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Emerge of colorectal cancer in Lynch syndrome despite colonoscopy surveillance: A challenge of hide and seek

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ABSTRACT

Even with colonoscopy surveillance, Lynch syndromes (LS) carriers still develop colorectal cancer (CRC). The cumulative incidence of CRCs under colonoscopy surveillance varies depending on the affected mismatch repair (MMR) gene. However, the precise mechanisms driving these epidemiological patterns remain incompletely understood. In recent years, several potential mechanisms explaining the occurrence of CRCs during colonoscopy surveillance have been proposed in individuals with and without LS. These encompass biological factors like concealed/accelerated carcinogenesis through a bypassed adenoma stage and accelerated progression from adenomas. Alongside these, various colonoscopy-related factors may contribute to formation of CRCs under colonoscopy surveillance, like missed yet detectable (pre)cancerous lesions, detected yet incompletely removed (pre)cancerous lesions, and colonoscopy-induced carcinogenesis due to tumor cell reimplantation. In this comprehensive literature update, we reviewed these potential factors and evaluated their relevance to each MMR group in an attempt to raise further awareness and stimulate research regarding this conflicting phenomenon.

1. Introduction

Lynch syndrome (LS) stands as the most common inherited (colorectal) cancer syndrome, originating from constitutional (likely) pathogenic variants in one of the mismatch repair (*path_MMR*) genes. These genes include *MLH1* (OMIM #609310), *MSH2* (OMIM #120435), *MSH6* (OMIM #614350), and *PMS2* (OMIM #614337) (Peltomaki, 2016). The diverse penetrance and expressivity of these genes, among other factors, could imply the existence of four distinct inherited Lynch syndromes, each linked to a specific MMR gene (Moller et al., 2023).

Despite the recommend colonoscopy with polypectomy as a preventive measure against colorectal cancer (CRC) in all *path_MMR* carriers (Seppala et al., 2021; Moller et al., 2022), numerous reports have indicated a notable incidence of CRC in these carriers, even with regular surveillance colonoscopy (Moller et al., 2022; Dominguez-Valentin et al., 2020; Moller, 2022; Moller et al., 2017; Seppala et al., 2017). The development of CRCs under colonoscopy surveillance poses a considerable challenge in current LS management, and sparked a debate regarding the effectiveness of regular colonoscopy surveillance in detecting adenomas and reducing CRC risk. In fact, recent analysis of the Prospective Lynch Syndrome Database (PLSD) and the retrospective cohort reported by the International Mismatch Repair

Abbreviations: ADR, adenoma detection rate; CRC, colorectal cancer; ESGE, European Society of Gastrointestinal Endoscopy; IMRC, International Mismatch Repair Consortium; DMMR, mismatch repair deficiency/deficient; MMR-DCF, mismatch repair deficient crypt focus; MSI, microsatellite instable/instability; LS, Lynch syndrome; *path_MMR,*, likely pathogenic variant of one of the mismatch repair genes; *path_MLH1,*, likely pathogenic variant of one of the *MLH1* gene alleles; *path_MSH2,*, likely pathogenic variant of one of the *MSH2* gene alleles; *path_MSH6,*, likely pathogenic variant of one of the *MSH6* gene alleles; *path_PMS2,*, likely pathogenic variant of one of the *PMS2* gene alleles; PCCRC, post-colonoscopy colorectal cancer; PLSD, Prospective Lynch Syndrome Database; WLE, white-light endoscopy.

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Consortium (IMRC) revealed an increased incidence of CRC in *path_MLH1* and *path_MSH2* carriers undergoing regular colonoscopy surveillance, no reduction for *path_MSH6* carriers, and a potential reduction in *path_PMS2* carriers below 50 years of age (Moller et al., 2022). However, despite these findings, the mortality associated with CRC was found to be low, likely attributed to early diagnosis, treatment, and the natural good prognosis of microsatellite instable (MSI) cancers (Dominguez-Valentin et al., 2023). Sanchez et al. (2022). demonstrated that time intervals of less than three years do lower the risk of CRC diagnosis following colonoscopy, and showed that adenoma detection is improved following adequate bowel preparation, complete colonoscopies, and pan-chromoendoscopy, highlighting the crucial role of colonoscopy quality in this context.

Gaining a deeper understanding of the underlying mechanisms driving CRC development under colonoscopy surveillance in *path_MMR* carriers is crucial in assessing the effectiveness of such surveillance and may also shed light on the variations in incidence among the different MMR groups. Over the past years, multiple potential mechanisms that could account for the CRC diagnoses in *path_MMR* carriers undergoing colonoscopy surveillance have been proposed, including both biological and colonoscopy-related factors. Following a discussion of the terminology and incidence of CRCs under colonoscopy surveillance, this literature update examines these potential factors and assesses their relevance to each MMR group in an attempt to raise further awareness and stimulate research regarding this conflicting phenomenon.

2. Terminology for CRCs under colonoscopy surveillance

Numerous different and overlapping terms to describe CRCs diagnosed under colonoscopy surveillance have been proposed and used, making it increasingly challenging to evaluate and compare the literature. In line with the most recent (2018) recommendations of the World Endoscopy Organization (Rutter et al., 2018), cancers diagnosed after a colonoscopy in which no cancer was diagnosed should be referred to as "post-colonoscopy CRCs" (PCCRCs; Fig. 1). PCCRCs are further classified into "interval cancers", which are identified before the next recommended screening or surveillance examination, and "non-interval cancers", which are identified at (type A) or after (type B) a recommended surveillance interval, or where no subsequent surveillance interval for repeat examination was recommended (type C), up to 10 years after the

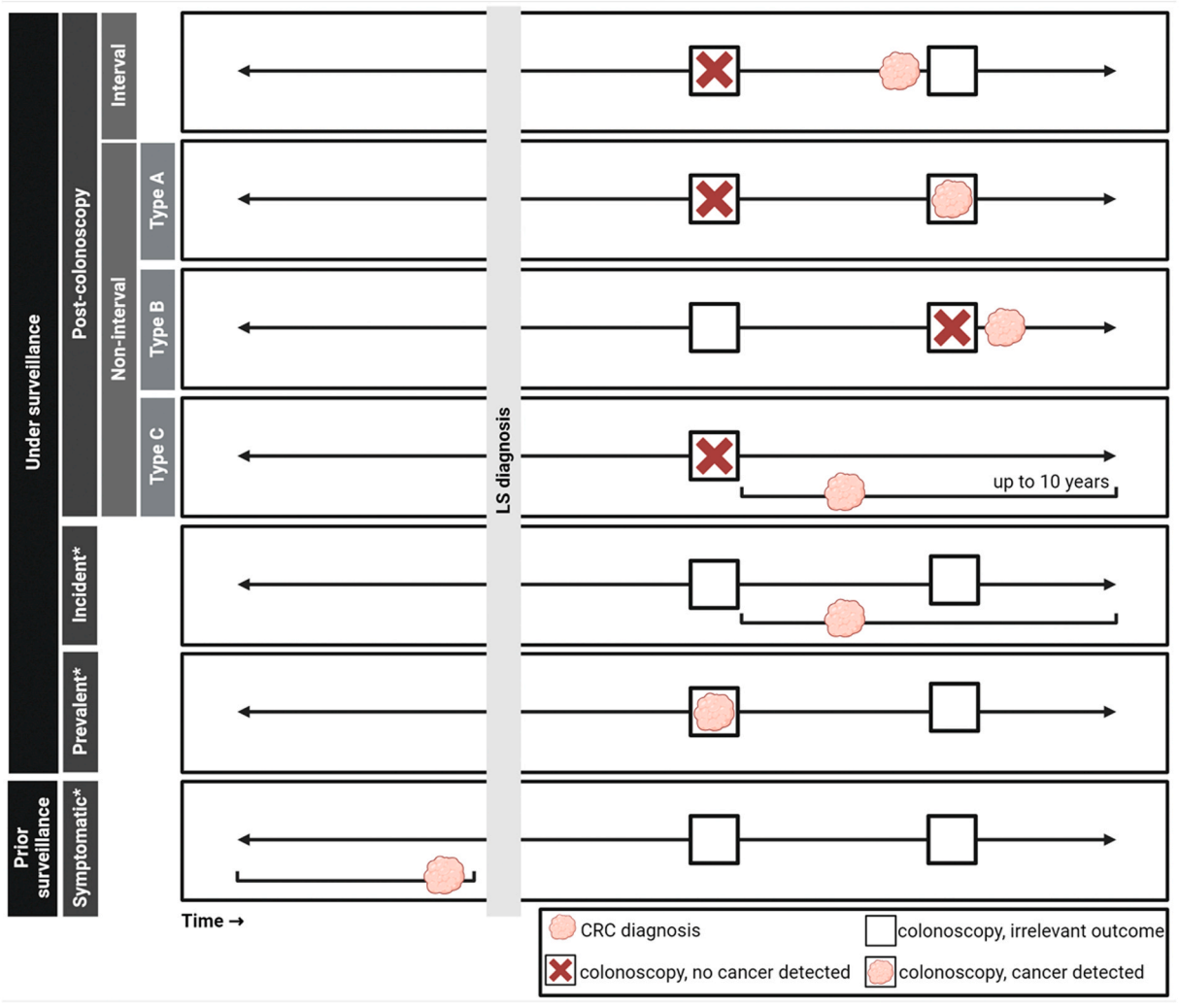

Fig. 1. Terminology of CRCs diagnosed under or prior to colonoscopy surveillance. PCCRCs diagnosed after a colonoscopy in which no cancer was diagnosed, and may be subdivided into interval and non-interval cancers. Interval CRCs are identified before the next recommended screening or surveillance examination, whereas non-interval CRCs are identified at (type A) or after (type B) a recommended surveillance interval, or where no subsequent surveillance interval for repeat examination was recommended (type C), up to 10 years after the colonoscopy (Rutter et al., 2018). Incident CRCs occur in the frame of regular surveillance but irrespective of the result of the previous colonoscopy and time to next colonoscopy, whereas prevalent CRCs are identified during the index colonoscopy. Symptomatic CRCs are diagnosed before the initial surveillance colonoscopy, typically due to the manifestation of symptoms. *Term not included in World Endoscopy Organization recommendations (Rutter et al., 2018). Created with BioRender.com. *CRC, colorectal cancer; LS, Lynch syndrome; PCCRC, post-colonoscopy CRC.*

colonoscopy (Rutter et al., 2018). While not formally acknowledged by the World Endoscopy Organization, alternative terms commonly employed in literature encompass "prevalent CRC", signifying the CRC identified during the index colonoscopy (i.e. prevalence screen), and "incident" CRC, indicating cancer occurring in the frame of regular surveillance but irrespective of the result of the previous colonoscopy and time to next colonoscopy. Moreover, the designation "symptomatic" CRC is utilized to describe CRC diagnosed before the initial surveillance colonoscopy, typically due to the manifestation of symptoms, but may be misleading, as CRCs that develop under colonoscopy surveillance may also cause symptoms that trigger the diagnosis (e.g. interval CRC, type B/C non-interval CRC).

3. Incidence of CRCs under colonoscopy surveillance by MMR gene

The cumulative incidences of CRC with and without colonoscopy surveillance vary based on the affected MMR gene, with higher CRC rates under colonoscopy surveillance being observed for *path_MLH1* (36–52%) and *path_MSH2* (30–50%) carriers compared to *path_MSH6* (10–17%) and *path_PMS2* (3–11%) carriers, as indicated by the PLSD (Table 1) (Moller et al., 2022; Dominguez-Valentin et al., 2023). It is essential to highlight that these incidences are derived from patients undergoing regular colonoscopy surveillance in expert centers. Additionally, age and sex play influential roles (Dominguez-Valentin et al., 2020, 2023), with confidence intervals related to age- and sex-specific incidences being particularly wide for *MSH6* CRCs and *PMS2* CRCs, reflecting the relative scarcity of carriers with pathogenic variants in these genes within datasets like the PLSD (Moller et al., 2022; Dominguez-Valentin et al., 2020, 2023). Furthermore, familial risk factors contribute to substantial within-gene variation in CRC risk with and without colonoscopy surveillance, underscoring the importance of personalized risk assessment for precision prevention and early detection of CRC in *path_MMR* carriers (International Mismatch Repair C., 2021).

Table 1
Cumulative incidence and mortality of CRC under colonoscopy surveillance categorized by MMR gene defects, as per the PLSD.

path_MMR	Moller et al (Moller et al., 2022).[a]		Dominguez-Valentin et al (Dominguez-Valentin et al., 2023).[b,c]			
	Cumulative incidence at 70 years		Cumulative incidence at 65 years		Mortality at 75 years	
	Male	Female	Male	Female	Male	Female
path_MLH1	52%	41%	48%	36%	6%	5%
path_MSH2	50%	39%	42%	30%	5%	4%
path_MSH6	13%	17%	13%	10%	2%	1%
path_PMS2	11%	8%	10%	3%	1%	0%

CRC, colorectal cancer; MMR, mismatch repair; path_MMR, (likely) pathogenic variant of one of the mismatch repair genes; path_MLH1, (likely) pathogenic variant of one of the MLH1 gene alleles; path_MSH2, (likely) pathogenic variant of one of the MSH2 gene alleles; path_MSH6, (likely) pathogenic variant of one of the MSH6 gene alleles; path_PMS2, (likely) pathogenic variant of one of the PMS2 gene alleles; PLSD, Prospective Lynch Syndrome Database

[a] 8153 *path_MMR* carriers were included from the first prospectively planned and performed colonoscopy and were prospectively followed with a median follow-up time of 8.3 years.

[b] 8500 *path_MMR* carriers were included from the first prospectively planned and performed colonoscopy and were prospectively followed with a median follow-up time of 8.4 years.

[c] The cumulative incidence and mortality rates that are provided were based on colon cancer only, excluding rectal cancer.

4. Biological factors

From a biological perspective, there are at least two (hypothetical) ways cancer prevention by regular colonoscopy surveillance might be rendered ineffective, including (i) carcinogenesis with a skipped adenoma phase and (ii) accelerated progression from an adenoma (Fig. 2) (Ahadova et al., 2021).

For a long time the prevailing hypothesis was that CRCs develop from adenomas, which would first form independently of DNA mismatch repair deficiency (dMMR). At some point, a somatic mutation in a MMR gene would serve as a second hit, triggering the onset of carcinogenesis (Helderman et al., 2021). However, following the discovery of dMMR crypt foci (MMR-DCFs), which may serve as alternative precursors for the development of CRCs in *path_MMR* carriers (Kloor et al., 2012; Shia et al., 2015; Pai et al., 2018), two additional pathways initiated by dMMR were proposed by Ahadova et al (Ahadova et al., 2018). MMR-DCFs can either develop into dMMR adenomas when a second hit in an MMR gene is followed by, for instance, two *APC* mutations, which then progress to carcinomas (referred to as the MMR-DCF-adenoma-carcinoma pathway). Alternatively, MMR-DCFs may directly form carcinomas (known as the MMR-DCF-carcinoma pathway), which exhibit immediate invasive growth and bypass an adenoma stage.

The conventional adenoma-carcinoma pathway may be of relatively minor significance in the development of tumors under colonoscopy surveillance, given the probability that this pathway is detectable during colonoscopy. The alternative two pathways, however, may hypothetically contribute to the development of CRCs under colonoscopy surveillance. By possibly bypassing the adenoma phase, cancers emerging through the MMR-DCF-carcinoma pathway lack a clearly visible precursor lesion, making their detection at the precancerous stage challenging during colonoscopy due to the small size of these crypts. If validated, this implies that relying on colonoscopy to detect and remove only visible lesions would not substantially prevent CRC in individuals with *path_MMR* variants (Helderman et al., 2021; Ahadova et al., 2018; Ahadova et al.; Bajwa-Ten Broeke et al., 2021; Helderman et al., 2023). Alternatively, an accelerated progression from an adenoma, such as through the MMR-DCF-adenoma-carcinoma pathway, where dMMR is an early event, could potentially occur entirely within a colonoscopy interval. In such cases, there may be insufficient time for precancerous lesions to be removed by colonoscopy, which may also lead to the development of CRCs under colonoscopy surveillance. The degree of evidence differs for both concepts and across MMR groups, and this will be addressed in the subsequent sections.

It is important to note that the development of CRC through sessile serrated lesions and the serrated neoplasia pathway is yet another possible pathway in *path_MMR* carriers. However, the detection of sessile serrated lesions in *path_MMR* carriers during colonoscopy is similar to that in a matched population, indicating that this pathway does not appear to be specific to LS (Vleugels et al., 2018). There is currently a lack of data regarding the prevalence of CRCs originating from serrated lesions *path_MMR* carriers.

4.1. Concealed/accelerated carcinogenesis with bypassed adenoma stage

4.1.1. CTNNB1 mutations and the MMR-DCF-carcinoma pathway

Possible relevance to each MMR group:

- *MLH1 syndrome: high relevance*
- *MSH2/MSH6/PMS2 syndromes: no/low relevance*

Over the past years, multiple molecular studies of *MLH1* CRCs have associated gain-of-function mutations in exon 3 of the *CTNNB1* gene with an invasive growth pattern and the MMR-DCF carcinoma pathway (Helderman et al., 2021; Ahadova et al., 2018; Ahadova et al.; Bajwa-Ten Broeke et al., 2021; Helderman et al., 2023). *CTNNB1*

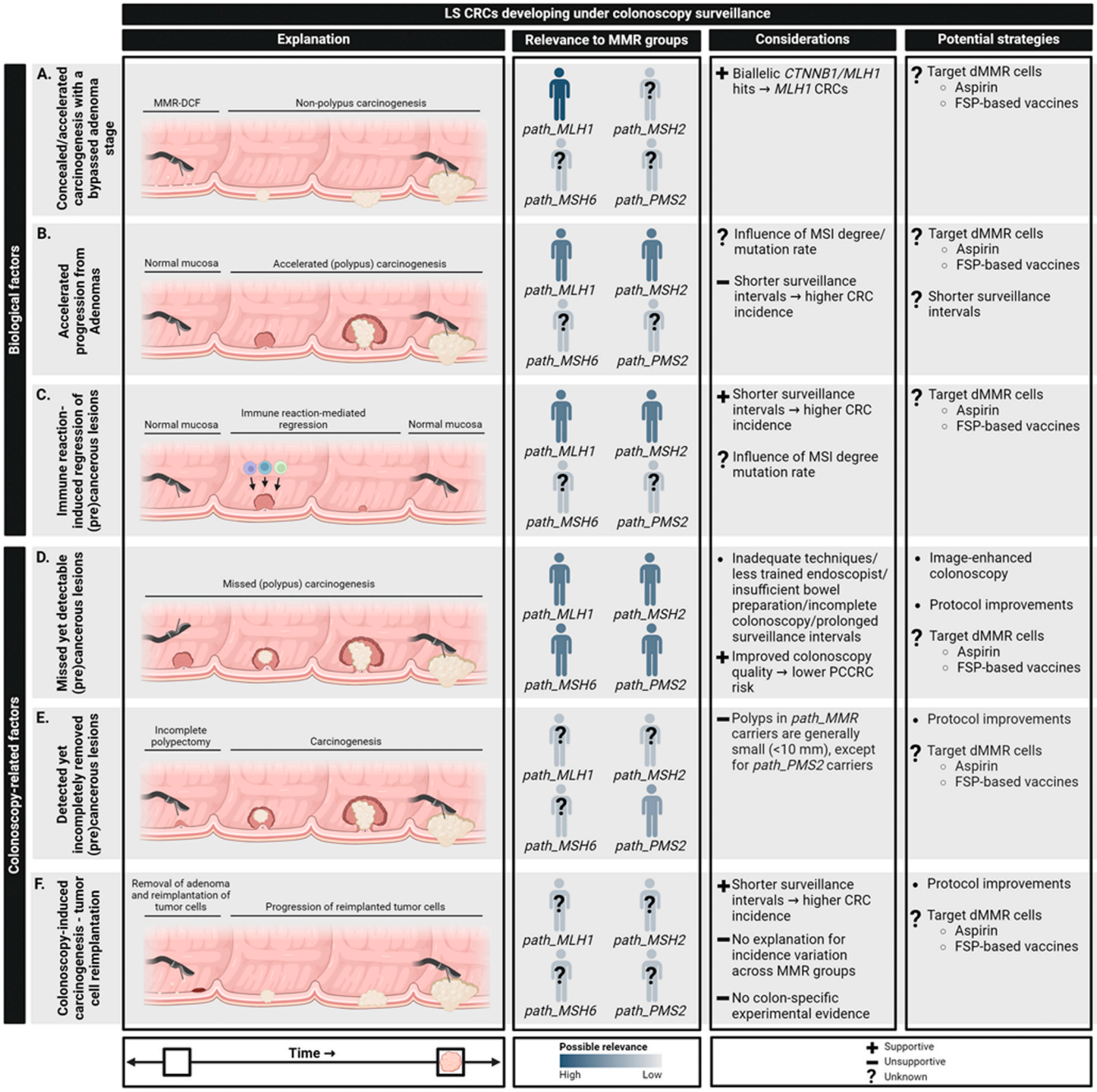

Fig. 2. Proposed factors involved in the development of CRCs under colonoscopy surveillance in *path_MMR* carriers. Both biological and colonoscopy-related factors may contribute to the development of CRCs under colonoscopy surveillance. Potential biological factors include (**A**) concealed/accelerated carcinogenesis with a bypassed adenoma phase, which may be difficult to detect during colonoscopy, (**B**) and accelerated progression from adenomas, which may entirely take place within a colonoscopy interval. Moreover, (**C**) the interplay with the immune system may play a role, for instance through immune reaction-induced regression of (precursor) lesions. Colonoscopy-related factors that might be involved include (**D**) missed yet detectable (pre)cancerous lesions due to poor colonoscopy quality (e.g. inadequate techniques, inadequate quality and/or limited experience of the endoscopist, insufficient bowel preparation and/or incomplete colonoscopies) or prolonged surveillance intervals, (**E**) detected yet incompletely removed (pre)cancerous lesions due to incomplete polypectomy, and (**F**) colonoscopy-induced carcinogenesis due to the reimplantation of tumor cells following the removal of (pre)cancerous lesions. For each potential factor, the possible relevance to each MMR group, current considerations regarding their level of evidence and the potential strategies to tackle the phenomenon are discussed. Created with BioRender.com. *CRC, colorectal cancer; dMMR, mismatch repair deficiency/deficient; FSP, frameshift peptide; LS, Lynch syndrome; MMR-DCF, mismatch repair deficient crypt focus/foci; path_MLH1, (likely) pathogenic variant of one of the MLH1 gene alleles; path_MSH2, (likely) pathogenic variant of one of the MSH2 gene alleles; path_MSH6, (likely) pathogenic variant of one of the MSH6 gene alleles; path_PMS2, (likely) pathogenic variant of one of the PMS2 gene alleles.*

encodes for β-catenin, which is at the center of the Wnt/β-catenin signaling pathway. This signaling pathway plays an important role in cell proliferation and differentiation, as well as in multiple other cellular processes (White et al., 2012). In the absence of active Wnt signaling, β-catenin is captured in the cytoplasm by a complex of proteins, including APC, and tagged for destruction by glycogen synthase kinase-3β (GSK-3β). In the presence of Wnt-signaling, GSK-3β is shut down, allowing β-catenin to move into the nucleus and influence transcription of growth-promoting genes (Helderman et al., 2021; White et al., 2012).

Overactivation of the Wnt/β-catenin signaling pathway prevents the

outmigration of enterocytes from colonic crypts, where they would die 3–4 days after they were formed (Helderman et al., 2021; White et al., 2012). As the latter is essential for tumor cells to acquire additional driver mutations, approximately 90% of all CRCs in the general population is estimated to have a disordered Wnt/β-catenin signaling pathway (White et al., 2012; Yaeger et al., 2018). For CRC in general, biallelic loss-of-function mutations in *APC* involve the most common route to achieve β-catenin stabilization, and are associated with carcinoma development through an intermediate adenoma stage (i.e. the (MMR-DCF) adenoma-carcinoma pathway) (Ahadova et al., 2018). In contrast, activating mutations of *CTNNB1* were found to be enriched in *MLH1* CRCs compared to sporadic MSI CRCs, with the majority of *CTNNB1*-mutant *MLH1* CRCs presenting with a histological appearance suggestive of immediate invasive growth and lacking evidence of polypous growth. These findings led to the hypothesis that *CTNNB1*-mutant *MLH1* CRCs represent a distinct group that emerges from precursors other than adenomas, such as the MMR-DCF, and therefore contribute to the MMR-DCF carcinoma pathway (Ahadova et al.).

Several successive studies provided further evidence of a potential causative role for somatic *CTNNB1* mutations in the MMR-DCF carcinoma pathway and the development of *MLH1* CRCs under colonoscopy surveillance. For instance, we and others have shown that approximately 50% of the *MLH1* CRCs contain somatic *CTNNB1* mutations (Helderman et al., 2021; Ahadova et al., 2018; Engel et al., 2020; Ten Broeke et al., 2018a), which is compatible with the high cumulative incidence (36–52%) of CRC in *path_MLH1* carriers under surveillance (Moller et al., 2022; Dominguez-Valentin et al., 2023). On the other hand, we found *CTNNB1* variants to be scarce in CRCs of *path_MSH2*, path_*MSH6* and *path_PMS2* carriers (Helderman et al., 2023; Ten Broeke et al., 2018a), with the latter two groups of individuals unfrequently (3–17%) presenting with CRC while under colonoscopy surveillance.

It has recently been proposed that the strikingly high abundance of *CTNNB1* variants in *MLH1* CRCs can be attributed to a singular genomic event facilitated by the close genomic neighborhood of *MLH1* and *CTNNB1*. This proximity allows for biallelic hits in *MLH1* and *CTNNB1* through a copy number-neutral loss of heterozygosity event affecting the chromosome 3p22.1–2 region, containing both, *CTNNB1* and *MLH1* genes, which simultaneously triggers CTNNB1 activation and MLH1 inactivation. This "two-in-one hit" model may considerably accelerate the process of carcinogenesis due to the occurrence of two driver hits in a singular event, and is not observed for any of the other MMR genes, as they are located on other chromosomes, making a double-hit mutation together with *CTNNB1* highly unlikely. Consequently, the *CTNNB1*-driven MMR-DCF carcinoma pathway would primarily apply to *MLH1* CRCs and is likely to play no or a only marginal role in other LS CRCs that would have to acquire double somatic activating *CTNNB1* mutations through alternative mechanisms.

There are still numerous questions surrounding the involvement of *CTNNB1* in the MMR-DCF carcinoma pathway and the development of *MLH1* CRCs under colonoscopy surveillance that needs to be answered. For instance, it remains unknown why *CTNNB1* and not *APC* mutations are linked to concealed/accelerated carcinogenesis without an intermediate adenoma phase, especially given the related functions of the respective proteins. This discrepancy may imply that APC serves additional tumor-suppressive roles beyond its involvement in β-catenin degradation, potentially specifically related to polyp formation. Alternatively, Wnt-independent β-catenin functions, such as involvement in cell-cell adhesion may contribute to invasive growth of affected tumor cells (Arnold et al., 2020). Furthermore, it remains unclear whether the incidence and prevalence of MMR-DCF in the normal mucosa of *path_*MMR carriers varies depending on the affected MMR gene. Given the higher reported incidences of CRCs under colonoscopy surveillance in *path_MLH1* and *path_MSH2* carriers compared to *path_MSH6* and *path_PMS2* carriers, one might speculate that the first two MMR groups could exhibit higher frequencies of MMR-DCF. However, such differences were not observed during a recent study of Brand et al (Brand et al., 2020)., though the limited sample size of this study warrants further investigations.

4.1.2. Potential role of somatic mutations in other genes

Possible relevance to each MMR group:

- *MLH1/MSH2/MSH6/PMS2 syndromes: no/low relevance*

Though speculative, there may be a potential role for somatic mutations in genes other than *CTNNB1* in the process of concealed/accelerated carcinogenesis without an adenoma stage. This could be particularly pertinent for *path_MSH2* carriers, who, like *path_MLH1* carriers, frequently develop CRCs under surveillance, but typically do not exhibit *CTNNB1* mutations in their CRCs.

Many prior molecular studies have utilized limited hotspot panels, potentially overlooking LS CRC-specific somatic mutations that could be pivotal in the MMR-DCF carcinoma pathway. One conceivable candidate gene in this context is *RNF43*, which, like *CTNNB1*, encodes a component of the Wnt/β-catenin signaling pathway (Helderman et al., 2021), and along with *BRAF* mutations, is thought to drive the serrated neoplasia pathway (Yan et al., 2017). Subsequent studies that investigate the presence of mutations in *RNF43* and other genes in LS CRCs developing both during and prior to colonoscopy surveillance would be crucial in testing this hypothesis.

4.2. Accelerated progression from adenomas

Possible relevance to each MMR group:

- *MLH1/MSH2 syndromes: low/moderate relevance*
- *MSH6/PMS2 syndromes: no/low relevance*

Carcinogenesis without an adenoma stage, in particular the one suggested by the "two-in-one hit" model, could be perceived as accelerated, as two hits occur in a single event. However, carcinogenesis with an adenoma stage may also exhibit an accelerated progression. Due to the rapid accumulation of mutations following dMMR, the diversity of the genome of dMMR cells increases per cell division (Weinberg, 2014). Hypothetically, the latter could have multiple consequences, including a higher risk of cell death, in case disruptive mutations are acquired in proteins and/or pathways essential for cell survival. At the same time, it may also increase the chance of a cell to acquire cancer driver mutations, thereby potentially accelerating the process of carcinogenesis as compared to MMR-proficient tumors (Weinberg, 2014). Such accelerated progression could in theory leave no time for removal of the lesion at a precancerous stage, and may especially apply for the MMR-DCF (adenoma-)carcinoma pathway(s), in which dMMR is an early event.

In the context of LS, two important factors that could influence the mutational rate include the timing and degree of dMMR. Regarding the timing of dMMR, it could be envisioned that more mutations will accumulate in tumors in which the second hit of the wild type MMR allele is an early event, which for example is the case in MMR-DCF. Regarding the degree of dMMR, the functional redundancy of MSH6 and PMS2 in MMR may be of relevance. In the absence of MSH6, MSH2 may form an alternative heterodimer with MSH3, while MLH1 does the same with MLH3 or PMS1 in case of PMS2 deficiency (Helderman et al., 2021). Consequently, the absence of MSH6/PMS2 activity may result in a slower mutational rate/lower number of mutations as compared to that observed during MLH1/MSH2 deficiencies. Such differences in mutation patterns have recently been observed (Helderman et al., 2021; Ahadova et al., 2018; Helderman et al., 2023; Ten Broeke et al., 2018a) and are in line with the previously observed lower prevalence of CRCs under surveillance in *path_MSH6* and *path_PMS2* versus *path_MLH1* and *path_MSH2* carriers (Moller et al., 2022; Dominguez-Valentin et al., 2023), as well as by an earlier report demonstrating that advanced adenomas (defined as adenomas with a villous component, high-grade

dysplasia, and/or ≥10 mm in size) and CRC were detected after a significantly longer follow-up period in *path_MSH6* carriers compared to *path_MLH1*, *path_MSH2*, and *path_PMS2* carriers (Goverde et al., 2020). While it is speculative, it is therefore anticipated that the accelerated progression from adenomas will have a more pronounced impact on *path_MLH1* and *path_MSH2* carriers compared to *path_MSH6* and *path_PMS2* carriers. Interestingly, it has been documented that the majority (around 80%) of adenomas in *path_MLH1* and *path_MSH2* carriers are in fact dMMR (Ahadova et al., 2018; Sekine et al., 2017), though normal PMS2 expression was detected in adenomas from *path_PMS2* carriers (Bajwa-Ten Broeke et al., 2021) and dMMR/MSI in adenomas from individuals without LS is very rare (Vink-Borger et al., 2024). The MMR status of adenomas in *path_MSH6* and *path_PMS2* carriers has not been assessed in (large) cohorts to date.

A crucial distinction between concealed/accelerated carcinogenesis by bypassing the adenoma stage and accelerated progression from adenomas lies in the expectation that shorter colonoscopy surveillance intervals would lead to a decreased incidence of CRCs in the latter scenario, as this would increase the chance of detecting the precancerous adenomas. In contrast, in the first scenario, shorter surveillance intervals would not render the hidden precursor lesions visible, leaving the incidence of CRC under colonoscopy surveillance unaffected. Interestingly, some of the epidemiological studies comparing CRC incidence amongst *path_MMR* carriers in the context of one- to three-year intervals did not demonstrate a decreased incidence following shorter colonoscopy surveillance. If confirmed, these results would question a potential role for accelerated progression from adenomas in the development of CRCs under colonoscopy surveillance and indicate involvement of other (biological) factors (Seppala et al., 2017; Dominguez-Valentin et al., 2019; Engel et al., 2018; Seppala et al., 2019).

4.3. Immune reaction-induced regression of (pre)cancerous lesions

Possible relevance to each MMR group:

- *MLH1/MSH2 syndromes: low/moderate relevance*
- *MSH6/PMS2 syndromes: no/low relevance*

Since the immune system is able to induce the regression of adenomas/carcinomas by reacting to neoantigens presented by the tumor cells, the probability of developing CRCs may be described as a balance between carcinogenic mechanisms that lead to generation of cancer cells and the host's immune system which simultaneously tries to remove these cancer cells (Ahadova et al., 2021). Although unexplored at the moment of writing, this balance/interaction could potentially also play a role in the development of CRCs under colonoscopy surveillance in *path_MMR* carriers.

One conceivable theory explaining the potential elevated incidence of *MLH1* CRCs and *MSH2* CRCs under colonoscopy surveillance suggests that (precursor) lesions could potentially be targeted and eliminated by the immune system over time (Ahadova et al., 2021). With shorter surveillance intervals, there might not be sufficient time for these lesions to naturally regress, resulting in heightened detection rates. Alternatively, this immune reaction may initially reduce tumor size, potentially to a such an extent that the lesion is not (clearly) visible during colonoscopy, following which a subpopulation of tumor cells may eventually escape from the immunological pressure and invade surrounding tissue.

While currently underexplored, there is a potential for various immunological distinctions between the MMR groups, as suggested by previous research. For instance, our recent observations indicate a lower presence of dMMR signature-associated INDELs in *MSH6* CRCs compared to CRCs from the other three MMR groups (Helderman et al., 2023). This suggests that *MSH6* CRCs may exhibit a lower quantitative degree of MSI (e.g. lower INDEL mutational load), potentially leading to a weaker immune response compared to typical MSI CRCs. Furthermore, a study by Bohaumilitzky et al (Bohaumilitzky et al., 2022). found no variation in normal mucosa immune infiltration among different *path_MMR* carriers (*MLH1, MSH2* and *MSH6*), and a study by Bajwa – Ten Broeke et al (Bajwa-Ten Broeke et al., 2021). revealed lower frequencies of intra-tumoral $CD3^+$ T cells when looking at CRCs in *path_PMS2* carriers compared to CRCs in *path_MLH1* and *path_MSH2* carriers. Future in-depth studies focusing on the immune profile of CRCs within each MMR group are imperative to further uncover potential disparities and understand whether they correlate with variations in the incidence of CRCs under colonoscopy surveillance. Additionally, exploring the immune profile of CRCs that develop under colonoscopy surveillance compared to those that do not, along with potential immune reactivity directed towards precancerous lesions like MMR-DCF, holds significant promise for advancing our understanding in this area.

5. Colonoscopy-related factors

Apart from biological factors, several non-molecular, colonoscopy-related factors have been suggested as potential contributors to the development of CRCs during colonoscopy surveillance. These include instances (i) where (pre)cancerous lesions may have been missed despite being detectable, possibly due to inadequate colonoscopy quality or prolonged surveillance intervals, (ii) where the removal of (pre) cancerous lesions was incomplete, or more speculatively, (iii) where tumor cells may have been reimplanted following the colonoscopy procedure (Fig. 2) (Ahadova et al., 2021; Ehlken et al., 2022; Backes et al., 2019). It is crucial to emphasize that if future studies confirm the potential for invasive carcinoma to develop directly from MMR-DCF in *path_MMR* carriers, relying on colonoscopy that identifies and removes only visible lesions will not substantially prevent CRC, calling for alternative, primary prevention approaches. However, it may facilitate the detection of (curable) CRC originating from adenomas, and to contribute to low CRC-associated mortality (Seppala et al., 2017).

Since we anticipate similar colonoscopy quality among *path_MLH1*, *path_MSH2*, *path_MSH6*, and *path_PMS2* carriers, colonoscopy-related factors do not seem to directly explain the observed variations in CRC incidence during surveillance across *path_MMR* groups. Nevertheless, one potential factor contributing to this discrepancy could be polyp size, as larger, more easily detectable polyps tend to be more prevalent in *path_PMS2* carriers compared to *path_MLH1*, *path_MSH2*, and *path_MSH6* carriers (Goverde et al., 2020). Alternatively, it could be envisioned that the colonoscopy-related factors account for a comparable part of the CRCs diagnosed under surveillance in all *path_MMR* groups, whereas the inherent biological differences in the mechanisms of carcinogenesis between the MMR groups potentially contribute to the remaining ("extra") CRCs that develop under surveillance predominantly in *path_MLH1* and *path_MSH2* carriers. Interestingly, both colonoscopy-related and biological factors may interact in this context, as our research (Helderman et al., 2023), as well as that of others (Terui et al., 2013), has demonstrated that *MSH6* CRCs are more often located distally compared to *MLH1* CRCs. This distinction might potentially reduce the likelihood of adenoma being overlooked during an incomplete colonoscopy and make them more amenable to removal via polypectomy.

5.1. Missed yet detectable (pre)cancerous lesions

Ensuring a high-quality colonoscopy examination is regarded as a pivotal factor for the optimal effectiveness of surveillance colonoscopy. Therefore, surveillance colonoscopies for individuals with LS should adhere to the European Society of Gastrointestinal Endoscopy (ESGE) quality criteria for colonoscopy (Kaminski et al., 2014, 2017; van Leerdam et al., 2019a, 2019b). Detectable (pre)cancerous lesions may be missed if these quality criteria are not met, for instance due to the use inadequate techniques, inadequate quality and/or limited experience of the endoscopist, inadequate bowel preparation and/or incomplete examination. Moreover, (pre)cancerous lesions may not be detected if the

surveillance intervals are too long, potentially allowing cancer to progress within a single interval.

5.1.1. Inadequate colonoscopy quality

Possible relevance to each MMR group:

- *MLH1/MSH2/MSH6/PMS2 syndromes: no/low/moderate relevance*

5.1.1.1. Inadequate technique(s). The use of older processors in combination with lower-quality endoscopes lacking high definition endoscopes and near focus capability may result in (pre)cancerous lesions to be missed. On the other hand, utilizing high-definition endoscopy systems, as recommended by the ESGE (van Leerdam et al., 2019a), could potentially enhance the adenoma detection rate (ADR). Various endoscopic techniques have undergone evaluation, including (high--definition) white-light endoscopy (WLE), dye-based chromoendoscopy and virtual chromoendoscopy (i.e. narrow band imaging). High-definition WLE is the current golden standard according to the ESGE, though the latest ESGE guidelines acknowledge the potential benefit of chromoendoscopy in individuals with LS (Hassan et al., 2020). Several studies employing a back-to-back design and standard-definition endoscopes have indicated the superiority of dye-based chromoendoscopy over white-light endoscopy (WLE), with WLE adenoma miss rates ranging from 52% to 74% (Huneburg et al., 2009; Hurlstone et al., 2005; Lecomte et al., 2005; Rahmi et al., 2015). However, another back-to-back study (Stoffel et al., 2008), as well as two recent multicenter randomized trials in *path_MMR* carriers (Haanstra et al., 2019; Rivero-Sanchez et al., 2020), have shown no significant difference in adenoma/neoplasia detection rate between standard/high-definition WLE and dye-based chromoendoscopy. Virtual chromoendoscopy (i.e., narrow band imaging) demonstrated superiority to WLE in two back-to-back studies in individuals with LS (Bisschops et al., 2017; East et al., 2008), but was found to be inferior to dye-based chromoendoscopy in another back-to-back study (Huneburg et al., 2009). Therefore, the current role of virtual chromoendoscopy in the surveillance of *path_MMR* carriers is not yet firmly established. Artificial intelligence-assisted colonoscopy using computer-aided diagnosis might provide another candidate approach, yet the diagnostic benefit remains to be proven (Barua et al., 2022; Wei et al., 2023; Huneburg et al., 2023; Taghiakbari et al., 2021).

5.1.1.2. Inadequate quality and/or limited experience of the endoscopist. The competence and expertise of the endoscopist performing the procedure are pivotal in achieving high-quality outcomes, particularly in the context of surveillance colonoscopies for *path_MMR* carriers, which should adhere to the ESGE quality criteria for colonoscopy (Kaminski et al., 2017; van Leerdam et al., 2019a). Insufficient skills and limited experience may lead to incomplete colonoscopies and reduced ADR. This is exemplified by the findings of Toledo et al (van Toledo et al., 2022)., who demonstrated an inverse relationship between the proximal serrated polyp detection rate of an endoscopist and the incidence of PCCRC based on data from the Dutch fecal immunochemical test-based colorectal cancer screening program. Such factors can contribute to diminished inter- and intra-reproducibility, as underscored by a meta-analysis of various back-to-back colonoscopy studies, revealing that approximately 20% of adenomas go undetected (van Rijn et al., 2006).

5.1.1.3. Insufficient bowel preparation and/or incomplete colonoscopies. A recent multicenter study focused on *path_MMR* carriers without a prior history of CRC undergoing colonoscopy surveillance revealed that both adequate bowel preparation and complete colonoscopies were significantly associated with an improved ADR (Sanchez et al., 2022). Notably, the 10-year cumulative risk of PCCRC was found to be significantly lower in *path_MMR* carriers who received complete and adequately prepared colonoscopies with intervals of less than three years, in comparison to those who underwent colonoscopies that did not meet these criteria (2.8% vs 7.1%; $P<0.001$). In light of these findings, the ESGE recommends repeating the colonoscopy within three months prior to entering the two-year surveillance period if either bowel preparation (Boston Bowel Preparation Scale < 2 in one of the colon segments) was suboptimal in one of the colon segments, or if the procedure was incomplete (van Leerdam et al., 2019a).

Though comparable to the concept of concealed carcinogenesis through bypassing the adenoma stage, the concept of missed (pre) cancerous lesions due to inadequate colonoscopy quality assumes that if we improve colonoscopy quality, for instance by applying better techniques or training or continuous benchmarking, we would detect the previously undetected lesions. Concealed carcinogenesis by bypassing the adenoma stage, on the other hand, may involve (pre)cancerous lesions that are not macroscopically visible at all, and might require other approaches for proper identification. In order to understand the development of CRCs under colonoscopy surveillance, details about the quality of the colonoscopy (completeness, withdrawal time, adequate bowel preparation, interval) and preferably also about the quality of the endoscopy (ADR, caecal intubation rate) are essential. Unfortunately, this information is missing in most epidemiological studies (Moller et al., 2022, 2017; Engel et al., 2018, 2010; Moller et al., 2018).

5.1.2. Prolonged surveillance intervals

Possible relevance to each MMR group:

- *MLH1/MSH2/MSH6/PMS2 syndromes: no/low relevance*

Apart from suboptimal colonoscopy quality, there is a risk of overlooking detectable (pre)cancerous lesions due to excessively long surveillance intervals, potentially allowing cancer to progress within a single interval. As mentioned earlier, the epidemiological data on the incidence of LS CRC in relation to various surveillance intervals is conflicting. This includes studies that indicate a lower CRC incidence with shorter surveillance intervals (Sanchez et al., 2022; Aronson et al., 2023), studies that show no significant difference in CRC incidence across different intervals (Engel et al., 2018), and studies indicating that colonoscopy surveillance does not necessarily decrease CRC incidence but rather lowers mortality associated with CRC (Moller et al., 2022; Dominguez-Valentin et al., 2023). These inconsistencies may stem from a lack of data on colonoscopy quality in some of these studies (Moller et al., 2022; Engel et al., 2018), and hinder the establishment of a consensus on the optimal surveillance intervals, which currently differ between countries. The most recent recommendations from the ESHG advocate for high-quality surveillance colonoscopy every two years in asymptomatic *path_MMR* carriers, regardless of the specific affected MMR gene in the germline (van Leerdam et al., 2019a). On the other hand, the European Hereditary Tumour Group (EHTG) and European Society of Coloproctology (ESCP) suggest colonoscopy surveillance intervals of two to three years for *path_MLH1*, *path_MSH2*, and *path_MSH6* carriers, and five-year intervals for *path_PMS2* carriers (Seppala et al., 2021). This is because individuals in the latter group have a considerably lower CRC risk and mainly develop CRC through the adenoma-carcinoma pathway. For *path_MLH1* and *path_MSH2* carriers, surveillance is currently recommended from the age of 25, while for *path_MSH6* and *path_PMS2* carriers, it may commence from the age of 35 years (Seppala et al., 2021; van Leerdam et al., 2019a).

5.2. Detected yet incompletely removed (pre)cancerous lesions

Possible relevance to each MMR group:

- *MLH1/MSH2/MSH6 syndromes: no/low relevance*
- *PMS2 syndrome: low/moderate relevance*

After identifying precancerous lesions during colonoscopy, they are typically removed through polypectomy. Incomplete removal of these lesions may contribute to the subsequent development of CRC in the same colonic segment, as it permits (pre)cancerous cells to progress towards malignancy. Factors that increase the risk of incomplete polyp removal include a proximal location of the polyp, a sessile serrated histology, and a polyp size larger than 10 mm (Djinbachian et al., 2020; Lee et al., 2015; Ma et al., 2022; Pedersen et al., 2021). Additionally, patients who undergo a piecemeal polyp resection may face a higher risk of incomplete removal compared to those who undergo an en bloc resection (Zhang et al., 2018).

For *path_MMR* carriers, the phenomenon of detected yet incompletely removed (pre)cancerous lesions may be of less significance, as the majority (approximately 90%) of polyps in these individuals are small (< 10 mm) (Goverde et al., 2020). Interestingly, larger polyps (> 10 mm) seem to be more common in *path_PMS2* carriers compared to *path_MLH1*, *path_MSH2*, and *path_MSH6* carriers (Goverde et al., 2020). This contrasts with the incidence of CRCs under colonoscopy surveillance, which is lower for *path_PMS2* carriers as compared to other *path_MMR* carriers, and therefore questions the significance of incomplete polypectomy in the development of CRCs under colonoscopy surveillance.

In order to minimize the risk for incomplete polyp resection, it is advised to adhere to the colorectal polypectomy and endoscopic mucosal resection recommendations provided by the ESGE (Ferlitsch et al., 2017). In brief, cold snare polypectomy is recommended for achieving en bloc resection in sessile or flat lesions smaller than 10 mm. On the other hand, hot snare polypectomy is advised for noninvasive sessile or flat lesions ranging from 10 to 19 mm, as well as for pedunculated lesions. In cases of noninvasive sessile or flat lesions that measure 20 mm or larger, en bloc endoscopic mucosal resection or the alternative piecemeal endoscopic mucosal resection is advised. The recommended timeframe for assessing the scar for any remaining tissue following piecemeal endoscopic mucosal resection is uncertain. Nevertheless, it is advised to conduct a follow-up colonoscopy at six months. When dealing with sessile or flat lesions suspected of submucosal invasion, it is recommended to refer the patient for surgery, following colonic tattoo placement 3 cm distal to the lesion (Ferlitsch et al., 2017). The safety of local excision methods such as endoscopic submucosal dissection or endoscopic full-thickness resection for early invasive cancers in individuals with Lynch syndrome has not been established yet (Langers et al., 2019).

5.3. Colonoscopy-induced carcinogenesis

Possible relevance to each MMR group:

- *MLH1/MSH2/MSH6/PMS2 syndromes: no/low relevance*

In addition to inadequate colonoscopy quality and incomplete polypectomy, it has been hypothesized that colonoscopy itself may induce the formation of precancerous lesions, for instance through the reimplantation of tumor cells triggered by colonoscopy (Ehlken et al., 2022; Backes et al., 2019). This provocative hypothesis is supported by findings of Engel et al (Engel et al., 2018)., who demonstrated that shorter colonoscopy intervals were not associated with lower CRC incidence, and resulted in an international discussion regarding the credibility of colonoscopy surveillance. However, with no data about the quality of the colonoscopy we cannot judge the relevance of these results. Furthermore, as there is no colon-specific experimental evidence to date, the concept of carcinogenesis induced by colonoscopy remains speculative and should be carefully evaluated in future studies.

The concept of tumor cell reimplantation triggered by colonoscopy was recently introduced by Backes et al (Backes et al., 2019). and Ehlken et al (Ehlken et al., 2022)., who detected viable tumor cells on the endoscope channels and accessories of endoscopes following the removal of primary tumors from patients who later presented with metachronous tumor lesions. Though further experimental evidence is essential to prove this concept, it could be especially relevant for PCCRCs that developed after the removal of a polyp. As discussed earlier, PCCRCs are cancers diagnosed after a colonoscopy in which no "cancer" was detected, according to the World Endoscopy Organization (Rutter et al., 2018). Considering the fact that adenomas are strictly speaking not considered "cancer", adenomas could in theory be detected during the colonoscopy prior to the diagnosis of a PCCRC, raising the hypothesis that PCCRCs may arise from reimplanted tumor cells that originate from a removed adenoma during the previous colonoscopy.

Although adenomas can be detected in all MMR groups, prior epidemiological studies have revealed that the occurrence of (advanced) adenomas is most pronounced among *path_MSH2* carriers compared to other MMR groups (Engel et al., 2020; Bucksch et al., 2022). Hence, the hypothetical scenario of a PCCRC emerging after the removal of an adenoma during a previous colonoscopy may apply predominantly to *path_MSH2* carriers, though this remains speculation as experimental evidence is lacking.

6. Conclusion and future perspective

The development of CRCs under colonoscopy surveillance is complex and probably differs from PCCRC development in individuals without LS. It conceivably relies on (combinations of) biological and colonoscopy-related factors, which seem dependent on the MMR gene affected in the germline, as illustrated by the wide variation in incidence differences between the MMR groups.

From a biological perspective, considerable evidence suggests a relation between activating *CTNNB1* mutations and the MMR-DCF carcinoma pathway in *path_MLH1* carriers (Helderman et al., 2021; Ahadova et al., 2018; Engel et al., 2020; Ten Broeke et al., 2018a), though it is not directly proven whether the latter could in fact result in the development of *MLH1* CRCs under colonoscopy surveillance. Other somatic variants may hypothetically (additionally) be of importance to drive concealed/accelerated progression without an intermediate adenoma stage, while accelerated progression from adenomas could (also) be of importance in both *path_MLH1* and *path_MSH2* carriers. Each of the biological factors accentuate the need for targeting dMMR cells, which if performed in a preventative setting, may for instance counter cancerous outgrowth from MMR-DCF. Potential candidate approaches that are currently under investigation in randomized clinical trials include regular aspirin intake (Burn et al., 2011, 2020) and frameshift neoantigen-based vaccines (Gebert et al., 2021; Hernandez-Sanchez et al., 2022; Kloor et al., 2020; Leoni et al., 2020).

Future experimental studies are essential to better understand these biological factors in each MMR group. Crucial to consider in these upcoming studies is the importance of incorporating CRCs and/or *path_MMR* carriers both with and without colonoscopy surveillance. The discrimination between these groups during analyses is essential, as numerous existing fundamental and epidemiological studies frequently lack either a control group without colonoscopy surveillance or, conversely, a group with colonoscopy surveillance, making it challenging to discern outcomes influenced by colonoscopy from those that are not. Preferably, these fundamental studies will focus on unbiased, population-based cohorts using methods technically suited for identifying LS-specific somatic mutations. The inclusion of tissue representing initial stages of tumor progression (e.g. normal tissue, MMR-DCF, adenomas, serrated lesions, adenomatous/ serrated parts of carcinomas) in molecular analyses might shed further light on potential precursor lesions and the entire process of carcinogenesis in each MMR group. Epidemiological studies comparing *path_MMR* carriers with and without colonoscopy surveillance may rely on retrospective cohorts (Moller et al., 2022; ten Broeke et al., 2015; Ten Broeke et al., 2018b) or should take into account countries where colonoscopy surveillance is not standard, as prospectively including groups without surveillance would

be ethically unfeasible in most countries.

From a colonoscopy-related perspective, most evidence supports the concept of missed yet detectable (pre)cancerous lesions due to poor colonoscopy quality, with multiple studies showing that timely high-quality colonoscopy reduces PCCRC risk (Sanchez et al., 2022; Perrod et al., 2018). This concept may be tackled by improving the quality of colonoscopy, the use of image-enhancing techniques and maybe also by the upcoming introduction of artificial intelligence-assisted colonoscopy. On the other hand, the current level of evidence remains limited for the concepts of detected yet incompletely removed (pre)cancerous lesions and colonoscopy-induced carcinogenesis, which therefore needs attention in future studies. Strategies to avoid colonoscopy-induced carcinogenesis through tumor cell reimplantation may involve simple protocol adaptations (e.g. submucosal tattooing before taking biopsies) and the placement of the tattoo at a safe distance from the tumor to avoid tumor penetration (Backes et al., 2019). Strategies that target dMMR cells may be effective already in a preventive setting and could therefore in the future perhaps change medical care of *path_MMR* carriers, thereby limiting any of the potential harms of colonoscopy surveillance.

In conclusion, many questions remain to be answered regarding the mechanisms that underly the development of CRCs under colonoscopy surveillance, particularly in relation to the specific affected MMR gene and of the quality of colonoscopy. Future studies into both the biological and colonoscopy-related factors would be essential to gain a better understanding of this conflicting phenomenon, and preferably should have a gene-specific approach. These studies may eventually find application in the prevention/early detection strategies adapted for the needs of the specific MMR gene groups, which would be essential for the optimal medical care of LS carriers.

Search strategy

To retrieve relevant literature on the topic, we searched PubMed up to December 2023 for articles using the following search strategy:

("Colorectal Neoplasms, Hereditary Nonpolyposis"[Majr] OR "Familial Nonpolyposis"[ti] OR "Hereditary Nonpolyposis"[ti] OR "HNPCC"[ti] OR "Lynch"[Ti] OR "MLH1"[ti] OR "MSH2"[ti] OR "MSH6"[ti] OR "PMS2"[ti] OR "EPCAM"[ti] OR "Mismatch repair"[ti] OR "MMR"[ti] OR "MSI"[ti] OR "Microsatellite instab"[ti] OR "Microsatellite-instab*"[ti] OR "Microsatellite unstab*"[ti] OR "Microsatellite-unstab*"[ti])* AND *("Colonoscopy"[Mesh] OR "Colonoscop*"[tiab] OR "Endoscop*"[tiab] OR "Sigmoidoscop*"[tiab] OR "Post colonoscop*"[tiab] OR "Post-colonoscop*"[tiab] OR "PCCRC"[tiab] OR "Interval"[tiab] OR "Incident"[Tiab] OR "Prevalent"[Tiab] OR "Symptomatic"[Tiab] OR "Surveillance"[Tiab])* AND *("Neoplasms"[Majr] OR "Neoplas*"[tiab] OR "Tumor*"[tiab] OR "Tumour*"[tiab] OR "Cancer*"[tiab] OR "Malignan*"[tiab] OR "Oncolog*"[tiab] OR "Carcinoma*"[tiab] OR "Adenoma*"[tiab] OR "Adenocarcinoma*"[tiab]) AND ("Colorectal"[tiab] OR "Colon*"[tiab] OR "Rectal"[tiab] OR "Rectum"[tiab])*

Articles were included if they met the following criteria: (i) publication in English, (ii) concentration on confirmed *path_MMR* carriers, and (iii) exploration of carcinogenetic mechanisms and/or the particular development of colorectal cancer (CRC) under colonoscopy surveillance.

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CRediT authorship contribution statement

NCH: Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **MEvL:** Conceptualization, Writing – review & editing. **MK:** Conceptualization, Writing – review & editing. **AA:** Conceptualization, Writing – review & editing. **MN:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

None

Data Availability

No datasets were generated or analyzed during the current study.

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