Juvenile polyposis syndrome

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INTRODUCTION

Juvenile polyposis syndrome (JPS) is an autosomal dominant condition characterized by multiple hamartomatous polyps throughout the gastrointestinal tract. Individuals with JPS are at increased risk for colorectal and gastric cancer [1,2]. In contrast to JPS, sporadic juvenile polyps of the colon occur in up to 2 percent of children under the age of 10 years, are usually solitary, and are not associated with an increased cancer risk [3].

This topic will review the clinical manifestations, diagnosis, and management of JPS. The clinical manifestations and diagnosis of other hamartomatous polyposis syndromes (eg, Peutz-Jeghers syndrome, Cowden syndrome, and Bannayan-Riley-Ruvalcaba syndrome) and adenomatous polyposis syndromes (eg, familial adenomatous polyposis and *MUTYH*-associated polyposis) are discussed in detail, separately [4]. (See "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management" and "PTEN hamartoma tumor syndromes, including Cowden syndrome" and "Clinical manifestations and diagnosis of familial adenomatous polyposis" and "*MUTYH*-associated polyposis".)

EPIDEMIOLOGY

JPS is rare, with an estimated incidence of 1 in 100,000 individuals [1,5,6].

GENETICS

Genetic mutations — JPS is an autosomal dominant condition with incomplete penetrance [7]. JPS occurs as a result of germline mutations in the *SMAD4* (*MADH4*) or bone morphogenetic protein receptor type-1A (*BMPR1A*) genes, which are related to the transforming growth factor-beta (TGF-beta) signaling pathway [8,9]. Mutations in *SMAD4* or *BMPR1A* are identified in approximately 40 to 60 percent of JPS patients [6,10]. While 75 percent of patients have a family history of juvenile polyposis, approximately 25 percent of patients have de novo mutations [11,12].

The *SMAD4* gene is located on chromosome 18q21.1 and encodes for a cytoplasmic mediator of the TGF-beta signaling pathway. *SMAD4* forms heteromeric complexes with other proteins of the *SMAD* family, and these complexes then act within the nucleus [7,13]. The *BMPR1A* (*ALK3*) gene is located on chromosome 10q22-23 and encodes a serine/threonine kinase receptor protein that is also involved in the TGF-beta signaling pathway. Upon activation, *BMPR1A* phosphorylates *SMAD* family proteins [7].

Genotype-phenotype correlation — Individuals with *SMAD4* mutations may have more profuse polyposis of the upper gastrointestinal tract and a higher risk of cancer (specifically gastric) as compared with individuals with a *BMPR1A* mutation [6,10,14].

Patients with a recurrent 10q22q23 deletion, which includes the *BMPR1A* gene and often the adjacent *PTEN* gene, exhibit a more severe phenotype (juvenile polyposis of infancy) within the first few years of life [15]. There have been a few reports of individuals with this deletion who also exhibited severe juvenile polyposis as well as gastric adenocarcinoma [16].

CLINICAL MANIFESTATIONS

Gastrointestinal symptoms

Juvenile polyposis in adults — Most patients are symptomatic by age 20 years [17]. Overall, 90 percent of patients present with bleeding or anemia due to gastrointestinal polyps [6]. Rectal bleeding is the most common presenting symptom. Other symptoms include abdominal pain due to obstruction from intussusception, diarrhea due to protein-losing enteropathy, and rectal prolapse of polyps [1,12,17,18].

Polyps usually begin to appear in the first decade of life, and patients can develop between five to hundreds of polyps in their lifetime. Polyps occur predominantly in the colorectum (98 percent) but can occur in the stomach (14 percent), duodenum (7 percent), jejunum, and ileum (7 percent). Up to 70 percent of colonic polyps develop in the proximal colon [19]. Generalized juvenile polyposis refers to polyps in the upper and lower gastrointestinal tract, and juvenile

polyposis coli refers to polyps of the colon and rectum. (See "Etiologies, clinical manifestations, and diagnosis of mechanical small bowel obstruction in adults" and "Intussusception in children" and "Protein-losing gastroenteropathy", section on 'Clinical features'.)

Juvenile polyposis of infancy — Juvenile polyposis of infancy is a rare variant of JPS in which juvenile polyps occur in both the upper and lower gastrointestinal tract (including the small bowel) and polyps develop within the first few years of life. In the stomach, juvenile polyps can be more difficult to recognize and often resemble hyperplastic polyps or other hamartomatous gastric polyps [6]. The antropyloric region is the most common site for gastric polyps [19]. Symptoms include diarrhea, bleeding, and intussusception. Macrocephalus and hypotonia may also occur, and patients often die at an early age [20].

Endoscopic and histologic features — Juvenile polyps are hamartomas that develop from an abnormal collection of tissue elements normally present within the intestinal tract (picture 1). In addition, individuals with JPS are at risk for other types of polyps (ie, inflammatory, hyperplastic, adenomatous). Up to 75 percent of JPS patients have polyp diagnoses other than juvenile polyps, with some having up to five or six different polyp types diagnosed throughout the years [18].

Endoscopically, juvenile polyps vary in size from small sessile nodules to large pedunculated lesions measuring several centimeters. Smaller polyps are often rounded and smooth, while larger polyps may be multilobulated. A small white exudate may also be found [12].

The histologic appearance of juvenile polyps is characterized by both abundant lamina propria, which may be edematous and contain inflammatory cells, and dilated glands forming mucin-filled cysts. While JPS is a hamartomatous polyp syndrome, adenomatous changes are also thought to play a role in the development of malignancy. Adenomatous changes have been demonstrated in up to 50 percent of juvenile polyps in JPS [1,12]. (See 'Gastrointestinal cancer risk' below.)

Associated extraintestinal conditions — JPS due to *SMAD4* mutations may also be associated with hereditary hemorrhagic telangiectasia (HHT) [21,22]. The most common clinical manifestations of HHT are telangiectasias of the skin and buccal mucosa, epistaxis, and iron deficiency anemia from gastrointestinal telangiectasia; pulmonary, hepatic, cerebral, and rare arteriovenous malformations. It is estimated that 32 percent of individuals with *SMAD4* pathogenic variants will exhibit features of HHT, although the proportion may be considerably higher [23]. There are case reports of germline mutations in the *ENG* gene that result in HHT in patients with JPS [24]. The *ENG* gene, located on chromosome 9q34.1, encodes for the protein endoglin, which is an accessory protein of transforming growth factor-beta signaling. However,

there are insufficient data to suggest that a mutation in the *ENG* gene predisposes to JPS [25]. (See "Clinical manifestations and diagnosis of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)", section on 'Genetics'.)

Other conditions associated with JPS include cardiac (eg, mitral valve prolapse), vascular (eg, arterial aneurysms), skeletal, and cranial abnormalities [1]. (See "Clinical manifestations and diagnosis of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)", section on 'Clinical features'.)

Gastrointestinal cancer risk — Individuals with JPS are at increased risk for colorectal cancer. The cumulative risk of colorectal cancer is 17 to 22 percent by age 35 years and 68 percent by age 60 years [26,27]. The mean age at colorectal cancer diagnosis in patients with JPS is 34 years, is earlier as compared with sporadic colorectal cancer.

Individuals with JPS are also at increased risk for gastric and duodenal cancer, with an estimated lifetime risk of 11 to 20 percent, with a greater risk of gastric cancer in *SMAD4* mutations carriers, and a mean age at diagnosis of 58 years (range 21 to 73 years) [1,12,19,26].

DIAGNOSIS

When to suspect JPS — A diagnosis of JPS should be considered in patients with multiple (>5) juvenile polyps in the gastrointestinal tract or a juvenile polyp and a family history of juvenile polyps.

Clinical diagnosis — A clinical diagnosis of JPS is based on the presence of at least one of the following criteria and the absence of clinical manifestations of other hamartomatous polyposis syndromes (see 'Differential diagnosis' below) [1,12]:

- Five or more juvenile polyps in the colorectum [6,10]
- Two or more juvenile polyps in other parts of the gastrointestinal tract
- Any number of juvenile polyps in a person with a known family history of juvenile polyps in a first-degree relative

Genetic testing — Individuals who meet clinical criteria for JPS should undergo genetic testing for a germline mutation in the *BMPR1A* and *SMAD4* genes. Genetic testing in an individual who meets clinical criteria for JPS serves to confirm the diagnosis and to counsel at-risk family members. However, approximately 40 percent of JPS patients have no germline mutation. If a pathogenic variant has not been identified in a family and the tested individual does not have a

pathogenic variant, patients with such indeterminate test results are still considered at risk and are managed as patients with positive genetic test results. (See 'Management' below.)

DIFFERENTIAL DIAGNOSIS

JPS can be differentiated from other disorders that present with multiple hamartomatous gastrointestinal polyps based on the clinical presentation, histologic findings, and genetic testing.

- **Phosphatase and tensin homolog (*PTEN*) hamartoma tumor syndrome** – Hamartomatous polyps of the small intestine can be associated with Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome (BRRS). Cowden syndrome and BRRS are associated with germline mutations in *PTEN1*. BRRS is characterized by macrocephaly, lipomas, vascular abnormalities, and developmental delay. Cowden syndrome has characteristic skin and oral findings including trichilemmomas, acral keratoses, and facial papules/oral papillomas. Pigmented spots in BRRS and Cowden syndrome characteristically occur on the glans penis in males [3,12]. (See "PTEN hamartoma tumor syndromes, including Cowden syndrome", section on 'Cowden syndrome' and "PTEN hamartoma tumor syndromes, including Cowden syndrome", section on 'Bannayan-Riley-Ruvalcaba syndrome'.)

- **Peutz-Jeghers syndrome** – Peutz-Jeghers syndrome is an autosomal dominant syndrome characterized by multiple hamartomatous Peutz-Jeghers-type polyps in the gastrointestinal tract, mucocutaneous pigmentation, and an increased risk of gastrointestinal and non-gastrointestinal cancer. Peutz-Jeghers syndrome is associated with germline mutations in the *STK11* (*LKB1*) gene encoding a serine/threonine kinase mapped to chromosome 19p13.3 [12,28]. (See "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management".)

- **Nevoid basal cell carcinoma syndrome** – Nevoid basal cell carcinoma syndrome is an autosomal dominant condition due to mutations in the *PTCH1* gene and is characterized by multiple basal cell carcinomas, palmar and plantar pitting, and macrocephaly. Rarely, patients may have multiple gastric hamartomatous polyps [29]. (See "Nevoid basal cell carcinoma syndrome (Gorlin syndrome)".)

MANAGEMENT

Individuals with a pathogenic germline mutation in the *BMPR1A* and *SMAD4* genes, and individuals with a clinical diagnosis of JPS who have not undergone genetic testing or who have indeterminate genetic test results, should be screened for manifestations of JPS. Although the association between JPS and a 10q22.3q23.1 deletion is still unclear, patients who have this deletion follow the same surveillance protocol [16].

Guidelines for cancer screening in patients with JPS have been proposed by several groups and are largely based on expert opinion and limited observational data [12,30,31]. Our recommendations are largely consistent with the guidelines issued by the US Multi-Society Task Force on Colorectal Cancer and the National Comprehensive Cancer Network [12,32,33].

Routine measures — Individuals with JPS should undergo an annual physical examination including a cardiovascular examination [1]. We monitor a complete blood count annually to evaluate for iron deficiency anemia secondary to blood loss.

Individuals with pathogenic variants in *SMAD4* should have a thorough family history and personal history for clinical manifestations and complications of HHT, including epistaxis, gastrointestinal bleeding, and others. (See "Clinical manifestations and diagnosis of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)".)

All symptoms attributable to telangiectasia, arteriovenous malformations (AVMs), or bleeding should be thoroughly evaluated. Decisions regarding screening of asymptomatic individuals, including the specific tests and age at which to initiate them, are best done in consultation with an HHT center and/or facilitated by a clinician with expertise in HHT management. (See "Hereditary hemorrhagic telangiectasia (HHT): Evaluation and therapy for specific vascular lesions" and "Hereditary hemorrhagic telangiectasia (HHT): Routine care including screening for asymptomatic AVMs".)

Screening and management — Surveillance of the gastrointestinal (GI) tract in affected or at-risk JPS patients should include screening for colon, stomach, and small bowel cancers.

Colorectal cancer — Screening for colorectal cancer with colonoscopy should be performed every one to three years, beginning between the ages of 12 and 15 years or earlier in patients who present with symptoms [13,33]. If polyps are found, colonoscopy should be repeated annually; otherwise, colonoscopy intervals can be increased to every one to three years [12,33].

Gastrointestinal tract polyps can usually be resected endoscopically [17]. (See "Endoscopic removal of large colon polyps".)

Potential indications for colectomy and ileorectal anastomosis (IRA) or proctocolectomy and ileal pouch anal anastomosis include:

- Severe symptoms related to colonic neoplasia (eg, severe gastrointestinal bleeding)
- Colorectal cancer, adenoma with high-grade dysplasia or multiple adenomas >6 mm
- Marked increases in polyp number on consecutive exams
- Inability to adequately survey the colon because of multiple polyps

The remaining rectum or pouch should be surveyed every 12 months following colectomy. Approximately half of the patients undergoing IRA will eventually require proctectomy [12]. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management", section on 'Surgery'.)

Upper gastrointestinal tract cancer — We survey the upper GI tract with upper endoscopy starting at the age of 12 years. If polyps are detected, upper endoscopy is repeated annually. In the absence of upper gastrointestinal tract polyps, upper endoscopy can be performed every two to three years [12].

Patients with JPS also require evaluation of the small bowel for polyps. However, the timing and intervals for small bowel screening are not well defined. The small bowel can be evaluated using wireless capsule endoscopy, small bowel imaging, or small bowel enteroscopy (eg, double balloon enteroscopy). We perform a baseline exam starting in the teenage years and then repeat it periodically based upon the presence of polyps or symptoms, including anemia or protein-losing enteropathy. In patients with advanced dysplasia, gastric cancer, or massive gastric polyposis that cannot be effectively managed endoscopically, complete or partial gastrectomy is warranted.

Reproductive counseling — Individuals of reproductive age should be offered carrier testing and prenatal testing options including preimplantation genetic diagnosis. JPS is an autosomal dominant disorder and can be transmitted by either parent to approximately 50 percent of their offspring. Carrier testing can be offered to the partner to determine if they are carriers of pathogenic variants in the same gene.

Counseling at-risk family members — Genetic testing for at-risk relatives may be considered as early as 12 years. Age of polyposis onset for relatives may help guide the timing [32].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hereditary colorectal cancer syndromes".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Colon and rectal cancer screening (The Basics)" and "Patient education: Colonoscopy (The Basics)")
- Beyond the Basics topics (see "Patient education: Screening for colorectal cancer (Beyond the Basics)" and "Patient education: Colonoscopy (Beyond the Basics)" and "Patient education: Flexible sigmoidoscopy (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Epidemiology** – JPS is a rare autosomal dominant syndrome characterized by multiple juvenile-type hamartomatous polyps in the gastrointestinal tract. The incidence of JPS is approximately 1 in 100,000 individuals. (See 'Epidemiology' above.)
- **Genetics** – JPS occurs as a result of germline mutations in the *SMAD4 (MADH4) and BMPR1A genes*. While 75 percent of patients have a family history of juvenile polyposis, approximately 25 percent are de novo mutations. However, approximately 40 percent of patients who meet clinical criteria for JPS have no germline mutation. (See 'Genetics' above.)

- **Clinical manifestations** – Most patients are symptomatic by age 20 years. Rectal bleeding is the most common presenting symptom. Other symptoms include abdominal pain due to obstruction from intussusception, diarrhea due to protein-losing enteropathy, and rectal prolapse of polyps. Juvenile polyposis of infancy is a rare variant of JPS in which juvenile polyps occur in both the upper and lower gastrointestinal tract (including the small bowel) and polyps develop within the first few years of life. Individuals with JPS are at increased risk for colorectal and gastric cancer. (See 'Gastrointestinal symptoms' above.)

- **Endoscopic features** – Endoscopically, juvenile polyps vary in size from small sessile nodules to large pedunculated lesions measuring several centimeters. The histologic appearance of juvenile polyps is characterized by both abundant lamina propria, which may be edematous and contain inflammatory cells, and dilated glands forming mucin-filled cysts. (See 'Endoscopic and histologic features' above.)

- **Associated conditions** – JPS due to *SMAD4* mutations may also be associated with hereditary hemorrhagic telangiectasia (HHT). Other associated conditions in patients with JPS include cardiovascular and neurological malformations as well as autoimmune disorders. (See 'Associated extraintestinal conditions' above.)

- **Diagnosis** – A clinical diagnosis of JPS is based on the presence of at least one of the following and the absence of clinical manifestations of other hamartomatous polyposis syndromes:

  - Five or more juvenile polyps in the colorectum
  - Two or more juvenile polyps in other parts of the gastrointestinal tract
  - Any number of juvenile polyps in a person with a known family history of juvenile polyps in a first-degree relative

  Individuals who meet clinical criteria for JPS should undergo genetic testing for a germline mutation in the *BMPR1A* and *SMAD4* genes. (See 'Diagnosis' above.)

- **Management** – Our approach to the management of patients with JPS is as follows:

  - Annual physical examination including a cardiovascular examination with a complete blood count to evaluate for iron deficiency anemia. Screening for clinical manifestations and complications of HHT-associated vascular lesions in patients with pathogenic mutations in *SMAD4*. (See 'Routine measures' above.)

  - Colonoscopy and esophagogastroduodenoscopy beginning between the ages of 12 and 15, repeated annually if polyps are demonstrated or every two to three years in the

absence of polyps. Additional evaluation of small bowel based on the polyp burden and in patients with iron deficiency anemia or abdominal pain. (See 'Screening and management' above.)

- Gastrointestinal tract polyps in JPS can usually be resected endoscopically. Potential indications for colectomy and ileorectal anastomosis or proctocolectomy and ileal pouch anal anastomosis include:
  - Severe symptoms related to colonic neoplasia (eg, severe gastrointestinal bleeding)
  - Colorectal cancer, adenoma with high-grade dysplasia or multiple adenomas >6 mm
  - Marked increases in polyp number on consecutive exams
  - Inability to adequately survey the colon because of multiple polyps (see 'Screening and management' above)

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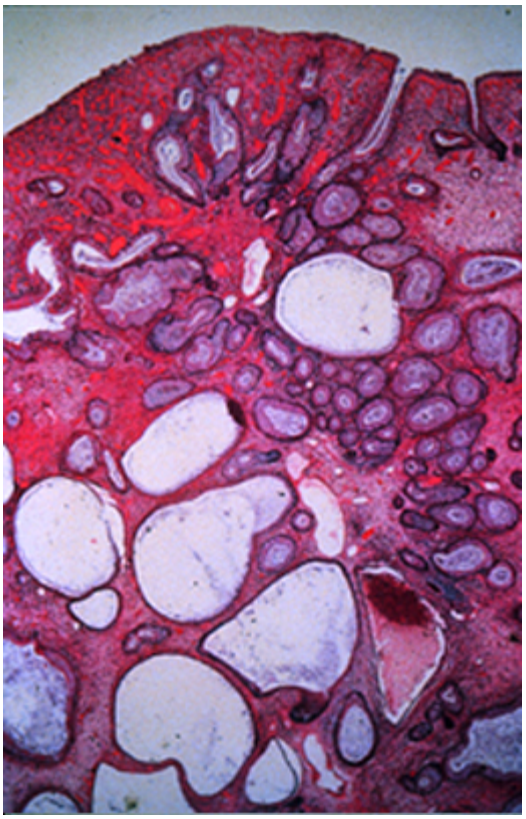
GRAPHICS

Juvenile colonic polyp

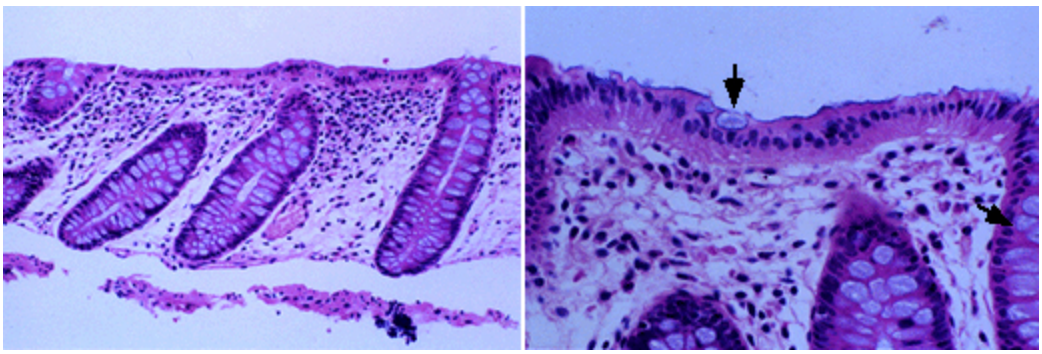


Low power view of a juvenile colonic polyp shows dilated cystic crypts and abundant, mildly inflamed lamina propria.

Courtesy of Robert Odze, MD.

Graphic 72376 Version 1.0

Normal colon



Low (left) and high (right) power views of a biopsy of a normal colon. Low power reveals straight crypts and mild lamina propria mononuclear cell

infiltration. High power shows the surface enterocytes with interspersed goblet cells (arrows).

Courtesy of Robert Odze, MD

Graphic 81083 Version 6.0

Contributor Disclosures

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