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INVITED REVIEW



The “unnatural” history of colorectal cancer in Lynch syndrome: Lessons from colonoscopy surveillance

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Abbreviations: ADR, adenoma detection rate; CI, confidence interval; CRC, colorectal cancer; FSP, frameshift peptide; HNPCC, hereditary nonpolyposis colorectal cancer; IBD, inflammatory bowel disease; InSIGHT, International Society for Inherited Gastrointestinal Tumors; LS, Lynch syndrome; MMR, mismatch repair; MMR-DCF, mismatch repair-deficient crypt foci; MSI, microsatellite instability; PLSD, Prospective Lynch Syndrome Database.

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Abstract

Individuals with Lynch syndrome (LS), one of the most common inherited cancer syndromes, are at increased risk of developing malignancies, in particular colorectal cancer (CRC). Regular colonoscopy with polypectomy is recommended to reduce CRC risk in LS individuals. However, recent independent studies demonstrated that a substantial proportion of LS individuals develop CRC despite regular colonoscopy. The reasons for this surprising observation confirmed by large prospective studies are a matter of debate. In this review, we collect existing evidence from clinical, epidemiological and molecular studies and interpret them with regard to the origins and progression of LS-associated CRC. Alongside with hypotheses addressing colonoscopy quality and pace of progression from adenoma to cancer, we discuss the role of alternative precursors and immune system in LS-associated CRC. We also identify gaps in current knowledge and make suggestions for future studies aiming at improved CRC prevention for LS individuals.

KEYWORDS

colonoscopy surveillance, colorectal cancer, incident cancer risk, Lynch syndrome, microsatellite instability, mismatch repair deficiency

1 | NATURAL HISTORY OF LYNCH SYNDROME-ASSOCIATED COLORECTAL CANCER

The most common inherited colorectal cancer syndrome, Lynch syndrome (LS), is caused by inherited pathogenic germline variants of DNA mismatch repair (MMR) genes responsible for correction of mismatches during DNA replication: *MLH1*, *MSH2*, *MSH6* and *PMS2*.¹ In addition, deletions involving the *EPCAM* gene may silence the adjacent *MSH2* gene. The prevalence of pathogenic MMR gene variants predisposing to LS in the general population is estimated to be 1:250 or even higher.²⁻⁵ LS is inherited as an autosomal-dominant trait, meaning that carriers of a monoallelic pathogenic germline variant (insight-database.org⁶), hereafter referred to as “carriers” or “*MLH1/MSH2/MSH6/PMS2* carriers”, have an increased lifetime cancer risk. However, for LS-associated cancers to develop, somatic second hits that inactivate the remaining functional MMR allele are required (consistent with Knudson's two-hit hypothesis).^{7,8} As a consequence of MMR deficiency, mismatch mutations can accumulate resulting in hypermutated tumors with >10 point mutations per megabase.⁹ MMR deficiency also leads to the accumulation of insertion/deletion of

mutations at short repetitive sequences (microsatellites), as polymerase slippage-induced insertion/deletion loops are not repaired during DNA replication, and the mutation is passed on to subsequent cell generations.¹⁰ Insertion/deletion of mutations alter the length of microsatellites, resulting in the genetic phenotype of microsatellite instability (MSI).

Microsatellite mutations residing in protein-encoding regions of the genome can lead to loss of function of tumor suppressor genes, thereby contributing to cancer development and also to the generation of frameshift peptide (FSP) neoantigens. Certain MSI-related FSP neoantigens can encompass neoepitopes completely unknown to the host's immune system. This mechanism is commonly considered to be responsible for the high immunogenicity of MSI tumors¹¹ that has been demonstrated by several studies showing dense local immune infiltration¹²⁻¹⁴ and reactivity of these immune cells to FSPs.^{15,16} The immunogenicity of MSI tumors is also a likely reason for the observed favorable prognosis of MSI cancers and their response to immune checkpoint blockade therapy.^{14,17-19}

The most common clinical manifestations of LS are colorectal cancer (CRC) and endometrial cancer. Prior to the discovery of LS-causing MMR gene variants in the early 1990s, namely those affecting *MSH2*

and *MLH1*,²⁰⁻²² the syndrome had been termed hereditary non-polyposis colorectal cancer (HNPCC) syndrome.²³ HNPCC defined the high CRC risk and underlined the major phenotypic difference between the syndrome and familial adenomatous polyposis (FAP): FAP presents with hundreds to thousands of colonic adenomatous polyps, while the number of polyps in LS patients is not substantially changed in comparison to the general population.²⁴⁻²⁶ Even though polyposis is not part of the LS phenotype, benign polyp precursor lesions of LS CRC have been detected.^{27,28} This suggested that polyp removal may be an effective measure for CRC prevention in LS and led to international clinical guidelines recommending regular colonoscopy in LS patients.

2 | PERFORMANCE OF COLONOSCOPY FOR CRC PREVENTION IN THE GENERAL POPULATION AND IN LS

In the general population, colonoscopy with polypectomy has been associated with a reduction in CRC risk and improved survival through early detection of CRC.²⁹⁻³² In an observational re-analysis of the National Polyp Study (US) undertaken in the general population, screening colonoscopy with polypectomy reduced the risk of CRC death by 53% in 15 years of follow-up,³³ and the incidence of CRC was reduced by at least 66%.³⁴ A more recent population-based study (Germany) by Brenner et al³¹ reported a 77% risk reduction for CRC in individuals who had a screening colonoscopy in the 10 years prior to assessment. Interestingly, and similar to other studies,^{30,32,35} the risk reduction by colonoscopy was higher for left-sided CRC (84%) compared to right-sided CRC (56%). The preventive effect of colonoscopy on right-sided CRC was particularly limited in the younger age group, with only a 26% risk reduction in patients aged between 50 and 59 years. Although this study did not identify a difference in risk reduction between patients with and without a family history of CRC, the limited efficacy of colonoscopy particularly in young patients and for the right-sided colon is intriguing.^{36,37} It may in part relate to more limited efficacy of colonoscopy to prevent CRC in LS, a disease

predisposition known to be associated with an increased proportion of right-sided CRCs and earlier onset compared to the general population.³⁸

In LS, CRC risk and its reduction by colonoscopy surveillance have been analyzed by several studies with different designs. Retrospective studies largely covering the time period before the introduction of regular colonoscopy reported up to 78% “natural” (without surveillance) risk of developing CRC in individuals with HNPCC.^{39,40} A landmark non-randomized controlled study by Jarvinen et al⁴¹ reported halving of CRC risk by 3-yearly colonoscopy in HNPCC, including a group of proven MMR carriers. However, LS patients under regular colonoscopy still had up to 15% risk of developing CRC in 10 years.⁴¹⁻⁴⁹ A summary of studies assessing CRC risk in LS carriers under surveillance independent of the affected MMR gene is presented in Table 1. Differences in the CRC risk observed between the studies can be explained by the variations in study design (retrospective vs prospective), colonoscopy protocols, eligibility criteria and censoring strategies.

In line with these observations, the Prospective Lynch Syndrome Database (PLSD, plsd.eu), the largest prospective database of known MMR carriers, demonstrated the development of a substantial number of CRCs despite colonoscopy with polypectomy.⁵⁰ Even in LS patients undergoing regular colonoscopy surveillance, CRC was the most frequent first cancer observed,⁵¹ becoming clinically manifest as “incident cancers” (ie, diagnosed after the beginning of surveillance period). These findings were confirmed in an independent large series of MMR carriers.⁵² In between-country comparisons, point estimates of the incidence of CRC in *MLH1* carriers who underwent colonoscopy every 1 or 2 years were insignificantly higher⁵³ or similar⁵⁴ to those receiving colonoscopy only every 3 to 3.5 years. Neither stage of CRC^{54,55} nor survival⁵⁶ after diagnosis of CRC were associated with time since last colonoscopy. Notably, adjusting for country of origin to minimize a potential influence of country-specific factors did not change the results.⁵⁴ Previous studies also did not detect a significant variant-specific influence on penetrance of LS,⁵⁷ indicating that a potential effect of founder mutations⁵⁸ on the observed correlations is minor at most.⁵³ These observations support the concept that

TABLE 1 CRC risk under surveillance in LS variant carriers independent of the affected MMR gene

Study	Setting	Colonoscopy interval (years)	Observation time	CRC incidence
Jarvinen et al ⁴¹	Prospective	3	15 years	18%
De vos tot Nederveen Cappel et al ⁴⁴	Retrospective	2 to 3	10 years	10.5% (95% CI: 3.8-17.2)
Mecklin et al ⁴²	Prospective	2 to 3	Age 60	Men: 35% (95% CI: 16%-49%) Women: 22% (95% CI: 7%-34%)
Järvinen et al ⁴⁵	Prospective	2 to 3	11.5 years	12.4%
Stupart et al ⁴⁶	Prospective	1 to 2	5 years	11%
Engel et al ⁴⁷	Prospective	1 to 2	Age 60	23% (95% CI: 14.8%-31.2%)
Vasen et al ⁴⁸	Retrospective	1 to 2	10 years	6% (95% CI: 2.7%-8.7%)
Newton et al ⁴⁹	Retrospective	2	Age 70	25% (95% CI: 17-32%)
Engel et al ⁵⁴	Prospective	1 to 3	10 years	8.4% (95% CI: 7.1%-10.2%)

TABLE 2 Cumulative CRC risk in confirmed LS variant carriers depending on the affected MMR gene reported by the largest studies published in the last decade

Study	Surveillance ^a	Gender	Cumulative colorectal cancer risk at the age of 70 ^b (95% CI)			
			MLH1	MSH2	MSH6	PMS2
Bonadona et al ⁶⁶	No	Both	41% (25%-70%)	48% (30%-77%)	12% (8%-22%)	n.a.
Dowty et al ⁵⁷	No	Male	34% (25%-50%)	47% (36%-60%)	n.a.	n.a.
		Female	36% (25%-51%)	37% (27%-50%)		
Broeke et al ⁶⁷	No	Male	n.a. ^c	n.a.	n.a.	13% (8%-22%)
		Female				12% (7%-21%)
Dominguez-Valentin et al ⁵²	Yes	Male	53% (45%-62%)	46% (37%-59%)	12% (5%-35%)	3% (1%-35%)
		Female	44% (37%-52%)	42% (35%-50%)	20% (12%-41%)	

^aSurveillance here refers to studies that included data only from patients undergoing regular colonoscopy with polypectomy. Note that the first three studies are based on often not fully documented retrospective cohorts including patients with differing colonoscopy exposures and censoring at the time of first colonoscopy or first polypectomy.

^bAll studies reported the cumulative CRC risk at the age of 70 years, except for Broeke et al that reported the cumulative CRC risk at the age of 80.

^cn.a. not analyzed.

reducing colonoscopy intervals below 2 years is generally not associated with a clinical benefit in LS.

Moreover, LS carriers with a history of previous CRC and hemicolectomy, or with a history of previous extracolonic cancer, present with a similarly high CRC risk as LS carriers without previous history of cancer.⁵⁹ Therefore, the option of more radical surgery at first CRC should be discussed with patients; alternatively, stringent surveillance measures for controlling CRC risk in LS patients have to be maintained also after first cancer diagnosis.⁶⁰⁻⁶⁴

Importantly, CRC risk and colonoscopy efficacy depend on the affected MMR gene: *MLH1* and *MSH2* carriers had a lifetime CRC risk of up to 50%,^{57,65,66} which remained high despite regular colonoscopy surveillance.^{52,57} On the other hand, *MSH6*^{65,66} and *PMS2*⁶⁷ carriers had a substantially lower lifetime CRC risk, which might be further reduced by colonoscopy surveillance in *MSH6* carriers or even become unmeasurably low in *PMS2* carriers^{52,57,68} (Table 2, Figure 1).

Difference in the protection against CRC afforded by colonoscopy in the general population compared to LS suggests that any biological differences between LS and sporadic CRC in the general population maybe important determinants of the success of colonoscopy in cancer prevention in these two settings. In recent years, several hypotheses have been proposed to explain the observed epidemiologic data.^{55,69} We discuss current hypotheses and consider the most likely explanations for the reported observations.

3 | HYPOTHESES EXPLAINING CRC DESPITE SURVEILLANCE IN LS

3.1 | “Missed” lesions

One hypothesis to explain the occurrence of incident CRC in LS patients under colonoscopic surveillance is failure to identify or successfully remove adenomas. According to this hypothesis, improving

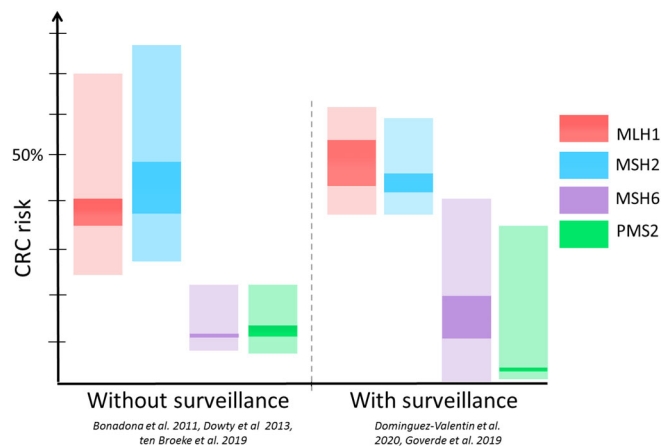


FIGURE 1 Schematic illustration of the effect of surveillance on CRC risk for different MMR gene variant carriers (based on the data summarized in Table 2). The CRC incidence is reduced by colonoscopy in *PMS2* carriers, and might be reduced by colonoscopy in *MSH6* carriers, whereas in *MLH1* and *MSH2* carriers CRC incidence seems not to be substantially influenced by colonoscopy surveillance. The darker shades represent the range of average risks reported by different studies for males and females, whereas the brighter shades represent the range of reported confidence intervals. Note: Influence of different penetrance in carriers of variant in different MMR genes on the colonoscopy efficacy cannot be formally excluded

the quality of colonoscopy would lead to improved detection and removal of adenomas and reduce incident cancers (Figure 2, “missed lesions”). The claim is that if colonoscopy is of high quality, all/most CRC in LS may be prevented.

Several factors impacting colonoscopy quality should be considered, including time-trends in techniques used, knowledge of what to look for, and inter-observer and intra-observer reproducibility. An incomplete colonoscopy that does not reach the caecum, inadequate bowel preparation, an inexperienced examiner, short withdrawal time

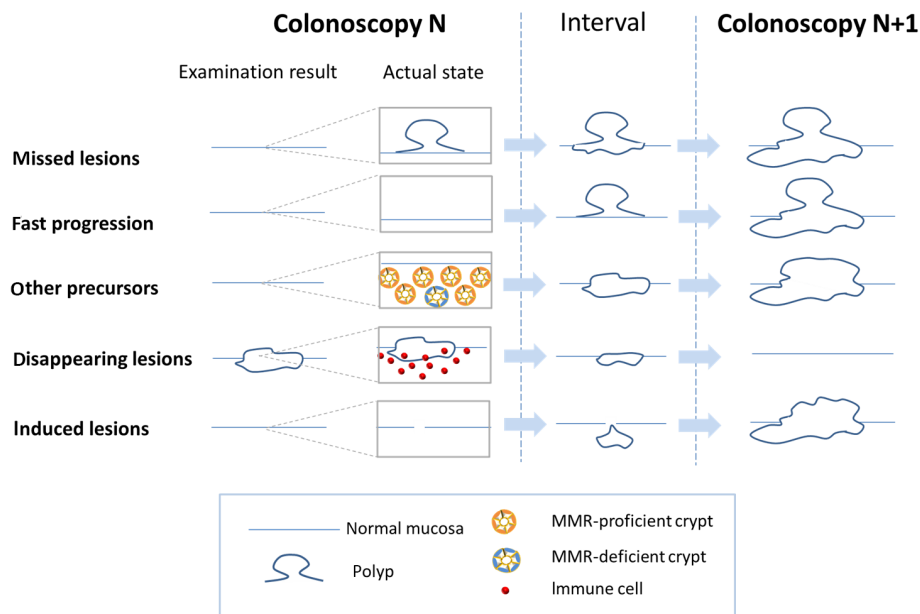


FIGURE 2 Summary of discussed hypotheses for CRC incidence in LS despite regular colonoscopy. The figure schematically summarizes the discussed hypotheses, including missed lesions, fast progression, alternative precursors, disappearing lesions and induced lesions, showing the hypothetical snapshots of colon during colonoscopy examination, of CRC progression/regression in the time intervals between colonoscopy examinations and of colon during the next examination

and the use of chromoendoscopy represent factors that may affect the likelihood of detecting polyps. In particular, small polyps or non-pedunculated flat lesions characteristic for LS may be overlooked.^{70,71} A recent systematic review and meta-analysis demonstrated an adenoma miss rate as high as 33% in patients at increased CRC risk.⁷¹ However, the majority of the studies conducted have not reported detailed quality measures for colonoscopy.^{71,72}

Due to the wide acceptance of the adenoma-carcinoma model, adenomas removed have been often used as surrogate marker for CRCs prevented. One attempt to standardize colonoscopy quality across centers is the definition of the “adenoma detection rate” (ADR), describing the proportion of colonoscopies that result in the detection of an adenoma. In fact, ADR has been shown to inversely correlate with the risk of incident cancer.^{73,74} However, using ADR for assessing surveillance quality in LS setting with regular examinations evidently has limitations, as population characteristics, namely the growth dynamics of adenomas in a given population, directly affect ADR. Accordingly, the highest possible and the lowest recommendable ADR for current LS surveillance colonoscopies are unknown and may depend on the distribution of pathogenic variants in the cohort, the extent of previous colectomies and the frequency of carriers ascertained without previous CRC. ADRs so far reported by independent studies vary: one large study that pooled prospective surveillance data from three different countries showed an average ADR of 16% per examination,⁵⁴ but ADR values as low as 10.6% and as high as 52.5% have been reported both before and after the implementation of a quality-improvement program.^{73,75-79} A universal ADR cannot be determined due to geographical differences in adenoma risk as well as different target populations used to determine the ADR. Another important limitation of the ADR as a marker for high-quality colonoscopy is lack of information on the completeness of adenoma resection, as detected adenomas, when not completely resected, may also lead to incident cancer development.⁸⁰

There is evidence that more sophisticated endoscopic modalities could lead to more efficient detection of adenomatous lesions during LS surveillance colonoscopy.^{72,78,81-83} For example, it has been shown that chromoendoscopy, virtual chromoendoscopy (I-SCAN) and narrow-band imaging approaches allow detection of significantly more adenomas compared to standard colonoscopy.^{78,81-83} A recent study reporting an optimized colonoscopy surveillance program suggested improvements in the cancer detection rate in LS without altering the ADR.⁷⁵ Another randomized controlled study analyzing neoplasia detection rates in LS at baseline and follow-up colonoscopy did not find a significant added value for chromoendoscopy over high-definition white-light endoscopy for the proximal colon,⁷⁷ nor did a randomized non-inferiority study comparing these two techniques for LS surveillance.⁸⁴ However, a clear time-trend toward higher ADR after the introduction of high-definition endoscopy has been observed by a recent study, also reporting development of incident cancers after the high-quality penultimate colonoscopy.⁸⁵

Currently, it is not known how much optimization of colonoscopy—relating to all of the factors affecting colonoscopy quality discussed earlier—would reduce the occurrence of CRC in LS. Randomized controlled trials analyzing the impact of novel sensitive endoscopy techniques, including those using artificial intelligence-based approaches, on the ADR and on cancer incidence in LS are needed to clarify and quantify the contribution of “missed” lesions to incident cancers.

The surveillance colonoscopies currently reported in prospective studies have largely been conducted at highly specialized centers in different parts of the world. Given their expertise, and their ability to very effectively prevent CRC in the general population, it seems unlikely that inter-observer differences or technical limitations could be the only explanations for the high proportion of LS patients developing incident cancer while under regular colonoscopy surveillance. Although optimization of colonoscopy may reduce occurrence of CRC in LS, the extent of cancer prevention needs to be quantified in

prospective, ideally randomized international multicenter studies. To this end, time-trends will now be analyzed in the PLSD.

3.2 | Fast progression of newly formed adenomas

Another possible explanation for occurrence of CRC in LS carriers despite colonoscopy surveillance is provided by the hypothesis of accelerated progression from adenoma to carcinoma. This proposes that CRCs in LS develop from adenomas, but progression is so fast that there is often no time to detect and remove the lesion at pre-cancerous adenoma phase (Figure 2, “fast progression”). Several observations support this concept. In the general population, CRC formation usually involves a benign polypoid precursor stage and the transformation to invasive cancer appears to take 10 years or more.⁸⁶ This is why 10-yearly colonoscopy intervals are considered sufficient to successfully lower the incidence of CRC in the general population.^{87,88} In LS, however, the progression to CRC has been suggested to be accelerated compared to the general population.⁸⁹⁻⁹² The different progression times indicate that there are biological differences between CRC development in LS carriers and the general population.

A study estimating the polyp dwell time has demonstrated a time period of approximately 3 years being required for the development of an advanced lesion, with an equal dwell time to adenoma as to cancer formation.⁹³ Calculations of longitudinal parameters, such as progression time, based on cross-sectional observations have to be interpreted with caution. However, equal dwell times of adenomas and cancers could have two possible reasons: either the progression from adenoma to carcinoma is very fast, or dwell time to adenoma and dwell time to carcinoma are not always connected by one linear progression, but rather represent two distinct branches of progression with different end points.

The hypothesis of accelerated progression is also consistent with the minor differences in adenoma incidence in LS compared to the general population.^{25,26} This finding has been interpreted as supporting evidence for the hypothesis that elevated CRC risk in LS patients does not result from an increased likelihood of adenoma initiation as in FAP, but rather from accelerated progression of pre-existing adenomas into cancer due to acquisition of MMR deficiency and an increased mutation rate.^{89,91,94,95} The hypothesis of faster progression was further supported by the correlation of MMR deficiency with larger size and higher grade of adenomas in LS,^{25,96-100} though some studies reported high-grade dysplasia and MSI phenotype in lesions smaller than 5 mm.²⁵

Although it seems highly likely that a subset of LS CRCs follow the tumorigenesis model proposed by the hypothesis of accelerated progression, other evidence suggests that many CRCs in LS, perhaps even the majority, do not. As discussed earlier, application of colonoscopy surveillance every 3 years has led to halving of the CRC risk and a reduction in CRC-related mortality; however, further improvement was not achieved by shortening colonoscopy intervals from 3 years down to 1 year, as shown by a PLSD study.⁵³ This was also confirmed

by a large prospective observational study of three European LS registries comparing the outcomes of different surveillance protocols in three countries and showing no difference in the incidence of CRC between the three different colonoscopy intervals (annual, 2- and 3-yearly colonoscopy).⁵⁴ There was also no difference in the stage of CRCs detected, a finding which was later confirmed by studies of the PLSD.⁵⁵ A recent study in the PLSD reported no difference in CRC survival associated with the time since last colonoscopy prior to CRC diagnosis.⁵⁶ In summary, these reports question the assumptions underlying current clinical guidelines for colonoscopy in carriers: AGA: 1-2-year interval (GRADE low-quality evidence)¹⁰¹; ACG: at least 2-year interval (moderate quality and very low-quality evidence for annual interval)¹⁰²; ASCO & ESMO: 1-2 year interval¹⁰³; ESGE: 2-year interval (moderate-quality evidence)¹⁰⁴; updated guidelines of EHTG are currently in preparation.

Interestingly, the success of colonoscopic surveillance could depend on which MMR gene is involved. For example, *PMS2* carriers undergoing regular colonoscopy have negligible CRC risk, especially at young ages,^{52,105} and low CRC risks have also been shown for *MSH6* carriers under surveillance.^{52,57} Such observations, further corroborated by distinct molecular characteristics of tumors from different MMR carriers,¹⁰⁶ could point to biological differences between colorectal tumorigenesis in different genetic backgrounds: the apparently hard-to-detect cancer precursors present in *MLH1* and *MSH2* carriers seem to be absent or very rare in *PMS2* or *MSH6* carriers and the general population. These differences should be considered when formulating guidelines for management of LS.

3.3 | Not all CRCs in LS develop in a macroscopically visible adenoma, and not all adenomas are precursors

In recent years, evidence for colonoscopically invisible precursor lesions, or alternative, “adenoma-free” progression routes to cancer, has accumulated. Such routes could start from mismatch repair-deficient crypt foci (MMR-DCF) that are found in the normal-looking colonic mucosa of LS carriers but not in sporadic MSI CRC patients (Figure 2, “other precursors”).^{107,108} These lesions are not only undetectable by colonoscopy, but also microscopically unidentifiable, unless MMR protein staining is performed.^{107,108} MMR-DCF exhibit MSI and carry mutations in microsatellite-bearing genes, also found in advanced lesions¹⁰⁹, suggesting their potential as cancer precursors.

Molecular analysis of LS CRC in fact indicates that MMR deficiency is often an early or even initiating event,^{110,111} which frequently precedes canonical mutations affecting the genes *APC* and *KRAS*.¹¹² Moreover, it has been demonstrated that a substantial proportion of LS-associated CRC may develop without an adenomatous phase: LS CRCs that did not display features of cancer-adjacent adenoma cells were associated with specific molecular alterations, mainly *CTNNB1* and *TP53* mutations.^{96,99} This observation indicates the

possibility that alternative molecular progression events, similar to inflammatory bowel disease (IBD)-associated colorectal neoplasia that are commonly initiated by APC-independent events,^{113,114} are associated with the lack of polypoid precursor lesions.¹¹⁵ This pathway of progression seems to be less common in *PMS2*-associated CRC, an observation that may reflect the minimal risk of cancers in *PMS2* carriers under surveillance.¹¹⁶

Thus, existing data strongly suggest that the assumption of a sequential model of colorectal carcinogenesis in LS where CRC is always preceded by an adenoma is wrong or, at least, a considerable oversimplification.^{117,118} Thus, accounting for the diversity of colorectal carcinogenesis suggested by Jeremy Jass,^{117,118} it is important to acknowledge the heterogeneity of LS CRCs. Instead of seeking one model for all cases, at least three pathways should be considered: (a) progression from an adenoma with secondary inactivation of the MMR system, (b) progression from an initially MMR-deficient adenoma and (c) progression from MMR-DCF directly to invasive cancer without adenoma formation.¹¹⁰

If there is more than one pathway to CRC in LS, what is the relative contribution of each? This question is difficult to answer precisely. Importantly, LS carcinogenesis might be influenced by the "observation" itself having an effect on the observed data. Here, the process of observation, that is, colonoscopy, may affect the disease status, either because the relative contributions of the three pathways are changed by removing adenomas, or because of the colonoscopy-mediated effects influencing carcinogenesis (as discussed later). The results reported by PLSD, in which cancers continued to develop despite colonoscopy, may reflect the effect of colonoscopy blocking progression from adenomas as precursors, and thereby increasing the proportion of CRCs progressing through a different molecular pathway, potentially similar to nonpolypoid CRCs in IBD patients,¹¹⁵ via direct invasive growth without a polypoid precursor. Notably, molecular evidence from CRCs suggest that the proportion of cancers progressing through the second and the third, MMR deficiency-initiated pathways outweigh the proportion of cancers progressing through the first, adenoma-initiated pathway in LS.¹¹⁰

This conclusion has wide-ranging implications. First, it explains why even high-quality, short-interval colonoscopy with meticulous inspection of the intestinal mucosa and removal of all polyps cannot completely prevent LS-associated CRC, as CRC may develop without ever passing through a detectable non-invasive phase. Second, it predicts that any approach targeting MMR-deficient cells should be very effective in preventing the majority of LS-associated CRCs, particularly non-polypous cancers. Third, studies assessing CRC development in LS need to account for colonoscopy surveillance as a factor in the populations studied. Fourth, a better understanding of non-adenoma precursors is needed to define suitable end points for prevention trials and improve prevention and surveillance strategies. This is underlined by the observation of the CAPP2 study that, similar to observations in the general population,¹¹⁹ reported a significant reduction in incidence of CRC, but not of colorectal adenomas, upon regular aspirin use.¹²⁰

Conceptually, the hypothesis of invisible lesions is very similar to the hypothesis of missed lesions, with one very important difference:

the hypothesis of missed lesions assumes that an improvement of colonoscopy techniques, shorter surveillance intervals or better training of gastroenterologists will make the invisible visible, at a phase of pre-invasive tumor development. Whether this is true and to what extent, remains to be demonstrated in prospective studies.

4 | HYPOTHESES ADDRESSING THE HIGHER CRC INCIDENCE OBSERVED WITH MORE FREQUENT COLONOSCOPY SURVEILLANCE

4.1 | Overdiagnosis and disappearing lesions

The trend toward higher CRC incidence in groups of LS patients subjected to colonoscopy with shorter intervals⁵³ is surprising and could be explained by the spontaneous disappearance of colonic lesions. This is theoretically possible for precancerous lesions or even for invasive cancers (Figure 2, "disappearing lesions").⁵⁵ If true, longer colonoscopy intervals may tend to result in fewer identified lesions, because one has to look frequently to catch lesions destined to disappear between colonoscopies. Shortening of the colonoscopy interval could lead to detection of lesions that otherwise would have been eliminated by patient's immune system. Biological support for this hypothesis comes from data on MMR-DCF prevalence and LS penetrance: the number of MMR-DCF per LS patient is estimated to be 1000 times or more the numbers of manifest cancers.¹⁰⁷ On the one hand, such a low progression rate might be explained by acquisition of growth-repressing mutations leading to apoptosis or oncogenic mutations leading to oncogene-induced senescence of MMR-DCF; on the other hand, immune responses against these lesions could contribute to their elimination. It is known that LS-associated cancers are highly immunogenic, as shown by dense immune infiltration and Crohn's-like reactions observed in these tumors,^{12,14} as well as their response to immune checkpoint blockade therapy.^{16,19} LS-associated CRCs, as well as MMR-DCFs, have been shown to carry coding microsatellite mutations, resulting in the generation of FSPs that can elicit strong immune responses and cause *in vitro* killing of FSP-expressing cells by T cells.¹²¹ Moreover, systemic cellular immune responses to FSP have been found in the blood of healthy LS carriers,¹⁵ suggesting that FSP neoantigen-specific T cells may eliminate MMR-deficient lesions that might include both MMR-DCFs and more advanced lesions. Indeed, it has been shown that adenomas can regress,¹²²⁻¹²⁴ and even cancers can be attacked by immune responses of the host and should be particularly vulnerable in LS due to a high tumor mutational burden and tumor-associated antigen load.¹²⁵⁻¹²⁸ The low probability of lymph node and distant metastases and the good prognosis of LS-related CRC may also reflect the immune system's capability to restrain CRC.

It would be interesting to monitor the progression rate of adenomas in LS over time; however, due to ethical considerations such a study could not reasonably be conducted in humans. Recently developed organoid models may facilitate research into carcinogenic

cascades in multiple organs. The favorable culture time and ability to retain genetic stability over time of such models may help to circumvent the complexity of *in vivo* studies of adenomas, carcinomas and immune response in humans.¹²⁹

In short, the probability for developing a malignancy may be described as a balance between the carcinogenic mechanisms producing CRCs and the host's immune system removing them.

Alternatively, higher CRC incidence upon shorter colonoscopy intervals could be explained by the different penetrance of pathogenic variants in the same MMR gene (eg, strong founder mutation effect in the Finnish population⁵⁸). Currently available data do not suggest a major influence of this factor,^{53,57} though future studies are warranted.

4.2 | Induced lesions

The observation of a higher CRC incidence occurring in the context of shorter colonoscopy intervals is also consistent with colonoscopy itself playing a role in the pathogenesis of CRC (Figure 2, "induced lesions"). However, given the success story of colonoscopy in CRC prevention in the general population, this theoretical possibility seems unlikely in practice. Despite this, at least two colonoscopy-associated factors can be proposed that might favor tumor progression under certain circumstances. First, bowel preparation prior to colonoscopy affects the microbiome composition of the colon in a persisting way.¹³⁰ The impact of certain bacterial species in the development of CRC through modulation of the immune response has been extensively studied;¹³¹⁻¹³⁴ and it is conceivable that bowelpreparation-initiated microbiome changes may be related, positively or negatively, with CRC progression in the individual being examined. It is possible that such effects, even if minor at the individual level, may become detectable in a larger population. A second factor linked to the examination procedure itself is mechanical irritation. In theory, local pressure, distension and abrasion by the endoscope could lead to micro-injuries of the mucosal surface, particularly if biopsies are taken, disturbing cell-cell contacts and damaging the mucosa. This could lead to the initiation or acceleration of a malignant process, particularly if MMR-deficient cells are in the vicinity. A recent study analyzing the impact of colonoscopy on the development of metachronous CRC has shown the possibility of tumor seeding during colonoscopy; the risk of such tumor cell spreading was estimated to be 0.3% to 0.6%.¹³⁵ However, the authors are not aware of any further experimental evidence supporting these theories so far. Therefore, colonoscopy will remain one central pillar of cancer prevention in LS with a reported risk of severe complications of, at most, 0.3%.^{136,137}

5 | SUMMARY

CRC incidence in LS remains high despite regular colonoscopy. Although technical limitations may explain some incident cancers, strong evidence indicates that multiple CRC precursors in LS follow

distinct fates of persistence, progression or regression depending on several factors. If we acknowledge these possibilities, we can better interrogate the biologic diversity and complexity of LS. By designing clinical trials that produce data analyzable for the distinct pathways separately, we will learn more about LS carcinogenesis. This knowledge will be essential to refine prevention and treatment strategies for LS patients.

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CONFLICT OF INTEREST

Potential financial conflict of interest outside the present work: Toni Seppälä is CEO and co-owner of Healthfund Finland. Potential personal conflict of interest: Finlay Macrae is practicing, publically funded colonoscopist; counselor of the International Society for Gastrointestinal Hereditary Tumors.

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