https://doi.org/10.33878/2073-7556-2022-21-2-10-24

CLINICAL GUIDELINES
Adenomatous Polyposis Syndrome

Yuri A. Shelygin, Evgeny N. Imyanitov, Sergey I. Kutsev, Sergey I. Achkasov, Sergey V. Vasiliev, Sergey A. Frolov, Vladimir N. Kashnikov, Alexander M. Kuzminov, Evgeny G. Rybakov, Vladimir V. Strelnikov, Dmitry V. Vyshegorodtsev, Alexey S. Tsukanov, Alexey I. Moskalev, Dmitry Yu. Pikunov

Developers of Clinical Recommendations:
Association of Coloproctologists of Russia;
Association of Medical Geneticists

Coding according of the International Statistical Classification of Diseases and Health-Related Problems: **D12**

Age group: **adults**

Year of approval: 2022

There are no conflicts of interest for all the listed authors.

LIST OF ABBREVIATIONS

APS — adenomatous polyposis syndrome
ROA — rectal occlusion apparatus (anal sphincter)
CRC — colorectal cancer
CT — computed tomography
MAP — *MutYH*-associated polyposis
MRI — magnetic resonance imaging
TRUSE — transrectal ultrasound examination
Ultrasound — ultrasound examination
EGDS — esophagogastroduodenoscopy

TERMS AND DEFINITIONS

The autosomal dominant type of inheritance is a type of inheritance characterized by the following signs: each sick descendant has a sick parent; the disease occurs in persons of both sexes; the risk of inheritance of the disease for the children of the affected parent is 50%; in healthy descendants of the patient, all children should be healthy.

An autosomal recessive type of inheritance is a type of inheritance of a trait characterized by the following signs: the disease occurs in persons of both sexes; there are breaks in the pedigree; sick children can be born to healthy parents; if both parents are sick, then all their children will also be sick.

Proband is a person from whom the compilation of a pedigree begins to study the process of inheritance of a disease among members of the same family.

The family tree is a graphical representation of family history data, in addition to the nature of family ties between family members, reflects information about the manifestation of a trait, health status or pathology among relatives, provides visual information about the nature of inheritance of the trait.

Germinal (hereditary) mutations are any genetic changes that take place inside the progenitor cells of germ cells; they are determined in all cells of the body.

Adenoma is a benign tumor originating from the glandular epithelium.

Polyp is a collective term used to refer to various pathological tissue growths over the mucous membrane.

Dentate adenoma is a variant of a polyp that occupies an intermediate position between adenomas and hyperplastic polyps, a characteristic feature of which is a pronounced expansion of the basal sections and horizontal growth of crypts along the muscular plate of the mucous membrane.

Hyperplastic polyp is a polyp formed as a result of focal hyperplasia and morphologically unrelated to benign intestinal tumors.

Desmoid tumor (desmoid, desmoma, aggressive fibromatosis) is a rare, locally invasive, non-metastatic tumor that develops from musculoaponeurotic structures and occupies an intermediate position between benign and malignant neoplasms. The most common localization is the anterior abdominal wall, upper and lower extremities, mesentery of the small intestine.

1. BRIEF INFORMATION ON THE DISEASE OR CONDITION (GROUP OF DISEASES OR CONDITIONS)

1.1 Definition of a Disease or Condition (Group of Diseases or Conditions)

Adenomatous polyposis syndrome is a rare hereditary disease characterized by the development of multiple (more than 20) colon adenomas at a young age with their inevitable malignant transformation in case of untimely surgical treatment [1–2].

1.2 Etiology and Pathogenesis of a Disease or Condition (Group of Diseases or Conditions)

The etiological cause of the development of the APS is the presence of a germinal mutation in one of the genes encoding proteins that regulate intercellular adhesion and apoptosis (*APC, MutYH*).

The *APC* (adenomatous polyposis coli) gene was identified and mapped by two independent groups of researchers in 1986–1991 [3–5]. It is located on the long arm of chromosome 5 in the 5q22 region, and includes 16 exons, of which 15 encode a protein containing 2,843 amino acids [6]. The *APC* gene is responsible for the synthesis of a specific protein that functions as a tumor suppressor, ensuring normal proliferation in the cells of the gastrointestinal mucosa. Mutations in the *APC* gene lead to the synthesis of a 'shortened' protein, which loses the function of suppressing increasing epithelial dysplasia, and are the cause of the development of an autosomal dominant hereditary syndrome — familial adenomatosis of the colon, which is characterized by the development of multiple adenomas with their subsequent malignant transformation in 100% of cases [7,8]. The most common types of mutations in the *APC* gene are deletion, insertion with a reading frame shift and nonsense mutation. Deletion is characterized by the loss of one or more nucleotides, the number of which is not a multiple of 3, from a normal DNA chain; insertion is the insertion of one or more nucleotides, the number of which is not a multiple of 3, into a DNA molecule; and nonsense mutation is a type of mutation in which the formation of a premature stop codon occurs [9].

To date, more than 2,000 unique pathogenic hereditary mutations in the *APC* gene have been described; but new mutations are regularly found in ongoing studies, which is due to both the heterogeneous population affiliation of the probands and the nature of the gene itself [8,9]. An autosomal dominant type of inheritance is characteristic for the transmission of mutations in the *APC* gene, which has a number of features:

- The trait occurs, as a rule, in each generation, which is called vertical inheritance;
- Male and female individuals are affected with the same frequency;
- Sick men and women equally transmit the trait to offspring — boys and girls;
- A sick family member, as a rule, has a sick parent (less often parents);
- The probability of having a sick child if both parents are sick is 75%, if one of them is sick — 50%.

In 2002, biallelic mutations in the *MutYH* gene located on the first chromosome in the 1p34 region were described for the first time [10]. This gene encodes a DNA excision repair protein involved in the reduction of oxidative damage to guanine. ***MutYH*-associated polyposis** is an autosomal recessive disease characterized by the development of multiple colon adenomas and the risk of CRC on their background, reaching 80% in case of late diagnosis and treatment. A characteristic feature of APS caused by mutation in the *MutYH* gene is the presence in the colon, along with adenomatous polyps, also creeping **dentate adenomas**, hyperplastic polyps, mixed polyps (hyperplastic and adenomatous) [11,12]. An autosomal recessive type of inheritance is characteristic of the *MutYH* gene mutation transmission, which has a number of features:

- The trait is rare, not in every generation;
- Sick children are born, as a rule, to healthy parents;
- Mostly siblings (brothers, sisters) are sick;
- Healthy children may be born to a sick parent;
- Male and female individuals are affected with the same frequency;
- The probability of having a sick child in a marriage of two heterozygotes is 25% for each subsequent child, regardless of the number of already existing sick children.

At the birth of a child, clinical signs of APS do not appear. In the future, as the body grows, the appearance of small polyps on the mucous membrane of the colon is detected [13,14].

1.3 Epidemiology of a Disease or Condition (Group of Diseases or Conditions)

In 2018, more than 74,000 new cases of CRC were detected in the Russian Federation [15]. About 5–10% occur in cases of cancer with a known molecular genetic cause, while up to 1% of cases are caused by APS [16], which is

the second most common genetically determined syndrome after Lynch syndrome [17,18]. The prevalence of mutations in the *APC* gene in Europeans, according to various estimates, is from 1:6,850–1:31,250 [19,20].
The frequency of occurrence of allelic mutations in the *MutYH* gene, according to various estimates, is 1:20,000–1:60,000 [19,21].

1.4 Features of Coding a Disease or Condition (Group of Diseases or Conditions) According to the International Statistical Classification of Diseases and Health-Related Problems

ICD-10 codes

Class — Neoplasms (C00-D48) (II).
Block — Benign neoplasms (D10-D36).
Code — D12 — Benign neoplasm of the colon, rectum, anus, and anal canal:
D12.0 — Caecum
D12.1 -Vermiform process
D12.2 — Ascending colon
D12.3 — Transverse colon
D12.4 — Descending colon
D12.5 — Sigmoid colon
D12.6 — Colon of unspecified part, including:
- Adenomatosis of the colon
- Large intestine
- Polyposis (congenital) of the colon

D12.7 — Rectosigmoid compound
D12.8 — Rectum
D12.9 — Anus and anal canal

1.5 Classification of a Disease or Condition (Groups of Diseases or Conditions)

Polyposis syndromes include situations when 20 or more colon polyps are detected. All of them are united by the concept of "adenomatous polyposis syndrome".
APS is classified according to the clinical course and variant of the genetic mutation. The classification is used to determine the severity of the disease and the choice of treatment tactics [1,2]. The following clinical forms of the disease are distinguished:
1. The classical form is the most common form, which is characterized by the presence of hundreds or thousands (i.e. more than 100) polyps in the colon, and their malignant transformation occurs at the age of 18–40 years. The first symptoms of the disease may appear already in childhood. In addition, patients with the classical form of the disease may develop severe metabolic disorders and anemia, which often cause children to lag behind in physical development [2,23]. In the classical form of APS, mutations in the *APC* gene are detected in about 80% of observations. In other cases, the presence of the wild-type *APC* gene is detected.
In the classical form of APS, Gardner syndrome and Turco syndrome are additionally distinguished.
- *Gardner syndrome* is a combination of APS with soft tissue tumors, osteomas of the skull bones. Most often there are desmomas — highly differentiated connective tissue tumors localized in the anterior abdominal wall, mesentery of the small or large intestine, sometimes in the intermuscular layers of the back and shoulder girdle. By their structure, tumors are not malignant, do not metastasize, but are prone to aggressive locally destructive growth and frequent recurrence.
- *Turcot syndrome* is APS in combination with malignant tumors of the central nervous system — medulloblastomas.

2. The weakened form is characterized by the presence of 20 to 100 polyps in the large intestine, localized mainly in the proximal parts. Clinical manifestations occur at the age of 40–45 years, and polyp malignancy occurs at the age of over 50 years. The weakened form occurs in about 8% of patients with APS. With a weakened form of APS, mutations in the *APC* gene are detected in about 20% of observations. In other cases, when 20–99 polyps are detected, the presence of the wild-type *APC* gene is detected.
3. *MutYH*-associated polyposis (MAP) caused by the presence of 2 non-allelic mutations in the *MutYH* gene, in contrast to the classical and weakened forms, in which mutations occur in the *APC* gene [24–27].
Despite the localization of mutations in different genes, MAP can manifest itself as a classical form of APS (100 or more polyps) and weakened form (20–99 polyps). Unlike the classical and weakened forms of APS, MAP **always** reveals 2 mutations in the *MutYH* gene.
4. Preclinical Form. This variant of the disease includes clinical situations when a relative of a patient with APS had a characteristic mutation, but colonoscopy did not reveal colon polyps.

1.6 Clinical Picture of a Disease or Condition (Group of Diseases or Conditions)

The most frequent manifestations of the disease *in the classical form of APS* are changes in the frequency and consistency of stool — diarrheal syndrome, metabolic disorders, as well as the presence of blood and mucus

impurities in the stool, abdominal pain. In addition, the characteristic symptoms are also general weakness, dizziness, which develop against the background of anemia. The first symptoms appear at the age of 14–16 years, and malignant degeneration of polyps occurs at the age of 18–40 years. With late treatment, there may be signs of intestinal patency disorders.

With a weakened form of APS, the main complaints in patients are the discharge of blood, mucus from the anus. At the same time, the first symptoms of the disease appear at the age of 20–45 years, and malignant degeneration of polyps often occurs at the age of over 40 years. Most often, the diagnosis of a weakened form of APS is established as a result of examination for clinical symptoms characteristic of the presence of a malignant tumor of the colon.

MutYH-associated polyposis is similar in clinical picture to the weakened form of APS.

In addition, patients with APS have a high risk of developing malignant neoplasms of extra-intestinal localization: duodenal, stomach, thyroid, brain cancer, hepatoblastomas (may occur in children), tumors of the hepatobiliary system [23].

2. DIAGNOSIS OF A DISEASE OR CONDITION, MEDICAL INDICATIONS AND CONTRAINDICATIONS TO THE USE OF DIAGNOSTIC METHODS

Diagnosis of APS is based on the clinical picture of the disease, family history data, endoscopic picture and molecular genetic study.

When establishing the diagnosis of APS, it is necessary to carry out differential diagnosis with other diseases and hereditary syndromes:

- Colon cancer
- Lynch syndrome
- Peitz-Jaegers syndrome
- Juvenile polyposis

Diagnosis Principles

The diagnosis of APS is established on the basis of the clinical picture (the presence of 20 or more colon polyps) and the results of genetic studies indicating the presence and localization of mutations in the gene. The last two criteria are especially important for a clinical geneticist, whose participation in the APS diagnosis is necessary as part of the multidisciplinary team work.

In the presence of 100 or more colon polyps, a diagnosis of the classical form of APS is established. When a mutation is detected in the *APC* gene, the localization of the mutation is indicated. For example:

"Adenomatous polyposis syndrome, classical form. Mutation in the *APC* gene c.2730-2737del8."

If a mutation in the *APC* gene is not detected in the patient, then the presence of the wild-type *APC* gene is established. In this case, the diagnosis is formulated as follows:

"Adenomatous polyposis syndrome, classical form. The wild-type *APC* gene."

With the classical form of APS and the detection of a soft tissue tumor, a diagnosis of Gardner syndrome is established, and also the nature, localization and size of the soft tissue tumor are indicated, for example:

"Adenomatous polyposis syndrome, classical form. Mutation in the *APC* gene c.2730-2737del8. Gardner syndrome, desmoma of the anterior abdominal wall 6 × 13 cm."

With the classical form of APS and the detection of a tumor of the posterior cranial fossa, the diagnosis of Turko syndrome is established. This part of the diagnosis is formed by a neurosurgeon, for example:

"Adenomatous polyposis syndrome, classical form. Mutation in the *APC* gene c.2730-2737del8. Turko syndrome, medulloblastoma of the cerebellum."

When 20–99 colon polyps are detected, the weakened form of APS is diagnosed. With the weakened form, the number and size of the identified polyps must be indicated, as well as the localization of the mutation in the *APC* gene, for example:

"Adenomatous polyposis syndrome, weakened form (52 colon polyps, 3–28 mm). Mutation in the *APC* p.Arg405X gene."

If in the presence of 20–99 colon polyps a mutation in the *APC* gene is not detected, then the wild type of the *APC* gene is stated, for example:

"Adenomatous polyposis syndrome, weakened form (34 colon polyps, 8–34 mm), wild-type *APC* gene."

If a mutation in the *APC* gene is detected in the patient's relatives, then even in the absence of colon polyps, it is necessary to diagnose APS, while the localization of the mutation is necessarily indicated, for example:

"Adenomatous polyposis syndrome, preclinical form. Mutation in the *APC* gene c.2730-2737del8."

If a patient has 2 biallel mutations in the *MutYH* gene, the diagnosis of MAP is established, while the number and size of polyps are indicated, as well as the localization of mutations in the *MutYH* gene, for example:

"Adenomatous polyposis syndrome. *MutYH-associated* polyposis (14 polyps, 6–25 mm). Mutations in the *MutYH* p.R231H and p.G382D gene."

With MAP, if the number of polyps is more than 100, then the exact number and size of polyps are not indicated, for example:

"Adenomatous polyposis syndrome. *MutYH-associated* polyposis (more than 100 polyps). Mutations in the *MutYH* p.R231H and p.G382D gene."

If 2 mutations in the *MutYH* gene are detected in the patient's relatives, even in the absence of polyps during colonoscopy, the diagnosis of APS is established, for example:

"Adenomatous polyposis syndrome. *MutYH*-associated polyposis. Mutations in the *MutYH* p.R231H and p.G382D gene. Preclinical stage."

When a malignant tumor of the colon is detected in APS, a cancer diagnosis should be the first in the diagnosis establishment, for example:

"Cancer of the ascending intestine T4N0M0. Adenomatous polyposis syndrome, the classical form. Mutation in the *APC* gene c.2730-2737del8."

2.1 Complaints and Anamnesis

Patients with APS are most characterized by complaints of frequent, loose stools, abdominal pain, the presence of pathological impurities in the stool (blood, mucus). Some patients may complain of general weakness, weight loss, bloating, nausea.

• For all patients who, according to their anamnesis and instrumental examination, have (had) a total of more than 20 colon polyps, as well as those who have a family history of APS or a history of having any number of polyps in the colon had extra-intestinal manifestations of APS (multiple duodenal/gastric adenomas, desmoid tumors, papillary thyroid cancer, epidermal cysts, osteomas), it is **recommended** to compile a pedigree with subsequent analysis of the type of inheritance characteristic of this family (autosomal dominant, autosomal recessive) [24,28–30].

Category of recommendations — A (Level of evidence — 1)

2.2 Physical Examination

All patients with suspected APS should undergo a physical examination:

- *General examination;*
- *Examination and palpation of the abdomen;*
- *External examination of the perineum and anus;*
- *Digital rectal examination.*

During the general examination of the patient, attention is paid to the body mass index, pallor and dryness of the skin, the presence/absence of extra-intestinal manifestations (soft tissue tumors, sebaceous glands). The examination and palpation of the abdomen is carried out in order to identify tumors of the abdominal organs, desmoid tumors and to assess the condition of the inguinal lymph nodes.

The examination of the perianal area is carried out on a gynecological chair in the position of the patient on his back with his legs maximally brought to the abdomen, and if impossible — in the side position.

During an external examination of the perineum and anus, attention is paid to changes in the perianal skin, the shape of the anus, its gaping, the presence of any changes and deformities. Digital rectal examination assesses the presence or absence of polyps in the lower ampullary rectum and their size, as well as the presence or absence of malignant neoplasms on their background. Attention should be paid to the tone and volitional contractions of the anal sphincter to assess the condition of the rectal occlusion apparatus(ROA).

2.3 Laboratory Diagnostic Tests

• All patients with suspected APS are **recommended** to undergo a molecular genetic blood test for the presence of mutations in the *APC/MutYH* genes [31–36].

Category of recommendations — C (Level of evidence — 4)

Comments: *This method allows to establish not only the presence of the disease in the patient, but also to determine the probability of its development in a still healthy child. All patients with more than 20 adenomatous polyps in the colon need to perform DNA diagnostics of the entire coding sequence of APC/MutYH genes. Moreover, if a patient has more than 100 polyps, then in order to save time, it is advisable to start the study with the APC gene, and if their number is from 20 to 100, then with the MutYH gene [19,21,22,34].*

Technique: blood is taken from a patient with APS, the coding regions of the APC/MutYH genes are examined. If a mutation is detected, blood is taken from his/her blood relatives. Since mutations in blood relatives are localized in the same parts of the gene as in the patient, a targeted study of the identified affected part of the gene is carried out. If the presence of a mutation is confirmed, the patient under study is diagnosed with APS and an endoscopic examination is prescribed.

• All blood relatives of the patient with a confirmed presence of a mutation in the *APC/MutYH* genes (children, siblings, nephews and nieces) are recommended to undergo a molecular genetic study to search for a similar mutation, in case of detection of which they should undergo lifelong clinical monitoring and timely surgeries to avoid malignant transformation of polyps [31–33].

Category of recommendations — C (Level of evidence — 5)

In the absence of mutations in the APC and MutYH genes in patients with a clinical picture of APS, the expediency of genetic testing of all his/her blood relatives disappears. But all these relatives are potentially at risk of developing colon cancer and need lifelong monitoring.

In addition, iron deficiency anemia can be diagnosed in patients with suspected APS according to the results of a general (clinical) blood test, and a biochemical blood test can reveal electrolyte and metabolic disorders, hypoproteinemia (in particular, hypoalbuminemia).

2.4 Instrumental Diagnostic Examinations

• It is **recommended** for all patients with suspected APS to undergo a total colonoscopy with multiple biopsy (if necessary) [17,19,26, 28].

Category of recommendations — C (Level of evidence — 5)

Comments: *Colonoscopy is the main and most accurate method of diagnosing APS. In this study, the extent of lesion on various parts of the colon by polyps is determined, which directly influences the choice of treatment tactics. With the help of a biopsy, data on the malignant transformation of polyps in various parts of the colon are obtained.*

• It is **recommended** for all patients with APS to undergo EGDS to determine the presence/absence of polyps in the stomach, duodenum and their malignant transformation [37–41].

Category of recommendations — C (Level of evidence — 4)

• CT of the abdominal cavity and pelvis is **recommended** for all patients with APS in order to exclude tumors of extra-intestinal localization and desmoid tumors of intraabdominal localization [35,36,42,43].

Category of recommendations — C (Level of evidence — 4)

Comments: *In the presence of malignant tumors against the background of APS, CT scans of the chest organs are additionally performed to determine the prevalence of the malignant process and diagnose distant tumor metastasis.*

• When planning a surgery with the formation of a small intestinal reservoir in a patient with APS, it is **recommended** to conduct a physiological study of the functions of the sphincter occlusion apparatus of the rectum to exclude the initial incontinence of the anal sphincter, which may negatively affect the functional results of the surgery [44,45].

Category of recommendations — C (Level of evidence — 5)

• In the presence of malignant rectal tumors against the background of APS, it is **recommended** to perform magnetic resonance imaging of the pelvis to assess the presence of malignant transformation and the depth of invasion [35,51,59].

Category of recommendations — B (Level of evidence — 3)

Comments: *If a patient with APS has a neoplasm with suspected malignancy or a malignant tumor of the colon, it is necessary to conduct additional examination methods provided for by Clinical Recommendations for the diagnosis and treatment of colon cancer, rectal cancer.*

2.5 Other Diagnostic Tests

They are not available.

3. TREATMENT, INCLUDING DRUG AND NON-DRUG THERAPY, DIET THERAPY, ANESTHESIA, MEDICAL INDICATIONS AND CONTRAINDICATIONS TO THE USE OF TREATMENT METHODS

3.1 Conservative Treatment

There are no methods of non-surgical treatment of APS [1,2,35,47].

3.2 Surgical Treatment

Currently, the main method of treating APS is surgical. At the same time, the APS treatment should be performed in specialized hospitals, since the incidence of complications and the functional outcome significantly depend on the qualifications of the surgeon (in particular, on the number of similar surgeries performed) [48].

• When performing surgeries in patients with APS, it is **recommended** to use laparoscopic technologies if technically possible [49,50,83,84].

Category of recommendations — A (Level of evidence — 2)

Comments: *The use of laparoscopic technologies reduces surgical trauma, reduces the level of perioperative*

complications, provides the possibility of early activation of the patient, as well as shortening the rehabilitation period [50]. In addition, in patients with APS the use of laparoscopic technologies reduces the risk of infertility by 90% [83].

3.2.1 Classical Form of APS

Taking into account the genetically determined nature of the disease (hence, the lack of conservative treatment options), as well as the obligate-precancerous status of the disease, the only possible method of surgical treatment is the removal of the target organ — the colon.

- With the confirmed classical form of APS, all patients are **recommended** to undergo coloproctectomy with the formation of a small intestinal reservoir, reservoir-anal anastomosis, preventive ileostomy [52,53, 86].

Category of recommendations — C (Level of evidence — 4)

Comments: *Taking into account the young age of patients (in the classical form of the disease, manifestation occurs in 2–3 decades of life), with the potential purpose of social adaptation after removal of the colon, a plastic stage of surgery is performed — the formation of a reservoir from the distal loop of the ileum, the reduction of the resulting structure into the pelvic cavity with the imposition of a reservoir-anal anastomosis and a preventive double-barreled ileostomy [53].*

To improve the quality of life of patients, during surgery it is possible to preserve 1–2 cm of the rectal wall in the supra anal area for the formation of an anastomosis by hardware. If it is impossible to form an anastomosis using a stitching device, abdominal-anal resection of the rectum should be performed and a manual reservoir-anal anastomosis should be applied. Despite the fact that a small fragment of the mucous membrane is preserved when using a stitching device, the risk of cancer in this area is low and corresponds to that in the formation of a manual anastomosis [54].

Reconstructive surgery to restore intestinal continuity — closure of the ileostomy — is performed not earlier than 1.5–2 months after the initial surgery, provided that the sutures of the small intestine reservoir are consistent, as well as reservoir-anal anastomosis (according to the results of retrograde radiological examination with contrast — reservoir imaging) [2].

- A patient with the classical form of APS, in the presence of contraindications to the formation of a small intestinal reservoir and a reservoir-anal anastomosis, is **recommended** to undergo a coloproctectomy with the formation of a terminal ileostomy [35].

Category of recommendations — C (Level of evidence — 5)

Comments: *Contraindications to performing coloproctectomy with the formation of a small intestinal reservoir and reservoir-anal anastomosis are: the presence of a desmoid tumor involving the mesentery of the small intestine, as well as anatomical features of the mesentery of the small intestine, excluding the possibility of relegation to the pelvic cavity; the presence of low-lying rectal cancer with germination into surrounding tissues and infiltration of pelvic floor elements; as well as the patient's refusal of the plastic component of the surgery in favor of the formation of a permanent ileostomy (due to personal preferences or malfunction of the rectal occlusion apparatus) [35].*

3.2.2 Weakened form of APS

The choice of the method of surgical treatment of the weakened form of APS depends on the age of the manifestation of the disease, the number, type, size and localization of the identified colon polyps, as well as the results of genetic research.

- A patient with the weakened form of APS, with the possibility of complete endoscopic colon sanitation and the presence of no more than 10 polyps > 1 cm in size, is **recommended** to undergo endoscopic removal of colon polyps [55,87].

Category of recommendations — C (Level of evidence — 5)

Comments: *It should be remembered that regardless of the results of endoscopic polypectomy, patients require regular dynamic monitoring, since this method is exclusively supportive and cannot replace radical surgery [55]. Contraindications to endoscopic polypectomy are: suspicion of the presence of malignancy in any of the polyps, the presence of high-grade dysplasia in the polyp tissue according to the results of biopsy, a significant increase in the number and size of polyps in the period between the two nearest colonoscopies [55].*

- With the weakened form of APS and the detection of a biallel mutation in the *MutYH* gene, as well as with the detection of an insignificant number of polyps in the rectum, colectomy with the formation of an ileorectal anastomosis is **recommended** [35,56,57].

Category of recommendations — C (Level of evidence — 4)

Comments: *The clinical picture of APS caused by the mutation in the MutYH gene is characterized by a predominant lesion of the right colon and an insignificant number*

of polyps in the rectum, and therefore its preservation is possible during surgical treatment [56]. If the weakened form of APS is detected in patients over 45 years of age with no signs of polyp malignancy and a predominant lesion of the right colon, it is also possible to preserve the rectum and form an ileorectal anastomosis. After performing this surgery, patients need annual endoscopic monitoring with the removal of newly formed polyps in the rectum [57].

3.2.3 MAP

- A patient with MAP in the presence of 20–99 polyps and the possibility of complete endoscopic colon sanitation (in the presence of no more than 10 polyps > 1 cm in size) is **recommended** to undergoendoscopic removal of colon polyps [12, 87].

Category of recommendations — C (Level of evidence — 5).

- When detecting a biallel mutation in the *MutYH* gene, as well as when detecting a small number of polyps in the rectum, it is **recommended** to perform a colectomy with the formation of an ileorectal anastomosis [35,56,57].

Category of recommendations — C (Level of evidence — 5).

- With MAP with the number of polyps of 100 or more, all patients are **recommended** to undergo coloproctectomy with the formation of a small intestinal reservoir, reservoir-anal anastomosis, preventive ileostomy [12,86].

Category of recommendations — C (Level of evidence — 4).

3.3 Treatment of CRC on the Background of APS

In most cases, the diagnosis of APS reveals the presence of single or synchronous multiple malignized tumors of the colon. At the same time, the symptoms of CRC often play a leading role in the clinical picture.

When detecting a malignant colon tumor in a patient with APS, it is advisable to conduct neoadjuvant /adjuvant treatment (if necessary) for CRC (see clinical recommendations 'Malignant neoplasms of the colon and rectosigmoid department' and 'Rectal cancer') [58,59]. With the development of CRC against the background of APS, the priority is the treatment of oncological disease according to its localization and degree of prevalence [58,59].

- In the surgical treatment of a patient with CRC on the background of APS, it is **recommended** to perform surgery according to the oncological principles set out in the 'Clinical guidelines for the diagnosis and treatment of colon and rectal cancer' [58,59], supplementing it with the removal of the remaining parts of the colon.

Category of recommendations — C (Level of evidence — 5).

3.4 Treatment of Desmoid Tumors in Patients with APS

Desmoid tumors are histologically benign, but potentially locally aggressive neoplasms that affect about 15% of patients with APS. Unlike other desmoid tumors, APS-associated desmoids are usually located in the abdominal cavity and involve the mesentery of the small intestine. Most of them occur after surgery. Risk factors for the development of desmoids are considered to be the presence of such tumors in the family history, intra-abdominal surgeries, as well as the location of the pathogenic mutation in the range from 148 to 1,800 codons in the *APC* gene [60]. If these factors coincide, the risk of developing an intra-abdominal desmoid tumor reaches 65% [61].

There are no proven predictors of desmoid tumor growth. Some of them may spontaneously stop growing, some regress, and others continue to grow nonstop. In a small number of patients, this growth may be rapid and uncontrolled.

- When a desmoid tumor located in the thickness of the abdominal wall or in the abdominal cavity is detected in patients with APS, conservative therapy with high-dose drugs of the antiestrogen group in combination with a nonsteroidal anti-inflammatory drug from the group of acetic acid derivatives and related compounds is **recommended** [35,88].

Category of recommendations — C (Level of evidence — 5).

Comments: *Due to the insignificant quantity and quality (retrospective, uncontrolled) of the studies conducted, there is no convincing data on priority methods of treatment of desmoid tumors. However, in a prospective cohort study involving 64 patients with desmoid intraperitoneal tumors that occurred against the background of APS, after treatment with high-dose estrogen receptor modulators in combination with a nonsteroidal anti-inflammatory drug from the group of acetic acid derivatives, a tumor response (in the form of stabilization or regression) was demonstrated in 85% of cases after at least 1 year of treatment with high-dose estrogen receptor modulators in combination with a nonsteroidal anti-inflammatory drug*

from the group of acetic acid derivatives. After achieving a positive response, the dose of drugs was reduced in 60% of patients, against this background, only one recurrence of the tumor was noted after 10 years [62]. Thus, the role of surgical treatment of desmoid tumors should be limited to the correction of secondary changes due to the local nature of tumor growth — obstruction of the gastrointestinal tract, urinary tract, etc.

4. MEDICAL REHABILITATION AND SPA TREATMENT, MEDICAL INDICATIONS AND CONTRAINDICATIONS TO THE USE OF REHABILITATION METHODS, INCLUDING THOSE BASED ON THE USE OF NATURAL THERAPEUTIC FACTORS

There are no specific rehabilitation measures for patients with APS. In a number of patients in whom surgeries for APS resulted in the formation of a small intestinal reservoir and a reservoir-anal anastomosis, a decrease in the holding function is possible. Medical rehabilitation measures are aimed at the fastest possible recovery in the postoperative period, achieving a socially acceptable degree of adaptation of patients in society after surgical treatment. At the same time, rehabilitation of such patients is carried out in three stages: the 1st stage (early rehabilitation) is carried out immediately after surgery on the 14th day. The main tasks are: restoration of normal functioning of the gastrointestinal tract, control of homeostasis, relief of postoperative pain syndrome, activation of the patient, healing of postoperative wounds. The second stage of rehabilitation begins after 15 days and continues as necessary in the future, aimed at the final healing of postoperative wounds with monitoring of the activity of the gastrointestinal tract and the other body systems. This stage can be carried out both on an outpatient basis and in a day- or 24-hourhospital. The third stage of rehabilitation is carried out in the late postoperative period in patients with both permanent ileostomy and before reconstructive and recovery surgery.

The main rehabilitation actions at this stage are compensation of the gastrointestinal tract function, as well as measures aimed at identifying and correcting the function of the rectal occlusion apparatus.

Patients with APS who have undergone surgery with the formation of a temporary/permanent ileostomy need to use colostomy bags and stoma care products [63]. To care for the stoma in the early postoperative period, a special postoperative colostomy bag is used, which is glued immediately after the surgery. A hole corresponding to the size of the stoma is cut out in the plate. A transparent bag and a removable lid allow to monitor the condition of the stoma in the early postoperative period. For further care of the stoma, a one- or two-component system is selected for the patient, taking into account the functional features of the stoma, the relief of the peristomal area, individual preferences and the patient's training opportunities.

- In patients with APS, before performing reconstructive and recovery surgery, it is recommended to examine the sphincter (occlusion) apparatus functions of the rectum (sphincterometry, profilometry, a study of conduction along the sacral nerve), with the followed consultations with a doctor of functional diagnostics when functional disorders are detected [45].

Category of recommendations — C (Level of evidence — 5).

Comments: *In a number of patients whose surgeries for APS resulted in the formation of a small intestinal reservoir, there may be a decrease in the holding function due to the removal of an ampoule of the rectum and intraoperative traumatization of the occlusion apparatus due to the formation of a reservoir-anal anastomosis [64,85].*

- If a patient with APS who underwent coloproctectomy with the formation of a small-intestinal reservoir and reservoir-anal anastomosis is found to have 2–3 degree anal sphincter incontinence before reconstructive surgery, it is **recommended** to conduct a 10-day cycle of electrostimulation using biofeedback therapy and tibial neuromodulation in a day or 24-hourhospital in order to improve the expected quality of life of patients [46, 65].

Category of recommendations — C (Level of evidence — 4).

Comments: *In the rehabilitation of patients with anal sphincter incontinence, according to the literature, a treatment method based on biofeedback (BFB) has found wide application aimed at improving the contractility of the muscles of the external sphincter and pelvic floor by increasing both the strength and duration of arbitrary compression [46, 65]. This method involves the body's own resources in the rehabilitation process with the development of the right skills at the level of creating new conditioned reflex connections. The method of tibial neuromodulation is also effective, in which an electric current along one nerve pathway modulates pre-existing activity in other nerve pathways or centers. Percutaneous electrical stimulation of the posterior tibial nerve is used for functional*

diseases of the pelvic organs, since fibers from the II and III sacral segments of the spinal cord pass through the posterior tibial nerve, which play a significant role in the innervation of the rectum, bladder and their sphincters. It has been proved that the muscle structures of the disabled occlusion apparatus can respond to biofeedback therapy and tibial neuromodulation with an increase in both tone and strength of volitional contractions [46, 65]. Stimulation of the tibial nerve is carried out using a cutaneous stimulating electrode, which allows the patient to continue the course of treatment independently at home after a course of preliminary training. In this case, the course of treatment with daily stimulation sessions can be extended up to 1–3 months.

The effectiveness of the BFB therapy is monitored before and after each course of procedures by a comprehensive physiological study of the function of the rectal occlusion apparatus (sphincterometry + physiological study of the reservoir function of the formed reservoir). With an improvement in the tone and contractility of the anal sphincters, the question of performing reconstructive and recovery surgery aimed at resuming the natural passage through the gastrointestinal tract can be raised [46].

5. PREVENTION AND DISPENSARY SUPERVISION, MEDICAL INDICATIONS AND CONTRAINDICATIONS TO THE USE OF PREVENTION METHODS

Taking into account the fact that APS is a hereditary disease, there is no specific prevention of it [1,2].

Despite this, there is evidence of the study of the use of nonsteroidal anti-inflammatory drugs as chemoprophylactic agents in patients with APS. At the same time, it was demonstrated that the administration of nonsteroidal anti-inflammatory drugs from the group of acetic acid derivatives, as well as from the group of coxibs, reduces the number and size of polyps in the short term [66–69]. However, long-term cancer prevention as an endpoint was not achieved in large randomized trials [70–72].

Considering APS as an obligate precancerous disease, it is important to clarify that the only way to prevent CRC is timely surgical treatment described in paragraph 3. Preventive measures also include careful collection of a family history of a patient with APS, conducting the necessary genetic research and a comprehensive examination of the closest blood relatives for timely detection of patients with APS before the onset of clinical symptoms.

APS is often accompanied by the development of multiple polyps also in the upper gastrointestinal tract (stomach, duodenum). At the same time, fundal gland polyps are detected in 80% of patients with APS [73] and are completely benign formations without malignant potential, without increasing the risk of developing stomach cancer [74]. At the same time, the presence of adenomatous polyps in the duodenum in APS is associated with the risk of cancer in 5% of cases [75].

- Patients with APS are **recommended** to undergo esophagogastroduodenoscopy from the age of 25 years, and in those patients diagnosed with APS at a later age — from the moment of diagnosis of APS [35, 41].

Category of recommendations — C (Level of evidence — 5).

Comments: *Given the incidence of duodenal cancer reaching 5%, preventive removal of the organ is not used. At the same time, for those patients whose duodenal cancer was diagnosed during dynamic follow-up, an advantage in survival was demonstrated compared to those who went to the doctor already with clinical symptoms [76]. Currently, it is customary to use Spigelman, A.D.'s classification for stagingduodenal lesions and determining observation intervals (Table 1).*

- All patients with APS who have undergone coloproctectomy with the formation of ileorectal/reservoir-anal anastomosis are **recommended** to undergo an annual endoscopic examination of the remaining part of the rectum, the small intestine reservoir [12,35,36].

Category of recommendations — C (Level of evidence — 5).

Comments: *In the part of the rectum remaining after surgery, new polyps may appear, which, in the absence of the necessary control, are prone to malignancy. In addition, 12–18 months after the closure of the ileostomy, morphological changes of the epithelial lining develop in the reservoir, characterized by flattening and reduction of the number of villi, leading to their atrophy ("colonic metaplasia"), which potentially leads to the risk of malignant transformation of the mucous membrane of the reservoir [79,80]. Thus, out of 212 patients observed within the framework of the Netherlands Polyposis Registry, the cumulative risk of developing adenoma in the small intestine reservoir at 10-year follow-up was 45%: twenty-five patients (11.8%) developed adenoma with severe dysplasia, and four patients (1.9%) developed carcinoma. The cumulative risk of developing cancer in the reservoir at 10-year follow-up was 1% [81].*

Table 1. *Classification of duodenal lesions in APS and appropriate management tactics (according to Spigelman A.D. [77,78]).*

	Number of points		
	1	**2**	**3**
Number of polyps	1-4	5-20	> 20
Polyp size, mm	1-4	5-10	> 10
Histological structure	Tubular	Tubular-villous	Villous
Degree of dysplasia	Weak	Moderate	Severe

Total points	**Stage**	**Recommended tactics**
0	0	EGDS after 5 years
1-4	I	EGDS after 5 years
5-6	II	EGDS after 3 years
7-8	III	EGDS after one year, endoscopic intervention is possible
9-12	IV	EGDS after 6–12 months or endoscopic/surgical treatment

- All patients who have undergone surgery for APS are **recommended** to undergo an annual comprehensive ultrasound/CT of the abdominal cavity and pelvic organs for timely detection of possible desmoid tumors [89,90].

Category of recommendations — A (Level of evidence — 1).

Comments: *APS-associated desmoids, as a rule, are located in the abdominal cavity, involve the mesentery of the small intestine and occur after surgery. Risk factors for the development of desmoids are considered to be the presence of such tumors in the family history, surgeries in the abdominal cavity, as well as the location of a pathogenic mutation from 148 to 1,800 codon in the APC gene [60]. If these factors coincide, the risk of developing an intra-abdominal desmoid tumor reaches 65% [61,82].*

6. ORGANIZATION OF MEDICAL CARE

Medical care, with the exception of medical care within the framework of clinical approbation, in accordance with Federal Law No. 323-FZ of 21.11.2011 (ed. of 47 25.05.2019) 'On the basics of protecting the health of citizens in the Russian Federation' is organized and provided:

1) In accordance with the regulations on the organization of medical care by type of medical care, which is approved by the authorized federal executive authority.
2) In accordance with the procedures for providing assistance in the "Coloproctology" profile, which is mandatory for all medical organizations on the territory of the Russian Federation.
3) Based on these clinical recommendations.
4) Taking into account the standards of medical care approved by the authorized federal executive authority.

Primary specialized medical and sanitary care for APS patients is provided by a coloproctologist, oncologist, gastroenterologist, and other specialist doctors in medical organizations licensed to provide appropriate types of medical activities.

In case of suspicion or detection of APS in a patient, internists, district internists, general practitioners (family doctors), specialist doctors, secondary medical workers, in accordance with the established procedure, refer the patient for consultation to a medical organization that has a coloproctologist's office and/or an outpatient coloproctology center (unit) to provide him/her with primary specialized health care. Consultation in the specified structural units of the medical organization must be carried out no later than 15 working days from the date of issuance of the referral for consultation.

The coloproctologist organizes a timely qualified examination of the patient, including determining the severity of clinical symptoms, endoscopic examination, taking biopsy material and consulting a geneticist. The geneticist finds out the family history, draws up a pedigree and prescribes DNA diagnostics in the genetics laboratory.

If treatment and in-depth examination in inpatient conditions are necessary, the patient is referred by the attending physician to the coloproctology unit or other medical organization providing inpatient medical care to patients in the "Coloproctology" profile.

A coloproctologist of a medical organization that includes a coloproctologist's office, an outpatient coloproctology center (unit), directs the patient to

medical organizations that have a coloproctology unit and a genetic laboratory in their structure to provide medical care in inpatient conditions (in case it is impossible to establish a diagnosis when providing primary specialized medical care), to provide specialized, including high-tech, medical care. The deadline for the start of specialized, with the exception of high-tech, medical care is determined by the decision of the commission for the selection of patients for hospitalization, depending on the severity of clinical symptoms; the period should not exceed 30 calendar days from the date of issuance of the referral for hospitalization.

Specialized, including high-tech, medical care for APS is provided by coloproctologists in medical organizations that have a coloproctology unit, have a license, the required material and technical base, certified specialists in inpatient and day hospital conditions, and includes diagnostics and treatment of APS that require the use of special methods and complex unique medical technologies as well as medical rehabilitation.

Indications for hospitalization in a 24-houror day hospital of a medical organization providing specialized, including high-tech, medical care for APS are determined by a coloproctologist with, if necessary, a multidisciplinary consultation.

The indication for hospitalization of a patient to a medical organization in an emergency or urgent form is:

1) The presence of complications of APS that require specialized medical care in an emergency and urgent form.
2) The presence of complications of the APS treatment that require specialized medical care in an emergency and urgent form.

The indication for hospitalization to a medical organization in a planned form is:

1) The need to perform complex diagnostic medical interventions that require follow-up in a 24-hour or day hospital.
2) The presence of indications for specialized treatment of APS (surgery), requiring observation in a 24-houror day hospital.

The indication for the patient discharge from the medical organization is:

1) Completion of a course of treatment or one of the stages of providing specialized, including high-tech, medical care, in a 24-houror day hospital, provided there are no complications of treatment requiring medication correction and/or medical interventions in a hospital setting.
2) Refusal by the patient or his/her legal representative from specialized, including high-tech, medical care in a 24-houror day hospital, established by the consultation of the medical organization providing APS treatment, provided there are no complications of the underlying disease and/or treatment requiring medication correction and/or medical interventions in inpatient conditions.

The need to transfer the patient to another medical organization according to the appropriate profile of medical care. The conclusion on the expediency of transferring the patient to a specialized medical organization is carried out after a preliminary consultation on the provided medical documents and /or a preliminary examination of the patient by specialist doctors of the medical organization to which the transfer is planned.

7. ADDITIONAL INFORMATION (INCLUDING FACTORS AFFECTING THE OUTCOME OF THE DISEASE OR CONDITION)

It is not available.

Criteria for assessing the quality of medical care

№	Quality criteria	Category of recommendations	Level of evidence
1.	All patients with suspected APS underwent colonoscopy	A	2
2.	All patients with APS underwent EGDS	B	3
3.	All patients with APS underwent CT of the abdominal cavity and pelvis	C	4
4.	All patients with suspected APS underwent a molecular genetic blood test for the presence of mutations in the *APC/MutYH* genes	A	2
5.	Sphincterometry was performed in patients who are planning to form a small intestinal reservoir	C	4
6.	Coloproctectomy was performed in the classical form of APS	C	5
7.	Colectomy was performed with the formation of an ileorectal anastomosis with the weakened form of APS	C	4

REFERENCES

1. Guide of coloproctology (edited by Yu.A.Shelygin, L.A. Blagodarny). M.: Litterra. 2012; 596 p. (in Russ.).
2. Tsukanov A.S., Shelygin Yu.A., Frolov S.A., Kuzminov A.M. Familial adenomatosis of the colon. *Surgeon*. 2017;3:14–24. (in Russ.).
3. Groden J, Thliveris A, Samowitz W, et al. Identification and characterization of the familial adenomatous polyposis coli gene. *Cell*. 1991;66:589–600.
4. Herrera L, Kakati S, Gibas L, et al. Gardner syndrome in man with an interstitial deletion of 5q. *Am J Med Genet*. 1986;25:473–476.
5. Joslyn G, Carlson M, Thliveris A, et al. Identification of deletion mutations and three new genes at the familial polyposis locus. *Cell*. 1991;66:601–613.
6. Nallamilli BRR, Hegde M. Detecting *APC* gene mutations in familial adenomatous polyposis (FAP). *Curr Protoc Hum Genet.* 2017;92:10.8.1–10.8.16. DOI: 10.1002/cphg.29
7. Fodde R. The *APC* gene in colorectal cancer. *Eur J Cancer*. 2002;38(7):867–871.
8. Tsukanov A.S., Pospekhova N.I., Shubin V.P., Kuzminov A.M., et al. Mutations in the *APC* gene in Russian patients with classic form of familial adenomatous polyposis. *Russian Journal of Genetics*. 2017;53(3):369–375.
9. Kastrinos F, Syngal S. Inherited Colorectal Cancer Syndromes. *Cancer J*. 2011;17(6):405–415.
10. Al-Tassan N, Chmiel NH, Maynard J, et al. Inherited variants of *MYH* associated with somatic G:C/T:A mutations in colorectal tumors. *Nature Genetics*. 2002;30:227–232.
11. Kantor M, Sobrado J, Patel S, et al. Hereditary Colorectal Tumors: A Literature Review on *MutYH*-associated Polyposis. *Gastroenterology Research and Practice*. 2017;2017:8693182. DOI: 10.1155/2017/8693182
12. Nielsen M, Infante E, Brand R. *MutYH* Polyposis. In: Adam M.P., Ardinger H.H., Pagon R.A. et al., editors. Gene Reviews® [Internet]. Seattle (WA): University of Washington, Seattle. 2012; 4 [Updated 2019 Oct].
13. Galiatsatos P, Foulkes WD. Familial adenomatous polyposis. *Am J Gastroenterol*. 2006;101(2):385–398.
14. Septer S, Lawson CE, Anant S, Attard T. Familial adenomatous polyposis in pediatrics: natural history, emerging surveillance and management protocols, chemopreventive strategies, and areas of ongoing debate. *Fam Cancer*. 2016;15(3):477–485.
15. Malignant neoplasms in Russia in 2018 (morbidity and mortality) (edited by A.D. Kaprin, V.V. Starinsky, G.V. Petrova). Moscow: P.A. Herzen Institute of Medical Research — Branch of the Federal State Budgetary Institution "NMIC of Radiology" of the Ministry of Health of Russia. 2019; pp. 11-12. (In Russ.).
16. Tsukanov A.S., Shubin V.P., Pospekhova N.I., Sachkov I.Yu., et al. Hereditary cancers of the gastrointestinal tract. *Practical oncology*. 2014;15(3):126–133. (In Russ.).
17. Rozen P, Macrae F. Familial adenomatous polyposis: The practical applications of clinical and molecular screening. *Fam Cancer.* 2006;5:227–235.
18. Tsukanov A.S., Pospekhova N.I., Shubin V.P., et al. Differential diagnosis of Lynch syndrome from other forms of non-polypous colorectal cancer among Russian patients. *Russian Journal of Gastroenterology, Hepatology, Coloproctology.* 2014;24(2):78–84. (In Russ.).
19. Grover S, Kastrinos F, Steyerberg EW, et al. Prevalence and phenotypes of APC and *MutYH* mutations in patients with multiple colorectal adenomas. *JAMA*. 2012;308:485–492.
20. Scheuner M, McNeel T, Freedman A. Population prevalence of familial cancer and common hereditary cancer syndromes. The 2005 California Health Interview Survey. *Genet Med*. 2010;12:726–735.
21. Tsukanov A.S., Shubin V.P., Kuzminov A.M. et al. Differential diagnosis of *MutYH*-associated polyposis and sporadic colon polyps. *Russian Journal of Gastroenterology, Hepatology, Coloproctology.* 2018;28(6):51–57. (In Russ.). DOI: 10.22416/1382-4376-2018-28-6-51-57
22. Grover S, Kastrinos F, Steyerberg EW, et al. Prevalence and Phenotypes of *APC and MutYH* Mutations in Patients with Multiple Colorectal Adenomas. JAMA. 2012;308(5):485–492.
23. Dinarvand P, Davaro EP, Doan JV, et al. Familial Adenomatous Polyposis Syndrome: An Update and Review of Extraintestinal Manifestations. *Arch Pathol Lab Med*. 2019;143(11):1382–1398.
24. Brensinger JD, Laken SJ, Luce MC, et al. Variable phenotype of familial adenomatous polyposis in pedigrees with 3′ mutation in the *APC* gene. *Gut*. 1998;43(4):548–552.
25. Soravia C, Berk T, Madlensky L, et al. Genotype-phenotype correlations in attenuated adenomatous polyposis coli. *Am J Hum Genet.* 1998;62:1290–1301.
26. Lal G, Gallinger S. Familial adenomatous polyposis. *Seminars in Surgical Oncology*. 2000;18:314–323.
27. Novelli M. The pathology of hereditary polyposis syndromes. *Histopathology*. 2015;66(1):78–87.
28. Barrow P, Khan M, Lalloo F, Evans DG, et al. Systematic review of the impact of registration and screening on colorectal cancer incidence and mortality in familial adenomatous polyposis and Lynch syndrome. *Br J Surg*. 2013;100:1719–1731.
29. Riley BD, Culver JO, Skrzynia C, et al. Essential elements of genetic cancer risk assessment, counseling, and testing: updated recommendations of the National Society of Genetic Counselors. *J Genet Couns*. 2012;21:151–161.
30. Brensinger JD, Laken SJ, Luce MC, et al. Variable phenotype of familial adenomatous polyposis in pedigrees with 3′ mutation in the *APC* gene. *Gut*. 1998;43(4):548–552.
31. Talseth-Palmer BA. The genetic basis of colonic adenomatouspolyposis syndromes. *Hereditary Cancer in Clinical Practice.* 2017;15:5. DOI 10.1186/s13053-017-0065-x
32. Jass JR. Colorectal polyposes: from phenotype to diagnosis. *Pathol Res Pract*. 2008;204(7):431–47.

33. Friedl W, Caspari R, Sengteller M, et al. Can *APC* mutation analysis contribute to therapeutic decisions in familial adenomatous polyposis? Experience from 680 FAP families. *Gut*. 2001;48:515–521.
34. Tsukanov A.S. Strategy of complex molecular genetic study of hereditary forms of colorectal cancer in Russian patients (abstract. ... doctor of medical sciences). Moscow. 2017; 48 p. (In Russ.).
35. Herzig D, Hardiman K, Weiser M, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Inherited Polyposis Syndromes. *Dis Colon Rectum.* 2017;60(9):881–894.
36. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol.* 2015;110(2):223–263.
37. Groves CJ, Saunders BP, Spigelman AD, Phillips RK. Duodenal cancer in patients with familial adenomatous polyposis (FAP): results of a 10-year prospective study. *Gut*. 2002;50:636–634.
38. Spigelman A, Talbot I, Williams C, et al. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. *Lancet*. 1989;334(8666):783–785.
39. Brosens LA, Keller JJ, Offerhaus GJA, et al. Prevention and management of duodenal polyps in familial adenomatous polyposis. *Gut*. 2005;54(7):1034–1043.
40. Leone PJ, Mankaney G, Sarvapelli Sh, et al. Endoscopic and histologic features associated with gastric cancer in familial adenomatous polyposis. *Gastrointest Endosc*. 2019;89(5):961–968.
41. Kallenberg FGJ, Bastiaansen BAJ, Dekker E, Cap-assisted forward-viewing endoscopy to visualize the ampulla of Vater and the duodenum in patients with familial adenomatous polyposis. *Endoscopy*. 2017;49(2):181–185.
42. de Marchis ML, Tonelli F, Quaresmini D, et al. Desmoid Tumors in Familial Adenomatous Polyposis. *Anticancer Res.* 2017;37(7):3357–3366.
43. Campos FG, Martinez CA, Novaes M, Nahas SC. Desmoid tumors: clinical features and outcome of an unpredictable and challenging manifestation of familial adenomatous polyposis. *Fam Cancer*. 2015;14(2):211–219.
44. Budtuev A.S., Pikunov D.Yu., Rybakov E.G., Sevostyanov S.I. Low anterior rectal resection syndrome and methods of its surgical correction. *Bulletin of Surgery named after I.I. Grekov*. 2014;173(4):106–110. (in Russ.).
45. Podberezskaya A.A., Salmin R.M., Mogilevets E.V., et al. Modern surgical methods of treatment of colon polyposis. *Journal of Grodno State Medical University.* 2016;4(56):26–29. (in Russ.).
46. Fomenko O.Yu., Achkasov S.I., Titov A.Yu. et al. Modern possibilities of improving the functional state of the locking device in patients with the presence of preventive intestinal stomas. *Russian Journal of Gastroenterology, Hepatology, Coloproctology*. 2015;25(5):77–83. (in Russ.).
47. Roncucci L, Pedroni M, Mariani F. Attenuated adenomatous polyposis of the large bowel: Present and future. *World J Gastroenterol.* 2017;23(23):4135–4139.
48. Burns EM, Bottle A, Aylin P, et al. Volume analysis of outcome following restorative proctocolectomy. *Br J Surg.* 2011;98:408–417.
49. Sylla P, Chessin DB, Gorfine SR. et al. Evaluation of onestage laparoscopic-assisted restorative proctocolectomy at a specialty center: comparison with the open approach. *Dis Colon Rectum*. 2009;52(3):394–399.
50. Zhang H, Hu S, Zhang G, et al. Laparoscopic versus open proctocolectomy with ileal pouch-anal anastomosis. *Minim Invasive Ther Allied Technol*. 2007;16(3):187–191.
51. Norenberg D, Sommer WH, Thasler W, et al. Structured Reporting of Rectal Magnetic Resonance Imaging in Suspected Primary Rectal Cancer: Potential Benefits for Surgical Planning and Interdisciplinary Communication. *Invest Radiol.* 2017;52(4):232–239.
52. Ellis CN. Colonic adenomatous polyposis syndromes: clinical management. *Clin Colon Rectal Surg.* 2008;21:256–262.
53. Aziz O, Athanasiou T, Fazio VW, et al. Meta-analysis of observational studies of ileorectal versus ileal pouch-anal anastomosis for familial adenomatous polyposis. *Br J Surg*. 2006;93:407–417.
54. Tajika M, Niwa Y, Bhatia V, et al. Risk of ileal pouch neoplasms in patients with familial adenomatous polyposis. *World J Gastroenterol*. 2013;19:6774–6783.
55. Lynch PM, Morris JS, Wen S, et al. Proposed staging system and stage-specific interventions for familial adenomatous polyposis. *Gastrointest Endosc*. 2016;84(1):115–125.
56. Knudsen A, Bisgaard M, Bulow S. Attenuated familial adenomatous polyposis (AFAP). A review of the literature. *Fam Cancer*. 2003;2:43–55.
57. Nascimbeni R, Pucciarelli S, Di Lorenzo D, et al. Rectum-sparing surgery may be appropriate for biallelic *MutYH*-associated polyposis. *Dis Colon Rectum*. 2010;53:1670–1675.
58. Clinical recommendations "Malignant neoplasms of the colon and rectosigmoid department", 2020. http://cr.rosminzdrav.ru/recomend/396 1. (in Russ.).
59. Clinical recommendations "Rectal cancer", 2020. http://cr.rosminzdrav.ru/recomend/554_2. (in Russ.).
60. Nieuwenhuis MH, Lefevre JH, Bulow S, et al. Family history, surgery, and *APC* mutation are risk factors for desmoid tumors in familial adenomatous polyposis: an international cohort study. *Dis Colon Rectum.* 2011;54:1229–1234.
61. Speake D, Evans DG, Lalloo F, et al. Desmoid tumours in patients with familial adenomatous polyposis and desmoid region adenomatous polyposis coli mutations. *Br J Surg*. 2007;94:1009–1013.
62. Quast DR, Schneider R, Burdzik E, et al. Long-term outcome of sporadic and FAP-associated desmoid tumors treated with high-dose selective estrogen receptor modulators and sulindac: a single-center long-term observational study in 134 patients. *Fam Cancer*. 2016;15:31–40.
63. Clinical recommendations "Intestinal stoma in adults". 2017. http://akr-online.ru/press/clinical-guidelines/recommendationstoma.pdf. (in Russ.).

64. Annibali R, Oresland T, Hulten L. Does the level of stapled ileoanal anastomosis influence physiologic and functional outcome? *Dis Colon Rectum*. 1994;37:321–329.
65. Fomenko O.Yu., Achkasov S.I., Titov A.Yu. et al. The role of anorectal manometry, BOS therapy and tibial neuromodulation in the diagnosis and conservative treatment of anal incontinence in the elderly. *Clinical gerontology*. 2015;5(6):16–20. (in Russ.).
66. Labayle D, Fischer D, Vielh P, et al. Sulindac causes regression of rectal polyps in familial adenomatous polyposis. *Gastroenterology*. 1991;101:635–639.
67. Steinbach G, Lynch PM, Phillips RKS, et al. The effect of celecoxib, a cyclooxygenase- 2 inhibitor, in familial adenomatous polyposis. *N Engl J Med*. 2000;342:1946–1952.
68. Nugent KP, Farmer KC, Spigelman AD, et al. Randomized controlled trial of the effect of sulindac on duodenal and rectal polyposis and cell proliferation in patients with familial adenomatous polyposis. *Br J Surg*. 1993;80:1618–1619.
69. Higuchi T, Iwama T, Yoshinaga K, et al. A randomized, double-blind, placebo-controlled trial of the effects of rofecoxib, a selective cyclooxygenase-2 inhibitor, on rectal polyps in familial adenomatous polyposis patients. *Clin Cancer Res*. 2003;9:4756–4760.
70. Tonelli F, Valanzano R, Messerini L. et al. Long-term treatment with sulindac in familial adenomatous polyposis: is there an actual efficacy in prevention of rectal cancer? *J Surg Oncol*. 2000;74:15–20.
71. Cruz-Correa M, Hylind LM, Romans KE, et al. Long-term treatment with sulindac in familial adenomatous polyposis: a prospective cohort study. *Gastroenterology*. 2002;122:641–645.
72. International Society for Gastrointestinal Hereditary Tumours-InSiGHT. *Fam Cancer*. 2015; 14(Suppl 1): 1-91.
73. Bianchi LK, Burke CA, Bennett AE, et al. Fundic gland polyp dysplasia is common in familial adenomatous polyposis. *Clin Gastroenterol Hepatol*. 2008;6:180–185.
74. Walton S-J, Frayling IM, Clark SK, et al. Gastric tumours in FAP. *Fam Cancer*. 2017;16:363–369.
75. Vasen HF, Bulow S, Myrh0j T, et al. Decision analysis in the management of duodenal adenomatosis in familial adenomatous polyposis. *Gut*. 1997;40:716–719.
76. Bulow S, Christensen IJ, H0jen H, et al. Duodenal surveillance improves the prognosis after duodenal cancer in familial adenomatous polyposis. *Colorectal Dis*. 2012;14:947–952.
77. Spigelman AD, Williams CB, Talbot IC, et al. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. *Lancet*. 1989;2:783–785.
78. Groves CJ, Saunders BP, Spigelman AD, et al. Duodenal cancer in patients with familial adenomatous polyposis (FAP): results of a 10-year prospective study. *Gut*. 2002;50:636–641.
79. Shepherd NA, Jass JR, Duval I, et al. Restorative proctocolectomy with ileal reservoir: pathological and histochemical study of mucosal biopsy specimens. *J Clin Pathol*. 1987;40:601–607.
80. Setti Carraro PG, Talbot IC, Nicholls JR. Patterns of distribution of endoscopic and histological changes in the ileal reservoir after restorative proctocolectomy for ulcerative colitis. A long-term follow-up study. *Int J Colorectal Dis*. 1998;13:103–107.
81. Friederich P, de Jong AE, Mathus-Vliegen LM, et al. Risk of developing adenomas and carcinomas in the ileal pouch in patients with familial adenomatous polyposis. *Clin Gastroenterol Hepatol*. 2008;6:1237–1642.
82. Speake D, Evans DG, Lalloo F, et al. Desmoid tumours in patients with familial adenomatous polyposis and desmoid region adenomatous polyposis coli mutations. *Br J Surg*. 2007;94:1009–1013.
83. Ahmed Ali U, Keus F, Heikens JT, et al. Open versus laparoscopic (assisted) ileo pouch anal anastomosis for ulcerative colitis and familial adenomatous polyposis. *Cochrane Database Syst Rev*. 2009; (1) CD006267.
84. Ueno H, Kobayashi H, Konishi T, et al. Prevalence of laparoscopic surgical treatment and its clinical outcomes in patients with familial adenomatous polyposis in Japan. *Int J Clin Oncol*. 2016;21(4):713–722.
85. Fazio VW, Ziv Y, Church JM, et al. Ileal pouch-anal anastomoses complications and function in 1005 patients. *Ann Surg*. 1995;222:120–127.
86. Vasen HF, van Duijvendijk P, Buskens E, et al. Decision analysis in the surgical treatment of patients with familial adenomatous polyposis: a Dutch-Scandinavian collaborative study including 659 patients. *Gut*. 2001;49(2):231–5.
87. NCCN Clinical Practice Guidelines in Oncology Genetic/Familial High-Risk Assessment: Colorectal version 1.2021.
88. Vasen HF, Möslein G, Alonso A, Aretz S, et al. Guidelines for the clinical management of familial adenomatous polyposis (FAP). *Gut*. 2008;57(5):704–13.
89. Aelvoet AS, Struik D, Bastiaansen BA J, et al. Colectomy and desmoid tumours in familial adenomatous polyposis: a systematic review and meta-analysis. *Familial Cancer*. (2022), DOI: 10.1007/s10689-022-00288-y
90. Jannasch O, Evert M, Rapp L, Lippert H, Meyer F. Aktuelle Diagnostik und Therapie von Desmoidtumorenbei Patienten mit familiärer adenomatöser Polyposis — auschirurgischer Sicht [Current diagnosis and treatment of desmoid tumours in patients with familial adenomatous polyposis — the surgical view]. *Zentralbl Chir*. German. 2010;135(1):34–43. DOI: 10.1055/s-0028-1098794