisionCHD [0440U])
  - ST2 testing (eg, Cardio IQ ST2 [83006])
- Comprehensive or multicondition multigene panels, including but may not be limited to:
  - Arrhythmia Panel
  - AtheroGxOne
  - Cardiomyopathies Del/Dup Panel
  - Cardiomyopathy and Arrhythmia Panel

- Cardiomyopathy Panel
- CardioNext
- CMNext
- Combined Cardiac Panel
- Comprehensive Cardiomyopathy Multi-Gene Panel
- DCMNext
- GeneSeq: Cardio-Familial Arrhythmia Panel
- GeneSeq: Cardio Familial Cardiomyopathy Profile
- Genomic Unity Cardiac Ion Channelopathies Analysis
- HCMNext
- Invitae Arrhythmia and Cardiomyopathy Comprehensive Panel
- Invitae Arrhythmia Comprehensive Panel
- Invitae Arrhythmogenic Cardiomyopathy Panel
- Invitae Cardiomyopathy Comprehensive Panel
- Invitae Hypertrophic Cardiomyopathy Panel
- LongQTNext
- Pan Cardiomyopathy Panel
- RhythmNext

- Health and wellness single nucleotide polymorphism (SNP) genotyping tests (eg, Cardiac Healthy Weight DNA Insight, Healthy Woman DNA Insight)

These are considered experimental/investigational as they are not identified as widely used and generally accepted for the proposed uses as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for **genetic testing for cardiac conditions** for **ANY** genes, indications or tests other than those listed above including:

- Brugada syndrome

- Individual to be tested has an affected first-, second- or third-degree relative with a negative genetic testing result for the associated condition

- KFV detection analysis using either of the following methods:

  - Multigene panel that includes the KFV

  - Sequencing, deletion/duplication analysis or large genomic rearrangement analysis (conducted individually, as comprehensive testing or sequentially) without KFV results of a first, second- or third-degree relative

- Deletion/duplication information is obtained as part of the sequencing procedure but submitted as an independent analysis

These are considered not medically necessary as defined in the member's individual certificate. Please refer to the member's individual certificate for the specific definition.

Humana members may **NOT** be eligible under the Plan for **multigene panels** unless ALL genes in the panel meet disease- or gene-specific criteria (Refer to Coverage Determination section or Limitations section for single genes in a panel). These are considered experimental/investigational as they are not identified as widely used and generally accepted for the proposed uses as reported in nationally recognized peer-reviewed medical literature published in the English language.

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)	**Not Covered**
81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)	**Not Covered if used to report any test outlined in Coverage Limitations section**
81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)	**Not Covered**
81229	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities	**Not Covered if used to report any test outlined in Coverage Limitations section**
81240	F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant	**Not Covered if used to report any test outlined in Coverage Limitations section**
81241	F5 (coagulation factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant	**Not Covered if used to report any test outlined in Coverage Limitations section**
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)	**Not Covered**

81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G>A, c.173+1000C>T)	**Not Covered**
81381	HLA Class I typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, B*57:01P), each	**Not Covered if used to report any test outlined in Coverage Limitations section**
81400	MOLECULAR PATHOLOGY PROCEDURE LEVEL 1	**Not Covered if used to report any test outlined in Coverage Limitations section**
81401	MOLECULAR PATHOLOGY PROCEDURE LEVEL 2	**Not Covered if used to report any test outlined in Coverage Limitations section**
81402	MOLECULAR PATHOLOGY PROCEDURE LEVEL 3	**Not Covered if used to report any test outlined in Coverage Limitations section**
81403	MOLECULAR PATHOLOGY PROCEDURE LEVEL 4	**Not Covered if used to report any test outlined in Coverage Limitations section**
81404	MOLECULAR PATHOLOGY PROCEDURE LEVEL 5	**Not Covered if used to report any test outlined in Coverage Limitations section**
81405	MOLECULAR PATHOLOGY PROCEDURE LEVEL 6	**Not Covered if used to report any test outlined in Coverage Limitations section**
81406	MOLECULAR PATHOLOGY PROCEDURE LEVEL 7	**Not Covered if used to report any test outlined in Coverage Limitations section**
81407	MOLECULAR PATHOLOGY PROCEDURE LEVEL 8	**Not Covered if used to report any test outlined in Coverage Limitations section**
81408	MOLECULAR PATHOLOGY PROCEDURE LEVEL 9	**Not Covered if used to report any test outlined in Coverage Limitations section**

81413	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A	**Not Covered**
81414	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1	**Not Covered if used to report any test outlined in Coverage Limitations section**
81439	Hereditary cardiomyopathy (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (eg, DSG2, MYBPC3, MYH7, PKP2, TTN)	**Not Covered if used to report any test outlined in Coverage Limitations section**
81479	Unlisted molecular pathology procedure	**Not Covered if used to report any test outlined in Coverage Limitations section**
83006	Growth stimulation expressed gene 2 (ST2, Interleukin 1 receptor like-1)	**Not Covered**
85415	Fibrinolytic factors and inhibitors; plasminogen activator	**Not Covered if used to report any test outlined in Coverage Limitations section**
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family	
0237U	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia), genomic sequence analysis panel including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions	**Not Covered**
0401U	Cardiology (coronary heart disease [CAD]), 9 genes (12 variants), targeted variant genotyping, blood, saliva, or buccal swab, reported as a genetic risk score for a coronary event	**Not Covered** **New Code Effective 07/01/2023**

0439U	Cardiology (coronary heart disease [CHD]), DNA, analysis of 5 single-nucleotide polymorphisms (SNPs) (rs11716050 [LOC105376934], rs6560711 [WDR37], rs3735222 [SCIN/LOC107986769],rs6820447 [intergenic], and rs9638144 [ESYT2]) and 3 DNAmethylation markers (cg00300879 [transcription start site {TSS200} of CNKSR1], cg09552548[intergenic], and cg14789911 [body of SPATC1L]), qPCR and digital PCR, whole blood, algorithm reported as a 4-tiered risk score for a 3-year risk of symptomatic CHD	**Not Covered** **New Code Effective 04/01/2024**
0440U	Cardiology (coronary heart disease [CHD]), DNA, analysis of 10 single-nucleotide polymorphisms (SNPs) (rs710987 [LINC010019], rs1333048 [CDKN2B-AS1], rs12129789 [KCND3], rs942317 [KTN1-AS1], rs1441433 [PPP3CA], rs2869675 [PREX1], rs4639796 [ZBTB41], rs4376434 [LINC00972], rs12714414 [TMEM18], and rs7585056 [TMEM18]) and 6 DNAmethylation markers (cg03725309 [SARS1], cg12586707 [CXCL1, cg04988978 [MPO], cg17901584 [DHCR24-DT], cg21161138 [AHRR], and cg12655112[EHD4]), qPCR and digital PCR, whole blood, algorithm reported as detected or not detected for CHD	**Not Covered** **New Code Effective 04/01/2024**
0466U	Cardiology (coronary artery disease [CAD]), DNA, genomewide association studies (564856 single-nucleotide polymorphisms [SNPs], targeted variant genotyping), patient lifestyle and clinical data, buccal swab, algorithm reported as polygenic risk to acquired heart disease	**Not Covered** **New Code Effective 07/01/2024**
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**
S0265	Genetic counseling, under physician supervision, each 15 minutes	
S3861	Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada Syndrome	**Not Covered**
S3865	Comprehensive gene sequence analysis for hypertrophic cardiomyopathy	**Not Covered**
S3866	Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family	**Not Covered if used to report any test outlined in Coverage Limitations section**

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Appendix

Appendix A
Pre- and Post-Test Genetic Counseling Criteria

Pre- and post-test genetic counseling performed by any of the following qualified medical professionals
Genetic counselor who is board-certified or board-eligible by the American Board of Medical Genetics and Genomics (ABMGG) or American Board of Genetic Counseling, Inc (ABGC) and is not employed by a commercial genetic testing laboratory; **OR**
Genetic clinical nurse (GCN) or advanced practice nurse in genetics (APNG) who is credentialed by the Genetic Nursing Credentialing Commission (GNCC) or the American of Nurses Credentialing Center (ANCC) and is not employed by a commercial genetic testing laboratory; **OR**
Medical geneticist who is board-certified or board-eligible by ABMGG; **OR**
Treating physician who has evaluated the individual to be tested and has completed a family history of three generations

Appendix B
Family Relationships

Degree of Relationship	Definition
First-degree	Child, full-sibling, parent

Second-degree	Aunt, uncle, grandchild, grandparent, nephew, niece, half-sibling
Third-degree	First cousin, great aunt, great-uncle, great-grandchild, great-grandparent, half-aunt, half-uncle

Change Summary

- 07/25/2024 Annual Review, No Coverage Change.