Juvenile Polyposis Syndrome: **SMAD4 Gene Sequencing**

**Test Code:** UT  
**Turnaround time:** 4 weeks  
**CPT Codes:** 81479 \*1

### Condition Description

Juvenile polyposis syndrome (JPS) is an autosomal dominant condition characterized by predisposition to hamartomatous polyps in the gastrointestinal (GI) tract, specifically in the stomach, small intestine, colon, and rectum. The term "juvenile" refers to the type of polypl rather than to the age of onset of polyps. Most individuals with JPS have some polyps by age 20 years; some may have only four or five polyps over their lifetime, whereas others in the same family may have more than a hundred. If the polyps are left untreated, they may cause bleeding and anemia. Most juvenile polyps are benign; however, malignant transformation can occur. Most of this increased risk is attributed to colon cancer, but cancers of the stomach, upper GI tract, and pancreas have been reported. The incidence of colorectal cancer is 17%-22% by age 35 years and approaches 68% by age 60 years. The median age is 42 years. The incidence of gastric cancer is 21% in those with gastric polyps.

JPS is clinically diagnosed if any one of the following findings is present: more than five juvenile polyps of the colorectum; multiple juvenile polyps throughout the GI tract; any number of juvenile polyps and a family history of juvenile polyps. Juvenile polyps are hamartomas with a distinct histology that differs from that of adenomas. The genes known to be associated with JPS are **SMAD4** and **BMPR1A**. Approximately 20% of individuals with JPS have mutations in **SMAD4** (18q21.1); approximately 20% have mutations in **BMPR1A**. Recent studies suggest that deletion/duplication testing can identify an additional 9%-14% of mutations in **SMAD4**. Approximately 75% of individuals with JPS have an affected parent; approximately 25% of probands with JPS have no previous history of polyps in the family and may have the disorder as the result of a new gene mutation.

A combined syndrome of JPS and hereditary hemorrhagic telangiectasia (HHT) (termed JPS/HHT) may be present in 15%-22% of individuals with an **SMAD4** mutation. Some clinicians suggest that patients with juvenile polyposis who have a **SMAD4** mutation should be screened for the vascular lesions associated with hereditary hemorrhagic telangiectasia, especially occult arteriovenous malformations in visceral organs that may otherwise present suddenly with serious medical consequences.

For patients with suspected JPS, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate. Click here for the GeneTests summary on this condition.

### Genes

**SMAD4**

### Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of juvenile polyposis syndrome
- Individuals at-risk for juvenile polyposis syndrome due to family history

### Methodology

PCR amplification of 11 exons contained in the **SMAD4** gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

### Detection

Clinical Sensitivity: Approximately 20% of individuals with JPS have mutations in SMAD4. Mutations in the promoter region, some mutations in the
introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%

<table>
<thead>
<tr>
<th>Specimen Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submit only 1 of the following specimen types</td>
</tr>
<tr>
<td>* Preferred specimen type: Whole Blood</td>
</tr>
</tbody>
</table>

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) or ACD (yellow top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

<table>
<thead>
<tr>
<th>Special Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.</td>
</tr>
<tr>
<td>Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Related Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Deletion/duplication analysis of the <strong>SMAD4</strong> gene by CGH array is available for those individuals in whom sequence analysis is negative (UU).</td>
</tr>
<tr>
<td>- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.</td>
</tr>
<tr>
<td>- Prenatal testing is available to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.</td>
</tr>
</tbody>
</table>