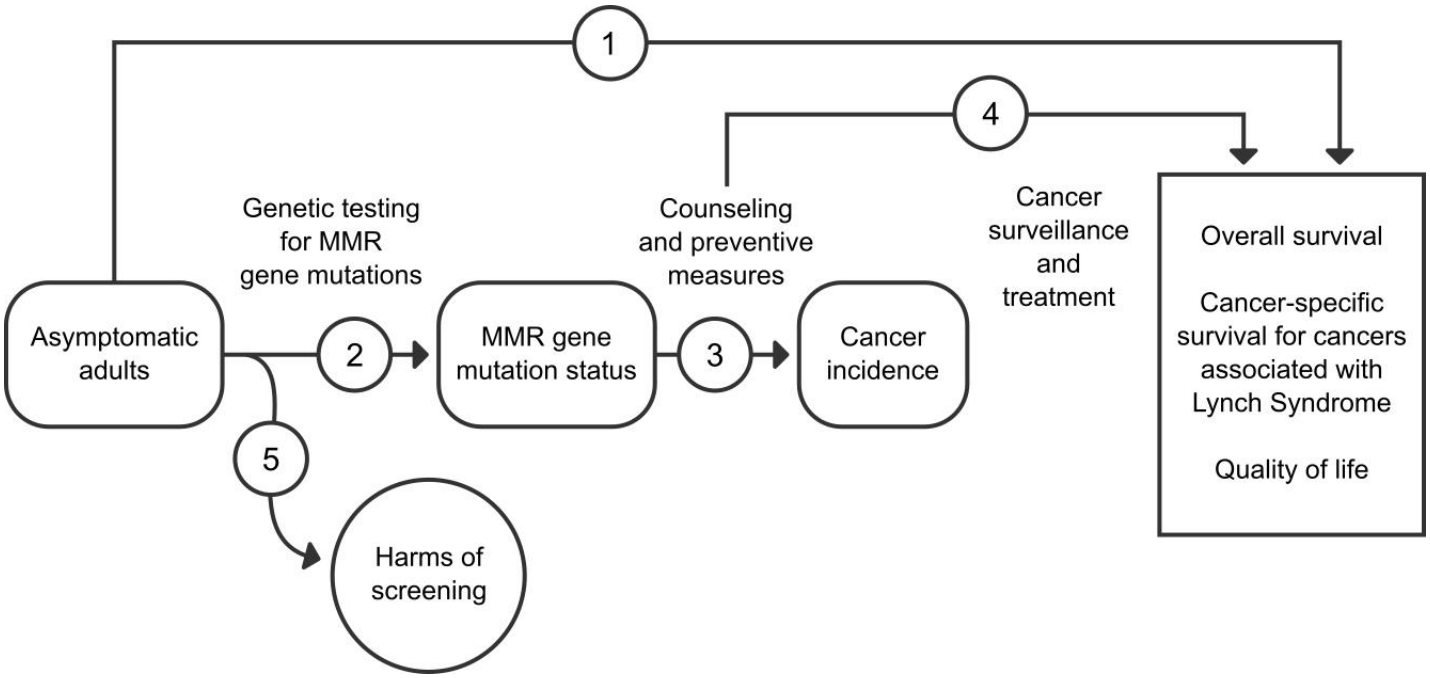
Supplementary Material 1: Analytic Framework



Supplementary Material 2: Tables S1-S23

Title: Should we screen the general population for Lynch Syndrome with genetic testing? A systematic review

Journal: Pharmacogenomics and Personalized Medicine

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Table S1: Electronic search strategy for PubMed

Search String	Search Terms	Number of Results
#1	Search ("Colorectal Neoplasms, Hereditary Nonpolyposis"[MeSH] OR "Colorectal Neoplasms, Hereditary Nonpolyposis"[tw] OR "Hereditary Nonpolyposis Colorectal Neoplasms"[tw] OR "Familial Nonpolyposis Colon Cancer"[tw] OR "Hereditary Nonpolyposis Colorectal Cancer"[tw] OR "Colorectal Cancer Hereditary Nonpolyposis"[tw] OR "Lynch Syndrome I"[tw] OR "Lynch Cancer Family Syndrome I"[tw] OR "Lynch Syndrome"[tw] OR "Syndrome, Lynch"[all fields] OR "Colon Cancer, Familial Nonpolyposis"[all fields] OR "Hereditary Nonpolyposis Colon Cancer"[tw] OR "hereditary non-polyposis"[tw] OR "hereditary nonpolyposis"[tw])	4770
#2	Search ("Lynch Syndrome II"[MeSH] OR "Lynch Syndrome II"[tw] OR "Lynch cancer family syndrome 2"[tw] OR "Lynch Cancer Family Syndrome II"[tw] OR "Colon Cancer, Familial Nonpolyposis, Type 2"[all fields] OR "Colorectal Cancer, Hereditary Nonpolyposis, Type 2"[all fields])	131
#3	Search (MLH1[TW] OR MSH2[TW] OR MSH6[TW] OR PMS2[TW] OR hMLH1[tw] OR hMSH2[tw] OR hMSH6[tw] OR hPMS2[tw])	5762
#4	Search (MLH3[tw] OR hMLH3[tw])	120
#5	Search (("DNA Mismatch Repair"[MeSH] OR "DNA Mismatch Repair"[tw] OR "Mismatch Repair"[tw] OR MMR[tw]) AND (test[tw] OR tests[tw] OR testing[tw] OR screen[tw] OR screens[tw] OR screening[tw])	1976
#6	Search (#1 OR #2)	4770
#7	Search (#6 AND #3)	2027
#8	Search (#6 AND (#3 OR #4))	2029
#9	Search (#6 AND (#3 OR #5))	2309
#10	Search (#6 AND (#3 OR #4 OR #5))	2311
#11	Search (Autobiography[Publication Type] OR Bibliography[Publication Type] OR Biography[Publication Type] OR Case Reports[Publication Type] OR Classical Article[Publication Type] OR comment[Publication Type] OR Congresses[Publication Type] OR Consensus Development Conference[Publication Type] OR Dictionary[Publication Type] OR Directory[Publication Type] OR Editorial[Publication Type] OR Electronic supplementary materials[Publication Type] OR Festschrift[Publication Type] OR In Vitro[Publication Type] OR Interactive Tutorial[Publication Type] OR Interview[Publication Type] OR Lectures[Publication Type] OR Legal Cases[Publication Type] OR Legislation[Publication Type] OR Letter[Publication Type] OR News[Publication Type] OR Newspaper article[Publication Type] OR Patient Education Handout[Publication Type] OR Personal Narratives[Publication Type] OR Periodical Index[Publication Type] OR Pictorial works[Publication Type] OR Popular works[Publication Type] OR Portraits[Publication Type] OR Scientific Integrity Review[Publication Type] OR Video Audio Media[Publication Type] OR Webcasts[Publication Type])	3639651
#12	Search (#10 NOT #11)	1986
#13	Search (#10 NOT #11) Filters: Humans	1803
#14	Search (#10 NOT #11) Filters: Other Animals	114
#15	Search (#14 NOT #13)	36
#16	Search (#12 NOT #15)	1950
#17	Search (#12 NOT #15) Filters: English	1817
#18	Search (#12 NOT #15) Filters: Publication date from 2006/06/01; English	879

Table S2. Eligibility Criteria

	Inclusion	Exclusion
Population	Questions 1 & 2 (overarching question and analytic validity): 1) Asymptomatic adults without previous or current diagnosis of colorectal, endometrial, ovarian, stomach, small bowel, pancreatic, hepatobiliary system, renal pelvic, or ureter cancer(s); and without a family history of Lynch Syndrome or a strong family history of cancers associated with Lynch Syndrome 2) Adults with a family history of Lynch Syndrome or a strong family history of cancers associated with Lynch Syndrome (eg, studies that focus on family members of new colorectal cancer patients with Lynch Syndrome). Questions 3 (cancer incidence), 4 (survival and quality of life), & 5 (harms of screening/intervention): 1) Asymptomatic adults (and their family members) with an MMR gene mutation associated with Lynch Syndrome who were identified by general population screening 2) Secondarily, adult family members with an MMR gene mutation that were identified by genetic testing after a family member was diagnosed with a Lynch-associated cancer Question 5 only: Asymptomatic adults (and their family members) lacking an MMR gene mutation but being screened for a mutation (in addition to the above described eligible populations)	All Questions: Age <18 years Questions 1, 3, 4, 5: Individuals with cancer diagnoses
Tests	Questions 1, 3, 4, & 5: Testing for the following germ line MMR gene mutations: *MLH1*, *MSH2*, *PMS2*, and *MSH6* (NOTE: not limited to targeted next-generation sequencing to be an eligible study) Question 2: Targeted Next-Generation sequencing (aka massively parallel sequencing) for the following germ line MMR gene mutations: *MHL1*, *MSH2*, *PMS2*, and *MSH6*. Other methods of testing for these MMR gene mutations are not eligible for Question 2.	Tumor tissue testing (eg, MSI testing and immunohistochemistry [IHC] testing uses the tumor sample)
Interventions	Questions 3, 4, & 5: Genetic counseling, early or more frequent colonoscopy and removal of polyps, prophylactic hysterectomy and salpingo-oophorectomy, transvaginal ultrasound, endometrial biopsy, CA 125, annual urinalysis and cytologic examination, annual skin examination and removal of pre-cancerous lesions	
Comparators	Question 1: No testing Question 2: Sanger sequencing (a.k.a., sequencing or traditional sequencing) or deletion/duplication testing Questions 3, 4, & 5: Usual care (ie screening for specific cancers as recommended or typically used for the general population) or no screening	
Outcomes	Questions 1 & 4: Overall survival, cancer-specific survival, quality of life Question 2: Sensitivity/specificity, reliability, reproducibility Question 3: Cancer incidence Question 5: Overdiagnosis, false positive results leading to unnecessary interventions; adverse events caused by screening measures or preventive interventions (eg, perforation of the colon during colonoscopy, perioperative mortality after hysterectomy); disease-specific distress; anxiety; burden of responsibility to communicate results of a positive test with family; negative test results leading to avoidance of routine screening procedures or risky behavior; increased health care expenses, opportunity costs, and other costs; and loss of insurance or inability to be insured	

	Inclusion	Exclusion
Setting	Developed countries	
Study design	Question 1: • 1st tier: RCTs comparing screened and unscreened groups • 2nd tier: Non-randomized controlled trials, prospective cohort studies • 3rd tier: Retrospective cohort studies • 4th tier: Modeling studies (cost-benefit analyses, cost-effectiveness analyses) Question 2: • Test and re-test of samples, or validation studies (including those from manufacturers) Questions 3 & 4: • 1st tier: RCTs comparing those who receive counseling or preventive measures with usual care or with no intervention; • 2nd tier: Non-randomized controlled trials, prospective cohort studies • 3rd tier: Retrospective cohort studies Question 5: • 1st tier: RCTs comparing screened and unscreened groups • 2nd tier: Non-randomized controlled trials, prospective cohort studies • 3rd tier: Retrospective cohort studies and case-control studies • 4th tier: Modeling studies (cost-benefit analyses, cost-effectiveness analyses), cross-sectional studies (eg focus groups, surveys)	Systematic reviews (but we identified systematic reviews and we made sure they did not find studies that we missed)

Note: All tiers are eligible.

Abbreviations: CA 125, cancer antigen-125; MMR, mismatch repair; MSI, microsatellite instability; PICOTS, populations-interventions-comparators-outcomes-timing-settings of interest; RCT, randomized controlled trial; RoB, risk of bias

Table S3. Detailed Risk of Bias Form for Dinh et al, 2011[1]

ROB Question	Response	Comments
1. What is the study design?	Modeling study	
2. For RCTs, were randomization and allocation concealment adequate?	NA	
3. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	Yes	
4. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	Yes	
5. Did the study guard against risk of survivor bias?	NA	Modeling study
6. Were groups similar at baseline?	Yes	Modeling study, groups same at baseline
7. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	NA	Modeling study
8. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	NA	Modeling study, outcomes not assessed (modeled using published literature)
9. Was overall attrition less than 30%?	NA	Modeling study
10. Was differential attrition less than 15%?	NA	Modeling study
11. Does the analysis control for baseline differences between groups?	NA	Modeling study
12. Does the analysis account for differences in treatment received by the groups?	Yes	
13. Are the statistical methods used to assess the outcomes appropriate?	Yes	
The following questions are only for modeling studies		
14. Was an appropriate, comprehensive search used to find data inputs? (how reliable are the inputs?)	Partially, and Can't Determine	Unclear how investigators selected the studies to use for their inputs. They used the EGAPP report for many of them (ie, reference 1: Palomaki et al), and that report had used an appropriate comprehensive search. For the inputs for which the investigators didn't use that review, cannot determine if an appropriate search was used.
15. Were appropriate, clinically relevant strategies/interventions evaluated?	Partially	Partially, with some caveats (see comments below related to the PREMM risk prediction model and the 30% IHC/MSI testing availability).
16. Was an appropriate comparison used?	Yes	They included tumor testing and then offering testing to family members of those with positive tests in the control group.
17. Were all the appropriate health benefits, harms, and costs described and included?	Partially	Most of them were, but they did not include indirect costs or time costs (included direct costs only) and did not consider newest treatments. See other comments below.
18. Were appropriate sensitivity analyses conducted? (especially for any variables that were not based on data from published literature)	Partially	A number of additional sensitivity analyses would be needed to address several potential limitations (see comments below).

19. Is the base case broadly applicable/generalizable to our Key Question(s)?	Yes	

ROB Question	Response	Comments
20. Was the analysis conducted from the societal perspective?*	Partially	They explain that it was from the societal perspective for the part on QALYs. However, for the cost inputs, they only included direct costs (no patient time costs or indirect costs were considered).
21. Was a lifetime horizon used? (if not, provide comments about the time horizon used and potential for risk of bias)	Yes	
22. Were costs and outcomes adjusted for differential timing (eg, discounting costs)?	Yes	The investigators ran sensitivity analyses for different discounting approaches.
ROB Ratings		
Outcomes Addressed	**Rating**	**Rationale**
Improved overall survival, and quality of life	Medium (cost-effectiveness, measured with QALYs gained) High (clinical effectiveness, measured with absolute life-years saved)	Medium ROB for the universal screening strategy cost-effectiveness assessment (given the limitations below, many biasing the results in favor of the intervention, but the intervention was not found to be cost-effective). High ROB for the clinical effectiveness assessment of universal screening (given the limitations below, many biasing the results in favor of the intervention, and the lack of sensitivity analyses to explore key assumptions) and high ROB for all models using the PREMM risk prediction. The details of how well the PREMM risk prediction model performs are a key underlying assumption. This does not report information about the model performance characteristics, and that model was built from a population that is different from the population that they are applying it to (assumption that it would work well when developed and validated in a group that was referred for genetic testing and individuals with CRC, and then applying the model to the general US population). The authors estimated that only 30% of those diagnosed with CRC have access to MSI and IHC testing (p. 19), thus making the control group intervention less effective than it would be if implemented more broadly, biasing the analysis in favor of the intervention. Additionally, there is no sensitivity analysis exploring the impact of this decision (eg, with 80% of those with CRC getting MSI/IHC). Did not include other cancers for the probands (non-CRC or non-endometrial cancer). Lack of consideration of indirect costs biases the model in favor of the intervention group (because it does not include costs of doing more screening colonoscopies, biopsies, ultrasounds, and TAHBSOs; this did not fully use a societal perspective). Costs, as the authors note, did not consider newer treatments (molecular targeting agents).
Outcomes Addressed	**Rating**	**Rationale**
		Some strengths: Use of Archimedes model. Inputs from Palomaki EGAPP review for many things. They used conservative estimates for analytic sensitivity (used 90%) and this would be better with the technology we're considering in our review.

Abbreviations: CRC, colorectal cancer; EGAPP, Center for Disease Control's Evaluation of Genomic Applications in Practice and Prevention; IHC, immunohistochemistry; MSI, microsatellite instability; NA, not applicable; QALY, quality-adjusted life year(s); RCT, randomized controlled trial; ROB, risk

of bias; TAHBSO, total abdominal hysterectomy with bilateral salpingo-oophorectomy.

Table S4. Detailed Risk of Bias Form for Hansen et al, 2014[2]

ROB Question	Response	Comments
Domain 1: Patient Selection		
1. Was a consecutive or random sample of patients enrolled?	NA	
2. Was a case-control design avoided?	Yes	
3. Did the study avoid inappropriate exclusions?	Unclear	Unclear description of how investigators selected their samples
4. What is the likelihood that the selection of patients could have introduced bias (ie, low, medium, or high)?	Low	
Domain 2: Index Test(s)		
5. Were the index test results interpreted without knowledge of the results of the reference standard?	No	
6. If a threshold was used, was it pre-specified?	NA	
7. What is the likelihood that the conduct or interpretation of the index test could have introduced bias (ie, low, medium, or high)?	Unclear	
Domain 3: Reference Standard		
8. Is the reference standard likely to correctly classify the genetic markers?	Yes	
9. Were the reference standard results interpreted without knowledge of the results of the index test?	Yes	
10. What is the likelihood that the reference standard, its conduct, or its interpretation could have introduced bias (ie, low, medium, or high)?	Low	
Domain 4: Flow and Timing		
11. Did all patients receive a reference standard?	Yes	
12. Did patients receive the same reference standard?	Yes	
13. Were all patients included in the analysis?	No	
14. What is the likelihood that the patient flow could have introduced bias (ie, low, medium, or high)?	Low	
Outcomes Addressed	**Overall Rating**	**Rationale**
Sensitivity of targeted next-generation sequencing versus Sanger sequencing for MMR gene mutations Specificity of targeted next-generation sequencing versus Sanger sequencing for MMR gene mutations	Low	The selection of which mutations (ie, which samples) to investigate wasn't explained. Presumably, the investigators were trying to evaluate a diverse set of the kinds of mutations that one would encounter clinically (ie, 14 deletions, 7 duplications, and 2 indels). This is reasonable, but it would have been ideal had they either had a larger sample or explained their rationale. This selection of mutations is, thus, a

		potential strength of the study, but it undeniably introduces some modest element of possible bias.

Abbreviations: NA, not applicable; RCT, randomized controlled trial; ROB, risk of bias.

Table S5. Detailed Risk of Bias Form for Pritchard et al, 2012[3]

ROB Question	Response	Comments
Domain 1: Patient Selection		
1. Was a consecutive or random sample of patients enrolled?	NA	
2. Was a case-control design avoided?	Yes	
3. Did the study avoid inappropriate exclusions?	Unclear	How investigators selected their samples not described in much detail
4. What is the likelihood that the selection of patients could have introduced bias (ie, low, medium, or high)?	Low	
Domain 2: Index Test(s)		
5. Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
6. If a threshold was used, was it pre-specified?	NA	
7. What is the likelihood that the conduct or interpretation of the index test could have introduced bias (ie, low, medium, or high)?	Low	
Domain 3: Reference Standard		
8. Is the reference standard likely to correctly classify the genetic markers?	Yes	
9. Were the reference standard results interpreted without knowledge of the results of the index test?	Yes	
10. What is the likelihood that the reference standard, its conduct, or its interpretation could have introduced bias (ie, low, medium, or high)?	Low	
Domain 4: Flow and Timing		
11. Did all patients receive a reference standard?	No	
12. Did patients receive the same reference standard?	Yes	
13. Were all patients included in the analysis?	No	
14. What is the likelihood that the patient flow could have introduced bias?	Low	
ROB Ratings		
Outcomes Addressed	**Rating**	**Rationale**

Sensitivity of targeted next-generation sequencing versus Sanger sequencing for MMR gene mutations Specificity of targeted next-generation sequencing versus Sanger sequencing for MMR gene mutations	Low	The investigators use the term "blinded", which might mean that the analysis of the MPS results was done without knowing the nature of the mutation found in prior Sanger sequencing. This is a reasonable assumption, but it isn't clearly spelled out in the paper. Regardless, this is a fairly straightforward study with little chance of significant bias.

Abbreviations: MPS, massively parallel sequencing; NA, not applicable; RCT, randomized controlled trial; ROB, risk of bias.

Table S6. Detailed Risk of Bias Form for Breheny et al, 2006[4]

ROB Question	Response	Comments
1. What is the study design?	Modeling study	
2. For RCTs, were randomization and allocation concealment adequate?	NA	
3. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	Yes	
4. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	Yes	All patient selection modeled on individuals entering Familial Cancer Programme in GSWA
5. Did the study guard against risk of survivor bias?	NA	
6. Were groups similar at baseline?	Can't Determine	Unclear if modeling study automatically selects patients in a manner that assures ideal similarity between groups
7. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	NA	
8. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Yes	
9. Was overall attrition less than 30%?	NA	
10. Was differential attrition less than 15%?	NA	
11. Does the analysis control for baseline differences between groups?	Can't Determine	
12. Does the analysis account for differences in treatment received by the groups?	Can't Determine	
13. Are the statistical methods used to assess the outcomes appropriate?	Can't Determine	
The following questions are only for modeling studies		
14. Was an appropriate, comprehensive search used to find data inputs? (how reliable are the inputs?)	Can't Determine	
15. Were appropriate, clinically relevant strategies/interventions evaluated?	Yes	Consistent with national Australian clinical practice guidelines (see pg. 99 under "Costs").
16. Was an appropriate comparison used?	Yes	
17. Were all the appropriate health benefits, harms, and costs described and included?	Partially	Complications from medical interventions not incorporated, nor were intangible costs or benefits (pg. 101)
18. Were appropriate sensitivity analyses conducted? (especially for any variables that	Can't Determine	No description of how sensitivity analyses were selected.

were not based on data from published literature)		
19. Is the base case broadly applicable/generalizable to our Key Question(s)?	Partially	Australian national data used to generate base cases for clinical screening and interventions and outcomes, but base case for cost data likely not broadly generalizable because they are drawn from regional sources (see pg. 99).
20. Was the analysis conducted from the societal perspective?*	Partially	Only direct costs assessed.

ROB Question	Response	Comments
21. Was a lifetime horizon used? (if not, provide comments about the time horizon used and potential for risk of bias)	Partially	Only ages 25-70 considered in analyses, in accordance with Australian national clinical guidelines for HNPCC surveillance.
22. Were costs and outcomes adjusted for differential timing (eg, discounting costs)?	Yes	Costs incurred in future were discounted at rate of 5% per annum.
ROB Ratings		
Outcomes Addressed	**Rating**	**Rationale**
Harms related to interventions	Medium	Unclear whether the study modeled expected baseline differences.

Abbreviations: GSWA, Genetic Services of Western Australia; HNPCC, hereditary nonpolyposis colorectal cancer; NA, not applicable; pg., page; RCT, randomized controlled trial; ROB, risk of bias;

Table S7. Detailed Risk of Bias Form for Jarvinen et al, 2000[5]

ROB Question	Response	Comments
1. What is the study design?	Retrospective cohort study	
2. For RCTs, were randomization and allocation concealment adequate?	NA	
3. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	Yes	
4. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	Yes	
5. Did the study guard against risk of survivor bias?	Yes	
6. Were groups similar at baseline?	Can't Determine	Overall groups similar in terms of age and sex, but unclear whether mutation-positive versus mutation-negative patients in each group also similar.
7. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	Can't Determine	
8. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Yes	Study does not report deaths among mutation-positive subjects and controls.
9. Was overall attrition less than 30%?	Can't Determine	The authors imply that some attrition might have occurred, even though they do not report how much.
10. Was differential attrition less than 15%?	Can't Determine	The authors imply that some attrition might have occurred, even though they do not report how much.
11. Does the analysis control for baseline differences between groups?	Can't Determine	The authors acknowledge not having information about certain baseline characteristics, such as socioeconomic status, that might have affected participants' decisions to accept or not accept screening.
12. Does the analysis account for differences in treatment received by the groups?	Yes	ITT analysis used to account for contamination in control group: 20% of patients requested screening after beginning study.
13. Are the statistical methods used to assess the outcomes appropriate?	Yes	ITT analysis used to adjust for attrition in screening group and contamination in control group.

ROB Ratings		
Outcomes Addressed	**Rating**	**Rationale**
Overall survival Cancer-specific survival Harms related to interventions	Medium	Unclear how much overall and differential attrition took place; if outcome assessment was blinded; if baseline characteristics besides age and sex were similar between groups, like socioeconomic status (which the authors admit may have influenced patients' choice to receive screening). Potential risk of ascertainment bias, but unclear to what extent because of lack of baseline characteristic reporting.

Abbreviations: ITT, intent-to-treat; NA, not applicable; RCT, randomized controlled trial; ROB, risk of bias

Table S8. Detailed Risk of Bias Form for Renkonen-Sinisalo et al, 2007[6]

ROB Question	Response	Comments
1. What is the study design?	Retrospective cohort study	
2. For RCTs, were randomization and allocation concealment adequate?	NA	
3. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	No	No, different criteria were used. Different time period and durations of follow-up. One group were those with positive mutation and underwent surveillance and were followed prospectively. The control group were cases of people with endometrial cancer who had undergone hysterectomy. They mainly compare the cases of people who developed endometrial cancer within the surveillance group versus the endometrial cancer cases (mostly from the past)
4. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	No	Non-equivalent selection of patients in screening and no-screening groups based on very different follow-up periods (screening: 1996-2005; no-screening: 1963-2005).
5. Were groups similar at baseline?	Can't Determine	Baseline characteristics not reported for mutation-positive women. Median ages reported for mutation-positive women in surveillance and control groups.
6. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	Can't Determine	
7. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Yes	
8. Was overall attrition less than 30%?	NA	Women selected based on whether they attended ≥1 post-test screening visit, or whether they declined screening, or were ineligible or unavailable for it.
9. Was differential attrition less than 15%?	NA	See comment for overall attrition.
10. Does the analysis control for baseline differences between groups?	No	
11. Does the analysis account for differences in treatment received by the groups?	No	
12. Are the statistical methods used to assess the outcomes appropriate?	No	No adjustment for potential confounders

ROB Ratings		
Outcomes Addressed	**Rating**	**Rationale**
Overall survival Cancer-specific survival	High	High risk of selection bias and confounding due to non-equivalent selection of screening and no-screening groups. Non-concurrent control group with different (longer) follow up. Surveillance group included patients diagnosed with cancer and treated during the pre-specified follow-up period (1996-2005), while no-screening group included patients diagnosed and treated within a much larger follow-up period (1963-2005). No explanation given for this decision. No baseline information provided for groups to assess comparability, and only median ages reported for women diagnosed with cancer within each group. Unclear if statistical analyses controlled for potential confounders.

Abbreviations: NA, not applicable; RCT, randomized controlled trial; ROB, risk of bias

Table S9. Detailed Risk of Bias Form for Schmeler et al, 2006[7]

ROB Question	Response	Comments
1. What is the study design?	Retrospective cohort study	
2. For RCTs, were randomization and allocation concealment adequate?	NA	
3. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	Yes	Only followed those for whom there were records available, not sure whether there are any systematic differences between those not included in study.
4. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	Yes	Excluded women who didn't have any matched controls within age range.
5. Did the study guard against risk of survivor bias?	Can't Determine	
6. Were groups similar at baseline?	Can't Determine	Study did not have information about potential confounding factors, such as BMI or other variables specific to gynecological cancers. Also, patients not matched based on specific mutation, although authors cite prior research and incidence data from this study to suggest that mutation types most likely did not affect the findings.
7. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	Can't Determine	
8. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Yes	Follow-up time different for groups, but those with surgery were followed longer, so this limits any bias of not learning of cancer incidences
9. Was overall attrition less than 30%?	Yes	17% of eligible women not included in the study because of missing follow-up information
10. Was differential attrition less than 15%?	Can't determine	No information provided about how many women who were excluded for missing follow-up information had received prophylactic surgery, and among those, how which types they had received

11. Does the analysis control for baseline differences between groups?	Can't Determine	The study controls for age by matching controls, but they did not collect data on other differences, such as BMI or use of birth control

ROB Question	Response	Comments
12. Does the analysis account for differences in treatment received by the groups?	No	The study is limited because it does not compare screening measures taken amongst the women. The authors specifically mention that screening information was not available as a limitation of the study.
13. Are the statistical methods used to assess the outcomes appropriate?	Yes	
ROB Ratings		
Outcomes Addressed	**Rating**	**Rationale**
Overall survival Cancer-specific survival	Medium	Unclear how screening measures differed between women receiving prophylactic surgery and those who did not. Also unclear to which extent baseline characteristics differed between groups or whether the investigators accounted for any differences that were present.
Harms related to interventions	Low	This study has a small sample size and found only one incident of complications. Authors note that prophylactic hysterectomy and bilateral salpingo-oophorectomy can also lead to premature menopause, but no information available about its incidence or that of resulting issues.

Abbreviations: BMI, body mass index; NA, not applicable; RCT, randomized controlled trial; ROB, risk of bias

Table S10. Detailed Risk of Bias Form for Stuckless et al, 2012[8]

ROB Question	Response	Comments
1. What is the study design?	Retrospective cohort study	
2. For RCTs, were randomization and allocation concealment adequate?	NA	
3. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	Yes	
4. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	Yes	
5. Did the study guard against risk of survivor bias?	No	The investigators' attempt to guarding against survivor bias, as I'm interpreting it, involves comparing outcomes in the screened group with those of non-screened participants who were alive, disease-free, and age and sex-matched. That means the analysis is ignoring data from participants who had already been diagnosed with CRC or died at baseline. There is no mention of how this statistical approach affects the actual numbers analyzed.
6. Were groups similar at baseline?	No	Baseline differences in age between groups after being stratified by sex. Very large differences in percentage of men and women in the non-screened group who had died before the baseline assessment.

7. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	Can't Determine	Blinded assessment of mortality outcomes was possible, but there is not enough information to know whether blinding was used. For example, CRC assessors could have been different individuals than those collecting demographic data.

ROB Question	**Response**	**Comments**
8. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Yes	
9. Was overall attrition less than 30%?	NA	Patients "lost to follow-up" were considered ineligible for the analysis. Therefore, attrition was NA for this study.
10. Was differential attrition less than 15%?	NA	See explanation for overall attrition question.
11. Does the analysis control for baseline differences between groups?	Yes	
12. Does the analysis account for differences in treatment received by the groups?	Partially	Figure 3 presents comparative data for CRC rates among mutation carriers in the screened group, but only for those who received ≥2 colonoscopies after 1994 (see Fig. 3 on pg. 442). Furthermore, no statistical analyses were used to evaluate the association of compliance with CRC incidence rates. Compliance information was not fully available for one of several Lynch Syndrome families, and compliance rates might have been underestimated if colonoscopy reports were missed.
13. Are the statistical methods used to assess the outcomes appropriate?	Yes	
ROB Ratings		
Outcomes Addressed	**Rating**	**Rationale**
Overall survival Cancer-specific survival	High	High risk of selection bias and survivor bias, retrospective design, major problem with the majority of the non-screened group being historical controls, and risk of volunteer bias in the screening group. Almost essentially a historical, non-concordant comparison because of the much larger proportion of non-screened participants who had died or been diagnosed with CRC at baseline, compared with the screened group. The investigators' approach to guarding against survivor bias is problematic because it involves ignoring data from CRC-diagnosed or deceased participants. In addition, unclear how differences in colonoscopy compliance affected outcomes in the screened group.

Abbreviations: CRC, colorectal cancer; NA, not applicable; NR, not reported; pg., page; RCT, randomized controlled trial; ROB, risk of bias

Table S11. Detailed Risk of Bias Form for Stuckless et al, 2013[9]

ROB Question	Response	Comments
1. What is the study design?	Retrospective cohort study	
2. For RCTs, were randomization and allocation concealment adequate?	NA	
3. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	Yes	
4. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	No	For the intervention group, majority of subjects were from the 1990s or later because that is when screening was offered more; for the control group, a lot more of them are further back, born after 1910. Historical controls could be considered inappropriate and they should have perhaps only used control groups from same time period (because of changes in treatment, awareness, colonoscopy, other testing, etc.)
5. Did the study guard against risk of survivor bias?	Yes	
6. Were groups similar at baseline?	No	Much higher proportion of both control groups born 1910-1950 than after 1950 (see Table 1). No other information reported to assess comparability of groups; some women in the non-screened group were not screened because they had hysterectomies.
7. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	Can't Determine	
8. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Can't Determine	No information provided about how outcomes were ascertained for most things, or about whether they had similar length of follow up for the groups being compared
9. Was overall attrition less than 30%?	Yes	Looks like about 13% overall (25/197)
10. Was differential attrition less than 15%?	Can't Determine	They never received records for 9, and 14 were lost to follow-up; they don't report which group these people were in. This is 25 total subjects, and the final/analyzed intervention group is small (N=54), so this could possibly be a large % differential attrition
11. Does the analysis control for baseline differences between groups?	No	For the 2nd control group, they matched for age, but nothing else was controlled for
12. Does the analysis account for differences in treatment received by the groups?	No	And this could potentially be important for the mortality outcomes, as treatments changed from 1910 to later; nothing done in analysis to account for how those with hysterectomies may affect the non-screening group (but overall this was a small number)
13. Are the statistical methods used to assess the outcomes appropriate?	No	None

ROB Ratings		
Outcomes Addressed	**Rating**	**Rationale**
Overall survival Cancer-specific survival	High	High risk of selection bias, measurement bias, and confounding. Use of historical controls raises concern for bias. Specifically, a much higher proportion of both control groups born 1910-1950 than after 1950, and no other information provided to allow for comparison of the groups. No information about whether follow-up time was similar for the groups being compared (see pg. 360: median of 8.5 years from entry into screening to death or last follow-up). Does not report masking of outcome assessors, or details of ascertainment of outcomes. Analyses don't adjust for any potential confounders.

Abbreviations: NA, not applicable; pg., page; RCT, randomized controlled trial; ROB, risk of bias

Table S12. Detailed Risk of Bias Form for Stupart et al, 2009[10]

ROB Question	Response	Comments
1. What is the study design?	Prospective cohort study	
2. For RCTs, were randomization and allocation concealment adequate?	NA	
3. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	Yes	
4. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	Yes	
5. Did the study guard against risk of survivor bias?	Yes	Prospective design
6. Were groups similar at baseline?	Can't Determine	No consideration of or adjustment for potential confounders
7. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	Can't Determine	
8. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Yes	Duke's cancer staging system
9. Was overall attrition less than 30%?	Yes	
10. Was differential attrition less than 15%?	Yes	
11. Does the analysis control for baseline differences between groups?	Can't Determine	No consideration of or adjustment for potential confounders
12. Does the analysis account for differences in treatment received by the groups?	Yes	
13. Are the statistical methods used to assess the outcomes appropriate?	Yes	
ROB Ratings		
Outcomes Addressed	**Rating**	**Rationale**
Overall survival Cancer-specific survival	Low	Uncertain about the presence of some potential confounding factors, but no major reasons for concern about ROB.

Abbreviations: NA, not applicable; RCT, randomized controlled trial; ROB, risk of bias

Table S13. Detailed Risk of Bias Form for Vasen et al, 1998[11]

ROB Question	Response	Comments
1. What is the study design?	Modeling study	
2. For RCTs, were randomization and allocation concealment adequate?	NA	
3. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	Yes	
4. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	Yes	Only men included in modeled sample to avoid confounding by female carriers' risk of developing endometrial cancer
5. Did the study guard against risk of survivor bias?	NA	Modeling study
6. Were groups similar at baseline?	Yes	Modeling study, groups same at baseline
7. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	NA	Modeling study
8. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Yes	Modeling study (see references 14-15)
9. Was overall attrition less than 30%?	NA	Modeling study
10. Was differential attrition less than 15%?	NA	Modeling study
11. Does the analysis control for baseline differences between groups?	NA	Modeling study
12. Does the analysis account for differences in treatment received by the groups?	Partially	The study modeled different scenarios for different treatment based on stage of cancer. However, its analysis did not take noncompliance with the recommended surveillance plan into account.
13. Are the statistical methods used to assess the outcomes appropriate?	Can't Determine	Authors state that "Decision Maker" software used to calculate cost outcomes, but no data on analyses provided.
The following questions are only for modeling studies		
14. Was an appropriate, comprehensive search used to find data inputs? (how reliable are the inputs?)	Partially	Unclear how exhaustive the literature review was; this does not describe a systematic review process. The investigators drew from numerous relevant sources for their data inputs, but they could not find studies for all. This led them to exclude women and assume several points, such as how often polypectomy was needed. They noted that the assumption was likely an overestimate, so costs may be lower.
15. Were appropriate, clinically relevant strategies/interventions evaluated?	Partially	The surveillance and polypectomy strategies were relevant and appropriate to consider. However, the model did not consider the use of newer molecular targeting agents along with other downstream treatments of cancer.
16. Was an appropriate comparison used?	Yes	None
17. Were all the appropriate health benefits, harms, and costs described and included?	No	Indirect costs not considered in the cost-effectiveness analysis. Also, harms of screening or polypectomies were not discussed, nor were costs of surgery that could be relevant in some cases.

ROB Question	Response	Comments
18. Were appropriate sensitivity analyses conducted? (especially for any variables that were not based on data from published literature)	Partially	Sensitivity analyses accounted for varying CRC risks and proportions of early stage CRC diagnosed during surveillance, but not length of intervals between polypectomies (ie, 5 versus 10 years) at age 40 and later (see Table 3).
19. Is the base case broadly applicable/generalizable to our Key Question(s)?	Partially	Key inputs for costs of surveillance and CRC treatment based on individual study data now >10 years out-of-date. However, estimated CRC risk in HNPCC patients likely stable. In addition, not broadly generalizable because women were not included.
20. Was the analysis conducted from the societal perspective?*	No	Only direct costs of screening, polypectomies, and CRC treatment considered in cost analysis (see references 14-15)
21. Was a lifetime horizon used? (if not, provide comments about the time horizon used and potential for risk of bias)	Yes	Began at age 25, when CRC surveillance generally started
22. Were costs and outcomes adjusted for differential timing (eg, discounting costs)?	Yes	Costs adjusted using both different discounts and intervals between screening examinations
ROB Rating		
Outcomes Addressed	**Rating**	**Rationale**
Health care expenses associated with screening measures or preventive interventions	Medium	This study's analyses were not based on a societal perspective, and they did not consider several important variables that could affect the real-world effectiveness of screening, including a) the lengths of intervals between polypectomies at age 40 and later, and b) noncompliance with screening recommendations. Also unclear how appropriate or comprehensive the search used to retrieve data inputs for the model was, since only individual studies were cited as supporting evidence. Strengths of the study included the use of discounting costs, the use of sensitivity analyses for varying CRC risks and intervals between screening examinations, and the use of a lifetime horizon.

Abbreviations: CRC, colorectal cancer; HNPCC, hereditary nonpolyposis colorectal cancer; NA, not applicable; RCT, randomized controlled trial; ROB, risk of bias

Table S14. Detailed Risk of Bias Form for Yang et al, 2011[12]

ROB Question	Response	Comments
1. What is the study design?	Modeling study	
2. For RCTs, were randomization and allocation concealment adequate?	NA	
3. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	Yes	
4. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	Yes	Unclear how many women were included in the modeled sample
5. Did the study guard against risk of survivor bias?	NA	Modeling study
6. Were groups similar at baseline?	Yes	Modeling study, groups same at baseline

ROB Question	Response	Comments
7. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	NA	Modeling study
8. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	NA	Modeling study
9. Was overall attrition less than 30%?	NA	Modeling study
10. Was differential attrition less than 15%?	NA	Modeling study
11. Does the analysis control for baseline differences between groups?	NA	Modeling study
12. Does the analysis account for differences in treatment received by the groups?	Yes	
13. Are the statistical methods used to assess the outcomes appropriate?	Yes	
The following questions are only for modeling studies		
14. Was an appropriate, comprehensive search used to find data inputs? (how reliable are the inputs?)	Can't Determine	Unclear how exhaustive the literature review was; this does not describe a systematic review process. Also, most of the sources cited in Table 1 do not match the references appearing in the bibliography.
15. Were appropriate, clinically relevant strategies/interventions evaluated?	Partially	The prophylactic surgery, gynecological surveillance, and gynecological examination strategies were relevant and appropriate to consider. However, the model did not consider the use of newer molecular targeting agents along with other downstream treatments of cancer.
16. Was an appropriate comparison used?	Yes	
17. Were all the appropriate health benefits, harms, and costs described and included?	Partially	Non-fatal surgical complications not described or considered. Time costs (other than those directly related to surgery) and other indirect costs were not considered; eg, time costs related to recovery (beyond the recovery room) from surgery, follow up visits, and gynecological surveillance not included
18. Were appropriate sensitivity analyses conducted? (especially for any variables that were not based on data from published literature)	Yes	Univariate and multivariate sensitivity analyses were conducted.
19. Is the base case broadly applicable/generalizable to our Key Question(s)?	Partially, but can't determine for some aspects	Some key inputs based on SEER data now >10 years out-of-date. Also, some of the references supporting base assumptions do not appear as cited in the article's bibliography.
20. Was the analysis conducted from the societal perspective?*	Partially	The analysis included cost of prophylactic procedures included operating room and recovery room time, as well as physician and nursing time required for the procedure. However, it did not consider the direct or indirect costs of non-fatal surgical complications, or time costs other than those related to surgery.
21. Was a lifetime horizon used? (if not, provide comments about the time horizon used and potential for risk of bias)	Yes	
22. Were costs and outcomes adjusted for differential timing (eg, discounting costs)?	Yes	The sensitivity analyses applied different discount rates, as well.

ROB Ratings		
Outcomes Addressed	**Rating**	**Rationale**
Health care expenses associated with screening measures or preventive interventions	Medium	The use of univariate and multivariate sensitivity analyses testing the model's robustness are an important strength. Newer molecular targeting agents were not considered in this model, and including them might have reduced the predicted cost differences between the screening/treatment groups (ie, toward supporting the null hypothesis). Also, the effect of non-fatal surgical complications on QALYs and costs of care were not taken into account in the model, which biases the findings in favor of prophylactic surgery.

Abbreviations: NA, not applicable; QALY, quality-adjusted life year(s); RCT, randomized controlled trial; ROB, risk of bias; SEER, Surveillance Epidemiology and End Results database

Table S15. Overarching question: evidence that screening asymptomatic adults with genetic testing for MMR gene mutations (*MLH1*, *MSH2*, *PMS2*, and *MSH6*) leads to improved overall survival, cancer-specific survival, or quality of life

Number of Studies; N of Subjects	Risk of Bias Design	Consistency	Directness	Precision	Results	Overall Strength of Evidence (Insufficient, Low, Moderate, or High)
Lynch Syndrome (HNPCC)						
1 [1]	High (for the clinical effectiveness assessment of universal screening and for all of the models using the PREMM risk prediction) Medium (for the universal screening strategy cost-effectiveness assessment) Modeling study	Unknown, single study	Indirect (model that relied on compiling various evidence sources and assumptions)	Unknown (estimates of precision not provided)	See Outcomes table	Insufficient

HNPCC = hereditary non-polyposis colorectal cancer; MMR = mismatch repair; N = number (of subjects)

Table S16. Sensitivity of targeted next-generation sequencing versus Sanger sequencing for MMR gene mutations

Number of Studies; N of Subjects	Risk of Bias Design	Consistency	Directness	Precision	Results	Overall Strength of Evidence (Insufficient, Low, Moderate, or High)
Lynch Syndrome (HNPCC)						
2;[2,3] N=103	Low Test and re-test of samples for validation studies	Consistent	Direct	Precise	Hansen, 2014:[2] 95% (123/123); however 5% probability of false negative not being in sample) Pritchard, 2012:[3] 99.4% (222/224)	High

HNPCC = hereditary non-polyposis colorectal cancer; MMR = mismatch repair; N = number (of subjects)

Table S17. Specificity of targeted next-generation sequencing versus Sanger sequencing for MMR gene mutations

Number of Studies; N of Subjects	Risk of Bias Design	Consistency	Directness	Precision	Results	Overall Strength of Evidence (Insufficient, Low, Moderate, or High)
Lynch Syndrome (HNPCC)						
2;[2,3] N=103	Low Test and re-test of samples for validation studies	Consistent	Direct	Precise	Hansen, 2014:[2] 46% [a] (146/316) after processing, then 89% Pritchard, 2012:[3] 99.4% (1012/1018)	High

[a] Their "specificity" is actually a positive predictive value, because they would consider variants matching the reference sequence to inflate the numbers of true negatives.
HNPCC = hereditary non-polyposis colorectal cancer; MMR = mismatch repair; N = number (of subjects)

Table S18. Colorectal cancer incidence

Number of Studies; N of Subjects	Risk of Bias Design	Consistency	Directness	Precision	Results	Overall Strength of Evidence (Insufficient, Low, Moderate, or High)
Early or more frequent colonoscopy and removal of polyps versus no screening						
3;[5,8,10] N=590	Medium Prospective cohort (n=2), retrospective cohort (n=1)	Consistent	Direct	Precise	Favors early or more frequent colonoscopy vs. no screening.	Moderate

n or N = number (of subjects or studies); vs. = versus

Table S19. Endometrial cancer incidence: organized by intervention type

Number of Studies; N of Subjects	Risk of Bias Design	Consistency	Directness	Precision	Results	Overall Strength of Evidence (Insufficient, Low, Moderate, or High)
Gynecological screening versus no screening						
2;[6,9] N=421 [a,b]	High Retrospective cohort	Consistent	Direct	Imprecise	No statistically significant differences between screening and no-screening groups.	Low
Prophylactic hysterectomy (with or without salpingo-oophorectomy)						
1;[7] N=271	Medium Retrospective cohort	Unknown, single study	Direct	Precise	The surveillance group had lower incidence of endometrial cancer (none) than the control group.	Low

[a] CRC incidence outcomes following gynecological screening from Stuckless et al (2013) should be disregarded.[9]
[b] Data from Stuckless et al, 2013 based only on statistical comparisons of matched case-and-control group pairs.[9]
CRC = colorectal cancer; N = number (of subjects)

Table S20. Ovarian cancer incidence: organized by intervention type

Number of Studies; N of Subjects	Risk of Bias Design	Consistency	Directness	Precision	Results	Overall Strength of Evidence (Insufficient, Low, Moderate, or High)
Gynecological screening versus no screening						
1;[9] N=108 [a]	High Retrospective cohort	Unknown, single study	Direct	Precise	No difference in cumulative incidence of ovarian cancer in the screened group vs. non-screened group of matched controls.	Insufficient
Prophylactic salpingo-oophorectomy versus usual care						
1;[7] N=271	Medium Retrospective cohort	Unknown, single study	Direct	Imprecise	The surveillance group had lower incidence of endometrial cancer (none) than the control group.	Insufficient

[a] Data from Stuckless et al, 2013 based only on statistical comparisons of matched case-and-control group pairs.[9]
N = number (of subjects); vs. = versus

Table S21. Overall survival: organized by intervention type

Number of Studies; N of Subjects	Risk of Bias Design	Consistency	Directness	Precision	Results	Overall Strength of Evidence (Insufficient, Low, Moderate, or High)
Gynecological screening versus no screening						
1;[9] N=108 [a]	High Retrospective cohort	Unknown, single study	Direct	Precise	Mean survival was substantially better in the screened group (3/54) vs. matched controls (29/54) (p=0.000)	Insufficient
Prophylactic gynecological surgery (hysterectomy or bilateral salpingo-oophorectomy) versus no surgery						
1;[7] N=271	Medium Retrospective cohort	Unknown, single study	Direct	Precise	Prophylactic gynecological surgery led to higher rates of overall survival.	Insufficient
Early or more frequent colonoscopy and removal of polyps versus no screening						
3;[5,8,10] N=590	Medium Prospective cohort (n=2); retrospective cohort (n=1)	Consistent	Direct	Precise [b]	Early or more frequent colonoscopies led to higher rates of overall survival.	Moderate

[a] Data from Stuckless et al, 2013 based only on statistical comparisons of matched case-and-control group pairs.[9]
[b] The entire width of the 95% confidence interval includes a moderate to large effect.
n or N = number (of subjects or studies); vs. = versus

Table S22. Cancer-specific survival: organized by intervention and cancer types

Number of Studies; N of Subjects	Risk of Bias Design	Consistency	Directness	Precision	Results	Overall Strength of Evidence (Insufficient, Low, Moderate, or High)
Gynecological screening versus no screening: Endometrial cancer						
2;[6,9] N=421 [a]	High Retrospective cohort	Consistent	Direct	Imprecise	No statistically significant differences in endometrial cancer-specific survival between screened and non-screened groups, but screened patients tended to have better survival rates.	Insufficient
Gynecological screening versus no screening: Ovarian cancer						
1;[9] N=108 [a]	High Retrospective cohort	Unknown, single study	Direct	Imprecise	No statistically significant differences in ovarian cancer-specific survival between screened and non-screened groups, but screened patients tended to have better survival rates.	Insufficient
Prophylactic salpingo-oophorectomy versus usual care: Endometrial cancer						
1;[7] N=271 [b]	Medium Retrospective cohort	Unknown, single study	Direct	Imprecise	The prophylactic salpingo-oophorectomy group had fewer endometrial cancer deaths (none) than the control group, although statistical significance is unclear.	Insufficient
Prophylactic salpingo-oophorectomy versus usual care: Ovarian and colon cancer						
1;[7] N=271 [b]	Medium Retrospective cohort	Unknown, single study	Direct	Imprecise	The prophylactic salpingo-oophorectomy group had fewer deaths (none) from ovarian and colon cancer than the control group, although statistical significance is unclear.	Insufficient

Prophylactic salpingo-oophorectomy versus usual care: Colon cancer						
1;[7] N=271 [b]	Medium Retrospective cohort	Unknown, single study	Direct	Imprecise	The prophylactic salpingo-oophorectomy group had fewer deaths from colon cancer than the control group, although statistical significance is unclear.	Insufficient
Prophylactic salpingo-oophorectomy versus usual care: Other Lynch syndrome-associated cancers						
1;[7] N=271 [b]	Medium Retrospective cohort	Unknown, single study	Direct	Imprecise	The prophylactic salpingo-oophorectomy group had fewer deaths (none) from other Lynch syndrome-associated cancers than the control group, although statistical significance is unclear.	Insufficient
Early or more frequent colonoscopy and removal of polyps versus no screening						
1;[10] N=178 [c]	Low Prospective cohort	Unknown, single study	Direct	Imprecise	Early or more frequent colonoscopies associated with fewer deaths from colorectal cancer.	Low

[a] Data from Stuckless et al, 2013 based only on statistical comparisons of matched case-and-control group pairs.[9]
[b] Mortality information for other, non-Lynch syndrome-associated cancers also reported, but not included in SOE grade assessments for prophylactic salpingo-oophorectomy vs. usual care because they are not outcomes being focused on in this review.[7]
[c] Mortality information for other cancer types also reported but not Lynch syndrome-associated, including breast, renal cell, and neuroendocrine liver. Not included in SOE grade assessments for early or more frequent colonoscopies vs. no screening because they are not outcomes being focused on in this review.[10]
N = number (of subjects); SOE = strength of evidence; vs. = versus

Table S23. Health care expenses associated with screening measures or preventive interventions

Number of Studies; N of Subjects	Risk of Bias Design	Consistency	Directness	Precision	Results	Overall Strength of Evidence (Insufficient, Low, Moderate, or High)
Intensive colorectal cancer surveillance and surgery versus general population surveillance						
1;[4] N=NA	Medium Modeling study	Unknown, single study	Indirect (model that relied on compiling various evidence sources and assumptions)	Unknown (estimates of precision not provided)	HNPCC testing delayed onset of colorectal cancer by 8 years with net cost savings[a] for both males and females when compared with population surveillance[b].	Insufficient
Intensive colorectal cancer surveillance versus no screening						
1;[11] N=NA	Medium Modeling study	Unknown, single study	Indirect (model that relied on compiling various evidence sources and assumptions)	Unknown (estimates of precision not provided)	Surveillance every 2.5 years leads to an increased life expectancy of 6.9 years and a decreased cost compared to no screening. Risk of developing cancer while undergoing surveillance and the stage of diagnosis of cancer during surveillance were important variables.	Insufficient
Intensive gynecological screening versus annual gynecological exam with or without screening						
1;[12] N=NA	Medium Modeling study	Unknown, single study	Indirect (model that relied on compiling various evidence sources and assumptions)	Unknown (estimates of precision not provided)	Prophylactic hysterectomy and salpingo-oophorectomy was more cost effective (cost vs. QALYs) than annual gynecological surveillance[c] or usual care. This was true for all ages, but most cost effective at younger ages.	Insufficient

[a] Breheny et al, 2006:[4] Costs reflect standards of care in Western Australia from 2001-2002 and reported in Australian dollars.
[b] Breheny et al, 2006:[4] Population surveillance includes fecal occult blood test, flexible sigmoidoscopy, and colorectal cancer treatment.
[c] Yang et al, 2011:[12] Annual gynecological surveillance includes transvaginal ultrasound, endometrial biopsy, and serum CA125 testing.
CA125 = cancer antigen-125; HNPCC = hereditary non-polyposis colorectal cancer; N = number (of subjects); NA = not applicable; QALY = quality-adjusted life year; vs. = versus

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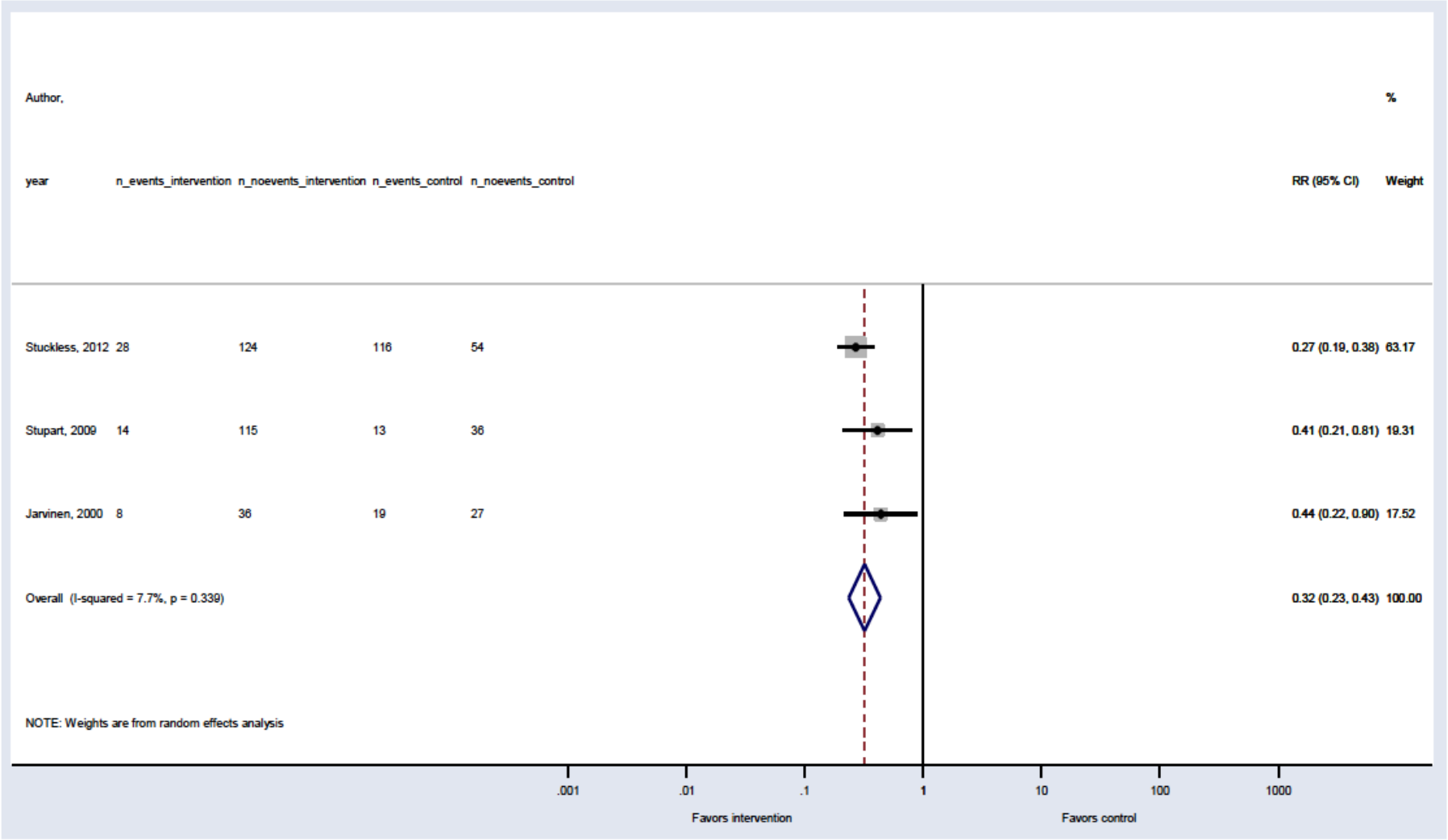
Supplementary Material 3

Association between early or more frequent colonoscopy and colorectal cancer incidence among adult family members with an associated MMR gene mutation



Supplementary Material 4

Association between early or more frequent colonoscopy and overall survival among adult family members with an associated MMR gene mutation