GENESEQ® CARDIO

# Genetic Testing for Familial Cardiac Disease

labcorp

# A comprehensive portfolio and access to deep expertise to support you in assessing genetic risks for cardiac disease in your patients and their families.

GeneSeq® Cardio offers comprehensive genetic testing for clinical indications associated with cardiomyopathies, arrhythmias, aortopathies, RASopathies, congenital heart defects, early-onset coronary artery disease and familial hypercholesterolemia. Identification of a pathogenic variant(s) in genes associated with these cardiovascular disorders is helpful in confirming a clinical diagnosis, defining a genetic etiology and directing treatment options. This information can also be used to identify at-risk family members, thereby allowing for earlier initiation of preventative treatment and reducing the risk of heart attack, stroke and sudden cardiac death. Labcorp also offers full gene sequencing* for all genes included into GeneSeq® Cardio panels.

# Gene/panel testing options

| Test Name | | Test No. |
|---|---|---|
| **GeneSeq® Cardio: Familial Cardiomyopathy Panel** | | **482207** |
| Genes assessed (67) | *ABCC9, ACTC1, ACTN2, ALMS1, ALPK3, ANKRD1, APOA1, BAG3, CALR3, CAV3, CRYAB, CSRP3, DES, DMD, DNAJC19, DOLK, DSC2, DSG2, DSP, DTNA, EMD, EYA4, FHL1, FKRP, FKTN, FLNC, GLA, JPH2, JUP, LAMA4, LAMP2, LDB3, LMNA, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYLK2, MYOT, MYOZ2, MYPN, NEBL, NEXN, PDLIM3, PKP2, PLN, PRDM16, PRKAG2, RBM20, RYR2, SCN5A, SGCD, SLC25A4, TAFAZZIN, TCAP, TGFB3, TMEM43, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TRIM63, TTN*, TTR, VCL* | |
| **GeneSeq® Cardio: Familial Arrhythmia Panel** | | **482225** |
| Genes assessed (51) | *AKAP9, ANK2, CACNA1C, CACNB2, CALM1, CALM2, CALM3, CASQ2, CAV3, CTNNA3, DES, DSC2, DSG2, DSP, FLNC, GJA5, GPD1L, HCN4, JUP, KCNA5, KCND2, KCND3, KCNE1, KCNE2, KCNE3, KCNE5, KCNH2, KCNJ2, KCNJ5, KCNJ8, KCNQ1, LIG3, NPPA, PKP2, PLN, PRKAG2, RANGRF, RYR2, SCN10A, SCN1B, SCN2B, SCN3B, SCN4B, SCN5A, SLMAP, SNTA1, TECRL, TGFB3, TMEM43, TRDN, TRPM4* | |
| **GeneSeq® Cardio: Familial Aortopathy Panel** | | **482189** |
| Genes assessed (28) | *ACTA2, BGN, CBS, COL3A1, COL5A1, COL5A2, EFEMP2, FBN1, FBN2, FLNA, LOX, MAT2A, MED12**, MFAP5, MYH11, MYLK, NOTCH1, PLOD1, PRKG1, SLC2A10, SMAD2, SMAD3, SMAD4, SMAD6, TGFB2, TGFB3, TGFBR1[+], TGFBR2* | |
| **GeneSeq® Cardio: Noonan Syndrome/RASopathies Panel** | | **482279** |
| Genes assessed (20) | *BRAF, CBL, HRAS, KRAS, LZTR1, MAP2K1, MAP2K2, MRAS, NF1, NRAS, PPP1CB, PTPN11, RAF1, RASA2, RIT1, RRAS, SHOC2, SOS1, SOS2, SPRED1* | |
| **Noonan Syndrome, Fetal Analysis** | | **482299** |
| Genes assessed (19) | *BRAF, CBL, HRAS, KRAS, LZTR1, MAP2K1, MAP2K2, MRAS, NRAS, PPP1CB, PTPN11, RAF1, RASA2, RIT1, RRAS, SHOC2, SOS1, SOS2, SPRED1* | |
| **GeneSeq® Cardio: Familial Congenital Heart Disease Panel** | | **482318** |
| Genes assessed (17) | *CHD7, ELN, FOXH1, GATA4, GATA6, GDF1, HAND1, JAG1, NKX2-5, NKX2-6, NOTCH1, NR2F2, SMAD6, TBX1[++], TBX5, TBX20, ZFPM2* | |
| **GeneSeq® Cardio: Familial Hypercholesterolemia Panel** | | **482261** |
| Genes assessed (4) | *APOB***, LDLR, LDLRAP1, PCSK9* | |
| **GeneSeq® Cardio: Early-onset Coronary Artery Disease/ Familial Hypercholesterolemia Panel** | | **482243** |
| Genes assessed (12) | *ABCA1, ABCG5, ABCG8, APOA1, APOA5, APOB***, APOC3, LDLR, LDLRAP1, LPL, PCSK9, PON2* | |

*Exons 154 and 155 are not included.
**Only the c.3020A>G (p.N1007S) MED12 mutation is sequenced.
***Partial sequencing is performed for APOB (556 bp of exon 26).
[+] Exon 1 is not included.
[++] Exon 3 excludes the chr22:19748428-19748611 region.

# Single gene analysis options

| Test Name | Genes Description | Test No. |
|---|---|---|
| *FBN1* (Marfan syndrome) Full Gene Sequencing | *FBN1* full gene sequencing | **482336** |
| GeneSeq® PLUS, *TTR* | *TTR* (Transthyretin amyloidosis) full gene sequencing | **482353** |
| GeneSeq® Cardio Single Gene Analysis | Full gene sequencing for any gene(s) on any of the GeneSeq Cardio panels | **485149** |
| GeneSeq® Cardio Targeted Variant Analysis | Targeted variant analysis for any gene(s) on any of the GeneSeq Cardio panels | **485208** |

Visit the online Test Menu at **Labcorp.com** for more information, including test methodology and specimen requirements. Panels can be ordered alone or in combination. To request specimen collection supplies, please call 866-647-0735.

### Clinical Utility

- Confirm or support a clinical diagnosis or suspected diagnosis
- Differentiate between disorders with phenotypically similar clinical presentations
- Identify the need for regular cardiac screening, lifestyle changes, or pharmacological or surgical intervention to prevent the progression of cardiac disease and secondary complications
- Facilitate genetic testing for family members that may also be at risk for heart attack, stroke or sudden cardiac death

### GeneSeq® Cardio: Familial Cardiomyopathy Panel

Inherited cardiomyopathies encompass a heterogeneous group of disorders that affect the cardiac muscle and lead to an increased risk for arrhythmias, thrombolytic events, and sudden cardiac death (SCD). The major types of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy, and restrictive cardiomyopathy. The most common cardiomyopathies, HCM and DCM, have a prevalence of 1/500 and 1/2500, respectively.[1] Rarer types include left ventricular non compaction and amyloid-associated cardiomyopathies, such as transthyretin amyloidosis and apolipoprotein A-1 amyloidosis.

Common clinical signs of cardiomyopathies are those that are observed in heart failure such as reduced ejection fraction, fatigue, peripheral edema, dyspnea on exertion and syncope. Identification of at-risk individuals can be challenging, since abnormal electrocardiogram or echocardiogram profiles may not always be clear, patients may be asymptomatic, age of onset varies with etiology, and SCD may be the presenting clinical manifestation.

Cardiomyopathies have an autosomal dominant, autosomal recessive, X-linked, or mitochondrial mode of inheritance. Reduced penetrance and variable expressivity are often observed. Identification of a pathogenic variant may help confirm a diagnosis, aid in medical management and determining the prognosis, and allow for cascade testing of at-risk family members.

### GeneSeq® Cardio: Familial Arrhythmia Panel

Arrhythmias are a heterogeneous group of disorders that result in a disruption of cardiac rhythm and can lead to a high risk of sudden cardiac death. Commonly recognized arrhythmia disorders include long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, atrial fibrillation and arrhythmogenic right ventricular cardiomyopathy.

While their clinical presentations are generally similar and may include syncope, palpitations, dizziness, dyspnea, stroke and/or sudden cardiac death, each of these disorders has a different etiology and prognosis. Age of onset varies by condition and can, in some cases, occur during early childhood or adolescence.

Inherited arrhythmias are caused by pathogenic variants in the ion channels of the cardiac muscle and their interacting proteins.[2] The majority of these variants have an autosomal dominant mode of inheritance with reduced penetrance and variable expressivity; however, autosomal recessive and X-linked modes of inheritance are also observed. Identification of a pathogenic variant may help confirm a diagnosis, aid in medical management and allow for genetic testing of at-risk family members who may not have clinical signs of disease.

### GeneSeq® Cardio: Familial Aortopathy Panel

Aortopathies encompass a variety of disorders that lead to asymptomatic aortic enlargement/dilation and may result in life-threatening aneurysms and/or dissections. Early diagnosis is critical in order to slow aortic dilation and prevent aortic dissection or rupture; however, overt disease symptoms are generally absent until an acute event occurs. Common signs and symptoms of aortic dissection may include pain in the back, jaw or chest, hypo- or hyper-tension, severe abdominal pain, nausea, dizziness and rapid heartbeat.

It is estimated that approximately 20% of thoracic aortic aneurysms/ dissections (TAAD) are inherited and can be nonsyndromic or part of a multisystem syndrome.[3] Examples of common aortopathy syndromes include Marfan syndrome, Loeys-Dietz syndrome or Ehlers-Danlos syndrome. TAADs have autosomal dominant, autosomal recessive and X-linked modes of inheritance. Identification of pathogenic variants may provide clinically actionable information that leads to prophylactic measures and surgical intervention, which varies considerably between different syndromic forms of TAAD. Identification of pathogenic variants will also help facilitate genetic testing of at-risk family members.

### GeneSeq® Cardio: Noonan Syndrome /RASopathies Panel

Noonan Syndrome and related conditions, also known as the RASopathies, are a group of congenital disorders with overlapping phenotypes and a shared molecular basis for disease. These disorders include Noonan syndrome, Noonan syndrome with loose anagen hair, Noonan syndrome with multiple lentigines, Cardiofaciocutaneous syndrome, Costello syndrome, Neurofibromatosis type 1 and Legius syndrome. Noonan syndrome, the most common RASopathy, is estimated to affect between 1 in 1000-2500 individuals.[4]

Common signs and symptoms of the RASopathies include short stature, facial dysmorphisms, developmental delay, an increased risk for certain cancers and congenital heart defects, including pulmonary valve stenosis. The clinical findings may be highly variable even among family members.

The RASopathies are caused by pathogenic variants in the RAS/MAPK signaling pathway that are inherited in an autosomal dominant manner. One exception, *LTZR1,* is also associated with autosomal recessive Nooanan syndrome.[4] Many cases of Noonan syndrome and the majority of cases of Costello syndrome and Cardiofaciocutaneous syndrome are observed to be the result of *de novo* variants.

### Noonan Syndrome, Fetal Analysis

Noonan syndrome and related conditions are congenital disorders that are typically diagnosed early in life. Signs and symptoms may manifest prenatally. The most common prenatal ultrasound findings are increased nuchal translucency, cystic hygroma, hydrops fetalis, pleural effusion, polyhydramnios, distended jugular lymphatic sacs and cardiac and renal anomalies. Prenatal testing is recommended in the presence of abnormal ultrasound findings suggestive of a Noonan spectrum disorder or if a family member was previously diagnosed with a Noonan spectrum disorder.

### GeneSeq® Cardio: Familial Hypercholesterolemia Panel

Familial Hypercholesterolemia (FH) is a common yet largely underdiagnosed genetic disorder that is estimated to occur in greater than 1 in 250 individuals.[5,6] FH is characterized by very high blood low-density lipoprotein (LDL) levels, which lead to abnormal lipid deposition in body tissues. These individuals have an increased risk of early onset coronary artery disease (CAD), which can lead to heart attack, stroke and premature death.

Signs and symptoms of FH include high serum LDL levels, xanthomas and CAD. While diet and lifestyle changes are generally recommended as the first-line treatment for hypercholesterolemia, especially in children, these measures are rarely effective by themselves in patients with familial hypercholesterolemia (FH).[7] Patients with FH may require pharmacological intervention starting in childhood.[7,8]

FH typically exhibits autosomal dominant inheritance with more than 90% of cases caused by pathogenic variants in the *LDLR, APOB* and *PCSK9* genes.[9] A recessive form is also known to be caused by pathogenic variants in *LDLRAP1.* The diagnosis of FH at an early age is critical for medical intervention, as undiagnosed or misdiagnosed individuals may have significantly shortened life spans. Early identification also allows for subsequent testing of at-risk family members.

## GeneSeq® Cardio: Early-onset Coronary Artery Disease/ Familial Hypercholesterolemia e Panel

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality in the United States.[10] CAD is caused by atherosclerosis, a progressive narrowing and hardening of arteries and blood vessels that can lead to an increased risk of cardiovascular disease, heart attack and premature death. Risk factors include cigarette smoking, hypertension, diabetes, and various forms of dyslipidemia, most notably hypercholesterolemia. The familial form, known as familial hypercholesterolemia (FH), occurs in greater than 1 in 250 individuals.[6]

Signs and symptoms of CAD or FH may include angina, cold sweats, dizziness, nausea, shortness of breath, sleep disturbances, weakness, xanthomas and corneal lipid rings. Some individuals may not exhibit overt symptoms until they experience a life threatening acute cardiac event such as heart attack or sudden cardiac arrest.

Pathogenic variants in genes *APOB, LDLR, LDLRAP1* and *PCSK9* account for more than 90% of FH cases.[9] An increased risk of CAD is also associated with pathogenic variants in the lipid biosynthesis and metabolism genes *ABCA1, ABCG5, ABCG8, APOA1, APOA5, APOC3, LPL,* and *PON2.*[11-15] FH and early-onset CAD are inherited in both an autosomal dominant and autosomal recessive manner. Reduced penetrance can also be observed. Early identification of individuals with pathogenic variants in genes associated with CAD or FH may allow for timely initiation of treatment that may help prevent early-onset CAD and allow for subsequent testing of at-risk family members.

## GeneSeq® Cardio: Familial Congenital Heart Disease Panel

Congenital heart defects (CHD) are the most commonly occurring birth defects, affecting ~1% of live births and ~10% of stillbirths.[16,17] CHDs are a significant cause of neonatal morbidity and mortality. They have a heterogeneous etiology that can be explained by a single gene disorder in ~3-5% of cases.[18] CHDs can occur in isolation or as part of a syndrome and are inherited in an autosomal dominant, autosomal recessive or X-linked mode of inheritance. Up to 10% of CHDs are the result of *de novo* variants.[19] Identification of a pathogenic variant may help confirm a diagnosis of inherited CHDs, assist with clinical management of CHDs and facilitate the identification of at-risk family members.


**References**

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