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Translation of the article

Peutz-Jeghers syndrome: what has been known for 125 years of research? (review)

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ABSTRACT *The Peutz-Jeghers syndrome (PJS) is an extremely rare autosomal dominant hereditary disease characterized by the growth of hamartomatous polyps in the gastrointestinal tract, mucocutaneous pigmented macules and an increased risk of malignant neoplasms of various localizations. In most cases the PJS is associated with the presence of a mutation in the STK11 gene, but not all patients have this mutation. This review presents the historical aspects of the first data on PJS, considers the clinical manifestations of the disease, current diagnostic methods, as well as recent knowledge about the genetic causes, risk of malignant neoplasms in patients with PJS, existing guidelines for screening and treatment of patients with PJS.*

However, the presence of a number of unresolved issues in genetics, monitoring and treatment indicates the need for further research.

KEYWORDS: *Peutz-Jeghers syndrome, hamartomatous polyps, lentiginosis, STK11*

CONFLICT OF INTEREST: *The authors declare no conflict of interest.*

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The Peutz-Jeghers syndrome (PJS) is an extremely rare autosomal dominant hereditary disease, which is characterized by the growth of multiple hamartomic polyps in the gastrointestinal tract and mucosa and skin pigmentation, as well as a high risk of malignant transformation in different sites [1]. At the same time, PJS occupies the second place in the incidence among hereditary polyposis of the gastrointestinal tract after adenomatous polyposis syndromes [2,3]. According to literary data, the incidence is approximately 1 case per 50,000–200,000 newborns [4,5]. About 55% of patients have a family history [6].

History of the disease

In 1896, the London physician Hutchinson, J. described a clinical case of twin sisters with the "unique inky pigmentation of the lips and mouth" and an unusual fate — one sister died of bowel obstruction at the age of 20, and the second died of breast cancer at the age of 52 [7]. Then in 1921, the Dutch physician Peutz, J. reported about a family with intestinal polyposis and mucocutaneous pigmentation [8].

In 1949, Dr. Jeghers H. together with his colleagues published his own data on ten cases of such polyposis in the one family, emphasizing the autosomal dominant type of inheritance of the disease [9]. As a result, in 1954, Bruwer A. et al., working at the Mayo clinic, introduced the eponym "Peutz-Jeghers syndrome", which is still used to refer to the syndrome [10].

Clinical Picture

The Peutz-Jeghers syndrome (PJS) is clinically characterized by the presence of gastrointestinal hamartomas and mucosa and skin pigmentation [1,2,11], also called lentigo [12].

The first clinical symptoms that occur with PJS, such as anemia, nausea, abdominal pain, bowel

obstruction, blood in the stool, and prolapse of polyps from the anus, can occur in various diseases [13]. However, most often, pediatric surgeons face with clinical manifestations of the disease. The most common and significant manifestation of the disease in children and adolescents is intestinal obstruction caused by intussusception of the small intestine with a concomitant risk of intestinal infarction, and gastrointestinal bleeding [11, 12], which necessitate urgent medical care, often requiring surgery.

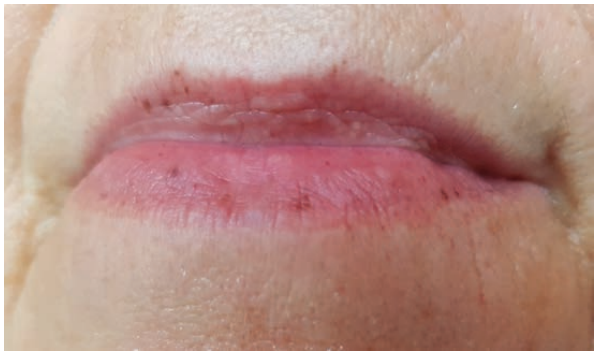

Figure 1. *Perioral lentiginoses*

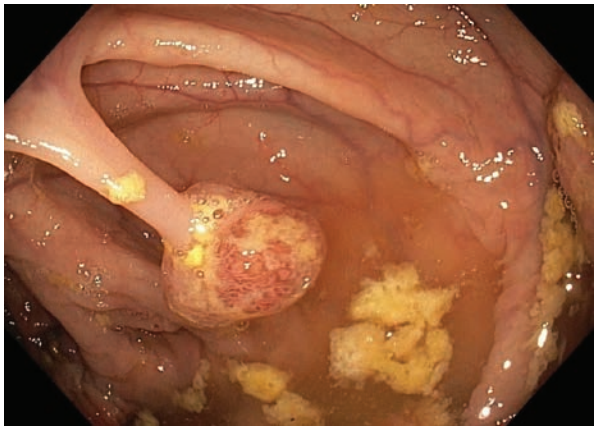

Figure 2. *Hamartomatous polyp of the colon in Peutz-Jeghers syndrome detected by colonoscopy*

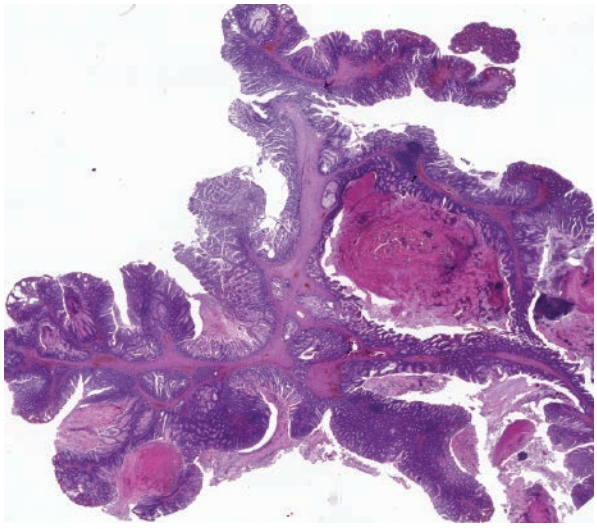

Figure 3. *Typical morphological structure of the hamartomatous polyp in Peutz-Jeghers syndrome. Hematoxylin-eosin staining*

In Hinds, R. study on the impact of pediatric screening in PJS, approximately 30% of the patients needed surgery at the age under 10 years and 68% aged under 18 years. Seventy percent (70%) of the initial laparotomies were performed urgently for intestinal obstruction [14].

In 60–90% of patients, hamartomas are localized in the small intestine, in 50–64% of patients — in the large intestine, in 25% of patients — in the stomach [11,15]. The order of their prevalence: jejunum, ileum, duodenum, then colon and stomach [16]. Polyps in PJS are most often arranged in groups, and their size can vary from a few millimeters to several centimeters [1].

Hamartomic polyps develop in the first decade of life and are observed in 33% of patients by the age of 10 years, and in 50–60% of patients by the age of 20 years [11, 16]. Also, polyps with PJS can be detected in extra-intestinal sites, such as the gallbladder, bronchi, bladder and ureters [6,11,12,17].

According to the literature, up to 95% of intussusception occurs in the small intestine and only about 5% — in the large intestine [18,19]. This is consistent with the fact that hamartomas are mainly localized in the jejunum and play a leading role in the development of the clinical manifestation. Intussusception is usually caused by hamartomas with a diameter of over 15 mm, and the size of the polyp is the most important risk factor for the development of small intestine intussusception and intestinal obstruction. The risk of intussusception does not depend on gender, family history, or the status of a mutation in the *STK11* gene [18].The cumulative risk of intussusception is estimated at 50–68% in childhood [20]. The average age of the first intussusceptions is between 10 and 16 years, the earliest episodes are observed from 1 to 5 years [12]. A Korean study showed that the average age of onset of the first symptoms is 12.5 years [20].

Another characteristic feature of PJSis the presence of perioral lentiginosis, which occurs in more than 95% of cases and provides significant assistance in making a correct diagnosis (Figure 1).

Most often, pigmentation appears in childhood at the age of over 5 years around the natural orifices: the mouth, nostrils, perianal area, as well as in the palms, fingertips and toes. In the vast majority of cases, pigment spots persist throughout life, especially on the mucosa, but they may fade or disappear after puberty [12,15].

The appearance of pigment spots is associated with an increase in melanin secretion in basal cells, probably due to inflammatory blockade during the migration of melanin from melanocytes to keratinocytes [15]. However, perioral lentiginosis is not pathognomonic for PJS, it can also be found in patients with Carney complex [21] and LEOPARD syndrome [22].

The clinical criteria for the diagnosis of PJS were established by WHO in 2000, and then revised by the European Consensus of Experts in 2007. The clinical diagnosis of PJS is established if one of the following criteria is present [11,12,15,18]:

1. Two or more histologically confirmed hamartomic polyps;
2. Any number of hamartomic polyps found in a single patient with a confirmed family history;
3. The presence of peculiar mucosal skin pigmentation in a patient who has relatives with confirmed PJS;
4. Any number of hamartomic polyps in a patient who also has a peculiar pigmentation of the mucous layer.

Aretz S. et al. showed a correlation of the diagnostic criteria of PJS with the incidence of detection of mutations in the *STK11* gene.

Of the 71 patients who met the PJS criteria, more than 94% had an identified mutation [23].

Morphology of Polyps

The appearance of PJS polyps may endoscopically resemble hyperplastic polyps [15], but according to the histological structure, PJS polyps are classified as hamartomas [12].

The term "hamartoma" (in the ancient Greek αμαρτημα means "sin", "flaw" and -ωμα comes from ογκωμα that means "tumor") is a nodular benign tumor-like lesion, which is a tissue abnormality of development. It was first used in 1904 by the German pathologist Albrecht, E. [24].

Hamartomas consist of the same tissue components as the organ where they are sited. At the same time, they differ in the abnormal structure and in the degree of differentiation of tissues. Most of the hamartomas have a pedicle that contains epithelial components typical of a particular part of the gastrointestinal tract (Fig. 2) [15].

Polyps in the Peutz-Jeghers syndrome are distinguished from others by the presence in the stroma of tree-branching bundles of smooth muscles originating from the own muscular lamina of the mucous membrane. The smooth muscle bundles are covered with elongated and branched glands lined with mature epithelium.

Crypts and glands are often elongated, the mucous layer draped over the core of the stretching muscle bundles extending from the pedicle to the head of the polyp (Fig. 3) [19,25,26].

For a more reliable diagnosis of PJS, it is necessary to conduct an immunohistochemical study, in which desmin-positive smooth muscle fibers are detected around these lobules [19], which is a pathognomic feature of hamartomic polyps.

Although the morphology of hamartomas differs from other polyps, it is not completely specific.

The criterion for a confident pathomorphological verification of a hamartomic polyp is the presence of an appropriate medical history or genetic proof of the disease. Otherwise, in the conclusion of the morphological study, it should be written: the polyp corresponds to the polyp of Peutz-Jeghers type [25].

Hamartomic polyps should also be differentiated from mucosal prolapse, which can occur in different parts of the gastrointestinal tract, and therefore different diagnoses can be established, such as mucosal prolapse syndrome, cloacogenic polyp and solitary rectal ulcer syndrome. Similar to hamartoma polyps, these lesions are characterized by the presence of proliferating muscle fibers in the center, surrounded by a normal or reactive mucosa, which is believed to be secondary to the prolapse or protrusion of the mucosa into the lumen of the gastrointestinal tract [25].

Another feature observed as a result of mucosal prolapse is "pseudo-invasion", which can be mistaken for invasive carcinoma. The absence of atypia during histological examination helps to exclude cancer [20].

However, to date, the diagnosis of PJS is largely based on pathomorphology of the polyp [19].

Table 1. *Cumulative cancer risk in Peutz-Jeghers syndrome [47]*

Localization of cancer	Overall risk of cancer in the population, %	Peutz-Jeghers syndrome	
		Cancer risk, %	Average age of cancer diagnosis, years
Large intestine	5	39	42–46
Stomach	< 1	29	30–40
Small intestine	< 1	13	37–42
Mammary glands	12.4	32–54	37–59
Ovaries	1.6	21	28
Cervix	< 1	10	34–40
The body of the uterus	2.7	9	43
Pancreas	1.5	11–36	41–52
Testicles (Sertoli cell tumor)	< 1	9	6–9
Lungs	6.9	7–17	47

Genetic aspects of the disease

In 1998, the *STK11* (serine/threonine kinase gene) gene, formerly known as the LKB1 (hepatic kinase) gene, located on chromosome 19p13.3, was mapped by two independent groups of researchers: Jenn D. et al. [27], as well as Nemminki A. et al. [[28]. Hereditary mutations of the *STK11* gene were detected in 5 and 12 patients with PJS from unrelated families, respectively. It was proved that germinal mutations in this gene cause the Peutz-Jeghers syndrome [28,29]. The penetrance of the *STK11* mutation was 100% [12].

It should be noted that the STK11 gene is rarely mutated in most types of tumors of sporadic origin. So, according to Sanchez-Cespedes M. et al., a mutation in the *STK11* gene occurred only in 4% of pancreatic cancer cases [30]. At the same time, in the study of Resta N. in sporadic colorectal cancer, somatic mutations in the *STK11* gene were not detected at all [31].

The *STK11* gene includes 10 exons, 9 of which encode the protein serine-threonine kinase containing 433 amino acids [28]. *STK11* protein expression is observed in all adult and fetal tissues, but to varying degrees [27,28,32]. Protein expression is particularly pronounced in the heart, esophagus, pancreas, liver, testicles, and skeletal muscles [30]. In addition, it's over expression in the small intestine and gastric tissue of the fetus was noted in comparison with adults, which indicated the role of *STK11* in the development of gastrointestinal polyps [33]. The loss of the *STK11* protein affects cell polarity, epithelial transition to the mesenchyma, apoptosis, angiogenesis, and cell cycle inhibition [33,34]. As a result, the *STK11* mutation leads to the displacement of the epithelium with secondary changes due to the loss of the mucous layer and the formation of "hamartomic" polyps typical for PJS [25].

The loss of the wild-type allele in hamartomas and adenocarcinomas occurring in patients with PJS suggests that *STK11* is a tumor suppressor gene.

Mutations in the *STK11* gene promote oncogenesis through various mechanisms, such as angiogenesis induction, apoptosis, and loss of cell polarity [35].

Pathogenic mutations in the *STK11* gene are usually detected in 75–94% of patients with a characteristic clinical picture of PJS using traditional methods of screening for mutations, such as direct sequencing of individual exons and searching for large inserts/deletions.

Various types of mutations were found, including small insertions, deletions, defects in the splicing sites, and large rearrangements. In about 30% of cases, partial or complete deletions of the gene are detected, and in 64% — point mutations [27]. To date, a total of about 200 different mutations of the STK11 germ line gene have been registered [36]. Most studies were conducted in Western European populations, but the study of Latin American patients with PJS revealed 2 new mutations in exon 2 (c. 350_351insT) and exon 6 (c.811_813delAG) of the STK11 gene [37].

Amos, C. et al. reported of the genotype-phenotypic correlation in PJS. The authors concluded that people with missense mutations showed the symptoms later than patients with other types of mutations in *STK11* [38].

Schumacher, V. et al. suggested that mutations in protein-coding domains and ATP binding were rarely associated with cancer, and the missense mutations in the C-terminus and in the part of the gene encoding protein domains for substrate recognition were more often associated with malignant neoplasms, whereas in patients with breast carcinoma, mutations leading to protein shortening prevailed [35].

Mehenni H. et al. studied 49 families with PJS with identified mutations and found 32 cancers. They concluded that mutations in exon 6 of the *STK11* gene have a high cancer risk [39].

In turn, Giardiello F. et al. analyzed the data of 240 patients with PJS with a mutation in the *STK11* gene. However, no differences were found between individuals with missense mutations and mutations leading to protein shortening, as well as between familial and sporadic cases, although it was suggested that carriers of the mutation in exon 3 had a higher cancer risk [40].

These studies were done on small samples of patients. Therefore, it is difficult to draw final conclusions based on the presented results [39].

Hearle N.et al., having analyzed the clinical data of 419 patients with PJS, 297 of whom had a mutation in the *STK11* gene, concluded that the type and location of the mutation did not affect the cancer risk [41].

Thus, there was no clear genotype-phenotypic correlation in PJS. In addition, there were no significant differences in the clinical picture between patients with the *STK11* mutation and those in whom the mutation was not identified [12].

It should be noted that to date, no other gene that causes PJS has been detected in patients without an identified mutation in *STK11* [11,12].

Cancer risk

Until 1987, the Peutz-Jeghers syndrome was considered a condition without malignant potential [42]. Giardiello F. et al. noted an 18-fold increase in the risk of developing malignant tumors of the digestive tract and extra-intestinal localization in patients with PJS throughout their life compared to the general population [43].

In a Japanese study involving 222 patients with PJS, 60% of deaths at the age of over 30 years were associated with malignancies [44].

In a systematic review of twenty cohort studies involving 1,644 patients with PJS, conducted by Van Lier et al., 349 of whom developed 384 malignancies. The mean age of cancer diagnosis was 42 years [45].

One of the largest multicenter studies involving a group of patients with PJS from Europe, Australia, and the United States is the one by Hearle, N. et al. Out of the 419 patients (including 297 with the *STK11* mutation), 85 patients were diagnosed with 96 cancers. The cancer risk at the age of 20, 30, 40, 50, 60, and 70 years old was 2%, 5%, 17%, 31%, 60%, and 85%, respectively. The most common cancers were of gastrointestinal origin: gastroesophageal, small intestine, colorectal, and pancreatic. The risk of these types of cancer at the age of 30, 40, 50, and 60 years was 1%, 9%, 15%, and 33%, respectively [41].

More recent Italian and Dutch studies have produced similar results. Thus, according to the AIFEG (Italian Association for the Study of Familial and Hereditary Tumors of the Gastrointestinal Tract), the cumulative cancer risk in PJS is 20% — aged 40 years, 43% — aged 50 years, 71% — aged 60 years, 89% — after 65 years old [46]. According to Van Lier et al., this risk reaches 20 ± 5% at the age of 40 years, 36 ± 5% — aged 50 years, 58 ± 7% — 60 years, 76 ± 8% aged 70 years [45]. The cumulative cancer risk is presented in Table 1.

Table 2. *Recommendations for screening for patients with Peutz-Jeghers syndrome [6]*

Cancer screening	Screening start age (years)	Interval (years)	Medical examination types
Large intestine	25	2	Colonoscopy
Stomach and small intestine	10	2	Esophagogastroduodenoscopy, radiography of the small intestine, VCE, BES
Pancreas	30	1–2	Ultrasound
Mammary glands	20	2	Mammography
Uterus	20	1	Transvaginal or trans abdominal ultrasound examination
Cervix	20	1	Smear for cytological examination
Testicles	10	1	Physical examination, ultrasound examination

Due to the increased risk of breast cancer, Chen, H. et al. noted a significantly higher risk of cancer in women with PJS than in men ($p < 0.05$) [48]. The risk of breast cancer is estimated by Hearle N. at 8% at the age of 40 years and 31% aged 60 years [41]. As in patients with mutations in the *BRCA1/2* genes, there is an increased risk of bilateral cancer. The main histological type is invasive ductal carcinoma, but infiltrative lobular carcinomas are also possible [15,49]. Also, in Hearle N.'s study it was shown that the cancer risk of all types increases at the age over 50 years [41]. However, this fact is not taken into account in most recent surveillance protocols [11]. In addition, the authors note a high risk of lung, kidney, prostate, bone cancer, and leukemia [41]. Kaplan-Meyer's analysis showed that the cancer risk was the same in patients with PJS with an identified *STK11* mutation and without a detectable mutation. Besides, the type of *STK11* mutation did not significantly affect the cancer risk [24].

The question of the occurrence of gastrointestinal cancer in PJS and the role of hamartomic polyps in the development of the tumor remains unclear to this day. It has been suggested that there is a unique hamartoma-adenoma-carcinoma way [50,51]. This hypothesis is confirmed by the detection of adenomatous foci in hamartomic polyps, as well as advanced cancer [52]. Other researchers have shown that hamartomic polyps do not have a malignant potential. Malignant transformation in it is considered only as a rare event that confirms this hypothesis [53]. Latchford, A. et al., in a single-center study of almost 2,500 removed hamartoma polyps, detected dysplasia/atypia in only 6 (0.24%) of them [54].

At the same time, the absence of malignant potential in hamartomic polyps may mean that cancer occurs against the background of mucosal instability, presumably through the usual ways of carcinogenesis [15].

Thus, in patients with PJS, there is a need for early screening of cancer of various sites.

Medical checkup

The presence of classical mucosal pigmentation suggests a diagnosis even before prognostic testing, but the spots may be absent in the first few years of life or may be invisible even in a person with a genetic diagnosis of PJS. Therefore, the absence of lentiginos is cannot completely exclude PJS [12].

Molecular analysis of the *STK11* gene is recommended for all patients with clinical suspicion of PJS in order to identify all carriers of the mutation and put them on lifelong clinical monitoring. If the proband mutation is not identified, then other blood relatives are not administered molecular diagnostics. In this regard, it is necessary to conduct a thorough clinical monitoring of all relatives from childhood in order to identify the clinical signs of PJS in a timely manner [15].

Genetic testing can be performed on a blood sample or a buccal sample [12]. With the advent of new

methods of full-exon and full-genome sequencing, as well as the MLPA method, the possibility of detecting new mutations in patients with PJS has been significantly expanded.

Thus, in Russian patients, 3 new mutations that were not previously described in the Human Gene Mutation Database were identified [55].

The protocols for monitoring patients with PJS have two main goals. One of them is the detection of hamartomas that can cause intussusception/obstruction or bleeding/anemia. The other is the detection of cancer at an early stage. Therefore, the indications for screening depend on age: complications associated with polyps can occur in childhood, while the risk of cancer is mainly attributed to the adult population [11,15,29].

Most guidelines recommend performing contrast X-ray of the small intestine starting at the age of 8 years and at intervals ranging from 2 to 5 years [12,48].

In patients with PJS, it is also possible to use ultrasound (US) diagnostics to examine the small intestine in order to detect intussusception, and in thin children, the polyp that caused intussusception can be visualized. However, the use of ultrasound for screening small intestine polyps is not always informative [12].

Taking into account the risk of radiation exposure, computed tomography (CT) should be performed only after ultrasound examination in patients with acute intestinal obstruction to verify invaginate while maintaining diagnostic uncertainty[12].

The sensitivity and specificity of CT in adult patients are assessed as 93% and 99%, respectively [56]. New options for examining the small intestine in PJS have recently appeared.

These are videocapsular endoscopy(VCE), balloon enteroscopy (BES), magnetic resonance imaging enterography (MRI-enterography), virtual colonoscopy [57,58]. These methods have become widely available for clinical practice.

The advantage of BES is that it allows not only to visualize the polyp, but also makes it possible to endoscopically remove small intestine polyps.

This can prevent such a complication as intussusception, reduce the incidence of laparotomies, and thus improve treatment outcomes [18,22]. However, it has been suggested that it is impossible to perform BES in patients with PJS in the case of previously undergone abdominal surgery.

Postoperative intra-abdominal adhesions may interfere with the free movement of the device through the small intestine, affecting the depth of the maximal search [59].

Postgate, A. et al. compared the effectiveness of small intestine X-ray examination with barium and video capsule endoscopy in children with PJS.

At the same time, there were no significant differences in the detection of polyps > 1 cm, but more polyps < 1 cm were detected by the VCE. A much better tolerance of VCE was also noted [60].

Currently, many diagnostic units use only VCE, since with equal diagnostic significance with X-ray examination with barium, there is no radiation load in VCE [11]. However, it is recognized that the duodenum and the proximal jejunum are the most difficult to study with VCE due to the rapid passage of the capsule and the relatively narrow lumen of the intestine.

In addition, it should also be noted that one of the most serious complications of VCE is the jamming of the capsule in any of the sections of the gastrointestinal tract, which usually requires surgeries.

In the studies by Caspari R. et al., MRI-enterography and VCE were compared. At the same time, a lower sensitivity of MRI-enterography was revealed when detecting small intestine polyps < 15 mm. However, despite this, the authors concluded that MRI-enterography provides the advantage of a more accurate assessment of the polyp size and its localization in a particular segment of the small intestine [58].

The study of the role of virtual enteroscopy in small intestine with PJS done by Su X. et al. showed a higher diagnostic accuracy of this method in the detection of small intestine tumors [61].

Thus, recent methods allow detecting most polyps in patients with PJS. Missed polyps are usually less than 10 mm in size and are considered clinically insignificant [57].

Given the increased cancer risk, all patients with PJS should be screened for the timely detection of possible malignancies. Lifelong screening is mandatory on a regular basis (Table 2). It is also

necessary to examine all relatives of the first degree of kinship [1].

Differential diagnosis

Hamartomic polyps are not pathognomonic for PJS, as they are also found in other hamartotic polyposes: juvenile polyposis (associated with mutations in the *SMAD4* or *BMPR1A* genes) and Cowden syndrome (associated with a mutation in the *PTEN* gene), in which there is also dysmorphia (macrocephaly), often mucosal lesions and an increased risk of breast, thyroid and colon cancer [15].

However, juvenile polyps differ from those in PJS in that their glands are filled with mucus, there is a large amount of stroma between the crypts with signs of edema and inflammation, and there are practically no smooth muscular layers [17,23]. In Cowden syndrome, inflammatory and hyperplastic polyps are detected [62]. Polyps in PJS differ from adenomatous ones by the presence of tree-branching bundles of smooth muscles in the stroma, which originate from the own muscle plate of the mucous layer [23].

At the dermatological level, PJS should be differentiated from Carney complex [21] and LEOPARD syndrome [22].

In the past, intussusception of the small intestine was the main cause of death in patients with PJS [18]. Intussusception occurs when the proximal parts of the intestine and its associated mesentery slip behind the polyp into the lumen of the adjacent distal segment, resulting in intestinal obstruction, ischemia, necrosis, and perforation. Retrospective data indicates the risk of intussusception and emergency laparotomy in 70% of patients with PJS under the age of 18, but this occurred before the introduction of the small bowel surveillance program [12,14]. Untimely detection of large polyps of the small intestine leads to the need for repeated surgical procedures with intestinal resection, which can lead to short bowel syndrome and impaired absorption [6].

In a study by Van Lier, M. et al. in a group of 110 patients with PJS, the mean size of the polyp leading to intussusception in the small intestine was 35 mm (15–60 mm) [18]. In addition to the size of the polyps, there are no other predictors to determine which patients with PJS will develop intussusception[18,63]. Patients were recommended laparotomy with intraoperative enteroscopy to remove small intestine polyps with a diameter of over 1.5 cm [6].

Recently, a more active approach to treatment has been proposed — performing an endoscopic examination with simultaneous polypectomy [64–66]. Latchford A., Van Lier M. recommend the removal of polyps with a size of 10 mm or more, since the purpose of polypectomy is to prevent intussusception [12,18].

The method of choice hamartomas removal should be made individually, depending on the site and size of the polyp, based on a previous examination. Endoscopic, surgical, and combined approaches have their advantages and disadvantages. Endoscopic polypectomy for PJS requires experience and should only be performed by an expert in this field. The risk of intestinal perforation during a polypectomy in PJS is higher than in other gastrointestinal polyps. In polypectomy, it is necessary to use methods that reduce the risk of perforation and bleeding, including mucosal lifting, endoclips, latex loops and an electrosurgical knife [12,48].

Balloon enteroscopy makes it possible to remove small intestine polyps without laparoscopy. There is more information about the safety of the BES. Sakamoto H. suggests polypectomy with double balloon enteroscopy as an alternative to surgery [67].

There is no data on the size of hamartomic polyps that should be removed from the stomach or colon, but endoscopic polypectomy from these organs carries the same risk of complications as when removing polyps from the small intestine.

It is believed that small polyps of the stomach and large intestine in size between 3 and 5 mm do not require removal. For larger polyps, the optimal strategy should be chosen: either endoscopic polypectomy or laparoscopic wedge resection [12].

Currently, experimental studies are being conducted on the use of various chemotherapeutic agents to prevent the growth of polyps.

Studies in mice have shown that rapamycin (an immunosuppressant), when used daily for a long

period, is effective in reducing the number and size of polyps in a mouse model of PJS [68].
The immunosuppressant Everolimus is also being studied as a potential agent for the treatment of PJS. Kuwada S. reports of the first experience of its use in patients with PJS [69].
Thus, to date, no chemoprophylaxis strategy has been developed for PJS, and therefore pharmacological agents for the treatment of PJS cannot yet be recommended for widespread use [12].

CONCLUSION

In conclusion, it should be noted that despite more than a century of observation of patients with a rare hereditary disease, Peutz-Jeghers syndrome, there are currently a significant number of issues that have not been resolved. First of all, this concerns the molecular and genetic basis of the disease, since not all patients can be identified with a mutation, which may be due to the method of performing DNA diagnostics. In addition, patients may have a mutation in an alternative gene that has not yet been described as associated with this syndrome. Third, somatic mosaicism may be present [43]. With the modern development of genetics and the success in studying the human genome, it is possible to search for quite likely additional genetic causes of PJS.
Another unclear issue is the mechanism of development of malignant neoplasms in patients with PJS and the spectrum of malignant tumors. The risk of developing a malignant tumor may vary depending on ethnicity, environment, and lifestyle [70]. Thus, the surveillance programs for malignant tumors offered by Western countries cannot be accepted unconditionally for Russian patients.
It remains relevant to continue the study in order to identify all possible clinical and genetic characteristics of patients with PJS.
Given the rare occurrence of PJS and the lack of necessary experience in such patients in the general hospital network, it is necessary to develop clear criteria for early diagnosis of the disease to prevent the development of acute intestinal obstruction, indications for a particular treatment method, as well as further monitoring of patients with PJS in the Russian population.

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