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Colorectal cancer risk in hamartomatous polyposis syndromes

Fábio Guilherme Campos, Marleny Novaes Figueiredo, Carlos Augusto Real Martinez

Fábio Guilherme Campos, Surgery at University of São Paulo, Medical School, São Paulo SP 01411-000, Brazil
Fábio Guilherme Campos, Colorectal Surgery Division, Gastroenterology Department, Hospital das Clínicas, University of São Paulo, Medical School, São Paulo SP 01411-000, Brazil
Marleny Novaes Figueiredo, Colorectal Surgery Division, University of São Paulo, Medical School, São Paulo SP 01411-000, Brazil
Carlos Augusto Real Martinez, Surgery at University of Campinas, Medical School (UNICAMP), São Paulo 01411-000, Brazil
Carlos Augusto Real Martinez, Colorectal Surgery Division, Gastrocentro Hospital, University of Campinas, Medical School, São Paulo 01411-000, Brazil
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Correspondence to: Fábio Guilherme Campos, MD, Colorectal Surgery Division, Gastroenterology Department, Hospital das Clínicas, University of São Paulo, Medical School, Rua Padre João Manoel, 222 Cj 120, São Paulo SP 01411-000, Brazil. fgmcampos@terra.com.br
Telephone: +55-11-30647010
Fax: +55-11-30610108
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Abstract

Colorectal cancer (CRC) is a major cause of morbidity and mortality around the world, and approximately 5% of them develop in a context of inherited mutations leading to some form of familial colon cancer syndromes. Recognition and characterization of these patients have contributed to elucidate the genetic basis of CRC. Polyposis Syndromes may be categorized by the predominant histological structure found within the polyps. The aim of the present paper is to review the most important clinical features of the Hamartomatous Polyposis Syndromes, a rare group of genetic disorders formed by the peutz-Jeghers syndrome, juvenil polyposis syndrome and PTEN Hamartoma Tumor Syndrome (Bannayan-Riley-Ruvalacaba and Cowden Syndromes). A literature search was performed in order to retrieve the most recent and important papers (articles, reviews, clinical cases and clinical guidelines) regarding the studied subject. We searched for terms such as "hamartomatous polyposis syndromes", "Peutz-Jeghers syndrome", "juvenile polyposis syndrome", "juvenile polyp", and "PTEN hamartoma tumour syndrome" (Cowden syndrome, Bananyan-Riley-Ruvalcaba). The present article reports the wide spectrum of disease severity and extraintestinal manifestations, with a special focus on their potential to develop colorectal and other neoplasia. In the literature, the reported colorectal cancer risk for Juvenile Polyposis, Peutz-Jeghers and PTEN Hamartoma Tumor Syndromes are 39%-68%, 39%-57% and 18%, respectively. A review regarding cancer surveillance recommendations is also presented.

Key words: Hereditary GI cancer syndromes; Peutz-Jeghers; Juvenile polyposis; Cowden syndrome; PTEN tumor

Core tip: This is a brief review about clinical presenta-

tion, diagnosis, molecular features and surveillance recommendations regarding hamartomatous polyposis syndromes: Peutz-jeghers syndrome, juvenil polyposis Syndrome and PTEN Hamartoma Tumor Syndrome (Bannayan-Riley-Ruvalacaba and Cowden Syndromes).

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INTRODUCTION

Colorectal polyps may be histologically classified as neoplastic, hyperplastic, hamartomatous or inflammatory. Some of these polyps may develop sporadically or as part of a polyposis syndrome. Hereditary Polyposis Syndromes account for approximately 1% of all cases of colorectal cancer (CRC) and are associated with a broad spectrum of extra-colonic tumors. Each syndrome has its own genetic basis, polyp histology and distribution, clinical features, and malignancy risk.

Taking into account the histological nature of the polyp, the gastrointestinal syndromes may derive from adenomas (familial adenomatous polyposis, MutYH-associated polyposis), from hyperplastic polyps (serrated polyposis syndrome), from hamartomas [Peutz-Jeghers Syndrome (PJS), Juvenile Polyposis Syndrome (JPS), PTEN Hamartoma Tumor Syndrome] or from mixed polyps (Hereditary Mixed Polyposis Syndrome).

Hamartomatous polyp usually appear macroscopically as pedunculated, cherry-red lesions. They vary in size and its characteristic histological structure allows the distinction between a Peutz-Jeghers and Juvenile Polyp[1]. Peutz-Jeghers polyps (Figure 1) are tipically multilobulated with a papillary surface and branching bands of smooth muscle covered by hyperplastic glandular mucosa. A Juvenile Polyp (Figure 2) exhibits a normal epithelium with a dense stroma, an inflammatory infiltrate and a smooth surface with dilated, mucus-filled cystic glands in the lamina propria. For this reason, it might be difficult to distinguish it from an inflammatory polyp.

The clinical significance of the Hamartomatous Polyposis Syndromes lies on their association with colorectal and other extracolonic malignancies (gastrointestinal, urogenital, breast and thyreoid)[2]. Thus, knowledge of their genetic basis and clinical expressions help establish diferential diagnosis and allow the construction of screening, surveillance and treatment recomendations, that should differ from the general population.

Genetic data and prevalence of PJS, JPS and PTEN Hamartoma Tumor Syndrome (Bannayan-Riley-Ruvalacaba and Cowden Syndromes) are presented in Table 1.

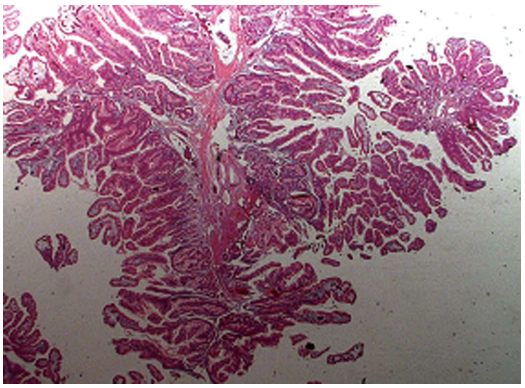

Figure 1 Histological features of a Peutz-Jeghers polyp. Note that they are typically multilobulated with a papillary surface and branching bands of smooth muscle covered by hyperplastic glandular mucosa.

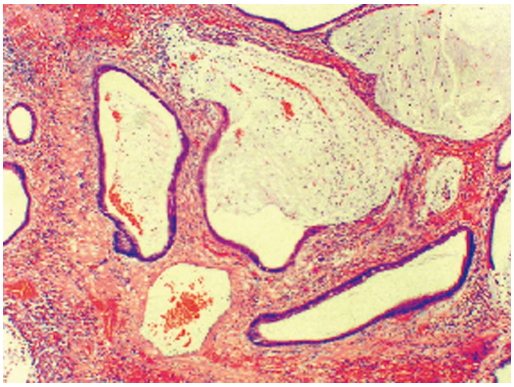

Figure 2 A Juvenile Polyp exhibiting a normal epithelium with a dense stroma, an inflammatory infiltrate and a smooth surface with dilated, mucus-filled cystic glands in the lamina propria.

Table 1 Genetic features and prevalence of pure Hamartomatous Polyposis Syndromes

Syndrome	Mode of inheritance	Gene	Incidence
Juvenile Polyposis	AD	*SMAD4/DPC4* *BMPR1A*	1:100 to 1:160 thousand
Peutz-Jeghers	AD	*STK11/LKB1*	1:60 mil a 1:300 thousand
BRRS	AD	*PTEN*	Rare
Cowden	AD	*PTEN, SDH* and *KLLN* epimutations	1:200 thousand

BRRS: Bannayan-Riley-Ruvalacaba syndrome; AD: Autosomal dominant; *SDH*: *Succinate dehydrogenase* (B and C subunits); *KLLN*: *p53 target* gene.

The aim of the present paper was to review the most important clinical features of the Hamartomatous Polyposis Syndromes, focusing on their potential to develop neoplasia, especially colorectal. This review was based on a literature search in order to retrieve the most recent and important papers (articles, reviews, clinical cases and clinical guidelines) regarding the subject. We searched for terms such as "hamartomatous polyposis syndromes", "PJS", "JPS", "juvenile polyp", and "PTEN hamartoma tumour syndrome" (Cowden

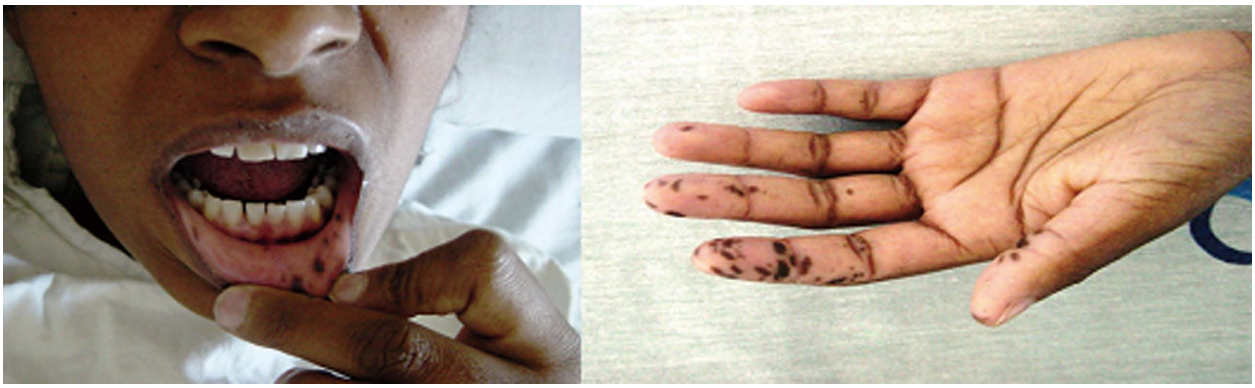

Figure 3 Mucocutaneous pigmentation in Peutz-Jeghers Syndrome.

Table 2 Clinical features and colon cancer risk in Hamartomatous Polyposis Syndromes, according to literature series

Syndrome	Main clinical features polyp distribution	Increased risk of other tumors	Colon cancer risk
Juvenile Polyposis	Juvenile polyps Distribution: large bowel (mainly), small bowel, stomach	Gastric and colorectal	39%-68%
Peutz-Jeghers	Peutz-Jeghers polyps Typical melanotic oral and dermic pigmentations Distribution: small bowel, large bowel, stomach	Gastric, small bowel, pancreas, colorectal, ovary, uterus, breasts, sex cords	39%-57%
PTEN	Mucocutaneous tumors (multiple trichilemmomas) Distribution: Small bowel, large bowel, stomach	Breast, thyroid, retina and uterus cancer	18%

syndrome, Bananyan-Riley-Ruvalcaba).

Table 2 presents the main clinical features and the reported malignancies described in association with these syndromes, revealing how heterogeneous this group is regarding polyp distribution and neoplasia risks.

The Hereditary Mixed Polyposis Syndrome is not discussed here cause this entity encompass polyps with distinct histologies (adenomas, serrated, hyperplastic, juvenile, mixed juvenile-adenomatous or hyperplastic adenomatous)[3]. In the same context, other syndromes where hamartomatous polyps are present (Multiple endocrine neoplasia type 2B, Gorlin, Neurofibromatosis type 1, Birt-Hogg-Dubbé and Cronkhite-Canada) have not either been included in this revision.

PJS

History and genetics

The association of mucosal pigmentation and gas trointestinal polyposis was first described by the English Sir Jonathan Huchinson in 1896. Although this condition has received many denominations throughout time, it was only after the work of the Dutch Peutz[4] (1886-1957) in 1921 and the American Jeghers[5] (1944), who firmed the disease features, that this association was nominated PJS.

Gastrointestinal polyps from PJS present distinct features from those found in other Hamartomatous Syndromes, such as the presence of a muscular component infiltrating the conective tissue in a pattern of ramification. Although a good pathologist should be able suggest the diagnosis based on histology, the establishment of a hamartomatous polyposis syndrome should be based on molecular features, as clinical manifestations may differ slightly.

PJS is inherited by an autosomal-dominant gene that is responsible either by the polyposis and the pigmentation. Nevertheless, some isolated cases have been reported. The genetic mutation occurs in a supressor gene that codifies the serina/threonina kinase (LKB1 ou STK11), located in chromossome 19p13.3[6]. Germline mutations of this gene lead to hamartoma formation, and other somatic mutations may transform hamartomas into adenomas and subsequently carcinomas[7]. The multiple mutations identified in gene LKB1 are responsible by the phenotypic variability of PJS, including the development of aggressive cases and other that never developed cancer.

Clinical features

PJS is characterized by the triad mucocutaneous melanic pigmentation, intestinal polyposis and familial history. Diagnostic criteria of PJS include two or more hamartomatous polyps in the gastrointestinal tract *or* one confirmed Peutz-Jeghers polyp with a family history of PJS or typical perioral pigmentation[8].

The pigmentation is manifested by dark black or blue spots around the lips, eyes and extremities (hands and feet), but are also found in the neck, thorax and perineum. They are formed by smooth melanin deposits in a round or oval shape, rarely confluent, with a 1 cm maximal diameter (Figure 3). They may appear since the neonatal period or even after the begining of the gastrointestinal symptoms[9].

The most important clinical manifestations are

Table 3 Cumulative cancer risk by site and age in Peutz-Jeghers Syndrome (Hearle *et al*[18])

Cancer/Age	20 yr	30 yr	40 yr	50 yr	60 yr	70 yr
All cancers	2	5	17	31	60	85
Gastrointestinal	-	1	9	15	33	57
Breast	-	-	8	13	31	45
Gynecological	-	1	3	8	18	18
Pancreas	-	-	3	5	7	11
Lung	-	-	2	4	13	17

secondary to the polyps, that may affect the small bowel (70%-95%), colon (27%), stomach (25%) and colorectum (24%-50%); the jejunum is more commonly involved than duodenum and ileum[10]. Gastrointestinal symptoms usually develop during the second and third decades, with abdominal pain resulting from hiperperistalism or polyp invagination. PJS polyps may may also cause obstruction, prolapse through the rectum, bleeding and anemia. Isolated polyps may rarely develop in the absence of other clinical features and are not associated with gastrointestinal cancer risk[11].

Risk of malignancy

Since its classical description in 1944[5], numerous cases of PJS associated with gastrointestinal (duodenum, jejunum, pancreas, stomach and colon) or extra-intestinal carcinomas (breast, ovary, cervix, thiroid, lung, pancreas and testicles) have been reported[2]. The supposed carcinogenesis is based on the controversial idea that the hamartomas may develop carcinomas as adenomatous and malignant alteration have been described in hamartomas[12,13].

It's been estimated that lifetime risk of any gastrointestinal cancer approaches 70% (mainly colorectal at 39% and pancreatic at 36%). Additional tumors (breast, sex chord in females, adenoma malignum of the cervix, Sertoli cell tumors of the tests, *etc.*) increase patient's lifetime risk to near 90%[14,15].

In a Dutch group of 133 PJS from 54 families, Van Lier *et al*[16] found 37% cancers, and CRC was the most common malignancy (14%). Compared to the general population, this report confirms a 9 fold increased cancer risk, a higher risk among women (20 fold) compared to men (5 fold), a 3.5 fold increased mortality rate and that gastrointestinal cancers develop at young age. In a recent paper, Beggs *et al*[17] reported a high rate of extracolonic tumors such as gastric (29%), small bowel (13%), pancreatic (36%), breast (54%), ovarian (21%), lung (15%), cervical (10%) and uterine/testicular (9% each).

In another paper[18], CRC turned to be the most common luminal gastrointestinal cancer (17/40) among 419 patients with 297 documented mutations, with a cumulative risk of 3%, 5%, 15% and 39% at ages 40, 50, 60 and 70 years, respectively (Table 3). The risk of developing cancer at any site was four fold that observed in the general population. In females with PJS, the risk of breast cancer was also increased six fold over the population and is comparable to the BRCA mutations.

Similarly, in a metanalysis to evaluate the risk of many tumors, Giardiello *et al*[19] grouped 107 men and 106 women from 79 families, and reported estimated cumulative cancer risks of 54% for breast, 39% for colorectal, 36% for pancreas, 29% for stomach and 21% for ovarian cancer by 64 years of age.

Management of PJS is based on the treatment of symptomatic benign conditions, large polyps and surveillance of malignant tumors. For this reason, endoscopic resection of polyps larger than 1.5 cm is advisible, even in asymptomatic patients. Patients scheduled to a conservative follow-up must undergo periodic examination after 30 years of age, with bienal evaluation of superior and inferior digestive tract, anual pelvic, testicular and abdominal ultrasound (mainly for pancreas) and anual mammography after 25 years Family member should be equally examinated[20].

JPS

Genetics and history

JPS is a rare genetic disease that exhibits incomplete penetrance and heterogeneity, with positive familiar history appearing in only 20% to 50% of patients. There were described germinative mutations in the *SMAD4* (*MADH4*) (chromosome 18q21.1) and in the *BMPR1A* (chromosome 10q 21-22) genes[21,22]. The genetic mutations have not been identified in all cases of JPS. *SMAD4* mutations are more common and predispose to polyposis in the upper digestive tract[23]. *BMPR1A* mutations are found in 40%-100% of families without *SMAD4* mutation.

Pathological features of polyps in children were described many years ago, at the same time when the term juvenile polyp was coined by Horrilleno *et al*[24] in 1957. But it was Morson in 1962 who established those polyps as hamartomas[25], and McColl *et al*[26] in 1964 defined the JPS as a distinct entity.

Clinical features

When discovered as isolated sigmoid or rectal lesions during infancy, Juvenile polyps may cause bleeding, hematochezia, intussusception, or even self-amputation (Figure 4). In this cases, the risk of malignization is very low. Once recognized, they should undergo endoscopic resection.

On the other hand, development of JPS is much more less frequent, being characterized by numerous hamartomatous polyps in the intestine and other parts of the gastrointestinal tract. Diagnostic criteria include: (1) more than 5 juvenile polyps in the colorectum; and (2) multiple juvenile polyps throughout the gastrointestinal tract or one or more polyp and a positive family history of juvenile polyposis[27-29].

During infancy, the polyposis may affect all the digestive tract, and the prognosis is dependent on this

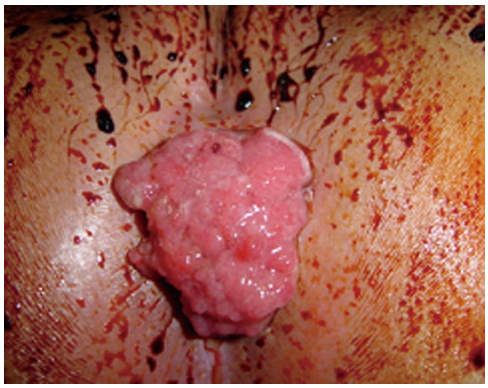

Figure 4 Prolapsed polyp through the anus in a patient with Juvenile Polyposis.

involvement (referred as JP of infants). These cases are not associated with familiar history[28]. Within the other forms of the disease, the polyposis may appear during the second or third decades, more rarely (15%) in adults. Within the gastrointestinal tract, the most affected sites are the colorectum (98%), stomach (14%), jejunum/ileum (7%) and duodenum (2%)[29]. Similarly, in 262 patients with PJS, Höfting *et al*[30] reported colorectal, gastric and intestinal lesions in 98%, 13.6% and 8.8% of them, respectively.

Some patients may refer familar history suggesting an autosomal dominant pattern of inheritance[31]. Some congenital abnormalities have been described in 15%-20% (midgut malrotation, cardiac anomalies, cleft palate, supranumerary teeth, macrocephaly, hydrocephalus, polydactyly, mesenteric lymphangioma, *etc.*), mainly in patients not referring familiar history. *SMAD4* mutations are associated with JPS and hereditary hemorrhagic telangiectasia, and some carriers may present symptoms from both conditions. Conective tissue disorders have been documented in approximately one-fifth of these patients, such as enlarged aortic root, aortic and mitral insufficiency, aortic dissection and others[32].

Risk of malignancy

Carcinomas from many locations have been reported within a wide variation of lifetime cumulative cancer risk[33,34]. The estimated lifetime risk of gastrointestinal cancer in JPS family members varies from 9% to 50%[22]. Although most of these tumors consist of colon cancer, tumors arising in the stomach, upper gastrointestinal tract and pancreas have also been reported. The estimated risk for CRC is 17%-22% by age 35[35] and a lifetime risk of gastric and duodenal cancer of 10%-21%[15,36].

Specialized centres have reported adenomatous features or adenomas associated with juvenile polyps in 2 a 15% of the patients, suggesting a possible histogenical mechanism to carcinogenesis[33,37,38]. Otherwise, it is not known if those adenomas are formed through a total conversion of a juvenile polyp or if they represent "*de novo*" lesions.

Isolated juvenile polyps should be endoscopically or surgically excised, depending on location. In PJS patients, regular endoscopic examinations is considered a more conservative approach after 15 years of age. There is a tendency to manage the patient according with symptoms severity and polyp features (number, accelerated growing and displasia). In the case of few polyps, polypectomy is indicated. A prophylactic colectomy (Ileal-rectal anastomosis or pouch surgery has been advocated by others, especially in patients with adenomatous features, displasia and a strong history of CRC[39,40].

Some studies showed that up to half of patients required a completion proctectomy after initial total colectomy. Annual endoscopic surveillance of the rectum and ileal mucosa is advisable after surgery in order to detect recurrent polyps. First-degree relatives must be screened by colonoscopy from the second decade of life up to the age of 70[15,22,31].

PTEN HAMARTOMATOUS TUMOR SYNDROME

Genetics and clinical features

PTEN Hamartomatous Tumor Syndrome (PHTS) groups patients diagnosed with either Cowden (CS) or Bannayan-Riley-Ruvalcaba syndromes (BRRS). Both are inherited in an autosomal dominant pattern and develop due to mutations of the *PTEN* gene (phosphatase and tensin homolog), a tumor suppressor gene located on 10q23.3. PTEN mutations have been recently found in only 25% of CS patients. Other patients were described as having SDH gene mutations (succinate dehydrogenase B and C) or KLLN epimutations in 10% and 30% of the cases, respectively[41].

While BRRS is usually diagnosed during infancy, CS prevails in adults. Mucocutaneous features allow early recognition of CS, manifesting before the neoplastic changes. They appear in 80% of the patients and are represented by multiple facial triquilemomas, oral mucosa papilomatosis and hand queratosis (Figure 5). Colorectal polyps are small, sessile and asymptomatic, being found in 35%-65% of patients[42].

Cowden's syndrome should be screened for the development of various cancers, such as thyroid (10%), breasts (30%-50%), endometrium and colorectal. Less than 10% of patients develop Central Nervous System tumors[43].

BRRS is characterized by intestinal polyposis (45% of patients) associated with dermatological lesions (pigmented macules of the glans penis)[44]. Extraintestinal manifestations have been described such as macrocephaly, subcutaneous lipomas, vascular malformations, high birth weight and central nervous system anomalies[45].

Cancer risks in PHTS

CRC risk in PHTS has been evaluated in the past few years. In a study of 127 patients with PTEN mutations

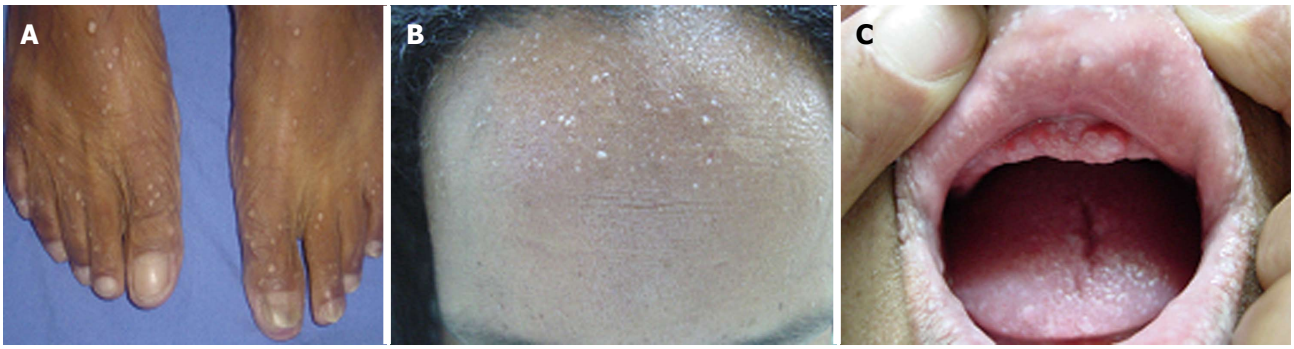

Figure 5 Feet queratosis (A), multiple facial triquilemomas (B) and oral mucosa papilomatosis (C) in a patients with Cowden's Syndrome.

Table 4 Recommendations for screening and surveillance according to the literature[17,40,48-51,53]

Syndrome	Screening	Work-up	Interval
Peutz-Jeghers	18-25 yr	Endoscopy (upper/lower)	2-3 yr
	25 yr	MRI and mammography	Annual
	10 yr	Testicular examination	Annual
	30 yr	MRI or CT (pancreas)	1-2 yr
Juvenile Polyposis	15-18 yr	Upper endoscopy	1-3 yr
		Colonoscopy	1-3 yr
		Upper endoscopy and video capsule endoscopy for HHT	3 yr
PTEN	After 25 yr	Colonoscopy	3-5 yr
		Mamography/thyroid US	Annual

US: Ultrasound; CT: Computorized tomography; MRI: Magnetic resonance imaging; HHT: Hereditary hemorrhagic telangiectasia.

(62 colonoscopies), Heald *et al*[46] found a wide spectrum of polyps and 13% CRC diagnosed in patients under 50 years of age. In a multi-national cohort of 3399 patients with CS (368 with PTEN mutations), Tan *et al*[47] reported a significantly increased incidence of CRC (10 fold), breast (20 fold), thyroid (50 fold), endometrium (40 fold), kidney (30 fold) and melanoma (8 fold).

In a group of 156 patients from 101 families with PTEN mutations, Nieuwenhuis *et al*[48] reported a cumulative risk of 70% for benign gastrointestinal polyps and 18% for CRC at age 60, respectively. This three to four-fold increase in CRC risk led the authors to recommend colonoscopy after 40 years of age.

Recommendations for screening and surveillance

Besides rare, recognition and screening of any Hamartomatous Polyposis Syndromes is a great deal for the patient, as these disorders may manifest important complications due to polyp bleeding or intestinal obstruction. Family members at risk should be fully evaluated after the second decade of life even if they are asymptomatic.

Once diagnosis is established, upper and lower endoscopic investigation (as well as radiological images) should be performed every 2 to 5 years[42,46]. Moreover, especial attention should be driven to extraintestinal malignancies at risk such as breasts, thyroid, uterus and others[47].

Gastrointestinal surveillance aims to reduce the polyp burden, its complications and cancer development. Furthermore, polyp management may reduce surgical intervention and prevent resection or emergency surgery, as demonstrated for PJS[49]. As the chance of malignant degeneration of colonic polyps has also been recognized in all hamartomatous polyposis syndromes, screening colonoscopy should be advised for all patients. Current recommendations for screening and surveillance according to recent publications[17,40,48,50,51] are resumed in Table 4.

Surveillance of the breast, colon and rectum and the small intestines should be established for PJS patients[51]. After comparing surveillance programs already published, Beggs *et al*[17] proposed to postpone the gastrointestinal screening till the late teens, with repeated exams each three years till 50 years of age (and each 1-2 years thereafter). Colonoscopy should be performed every 2-5 years from 25 years of age.

Recommendations regarding JPS families include colonoscopy every 1-2 years starting at 15-18 years and upper endoscopy with a 1-2 year interval from 25 years of age[22,52]. The group from the St. Mark's Hospital[53] showed that colonic polyps predominated in the right colon and that carpeting disease represents a special concern. They recommend upper and lower gastrointestinal endoscopy every 1-3 years starting at 12 years. Moreover, they advise annul full blood count and cardiovascular examination and screening for HHT (hereditary-hemorrhagic telangiectasia) symptoms (mainly A-V malformations) in *SMAD4* mutation carriers.

Finally, PTEN-mutations carriers are suggested to perform dermatological examination, neurological, psychological testing, and thyroid ultrasound from the late teens. After 30 years, women should undergo annual mammogram, endometrial examination and transvaginal ultrasound[47]. Biannual colonoscopy is advised after 40 years of age[48].

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