REVIEW ARTICLE

Impact of Mutations in DNA Repair Genes in Lynch Syndrome: A Systematic Literature Review

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ABSTRACT

Introduction: Lynch syndrome (LS), also known as hereditary nonpolyposis colorectal cancer, is a genetic condition that significantly increases the risk of developing colorectal cancer and other types of cancer. This syndrome is caused by mutations in DNA repair (MMR) genes, which are responsible for correcting errors that occur during DNA replication.

Methodology: Scientific databases such as PubMed, Scopus, and Web of Science were consulted for this systematic review. Studies that addressed mutations in MMR genes (MLH1, MSH2, MSH6, PMS2 and EPCAM) and their association with Lynch syndrome were included. Studies that did not present relevant clinical data or that were not systematic reviews were excluded..

Results: The results showed that mutations in MMR genes are responsible for approximately 1-7% of all cases of colorectal cancer. The most common mutations are found in the MLH1 (50%) and MSH2 (40%) genes, while MSH6, PMS2 and EPCAM represent a smaller proportion1. These mutations lead to genomic instability, resulting in a high rate of mutations in tumour cells, which contributes to the development of cancer.

Conclusion: The systematic review demonstrated that mutations in DNA repair genes have a significant impact on Lynch Syndrome, increasing the risk of colorectal cancer and other types of cancer. Identifying these mutations is crucial for early diagnosis and implementation of screening and prevention programs. Furthermore, understanding the molecular basis of the syndrome may lead to the development of new targeted therapies.

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What do we already know about this topic?
Lynch syndrome is the most common inherited form of colorectal cancer, accounting for approximately 3% of cases. This syndrome is associated with mutations in DNA repair genes such as MLH1, MSH2, MSH6 and PMS2. These mutations result in microsatellite instability (MSI), which is characterized by the accumulation of errors in DNA during cell replication, leading to malignant transformation of cells and the development of cancers. In addition to colorectal cancer, individuals with Lynch syndrome have an increased risk of cancers of the endometrium, ovary, stomach, small intestine, urinary tract, liver and central nervous system. Advances in understanding these mutations have enabled the development of genetic tests to identify individuals at risk, facilitating preventive interventions and regular surveillance. Early detection of specific mutations also allows for more personalized treatment approaches. Systematic literature reviews highlight the importance of continued studies to elucidate genetic variations and their clinical implications, identifying gaps in current knowledge and suggesting further research to better understand the mechanisms underlying mutations in DNA repair genes and their impact on Lynch syndrome.
What is the main contribution to Evidence-Based Practice from this article?
The article "Impact of DNA Repair Gene Mutations on Lynch Syndrome: A Systematic Review" makes a significant contribution to evidence-based practice by providing a comprehensive synthesis of current knowledge on DNA repair gene mutations and their clinical implications in Lynch Syndrome. Firstly, the article highlights the importance of genetic testing to detect mutations associated with Lynch Syndrome. Early identification of these genes allows for preventive interventions and regular surveillance, increasing the effectiveness of patient screening and treatment. This facilitates early detection of the syndrome, which is crucial for the adoption of preventive measures and regular screening. Secondly, the systematic review identifies how specific mutations in DNA repair genes can influence treatment options. This knowledge promotes more personalized and effective therapeutic approaches, allowing treatments to be tailored according to the individual genetic characteristics of patients. In addition, the article emphasizes the need for public health policies that consider the genetic characteristics of Lynch Syndrome. Implementing screening and prevention programs that take these characteristics into account can significantly improve patients' quality of life and the efficiency of health care. Finally, the review highlights areas where knowledge is limited, suggesting the need for further research to better understand the genetic mechanisms involved and develop new strategies for managing the syndrome. Identifying these gaps in current knowledge encourages future studies that can deepen our understanding and improve the treatment and prevention of Lynch Syndrome. These contributions are essential to improving the diagnosis, treatment and prevention of Lynch Syndrome, directly impacting patients' quality of life and the efficiency of health care.
What are this research's implications towards health policy?
The article "Impact of DNA Repair Gene Mutations on Lynch Syndrome: A Systematic Review" presents significant implications for theory, practice, and health policy. Theory: The article expands knowledge about DNA repair gene mutations and their influence on Lynch Syndrome. It refines existing theoretical foundations and suggests new directions for future research, providing a deeper understanding of the genetic mechanisms involved. Practice: In clinical practice, the article highlights the importance of genetic testing for the early detection of Lynch Syndrome. Early identification of these mutations allows for more effective preventive interventions and regular surveillance, which increases the effectiveness of patient screening and treatment. In addition, the systematic review identifies how specific DNA repair gene mutations may influence treatment options, promoting more personalized and effective therapeutic approaches. Policy: In terms of public health policy, the article emphasizes the need for screening and prevention programs that consider the genetic features of Lynch Syndrome. Implementing policies that promote genetic testing and regular surveillance can significantly improve early detection of the syndrome and the quality of life of patients. Health policies should include strategies based on genetic evidence to be most effective.

Authors' Contributions Statement:
Dobroski, Alexia Uriadenik Bastos, lead author, wrote introduction and methodology. Duarte, Bruno Pelinson Fogaça, co-author, wrote introduction and results. Tanganelli, Caroline Baptista, co-author, wrote methodology and introduction. Neto, Elias M. Oliveira, co-author, wrote introduction and results. Naddeo, Marcelo, co-author, wrote introduction and discussion. Valdujo, Nathália Simões, co-author, wrote introduction and discussion. Maluf, Gabriel, co-author, wrote introduction and discussion. Uyeda, Mari, co-author, wrote results and conclusion and reviewed all the material.

Introduction:

Lynch Syndrome (LS), also known as hereditary nonpolyposis colorectal cancer (HNPCC), is the most common form of hereditary colorectal cancer (CRC). It results from germline mutations in genes of the DNA mismatch repair (MMR) system, specifically MSH2, MLH1, MSH6, and PMS2 (Grigorie, Potlog, & Alexandrescu, 2025; Lynch et al., 2009). Individuals with MMR mutations have a significantly increased risk of developing CRC and endometrial cancer (Costa et al., 2023). LS is inherited in an autosomal dominant manner, meaning that each child of a carrier has a 50% chance of inheriting the mutation. LS carriers have an increased risk of several

cancers, including ovarian, stomach, small intestine, hepatobiliary tract, urinary tract, brain and skin cancers, in addition to CRC (Costa et al., 2023). The lifetime risk of developing CRC ranges from 47-78% in men and 30-57% in women, while the risk of endometrial cancer ranges from 25-61% (Vasen et al., 2007; Ramsoekh et al., 2009; Alarcon et al., 2007). Identifying genetic modifying factors that influence the penetrance of MMR mutations is a significant challenge. Characterizing these factors could have important clinical implications, allowing for tailoring of follow-up and investigations according to the modifying alleles. Overall, LS accounts for 0.3% to 2.4% of CRCs, with an estimated overall prevalence of approximately 1:3100 in the population (Cairns et al., 2010; Vasen et al., 2010). The risk of developing a second primary CRC in individuals with LS is estimated to be 16% within 10 years (Peltomäki, Nyström, Mecklin, & Seppälä, 2023). The risk of LS-related cancer in first- or second-degree relatives is approximately 45% for men and 35% for women by age 70 (Grigorie, Potlog & Alexandrescu, 2025, Vasen et al., 2007).

LS is caused by mutations in DNA MMR genes, including MLH1, MSH2, MSH6, and PMS2. Loss of DNA repair activity due to mutations in both alleles of these genes results in the inability to correct base-base mismatches and small insertions and deletions, leading to mutations that can progress to cancer (Umar et al., 2004). Mutations occur especially in repetitive DNA sequences, such as microsatellites, resulting in microsatellite instability (MSI). Global data indicate that MLH1 is responsible for 39% of cases, MSH2 for 34%, MSH6 for 20% and PMS2 for 8% of mutations recorded in the International Society for Hereditary Gastrointestinal Tumors (InSiGHT) database. Studies have focused on identifying modifier genes in LS and investigating genes associated with the development of CRC. One of the first genetic modifiers identified was a CA repeat polymorphism in the IGF1 gene promoter, associated with an increased risk of CRC (Zecevic et al., 2006; Reeves et al., 2008). Other studies have investigated genes encoding xenobiotic-metabolizing enzymes, such as GSTT1 and GSTM1, with mixed results (Seppälä et al., 2021, Felix et al., 2006; Pande et al., 2008). Recently, genome-wide association studies (GWAS) have identified SNPs associated with CRC risk in the general population, which also act as risk modifiers in patients with highly penetrant MMR mutations. For example, the SNPs rs16892766 (8q23.3) and rs3802842 (11q23.1) have been associated with CRC risk in MMR mutation carriers (Grigorie, Potlog & Alexandrescu, 2025, Wijnen et al., 2009).

The second strategy to detect modifier genes in LS patients relies on GWAS that identify SNPs (single nucleotide polymorphisms) associated with CRC risk in the general population. The hypothesis is that these SNPs, which are risk factors for CRC, may act as risk modifiers in patients with highly penetrant mutations. Wijnen et al. (2009) reported significant associations of the SNPs rs16892766 (8q23.3) and rs3802842 (11q23.1) with CRC risk in 675 Dutch carriers of MMR mutations from 127 families (Grigorie, Potlog & Alexandrescu, 2025).

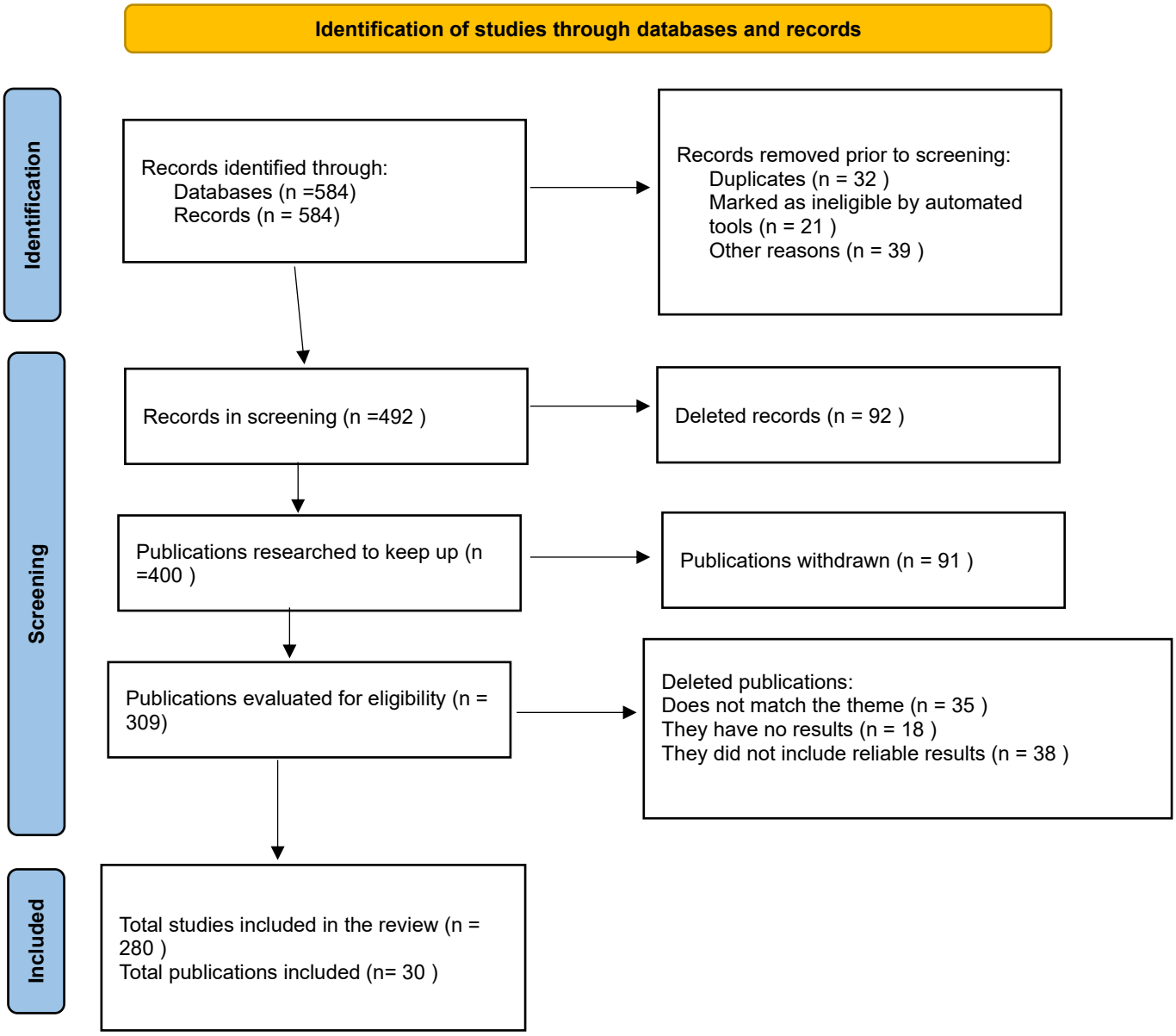
Methodology

The objective of this systematic review was to analyze the impact of mutations in MMR genes on LS. This study aims to understand how these mutations influence the pathogenesis, diagnosis, treatment and prognosis of LS. For this purpose, the following inclusion criteria were used: Studies that investigated mutations in MMR genes (MSH2, MLH1, MSH6, PMS2, PMS1) and their relationship with LS; Studies

published in English, Portuguese or translated into these languages; Studies that included relevant clinical and molecular data.
The exclusion criteria were: Studies that did not specifically address mutations in MMR genes; Opinion articles, editorials and non-systematic reviews; and Studies with very small sample sizes (less than 10 participants).
The search was conducted in the following databases: PubMed, Scopus, Web of Science and Google Scholar. Keywords used will include: "Lynch syndrome," "DNA mismatch repair genes," "MSH2," "MLH1," "MSH6," "PMS2," "mutation," and "colorectal cancer." Filters will be applied for articles published in the last 10 years, human studies, and clinical and molecular studies.
Study selection was performed in three stages. The first screening involves reviewing the titles and abstracts to identify potentially relevant studies. The second screening involves reading the selected articles in full to verify compliance with the inclusion criteria. The third screening involves reviewing the included studies to ensure their quality and relevance. The results were interpreted to discuss the impact of MMR gene mutations on LS, considering the limitations of the included studies. The discussion will address the clinical implications of the findings for the diagnosis, treatment, and prevention of LS.

Results:

Prisma Flowchart
Electronic databases, including PubMed, Scopus, and Web of Science, were searched using terms related to LS, DNA repair gene mutations, and systematic review. In addition, the references of the included studies were checked to identify additional relevant studies. After removing duplicates, the titles and abstracts of the identified studies were assessed to verify whether they met the previously defined inclusion criteria. Studies that did not meet the inclusion criteria were excluded. The full texts of potentially relevant studies were obtained and assessed in detail for eligibility, and studies that did not provide sufficient data or did not meet the inclusion criteria were excluded.
Data on DNA repair gene mutations, patient characteristics, methodologies used, and outcomes were extracted from the included studies.
The results of the included studies were synthesized qualitatively and, where possible, quantitatively. Patterns and trends in DNA repair gene mutations and their impact on Lynch syndrome were identified. The results were discussed in terms of their clinical and scientific implications.



Diagnosis/tests:

The Amsterdam Criteria (AC) II and the revised Bethesda criteria are used to diagnose LS. Proposed in 1989, the AC were revised in 1999 to include extracolonic tumors (Vasen et al., 2007). The Bethesda guidelines, developed in 1997 and revised in 2004, use techniques such as immunohistochemistry (IHC), MSI, and MMR to select tumors for testing and identify individuals with LS. All of the Amsterdam criteria must be met, while only one Bethesda criterion is required..

TABLE 1 Lifetime Cancer Risk in LS

Cancer	Estimated lifetime cancer risk for individuals with LS (%)	Estimated lifetime risk of cancer in the general population (%)
Colorectal at 70 years old	Man: 38 Women: 31	Man: 5 Women: 6
Endometrium	Women: 33	Women: 2–3
Gastric	0.7	1
Ovary	Women: 9	Women: 1–2
Small intestine	0.6	0.01
Bladder	4	1–3
Urinary Tract	1.9–8.4	4
Brain	4	0.6
Kidney, renal pelvis	3	1
Biliary tract	0.6	0.5
Pancreas	0.4–3.7	1.4
Prostate	Man: 9.1–30.0	Man: 13.2
Mama	Women: 5.4–14.4	Women: 12.9

Source: The Author

TABLE 2 Criteria used to aid the diagnosis of LS

AC II	Revised Bethesda guidelines
At least three separate relatives with CRC or LS-associated cancer	CRC diagnosed in a patient aged <50 years
One relative must be an FDR of the other two	Presence of synchronous, metachronous colorectal tumors or other SL-related tumors, regardless of age
At least two successive generations affected	CRC with MSI-H phenotype diagnosed in a patient aged <60 years
At least one tumor must be diagnosed before age 50	At least one tumor must be diagnosed before age 50
FAP excluded in case(s) of CCR	CRC patient with two or more FDRs or SDRs with SL-related tumor, regardless of age
Pathologically verified tumors	

Source: The Author

The Bethesda criteria for LS include MSI testing. The National Cancer Institute (NCI) recommends a panel of five markers: two mononucleotides (BAT25 and BAT26) and three dinucleotides (D2S123, D5S346, and D17S250). Tumours without instability are considered microsatellite stable (MSS). Tumours with one altered marker are MSI-low (MSI-L), and those

with two or more altered markers are MSI-high (MSI-H) (Umar et al., 2004). In some cases, an additional panel of five markers is used; if 3 out of 10 are unstable, the tumour is classified as MSI-H, and if two or fewer are unstable, MSI-L. Limitations of MSI testing include the silencing of MLH1 in non-hereditary cancers, resulting in MSI in approximately 15% of sporadic CRC cases (Vasen et al., 2007). Up to 50% of suspected LS cases are not confirmed by mutations in known MMR genes (Umar et al., 2004). Therefore, the Bethesda criteria have been criticized for being insensitive and non-specific, resulting in 25% of all CRCs being tested. This has led to the development of additional tests for the diagnosis of LS. Current evidence recommends including genetic testing for LS (EGAPP, 2009):

1. Assessment of tumour tissue for MSI by molecular MSI testing and/or IHC of MMR proteins (MLH1, MSH2, MSH6 and PMS2).
2. Molecular testing of the tumour for MLH1 gene methylation and/or somatic BRAF V600E mutation to distinguish sporadic from hereditary tumours. The presence of the BRAF V600E mutation makes SL unlikely (Vasen et al., 2007).
3. Genetic testing of MMR genes to identify constitutional (germline) mutations when findings are consistent with LS.

Prognosis

CRC in LS evolves more rapidly through the adenoma-carcinoma sequence than in sporadic cases, occurring in 2–3 years rather than 8–10 years (Umar et al., 2004; Aarnio et al., 1998). Adenomas in LS tend to arise in younger individuals, are larger, and are more dysplastic. Studies indicate that CRC patients in LS families have a higher survival rate than patients with sporadic CRC (Aarnio et al., 1995), possibly due to a lower propensity for metastasis and more active immunologic mechanisms in MSI tumours.

In addition, there is a genotype-phenotype correlation in LS. Carriers of the MSH6 mutation have a lower overall risk of cancer compared with carriers of the MLH1 or MSH2 mutations (Vasen et al., 2013). Carriers of mutations in MMR genes have a high risk of developing CRC (25–70%) and endometrial cancer (30–70%), as well as an increased risk of other tumours (Vasen et al., 2013).

Understanding these factors and using genetic testing can aid in the diagnosis and management of LS, as described in Table 3, which provides an overview of the tests available to identify the syndrome.

TABLE 3 Overview of tests to aid in the diagnosis of LS

Test	Description
MSI	Preliminary testing performed on tumour tissue. Those with high instability proceed to DNA analysis or IHC. However, the presence of MSI in the tumour alone is
IHC	Preliminary test performed on tumour tissue to identify one of the four MMR proteins (MLH1, MSH2, MSH6, and PMS2). Those with negative staining undergo DNA analysis of the indicated gene/genes The IHC test helps identify the MMR gene that is likely to harbor a constitutional ('germline') mutation, as abnorm
MLH1 methylation and/or BRAF V600E testing of tumour tissue	Preliminary molecular genetic testing performed on tumour tissue from patients with negative MLH1 staining on IHC The presence of BRAF V600E mutation or MLH1 hypermethylation makes LS unlikely
DNA analysis of MMR genes (MLH1, MSH2, MSH6, PMS2)	Diagnostic test, usually performed on blood. DNA analysis (gene sequencing, deletion/duplication testing) of MLH1, MSH2, MSH6, PMS2

Source: The Author

Disease management

Surveillance

LS is hereditary, making identification of family members carrying mutations in the MMR genes essential. Colonoscopic surveillance and possibly surgical interventions can be offered to high-risk individuals. However, screening for mutations is expensive and time-consuming, as it can involve analysis of four genes with broad mutational spectra (Vasen et al., 2007).

The British Society of Gastroenterology (BSG) and the Association for Coloproctology of Great Britain and Ireland (ACPGBI) recommend surveillance for individuals at high risk of gastrointestinal malignancy based on the following criteria:

- Family history consistent with an autosomal dominant cancer syndrome.
- Pathognomonic features of a polyposis syndrome in person or in a close relative.
- Presence of a constitutional pathogenic mutation in a CRC susceptibility gene.
- Molecular features of a familial syndrome in a CRC in a FDR.

Vasen et al. (2007) highlight a study in which 10-year surveillance in 22 families with LS reduced the development of CRC by 60% and decreased mortality (Vasen et al., 2010; Järvinen, Mecklin & Sistonen, 1995). Adequate surveillance also avoids the need for intensive surveillance for those without a genetic defect, saving costs and reducing risks (Vasen et al., 2007).

Full colonic surveillance should begin at age 25, with colonoscopies every 18 months due to

the occurrence of interval cancers in some series. Surveillance continues until age 70–75 or until comorbidity makes the procedure inappropriate. If a causal mutation is identified in a relative and the patient is not a carrier, surveillance should cease and general population risk measures should be applied. Families meeting the Amsterdam criteria but without evidence of MMR gene defects require less frequent colonoscopic surveillance. Gastrointestinal surveillance should cease for individuals who test negative for a pathogenic germline mutation present in the family unless there is a significant finding on a previous colonoscopy. The evidence for upper gastrointestinal surveillance is limited, but it is suggested that it may be beneficial.
Debate continues about the appropriate age and frequency of surveillance (Vasen et al., 2007). The situation is more complex when the individual has no detectable DNA alteration associated with LS or when an alteration of uncertain significance is identified. Vasen et al. (2007) suggest that approximately 30% of families fall into this category, and recommend a less intensive surveillance protocol, such as a colonoscopy every 3–5 years, starting 5–10 years before the first diagnosis of CRC or after age 45.

Surgical treatment
Patients with LS have an increased risk of developing multiple synchronous and metachronous CRCs. The recommended surgery, whether total or subtotal colectomy, depends on the location and stage of the tumour. Adenomas in LS are usually in the proximal colon, favoring subtotal colectomy, which removes most of the colon, leaving a small portion for reconnection with the rectum. Prophylactic colectomy may be discussed for mutation carriers with difficult colonoscopy or difficult-to-remove adenomas, although this approach is controversial.

Chemotherapy
At least three chemotherapeutic agents are effective in the treatment of RCC: 5-FU (fluorouracil) with or without leucovorin (folinic acid), oxaliplatin, and irinotecan. However, MSI-H tumours are often resistant to 5-FU-based chemotherapy, and prospective clinical trials are needed before definitive recommendations can be made (Vasen et al., 2007).
Epidemiological studies have shown that nonsteroidal anti-inflammatory drugs, such as aspirin, reduce the risk of CRC (Aarnio et al., 1998). A recent study found that daily aspirin decreased the incidence of CRC in LS patients after 56 months of follow-up (Burn et al., 2011). Although the exact mechanisms are unknown, aspirin is thought to be pro-apoptotic in the early stages of CRC development.
The CAPP2 trial demonstrated that aspirin treatment for up to 3 years reduced the incidence of LS-associated cancers, including CRC, by 63% a decade later (Burn et al., 2011). An additional dose-ranging trial (CAPP3) is planned for LS patients worldwide, highlighting the importance of identifying individuals and families with LS.

Description of technologies under evaluation

Immunohistochemistry
For families with suspected mutations in the MMR genes, IHC analysis for MSH2, MLH1, and MSH6 proteins in tumour tissue is the first step to confirm MMR deficiency. Pathogenic mutations often result in the absence or abnormal localization of the protein (cytoplasm rather than nucleus). Tumour tissue from patients with LS shows negative or less intense nuclear staining compared to surrounding

normal tissue (Bonis et al., 2007; Müller et al., 2004).

Microsatellite instability test
MSI refers to the variation in microsatellite repeat patterns observed in amplified DNA from defective MMR compared with normal DNA. Microsatellites, which are repetitive mono- or dinucleotide DNA sequences, are particularly susceptible to defects in MMR. MSI is common in tumours from patients with MMR mutations and who meet the Amsterdam criteria, and microsatellite analysis is often used as the first screening test for LS (Bonis et al., 2007; Müller et al., 2004).

BRAF V600E and methylation testing
The presence of MSI in the tumour is not sufficient to diagnose LS, since 10-15% of sporadic CRCs also exhibit MSI (Oliveira et al., 2004). In non-LS tumours, MSI is usually caused by hypermethylation of the MLH1 gene associated with mutations in the BRAF gene (V600E). The identification of these alterations indicates that the patient does not have a germline LS mutation. Table 4 describes the types of mutations that are associated with.

TABLE 4 Types of mutations associated with LS.

Mutation	Description
Missense	A change in a DNA base pair that results in the substitution of one amino acid for another in the protein produced by a gene.
Nonsense	A change in a DNA base pair that results in a premature signal to stop building a protein. This type of mutation results in a shortened protein that may function improperly or not at all.
Insertion	Changes the number of DNA bases in a gene by adding a piece of DNA. As a result, the protein made by the gene may not function properly.
Deletion	Changes the number of DNA bases by removing a piece of DNA. Small deletions can remove one or a few base pairs within a gene, while larger deletions can remove an entire gene or several neighboring genes. The deleted DNA can alter the function of the resulting protein(s).
Duplication	It consists of a piece of DNA that is copied abnormally one or more times. This type of mutation can alter the function of the resulting protein.
Frameshift mutation	Frameshift mutation occurs when the addition or loss of DNA bases changes the reading frame of a gene. A reading frame consists of groups of three bases that each code for an amino acid. A frameshift mutation changes the grouping of these bases and changes the code for amino acids. The resulting protein is usually nonfunctional. Insertions, deletions, and duplications can all be frameshift mutations..
Splice site	Causes abnormal mRNA processing, usually leading to in-frame deletions of entire exons or out-of-frame mRNA mutations, leading to nonsense-mediated decay of mRNA. Mutations may be located deep in intronic sequences
Promoter	Mutations in the control region of a gene that lead to its non-expression. Epigenetic mutations, i.e. abnormal methylation of CpG sites, can give rise to the same effect.

Source: The Author

TABLE 5 Genetic testing in SL

Test	Description	Comment
High-throughput screening techniques	SSCP CSGE DGGE DHPLC	All of these methods take advantage of the observation that altering DNA confers chemical properties that allow it to be differentiated from normal DNA.
DNA sequencing	This can be used after a high-throughput screening technique or as a primary approach when IHC patterns allow targeting of an MMR gene.	It does not reliably allow the detection of deletions or rearrangements, which are also important in LS.
Methods for detecting major structural abnormalities of DNA.		Large structural DNA abnormalities are an important cause of LS (5–25% of cases, depending on the gene) but are often not detected by high-throughput screening techniques or DNA sequencing.
Conversion analysis.	Only a single allele is analyzed at a time. This can increase the throughput of genetic testing, but it is technically complicated, expensive, and not widely available.	

Source: The Author

Conclusion

Studies have shown that mutations in DNA repair genes not only increase the risk of developing CRC but are also associated with several other types of cancer, such as endometrial, ovarian, stomach, small intestine, urinary tract, liver and brain cancer. Early identification of these mutations through genetic testing may allow for more intensive surveillance strategies and preventive interventions, such as prophylactic surgery and the use of aspirin, which has been shown to reduce the risk of cancer in carriers of LS mutations.

Throughout this analysis, it became clear that the MLH1, MSH2, MSH6, PMS2 and EPCAM genes play crucial roles in maintaining genomic integrity. Mutations in these genes compromise the error correction mechanism during DNA replication, resulting in genomic

instability which is a hallmark of LS. The prevalence of these mutations varies, with MLH1 and MSH2 being the most commonly affected. This genomic instability is a key factor in the development of malignant tumours, as it allows the accumulation of mutations in oncogenes and tumour suppressor genes.
The clinical impact of these mutations is profound. Patients with LS face a significantly increased risk of developing cancer at an earlier age than the general population. This highlights the importance of genetic screening and counselling for individuals with a family history of colorectal cancer and other malignancies associated with the syndrome. Early identification of mutations in MMR genes allows for preventive interventions, such as regular colonoscopies, which can detect and remove precancerous polyps before they progress to cancer.
In addition, understanding the molecular mechanisms underlying cancer development in LS has significant implications for developing new therapies. For example, immunotherapy has emerged as a promising approach for patients with LS-associated cancers, due to the high mutational burden and the presence of neoantigens that can be targeted by the immune system.
The systematic review also highlights the need for further research to fully understand the implications of the less common mutations in the PMS2 and EPCAM genes. Future studies should focus on the correlation between different specific mutations and the risk of developing cancers other than colorectal cancer, such as endometrial, gastric and ovarian cancer, which are also frequently observed in patients with LS.
In conclusion, mutations in DNA repair genes play a central role in the pathogenesis of LS. Early detection and appropriate management of these mutations are crucial for effective prevention and treatment of cancer. This systematic review contributes to a greater understanding of the syndrome and emphasizes the importance of genetic screening and personalized treatment. With continued advancement of research, it is expected that new therapeutic and preventive strategies will emerge, significantly improving the quality of life and survival of patients affected by LS.

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Abbreviations:
AC - Amsterdam Criteria, **ACPGBI** - Coloproctology Association of Great Britain and Ireland, **AFM** - American Founder Mutation, **BSG** - British Society of Gastroenterology, **CCR** - Colorectal Cancer, **CpG** – C-phosphate -G, **CSGE** - Conformation-Sensitive Gel Electrophoresis, **DGGE** - Denaturing Gradient Gel Electrophoresis, **DHPLC** - High Performance Denaturing Liquid Chromatography, **FAP** - Familial Adenomatous Polyposis, **FDR** - First Degree Relative, **GWAS** - Genome-Wide Association, **HNPCC** - Hereditary Nonpolyposis Colorectal Cancer, **IHC** - Immunohistochemistry, **InSiGHT** - International Hereditary Gastrointestinal Tumor Society, **MLPA** - Multiplex Ligation-Dependent Probe Amplification, **MMR - DNA** Mismatch Repair System, mRNA - Messenger Ribonucleic Acid, **MSI** - Microsatellite Instability, **MSI-H** - High Microsatellite Instability, **MSI-L** - Low Microsatellite Instability, **MSS** - Stable Microsatellites, **NCI** - National Cancer Institute, **SDR** - Second Degree Relative, **SL** – Lynch Syndrome, **SSCP** - Single-Strand Conformational Polymorphism.

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