

Hamartomatous polyposis syndromes

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SUMMARY

The hamartomatous polyposis syndromes are a heterogeneous group of disorders that share an autosomal-dominant pattern of inheritance and are characterized by hamartomatous polyps of the gastrointestinal tract. These syndromes include juvenile polyposis syndrome, Peutz–Jeghers syndrome and the *PTEN* hamartoma tumor syndrome. The frequency and location of the polyps vary considerably among syndromes, as does the affected patient's predisposition to the development of gastrointestinal and other malignancies. Although the syndromes are uncommon, it is important for the clinician to recognize these disorders because they are associated with considerable morbidity and mortality, not only from malignancy but also from nonmalignant manifestations such as bleeding, intussusception, and bowel obstruction. Each hamartomatous polyposis syndrome has its own distinctive organ-specific manifestations and each requires a different surveillance strategy, which makes accurate diagnosis crucial for appropriate patient management. The availability of clinical genetic testing for these disorders means that appropriate recognition allows for timely referral for cancer genetic counseling, and often allows for predictive testing in at-risk family members. Promisingly, an understanding of the molecular pathogenesis of these disorders offers insights into the mechanisms underlying the development of sporadic malignancy, and enables rational selection of targeted therapies that warrant further investigation.

KEYWORDS cancer, hamartomatous polyposis syndromes, inherited

REVIEW CRITERIA

This Review is based on a PubMed search performed in January 2007 with the following terms alone or in combination: "hamartomatous polyps", "hamartomas", "juvenile polyposis syndrome", "juvenile polyps", "Peutz–Jeghers syndrome", "Cowden syndrome", "Bannayan–Riley–Ruvalcaba syndrome", "BRRS", "*PTEN* hamartoma tumor syndrome", "small bowel polyps", "*PTEN*", "*BMPRIA*", "*LKB1*", "*SMAD4*", "germline", "mTOR inhibitors", "rapamcyin". Full-length, original research and review articles published in English were used.

CME

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Identify the different autosomal dominant types of hamartomatous polyposis syndromes.
- 2 Describe the risk for cancer associated with juvenile polyposis syndrome.
- 3 List clinical features of and cancer risks associated with Peutz–Jeghers syndrome.
- 4 List the types of cancers that Cowden's syndrome predisposes to.
- 5 Describe surveillance strategies recommended for the hamartomatous polyposis syndrome *PTEN* hamartoma tumor syndrome.

INTRODUCTION

The hereditary gastrointestinal polyposis syndromes can be broadly divided into those in which the polyps are predominantly adenomatous and those in which the polyps are predominantly hamartomatous. Hamartomatous polyps are composed of the normal cellular elements of the gastrointestinal tract, but have a markedly distorted architecture. The hamartomatous polyposis syndromes are a heterogeneous group of disorders that are inherited in an autosomal-dominant manner. The syndromes include juvenile polyposis syndrome (JPS), Peutz–Jeghers syndrome (PJS), and *PTEN* hamartoma tumor syndrome (PHTS). PHTS includes Cowden syndrome, Bannayan–Riley–Ruvalcaba syndrome (BRRS), and all syndromes in which there are germline *PTEN* mutations.

The hamartomatous polyposis syndromes are uncommon—together, they account for fewer

than 1% of colon cancer cases in North America.¹ Nonetheless, it is important that these syndromes are recognized and managed appropriately for several reasons. First, most of these syndromes are associated with a markedly increased risk for the development of colon cancer. Second, they are associated with the development of extra-colonic manifestations, both malignant and nonmalignant, which often result in considerable morbidity and mortality. Insights into the molecular pathogenesis of malignancy in these rare disorders have advanced our knowledge of the pathogenesis of their sporadic counterparts. This advancement is illustrated by the evolution of the concept of the hamartoma to carcinoma sequence,² which is an alternative sequence to the adenoma to carcinoma paradigm of colorectal cancer pathogenesis.

Although the field of hamartomatous polyposis is broad, in this Review we discuss the diagnosis and clinical features of the different hamartomatous polyposis syndromes, the risk of malignancy associated with each syndrome, appropriate surveillance recommendations, and what is known about the genetics of these syndromes. Other disorders that are associated with the presence of hamartomatous polyps are briefly discussed, and the Review additionally summarizes the potential for targeted therapy of hamartomatous polyposis syndromes and the malignant potential of hamartomatous polyps.

PEUTZ-JEGHERS SYNDROME

Diagnosis and clinical features

PJS, which has an incidence of 1 in 150,000 in North America and Western Europe,³ is characterized by the presence of hamartomatous polyps in the gastrointestinal tract, and is associated with a distinctive mucocutaneous pigmentation. Polyps occur most commonly in the small intestine (64%), although involvement of the colon (53%), stomach (49%), and rectum (32%) is also seen.⁴ Polyps have also been found in the upper and lower respiratory tract and bladder.⁵ There are usually fewer than 20 polyps present in each case, and the polyps vary in size from several millimeters to more than 5 cm in diameter.⁶ Patients usually present with PJS in the second or third decade of life, and the presenting symptoms include abdominal pain, rectal bleeding, anemia, small intestinal intussusception, bowel obstruction, and rectal prolapse of polyps.⁵

The characteristic pigmentation, which is usually dark blue to dark brown in color, is present in 95% of patients with PJS and is most commonly

seen on the vermillion border of the lips, the buccal mucosa, and the hands and feet.⁴ Perinasal, perianal, genital, and periorbital pigmentation can also be observed, but this pigmentation often fades after puberty. In contrast to the lentiginos seen in individuals with PJS, common freckles spare the buccal mucosa, and are usually rare around the lips and nose.

The diagnostic criteria for PJS include the presence of characteristic mucocutaneous pigmentation, the presence of small-bowel hamartomatous polyps and a family history of PJS. Patients need to fulfill two of these three criteria for a clinical diagnosis of PJS to be made.⁷

On endoscopy, the polyps seen in patients with PJS have no defining features, although they can develop long stalks that predispose the intestine to intussusception.⁵ Microscopically, extensive smooth-muscle proliferation, with an elongated, arborized pattern of polyp formation, can be seen (Figure 1).⁸ This characteristic microscopic appearance of PJS polyps enables experienced gastrointestinal pathologists to confirm the clinical diagnosis.

Cancer risk

PJS is associated with a markedly increased risk of malignancy that is not confined to the gastrointestinal tract. A meta-analysis found that, compared with the general population, patients with PJS have a relative risk (RR) of greater than 15 for developing any type of cancer.⁹ According to this meta-analysis, the cumulative risk of developing any type of cancer was 93% by the time a PJS patient was 65 years old. Very high RRs for the development of cancer were observed for the small intestine (520), stomach (213), pancreas (132), colon (84), and esophagus (57), with RRs of greater than 10 for the development of breast, lung and ovarian cancer.

A follow-up study restricted to patients with PJS who had a germline mutation in the tumor suppressor gene *STK11* (also known as *LKB1*) confirmed that these patients have a very high risk of developing cancer.¹⁰ The cumulative risk of developing any type of cancer was 81% by the time these patients were 70 years of age, the cumulative risk of developing any gastrointestinal cancer (including small intestine, colorectal, esophageal and pancreatic cancer) was 66% by the time they were 70 years of age, and for female patients the cumulative risk of developing breast cancer was 32% by the time they were 60 years of age.¹⁰

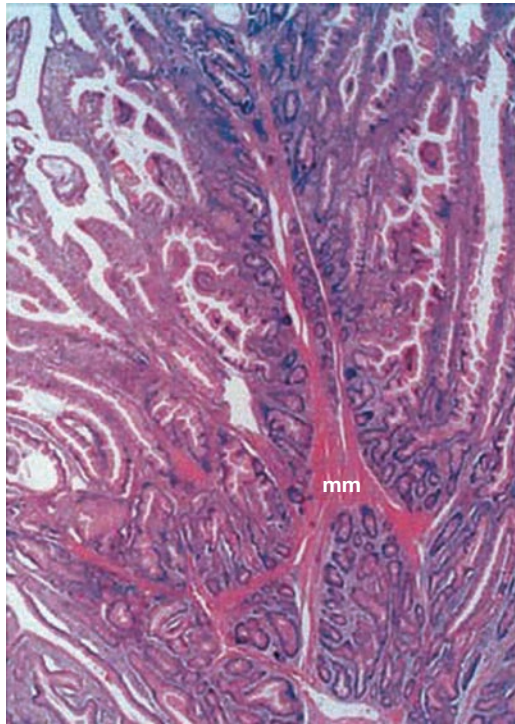


Figure 1 A typical Peutz–Jeghers syndrome polyp demonstrating the arborizing pattern of smooth-muscle proliferation. Abbreviation: mm, muscularis mucosa. Permission obtained from Macmillan Publishers Ltd © Bronner (2003)⁷⁹ *Modern Pathology* **16**: 359–365.

PJS also predisposes females to development of cervical adenoma malignum, a rare and very aggressive adenocarcinoma of the cervix.¹¹ In addition, females with PJS commonly develop benign ovarian sex-cord tumors with annular tubules, whereas males with PJS are predisposed to development of Sertoli-cell testicular tumors,¹² although neither of these two tumor types is malignant, they can cause symptoms related to increased estrogen production.

Surveillance recommendations

Surveillance recommendations for the hamartomatous polyposis syndromes are based on expert opinion, but no randomized trials have evaluated the efficacy of surveillance for the management of these disorders. The surveillance recommendations for patients with PJS are complex, and focus on the increased risk of gastrointestinal, gynecologic, breast, and testicular neoplasms. A strategy proposed in 2006 by Giardiello and Trimbath is illustrated in Figure 2.⁸

Surveillance and management of polyposis of the small intestine has been markedly improved

by advances in capsule and double-balloon endoscopy. Although the precise role of these techniques in the management of patients with PJS has not yet been established, they will undoubtedly prove useful in the nonsurgical treatment of patients with polyps of the small intestine,¹³ and might replace surveillance performed by small-bowel barium follow-through.

Genetics

Germline mutations of *STK11* are documented in up to 70–80% of patients with PJS; up to 15% of cases have germline deletions of all or part of *STK11*.¹⁴ Although the classic clinical and histopathologic features of PJS might sometimes obviate the need for genetic testing, analysis of germline *STK11* mutations can be helpful when the clinical features are subtle or when the histological diagnosis is in question.¹⁵ *STK11* encodes a serine–threonine kinase that modulates cellular proliferation, controls cell polarity, and seems to have an important role in responding to low cellular energy levels.¹⁶ In the performance of this last role, the STK11 protein is involved in the inhibition of AMP-activated protein kinase (AMPK), and signals downstream to inhibit the mTOR (mammalian target of rapamycin; also known as FRAP; FKBP12-rapamycin complex-associated protein) pathway;¹⁷ the mTOR pathway is dysregulated in patients with PJS and in patients with PHTS (Figure 3). Genotype–phenotype correlation suggests that patients with PJS who have mutations in *STK11* that result in truncation of the encoded STK11 protein have a significantly earlier age of onset than those who have a missense mutation or no detectable mutation of *STK11*.¹⁸ Interestingly, heterozygous *Stk11* knockout mice develop hamartomatous polyps in the stomach and small intestine, but the predominant malignancy they develop is hepatocellular carcinoma, which is not a malignancy characteristic of human PJS.¹⁹

PTEN HAMARTOMA TUMOR SYNDROME

Diagnosis and clinical features

The term PHTS was developed to unify the heterogeneous group of disorders that are all caused by germline mutations of the tumor suppressor gene *PTEN*.²⁰ PHTS encompasses the disorders Cowden syndrome, BRRS, and Proteus syndrome. Several other disorders have also been associated with germline *PTEN* mutations, but a detailed discussion of this group of disorders is beyond the scope of this Review, and the prevalence of polyposis in many of these disorders is unknown.

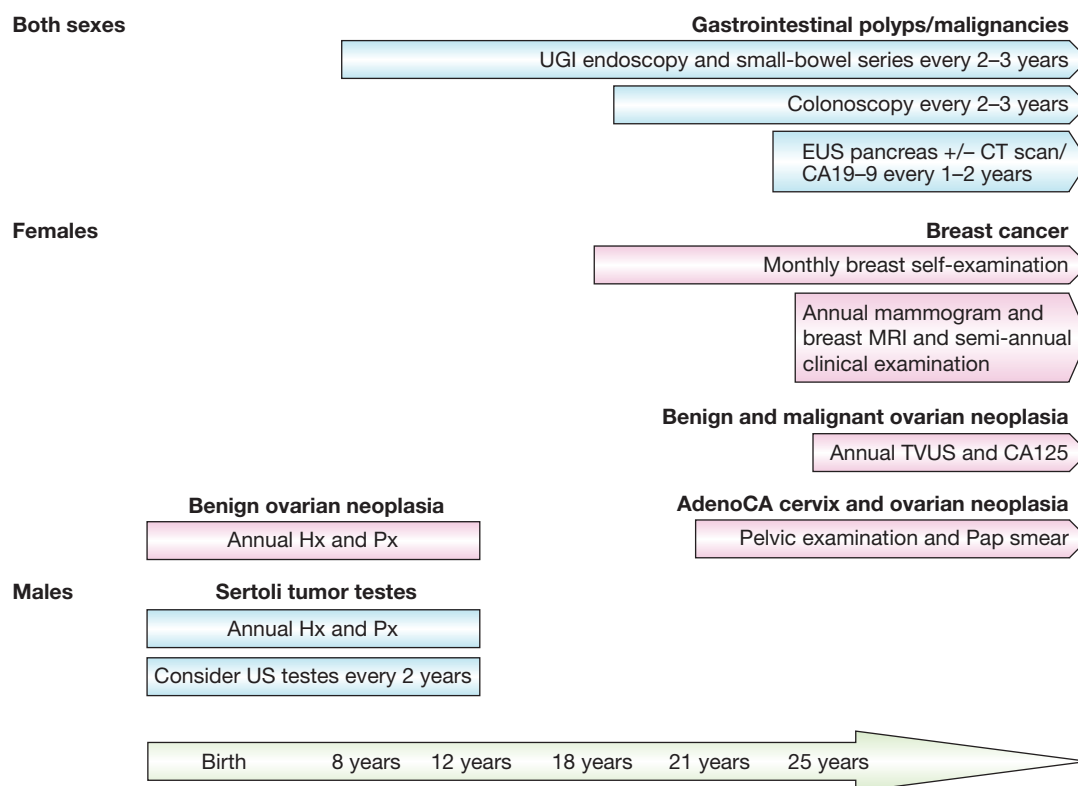


Figure 2 The suggested age-range-specific surveillance recommendations for patients with Peutz–Jeghers syndrome. Abbreviations: EUS, endoscopic ultrasound; Hx, history; Pap smear, Papanicolaou smear; Px, physical examination; TVUS, transvaginal ultrasound; UGI, upper gastrointestinal; US, ultrasound. Adapted from data presented in Reference 8.

Cowden syndrome is an uncommon, under-recognized disorder with an estimated incidence of 1 per 200,000 of the population, at least in Europe and North America;²¹ the syndrome confers an increased risk of breast, thyroid, and endometrial cancer. Other features of the disorder include the following: macrocephaly; gastrointestinal polyps; benign breast, thyroid, and endometrial manifestations; and characteristic mucocutaneous lesions (Table 1). Many of the benign manifestations are hamartomatous in nature, and Cowden syndrome has previously been referred to as the multiple hamartoma syndrome. Operational diagnostic criteria for Cowden syndrome are updated annually by the National Comprehensive Cancer Network.²²

BRRS is characterized by the presence of multiple lipomas, gastrointestinal hamartomatous polyps, macrocephaly, hemangiomas, developmental delay and, in males, pigmented macules on the glans penis.²³ Formal diagnostic criteria have not been established.

Proteus syndrome is a complex multisystem disorder that is characterized by congenital

malformations, hemihypertrophy, hamartomatous overgrowths, epidermal nevi and hyperostosis.²⁴

Historically, it was felt that gastrointestinal polyps were more commonly seen in patients with BRRS than in patients with Cowden syndrome, as these polyps are present in approximately 50% of patients with BRRS.²³ It is possible, however, that asymptomatic polyps are at least as common in patients with Cowden syndrome. Series have suggested that diminutive colonic polyps, mostly present distal to the hepatic flexure, occur in 60–90% of patients with Cowden syndrome.^{25–27} One small study of patients with this syndrome, which has been presented in abstract form only, reported that such polyps have a markedly varied histology, with adenomatous, juvenile, hyperplastic, lipomatous, and ganglioneuromatous polyps all being described.²⁶ Whether such varied polyp pathology is common in patients with Cowden syndrome is, however, questioned by some in the field.

Another manifestation of Cowden syndrome is glycogenic acanthosis. This manifestation is

