Thieme

Endoscopic management of Lynch syndrome and of familial risk of colorectal cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline

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MAIN RECOMMENDATIONS

ESGE recommends that individuals with Lynch syndrome should be followed in dedicated units that practice monitoring of compliance and endoscopic performance measures.

Strong recommendation, low quality evidence, level of agreement 100 %.

ESGE recommends starting colonoscopy surveillance at the age of 25 years for *MLH1* and *MSH2* mutation carriers and at the age of 35 years for *MSH6* and *PMS2* mutation carriers.
Strong recommendation, moderate quality evidence, level of agreement 100 %.

ESGE recommends the routine use of high-definition endoscopy systems in individuals with Lynch syndrome.
Strong recommendation, high quality evidence, level of agreement 100 %.

ESGE suggests the use of chromoendoscopy may be of benefit in individuals with Lynch syndrome undergoing colonoscopy; however routine use must be balanced against costs, training, and practical considerations.
Weak recommendation, moderate quality evidence, level of agreement 89 %.

ESGE recommends definition of familial risk of colorectal cancer as the presence of at least two first-degree relatives with colorectal cancer or at least one first-degree relative with colorectal cancer before the age of 50 years.
Strong recommendation, moderate quality evidence, level of agreement 92 %.

ESGE recommends colonoscopy surveillance in first-degree relatives of colorectal cancer patients in families that fulfill the definition of familial risk of colorectal cancer.
Strong recommendation, moderate quality evidence, level of agreement 100 %.

SOURCE AND SCOPE

This Guideline is an official statement of the European Society of Gastrointestinal Endoscopy (ESGE). It provides an overview of the endoscopic management of individuals with Lynch syndrome and individuals with familial risk of colorectal cancer. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was adopted to define the strength of recommendations and the quality of evidence.

1 Introduction

Colorectal cancer (CRC) is the fourth most incident cancer and the second leading cause of cancer-related deaths in Europe [1]. While the majority of CRC is sporadic, twin studies have shown that up to 35 % of CRC cases have a familial component [2].

In 2 % – 5 % of CRC cases a genetic origin has been identified [3]. The most common hereditary CRC syndrome is caused by a constitutional pathogenic variant in one of the DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) or the 3' end of the *EpCAM* gene; it is also known as Lynch syndrome (LS) and was previously termed hereditary non-polyposis colorectal cancer (HNPCC) [3]. Among CRC cases about 2 % – 4 % are caused by LS [4]. As well as increased CRC risk, individuals with LS have a higher risk of developing endometrial, gastric, small-bowel, biliary tract, ovary, urinary tract, brain, and skin cancers. Because of the high cancer risk, it is of great importance that clinicians recognize individuals with LS in order to make appropriate management decisions for both the patient and their at-risk family members. CRC cases associated with polyposis syndromes are discussed in a separate guideline [5].

However, for most cases of CRC with a familial component, no genetic origin is found. The CRC risk in this heterogeneous group of individuals varies. The actual CRC risk depends on the number of family members affected and the age at diagnosis of any affected family member [6], and surveillance should be offered to these individuals based on their estimated CRC risk.

This Guideline provides an overview of the endoscopic management of individuals with LS. Furthermore, we aimed to define familial risk of CRC for those individuals at high risk for CRC to whom, therefore, surveillance should be offered. Since endoscopic management strategies for LS and familial risk of CRC vary widely, we aimed to gain consensus among European experts by using a Delphi process.

2 Methods

The ESGE commissioned this Guideline (Guideline Committee chair, J.v.H.) and appointed a Guideline leader (M.v.L), who invited the listed authors to participate in the project development. The key questions were prepared by the coordinating

ABBREVIATIONS

ADR	adenoma detection rate
CE	chromoendoscopy
CI	confidence interval
CRC	colorectal cancer
CT	computed tomography
ESGE	European Society of Gastrointestinal Endoscopy
FDR	first-degree relative
FIT	fecal immunochemical test
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HR	hazard ratio
HNPCC	hereditary non-polyposis colorectal cancer
LS	Lynch syndrome
MMR	mismatch repair
MRI	magnetic resonance imaging
OR	odds ratio
RR	relative risk
SIR	standardized incidence ratio
VCE	video capsule endoscopy
WLE	white-light endoscopy

team (M.v.L. and V.R.) and then approved by the other group members. The coordinating team established task force subgroups, each with its own leader and divided the key topics among those task forces (Appendix 1s; see online-only Supplementary Material).

The process of developing the Guideline included telephone conferences, meetings, and online and face-to-face discussions among the members from July 2018 until July 2019. Searches were performed in MEDLINE, Embase, and the Cochrane Library. Articles were selected through title and abstract screening followed by full-text screening. The results of the search were presented to all group members and consensus statements were created.

Evidence levels and recommendation strengths were assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [7]. Further details on the methodology of ESGE guidelines have been reported elsewhere [8].

Since literature on familial risk of colorectal cancer and LS is limited, a Delphi process, usually consisting of two rounds, was used in order to obtain consensus [9]. All members, except for the research fellows, were asked to complete the online Delphi questionnaire in isolation, and responses were anonymized to prevent participants from influencing one another [10]. In each round, members were asked to rate all the statements with their level of agreement using a seven-point Likert scale: "Very strongly agree", "Strongly agree", "Agree", "Neither agree nor disagree", Disagree", "Strongly disagree", or "Very strongly disagree" [11]. If the statement was not within their area of expertise, participants could opt out. Secondly, participants were asked whether the statement was clear, and had the opportunity to make suggestions for improvement. After the Delphi round, all statements were discussed and adjusted, if necessary, during a face-to-face meeting. Consensus was reached when ≥80 % of the group members had voted either "Very strongly agree", "Strongly agree", or "Agree" during the second Delphi round. Third and fourth Delphi rounds were organized only for the statements regarding advanced imaging.

In July 2019, a draft prepared by M.v.L. and V.R. was sent to all group members. After the agreement of all group members had been obtained, the manuscript was reviewed by a member of the ESGE Governing Board and an external reviewer, and was sent for further comments to the ESGE national societies and individual members. After this, it was submitted to *Endoscopy* for publication. This Guideline was issued in 2019 and will be considered for update in 2024. Any interim updates will be noted on the ESGE website: http://www.esge.com/esge-guidelines.html.

3 Lynch syndrome

3.1 Background

This part of the Guideline focuses on individuals with LS, defined as those with a constitutional pathogenic variant in one of the mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, *PMS2*, or deletions in the 3' region of the *EpCAM* gene. The key for identification of LS among CRC cases is testing for MMR deficiency on the tumor tissue, and this is currently the strategy of choice in all individuals diagnosed under the age of 70 years with CRC [12).

It is estimated that at the population level, the prevalence of LS is 1 in 279 (95 % confidence interval [CI] 192 – 493) [13]. Individuals with LS are at risk of early-onset CRC and have a high cumulative lifetime risk of CRC that ranges between 15 % and 70 % at age 70 [14 – 18]. The adenoma – carcinoma sequence seems to be accelerated, with a reported dwell time as low as 35 months compared with the 10 – 15 years in sporadic CRCs [17].

To prevent CRC development or to detect CRC at an early stage, colonoscopy surveillance in LS is essential. Regular colonoscopy surveillance in individuals with LS significantly reduced CRC incidence and associated mortality by more than 50 % [18, 19]. Individuals with LS also have a higher risk of other gastrointestinal malignancies for which endoscopic surveillance may be an option.

3.2 Colonoscopy surveillance

3.2.1 Quality standards

RECOMMENDATION

ESGE recommends that individuals with Lynch syndrome should be followed in dedicated units that practice monitoring of compliance and endoscopic performance measures.

Strong recommendation, low quality evidence, level of agreement 100 %.

Colonoscopy reduces the incidence and mortality of CRC [18 – 21] in individuals with LS. Post-colonoscopy CRCs are defined by the World Endoscopy Organization as cancers appearing after a colonoscopy in which no cancer is diagnosed, and encompass both interval cancers and non-interval cancers [22]. Interval cancers are those detected before the next recommended surveillance examination. Non-interval cancers are subdivided into cancers detected at (type A) or after (type B) a recommended surveillance interval or when no subsequent surveillance interval was recommended (type C), up to 10 years following the colonoscopy.

Epidemiological studies have reported that the cumulative CRC rate at 70 years among individuals with LS undergoing colonoscopy surveillance can be as high as 46 % among *MLH1*, 35 % among *MSH2*, 20 % among *MSH6*, and 10 % among *PMS2* pathogenic mutation carriers [15]. Some authors postulate that some post-colonoscopy CRCs in LS may emerge from MMR-deficient crypt foci without a polypoid growth pattern and therefore can be difficult to detect by colonoscopy [23]. However, retrospective descriptive studies evaluating post-colonoscopy CRC showed associations with incomplete examination [24 – 28], inadequate bowel preparation [24 – 27, 29], and possible incomplete resection of lesions [24, 30]. Moreover, recommendations on the interval between colonoscopies are not always adhered to and the lack of compliance has been

reported as another important factor in post-colonoscopy CRC [26–28, 31–38].

Furthermore, high miss rates for colorectal neoplasia (12 %–74 %) have been reported in several back-to-back colonoscopy studies [39–46]. Therefore, it can be concluded that high quality standards for colonoscopy are not always met in individuals with LS. However, the evidence regarding key performance indicators for colonoscopy in individuals with LS is limited [24–30].

Adherence to the recommended surveillance intervals is important. Some studies have demonstrated that provision of genetic testing [37] and implementation of standardized surveillance programs [38, 47] improve compliance. National registries associated with surveillance programs offering regular endoscopic surveillance through the use of reminders show high compliance rates [26–28, 31–36, 38].

For these reasons, individuals with LS should be followed in dedicated units (national registries, genetic counseling centers, or high-risk cancer centers) where endoscopic surveillance recommendations are monitored in order to improve adherence and to audit the quality of the surveillance program. It should be emphasized that surveillance colonoscopies in individuals with LS should meet the ESGE quality criteria for colonoscopy [48, 49].

3.2.2 Symptomatic LS individuals

RECOMMENDATION

ESGE recommends performance of endoscopy earlier than the planned surveillance procedure if an individual with LS is symptomatic.

Strong recommendation, low quality evidence, level of agreement 100 %.

This Guideline discusses surveillance intervals for asymptomatic individuals with LS. However, individuals having specific complaints, such as anemia, rectal blood loss, or abdominal pain, should be seen by a gastroenterologist and endoscopies might be indicated at an earlier point in time.

3.2.3 Colonoscopy surveillance: starting age

RECOMMENDATION

ESGE recommends starting colonoscopy surveillance at the age of 25 years for *MLH1* and *MSH2* mutation carriers and at the age of 35 years for *MSH6* and *PMS2* mutation carriers.

Strong recommendation, moderate quality evidence, level of agreement 100 %.

The appropriate age to start surveillance in order to achieve optimal efficacy has not been established in clinical trials. Thus, the starting age is estimated on the basis of the individual risk of developing advanced adenomas and CRC at a certain age. It has been demonstrated that both the risk of developing early-onset CRC, as well as the overall CRC risk depend on the MMR gene involved [14, 16, 28, 50–53]. In a recent international prospective cohort study including over 3000 unaffected mutation carriers, the cumulative CRC incidence was 46 %, 43 %, 15 %, and 0 % for carriers of *MLH1*, *MSH2*, *MSH6*, and *PMS2* pathogenic variants, respectively, after a mean follow-up time of 7.8 years [16]. Of note, carriers of pathogenic variants of the *MSH6* and *PMS2* gene had no CRC before 40 years of age. Other studies confirmed that the age of CRC onset in carriers of pathogenic variants of the *MSH6* and *PMS2* genes was delayed by 10 years compared to carriers of *MLH1* and *MSH2* pathogenic variants [52, 53], with very low CRC risk before the age of 30 years [51, 52]. Similarly, there was an extremely low risk of developing advanced adenoma (mean number of neoplastic lesions for ages 20–29 years, 1.3 ± 0.5) or CRC (1 % in 5 years) before the age of 30 for carriers of pathogenic variants of the *MLH1* and *MSH2* genes [52, 53], with very high numbers needed to screen to prevent one CRC death [54]. It is important to take into consideration that, to prevent ascertainment bias, index cases are not included in the retrospective and prospective cohort studies. Mainly among index cases, carriers with a pathogenic MMR variant may present with CRC at a younger age than the proposed starting age for surveillance. However, in view of the cancer risks and the very high numbers needed to screen to detect one lesion at colonoscopy [17, 54] it seems justified to defer the start of colonoscopy surveillance to the age of at least 25 years for carriers of pathogenic variants of the *MLH1* and *MSH2* gene and 35 years for carriers of pathogenic variants of the *MSH6* and *PMS2* genes. A summary of the evidence is provided in **Table 1s** (Appendix 2, online-only Supplementary Material).

There is no evidence that colonoscopy prior to the age of the youngest CRC diagnosis in the family is beneficial; however it may be advised on an individual basis having fully counseled the individual about the risks and benefits of the procedure.

3.2.4 Colonoscopy surveillance interval

RECOMMENDATION

ESGE recommends a high quality surveillance colonoscopy every 2 years in asymptomatic individuals with Lynch syndrome.

Strong recommendation, moderate quality evidence, level of agreement 90 %.

RECOMMENDATION

ESGE recommends to repeat complete colonoscopy within 3 months in the case of a colonoscopy of suboptimal quality (poor bowel preparation or incomplete procedure).

Strong recommendation, moderate quality evidence, level of agreement 90 %.

Randomized controlled trials for surveillance in LS mutation carriers are unavailable; therefore we have to rely on retrospective or prospective observational studies that indirectly

compare rates of post-colonoscopy CRC and their stage distribution with different surveillance intervals. A summary of these studies is provided in **Table 2s**. Post-colonoscopy CRCs were observed irrespective of the 1-, 2-, or 3-year colonoscopy surveillance interval used in each of the published studies [14–17, 28, 50–55]. In a recent large international study involving 2747 carriers of pathogenic variants of the *MLH1*, *MSH2*, or *MSH6* genes, reporting on over 16 000 colonoscopies, no differences in post-colonoscopy CRC rates or CRC stage distribution were observed among three different surveillance policies used, in LS registries from Germany (1-year interval), the Netherlands (1–2-year interval), and Finland (2–3-year interval) [35]. Furthermore, in multiple studies the average time from the date of colonoscopy to CRC diagnosis was between 24 and 36 months, which may support intervals longer than 1 year [31, 32, 56]. Of note, overall survival rates in patients diagnosed with post-colonoscopy CRC within surveillance programs were excellent and exceeded 90 % [24, 27, 32, 36, 56, 57].

As the data on colonoscopy quality in the studies comparing different surveillance intervals were limited, as were the data on compliance to assigned surveillance intervals and the evidence for a stratified approach for the different constitutional pathogenic variants in the MMR genes, it seems justified to propose a uniform 2-year interval irrespective of the pathogenic variant.

The evidence for the increased risk for metachronous CRC in individuals with LS after polyp removal or CRC resection is not unequivocal [31, 32, 35, 58]. In a study from the Netherlands neither the presence of an adenoma, nor its characteristics were associated with an increased risk for CRC [32]. However, Engel et al. showed that a prevalent adenoma at index colonoscopy was actually associated with a higher cumulative CRC incidence [35]. Besides, it was suggested that incomplete removal of an adenoma might be a significant contributor to the risk of post-colonoscopy CRC [24]. In other studies the risk of developing a metachronous adenoma or CRC after surgery for CRC (segmental or subtotal colectomy) was relatively low, providing that surveillance was performed within 2 years [27, 58]. Awaiting further evidence, shortening surveillance intervals to less than 2 years should only be considered in special situations. Currently, limited data support a longer surveillance interval for carriers of a pathogenic variant of *MSH6* and *PMS2*, who do carry a lower cumulative CRC incidence. It has been suggested that *PMS2*-associated CRCs do have a distinct tumor biology, which may support a longer surveillance interval for *PMS2* carriers if the data are confirmed [59].

A high quality examination is considered to be one of the key factors for optimal effectiveness of surveillance colonoscopy, and therefore, surveillance colonoscopies in individuals with LS should meet the ESGE quality criteria for colonoscopy [24, 48, 49] (see also above). Perrod et al. evaluated a surveillance program that assigned surveillance intervals based on the quality of the previous colonoscopy (cleanness, completeness, and use of chromoendoscopy), and demonstrated an improvement in quality, a reduction in post-colonoscopy CRC, and increased detection of flat dysplasia [60]. So when suboptimal bowel preparation (Boston Bowel Preparation Scale <2 in one of the colon segments) is found or the procedure is incomplete, colonoscopy should be repeated within 3 months before entering the 2-year surveillance period.

3.2.5 Colonoscopy surveillance: advanced imaging techniques

RECOMMENDATION

ESGE recommends the routine use of high-definition endoscopy systems in individuals with Lynch syndrome.
Strong recommendation, high quality evidence, level of agreement 100 %.

RECOMMENDATION

ESGE suggests the use of chromoendoscopy may be of benefit in individuals with Lynch syndrome undergoing colonoscopy; however routine use must be balanced against costs, training, and practical considerations.
Weak recommendation, moderate quality evidence, level of agreement 89 %.

In the literature, seven studies compared indigo carmine chromoendoscopy with white-light endoscopy (WLE) in individuals with LS (**Table 3As**) [39–41, 44, 45].

Three small single-center studies with a back-to-back design and standard-definition endoscopes demonstrated that chromoendoscopy was superior to WLE, reporting a WLE adenoma miss rate ranging from 61 % to 74 % [39, 40, 45]. Very recently another back-to-back multicenter study, in which the second pass was performed by a different gastroenterologist, again demonstrated superiority of standard-definition chromoendoscopy over standard-definition WLE, reporting an adenoma miss rate of 52 % [41]. However, all these studies are methodologically flawed as the back-to-back design entails that the second pass is always done with chromoendoscopy, which may have led to an overestimation of the effect of chromoendoscopy over WLE.

Three parallel trials with a control arm are available [44, 61, 62]. A small back-to-back study with two arms, namely WLE followed by either intensive inspection of over 20 minutes or WLE-chromoendoscopy, showed no significant difference in adenoma miss rate between the two strategies [44]. Recently, two large multicenter randomized parallel trials did not demonstrate benefit for chromoendoscopy compared to WLE [61, 62]. A Dutch study in 246 individuals with constitutional pathogenic variants in one of the MMR genes showed no difference in neoplasia detection rate between chromoendoscopy and WLE, both at baseline colonoscopy (27 % versus 30 %, respectively, P = 0.56), and at the 2-year follow-up colonoscopy (26 % versus 28 % respectively, P = 0.81) [61]. A multicenter non-inferiority Spanish study in 256 carriers with a constitutional pathogenic variant in one of the MMR genes showed similarly high adenoma detection rates (ADRs), for high-definition WLE and chromoendoscopy (ADR 28.1 %, 95 %CI 21.1 %–36.4 % versus 34.4 %, 95 %CI 26.4 %–43.3 %, respectively; P = 0.28) [62]. However,

there was a non-statistically significant trend regarding the detection rate of flat adenomas in favor of pancolonic chromoendoscopy (24.2 %, 95 %CI 17.1 % – 32.6 %) compared with WLE (14.8 %, 95 %CI 9.2 % – 22.2 %) (P = 0.06). Of note, only high-level detector endoscopists were involved in both studies, and in the second one all the endoscopes were high-definition.

Virtual chromoendoscopy was superior to WLE in two back-to-back studies in individuals with LS (**Table 3Bs**) [42, 43]. On the other hand, virtual chromoendoscopy was inferior to dye-based chromoendoscopy in two back-to-back studies [40, 63]. Thus, at present the role of virtual chromoendoscopy in the surveillance of individuals with LS is not yet well established.

Comment: Utility of chromoendoscopy In the past 10 years, detection rates for colorectal lesions have gradually increased, because of improvements in endoscopic technology as well as the implementation of quality indicators in screening colonoscopy. The incremental effect of chromoendoscopy over WLE for detecting adenomas in LS may have been overestimated because of the methodological limitations in most previous studies. In fact, in back-to-back studies WLE ADRs ranged from 9 % to 23 % and in the two recent parallel studies WLE ADRs ranged from 26 % to 28 %. This might imply that a thorough inspection by high-level detector endoscopists and the use of high-definition endoscopes might outweigh the advantageous effect of chromoendoscopy. Nevertheless, for low-level detector endoscopists or when high definition is not available, the use of chromoendoscopy still remains advisable.

3.3 Gastric surveillance

RECOMMENDATION

ESGE does not recommend routine gastric surveillance in individuals with Lynch syndrome.

Strong recommendation, low quality evidence, level of agreement 100 %.

RECOMMENDATION

ESGE suggests (non-invasive) testing for *Helicobacter pylori* in individuals with Lynch syndrome.

Weak recommendation, moderate quality evidence, level of agreement 90 %.

Individuals with LS have a cumulative lifetime risk ranging from 0.7 % to 13 % of developing gastric cancer [64]. Data show a trend towards an increased prevalence of gastric cancer for carriers of pathogenic variants of the *MLH1* or *MSH2* genes compared with carriers of a pathogenic variant of the *MSH6* gene [64]. Most of the gastric cancers were diagnosed in individuals older than 45 years, with reported median ages ranging from 55 to 64 years (overall ranges 27 – 85) [65 – 68]. Among all individuals with LS who developed gastric cancer, 0 – 31 % had a family history of gastric cancer [65 – 68].

There are no RCTs evaluating the effect of gastric surveillance in individuals with LS, but three observational studies have been published [68 – 70] (**Table 4s**). In two retrospective observational cohort studies about 30 % of the individuals with LS had undergone an esophagogastroduodenoscopy [68, 69]. In a Turkish study, 19.1 % of the mutation carriers had *H. pylori* gastritis, atrophic gastritis, or gastrointestinal metaplasia [69]. A positive family history was not significantly associated with having abnormal esophagogastroduodenoscopy findings [69]. In a Dutch study, esophagogastroduodenoscopy revealed gastric cancer in 8 individuals (6.1 %), biopsies confirmed inflammation in 23 (17.4 %), intestinal metaplasia in 4 (3.0 %), and no pathological or endoscopic abnormalities in 97 (73.5 %) [68]. Of these individuals with LS, 20 % were *H. pylori*-positive [68]. In a non-randomized comparative Finnish study, a single esophagogastroduodenoscopy was performed both in carriers of a pathogenic variant in the *MLH1* gene (median age 49 years) and in mutation-negative family members (median age 51 years) [70]. In individuals with a pathogenic variant of the *MLH1* gene, *H. pylori* infection was observed in 26 %, atrophy in 14 %, and intestinal metaplasia in 14 %; these findings were similar to those in the control group [70]. So in view of the apparently limited gastric cancer risk in individuals with LS and lack of evidence regarding benefit of gastric surveillance, such surveillance is not routinely recommended.

A meta-analysis including 7 randomized controlled trials in the general population showed that *H. pylori* eradication reduces gastric cancer incidence by 35 % [71]. Furthermore, population screening for *H. pylori* has been found to be cost-effective [72]. Although no direct evidence is present, one could assume that individuals with LS would also benefit from *H. pylori* screening and eradication.

3.4 Small-bowel surveillance

RECOMMENDATION

ESGE does not recommend routine small-bowel surveillance in individuals with Lynch syndrome.

Strong recommendation, moderate quality evidence, level of agreement 100 %.

In individuals with LS, the cumulative risk of developing small-bowel cancer before the age of 70 years ranged from 0.6 % (95 %CI 0.1 % – 1.3 %) to 7.2 % (95 %CI 1.5 % – 12.9 %) in carriers of a pathogenic variant of the *MLH1* gene [64]. There is a 100-fold increase in the risk of developing small-bowel cancer in individuals having LS compared with the general population [73]. The incidence of small-bowel cancer in individuals with LS was highest among carriers of pathogenic variants of the *MLH1* or *MSH2* genes and most often seen in males (57 % – 79 %) [74 – 76]. The median age of diagnosis varied from 39 to 53 years [77 – 83]. The majority of the small-bowel cancers were located in the duodenum or jejunum [77 – 82] and histology showed adenocarcinoma in 81 % to 100 % of the cases [79, 81].

Two studies have investigated the use of video capsule endoscopy (VCE) in asymptomatic carriers of a pathogenic vari-

ant and observed small-bowel neoplasia prevalences of 1.5 % and 8.6 % [84, 85] (**Table 5s**). In a Dutch study including 200 individuals with LS, one patient was diagnosed with a T2N0Mx duodenal cancer 7 months after a negative VCE [84]. The other study, among 35 individuals with LS, reported no small-bowel cancers after a mean follow-up of 40 months [85]. Furthermore, 70 % of individuals had a false-positive finding, resulting in unnecessary invasive secondary procedures such as balloon-enteroscopy or magnetic resonance imaging (MRI) enteroclysis [84]. The second study compared VCE with computed tomography (CT) enteroclysis and showed that CT enteroclysis missed two of the three cases of small-bowel neoplasia [85]. Another study demonstrated that repeat VCE after a mean interval of 2.2 years in 78 % of the asymptomatic individuals with LS resulted in no detection of small-bowel neoplasia [86].

In a recent French prospective study among 154 individuals with LS, that evaluated the yield of esophagogastroduodenoscopy performed every 3 – 4 years on the occasion of a colonoscopy, a total of 3 duodenal adenocarcinoma cases and 4 duodenal adenoma cases were found [87]. Of the 7 individuals with duodenal neoplasia, 3 were carriers of a pathogenic variant in the *MSH2* gene.

Currently, the reported prevalence of small-bowel neoplasia among asymptomatic individuals with LS is low and the benefit of small-bowel surveillance is not clear; routine surveillance of the small bowel is not recommended. A large prospective study is necessary to determine the value of surveillance esophagogastroduodenoscopy for both the gastric and duodenal cancer risk in individuals with LS.

4 Familial risk of colorectal cancer

4.1 Definition

In about 20 % – 30 % of individuals diagnosed with CRC, a familial history of CRC is reported [3]. The CRC risk in individuals with a family history of CRC depends on the number of affected family members and the age of diagnosis of CRC in the family. According to various guidelines, individuals with a family history of CRC should undergo more intensive surveillance strategies than the general population, starting at an earlier age [88 – 90]. However, definitions of who should undergo more intensive surveillance show wide geographic variation.

RECOMMENDATION

ESGE recommends definition of familial risk of colorectal cancer as the presence of at least two first-degree relatives with colorectal cancer or at least one first-degree relative with colorectal cancer before the age of 50 years.

Strong recommendation, moderate quality evidence, level of agreement 92 %.

Five meta-analyses have evaluated the influence of family history on relative and absolute risk of CRC [91 – 95]. In a recently published systematic review and meta-analysis, Wong et al. found that individuals having at least one first-degree relative (FDR) with CRC had a lower increased risk of developing CRC (relative risk [RR] 1.76, 95 %CI 1.57 – 1.97; $P<0.001$) [91] than previously reported risk estimates (RRs ranging from 2.24 to 2.26) [92 – 94]. This lower estimate of the risk of developing CRC among FDRs was confirmed by a recent meta-analysis that grouped risk estimates by study design; it reported a pooled RR among cohort studies of 1.67 (95 %CI 1.52 – 1.82) and a pooled RR among case–control studies of 2.22 (95 %CI 2.00 – 2.48) in the presence of at least one FDR with CRC (**Table 6s**) [95]. A higher pooled RR was found in the presence of two or more FDRs, with pooled RRs of CRC of 2.40 (cohort) and 2.81 (case–control) [95]. When CRC was diagnosed before the age of 50 years in an FDR, the pooled RRs were 3.26 (95 %CI 2.82 – 3.77; cohort) and 3.57 (95 %CI 1.07 – 11.85; case–control) [95]. Since cohort studies are less likely to contain recall bias, the authors considered the summary estimates of cohort studies to be closer to the truth. These RRs corresponded to a cumulative absolute risk for CRC, at 85 years in Western Europe, of 4.8 % (95 %CI 2.7 % – 8.3 %) for those with one affected FDR, increasing to 8.2 % (95 %CI 6.1 % – 10.9 %) for those with two or more affected FDRs, and of 11 % (95 %CI 9.5 % – 12.4 %) when there was an affected FDR below the age of 50 years at diagnosis [95]. Individuals having at least one second-degree relative with CRC showed no clinically significant increased risk of developing CRC with a pooled RR among cohort studies of 1.09 (95 %CI 1.03 – 1.15).

Previously published guidelines have reported that familial risk of CRC should be defined as having a relevantly increased risk of developing CRC, often set at two to three times the general population risk [89, 96, 97]. Therefore ESGE proposes to define familial risk of CRC as being present in those having two or more FDRs with CRC or one FDR with CRC below the age of 50 years.

4.2 Surveillance in familial risk of CRC

4.2.1 Protective effect

RECOMMENDATION

ESGE recommends colonoscopy surveillance in first-degree relatives of CRC cases in families that fulfill the definition of familial risk of colorectal cancer.

Strong recommendation, moderate quality evidence, level of agreement 100 %.

Only two studies have addressed the protective effect of colonoscopy in individuals with at least one FDR with CRC [98, 99] (**Table 7s**). Dove-Edwin et al. registered the outcomes of screening colonoscopy in a clinic for high-risk families during 16 years, with the aim of determining to what extent individuals with various family histories of CRC (specified in **Table 7s**) benefit from colonoscopic surveillance [98]. Among 1678 individuals, the observed number of CRC cases was lower than the expected number of cases in the absence of surveillance, with a reduction in CRC incidence of 80 % and a reduction of CRC mor-

tality of 81 %. However, this study has several limitations such as the lack of a robust control group as well as the possibility of underreporting of CRC cases since the study relied on UK National Health Service (NHS) registry data. In the second study, Hatfield et al. described the findings of screening colonoscopy in a cohort of 20 families and 332 individuals with type X familial risk of CRC (families fulfilling the Amsterdam criteria, but with MMR-proficient tumors), including 162 individuals receiving colonoscopy surveillance and 162 not receiving surveillance. In this study they found that surveillance colonoscopy reduced both CRC incidence (men, RR 0.27 [95 %CI 0.10 – 0.71]; women, RR 0.19 [95 %CI 0.07 – 0.48]) and CRC-related mortality (men, RR 0.38 [95 %CI 0.15 – 0.94]; women, RR 0.19 [95 %CI 0.07 – 0.49]) [99]. This study also had several limitations such as the non-randomized allocation of the intervention, historical controls, retrospective data collection, and incomplete medical records.

In summary, in individuals with a significant family history of CRC, colonoscopy surveillance seems to reduce CRC incidence and mortality; however, more studies are needed in order to know to what extent.

4.2.2 Surveillance intervals

RECOMMENDATION

ESGE recommends a 5-year surveillance interval for colonoscopy after a normal high quality baseline examination in the setting of familial risk of colorectal cancer.

Strong recommendation, low quality evidence, level of agreement 83 %.

RECOMMENDATION

ESGE recommends that follow-up after polyp excision in individuals with familial risk of colorectal cancer should follow the surveillance guidelines for the general population.

Strong recommendation, moderate quality evidence, level of agreement 92 %.

Previous guidelines recommend an interval between colonoscopies of 5 years in those with a family history of CRC [88, 89]. Different studies have analyzed the risk of developing CRC or advanced neoplasia after a negative colonoscopy among individuals with at least one FDR with CRC (excluding individuals with LS). The vast majority of these studies do not show any increase in risk of metachronous neoplasia after colonoscopy (**Table 7s**).

In a population-based case–control study, Brenner et al. showed that the risk of developing CRC is low up to 20 years after a negative colonoscopy [100]. The odds ratio (OR) for developing CRC for individuals with at least one FDR with CRC was 0.66 (95 %CI 0.27 – 1.58) within 5 – 9 years after a negative colonoscopy and 0.47 (95 %CI 0.14 – 1.59) more than 10 years after a negative colonoscopy. The protective effect in individuals without a family history was higher, with an OR of 0.23 (95 %CI 0.15 – 0.36) within 5 – 9 years and 0.33 (95 %CI 0.23 – 0.48) for more than 10 years after a negative colonoscopy. Furthermore, Samadder et al. performed an observational cohort study including 131 349 individuals and found that, compared with the general population of Utah, the standardized incidence ratio (SIR) for CRC was consistently low until 10 years after a negative colonoscopy, but in individuals with at least one FDR with CRC this risk reduction only extends until 5 years after a negative colonoscopy [101]. In the latter group a first negative colonoscopy was associated with a statistically significant reduced incidence of CRC for only the first 5 years (SIR 0.39, 95 %CI 0.13 – 0.64); after this 5-year interval, the negative colonoscopy was no longer protective for CRC (SIR 0.74, 95 %CI 0.32 – 1.16). However, this study has some limitations, with the very small numbers of observed CRC cases after 5 years limiting the statistical power of the results.

Surveillance after polyp excision According to the studies evaluating the yield of colonoscopy after adenoma removal, there is no evidence that supports shortening the surveillance interval in individuals with a family history of CRC (**Table 7s**). There is only one randomized controlled trial comparing different colonoscopy intervals (6 versus 3 years) in people with a family history of CRC [102]. In this study that included 528 individuals (with one affected FDR aged < 50 years or two affected FDRs) with 0 – 2 adenomas at baseline, Hennink et al. found no significant difference in the proportion of individuals with advanced adenomas at the first follow-up examination at 6 years (6.9 %) versus 3 years (3.5 %), with a crude OR of 2.0 (CI 0.9 – 4.7). The authors concluded that, in view of the relatively low rate of advanced adenomas at 6 years and the very low risk of CRC (only one CRC was detected in the 3-year arm), a 6-year surveillance interval should be considered as appropriate.

Based on the limited evidence, a 5-year surveillance interval is advised after a negative colonoscopy for individuals with familial risk of CRC. Furthermore, surveillance guidelines for average-risk populations after adenoma removal can be followed.

4.2.3 Starting age for colonoscopy surveillance

RECOMMENDATION

ESGE recommends starting colonoscopy surveillance at the age of 40 years when there is a familial risk of colorectal cancer.

Strong recommendation, moderate quality evidence, level of agreement 92 %.

The majority of guidelines recommend starting colonoscopy screening in individuals with a family history of CRC (mostly defined as an affected FDR aged less than 60 years or two affected FDRs) at 40 years of age or 10 years earlier than the age of the youngest index case [88, 89]. The rationale for age 40 years initially comes from the study of Fuchs et al. [103] (**Table 8s**). In this study, for 40-year-old individuals with a family history of CRC, the cumulative incidence of CRC was comparable to that

of 50-year-old individuals without a family history. Hemminki & Li in a large prospective cohort study found similar results, reporting an SIR of 2.01 (95 %CI 1.71 – 2.33) for individuals aged 40 – 49 years at diagnosis, with at least one affected FDR with CRC, compared with an SIR of 1.18 (95 %CI 0.99 – 1.39) for individuals over 50 years at diagnosis [104]. Other studies found an increase of CRC incidence and mortality at an age younger than 50 years in relatives of CRC patients [105 – 107]. CRC incidence was increased with an RR of 2.07 (95 %CI 0.99 – 3.80) for relatives aged 50 years and less [105]. The CRC standardized mortality ratio ranged between 12.5 (95 %CI 1.52 – 45.14) and 3.66 (95 %CI 1.47 – 7.55) in individuals between 35 and 55 years [106]. Additionally, a case–control study found that individuals younger than 50 years had a significantly higher relative risk of CRC compared to those older than 50 years of age (RR < 50 years 8.54 [95 %CI 1.9 – 39] vs. RR ≥ 50 years 1.87 [95 %CI 1.4 – 2.8]) [107]. This is confirmed by another case–control study including 18 208 CRC patients from a cancer registry that did find an increased risk for FDR at younger ages (< 50 years), and although FDRs in both age groups (< 50 and > 50 years) were consistently at increased cancer risk, FDRs of young-onset CRC cases (< 40 years old) had the highest familial risk when they were younger than 50 years of age (HR 7.0 [95 % CI 2.86 – 17.09]) [108].

There is no evidence that colonoscopy 10 or 5 years prior to the youngest CRC diagnosis in the family is beneficial; however it may be advised on an individual basis having fully counseled an individual about the risks and benefits of the procedure.

Based on these results, we do advise to start colonoscopy surveillance at the age of 40 years for individuals with familial risk of colorectal cancer.

On the other hand, all these results come from observational studies and are based on relative risk estimates. In a recent systematic review and meta-analysis, the absolute risk estimates for CRC at different ages were calculated [95]. The results showed that the risk of CRC is less than 1 % in the next 10 years for 40-year-old individuals fulfilling the criteria for familial risk of CRC, and moves to close to 2 % in the next 10 years for these individuals at 50 years. In the near future when more evidence is available, these results may support starting surveillance for individuals with familial risk of CRC at 50 years.

Comments

This Guideline provides a framework for the endoscopic management of individuals with LS, and proposes a definition of familial risk of colorectal cancer to identify the group of individuals in whom colonoscopy surveillance is justified, as they have a high risk (RR > 2.5) for developing CRC.

Evidence is limited in several areas and further research is needed. Such areas include, among others: evaluation of the optimal starting ages and intervals for colonoscopy surveillance among individuals with LS and those with familial risk of CRC; the yield of stomach and small-bowel surveillance in LS; and the yield of fecal immunochemical test (FIT) screening among individuals at familial risk of CRC.

Disclaimer

The legal disclaimer for ESGE guidelines [8] applies to this Guideline.

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Competing interests

E. Dekker was an advisory board chair for Cancer Prevention Pharmaceuticals (2019) and is a Co-Editor for *Endoscopy*. M.F. Kaminski has received speaker's, teaching, and consultancy fees from Olympus (2017 to present) and speaker's and teaching fees, and a loan of equipment from Fujifilm (2019). H. Neuman has provided consultancy services to Fujifilm and Pentax (2012 to present). M. Pellisé has received consultancy fees from Norgine Iberia (2019), speaker's fees from Casen Recordati (2017 – 2019), Olympus (2017), and Jansen (2018), and is a Co-Editor for Endoscopy; her department has received an equipment loan from Fujifilm (2017 to present) and a research donation from Fujifilm (2019). J.E. van Hooft has received lecture fees from Medtronics (2014 – 2015) and Cook Medical (2019), and consultancy fees from Boston Scientific (2014 – 2017); her department has received research grants from Cook Medical (2014 – 2018) and Abbott (2014 – 2017). F. Balaguer, R. Jover, A. Latchford, L. Ricciardiello, V.H. Roos, M. Rupińska, J.-C. Saurin, P.J. Tanis, M. E. van Leerdam, and A. Wagner have no competing interests.

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Supplementary material: Endoscopic management of Lynch syndrome and of familial risk of colorectal cancer: ESGE Guideline

Appendix 1s: Topics and key questions

1. Statements regarding Lynch syndrome	**Task forces (leads in bold)**
What are the quality standards for colonoscopy in Lynch syndrome patients?	**Monique van Leerdam/ Victorine Roos**
What is the appropriate age to start colonosocpy surveillance in Lynch syndrome patients?	Maria Pellisé
What is the optimal interval of colonoscopy surveillance in Lynch syndrome patients?	Michal Kaminski/ Maria Rupinska
What is the role of advanced imaging techniques in colonoscopy surveillance in Lynch syndrome patients?	
What is the role of gastric surveillance (including *H. Pylori* eradication) in Lynch syndrome patients?	
Is there a role for small-bowel surveillance in Lynch syndrome patients?	
2. Statements regarding familial colorectal cancer	
What is the influence of family history on relative and absolute risk of developing CRC?	**Rodrigo Jover**
Does colonoscopy reduce the CRC incidence and/or mortality in people with family history of CRC?	Monique van Leerdam/ Victorine Roos
What is the optimal time interval for screening colonoscopies in people with family history of CRC?	Evelien Dekker
What is the optimal age to start screening colonoscopy in people with family history of CRC?	

Appendix 2s: Summary tables

Table 1s. Summary table: Starting age for colonoscopy surveillance in Lynch syndrome

First Author [Ref in Guideline]	Year of publication	Study design	Study sample and mutation distribution	Male/ female ratio	Age	Intervention	Comparison	Follow-up time	Outcomes: cumulative CRC risk	Outcomes: CRC risk by age	Index case
Hendriks [51]	2004	Register study	146 MSH6	59/87	NR	NR	MLH1/ MSH2 mutation carriers	NR	Mean CRC risk: MLH1; MSH2; MSH6 At 30 years, men: 4.1% (0.1-7.9); 2.0% (0-4.4); 1.7% (0-5.0) At 50 years, men: 31% (19-41); 39% (28-48); 63% (49-73) At 70 years, men: 65% (39-80); 63% (49-73); 69% (42-83) At 30 years, women: 4.3% (0.9-7.7); 0%; 0% At 50 years, women: 26% (17-34); 30% (18-40); 10% (2.4-17) At 70 years, women: 53% (33-66); 68% (43-82); 30% (12-44)	The mean age at CRC diagnosis males; females: MLH1: 43 years; 43 years. MSH2: 44 years; 44 years. MSH6: 55 (26-84) years; 57 (41-81) years.	Included
Plaschke [52]	2004	Register study	396 MSH6	NR	NR	Colonoscopy surveillance every 1-2 years	1579 MLH1/ MSH2 mutation carriers	NR	Frequency CRC: MSH6: 61 MLH1/MSH2: 563	Median age of CRC onset: MSH6: 54 (51-56) years MLH1/MSH2: 44 (43-45) years	Included
Ramsoekh [14]	2009	Retrospective cohort study	70 MLH1, 67 MSH2, 109 MSH6.	92/154	At the time of mutation analysis: mean 49± 16 years	Colonoscopy surveillance in 194/246 MMR mutation carriers	NA	Mean 7±4 years	At age 70 years males; females: MLH1: 78%; 57% MSH2: 57%; 52% MSH6: 54%; 30%	Median age of CRC onset: males; female: MLH1: 45 (33-63) years; 50 (25-79) years MSH2: 43 (20-51) years; 44 (29-82) years MSH6: 48 (32-84) years; 53 (34-61) years	Included

Vasen [28]	2010	Retrospective cohort study	290 MLH1, 328 MSH2, 127 MSH6.	308/437	At start evaluation: mean 42 (16-82) years	Surveillance colonoscopy every 1-2 years	NA	Mean 7.2 (0.4-13.7) years	All MMR mutation carriers: 6% (2.7-8.7) after the 10-year follow-up period. MLH1: 19/290 (6.6%) MSH2: 13/328 (4.0%) MSH6: 1/127 (0.8%)	CRC incidence males and females: <40 years: 11/337 (3.3%) ≥40 years: 22/408 (5.4%)	Excluded
Edelstein [17]	2011	Retrospective cohort study	30 MLH1, 24 MSH2.	21/33	At first colonoscopy: mean 39.5±10.8 years	Colonoscopy surveillance with interval of 1.7 ±1.2 years	NA	Mean 9.3 years	NR	Mean numbers of neoplastic lesions: 20-29 years: 1.3±0.5 30-39 years: 1.8±1.4 40-49 years: 2.2±1.8 50-59 years: 3.5±2.9 60-69 years: 5.3± 5.1 70–79 years: 7.6±6.8	Excluded
Lee [58]	2013	Retrospective cohort study	16 MSH6, 7 PMS2	NR	NR	NR	NA	NR	NR	Mean age at CRC diagnosis: 48.5 (32-70) years in MSH6 and 40.7 (22-57) years in PMS2.	Included
Jenkins [54]	2015	Meta-analysis	508 MLH1 families, 606 MSH2 families.	NR	NR	NR	NA	NR	NR	CRC incidicence males; females: 20-29 years: 1.4%; 1.0% 30-39 years: 4.8%; 3.3% 40-49 years: 7.6%; 6.2% 50-59 years: 14.0%; 8.7% 60-69 years: 9.0%; 6.3% 70-79 years: 7.6%; 5.4%	Excluded
Sanchez [53]	2017	Retrospective study of prospectively observed data	449 MLH1, 371 MSH2, 197 MSH6, 68 PMS2.	478/630	Mean age at inclusion was 45.2+15.	Colonoscopy surveillance	NA	Mean 67.5±57.8 months	At age 70 years: MLH1: 25.6% (13.2-38.2) MSH2: 22.1% (11.3-35.1) MSH6: 6.3% (0-12.8) PMS2: 25.6% (13.2-38.2)	NR	Excluded
Ten Broeke [50]	2018	Multicenter, register study	513 PMS2	NR	NR	NR	General population	NR	At age 80 years males; females: PMS2: 13% (7.9-22); 12% (6.7-21%). General population: 6.6%; 4.7%.	Males <40 years: HR 6.51 (2.03-20.9) Males >70 years: HR 1.70 (0.89-3.24) Females <40 years: HR 6.48 (2.24-18.8) Females >70 years: HR 2.23 (1.21-4.12)	Excluded
Lamba [55]	2019	Prospectively maintained national database	98 MLH1, 159 MSH2, 103 MSH6, 21 PMS2.	NR	NR	Colonoscopy surveillance every 1-2 years from age 25	NA	Median 4.43 (1-28) years	All MMR mutation carriers: 2.49% (95%CI 1.18-5.23) at 5 years of surveillance. At age 70 years males and females: MLH1: 17.7% MSH2: 17.8% MSH6: 8.5% PMS2: 0	Mean age at CRC diagnosis: 54 years, 55.5% female.	Excluded

Moller [15,16]	2017; updated in 2018	Multicentre prospective study	1473 MLH1, 1060 MSH2, 462 MSH6 and 124 PMS2.	885/1057	At inclusion: mean 41 to 55 years	Colonoscopy surveillance	NA	Mean 7.8 years	MLH1: 46% MSH2: 35% MSH6: 49% PMS2: 10%	CRC incidence males and females: MLH1; MSH2; MSH6; PMS2 At 40 years: 12.7% (8.6-16.9); 8.9% (4.0-13.7); 0; 0 At 50 years: 25.0% (20.0-30.0); 19.4% (13.0-25.8); 1.8% (0.0-5.4); 0 At 60 years: 34.6% (28.9-40.3); 27.1% (19.9-34.3); 5.6% (0.0-11.9); 0 At 70 years: 40.1% (33.5-46.7); 40.8% (31.6-50.1); 15.0% (3.3-26.6); 0 At 75 years: 45.8% (37.8-53.9); 43.0% (33.2-52.8), 15.0% (3.3-26.6), 0	Excluded

Legend. NR, Not reported; CRC, colorectal cancer; MMR, mismatch repair; NA, Not Applicable.

Table 2s. Summary table: Colonoscopy surveillance intervals in Lynch syndrome

First author [Ref. in Guideline]	Year of publication	Study design	Study sample and mutation distribution	Male/female per subgroup	Age (mean±SD, or median [range]) per subgroup	Intervention: colonoscopy interval	Comparison	Outcome/ Findings
Jarvinen [18]	2000	Prospective, controlled non-randomized trial	252 at-risk members of 22 families with HNPCC.	Surveillance group: 73/60. Non-surveillance group: 59/60.	Age at the beginning of the study: Surveillance group: 38.1±10 years. Non-surveillance group: 38.8±12 years.	Colonoscopy screening every 3 years	No surveillance	Surveillance group: CRC incidence 8 (6%) overall, CRC reduction rate of 62%. CRC rate mutation positive subjects: 18%. CRC related deaths: 0. Overall death rates: 10 and 4 in mutation- positive subjects. Non-surveillance group: CRC incidcence 19 (16 %, P= 0.014). CRC rate mutation positive subjects: 41% (P= 0.02). CRC relates deaths: 9. Overall death rates: 26 subjects (p= 0.03) and 12 in mutation-positive subjects (P=0.05).
de Vos tot Nederveen Cappel [27]	2002	Retrospective registry based cohort study	199 LS with proven mutation. 1. No CRC before index colonoscopy. 2. After partial or segmental colectomy due to CRC.	NR	NR	Colonoscopy surveillance every 2-3 years. 1. No CRC before index colonoscopy.	2. After partial or segmental colectomy due to CRC	The 10-year cumulative risk of developing CRC: 1. No CRC before index colonoscopy: 10.5 (95 percent confidence interval, 3.8-17.2). 2. After partial colectomy due to CRC: 15.7 (95 percent confidence interval, 4.1-27.3) and 3.4 percent after subtotal colectomy. 12 CRC were detected in proven mutation carriers, 10 of them were early CRC (Dukes A&B). Number of CRCs within 1-2 years from colonoscopy: 4, number of CRCs beyond 2 years from colonoscopy: 8.

de Jong [32]	2006	Retrospective cohort study	Registry: 110 families (45 MLH1, 53 MSH2, 12 MSH6), 666 proven or obligate mutation carriers. Study: 330 mutation carriers.	Registry: 324/342	NR	Until 1995: colonoscopy or sigmoidoscopy in combination with a barium enema every 2–3 years starting between 20 and 25 years of age. From 1995: colonoscopy every 1–2 years. Adenoma-group	Adenoma-free group	CRC diagnosis during surveillance: 41/330, 34(83%) diagnosed between 40 - 60 y/o. Mean age at diagnosis: 49.3 (26.1-66.2) years. 21/34 CRCs detected >2 years after the previous colonoscopy. If interval would be 1 year (for subjects aged 40– 60 years), an additional number of 8 CRC probably would have been detected at an earlier stage. All CRCs diagnosed 12 - 24 months after previous colonoscopy were already at Duke A and B stage. CRC incidence: 5/141 (3.5%) in the adenoma group vs 31/992 (3.1%) in the adenoma- free group.
Mecklin*	2007	Retrospective registry based cohort study	Cohort (n=420)	NR	Median age at beginning of surveillance: 36.0 (20-74) years.	Colonoscopy surveillance every 2-3 years	NA	The cumulative risk of adenoma by age 60: 68% (95% confidence interval [CI], 50%–80%) in men and 48% (95% CI, 29%–62%) in women. The estimated cumulative risk up to age 60 years for the development of cancer found as a result of surveillance at an interval of 2–3 years was 35% (95% CI, 16%–49%) in men and 22% (95% CI, 7%–34%) in women.
Stupart [57]	2009	Prospective cohort study	178 MLH1: Surveillance group: 129. Non-surveillance group: 49	Surveillance group: 58/71. Non-surveillance group: 26/23	Surveillance group: mean 33±12.2 years Non-surveillance group: 35±13.0 years	Colonoscopy every 2 years until age 30, annually thereafter.	Non surveillance	Surveillance group: CRC diagnosis 14⁄129 (11%). Earlier CRC stage than in the nonsurveillance group (P = 0.032). Death from CRC 3/129 (2%). Non-surveillance group: CRC diagnosis 13⁄49 (27%) (P = 0.019). Death from CRC: 6/ 49 (12%) (P = 0.021).
Engel [34]	2010	Prospective, multicenter, cohort study	HNPCC families (n=1126): CRC negative (n=402) veruss CRC positive (n=724). 1. MUT group: Pathogenic germline mutation in a mismatch repair gene (633 families): 222 MLH1, 337 MSH2, 63 MSH6, 11 not tested. 2. MSI group: Without mutation but with microsatellite instability (296 families). 3. MSS group: Fulfilled Amsterdam criteria without microsatellite instability (117 families).	Total: 558/568	Age at inclusion: 44.0 (37.0–53.9) years.	CRC negative: 1 year interval	CRC positive: 1 year interval	Cumulative age-dependent CRC risk: CRC negative group at 60 years: similar in the MUT and MSI groups (P = .80; 23.0% at the age of 60 years for the 2 groups combined; 95% confidence interval [CI], 14.8%–31.2%), significantly lower in the MSS group (1.8% at the age of 60 years; 95% CI, 0.0%–5.1%; MUT/MSI vs MSS, P = .01). CRC positive group at 60 years: 23.7% (95% CI, 14.5%–32.9%) to develop a metachronous CRC within 20 years after the first CRC. Median time between the CRCs detected through follow-up colonoscopy and the preceding colonoscopy was 11.3 months. Compliance: 81% of colonoscopies completed within 15 months.

Vasen [28]	2010	Retrospective cohort study	Lynch syndrome cohort (n=745): 290 MLH1, 328 MSH2, 127 MSH6. non-Lynch syndrome cohort (n=344).	Lynch syndrome cohort: 308/437. non-Lynch syndrome cohort: 157/187	Lynch syndrome cohort: Mean age at start evaluation: 42 (16-82) years. Non-Lynch syndrome cohort: Mean age at start evaluation: 47 (18-88) years.	1-2 year interval in Lynch syndrome	non-Lynch syndrome	Cumulative CRC risk : 6% after 10 years of follow-up. CRC: MSH6 1/127, MLH1 19/290, MSH2 13/328 (univariate analysis: HR, 0.74 (95% CIs: 0.52–1.04), P .08). In the multivariate analysis, these variables remain borderline.
Stuckless [36]	2012	Retrospective cohort study	Cohort (n=322): Screened: 152 MSH2 Non-screned: 170 MSH2	54/98	Age at screening: Male: 36 years Female: 38 years	1-2 year interval	No screening	Screened versus non-screened group: Males: Interval CRC 41 (27%), median time from last screening 1.7 years. Median age to CRC: 58 years versus 47 years (p<0.01). Median survival: 66 years versus 62 years (p=0.034). Females: Interval CRC 10 (15%), median time from last screening 2.1 years. Median age to CRC: 79 years versus 57 years (p<0.01). Median survival: 80 years versus 63 years (p<0.01).
Haanstra [24]	2013	Retrospective, multicenter registry study	Cohort: 2,101 registered relatives (about 70 % of them being proven carriers). In 29 LS patients (all proven mutation carriers), 31 interval cancers were detected within or at 24 months of previous colonoscopy between 1995 and 2011. 14 MLH1, 17 MSH2.	14/17	Age: 52.0 (34.9–73.3)years	Colonoscopy surveillance every 1-2 years starting at the age 20-25.	NA	Of all interval cancers, 77 % were at local stage (T1-3N0Mx), 39% had a previous CRC. In 3 patients (9%) with an incomplete previous colonoscopy, CRC was located in the unexamined colon. In 6/9 patients with an adenoma during previous colonoscopy, the cancer was detected in the same colonic segment as the previously removed adenoma. 16/31 interval CRCs had unreported bowel preparation.
Newton [26]	2015	Retrospective, multicenter registry study	Screened population (n=227): 85 MLH1, 119 MSH2, 21 MSH6, 2 PMS2. Unscreened population (n=689).	NR	NR	Colonoscopy at least every 2 years from the age of 25.	Unscreened population.	Cumulative incidence of CRC to the age of 70: Screened population: 25% (95% CI 17–32%) in the surveillance population. Unscreened population: 81% (95% CI 78–84%) (P < 0.0001). Screened population: CRC diagnosis 19 (8.4%) after median surveillance of 4.4 years (8 among patients who had no prior CRC). All CRCs diagnosed within 2 years were early stage (A & B); 2 CRCs were advanced (Dukes C) after 35 and 51

								months, but the first patient was after prior CRC surgery.
Seppala [56]	2017	Prospective cohort	Finnish cohort: 505 MLH1. non-Finnish cohort: 439 MLH1.	Finnish cohort: 246/259. non-Finnish cohort: 184/255.	Age at inclusion: Finnish cohort: 35.2 ± 12.1 non-Finnish cohort: 36.1±11.0	Finnish: 3 year interval	non-Finnish: 1-2 year interval	Finnish cohort: Cumulative CRC incidences at 70 years: 41% for males and 36% for females. Time from last colonoscopy to CRC: 32.7 months. Ten-year overall survival after CRC: 88%. non-Finnish cohort: Cumulative CRC incidence at 70 years: 58% for males and 55% for females (p>0.05). Time from last colonoscopy to CRC: 31.0 months (p>0.05). Ten-year overall survival after CRC: 91% (p>0.05).
Anyla [31]	2018	Prospective cohort	Cohort (n=121): 43 MLH1, 51 MSH2, 3 MSH6, 1 PMS2, 1 TASCD1, 1 MLH1 + variant MSH2, 21 no mutation found.	71/50	44 (16-70) years	2 year interval	NA	Metachronous CRC: 39 (32.2%) after a median interval of 24 (6–57) months since last colonoscopy. More commonly in MSH2 mutation carriers (58 vs. 35%, p = 0.001).
Engel [35]	2018	Retrospective, registry based study	Cohort 1 (n=1709): Germany: 127 MLH1, 201 MSH2, 59 MSH6. Netherlands: 218 MLH1, 276 MSH2, 152 MSH6. Finland: 536 MLH1, 104 MSH2, 36 MSH6. Cohort 2 (n=2747): Germany: 273 MLH1, 306 MSH2, 61 MSH6. Netherlands: 67 MLH1, 60 MSH2, 33 MSH6. Finland: 186 MLH1, 39 MSH2, 13 MSH6.	Cohort 1: Germany: 154/233 Netherlands: 255/391 Finland: 320/356 Cohort 2: Germany: 369/271 Netherlands: 84/76 Finland: 133/105	Age at index colonoscopy Cohort 1: Germany: 40.9 ± 12.0 Netherlands: 41.3 ± 12.5 Finland: 39.0 ± 13.4 Cohort 2: Germany: 48 ± 11.4 Netherlands: 52.3 ± 11.1 Finland: 53.5 ± 11.8	Cohort 1: no CRC before index colonoscopy Surveillance interval: Germany: 1 yearly Netherland: 1-2 yearly Finland: 2-3 yearly	Cohort 2: first CRC before index colonoscopy Surveillance interval: Germany: 1 yearly Netherland: 1-2 yearly Finland: 2-3 yearly	Cohort 1: Incident CRC 144 patients. Cumulative CRC incidence first CRC after 10 years of follow-up: 8.4% (7.1-10.2). Cohort 2: Incident CRC 128 patients. Cumulative CRC incidence metachronous CRC after 10 years of follow-up: 14.1% (11.5-16.8). Surveillance interval within recommended interval: Germany: 76% Netherlands: 87% Finland: 88% No significant differences in cumulative CRC incidence or CRC stage at detection among countries.

Perrod [60]	2018	Prospective cohort study	Before inclusion (n=118): 46 MLH1, MSH2 52, MSH6 18, 2 PMS2. After inclusion (n=144): 56 MLH1, 64 MSH2, 22 MSH6, 2 PMS2	Before inclusion: 38/80. After inclusion: 50/94	Before inclusion: 46±13 years. After inclusion 51±13 years.	Optimized screening program (PRED-IdF) allowing an adjustment of the interval between colonoscopies, depending on bowel preparation, chromoendoscopy achievement and adenoma detection.	Before PRED-IdF	Optimal colonoscopy rate: 304/353 (86%) versus 87/211 (41%), p < 0.0001. CRC detection rate: 1/353 (0.3%) versus 6/211 (2.8%), p = 0.012. ADR: 99/353 (28%) versus 60/211 (28.8%), p>0.05. PDR: 167/353 (48.1%) versus 90/211 (42.2%), p>0.05.
Lee [58]	2012 (supplement) Full text not available	Retrospective cohort study	Cohort (n=64): 43 MLH1 17 MSH2, 4 MSH6.	NR	NR	Postoperative endoscopic surveillance, median interval 12 months.	NA	After segmental colectomy, 4 patients (6.25%) had mCRC in the follow up period. Adenoma was detected in 16 patients in the remnant colon and rectum. 1 year and 2 years adenoma free survival rate: 93.2% and 91.4% respectively. 3 and 4 years adenoma free survival rate: 79.8% and 76.0% respectively.
Lamba [55]	2017 Conference Abstract	Observational study of national database	Cohort (n=381): 98 MLH1, 159 MSH2, 103 MSH6, 21 PMS2).	NR	Mean age at enrollment: 43 years.	Colonoscopy every 1-2 years from the age of 25 years.	NR	The overall risk of developing CRC during surveillance was 2.49% (95%CI 1.18-5.23) at 5 years. The estimated cumulative risk of developing CRC for MLH1, MSH2 and MSH6 carriers by 70 years of age was 17.7%, 17.8% and 8.5% respectively. 18 CRC cases (8 MLH1, 8 MSH2, 2 MSH6, 0 PMS2) after a median follow-up of 6.5 years (range 1-16), mean age at diagnosis 54 years and 55.5% were female. Fifteen patients (83%) had colonoscopy <24 months before CRC, 3 patients an interval of 28 (27-41) months. Six patients (33%) had an adenomatous polyp resected from the same site as CRC, 1 had suboptimal bowel preparation. Seventeen patients (94.4%) were diagnosed with stage 0-II CRC and no CRC-related mortality was observed.

Legend. HNPCC, Hereditary Non-polyposis Colorectal Cancer; CRC, colorectal cancer; LS, Lynch syndrome; MSI, Microsatellite instable; MSS, Microsatellite stable; ADR, Adenoma detection rate; PDR, polyp detection rate.

*Mecklin JP, Aarnio M, Laara E, et al. Development of colorectal tumors in colonoscopic surveillance in Lynch syndrome. Gastroenterology 2007; 133: 1093-1098

Table 3As. Summary table: Advanced imaging techniques in surveillance of Lynch syndrome: dye based chromoendoscopy versus white light and NBI

First Author [Ref. in Guideline]	Year of publication	Study design	Study sample and mutation distribution	Intervention	Comparison	Results
Hurlstone [45]	2005	Unicenter Back-to-back sequential	MMR (84%) ± Amsterdam II. N=25	Conventional colonoscopy with targeted CE followed by indigo carmine pancolonic CE SD	NA	Number of adenomas: WLE: 11 CE: 32 ADR WLE: 28% ADR CE: 68% P = 0.001
Lecompte [39]	2005	Unicenter Back-to-back sequential	MMR (50%) ± Amsterdam N=33	Conventional colonoscopy followed by Indigo carmine CE proximal to splenic flexure SD	NA	Number of adenomas in the proximal colon WLE: 3 CE: 11 ADR WLE: 9% ADR CE: 30% P=0.045
Stoffel [44]	2008	Multicenter, Randomized Two arms Back to back parallel	MMR 85% ± Amsterdam N=54	First pass WLE Second pass: 1. Indigo carmine pancolonic CE	First pass WLE Second pass: 2. At least 20 minutes WLE inspection, SD	Number of adenomas First pass: WLE: 10 (4 in arm CE; 6 in ≥20'inspection) Second pass: CE: 3 WLE ≥ 20'inspection: 7 P= 0.77 ADR first pass WLE: 15% ADR second pass CE: 11% ADR second pass WLE ≥20': 19% P = 0.27

Hüneburg [40]	2009	Unicenter Back-to-back Two arms **Polyps were not removed in the first pass	MMR 89% ± Amsterdam N=109	WLE follow by Indigo carmine pancolonic CE SD/HD	NBI followed by Indigo carmine pancolonic CE SD/HD	Number of adenomas: WLE: 7 CE after WLE: 13 (P= <0.032) NBI: 11 CE after NBI: 39 (P=0.001) ADR WLE: 15% ADR CE: 19% (P= n.s.) ADR NBI: 14% ADR CE: 35% (P= 0.04)
Rahmi [41]	2015	Multicenter Back-to-back Different endoscopist second pass	MMR 100% N=78	Standard endoscopy followed by Indigo carmine pancolonic CE SD	NA	Number of adenomas WLE: 26 CE:29 ADR WLE: 23% ADR CE: 41% (P < 0.001)
Haanstra [61]	2019	Multicenter; randomized; Parallel	MMR 100% N=246	Indigo carmine CE proximal to splenic flexure SD/HD	Conventional WLE SD/HD	ADR Whole colon WLE: 27% CE: 30% (P= 0.56) ADR Proximal colon: WLE 16% CE:24% (P=0.013)
Rivero-Sánchez [62]	2019	Multicenter; randomized; Parallel Non-inferiority	MMR 100% N= 256	WLE HD * High adenoma detectors	Indigo carmine pancolonic CE HD * High adenoma detectors	WLE ADR: 28.1% (95% CI 21.1 – 36.4%) CE ADR: 34.4% (95% CI 26.4 – 43.3%) P= 0.2 (WLE non- inferior to CE)

Legend. NBI, Narrow-band imaging; SD, standard definition; HD, high definition; MMR, mismatch repair; WLE, white-light endoscopy; CE, Chromoendoscopy; ADR, Adenoma Detection rate; n.s, not significant; CI, confidence interval

Table 3Bs. Summary table: Advanced imaging techniques in surveillance of Lynch syndrome: virtual chromoendoscopy vs white light and CE

First Author [Ref. in Guideline]	Year of publication	Study design	Study sample and mutation distribution	Intervention	Comparison	Results
East [43]	2005	Unicenter Back-to-back sequential	MMR (13%) ± Amsterdam II. N=62	WLE followed by NBI Exera II proximal to sigmoid colon HD	NA	Number of adenomas: WLE: 25 NBI: 46 ADR WLE: 27% ADR NBI: 42% P=0.004
Hüneburg [40]	2009	Unicenter Back-to-back Two arms **Polyps were not removed in the first pass	MMR 89% ± Amsterdam N=109	WLE follow by Indigo carmine pancolonic CE SD/HD	NBI followed by Indigo carmine pancolonic CE SD/HD	Number of adenomas: WLE: 7 CE after WLE: 13 NBI: 11 CE after NBI: 39 ADR WLE: 15% ADR CE: 19% ADR NBI: 14% ADR CE: 35%
Bisschops [42]	2017	Unicenter, Back-to-back Cross-over	MMR 64% N=61	WLE followed by i-scan HD	i-scan followed by WLE HD	Number of adenomas -First pass WLE: 5 second pass i-scan:8 Miss rate 62% -First pass i-scan 15 Second pass WLE 2 Miss rate 12% (P=0.007) ADR WLE: 19%->IScan: 16% ADR iscan:30%->WLE 7% (P=0.098)

Samaha [63]	2018 Conference Abstract	Multicenter Back-to-back sequential Non-inferiority	MMR (100%) N= 138	First pass: NBI Second pass: Indigo carmine CE HD	NA	Number of adenomas: NBI:39 CE 75 ADR NBI: 20.3% ADR CE: 30.4% (NBI inferior to CE)

Legend. NBI, Narrow-band imaging; HD, high definition; SPS, serrated polyposis syndrome; WLE, white-light endoscopy; CE, Chromoendoscopy; CI, confidence interval

Table 4s. Summary table: Gastric surveillance in Lynch syndrome

Study characteristics					Gastroscopy findings								H. Pylori testing		
First Author [Ref. in Guideline]	**Year of public-ation**	**Study design**	**Size study sample**	**Study sample surveillance**	**Proportion abnormal surveillance**	**Neoplasia**	**Inflam-mation**	**Peptic ulcer disease**	**Gastric intestinal metaplasia**	**Reactive gastro-pathy**	**Gastric polyps**	**Gastric atrophy**	**Proportion undergoing H. pylori testing**	**Type of H. pylori testing**	**Positivity rate**
Renkonen [70]	2002	Prospective clinical trial	73 MMR positive	73 MMR positive	NR	1/73	23/73	NR	10/73	20/73	6/73	10/73	NR	Biopsy during endoscopy when indicated	19/73
			32 MMR negative	32 MMR negative	NR	0/32	11/32	NR	6/32	9/32	2/32	7/32	NR		9/32
Soer [68]	2016	Retrospective cohort study	443 MMR mutation carriers	132 patients	35/132	8/35	23/35	NR	4/35	NR	NR	NR	20/43	Serology (42%), Rapid urease test (9%), Urea breath test (2%), Stool antigen (19%), Histology (24%), Unknown (3%)	42
Galiatsatos [69]	2017	Retrospective cohort study	66 mutation-proven Lynch syndrome patients	21 patients	10/21	0/10	0/10	1/10	2/10	4/10	NR	0/10	NR	Biopsy during endoscopy when indicated	2/10

Legend. MMR, mismatch repair; NR, Not reported.

Table 5s. Small-bowel surveillance in Lynch syndrome

First Author [Ref. in Guideline]	Year of publication	Study design	Sample size	Intervention	Findings	Secondary procedures	Outcomes
Saurin [85]	2010	Prospective comparative study	35	VCE vs CT enteroclysis	VCE (31/35): Certain: polyp (n=1), ileal tumor (n=1) Uncertain: polyps (n=4), enlarged irregular folds (n=5). CT enteroclysis 35/35: Certain: - Uncertain: 7 patients (including tumor).	VCE: Polyp: DBE failed, surgical resection (adenoma 10mm and jejunal carcinoma T3N0M0). Uncertain: DBE or duodenoscopy (n=4): 4mm adenoma (n-1). CT enteroclysis: Uncertain: DBE (n=7): DBE failed, surgery (n=1).	Prevalence of small bowel neoplasia 8,6%. CT enteroclysis missed the two adenomas.
Samaha	2012	Conference Abstract	46	VCE	NR	NR	Prevalence small bowel neoplasia 2%.
Haanstra [84]	2015	Prospective multicenter trial	200	VCE	Polyps >1cm: n=17. Polyps <1cm (no investigation): n=6.	Gastroduodenoscopy (n=10): TisN0Mx adenocarcinoma (n=1), TVA (n=1), inflammation (n=1), brunner's gland (n=2), heterotopic gastric mucosa (n=1), NA (n=4). SBE/ DBE (n=6): lymphoid hyperplasia (n=1), NA (n=5)	Prevalence small bowel neoplasia 1,5%: >50 years within reach of gastroduodenoscope. Follow-up: 7 months after negative VCE, duodenal cancer (T2N0Mx).
Haanstra [86]	2017	Prospective multicenter trial	155/200	VCE	Polyps >1cm: n=13. Polyps <1cm (no investigation): n=2.	Gastroduodenoscopy (n=5): brunner's gland (n=1), swollen normal mucosa (n=1), polyp (normal mucosa) <5mm (n=1), NA (n=2) SBE/ DBE (n=8): polyp (lymphoid hyperplasia) 6-9mm (n=1), polyp (FGP) <5mm (n=1),	No small bowel neoplasia.

						thickened mucosa (n=1), NA (n=5)	
Hammoudi [87]	2019	Retrospective cohort study	154	Upper endoscopy, performed every 3–4 years, in the occasion of a colonoscopy, according to our PRED-IdF guidelines.	≥1 duodenal lesion: 7 (4.5%), median age at diagnosis was 58 years (range: 49–73). Three lesions were invasive adenocarcinomas. MLH1: 2.4% (1 out of 41). MSH2: 7.1% (6 out of 85). OR: 5.17, IC95% (0.8–60.07), p = 0.1307.	NA	NA

Legend. VCE, Video capsule endoscopy; MR, Magnetic Resonance; CT, Computer tomography; NR, Not reported; TVA, tubulovillous adenoma; NA, Not Applicable; SBE, Single balloon endoscopy; DBE, Double balloon endoscopy; FGP, Fundic gland polyp; NA, Not Applicable.

Table 6s. Family history and risk of developing colorectal cancer: overview of Wong et al. and Roos et al.

Family history	First Author, Ref. [91] in Guideline	Year of publication	Number of studies included	Oveall risk estimate (95%CI)	First Author, Ref. [95] in Guideline	Year of publication	Number of studies included	Case-control study risk estimate (95%CI)	Number of studies included	Cohort study risk estimate (95%CI)
1 FDR	Wong	2018	7	1.82 (1.51-2.18)	Roos	2019	8	1.92 (1.53-2.41)	3	1.37 (0.76-2.46)
≥1 FDR	Wong	2018	63	1.76 (1.57-1.97)	Roos	2019	41	2.22 (2.00-2.48)	12	1.67 (1.52-1.82)
≥2 FDR	Wong	2018	9	2.68 (1.92-3.74)	Roos	2019	8	2.81 (1.73-4.55)	3	2.40 (1.76-3.28)
FDR <50 years	Wong	2018	4	3.55 (1.84-6.83)	Roos	2019	2	3.57 (1.07-11.85)	4	3.26 (2.82-3.77)
FDR <60 years	Wong	2018	NR	NR	Roos	2019	3	2.40 (2.12-2.73)	4	2.02 (1.59-2.57)

FDR, first-degree relative; CI, confidence interval; NR, Not reported.

Table 7s. Surveillance in familial risk of colorectal cancer: intervals and outcomes

First author [Ref. in Guideline]	Year of publication	Study design	Study sample size	Age range	Definition of family history	Method of family history assessment	Lynch syndrome excluded?	Intervention: surveillance interval	Comparison	Outcome
Dove-Edwin [98]	2005	Prospective, observational cohort study	Group 1 = 197 individuals Group 2 = 536 individuals Group 3 = 391 individuals Group 4 = 554 individuals	20-82 years	Group 1: 1 FDR with CRC <45 yo Group 2: 2 FDR or 1 FDR + 1 SDR Group 3: ≥3 individuals affected over two generations, one a FDR of the other two, but no cases diagnosed <50 yo Group 4: HNPCC	NR	Group 4	Offered from age 25. 5-year intervals or 3-year intervals if an adenoma was diagnosed. Later, individuals in a family with HNPCC were offered colonoscopy every 1-3 years.	NA	Families with moderate risk (group 1-3): Advanced adenoma and CRC under age <45 on initial colonoscopy: 1.1% and 0%. On follow-up colonoscopy (5-year interval) if advanced neoplasia was absent initially (1.7% and 0.1%, respectively). Advanced neoplasia on initial colonoscopy: 12% of advanced neoplasia on follow-up (3-year interval). Multiple adenomas on initial colonoscopy: 41% had an adenoma on follow-up (3-yearly surveillance), but 0% had advanced neoplasia. Incidence of CRC: 80% lower (P = 0.00004) than the expected incidence in the absence of surveillance when the family history was taken into account. Significant reduction in mortality: 81% in moderate-risk

Brenner [100]	2011	Population-based case-control study	FH among first diagnosed CRC cases = 232 (14.1%) FH among controls = 192 (10.4%)	≥30 years	≥1FDR	Standardized interviews or questionnaire to those individuals not willing to participate in a personal interview.	NR	Colonoscopy surveillance interval after previous negative colonoscopy: 1-10 years.	No colonoscopy surveillance.	Risk remained low for each of the time intervals within 20 years following negative colonoscopy in people with (aOR=0.27, 95%CI 0.17-0.43) and without CRC (OR=0.19, 95%CI 0.15-0.24) in a FDR vs. no colonoscopy.
Hennink [102]	2015	Multicenter randomized controlled trial	Patients with <3 adenomatous polyps at baseline: Group A (6 years surveillance) = 262. Group B (3 and 6 years surveillance) = 266.	45-65 years	1 FDR with CRC <50 years 2FDR with CRC at any age	Medical (99%) and pathology (47%) reports. Verified.	Excluded	Group A: 6 year surveillance interval	Group B: 3 year surveillance interval	Advanced adenomatous polyps at first follow-up: group A (6.9%) versus 3 years in group B (3.5%) (crude OR, 2.0; 95%CI 0.89 to 4.7; P=0.09) (adjusted OR, 2.44; 95%CI 1.03 to 5.78; P=0.044). Advanced adenomatous polyps at the final follow-up at 6 years: group A (6.9%) versus 6 years in group B (3.4%) (crude OR, 2.1; 95%CI 0.89 to 5.0; p=NS) (adjusted OR, 2.61; 95%CI 1.06 to 6.45; P=0.038).
Samadder [101]	2017	Cohort study	First negative colonoscopy & Family history = 7,515 First negative colonoscopy & No family history = 138,864	50-80 years	≥1FDR	Linkage between the Utah Population Database and the Utah Cancer Registry. Not ascertainment.	Excluded	Family history: 5 year surveillance interval	No family history: 10 year interval.	Family history: the SIR for CRC overall was significantly reduced up to 5 years (SIR 0.39, 95%CI 0.13–0.64) following a negative colonoscopy, and 5-10 years (SIR 0.74, 95%CI 0.32–1.16). No family history: the SIR for CRC overall was significantly reduced up to 10 years following that index procedure (SIR 0.28, 95% CI: 0.24–0.33).

Hatfield [99]	2018	Case-control study	324 individuals (162 screened; 162 unscreened)	The median ages of males and females at entry into screening; 44.8 (95% CI 42.2–47.4) vs. 44.5 (41.8–47.2) years.	Family members eligible for study were born after 1909, were FDR of incident CRC cases, and presumed to be at 50% a priori risk for a inheriting genetic CRC susceptibility factor.	FCCTX families were identified from population-based cohorts where incident cases with CRC were recruited into the Newfoundland Familial Colorectal Cancer Registry between 1999 and 2003, or had been referred to the Provincial Medical Genetics Program.	Yes	Follow-up colonoscopies at 1–2-year intervals	Unscreened control group from the families, matched for age at entry into screening and for sex.	INCIDENCE OF CRC: 12% of males developed CRC after 30 years of follow-up, compared to 46% of unscreened males (RR=0.27; 95% CI: 0.10–0.71). Regarding females, 7% had developed CRC after 30 years of follow-up, compared to 49% of unscreened females (RR=0.19; 0.07–0.48). MORTALITY: survival was significantly better in screened compared to unscreened males (RR = 0.38). At 30 years of follow-up, 45.5% of males had died in the screened group compared to 62.8% in the unscreened group. In screened females, mortality at 30 years of follow-up was 7.2%, whereas in unscreened females, it was 60.4% (RR = 0.14).

Legend. FDR, First-degree relative; NR, Not reported; HNPCC, Hereditary Non Polyposis Colorectal Cancer; NA, Not Applicable; CRC, Colorectal cancer; FH, Family history; (a)OR, (adjusted) Odds Ratio; NS, Not significant; CI, confidence interval; SIR, Standardized Incidence Ratio; FCCTX, Familial colorectal cancer type X.

Table 8s. Starting age for colonoscopy surveillance in familial risk of colorectal cancer

First Author [Ref. in Guideline]	Year of Publication	Study	Definition of family history	Method of family history assessment	Lynch syndrome excluded?	Risk: Type of cancer	FH: Type of cancer	Age of person at risk
Fuchs [103]	1994	Prospective cohort study	≧1 FDR	Questionnaire and medical records and pathology reports.	NR	CRC	CRC	For participants under the age of 45 years who had one or more affected first-degree relatives, the relative risk was 5.37 (95%CI 1.98 to 14.6), and the risk decreased with increasing age (P for trend, < 0.001).
Hemminki [104]	2001	Prospective cohort study	≧1 FDR	NR	NR	CRC	CRC	**SIR for CRC in offspring by their age:** <40 years --> SIR 2.20 (95%CI 1.74-2.70) 40-49 years --> SIR 2.01 (95%CI 1.71-2.33) >50 years --> SIR 1.18 (95%CI 0.99-1.39)
Andrieu [105]	2003	Case-control study	FDR+SDR	Verified through the local cancer registers, and medical care centres', GPs' or specialists' records.	"Only three families (0.4%) fulfilled the Amsterdam criteria of 3 cases of CRC"	CRC	CRC	Risk of developing CRC: ≤ 50 years: RR 2.07 (95%CI 0.99-3.80) 51-60 years: RR 1.67 (95%CI 0.97-2.68) 61-70 years: RR 1.28 (95%CI 0.85-1.85) > 70 years: RR 1.60 (95%CI 1.19-2.10)
Johns {106]	2002	Retrospective cohort study	≧1 FDR	Medical reports	Not excluded, however birth prevalence of mutations is only approximately 1 in 2,800.	CRC	CRC	Cumulative CRC risk in first-degree relatives of CRC cases 30 years --> 0.2 (0.08-0.7) 35 years --> 0.6 (0.3-1.3) 40 years --> 0.6 (0.3-1.3) 45 years --> 1.4 (0.9-2.3) 50 years --> 1.8 (1.2-2.8) 55 years --> 2.8 (2.0-4.0) 60 years --> 3.6 (2.6-4.9) 65 years --> 5.8 (4.4-7.7) 70 years --> 6.9 (5.3-9.0) 75 years --> 8.5 (6.4-11.1)

Kune [107]	1989	Case-control study	≧1 FDR	Questionnaire	NR	CRC	CRC	When relative risks were estimated by age in 2 groups, a statistically significant association was found between FH of CRC and the respondent's age of less than 50 years (RR l< 50 years = 8.54, 95%CI 1.9-39; RR 50 years or older = 1.87, 95% CI = 1.4-2.8; and p value associated with the difference between the 2 age groups = 0.05
Samadder [108]	2015	Case-control study	FDR+SDR	NR	Patients with known hereditary cancer syndromes other than FAP (in particular Lynch syndrome) and IBD could not specifically be excluded; however, these conditions account for less than 3% of all CRCs and are therefore unlikely to modify the statistical associations demonstrated.	CRC	CRC	Risk of CRC <50 years --> HR 2.28 (95%CI 1.86-2.80) ≧50 years --> HR 1.81 (95%CI 1.71-1.92)

Legend. FDR, First-degree relative; NR, Not reported; CRC, Colorectal cancer; CI, confidence interval; SIR, Standardized Incidence Ratio; SDR, Second Degree Relative; RR, Relative Risk; HR, Hazard Ratio.