EIF2AK4-Associated Disorders

**Indications for Ordering**
- Confirm diagnosis and genetic etiology of pulmonary capillary hemangiomatosis (PCH) or pulmonary veno-occlusive disease (PVOD) in a symptomatic individual
- Predictive testing for at-risk relatives of an individual with an EIF2AK4-associated disorder
- Carrier testing for the reproductive partner of an individual known to carry one or more EIF2AK4 gene variants

**Test Description**
Polymerase chain reaction followed by bidirectional sequencing of the entire EIF2AK4 gene coding region and intron/exon boundaries

**Tests to Consider**

**Primary test**
**EIF2AK4-Associated Disorders (EIF2AK4) Sequencing** 2010696
- Preferred test to confirm diagnosis or assess carrier status for an EIF2AK4-associated disorder, pulmonary capillary hemangiomatosis (PCH), and pulmonary veno-occlusive disease (PVOD), especially when molecular testing for variants in other genes associated with pulmonary arterial hypertension (PAH) has not identified a cause

**Related test**
**Pulmonary Arterial Hypertension (PAH) Panel, Sequencing and Deletion/Duplication** 2009345
- Preferred test to confirm diagnosis of pulmonary arterial hypertension (PAH), especially in those with known family history
  - Genes – ACVRL1, BMPR2, CAV1, EIF2AK4, ENG, KCNK3

**Disease Overview**

**Incidence** – rare

**Symptoms**
- Progressive dyspnea
- Cough
- Hemothysis
- Fatigue
- Weight loss
- Pulmonary arterial hypertension

**Diagnostic issues**
Variable presentation depending on the affected lung structures
- PCH may mimic idiopathic PAH, PVOD, or pulmonary hemosiderosis

**Pathophysiology**
Two different histological patterns of disease currently associated with EIF2AK4 variants – PCH and PVOD
- PCH – uncontrolled proliferation of capillaries in the pulmonary interstitium
  - Capillary invasion may impact the pulmonary veins or arteries, alveolar walls and alveolar space, intralobular fibrous septa and bronchi, pericardium, pleura, and/or mediastinal lymph nodes
- PVOD
  - Occlusion or narrowing of pulmonary veins and venules by fibrous tissue
  - Dilatation of alveolar capillaries and capillary proliferation may be noted
  - Dilatation of lymphatics can occur

**Genetics**
**Gene** – EIF2AK4

**Inheritance** – autosomal recessive

**Test Interpretation**

**Sensitivity/specificity**
- Clinical sensitivity
  - >90% for heritable EIF2AK4-related disorders
  - <10% for PAH
- Analytical sensitivity/specificity – 99%

**Results**
- Positive
  - Two pathogenic variants identified on opposite chromosomes
    - Confirms a diagnosis of PCH/PVOD
  - One pathogenic variant identified
    - Individual is at least a carrier of an EIF2AK4-associated disorder
- Negative – no pathogenic EIF2AK4 gene variant detected
  - Reduces but does not exclude the possibility of a hereditary form of PAH, PCH, or PVOD
- Inconclusive – one or more gene variants detected, but whether pathogenic or benign is unclear
Limitations

- Not detected
  - Deep intronic and regulatory region variants
  - Large exonic deletions and duplications
- Diagnostic errors can occur due to rare sequence variations