



## Review article

## Effect of genetic profiling on surgical decisions at hereditary colorectal cancer syndromes

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## ABSTRACT

Hereditary colorectal cancer syndromes, such as Lynch syndrome and familial adenomatous polyposis (FAP), present significant clinical challenges due to the heightened cancer risks associated with these genetic conditions. This review explores genetic profiling impact on surgical decisions for hereditary colorectal cancer (HCRC), assessing options, timing, and outcomes. Genotypes of different HCRCs are discussed, revealing a connection between genetic profiles, disease severity, and outcomes. For Lynch syndrome, mutations in the *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes guide the choice of surgery. Subtotal colectomy is recommended for patients with mutations in *MLH1* and *MSH2*, while segmental colectomy is preferred for those with *MSH6* and *PMS2* mutations. In cases of metachronous colon cancer after segmental colectomy, subtotal colectomy with ileorectal anastomosis is advised for all mutations. Surgical strategies for primary rectal cancer include anterior resection or abdominoperineal resection (APR), irrespective of the specific mutation. For rectal cancer occurring after a previous segmental colectomy, proctocolectomy with ileal pouch-anal anastomosis (IPAA) or APR with a permanent ileostomy is recommended. In

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FAP, surgical decisions are based on genotype-phenotype correlations. The risk of desmoid tumors post-surgery supports a single-stage approach, particularly for certain *APC* gene variants. Juvenile Polyposis Syndrome (JPS) surgical decisions involve genetic testing, polyp characteristics with attention to vascular lesions in *SMAD4* mutation carriers. However, genetic profiling does not directly dictate the specific surgical approach for JPS. In conclusion this review highlights the critical role of personalized surgical plans based on genetic profiles to optimize patient outcomes and reduce cancer risk. Further research is needed to refine these strategies and enhance clinical guidelines.

## 1. Introduction

Colorectal cancer, one of the most prevalent and lethal malignancies worldwide, presents a multifaceted challenge to both patients and healthcare providers. Its occurrence and progression are influenced by a complex interplay of genetic, environmental, and lifestyle factors. However, for a subset of individuals, the risk of developing colorectal cancer is primarily rooted in their genetic makeup [1]. Hereditary colorectal cancer (HCRC) syndromes, exemplified by Lynch syndrome and familial adenomatous polyposis (FAP), constitute a distinctive and clinically intricate subset of colorectal malignancies [2]. These syndromes are characterized by germline mutations in specific genes, resulting in a significantly heightened risk of colorectal cancer development. In recent years, genetic profiling has emerged as an invaluable tool in the management of HCRC, offering insights into the genetic underpinnings of the disease [3]. The utilization of genetic profiling has notably influenced surgical decisions, enhancing risk assessment, refining treatment strategies, and guiding postoperative management for individuals affected by these syndromes [4]. FAP is an autosomal dominant polyposis syndrome caused by *APC* gene mutations, leading to nearly 100 % colorectal cancer risk if untreated [5]. Prophylactic surgery, such as total abdominal colectomy or total proctocolectomy, is recommended to prevent cancer [6]. In Lynch syndrome, caused by *MLH1*, *MSH2*, *MSH6*, or *PMS2* mutations, total abdominal colectomy is advised in the presence of colon cancer due to the high chance of metachronous colorectal cancer development [6,7]. The effect of genetic profiling extends beyond mere identification to encompass critical implications for risk assessment and early detection, enabling tailored surveillance and screening strategies [8]. This comprehensive review aims to investigate the influence of genetic profiling on surgical decisions in HCRC. It will delve into the significance of genetic testing, including various types of genetic tests, genetic counseling, and their role in screening and diagnosis. The study will also examine the impact of genetic profiling on surgical decision-making, encompassing surgical options, timing of surgery, and surgical outcomes.

## 2. Definition and significance of hereditary colorectal cancer syndromes

HCRC syndromes are a group of genetic conditions that significantly increase an individual's risk of developing colorectal cancer. These syndromes are characterized by the inheritance of specific gene mutations that predispose affected individuals to the development of colorectal tumors. It's important to note that while these syndromes increase the risk of colorectal cancer, they are relatively rare, and most cases of colorectal cancer are sporadic [9].

Hereditary non-polyposis colorectal cancer (HNPCC), characterized as an autosomal dominant cancer syndrome, is responsible for approximately 1.7–4.2 % of all cases of colorectal cancer on a global scale, equivalent to 3 to 8 cases per one million individuals. It is notably linked to Lynch syndrome (Muir-Torre syndrome), which is the most prevalent form of HCRC [10]. Typically, Lynch syndrome presents with flat polyps located in the right colon, which give rise to colorectal cancer and other malignancies, such as endometrial, stomach, ovarian, pancreatic, ureter and renal pelvis, cerebral glioblastoma, biliary tract, small intestine cancer, sebaceous carcinomas, and keratoacanthomas. Notably, endometrial cancer tends to manifest in relatively young women [11]. Individuals affected by Lynch syndrome typically exhibit fewer than ten adenomatous polyps over the course of their lifetime [12]. Adenomas are commonly observed in patients below the age of 40 and frequently display a villous growth pattern coupled with moderate to high-grade dysplasia. In the case of individuals with Lynch syndrome, adenomas tend to progress into cancers more rapidly than they do in individuals without the syndrome who have adenomas [13,14]. Furthermore, both adenomas and colon tumors linked to Lynch syndrome are predominantly located on the ascending colon. These tumors also display distinct characteristics, including poorly differentiated medullary-type carcinoma, mucinous adenocarcinoma, the presence of signet-ring cells, and a Crohn's disease-like reaction with infiltrating lymphocytes [15]. HPCC, or Hereditary Polyposis Colorectal Cancer, is a relatively rare condition, accounting for approximately 3–5 % of all reported cases of colorectal cancer worldwide. This translates to an incidence rate of 5–9 cases per million individuals across the globe. Within this classification of genetic disorders, HPCC encompasses a diverse range of distinct syndromes, and among them, FAP stands out as a particularly well-recognized and noteworthy condition. FAP is not only prevalent within the HPCC spectrum but also holds a prominent place in the broader landscape of hereditary colorectal disorders [16]. FAP is distinguished by the presence of numerous adenomatous polyps in the colon, ranging from hundreds to thousands, with the potential to progress to colorectal cancer. However, FAP is responsible for only 1 % of the colorectal cancer cases. The impact of FAP extends beyond the colon, encompassing a wide spectrum of extracolonic manifestations, including desmoid tumors, osteomas, epidermoid cysts, papillary thyroid carcinoma, pancreatic carcinoma, gastric cancer, duodenal cancer, hepatobiliary tumors, and central nervous system (CNS) tumors. This comprehensive array of potential health concerns associated with FAP highlights the intricate and severe nature of this hereditary condition, necessitating diligent medical surveillance and management to address both the colorectal and

extracolonic aspects of the disease [17]. Juvenile Polyposis Syndrome (JPS) is a rare autosomal dominant hereditary disorder characterized by the formation of multiple juvenile polyps within the gastrointestinal (GI) tract, predominantly in the colon, but also affecting the stomach and small intestine. Onset of symptoms typically occurs during childhood and includes gastrointestinal bleeding, anemia, and abdominal pain. While juvenile polyps themselves are generally benign, individuals with JPS face an elevated risk of gastrointestinal malignancies, notably colorectal cancer [18]. Peutz-Jeghers syndrome (PJS) is an uncommon autosomal dominant genetic disorder characterized by the emergence of hamartomatous polyps within the gastrointestinal tract and distinctive mucocutaneous pigmentation patterns. These benign polyps, distributed throughout the stomach, small intestine, and colon, carry the potential for complications such as intestinal obstruction and hemorrhage. The characteristic mucocutaneous pigmentation, presenting as dark pigmented spots on the lips, buccal mucosa, and extremities, manifests early in childhood [19].

### 3. Genetic testing in hereditary colorectal cancer syndromes

Genetic profiling of HCRC syndromes has significantly advanced understanding of the molecular basis of these conditions, leading to more personalized approaches for prevention and treatment. The identification of specific genetic markers associated with HCRC syndromes has enabled the development of targeted screening and management strategies [20].

#### 3.1. Genetic profiling of lynch syndrome

The suspicion of Lynch syndrome should arise when evaluating an individual known as a proband who exhibits specific criteria. These criteria involve identifying tumors that are part of the Lynch syndrome spectrum, with a notable focus on colorectal cancer but not limited to it. Microsatellite instability (MSI) status stands out as a sanctioned biomarker for clinical application in colorectal cancer by regulatory authorities. The current guidelines advise conducting MSI testing for the majority of patients following a colorectal cancer diagnosis, serving dual purposes of screening for hereditary syndromes and assessing prognostic and treatment implications [21]. Suspicion arises when tumor tissue testing reveals either high MSI, a loss of expression of one or more mismatch repair (*MMR*) gene products (*MLH1*, *MSH2/EPCAM*, *MSH6* or *PMS2*) through immunohistochemistry (IHC), PCR-based method MSI, or identification of a pathogenic variant in an *MMR* gene [22,23]. The distinct *MMR* genes linked to HNPCC encompass *hMLH1* positioned on chromosome 3p22, *hMSH2* and *hMSH6* on chromosome 2p16, *hPMS1* on chromosome 2q32, *hPMS2* on chromosome 7p22, *hMSH3* on chromosome 5q14.1, and *EXO1* on chromosome 1q43. Notably, mutations in *hMLH1*, *hMSH2*, and *hMSH6* collectively contribute to around 75–80 % of HNPCC cases. However, the genetic origins of the remaining 20–25 % of HNPCC cases remain undisclosed [10]. The collaboration between the *MLH1* and *PMS2* proteins results in the formation of the MutL $\alpha$  complex, a pivotal component in DNA mismatch repair. MutL $\alpha$  coordinates the recruitment of various proteins essential for the repair process, including DNA helicase, single-stranded-DNA binding-protein (RPA), and DNA polymerases [24,25]. Simultaneously, the *MSH2* protein forms a dimer with *MSH6*, employing a sliding clamp model to identify mismatches. This model functions as a protein scanning mechanism, detecting errors within the DNA sequence. These molecular interactions underscore the synchronized actions of these protein dimers, ensuring the precision and fidelity of DNA replication and repair mechanisms [26]. In the context of testing for MSI, specific markers such as BAT25/26, D2S123, D5S346, and D17S250 are utilized in PCR-based methodologies to investigate the instability present in these particular loci. This group of markers includes both mononucleotide repeats (BAT25/26) and dinucleotide repeats (D2S123, D5S346, D17S250) and forms a 5-marker panel specifically employed for evaluating MSI [27]. MSI status is divided into three categories: MSI-High (MSI-H) denotes tumors with instability in over 30 % of examined markers, strongly suggesting the presence of Lynch syndrome; MSI-Low (MSI-L) indicates tumors with instability in fewer than 30 % of markers, often associated with sporadic cancers; and Microsatellite Stable (MSS) characterizes tumors demonstrating stability across all tested markers, making Lynch syndrome unlikely in such cases [28].

#### 3.2. Genetic profiling of familial adenomatous polyposis

Comprehensive genetic testing for FAP is centered on examining the *APC* gene, located on chromosome 5q21.2, where pathogenic alterations drive the development of numerous adenomatous polyps in the colon and rectum. This involves detailed direct sequencing to detect point mutations, small insertions, or deletions [29]. Additionally, techniques such as Multiplex Ligation-dependent Probe Amplification (MLPA) and *APC* gene deletion/duplication analysis are employed to scrutinize larger structural variations [30]. Methylation analysis of the *APC* gene promoter region provides insights into potential modifications in gene regulation [31]. The *APC* gene functions as a tumor suppressor, overseeing the synthesis of *APC*, a substantial and multifunctional tumor-suppressing protein. This protein serves as a crucial "gatekeeper," preventing the formation of tumors. Specifically, *APC* regulates  $\beta$ -catenin, a protein integral to cellular communication, signaling, growth, and controlled destruction. Unchecked  $\beta$ -catenin activity can lead to the onset of various cancers. An impairment in the *APC* gene compromises the effectiveness of *APC*, increasing the likelihood that some cells, which should have been restrained by *APC*, will persistently develop and transition into cancerous cells over time. In the context of familial polyposis, these anomalies typically manifest as polyps—minute irregularities on the surface of the intestinal tract [32]. In addition to the *APC* gene, there are other genes that can be associated with familial adenomatous polyposis, albeit in rarer cases. Mutations in the *MUTYH* gene, which is involved in DNA repair, can also lead to a condition called *MUTYH*-associated polyposis (MAP), characterized by the development of polyps in the colon. *MUTYH* is situated on chromosome 1p34.3–p32. Nevertheless, individuals carrying monoallelic *MUTYH* mutations within families affected by MAP did not exhibit an elevated risk of colorectal cancer [33].

### 3.3. Genetic profiling of Juvenile Polyposis Syndrome

Various molecular genetic testing strategies are available for individuals suspected of having JPS, including *BMPR1A* and *SMAD4* (commonly referred to as *MADH4/DPC4*) concurrent testing, serial single-gene testing, multigene panel use, and more comprehensive genomic testing. For those with clinical features suggestive of JPS, *BMPR1A* and *SMAD4* concurrent testing involves initial sequence analysis, including the examination of promoter regions, and gene-targeted deletion/duplication analysis. If no pathogenic variant is identified, the consideration of a multigene panel, encompassing genes like *PTEN*, is recommended [34]. Serial single-gene testing is an alternative, beginning with sequence analysis and deletion/duplication analysis of *SMAD4*, followed by similar analysis of *BMPR1A* if no *SMAD4* pathogenic variant is found. Additional molecular genetic testing of HHT-related genes may be considered if *SMAD4* or *BMPR1A* pathogenic variants are not identified. A multigene panel, including *BMPR1A*, *SMAD4*, and other relevant genes, particularly *PTEN*, may be considered for individuals with JPS. It's important to note that the genes included in multigene panels and their sensitivity may vary, and understanding the limitations of the panel is crucial for interpretation. Chromosomal microarray analysis for detecting deletions in the 10q22-q23 region, involving *BMPR1A* or both *BMPR1A* and *PTEN*, may reveal additional clinical features [35,36].

### 3.4. Genetic profiling of Peutz-Jeghers syndrome

In the molecular diagnosis of PJS, various genetic testing approaches are considered based on the phenotype observed. Single-gene testing initiates with sequence analysis of *STK11*, aiming to identify small intragenic deletions/insertions, missense, nonsense, and splice site variants. However, limitations exist, as certain sequencing methods may not detect single-exon, multiexon, or whole-gene deletions/duplications. If no variant is detected through sequencing, subsequent gene-targeted deletion/duplication analysis is performed simultaneously to decrease turnaround time. In cases where no pathogenic *STK11* variant is identified, exploring an alternate DNA source for somatic mosaicism is recommended. Additionally, a multigene panel, encompassing *STK11* and relevant genes, may be considered, though variations in gene inclusion and panel sensitivity exist among laboratories [37,38] (Table 1).

## 4. Genetic counseling for hereditary colorectal cancer syndromes

Genetic counseling for HCRC is a comprehensive process that involves assessing an individual's familial and personal medical history, discussing the option of genetic testing, and providing information about the associated risks and implications. Genetic counselors play a key role in supporting informed decision-making, educating individuals about the genetics of colorectal cancer, and addressing psychosocial aspects of the genetic testing process. Through personalized risk management strategies, coordination with healthcare providers, and facilitating family communication, genetic counselors empower individuals to navigate their hereditary cancer risk with knowledge and emotional support. Staying abreast of genetic advancements, these professionals contribute to ongoing updates and improvements in the management of HCRC [39,40]. In the initial step of genetic counseling, suspected individuals and their families, spanning at least two generations, should undergo a detailed investigation of colorectal cancer, endometrial cancer, and

**Table 1**  
Approach to testing Strategies, genes involved, and clinical implications of different hereditary colorectal cancer syndromes.

Hereditary colorectal cancer syndromes	Genetic Markers/Testing Strategies	Inheritance pattern	Genes Involved	Clinical Implications
Lynch Syndrome	- Criteria for suspicion: specific tumors within Lynch syndrome spectrum, emphasizing colorectal cancer. - Testing methods: MSI, IHC, PCR, identification of MMR gene variants.	Autosomal dominant	- MMR genes: hMLH1, hMSH2, hMSH6, hPMS1, hPMS2, hMSH3, EXO1. On chromosomes (3p21.3; 2p22-p21; 2p16; 2q31-33; 7p22; 18q21) - MutL $\alpha$ complex formation involving MLH1 and PMS2. - MSH2-MSH6 dimer for mismatch detection.	- MSI Status: MSI-High (Lynch syndrome likely), MSI-Low, Microsatellite Stable (Lynch syndrome unlikely). - Implications for prognosis and treatment.
Familial Adenomatous Polyposis (FAP) and MUTYH associated polyposis	- Comprehensive testing of APC gene (direct sequencing, MLPA, deletion/duplication analysis, methylation analysis).	-Autosomal dominant -Autosomal recessive	- APC gene on chromosome 5q21.2. - Other genes (rare cases): MUTYH on chromosome 1p34.3-p32.	- APC as tumor suppressor. - Development of adenomatous polyps. - Risk of colorectal cancer.
Juvenile Polyposis Syndrome (JPS)	- Testing strategies: BMPR1A and SMAD4 concurrent testing, serial single-gene testing, multigene panels.	Autosomal dominant	- BMPR1A (on chromosome 10q22-q23), SMAD4 (MADH4/DPC4), PTEN (for multigene panels).	- Clinical features guide testing approach. - Consideration of multigene panels for comprehensive evaluation.
Peutz-Jeghers Syndrome (PJS)	- Testing approaches: Single-gene testing (STK11), deletion/duplication analysis, alternative DNA source for mosaicism, multigene panels.	Autosomal dominant	- STK11 (on chromosome 19p13.3). - Other relevant genes (for multigene panels).	- Diagnosis based on phenotype. - Consideration of alternate DNA sources. - Variability in gene inclusion and panel sensitivity.

other malignancies. Generating a comprehensive family pedigree is crucial for assessing familial cancer risk, understanding inheritance patterns, and identifying the proband [41].

#### 4.1. Genetic counseling for lynch syndrome

Genetic counseling for Lynch syndrome involves informing individuals about the complexities of genetic testing, emphasizing potential challenges in interpreting results, such as variants of unknown significance (VUS) and the sensitive nature of genetic information shared within families [42]. The shift from traditional single-gene tests to NGS multi-gene panels is highlighted, emphasizing benefits like simultaneous screening of multiple genes, reduced turnaround time, and cost-effectiveness. However, challenges, including interpreting incidental findings and VUS, are acknowledged [43]. Family counseling addresses the importance of detailed pedigrees in identifying at-risk members and recognizes the role of family relationships in disclosure dynamics. The discussion extends to family planning options, incorporating ethical considerations and legal implications surrounding prenatal and preimplantation genetic diagnoses, with consensus-building emphasized for informed decision-making [44]. The family pedigree is instrumental in clinical decision-making, helping determine eligibility for confirmatory genetic testing based on criteria like the Amsterdam II or revised Bethesda guidelines. Computational models like PREMM1,2,6 and MMRpro, assessing Lynch syndrome probability, rely on family pedigree information when direct tumor sequencing is impractical. Additionally, the family pedigree assists in efficiently guiding genetic testing, distinguishing individuals who may benefit from those with no Lynch syndrome risk. It also serves as educational material for patients and their families [45]. Screening universally for *MMR* deficiency is advocated for all colorectal or endometrial tumors, without regard to the age at diagnosis. This encompasses cases of colorectal cancer diagnosed before the age of 50, instances of synchronous or metachronous colorectal or other Lynch syndrome-associated tumors, irrespective of age, and situations where colorectal cancer is identified in a first-degree relative under the age of 50 [46,47]. The Revised Bethesda criteria further pinpoint individuals with colorectal cancer diagnosed in two or more first- or second-degree relatives, regardless of age. The process involves assessing MSI or conducting immunohistochemical analysis, with negative outcomes suggesting a lower likelihood of Lynch syndrome. Additional examinations, such as *MLH1* promoter methylation and/or *BRAF* p.V600E variant testing, are recommended for specific MSI patterns [48]. Subsequent steps involve scrutinizing methylation status, genetic variant testing for *MSH2*, *MSH6*, *MLH1*, and *PMS2*, as well as considering *EPCAM* deletion. The results guide the determination of Lynch syndrome and provide insights for testing at-risk family members based on the identified variants or their absence [49].

#### 4.2. Genetic counseling for familial adenomatous polyposis

Genetic counseling for FAP is an essential component of managing individuals and families affected by this hereditary condition. FAP is an autosomal dominant genetic disorder characterized by the development of numerous adenomatous polyps in the colon, leading to a high risk of colorectal cancer [50]. Testing for hereditary colorectal polyposis is recommended for individuals meeting specific criteria. This includes those with a personal history of 20 or more cumulative adenomas, the presence of multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE), and individuals with a personal history of between 10 and 19 cumulative adenomas, a desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, unilateral CHRPE, or those meeting the criteria for serrated polyposis syndrome with at least some adenomas [12]. Genetic counseling and consistent monitoring are essential for tailoring the treatment of families affected by cancer due to *APC* gene expression deficiency. Presently, there are over 2000 documented pathogenic variations in the *APC* gene, predominantly located in the mutation cluster region (MCR) at the 5'-ends of exon 15 [51]. Notably, codons 1309 and 1061 serve as hotspots for mutations, representing approximately 17 % and 11 % of all germline *APC* mutations, respectively [52]. Individuals with MCR mutations typically experience a more unfavorable prognosis, with early manifestation of their condition. Identifying the precise *APC* mutation within a family can facilitate targeted sequencing tests for at-risk family members who have yet to exhibit symptoms [53]. Childhood DNA testing, prenatal diagnosis (PND), and preimplantation genetic diagnosis (PGD) are viable options for individuals from families at elevated risk of FAP [54]. In the majority of cases, FAP follows an autosomal dominant pattern, with an affected parent passing on the condition to their offspring. This familial pattern allows for cascade genetic counseling and testing to identify at-risk family members. However, a significant proportion (about 25 %) of FAP cases result from de novo pathogenic variants, not inherited from either parent. In such cases, where the variant cannot be identified in the parents' DNA, the concept of germline mosaicism is introduced. This concept influences the recommendation for testing, suggesting that while testing siblings of an affected individual is advisable, it is not typically indicated for aunts, uncles, and cousins of the proband unless clear evidence of familial inheritance is present. The nuanced approach to genetic testing considers both familial patterns and de novo variants, ensuring a comprehensive understanding of the genetic basis of FAP within a family context [55].

#### 4.3. Genetic counseling for Juvenile Polyposis Syndrome

JPS follows an autosomal dominant inheritance pattern, wherein up to half of affected individuals inherit the condition from an affected parent. Intriguingly, around 50 % of individuals diagnosed as probands with JPS lack a familial history of polyps, indicating the potential occurrence of a de novo pathogenic variant. In the context of familial inheritance, each child born to an affected individual carries a 50 % likelihood of inheriting the pathogenic variant and subsequently developing JPS [18]. For pregnancies at an increased risk, prenatal testing becomes a viable option, providing insights into the genetic status of the developing fetus. Additionally, advancements in genetic technology have paved the way for PGD, offering prospective parents the opportunity to screen embryos for

the pathogenic variant before implantation, thus mitigating the risk of JPS transmission in subsequent generations when the familial variant is known [56]. Genetic testing for the prediction of particular familial mutation has been found in either affected parents or sibling. If there is no identified pathogenic gene mutation in the affected parent or sibling, the child is ineligible for predictive genetic testing and would need to undergo endoscopic screening instead [57]. It's crucial to recognize that a gene mutation may only be identified in around 40 %–60 % of individuals with JPS. In instances where no pathogenic *SMAD4* or *BMPRIA* variant is found, opting for a multigene panel that includes *PTEN* is recommended [58].

#### 4.4. Genetic counseling for Peutz-Jeghers syndrome

The combined probability of gastrointestinal tumor development in individuals with PJS is approximately 20 % by the age of 40, rising to more than 70 % in patients reaching their eighth decade of life. The uncertainty surrounding this risk, coupled with the substantial clinical implications of PJS, has a notable impact on the overall quality of life experienced by individuals affected by this syndrome [59]. During genetic counseling, individuals with PJS have expressed a consideration for prenatal testing if identified as carriers of the pathogenic *STK11* mutation. This proactive approach aims to prevent the birth of children affected by the syndrome. Valuable options for families at an elevated risk of PJS include PND and PGD. There is limited literature available on the utilization of PND and PGD in the context of PJS. In one case described by Wang et al., a positive PND result for PJS was reported, leading to the decision to proceed with the pregnancy, and PGD was subsequently recommended for future pregnancies [60]. An additional study conducted by Woo et al. surveyed 38 individuals with PJS, revealing that 40 % adjusted their reproductive choices due to the syndrome, and 33 % expressed reluctance to have children due to the associated risks, emphasizing the necessity for reproductive counseling [61]. Another survey by Van Lier et al. involving 52 PJS patients indicated that PJS influenced family planning decisions for nearly a third of respondents, with considerations including termination and acceptance of PGD. In light of these findings and experiences with other predisposition syndromes, it is proposed that PJS should be acknowledged as an indication for PND and PGD, underscoring the importance of counseling individuals with PJS about their reproductive options [62]. While some studies have identified specific mutations in the *STK11* gene during PND and PGD testing, enhancing the precision and effectiveness of these genetic screening methods [63], findings from specific studies others indicated that in instances of prenatal testing, it was reported that the mutation was not inherited by the fetus, and as a result, the pregnancy proceeded [64] (Fig. 1).

### 5. Surgical options and decision making

Surgery for HNPCC can serve both therapeutic and prophylactic purposes, primarily addressing colon cancer. Surgical choices encompass either segmental resection or total abdominal colectomy (TAC) [65]. The preference for TAC arises from the elevated risk of metachronous neoplasia in the remaining colon. While retrospective studies indicate a reduced risk of metachronous colon cancer following TAC compared to segmental resection, there is a lack of prospective trials supporting a definitive survival advantage for TAC [66]. The likelihood of developing metachronous colon cancer after partial colectomy ranges from 11 to 45 % over 8–13 years. Segmental resection carries a cumulative risk of metachronous colon cancer, reaching 62 % at 30 years. The degree of segmental resection is inversely linked to the risk of metachronous cancer. Survival rates at 5 and 10 years show no substantial disparity between TAC and segmental resection for individuals with HNPCC and colon cancer [67].

#### 5.1. Surgical decision for lynch syndrome

It is recommended that individuals with Lynch syndrome who have completed childbearing or are postmenopausal undergo total abdominal hysterectomy and bilateral salpingo-oophorectomy simultaneously to minimize the risk of endometrial and ovarian cancers

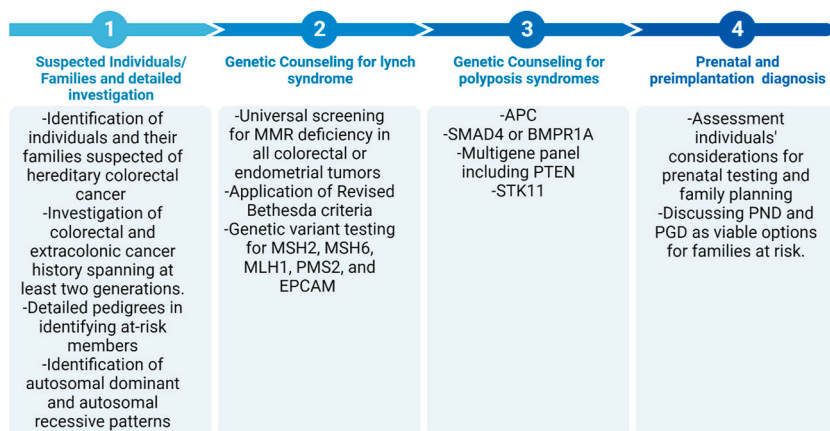


Fig. 1. Genetic counseling steps for hereditary colorectal cancer syndromes.

[68]. Malik et al. conducted a systematic review and meta-analysis to assess the risk of MCC and mortality in Lynch syndrome following either segmental or extensive colectomy. The findings of this study suggested a fivefold greater risk of MCC after segmental colectomy compared to extensive colectomy in individuals with Lynch syndrome [69]. Approximately 20 %–30 % of individuals diagnosed with Lynch syndrome may develop rectal cancer, and within this group, 15 %–24 % initially present with rectal cancer. Surgical options include either a low anterior resection or abdomino-perineal resection, depending on sphincter involvement [70]. Another option is an extended resection, involving the removal of all colorectal tissue at risk. This extended resection can be accomplished through a total proctocolectomy with an end ileostomy (TPC-EI) or, more commonly, a restorative ileal pouch-anal anastomosis (IPAA) [71]. Preventive surgical interventions for Lynch Syndrome encompass primary, secondary, and tertiary measures. In cases where a patient lacks colonic lesions, primary prophylactic colorectal surgery is generally not recommended, and endoscopic management is favored, associated with a 70 % reduction in the risk of death as per earlier statistical models [72]. However, primary prophylactic colon surgery may be considered for lynch syndrome patients with endometrial cancer (EC), particularly if it represents the initial manifestation of lynch syndrome, owing to the heightened subsequent risk of colorectal cancer [73]. Secondary prophylactic surgery is primarily directed at colorectal cancer, dysplasia, or adenoma, providing choices such as segmental or total colectomy based on lesion location. Surgical decisions take into account patient-specific factors, morbidity, functional consequences, impact on quality of life, and the risk of developing metachronous lesions. Tertiary prophylactic surgery pertains to cases where the lynch syndrome diagnosis is established post-operatively, involving strategies ranging from endoscopic surveillance to extended surgical resection. For women with lynch syndrome, discussions and gynecologic examinations regarding prophylactic surgery typically commence at age 45 or five years before the occurrence of the first family case of endometrial cancer, acknowledging the intricacies of decision-making due to uncertainties in lynch syndrome diagnosis at the time of surgery.

### 5.2. Surgical decision for familial adenomatous polyposis

Prophylactic colorectal surgery is crucial in managing FAP, given the absolute risk of colorectal cancer by the age of 40 if left untreated [74]. Surgical decision-making, encompassing the timing of prophylactic surgery, extent of bowel resection, and type of reconstruction, is intricately guided by patient-specific factors and disease characteristics [75]. FAP patients have three primary surgical options, including subtotal colectomy with ileorectal anastomosis (IRA), total proctocolectomy with or without mucosectomy and IPAA, and TPC-EI. Key principles of oncologic bowel resection involve the high ligation of the primary blood supply to the bowel and removal of its mesentery [76]. Colectomy is typically recommended when there are multiple polyps exceeding 10 mm in size, polyps displaying high-grade dysplasia, or a notable rapid increase in the polyp count [77]. However, the decision should involve both the healthcare provider and the patient, considering social, educational, and career aspects. Optimal timing aligns with the severity of polyposis and the patient's preferences, ensuring a medically sound decision that respects their overall life circumstances [78]. After deciding on the need for colectomy, the next step involves choosing the type of operation – either subtotal colectomy with IRA/ISA or a more extensive proctocolectomy with IPAA. Performing end ileostomy is rare but may be necessary in specific cases. The decision to preserve the rectum depends on the rectal polyp burden at colectomy, with rectal cancer risk varying [79]. Introduction of Ileal Pouch-Anal Anastomosis (IPAA) in 1978 significantly reduced rectal cancer incidence after colectomy. In low-polyp burden cases like MAP, IRA is a reasonable choice, provided strict endoscopic surveillance [80]. After undergoing colectomy, individuals with MAP encounter the potential risk of developing metachronous colorectal cancer, with reported rates as elevated as 17 %. This heightened risk may be attributed to an accelerated process of carcinogenesis [81].

### 5.3. Surgical decision for Juvenile Polyposis Syndrome

The decision to opt for surgical intervention in JPS is contingent upon several pivotal factors, underscoring the imperative for timely medical action. These factors encompass an excessive accumulation of polyps, substantial blood loss leading to persistent anemia, and the identification of juvenile polyps displaying characteristics indicative of severe dysplasia or malignancy. Furthermore, a pronounced familial predisposition to colorectal cancer amplifies the necessity for contemplating surgical measures. Within the spectrum of surgical interventions for JPS, colectomy emerges as a prominent option, encompassing variations from segmental or subtotal colectomy to the more encompassing total colectomy. This procedure entails an IRA, offering a surgical remedy to alleviate the impact of the polyp burden and associated complications. Conversely, an alternative viable approach involves a TPC with IPAA [82,83].

### 5.4. Surgical decision for Juvenile Polyposis Syndrome

For PJS patients with polyps exceeding 0.5 cm detected during upper endoscopy and colonoscopy, it is advisable to consider endoscopic removal [84]. Resection of other small bowel polyps, particularly those surpassing 1 cm or causing symptoms, is recommended to minimize the risk of complications associated with polyps, including anemia, bleeding, obstruction, malignancy, and the potential requirement for urgent surgery [85]. Progress in small bowel endoscopy has elevated the efficacy of non-surgical approaches to small bowel polyps. Successful polyp extraction has been documented with balloon-assisted enteroscopy, encompassing both single and double balloon procedures [84]. The use of double balloon enteroscopy may present challenges in individuals with a history of abdominal surgery, marked by peritoneal adhesions and altered anatomy. Those with PJS confront an increased likelihood of perforation during polyp removal due to serosal invagination within the polyp stalk [86]. Surgical intervention becomes necessary when endoscopic management of polyps is unachievable due to their size or number, or in the presence of neoplasia. Surgery may also

be indicated for patients with small bowel obstruction or intussusception. In cases of laparotomy for individuals with PJS, intra-operative enteroscopy is recommended for the identification and excision of small bowel polyps [87].

## 6. The impact of genetic profiling on surgical decisions and timing

The influence of genetic profiling on surgical decisions in Lynch syndrome is profound. The identification of specific genetic mutations associated with Lynch syndrome has significantly impacted the approach to surgical interventions. With a deeper understanding of the genetic factors involved, healthcare professionals can tailor surgical strategies to the individual's unique genetic profile. Research findings have indicated the occurrence of metachronous colon cancer following surgical procedures for rectal cancer in individuals with *path\_MMR* mutations [88]. Nevertheless, the documented instances of such occurrences are notably lower compared to those of colon cancer [89]. Consequently, there is insufficient empirical evidence to advocate for extended surgery specifically targeting primary rectal cancers in individuals with *path\_MMR* mutations. Consequently, both national and international guidelines suggest anterior resection or abdominoperineal resection (APR) as the preferred primary surgical interventions in these cases [90]. For patients with rectal cancer subsequent to prior segmental colectomy, the European expert group recommends either proctocolectomy with IPAA or APR with a permanent ileostomy. However, it's important to note that there is a lack of available data to substantiate this recommendation [88]. Individuals with variants in *MLH1* and *MSH2* genes face an elevated risk of developing metachronous colorectal cancer according to current research, emphasizing the potential benefits of extended surgical interventions. Engaging in more extensive surgery in these cases could potentially reduce the necessity for subsequent bowel surgeries [91]. Nevertheless, performing an extended resection does not directly contribute to an improvement in colorectal cancer-related mortality [92]. Reduced cumulative risks of both primary and metachronous colorectal cancer in individuals carrying variants in *MSH6* and *PMS2* genes justify the adoption of standard segment resection. However, for *MSH6* and *PMS2* patients with a history of challenging surveillance colonoscopies, there is a rationale for considering extended bowel resection. This is due to the potential complications arising from postoperative bowel adhesions that could further hinder the effectiveness of subsequent endoscopic procedures [88]. The surgical options for colorectal cancer in individuals with *path\_MMR* mutations vary based on the specific gene involved. For primary colon cancer, subtotal colectomy is recommended for those with *Path\_MLH1* and *Path\_MSH2* mutations, while segmental colectomy is suggested for those with *Path\_MSH6* and *Path\_PMS2* mutations. In cases of metachronous colon cancer after segmental colectomy, the preferred approach is subtotal colectomy with ileorectal anastomosis for all *path\_MMR* mutations. For primary rectal cancer in *path\_MMR* carriers, the recommended surgical procedure is anterior resection or APR, regardless of the specific *path\_MMR* mutation. In instances where rectal cancer occurs after a previous segmental colectomy, the European expert group advises either proctocolectomy with IPAA or abdominoperineal resection with a permanent ileostomy for all *path\_MMR* mutations. It is noteworthy that these recommendations are based on available data and expert opinion, as there may be limited empirical evidence to support certain surgical options [93].

Genotyping the *APC* gene emerges as a valuable tool for tailoring the management of individuals with FAP [94]. Sarvepalli and collaborators devised a predictive model that demonstrated accuracy levels surpassing 80 % in predicting the probability of surgery within a 2- or 5-year timeframe. Notably, they classified the correlation between genotype and phenotype into four distinct groups: attenuated phenotype (involving mutations in codon <157 or >1595, or alternatively spliced 9th exon), intermediate phenotype (encompassing mutations in codon 157–1249 and 1464–1595, excluding alternatively spliced 9th exon), severe phenotype (linked to mutations in codon 1250–1464), and large *APC* deletion. The study underscored a substantial connection between the severity of the phenotype and the time elapsed between the initial colonoscopy and the inaugural prophylactic surgery. Specifically, the cohort characterized by large *APC* deletions demonstrated the briefest duration before undergoing surgery [95]. Certain patients manifest a less severe variant of FAP termed attenuated FAP (aFAP). This distinction from classical FAP relies on factors such as polyp phenotype and family history. Those with aFAP typically present with a lower number of colorectal polyps (ranging from few to one-hundred), experience onset later in life, and often have rectal sparing. The risk of CRC is estimated to be around 70 % by the age of 80, occurring at an average age of approximately 30 years. Given the later onset, the use of colonoscopy with polypectomy is frequently effective, potentially delaying the necessity for surgery until patients reach their 30s or 40s [96]. Recent research conducted by Mori et al., in 2023 [97] proposes that distinct interventional strategies based on genotypes can be considered in the clinical management of FAP patients. Specifically, they observed that individuals with certain germline variants in attenuated FAP-associated regions (Genotype-1) exhibited a lower risk of colorectal cancer stages II–IV compared to those with other variants (Genotype-2). The study highlighted that the risk of developing stage II–IV CRC significantly increased at different ages for Genotype-1 and Genotype-2 patients, suggesting a potential basis for guiding the timing of prophylactic (procto)colectomy. Despite these promising findings, it is imperative to note that the proposed approach awaits validation through further prospective studies, particularly those focusing on long-term endoscopic intervention and determining the optimal age for prophylactic (procto)colectomy. Therefore, while genotyping of the *APC* gene can provide valuable insights, the decision-making process regarding the type of surgery in FAP should be comprehensive. This involves a thorough assessment of the patient's condition, considering factors such as the number and size of polyps, the presence of symptoms, and the overall health status. The integration of genetic information into the broader clinical context ensures a more nuanced and personalized approach to surgical decisions for individuals with FAP. There is indication that the likelihood of developing desmoid tumors rises after abdominal surgery, with a potentially higher risk associated with procedures necessitating two stages. Those with an elevated risk for desmoids, such as women, individuals with *APC* pathogenic variants in codons 1395–1493, and those with a family history of desmoids, are advised to contemplate a surgical approach that is likely to be completed in a single stage. This is recommended to minimize the necessity for a subsequent surgery [5].

As mentioned JPS is associated with germline mutations in certain genes, including *SMAD4* and *BMPRIA*. These mutations are



associated with an increased risk of juvenile polyps in the gastrointestinal tract, including the colon and rectum. However, the association between specific genes and the degree of dysplasia in the polyps is not always straightforward and might not help choosing the best surgical option. Mostly, finding the best option for the surgery requires a combination of genetic testing, the extent and location of polyps, and individual patient characteristics [98]. Individuals harboring *SMAD4* pathogenic mutations should be mindful of vascular lesions associated with hereditary hemorrhagic telangiectasia (HHT) [99].

Surveillance in PJS advises polypectomy, primarily to avert complications rather than significantly altering cancer risk, given the absence of dysplasia in PJS polyps. The primary objective of polypectomy is to prevent complications such as anemia and bleeding, but quantifying this prevention is challenging, and there is a lack of supporting data. In children with PJS, intussusception poses a notable clinical concern, with a cumulative risk ranging from 50 % to 68 % during childhood. Limited therapeutic options are available for the management of PJS concurrent with rectal cancer [100]. Surgical approaches are typically employed to address PJS-related complications, like small bowel intussusception or neoplastic lesions, often necessitating enterectomy. Notably, there is a lack of research specifically investigating laparoscopic restorative proctocolectomy with IPAA in PJS patients [101] (Fig. 2).

### 7. Critical view

The application of genetic profiling technologies in surgical decision-making is heavily dependent on the precision and reliability of these tools [102]. Challenges persist in obtaining consistently accurate genetic data, encompassing issues from interpreting variants to identifying new mutations. Additionally, the integration of diverse genetic information into a unified framework for surgical planning necessitates continuous refinement of analytical methods [103]. The American College of Medical Genetics and Genomics (ACMG) has developed a system to classify genetic variants into five categories based on their potential to cause disease: Pathogenic (P), Likely Pathogenic (LP), Variant of Uncertain Significance (VUS), Likely Benign (LB), and Benign (B). This classification system aids clinicians in understanding the clinical significance of genetic variants and tailoring patient care accordingly. Variants identified as pathogenic or likely pathogenic are considered actionable from a clinical standpoint, necessitating specific monitoring and treatment for associated diseases. On the other hand, Variants of Uncertain Significance (VUS) present a challenge due to the uncertainty surrounding their impact on gene function. This uncertainty complicates their role in genetic disorders, emphasizing the need for ongoing monitoring and thorough genetic counseling to evaluate their clinical significance [104]. Another notable challenge emerges in translating genetic findings into actionable insights for surgeons. Clinicians are confronted with the intricate task of interpreting complex genetic data, comprehending the nuanced implications of specific mutations, and assessing their relevance to surgical strategies [105]. Bridging the gap between genetic knowledge and practical clinical application requires collaborative efforts in education and multidisciplinary approaches. With the increasing prevalence of genetic profiling, effective communication between healthcare providers and patients becomes paramount [106]. Navigating the delicate balance of conveying potential risks and benefits, uncertainties, and the enduring impact of surgical decisions presents ethical and communication challenges. The evolving landscape of genetic testing also prompts considerations regarding the appropriate scope and depth of informed consent processes. Ongoing research efforts are essential for advancing the understanding of the genetic foundations of HCRC syndromes. The refinement of predictive models that encompass a broader spectrum of genetic factors, environmental influences, and lifestyle considerations is crucial for enhancing the accuracy and clinical significance of genetic profiling, ultimately enabling more precise surgical recommendations [107]. Looking ahead, the future of genetic profiling involves embracing multi-omics strategies that extend beyond DNA

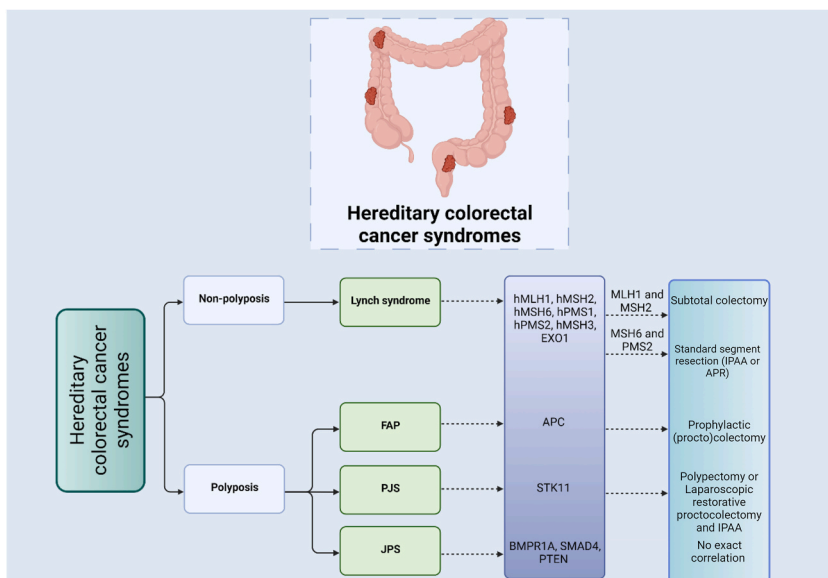


Fig. 2. Illustration of the impact of various genetic profiles on the surgical approach in the management of hereditary colorectal cancer syndromes.

sequencing. Integrating data from genomics, transcriptomics, epigenomics, and proteomics will furnish surgeons with a comprehensive molecular landscape, offering a more holistic perspective on the disease and its potential trajectories [108]. This comprehensive approach holds the potential to uncover novel therapeutic targets and guide personalized surgical interventions. As artificial intelligence progresses, the analysis of data illustrating the connection between the genotype and phenotype in HCRCs can aid in distinguishing various patient classifications and forecasting the results of ongoing surgical procedures [109].

## 8. Conclusions

In conclusion, this review underscores the pivotal role of genetic profiling in guiding surgical decisions for HCRC syndromes such as Lynch syndrome and FAP. The understanding of genotypes, particularly mutations in genes like MLH1, MSH2, MSH6, PMS2, and APC, allows for tailored surgical strategies that optimize patient outcomes and mitigate cancer risks. For instance, subtotal colectomy is recommended for Lynch syndrome patients with MLH1 and MSH2 mutations, while segmental colectomy is preferred for those with MSH6 and PMS2 mutations. The genotype-phenotype correlations in FAP further inform surgical timing and approaches, with considerations for desmoid tumor risks influencing the choice of single-stage surgeries. The findings highlight the importance of personalized surgical plans that account not only for the genetic profile but also for the individual's cancer history and risk of metachronous cancer. Such personalized strategies are essential in improving long-term survival and quality of life for patients with HCRC. Despite these advances, further research is necessary to refine these surgical guidelines and ensure they remain aligned with the latest genetic discoveries and clinical practices. This ongoing research will enhance the precision of clinical decision-making and the efficacy of surgical interventions for HCRC.

### CRedit authorship contribution statement

**Yasaman Goudarzi:** Writing – review & editing, Writing – original draft. **Khaterehsadat Monirvaghefi:** Writing – review & editing, Writing – original draft, Conceptualization. **Salar Aghaei:** Writing – original draft, Visualization. **Seyed Siamak Amiri:** Writing – review & editing, Writing – original draft. **Mahdi Rezaei:** Writing – original draft. **Atefeh Dehghanitafti:** Visualization, Conceptualization. **Ali Azarpey:** Writing – original draft. **Alireza Azani:** Writing – original draft, Visualization. **SeyedAbbas Pakmehr:** Writing – original draft. **Hamid Reza Eftekhari:** Writing – original draft, Visualization, Conceptualization. **Safa Tahmasebi:** Writing – original draft. **Shahriar Zohourian Shahzadi:** Visualization, Project administration, Conceptualization. **Mansour Rajabivahid:** Writing – review & editing, Project administration.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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