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Evidence Summary 15-16 REQUIRES UPDATING

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Cancer Screening for Persons at Risk for or Affected with Lynch Syndrome Evidence Summary

J. Tinmouth, C. Zwaal, R. Gryfe, J.C. Carroll, N. Baxter, B.R. McCurdy and S.E. Ferguson

An assessment conducted in March 2024 indicated that Evidence Summary (ES) 15-16 REQUIRES UPDATING. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

You can access ES 15-16 here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/43271

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Executive Summary

J. Tinmouth, C. Zwaal, R. Gryfe, J.C. Carroll, N. Baxter, B.R. McCurdy and S.E. Ferguson

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EXECUTIVE SUMMARY

Cancer Care Ontario's Prevention and Cancer Control portfolio with the Program in Evidence-Based Care developed this report to evaluate the existing evidence so as to inform the development of screening recommendations and risk reduction strategies for persons affected or at risk for Lynch syndrome in Ontario's colorectal cancer (CRC) screening program (ColonCancerCheck). Lynch syndrome is an autosomal dominant genetic condition. These recommendations will inform program design and policy for screening in Ontario.

The main objectives of this evidence review were to identify, among persons affected or at risk for Lynch syndrome:

i. The risk for Lynch syndrome cancers;
ii. Screening protocols that are effective for each Lynch syndrome cancer;
iii. Risk reduction strategies that are effective for each Lynch syndrome cancer;
iv. The most effective surveillance protocol for persons with a CRC who do not have a total proctocolectomy.

A systematic review of the evidence was performed and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method was used to evaluate the quality of the evidence for each of the outcomes.

SUMMARY OF FINDINGS

The Working Group developed the following conclusions. Outcomes vary for each question and cancer. Please see Section 2 of the evidence summary for more details.

What is the risk for Lynch syndrome cancers for people affected or at risk for Lynch syndrome? Are there differences in risk for various germline mutations?

The quality of the evidence was not graded, as the methodology is not appropriate to the question.

Persons affected or at risk for Lynch syndrome appear to be at highest risk of CRC and endometrial cancer (EC). In addition, there appears to be an increased lifetime risk of ovarian, gastric, bladder, urothelial, small intestine, hepatobiliary, and brain cancers in persons with Lynch syndrome [1-29]. There is a possible increase in the lifetime risk of breast, prostate, pancreatic and hematologic cancer in persons with Lynch syndrome. There is some uncertainty for risk by gene mutation type however; different gene mutations likely confer

different risks by type of cancer. For most cancers, persons with *MLH1* and *MSH2* mutations are at highest risk while those with *MSH6* and *PMS2* mutations appear to be at lower risk. However, sample sizes are small and for some cancers, associations have not been extensively investigated [2,8-10,13,14,28]. Further study is warranted.

For each Lynch syndrome cancer, what cancer screening protocols are effective for people affected or at risk for Lynch syndrome?

Colorectal cancer screening for people affected or at risk for Lynch syndrome

There is weak but consistent evidence to support the use of colonoscopy for CRC screening in persons with Lynch syndrome.

The certainty of the evidence to support the use of colonoscopy for CRC screening in persons with Lynch syndrome is very low. In the included studies, fewer persons with Lynch syndrome were diagnosed with CRC or died from CRC during follow-up among those who were screened with colonoscopy compared with those who did not have colonoscopy during the follow-up period. There were no significant complications reported such as perforation or bleeding; however these are rare complications and the sample was small making reliable estimates for adverse events difficult. A small percentage in one study did report discomfort during the colonoscopy [30]. There were no studies on screening tests other than colonoscopy in persons with Lynch syndrome. There were studies on new endoscopic techniques (narrow-band imaging, autofluorescence endoscopy, and chromocolonoscopy); however the evidence was insufficient to support the use of these techniques over conventional white light colonoscopy.

The evidence to support conclusions regarding the age at which to initiate or stop screening with colonoscopy in persons with Lynch syndrome is insufficient.

The certainty of the evidence regarding the age of initiation for the use of colonoscopy for CRC screening in persons with Lynch syndrome is very low. The risk of CRC in persons with Lynch syndrome increases with age, with those aged 30 years and over at extremely high risk. Those aged 20 to 30 years appear to be at comparable risk to those aged 60 to 69 in the general population. There is no evidence for age of cessation.

There is no evidence regarding the intervals between colonoscopies in persons with Lynch syndrome. Most studies used intervals of one to two years but none of the studies compared different intervals.

There are no data on the effectiveness of CRC screening by gene mutation.

Screening for endometrial cancer in women affected or at risk for Lynch syndrome

There is insufficient evidence to support the use of routine or directed (for thickened endometrium on transvaginal ultrasound (TVUS)) endometrial biopsy (EB) for EC screening in women with Lynch syndrome.

The certainty of the evidence for the use of routine or directed EB for EC screening in women with Lynch syndrome is very low. A single small study compared women who were screened with routine or directed endometrial biopsy with those who were not screened during the follow-up period [31]. In this study, there was no significant difference in EC-related death between the two groups. The incidence of complex atypical hyperplasia (CAH) and EC was higher in the control group than the screened group with comparable hysterectomy rates in the two groups, suggesting possible contamination. There were two small studies comparing routine versus directed biopsy. One found a significant difference ($p=0.026$) where the use of routine EB resulted in more CAH and EC found than directed EB (6.3% versus 1.4% of visits). The other study was non-significant and neither study included a non-screened control group [32,33].

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Most studies did not report on complications; one study reported cancer worry and procedure-related discomfort [32].

There is no evidence regarding ages of initiation or cessation of EC screening or intervals between screening examinations. Most studies recommended that screening start at 30 to 35 years of age and used intervals of one to three years but there were no studies comparing different start ages or intervals.

There are no data on the effectiveness of EC screening by gene mutation.

Screening for ovarian cancer in women affected or at risk for Lynch syndrome

There is insufficient evidence to support the use of TVUS with or without CA-125 or physical examination for ovarian cancer (OC) screening in women with Lynch syndrome.

The certainty of the evidence to support the use of TVUS with or without CA-125 or physical examination for OC screening in women with Lynch syndrome is very low. There was no significant difference in the incidence of or death from OC during follow-up among those who were screened with TVUS + CA-125 compared with those who were not screened during the follow-up period. However, in the only controlled study to date, the control group had rates of hysterectomy and oophorectomy similar to cases, again suggesting possible contamination [31]. Most studies did not report on complications; one study reported cancer worry [32]. Some studies also studied TVUS alone or TVUS with physical examination ± CA-125 but none of these studies included a non-screened control group.

There is no evidence regarding ages of initiation or cessation of OC screening or intervals between screening examinations. Most studies recommended that screening start at 25 to 35 years of age and used intervals of one to three years but there were no studies comparing different start ages or intervals [30,34-38].

There are no data on the effectiveness of OC screening by gene mutation.

Small bowel cancer screening for people affected or at risk for Lynch syndrome

There is insufficient evidence to support the use of capsule endoscopy and computed tomographic enteroclysis for small bowel cancer (upper gastrointestinal cancer, UGI) screening in people with Lynch syndrome.

There were no controlled studies on this topic.

Urinary tract cancer screening for people affected or at risk for Lynch syndrome

There is insufficient evidence to support the use of urine cytology for urinary tract cancer (UTC) screening in people with Lynch syndrome.

The certainty of the evidence to support the use of urine cytology for UTC screening in people with Lynch syndrome is very low. There was one study on this topic: it had poor compliance and did not find a significant difference in the incidence of or death from UTC during follow-up among those who were screened with urine cytology compared with those who were not screened during the follow-up period [39]. Complications were not reported.

There is no evidence regarding ages of initiation or cessation of UTC screening or intervals between screening examinations.

Upper gastrointestinal cancer screening for people affected or at risk for Lynch syndrome

There is insufficient evidence to support the use of gastroscopy for UGI screening in people with Lynch syndrome.

The certainty of the evidence to support the use of gastroscopy for UGI screening in people with Lynch syndrome is very low. There was one small study on this topic: it did not find a significant difference in the incidence of UGI cancer during a three to four year follow-up period among those with Lynch syndrome compared with those family members without

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Lynch syndrome, both of whom were screened once with gastroscopy [40]. Complications and deaths from UGI cancers were not reported.

There is no evidence regarding ages of initiation or cessation of UGI screening or intervals between screening examinations.

For each Lynch syndrome cancer, what risk reduction strategies are effective for people affected or at risk for Lynch syndrome?

Use of prophylactic or risk reducing surgery to prevent endometrial or ovarian cancer

There is weak evidence to support the use of prophylactic surgery to prevent EC or OC in persons with Lynch syndrome.

The certainty of the evidence to support the use of prophylactic surgery to prevent EC or OC in persons with Lynch syndrome is very low. Fewer women were diagnosed with EC or OC among those in the prophylactic surgery group during follow-up (all diagnosed at the time of surgery and none after) than among the non-surgical controls; however it was not possible to determine the magnitude of this benefit [38]. There were no EC or OC-related deaths among those that received prophylactic surgery while a small number of women died from these cancers among the non-surgical controls [41]. There were harms due to prophylactic surgery reported in the included studies however, these data were sparse (e.g., no data on long-term effects, quality of life, psychological consequences), perhaps because of the nature of the studies or because harms were not the focus of the study. Our search strategy was not specifically focused on harms; therefore we may have missed studies on this topic. There are no data to determine optimal ages of initiation and benefit by gene mutation.

Use of extended colectomy in persons with colorectal cancer and Lynch syndrome

There is consistent but weak evidence to support extended colectomy in persons with CRC and Lynch syndrome.

The certainty of the evidence to support extended colectomy in persons with CRC and Lynch syndrome is low. There were fewer deaths and metachronous CRCs among those who received extended colectomy compared with those who had a segmental colectomy [42-47]. While it was not possible to determine the magnitude of this benefit, there is consistent clinically important reduction in the incidence of metachronous CRCs across studies. There were harms reported with both surgical approaches; however these were restricted to surgical complications (e.g., no data on long-term effects including function, quality of life, psychological consequences). Our search strategy was not specifically focused on harms therefore we may have missed studies on this topic. There are no data to determine benefit by gene mutation.

Use of aspirin/non-steroidal anti-inflammatory drugs to prevent colorectal cancer

There is very weak evidence to support the use of aspirin/non-steroidal anti-inflammatory drugs to prevent CRC in persons with Lynch syndrome.

The certainty of the evidence is low. The anticipated desirable effects are uncertain: while there is randomized controlled trial evidence suggesting a potentially large reduction in CRC incidence with aspirin use, the 95% confidence interval (CI) around the estimate is wide and includes the null [48]. There are no data on the outcome of cancer-related death. There was a balance in anticipated harms (more bleeding with aspirin but fewer cardiovascular events). Given the potential for benefit and negligible harms, use of aspirin prophylaxis should be discussed with persons with Lynch syndrome. There are no data to determine optimal ages of initiation and cessation, dosing, and benefit by gene mutation.

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Use of resistant starch to prevent colorectal cancer

There is insufficient evidence to support the use of resistant starch to prevent CRC in persons with Lynch syndrome.

The certainty of the evidence is low. The anticipated desirable effects are uncertain. In the one randomized controlled trial, the 95% CI was wide and included the null; in addition, the point estimate of the relative risk was close to null [49]. The anticipated harms were small. There are no data to determine optimal ages of initiation and cessation, dosing, and benefit by gene mutation.

Use of lifestyle modifications to prevent cancer

There is very weak evidence to support the use of some lifestyle modifications to prevent CRC and insufficient evidence for other Lynch-associated cancers.

The certainty of the evidence to support the use of lifestyle modifications to prevent CRC in persons with Lynch syndrome is very low. There are some data to indicate higher risk of CRC in those persons who are obese compared with those who are not obese [50]. There may also be benefit to diets high in fruit and/or tea intake, the use of calcium or multivitamin supplements and vigorous exercise for the prevention of CRC [51-55]. The data on other Lynch-associated cancers are sparse: one study found a higher risk of EC in women with diabetes or long-term use of hormone replacement therapy [56]. There are no data on the optimal ages of initiation and cessation, timing, and benefit by gene mutation. In the studies of vitamins and other supplements, there is insufficient data to recommend a dose.

What is the most effective surveillance protocol for persons with a colorectal cancer and a known or suspected Lynch syndrome germline mutation who did not have a total proctocolectomy?

There is no evidence to inform the most effective colonoscopy surveillance protocol for persons with CRC and Lynch syndrome who did not have an extended colectomy.

Descriptive data from the literature indicates median time from initial surgery to metachronous CRC was approximately six years (range, 0.1 to 16 years) for segmental resection [42,43,45,57] and 19 years for extended colectomy (range, 1.3 to 26 years) [42,43,45,47]. The median time from previous endoscopy to CRC was approximately 3 years (range, 0.5 to 7.5 years) [42,43,47,57] for segmental resection and 3.8 years for extended colectomy (range, 3.4 to 7.5 years) [42,43,47]. Most studies used colonoscopy surveillance intervals of one to two years [42,44,46,58,59].

CONCLUSION

In summary, there is only low to very low-quality evidence to guide the management of persons with Lynch syndrome and at risk of Lynch syndrome in terms of their risk of cancer, recommended surveillance and lifestyle modifications.

There are significant limitations to this review including: small sample sizes for many studies; a lack of meaningful data on undesirable harms and benefits; an absence of studies addressing questions of interest; and the design limitation of the included studies. The lack of controlled trials increases the vulnerability to issues of confounding as well as selection and recall bias.

Future research regarding the determination of cancer risk for sex and gene mutation type as well as a better understanding of role of age needs to be conducted. More research is

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needed concerning risk reduction strategies along with the timing, amounts, and dosing of medication or supplements.

However, in some areas where there is insufficient evidence, it is unlikely that high quality studies will be conducted for multiple reasons: 1) the very low numbers of people affected or at risk for Lynch syndrome; 2) unwillingness of subjects to be randomized to "placebo" (e.g., anecdotally, there is high uptake of risk-reducing surgeries in among women at risk for endometrial cancer); 3) it has become accepted practice to offer screening in some of the above scenarios based on limited data; and 4) for many cancers, other than CRC and EC, the rate of the cancer is very low making the development of meaningful conclusions very difficult.

NEXT STEPS

This evidence summary reports what is known about the management of persons with or at risk of Lynch syndrome. However, the evidence summary is necessary but not sufficient to guide the development of screening recommendations as other context-specific criteria must be considered. In addition, Cancer Care Ontario must also consider issues incompletely addressed by the evidence such as patient preference and potential harms. An expert panel including primary care physicians, colorectal surgeons, gastroenterologists, pathologists and members of the public will be convened to provide guidance on how to incorporate the evidence summarized here in light of these other issues.

Cancer Care Ontario will use findings from this evidence summary as well as expert panel recommendations to guide the development and design of Ontario's high-risk colorectal cancer screening program.

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Evidence Summary 15-16: Section 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Cancer Screening for Persons at Risk for or Affected with Lynch Syndrome Evidence Summary

Systematic Review

J. Tinmouth, C. Zwaal, R. Gryfe, J.C. Carroll, N. Baxter, B.R. McCurdy and S.E. Ferguson

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THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (MOHLTC). All work produced by the PEBC is editorially independent from the MOHLTC.

INTRODUCTION

Lynch syndrome is an autosomal dominant genetic condition that is associated with a high risk of colorectal cancer (CRC), endometrial cancer (EC), and various other cancers frequently diagnosed at an early age [60]. It is caused by a mutation of genes in the DNA mismatch repair (MMR) pathway: *MLH1*, *MSH2*, *MSH6* or *PMS2*. Genetic testing for Lynch syndrome can confirm the diagnosis and identify at-risk people who require surveillance, and aid in surgical and chemoprevention management [61].

The purpose of the evidence summary is to evaluate the existing evidence so as to inform the development of screening recommendations and risk reduction strategies for persons affected or at risk for Lynch syndrome in Ontario's CRC screening program (ColonCancerCheck). These recommendations will inform program design and policy for screening in Ontario.

The main objectives are to identify, among persons affected or at risk for Lynch syndrome:

i. The risk for Lynch syndrome cancers;
ii. Screening protocols that are effective for each Lynch syndrome cancer;
iii. Risk reduction strategies that are effective for each Lynch syndrome cancer;
iv. The most effective surveillance protocol for persons with a CRC who did not have a total proctocolectomy.

INTENDED USERS

The primary user is the Cancer Screening Program at Cancer Care Ontario. Other stakeholders include primary care physicians, colorectal surgeons, gastroenterologists, and pathologists.

RESEARCH QUESTIONS

These research questions were developed to direct the search for available evidence on screening recommendations and risk reduction strategies for people affected or at risk for Lynch syndrome.

QUESTION 1: What is the risk for Lynch syndrome cancers for people affected or at risk for Lynch syndrome? Are there differences in risk for various germline mutations?

QUESTION 2: For each Lynch syndrome cancer, what cancer screening protocols are effective for people affected or at risk for Lynch syndrome?
For those cancers, identify the following:

- Which cancer screening modalities have been found to be effective by cancer type?
- What is the evidence for ages of screening initiation and cessation?
- What is the evidence for intervals between screening tests?
- Are there differences in effectiveness for various germline mutations?

QUESTION 3: For each Lynch syndrome cancer, what risk reduction strategies are effective for people affected or at risk for Lynch syndrome?

- What is the evidence for ages of initiation and cessation?
- What is the evidence for timing of the strategy?
- What is the evidence for each gene mutation?

QUESTION 4: What is the most effective colonoscopy surveillance protocol for persons with a colorectal cancer and a known or suspected Lynch syndrome germline mutation who did not have a total proctocolectomy?
Specifically:

- What is the evidence for frequency of colonoscopy surveillance?
- What is the evidence for age of cessation of surveillance?
- What is the evidence for each gene mutation?

TARGET POPULATION

People affected or at risk for Lynch syndrome or Lynch-like syndrome. People affected with Lynch syndrome are defined as:

- People with a Lynch syndrome cancer and a known Lynch syndrome germline mutation;
- People with a known Lynch syndrome germline mutation.

People at risk for Lynch syndrome or Lynch-like syndrome, defined as:

- People with a Lynch syndrome cancer and a germline mutation of unknown significance (considered Lynch-like syndrome);
- People with a Lynch syndrome cancer and evidence of MMR protein loss but who do not have a germline mutation and where sporadic microsatellite instability (MSI) has reasonably been ruled out (considered Lynch-like syndrome);

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- A relative of someone with confirmed Lynch syndrome; this relative has not undergone genetic testing. (Note: consider first-degree relative separately from second-degree relative if possible).

Relatives of those at risk for Lynch syndrome or of those with Lynch-like syndrome:

- For example, (1) a relative of a person with a Lynch syndrome cancer and a germline mutation of unknown significance; this relative also has the germline mutation of unknown significance; or (2) a relative of a person with a Lynch syndrome cancer and evidence of MMR protein loss but who does not have a germline mutation and where sporadic MSI has reasonably been ruled out; this relative does not have a germline mutation.

METHODS

This evidence summary was developed by a Working Group consisting of a gastroenterologist, a gynecologic oncologist, two surgical oncologists, a primary care physician, a representative of the ColonCancerCheck program and a health research methodologist.

The Working Group was responsible for reviewing the identified evidence and drafting the summary. Conflict of interest declarations for all authors are summarized in Appendix 1 and were managed in accordance with the *PEBC Conflict of Interest Policy*.

This evidentiary review was developed using a planned two-stage method summarized here and described in more detail below.

1. Search and evaluation of existing guidelines: If one or more systematic reviews from existing guidelines were identified that address the research questions and were of reasonable quality, then those systematic reviews would form the core of the evidentiary base.
2. Systematic review of the primary literature: This review would focus on those areas not covered by existing reviews if any are located and accepted.

Search for Existing Guidelines

The following databases were searched in August 2016 for existing evidence-based practice guidelines that addressed one or more of the preceding clinical questions: the Cancer Guidelines Database, the National Guideline Clearinghouse, and the Canadian Medical Association (CMA) Infobase. As well, MEDLINE and EMBASE and an Internet search using the Google search engine was conducted using the phrases “hereditary non polyposis CRC”, “HNPCC” and “Lynch syndrome” to identify any additional relevant guidelines. Included guidelines comprised those with guidance for screening for cancers for people with Lynch syndrome. The search was limited to the English language due to the unavailability of translation services. If more than one guideline was identified that addressed a particular research question, then guidelines were selected for further assessment based on currency, clarity, and applicability. Practice guidelines that were selected for further consideration were assessed for reporting quality using the AGREE II [62]. Three guidelines were found that were considered to be of good quality, but the guideline on genetic evaluation and management of Lynch syndrome from the U.S. Multi-Society Task Force on Colorectal Cancer (USMSTF) [61] was found to be the most relevant and useful to answer the research questions.

Search for Primary Literature

Since the guideline from the USMSTF systematically searched all relevant evidence until 2012, a systematic review of the primary literature including systematic reviews was

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conducted to update the review. The following criteria were written to update the literature search from the USMSTF guideline.

Literature Search Strategy

The literature was searched for new primary studies published after the end search date of USMSTF guideline. A systematic search was conducted in OVID MEDLINE (2012 to August 15, 2016), EMBASE (2012 to August 15, 2016) and the Cochrane library (August 2016). Details of the literature search strategy are included in Appendix 2. A literature search was conducted in OVID MEDLINE (2016 to January 25, 2018) and EMBASE (2016 to January 25, 2018) to update the search from August 2016 using the same search terms as in the August 2016 search.

Systematic Review Criteria and Protocol

Identified systematic reviews were evaluated based on their clinical content and relevance. Relevant systematic reviews were assessed using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) [63] tool to determine whether or not existing systematic reviews met a minimum threshold for methodological quality and could be considered for inclusion in the evidence-base. In cases where multiple systematic reviews were identified for a particular outcome, only evidence from the most recent systematic review with the highest quality was used in the evidence base.

Systematic reviews were included if:

- They addressed at least one of the research questions;
- They evaluated randomized control trials (RCTs) or non-RCTs of people with Lynch syndrome;
- The literature search strategy for the systematic review was reproducible (i.e., reported) and appropriate; and
- The systematic review reported the sources searched, as well as the dates that were searched.

Primary Study Selection Criteria and Protocol

Studies included in the USMSTF guideline [61] as well as any new primary studies identified via our systematic review were assessed in order to complete the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) [64]. Articles in reference lists from included studies were also searched. The criteria for the primary literature are described below.

Inclusion Criteria:

1. Randomized controlled trials (RCTs), cohort/case-control studies with a minimum study size of n=30; and
2. The population of the study consisted of people affected by Lynch syndrome or Lynch-like syndrome or relatives of those at risk for Lynch syndrome or Lynch–like syndrome; and
3. Evaluated the risk of getting a Lynch syndrome cancer; or
4. Evaluated screening protocols for Lynch syndrome cancers; or
5. Evaluated risk reduction strategies other than screening; or
6. Evaluated surveillance protocols after segmental proctocolectomy; and
7. English language because of unavailability of translation; and
8. Published in 2012 or later (to update the USMSTF guideline).

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Exclusion Criteria:

1. Letters, comments or editorials;
2. Non-systematic reviews; and
3. Non-English-language publications.

All results from the OVID literature search were put into reference management software (EndNote X6), where duplicate citations were removed. A review of the titles and abstracts that resulted from the search was performed by one reviewer (CZ). For those items that warranted full-text review, one reviewer (CZ) reviewed each item and consulted a second reviewer (JT) whenever there was uncertainty.

Data Extraction and Assessment of Study Quality and Potential for Bias

Data from the included studies were independently extracted by CZ. If there was more than one publication for the same study, only the most updated or recent versions of the data were reported in the results. All extracted data and information were audited by an independent auditor.

Important quality features, such as study type, study population, randomization details, sample size, intention-to-treat analysis, and length of follow-up were extracted for each RCT.

The RCTs were assessed using Cochrane's Risk of Bias tool [65] where six domains of bias are assessed: random sequence generation, allocation concealment, blinding participants, personnel and outcome assessment, incomplete outcome data, selective reporting, and other concerns. Each domain was judged as being at low, high, or an unclear risk of bias.

The quality of cohort and case-control studies was assessed using a modified ROBINS-I Tool [66] where seven domains of bias are assessed: confounding, selection of participants, measures of intervention and outcomes, departure from intervention, incomplete outcome data, selective reporting, and other concerns. The judgment of each domain includes three categories: low, high, or unclear risk of bias.

The GRADE method for assessing the quality of aggregate evidence was used for each comparison and outcome. The Working Group used the GRADE system for ranking outcomes and scored each outcome from the evidence review for Questions 2 and 3 on a scale from critically important, important but not critical, or of limited importance in the development of recommendations for the CRC screening program. The Working Group members believed that the use of GRADE was not applicable to the outcomes examined in Question 1. GRADE was also not used in Question 4 since there were no studies identified that addressed the question.

Synthesizing the Evidence

Due to the expected clinical heterogeneity among studies (e.g., disease types, treatment status), the nature of the interventions, and the outcomes assessed, meta-analysis was not planned.

Process for Developing Conclusions

The Working Group members met in-person on two occasions and held two teleconferences to develop evidence-based conclusions through consensus. For each comparison or outcome, the Working Group assessed the quality of the body of evidence for each outcome using the GRADE process [64]. Five factors were assessed for each outcome in each comparison, including the risk of bias, inconsistency, indirectness, imprecision and publication bias. Observational studies began as low quality and RCTs as high quality; the

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quality of the evidence was downgraded when serious threats were identified to one or more factors. At the meetings, the Working Group members discussed each comparison or outcome and agreed on the overall certainty of the evidence across outcomes (Table 1), whether the desirable anticipated effects were large, the undesirable anticipated effects were small, and how they related. Conclusions were developed that reflected these Working Group discussions for each comparison or outcome.

Table 1. Definition of the grades for quality of the evidence.

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

RESULTS

Literature Search Results

The search for primary literature beyond the USMSTF review yielded 1559 citations, of which 300 met the inclusion criteria and were retrieved for full-text review (PRISMA flow diagram – Appendix 3). The updated search yielded 320 citations, 22 of which met the inclusion criteria and were retrieved for full-text review. In total, 84 articles (44 from the search [1-10,12,31,32,37,38,43-47,50-59,67-79], plus 40 articles from the USMSTF [11,14-31,33-36,39-42,48,49,80-90] were selected for inclusion and were evaluated using Cochrane's Risk of Bias tool [65] or the ROBINS tool [91] (see Appendix 4 Tables A4-3 to A4-7 for scores).

The above search also identified 28 systematic reviews, 19 of which were retrieved for full-text review. Five systematic reviews were selected for inclusion and were evaluated for quality using the AMSTAR [63] (see Appendix 4 Table A4-2 for scores). Two of the systematic reviews concerned CRC screening [74,75]: one examined extended versus segmental colectomies [78], one summarized ovarian cancer (OC) surveillance [70] and one reviewed data on urinary tract cancer (UTC) [72]. Studies selected for inclusion are presented in Table 2.

Table 2. Studies selected for inclusion.

Research Question	Number of sources that were included
What is the risk for Lynch syndrome cancers for people affected or at risk for Lynch syndrome?	27 cohort studies [1-20,23-29,83,88]
For each Lynch syndrome cancer, what cancer screening protocols are effective for people affected or at risk for Lynch syndrome?	4 systematic reviews [70,72,74,75] 23 cohort studies [30-40,42,68,69,71,80,82,85,87,89,90,92,93]
For each Lynch syndrome cancer, what risk reduction strategies other than screening are effective for people affected or at risk for Lynch	3 RCTs [48,49,84] 18 cohort studies [38,41-47,50-57,76,79]

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syndrome?	
What is the most effective surveillance protocol for persons with a colorectal cancer and a known or suspected Lynch syndrome germline mutation who did not have a total proctocolectomy?	1 systematic review [78] 11 cohort studies [42-47,57-59,77,79]

Abbreviations: RCT: randomized controlled trial

Study Design and Quality

The USMSTF guideline was evaluated for reporting quality using the AGREE II [62]. As well, the relevance of the guideline was evaluated for context and its applicability in Ontario.

The systematic reviews were assessed using the AMSTAR criteria [63]. Using these criteria, the scores of the reviews varied, but all reviews had a comprehensive literature search, used appropriate methods to combine the findings of the included studies, and included a conflict of interest statement. Common limitations were a lack of a list of excluded studies and a lack of assessment of publication bias. The systematic reviews focused on different interventions, populations and outcomes, and provided valuable information to inform the objective of the guideline.

The primary studies included all levels of evidence: RCTs, prospective and retrospective cohort studies, and case-control studies. There were many methodological issues with the evidence. The most common limitations overall were small study sizes, small number of events, high attrition rates, lack of power calculations, and lack of blinding of participants and assessors (see Appendix 4 for quality assessment tables).

Conclusions about Importance of Outcomes

The Working Group members decided that the outcomes varied among questions and thus ranking the outcomes should occur independently for each question. Outcomes were not ranked for Questions 1 and 4, as the GRADE methodology, which is intended to rate the quality of evidence in reviews that examine alternative management strategies, was not thought to be applicable to these questions. Question 1 examined risk of cancer (without comparators) and for Question 4, the literature search failed to identify studies that compared different surveillance protocols. For Questions 2 and 3, there was complete or near complete agreement among Working Group members that cancer-related death and cancer incidence were critically important outcomes; for Question 2, participation with the screening test and cancer detection were also believed to be critically important (Tables 3 to 5).

There was greater variability in the ranking of the remaining outcomes, most of which were considered important but not critical, except for pre-cancerous lesion detection and incidence outcomes in studies of risk-reducing surgical interventions.

Outcomes

Question 1. What is the risk for Lynch syndrome cancers for people affected or at risk for Lynch syndrome? Are there differences in risk for various germline mutations?

Twelve studies that examined the increased cancer risk of people with Lynch syndrome were identified in the literature search [1-10,12,13]. Combining these data with the 18 studies from the USMSTF guideline [11,14-26,28,29,83,88], it was found that lifetime risk for many cancers in people with Lynch syndrome (Tables 7 and 8) is high. The risk estimates were assessed using the number studies for that cancer, the magnitude of the cumulative risk or

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standardized incidence ratio (SIR) and the consistency of the findings among the studies examining that cancer.

Persons affected or at risk for Lynch syndrome were at highest risk for CRC and EC where there were multiple studies with consistent results showing very high SIR or cumulative risk values. The cumulative risk for CRC by age 70 varied from 10% to 82% [1,2,6,10,12,13,15,16,18,20,22-29] compared with 4.45% in the general population [94]. The cumulative risk by age 70 for EC was 12% to 71% [1,2,6,12,13,15,16,18,20,22,23,25-29] compared with 2.87% in the general population [94]. The SIR for CRC ranged from 10 to 68 and for EC from 31 to 62 for persons affected or at risk for Lynch syndrome [2,6,12,13,15,16,18,20,22,23,25-29].

Persons with Lynch syndrome were also at increased risk of OC as well as gastric, bladder, urothelial, small intestinal cancer, hepatobilliary and brain cancers [1-4,9,12-17,20-22,27]. Various studies show an increased range in cumulative risk and SIR compared with the general public [61]. There was a possible increase in lifetime risk of breast, prostate, pancreatic and hematologic cancers in this population. There are fewer studies examining those cancers and risks are inconsistent among studies (Tables 7 and 8).

For most cancers, persons with *MLH1*, *MSH2* and *MSH6* mutations are at highest risk while those with *PMS2* mutations appear to be at lower risk (Tables 8 and 9). However, the sample sizes are small in these studies and for some cancers; associations have not been extensively investigated. Further study is warranted to better delineate risk of cancer type by gene mutation (also, see Appendix 5 for raw data and study characteristics).

Question 2. For each Lynch syndrome cancer, what cancer screening protocols are effective for people affected or at risk for Lynch syndrome?

Conclusion about Importance of Outcomes

There was complete or near-complete agreement among the Working Group members that cancer-related death, participation with the screening test, cancer detection and cancer incidence were critical outcomes (Table 3). There was greater variability in the ranking of the remaining outcomes, all of which were considered important but not critical.

Table 3. Working Group members ranking of outcomes by importance for Question 2.

Outcomes	Working Group members (n)		
	Critical	Important but not critical	Of limited importance
Cancer-related death	5	0	0
Participation with the screening test	5	0	0
Cancer incidence (over time)	4	1	0
Cancer detection rate (from the test)	4	1	0
Harms (e.g. false positives, unnecessary treatment, distress, different risks)	2	3	0
Pre-cancerous lesion (e.g. polyp) incidence	1	3	1
Pre-cancerous lesion (e.g. polyp) detection	1	3	1

There were four systematic reviews [70,72,74,75], eleven CRC studies [30,42,68,69,71,82,87,92,93] and 10 EC and OC studies [30-38,85] and one study each for small bowel [80], urinary [39]and gastric [40] cancer.

Colorectal cancer screening for people affected or at risk for Lynch syndrome

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Evidence for the effectiveness of CRC screening included two systematic reviews [74,75], and eleven studies, three from the updated search [68,69,71] and eight from the USMSTF [30,42,82,87,89,90,92,93]. The characteristics and GRADE evidence profile for the studies can be found in Tables 10 and 11.

One meta-analysis conducted by Jenkins et al. examined age- and sex-specific CRC five-year risks for persons with *MLH1* and *MSH2* mutations using four cohort studies and provides some indirect evidence on age of initiation. The benefit of annual colonoscopy was evaluated by estimating the number needed to screen to prevent one CRC death [74]. They found that short-term (five-year) risk of CRC is dependent on age and is the highest for people in their 50s. The five-year CRC risk for those in their 50s is approximately 10 times greater than for those in their 20s. However, there is a large increase in risk from persons in their 20s to those in their 30s. The risk increases from 1 in 71 (1.4%) men and 1 in 102 (1.0%) women in their 20s to 1 in 21 (4.8%) men and 1 in 30 (3.3%) women among persons 30 to 39 years of age. Annual colonoscopy in 155 men or 217 women in their 20s was estimated to prevent one death from CRC over 5 years while resulting in approximately one serious complication. In comparison, annual colonoscopy in 45 men or 66 women in their 30s would prevent one death from CRC over five years while resulting in almost no serious complications.

Haanstra et al. conducted a systematic review, searching between 1980 and 2012, and found six studies in which new endoscopic techniques were investigated in Lynch syndrome: narrow-band imaging (n=1), autofluorescence endoscopy (n=1), and chromocolonoscopy (n=4) [75]. They concluded that none of these techniques appeared to show clear superiority over conventional white light colonoscopy for Lynch syndrome subjects, but that chromocolonoscopy seemed to be the most promising. One cross-sectional study compared the number of adenomas found in Lynch syndrome patients examined first by standard colonoscopy and then by chromocolonoscopy performed by a second gastroenterologist blinded to the findings of the first colonoscopy [71]. Significantly more patients with at least one adenoma were identified by chromocolonoscopy (32 of 78, 41%) than by standard colonoscopy (18 of 78, 23%; $p < 0.001$). However these findings are biased in favor of chromocolonoscopy as the order of the two procedures was not randomized and chromocolonoscopy always followed standard colonoscopy. There were no studies on screening tests other than colonoscopy in persons with Lynch syndrome.

Three cohort studies compared persons with Lynch syndrome who had colonoscopy screening with a similar population without colonoscopy screening [87,92,93]. All studies found that the screened group of Lynch syndrome patients had significantly fewer deaths from CRC (5% vs. 29%; 2% vs. 12%; 0% vs. 8%, respectively) and significantly lower CRC incidence than the non-screened group (18% vs. 68%; 7% vs. 27%; 6% vs. 16%, respectively). Two studies did not report any complications or harms in either the screened or unscreened group [81,87]. One non-comparative study that followed 242 Lynch syndrome patients for 11.5 years reported three painful colonoscopies [30]. Six studies [30,81,82,87,89,93] reported that the compliance rate varied from 72% [81] to 96% [30] or that most Lynch syndrome patients complied with the screening protocols [82,87,89,93]. There is no evidence regarding the intervals between colonoscopies in person with Lynch syndrome. One study [68] attempted to compare a program with intervals between colonoscopies planned for three years to other programs with one to two year intervals but the intervals were similar in length (32.7 vs. 31.0 months; $p>0.05$) as were the number of CRC found (51 vs. 50; $p>0.05$). Ten studies used screening intervals that varied from one to three years [30,42,68,69,82,87,89,90,92,93]. There was no direct evidence for age of initiation or cessation of screening or for CRC screening effectiveness by gene mutation.

Screening for endometrial cancer in women affected or at risk for Lynch syndrome

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Evidence from 10 cohort studies (three from our search and seven from the USMSTF) was used to assess the use of screening for EC in women affected or at risk for Lynch syndrome (Tables 12 and 13) [30-38,85]. One study compared a screened cohort of 54 women screened with routine or directed endometrial biopsy (EB) (for thickened endometrium on transvaginal ultrasound (TVUS)) to a historical matched non-screened group and found no significant difference in death due to EC (p=0.079) but did find significantly fewer complex atypical hyperplasia (CAH) lesions and ECs in the screened group compared with the non-screened group over 4.5 years (p=0.017) [31]. However, there were comparable hysterectomy rates in the two groups, suggesting possible contamination. Two studies compared two different screening strategies over two time periods: TVUS with directed EB because of endometrial thickening versus TVUS plus routine EB [32,33]. There were no EC related deaths in either group for both studies. One study [33] found significantly fewer CAH/ECs with TVUS + routine EB than TVUS + directed EB (p=0.026), while the other study [32] did not (p=0.429).

There were no deaths due to EC in the studies without a comparator [30,34,35] and 1% to 18% of patients were diagnosed with CAH/EC [30,34]. There were no studies that reported on complications but Helder-Woolderink et al. reported that 8 of 10 of preventive operations were performed because of cancer worries and/or anxiety for invasive and painful endometrial sampling procedures annually [32]. The compliance and participation rates ranged from 76% to 97% for at least one screen [30,34]. The median number of visits ranged from one to three per patient [32].

There were no studies examining ages at initiation or cessation of EC screening or intervals between screening examinations. Most studies recommended that screening start at ages 30 to 35 years and used intervals of one to three years but there were no studies comparing different start ages or intervals.

There were no data on the effectiveness of EC screening by gene mutation.

Screening for ovarian cancer in women affected or at risk for Lynch syndrome

Eight studies [30-33,35,37,38,85] measured screening outcomes for OC in women affected or at risk for Lynch syndrome (Tables 13 and 14).

Only one study by Stuckless et al. compared a screened population (TVUS+CA-125) with a non-screened population and found no significant differences in OC-related death or OC incidence (p=1.0); however, the control group had rates of hysterectomy and oophorectomy similar to the cases, again suggesting possible contamination [31]. Five observational studies with no non-screened control group examined TVUS alone or with CA-125 or with a physical examination [30,32,33,35,36]. No deaths due to OC were found over a follow-up ranging from 8-11.5 years and the incidence of OC ranged from 0% to 6%.

There were no studies examining age of initiation or cessation of screening for OC, or intervals between screening exams. Most studies recommended that screening start at ages 25 to 35 years and used intervals of one to three years but there were no studies comparing different start ages or intervals [30,34-38].

There were no studies on the effectiveness of OC screening by gene mutation.

Small bowel cancer screening for people affected or at risk for Lynch syndrome

One prospective case series from France evaluated capsule endoscopy (CE) and computed tomography enteroclysis (CTE) by performing both tests on 35 Lynch syndrome patients [80]. Two jejunal adenomas were found by CE but not by CTE and one jejunal adenocarcinoma was found by both tests (Tables 15 and 16). There were no studies examining age of initiation or cessation of screening for small bowel cancer, intervals between screens or the effectiveness of screening different gene mutation groups.

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Urinary tract cancer screening for people affected or at risk for Lynch syndrome

One recent systematic review by Mork et al., with the aim of informing urologists about Lynch syndrome, examined retrospective studies, reviews and guidelines of various aspects of UTC and Lynch syndrome, and concluded that there was no ideal screening test (i.e., urinalysis, cytology, nuclear matrix protein-22, renal ultrasound) or interval of screening for UTC [72].

One retrospective cohort study from Denmark linked patients from the Danish HNPCC registry to Patobank, the National Danish Pathology database, to evaluate whether the use of urine cytology (UC) was appropriate for UTC screening [39]. There were no deaths due to UTC reported in the study and the incidence of UTC was the same for the screened and unscreened groups. Only 0.1% of UC examinations (2 of 1868) led to a diagnosis of an asymptomatic UTC, and there were 22 false positives. As well, adherence to screening was only 29% (Tables 15 and 16). There were no studies regarding the age of initiation or cessation of screening, intervals of screening examinations or the effectiveness of screening different gene mutation groups.

Upper gastrointestinal cancer screening for people affected or at risk for Lynch syndrome

In one prospective case series published in 2002, gastroscopy was performed in 73 gene mutation positive subjects and 32 relatives. One duodenal cancer was found in the mutation positive group [40]. There was no significant difference between the groups for: *Helicobacter pylori* infection (p=0.7), gastric atrophy (p=0.4), intestinal metaplasia (p=0.8), gastric polyps (p=NR) or inflammation (p=0.9) (Tables 15 and 16). There were no studies investigating the age of initiation or cessation of screening, intervals of screening examinations or the effectiveness of screening different gene mutation groups.

Question 3. For each Lynch syndrome cancer, what risk reduction strategies are effective for people affected or at risk for Lynch syndrome?

Conclusions about the Importance of Outcomes

The Working Group ranked the outcomes for importance separately for surgical and non-surgical interventions (Tables 4 and 5). There was complete agreement among Working Group members that cancer related death and cancer incidence were of critical importance. Harms from and participation with the risk-reducing intervention were deemed to be very important. Cancer detection rate was important but not critical. While pre-cancerous lesion incidence and detection were believed to be less important for surgical interventions, they were not ranked for non-surgical interventions.

Table 4. Working Group members ranking of outcomes by importance for surgical interventions.

Outcomes available in the evidence found	Working Group members (n)		
	Critical	Important but not critical	Of limited importance
Cancer-related death	5	0	0
Cancer incidence (over time)	5	0	0
Harms (e.g. false positives, unnecessary treatment, distress, different risks)	3	2	0
Compliance and participation	2	3	0
Cancer detection rate (from the test)	1	3	1
Pre-cancerous lesion (e.g. polyp) detection	0	2	3
Pre-cancerous lesion (e.g. polyp) incidence	0	0	5

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Table 5. Working Group members ranking of outcomes by importance for non-surgical interventions or life-style factors.

Outcomes available in the evidence found	Working Group members (n)		
	Critical	Important but not critical	Of limited importance
Cancer incidence (over time)	5	0	0
Cancer-related death	4	1	0
Harms (e.g. false positives, unnecessary treatment, distress, different risks)	3	2	0
Compliance and participation	1	4	0
Pre-cancerous lesion (e.g. polyp) incidence	0	5	0

There were 21 studies that examined risk reduction strategies in people with Lynch syndrome [38,41,42,44-57,76,79,84] (Tables 17 to 19).

Use of extended colectomy in persons with colorectal cancer and Lynch syndrome

There were six cohort studies that compared extended (total) colectomy (TC) and segmental colectomy (SC) in Lynch syndrome CRC patients for the outcome of CRC incidence [42-47]. Two studies found that CRC related death occurred more often in those Lynch syndrome patients with SC versus TC (33% vs. 9.5%; 1.8% vs. 0, respectively) [42,47]. Heneghan et al. performed a meta-analysis using five of the studies and found metachronous cancers occurred more frequently after SC than after TC (23.5% vs. 6.8%; odds ratio, 3.679; $p < 0.005$) [78]. One study reported on harms for both groups being a second abdominal surgery due to adhesions causing bowel obstruction caused by the first surgery SC=4, TC=2 [45] (Tables 17 and 18). There were no studies that provided data to determine benefit by gene mutation.

Use of prophylactic surgery to prevent endometrial or ovarian cancer

Two retrospective studies were conducted that compared the incidence of EC and OC in women who elected to have a risk-reducing hysterectomy (RRH) with or without a bilateral salpingo-oophorectomy (BSO) [38,41]. Tzortzaros et al. compared 41 women who had a RRH and/or BSO with 45 women who had had some type of clinical surveillance [38]. The difference in cumulative proportion free from either EC or OC cancer diagnosis at 70 years of age between the surgery and surveillance groups was not significant (0.88 vs. 0.52, p=0.079). Schmeler et al. compared 61 women who underwent RRH and/or BSO with matched controls [41]. The incidence density of EC was significantly lower for those women who had RRH compared with control ($p<0.001$) while there was no significant difference in the incidence density of OC for women who had RRH and BSO compared with control (p=0.09). No new cancers were found after surgery in women who underwent RRH and/or BSO although altogether, five EC and two CAH were found during surgery. There was little information on harms; one woman had a complication from the surgery but other harms or benefits were not evaluated (Tables 17 and 18). There were no studies that examined the optimal age of initiation for the use of risk-reducing prophylactic surgery or its effectiveness by gene mutation.

Use of aspirin/non-steroidal anti-inflammatory drugs/resistant starch to prevent colorectal cancer

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One RCT [84] and one retrospective cohort study [76] were conducted among persons with Lynch syndrome to try to determine whether aspirin decreases the incidence of CRC. In the CAPP2 study, the point estimate suggested a reduction in risk for CRC after 55 months of follow-up in those in the aspirin (600mg) group compared with the placebo group in the intention to treat analysis (hazard ratio (HR)=0.63; 95% CI, 0.35 to 1.13; p=0.12), however the confidence interval was wide and included the null [48]. The point estimate for the risk of CRC after 55 months of follow-up for those taking 30g of resistant starch compared with the placebo group was greater than one (HR=1.40; 95% CI, 0.78 to 2.56; p=0.26), indicating a lack of protective effect [49]. There was no significant difference in identified harms (ulcers, cerebrovascular or cardiovascular events) among the aspirin, resistant starch or placebo groups and no difference in compliance among the three groups [84]. The retrospective study [76] found a significant reduction in the risk of CRC for those who used aspirin (HR=0.43; 95% CI, 0.25 to 0.75; p=0.003) or ibuprofen (HR=0.35; 95% CI, 0.19 to 0.63; p=0.001) or both (HR=0.41; 95% CI, 0.28 to 0.61; p<0.001) for at least twice a week for a month or longer compared with those who reported taking those medications less frequently than that. The study controlled for potential confounders such as alcohol consumption, cigarette smoking, hormone replacement therapy, and multivitamin use (Tables 17 and 18). Neither study reported on the outcome of cancer-related death. There was no evidence regarding the age of initiation or cessation or optimal dosing for these strategies, nor data regarding the effectiveness for different gene mutations.

Use of lifestyle modifications to prevent cancer

Seven studies examined lifestyle modifications and potential confounders to reduce the risk for cancer in people with Lynch syndrome; six examined risks for CRC [50-55] and one study examined risks for EC [56] (Tables 18 and 19).

A prospective study examined the body mass index of people in the CAPP2 study and the risk of CRC [50]. For obese participants, the risk of CRC was significantly higher (HR 2.34; 95% CI=1.17 to 4.670; p=0.020) than for normal weight people. When stratified by gene mutation, obesity was significantly associated with CRC among those *MLH1* carriers (HR 3.72; 95% CI=1.41 to 9.81; p=0.008) but not *MSH2* or MSH6 carrier. The association between obesity and CRC was restricted to those not on aspirin.

Chau et al.[52] used data from the Colon Cancer Family Registry to compare never users and users of multivitamin, calcium and folic acids intake for at least three years. They found a significant reduction in risk for CRC among multivitamin users (HR=0.47; 95% CI, 0.32 to 0.69; p<0.001), calcium users (HR=0.42; 95% CI, 0.23 to 0.74; p=0.003) and a non-significant decrease for folic acid users (HR=0.87; 95% CI=0.36 to 2.08; p=0.76). Kazima et al. [55], in a retrospective study, surveyed risk factors over the preceding five years by administering a questionnaire to gene mutation carriers from a hereditary nonpolyposis colorectal cancer registry in Taiwan. They found a reduced risk of CRC among those with high fruit and tea intake. There was also a significant reduction in CRC risk for any amount of physical activity among the entire study population (HR=0.62; 95% CI, 0.41 to 0.88; p=0.009) and specifically for *MLH1* carriers (HR=0.54; 95% CI, 0.34–0.83; p=0.005). There was an increased risk of CRC for those with Hakka ethnicity (HR=1.62; 95% CI=1.09–2.34; p=0.015) and those with a manual occupation (HR=1.56; 95% CI=1.07 to 2.27; p=0.021). Jung et al. [54], Botma et al. [53], and Brouwer et al. [51] followed participants in the GEOlynch study for 28 months and using a food frequency questionnaire, compared the risk of CRC for the highest and lowest tertiles of consumption of various foods and supplements. Botma et al. [53] did not find a substantial difference in risk of colorectal adenomas for persons with Lynch syndrome on different diets (prudent, meat, snack, and cosmopolitan) but those who ate more of a snack diet and meat diet had a tendency towards higher risk for colorectal adenomas than the other diets types

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(HR=2.16; 95% CI, 1.03 to 4.49; p=0.12; HR=1.70; 95% CI, 0.83 to 3.52; p=0.21) while those that ate a more prudent or sensible diet had a tendency towards lower risk for colorectal adenomas (HR=0.73; 95% CI, 0.32 to 1.66; p=0.78). Brouwer et al. [51] used the dietary inflammatory index to analyze the composition of food intake, and compared those with high inflammatory diets to low inflammatory diets and did not find a difference in incidence of CRC between those groups (Tables 18 and 19). Jung et al. [54] did not find a difference in the risk of CRC in persons in the highest tertile of folate, dietary vitamin B2, B6 and B12, and methionine consumption compared with those in the lowest. These studies did not provide data to determine optimal ages of initiation and cessation, and timing of the lifestyle modification.

Staff et al. [56] surveyed 136 women registered in the Finnish Lynch Syndrome Registry using a questionnaire on life style factors. In the multivariate analysis, there was an increased risk for EC for women with diabetes (HR=4.18; 95% CI, 1.52 to 11.52; p=0.006) and for those who were on hormone replacement therapy for nine years (HR=1.07; 95% CI, 1.02 to 1.13; p=0.010).

Questions 4. What is the most effective surveillance protocol for persons with a colorectal cancer and a known or suspected Lynch syndrome germline mutation who did not have a total proctocolectomy?

Five cohort studies [42,58,59,77,79] and one systematic review [78] (of six studies [43-47,57]) that reported various surveillance protocols for those Lynch syndrome patients treated surgically for CRC with segmental resection. The focus of the systematic review was to compare the surgical approaches: SC versus TC for the management of CRC in people with Lynch syndrome however, some studies also reported data from surveillance [78]. The six studies in the systematic review and the five studies from the literature search reported variation in the design of the surveillance programs and the median times to cancer. There were no studies comparing different surveillance protocols in this population however, we were able to abstract data from surveillance in the 10 studies described above.

All studies used colonoscopy for surveillance. Four of the studies provided no information about their surveillance protocol [43,45,57,79]; in the other seven studies, the recommended surveillance intervals ranged from one to three years [42,44,46,47,58,59,77]. Five studies reported the average times between colonoscopies, which ranged from one year to 28.7 years for the SC group and from one to six years for the TC group [42,43,45,46,57]. The median time to a second cancer from the index surgery in the SC group was approximately 6 years (range: 0.1 to 16 years) and 19 years for the TC group (range: 1.3 to 26 years) [42,43,45,57,59,79]. Four studies reported that the median time from the last surveillance examination to CRC was approximately three years (range: 0.5 to 7.5 years) in those treated with SC [42,43,47,57]. One study reported a median of 3.8 years for those treated with TC (range: 3.4-7.5 years) and five found the CRCs within four years from the last surveillance examination [42,43,47,58,77] (Table 20).

Ongoing, Unpublished, or Incomplete Studies

Ongoing, unpublished, and incomplete studies are reported in Table 6.

Table 6. Ongoing studies.

Name	Type		Protocol ID
Chromoendoscopy to Decrease the Risk of Colorectal Neoplasia	Interventional	Endpoints of the study are the number of adenomas, advanced	NCT00905710

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in Lynch syndrome (ChromoLynch)		adenomas, carcinomas at baseline and the number of the number of adenomas, advanced adenomas, carcinomas, complications and the number of patients requiring colectomy at 2-year follow-up.	
Assessment of the Effect of a Daily Chemoprevention by Low-dose Aspirin of New or Recurrent Colorectal Adenomas in Patients With Lynch syndrome (AAS-Lynch)	Interventional	The proposed trial will evaluate the effect of aspirin 300 mg/d and 100 mg/d during 4 years vs placebo, in a 4 groups randomised parallel design in Lynch syndrome patients.	NCT02813824
A Randomised Double Blind Dose Non-inferiority Trial of a Daily Dose of 600mg Versus 300mg Versus 100mg of Enteric Coated Aspirin as a Cancer Preventive in Carriers of a Germline Pathological Mismatch Repair Gene Defect, Lynch syndrome (CaPP3 Israel)	Interventional Phase 3	A randomized double blind dose non-inferiority trial of a daily dose of 600mg versus 300mg versus 100mg of enteric coated aspirin as a cancer preventive in carriers of a germline pathological mismatch repair gene defect, Lynch syndrome. Project 3 in the Cancer Prevention Programme (CaPP3).	NCT02497820
High Definition White-Light Colonoscopy vs. Chromoendoscopy for Surveillance of Lynch syndrome	Interventional	A prospective multicenter randomized non-inferiority study. The principal aim is to compare the adenoma detection rate with WLE vs. CE.	NCT02951390
Mesalamine for Colorectal Cancer Prevention Program in Lynch syndrome (MesaCAPP)	Interventional Phase 2	Multicenter, multinational, randomized, 3-arm, double-blind, phase II clinical study with 2400mg Mesalamine, 1200mg Mesalamine or placebo for prevention of neoplasia in Lynch syndrome patients for 2 years.	NCT03070574
Capsule Endoscopy in Lynch syndrome for Small Intestinal Tumour Screening (CELSIUS)	Interventional Phase 1	The aim of the study is to determine the prevalence and incidence of small bowel neoplasia in Lynch syndrome patients using small bowel CE and DBE.	NCT00898768
A Phase Ib Biomarker Trial of Naproxen in Patients at Risk for DNA Mismatch Repair Deficient Colorectal Cancer	Interventional Phase 1	Randomized phase Ib trial to study the side effects and best dose of naproxen in preventing deoxyribonucleic acid (DNA) mismatch repair deficient colorectal cancer in patients with Lynch syndrome.	NCT02052908

DISCUSSION

In summary, we have found only low to very low-quality evidence to guide the management of persons with Lynch syndrome and at risk of Lynch syndrome in terms of their risk of cancer, recommended surveillance and lifestyle modifications. There appears to be a definite risk of colorectal cancer (CRC) and endometrial cancer (EC) and a likely risk of

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ovarian cancer (OC) as well as gastric, bladder, urothelial, small intestine cancer, hepatobiliary, and brain cancer in persons with Lynch syndrome and at risk of Lynch syndrome. There is weak evidence to support colonoscopy to screen for CRC, prophylactic surgery to prevent EC or OC, extended colectomy in persons with CRC, aspirin/non-steroidal anti-inflammatory drugs, diets high in fruit, use of calcium or multivitamin supplements and vigorous exercise to prevent CRC in persons with Lynch syndrome or at risk for Lynch syndrome. The data on other types of surveillance or preventative strategies are insufficient or non-existent.

Limitations

There are significant limitations to this review, including the small sample sizes for many studies, the lack of meaningful data on undesirable harms and benefits, an absence of studies addressing questions of interest, and the design limitations of the included studies, such as the paucity of randomized controlled trials.

There was variation in the risk estimates reported for many of the questions in this review. The reasons for variation may be related to variation in the underlying study populations and the small sample sizes of many studies. As an example of the former limitation, some studies restricted the study population to only those people tested for DNA mismatch repair mutations while others allowed relatives of those with Lynch syndrome (without requiring genetic testing) who may be at a lower risk (Appendix 5). Studies with smaller sample sizes are vulnerable to less precise estimates, which may contribute to the observed variation. Finally, the composition of study populations may have varied by gene mutation type, which may also have contributed to variation in the estimates of risk, particularly in smaller studies.

Undesirable effects and harms were not evaluated in any meaningful way in the included studies and therefore, for most questions, the data are insufficient to address this issue. In part, the lack of data on this topic may be due to our search strategies, which did not search specifically for harms. Of the 85 studies reviewed, only three studies reported on harms; three painful colonoscopies were reported in one study [30], another reported one complication from surgery [41] while another study reported that women opted for surgery because of cancer worries and anxiety about yearly painful endometrial sampling procedures [32]. Another limitation of our review is that we did not include patient representatives in the Working Group; therefore, no comment can be made on the data from a patient's perspective.

There were a number of questions that were of interest but could not be answered because there were no published studies found. For example, there was no evidence regarding oral contraceptives in women at risk for Lynch syndrome, although the risk for EC has been shown to be reduced in the general population with the use of oral contraceptives [95]. Although it is not uncommon that persons with Lynch syndrome are treated with segmental colectomy there, are no published clinical trials on the role of completion colectomy or on the appropriate surveillance protocols for these persons. In addition, it would appear reasonable to conduct surveillance using colonoscopy in this population; however, there are insufficient data to recommend a specific interval between colonoscopies.

Lastly, the included studies were of low or very low quality, as such, all recommendations were based on weak evidence. There were very few controlled trials and as such, confounding could have occurred. Furthermore, many studies were vulnerable to selection bias and recall bias.

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Future Research

There is ample room for future research in persons with Lynch syndrome. Some research, as noted above, is ongoing. For example, the use of aspirin and/or non-steroidal anti-inflammatory drugs is of considerable interest given the data presented above. It is noted that the dose of aspirin (600 mg/day) used in the literature to date is quite high. Currently, there is an RCT being conducted (CAPP3) that is looking into lower doses of aspirin.

Other areas of future research that are of interest include a better determination of cancer risk by age, sex and gene mutation type. In addition, a more detailed understanding of the role of age would be useful. In a study outside of our research question, Ryan et al., studied 1063 people with Lynch syndrome, comparing the age of diagnosis for various cancers and gene mutation types [96]. They found that men and women with *MSH6* mutations were diagnosed with CRC and EC at later ages than those with other gene mutations and women with truncating *MLH1* mutations were diagnosed with EC at later ages than those with other gene mutations. Another interesting area might be to better understand the "inflection" point by cancer type and gene mutation; that is, the age at which the incidence of these cancers appears to rise instead of reporting median age.

There are some areas where there may be limited opportunity for further study given the current practice. For example, the American College of Obstetricians and Gynecologists recommend that risk-reducing hysterectomy (RRH) and bilateral salpingo-oophorectomy be discussed with women with Lynch syndrome by their early to mid-40s as a risk-reducing option. Uptake of this practice may limit studies examining the benefit of RRH in women with Lynch syndrome; however, there are other opportunities for study in this area such as the risks of surgery, medical management of menopause, and fertility.

NEXT STEPS

This evidence summary reports what is known about the management of persons with or at risk of Lynch syndrome. However, the evidence summary is necessary but not sufficient to guide the development of screening recommendations as other context-specific criteria must be considered. In addition, the program must also consider issues not well addressed by the evidence such as patient preference and potential harms. An expert panel including primary care physicians, colorectal surgeons, gastroenterologists, pathologists and members of the public will be convened to provide guidance on how to incorporate the evidence summarized here in light of these other issues.

Cancer Care Ontario will use findings from this evidence summary, as well as expert panel recommendations to guide the development and design of Ontario's high-risk colorectal cancer screening program.

INTERNAL REVIEW

The evidence summary was reviewed by the Director of the PEBC. The Working Group is responsible for ensuring the necessary changes are made.

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INFLUENCE

Table 7. Summary of cumulative risk by age 70 and standardized incidence ratio ranges of all gene mutations and sexes of Lynch syndrome cancers for people affected or at risk for Lynch syndrome.

Cancer	General Population Cumulative Risk % (by age 70 years) [61]	Cumulative Risk % (by age 70 years)	Standardized Incidence Ratio	Median Age at Diagnosis (years) (range)	References
Colorectal	4.4	10-82	10-68	43-60	[1,2,6,10,12,13,15,16,18,20,22-29]
Endometrium	2.9	12-71	31-62	44-58	[1,2,6,12,13,15,16,18,20,22,23,25-29]
Ovary	1.3	1-24	3-19	43-54	[1,12-15,20,21,25,27,28]
Gastric	0.5	0.2-20	3-10	48-69	[4,12-15,17,20-22,27,28]
Bladder	2.4	0-16	4-16	53-71	[4,9,13,14,16]
Urothelial	1.6	0-27	1-122	46-69	[2,4,9,12,13,15,16,20,27,28]
Small Intestinal Cancer	<1	0-12	0-251	46-55	[13-15,20,21]
Breast	14.7	2-19	1-5	52-60	[5,13,14,20,28]
Prostate	11.6	0-29	1-5	54-65	[7,8,11,13,14,19,28]
Pancreatic	1.6	0.4-1	2-11	64-65	[13,20]
Hepatobiliary	1.0	0-3	4-10	50-62	[13,15,20,28]
Hematologic	-	-	2-7	57	[13,28]
Brain	0.6	0-6	4-9	41-68	[3,13,20,21,27]

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Table 8. Gene-specific cumulative risk by age 70 of Lynch syndrome cancers for people affected or at risk for Lynch syndrome: Summary table.

Cumulative Risk % by age 70 years range						
Cancer	***MLH1***	***MSH2***	***MSH6***	***PMS2***	**Those Studies incorporating All Genes**	**Reference**
Colorectal	34-60	35-64	10-69	10-20	10-82	[1,2,6,10,12,13,15,16,18,22-29]
Endometrium	18-54	21-51	16-71	12-24	12-71	[1,2,6,12,13,15,16,18,20,22,23,25-29]
Ovary	3-20	6-24	0-1	0	0-24	[1,12-15,20,21,25,27,28]
Gastric	2-20	0.2-9	0-10	-	0-20	[4,12-15,17,20-22,27,28]
Bladder	0-11	3-12	0-2	-	0-16	[4,9,13,14,16]
Urothelial (UT+UUT)	0.2-16	0-27	0-9	-	0-27	[1,2,4,9,12,13,15,16,20,27,28]
Small intestinal cancer	0.4-8	1-8	0-3	-	0-12	[13-15,20,21]
Breast	17-19	2-11	12	-	2-19	[5,13,14,20,88]
	MLH1 + *MSH2*: 13					
Prostate	0	18	4	-	0-29	[7,8,11,13,14]
Pancreatic	-	1	-	-	0.4-1	[13,20]
Hepatobiliary	2-3	0-0.4	0	-	0-3	[13,15,20,28]
Hematologic	-	-	-	-	-	-
Brain	0.3-2	1-6	0-0.8	-	0-6	[3,13,20,21,27]

Abbreviations: MLH = mutL homolog; MSH = mutS homolog; PMS = postmeiotic segregation; UT = urinary tract; UUT = upper urinary tract

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Table 9. Gene-specific standardized incidence ratios of Lynch syndrome cancers for people affected or at risk for Lynch syndrome: Summary table.

Standardized Incidence Ratio range						
Cancer	***MLH1***	***MSH2***	***MSH6***	***PMS2***	**Those Studies incorporating All genes**	**Reference**
Colorectal	39	11	17	15	10-68	[2,10,13,28]
Endometrial	35	45	50	-	31-62	[13,28]
Ovary	3	6	-	-	3-19	[13,14,28]
Gastric	3-5	6-7	8	-	3-10	[13,14,17,28]
Bladder	4	12	-	-	4-16	[13,14]
Urothelial (UT+UUT)	1-10	7-18	-	-	8-122	[9,13,14,28]
Small Intestinal Cancer	41	109	-	116	0-251	[13,14]
Breast	1	2	5	-	1-5	[13,14,28]
Prostate	1	4	1	-	1-5	[8,13,14,28]
Pancreatic	-	4	-	-	4-11	[13,28]
Hepatobiliary	8	4	10	-	4-10	[13,28]
Hematologic	-	7	-	-	2-7	[13,28]
Brain	-	9	-	-	4-9	[13,28]

Abbreviations: MLH = mutL homolog; MSH = mutS homolog; NHL= non-Hodgkin's lymphoma; PMS = postmeiotic segregation; UT = urinary tract; UUT = upper urinary tract

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Table 10. GRADE summary table for colorectal cancer screening for people with Lynch syndrome.

Patients or population: Lynch syndrome Patients Setting: Colorectal Cancer Screening Intervention: Screening (colonoscopy)											
Outcomes	Study Design	Intervention	Comparison	Number of Participants (studies)	Main findings	Risk of Bias	Consistency	Directness	Precision	Other (publication bias)	Quality of Evidence (GRADE)
Colorectal Cancer											
Colonoscopy vs. Chromocolonoscopy											
Pre-cancerous lesion detection Importance: Important -1 study	Cross-sectional [71] (Rahmi, 2015)	Colonoscopy	Chromo-colonoscopy	78 MMR germline mutation carriers	Colonoscopy group: At least 1 adenoma 18/78 (23%) Chromocolonoscopy group: 32/78 (41%) p<0.001	Serious[1]	Not Serious	Serious[2]	Serious[3]	Serious[4]	Very low
Harms or Complications Importance: Important -1 study	Cross-sectional [71] (Rahmi, 2015)	Colonoscopy	Chromo-colonoscopy	78 MMR germline mutation carriers	No complications in either group	Serious[1]	Not Serious	Serious[2]	Serious[3]	Not Serious	Very low
Colonoscopy vs. No Colonoscopy											
Cancer Related Death Importance: Critical -3 studies	Retrospective Cohort [92] (Stuckless, 2012) Program Recommended COL=1-2 yrs	Screening with colonoscopies	No colonoscopy	322 *MSH2* mutation carriers Screened group: 152 in screening program	Screened group Death due to CRC<8* (5%) Non screened Death due to CRC=50 (29%) p=0.000	Serious[1,5]	Not Serious	Not Serious	Serious[3]	Not Serious	Very low

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	Starting at age 20-25 yrs F/U=12 yrs			Non-screened: 170 historical control							
	Prospective Cohort [93] (Stupart, 2009) Program Recommended COL=2 yrs until age of 30, then annually. Starting at age 18. F/U=18 yrs	Screening with colonoscopies	No colonoscopy	178 subjects with MMR mutation of *MLH1* Screened group: 129 Non screened group: 49	Screened group Deaths due to CRC= 3 (2%) Non screened Death due to CRC= 6 (12%) p=0.021						
	Prospective Cohort [87] (Jarvinen, 2000) Program Recommended COL = 3 yrs F/U=15 yrs	Screening with colonoscopies	No colonoscopy	252 persons from families with HNPCC Screened group: 133 had COL Non screened group: 119	Screened group Death due to CRC=0 (0%) Non screened Death due to CRC=9 (8%) p<0.001						
Colorectal Cancer Incidence Importance: Critical -3 studies	Retrospective Cohort (Stuckless, 2012) [92] Program Recommended COL = 1-2 yrs Starting at age 20-25 yrs F/U=12 yrs	Screening with colonoscopies	No colonoscopy	322 *MSH2* mutation carriers Screened group: 152 in screening program Non screened: 170 historical control	Screened group CRC=28 (18%) Non screened CRC=116 (68%) p=0.000	Serious[1,5]	Not Serious	Not Serious	Serious[3]	Not Serious	Very low
	Prospective Cohort [93] (Stupart, 2009)	Screening with colonoscopies	No colonoscopy	178 subjects with MMR mutation of *MLH1*	Screened group CRC= 9 (7%) Non screened						

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	Program Recommended COL=2 yrs until age of 30, then annually. Starting at age 18. F/U=18 yrs			Screened group: 129 Non screened group: 49	CRC= 13 (27%) p=0.019						
	Prospective Cohort [87] (Jarvinen, 2000) Program Recommended COL=3 yrs F/U=15 yrs	Screening with colonoscopies	No colonoscopy	252 persons from families with HNPCC Screened group: 133 Non screened group: 119	Screened group CRC =8 (6%) Non screened CRC=19 (16%) p=0.014						
Pre-cancerous lesion incidence Importance: Important -1 study	Prospective cohort [87] (Jarvinen, 2000) Program Recommended COL=3 yrs F/U=15 yrs	Screening with colonoscopies	No colonoscopy	252 persons from families with HNPCC Screened group: 133 Non screened group: 119	Screened group: Adenomas: 31 (23%) Non screened: Adenomas: 4 (3%) p=0.001	Serious[1]	Not Serious	Not Serious	Serious[3]	Not Serious	Very low
Cancer Detection Importance: Important -1 study	Prospective cohort [87] (Jarvinen, 2000) Program Recommended COL=3 yrs F/U=15 yrs	Screening with colonoscopies	No colonoscopy	252 persons from families with HNPCC Screened group: 133 Non screened group: 119	Screened: CRC=2 (1.5%) Dukes A=1 Dukes B=1 Non Screened: CRC=2 (1.7%) Dukes A=1 Dukes B=1	Serious[1]	Not Serious	Not Serious	Serious[3]	Not Serious	Very low
Complications or Harms Importance: Important -2 studies	Retrospective Cohort [92] (Stuckless, 2012) Program Recommended COL=1-2 yrs	Screening with colonoscopies	No colonoscopy	322 *MSH2* mutation carriers Screened group: 152 in screened program	No complications reported	Serious[1]	Not Serious	Not Serious	Serious[3]	Not Serious	Very low

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	Starting at age 20-25 yrs F/U=12 yrs			Non screened: 170 historical control							
	Prospective Cohort [87] (Jarvinen, 2000) Program Recommended COL=3 yrs F/U=15 yrs	Screening with colonoscopies	No colonoscopy	252 persons from families with HNPCC Screened group: 133 had COL Non screened group: 119	No significant complications reported for either group						
Colonoscopy – No comparison											
Cancer Related Death Importance: Critical -5 studies	Prospective Cohort [90] (Vasen, 2010) Program Recommended COL= 1-2 yrs Starting at age 20-25 yrs F/U=7.2 yrs	Screening with colonoscopies	None	745 MMR mutation carriers	Death due to CRC=0 (0%)	Serious[1]	Not Serious	Serious[2]	Serious[3]	Not Serious	Very low
	Prospective Cohort [89] (Engel, 2010) Program Recommended COL =1yr Starting at age 25 yrs F/U=NR	Screening with colonoscopies	None	402 mutation carriers or relatives	Death due to CRC=0 (0%)						
	Prospective Cohort [30] (Jarvinen, 2009) Program	Screening with colonoscopies	None	242 MMR mutation – positive subjects	Death due to CRC=3 (1%)						

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	Recommended COL=< 3 yrs F/U=11.5 yrs										
	Prospective Cohort [82] (Dove-Edwin, 2005) Program Recommended COL=5 yrs: 3 if adenoma detected; Approx. 1995, every 1-3 yrs Starting at age 25 F/U=15 yrs	Screening with colonoscopies	None	554 members of 290 families in whom a mutation for HNPCC has been found	Death due to CRC=3 (0.5%)						
	Prospective Cohort [42] (de Vos tot Nederveen Cappel, 2002) Program Recommended COL=< 2 yrs Starting at age 20-25 yrs F/U=13 yrs	Large bowel investigation	None	887 members of 114 HNPCC or MMR-positive families	Death due to CRC=2 (0.2%)						
Cancer Incidence Importance: Critical -7 studies	Prospective Cohort [68] (Seppala, 2017) Program Recommended COL=1-3 yrs F/U=9.2 yrs	Screening with colonoscopies	None	944 families MMR mutation positive subjects	Total CRC=101 (9.3%)	Serious1	Serious[6]	Not Serious	Serious[3]	Not Serious	Very low
	Prospective Cohort [69] (Lindberg, 2017)	Screening with colonoscopies	None	235 families MMR mutation positive	Total CRC=53 (2%)						

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	Program Recommended COL=2 yrs F/U=24 yrs										
	Prospective Cohort [90] (Vasen, 2010) Program Recommended COL= 1-2 yrs Starting at age 20-25 yrs F/U=7.2 yrs	Screening with colonoscopies	None	745 MMR mutation carriers	Total CRC=33 (4.4%)						
	Prospective Cohort [89] (Engel, 2010) Program Recommended COL =1yr Starting at age 25 yrs F/U=NR	Screening with colonoscopies	None	402 mutation carriers or relatives	Total CRC=20 (5%)						
	Prospective Cohort [30] (Jarvinen, 2009) Program Recommended COL=<3 yrs F/U=11.5 yrs	Screening with colonoscopies	None	242 MMR mutation – positive subjects	Total Screened after 1st exam CRC=21 (9%)						
	Prospective Cohort [82] (Dove-Edwin, 2005) Program Recommended COL=5 yrs: 3 if adenoma detected;	Screening with colonoscopies	None	554 members of 290 families in whom a mutation for HNPCC has been found	Total Screened CRC=11 (2%)						

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	later 1-3 yrs Starting at age 25 yrs F/U=15 yrs										
	Prospective Cohort [42] (de Vos tot Nederveen Cappel, 2002) Program Recommended COL=< 2 yrs Starting at age 20-25 yrs F/U=13 yrs	Large bowel investigation	None	887 members of 114 HNPCC or MMR-positive families	Total CRC=21 (2%)						
Cancer Detection Importance: Critical -5 studies	Prospective Cohort [69] (Lindberg, 2017) Program Recommended COL=2 yrs F/U=24 yrs	Screening with colonoscopies	None	235 families MMR-mutation positive	Initial Screen CRC=43 (4.6%)	Serious[1]	Serious[6]	Not Serious	Serious[3]	Not Serious	Very low
	Retrospective Cohort [92] (Stuckless. 2012) Program Recommended COL=1-2 yrs Starting at age 20-25 yrs F/U=12 yrs	At least 2 colonoscopies	No colonoscopy	322 *MSH2* mutation carriers: Screened group: 152 in screening program	Screened group Initial Screen CRC=1 (0.6%)						
	Prospective Cohort [89] (Engel, 2010) Program Recommended COL	Screening with colonoscopies	None	402 mutation carriers or relatives	Initial Screen CRC=12 (3%)						

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	=1yr Starting at age 25 yrs F/U=NR										
	Prospective Cohort [30] (Jarvinen, 2009) Program Recommended COL=<3 yrs F/U=11.5 yrs	Screening with colonoscopies	None	252 persons from families with HNPCC Screened group: 133 had COL	Initial Screen CRC=9 (8%)						
	Prospective Cohort [82] (Dove-Edwin, 2005) Program Recommended COL=5 yrs: 3 if adenoma detected; later 1-3 yrs Starting at age 25 yrs F/U=15 yrs	Screening with colonoscopies	None	554 members of 290 families in whom a mutation for HNPCC has been found	Initial Screen CRC=5 (0.9%)						
Compliance and Participation Importance: Critical -6 studies	Retrospective Cohort [92] (Stuckless, 2012) Program Recommended COL=1-2 yrs Starting at age 20-25 yrs F/U=12 yrs	Screening with colonoscopies	No colonoscopy	322 *MSH2* mutation carriers Screened group: 152 in screening program Non screened: 170 historical control	Had at least 2 screens: 109/152 (72%) F=68, M=41 Every 1-2 years: 46/152 (30%) F=28, M=18	Serious[1]	Serious[6]	Not Serious	Serious[3]	Not Serious	Very low
	Prospective Cohort [89] (Engel, 2010) Program Recommended COL	Screening with colonoscopies	None	402 mutation carriers or relatives	75% of COL were performed within 15 months						

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	=1yr Starting at age 25 yrs F/U=NR										
	Prospective Cohort [30] (Jarvinen, 2009) Program Recommended COL=<3 yrs F/U=11.5 yrs	Screening with colonoscopies	None	242 MMR mutation – positive subjects	Completed at least 3 =232 (95.9%) Completed at least 1 =240 Completed 0 =2						
	Prospective Cohort [93] (Stupart, 2009) Program Recommended COL=2 yrs until age of 30, then annually Starting at age 18. F/U=18 yrs	Screening with colonoscopies	No colonoscopy	178 subjects with MMR mutation of *MLH1* Screened group: 129 Non screened group: 49	Median number of Col=3 (1-12)						
	Prospective Cohort [82] (Dove-Edwin, 2005) Program Recommended COL=5 yrs: 3 if adenoma detected; later 1-3 yrs Starting at age 25 yrs F/U=15 yrs	Screening with colonoscopies	None	554 members of 290 families in whom a mutation for HNPCC has been found	Median number of years between colonoscopies= 3.3 yrs						
	Prospective Cohort [87] (Jarvinen, 2000) Program Recommended COL=3 yrs	Screening with colonoscopies	No colonoscopy	252 persons from families with HNPCC Screened group: 133 Non screened	Had at last 4 screens: 123/133 (93%) 10 non-compliant subjects (5 died from non CRC causes and 4 had negative gene test results and 1						

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	F/U=15 yrs			group: 119	dropped out)						
Pre-cancerous lesion incidence Importance: Important -3 studies	Prospective Cohort [69] (Lindberg, 2017) Program Recommended COL=2 yrs F/U=24 yrs	Screening with colonoscopies	None	235 families MMR-mutation positive	High risk adenomas=12 Intermediate risk: 83	Serious[1]	Not Serious	Not Serious	Serious[3]	Not Serious	Very low
	Prospective Cohort [89] (Engel, 2010) Program Recommended COL =1yr Starting at age 25 yrs F/U=NR	Screening with colonoscopies	None	402 mutation carriers or relatives	Advanced Adenomas=15 (3.7%)						
	Prospective Cohort [30] (Jarvinen, 2009) Program Recommended COL=<3 yrs F/U=11.5 yrs	Screening with colonoscopies	None	242 MMR mutation – positive subjects	74 pts. had 1 or more adenomas removed						
Pre-cancerous lesion detection Importance: Important -3 studies	Prospective Cohort [69] (Lindberg, 2017) Program Recommended COL=2 yrs F/U=24 yrs	Screening with colonoscopies	None	235 families MMR-mutation positive	Initial Screen: Adenomas=108 High risk adenomas=29 Multiple simple=8 Simple=71	Serious[1]	Not Serious	Not Serious	Serious[3]	Not Serious	Very low
	Prospective Cohort [89]	Screening with colonoscopies	None	402 mutation carriers or relatives	Initial Screen: Advanced Adenomas=15						

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	(Engel, 2010) Program Recommended COL =1yr Starting at age 25 yrs F/U=NR										
	Prospective Cohort [82] (Dove-Edwin, 2005) Program Recommended COL=5 yrs: 3 if adenoma detected; later 1-3 yrs Starting at age 25 yrs F/U=15 yrs	Screening with colonoscopies	None	554 members of 290 families in whom a mutation for HNPCC has been found	Initial Screen: High risk adenomas=9 Intermediate risk: 43						
Complication or Harms Importance: Important -2 studies	Prospective Cohort [90] (Vasen, 2010) Program Recommended COL= 1-2 yrs Starting at age 20-25 yrs F/U=7.2 yrs	Screening with colonoscopies	None	745 MMR mutation carriers	There were no perforations or deaths because of colonoscopies.	Serious[1]	Not Serious	Not Serious	Serious[3]	Not Serious	Very low
	Prospective Cohort [30] (Jarvinen, 2009) Program Recommended COL=<3 yrs F/U=11.5 yrs	Screening with colonoscopies	None	242 MMR mutation – positive subjects	3 (1.2%) had painful colonoscopy						

Abbreviations: COL = colonoscopy; CRC = colorectal cancer; F = female; HPNCC = hereditary non-polyposis colorectal cancer; LS = Lynch syndrome; M = male; MMR = mismatch repair gene; NR = not reported; pt = patient; vs. = versus; yr = year
Note: Large bowel investigation includes: Endoscopy or Barium Enema or Sigmoidoscopy or Sigmoidoscopy + Barium Enema

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Footnotes:

1- Because the studies are prospective and/ or retrospective design and there is a risk of bias in the results
2- Because there are only a few small studies
3- Because the event rate is low
4- Because there is confirmatory bias as chromocolonoscopy is always done 2nd
5- Because of the use of historical controls there was evidence of survival bias
6- Because there are no comparisons

* - The authors assumed < 8 here, not clear in study

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Table 11. Colorectal cancer screening studies, protocols, incidence, and detection rates for people with Lynch syndrome.

Study	Population	Study Design	Screening method	Interval	Age of Initiation (years)	Pre-cancerous lesion detection	Pre-cancerous lesion incidence	Cancer detection (95% CI)	Cancer incidence (95% CI)	Cancer Death	Ad-herence	Harms and complications	Comments
Seppala, 2017 [68] The Mallorca Group	505 LS carriers from Finland and 439 LS carriers from other countries	Prospective cohort Mean FU Finnish= 9.2 yrs (SD=5.9) Non-Finnish= 7.5 yr (SD=5.2) Total: 8.4 (SD 5.7)	COL	Finnish= 3 yr Non-Finnish 1-2 yr	Finnish= 35.2 yrs Non-Finnish =36.1 yrs; p>0.05	NR	NR	NR	CRC=101 Finnish=51 Non-Finnish =50	NR	NR	NR	Interval between colonoscopies did not differ. Finnish=32.7 (SD 13.6) mos; Non-Finnish =31.0 (SD 23.4) mos; p>0.05
Lindberg, 2017 [69] National Danish HNPCC register	298 LS families and for affected individuals and their first-degree relatives in FCC families	Prospective cohort Mean FU =5.9 (range 0-23) Data collected 1991-2014	COL	2 yrs Mean interval was 2.3 years	44 (mean age) (range=18 -86)	High risk adenomas=9 (1%)	High risk adenomas= 12 (0.5%)	CRC=43 (4.6%)	CRC=53 (2.0%)	NR	NR	NR	96 CRC (2.7%) (CI=2.2-3.3)
Rahmi, 2015 [71] (France) To compare COL vs choromcolono-scopy	78 pts with proven MMR germline mutation; at least 30 yrs old; asymptomatic required screening COL in accord with international guidelines	Cross-sectional multi-center	Standard COL vs. standard COL + chromoco-lonoscopy	NA	45 (median age)	COL: Patients with at least one adenoma: 18/78 (23%) Chromocolono -scopy: Patients with at least one adenoma: 32/78 (41%) Absolute difference= 18%; 95% CI, 8.4-24.9, p<<0.001	NA	None	NR	NR	NR	Pts reported no complications	Screening done only once; participants were enrolled in referral centres Bias –will never be less adenomas found in chromocolono-scopy because done second and polyps removed in first COL

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Stuckless, 2012 [92] (Canada) Pts identified through provincial medical genetics program. To test the effectiveness of COL, after initial COL	322 *MSH2* mutation carriers Screened group: 152 carriers entered a screening program, (F=98, M=54) Non-screened: 170 Most had a prior CRC or died before screening program implemented	Retrospec-tive Cohort 1994-2006 Median follow-up from entry into screening to death or last FU 9 yrs (M) or 11 yrs (F) Data collected 2006-2009	COL	1-2 yrs	20-25 Actual median age at screening F=36, M=38	NR (no information on initial COL)	NR	NR	Screened: Total: CRC=28 (M=14, F=14) During screening: CRC=7 Interval CRC=21 Median time to diagnosis =1.7 yrs M =2.1 yrs F (this info only for interval cancers) Non-screened: CRC=116 (M=74, F=42) OR=3.4 (95% Ci: 2.1-5.4) p<0.0001	Screened: Death due to CRC<8 Non-screened: Death due to CRC=50 OR=5.6 (95% CI: 2.5-12.1) p<0.0001	Had at least 2 screens: F=68, M=41 Every 1-2 years: F=28, M=18	No information about harms	Median age to CRC later in screened vs. non-screened (expected outcome) (RR=0.29, 95% CI=0.16-0.53) Median survival, for screened vs. non-screened (expected outcome): Males: 66 vs.62 yrs (RR=0.38; 95% CI 0.13–1.0) Females: 80 vs. 66 yrs (RR=0.19; 95% CI 0.085–0.44)
Vasen, 2010 [90] (Netherlands) Dutch Lynch Syndrome	745 MMR mutation carriers (F=437, M=308) Belonging to 205 families:	Prospective cohort 1995-2009 Mean FU =7.2 yrs	COL	1-2 years Mean interval =16 mos	20-25 Actual median age at start 42 (range,	NR	NR	NR	Screened: CRC=33 (4.4%)	Screened: death due to CRC=0	NR	There were no perforations or deaths because of colonoscopi es.	

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Registry	MLH1=75, MSH2=87, MSH6=43.				16 -82)								
Engel, 2010 [89] (Germany) German Hereditary Non-Polyposis Colorectal Cancer Registry	402 mutation carriers or relatives (F=249, M=153)	Prospective cohort 1999-2007 Mean FU =NR	COL	1 year Median Interval =12.2 mos	25	Advanced adenomas = 15	Advanced adenomas =15	Initial exam: CRC=12	Screened: CRC=9 Interval: CRC=11	Screened: death due to CRC=0	75% of COL were performed within 15 months	No information about harms	
Järvinen, 2009 [30] (Finland) A group of mutation carriers followed-up and invited to screening program	242 MMR mutation positive subjects; (119 M, 123 F) From 57 families with 14 different mutations: 9 in *MLH1*, 5 in *MSH2*	Prospective cohort 11.5 yrs FU Mutation testing started 1995-1999	COL	Maxi-mum 3 years At a later stage approx. ½ had biennial because they were in another research project (CAPP)	Median age: 36 yrs (range, 18 -72) (for whole study) (no recommendation to start)	NR	Adenomas =74 pts One or more removed from 74 mutation carriers (30.6%)	Initial exam: CRC=9 Dukes Stage A=6 Stage B=2 Stage C=1	Screened CRC=30 Total: Dukes Stage A=17 Stage B=7 Stage C=6* Interval btwn exams <2 yrs Dukes Stage A=3 Stage B=2 Stage C=0 Interval btwn exams >2 yrs Dukes Stage A=8 Stage B=3 Stage C=5	Deaths due to CRC=3* *Found at Stage C	COL: 95.9% compliance (3.3% dropped out after 1 or 2 exams, 0.8% did not attend any)	3 pts (1.2%) had painful COL	
Stupart, 2009 [93]	178 subjects with MMR	Prospective Cohort	COL	Every 2 years	18	NR	Screened: Adenomato	NR	Screened:	Screened: Deaths	Median number of	No information	

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(South Africa) The aim of this study was to investigate whether surveillance colonoscopy improves the survival in subjects with MMR	mutation of *MLH1* 129 had screening: 49 declined	1988-2007 Median F/U: 5 yrs		until age 30, then annually	Median age 33		us polyps =29 High-grade dysplasia=11		Total CRC=14 (7%) Non-screened: CRC=13 (27%)	due to CRC=3 (2%) Non-screened: Death due to CRC=6 (12%) p=0.021	COL=3 (1-12) over median F/U of 5 yrs	about harms	
Dove-Edwin, 2005 [82] (UK) Participants from family registry from a clinic. Participants were split into 4 at risk groups. We are only looking at the one high-risk group who fits our population.	554 members of 290 families who fulfill the (ACI or ACII) and in whom a mutation for HNPCC has been found	Prospective Cohort 1987-2003	COL	Five yr intervals or three yr intervals if an adenoma was detected Later, indivi-duals in a family with HNPCC CRC were offered COL every 1-3 yrs	25 Median age 38 (20-82) for 1st COL	Adenomas= 108 Includes simple (71), multiple simple (8) and high risk adenomas (29)	Adenomas= 144	Initial COL CRC: 5	Total: CRC=11 During Surveillance: CRC=8 Interval: CRC=3	Deaths due to CRC=3	The median number of yrs between success-ive COL was: 3.3yrs	No information about harms	
de Vos tot Nederveen Cappel, 2002 [42] (Netherlands) To examine the stage of	887 members of 114 HNPCC or MMR-positive families and in family members who underwent partial or subtotal colectomy who had completed	Prospective Cohort Of family registry surveillance program 1987-2000	COL Tumour stage with more frequent (≤ 2 yrs) vs. less frequent surveillance;	2 yrs or less Mean FU from 1st exam was 6.6 (Range =0.2-25.5)	20-25 First exam: Mean age=37, (Range =17-68) 2002 Mean age of	NR	NR	NR	CRC=21 (5 *MLH1*, 6, *MSH2*, 1 *MSH6*, 9 unknown) Interval btwn exams <2 yrs: 6 pts Dukes	Death due to CRC=2	NR	No information about harms	Earlier stage CRC with more frequent COL The number of pts that had more or less frequent COL not provided In 6 of 21 CRC

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the screening-detected tumours in relation to the surveillance interval	at least 1 exam with no CRC (199 MMR mutation carriers; 513 untested)				diagnosis =47 (35-57)				stage A=1 (*MSH2*) Stage B=5 (1 *MLH1*, 2 *MSH2*, 3 unk) Interval >2 yrs=15 pts Dukes stage A=4 (1 double) (3 *MLH1*, 1 unk) Stage B=7 (MHL1, 3 *MSH2*, 3 unk) Stage C=5 (*MLH1*, *MSH6*, 3 unk)				cases in whole study, pts were not given a complete COL in the previous examination but a sigmoidoscopy and/or a barium enema instead 4 –SS+BE 2-BE
Järvinen, 2000 [87] (Finland) To test the efficacy of screening	252 at-risk persons from 22 families with HNPCC 19 families had *MLH1* 1 family had *MSH2* 2 families are unknown Not all subjects had mutation All invited for COL screening	Prospective Cohort FU of Järvinen, 1995 15 yr study period 1982-1998 (1st COL btwn 1982-1986)	133 in "screened" group: 1st round: 43 had COL; 90 had DCBE and sigmoidoscopy 4th round: 100% had COL 119 in "non-screened" group: 24 had COL during study	3 yrs	Range 20-66	NR	Screened: Adenomas= 31 (23%) Non Screened: Adenomas= 4 (3%) p=0.001	Screened: CRC=2 Dukes A=1 Dukes B=1 Non Screened: CRC=2 Dukes A=1 Dukes B=1	Screened: CRC=6 (4.5%) Dukes A=2 Dukes B=4 Non screened: CRC= 17(14%) Dukes A=2 Dukes B=6 Dukes C=1 Dukes D=8 RR 0.38 (95% CI 0.17–0.83) p=0.014	Screened: Deaths due to CRC=0 Non-screened: Deaths due to CRC=9 p<0.001	Completed or nearly completed all rounds with some delays in 123 study subjects (93%) 10 non-compliant subjects	No significant complications	

Abbreviations: ACI = Amsterdam criteria I; ACII = Amsterdam criteria II; AMS = Amsterdam; BE = barium enema; CAPP = Colorectal Adenoma/carcinoma Prevention Programme; CI = confidence interval; COL: Colonoscopy; CRC = colorectal cancer; CT = computed tomography; DCBE = double contrast barium enema; F = female; FCC = familial colorectal cancer; FDR = first-degree relative; FU = follow up; HPNCC =

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hereditary non-polyposis colorectal cancer; LS = Lynch syndrome; M = male; MMR = mismatch repair gene; NR = not reported; pt = patient; R = range; RR= risk ratio; SDR = second-degree relative; SS = sigmoidoscopy; vs. = versus; yr = year

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Table 12. GRADE summary table for endometrial cancer screening for people with Lynch syndrome.

Patients or population: Lynch syndrome Patients Setting: Gynecological Cancer Screening – Endometrial Cancer Intervention: Screening (TUV; EB; Ca-125)											
Outcomes	Studies	Intervention	Comparison	Number of Participants (studies)	Main findings	Risk of Bias	Consistency	Directness	Precision	Other Publication bias	Quality of Evidence (GRADE)
Endometrial Cancer											
Screening vs. No Screening											
Cancer Related Death Importance: Critical -1 study	Retrospective Cohort [31] (Stuckless, 2013) Program Recommended both TVUS plus EB (Interval NR) F/U=4.5 yrs	TVUS + directed EB	No screening	174 women from 17 families with *MSH2* gene mutation Screened: 54 women with at least 1 screening exam Non screened 54 matched controls with no screening	Screened: Death due to EC=0 (0%) Non-screened: Death due to EC=3 (6%) p=0.079	Serious[1]	Not Serious	Not Serious	Serious[2]	Not Serious	Very low
Precancerous Lesion and Cancer Incidence Importance: Critical -1 study	Retrospective Cohort [31] (Stuckless, 2013) Program Recommended both TVUS plus EB (Interval NR) F/U=4.5 yrs	TVUS+ directed EB or routine EB	No screening	174 women from 17 families with *MSH2* gene mutation Screened: 54 women with at least 1 screening exam	Screened: Total: CAH/EC=7 (13%) During screening: CAH/EC=3 Interval/Symptoms: CAH/EC=4 Non-screened: Total: CAH/EC=20	Serious[1]	Not Serious	Not Serious	Serious[2]	Not Serious	Very low

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				Non screened 54 matched controls with no screening	(37%) p=0.017						
Screening with TVUS with directed EB vs. Screening with TVUS plus routine EB											
Cancer Related Death Importance: Critical -2 studies	Retrospective Cohort [32] (Helder-Woolderink, 2013) Program Recommended Annual Exams Starting at age 30 yrs F/U=9 yrs	TVUS + directed EB 2003-2007	TVUS + routine EB 2008-2012	75 women with LS or FDR at 50% risk of carrying the LS mutation	Death due to EC=0 (0%) Vs. Death due to EC=0 (0%)	Serious[1]	Not Serious	Not Serious	Serious[2]	Not Serious	Very low
	Prospective Cohort [33] (Gerritzen, 2009) Program Recommended Annual Exams Starting at age 30 yrs F/U=8 yrs	TVUS + directed EB 1997-2006	TVUS + routine EB 1997-2006	100 women from families with MMR mutation or fulfilled the AMS criteria	Death due to EC=0 (0%) Vs. Death due to EC=0 (0%)						
Precancerous lesion and Cancer Incidence Importance: Critical -2 studies	Retrospective Cohort [32] (Helder-Woolderink, 2013) Program Recommended Annual Exams Starting at age 30 yrs F/U=9 yrs	TVUS + directed EB 2003-2007	TVUS + routine EB 2008-2012	75 women with LS or FDR at 50% risk of carrying the LS mutation	TVUS First: Total: CAH/EC=2 (2.6%) During screening: CAH/EC=2 Interval/Symptoms: CAH/EC=0 Vs. TVUS+EB: Total: CAH/EC=1 (1.3%) p=0.429 (calculated) During screening: CAH/EC=1 Interval/Symptoms: CAH/EC=0	Serious[1]	Not Serious	Not Serious	Serious[2]	Not Serious	Very low

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	Prospective Cohort [33] (Gerritzen, 2009) Program Recommended Annual Exams Starting at age 30 yrs F/U=8 yrs	TVUS + directed EB 1997-2006	TVUS + routine EB 1997-2006	100 women from families with MMR mutation or fulfilled the AMS criteria	TVUS First: Total: CAH/EC=2 (1.4%) During screening: CAH/EC=2 Interval/Symptoms: CAH/EC=0 Vs. TVUS+EB: Total: CAH/EC=4 (6.3%) p=0.026 During screening: CAH/EC=4 Interval/Symptoms: CAH/EC=0						
Complications or Harms Importance: Important -1 study	Retrospective Cohort [32] (Helder-Woolderink, 2013) Program Recommended Annual Exams Starting at age 30 yrs F/U=9 yrs	TVUS + directed EB 2003-2007	TVUS + routine EB 2008-2012	75 women with LS or FDR at 50% risk of carrying the LS mutation	8 of 10 of preventive operations were performed because of cancer worries and/or anxiety for invasive and painful endometrial sampling procedures annually	Serious[1]	Not Serious	Not Serious	Serious[2]	Not Serious	Very low
Compliance and participation Importance: Critical -1 study	Retrospective Cohort [32] (Helder-Woolderink, 2013) Program Recommended Annual Exams Starting at age 30 yrs F/U=9 yrs	TVUS + directed EB 2003-2007	TVUS + routine EB 2008-2012	75 women with LS or FDR at 50% risk of carrying the LS mutation	TVUS + directed EB: Median visits: 3/pt (1-6) Interval: 36 mos (1-60) Vs. TVUS+ routine EB: Median visits: 2/pt (1-3) Interval: 28 mos	Serious[1]	Not Serious	Not Serious	Serious[2]	Not Serious	Very low

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					(2-51)						
Screening – No comparison											
Cancer Related Death Importance: Critical -3 studies	Prospective Cohort [30] (Jarvinen, 2009) Program Recommended Exams 2-3 yrs Starting at age 35 yrs F/U=11.5 yrs	TVUS+ routine EB	None	103 MMR mutation – positive women	Death due to EC=0	Serious[1]	Not Serious	Not Serious	Serious[2]	Not Serious	Very low
	Retrospective Cohort [35] (Renkonen-Sinisalo, 2006) Program Recommended Exams 2-3 yrs Starting at age 30-35 yrs F/U=9 yrs	TVUS+ routine EB	None	175 women with MMR mutations from 103 families	Death due to EC=0						
	Prospective Cohort [34] (Dove-Edwin, 2002) Program Recommended Exams every 1 or 2 yrs Starting at age 30-35 yrs F/U=10 yrs	Only TVUS	None	292 women from HNPCC (AMS criteria positive) or HNPCC-like families	Death due to EC=0						
Precancerous lesion and Cancer Incidence Importance: Critical	Retrospective Cohort [38] (Tzortzatos 2015) Program Recommended Annual Exams F/U=18 yrs	TVUS + directed EB	None	45 women with LS and clinical and screening information	Total: CAH/EC=7 (16%) During screening: CAH/EC=3 Interval/Symptoms: CAH/EC=4	Serious[1]	Serious[4]	Serious[3]	Serious[2]	Not Serious	Very low

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-7 studies	Retrospective Cohort [37] (Ketabi, 2014) Program Recommended Biennial Exams F/U=10 yrs	PE + TVUS + directed EB	None	236 women from LS families	Total: CAH/EC=16 (7%) During screening: CAH/EC=8 Interval/Symptoms: CAH/EC=8						
	Prospective Cohort [30] (Jarvinen, 2009) Program Recommended Exams 2-3 yrs Starting at age 35 yrs F/U=11.5 yrs	TVUS+ routine EB	None	103 MMR mutation – positive women	Total: CAH/EC=19 (18%) During screening: CAH/EC=17 Interval/Symptoms: CAH/EC=2						
	Case Series [85] (Lécuru, 2008) Not a program	Hysteroscopy and EB	None	62 women (13 with MMR mutation, 49 met ACII) who had at least 1 hysteroscopy	Total: CAH/EC=3 (5%) During screening: CAH/EC=0 Interval/Symptoms: CAH/EC=3						
	Retrospective Cohort [35] (Renkonen-Sinisalo, 2006) Program Recommended Exams 2-3 yrs Starting at age 30-35 yrs F/U=9 yrs	CE+ TVUS+ routine EB	None	175 women with MMR mutations from 103 families	Total: CAH/EC=19 (11%) During screening: CAH/EC=16 Interval/Symptoms: CAH/EC=3						
	Prospective Cohort [36] (Rijcken, 2003) Program Recommended Annual Exams Starting at age 30-35	PE + TVUS+ directed EB	None	41 women with MMR mutations or fulfilled ACII	Total: CAH/EC=4 (10%) During screening: CAH/EC=3 Interval/Symptoms: CAH/EC=1						

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	yrs F/U=10 yrs										
	Prospective Cohort [34] (Dove-Edwin, 2002) Program Recommended Exams every 1 or 2 yrs Starting at age 30-35 yrs F/U=11 yrs	Only TVUS	None	292 women from HNPCC (AMS criteria positive) or HNPCC-like families	Total: CAH/EC=2 (0.7%) During screening: CAH/EC=0 Interval/Symptoms: CAH/EC=2						
Compliance and Participation Importance: Critical -5 studies	Retrospective Cohort [37] (Ketabi, 2014) Program Recommended Biennial Exams Starting at age 25 yrs F/U=10 yrs	PE + TVUS + directed EB	None	236 women from LS families	46% every 2nd yr Mean=2.2 visits (1-11) Yrs btwn=3.54 Completed at least 3 Completed at least 1 Completed 0=2	Serious[1]	Serious[4]	Serious[3]	Serious[2]	Not Serious	Very low
	Prospective Cohort [30] (Jarvinen, 2009) Program Recommended Exams 2-3 yrs Starting at age 35 yrs F/U=11.5 yrs	TVUS+ routine EB	None	103 MMR mutation – positive women	97.1%						
	Case Series [85] (Lécuru, 2008) Not a program	Hysteroscopy and EB	None	62 women (13 with MMR mutation, 49 met ACII) who had at least 1 hysteroscopy	3 cases of non-compliance for hysteroscopy						
	Retrospective Cohort [35] (Renkonen-Sinisalo, 2006)	CE+TVUS+ directed EB	None	175 women with MMR mutations from 103 families.	Attended only 1 visit: 53						

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	Program Recommended Exams 2-3 yrs Starting at age 30-35 yrs F/U=9 yrs										
	Prospective Cohort [34] (Dove-Edwin, 2002) Program Recommended Exams every 1 or 2 yrs Starting at age 30-35 yrs F/U=11 yrs	Only TVUS	None	292 women from HNPCC (AMS criteria positive) or HNPCC-like families	Attended at least 1 scan: 222 (76%)						

Abbreviations: ACI = Amsterdam criteria I; ACII = Amsterdam criteria II; AMS = Amsterdam; CAH = complex atypical hyperplasia; EB = endometrial biopsy, endometrial sampling, hysteroscopy and/or curettages; EC = endometrial cancer; FDR = first-degree relative; HPNCC = hereditary non-polyposis colorectal cancer; LS = Lynch syndrome; MMR = Mismatch repair gene; MSH: mutS homolog NR = not reported; pt = patient; RRS = risk reduction surgery; SH = simple hyperplasia; TVUS = transvaginal ultrasound; vs. = versus; yr = year

Footnotes:

1- Because the studies are prospective and/or retrospective design and small and there is a risk of bias in the results
2- Because there are only a few small studies
3- Because the event rate is low
4- Because there are no comparisons and different screening programs

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Table13. Endometrial and ovarian cancer screening studies, protocols, incidence and detection rates for people with Lynch syndrome.

Study	Population	Study Design	Screening method	Interval	Age of Initiation (years)	Pre-cancerous lesion detection (prevalent)	Pre-cancerous lesion incidence	Cancer detection (95% CI)	Cancer incidence (95% CI)	Cancer Death	Ad-herence	Harms and complications	Comments
Tzortzatos 2015 [38] (Sweden) Nationwide study to examine which diagnostic modalities were used and the clinical outcome	45 women with LS and clinical and screening information From a study of 86 women: 45 attended screening visits and 41 underwent prophylactic surgery: At surgery: Median age 53 (40-77) Found: CAH/EC=4 Median age: 47.5 (42-58)	Retrospective 1994-2013 All women had TVUS and then EB according to Swedish guidelines, when endometrial thickness was abnormal	TVUS - 45 women (100%) Directed EB -28/45 women (62%) for thickened endometrium Ca-125 -27 women (29%)	Annual	All: 41 (24-84) Women who had EB: 57 (47-84) EB-CAH/EC Diagnosis=48 yrs Interval EC=46.5 yrs	Screened: Initial: EB: CAH=1 (*MLH1*)	Screened: EB: CAH=1 (*MLH1*) TVUS=0	Screened: Initial: EB: EC=1 (*MSH6*) TVUS=0	Screened: Total: EC=6 EB: EC=2 (1 *MLH1*; 1 *MSH6*) (normal TVUS) Interval cancer: EC=4 EB: EC=2 (2 *MSH2*; 1 *MLH1*; 1 *MSH6*) Total: OC=2 TVUS=2 (2 *MSH2*) Ca125=1 (but also only used on that one; *MSH2*)	NR	NR	NR	TVUS – did not detect any endometrial thickening in screening, only interval cancers For OC, pts had screening every 3 months Of those that had a RRS 9.8% had a EC/CAH
Ketabi, 2014 [37] (HNPCC registry Denmark)	2959 women from LS, AMS positive, and AMS-like families in HNPCC	Retrospective Cohort 1991-2011	Pelvic exam +TVUS Directed EB for thickened	Biennial Average surveillance period	25 Mean age at 1st visit: LS=39 (19-78)	NR	Screened: Total: CAH 5: During	Screened: Initial: EC= 2 (*MLH1*, *MSH2*)	Screened Total: EC=11 During screening:	NR	Compliance: 46% -1 every 2nd yr; 13% -1	NR	The majority of women with EC (10 of 13) and all CAH women had

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To evaluate the results of EC Surveillance in families with HNPCC	registry Surveillance data on 1/3 of study population: LS= 236; AMS positive= 269; AMS-like= 366 Women with RRS excluded		endometrium and/or postmenopausal/ irregular bleeding	was 7.9 yrs (range 0.1–21.7)	CAH diagnosis:46-52 yrs EC diagnosis:40-70 yrs OC Diagnosis:37-42 yrs		screening CAH=3 (1 *MLH1*, 1 *MSH2*, 1 *MSH6*) EB=3 TVUS=1 Interval: CAH=2 (1 *MLH1*, 1 *MSH2*) EB=2 TVUS=1	EB=2 TVUS=2	EC=5 (3 *MLH1*, 2 *MSH6*) EB=5 TVUS=4 Interval: EC=5 (1 *MLH1*, 3 *MSH2*, 1 *MSH6*) EB=5 TVUS=0 Symptom: (>4 yr interval) EC=1 (MHL1) EB=1 TVUS=0 _____ OC=4 During screening: OC=1 TVUS=1 (*MSH2*) Interval: OC=2 (*MLH1*, *MSH2*) TVUS=2 Symptoms: (>4 yr interval) OC=1 (*MSH2*) TVUS=1		every 3-4th yr; 40% -less than 1 visit every 4 yrs. 46% <3 yrs between visits Mean # of visits: 2.2 per woman (1-11)		experienced symptoms of menorrhagia, metrorrhagia, or postmenopausal bleeding prior t o their visits (age range 40-70) Note: 10 of 16 had normal TVUS 3.5% women had EB (62 EB procedures)

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Helder-Woolderink, 2013 [32] (Family Cancer Clinic, Netherlands) Aim –to compare added value of routine EB to screening with TVUS	75 women with LS or FDR at 50% risk of carrying the LS mutation Total 266 visits	Retrospective cohort Period 1 =2003-2007	Period 1: 44 women had screening visits TVUS: 117 visits (100%) EB: N=14 (12%) (Only if TVUS was abnormal)	Annual	Program – over 30 yrs Age at 1st visit 38 (R=26-61)	NR	Screened: Total: CAH=1 TVUS f/b EB=1 (*MLH1*)	NR	Screened: EC=1 TVUS f/b EB=1 _____ OC=0	Death due to EC=0	NR 266 screening visits in 300 person years Period 1: Median visits: 3/pt (1-6) Interval: 36 mos (1-60)	8 of 10 of preventive operations were performed because of cancer worries and/or anxiety for invasive and painful endometrial sampling procedures annually.	Ca125 data not shown No interval cancers during either period. Period 1: TVUS visits =117 EB=14 CAH/EC=2 Period 2: TVUS=149 EB=117 CAH/EC=1
		Period 2 =2008-2012	Period 2: 63 women had screening visits TVUS: 149 visits (100%) EB: 117 visits (79%)	Annual	41 (R=23-67)	NR	CAH=1 EB=1 (*MSH2*)	NR	EC=0 p=0.429 _____ OC=0	Death due to EC=0	Period 2: Median visits: 2 /pt (1-3) Interval: 28 mos (2-51)		
Stuckless, 2013 [31] (Canada) People identified through provincial medical genetics programme. To measure impact of screening	174 women from 17 families with *MSH2* gene mutation Screened: 54 pts with at least 1 screening examination prior to onset of diagnosis Non-screened matched controls: 54 randomly matched women	Retrospective cohort 2006-2010	TVUS, EB and Ca-125 Screening for EC consisted of both directed EB or routine EB; For OC, both TVUS and CA-125 No other information on the program	NR	Median age=36	NR	NR	Screened: Initial: EC=2 (*MSH2*) EB=2 TVUS=2	Screened: Total: EC=7 (*MSH2*) During screening: EC=3 Interval: EC=4 Non-screened matched controls: EC=20 p=0.017 _____	Screened: Death due to EC=0 OC=2 Non-screened: Death due to EC=3 OC=3 Death due to gyne	NR	NR	Stage I/II cancer diagnosed in 92% of screened pts compared with 71% in non-screened control group (p =0.17) Median age to EC was 54 yrs compared with 57 yrs in matched controls (p= 0.77)

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	without any screening (historical)		reported						Screened: Total: OC=6 (*MSH2*) During Screening: OC=1 Interval: OC=5 Non-screened matched controls: OC=6	cancer p=0.147			29% of matched controls had a hysterectomy alone or with BSO, RSO or LSO and 22% of cases (BSO:15% case, 11% matched controls, p=0.25)
Järvinen, 2009 [30] (Finland) Following mutation carriers over 10 yrs who were invited for screening	103 MMR mutation – positive subjects; From 57 families with 14 different mutations: 9 in *MLH1*, 5 in *MSH2*.	Prospective cohort of program 11.5 yrs FU Mutation testing started 1995-1999	Routine EB and TVUS for each visit	2-3 yrs	35 yrs Median age: 36 yrs (18 -72) (for whole study) EC Diagnosis median age=49 yrs OC Diagnosis median age=45 yrs	NR 48 (47%) had prophylactic hysterectomy during the study	Premalignant adenomatous hyperplasia =7	NR	Screened: Total: EC=19 (18%) During screening: EC=17 (1 during RRS &colectomy for CRC) EC stage: Stage1=13, Stage 2=2 Stage 3=2 Symptoms: EC=2 Stage 1=2 _____ Total: OC=6 During screening: OC=3 OC stage: Stage1=2 Stage 2=1 Symptoms:	No deaths due to EC or OC.	EC screening: 97.1% compliance (3 did not attend any)	NR	No other information about when TVUS or EB occurred 48 women had RRS during the study: 7 for premalignant adenomatous hyperplasia (PAH), 11 for other benign causes, 6 for OC, 24 for cancer prophylaxis Two of the patients in the symptoms detected cancers did not attend any screening. 1 for EC and 1 for OC

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									OC=3 OC stage: Stage1=2 Stage 3=1				
Gerritzen, 2009 [33] (Netherlands) To assess the efficacy of surveillance at a family cancer clinic	100 women from families: with MMR mutation or with mutation status not known	Prospective Cohort Period 1: 1997-2006: (8 yrs)	Period 1: Pelvic examination, TVUS, directed EB, Ca-125. EB only when indicated by TVUS 221 visits TVUS=221 EB=32 CAH/EC=3	Annual Median FU=1 (range 0-16)	30 (Median 46, range, 23-72)	NR	Screened: During screening: CAH=1 (*MSH6*) EB=1	Screened: Initial: EC=1 (*MSH2*) Stage IIIC EB=1	Screened: During screening: EC=1 (*MLH1*) Stage IC EB=2 TVUS=1	Death due to EC=0	Median number of visits =1 (Range, 1-16) Median follow-up was 1 yr Mean FU was 2 yrs	No information on harms.	Before 2006: 221 visits; 1.4% of visits found a (pre)malignancy; After 2006: 64 visits; 6.3% of visits resulted in found (pre)malignancies, p=0.026 No Interval carcinomas 15 surgeries 8 surgeries for OC due to TVUS or CA-125 found: 5 normal ovaries; 1 borderline malignancy, 1 mature teratoma; 1 OC
		Period 2: 2006-2008	Period 2: Pelvic examination, TVUS, routine EB, Ca-125. 64 visits TVUS-64 EB=64 AH/EC=4	Annual Mean FU=2.8	30 (Median 46, range, 23-72)	NR	Screened: During screening: Total CAH=2 (2 *MLH1*) EB=2 SAH=1 (*MLH1*) EB=1 TVUS =1	NA	Screened: During screening: After 2006: EC =1 (*MSH6*) EB=1 _____ OC=1 (*MSH2*) Stage IIIC TVUS =1 Ca-125=1	Death due to OC=1			
Lécuru, 2008 [85] (France) To report on the value of hysteroscopy and EB to detection CAH and EC,	62 women (13 with MMR mutation, 49 met ACII) who had at least 1 hysteroscopy	Consecutive Case Series 1999-2006	Hysteroscopy and endometrial biopsy Hysteroscopy attempts =125, with	Annual (TVUS, Pelvic exam and CA-125) Median FU: 19 months	NR Mean age=42 (±11.3)	NR	0	NR	Screened: Total: EC=3 During screening EC=0 Interval: EC=3 Stage IB, IB, IC	NR	Hysteroscopy: 3 cases of non-compliance	NR	Compared EB with hysteroscopy and found it to be 100 % sensitive for cancer

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and the accuracy of hysteroscopy			11 failures EB attempts =116, with 12 failures	(Range, 1-97 months)					EB=3 Hysteroscopy=3				
Renkonen-Sinisalo, 2006 [35] (Finland) All LS women in Finland asked, 175 entered the program. Report of the results of EC screening	175 women with MMR mutations from 103 families 83 symptomatic positive EC patients diagnosed and treated btwn 1963-2004. (Historical control group)	Retrospective Cohort 1996-2005	TVUS + routine endometrial biopsy 503 screening visits; clinical exam -100%, TVUS -94%, EB -74%	Biennially or 3-year Median FU=3.7 (Range, 0-13)	30-35	NR	Screened: Total premalignant hyperplasia =5 CAH=4 (4 *MLH1*) SAH=1 (*MLH1*) EB=1 TVUS=3	Screened: Initial: EC=1 (found during RRS) Stage IB	Screened: Total: EC=14 During screening: EC=11 (8 *MLH1*, 2 *MSH2*, 1 *MSH6*) Stage IA=5 Stage IB=4 Stage IIB=1 Stage IIIA=1 EB=11 TVUS=4 Interval: EC=3 (2 *MLH1*) Stage IA Stage IB Non screened: EC=83 _____ Screened: Total: OC=4 Interval: OC=4 Symptoms: OC=2 Surgery for EC or CH; OC=2 (*MLH1*) TVUS=0	Death due to EC: Screened =0 Non-screened Control =6	53 women only attended 1 visit	No information on harms	Biopsy diagnosed 8 of 11 ECs 4 cases of OC, none found by ultrasound: 2 were interval cancers, 2 found at surgery (those from the same families who were diagnosed and treated between 1963-2004) 59 (34%) women underwent hysterectomy during the study (43 RRS)

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Rijcken, 2003 [36] (Netherlands) To evaluate the 10 year experience with the screening program	41 women with MMR mutations or fulfilled ACII	Prospective Cohort 1991-2001	Pelvic examination, TVUS, Ca-125 Directed Endometrial sampling if indicted by TVUS	Annual	30-35 Median age for 1st=37 yrs (range, 27-60)	NR	Screened: Total: CAH=3 During screening: CAH=3 EB=3 TVUS=3	NR	Screened: Total: During screening: EC=0 Interval: EC=1 _____ Total: OC=0 CA-125=0	No deaths occurred	Followed for median of 5 yrs (range, 5 month-11 yrs) Good Compliance	NR	No MMR status 17 TVUS in 11 women indicted endometrial sampling
Dove-Edwin, 2002 [34] (UK and Netherlands) Information on the outcome of screening for two family/hereditary cancer clinics	292 women from HNPCC (AC positive) or HNPCC-like families Results available from 269 women	Prospective Cohort 1986-1997	TVUS	Annual or biennial	Age range: 30-35 Range for study: 25-65 Median age for first scan: UK HNPCC group: 40, (24-64) HNPCC-like: 45 (20-71) Netherlands: 42 (23-68)	NR	NR	None	Screened: Total: EC=2 During screening: EC=0 Interval: EC=2 (2 *MLH1*) TVUS=0	No deaths from EC	222 (83%) attended at least one scan	No information about harms	Age of diagnosis 51 and 46 yrs

Abbreviations: ACI = Amsterdam criteria I; ACII = Amsterdam criteria II; AMS = Amsterdam; BSO = bilateral salpingo-oophorectomy; CAH = complex atypical hyperplasia; CH = complex hyperplasia; CI = confidence interval; CRC = colorectal cancer; CT = computed tomography; EB = endometrial biopsy, endometrial sampling, hysteroscopy and/or curettages; EC = endometrial cancer; F = female; FDR = first-degree relative; FU = follow up; HPNCC = hereditary non-polyposis colorectal cancer; LS = Lynch syndrome; M = male; MMR = Mismatch repair gene; NR = not reported; OC = ovarian cancer; OHES = outpatient hysteroscopy and endometrial sampling; PH = prophylactic hysterectomy; pt = patient; R = range; RR= risk ratio; RRS –risk reduction surgery; SDR = second-degree relative; SH = simple hyperplasia ; TVUS = transvaginal ultrasound; vs. = versus; yr = year

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Table 14. GRADE summary table for ovarian cancer screening for people with Lynch syndrome

Patients or population: Lynch syndrome Patients Setting: Gynecological Cancer Screening – Ovarian Cancer Intervention: Screening (TUV; Ca-125)											
Outcomes	Studies	Intervention	Comparison	Number of Participants (studies)	Main findings	Risk of Bias	Consistency	Directness	Precision	Other Publication bias	Quality of Evidence (GRADE)
Ovarian Cancer											
Screening vs. No Screening											
Cancer-Related Death Importance: Critical -1 study	Retrospective Cohort [31] (Stuckless, 2013) Program Recommended both TVUS plus CA-125 (Interval NR) F/U=4 yrs	TVUS + Ca-125	No screening	174 women from 17 families with *MSH2* gene mutation Screened: 54 women with at least 1 screening exam Non screened 54 matched controls with no screening	Screened: Death due to OC=2 (4%) Non-screened: Death due to OC=3 (6%)	Serious[1]	Not Serious	Not Serious	Serious[2]	Not Serious	Very low
Cancer Incidence Importance: Critical -1 study	Retrospective Cohort [31] (Stuckless, 2013) Program Recommended both TVUS plus Ca-125 (Interval NR)	TVUS + Ca-125	No screening	174 women from 17 families with *MSH2* gene mutation Screened: 54 women with at least 1 screening exam	Screened: Total: OC=6 (11%) During screening: EB=1: TVUS=2 Interval/Symptoms: EB=5: TVUS=0 Non-screened: Total: OC=6 (11%)	Serious[1]	Not Serious	Not Serious	Serious[2]	Not Serious	Very low

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	F/U=4 yrs			Non screened 54 matched controls with no screening	p=1.0						
Screening Programs											
Cancer Related Death Importance: Critical -5 studies	Retrospective Cohort [32] (Helder-Woolderink, 2013) Program Recommended Annual Exams Starting at age 30 yrs F/U=9 yrs	TVUS + Ca-125	None	75 women with LS or FDR at 50% risk of carrying the LS mutation	Death due to OC=0	Serious[1]	Not Serious	Serious[3]	Serious[2]	Not Serious	Very low
	Prospective Cohort [33] (Gerritzen, 2009) Program Recommended Annual Exams Starting at age 30 yrs F/U=8 yrs	TVUS + Ca-125	None	100 women from families: with MMR mutation or fulfilled the AMS criteria	Death due to OC=0						
	Prospective Cohort [36] (Rijcken, 2003) Program Recommended Annual Exams F/U=10 yrs	PE + TVUS +Ca-125	None	41 women with MMR mutations or fulfilled ACII	Death due to OC=0						
	Retrospective Cohort [35] (Renkonen-Sinisalo,	CE+TVUS+ Ca-125	None	175 women with MMR mutations from 103 families	Death due to OC=0						

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	2006) Program Recommended Exams 2-3 yrs F/U=9 yrs										
	Prospective Cohort [30] (Jarvinen, 2009) Program Recommended Exams 2-3 yrs Starting at age 35 yrs F/U=11.5 yrs	TVUS	None	103 MMR mutation – positive women	Death due to OC=0						
Cancer Incidence Importance: Critical -5 studies	Retrospective Cohort [38] (Tzortzatos, 2015) Program Recommended Annual Exams F/U=18 yrs	TVUS + Ca-125	None	45 women with LS and clinical and screening information	Total: OC=2 (4%) During screening: OC=2 Interval/Symptoms: OC=0	Serious[1]	Serious[4]	Serious[3]	Serious[2]	Not Serious	Very low
	Retrospective Cohort [32] (Helder-Woolderink, 2013) Program Recommended Annual Exams Starting at age 30 yrs F/U=9 yrs	TVUS + Ca-125	None	75 women with LS or FDR at 50% risk of carrying the LS mutation	Total: OC=0 During screening: OC=0						
	Prospective Cohort [33] (Gerritzen, 2009)	TVUS + Ca-125	None	100 women from families: with MMR mutation or	Total: OC=1 (1%) During screening: OC=1						

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	Program Recommended Annual Exams Starting at age 30 yrs F/U=8 yrs			fulfilled the AMS criteria							
	Prospective Cohort [36] (Rijcken, 2003) Program Recommended Annual Exams Starting at age 30-35 yrs F/U=10 yrs	PE + TVUS + Ca-125	None	41 women with MMR mutations or fulfilled ACII	Total: OC=0 During screening: OC=0 Interval/Symptoms: OC=0						
	Retrospective Cohort [37] (Ketabi, 2014) Program Recommended Biennial Exams Starting at age 25 yrs F/U=10 yrs	PE + TVUS	None	236 women from LS families	Total: OC=4 (2%) During Surveillance: OC=1: TVUS=1 Interval/Symptoms: OC=3: TVUS=3						
	Prospective Cohort [30] (Jarvinen, 2009) Program Recommended Exams 2-3 yrs Starting at age 35 yrs F/U=11.5 yrs	TVUS	None	103 MMR mutation – positive women	Total: OC= 6 (6%) During screening: OC=3: TVUS=3 Interval/Symptoms: OC=3						
	Retrospective Cohort [35]	CE+TVUS+ Ca-125	None	175 women with MMR mutations from 103 families.	Total: OC=4 (0.2%) During screening:						

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	(Renkonen-Sinisalo, 2006) Program Recommended Exams 2-3 yrs Starting at age 30-35 yrs F/U=9 yrs				OC=0 Interval/Symptoms: OC=4						
Compliance and Participation Importance: Critical -3 studies	Retrospective Cohort [32] (Helder-Woolderink, 2013) Program Recommended Annual Exams Starting at age 30 yrs F/U=9 yrs	TVUS + Ca-125 2003-2007	TVUS 2008-2012	75 women with LS or FDR at 50% risk of carrying the LS mutation	Median visits: 3/pt (1-6) Interval: 36 mos (1-60) Vs. Median visits: 2/pt (1-3) Interval: 28 mos (2-51) Of 63 women who attended screening visits, 100% had TVUS and 79% of women had EB	Serious[1]	Serious[4]	Serious[3]	Serious[2]	Not Serious	Very low
	Retrospective Cohort [37] (Ketabi, 2014) Program Recommended Biennial Exams Starting at age 25 yrs F/U=10 yrs	PE + TVUS	None	236 women from LS families	46% every 2nd yr Mean=2.2 visits (1-11) Yrs btwn=3.54						
	Prospective Cohort [30] (Jarvinen, 2009) Program Recommended Exams 2-3 yrs Starting at age 35 yrs	TVUS	None	103 MMR mutation – positive women	97.1% (3 did not attend any)						

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	F/U=11.5 yrs										
	Retrospective Cohort [35] (Renkonen-Sinisalo, 2006) Program Recommended Exams 2-3 yrs Starting at age 30-35 yrs F/U=9 yrs	CE+TVUS+ Ca-125	None	175 women with MMR mutations from 103 families	53 attended at least 1 visit						

Abbreviations: ACI = Amsterdam criteria I; ACII = Amsterdam criteria II; AMS = Amsterdam; CA-125 = cancer antigen 125; CE =clinical exam; FDR = first-degree relative; HPNCC = hereditary non-polyposis colorectal cancer; LS = Lynch syndrome; MMR = Mismatch repair gene; MSH: mutS homolog NR = not reported; OC = ovarian cancer; pt = patient; RRS = risk reduction surgery; TVUS = transvaginal ultrasound; vs. = versus; yr = year

Footnotes:

1- Because the studies are prospective and/or retrospective design and there is a risk of bias in the results
2- Because there are only a few small studies
3- Because the event rate is low
4- Because there are no comparisons

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Table 15. GRADE summary table for small bowel, urinary and gastric cancer screening for people with Lynch syndrome.

Patients or population: Lynch syndrome Patients Setting: Other Cancer Screening (Small Bowel, Urinary, Gastric) Intervention: Screening (Capsule Endoscopy, CT Enteroclysis, Urine Cytology, Upper GI Endoscopy)											
Outcomes	Studies	Intervention	Comparison	Number of Participants (studies)	Main findings	Risk of Bias	Consistency	Directness	Precision	Other (Publication bias)	Quality of Evidence (GRADE)
Small Bowel Cancer											
Screened											
Cancer-Related Death Importance: Critical -1 study	Prospective Consecutive Series [80] (Saurin, 2010)	Capsule endoscopy and CT Enteroclysis screening of small bowel	None	35 pts with MMR mutations	No deaths	Serious[1]	Serious[2]	Not Serious	Serious[2,3]	Not Serious	Very low
Harms and complications Importance: Critical -1 study	Prospective Consecutive Series [80] (Saurin, 2010)	Capsule endoscopy and CT Enteroclysis screening of small bowel	None	35 pts with MMR mutations	No complications.	Serious[1]	Serious[2]	Not Serious	Serious[2,3]	Not Serious	Very low
Cancer Detection Importance: Important -1 study	Prospective Consecutive Series [80] (Saurin, 2010)	Capsule endoscopy and CT Enteroclysis screening of small bowel	None	35 pts with MMR mutations	Jejunal adenocarcinoma =1 CE=1 CTE=1	Serious[1]	Serious[2]	Not Serious	Serious[2,3]	Not Serious	Very low
Precancerous lesion detection	Prospective Consecutive Series [80]	Capsule endoscopy and CT	None	35 pts with MMR mutations	Jejunal adenoma=2	Serious[1]	Serious[2]	Not Serious	Serious[2,3]	Not Serious	Very low

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Importance: Important -1 study	(Saurin, 2010)	Enteroclysis screening of small bowel									
Urinary Tract Cancer											
Screened vs. Non-screened											
Cancer Related Death Importance: Critical -1 study	Retrospective Study [39] (Myrhøj, 2008) Program recommended biennial UC	Urine Cytology	No screening	977 at-risk persons in families with HNPCC; fulfilling the ACI or ACII; or suspected to have HNPCC who had UC completed at COL screening	No deaths due to UTC reported	Serious[1]	Serious[2]	Not Serious	Serious[2,3]	Not Serious	Very low
Cancer Incidence Importance: Critical -1 study	Retrospective Study [39] (Myrhøj, 2008) Program recommended biennial UC	Urine Cytology	No screening	977 at-risk persons in families with HNPCC; fulfilling the ACI or ACII; or suspected to have HNPCC who had UC completed at COL screening	Found within screening program: UTC=7: UC=2 Interval: UTC=5; UC=0 Found outside of screening program: UTC=7 Symptoms: UTC=5 Other surveillance: UTC=2	Serious[1]	Serious[2]	Not Serious	Serious[2,3]	Not Serious	Very low
Compliance and Participation Importance: Critical -1 study	Retrospective Study [39] (Myrhøj, 2008) Program recommended biennial UC	Urine Cytology	No screening	977 at-risk persons in families with HNPCC; fulfilling the ACI or ACII; or suspected to have HNPCC who had UC	977/3411 (29%)	Serious[1]	Serious[2]	Not Serious	Serious[2,3]	Not Serious	Very low

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				completed at COL screening							
Gastric Cancer											
Screened MMR vs. Screened non MMR											
Cancer Death Importance: Critical -1 study	Prospective Case series [40] (Renkonen-Sinisalo, 2002)	Upper gastrointestinal endoscopy (gastroscopy) with gastric biopsies	Mutation negative family members	73 pts with MMR mutation; 32 MMR mutation – negative family members	Death due to Duodenal cancer=1	Serious[1]	Serious[2]	Not Serious	Serious[2,3]	Not Serious	Very low
Cancer Detection Importance: Important -1 study	Prospective Case series [40] (Renkonen-Sinisalo, 2002)	Upper gastrointestinal endoscopy (gastroscopy) with gastric biopsies	Mutation negative family members	73 pts with MMR mutation; 32 MMR mutation – negative family members	Screened: MMR carriers: Duodenal C=1 Screened Controls: Duodenal C=0	Serious[1]	Serious[2]	Not Serious	Serious[2,3]	Not Serious	Very low
Precancerous lesion detection Importance: Important -1 study	Prospective Case series [40] (Renkonen-Sinisalo, 2002)	Upper gastrointestinal endoscopy (gastroscopy) with gastric biopsies	Mutation negative family members	73 pts with MMR mutation; 32 MMR mutation – negative family members	Screened: MMR carriers: Gastric polyps=6 Screened Controls: Gastric polyps=2	Serious[1]	Serious[2]	Not Serious	Serious[2,3]	Not Serious	Very low

Abbreviations: ACI = Amsterdam criteria I; ACII = Amsterdam criteria II; CE = Capsule enterology; CRC = colorectal cancer; COL = Colonoscopy; CT = computed tomography; CTE = computed tomography enteroclysis; HPNCC = hereditary non-polyposis colorectal cancer; LS = Lynch syndrome; MMR = mismatch repair gene; pt = patient; UC = urine cytology; UTC = urinary tract cancer; vs. = versus; yr = year

Footnotes:

1- Because the study is a retrospective design and there is a risk of bias in the results
2- Because there is only 1 study
3- Because the event rate is low

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Table 16. Small bowel, urinary and gastric cancer screening studies, protocols, incidence and detection rates for people with Lynch syndrome.

Study	Population	Study Design	Screening method	Interval	Age of Initiation (years)	Pre-cancerous lesion detection (prevalent)	Pre-cancerous lesion incidence	Cancer detection (95% CI)	Cancer incidence (95% CI)	Cancer Death	Adherence	Harms and complications	Comments
Saurin, 2010 [80] (Small bowel) (France) To evaluate capsule endoscopy and CT enteroclysis	35 pts with MMR mutations	Prospective Consecutive Series	Capsule endoscopy and CT Enteroclysis screening of small bowel	None Mean FU 40.8 months (Range, 23-62)	Mean age 47 (Range, 25-70)	Jejunal adenoma =2 (both *MLH1*) CE=2 CTE=0	NA	Jejunal adenocarcinoma=1 (*MLH1*) CE=1 CTE=1	NA	No deaths	Not applicable No information on harms	No complications	Capsule endoscopy found all lesions; CT enteroscopy found cancer but missed adenomas
Myrhøj, 2008 [39] (Urinary Tract Cancer) (Denmark) To evaluate if UC is appropriate for screening UTC Patients from Danish HNPCC registry. Data from Patobank – National Danish Pathology database	977 at-risk persons in families with HNPCC; fulfilling the ACI or ACII; or suspected to have HNPCC 197 people proven carriers, 67 at risk from families with proven MMR, 467 at risk persons from families fulfilling AC, 287	Retrospective Cohort 1991-2005 (3588 UCs performed at 1868 colonoscopy screening procedures)	UC	Biennial Median= 2.8 yrs, (Range, 0-11.5)	25 Median age=47 (Range, 25-84) Median age at diagnosis :61 (Range, 32-78)	NR	38 of 1868 had atypical or malignant cells 10 were benign 24 of 38 had extended screening with cystoscopy or excretory urography or CT urography 22 of these had normal results 14 were	NR	Total: UTC=14 Within screening program: UTC=7 UC: UTC=2 (*MSH2*, MMR unknown) Interval: UTC=5 Symptoms: UTC=5 Found outside of screening program: UTC=7	No deaths due to UTC reported	977/3411 (29%)	No information about harms	0.1 % of UC examinations lead to diagnosis of urothelial tumour (2) 10 times more (22) UC examinations lead to false-positive diagnosis Sensitivity of UC was 29 %

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	persons from families suspected of HNPCC))						ignored but did not have UTC 2 had UTC found by UC		Symptoms: UTC=5 Other : UTC=2 -This includes all people in the Patobank database				
Renkonen-Sinisalo, 2002 [40] (Gastric) (Finland) To determine whether there are any premalignant lesions to search for in gastric surveillance	73 pts with MMR mutation; 32 MMR mutation – negative family members	Prospective Case Series 1996-1998	Upper gastrointestinal endoscopy (gastroscopy) with gastric biopsies (105 performed)	Not applicable –only done once	Median age=49 yrs	Screened: MMR carriers: Gastric polyps=6 Controls: Gastric polyps=2	NA	Screened: MMR carriers: Duodenal C=1 (*MLH1*) Controls: Duodenal C=0	NA	Death due to duodenal cancer MMR carriers: Duodenal =1 (*MLH1*) Controls: Duodenal =0	NA	No information about harms	No statistical difference between gene-positive and gene-negative groups for: *H pylori*, atrophy, intestinal metaplasia, gastric polyps or inflammation

Abbreviations: ACI = Amsterdam criteria I; ACII = Amsterdam criteria II; AMS = Amsterdam; CI = confidence interval; CRC = colorectal cancer; CT = computed tomography; F = female; FDR = first-degree relative; FU = follow up; HPNCC = hereditary non-polyposis colorectal cancer; LS = Lynch syndrome; M = male; MMR = Mismatch repair gene; NR = not reported; pt = patient; R = range; RR= risk ratio; RRS = risk reduction surgery; SDR = second-degree relative; SH = simple hyperplasia; UC = urine cytology; UTC = urinary tract tumours; vs. = versus; yr = year,

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Table 17. GRADE Summary Table for Surgery or Chemo-prevention Risk Reduction Strategies.

Patients or population: Lynch syndrome Patients Setting: Risk Reduction Strategies Intervention: Surgery or Chemo-prevention Comparison: No surgery or Control										
Outcomes	Intervention	Comparison	Number of Participants (studies)	Main findings	Quality of evidence (Risk of Bias)	Consistency	Directness	Precision	Publi-cation bias	Quality of Evidence (GRADE)
Surgery vs. No Surgery for Gynecologic Cancers										
Endometrial Cancer Death Retrospective case control Importance: Critical	Surgery PH and/or BSO [41] (Schmeler, 2006)	Matched non-surgical controls	315 women 61 PH 47 PH & BSO 210 controls	Surgery group Death due to EC=0 Control group Death due to EC=3	Serious[1]	Not serious	Not serious	Serious[2]	Not serious	Very low
Ovarian Cancer Death Retrospective case control Importance: Critical	Surgery PH and/or BSO [41] (Schmeler, 2006)	Matched non-surgical controls	315 women 61 PH 47 PH & BSO 210 controls	Surgery group Death due to OC=0 Control group Death due to OC=1	Serious[1]	Not serious	Not serious	Serious[2]	Not serious	Very low
Endometrial Cancer Incidence 2 studies Retrospective and Retrospective case control	Surgery PH and/or BSO [38] (Tzortzatos, 2015)	Screening	86 women 41 surgery 45 screening	Surgery group: During surgery: 2 EC After surgery: 0 EC Screening group 7 EC	Serious[1]	Not serious	Not serious	Serious[3]	Not serious	Very low
	Surgery PH and/or BSO	Matched non-surgical	315 women 61 PH	Surgery group During surgery:	Serious[1]					

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Importance: Critical	[41] (Schmeler, 2006)	controls	47 PH & BSO 210 controls	3 EC After surgery: 0 EC Control group 69 EC, p<0.001						
Ovarian Cancer Cancer Incidence 2 studies Retrospective and Retrospective Case Control Importance: Critical	Surgery PH and/or BSO [38] (Tzortzatos 2015)	Screening	86 women 41 surgery 45 screening	Surgery group During surgery: 0 OC After surgery: 0 OC Screening group 2 OC, p=0.079	Serious[1]	Not serious	Not serious	Serious[3]	Not serious	Very low
	Surgery PH and/or BSO [41] (Schmeler, 2006)	Matched non-surgical controls	315 women 61 PH 47 PH & BSO 223 OC controls	Surgery group During surgery: 0 OC found After surgery: 0 OC Control group 12 OC, p=0.09	Serious[1]					
Harms (Surgical complications) Importance: Critical	Surgery PH and/or BSO [41] (Schmeler, 2006)	Matched non-surgical controls	315 women 61 PH 47 PH & BSO 210 EC controls 223 OC controls	1 patient Rate=1.6 percent	Serious[1]	Not serious	Not serious	Serious[3]	Not serious	Very low
Extended colectomy vs. segmental colectomy for colorectal cancer										
Colorectal Cancer Related Death 2 Prospective studies Importance:	Extended Colectomy [47] (Stupart, 2011)	Segmental Colectomy	60 CRC patients with LS SC=39 TC=21	Death due to CRC SC: 13 TC: 2	Serious[1]	Not serious	Not serious	Serious[3]	Not serious	Very Low
	Extended Colectomy [42] (de Vos tot	Segmental Colectomy	139 CRC patients with LS SC=110	Deaths due to CRC SC:2 TC=0						

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	Nederveen Cappel, 2002)		TC=29							
Colorectal Cancer Incidence 6 studies: 3 Retrospective and 3 Prospective Importance: Critical	Extended Colectomy [47] (Stupart, 2011)	Segmental Colectomy	60 CRC patients with LS SC=39 TC=21	CRC Incidence after SC or TC: SC=8 (21%) TC=2 (9.5%)	Serious[1]	Not serious	Not serious	Not Serious	Not serious	Low
	Extended Colectomy [46] (Parry, 2011)	Segmental Colectomy	382 CRC patients with LS SC=332 TC=50	CRC Incidence after SC or TC: SC=79 (42%) TC=0 (0%)						
	Extended Colectomy [45] (Natrajan, 2010)	Segmental Colectomy	106 LS patients either CRC diagnosis or prophylactic (8 –included in TC) SC=69 TC=37	CRC Incidence after SC or TC: SC=23 (33.3%) TC=4 (10.8%)						
	Extended Colectomy [43] (Kalady, 2010)	Segmental Colectomy	296 CRC patients with HNPCC (AMCII) SC=253 TC=43	CRC Incidence after SC or TC: SC=55 (25%) TC=3 (8%)						
	Extended Colectomy [42] (de Vos tot Nederveen Cappel, 2002)	Segmental Colectomy	139 CRC patients with LS SC=110 TC=29	CRC Incidence after SC or TC: SC=13 (11.8%) TC=1 (3.4%)						
	Extended Colectomy	Segmental Colectomy	54 patients from 22	CRC Incidence after SC or TC:						

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	[44] (Mecklin, 1993)		HNPCC families SC=37 TC=17	SC=15 (41%) TC=4 (24%)						
Harms Retrospective Cohort Importance: Critical	Extended Colectomy [45] (Natrajan, 2010)	Segmental Colectomy	106 LS patients either CRC diagnosis or prophylactic (8 –included in TC) SC=69 TC=37	Second abdominal surgery due to complication of the first surgery: adhesions causing bowel obstruction SC=4 TC=2	Serious[1]	Not serious	Not serious	Serious[2]	Not serious	Very low
Aspirin vs. No Aspirin for Colorectal Cancer										
Colorectal Cancer Incidence [48] (Burn, 2011) 1 RCT Importance: Critical	Aspirin	Placebo	861 from 43 centres	Time to first CRC hazard ratio (CI) by per protocol analysis, after 55.7 months mean follow-up HR=0.63 (0.35–1.13) p=0.12	Not serious	Not serious	Not serious	Serious[5]	Not serious	Low
Colorectal Cancer Incidence [76] (Ait Ouakrim, 2015) 1 RC 1997-2012	Aspirin	Control	1858 from USA, AUS, CAN	Never user: HR=1 (CI) Aspirin: Ever user: HR=0.43 (0.25 to 0.75) p=0.003 Ibuprofen: Ever user: HR=0.35 (0.19 to 0.63) p=0.001 For both: Ever: HR=0.41 (0.28 to 0.61) p<0.001	Serious[1]	Not serious	Not serious	Serious[5]	Not serious	Very low
Harms [84] (Burn, 2008) 1 RCT Importance:	Aspirin	Placebo	746 from 43 centres	Aspirin vs. placebo: Gastric ulcers or bleeding: 11 vs. 9 pts Cerebrovascular events: 2 vs.3 pts	Not serious	Not serious	Not serious	Serious[5]	Not serious	Moderate

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Critical				Cardiovascular events: 1 vs.5 pts						
Compliance [84] (Burn, 2008) 1 RCT Importance: Very Important	Aspirin	Placebo	746 from 43 centres	80% of the time, 81% complied with the use of Aspirin No difference in compliance between the aspirin and placebo groups	Not serious	Not serious	Not serious	Serious[5]	Not serious	Moderate
Resistant Starch vs. No Resistant Starch for Colorectal Cancer										
Colorectal Cancer Incidence [49] 1 RCT (Mathers, 2012) Importance: Critical	Resistant starch	Placebo	918 from 43 centres	CRC by starch at median follow-up of 52.7 months. Per-protocol analysis HR=1.09 (0.55–2.19, p=0·80)	Not serious	Not serious	Not serious	Serious[5]	Not serious	Low
Harms [84] (Burn, 2008) 1 RCT Importance: Critical:	Resistant starch	Placebo	746 from 43 centres	Resistant starch vs. placebo gastric ulcers or bleeding: 8 vs. 7 pts cerebrovascular events: 3 vs.2 pts cardiovascular events: 5 vs.1 pts	Not serious	Not serious	Not serious	Serious[5]	Not serious	Moderate
Compliance [84] (Burn, 2008) 1 RCT Importance: Very Important	Resistant starch	Placebo	746 from 43 centres	77% of the participants complied	Not serious	Not serious	Not serious	Serious[5]	Not serious	Moderate

Abbreviations: BSO = bilateral salpingo-oophorectomy; CI = confidence interval; CRC = colorectal cancer; EC = endometrial cancer; HNPCC = hereditary non-polyposis colorectal cancer; HR = hazard ratio; OC = ovarian cancer; PH = prophylactic surgery; pts = patients; RC = retrospective cohort; RCT = randomized controlled trial; SC = segmental colectomy; TC = total colectomy; vs. = versus

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Footnotes:
1 –Because the study(ies) is/are of a retrospective or prospective cohort design and there is a risk of bias in the results
2 –Because there is only 1 small study
3 -Because there are only 2 small studies
4 -Surgical complications – 1 patient had a ureteral injury during the PH/BSO, which was repaired.
5 -Because there is only 1 study and the confidence limits are wide

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Table 18. Data summary of risk reduction strategies: surgery, chemo-prevention, lifestyle.

Study	Population	Study Design	Strategy	Age (range)	Findings	Comments
Endometrial or Ovarian Cancer						
Surgery						
Tzortzatos, 2015 [38]	86 women attended screening visits 41 women with LS who underwent PH and/or BSO 32 -PH&BSO 7 -PH only 2 -BSO only 45 women with LS and clinical and surveillance information	Retrospective cohort 1994-2013 Swedish nationwide study –use of medical records	Hysterectomy and/or bilateral salpingo-oophorectomy	Median 53 (40-77) Median age of EC/CAH 47.5 (42-58)	For women with PH and/or BSO: 2 CAH found during surgery • 2 *MLH1* 2 EC found during surgery • 1 *MLH1* • 1 *MSH2* No cancers found after surgery For women with annual screening: 7 EC • 3 *MLH1* • 2 *MSH2* • 2 *MSH6* 2 CAH • 2 *MLH1* 2 OC • 2 *MSH2* Cumulative proportion free from cancer diagnosis at 70 yrs: Women with PH and/or BSO: 0.88 Women with annual screening: 0.52, p=0.079	Women with prophylactic or risk reducing surgery have a higher (although not statistically significant) cumulative proportion free from cancer diagnosis through the years No information on complications
Schmeler, 2006 [41]	315 women with LS 61 underwent PH (14 PH only; 47 underwent PH&BSO)	Retrospective case control 1973-2004 From 3 heredity cancer registry	To determine the reduction in the risk of gynecologic cancers associated with prophylactic hysterectomy	Median age for PH 41 (20-63) Median age of EC 46 (30-69)	3 EC found at time of PH surgery. No EC or OC or peritoneal cancer found after surgery 69 EC found in control (33%) • 22 *MLH1* • 47 *MSH2*	Control women were matched for age(DOB within 5yrs) had been treated at the same institutions, and had been alive, with an intact uterus (or ovaries for OC pts) and no history of gynecologic cancer, at the time the

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	Matched controls without gynecologic surgery (210 for EC, 223 for OC)	centres in the USA	and bilateral salpingo-oophorectomy	Median age for PH&BSO 41 (20-58) Median age for OC 42 (31-48)	12 OC found in control (5%) • 5 *MLH1* • 7 *MSH2* Incidence density (cases/woman yrs) PH=0.000 Control EC=0.045, p<0.001 PH& BSO=0.000 Control OC=0.005, p=0.09 Cumulative incidence at 20 years: PH=0 Control EC=0.6 PH & BSO=0 Control OC=0.1	women with whom they were matched underwent hysterectomy or PH and BSO The surgical complication rate was 1.6 percent Years follow-up: PH=13.3 (0.5-38.0) PH& BSO=11.2 (0.5-38.0) Control EC=7.4 (0.1-35.0) Control OC=10.6 (0.1-41.0)
Colorectal Cancer						
Segmental and Total Protocolectomy (SC and TC)						
Messick, 2014 [79]	38 CRC patients with LS	Retrospective Cohort No suggested screening protocol provided	SC=35 TC=3 24/38 (63%) of patients had COL	Of initial diagnosis: 48 (27-77). (No age of CRC incidence in FU)	CRC Incidence after SC and TC: 19 CRC in 16 pts Median time to second cancer from index cancer: Both SC and TC: 84 months (1-37) Deaths due to CRC=5 No information about the type of index surgery and number of CRC related deaths	No comparisons between type of surgery and CRC development or death
Kalady, 2012 [57]	50 HNPCC patients from single institution database To define the neoplastic risk in the remaining colon after proctectomy	Retrospective Cohort No suggested screening protocol provided	SC=50 TC=0 SC: 33 (66%) had COL	Mean age at index surgery: 53 (SD=14)	CRC Incidence after SC and TC: SC=5 pts (15.2%) TC=0 Median time to second cancer from index cancer: SC: 72 months (42-192) Median time from previous endoscopy to cancer (CRC=5)=42 mos (24-62)	17 of 33 patients (51.5%) developed high-risk adenoma or cancer after proctectomy

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	for rectal cancer				No information about death due to CRC	
Stupart, 2011 [47]	60 with HNPCC from one unit in Cape Town To determine the risk of MCC after SC or TC in HNPCC patients	Prospective Cohort Suggested screening protocol was annual	SC=21 TC=39 SC: 22 (56%) had COL TC: 15 (71%) had flex sig	Mean age at initial diagnosis: SC: 44 (± 11.0) TC: 41 (± 7.9)	CRC Incidence after SC and TC: SC= 8 (21%) TC= 2 (9.5%) Mean time to second cancer from index cancer: SC: NR TC: 19 years Death due to CRC: SC: 13 TC: 2	All offered yearly endoscopic surveillance Both groups likely to attend at least one exam p=0.39. TC attended more often (p=0.015)
Parry, 2011 [46]	382 LS patients from Colon Cancer Family Registry To compare the risks of MCC for patients undergoing SC or TC	Retrospective Cohort Suggested screening protocol was 1-2 yrs	SC=332 TC=50 SC: 289 (78%) had at least 1 COL TC: 37 (74%) had flex sig	Mean age at first diagnosis: 46 (SD=11)	CRC Incidence after SC and TC: SC=74 (22 %) TC=0 Median time to second cancer from index cancer: NR No information about death due to CRC	Cumulative risk of MCC was 16% (95% CI 10% to 25%) at 10 years, 41% (95% CI 30% to 52%) at 20 years and 62% (95% CI 50% to 77%) at 30 years after segmental colectomy. Risk of MCC was reduced by 31% (95% CI 12% to 46%; p<0.002) for every 10 cm of bowel removed
Natarajan 2010 [45]	106 LS patients who underwent segmental or subtotal colectomy either with no CRC diagnosis or at CRC diagnosis. From Creighton University Heredity Cancer Centre	Retrospective Cohort No suggested screening protocol provided	SC=69 TC=37 Total # of COL=80/116	Mean age at first diagnosis: 45.5	CRC Incidence after SC and TC: SC=23 (33.3%) TC=4 (10.8%) Median time to second cancer from index cancer: SC: 16-175 months TC: 6-160 months No information about death due to CRC A second abdominal surgery due to complication of the first surgery: TC=2 SC=4, all with adhesions causing bowel obstruction	Frequency of exams in both groups ranged btwn 1-6 yrs Times to subsequent colorectal cancer and subsequent abdominal surgery were significantly shorter in the TC group (p<0.006 and p<0.04, respectively). No significant difference was identified with respect to survival time between (no numbers given)
Kalady, 2010 [43]	296 HNPCC (AMCII) patients from	Retrospective Cohort	SC=253 TC=43	Mean age at index surgery:	CRC Incidence after SC and TC: SC= 55 (25%) TC=3 (8%)	In 74 patients (33%), 256 adenomas were detected, including 140 high-risk

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	single institution database To define subsequent adenoma burden and risk of cancers depending on surgery	No suggested screening protocol provided.	SC: 221 (87%) had a COL TC: 38 (88%) had endoscopy	52 (SD=14)	Median time to second cancer from index cancer (months): SC: 69 (IQR 162) TC: 227 (IQR 59) Median time from previous endoscopy to CRC SC: 18 months TC: 41,45,90 months No information about death due to CRC	adenomas in 48 patients (22%)
de Vos tot Nederveen Cappel, 2002 [42]	139 LS patients A part of a family registry surveillance program study with: 887 members of 114 HNPCC or MMR-positive families (199 MMR mutation carriers; 513 untested)	Prospective Cohort Screening Program for surveillance: Before 1996: 2-3 yrs, After 1996: 1-2 yrs	SC=110 TC=29 Intervals: Until 1996: every 2-3 yrs, After 1996; every 1-2 yrs	Age of 2nd diagnosis: Partial colectomy group: Mean=47 (25-58) Total colectomy group: 46	CRC Incidence after SC and TC: SC=13 (11.8%) TC=1 (3.4%) Median time to second cancer from index cancer: NR Death due to CRC: SC: 2 TC: 0	15.7 % risk of developing CRC with partial colectomy (13 pts) vs. 3.4 % with subtotal colectomy at 10 yrs (1 pt) The number of pts that had more or less frequent colonoscopies not provided 4 of 13 CRC detected at first exam; 9 detected within 2 yrs of last negative exam
Mecklin, 1993 [44]	54 patients from 22 HNPCC families	Prospective Cohort Suggested screening protocol every 2 yrs	SC=37 TC=17	Mean age of 1st diagnosis: 37 (27-43)	CRC Incidence after SC and TC: SC=8 (21.6%) TC=2 (11.8%) Median time to second cancer from index cancer: NR No CRC related deaths	Adenomas or adenocarcinomas were diagnosed in 41 % (I5/37) of the patients treated by segmental colonic resection and in 24 % (4/17) of those treated by segmental resection. Extracolonic carcinoma was diagnosed in 12 (30 percent) of the 40 patients during the long-term follow-up
Chemo-prevention Aspirin or Resistant Starch or Non-steroidal Anti-inflammatory Drugs						
Mathers, 2012 [49]	714 people with LS in study to examine the long term	Long-term follow-up report on RCT, 2 × 2 design	463 randomized to resistant-starch (30 g/d) 455 randomized		53 individuals=primary CRC 27 resistant starch 26 placebo Time to first CRC HR (CI)	Resistant starch is a specific form of dietary fibre that is not digested in the small bowel

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	effects of resistant starch on hereditary CRC	Intervention lasted a mean of 29 months CAPP2	to placebo		Intention to treat: HR=1.40 (0.78–2.56, p=0.26)	For those completing 2 yrs of intervention, no effect on incidence of CRC by starch at median follow-up of 52.7 months.
Burn, 2011 [48]	861 people with LS in study to examine the long term effects of Aspirin on hereditary CRC	Long-term follow-up report on RCT 2 × 2 design CAPP2	427 randomized to aspirin (600 mg/d); 434 randomized to placebo		600 mg aspirin/d for mean of 25 months reduced cancer incidence after 55.7 months Time to first CRC HR (CI) Intention to treat: HR=0.63 (0.35–1.13), p=0.12	Non CRC LS cancers (CI) Intention-to treat analysis: HR=0.63 (0.34-1.19), p=0.16
Burn, 2008 [84]	746 people with LS in study to examine the effects of Aspirin and/or resistant starch on hereditary CRC	RCT, 2 × 2 design CAPP2	727 randomized to resistant starch (30 g/d) or placebo; 693 randomized to aspirin (600 mg/d) or no aspirin 2 years	Mean age in analysis 46 (R=25-79)	141 participants developed a colonic adenoma or carcinoma Neoplasia: Aspirin vs placebo: (18.9% vs.19.0%) Starch vs. placebo: (18.7% vs. 18.4%) Advanced Neoplasia: Aspirin vs placebo: (7.4% and 9.9%) Starch vs. placebo: (8.7% vs. 9.5%) Adverse events between groups were similar. Aspirin vs. placebo: gastric ulcers or bleeding: 11 vs. 9 pts cerebrovascular events: 2 vs. 3 pts cardiovascular events: 1 vs. 5 pts Resistant starch vs. placebo: gastric ulcers or bleeding: 10 vs. 10 pts cerebrovascular events: 3 vs.2 pts cardiovascular events: 5 vs.1 pts	No effect on incidence of colorectal adenoma / cancer by starch or aspirin or both. Average duration of participation was 29 months (7-74) No difference in compliance between groups 81% for aspirin, 77% for starch
Ait Ouakrim, 2015 [76]	714 were diagnosed with CRC 1858 identified with mutation	Retrospective cohort 1997-2012 Compared	Aspirin and ibuprofen or both intake Never user, 2x/week for: <1	714 were diagnosed with CRC (38%) Median	Never user: HR=1 (ref) Aspirin: Ever user: 0.43 (0.25 to 0.75), p=0.003 1 mo to 4.9 yr: HR=0.49 (0.27 to 0.90), p=0.02; ≥5 yr: HR=0.25 (0.10 to 0.62), p=0.003	Never users are defined as carriers who reported not having taken either aspirin or ibuprofen or both for at least one month

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	in MMR gene From Colon Cancer Family Registry (USA, CAN, AUS, New Zealand)	aspirin and ibuprofen use in LS population between those with CRC and those without	month; 1 month-4.9 yrs; or ≥5 yrs	age with CRC=42.0 (R=19-75) Without CRC=41.0 (R=18-85)	Ibuprofen: Ever user: 0.35 (0.19 to 0.63) p=0.001 1 mo to 4.9 yr: HR=0.38 (0.18 to 0.79), p=0.009; ≥5 yr: HR=0.26 (0.10 to 0.69), p=0.007 For both: Ever: HR= 0.41 (0.28 to 0.61), p<0.001 1mo-5 yr: HR=0.44 (0.27 to 0.69), p<0.001; ≥5yr: HR=0.34 (0.19 to 0.62), p<0.001 ***MLH1*** Never user N=600, HR=1 (Ref) Aspirin-only user N=30, HR=0.34 (0.13 to 0.86) p=0.02 Ibuprofen-only user N=40, HR=0.91 (0.32 to 2.55) p=0.86 Aspirin and/or ibuprofen user N=81,HR=0.43 (0.21 to 0.87) p=0.02 ***MSH2*** Never user N=751, HR=1 (Ref) Aspirin-only user N=51, HR=0.52 (0.19 to 1.45) p=0.22 Ibuprofen-only user N=53, HR=0.27 (0.08 to 0.85) p=0 .03 Aspirin and/or ibuprofen user N=122, HR=0.39 (0.20 to 0.74) p=0.004 ***MSH6*** Never user N=148, HR=1 (Ref) Aspirin-only user N=21, HR=0.23 (0.04 to 1.06) p=0.06 Ibuprofen-only user N=24, HR=0.16 (0.03 to 0.72) p=0.02 Aspirin and/or ibuprofen user N=56, HR=0.27 (0.04 to 1.75) p=0.17 ***PMS2*** Never user N=73, HR=1 (Ref) Aspirin-only user N=15, HR=1.78 (0.56 to 5.67) p=0.33 Ibuprofen-only user N=9, HR=1.60 (0.33 to 7.59) p=0.55 Aspirin and/or ibuprofen user N=27, HR=0.70 (0.33 to 1.47) p=0.35	Ever user was defined as having taken either aspirin or ibuprofen or both for at least twice a week for a month or longer Were able to adjust for recognized potential confounding variables, including alcohol consumption, cigarette smoking, hormone replacement therapy, and multivitamin use Unable to assess gradient risk
Lifestyle –effect of diet, exercise, smoking, BMI on risk of CRC or EC cancer						

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Brouwer, 2017 [51]	457 people with LS from GEOLynch study Netherlands To investigate associations between dietary intakes and CRT development	Prospective cohort Median FU time=59 mos. July 2006 -July 2008	Food frequency questionnaire Dietary to calculate the adapted dietary inflammatory index (ADII) and risk of CRC Identified tertiles of inflammatory diets	Median age 49	CRT=182 CRC=18 Compared high inflammatory diets to low inflammatory diets for CRT risk HR=1.37 (95% CI: 0.80, 2.34)	Controlling for NSAID use did not make the HR significant, but it was larger: HR=1.60 (95% CI: 0.88, 2.93) of developing CRTs Controlled for age, smoking status, education and number of colonoscopies during FU.
Staff, 2016 [56]	136 women with LS Finnish LS Registry	Retrospective cohort 61% response rate	Lifestyle factors, medical and reproductive history data collected via postal questionnaire and risk of EC	Median age=58	EC=50 median age=49.5 PH performed on 52/86 of EC unaffected women median age=45 Multivariate analysis Diabetes HR=4.18 (95% CI 1.52–11.52), p=0.006 Duration of hormone replacement therapy (HRT) HR=1.07 (95% CI 1.02–1.13), p=0.010	The duration of hormonal replacement therapy use was categorized using the median duration (9 years) as the cutoff point. Data are presented only from ever users of hormone replacement therapy (n=61)
Chau, 2016 [52]	744 carriers with CRC 1966 identified with mutation in MMR gene From Colon Cancer Family Registry (USA, CAN, AUS, New Zealand)	Retrospective cohort 1997-2012	Lifestyle factors and supplement intake was collected at time of recruitment	744 were diagnosed with CRC Mean age =42.4	Compared with never users, a decreased CRC risk associated with: Multivitamin intake for at least 3 years HR =0.47 (95% CI 0.32–0.69), p<0.001 Calcium intake for at least 3 years: HR= 0.42, 95% CI 0.23–0.74), p=0.003 Folic Acid intake for at least 3 years: HR = 0.87 (95% CI 0.36–2.08) p=0.76	Ever users of supplements were defined as those who answered ‘yes’ to ‘Have you ever taken (supplement) at least twice a week for 1 month or longer?’ Never users were defined as those who answered ‘no’ to ‘Have you ever taken (supplement) at least twice a week for 1 month or longer Adjusted for recent BMI, red meat intake and fruit and vegetable intake No association for Folic Acid and CRC risk (p=0.82)
Movahedi,	937 people	Prospective	BMI categories:	At cohort	No significant increase in risk regardless	CAPP2 study

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2015 [50]	with LS in CAPP2 study To examine whether overweight or obese patients with LS may be at enhanced cancer risk compared with normal-weight patients with LS	cohort 1999-2005	Underweight: <18.5; Normal weight 18.5 to 24.99; Overweight, 25 to 29.99; and Obese ≥30 kg/m^2	entry median age=44.9 (Q1-Q3; 36-53)	of BMI for adenomas For obese participants, CRC risk HR=2.34 (95% CI, 1.17 to 4.67; p=0.02), no significant increase for other LS related cancers Obese participants with *MLH1* mutation HR=3.72 (1.41 to 9.81) p=0.008, the HR not significant for *MSH2* There was a linear increase in HR for CRC with increasing BMI. The greater CRC risk associated with each 1-kg/m2 increase in BMI seemed to be stronger for men (HR, 1.12; 95% CI, 1.02 to 1.24; p=0.02) than for women (HR, 1.06; 95% CI, 0.99 to 1.13)	In patients with LS randomly assigned to placebo, there was a significant association between increased BMI and CRC risk HR=1.10 (1.03 to 1.17), p=0.001 No evidence of an increased risk among those randomly assigned to aspirin, HR=1.00 (0.90 to 1.12), non-significant
Jung, 2014 [54]	470 people with LS from GEOLynch study Netherlands To investigate associations between dietary intakes of folate, vitamins B2, B6, B12, and methionine and CRT development	Prospective cohort July 2006 -July 2008	Food frequency questionnaire Dietary B vitamin and folate intake and risk of CRC	Median age 49	131 people developed a CRT during a median person time of 28 months in study HR (95% CI) for CRC development in the highest tertile (with lowest tertile as a comparison) were: 1.06 (0.59–1.91) for folate; 0.77 (0.39–1.51) for vitamin B2; 0.98 (0.59–1.62) for vitamin B6; 1.24 (0.77–2.00) for vitamin B12; and 1.36 (0.83–2.20) for methionine	In this LS population, intake of dietary folate, other B vitamins, and methionine were not associated with CRT development HRs were adjusted for age, sex, number of colonoscopies during person-time, NSAID use, and physical activity
Botma, 2013 [53]	486 people with LS from GEOLynch study Netherlands To examine the association of	Prospective cohort -20 months median follow-up July 2006-July 2008	Food frequency questionnaire Four dietary patterns were identified: a ‘‘Prudent,’’ ‘‘Meat,’’ ‘‘Snack,’’ and ‘‘Cosmopolitan’’	Median age 49	Colorectal adenomas were detected in 58 people Compared with the lowest tertile in each pattern the HR (95%CI) for colorectal adenomas for the highest tertiles were: Prudent: HR =0.73 (0.32-1.66), p=0.78 Meat: HR=1.70 (0.83-3.52), p=0.21	Prudent – fruits, vegetables, whole grains, nonfat yogurt, green and herbal teas, fish, chicken and added sweets Meat – chicken, beef, pork, minced, and processed meats and coffee, negative on whole grains, peanut butter

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	dietary patterns with colorectal adenomas		pattern		Snack: HR=2.16 (1.03-4.49), p=0.12 Cosmopolitan: HR=1.25 (0.61-2.55), p=0.56 HRs were adjusted for age, sex, smoking habits, colorectal adenoma history, and extent of colon resection	cakes, cookies, veggies Snack – chips, fried snacks, fast food snacks, spring rolls, mayonnaise, cooking fat and butter, ketchup, sweets, and diet sodas Cosmopolitan - leafy vegetables, tomatoes, and allium vegetables, refined grains, fish, dressings, tomato sauce, cream, low-fat margarine, sweet sandwich spread, and wine
Kamiza, 2015 [55]	209 *MLH1* and 92 *MSH2* germline mutation carriers in Taiwan To investigate risk factors associated with CRC development	Retrospective cohort May 2002-February 2012	Questionnaire for 5 years preceding by nurses and biennial follow-up for 10 years to obtain information about morbidity		During the follow-up, 147 (48.8%) carriers developed histologically confirmed CRC, and 109 (74.1%) were diagnosed with adenocarcinoma Multivariate Cox Proportional hazard model results All: Hakka Ethnicity: HR=1.62 (1.09–2.34), p=0.015 Occupation: Manual: HR=1.56 (1.07–2.27), p=0.021 Physical Activity: HR=0.62 (0.41–0.88), p=0.009 *MLH1*: Hakka Ethnicity: HR=1.72 (1.16–2.55), p=0.006 Physical Activity: HR=0.54 (0.34–0.83), p=0.005 *MSH2*: Blood Group type B, (compared with type O) HR=2.64 (1.06-6.58), p=0.036	Factors looked at: sex, education, ethnicity, occupation, blood group, physical activity, cigarette smoking, alcohol drinking, tea consumption, coffee consumption, and intake of meat, vegetables, fruits, seafood, and staple foods. Factors associated with increased risk of CRC: All: Hakka ethnicity, manual labour MHL1: Hakka ethnicity, manual labour *MSH2*: Blood type B, alcohol drinking Decreased Risk: All: regular physical activity, tea and high fruit consumption MHL1: college education, regular physical activity, tea and high fruit consumption *MSH2*: none

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Abbreviations: BMI = body mass index; BSO = bilateral salpingo-oophorectomy; CAH = complex atypical hyperplasia; CAPP2 = Colorectal Adenoma/carcinoma Prevention Programme 2; CI = confidence interval; CRC = colorectal cancer; CRT = colorectal tumour; DOB = date of birth; EC = endometrial cancer; HR = hazard ratio; LS = Lynch syndrome; MLH = mutL homolog; MMR = mismatch repair; MSH = mutS homolog; NSAID = nonsteroidal anti-inflammatory drug; OC = ovarian cancer; PH = prophylactic surgery; RCT = randomized controlled trial; yr = year

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Table 19. GRADE Summary Table for Lifestyle Factors Risk Reduction Strategies.

Patients or population: Lynch syndrome Patients Setting: Risk Reduction Strategies Intervention: Lifestyle Factors Comparison: Less vs. More										
Outcomes	Intervention	Comparison	Number of Participants (studies)	Main findings	Quality of evidence (Risk of Bias)	Consistency	Directness	Precision	Publi-cation bias	Quality of Evidence (GRADE)
BMI										
Colorectal Cancer Incidence [50] (Movahedi, 2015) 1 Prospective Cohort Importance: Critical	Overweight (BMI=25-29.9 kg/m^2)	Under - Normal weight (BMI<25 kg/m2)	937 *MLH1*=438 *MSH2*=276 Under-normal weight=432 Overweight =321 Obese=143	55 people developed CRC (*MLH1*=28, *MSH2*=20) All: HR=1.09 (0.57 to 2.11) p=ns *MLH1*: HR=1.19 (0.47 to 3.01) p=ns *MSH2*: HR=1.26 (0.44 to 3.60) p=ns	Serious[1]	Not serious	Not serious	Serious[2]	Not serious	Very Low
	Obese (BMI≥30 kg/m^2)	Under - Normal weight (BMI<25 kg/m^2)		All: HR=2.34 (1.17 to 4.67) p=0.02 *MLH1*: HR=3.72 (1.41 to 9.81) p=0.008 *MSH2*: HR=1.59 (0.47 to 5.44) p=ns						
Diabetes and Hormone Replacement Therapy –EC Risk										
Endometrial Cancer Incidence [56] (Staff, 2016) 1 Retrospective Cohort Importance:	Median value for hormone replacement therapy was 9 years: >9 years Diabetes: yes	For hormone replacement therapy: < 9 years Diabetes: no	136 women with LS	Multivariate analysis Duration of hormone replacement therapy (HRT) HR=1.07 (95% CI 1.02–1.13), p=0.010; Diabetes HR=4.18 (95% CI 1.52–11.52), p=0.006	Serious[1]	Not serious	Not serious	Serious[2]	Not serious	Very Low

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Critical										
Diet										
Colorectal Cancer Incidence [51] (Brouwer, 2017) 1 Prospective Cohort Importance: Critical	Highest tertile	Lowest tertile	457 59 months followed	182 people developed CR tumour and 18 developed CRC Compared high inflammatory diets to low inflammatory diets for CRT risk HR=1.37 (95% CI: 0.80-2.34)	Serious[1]	Not serious	Not serious	Serious[2]	Not serious	Very Low
Colorectal Cancer Incidence [52] (Chau, 2016) 1 Prospective Cohort Importance: Critical	Highest tertile	Lowest tertile	1966	744 people developed CRC Multivitamin intake for at least 3 years: HR=0.47 (0.32–0.69), p<0.001 Calcium intake for at least 3 years: HR=0.42 (0.23–0.74) p=0.003 Folic Acid for at 3 year intake: HR=0.87 (0.36–2.08) p=0.76	Serious[1]	Not serious	Not serious	Serious[2]	Not serious	Very Low
Colorectal Cancer Incidence [54] (Jung, 2014) 1 Prospective Cohort Importance: Critical	Highest tertile	Lowest tertile	470 20 months followed	131 people developed CR tumour HR (CI) Folate, HR=1.06 (0.59–1.91) Vitamin B2, HR=0.77 (0.39–1.51) Vitamin B6, HR=0.98 (0.59–1.62) Vitamin B12, HR=1.24	Serious[1]	Not serious	Not serious	Serious[2]	Not serious	Very Low

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				(0.77–2.00) for; and Methionine, HR=1.36 (0.83–2.20)						
Colorectal Cancer Incidence [53] (Botma, 2013) 1 Prospective Cohort Importance: Critical	Highest tertile	Lowest tertile	486 20 months followed	58 people developed CR adenoma Prudent: HR=0.73 (0.32-1.66), p=0.78 Meat: HR=1.70 (0.83-3.52), p=0.21 Snack: HR=2.16 (1.03-4.49), p=0.12 Cosmopolitan: HR =1.25 (0.61-2.55), p=0.56	Serious[1]	Not serious	Not serious	Serious[2]	Not serious	Very Low
Colorectal Cancer Incidence [55] (Kamiza, 2015) 1 Retrospective Cohort Importance: Critical	Highest tertile	Lowest tertile	209 *MLH1* 92 *MSH2* For 5 yrs	147 people developed CRC Meat intake: HR=0.99 (0.65–1.52) p=0.989 Vegetable intake: HR=0.93 (0.63–1.73) p=0.717 Fruit intake: HR=0.60 (0.38–0.94) p=0.026 Seafood intake: HR=0.93 (0.57–1.53) p=0.789 Staple intake: HR= 0.86 (0.55–1.33) p=0.501	Serious[3]	Not serious	Not serious	Serious[4]	Not serious	Very low
Physical Activity										
Colorectal Cancer Incidence [55] (Kamiza, 2015) 1 Retrospective	Yes, based on vigorous physical activity weekly (i.e. jog 16 km, swim 3.2 km,	No	209 *MLH1* 92 *MSH2* For 5 yrs	147 people developed CRC All: HR=0.62 (0.41-0.86) p=0.009 *MLH1*: HR=0.54 (0.34-0.83) p=0.005	Serious[3]	Not serious	Not serious	Serious[4]	Not serious	Very low

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Cohort Importance: Critical	or sports over 5 hrs)			*MSH2*: HR=0.64 (0.26-1.59) p=0.337						

Abbreviations: BMI = body mass index; CI = confidence interval; CR = colorectal; CRC = colorectal cancer; CRT = colorectal tumour; HR = hazard ratio; hrs = hours; MLH = mutL homolog; MSH = mutS homolog; RCT = randomized controlled trial; PC = prospective cohort: RC = retrospective cohort; yr = year

Footnotes:
1 – Because the study is a prospective design; the measurements of BMI and food intake were self-reported; there may be misclassification bias, selection bias, recall bias; unaccounted for confounding.
2 – Because there is only 1 study for this category; the confidence intervals are large.
3 - Because of the retrospective design and therefore there is a risk of bias in the results; selection bias, misclassification bias, recall bias and confounding.
4 – Because there is only 1 study for this category.

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Table 20. Summary of results for segmental colectomy and total (extended) proctocolectomy studies.

Study	Study Design	Number of participants (SC/TC)	Median follow-up (years)		Mean interval between screens (years)		CRC incidence after surgery		Median time from index surgery to metachronous cancer (years)		Median time from last screening exam to metachronous cancer (years)		Mean number of screening exams/person	
			SC	TC	SC	TC	SC %	TC%	SC	TC	SC	TC	SC	TC
Renkonen-Sinisalo, 2017 [59]	Retrospective Cohort Screening protocol was 2 yrs	144/98	14.6-25 yrs		-	-	36	5	8.2		-	-	-	-
Kim, 2017 [77]	Retrospective Cohort Screening protocol was 1-2 yrs	76/30	6.4 (0.75-14.5)	5.6 (1.5-13.5)	-	-	13	0	-	-	3 CRC < 1yr 5 CRC = 1yr 2 CRC > 1yr 3 FU loss	0	-	-
Moller, 2017 [58]	Prospective Cohort Screening protocol was different for regions. 1 yr, 2 yr or 3 yr intervals	821	Females: F/U = 6.1 yrs Males: F/U = 6.0 yrs		-		147		-		60 (46%) <2 yrs 102 (78%) <3 yrs		-	
Messick, 2014 [79]	Retrospective Cohort No suggested screening protocol provided	35/3 24/38 (63%) of patients had COL	8.5 (range, 0.1–38.5)		-		19 CRC in 16 pts		8 (1-37)		-		4 per pt over 8.5 yr (1-37.5)	
Kalady, 2012 [57]	Retrospective Cohort	50/0	Mean F/U	-	28.7 (±25.9)	-	15.2 (5 pts)	-	6 (3.5-16)	-	3.5 (2-5.2)	-	0.79 ±1.6 per yr	-

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	No suggested screening protocol provided	SC: 33 (66%) had COL	=10.7 yrs (± 7.6)											
Stupart, 2011 [47]	Prospective Cohort Suggested screening protocol was annual	39/21 SC: 22 (56%) had COL TC: 15 (71%) had flex sig	Median F/U=8 yrs (0-34)	Median F/U=6 yrs (1-30)	-	-	21.0 (8 pts)	9.5 (2 pts)	-	Mean =19 yrs	2 CRC < 1yr 6 CRC > 2yr	1 CRC<1yr 1 CRC> 4yr	3 (± 2.2)	5 (± 3.2)
Parry, 2011 [46]	Retrospective Cohort Suggested screening protocol was 1-2 yr	332/50 SC: 289 (78%) had at least 1 COL TC: 37 (74%) had flex sig	Mean F/U=9 (SD=8)	Mean F/U=8 (SD=6)	1.7 (1.5-1.8)	1.33 (1.1-1.7)	22.0 (74 pts)	0	-	0	-	0	Average frequency 54% every year	Average frequency 25% every year
Natarajan 2010 [45]	Retrospective Cohort No suggested screening protocol provided	69/37 Total # of COL=116/80	Median F/U =12 (5-20)	Median F/U=12 (5-20)	1-6	1-6	33.3 (23 pts)	10.8 (4 pts)	NR (0.5-13)	NR (1.3-14.8)	-	-	1.7/pt	2.2/pt
Kalady, 2010 [43]	Retrospective Cohort No suggested screening protocol provided	253/43 SC: 221 (87%) had a COL TC: 38 (88%) had endoscopy	Median F/U =8.7 (IQR 16.1)	Median F/U =8.7 (IQR 18.1)	2.1 (±1.8)	2.2 (± 1.5)	25.0 (55 pts)	8.0 (3 pts)	5.8 (IQR 13.5)	18.9 (IQR 4.9)	2.8 (0.5-7.5)	3.8 (3.4-7.5)	0.7 ± 0.3 /yr	0.6 ±0.3/yr
de Vos tot Nederveen Cappel, 2002 [42]	Prospective Cohort Screening Program for surveillance:	110/29	7.1 (0.1-15.3)	5 (1-15)	21.8 (7 pts)	5 (7 pts)	11.8 (13 pts)	3.4 (1 pt)	NR (0.1-12)	NR (3-4)	4 CRC < 1yr 9 CRC < 2yr	1 CRC < 2yr	-	-

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	Before 1996: 2-3 yr After 1996: 1-2 yr													
Mecklin, 1993 [44]	Prospective Cohort Suggested screening protocol every 2 yr	37/17	10.7 (1-30)	5.8 (1-15)	-	-	21.6 (8 pts)	11.8 (2 pts)	-	-	-	-	-	-

Abbreviations: COL = colonoscopy; CRC = colorectal cancer; F/U = follow=up; flex sig = flexible sigmoidoscopy; IQR = interquartile range; pts = patients; SC = segmental colectomy; TC = total colectomy; yr = year
Note: Not all of these studies are in the systematic review from Heneghan, 2015. Three were found in the literature search –de Vos tot Nederveen Cappel is also in question 2 data

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Appendix 1: Members of the Working Group and their COI declaration (see the PEBC Conflict of Interest (COI) Policy)

Name	Affiliation	Declarations of interest
Jill Tinmouth Working Group Chair Gastroenterologist	Cancer Care Ontario Sunnybrook Health Sciences Centre University of Toronto	None declared
Nancy Baxter Surgeon	St. Michael's Hospital, University of Toronto	None declared
Sarah Ferguson Gynecological Oncologist	Princess Margaret Hospital, University Health Network	Principal investigator for a clinical trial involving an object of study; Published paper on object of study
June Carroll Family Physician	Mount Sinai Hospital, University of Toronto	Co-investigator on grant involving an object of study; Published three papers on object of study
Robert Gryfe Colon & Rectal Surgeon	Mount Sinai Hospital, University Health Network	Terry Fox Research Institute and Co-investigator on research grant Canadian Agency for Drugs and Technologies in Health reviewer
Bronwen McCurdy Group Manager, ColonCancerCheck / GI Endoscopy	Cancer Care Ontario	None declared
Caroline Zwaal Health Research Methodologist	Program in Evidence-Based Care McMaster University Hamilton, Ontario	None declared

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Appendix 2: Literature Search Strategy

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

#	Searches	Results
1	exp Colorectal Neoplasms, Hereditary Nonpolyposis/	4056
2	hereditary nonpolyposis.tw.	1931
3	hereditary non-polyposis.tw.	1253
4	HNPCC.tw.	2209
5	Lynch Syndrome.tw.	2016
6	(Muir Torre Syndrome or Muir-Torre Syndrome).tw.	346
7	Turcot Syndrome.mp.	146
8	1 or 2 or 3 or 4 or 5 or 6 or 7	6068
9	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.	2015628
10	8 not 9	5547
11	limit 10 to english	4971
12	limit 11 to yr="2012-current"	1291

Database(s): Embase 1974 to 2016 August 12

Search Strategy:

#	Searches	Results
1	exp Colorectal Neoplasms, Hereditary Nonpolyposis/	3553
2	hereditary nonpolyposis.tw.	2139
3	hereditary non-polyposis.tw.	1487
4	HNPCC.tw.	2721
5	Lynch Syndrome.tw.	3183
6	(Muir Torre Syndrome or Muir-Torre Syndrome).tw.	427
7	Turcot Syndrome.mp.	301
8	1 or 2 or 3 or 4 or 5 or 6 or 7	7818
9	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.	2598626
10	8 not 9	7249
11	limit 10 to english	6589
12	limit 11 to yr="2012-current"	2492
13	limit 12 to exclude medline journals	268

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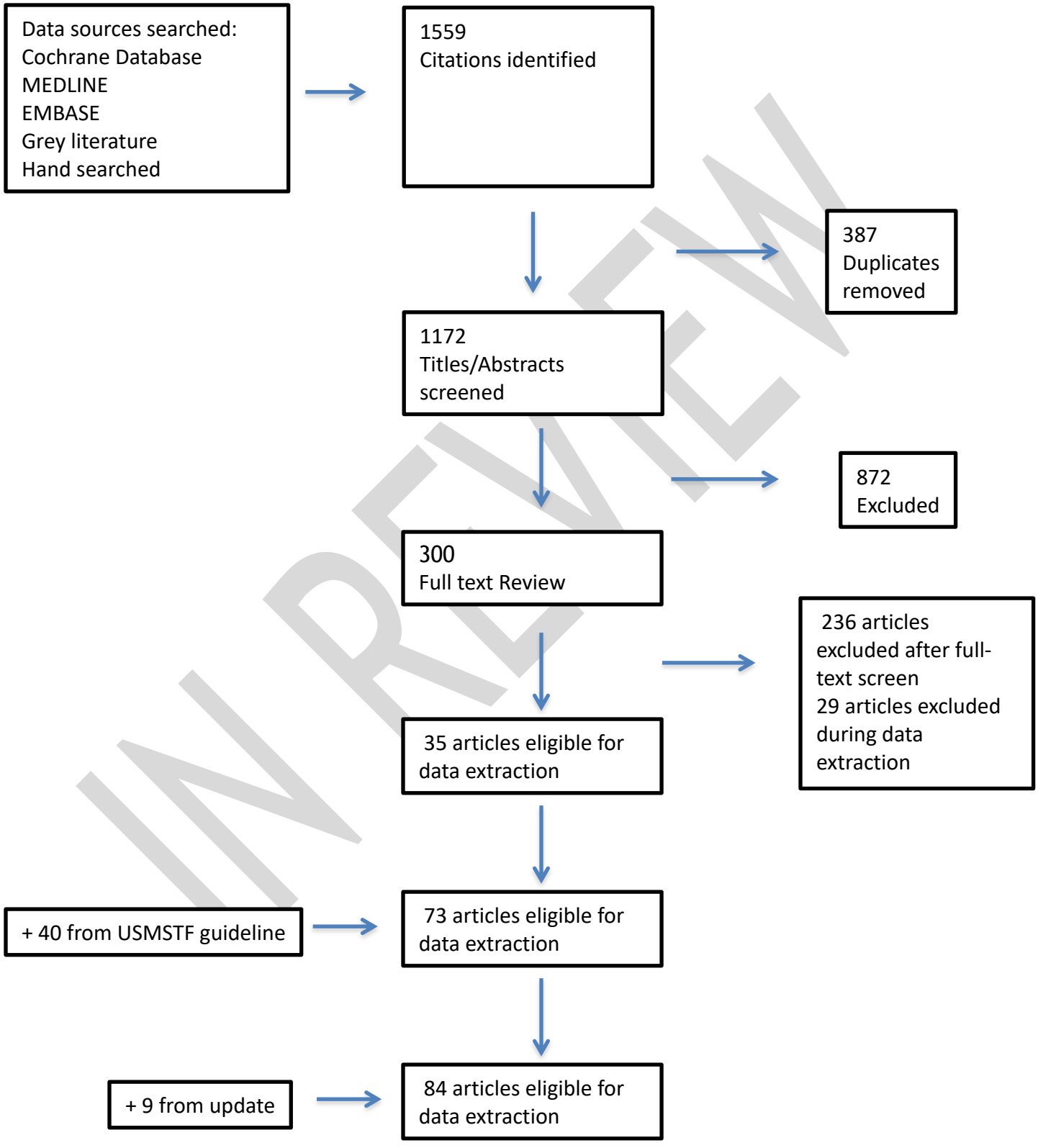
Appendix 3: PRISMA Flow Diagram



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Appendix 4. Quality Assessment Tables

Table A4-1: AGREE II Scores for Guidelines.

Domain	Guideline on Genetic Evaluation and Management of Lynch Syndrome: a consensus statement by the USMSTF on CRC 2014 Giardiello et al., 2014
Scope and Purpose	64
Stakeholder Involvement	58
Rigour of Domain	60
Clarity and Presentation	86
Applicability	0
Editorial Independence	75
Number of Reviewers	2

Abbreviations: CRC = colorectal cancer; USMSTF = U.S. Multi-Society Task Force

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Table A4-2. PRISMA scores for Systematic Reviews.

AMSTAR Checklist	1. Was an *a priori* design provided?	2. Was there duplicate study selection and data extraction?	3. Was a comprehensive literature search performed?	4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	5. Was a list of studies (included and excluded) provided?	6. Were the characteristics of the included studies provided?	7. Was the scientific quality of the included studies assessed and documented?	8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	9. Were the methods used to combine the findings of studies appropriate?	10. Was the likelihood of publication bias assessed?	11. Was the conflict of interest included?
Heneghan 2015 [78] (5/11)	Can't Answer	No	Yes	No	No	Yes	No	Yes	Yes	No	Yes
Helder-Woolderink 2016 [70] (7/11)	Can't Answer	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Mork 2015 [72] (4/11)	Can't Answer	No	Yes	No	No	No	No	Yes	Yes	No	Yes
Jenkins 2015 [74] (4/11)	Can't Answer	No	Yes	No	No	Yes	No	No	Yes	No	Yes
Haanstra 2013 [75] (6/11)	Can't Answer	No	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes

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Table A4-3. Quality assessment for RCTS using the RISK OF BIAS Tool.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other /Comment	Overall Risk of Bias Judgment
Burn, 2008 [84]	Low	Low	Low	Low	Moderate	Low	CRC ascertainment not standardized across centres	Low
Burn, 2011 [48]	Low	Low	Low	Low	Moderate	Low		Low
Mathers, 2012 [49]	Low	Low	Low	Low	Moderate	Low		Low

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Table A4-4. Question 1: Quality Assessment For Non-randomized studies using ROBINS (ACROBAT-NRSI) Risk of Bias Tool for Non-randomized Studies.

Study	Type of Study	Confounding	Selection of participants	Measurement of interventions	Departure from intervention	Missing data	Measurement of outcomes	Selection of reported results	Overall Risk of Bias Judgement
Moller, 2017 [1]	Prospective Cohort	Moderate	Moderate	Low	Low	Low	Low	Low	Low-moderate
Win, 2015 [2]	Retrospective Cohort	Low	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Therkildsen, 2015 [3]	Retrospective Cohort	Low	Moderate	Low	Low	Moderate	Low	Low	Low-moderate
Joost, 2015 [4]	Retrospective Cohort	Low	Moderate	Low	Low	Moderate	Low	Low	Low-moderate
Harkness, 2015 [5]	Retrospective Cohort	Low	Moderate	Low	Low	Moderate	Low	Moderate	Low-moderate
Castellsague, 2015 [6]	Retrospective Cohort	Low	Moderate	Low	Low	Low	Low	Low	Low
Rosty, 2014 [7]	Retrospective Cohort	Low	Moderate	Low	Low	Moderate	Low	Moderate	Low-moderate
Haraldsdottir, 2014 [8]	Retrospective Cohort	Low	Moderate	Low	Low	Low	Low	Low	Low
Skeldon, 2013 [9]	Retrospective Cohort	Low	Moderate	Low	Low	Low	Low	Low	Low
Rodriguez-Soler, 2013 [10]	Retrospective Consecutive series	Low	Moderate	Moderate	Low	Low	Low	Low	Low-moderate
Dowty, 2013 [12]	Retrospective Cohort	Low	Low	Moderate	Low	Moderate	Low	Low	Low-moderate
Win, 2012 [13]	Retrospective Cohort	Low	Moderate	Low	Low	Low	Low	Low	Low

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Table A4-5. Question 2: Quality Assessment For Non-randomized studies using ROBINS (ACROBAT-NRSI) Risk of Bias Tool for Non-randomized Studies.

Study	Type of Study	Confounding	Selection of participants	Measurement of interventions	Departure from intervention	Missing data	Measurement of outcomes	Selection of reported results	Overall Risk of Bias Judgement
Seppala, 2017 [68]	Prospective cohort	Low	Moderate	Low	Low	Low	Low	Low	Low
Lindberg, 2017 [69]	Prospective cohort	Low	Moderate	Low	Low	Low	Low	Low	Low
Rahmi, 2015 [71]	Prospective cohort	Low	Moderate	Low	Low	Low	Low	Low	Low
Tzortzatos, 2015 [38]	Retrospective cohort	Low	Moderate	Low	Low	Low	Moderate	Low	Low-moderate
Ketabi, 2014 [37]	Retrospective cohort	Low	Moderate	Low	Low	High	Moderate	Low	Low-moderate
Helder-Woolderink, 2013 [32]	Prospective cohort	Low	Moderate	Low	Low	Moderate	Low	Moderate	Low-moderate
Stuckless, 2013 [31]	Prospective cohort	Low	High	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Stuckless, 2012 [92]	Retrospective cohort	Low	High	Moderate	Moderate	Moderate	Low	Moderate	Moderate
Vasen, 2010 [90]	Prospective cohort	Low	Moderate	Moderate	Low	Low	Low	Low	Low
Saurin, 2010 [80]	Consecutive series	Low	Moderate	Low	Low	Moderate	Low	Moderate	Moderate
Engel, 2010 [89]	Prospective cohort	Moderate	Moderate	Low	Low	Moderate	Low	Moderate	Moderate
Stupart, 2009 [93]	Prospective cohort	Low	Moderate	Low	Low	Moderate	Low	Low	Low-moderate
Järvinen, 2009 [30]	Prospective cohort	Low	High	Moderate	Low	High	Moderate	High	High
Gerritzen, 2009 [33]	Prospective cohort	Low	Moderate	Low	Low	Moderate	Moderate	Low	Moderate
Myrhøj, 2008 [39]	Retrospective cohort	Low	High	High	High	High	Moderate	Moderate	High
Lécuru,	Consecutive	Moderate	High	Low	Moderate	Moderate	Moderate	Moderate	Moderate

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2008 [85]	series								
Renkonen-Sinisalo, 2006 [35]	Prospective cohort	Moderate	High	Moderate	Moderate	Moderate	High	Moderate	Moderate
Dove-Edwin, 2005 [82]	Prospective cohort	Low	Moderate	Moderate	Moderate	High	Moderate	Moderate	Moderate
Rijcken, 2003 [36]	Prospective cohort	Low	Moderate	Low	Low	Low	Moderate	Low	Moderate
Renkonen-Sinisalo, 2002 [40]	Prospective Cohort	Low	High	Moderate	Moderate	Low	Low	Moderate	Moderate
Dove-Edwin, 2002 [34]	Prospective cohort	Low	Moderate	Moderate	Moderate	Moderate	High	High	Moderate
de Vos tot Nederveen Cappel, 2002 [42]	Prospective cohort	Low	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Moderate
Järvinen, 2000 [87]	Prospective cohort – follow-up	Low	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Moderate
Järvinen, 1995 [86]	Prospective cohort	Low	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Moderate

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Table A4-6. Question 3: Quality Assessment For Non-randomized studies using ROBINS (ACROBAT-NRSI) Risk of Bias Tool for Non-randomized Studies.

Study	Type of Study	Confounding	Selection of participants	Measurement of interventions	Departure from intervention	Missing data	Measurement of outcomes	Selection of reported results	Overall Risk of Bias Judgement
Brouwer, 2017 [51]	Prospective cohort	Low	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Staff, 2016 [56]	Retrospective cohort	Low	Moderate	Moderate	Low	Moderate	Serious	Low	Moderate
Chau, 2016 [52]	Retrospective cohort	Low	Serious	Moderate	Low	Moderate	Serious	Low	Moderate
Tzortzatos, 2015 [38]	Retrospective cohort	Moderate	Serious	Low	Low	Low	Low	Low	Moderate
Movahedi, 2015 [50]	Prospective cohort	Low	Serious	Moderate	Moderate	Low	Moderate	Low	Moderate
Kamiza, 2013 [55]	Retrospective cohort	Low	Serious	Moderate	Low	Moderate	Serious	Low	Moderate
Ait Ouakrim, 2015 [76]	Retrospective cohort	Low	Serious	Moderate	Low	Moderate	Serious	Low	Moderate
Jung, 2014 [54]	Prospective cohort	Low	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Botma, 2013 [53]	Prospective cohort	Low	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Schmeler, 2006 [41]	Retrospective case control	Moderate	Serious	Low	Low	Low	Low	Low	Moderate

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Table A4-7. Question 4: Quality Assessment For Non-randomized studies using ROBINS (ACROBAT-NRSI) Risk of Bias Tool for Non-randomized Studies.

Study	Type of Study	Confounding	Selection of participants	Measurement of interventions	Departure from intervention	Missing data	Measurement of outcomes	Selection of reported results	Overall Risk of Bias Judgement
Renkonen-Sinisalo, 2017[59]	Retrospective Cohort	Low	Low	Low	Low	Low	Low	Low	Low
Kim, 2017 [77]	Retrospective Cohort	Low	Low	Low	Low	Moderate	Moderate	Moderate	Low-moderate
Moller, 2017 [58]	Prospective Cohort	Low	Low	Low	Low	Low	Moderate	Low	Low
Messick 2014 [79]	Retrospective Cohort	Low	Moderate	Moderate	Low	High	Moderate	Moderate	Moderate
Kalady, 2012 [57]	Retrospective Cohort	Low	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Moderate
Stupart, 2011 [47]	Prospective Cohort	Low	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Parry, 2011 [46]	Retrospective Cohort	Low	Moderate	Moderate	Low	High	Moderate	Moderate	Moderate
Natarajan 2010 [45]	Retrospective Cohort	Low	Moderate	Moderate	Low	High	Moderate	Moderate	Moderate
Kalady, 2010 [43]	Retrospective Cohort	Low	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Moderate
Mecklin, 1993 [44]	Prospective Cohort	Low	Moderate	Moderate	Low	High	Moderate	Low	Moderate

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Appendix 5. Additional information for Question 1

Table A5-1. Gene-specific cumulative risk by age 70, standardized incidence ratios and relative risk of Lynch syndrome cancers for people affected or at risk for Lynch syndrome.

Cancer	Cumulative Risk % (by age 70 years)	Standardized Incidence Ratio (95% CI)	Relative Risk	Median age at diagnosis (years) (range)	Number of subjects	References
Colorectal						
All mutations		All=10 (7-13)[2]	-	All=54(SD=12)	186 MC	Win, 2015 [2]
		All=20 (12-33)[3]		All=49 (26-75)	365 MC	Win, 2012 [13]
	M=70 (61-79)			NA	226 MC	van der Post, 2010 [16]
	F=57 (47-66)			NA	232 MC	van der Post, 201 0[16]
	M=54 (51-58)			NA	839 MC	Barrow, 2009 [20]
	F=46 (43-50)			NA	839 MC	Barrow, 2009 [20]
	M=47 (12-98)			NA	36 FAM	Alarcon, 2007 [23]
	F=33 (24-54)			NA	36 FAM	Alarcon, 2007 [23]
	M=27 (13- 51) (1+2)			NA	397 MC	Quenberger, 2005 [24]
	F=22(11-44)			NA	397 MC	Quenberger, 2005 [24]
	M=69 (NA)			M=55 (53-58)	190 REL	Hampel, 2005 [25]
	F=52 (NA)			F=60 (58-63)	183 REL	Hampel, 2005 [25]
	All=82 (NA)	All=68 (56-81)[4]		NA	360 MC	Aarnio, 1999 [28]
	M=74 (NA)			M=47 (31-79)	32 MC	Dunlop, 1997 [29]
	F=30 (NA)			F=50 (41-67)	35 MC	Dunlop, 1997 [29]
Suspected LS	-	All=3 (3-5)[2]	-	All=49 (SD=12)	271 MC	Win, 2015 [2]
LS	-	All=6 (4-10)[5]	-	All=48 (NA)	80 MC	Rodriguez-Soler, 2013 [10]
LLS	-	All=2 (1-4)[5]	-	All=54 (32-81)	177 LLS	Rodriguez-Soler, 2013 [10]
MLH1	M=47 (37-56)		-	NA	430 MC	Moller, 2017 [1]
	F=45 (31-59)			NA	514 MC	Moller, 2017 [1]
	M=34 (25-50)			M=45 (SD=13)	166 FAM	Dowty, 2013 [12]
	F=36 (25-51)			F=50 (SD=16)	166 FAM	Dowty, 2013 [12]
		All=39 (18-75)			9 MC	Win, 2012 [13]
	All=41 (25-70)			All=45 (15-90)	248 FAM	Bonadona, 2011 [15]
	M=57 (45-69)			NA	138 REL	van der Post, 2010 [16]
	F=50 (37-64)			NA	148 REL	van der Post, 2010 [16]
	All=60 (NA)			All=43 (16-81)	34 FAM	Vasen, 2001 [27]

MSH2	M=37 (20-54)				291 MC	Moller, 2017 [1]
	F=33 (16-49)				325 MC	Moller, 2017 [1]
	M=47 (36-60)		-	M=47 (SD=13)	224 FAM	Dowty, 2013 [12]
	F=37 (27-50)			F=47 (SD=15)	224 FAM	Dowty, 2013 [12]
		All=11 (3-28)			4 MC	Win, 2012 [13] [15]
	All=48 (30-77)			All=44 (16-95)	256 FAM	Bonadona, 2011
	M=43 (35-52)			NA	248 REL	van der Post, 2010 [16]
	F=47 (37-58)			NA	213 REL	van der Post, 2010 [16]
	All=64 (NA)			All=44 (16-90)	40 FAM	Vasen, 2001 [27]
MSH6	M=14 (0-32)			NA	135 MC	Moller, 2017 [1]
	F=26 (0-54)				170 MC	Moller, 2017 [1]
			All=OR:2.2 (0.3-16)	All=44 (10-59)	11 FAM	Castellsague, 2015 [6]
		All=17 (2-62)			2 MC	Win, 2012 [13]
	All=12 (8-22)			All=54 (24-85)	33 FAM	Bonadona, 2011 [15]
	M=31 (20-42)			NA	156 REL	van der Post, 2010 [16]
	F=22 (13-31)			NA	158 REL	van der Post, 2010 [16]
	M=22 (14-32)			M=59 (47-85)	1043 MC	Baglietto, 2010 [18]
	F=10 (5-17)			F=60 (36-82)	1043 MC	Baglietto, 2010 [18]
	M=69 (42-83)			M=55 (26-84)	59 MC	Hendriks, 2004 [26]
	F=30 (12-44)			F=57 (41-81)	87 MC	Hendriks, 2004[26]
PSM2	All=0			NA	77 MC	Moller, 2017 [1]
		All=15 (0-86)			1 MC	Win, 2012 [13]
	M=20 (11-34)			NA	39 FAM	Senter, 2008 [22]
	F=15 (8-26)			NA	39 FAM	Senter, 2008 [22]
Endometrium						
All mutations		F=40 (28-56)[3]	-	F=50 (35-69)	382 MC	Win, 2012 [13]
		F=31 (11-66)[3]		F=53 (42-66)	215 MC	Win, 2012 [13]
	F=35 (27-44)			NA	232 MC	van der Post, 2010 [16]
	F=28 (25-32)			F=49 (CI=47-51)	839 MC	Barrow, 2009 [20]
	F=14 (6-20)			NA	36 FAM	Alarcon, 2007 [23]
	F=32 (11-70)			NA	397 MC	Quenberger, 2005 [24]
	F=54 (NA)			F=58 (57-60)	321 MC	Hampel, 2005 [25]
	F=60 (NA)	F=62 (44-86)[4]		NA	183 MC	Aarnio, 1999 [28]
	F=42 (NA)			F=54 (45-68)	35 MC	Dunlop, 1997 [29]
MLH1	F=34 (24-44)		-	NA	514 MC	Moller, 2017 [1]
	F=18 (9-34)			F=48 (SD=11)	166 FAM	Dowty, 2013 [12]
		F=35 (21-64)[3]		NA	316 MC	Win, 2012* [13]
	F=54 (20-80)			F=49 (26-75)	248 FAM	Bonadona, 2011 [15]

	F=27 (21-33)			NA	148 REL	van der Post, 2010 [16]
	F=29 (24-34)			NA	839 MC	Barrow, 2009 [20]
	F=25 (NA)			NA	34 FAM	Vasen, 2001 [27]
MSH2	F=51 (33-69)				325 MC	Moller, 2017
	F=30 (18-45)		-	F=47 (SD=9)	224 FAM	Dowty, 2013 [12]
	F=21 (8-77)			F=48 (27-69)	256 FAM	Bonadona, 2011 [15]
	F=26 (17-35)			NA	213 REL	van der Post, 2010 [16]
		F=45 (26-71)[3]		NA	357 MC	Win, 2012* [13]
	F=24 (20-29)			NA	839 MC	Barrow, 2009 [20]
	F=37 (NA)			NA	40 FAM	Vasen, 2001 [27]
MSH6	F=49 (25-74)				170 MC	Moller, 2017 [1]
			F=OR:7.5(3.07–18.36)	F=44 (10-59)	11 FAM	Castellsague, 2015 [6]
		F=50 (0-185)[3]		NA	49 MC	Win, 2012* [13]
	F=16 (8-32)			F=55 (40-87)	33 FAM	Bonadona, 2011 [15]
	F=33 (22-43)			NA	158 REL	van der Post, 2010 [16]
	F=26 (18-36)			F=51 (32-80)	1043 MC	Baglietto, 2010* [18]
	F=49 (35-62)			NA	839 MC	Barrow, 2009 [20]
	F=71 (50-83)			F=54 (43-65)	87 MC	Hendriks, 2004 [26]
PMS2	F=24 (0-52.8)			NA	48 MC	Moller, 2017 [1]
	F=15 (6-35)			NA	39 FAM	Senter, 2008 [22]
Ovary						
All mutations		F=4 (1-8)[3]	-	F=52 (48-61)	382 MC	Win, 2012 [13]
		F=19 (4-55)[3]		F=52 (45-56)	241 MC	Win, 2012 [13]
	F=8 (6-10)	F=14 (10-18)[6]		F=44 (26-58)	1107 MC	Engel, 2012 [14]
	F=14 (NA)			F=54 (54-55)	321 MC	Hampel, 2005 [25]
	F=6 (4-8)			F=43 (CI=38-48)	839 MC	Barrow, 2009 [20]
	F=7 (5-9)			NA	2683 MC+PMC	Watson, 2008 [21]
	F=12 (NA)	F=13 (5-25)[4]		NA	183 MC	Aarnio, 1999 [28]
MLH1	F=11 (3-20)		-		514 MC	Moller, 2017 [1]
	F=13 (6-26)			F=48 (SD=13)	166 FAM	Dowty, 2013 [12]
		F=3 (0-8)[3]		NA	316 MC	Win, 2012* [13]
	F=5 (NA)			NA	806 MC	Engel, 2012* [14]
	F=20 (1-65)			F=45 (34-58)	248 FAM	Bonadona, 2011 [15]
	F=5.5 (3-8)			F=43 (CI=38-48)	340 MC	Barrow , 2009* [20]
	F=4 (2-6)			NA	2683 MC+PMC	Watson, 2008 [21]
	F=3.4 (0-7)			F=51 (35-75)	34 FAM	Vasen, 2001 [27]
MSH2	F=15 (6-24)			NA	325 MC	Moller, 2017 [1]
	F=10 (4 -21)		-	F=49 (13)	224 FAM	Dowty, 2013 [12]

		F=6 (1-13)[3]		NA	357 MC	Win, 2012* [13]
	F=6 (NA)			NA	1004 MC	Engel, 2012* [14]
	F=24 (3-52)			F=43 (20-58)	256 FAM	Bonadona, 2011 [15]
	F=8 (5-10)			F=43 (CI=38-48)	443 MC	Barrow, 2009* [20]
	F=8 (5-13)			NA	2683 MC+PMC	Watson, 2008 [21]
	F=10 (3-18)			F=45 (37-58)	40 FAM	Vasen, 2001 [27]
MSH6	F=0			NA	170	Moller, 2017 [1]
	F=0			NA	308 MC	Engel, 2012* [14]
	F=1 (0-3)			F=46 (39-55)	33 FAM	Bonadona, 2011 [15]
	F=0			F=43 (CI=38-48)	56 MC	Barrow , 2009* [20]
Gastric						
All mutations		All=6 (2-10)[3]	-	All=69 (55-79)	764 MC	Win, 2012 [13]
		All=10 (1-35)[3]		All=59 (31-88)	446 MC	Win, 2012 [13]
	M=7 (3-10)	M=10 (6-15)[6]		M=51 (28-78)	1011 MC	Engel, 2012 [14]
	F=3 (1-4)	F=7 (4-13)[6]		F=49 (40-58)	1107 MC	Engel 2012 [14]
	All=1 (0.08-4)			All=52 (24-81)	537 FAM	Bonadona, 2011 [15]
	M=6 (3-9)	M=4 (2-6)[7]		All=55 (27-82)	2014 MC	Capelle, 2010 [17]
	F=2 (0.6-3)	F=3 (1-6)[7]		All=55 (27-82)	2014 MC	Capelle, 2010 [17]
	All=9 (8-11)			M=56 (52-60)	839 MC	Barrow, 2009* [20]
	All=9 (8-11)			F=61 (58-65)	839 MC	Barrow, 2009* [20]
	All=6 (4-8)			NA	2683 MC+PMC	Watson, 2008 [21]
	All=13 (NA)	All=7 (4-12)[4]		NA	360 MC	Aarnio, 1999 [28]
MLH1	M=20 (10-35)		-	M=48 (SD=14)	166 FAM	Dowty, 2013 [12]
	F=8 (3-20)			F=57 (SD=21)	166 FAM	Dowty, 2013 [12]
		All=5 (0-10)[3]		NA	316 MC	Win, 2012 [13]
	All=6 (0.2-17)			All=52 (24-81)	248 FAM	Bonadona, 2011 [15]
		All=3 (1-6)[7]		NA	737 MC	Capelle, 2010 [17]
	All=11 (8-14)			NA	340 MC	Barrow, 2009 [20]
	All=6 (4-9)			NA	2683 MC+PMC	Watson, 2008 [21]
	All=2 (0-4.7)			All=53 (39-74)	34 FAM	Vasen, 2001 [27]
MSH2	M=2 (0.4-12)		-	M=53 (SD=13)	224 FAM	Dowty, 2013 [12]
	F=9 (4-21)			F=54 (SD=18)	224 FAM	Dowty, 2013 [12]
		All=7 (1-14)[3]		NA	357 MC	Win, 2012 [13]
	All=0.2 (0-10)			All=52 (30-79)	256 FAM	Bonadona, 2011 [15]
		All=6 (3-10)[7]		NA	897 MC	Capelle, 2010 [17]
	All=8 (5-10)			NA	443 MC	Barrow, 2009 [20]
	All=5 (3-8)			NA	2683 MC+PMC	Watson, 2008 [21]
	All=4 (0.5-8)			All=51 (23-82)	40 FAM	Vasen, 2001 [27]

MSH6		All=8 (0-29)[3]	-	NA	49 MC	Win, 2012 [13]
	All=0			All=63 (45-81)	33 FAM	Bonadona, 2011 [15]
	All=10 (3-17)				56 MC	Barrow, 2009 [20]
Bladder						
All mutations	M=4 (3-5)		-	All=61 (24-82)	75 FAM	Joost, 2015 [4]
	F=3 (2-4)			All=61 (24-82)	75 FAM	Joost, 2015 [4]
		All=7 (4-11)[3]		All=65 (54-84)	764 MC	Win, 2012 [13]
	M=6 (3-8)	M=8 (5-14)[6]		M=53 (34-75)	1011 MC	Engel, 2012 [14]
	F=4 (1-6)	F=16 (9-28)[6]		F=55 (43-74)	1107 MC	Engel, 2012 [14]
	M=16 (6-26)			All=60 (41-84)	226 MC	van der Post, 2010 [16]
	F=2 (0-5)			All=60 (41-84)	232 MC	van der Post, 2010 [16]
MLH1	All=3 (1-4)		-	All=59 (NA)	75 FAM	Joost, 2015** [4]
		All=4 (1-9)[3]		NA	316 MC	Win, 2012 [13]
	All=1 (NA)			NA	806 MC	Engel, 2012 [14]
	M=11 (0-25)			NA	138 REL	van der Post, 2010 [16]
	F=0			NA	148 REL	van der Post, 2010 [16]
MSH2	All=4 (3-6)		-	All=59 (NA)	75 FAM	Joost, 2015** [4]
		All=12 (7-20)[3]		NA	357 MC	Win, 2012 [13]
	All=8 (NA)			NA	1004 MC	Engel, 2012 [14]
	M=12 (4-20)			NA	248 REL	van der Post, 2010 [16]
	F=3 (0-4)			NA	213 REL	van der Post, 2010 [16]
MSH6	All=2 (0.4-3)	-	-	All=71 (NA)	75 FAM	Joost, 2015** [4]
	All=1 (NA)			NA	308 MC	Engel, 2012 [14]
	M=1 (0-4)			NA	156 REL	van der Post, 2010 [16]
	F=0			NA	158 REL	van der Post, 2010 [16]
Urinary Tract						
All mutations	All=7 (6-8)		-	All=62 (36-89)	75 FAM	Joost, 2015 [4]
		All=12 (8-18)[3]		All=60 (35-78)	316 MC	Win, 2012 [13]
		All=10 (1-34)[3]		All=62 (55-68)	446 MC	Win, 2012 [13]
	M=9 (5-14)	M=100 (65-148)[6]		M=52 (32-73)	1011MC	Engel, 2012 [14]
	F=6 (3-9)	F=122 (74-188)[6]		F=57 (41-74)	1107 MC	Engel, 2012 [14]
	All=2 (0.3-5)			All=55 (30-82)	537 FAM	Bonadona, 2011 [15]
	M=25 (8-42)			NA	226 MC	van der Post, 2010 [16]
	F=7 (0-16)			NA	232 MC	van der Post, 2010 [16]
	All=3 (2-4)			NA	839 MC	Barrow, 2009 [20]
	All=8 (6-10)			NA	2683 MC+PMC	Watson, 2008 [21]
	All=4 (NA)	All=8 (2-18)[4]		NA	360 MC	Aarnio, 1999 [28]
MLH1	M=1 (0.1-10)		-	M=46 (SD=18)	166 FAM	Dowty, 2013 [12]

	F=3 (1-13)			F=57 (SD=11)	166 FAM	Dowty, 2013 [12]
		All=10 (4-18)[3]		NA	316 MC	Win, 2012 [13]
	All=2 (NA)			NA	806 MC	Engel, 2012* [14]
	All=0.2 (0-3)			All=60 (37-67)	248 FAM	Bonadona, 2011 [15]
	M=16 (0-39)			NA	138 REL	van der Post, 2010 [16]
	F=2 (0-7)			NA	148 REL	van der Post, 2010 [16]
	All=4 (2-6)			NA	340 MC	Barrow, 2009 [20]
	M=4 (2-8)			NA	2683 MC+PMC	Watson, 2008 [21]
	F=1 (0.4-3)			NA	2683 MC+PMC	Watson, 2008 [21]
	All=1 (0-4)			All=63 (52-72)	34 FAM	Vasen, 2001 [27]
MSH2	M=8 (3-19)		-	M=56 (SD=11)	224 FAM	Dowty, 2013 [12]
	F=10 (4-23)			F=58 (SD=13)	224 FAM	Dowty, 2013 [12]
		All=18 (10-27)[3]		NA	357 MC	Win, 2012 [13]
	All=15 (NA)			NA	1004 MC	Engel, 2012* [14]
	All=2 (1-8)			All=54 (37-82)	256 FAM	Bonadona, 2011 [15]
	M=18 (5-31)			NA	248 REL	van der Post, 2010 [16]
	F=8 (0-15)			NA	213 REL	van der Post, 2010 [16]
	All=0			NA	443 MC	Barrow, 2009 [20]
	M=27 (20-38)			NA	2683 MC+PMC	Watson, 2008 [21]
	F=12 (8-18)			NA	2683 MC+PMC	Watson, 2008 [21]
	All=12 (4-20)			All=56 (40-72)	40 FAM	Vasen, 2001 [27]
MSH6	All=2 (NA)	-	-	NA	308 MC	Engel, 2012* [14]
	All=0.7 (0-2)			All=65 (30-75)	33 FAM	Bonadona, 2011 [15]
	M=3 (0-8)			NA	156 REL	van der Post, 2010 [16]
	F=0			NA	158 REL	van der Post, 2010 [16]
Upper Urinary Tract						
All mutations	M=4(3-5)	-	-	All=62 (36-89)	75 FAM	Joost, 2015 [4]
	F=5 (4-7)			All=62 (36-89)	75 FAM	Joost, 2015 [4]
	M=26 (9-43)			NA	226 MC	van der Post, 2010 [16]
	F=7 (0-16)			NA	232 MC	van der Post, 2010 [16]
MLH1	All=2 (0.7-3)		-	All=59 (NA)	75 FAM	Joost, 2015** [4]
	M=16 (0-39)			NA	138 REL	van der Post, 2010 [16]
	F=2 (0-7)			NA	148 REL	van der Post, 2010 [16]
		All=1.0 (NA)			129 MC	Skeldon, 2013 [9]
MSH2	All=7 (5-9)		-	All=61 (NA)	75 FAM	Joost, 2015** [4]
	M=18 (5-31)			NA	248 REL	van der Post, 2010 [16]
	F=8 (0-15)			NA	213 REL	van der Post, 2010 [16]

		All=7.0 (NA)			177 MC	Skeldon, 2013 [9]
MSH6	All=3 (1-4)	-	-	All=69 (NA)	75 FAM	Joost, 2015** [4]
	M=3 (0-8)			NA	156 REL	van der Post, 2010 [16]
	F=0			NA	158 REL	van der Post, 2010 [16]
Small Intestinal Cancer						
All mutations		All=73 (40-111)[3]	-	All=55 (31-67)	764 MC	Win, 2012 [13]
	M=12 (6-18)	M=251 (177-346)[6]		M=46 (25-73)	1011MC	Engel, 2012 [14]
	F=4 (1-6)	F=112 (65-180)[6]		F=46 (23-71)	1107 MC	Engel, 2012 [14]
	All=1 (0.1-1)			All=51 (29-71)	537 FAM	Bonadona, 2011 [15]
	All=2 (2-3)			NA	839 MC	Barrow, 2009 [20]
	M=6 (4-9)			NA	2683 MC+PMC	Watson, 2008 [21]
	F=3 (2-5)			NA	2683 MC+PMC	Watson, 2008 [21]
		All=0 (0-131)[4]		NA	360 MC	Aarnio, 1999 [28]
MLH1		All=41 (9-91)[3]		NA	316 MC	Win, 2012 [13]
	All=8 (NA)		-	NA	806 MC	Engel, 2012 [14]
	All=0.4 (0.1-3)			All=47 (20-90)	248 FAM	Bonadona, 2011 [15]
	All=4 (3-6)			NA	340 MC	Barrow, 2009 [20]
	All=7 (2-13)			All=50 (35-75)	34 FAM	Vasen, 2001 [27]
MSH2		All=109 (53-180)[3]		NA	357 MC	Win, 2012 [13]
	All=8 (NA)		-	NA	1004 MC	Engel, 2012 [14]
	All=1 (0-5)			All=48 (29-71)	256 FAM	Bonadona, 2011 [15]
	All=1 (0.5-2)			NA	443 MC	Barrow, 2009 [20]
	All=4 (0.5-8)			All=51 (31-69)	40 FAM	Vasen, 2001 [27]
MSH6	All=0			NA	33 FAM	Bonadona, 2011 [15]
	All=3			NA	308 MC	Engel, 2012 [14]
	All=0			NA	56 MC	Barrow, 2009 [20]
PSM2		All=116 (0-507)[3]		NA	42 MC	Win, 2012 [13]
Breast						
All mutations	-	F=2 (1-3)[3]	-	F=60 (35-69)	382 MC	Win, 2012 [13]
		F=4 (2-8)[3]		F=56 (42-62)	241 MC	Win, 2012 [13]
	F=14 (10-19)	F=2 (1-2)[6]		F=52 (30-76)	1107 MC	Engel, 2012 [14]
		F=1 (0.4-4)[4]		NA	183 MC	Aarnio, 1999 [28]
MLH1	F=19 (11-26)		-	NA	261 REL	Harkness, 2015 [5]
		F=1 (0.2-2)[3]		NA	316 MC	Win, 2012* [13]
	F=17 (NA)			NA	806 MC	Engel, 2012 [14]
	F=18 (12-24)			NA	340 MC	Barrow, 2009 [20]
MSH2	F=8 (3-12)		-	NA	345 REL	Harkness, 2015 [5]

		F=2 (1-4)[3]		NA	347 MC	Win, 2012* [13]
	F=11 (NA)			NA	1004 MC	Engel, 2012* [14]
	F=2 (0-3)			NA	443 MC	Barrow, 2009 [20]
MLH1+MSH2	F=13 (9-18)		-	NA	606 REL	Harkness, 2015 [5]
MSH6	-	F=5 (0-13)[3]	-	NA	49 MC	Win, 2012* [13]
	F=12 (NA)			NA	308 MC	Engel, 2012* [14]
Prostate						
All mutations			M=3.2 (2.0-6.3)	M=62 (45-74)	32 MC	Rosty, 2014 [7]
		M=5 (2-9)[8]		M=64 (55-82)	188 MC	Haraldsdottir, 2014 [8]
	M=17 (10-24)			M=65 (38-89)	4127 REL	Raymond, 2013 [11]
		M=2 (1-3)[3]		M=64 (55-77)	382 MC	Win, 2012 [13]
		M=2 (0.5-7)[3]		M=54 (50-62)	205 MC	Win 2012 [13]
	M=9 (4-14)	M=2 (1-4)[6]		M=59 (50-74)	1011 MC	Engel, 2012 [14]
	M=29 (SE=0.088)			M=60 (53-68)	106 MC	Grindeldal, 2009 [19]
		M=3 (0.8-7)[4]		NA	177 MC	Aarnio, 1999 [28]
MLH1	-	M=1 (0-2)[3]	-	NA	316 MC	Win, 2012* [13]
	M=0			NA	806 MC	Engel, 2012* [14]
MSH2	-		M=5.8 (2.6-20.9)	NA	32 MC	Rosty, 2014 [7]
		M=4 (2-5)[3]		NA	357 MC	Win, 2012* [13]
	M=18 (NA)			NA	1004MC	Engel, 2012* [14]
MSH6	-	M=1 (0-3)[3]	-	NA	49 MC	Win, 2012* [13]
	M=4 (NA)			NA	308 MC	Engel, 2012* [14]
Pancreatic						
All mutations	-	All=2 (0-4)[3]	-	All=65 (46-67)	764 MC	Win, 2012 [13]
		All=11 (3-48)[3]		All=64 (63-65)	446 MC	Win, 2012 [13]
	All=0.4 (0-1)			NA	839 MC	Barrow, 2009 [20]
		All=4 (1-13)[4]		NA	360 MC	Aarnio, 1999 [28]
MSH2	-	All=4 (0-9)[3]	-	NA	357 MC	Win, 2012 [13]
	All=1 (0-1)				443 MC	Barrow, 2009 [20]
Hepatobiliary						
All mutations		All=6 (2-11)[3]		All=62 (39-73)	764 MC	Win, 2012 [13]
	All=1 (0.07-2)		-	All=54 (28-97)	537 FAM	Bonadona, 2011 [15]
	All=1 (1-2)			M=NA	839 MC	Barrow, 2009 [20]
	All=1 (1-2)			F=60 (CI 32-68)	839 MC	Barrow, 2009 [20]
	All=2 (NA)	All=9 (1-33)[4]		NA	360 MC	Aarnio, 1999 [28]
MLH1		All=8 (2-18)[3]		NA	316 MC	Win, 2012 [13]
	All=2 (0-15)		-	All=50 (39-64)	248 FAM	Bonadona, 2011 [15]
	All=3 (1-5)				340 MC	Barrow, 2009 [20]
MSH2		All=4 (0-10)[3]	-	NA	357 MC	Win, 2012 [13]

	All=0.02 (0-0.2)			All=57 (28-97)	256 FAM	Bonadona, 2011 [15]
	All=0.4 (0-1)				443 MC	Barrow, 2009 [20]
MSH6		All=10 (0-39)[3]	-	NA	49 MC	Win, 2012 [13]
	All=0			NA	33 FAM	Bonadona, 2011 [15]
	All=0				56 MC	Barrow, 2009 [20]
Hematologic						
All mutations	-	All=3 (1-6)[3]	-	All=57 (41-75)	764 MC	Win, 2012 [13]
		All=2 (0.1-12)[4]		NA	360 MC	Aarnio, 1999 [28]
MSH2	-	All=7 (1-13)[3]	-	NA	357 MC	Win, 2012 [13]
Brain						
All mutations	-	All=4 (1-10)[3]	-	All=68 (62-80)	764 MC	Win, 2012 [13]
	All=3 (2-5)			M=56 (CI 9-102)	839 MC	Barrow, 2009 [20]
	All=3 (2-5)			F=50 (CI 29-71)	839 MC	Barrow, 2009 [20]
	All=2 (1-3)			NA	6041 REL	Watson, 2008 [21]
	All=4 (NA)	All=5 (1-12)[4]		NA	360 MC	Aarnio, 1999 [28]
MLH1	All=0.5 (0-1)	-	-	All=42 (2-73)	865 MC	Therkildsen, 2015 [3]
	All=0.3 (0-0.6)			NA	340 MC	Barrow, 2009 [20]
	All=2 (1-3)			NA	6041 REL	Watson, 2008 [21]
				All=45 (21-78)	34 FAM	Vasen, 2001 [27]
MSH2	All=2 (2-3)		-	All=42 (2-73)	1522 MC	Therkildsen, 2015 [3]
		All=9 (2-20)[3]		NA	357 MC	Win, 2012 [13]
	All=6 (4-9)			NA	443 MC	Barrow, 2009* [20]
	All=2 (2-4)			NA	6041 REL	Watson, 2008 [21]
	All=1 (0-3)			All=41 (2-73)	40 FAM	Vasen, 2001 [27]
MSH6	All=1 (0.2-1)	-	-	All=42 (2-73)	775 MC	Therkildsen, 2015 [3]
	All=0			NA	56 MC	Barrow, 2009 [20]

Abbreviations: CI = confidence interval; CRC = colorectal cancer; EC = endometrial cancer; F = female; FAM = families; LS = Lynch syndrome; LLS = Lynch-like syndrome; M = male; MC = mutation carrier; MC+PMC = probable mutation carriers; MLH = mutL homolog; MSH = mutS homolog; NA = not available; OR = odds ratio; PMS = postmeiotic segregation; REL = mutation carrier plus first-degree relatives; SD = standard deviation

Notes:

* Cannot tell how many of the women or men have a specific mutation. Only total number of each sex given.

** Did not subdivide mutation carriers into specific mutation types

Databases:

1. Cancer Incidence in Five Continents, Vol. VII (Win, 2015)
2. Cancer Incidence in Five Continents (Win, 2012)
3. Central population register and local parish records (Aarnio, 1999)
4. Spanish regional registers (Rodriguez-Soler, 2013)

5. German HNPCC Consortium and the registry of the Netherlands Foundation for the Detection of Hereditary Tumors (Engel, 2012)
6. Dutch Hereditary Cancer Registry (Capelle, 2010)
7. Surveillance, Epidemiology, and End Results Registry (Haraldsdottir, 2014)

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Table A5-2. Characteristics of risk of Lynch syndrome cancers studies.

Study	Study design	Population	Database/country/ Registry/ case and control	Risk for Type of Cancer	Comments
Colorectal Cancer					
Win, 2015	Retrospective Cohort study	• First-degree relatives of people with incident invasive CRC (probands) recruited by the Colon Cancer Family Registry between 1997 and 2007. • Participants were followed up approximately every 5 years after baseline to update information across all the study centres. • Based on all available baseline and follow-up data until 2012. • Categorized the probands into four groups we took data for: • 1799 people -'Suspected Lynch syndrome': probands with a CRC that had *MLH1/PMS2* loss with no evidence of *MLH1* methylation and/or BRAF V600E mutation or had *MSH2/MSH6* loss or solitary loss of *PMS2* or *MSH6* or were MSI-H, for which no MMR germline mutation had been identified. • 1239 people -'Lynch syndrome': probands known to carry a pathogenic MMR germline mutation.	Case: Colon Cancer Family Registry from USA, Canada and Australia. Control: Incidence rates for general population from: Cancer Incidence in Five Continents, Vol. VII (1988–1992). Lyon: IARC CancerBase No.7, 2005.	Colorectal cancer	A greater risk of CRC was estimated for first-degree relatives if CRC cases were diagnosed before age 50 years, had proximal colon cancer or if their tumours had any of the following: expanding tumour margin, peritumoral lymphocytes, tumour-infiltrating lymphocytes or synchronous CRC.
Rodriguez-Soler, 2013	Retrospective Cohort study	• 1689 consecutive CRC patients between March 2006-December 2007 • patient split into LS, LLS and sporadic • 13 families with LS • 25 families with LLS	Case: Two nationwide multicenter studies: EPICOLON I and EPICOLON II – Spain Control: Incidence rates for Gen pop calculated from Spanish regional registers	Colorectal cancer	The risk of cancer in families with LLS is lower that of families with Lynch syndrome but higher than that of families with sporadic CRC.

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Colorectal Cancer and Endometrial Cancer					
Dowty, 2013	Retrospective Cohort Study	• 17576 members of 166 *MLH1* and 224 *MSH2* mutation-carrying families. • Recruited between 1997-2010 • Includes clinic and population based families. • Families were recruited via probands who were either recently diagnosed CRC cases ascertained through population-complete cancer registries in the USA (Puget Sound, Washington State; the State of Minnesota; Los Angeles, California; Arizona; Colorado; New Hampshire; North Carolina; and Hawaii), Australia (Victoria), and Canada (Ontario) (population-based recruitment). • Or were persons from multiple-case families referred to family cancer clinics in Australia (Melbourne, Adelaide, Perth, Brisbane, and Sydney), New Zealand (Auckland), and the USA (Mayo Clinic, Rochester, Minnesota and Cleveland) (clinic-based recruitment).	Colon Cancer Family Registry USA Cumulative risk	Colorectal cancer, endometrial cancer	Estimates of CRC and EC cumulative risks for *MLH1* and *MSH2* mutation carriers are the most precise currently available.
Castellsague, 2015	Retrospective Cohort study	• Tested positive for a truncating mutation in the *MSH6* gene and fulfills Amsterdam and Bethesda criteria. • 11 French-Canadian families from Quebec. Studied 11 probands and 27 family members. • Additionally 6433 newborns, 187 CRC cases, 381 EC cases and 179 additional controls.	Case: Hospitals from Quebec Control: Incidence estimated allele frequency and the 2011 Quebec population	The association between *MSH6* mutation and risk to develop CRC, EC and OC was estimated by calculating odds ratio.	Investigating novel *MSH6* mutation and relation to Lynch syndrome.
Breast Cancer					
Harkness, 2015	Retrospective Cohort study	• 106 *MLH1* and 118 *MSH2* families • There were 157 *MLH1*, 219 *MSH2* and 53 *MSH6* mutation carriers and positive obligates.	Regional Genetics Service at St Mary's Hospital	Breast cancer	The risk to age 70 years for *MLH1* was 18.6%, for *MSH2*, 11.2%. The

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		• Mutation status was unknown for 206 *MLH1*, 262 *MSH2* and 31 *MSH6* female FDRs. • Just Breast cancer –no differentiation whether invasive or DCIS.	Cumulative Risk		difference between *MLH1* and *MSH2* carriers was statistically significant (p=0.014).
Prostate Cancer					
Rosty, 2014	Retrospective Cohort study	• 32 MMR mutation carriers (23 *MSH2*, 5 *MLH1* and 4 *MSH6*). • From between 1997-2010	Case: Australian, New Zealand, Mayo Clinic and Ontario Colon Cancer Family Registry between 1997 and 2010 Relative risk	Prostate cancer	Prostate cancer was the first or only diagnosed tumour in 37 % of carriers.
Haraldsdottir, 2014	Retrospective Cohort study	188 CRC males diagnosed with LS from 1998-2012 11 diagnosed with prostate cancer MMR gene mutation All patients prostate cancer *MLH1* 51 (27.1%) 1 (9.1%) *MSH2* 87 (46.3%) 7 (63.6%) *MSH6* 24 (12.8%) 2 (18.2%) *PMS2* 26 (13.8%) 1 (9.1%)	Case: Ohio Lynch syndrome Project at Ohio State University cohort Control: general population using Surveillance, Epidemiology and End Results registry 1999-2009	Prostate cancer	Males with Lynch syndrome had a nearly fivefold increased risk of developing prostate cancer but did not appear to have earlier onset or a more aggressive phenotype.
Urinary Tract Cancers					
Joost, 2015	Retrospective Cohort study	• 288 Lynch syndrome families ○ Lynch syndrome mutation carriers (n=1349) ○ First-degree relatives (n=1886) • In total, 136 cancers in 97 patients from 75 families.	The National Danish Hereditary Nonpolyposis Colorectal Cancer Register was utilized to estimate the cumulative life-time risk	Urothelial cancer in upper urinary tract and bladder	These tumours predominantly develop in individuals with mutations in *MSH2* (73%).
Skeldon, 2013	Retrospective Cohort study	• Cancer data from 321 people with known MMR mutation.	Case: Familial Gastrointestinal Cancer Registry in Toronto,	Bladder cancer	Eleven of 177 patients with *MSH2* mutations (6.21%, p

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			1980-2007 Control: Standardized incidence ratios from the Ontario Cancer Registry, using the Surveillance Epidemiology and End Results public database were used to compare cancer risk in patients with MMR mutations with the Canadian population.		< 0.001 compared with the Canadian population) were found to have BCa, compared with 3 of 129 patients with *MLH1* mutations (2.32%, p > 0.05) LS patients with *MSH2* mutations are at an increased risk for not only UTUC but also BCa.
Brain Cancer					
Therkidson, 2015	Retrospective Cohort study	• 288 Lynch syndrome families ○ Lynch syndrome mutation carriers (n=1349) ○ First-degree relatives (n=1886)	The National Danish Hereditary Nonpolyposis Colorectal Cancer Register was utilized to estimate the cumulative life-time risk	Glioblastomas, astrocytomas and oligodendroglio mas	
All Lynch syndrome Cancers					
Moller, 2017	Prospective Cohort Study	• 1942 mutation carriers followed for over 7.1 years • 944 *MLH1*, 616 *MSH2*, 305 *MSH6* and 77 *PMS2* • 1057 were females and 885 were males	European Majorca group Database from 10 countries	Colorectal, endometrial and ovarian cancers	Only those who never had cancer before were included. All prevalent cancers and cases< 1 year prospective observation time were excluded.
Win, 2012	Prospective Cohort study	• 764 carriers of an MMR gene mutation following CRC • 316 *MLH1*, 357 *MSH2*, 49 *MSH6*, and 42 *PMS2* • Just breast cancer no information on type	Case: Colon Cancer Family Registry Control: Cancer incidences for the general population were	Extra-colonic cancer following CRC in Lynch syndrome	Estimated risk of developing extra-colonic cancer 10-20 yrs after CRC using Kaplan-Meier method.

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			obtained from Cancer Incidence in Five Continents		

Abbreviations: BCa = bladder cancer; BRAF = proto-oncogene B-Raf; CRC = colorectal cancer; EC = endometrial cancer; FDR = first-degree relatives; GHBMR = General Hospital of Beijing Military Region; LS = Lynch syndrome; LLS = Lynch-like syndrome; MLH = mutL homolog; MMR = mismatch repair; MSH = mutS homolog; MSI-H = microsatellite instability-high; PMS = postmeiotic segregation; OC = ovarian cancer; UTUC = upper tract urothelial carcinoma; yr = year

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