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%.

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

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.

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team (M.v.L. and V.R.) and then approved by the other group members. The coordinating team established task force sub-groups, 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 pathogenic variants of the MLH1 and MSH2 genes [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 2a. 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 polyectomy 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 3a) [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 (ADR), 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 3B) [42, 43]. On the other hand, virtual chromoendoscopy was inferior to dye-based chromoendoscopy in two back-to-back studies [40, 63]. This, 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 esophagastroduodenoscopy [68, 69]. In a Dutch 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 esophagastroduodenoscopy findings [69]. In a Dutch study, esophagastroduodenoscopy 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) enterolysis [84]. The second study compared VCE with computed tomography (CT) enterolysis and showed that CT enterolysis 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-E 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-
mortality 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

<table>
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<th>RECOMMENDATION</th>
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<tbody>
<tr>
<td>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.</td>
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<tr>
<td>Strong recommendation, low quality evidence, level of agreement 83%.</td>
</tr>
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</table>

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 7).

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 7). 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

<table>
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<tr>
<td>ESGE recommends starting colonoscopy surveillance at the age of 40 years when there is a familial risk of colorectal cancer.</td>
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<tr>
<td>Strong recommendation, moderate quality evidence, level of agreement 92%.</td>
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</tbody>
</table>

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 8). 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 from Medtronics (2017–2018) and Cook Medical (2019), and 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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