Juvenile Polyposis *SMAD4* and *BMPR1A* Sequencing and Deletion/Duplication

**Indications for Ordering**

**SMAD4** Sequencing and Deletion/Duplication
- Confirm a diagnosis of juvenile polyposis syndrome (JPS) or JPS/ hereditary hemorrhagic telangiectasia (HHT) syndrome in symptomatic individuals
- Confirm a diagnosis of HHT in symptomatic individuals if no variant was previously detected in the *ENG* and *ACVRL1* genes by sequencing and deletion/duplication

**BMPR1A** Sequencing and Deletion/Duplication
- Confirm a diagnosis of JPS syndrome in symptomatic individuals

**Contraindications for ordering**
- Do not use for presymptomatic or diagnostic testing when a causative *BMPR1A* or *SMAD4* variant has previously been identified in the family
  - To test individuals for a specific variant, use the more cost-effective Familial Mutation, Targeted Sequencing test and provide a copy of the lab report detailing the familial variant
- *BMPR1A* testing should not be ordered for HHT
  - Gene is not causative for HHT or JPS/HHT
- Do not use for prenatal testing

**Test Description**
- Polymerase chain reaction/bidirectional sequencing of the entire *SMAD4* and *BMPR1A* coding regions and intron/exon borders
- Multiplex ligation-dependent probe amplification for large deletion/duplication analysis

**Tests to Consider**

**Primary tests**

- *Juvenile Polyposis (SMAD4) Sequencing and Deletion/Duplication 2001971*
  - Diagnostic and predictive testing for JPS or JPS/HHT
- *Juvenile Polyposis Syndrome (BMPR1A) Sequencing and Deletion/Duplication 2004992*
  - Diagnostic and predictive testing for JPS

**Related tests**

- *Juvenile Polyposis (SMAD4) Sequencing 0051510*
  - Diagnostic and predictive testing for JPS or JPS/HHT
- *Juvenile Polyposis Syndrome (BMPR1A) Sequencing 2004988*
  - Diagnostic and predictive testing for JPS
- *Familial Mutation, Targeted Sequencing 2001961*
  - Useful when a pathogenic familial variant identifiable by sequencing is known

**Disease Overview**

**Prevalence**
- JPS – 1/16,000-100,000
- JPS/HHT – unknown

**Symptoms**

**JPS**
- Multiple juvenile (hamartomatous) polyps in the stomach, small intestine, colon, and rectum
  - “Juvenile” – refers to particular type of hamartomatous polyp, not age of onset
- Onset varies from childhood to middle age
  - By age 20, most affected individuals have some polyps
- Gastrointestinal (GI) tract cancer risk estimates
  - ~20% by 35 years
  - Approaches 70% by 60 years

**HHT**
- Recurrent nosebleeds
- Telangiectases (mouth, face, hands, GI tract)
- Brain, lung, and liver arteriovenous malformations
  - Brain arteriovenous malformations are congenital and are at risk to bleed during infancy and early childhood

**JPS/HHT**
- Characterized by manifestation of both JPS and HHT

**Diagnostic issues**

DNA testing recommended for individuals with at-risk relatives
- In infancy for JPS/HHT
- By 15 years for JPS
Screening and medical management issues

- Screening/detection
  - Individuals with a variant in either gene should begin GI tract screening by 15 years
    - CBC
    - Colonoscopy (lower endoscopy)
    - Upper endoscopy
  - Screening should begin earlier if rectal bleeding, anemia, abdominal pain, constipation, or diarrhea occur
- Disease management
  - Usually involves routine endoscopy with removal of polyps to reduce risk of bleeding, obstruction, and cancer
  - Occasionally, large numbers of polyps may necessitate removal of a portion of the stomach or intestine

Genetics

Genes – SMAD4, BMPR1A

Inheritance – autosomal dominant for JPS and JPS/HHT syndrome

Penetrance – germline JPS variants predicted to be >90% for polyp development

De novo variants – 25% of JPS cases

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity
  - SMAD4 or BMPR1A variants are causative for ~50% of JPS
    - 28% of individuals with JPS have SMAD4 variants
    - 21% detectable by sequencing (Aretz, 2007; Calva-Cerqueira, 2009; van Hattem, 2008)
    - 7% detectable by large deletion/duplication analysis (Aretz, 2007; Calva-Cerqueira, 2009; van Hattem, 2008)
  - 20-25% of patients with JPS have BMPR1A variants (Howe, 2004; Sayed, 2002)
    - ~18% detectable by sequencing (Aretz, 2007; Calva-Cerqueira, 2009; Calva-Cerqueira, 2010; van Hattem, 2008)
    - ~4% detectable by large deletion/duplication analysis (Aretz, 2007; Calva-Cerqueira, 2009; van Hattem, 2008)
  - JPS/HHT syndrome
    - Nearly 100% of individuals have a variant in SMAD4
      - ~95% detectable by sequencing
      - ~5% detectable by large deletion/duplication analysis
    - SMAD4 variants are causative for ~1-3% of HHT (Prigoda, 2006)
- Analytical sensitivity/specificity for sequencing and MLPA for SMAD4 and BMPR1A – 99%

Results

- Positive – pathogenic variant detected
  - Predicted to cause JPS, JPS/HHT, or HHT
- Negative – no pathogenic variant detected
  - Does not rule out JPS, JPS/HHT, or HHT due to possibility of undetectable SMAD4 or BMPR1A variants
  - Medical management of patient should rely on clinical findings and family history
- Uncertain
  - Gene variant detected, but whether variant is benign or pathogenic is unclear
  - Medical management of patient should rely on clinical findings and family history
- Juvenile Polyposis Patient History Form documenting patient symptoms and family history of both JPS and HHT is required with specimen submission for optimal test interpretation

Limitations

- Not determined or evaluated
  - Regulatory region or deep intronic variants
  - Breakpoints of large deletions/duplications
  - Variants in genes other than SMAD4 or BMPR1A
  - Large deletions/duplications of exons 7 and 8 in BMPR1A gene may not be detected
  - Diagnostic errors can occur due to rare sequence variations

References