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NLM Citation: Larsen Haidle J, MacFarland SP, Howe JR. Juvenile Polyposis Syndrome. 2003 May 13 [Updated 2022 Feb 3]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Juvenile Polyposis Syndrome

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Created: May 13, 2003; Updated: February 3, 2022.

Summary

Clinical characteristics

Juvenile polyposis syndrome (JPS) is 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 100. If the polyps are left untreated, they may cause bleeding and anemia. Most juvenile polyps are benign; however, malignant transformation can occur. Risk for GI cancers ranges from 11% to 86%. Most of this increased risk is attributed to colon cancer, but cancers of the stomach, upper GI tract, and pancreas have also been reported. A combined syndrome of JPS and hereditary hemorrhagic telangiectasia (HHT) is present in most individuals with an *SMAD4* pathogenic variant.

Diagnosis/testing

The diagnosis of JPS is established in a proband with any of the following: more than five juvenile polyps of the colorectum; multiple juvenile polyps throughout the GI tract; or any number of juvenile polyps and a family history of juvenile polyposis. Identification of a heterozygous pathogenic variant in *SMAD4* or *BMPR1A* confirms the diagnosis if clinical features are inconclusive.

Management

Treatment of manifestations: Colonoscopy with endoscopic polypectomy to reduce the risk of cancer, bleeding, and intestinal obstruction. When a large number of polyps are present, removal of all or part of the colon or stomach may be necessary. Iron replacement and red blood cell transfusion as needed for anemia; treatment as needed for manifestations of HHT, arteriovenous malformations, aortopathy, and/or valvular disease per cardiologist and cardiothoracic surgeon.

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Surveillance: Assess for rectal bleeding, anemia, abdominal pain, constipation, diarrhea, or change in stool size, shape, and/or color at each visit; complete blood count as needed based on symptoms; colonoscopy and upper endoscopy every three years beginning at age 15 years or earlier if symptomatic or if polyps were present on the prior colonoscopy. For individuals following surgical resection: endoscopic evaluation of the remaining colon, rectum, and ileal pouch. In individuals with (or at risk for) *SMAD4*-related JPS, follow HHT surveillance guidelines and consider transthoracic echocardiogram.

Evaluation of relatives at risk: It is appropriate to evaluate apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from early surveillance and intervention. Evaluations include molecular genetic testing (if the pathogenic variant in the family is known) and gastrointestinal and hematologic evaluations if the pathogenic variant in the family is not known.

Genetic counseling

JPS is inherited in an autosomal dominant manner. Up to half of individuals with JPS have an affected parent; approximately 50% of probands with JPS have no previous history of polyps in the family and may have the disorder as the result of a *de novo* pathogenic variant. Each child of an affected individual has a 50% chance of inheriting the pathogenic variant and developing JPS. Prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible if the pathogenic variant in the family is known.

GeneReview Scope

Juvenile Polyposis Syndrome: Included Phenotypes
• Juvenile polyposis syndrome (JPS) • Juvenile polyposis syndrome / hereditary hemorrhagic telangiectasia (JPS/HHT)

For synonyms and outdated names see Nomenclature.

Diagnosis

Suggestive Findings

Juvenile polyposis syndrome (JPS) **should be suspected** in a proband with the following clinical and histopathologic features.

Clinical features

- Anemia, rectal bleeding, or prolapse of rectal polyp
- More than one juvenile polyp
- One or more juvenile polyps and a family history of JPS

Note: "Juvenile" refers to the polyp histopathology, not the age of onset of polyps.

Histopathologic features. Juvenile polyps are hamartomas that develop from an abnormal collection of tissue elements normally present at this site. Juvenile polyps show a normal epithelium with a dense stroma, an inflammatory infiltrate, and a smooth surface with dilated, mucus-filled cystic glands in the lamina propria. Muscle fibers and the proliferative characteristics of adenomas are typically not seen in juvenile polyps.

Note: Variability in histopathology has been reported in polyps associated with juvenile polyposis syndrome / hereditary hemorrhagic telangiectasia (JPS/HHT) (see Clinical Characteristics) [Aretz et al 2007].

Establishing the Diagnosis

The diagnosis of JPS **is established** in a proband with **any one** of the following features:

- More than five juvenile polyps of the colon or rectum
- Multiple juvenile polyps of the upper and lower gastrointestinal tract
- Any number of juvenile polyps and a family history of juvenile polyposis
- Identification of a heterozygous pathogenic (or likely pathogenic) variant in one of the genes listed in Table 1

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous variant of uncertain significance in one of the genes listed in Table 1 does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include ***BMPR1A* and *SMAD4* concurrent testing**, **serial single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**.

- ***BMPR1A* and *SMAD4* concurrent testing** can be considered in individuals with clinical features suggestive of JPS. Sequence analysis including analysis of promoter regions as well as gene-targeted deletion/duplication analysis of *BMPR1A* and *SMAD4* is performed first. If no pathogenic variant is found, consider use of a multigene panel that includes *PTEN* and other genes of interest (see Differential Diagnosis, Table 3).
- **Serial single-gene testing** can be considered in individuals with clinical features suggestive of JPS/HHT (see Table 2 and HHT).
    1. Sequence analysis and deletion/duplication analysis of *SMAD4* is performed first.
    2. Sequence analysis and deletion/duplication analysis of *BMPR1A* should be considered next if no *SMAD4* pathogenic variant is identified.
    3. Consider molecular genetic testing of additional HHT-related genes if an *SMAD4* or *BMPR1A* pathogenic variant has not been identified.
- **A multigene panel** that includes *BMPR1A*, *SMAD4*, and other genes of interest (see Differential Diagnosis) – in particular *PTEN* (see *) – may be considered in individuals with JPS. Note: (1) The genes included and the sensitivity of multigene panels vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. (5) Understanding the limitations of the panel is critical for interpreting a negative test result and determining if additional testing is required. It is important to ensure that the panel provides the best coverage for those genes with the highest clinical suspicion, and includes analysis of the promoter regions.

  Deletions of 10q22-q23 detectable by **chromosomal microarray analysis** including either *BMPR1A* or both *BMPR1A* and *PTEN* may be associated with additional clinical features with or without juvenile polyposis or with severe early-onset JPS [Delnatte et al 2006, Salviati et al 2006, van Hattem et al 2008,

Calva-Cerqueira et al 2009, Breckpot et al 2012, Oliveira et al 2013, Alimi et al 2015]. Hamartomatous polyposis and 10q22-q23 deletions have been reviewed by Dahdaleh et al [2012].

* If no pathogenic variant is found, molecular genetic testing of *PTEN* is appropriate to determine if the individual has *PTEN* hamartoma tumor syndrome rather than JPS (see also Genetically Related Disorders).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Juvenile Polyposis Syndrome

Gene [1]	Proportion of JPS Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detectable by Method	
		Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
BMPR1A	28% [5]	69%-85% [5, 6]	15% [5]
SMAD4	27% [5]	83% [5]	17% [5]
Unknown [7]	45%	NA	

NA = not applicable

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

5. Aretz et al [2007], van Hattem et al [2008], Calva-Cerqueira et al [2009], Latchford et al [2012]

6. Sequence analysis of the *BMPR1A* promoter region identified a pathogenic variant in 6/65 individuals with JPS who did not have a *BMPR1A* or *SMAD4* pathogenic variant identified on sequencing of the coding regions or deletion/duplication testing [Calva-Cerqueira et al 2010]. Sequence analysis that includes the promoter region increases the proportion of pathogenic variants detected by sequencing.

7. Two individuals with early-onset JPS have been found to have *ENG* pathogenic variants. Neither had clinical symptoms of HHT, which is known to be associated with *ENG* pathogenic variants; however, neither had yet reached the age at which symptoms of HHT commonly manifest [Sweet et al 2005, Howe et al 2007].

Clinical Characteristics

Clinical Description

Juvenile Polyposis Syndrome (JPS)

JPS is characterized by predisposition to hamartomatous polyps in the gastrointestinal (GI) tract, specifically in the stomach, small intestine, colon, and rectum. "Generalized juvenile polyposis" refers to polyps of the upper and lower GI tract. "Juvenile polyposis coli" refers to polyps of the colon only.

The polyps vary in size and shape: some are flat (sessile), whereas others have a stalk (pedunculated). The number of polyps in individuals with JPS varies. Some individuals may have only four or five polyps over their lifetime; others in the same family may have more than 100.

Bleeding may result from sloughing of the polyp or its surface epithelium with the passage of stool. If the polyps are left untreated, they may cause bleeding and anemia.

Juvenile polyps develop from infancy through adulthood. Most individuals with JPS have some polyps by age 20 years.

In juvenile polyposis of infancy, associated with a contiguous deletion of *BMPR1A* and *PTEN*, polyps develop within the first few years of life and are accompanied by hypoproteinemia, protein-losing enteropathy, diarrhea, anemia, anasarca, and failure to thrive [Taylor et al 2021].

Cancer risks associated with JPS. Most juvenile polyps are benign; however, malignant transformation can occur. Lifetime estimates of developing GI cancers in families with JPS range from 11% to 86%, with variability by region, time period included, and associated gene [Latchford et al 2012, Aytac et al 2015, Ishida et al 2018, Blatter et al 2020, MacFarland et al 2021]. In the largest study thus far of individuals with JPS caused by *SMAD4*/*BMPR1A* pathogenic variants, 15% of individuals developed cancer, which is consistent with other more recent studies [Blatter et al 2020]. Of individuals treated surgically and followed with surveillance, four of 27 individuals with *SMAD4* pathogenic variants and none of eight individuals with *BMPR1A* pathogenic variants developed cancer [Aytac et al 2015]. Most of the increased risk is attributed to colorectal cancer; cancers of the stomach, upper GI tract, and pancreas have also been reported:

- The incidence of colorectal cancer is 17%-22% by age 35 years and approaches 68% by age 60 years. The median age at diagnosis is 42 years.
- The incidence of gastric cancer is 21% in those with gastric polyps.
- The relative risk for colorectal cancer was 34.0% in individuals with JPS. The mean age of diagnosis of colorectal cancer was 43.9 years, with a cumulative lifetime risk of 38.7% [Brosens et al 2007].

Historically, the cancer incidence in one large family with a germline *SMAD4* pathogenic variant suggested a lifetime risk for colorectal cancer of approximately 40%, and a lifetime risk for upper GI cancers of 20% [Howe et al 1998]. However, these cancer rates may change over time with the implementation of screening of young at-risk individuals and the removal of polyps before cancer develops.

Juvenile Polyposis Syndrome / Hereditary Hemorrhagic Telangiectasia (JPS/HHT)

Individuals with JPS/HHT have variable findings of juvenile polyposis and HHT (see Table 2). Most individuals with JPS who have an *SMAD4* germline pathogenic variant have one or more clinical features of HHT. The findings of HHT may manifest in early childhood. A high frequency of pulmonary arteriovenous malformations (with digital clubbing) and epistaxis has been consistently noted in individuals with *SMAD4*-related HHT. Conversely, telangiectases do not appear to be a constant feature. Additional complications reported in individuals with JPS/HHT include anemia, migraine headaches, and exercise intolerance.

Table 2. Clinical Features of *SMAD4*-Related Hereditary Hemorrhagic Telangiectasia

Clinical Feature	% of Individuals w/Clinical Feature	Age of Onset
Epistaxis	61%-71% [1, 2]	Childhood [3]
Telangiectases	57% [2]	Often after 30 yrs [4]
Mucocutaneous telangiectases	48% [3]	5-65 yrs [3]
Pulmonary AVM	53%-81% [2, 3]	Birth-52 yrs [3]

Table 2. continued from previous page.

Clinical Feature	% of Individuals w/Clinical Feature	Age of Onset
Hepatic AVM	38% [3]	21-52 yrs [3]
Intracranial AVM	4% [3]	Mean 11 yrs (±7 yrs) [1]
Aortopathy	38% [4]	Median 24 yrs (range 21-48 yrs) [5, 6]
Intrapulmonary shunting on echocardiogram	61% [3]	5-59 yrs [3]

AVM = arteriovenous malformation
1. Nishida et al [2012]
2. O'Malley et al [2012]
3. Wain et al [2014] reported the frequency of HHT-related symptoms in a cohort of 34 individuals with *SMAD4* pathogenic variants.
4. See Hereditary Hemorrhagic Telangiectasia.
5. Heald et al [2015]
6. Jelsig et al [2016]

Thoracic aortic disease (e.g., aortic root dilatation, aneurysm, and aortic dissection) and mitral valve dysfunction have been reported in individuals with *SMAD4* pathogenic variants [Heald et al 2015].

Expanding phenotype. There are reports of individuals with an *SMAD4* pathogenic variant who also presented with retinitis pigmentosa, retinal detachment, joint laxity, and/or a marfanoid habitus. Data for these findings is limited and it is unclear if these are features of the *SMAD4*-related JPS/HHT phenotype. More work is needed to assess the frequency of these findings to determine medical management recommendations. Providers may wish to be aware of these reports and evaluate individuals on a case-by-case basis.

Genotype-Phenotype Correlations

Genotype-phenotype correlations in general are weak; family members with JPS and the same pathogenic variant can have a few polyps or more than 100. The age at which polyps develop can vary from the first decade to beyond the fourth decade among affected members of the same family. Some generalizations:

- Individuals with *SMAD4*-related JPS are more likely to have a personal or family history of upper GI polyps than individuals with a *BMPR1A* pathogenic variant or those with no known pathogenic variant. The gastric phenotype in individuals with an *SMAD4* pathogenic variant tends to be more aggressive with significant polyposis, anemia, and a higher risk for gastric cancer [Aytac et al 2015, Blatter et al 2020, MacFarland et al 2021]. Gastric cancer was reported almost exclusively in individuals with *SMAD4*-related JPS (27% of *SMAD4*-associated cancers vs 0% of *BMPR1A*-associated cancers) [Blatter et al 2020].
- Colorectal cancer occurs more frequently than other cancers in *BMPR1A*-related JPS (88% of *BMPR1A*-associated cancers vs 58% of *SMAD4*-associated cancers) [Blatter et al 2020].
- Individuals with either an *SMAD4* or *BMPR1A* pathogenic variant are more likely than those without a pathogenic variant identified to have more than ten lower GI polyps and a family history of GI cancer [Burger et al 2002, Friedl et al 2002, Sayed et al 2002, MacFarland et al 2021]. They are also more likely to be older at diagnosis and at higher risk of requiring colectomy [MacFarland et al 2021].
- There is some evidence that in individuals without a germline *BMPR1A* or *SMAD4* pathogenic variant, polyp burden may decrease in adulthood and cancer risk may be lower [MacFarland et al 2021], but this requires further research.
- JPS/HHT is associated with *SMAD4* pathogenic variants.

Penetrance

One study evaluating 34 affected individuals with an *SMAD4* pathogenic variant from 20 families revealed that 31/32 (97%) developed colonic polyps (diagnosed between ages 4 and 51 years), 21/31 (68%) developed gastric polyps, and 76% had some feature of HHT [Wain et al 2014]. In some instances, HHT-related symptoms in

individuals with an *SMAD4* pathogenic variant may be present prior to the onset of polyps [Author, personal observations]. Similar information is not available for individuals with a *BMPR1A* pathogenic variant. However, Aytac et al [2015] reported a similar colon and small bowel phenotype among individuals with an *SMAD4* or *BMPR1A* pathogenic variant in the number and location of the polyps and surgical rates.

Nomenclature

Familial juvenile polyposis is an older term used to distinguish between simplex (i.e., a single affected individual in a family) and familial cases.

Prevalence

The incidence of JPS has been estimated to range between 1:16,000 and 1:100,000.

Genetically Related (Allelic) Disorders

BMPR1A

Germline *BMPR1A* pathogenic variants were identified in affected members of six families with features of hereditary mixed polyposis syndrome. The polyps were reported to be of mixed adenomatous, hyperplastic, and atypical juvenile histology [Cao et al 2006, Cheah et al 2009, O'Riordan et al 2010, Miyahara et al 2020] (see Differential Diagnosis).

Deletions of 10q22-q23 that include *PTEN* and *BMPR1A* have been identified in individuals with juvenile polyposis of infancy; polyps develop within the first few years of life and are accompanied by hypoproteinemia, protein-losing enteropathy, diarrhea, anemia, anasarca, and failure to thrive.

One individual with an intragenic *BMPR1A* deletion was reported to have dysmorphic facies, atrioventricular septal defect, short stature, and delayed puberty [Breckpot et al 2012].

Homozygous *BMPR1A* missense variants (p.Arg406Lys) were identified in an individual with growth failure, atrial septal defect, airway abnormalities (laryngomalacia, subglottic stenosis), and developmental delay [Russell et al 2019].

SMAD4

Heterozygous gain-of-function *SMAD4* pathogenic variants affecting amino acid 496 or 500 are associated with Myhre syndrome. Myhre syndrome is a connective tissue disorder with multisystem involvement including cardiovascular disease, respiratory disease, gastrointestinal disease, thickened skin, proliferative fibrosis and scarring, cognitive impairment, facial dysmorphism, and short stature. To date, no cancers consistent with the typical juvenile polyposis syndrome (JPS) phenotype have been reported in individuals with Myhre syndrome. However, early-onset endometrial cancer and benign brain tumors have been reported in individuals with Myhre syndrome [Lin et al 2020].

Sporadic tumors (including colorectal cancer and pancreatic tumors) occurring as single tumors in the absence of any other findings of JPS frequently harbor a somatic variant in *SMAD4* that is **not** present in the germline [Chen et al 2014]. In these circumstances predisposition to these tumors is not heritable. For more information, see Cancer and Benign Tumors.

Differential Diagnosis

A juvenile polyp can result from genetic predisposition or chance. It should be noted that 1% to 2% of individuals in the general population develop a solitary juvenile polyp and do not meet diagnostic criteria for juvenile polyposis syndrome (JPS).

Genetic predisposition syndromes characterized by the presence of polyps are summarized in Table 3.

Table 3. Polyp Predisposition Syndromes in the Differential Diagnosis of Juvenile Polyposis Syndrome

Gene(s) / Genetic Mechanism	Disorder	MOI	Polyp Phenotype	Additional Characteristics
APC	Familial adenomatous polyposis (See *APC*-Associated Polyposis Conditions.)	AD	GI polyposis; multiple adenomatous polyps	Osteomas, dental anomalies, congenital hypertrophy of retinal pigment epithelium, desmoid tumors, thyroid cancer, risk of hepatoblastoma, medulloblastoma, & other assoc cancers
AXIN2	Polyposis & oligodontia (OMIM 608615)	AD	GI polyposis, adenomas	Absent teeth, colon cancer
GALNT12	Polyposis (OMIM 608812)	AD	GI polyposis, adenoma	Preliminary evidence of assoc w/colon cancer
GREM1 overexpression [1]	Hereditary mixed polyposis syndrome (OMIM 601228)	AD	Juvenile polyps & multiple addl types of polyps: serrated, Peutz-Jeghers polyps, adenomas	Significant colorectal cancer risk
MLH1 *MSH2* *MSH6* *PMS2* *EPCAM*	Lynch syndrome	AD	Colorectal polyps; few adenomatous polyps	Significant colorectal cancer risk; cancers of endometrium, ovary, stomach, small intestine, hepatobiliary tract, upper urinary tract, brain, &skin
MLH1 *MSH2* *MSH6* *PMS2*	Constitutional mismatch repair deficiency (See Lynch Syndrome, Molecular Genetics.)	AR	Colorectal polyps, many early onset adenomatous polyps	Significant cancer risk starting in early childhood incl brain tumors, leukemias/lymphomas, & colon cancers
MSH3	Polyposis (OMIM 617100)	AR	GI polyposis, adenomas	Colon cancer
MUTYH	*MUTYH*-associated polyposis	AR	GI polyposis; multiple colonic adenomatous polyps; duodenal adenomas; additional types of polyps: serrated, hyperplastic/ sessile serrated, mixed	Significant colorectal cancer risk; cancers of duodenum, stomach, ovary, & bladder
NTHL1	Polyposis (OMIM 616415)	AR	GI polyposis, adenomas	Colon cancer
PTCH1 *SUFU*	Nevoid basal cell carcinoma syndrome	AD	Gastric polyps	Multiple jaw keratocysts, basal cell carcinoma, macrocephaly, frontal bossing, coarse facial features, facial milia

Table 3. continued from previous page.

Gene(s) / Genetic Mechanism	Disorder	MOI	Polyp Phenotype	Additional Characteristics
PTEN	*PTEN* hamartoma tumor syndrome	AD	Variable polyp types, mainly hamartomatous polyps incl juvenile polyps, also tubular adenomas, ganglioneuromas, serrated polyps	Benign & malignant tumors of thyroid, breast, & endometrium; vascular malformations; ASD, DD; macrocephaly, trichilemmomas, papillomatous papules, lipomas, pigmented macules of glans penis
RNF43	Serrated polyposis syndrome (OMIM 617108)	AD	GI polyposis, hyperplastic, sessile serrated adenomas, adenomas	Colon cancer
STK11	Peutz-Jeghers syndrome	AD	GI polyposis; polyps have smooth muscle hyperplasia as prominent feature.	Mucocutaneous pigmentation cancer risk incl breast, colon, pancreatic, ovarian, stomach, lung, & small intestine

AD = autosomal dominant; AR = autosomal recessive; ASD = autism spectrum disorder; DD = developmental delay; GI = gastrointestinal; MOI = mode of inheritance
1. Duplications of 15q13-q14 lead to overexpression of *GREM1*.

ACVRL1-, *ENG*-, and *GDF2*-related hereditary hemorrhagic telangiectasia and other genes associated with vascular dysplasia syndromes including *EPHB4* and *RASA1* (see Capillary Malformation-Arteriovenous Malformation Syndrome) can be considered in the differential diagnosis of individuals with gastrointestinal bleeding and anemia who do not have polyposis.

Management

Clinical practice guidelines for juvenile polyposis syndrome have been published [Achatz et al 2017, Cohen et al 2019, NCCN 2021].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with juvenile polyposis syndrome (JPS), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Juvenile Polyposis Syndrome

System/Concern	Evaluation	Comment
Gastrointestinal	Assess for abdominal pain, rectal bleeding, constipation, diarrhea, or change in stool size, shape, &/or color.	At diagnosis
	• Complete blood count • Colonoscopy • Upper endoscopy	By age 15 yrs or earlier if symptomatic
Hematologic/ Cardiovascular	• Evaluate for complications related to HHT. • Consider transthoracic echocardiogram.	• At diagnosis in those w/*SMAD4* pathogenic variant • Note: Recommended age at first transthoracic echocardiogram has not been determined.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of JPS to facilitate medical & personal decision making

HHT = hereditary hemorrhagic telangiectasia; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Juvenile Polyposis Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
GI polyps	Colonoscopy w/endoscopic polypectomy	To ↓ morbidity by ↓ risk for cancer, bleeding, or intestinal obstruction
	• Partial or total gastrectomy • Partial or total colectomy (subtotal colectomy w/ ileorectal anastomosis or proctocolectomy w/ ileoanal pouch) [1]	May be necessary in those w/many polyps to alleviate symptoms &/or ↓ cancer risk
Anemia	• Iron replacement (oral or parenteral if needed) • Red blood cell transfusion as needed	May be improved by polypectomy or surgery (gastrectomy/colectomy)
GI bleeding	See Hereditary Hemorrhagic Telangiectasia, Management.	In those w/*SMAD4* pathogenic variant
Epistaxis		
AVMs/ Aortopathy/ Valvular disease	Treatment per cardiologist & cardiothoracic surgeon	

AVM = arteriovenous malformation; GI = gastrointestinal
1. The preferred procedure is debated. The number of colonic or rectal polyps does not appear to correlate with the need for proctectomy [Oncel et al 2005].

Surveillance

The surveillance recommended in Table 6 is for individuals with an *SMAD4* or *BMPR1A* pathogenic variant identified by molecular genetic testing, individuals with a clinical diagnosis of JPS, or individuals with a family history of JPS who have not undergone molecular genetic testing or whose molecular genetic test results were uninformative.

Table 6. Recommended Surveillance for Individuals with Juvenile Polyposis Syndrome

System/Concern	Evaluation	Frequency
Gastrointestinal	Assess for rectal bleeding, anemia, abdominal pain, constipation, diarrhea, or change in stool size, shape, &/or color.	At each visit
	Complete blood count	As needed based on symptoms
	• Colonoscopy • Upper endoscopy • Note: Following surgical bowel resection, continue screening for polyps in remaining colon, rectum, & ileal pouch.	• Every 3 yrs beginning at age 15 yrs or earlier if symptomatic • If polyps are found: following polyp treatment, annual screening until no polyps are found, then screening every 3 yrs • In those w/o germline *SMAD4* or *BMPR1A* pathogenic variant: every 5 yrs in adulthood if no polyps are found
Hematologic / Cardiovascular	• See Hereditary Hemorrhagic Telangiectasia, Surveillance. • Consider transthoracic echocardiogram.	Note: To date, frequency of echocardiography monitoring for aortopathy has not been determined. [1]

1. Teekakirikul et al [2013], Heald et al [2015]

Agents/Circumstances to Avoid

SMAD4-related HHT

- Individuals with significant epistaxis are advised to avoid vigorous nose blowing, lifting of heavy objects, straining during bowel movements, and finger manipulation in the nose. Some individuals with HHT experience increased epistaxis after drinking alcohol.
- Most otolaryngologists with experience treating individuals with HHT advise against electric and chemical cautery and transcatheter embolotherapy for treatment of recurrent nosebleeds.
- Anticoagulants including aspirin and nonsteroidal anti-inflammatory agents such as ibuprofen that interfere with normal clotting should be avoided unless required for treatment of other medical conditions. In one study, lower-dose agents, particularly anti-platelet agents, were not associated with hemorrhage in a high proportion of affected individuals. The findings support the use of antiplatelet or anticoagulant agents, with caution, if there is a very strong indication for their use [Devlin et al 2013].
- Scuba diving should be avoided unless contrast echocardiography performed within the last five years was negative for evidence of a right-to-left shunt.
- Liver biopsy should be avoided [Buscarini et al 2006].

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from early surveillance and intervention.

In families in which findings suggest JPS or families with a known *BMPR1A* pathogenic variant, evaluations can include:

- Molecular genetic testing at or prior to age 15 years if the pathogenic variant in the family is known;
- If the familial pathogenic variant is not known, complete blood count (CBC) and lower intestinal endoscopy in individuals age 15 years an older. Normal results do not rule out a diagnosis of JPS (see Surveillance for additional recommendations).

In families in which findings suggest juvenile polyposis syndrome / hereditary hemorrhagic telangiectasia (JPS/HHT) or families with a known *SMAD4* pathogenic variant:

- Molecular genetic testing before age 15 years for children at risk for a known familial *SMAD4* pathogenic variant should be offered because the surveillance for HHT-related findings begins earlier in childhood than the surveillance for polyps.
- In families in which findings suggest JPS/HHT but the familial pathogenic variant is not known:
  - CBC and lower intestinal endoscopy in individuals age 15 years an older, or earlier if symptoms of polyposis. Normal results do not rule out a diagnosis of JPS (see Surveillance for additional recommendations).
  - In individuals older than age 40 years, targeted medical history and clinical examination for features of HHT. The absence of mild but recurrent epistaxis and subtle telangiectases in characteristic locations on careful examination is reassuring (see Hereditary Hemorrhagic Telangiectasia).
  - In individuals age 40 years and younger, targeted medical history and clinical examination for features of HHT as well as initial evaluation for brain and pulmonary arteriovenous malformations, as features of HHT may not be identified by medical history and clinical examination in younger individuals

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

See Hereditary Hemorrhagic Telangiectasia, Pregnancy Management.

Therapies Under Investigation

In individuals with juvenile polyposis of infancy due to deletion of both *BMPR1A* and *PTEN*, sirolimus has been investigated as an intervention to decrease polyp burden [Busoni et al 2019]. In a small case series, sirolimus therapy reduced symptoms including bleeding and enteropathy, and also reduced rate of colectomy [Taylor et al 2021].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Other

No known chemoprevention options are effective for juvenile polyps.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Juvenile polyposis syndrome (JPS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Up to half of individuals diagnosed with JPS have an affected parent.

- Approximately 50% of individuals diagnosed with JPS have no previous history of polyps in the family and may have the disorder as the result of a *de novo* pathogenic variant [Restrepo et al 1978, Coburn et al 1995].
- If the proband appears to be the only affected family member (i.e., a simplex case), evaluation of the parents is recommended in order to clarify their genetic/clinical status and to assess the risk of JPS in sibs and other relatives. Recommendations for the evaluation of parents of a proband include the following:
  - Molecular genetic testing if a causative *SMAD4* or *BMPR1A* pathogenic variant has been identified in the proband
  - Screening/surveillance for JPS (and hereditary hemorrhagic telangiectasia [HHT] if findings in the proband suggest JPS/HHT) if a pathogenic variant has not been identified in the proband
- If the proband has a known pathogenic variant that cannot be identified in either parent and parental identified testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with JPS may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance and variable expressivity, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or appropriate molecular genetic testing has been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- Intrafamilial variability (including variable symptoms, ages of onset, and cancer risks) has been reported among family members who are heterozygous for the same *SMAD4* or *BMPR1A* pathogenic variant.
- If the proband has a known JPS-causing pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Lamireau et al 2005].
- If the genetic status of the parents is unknown (and/or a molecular diagnosis has not been established in the proband), sibs should be considered at risk for JPS (regardless of whether parents have had manifestations of the disorder) and offered molecular genetic testing and screening/surveillance for JPS (and HHT if findings in the proband suggest JPS/HHT).

Offspring of a proband. Each child of an individual with JPS has a 50% chance of inheriting the causative pathogenic variant and having an increased risk of developing JPS.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected and/or is known to have the pathogenic variant identified in the proband, the parent's family members may be at risk and may benefit from molecular genetic testing and/or surveillance.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early surveillance and intervention.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Genetic cancer risk assessment and counseling. For a comprehensive description of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see Cancer Genetics Risk Assessment and Counseling – for health professionals (part of PDQ®, National Cancer Institute).

Molecular genetic testing of asymptomatic individuals younger than age 18 years. If the JPS-causing pathogenic variant has been identified in a family, predictive molecular genetic testing can be used to identify family members who would benefit from early screening.

- **Families with a known *BMPR1A* pathogenic variant.** Since surveillance for asymptomatic individuals at risk for JPS is recommended beginning at age 15 years, it is appropriate to consider predictive genetic testing for JPS around this age or earlier. If parents are concerned about their child's ability to cope with the significance of test results, the disclosure of the molecular genetic testing information, but not surveillance, can be delayed.

  If symptoms of JPS appear before age 15 years, surveillance should begin at that time and disclosure of molecular genetic test results may be a reasonable option. It is important to consider the risks and benefits for children of learning this information at a young age and to consider ways to discuss this information with children and to answer their questions.

- **Families with a known *SMAD4* pathogenic variant.** Predictive molecular genetic testing before age 15 years should be offered because the surveillance for HHT-related findings begins earlier in childhood (see Hereditary Hemorrhagic Telangiectasia) than the surveillance for polyps.

See Management, Evaluation of Relatives at Risk for recommended evaluations of at-risk relatives when the familial pathogenic variant is not known.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the JPS-causing pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for JPS are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Cancer Institute (NCI)**

Email: NCIinfo@nih.gov
Colorectal Cancer—Patient Version

- **American Cancer Society**
  Phone: 800-227-2345
  cancer.org
- **International Society for Gastrointestinal Hereditary Tumours (InSiGHT)**
  insight-group.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Juvenile Polyposis Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
BMPR1A	10q23.2	Bone morphogenetic protein receptor type-1A	BMPR1A database	BMPR1A	BMPR1A
SMAD4	18q21.2	Mothers against decapentaplegic homolog 4	SMAD4 database	SMAD4	SMAD4

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Juvenile Polyposis Syndrome (View All in OMIM)

174900	JUVENILE POLYPOSIS SYNDROME; JPS
175050	JUVENILE POLYPOSIS/HEREDITARY HEMORRHAGIC TELANGIECTASIA SYNDROME; JPHT
600993	SMAD FAMILY MEMBER 4; SMAD4
601299	BONE MORPHOGENETIC PROTEIN RECEPTOR, TYPE IA; BMPR1A

Molecular Pathogenesis

The mechanism of juvenile polyp formation as a consequence of germline pathogenic variants in *SMAD4* or *BMPR1A* is not known. Although *SMAD4* is a tumor suppressor gene, loss of heterozygosity has not been definitively demonstrated to cause polyp development. Furthermore, whether such changes would affect cells in the epithelium, the lamina propria, or both is also not known. *BMPR1A* is not known to be a tumor suppressor gene, although few studies have examined it in cancer.

SMAD4 is the common intracellular mediator of the TGF-β superfamily signaling pathways. *BMPR1A* encodes a type I cell surface receptor for the BMP pathway. Ligands, such as TGF-β or BMP, bind to a receptor and activate signaling pathways involving regulatory SMAD proteins, which form protein complexes with SMAD4 that migrate to the nucleus and bind directly to DNA sequences to regulate transcription [Heldin et al 1997, Gómez Pinto et al 2018]. The downstream genes under the control of these signaling pathways are still being actively investigated.

Most *BMPR1A* pathogenic variants occur in the protein kinase domain and occasionally in the cysteine-rich region of the extracellular domain. No pathogenic variants have been described in the transmembrane domain [Howe et al 2004]. In vitro studies have shown that proteins resulting from JPS-related *BMPR1A* pathogenic

missense variants are retained in the cytoplasm and do not traffic to the cell membrane like the wild type protein [Howe et al 2013].

Most *SMAD4* pathogenic variants occur in the MH2 domain, which plays an important role for nuclear localization, interaction with other SMAD proteins, and transcriptional activation. In vitro studies demonstrate that pathogenic nonsense variants lead to significantly reduced bone morphogenetic protein signaling, with less of an effect for missense variants [Carr et al 2012].

Mechanism of disease causation. Unknown

Cancer and Benign Tumors

Somatic *SMAD4* variants that are **not** present in the germline have been reported in colorectal, pancreatic, and prostate cancers occurring as single tumors in the absence of any other findings of juvenile polyposis syndrome [Chen et al 2014, McCarthy & Chetty 2018].

Chapter Notes

Author Notes

Dr James R Howe is a surgical oncologist and primary researcher in the field of juvenile polyposis syndrome. Joy Larsen Haidle is a genetic counselor with the Cancer Genetics program at North Memorial Health Cancer Center who is actively involved in the development of genetic counseling guidelines with Dr Howe's research program.

Dr Suzanne P MacFarland is a pediatric oncologist and cancer predisposition researcher in the field of juvenile polyposis syndrome. She runs a multidisciplinary polyposis clinic at the Children's Hospital of Philadelphia.

Revision History

- 3 February 2022 (sw) Comprehensive update posted live
- 9 March 2017 (sw) Comprehensive update posted live
- 3 December 2015 (jrh) Revision: corrections to Genetically Related Disorders
- 22 May 2014 (me) Comprehensive update posted live
- 29 September 2011 (me) Comprehensive update posted live
- 9 September 2008 (me) Comprehensive update posted live
- 22 February 2007 (cd) Revision: prenatal diagnosis available for *BMPR1A* mutations
- 2 November 2006 (cd) Revision: prenatal diagnosis available for *SMAD4* mutations
- 13 June 2005 (me) Comprehensive update posted live
- 20 May 2004 (cd) Revision: Genetic Counseling
- 27 October 2003 (cd) Revision: Statements and Policies
- 13 May 2003 (me) Review posted live
- 4 January 2003 (jrh) Original submission

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