Juvenile Polyposis Syndrome: *SMAD4* Gene Deletion/Duplication

**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 polyp 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 three 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 polypos 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.

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 in individuals who have tested negative for sequence analysis
- Individuals at-risk for juvenile polyposis syndrome due to family history who have tested negative for sequence analysis

**Methodology**

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

**Detection**

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient’s clinical and/or biochemical phenotype.

**Specimen Requirements**

Submit only 1 of the following specimen types

**Type: DNA, Isolated**

**Specimen Requirements:**
- Microtainer
- 3µg
- Isolation using the Perkin Elmer™ Chemagen™ 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 72 hours of collection. Do not freeze.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Sequencing analysis of the SMAD4 gene is available (UT) and is required before deletion/duplication analysis.
- 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.