

Current status of familial gastrointestinal polyposis syndromes

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Abstract

Because of the rarity of familial gastrointestinal cancer-predisposing syndromes, their exploration in literature

is not extensive. In this review, an update of the clinicopathological and molecular criteria of gastrointestinal familial polyposis syndromes with potential malignant transformation is performed. In addition, a guide for screening and surveillance was synthesized and a distribution of gene mutations according to the specific syndromes and geographic distribution was included. The following inherited polyposis syndromes were analyzed: familial adenomatous polyposis, the hamartomatous familial polyposis (Juvenile polyposis, Peutz-Jeghers syndrome, Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, hereditary mixed polyposis syndrome, Gorlin syndrome, Birt-Hogg-Dube syndrome, neurofibromatosis type I and multiple endocrine neoplasia syndrome 2B), Li-Fraumeni syndrome, and MUTYH-associated adenomatous polyposis. For proper medical care, subspecialization of gastroenterologists, pathologists, and geneticists in the field of familial diseases should be introduced in the medical curriculum.

Key words: Inherited polyposis syndromes; Hereditary cancer; Stomach; Intestine; Colorectal

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Core tip: In this review the clinicopathological and histological aspects of inherited polyposis syndromes of the gastrointestinal tract are explored in detail. In addition, a guide for surveillance is proposed.

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INTRODUCTION

The familial cancer-predisposing syndromes of the

gastrointestinal tract are heterogeneous groups of diseases with the lifetime risk of gastrointestinal cancer generally low but their associated morbidities should be very attentively examined for developing specific programs of familial screening. Because these syndromes are relatively rare in the daily activity, management of their diagnosis and therapy is difficult.

These syndromes include, in particular, the following inherited polyposis syndromes: familial adenomatous polyposis (FAP), hamartomatous polyposis syndromes (Juvenile polyposis, Peutz-Jeghers syndrome, Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, hereditary mixed polyposis syndrome, Gorlin syndrome, Birt-Hogg-Dube syndrome, neurofibromatosis type I, and multiple endocrine neoplasia syndrome 2B), Li-Fraumeni syndrome, and *MUTYH*-associated adenomatous polyposis. They are usually diagnosed from the stomach to the rectum, the esophagus and anal canal being only secondarily involved^[1-30]. Although Cronkhite-Canada- and Proteus syndrome^[22] are also polyposis syndromes of the gastrointestinal tract, they do not present familial predisposition and are not included in this paper.

In this review, an update of clinicopathological criteria used for diagnosis of the inherited cancer-predisposing syndromes of the gastrointestinal tract and identification of eligible families was performed, followed by revision of criteria of screening and surveillance in the daily practice. A synthesis of data regarding the molecular profile of hereditary syndromes and their geographic particularities are synthesized in Table 1, based on our experience and literature data^[1-36].

CLINICOPATHOLOGICAL AND MOLECULAR FEATURES

FAP

FAP is a rare autosomal dominant syndrome (1:8300 live births), that is characterized by the presence of hundreds to thousands of adenomatous polyps scattered throughout colorectal mucosa^[36] (Figure 1). It is produced through mutations of the adenomatous polyposis coli (*APC*) gene that was firstly described in 1991^[1]. The risk for rectal adenocarcinomas is 87% up to 45 years of age and rise by 100% in older ages, but other colorectal segments can also be affected^[1,28]. FAP-related colorectal cancer (CRC) represent < 1% of all CRC cases^[36].

Other extracolonic associated lesions include small bowel, periampullary and gastric adenomatous polyps, adrenal adenomas and carcinomas^[32]. The lifetime risk of occurrence of duodenal polyps is almost 100%^[28]. The second and third portion of duodenum, including the periampullary region, are more predisposed to present adenomas^[28].

Regarding the stomach, the adenomatous polyps were reported to occur in 12%-84% of patients with FAP but less than half of them are focally dysplastic

and below 1% present malignant transformation^[2,3]. They are located mostly in the antrum, followed by gastric fundus^[2,28]. However, fundic gland polyps can also occur sporadically not only within FAP^[2]. The reported incidence of sporadic fundic gland polyps is about 1%-2% of all middle-aged healthy females who underwent upper endoscopy, more rare in males (30% of all cases) while the familial ones are usually multiple, occur at younger ages, and have an equal gender distribution^[3]. Microscopically, the fundic gland polyps consist of cystically dilated oxyntic glands lined by parietal cells, chief cells, and neck cells, with apical mucin bubbles^[2,4,5]. Dysplasia occurs in the covering neck cells and/or foveolar epithelium and dysregulation of epithelial proliferation is immunohistochemically (IHC) proved by loss of the normal inverse topographic distribution of Ki-67 proliferation marker and the cyclin-dependent kinase inhibitor p21 (*WAF1/CIP1*)^[2,4-6]. In these cases, for unknown reasons, a more increased risk for gastric intestinal-type adenocarcinomas have been reported in Japanese and Korean populations (four-fold) while no significant risk, when compared with the general population, was encountered in the Western countries (two-fold)^[2,4-6]. Although FAP syndrome is not rare in Romanian patients, we did not have cases with associated gastric lesions (personal communication).

Gardner's syndrome is a variant of FAP characterized by *APC* mutation-related gastrointestinal polyps and associated osteomas, dental abnormalities (supranumerary teeth), epithelial and mesenchymal tumors of the skin (epidermoid cysts, lipoma, fibroma, leiomyoma), desmoid tumors (most frequently in the abdominal wall or intra-abdominal), congenital hypertrophy of the retinal pigment epithelium and tumors of the thyroid gland^[28,32,34]. Congenital hypertrophy of the retinal pigment epithelium is the commonest extracolonic manifestation of FAP that occurs in 70%-80% of patients^[28]. It is characterized by occurrence of gray-brown round lesions in the retina, the clinical significance being not known yet^[28].

In Turcot's syndrome, the FAP is associated with tumors of the central nervous system, especially medulloblastoma^[32].

The attenuated FAP (AFAP) is a less severe form of FAP that is characterized by predominance of proximally located polyps of the colon (10-99 adenomatous polyps), a later age of onset and a lower risk (lifetime cumulated risk < 70%) for developing CRC^[7,32].

MUTYH-associated polyposis

It is an autosomal recessive syndrome produced through mutations of the *mutY* homolog (*MUTYH*) gene that was firstly described in 2002 in three members of a British family^[27,28,35]. *MUTYH*-associated polyposis (MAP) is clinically similar to the AFAP, being characterized by the early-onset of multiple adenomatous polyps of the colorectal segments (10-99 adenomatous or serrated polyps), with risk for malignant transformation,

Table 1 The molecular profile and geographic particularities of inherited gastrointestinal cancer-predisposing syndromes^[1-36]

Name of the syndrome	Mutated genes	Type of mutation	Geographic particularities
FAP	APC: Exon 15 - first half (54% of patients with FAP)	Classic phenotype: mutations between codons 178 and 309, and between 409 and 1580 (exons 5-8 and 9-14) Germline truncation (C > T), especially at codons 1309 and 1061: Nonsense mutations (28%) Small insertions (10%) Small deletions (46%)	NS
	APC: Chromosome arms 5q, 8p, 17p and 18q	LOH	NS
	β -catenin: Exon 3 (15%)	NS	NS
	APC/ β -catenin (28%)	NS	NS
	K-ras: Codon 12 (3%) - associated mutation	GGT to TGT/GTT	NS
Gardner syndrome	APC: Long arm of chromosome 5	Interstitial deletion	NS
	APC: Patients with congenital hypertrophy of the retinal pigment epithelium	Truncating mutations between codons 311 and 1465	NS
	APC: Patients with desmoid tumor	Downstream codon 1400 (1445-2011)	NS
	APC: Patients with gastro-duodenal adenomas	Mutations at the 3' before codon 1395 and between codons 564 and 1493	NS
	APC: Patients with hepatoblastomas	Mutations at the 5' to the mid region between codons 141 and 1751	NS
AFAP	APC: Patients with thyroid tumors	Mutations between codons 140 and 1309	NS
	APC	Somatic G:C→T:A	NS
	APC: Exons 3 and 4 (5' end of the gene), exon 9, and the very 3' end of the gene beyond codon 1595	Truncating mutation	NS
MUTYH-associated polyposis	APC: Variants	Missense mutations I1307 K N1026S E1317Q	I1307K: almost exclusively in Ashkenazi Jewish descendants - detected in 6% of all family members, with 10%-20% lifetime risk of developing CRC N1026S: Identified in one Spanish AFAP family (all members) E1317Q: NS
	MUTYH: Located on the chromosome 1p34.3-p32.1, contains 16 exons	Germline biallelic inactivation	Absent in Asia (Japan, Taiwan, South Korea)
		Missense mutations: p.Y179C - exon 7 (c.536A > G; p.Tyr179Cys) p.G396D - exon 13 (c.1187g > A;p.Gly396Asp)	Specific for Eastern, Southern, and Central Europe, North America, European inhabitants from Canada, and Sephardi Jews
		Missense mutation p.Ala385ProfsX23 p.E410GfsX43 Missense mutation p.Y104X Missense mutation p.E480X	Absent in Finland, India, Pakistan, Tunisia, Singapore, and Ashkenazi Jewish
	MUTYH variants	Heterozygous mutations	Specific for Northern Europe Specific for Tunisia Specific for Pakistan Specific for India Asia (Japan, Taiwan, South Korea): p.Arg19; p.Arg109Trp; p.Gly286Glu Southern Europe: p.Glu480del Pakistan: p.Tyr104 India: p.Glu480
Juvenile polyposis syndrome (pure type)	K-ras: Codon 12 - associated mutation (64%), usually in patients with sessile serrated adenomas	c.34G > T	NS
	MADH4/SMAD4/DPC4: Chromosome 18q21.1 (30%)	NS	NS
	BMPR1A: Chromosome 10q23 (20%-30%) Other genes (49%) ENG: exons 11, 12 PTEN: chromosome 10q23.3	Large deletions NS	NS NS
Juvenile polyposis + hemorrhagic telangiectasia	MADH4/SMAD4/DPC4: Chromosome 18q21.1	NS	NS
	STK11: Chromosome 19p13.3 or 19q13.4 (50%-94%)	NS	NS
Peutz-Jeghers syndrome	TGF- β PTEN: Chromosome 10q23.3	NS	NS

Peutz-Jeghers syndrome + primary pulmonary hypertension	<i>ALK1/ACVRL1</i>	NS	NS
Cowden syndrome	<i>PTEN</i> : Chromosome 10q23.3 (13-85%)	Nonsense mutations missense mutations frameshift mutations Large deletions	NS
Bannayan-Riley- Ruvalcaba syndrome	<i>PTEN</i> : Chromosome 10q23.3 (60%-65%)	NS	NS
Hereditary mixed polyposis syndrome	<i>BMPRIA</i> : Chromosome 10q23 <i>GREM1</i>	NS	NS
Li-Fraumeni syndrome – classic type	<i>p53</i> : Exons 4-9 (23%-50%)	NS	NS
Unclassified/ unexplained polyposis syndromes (50%)	<i>PTEN</i> : Chromosome 10q23.3 Other genes: <i>BMPR2</i> , <i>ACRV1</i> , <i>SMAD1</i> , <i>SMAD2</i> , <i>SMAD3</i> , <i>SMAD5</i> , <i>SMAD7</i> (22%)	Nonsense mutations missense mutations frameshift mutations NS	NS

FAP: Familial adenomatous polyposis; BMPR: Bone morphogenetic protein receptor; CRC: Colorectal cancer; ENG: Endoglin; FAP: Familial adenomatous polyposis syndrome; LOH: Loss of heterozygosity; NS: Non-specified; TGF: Transforming growth factor.



Figure 1 Macroscopic aspect of the colonic mucosa in a 43 years old male with classic Familial adenomatous polyposis.

and infrequent extracolonic manifestations^[25-28]. The phenotype of MAP is less severe than classic FAP^[36]. In some of the cases, MAP-related CRC can be developed without the polyposis background, the differential diagnosis with Lynch syndrome being difficult^[35].

Juvenile polyposis syndrome

It is a rare autosomal dominant hereditary syndrome (1:100000-160000 live births) characterized by identification of 1-100 hamartomatous polyps throughout the gastrointestinal tract, mostly in the colorectal segments, diagnosed in young patients^[8-12]. Microscopically, these polyps are covered by normal columnar epithelium and present mucus-filled tortuous dilated glands lined by columnar epithelium in the lamina propria; the dense stroma is edematous and rich in inflammatory infiltrate predominantly composed of plasma cells^[8,11,13]. The clinical diagnosis is based on at least one of the following Jass's modified criteria^[6,12]: (1) Multiple juvenile polyps throughout the gastrointestinal tract; (2) At least five colorectal juvenile polyps; or (3) Any number of juvenile polyps identified in patients with a family history of juvenile polyps. These polyps can present malignant transformation, the lifetime risk being about 34%-38% for colorectal segments and 21% for stomach^[9,10,12]. Juvenile polyposis-related gastric cancers are rather produced through *SMAD4* than *BMPRIA* mutation genes^[12]. Association with hereditary

hemorrhagic telangiectasia also known as Osler-Weber-Rendu syndrome have been reported in about 20% of the cases; protein-losing enteropathy can also be associated^[9,13].

Peutz-Jeghers syndrome

This syndrome is a rare autosomal dominant inherited disorder (1:8300-200000 live births) associated with a lifetime hazard for cancer up to 93%, which occurs as a consequence of a germline mutation in the *STK11* gene^[12,14-16]. It is characterized by familial gastrointestinal hamartomatous polyposis and 1-5 mm mucocutaneous melanic spots around the mouth, in the buccal mucosa, on the fingertips and toes, and, infrequently, on the eyelid and sole of the foot^[16]. The spots occur in first years of life; the skin spots spontaneously disappear at puberty but mucosal spots remains visible per life^[16].

Regarding the polyps, the upper jejunum is most frequently involved (78%), followed by colon and stomach (24%)^[15-19]. Solitary gastric polyps can occur rarely, less than 30 cases being reported to 2012^[17]. Microscopically, the gastrointestinal hamartomatous polyps, that can undergo focal or total malignant transformation, are characterized by hyperplastic mucosal glands with periglandular proliferation of smooth muscle fibers^[16,17]. Arborizing pattern of smooth muscle proliferation is characteristic^[15,16]. In solitary polyps of the stomach, it was suggested that the branching of

the muscularis mucosae are not so well developed in the subsequent layers^[15,17]. Gallbladder, bronchi, urinary bladder, and the ureter can also present hamartomatous polyps with similar histological architecture and further possible malignization^[12].

Multiple synchronous or metachronous colonic and extra-colonic carcinomas of different organs like breast (54%), pancreas (36%), stomach (29%), ovary (21%), small bowel (13%), or other organs (cervix, uterus, testes, lung, appendix), can be associated in the same patient or his first-degree relatives, with a cumulative risk over 90%^[12,15-18]. Associated lymphomas and sex-cord tumors were also encountered^[16].

For a final diagnosis, one of the following criteria should be filled^[12,14-19]: (1) At least two histologically proved Peutz-Jeghers polyps; (2) At least one histologically proved Peutz-Jeghers polyp in a patient with specific mucocutaneous spots; (3) Identification of at least one Peutz-Jeghers polyp in a patient with at least one relative with confirmed diagnosis of Peutz-Jeghers syndrome; and (4) Specific mucocutaneous spots in a patient with at least one relative with confirmed diagnosis of Peutz-Jeghers syndrome.

Cowden syndrome

It is an autosomal dominant hereditary syndrome that occur in 1:200000 live births (more frequent in Asian population). It is characterized by synchronous or metachronous tumors in multiple organs that occur in one patient or in members of his family. This familial gastrointestinal hamartomatous polyposis occurs as a result of mutations in the phosphatase and tensin (*PTEN*) gene.

The clinical diagnosis is based on the following International Cowden Consortium major criteria, modified by the National Comprehensive Cancer Network Cowden syndrome^[9,12,14,19,20]: macrocephaly (75%-97% of the cases - 58 cm for women and 60 cm for men), multiple (at least 3) gastrointestinal hamartomas including ganglioneuromas but excluding hyperplastic polyps (50%), dysplastic gangliocytomas of the cerebellum associated with seizures, tremors, and disorders of coordination (Lhermitte-Duclos syndrome), breast cancer (37%), nonmedullary (follicular) thyroid carcinoma (16%), endometrial cancer, and macular pigmentation of the glans penis. The mucocutaneous lesions are considered as pathognomonic (major criteria) only if the following associations are identified^[12,20]: At least three trichilemmomas (at least one being biopsically proved), at least three acral keratoses, at least three mucocutaneous neuromas, or oral papillomas (at least three without biopsy or at least one biopsically proved). The minor criteria are presence of benign lesions of the breast (fibrocystic change, benign epithelial tumors), thyroid (multinodular goiter, adenoma, papillary carcinoma), single lesion of the gastrointestinal tract (adenoma, lipoma, hamartoma), at least three lipomas, testicular lipomatosis, malformations or tumors of the

urogenital tract, vascular malformations, and mental retardation ($IQ \leq 75$)^[12,19,20]. Recently, the autism spectrum disorders, colon/renal cancer, and esophageal glycogenic acanthosis (at least three) were included in the minor criteria^[12]. For a final diagnosis, the following associations are necessary: at least three major criteria [at least one being macrocephaly, Lhermitte-Duclos syndrome (in adults), or gastrointestinal hamartomas], two major and three minor, or three minor criteria^[12,19,20]. Absence of one of the associated criteria allows the diagnosis of the "Cowden syndrome-like family"^[19].

Gastrointestinal hamartomas occur in 50% of patients with Cowden syndrome, being currently considered the second most common feature, after macrocephaly^[19]. The estimated lifetime risk for malignancy at the age of 70 is 85% for any cancer, 77%-85% for breast and 35%-38% for thyroid cancer, 33% for renal cancer, 28% for endometrial, 7%-15% for CRC and 6% for melanoma^[12,15,20,21]. Gastric malignancy is rarely associated, 1/100 patients with Cowden syndrome being affected^[20].

Other hamartomatous polyposis syndromes

Besides Cowden syndrome, *PTEN* gene mutations were described in patients with Bannayan-Riley-Ruvalcaba and hereditary mixed polyposis syndrome^[7,12].

Bannayan-Riley-Ruvalcaba syndrome is an autosomal dominant disorder characterized by hamartomatous polyps of the small intestine and colon (25% of the cases) along with genital spots, macrocephaly, subcutaneous/visceral lipomas including lipomatosis of the glans penis, hemangiomas, and mental retard^[7].

In some cases, identification of the specific genetic syndrome is very difficult, the recommended diagnosis being hereditary mixed polyposis syndrome. In this category, association of atypical juvenile polyps, hyperplastic polyps, sessile serrated adenomas, and adenomatous polyps can be associated with increased risk for CRC^[7].

Other very rare familial hamartomatous syndromes that can include hamartomatous polyps of the gastrointestinal tract are the following^[7,12]: Gorlin syndrome (consequence of *PTCH1* mutations), characterized by hyperkeratosis of palms, soles, and jaw, skeleton abnormalities, macrocephaly, frontal bossing, and associated medulloblastoma and basal-cell carcinomas; multiple endocrine neoplasia syndrome 2B (consequence of *RET* mutations), characterized by neuromas of the lips and tongue, and associated pheochromocytoma and medullary thyroid cancer; neurofibromatosis type I (consequence of *NF1* mutations), characterized by café au lait spots, axillaries and inguinal freckling, and associated neurofibromas, gliomas, malignant peripheral nerve sheath tumors, and tumors of the breast; and Birt-Hogg-Dube syndrome (consequence of *FLCN* mutations), characterized by spontaneous pneumothorax and associated fibrofolliculomas of the skin, and renal tumors.

Li-Fraumeni syndrome

It is an autosomal dominant hereditary cancer syndrome characterized by mutations in the *p53* gene that determines occurrence of leukemia, carcinomas of the breast and adrenal glands, brain tumors, sarcomas of the soft tissues and bone, *etc*^[19-21,23-26]. The classic Li-Fraumeni syndrome criteria of eligible families include one family member diagnosed with sarcoma before 45 years of age, a first-degree relative with any type of cancer before 45 years of age, and a first/second relative with any cancer diagnosed before 45 years of age or a sarcoma at any age^[19,20]. Similar to Cowden syndrome, absence of one of the associated criteria allows the diagnosis of the "Li-Fraumeni syndrome-like family"^[19,23,24].

Gastric carcinoma, preponderantly located in the proximal stomach, is reported to occur in about 2%-5% of carriers with *p53* mutations at the median age of 36 years, ranging between 12 and 74 years^[24]. Association of early-onset gastric carcinoma and CRC can involve in 10%-28% of the families with classic Li-Fraumeni syndrome, but carcinomas of the lung, melanomas, lymphomas, and germ cell tumors have also been reported^[24]. The incidence of Li-Fraumeni-related gastric cancer is higher in Asian population (Japan and South Korea), when compared with people from United States, being supposed that *p53* mutation could enhance the carcinogenic effect of *H. pylori*^[24].

GENETIC COUNSELING AND CRITERIA FOR SURVEILLANCE

In patients with *FAP* and *FAP-variants* including *Gardner syndrome*, *Turcot syndrome*, and *AFAP*, the main goal of surveillance is to detect the CRC in early stages^[28], combining molecular and clinical approaches^[33].

The clinico-genetic screening should be performed in all first degree relatives of a patient with *FAP* and should be started, when it is possible, from the mid adolescence^[28].

The genetic screening consists in attentively examination of the *APC* gene, according to the particularities presented in Table 1, after a proper genetic counseling of the patient who should be asked for the informed consent. The gold standard method is the full sequencing of the *APC* gene, to examine all the 15 exons^[28]. The mutation cluster region (mutational hotspot of *APC* gene) is the 5'part of exon 15 from codon 1250 to 1464^[28]. If no mutations are detected, the current guidelines recommend to continue testing for large gene rearrangements^[28,35].

From colonoscopy point of view, it is worthy noticing that the small polyps are mostly limited to the recto-sigmoid at the time of adolescence and only thereafter increase in size and number^[28]. However, because half of patients develop adenomatous polyps before puberty and 95% by 35 years, sigmoidoscopy screening is recommended starting at age 12-14 years old

and performed every two years in mutation carriers. Identification of adenomas is an indicator for annually total colonoscopy, with biopsies from the suspect areas, until colectomy will be performed, depending on the individual endoscopic features^[1,28]. Prophylactic colectomy is recommended for multiple ulcerated polyps larger than 1 cm that shows high-grade dysplasia^[28]. The type of resection depends on the patient's age and personal decision, number and extension of polyps, and also by the macroscopic aspect of the tumors^[28].

At risk family members carrying germline mutations near codon 1300 can present early-onset CRC in their childhood and colonoscopy surveillance should also begin before puberty^[32,33]. On the other hand, if the carrying germline mutations suggest risk for *AFAP*, screening should be carried out every two years from the age of 18-20 years, with focused attention on identification of the right-sided distribution of adenomas. Once adenomatous polyps are identified, endoscopic polypectomy followed by annually total colonoscopy is recommended, followed by colectomy in case of large ulcerated polyps with high-grade dysplasia^[28,32]. Postoperative endoscopic follow-up is necessary in patients with rectal remnant, to detect the possible carcinoma of the ileo-anal pouch^[28].

For classic *FAP*, flexible sigmoidoscopy remains the standard of care, whereas in patients with *FAP* variants the proximal colon should also be explored through total colonoscopy. Modern imagistic methods such as capsule endoscopy and/or entero-CT-scan or entero-MRI can also be used for complex investigations. Because duodenal cancer is the second cause of death of patients with *FAP*, with 5% lifetime risk^[28], gastrointestinal endoscopy is recommended to be carried out every 5 years after identification of the colorectal polyps^[28].

Besides the risk for gastrointestinal cancer, the protocol of surveillance should also take into account the extraintestinal manifestations, including papillary carcinoma of the thyroid (the third commonest tumor in patients with *FAP*, with a risk of about 160 times higher than in general population, and a male to female ratio of 1:17), pancreatic carcinoma but also the central nervous system tumors and neuroblastomas^[14,28], based on the genetic particularities shown in Table 1.

Annually thyroid palpation, eventually completed by cervical ultrasonography, is recommended starting at the age 25 years^[28,36]. Because patients with *FAP* present 1000-fold increased risk developing desmoid tumor, compared to the general population^[34], diagnosis of such tumors, mostly in the abdominal wall, should be followed by a total colonoscopy, especially in young people. Although benign, due to highly recurrence rate, desmoids tumor represents one of the main causes of death of patients with *FAP*^[28].

For patients diagnosed with *MAP*, the surveillance is identically to those used for *AFAP*. The colonoscopy surveillance begins at 18-20 years old being carried out every two years and annually after adenomas detection. Upper endoscopy is also recommended every five years

starting at the age of 25-30 years old, to explore the duodenal segments^[28,36]. Screening for extra-intestinal manifestations is not recommended. Biallelic *MUTYH* gene mutations should be suspected and explored in patients with colorectal polyposis diagnosed before the age of 50 years, especially in associated serrated adenomas. In first degree relatives the two most common mutations, p.G396D and p.Y179C, should be determined. Identification of at least one of the two missense mutations should be followed up by full gene sequencing^[28]. Sequencing should also be done in non-Caucasian suspected patients, focusing on the specific geographic and ethnic particularities shown in Table 1.

For juvenile polyposis syndrome, annual upper and lower endoscopies are recommended to be performed in the *MADH4/SMAD4* carriers by the mid-teens or at the time of initial symptoms, most of the cases being diagnosed around the age of 40 years^[8-13]. Modern imagistic methods such as capsule endoscopy and/or entero-CT-scan or entero-MRI can also be used^[37].

In the bioptic specimens of gastrointestinal polyps, loss or partial loss of the epithelial expression of SMAD4 protein, with or without retained stromal expression, can be a first sign of suspected *SMAD4* mutation^[11]. Proctocolectomy or subtotal colectomy should be considered in patients with multiple polyps, severe symptoms, and/or history of familial CRC, but a specific guideline does not exist^[12]. According to the British Society of Gastroenterology and Association of Coloproctology for Great Britain and Ireland, in asymptomatic family at-risk members, including the proved *SMAD4/ BMPR1A* mutations, every 1-2 years colonoscopy is recommended from age 15-18 years until age 70 years and gastroduodenoscopy from the age of 25 years^[12,29].

In *SMAD-4* mutation-carriers, investigation for a possible associated hereditary telangiectasia is also recommended^[13]. Because severe gastrointestinal bleeding can be associated in these syndromes, long-time intravenous using of low doses of the antiangiogenic (anti-VEGF) drugs such as bevacizumab (2 mg/kg per course, every 3 wk) have been recently proposed^[30]. Identification of a pulmonary associated vascular malformation and a dilated thoracic aorta is mandatory to avoid bleeding complications^[12].

Decreased SMAD4 expression can also activate the transforming growth factor- β and, as a consequence, breast epithelial malignant proliferation can occur, as in one of the previously reported cases^[31]. Duodenal and pancreatic tumors can also occur in these patients^[14].

In patients with Peutz-Jeghers syndrome, surveillance for tumors of the colorectum, small intestine, breast, pancreas, and sex-cord tumors should be performed^[12,14]. Endoscopic examination of the gastrointestinal tract is recommended to be performed every 3 years beginning from the age of 18 years (and every 1-2 years after the age of 50 years) while suspicion for breast cancer should be excluded based on annual ultrasound examinations from the age of 25-30 years completed by

annual mammography from the age of 50 years^[12,15]. In symptomatic children, periodic gastrointestinal endoscopy should be done^[12]. In patients with Peutz-Jeghers syndrome, the capsule endoscopy proved to have a higher diagnostic sensitivity than the Barium-contrast X-Ray and entero-MRI but the size and location of polyps are difficult to be evaluated^[37].

No guidelines for screening of other cancers have been implemented to date.

For Cowden syndrome, being known that breast cancer and thyroid cancer occurs in 25%-50% of females and 3%-10% of all patients, respectively, a personal and familial cancer surveillance for these associated malignancies and also for endometrial cancer in females would be necessary^[12,19]. Currently, the gastrointestinal tract surveillance is not routinely recommended below 50 years of age, although an earlier endoscopic colonic and gastric surveillance beginning at the age of 30-35 years with follow-up every 1-2 years was recently suggested, especially for Asian population^[20]. However, annual mammogram and vaginal ultrasound with endometrial sampling should be done from age 30 years for women and biannual colonoscopy and renal ultrasound examination from age 35-40 years in both males and females are recommended in the most recent studies^[12]. Annual thyroid examination should begin from age 18 or 5-10 years before the earliest thyroid tumor in the family^[12].

For the other previously nominated hamartomatous polyposis syndromes, the childhood surveillance should take into account the gastrointestinal and extra-gastrointestinal complications such as bleeding, severe anemia, intussusception, whereas the adults should be examined to detect malignancies in early stages, similar to patients with Cowden syndrome^[7,12].

In patients with Li-Fraumeni syndrome, although germline *p53* mutations can be identified in the family members, it is difficult to establish the rules of surveillance, because tumors can occur in every organ^[19]. In these "p53 families", screening program is recommended to begin at earlier ages including investigations for breast, colorectal, and gastric cancer detection^[19]. However, the guidelines of the National Comprehensive Cancer Network Surveillance recommend colonoscopy as part of the surveillance protocol in these carriers^[20].

Because some of the inherited polyposis syndromes remain unexplained/unclassified, the genetic screening should take into account, after a meticulous histological examination, a minimal number of gene mutations, respectively the genes *SMAD4*, *BMPR1A*, *STK11*, and *PTEN*^[14]. The surveillance protocol should also take into consideration the other nontumor complications such as intussusceptions, ileus, gastrointestinal hemorrhage, and anemia^[21].

CONCLUSION

Despite the well-conducted screening programs worldwide, the accurate diagnosis of inherited cancer-

predisposing syndromes of gastrointestinal tract remains difficult. Lack of experience of both gastroenterologists and pathologists, due to rare occurrence of these syndromes, increases the difficulty. Subspecialization in the field of familial malignancies and founded of specialized medical centers in this field is essential for future proper medical care.

Because of geographic and ethnic particularities of gene mutations, national and international guidelines of screening and surveillance in these risk families should be elaborated. Development of the IHC markers that could predict specific gene mutation is a cheaper method that can be routinely used to detect these familial cases. Although rare, association of multiple tumors in the same patient is a time- and money-consuming management, the reason why a proper screening and surveillance could benefit both the patient and medical care system.

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