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REVIEW

Progress Report: New insights into the prevention of CRC by colonoscopic surveillance in Lynch syndrome

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Abstract

Lynch syndrome is the most frequent hereditary colorectal cancer (CRC) syndrome, affecting approximately 1 in 300 in the Western population. It is caused by pathogenic variants in the mismatch repair (MMR) genes including *MLH1*, *MSH2* (*EPCAM*), *MSH6* and *PMS2*, and is associated with high risks of CRC, endometrial cancer and other cancers. In view of these risks, carriers of such variants are encouraged to participate in colonoscopic surveillance programs that are known to substantially improve their prognosis. In the last decade several important studies have been published that provide detailed cancer risk estimates and prognoses based on large numbers of patients. These studies also provided new insights regarding the pathways of carcinogenesis in CRC, which appear to differ depending on the specific MMR gene defect. In this report, we will discuss the implications of these new findings for the development of new surveillance protocols.

Keywords Surveillance · Hereditary colorectal cancer · Lynch syndrome · Pathways carcinogenesis · "de novo" colorectal cancer

Introduction

Several important studies have recently been reported that provide new insights into the value of colonoscopic surveillance in the prevention of colorectal cancer (CRC) in Lynch syndrome. Lynch syndrome (LS) is the most common inherited form of CRC and is responsible for around 3% of all CRCs, affecting approximately 1/300 in the Western population [1]. Lynch syndrome is an autosomal dominant inherited syndrome caused by a pathogenic variant in one of the mismatch repair (MMR) genes (*MLH1*, *MSH2/EPCAM*, *MSH6,* or *PMS2*) [2]. Carriers of MMR gene variants have a high risk of developing CRC, endometrial cancer and some other cancers, depending of the underlying MMR gene defect [3]. Surveillance of the colorectum was recommended over 30 years ago by Henry Lynch [4, 5]. Today there is general consensus that colonoscopic surveillance is highly effective and substantially improves the prognosis of CRC. However, as surveillance is not completely successful in preventing CRCs, a keen subject of debate over the last three decades has been the question of how to improve the screening protocol to prevent *all* CRCs. The main solutions put forward include shorter screening intervals [6, 7], and improving the quality of colonoscopies [8].

In this report, we highlight several ground breaking studies on colorectal carcinogenesis and the prevention of CRC in LS, and discuss their implications for new surveillance guidelines. First, we provide a short summary of evidence supporting a beneficial effect of colonoscopic surveillance, and then offer possible explanations for the limited efficacy of the current surveillance program for CRC prevention.

I want to dedicate this report to Henry Lynch, who passed away on June the 2nd, 2019 at the age of 91. Henry spent practically his whole life researching hereditary cancer and in doing so saved the lives of countless individuals genetically predisposed to cancer. As Henry and I had the same goals in research, we successfully collaborated as colleagues and friends for more than 30 years. He is still sorely missed.

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Effectiveness of colonoscopic surveillance over the last four decades

Studies undertaken in the 1980′s in Finland and The Netherlands showed that colonoscopic surveillance of families with Hereditary Non-Polyposis Colorectal Cancer (HNPCC), later diagnosed as LS families, had a high yield of precursor lesions and CRC and led to a shift in CRC stages [9, 10], with screen-detected CRC showing only locally-restricted disease (Dukes A & B).

In the mid-1980′s, Järvinen et al. began a "non-randomised controlled trial" comparing 3-yearly colonoscopic surveillance versus no surveillance in (suspected) Lynch syndrome/HNPCC families. The Finnish investigators were able to establish a large control group because in those early years, many high-risk individuals refused surveillance or initially could not be traced. As this study was the first and undoubtedly also the last controlled trial with a 'no surveillance arm' in Lynch syndrome, this investigation remains the most important study in the field today.

The results showed that 3-yearly colonoscopic surveillance (and polypectomy) reduced CRC by 62%, and also significantly improved survival. The investigators also concluded that the adenoma-carcinoma sequence is a feature of the development of CRC in LS. Furthermore, the study demonstrated that ~40% of cancers were not prevented when a 3-year interval was used (circa 13% of patients under surveillance developed CRC after 10 years follow-up) [11, 12].

In 1995, Dutch investigators published a registry case series of suspected LS patients who developed CRC within 2–3 years after a normal colonoscopy, also suggesting that a 3-year screening interval might be too long [6].

Between 2007 and 2010, three large LS registries in Finland, Germany and The Netherlands reported the results of prospective long-term surveillance [7, 13, 14]. As with the study by Järvinen, substantial CRC risk was still present despite surveillance (22–35% risk by age 60 years or 7%/10 years follow-up). Nevertheless, all three studies found a good overall prognosis for patients with screen-detected CRC, with no mortality in the Finnish and Dutch series and only local CRC in 41 (95%) out of 43 CRCs in the German registry. Other surveillance studies have reported similar results [15–17].

Explanations for the development of CRC under surveillance

Possible explanations for a high frequency of CRC despite intensive surveillance are that adenomas were missed during a previous colonoscopy or that a deficiency of MMR function accelerates the initiation and progression of the adenoma-carcinoma sequence. A third explanation is that the carriers of an MMR gene defect develop CRC directly from non-adenomatous mucosa ("de novo" CRC) [6]. These and other explanations are discussed in more detail in Ahadova et al. [18]. Here we briefly discuss the original hypotheses.

Regarding the first explanation, it is certainly possible that adenomas are missed during colonoscopy in LS as this is known to occur in an average risk population [19]. A proportion of the remaining CRC risk could therefore be attributed to development of cancer from 'missed adenomas'. As a consequence, it is of the utmost importance that no effort is spared in the improvement of the technical performance of colonoscopies [20–23].

Various studies have shown that LS patients develop adenomas 2–4 times more frequently than average-risk individuals [24, 25] and that they develop adenomas at a younger age [24–26]. Another important finding was the identification of MMR-deficient crypt foci in the normal colon of virtually all carriers of an MMR pathogenic variant (PV), reported by Matthias Kloor et al. in 2012 [27]. These novel lesions show loss of MMR protein expression but are neither dysplastic nor hyperplastic and should be differentiated from aberrant crypt foci that show histomorphological alterations [28]. MMR-deficient crypt foci represented the first evidence of the potential initiating role of MMR deficiency in the development of LS CRC, further supported by the observation in LS precancerous lesions (adenomas) reported by several independent research groups. Sekine et al. showed that the majority (79%) of adenomas in *MLH1* and *MSH2*-PV carriers are MMR-deficient [29]. These adenomas were found to carry *APC* or *CTNNB1* mutations less frequently (37%) but to carry frameshift *RNF43* mutations involving mononucleotide repeats more frequently (66%) than MMR-proficient adenomas. About half of the *APC* mutations detected in adenomas were also (frameshift) mutations involving repeat sequences. Ahadova et al. [30] investigated the frequency of MMR-deficiency in adenomas from LS patients by systematic literature analysis and by histochemistry of 21 adenomas, reporting MMR deficiency in 77% of a total of 640 lesions. In addition, most (75%) *APC* mutations detected in MMR-deficient LS-associated tumours showed the mutational signatures of MMR deficiency [30]. Together, these findings suggest that MMR deficiency often precedes and initiates adenoma formation in LS, which may partly explain the increased CRC risk.

There is also ample evidence that carcinogenesis is accelerated in LS. As far back as the 1980′s Mecklin et al. reported a high frequency of advanced adenomas in HNPCC families [31]. Jass et al. compared the incidence of adenomas in HNPCC to an age-matched autopsy series and found that HNPCC more often showed advanced aggressive adenomas

at a young age. These authors concluded that because adenomas are relatively uncommon, individually they must have a high malignant conversion rate [25]. Later studies also reported a high frequency of advanced adenomas in LS [24, 32].

Recently, Ahadova et al. proposed that some CRCs in LS may develop 'de novo' from MMR-deficient crypt foci [33]. This proposed new pathway of LS-associated CRC carcinogenesis is characterized by immediate invasive growth from non-polypous mucosa and the presence of mutations in the *CTNNB1* gene, which is known to be involved in the Wnt Pathway and to be particularly associated with hereditary MSI carcinogenesis [34–36]. These cancers appear to grow submucosally and may escape detection during colonoscopy.

Based on these findings and on additional studies [30], Ahadova et al. proposed three types of carcinogenesis in LS: (1) progression from MMR-proficient adenomas; (2) progression from MMR-deficient crypt foci, with development of adenoma followed by accelerated growth; and (3) progression from MMR-deficient crypt foci, with development of invasive cancer without polyp formation (Table 1).

In summary, we can conclude that one or a combination of the abovementioned explanations is responsible for the substantial risk of CRC under surveillance.

New insights for prevention of Lynch syndrome-associated CRC

In the last two decades, several important studies have been initiated by a European collaborative group focused on hereditary CRC, originally known as the 'Mallorca group' and now called the European Hereditary Tumour Group (EHTG). The first of these, the Prospective Lynch Syndrome Database (PLSD) established by Pål Møller and other members, was launched with the aim of prospectively evaluating the cancer risk and prognosis of a large series of LS patients. A second study was initiated by Juul Wijnen and aimed to collect a large series of families with *PMS2* to evaluate cancer risk. A third international study was proposed by Christoph Engel, the so-called 3 countries (Germany, Finland and The Netherlands) study (3CS), which prospectively evaluated the effect of different surveillance intervals on the incidence of CRC. Each of these initiatives recently produced a series of very important papers that provide groundbreaking insights into the prevention of CRC in LS.

Table 1 Pathways of CRC carcinogenesis in Lynch syndrome, as proposed by Ahadova et al. [30]

Pathway type 1	Progression from MMR-proficient adenomas
Pathway type 2	Progression from MMR-deficient crypt foci, with development of adenoma followed by accelerated growth
Pathway type 3	Progression from MMR-deficient crypt foci, with development of invasive carcinoma without adenoma

PLSD studies

The Prospective LS Database (PLSD) has collected follow-up data from more than 3000 carriers of a pathogenic variant, mainly found in the *MLH1, MSH2* and *MSH6* genes. 'Prospective' means that the moment of observation began with the first surveillance colonoscopy in the setting of structured follow-up, which could be either recent or 1–3 decades ago. The studies made possible by the PLSD have provided detailed cancer risk estimates for patients without a previous cancer [37] and for those with a previous cancer [38]. In a third study [39], cancer risks were reported up to the age of 75 years. In the most recent PLSD study, the original series and a validation cohort of LS patients were compared for cancer risks. Similar risks were found, after which the two cohorts could be merged. The resulting cohort now has around 6300 carriers of a pathological MMR variant, including 400 *PMS2* PV carriers [3]. In agreement with previous reports, studies by Møller et al. also showed a high CRC risk despite colonoscopic surveillance, with a cumulative CRC incidence at age 75 years of 57% and 48% for male and female *MLH1* PV carriers, respectively, 51% and 47% for male and female *MSH2* PV carriers, respectively, 18% and 20% for male and female *MSH6* PV carriers, respectively, and 10% (both sexes) for *PMS2* PV carriers [3]. In contrast to the high CRC rates that occur despite surveillance, the survival of patients with CRC was very good (colon cancer 5-year survival of 95%), although the survival of patients with rectosigmoid cancers was lower (5-year survival of 75%). The authors have developed a web-based tool (www.plsd.eu) that can be used to calculate an individual's cancer risk based on current age, sex and underlying MMR PV [3].

Additional PLSD studies have demonstrated that the cumulative CRC incidence in *MLH1* PV carriers is independent of surveillance intervals [40], and that CRC stage or survival in *MLH1* and *MSH2* PV carriers is not related to the time since the last colonoscopy [41, 42].

PMS2 studies

A second initiative, proposed by Wijnen et al. aimed to collect a large series of individuals with *PMS2* PV in order to calculate reliable risk estimates for CRC and other cancers. Wijnen and colleagues were able to collect 98 families, including 377 proven MMR PV carriers from European countries. In their first report, *PMS2* cancer risks were calculated using (modified) segregation analysis [43] and were found to be significantly lower (CRC: 19% for male carriers

and 11% for female carriers by age 70 years; EC: 12%) compared to other MMR PVs, together with a significantly later onset of CRC. As described by ten Broeke et al. [44], this cohort was later extended to include families from around the world, eventually totalling 284 families with 513 PV carriers. The reported CRC risks were even lower than those found in the previous study (CRC risk at age 80 years 13% for males and 12% for females), although the EC risk was similar. No increases in risk were found for other cancers.

Three-countries studies (3CS)

The third initiative was made possible by the collaboration of LS registries in Germany, Finland and The Netherlands, and was coordinated by Christoph Engel. The aim of the first of the 3CS studies was to compare the results of colonoscopic surveillance in the 3 countries, facilitated by the use of different surveillance intervals (annual surveillance in Germany, 1–2 yearly surveillance in the Netherlands and 2–3 yearly surveillance in Finland). Follow-up data were collected from 2747 carriers of an *MLH1, MSH2* or *MSH6* PV. Unexpectedly, the study did not show lower CRC incidences or earlier CRC stages as a result of shorter colonoscopic surveillance intervals (annual vs. 1–2 yearly and 2–3 yearly) [45]. CRC risk was actually found to be primarily dependent on a number of independent risk factors, including (1) the presence of a prior CRC diagnosis, (2) male sex, (3) *MLH1* or *MSH2* carrier status (in contrast to *MSH6* carrier status), (4) age > 40 years at the index colonoscopy, and (5) presence of an adenoma at the index colonoscopy.

In the second 3CS study, Engel et al. studied associations between LS-associated pathogenic variants (*MLH1, MSH2* and *MSH6*), the risk of (advanced) adenoma and CRC, and somatic mutations in *APC* and *CTNNB1* [46]. The study showed that the risk of advanced adenoma was significantly higher in *MSH2* PV carriers (17.8%) compared to *MLH1* PV carriers (7.7%), whereas the risk of CRC was similar in these PV carriers (11% at 10 years) but significantly higher compared to risk in *MSH6* PV carriers (5%).

Somatic mutations in *APC* were more frequently found in tumours from *MSH2* PV carriers compared to tumours from *MLH1* PV carriers (75% vs. 11%), whereas somatic mutations in *CTNNB1* were more common in tumours from *MLH1* PV carriers than in *MSH2*-associated tumours (50% vs. 7%). Three tumours from *MSH6* PV carriers showed *APC* mutations but no *CTNNB1* mutations (46). In another recent study by ten Broeke et al. [47], the molecular profile of tumours from *PMS2* PV, *MLH1* PV and *MSH2* PV carriers was investigated. Differences in the proportions of various genes (*APC, RAS, T53, FBXW7*) were found, but the most notable finding was the total lack of *CTNNB1* mutations in *PMS2* tumours (0 out of 20 tumours), compared to *CTNNB1* mutation frequencies of 58% in *MLH1* tumours and 6% in *MSH2* tumours. Another important finding was the high proportion of MMR-proficient adenomas in *PMS2* PV carriers. The findings are summarized in Table 2.

The combined results of clinical and molecular studies suggest that cancer in carriers of the various pathogenic MMR variants may be driven by different pathways. The relatively high frequency of *CTNNB1* mutations and the low frequency of *APC* mutations found in *MLH1* PV carriers, in combination with the high risk of CRC and lower risk of advanced adenoma (compared to *MSH2* PV carriers), suggest that the dominant pathway might be via immediate development of invasive CRC from MMR-deficient crypt foci without adenoma formation (i.e., pathway Type 3) [30].

Table 2 Clinical-molecular findings and the most likely involved dominant pathway of carcinogenesis in carriers of various LS pathogenic variants

Pathogenic MMR variant	CRC risk at age 75 years	Advanced adenomas at 10-years follow-up[3]	Somatic mutations in tumours	Probable dominant pathway[a]
MLH1	High (~50%)[1]	7.7%	*CTNNB1*: 50%[3]/58%[4] *APC:* 11[3]/13%[4]	Type 3
MSH2	High (~50%)[1]	17.8%	*CTNNB1*: 7%[3]/6%[4] *APC:* 75[3]/33%[4]	Type 2
MSH6	Moderate (~20%)[1]	9.4%	*CTNNB1:* 0 out of 3[3] *APC:* 3 out of 3[3]	Type 1
PMS2	Low (~10%)[2]	Not available	*CTNNB1*: 0%[4] *APC:* 30%[4]	Type 1

[a]Ahadova et al. (2018) [30]

[1]Dominguez-Valentin et al. (2020) [3]

[2]ten Broeke et al. (2018) [44]

[3]Engel et al. (2020) [46]

[4]ten Broeke et al. (2018) [47]

In contrast, findings in *MSH2* PV carriers, including a low frequency of *CTNNB1* mutations, a high frequency of *APC* mutations, together with a high risk of CRC and advanced adenomas, may indicate that pathway Type 2 is the dominant pathway in these carriers. In *MSH6* PV and *PMS2* PV carriers, the lack of *CTNNB1* mutations and the high frequency of *APC* mutations in combination with the low risk of CRC suggests that carcinogenesis from MMR-proficient adenoma to cancer may be the dominant pathway (Type 1) (Table 2).

Discussion

What do these studies teach us in relation to colonoscopic surveillance for the prevention of CRC in LS? Firstly, the PLSD studies in particular, with the largest collection of carriers to date, confirmed the overall relatively good survival of patients with CRC detected under surveillance. Secondly, the PLSD, 3CS and *PMS2* studies demonstrated large differences in adenoma and/or CRC risk between the four groups of MMR PV carriers. Thirdly, the 3CS and PLSD studies showed that annual colonoscopic surveillance does not lead to lower CRC incidence and lower stages of CRC compared to longer intervals.

The favourable prognosis of CRC LS patients might be explained by a strong immune response, which may restrict tumour growth [18]. Systemic immune responses against MMRd-induced frameshift peptides had been demonstrated, supporting the concept of continuous immune surveillance in LS [48]. This slow growth might also explain the lack of influence of shorter surveillance intervals on the CRC stage [45].

Some very interesting observations have been made in clinical and molecular studies, suggesting that the four groups of MMR PV carriers may follow distinct carcinogenic pathways. Based on these differences, surveillance protocols could be adjusted to suit each of the four MMR gene groups, which might further improve the prognosis.

The type of carcinogenesis found in tumours from different MMR PV carriers appears to depend on the moment and degree of MMR loss-of-function during cancer development. Apparently, complete loss of MMR function already commonly occurs at an early stage of carcinogenesis in *MLH1* and *MSH2* PV carriers, or may even be an initiating event giving rise to MMRd crypt foci. In *MSH6* and *PMS2* PV carriers some MMR function may remain, due to compensation for mutated *MSH6* and *PMS2* by other MMR genes such as *MSH3, MLH3*, and *PMS1* [49]. This may explain why MMR deficiency occurs much later in the adenoma-carcinoma sequence in these carriers.

What are the implications of these new findings for the surveillance protocol?

Pathway Type 3 probably dominates in *MLH1* tumours, which is associated with the submucosal growth of cancer or flat lesions that are hard to detect during endoscopy (Table 2). However, as discussed above, the study by Järvinen et al. [12] demonstrated that polypectomy was effective despite the inclusion of mainly *MLH1* PV carriers, suggesting that other pathways are also involved. In view of the potential development of small CRCs while skipping the adenoma phase, surveillance at 2 year intervals appears appropriate in these carriers. Even shorter intervals do not appear to be safer, as annual colonoscopy did not lead to a lower incidence of CRC in the above-mentioned 3CS study [45]. In tumours from *MSH2* PV carriers, studies indicate that loss of MMR function leads to initiation of adenomas followed by fast progression, processes compatible with Type 2 pathway carcinogenesis. In this group of carriers the optimal interval between colonoscopies is probably 2 years, especially in view of the lack of effectiveness of even shorter surveillance intervals in the 3CS study [45]. On the other hand, this study, did not prove that a 2–3 year or, in particular, a 3-year interval is completely safe in *MLH1 and MSH2* PV carriers because age, sex, mutation, and previous neoplasia were used to individually adjust colonoscopy intervals and in 30–40% of patients in the 2–3 year cohort, the median colonoscopy interval actually was approximately 2 years [45].

As mentioned above, the risk of an incident CRC in the 3CS study was largely dependent on a number of (independent) risk factors, including the presence of a prior CRC diagnosis, male sex, *MLH1* or *MSH2* carrier status (in contrast to *MSH6* carrier status), age > 40 years at the index colonoscopy, and presence of an adenoma at the index colonoscopy [45]. Engel et al. calculated that patients with 4 or 5 risk factors had a 10-year CRC risk of 18·4%, while the risk in patients with none or only 1 risk factor was 4·1% [45]. In view of these findings, more frequent colonoscopic surveillance might be appropriate in *MLH1* and *MSH2* PV carriers with multiple risk factors but more studies are needed to validate such risk-adjusted surveillance strategy [45].

Regarding *MSH6* PV carriers, the finding of *APC* somatic mutations in the absence of *CTNNB1* mutations in the few *MSH6* tumours available in the 3CS study should be confirmed in a larger series. However, these preliminary findings, together with reports that indicate that adenomas in *MSH6* PV carriers are mainly MMR proficient [50, 51], suggest that pathway Type 1 carcinogenesis is the dominant route of progression. Furthermore, surveillance was recently shown to be very effective in this group of carriers [52], as no CRCs were detected during 915 surveillance colonoscopies in 143 *MSH6* PV carriers, probably because there seems to be more time to identify and remove initially MMR-proficient adenomas [52]. In the 3CS study, the risk of an advanced adenoma and incident CRC in 354 *MSH6*

PV carriers at 10 years follow-up was only 9.4% and 4.7%, respectively [46]. In view of these findings, a 2–3 yearly or 3-yearly colonoscopy is likely the optimal option.

The molecular findings in *PMS2* tumours, together with the low risk of CRC and the fact that most adenomas are MMR proficient [47], suggest that CRCs develop according to pathway Type 1 carcinogenesis. Similarly to *MSH6* carriers, most adenomas can be detected and removed by colonoscopy in this group of carriers, explaining the nearly complete CRC prevention by colonoscopy in *PMS2* PV carriers as reported by the recent PLSD study [3]. In view of the low risk of CRC and the apparent absence of accelerated progression of adenomas, a 3–5 year or 5 year interval might be recommended [44].

The most recent CRC surveillance protocols for LS patients are summarized in Table 3 [53–57]. The differences between these protocols, together with the surveillance recommendations suggested above, reflect how difficult it is to directly deduce screening interval recommendations from the existing data in the absence of prospective studies. It is clear that more studies are needed to substantiate the recommendations.

In view of the large differences in cancer risks and molecular findings between different groups of carriers, and the necessary adjustments in surveillance protocols, it is important that the terminology of LS is reconsidered to clarify the fact that we are dealing with clinically distinct syndromes [3]. A few years ago we suggested that the pathogenic gene variant involved should be included in the name of the syndrome (e.g. *MLH1*-Lynch syndrome, etc.) [58], in the belief that the use of these new terms will help to improve personalized care for patients with Lynch syndrome.

To summarize, there is convincing evidence that distinct pathways are involved in carcinogenesis driven by the various MMR gene PVs. Based on this new knowledge, the development of CRC during surveillance can be better explained and should allow surveillance protocols to be improved.

Table 3 Recent guidelines for colonoscopic surveillance in Lynch syndrome (see text for references)

Pathogenic variant	Colonoscopy interval	Lower age limits
American Gastroenterological Association Institute Guideline 2015		
MLH1/MSH2/MSH6/PMS2	1–2 years	20–25 years or 5 years before youngest case in family
American College of Gastroenterology 2015		
MLH1/MSH2/MSH6/PMS2	at least every 2 years[a]	20–25 years[b]
British Society Gastroenterology & Association of Coloproctology of Great Britain & Ireland & UK Cancer Genetics Group Guidelines 2020[c]		
MLH1/MSH2	2 years	25 years
MSH6/PMS2	2 years	35 years
European Hereditary Tumour Group (EHTG) & European Society of Coloproctology guidelines 2020		
MLH1/MSH2	2–3 years[d]	25 years
MSH6	2–3 years[d]	35 years
PMS2	5 years	35 years
National comprehensive guidelines 2020 (www.nccn.org)		
MLH1/MSH2 (& *EPCAM*)	1–2 years[e]	20–25 years or 2–5 years prior to earliest CRC if diagnosed before 25 years
MSH6/PMS2	1–2 years[e]	30–35 years or 2–5 years prior to earliest CRC if diagnosed before 30 years
European Society of Gastrointestinal Endoscopy Guidelines 2019		
MLH1/MSH2	2 years	25 years
MSH6/PMS2	2 years	35 years

[a]Annual colonoscopy should be considered in mutation carriers

[b]Consider starting surveillance at 25–30 years in *MSH6* and *PMS2* mutation carriers

[c]Supported by the European Hereditary Tumour Group (EHTG)

[d]2 years is recommended in patients with a previous CRC

[e]Patients who may benefit from a shorter 1 versus 2 year interval include those with risk factors such as a history of CRC, male sex, *MLH1/MSH2* pathogenic variants, age > 40 years, history of adenomas

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

References

1. Win AK, Jenkins MA, Dowty JG, Antoniou AC, Lee A, Giles GG et al (2017) Prevalence and penetrance of major genes and polygenes for colorectal cancer. Cancer Epidemiol Biomark Prev 26(3):404–412
2. Biller LH, Syngal S, Yurgelun MB (2019) Recent advances in Lynch syndrome. Fam Cancer 18(2):211–219
3. Dominguez-Valentin M, Sampson JR, Seppala TT, Ten Broeke SW, Plazzer JP, Nakken S et al (2020) Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med 22(1):15–25
4. Lynch HT, Smyrk TC, Watson P, Lanspa SJ, Lynch JF, Lynch PM et al (1993) Genetics, natural history, tumor spectrum, and pathology of hereditary nonpolyposis colorectal cancer: an updated review. Gastroenterology 104(5):1535–1549
5. Lynch HT, Watson P, Lanspa SJ, Marcus J, Smyrk T, Fitzgibbons RJ Jr et al (1988) Natural history of colorectal cancer in hereditary nonpolyposis colorectal cancer (Lynch syndromes I and II). Dis Colon Rectum 31(6):439–444
6. Vasen HF, Nagengast FM, Khan PM (1995) Interval cancers in hereditary non-polyposis colorectal cancer (Lynch syndrome). Lancet 345(8958):1183–1184
7. Engel C, Rahner N, Schulmann K, Holinski-Feder E, Goecke TO, Schackert HK et al (2010) Efficacy of annual colonoscopic surveillance in individuals with hereditary nonpolyposis colorectal cancer. Clin Gastroenterol Hepatol 8(2):174–182
8. Haanstra JF, Kleibeuker JH, Koornstra JJ (2013) Role of new endoscopic techniques in Lynch syndrome. Fam Cancer 12(2):267–272
9. Mecklin JP, Jarvinen HJ, Aukee S, Elomaa I, Karjalainen K (1987) Screening for colorectal carcinoma in cancer family syndrome kindreds. Scand J Gastroenterol 22(4):449–453
10. Vasen HF, den Hartog Jager FC, Menko FH, Nagengast FM (1989) Screening for hereditary non-polyposis colorectal cancer: a study of 22 kindreds in The Netherlands. Am J Med 86(3):278–281
11. Jarvinen HJ, Mecklin JP, Sistonen P (1995) Screening reduces colorectal cancer rate in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 108(5):1405–1411
12. Jarvinen HJ, Aarnio M, Mustonen H, Aktan-Collan K, Aaltonen LA, Peltomaki P et al (2000) Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 118(5):829–834
13. Mecklin JP, Aarnio M, Laara E, Kairaluoma MV, Pylvanainen K, Peltomaki P et al (2007) Development of colorectal tumors in colonoscopic surveillance in Lynch syndrome. Gastroenterology 133(4):1093–1098
14. Vasen HF, Abdirahman M, Brohet R, Langers AM, Kleibeuker JH, van Kouwen M et al (2010) One to 2-year surveillance intervals reduce risk of colorectal cancer in families with Lynch syndrome. Gastroenterology 138(7):2300–2306
15. Stupart DA, Goldberg PA, Algar U, Ramesar R (2009) Surveillance colonoscopy improves survival in a cohort of subjects with a single mismatch repair gene mutation. Colorectal Dis 11(2):126–130
16. Newton K, Green K, Lalloo F, Evans DG, Hill J (2015) Colonoscopy screening compliance and outcomes in patients with Lynch syndrome. Colorectal Dis 17(1):38–46
17. Stuckless S, Green JS, Morgenstern M, Kennedy C, Green RC, Woods MO et al (2012) Impact of colonoscopic screening in male and female Lynch syndrome carriers with an MSH2 mutation. Clin Genet 82(5):439–445
18. Ahadova A, Seppala TT, Engel C, Gallon R, Burn J, Holinski-Feder E et al (2020) The "unnatural" history of colorectal cancer in Lynch syndrome: Lessons from colonoscopy surveillance. Int J Cancer. https://doi.org/10.1002/ijc.33224
19. Zhao S, Wang S, Pan P, Xia T, Chang X, Yang X et al (2019) Magnitude, risk factors, and factors associated with adenoma miss rate of tandem colonoscopy: a systematic review and meta-analysis. Gastroenterology 156(6):1661–1674
20. Latchford A (2020) How should colonoscopy surveillance in Lynch syndrome be performed? Gastroenterology 158(4):818–819
21. Haanstra JF, Dekker E, Cats A, Nagengast FM, Hardwick JC, Vanhoutvin SA et al (2019) Effect of chromoendoscopy in the proximal colon on colorectal neoplasia detection in Lynch syndrome: a multicenter randomized controlled trial. Gastrointest Endosc 90(4):624–632
22. Rivero-Sanchez L, Arnau-Collell C, Herrero J, Remedios D, Cubiella J, Garcia-Cougil M et al (2020) White-light endoscopy is adequate for Lynch syndrome surveillance in a randomized and noninferiority study. Gastroenterology 158(4):895–904
23. Argillander TE, Koornstra JJ, van Kouwen M, Langers AM, Nagengast FM, Vecht J et al (2018) Features of incident colorectal cancer in Lynch syndrome. United Eur Gastroenterol J 6(8):1215–1222
24. De Jong AE, Morreau H, Van Puijenbroek M, Eilers PH, Wijnen J, Nagengast FM et al (2004) The role of mismatch repair gene defects in the development of adenomas in patients with HNPCC. Gastroenterology 126(1):42–48
25. Jass JR, Stewart SM (1992) Evolution of hereditary non-polyposis colorectal cancer. Gut 33(6):783–786
26. Love RR (1986) Adenomas are precursor lesions for malignant growth in nonpolyposis hereditary carcinoma of the colon and rectum. Surg Gynecol Obstet 162(1):8–12
27. Kloor M, Huth C, Voigt AY, Benner A, Schirmacher P, von Knebel DM et al (2012) Prevalence of mismatch repair-deficient crypt foci in Lynch syndrome: a pathological study. Lancet Oncol 13(6):598–606
28. Pedroni M, Sala E, Scarselli A, Borghi F, Menigatti M, Benatti P et al (2001) Microsatellite instability and mismatch-repair protein expression in hereditary and sporadic colorectal carcinogenesis. Cancer Res 61(3):896–899
29. Sekine S, Mori T, Ogawa R, Tanaka M, Yoshida H, Taniguchi H et al (2017) Mismatch repair deficiency commonly precedes adenoma formation in Lynch syndrome-associated colorectal tumorigenesis. Mod Pathol 30(8):1144–1151
30. Ahadova A, Gallon R, Gebert J, Ballhausen A, Endris V, Kirchner M et al (2018) Three molecular pathways model colorectal carcinogenesis in Lynch syndrome. Int J Cancer 143(1):139–150
31. Mecklin JP, Sipponen P, Jarvinen HJ (1986) Histopathology of colorectal carcinomas and adenomas in cancer family syndrome. Dis Colon Rectum 29(12):849–853
32. Rijcken FE, Hollema H, Kleibeuker JH (2002) Proximal adenomas in hereditary non-polyposis colorectal cancer are prone to rapid malignant transformation. Gut 50(3):382–386
33. Ahadova A, von Knebel DM, Blaker H, Kloor M (2016) CTNNB1-mutant colorectal carcinomas with immediate invasive

growth: a model of interval cancers in Lynch syndrome. Fam Cancer 15(4):579–586
34. Miyaki M, Iijima T, Kimura J, Yasuno M, Mori T, Hayashi Y et al (1999) Frequent mutation of beta-catenin and APC genes in primary colorectal tumors from patients with hereditary nonpolyposis colorectal cancer. Cancer Res 59(18):4506–4509
35. Johnson V, Volikos E, Halford SE, Eftekhar Sadat ET, Popat S, Talbot I et al (2005) Exon 3 beta-catenin mutations are specifically associated with colorectal carcinomas in hereditary non-polyposis colorectal cancer syndrome. Gut 54(2):264–267
36. Huels DJ, Ridgway RA, Radulescu S, Leushacke M, Campbell AD, Biswas S et al (2015) E-cadherin can limit the transforming properties of activating beta-catenin mutations. EMBO J 34(18):2321–2333
37. Moller P, Seppala T, Bernstein I, Holinski-Feder E, Sala P, Evans DG et al (2017) Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. Gut 66(3):464–472
38. Moller P, Seppala T, Bernstein I, Holinski-Feder E, Sala P, Evans DG et al (2017) Incidence of and survival after subsequent cancers in carriers of pathogenic MMR variants with previous cancer: a report from the prospective Lynch syndrome database. Gut 66(9):1657–1664
39. Moller P, Seppala TT, Bernstein I, Holinski-Feder E, Sala P, Gareth Evans D et al (2018) Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. Gut 67(7):1306–1316
40. Seppala T, Pylvanainen K, Evans DG, Jarvinen H, Renkonen-Sinisalo L, Bernstein I et al (2017) Colorectal cancer incidence in path_MLH1 carriers subjected to different follow-up protocols: a prospective Lynch syndrome database report. Hered Cancer Clin Pract 15:18
41. Dominguez-Valentin M, Seppala TT, Sampson JR, Macrae F, Winship I, Evans DG et al (2019) Survival by colon cancer stage and screening interval in Lynch syndrome: a prospective Lynch syndrome database report. Hered Cancer Clin Pract 17:28
42. Seppala TT, Ahadova A, Dominguez-Valentin M, Macrae F, Evans DG, Therkildsen C et al (2019) Lack of association between screening interval and cancer stage in Lynch syndrome may be accounted for by over-diagnosis; a prospective Lynch syndrome database report. Hered Cancer Clin Pract 17:8
43. ten Broeke SW, Brohet RM, Tops CM, van der Klift HM, Velthuizen ME, Bernstein I et al (2015) Lynch syndrome caused by germline PMS2 mutations: delineating the cancer risk. J Clin Oncol 33(4):319–325
44. Ten Broeke SW, van der Klift HM, Tops CMJ, Aretz S, Bernstein I, Buchanan DD et al (2018) Cancer risks for PMS2-associated Lynch syndrome. J Clin Oncol 36:2961
45. Engel C, Vasen HF, Seppala T, Aretz S, Bigirwamungu-Bargeman M, de Boer SY et al (2018) No difference in colorectal cancer incidence or stage at detection by colonoscopy among 3 countries with different Lynch syndrome surveillance policies. Gastroenterology 155(5):1400–1409
46. Engel C, Ahadova A, Seppala TT, Aretz S, Bigirwamungu-Bargeman M, Blaker H et al (2020) Associations of pathogenic variants in MLH1, MSH2, and MSH6 with risk of colorectal adenomas and tumors and with somatic mutations in patients with Lynch syndrome. Gastroenterology 158(5):1326–1333
47. Ten Broeke SW, van Bavel TC, Jansen AML, Gomez-Garcia E, Hes FJ, van Hest LP et al (2018) Molecular background of colorectal tumors from patients with Lynch syndrome associated with germline variants in PMS2. Gastroenterology 155(3):844–851
48. Schwitalle Y, Kloor M, Eiermann S, Linnebacher M, Kienle P, Knaebel HP et al (2008) Immune response against frameshift-induced neopeptides in HNPCC patients and healthy HNPCC mutation carriers. Gastroenterology 134(4):988–997
49. Peltomaki P (2016) Update on Lynch syndrome genomics. Fam Cancer 15(3):385–393
50. Yurgelun MB, Goel A, Hornick JL, Sen A, Turgeon DK, Ruffin MTT et al (2012) Microsatellite instability and DNA mismatch repair protein deficiency in Lynch syndrome colorectal polyps. Cancer Prev Res (Phila) 5(4):574–582
51. Walsh MD, Buchanan DD, Pearson SA, Clendenning M, Jenkins MA, Win AK et al (2012) Immunohistochemical testing of conventional adenomas for loss of expression of mismatch repair proteins in Lynch syndrome mutation carriers: a case series from the Australasian site of the colon cancer family registry. Mod Pathol 25(5):722–730
52. Goverde A, Eikenboom EL, Viskil EL, Bruno MJ, Doukas M, Dinjens WNM et al (2020) Yield of Lynch syndrome surveillance for patients with pathogenic variants in DNA mismatch repair genes. Clin Gastroenterol Hepatol 18(5):1112–1120
53. Rubenstein JH, Enns R, Heidelbaugh J, Barkun A, Clinical GC (2015) American Gastroenterological Association Institute guideline on the diagnosis and management of Lynch syndrome. Gastroenterology 149(3):777–782
54. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW et al (2015) ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 110(2):223–262
55. van Leerdam ME, Roos VH, van Hooft JE, Balaguer F, Dekker E, Kaminski MF et al (2019) Endoscopic management of Lynch syndrome and of familial risk of colorectal cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 51(11):1082–1093
56. Monahan KJ, Bradshaw N, Dolwani S, Desouza B, Dunlop MG, East JE et al (2020) Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). Gut 69(3):411–444
57. Seppala TT, Latchford A, Negoi I, Sampaio Soares A, Jimenez-Rodriguez R, Sanchez-Guillen L et al (2020) European guidelines from the EHTG and ESCP for Lynch syndrome: an updated third edition of the Mallorca guidelines based on gene and gender. Br J Surg. https://doi.org/10.1002/bjs.11902
58. Vasen HF, Tomlinson I, Castells A (2015) Clinical management of hereditary colorectal cancer syndromes. Nat Rev Gastroenterol Hepatol 12(2):88–97