Hereditary Colorectal Cancer Syndromes

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Abstract

Context: In recent decades, there has been an increase in hereditary colorectal cancer cases in individuals under 50 years of age. Several studies have revealed similar pathologies in both molecular and clinical variations of hereditary colorectal neoplasms. We subdivided those new pathologies derived from the two groups in which hereditary colorectal cancer is classified: polyposis syndromes and non-polyposis syndromes.

Evidence Acquisition: The scientific search was done up to October 2020. The search was limited to predefined keywords. The inclusion criteria were articles relevant to the search criteria (keywords). Afterward, R. F. and M. Y. looked for the associated articles, removed duplicates, and selected relevant information for our review manuscript. We included 80 scientific articles that met the established criteria.

Results: The syndromes were divided according to the presence or absence of polyps, their histological type, and the classification or subclassification. Also, we explained the type of inheritance, the affected genes, the clinical manifestations, the mean age of presentation of the disease, and the polyp histology when available. Accordingly, in this article, we facilitated the identification of each syndrome for the reader.

Conclusion: Despite representing a low proportion of CRC cases, hereditary CRC has shown a rising trend over the last years. The development of genetic research has led to the establishment, modification, and redefinition of molecular and clinical criteria associated with this pathology. However, there is a small group of patients that don't have molecular or clinical criteria belonging to any classification. Also, the limited access and high cost associated with molecular analysis complicates the study of these pathologies and therefore leads to insufficient diagnosis and general treatment. For these reasons, novel genetic branches of hereditary CRC remain to be investigated, after which comprehensive treatment plans can be devised for patients.

Keywords: Colorectal neoplasms, Polyps, Colonic polyps, Intestinal polyposis, Hereditary nonpolyposis
familial in 25%, hereditary in 5%, and associated with inflammatory diseases in 1% of cases. In recent decades, there has been an increase in cases in people under 50 years of age, associated with hereditary forms (3) and somatic or other mutations that confer a hereditary predisposition to CRC.

Several studies have revealed similar pathologies in both molecular and clinical variations of hereditary CRC syndromes. In this review, we subdivided those new pathologies derived from the two large groups in which hereditary CRC is classified: polyposis syndromes and non-polyposis syndromes (2).

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**Results**

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1 Polyposis Syndromes

1.1 Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited disorder secondary to a germline mutation in the Adenomatous Polyposis Coli (APC) gene, 5q21-q22. The incidence is 1/10000. The main presentation is >100 polyps throughout the colorectum. The polyps develop in the first 10 years of life but in most cases are diagnosed at puberty, usually causing symptoms at the age of 30-35 years. About 70% of cases have a family history of cancer and colorectal polyps (4). If the patient is not treated by colectomy, the lifetime risk of colorectal carcinoma is 100% (5).

In 40% of cases, FAP is associated with extracolonic manifestations, the most frequent of which are:

- Gastrointestinal (GI) lesions with polyps of the upper digestive tract, with gastric or duodenal adenomas occurring in 90% of cases approximately at the age of 38 y. Carriers are at an increased risk (25-60%) of developing fundic gland polyps. Duodenal, papilla of Vater, and periampullary adenomas are observed in 58% to 74% of FAP carriers. It should be noted that in FAP, desmoid tumors are the first cause of death from extracolonic cancers and periampullary adenomas represent the second.

Duodenal polyps can be classified in terms of severity according to the system developed by Spigelman and colleagues (6). This classification describes five (0–IV) stages. Points are given for number, size, histology, and severity of dysplasia of polyps (Table 1) (7).

Stage I indicates mild disease, whereas stages III-IV imply severe duodenal polyposis (7). Approximately 70–80% of FAP patients have stage II or stage III duodenal disease, and 20–30% have stage I or stage IV disease (9). The estimated incidence of stage IV duodenal disease is 50% at age 70 years (10, 11).

- Dental abnormalities (11-27%) (3).
- Extra-intestinal neoplasms (thyroid 2-3%, hepatoblastoma 1%, central nervous system 1%) (6).
- Gardner syndrome is identified by the presence of intestinal polyposis and soft tissue tumors like desmoids and fibroids (10-15%), osteomas (50-90%), and epidermoid cysts (50%). Patients may develop osteomas of the mandible and skull, epidermal cysts, or fibromatosis with pruritus, inflammation, and rupture. Congenital hypertrophy of the retinal epithelium develops in 70-80% of cases, featuring multiple, bilateral, pigmented ocular fundus lesions (12).
- Turcot syndrome, known as the atypical form of FAP (3), is characterized by brain neoplasms (e.g., medulloblastoma and glioblastoma) and the clinical features of colorectal polyposis (13). This syndrome is associated with mutations in the MMR genes (3).

The APC gene encodes a scaffolding protein, which works as a tumor suppressor in the Wnt signaling pathway to decrease the action of β-catenin. The lack of functioning of APC gives rise to the accumulation of catenin B, upregulating several genes responsible for the proliferation, differentiation, and apoptosis of cells. The APC gene also intervenes in the fixation of microtubules; the mutation of this gene results in severe duodenal polyposis and soft tissue tumors like desmoid tumors in 58% to 74% of FAP carriers. It should be noted that in FAP, desmoid tumors are the first cause of death from extracolonic cancers and periampullary adenomas represent the second.

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**Table 1:** Spigelman classification for duodenal polyposis in familial adenomatous polyposis.

<table>
<thead>
<tr>
<th>Author</th>
<th>Criterion</th>
<th>1 Point</th>
<th>2 Points</th>
<th>3 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spigelman et al. (8)</td>
<td>Polyp number</td>
<td>1 - 4</td>
<td>5 - 20</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Spigelman et al. (8)</td>
<td>Polyp size (mm)</td>
<td>1 - 4</td>
<td>5 - 10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Spigelman et al. (8)</td>
<td>Histology</td>
<td>Tubular</td>
<td>Tubulovillous</td>
<td>Villous</td>
</tr>
<tr>
<td>Spigelman et al. (8)</td>
<td>Dysplasia</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Stage 0: 0 points / Stage I: 1 - 4 points / Stage II: 5 - 6 points / Stage III: 7 - 8 points / Stage IV: 9 - 12 points. A low degree of dysplasia according to current classification; a high degree of dysplasia.
Hereditary colorectal cancer

1. Abundant polyposis that presents an aggressive phenotype, with early occurrence of polyposis, symptoms, and death associated with CRC in an average period of 10 years earlier than typically indicated. Deletions in codon 1309 and truncation mutations in codons 1250 and 1464 are related to the phenotype.

2. Intermediate polyposis, with most mutations located between codon 157 and codon 1595.

3. Attenuated polyposis, described by a decreased number of polyps (10-100) with a later age of onset and reduced incidence of CRC (3).

Clinical diagnostic criteria include patients who have had at least 10-20 cumulative colorectal adenomatous polyps, a member of the family with 10 or more adenomatous polyps, or extracolonic manifestations.

APC genetic tests are designated for FAP confirmation, specifically if the patient has first-degree relatives under the age of 40 who have not yet developed the disease (14).

When a patient is diagnosed with FAP, the protocol consists of screening first-degree relatives, following these specifications:

- If a causal mutation is detected in the index case, a genetic study should be performed on the relatives and colonoscopy should only be performed on relatives who carry the mutation.

- If a causal mutation is not detected in the index case or genetic analysis is not available, all immediate family members should be evaluated with colonoscopy every 1-2 years from 10-15 years of age, with endoscopic resection of the polyps and high endoscopy from the age of 25.

- For the treatment of FAP, in situations where endoscopic control of polyps is technically impossible, prophylactic surgery is indicated, usually between the ages of 15-25 (3).

Surgical treatment is based on total proctocolectomy with or without ileoanal reservoir and total colectomy plus ileorectal anastomosis (IRA) depending on the age, the presence and severity of symptoms, the extent of rectal polyposis, and the existence and location of desmoid cancer or tumors.

Total proctocolectomy with definitive end ileostomy construction decreases the occurrence of CRC. The main indication for this technique is in cases where the patient has a neoplasm of the rectum which, due to its location close to the anal margin, does not allow the restoration of intestinal transit, as well as in patients who require a total colectomy with the removal of the rectum and who, due to some associated problems, do not allow a proctocolectomy with an ileal reservoir to be performed.

Restorative proctocolectomy is also recommended in patients with Gardner syndrome because of the risk of desmoid tumor occurrence after colectomy and IRA, which could make subsequent proctocolectomy unfeasible.

Total colectomy plus IRA is indicated when the rectum is not affected; however, periodic rectoscopic monitoring of the rectal mucosa should be performed.

In young people, surgery is recommended as prophylaxis against CRC. Suggested options are total proctocolectomy and ileoanal pouch or IRA. The treatment for duodenal cancer and desmoid tumors, which should be identified and treated in the early stages, is total colectomy. Upper endoscopy is performed to decrease the risk of the development of duodenal cancer.

Progressive tumors or unresectable diseases may be controlled with cytotoxic chemotherapy followed by surgery. There is evidence of regression of adenomas by prolonged treatment with non-steroidal anti-inflammatory drugs (NSAIDs; sulindac and celecoxib, among others) (15). However, polyps reappear when treatment is interrupted and the administration of such drugs does not eliminate the risk of neoplastic transformation. The administration of NSAIDs is only accepted as an adjuvant therapy to surgery as they are associated with increased cardiovascular, GI, and renal risks.

The main objectives of management are prevention and the maintenance of an adequate quality of life; all patients should have regular follow-ups (16).

The National Comprehensive Cancer Network recommends a baseline upper GI endoscopic examination at 25–30 years of age. Guidelines for continued endoscopic surveillance after baseline examination have been developed according to the Spigelman stage by several authorities (7); recommendations include every 4 years in stage 0, every 2-3 years in stages I-II, and every 6-12 months in stages III-IV, with surgery being considered in stage III and indicated in stage IV.

There are two pathological subtypes of FAP (17):

1.1.1 Attenuated Familial Adenomatous Polyposis
Attenuated familial adenomatous polyposis (AFAP) presents an autosomal dominant inheritance pattern and is related to variations in the APC gene, though with a higher proportion of de novo cases (3). It is characterized by the presence of fewer than 100 polyps, the late development of colorectal adenomas, and a reduced risk of CRC. The most common location of adenomas is proximal to the splenic flexure. Macroscopically, a flat morphology is observed. About 10% of AFAP cases carry an APC mutation and 7% carry a mutation in the MUTYH gene. Unfortunately, studies of the mutations are still limited (17).

1.1.2 MUTYH-associated Polyposis
The MUTYH mutation was first described in 2002. It features an autosomal recessive inheritance pattern. Al-Tassan and researchers investigated a British family in which three siblings presented multiple colorectal adenomas and CRC (18). The disease is caused as a consequence of biallelic mutations in the
MYH gene (MutY gene orthologs in Escherichia coli). Patients usually present between 10 and 100 adenomas and extracolonic manifestations are very rare. Also, up to 30% of CRC cases in the context of MUTYH mutation lack polyposis.

In patients with the PAFA phenotype, the diagnosis is based on a genetic study guided by family history. If there is a dominant familial pattern, the first step is to start with the APC study and, if negative, continue with the MYH gene. On the contrary, if the familial pattern is recessive, the study must begin with MYH and continue with APC if no mutation is found in the former (19).

### 1.2 Hamartomatous Polyposis

Hamartomatous polyposis syndromes represent a group of autosomal dominant conditions related to mutations in the phosphatase and tensin homolog (PTEN) gene (10q23), with a low degree of premalignancy (3). The PTEN gene is important for cell proliferation, cell cycle evolution, and apoptosis. PTEN gene mutations negatively regulate the phosphatidylinositol-3-kinase-AKT enzyme. The loss of function of this gene contributes to oncogenesis; for this reason, it is considered like a tumor suppressor gene (20).

#### 1.2.1 Juvenile Polyposis Syndrome

Juvenile polyposis syndrome (JPS) is the most frequent hamartomatous polyposis syndrome. Patients have hundreds of polyps in the colon and rectum (14). The lifetime risk of development into adenomas and carcinomas is approximately 40% (21). The two forms of presentation are sporadic and familial; both have autosomal dominant inheritance patterns with variable penetrance (22). Roughly 20-50% of cases present a family history of polyps (23).

In the absence of the extraintestinal manifestations, the diagnosis of JPS is established with the presentation of at least one of the following criteria (24, 25):

1. Greater than five juvenile polyps in the colon or rectum.
2. Juvenile polyps in other parts of the GI tract.
3. The presence of positive family history with any number of juvenile polyps.

Juvenile polyposis in childhood is the most aggressive form and has the worst prognosis. The disease manifests with bloody diarrhea, protein-losing enteropathy, anasarca, anemia, intussusception, hypoproteinemia, or rectal prolapse. Macrocephaly, clubbing, and hypotonia may also occur.

Juvenile colonic polyposis and generalized juvenile polyposis usually occur before the age of 20, presenting in the form of rectal bleeding, rectal polyp prolapse, abdominal pain, diarrhea, and anemia (22).

About 50% of cases have mutations in the SMAD4 (18q21) and BMPR1A (10q21-22) genes, and 25% have no family history. The malignant degeneration of GI tract polyps increases with age, so it is necessary and important to perform a genetic study to establish prognosis and treatment. If there is a mutation in SMAD4 in the family, the genetic study should be performed in the first six months due to hereditary telangiectatic hemorrhage risks (14).

The American College of Gastroenterology recommends the following steps for the management and surveillance of patients (25):

1. Surveillance of the GI tract for affected or at risk JPS patients should include screening for colon, stomach, and small bowel cancers.
2. Colectomy and IRA or proctocolectomy and ileal pouch-anal anastomosis (IPAA) is indicated for polyp-related symptoms, or when the polyps cannot be managed endoscopically.
3. Cardiovascular examination for the evaluation of hereditary hemorrhagic telangiectasia should be considered in SMAD4 mutation carriers (conditional recommendation).

Treatment is surgical, and total colectomy plus IRA or total proctocolectomy plus ileoanal anastomosis can be performed, always with follow-up of the residual colonic segment. Some authors recommend prophylactic colectomy at 20 years of age (23). In the case of high stretch polyps, endoscopic resection should be attempted and if this possibility does not exist, surgery should be considered (14).

The screening recommendations that should be performed are (26, 27):

1. Screening starts with continuous monitoring for symptoms in individuals with JPS.
2. Screening including a blood test, colonoscopy, and an upper endoscopy should be done by the time the person with JPS is 15 years old or when symptoms first appear. If results are negative, screening should be repeated in 3 years.
3. If only a few polyps are found, polyps should be removed and screening should be done every year until no polyps are found. Then, screening can be done every three years.
4. In the case of surgery, screening should be done yearly until no more polyps are found; then, screening can be done every three years (28).

#### 1.2.2 Peutz-Jeghers Syndrome

The first description of this Peutz-Jeghers syndrome (PJS) was made by Dr. Conner in 1895, although in 1921 Dr. J. Peutz described the relationship between mucocutaneous pigmentation and intestinal polyposis by studying 7 family members across 3 generations. In 1949, Dr. Jeghers published the description of the symptoms of the disease, recognizing a dominant hereditary character with a simple Mendelian pattern, accompanied by a high risk of cancer (29).

This syndrome is an autosomal dominant condition described as the development of polyps in the GI tract together with mucocutaneous pigmentation (30). The incidence is between approximately 1/50,000 and 1/200,000 live births (31). Mucocutaneous hyperpigmentation (32) occurs in 95% of patients
and is primarily located in the perioral and oral region, although it may also occur in other sites such as the face, elbows, fingers, soles of the feet, perineum and, rarely, in the GI mucosa (29).

The histological features characteristically include a frond-like elongated epithelial component, cystic gland dilatation extending into the submucosa or muscularis propria, and arborizing smooth muscle extending into the polyp fronds (juvenile polyps have a lamina propria lacking smooth muscle) (33).

Polyps are found throughout the GI tract but 60-90% are in the small bowel and 50-64% occur in the colon (34). They may also be found at extraintestinal sites such as the gallbladder, bronchi, bladder and ureter (35). Gastrointestinal polyps may cause GI bleeding, anemia, and abdominal pain due to intussusception, obstruction, or infarction. Polyp-related symptoms usually arise in childhood and are seen by the age of 10 years in 33% of cases and by 20 years in 50%.

The cause of this syndrome is mutations of the suppressor gene STK1 (LKB1) (36, 37) on chromosome 19p13.3 (38, 39). This gene belongs to the family of kinases and threonines and encodes a serine-threonine-kinase involved in the mTOR pathway. Pathogenetic mutations have been found in more than 90% of patients presenting clinical characteristics, and 25% of patients feature de novo mutations (40). The mutations reported in the Human Genome Mutation database are mostly deletions and insertions (3).

The diagnostic criteria of the European Council described by Beggs et al. 2010 (30) include:
- Two or more histologically confirmed Peutz-Jeghers (PJ) polyps.
- Any number of PJ polyps and a family history of PJS.
- Mucocutaneous pigmentation and a family history of PJS.
- Any number of PJ polyps and mucocutaneous pigmentation.

This is while the Mayo Clinic suggests the identification of a pathogenic mutation in the STK11 as the criterion for diagnosis. The study of STK11 mutations presents a sensitivity of 70% in families with STK11-associated PJS, and slightly lower sensitivity in patients with sporadic PJS.

In PJS, surveillance protocols have specific purposes (30):
- To detect sizeable GI polyps that could cause intussusception, obstruction, bleeding, and anemia.
- To detect cancer at an early stage.

Screening consists of an initial colonoscopy and upper endoscopy at the age of 20 years. Subsequently, an annual flexible sigmoidoscopy is indicated (41).

To prevent benign and malignant complications, patients require endoscopic polypectomy for polyps larger than 5 mm in diameter. Colectomy is reserved for complications (obstruction/bleeding) and for patients in whom the polyps develop adenomatous characteristics (29).

1.2.3 Cowden Syndrome

Cowden syndrome (CS) is an autosomal dominant disorder caused by germline mutations in the PTEN gene (42-44) and is part of the PTEN hamartoma tumor syndrome (45-48). It was first described in 1963 by Lloyd and Dennis under the name of the first patient. The prevalence of CS can be estimated as 1 case for every 200,000 to 250,000 people, predominantly occurring in women and white people (49). The risk of CRC in patients with CS is about 9%, with a mean onset age of 30 years (50). A distinctive feature in patients with CS is the presence of multiple hamartomas in the three layers of embryonic cells.

Individuals with CS have an increased risk of nonmalignant tumors as well as specific malignancies, including breast cancer, thyroid, endometrial, colorectal, and renal cancer (51, 52), as well as several benign manifestations such as macrocephaly and cerebellar gangliocytoma (53, 54).

The International Cowden Syndrome Consortium (ICSC) established the clinical diagnostic criteria where the characteristics of the syndrome are grouped into pathognomonic, major, and minor criteria (Table 2).

A clinical diagnosis is made if the patient has pathognomonic skin lesions confirmed by biopsy, two or more major criteria (including macrocephaly), one major criterion and three or more minor criteria, or four or more minor criteria (57).

The molecular diagnosis is made with the detection of pathogenic variants of the heterozygous germline PTEN gene; when the PTEN test is negative, patients may have KLLN hypermethylation or other mutations in genes such as SDHB/C/D, PIK3CA, AKT1 (58). Other candidate genes in research are SEC23B and USF3 (59).

Given that patients with CS are at an increased risk for certain cancers, treatment focuses on screening for high-risk cancer. Therefore, a colonoscopy is performed every five years from the age of 35. However, if polyps are detected, the frequency of colonoscopy should increase. Treatment is symptom-based and multidisciplinary since CS has multisystemic involvement (50).

1.2.4 Bannayan-Riley-Ruvalcaba Syndrome

Similar to CS, the Bannayan-Riley-Ruvalcaba syndrome (BRRS) is classified within the PTEN spectrum. The inheritance associated with BRRS shows autosomal dominance alongside sporadic cases. The prevalence is about 1-2/200,000.

In this condition, the clinical manifestations can be macrocephaly, multiple non-cancerous tumors (hemangiomas and lipomas), mental and psychomotor retardation, Hashimoto’s thyroiditis, pigmentation on the penis and hamartomas, as well as some manifestations of CS.

The molecular diagnostic is searching for a mutation
of the PTEN gene; 50-60% have it, while 10% have deletions in this gene and the diagnosis is uncertain in the remaining cases (60).

Given the fact that there are no clinical diagnostic criteria of an international consensus, some authors consider the diagnosis if patients manifest three of the following four characteristics: macrocephaly, lipomatosis, hemangiomas, and mottled pigmented macules on the penis; others make the diagnosis with two of the following three characteristics: macrocephaly, hamartomas (including at least one lipoma, hemangioma, or intestinal polyp), and macules on the penis (61).

Treatment is symptomatic; screening for high-risk cancer must be performed as in CS.

1.2.5 Hereditary Mixed Polyposis Syndrome

The hereditary mixed polyposis syndrome is a rare pathology subject to autosomal dominant inheritance. Recent studies revealed that the GREM1 gene in the 15q13.3 region can be identified as the cause of this pathology. Additionally, this gene could have duplications that lead to overexpression. Hence, the pathogenesis turns out to be different from Lynch syndrome (LS) and FAP (62). The studies were carried out in several Jewish families (e.g., Ashkenazi). The fact that the overexpression of GREM1 affects the Bone Morphogenetic Protein (BMP) pathway turns into a possible cause of the generation of polyps and their neoplastic transformation (63).

In this syndrome, patients present several histological types of colorectal polyps (juvenile, serrated, Peutz-Jeghers, tubular, villous and tubulovillous adenomas, and/or hamartomas). The average age at which polyps were detected in a family was 28 years, though they can appear at the age of 20, 18, or earlier. The molecular diagnosis is performed by finding duplications in the GREM1 gene. The National Comprehensive Cancer Network suggests that GREM1 carriers should begin colonoscopies between the age of 25 and 30 years and repeat them every 2 or 3 years. The colonoscopy should be done every year if polyps are found (64).

1.3 Serrated Polyposis Syndrome

One of the major features that characterize serrated polyposis syndrome (SPS) is the presence of numerous colonic serrated polyps (SPs) alongside a substantially increased CRC risk (25-59%). It was discovered in 1980 and is also known as hyperplastic polyposis.

Since no genetic mutations have been recognized, the diagnosis of SPS is based on clinical criteria defined by the World Health Organization. Among these criteria, we can find:

1. At least five SPs proximal to the sigmoid, with two or more of these being ≥10 mm;
2. Any number of SPs proximal to the sigmoid in an individual who has a first-degree relative with SPS;
3. ≥20 SPs of any size distributed throughout the colon (65).

In SPS, close endoscopic surveillance is essential.

Table 2: The international Cowden syndrome consortium diagnostic criteria for Cowden syndrome (55, 56).

<table>
<thead>
<tr>
<th>Category</th>
<th>Clinical criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathognomonic criteria</td>
<td>Adult with Lhermitte-Duclos disease (LDD; includes cerebellar dysplastic gangliocytoma) Mucocutaneous lesions: facial trichilemmomas, acral keratoses, papillomatous lesions, mucosal lesions Pigmented macules of the glans penis or “penile freckling”</td>
</tr>
<tr>
<td>Major criteria</td>
<td>Breast cancer Thyroid cancer (non-medullary), especially follicular Macrocephaly with an occipital frontal circumference ≥97th percentile Endometrial cancer</td>
</tr>
<tr>
<td>Minor criteria</td>
<td>Other thyroid lesions such as adenomas or multinodular goiter Intellectual disability with an IQ of ≤ 75 Hamartomatous intestinal polyps Fibrocystic breast disease Lipomas Fibromas Genitourinary tumors (especially renal cell carcinoma) or malformations Uterine fibroids</td>
</tr>
<tr>
<td>Operational diagnosis</td>
<td>Any of the following: Mucocutaneous lesions alone if: a) There are six or more facial papules, of which three or more must be trichilemmomas. b) Cutaneous facial papules and oral mucosal papillomatosis. c) Oral mucosal papillomatosis and acral keratoses. d) Palmoplantar keratoses. Two or more major criteria but one must include macrophaly or LDD. One major and three minor criteria. Four minor criteria.</td>
</tr>
<tr>
<td>in an individual</td>
<td></td>
</tr>
<tr>
<td>Operational diagnosis</td>
<td>One pathognomonic criterion. Any major criterion with or without minor criteria. Two minor criteria. History of Bannayan-Riley-Ruvalcaba syndrome.</td>
</tr>
<tr>
<td>in a family where one individual has CS</td>
<td></td>
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</tbody>
</table>
in the prevention of CRC development (66). The follow-up will be done preferably with annual chromoendoscopy involving the use of biological dyes to augment the detection of the serrated lesions, with resection of all polyps. In the case of diagnosing CRC or if endoscopic treatment is impossible for controlling the disease, a total colectomy with IRA and strict endoscopic control of the rectum should be performed. First-degree relatives should have a colonoscopy every five years starting at age 40 or 10 years before the age of earliest onset in the family (64).

2. Non-Polyposis Syndromes

2.1 Lynch Syndrome

Lynch syndrome (LS) is present among 3 to 5% of all patients with CRC, representing the main cause of hereditary CRC with an incidence of 40 to 50 new cases per 100,000 every year (2). The syndrome has autosomal dominant inheritance with incomplete penetrance, which implies that not all patients with genetic involvement will present the disease.

The molecular mechanism that affects LS is microsatellite instability (MSI). It is caused by multiple somatic mutations that affect repetitive fragments of DNA (microsatellites) distributed throughout the genome, as a consequence of mutations in the genes responsible for their repair, called mismatch repair system or mismatch repair (MMR). The affected genes are MLH1 (50%), MSH2 (40%), MSH6 (7-10%), and PMS2 (5%) (67). Furthermore, deletions in the EPCAM gene lead to hypermethylation of the MSH2 promoter, and its subsequent silencing is another cause. Mutations in MLH1 are associated with a higher prevalence of CRC in isolation (type 1 of LS), while mutations in MSH2 also result in extracolonic manifestations (type 2 of LS), where endometrial cancer is the second most frequent cancer after CRC. Other tumors that also feature in type 2 LS include gastric, ovarian, small intestine, urinary tract, hepatobiliary, or brain neoplasms (6). According to the MMR mutation, the age at which cancer can appear may vary; mutations in MLH1 and MLH2 result in early presentation (27-46 years), while mutations in MSH2 have a late presentation (61 years) (14).

The screening process to identify people at risk for LS is based on clinical and molecular diagnostic criteria. Furthermore, the clinical diagnostic criteria have evolved for better sensitivity. The first official set of diagnostic criteria was the Amsterdam I criteria, which later turned out to be restrictive as it excludes families with extracolonic manifestations or with few members that have CRC. However, it helped to identify the mutated genes in this pathology. Hence, the Bethesda criteria were formed, which included patients with CRC and a high probability of presenting MMR alterations. Both were updated giving the revised Amsterdam II criteria and the revised Bethesda criteria. Although the former failed to diagnose up to 68% of patients with LS, the latter featured improved diagnosis and sensitivity (68, 69) (Table 3).

The sensitivity of the Amsterdam II criteria is 87, 62, 38, and 48% in identifying patients with pathogenic germline variants in the MLH1, MSH2, PMS2, and MSH6 genes, respectively. The sensitivity for the revised Bethesda criteria in identifying patients with SL is >94%, but its specificity is 25% (74).

The molecular detection of LS is the key to diagnosing this pathology. After some investigations, it was discovered that a group of patients who met the Amsterdam criteria did not present alterations in the MMR genes, and their relatives had a lower incidence of CRC relative to families with LS. Furthermore, the risk associated with developing extracolonic cancer was small. For those patients with these peculiarities, the name of Familial CRC Type X was suggested alongside the label of Lynch-like syndrome (LLS). The predictive value of the Amsterdam and Bethesda criteria reaches 50 and 20%, respectively, which makes the use of complementary tools such as MSI testing and immunohistochemistry (IHC) necessary for the proper diagnosis and management of these patients (75).

The tumor tissue must be studied with IHC using the Bethesda panel of five MSI markers (BAT25, BAT26, D2S123, D5S346, and D17S250). The results are classified as high-MSI when two or more different bands differ in their patterns in tumor tissue compared with non-tumor tissue, low-MSI when one of the markers show differences, or stable when there is no alteration. The IHC assesses the expression of proteins such as MLH1, MSH2, MSH6, PMS2, or EPCAM. The underexpression of a protein in the tumor is inferred to be the mutated gene. Both studies are carried out in patients with CRC and/or other types of tumors related to SL, as well as early age of presentation or positive family history (76).

The CRC of the LS is located mainly in the proximal colon, with 70% occurring near the splenic flexure. It is a poorly differentiated tumor with histological characteristics of mucinous cells, signet ring cells, a medullary growth pattern, abundant synchronous infiltrating lymphocytes in the tumor, and/or metachronous CRC. The main objective is the prevention of the development of CRC as well as extracolonic neoplasms once the diagnosis of LS is made and the follow-up of the relatives is done considering the higher CRC risk in these patients compared with the general population.

No specific treatment has been given for LS, so prevention and family monitoring are the key to managing these patients.

In matters of prevention, it is recommended that a colonoscopy should be done each year or every two years. The suggested age for starting this procedure is estimated to be around 20-25 years or 5 years before the age of disease onset in the youngest family member (16). In some clinical cases, the start of surveillance may be delayed (e.g., later age of onset for colonoscopy in PMS2 carriers). In early-stage patients, surgical
The case for FOLFOX or CAPOX has become widely accepted for stage III CRC, as is II or III CRC. Nonetheless, adjuvant chemotherapy with 5-fluorouracil does not provide a survival benefit for stage III CRC, in line with other studies. It was found that patients with BMI ≥30 kg/m² had a significant risk factor for CRC among those who received a placebo instead of aspirin. This seems to imply that the chemopreventive effects of aspirin in LS are elevated in obese people. Other studies reveal a chemopreventive benefit from the use of ibuprofen, multivitamins, supplemental calcium, and progestogens; however, further investigations are needed. Adjuvant therapy based on 5-fluorouracil (5-FU) does not provide a survival benefit for stage II or III CRC. Nonetheless, adjuvant chemotherapy has become widely accepted for stage III CRC, as is the case for FOLFOX or CAPOX.

### 2.2 Lynch-like Syndrome

As a subdivision of LS, Lynch-like syndrome (LLS) represents the group of patients who fulfill the clinical diagnosis of LS but not the molecular diagnosis; such patients exhibit MSI but do not have the germline pathogenic variants in MMR genes (77). LLS accounts for up to 60-70% of cases where LS is clinically suspected. Given the fact that there are no genetic alterations, it is believed that the mutations occur in intronic areas and promoters. Therefore, studies should be continued to facilitate molecular diagnosis.

Just as in LS, the goal is to avert the development of CRC, so vigilance is the key to managing these patients. The frequency of colonoscopy is individualized based on the personal records and family history of CRC.

### 2.3 Constitutional Mismatch Repair Deficiency

Constitutional mismatch repair deficiency is a strange disease with autosomal recessive inheritance and the development of CRC in childhood. Other manifestations include intestinal adenomas of the upper and lower digestive tract, brain tumors, hematological neoplasms, and embryonic tumors.

### Table 3: Evolution of clinical diagnostic criteria for Lynch syndrome.

<table>
<thead>
<tr>
<th>Amsterdam I criteria / Vasen H et al. (70)</th>
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<tbody>
<tr>
<td>1. One must be a first-degree relative of the other two.</td>
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<tr>
<td>2. At least two successive generations must be affected.</td>
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<tr>
<td>3. At least one of the relatives with CRC must have received the diagnosis before the age of 50 years.</td>
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<td>4. Familial adenomatous polyposis must have been excluded.</td>
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<tr>
<th>Bethesda guidelines / Boland C et al. (71)</th>
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<tbody>
<tr>
<td>1. Individuals with cancer in families that meet the Amsterdam criteria.</td>
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<tr>
<td>2. Individuals with two hereditary non-polyposis colorectal cancer (HNPCC)-related cancers, including synchronous and metachronous CRC.</td>
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<tr>
<td>3. Individuals with CRC and a first-degree relative with HNPCC-related cancer and/or a colorectal adenoma; one of the cancers diagnosed at age &lt;45 years, and the adenoma diagnosed at age &lt;40 years.</td>
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<td>4. Individuals with CRC or endometrial cancer diagnosed at age &lt;45 years.</td>
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<td>5. Individuals with right-sided CRC with an undifferentiated pattern (solid/cribriform) on histopathology diagnosed at age &lt;45 years.</td>
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<td>6. Individuals with signet-ring-cell-type CRC diagnosed at age &lt;45 years.</td>
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<td>7. Individuals with adenomas diagnosed at age &lt;40 years.</td>
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<tr>
<th>Amsterdam II criteria / Vasen H et al. (72)</th>
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<tbody>
<tr>
<td>1. One must be a first-degree relative of the other two.</td>
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<tr>
<td>2. At least two successive generations must be affected. At least one of the relatives with cancer associated with HNPCC should have received the diagnosis before the age of 50 years.</td>
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<tr>
<td>3. Familial adenomatous polyposis should have been excluded in any relative with CRC.</td>
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<td>4. Tumors should be verified whenever possible.</td>
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<tr>
<th>Revised Bethesda guidelines / Laghi L et al. (73)</th>
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<tbody>
<tr>
<td>1. Individuals with CRC diagnosed at age &lt;50 years.</td>
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<tr>
<td>2. Presence of synchronous, metachronous CRC, or other HNPCC-associated tumors.</td>
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<tr>
<td>3. CRC with the MSI-H histology diagnosed at age &lt;60 years.</td>
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<tr>
<td>4. CRC diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed at age &lt;50 years.</td>
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<tr>
<td>5. CRC diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.</td>
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* Colorectal, endometrial, ovarian, gastric, hepatobiliary, or small-bowel cancer or transitional cell carcinoma of the renal pelvis or ureter. *Colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir—Torre syndrome, and carcinoma of the small bowel. Presence of tumor-infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern.
The diagnosis is made by finding the biallelic alterations of the MMR genes. Cases have been described of patients with pathogenic variants in a homozygous state in the MLH1, MSH2, MSH6, and PMS2 genes, which can result in the presentation of CRC or small intestine cancer in the second decade of life (74).

Surveillance is performed with upper GI endoscopy and capsule endoscopy annually from 8 years of age and annual colonoscopy from 6 years of age (14).

2.4 Familial Colorectal Cancer Type X

In recent years, a new entity called familial colorectal cancer type X (FCCTX) has been described to designate those families that comply with the Amsterdam II criteria but do not show detectable mutations in the MMR genes. The responsible mutations are yet to be identified. Unlike LS, there is no higher incidence of extracolonic neoplasms and the development of CRC occurs in later ages, as in sporadic CRC in patients older than 50 years.

The location of the tumor predominates in the rectum or left colon and the progression from adenoma to carcinoma is slow. CRC of type X families shows a medium-high degree of differentiation alongside a pattern of infiltration, glandular growth, and necrosis similar to that of stable sporadic tumors (14).

The recommended follow-up for family members with FCCTX is a colonoscopy every 3-5 years starting at the age of 45 years, or 5 to 10 years before the lowest age of diagnosis of CRC in the family (78).

2.5 Polymerase Proofreading Associated Polyposis

Since 2013, polymerase proofreading associated polyposis (PPAP) has been designated as the reason for multiple adenomas or early-onset CRC, which is similar to LS and FAP. The POLE gene is responsible for the synthesis of the leading strand during DNA replication. In addition to DNA binding and polymerase domains, POLE has proofreading capacity through the POLE exounuclease domain. This capacity is essential for the maintenance of replication fidelity and may act not only on newly misincorporated bases but also on mismatches produced by non-proofreading polymerases (79).

POLD1 encodes the catalytic and proofreading subunit of POLD and thus participates in the mismatch and base excision repair pathways (80). The molecular diagnosis of PPAP is made by detecting mutations in POLD1 and/or POLE. Surveillance is done with colonoscopy from the age of 25-30 years, repeated every 2-3 years if negative. If polyps are found, follow-up should be done every year, and if they cannot be removed with polypectomy, surgery is considered (14).

Overall, hereditary colorectal neoplasms are divided into two general groups (Figure 1). A summary of the various hereditary CRC syndromes is provided in Table 4.

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**Figure 1:** Classification of hereditary colorectal cancer syndromes.
Conclusion

Despite representing a low proportion of CRC cases, hereditary CRC has shown a rising trend over the last years. The development of genetic research has led to the establishment, modification, and redefinition of molecular and clinical criteria associated with this pathology. However, there is a small group of patients that don’t have molecular or clinical criteria belonging to any classification. Also, the limited access and high cost associated with molecular analysis complicates the study of these pathologies and therefore leads to insufficient diagnosis and general treatment. For these reasons, novel genetic branches of hereditary CRC remain to be investigated, after which comprehensive treatment plans can be devised for patients.

Acknowledgments

No financial or material support was needed.

Conflicts of Interests: None declared.
Hereditary colorectal cancer

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67. Anna Colorectal Res 2020;8(4)