

# Hereditary Hamartomatous Polyposis Syndromes: Understanding the Disease Risks As Children Reach Adulthood

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**Abstract:** Hamartomatous polyposis syndromes are a rare group of hereditary autosomal dominant disorders that comprise less than 1% of all hereditary colorectal cancers. Hamartomatous polyps, in and of themselves, are benign entities; however, these hamartomatous polyposis syndromes have a malignant potential for the development of colorectal cancer as well as extracolonic cancers. Early detection and proper surveillance are vital to minimizing the risk of carcinoma. This article provides a critical review of the clinical presentation, pathology, genetics, and screening and surveillance guidelines of juvenile polyposis syndrome, PTEN hamartoma tumor syndrome, and Peutz-Jeghers syndrome.

**H**amartomatous polyposis syndromes are a rare group of hereditary autosomal dominant disorders that comprise less than 1% of all hereditary colorectal cancers.<sup>1-3</sup> Hamartomatous polyps, in and of themselves, are benign entities comprised of cells that are indigenous to the area in which they are found (ie, all cell layers with a mesenchymal predominance). However, these hamartomatous polyposis syndromes have a malignant potential for the development of colorectal cancer as well as extracolonic cancers. The progression of hamartomatous polyps to carcinoma is still being elucidated. Unlike adenomatous polyps, in which malignant transformation progresses through the adenoma-carcinoma sequence via a gatekeeper or caretaker defect, in hamartomatous polyps, a proposed hamartoma-carcinoma sequence hypothesis involves a landscaper defect in which stromal elements create a local environment that promotes epithelial dysplasia and ultimately leads to carcinoma.<sup>4</sup>

The hamartomatous polyposis syndromes include juvenile polyposis syndrome (JPS); PTEN hamartoma tumor syndrome, which includes Cowden syndrome (CS) and Bannayan-Riley-Ruvalcaba syndrome (BRRS); and Peutz-Jeghers syndrome (PJS). Due to the

## Keywords

Hamartomatous polyposis syndromes, juvenile polyposis syndrome, PTEN hamartoma tumor syndrome, Peutz-Jeghers syndrome

rarity of these conditions, a thorough understanding of their clinical presentation, including extraintestinal manifestations (gross and histopathologic), and genetics is important. For pediatric gastroenterologists, understanding how to recognize and establish the appropriate diagnosis and cancer risk and following appropriate screening and surveillance guidelines is crucial for early detection to minimize the risk of carcinoma as children reach adulthood.

## Juvenile Polyposis Syndrome

### *Clinical Presentation*

Juvenile polyps are the most common type of pediatric gastrointestinal polyps. Solitary juvenile polyps can develop at any age, though they appear most frequently in preschool children and have an incidence of 2% in children under 10 years of age. Solitary polyps are generally located in the rectosigmoid area and are usually considered to be a separate entity from JPS, which has an incidence of 1 in 100,000–160,000 individuals.<sup>5,6</sup> A family history of juvenile polyps is found in 20–50% of patients with JPS, with an autosomal dominant inheritance pattern of variable penetrance.<sup>1,7-10</sup>

In JPS, affected individuals develop multiple gastrointestinal juvenile polyps, predominantly in the colon, though the condition may also affect the rest of the gastrointestinal tract.<sup>11-13</sup> JPS has been phenotypically classified into 3 categories<sup>14</sup>: juvenile polyposis coli, in which polyp growth affects only the colon; the rare and often fatal form of JPS called juvenile polyposis of infancy, which is characterized by diarrhea, protein-losing enteropathy, bleeding, and rectal prolapse<sup>15</sup>; and generalized juvenile polyposis, in which polyp growth can affect the colon, stomach, and small bowel. As opposed to solitary juvenile polyps, which occur in children most commonly at 4–5 years of age, JPS presents in the first or second decade of life, with an average age of 18.5 years at the time of diagnosis.<sup>12,16</sup> Typical presenting symptoms include rectal bleeding, anemia, abdominal pain, diarrhea, intussusception, obstruction, and polyp prolapse, though many JPS patients may be asymptomatic.<sup>8,17,18</sup>

### *Extraintestinal Manifestations*

Multiple extraintestinal manifestations have been reported with JPS, including heart defects, polydactyl, clubbing, intestinal malrotation, Meckel diverticulum, hydrocephalus, macrocephaly, hypertelorism, cleft lip, cleft palate, double renal pelvis and ureter, bifid uterus and vagina, undescended testes, and supernumerary teeth.<sup>13,16,19</sup> These abnormalities have been reported in approximately 11–20% of cases,<sup>8,19,20</sup> mainly in case reports. However, due to the overlap of JPS, CS, and BRRS, the true inci-

dence of extraintestinal manifestations based upon these case reports is difficult to interpret. JPS and hereditary hemorrhagic telangiectasia (HHT) have also been reported together.<sup>21</sup> Further credence to this association has been made with the recent report of 2 JPS patients having a germline mutation in the *ENG* gene, which is the causative gene in HHT.<sup>22</sup>

### *Diagnosis*

The diagnosis of JPS is clinically established based upon the presence of at least 1 of the following criteria<sup>18,23,24</sup>: at least 3–10 polyps detected on colonoscopy; polyps located outside of the colon; and any number of polyps in a patient with a family history of juvenile polyps. The number of polyps needed to establish the diagnosis of JPS varies in the literature. Sachatello and associates proposed 10 polyps as the benchmark; however, this number was reduced to 5 polyps by Jass and colleagues and then to 3 polyps by Giardiello and coworkers.<sup>18,23,24</sup> There is currently no clear consensus on the number of polyps to use for diagnosis, hence the range of 3–10 listed above.

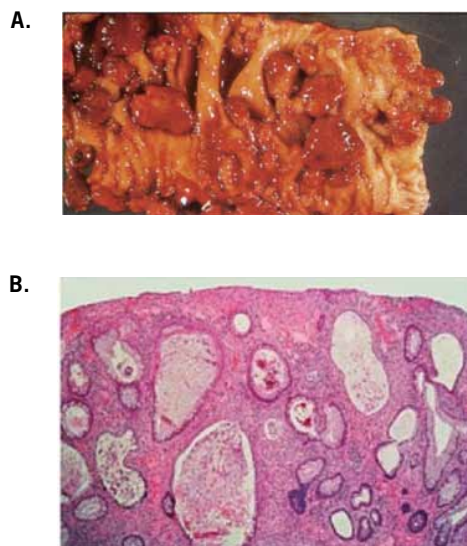
### *Gastrointestinal Pathology*

The gross appearance of a juvenile polyp is spherical to slightly lobular in shape, and most are pedunculated with long stalks.<sup>25</sup> In patients with JPS, polyps may have a multilobulated appearance of a villiform or papillary shape.<sup>8</sup> Jass and colleagues reported that approximately 20% of polyps have the latter appearance.<sup>18</sup> Polyp size can range from several millimeters to 3 cm (Figure 1A). These polyps are typically very vascular, with a smooth and glistening appearance on the surface; however, they may also have an ulcerated surface from auto-infarction.

The histologic appearance of juvenile polyps shows multiple large mucus-filled glands lined with columnar epithelium (Figure 1B). The lamina propria usually has an inflammatory cell component.<sup>18</sup> Smooth muscle components are not present in juvenile polyps, which distinguishes them from PJS polyps, but not from polyps of the other hamartomatous polyposis syndromes.<sup>26,27</sup>

### *Genetics*

A family history of JPS is found in 20–50% of patients with JPS, with an autosomal dominant inheritance pattern of variable penetrance.<sup>17,18</sup> Three genes have been associated with JPS: *SMAD4*, *BMPRIA*, and *ENG*, all of which are part of the transforming growth factor- $\beta$  (TGF- $\beta$ ) superfamily of proteins.<sup>27</sup> The *PTEN* gene mutation in patients with juvenile polyposis is a controversial topic. It is generally thought that patients with the *PTEN* gene mutation likely represent CS or BRRS patients who have not yet expressed the extraintestinal clinical features of these conditions.<sup>27-29</sup>



**Figure 1.** Resection of a colon from a patient with juvenile polyposis syndrome containing multiple juvenile polyps (A).

Reproduced from Demetris AJ, Finkelstein SD, Nalensnik MA, et al. Slide carousel of GI pathology course for medical students. Available at: <http://www.pathology.pitt.edu/lectures/gi/>. © Department of Pathology, University of Pittsburgh School of Medicine.

Histologic image of a juvenile polyp showing its characteristic large cystic spaces and a lamina propria with an inflammatory cell component (B).

Reproduced from Mulholland M, Lillemoe K, Doherty G, Maier R, Upchurch G. *Greenfield's Surgery: Scientific Principles and Practice*. 4th ed. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2006.

The *SMAD4* gene, located on chromosome 18q21.1, was first identified by Howe using gene linkage analysis on affected families with JPS.<sup>30,31</sup> Germline mutations in the *SMAD4* gene have a prevalence of 20% in JPS patients.<sup>32</sup> Patients with the *SMAD4* mutation are more likely to have upper gastrointestinal polyps. A subset of JPS patients also has HHT, which has been linked to patients with *SMAD4* mutations. Multiple types of mutations have been reported in the *SMAD4* gene, including missense, nonsense, deletions, and insertions; however, the most common mutation is the one originally discovered by Howe (the 4-base pair deletion in exon 9).<sup>33</sup> *SMAD4* is an intracellular mediator in the TGF- $\beta$  signaling pathway. It binds to other members of the SMAD family and is involved in transcriptional activation and nuclear localization.<sup>26,34,35</sup> In JPS, *SMAD4* is thought to act as a tumor suppressor gene, and the inactivation of *SMAD4* in the unaffected allele is an important step in

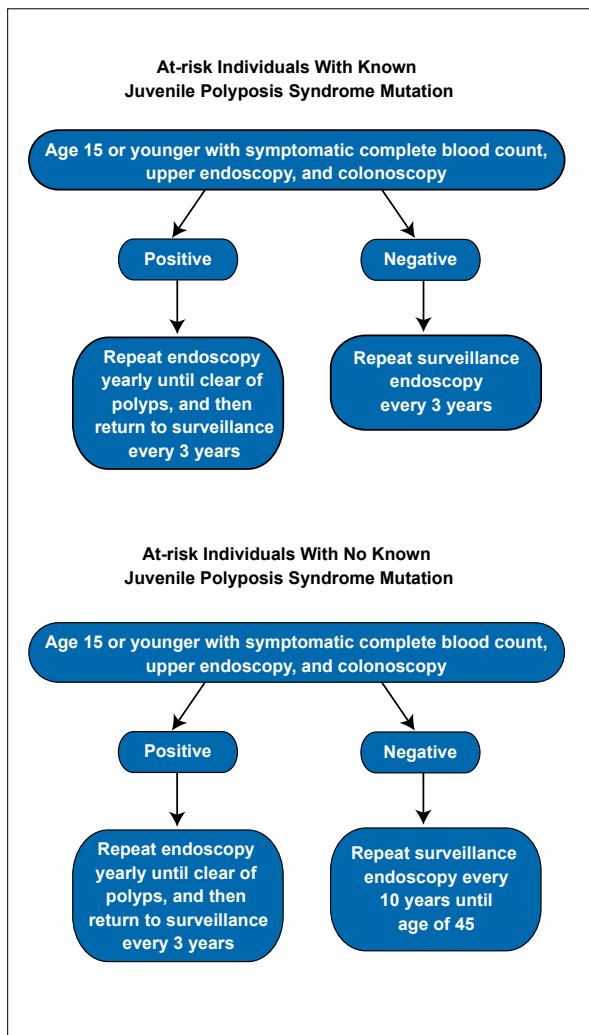
polyp development.<sup>36</sup> These data are supported by the *SMAD4* knockout mouse model.<sup>37-39</sup>

The bone morphogenetic protein receptor type IA (*BMPRIA*) gene is located on chromosome 10q22-23 and was reported by Howe and associates in 2001.<sup>40-42</sup> Germline mutations in the *BMPRIA* gene have a prevalence of 20% in JPS patients.<sup>32</sup> *BMPRIA* is a type I serine/threonine kinase receptor protein that is bound to a type II serine/threonine kinase receptor protein.<sup>34</sup> This receptor complex is also involved in the TGF- $\beta$  signaling pathway upstream of *SMAD4*. It phosphorylates *SMAD* proteins that then bind to *SMAD4*.<sup>43,44</sup> *BMPRIA* knockout mice are homozygous lethal, whereas heterozygous mice appear normal with no polyp development.<sup>45</sup>

*ENG* has recently been shown to be present in 2 patients with JPS; however, its role as a predisposition gene still requires additional confirmation.<sup>22,46</sup> The *ENG* gene is located on chromosome 9q34.1.<sup>47</sup> *ENG* encodes the protein endoglin, which is an accessory protein of the TGF- $\beta$  signaling pathway.<sup>48</sup> Endoglin signaling is initiated by the binding of TGF- $\beta$  in combination with TBR-II and results in a series of activation steps leading to transcriptional activity. Endoglin inhibition appears to have an inhibitory effect on TGF- $\beta$  in endothelial cells.<sup>48,49</sup> *ENG* knockout mice are homozygous lethal, and heterozygous mice exhibit large numbers of irregular, dilated, and thinner-walled vessels and serve as a model for HHT. There is no reported polyp growth in this mouse model.<sup>50</sup>

### Cancer Risk

Individuals with JPS are at risk for the development of colorectal, gastric, small intestinal, and pancreatic cancers. The risk of developing colorectal cancer from solitary juvenile polyps is thought to be negligible or nonexistent. However, individuals with JPS are at risk for developing adenomatous change and carcinoma. The incidence of colorectal cancer has been reported by Jass and associates to be 20.7%, with a mean age of 34 years (age range, 15–59 years) and an estimated cumulative colorectal cancer risk of 68% by 60 years of age.<sup>18</sup> Coburn and colleagues reported a colorectal cancer risk of 17%, with a mean age of 35 years (age range, 15–59 years) at diagnosis.<sup>17</sup> Howe and coworkers reported a colorectal cancer risk of 38% and a cumulative risk of gastrointestinal cancer of 55%, with a mean age of 43 years (age range, 17–68 years).<sup>51</sup> There have been multiple case reports documenting gastric adenocarcinomas and pancreatic adenocarcinomas.<sup>52-54</sup> In an Iowa kindred, Howe and colleagues reported 4 gastric carcinomas, 1 duodenal carcinoma, and 1 pancreatic carcinoma, with an overall risk of upper gastrointestinal cancer of 21% in patients with JPS.<sup>51</sup> In a review of JPS patients, Coburn and associates reported 1 gastric carcinoma and 1 duodenal carcinoma.<sup>17</sup>



**Figure 2.** Proposed algorithm for endoscopic surveillance of juvenile polyposis syndrome.

### Screening and Management

There are no standardized screening and surveillance guidelines for the management of JPS. Two proposed guidelines have been published, one by Howe and coworkers and another by Dunlop.<sup>55,56</sup> Howe and coworkers suggested that genetic testing be performed in patients at risk for JPS. According to their guidelines, a complete blood count (CBC), upper endoscopy, and colonoscopy should be performed for JPS in all at-risk patients when symptoms present or in asymptomatic patients by 15 years of age. If no polyps are found, a repeat colonoscopy should be performed every 3 years. If a genetic mutation is present, screening with upper endoscopy, colonoscopy,

and CBC should also be performed every 3 years; however, if no genetic mutation is present and no polyps are found at the initial endoscopy, a repeat endoscopy should be performed every 10 years until 45 years of age. If no polyps are found by 45 years of age, standard colorectal cancer screening should be used (Figure 2).<sup>55</sup> Wirtzfeld and colleagues critiqued the every-10-year screening intervals for at-risk JPS patients without genetic mutations by claiming that, due to the genetic heterogeneity of JPS, a 10-year interval may be too long of a period of time to go without screening.<sup>3</sup>

Dunlop's proposed guidelines for JPS screening starts at 15–18 years of age for colonoscopy in asymptomatic at-risk patients and at 25 years of age for upper endoscopy. If a genetic mutation is found and no polyps are detected at the time of the initial endoscopy, screening should continue until 70 years of age; however, if no genetic mutation is found and no polyps are detected at the initial endoscopy, repeat endoscopy should be performed every 1–2 years until 35 years of age.<sup>56</sup>

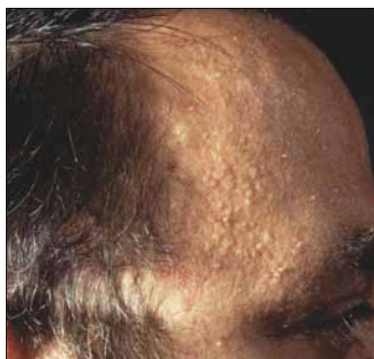
Both sets of authors agree that any found polyps should be removed endoscopically. Endoscopy should then be repeated yearly until no polyps are detected, at which point screening should return to every 3 years, according to Howe and coworkers, or every 1–2 years, according to Dunlop.

The indications for surgery include a large polyp burden that cannot be managed endoscopically, polyps with adenomatous change, severe diarrhea with hypoproteinemia, or gastrointestinal bleeding with anemia. There are no standards for the type of surgery. Surgical options include subtotal colectomy with ileorectal anastomosis and total colectomy with J-pouch ileoanal anastomosis.<sup>57,58</sup> Regardless of the surgery performed, endoscopic surveillance is recommended after surgery for polyp recurrence in the pouch.<sup>57,58</sup>

Gastric polyps should be removed endoscopically; however, this guideline may be challenging due to the number of polyps found. Indications for total or subtotal gastrectomy include severe anemia due to chronic bleeding, adenomatous change, or adenocarcinoma.<sup>26</sup>

### PTEN Hamartoma Tumor Syndrome

PTEN hamartoma tumor syndrome is the term that has been used recently to describe both CS and BRRS.<sup>59</sup> These disorders are both caused by mutations in the *PTEN* gene and are both characterized by extraintestinal manifestations more than intestinal polyposis. The clinical presentations for the diseases will be discussed separately in this paper, though it should be noted that the differences between them are likely due to the variable phenotypic expression seen in *PTEN* gene mutations.<sup>59-62</sup>



A.



B.

**Figure 3.** Multiple skin-colored facial warty papules representing trichilemmomas (A). Multiple reddish confluent papules on the oral mucosa revealing a cobblestone appearance (B).

Both figures are reproduced from Wolff K, Johnson RA, Fitzpatrick TB. *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*. 6th ed. New York, New York: McGraw-Hill Medical; 2009.



**Figure 4.** Glycogenic acanthosis of the esophagus in a patient with Cowden syndrome.

### Cowden Syndrome

**Clinical Presentation** CS is a rare autosomal dominant syndrome, with a reported incidence of 1 in 200,000 individuals.<sup>63</sup> This syndrome is characterized by macrocephaly, mucocutaneous lesions (such as facial trichilemmoma), acral keratosis, and papillomatous papules (Figure 3). It is also associated with thyroid, breast, and endometrial manifestations, including cancer in all of these areas.<sup>26,27,64</sup> CS has been linked to Lhermitte-Duclos disease, which is characterized by hamartomas of the cerebellum.<sup>65</sup> Hamartomatous polyps throughout the gastrointestinal tract are associated with this syndrome but are not as common as the extraintestinal findings associated with the syndrome. The incidence of gastrointestinal polyps in CS varies in the literature, ranging anywhere from 30% to 85%.<sup>64,66,67</sup> It is generally thought that the incidence of gastrointestinal polyps in CS is less than that of BRRS, though this belief is debated in the literature.<sup>66</sup> Another gastrointestinal manifestation of CS is glycogenic acanthosis of the esophagus (Figure 4), which involves large benign glycogen-filled epithelial cells that are gray to white in color.<sup>68</sup>

**Extraintestinal Manifestations** As stated above, extraintestinal manifestations are the hallmark of the syndrome and summarized in Table 1.

**Table 1.** Extraintestinal Manifestations of Cowden Syndrome With Their Diagnostic Criteria

Manifestation	Type of criteria
Facial trichilemmomas	Pathognomonic
Acral keratoses	Pathognomonic
Papillomatous papules	Pathognomonic
Lhermitte-Duclos disease	Pathognomonic
Breast adenocarcinoma	Major
Fibrocystic breast disease	Minor
Thyroid multinodular goiter	Minor
Thyroid adenoma	Minor
Thyroid carcinoma	Major
Uterine leiomyomas	Minor
Endometrial carcinoma	Major
Bicornuate uterus	Minor
Macrocephaly	Major
Developmental delay	Minor
Lipomas	Minor
Fibromas	Minor
Renal cell carcinoma	Minor
Melanoma	Minor

**Diagnosis** The diagnosis of CS is based upon pathognomonic, major, and minor criteria. These criteria are updated by the National Comprehensive Cancer Network (NCCN) and can be accessed via the Web site [www.nccn.org](http://www.nccn.org).<sup>27</sup> A working diagnosis can be established by fulfilling 1 pathognomonic criterion; 2 major criteria; 1 major and 3 or more minor criteria; or 4 or more minor criteria. These criteria are listed in Table 1.

**Table 2.** Extraintestinal Manifestations of Bannayan-Riley-Ruvalcaba Syndrome

- Macrocephaly
- Developmental delay
- Accelerated growth of first metacarpal and first proximal and middle phalanges
- Joint hyperflexibility
- Pectus excavatum
- Scoliosis
- Genital pigmentation
- Lipomas
- Hemangiomas
- Lipid storage myopathy

***Bannayan-Riley-Ruvalcaba Syndrome***

**Clinical Presentation** The term BRRS was first used by Gorlin and coworkers to describe 3 clinically similar autosomal dominant syndromes: Riley-Smith syndrome, Bannayan-Zonana syndrome, and Ruvalcaba-Myhre-Smith syndrome.<sup>69</sup> BRRS is characterized by macrocephaly; developmental delays; pigmented speckling of the penis; lipomas; and hamartomatous polyps of the intestine.<sup>69,70</sup> The incidence of gastrointestinal polyps in BRRS has been reported to be 45%.<sup>69</sup>

**Extraintestinal Manifestations** As with CS, the extraintestinal manifestations of this syndrome are its hallmark and are summarized in Table 2.

**Diagnosis** Due to the rarity of this syndrome, there are no formal diagnostic criteria for BRRS. The diagnosis of BRRS should be considered when a patient exhibits 1 or more extraintestinal manifestations with or without polyps, or has a family history of BRRS or CS.

**Cowden Syndrome and Bannayan-Riley-Ruvalcaba Syndrome Gastrointestinal Pathology** The appearance of polyps within the gastrointestinal tract in both CS and BRRS resembles the gross and histologic appearance of juvenile polyps.<sup>69</sup> Therefore, when juvenile polyps are detected, physicians should evaluate the patient for possible extraintestinal manifestations of CS and BRRS.

**Cowden Syndrome and Bannayan-Riley-Ruvalcaba Syndrome Genetics** CS and BRRS have an autosomal dominant inheritance pattern with variable penetrance. Both syndromes have been associated with the *PTEN* gene, which is located on chromosome 10q22-23. CS was linked to chromosome 10q22-23 by Nelen and associates, and the *PTEN* gene was later identified at this locus

**Table 3.** Cowden and Bannayan-Riley-Ruvalcaba Syndrome Management

- **Thyroid**
  - Annual thyroid ultrasound starting at age 18
- **Breast**
  - Biannual breast examination at age 25 or 5–10 years from the earliest known family member with breast cancer
  - Annual mammography and breast magnetic resonance imaging screening at ages 30–35 or 5–10 years from the earliest known family member with breast cancer
- **Endometrial cancer**
  - Endometrial suction biopsies between the ages of 35–40 or 5 years before the earliest known family member, then followed by annual endometrial ultrasound
- **Renal cell carcinoma**
  - Annual urine analysis and renal ultrasound
- **Melanoma**
  - Annual dermatologic examination

by Liaw and colleagues, and confirmed by Nelen and coworkers, as well as Lynch and associates.<sup>63,71-73</sup> Marsh and colleagues then found an association between *PTEN* and BRRS.<sup>74</sup> The *PTEN* gene is found in 80% of CS patients and 60% of BRRS patients.<sup>62,75</sup> CS and BRRS are allelic diseases in which a mutation of the *PTEN* gene is found in all exons except 1, 4, and 9 in CS. In BRRS, mutations occur preferentially in exons 6 and 7 and are also associated with balanced translocations and deletions.<sup>62,63,71,72,74</sup> It has been hypothesized that the differential expression of the *PTEN* gene correlates with the different phenotypes seen in CS and BRRS.<sup>76</sup>

The *PTEN* gene is a tumor suppressor gene that is also a tyrosine phosphatase that dephosphorylates tyrosine, serine, and threonine.<sup>77</sup> *PTEN* is a negative regulator of the Akt/PKB signaling pathway,<sup>77,78</sup> which controls the levels of phosphoinositol triphosphate. *PTEN* is also involved in regulating cell cycle, apoptosis, and angiogenesis.<sup>78,79</sup>

**Cancer Risk** Individuals with CS are at risk for developing breast, thyroid, and endometrial cancers. The risk of adenocarcinoma of the breast has been reported to range from 30% to 50% in women with CS.<sup>27,64,66</sup> In addition, there are reports of breast cancer in men with CS.<sup>80</sup> Individuals with CS are also subject to benign conditions of the breast such as fibrocystic disease.<sup>64</sup> Thyroid abnormalities such as multinodular goiter and thyroglossal duct cysts are associated with this syndrome, as well as a 10% risk of thyroid cancer. CS patients also have a risk of



**Figure 5.** Multiple dark-brown lentiginos on the vermilion border of the lip and buccal mucosa in a patient with Peutz-Jeghers syndrome.

Reproduced from Swartz MH. *Textbook of Physical Diagnosis: History and Examination*. 4th ed. Philadelphia, Pennsylvania: WB Saunders; 2002:295.

leiomyomas, as well as an up-to-10% risk of endometrial cancer.<sup>64,81</sup> Renal cell cancer has also been associated with CS.<sup>64</sup> The risk of developing gastrointestinal carcinoma in CS is unclear at this point. It has been reported by some studies that there is no increased risk of gastrointestinal cancer; however, there are multiple case reports of gastric and colorectal cancer.<sup>64,82-84</sup>

In BRRS, the cancer risk is unclear. The limited number of patients with this disease makes it difficult to determine the risk; however, there have been case reports of breast and endometrial cancer.<sup>62,85</sup> With additional evidence supporting the idea that CS and BRRS are variable phenotypic expressions in the *PTEN* gene, it is therefore recommended that individuals with BRRS be considered at risk for malignancy, as with CS.

**Screening and Management** Individuals with CS and BRRS who have mutations in the *PTEN* gene should be screened according to the CS guidelines summarized in Table 3.<sup>1,5,59,68,86</sup> These guidelines include breast cancer screening with self and clinical breast examinations, in addition to annual mammography and breast magnetic resonance imaging for breast cancer beginning at 25 years of age or 5–10 years earlier than the youngest case in the family. Thyroid cancer screening involves clinical examinations and yearly thyroid ultrasounds starting at 18 years of age. Endometrial cancer screening with endometrial biopsies should be performed at 35–40 years of age or 5 years earlier than the youngest case in the family. Renal cell cancer screening can be performed with yearly urinalysis and ultrasound.<sup>1,5,68,86</sup> Updated guidelines for CS screening can be found on the NCCN Web site.<sup>59</sup>



**Figure 6.** Polyps from a patient with Peutz-Jeghers syndrome are pedunculated and tend to be large and multilobulated.

Reproduced from Mulholland M, Lillemoe K, Doherty G, Maier R, Upchurch G. *Greenfield's Surgery: Scientific Principles and Practice*. 4th ed. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2006.

## Peutz-Jeghers Syndrome

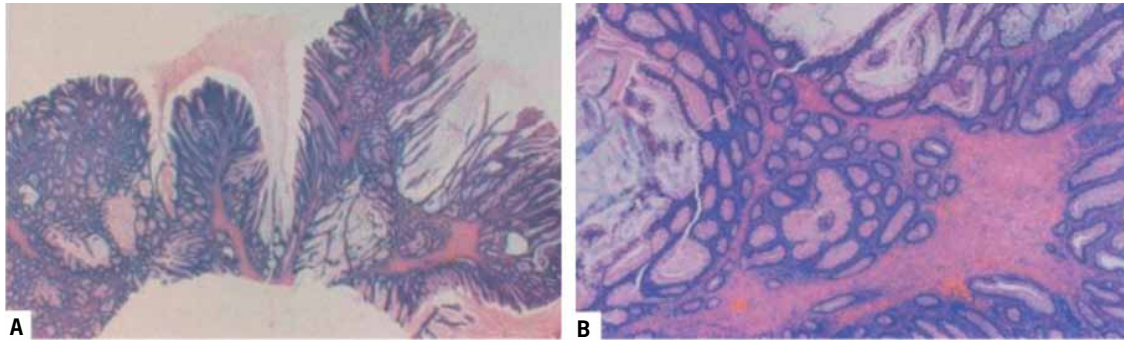
### Clinical Presentation

PJS, as with the other hamartomatous syndromes, is an autosomal dominant syndrome that is typified by its characteristic mucocutaneous pigmentation and intestinal hamartomatous polyps. The incidence of PJS is reported to be 1 in 150,000 to 200,000 individuals.<sup>86,87</sup> Pigmentation is seen around the vermilion border of the lips in over 95% of cases, with the buccal mucosa being the second most common site (80%; Figure 5).<sup>88,89</sup> Other areas of pigmentation include the hands, feet, genitals, and around the nose and eyes. Pigmentation typically presents in early childhood and starts to fade with age usually after the start of puberty.<sup>90,91</sup>

Hamartomatous polyps in PJS are commonly found in the small intestine; however, they are also found in the stomach and colon. The number of polyps in the intestine may range from 1 to a complete carpeting of the gastrointestinal tract (Figure 6).<sup>89,92</sup> The most common presentation of PJS is abdominal pain secondary to intussusception. Other clinical presentations include anemia, melena, hematochezia, hematemesis, and obstruction. Approximately one third of PJS patients present in the first decade of life, with up to 60% presenting by the second or third decade.<sup>90,93,94</sup>

### Extraintestinal Manifestations

In PJS, polyps have been reported outside of the gastrointestinal tract, including areas involving the nose, bronchi, renal pelvis, and bladder.<sup>95</sup> Polyps have also been reported in the gallbladder and bile ducts; however, polyps in the



**Figure 7.** Histologic image of a Peutz-Jeghers polyp showing its characteristic histologic appearance, which consists of smooth muscle proliferation in the shape of a tree branch (a process that is called arborization) (A). Enlargement of a Peutz-Jeghers polyp showing smooth muscle proliferation (B).

Both images reproduced from Boland CR. The colon, rectum, and anus. In: Feldman M, ed. *Gastroenterology and Hepatology: The Comprehensive Visual Reference*. Philadelphia, Pennsylvania: Churchill Livingstone; 1996.

gallbladder have been histologically adenomatous and not hamartomatous.<sup>96</sup> Bile duct polyps have presented with jaundice secondary to obstructive symptoms.<sup>97,98</sup> PJS is also associated with various malignancies that will be described below.

### Diagnosis

The diagnosis of PJS is clinically established on the presence of histologic tissue that is consistent with hamartomatous polyps and 2 of the following criteria<sup>99</sup>: a family history of PJS; the presence of mucocutaneous pigmentation; and the presence of small-bowel polyps.

### Pathology

The gross appearance of a polyp in PJS is typically pedunculated with long stalks. These polyps tend to be multilobulated and have a villiform or papillary shape. Polyp size can range from 0.5 cm to 5 cm in diameter. The polyp has a characteristic histologic appearance consisting of smooth muscle proliferation in a tree branch, a process that is called arborization (Figure 7).<sup>100</sup> The epithelium that covers the smooth muscle can become displaced into the submucosa and muscularis propria, giving a pseudocarcinoma appearance of a mucinous adenocarcinoma.<sup>101</sup>

### Genetics

PJS, as with the other hamartomatous syndromes, has an autosomal dominant pattern of inheritance with both familial and sporadic transmission.<sup>102</sup> The gene associated with PJS is a serine-threonine kinase that is located on chromosome 19p13.3.<sup>103,104</sup> Hemminki and coworkers and Jenne and associates independently identified the gene in this region as *LKB1/STK11*.<sup>105,106</sup> This gene has been reported in 80% of patients with PJS.<sup>107</sup> Common mutations are frameshift and nonsense mutations in exons

1–6; however, large deletion mutations missed by direct sequencing have been recently described using multiple ligation probes.<sup>107</sup>

*LKB1/STK11* is a tumor suppressor gene that encodes a serine-threonine kinase that phosphorylates and activates members of the AMPK-related subfamily of protein kinases.<sup>108</sup> *LKB1/STK11* has an essential role in G1 cell cycle arrest, cell polarity, p53-dependent apoptosis, and cellular energy levels.<sup>109,110</sup> *LKB1* (+/-) mice develop gastrointestinal polyps with histologic characteristics resembling those of human PJS polyps.<sup>111</sup>

### Cancer Risk

Individuals with PJS are at risk for the development of colorectal, gastric, small intestinal, esophageal, and pancreatic cancers. PJS patients are also at risk for extraintestinal cancer such as lung, breast, ovarian, testicular, and endometrial cancers.<sup>26,27,90</sup> A meta-analysis showed that the risk of developing any type of cancer by 64 years of age was 93% (relative risk of 15).<sup>112</sup> Lim and colleagues evaluated the St. Mark's polyp registry and found that the relative risk of developing any type of cancer was 47% by 65 years of age in PJS patients with known genetic mutations in *LKB1/STK11*.<sup>113</sup> More recently, a study looking at 419 PJS patients, 297 of whom had documented mutations, showed the risk of cancer to be 60% by 60 years of age and 85% by 70 years of age.<sup>114</sup> This same study reported the risks of developing gastrointestinal cancer (31%), breast cancer (31%), gynecologic cancer (18%), pancreatic cancer (7%), and lung cancer (13%) by 60 years of age.<sup>114</sup> Individuals with PJS are also at risk for developing rare sex cord tumors. Women are at risk for sex cord tumors with annular tubules that are benign, and men are at risk for developing Sertoli cell tumors, which result in feminization.

**Table 4.** Peutz-Jeghers Syndrome Surveillance Recommendations

Cancer screening by organ	Disease	Diagnostic testing	Screening interval	Age interval to be screened
Testes	Sertoli tumor	<ul style="list-style-type: none"> <li>History and physical examination</li> <li>Testicular ultrasound</li> </ul>	1 year	Birth to age 12
			2 years	
Ovary	Ovarian carcinoma	<ul style="list-style-type: none"> <li>Transvaginal ultrasound</li> <li>CA-125</li> </ul>	1 year 1 year	Start at age 25
Cervix and uterus	Cervical and uterine carcinoma	<ul style="list-style-type: none"> <li>Pelvic examination and pap smear</li> </ul>	1 year	Start at age 21
Breast	Breast carcinoma	<ul style="list-style-type: none"> <li>Breast self-examination</li> <li>Clinical breast examination</li> <li>Mammography or magnetic resonance imaging</li> </ul>	1 month	Start at age 18 Start at age 25 Start at age 25
			6 months	
			1 year	
Pancreas	Pancreatic carcinoma	<ul style="list-style-type: none"> <li>Endoscopic ultrasound (computed tomography scan as an alternative)</li> <li>CA 19-9</li> </ul>	1–2 years	Start at age 25 Start at age 25
			1–2 years	
Gastrointestinal tract	Gastric carcinoma, small-bowel polyps, and small-bowel carcinoma	<ul style="list-style-type: none"> <li>Upper gastrointestinal endoscopy and upper gastrointestinal small bowel follow-through</li> <li>Colonoscopy</li> </ul>	2–3 years	Start at age 8 Start at age 25
	Colorectal carcinoma		2–3 years	

Both of these tumors arise from the same embryonic tissue.<sup>115,116</sup>

### Screening and Management

Individuals at risk for PJS should be evaluated at birth for pigmented spots, precocious puberty, and testicular tumors. Asymptomatic at-risk individuals should undergo genetic testing for the affected member's mutation in the *STK11/LKB1* gene at 8 years of age.<sup>90</sup> If the at-risk family member does not have a genetic mutation, they are not thought to have PJS. However, genetic testing is only useful if the family member with PJS has a known *STK11/LKB1* mutation. If the family member with PJS has a mutation that is unidentifiable, endoscopic surveillance, as apposed to genetic testing, should be performed in at-risk family members. These asymptomatic at-risk individuals should, at the bare minimum, undergo small-bowel contrast studies every 2 years until 25 years of age. Alternatively, this group of at-risk patients should undergo upper endoscopy, colonoscopy, and small-bowel contrast study every 6 years starting at 12 years of age until 24 years of age. Any at-risk patients with pigmentation should undergo the PJS surveillance guidelines, as outlined below.

The PJS surveillance guidelines proposed by Giardiello and Trimbath<sup>90</sup> (Table 4) include upper endoscopy and small-bowel contrast study starting at 8 years of age every 2–3 years. Starting at 18 years of age, colonoscopy should be performed every 2–3 years in coordination with upper endoscopy and small-bowel contrast study. Pancreatic screening should begin at 25–30 years of age, with endoscopic ultrasound every 1–2 years, with possible computed tomography scan and CA 19-9 cancer marker. For women, breast cancer screening with self and clinical breast examinations should begin at 18 years of age. Annual mammography and/or breast magnetic resonance imaging should begin at 25 years of age or 5–10 years earlier than the youngest case in the family. Other genitourinary cancers should be evaluated starting at 21 years of age, with yearly transvaginal ultrasound and CA-125 cancer markers, as well as yearly pelvic examinations and pap smears. Men should undergo yearly testicular examinations starting at birth and testicular ultrasounds every 2 years up until 12 years of age.<sup>27,93</sup> Capsule endoscopy may replace small-bowel contrast studies in the future.

Polyps found in the stomach and colon should be removed at the time of surveillance endoscopy. Polyps

detected in the small bowel that are 1–1.5 cm or larger in size should also be removed.<sup>90,117,118</sup> In the past, removal was performed by push enteroscopy or laparotomy by either polypectomy or, in the case of very large polyps, bowel resection. However, advances in enteroscopy with the use of double- and single-balloon technology, and now spiral enteroscopy, allow for more of the small bowel to be reached without requiring laparotomy.

## References

- Attard TM, Young RJ. Diagnosis and management of gastrointestinal polyps: pediatric considerations. *Gastroenterol Nurs*. 2006;29:16-22; quiz 3-4.
- Nagy R, Sweet K, Eng C. Highly penetrant hereditary cancer syndromes. *Oncogene*. 2004;23:6445-6470.
- Wirtzfeld DA, Petrelli NJ, Rodriguez-Bigas MA. Hamartomatous polyposis syndromes: molecular genetics, neoplastic risk, and surveillance recommendations. *Ann Surg Oncol*. 2001;8:319-327.
- Kinzler KW, Vogelstein B. Landscaping the cancer terrain. *Science*. 1998;280:1036-1037.
- Burt RW, Bishop DT, Lynch HT, Rozen P, Winawer SJ. Risk and surveillance of individuals with heritable factors for colorectal cancer. WHO Collaborating Centre for the Prevention of Colorectal Cancer. *Bull World Health Organ*. 1990;68:655-665.
- Chow E, Macrae F. A review of juvenile polyposis syndrome. *J Gastroenterol Hepatol*. 2005;20:1634-1640.
- Alhan E, Unuvar E, Gumustekin E. Juvenile polyps of the colon and rectum. *Turk J Pediatr*. 1988;30:99-103.
- Desai DC, Neale KF, Talbot IC, Hodgson SV, Phillips RK. Juvenile polyposis. *Br J Surg*. 1995;82:14-17.
- Pillai RB, Tolia V. Colonic polyps in children: frequently multiple and recurrent. *Clin Pediatr (Phila)*. 1998;37:253-257.
- Reed K, Vose PC. Diffuse juvenile polyposis of the colon: a premalignant condition? *Dis Colon Rectum*. 1981;24:205-210.
- Sachatello CR, Pickren JW, Grace JT Jr. Generalized juvenile gastrointestinal polyposis. A hereditary syndrome. *Gastroenterology*. 1970;58:699-708.
- Coffin CM, Dehner LP. What is a juvenile polyp? An analysis based on 21 patients with solitary and multiple polyps. *Arch Pathol Lab Med*. 1996;120:1032-1038.
- McColl I, Bussey HJ, Veale AM, Morson BC. Juvenile polyposis coli. *Proc R Soc Med*. 1964;57:896-897.
- Sachatello CR, Hahn IS, Carrington CB. Juvenile gastrointestinal polyposis in a female infant: report of a case and review of the literature of a recently recognized syndrome. *Surgery*. 1974;75:107-114.
- Ruyman FB. Juvenile polyps with cachexia. Report of an infant and comparison with Cronkhite-Canada syndrome in adults. *Gastroenterology*. 1969;57:431-438.
- Veale AM, McColl I, Bussey HJ, Morson BC. Juvenile polyposis coli. *J Med Genet*. 1966;3:5-16.
- Coburn MC, Pricolo VE, DeLuca FG, Bland KI. Malignant potential in intestinal juvenile polyposis syndromes. *Ann Surg Oncol*. 1995;2:386-391.
- Jass JR, Williams CB, Bussey HJ, Morson BC. Juvenile polyposis--a precancerous condition. *Histopathology*. 1988;13:619-630.
- Desai DC, Murday V, Phillips RK, Neale KF, Milla P, Hodgson SV. A survey of phenotypic features in juvenile polyposis. *J Med Genet*. 1998;35:476-481.
- Bussey HJ, Veale AM, Morson BC. Genetics of gastrointestinal polyposis. *Gastroenterology*. 1978;74:1325-1330.
- Inoue S, Matsumoto T, Iida M, Hoshika K, Shimizu M, et al. Juvenile polyposis occurring in hereditary hemorrhagic telangiectasia. *Am J Med Sci*. 1999;317:59-62.
- Sweet K, Willis J, Zhou XP, Gallione C, Sawada T, et al. Molecular classification of patients with unexplained hamartomatous and hyperplastic polyposis. *JAMA*. 2005;294:2465-2473.
- Giardiello FM, Hamilton SR, Kern SE, Offerhaus GJ, Green PA, et al. Colorectal neoplasia in juvenile polyposis or juvenile polyps. *Arch Dis Child*. 1991;66:971-975.
- Sachatello CR. Polypoid diseases of the gastrointestinal tract. *J Ky Med Assoc*. 1972;70:540-544.
- Horrilleno EG, Eckert C, Ackerman LV. Polyps of the rectum and colon in children. *Cancer*. 1957;10:1210-1220.
- Calva D, Howe JR. Hamartomatous polyposis syndromes. *Surg Clin North Am*. 2008;88:779-817, vii.
- Zbuk KM, Eng C. Hamartomatous polyposis syndromes. *Nat Clin Pract Gastroenterol Hepatol*. 2007;4:492-502.
- Eng C. To be or not to BMP. *Nat Genet*. 2001;28:105-107.
- Eng C, Ji H. Molecular classification of the inherited hamartoma polyposis syndromes: clearing the muddied waters. *Am J Hum Genet*. 1998;62:1020-1022.
- Howe JR, Ringold JC, Summers RW, Mitros FA, Nishimura DY, Stone EM. A gene for familial juvenile polyposis maps to chromosome 18q21.1. *Am J Hum Genet*. 1998;62:1129-1136.
- Howe JR, Roth S, Ringold JC, Summers RW, Järvinen HJ, et al. Mutations in the SMAD4/DPC4 gene in juvenile polyposis. *Science*. 1998;280:1086-1088.
- Howe JR, Sayed MG, Ahmed AF, Ringold J, Larsen-Haidle J, et al. The prevalence of MADH4 and BMPR1A mutations in juvenile polyposis and absence of BMPR2, BMPR1B, and ACVR1 mutations. *J Med Genet*. 2004;41:484-491.
- Merg A, Howe JR. Genetic conditions associated with intestinal juvenile polyps. *Am J Med Genet C Semin Med Genet*. 2004;129C:44-55.
- Heldin CH, Miyazono K, ten Dijke P. TGF-beta signalling from cell membrane to nucleus through SMAD proteins. *Nature*. 1997;390:465-471.
- Massague J. TGFbeta signaling: receptors, transducers, and Mad proteins. *Cell*. 1996;85:947-950.
- Hahn SA, Schutte M, Hoque AT, Moskaluk CA, da Costa LT, et al. DPC4, a candidate tumor suppressor gene at human chromosome 18q21.1. *Science*. 1996;271:350-353.
- Sirard C, de la Pompa JL, Elia A, Irie A, Mirtsos C, et al. The tumor suppressor gene Smad4/Dpc4 is required for gastrulation and later for anterior development of the mouse embryo. *Genes Dev*. 1998;12:107-119.
- Takaku K, Oshima M, Miyoshi H, Matsui M, Seldin MF, Taketo MM. Intestinal tumorigenesis in compound mutant mice of both Dpc4 (Smad4) and Apc genes. *Cell*. 1998;92:645-656.
- Yang X, Li C, Xu X, Deng C. The tumor suppressor SMAD4/DPC4 is essential for epiblast proliferation and mesoderm induction in mice. *Proc Natl Acad Sci U S A*. 1998;95:3667-3672.
- Howe JR, Bair JL, Sayed MG, Anderson ME, Mitros FA, et al. Germline mutations of the gene encoding bone morphogenetic protein receptor 1A in juvenile polyposis. *Nat Genet*. 2001;28:184-187.
- Kim IJ, Park JH, Kang HC, Kim JH, et al. Identification of a novel BMPR1A germline mutation in a Korean juvenile polyposis patient without SMAD4 mutation. *Clin Genet*. 2003;63:126-130.
- Zhou XP, Woodford-Richens K, Lehtonen R, Kurose K, Aldred M, et al. Germline mutations in BMPR1A/ALK3 cause a subset of cases of juvenile polyposis syndrome and of Cowden and Bannayan-Riley-Ruvalcaba syndromes. *Am J Hum Genet*. 2001;69:704-711.
- Mehra A, Wrana JL. TGF-beta and the Smad signal transduction pathway. *Biochem Cell Biol*. 2002;80:605-622.
- Reddi AH. Bone morphogenetic proteins: an unconventional approach to isolation of first mammalian morphogens. *Cytokine Growth Factor Rev*. 1997;8:11-20.
- Mishina Y, Suzuki A, Ueno N, Behringer RR. Bmpr encodes a type I bone morphogenetic protein receptor that is essential for gastrulation during mouse embryogenesis. *Genes Dev*. 1995;9:3027-3037.
- Howe JR, Haidle JL, Lal G, Bair J, Song C, et al. ENG mutations in MADH4/BMPR1A mutation negative patients with juvenile polyposis. *Clin Genet*. 2007;71:91-92.
- Fernandez-Ruiz E, St-Jacques S, Bellon T, Letarte M, Bernabeu C. Assignment of the human endoglin gene (END) to 9q34-->qter. *Cytogenet Cell Genet*. 1993;64:204-207.
- Fonsatti E, Del Vecchio L, Altomonte M, Sigalotti L, Nicotra MR, et al. Endoglin: an accessory component of the TGF-beta-binding receptor-complex with diagnostic, prognostic, and bioimmunotherapeutic potential in human malignancies. *J Cell Physiol*. 2001;188:1-7.
- Dallas NA, Samuel S, Xia L, Fan F, Gray MJ, et al. Endoglin (CD105): a marker of tumor vasculature and potential target for therapy. *Clin Cancer Res*. 2008;14:1931-1937.
- Bourdeau A, Dumont DJ, Letarte M. A murine model of hereditary hemorrhagic telangiectasia. *J Clin Invest*. 1999;104:1343-1351.

51. Howe JR, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. *Ann Surg Oncol*. 1998;5:751-756.
52. Watanabe A, Nagashima H, Motoi M, Ogawa K. Familial juvenile polyposis of the stomach. *Gastroenterology*. 1979;77:148-151.
53. Yoshida T, Haraguchi Y, Tanaka A, Higa A, Daimon Y, et al. A case of generalized juvenile gastrointestinal polyposis associated with gastric carcinoma. *Endoscopy*. 1988;20:33-35.
54. Stemper TJ, Kent TH, Summers RW. Juvenile polyposis and gastrointestinal carcinoma. A study of a kindred. *Ann Intern Med*. 1975;83:639-646.
55. Howe JR, Ringold JC, Hughes JH, Summers RW. Direct genetic testing for Smad4 mutations in patients at risk for juvenile polyposis. *Surgery*. 1999;126:162-170.
56. Dunlop MG. Guidance on gastrointestinal surveillance for hereditary non-polyposis colorectal cancer, familial adenomatous polyposis, juvenile polyposis, and Peutz-Jeghers syndrome. *Gut*. 2002;51(suppl 5):V21-27.
57. Oncel M, Church JM, Remzi FH, Fazio VW. Colonic surgery in patients with juvenile polyposis syndrome: a case series. *Dis Colon Rectum*. 2005;48:49-55; discussion -6.
58. Scott-Conner CE, Hausmann M, Hall TJ, Skelton DS, Anglin BL, Subramony C. Familial juvenile polyposis: patterns of recurrence and implications for surgical management. *J Am Coll Surg*. 1995;181:407-413.
59. Zbuk KM, Eng C. Cancer phenomics: RET and PTEN as illustrative models. *Nat Rev Cancer*. 2007;7:35-45.
60. Arch EM, Goodman BK, Van Wesep RA, Liaw D, Clarke K, et al. Deletion of PTEN in a patient with Bannayan-Riley-Ruvalcaba syndrome suggests allelism with Cowden disease. *Am J Med Genet*. 1997;71:489-493.
61. Celebi JT, Tsou HC, Chen FF, Zhang H, Ping XL, et al. Phenotypic findings of Cowden syndrome and Bannayan-Zonana syndrome in a family associated with a single germline mutation in PTEN. *J Med Genet*. 1999;36:360-364.
62. Marsh DJ, Kum JB, Lunetta KL, Bennett MJ, Gorlin RJ, et al. PTEN mutation spectrum and genotype-phenotype correlations in Bannayan-Riley-Ruvalcaba syndrome suggest a single entity with Cowden syndrome. *Hum Mol Genet*. 1999;8:1461-1472.
63. Nelen MR, van Staveren WC, Peeters EA, Hassel MB, Gorlin RJ, et al. Germline mutations in the PTEN/MMAC1 gene in patients with Cowden disease. *Hum Mol Genet*. 1997;6:1383-1387.
64. Starink TM, van der Veen JB, Arwert F, de Waal LP, de Lange GG, et al. The Cowden syndrome: a clinical and genetic study in 21 patients. *Clin Genet*. 1986;29:222-233.
65. Albrecht S, Haber RM, Goodman JC, Duvic M. Cowden syndrome and Lhermitte-Duclos disease. *Cancer*. 1992;70:869-876.
66. Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. *J Med Genet*. 2000;37:828-830.
67. Marra G, Armelao F, Vecchio FM, Percepe A, Anti M. Cowden's disease with extensive gastrointestinal polyposis. *J Clin Gastroenterol*. 1994;18:42-47.
68. McGarrity TJ, Wagner Baker MJ, Ruggiero FM, Thiboutot DM, Hampel H, et al. GI polyposis and glycogenic acanthosis of the esophagus associated with PTEN mutation positive Cowden syndrome in the absence of cutaneous manifestations. *Am J Gastroenterol*. 2003;98:1429-1434.
69. Gorlin RJ, Cohen MM Jr, Condon LM, Burke BA. Bannayan-Riley-Ruvalcaba syndrome. *Am J Med Genet*. 1992;44:307-314.
70. Ruvalcaba RH, Myhre S, Smith DW. Sotos syndrome with intestinal polyposis and pigmentary changes of the genitalia. *Clin Genet*. 1980;18:413-416.
71. Liaw D, Marsh DJ, Li J, Dahia PL, Wang SI, et al. Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. *Nat Genet*. 1997;16:64-67.
72. Lynch ED, Ostermeyer EA, Lee MK, Arena JE, Ji H, et al. Inherited mutations in PTEN that are associated with breast cancer, cowden disease, and juvenile polyposis. *Am J Hum Genet*. 1997;61:1254-1260.
73. Nelen MR, Padberg GW, Peeters EA, Lin AY, van den Helm B, et al. Localization of the gene for Cowden disease to chromosome 10q22-23. *Nat Genet*. 1996;13:114-116.
74. Marsh DJ, Dahia PL, Zheng Z, Liaw D, Parsons R, et al. Germline mutations in PTEN are present in Bannayan-Zonana syndrome. *Nat Genet*. 1997;16:333-334.
75. Marsh DJ, Coulon V, Lunetta KL, Rocca-Serra P, Dahia PL, et al. Mutation spectrum and genotype-phenotype analyses in Cowden disease and Bannayan-Zonana syndrome, two hamartoma syndromes with germline PTEN mutation. *Hum Mol Genet*. 1998;7:507-515.
76. Sarquis MS, Agrawal S, Shen L, Pilarski R, Zhou XP, Eng C. Distinct expression profiles for PTEN transcript and its splice variants in Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome. *Am J Hum Genet*. 2006;79:23-30.
77. Suzuki A, de la Pompa JL, Stambolic V, Elia AJ, Sasaki T, et al. High cancer susceptibility and embryonic lethality associated with mutation of the PTEN tumor suppressor gene in mice. *Curr Biol*. 1998;8:1169-1178.
78. Waite KA, Eng C. Protean PTEN: form and function. *Am J Hum Genet*. 2002;70:829-844.
79. Chow LM, Baker SJ. PTEN function in normal and neoplastic growth. *Cancer Lett*. 2006;241:184-196.
80. Fackenthal JD, Marsh DJ, Richardson AL, Cummings SA, Eng C, et al. Male breast cancer in Cowden syndrome patients with germline PTEN mutations. *J Med Genet*. 2001;38:159-164.
81. Hanssen AM, Fryns JP. Cowden syndrome. *J Med Genet*. 1995;32:117-119.
82. Carlson GJ, Nivatvongs S, Snover DC. Colorectal polyps in Cowden's disease (multiple hamartoma syndrome). *Am J Surg Pathol*. 1984;8:763-770.
83. Hamby LS, Lee EY, Schwartz RW. Parathyroid adenoma and gastric carcinoma as manifestations of Cowden's disease. *Surgery*. 1995;118:115-117.
84. Kato M, Mizuki A, Hayashi T, Kunihiro T, Nagata H, et al. Cowden's disease diagnosed through mucocutaneous lesions and gastrointestinal polyposis with recurrent hematochezia, unrevealed by initial diagnosis. *Intern Med*. 2000;39:559-563.
85. Longy M, Coulon V, Duboue B, David A, Larrègue M, et al. Mutations of PTEN in patients with Bannayan-Riley-Ruvalcaba phenotype. *J Med Genet*. 1998;35:886-889.
86. Boardman LA. Heritable colorectal cancer syndromes: recognition and preventive management. *Gastroenterol Clin N Amer*. 2002;31:1107-1131.
87. Kutscher AH, Zegarelli EV, Rankow RM, Slaughter TW. Incidence of Peutz-Jeghers syndrome. *Am J Dig Dis*. 1960;5:576-577.
88. Traboulsi EI, Maumenee IH. Periocular pigmentation in the Peutz-Jeghers syndrome. *Am J Ophthalmol*. 1986;102:126-127.
89. Utsunomiya J, Gocho H, Miyayama T, Hamaguchi E, Kashimura A. Peutz-Jeghers syndrome: its natural course and management. *Johns Hopkins Med J*. 1975;136:71-82.
90. Giardiello FM, Trimboth JD. Peutz-Jeghers syndrome and management recommendations. *Clin Gastroenterol Hepatol*. 2006;4:408-415.
91. Kyle J. Peutz-Jeghers syndrome. *Scottish Med J*. 1961;6:361-367.
92. Westerman AM, Wilson JH. Peutz-Jeghers syndrome: risks of a hereditary condition. *Scand J Gastroenterol*. 1999;230:64-70.
93. Brosens LA, van Hattem WA, Jansen M, de Leng WW, Giardiello FM, Offerhaus GJ. Gastrointestinal polyposis syndromes. *Curr Mol Med*. 2007;7:29-46.
94. Tovar JA, Eizaguirre I, Albert A, Jimenez J. Peutz-Jeghers syndrome in children: report of two cases and review of the literature. *J Pediatr Surg*. 1983;18:1-6.
95. Dormandy TL. Gastrointestinal polyposis with mucocutaneous pigmentation (Peutz-Jeghers syndrome). *N Engl J Med*. 1957;256:1186-1190; concl.
96. Foster DR, Foster DB. Gall-bladder polyps in Peutz-Jeghers syndrome. *Postgrad Med J*. 1980;56:373-376.
97. Gentile AT, Bickler SW, Harrison MW, Campbell JR. Common bile duct obstruction related to intestinal polyposis in a child with Peutz-Jeghers syndrome. *J Pediatr Surg*. 1994;29:1584-1587.
98. Parker MC, Knight M. Peutz-Jeghers syndrome causing obstructive jaundice due to polyp in common bile duct. *J R Soc Med*. 1983;76:701-703.
99. Giardiello FM, Welsh SB, Hamilton SR, Offerhaus GJ, Gittelsohn AM, et al. Increased risk of cancer in the Peutz-Jeghers syndrome. *N Engl J Med*. 1987;316:1511-1514.
100. Jass JR. Gastrointestinal polyposes: clinical, pathological and molecular features. *Gastroenterol Clin North Am*. 2007;36:927-946, viii.
101. Shepherd NA, Bussey HJ, Jass JR. Epithelial misplacement in Peutz-Jeghers polyps. A diagnostic pitfall. *Am J Surg Pathol*. 1987;11:743-749.
102. Bartholomew LG, Moore CE, Dahlin DC, Waugh JM. Intestinal polyposis associated with mucocutaneous pigmentation. *Surg Gynecol Obstet*. 1962;115:1-11.
103. Hemminki A, Tomlinson I, Markie D, Järvinen H, Sistonen P, et al. Localization of a susceptibility locus for Peutz-Jeghers syndrome to 19p using comparative genomic hybridization and targeted linkage analysis. *Nat Genet*. 1997;15:87-90.
104. Mehenni H, Blouin JL, Radhakrishna U, Bhardwaj SS, Bhardwaj K, et al. Peutz-Jeghers syndrome: confirmation of linkage to chromosome 19p13.3 and identification of a potential second locus, on 19q13.4. *Am J Hum Genet*. 1997;61:1327-1334.
105. Hemminki A, Markie D, Tomlinson I, Avizienyte E, Roth S, et al. A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. *Nature*. 1998;391:184-187.
106. Jenne DE, Reimann H, Nezu J, Friedel W, Loff S, et al. Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase. *Nat Genet*. 1998;18:38-43.

107. Volikos E, Robinson J, Aittomäki K, Mecklin JP, Järvinen H, et al. LKB1 exonic and whole gene deletions are a common cause of Peutz-Jeghers syndrome. *J Med Genet.* 2006;43:e18.
108. Forcet C, Etienne-Manneville S, Gaude H, Fournier L, Debilly S, et al. Functional analysis of Peutz-Jeghers mutations reveals that the LKB1 C-terminal region exerts a crucial role in regulating both the AMPK pathway and the cell polarity. *Hum Mol Genet.* 2005;14:1283-1292.
109. Forcet C, Billaud M. Dialogue between LKB1 and AMPK: a hot topic at the cellular pole. *Sci STKE.* 2007;2007:pe51.
110. Marignani PA. LKB1, the multitasking tumour suppressor kinase. *J Clin Pathol.* 2005;58:15-19.
111. Miyoshi H, Nakau M, Ishikawa TO, Seldin MF, Oshima M, Taketo MM. Gastrointestinal hamartomatous polyposis in Lkb1 heterozygous knockout mice. *Cancer Res.* 2002;62:2261-2266.
112. Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. *Gastroenterology.* 2000;119:1447-1453.
113. Lim W, Hearle N, Shah B, Murday V, Hodgson SV, et al. Further observations on LKB1/STK11 status and cancer risk in Peutz-Jeghers syndrome. *Br J Cancer.* 2003;89:308-313.
114. Hearle N, Schumacher V, Menko FH, Olschwang S, Boardman LA, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. *Clin Cancer Res.* 2006;12:3209-3215.
115. Cantu JM, Rivera H, Ocampo-Campos R, Bedolla N, Cortés-Gallegos V, et al. Peutz-Jeghers syndrome with feminizing sertoli cell tumor. *Cancer.* 1980;46:223-228.
116. Scully RE. Sex cord tumor with annular tubules a distinctive ovarian tumor of the Peutz-Jeghers syndrome. *Cancer.* 1970;25:1107-1121.
117. Hinds R, Philp C, Hyer W, Fell JM. Complications of childhood Peutz-Jeghers syndrome: implications for pediatric screening. *J Pediatr Gastroenterol Nutr.* 2004;39:219-220.
118. McGrath DR, Spigelman AD. Preventive measures in Peutz-Jeghers syndrome. *Fam Cancer.* 2001;1:121-125.

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