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.

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 aorta. 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 contractual arachnodactyly all have TAAD as part of their clinical spectrum.

Pulmonary Arterial Hypertension
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.
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.

Note: This test does not detect the retrotransposon insertion in the 3' UTR of the FKTN gene common in some Asian populations. For patients with suspected Fukuyama congenital muscular dystrophy, testing for the FKTN insertion is recommended. Analysis for the FKTN insertion is available as a separate assay.

References:

- American Heart Association.
- GeneReviews.
- OMIM.

Genes

| ABC9, ACTA2, ACTC1, ACTN2, ACVRL1, AKAP9, ANK2, ANKRD1, BAG3, BMPR2, BRAF, CACNA1C, CACNB2, CALM1, CASQ2, CAV1, CAV3, CBS, COL3A1, COL5A1, COL5A2, CRYAB, CSRP3, CTNNA3, DES, DMD, DSC2, DSG2, DSP, DTNA, EMD, ENG, FBX1, FBX2, FHL2, FKTN, FLNA, GAA, GATAD1, GJA5, GLA, GP1D1, HCN4, JPH2, JUP, KCNA5, KCND3, KCNE1, KCNE2, KCNE3, KCNH2, KCNJ5, KCNJ8, KCNQ1, KRAS, LAMA4, LAMP2, LDB3, LAMA4, MAP2K1, MAP2K2, MED12, MYBPC3, MYH11, MYH6, MYH7, MYL2, MYL3, MYL5, MYLK, MYL2, MYOZ2, MYPN, NEBL, NEXN, NXK2-5, NPPA, NRG5, PDLIM3, PKP2, PLN, PRDM16, PRKAG2, PTPN11, RAF1, RANGRF, RBM20, RIT1, RYR2, SCN1B, SCN3B, SCN4A, SCN5A, SCGD, SK1, SLC22A5, SLC2A10, SMAD3, SNTA1, SOD1, TAZ, TCAP, TGFBR2, TGFBR3, TGFBR2, TMEM43, TMPO, TNCC1, TNIN3, TNNT2, TPM1, TRDN, TRPM4, TTN, TTR, VCL |

Indications

This test is indicated for:

- Individuals with a cardiovascular condition.

Methodology

Next Generation Sequencing: In-solution hybridization of all coding exons is performed on the patient’s genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

Detection

Next Generation Sequencing: Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions/duplications will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype.

Analytical Sensitivity: ~99%.

Specimen Requirements
Submit only 1 of the following specimen types

**Type: DNA, Isolated**

**Specimen Requirements:**
- Microtainer
- 15µg
- Isolation using the Perkin Elmer™Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

**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 24 hours of collection. Do not refrigerate or freeze.

**Type: Saliva**

**Specimen Requirements:**
- Orangene™ Saliva Collection Kit
- Orangene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

**Specimen Collection and Shipping:**
- Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

**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: Deletion/Duplication Panel.