



## Disease Information

Juvenile polyposis syndrome (JPS) is an autosomal dominant disorder occurring in 1/100,000-1/160,000<sup>1</sup> individuals that predisposes to development of polyps in the gastrointestinal tract. Diagnostic criteria for typical JPS require at least three to five colorectal juvenile polyps, juvenile polyps throughout the gastrointestinal tract, or any number of juvenile polyps and a positive family history.<sup>2</sup>

The term 'juvenile' refers to the particular morphology of the polyps, which are hamartomas. Malignant transformation can occur with risk of gastrointestinal cancer ranging from 9% to 50%.<sup>3</sup> Polyps are almost always found in the colon and rectum but also occur in the stomach and small intestine. Juvenile polyposis of infancy involves the entire digestive tract and has the poorest prognosis.<sup>1</sup> Most other patients develop symptoms by age 20 though some are not diagnosed until the third decade of life. Common symptoms include gastrointestinal bleeding, anemia, diarrhea, and abdominal pain. Early detection of JPS allows for better treatment of polyps and surveillance of at-risk individuals.

Defects in the *BMPR1A* and *SMAD4* genes cause approximately equal numbers of JPS cases, together accounting for 45-60% of JPS. Sequence variant mutations explain about 40-45% of cases, and the remaining 10-15% of detectable cases are caused by gross deletions of either gene.<sup>2,4,5</sup>

*SMAD4* mutations may cause a combined syndrome of Hereditary Hemorrhagic Telangiectasia (HHT) with JPS as reported in 22% of JPS patients with *SMAD4* mutations.<sup>6</sup> Therefore, clinical evaluation for HHT symptoms is recommended for these patients.<sup>4,6</sup> *PTEN* gene mutations have been reported in a small number of JPS patients, so *PTEN* sequencing may be considered in *BMPR1A*- and *SMAD4*-negative patients.<sup>4</sup> *PTEN* testing is available separately from Ambry Genetics.

## Testing Benefits & Indications

Genetic testing can complement pathology findings to enable:

- confirmation of diagnosis in symptomatic individuals
- appropriately increased or decreased surveillance in relatives who are tested

## Test Description

Juvenile Polyposis AMPLIFIED™ includes concurrent sequence analyses of the *BMPR1A* and *SMAD4* genes with reflex testing to gross deletion/duplication analyses of both genes if no causative mutation is found by sequence analysis. PCR-based double-stranded automated sequencing is performed in the sense and antisense directions for coding exons 3-13 of *BMPR1A* and exons 1-11 of *SMAD4*, plus at least 20 bases into the 5' and 3' ends of all the introns. If no mutation is detected, analysis of both genes for gross deletions/duplications of any exon is performed by MLPA.

Other test options available are sequence analysis for only one of the genes, deletion/duplication analysis for the pair of genes without sequence analysis, or specific mutation analysis for individual *BMPR1A* or *SMAD4* mutations known to be in the family.

## Mutation Detection Rate

The Juvenile Polyposis AMPLIFIED™ test is designed and validated to detect approximately 99% of described mutations in *BMPR1A* and *SMAD4* (analytic sensitivity). These detectable mutations account for approximately 45-60% of JPS cases (clinical sensitivity).

### Turn-Around-Time

Juvenile Polyposis AMPLIFIED™	14 – 28 days
<i>BMPR1A</i> gene sequence analysis	10 – 21 days
<i>SMAD4</i> gene sequence analysis	10 – 21 days
Deletion/duplication analysis of both genes	10 – 14 days
Specific mutation analysis	10 – 14 days

### Specimen Requirements

**Blood:** Collect 3-5 cc from adult or 2 cc minimum from child into EDTA purple-top tube (first choice) or ACD yellow-top tube (second choice). Store at room temperature or refrigerate. Ship at room temperature.

**Blood Spot:** Call for availability.

**Saliva:** Collect 2 ml into Oragene™ DNA Self Collection container. Store and ship at room temperature.

**DNA:** Send 20 µg in TE at 50-100 ng/µl. Store frozen and ship on ice or dry ice.

**Prenatal:** Prenatal testing is available. Please call an Ambry Genetic Counselor to discuss your case.

### CPT Codes

Juvenile Polyposis AMPLIFIED™	83891, 83894x20, 83898x19, 83900,83901x28, 83904x33, 83909x34, 83912x3
<i>BMPR1A</i> gene sequence analysis	83891, 83894x10, 83898x9, 83904x18, 83909x18, 83912
<i>SMAD4</i> gene sequence analysis	83891, 83894x11, 83898x10, 83904x15, 83909x15, 83912
Deletion/duplication analysis of both genes	83891, 83900, 83901x28, 83909, 83912
Specific mutation analysis	83891, 83894x2, 83898, 83904x2, 83909x2, 83912

### References

- <sup>1</sup> Chow E and Macrae F. *J Gastroenterol Hepatol*. 2005;20:1634-1640.
- <sup>2</sup> Van Hattem WA, Brosens LAA, de Leng WW, et al. *Gut*. 2008;57:623-627.
- <sup>3</sup> Merg A and Howe JR. *Am J Med Genet Part C (Semin Med Genet)*. 2004;129C:44-55.
- <sup>4</sup> Aretz S, Stienen D, Uhlhaas S, et al. *J Med Genet*. 2007;44:702-709.
- <sup>5</sup> Calva-Cerqueira D, Chinnathambi S, Pechman B, et al. *Clin Genet*. 2009;75:79-85.
- <sup>6</sup> Gallione CJ, Repetto GM, Legius E, et al. *Lancet*. 2004;363:852-859.