Vascular Malformations, 14 Genes

Indications for Ordering

Confirm clinical diagnosis of a vascular malformation disorder
- Capillary malformation-arteriovenous malformation syndrome (CM-AVM)
- Cerebral cavernous malformation (CCM)
- Glomuvenous malformation (GVM)
- Hereditary hemorrhagic telangiectasia (HHT)
- Juvenile polyposis syndrome/hereditary hemorrhagic telangiectasia (JPS/HHT)
- Multiple cutaneous and mucosal venous malformations (VMCM)
- Parkes Weber syndrome (PKWS)
- PTEN-related Proteus syndrome
- Pulmonary arterial hypertension (PAH)

Test Description

- Next generation sequencing for targeted capture of all coding exons and exon/intron junctions followed by massively parallel sequencing
  - Sequence variants reported are confirmed by Sanger sequencing
- Deletion/duplication analysis by custom-designed comparative genomic hybridization (CGH) array

Tests to Consider

Primary tests
Vascular Malformations Panel, Sequencing and Deletion/Duplication, 14 Genes 2007384
- Preferred DNA test to confirm clinical diagnosis of a genetic-related vascular malformation disorder

Related tests
Consider if patient/family has classic symptoms of HHT
- Hereditary Hemorrhagic Telangiectasia (HHT) Panel, Sequencing Deletion/Duplication, 5 Genes 2009337
- Hereditary Hemorrhagic Telangiectasia (ACVRL1 and ENG) Sequencing and Deletion/Duplication with Reflex to Juvenile Polyposis (SMAD4) Sequencing and Deletion/Duplication 2009008
- Hereditary Hemorrhagic Telangiectasia (ACVRL1 and ENG) Sequencing and Deletion/Duplication 0051381
- Hereditary Hemorrhagic Telangiectasia (ACVRL1 and ENG) Sequencing 0051380

Consider if clinical suspicion for PTEN-related disorder is high
- PTEN-Related Disorders (PTEN) Sequencing and Deletion/Duplication 2002470
- PTEN-Related Disorders (PTEN) Sequencing 2002722

Consider if clinical suspicion for CM-AVM syndrome is high
- RASA1-Related Disorders (RASA1) Sequencing 2002730

Consider for individuals with a clinical phenotype of juvenile polyposis
- Juvenile Polyposis (SMAD4) Sequencing and Deletion/Duplication 2001971
- Juvenile Polyposis (SMAD4) Sequencing 0051510

Consider for individuals with PAH and no other vascular findings
- Pulmonary Arterial Hypertension (PAH) Panel, Sequencing and Deletion/Duplication, Multigene 2009345
- Familial Mutation, Targeted Sequencing 2001961
  - Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Vascular malformation syndromes are caused by defects of blood vessels
- Typically categorized according to
  - Vessel type affected (venous, arterial, capillary, or combined)
  - Fast- vs. slow-flow lesions
- Most vascular malformations are sporadic
- Inherited forms are characterized by multiple lesions, which are often smaller and less often congenital than their sporadic counterparts

Symptoms
- Hemorrhage
- Effects of shunting through high-flow lesions (eg, cases of congestive heart failure)
- Localized pain
- Destruction/deformation of surrounding tissue
- Localized intravascular coagulopathy (LIC)
- Stroke
- Effects of resistance through occluded vessels

Genetics

Genes – see table
- Clinical variability is high and penetrance is often age related and reduced
Test Interpretation

Clinical sensitivity – dependent upon specific disorder

Results
- Positive – one copy of a pathogenic variant detected in ACVRL1, BMP9/GDF2, BMPR2, CAV1, CCM1/KRIT1, CCM2, CCM3/PDCD10, ENG, GLMN, KCNK3, PTEN, RASA1, SMAD4, or TEK gene
  - Confirms affected status for related disorder
- Negative – no pathogenic variant detected in ACVRL1, BMP9/GDF2, BMPR2, CAV1, CCM1/KRIT1, CCM2, CCM3/PDCD10, ENG, GLMN, KCNK3, PTEN, RASA1, SMAD4, or TEK gene
  - Decreases but does not exclude likelihood of diagnosis of a heritable vascular malformation disorder in a clinically affected individual
- Inconclusive – variants of unknown clinical significance may be identified in any of the 14 genes tested

Limitations
- Some small deletions or insertions may not be detected by massively parallel sequencing
- Not determined or evaluated
  - Variants in genes not listed
  - Deep intronic or regulatory region variants
  - Breakpoints of large deletions/duplications
- Copy number variants <1,000 base pairs may or may not be detected in the targeted genes
- Diagnostic errors may occur due to rare sequence variations

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene Description</th>
<th>NM #</th>
<th>OMIM #</th>
<th>Condition</th>
<th>Inheritance</th>
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**AD** = autosomal dominant