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CLINICAL PRACTICE GUIDELINES

Diagnosis and Management of Cancer Risk in the Gastrointestinal Hamartomatous Polyposis Syndromes: Recommendations From the US Multi-Society Task Force on Colorectal Cancer

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The gastrointestinal hamartomatous polyposis syndromes are rare, autosomal dominant disorders associated with an increased risk of benign and malignant intestinal and extraintestinal tumors. They include Peutz-Jeghers syndrome, juvenile polyposis syndrome, the *PTEN* hamartoma tumor syndrome (including Cowden's syndrome and Bannayan-Riley-Ruvalcaba syndrome), and hereditary mixed polyposis syndrome. Diagnoses are based on clinical criteria and, in some cases, confirmed by demonstrating the presence of a germline pathogenic variant. The best understood hamartomatous polyposis syndrome is Peutz-Jeghers syndrome, caused by germline pathogenic variants in the *STK11* gene. The management is focused on prevention of bleeding and mechanical obstruction of the small bowel by polyps and surveillance of organs at increased risk for cancer. Juvenile polyposis syndrome is caused by a germline pathogenic variant in either the *SMAD4* or *BMPR1A* genes, with differing clinical courses. Patients with *SMAD4* pathogenic variants may have massive gastric polyposis, which can result in gastrointestinal bleeding and/or protein-losing gastropathy. Patients with *SMAD4* mutations usually have the simultaneous occurrence of hereditary hemorrhagic telangiectasia (juvenile polyposis syndrome–hereditary hemorrhagic telangiectasia overlap syndrome) that can result in epistaxis, gastrointestinal bleeding from mucocutaneous telangiectasias, and arteriovenous malformations. Germline pathogenic variants in the *PTEN* gene cause overlapping clinical phenotypes (known as the *PTEN* hamartoma tumor syndromes), including Cowden's syndrome and related disorders that are associated with an increased risk of gastrointestinal and colonic polyposis, colon cancer, and other extraintestinal manifestations and cancers. Due to the relative rarity of the hamartomatous polyposis syndromes, recommendations for management are based on few studies. This U.S Multi-Society Task Force on Colorectal Cancer consensus statement summarizes the clinical features, assesses the

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Abbreviations used in this paper: AVM, arteriovenous malformation; BMP, bone morphogenetic protein; BRRS, Bannayan-Riley-Ruvalcaba syndrome; CI, confidence interval; CL, confidence limits; CR, cumulative risk; CRC, colorectal cancer; CS, Cowden's syndrome; EGD, esophagogastroduodenoscopy; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HHT, hereditary hemorrhagic telangiectasia; HMPS, hereditary mixed polyposis syndrome; JPS, juvenile polyposis syndrome; MRE, magnetic resonance enterography; MRI, magnetic resonance imaging; PHTS, *PTEN* hamartoma tumor syndrome; PJS, Peutz-Jeghers syndrome; RR, relative risk; SIR, standardized incidence ratio; USMSTF, US Multi-Society Task Force on Colorectal Cancer; VCE, video capsule endoscopy.

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current literature, and provides guidance for diagnosis, assessment, and management of patients with the hamartomatous polyposis syndromes, with a focus on endoscopic management.

The gastrointestinal hamartomatous polyposis syndromes are rare, autosomal dominant disorders associated with an increased risk of benign and malignant intestinal and extraintestinal tumors. Nevertheless, there has been tremendous progress in recent years, both in understanding the underlying genetics that underpin these disorders and in elucidating the biology of associated premalignant and malignant conditions. Emerging data in affected populations focus increasingly on those with defined cancer susceptibility germline pathogenic variants leading to less heterogeneity in terms of quantifying cancer risk.

The US Multi-Society Task Force on Colorectal Cancer (USMSTF) is a group of colorectal cancer (CRC) content experts appointed by the American College of Gastroenterology, American Gastroenterological Association, and American Society for Gastrointestinal Endoscopy, supplemented at times by other experts to complement existing expertise. In this USMSTF Consensus Statement, the gastrointestinal hamartomatous polyposis syndromes were chosen because of recent progress in understanding these diseases. The following entities reviewed are: Peutz-Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), *PTEN* hamartoma tumor syndrome (PHTS, including Cowden's syndrome [CS] and Bannayan-Riley-Ruvalcaba syndrome [BRRS]), and hereditary mixed polyposis syndrome (HMPS). Germline alterations are known to cause each of these disorders, but the diagnosis can also be made on the basis of clinical criteria.

Although there are essentially no long-term prospective controlled studies of comparative effectiveness of management strategies for these syndromes, there have been consensus statements by expert panels that made management recommendations for these disorders. The goal of this USMSTF Statement was to review the literature focusing on the most recent data, synthesize both the data and the suggested approaches to diagnosis and management by other expert groups, and present the consensus recommendations of the USMSTF (Table 1). Review of summary tables, conference calls, and revisions of iterative drafts, including recommendation statements, were used to reach consensus, at which time documents were forwarded to Governing Boards for approval. As our USMSTF is a group of individuals with expertise in gastroenterology and gastrointestinal malignancies, we have reserved our management recommendations to these areas and defer to other expert groups' recommendations for other cancers (which are reviewed here). This document therefore recommends clinical approaches to diagnosing and managing these conditions that affect children and adults, focuses on cancer risk, and provides insights into future research opportunities.

Methods

A computer-aided PubMed search was performed from 2000 to 2018, with additional back searches as required, and consisted of the following search terms: *hamartoma*, *hamartomatous polyp*, *hamartoma syndrome*, *Peutz-Jeghers syndrome*, *juvenile polyp*, *juvenile polyposis*, *Cowden's syndrome*, *Cowden's disease*, *PTEN-hamartoma*, *Bannayan-Riley-Ruvalcaba syndrome*, *hyperplastic polyposis*, *serrated polyposis*, and *hereditary mixed polyposis syndrome*. Only English-language articles were reviewed. Published articles were selected on the basis of relevance to the diagnosis or clinical management of these diseases. Emphasis was placed on the risk for gastrointestinal cancer in these disorders to gain consensus on rational and reasonable strategies for management once these diseases are diagnosed in a family. The document was approved by the governing boards of each of the sponsoring gastroenterology societies.

The USMSTF approach to an adapted use of Grading of Recommendations Assessment, Development and Evaluation (GRADE) has been described previously.[1] In brief, the GRADE process categorizes the quality of the evidence as high, moderate, low, or very low on the basis of the strength of underlying studies, and that categorization can be adjusted on the basis of study limitations. For example, randomized trials begin as high-quality evidence and observational studies as low-quality evidence, but their quality may be adjusted up or down on the basis of specific study factors. Although the GRADE process entails a formal meta-analysis to assess the quality of evidence for each recommendation, the USMSTF employs a modified, qualitative approach for this assessment. The GRADE process separates evaluation of the quality of the evidence to support a recommendation from the strength of that recommendation. This is done in recognition of the fact that, although the quality of the evidence can influence the strength of the recommendation, other factors can influence a recommendation, such as adverse effects, patient preferences, values, and cost. Generally, strong recommendations mean that most informed patients would choose the recommended management. Weak recommendations mean that patients' choices will vary according to their values and preferences, and clinicians should ensure that patient care is in keeping with their values and preferences. When the quality of the evidence to support a recommendation is low or very low, or if there is a close balance between desirable and undesirable consequences, then usually only a weak recommendation would be warranted. Weaker recommendations are indicated by phrases such as "we suggest," and stronger recommendations are typically stated as "we recommend."

However, the relative infrequency of, and absence of controlled prospective trials of the interventions (eg, to prevent cancer) in, these syndromes leave all of the recommendations without a robust basis of underlying evidence. Thus, all of the interventional recommendations fall (at best) into the "low quality of evidence" GRADE category, indicating that the true effect of the interventions may be markedly different than estimated at this time, and that further research is likely to impact or change our confidence in the effects. As such, this review is intended to establish a starting point for future research into the care of patients with the hamartomatous polyposis syndromes.

Table 1. Questions and Recommendations of Best Practice

Which individuals with hamartomatous polyps should be referred for genetic evaluation?

We recommend patients with any of the following undergo a genetic evaluation: 2 or more lifetime hamartomatous polyps, a family history of hamartomatous polyps, or a cancer associated with a hamartomatous polyposis syndrome in first or second-degree relatives. Genetic testing (if indicated) should be performed using a multigene panel test. *(Strong recommendation, low quality of evidence)*

Peutz-Jeghers syndrome

Who should undergo a genetic evaluation for Peutz-Jeghers syndrome?

We recommend genetic evaluation for any individual with the following: 1) 2 or more histologically confirmed Peutz-Jeghers polyps, 2) any number of Peutz-Jeghers polyps in an individual who has a family history of Peutz-Jeghers syndrome in a first-degree relative, 3) characteristic mucocutaneous pigmentation in a person with a family history of Peutz-Jeghers syndrome, 4) any number of Peutz-Jeghers polyps in a person with the characteristic mucocutaneous pigmentation of Peutz-Jeghers syndrome. *(Strong recommendation, low quality of evidence)*

Which organs should undergo surveillance when caring for a patient with Peutz-Jeghers syndrome?

Patients with Peutz-Jeghers syndrome are at increased risk for cancer in multiple organs including cancer of the breast, small bowel, colon, stomach, pancreas, ovaries, testes, and lungs.

Given this risk, we recommend a multidisciplinary approach to cancer surveillance in these organs *(Strong recommendation, low quality of evidence)*

How and when should small bowel surveillance be performed in Peutz-Jeghers syndrome?

We recommend that baseline small bowel surveillance using video capsule endoscopy or magnetic resonance enterography be performed between ages 8-10 years or earlier if the patient is symptomatic. If no polyps are found at the initial examination, surveillance should resume at age 18. Because of the risk of small bowel intussusception, small bowel surveillance in adulthood is recommended to continue throughout life every 2-3 years. *(Strong recommendation, low quality of evidence)*

What is the recommended approach to endoscopic surveillance of the colon, stomach, and duodenum in Peutz-Jeghers syndrome?

We suggest a baseline upper gastrointestinal endoscopy between the ages of 8 and 10 years, which could be performed at the time of capsule placement for small bowel surveillance or if polyps are identified on magnetic resonance enterography. Although the initiation age for colonoscopy remains uncertain, we also suggest initiation of colonoscopy at same time as esophagogastroduodenoscopy. In those in whom characteristic polyps are detected, both colonoscopy and esophagogastroduodenoscopy should be repeated every 2–3 years. In those in whom there are no Peutz-Jeghers polyps at baseline, surveillance is repeated at age 18 years, or sooner should symptoms arise, and then every 3 years. *(Weak recommendation, very low quality of evidence)*

What size polyps found on small bowel imaging in Peutz-Jeghers syndrome should be removed?

We recommend polypectomy of small bowel polyps that are symptomatic or $\geq$10 mm to prevent intussusception and other complications, such as bleeding.*(Strong recommendation, low quality of evidence)*

What is the recommended pancreatic cancer surveillance in Peutz-Jeghers syndrome?

We suggest annual pancreatic cancer surveillance with either magnetic resonance cholangiopancreatography or endoscopic ultrasound starting at age 35 years. *(Weak recommendation, low quality of evidence)*

Juvenile Polyposis Syndrome

Who should undergo a genetic evaluation for juvenile polyposis syndrome?

We recommend genetic evaluation for any individual with 1) 5 or more juvenile polyps of the colon or rectum; or 2) 2 or more juvenile polyps in other parts of the gastrointestinal tract; or (3) any number of juvenile polyps and 1 or more first-degree relatives with juvenile polyposis syndrome. *(Strong recommendation, low quality of evidence)*

Which organs should undergo surveillance when caring for a patient with juvenile polyposis syndrome?

Juvenile polyposis syndrome patients are at increased risk for cancer in multiple organs including cancer of the colon and stomach.

Given this risk, we recommend patients with juvenile polyposis syndrome undergo surveillance of the colon and stomach. *(Strong recommendation, low quality of evidence)*

At what age should colonoscopic and upper endoscopic surveillance begin in individuals identified with juvenile polyposis syndrome?

We suggest initiating colonoscopic and upper endoscopic surveillance at age 12–15 years, or earlier if symptomatic. Surveillance should be repeated every 1–3 years depending on polyp burden. *(Weak recommendation, low quality of evidence)*

Which patients with juvenile polyposis syndrome should undergo screening for hereditary hemorrhagic telangiectasia?

We suggest patients with SMAD4 pathogenic variants be clinically evaluated for HHT at the time of the diagnosis, including screening for and appropriate management of cerebral and pulmonary AVMs. *(Weak recommendation, low quality of evidence)*

PTEN hamartoma tumor syndrome

Which gastrointestinal findings should prompt a genetic evaluation for *PTEN* hamartoma tumor syndrome?

We recommend individuals with multiple gastrointestinal hamartomas or ganglioneuromas undergo genetic evaluation for Cowden's syndrome and related conditions. *(Strong recommendation, low quality of evidence)*

Which organs should undergo surveillance for cancer when caring for a patient with *PTEN* hamartoma tumor syndrome?

In PTEN hamartoma tumor syndrome, patients are at increased risk for cancer in multiple organs, including cancer of the breast, thyroid, kidney, uterus, colon, and skin.

Given this risk, we recommend a multi-disciplinary approach to cancer surveillance in these organs. *(Strong recommendation, low quality of evidence)*

What is the recommended colonoscopic surveillance in individuals identified with *PTEN* hamartoma tumor syndrome?

We suggest colonoscopy surveillance to begin at age 35 years (or 10 years younger than age of any relative with colorectal cancer), repeated at intervals no greater than 5 years, depending on polyp burden. *(Weak recommendation, low quality of evidence)*

NOTE. Specific circumstances may merit modification of the recommendations. In cases where very-early-onset cancers develop, the above statements may be modified to start surveillance 10 years earlier than the youngest cancer diagnosis in the family.

Cancer Family History Assessment and Referral for Genetic Testing in Gastroenterology Practice

Question: Which individuals with hamartomatous polyps should be referred for genetic evaluation?
Recommendation: We recommend patients with any of the following undergo a genetic evaluation: 2 or more lifetime hamartomatous polyps, a family history of hamartomatous polyps, or a cancer associated with a hamartomatous polyposis syndrome in first- or second-degree relatives. Genetic testing (if indicated) should be performed using a multigene panel test. *(Strong recommendation, low quality of evidence)*

Hereditary cancer syndromes account for approximately 5%–10% of new cancer diagnoses and many of the cancers that arise in families with undiagnosed hereditary cancer syndromes are preventable. The identification of individuals with a hereditary gastrointestinal cancer syndrome requires a thorough evaluation of the patient's personal and family history of cancer. The collection and assessment of family cancer history is a valuable tool for cancer interception and prevention and can be critical in the identification of genetic susceptibility. An accurate family history is one that collects the following information: 1) type of cancer, 2) age at diagnosis of each primary cancer, 3) lineage (maternal or paternal), 4) ethnicity (people of some ethnicities, such as those with Ashkenazi Jewish ancestry, are at greater risk for certain cancers), and 5) results of any previous cancer-related genetic testing.[2]

Features of a patient's personal history and clinical characteristics may suggest an inherited susceptibility to cancer. Although it is not rare to identify individuals with an isolated hamartomatous polyp (particularly an isolated juvenile polyp), other features may prompt further evaluation for an underlying hereditary syndrome. Features associated with the hamartomatous polyposis syndromes are outlined in detail in this document and include early age at cancer onset, multiple cancers in close relatives, unusual numbers of hamartomatous polyps, or associated dermatologic findings. Genetic evaluation may include genetic counseling and/or genetic testing.

Genetic counseling is a key component to hereditary cancer risk assessment. The purpose of genetic counseling is to educate individuals about the genetic and biologic factors that are related to a patient's cancer diagnosis or risk of disease. Counseling helps an individual understand the relevant genetic, medical, and psychosocial information to make informed decisions about their health care. This includes reviewing and expanding the following: family history information, elements of genetic testing, tailored cancer risks associated with a pathogenic variant, impact on medical management, reproductive issues and options, confidentiality of results, risks with genetic discrimination, potential significance of test results for other family members, and other pertinent topics. Practice guidelines from the American College of Medical Genetics and Genomics and National Society of Genetic Counselors are available for details regarding the elements and process of genetic counseling.[3] Although traditional models of genetic evaluation and testing included a certified genetic counselor, alternative models exist and are emerging that include provisions for pretest counseling to be provided by physicians and other health care providers in order to deal with the increasing demand for genetic testing. If a patient is found to be a carrier of a germline pathogenic variant, or the results are ambiguous due to the finding of a variant of uncertain significance, the help of a genetics provider for post-test counseling and education is recommended. In the current era, the vast majority of genetic testing for inherited cancer risk predisposition is performed using a multigene panel testing approach.[4] Some patients or families may elect to decline genetic testing due to concerns about risk to confidentiality and insurance; in these cases, surveillance may still be indicated in the presence of a concerning clinical and/or family history.

If a germline pathogenic variant is identified, other family members should be offered testing for clarification of their own risk. This testing may facilitate initiation of screening for associated cancers before symptomatic manifestations occur and reduce the morbidity and mortality associated with the syndrome. For example, early small bowel surveillance may find a polyp that could be removed from a child with a pathogenic variant in *STK11* before leading to intussusception. It is important to recognize that genetic testing may not identify pathogenic variants in every family suspected of a hereditary syndrome. However, there may be clinical features in the family history that suggest a familial predisposition to cancer and suggest more intensive surveillance recommendations. Referral to Centers of Excellence might be particularly helpful when genetic testing results are ambiguous in the setting of suspicious features and prophylactic surgery is being considered. Lastly, in the era of multigene panel testing, there may be a scenario in which a germline variant is found incidentally associated with an unsuspected syndrome. In these cases, patients may be eligible for cancer screening and surveillance as outlined. However, phenotype and cancer risk compared with patients with classic familial features are not established and are areas of active research. Enlisting the assistance of a genetic specialist may be particularly helpful in interpreting ambiguous results and providing management recommendations in these cases.

When children are identified with a hamartomatous polyposis syndrome, their transition of care to adulthood for cancer surveillance is a unique aspect that bears consideration. It is imperative to transition adolescents with life-long medical conditions from child-centered to adult-centered care. Preparation for this transition takes place throughout childhood and adolescence to achieve independent health management in adulthood. Steps required are individualized based on the developmental needs of the patient. Inherited conditions involve generational factors, as multiple family members may be affected. Health care providers can assist

in the transition of care by coordinating screening and surveillance to ensure patients receive recommended care.[5]

Gastrointestinal Hamartomatous Polyposis Syndromes

The hamartomatous polyposis syndromes are rare entities with an estimated prevalence of 1/100,000–200,000,[6,7] but this has not been measured directly in any population. The term *hamartoma* implies a non-neoplastic tumor with a markedly distorted architecture composed of an abnormal mixture of cells and tissue normally present in that particular area. The diagnosis is based on the presence of a pathogenic germline variant or meeting clinical criteria for the syndrome. The hamartomatous polyposis syndromes are distinct from Lynch syndrome and the adenomatous polyposis syndromes, based on the presence of hamartomas (Figures 1 and 2). Certain hamartomatous polyps of the gut have a unique histopathological appearance, such as those associated with PJS, PHTS, JPS, and HMPS.[8] Hamartomas are not typically characterized by dysplasia, but some evidence suggests the existence of a hamartoma–carcinoma pathway in some of these polyps.

Peutz-Jeghers Syndrome

Question: Who should undergo a genetic evaluation for Peutz-Jeghers syndrome?
Recommendation: We recommend genetic evaluation for any individual with the following: 1) 2 or more histologically confirmed Peutz-Jeghers polyps, 2) any number of Peutz-Jeghers polyps in an individual who has a family history of Peutz-Jeghers syndrome in a first-degree relative, 3) characteristic mucocutaneous pigmentation in a person with a family history of Peutz-Jeghers syndrome, and 4) any number of Peutz-Jeghers polyps in a person with the characteristic mucocutaneous pigmentation of Peutz-Jeghers syndrome. *(Strong recommendation, low quality of evidence)*

Clinical Features

PJS was the first hamartomatous polyposis syndrome described, by Peutz in Holland in 1921 and by Jeghers, McKusick, and Katz in the United States in 1949.[9] The clinical recognition of PJS was facilitated by the characteristic mucocutaneous freckling around the mouth and multiple cerebriform-appearing polyps due to smooth muscle bands coursing through the polyp (Figures 1*A* and 2*A–C*, and Table 2). Hamartomatous polyps vary in size and may have a characteristic histologic structure, which makes it possible to distinguish the PJ polyp. PJ polyps are typically composed of branching bands of smooth muscle covered by hyperplastic glandular mucosa.[10] PJS polyps may develop in the stomach, small intestine, and colon. Rectal bleeding with anemia is the most common presentation, followed by abdominal pain, diarrhea, and intussusception. The clinical management in early life is initially focused on preventing complications of small bowel polyposis–related obstruction and bleeding and, in adulthood, the focus is primarily on management of cancer risk.

Diagnosis

The diagnostic clinical features of PJS include the presence of 2 or more histologically confirmed PJ polyps; any number of PJ polyps in an individual who has a family history of PJS in a first-degree relative; characteristic mucocutaneous pigmentation in a person with a family history of PJS; or any number of PJ polyps in a person with the characteristic mucocutaneous pigmentation of PJS.[11]

Genetics

In 1997, a genetic locus for PJS was mapped to chromosome 19p13.3,[12] which in 1998 led to the cloning of the *STK11* (serine/threonine kinase) gene, which encodes the LKB1 (liver kinase B1) protein, and linkage to PJS.[13] *STK11* functions like a tumor suppressor gene, regulates cell growth via adenosine monophosphate–activated protein kinase,[14] and negatively regulates mTOR signaling.[15]

PJS is inherited in an autosomal dominant fashion with an inactivating germline pathogenic variant inherited from the affected parent. It was initially assumed that the polyps occurred after the loss of the second, wild-type, allele inherited from the unaffected parent in a somatic tissue according to the classic "two-hit" model of Knudson.[16] However, loss of the wild-type allele (ie, the second hit) is not an obligatory feature of PJ polyps.[17] Moreover, recent data in mice indicate that the presence of a single inactivating germline pathogenic variant (ie, haploinsufficiency), as occurs in individuals with PJS, promotes the development of gastrointestinal polyposis, and that loss of the wild-type allele is not necessary for the formation of the polyps in these mice. Furthermore, conditional knockout of the *STK11* gene targeted to gastrointestinal smooth muscle cells yields the same polyposis phenotype in mice.[18] Evidence suggests that LKB1 deficiency in either T cells[19] or mesenchymal cells[18,19] leads to immune cell proliferation in the stroma. Stromal deficiency of LKB1 leads to tumor formation (in mice) via the interleukin-11–JAK/STAT3 (Janus kinase/signal transducer and activator of transcription 3) pathway, and administration of the JAK1/2 inhibitor ruxolitinib dramatically reduces polyposis in mice.[20] The phenomenon of stromal-driven epithelial polyp development may be referred to as a "landscaper" genetic effect.[21] These discoveries raise the possibility of the development of novel preventive pharmacological interventions for patients.

Genotype–phenotype relationships reveal that missense alterations in *STK11* are associated with later onset of symptoms than other sequence variations.[11,22] Some of the germline pathogenic variants in *STK11* are *Alu*-mediated deletions and inversions.[23] Deletions and inversions are

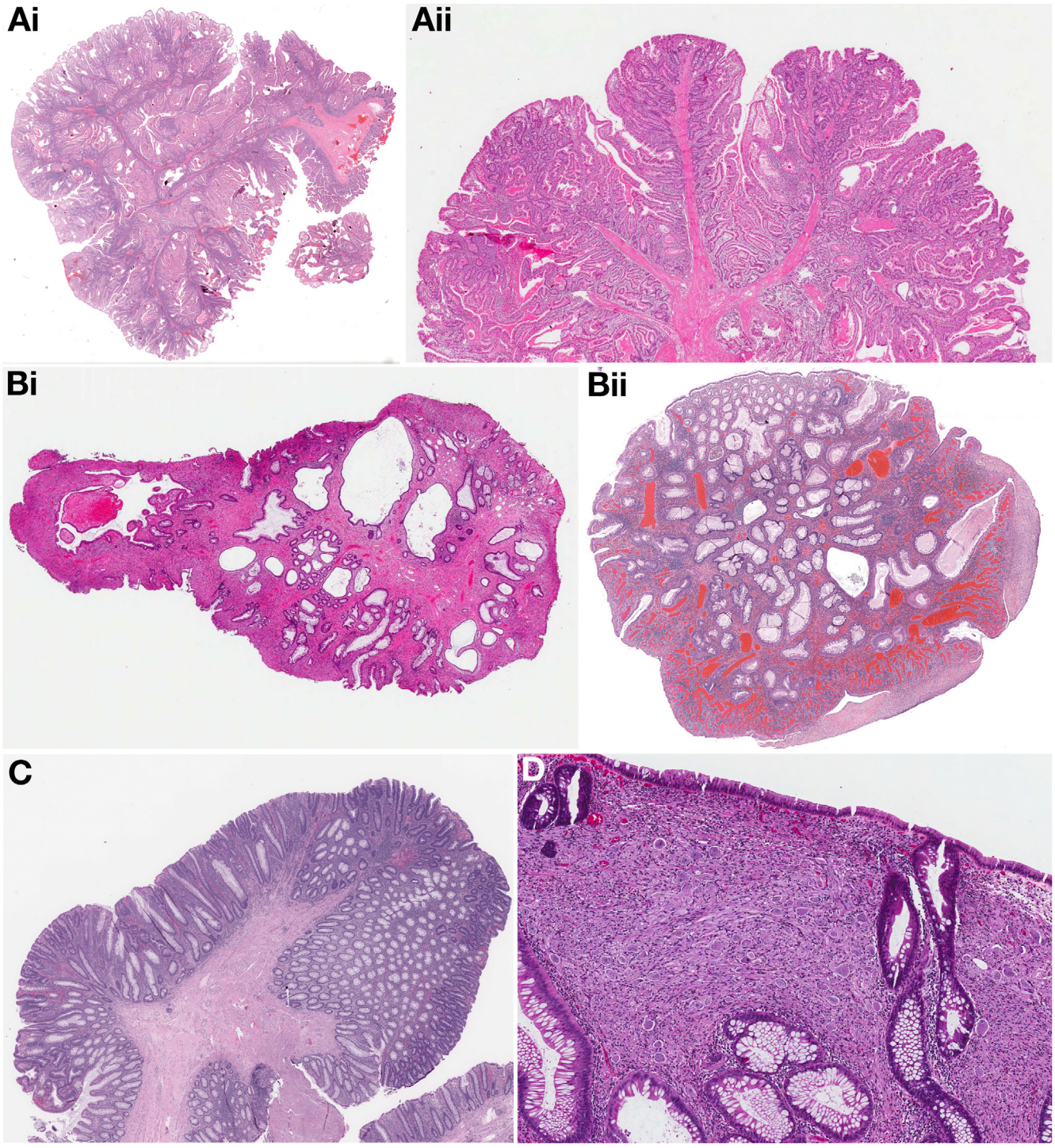

Figure 1. Histologic characteristics of polyps. hamartomatous polyps. Images courtesy of Drs Aaron Pollett and Thomas Plesec. (*A*) Peutz-Jeghers polyp: pathognomonic broad bands of mucosal smooth muscle seen throughout the lesion. (*B*) Juvenile polyp: characteristic chronic inflammatory infiltrate and cystic dilatation. (*C*) Adenomatous polyp: characteristic hypercellularity with glandular crowding, enlarged nuclei, increased mitotic activity and reduced goblet cells. By definition, all tubular adenomas show epithelial dysplasia. (*D*) Ganglioneuroma: benign neuroectodermal tumor composed of ganglion and Schwann cells.

likely to completely inactivate a gene, whereas a missense pathogenic variant may have an intermediate effect on protein function. Approximately 15% of *STK11* pathogenic variants in PJS involve large genetic deletions.[24] Therefore, genetic diagnostic platforms must include strategies to detect these types of germline variations; at least some of the "missing" germline pathogenic variants may involve obscure rearrangements of the *STK11* gene.

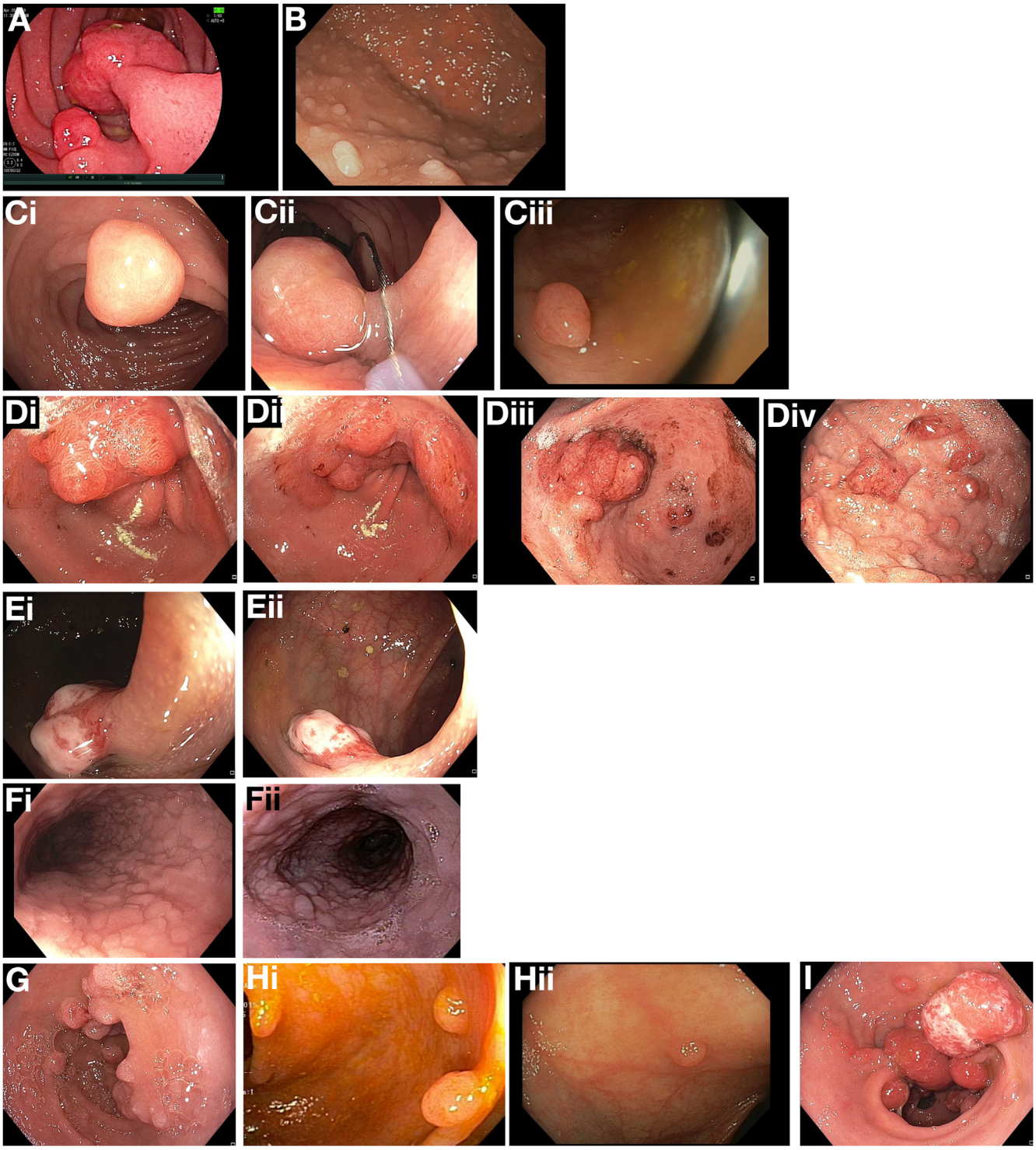

Figure 2. Endoscopic images of hamartomatous polyposis syndromes. Endoscopic photos provided courtesy of Swati Patel, MD, Gregory Idos, MD, and Carol Burke, MD. (*A*) Peutz-Jeghers small bowel polyps. (*B*) Peutz-Jeghers gastric polyps. (*C*) Peutz-Jeghers colon polyps. (*D*) Juvenile polyposis gastric polyps. (*E*) Juvenile polyposis colon polyp. (*F*) Cowden syndrome associated–esophageal glycogenic acanthosis. (*G*) Cowden syndrome small bowel polyps. (*H*) Cowden syndrome colon polyps. (*I*) Cowden syndrome gastric polyps.

Table 2. Clinical Features of Gastrointestinal Hamartomatous Polyposis Syndromes

Syndrome	"Commercially available gene testing"	Polyps	Clinical features
PJS	*STK11*	Peutz-Jeghers polyps (pathologically characteristic)	Childhood: Labial pigmentation; gastrointestinal bleeding and intussusception Adults: Increased risk for multiple cancers
JPS	*SMAD4 or BMPR1A*	Juvenile (inflammatory) polyps; juvenile polyps and inflammatory polyps are pathologically indistinct	Childhood: Gastrointestinal bleeding, auto-amputation of polyps; anemia Adults: CRC and gastric cancer
CS	*PTEN* (inactivation) *WWP1* (gain-of-function)	Hyperplastic polyps; juvenile-like polyps; ganglioneuromas; lipomas; hamartomas;adenomas	Childhood: none Adults: multiple cancer risks
BRRS	*PTEN*	Same as for CS	Developmental delay, hemangiomas, lipomas, gastrointestinal polyps
HMPS	*GREM1* (duplication upstream of promoter)	Pathologically mixed with features of adenoma, hyperplastic polyps, inflammatory polyps	Increased risk of colonic polyposis and CRC

Cancer Risk

Question: Which organs should undergo surveillance when caring for a patient with Peutz-Jeghers syndrome?
Recommendation: Patients with Peutz-Jeghers syndrome are at increased risk for cancer in multiple organs, including cancer of the breast, small bowel, colon, stomach, pancreas, ovaries, testes, and lungs. Given this risk, we recommend a multidisciplinary approach to cancer surveillance in these organs. *(Strong recommendation, low quality of evidence)*

Very high lifetime risks of cancer occur in multiple organs in patients with PJS, inside and outside the gut. Intratubular large-cell hyalinizing Sertoli cell neoplasms, ovarian sex cord tumors, and adenoma malignum of the uterine cervix, although not common, are linked to PJS[25] (Table 3).

The lifetime risk of colon, stomach, and small bowel cancer has been estimated at 12%–39%, 29%, and 13% respectively[6,26–28] (Table 3). Most CRCs occur after the mid-20s (range, 27–71 years, median age 46 years), but these malignancies have been reported in teenage years as well.[26] Mean age at diagnosis of gastric adenocarcinoma ranges between 30 and 40 years and of small intestinal cancer between 37 and 42 years.[26,27,29]

In a meta-analysis of 210 cases reported in 6 publications (retrospective cohort studies with kindred-based ascertainment from the United States, United Kingdom, and The Netherlands) on PJS that were based on clinical and histologic criteria with varying types of ascertainment, the relative risk (RR) for any cancer was 15.2 (95% confidence limits [CL], 2 and 19) compared with a variety of time period–specific US-based registries. Significantly increased age-adjusted cancer risks were noted for the small intestine (RR, 520; 95% CL, 220 and 1306; cumulative risk [CR], 13%), stomach (RR, 213; 95% CL, 96 and 368; CR, 29%), pancreas (RR, 132; 95% CL, 44 and 261; CR, 36%), colon (RR, 84; 95% CL, 47 and 137; CR, 39%), esophagus (RR, 57; 95% CL, 2.5 and 557; CR, 0.5%), ovary (RR, 27; 95% CL, 7.3 and 68; CR, 21%), lung (RR, 17.0; 95% CL, 5.4 and 39; CR, 15%), uterus (RR, 16.0; 95% CL, 1.9 and 56; CR, 9%), testes (RR, 4.5; 95% CL, 0.12 and 25; CR, 9%), and breast (RR, 15.2; 95% CL, 7.6 and 27; CR, 54%).[26] Mean age at the time of cancer diagnosis was 42.9 years. The absolute risk of developing any cancer between the ages of 15 and 64 was estimated to be 93%.

The risk of cancer in PJS was revisited in 2 follow-up studies that included some who were members of the original cohort.[28,30] The lattermost report included some of the original 210 cases and expanded to 419 cases, in which 297 had confirmed germline pathogenic variants in *STK11*.[28] The cumulative incidences of cancer by decade from age 20 to 70 years were 2%, 5%, 17%, 31%, 60%, and 85% respectively, confirming the initial estimates and tumor spectrum—predominantly the gastrointestinal tract and breast. Cancer risks were the same in those with a clinical diagnosis but no detectable germline pathogenic variant in the *STK11* gene.

Several collaborative studies from Europe and the United States again found similar risks for cancer.[29,31] A systematic review of 20 cohort studies looking at 1644 patients with PJS confirmed at least 1 cancer in >90% of patients with PJS at a mean age of 42 years.[29] CRC was the most commonly diagnosed tumor, followed by cancers of the breast, small intestine, stomach, lung, pancreas, cervix, ovary, bile ducts, and testicles. A multicenter study from Italy of 119 *STK11* pathogenic variant carriers reported an overall RR for cancer of

Table 3. Risk of Cancer in Hamartomatous Polyposis Syndromes

Site	General population risk,[a] %	Syndrome risk, %	Mean age at diagnosis, *y*	Reference
PJS				
Colorectal	4.3	39	42–46	26, 29
Stomach	<1	29	30–40	26, 29
Small bowel	<1	13	37–42	26, 29
Breast	12.9	32–54	37–59	26, 28, 29
Ovarian (mostly SCTAT)	1.2	21	28	26
Cervix (adenoma malignum)	<1	10–23	34–40	26
Uterus	3.1	9	43	26, 29
Pancreas	1.7	11–36	41–52	26, 28, 29, 32
Testicular (Sertoli cell tumor)	<1	9	6-9	26, 29
Lung	6.3	7–17	47	26, 28, 29
JPS				
Colon	4.3	39	44	86
Stomach	<1	5–21	54	65, 67, 89
CS				
Breast	12.9	25–85	38–46	100, 101, 102
Thyroid	1.3	3–38	31–38	100, 101, 102
Uterus	3.1	5–28	25	95, 100, 101, 102
Kidney (renal cell)	1.7	15–34	40	97, 100, 104
Colon	4.3	9–18	35	100–103, 106
Melanoma	2.3	6	3[b]	100, 101
HMPS				
Colon	4.3	Increased	—	119–121

SCTAT, sex cord tumors with annular tubules.
[a]National Cancer Institute. Surveillance, Epidemiology, and End Results Cancer Statistics Review 1975–2017. Lifetime risk (%) of being diagnosed with cancer by site, 2017.
[b]Youngest age of onset.

22.0 in women (in part because of additional risks for cervical cancers) and 8.6 in men, compared with an Italian-based general population registry, and a cumulative risk of cancer reaching 89% by age 65 years.[27] A more recent study from China confirmed elevated cancer risks (albeit somewhat lower than the American and European data), early age of onset, and a similar tumor spectrum.[32]

Surveillance of Affected Individuals

The effectiveness of cancer surveillance in PJS has not been evaluated in controlled studies. Consequently, surveillance recommendations have been developed by consensus groups and expert opinion analyzing cancer risks and published organ-specific surveillance protocols (Tables 3 and 4).[11,33–35]

Question: How and when should small bowel surveillance be performed in Peutz-Jeghers syndrome?
Recommendation: We recommend that baseline small bowel surveillance using video capsule endoscopy or magnetic resonance enterography be performed between ages 8 and 10 years or earlier if the patient is symptomatic. If no polyps are found at the initial examination, surveillance should resume at age 18 years. Because of the risk of small bowel intussusception, small bowel surveillance in adulthood is recommended to continue throughout life every 2–3 years. *(Strong recommendation, low quality of evidence)*

Gastrointestinal Polyposis and Cancer

Gastric, small bowel, and colorectal polyposis occur in 88%–100% of patients, with the majority appearing in the small bowel (60%–90%) and colon (50%–64%).[36] Polyps can vary in number (1–100) and size (0.1–3 cm in diameter) and age of onset of symptoms may vary. Polyp growth begins in childhood by age 10 years (33%), with most experiencing symptoms such as bleeding, abdominal pain, intussusception, or obstruction (68%) by age 18 years.[37] In affected or at-risk individuals, early surveillance with esophagogastroduodenoscopy (EGD), colonoscopy, and small bowel imaging with video capsule endoscopy (VCE) and/or magnetic resonance enterography (MRE) is recommended to begin at age 8 years.[11,33–35]

Intussusception is rare in children younger than 5 years, and the precise risk of intussusception between 5 and 18 years of age is unknown. Retrospective registry data report that 23 of 34 adults with PJS (68%) had undergone laparotomy by the age of 18 years, 70% of which were performed as an emergency. By the age of 10 years, 30% had required a laparotomy.[37] In a single-institution study of 379 pediatric patients who underwent pneumatic reduction for intussusception (from all causes), one-quarter required operative management.[38] There is a paucity of studies that assess modalities to evaluate the small bowel in patients with PJS. Retrospective data comparing VCE to small bowel barium studies have reported VCE as a useful diagnostic tool

Table 4. Surveillance Guidelines in Hamartomatous Polyposis Syndromes

	ACG 2015		NCCN 2020		ESPGHAN 2019		USMSTF 2020		
Examination	Age of initiation, *y*	Interval, *y*	Age of initiation, *y*	Interval, *y*	Age of initiation, *y*	Interval, *y*	Age of initiation, *y*	Interval, *y*	Evidence grade
JPS									
Colonoscopy	12–15	1–3	15	2–3	12–15	—	12–15	1–3	Low
Upper endoscopy	12–15	1–3	15	2–3	Late teens[a]	—	12–15	1–3	Low
Screen for vascular lesions	≤6 mo	—	≤6 mo	—	At diagnosis	—	≤6 mo[b]	—	—
PJS									
Colonoscopy	8, 18[c]	3	Late teens	2–3	8	3	8–10, 18[c]	2–3	Very low
Upper endoscopy	8, 18 [c]	3	Late teens	2–3	8	3	8–10, 18[c]	2–3	Very low
VCE	8, 18 [c]	3	~8–10[d]	2–3	8	3	8, 18[c]	2–3	Low
CT or MRE of small bowel	—	—	~8–10[d]	2–3	—	—	—	—	—
MRI/MRCP or EUS of pancreas	30	1–2	~30–35[e]	1–2	—	—	35	1	Low
MRI and/or mammogram	25	1	~25	1	—	—	—	—	—
Physical examination	Birth to teenage	1	~10	1	—	—	—	—	—
Pelvic examination and Pap smear	25[f]	1	~18–20	1	—	—	—	—	—
Testicular examination	Birth to teenage	1	~10	1	—	—	—	—	—
PHTS									
Colonoscopy	15	2	35	5	—	—	35	5	Low
Upper endoscopy	15	2–3	—	—	—	—	—	—	—
Thyroid examination and US	Adolescence	1	7	1	—	—	—	—	—
MRI and/or mammogram	30–35	1	30-35	1	—	—	—	—	—
Endometrial sampling	30–35	1	—	1–2	—	—	—	—	—
Urinalysis or renal US	18	1	40	1–2	—	—	—	—	—
Skin examination	~18	1	At diagnosis	1	—	—	—	—	—

ACG, American College of Gastroenterology; CT, computed tomography; ESPGHN, European Society for Paediatric Gastroenterology Hepatology and Nutrition; EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography; NCCN, National Comprehensive Cancer Network.

[a]Upper gastrointestingal screening in JPS *SMAD4* carriers is indicated in asymptomatic patients starting in late teens. For non-*SMAD4* JPS patients, upper endoscopic screening is only indicated if the patient has relevant symptoms or anemia not explained by colonic polyps.

[b]*SMAD4* mutation carriers should be clinically evaluated for HHT at the time of the diagnosis, including screening for, and appropriate management of, cerebral and pulmonary AVMs.

[c]First procedure at 8 years of age; if polyps present, repeat every 3 years; if no polyps, restart at 18 years of age and every 3 years.

[d]Baseline at age 8–10 years of age with follow-up interval based on findings but at least by age 18 years of age, then every 2–3 years, although this may be individualized by at least age 18 years, then every 2–3 years, although this may be individualized, or with symptoms).

[e]Based on clinical judgment, early initiation age may be considered, such as 10 years younger than the earliest age of onset in the family.

[f]ACG 2015 Guidelines recommend transvaginal ultrasound as part of surveillance beginning at age 25 years.

in PJS. A retrospective study from France included 27 children who underwent at least 1 VCE.[39] The authors found VCE was a useful diagnostic tool, however, findings at VCE may not predict future bowel obstructions. Although VCE may not predict future bowel obstructions, it has a greater sensitivity in detecting small bowel polyps compared with MRE and provides patients with another alternative if they are unable to undergo MRE. Ten children with PJS with polyps >15 mm identified by VCE and MRE underwent single-balloon enteroscopy.[40] In this small study, single-balloon enteroscopy was effective for treating small bowel polyps. Further larger, multicenter studies are warranted to accurately determine the safety of therapeutic single-balloon enteroscopy in children.[7] Based on the published data, VCE or MRE is recommended between ages 8 and 10 years in asymptomatic patients. Investigations should commence earlier if patients have symptoms. If no polyps are found on the baseline investigation, repeat small bowel evaluation may commence at age 18 years. If polyps are found, further investigation and surveillance should be individualized based on polyp size and location. Because of the risk of small bowel intussusception, small bowel surveillance in adulthood continues throughout life every 2–3 years. If polyps are present in the colon or stomach, EGD or colonoscopy is continued as necessary every 2–3 years.

Question: What is the recommended approach to endoscopic surveillance of the stomach, duodenum, and colon in Peutz-Jeghers syndrome?
Recommendation: We suggest a baseline upper gastrointestinal endoscopy between the ages of 8 and 10 years, which could be performed at the time of capsule placement for small bowel surveillance or if polyps are identified on magnetic resonance enterography. Although the initiation age for colonoscopy remains uncertain, we also suggest initiation of colonoscopy at the same time as esophagogastroduodenoscopy. In those in whom characteristic polyps are detected, both colonoscopy and esophagogastroduodenoscopy should be repeated every 2–3 years. In those in whom there are no Peutz-Jeghers polyps at baseline, surveillance is repeated at age 18 years, or sooner should symptoms arise, and then every 3 years. *(Weak recommendation, very low quality of evidence)*

Management of Polyposis

Although the malignant potential of PJ polyps is unknown and the evidence of benefit from gastrointestinal surveillance is not robust, endoscopic removal of polyps is recommended to prevent polyp-related complications and to reduce the risk of cancer. In a study of long-term outcomes of gastrointestinal procedures from a PJ polyposis registry, investigators tracked the results of 776 procedures among 63 patients with PJS at a median age of 20 years (range, 3–59 years). A total of 2461 polypectomies were performed; more than 1000 polyps were removed during colonoscopy and more than 400 polyps were removed during EGD, and the remaining polyps were removed by means of enteroscopy or laparotomy of the small bowel.[41] A substantial proportion of patients required intervention for removal of large polyps and the authors concluded that surveillance reduced polyp burden and likelihood of polyp-related complications, and provided cancer surveillance. Therefore, we recommend polypectomy for polyps in the stomach and colorectum that are >0.5 cm in size on endoscopic surveillance and an attempt to remove all polyps if endoscopically feasible.[33,35,42,43]

In the small bowel, balloon enteroscopy and MRE have similar diagnostic yields for lesions ≥15 mm, but endoscopy permits polyp removal.[43] Consequently, removal, preferably by enteroscopy, of small intestinal polyps that are symptomatic or rapidly growing, or asymptomatic polyps that are >1.0–1.5 cm in size, has been recommended.[33,35,37,42,44,45] Surgery is often needed when small bowel intussusception occurs. Some authorities recommend an attempt to clear the small intestine of polyps during laparotomy by means of intraoperative endoscopy with polypectomy or, for larger polyps, by means of enterotomy. This "clean sweep" approach appears to decrease the need for recurrent small bowel surgery.[46] Thus, the early management focus is on large hamartomatous polyps and their tendency to obstruct the gut or bleed. As children grow older and transition into adulthood, the focus shifts to managing the cancer risk.

Question: What size polyps found on small bowel imaging in Peutz-Jeghers syndrome should be removed?
Recommendation: We recommend polypectomy of small bowel polyps that are symptomatic or ≥10 mm to prevent intussusception and other complications, such as bleeding. *(Strong recommendation, low quality of evidence)*

Breast Cancer

Invasive ductal adenocarcinoma poses the greatest risk of early malignancy to patients with PJS (24%–54% lifetime risk in women) and often presents at a young age (range, 19–61 years in 1 study).[26,47] The risk of breast cancer in women with PJS is within the same range as women affected by *BRCA-1* or *BRCA-2* pathogenic variants (40%–85% lifetime risk for breast cancer).[26,48] Therefore, consensus opinion surveillance recommendations by groups that include breast cancer experts[49,50] include monthly breast self-examination starting at age 18 years, biannual clinical breast examination starting at age 25 years, annual breast magnetic resonance imaging (MRI) from ages 25–29 years, and mammography with consideration of tomosynthesis (3-dimensional mammography) alternating every 6 months with breast MRI with contrast from ages 30 to 75 years.[6,11] The option of prophylactic mastectomy might be discussed on a case-by-case basis, factoring in family history. In patients with PJS, referral to a breast cancer specialist for management of breast cancer surveillance is reasonable, and a multidisciplinary approach including a breast surgeon is recommended when prophylactic mastectomy is being considered.

Question: What is the recommended pancreatic cancer surveillance in Peutz-Jeghers syndrome?
Recommendation: We suggest annual pancreatic cancer surveillance with either magnetic resonance cholangiopancreatography or endoscopic ultrasound starting at age 35 years. *(Weak recommendation, low quality of evidence)*

Pancreas Cancer

Pancreatic cancer is the third most frequently occurring malignancy in patients with PJS. The lifetime risk of pancreatic ductal adenocarcinoma is between 11% and 36%, presenting, on average, at ages 41–52 years, with 95% of cases occurring after age 24 years.[6,26,28,51,52] PJS is associated with the highest relative risk of all pancreatic cancer syndromes, with the exception of hereditary pancreatitis (25%–40% lifetime risk).[43] Consequently, a high-risk pancreatic surveillance protocol is recommended. The consensus recommendations of the International Cancer of the Pancreas Screening Consortium[53] recommend pancreas MRI/magnetic resonance cholangiopancreatography and/or endoscopic ultrasound every 1–2 years starting from age 40 years, for which evidence suggests that these cancers can be found in earlier stages.[54] The National Comprehensive Cancer Network Guidelines recommend initiating pancreatic cancer surveillance between the ages of 30 and 35 years. Due to reports of pancreatic cancer diagnoses in patients with PJS before the age of 40 years,[26] the USMSTF suggests initiating annual surveillance at age 35 years with MRI/magnetic resonance cholangiopancreatography and/or endoscopic ultrasound. Ideally, these examinations would alternate on an annual basis, as they are complementary. In addition, routine fasting glucose and hemoglobin A1c at initiation of screening is recommended by the Cancer of the Pancreas Screening Consortium. At the current time, the USMSTF awaits definitive data before making a recommendation regarding fasting glucose and hemoglobin A1c. Recent updates to the Cancer of the Pancreas Screening Guidelines detail surveillance protocols and management recommendations based on imaging and endoscopic findings.[55]

Gynecological Cancers

The lifetime risks for ovarian, uterine, and cervical cancer are estimated at 21%, 9%, and 10%–23%, respectively, with mean age at presentation of 28–35 years, 43 years, and 34–40 years, respectively.[6,26,27] Of note, almost all ovarian tumors in patients with PJS are sex cord tumors with annular tubules, and rarely cystadenomas or granulosa cell tumors. Sex cord tumors with annular tubule neoplasms are a heterogeneous group of benign or malignant neoplasms, but the tumors rarely have lymph node metastasis.[26] Also, an unusual percentage of cervical cancers in patients with PJS are adenoma malignum, a rare, well-differentiated, cervical adenocarcinoma that is associated with a poor prognosis and difficult to diagnose on Pap smear. A high level of suspicion is required for diagnosis.[56] Recommendations for gynecological surveillance are pelvic examination with Pap smear and transvaginal ultrasound annually starting at age 25 years.[33,35]

Testicles

The estimated risk of testicular cancer in male patients with PJS is 9%, mean age at diagnosis is 9 years (range, 3–20 years).[6,26,27] These tumors present as testicular masses. The tumors are Sertoli cell tumors that can cause gynecomastia and other signs of hyperestrogenism and occasionally virilization and/or accelerated height growth.[26] Accelerated height velocity can be challenging to detect as adolescents have "growth spurts" as part of normal maturation and development. Expert opinion recommends annual history and physical examination (including self-examination) with observation for feminizing changes and examination of the testicles[6,34,35]; based on the range of age at diagnosis of this tumor, examination should start from birth. Ultrasound of the testicles every 2 years from birth to age 12 years has been suggested.[44]

Lung

The lifetime risk of lung cancer in patients with PJS has been estimated between 7% and 17%,[6,26–28,30] compared with 0.2%–0.6% in nonsmokers in the general population.[57] The cumulative risk of lung cancer in PJS surpasses 5% by age 55 years.[6] Of note, lung cancer risk in patients with PJS has not been calculated with adjustment for smoking status. The RRs of lung cancer in patients with PJS compared with nonsmokers are similar to people with a more than 30 pack-year history of smoking who have quit for 10–15 years (hazard ratio, 14.8).[58] Currently, the American College of Chest Physicians, American Society of Clinical Oncology, and American Cancer Society recommend low-dose computed tomography annually for individuals with this level of cumulative risk for lung cancer from ages 55 to 74 years.[59,60] There are no data to show benefit of lung cancer surveillance in patients with PJS. Lung cancer surveillance with annual low-dose computed tomography, as performed in smokers at high risk for lung cancer, may be considered in patients with PJS. Smoking cessation counseling in patients with PJS is advisable to mitigate risk.[33,34]

Chemoprevention

Currently, there are no known chemopreventive agents in clinical practice that slow or prevent the development of intestinal polyps and cancers in PJS. Pathogenic variants in the *STK11 gene* decrease inhibition of mTOR leading to the development of intestinal polyps. A trial examining the oral selective mTOR inhibitor, everolimus, was stopped prematurely because of poor patient accrual. Only 2 patients were enrolled, 1 with pancreatic cancer that progressed and another patient who withdrew from the protocol because of severe complications from the medication.[61]

In a murine model of PJS, treatment with celecoxib, a COX2 inhibitor, resulted in a >50% reduction in polyp burden. When used in patients with PJS with diffuse

polyposis in the body of the stomach (tens to hundreds), 2 of 6 had a significant reduction in polyp number, as assessed by 5 independent evaluators, after administering celecoxib (200 mg twice per day for 6 months).[62]

Summary

PJS is associated with a very high cumulative lifetime risk of cancer of multiple organs, including, but not limited to, the gastrointestinal tract. Intensive surveillance is recommended to prevent and manage complications of polyposis and identify cancer at an early stage. The development of polyposis and the cancer risks may be a reflection of the effects of haploinsufficiency of the LKB1 protein, for which there are possible medical therapies to be explored. It is unclear whether the basic mechanisms responsible for hamartoma formation in younger life are the same as those that create the risks for cancer later in life. Simulation models and clinical trials are needed to optimize endoscopic surveillance frequencies and the use of imaging modalities in adults. In addition, collaborative multicenter consortia may help facilitate chemoprevention trials in the future.

Juvenile Polyposis Syndrome

Question: Who should undergo a genetic evaluation for juvenile polyposis syndrome?
Recommendation: We recommend genetic evaluation for any individual with 1) 5 or more juvenile polyps of the colon or rectum; 2) 2 or more juvenile polyps in other parts of the gastrointestinal tract; or 3) any number of juvenile polyps and 1 or more first-degree relatives with juvenile polyposis syndrome. *(Strong recommendation, low quality of evidence)*

Clinical Features

JPS is an autosomal dominant inherited condition in which multiple juvenile polyps are found in the colorectum (98% of affected patients) (Figure 1*B*), stomach (14%), jejunum and ileum (7%), and duodenum (7%).[63–65] The incidence of JPS is between 1 in 100,000 and 1 in 160,000 individuals.[65] The polyps in JPS vary in size from small sessile nodules to pedunculated lesions that are $\geq$3 cm in diameter. Histologically, the typical juvenile polyp has a distinctive cystic architecture, dilated mucus-filled glands, a prominent lamina propria, and Paneth cells enmeshed within a dense infiltration of inflammatory cells. In patients with germline pathogenic variants in *SMAD4,* additional features of gastric polyposis, gastric cancer, and a JPS–hereditary hemorrhagic telangiectasia (HHT) overlap syndrome are common. The management of JPS is based on decreasing the risk of bleeding and gastric and colorectal cancer through polypectomy. Patients with JPS-HHT overlap syndrome should have lifelong HHT surveillance. One study also demonstrated that as many as 38% may have thoracic aorta abnormalities.[66]

Juvenile polyps are most often solitary and are not syndromic, occurring sporadically in infants and children. A typical history associated with a solitary juvenile polyp is the asymptomatic passing of a polyp into an infant's diaper. Juvenile polyps appear endoscopically to have a smooth red surface, may be sessile or pedunculated, and pathologically are characterized by cystic dilatation of mucus-filled glands suspended in an inflamed stroma (Figures 1*B* and 2*D* and *E*). These lesions may also be called retention polyps or inflammatory polyps because of their microscopic appearance.

Diagnosis

The diagnosis of JPS is made based on clinical criteria or identification of a germline pathogenic variant in *SMAD4* or *BMPR1A*. The clinical diagnosis of JPS is made when a person has any 1 of the following: 1) 5 or more juvenile polyps of the colon or rectum; 2) any number of juvenile polyps in parts of the gastrointestinal tract other than the colon; or 3) any number of juvenile polyps and 1 or more first-degree relatives with JPS.[65]

Genetics

JPS is an autosomal dominant disorder with approximately 75% of cases inherited from a parent and 25% representing de novo pathogenic variants.[64] Approximately 60% of patients with JPS have a pathogenic variant in the *BMPR1A* or *SMAD4* gene.[67] Rarely (1 in 1,000,000) individuals develop features of JPS and PHTS, known as juvenile polyposis of infancy, due to a large deletion encompassing both the *BMPR1A* and *PTEN* genes.

In a study from the Cleveland Clinic of 35 patients with JPS, germline pathogenic variants in *SMAD4* and *BMPR1A* were associated with similar colonic polyposis phenotypes, but *SMAD4* pathogenic variant carriers were more likely to have more gastric polyps, and an 11% risk of gastrointestinal cancer.[68] However, no gastric cancers were reported in patients with *BMPR1A* pathogenic variants in 8 patients followed for a mean of 11 years.

However, germline pathogenic variants in other genes may cause a hamartomatous polyp phenotype. In a study of 49 patients referred to the Cleveland Clinic for unexplained hamartomatous or hyperplastic polyps, germline pathogenic variants were found in multiple genes, including *endoglin* (*ENG*, a gene associated with HHT*)*, *STK11* (the PJS gene), *SMAD4*, *BMPR1A*, and *PTEN*.[69] In a later study from this group of 603 patients with a "moderate load of gastrointestinal polyps" with at least 1 confirmed to be a hamartoma or hyperplastic polyp, 13% were found to have a germline pathogenic variant in at least 1 of the genes listed above and 20% of the cohort had a personal history of CRC.[70]

As discussed in the context of PJS, it has been traditionally thought that a germline pathogenic variant associated with a hereditary colon cancer syndrome did not change the biology of the normal tissues and a second (somatic) hit was required for a tumor to form. In fact, allelic loss of the *SMAD4* locus was found in the epithelial component of juvenile polyps of patients with JPS (together

with a germline pathogenic variant in *SMAD4*) using in situ hybridization, but not in the inflammatory or stromal cells. This was compatible with the Knudson 2-hit model.[71] However, another group has reported that SMAD4 haploinsufficiency (ie, a lower dose of the gene product due to the specific type of germline pathogenic variant) causes the JPS phenotype in humans, supported by data from mice.[72] However, just as in PJS, being haploinsufficient for *SMAD4* (ie, just the germline pathogenic variant), is associated with partially diminished transforming growth factor–β signaling, at least in mice,[72] as this alters proliferation in T cells, which contributes to the development of polyps and cancer.[73,74] Specific deletion of *SMAD4* in mouse T cells leads to up-regulation of the Th17-inflammatory pathway in the stroma, and the growth of large polyps in the gastrointestinal tracts of mice.[73,74] This raises the question of whether there is abnormal regulation of immune cells in JPS, and may explain the inflammatory appearance of juvenile polyps independent of abnormal biology in the epithelium—another landscaper mechanism, as discussed above for PJS. These observations may have important clinical implications for future attempts to halt the appearance or growth of the inflammatory polyps. However, allelic loss (ie, a somatic variants as the second hit) occurs in at least some polyps of JPS patients.[75,76]

Juvenile Polyposis Syndrome–Hereditary Hemorrhagic Telangiectasia Overlap Syndrome

HHT occurs in approximately 15%–81% of patients with a germline *SMAD4* pathogenic variant.[77,78] The clinical features of HHT, such as epistaxis, obscure gastrointestinal bleeding, digital clubbing, visceral arteriovenous malformations (AVMs), and mucocutaneous telangiectasias should be sought in *SMAD4* patients. International guidelines (outlined below) recommend that surveillance and treatment for HHT complications are necessary for all *SMAD4* carriers.[79]

Juvenile Polyposis of Infancy

Juvenile polyposis of infancy is a severe form of juvenile polyposis. This disease presents in the first 2 years of life with diarrhea, abdominal pain, rectal bleeding, refractory anemia, hypoalbuminemia, and enteropathy. Case reports indicate that a large deletion in the long arm of chromosome 10 (10q23), encompassing the *PTEN* and *BMPR1A* genes, is associated with the development of the disease.[69,80–83]

Question: Which organs should undergo surveillance when caring for a patient with juvenile polyposis syndrome?
Recommendation: Patients with juvenile polyposis syndrome are at increased risk for cancer in multiple organs, including cancer of the colon and stomach.
Given this risk, we recommend patients with juvenile polyposis syndrome undergo surveillance of the colon and stomach. *(Strong recommendation, low quality of evidence)*

Gastrointestinal Polyposis and Cancer

In a retrospective chart review study of 257 children with juvenile polyps at a single-referral center, patients presented at a median age of 5.6 years, and at colonoscopy 39% had multiple polyps.[84] Among 192 patients who underwent complete colonoscopy at initial diagnosis, 117 (60.9%) had a single polyp and 75 (39.1%) had multiple polyps. These lesions recurred in 21 of 47 patients (44.7%) after an initial eradication, including 3 of 18 presenting with a single polyp, and neoplasia was found in 3.9% of lesions. Patients with JPS often have a variable presentation of polyp distribution, which may occur throughout the colon and/or stomach and the cancer risk is attributable to the presence of dysplasia in the polyps. One study of 78 juvenile polyps from 12 patients with JPS and 34 patients with sporadic juvenile polyps reported that dysplasia was present in 31% of the polyps from patients with JPS but in none of the polyps from patients with sporadic juvenile polyps.[85] Dysplasia in polyps from patients with JPS was associated with somatic variants in the *APC* gene.[85] In a longitudinal study from St Mark's Hospital of 44 patients with JPS from 30 kindreds, a total of 787 polyps (juvenile and adenomatous) were resected, and 65 of 787 (8.3%) contained mild/moderate architectural dysplasia, and 20 additional polyps (2.5%) were adenomatous.[65]

Patients with JPS are at increased risk for cancer principally in the stomach and colon (Table 3). In a small cohort of patients with JPS (n = 84) relative to age-, sex-, and race-matched controls, the RR of CRC was estimated to be 34 (95% CL, 14.4 and 65.7), with a cumulative lifetime risk of CRC reaching 38.7%.[86] The CRCs were diagnosed at a mean age of 43.9 years. Interestingly, no other gastrointestinal cancers were noted in this cohort, but the numbers were small and the duration of the study was short. Individuals with gastric polyposis, usually in association with pathogenic variants in *SMAD4* are also at risk for gastric cancer, with the lifetime risk estimated to be at least 30% and median age of diagnosis is 58 years; this has not been reported in association with *BMPR1A* pathogenic variants.[67,87–91] Estimates of gastrointestinal cancer risk range from 11%[68] to 55%,[89] but none of the studies are prospective long-term studies (which would lead to underestimates), and all are prone to referral-based ascertainment bias (overestimates).

Question: At what age should colonoscopic and upper endoscopic surveillance begin in individuals identified with juvenile polyposis syndrome?
Recommendation: We suggest initiating colonoscopic and upper endoscopic surveillance at age 12–15 years, or earlier if symptomatic. Surveillance should be repeated every 1–3 years depending on polyp burden. *(Weak recommendation, low quality of evidence)*

Management of Polyposis

The goal of surveillance in JPS is to mitigate symptoms related to the disorder and decrease the risk of

complications from the manifestations, including cancer. Colonoscopy should be first performed at age 12–15 years and repeated every 1–3 years, depending on polyp burden found, with removal of all polyps when feasible or at least all polyps ≥5 mm. Upper endoscopy should be first performed at age 12–15 years and repeated every 1–3 years depending on polyp burden found, with removal of polyps ≥5 mm. Due to the possible presence of intestinal telangiectasias, an annual history and physical examination and complete blood counts to monitor for rectal bleeding and/or anemia should begin at age 12–15 years in patients with a germline *SMAD4* pathogenic variant.

Endoscopic polypectomy is recommended for colorectal polyposis management. Surgery with colectomy and ileorectal anastomosis is recommend for patients with CRC, endoscopically unmanageable colon polyp burden and uncontrolled anemia from colonic bleeding.[33] In some cases, proctocolectomy is necessary for rectal cancer or advanced polyp burden of the rectum. Colectomy in patients with JPS should be reserved for patients with polyp burdens that cannot be managed by polypectomy, persistent blood loss leading to severe anemia or hypoalbuminemia, or cancer. A decision to proceed to colectomy should be reviewed with gastroenterologists and surgeons with expertise in caring for individuals with hereditary polyposis syndromes.

The risk of gastric cancer is a concern in patients with JPS with *SMAD4* pathogenic variants and gastric polyposis. There is a paucity of published data evaluating the stomach and small bowel in pediatric patients with JPS. Those with upper gastrointestinal symptoms, or with anemia not explained by colonic polyps, should undergo evaluation with upper endoscopy.[92] In pediatric patients without *SMAD4* pathogenic variants, according to the existing data, gastroscopy is not indicated unless the child has symptoms.[92] In asymptomatic patients with *SMAD4* pathogenic variants, it is prudent to assess the upper tract between the ages of 12 and 15 years. At the time of this publication, it is uncertain as to whether *BMPR1A* pathogenic variants are associated with gastric cancer risk, and that pending new evidence, upper endoscopy surveillance is suggested at intervals similar to those recommended for *SMAD4* carriers. In adults, partial or complete gastrectomy is indicated in patients with gastric cancer, high-grade dysplasia, inability to adequately survey or endoscopically control polyposis, persistent anemia or gastrointestinal bleeding from gastric polyposis or angioectasia, symptoms of gastric outlet obstruction, or protein-losing gastropathy.[63,64]

Question: Which patients with juvenile polyposis syndrome should undergo screening for hereditary hemorrhagic telangiectasia?
Recommendation: We suggest patients with SMAD4 pathogenic variants be clinically evaluated for hereditary hemorrhagic telangiectasia at the time of the diagnosis, including screening for and appropriate management of cerebral and pulmonary arteriovenous malformations. *(Weak recommendation, low quality of evidence)*

Management of Juvenile Polyposis Syndrome–Hereditary Hemorrhagic Telangiectasia

As recommended by HHT Foundation International, patients with *SMAD4* pathogenic variants should be screened for vascular findings associated with HHT.[79,93] Children with possible or confirmed HHT should be screened for brain AVMs at the time of diagnosis and undergo at least 1 follow-up MRI at puberty because brain AVM development appears to correlate with times of growth. Lung AVM screening and surveillance is recommended at diagnosis and then every 3–5 years with pulse oximetry testing and consideration of transthoracic contrast echocardiogram. In adulthood, surveillance should include annual hemoglobin or hematocrit for all patients older than 35 years. Transthoracic contrast echocardiogram as a screen for pulmonary AVMs should be performed at the time of diagnosis, within 5 years preceding planned pregnancy, after pregnancy, and otherwise every 5–10 years. Physicians should consider referring these patients to HHT Centers of Excellence for this evaluation. Brain MRI with and without contrast should be performed at birth or at the time of diagnosis to screen for cerebral vascular malformations.

Chemoprevention

No known effective chemoprevention strategies exist for the development of polyposis in patients with JPS.

Summary

BMPR1A and *SMAD4* gene alterations are responsible for JPS, yet only 60% of patients will have a pathogenic alteration identified. The clinical overlap syndromes include JPS-HHT in patients with a *SMAD4* pathogenic variant and juvenile polyposis of infancy in patients with a combined *BMPR1A* and *PTEN* deletion. The symptoms of JPS are usually related to bleeding from colorectal polyposis or in *SMAD4*-related JPS to gastric polyposis or manifestations of HHT. Cancer risk in JPS is elevated, mainly in the colon and stomach (39%–68%), and is largely associated with *SMAD4* pathogenic variants.[94] Excess risk of nongastrointestinal cancer is not reported in JPS.

PTEN-Hamartoma Tumor Syndrome

Clinical Features

Question: Which gastrointestinal findings should prompt a genetic evaluation for *PTEN* hamartoma tumor syndrome?
Recommendation: We recommend individuals with multiple gastrointestinal hamartomas or ganglioneuromas undergo genetic evaluation for Cowden's syndrome and related conditions. *(Strong recommendation, low quality of evidence)*

PHTS includes a variety of phenotypic variations known as CS, BRRS, and Proteus syndrome. The clinical diagnosis of

the PHTS is made in patients meeting the revised diagnostic criteria, which include the presence of hamartomas of the skin and gastrointestinal tract (see Figures 1*D* and 2*F–H*), mucocutaneous lesions, macrocephaly, and an increased risk of benign and malignant lesions of the breast, thyroid, and endometrium.[95]

Diagnosis

The genetic diagnosis of PHTS is established with a germline pathogenic variant in the phosphatase and tensin homolog (*PTEN*) gene. The clinical criteria for the diagnosis of CS is complex, and can be found at the National Comprehensive Cancer Network website.[49] The discussion for this article will focus on the manifestations and management of patients with a confirmed diagnosis of PHTS.

Genetics

Question: Which organs should undergo surveillance for cancer when caring for a patient with *PTEN* hamartoma tumor syndrome?
Recommendation: In PTEN hamartoma tumor syndrome, patients are at increased risk for cancer in multiple organs, including cancer of the breast, thyroid, kidney, uterus, colon, and skin.
Given this risk, we recommend a multidisciplinary approach to cancer surveillance in these organs. *(Strong recommendation, low quality evidence)*

The *PTEN* gene encodes a dual-function phosphatase that negatively regulates the growth-promoting activity of the phosphatidylinositol 3-kinase pathway. The PHTS family of syndromes are caused by inactivating pathogenic variants in *PTEN*, making it a classic tumor suppressor gene.[96] Germline pathogenic variants in the *PTEN* gene lead to heterogeneous phenotypes called PHTS, which includes CS, BRRS, and some cases of the *PTEN*-related Proteus syndrome (not considered further here).[97,98] Germline pathogenic variants in *PTEN* are associated with other systemic nonpolyposis phenotypes, including abnormalities of the central nervous system and skeleton, but these will not be discussed here in detail. Patients with CS are also at risk for dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease), but the specific genetic basis of this and the other protean manifestations of germline pathogenic variants in *PTEN* are not yet understood. Interestingly, gain-of-function germline pathogenic variants in the *WWP1* gene, an E3 ubiquitin ligase commonly up-regulated in cancers, inhibits the activity of *PTEN*, causes a CS-like syndrome (oligopolyposis and cancer-prone phenotype), and provides some insight into what may be responsible for PHTS in the absence of germline variants in *PTEN*.[99]

Cancer Risk

Cancer risks for patients with germline pathogenic variants in *PTEN* are very high. The International Cowden Consortium reported in 2012 on 368 individuals with germline pathogenic variants in *PTEN*. Elevated standardized incidence ratios (SIRs) were found for carcinomas of the breast (SIR, 25.4; 95% CL, 19.8 and 32.0), thyroid (SIR, 51.1; 95% CL, 38.1 and 67.1), endometrium (SIR, 42.9; 95% CL, 28.1 and 62.8), colorectum (SIR, 10.3; 95% CL, 5.6 and 17.4), kidney (SIR, 30.6; 95% CL, 17.8 and 49.4), and melanoma (SIR, 8.5; 95% CL, 4.1 and 15.6). This led to cumulative lifetime risks for cancer of the breast at 85.2% (95% CL, 71.4% and 99.1%), thyroid 35.2% (95% CL, 19.7% and 50.7%), endometrium 28.2% (95% CL, 17.1% and 39.3%), colorectum 9.0% (95% CL, 3.8% and 14.1%), kidney 33.6% (95% CL, 10.4% and 56.9%), and melanoma 6% (95% CL, 1.6% and 9.4%).[100]

A multicenter study from France estimated cancer risks in 154 patients with a germline pathogenic variant in *PTEN*.[101] SIRs for female breast cancer were 39.1 (95% confidence interval [CI], 24.8–58.6), thyroid cancer 43.2 (95% CI, 19.7–82.1) in women and 199.5 (95% CI, 106.39–342.03) in men, melanoma 28.3 (96% CI, 7.6–35.4) in women and 39.4 (95% CI, 10.6–100.9) in men, and endometrial cancer 48.7 (95% CI, 9.8–142.3). Estimated cumulative lifetime risks by age 70 years were 85% for any cancer, 77% for female breast cancer, and 38% for thyroid cancer. Median age for developing cancer was 36 years. Although 85% were reported to have colonic polyps of any variety, risks for gastrointestinal cancer were not reported to be elevated in this series. However, a review of 211 patients with CS from the Mayo Clinic, including a review of the literature, reported a 16% lifetime risk for CRC. In this study, only 46% had a proven germline pathogenic variant in *PTEN*, and the cumulative risk for any cancer by age 70 years was 89%.[102]

In a study of 2548 patients who met "relaxed" International Cowden's Consortium criteria for CS with 5 or more gastrointestinal polyps in which at least 1 was considered hyperplastic or hamartomatous, germline pathogenic variants in *PTEN* were found in 127 (5%).[103] At endoscopy, gastrointestinal polyps were found throughout the gut, and one-half were considered "hyperplastic." In this group, 13% of those who underwent colonoscopy developed CRC (7.1% of the entire series of patients), all before age 50 years (the youngest was 35 years old), with a SIR for CRC of 224.1 (95% CI, 109.3–411.3).

A multicenter study from 9 countries of 180 carriers of germline pathogenic variants in *PTEN* estimated the cumulative risk of any cancer or Lhermitte-Duclos disease by age 60 years was 56% for men and 87% for women.[104] Increased risk was reported for cancers of the breast, thyroid, endometrium, skin, kidneys, colorectum, and lungs. An earlier report from this group on 156 patients reported that benign gastrointestinal polyps were found in 31% of patients at a mean age of 38 years (range, 18–62 years) and most were considered "hamartomas."[105] The cumulative risk of developing polyps was 70% by age 60 years. The cumulative risk of developing CRC was 18% by age 60 years (occurring between ages 53 and 62 years), suggesting that surveillance colonoscopy might not be necessary in early adult life.

Gastrointestinal Polyps and Polyposis

Gastrointestinal polyps are frequently found in patients with germline pathogenic variants in *PTEN*, with variable prevalence. Estimates suggest that 35%–93% of patients with CS have gastrointestinal polyps, but in some reports the germline basis of the disease was not known and a uniform interpretation of nonadenomatous polyps had not been established.[103,106] The wide range of estimated polyp prevalence is probably a reflection of the heterogeneity of the disease and challenges in making definitive diagnoses outside of germline tests. Gastrointestinal polyps include hyperplastic polyps, inflammatory polyps, ganglioneuromas, lipomas, adenomas, and the nonspecific term *hamartomas*.

A prospective study of 127 *PTEN* pathogenic variant carriers from 2548 subjects in an International Cowden Consortium study in which 69 underwent endoscopic studies found that 64 (93%) had gastrointestinal polyps.[103] Of that group, one-half had hyperplastic polyps, but all of the above-listed polyps (plus adenomas) were also found. The number of polyps ranged from 1 to "innumerable," and were distributed throughout the gut.

BRRS is caused by germline pathogenic variants in the *PTEN* gene.[98,107] It is a pediatric condition associated with macrocephaly, developmental delay, gastrointestinal hamartomatous polyps, and pigmented macules on the toes and glans penis. It has also been called the Bannayan-Zonana or Ruvalcaba-Riley-Smith syndrome. Inexplicably, members of the same family may have features of either BRRS or CS,[108] and some cases of BRRS do not have detectable pathogenic variants in *PTEN*.[109] Confusing overlap between CS and JPS can occur when, as mentioned above, a chromosomal deletion occurs on chromosome 10q22.3-q24.1. This leads to the loss of both *PTEN* and *BMPR1A*[28]; a situation that can also look like BRRS, also known as juvenile polyposis of infancy (see section on JPS).[110,111]

In a smaller study of 19 patients with CS (in which only 12 were shown to have germline pathogenic variants in *PTEN*), pan-colonic polyps were found in 58%, pan-gastrointestinal polyps in 42%, and the pathological interpretation of the polyps included inflammatory polyps in 95%, but also adenomas, lipomas, and ganglioneuromas.[112] Moreover, there was more than 1 pathological variety in 79% of patients, indicating the clinical heterogeneity in this entity. Esophageal glycogenic acanthosis is also found in PHTS, which is a benign condition and there is no reported increased risk for esophageal cancer.[113]

Question: What is the recommended colonoscopic surveillance in individuals identified with *PTEN* hamartoma tumor syndrome?
Recommendation: We suggest colonoscopy surveillance to begin at age 35 years (or 10 years younger than age of any relative with colorectal cancer), repeated at intervals no greater than 5 years, depending on polyp burden. *(Weak recommendation, low quality of evidence)*

Surveillance of Affected Individuals

Surveillance recommendations are provided in Table 4. The assessment at diagnosis of CS/PHTS should include a complete (and especially dermatologic and neurologic) clinical examination, mammography and breast MRI, thyroid ultrasound, transvaginal ultrasound, upper gastrointestinal endoscopy, colonoscopy, and renal ultrasound. Although there are no data regarding risk-reduction surgery in women with CS, the option for risk-reducing mastectomy and hysterectomy should be discussed on a case-by-case basis.

The risk of CRC in patients with CS is estimated to be up to 9%–18% lifetime risk with mean age at diagnosis of 44 years, but ranging from 35 to 49 years.[100,102,103,105,114,115] Consequently, expert opinion recommends colonoscopy starting at age 35 years unless symptomatic or if a close relative has had colon cancer before age 40 years, then start 10 years before the earliest known colon cancer in the family and repeat every 5 years or more frequently if the patient is symptomatic or polyps are found. This recommendation differs from a recent American College of Gastroenterology Guideline,[32] which recommends initiating colonoscopy at age 15 years. Recent evidence suggesting later onset of significant colon cancer risk informed our recommendations.

Colectomy is rarely required in patients with CS and is reserved for patients with CRC or in whom surveillance and clearing of premalignant lesions is not endoscopically feasible.

Breast Cancer

The management of breast cancer risk begins at age 25 years with clinical breast examination every 6–12 months; annual mammography and breast MRI surveillance starting between ages 30 and 35 years or 5–10 years before the earliest known breast cancer in the family.[49] In patients with PHTS, referral to a breast cancer specialist for management of breast cancer surveillance is reasonable and a multidisciplinary approach, including a breast surgeon, is recommended when prophylactic mastectomy is being considered.

Endometrial Cancer

The management of endometrial cancer risk begins between the ages of 30 and 35 years. Endometrial cancer can often be detected early on the basis of symptoms, and women should be educated regarding seeking medical attention on the basis of symptoms, including abnormal uterine bleeding or postmenopausal bleeding. Endometrial biopsy is sensitive and specific for endometrial cancer and surveillance via biopsy every 1–2 years can be considered.[33,49]

Thyroid Cancer

An annual thyroid ultrasound should be performed, beginning at the time of PHTS diagnosis (including in childhood).[33,49]

Renal Cancer

The recommended management of kidney cancer risk is an annual renal ultrasound and/or renal MRI starting at age 40 years if there is a family history of renal cancer, or every 2 years if not.[33,49]

Melanoma

The management of melanoma risk includes an annual clinical skin examination beginning at age 18 years.[33]

Summary

Germline pathogenic variants in *PTEN* are associated with variety of gastrointestinal hamartomatous polyps and a markedly increased risk of cancer, but largely in non-gastrointestinal organs. There is a moderate increase in the risk of CRC, but it may be that the age of risk is such that colonoscopic surveillance can be withheld until age 35 years or later or 10 years younger than the age of the youngest relative with CRC. However, the reports of CRC risk have been variable,[95,116] and no surveillance recommendation has been rigorously evaluated. The principal organs at risk for cancer include the breast, thyroid, endometrium, and colorectum.

Hereditary Mixed Polyposis Syndrome

The Genetic Basis of the Disease and Cancer Risk

HMPS is a rare autosomal dominant disease reported in only a few families. It is characterized by attenuated colonic polyposis. The polyps include adenomas, hyperplastic, and a particular polyp with an admixture of variable histologies including adenomatous, hyperplastic, juvenile, and mixed polyps.[117] In the original HMPS kindred described by Whitelaw et al,[118] 13 members were diagnosed with CRC and 23 developed multiple polyps of several different histologic types (adenomatous, hyperplastic, and juvenile). HMPS has been associated with large duplications of the promoter region or entire *GREM1* gene.[119–121] These unusual pathogenic variants increase the expression of the gene product, which then inhibits the bone morphogenetic protein (BMP) pathway.[119] This promoter duplication was found in 0.7% of Ashkenazi Jews in Israel who met clinical criteria for Lynch syndrome.[120] The largest series reported 4 families with 16 affected members; the onset of polyposis starts in the late 20s, which is when colonoscopic surveillance should begin.[122] There are not enough data to know the optimal surveillance intervals or whether extraintestinal neoplasia is a risk. The underlying genetic basis of the majority of HMPS families is unknown.

Future Research Considerations

The hamartoma syndromes are rare and it is difficult for single institutions or even collaborative centers to accumulate enough cases and follow them prospectively long enough to develop robust conclusions about cancer risk. Modeling, simulation, and collaborative multicenter clinical studies can be used to help clarify the benefits and risks of various interventions and surveillance programs. The management of these diseases changes dramatically when the patient matures from childhood to adulthood—which is where almost all of the cancer risk lies. Important knowledge gaps are listed in Table 5 and expanded upon below.

Peutz-Jeghers Syndrome

As indicated above, *STK11/LKB1* pathogenic variants result in up-regulation of inflammatory cytokines and promotion of overgrowth of both stromal and normal gastrointestinal epithelium, driving polyp formation (Table 5). Up-regulation of cytokines is associated with hyperactivation of JAK-STAT, which contributes to inflammation and cancer. Inhibition of JAK-STAT significantly reduced polyp growth in mice. Consequently, the JAK inhibitor ruxolitinib (already clinically approved for myeloproliferative disease) may have therapeutic potential in patients with PJS.[21] Also, LKB1 activity inhibits the activation of adenosine monophosphate–dependent protein kinase. Loss of LKB1 activity results in adenosine monophosphate–dependent protein kinase activation with up-regulation of mTORC1 signaling contributing to growth of PJS polyposis. Targeting of adenosine monophosphate–dependent protein kinase activation is currently being investigated.[123]

Juvenile Polyposis Syndrome

Of note is the mouse model of juvenile polyposis created by a conditional knockout of the *SMAD4* gene only in T-cell populations.[73] These animals spontaneously developed massive polyps within the gastroduodenal region. The epithelium in the polyps contained increased expression of pro-inflammatory cytokines, particularly interleukin-11, a cytokine known to promote gastric epithelial cell survival and hyperplasia with evidence of increased TH17 cell activity. This suggests possible therapeutic targets for the future chemoprevention of juvenile polyposis.

Summary and Conclusions

Among the gastrointestinal hamartomatous polyposis syndromes, PJS is the best understood. The polyps are readily identified as PJ polyps pathologically, and only 1 known gene (*STK11*) is associated with this entity. The phenotype is clinically distinct. Not all patients (or families) have detectable germline pathogenic variants in *STK11*, so additional genes in this pathway are possibly contributors to this entity. The polyps may evolve through an expansion of elements of the gut stroma due to haploinsufficiency of *STK11*. In children, the main risks are for gastrointestinal obstruction and bleeding. Later in adult life, a very high risk of intestinal and extraintestinal cancers exists. The major organs at risk for cancer (in order of decreasing relative risk) include the small intestine, stomach, pancreas, colon, esophagus, ovary, lung, uterus, and breast, with estimated lifetime risks for any cancer reaching >90%. The ovaries and testes are also at risk for rare variant tumors. The

Table 5. Areas Requiring Further Investigation in Hamartomatous Polyposis Syndromes

1. Discover the germline variants in families with clinically recognizable syndromes who do not have germline mutations in the genes known to be associated with these syndromes.
2. Understand the effects of haplo-insufficiency of *STK11* in PJS and the *SMAD4* in JPS on the development of polyposis.
3. Identify safe and effective pharmacological interventions for the inhibition of polyp formation children and adults with the hamartomatous polyposis syndromes.
4. Determine whether pharmacological intervention can mitigate cancer risk in PJS and JPS in adults (independent of the polyposis risk).
5. Develop simulation models in adults with a hamartomatous polyposis syndrome to determine the optimal endoscopic frequency.
6. Design and implement studies to determine the best imaging modalities and surveillance intervals in adults with a hamartomatous polyposis syndrome.
7. Determine whether the hamartomatous phenotype in pediatric patients predicts the cancer risk in adulthood.
8. Perform outcomes studies evaluating the transition of care in pediatric polyposis patients entering adult life, including outcomes such as compliance with surveillance.
9. Determine difference in phenotype and cancer risk in individuals who meet clinical criteria, but do not have an identifiable pathogenic variant compared to those with a germline pathogenic variant in a hamartomatous polyposis syndrome.
10. Determine the lifetime cancer risks in patients with a pathogenic variant, but without clinical manifestations (those identified incidentally on multigene panel testing).
11. Quantify the frequency of mosaicism as a cause of the hamartomatous polyposis syndromes.
12. Determine the optimal modality of small bowel evaluation in individuals with PJS.

screening and surveillance strategies change dramatically when the children reach adulthood.

JPS has principal risks for obstruction and bleeding in the pediatric ages, but the management in adults shifts to cancer risks in the stomach and colon. Importantly, unlike PJS, the gastrointestinal cancers tend to arise within the juvenile polyps, suggesting that polyp removal might prevent cancer. Cancer risk is linked to germline pathogenic variants in the *SMAD4* gene rather than the *BMPR1A* gene. The polyps are histologically inflammatory in nature, and their growth may be driven by haploinsufficiency of *SMAD4* in the immune cells of the polyp stroma. The management focuses on the polyps in children and cancers later in life, when endoscopic approaches are the mainstay of surveillance.

The hamartoma syndromes associated with germline pathogenic variants in *PTEN* raise a completely different clinical challenge. Although nearly all patients with PHTS have a variety of different hamartomatous gastrointestinal polyps, studies suggest an increased risk of cancer in this setting.[100,103] The extracolonic cancer risks are greatest for the breast, thyroid, melanoma, and endometrium. The absolute risk for CRC appears to be increased, ranging from 9% to 18% during a lifetime, and the rest of the gastrointestinal tract does not have an established increase in cancer risk. The age for beginning surveillance for CRC remains to be determined, but the early onset of CRC provides some suggestions. Be aware that the *PTEN* gene and *BMPR1A* are located near one another on chromosome 10q, and that large-scale chromosomal deletions could adversely affect both genes, complicating the clinical picture. Long-term prospective studies of mutation carriers are still needed to further clarify the risk of cancer and the role of surveillance in these syndromes. With increases in genetic testing and evaluation, future studies will be conducted with more robust cohorts of genetically characterized, less heterogeneous populations. However, there is also a need to study patients and families with unusual phenotypes where no genotype can be found.

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Conflicts of interest
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