Pulmonary arterial hypertension (PAH) is increased pulmonary artery pressure in the absence of common causes of pulmonary hypertension, such as lung, heart, or thromboembolic chronic diseases. It is thought that both genetic and environmental factors that alter vascular structure and function contribute to the pathogenesis of PAH.

Thoracic aortic aneurysm and dissection (TAAD) has a highly variable presentation and age of onset. It is characterized by dilation and dissections of the ascending aorta and/or ascending aortic arch. An aneurysm involving the descending thoracic aorta is observed rarely. Without surgical repair of the ascending aorta, individuals with TAAD have continual enlargement of the ascending aorta that leads to an acute aortic dissection. Isolated TAAD is typically inherited in an autosomal dominant manner with variable expression and reduced penetrance. Only about 20% of familial non-syndromic TAAD is attributed to pathogenic variants in known genes.

The prevalence of HCM is approximately 1 in 500 and ~55-70% of cases are caused by a mutation in one of the genes that encode a part of the myocardium. The onset of HCM is usually during adolescence or young adulthood; however, it can range from infancy to much later in adult life. Other features include syncope, presyncope, shortness of breath, chest pain, orthostasis, dizziness, lightheadedness, syncope, rapid heartbeat, shortness of breath, chest pain, and sudden cardiac arrest.

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is characterized by cardiac electrical instability. This instability can be exacerbated by acute activation of the adrenergic nervous system, such as during exercise or extreme emotional events. These episodes have an underlying cause of ventricular tachycardia, which may progress into ventricular fibrillation.

Dilated cardiomyopathy can range from asymptomatic to progressive heart failure. Other features include syncope, presyncope, shortness of breath, chest pain, orthostasis, and palpitations. The onset of HCM is usually during adolescence or young adulthood; however, it can range from infancy to much later in adult life. The prevalence of HCM is approximately 1 in 500 and ~55-70% of cases are caused by a mutation in one of the genes that encode a part of the sarcosome.

Familial left ventricular noncompaction (LVNC) is an autosomal dominant or X-linked cardiomyopathy. The distinct diagnostic features of LVNC (a thick, bilayered myocardium, deep intertrabecular recesses, and prominent ventricular trabeculations) are secondary to an arrest of myocardial maturation during embryo development. Individuals with LVNC may be symptomatic or asymptomatic. Major complications of LVNC include heart failure, thromboembolic events, arrhythmias, and sudden cardiac death. Diagnosis can occur prenatally through late adulthood. The manifestation of LVNC is extremely variable, even within the same family. Approximately 30% of isolated LVNC are caused by a mutation in one of the genes that encode a part of the sarcomere.

Long QT Syndrome (LQTS) is characterized by a QT interval that is prolonged on the surface electrocardiogram and a predisposition to early afterdepolarizations and torsades de pointes. LQTS can present clinically with palpitations, presyncope, syncope, or sudden cardiac death.

Marfan Syndrome, Thoracic Aortic Aneurysm & Dissection (TAAD), and Related Disorders
Thoracic aortic aneurysm and dissection (TAAD) has a highly variable presentation and age of onset. It is characterized by dilation and dissections of the ascending thoracic aorta and/or ascending aortic arch. An aneurysm involving the descending thoracic aorta is observed rarely. Without surgical repair of the ascending aorta, individuals with TAAD have continual enlargement of the ascending aorta that leads to an acute aortic dissection. Isolated TAAD is typically inherited in an autosomal dominant manner with variable expression and reduced penetrance. Only about 20% of familial non-syndromic TAAD is attributed to pathogenic variants in known genes.

TAAD can also be present as part of a genetic syndrome. Marfan syndrome, Loey-Dietz syndrome, Ehlers-Danlos syndrome vascular type, multisystemic smooth muscle dysfunction syndrome, and congenital contractualarachnodactyly all have TAAD as part of their clinical spectrum.
Familial cases of PAH are usually inherited in an autosomal dominant manner. With the identification of pathogenic variants in genes known to cause PAH, what was previously thought to be idiopathic PAH is now known to be genetic. A pathogenic variant in the BMPR2 gene causes ~70% of hereditary cases of PAH and in 10-40% of idiopathic PAH. Pathogenic variants in the CAV1 gene cause PAH.

Heterozygous pathogenic variants in the ENG and ACVRL1 (previously known as ALK1) genes cause hereditary hemorrhagic telangiectasia (HHT). HHT is an autosomal dominant vascular disorder characterized by acquired cutaneous telangiectasias and arteriovenous malformations that can lead to the development of PAH.

Restrictive Cardiomyopathy
Restrictive cardiomyopathy (RCM) is a primary myocardial disorder in which the main feature, restrictive ventricular physiology, develops early in the disease. RCM is characterized by inadequate ventricular relaxation during diastole. Onset can range from childhood to late adult hood. Major complications of RCM can include congestive heart failure, cerebrovascular accidents, and arrhythmias. Cardiac restriction may occur secondary to many genetic syndromes, such as Pompe disease and Fabry disease.

Short QT Syndrome
Short QT syndrome (SQTS) is characterized by an abnormally short QT interval and susceptibility to both ventricular tachyarrhythmias and atrial fibrillation.

Sudden Cardiac Arrest
Sudden cardiac arrest is the abrupt loss of heart function due to a malfunction in the heart’s electrical system, such as an arrhythmia. The individual may or may not have been diagnosed with heart disease.

References:
- American Heart Association.
- GeneReviews.
- OMIM.

**Genes**

- ABC9, ACTA2, ACTC1, ACTN2, ACVRL1, AKAP9, ANK2, ANKRD1, BAG3, BMPR2, BRAF, CACNA1C, CACNB2, CASQ2, CAV1, CAV3, CBS, COL3A1, COL5A1, COL5A2, CRYAB, CSRP3, DES, DMD, DSC2, DSG2, DSP, DTNA, EMD, ENG, FBN1, FBN2, FHL2, FKTN, FLNA, GAA, GATAD1, GLA, GPD1L, HCN4, HRAS, JPH2, JUP, KCNE1, KCNE2, KCNE3, KCN2, KCNJ5, KCNJ8, KCNQ1, KRAS, LAMA4, LAMP2, LDB3, LMNA, MAP2K1, MAP2K2, MED12, MYBPC3, MYH11, MYH6, MYH7, MYL2, MYL3, MYLK, MYLK2, MYOZ2, MYL6, NEBL, NEXN, NKKX2.5, NRAS, PKP2, PLN, PRKAG2, PTPN11, RAF1, RANGRF, RBM20, RIT1, RYR2, SCN1B, SCN3B, SCN4B, SCN5A, SGCD, SKI, SLC2A10, SMAD3, SNTA1, SOS1, TAZ, TCAP, TGFBR2, TGFBRI, TGFBRII, TMEM43, TMPO, TNNC1, TNNI3, TNNI2, TPM1, TTN, TTR, VCL

**Indications**

This test is indicated for:
- Individuals with a cardiovascular condition.

**Methodology**

**Deletion/Duplication Analysis:** DNA isolated from peripheral blood is hybridized to a gene-targeted CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes that cover the entire genomic region.

**Detection**

**Deletion/Duplication Analysis:** Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient’s clinical and/or biochemical phenotype.

**Specimen Requirements**

**Submit only 1 of the following specimen types**

**Type:** DNA, Isolated

**Specimen Requirements:**
- Microtainer
- 3µg
- Isolation using the Perkin Elmer™Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

**Disclaimer:** This information is confidential and subject to change without notice. It may not be reproduced in whole or part unless authorized in writing by an authorized EGL representative.
Specimen Collection and Shipping:
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Whole Blood (EDTA)

Specimen Requirements:
EDTA (Purple Top)
Infants and Young Children (2 years of age to 10 years old): 3-5 ml
Older Children & Adults: 5-10 ml
Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Related Tests

- Individual gene sequencing analysis and deletion duplication analysis are available for the CAV3, DES, DMD, EMD, GAA, GLA, LAMP2, LMNA, RYR2, SGCD, and TCAP genes.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.
- Comprehensive Cardiovascular: Sequencing Panel.