CADTH

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DNA Mismatch Repair Deficiency Tumour Testing for Patients With Colorectal Cancer: A Health Technology Assessment

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David Kaunelis designed and executed the search strategies and wrote the search methods for the patient preferences review.

Conflicts of Interest

No authors declared conflicts of interest.

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Table of Contents

Abbreviations

5-FU	fluorouracil
BG	Bethesda Guidelines
CEAC	cost-effectiveness acceptability curve
CRC	colorectal cancer
dMMR	deficient mismatch repair
ECOG	Eastern Cooperative Oncology Group
HNPCC	hereditary non-polyposis colorectal cancer
HTERP	Health Technology Expert Review Panel
ICER	incremental cost-effectiveness ratio
IHC	immunohistochemistry
LR	likelihood ratio
LS	Lynch syndrome
MSI	microsatellite instability
PCR	polymerase chain reaction
pMMR	proficient mismatch repair
QALY	quality-adjusted life-year
rBG	revised Bethesda Guidelines
SROC	summary receiver operator characteristic
WTP	willingness to pay

1. Protocol Deviations

Methodological discrepancies between the report and the published Protocol.[1]

Study Question	Pre-planned Methodology	Protocol Change	Rationale
Q1	Study selection based on the PICOs in the Protocol	Additional exclusion criteria: – Unable to confirm each tumour sample is linked to only 1 patient or family – Outcomes only for < 10 patients – < 3 IHC test proteins reported	Based on expert opinion: Additional exclusion criteria recommended to ensure included studies are as methodologically strong and as relevant to the Canadian clinical context as possible.
Q2		None	Not applicable.
Q3	Study selection based on the PICOs in the Protocol	Additional exclusion criterion – Outcomes only for < 10 patients	Based on expert opinion: Additional exclusion criteria recommended to ensure included studies are as methodologically strong as possible.
Q4	Study population: CRC patients (any age, any stage) who do not receive adjuvant chemotherapy	Study population: stage II or III CRC patients (any age) who do not receive adjuvant chemotherapy	Based on expert opinion: The recommendations committee would base its recommendations on the studies of stage II and stage III CRC patients who received adjuvant chemotherapy and those who did not. Therefore, to be consistent with the patient population included for Question 5, Question 4 was also modified to include stage II and stage III CRC patients.
Q5	Study population: CRC patients (any age, any stage) undergoing adjuvant chemotherapy	Study population: stage II and stage III colon cancer patients (any age) undergoing adjuvant chemotherapy	Based on expert opinion: Studies including stage II and III colon cancer should be included, because: 1) Decisions on adjuvant chemotherapy are not relevant for stage I and stage IV colorectal cancer. 2) Decisions on adjuvant chemotherapy are not relevant to rectal cancer; so data from colon cancer patients should be considered for this question.
Q6		None	Not applicable.
Q7	Intervention: dMMR testing of any type	Refinements to the eligibility criteria to exclude the following from the list of	These interventions are outside the scope of the HTA and the policy concern. They were not listed as

Study Question	Pre-planned Methodology	Protocol Change	Rationale
	(tumour and/or germline)	eligible interventions: direct to consumer testing, pre-implantation genetic diagnostic testing	explicit exclusion criteria in the protocol as they were not anticipated to arise in the search.
Q7	Coding will take place independently by 2 reviewers, and at least 1 code will be applied to each result statement	As opposed to double coding all of the included data as planned in the Protocol, descriptive coding was conducted by 2 researchers during a pilot phase for 20 of the included articles, after which 1 reviewer coded the data for the remaining articles and a second reviewer verified the coding. Disagreements were resolved through discussion.	There was a high level of agreement between the 2 reviewers during the pilot phase of descriptive coding. For efficiency, subsequent descriptive coding was conducted by 1 reviewer with a second reviewer verifying the coding.

CRC = colorectal cancer; dMMR = deficient mismatch repair; HTA = health technology assessment; IHC = immunohistochemistry; PICOs = Population, Intervention, Comparators, Outcomes study type.

2. Context and Policy Issues

2.1 Disease and Technology Background

Colorectal cancer (CRC) is one of the most common malignancies, representing the third most common cancer in men and the second in women worldwide.[2] CRC ranks second to lung cancer in the list of leading causes of cancer deaths in men in developed countries.[2] Approximately 3% to 5% of CRCs are attributable to a hereditary cancer predisposition related to DNA mismatch repair (MMR) deficiency.[3] MMR is a process that corrects mismatches generated during normal DNA replication, recombination, and damage. Deficient MMR (dMMR) results in an inability to correct DNA replication errors; one consequence of this is microsatellite instability (MSI).

Lynch syndrome (LS) is the most common familial CRC syndrome.[4] Individuals with LS — also referred to as hereditary nonpolyposis colorectal cancer (HNPCC) — have hereditary (germline) defects in one of their genes that encode for an MMR protein. This predisposes them to colorectal and other types of cancer. People with LS have a 70% to 80% lifetime risk of developing any type of cancer.[5]

The tumours of patients with CRC can be screened for evidence of dMMR that may be attributed to LS. This will enable genetic testing, counselling, cancer surveillance (e.g., through frequent colonoscopic or endometrial screening examinations), and prophylaxis (e.g., risk-reducing colorectal or gynecological surgeries) for CRC patients, as well as for their family members. Tumour testing for dMMR may improve outcomes for patients and their family members, as the latter may also have LS and therefore be at an increased risk of cancer.[5] Aside from being a marker suggestive of LS, tumour dMMR also appears to have utility in the management of CRC by providing prognostic information for patients with stage II tumours.[5] MMR-deficient tumours are associated with improved stage-adjusted, disease-free, and overall survival rates, and a lower chance of progression, when compared with non-dMMR tumours.[6] This could be attributable to a better immunologic response to the tumour (greater number of cytotoxic tumour-infiltrating lymphocytes) in CRC patients with tumour dMMR-positive results.[7] In addition, tumour dMMR status may have predictive value for the effectiveness of 5-fluorouracil–based adjuvant chemotherapy, favouring non-dMMR tumours.[6]

Germline genetic testing by sequencing is considered the gold standard for detection of a germline mutation in MMR genes (LS). However, as mutations in one of four MMR genes can underlie LS, and because of the time-consuming nature and considerable economic burden associated with testing four MMR genes, the decision to offer germline genetic testing to diagnose LS is commonly made in a stepwise manner.[8] A detailed family history and clinical findings in CRC patients are often used as the first steps to identify potentially hereditary CRC cases.[9] Clinicopathological criteria and the revised Bethesda Guidelines (rBG)[10] have been formulated as clinical tools for pre-selecting patients with a higher probability of carrying an MMR mutation and who should undergo dMMR tumour testing. For instance, The Ottawa Hospital's pathology service follows the rBG[10] to select tumours for MSI/dMMR testing. The BC Cancer Agency's genetics program[11] currently offers dMMR tumour testing to all newly diagnosed CRC patients younger than 40 years of age, regardless of pathology findings, or to CRC patients at any age with a significant family history of LS-related cancers.

Tumour MMR deficiency can be assessed by either MSI testing of tumours to detect abnormalities in tumour DNA replication (i.e., the length of alteration of microsatellite sequences) or by testing tumours for loss of expression of proteins involved in MMR (i.e.,

MLH1, MSH2, MSH6, and PMS2) as a precursor to gene sequencing. Protein deficiency is tested by immunohistochemistry (IHC) of tumour tissue, whereas the MSI assay tests tumour DNA for MSI using a polymerase chain reaction (PCR)–based method. Experts and recent literature agree that IHC-based detection of MMR defects is as accurate as PCR-based microsatellite analysis, while being cheaper and providing the major advantage of distinguishing the defective MMR protein to guide subsequent germline genetic testing.[12-15]

In a subset of CRC patients for whom the tumour IHC analysis reveals a lack of MLH1 protein expression, a somatic (non-inherited) event is often responsible for the tumour MMR deficiency. These cases are due to somatically acquired hypermethylation of the MLH1 promotor, which is seen in the presence of somatic BRAF V600E mutations. Therefore, additional testing for the BRAF V600E (as an indicator of the likelihood of MLH1 promoter methylation) or direct MLH1 promotor methylation can be used as part of diagnostic tumour testing algorithms to exclude likely sporadic CRC cases.[16] These tests can be conducted simultaneously with the initial IHC, or they can be ordered automatically upon an initial test result indicative of dMMR (reflex testing).

2.2 Policy and Practice Issues

Testing tumours for dMMR has been identified as a practice that is potentially over-utilized. According to clinical experts, dMMR tumour testing appears to be transitioning from an approach aimed at identifying patients and families with LS into a tumour phenotyping procedure that can be used to predict the prognosis of CRC and to guide for adjuvant chemotherapy decisions. The use of a test with a prognostic and predictive value falls under the realm of “personalized medicine.” According to oncology and pathology experts, this recent application of dMMR tumour testing is the major driver of new test requisitions. This transition has led to an increased demand for the test, with unclear benefits for the patient or family members. In general, there is a lack of clarity regarding when the tests should be ordered and the impact of tumour dMMR status on CRC outcomes in the current era of oxaliplatin- and irinotecan-based chemotherapy. The central question, however, is whether universal dMMR tumour testing of CRC tumours is a viable and desirable option, given the known limitations of LS pre-selection criteria based on age, history, and pathology, and recognizing the potential utility of tumour dMMR status for personalizing cancer therapy. Missed cases of LS resulting from a targeted tumour dMMR testing strategy that is restricted to pre-selected high-risk individuals (e.g., selected based on the rBG) can be problematic and costly for the system, which would potentially support broader (universal) dMMR tumour testing of all CRC tumours. Alternatively, universal tumour testing carries with it additional costs associated with testing all CRC patients, most of whom will not have LS.

In summary, there is uncertainty regarding:

- Optimal eligibility criteria for dMMR tumour testing in:
    - CRC patients to identify new families with LS
    - CRC patients to inform prognosis or prediction of response to chemotherapy.
- The cost-effectiveness of tumour screening strategies and algorithms in:
    - CRC patients to identify new families with LS
    - CRC patients to inform prognosis or prediction of response to chemotherapy.

3. Research Questions

1. What is the clinical validity of IHC- or PCR-based dMMR testing, compared with germline sequencing, for detecting LS:
   a. When screening all CRC patients?
   b. When screening only patients at high risk of LS (e.g., selected based on BG/rBG)?
2. What is the clinical utility of screening CRC patients for LS by IHC- or PCR-based dMMR testing for improving health outcomes of family members?
3. What is the clinical validity of molecular tests subsequent to dMMR testing for ruling out a germline mutation in MMR genes?
   a. What is the clinical validity of BRAF V600E testing by PCR for ruling out an MMR gene mutation in a CRC tumour with no MLH1 protein expression?
   b. What is the clinical validity of BRAF V600E testing by IHC for ruling out an MMR gene mutation in a CRC tumour with no MLH1 protein expression?
   c. What is the clinical validity of MLH1 promoter hypermethylation testing for ruling out an MMR gene mutation in a CRC tumour with no MLH1 expression?
4. What is the clinical utility of dMMR testing for improving health outcomes of CRC patients who do not receive adjuvant chemotherapy?
5. What is the clinical utility of dMMR testing for improving health outcomes of colon cancer patients who receive adjuvant chemotherapy?
6. What is the cost-effectiveness of dMMR testing in newly diagnosed CRC patients, considering the following two sub-questions?

   a. What is the comparative cost-effectiveness of the following four dMMR testing strategies, taking into account their impact on the choice of using adjuvant chemotherapy for the CRC patient or not, and on cancer prevention of first-degree family members of the CRC patient:

      - dMMR testing in all CRC patients
      - dMMR testing all CRC patients younger than 70 years old
      - dMMR testing only patients at high risk of LS based on the rBG
      - No dMMR testing in any CRC patients.

   b. What is the comparative cost-effectiveness of the following dMMR reflex testing algorithms for screening CRC patients for LS?

      - Initial four-panel IHC test (MLH1, MSH2, MSH6, PMS2), followed by germline testing if abnormalities are found in any gene
      - Initial four-panel IHC test (MLH1, MSH2, MSH6, PMS2), followed by BRAF testing if the MLH1 protein is abnormal, or germline testing if abnormalities are found in MSH2, MSH6, PMS2, or MLH1 with normal BRAF

- Initial four-panel IHC test (MLH1, MSH2, MSH6, PMS2), followed by promoter hypermethylation if the MLH1 protein is abnormal, or germline testing if abnormalities are found in MSH2, MSH6, PMS2, or MLH1 without hypermethylation

- Single-step MMR + BRAF V600E IHC. Genetic testing if abnormal MSH2, MSH6, or PSM2; or abnormal MLH1 with normal BRAF

- Single-step MMR + BRAF V600E IHC. If MLH1 is abnormal and BRAF is normal, follow with MLH1 promoter hypermethylation. Genetic testing if abnormal MSH2, MSH6, or PSM2; or abnormal MLH1and normal BRAF without promoter hypermethylation

7. What are the perspectives of CRC patients, their family members, and caregivers regarding the value and impact of dMMR testing on their health, health care, and lives?

Clinical Review: Clinical Validity of dMMR Testing

1. What is the clinical validity of IHC- or PCR-based dMMR testing, compared with germline sequencing, for detecting LS:
   a. When screening all CRC patients?
   b. When screening only patients at high risk of LS (e.g., selected based on BG/rBG)?

4. Methods

4.1 Literature Search Strategies

The literature search was performed by an information specialist using a search strategy peer-reviewed according to PRESS guidance.[17]

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946 to current) with in-process records and daily updates via Ovid; Embase (1974 to 2015 Feb 20) via Ovid; The Cochrane Library (2015, Issue 1) via Wiley; and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were hereditary nonpolyposis colorectal neoplasms and microsatellite instability (MSI), DNA mismatch repair (dMMR), or germline mutation testing (reference standard test).

A filter was applied to limit retrieval to studies reporting analytical or clinical validity, with evidence of the tests' sensitivity and specificity, for MSI or dMMR searches. A filter was not applied to germline mutation test searches in order to mitigate the possible risk of missing relevant studies. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year, but was limited to the English or French language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies. The initial search was run from February 23 to 24, 2015. A search update was conducted on March 1, 2016. Additional articles that were published since the initial search and that met the selection criteria but were not included in the analysis are provided in Appendix 2.

Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist (www.cadth.ca/resources/finding-evidence/grey-matters), which includes the websites of regulatory agencies, health technology assessment agencies, clinical guideline repositories, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by

reviewing the bibliographies of key papers and through contacts with appropriate experts. See Appendix 1 for more information on the grey literature search strategy.

4.2 Selection Criteria and Methods

Studies suitable for inclusion were selected from those identified through the literature search, using the criteria listed below.

Population	CRC patients at any age, any stage for whom tumour tissue is available for testing: a. all patients (unselected) b. high-risk patients (pre-selected; e.g., meeting BG)
Intervention	PCR- or IHC-based dMMR testing
Comparator (Reference Standard)	Germline mutation analysis
Outcomes	Diagnostic test performance for detecting LS: • sensitivity • specificity • positive and negative predictive values • AUC • rates of false positive tests • rates of false negative tests • overall diagnostic accuracy
Study Types	RCTs, prospective or retrospective observational (non-randomized) studies (cross-sectional diagnostic studies, cohort, case-control)

AUC = area under the receiver operating characteristic curve; CRC = colorectal cancer; dMMR = deficient mismatch repair; IHC = immunohistochemistry; LS = Lynch syndrome; rBG = revised Bethesda Guidelines; RCT = randomized controlled trial.

4.3 Exclusion Criteria

Studies were excluded if they:

- were published before 2000, due to differences in PCR- and IHC-based testing methods compared with current testing methods generally affecting studies conducted prior to 1998
- included only *aggregated* diagnostic accuracy results of combined CRC or non-CRC patients, or LS family members (i.e., CRC results unable to be abstracted separately)
- included results for fewer than 10 patients, families, or tumours
- did not perform PCR- and/or IHC-based testing on tumours
- included results of only patients who were germline tested if they scored positively for PCR-based (MSI-H or MSI-L) or IHC-based (loss of expression [LoE] for any protein) testing
- used fewer than five panel markers for PCR-based testing, or fewer than three proteins for IHC-based testing with results for all proteins combined or combinable

- had discrepancies between results presented in the text and tables, which could not be resolved

  or

- were duplicate publications, narrative reviews, or editorials.

Two reviewers (KC and CV) independently screened the titles and abstracts of records identified in the literature search for relevance using a predefined checklist (Appendix 3). Any discrepancies between reviewers were resolved by discussion. Full-text copies of any items that passed title and abstract review were retrieved. These studies were assessed by one experienced reviewer for inclusion (KC or CV) using a checklist (Appendix 8), which incorporated explicit predetermined criteria as previously outlined. A second reviewer was consulted when necessary, and any disagreement between reviewers was discussed until consensus was reached.

Any primary studies that presented test accuracy values, sensitivity and specificity measures, or sufficient data to construct 2 × 2 or 1 × 2 contingency tables, to calculate the diagnostic performance of MSI (i.e., PCR-based test) and/or dMMR (i.e., IHC-based test) compared with the reference test (germline mutation analysis) were included. Identified systematic reviews, health technology assessments (HTAs), and guideline documents were also reviewed for potentially relevant primary studies; however, pooled analyses without individual study-level data presented in these documents were not considered for inclusion in this review.

4.4 Data Extraction

One reviewer performed data extraction for each article (KC or CV) using pre-drafted data extraction forms (Appendix 15). A second reviewer (KC or RH) checked the abstracted data for accuracy. The reviewers piloted data extraction forms a priori, and performed a calibration exercise using 10 studies to ensure consistency between the reviewers.

4.5 Critical Appraisal of Individual Studies

One reviewer critically appraised the selected studies based on the QUADAS-2 instrument[18] for the evaluation of diagnostic accuracy studies (Appendix 13). QUADAS-2 is a tool that evaluates the risk of bias in selection of patients, index test, reference standard, and flow and timing of the study. A second reviewer verified the critical appraisal assessments of individual studies.

4.6 Data Analyses and Synthesis

4.6.1 Outcomes

Statistical outcomes that provided diagnostic accuracy of each test (i.e., PCR- or IHC-based), relative to germline testing, included sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR–), positive predictive value (PPV), or negative predictive value (NPV). A definition of each outcome is provided in Table A1. Details on each of these outcomes are provided in Appendix 19.

Table A1: Definitions of Diagnostic Accuracy Measures

Measure	Definition	Formula
Sensitivity	The proportion of persons with the disease who are correctly identified by a test	TP/(TP + FN)
Specificity	The proportion of persons without a disease who are correctly identified by a test	TN/(TN + FP)
Positive Likelihood Ratio	The probability of a person who has the disease testing positive divided by the probability of a person who does not have the disease testing positive	SENS/(1 – SPEC)
Negative Likelihood Ratio	The probability of a person who has the disease testing negative divided by the probability of a person who does not have the disease testing negative	(1 – SENS)/SPEC
Positive Predictive Value	The proportion of patients with positive test results who are correctly diagnosed	TP/(TP + FP), or equivalently SENS × Prev / (SENS × Prev + [1 – SPEC] × [1 – Prev])
Negative Predictive Value	Proportion of patients with negative test results who are correctly diagnosed	TN/(TN + FN), or equivalently SPEC × (1 – Prev) / ([1 – SENS] × Prev + SPEC × [1 – Prev])

FN = false negative; FP = false positive; Prev = prevalence; SENS = sensitivity; SPEC = specificity; TN = true negative; TP = true positive.

In this report, measures of sensitivity, specificity, LR+, LR–, PPV, NPV, and the global measure of overall diagnostic accuracy are used for the purpose of reporting estimates of diagnostic performance of either dMMR test (i.e., PCR- or IHC-based) relative to the reference standard germline mutation testing.

4.6.2 Comparisons

Each of the diagnostic performance measures were estimated for each test, PCR- or IHC-based, relative to germline testing as the reference standard.

The analysis of the diagnostic test performance involves two steps. In the first step, the direct comparison between the index test and the reference standard — i.e., PCR-based test versus germline testing or IHC-based test relative to germline testing — was estimated for each study. When there was more than one study with the same test type, the results of multiple studies were meta-analyzed to create one pooled estimate. The meta-analytic summary for all diagnostic accuracy outcomes across all studies was conducted with STATA using the command "midas".[19] Midas data synthesis is performed within the bivariate mixed-effects binary regression modelling framework using a multilevel mixed-effects logistic regression. This analysis models the variance and mixed effects between and within studies, as well as modelling the mixed effects that occur between sensitivity and specificity.

4.6.3 Heterogeneity

For descriptive purposes, to inspect whether the studies were similar enough to be compared indirectly under the assumptions of similarity, we provided an estimate of disease prevalence for each test (PCR or IHC), as well as providing an assessment of heterogeneity within each test

(e.g., sensitivity of PCR-based test). The presence of heterogeneity is expected in meta-analysis of diagnostic accuracy, and the typical thresholds for I^2 that are often applied to outcomes such as relative risk for the degree of heterogeneity have not been established, according to the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy*.[20]

Heterogeneity was explored graphically, by plotting sensitivity and false positive rate (1 – specificity) for individual studies against the fitted summary receiver operator characteristic (SROC) curve. Potential sources of heterogeneity were not prospectively defined in the Protocol, but in discussion with expert consultants, we identified the following for PCR-based tumour testing: the number of markers tested, the threshold used for a positive test, the number of genes sequenced for the reference comparator, and the study design. The number of markers tested was dichotomized as equal to five markers (reference level) and greater than five markers. Higher threshold was represented by studies that used MSI-H (positive) and MSI-L (negative; reference level), and lower threshold by studies that used MSI-H/MSI-L (positive) or MSI (positive). The number of genes sequenced was dichotomized as two genes (reference level) and more than two genes. Study design was dichotomized as observational non–case-control (reference) and case-control or unclear design. For IHC-based tumour testing, we identified the number of proteins assayed. We calculated summary estimates and confidence intervals (CIs) for sensitivity and specificity for each pair of subgroups, and plotted and compared SROC curves. We used multivariate regression to test the effect of each variable individually.

4.6.4 Missing data

For studies that did not report all of the statistical parameters and CIs, wherever possible the missing parameters and CIs were derived using available information. Specifically, not all studies reported the elements of the 2 × 2 contingency table; i.e., number of true positive, false positive, true negative, and false negative. These latter values are required for meta-analysis of diagnostic accuracy studies.

To derive the missing information, we relied on the assumption that we can re-create the elements of the 2 × 2 table by using available information, described below.[21]

In most cases, the sensitivity and specificity were provided without CIs. When the CIs were not provided, we can, based on the total study sample size, iteratively estimate the unique 2 × 2 table that would create the study's sensitivity and specificity. When CIs were provided, we assumed that they were derived with binomial approximation methods, which is the most common statistical distribution, according to the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy*.[20] From the available estimate and CI, we iteratively estimated the unique number of true positives and false negatives to re-create the CI. After a similar exercise for the non-disease cases, the numbers of true negatives and false positives were derived. With the derived 2 × 2 table estimates, the estimates and CIs were re-created to ensure approximate consistency, as well as being verified with other estimates such as PPVs. Studies that reported estimates with insufficient decimal places — e.g., sensitivity of 0.94 instead of 94.4% — led to the creation of a range of possible values in the 2 × 2 table, which can lead to inconsistencies between the derived 2 × 2 table and that in the original study. To minimize such discrepancies, the mean estimated values of the 2 × 2 estimates were used.

Sensitivity analysis was conducted by analyzing only the data for which no imputation was required. Due to a low number of studies that required imputation, there were an insufficient number of studies available to separately combine those that required imputation.

5. Summary of Clinical Evidence

5.1 Quantity of Research Available

A total of 2,489 citations were identified through the literature search, with 2,134 citations excluded during the title and abstract review phase because they did not meet the screening criteria. Full-text copies of the remaining 355 articles were retrieved. Of these, 322 did not meet the eligibility criteria and were excluded, leaving 33 articles for abstraction.[22-54] However, two of these studies[39,44] were deemed ineligible at the data analysis phase, leaving a total of 31 studies for analysis. The reference lists of three review publications[55-57] identified during scoping were also reviewed for potentially relevant primary studies, and we confirmed that all relevant studies cited by these documents had already been considered for inclusion. The study selection process is presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Appendix 20).

5.2 Summary of Study Characteristics

A total of 31 studies were included in the final analyses — all observational studies, with one mixed prospective/retrospective,[22] 24 retrospective,[23-26,29-34,37,38,41-43,45-48,50-54] and six prospective.[27,28,35,36,40,49] Data abstracted from these studies were used to calculate the accuracy of tumour MSI status by PCR- or MMR protein expression by IHC for identifying patients with LS. We summarized studies according to basic characteristics of interest, including the country in which data were collected, criteria used to select patients for study participation, test details, and which diagnostic accuracy outcomes were reported or imputed from data in each study (Appendix 25).

The majority of the included studies involved patients from European countries (61%, 19 of 31),[24,28,30-32,34,36,37,41-43,45-49,52-54] or Australia and/or North America (23%, seven of 31).[25,26,29,38,40,50,51] Most of the studies reported using pre-selection criteria (84%, 26 of 31) such as age, family history, a published set of structured criteria (e.g., Amsterdam or Bethesda), or a combination of any of these. Five studies (16%)[25,26,28,30,52] either did not report whether criteria were used or details of the criteria used.

All 27 studies[22-25,27,28,31-38,40,42,43,45-54] that reported PCR-based MSI test accuracy outcomes used a minimum of five microsatellite markers, and nine of these studies used six or more microsatellite markers, alone or in combination with a five-marker panel. Of the 17 studies[22-30,34,36,37,40-42,45,46] reporting MMR protein expression by IHC-based test accuracy outcomes, eight tested for loss of expression (LoE) in four proteins (MLH1, MSH2, MSH6, PMS2), and nine tested for LoE in three proteins (MLH1, MSH2, MSH6). Of the 31 total studies included in the analysis, 12[32,33,35,38,43,47-51,53,54] sequenced only two genes for their reference standard testing (MLH1, MSH2), 18[22-28,30,31,34,36,37,40-42,45,46,52] used three or more genes, and one study[29] did not report its germline methodology.

If pathogenic germline results were reported in studies separately from non-pathogenic, only pathogenic diagnostic accuracy results were abstracted.

5.3 Summary of Critical Appraisal

Details of the individual study critical appraisal are provided in Appendix 30.

5.3.1 Risk of bias

The majority (27 of 31) of studies[22-27,31-38,40-43,45-47,49-54] avoided a case-control design. Because case-control studies do not reflect the natural prevalence of disease, they are ill-suited for

determining PPVs and NPVs as they overestimate diagnostic accuracy estimates. While a case-control design was avoided by most studies, in five studies[24,46,54-56] it was unclear whether a consecutive sample was used. One study (Loukola 2001)[54] enriched the proportion of germline mutation-positive patients by adding 10 patients with a known mutation to the study population, which would again overestimate the diagnostic accuracy estimates. However, all studies avoided inappropriate exclusions. The index test was described and positive results were defined in all studies. In each study, the reference standard (germline mutational analysis) was likely to classify patients appropriately. However, in some studies, only two of the four dMMR genes of interest (MLH1, MSH2, MSH6, and PMS2) were sequenced, which may lead to a misclassification of some index test results. Additionally, in six of the 31 studies,[23,29,38,45,46,51] the reference standard and index tests were interpreted independently, without knowledge of results of the other test. In the remaining studies, results from one test were known when interpreting the other, or it was unclear whether they were interpreted independently. In 12 studies, not all patients were included in the analysis.[23,29,32,33,35,37,40,41,45-47,49]

5.3.2 Applicability

There were few applicability concerns, as the patients and index test in the studies matched the review questions. The main applicability concern was regarding the reference standard. While the reference standard in all studies was germline mutational testing, some studies sequenced two of the four dMMR genes of interest, which may not be reflective of current clinical practice and, as mentioned, may lead to a misclassification of some patients (i.e., an increase in false positive or true negative results).

5.4 Summary of Findings

5.4.1 Diagnostic performance of PCR- and IHC-based tests of dMMR status

Using germline mutation testing as the reference standard, the diagnostic test performance of PCR- and IHC-based testing is presented in Table A2 and Table A3, respectively. Data available for a total of 3,603 MSI and 2362 MMR IHC patients or samples were pooled. Case-control studies do not reflect true prevalence of the disease, because the number of true disease and non-disease cases is often selected at a 1:1 ratio. The estimation of predictive values relies on the study level of prevalence (which is often 1:1 cases:controls but may be more accurate in cohort studies), or a literature value must be substituted into the estimation.

For MSI-based studies, three studies did not provide all of the 2 × 2 elements (true positive [TP], false positive [FP], true negative [TN], false negative [FN]) directly in the published manuscript,[23,35,40] while two MMR IHC studies did not provide all of the 2 × 2 elements.[29,30] For these studies, sufficient information was available to indirectly estimate the missing data (e.g., Warrier[29] 0.949 sensitivity for 33 disease positive cases leads to 0.949 × 33 = 31 TP and 2 FN).

A forest plot of all PCR test data is provided in Figure 1. A forest plot of all MMR IHC test data is provided in Figure 3.

5.4.2 PCR-based tumour MSI testing

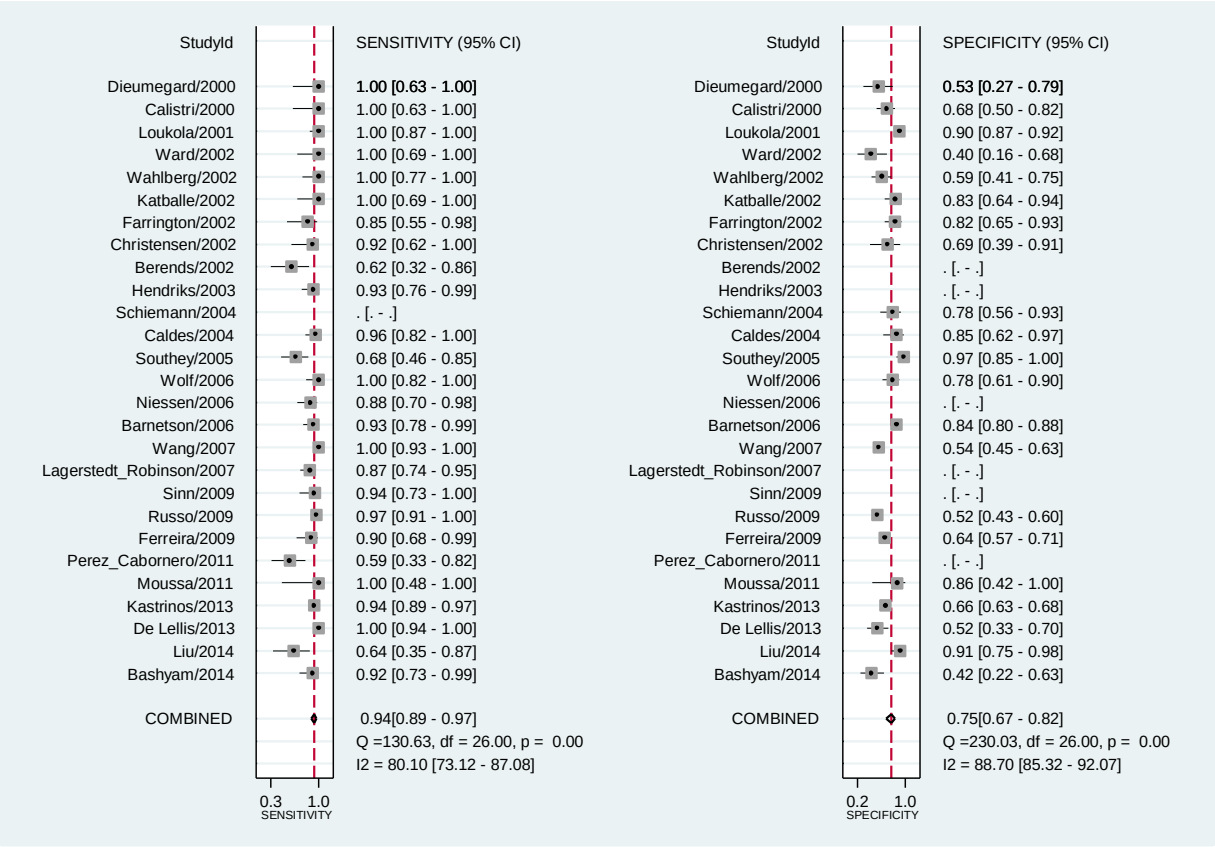
a) Heterogeneity of PCR-based MSI testing

The scatter of points around the SROC curve indicates heterogeneity. The shape of the confidence ellipse around the summary estimate of sensitivity and FP rate (1 – specificity) suggests greater variability in specificity than in sensitivity.

Figure 2 shows the ROC with summary estimate (circle and dotted ellipse) and scatter plot of sensitivity and specificity (triangles, for studies reporting data for both sensitivity and specificity). There did not appear to be any notable outliers.

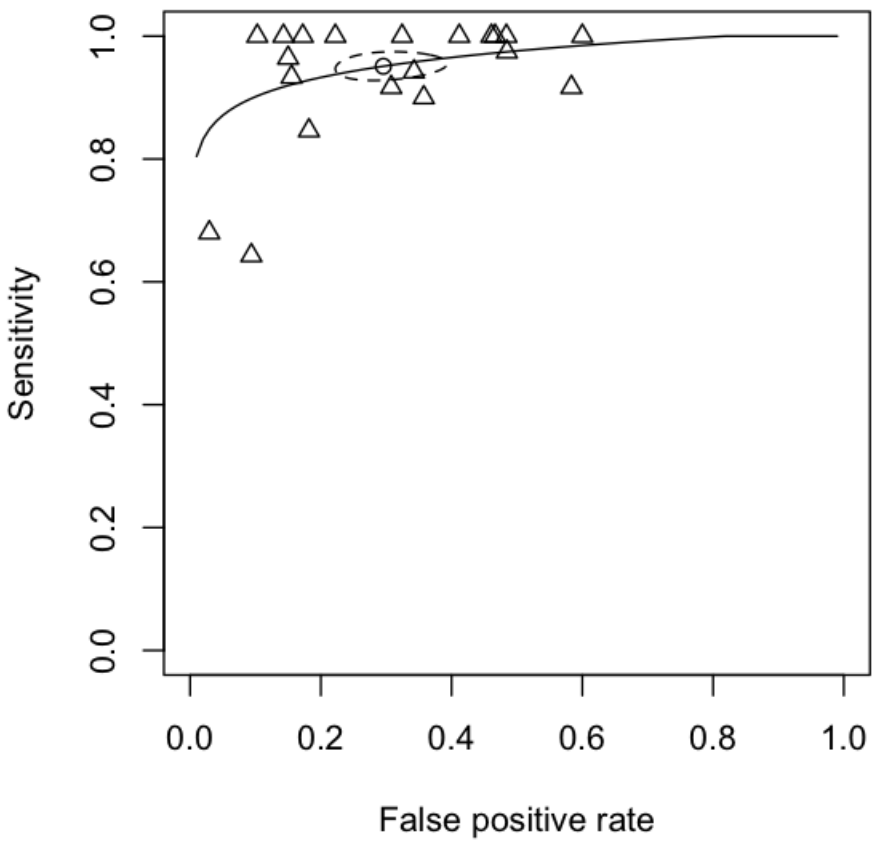
We explored the effect on heterogeneity of number of markers tested, threshold for a positive test, number of germline genes sequenced, and study design (Table A2). The number of markers tested was dichotomized as equal to five markers (reference level) and greater than five markers. Higher threshold was represented by studies that used MSI-H (positive) and MSI-L (negative; reference level), and lower threshold by studies that used MSI-H/MSI-L (positive) or MSI (positive). The number of genes sequenced was dichotomized as two genes (reference level) and more than two genes. Study design was dichotomized as observational non–case-control (reference) and case-control or unclear design. For the three covariates, number of markers, the threshold for a positive test, and study design, the two SROCs diverged at lower FP rates, but the confidence ellipses overlapped, and meta-regression did not show a significant effect. For the number of genes sequenced for the reference standard, the two SROCs were almost superimposed, but the confidence ellipses also overlapped, and meta-regression did not show a significant effect. Thus, none of the covariates, as dichotomized, had a significant effect on heterogeneity. No obvious source of heterogeneity was identified; pooled summaries of sensitivity and specificity are presented.

Figure 1: Forest Plot, All PCR-Based Data



CI = confidence interval; PCR = polymerase chain reaction.

Figure 2: ROC Curve for PCR-Based Tumour MSI Testing



MSI = microsatellite instability; PCR = polymerase chain reaction; ROC = receiver operator characteristic.

b) Sensitivity of PCR-based MSI testing

The overall sensitivity for pooled MSI studies was 0.940 (95% CI, 0.894 to 0.967). When analyses were restricted to studies using five markers, sensitivity was 0.947 (95% CI, 0.891 to 0.975), compared with studies using more than five markers (0.931, 95% CI, 0.856 to 0.968). When only MSI-H (based on classifications in the included studies) results were included, sensitivity was 0.915 (95% CI, 0.845 to 0.956), compared with a combination of MSI-H/L which had a sensitivity of 0.963, 95% CI, 0.824 to 0.993. When results from the 11 studies reporting germline sequencing using only two proteins (MLH1 and MSH2) were pooled, sensitivity increased to 0.972 (95% CI, 0.935 to 0.989).

c) Specificity of PCR-based MSI testing

The overall specificity for pooled MSI studies was 0.754 (95% CI, 0.670 to 0.823). When the PCR-based MSI test was based on five markers, the specificity was 0.770 (95% CI, 0.664 to 0.850) and with more than five markers, specificity was 0.684 (95% CI, 0.571 to 0.779). When studies were categorized using high (H) or low (L) cut-offs, the specificity for MSI-H positive results alone was 0.777 (95% CI, 0.676 to 0.853), compared with combined MSI-H/L 0.794 (95% CI, 0.656 to 0.887). When results from the 11 studies reporting germline sequencing using only two proteins (MLH1 and MSH2) were pooled, specificity decreased to 0.660 (95% CI, 0.571 to 0.738).

Table A2: Pooled Sensitivity and Specificity, PCR-Based MSI Test

	Studies (n)	Sensitivity (95% CI)	I^2	Studies (n)	Specificity (95% CI)	I^2
Overall PCR-Based MSI Test	26	0.940 (0.894 to 0.967)	80%	21	0.754 (0.670 to 0.823)	89%
5 Markers	18	0.947 (0.891 to 0.975)	82%	12	0.770 (0.664 to 0.850)	90%
> 5 Markers	11	0.931 (0.856 to 0.968)	77%	9	0.684 (0.571 to 0.779)	69%
MSI-H	19	0.915 (0.845 to 0.956)	81%	13	0.777 (0.676 to 0.853)	92%
MSI-H/MSI-L	6	0.963 (0.824 to 0.993)	83%	5	0.794 (0.656 to 0.887)	83%
2 Protein Reference Standard	11	0.972 (0.935 to 0.989)	40%	11	0.660 (0.571 to 0.738)	68%

CI = confidence interval; H = high; L = low; MSI = microsatellite instability; PCR = polymerase chain reaction.

d) Impact of missing data for PCR-based MSI testing

There were three studies that did not have all elements for analysis requiring imputation,[23,35,40] and after these studies were removed from the analysis, the estimate of sensitivity changed from 0.940 to 0.947 (95% CI, 0.903 to 0.972) with an I^2 value of 76%, and the estimate of specificity changed from 0.754 to 0.711 (95% CI, 0.617 to 0.789), I^2 = 90%.

5.4.3 IHC-based tumour testing

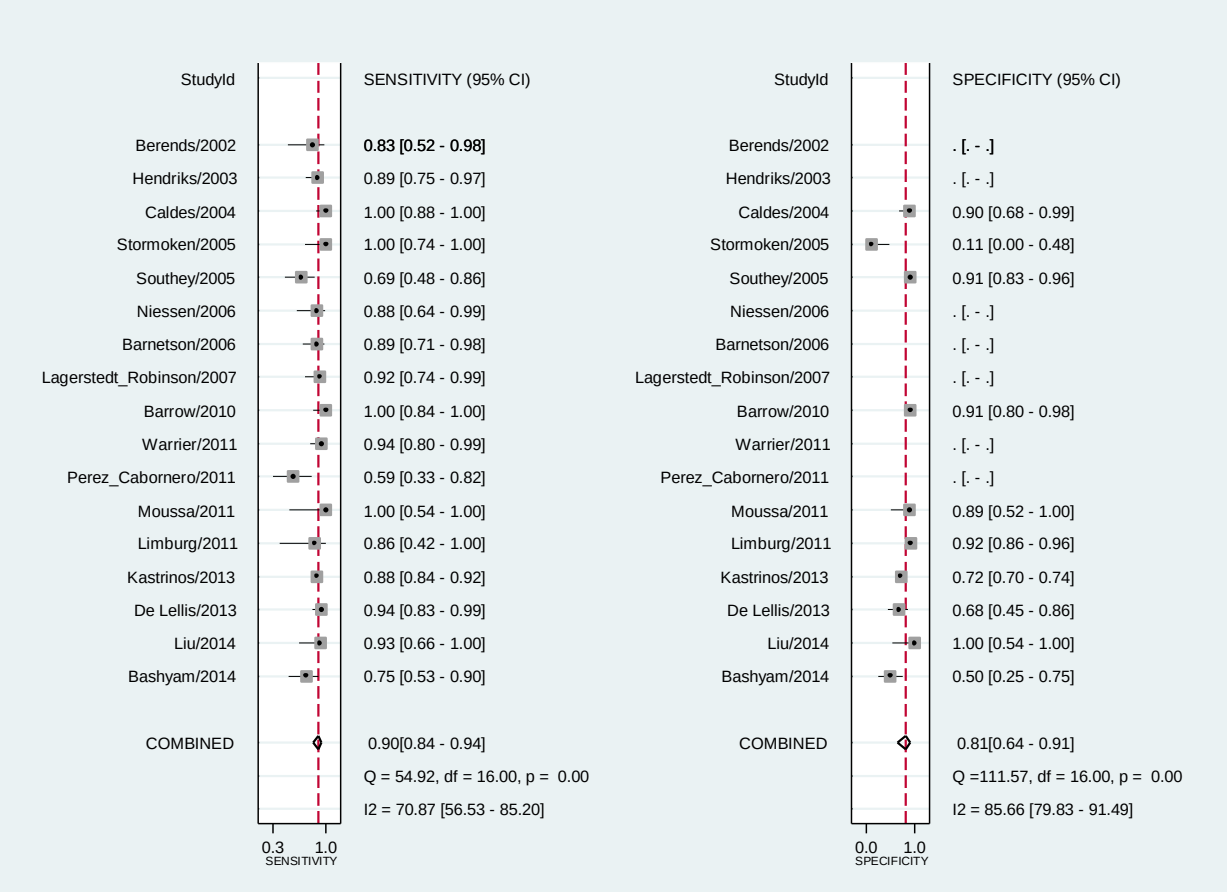
a) Heterogeneity of MMR IHC-based testing

The scatter of individual study points around the SROC curve indicates heterogeneity (although the points represent only that subset that includes estimates for both sensitivity and specificity). The shape of the confidence ellipse around the summary estimate of sensitivity and FP rate (1 – specificity) suggests greater variability in specificity than in sensitivity.

Figure 4 shows the ROC with summary estimate (circle and dotted ellipse) and scatter plot of sensitivity and specificity (triangles, for studies with data reported for both).

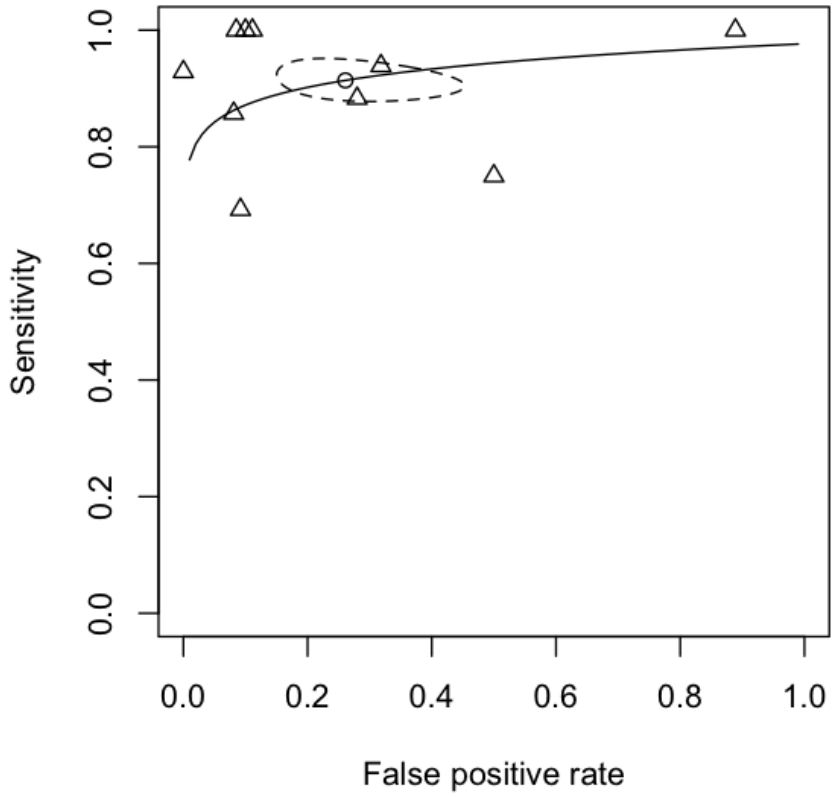
We explored the effect on heterogeneity of number of proteins assayed. The number of proteins was dichotomized as three proteins and more than three proteins. The two SROCs diverged at lower FP rates, but the confidence ellipses overlapped, and meta-regression did not show a significant effect. No obvious source of heterogeneity was identified; pooled summaries of sensitivity and specificity are presented.

Figure 3: Forest Plot, All MMR IHC-Based Data



CI = confidence interval; IHC = immunohistochemistry; MMR = mismatch repair; PCR = polymerase chain reaction.

Figure 4: ROC Curve for IHC-Based Tumour Testing



IHC = immunohistochemistry; ROC = receiver operator characteristic.

b) Sensitivity of MMR IHC-based testing

The overall estimate of sensitivity for IHC was 0.900 (95% CI, 0.841 to 0.939). When studies were categorized into having IHC analysis conducted with three proteins, the sensitivity was 0.907 (95% CI, 0.816 to 0.955), compared with analyses conducted using four proteins (sensitivity 0.900 [95% CI, 0.806 to 0.951]).

c) Specificity of MMR IHC-based testing

The overall estimate of specificity for IHC was 0.810 (95% CI, 0.643 to 0.910). When studies were categorized into having IHC analysis conducted with three proteins, the specificity was 0.851 (95% CI, 0.367 to 0.983), compared with analyses conducted using four proteins (specificity 0.853 [95% CI, 0.698 to 0.936]).

Table A3: Pooled Sensitivity and Specificity, MMR IHC-Based Test

	Studies (n)	Sensitivity (95% CI)	Studies (n)	Specificity (95% CI)
Overall MMR IHC-Based Test	17	0.900 (0.841 to 0.939)	10	0.810 (0.643 to 0.910)
3 Proteins	9	0.907 (0.816 to 0.955)	4	0.851 (0.367 to 0.983)
4 Proteins	8	0.900 (0.806 to 0.951)	6	0.853 (0.698 to 0.936)

CI = confidence interval; IHC = immunohistochemistry; MMR = mismatch repair.

d) Impact of missing data for MMR IHC-based testing

There were two studies that did not have all elements for analysis requiring imputation,[29,30] and after these studies were removed from the analysis, the estimate of sensitivity changed from 0.900 to 0.947 (95% CI, 0.903 to 0.972) with an I^2 value of 68%, and the estimate of specificity changed from 0.810 to 0.711 (95% CI, 0.617 to 0.789), I^2 = 84%.

Interpreting diagnostic test results using Fagan's nomogram — screening high-risk patient subgroups: A pre-test probability, or the prevalence of a condition in a given population, can be used in combination with an LR to "modify the pre-test probability of that condition, yielding a new post-test probability."[58] LRs "indicate the extent to which a given diagnostic test result will increase or decrease the pre-test probability of the target disorder."[58] A useful clinical tool called Fagan's nomogram[59] converts a pre-test to a post-test probability using LRs. We therefore calculated relevant LRs in order to provide nomographic examples of the post-test probability of LS actually being present in a CRC population tested with either MSI- or MMR IHC-based tumour tests, versus a CRC population that is first pre-screened using the revised Bethesda criteria and then the tumour tested by MSI or MMR IHC.

Briefly, to generate a post-test probability using a nomogram, the pre-test probability relevant to the context (leftmost column) and the relevant LR (middle column) are found, and a straight line is drawn between the two points, extending the line past the rightmost column (post-test probability). The point where the line crosses the post-test probability column indicates the converted value.

The calculated positive LRs (MSI = 3.8, MMR IHC = 4.7) fell into the 2 to 5 category (Table A4), commonly interpreted as meaning a positive test would generate a small, but sometimes important, shift in the probability of disease.[60] Based on each LR+, with a pre-test probability (i.e., population prevalence of true cases/total cases) of disease of 18% (MSI) or 19% (MMR IHC) as seen in our included studies on average, which may not accurately reflect the incidence

of the disease in Canada, a positive test result would produce a post-test probability of disease of 46% for PCR and 53% for IHC.

Table A4: Prevalence, LR+, LR–, PPV, NPV, MSI- and MMR IHC-Based Tests

	PCR (95% CI)	IHC (95% CI)
Studies (n); patients (N)	27; 3,603	17; 2,362
Prevalence: mean (min, max)	0.175 (0.055, 0.659)	0.191 (0.045, 0.700)
LR+	3.8 (2.8 to 5.1)	4.7 (2.3 to 9.6)
LR–	0.08 (0.05 to 0.14)	0.12 (0.08 to 0.21)
PPV	0.578 (0.474 to 0.683)	0.721 (0.551 to 0.892)
NPV	0.997 (0.992 to 0.999)	0.987 (0.964 to 0.999)

CI = confidence interval; IHC = immunohistochemistry; LR+ = positive likelihood ratio; LR– = negative likelihood ratio; MMR = mismatch repair; MSI = microsatellite instability; NPV = negative predictive value; PPV = positive predictive value.

Table A5: Interpretation of Likelihood Ratios

Positive LR	Negative LR	Interpretation
> 10	< 0.1	Generate large and often conclusive shifts in probability of disease
5 to 10	0.1 to 0.2	Generate moderate shifts in probability
2 to 5	0.2 to 0.5	Generate small, but sometimes important, shift in probability
1 to 2	0.5 to 1	Alter probability to a small, and rarely important, degree

LR = likelihood ratio.

The negative LRs (MSI = 0.08, MMR IHC = 0.12), fell into the < 0.1 and 0.1 to 0.2 categories, respectively (Table A5). Therefore, an LR– for MSI of 0.08 would indicate that a negative test result generates a large and often conclusive shift in the probability of disease. Based on the LR–, with a pre-test probability of disease of 18% for MSI and 19% for MMR IHC, as was seen in these studies on average, a negative test result would produce a post-test probability of disease of 2% for MSI- (Figure 6) and 3% for MMR IHC-based testing (Figure 7).

Figure 5: Fagan's Nomogram — All Microsatellite Instability–Based Data, Prevalence of Studies = 0.18

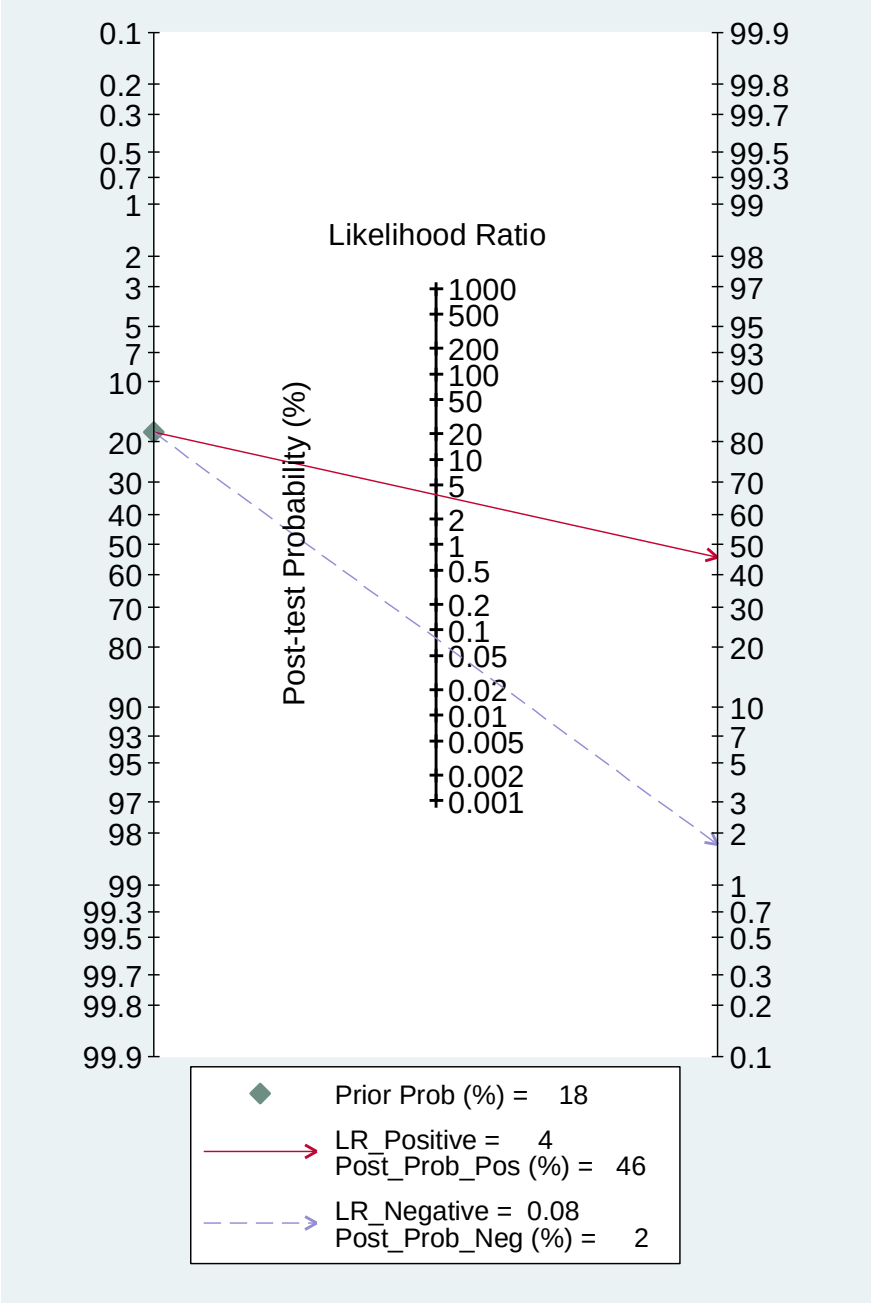
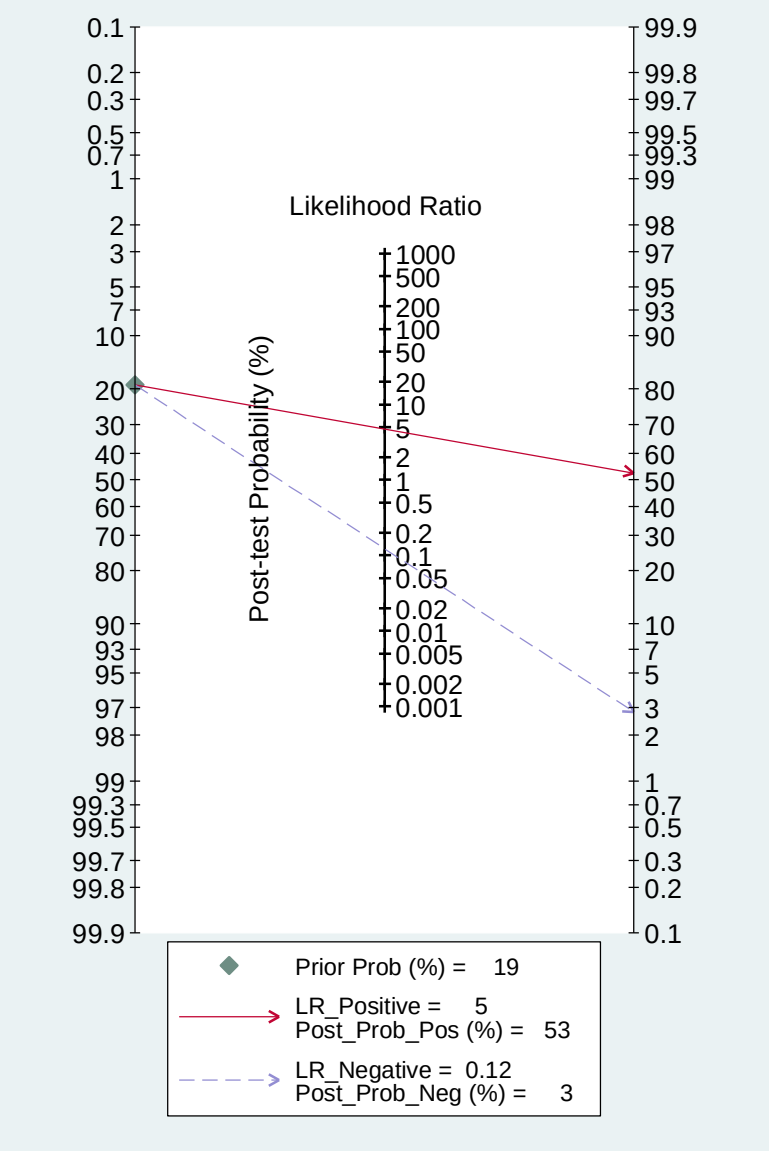


Figure 6: Fagan's Nomogram — MMR IHC, Based on Study Data Estimate of Prevalence 0.19

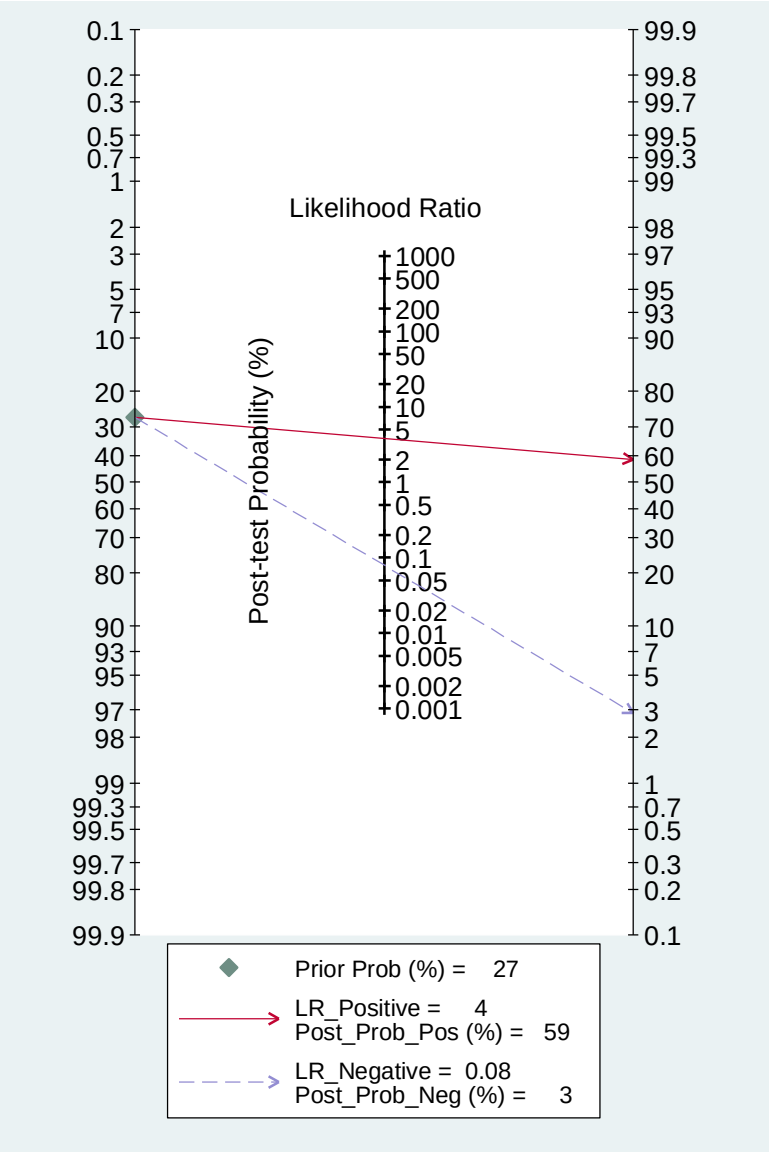


IHC = immunohistochemistry; LR = likelihood ratio; MMR = mismatch repair.

e) Benefit of pre-screening criteria

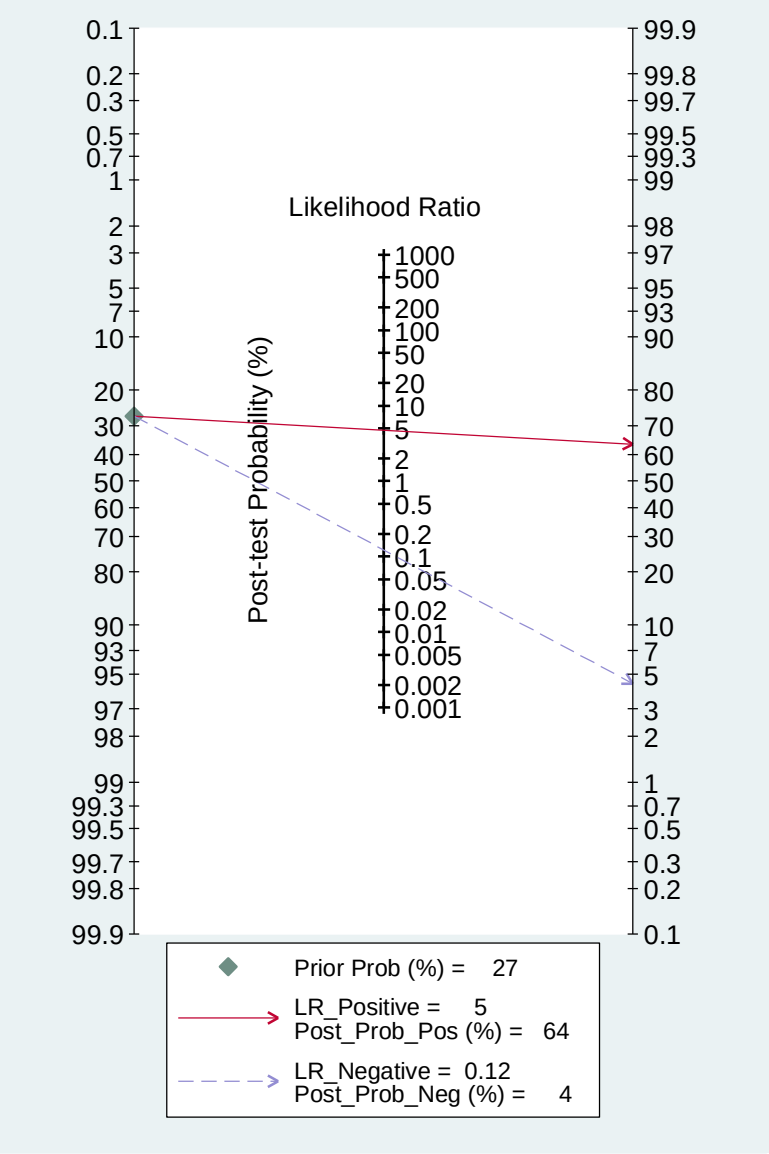
If the pre-test probability (prevalence) of disease was higher due to the application of clinical screening criteria such as the rBG criteria (literature systematic review based estimate of 27%[61]) in comparison with an unscreened CRC population, the MSI-based tumour test would predict a post-test probability of disease with a positive test of 59% and with a negative test 3% (Figure 7). The MMR IHC-based tumour test would predict a post-test probability of disease with a positive test of 64% and with a negative test 4% (Figure 8).

Figure 7: Fagan's Nomogram — All MSI-Based Data, After Applying Revised Bethesda Guidelines Criteria Possible Literature Value of Prevalence = 0.27



LR = likelihood ratio; MSI = microsatellite instability.

Figure 8: Fagan's Nomogram — MMR IHC, After Applying Revised Bethesda Guidelines Criteria Possible Literature Value of Prevalence = 0.27



IHC = immunohistochemistry; LR = likelihood ratio; MMR = mismatch repair.

Clinical Review: Health Outcomes of dMMR Testing for Family Members

2. What is the clinical utility of screening CRC patients for LS by IHC- or PCR-based dMMR testing for improving health outcomes of family members?

6. Methods

6.1 Literature Search Strategies

The literature search was performed by an information specialist using a peer-reviewed search strategy according to PRESS guidance.[17]

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946 to current) with in-process records and daily updates via Ovid; EMBASE (1974 to 2015 Feb 20) via Ovid; The Cochrane Library (2015, Issue 1) via Wiley; and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH, and keywords. The main search concepts were family members and hereditary nonpolyposis colorectal neoplasms (HNPCC) and microsatellite instability (MSI) or DNA mismatch repair (dMMR).

No filter was applied to limit retrieval to particular study types. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year, but was limited to the English or French language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies. The search was run from February 23 to 24, 2015. A search update was conducted on March 1, 2016. Additional articles that were published since the initial search and that met the selection criteria but were not included in the analysis are provided in Appendix 2.

Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist (www.cadth.ca/resources/finding-evidence/grey-matters), which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry. See Appendix 1 for more information on the grey literature search strategy. The references of six guideline/review documents,[55,57,62-65] identified in the scoping review, were reviewed to identify additional studies of potential relevance to this study question.

6.2 Selection Criteria and Methods

Studies suitable for inclusion were selected from those identified through the literature search, using the criteria listed below.

Population	CRC patients, at any age, any stage, diagnosed with LS
Intervention	Screening with dMMR testing
Comparator	No screening
Outcomes	Clinical and cancer-related outcomes of relatives of CRC patients diagnosed with LS (e.g., patient management decisions, survival rates, cancer prevention)
Study Types	Randomized controlled trials, prospective or retrospective observational (non-randomized) studies (cross-sectional diagnostic studies, cohort, case-control)

6.3 Exclusion Criteria

Studies were excluded if they included patients with other types of cancer and did not present results for CRC patients separately, or if they recruited members of families suspected of having LS (but not CRC patients). Duplicate publications, narrative reviews, and editorials were also excluded.

Two reviewers (NA, CV) independently screened the titles and abstracts for relevance using a predefined checklist (Appendix 4). Any discrepancies between reviewers were resolved by discussion. Full texts of relevant titles and abstracts were retrieved, and assessed by two independent reviewers (NA, CV) to make inclusion and exclusion decisions, using explicit predetermined criteria (Appendix 9). Discrepancies between the reviewers were resolved by discussion, consulting a third reviewer when necessary.

6.4 Data Extraction

Not applicable — no studies relevant to this question were identified in this review.

6.5 Critical Appraisal of Individual Studies

Not applicable — no studies relevant to this question were identified in this review.

6.6 Data Analyses and Synthesis

Not applicable — no studies relevant to this question were identified in this review.

7. Summary of Clinical Evidence

7.1 Quantity of Research Available

A total of 878 potential citations were identified by the clinical search, with 839 citations being excluded during the title and abstract review based on irrelevance to the inclusion criteria. The full-text documents of the remaining 39 articles were retrieved. None of the 39 articles met the eligibility criteria for this question. A PRISMA diagram demonstrating the study selection process is presented in Appendix 21. The list of excluded studies is available upon request.

7.2 Summary of Study Characteristics

Not applicable — no studies relevant to this question were identified in this review.

7.3 Summary of Critical Appraisal

Not applicable — no studies relevant to this question were identified in this review.

7.4 Summary of Findings

No studies examining the utility of PCR-based or IHC-based dMMR tumour testing for improving health outcomes of family members were identified in this review.

Because of the lack of evidence examining the full pathway from initial dMMR tumour test to family member outcomes, a supplementary Rapid Response review was conducted to address the mortality and morbidity benefits of dMMR tumour testing and subsequent cancer surveillance in CRC patients with dMMR tumours, and their relatives.[66] This review examined the benefits of increased surveillance of family members of patients with or without dMMR tumours compared with no change in surveillance or monitoring. Four studies (including one HTA) compared surveillance of members of LS families to non-surveillance. These studies found that surveillance was associated with a decreased risk of colorectal and extra-colonic cancers, early cancer detection, and better survival in members of LS families regardless of mutation status.

Six studies compared surveillance of mutation carriers with non–mutation carriers within LS families, or surveillance of LS versus non-LS families. During surveillance, higher rates of colorectal or other cancers were detected in mutation carriers or members of LS families compared with non–mutation carriers or members of non-LS families. However, no difference was observed in the risk of mortality between mutation-positive and mutation-negative individuals, which suggests a potential benefit of screening for LS for family members.

Clinical Review: Clinical Validity of Tests Subsequent to dMMR Testing

3. What is the clinical validity of molecular tests subsequent to dMMR testing for ruling out a germline mutation in MMR genes?
   a. What is the clinical validity of BRAF V600E testing by PCR for ruling out an MMR gene mutation in a CRC tumour with no MLH1 protein expression?
   b. What is the clinical validity of BRAF V600E testing by IHC for ruling out an MMR gene mutation in a CRC tumour with no MLH1 protein expression?
   c. What is the clinical validity of MLH1 promoter hypermethylation testing for ruling out an MMR gene mutation in a CRC tumour with no MLH1 expression?

8. Methods

8.1 Literature Search Strategies

The literature search was performed by an information specialist using a search strategy peer-reviewed according to PRESS guidance.[17]

One previously identified systematic review and meta-analysis[67] with 57 studies of potential relevance for this question was updated with a search of the current literature. While there were concerns regarding search limitations of the systematic review (i.e., only the PubMed database was searched, and a full description of search terminology was not provided), this limitation was mitigated by the extensive number of studies relevant to our research question that Parsons et al.[67] included in their analysis.

Published literature was identified by searching the following bibliographic databases with a database entry date limit of 2011 to the present, which is based on the last recorded date on which searching was performed in the previously identified review: MEDLINE (1946 to current) with in-process records and daily updates via Ovid; Embase (1974 to 2015 Feb 20) via Ovid; The Cochrane Library (2015, Issue 1) via Wiley; and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH, and keywords. The main concepts for this search were any type of colorectal neoplasms and immunohistochemical DNA mismatch repair (dMMR) testing of MLH1, and BRAF V600E or MLH1 hypermethylation.

No filter was applied to limit retrieval to particular study types. Where possible, retrieval was limited to the human population and English or French documents. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies. The search was conducted from February 23 to 24, 2015. A search update was conducted on March 1, 2016. Additional articles that were published since the initial search and that met the selection criteria but were not included in the analysis are provided in Appendix 2.

Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist (www.cadth.ca/resources/finding-evidence/grey-matters), which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry. See Appendix 1 for more information on the grey literature search strategy.

8.2 Selection Criteria and Methods

Studies suitable for inclusion were selected from those identified through the literature search, using the criteria listed below:

Population	CRC patients, at any age, any stage, for whom dMMR tumour test by IHC indicates no MLH1 expression
Intervention	BRAF V600E tumour testing by genotyping (PCR) MLH1 promoter hypermethylation tumour testing BRAF V600E testing by IHC
Comparator (Reference Standard)	Germline mutation analysis
Outcomes	Diagnostic test performance for differentiating LS from sporadic CRC: • Sensitivity • Specificity • PPV and NPV
Study types	RCTs, prospective or retrospective observational (non-randomized) studies (cross-sectional diagnostic studies, cohort, case-control)

8.3 Exclusion Criteria

Studies were excluded if they did not meet the selection criteria. Duplicate studies, narrative reviews and small studies, defined as those that reported relevant data for fewer than 10 patients, were also excluded.

Two reviewers (JJ, CV) independently screened the titles and abstracts for relevance using a predefined checklist (Appendix 5). Any discrepancies between reviewers were resolved by discussion. Full texts of relevant titles and abstracts were retrieved, and assessed by two independent reviewers to make inclusion and exclusion decisions, using explicit predetermined criteria (Appendix 10). Discrepancies between the reviewers were resolved by discussion, and a third reviewer was consulted when necessary.

8.4 Data Extraction

One reviewer performed data extraction for each article (KG) using pre-drafted data extraction forms (Appendix 16). A second reviewer (GB) checked the abstracted data for accuracy. The reviewers piloted data extraction forms a priori, and performed a calibration exercise using 10 studies to ensure consistency between the reviewers.

8.5 Critical Appraisal of Individual Studies

One reviewer critically appraised the selected studies based on the QUADAS-2 instrument[18] for the evaluation of diagnostic accuracy studies (Appendix 13). QUADAS-2 is a tool that evaluates the risk of bias in selection of patients, index test, reference standard, and flow and timing of the study. A second reviewer verified the critical appraisal assessments of individual studies.

8.6 Data Analyses and Synthesis

8.6.1 Outcomes

Statistical outcomes that provided estimates of diagnostic test accuracy included sensitivity, specificity, PPV, and NPV. A definition of each outcome measure is provided below. Details on each of these outcomes are provided in Appendix 19.

Table C1: Definitions of Diagnostic Accuracy Measures

Measure	Definition	Formula
Sensitivity	The proportion of persons with the disease who are correctly identified by a test	TP/(TP + FN)
Specificity	The proportion of persons without a disease who are correctly identified by a test	TN/(TN + FP)
Positive Predictive Value	the proportion of patients with positive test results who are correctly diagnosed	TP/(TP + FP)
Negative Predictive Value	proportion of patients with negative test results who are correctly diagnosed	TN/(TN + FN)

FN = false negative; FP = false positive; TN = true negative; TP = true positive.

In this report, measures of sensitivity, specificity, PPV, and NPV are used for the purpose of reporting the diagnostic performance of three tests using germline MMR gene testing as the reference standard: 1) PCR-based BRAF mutation tumour testing; 2) IHC-based BRAF mutation tumour testing; and 3) tumour MLH1 promoter hypermethylation testing.

8.6.2 Comparisons

Each of the diagnostic performance measures were estimated for each test, tumour PCR-based BRAF mutation testing, tumour IHC-based BRAF mutation testing, or tumour MLH1 promoter hypermethylation testing, relative to germline MMR gene testing as the reference standard.

The analysis of the diagnostic test performance involves two steps. In the first step, the direct comparison between the index tumour test and the reference standard — i.e., PCR-based BRAF mutation testing relative to germline testing, IHC-based BRAF mutation testing relative to germline testing, or MLH1 promoter hypermethylation testing relative to germline MMR gene testing — was estimated for each study. When there was more than one study with the same test type, the results of multiple studies of the same test for a particular condition were meta-analyzed to create one pooled estimate. The meta-analytic summary for all diagnostic accuracy outcomes across all studies was conducted with STATA using the command "midas".[19] Midas data synthesis is performed within the bivariate mixed-effects binary regression modelling framework using a multilevel mixed-effects logistic regression. This analysis models the variance and mixed effects between and within studies, as well as modelling the mixed effects that occur between sensitivity and specificity.

8.6.3 Heterogeneity

For descriptive purposes, to inspect whether the studies were similar enough to be compared indirectly under the assumptions of similarity, we provided an assessment of heterogeneity within each test (e.g., sensitivity of MLH1 promoter hypermethylation). The presence of heterogeneity is expected in meta-analysis of diagnostic accuracy, and the typical thresholds for I^2 that are often applied to outcomes such as relative risk for the degree of heterogeneity have not been established, according to the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy*.[20]

Because of the small number of studies and lack of pre-specified variables that may contribute to differences between studies, heterogeneity was explored by the removal of outliers and the effects on sensitivity and specific were reported.

9. Summary of Clinical Evidence

9.1 Quantity of Research Available

A total of 934 potential citations were identified by the systematic search and bibliographic review of the previously identified Parsons et al. systematic review.[67] During title and abstract review, 839 of these citations were excluded because they were irrelevant to the question of interest. Full-text documents of the remaining 95 articles were retrieved. Among these articles, 83 were excluded during second-level screening. Forty studies were excluded because they did not contain relevant outcomes. Twenty studies were excluded because they evaluated an irrelevant study population. Ten studies were excluded because they did not include a relevant reference standard (i.e., germline mutation testing). Seven studies were excluded because they had relevant data for fewer than 10 patients. Four studies were excluded because of irrelevant study design, while two studies were excluded because they were based on duplicate data of one of the included studies.[16] Appendix 22 shows the PRISMA flowchart of the process used to identify and select studies for the review and the main reasons for exclusion.

9.2 Summary of Study Characteristics

Appendix 26 provides an overview of the 12 included studies. All of the included articles were published between 2003 and 2013. Two of the included studies were conducted in Australia,[68,69] two in the USA,[61,70] one in the USA and Canada,[71] and one in each of the following countries: Switzerland,[72] Spain,[16] Germany,[73] France,[74] the Netherlands,[75] Slovakia,[76] and Taiwan.[77] In four of the studies,[69,73,75,76] all or the majority of the starting population included patients who met clinical criteria (Amsterdam or rBG) for LS, also known as HNPCC. In two studies,[68,72] the starting population included CRC patients known to have or suspected of having HNPCC. The remaining studies involved patients who had undergone bowel resection for CRC. The number of patients in the starting population of the included studies was generally much larger than the number of data points used to derive the diagnostic accuracy study. This is because the usable data from the studies include only patients who have lack of tumour expression of the MLH1 protein, have the corresponding germline MLH1 mutation status, and have either tumour BRAF mutation or MLH1 promoter hypermethylation status results available.

Seven studies[16,69,70,72-74,77] conducted both tumour PCR and sequencing for the BRAF mutation and MLH1 promoter hypermethylation tests, but two of these studies[70,73] did not report data relating to one of the two tests. One study conducted only tumour tests to identify the BRAF mutation[68] and the remaining four studies conducted only the tumour MLH1 promoter methylation tests.[61,71,75,76]

The eight studies that conducted tumour tests for the BRAF mutation appear to have used standard PCR-based assay protocols to identify the sequence of DNA proteins in the tumour samples. Two studies[72,74] identified the commercial assay kit they used: BigDye Terminator Sequencing Kit. One study[68] used the standard PCR protocol as verification for an allele-specific PCR protocol that was used to identify the BRAF mutation.

All but one[72] MLH1 promoter hypermethylation test utilized the bisulphite conversion method. Bisulphite deaminates unmethylated cytosine, causing its chemical conversion to uracil upon alkaline desulfonation, but converts methylated cytosine much more slowly. The selective conversion, following PCR and sequencing of cloned amplified DNA, the presence of unmethylated cytosine is clearly detected.[78] Bouzourene et al.[72] used an electrophoresis protocol to determine the hypermethylation status of their samples. Of the 10 studies that completed these methylation tests, eight reported the protocol that was utilized. One study used

single-strand conformation analysis,[72] the only non-bisulphite protocol. Two studies[71,75] used a commercially available kit called MethyLight (Qiagen). Two other studies[73,74] used a combined bisulphite restriction analysis (COBRA) that is reported to be compatible with paraffin-embedded DNA samples.[79] One study[16] used two commercially available protocols in their analyses (MethyLight and SALSA, which are allele-specific methylation protocols[77]). One study used a methylation-specific PCR (MS-PCR) protocol and a second study[74] used both MS-PCR and COBRA.

9.3 Summary of Critical Appraisal

Details of the individual study critical appraisal are provided in Appendix 31.

9.3.1 Risk of bias

All 12 studies included for this research question[16,61,68-77] avoided a case-control design. As case-control studies do not reflect the natural prevalence of disease, they are ill-suited for determining PPVs and NPVs. While a case-control design was avoided by all studies, in four studies[61,70,72,76] it was unclear whether a consecutive or random sample was used. Three of these studies[61,70,72] selected patients from previous or ongoing studies by the same researchers. However, all studies avoided inappropriate exclusion criteria. The index test was described and positive results were defined in all studies. In each study, the reference standard (germline MMR mutational analysis) was likely to classify patients appropriately. In two studies,[69,77] the index test was interpreted without knowledge of the results of the reference standard, and in three studies,[69,76,77] the reference standard was interpreted without knowledge of the index test results. In the remaining studies, it was unclear whether the tests were interpreted independently. In seven studies,[16,68,69,71,73-75] not all patients were included in the analysis.

9.3.2 Applicability

There were no major applicability concerns, as the patient population, index tests, and reference standards matched the research questions.

9.4 Summary of Findings

Tumour BRAF mutation testing and MLH1 promoter hypermethylation testing may be helpful in reducing the likelihood of LS being diagnosed in patients shown to have dMMR tumours by detecting MMR dysfunction that is somatic in origin (non-LS, or “likely sporadic CRC”). Therefore, diagnostic accuracy for these tumour tests is presented in terms of their ability to detect likely sporadic CRC, which reduces the likelihood of germline mutations.

9.4.1 Sensitivity and specificity of tumour-based BRAF (PCR-based), BRAF (IHC-based) and MLH1 promoter hypermethylation testing to detect likely sporadic CRC

Table C2 presents pooled estimates for sensitivity and specificity for the tumour tests PCR-based BRAF mutation testing, IHC-based BRAF mutation testing, and MLH1 promoter hypermethylation testing to detect likely sporadic CRC in patients showing lack of tumour expression of the MLH1 protein. As shown, the pooled sensitivity of PCR-based BRAF is estimated to be 0.57 (95% CI, 0.45 to 0.69). The sensitivity of MLH1 promoter hypermethylation is estimated to be 0.82 (95% CI, 0.62 to 0.93). A single study was identified that evaluated the diagnostic accuracy of IHC-based BRAF mutation testing. Based on data from this one study, the sensitivity of IHC-based BRAF is estimated to be 0.36 (95% CI, 0.14 to 0.51).[69]

Table C2: Pooled Sensitivity and Specificity to Detect Likely Sporadic CRC for PCR-Based BRAF, MLH1 Promoter Hypermethylation, and IHC-Based BRAF

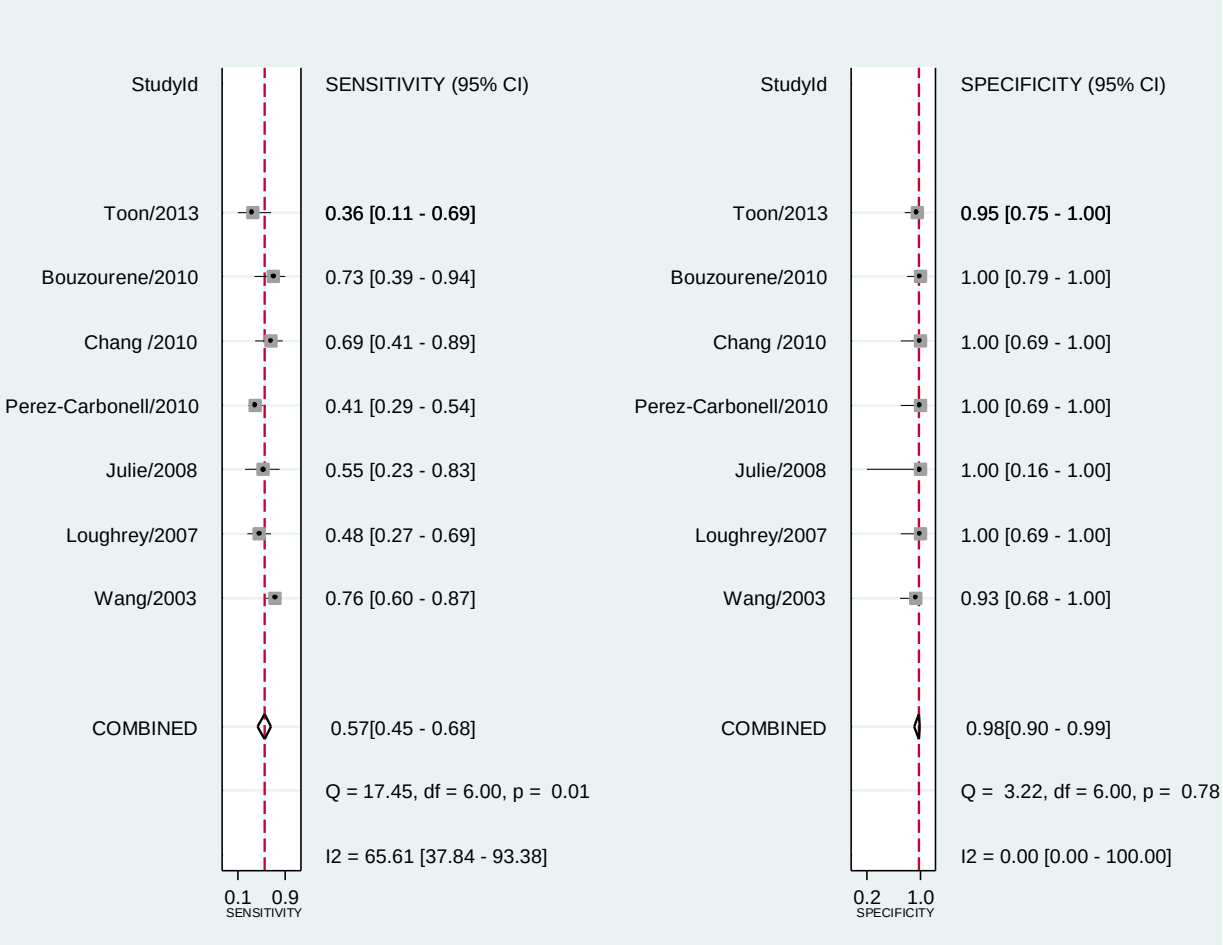
	Studies (n)	Sensitivity (95% CI)	Studies (n)	Specificity (95% CI)
BRAF-PCR	7	0.57 (0.45 to 0.69)	7	0.98 (0.90 to 0.99)
MLH1 Promoter Hypermethylation	8	0.82 (0.618 to 0.93)	9	0.96 (0.74 to 0.99)
BRAF-IHC	1	0.36 (0.14 to 0.51)	1	0.90 (0.78 to 0.98)

CRC = colorectal cancer; IHC = immunohistochemistry; PCR = polymerase chain reaction.

The pooled specificity of PCR-based BRAF is estimated to be 0.98 (95% CI, 0.90 to 0.99). The pooled specificity of MLH1 promoter hypermethylation is estimated to be 0.96 (95% CI, 0.74 to 0.99). Based on data from a single study, the specificity of IHC-based BRAF is estimated to be 0.90 (95% CI, 0.78 to 0.98).

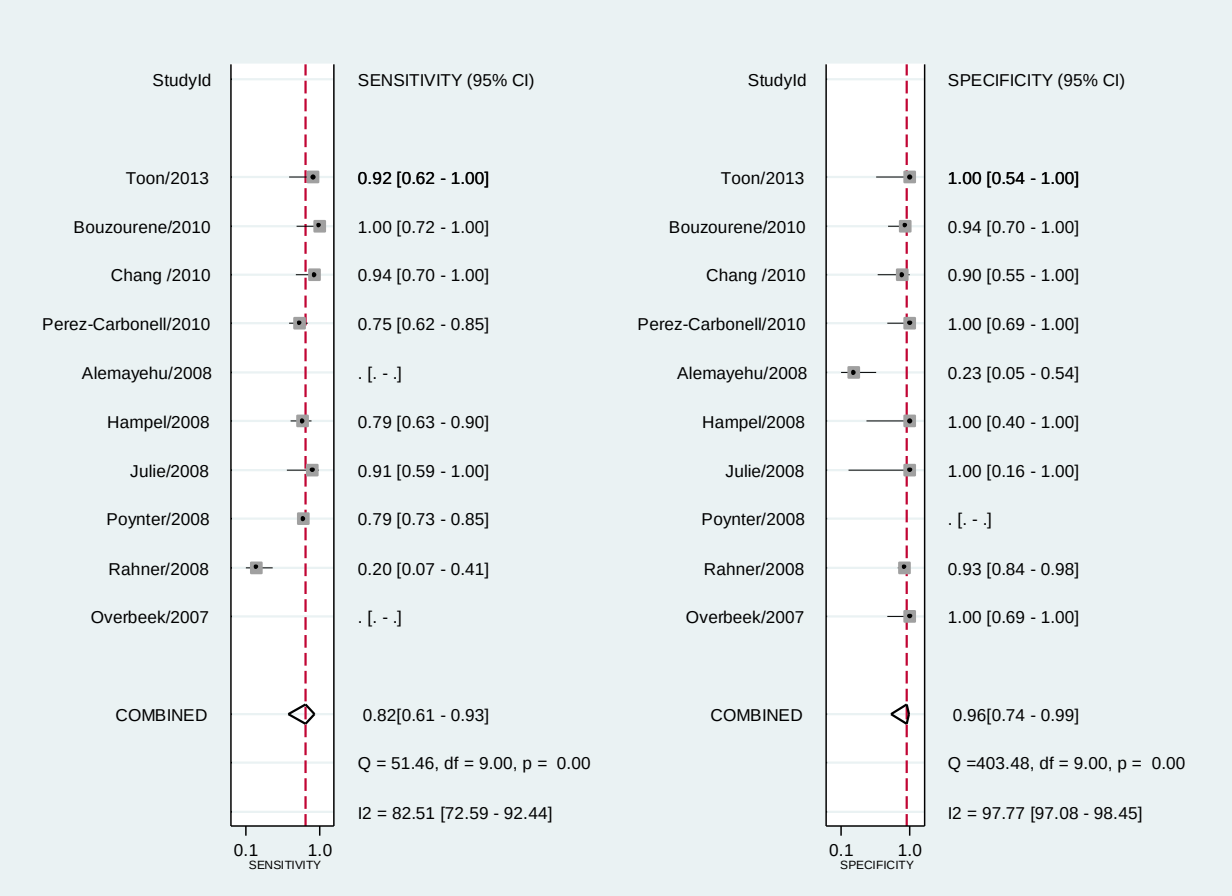
Forest plots for sensitivity and specificity of the PCR-based BRAF mutation test are presented in Figure 9. Forest plots for sensitivity and specificity of MLH1 promoter hypermethylation are presented in Figure 10. As shown in the forest plots, there appears to be an outlier among studies contributing to the pooled estimate of sensitivity for MLH1 promoter hypermethylation (Rahner 2008).[73] There also appears to be an outlier among studies contributing to the pooled estimate of specificity of MLH1 promoter hypermethylation (Alemeayehu 2008).[76] If these two studies are removed, the sensitivity for MLH1 promoter hypermethylation is 0.80 (95% CI, 0.76 to 0.85; $I^2 = 11\%$). When these studies are removed, the specificity of MLH1 promoter hypermethylation becomes 0.97 (95% CI, 0.87 to 0.99; $I^2 = 0\%$).

Figure 9: Forest Plots for Sensitivity and Specificity for BRAF-PCR



CI = confidence interval; PCR = polymerase chain reaction.

Figure 10: Forest Plots for Sensitivity and Specificity for MLH1 Promoter Hypermethylation



CI = confidence interval.

9.4.2 Positive predictive value and negative predictive Value of tumour-based BRAF-PCR, BRAF-IHC, and MLH1 promoter hypermethylation tests for likely sporadic CRC

Predictive values identify the proportion of patients who are correctly identified as having likely sporadic CRC after they have had the index tumour test. These values are dependent upon the prevalence of the condition under evaluation, along with the sensitivity and the specificity of the tests under evaluation. The mean prevalence of likely sporadic CRC among the BRAF-PCR, MLH1 promoter hypermethylation, and BRAF-IHC studies was 0.74, 0.64, and 0.46, respectively. Table C3 presents the predictive values for the BRAF-PCR, BRAF-IHC, and MLH1 promoter hypermethylation tests. BRAF-PCR and MLH1 promoter hypermethylation tests have high PPVs and low I^2 values, giving confidence that those patients who have a positive test will have no germline mutation and have likely sporadic CRC. Data from one study indicate that BRAF-IHC has a lower PPV, suggesting that approximately 33% of the patients who have a positive test will in fact have a germline mutation.

The NPVs give a picture of uncertainty. Approximately 83% of patients who have a negative MLH1 promoter hypermethylation test will have a germline mutation. When the BRAF-PCR test is utilized, approximately 68% of those with a negative BRAF-PCR will have a germline

mutation. Based on data from one study, 72% of those with a negative BRAF-IHC will have a germline mutation.

Table C3: Predictive Values for the BRAF-PCR, BRAF-IHC, and MLH1 Promoter Hypermethylation Tests

	Studies (n)	Positive Predictive Values (95% CI)	Studies (n)	Negative Predictive Values (95% CI)
BRAF-PCR	7	0.96 (0.92 to 0.99)	7	0.68 (0.66 to 0.70)
BRAF-IHC	1	0.67 (0.26 to 0.94)	1	0.72 (0.62 to 0.79)
MLH1 Promoter Hypermethylation	7	0.94 (0.89 to 0.99)	7	0.83 (0.78 to 0.87)

CI = confidence interval; IHC = immunohistochemistry; PCR = polymerase chain reaction.

From these analyses, tumour MLH1 promoter hypermethylation testing has the highest sensitivity (0.82 versus 0.57 for BRAF-PCR and 0.36 for BRAF-IHC) to detect likely sporadic CRC. Therefore, MLH1 promoter hypermethylation testing appears to have the best ability to significantly reduce the likelihood of LS being present. PCR-based BRAF mutation tumour testing has the highest specificity (0.98 versus 0.96 for MLH1 promoter hypermethylation testing and 0.90 for BRAF-IHC). Therefore, PCR-based BRAF mutation tumour testing to reduce the likelihood of diagnosing LS will result in the fewest number of patients with LS being misdiagnosed as having likely sporadic CRC. Conclusions about the diagnostic accuracy of IHC-based BRAF mutation tumour testing are difficult, due to a limited amount of published data available.

Clinical Review: Clinical Utility of dMMR Testing

Due to the overlap in studies addressing Questions 4 and 5, the results for these questions are presented together:

4. What is the clinical utility of dMMR testing for improving health outcomes of CRC patients who do not receive adjuvant chemotherapy?
5. What is the clinical utility of dMMR testing for improving health outcomes of colon cancer patients who receive adjuvant chemotherapy?

10. Methods

10.1 Literature Search Strategies

The literature search was performed by an information specialist using a search strategy peer-reviewed according to PRESS guidance.[17]

Three previously identified systematic reviews/meta-analyses,[6,80,81] which identified 62 unique studies of potential relevance for these two questions, were updated with a new search of the literature published after the date of the latest search from the review by Des Guetz et al.[80] The one concern regarding the quality of these reviews is that in two of the reviews, only the PubMed database was searched, with non-transparent terminology. However, other sources were included such as bibliographies of reviews.

In a new search, published literature was identified by searching the following bibliographic databases: MEDLINE (1946 to current) with in-process records and daily updates via Ovid;

Embase (1974 to current) via Ovid; The Cochrane Library (2015, Issue 1) via Wiley; and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH, and keywords. The main search concepts were survival or prognosis, and colorectal neoplasms and microsatellite instability (MSI) or DNA mismatch repair (dMMR).

No filter was applied to limit retrieval to particular study types. Where possible, retrieval was limited to the human population and English or French documents, with a database entry date limit of 2008 to February 2015, which is based on the last recorded date that searching was performed in the previously identified reviews. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies. The search was conducted from February 23 to 24, 2015. A search update was conducted on March 1, 2016. Additional articles published since the initial search and that met the selection criteria but were not included in the analysis are provided in Appendix 2.

Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist (www.cadth.ca/resources/finding-evidence/grey-matters), which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry. See Appendix 1 for more information on the grey literature search strategy.

10.2 Selection Criteria and Methods

Studies suitable for inclusion were selected from those identified through the literature search, including those identified through the three previously identified systematic reviews, using the criteria listed below.

Population	*Question 4*: stage II or III CRC patients (any age) who do not receive adjuvant chemotherapy *Question 5*: stage II and stage III colon cancer patients (any age) undergoing adjuvant chemotherapy
Intervention/ Study Test	Positive deficient mismatch repair (dMMR) tumour test; dMMR: MSI-high, MSI-high/MSI-low, suggestive IHC
Comparators	Negative dMMR tumour test; proficient mismatch repair (pMMR: microsatellite stable, non-suggestive IHC)
Outcomes	Survival rates in CRC patients (progression-free survival, overall survival), recurrence rates, death rates
Study Types	RCTs, prospective or retrospective observational (non-interventional) studies with a control group (cohort, case-control)

It should be noted that the stage and type of CRC were not pre-specified in the published protocol.[1] However, consultations with clinical experts resulted in the following suggestions for changes to inclusion criteria: First, it was agreed that the study questions about the prognostic and predictive values of dMMR tumour testing are applicable only to stage II and III CRC. This was mainly because adjuvant chemotherapy was not considered as a standard treatment option for stage I (for which resection of the affected polyp or section of intestine and nearby lymph nodes is the standard treatment) or stage IV CRC patients (for whom chemotherapy is usually given as a primary treatment option). Therefore, studies that included patients with stage I or IV

CRC were not included in the review for Question 5. In order to be consistent with the patient population analyzed for Question 4, Question 4 was also intended to include stage II and stage III CRC patients. Additionally, because clinical experts have suggested that rectal cancer is usually treated with adjuvant radiation therapy or a combination of radiation therapy and chemotherapy, the study population for Question 5 was limited to colon cancer patients.

10.3 Exclusion Criteria

Studies were excluded if they:

- did not include a clear explanation about the type and staging of cancer, type of adjuvant chemotherapy, and the proportion of study participants who received chemotherapy
- did not report the study outcomes separately for patients who were treated with adjuvant chemotherapy and those who were not
- presented the study outcomes in the form of graphs only
- did not include sufficient outcome data (e.g., reported *P* values only)
- did not perform MSI and/or IHC testing on tumours

  or

- were duplicate publications, narrative reviews, or editorials.

Two reviewers (NA and CV) independently screened the titles and abstracts of records identified in the literature search for relevance using a predefined checklist (Appendix 6). Any discrepancies between reviewers were resolved by discussion until consensus was reached. Full-text copies of any items that passed title and abstract review, as well as of the 52 primary studies identified from previously published systematic reviews, were retrieved and assessed by two independent reviewers for inclusion (NA and CV or JJ) using a checklist (Appendix 11), which incorporated explicit predetermined criteria. A third reviewer was consulted when necessary, and any disagreement between reviewers was discussed until consensus was reached.

For the review of literature related to Question 4, we included studies that involved colon cancer, rectal cancer, or a mix of colon and rectal cancer patients, while the review for Question 5 included studies that focused on colon cancer. Systematic reviews, HTAs, and guideline documents identified during scoping were also reviewed for potentially relevant primary studies. The review of systematic reviews resulted in the identification of 52 primary studies of potential relevance for Questions 4 and 5, full-text copies of which were retrieved and assessed for relevance.

10.4 Data Extraction

One reviewer performed data extraction for each article (NA or JJ) using pre-drafted data extraction forms (Appendix 17). A second reviewer (GB or NA) checked the abstracted data for accuracy. The reviewers piloted data extraction forms a priori, and performed a calibration exercise using five studies to ensure consistency between the reviewers.

10.5 Critical Appraisal of Individual Studies

The methodological quality of the randomized controlled trials (RCTs) was assessed using the Cochrane Risk of Bias tool.[82] This tool contains six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. Within each domain, the risk of bias was graded as high, low, or unclear, according to the guidance provided in the *Cochrane Handbook for Systematic Reviews of Intervention*.[82] For the assessment of the methodological quality of non-randomized trials and observational studies, in addition to the four common sources of bias (selection, performance, attrition, and detection biases), other criteria suggested by the *Cochrane Handbook* were also considered, such as appropriateness of the study design and adequate control of confounding[83] (Appendix 14). One reviewer conducted the quality assessment of each study, which was checked by a second reviewer.

10.6 Data Analyses and Synthesis

Comparability of the studies was explored through a description of the methodological characteristics of the included studies (i.e., population, interventions, and outcome measures). When two or more comparable studies measuring the same quantitative outcomes were identified, pooled estimates of the outcome measures were calculated with meta-analysis. Data from all selected studies, including those identified by the previous systematic reviews and meta-analysis, were included in our analysis. When the studies were not comparable in terms of population, interventions, or outcome measures, a formal meta-analysis was not performed. Instead, the individual studies were described and synthesized using a narrative approach.

10.7 Meta-analysis

The outcomes for the prognostic implications of dMMR tumour testing (Study Questions 4 and 5) were estimates of the relative risk (RR) of overall survival (OS), disease-free survival (DFS), or recurrence rates of cancer for patients with dMMR tumours relative to those with proficient tumour DNA mismatch repair (pMMR). The data most often available for abstraction were unadjusted hazard ratios (HRs) for dMMR versus pMMR, while a few studies provided the raw number of events in both groups from the trial to allow a direct estimation of a RR. Thus, meta-analysis was conducted by pooling the unadjusted HRs using the software STATA SE 14.1.[84] There were not sufficient raw data available to use the Cochrane Collaboration's software Review Manager 5.3, which requires the number of events and non-events for each study.[85]

10.8 Heterogeneity

When there was more than one study, pooling of the RR of two or more studies was conducted with the command "metan" in STATA under a random-effects assumption using the method by DerSimonian and Laird, and the estimate of heterogeneity was generated from the Mantel–Haenszel model. Because of anticipated clinical heterogeneity, results were stratified by pre-specified subgroups of stage of cancer and type of chemotherapy regimen. Statistical heterogeneity across the remaining studies was assessed descriptively with I^2, with greater than 50% being moderate heterogeneity and greater than 70% being considerable heterogeneity as suggested by the *Cochrane Handbook of Systematic Reviews*.[86] The formal test for heterogeneity with the Q statistic (based on chi-squared, where I^2= (Q–df)/Q) was also provided, but because there were few studies when meta-analysis was conducted, possible causes of heterogeneity could not be explored with post-hoc subgroup analyses, sensitivity analyses (e.g., based on study quality) or other appropriate methods, such as repeating the analysis after excluding outliers. If there were only two studies in one meta-analysis and high statistical heterogeneity was detected, a narrative description of each of the two studies is provided.

10.9 Missing Data

Few studies reported all of the required data to conduct the meta-analysis and different methods were used to impute the missing data. To derive the missing information, we relied on the assumption that CIs for RR are often generated with a binomial distribution.[21]

Specifically, the 95% CIs for RR were assumed to be [exp(ln(RR)–1.96 SEln(RR), exp(ln(RR)+1.96 SEln(RR)], where SEln(RR) is the standard error (SE) of the natural log of the RR. Most often, the 95% CIs were provided and the SEln(RR) was estimated. Only a few studies provided for the number of events to allow the direct estimation of the SE of the natural log of RR with SEln(RR) =sqrt [(1/(number of events in dMMR) – (1/(number of subjects in dMMR)) + (1/ number of events in dMMR) – (1/(number of subjects in pMMR))].

In addition, the *P* values for each study were confirmed or newly estimated with the Microsoft Excel command = NORM.DIST(-(ABS(ln(RR)/SEln(RR))),0,1,2)*2, which is the two-sided *P* value for the z statistic for the difference from the value of 0 of the ln(RR) with standard error SEln(RR).

11. Summary of Clinical Evidence

11.1 Quantity of Research Available

The database search yielded a total of 1427 citations, of which 1,161 were excluded during the title and abstract review phase because they did not meet the screening criteria. Full-text copies of 265 articles were retrieved, while one article that was not available in full-text format was excluded from the review. Bibliographic review of the six identified systematic reviews,[6,55,80,87-89] two of which were identified during scoping,[6,80] yielded 52 additional references whose full-text documents were retrieved. Thus, a total of 311 full-text articles were screened for inclusion. Of these 311 articles, 107 did not provide sufficient information on the chemotherapy status of the study participants and were excluded, and the remaining 204 articles were categorized based on the chemotherapy status of the study participants for further screening. Sixty of these studies recruited CRC patients who did not receive adjuvant chemotherapy (chemo–), and were deemed relevant to Question 4, while 78 studies included CRC patients who received adjuvant chemotherapy following surgical resection of their tumours (chemo+), which were considered relevant to Question 5. The remaining 66 studies included a mix of patients who had or had not undergone adjuvant chemotherapy (chemo+ and chemo–). Of these 66 studies, 45 that did not present outcome data separately for chemo+ and chemo– arms were excluded, leaving 21 articles, which were deemed relevant to both Question 4 and Question 5. As a result, a total of 81 articles were screened for Question 4 and 99 articles for Question 5. After application of question-specific eligibility criteria, the review resulted in the inclusion of seven studies for Question 4 and 12 studies for Question 5.

The study selection process is presented in a PRISMA flowchart (Appendix 23).

11.2 Summary of Study Characteristics

11.2.1 CRC patients who do not receive adjuvant chemotherapy

Appendix 27 provides an overview of the seven studies that met the inclusion criteria for Question 4.[3,43,90-94] The included articles were published between 2000 and 2011, and were conducted in Australia,[94] Germany,[92] Ireland,[90] Italy,[93] the Netherlands,[95] the United Kingdom,[91] or the United States,[3] one in each country. Two studies included CRC patients who were enrolled in previously conducted RCTs.[3,91] The remaining five studies seemed to have prospective cohort,[90,93] historical cohort,[92,94] or case-control[95] study designs.

Four of the seven studies conducted PCR-based MSI tumour testing,[90,92,94,95] one used IHC testing,[91] and two used MSI and/or IHC testing strategies[3,93] for the detection of DNA dMMR.

The prognostic effect of dMMR tumour testing was reported in terms of OS in four studies,[90,92-94] DFS in one study,[95] and relapse rate in three studies.[3,91,95] Three of the studies reported on the outcomes of stage II,[90,91,95] and four of them on stage III[3,92-94] CRC patients.

11.2.2 Colon cancer patients who receive adjuvant chemotherapy

Appendix 28 provides an overview of the 12 studies that met the inclusion criteria for Question 5.[3,92,96-105] The included articles were published between 2001 and 2015. One multinational study was conducted in Europe,[96] three studies in the United States,[3,100,105] three in Korea,[97,99,102] two in France,[101,103] and one in each of the following countries: China,[98] Germany,[92] and the Netherlands.[104]

Five studies included colon cancer patients who were enrolled in previously conducted RCTs.[3,96,100,104,105] The remaining seven studies seemed to have prospective,[102] or historical[3,96,100,104,105] cohort study designs. All of the 12 included studies reported on stage III colon cancer.[3,92,96-105] Two studies also reported on the outcomes of stage II colon cancer patients.[96,102]

Six of the 12 studies conducted PCR-based MSI tumour testing,[92,96,97,99,104,105] two used IHC testing,[98,103] and four used MSI and/or IHC testing strategies[3,100-102] for the detection of DNA dMMR.

The prognostic effect of dMMR tumour testing in patients with stage II and III colon cancer who received adjuvant chemotherapy following surgical resection of their primary tumours was reported in terms of DFS in 10 studies,[96-105] OS in eight studies,[92,96-98,100-102,105] and relapse rate in three studies.[3,103,104]

11.3 Summary of Critical Appraisal

11.3.1 CRC patients who do not receive adjuvant chemotherapy

Appendix 32 provides details about the critical appraisal of included studies for Question 4. The majority of studies included for Question 4 were non-randomized studies and are therefore at risk of selection bias.[90,92-95] While two studies (Hutchins, Sinicrope)[3,91] were based on participants in a randomized trial, the analyses were based on subgroups in each treatment arm, removing the benefits of randomization. Study groups were comparable at baseline in two studies,[90,95] and it was unclear if they were comparable in one.[91] In four studies, there were differences in baseline characteristics in the study groups that were not accounted for at the design stage.[3,92-94] All studies were at low risk of reporting bias due to selective reporting of the main outcome and all studies were at low risk of detection bias due to differences in how outcomes were determined between groups. In four studies, the risk of performance bias, due to potential differences in care provided to the two groups, was considered to be high[92,94] or unclear.[91,95]

11.3.2 Colon cancer patients who receive adjuvant chemotherapy

Appendix 33 provides details about the critical appraisal of included studies for Question 5. All included studies for Question 5 involved non-random allocation. While this increases the risk of selection bias, baseline patient characteristics were comparable between groups in five studies.[97,98,100,104,105] None of the studies were at high risk of detection or reporting bias; there was no evidence of systematic differences between groups in how outcomes were determined

or of selective reporting of outcomes. The risk of performance bias was high or unclear in all studies, except two in which blinding occurred.[98,101] Potential confounders were described in most studies; however, they were not controlled or adjusted for in the analyses; four studies adjusted for confounding using multivariable regression.[3,99,100,102]

11.4 Summary of Findings

11.4.1 CRC patients who do not receive adjuvant chemotherapy

Tables D1 and D2 show the RRs, along with their 95% CIs, for the comparison of chemo-CRC patients who had a dMMR tumour versus those with a tumour with pMMR in stage II and III CRC, respectively. These relative effect measures have been estimated based on HRs that represented the probability of death (not survival) for OS, and the probability of death or disease relapse for DFS rates. Therefore, RRs smaller than 1 indicate a lower probability of death (better survival) in patients with dMMR tumours than in those with pMMR tumours. More details on the definitions of the reported outcomes and follow-up times are reported in Appendix 35.

Table D1: Estimated Relative Effect Measures for the Comparison of Stage II Colorectal Cancer Patients With dMMR Tumours Versus Those With pMMR Tumours Who Did Not Receive Adjuvant Chemotherapy

Author, Year	Outcome	RR	95% CI		*P* Value
			Lower limit	Upper limit	
Brosens, 2011[95]	DFS	0.40	0.15	1.04	0.060
Curran, 2000[90]	OS	0.95	0.41	2.17	0.900
Brosens, 2011[95]	Relapse	0.33	0.09	1.25	0.161
Hutchins, 2011[91]	Relapse	0.54	0.30	0.97	0.040

CI = confidence interval; DFS = disease-free survival; dMMR = deficient mismatch repair; OS = overall survival; pMMR = proficient mismatch repair; RR = relative risk.

Table D2: Estimated Relative Effect Measures for the Comparison of Stage III Colorectal Cancer Patients With dMMR Tumours Versus Those With pMMR Tumours Who Did Not Receive Adjuvant Chemotherapy

Author, Year	Outcome	RR	95% CI		*P* Value
			Lower limit	Upper limit	
Dietmaier, 2006[92]	OS	0.99	0.49	1.98	0.993
Lanza, 2006[93]	OS	0.66	0.49	0.88	0.005
Elsaleh, 2001[94]	OS	0.89	0.58	1.40	0.644
Sinicrope, 2011[3]	Relapse	0.75	0.51	1.11	0.344

CI = confidence interval; DFS = disease-free survival; dMMR = deficient mismatch repair; OS = overall survival; pMMR = proficient mismatch repair; RR = relative risk.

The results of the pooled analyses of the reported outcome measures are displayed in Table D3, and the corresponding forest plots are shown in Appendix 36.

a) Outcomes in stage II CRC

Due to paucity of data, the pooled analysis was limited to one outcome: relapse rate. The pooled results from two studies involving stage II CRC[91,95] showed statistically lower relapse rates in patients with dMMR tumours when compared with those who had pMMR tumours (pooled RR, 0.50; 95% CI, 0.29 to 0.85; *P* = 0.011). No heterogeneity was detected between the

two studies (I^2 = 0%). Limited data from one individual study each suggested that there were no statistically significant differences between patients with dMMR tumours and those with pMMR tumours in terms of DFS (RR, 0.40; 95% CI, 0.15 to 1.04; *P* = 0.06)[95] and OS (RR, 0.95; 95% CI, 0.41 to 2.17; *P* = 0.900).[90]

b) Outcomes in stage III CRC

Due to paucity of data, the pooled analysis was limited to one outcome: OS. The pooled results from three studies involving stage III CRC[92-94] showed a statistically improved OS in patients with dMMR tumours, when compared with those with pMMR tumours (RR, 0.75; 95% CI, 0.59 to 0.94; *P* = 0.014). No heterogeneity was detected between the studies (I^2 = 0%) Limited data from a single study suggested that there was no statistically significant difference between patients with dMMR tumours and those with pMMR tumours in terms of relapse rate (RR, 0.75; 95% CI, 0.51 to 1.11); *P* = 0.344).[3] None of the included studies reported on DFS in stage III CRC patients who did not receive adjuvant chemotherapy according to their tumour dMMR status.

Table D3: Meta-analyses of the Outcomes Reported in the Studies Included for Question 4

Outcome	Number of Studies	Pooled RR	95% CI		*P* value	I^2
			Lower limit	Upper limit		
Stage II CRC						
DFS	1[95]	0.40	0.15	1.04	0.060	NA
OS	1[90]	0.95	0.41	2.17	0.900	NA
Relapse	2[91,95]	0.50	0.29	0.85	0.011	0%
Stage III CRC						
OS	3[92-94]	0.75	0.59	0.94	0.014	0%
Relapse	1[3]	0.75	0.51	1.11	0.344	NA

CI = confidence interval; CRC = colorectal cancer; DFS = disease-free survival; NA = not applicable; OS = overall survival; RR = relative risk.

11.4.2 Colon cancer patients who receive adjuvant chemotherapy

The outcome variables (DFS, OS, and relapse rate) were included in separate pooled analyses based on the stage of colon cancer (i.e., stage II and III). Then, within each category, subgroup analyses were carried out to explore potential variability in pooled estimates of effect based on the type of adjuvant chemotherapy. The subgroups were defined as follows: 1) 5-FU, if the patients received fluorouracil (5-FU or capecitabine) with or without either folinic acid (leucovorin) or levamisole or both; 2) oxaliplatin-based, if the patients were treated with 5-FU plus oxaliplatin with (FOLFOX) or without (XELOX) folinic acid; 3) irinotecan-based, if the patients received 5-FU plus irinotecan and folinic acid (FOLFIRI); and 4) mixed, if the study participants underwent various treatment protocols. More details on the definitions of outcome variables and adjuvant chemotherapy regimens used in the included studies are provided in Appendices 8B and 9B.

Tables D4 and D5 show the RRs along with their 95% CIs for the comparison of chemo+ patients whose tumours exhibited dMMR versus those who had pMMR tumours in stage II and III colon cancer, respectively. These relative effect measures have been estimated based on HRs that represented the probability of death (not survival) for OS, and the probability of death or disease relapse for DFS rates. Therefore, RRs (HRs) smaller than 1 indicate a lower probability of death (better survival) in patients with dMMR tumours than in those with pMMR

tumours. More details on the definitions of the reported outcomes and follow-up times are reported in Appendix 35.

Table D4: Estimated Relative Effect for the Comparison of Stage II Colon Cancer Patients With dMMR Tumours Versus Those With pMMR Tumours Who Received Adjuvant Chemotherapy

Author, Year	Outcome	RR	95% CI		*P* Value
			Lower limit	Upper limit	
5-FU					
Klingbiel, 2015[96]	DFS	0.22	0.05	0.91	0.037
Yoon, 2011[102]	DFS	0.60	0.54	0.66	< 0.001
Klingbiel, 2015[96]	OS	0.18	0.02	1.32	0.092
Yoon, 2011[102]	OS	0.00	0.00	0.001	< 0.001
Irinotecan-based					
Klingbiel, 2015[96]	DFS	0.30	0.09	0.96	0.042
Klingbiel, 2015[96]	OS	0.14	0.02	1.03	0.053
Mixed treatment					
Klingbiel, 2015[96]	DFS	0.26	0.10	0.65	0.004
Klingbiel, 2015[96]	OS	0.16	0.04	0.64	0.010

5-FU = fluorouracil; CI = confidence interval; DFS = disease-free survival; dMMR = deficient mismatch repair; OS = overall survival; pMMR = proficient mismatch repair; RR = relative risk.

Table D5: Estimated Relative Effect for the Comparison of Stage III Colon Cancer Patients With dMMR Tumours Versus Those With pMMR Tumours Who Received Adjuvant Chemotherapy

Author, Year	Outcome	RR	95% CI		*P* Value
			Lower limit	Upper limit	
5-FU					
Klingbiel, 2015[96]	DFS	0.56	0.32	0.96	0.035
Li, 2013[98]	DFS	0.60	0.26	1.43	0.250
Bertagnolli,2011[100]	DFS	0.98	0.74	1.30	0.910
Yoon, 2011[102]	DFS	0.50	0.44	0.57	0.030
Zaanan, 2010[103]	DFS	0.66	0.38	1.15	0.142
Westra, 2005[104]	DFS	0.69	0.49	0.97	0.000
Watanabe, 2001[105]	DFS	0.94	0.89	0.99	0.020
Klingbiel, 2015[96]	OS	0.51	0.26	1.00	0.050
Li, 2013[98]	OS	0.60	0.25	1.41	0.249
Bertagnolli,2011[100]	OS	0.97	0.77	1.23	0.810
Yoon, 2011[102]	OS	1.10	0.95	1.26	0.830
Dietmaier, 2006[92]	OS	0.89	0.32	2.52	0.869
Watanabe, 2001[105]	OS	1.21	0.90	1.63	0.200
Sinicrope, 2011[3]	Relapse	0.67	0.47	0.94	0.019
Zaanan, 2010[103]	Relapse	1.30	0.71	2.39	0.399

Author, Year	Outcome	RR	95% CI		*P* Value
			Lower limit	Upper limit	
Westra, 2005[104]	Relapse	0.67	0.37	1.21	0.235
Oxaliplatin-based					
Kim, 2013[99]	DFS	0.83	0.38	1.79	0.635
Oh, 2013[97]	DFS	1.05	0.55	2.02	0.874
Zaanan, 2011[101]	DFS	0.30	0.10	0.90	0.032
Zaanan, 2010[103]	DFS	0.17	0.04	0.68	0.012
Oh, 2013[97]	OS	0.96	0.86	1.07	0.437
Zaanan, 2011[101]	OS	0.30	0.04	2.12	0.227
Oh, 2013[97]	Relapse	0.93	0.38	2.28	0.865
Zaanan, 2010[103]	Relapse	0.00	0.00	1.69	0.121
Irinotecan-based					
Klingbiel, 2015[96]	DFS	0.82	0.48	1.40	0.467
Bertagnolli,2011[100]	DFS	1.19	0.96	1.48	0.120
Klingbiel, 2015[96]	OS	0.94	0.52	1.72	0.841
Bertagnolli,2011[100]	OS	1.06	0.86	1.30	0.600
Mixed treatments					
Klingbiel, 2015[96]	DFS	0.67	0.46	0.99	0.044
Li, 2013[98]	DFS	0.60	0.27	1.32	0.204
Bertagnolli,2011[100]	DFS	0.82	0.60	1.11	0.199
Klingbiel, 2015[96]	OS	0.70	0.44	1.09	0.114
Li, 2013[98]	OS	0.73	0.33	1.61	0.435
Bertagnolli,2011[100]	OS	0.88	0.63	1.22	0.443

5-FU = fluorouracil; CI = confidence interval; DFS = disease-free survival; dMMR = deficient mismatch repair; OS = overall survival; pMMR = proficient mismatch repair; RR = relative risk.

The results of the meta-analyses of the reported outcome measures are displayed in Table D6, and the corresponding forest plots are shown in Appendix 37.

a) Outcomes in stage II colon cancer

The pooled analysis of data from two studies involving stage II colon cancer[96,102] showed that there was no statistically significant difference, in terms of DFS and OS rates, between dMMR and pMMR tumours in patients who received 5-FU. The limited data from the study by Klingbiel et al.[96] indicated that, when compared with patients with pMMR tumours, patients with stage II dMMR tumours could benefit from 5-FU plus irinotecan in terms of DFS (RR = 0.30; 95% CI, 0.09 to 0.98); *P* = 0.046), but not OS (RR = 0.14; 95% CI, 0.02 to 1.00; *P* = 0.051).

A high level of heterogeneity (I^2= 97.0%; *P* value < 0.001) was observed between the two studies that were included in the subanalysis for OS in 5-FU recipients.[96,102] The diversity of inclusion criteria, source of study data, and length of follow-up between the two studies are likely to have contributed to the observed heterogeneity of their outcome measures. The study by Klingbiel et al.[96] recruited colon cancer patients who received adjuvant chemotherapy from the Pan-European Trial in Adjuvant Colon Cancer (PETAAC) multinational study with an 84-month follow-up, while Yoon et al.[102] prospectively enrolled all patients who underwent surgical resection and received

adjuvant chemotherapy, at a single medical centre in Korea, and followed them for up to 48 months. Both studies restricted their inclusion criteria to patients who were younger than 75 years of age, but Yoon et al. also limited their study population to those who had an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1. The ECOG score describes a patient's level of functioning in terms of self-care, daily activity, and physical ability (walking, working, etc.) and consists of five levels, with 0 representing no-restriction of function and 5 representing death.[106] Another factor contributing to the heterogeneity is the lack of death event (100% OS) in the dMMR tumour arm in Yoon's study, which has resulted in a RR of 0 for overall probability of death. A sensitivity analysis, which was performed by adding a single death event to the dMMR tumour arm in this study, resulted in a RR of 0.12, which is not clinically different from that reported by Klingbiel at al. (RR = 0.18).

b) Outcomes in stage III colon cancer

The results of our pooled analysis showed a statistically improved DFS in subgroups of dMMR tumour patients who received 5-FU (RR = 0.70; 95% CI, 0.51 to 0.96; *P* = 0.026), when compared with those with pMMR tumours. Similar results were obtained for DFS in mixed chemotherapy regimens (RR = 0.74; 95% CI, 0.59 to 0.94; *P* = 0.011), with no between-study heterogeneity. However, no statistical difference was found between the tumour dMMR and pMMR groups of patients who received oxaliplatin-based adjuvant chemotherapy.

There was significant heterogeneity in the meta-analysis for DFS in the 5-FU subgroup, which indicated potential methodological differences (I^2 = 93.0%; *P* < 0.001). A closer examination of the seven studies included in this meta-analysis[96,98,100,102-105] revealed a possibility of different risk profiles between patients included in the study by Yoon et al.[102] and those recruited by the remaining six studies. Yoon's study limited the inclusion criteria to patients who were younger than 75 years of age and had a better functional status (ECOG score of 0 or 1). It has been shown that CRC patients with higher ECOG score have a lower response to chemotherapy and higher morbidity and mortality rates.[107] Therefore, with the hypothesis that the restriction of study population to younger patients with better ECOG performance scores might have resulted in between-study variability, the pooled analysis was repeated without the Yoon study. After exclusion of this study, the pooled RR remained statistically significant (RR = 0.82; 95% CI, 0.69 to 0.98), but heterogeneity decreased (I^2 = 44.6%; *P* = 0.01).

Our pooled analysis did not find any statistical differences between patients with dMMR tumours and those with pMMR tumours in terms of OS or relapse rates for any of the reported chemotherapy regimens (see Table D6 for details). However, a high level of heterogeneity (I^2 = 92.4%; *P* value < 0.001) was present in the subanalysis for two studies reporting on relapse rates of patients who received oxaliplatin-based chemotherapy.[97,103] As shown in Table D6, the CI for the pooled estimate of effect includes values between 0 and 100, which indicates a high level of uncertainty. This could have resulted from the relatively smaller sample sizes in dMMR tumour groups, when compared with those in the pMMR tumour groups, in both studies (16 versus 111 in the study by Oh et al.[97] and 12 versus 97 in Zaanan et al. [2010][103]). Additionally, in the Zaanan study, no relapse occurred in the dMMR tumour group during follow-up, which resulted in an RR of 0 for this outcome. Our sensitivity analysis predicted that the pooled effect size would have been equal to 0.44, had a single relapse happened in the dMMR tumour group in this study. This high level of heterogeneity between these two studies meant that interpretation of the pooled RR for relapse rate was not appropriate, and that the results of these studies should be interpreted individually. However, no statistically significant differences were reported between the dMMR and pMMR patients, who received oxaliplatin-based chemotherapy in terms of relapse rates in either

the study by Oh et al.[97] (RR = 0.93; 95% CI, 0.38 to 2.28; *P* = 0.865) or the one by Zaanan et al.[103] (RR = 0.93; 95% CI, 0.38 to 2.28; *P* = 0.865) (Table D5).

Table D6: Meta-analyses of the Outcomes Reported in the Studies Included for Question 5

Outcome	Chemotherapy Type	Number of Studies	Pooled RR	95% CI		*P* Value	I^2
				Lower limit	Upper limit		
Stage II colon cancer							
DFS	5-FU	2[96,102]	0.48	0.21	1.08	0.075	45%
	Irinotecan-based	1[96]	0.30	0.09	0.96	0.042	NA
	Mixed	1[96]	0.26	0.10	0.65	0.004	NA
OS	5-FU	2[96,102]	0.005	0.000	5.11	0.134	97%
	Irinotecan-based	1[96]	0.14	0.02	1.03	0.053	NA
	Mixed	1[96]	0.16	0.04	0.64	0.010	NA
Stage III colon cancer							
DFS	5-FU	7[96,98,100,102-105]	0.70	0.51	0.96	0.026	93%
	Oxaliplatin-based	4[97,99,101,103]	0.55	0.26	1.16	0.115	62%
	Irinotecan-based	2[96,100]	1.07	0.78	1.49	0.670	37%
	Mixed	3[96,98,100]	0.74	0.59	0.94	0.011	0%
OS	5-FU	6[92,96,98,100,102,105]	1.01	0.85	1.20	0.937	36%
	Oxaliplatin-based	2[97,101]	0.82	0.37	1.79	0.615	27%
	Irinotecan-based	2[96,100]	1.04	0.86	1.27	0.666	0%
	Mixed	3[96,98,100]	0.80	0.62	1.04	0.091	0%
Relapse	5-FU	3[3,103,104]	0.80	0.53	1.18	0.256	47%
	Oxaliplatin-based	2[97,103]	0.01	0.00	100.35	0.343	92%

5-FU = fluorouracil; CI = confidence interval; DFS = disease-free survival; dMMR = deficient mismatch repair; OS = overall survival; pMMR = proficient mismatch repair; RR = relative risk.

Economic Review: Cost-Effectiveness of dMMR Testing

6. What is the cost-effectiveness of dMMR testing in newly diagnosed CRC patients considering the following two sub-questions?

    c. What is the comparative cost-effectiveness of the following four dMMR testing strategies, taking into account their impact on the choice of using adjuvant chemotherapy for the CRC patient or not and on cancer prevention of first-degree family members of the CRC patient:

        - dMMR testing in all CRC patients
        - dMMR testing all CRC patients younger than 70 years old
        - dMMR testing only patients at high risk of LS based on the rBG
        - No dMMR testing in any CRC patients.

    a. What is the comparative cost-effectiveness of the following dMMR reflex testing algorithms for screening CRC patients for LS?

        - Initial four-panel IHC test (MLH1, MSH2, MSH6, PMS2), followed by germline testing if abnormalities are found in any gene
        - Initial four-panel IHC test (MLH1, MSH2, MSH6, PMS2), followed by BRAF testing if the MLH1 gene is abnormal, or germline testing if abnormalities are found in MSH2,MSH6,PMS2, or MLH1 with normal BRAF
        - Initial four-panel IHC test (MLH1, MSH2, MSH6, PMS2), followed by promoter hypermethylation if the MLH1 gene is abnormal, or germline testing if abnormalities are found in MSH2, MSH6, PMS2, or MLH1 without hypermethylation
        - Single-step MMR + BRAF V600E IHC. Genetic testing if abnormal MSH2, MSH6, or PSM2; or abnormal MLH1 with normal BRAF
        - Single-step MMR + BRAF V600E IHC. If MLH1 is abnormal and BRAF is normal, follow with MLH1 promoter hypermethylation. Genetic testing if abnormal MSH2, MSH6, or PSM2; or abnormal MLH1/normal BRAF without promoter hypermethylation

12. Methods

12.1 Literature Search Strategies

A review of the economic literature was undertaken to provide evidence to answer research Question 6. We reviewed the systematic reviews, meta-analyses, and HTAs identified during scoping to determine whether the research question(s), search strategies, inclusion, and exclusion criteria used in each systematic review, meta-analysis, and HTA matched the requirements of research Question 6.

A well-conducted, previously identified HTA by Snowsill et al.,[57] which identified 28 economic evaluations of potential relevance to this review, was updated with a search of the current literature. The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946 to current) with in-process records and daily updates via Ovid; EMBASE (1974 to 2015 Feb 20) via Ovid; The Cochrane Library (2015, Issue 1) via Wiley; and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH, and keywords. The main search concepts were hereditary nonpolyposis colorectal neoplasms (HNPCC) and microsatellite instability (MSI) or DNA mismatch repair (dMMR).

A filter was applied to limit retrieval to cost-effectiveness or cost-utility studies. Where possible, retrieval was limited to English or French documents and a database entry date of 2012 to the current date, which was based on the last recorded date on which searching was performed in the previously identified review. Conference abstracts were excluded from the search results. (See Appendix 1 for the detailed search strategies.) The search was conducted from February 23 to 24, 2015.

Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist (www.cadth.ca/resources/finding-evidence/grey-matters) which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry. See Appendix 1 for more information on the grey literature search strategy.

12.1.1 Selection criteria and methods

Studies suitable for inclusion were selected from those identified through the literature search, using the criteria listed in Table E1.

Table E1: Research Question of Interest for Economic Literature Review

Population	Intervention and Comparator	Outcome
Newly diagnosed CRC patients	At least 2 of the following screening strategies to identify patients who might have LS 1) No dMMR tumour screening 2) Tumour screen if meet 1 of the rBG 3) Tumour screen if younger than 70 years of age 4) Universal tumour screening **OR** At least 2 of the following reflex testing strategies to identify patients who might have LS 1) All patients to germline testing if abnormal tumour MMR IHC 2) Tumour PCR-based BRAF mutation test if abnormal MLH1 IHC; if normal BRAF or	Incremental cost per QALY Incremental cost per life-year Incremental cost per LS case detected

Population	Intervention and Comparator	Outcome
	abnormal IHC for other MMR proteins, send to germline MMR gene testing 3) MLH1 promoter hypermethylation if abnormal MLH1 IHC; if normal MLH1 promoter methylation or abnormal IHC for other MMR proteins, send to germline MMR gene testing 4) Tumour IHC-based mutated BRAF protein expression for all patients; if MLH1-IHC abnormal and BRAF-IHC normal, or abnormal IHC for other MMR proteins, send to germline MMR gene testing 5) Tumour IHC-based mutated BRAF expression for all patients; if MLH1 IHC abnormal and BRAF normal, tumour MLH1 promoter hypermethylation test. If BRAF-IHC normal and MLH1 promoter methylation normal, send to germline MMR gene testing. If IHC expression abnormal for other MMR genes, send to germline MMR gene testing. **OR** At least 2 of the following adjuvant chemotherapy strategies: 1) Tumour dMMR status is used for adjuvant chemotherapy decisions 2) Tumour dMMR status is not used for adjuvant chemotherapy decisions	

CRC = colorectal cancer; dMMR = deficient mismatch repair; IHC = immunohistochemistry; LS = Lynch syndrome; MMR = mismatch repair; PCR = polymerase chain reaction; QALY = quality-adjusted life-year; rBG = revised Bethesda Guidelines.

Two reviewers (GB, JJ) independently screened the titles and abstracts for relevance using a predefined checklist (Appendix 7). Studies were excluded if they did not meet the selection criteria. Any discrepancies between reviewers were resolved by consensus. Full-text copies of relevant titles and abstracts were retrieved, and assessed by two independent reviewers to make inclusion and exclusion decisions, using explicit predetermined criteria (Appendix 12). Discrepancies between the reviewers were resolved by consensus, and a third reviewer was consulted when necessary.

12.1.2 Data extraction

One reviewer performed data extraction for each article (GB) using pre-drafted data extraction forms (Appendix 18). A second reviewer (JJ) checked the abstracted data for accuracy.

12.1.3 Critical appraisal of individual studies

To help critically appraise the economic studies, the Scottish Intercollegiate Guidelines Network (SIGN) assessment tool was used.[108] This assessment tool includes 10 questions regarding the internal validity of the economic evaluation and two questions regarding the overall quality of the economic evaluation.

12.1.4 Data analyses and synthesis

A literature review involving a narrative summary of each included economic study was conducted. The cost-effectiveness results presented for each included study are focused on interventions that are common to those being evaluated in the primary economic analysis. In some of the included studies, incremental cost-effectiveness ratios (ICERs) between interventions of interest are not reported. However, they can be calculated based on other information provided in the publication (e.g., expected total costs and quality-adjusted life-years [QALYs] for interventions). In these cases, we present the calculated incremental cost-effectiveness as part of the narrative reviews.

13. Summary of Evidence

13.1 Quantity of Research Available

A total of 497 potential citations were identified by the systematic search. During title and abstract review, 435 of these citations were excluded because they were irrelevant to the question of interest. Full-text documents of the remaining 42 articles were retrieved. Among these articles, 30 were excluded during full-text screening. Seventeen studies were excluded because the starting population was not newly diagnosed CRC patients. Nine studies were excluded because they did not include at least two relevant comparators. Three studies were excluded because they did not include an economic evaluation. One study was excluded because it did not include a relevant cost-effectiveness outcome. Appendix 24 shows the PRISMA flowchart of the process used to identify and select studies during the review and the main reasons for exclusion.

13.2 Summary of Study Characteristics

Appendix 29 provides an overview of the characteristic of the 12 included studies. As shown, in seven of the included studies, the cost-effectiveness economic outcome used was the cost per MMR germline mutation carrier ("LS case") detected.[56,109-114] The other five studies projected outcomes beyond the number of LS cases detected. Three of these studies used a primary outcome of cost per life-year, while two studies used the cost-effectiveness outcome of cost per QALY.[115-117] Seven studies evaluated at least two of the LS screening strategies of interest in the primary economic evaluation.[111,113,115-119] Among studies using the cost per LS detected outcome, one study included universal and rBG screening,[111] while one included age younger than 70 years and "no testing" screening strategies. Among studies that used cost per life-year or cost per QALY as their outcome, three studies included no screening, rBG, and universal screening strategies;[115,117,118] one study included no testing and universal screening strategies;[116] and one study included no testing and screening patients younger than 70 years old.[119]

Seven studies evaluated at least two of the reflex testing strategies that are of interest to this review.[56,109,110,112,114,116,119] Among studies using the cost per LS case detected as their outcome, two studies included no supplementary tumour tests, tumour PCR-based BRAF testing for those with an abnormal MLH1 IHC expression, and MLH1 promoter hypermethylation testing for patients with an abnormal MLH1 IHC expression.[110,112] Two studies included a strategy with no supplementary tumour testing and a strategy with tumour PCR-based BRAF mutation testing for patients with an abnormal MLH1 IHC expression.[56,109] One study included no supplementary tumour testing and MLH1 promoter hypermethylation testing for patients with abnormal MLH1 IHC expression.[114] Both studies that used cost per life-year or cost per QALY as their outcome included a strategy of no supplementary tumour testing and a strategy of tumour PCR-based BRAF mutation testing for patients with an abnormal MLH1 IHC expression.[116,119] None of the

studies included reflex testing strategies that included tumour IHC-based mutated BRAF protein expression as supplementary testing.

None of the identified economic evaluations have assessed the impact of using tumour dMMR status to determine adjuvant chemotherapy.

13.3 Summary of Critical Appraisal

An assessment of each of the included economic evaluations, by item in the SIGN assessments, is provided in Table E2. As shown, based on Question 2.1 (i.e., how well was the study conducted?), all economic evaluations were judged to be of at least acceptable quality, with five of the economic studies judged to be of high quality.[115,116,118-120]

Table E2: Critical Appraisal Checklist for Included Studies

First Author, Year	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	1.10	2.1	2.2
Bessa, 2008[109]	Y	N	N	U	U	NA	N	N	N	U	+	Y
Gausachs, 2012[110]	Y	N	N	U	U	NA	Y	N	N	U	+	Y
Gould-Suarez, 2014[111]	Y	N	N	U	U	NA	Y	N	N	U	+	Y
Gudgeon, 2011[112]	Y	N	N	U	U	NA	Y	N	Y	U	+	Y
Ladabaum, 2011[115]	Y	Y	Y	U	U	Y	Y	Y	Y	Y	++	Y
Wang, 2012[118]	Y	Y	Y	U	U	Y	Y	N	Y	Y	++	Y
Mvundura, 2010[116]	Y	N	N	U	U	Y	Y	N	Y	Y	++	Y
Palomaki, 2009[56]	Y	N	N	U	U	NA	N	N	Y	U	+	Y
Severin, 2015[120]	Y	N	N	U	U	Y	Y	N	Y	Y	++	Y
Snowsill, 2015[119]	Y	Y	N	U	U	Y	Y	Y	Y	Y	++	Y
Yan, 2008[114]	Y	N	N	U	U	NA	N	N	N	U	+	Y
Gudgeon, 2013[113]	Y	N	N	U	U	NA	Y	N	N	U	+	Y

N = no; NA = not applicable U = unclear; Y = yes.
Note: High Quality: ++; Acceptable: +; Unacceptable: 0

13.4 Summary of Findings

A number of published economic evaluations have compared different screening strategies and the use of tumour BRAF and MLH1 promoter hypermethylation testing as part of reflex testing for LS. A detailed description of each study can be found in Appendix 38. No published economic studies were identified that evaluated the use of tumour dMMR testing to inform adjuvant chemotherapy decisions.

A number of published economic evaluations have compared at least two of the screening strategies that are of interest to our primary economic evaluation[57,111,115,116,118,120] (i.e., no testing, rBG, younger than 70 years, universal testing) although none have compared all four strategies together. Cost-effectiveness estimates varied by study, given that different outcome definitions and perspectives were taken. The incremental cost-effectiveness of universal screening versus no screening varied from US$22,522 per life-year gained[116] to €$98,149 per life-year gained.[120] The incremental cost-effectiveness of using the rBG criteria compared with no screening varied from US$30,000 per life-year gained[116] to €$77,268 per life-year gained.[120] The cost-effectiveness of universal screening compared with screening using the rBG criteria ranged from US$62,624 per life-year gained[116] to €$254,011 per life-year gained.[120] Two studies included screening CRC patients younger than 70 years. Snowsill reported that the incremental cost per QALY of screening CRC patients younger than 70 years old compared with no screening was £11,268,[119] while Gudgeon et al. estimated the incremental cost per LS case detected for universal screening compared with screening patients younger than 70 years old to be US$26,917.[113]

Variation in cost-effectiveness results in screening strategies between studies is likely due to differences in the assumed diagnostic accuracy of diagnostic tests, the testing strategy considered (e.g., IHC, germline, rule out supplemental tests), the costs of the diagnostic test, assumptions regarding the impact of LS-related cancer prevention and interventions, and the yield of relatives diagnosed with LS through testing for each CRC proband (person initially tested and diagnosed).

Some published studies have found that using supplementary tests in patients who show lack of expression in the MLH1 protein before germline testing may lead to lower costs and no loss of effectiveness compared with sending all patients to germline genetic testing with an abnormal IHC-based MMR test.[57,109,114,115,118] In these cases, the supplemental tests were assumed to have perfect specificity in detecting likely sporadic CRC and therefore not result in any false negative findings. Otherwise, if the specificity of tumour BRAF or tumour MLH1 promoter hypermethylation was not 100%, supplemental testing before sending patients with lack of expression of MLH1 protein would save money but would lead to fewer LS cases detected compared with sending all patients for germline testing without these exclusion tests.[56,110,112,121] For those studies that used the number of LS cases detected as their outcomes, the ICER of sending patients straight to germline genetic testing compared with using a supplemental test first ranged from £7,911[110] per LS case detected to US$3.8 million per LS case detected.[112] Mvundura et al. estimated the incremental cost per life-year of sending all patients showing tumour dMMR to germline genetic testing compared with sending patients with lack of tumour expression of MLH1 protein to tumour BRAF first to be US$273,915. Among the studies that included both reflex testing strategies with tumour BRAF and with tumour MLH1 promoter hypermethylation, one found the hypermethylation-based testing strategy to be cheaper and to result in the same number of LS cases detected than a strategy that included BRAF testing.[110] Others have reported tumour BRAF-based strategies to both cost more and be more effective. One study estimated the incremental cost per LS detected of a tumour BRAF-based reflex testing strategy to be US$19,007 compared with tumour MLH1 promoter hypermethylation–based reflex testing strategy,[112] while another study reported an ICER of £27,149/QALY.[119]

Variation in cost-effectiveness results of reflex testing strategies is likely due to differences in the assumed diagnostic accuracy of the supplemental tests, and the costs of testing in the various studies.

Although the findings from published economic evaluations on tumour dMMR testing provide some insights into the cost-effectiveness of different ways to implement tumour dMMR testing in newly diagnosed CRC patients, there remains a need to conduct a *de novo* economic evaluation. First, none of the published economic evaluations adopted a Canadian perspective. In addition, none of the publications evaluated all of the combinations of screening and reflex testing strategies that are relevant to the Canadian health care practices and of interest to this review. Finally, none of the identified studies considered the impact of using tumour dMMR status on guiding adjuvant chemotherapy choice.

Primary Economic Evaluation

14. Methods

14.1 Type of Economic Evaluation

A cost-utility analysis was conducted to compare various interventions related to tumour dMMR testing in newly diagnosed CRC patients and the subsequent identification of LS among the relatives of probands. A cost-utility analysis incorporates both mortality and quality of life impacts of a disease. The use of the cost per QALY outcome also allows for comparison with economic evaluations of other conditions and treatments.

14.2 Target Population

The starting target population of the model is individuals who are newly diagnosed with CRC. The model considers family as an aggregate by including probands with cancer and female or male relatives of newly diagnosed CRC patents who do not have a cancer but may be affected by the diagnosis of LS.

14.3 Comparators

There are multiple layers to the various treatment comparators that are evaluated in the economic evaluation. The first layer is made up of the various strategies to screen newly diagnosed CRC patients for LS. These strategies include:

1) No screening
2) Screening individuals who meet at least one criterion of the rBG
3) Screening individuals who are younger than 70 years old
4) Screening all patients.

Among the population eligible for screening, as determined by the respective screening strategy, the initial screen is assumed to be a four MMR protein IHC tumour test. The second layer, referred to as reflex testing strategies, consists of strategies that vary in terms of the sequence of testing to determine whether CRC patients would go on to receive germline genetic testing. Although all patients showing lack of expression in one of the MMR proteins could receive germline genetic testing, tumour BRAF mutation and MLH1 promoter hypermethylation tests can be used to help identify likely sporadic CRC cases, and therefore avoid the use of expensive germline genetic testing. Tumour BRAF testing can be done by either PCR or IHC-based techniques. The various reflex testing strategies being considered in the analysis are:

A. All to germline: All patients with tumours showing LoE of at least one of the four MMR proteins receive germline genetic testing.

B. Tumour BRAF mutation detection by PCR-based technique: Patients with tumours that have LoE in MLH2, PMS2, or MLH6 proteins receive germline genetic testing. Patients with tumours that show LoE of the MLH1 protein have their tumours tested for the BRAF V600E mutation by means of a PCR-based technique. Those patients with tumours that test

positive for the BRAF mutation are assumed to have sporadic CRC and therefore are not given a germline genetic test. Patients whose tumours test negative for the BRAF V600E mutation would go on to receive germline genetic testing;

C. **Tumour MLH1 promoter hypermethylation:** Patients with tumours that lack expression of MSH2, PMS2, or MSH6 proteins receive germline genetic testing. Patients with tumours that lack expression of the MLH1 protein have their tumours tested for MLH1 promoter hypermethylation. Those patients with tumours that show MLH1 promoter hypermethylation are assumed to have sporadic CRC and therefore are not given a germline genetic test. Patients with tumours that do not show MLH1 promoter hypermethylation go on to receive germline genetic testing.
D. **Tumour BRAF mutation detected by IHC-based technique:** All patients receive BRAF V600E tumour testing by means of an IHC-based technique. Patients whose tumours lack expression ofMSH2, PMS2, or MSH6 proteins receive germline genetic testing. Those patients with tumours that test positive for BRAF V600E are assumed to have sporadic CRC and, therefore, are not given a germline genetic test. Patients with tumours that test negative for the BRAF mutation and lack MLH1 protein expression go on to receive germline genetic testing.
E. **Tumour BRAF mutation detection by IHC and MLH1 promoter hypermethylation testing**- All patients receive tumour BRAF V600E mutation testing by means of IHC-based technique. Patients with tumours that lack expression of MSH2, PMS2, or MSH6 proteins receive germline genetic testing. Those patients with tumours that test positive for the BRAF V600E mutation are assumed to have sporadic CRC and therefore are not given a germline genetic test. Patients with tumours that have a negative BRAF V600E test but show LoE of the MLH1 protein receive a tumour MLH1 promoter hypermethylation test. Patients with tumours that test positive for MLH1 promoter hypermethylation are assumed to have sporadic CRC and are therefore not given germline genetic testing. Patients with tumours that do not show MLH1 promoter hypermethylation go on to receive germline genetic testing.

The third layer relates to whether tumour dMMR status results are used to guide decisions on adjuvant chemotherapy for stage 2 colon cancer patients who are at high risk of cancer recurrence. In total, 32 strategies are evaluated and a listing is provided in Appendix 39.

14.4 Perspective

The analysis was taken from the perspective of a publicly funded health care system. The costs from this perspective include the costs of medications that are covered in the provincial formularies for eligible patients and their relatives, in-patient costs, diagnostic tests, and physician fees for services that are covered in provincial fee schedules. Indirect costs, such as productivity losses, were not considered.

14.5 Time Horizon

A lifelong time horizon for both the newly diagnosed CRC patients and their relatives was used in the model.

14.6 Modelling

The current model estimates the expected costs, life-years, and QALYs of various screening and treatment strategies related to tumour dMMR testing in newly diagnosed CRC patients and the healthy relatives of patients identified to have LS. In patients with CRC, these strategies comprise different ways of using tumour dMMR testing to screen and test for LS, and on the use

of tumour dMMR status to support adjuvant chemotherapy choices. An illustrative overview of how LS screening and reflex testing strategies affect newly diagnosed CRC patients and their relatives is provided in Appendix 40. Screening and reflex testing strategies can lead to the identification of LS in the CRC patient and subsequent carrier testing in their family members. The model incorporates the impact of taking preventive measures to reduce the probability or eliminate the potential of developing three cancers (i.e., colorectal, endometrial, and ovarian cancer) that are associated with LS. For family members of the newly diagnosed CRC patient, the model incorporates the development of the first and second CRC, and, among female relatives, the development of gynecological cancers (i.e., endometrial, ovarian). For the CRC patient, the model incorporates the development of a second CRC, and gynecological cancers for female patients. People identified as having LS are offered biannual colonoscopy starting at age 25. Females identified as having LS are offered total abdominal hysterectomy at the end of child-bearing, which was assumed to be 45 years of age. Knowing the tumour dMMR status of newly diagnosed CRC patients may also be useful for decision-making regarding adjuvant chemotherapy choice.

The model can be thought of as being made up of a number of different modules, as shown in Figure 11. The starting point is the screening and reflex testing module in patients with newly diagnosed CRC. In this module, the number of CRC patients correctly identified as having LS, along with the average screen and testing costs per CRC patient, is calculated for each of the various combinations of LS screening and LS reflex testing strategies. For each CRC patient correctly diagnosed as having LS, this would then impact the relative identification module that estimates both the number of relatives identified as having LS and the carrier testing and genetic counselling costs needed to identify these patients.

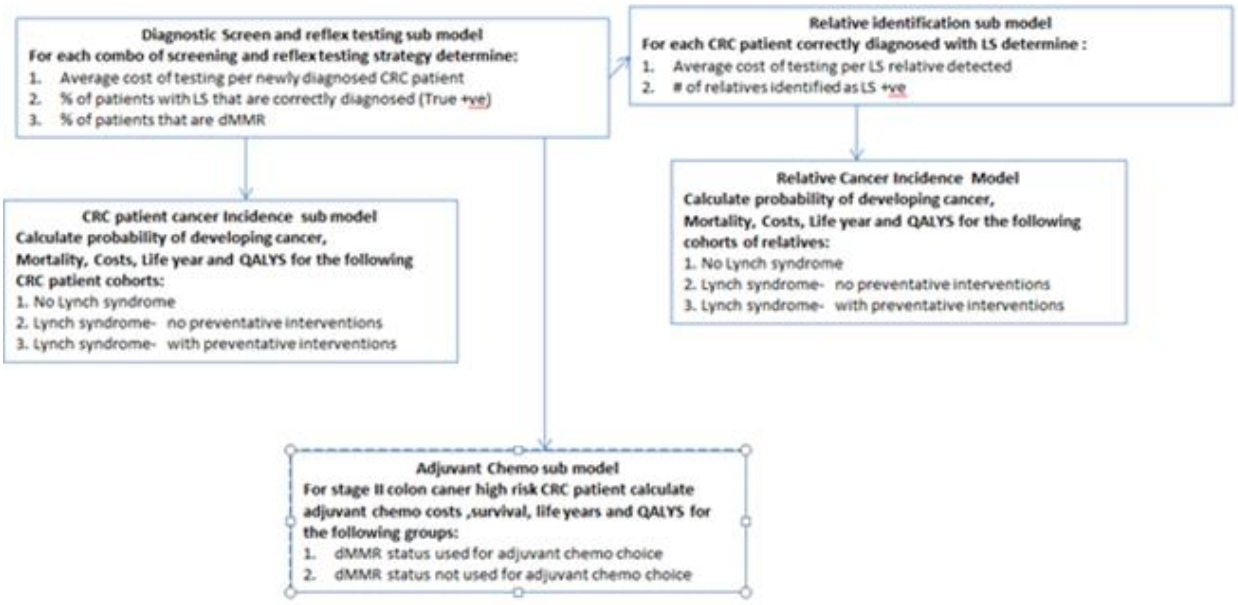
In the relatives' cancer incidence module, the lifetime expected costs, life-years, and QALYS are estimated for different cohorts of patients: those without LS; those with LS who do not receive preventive interventions; and those with LS who do receive preventive interventions. Individuals with LS may not receive preventive interventions for one of two reasons. First, they might not be offered the interventions because they were not positively identified as having LS. Second, they may have been diagnosed with LS but refused preventive treatment. Lifetime costs and outcomes for the different cohorts are based upon the probability of developing LS-related cancers over time, along with their mortality and quality-of-life impacts. It was assumed that the median age of relatives in the model was 38 years, as this was the midpoint of the age distribution for first colonoscopy that was reported in individuals at high risk of LS.[122] The starting age of relatives was varied in sensitivity analysis. Family members were assumed to not have had a CRC or gynecological cancer when entering the model.

The CRC patient cancer module is very similar to the relatives' cancer incidence module, with the exception of the following differences: Because CRC patients were starting the model with an incident CRC, they were assumed to only be at risk for a second CRC or a gynecological cancer (females only). Individuals were assumed to be at risk for another LS-related cancer only after five years following their cancer diagnosis. The assumed starting age for the CRC patient was 51 years.[122]

In the adjuvant chemotherapy submodel, which applied only to the patient, two options were available: using tumour dMMR test status, or not using tumour dMMR test status to guide adjuvant chemotherapy choice. Each option would affect the costs, life-years, and QALYs during the first five years of treatment of CRC. Based on expert opinion, the use of tumour

dMMR status on chemotherapy choice was applied only on a subset of patients with stage II colon cancer at high risk of cancer recurrence and applied only to the first cancer case.

Figure 11: Submodels Making Up Overall dMMR Model



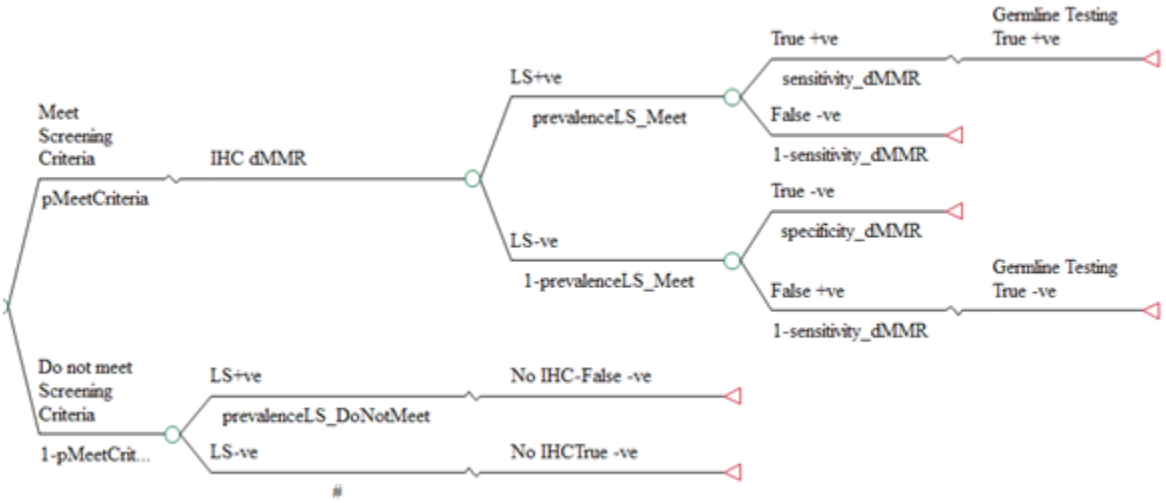
CRC = colorectal cancer; dMMR = deficient mismatch repair; LS = Lynch syndrome; QALY = quality-adjusted life-year.

14.6.1 Screening and reflex testing submodel

The generic structure for the LS screening and reflex testing submodel is presented in Figure 12. This structure reflects the “all screening” strategy combined with the “all to germline testing reflex” testing strategy that would have followed after an initial tumour MMR IHC screen. Patients are first categorized as either meeting or not meeting the screening criteria being evaluated (e.g., no screen, BG, younger than 70 years, universal). There is an underlying prevalence of LS depending on whether patients meet or do not meet the screening criteria. Patients who meet the screening criteria are given a four-panel (MLH1, PMS2, MSH2, and MSH6) IHC-based dMMR tumour test. Based upon the sensitivity and specificity of the tumour MMR IHC screen, patients who meet the screening criteria are classified as being a TP, FN, TN, or FP for LS. In the reflex testing strategy presented in Figure 12, it is assumed that all patients who have a positive tumour dMMR test would proceed with a germline genetic test. The germline genetic test was assumed to be 100% accurate. Patients who have an FP diagnosis based on their tumour dMMR test would be considered TNs after germline testing. Patients who do not meet the screening criteria are not given a tumour dMMR test and therefore assumed to not have LS. Among these individuals, if they in fact have LS, they would be considered to have an FN diagnosis.

Palomaki et al.[56] reported that 32% of all LS diagnoses involve the *MLH1* gene. Additionally, it was reported that 70% of all abnormal IHC dMMR tumour tests demonstrate lack of expression of MLH1 protein. Based on these data, the model assumed that 32% of all true positive MMR IHC tumour test results would show a lack of expression of MLH1 protein.

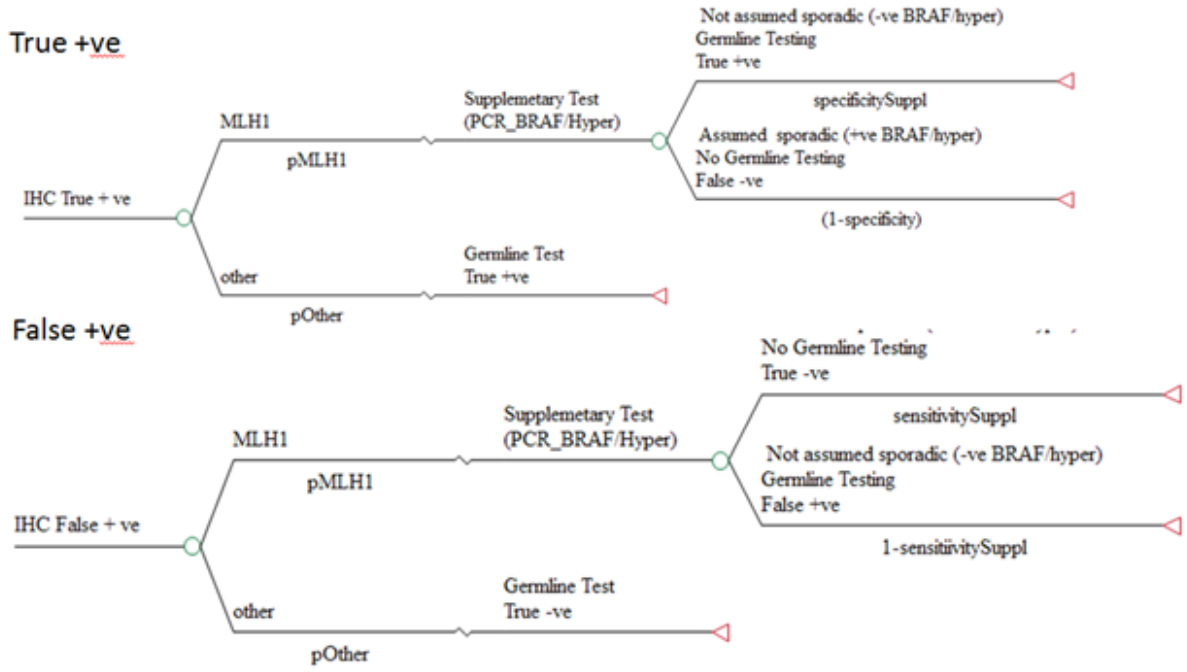
Figure 12: Graphical Representation of Overall Screen and Reflex Testing Model



dMMR = deficient mismatch repair.

Modifications to the structure of the submodel for the PCR-BRAF and MLH1 promoter hypermethylation reflex tumour testing strategies are shown in Figure 13. As shown, changes to the structure are made when there are positive tumour dMMR findings (i.e., FPs and true positives). Specifically, it is assumed that if patients show lack of expression of the MLH1 protein in their dMMR IHC tumour test, a supplementary tumour test (PCR-based BRAF, or MLH1 promoter hypermethylation) would be applied to try to detect likely sporadic CRC and therefore exclude LS, thereby avoiding the need for germline genetic testing in some patients. Specifically, patients with tumours that test positive for either the BRAF mutation, using the PCR test, or MLH1 promoter hypermethylation are assumed to have sporadic CRC and therefore do not undergo germline genetic testing. For FP patients with lack of tumour expression of the MLH1 protein, the sensitivity of the supplementary tumour test to detect likely sporadic CRC (non-LS) would determine the proportion of patients who would avoid having unnecessary and costly germline testing. For patients with a TP LS diagnosis, the specificity of the supplemental tumour test would determine the proportion of patients who would correctly go on to receive germline genetic test and remain correctly diagnosed as having LS. If specificity of the supplementary tumour test is less than 100%, then supplementary tumour testing would result in more FN diagnoses.

Figure 13: Modifications Made to Screen and Reflex Testing Model When Supplementary Tests Are Used



IHC = immunohistochemistry; PCR = polymerase chain reaction; SUPPL = supplementary.

The structure for the IHC-based BRAF reflex tumour testing strategy is similar to the PCR-based BRAF reflex tumour testing strategy with the exception that IHC-based BRAF tumour testing is conducted on all newly diagnosed CRC patients as an add-on to their tumour MMR IHC tests, instead of being conducted only on those who show a lack of expression of the MLH1 protein in their MMR IHC panel. Even though IHC-based BRAF tumour testing is conducted on all newly diagnosed CRC patients, the results of the IHC-based BRAF tumour test is only informative for patients whose tumours show a lack of expression of the MLH1 protein.

The structure of the tumour IHC-based BRAF plus MLH1 promoter hypermethylation strategy is similar to the structure for the tumour IHC-based BRAF strategy. The difference is that, in this strategy, patients lacking expression of the MLH1 protein and who test negative for a somatic BRAF mutation are then given a MLH1 promoter hypermethylation tumour test. Individuals with either an abnormal IHC-based BRAF tumour test and an abnormal MLH1 promoter methylation tumour test are assumed to have sporadic CRC and therefore will avoid germline genetic testing.

In addition to the cost of tumour MMR IHC panel, germline genetic test, tumour BRAF, and tumour MLH1 promoter hypermethylation test, all individuals undergoing germline genetic testing will incur the costs of genetic counselling before germline testing.

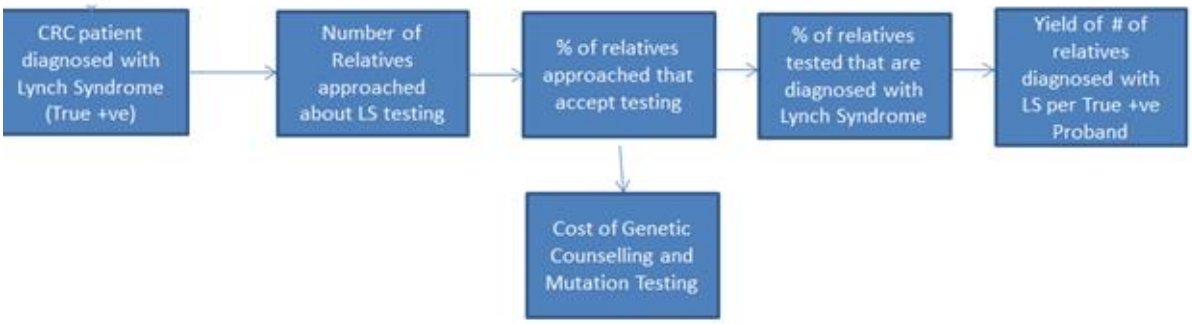
14.6.2 Relative identification submodel

For each CRC proband identified as having LS, the number of relatives who would be contacted and subsequently diagnosed as having LS needs to be estimated. This is determined through the patient identification submodel. The structure of this model is shown in Figure 14. It is

assumed that cascade testing is used to identify relatives with LS. As shown, for each proband, the number of relatives who are approached for testing is first estimated. Next, the percentage of relatives approached who would accept testing is determined. Germline genetic testing (i.e., carrier testing) and genetic counselling costs are applied to relatives who are tested for LS. Finally, the yield in terms of the number of relatives identified as having LS per proband is determined by multiplying the number of relatives tested for LS by the incidence of LS among relatives.

An FN diagnosis of CRC patients during the screening and reflex testing stage (i.e., CRC patients with LS who are not diagnosed as having LS) would have implications for the identification of relatives. In such circumstances, the patient's relatives would not receive carrier testing and those relatives with LS will remain undiagnosed.

Figure 14: Structure of Patient's Relatives Identification Submodel



CRC = colorectal cancer; LS = Lynch syndrome.

14.6.3 Cancer incidence submodel

The cancer incidence submodels (applicable to both relatives and CRC patients) relied on a Markov cohort models structure with one-year cycles to estimate the expected costs, life-years, and QALYs for different cohorts of individuals. These include: 1) Individuals without LS; 2) Individuals with LS who undergo preventive interventions; 3) individuals with LS who do not undergo preventive interventions. Individuals with LS who do not undergo preventive measures include those who were never diagnosed with LS and those who were diagnosed with LS but elected not to undergo preventive interventions. The cohort is at risk each year of CRC, endometrial cancer (females only), and ovarian cancer (females only). In the relative cancer incidence submodel, individuals are at risk for up to two incident CRCs, whereas in the CRC patient cancer incidence submodel, individuals are at risk of only one additional CRC, given that these patients are already diagnosed with their first CRC. Patients with LS are at increased risk of cancer compared with patients without LS; however, patients with LS who undergo preventive interventions (i.e., biannual colonoscopy, total abdominal hysterectomy) would have decreased risk of cancer in the model.

Patients who have had incident cancer have an increased risk of death for five years post-diagnosis. Individuals are assigned cancer-specific resource costs and utility values during the first five years post-diagnosis. Background mortality and general population utility values are assigned to patients if they did not have an incident cancer diagnosis within the last five years.

14.6.4 Adjuvant chemotherapy submodel

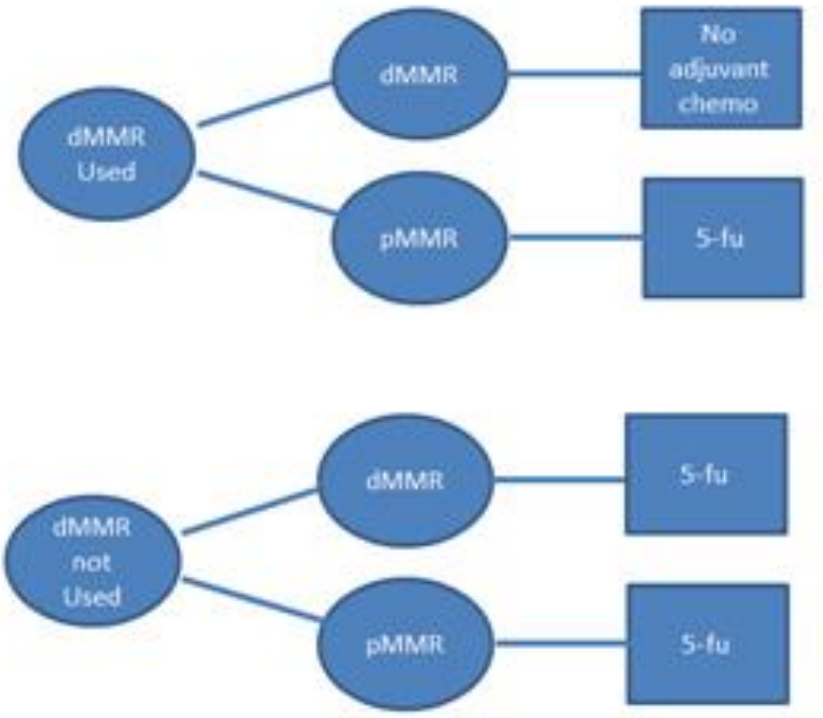
The adjuvant chemotherapy submodel estimates the five-year expected costs, life-years, and QALYs for CRC patients under two scenarios: 1) tumour dMMR status used to guide adjuvant chemotherapy choice or 2) tumour dMMR status not used to guide adjuvant chemotherapy choice. Based on expert opinion, the model considered only the impact of using tumour dMMR status for adjuvant chemotherapy for stage II colon cancer patients who are at high risk of cancer recurrence and applied only to their first cancer.

This represents a relatively small percentage of all newly diagnosed CRC patients. The American Cancer Society estimated that among the incident CRC cases, 70.1% were colon cancer cases. Furthermore, based on data from Saskatchewan, Manitoba, and Alberta, 28% of their CRC cases were diagnosed as stage II cancer.[123] Quah et al.[124] investigated the impact of different prognostic factors on DFS among stage 2 colon cancer patients who did not receive adjuvant chemotherapy. Among the 448 patients in their study, 140 (31%) were considered to have at least one prognostic factor considered "high risk" (i.e., tumour stage T4, preoperative carcinoembryonic antigen (CEA) > 5 ng/mL, presence of lymphovascular or perineural invasion). Together, these data implied that 6.1% (70.1% × 28% × 31%) of all newly diagnosed patients would be considered stage II high-risk colon cancer patients.

Expert opinion informed the treatment algorithm for adjuvant chemotherapy choice. As shown in Figure 15, if tumour dMMR status is used in adjuvant chemotherapy choice, patients with tumours that are dMMR were assumed to not receive adjuvant chemotherapy, while patients with tumours that are pMMR were assumed to receive a regimen of 5-FU alone. If tumour dMMR status is not used in adjuvant chemotherapy choice, then all stage II high-risk colon cancer patients were assumed to receive a regimen of 5-FU alone.

Expected costs, life-years, and QALYs for five years post-diagnosis were estimated for the two strategies (tumour dMMR status used in adjuvant chemotherapy choice, or tumour dMMR status not used in adjuvant chemotherapy choice). Based on data from Andre et al.,[125] it was assumed that 0.094 of all patients would have dMMR tumours while the rest would have pMMR tumours. Patients were at risk of death each year. The probability of death was dependent on both the patient's tumour's MMR status and on whether they received adjuvant chemotherapy. Chemotherapy costs were applied in the first year of the model and other CRC-related costs were applied subsequent to the first year post–CRC diagnosis. A disutility is applied for six months for patients undergoing adjuvant chemotherapy. For some LS screening strategies (rBG, age younger than 70, universal), some or all CRC patients will already have had tumour MMR testing. For these patients, no additional costs for tumour MMR IHC testing are incurred. For CRC patients who did not have MMR tumour testing as part of the screening strategies, tumour MMR IHC test costs are applied to the proportion of patients who have stage II colon cancer and are at high risk of recurrence.

Figure 15: Algorithm for Adjuvant Chemotherapy Submodel



5-FU = fluorouracil; dMMR = deficient mismatch repair; pMMR = proficient mismatch repair.
Note: 5-FU refers to a chemotherapy strategy involving 12 cycles of bolus plus continuous infusion of 5-FU (bolus: 400 mg/m^2; continuous infusion: 600 mg/m^2) plus leucovorin (200 mg/m^2).

14.6.5 Clinical model parameters

A number of clinical model input parameters are included in the model. These include LS prevalence data, the diagnostic accuracy of various diagnostic tests, cancer incident rates, effectiveness of prophylactic interventions, mortality rates, utility values, and the number of relatives identified as having LS for each CRC proband. Details of these parameter values and their sources are provided below.

14.6.6 Lynch syndrome prevalence

Table F1 shows prevalence-related data that were used in the model. Specifically, Table F1 shows the proportion of patients who meet each screening criterion (e.g., rBG), along with the prevalence of LS among CRC patients who do or do not meet the screening criteria. This information is based on supplemental data provided in a study investigating LS screening among CRC patients.[126] The entire study included 1,566 patients and found the overall prevalence of LS among CRC patients to be 2.81%.

Table F1: Prevalence of Lynch Syndrome According to Colorectal Cancer Patients Who Meet Various Screening Criteria

		Prevalence of Lynch Syndrome	
Screening Criterion	Percentage Who Meet Criteria	Those who meet criteria	Those who do not meet criteria
No Screening	0.00%	-	2.81%
Revised Bethesda Guidelines	26.76%	6.92%	1.31%
Younger than 70 years	64.62%	3.75%	1.08%
Universal Screening	100.00%	2.81%	-

14.6.7 Diagnostic accuracy of dMMR tumour and supplementary reflex tumour testing

The diagnostic accuracy estimates of dMMR tumour testing to detect LS and supplementary tumour tests to detect likely sporadic CRC were based on findings from the clinical review. A summary of the sensitivity and specificity values used in the model are shown in Table F2. No data were found on the diagnostic accuracy of MLH1 promoter hypermethylation tumour testing after a negative IHC-BRAF tumour test. Therefore, it was assumed to have the same diagnostic accuracy of MLH1 promoter hypermethylation tumour test that did not succeed a negative IHC-BRAF tumour test.

Table F2: Tumour dMMR Screening and Reflex Supplementary Tumour Testing Diagnostic Accuracy

Diagnostic Tumour Test		Sensitivity (95% CI)	Specificity (95% CI)
Detect Lynch syndrome			
Four MMR protein IHC test		0.90 (0.84 to094)	0.81 (0.64 to 0.91)
Detect likely sporadic CRC			
PCR-BRAF V600E		0.57 (0.45 to 0.69)	0.98 (0.90 to 0.99)
MLH1 promoter hypermethylation		0.82 .0.61 to 0.93)	0.96 (0.74 to 0.99)
IHC-BRAF V600E		0.36 (0.14 to 0.51)	0.90 (0.78 to 0.98)
Detect likely sporadic CRC after a negative IHC-BRAF test			
MLH1 promoter hypermethylation		0.82 (0.61 to 0.93)	0.96 (0.74 to 0.99)

CI = confidence interval; CRC = colorectal cancer; IHC = immunohistochemistry; MMR = mismatch repair; PCR = polymerase chain reaction.

14.6.8 Cancer incidence rates

For individuals without LS, the annual probability of developing CRC was determined based on the Surveillance, Epidemiology, and End Results Program (SEER) database. The SEER database includes the annual incidence rates of CRC in the US by gender and according to age ranges.[127] Using these data, age- and gender-specific probabilities of developing CRC were derived for individuals without LS. The age-dependent probability of women without LS of developing endometrial or ovarian cancer was also derived from SEER data.[128]

A study by Bonadona et al.[129] was used to estimate the annual probability of being diagnosed with various types of cancer over time for individuals with LS. Bonadona estimated the cumulative risk of developing cancer among 537 families with confirmed LS in France. There were 1,633 mutation carriers in the study, of which 844 were diagnosed with an LS-related cancer. The study estimated the cumulative risk of being diagnosed with CRC to be 13% by age 50 and 35% by age 70. The cumulative risk of endometrial cancer was estimated to be 8% by

age 50 and 34% by age 70. The cumulative risk of ovarian cancer was estimated to be 3% by age 50 and 8% by age 70. The study provided cumulative risk of CRC among people with LS at 10-year increments from ages 20 to 70. These data were used to estimate age- and gender-specific probabilities of being diagnosed with CRC for people with LS who do not undergo regular CRC screening or prophylaxis interventions. The annual probability of CRC, endometrial cancer, and ovarian cancer used in the model are shown in Table F3. It is recognized that the cancer risks are variable and MMR is gene-specific, but the figures used here are the composite risks observed by Bonadona et al.[129]

Table F3: Annual Incidence Rates of Cancer for Patients With Lynch Syndrome Without Regular Surveillance or Prophylaxis Interventions

Age Group (Years)	Colorectal	Endometrial	Ovarian
20 to 30	0.0020	0	0
30 to 40	0.0031	0.0020	0.0010
40 to 50	0.0088	0.0063	0.0020
50 to 60	0.0134	0.0176	0.0042
60 to 70	0.0155	0.0153	0.0011

In sensitivity analysis, data from a Canadian study[130] were used to derive the annual probability of being diagnosed with CRC for individuals with LS. In this Canadian-based study, data were collected from first-degree and second-degree relatives of 32 probands from the Ontario Familial Colorectal Cancer Registry. Blood samples were available for only a fraction of the 620 first- and second-degree relatives in the study, in which a total of 60 mutation-positive relatives were identified. The study estimated the cumulative risk of developing CRC by age 70 to be 60% for males and 47% for females.

The risk of a second CRC was assumed to be the same as the risk of a first incident CRC.

14.6.9 Impact of regular colonoscopy screening on the probability of developing CRC

Regular colonoscopy screening was assumed to decrease CRC incidence and mortality. The impact of colonoscopy screening on the development of CRC among people with LS was based on a study by Jarvinen et al.[131] In this 10-year Finnish study, the frequency of CRC diagnosis among 133 members of HNPCC families who underwent regular colonoscopy surveillance was compared with 119 individuals who refused screening. Screened patients underwent colonoscopy every three years. Among the asymptomatic study patients, the RR of developing CRC was found to be 0.44 (95% CI, 0.22 to 0.90) for patients undergoing regular screening compared with those not undergoing regular screening. Similar results were found in a South African study in which patients with an MLH1 mutation who were screened for CRC by colonoscopy had a RR of being diagnosed with CRC of 0.42 (95% CI, 0.21 to 0.82) compared with control subjects who did not undergo colonoscopy screening. In order to calculate the age- and gender-specific annual probability of developing CRC among peoples with LS who undergo regular colonoscopy, the baseline probability of developing CRC among people with LS was multiplied by the RR of developing CRC in the presence of colonoscopy screening. The impact of colonoscopy screening on mortality is discussed in a later section.

It was assumed that 81%[56] of probands and relatives diagnosed with LS would undergo biannual colonoscopy starting at age 25 to age 70 years.

14.6.10 Colonoscopy complications

Based on a Canadian study,[132] it was assumed the probability of bleeding complications per colonoscopy was 0.00085, while the probability of perforation per colonoscopy was assumed to be 0.00164. The probability of death per colonoscopy was assumed to be 0.000074.

14.6.11 Impact of total abdominal hysterectomy on endometrial and ovarian cancer on the probability of developing endometrial and ovarian cancer

It was assumed that 0.19 of female probands and 0.18 female relatives diagnosed with LS would undergo abdominal hysterectomy at the end of child-bearing (i.e., age 45).[115] It was further assumed that abdominal hysterectomy would eliminate the chance of developing endometrial and ovarian cancer.

14.6.12 Mortality post–incident cancers

General population mortality was based on Canadian life tables.[133,134] Mortality from colorectal, ovarian, and endometrial cancer was calculated using information from the SEER database.[135-137] Specifically, SEER provides both the proportion of patients diagnosed by stage of disease, and the five-year relative survival by cancer stage at diagnosis. Together, this was used to derive a weighted five-year relative survival rate for each type of cancer, which was estimated to be 0.64, 0.82, and 0.45 for CRC, endometrial, and ovarian cancer, respectively (Table F4). Relative survival rate was multiplied by age- and gender-specific mortality to derive cancer-specific survival that was applied up to five years post-diagnosis. General population mortality was assumed for patients who were still alive after five years post–cancer diagnosis.

Table F4: Five-Year Relative Survival by Type of Cancer

	Colorectal (With Regular Surveillance)		Endometrial		Ovarian	
Stage	Proportion at diagnosis	Relative survival	Relative survival	Relative survival	Proportion at diagnosis	Relative survival
Localized	0.40	0.898	0.69	0.95	0.15	0.92
Regional	0.36	0.705	0.21	0.68	0.18	0.72
Distant	0.20	0.129	0.09	0.18	0.61	0.27
Unstaged	0.04	0.332	0.03	0.48	0.06	0.22
Weighted		0.64		0.82		0.45

Patients undergoing regular CRC surveillance may be diagnosed at earlier stages of the cancer and therefore have better survival than patients diagnosed because of symptoms. Among LS patients diagnosed with CRC, both Jarvinen[131] and Stupart[138] found that LS patients who underwent regular colonoscopy were diagnosed at earlier stages than patients who had not undergone regular colonoscopy surveillance. Table F5 shows the distribution of stage diagnosis for patients diagnosed of CRC who were in the surveillance arm of these two studies. Diagnosis stage was based on Dukes staging in these two studies,[131,138] in which 22 surveilled patients developed CRC with the proportion of patients in each Dukes stage reported in Appendix 41. Based on expert opinion, Dukes staging can be mapped to cancer staging used by SEER, with Dukes A and B mapped to localized cancer, Dukes C mapped to regional cancer, and Dukes D mapped to distant cancer.

Based on this mapping, it can be inferred that 73% of CRC patients diagnosed through colonoscopy surveillance would be diagnosed with localized cancer, while the remainder would be diagnosed with regional cancer. As shown in Table F5, this distribution of cancer staging in patients undergoing regular colonoscopy, along with the SEER relative survival rates by CRC stage, can be combined to derive an weighted five-year relative survival rate of 0.84 in patients diagnosed with CRC through regular surveillance.

Table F5: Relative Survival After Colorectal Cancer Diagnosis for Lynch Syndrome Patients Diagnosed Through Regular Surveillance

Stage	Proportion at Diagnosis	5-Year Relative Survival
Localized	0.73	0.898
Regional	0.27	0.705
Distant	0.00	0.129
Unstaged	0.00	0.332
Weighted relative survival		0.845

14.6.13 Mortality used in the adjuvant chemotherapy submodel

Question 5 of the clinical review identified two studies, Klingbiel[96] and Yoon,[102] that reported overall five-year survival for patients with stage II colon cancer who underwent adjuvant chemotherapy with 5-FU leucovorin according to their tumour dMMR status. In particular, as Klingbiel[96] presented survival curves, five-year survival rates were abstracted from these curves using DigitizeIt software. As shown in Table F6, the weighted five-year OS from these studies was estimated to be 0.988 for patients with dMMR tumours and 0.916 for patients with pMMR tumours. Annual mortality rates for patients treated with adjuvant chemotherapy (0.026 for pMMR, 0.0008 for dMMR) were derived from the five-year survival estimates.

Table F6: Weighted Overall 5-Year Survival for Stage II Colon Cancer After Fluorouracil Adjuvant Chemotherapy

	dMMR		pMMR	
	N	5-year OS	N	5-year OS
Yoon[102]	60	1	148	0.95
Klingbiel[96]	86	0.98	309	0.90
Weighted 5-year survival		0.988		0.916

dMMR = deficient mismatch repair; OS = overall survival; pMMR = proficient mismatch repair.

The mortality impact of 5-FU–based adjuvant chemotherapy compared with no adjuvant chemotherapy was derived from two studies.[139,140] In both studies, patients' tumour's MMR status from several colon cancer studies were used to estimate survival according to the tumour dMMR status and whether patients received 5-FU–based chemotherapy or no adjuvant chemotherapy. The HR for death among patients with dMMR tumours was reported to be 2.95 (95% CI, 1.02 to 8.54),[140] while the HR for death among patients with pMMR tumours was reported to be 0.67 (95% CI, 0.39 to 1.15).[139] This indicates that 5-FU–based adjuvant chemotherapy increases mortality among patients with dMMR tumours, but decreases mortality among patients with pMMR tumours.

In order to estimate annual mortality for patients who did not undergo adjuvant chemotherapy, the inverse of the above-mentioned HRs were applied to the estimated annual mortality rates among patients who did receive adjuvant chemotherapy. This results in the annual mortality among patients not receiving chemotherapy to be 0.0003 among patients with dMMR and 0.039 among patients with pMMR tumours.

14.6.14 Utilities

Background age- and sex-specific utility values were used in the model, based on a study by Kind et al. (Appendix 44).[141] Utility weights were applied to the background utility values during the first five years post–incident cancer. A utility weight of 0.73 and 0.76 was applied to patients after incident CRC[142] and gynecological cancer,[143] respectively. For patients undergoing adjuvant chemotherapy, a disutility of 0.226[144] was applied during the six-month chemotherapy period.

14.6.15 Number of relatives identified as having Lynch syndrome, per proband

Data from a previously published systematic review[145] were used to estimate, for each proband, the number of relatives identified as having LS by cascade testing. The systematic review focused on the uptake of LS testing among first-degree relatives of CRC probands, but also included studies that included more distant relatives. Because the current model assumes cascade testing, data from studies that were solely based on first-degree relatives were excluded. It was estimated that 17.63 relatives would be approached per proband,[145] 29.11% of these relatives would accept genetic testing for LS, and 40.1% of these relatives tested would have a germline mutation indicative of LS. This results in 2.10 relatives being identified and diagnosed with LS, per proband identified as having LS. Appendix 42 provides further details on these calculations.

14.7 Resource Costs Model Variables

A summary of resource costs values is provided in Table F7. Costs related to screening and reflex testing were based on the costing data from a public hospital in British Columbia, Canada (expert opinion, 2016 Jan). In a sensitivity analysis, the model was run using costs from a private diagnostic laboratory in Alberta for 4 MMR protein IHC panel, germline genetic testing, PCR-based BRAF V600E tumour test and IHC-based BRAF V600E tumour test (Dr. Kamnasaran: personal communication, 2016 Jan).

An overall annual cost of treating CRC was based on a Canadian cost-effectiveness study of CRC screening.[146] The authors presented the costs of CRC by stage and by year of diagnosis. The current model assumes that patients with LS who are diagnosed with CRC through colonoscopy surveillance have a different distribution than those who are not receiving regular colonoscopy (Table F4 and F5). Therefore, different first- and subsequent-year costs were calculated for patients with LS, depending on whether they underwent colonoscopy surveillance.

Canadian costs for gynecological cancers by year since diagnosis was not identified in a targeted search. However, the National Cancer Institute (NCI) published estimates of US-based annual costs of various types of cancer, including ovarian and colorectal cancer.[147] To estimate Canadian annual costs for gynecological cancer, Canadian CRC costs were multiplied by the relative costs of ovarian to colorectal cancer costs estimated from the US-based NCI publication.

The costs of colonoscopy[148] and related complications[149] were based on various Canadian published studies. The cost of total abdominal hysterectomy was also based on a Canadian

publication and included related in-patient costs, surgeon fees, and anesthesiologist fees.[126] All costs are inflated to 2015 Canadian dollars using the health care component of the consumer price index.

The unit costs of adjuvant chemotherapy medications were based on information provided by the drug manufacturers. The six-month adjuvant chemotherapy drug regimen used in the model was based on the 5-FU alone (without oxaliplatin) treatment that was studied in the MOSAIC trial. Details of the calculations of the cost of this adjuvant chemotherapy regimen are provided in Appendix 43.

Table F7: Summary of Resource Costs Used in the Model

Cost Variable	Model Value	Source
Testing costs used in base case		
4 MMR protein IHC panel	$60.63	(Expert opinion, 2016 Jan)
Tumour PCR-based BRAF test	$350	
Tumour MLH1 promoter hypermethylation	$390	
Tumour IHC-based BRAF test	$22.62	
Germline MMR gene testing	$1600	
Genetic counselling	$506	
LS genetic testing for relative (carrier testing)	$275	
Alternative testing costs used in sensitivity analysis[a]		
4 MMR protein IHC panel	$1,215	(Dr. Deepak Kamnasaran, CEN4GEN Institute for Genomics and Molecular Diagnostics, Edmonton, AB: personal communication, 2016 Feb)
Tumour PCR-based BRAF test	$690	
Tumour MMR gene mutation testing		
MLH1, MSH2	$1,780	
MSH6, PMS2	$2,199	
Colorectal cancer		
First year of diagnosis		
No LS-No surveillance	$40,248	Telford[146]
No LS-Surveillance	$40,248	Telford[146]
LS-No Surveillance	$40,248	Telford[146]
LS-Surveillance	$27,405	Telford[146]
Years 2 to 5 since diagnosis		
No LS-No surveillance	$808.69	Telford[146]
No LS-Surveillance	$808.69	Telford[146]
LS-No Surveillance	$808.69	Telford[146]
LS-Surveillance	$818.86	Telford[146]
Year of death (same for everyone)	$20,067	Telford[146]
Gynecological cancer		
First year of diagnosis	$64,554	NCI,Telford[146,147]
Subsequent year of diagnosis	$1,612	NCI,Telford[146,147]
Year of death	$22,225	NCI,Telford[146,147]
Colonoscopy	$395	Shahara[148]
Colonoscopy complications		
Perforation	$34,581	Heitman[149]
Bleeding	$3,537	Heitman[149]
Total abdominal hysterectomy	$7,414	Kwon[126]

Cost Variable	Model Value	Source
Adjuvant chemotherapy		
Leucovorin	0.5616/mg	manufacturer
5-FU	0.0442/mg	manufacturer
Six-month adjuvant chemotherapy regimen	$6,574.51	calculated

5-FU = fluorouracil; IHC = immunohistochemistry; LS = Lynch syndrome; PCR = polymerase chain reaction; MMR = mismatch repair.
[a] Fees from this source may vary depending on factors such as promotions, change in proprietary methods, etc.

14.8 Discount Rate

In accordance with CADTH guidelines[150] a 5% discount was applied to costs, life-years, and QALYs.

14.9 Uncertainty and Variability

The overall parameter uncertainty of the model was assessed by means of probabilistic sensitivity analysis (PSA). In PSA, parameter values are defined as distributions instead of specific values. The model is simulated a large number of times and during each simulation, the model parameters take on a value from their defined distribution. Beta distributions were used for utility and probability parameters such as diagnostic accuracy. Log-normal distributions were used for RR parameters. Cost parameters were defined by gamma distributions.

The expected costs and outcomes (e.g., QALYs) for all comparators are recorded in each simulation. Results across all simulations provide a distribution of the cost-effectiveness results incorporating the uncertainty in the model parameters. This uncertainty is expressed on the cost-effectiveness acceptability curves (CEACs). CEACs show the probability that each comparator is cost-effective across a range of willingness to pay (WTP) values for an additional unit of outcome (e.g., QALY).

One-way sensitivity analyses were conducted to investigate the impact of changing the values of individual model parameters. One-way sensitivity analysis was conducted on the overall prevalence of LS, the number of LS relatives identified per LS diagnosed proband, the proportion of CRC patients and relatives who undergo preventive interventions, and the starting age of both CRC patients and their relatives. Sensitivity analyses were also undertaken assuming a higher risk of CRC for patients with LS, and assuming diagnostic accuracy of IHC-based BRAF tumour testing was the same as the diagnostic accuracy of PCR-based BRAF tumour testing. Scenario analysis was also completed using molecular diagnostic test costs based on an alternative source from a private diagnostic laboratory rather than from a public hospital setting.

14.10 List of Assumptions

The starting age for patients newly diagnosed with CRC is 51.
The proportion of males starting in this model is 50%.
The overall prevalence rate of LS among all newly diagnosed CRC patients is 0.028.
The diagnostic accuracy of MLH1 promoter hypermethylation to detect likely sporadic CRC among patients with tumours that show lack of expression of the MLH1 protein after a negative IHC-based BRAF tumour test is the same as the diagnostic accuracy of MLH1 promoter hypermethylation among all patients with tumours that show lack of expression of MLH1 protein.
It was assumed that all patients with a mismatch repair protein deficiency that is not suspected to be likely sporadic CRC following the reflex testing strategy would accept germline testing.
Germline testing is assumed to be 100% accurate.
For each CRC patient who is diagnosed with LS, 2.1 relatives will be identified through cascade testing as having LS.
The starting age of relatives of CRC patients is 41.
Relatives are at risk for up to 2 incident CRCs and 1 gynecological cancer (assume females will have hysterectomy if they have an incident gynecological cancer and will not be at risk for a 2nd gynecological cancer).
CRC patients are at risk for 1 incident CRC (they enter the model already having 1 CRC) and 1 gynecological cancer (assumes that after gynecological cancer, females will undergo hysterectomy and will not be at risk for a 2nd gynecological cancer).
The proportion of CRC patients and relatives diagnosed with LS who will undergo biannual colonoscopy is 0.81.
Individuals diagnosed with LS who undergo biannual colonoscopy will start receiving colonoscopy at age 25 or at the age they are diagnosed with LS and until the age of 80, or until 2 cases of CRC have occurred.
Biannual colonoscopy for individuals with LS will reduce the annual probability of being diagnosed with CRC by 68%.
The proportion of female CRC patients and relatives diagnosed with LS who will undergo total abdominal hysterectomy is 0.20.
Females will undergo total abdominal hysterectomy at the end of child-bearing, which was assumed to be the age of 45 years, or at the age they are diagnosed with LS (if after the age of 45).
Total abdominal hysterectomy will eliminate the risk of endometrial and gynecological cancers.
Mortality for patients after 5 years post–cancer diagnosis is the same as mortality of the general population.
In modelling the use of dMMR status to guide chemotherapy decisions, it was assumed patients who were not screened initially but were classified as stage II high-risk colon cancers would be subsequently screened to ascertain dMMR status. The outcome of screening was assumed to have no impact on relative identification for LS.

CRC = colorectal cancer; dMMR = deficient mismatch repair; IHC = immunohistochemistry; LS = Lynch syndrome; PCR = polymerase chain reaction; MMR = mismatch repair.

15. Results

15.1 Base-Case Results

The base case expected costs, number of LS cases detected, life-years, and QALYs predicted by the model for all 32 comparators are shown in Appendix 45. The expected costs and outcomes represent those from both the CRC patients and their relatives. It is worth noting that a small proportion of these relatives are diagnosed with LS through cascade testing. Specifically, for each comparator, the proportion of relatives diagnosed with LS through carrier testing is equal to the proportion of the CRC patients who are diagnosed with LS through dMMR tumour and germline

genetic testing. The number of LS cases detected represents cases detected for both the CRC patients and their relatives. The results integrate the various submodels and incorporate adjuvant chemotherapy decisions based on tumour dMMR status.

Table F8 shows this information for the comparators that may be considered cost-effective depending on how much decision-makers are willing to pay for an additional QALY. These strategies make up what is referred to as the efficiency frontier. The remaining comparators are dominated (more costly, fewer QALYs) by other strategies or combinations of other strategies that make up the efficiency frontier. Because they are dominated, they would not be considered cost-effective regardless of how much a decision-maker is willing to pay for an additional QALY. In all of the comparators that make up the efficiency frontier, the use of dMMR tumour status to guide adjuvant chemotherapy decisions in stage II high-risk colon cancer patients is always considered cost-effective compared with not using dMMR tumour status to guide chemotherapy decision-making.

As shown in Table F8, a strategy of no dMMR tumour screening leads to the lowest expected costs ($63,517), and QALYs (37.9224). This makes intuitive sense, as this strategy leads to the fewest LS cases detected (0.00) and, therefore, no patients with LS will undergo preventive interventions to reduce incident cancers. A strategy of universal MMR tumour testing with all patients with dMMR tumours receiving germline genetic testing after their initial 4 MMR protein IHC panel leads to the highest expected cost ($63,978) and the highest number of expected QALYs (37.9481). This also makes intuitive sense, as screening all patients and sending all patients with dMMR tumours to germline testing without supplemental tumour tests (e.g., BRAF V600E, MLH1 promoter hypermethylation) leads to the greatest number of LS cases detected (0.0784). This is because supplemental tumour tests to detect likely sporadic CRC are not 100% specific, which would lead to FN results. All other strategies are not shown in Table F8 because they were dominated (strictly or extendedly) by other strategies.

Table F8: Base Case Expected Costs and Outcomes for Comparators on the Efficiency Frontier (Probabilistic Results)

Screening	Reflex Tumour Testing	Use dMMR for Chemo?	Costs	LS Cases Detected	Life-Years	QALYs
No Screening	Not applicable	yes	$63,517	0.0000	47.0278	37.9224
rBG	BRAF-IHC +MLH1 promoter hypermethylation	yes	$63,596	0.0495	47.0451	37.9386
rBG	MLH1 promoter hypermethylation	yes	$63,599	0.0510	47.0456	37.9391
Younger than 70	MLH1 promoter hypermethylation	yes	$63,707	0.0669	47.0512	37.9443
Universal	MLH1 promoter hypermethylation	yes	$63,807	0.0774	47.0549	37.9478
Universal	BRAF-PCR	yes	$63,871	0.0779	47.0550	37.9480
Universal	All receive germline testing	yes	$63,978	0.0784	47.0552	37.9481

dMMR = deficient mismatch repair; IHC = immunohistochemistry; LS = Lynch syndrome; PCR = polymerase chain reaction; QALY = quality-adjusted life-year; rBG = revised Bethesda Guidelines.
Note: Other strategies not shown because they were dominated (strictly or extendedly) by other strategies.

Table F9 shows incremental cost-effectiveness for the seven comparators that are part of the efficiency frontier in the base-case analysis. Moving from one comparator to the next results in higher QALYs and higher costs. The incremental cost per additional QALY gained also increases when moving from one comparator to the next.

The incremental cost per QALY in moving from a strategy of screening patients younger than 70 years old and using MLH1 promoter hypermethylation in reflex testing to a universal screening strategy with the same reflex testing strategy is $28,902/QALY. Using different reflex testing strategies in universal dMMR tumour screening would lead to higher expected QALYs and higher costs as more LS cases are detected, but with diminishing returns. The incremental cost per QALY of using PCR-based BRAF tumour testing compared with using MLH1 promoter hypermethylation testing in a universal screening strategy is $387,330/QALY. The incremental cost per QALY of sending all patients to germline testing after a positive dMMR tumour test compared with MLH1 promoter hypermethylation testing for patients showing a lack of expression on the MLH1 protein was found to be $651,283/QALY.

These results imply that screening CRC patients younger than 70 years old using MLH1 promoter hypermethylation in the reflex testing strategy would be considered the most cost-effective option if maximum WTP for a QALY is between $20,757 and $28,902. Universal screening with MLH1 promoter hypermethylation as part of the reflex testing strategy would be considered the most cost-effective option if maximum WTP for a QALY is between $28,902 and $387,330. Universal screening of CRC patients using PCR-based tumour BRAF testing as part of reflex testing would be considered the most cost-effective option if maximum WTP for a QALY is between $387,330 and $651,283.

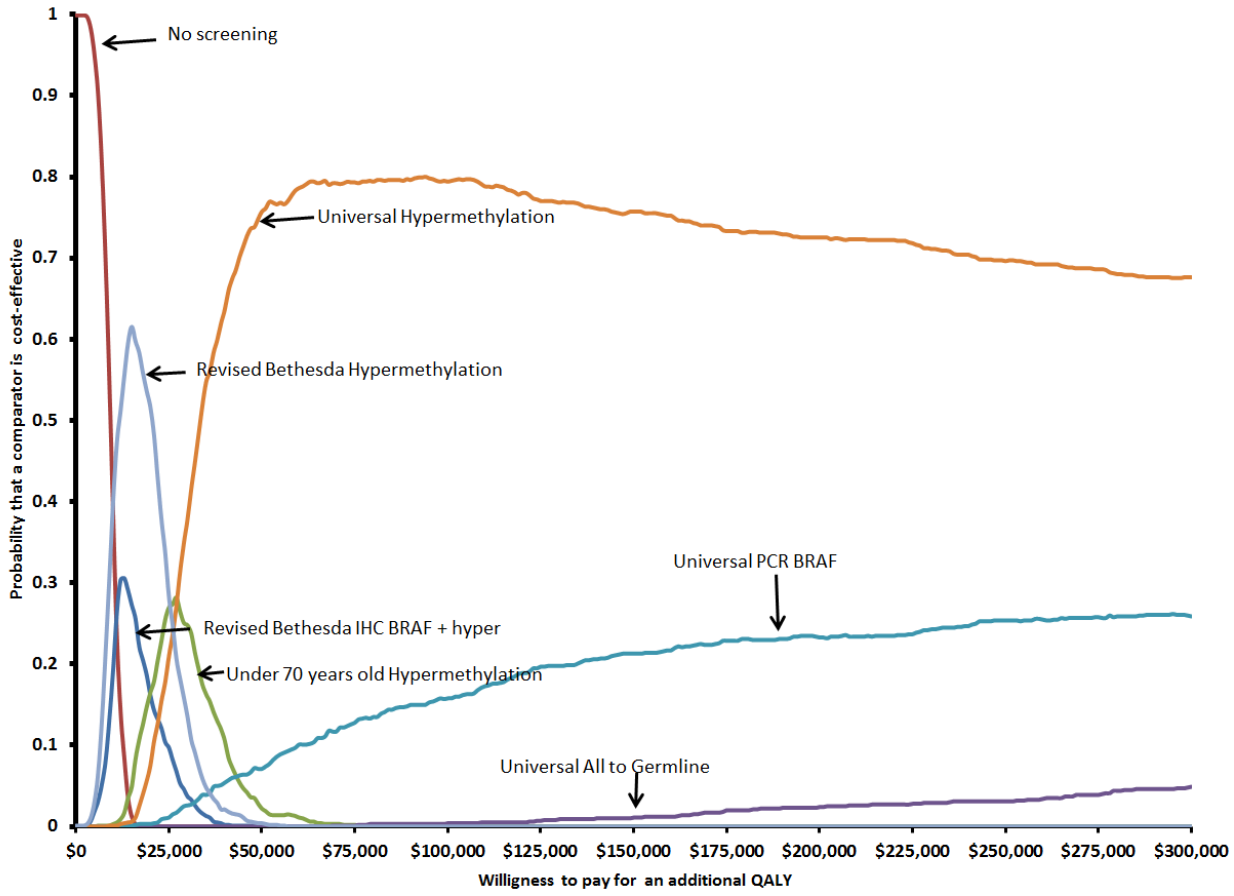
Table F9: Base Case Incremental Cost-Effectiveness Results for Comparators on the Efficiency Frontier (Probabilistic Results)

Screening	Reflex Tumour Testing	Use dMMR for Chemo?	Costs	Life-Years	QALYs	$/Life-Year	$/QALY
No Screening	Not applicable	yes	ref	ref	ref	ref	ref
rBG	BRAF-IHC + MLH1 promoter hypermethylation	yes	$79	0.0173	0.0162	$4,561	$4,866
rBG	MLH1 promoter hypermethylation	yes	$4	0.0006	0.0005	$6,368	$6,794
Younger than 70	MLH1 promoter hypermethylation	yes	$111	0.0061	0.0057	$19,455	$20,757
Universal	MLH1 promoter hypermethylation	yes	$211	0.0098	0.0092	$27,089	$28,902
Universal	BRAF-PCR	yes	$275	0.0100	0.0093	$363,043	$387,330
Universal	All receive germline testing	yes	$382	0.0101	0.0095	$610,447	$651,283

dMMR = deficient mismatch repair; IHC = immunohistochemistry; LS = Lynch syndrome; PCR = polymerase chain reaction; QALY = quality-adjusted life-year; rBG = revised Bethesda Guidelines; ref = reference.
Note: Other strategies not shown because they were dominated (strictly or extendedly) by other strategies.

Figure 16 presents the CEAC for the comparators that are part of the efficiency frontier. The CEAC shows the probability that each strategy is cost-effective for values of WTP for an additional QALY, ranging from $0 to $300,000/QALY. At a WTP value of $25,000 per QALY, a screening strategy based on rBG with reflex testing using MLH1 promoter hypermethylation had the highest probability of being cost-effective (0.28). Universal screening using MLH1 promoter hypermethylation in reflex testing had the highest probability of being cost-effective (0.76) if WTP for a QALY is $50,000. This strategy also had the highest probability of being cost-effective if WTP for a QALY was $100,000 (0.79), $200,000 (0.73), or $300,000 (0.68).

Figure 16: Cost-Effectiveness Acceptability Curves



IHC = immunohistochemistry; PCR = polymerase chain reaction.

15.2 Sensitivity Analysis

A number of sensitivity analyses were conducted on model parameters. For the one-way sensitivity analyses, the model's results were evaluated by halving or doubling a parameter's base-case values. In addition, scenario analyses were run that changed the model's assumptions and data sources, including CRC incidence rates for patients with LS, the diagnostic accuracy of IHC-based BRAF tumour testing, and the costs of molecular diagnostic tests.

Table F10 shows the incremental cost per QALY for interventions that make up the efficiency frontier when the starting ages of the CRC patient and of their relative are varied. As shown, the

incremental cost per QALY of a universal screening strategy combined with MLH1 promoter hypermethylation supplementary testing is $43,109 if the starting age of relative of newly diagnosed CRC patients is 25 years instead of 41 years. The incremental cost per QALY of this strategy is $29,225 if the starting age of relative is assumed to be 50 years. The impact of changing the starting age of the newly diagnosed CRC patient on the cost-effectiveness results was minimal.

Table F10: Incremental Cost per QALY for Comparators on the Efficiency Frontier Varying Starting Age of Relatives and of CRC patients

Screening	Reflex Tumour Testing	Use dMMR in Chemo?	Base Case	Age of Relatives (Years)		Age of CRC Patient (Years)	
				25	50	40	60
No Screening	Not applicable	yes	ref	ref	ref	ref	ref
rBG	BRAF-IHC + MLH1 promoter hypermethylation	yes	$4,866	$12,005	$3,601	$5,121	$5,633
rBG	MLH1 promoter hypermethylation	yes	$6,794	$14,501	$5,658	$6,977	$7,687
Younger than 70	MLH1 promoter hypermethylation	yes	$20,757	$32,569	$20,542	$20,413	$22,554
Universal	MLH1 promoter hypermethylation	yes	$28,902	$43,109	$29,225	$28,251	$31,227
Universal	BRAF-PCR	yes	$387,330	$506,939	$411,331	$373,177	$412,885
Universal	All receive germline testing	yes	$651,283	$848,513	$692,721	$627,188	$693,946

CRC = colorectal cancer; dMMR = deficient mismatch repair; IHC = immunohistochemistry; LS = Lynch syndrome; MMR = mismatch repair; PCR = polymerase chain reaction; QALY = quality-adjusted life-year; rBG = revised Bethesda Guidelines.
Note: Other strategies not shown because they were dominated (strictly or extendedly) by other strategies.

Table F11 shows cost-effectiveness results if the number of relatives identified as being LS positive for each LS-identified proband varied from 2.1. If only one relative was identified as LS per proband, the incremental cost per QALY for all strategies on the efficiency frontier became higher than in the base-case analysis. This was because fewer relatives are benefiting from the identification of LS among CRC patients. The incremental cost per QALY of universal screening with MLH1 promoter hypermethylation testing became $56,272. The incremental cost per QALY for all screening strategies on the efficiency frontier is progressively more cost-effective as more relatives were tested compared with the base case.

Table F11: Incremental Cost per QALY for Comparators on the Efficiency Frontier Varying the Number of Relatives Diagnosed With Lynch Syndrome per Proband

Screening	Reflex Tumour Testing	dMMR Used in Chemo?	Base Case	1 LS-Positive Relative	3 LS-Positive Relatives
No Screening	Not applicable	yes	ref	ref	ref
rBG	BRAF-IHC + MLH1 promoter hypermethylation	yes	$4,866	$12,861	$2,221
rBG	MLH1 promoter hypermethylation	yes	$6,794	$16,344	$3,636
Younger than 70	MLH1 promoter hypermethylation	yes	$20,757	$41,562	$13,875
Universal	MLH1 promoter hypermethylation	yes	$28,902	$56,272	$19,848
Universal	BRAF-PCR	yes	$387,330	$703,629	$282,709
Universal	All receive germline testing	yes	$651,283	$1,180,357	$476,284

CRC = colorectal cancer; dMMR = deficient mismatch repair; IHC = immunohistochemistry; LS = Lynch syndrome; MMR = mismatch repair; PCR = polymerase chain reaction; QALY = quality-adjusted life-year; rBG = revised Bethesda Guidelines.
Note: Other strategies not shown because they were dominated (strictly or extendedly) by other strategies.

Table F12 shows that, if it is assumed that 0.50 of LS-identified CRC patients and their relatives would undergo biannual colonoscopy, the incremental cost per QALY of a universal screening strategy with MLH1 promoter hypermethylation reflex testing became $50,177. If it is assumed that all LS-identified CRC patients and LS-identified relatives would undergo biannual colonoscopy, the incremental cost per QALY of a universal screening strategy with MLH1 promoter hypermethylation reflex testing became $22,382.

Table F12: Incremental Cost per QALY for Comparators on the Efficiency Frontier Varying the Percentage of Patients Who Undergo Biannual Colonoscopy

Screening	Reflex Testing	dMMR Used in Chemo?	Base Case	Percentage of Identified LS Patients Who Undergo Biannual CRC Colonoscopy	
				50%	100%
No Screening	Not applicable	yes	ref	ref	ref
rBG	BRAF-IHC + MLH1 promoter hypermethylation	yes	$4,866	$11,238	$2,913
rBG	MLH1 promoter hypermethylation	yes	$6,794	$14,363	$4,475
Younger than 70	MLH1 promoter	yes	$20,757	$36,982	$15,784

Screening	Reflex Testing	dMMR Used in Chemo?	Base Case	Percentage of Identified LS Patients Who Undergo Biannual CRC Colonoscopy	
				50%	100%
	hypermethylation				
Universal	MLH1 promoter hypermethylation	yes	$28,902	$50,177	$22,382
Universal	BRAF-PCR	yes	$387,330	$630,830	$312,708
Universal	All receive germline testing	yes	$651,283	$1,058,435	$526,511

CRC = colorectal cancer; dMMR = deficient mismatch repair; IHC = immunohistochemistry; LS = Lynch syndrome; MMR = mismatch repair; PCR = polymerase chain reaction; QALY = quality-adjusted life-year; rBG = revised Bethesda Guidelines.
Note: Other strategies not shown because they were dominated (strictly or extendedly) by other strategies.

As shown in Tale F13, varying the proportion of female CRC probands and LS-positive female relatives who undergo total hysterectomy had minimal effects on cost-effectiveness results. As the proportion of patients undergoing preventive interventions rose, the more cost-effective all the intervention strategies became.

Table F13: Incremental Cost per QALY for Comparators on the Efficiency Frontier Varying the Percentage of Females Who Undergo Total Hysterectomy

Screening	Reflex Tumour Testing	dMMR Used in Chemo?	Base Case	Percentage of Identified Female LS Patients Who Undergo Hysterectomy	
				10%	40%
No Screening	Not applicable	yes	ref	ref	ref
rBG	BRAF-IHC + MLH1 promoter hypermethylation	yes	$4,866	$5,407	$3,525
rBG	MLH1 promoter hypermethylation	yes	$6,794	$7,377	$5,349
Younger than 70	MLH1 promoter hypermethylation	yes	$20,757	$21,642	$18,557
Universal	MLH1 promoter hypermethylation	yes	$28,902	$29,964	$26,261
Universal	BRAF-PCR	yes	$387,330	$396,161	$365,314
Universal	All receive germline testing	yes	$651,283	$665,836	$614,999

CRC = colorectal cancer; dMMR = deficient mismatch repair; IHC = immunohistochemistry; LS = Lynch syndrome; MMR = mismatch repair; PCR = polymerase chain reaction; QALY = quality-adjusted life-year; rBG = revised Bethesda Guidelines.
Note: Other strategies not shown because they were dominated (strictly or extendedly) by other strategies.

The impact of varying the overall prevalence rates of LS among all newly diagnosed CRC patients on the cost-effectiveness results are shown in Table F14. In the base case, the prevalence of LS was 0.028. If the overall prevalence of LS is assumed to be 0.01, the incremental cost per QALY of universal screening with MLH1 promoter hypermethylation as part of reflex testing compared with screening patients younger than 70 years with the same reflex testing strategy is $80,333. If the overall prevalence of LS is assumed to be 0.06, the incremental cost per QALY of universal screening with MLH1 promoter hypermethylation was $13,790.

Table F14: Incremental Cost per QALY for Comparators on the Efficiency Frontier Varying the Overall Prevalence of Lynch Syndrome in CRC Patients

Screening	Reflex Tumour Testing	dMMR Used in Chemo?	Base Case	Overall Prevalence of LS (in Patients Diagnosed With CRC)	
				0.01	0.06
No Screening	Not applicable	yes	ref	ref	
rBG	BRAF-IHC + MLH1 promoter hypermethylation	yes	$4,866	$12,760	$2,546
rBG	MLH1 promoter hypermethylation	yes	$6,794	$19,627	$3,024
Younger than 70	MLH1 promoter hypermethylation	yes	$20,757	$57,458	$9,973
Universal	MLH1 promoter hypermethylation	yes	$28,902	$80,333	$13,790
Universal	BRAF-PCR	yes	$387,330	$1,111,093	$174,678
Universal	All receive germline testing	yes	$651,283	$1,894,914	$285,888

CRC = colorectal cancer; dMMR = deficient mismatch repair; IHC = immunohistochemistry; LS = Lynch syndrome; MMR = mismatch repair; PCR = polymerase chain reaction; QALY = quality-adjusted life-year; rBG = revised Bethesda Guidelines.
Note: Other strategies not shown because they were dominated (strictly or extendedly) by other strategies.

Table F15 presents cost-effectiveness results if the costs for diagnostic tests (tumour MMR protein IHC [$1,215] PCR-BRAF [$690], and germline genetic testing [$1,780 for *MLH1* or *MSH2* genes; $2,199 for *MSH6* and *PMS2* genes]) were based on an alternative source, a private molecular diagnostic laboratory in Alberta, Canada (Dr. Kamnasaran: personal communication, 2016 Feb). As shown, cost-effectiveness results were quite different using these costs. The incremental cost per QALY of screening CRC patients younger than 70 years old using MLH1 promoter hypermethylation in the reflex testing strategy compared with screening CRC patients by the Bethesda criteria with the same reflex testing strategy is $103,000. The incremental cost per QALY of universal screening using MLH1 promoter hypermethylation in the reflex testing strategy is $143,932 compared with screening CRC patients younger than 70 years old with the same reflex testing strategy.

Table F15: Incremental Cost per QALY for Comparators on the Efficiency Frontier Using Alternative Testing Costs (Private Lab)

Screening	Reflex Tumour Testing	dMMR Used in Chemo?	Base Case	Alternative Testing Costs
No Screening	Not applicable	yes	ref	x
No Screening	Not applicable	no	x	ref
rBG	BRAF-IHC + MLH1 promoter hypermethylation	yes	$4,866	x
rBG	MLH1 promoter hypermethylation	yes	$6,794	$24,240
Younger than 70	MLH1 promoter hypermethylation	yes	$20,757	$103,000
Universal	MLH1 promoter hypermethylation	yes	$28,902	$143,932
Universal	BRAF-PCR	yes	$387,330	x
Universal	All receive germline testing	yes	$651,283	$577,726

dMMR = deficient mismatch repair; IHC = immunohistochemistry; LS = Lynch syndrome; MMR = mismatch repair; PCR = polymerase chain reaction; QALY = quality-adjusted life-year; rBG = revised Bethesda Guidelines.
Note: Other strategies not shown because they were dominated (strictly or extendedly) by other strategies.

Only one study identified in the clinical review included data to inform diagnostic accuracy estimates for IHC-based BRAF tumour testing. In this study,[69] the sensitivity and specificity of BRAF-IHC tumour testing was very similar to that of BRAF-PCR tumour testing. Therefore, a sensitivity analysis was undertaken in which the diagnostic accuracy of the IHC-based BRAF tumour test is assumed to be the same as the diagnostic accuracy of PCR-based BRAF. The results of this sensitivity analysis are provided in Table F16. Under the reanalysis, the incremental cost per QALY of a universal screening strategy with BRAF-based IHC tumour test and MLH1 promoter hypermethylation compared with screening patients younger than 70 years old with the same reflex testing strategy is $25,534. The incremental cost per QALY of moving to a universal screening strategy with MLH1 promoter hypermethylation reflex testing is $212,542. The incremental cost per QALY of moving to universal testing with an BRAF-IHC reflex tumour testing strategy is $232,676.

Table F16: Incremental Cost per QALY for Comparators on the Efficiency Frontier if Assumed Diagnostic Accuracy of IHC-Based BRAF is the Same as PCR-Based BRAF

Screening	Reflex Tumour Testing	dMMR Used in Chemo?	Base Case	BRAF-IHC Diagnostic Accuracy Same as BRAF-PCR Diagnostic Accuracy (sens = 0.57, spec = 0.98)
No Screening	Not applicable	yes	ref	ref
rBG	BRAF-IHC + MLH1 promoter hypermethylation	yes	$4,866	$4,451
rBG	MLH1 promoter hypermethylation	yes	$6,794	x
Younger than 70	BRAF-IHC + MLH1 promoter hypermethylation	yes	x	$18,375
Younger than 70	MLH1 promoter hypermethylation	yes	$20,757	x
Universal	BRAF-IHC + MLH1 promoter hypermethylation	yes	x	$25,534
Universal	MLH1 promoter hypermethylation	yes	$28,902	$212,542
Universal	BRAF-PCR	yes	$387,330	x
Universal	BRAF-IHC	yes	x	$232,676
Universal	All receive germline testing	yes	$651,283	$805,937

dMMR = deficient mismatch repair; IHC = immunohistochemistry; LS = Lynch syndrome; MMR = mismatch repair; PCR = polymerase chain reaction; QALY = quality-adjusted life-year; rBG = revised Bethesda Guidelines; sens = sensitivity; spec = specificity.
Note: Other strategies not shown because they were dominated (strictly or extendedly) by other strategies.

In the base-case analysis, CRC incidence rates for individuals with LS were based on a study by Bonadona et al.[129] In this study, the cumulative probability of developing CRC by the age of 70 was 35%. A sensitivity analysis was run in which CRC incidence data were based on findings from Choi et al.[130] This Canadian study found higher incidence rates of CRC than Bonadona among patients with LS. Specifically, Choi reported a cumulative risk of CRC of 60% in men with LS and 47% in women with LS by the age of 70. This sensitivity analysis is presented in Table F17. As the risk of developing CRC increased in patients with LS, it became more cost-effective to screen. The incremental cost per QALY of a universal screening strategy with MLH1 promoter hypermethylation became $14,265. The incremental cost per QALY of a universal screening strategy with PCR-based BRAF tumour testing is $245,480 under this new set of assumptions.

Table F17: Cost per QALY for Comparators on the Efficiency Frontier if Use Colorectal Cancer Incidence Data for Lynch Syndrome Patients From Choi et al.[130]

Screening	Reflex Tumour Testing	dMMR Adjuvant Chemo?	Base Case	Choi et al. CRC Incidence
No Screening	Not applicable	yes	ref	x
rBG	BRAF-IHC + MLH1 promoter hypermethylation	yes	$4,866	x
rBG	MLH1 promoter hypermethylation	yes	$6,794	ref
Younger than 70	MLH1 promoter hypermethylation	yes	$20,757	$9,011
Universal	MLH1 promoter hypermethylation	yes	$28,902	$14,265
Universal	BRAF-PCR	yes	$387,330	$245,480
Universal	All receive germline testing	yes	$651,283	$415,752

CRC = colorectal cancer; dMMR = deficient mismatch repair; IHC = immunohistochemistry; LS = Lynch syndrome; MMR = mismatch repair; PCR = polymerase chain reaction; QALY = quality-adjusted life-year; rBG = revised Bethesda Guidelines.
Note: Other strategies not shown because they were dominated (strictly or extendedly) by other strategies.

Patient Experience and Preferences

7. What are the perspectives of CRC patients, their family members, and their caregivers regarding the value and impact of dMMR testing on their health, health care, and lives?

16. Methods

A systematic review and thematic synthesis of the literature relevant to the research question on patient experience and preferences was conducted. We developed a unique protocol a priori and followed those pre-specified methods throughout the project. Minor deviations and refinements to the study methods are outlined in the Protocol Deviation table at the front of this document.

16.1 Literature Search Strategy

The literature search was performed by an information specialist using a search strategy peer-reviewed according to the PRESS checklist.[17] Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; and Embase (1974–) via Ovid. A limited PubMed search was performed to capture records not indexed in MEDLINE. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH, and keywords. The main search concepts were related to the intervention and condition of interest: DNA mismatch repair, colorectal cancer, and genetic testing. Two separate searches were performed. The first search combined these main search concepts with patient and family factors, such as experiences, satisfaction, and preferences. The second search addressed psychosocial issues, including

attitudes, behaviour, and acceptance. The PsycINFO database (1967–), via Ovid, was additionally searched for search #2. See Appendix 46 for the detailed search strategy.

Retrieval was not limited by publication year or language of publication. Conference abstracts were excluded from search #1, but included in search #2. Regular alerts were established to update the search until the publication of the final report. Regular search updates were performed on databases that do not provide alert services.

16.2 Eligibility Criteria

Eligible reports were those published in the English or French language that describe studies of any design that explored or assessed perspectives on any type of dMMR testing of anyone eligible for such testing, including people diagnosed with CRC and their family members, and/or their personal (i.e., not clinical) caregivers. To be eligible, studies must have explored or assessed participants' own perspectives directly and not indirectly; for example, through another person. Studies that assessed clinician perspectives only were excluded. Further, reports that described results for a combined population — for example, of people with breast, ovarian, and colorectal cancer — were excluded unless results were presented separately for CRC patients. Selection criteria are presented in Table G1.

Table G1: Eligibility Criteria

	Include	Exclude
Population	– People with colorectal cancer, their family members and/or their caregivers	– General population-based samples
Intervention	– dMMR testing of any type (tumour and/or germline) with or without genetic counselling	– Genetic counselling only – Direct to consumer testing – Pre-implantation genetic diagnostic testing
Comparator	– No testing – No comparator – dMMR testing of any type (tumour and/or germline)	

Outcomes	– Perspectives
	– Experiences
	– Beliefs
		– Perspectives regarding:
		  – Prenatal and pre-implantation genetic testing
		  – Direct to consumer testing

dMMR = deficient mismatch repair.

16.3 Screening and Selecting Studies for Inclusion

Two reviewers (LW, KM) independently screened the titles and abstracts of all citations retrieved from the literature search based on the selection criteria. For citations for which it was difficult to determine eligibility on the basis of title and abstract alone, the full text of the article was retrieved and assessed before determining eligibility. Discrepancies between the two reviewers were resolved through discussion. A pilot screening exercise was conducted at the beginning of the review process, which involved the two reviewers independently screening 25 articles to assess reliability in application of the eligibility criteria. Given the high level of agreement between the two reviewers following this pilot exercise, the reviewers proceeded with the two-stage screening process as planned.

16.4 Data Collection and Extraction

Data collection involved extracting data from primary reports regarding study characteristics and study results as relevant to the research question. From each eligible article, both descriptive data and results were extracted by one reviewer (LW, KM, or SG) into a standardized electronic form (see Appendix 47). The extractions were subsequently verified by a second reviewer (LW, KM or SG), with discrepancies resolved through discussion. Descriptive data included such items as first author, article title, study objectives, participant characteristics, and study design. In addition, verbatim result statements relevant to the research question were extracted from each of the included reports into the same standardized electronic form. Result statements were typically presented within the "results" section of a report; however, before being extracted, each result statement was assessed to ensure it was differentiated from raw data, methods, external data, and researchers' conclusions and implications. The latter were not extracted. Only results presented within the main report were extracted. Data from figures were not extracted unless specific labels (i.e., numeric values) were provided.

16.5 Quality Assessment

One reviewer with experience in qualitative and descriptive research (LW, SG, or KM) independently assessed the quality of each study using standardized criteria, depending on the study design. One other reviewer (LW, SG, or KM) verified the assessments. Discrepancies were resolved through discussion. Critical appraisal forms are found in Appendix 48 for qualitative studies[151-155] and Appendix 49 for cross-sectional studies.[156,157]

As there are no agreed-upon quality criteria among the qualitative research community, the criteria used within this review were developed to suit the purpose and intended uses of the results. For example, Thomas and Harden[158] argue that appraisal criteria within syntheses of "views" studies need to move beyond quality of reporting criteria to criteria that can better assess whether results are rooted in participants' own perspectives and experiences. Further, the Cochrane Collaboration proposes quality criteria focused on researcher bias, and hence the believability of results. Believability is assessed by examining researcher efforts to make his or her influence and assumptions clear as well as support for the accuracy of results, typically provided through an audit trail.[152] Additional criteria focus on quality of reporting, the nature and appropriateness of the methodological approach and specific methods, and congruence between the research design and the reported research questions, data collection, analysis and interpretation.[152,159,160]

The results of the critical appraisal process are reported narratively and summarized in a table to highlight the strengths and limitations of each study. They were not used as the basis for excluding any studies deemed to be of low quality.

16.6 Data Analysis

16.6.1 Descriptive analysis

A descriptive analysis was conducted, with the goal of characterizing the set of included studies in terms of important study and patient characteristics (e.g., PICOS, sample size). Study and patient characteristics are summarized in tables, and accompanied by a narrative description.

16.6.2 Thematic analysis

We conducted a thematic analysis that proceeded through three stages: coding, developing descriptive themes and developing analytic themes. The analysis was conducted using NVivo 11.[161]

16.6.3 Coding (stage 1)

To begin, one reviewer (LW) read through all of the data, without applying any coding structure, to become familiar with the data set in its entirety and the main concepts to emerge. The data were then coded line by line for meaning and content, beginning with an a priori "start list" of codes developed based on the research question and a preliminary reading of the data. The start list included, for example, reasons for pursuing testing, or not pursuing testing, expectations regarding testing, disclosure of test results, and a range of psychological outcomes. As coding progressed, other codes not on the start list emerged inductively to capture unexpected content grounded in the results themselves; for example, the impact of testing, or disclosure of test results on family relationships and health behaviours. When new codes emerged, all data were recoded to search for further instances of the meaning captured by that code.

During a pilot coding phase, the first 20 reports were coded independently by two reviewers (of LW, SG, and KM), with at least one code applied to each result statement. Coding was then compared, and discussed among the review team, with discrepancies resolved and corresponding refinements made to the coding template. Given the high level of agreement between reviewers during this pilot phase, the remainder of the coding process involved one reviewer (LW) coding all data with a second reviewer (either SG or KM) verifying the coding. After a set of 20 articles were coded, and verified, the three reviewers met to discuss progress and again refine the coding template to reflect emergent concepts. When all reports were coded, all of the text assigned to each code was read to assess consistency in interpretation and application and to determine whether any additional levels of coding were needed. Regular discussions among the review team during this process helped refine the coding structure, resolve differences, and confer authenticity within the emergent categories.

16.6.4 Developing descriptive themes (stage 2)

In the second stage of the thematic analysis, the codes developed in the prior stage were organized into related areas to construct "descriptive" themes. In this process, two reviewers independently explored similarities and differences between codes and grouped together all similar codes. All codes were related to one another in a chronological structure, representing the time period from before testing, through testing, and post-testing.[158]

Once descriptive themes were identified, a draft summary of the results across the studies organized by each theme was written by one reviewer (one of LW, SG, or KM) and subsequently reviewed by a second reviewer (one of LW, SG or KM). Where relevant, reviewers explored similarities and differences in data across included studies of different designs (e.g., cross-sectional, qualitative description) and that included different populations (e.g., CRC patients, relatives, those with known and unknown mutation status).[162] In this way, the summaries represented the range of perspectives held by CRC patients and their family members and subgroups emerged for which certain results apply.[158] The summary at this stage remained close to the results of the included studies, with minimal interpretation.

16.6.5 Developing analytic themes (stage 3)

During the final stage, the "data-driven" descriptive themes that emerged through the prior stage were analyzed through consideration of the research questions to develop "theory driven" analytic themes.[158] In this stage, the reviewers used the descriptive themes that emerged in the prior stage to infer answers to the question of value and impact of dMMR testing as perceived by people with CRC and their family members. Reviewers made these inferences independently, and met frequently to discuss their interpretations. Through the process of group

discussion, analytic themes were refined until a set of themes merged that was inclusive of all of the initial descriptive themes and was sufficient to answer the research question.

Throughout all stages of the thematic analysis, explicit notes were kept to record decisions made regarding coding and theme development. An audit trail was developed in this manner as a key step to help ensure rigour in the analysis, and these notes were used when writing up the results in order to describe to readers how various conclusions were reached.

17. Results

A total of 1,638 citations were identified from the initial electronic database, alerts, and search updates. Of those, 1,488 were deemed ineligible and the full text of the remaining 150 citations was retrieved for eligibility screening, of which 61 were excluded, leaving 89 eligible reports for inclusion in this review. The study selection processes are presented in a PRISMA flow diagram Appendix 50. A list of included studies is provided in Appendix 52, and a list of excluded studies is provided in Appendix 52.

17.1 Descriptive Analysis

17.1.1 Study characteristics

Most of the included studies used a survey (n = 59; 66%) or cross-sectional (n = 6; 7%) design, one of which used cross-sectional data collected as part of an RCT. An additional 19 studies (21%) were qualitative descriptive studies, one was a grounded theory study (1%), and another used an unclear design that was of a qualitative nature (1%). Two further studies were pre-post studies (2%) while the study design for one study (1%) could not be classified due to poor reporting. Accordingly, most of the studies collected data using questionnaires (n = 62; 70%), structured interviews (n = 3; 3%), through a chart review (n = 7; 8%) or using preference elicitation methods (n = 1; 1%). Studies of a qualitative design collected data using interviews (n = 26; 29%), focus groups (n = 2; 2%) and observation (n = 1; 1%). Some studies used more than one data collection method, accounting for percentages that add to more than 100%.

The sample sizes across the 59 survey studies ranged from 21 to 1,127 participants, with a median of 107 participants (mean = 176). The six cross-sectional studies ranged in size from 65 to 591 participants, with a median of 125 participants (mean = 208). Of the two pre-post studies, one enrolled 42 participants, and the other enrolled 106 participants. For the 19 qualitative descriptive studies, sample sizes ranged from seven to 155 participants with a median of 24 participants (mean = 36). The one grounded theory study included 23 participants and the one qualitative study of unclear design enrolled 36 participants. The one study of unclear design enrolled 199 participants. All studies included only adults, and all but two included male and female populations. Two included studies included only adult females.

More than half of the included studies were conducted in the United States (n = 46; 52%). Ten were conducted in the Netherlands (11%), six in Finland (7%), five in Australia (6%), five in Canada (7%), and three in the United Kingdom (3%). Two studies each were conducted Belgium (2%), France (2%), Japan (2%), and Sweden (2%), and one each was conducted in China (1%), Germany (1%), Italy (1%), New Zealand (1%), South Africa (1%), and Canada and the United States (1%).

The included studies were published between 1996 and 2015: eight (9%) were published in the 1990s, 25 between 2000 and 2004 (28%), 31 between 2005 and 2009 (35%) and the remaining 25 published between 2010 and 2015 (28%).

The characteristics included studies are summarized in Appendix 53.

17.1.2 Participant characteristics

Forty-nine studies focused on relatives, including relatives of confirmed mutation carriers (n = 34; 38%), relatives of people with CRC who are at risk or suspected of a mutation (n = 8; 9%), relatives of people with CRC with unknown mutation status (n = 6; 7%) and relatives of people with either a confirmed mutation or suspected of a mutation (n = 1; 1%). Nineteen studies focused on CRC patients, with a confirmed or suspected mutation (n = 4; 4%) or an unknown mutation status (n = 15, 13%), three with populations undergoing testing (n = 3; 3%). Eight studies include both CRC patients and their relatives who are suspected of carrying a mutation (n = 7; 8%) and patients with indeterminate mutation status and their relatives (n = 1; 1%). Thirteen studies include people of known mutation status, including both CRC patients and their relatives. Eight (9%) include confirmed mutation carriers only; five (6%) include both confirmed carriers and non-carriers.

Participants in the included studies range in age from 18 years to 98 years. More than half of the included studies included participants with a mean age between 40 and 49 years (n = 16; 52%), while 18 studies (20%) included participants of a mean age of 50 to 59 years, seven (8%) included participants of a mean age of 60 years or older, and eight (9%) included participants of a mean age of younger than 40 years. Approximately one-third of the included studies (n = 28; 31%) included roughly equal proportions of males and females, while more than half (n = 47; 53%) included more female than male participants, and eight studies (9%) included more males than females. Two studies (2%) included exclusively females.

Race was not reported in more than half (n = 47; 53%) of the included studies. Of the 42 studies that did report the race of study participants, four (9%) included entirely white or Caucasian participants, 21 (50%) included more than 90% white or Caucasian participants and another 10 (24%) included between 80% and 89% white or Caucasian participants. The majority (93%) of participants in one study conducted in South Africa were of mixed ancestry (Coloured) and spoke Afrikaans.[163] In another study conducted in the United States, the majority of participants (79%) were of Japanese ancestry and another 12% were Hawaiian.[164] In a qualitative study conducted in the US that included participants from three families, one family was Caucasian, one was African-American, and one was Mexican-American.[165] In a related qualitative study that included participants from five families in the US, four families were Caucasian and one was Hispanic.[166]

Of the studies that reported the relationship status of study participants, 87% (46 of 53) included more than two-thirds of participants who were married or cohabiting. Of the studies that reported the proportion of participants with children (n = 35), 15 (43%) included between 80% and 100% of participants with children, 13 (37%) included between 70% and 79% of participants with children, and seven (20%) included less than 70% of participants with children.

The characteristics of participants within the included studies are summarized in Appendix 54.

17.2 Thematic Analysis

Following the first two stages of the analysis, the data were organized into 12 categories within three descriptive themes. In the next step of the analysis, the descriptive themes were analyzed through careful consideration of the research question to identify “analytic themes.” Analytic themes represent the essence of the data in direct relation to the research question. In this case, the analytic themes represent the value and impact of dMMR testing from the perspective

of people with CRC and their family members. Two analytic themes emerged in this process. Table G2 represents the emergent analytic structure, including categories, descriptive themes, analytic themes and their relationships. In the following section, we provide a descriptive representation of the data in terms of the two analytic themes, using results within the descriptive categories as support.

Table G2: Emergent Data Categories, Descriptive Themes, and Analytic Themes

Descriptive Themes	Categories	Analytic Themes	
Making a decision to learn mutation status	Decision-making process		Deciding to learn about one's mutation status is an individualized process with implications for the individual and their family
	Reasons for, and factors related to, learning mutation status		
	Reasons for not, and factors related to not, learning mutation status		
	Perceptions of genetic testing		
	Knowledge of genetic testing		
	Uptake of testing		
	Willingness to pay		
Learning mutation status	Expectations regarding testing		
Behaviours, feelings, and experiences after learning mutation status	Confidence in test results		
	Satisfaction with decision to learn mutation status		
	Impact of knowing mutation status	Living with knowledge of one's mutation status has individual and family implications	
	Disclosure and discussion of mutation status		

Analytic theme: Deciding to learn about one's mutation status is an individualized process with implications for the individual and their family: Participants represented in the included studies, including people with a diagnosis of CRC and their family members, see value in knowing whether hereditary cancer runs in their family. Participants described value in relation to either how they anticipated they would react to the information, or how they did react to the information about their mutation status. Generally, people with a diagnosis of CRC expressed perceived value in terms of the benefits to their family members, including clarifying their risk and offering the opportunity for prevention or early detection of CRC. Family members, however, expressed value for themselves and their family members, also in relation to an ability to clarify risk and participate in enhanced CRC surveillance. Perceived value was articulated when participants described their reasons for learning their mutation status, their perceptions of genetic testing, how they made the decision to pursue testing, and through their expressed confidence in the testing process and satisfaction with their decision to learn their mutation status. While perceived value was articulated in many ways, people do hold some reservations or hesitations about the testing process. Some barriers and disadvantages to testing were also articulated, and some people decline the offer for genetic testing or express regret regarding their decision to learn their mutation status.

The experience of deciding to learn about one's mutation status is influenced by several factors relevant to the individual and family, which interact to make the experience unique for each individual. First, deciding to learn about one's mutation status takes place in the context of relatively low levels of knowledge about genetic testing in general, and genetic testing for hereditary CRC specifically. Further, people's prior expectations of their mutation status will likewise influence their experience, as does the nature of family relationships and an individual's coping style and their baseline levels of depression, anxiety, and distress.

A more detailed synthesis of the data from the included primary studies in support of this analytic theme follows, organized by the descriptive categories as outlined in Table G2.

17.2.1 Reasons for, and factors related to, learning mutation status

Many reasons were cited as to why people wanted to learn their mutation status. Further, reasons in favour of learning one's mutation status were cited more frequently than reasons against learning one's mutation status.[164,167,168] One of the most common reasons was the wish to clarify risk for other family members, in particular children, or the felt need to inform children and other family members of their mutation status and associated risk. Among the cross-sectional studies in which participants identified this issue as a reason, the majority of included participants did so,[165,168-175] while this was raised as an issue in several other studies without specific proportions measured or reported.[164,165,167,168,168,176-182] In one study, none of the included participants described being motivated to seek genetic assessment in terms of implications for themselves, but only for their family members, in terms of treatment or screening for other cancers.[178]

Another group of studies cited participants' desire to learn about or adopt appropriate medical management strategies to manage future risk, as an important reason for pursing testing. Most commonly, people identified wanting to understand appropriate colorectal screening behaviours or other strategies to manage a future risk of developing cancer. This reason was cited by between 17%[170] and 95%[173] of participants in a range of included cross-sectional studies,[168,170,171,173,175,181,183] and generally without specific proportions measured or reported in other studies.[164,167,172] As reported by one family member of a confirmed mutation carrier, "for me, the testing lets you know one way or other, yes, it is there; and then it gives you a chance to do preventive measures and early detection so that there's hope."[165] Similarly, to help prepare for the future was mentioned as a reason for learning one's mutation status in several studies, although this reason was cited less frequently than to clarify risk, or to adopt medical management strategies. Related reasons included to help prepare for the future in general,[167,172,184] to help with marital decisions,[172,173,175] and to help with reproductive decisions.[172,173,175]

In a group of included qualitative studies, themes related to family duties, responsibilities, and family impact emerged as important in participant descriptions of their stated reasons for pursuing testing and learning their mutation status.[171,185,186] For example, in one study, participants indicated they were only tested so they could learn whether their children were at risk, in which case they could then encourage their children to get tested.[171] In another, the possibility that a parent's mutation could be inherited by their children was of primary concern, and therefore learning about the children's risk was stated as a primary reason for genetic testing.[186] In the words of one high-risk CRC patient: "Obviously, I'm interested for my kids. That's the biggest thing I want to get out of it."[185]

17.2.3 Reasons for, and factors related to, not learning mutation status

Anticipated adverse psychological reactions are commonly cited as reasons for not learning one's mutation status, although among a minority of participants in the included studies. The range of anticipated reactions included concern over becoming anxious or worried,[168,170,172,187] concern over undefined general adverse psychological effects,[181] worry about the impact on one's family or their reactions,[168,170,175] as well as fear of becoming upset,[182] feeling guilty about passing on a mutation,[168] and being fearful of getting cancer or having transmitted a faulty gene to one's children.[172]

Anticipated potential problems with obtaining insurance,[168,170,172,175,181,183,187,188] employment,[172,181,188] or a mortgage,[183] or other financial implications,[187] were likewise reported as reasons for not learning one's mutation status, but again by a minority of participants. One group of studies[168,172,181,187,188] included reference to insurance and employment concerns by between 1%[188]and 5%[168] of study participants, while another group of studies[170,175,183] cited these concerns more often, by between 30%[170] and 60%[175] of study participants. Poor family communication[187,189] and/or lack of contact information for family members[187,189] was also reported, and related to complex family structures and estrangement.[187]

In a qualitative study of newly diagnosed CRC patients, among those who declined genetic assessment one of the major cited barriers was timing. They felt they did not have the personal resources to face another appointment or procedure, or the time to travel to another facility.[178] Logistics and timing concerns were likewise cited in cross-sectional studies, but by less than 5% of included participants in each case. Such reasons included being on a long holiday,[187] dealing with a recent bereavement or caring for an unwell relative,[187] being too busy with other commitments,[187] having too far to travel to a clinic appointment,[187] and the time needed to wait for test results.[168] Cost was also cited as a reason for not pursuing testing, particularly if the test was not covered by insurance and there were resultant out-of-pocket costs.[164,181,185]

17.2.4 Willingness to pay

One study described participants' WTP for genetic testing.[190] CRC patients, their first-degree relatives, and a control group of participants were included and given a stated range of the cost of genetic counselling and testing of US$1,500 to $2,000, and also told that many health insurers would not cover these costs. In this context, most participants stated they would be very reluctant to pay out of pocket for a genetic test. Two individuals from the patient group were disinclined to pay for themselves but did feel an out-of-pocket expense would be worthwhile for family members. As one person said, "I can't see it would do any good. Not for me now. I would insist my kids did it and I would pay for them." None of the included first-degree relatives or participants from the control group stated they would pay for the test at the stated price range. When asked how much they would be willing to pay out of pocket for the genetic test, patients reported a range from US$0 to $100, relatives from US$50 to $500 and controls from US$10 to $200.

17.2.5 Perceptions of genetic testing

Participants in the included studies described perceived advantages and disadvantages, beliefs, and opinions of testing independent of decisions to pursue testing, which were captured in our analysis as "Perceptions of genetic testing." Described perceptions mirror the stated reasons for and against learning mutation status to a great extent, and similar to the described reasons for learning mutation status, perceived advantages were described more frequently than perceived disadvantages.[191,192] Although benefits to testing appeared to be highly endorsed, positive perceptions did not always translate into testing decisions.[166,167]

The primary perceived advantage regarding genetic testing appears to be a general benefit to knowing test results and the associated CRC-related risk[163,166,193] or obtaining certainty regarding personal or family risk for heritable cancer.[191,192] For example: “You can not know and have to worry that you were going to develop cancer or you could find out and there is a chance that I’d be clear…knowledge is where it’s all at…I can’t understand why anyone would not want to know."[193] In particular, value was described in relation to a future preventive value for children.[165,194] Among non-carriers, people cited as primary advantages “reassurance” and that they knew their children were not at risk anymore.[192]

Perceived disadvantages related to the burden of follow-up medical care, psychological burden, and possible insurance discrimination.[191,192] In one study, non-carriers describe difficulties in relation to carrier relatives; for example, survivor guilt, feeling excluded, and negative reactions.[192] In another study, barriers related to an uncertainty associated with test results, with more than one-third of people agreeing that the MSI test does not provide a definitive result.[191]

17.2.6 Decision-making process

When making a decision whether or not to undergo testing, participants in the included studies fell into one of two categories: those who sought information as well as clarification of their family history and weighed the perceived benefits and harms of learning their mutation status, and those for whom making a decision appeared more of a straightforward and less of an involved process.[176,178,182,188,193,195] In one qualitative study, the researchers reported being surprised at how little participants spoke about the process of making a decision or consenting to dMMR testing when prompted to talk about their experience and involvement with the clinical genetics service.[176] Some participants in this study reported limited, or no, knowledge and memory of dMMR testing, but instead demonstrated a belief that it is acceptable to be unconcerned about the testing procedure because of a broader responsibility to family members to undergo testing. Others represented the decision as one that required little consideration due to either perceived benefits to their family or an implicit trust in the medical system.[176] This result is replicated in a separate study and exemplified with the following quote: "I didn’t really do much thinking about it… I didn’t really worry too much, I was quite prepared to do it and quite prepared to know.”[193]

Specific contexts appeared to make decision-making more difficult, including conflicting or negative opinions of family members.[178,193] "[My brother] was saying he wouldn’t have the test and things like this… but he got called an idiot enough times, he changed his mind."[193] The timing of decision-making in relation to the disease process could likewise pose a barrier. In one study that focused on decision-making close to the time of diagnosis,[178] coping with a new diagnosis including new physical limitations, as well as fear, anxiety, sadness, and shock took precedence over making a decision regarding testing. Participants described needing to confront fears of death and the burden of cancer, and among these competing demands, genetic assessment was not viewed as a high priority.[178] Further, the physical constraints imposed by the cancer diagnosis and treatment, as well as a need to attend medical appointments, imposed barriers to accessing genetic services. For some participants, timing was a major barrier and people were challenged to set aside additional time and personal resources to travel to another facility for another assessment.[178]

17.2.7 Uptake of testing

Several of the included studies reported rates of testing and non-testing, and of learning and not learning test results among various populations, including people living with CRC and their relatives, as well as the length of time it took to initiate testing following knowledge of

eligibility.[163,164,166,170,172,180,187,189,195-199] Appendix 55 includes a summary of the reported rates of uptake among the various populations included in the studies. Some of the higher reported rates of testing include 81% of people with an HNPCC-associated cancer or suggestive family history,[170] 88% of people who are first-degree relatives of confirmed mutation carriers and who are estimated to be at 50% risk of carrying a mutation,[172] and 97% of siblings of confirmed carriers.[163] In one study that explored rates of testing following two different ethical protocols, one in which insurance implications were explicitly stated in the consent form and one in which they were not, 81% of relatives of people diagnosed with CRC before 45 years of age who did not have insurance implications spelled out underwent testing, compared with 49% who underwent testing when insurance implications were explicitly mentioned.[198] Two studies reported rates specifically among children of confirmed carriers as 74%[163] and 69%.[196] Among any first-degree relative, reported rates were 34%,[189] 51%,[170] 56%,[187] and between 46% and 64%.[166] In one such study, 50% of first-degree relatives older than 25 years declined the offer of testing, although 70% accepted CRC screening.[187]

In one study, the proportion of CRC patients agreeing to germline testing for LS was compared based on a universal versus a selective (i.e., high risk) screening strategy. No statistically significant difference was reported based on screening strategy ($P = 0.24$). Based on a selective screening process, 86.7% agreed to receive genetic counselling, and of those, 77.0% underwent testing. Based on a universal screening process, 58.3% agreed to receive genetic counselling, and of those, 92.9% underwent testing.[199]

Two studies described CRC patients who have been tested, but did not yet know their results. In one such study, 90% of CRC patients who consented to have their blood drawn for testing intended to learn results,[195] and in the other study, 74% of people at risk based on a young age at diagnosis or a family history of CRC responded that they wanted their results, with no difference between those with and without first- and second-degree relatives with CRC.[180]

The timing of testing in relation to learning eligibility status was explored in two studies. In one Kaplan–Meier analysis, half of eligible first-degree relatives underwent testing within three years[187] and half did so within 19.7 months of learning their eligibility.[187] Uptake of testing reached a plateau of 77% by 12 years, after which no further tests were performed.[187] A separate study included five families with an identified mutation and at least five other family members estimated to be at 50% risk.[166] In this study, in four of the five families, probands shared information about their carrier status with at least one relative within two weeks of learning their results, and in these families, at least one first-degree relative requested testing within two months.[166] Among all at-risk relatives in these families, most underwent testing within 12 to 14 months. The amount of time that had elapsed since the last family member had undergone genetic counselling or testing ranged from 18 to 46 months across the families.[166] In the other family, the first relative to request testing did so within two months of notification, and the at-risk relatives who did undergo testing did so within 31 months.[166]

17.2.8 Confidence in test results

Overall, participants in the included studies appeared to have confidence in their test results.[172,179,185,188,200] The two studies that report confidence levels both report high levels of confidence: from 86% up to 97%.[179,188] Both studies reported higher confidence among carriers versus non-carriers, and that confidence levels did not change over time.[179,188] In one study, non-carriers who reported cancer worry had significantly less confidence in their test results as compared with those who were not worried.[179]

17.2.9 Satisfaction with decision to learn mutation status

Similarly, satisfaction with testing decisions overall were high, although a small percentage of people expressed regret at their decision to undergo testing. In one subset of included studies, satisfaction was assessed by asking participants to report their level of satisfaction.[174,179,196,197] In these studies, between 89% and 97% of participants reported high levels of satisfaction with their testing decision, a result that was reported to be maintained for up to seven years follow-up in one study.[179] Another subset of included studies asked participants whether they would be willing to take the test again, given their current knowledge and experience. In two such studies that included family members of mutation carriers, 93%[179] and 95%[188] of respondents were willing to take the test again.[179] In contrast, in another study that included confirmed mutation carriers,[201] and another that included both people diagnosed with CRC as well as their relatives,[169] 9% and 8% respectively reported regret regarding their testing decision and stated that if they were asked to be tested again, they would decline. In one qualitative study, at least one participant hinted at some possible ambivalence about having taken the test: "We sort of went with the flow . . . I'm not sorry I did do it [take the test], but I'd perhaps think differently next time."[193] Finally, one included study measured satisfaction by asking participants whether they felt that they had accomplished their purpose through testing, and a majority of participants expressed that they had done so: between 66% and 100%, depending on the stated purpose. In this study, three of the 36 participants expressed regret over being tested.[169]

17.2.10 Expectations regarding testing

Several studies reported proportions of people who expected to carry a mutation for cancer. Generally, a higher proportion of people meeting high-risk criteria — for example, based on family history — anticipated positive test results as compared with first-degree relatives of people diagnosed with CRC, or people with a CRC diagnosis. Among people meeting high-risk criteria, 70% in one study[174] and 72% in a separate study[170] reported they anticipated positive test results or believed they carried an HNPCC mutation. In one study including first-degree relatives of people diagnosed with CRC, a slightly lower proportion (64%) of people reported believing that their likelihood of being a gene carrier was at least 50%.[202] Finally, in studies including people diagnosed with CRC, 34%,[203] 36%,[177] and 47%[181] of participants reported expecting to carry a mutation and 26%[177] and 29%[203] anticipated testing negative.

Some aspects that were reported to be associated with the expectation of a positive result include having a strong family history of CRC,[163,165,177,193,194,203-205] a personal history of cancer,[163,170,204] being diagnosed at a young age,[177,194,203] being at high versus intermediate risk,[177] physical resemblance to other family members who have been diagnosed,[163,206] a personality resemblance to other family members who have been diagnosed,[206] the presence of existing symptoms,[163] and luck.[206] Some aspects that were reported to be associated with the expectation of negative result include feeling healthy or cured of cancer,[177] being optimistic,[177] or because an individual's siblings had already been affected[171] Some people who expected to have a positive result were still concerned about the possibility that they might be gene carriers (64%).[181] Despite expecting positive results, some people remained fearful due to the expectation of needing to undergo frequent testing or that their cancer could recur.[204] Expectations regarding carrying a mutation were significantly and positively associated with intentions to pursue genetic testing.[170]

17.2.11 Knowledge of genetic testing

In six included studies, researchers assessed knowledge about genetic testing prior to study participation among people diagnosed with CRC and their first-degree relatives.[170,181,190,191,202,207] Overall, knowledge was low, with between 64%[170] and 82%[181] of study participants reporting

they had not previously heard or read anything about genetic testing for CRC. In one study in which researchers asked about information sources, 98% of at-risk CRC patients reported never having read articles about MSI testing, and 6% reported hearing about the test on either television, radio, or the Internet.[191] It is possible that people with a higher average household income are more aware of genetic testing.[170] In one study, researchers administered a knowledge based test to at-risk CRC patients. Approximately 43% of the study participants did not answer any of the items correctly and less than 20% of participants answered more than half of the items correctly.[191]

In one Canadian qualitative study, researchers described newly diagnosed CRC patients' understanding of genetics as primarily negative and characterized by "myths and misconceptions."[178] They found knowledge about genetics to be non-specific, difficult to relate to personal experience, and outside the tangible experience of most participants, in contrast to their knowledge of cancer. They described that some participants equated genetic assessment with psychological counselling, and others equated genetic assessment with eugenic aspects or risk stratification in the context of insurance. Of those who perceived genetic assessment in a positive way, the usefulness was related to a contribution to broader scientific knowledge or finding a cure for cancer, but not for personal benefit. Participants in this study were often surprised that a genetic link could exist, and also surprised that this potential had not been discussed with them by their physician.

Analytic Theme: Living with knowledge of mutation status has individual and family implications: Learning of one's mutation status has implications for individuals and their families that encompass behavioural changes, psychological impacts, changes in family relationships, and subsequent decisions regarding disclosure of mutation status. Through our review, it became apparent that living with knowledge of one's mutation status requires an individual to face a series of subsequent decisions, including whether to modify their behaviour — for example, to participate in recommended medical surveillance or engage in other preventive behaviours such as diet and lifestyle modifications — and whether to disclose their mutation status to whom, when, and how. Further, these decisions take place in the context of psychological change, including a range of positive and negative emotions as people learn to cope with knowledge of their mutation status. Living with knowledge of one's mutation status is a process that can include an initial period of shock, anger, and worry, and subsequently progress to acceptance and coping, at which time decisions about disclosure and behaviour changes can be made. The process is individualized, and varies based on many factors including personal mutation status (i.e., whether an individual is mutation-positive or mutation-negative), the mutation status of family members, personal and family history of cancer, the family dynamic, and individual coping style.

A more detailed synthesis of the data from the included primary studies in support of this analytic theme follows, organized by the descriptive categories as outlined in Table G2.

17.2.12 Behaviour modification, screening, and medical management

Some participants in the included studies reported feeling compelled to change their behaviour after learning their mutation status. For many carriers, this involved an increase in CRC screening and other behaviour modification to mitigate cancer risks. In some studies, people reported changing their diet in the wake of positive test results,[174,208] and in others people described a process of embracing life and living more fully.[192,205] Some participants also described feeling compelled to encourage other family members to learn their mutation status, or to undergo CRC screening.[163,165,186,194,204,205,209] Most often it was the proband,[166] or an older

family member[165,186] who was instrumental in encouraging others. However, for a few people, the desire not to upset family members prevented them from encouraging others, or some simply did not want to interfere or influence what was perceived as a personal choice.[166]

Living with the knowledge of their mutation status also meant that individuals were making choices about child-bearing. Being a carrier meant that some participants decided not to have children, or not to have more children, due to their increased cancer risk. This behaviour change was reported by 9% of participants in the one study that included this outcome.[210] In another study, the desire to have children was reported to remain unchanged after people learned their mutation status.[205] In both these studies, participants described being worried about their children's risk of developing cancer.

Screening and medical management was a repeated concept among included studies, and related to behaviour change after learning mutation status. Overall, carriers were more likely to undergo colorectal screening than non-carriers after learning their mutation status;[174,179,187,192,200,201,211-213] however, this was not always the case. In one study, no difference in screening behaviour between carriers and non-carriers was reported after learning test results,[197] and in another, study carriers were found to be less likely to pursue screening as compared with non-carriers.[169] The impact of inconclusive test results on screening behaviour was not always clear, with one study reporting that these people were less likely to undergo screening as compared with carriers.[214] Untested individuals were also less likely to undergo screening, and were more likely to cease screening, compared with carriers.[187] Compared with carriers, non-carriers had decreased rates of screening after receiving their test results in one study,[215] decreased intention to screen in another,[192] and were overdue for screening in another.[213] Further detail on screening and medical management by mutation status is provided in Appendix 56.

Frequency of screening and adherence to recommendations was influenced not only by mutation status, but also included an individual's emotional state;[193,204,208] their confidence in the test results (less confidence led to more screening);[193,200] their confidence in screening recommendations or the effectiveness of screening;[186,193] perceived control over developing cancer (more control over cancer led to more screening);[212] and the felt burden of regular medication examinations (higher burden led to less screening).[192,201,204,208] Other correlates of increased screening frequency are less certain, but may include being female, a personal history of cancer, or increasing age.[216] Reasons for not screening may include pregnancy,[187,200] young age,[187,189] awaiting genetic test results,[187] current illness,[187] lack of time,[189,201] belief that they were at low risk,[200] implications for insurance,[186] other risks associated with screening (i.e., bowel perforation),[186] and physical disability.[187]

17.2.13 Disclosure and discussion of mutation status

Another important concept for individuals living with their test result relates to the issue of disclosure of mutation status to others. Within the included studies, disclosure practices were represented as a series of decisions, including whether or not to disclose, who should disclose, whom to disclose to, when to disclose, and how to disclose. Again, family relationships greatly influenced disclosure practices and some individuals expressed a need for support from their genetic counsellors and health care professionals in this process. It also became apparent that the process of disclosing test results means that the individuals receiving the information are then faced with their own series of decisions, primarily whether to pursue testing and how to live with the result.

Overall, the notion of a felt responsibility to disclose one's mutation status to family members, so that relatives could understand their risk, was apparent in the included studies.[163,166,182,204,206,217,218] In some studies, people reported the reasons why they chose to disclose their mutation status, many of which revolved around a family responsibility, including to encourage others to get testing,[163,182,218] to encourage others to participate in screening,[205] or to gain emotional support.[218] The need to inform other family members was described as a personal responsibility.[217] As one individual said, "I did feel responsible for the remainder of the family. At least you can do something about it. I sure would feel guilty if cancer would be diagnosed with a family member and this person was not being screened because he was unfamiliar with this risk. I would reproach myself very much."[219] The intrinsic motivation to inform others was reinforced by external cues, such as suggestions by their physicians or genetic counsellors.[219]

Following the decision to disclose mutation status, a subsequent decision must be made about to whom to disclose. In some studies, the typical pattern of disclosure involved the nuclear family or immediate family.[163,165,166,220] In other studies, disclosure also included extended family.[174,197,218] Rates of disclosure of mutation status to a sibling was high, with four studies reporting more than 90% of individuals choosing to disclose to their siblings.[163,214,218] Disclosure rates to living parents[163,174,214,218] and spouses was also relatively high,[163,174,197,214] with disclosure to spouses ranging from 65%[174] to 91%.[214] Disclosure rates to children were more variable,[163,174,196,197,214,218] from a low of 27%[174] to a high of 90%.[218] Some participants reported that they would wait to disclose their mutation status to their children until the children were older and they were more able to understand, and act on, the information.[163,196,221] Rates of disclosure to health care providers were less commonly reported,[163,174,222] but in the studies that did report on this outcome, it ranged from a low of 21% of carriers[163] to a high of 68% of those at risk for LS.[174] Disclosure to a health care provider depended on the provider and the circumstance in which the visit was made, and the perceived relevance of disclosure to the purpose of the visit.[222] Participants reported deciding to disclose to a health care provider so that the provider was made aware of the patient's family history and cancer risk and also so that patients could seek advice and information regarding appropriate screening.[222] Overall, most persons seem satisfied with their decision to disclose their mutation status, although some reported regretting this decision.[167,174]

Another component of the decision to disclose mutation status is the decision regarding when to disclose. Some individuals disclose soon after learning their mutation status, from the same day[163] to a week or a few weeks following.[166,174] Others take longer to disclose, sometimes years after learning their mutation status.[163,166] Delaying disclosure was sometimes related to a death in the family,[205] taking time to accept the result,[205] or waiting until children were older.[163]

In some of the included studies, disclosure is described as a burdensome topic,[183] and some participants, including carriers and non-carriers, described the need for professional support during the disclosure process, in particular with family members.[194,205,223] Some participants reported they would have preferred professionally organized family information meetings, as they found the topic of disclosure complicated and emotional.[194] In one study, it was found that if the initial disclosure of mutation status had gone poorly, participants were less likely to continue disclosing their results; however, if the first few conversations had gone well, then the primary informant was more likely to persist through difficult conversations with family members.[219] Families with open communication about health issues were more likely to be understanding of genetic information, and react more positively upon learning the news of hereditary cancer in their family.[219]

17.2.14 Psychological impact

Several psychological impacts were reported among the set of included studies, including both positive and negative impacts for both carriers and non-carriers: acceptance, anger, anxiety, attitude about the future, burden, coping, depression, distress and grief, empowerment, envy, fear, guilt, hope, perceived impact on others, isolation, perceived control over developing cancer, perceived risk, quality of life, relief, sense of unfairness, shock, uncertainty, and worry.

In one study, the process of accepting personal knowledge of mutation status for carriers was reported to come with time, reflection upon the testing process, and learning new information.[205] In another study, acceptance of test results was reported to be influential in adhering to screening recommendations.[208] It is possible that carriers may feel differently about the future after learning their mutation status: in one study, carriers reported living more consciously and recognizing their time as precious.[174,192,205] The notion of people feeling empowered by the process of genetic testing and learning their family history emerged in the review,[165,192] as did a feeling of confidence among carriers in being able to control future cancer through medical management and screening, as compared with non-carriers.[192,212] It is possible, however, that some individuals will feel burdened by their mutation status, and overwhelmed by the continuous medical management after learning they are mutation carriers.[208]

Several studies examined the impact of learning mutation status on negative psychological emotions, including anxiety, worry, depression, distress, and a feeling of isolation due to the perception that others do not understand what someone is going through. Overall, it appears that carriers experience an increase in these emotions immediately after learning their mutation status but, for most people, they return to baseline over the course of time.[179,188,192,200,224-227] It is also possible that some mutation carriers experience a short-term increase in fear of dying and fear of cancer, but again, for most people, these feelings decrease with time.[224] There appears to be a small subset of the population, both carriers and non-carriers, who are highly distressed, anxious, or depressed before genetic testing, and for whom these feelings do not return to baseline after learning their mutation status.[225,226,228] Additionally, feelings of distress may not decrease for people with uninformative test results.[225] Experiencing cancer worry and anxiety was reported in one study to be related to an accurate understanding of cancer risk: in this study, carriers who understood their risk and non-carriers who misunderstood their risk reported higher levels of cancer worry.[229]

Feelings of guilt were reported by both carriers and non-carriers within the included studies. Non-carriers reported feeling guilty about their mutation status in relation to the mutation status of their family members,[171,192,205,228] and also relieved of the potential guilt of passing the mutation on to their children.[174] Carriers reported feeling guilty about passing a mutation on to their children[165,174,204,205,228] and also relieved of the guilt that their cancer could their fault.[194] Like guilt, a feeling of relief was also reported by both carriers and non-carriers. Carriers reported feeling relieved to learn their mutation status and also that there were preventive measures they could take to mitigate their risk.[192,193,204] Non-carriers reported feeling relieved to learn their mutation status, again in relation to not passing a mutation on to their children.[192,193]

Overall, quality of life for people undergoing genetic testing appears similar to peers in the general population.[188] There likewise appears to be no difference in quality of life between mutation carriers and non-carriers.[180,197,211,224] People with high levels of distress before testing may report a low quality of life after learning their mutation status, and those with low distress before testing may report a high quality of life after learning their mutation status.[225,226]

The process of genetic testing and learning one's mutation status appears to have an impact on their feelings regarding their family members. For example, some carriers reported worry for their children,[174,228] while others reported a feeling of hope for their children's future.[194] Non-carriers reported needing to cope with the fear and worry for their family members who were found to be mutation carriers.[205] Others reported being fearful when their family members did not want to pursue genetic testing or regular screening,[165] and some non-carriers reported feelings of distress when their mutation status differed from that of their family.[171] An individual's feelings appear to be influenced by their relationship with family members. For some individuals, the mutation status of their family members was more predictive of their emotions than their own individual test results.[230]

17.2.15 Impact on relationships

Learning one's mutation status has an impact on family function and relationships, which appears to be mediated by the nature of the family dynamic before testing, and during the process of testing. In one study, members of families assessed as being cohesive and with good communication often reported that the process of genetic testing brought their family closer together.[205] In contrast, among families assessed as having poor cohesion and poor communication, the process of genetic testing was divisive.[205]

A range of negative impacts on family functions and relationships were reported in the included studies; for example, dreading communication or reluctance to communicate with family members,[166,186,194,219,231] and feelings of exclusion by family members with differing status,[192,193] distress when family members had a different mutation status,[171] concern for family members who have not had testing,[192] and concern for family members undergoing colonoscopy.[186,205] Other impacts include feelings of survival guilt among non-carriers,[192] resentment or anger among mutation carriers toward family members from whom they inherited the mutation,[205] and worry among mutation carriers for missing their family members grow up.[205]

Similarly, a range of positive impacts on family function and relationships were reported, including being drawn closer to family members;[166,192] feeling supported;[166,211] experiencing more open communication among family members;[192] feelings of relief, pride, and familial solidarity;[171] and experiencing a personal growth that affects family members.[192]

The nature of family relationships was influential regarding the disclosure of mutation status among family members. When relationships were fragile, some people reported feeling it was more appropriate for health care professionals to disclose mutation status within their family, due to a concern that otherwise the information would not get passed on.[231] In one study, some participants reported the disclosure process to be difficult with certain family members who denied a possibility of hereditary cancer.[165]

17.3 Summary of Quality Assessment

Overall, the cross-sectional studies included in this analysis were of moderate quality. The body of literature adds the perspectives and experiences of patients with CRC and their families as they go through decision-making and the process of genetic testing to determine their gene mutation status and risk for CRC. It may not be appropriate, however, to generalize the findings based on the included studies to populations that were underrepresented (e.g., ethnicities other than Caucasian, persons of lower socioeconomic status, persons with little motivation to be tested) by these studies.

Although the sampling strategies of the included cross-sectional studies were congruent with the research designs and study objectives, it was generally unclear or unlikely that the target population was representative of the population for which the results could be generalized.[164,167,169,170,172,174,175,179-184,187-189,191,192,195,197,200-203,206,209-218,224,226-230,232-249] Study samples were commonly mostly Caucasian,[170,184,195,202,207,209,211,213-215,218,226,230,232,234,236,238,245] well educated,[170,184,202,207,210,216,218,227,230,236,238,240-242] insured,[170,184,210,214-216,230,234,245] highly motivated,[167,170,172,174,179,188,200-202,206,213,215,224,228-230,232,233,238,245-249] and/or individuals with a high socioeconomic status.[217,235] Seven study samples comprised mostly women,[201,209,218,227,240-242] and three reported that most participants were married or partnered.[184,209,238] Three studies[173,177,199] examined samples that were likely representative of the population to which the results will be generalized, one drew their study populations from a large database,[199] one[177] provided demographic characteristics that seemed representative of a larger CRC population, and one[173] was likely generalizable as long as it was not beyond the population with HNPCC seeking predictive testing.

For the cross-sectional and survey studies, the construct of the data collection methods (i.e., questionnaire) was variable across studies. The use of valid and reliable questionnaires is important in survey studies, and necessary to ensure that the tools used to ask questions of the participants are indeed capturing the concepts that they are supposed to assess. Approximately half of the survey studies used valid and reliable questionnaires for data collection.[170,174,177,180,184,188,191,195,198-200,203,206,211,216,223,226,228,230,232-236,238,239,246,247,249] However, this means that approximately half used questionnaires that were not valid or reliable, or had uncertain validity and reliability.[167,169,171-173,179,181,182,188,189,192,196,197,202,210,212,213,217,224,227,229,237,240-242,244,248,250] A few studies had questionnaires with construct or face validity; based on a subjective judgment, they appeared to ask questions that were appropriate and designed to measure the questions they asked, and were not prone to recall bias.[164,175,183,201,209,214,243] Two studies[215,243] did not use reliable questionnaires. Few studies made explicit mention that the data collection methods were piloted tested.[164,174,180,216,223,233,235] For many studies, it was uncertain whether pilot testing occurred, or that no pilot testing occurred.[167,169,181,182,196,198,200-202,210,212,217,227,228,238,240-242,244,246,247,249] Overall, while an almost equal number of studies employed valid and reliable methods, few studies reported pilot testing of these methods.

A summary of the major strengths and limitations within each included survey or cross-sectional study is provided in Appendix 57.

Overall, the quality of the included qualitative studies was moderate. This body of literature added depth to the included cross-sectional data by allowing the perspectives and experiences of CRC patients and their family members to be represented in their own words. The majority of qualitative study reports included clear research objectives and data collection strategies congruent with those objectives.[163,165,166,168,185,186,193,205,208,219,221,222] In four study reports, however, data collection strategies were not well reported; for example, who conducted interviews and their training, how long interviews lasted, where interviews took place, or what questions were asked.[145,171,178,190,231,251] Data analysis strategies were reported with varying degrees of detail and were of varying quality. For some studies, strategies were clearly reported, congruent with research objectives and rigorous,[163,165,166,168,170,185,186,193,205,208,222] while for other studies, the quality of the analytic approach was difficult to assess with the limited information provided.[145,171,178,194] For those reports with clearly described analytic strategies, most often the results reflected a diversity in perspectives across research participants.[165,166,168,185,186,193,205,208,219] In three studies, qualitative data were inappropriately

quantified, with reported results focusing on frequencies and counts of emergent concepts, which was incongruent with participant recruitment strategies.[163,222,231]

Most studies did not include a description of any attempt to enhance dependability,[145,163,165,178,185,186,190,193,194,205,219,221,222,251] and some likewise did not report any attempts to enhance credibility of data collection and analysis.[145,190,194,221,251] Of those studies that reported strategies to enhance credibility, the most common approaches used were independent coding by more than one researcher[163,165,166,168,176,178,185,186,193,208,219,222,231] and reporting of verbatim data in the form of quotes.[163,165,166,168,176,178,185,186,219,222,231] In two studies, member checking was used as another means to enhance credibility.[193,208] In the five study reports in which attempts to enhance dependability were described, the strategies used included peer review[166,176,208,231] and peer debriefing.[168] It is unclear in most cases whether attempts to enhance rigour were not conducted, or not reported.

The role of the researcher(s) and the relationship between researcher(s) and participants were inadequately explored across this body of literature.[145,163,165,168,170,171,178,185,186,190,193,194,205,208,219,222,231,251] With the exception of two study reports,[166,176] there was no reporting of researcher assumptions and biases, reflections on prior experiences with the dMMR testing and qualitative research, and any related potential influences on data collection and analysis. In one study report, Peterson[166] explored assumptions and preconceived notions of family functioning based on published models in relation to the research question and data collection through interviews; and in another study report, Shipman[176] provided a description of the co-construction of accounts of responsibility toward family members in relation to learning one's mutation status between the interviewer and participants. It is unclear whether such reflective exercises were not conducted, or not reported.

Sampling strategies were likewise reported with varying quality, challenging the assessment of this quality appraisal criterion in many cases.[145,166,171,178,185,186,190,208,222,251] In one study, it was clear a purposive sampling strategy was used that was congruent with the research questions,[165] and in another it was clear that sampling continued until data saturation was reached.[193] Several studies selected participants from among those involved in separate cohort studies.[166,221,231] While this could be an efficient and convenient approach, it is incongruent with the purposive intent of sampling in qualitative research. Further, in most cases, little description was provided of how participants were selected from among the target population and it was not reported whether sampling continued until data saturation was achieved. One study report described that researchers identified a random sample from a registry,[219] and another developed an age- and sex-matched sample,[190] although it would have been more congruent with the research objectives to sample based on characteristics that could influence mutation status disclosure practices[219] or screening behaviour,[190] — including, for example, age, number of children, sex and psychological distress — in order to achieve diversity in perspectives.

A summary of the major strengths and limitations within each included qualitative study is provided in Appendix 58.

18. Discussion

18.1 Summary of Main Findings

18.1.1 Clinical review

a) Diagnostic performance of dMMR tests in detecting LS

Based on the results of our review, the overall sensitivity and specificity for pooled PCR-based testing studies relative to germline testing, as the reference standard, are estimated to be 0.940 (95% CI, 0.894 to 0.967) and 0.754 (95% CI, 0.670 to 0.823), respectively. The overall sensitivity and specificity for pooled IHC-based testing studies relative to germline testing as the reference standard are 0.900 (95% CI, 0.841 to 0.939) and 0.810 (95% CI, 0.643 to 0.910) respectively. A higher test sensitivity indicates a higher avoidance of FN test results, meaning that fewer patients who are actually LS positive will be missed, while higher test specificity indicates a higher avoidance of FP results, meaning that fewer patients will be identified as LS-positive who are truly not. In the case of either a FN or FP test result, a patient could potentially be harmed, by either not receiving intervention that could be potentially helpful, or receiving intervention that could potentially be harmful because of the test result. Use of pre-screening criteria, such as the rBG criteria, increases the pre-test probability of LS, and results in a higher post-test probability following a positive test compared with universal testing. However, pre-screening criteria also increase the risk of missed cases (LS patients who do not meet pre-screening criteria screened out before testing) and increases the post-test probability of LS with a negative test compared with universal testing.

b) Clinical utility of PCR-based or IHC-based tumour tests for improving health outcomes for family members

No evidence was identified examining the effect of PCR- or IHC-based CRC tumour tests on the outcomes of family members. However, a supplementary review[66] was conducted to determine the effects of surveillance on family members of CRC patients once tumour MMR status is known. That review identified a total of nine studies that showed that surveillance of LS family members was associated with a decreased risk of CRC and extra-colonic cancers, and better survival regardless of mutation status. Despite the increased risk in CRC and other cancers, there was no difference in the risk of mortality between mutation-positive and mutation-negative individuals, indicating a potential benefit of screening for LS for family members

c) Diagnostic performance of supplementary (BRAF and MLH1 hypermethylation) tests in detecting sporadic (non-germline) mutations

The results of the review show that MLH1 promoter hypermethylation testing has the highest sensitivity (0.82 versus 0.57 for BRAF-PCR and 0.36 for BRAF-IHC) to detect likely sporadic CRC. Therefore, hypermethylation testing appears to have the best ability to rule out LS. PCR-based BRAF mutation testing has the highest specificity (0.98 versus 0.96 for hypermethylation testing and 0.90 for BRAF-IHC). Therefore, PCR-based BRAF mutation testing to rule out LS will result in the fewest number of patients with LS being misdiagnosed as having likely sporadic CRC. Our results are inconclusive about the diagnostic accuracy of IHC-based BRAF mutation testing, due to a limited amount published data available.

d) Prognostic value of dMMR testing for predicting morbidity and mortality rates in CRC patients

Pooled results from a limited number of studies on the association between dMMR status and tumour relapse or survival rates of CRC patients, who do not receive adjuvant chemotherapy, show that patients with stage II dMMR tumours have statistically lower rates of relapse and those with stage III dMMR tumours have statistically better survival rates than patients with pMMR tumours. Limited evidence from individual studies also suggests that there are no

differences between dMMR and pMMR tumours in terms of survival rates (DFS or OS) in stage II, and relapse rates in stage III CRC, when no chemotherapy is administered.

Pooled results comparing survival rates of dMMR with pMMR from two studies show a statistically better DFS in stage II dMMR patients who received 5-FU + irinotecan, but the difference was not statistically significant in those who received 5-FU alone. The OS was not statistically different between the dMMR and pMMR groups, in recipients of either of the chemotherapy regimens. No data were available on the outcomes of interest in stage II patients who received oxaliplatin-based chemotherapy.

The results of our meta-analyses suggest that among stage III colon cancer patients who receive 5-FU alone (with or without leucovorin or levamisole), dMMR was associated with a statistically improved DFS, but similar OS rates. No survival difference was found between stage III dMMR and pMMR patients who received oxaliplatin-based or irinotecan-based chemotherapy regimens.

Overall, the limited number of studies included in this review does not permit a definitive conclusion about the value of dMMR status in predicting prognosis of CRC patients, although the limited evidence included in our review may suggest beneficial effects of adjuvant chemotherapy in colon cancer patients who exhibit dMMR.

18.1.2 Economic evaluation

In order to evaluate the value for money of different ways of using tumour dMMR testing to detect CRC patients with LS and their relatives, and to use tumour dMMR testing to guide adjuvant chemotherapy decisions in stage II high-risk colon cancer patients, an economic model was created. The economic model synthesized data from the clinical review along with other data sources to estimate the expected costs and outcomes (QALYs) of various testing and screening options in a Canadian population of CRC patients. Combinations of different dMMR screening strategies, reflex testing strategies, and the use of tumour dMMR testing in guiding adjuvant chemotherapy decisions were compared.

Using the models' base-case results, the strategy of screening CRC patients younger than 70 years old using MLH1 promoter hypermethylation as the reflex testing strategy would be considered the most cost-effective option if maximum WTP for a QALY was between $20,757 and $28,902. Universal screening with MLH1 promoter hypermethylation as part of the reflex testing strategy would be considered the most cost-effective option if maximum WTP for a QALY was between $28,902 and $387,330. Universal screening of CRC patients using PCR-based BRAF tumour testing as part of reflex testing would be considered the most cost-effective option if maximum WTP for a QALY was between $387,330 and $651,283 (Table F9). Using tumour dMMR status to help guide adjuvant chemotherapy decisions in stage II high-risk colon cancer patients was found to always lead to lower costs and higher QALYs compared with not using dMMR status, regardless of the combination of screening and reflex testing strategy used. The use of dMMR testing with the aim of directing adjuvant chemotherapy decisions was explored only in stage II high-risk colon cancer patients. Research on the horizon may expand the role of dMMR testing in guiding actionable information that affects patient care. For instance, upcoming trials are exploring the impact of dMMR testing in guiding the selection of chemotherapy in stage IV colon cancer patients. It remains too early to explore the cost-effectiveness of dMMR in many of the roles to guide treatment decisions, and this present model could only evaluate the use of dMMR status to guide chemotherapy decisions in stage II colon cancer patients.

The model results were found to be fairly robust in sensitivity analyses, the exceptions being when patients with LS had a higher risks of developing CRC, when using costs based on those from a private Canadian laboratory, and when the diagnostic accuracy of IHC-based BRAF tumour testing was assumed to be the same as the diagnostic accuracy of PCR-based BRAF tumour testing.

Comparisons of this economic analysis with other published studies are difficult because no other studies have looked at all the different combinations of screening and reflex testing strategies considered relevant to the Canadian setting that this current model does. Our model found the incremental cost per QALY of universal dMMR tumour testing compared with testing patients younger than 70 years to be $28,902 when MLH1 hypermethylation was used as part of the reflex testing strategy. The incremental cost per LS case detected was calculated as $9,475. A number of studies, using life-years or QALYs as their outcomes, included both universal screening and screening based on rBG as comparators. The incremental cost per QALY of universal versus rBG screening can be estimated as $24,015 in the current model. This is lower than the incremental cost per life-year reported by Ladabaum et al.[115] ($63,624), and much lower for this same comparison derived from Severin[120] (€254,011 per life-year) and the cost per QALY derived from Wang[118] ($103,264). The higher cost-effectiveness found in Ladabaum and Wang compared with our model may have to do with the cost of the tumour MMR test. In the analyses by Ladabaum and Wang, the cost of an IHC-based dMMR tumour test was assumed to be $280, which is much higher than the costs used in our model ($60.33). The difference between our model and Severin[120] may be partially due to their assumptions on the number of relatives in which LS was detected per proband. In this study, the authors assumed 3.83 relatives per proband would be approached with 30% accepting testing and 50% of these patients being LS positive. This results in a yield of 0.57 relatives detected to have LS for each proband. This is much lower than the yield used in the current economic analysis (2.10). Additionally, Severin did not consider the impact of detecting LS on subsequent cancer prevention in the probands.

The current model found the incremental cost per QALY of using PCR-based BRAF tumour testing in the reflex testing strategy compared with using MLH1 promoter hypermethylation was $387,330 within the context of universal screening. This relatively high cost-effectiveness was due to the small difference in specificity to detect likely sporadic CRC between the two supplemental tests (0.98 for tumour PCR-based BRAF, 0.96 for MLH1 promoter hypermethylation). Although the higher specificity in PCR-based BRAF tumour testing would lead to fewer false negative LS diagnoses for the PCR-based BRAF test compared with testing for MLH1 promoter hypermethylation, the number of LS cases detected was small (0.0774 versus 0.0779; Table F8).

In the base-case analysis, the costs of diagnostic tests were from a British Columbia public hospital lab. Sensitivity analysis was conducted when the costs of diagnostic test were based on costs from a private laboratory in Alberta, where testing costs were much higher. Cost-effectiveness results were quite different when the alternative costs were used in the model. If the alternative costs were used, then screening using Bethesda criteria with MLH1 promoter hypermethylation in reflex testing would be cost-effective if WTP for a QALY was between $24,240 and $103,000. Screening CRC patients who are younger than 70 years old with MLH1 promoter hypermethylation would be cost-effective if WTP for a QALY was between $103,000 and $143,932. Universal screening using MLH1 promoter hypermethylation in reflex testing would be cost-effective if WTP for QALY was between $143,932 and $577,726. It is expected that the costs of germline testing will continue to decline over time, and this sensitivity analysis

suggests that this may affect the overall cost-effectiveness of dMMR testing and screening strategies.

There were limited data on the diagnostic accuracy of IHC-based BRAF tumour testing. A sensitivity analysis was conducted in which it was assumed that the diagnostic accuracy for IHC-based BRAF tumour testing is the same as the diagnostic accuracy of PCR-based BRAF tumour testing. In this sensitivity analysis, universal screening with IHC-based BRAF tumour testing and MLH1 promoter hypermethylation as part of the reflex testing strategy would be considered cost-effective if WTP for a QALY is between $25,534 and $212,542. Universal screening with MLH1 promoter hypermethylation as part of the reflex testing strategy would be considered cost-effective if WTP for a QALY is between $212,542 and $232,676.

18.1.3 Patient experience and preferences

The review of the literature regarding the value and impact of dMMR testing from the perspective of people living with CRC and of their family members uncovered many relevant issues relating to the test decision-making process, reasons for and against testing, perceptions and knowledge of genetic testing, uptake of testing, confidence in test results, satisfaction with the decision to be tested, and the varied impacts and behavioural changes after learning about one's mutation status. It became apparent that people are more concerned with knowing their mutation status — i.e., with learning the results of the test — than the testing process. The testing process was given little, if any, consideration; instead, participants tended to focus on the importance (or not) of understanding if hereditary CRC ran in their family, the implications of positive or negative mutation status, and how to live with the results. It also became clear that the perceived value and impact of knowing one's mutation status extends beyond the individual to their family. People with a diagnosis of CRC, and their family members, expressed perceived value in terms of the benefits to family members, who could then have the opportunity to clarify their own risk or participate in enhanced CRC surveillance programs. While overall people perceived value in knowing their mutation status, our review also demonstrates the unique experience for each person involved. Whether an individual is mutation positive or negative, their prior expectations of their mutation status, the mutation status of their family members, the nature of their family relationships, and their personal coping style all influence the experience of deciding whether or not to pursue testing, learning test results, and learning to live with the knowledge of their mutation status.

Our review suggests several areas of relevance to implementation of a dMMR testing program. First, it seems important to consider the range of impacts and considerations after someone has learned their mutation status. Learning one's mutation status introduces a whole new range of scenarios, including whether to participate in medical surveillance, whether to change one's lifestyle, learning to cope with and accept the results, and the need to make decisions about whether to disclose the results, and to whom and how. Many people describe at least some of these situations as troublesome, suggesting that following testing, there is a need for suitable and ongoing support. A small group of people, who are highly depressed, anxious or distressed before testing, may experience an exacerbation in these symptoms upon testing, whether they are mutation carriers or not. These people would likely benefit from enhanced counselling and support throughout the testing process. While these implementation considerations are important in any environment, they may be particularly relevant to consider in rural and remote settings, where access to services could be less than in more populated jurisdictions. Further, in our review, it also became clear that people are making decisions about testing, and living with their test results, in a low-literacy environment. Generally low levels of knowledge about genetic testing suggests a need for support for individuals — for example, as people turn to their

friends, colleagues, and family members for support in deciding whether to learn their mutation status — and, if they pursue testing, then to understand their related cancer risk and whether to implement desired behaviour or medical changes. It also suggests a need for support on a professional level, so that people are able to obtain support from their family physicians; for example, to implement recommended medical surveillance based on their mutation status. In our review, there is evidence to suggest that some people do not disclose their mutation status to their family physicians, in some cases due to a perceived lack of knowledge of LS, which could mean that some people have difficulty implementing recommended screening guidelines. There is also a suggestion within the included studies that non-carriers might not be as vigilant about screening, and perhaps even less so than the general population, further suggesting a need for physician education. It is important that family physicians can support people in obtaining the recommended surveillance, whether they are mutation positive or negative, and to also modify their lifestyle, if appropriate; for example, through diet and lifestyle changes or modification of other risk factors.

18.2 Strengths and Limitations

The clinical review provides a comprehensive review of available comparative evidence on: 1) the diagnostic performance of PCR-based and IHC-based dMMR tests, as well as supplementary BRAF and MLH1 hypermethylation testing for diagnosis of LS in CRC patients; 2) the value of dMMR status, determined by PCR-based or IHC-based dMMR tests, in predicting the prognosis (morbidity and mortality) in CRC patients who do not receive adjuvant chemotherapy, and colon cancer patients who undergo adjuvant chemotherapy after resection of their tumours. Strengths and limitations of the existing evidence are also highlighted in this report through appraisal of the quality of the included studies.

Despite the above-mentioned strengths, the following limitations should be considered in interpretation of this HTA.

Search strategies were designed de novo to comprehensively retrieve studies relevant to the six questions of interest, which served as the basis for this review. However, when previously identified systematic reviews related to the questions of interest existed, this resulted in narrow search date limits to retrieve a smaller pool of literature to be screened for some questions. While this resulted in some efficiency, there may be concerns that the identified reviews themselves were not comprehensive. Particularly for Question 3, there were concerns regarding search limitations of the systematic review (i.e., only the PubMed database was searched, and a full description of search terminology was not provided). This limitation was mitigated by the extensive number of studies relevant to our research question that the review[67] included in its analysis.

Most of the included studies for the evaluation of diagnostic performance of the study tests (Question 1 and Question 3) were methodologically variable (e.g., variable types or numbers of test markers or proteins), not designed as diagnostic accuracy studies, based on small sample sizes, and generally heterogeneous. Heterogeneity was explored through subgroup analyses (Question 1) or removal of outliers (Question 3), but no clear sources of heterogeneity were identified. While the presence of heterogeneity reduces the reliability of the pooled estimates, ROC analysis revealed that variation was greater for specificity than sensitivity. This may be less of a concern for a screening test where there is more tolerance for FPs (i.e., more patients screened in than screened out). Many studies for Question 1 used pre-selection criteria that may not accurately reflect the universal testing scenario. For example, the pre-test probability of

LS of 18% or 19% may be higher than the true pre-test probability in the general CRC population, although test sensitivity and specificity would not be affected.

Our review attempted to assess whether screening CRC patients for LS, using dMMR tests, could reduce morbidity and mortality rates of their family members (Question 2), but found no evidence, in the form of test-to-outcome studies, to address this question. However, a supplementary review[66] focused on the potential benefits of surveillance based on the knowledge of MMR status resulting from testing. This review found that surveillance of LS family members was associated with a decreased risk of CRC and extra-colonic cancers, and better survival regardless of mutation status. While mutation-carrying family members had a higher risk of CRC and other cancers, there was no difference in the risk of mortality between mutation-positive and mutation-negative individuals, suggesting a potential benefit of screening for LS for family members.

This review is not able to provide a definitive conclusion regarding the prognostic value of dMMR tests (Question 4 and Question 5) in CRC patients, for the following reasons: 1) a limited number of studies met the review's specific inclusion criteria (e.g., studies were required to report on the survival outcomes of colon cancer patients, based on their dMMR status, stage of colon cancer, and adjuvant administered chemotherapy regimens); 2) a limited, and for some comparisons insufficient, number of studies reporting on each study outcome (i.e., DFS, OS, or relapse rates) were found that allowed a meta-analysis to be performed; 3) there were some levels of heterogeneity across the studies, in terms of study populations, study designs, and reported outcomes that could seriously affect interpretation of the meta-analysis results. Although attempts were made to explore the sources of heterogeneity, comprehensive subgroup and sensitivity analyses could not be performed, due to the limited number of studies available.

There are a number of limitations to the economic analysis. No direct evidence of the effectiveness of tumour dMMR testing on long-term outcomes, such as incidence of cancer or mortality, was found in the literature. Therefore, the benefits of testing had to be extrapolated using various pieces of information. An important variable in the model was the reduction in CRC incidence that would result if LS patients underwent biannual colonoscopy. The evidence for this benefit was based on limited evidence. The economic model used a cohort approach. This means that all patients were assumed to have similar characteristics. This approach could bias estimates of the incremental benefit of increasing the breadth of tumour dMMR testing. For example, the model assumed that newly diagnosed CRC patients identified as having LS will result in an average of 2.1 relatives being diagnosed with LS and that the average age of relatives testing positive for LS is 41. However, these numbers could be quite different for older CRC patients. Moving from a strategy of screening patients younger than 70 to universal screening will result in additional LS cases being detected. However, the additional LS cases detected will be in CRC patients aged 70 years and older. The benefit being accrued to detecting older LS patients may be different from the benefit of detecting LS in CRC patients of average age. This is not presently captured in the current model.

One important limitation of the included studies describing patient experience and preferences is that the cross-sectional nature in many cases presupposed what issues were important to participants, instead of allowing those issues that participants identified as important to be explored. For example, a large body of cross-sectional literature regarding the psychological impact of testing was uncovered, including, for example, the impact of learning one's mutation status on depression, anxiety, and distress.[179,188,192,200,224-228] In the qualitative studies, which allowed those issues identified as important to participants to be explored, these negative

psychological impacts were raised, but infrequently. In the qualitative literature, more of a balance between positive and negative psychological impacts was found; for example, becoming empowered to implement preventive behaviours, learning to cope with results, and a bonding that can happen between family members who share a common mutation status. Another limitation is that many of the included studies included a primarily white, educated population with above-average incomes, which has implications for generalizability of the results to the Canadian population. It is possible that people who are not white, not highly educated, or have lower household incomes hold different perspectives and have had different experiences with learning their mutation status. Because we could not explore these issues with the studies included in this review, it is unclear whether the results reported here are generalizable across Canadian jurisdictions. A final limitation is with respect to the lack of published research regarding the potential prognostic value of dMMR testing, and related patient perspectives and experiences. No relevant literature was uncovered for inclusion in our review, and therefore our analysis excludes discussion of this use of test results. Future research to explore the value that people living with CRC might place on using knowledge of their dMMR status to guide treatment decisions would be valuable.

19. Conclusions

Based on the results of our review, both PCR-based and IHC-based tumour testing have similar sensitivity and specificity for detecting possible cases of LS, though IHC-based tumour testing has the added advantage of identifying which MMR protein is affected, which can guide follow-up testing to reduce the probability of a somatic mutation. Use of pre-screening criteria, such as the rBG criteria, can increase the prevalence of LS in the population being screened, but also increases the risk of missed cases (LS patients who do not meet pre-screening criteria screened out before testing). No evidence was identified that examined the effect of dMMR testing on the outcomes of family members. However, a supplementary review suggested a potential benefit of screening for LS for family members. Following initial tumour testing, additional tests can be done to identify probable somatic (non-inherited) events. MLH1 promoter hypermethylation testing appears to have the best ability to rule out LS. PCR-based BRAF mutation testing has the highest specificity. Therefore, using PCR-based BRAF mutation testing to rule out LS will result in the fewest number of patients with LS being misdiagnosed as having likely sporadic CRC. The results are inconclusive about the diagnostic accuracy of IHC-based BRAF mutation testing, due to a limited amount of published data available. Overall, the limited number of studies included in this review does not permit a definitive conclusion about the value of knowing dMMR status in predicting prognosis of CRC patients, although the evidence suggests beneficial effects of adjuvant chemotherapy in colon cancer patients who exhibit dMMR.

Using dMMR testing to help guide adjuvant chemotherapy decisions in patients with stage II colon cancer at high risk of recurrence leads to lower costs and higher QALYs compared with not using dMMR status to guide adjuvant chemotherapy decisions. Based on the current analysis, universal screening with hypermethylation as part of the reflex testing strategy would be considered the cost-effective strategy under most circumstances. Although there is no consensus on a WTP value for a QALY, it is likely within the range that this strategy would be considered to be cost-effective ($28,902 to $387,330). Conclusions would be similar for most sensitivity analyses, the exceptions being when patients with LS have a higher risk of developing CRC, when using costs based on those from a private Canadian laboratory, and when the diagnostic accuracy of IHC-based BRAF tumour testing was assumed to be the same as the diagnostic accuracy of PCR-based BRAF tumour testing.

Our review of the patient experience literature suggests that CRC patients and their family members consider knowledge of their mutation status to be a valuable piece of information. The perceived value is most often attributed to the benefit to one's family members, or oneself, in terms of potential to reduce future risk of cancer. The experience of learning one's mutation status, and learning to live with the knowledge of one's mutation status, is influenced by many factors, including personal mutation status, the mutation status of family members, personal and family history of cancer, the family dynamic, and individual coping style. These factors interact to make the experience unique for each individual. This review also highlights a need for support throughout the testing process, including making the decision as to whether or not to pursue testing, understanding test results, deciding whether to modify behaviour or lifestyle upon learning test results, and deciding whether or not to disclose test results and to whom, when, and how.

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Appendix 1: Literature Search Strategies

OVERVIEW	
Interface:	OvidSP
Databases:	EMBASE <1974-2015 Feb 20>, oemez Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE <1946 to current>, prmz **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	February 23-24, 2015
Study Types:	Question #1: Studies reporting analytical or clinical validity with evidence of tests' sensitivity and specificity Question #6: Cost-effectiveness and cost-utility studies All other questions: No study type filter(s) used
Limits:	English or French language Humans, where possible

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.mp	In MEDLINE=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier In Embase=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ed	In MEDLINE=Entry Date
.em	In Embase=Entry Week
.pt	Publication type
.tw	Textword; includes Title (TI), Abstract (AB), and Drug Trade Name (TN)

MULTI-DATABASE STRATEGY

Question #1

Line #	Searches	Results
1	exp Colorectal Neoplasms, Hereditary Nonpolyposis/ use prmz	3616
2	exp Hereditary Colorectal Cancer/ use oemezd	3056
3	HNPCC.tw.	4714
4	((hereditary or familial or inherited) adj3 (nonpolyposis or non-polyposis) adj3 (colorectal* or colo-rectal* or colorectum* or colo-rectum* or colon* or rectal*	6352

MULTI-DATABASE STRATEGY		
Question #1		
Line #	**Searches**	**Results**
	or rectum or sigmoid or anal or anus or perianal* or peri-anal* or circumanal* or circum-anal*) adj3 (cancer* or carcinoma* or neoplas*)).tw.	
5	lynch syndrome*.mp.	4370
6	(lynch* adj (cancer* or famil*)).tw.	46
7	or/1-6	11922
8	Microsatellite Instability/	9846
9	exp Microsatellite Repeats/ use prmz	33543
10	DNA Mismatch Repair/ use prmz	1629
11	Base Pair Mismatch/ use prmz	3947
12	Microsatellite DNA/ use oemezd	14483
13	Mismatch Repair/ use oemezd	6706
14	Base Mispairing/ use oemezd	4426
15	(dMMR or (MMR adj (abnormal* or deficienc* or test*)) or (error* adj phenotype* adj replication*) or replication error* or ((microsatellite* or micro-satellite*) adj (analy* or instabilit* or unstable)) or IMSI or MSI).tw.	21713
16	((mismatch* or mis-match*) adj2 repair*).tw.	16434
17	or/8-16	83577
18	exp "Sensitivity and Specificity"/	657401
19	exp "Reproducibility of Results"/ use prmz	288491
20	Reproducibility/ use oemezd	155619
21	diagnos*.mp.	5732550
22	(accurac* or sensitiv* or specific* or (detection* adj2 limit*) or (ROC adj (curve* or analys*)) or receiver operating characteristic* or signal-to-noise ratio* or predictive value*).tw.	7069425
23	(predict* or reliabilit* or reproducib* or validit*).ti.	565206
24	or/18-23	12358818
25	DNA Mutational Analysis/ use prmz	48646
26	Genetic Testing/ use prmz	27674
27	Germ-Line Mutation/ use prmz	7147
28	Nucleotide Sequence/ use oemezd	442739
29	Genetic Screening/ use oemezd	50345
30	Germline Mutation/ use oemezd	1341
31	((germline or germ-line) adj8 mutation*).tw.	26436
32	((genetic* adj test*) or gene test* or (mutation* adj analysis)).tw.	77574
33	or/25-32	629399
34	exp animals/	38018358
35	exp animal experimentation/ or exp animal experiment/	1851046
36	exp models animal/	1259150
37	nonhuman/	4492146
38	exp vertebrate/ or exp vertebrates/	36954274
39	or/34-38	39345502
40	exp humans/	29664676
41	exp human experimentation/ or exp human experiment/	347678
42	or/40-41	29666766

MULTI-DATABASE STRATEGY		
Question #1		
Line #	**Searches**	**Results**
43	39 not 42	9680332
44	(conference abstract or conference review).pt.	1822649
45	7 and 17 and (24 or 33)	5149
46	45 not (43 or 44)	4402
47	limit 46 to (english or french)	4104
48	remove duplicates from 47	2436

MULTI-DATABASE STRATEGY		
Question #2		
Line #	**Searches**	**Results**
1	exp Colorectal Neoplasms, Hereditary Nonpolyposis/ use prmz	3543
2	exp Hereditary Colorectal Cancer/ use oemezd	2991
3	HNPCC.tw.	4689
4	((hereditary or familial or inherited) adj3 (nonpolyposis or non-polyposis) adj3 (colorectal* or colo-rectal* or colorectum* or colo-rectum* or colon* or rectal* or rectum or sigmoid or anal or anus or perianal* or peri-anal* or circumanal* or circum-anal*) adj3 (cancer* or carcinoma* or neoplas*)).tw.	6313
5	lynch syndrome*.mp.	4230
6	(lynch* adj (cancer* or famil*)).tw.	46
7	or/1-6	11726
8	Family Health/	28436
9	Neoplastic Syndromes, Hereditary/ use prmz	1658
10	Familial Cancer/ use oemezd	10111
11	Pedigree/	103010
12	Pedigree Analysis/ use oemezd	6064
13	exp Consanguinity/ use oemezd	9147
14	Relative/ use oemezd	8280
15	(familial* or family* or families* or inherited or kindred* or proband or probands or relative or relatives).tw.	3024272
16	or/8-15	3075875
17	Microsatellite Instability/	9712
18	exp Microsatellite Repeats/ use prmz	32997
19	DNA Mismatch Repair/ use prmz	1566
20	Base Pair Mismatch/ use prmz	3900
21	Microsatellite DNA/ use oemezd	14017
22	Mismatch Repair/ use oemezd	6624
23	Base Mispairing/ use oemezd	4382
24	(dMMR or (MMR adj (abnormal* or deficienc* or test*)) or (error* adj phenotype* adj replication*) or replication error* or ((microsatellite* or micro-satellite*) adj (analy* or instabilit* or unstable)) or IMSI or MSI).tw.	21312
25	((mismatch* or mis-match*) adj2 repair*).tw.	16160
26	or/17-25	81919
27	exp animals/	37582283
28	exp animal experimentation/ or exp animal experiment/	1839306

MULTI-DATABASE STRATEGY		
Question #2		
Line #	**Searches**	**Results**
29	exp models animal/	1239006
30	nonhuman/	4454398
31	exp vertebrate/ or exp vertebrates/	36622291
32	or/27-31	38855213
33	exp humans/	29254155
34	exp human experimentation/ or exp human experiment/	345965
35	or/33-34	29256232
36	32 not 35	9600566
37	(conference abstract or conference review).pt.	1767833
41	7 and 16 and 26	4237
42	38 not (36 or 37)	3696
43	limit 39 to (english or french)	3430
44	remove duplicates from 40	2033

MULTI-DATABASE STRATEGY		
Question #3		
Line #	**Searches**	**Results**
1	exp Colorectal Neoplasms, Hereditary Nonpolyposis/ use prmz	3590
2	exp Hereditary Colorectal Cancer/ use oemezd	3033
3	((colorectal* or colo-rectal* or colon* or rectal* or rectum or sigmoid or anal or anus or perianal* or peri-anal* or circumanal* or circum-anal*) adj5 (cancer* or carcinoma* or neoplas* or tumor* or tumour*)).ti.	212472
4	HNPCC.tw.	4704
5	((hereditary or familial or inherited) adj3 (nonpolyposis or non-polyposis) adj3 (colorectal* or colo-rectal* or colorectum* or colo-rectum* or colon* or rectal* or rectum or sigmoid or anal or anus or perianal* or peri-anal* or circumanal* or circum-anal*) adj3 (cancer* or carcinoma* or neoplas*)).tw.	6336
6	lynch syndrome*.mp.	4322
7	(lynch* adj (cancer* or famil*)).tw.	46
8	or/1-7	218600
9	Microsatellite Instability/	9781
10	exp Microsatellite Repeats/ use prmz	33247
11	DNA Mismatch Repair/ use prmz	1595
12	Base Pair Mismatch/ use prmz	3921
13	Microsatellite DNA/ use oemezd	14370
14	Mismatch Repair/ use oemezd	6679
15	Base Mispairing/ use oemezd	4421
16	(dMMR or (MMR adj (abnormal* or deficienc* or test*)) or (error* adj phenotype* adj replication*) or replication error* or ((microsatellite* or micro-satellite*) adj (analy* or instabilit* or stabil* or stable or unstable)) or IMSI or MSI).tw.	21908
17	((mismatch* or mis-match*) adj2 repair*).tw.	16333
18	(hMLH1 or hMLH-1 or MLH1 or MLH-1).mp.	11524
19	(immunohistochem* or IHC).mp.	903717
20	or/9-19	983303

MULTI-DATABASE STRATEGY		
Question #3		
Line #	**Searches**	**Results**
21	DNA Methylation/	73825
22	((DNA adj methylation) or MLHHM or MLH1H or MethyLight or Methylation-Specific Multiplex Ligation-Dependent Probe Amplification or MS-MLPA or "(MS)-MLPA" or ((hMLH1 or hMLH-1 or MLH1 or MLH-1) adj5 (hypermethylation* or hyper-methylation* or methylated or methylation*)) or (MLH1 and (promoter adj2 methylation))).mp.	89236
23	"Proto-Oncogene Proteins B-raf".mp. use prmz	4203
24	B Raf kinase/ use oemezd	7273
25	(BRAF* adj2 screening).ti.	6
26	(BRAFP or "BRAF(V600E)" or "BRAF-(V600E)" or BRAFV600E* or (BRAF* adj3 V600E) or BRAF-V600E* or ((BRAF* or V600E) adj2 mutation*)).tw.	10547
27	(MBPIN or "MLH1 Hyp/BRAF (V600E)").tw.	1
28	or/21-27	104898
29	20 and 28	12715
30	(HNPCC BRAF or Lynch BRAF or (Lynch MLH1 adj3 (hypermethylation* or hyper-methylation* or methylated or methylation*))).tw.	3
31	exp animals/	37838734
32	exp animal experimentation/ or exp animal experiment/	1847086
33	exp models animal/	1251185
34	nonhuman/	4480184
35	exp vertebrate/ or exp vertebrates/	36779289
36	or/31-35	39163082
37	exp humans/	29515893
38	exp human experimentation/ or exp human experiment/	347022
39	or/37-38	29517981
40	36 not 39	9646696
41	(conference abstract or conference review).pt.	1810180
42	exp humans/	29254155
43	exp human experimentation/ or exp human experiment/	345965
44	or/42-43	29256232
45	41 not 44	9600566
46	(conference abstract or conference review).pt.	1767833
47	35 not (45 or 46)	1984
48	limit 47 to (english or french)	1918
49	remove duplicates from 48	1348

MULTI-DATABASE STRATEGY		
Question #4 & #5		
Line #	**Searches**	**Results**
1	exp Colorectal Neoplasms/ use prmz	151495
2	exp Colon Tumor/ use oemezd	219837
3	exp Rectum Tumor/ use oemezd	165257
4	((colorectal* or colo-rectal* or colon* or rectal* or rectum or sigmoid or anal or anus or perianal* or peri-anal* or circumanal* or circum-anal*) adj3 (cancer* or carcinoma* or neoplas* or tumor* or tumour*)).tw.	342622

MULTI-DATABASE STRATEGY		
Question #4 & #5		
Line #	**Searches**	**Results**
5	or/1-4	473039
6	Microsatellite Instability/	9712
7	exp Microsatellite Repeats/ use prmz	32997
8	DNA Mismatch Repair/ use prmz	1566
9	Base Pair Mismatch/ use prmz	3900
10	Microsatellite DNA/ use oemezd	14017
11	Mismatch Repair/ use oemezd	6624
12	Base Mispairing/ use oemezd	4382
13	(dMMR or (MMR adj (abnormal* or deficienc* or test*)) or (error* adj phenotype* adj replication*) or replication error* or ((microsatellite* or micro-satellite*) adj (analy* or instabilit* or unstable)) or IMSI or MSI).tw.	21312
14	((mismatch* or mis-match*) adj2 repair*).tw.	16160
15	or/6-14	81919
16	Prognosis/ use prmz	369282
17	Disease-Free Survival/ use prmz	45429
18	Survival Analysis/ use prmz	101574
19	Survival Rate/ use prmz	128652
20	"Predictive Value of Tests"/ use prmz	147049
21	Neoplasm Recurrence, Local/ use prmz	85371
22	Cancer Prognosis/ use oemezd	33793
23	exp Survival/ use oemezd	661601
24	Predictive Value/ use oemezd	65628
25	Cancer Recurrence/ use oemezd	85492
26	prognos*.ti.	235613
27	(prognos* adj (factor* or marker*)).ab.	166176
28	survival*.tw.	1456858
29	(predict* adj (factor* or marker*)).tw.	53128
30	(risk adj2 recurrence*).tw.	28738
31	or/16-30	2413167
32	(2008* or 2009* or 201*).ed.	6541467
33	(2008* or 2009* or 201*).em.	15100570
34	or/32-33	15100570
35	5 and 15 and 31 and 34	2482
36	exp animals/	37582283
37	exp animal experimentation/ or exp animal experiment/	1839306
38	exp models animal/	1239006
39	nonhuman/	4454398
40	exp vertebrate/ or exp vertebrates/	36622291
41	or/36-40	38855213
42	exp humans/	29254155
43	exp human experimentation/ or exp human experiment/	345965
44	or/42-43	29256232
45	41 not 44	9600566
46	(conference abstract or conference review).pt.	1767833

MULTI-DATABASE STRATEGY		
Question #4 & #5		
Line #	**Searches**	**Results**
47	35 not (45 or 46)	1984
48	limit 47 to (english or french)	1918
49	remove duplicates from 48	1348

MULTI-DATABASE STRATEGY		
Question #6 (Economic Review)		
Line #	**Searches**	**Results**
1	exp Colorectal Neoplasms/ use prmz	151495
2	exp Colon Tumor/ use oemezd	219837
3	exp Rectum Tumor/ use oemezd	165257
4	((colorectal* or colo-rectal* or colon* or rectal* or rectum or sigmoid or anal or anus or perianal* or peri-anal* or circumanal* or circum-anal*) adj3 (cancer* or carcinoma* or neoplas*)).tw.	321774
5	HNPCC.tw.	4689
6	((hereditary or familial or inherited) adj3 (nonpolyposis or non-polyposis) adj3 (colorectal* or colo-rectal* or colorectum* or colo-rectum* or colon* or rectal* or rectum or sigmoid or anal or anus or perianal* or peri-anal* or circumanal* or circum-anal*) adj3 (cancer* or carcinoma* or neoplas*)).tw.	6313
7	lynch syndrome*.mp.	4230
8	(lynch* adj (cancer* or famil*)).tw.	46
9	or/1-8	464327
10	Microsatellite Instability/	9712
11	exp Microsatellite Repeats/ use prmz	32997
12	DNA Mismatch Repair/ use prmz	1566
13	Base Pair Mismatch/ use prmz	3900
14	Microsatellite DNA/ use oemezd	14017
15	Mismatch Repair/ use oemezd	6624
16	Base Mispairing/ use oemezd	4382
17	(dMMR or (MMR adj (abnormal* or deficienc* or test*)) or (error* adj phenotype* adj replication*) or replication error* or ((microsatellite* or micro-satellite*) adj (analy* or instabilit* or unstable)) or IMSI or MSI).tw.	21312
18	((mismatch* or mis-match*) adj2 repair*).tw.	16160
19	DNA Mutational Analysis/ use prmz	47826
20	Genetic Testing/ use prmz	27106
21	*Nucleotide Sequence/ use oemezd	88981
22	Genetic Screening/ use oemezd	49256
23	(identif* or screen* or surveillance or test*).ti.	1467887
24	(molecular adj (tumor? or tumour?) adj test*).tw.	11
25	(mutation* adj (analys#s or identif* or screen* or surveillance or test*)).tw.	67011
26	or/10-25	1758902
27	"Costs and Cost Analysis"/ use prmz	42063
28	Cost-Benefit Analysis/ use prmz	61294
29	exp Models, Economic/ use prmz	10465
30	Quality-Adjusted Life Years/ use prmz	7290

MULTI-DATABASE STRATEGY		
Question #6 (Economic Review)		
Line #	**Searches**	**Results**
31	Economic Evaluation/ use oemezd	10134
32	Cost Effectiveness Analysis/ use oemezd	103830
33	Cost Utility Analysis/ use oemezd	5883
34	Statistical Model/ use oemezd	107652
35	Quality Adjusted Life Year/ use oemezd	13367
36	(econom* or pharmacoeconomic* or pharmaco-economic*).ti.	88107
37	(economic evaluation* or economic review*).tw.	16723
38	(cost* adj2 (util* or effective* or benefit? or analy*)).tw.	248489
39	(health adj2 utilit*).tw.	4480
40	(euroqol or eq5d or eq-5d or hui or hui1 or hui2 or hui3).mp.	15618
41	((utilit* adj2 (valu* or measure*)) or (time adj2 trade) or (standard adj2 gamble)).mp.	7283
42	((cost* or economic*) adj2 model*).tw.	14288
43	(qoly or qolys or hrqol or qaly or qalys or qale or qales or qald or qtime or daly or haly or hale or hql or hqol or h-qol or hrqol or hr-qol or hye or hyes).tw.	39955
44	(quality-adjusted life year* or quality-adjusted life expectanc* or disability-adjusted life or health-adjusted life).tw.	19481
45	or/27-44	586017
46	(2012* or 2013* or 2014* or 2015*).ed.	3016444
47	(2012* or 2013* or 2014* or 2015*).em.	7574846
48	or/46-47	7574846
49	9 and 26 and 45 and 48	740
50	(conference abstract or conference review).pt.	1767833
51	49 not 50	564
52	limit 51 to (english or french)	546
53	remove duplicates from 52	412

OTHER DATABASES		
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Cochrane Library Issues 1, 2015	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.	

Grey Literature

Dates for Search:	April 14-16, 2015
Keywords:	Included terms for Hereditary Nonpolyposis Colorectal Neoplasms (HNPCC) or lynch or microsatellite instability (MSI) or mismatch repair (dMMR).
Limits:	English or French language

Relevant websites from the following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based searching” (www.cadth.ca/resources/finding-evidence/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search.

Appendix 2: Results From Search Update (March 1, 2016)

A search update was conducted on March 1, 2016 to identify any studies published since the original search that met the selection criteria for Questions 1 to 5. These studies were not included in the main analysis. One study each for Questions 1, 4, and 5 met the inclusion criteria for this review.

Question 1

Pinheiro M, Pinto C, Peixoto A, Veiga I, Lopes P, Henrique R, et al. Target gene mutational pattern in Lynch syndrome colorectal carcinomas according to tumour location and germline mutation. Br J Cancer 2015;113(4):686-92.

Question 2

No new studies identified.

Question 3

No new studies identified

Question 4

Kim JE, Hong YS, Kim HJ, Kim K-P, Lee J-L, Park SJ, et al. Defective Mismatch Repair Status was not Associated with DFS and OS in Stage II Colon Cancer Treated with Adjuvant Chemotherapy. Ann Surg Oncol. 2015;22:630-7.

Question 5

Vogelaar F, Van EF, Reimers M, Van Der Linden J, Pruijt J, Van Den Brule A, et al. The prognostic value of Microsatellite Instability, KRAS, BRAF and PIK3CA mutations in stage II colon cancer patients. Mol Med. 2015 Dec 17;1-26.

Appendix 3: Title and Abstract Screening Checklist (Question 1)

Ref ID#: **Author:** **Year:**			
Did the study include:	**Yes (include)**	**Unclear (include)**	**No (Exclude)**
1) Patients of any age with **CRC** (any stage; unselected or selected based on non-molecular criteria such as Amsterdam or Bethesda criteria)?	☐	☐	☐
2) **dMMR** testing/screening for LS or HNPCC (**IHC**-based or **MSI/PCR**-based)?	☐	☐	☐
3) **Genetic testing** (germline mutation analysis)?	☐	☐	☐
4) Any of the following as the study outcomes? • Sensitivity • Specificity • PPV • NPV • Proportions TP, TN, FP, FN • LR+ • LR– • AUC	☐	☐	☐
5) Any of the following study designs: • Diagnostic study • RCT • Non-RCT/observational study (e.g., cohort, case-control, analytical cross-sectional) • Case series • Registry data • Systematic review/meta-analysis/HTA	☐	☐	☐
6) Publication date 2000 to present?	☐	☐	☐
Include for full-text review?	**Yes☐**		**No☐**

AUC = area under the curve; CRC = colorectal cancer; dMMR = deficient mismatch repair; HTA = health technology assessment; IHC = immunohistochemistry; LR+ = positive likelihood ratio; LR– = negative likelihood ratio; LS = Lynch syndrome; MSI = microsatellite instability; MSS = microsatellite stable; NPV = negative predictive value; ODA = overall diagnostic accuracy; PPV = positive predictive value; ROC = receiver operator curve; RCT = randomized controlled trial.

Appendix 4: Title and Abstract Screening Checklist (Question 2)

Ref ID: **First Author (year):**

	INCLUDE	EXCLUDE
STUDY TYPE (all questions)	☐ Diagnostic study, RCT, non-RCT/observational study (e.g., cohort, case-control, analytical cross-sectional), systematic review/meta-analysis/HTA ☐ Case series ☐ Registry data ☐ Unclear	☐ Laboratory-based genetic studies ☐ Case reports ☐ Editorials/comments
Question 2		
Population	☐ Patient of any age with CRC	☐ Patients with other types of cancer
Intervention	☐ dMMR testing/screening for Lynch syndrome or HNPCC (IHC-based or MSI PCR-based)	☐ Other tumour molecular testing ☐ Non-molecular testing/screening strategies
Comparator	☐ No testing/screening ☐ Unclear	☐ Other guidelines or pre-screening scheme, pathology studies predicting MSI/dMMR
Outcomes	☐ Clinical/cancer outcomes of family members ☐ Survival rates of family members ☐ Patient management decisions for family members (e.g., cancer prevention interventions) ☐ Psychological outcomes ☐ Unclear	☐ Other outcomes
Include for full-text review?	☐ Yes	☐ No

CRC = colorectal cancer; dMMR = deficient mismatch repair; HNPCC = hereditary non-polyposis colorectal cancer; HTA = health technology assessment; IHC = immunohistochemistry; MSI = microsatellite instability; PCR = polymerase chain reaction; RCT= randomized controlled trial.

Reviewer: **Date:**

Appendix 5: Title and Abstract Screening Checklist (Question 3)

	INCLUDE	EXCLUDE
STUDY TYPE	☐ Diagnostic study, RCT, non-RCT/observational study (e.g., cohort, case-control, analytical cross-sectional), systematic review/ meta-analysis/HTA ☐ Case series ☐ Registry data ☐ Unclear	☐ Laboratory-based genetic studies ☐ Case reports ☐ Editorials/comments
Population	☐ CRC patients for whom dMMR test by IHC indicates no MLH1 expression	☐ CRC patients for whom the results of dMMR test is not available at the time of BRAF V600E or MLH1 promoter hypermethylation testing
Intervention	☐ BRAF V600E (by genotyping or IHC methods) and/or MLH1 promoter hypermethylation testing for ruling out likely sporadic CRC	☐ Other testing technologies
Comparator	☐ Genetic testing (germline mutation analysis ☐ Unclear	☐ Other guidelines or pre-screening scheme, pathology studies predicting MSI/dMMR ☐ No comparator
Outcomes	☐ Diagnostic performance (sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values, proportions of true and false positive and negative test results, area under the ROC curve) ☐ Unclear	☐ Other outcomes
Include for full-text review?	☐ Yes	☐ No

CRC = colorectal cancer; dMMR = deficient mismatch repair; HNPCC = hereditary non-polyposis colorectal cancer; HTA = health technology assessment; IHC = immunohistochemistry; MSI = microsatellite instability; PCR = polymerase chain reaction; ROC = receiver operator curve; RCT = randomized controlled trial.

Appendix 6: Title and Abstract Screening Checklist (Questions 4 and 5)

Ref ID: **First Author (year):**

	INCLUDE	EXCLUDE
STUDY TYPE (all questions)	☐ Diagnostic study, RCT, non-RCT/observational study (e.g., cohort, case-control, analytical cross-sectional), systematic review/meta-analysis/HTA ☐ Case series ☐ Registry data ☐ Unclear	☐ Laboratory-based genetic studies ☐ Case reports ☐ Editorials/comments
Question 4		
Population	☐ Patient of any age with CRC (any stage) who do not receive adjuvant chemotherapy	☐ CRC patients receiving chemotherapy (Q5) ☐ Patients with other types of cancer
Intervention	☐ dMMR testing to detect MSI status	☐ Other molecular and non-molecular testing technologies
Comparator	☐ dMMR-positive versus dMMR-negative test results ☐ Unclear	☐ No testing ☐ Other testing technologies
Outcomes	☐ Progression/recurrence-free survival ☐ Overall survival ☐ Mortality rates ☐ Unclear	☐ Other outcomes
Include for full-text review?	☐ Yes	☐ No
Question 5		
Population	☐ Patient of any age with CRC (any stage) undergoing adjuvant chemotherapy following tumour resection	☐ CRC patients not receiving adjuvant chemotherapy (Q4)
Intervention	☐ dMMR testing to detect MSI status	☐ Other molecular and non-molecular testing technologies
Comparator	☐ dMMR-positive versus dMMR-negative test results ☐ Unclear	☐ No testing ☐ Other testing technologies
Outcomes	☐ Progression/recurrence-free survival ☐ Overall survival ☐ Mortality rates ☐ Unclear	☐ Other outcomes
Include for full-text review?	☐ Yes	☐ No

CRC = colorectal cancer; dMMR = deficient mismatch repair; HTA = health technology assessment; MSI = microsatellite instability; RCT = randomized controlled trial.

Reviewer: **Date:**

Appendix 7: Title and Abstract Screening Checklist (Question 6)

	INCLUDE	EXCLUDE
Question 6a		
Population	□ Patient of any age with CRC (any stage) At least two of the following LS screening strategies 1) No dMMR screening 2) Screen if meet one of the rBG 3) Screen if younger than 70 years old 4) Universal screening **OR** At least two of the following LS reflex testing strategies 5) All patients to germline testing if abnormal IHC 6) PCR-based BRAF if abnormal MLH1, if normal BRAF, or abnormal IHC for other genes send to germline testing 7) Promoter hypermethylation if abnormal MLH1, if normal hypermethylation, or abnormal IHC for other genes send to germline testing 8) IHC-based BRAF for all patients, if MLH1 abnormal and BRAF normal, or abnormal IHC for other genes send to germline testing. 9) IHC-based BRAF for all patients, if MLH1 abnormal and BRAF normal, promoter hypermethylation test. If IHC BRAF normal and hypermethylation normal, send to germline testing. If IHC dMMR abnormal for other genes, send to germline testing. **OR** At least two of the following adjuvant chemotherapy strategies 10) dMMR status is used for adjuvant chemotherapy decisions 11) dMMR status is not used for adjuvant chemotherapy decisions	□ Non-CRC patients
Intervention	□ Universal dMMR testing to screen for LS	□ Universal dMMR testing not a comparator
Comparator	□ Targeted dMMR testing to screen for LS	□ Targeted dMMR testing not a comparator
Outcomes	□ Incremental cost per QALY □ Incremental cost per life-year □ Incremental cost per LS detected □ Incremental cost per CRC case averted	□ Other outcomes
Include for full-text review?	□ Yes	□ No

CRC = colorectal cancer; dMMR = deficient mismatch repair; IHC = immunohistochemistry; LS = Lynch syndrome; QALY = quality-adjusted life-year; rBG = Revised Bethesda Guidelines.

Appendix 8: Full-Text Screening Checklist (Question 1)

Ref ID#:	**Author:**		**Year:**
Did the study include:	**Yes (include)**	**Unclear (include)**	**No (Exclude)**
1) **CRC** patients?	☐	☐	☐
2) **dMMR testing** for LS as the index test?	☐	☐	☐
3) **Genetic testing** (germline mutation analysis) as the reference standard?	☐	☐	☐
4) Any of the following as the study outcomes?* – Sensitivity – Specificity – PPV – NPV – Proportions TP, TN, FP, FN – LR+ – LR– – AUC	☐	☐	☐ ***Answer next question before excluding the article**
5) If the answer to Q4 is No, were sufficient data provided to construct 2 × 2 contingency tables?	☐	☐	☐
6) Any of the following study designs: – Diagnostic study – RCT – Non-RCT/observational study (e.g., cohort, case-control, analytical cross-sectional)	☐	☐	☐
7) **> 10 CRC-only patients** with test results reported (if mixed cancer population, must be able to determine CRC results separate from other cancers)?	☐	☐	☐
8) Is **each tumour analysis reported** linked to an individual patient (or in the case of families reported, is each tumour reported linked to a specific family/family member)?	☐	☐	☐
9) If the **germline test** is performed on a **sub-population** (i.e., those with MSI-high and/or -low [PCR test] and/or lack of protein expression [IHC test]), is LS germline status/prevalence reported for entire study population?	☐	☐	☐
Decision for including the study in the review:	☐ Yes		☐ No
Reason(s) for exclusion:	☐ Inappropriate study population ☐ No intervention of interest ☐ No/inappropriate comparator ☐ No relevant outcomes ☐ Irrelevant study type ☐ Not primary report of study ☐ Study description only ☐ Unable to confirm each tumour sample is linked to only 1 patient/family ☐ Outcomes only for <10 patients ☐ < 3 IHC test proteins reported ☐ Other:		

AUC = area under the curve; CRC = colorectal cancer; dMMR = deficient mismatch repair; HTA = health technology assessment; IHC = immunohistochemistry; LR+ = positive likelihood ratio; LR– = negative likelihood ratio; LS = Lynch syndrome; MSI = microsatellite instability; MSS = microsatellite stable; NPV = negative predictive value; ODA = overall diagnostic accuracy; PPV = positive predictive value; ROC = receiver operator curve; RCT = randomized controlled trial.

Reviewer: **Date:**

Appendix 9: Full-Text Screening Checklist (Question 2)

Ref#: **Author:** **Year:**			
Did the study include:	**Yes (include)**	**Unclear (include)[a]**	**No (exclude)**
1) Patient of any age with CRC	☐	☐	☐
2) dMMR testing/screening for LS or HNPCC as the index test?	☐	☐	☐
3) No testing/screening as the comparator?	☐	☐	☐
4) Any of the following as the study outcomes? – Clinical/cancer outcomes of family members – Survival rates of family members – Patient management decisions for family members (e.g., cancer prevention interventions) – Psychological outcomes	☐	☐	☐
5) Any of the following study designs: – RCT – Non-RCT/observational study (e.g., cohort, case-control, analytical cross-sectional) – Population-based cohort – Systematic review/meta-analysis/HTA	☐	☐	☐
Decision for including the study in the review:	☐ Yes		☐ No
Reason(s) for exclusion:	☐ Inappropriate study population ☐ No intervention of interest ☐ No/inappropriate comparator ☐ No relevant outcomes ☐ Irrelevant study type ☐ Not primary report of study ☐ Study description only ☐ Other:----------		

CRC = colorectal cancer; dMMR = deficient mismatch repair; HNPCC = hereditary non-polyposis colorectal cancer; LS = Lynch syndrome.
[a] Discuss with a second reviewer.

Reviewer: **Date:**

Appendix 10: Full-Text Screening Checklist (Question 3)

Ref#: **Author:** **Year:**			
Did the study include:	**Yes (include)**	**Unclear (include)[a]**	**No (Exclude)**
1) **CRC** patients for whom **dMMR test** by IHC **indicates no MLH1** expression?	☐	☐	☐
2) BRAF V600E (by genotyping or IHC methods) and/or MLH1 promoter hypermethylation testing as the index test(s) for ruling out likely sporadic CRC?	☐	☐	☐
3) Genetic testing (germline mutation analysis) as the comparator?	☐	☐	☐
4) Any of the following as the study outcomes? – Sensitivity – Specificity – PPV – NPV – Proportions TP, TN, FP, FN – LR+ – LR– – AUC	☐	☐	☐
5) Any of the following study designs: – Diagnostic study – RCT – Non-RCT/observational study (e.g., cohort, case-control, analytical cross-sectional) – Systematic review/meta-analysis/HTA	☐	☐	☐
Decision for including the study in the review:	☐ Yes		☐ No
Reason(s) for exclusion:	☐ Inappropriate study population ☐ No intervention of interest ☐ No/inappropriate comparator ☐ No relevant outcomes ☐ Irrelevant study type ☐ Not primary report of study ☐ Study description only ☐ Other:		

AUC = area under the curve; CRC = colorectal cancer; dMMR = deficient mismatch repair; HTA = health technology assessment; IHC = immunohistochemistry; LR+ = positive likelihood ratio; LR– = negative likelihood ratio; LS = Lynch syndrome; MSI = microsatellite instability; MSS = microsatellite stable; NPV = negative predictive value; ODA = overall diagnostic accuracy; PPV = positive predictive value; ROC = receiver operator curve; RCT = randomized controlled trial.

[a] Discuss with a second reviewer.

Reviewer: **Date:**

Appendix 11: Full-Text Screening Checklist (Questions 4 and 5)

Ref#: **Author:** **Year:**			
1) Did the study include:	Yes (include)	Unclear (include)[a]	No (Exclude)
– Stage II or III CRC patients not receiving adjuvant chemotherapy; or	☐Q4	☐Q4	☐
– Stage II or III colon cancer patients undergoing (adjuvant) chemotherapy following tumour resection?	☐Q5	☐Q5	☐
2) Did the study use dMMR testing to detect microsatellite instability status of the study participants?	☐	☐	☐
3) Did the study compare patients who had dMMR-positive (deficient) results with those who are MMR-proficient?	☐	☐	☐
4) Did the study report any of the following outcomes? – Progression/recurrence-free survival – Overall survival – Mortality rates	☐	☐	☐
5) Any of the following study designs: – RCT – Non-RCT/observational study (e.g., cohort, case-control, analytical cross-sectional) – Systematic review/meta-analysis/HTA	☐	☐	☐
Decision for including the study in the review:	Yes☐Q4 Yes☐Q5		No☐Q4 No☐Q5
Reason(s) for exclusion:	☐ Inappropriate study population ☐ No intervention of interest ☐ No/inappropriate comparator ☐ No relevant outcomes ☐ Irrelevant study type ☐ Not primary report of study ☐ Study description only ☐ Other:----------		

CRC = colorectal cancer; dMMR = DNA mismatch repair deficiency; HTA = health technology assessment; LS = Lynch syndrome.
[a] Discuss with a second reviewer.

Reviewer: **Date:**

Appendix 12: Full-Text Screening Checklist (Question 6)

	INCLUDE	EXCLUDE
Question 6a		
Population	☐ Patient of any age with CRC (any stage)	☐ Non-CRC patients
Intervention	☐ Universal dMMR testing to screen for LS	☐ Universal dMMR testing not a comparator
Comparator	☐ Targeted dMMR testing to screen for LS	☐ Targeted dMMR testing not a comparator
Outcomes	☐ Incremental cost per QALY ☐ Incremental cost per life-year ☐ Incremental cost per LS detected ☐ Incremental cost per CRC case averted	☐ Other outcomes
Include for full-text review?	☐ Yes	☐ No

CRC = colorectal cancer; dMMR = deficient mismatch repair; LS = Lynch syndrome; QALY = quality-adjusted life-year.

Appendix 13: QUADAS-2 Tool for the Quality Assessment of Diagnostic Accuracy Studies

State the review question

Patients (setting, intended use of index test, presentation, prior testing):
Index test(s):
Reference standard and target condition:

Draw a flow diagram for the primary study

Risk of bias and applicability judgments

Domain 1: Patient selection

A. Risk of bias	
Describe methods of patient selection:	
Was a consecutive or random sample of patients enrolled?	**Yes / No / Unclear**
Was a case-control design avoided?	**Yes / No / Unclear**
Did the study avoid inappropriate exclusions?	**Yes / No / Unclear**
Could the selection of patients have introduced bias? **Risk: Low / High / Unclear**	
B. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting):	
Is there concern that the included patients do not match the review question? **Concern: Low / High / Unclear**	

Domain 2: Index test(s)

A. Risk of bias	
Describe the index test and how it was conducted and interpreted:	
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes / No / Unclear**
If a threshold was used, was it pre-specified?	**Yes / No / Unclear**
Could the conduct or interpretation of the index test have introduced bias? **Risk: Low / High / Unclear**	
B. Concerns regarding applicability	
Is there concern that the index test, its conduct, or interpretation differ from the review question? **Concern: Low / High / Unclear**	

Domain 3: Reference standard

A. Risk of bias	
Describe the reference standard and how it was conducted and interpreted:	
Is the reference standard likely to correctly classify the target condition?	**Yes / No / Unclear**
Were the reference standard results interpreted without knowledge of the results of the index test?	**Yes / No / Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias? **Risk: Low / High / Unclear**	
B. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question? **Concern: Low / High / Unclear**	

Domain 4: Flow and timing

A. Risk of bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2 × 2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:	
Was there an appropriate interval between index test(s) and reference standard?	**Yes / No / Unclear**
Did all patients receive a reference standard?	**Yes / No / Unclear**
Did patients receive the same reference standard?	**Yes / No / Unclear**
Were all patients included in the analysis?	**Yes / No / Unclear**
Could the patient flow have introduced bias? **Risk: Low / High / Unclear**	

Appendix 14: Quality Assessment Form (Questions 4 and 5)

Domain	Yes	No	Unclear	Reviewer's comments
Study design				
Were there a relevant (external or internal) comparison?	☐	☐	☐	
How were the comparison groups formed?				
Randomization	☐	☐	☐	
Non-random allocation based on exposure ☐ cohort ☐ historical cohort	☐	☐	☐	
Non-random allocation based on outcome ☐ case-control	☐	☐	☐	
Allocation based on other factors (e.g., based on time difference, location difference, participant preference, etc.)	☐	☐	☐	
Based on outcome and exposure status at a particular point of time ☐ cross-sectional	☐	☐	☐	
Based on observation made on series of individuals ☐ case series	☐	☐	☐	
Other process:----------	☐	☐	☐	
Were the following key steps of the study carried out before the study was designed:				
Identification of participants?	☐	☐	☐	
Baseline assessment (prior to intervention)?	☐	☐	☐	
Assignment to intervention groups?	☐	☐	☐	
Assessment of outcomes?	☐	☐	☐	
Were the study groups comparable?	☐	☐	☐	
Risk of bias				
Selection bias due to systematic differences in baseline characteristics of the comparison groups	☐	☐	☐	
Performance bias due to systematic differences between the comparison groups in care provided or exposure to other factors	☐	☐	☐	
Detection bias due to systematic differences between the comparison groups in how outcomes are determined	☐	☐	☐	
Reporting bias due to selective reporting of the main outcome or class of outcomes	☐	☐	☐	
Risk of confounding				
Control for confounding at the design stage	☐	☐	☐	
Description of confounders	☐	☐	☐	
Adjustment for confounders	☐	☐	☐	

Domain		Yes	No	Unclear	Reviewer's comments
If yes, what method used?	stratification	☐	☐	☐	
	multivariable regression	☐	☐	☐	
	propensity score	☐	☐	☐	

Notes:
- Yes (high risk of bias), No (low risk of bias), and Unclear (lack of information or certainty).
- Yes (low risk of bias), No (high risk of bias), and Unclear (lack of information or certainty).

Reviewer: **Date:**

Appendix 15: Clinical Data Abstraction Form (Question 1)

STUDY	
Ref ID	
Author	
Publication Year	
Country	
Study Design	
Setting	

METHODOLOGY	
Type/stage of CRC	
Inclusion criteria	
Exclusion criteria	
Type of prior testing	
# Patients/Families/Samples tested	
# Patients/Families/Samples tested positive	
Only those who fulfilled criteria included?	

INTERVENTION/COMPARATOR			
	dMMR (MSI/PCR)	**dMMR (IHC)**	**Reference standard (germline testing)**
Test description			

POPULATION CHARACTERISTICS	
Mean age, year (SD)	
Median age, year (IQR, Range)	
Gender (% female)	
Stage of cancer (I, II, III, IV)	
Other	

RESULTS		
Outcome	**dMMR (MSI/PCR)**	**dMMR (IHC)**
Diagnostic test performance		
Name of test		
Total # tested		
# confirmed disease positive by reference standard		
# confirmed disease negative by reference standard		
# true positives		
# false positives		
# false negatives		
# true negatives		
Sensitivity (95% CI)		
Specificity (95% CI)		
Positive predictive value (95% CI)		
Negative predictive value (95% CI)		
Positive likelihood ratio (95% CI)		
Negative likelihood ratio (95% CI)		
Area under ROC (95% CI)		
Overall diagnostic accuracy (95% CI)		

CI = confidence interval; CRC = colorectal cancer; dMMR = deficient mismatch repair; IHC = immunohistochemistry; IQR = interquartile range; MSI = microsatellite instability; PCR = polymerase chain reaction; ROC = receiver operator curve; SD = standard deviation.

Appendix 16: Clinical Data Abstraction Form (Question 3)

STUDY	
Ref ID	
Author	
Publication Year	
Country	
Funding	

METHODOLOGY	
Study design	□ Single gate DS □ Double gate DS □ Systematic review/MA □ Other:
Setting	
Eligibility criteria	
Type/stage of CRC	
Other inclusion/exclusion criteria	
Prior testing (e.g., Bethesda screening criteria)	Type of the test: # tested: # tested positive/met the criteria:
Did the study only include patients who fulfilled prior testing criteria?	□ Yes □ No
Total # of CRC patients, if stated **# of patients with lack of MLH1 expression**	

INTERVENTION/COMPARATOR		
Index test (Choose more than one, if applicable)	**Technical details**	**Reference standard**
□ BRAF V600E □ MLH1 hypermethylation □ Other:		

POPULATION CHARACTERISTICS			
	BRAF V600E	**MLH1 hypermethylation**	**Reference standard**
Mean/median age, year (range)			
Gender (% female)			
Other important variables(unit) **1. ( )** **2. ( )**			

RESULTS				
Outcome	**BRAF V600E**	**MLH1 hypermethylation**	**Combined test** □ BRAF and MLH1 hypermethylation □ BRAF or MLH1 hypermethylation	***P* value (comparison)**
Diagnostic test performance				
Total number tested				
No true positives (%)				
No true negatives (%)				
No false positives (%)				
No false negatives (%)				
Sensitivity (95% CI)				
Specificity (95% CI)				
Positive likelihood ratio (95% CI)				
Negative likelihood ratio (95% CI)				
Positive predictive value (95% CI)				
Negative predictive value (95% CI)				
Area under ROC (95% CI)				

CI = confidence interval; CRC = colorectal cancer; dMMR = deficient mismatch repair; DS = diagnostic study; IQR = interquartile range; MA = meta-analysis; ROC = receiver operator curve.

Did the article report any data relevant to other study questions? □Yes: Q# □No

Reviewer: **Date:**

Appendix 17: Clinical Data Abstraction Form (Questions 4 and 5)

STUDY	
Ref ID	
First Author	
Publication Year	
Country	
Funding	
Setting	

METHODOLOGY	
Study design	□ RCT □ Non-RCTs (interventional) □ Observational studies:
Total sample size	
# not received adjuvant chemotherapy	
# received adjuvant chemotherapy	
Eligibility criteria	
Adjuvant chemotherapy protocol	
Reported outcomes	

RESULTS A. (Question 4) patients who did NOT receive adjuvant chemotherapy

Outcome	**Definition (follow-up months)**	**Event rates**									
		dMMR/MSI-positive (MMR-deficient)			**dMMR/MSI negative (MMR-proficient)**			**RR/Hazard Ratio dMMR vs. pMMR**			
		N	**#event**	**%**	**N**	**#event**	**%**	**RR**	**LCI**	**UCI**	***P* value**
Death											
Recurrence											
		Time to event data									
		probability	**LCI**	**UCI**	**probability**	**LCI**	**UCI**	RR	**LCI**	**UCI**	***P* value**
OS											
DFS											

RESULTS B. (Question 5) Patients who received adjuvant chemotherapy											
(treatment #1:) (n=)											
Outcome	Definition (follow-up months)	Event rates									
		dMMR/MSI-positive (MMR-deficient)			dMMR/MSI negative (MMR-proficient)			RR/Hazard Ratio dMMR vs. pMMR			
		N	#event	%	N	#event	%	RR	LCI	UCI	*P* value
Death											
Recurrence											
		Time to event data									
		Prob-ability	LCI	UCI	Prob-ability	LCI	UCI	RR	LCI	UCI	*P* value
OS											
DFS											
(treatment #2:) (n=)											
Outcome	Definition (follow-up months)	Event rates									
		dMMR/MSI-positive (MMR-deficient)			dMMR/MSI negative (MMR-proficient)			RR/Hazard Ratio dMMR vs. pMMR			
		N	#event	%	N	#event	%	RR	LCI	UCI	*P* value
Death											
Recurrence											
		Time to event data									
		Prob-ability	LCI	UCI	Prob-ability	LCI	UCI	RR	LCI	UCI	*P* value
OS											
DFS											

dMMR = deficient mismatch repair; DFS = disease-free survival; LCI = lower confidence interval; MMR = mismatch repair; MSI = microsatellite instability; OS = overall survival; RCT = randomized controlled trial; RR = relative risk; UCI = upper confidence interval; vs. = versus.

Did the article report any data relevant to other study questions? □Yes: Q# □No

Reviewer: **Date:**

Appendix 18: Data Abstraction Form (Question 6)

STUDY	
Ref ID	
Author	
Publication Year	
Country	
Funding	

METHODOLOGY	
Study Perspective	
Population	
Interventions and Comparators	
Study Design	□ Decision tree □ Markov model □ Microsimulation □ Patient level analysis Other:
Model Structure	**Were impacts of interventions on LS +ve probands considered in the model? (Y/N)** **If so, which ones** □ Colectomy □ CRC surveillance □ Hysterectomy □ Endometrial cancer surveillance □ Ovarian cancer surveillance □ Adjunctive chemotherapy Other: **Were impacts of interventions on relatives LS +ve probands considered in the model? (Y/N)** **If so, which ones** □ Colectomy □ CRC surveillance □ Hysterectomy □ Endometrial cancer surveillance □ Ovarian cancer surveillance □ Adjunctive chemotherapy Other: □ Microsimulation □ Patient level analysis
Outcomes	
Currency and Year	
Estimate of Cost-Effectiveness	
Conclusions From Authors	

+ve = positive; CRC = colorectal cancer; LS = Lynch syndrome.

Appendix 19: Details of Outcome Measures for Assessment of Diagnostic Test Performance

		Reference standard		
		Positive (Disease +)	Negative (Disease –)	Total
Index test	Positive	TP	FP	TP+FP
	Negative	FN	TN	FN+TN
	Total	TP+FN	FP+TN	TP+FP+TN+FN

TP = true positives; when the positive index test agrees with the positive reference standard.

FP = false positives; when the positive index test disagrees with the negative reference standard.

FN = false negatives; when the negative index test disagrees with the positive reference standard.

TN = true negatives; when the negative index test agrees with the negative reference standard.

From this 2 × 2 table, several tests of diagnostic performance can be made with confidence intervals (CIs).

Sensitivity: TP/(TP + FN): the proportion of persons with the disease who are correctly identified by a test; i.e., a test with a high sensitivity is useful for "ruling out" a disease if a person tests negative.

CI: $p \pm Z * \sqrt{\frac{p*(1-p)}{TP+FN}}$

Specificity: TN/(TN + FP). the proportion of persons without a disease who are correctly identified by a test. High specificity is important when the treatment or diagnosis is harmful to the patient.

CI: $p \pm Z * \sqrt{\frac{p*(1-p)}{TN+FP}}$

Positive Predictive Value (PPV): TP/(TP + FP): the proportion of patients with positive test results who are correctly diagnosed.

CI: $p \pm Z * \sqrt{\frac{p*(1-p)}{TP+FP}}$

Negative Predictive Value (NPV): TN/(TN + FN): proportion of patients with negative test results who are correctly diagnosed.

CI: $p \pm Z * \sqrt{\frac{p*(1-p)}{TN+FN}}$

Positive Likelihood Ratio (LR+): Indicates how much more likely it is to get a positive test in the diseased as opposed to the non-diseased group.

CI: $LR+ = \exp(\ln \frac{sensitivity}{1-specificity} \pm 1.96 * \sqrt{\frac{1-sensitivity}{TP} + \frac{specificity}{FP}})$

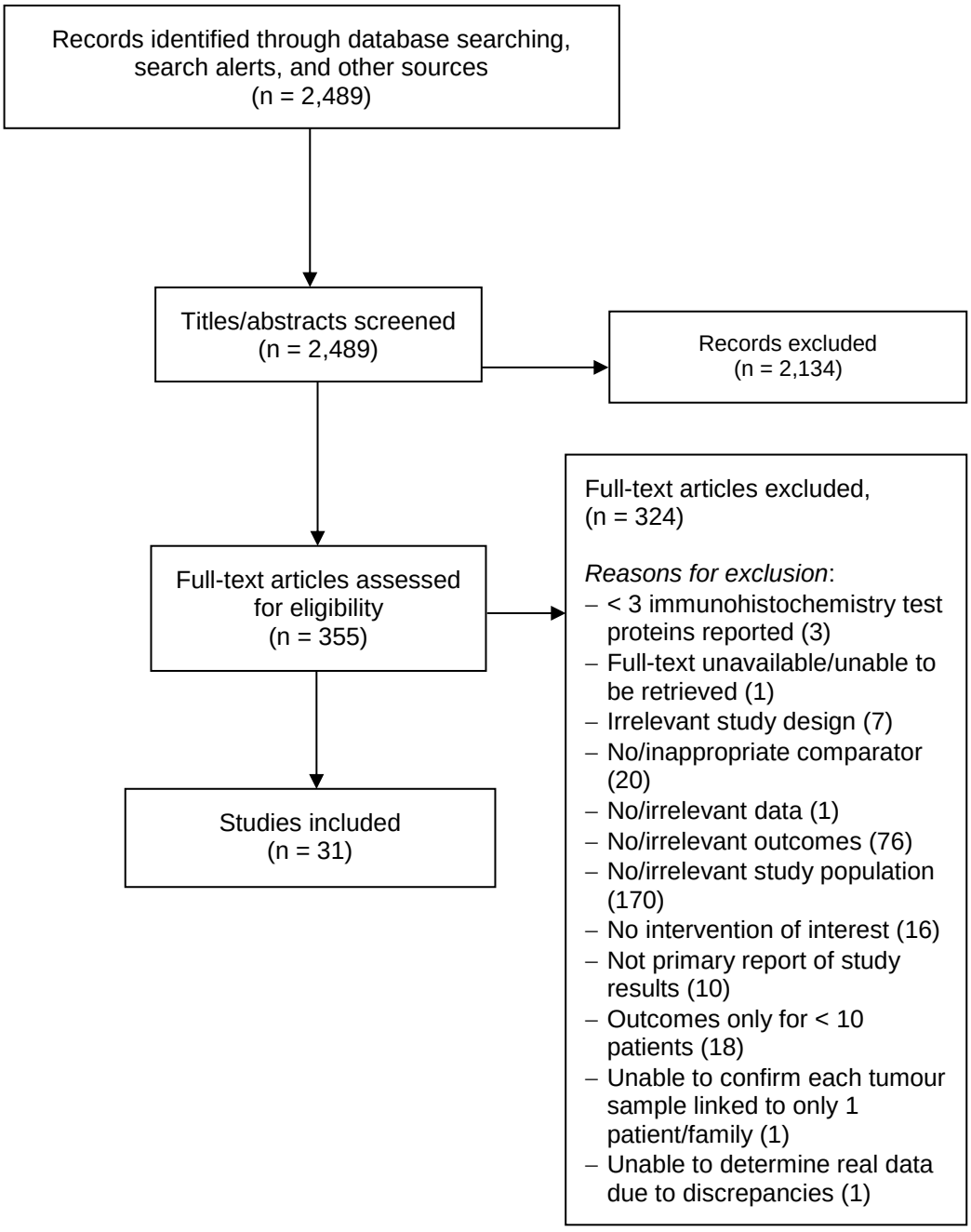
Negative Likelihood Ratio (LR–): Indicates how much more likely it is to get a negative test in the non-diseased as opposed to the diseased group.

CI: $LR- = \exp(\ln \frac{1-sensitivity}{specificity} \pm 1.96 * \sqrt{\frac{sensitivity}{FN} + \frac{1-specificity}{TN}})$

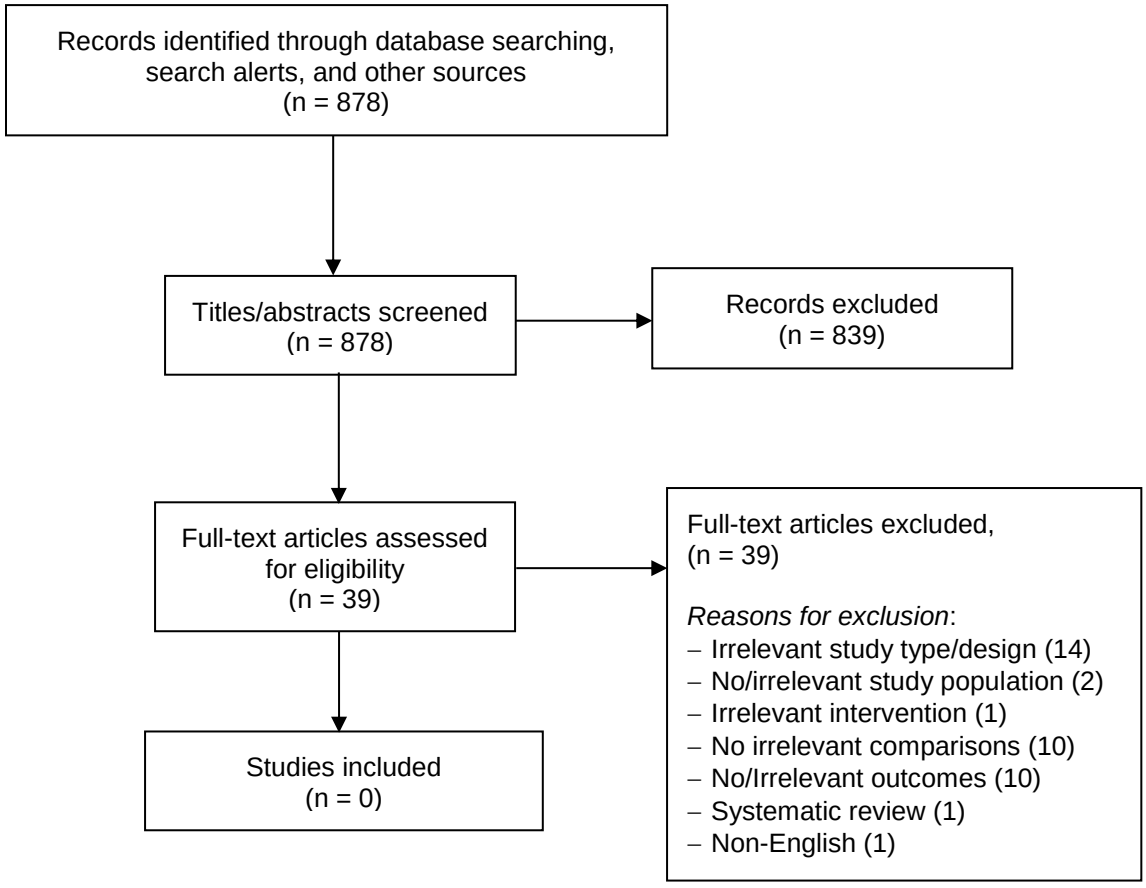
Overall diagnostic accuracy: (TP/TN)/(TP + FP + TN + FN). The proportion of correctly classified participants among all study participants.

CI: $p \pm Z * \sqrt{\frac{p*(1-p)}{TN+TP++FN+FP}}$

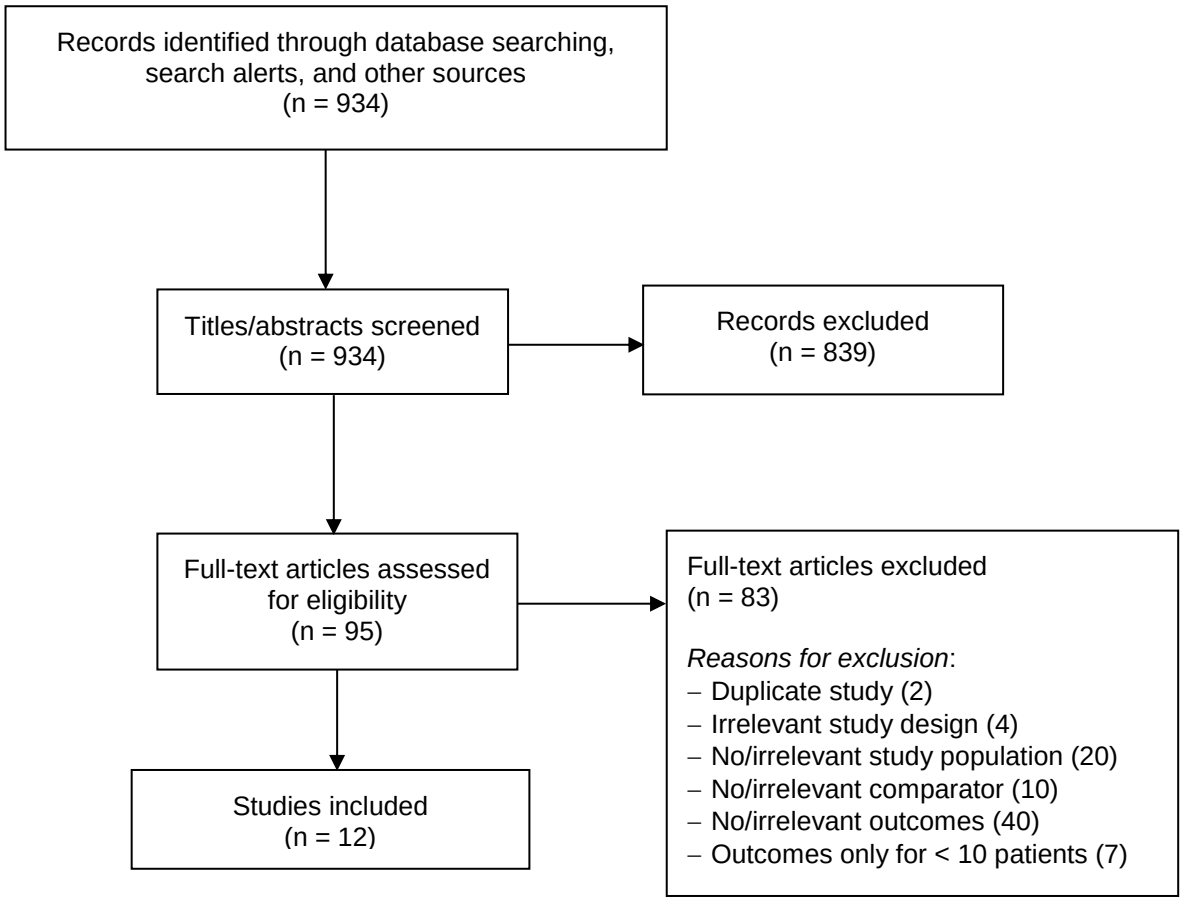
Appendix 20: Selection of Included Studies (Question 1)



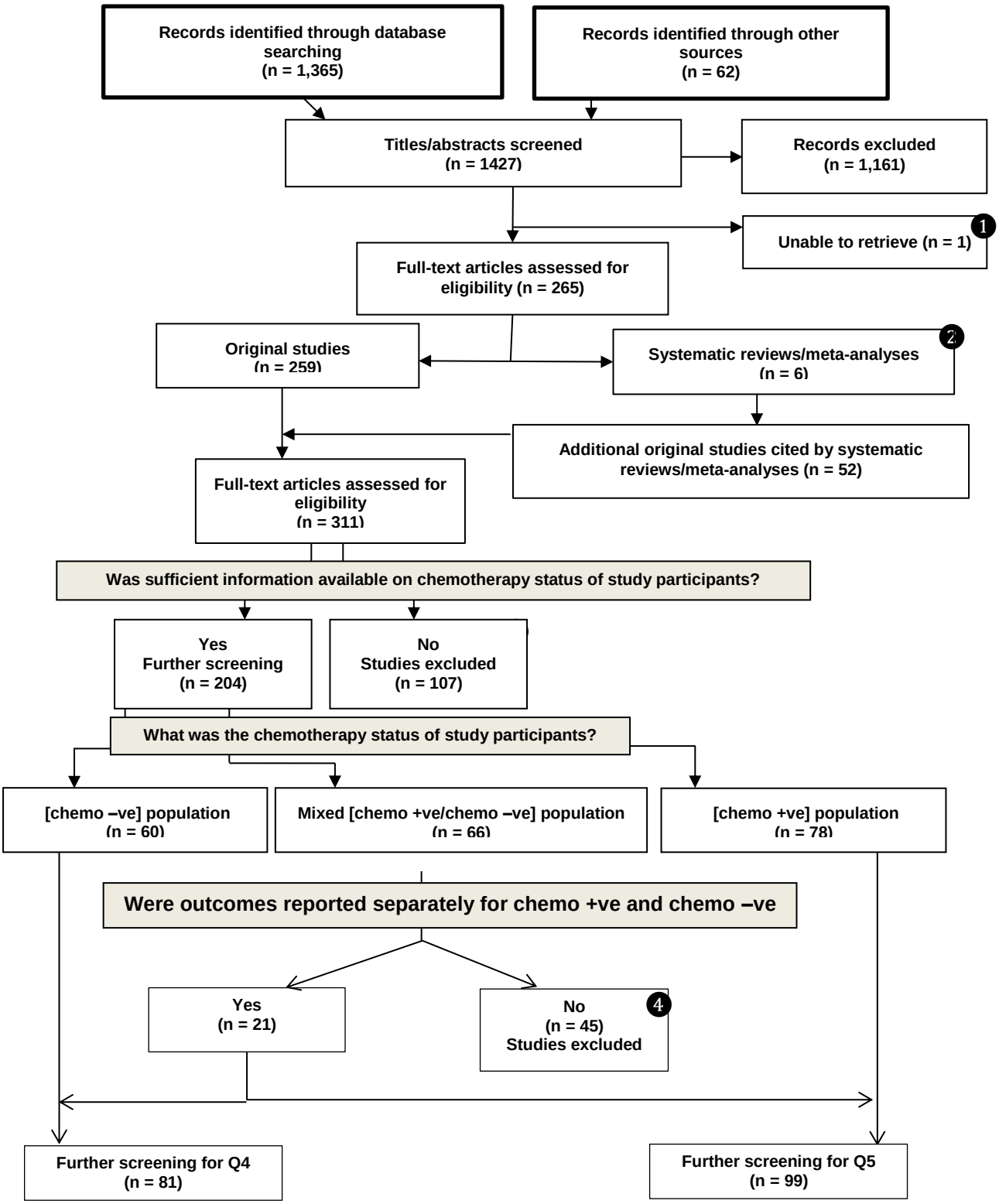
Appendix 21: Selection of Included Studies (Question 2)



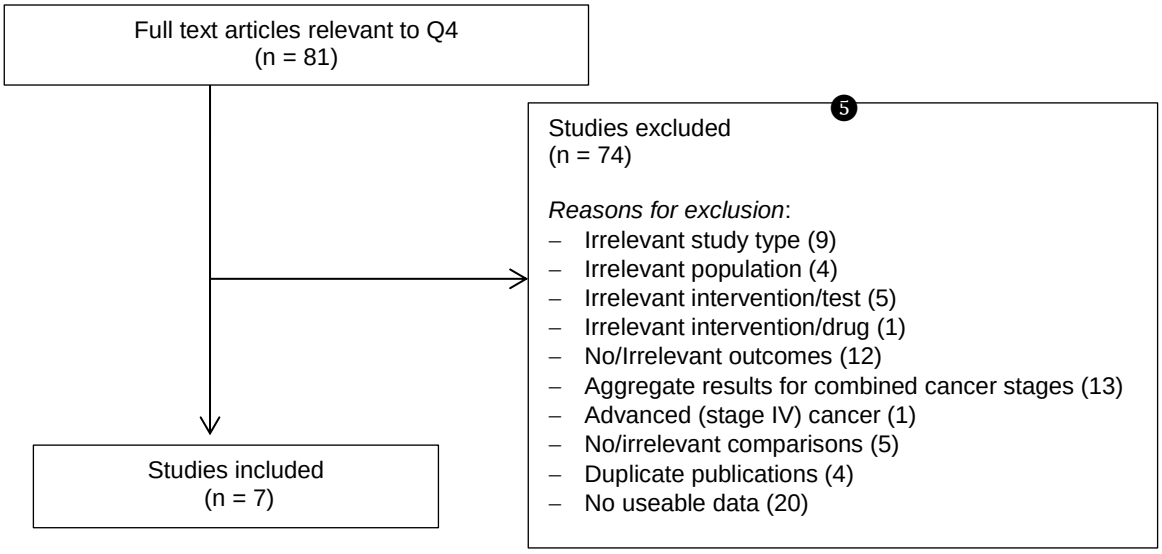
Appendix 22: Selection of Included Studies (Question 3)



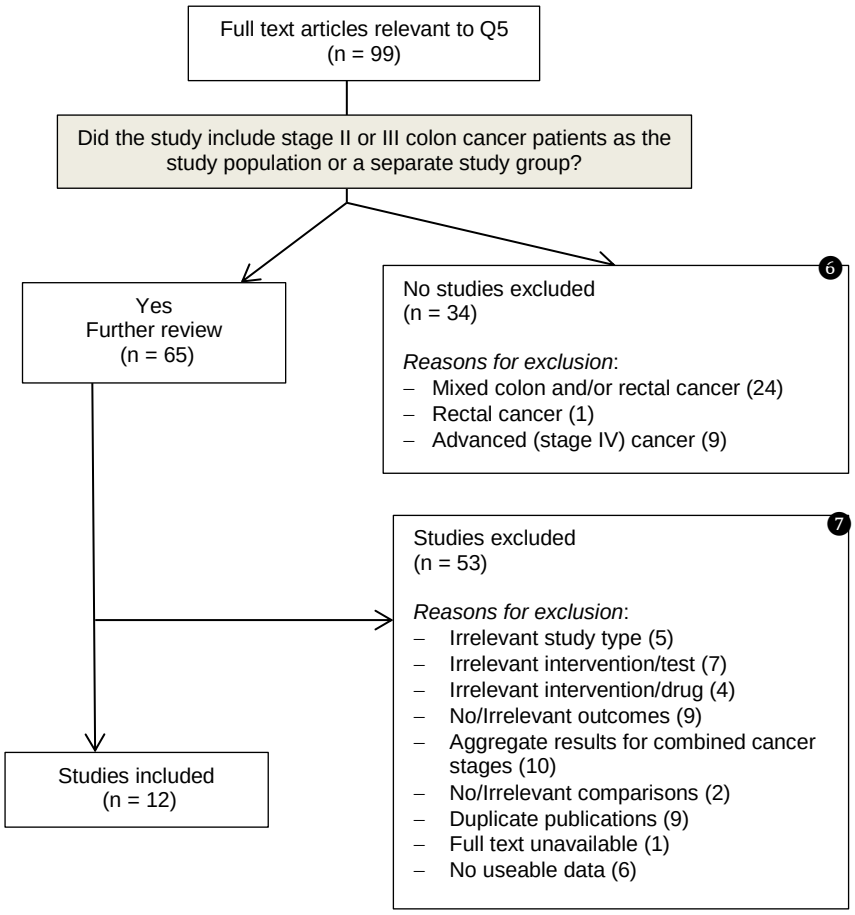
Appendix 23: Selection of Included Studies (Question 4 and 5)



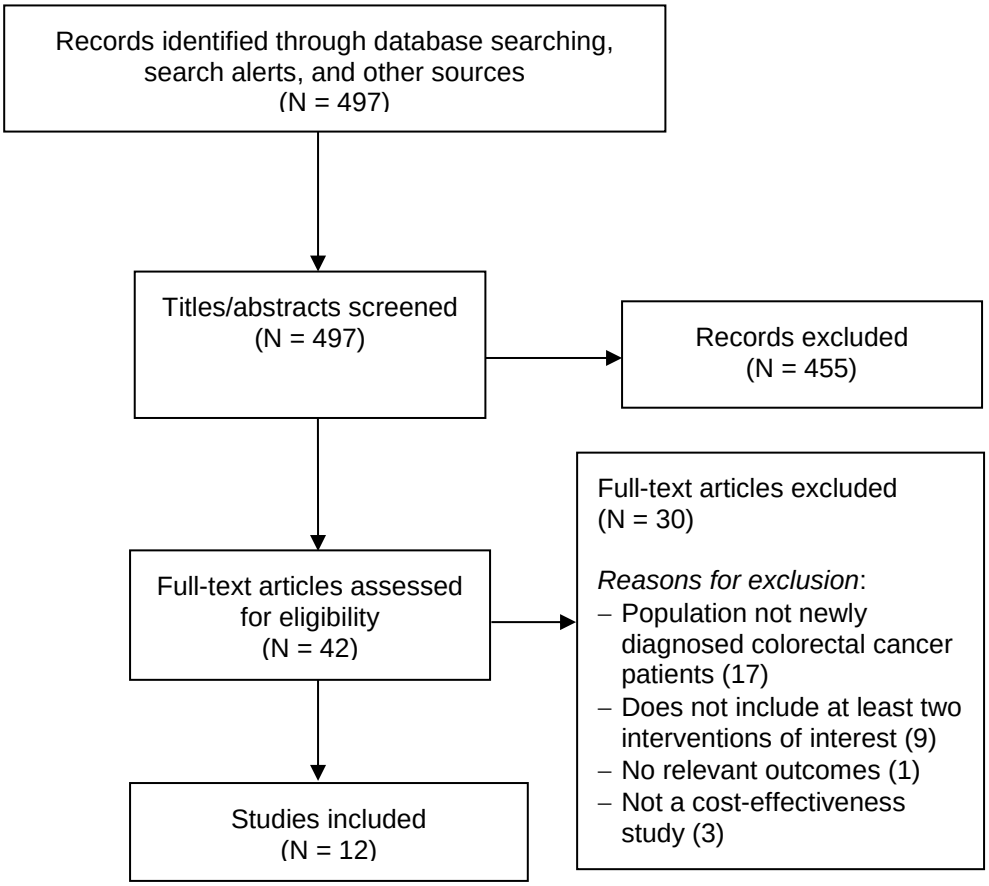
Study selection process for Q4



Study selection process for Q5



Appendix 24: Selection of Included Studies (Question 6)



Appendix 25: Characteristics of Included Studies (Question 1)

Author, Year	Country	Initial Study Population Selection Criteria	dMMR Test(s)		Germline Test(s)	Outcomes Reported	
			PCR, Markers (Type)	IHC, Proteins (Type)		Sens	Spec
Bashyam, 2014[22]	India	Samples fulfilling any of: rBG or AC-II	5 markers (BAT25, BAT26, D5S346, D17S250, D2S123); MSI-H (pos), MSI-L/MSS (neg)	4 proteins (MLH1, MSH2, MSH6, PMS2)	Sequencing by PCR-DNA using standard protocol in MLH1, MSH2, MSH6 Modified long-range PCR in PMS2, large deletions identified by MLPA Exonic rearrangement analyses by SALSA MLPA in all 4 MMR genes, confirmed by Q-PCR RT-PCR performed to confirm effect of specific mutations at transcript level Pathogenicity unclear	x	x
Liu, 2014[23]	Singapore	Pts fulfilling any of: AC-I, AC-II, or Japanese criteria	5 markers (BAT25, BAT26, NR21, NR24, MONO27); MSI-H (pos), MSI-L/MSS (neg)	4 proteins (MLH1, MSH2, MSH6, PMS2)	Mutations in exons scanned by high resolution melting assay, followed by direct targeted DNA sequencing in MLH1, MSH2, MSH6, PMS2, PMS1 Large fragment deletions/duplications evaluated by MLPA in MLH1, MSH2, MSH6, PMS2, EPCAM Pathogenic	x	x
De Lellis, 2013[24]	Italy	Pts fulfilling either: AC-I or AC-II	5 markers (BAT25, BAT26, D5S346, D2S123, DI7S250); MSI-H/MSI-L (pos), MSS (neg)	3 proteins (MLH1, MSH2, MSH6)	Initial screening with SSCP or DGGE in MLH1, MSH2, and negative cases screening by dHLPC and automated sequencing in MLH1, MSH2, MSH6 Probands negative for pathogenic nucleotide substitutions further screened by MLPA for extended rearrangements in MSH2, MLH1, EPCAM Pathogenic	x[a]	x[a]
Kastrinos, 2013[25]	Multiple (Canada, US, Australia)	None	10 markers (BAT25, BAT26, BAT40, MYCL, D5S346, D17S250, ACTC, D18S55, D10S197, BAT34C4); MSI-H (pos), MSI-L/MSS (neg)	4 proteins (MLH1, MSH2, MSH6, PMS2)	Mutations in MSH2, MLH1 detected using combined dHPLC/direct sequencing and MLPA Direct sequencing used to detect MSH6 mutations where no IHC staining of MSH6 Large genomic rearrangements analyzed by MLPA PMS2 mutations evaluated in some pts Pathogenic	x	x
Limburg, 2011[26]	Multiple (Canada, US)	None	-	3 proteins (MLH1, MSH2, MSH6)	Direct sequencing of MLH1, MSH2, MSH6 and large rearrangement testing by Southern blot analysis in conjunction with MLPA and duplication and deletion analyses performed for MLH1, MSH2 Pathogenic	x	x

Author, Year	Country	Initial Study Population Selection Criteria	dMMR Test(s)		Germline Test(s)	Outcomes Reported	
			PCR, Markers (Type)	IHC, Proteins (Type)		Sens	Spec
Moussa, 2011[27]	Tunisia	Pts Dx'd w/CRC or HNPCC spectrum cancer < 50 years, or > 50 years but known as having family history of cancers highly suggestive of LS at Dx Pts fulfilling any of: rBG, AC-I, AC-II, or none	5 markers (BAT25, BAT26, NR21, NR22, NR24); MSI-H (pos), MSS (neg)	4 proteins (MLH1, MSH2, MSH6, PMS2)	Large genomic rearrangements analyzed by MLPA in MLH1, MSH2 Entire coding regions, splice junctions, and promoter regions of MLH1, MSH2 screened for presence of point mutations MSH6 analyzed for all pts without a certain pathogenic mutation in MLH1 or MSH2, and PMS2 in 1 pt Pathogenic	x[a]	x[a]
Perez-Cabornero, 2011[28]	Spain	None	5 markers (BAT25, BAT26, D2S123, D5S346, D17S250); MSI-H (pos), MSI-L/MSS (neg)	3 proteins (MLH1, MSH2, MSH6)	General point mutation screening by HA-CAE in MLH1, MSH2, MSH6 and sequencing of fragments showing HA-CAE–altered pattern Genomic rearrangements of negative samples evaluated by MLPA Pathogenic	x[a]	
Warrier, 2011[29]	Australia	Pts w/ germline pos. LS Dx, & PCR-based test if proband Dx'd < 40 years or had AC-I family	-	4 proteins (MLH1, MSH2, MSH6, PMS2)	Germline analysis methods NR Pathogenicity NR	x	
Barrow, 2010[30]	UK	None	-	4 proteins (MLH1, MSH2, MSH6, PMS2)	Sequencing of MLH1, MSH2, MSH6 Pathogenic	x	x
Ferreira, 2009[31]	Netherlands, Portugal	Dx'd MMR carriers, pts Dx'd w/CRC < 50 years, or pts who had 2 or more LS-related cancers, incl. min. 1 CRC	3 markers (BAT25, BAT26, BAT40) used in some tumours, 3 additional markers (D2S123, D5S346, D17S250) in others; MSI-H (pos), MSI-L/MSS (neg)	-	Mutation analysis carried out by DGGE and direct sequencing for germline mutations in MLH1, MSH2, MSH6 MLPA used for large deletion detection, and deletions of > 1 exon in MLH1, MSH2 gene confirmed by Southern blot analysis Pathogenic	x	x
Russo, 2009[32]	Italy	Pts w/ HNPCC Dx based on: AC-I, AC-II, and family history	5 markers (BAT25, BAT26, D2S123, D5S346, D17S250); MSI (2+ pos markers)	-	Combination of different methods to look for alterations in MLH1, MSH2, including SSCP, DGGE, dHPLC, and direct sequencing, with negative cases tested by Southern blotting analysis, MLPA, or non-fluorescent multiplex PCR with HPLC All mutations identified by indirect methods confirmed by sequencing Pathogenic	x	x
Sinn, 2009[33]	Korea	Pts fulfilling any of: AC-II, BG & MSI pos., or MSI pos. & ‹ 60 years offered germline testing	5 markers (BAT25, BAT26, D2S123, D5S346, D17S250); MSI-H (pos), MSI-L/MSS (neg)	-	Genomic DNA sequenced for MLH1, MSH2 Confirmed "authenticity"	x	

Author, Year	Country	Initial Study Population Selection Criteria	dMMR Test(s)		Germline Test(s)	Outcomes Reported	
			PCR, Markers (Type)	IHC, Proteins (Type)		Sens	Spec
Lagerstedt Robinson, 2007[34]	Sweden	AC-II family, MSI pos. family, MSI neg. family w/ 1 pt ‹ 50 years, or MSI pos. early onset single pts offered germline testing	5 markers (BAT25, BAT26, D2S123, D5S346, D17S250); MSI-H (pos), MSI-L/MSS (neg)	4 proteins (MLH1, MSH2, MSH6, PMS2)	DGGE or sequencing used to screen for mutations in MLH1, MSH2, MSH6, PMS2 Rearrangement screening used RNA- or DNA-based methods, e.g., MLPA Pathogenic	x[a]	
Wang, 2007[35]	China	Pts w/ pathology Dx'd CRC + AC-I or AC-II, or suspected HNPCC (established using Japanese criteria + top 6 criteria from BG) w/ hMLH1/ hMSH2 germline mutations	9 markers (BAT25, BAT26, BAT40, D2S123, D18S58, D10S197, D5S36, D18S69, MYCL); MSI-H (pos), MSI-L/MSS (neg)	-	SSCP analysis of MLH1, MSH2, with PCR product sequencing Pathogenicity NR	x	x
Barnetson, 2006[36]	UK	Pts w/ Dx'd CRC < 55 years	5 markers (BAT25, BAT26, D2S123, D5S346, D17S250); MSI-H (pos), MSI-H/MSI-L (pos), MSI-L (pos), MSS (neg)	3 proteins (MLH1, MSH2, MSH6)	dHPLC or sequencing used to screen for mutations in MLH1, MSH2, MSH6 MLH1, MSH2 assessed by MLPA Pathogenic	x[a]	
Niessen, 2006[37]	Netherlands	Pts w/ Dx'd CRC < 50 years, or had > 2 HNPCC-related cancers, incl. min. 1 CRC	5 markers (BAT25, BAT26, D2S123, D5S346, D17S250); MSI-H (pos), MSI-L (neg), MSS not used	3 proteins (MLH1, MSH2, MSH6)	Mutation analysis carried out by DGGE and direct sequencing for germline mutations in MLH1, MSH2, MSH6 MLPA used for large deletion detection, and deletions of >1 exon in MLH1, MSH2 gene confirmed by Southern blot analysis Pathogenic	x[a]	
Wolf, 2006[38]	Australia	Pts fulfilling any of: rBG, BG, Rev. AC, or AC-II	5 markers for each of 2 groups (D5S346, HSCAP53L, D2S123, Bat26, D18S34 & D5S82, D2S134, D13S175, D11S904, Bat25); MSI-H (pos), MSS (neg)	-	Sequence analysis of MLH1, MSH2 Pathogenic	x	x
Southey, 2005[40]	Australia	Pts w/ Dx'd histologically confirmed CRC < 45 years	10 markers (D5S346, D17S250, D2S123, BAT25, BAT26, BAT40, MYB, TGF RII, IGFIIR, BAX); MSI-H (pos), MSI-H/MSI-L (pos), MSS (neg)	4 proteins (MLH1, MSH2, MSH6, PMS2)	Sequencing and dHPLC used to screen for mutations in MLH1, MSH2, MSH6, PMS2, with confirmation by PCR direct automated sequencing MLPA used for large genomic alterations in MLH1, MSH2 Pathogenic	x	x
Stormorken, 2005[41]	Norway	AC-I or AC-II families, 4 or more HNPCC-related cancers on 1 side of family, pts with very early	-	3 proteins (MLH1, MSH2, MSH6)	Pts sequenced for MLH1, MSH2 Negative cases lacking MMR protein expression analyzed for large rearrangements in MLH1, MSH2, with	x[a]	x[a]

Author, Year	Country	Initial Study Population Selection Criteria	dMMR Test(s)		Germline Test(s)	Outcomes Reported	
			PCR, Markers (Type)	IHC, Proteins (Type)		Sens	Spec
		onset CRCs, or pts with multiple primary CRCs or ECs			remaining cases sequenced for MSH6 Pathogenic		
Caldes, 2004[42]	Spain	HNPCC families, w/ prior test for MMR defect Families fulfilling any of: AC-I, Rev. AC, BG, or Familial Association of Colorectal Cancer	5 markers (BAT25, BAT26, D2S123, D5S346, D17S250); MSI-H (pos), MSS (neg)	3 proteins (MLH1, MSH2, MSH6)	DGGE or cycle sequencing analysis of MLH1, MSH2, MSH6 Negative MSI-H cases analyzed for genomic deletions in MLH1, MSH2 by Southern blotting Pathogenic	x	x
Schiemann, 2004[43]	Germany	Pts fulfilling either: AC or BG	5 markers (BAT25, BAT26, D2S123, D5S346, D17S250); MSI-H/MSI-L (pos), MSS (neg)	-	dHPLC analysis of MLH1, MSH2 Pathogenicity NR		x[a]
Hendriks, 2003[45]	Netherlands	Pts with known germline mutation fulfilling either: Rev. AC, suspected HNPCC (BG pos.), or late onset w/ 3 CRC pts in 2 to 3 generations w/out Dx < 50 years, or sporadic pts Dx'd < 40 years	5 markers (BAT25, BAT26, D2S123, D5S346, D17S250 + extended BAT40, MSH3, MSH6); MSI-H/MSI-L (pos), MSS (neg)	3 proteins (MLH1, MSH2, MSH6)	DGGE or Southern blotting to analyze MLH1, MSH2, MSH6 Pathogenic	x	
Berends, 2002[46,47]	Netherlands	Pts suspected of HNPCC fulfilling no criteria, or fulfilling any of: CRC or EC Dx'd < 50 years; pts w/ CRC, EC, or HNPCC-related tumour & 1 first-degree relative w/ CRC, EC, or HNPCC-related tumour Dx'd < 50 years; pts w/ 2+ HNPCC-related tumours irrespective of age at Dx; pts w/ colorectal adenoma or atypical endometrial hyperplasia & 1 first-degree relative w/ CRC or EC, both Dx'd < 50 years	6 markers (BAT25, BAT26, D2S123, D5S346, D17S250, BAT40); MSI-H (pos), MSI-L (neg), MSS not used	3 proteins (MLH1, MSH2, MSH6)	DGGE to analyze MSH6, confirmed by direct sequencing Sequencing of MLH1, MSH2 for nearly all pts No search for germline genomic deletions Pathogenic	x[a]	
Christensen, 2002[47]	Denmark	Pts suspected of belonging to HNPCC families, or fulfilling AC-I	5 markers (BAT26, D2S119, D3S1612, D5S404, D17S26) + 4 additional loci in AC pts (BAT25, D2S123, D5S346, D17S250); MSI-	-	Sequencing of MLH1, MSH2 Pathogenicity NR	x	x

Author, Year	Country	Initial Study Population Selection Criteria	dMMR Test(s)		Germline Test(s)	Outcomes Reported	
			PCR, Markers (Type)	IHC, Proteins (Type)		Sens	Spec
			H (pos), MSI-L/MSS (neg)				
Farrington, 2002[48]	UK	Pts w/ Dx'd CRC < 30 years	8 markers (D2S123, D5S82, D5S346, D13S160, BAT25, BAT26, BAT40, PAX6-I253); MSI (pos), MSS (neg)	-	Germline mutation analysis of MSH2, MLH1 Pathogenicity NR	x	x
Katballe, 2002[49]	Denmark	Pts suspected of belonging to HNPCC families, including fulfilling: AC-I or AC-II; Rev. AC-I (Dx'd CRC 50 to 55 years); Pts < 40 years w/ at least 1 CRC in family members; both proband & 1 first-degree relative had CRC < 55 years	5 markers (BAT26, D2S119, D3S1612, D5S404, D17S261) or 5 NCI markers (BAT25, BAT26, D2S123, D5S346, D17S250); MSI-H/MSI-L (pos), MSS (neg)	-	SSCP, heteroduplex, and sequencing of MLH1, MSH2 Pathogenic	x	x
Wahlberg, 2002[50]	USA	Families fulfilling any of: AC-I, Rev. AC, BG criteria 2, 3, 4, or 7, or HNPCC-like criteria	5 markers (BAT25, BAT26, D2S123, APC, Mfd15) + 5 marker extended panel (BAT40, MYCL, D18S69, D18S58, D10S197); MSI-H (pos), MSI-L/MSS (neg)	-	Sequencing of MLH1, MSH2 Pathogenic	x	x
Ward, 2002[51]	Australia	Pts germline tested for mutations in hMSH2/ hMLH1, fulfilling any of: AC-I, AC-II, or BG	6 markers (BAT25, BAT26, BAT40, D5S346, D2S123, D17S250); MSI-H (pos), MSS (neg)	-	DGGE and sequencing to analyze MLH1, MSH2 Pathogenic	x[a]	x[a]
Loukola, 2001[52]	Finland	None	5 markers (BAT25, BAT26, D2S123, D5S346, D17S250); MSI-H (pos), MSI-L/MSS (neg)	-	Direct genomic sequencing and Southern blotting of MLH1, MSH2, MSH6 Pathogenicity NR	x	x
Calistri, 2000[53]	Italy	Pts fulfilling any of: AC; partially documented HNPCC families; families meeting 2 out of 3 AC; pts w/ at least 1 first-degree relative w/ CRC; pts Dx'd at < 50 years w/ no family history of cancer; pts w/ multiple tumours and no family history of cancer	13 markers (BAT25, BAT26, BAT40, D2S123, D5S346, D17S250, D2S177, D3S1076, D5S433, D11S904, D17S796, D18S59, HUMTH01); MSI-H/MSI-L (pos), MSS (neg)	-	SSCP to analyze MLH1, MSH2 Pathogenic	x[a]	x[a]

Author, Year	Country	Initial Study Population Selection Criteria	dMMR Test(s)		Germline Test(s)	Outcomes Reported	
			PCR, Markers (Type)	IHC, Proteins (Type)		Sens	Spec
Dieumegard, 2000[54]	France	Pts fulfilling any of: ICG criteria for HNPCC; Strong family CRC history, missing at least 1 ICG criterion; pts Dx'd w/ CRC < 50 years, after verified absence of CRC & HNPCC spectrum tumours recorded in second-degree family members	20 markers (D2S116, D2S117, D2S119, D2S123, D2S147, D2S155, D2S391, D3S1277, D3S1298, D3S1561, D5S82, D5S299, CA7, D5S346, D7S481, D7S517, D7S531, D11S904, D13S175, D20S116); MSI >10% (pos), MSI <10% (neg)	-	SSCP to analyze MLH1, MSH2 Direct sequencing for aberrant single-strand DNA fragment samples Pathogenic	x[a]	x[a]

AC = Amsterdam criteria; BG = Bethesda Guidelines; CRC(s) = colorectal cancer(s); DGGE = denaturating gradient gel electrophoresis; dHPLC = denaturing high-performance liquid chromatography; dMMR = deficient mismatch repair; Dx = diagnose; EC(s) = endometrial cancer(s); HA-CAE = heteroduplex analysis by capillary array electrophoresis; HNPCC = hereditary non-polyposis colorectal cancer; HPLC = high-performance liquid chromatography; ICG = International Collaborative Group; IHC = immunohistochemistry; LS = Lynch syndrome; MLPA = multiplex ligation-dependent probe amplification; MMR = mismatch repair; MSI = microsatellite instability; MSS = microsatellite stable; neg = negative; NR = not reported; PCR = polymerase chain reaction; pos = positive; pt = patient; Q-PCR = quantitative PCR; rBG = Revised Bethesda Guidelines; Rev. = revised; RT-PCR = reverse transcription-PCR; Sens = sensitivity; Spec = specificity; SSCP = single-strand conformation polymorphism; w/ = with.

[a] Imputed data

Appendix 26: Characteristics of Included Studies (Question 3)

Author	Country	Initial Study Population	BRAF-PCR Test Method	Hypermethylation Test Method	BRAF-PCR		BRAF-IHC		Hypermethylation	
					sens	spec	sens	spec	sens	spec
Toon 2013[69]	Australia	1,403 CRC patients, BRAF-PCR and IHC completed on all patients. 51 CRC samples from a registry used for methylation status	Sequencing	Method not reported	x	x	x	x	x	x
Bouzourene 2010[72]	Switzer-land	Selected patients known to have MLH1 mutation + patients known to have sporadic CRC but loss of MLH1	Sequencing	Single-strand conformation analysis	x	x			x	x
Chang 2010[77]	Taiwan	561 CRC patients had MSI. IHC conducted on 158 patients who were MSI high or met BG criteria	Sequencing	MS-PCR	x	x			x	x
Perez-Carbonell 2010[16]	Spain	IHC performed on 2,265 CRC tumours	Sequencing	Bisulfite genomic sequencing (MethyLight & SALSA)	x	x			x	x
Aleayehu 2008[76]	Slovakia	22 patients who fulfilled AC, BG, or rBG criteria, plus 1 patient that was MSI high but did not fill criteria, plus 10 MSS patients	No BRAF sequencing	Bisulfite genomic sequencing						x
Hampel 2008[61]	USA	500 CRC tumours from patients treated in 6 hospitals had IHC	No BRAF sequencing	MS-PCR & COBRA					x	x
Julie 2008[74]	France	214 consecutive CRC patients tested for MSI. Tumours that were MSI high, had IHC testing (n = 21)	Sequencing	Bisulfite genomic sequencing (COBRA)	x	x			x	x
Poynter 2008[71]	USA/ Canada	1,222 CRC patients from 6 registries. IHC conducted in all MSI-H and MSI-L patients (n = 719)	No BRAF sequencing	Bisulfite genomic sequencing (MethyLight)					x	
Rahner 2008[73]	Germany	763 CRC patients who fulfilled at least one of the rBG criteria	Sequencing	Bisulfite genomic sequencing (COBRA)					x	x

Author	Country	Initial Study Population	BRAF-PCR Test Method	Hypermethylation Test Method	BRAF-PCR		BRAF-IHC		Hypermethylation	
					sens	spec	sens	spec	sens	spec
Loughrey 2007[68]	Australia	500 CRC tumours that were suspected to be HNPCC. 68 patients were MSI high or IHC deficient	allele-specific PCR + Sequencing	No hypermethylation test	x	x				
Overbleek 2007[75]	Nether-lands	667 tumours from family members suspected for Lynch syndrome because they either met the AC or the BG criteria or had history very close to the BG	No BRAF sequencing	Bisulfite genomic sequencing (MethyLight)						x
Wang 2003[70]	USA	293 consecutive tumours tested for MSI and IHC	Sequencing	Bisulfite genomic sequencing	x	x				

AC = Amsterdam criteria; BG = Bethesda Guidelines; COBRA = combined bisulphite restriction analysis; CRC = colorectal cancer; HNPCC = hereditary non-polyposis colorectal cancer; IHC = immunohistochemistry; MSI = microsatellite instability; MS-PCR = methylation-specific polymerase chain reaction; PCR = polymerase chain reaction; rBG = revised Bethesda criteria; sens = sensitivity; spec = specificity.

Appendix 27: Characteristics of Included Studies (Question 4)

Author, Year	Country	Type and Stage of Cancer	Eligibility Criteria		dMMR Testing			Reported Outcomes
			Inclusion	Exclusion	MSI	IHC	Definition of Instability	
Brosens, 2011[95]	Netherlands	Stage II colon	– Stage II colon cancer with or without relapse – Underwent surgery between 1990 and 2000	– Post-operative chemotherapy	5 mononucleotide markers using MSI Analysis System (Promega, Madison, USA)	NR	– MSI: instability in ≥ 2 markers – MSS: instability in 0 to 1 marker	Relapse rate, DFS
Hutchins, 2011[91]	UK	Stage II colorectal	– CRC patients participating in QUASAR RCT – Available tissue specimens	NR	-	hMLH1 and hMSH2	– dMMR: no nuclear staining in all tumour epithelial cells, positive infiltrating lymphocytes	Relapse rate
Sinicrope, 2011[3]	USA	Stage II and III colon (results presented for stage III only)	– Pathologically proven stage II or stage III colon cancer – Available tissue specimens – Received adjuvant chemotherapy regimens in the RCTs performed by NCCTG, FFCD, GIVIO, and NASBP – Recruitment period: variable	NR	NCCTG 91-46-53 study: BAT26 + IHC Other NCCTG studies: 5-10 NCI panel markers that includeedBAT26, BAT25, D5S346, D2S123 and D17S250; NASBP studies: 5 Bethesda/NCI panel markers + TGFßRII. FFCD study: BAT25 & BAT26 GIVIO study: BAT25 & BAT26 a	MLH1, MSH2, and MSH6 (one study; NCCTG 91-46-53)	By MSI – MSI-H: instability in ≥ 30% of markers (GIVIO study: instability at both BAT25 & BAT26 loci) – MSI-L: instability at < 30% of loci screened – MSSL: all loci stable – MSI-L and MSS grouped together as MSI-L/S By IHC – dMMR: loss of MLH1 or MSH2 or MSH6 protein expression, – pMMR: intact MMR protein expression	Relapse rate
Dietmaier, 2006[92]	Germany	stage III colon	– Primary lymph node positive stage III colon cancer reported to a clinical tumour registry centre between	NR	# markers: NR using international microsatellite standard panel (HNPCC MSI Test kit (Roche, Mannheim,	NR	– MSI-H: instability in >40% of markers – MSI-L: instability in <40% of markers – MSS: instability in 0 markers	Death rate

Author, Year	Country	Type and Stage of Cancer	Eligibility Criteria		dMMR Testing			Reported Outcomes
			Inclusion	Exclusion	MSI	IHC	Definition of Instability	
			1993 and 2001 – Received standard 5-FU–based adjuvant chemotherapy		Germany).			
Lanza, 2006[93]	Italy	Stage III colorectal	– Stage II or III colorectal adenocarcinoma (outcomes reported for stage III) – Underwent curative surgery between 1986 and 1995	– > 85 years of age – Multiple synchronous colon carcinomas – Idiopathic IBD – Preoperative radiation therapy – A malignant tumour detected within the past 5 years – Death from post-op complications or other causes – Lost to follow-up	7 markers (BAT26, BAT40, D18S58, D18S61, D17S855, D17S786) + other markers (in some of the patients)	MLH1 and MSH2	By MSI – MSI-H: instability in ≥ 30% instability in markers – MSI-L: instability < 30% – MSS = instability in 0 markers By IHC – dMMR: complete loss of nuclear staining of tumour cells for MLH1 or MSH2 expression – pMMR: normal expression of MLH1 and MSH2	OS (disease-specific)
Elsaleh, 2001[94]	Australia	Stage III colorectal	– Margin-negative stage III CRC – Diagnosed between January 1986 and December 1998 – Treated surgically in public hospitals in Australia.	NR	BAT26 mononucleotide	NR	NR	OS
Curran, 2000[90]	Ireland	Stage II colorectal	– Stage II CRC admitted for resection surgery between 1983 and 1989	– Pre- or post-operative chemo- or radiation-therapy	4 markers, D5S82 and D5S346 (chromosome 5q), TP53 (chromosome 17p), D18S474 andDCC1.1/1.2	NR	– MSI-H: instability in ≥ 2 markers	OS

Author, Year	Country	Type and Stage of Cancer	Eligibility Criteria		dMMR Testing			Reported Outcomes
			Inclusion	Exclusion	MSI	IHC	Definition of Instability	
					(chromosome 18q), D17S579 &NM23&D17S293 (chromosome 17q):			

5-FU = fluorouracil; CALGB = Cancer and Leukemia Group B; CRC = colorectal cancer; DFS = disease-,recurrence-, and/or relapse-free survival; dMMR = deficient mismatch repair; FFCD = Federation Francophone de la Cancérologie Digestive; GIVIO = Gruppo Italiano Valutazione Interventi in Oncologia; HNPCC = hereditary non-polyposis colorectal cancer; IBD = inflammatory bowel disease; IHC = immunohistochemistry-based dMMR testing; MSI = PCR-based microsatellite stability (dMMR) testing; MSI-H = high microsatellite instability; MSI-L = low microsatellite instability; MSS = microsatellite stable; NASBP = the National Cancer Institute of Canada; NCCTG = North Central Cancer treatment Group; NR = not reported; OS = overall survival (all cause or disease-specific); PETACC = Pan-European Trial in Adjuvant Colon Cancer; QUASAR= Quick and Simple and Reliable trial; RCT = randomized controlled trial.

Appendix 28: Characteristics of Included Studies (Question 5)

Author, Year	Country	Eligibility Criteria		dMMR Testing			Chemotherapy Regimens	Reported Outcomes
		inclusion	Exclusion	MSI	IHC	Definition of MSI		
Klingbiel, 2015[96]	Multinational (Europe)	– 18 to 75 years of age – Histologically proven stage II or stage III colon cancer – Available tumour specimens – Received adjuvant chemotherapy in the PETACC trial – Recruitment period: NR	NR	10 markers: BAT25, BAT26, D2S123, D5S346, TGFßRII, BAT40, D17S787, D18S69, D17S250, and D18S58)	NR	– MSI-H: instability in ≥ 3 markers – MSI-L: instability in 1 to 2 markers – MSS: instability in 0 markers – MSI-L and MSS grouped together as MSI-L/S	5-FU ± FA or FOLFIRI	DFS OS
Kim SH, 2013[99]	Korea	– Pathologically proven stage III colon cancer – Available tumour specimens – Received curative surgical resection followed by adjuvant chemotherapy between January 2005 and July 2011	– Cancer other than adenocarcinoma – Signet ring cell type without extracellular mucin production – Rectal cancer – Pre-op chemotherapy – Pre-op or post-op radiotherapy – Unavailability of MSI status	5 markers: BAT25, BAT26, MFD15, D2S123 and D5S346	NR-	– MSI-H: instability in ≥ 2 markers – MSI-L: instability in 1 marker – MSS: instability in 0 markers – MSI-L and MSS grouped together as MSI-L/S	FOLFOX	DFS
Li, 2013[98]	China	– Histologically proven stage III colon cancer – Available tumour specimens – Received curative surgical resection followed by adjuvant chemotherapy between January 2000 and December 2008	– < 18 years of age or > 85 years – Rectal cancer – Abdominopelvic radiotherapy – Severe complication – Changing drug regimen – Multi-primary cancer – Family history of cancer in 1st- or 2nd-degree relatives – Familial	NR	MLH1 and MSH2	– dMMR: complete lack of expression in MLH1 and MSH2 (< 10% tumour cell staining for each protein) – pMMR: nuclear staining in ≥ 11% tumour cells	FOLFOX/ XELOX or 5-FU alone	DFS OS (disease-specific)

Author, Year	Country	Eligibility Criteria		dMMR Testing			Chemotherapy Regimens	Reported Outcomes
		inclusion	Exclusion	MSI	IHC	Definition of MSI		
			adenomatous polyposis					
Oh, 2013[97]	Korea	– Stage III colon cancer – Underwent curative surgical resection between January 2003 and December 2010	– Treated by surgery alone – Treated with adjuvant chemotherapy other than FOLFOX	5 markers: D2S123, D17S250, D5S346, BAT25, BAT26	NR	– MSI-H: instability in ≥ 2 markers – MSI-L: instability in 1 marker – MSS: instability in 0 markers – MSI-L and MSS grouped together as MSI-L/S	FOLFOX4	DFS OS Relapse rate
Bertagnolli, 2011[100]	USA	– Histologically proven stage III colon cancer – Underwent complete surgical resection – Received adjuvant chemotherapy in CALGB 89803 trial – Recruitment period: NR	– Metastatic disease – Rectal cancer – Positive tumour margins – Chemotherapy started too long post-operative – Labs outside limits.	10 markers: BAT25, BAT26, D17S250, D5S346, ACTC, D18S55, BAT40, D10S197, BAT34c4 and MycL	MLH1 and MSH2	– MSI – MSI-H: instability at ≥ 50% of screened loci – MSI-L: instability in at least one but ≤ 50% of the loci – MSS: all loci stable – MSI-L and MSS grouped together as MSI-L/S – IHC – dMMR: nuclear staining I < 10% tumour cells related to either MLH1 or MSH2 – pMMR: retained expression	5-FU + Lev or FOLFIRI	DFS OS

Author, Year	Country	Eligibility Criteria		dMMR Testing			Chemotherapy Regimens	Reported Outcomes
		inclusion	Exclusion	MSI	IHC	Definition of MSI		
						(staining in ≥ 10% of tumour cells) of both proteins		
Sinicrope, 2011[3]	USA	– Pathologically proven stage II or stage III colon cancer – Available tissue specimens – Received adjuvant chemotherapy regimens in the RCTs performed by NCCTG, FFCD, GIVIO, and NASBP – Recruitment period: variable	– NR	NCCTG 91-46-53 study: BAT26 + IHC Other NCCTG studies: 5-10 NCI panel markers that include BAT26, BAT25, D5S346, D2S123 and D17S250; NASBP studies: 5 Bethesda/NCI panel markers + TGFßRII. FFCD study: BAT25 & BAT26 GIVIO study: BAT25 & BAT26	MLH1, MSH2, and MSH6 (one study; NCCTG 91-46-53)	– MSI – MSI-H: instability in ≥ 30% of markers (GIVIO study: instability at both BAT25 & BAT26 loci) – MSI-L: instability at < 30% of loci screened – MSSL: all loci stable – MSI-L and MSS grouped together as MSI-L/S – IHC – dMMR: loss of MLH1 or MSH2 or MSH6 protein expression – pMMR: intact MMR protein expression	5-FU + FA/Lev or 5-FU + FA + ɣ-interferon + Lev	Relapse rate
Yoon, 2011[102]	Korea	– < 75 years of age – An ECOG performance status of 0 or1 – Histologically confirmed colorectal adenocarcinoma – Underwent curative surgical resection	– HNPCC, corresponding to Amsterdam criterion I or II – FAP or attenuated FAP – Synchronous or metachronous CRC – History of pre-	5 markers: BAT25, BAT26, D5S346, D2S123 and D17S250	MLH1 and MSH2	– MSI – MSI-H: instability in ≥ 2 markers – MSI-L: instability in 1 marker – MSS: instability in 0	5-FU+FA / ca	DFS OS

Author, Year	Country	Eligibility Criteria		dMMR Testing			Chemotherapy Regimens	Reported Outcomes
		inclusion	Exclusion	MSI	IHC	Definition of MSI		
		followed by adjuvant chemotherapy between August 2003 and December 2007	operative radio-chemotherapy			markers – MSI-L and MSS grouped together as MSI-L/S – IHC – dMMR: nuclear staining > 10% of tumour cells for both MLH1 and MSH2		
Zaanan, 2011[101]	France	– Histologically proven stage III colon cancer – Available tumour specimens – Received curative surgical resection followed by adjuvant chemotherapy between June 2003 and December 2007	– Age < 18 years – Rectal cancer – Abdominopelvic radiotherapy – Dead within 30 days after surgery – Treated by surgery alone – Treated with chemotherapy other than FOLFOX – Chemotherapy and/or surveillance after surgery in another centre – Delay between surgery and chemotherapy > 8 weeks – Tissue samples unavailable – IHC test uninterpretable or clinical data were missing.	5 mononucleotide markers: NR21, NR24, NR27, BAT25 and BAT26	MLH1, MSH2 and MSH6	– MSI – MSI-H: instability in ≥ 3 markers – MSS: instability in < 3 markers – IHC – dMMR: loss of tumour MLH1, MSH2 or MSH6 protein expression (complete absence of tumour cell staining) – pMMR: normal tumour MLH1, MSH2 and MSH6 protein expression	FOLFOX4 or FOLFOX6	DFS OS Relapse rate

Author, Year	Country	Eligibility Criteria		dMMR Testing			Chemotherapy Regimens	Reported Outcomes
		inclusion	Exclusion	MSI	IHC	Definition of MSI		
Zaanan, 2010[103]	France	– Histologically proven stage III colon cancer – Underwent curative surgical resection followed by adjuvant chemotherapy between December 1997 and March 2006	NR	NR	MLH1, MSH2, and MSH6	– dMMR: the complete lack of expression (complete absence of nuclear staining of tumour cells) for MLH1, MSH2 or MSH6	5-FU + FA or FOLFOX	DFS
Dietmaier, 2006[92]	Germany	– Primary lymph node positive stage III colon cancer reported to a clinical tumour registry centre between 1993 and 2001 – Received standard 5-FU–based adjuvant chemotherapy	NR	# markers: NR Using international microsatellite standard panel (HNPCC MSI Test kit; Roche, Mannheim, Germany)	NR	– MSI-H: instability in > 40% of markers – MSI-L: instability in < 40% of markers – MSS: instability in 0 markers	5-FU	OS
Westra, 2005[104]	Netherlands	– Primary stage III colon cancer from CKVO 90-11 trial – Available tumour specimens – Received adjuvant chemotherapy – Recruitment period: NR	NR	9 markers (BAT25, BAT26, BAT40, MONO27, D3S2432, D7S1808, D7S3046, D7S3070, D10S1426) or 5 markers (BAT25, BAT26, D5S346, D2S123, D17S250)	NR	– MSI-H: instability in ≥ 3 of 9 markers or ≥ 2 of 5 markers – MSS: all other cases	5-FU + Lev ± FA	DFS (recurrence or disease-specific death)

Author, Year	Country	Eligibility Criteria		dMMR Testing			Chemotherapy Regimens	Reported Outcomes
		inclusion	Exclusion	MSI	IHC	Definition of MSI		
Watanabe, 2001[105]	USA	– Stage III or high-risk stage II colon cancer – Received adjuvant chemotherapy in the INT0032 and INT0089 trials, between August 1988 and July 1992	NR	10 markers (8 dinucleotides and 2 mononucleotides) (D18S69, D18S64, D18S55, D18S61, D18S58, D17S520, TGFßRII, TP53, p53VNTR, BAT26)	NR	– MSI-H: instability in ≥ 2 markers or ≥ 30% of loci	5-FU + Lev ± FA (high/low doses)	DFS OS

5-FU = 5 fluorouracil; ca = capecitabine; CALGB = Cancer and Leukemia Group B; CKVO = the Dutch Commissie Klinisch Vergelijkend Onderzoek group; CRC = colorectal cancer; DFS = disease-, recurrence-, and/or relapse-free survival; dMMR = deficient mismatch repair; ECOG = Eastern Cooperative Oncology Group; FA = folinic acid (leucovorin); FAP = familial adenomatous polyposis; FFCD = Federation Francophone de la Cancérologie Digestive; FOLFOX = 5-FU + leucovorin + oxaliplatin; FOLFIRI = 5-FU + leucovorin + irinotecan; GIVIO = Gruppo Italiano Valutazione Interventi in Oncologia; HNPCC = Hereditary nonpolyposis colorectal cancer; IHC = immunohistochemistry-based dMMR testing; INT = National Cancer Institute Gastrointestinal Intergroup; Lev = levamisole; MSI = PCR-based microsatellite stability (dMMR) testing; MSI-H = high microsatellite instability; MSI-L = low microsatellite instability; MSS = microsatellite stable; NASBP = the National Cancer Institute of Canada; NCCTG = North Central Cancer treatment Group; NR = not reported; OS = overall survival (all cause or disease-specific); PETACC = Pan-European Trial in Adjuvant Colon Cancer; pMMR = proficient mismatch repair; RCT = randomized controlled trial; XELOX = 5-FU (capecitabine) + oxaliplatin.

Appendix 29: Characteristics of Included Studies (Question 6)

Author	Setting	Outcome	Screening Strategy Evaluated				Reflex Testing Strategy Evaluated		
			No Testing	Revised Bethesda Guidelines	Younger than 70 Years	Universal	All to Germline	BRAF-PCR	Hyper methylation
Bessa,[109] 2008	Spain	Cost per LS case detected					x	x	
Gausachs,[110] 2012	Spain	Cost per LS case detected					x	x	x
Gould-Suarez,[111] 2014	USA	Cost per LS case detected		x		x			
Gudgeon,[112] 2011	USA	Cost per LS case detected					x	x	x
Gudgeon,[113] 2013	USA	Cost per LS case detected	x		x				
Palomaki,[56] 2009	USA	Cost per LS case detected					x	x	
Yan,[114] 2008	China	Cost per LS case detected					x		x
Ladabaum,[115] 2011	USA	Cost per life-year	x	x		x	x	x	
Mvundura,[116] 2010	USA	Cost per life-year	x			x	x	x	
Severin,[120] 2015	Germany	Cost per life-year	x	x		x			
Wang,[118] 2012	USA	Cost per QALY	x	x		x	x?	x?	
Snowsill,[119] 2015	UK	Cost per QALY	x		x		x	x	x

LS = Lynch syndrome; QALY = quality-adjusted life-year.

Appendix 30: Critical Appraisal of Included Studies (Question 1)

Strengths	Limitations
Bashyam, 2014[22]	
Patient Selection • A case-control designed was not used • Patient sample was consecutive • No patients were lost to follow-up *Index Test* • Threshold was pre-specified *Reference Standard* • Reference standard was likely to classify patients appropriately *Flow and Timing* • All patients in the study received the same reference standard • All patients were included in the analysis	*Patient Selection* • No limitations identified *Index Test* • Unclear if the index test was interpreted without knowledge of the reference standard *Reference Standard* • Unclear if the reference standard was interpreted without knowledge of the index test *Flow and Timing* • Index and reference test were conducted at the same time
Liu, 2014[23]	
Patient Selection • Patients were selected consecutively • A case-control design was avoided • The study avoided inappropriate exclusions *Index Test* • Index test results were interpreted by a pathologist and scientist blind to the reference standard results • A threshold was pre-specified *Reference Standard* • Reference standard results were interpreted without knowledge of the results of the index test • The reference standard was likely to classify patients appropriately *Flow and Timing* • No strengths identified	*Patient Selection* • No limitations identified *Index Test* • No limitations *Reference Standard* • No limitations identified *Flow and Timing* • Not all the patients received the reference standard • Unclear about the time interval between the index test and the reference standard • Not all patients were included in the analysis
De Lellis, 2013[24]	
Patient Selection • A case-control design was not used • The study avoided inappropriate exclusions *Index Test* • Threshold was pre-specified *Reference Standard* • The reference standard was likely to correctly classify the patients appropriately *Flow and Timing* • All patients in the study received the reference standard	*Patient Selection* • Unclear if patient sample was consecutive *Index Test* • Unclear if the index test results were interpreted without knowledge of the results of the reference standard *Reference Standard* • Unclear if the reference standard results were interpreted without knowledge of the results of the index test *Flow and Timing* • No limitations were identified

Strengths	Limitations
• All patients were included in the analysis • The index test and reference standard were performed within an appropriate timeframe	
Kastrinos, 2013[25]	
Patient Selection • Patients were selected consecutively • A case-control design was avoided • The study avoided inappropriate exclusions *Index Test* • A threshold was pre-specified *Reference Standard* • The reference standard was likely to classify patients appropriately *Flow and Timing* • All patients in the study received the reference standard • All patients were included in the analysis	*Patient Selection* • No limitations identified *Index Test* • Unclear if index test results were interpreted without knowledge of the results of the reference standard *Reference Standard* • Unclear if reference standard results were interpreted without knowledge of the index test *Flow and Timing* • Unclear about the time interval between the index test and the reference standard
Limburg, 2011[26]	
Patient Selection • Patients were selected consecutively • A case-control design was avoided • The study avoided inappropriate exclusions *Index Test* • A threshold was pre-specified *Reference Standard* • The reference standard results were interpreted without knowledge of the results of the index test • The reference standard was likely to classify patients appropriately *Flow and Timing* • All patients were included in the analysis • All patients in the study received the reference standard	*Patient Selection* • No limitations identified *Index Test* • Unclear if index test results were interpreted without knowledge of the results of the reference standard *Reference Standard* • No limitations identified *Flow and Timing* • Unclear about the time interval between the index test and the reference standard
Moussa, 2011[27]	
Patient Selection • Patients were selected consecutively • A case-control design was avoided • The study avoided inappropriate exclusions *Index Test* • A threshold was pre-specified *Reference Standard* • The reference standard was likely to classify patients appropriately	*Patient Selection* • No limitations identified *Index Test* • Unclear if index test results were interpreted without knowledge of the results of the reference standard *Reference Standard* • Unclear if reference standard results were interpreted without knowledge of the index test *Flow and Timing* • Unclear about the time interval between the index

Strengths	Limitations
Flow and Timing • All patients were included in the analysis • All patients in the study received the reference standard	test and the reference standard
Perez-Cabornero, 2011[28]	
Patient Selection • The study avoided inappropriate exclusions *Index Test* • A threshold was pre-specified *Reference Standard* • The reference standard was likely to classify the patients appropriately *Flow and Timing* • No strengths were identified • All patients were included in the analysis	*Patient Selection* • A case-control design was used *Index Test* • Unclear if index test results were interpreted without knowledge of the results of the reference standard *Reference Standard* • Unclear if reference standard results were interpreted without knowledge of the index test *Flow and Timing* • Unclear about the time interval between the index test and the reference standard • All patients in the study received the reference standard
Warrier, 2011[29]	
Patient Selection • The study avoided inappropriate exclusions *Index Test* • The index test results were interpreted without the knowledge of the results of the reference standard • A threshold was pre-specified *Reference Standard* • The reference standard results were interpreted without the knowledge of the results of the index test • The reference standard was likely to classify patients appropriately *Flow and Timing* • No strengths identified	*Patient Selection* • A case-control design was used *Index Test* • No limitations identified *Reference Standard* • No limitations identified *Flow and Timing* • Not all patients were included in the analysis • The index test and reference standard were completed at different times • Not all patients received the reference standard
Barrow, 2010[30]	
Patient Selection • Study avoided inappropriate exclusions *Index Test* • Index test results were interpreted by a gastrointestinal pathologist, who was blinded by mutational status • Threshold was pre-specified *Reference Standard* • Reference standard was likely to classify patients appropriately *Flow and Timing* • No patients were lost to follow-up	*Patient Selection* • A case-control design was used *Index Test* • No limitations identified *Reference Standard* • Unclear how reference standard was performed *Flow and Timing* • Not all patients received the reference standard • Index and reference tests were conducted at different times

Strengths	Limitations
Ferreira, 2009[31]	
Patient Selection • The study avoided inappropriate exclusions • A case-control design was not used *Index Test* • Threshold was pre-specified *Reference Standard* • The reference standard is likely to classify the patients appropriately • The reference standard results were interpreted without the knowledge of the results of the index test *Flow and Timing* • All patients in the study received the same reference standard • All patients were included in the analysis	*Patient Selection* • Some of the patients were used in a previous study with the same researchers *Index Test* • The index test was performed with the knowledge of the results of the reference standard *Reference Standard* • Unsure how the reference standard was performed *Flow and Timing* • The index test and reference standard were performed at the different times—time interval was unclear
Russo, 2009[32]	
Patient Selection Russo • Patients were selected consecutively • A case-control design was avoided • The study avoided inappropriate exclusions *Index Test* • A threshold was pre-specified *Reference Standard* • The reference standard was likely to classify the patients appropriately *Flow and Timing* • No strengths identified	*Patient Selection* • No limitations identified *Index Test* • Unclear if index test results were interpreted without knowledge of the results of the reference standard *Reference Standard* • Unclear if reference standard results were interpreted without knowledge of the index test *Flow and Timing* • Not all patients were included in the analysis • Unclear about the time interval between the index test and the reference standard • Not all the patients received the reference standard
Sinn, 2009[33]	
Patient Selection • Patients were consecutively selected • A case-control design was avoided • The study avoided inappropriate *Index Test* • Index results were interpreted without the knowledge of the results of the reference standard • A threshold was pre-specified *Reference Standard* • The reference standard was likely to classify patients appropriately *Flow and Timing* • No strengths identified	*Patient Selection* • No limitations identified *Index Test* • No limitations identified *Reference Standard* • The reference standard results were interpreted with the knowledge of the index test *Flow and Timing* • Not all patients received the reference standard • Not all patients were included in the analysis • The index test and reference standard were performed at the different times—time interval was unclear
Lagerstedt Robinson, 2007[34]	
Patient Selection • Patients were selected consecutively	*Patient Selection* • No limitations identified

Strengths	Limitations
• A case-control design was avoided • The study avoided inappropriate exclusions *Index Test* • A threshold was pre-specified *Reference Standard* • The reference standard was likely to classify patients appropriately *Flow and Timing* • All patients were included in the analysis	*Index Test* • Unclear if index test results were interpreted without knowledge of the results of the reference standard *Reference Standard* • Unclear if reference standard results were interpreted without knowledge of the index test *Flow and Timing* • Not all patients received the reference standard • Unclear about the time interval between the index test and the reference standard
Wang, 2007[35]	
Patient Selection • Patients were consecutively selected • A case-control design was avoided • The study avoided inappropriate exclusions *Index Test* • A threshold was pre-specified *Reference Standard* • The reference standard was likely to classify patients appropriately *Flow and Timing* • No strengths identified	*Patient Selection* • No limitations identified *Index Test* • Unclear if index test results were interpreted without knowledge of the results of the reference standard *Reference Standard* • Unclear if reference standard results were interpreted without knowledge of the index test *Flow and Timing* • Not all patients received the reference standard • Unclear about the time interval between the index test and the reference standard • Not all patients were included in the analysis
Barnetson, 2006[36]	
Patient Selection • Consecutive sample of patients were enrolled • No patients were lost to follow-up • A case-control design was not used • Minimized selection bias: researchers did not look at previous family history or test the tumour prior to selection *Index Test* • Threshold was pre-specified *Reference Standard* • Reference standard (germline mutational analysis) was likely to classify patients appropriately *Flow and Timing* • All patients were included in the analysis • All patients in the study received the same reference standard	*Patient Selection* • Age cut-off (≤ 55) with no explanation as to why *Index Test* • Index test results were interpreted with knowledge of the results of the reference standard *Reference Standard* • No limitations identified *Flow and Timing* • No limitations identified
Niessen, 2006[37]	
Patient Selection • Patients were selected consecutively • A case-control design avoided • The study avoided inappropriate exclusions	*Patient Selection* • No limitations identified *Index Test* • No limitations identified *Reference Standard*

Strengths	Limitations
Index Test • A threshold was pre-specified • The index test results were interpreted without the knowledge of the results of the reference standard *Reference Standard* • The reference standard was likely to classify patients appropriately *Flow and Timing* • No strengths identified	• Unclear if reference standard results were interpreted without knowledge of the index test *Flow and Timing* • Unclear about the time interval between the index test and the reference standard • Not all patients received the reference standard • Not all patients were included in the analysis
Wolf, 2006[38]	
Patient Selection • Patients were consecutively selected • The study avoided inappropriate exclusions • A case-control design was not used *Index Test* • The index test results were interpreted without knowledge of the results of the reference standard • A threshold was pre-specified *Reference Standard* • The reference standard results were interpreted without knowledge of the results of the reference standard • The reference standard was likely to classify patients appropriately *Flow and Timing* • All patients in the study received the reference standard • All patients were included in the analysis	*Patient Selection* • No limitations identified *Index Test* • No limitations identified *Reference Standard* • No limitations identified *Flow and Timing* • Unclear about the time interval between the index test and the reference standard
Southey, 2005[40]	
Patient Selection • Patients were selected consecutively • A case-control design was avoided • The study avoided inappropriate exclusions *Index Test* • A threshold was pre-specified • The index test results were interpreted without the knowledge of the results of the reference standard *Reference Standard* • The reference standard was likely to classify patients appropriately *Flow and Timing* • No strengths identified	*Patient Selection* • No limitations identified *Index Test* • No limitations identified *Reference Standard* • The reference standard results were interpreted with the knowledge of the index test *Flow and Timing* • Not all patients received the reference standard • Unclear about the time interval between the index test and the reference standard • Not all patients were included in the analysis
Stormorken, 2005[41]	
Patient Selection • Patients were selected consecutively	*Patient Selection* • No limitations identified

Strengths	Limitations
• A case-control design was avoided • The study avoided inappropriate exclusions *Index Test* • The index test results were interpreted without the knowledge of the results of the reference standard • A threshold was pre-specified *Reference Standard* • The reference standard was likely to classify patients appropriately *Flow and Timing* • No strengths identified	*Index Test* • No limitations identified *Reference Standard* • The reference standard results were interpreted with the knowledge of the results of the index test *Flow and Timing* • Not all patients received the reference standard • Unclear about the time interval between the index test and the reference standard • Not all patients were included in the analysis
Caldes, 2004[42]	
Patient Selection • The study avoided inappropriate exclusions • Patient selection was consecutive • A case-control design was not used *Index Test* • Threshold was pre-specified *Reference Standard* • Reference standard was likely to classify patients appropriately • Reference standard results were interpreted without knowledge of the results of the index test *Flow and Timing* • All patients in the study received the same reference standard • All patients were included in the analysis	*Patient Selection* • No limitations identified *Index Test* • Index test results were interpreted with knowledge of the results of the reference standard *Reference Standard* • No limitations identified *Flow and Timing* • The index test and reference standard were performed at the different times
Schiemann, 2004[43]	
Patient Selection • The study avoided inappropriate exclusions • A case-control design was avoided *Index Test* • A threshold was pre-specified *Reference Standard* • The reference standard was likely to classify patients appropriately *Flow and Timing* • All patients received the reference standard • All patients were included in the analysis	*Patient Selection* • Researchers were aware of the mutational status and IHC analysis of each patient *Index Test* • Index test results were interpreted with knowledge of the results of the reference standard *Reference Standard* • Reference standard results were interpreted with knowledge of the index test *Flow and Timing* • The index test and reference standard were performed at the different times—time interval was unclear
Hendriks, 2003[45]	
Patient Selection • Patients were selected consecutively • A case-control design was avoided	*Patient Selection* • No limitations were identified *Index Test*

Strengths	Limitations
• The study avoided inappropriate exclusions *Index Test* • The index test was interpreted by a pathologist and technician who were blinded by the germline mutational status of patients • A threshold was pre-specified *Reference Standard* • The reference standard results were interpreted without knowledge of the results of the index test • The reference standard was likely to classify patients appropriately *Flow and Timing* • All patients in the study received the same reference standard	• No limitations were identified *Reference Standard* • No limitations were identified *Flow and Timing* • The index test and reference standard were performed at the different times—time interval was unclear • Not all patients were included in the analysis
Berends, 2002[46]	
Patient Selection • The study avoided inappropriate exclusions *Index Test* • Index test results were interpreted without knowledge of the results of the reference standard • Threshold was pre-specified *Reference Standard* • Reference standard results were interpreted without knowledge of the results of the index test • The reference standard was likely to classify patients appropriately *Flow and Timing* • No strengths identified	*Patient Selection* • Unclear if patient selection was consecutive *Index Test* • No limitations identified *Reference Standard* • No limitations identified *Flow and Timing* • Not all patients were included in the analysis • Unclear if the index test and reference standard were performed at the same time
Christensen, 2002[47]	
Patient Selection • Patients were selected consecutively • A case-control design was not used • The study avoided inappropriate exclusions *Index Test* • Threshold was pre-specified *Reference Standard* • The reference standard was likely to correctly classify patients appropriately *Flow and Timing* • No strengths identified	*Patient Selection* • No limitations were identified *Index Test* • Unclear if index test results were interpreted without knowledge of the results of the reference standard *Reference Standard* • Unclear if reference standard results were interpreted without knowledge of the index test *Flow and Timing* • Not all patients received the reference standard • Not all patients were included in the analysis
Farrington, 2002[48]	
Patient Selection • The study avoided inappropriate exclusions	*Patient Selection* • A case-control design was used *Index Test*

Strengths	Limitations
Index Test • A threshold was pre-specified *Reference Standard* • The reference standard is likely to classify the patients appropriately *Flow and Timing* • All patients were included in the analysis	• Unclear if index test results were interpreted without knowledge of the results of the reference standard—some patients were tested in a previous study with the same researchers *Reference Standard* • Unclear how reference standard was performed in patients that had already been tested in a previous study with the same researchers • Unclear if reference standard results were interpreted without the knowledge of the results of the index test *Flow and Timing* • Unclear about the time interval between the index test and reference standard • Not all patients received the reference standard
Katballe, 2002[49]	
Patient Selection • Patients were selected consecutively • A case-control design was avoided • The study avoided inappropriate exclusions *Index Test* • A threshold was pre-specified *Reference Standard* • The reference standard results were likely to classify patients appropriately *Flow and Timing* • No strengths identified	*Patient Selection* • No limitations identified *Index Test* • Unclear if index test results were interpreted without knowledge of the results of the reference standard *Reference Standard* • Unclear if reference standard results were interpreted without knowledge of the index test *Flow and Timing* • Not all patients were included in the analysis • Not all the patients received the reference standard • Unclear about the time interval between the index test and the reference standard
Wahlberg, 2002[50]	
Patient Selection • Patients were consecutively selected • A case-control design was avoided • The study avoided inappropriate exclusions *Index Test* • A threshold was pre-specified *Reference Standard* • The reference standard was likely to classify patients appropriately • The reference standard results were interpreted without knowledge of the results of the index test *Flow and Timing* • All patients in the study received the reference standard	*Patient Selection* • No limitations identified *Index Test* • The index test results were interpreted with the knowledge of the results of the reference standard *Reference Standard* • No limitations identified *Flow and Timing* • The index test and reference standard were performed at different times
Ward, 2002[51]	
Patient Selection • Patients were consecutively selected • A case-control design was avoided • The study avoided inappropriate	*Patient Selection* • No limitations identified *Index Test* • No limitations identified

Strengths	Limitations
exclusions *Index Test* • The index test results were interpreted by two investigators independently, who were blinded by patient's mutational status • A threshold was pre-specified *Reference Standard* • The reference test results were interpreted without the knowledge of the results of the index test • The reference standard was likely to classify patients appropriately *Flow and Timing* • All patients were included in the analysis	*Reference Standard* • No limitations identified *Flow and Timing* • The index test and reference standard were performed at different times • All patients received the reference standard
Loukola, 2001[52]	
Patient Selection • The study avoided inappropriate exclusions • A case-control design avoided *Index Test* • A threshold was pre-specified *Reference Standard* • The reference standard was likely to classify the patients appropriately *Flow and Timing* • All patients received the reference standard • All patients were included in the analysis	*Patient Selection* • Patient selection was not consecutive; the researchers added 10 patients with a known germline mutation to enrich the proportion of germline mutation-positive patients *Index Test* • Unclear if index test results were interpreted without knowledge of the results of the reference standard *Reference Standard* • Unclear if reference standard results were interpreted without knowledge of the index test *Flow and Timing* • The index test and reference standard were performed at the different times—time interval was unclear
Calistri, 2000[53]	
Patient Selection • The study avoided inappropriate exclusions • A case-control design was not used *Index Test* • Threshold was pre-specified *Reference Standard* • The reference standard was likely to classify patients appropriately *Flow and Timing* • All patients were included in the analysis	*Patient Selection* • Unclear about if patient selection was consecutive, as some patients were from a previous study conducted by the same researchers *Index Test* • Unclear if index test results were interpreted without the knowledge of the results of the reference standard *Reference Standard* • Unclear if reference standard results were interpreted without knowledge of the index test *Flow and Timing* • Unclear if all patients received the reference standard
Dieumegard, 2000[54]	
Patient Selection • A case-control design was not used	*Patient Selection* • Unclear if patient sample was consecutive

Strengths	Limitations
• The study avoided inappropriate exclusions *Index Test* • The index test results were interpreted without the knowledge of the results of the reference standard • A threshold was pre-specified *Reference Standard* • The reference standard was likely to classify the patients appropriately *Flow and Timing* • All patients in the study received the reference standard • The index test and reference standard were performed within an appropriate timeframe • All patients were included in the analysis	*Index Test* • No limitations were identified *Reference Standard* • The reference standard results were interpreted with the knowledge of the results of the index test *Flow and Timing* • No limitations were identified

Appendix 31: Critical Appraisal of Included Studies (Question 3)

Strengths	Limitations
Toon, 2013[69]	
Patient Selection • Patient selection was consecutive • The study avoided inappropriate exclusions • A case-control design was avoided *Index Test* • The index test was interpreted without the knowledge of the results of the reference standard • A threshold was pre-specified *Reference Standard* • The reference standard was interpreted without the knowledge of the results of the index test • The reference standard was likely to classify patients appropriately *Flow and Timing* • No strengths identified	*Patient Selection* • No limitations identified *Index Test* • No limitations identified *Reference Standard* • No limitations identified *Flow and Timing* • The index test and reference standard were performed at different times • Not all patients received the reference standard • Not all patients were included in the analysis
Bouzourene, 2010[72]	
Patient Selection • The study avoided inappropriate exclusions • A case-control design was avoided *Index Test* • A threshold was pre-specified *Reference Standard* • The reference standard was likely to classify patients appropriately *Flow and Timing* • All patients received the reference standard • All patients were included in the analysis	*Patient Selection* • Some of the patients were selected from a previous study with the same researchers *Index Test* • Unclear if index test results were interpreted without knowledge of the results of the reference standard *Reference Standard* • Unclear if reference standard results were interpreted without knowledge of the index test *Flow and Timing* • The time interval between the index test and reference standard was unclear
Chang, 2010[77]	
Patient Selection • Patient selection was consecutive • The study avoided inappropriate exclusions • A case-control design was avoided *Index Test* • The index test results were interpreted without knowledge of the results of the reference standard • A threshold was pre-specified *Reference Standard* • The reference standard results were interpreted without knowledge of the results of the index test • The reference standard was likely to classify patients appropriately	*Patient Selection* • No limitations identified *Index Test* • No limitations identified *Reference Standard* • No limitations identified *Flow and Timing* • Not all patients received the reference standard • The time interval between the index test and reference standard was unclear

Strengths	Limitations
Flow and Timing • All patients were included in the analysis	
Perez-Carbonell, 2010[16]	
Patient Selection • The study avoided inappropriate exclusions • A case-control design was avoided • Patient selection was consecutive *Index Test* • A threshold was pre-specified *Reference Standard* • The reference standard was likely to classify patients appropriately *Flow and Timing* • No strengths identified	*Patient Selection* • No limitations identified *Index Test* • Unclear if the index test results were interpreted without the knowledge of the results of the reference standard *Reference Standard* • Unclear if the reference standard was interpreted without knowledge of the results of the index test *Flow and Timing* • Not all patients received the reference standard • Not all patients were included in the analysis • The time interval between the index test and reference standard was unclear
Alemayehu, 2008[76]	
Patient Selection • The study avoided inappropriate exclusions • A case-control design was avoided *Index Test* • A threshold was pre-specified *Reference Standard* • The reference standard results were interpreted without the knowledge of the index test • The reference standard was likely to classify patients appropriately *Flow and Timing* • All patients were included in the analysis • All patients received the reference standard	*Patient Selection* • Unclear if patient sample was consecutive *Index Test* • The index test results were interpreted with the knowledge of the reference standard *Reference Standard* • No limitations identified *Flow and Timing* • The index test and reference standard were completed at different times
Hampel, 2008[61]	
Patient Selection • The study avoided inappropriate exclusions • A case-control design was avoided *Index Test* • No strengths identified *Reference Standard* • The reference standard was likely to classify patients appropriately *Flow and Timing* • All patients were included in the analysis	*Patient Selection* • Most of the study patients were used by the same researchers in a previous study *Index Test* • Unclear if index test results were interpreted without knowledge of the results of the reference standard • Unclear if a threshold was pre-specified *Reference Standard* • The reference standard results were interpreted with the knowledge of the index test *Flow and Timing* • Not all patients received the reference standard • The time interval between the index test and reference standard was unclear
Julie, 2008[74]	
Patient Selection	*Patient Selection*

Strengths	Limitations
• Patient selection was consecutive • The study avoided inappropriate exclusions • A case-control design was avoided *Index Test* • A threshold was pre-specified *Reference Standard* • The reference standard was likely to classify patients appropriately *Flow and Timing* • No strengths identified	• No limitations identified *Index Test* • Unclear if index test results were interpreted without knowledge of the results of the reference standard *Reference Standard* • Unclear if reference standard results were interpreted without knowledge of the index test *Flow and Timing* • Not all patients received the reference standard • Not all patients were included in the analysis • The time interval between the index test and reference standard was unclear
Poynter, 2008[71]	
Patient Selection • Patient selection was consecutive • The study avoided inappropriate exclusions • A case-control design was avoided *Index Test* • A threshold was pre-specified *Reference Standard* • The reference standard was likely to classify patients *Flow and Timing* • No strengths identified	*Patient Selection* • No limitations identified *Index Test* • Unclear if the index test was interpreted without the knowledge of the results of the reference standard *Reference Standard* • Unclear if the reference standard was interpreted without knowledge of the results of the index test • Unclear how reference standard was performed *Flow and Timing* • Not all patients were included in the analysis • The index test and reference standard were performed at different times • Not all patients received the reference standard
Rahner, 2008[73]	
Patient Selection • Patient selection was consecutive • The study avoided inappropriate exclusions • A case-control design was avoided *Index Test* • A threshold was pre-specified *Reference Standard* • The reference standard was likely to classify patients appropriately *Flow and Timing* • No strengths identified	*Patient Selection* • No limitations identified *Index Test* • Unclear if the index test was interpreted without the knowledge of the results of the reference standard *Reference Standard* • Unclear if the reference standard was interpreted without knowledge of the results of the index test *Flow and Timing* • The time interval between the index test and reference standard was unclear • Not all patients received the reference standard • Not all patients were included in the analysis
Loughrey, 2007[68]	
Patient Selection • Patients selection was consecutive • The study avoided inappropriate exclusions • A case-control design was avoided	*Patient Selection* • No limitations identified *Index Test* • Unclear if the index test was interpreted without

Strengths	Limitations
Index Test • A threshold was pre-specified *Reference Standard* • The reference standard was likely to classify patients appropriately *Flow and Timing* • No strengths identified	the knowledge of the results of the reference standard *Reference Standard* • Unclear if the reference standard was interpreted without knowledge of the results of the index test *Flow and Timing* • Not all patients received the reference standard • The time interval between the index test and reference standard was unclear • Not all patients were included in the analysis
Overbeek, 2007[75]	
Patient Selection • Patient selection was consecutive • The study avoided inappropriate exclusions • A case-control design was avoided *Index Test* • A threshold was pre-specified *Reference Standard* • The reference standard was likely to classify patients appropriately *Flow and Timing* • No strengths identified	*Patient Selection* • No limitations identified *Index Test* • Unclear if the index test was interpreted without the knowledge of the results of the reference standard *Reference Standard* • Unclear if the reference standard was interpreted without knowledge of the results of the index test *Flow and Timing* • Not all patients received the reference standard • Not all patients were included in the analysis • The time interval between the index test and reference standard was unclear
Wang, 2003[70]	
Patient Selection • The study avoided inappropriate exclusions • A case-control design was avoided *Index Test* • A threshold was pre-specified *Reference Standard* • The reference standard was likely to classify patients appropriately *Flow and Timing* • All patients were included in the analysis	*Patient Selection* • Unclear if patient selection was consecutive—patients were selected from a number of ongoing studies *Index Test* • Unclear if the index test results were interpreted without the knowledge of the results of the reference standard *Reference Standard* • Unclear if the reference standard was interpreted without knowledge of the results of the index test *Flow and Timing* • Not all patients were given the reference standard • The reference standard and the index test were performed at different times

Appendix 32: Critical Appraisal of Included Studies (Question 4)

Study Author, Year	Strengths	Limitations
Brosens 2011[95]	– Study groups were comparable – Low risk of detection bias due to differences between groups in how outcomes were determined – Low risk of reporting bias due to selective reporting of the main outcome	– Non-random allocation (case-control design) – Unclear whether there was performance bias due to systematic differences between groups in care provided or exposure to other factors – No control for confounding at the design stage – No adjustment for confounders
Hutchins 2011[91]	– Low risk of detection bias due to differences between groups in how outcomes were determined – Low risk of reporting bias due to selective reporting of outcomes	– Non-random allocation based on participants in a randomized trial – Unclear risk of performance bias due to lack of blinding of study investigators – Confounders not clearly described; patient characteristics were reported by mutation status not treatment status
Sinicrope 2011[3]	– Low risk of detection bias due to differences between groups in how outcomes were determined – Low risk of reporting bias due to selective reporting of outcomes – Confounders described and adjusted for using multivariable regression	– Non-random allocation based on participants in a randomized trial – Study groups not comparable (risk of bias due to differences in the baseline characteristics of the comparison groups) – No control for confounding at the design stage
Dietmaier 2006[92]	– Low risk of detection bias due to differences between groups in how outcomes were determined – Low risk of reporting bias due to selective reporting of outcomes – Confounders described and adjusted for using multivariable regression	– Non-random allocation (historical cohort) – Study groups not comparable at baseline (different age at diagnosis) – High risk of performance bias due to differences in how care was provided (therapy was determined by the physician, and the majority who were treated were younger than age 70) – No control for confounding at the design stage
Lanza 2006[93]	– Low risk of detection bias due to differences between groups in how outcomes were determined – Low risk of reporting bias due to selective reporting of the main outcome – Low risk of performance bias due to differences between the comparison groups in care provided or exposure to other factors	– Non-random allocation (cohort study) – Study groups not comparable (risk of selection bias due to differences in the baseline characteristics of the comparison groups) – No control for confounding at the design stage

Study Author, Year	Strengths	Limitations
	– Confounders described	
Elsaleh 2001[94]	– Low risk of detection bias due to differences between groups in how outcomes were determined – Low risk of reporting bias due to selective reporting of main outcomes	– Non-random allocation – Risk of bias due to differences in study groups – Risk of performance bias due to differences in care provided or exposure to other factors (standard care at the study centre was changing during the study period)
Curran 2000[90]	– Study groups were comparable – Pathologists and technical investigators were blinded to outcomes and clinical details – Low risk of performance bias due to differences between the comparison groups in care provided or exposure to other factors – Low risk of detection bias due to differences between groups in how outcomes were determined – Low risk of reporting bias due to selective reporting of the main outcome – Confounders were described and accounted for using multivariable regression	– Non-random allocation based on exposure (cohort design)

Appendix 33: Critical Appraisal of Included Studies (Question 5)

Study Author, Year	Strengths	Limitations
Klingbiel 2015[96]	– Low risk of detection bias due to differences between groups in how outcomes were determined – Low risk of reporting bias due to selective reporting of outcomes	– Non-random allocation based on participants in a randomized trial – Study groups not comparable at baseline – Unclear risk of performance bias due to differences between the groups in terms of care provided or other factors – No control or adjustment for potential confounders
Kim 2013[99]	– Low risk of detection bias due to differences between groups in how outcomes were determined – Low risk of reporting bias due to selective reporting of outcomes – Description of potential confounders provided; confounders adjusted for by multivariable regression	– Non-random allocation based on exposure (historical cohort) – Potential for selection bias due to strict inclusion criteria – Unclear risk of performance bias due to differences between the groups in terms of care provided or other factors
Li 2013[98]	– Study groups were comparable – Low risk of selection bias due to differences in baseline characteristics – Low risk of performance bias (pathologists were blinded) – Low risk of detection bias due to differences between groups in how outcomes were determined – Low risk of reporting bias due to selective reporting of outcomes	– Non-random allocation based on exposure (historical cohort) – No control or adjustment for potential confounders
Oh 2013[97]	– Study groups were comparable – Low risk of detection bias due to differences between groups in how outcomes were determined – Low risk of reporting bias due to selective reporting of outcomes	– Non-random allocation – Unclear risk of performance bias due to differences between the groups in terms of care provided or other factors – No control or adjustment for potential confounders
Bertagnolli 2011[100]	– Study groups were comparable – Low risk of selection bias due to differences in baseline characteristics of the comparison groups	– Non-random allocation based on exposure – Unclear risk of performance bias due to differences between the groups in terms of care provided or other factors

Study Author, Year	Strengths	Limitations
	– Low risk of detection bias due to differences between groups in how outcomes were determined – Low risk of reporting bias due to selective reporting of outcomes – Description of confounders provided and adjusted for	
Sinicrope 2011[3]	– Low risk of detection bias due to differences between groups in how outcomes were determined – Low risk of reporting bias due to selective reporting of outcomes – Confounders described and adjusted for using multivariable regression	– Non-random allocation based on a participants in a randomized trial – Study groups not comparable (risk of bias due to differences in the baseline characteristics of the comparison groups) – No control for confounding at the design stage
Yoon 2011[102]	– Low risk of detection bias due to differences between groups in how outcomes were determined – Low risk of reporting bias due to selective reporting of outcomes – Confounders described and adjusted for using multivariable regression	– Study groups not comparable – Risk of selection bias due to differences in baseline characteristics of comparison groups – Unclear risk of performance bias due to differences between the groups in care provided
Zaanan 2011[101]	– Low risk of performance bias (pathologists were blinded) – Low risk of detection bias due to differences between groups in how outcomes were determined – Low risk of reporting bias due to selective reporting of outcomes – Confounders described	– Non-random allocation (historical cohort) – Study groups not comparable – Risk of selection bias due to differences in baseline characteristics of comparison groups – No control or adjustment for confounders
Zaanan 2010[103]	– Low risk of detection bias due to differences between groups in how outcomes were determined – Low risk of reporting bias due to selective reporting of outcomes – Confounders described	– Non-random allocation – Study groups not comparable – Risk of selection bias due to differences in baseline characteristics of comparison groups – Unclear risk of performance bias due to differences between the groups in care provided – Confounders not controlled or adjusted for
Dietmaier 2006[92]	– Low risk of detection bias due to differences between groups in how outcomes	– Non-random allocation (historical cohort) – Study groups not comparable at baseline (different age at diagnosis)

Study Author, Year	Strengths	Limitations
	were determined – Low risk of reporting bias due to selective reporting of outcomes – Confounders described and adjusted for using multivariable regression	– High risk of performance bias due to differences in how care was provided (therapy was determined by the physician, and the majority who were treated were younger than 70 years) – No control for confounding at design stage
Westra 2005[104]	– Study groups were comparable – Low risk of selection bias due to differences in baseline characteristics of the comparison groups – Low risk of detection bias due to differences between groups in how outcomes were determined – Low risk of reporting bias due to selective reporting of outcomes	– Non-random allocation – Unclear risk of performance bias due to differences between the groups in terms of care provided or other factors – No control or adjustment for potential confounders
Watanabe 2001[105]	– Study groups were comparable – Low risk of selection bias due to differences in baseline characteristics of the comparison groups – Low risk of detection bias due to differences between groups in how outcomes were determined – Low risk of reporting bias due to selective reporting of outcomes	– Non-random allocation based on participants in two randomized trials – Unclear risk of performance bias due to differences between the groups in terms of care provided or other factors – No control or adjustment for potential confounders

Appendix 34: Outcomes Reported by the Included Studies (Question 4)

Author, Year	Outcomes	Definition	Follow-up (Months)	Subgroups for Analysis
				Disease Stage
Brosens, 2011[95]	DFS	NR	60	Stage II
	Relapse	Occurrence of distant metastasis, confirmed by ultrasound, CT scan, and/or histology	36	
Hutchins, 2011[91]	Relapse	Time from random assignment to recurrence with censoring at last contact with patient or death without recurrence	NR (~10 years from graphs)	Stage II
Sinicrope, 2011[3]	Relapse	Proportion of patients without recurrence	60	Stage III
Dietmaier, 2006[92]	OS	Time to death from any cause	44.5 (med)	Stage III
Lanza, 2006[93]	OS	Time to CRC-related death (unrelated deaths were censored)	90.5 (med)	Stage III
Elsaleh, 2001[94]	OS	NR	76 (med)	Stage III
Curran, 2000[90]	OS	Time to cancer-related death	94.8 (med)	Stage II

CRC = colorectal cancer; CT = computerized tomography; DFS = disease-free survival; med = median; NR = not reported; OS = overall survival.

Appendix 35: Outcomes Reported by the Included Studies (Question 5)

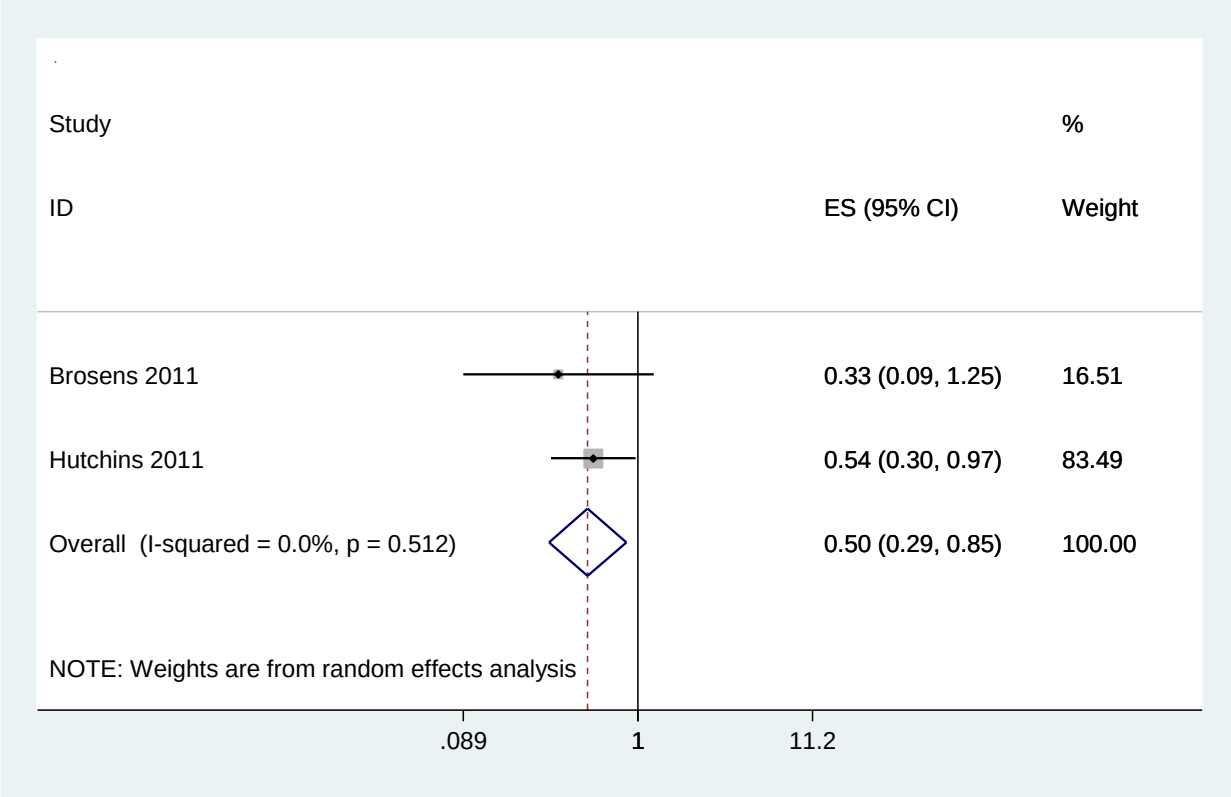
Author, Year	Outcomes	Definition	Follow-up (Months)	Subgroups for Analysis	
				Disease Stage	Adjuvant Chemotherapy
Klingbiel, 2015[96]	DFS	Time from randomization to recurrence (metastasis/second primary colon cancer) or death	84	Stage II Stage III	– 5-FU – IRI-based – Mixed
	OS	Time from randomization to death from any cause	84		
Kim, 2013[99]	DFS	Time from surgery to recurrence or death from any cause	36	Stage III	– 5-FU + OXI
Oh, 2013[97]	DFS	NR	43 med)	Stage III	– OXI-based
	OS	NR	43 (med)		
	Recurrence	NR	43 (med)		
Li, 2013[98]	DFS	Time from surgery to disease recurrence (first event, local or distant)	60	Stage III	– 5-FU – Mixed
	OS	Time from surgery to tumour-induced death	60		
Bertagnolli,2011[100]	DFS	Time from study entry to documented progression or death from any cause	60	Stage III	– 5-FU – IRI-based – Mixed
	OS	Time from study entry to death from any cause	60		
Sinicrope, 2011[3]	Recurrence	Local, intra-abdominal or distal recurrence	60	Stage III	– 5-FU
Zaanan, 2011[101]	DFS	Time from surgery to relapse or death from any cause	36	Stage III	– OXI-based
	OS	Time from surgery to death from any cause	60		
Yoon, 2011[102]	DFS	NR	48	Stage II	– 5-FU

Author, Year	Outcomes	Definition	Follow-up (Months)	Subgroups for Analysis	
				Disease Stage	Adjuvant Chemotherapy
	OS	NR	48	Stage III	
Zaanan, 2010[103]	DFS	Time from surgery to relapse or last contact	36	Stage III	– 5-FU – OXI-based
	Recurrence	Relapse or last contact	36		
Dietmaier, 2006[92]	OS	Death from any cause	44.5 (med)	Stage III	– 5-FU
Westra, 2005[104]	DFS	Time from randomization to documented recurrence or death from colon cancer	60	Stage III	– 5-FU
	Recurrence	Relapse or death from colon cancer or censored	60		
Watanabe, 2001[105]	DFS	NR	60	Stage III	– 5-FU
	OS	NR	60		

5-FU = fluorouracil ± leucovorin (±levamisole); DFS = disease-free survival; IRI-based = 5-FU + leucovorin irinotecan; med = median; NR = not reported; OS = overall survival; OXI-based = 5-FU ± leucovorin + oxaliplatin.

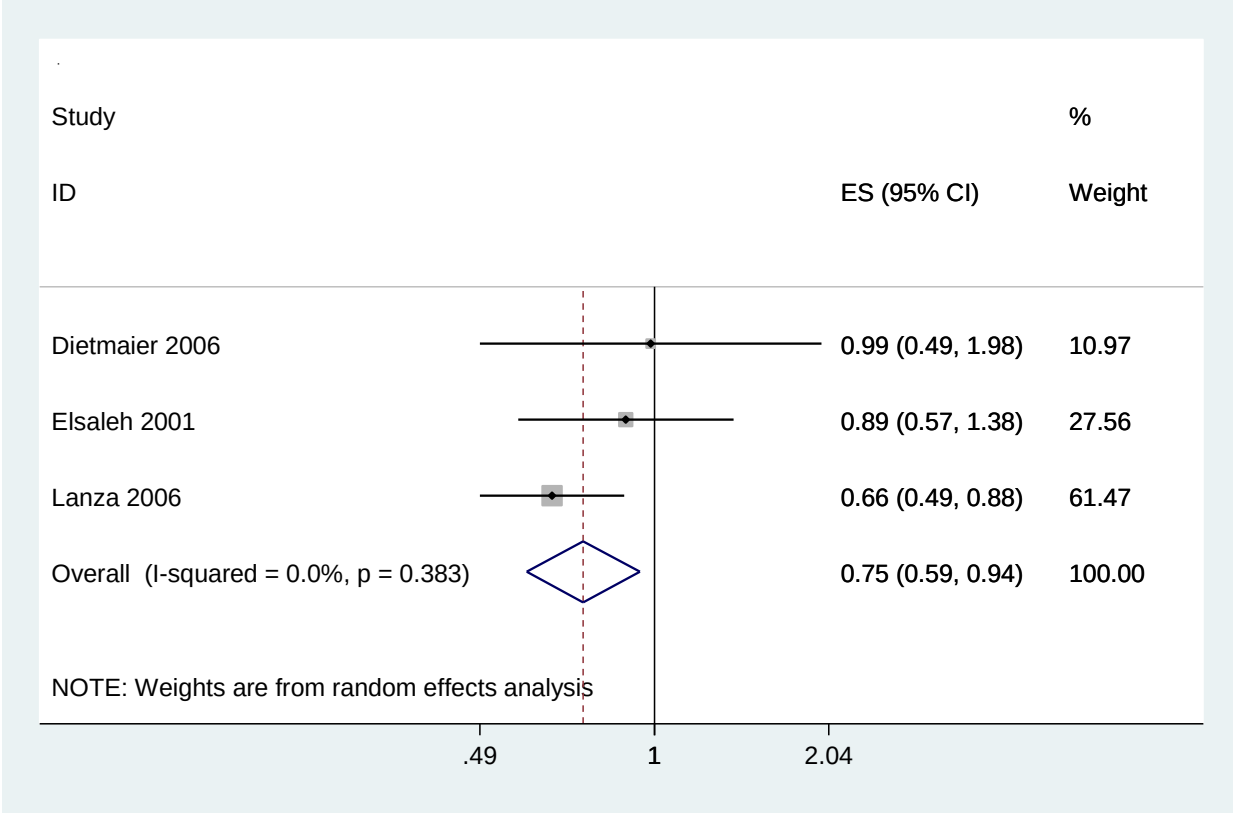
Appendix 36: Forest Plots of Outcome Comparisons Reported by the Included Studies (Question 4)

Figure 17: Meta-analysis Relapse Rates in Stage II Colorectal Cancer Patients With dMMR Tumours Versus Those With pMMR Tumours Who Did Not Receive Adjuvant Chemotherapy



CI = confidence interval; dMMR = deficient mismatch repair; ES = effect size; pMMR = proficient mismatch repair.

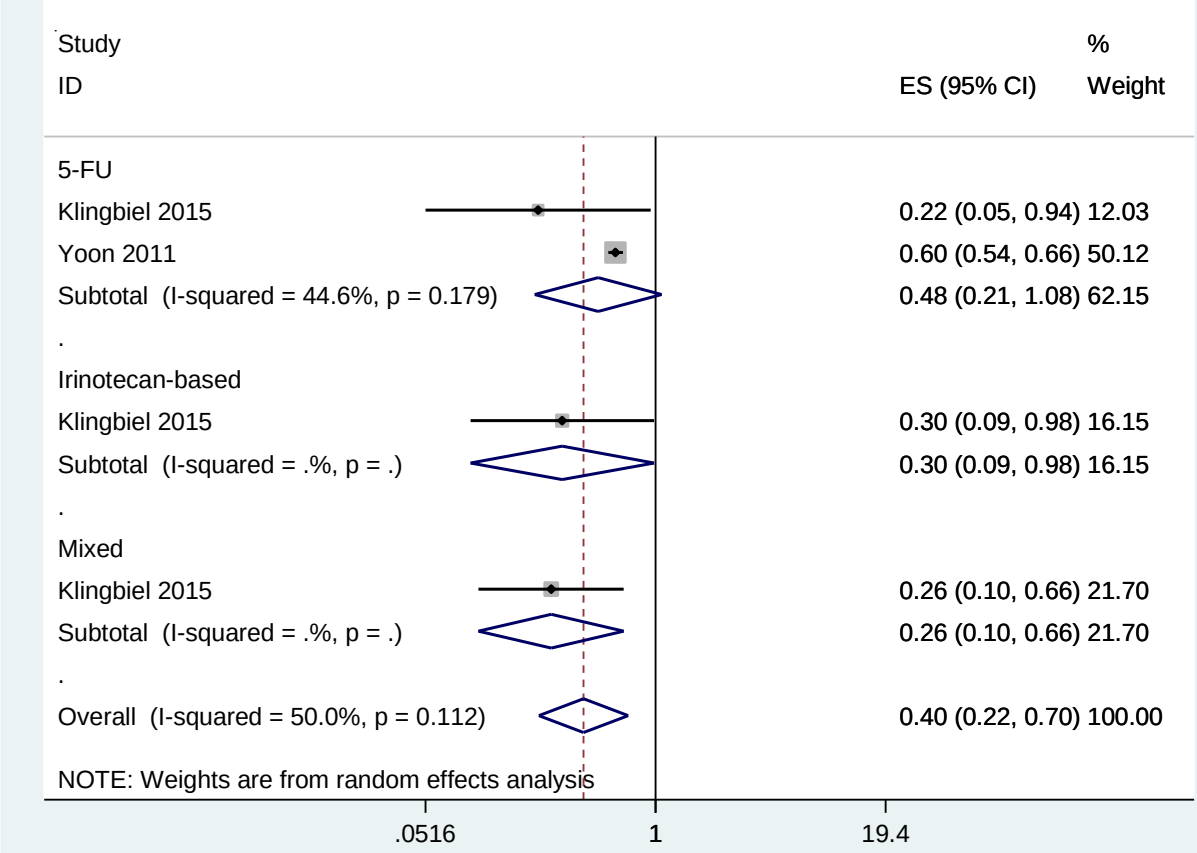
Figure 18: Meta-analysis Relapse Rates in Stage III Colorectal Cancer Patients With dMMR Tumours vs. Those With pMMR Tumours Who Did Not Receive Adjuvant Chemotherapy



CI = confidence interval; dMMR = deficient mismatch repair; ES = effect size; pMMR = proficient mismatch repair; vs. = versus.

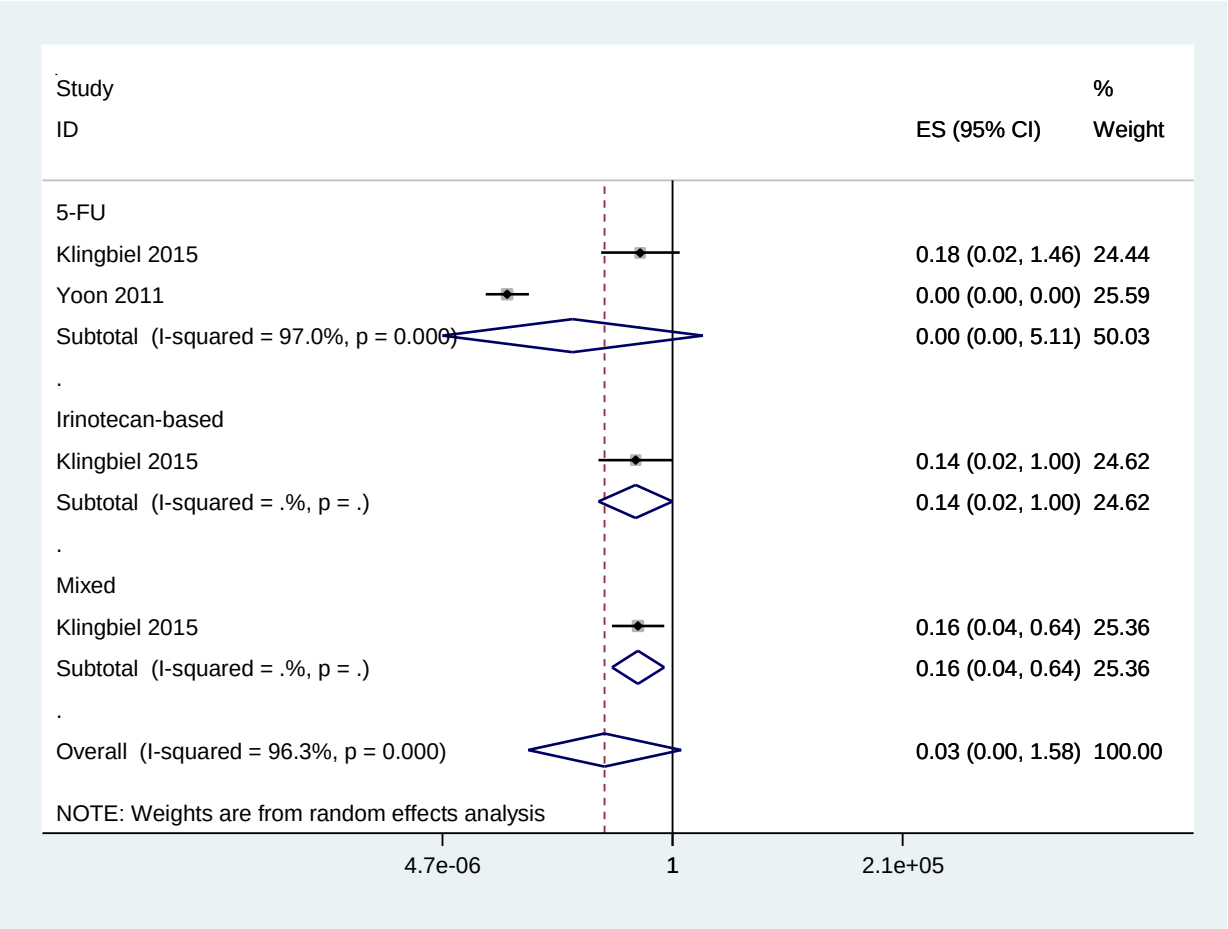
Appendix 37: Forest Plots of Outcome Comparisons Reported by the Included Studies (Question 5)

Figure 19: Meta-analysis of Disease-Free Survival Rates in Stage II Colon Cancer Patients With dMMR Tumours vs. Those With pMMR Tumours Who Received Adjuvant Chemotherapy



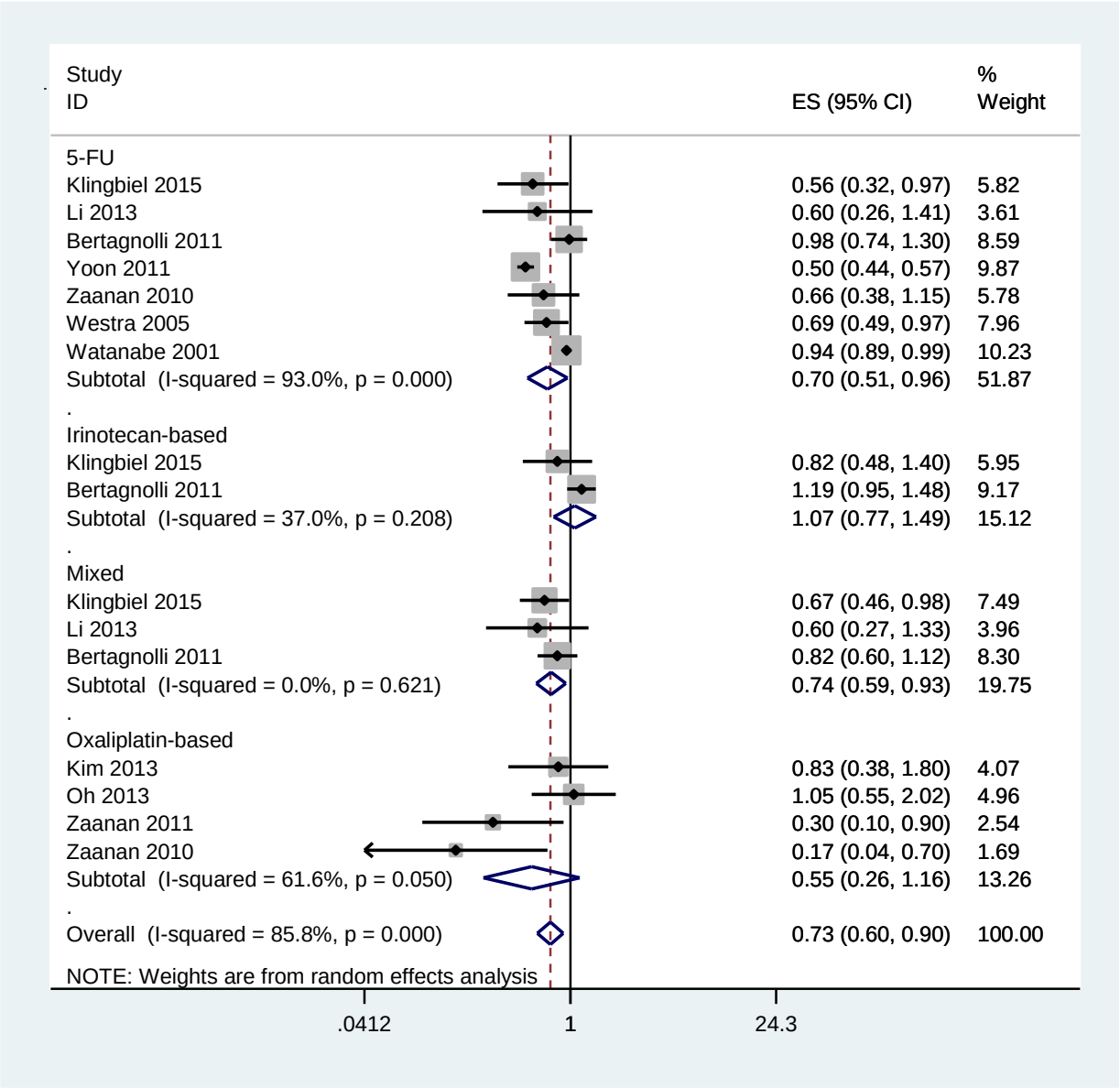
CI = confidence interval; dMMR = deficient mismatch repair; ES = effect size; pMMR = proficient mismatch repair; vs. = versus.

Figure 20: Meta-analysis of Overall Survival Rates in Stage II Colon Cancer Patients With dMMR Tumours vs. Those With pMMR Tumours Who Received Adjuvant Chemotherapy



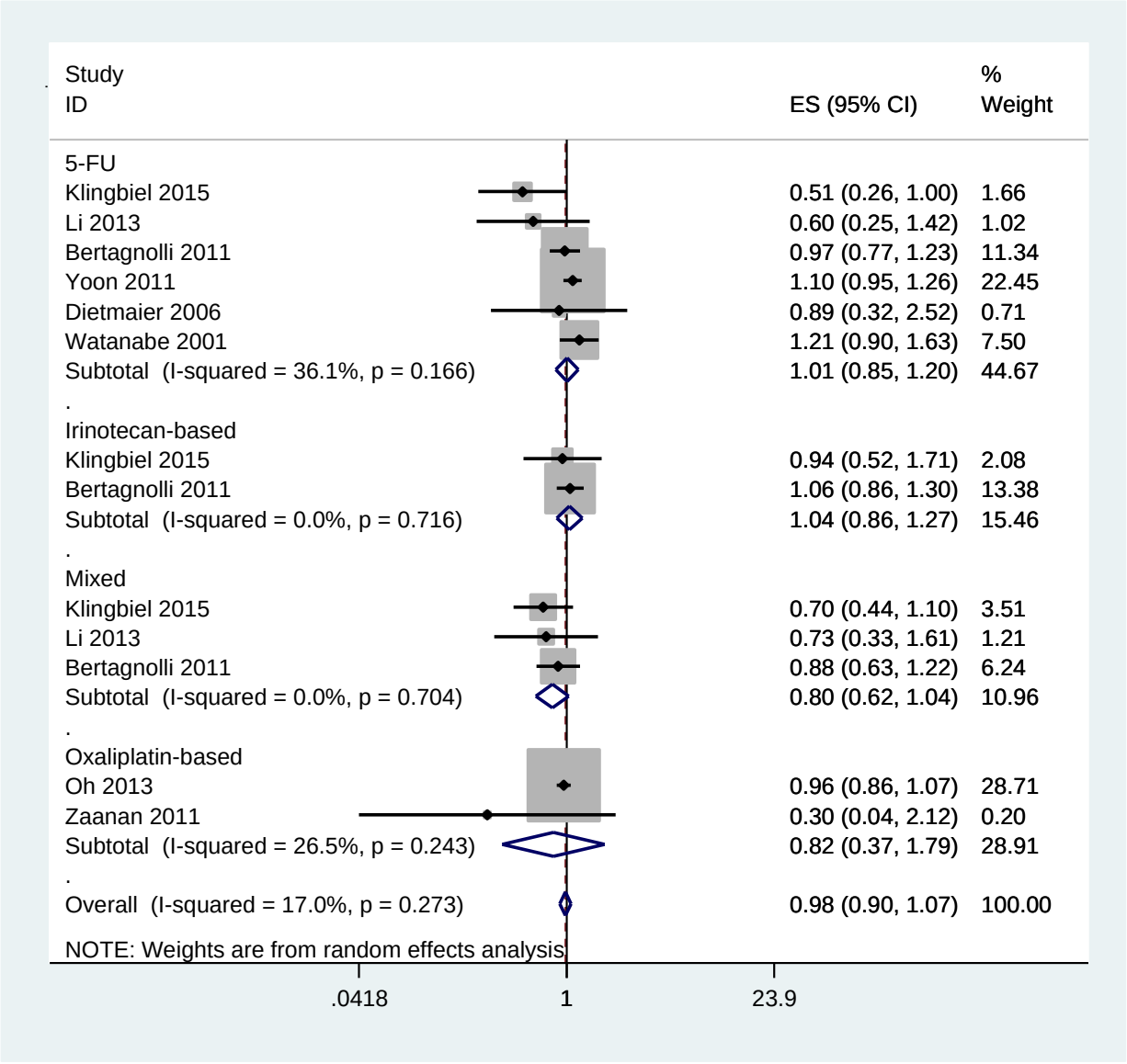
CI = confidence interval; dMMR = deficient mismatch repair; ES = effect size; pMMR = proficient mismatch repair; vs. = versus.

Figure 21: Meta-analysis of Disease-Free Survival Rates in Stage III Colon Cancer Patients With dMMR Tumours vs. Those With pMMR Tumours Who Received Adjuvant Chemotherapy



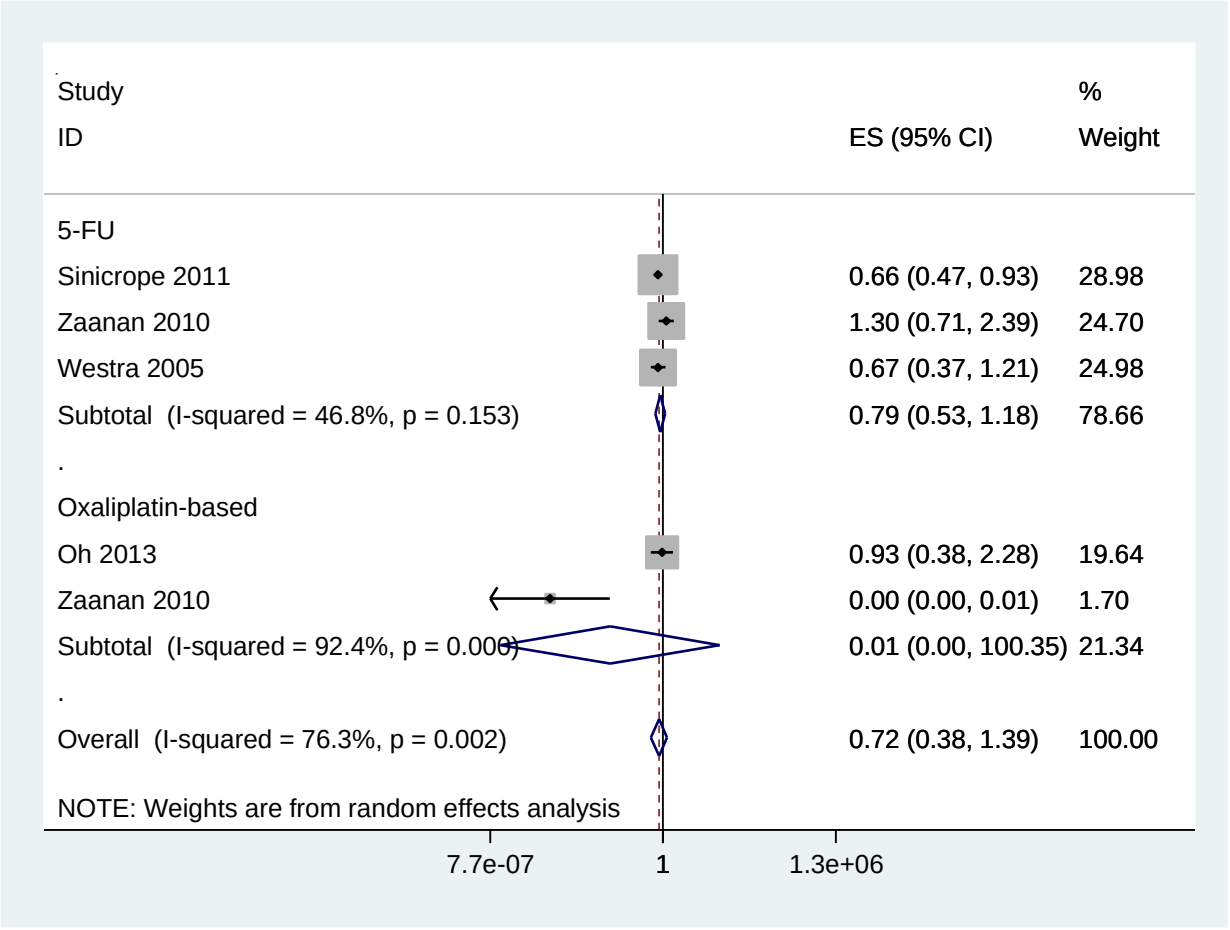
CI = confidence interval; dMMR = deficient mismatch repair; ES = effect size; pMMR = proficient mismatch repair; vs. = versus.

Figure 22: Meta-analysis of Overall Survival Rates in Stage III Colon Cancer Patients With dMMR Tumours vs. Those With pMMR Tumours Who Received Adjuvant Chemotherapy



CI = confidence interval; dMMR = deficient mismatch repair; ES = effect size; pMMR = proficient mismatch repair; vs. = versus.

Figure 23: Meta-analysis of Relapse Rates in Stage III Colon Cancer Patients With dMMR Tumours vs. Those With pMMR Tumours Who Received Adjuvant Chemotherapy



CI = confidence interval; dMMR = deficient mismatch repair; ES = effect size; pMMR = proficient mismatch repair; vs. = versus.

Appendix 38: Detailed Summary of Relevant Economic Evaluations

Bessa et al. (2008)
Bessa et al.[109] investigated the use of tumour BRAF V600E testing to help identify colorectal cancer (CRC) patients with germline mutations in the *MSH2*/*MLH1* genes. The authors conducted a cost-minimization analysis to estimate the difference in costs between two testing strategies; namely, one that included tumour BRAF mutational testing and one that did not.

In this analysis, consecutive patients from 25 Spanish hospitals with newly diagnosed CRC underwent both tumour microsatellite instability (MSI) and mismatch repair (MMR) protein immunohistochemistry (IHC) testing. Patients found to have tumours with MSI and/or a lack of expression of either MLH1 or MSH2 proteins through IHC analysis went on to receive both germline mutation testing and tumour BRAF mutation analysis. Among the 119 patients with tumour MMR deficiencies, eight were found to have a germline mutation and 22 patients had a somatic BRAF mutation. None of the patients with a somatic BRAF mutation had a germline mutation.

Using the clinical findings, the authors estimated the potential savings that would incur if tumour BRAF testing was included as part of the reflex testing strategies. It was assumed that patients with absent tumour MLH1 protein expression and a somatic BRAF mutation would avoid germline testing. Based on hospital billings, the costs of tumour MSI, MMR protein IHC testing, tumour BRAF V600E mutation and germline mutation tests (per gene) were assumed to be €100, €200, €100, and €1,200, respectively. Under a screening scenario in which the tumours of all newly diagnosed CRC patients would be tested for deficient mismatch repair (dMMR), the authors estimated that the inclusion of tumour BRAF testing as part of reflex testing would save €1,688 per mutation detected. Under a screening scenario in which newly diagnosed CRC patients meeting the revised Bethesda Guidelines (rBG) criteria would undergo dMMR testing, it was estimated that the inclusion of BRAF testing as part of reflex testing would save €375 per mutation detected.

Yan et al. (2008)
Yan et al.[114] investigated the molecular and clinical characteristics of CRC patients in China who were at risk for LS. As part of this study, the cost per mutation detected for reflex testing strategies including and not including MLH1 promoter methylation testing to avoid germline testing was estimated.

All study patients underwent tumour MSI testing and MMR IHC analysis. MLH1 promoter hypermethylation testing was conducted on tumours that lacked MLH1 protein expression. Germline mutation testing was completed for all patients showing tumour MSI or lack of expression of the MSH2, MLH1, or MSH6 proteins.

Of the 227 tumours analyzed, 64 showed a lack of expression in MLH1 protein and 28 germline mutations were found. Forty-three of the 64 tumours tested for MLH1 promoter hypermethylation were negative. None of the tumours showing MLH1 promoter hypermethylation had a germline mutation. The costs of tumour MSI, MMR IHC analysis, MLH1 promoter hypermethylation, and germline tests (per gene) were US$120, US$40, and US$40, respectively. Using the clinical results, the authors estimated the cost per mutation detected to be US$6,480 in the absence of hypermethylation testing. This compares to their estimate of

US$2,960 per mutation detected if the testing strategy included MLH1 promoter hypermethylation testing to avoid unnecessary germline testing.

Gudgeon et al. (2011)

Gudgeon et al.[112] compared the cost per Lynch syndrome (LS) case detected for a number of tumour MMR IHC reflex testing strategies for patients with newly diagnosed CRC. These included 1) no tumour BRAF or MLH1 promoter hypermethylation testing (i.e., direct sequencing); 2) tumour BRAF testing for patients with lack of MLH1 protein expression; 3) tumour MLH1 promoter hypermethylation testing for patients with lack of MLH1 protein expression; 4) tumour MLH1 promoter hypermethylation testing then tumour BRAF testing for MLH1 promoter hypermethylation–negative patients; 5) tumour BRAF testing, then tumour MLH1 promoter hypermethylation testing for BRAF-wild type patients. Tumour polymerase chain reaction (PCR)–based assay was assumed for BRAF tests. The first three strategies are of interest to this report.

Elements incorporated into this model include the cost of testing (tumour IHC [$230], tumour PCR-BRAF [$305], tumour MLH1 promoter methylation [$295], and germline MMR gene mutation [$1,355]), the diagnostic accuracy of the various tests, and the estimated prevalence of LS in all CRC patients (0.036). All costs were reported in 2010 US dollars.

The expected costs and outcomes of the three reflex testing strategies of interest, mentioned above, are shown in Table E3. Additionally, the incremental cost-effectiveness of these three strategies was calculated. As shown, conducting germline MMR gene analysis on all patients resulted in the highest cost and highest number of LS cases detected. The incremental cost per LS case detected was found to be US$19,007 for the strategy in which tumour MMR IHC was followed by tumour BRAF testing versus the strategy that had tumour MMR IHC followed by tumour MLH1 promoter hypermethylation. Similarly, the incremental cost per LS case detected of the tumour MMR IHC and direct germline MMR gene testing strategy, in comparison with the tumour IHC and BRAF strategy, was $3.8 million.

Table E3: Cost-Effectiveness for the Reflex Testing Strategies of Interest to This Report, Based on Gudgeon et al. Economic Analysis

Reflex Testing Strategy	Costs per 100 Patients	LS Detected per 100 Patients	Cost per LS Detected	Incremental Cost per LS Case Detected[a]
IHC, straight to sequencing	$44,244	3.3420	$11,266	$3,856,875
IHC + BRAF	$38,073	3.3404	$11,469	$19,007
IHC + MLH1 promoter hypermethylation	$37,020	3.2850	$13,355	Reference

IHC = immunohistochemistry; LS = Lynch syndrome.
[a] Calculated.

Palomaki et al. (2009)

As part of the supplemental Evaluation of Genomic Applications in Practice and Prevention (EGAPP) evidence review, Palomaki et al.[56] estimated the cost per LS case detected for four reflex testing strategies. Of interest to this review were two strategies: 1) tumour MMR IHC testing followed by germline MMR gene testing for the specific genes indicated by the IHC test; 2) tumour MMR IHC testing followed by tumour BRAF testing to indicate likely sporadic CRC,

which would avoid unnecessary germline MMR gene testing in patients who show lack of expression for the MLH1 protein.

Elements in this model included the cost of testing (i.e., IHC [$261], PCR-BRAF ($100), and germline mutation [$102 to $983, depending on gene]), the diagnostic accuracy of the various tests, and the estimated prevalence of LS in all CRC patients (0.03). In addition to the upfront testing of the CRC patient, the authors considered the costs of testing ($55) and genetic counselling of family members of the identified probands ($175). They assumed four relatives would be approached for each LS case detected, with 52% of these relatives accepting genetic counselling and 95% of counselled patients accepting genetic testing. The authors also included the number of LS cases detected in both probands and relatives. Results are presented assuming a cohort of 150,000 newly diagnosed CRC patients, with 100,000 of these patients accepting tumour dMMR testing. All costs were reported in 2007 US dollars.

The authors reported that, for a reflex testing strategy in which all tumour dMMR patients would go on to genetic testing, it would cost $46 million and result in 3,353 cases of LS detected in the 150,000-person cohort. The strategy that included tumour BRAF testing to indicate likely sporadic CRC was estimated to cost $41 million and result in 3,340 cases of LS detected for the 150,000 newly diagnosed CRC cohort. The incremental cost per LS case detected for the germline MMR gene testing strategy compared with tumour BRAF testing was $398,000. This implies that the strategy that included tumour BRAF testing following an IHC panel would be considered cost-effective if the willingness to pay for a case of LS detected is less than $398,000. Otherwise, the reflex testing strategy in which all patients with an abnormal IHC received germline MMR gene testing would be considered cost-effective.

Gausachs et al. (2012)

The cost-effectiveness of different testing strategies for patients with lack of tumour expression of the MLH1 protein was evaluated by Gausachs et al.[110] Specifically, they evaluated strategies in which 1) all patients went through direct germline MMR gene testing; 2) all patients were given tumour BRAF testing and those with negative results proceeded to germline MMR gene testing; and 3) all patients were given MLH1 promoter hypermethylation testing and those with normal results proceeded to germline MMR gene testing.

Diagnostic accuracy of tumour BRAF and MLH1 promoter hypermethylation tests to indicate likely sporadic CRC were based on the analysis of 122 CRC tumours of individuals who attended a German genetic counselling unit. Among tumours with loss of the MLH1 protein expression, one of 24 of the LS-positive cases (defined as having a germline MMR gene mutation) and 13 of 47 LS-negative cases (defined as no detectable germline MMR gene mutation) had a BRAF mutation. Similarly, one of 24 of the LS-positive cases and 31 of 47 of the LS-negative cases showed hypermethylation.

The authors' cost-effectiveness estimates included costs and number of LS cases detected for both the proband and the probands' relatives. The model included the costs of tumour BRAF testing (€110), tumour MLH1 promoter methylation testing (€110), and germline MMR gene testing (€1,100 for proband, €150 for relative). It was assumed that the mean number of first- and second-degree relatives per proband was 5 and that there was a 50% chance that a relative would be a mutation carrier.

The results of the cost-effectiveness analyses, as reported by the authors, are presented in Table E4. As shown, immediately sending all patients for germline testing was the most

expensive option, but it also resulted in the highest number of LS cases detected. The testing strategy that included MLH1 promoter hypermethylation testing resulted in the lowest expected costs. The number of LS cases detected were estimated to be equal for both the tumour BRAF and the MLH1 promoter hypermethylation testing strategies. This reflected the clinical findings in which, of the 24 LS-positive patients, one each of positive tumour BRAF and positive tumour MLH1 promoter hypermethylation result were found. The incremental cost per LS case detected for the all germline testing strategy compared with the tumour MLH1 promoter hypermethylation strategy was found to be €7,991. The tumour BRAF test strategy was found to result in the same number of LS cases detected as the MLH1 promoter hypermethylation strategy, but with higher costs. Therefore, it was considered to be dominated by the MLH1 promoter hypermethylation strategy. This indicated that a strategy of sending patients immediately to germline testing would be cost-effective if willingness to pay for a LS case detected was greater than €7,991.

Table E4: Cost-Effectiveness for the Reflex Testing Strategies of Interest to This Report, Based on Gausachs et al. Economic Analysis

MLH1 Testing Strategy	Costs per 1,000 Probands	LS Detected per 1,000 Probands	Cost per LS Detected	Incremental Cost per LS Case Detected
Tumour MLH1 promoter hypermethylation before germline	€959,577	1,134	€845	Reference
Germline testing	€1,353,521	1,183	€1,183	€7,991
Tumour BRAF test before germline	€1,235,615	1,134	€1,090	Dominated

LS = Lynch syndrome.

Gould-Suarez et al. (2014)

Gould-Suarez et al.[111] used a decision-analytic model to compare the cost-effectiveness of 10 different LS screening and reflex testing strategies. The 10 strategies differed by initial screening strategy (rBG, universal screening) and by reflex testing strategy (tumour MMR IHC with BRAF, tumour MSI, combination of tumour IHC and MSI, and all to germline testing). Two of these strategies were very similar to the screening and reflex testing strategies that are of interest to this report. Strategy #2 of this publication comprised four-panel tumour MMR IHC testing for patients meeting the rBG and tumour BRAF testing for those with non-expression of the MLH1 protein. This strategy also included tumour MSI testing if all four proteins were expressed by tumour MMR IHC with germline gene testing in cases of microsatellite instability (MSI > 30%). Strategy #8 of this paper was the same as strategy #2 in terms of the reflex testing strategy, except that the screening strategy was based on universal tumour testing. Therefore, a comparison of strategies #8 and #2 would provide an estimate of the cost-effectiveness between universal screening and screening based on the rBG, using an identical reflex testing based on tumour MMR IHC followed by tumour PCR-based BRAF testing if abnormal MLH1 protein expression, and germline MMR gene testing if normal tumour BRAF or abnormal IHC expression for the other MMR proteins.

Parameters in this model included the cost of the diagnostic test (i.e., IHC [$500], MSI [$415], BRAF [$314], and germline testing [$900 to $980, depending on the gene]), the diagnostic accuracy of detecting LS under the various tests and screening strategies (e.g., rBG), and the estimated prevalence of LS in all CRC patients (0.03). All costs are expressed in US dollars.

Table E5 presents the expected costs and number of LS cases detected for a universal tumour screening program versus a targeted tumour screening program based on rBG. As would be expected, the universal strategy resulted in more LS cases detected with higher costs compared with the rBG screening strategy. The incremental cost per LS detected for these two specific strategies (#2 and #8) was calculated as $141,973 per LS case detected.

Table E5: Cost-Effectiveness for the Screening Strategies of Interest to This Report, Based on Gould-Suarez et al. Economic Analysis

LS Screening Strategy	Costs per 150,000 Probands	LS Detected per 150,000 Probands	Cost per LS Detected	Incremental Cost per LS Case Detected[a]
Universal Testing (G-S strategy #8)[b]	$375,257,030	4,370	$85,881	$141,973
Revised Bethesda Guidelines (G-S strategy #2)[b]	$93,297,780	2,384	$23,480	Reference

G-S = Gould-Suarez et al.; IHC = immunohistochemistry; LS = Lynch syndrome; MMR = mismatch repair; MSI = microsatellite instability.
[a] Calculated.
[b] Reflex testing strategy consists of tumour IHC testing of MMR proteins. If MSH2.MSH6 or PMS2 is not expressed, patient receives germline MMR gene testing. If MLH1 protein is not expressed, patient receives tumour BRAF testing, followed by germline MMR gene testing if BRAF is negative. If all 4 MMR proteins are expressed, then tumour MSI testing; if MSI is unstable, germline testing of all 4 MMR genes is conducted.

Severin et al. (2014)

The cost-effectiveness of various LS testing strategies for newly diagnosed CRC patients in Germany was estimated by Severin et al.[120] The authors included several strategies that combined different screening strategies (no testing, universal testing, Amsterdam criteria, rBG criteria) and reflex testing strategies (tumour IHC without tumour BRAF, IHC with BRAF if non-expressed MLH1, IHC followed by tumour MSI for IHC positive, IHC followed by MSI for IHC negative, MSI followed with IHC for MSI-positive, MSI alone and direct germline MMR gene testing), resulting in a total of 22 strategies evaluated.

The cost per life-year was used as the cost-effectiveness outcome measure. A lifetime time horizon and a discount rate of 3% were used in the analysis, although the authors do not state whether the discount rate was applied to both costs and outcomes. The costs of testing and genetic counselling were included for both the newly diagnosed CRC patients and for their first-degree relatives (FDRs). The costs of CRC surveillance, colonoscopy complications, and CRC treatment for relatives were also included in the analysis.

The clinical impact of detecting LS in relatives of the patients was included in the model. Specifically, the impact on mortality resulting from CRC by detecting LS in FDRs was incorporated. This impact was integrated by assuming adherence to intense CRC surveillance for a large proportion of relatives diagnosed with LS. It was assumed that each CRC patient would have 3.8 FDRs and that 30% of FDRs would accept genetic counselling and be tested for LS. The model also examined the preventive impact of Aspirin as a risk-reducing medication. The clinical impact of LS detection on the newly diagnosed CRC patient was not included in the evaluation.

The authors presented cost-effectiveness results for the four strategies that were not strictly or extendedly dominated by other strategies. It is these strategies that make up the cost-

effectiveness efficiency frontier. Three of these four strategies correspond to screening strategies of interest in our primary economic evaluation, namely: no testing strategy, screening strategy based on rBG, and a universal screening strategy. In the latter two strategies, the reflex testing strategy consisted of a tumour MMR IHC panel followed by BRAF V600E mutational analysis for patients with an abnormal MLH1 protein expression and germline MMR gene testing in patients if normal BRAF or abnormal IHC expression for any of the other genes. Cost-effectiveness results for these three strategies are provided in Table E6. Total costs and effects are shown for 69,400 newly diagnosed CRC patients, corresponding to the projected 2012 incidence rates of CRC in Germany. As shown, the incremental cost per life-year of screening using the rBG criteria compared with no screening was estimated to be €77,268 per life-year gained (LYG). The incremental cost per LYG for universal screening compared with no screening was calculated to be € 98,149. The incremental cost per LYG of universal screening compared with screening based on rBG criteria was estimated to be €254,011.

Table E6: Cost-Effectiveness for the Screening Strategies of Interest to This Report, Based on Severin et al. Economic Analysis

LS Screening Strategy	Costs per 69,400 CRC Patients	LY per 69,400 CRC Patients	ICER (€/LY)	
			vs. no testing	efficiency frontier
No testing (Severin strategy 0)	€218,581,280	5,703,154	Reference	Reference
Revised Bethesda Guidelines[a] (Severin strategy B2)[b]	€242,028,209	5,703,458	€77,268	€77,268
Universal strategy (Severin strategy 2)[b]	€252,442,654	5,703,499	€98,149[a]	€254,011[a]

CRC = colorectal cancer; ICER = incremental cost-effectiveness ratio; LS = Lynch syndrome; LY = life-year; vs. = versus.
[a] Calculated.
[b] Reflex testing strategy consists of tumour IHC testing of MMR proteins. If MSH2, MSH6, or PMS2 proteins are not expressed, patient receives germline MMR gene testing. If MLH1 protein is not expressed, patient receives tumour BRAF testing, followed by germline MMR gene testing if BRAF is negative.

Ladabaum et al. (2011)

Ladabaum et al.[115] compared the cost-effectiveness of various LS screening strategies and tumour testing strategies for newly diagnosed CRC patients. There were 10 LS screening strategies evaluated based on clinical criteria (Amsterdam II, rBG), or prediction models (MMRpredict, MMRpro, PREMM). For each clinical criterion or prediction model, strategies were further stratified: patients either went directly to germline testing or had a tumour MMR IHC test as part of a reflex testing strategy before germline testing. Six different reflex testing strategies were evaluated: tumour IHC test of MMR proteins only, IHC with tumour BRAF testing, tumour MSI, MSI plus IHC, MSI plus IHC with BRAF testing, and germline MMR gene testing for all patients, with no testing evaluated as the reference strategy. Although not specified by the authors, it may be assumed that all newly diagnosed CRC patients are tested by various strategies (e.g., universal testing).

The model considered the costs and clinical impacts of LS detection for both the newly diagnosed CRC patients and their relatives, and incorporated the impact of detection on CRC, endometrial cancer, and ovarian cancer. Probands and relatives with confirmed mutation were offered annual colonoscopy starting at the age of 25. Females were offered annual gynecological screening starting at age 35 and abdominal hysterectomy and bilateral salpingo-

oophorectomy (TAH-BSO) at age 40. It was assumed that 0.19 of female probands would undergo TAH-BSO, while 0.18 of female relatives would undergo TAH-BSO. Surveillance was assumed to reduce CRC incidence by 58% and mortality by 76%. The model assumed no benefit of gynecological surveillance due to what the authors describe as lack of evidence of clinical benefit. TAH-BSO was assumed to be 100% effective in reducing the risk of gynecological cancers. Relatives of LS probands who refused testing and had a 50% chance of having LS were offered the same CRC and gynecological surveillance and preventive procedures. Similarly, mutation-negative CRC patients who met the Amsterdam criteria and had suspicious tumour features were offered the same surveillance and preventive interventions as their FDRs. The model assumed that each proband would have eight relatives contacted, of whom 0.52 would accept a germline test, and that 0.50 of relatives would be tested positive for LS.

Costs for testing procedures (tumour MSI, MMR IHC, BRAF, germline MMR gene testing), genetic counselling, screening and its complications, surgeries, and cancer care were included for both the newly diagnosed CRC patients and for their FDRs. All costs were expressed in 2010 US dollars. A discount rate of 3% was applied to both costs and outcomes.

The lifetime discounted costs and LYs per patient were presented for all strategies evaluated. Three of the screening strategies were similar to the no testing, rBG screening, and universal screening strategies that are of interest to this report. In the latter two strategies, the reflex testing strategy consisted of a tumour MMR IHC panel followed by germline testing if MMR IHC results were abnormal. The cost-effectiveness results of these three strategies are shown in Table E7. Compared with a no testing strategy, screening based on rBG criteria resulted in a cost per LY of US$30,600. The cost per LY of a universal screening strategy compared with no testing was calculated as US$36,962. The relative cost-effectiveness of a universal screening strategy compared with one based on patients meeting the rBG criteria was found to be US$62,624 per incremental LY gained. As part of the sensitivity analysis, the authors investigated the impact of implementing an age cut-off as a screening criterion, assuming a reflex testing strategy of MMR IHC plus BRAF tumour testing. The authors reported the incremental cost-effectiveness between having no age limit (i.e., universal) and an upper age limit of 70 years to be US$88,700 per LY gained. As the total expected costs and LYs for the 70-year-old cut-off strategy was not provided, the cost-effectiveness of this strategy in comparison with other screening strategies based on the rBG and the no testing strategy could not be calculated.

The authors also included a reflex testing strategy of tumour MMR IHC followed by BRAF to reduce the likelihood of LS after universal screening. The authors found that MMR IHC followed by BRAF tumour testing resulted in lower costs and the same number of LYs compared with tumour MMR IHC alone.

Table E7: Cost-Effectiveness for the Screening Strategies of Interest to This Report, Based on Ladabaum et al. Economic Analysis

LS Screening Strategy	Cost/CRC Patient	LYs/ Patient	ICER ($/LY)	
			vs. no testing	efficiency frontier
No testing (referent strategy)	$11,242	23.5071	reference	reference
Revised Bethesda Guidelines (reflex testing strategy: tumour MMR IHC)	$17,021	23.6915	$30,600	$30,600
Universal (reflex testing strategy: tumour MMR IHC)	$19,551	23.7319	$36,962[a]	$62,624[a]

CRC = colorectal cancer; ICER = incremental cost-effectiveness ratio; IHC = immunohistochemistry; LS = Lynch syndrome; LY = life-year; MMR = mismatch repair; vs. = versus.

[a] Calculated.

Wang et al. (2012)

Wang et al.[118] modified the economic model by Ladabaum et al. (2011),[115] described above, to incorporate quality-of-life (QoL) impacts. These included the impact from the possible awareness of having LS, having germline testing for LS, undergoing preventive total hysterectomy, and developing CRC or gynecological cancer. It was assumed that the QoL impact of cancer would last five years after diagnosis and the QoL impact of LS-related testing and preventive surgery would be 12 months in duration. CRC patients and relatives testing positive for LS through germline MMR gene testing had a utility value ranging from 0.622 to 0.697 applied for 12 months. Simply being offered a germline test was assumed to result in a utility of 0.660 for CRC patients and 0.719 for relatives of probands. Besides the QoL adjustments, there were no differences in the screening and testing strategies or the model inputs in the economic evaluation conducted by Wang et al.

Table E8 presents the cost-effectiveness results for a no testing strategy, a screening strategy based on the rBG criteria, and a universal screening strategy. Compared with no testing, the incremental cost per QALY of the screening strategy based on rBG and the universal screening strategy were found to be $51,691 and $60,961, respectively. The incremental cost per QALY of the universal screening strategy compared with the screening strategy based on rBG was estimated at $103,265.

The authors also included a reflex testing strategy of MMR IHC followed by BRAF tumour testing to reduce the likelihood of LS in universal screening. It is unclear whether this analysis was conducted correctly, as the expected costs for the strategy for tumour MMR IHC only and IHC with BRAF tumour testing were reversed between this paper and the paper by Ladabaum.[115]

Table E8: Cost-Effectiveness for the Screening Strategies of Interest to This Report, Based on Wang et al. Economic Analysis

LS Screening Strategy	Cost/CRC Patient	QALYs/ Patient	ICER ($/QALY)	
			vs. no testing	efficiency frontier
No testing (referent strategy)	$11,242	21.0649	Reference	Reference
Revised Bethesda Guidelines (reflex testing strategy: tumour MMR IHC)	$17,021	21.1767	$51,691*	$51,691*
Universal (reflex testing strategy: tumour MMR IHC)	$19,551	21.2012	$60,961*	$103,265*

CRC = colorectal cancer; ICER = incremental cost-effectiveness ratio; IHC = immunohistochemistry; LS = Lynch syndrome; QALY = quality-adjusted life-year; MMR = mismatch repair; vs. = versus.

[a] Calculated.

Mvundura et al. (2010)

The cost-effectiveness of various reflex testing strategies for newly diagnosed CRC patients were compared by Mvundura et al.[56] The four strategies of interest were: 1) MMR protein tumour IHC testing followed by BRAF mutation tumour testing for patients with no tumour expression of the MLH1 protein, and germline MMR gene testing if BRAF mutation tumour was negative or if abnormality in the other proteins; 2) tumour MMR IHC testing followed by germline testing for patients with abnormal MMR IHC; 3) tumour MSI testing with MSI-high patients going on to germline testing; 4) all patients go to germline testing without tumour MSI or IHC testing. In addition, a no testing strategy was considered. The authors assumed two screening scenarios; i.e., the universal screening and screening newly diagnosed CRC patients ≤ 50 years of age.

The clinical outcome of the model was LYs gained. The authors also estimated QALYs. Costs were presented in 2007 US dollars. Costs and outcomes were discounted at annual rate of 3%. The model included the impact of LS detection on family members at risk of developing CRC, but not on the probands. Family members who tested positive for LS were assumed to be offered colonoscopy surveillance every one to two years, starting at ages 20 to 25 years old. It was assumed that 79% of LS-positive relatives would comply with colonoscopy surveillance. A 60% reduction in CRC rates was applied to patients who compiled with regular colonoscopy. It was further assumed that patients with regular colonoscopy would be diagnosed at earlier stages of CRC. The authors state that relatives who do not have LS are offered colonoscopy every 10 years, starting at age 50. It does not appear that a clinical benefit of this screening option is incorporated into the model. It was assumed that four FDRs would be contacted per LS proband, and that half of these patients would agree to genetic testing. Furthermore, 0.46 of relatives tested were assumed to be LS positive. In sensitivity analysis, the authors assumed cascade testing would take place, with 12 relatives contacted per proband, and that 35% of these relatives would have LS.

Table E9 presents the ICERs reported in the publication for screening and testing strategies that are relevant to this report. As shown, the incremental cost per LY for universal screening compared with no testing was found to be $22,552 if tumour MMR IHC testing alone is used and $23,321 if BRAF mutation tumour testing is done on patients who lack tumour MLH1 protein expression before going on to germline gene testing. Assuming universal screening, the incremental cost-effectiveness of tumour MMR IHC alone versus IHC plus BRAF was estimated as US$273,915 per LY gained.

Table E9: Cost-Effectiveness for the Screening and Reflex Testing Strategies of Interest to This Report, Based on Mvundura et al. Economic Analysis

Treatment	Comparator	ICER (Incremental Cost/ LY)
Universal (tumour IHC alone)	No testing	$22,552
Universal (tumour IHC + BRAF)	No testing	$23,321
Universal (tumour IHC alone)	Universal (tumour IHC + BRAF)	$273,915

ICER = incremental cost-effectiveness ratio; IHC = immunohistochemistry; LY = life-year.

Snowsill et al. (2015)

Snowsill and colleagues[119] were commissioned by the National Institute for Health Research (NIHR) to conduct research evaluating the cost-utility of strategies that would identify LS in early onset CRC patients ≤ 50 years of age and their relatives. The results were published in both a health technology assessment (HTA) report (2014) and in a peer-reviewed publication (Snowsill et al. 2015). Of interest was the population of England and Wales. Nine strategies were evaluated in the economic model: 1a) No testing; 1b) No testing (Amsterdam II criteria for diagnosis); 2) tumour 4 MMR protein IHC test followed by germline genetic testing; 3) tumour IHC followed by BRAF (if abnormal MLH1) then germline genetic testing; 4) tumour MSI testing followed by germline genetic testing; 5) tumour MSI testing followed by tumour BRAF then germline genetic testing; 6) tumour MSI followed by tumour BRAF, followed by tumour MMR IHC then germline genetic testing; 7) tumour IHC followed by germline genetic testing (if MMR IHC abnormal); if MMR IHC test results found to be normal, follow strategy #5; 8) direct germline genetic testing.

Detection and interventions (surveillance and treatment) were conducted for both probands and relatives. The economic model assumed 1,699 probands to be identified each year with a prevalence of LS of 8.4% in probands. Five relatives were tested per proband and the prevalence of LS in relatives who were tested was 44%. Probands were considered LS positive if a mutation was found and, in the event of absence of a mutation, was assumed to be LS positive based on family history. If the probands declined genetic counselling or diagnostic testing, they would be classified as either LS assumed or LS negative, according to family history. Individuals who were classified as LS positive or LS assumed were offered biannual colonoscopic surveillance starting at age 25 and ending at age 75. Colonoscopy was assumed to reduce the incidence of an index CRC by 61% and reduce the incidence of a second CRC by 47%. The frequency of colonoscopies was every two years and patients were assumed to develop a maximum of two CRCs in their lifetime. No disutility measures were applied for occurrence of cancer, surveillance, or treatments. In the case of metastatic cancer, a disutility of 0.13 was applied. Utility was taken into account for the psychological impact of genetic counselling for four months.

Model elements included various costs (tests: tumour MSI, IHC, BRAF, germline genetic testing), genetic counselling, surveillance, and cancer treatment. Costs were reported in 2013-2014 UK pounds (GBP) and both costs and outcomes were discounted at 3.5%. Time horizon of the model was 100 years or until death.

Primary outcome of interests were total costs, QALYs, and ICERs for all strategies. Table E10 presents the results of the strategies that are relevant to this report. Compared with no testing, the incremental costs per QALY for screening patients based on the reflex testing strategies 1) tumour IHC, BRAF and germline and 2) tumour IHC, germline were £5,824, and £6,433 respectively. The screening strategies in the base case were limited to newly diagnosed CRC

patients who were younger than 50 years of age. Based on the results presented by Snowsill, the reflex testing strategy of tumour MMR IHC followed by tumour BRAF for those with abnormal MLH1 protein expression was equally effective and less costly than the testing strategy of sending all patients with abnormal MMR IHC findings to germline testing. The authors assumed that tumour BRAF testing would not lead to patients being falsely diagnosed as LS-negative (specificity for BRAF to detect likely sporadic CRC = 100%). In a scenario analysis, the authors replaced tumour BRAF testing with tumour MLH1 hypermethylation testing. The incremental cost per QALY of screening CRC patients younger than 50 years of age with tumour MMR IHC testing with MLH1 promoter hypermethylation testing compared with no testing was reported to be £5,901.

Although not shown in Table E10, the incremental cost per QALY of using tumour BRAF testing after MMR IHC testing compared with using MLH1 promoter hypermethylation testing can be calculated as £27,149.

As part of a scenario analysis, the authors changed the screening criteria from CRC patients younger than 50 years old to patients younger than 70 years old. The authors reported the cost per QALY of screening patients younger than 70 years old compared with no screening as £11,268.

Table E10: Cost-Effectiveness for the Screening and Reflex Testing Strategies of Interest to This Report, Based on Snowsill et al. Economic Analysis

LS Screening and Testing Strategy	Cost for 1,699 CRC Patients	QALYs for 1,699 CRC Patients	ICER ($/QALY)	
			vs. no testing	efficiency frontier
No testing (Snowsill 1(1))	£36,223,787	151,793	Reference	Reference
Age < 50 (tumour MMR IHC + MLH1 promoter hypermethylation) (Snowsill 3, scenario analysis 2)	£37,144,423	151,949	£5,901[a]	Extendedly dominated[a]
Age < 50 (tumour MMR IHC + BRAF) (Snowsill 3)	£37,155,626	151,953	£5,824[a]	£5,824[a]
Age < 50 (tumour MMR IHC alone) (Snowsill 2)	£37,253,017	151,953	£6,433[a]	Dominated by Age < 50 (tumour MMR IHC + BRAF)

CRC = colorectal cancer; ICER = incremental cost-effectiveness ratio; IHC = immunohistochemistry; LS = Lynch syndrome; QALY = quality-adjusted life-year; MMR = mismatch repair; vs. = versus.

[a] Calculated.

Gudgeon et al. 2013

In the study by Gudgeon et al. (2013),[113] various age cut-offs were evaluated with respect to their impact on cost per LS case detected. Acceptance rates of 100% and 50% were investigated for each age cut-off category of 50, 60, 70, and 80 years, and no age cut-off. Of relevance to this report is the evaluation of age cut-off at 70 years versus no age cut-off (universal screening). It was assumed that the reflex testing strategy was based on tumour MMR IHC including tumour BRAF and MLH1 promoter hypermethylation as supplementary tests.

This economic assessment considered the costs of testing (i.e., tumour IHC [$230], BRAF [$305], and MLH1 promoter hypermethylation [$295]), and the sensitivity of the screening protocol (91.5%). Clinical assumptions of the model included the proportion of total LS cases by each age cohort as well as the estimated prevalence of LS in CRC patients (3.6%). Cost for genetic counselling was not included in the model. All costs were reported in 2010 US dollars.

Cost-effectiveness results comparing universal screening with screening patients younger than 70 years old are shown in Table E11. As shown, the incremental cost per LS case detected for the universal screening strategy compared with screening only patients younger than 70 years old was estimated to be $26,917. If only 50% of CRC patients offered germline testing agreed to it, the cost per LS case detected was $44,933 for universal screening compared with an age-restricted screening criterion.

Table E11: Cost-Effectiveness for the Screening Strategy of Interest to This Report Assuming 100% Acceptance Rate for Screening, Based on Gudgeon et al. Economic Analysis

LS Screening Strategy	Cost to Screen and Test Age Cohort	# of LS Cases Detected	$/LS Detected
Age < 70 years[a]	$72,747	9.2	Reference
Universal testing[a]	$113,123	10.7	$ 26,917[b]

CRC = colorectal cancer LS = Lynch syndrome; MMR = mismatch repair; vs. = versus.

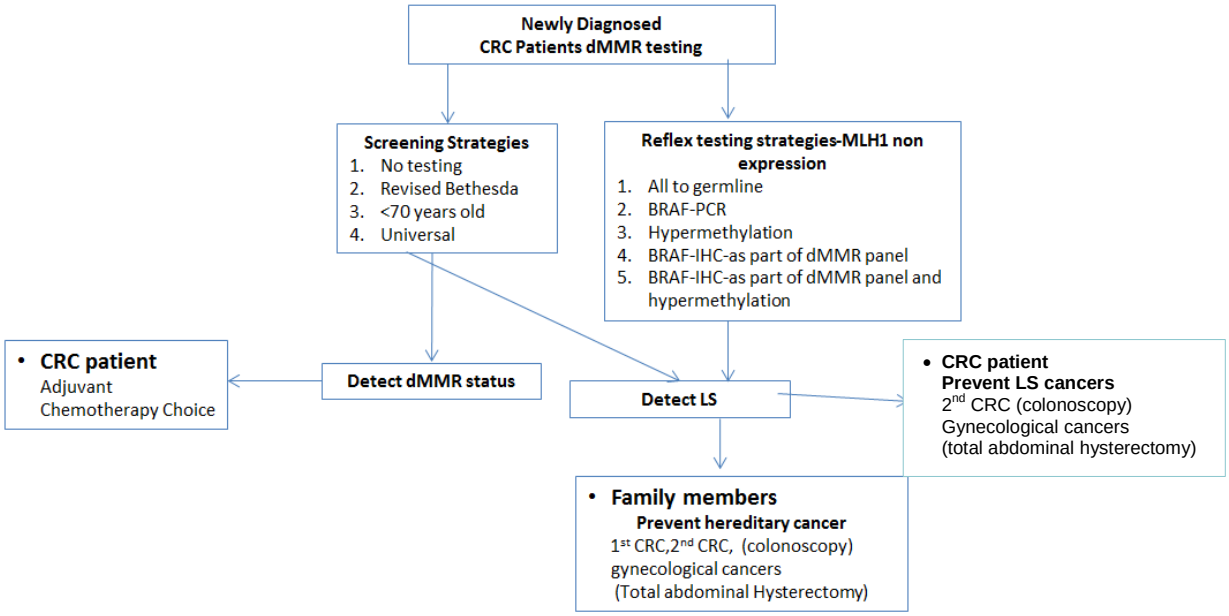
[a] Reflex testing strategy consists of tumour MMR IHC testing. If MSH2, MSH6, or PMS2 protein is not expressed, patient receives germline genetic testing. If MLH1 protein is not expressed, patient receives tumour BRAF testing, followed by MLH1 promoter hypermethylation testing if BRAF is negative. If both tumour BRAF and MLH1 promoter hypermethylation are normal, then patient receives germline testing.
[b] Calculated.

Appendix 39: List of Different Strategies Compared in the Model

Comparator	Screening Strategy	Reflex Tumour Testing Strategy	dMMR in Chemo Choice?
1	No Screening	Not applicable	No
2	No Screening	Not applicable	Yes
3	rBG	All receive germline testing	No
4	rBG	All receive germline testing	Yes
5	rBG	BRAF-PCR	No
6	rBG	BRAF-PCR	Yes
7	rBG	MLH1 promoter hypermethylation	No
8	rBG	MLH1 promoter hypermethylation	Yes
9	rBG	BRAF-IHC	No
10	rBG	BRAF-IHC	Yes
11	rBG	BRAF-IHC — MLH1 promoter hypermethylation	No
12	rBG	BRAF-IHC — MLH1 promoter hypermethylation	Yes
13	Younger than 70 years old	All receive germline testing	No
14	Younger than 70 years old	All receive germline testing	Yes
15	Younger than 70 years old	BRAF-PCR	No
16	Younger than 70 years old	BRAF-PCR	Yes
17	Younger than 70 years old	MLH1 promoter hypermethylation	No
18	Younger than 70 years old	MLH1 promoter hypermethylation	Yes
19	Younger than 70 years old	BRAF-IHC	No
20	Younger than 70 years old	BRAF-IHC	Yes
21	Younger than 70 years old	BRAF-IHC — MLH1 promoter hypermethylation	No
22	Younger than 70 years old	BRAF-IHC — MLH1 promoter hypermethylation	Yes
23	Universal	All receive germline testing	No
24	Universal	All receive germline testing	Yes
25	Universal	BRAF-PCR	No
26	Universal	BRAF-PCR	Yes
27	Universal	MLH1 promoter hypermethylation	No
28	Universal	MLH1 promoter hypermethylation	Yes
29	Universal	BRAF-IHC	No
30	Universal	BRAF-IHC	Yes
31	Universal	BRAF-IHC — MLH1 promoter hypermethylation	No
32	Universal	BRAF-IHC — MLH1 promoter hypermethylation	Yes

dMMR = deficient mismatch repair; IHC = immunohistochemistry; PCR = polymerase chain reaction; rBG = revised Bethesda Guidelines.

Appendix 40: Overview of Screening and Reflex Testing Strategies in Patients With Colorectal Cancer and Subsequent Carrier Testing in Their Relatives



CRC = colorectal cancer; dMMR = deficient mismatch repair; IHC = immunohistochemistry; LS = Lynch syndrome; PCR = polymerase chain reaction.

Appendix 41: Proportion of Patients With Diagnosed Colorectal Cancer, According to Dukes Staging

Stage at Diagnosis for Patients With Colorectal Cancer in Surveillance Arms				
Dukes staging at diagnosis				
	Jarvinen[131]	**Stupart[138]**	**Combined**	**Proportion**
A	3	7	10	0.455
B	5	1	6	0.273
C	0	6	6	0.273
D	0	0	0	0.000
Total	8	14	22	1

Appendix 42: Detailed Calculation to Determine Parameter Estimates for Relative Identification Submodel

Estimate of Number of Relatives Approached per Proband			
Study	**Relatives**	**Probands**	**Relatives per Proband**
Ramsoekh[252]	1118	112	9.98
Akatan Collan[172]	446	36	12.39
Lerman[253]	208	4	52.00
Lynch[254]	219	4	54.75
Baglietto[255]	3104	133	23.34
Pooled Estimate	**5095**	**289**	**17.63**

Estimate of Number and Percentage of Relatives Approached Who Are Tested			
Study	**# of Relatives Approached**	**# of Relatives Tested**	**% of Relatives Tested**
Ramsoekh[252]	1118	404	36%
Akatan Collan[172]	446	334	75%
Lerman[253]	208	90	43%
Lynch[254]	219	130	59%
Baglietto[255]	3104	525	17%
Pooled Estimate	**5095**	**1483**	**29.11%**

Estimate of Number and Percentage of Relatives Tested Who Have Lynch Syndrome			
Study	**# of Relatives Tested**	**# of Relatives Germline Mutation Positive**	**% of Relatives Germline Mutation Positive**
Ramsoekh[252]	404	151	37%
Akatan Collan[172]	334	94	28%
Lerman[253]	84	35	42%
Lynch[254]	130	47	36%
Baglietto[255]	525	278	53%
Pooled Estimate	**1477**	**605**	**41%**

Appendix 43: Detailed Cost Breakdown for a Year of Adjuvant Chemotherapy

Regimen: 5-FU + Leucovorin MOSAIC Trial[256]					
Drug	**Dose**	**Dose (mg) per Day**	**Admin Days per Cycle**	**Cost per mg**	**Cost per Cycle**
Leucovorin	200 mg/m^2	350	2	$0.5616	$393.12
5-FU (bolus)	400 mg/m^2	700	2	$0.0442	$61.90
5-FU (continuous infusion)	600 mg/m^2	1,050	2	$0.0442	$92.85
Chemo administrative costs per cycle					$172.10
Cost per 14-day cycle					$547.88
Cost for 12 cycles (6 months)					$6,574.51
Assumes a body surface area of 1.75 m^2					

5-FU = fluorouracil.

Appendix 44: Background Age- and Sex-Specific Utility Values

Utility Values by Age and Sex		
	Utility Values	
Age	Females	Males
35	0.91	0.91
45	0.85	0.84
55	0.81	0.78
65	0.78	0.78
75	0.71	0.75

Appendix 45: Detailed Deterministic Results From the Economic Model

Expected Number of LS Cases Detected, Costs, LYs, and QALYS for All Comparators Evaluated in the Model						
Screening	**Reflex Tumour Testing**	**Use dMMR for Chemo?**	**LS Cases Detected**	**Costs**	**LYs**	**QALYs**
No Screening	Not applicable	No	0.0000	$63,552	47.0275	37.9216
No Screening	Not applicable	Yes	0.0000	$63,517	47.0278	37.9224
rBG	All receive germline testing	No	0.0517	$63,678	47.0456	37.9385
rBG	All receive germline testing	Yes	0.0517	$63,642	47.0459	37.9393
rBG	BRAF-PCR	No	0.0514	$63,651	47.0455	37.9384
rBG	BRAF-PCR	Yes	0.0514	$63,615	47.0457	37.9392
rBG	MLH1 promoter hypermethylation	No	0.0510	$63,635	47.0454	37.9383
rBG	MLH1 promoter hypermethylation	Yes	0.0510	$63,599	47.0456	37.9391
rBG	BRAF-IHC	No	0.0500	$63,658	47.0451	37.9380
rBG	BRAF-IHC	Yes	0.0500	$63,622	47.0453	37.9388
rBG	BRAF-IHC — MLH1 promoter hypermethylation	No	0.0495	$63,631	47.0448	37.9378
rBG	BRAF-IHC — MLH1 promoter hypermethylation	Yes	0.0495	$63,596	47.0451	37.9386
Younger than 70 years old	All receive germline testing	No	0.0677	$63,853	47.0512	37.9438
Younger than 70 years old	All receive germline testing	Yes	0.0677	$63,816	47.0515	37.9446
Younger than 70 years old	BRAF-PCR	No	0.0673	$63,785	47.0511	37.9436
Younger than 70 years old	BRAF-PCR	Yes	0.0673	$63,748	47.0513	37.9445
Younger than 70 years old	MLH1 promoter hypermethylation	No	0.0669	$63,744	47.0509	37.9435
Younger than 70 years old	MLH1 promoter hypermethylation	Yes	0.0669	$63,707	47.0512	37.9443
Younger than 70 years old	BRAF-IHC	No	0.0656	$63,804	47.0505	37.9431
Younger than 70 years old	BRAF-IHC	Yes	0.0656	$63,767	47.0507	37.9439

Expected Number of LS Cases Detected, Costs, Lys, and QALYS for All Comparators Evaluated in the Model						
Screening	**Reflex Tumour Testing**	**Use dMMR for Chemo?**	**LS Cases Detected**	**Costs**	**LYs**	**QALYs**
Younger than 70 years old	BRAF-IHC — MLH1 promoter hypermethylation	No	0.0648	$63,736	47.0502	37.9428
Younger than 70 years old	BRAF-IHC — MLH1 promoter hypermethylation	Yes	0.0648	$63,698	47.0504	37.9436
Universal	All receive germline testing	No	0.0784	$64,017	47.0550	37.9473
Universal	All receive germline testing	Yes	0.0784	$63,978	47.0552	37.9481
Universal	BRAF-PCR	No	0.0779	$63,909	47.0548	37.9471
Universal	BRAF-PCR	Yes	0.0779	$63,871	47.0550	37.9480
Universal	MLH1 promoter hypermethylation	No	0.0774	$63,846	47.0546	37.9470
Universal	MLH1 promoter hypermethylation	Yes	0.0774	$63,807	47.0549	37.9478
Universal	BRAF-IHC	No	0.0759	$63,941	47.0541	37.9465
Universal	BRAF-IHC	Yes	0.0759	$63,902	47.0543	37.9473
Universal	BRAF-IHC — MLH1 promoter hypermethylation	No	0.0750	$63,832	47.0538	37.9462
Universal	BRAF-IHC — MLH1 promoter hypermethylation	Yes	0.0750	$63,793	47.0540	37.9470

dMMR = deficient mismatch repair; IHC = immunohistochemistry; LS = Lynch syndrome; LY = life-year; PCR = polymerase chain reaction; QALY = quality-adjusted life-year; rBG = revised Bethesda Guidelines.

Appendix 46: Literature Search Strategy (Question 7)

See the Literature Search Strategy section for more details on literature search methods.

Database Search

Overview	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations PsycINFO 1967 to present [search #2 only] **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	Patient and family factors search -- June 10, 2015 Psychosocial issues search – June 26, 2015
Alerts:	Bi-weekly search updates until project completion
Study Types:	No study design filters used
Limits:	Date limit: none Language limit: none Conference abstracts: excluded in search #1; included in search #2 Animal filter used [search #1 only]

Syntax Guide	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.tw	Text word
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.ot	Original title
.pt	Publication type
.es	Ethics subheading
.px	Psychology subheading
freq	Frequency of word
.jw	Journal title word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily
psyb	Ovid database code; PsycINFO 1967 to present

Multi-Database Search	
#	**Searches**
Search #1 – Patient and family factors search	
1	Microsatellite Instability/
2	exp Microsatellite Repeats/
3	DNA Mismatch Repair/
4	Base Pair Mismatch/
5	(dMMR or (MMR adj2 (abnormal* or deficienc* or test*)) or (error* adj3 phenotype* adj3 replication*) or replication error* or ((microsatellite* or micro-satellite*) adj2 (analy* or instabilit* or unstable)) or IMSI or MSI).tw.
6	((mismatch* or mis-match*) adj2 repair*).tw.
7	or/1-6
8	exp patient acceptance of health care/ or caregivers/
9	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) and (preference* or input or experience or experiences or value or values or perspective* or expectation* or choice* or choose* or choosing or "day-to-day" or participat* or acceptance or symptom or symptoms or limitations or survey* or focus group* or lives or interview* or quality of life or satisfaction or burden or attitude* or knowledge or lessons or reaction* or motivation* or intention* or involv* or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding)).ti.
10	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) adj2 (preference* or input or experience or experiences or value or values or perspective* or expectation* or choice* or choose* or choosing or "day-to-day" or participat* or acceptance or limitations or survey* or focus group* or lives or interview* or quality of life or satisfaction or burden or attitude* or knowledge or lessons or reaction* or motivation* or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding)).ab.
11	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) adj7 (preference* or input or experience or experiences or value or values or perspective* or expectation* or choice* or choose* or choosing or "day-to-day" or participat* or acceptance or limitations or survey* or focus group* or lives or interview* or quality of life or satisfaction or burden or attitude* or knowledge or lessons or reaction* or motivation* or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding)).ab. /freq=2
12	patient*.jw.
13	or/8-12
14	7 and 13
15	14 use pmez
16	Microsatellite Instability/
17	Microsatellite DNA/
18	Mismatch Repair/
19	Base Mispairing/
20	(dMMR or (MMR adj2 (abnormal* or deficienc* or test*)) or (error* adj3 phenotype* adj3 replication*) or replication error* or ((microsatellite* or micro-satellite*) adj2 (analy* or instabilit* or unstable)) or IMSI or MSI).tw.
21	((mismatch* or mis-match*) adj2 repair*).tw.

Multi-Database Search	
#	**Searches**
22	or/16-21
23	exp patient attitude/ or patient preference/ or patient participation/ or patient satisfaction/ or patient decision making/ or caregiver/ or relative/ or caregiver burden/ or caregiver support/
24	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) and (preference* or input or experience or experiences or value or values or perspective* or expectation* or choice* or choose* or choosing or "day-to-day" or participat* or acceptance or symptom or symptoms or limitations or survey* or focus group* or lives or interview* or quality of life or satisfaction or burden or attitude* or knowledge or lessons or reaction* or motivation* or intention* or involv* or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding)).ti.
25	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) adj2 (preference* or input or experience or experiences or value or values or perspective* or expectation* or choice* or choose* or choosing or "day-to-day" or participat* or acceptance or limitations or survey* or focus group* or lives or interview* or quality of life or satisfaction or burden or attitude* or knowledge or lessons or reaction* or motivation* or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding)).ab.
26	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) adj7 (preference* or input or experience or experiences or value or values or perspective* or expectation* or choice* or choose* or choosing or "day-to-day" or participat* or acceptance or limitations or survey* or focus group* or lives or interview* or quality of life or satisfaction or burden or attitude* or knowledge or lessons or reaction* or motivation* or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding)).ab. /freq=2
27	patient*.jw.
28	or/23-27
29	22 and 28
30	29 not conference abstract.pt.
31	30 use oemezd
32	15 or 31
33	exp animals/
34	exp animal experimentation/ or exp animal experiment/
35	exp models animal/
36	nonhuman/
37	exp vertebrate/ or exp vertebrates/
38	or/33-37
39	exp humans/
40	exp human experimentation/ or exp human experiment/
41	or/39-40
42	38 not 41
43	32 not 42
44	remove duplicates from 43
Search #2 – Psychosocial issues search	
#	**Searches**

Multi-Database Search	
#	**Searches**
1	exp colorectal neoplasms/
2	(colorectal adj3 (cancer* or carcinoma* or tumor* or tumour* or neoplasm*)).tw.
3	Lynch syndrome*.tw.
4	HNPCC.ti,ab.
5	or/1-4
6	(genetic* or hereditary or inherit* or heritable or familial or family history).tw.
7	exp Genetic Services/
8	6 or 7
9	Microsatellite Instability/
10	exp Microsatellite Repeats/
11	DNA Mismatch Repair/
12	Base Pair Mismatch/
13	(dMMR or (MMR adj2 (abnormal* or deficienc* or test*)) or (error* adj3 phenotype* adj3 replication*) or replication error* or ((microsatellite* or micro-satellite*) adj2 (analy* or instabilit* or unstable)) or IMSI or MSI).tw.
14	((mismatch* or mis-match*) adj2 repair*).tw.
15	or/9-14
16	exp Disclosure/
17	exp Self Disclosure/
18	exp Ethics/
19	Genetic Counseling/es, px
20	Genetic Services/es
21	Genetic Testing/es, px
22	social support/
23	Survivors/px
24	(counseling or counselling or counselor or counsellor or counsel or psychological or psycholog* or psychosocial or preference* or motivation* or intention* or behaviour* or behavior* or attitude* or moral or morals or morality or ethics or ethical or bioethic* or genethic* or confidential* or disclosure* or communication or acceptance or accepting or adjustment).ti.
25	((care or treatment) adj2 (duty or obligat*)).ti.
26	(inform* adj (choice* or decision*)).ti.
27	(social adj (responsib* or obligat*)).ti.
28	(harm or anxiety or threat or threatened or threatening).ti.
29	or/16-28
30	5 and (8 or 15) and 29
31	30 use pmez, psyb
32	exp *colorectal tumor/
33	(colorectal adj3 (cancer* or carcinoma* or tumor* or tumour* or neoplasm*)).tw.
34	Lynch syndrome*.tw.
35	or/32-34
36	(genetic* or hereditary or inherit* or heritable or familial or family history).tw.
37	exp *genetic service/
38	36 or 37
39	*microsatellite DNA/

Multi-Database Search	
#	**Searches**
40	*mismatch repair/
41	*base mispairing/
42	(dMMR or (MMR adj2 (abnormal* or deficienc* or test*)) or (error* adj3 phenotype* adj3 replication*) or replication error* or ((microsatellite* or micro-satellite*) adj2 (analy* or instabilit* or unstable)) or IMSI or MSI).tw.
43	((mismatch* or mis-match*) adj2 repair*).tw.
44	or/39-43
45	*survivor/
46	exp *medical ethics/
47	exp *genetic service/
48	(counseling or counselling or counselor or counsellor or counsel or psychological or psycholog* or psychosocial or preference* or motivation* or intention* or behaviour* or behavior* or attitude* or moral or morals or morality or ethics or ethical or bioethic* or genethic* or confidential* or disclosure* or communication or acceptance or accepting or adjustment).ti.
49	((care or treatment) adj2 (duty or obligat*)).ti.
50	(inform* adj (choice* or decision*)).ti.
51	(social adj (responsib* or obligat*)).ti.
52	(harm or anxiety or threat or threatened or threatening).ti.
53	or/45-52
54	35 and (38 or 44) and 53
55	54 use oemezd
56	31 or 55
57	remove duplicates from 56
	Duplicates then removed from search #1

Other Databases		
PubMed	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.	

Appendix 47: Data Abstraction Form (Question 7)

Reviewer Name:

STUDY CHARACTERISTICS	
Ref ID	
First author	
Publication title	
Publication year	
Country (where data were generated)	
Setting (where data were generated)	
Funding sources	
Ethics approval	□ Yes □ No Comments:
Study design	□ Descriptive survey □ Ethnography □ Phenomenology □ Grounded theory □ Qualitative description □ Other (specify):
Study objectives	
Eligibility criteria	
Recruitment method	
Sample size	
Participant characteristics	
Age	
Sex	
Cancer stage	
Other?	
Data collection methods	□ Questionnaire □ Interview □ Focus group □ Observation □ Document review □ Other (specify):

Data analysis methods	
STUDY RESULTS In the following table, extract verbatim result statements. Result statements will typically, but not always, be presented within the “results” section of a report. Result statements do not include raw data, study methods, external data, and researchers’ conclusions and implications.	
Result statements	

Appendix 48: Quality Assessment Instrument — Qualitative Studies

Reviewer Name:

STUDY CHARACTERISTICS	
Ref ID	
First author	
Publication year	
1. Was ethics approval obtained?	□ Yes □ No □ Unclear Comments:
STUDY DESIGN	
2. Was the study design clearly stated and justified?	□ Yes □ No □ Unclear Comments:
RESEARCH QUESTIONS AND OBJECTIVES	
3. Are the research questions and/or objectives clearly stated?	□ Yes □ No □ Unclear Comments:
4. Are the research questions suited to qualitative inquiry?	□ Yes □ No □ Unclear Comments:
PARTICIPANTS AND SAMPLING	
5. Is the sampling strategy clearly described?	□ Yes □ No □ Unclear Comments:
6. Is the sampling strategy congruent with the research questions and/or objectives?	□ Yes □ No □ Unclear Comments:

7. Did sampling continue until data saturation was reached?	□ Yes □ No □ Unclear Comments:
DATA COLLECTION	
8. Are the data collection strategies described with sufficient detail?	□ Yes □ No □ Unclear Comments:
9. Are the data collection strategies congruent with the research questions and/or objectives?	□ Yes □ No □ Unclear Comments:
DATA ANALYSIS	
10. Are the data analysis strategies described with sufficient detail?	□ Yes □ No □ Unclear Comments:
11. Are the data analysis strategies congruent with the research questions and/or objectives?	□ Yes □ No □ Unclear Comments:
RESULTS	
12. Are the results supported by and consistent with the data?	□ Yes □ No □ Unclear Comments:
13. Is it clear how the themes and concepts were derived from the data?	□ Yes □ No □ Unclear Comments:
14. Are results rooted in participants' own perspectives?	□ Yes □ No □ Unclear Comments:
15. Has the diversity of perspective and content been explored?	□ Yes □ No □ Unclear Comments:
CONFIRMABILITY	

16. Is the role of the researcher clearly described?	□ Yes □ No □ Unclear Comments:
17. Have the assumptions and biases of the researcher been clearly described?	□ Yes □ No □ Unclear Comments:
18. Have the effects of the researcher throughout the study process been clearly described?	□ Yes □ No □ Unclear Comments:
TRANSFERABILITY	
19. Is the study setting described with sufficient detail?	□ Yes □ No □ Unclear Comments:
20. Are study participants described with sufficient detail?	□ Yes □ No □ Unclear Comments:
CREDIBILITY	
21. Which of the following techniques were used to enhance credibility of results?	□ Member checking □ Peer debriefing □ Attention to negative cases □ Independent analysis by more than one researcher □ Reporting of verbatim data □ Other (specify):
22. Were the applied techniques to enhance credibility sufficient and appropriate?	□ Yes □ No □ Unclear Comments:
DEPENDABILITY	
23. Which of the following techniques were used to enhance dependability of results?	□ Peer review □ Debriefing □ Audit trail □ Triangulation □ Other (specify):

24. Were the applied techniques to enhance dependability sufficient and appropriate?	□ Yes □ No □ Unclear Comments:

Appendix 49: Quality Assessment Instrument — Cross-Sectional Studies

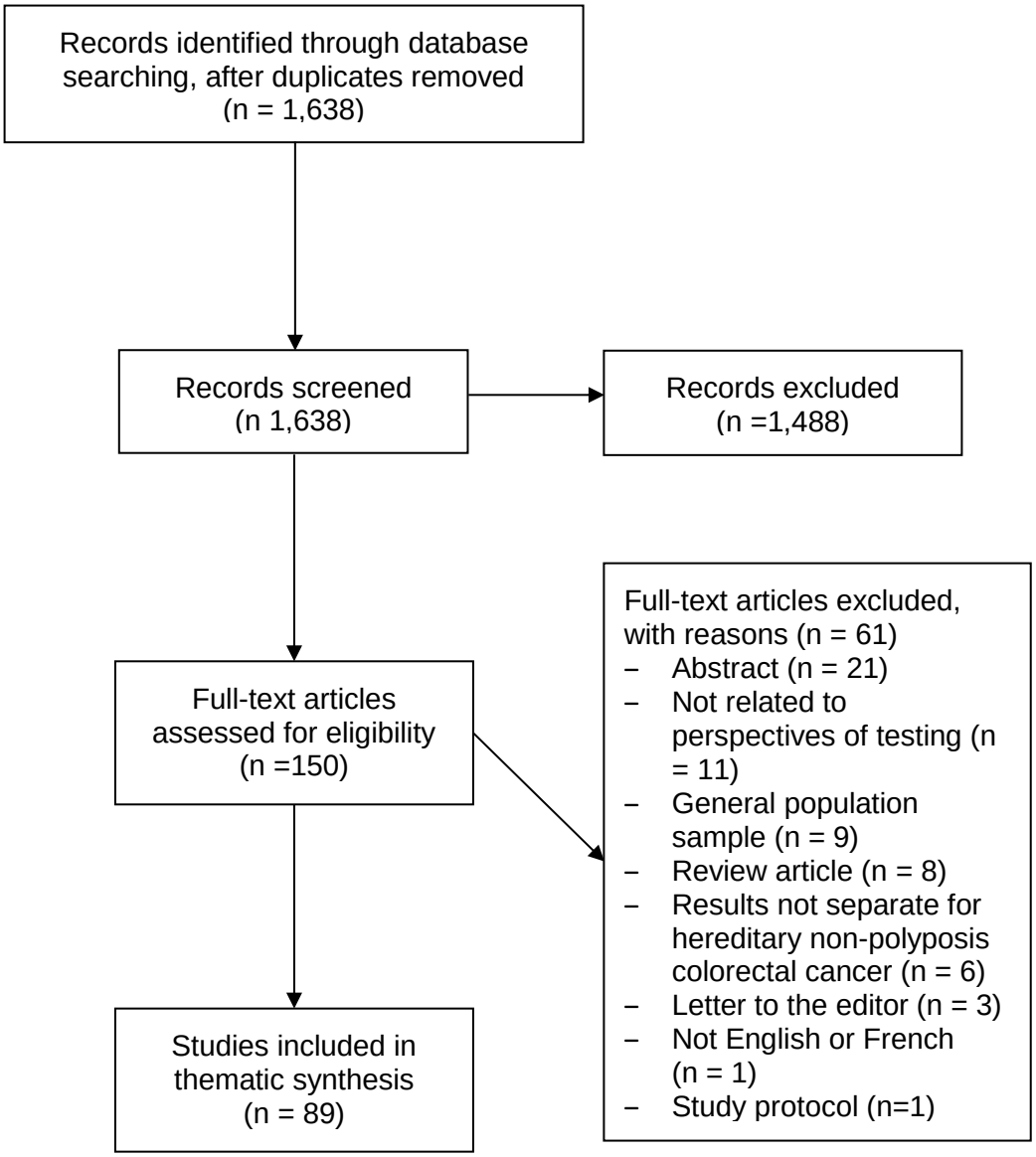
Reviewer Name:

STUDY CHARACTERISTICS	
Ref ID	
First author	
Publication year	
1. Was ethics approval obtained?	□ Yes □ No □ Unclear Comments:
RESEARCH QUESTION AND STUDY DESIGN	
2. Are the research questions and/or objectives clearly stated?	□ Yes □ No □ Unclear Comments:
3. Are the research questions suitable for a cross-sectional design?	□ Yes □ No □ Unclear Comments:
PARTICIPANTS AND SAMPLING	
4. Is the sampling strategy clearly described?	□ Yes □ No □ Unclear Comments:
5. Is the sampling strategy congruent with the research questions and/or objectives?	□ Yes □ No □ Unclear Comments:
6. Is the sample of participants representative of the target sample, or the population to which the findings will be generalized?	□ Yes □ No □ Unclear Comments:
7. Could the way the sample was obtained introduce selection bias?	□ Yes □ No □ Unclear Comments:

8. Was a sufficient sample size calculation provided?	□ Yes □ No □ Unclear Comments:
DATA COLLECTION	
9. Was a pilot test of data collection methods conducted?	□ Yes □ No □ Unclear Comments:
10. Was the study questionnaire valid?	□ Yes □ No □ Unclear Comments:
11. Was the study questionnaire reliable?	□ Yes □ No □ Unclear Comments:
DATA ANALYSIS	
12. Were the data analysis strategies appropriate for the type of data collected?	□ Yes □ No □ Unclear Comments:
13. Were all analyses planned a priori?	□ Yes □ No □ Unclear Comments:
RESULTS	
14. Was a satisfactory response rate achieved?	□ Yes □ No □ Unclear Comments:
15. Were all significant and non-significant quantitative results been reported?	□ Yes □ No □ Unclear Comments:

16. Were all qualitative results, resulting from open-ended questions, summarized and reported?	□ Yes □ No □ Unclear Comments:
DISCUSSION AND CONCLUSIONS	
17. Have the researchers drawn an appropriate link between the data and their conclusions?	□ Yes □ No □ Unclear Comments:
18. Have all potential biases been identified and discussed?	□ Yes □ No □ Unclear Comments:

Appendix 50: Selection of Included Studies (Question 7)



Appendix 51: List of Included Studies (Question 7)

Aktan-Collan K, Mecklin JP, Jarvinen H, Nystrom-Lahti M, Peltomaki P, Soderling I, et al. Predictive genetic testing for hereditary non-polyposis colorectal cancer: uptake and long-term satisfaction. Int J Cancer. 2000 Jan 20;89(1):44-50.

Aktan-Collan K, Haukkala A, Mecklin JP, Uutela A, Kaariainen H. Comprehension of cancer risk one and 12 months after predictive genetic testing for hereditary non-polyposis colorectal cancer. J Med Genet. 2001 Nov;38(11):787-92.

Aktan-Collan K, Haukkala A, Kaariainen H. Life and health insurance behaviour of individuals having undergone a predictive genetic testing programme for hereditary non-polyposis colorectal cancer. Community Genet. 2001;4(4):219-24.

Aktan-Collan K, Haukkala A, Mecklin JP, Uutela A, Kaariainen H. Psychological consequences of predictive genetic testing for hereditary non-polyposis colorectal cancer (HNPCC): a prospective follow-up study. Int J Cancer. 2001 Aug 15;93(4):608-11.

Aktan-Collan K, Kääriäinen H, Järvinen H, Peltomäki P, Pylvänäinen K, Mecklin JP, et al. Psychosocial consequences of predictive genetic testing for Lynch syndrome and associations to surveillance behaviour in a 7-year follow-up study. Fam Cancer. 2013 Dec;12(4):639-46.

Aktan-Collan KI, Kääriäinen HA, Kolttola EM, Pylvänäinen K, Järvinen HJ, Haukkala AH, et al. Sharing genetic risk with next generation: mutation-positive parents' communication with their offspring in Lynch syndrome. Fam Cancer. 2011 Mar;10(1):43-50.

Arver B, Haegermark A, Platten U, Lindblom A, Brandberg Y. Evaluation of psychosocial effects of pre-symptomatic testing for breast/ovarian and colon cancer pre-disposing genes: a 12-month follow-up. Fam Cancer. 2004;3(2):109-16.

Ashida S, Hadley DW, Vaughn BK, Kuhn NR, Jenkins JF, Koehly LM. The impact of familial environment on depression scores after genetic testing for cancer susceptibility. Clin Genet. 2009 Jan;75(1):43-9.

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Appendix 52: List of Excluded Studies, With Reasons (Question 7)

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Thesis
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Appendix 53: Characteristics of Included Studies (Question 7)

First Author Publication Year, Country of Origin[a]	Study Objectives	Study Design	Inclusion Criteria	Sample Size	Data Collection Methods
Aktan-Collan 2011, Finland[196]	1) To systematically investigate whether LS carriers inform their offspring about the mutation and possibilities of predictive genetic testing, and the outcome of this information; 2) to explore the challenges in the disclosure process, wish for professional support, and the gender impact on communication.	Survey	Adult (> 40) LS carriers who have children	248	Questionnaire
Aktan-Collan 2000, Finland[172]	To investigate acceptance of an independent predictive genetic test, satisfaction with taking the test and reasons for and against taking the test.	Survey	Adults (≥ 18) without cancer diagnosis and at 50% risk of HNPCC	Baseline: 446 1-month follow-up: 299 1-year follow-up: 271	Questionnaire
Aktan-Collan 2013[179]	1) To examine the long-term psychosocial consequences of genetic testing; 2) to determine how the results of the testing related to satisfaction with the decision to undergo testing; 3) to examine behaviour of attending post-testing colonoscopy surveillance among both carriers and non-carriers and the relation to psychosocial factors.	Survey	Adult members of family with verified LS mutation, without cancer diagnosis and at 50% risk of HNPCC	208	Questionnaire
Aktan-Collan 2001[224]	To study the possible association of the result with emotional consequences such as general anxiety, fear of cancer and death, satisfaction with life, and attitude to the future in those who have undergone HNPCC testing.	Survey	Adults without cancer diagnosis, and at 50% risk of HNPCC	271	Questionnaire
Aktan-Collan 2001[248]	1) To evaluate the number of insurance policies purchased in the course of the predictive genetic testing programme; 2) to describe the number of existing insurances, the actual purchase of insurance policies in pre- and post-test periods and the planned purchase of insurance policies after testing.	Survey	Adults without cancer diagnosis, and at 50% risk of HNPCC	271	Questionnaire

First Author Publication Year, Country of Origin[a]	Study Objectives	Study Design	Inclusion Criteria	Sample Size	Data Collection Methods
Aktan-Collan 2001[229]	To determine how the members of HNPCC families comprehended their predictive test results in terms of their risk of developing CRC and discuss what may have influenced this.	Survey	Adults (≥ 18) without cancer diagnosis, and at 50% risk of HNPCC in LS family with verified *MLH1* mutation	271	Questionnaire
Arver 2004, Sweden[188]	To prospectively evaluate the psychosocial consequences during the first year following pre-symptomatic testing with respect to anxiety, depression and quality of life in self-referred individuals tested for breast/ovarian or CRC genes known in their families.	Survey	Adult (> 18) female members of a family with verified mutation in *BRCA1*, *BRCA2*, *MLH1*, *MSH2*	21	Questionnaire
Balmana 2004, United States[243]	1) To explore potential differences in motivations and concerns about genetic testing among individuals at risk for HNPCC, FAP, and HBOC syndromes; and 2) to evaluate the influence of several clinical and demographic factors on the decision-making for undergoing genetic testing.	Survey	Eligible for genetic testing; at risk or affected by HNPCC, FAP, or HBOC	130 (HNPCC = 37)	Questionnaire
Barrow 2015, United Kingdom[187]	To assess the uptake of predictive testing and colorectal screening in FDRs of MMR mutation carriers and to elicit reasons for non-uptake and non-engagement.	Cross-sectional	Adults (> 18) FDR of MMR mutation carriers	591	Chart review
Broderson 2004, United Kingdom[244]	To investigate the anticipated emotional and behavioural reactions of patients at familial risk of CRC who are undergoing surveillance, to the offer of a genetic test for HNPCC.	Survey	Individuals with family history suggestive of hereditary cancer	437	Questionnaire
Bruwer 2013, South Africa[163]	To elucidate how mutation-positive individuals reacted to the news of their increased risk of developing CRC and how and when this information was communicated to their family.	Qualitative description	Adults (≥ 18) who are mutation positive	80	Interview, observation

First Author Publication Year, Country of Origin[a]	Study Objectives	Study Design	Inclusion Criteria	Sample Size	Data Collection Methods
Burton-Chase 2014, United States[222]	To evaluate the prevalence of gynecologic cancer screening among women with LS, their knowledge of LS risk and screening recommendations, and their perceptions regarding communication about LS with providers.	Qualitative description	Adult (≥ 25) females without a diagnosis of gynecologic cancer, who were LS mutation-positive or met Amsterdam II criteria	74	Interview, questionnaire
Carlsson 2007, Sweden[205]	To explore experiences from and perceived impact on life after genetic testing for HNPCC.	Qualitative description	Members of families with verified HNPCC mutation	19	Interview
Ceballos 2008, United States[237]	1) To assess willingness of CRC cases and relatives to receive genetic information that may indicate an increased risk for cancer; 2) to whom they would disclose genetic information; and 3) whether receiving genetic test results may influence future prevention behaviours.	Survey	Cases: Adults with CRC; FDR of cases	Cases = 45 Relatives = 102	Questionnaire
Claes 2004, Belgium[173]	To assess motivation, recall of cancer risks, and illness representations of individuals who had a predictive test for HNPCC as well as the short-term impact of predictive testing.	Survey	Members of families with verified dMMR mutation, without cancer diagnosis	40	Questionnaire, interview
Claes 2005, Belgium[192]	(1) To evaluate distress, illness representations, and health-related behaviour 1 year after disclosure of a predictive test result for HNPCC; (2) to delineate pre-test variables that would be associated with post-test distress and health-related behaviour.	Survey	Members of families with verified dMMR mutation, without cancer diagnosis	72	Questionnaire, interview
Codori 1999, United States[250]	To explore predictors of genetic testing for HNPCC in terms of psychological well-being and cancer prevention and early detection behaviours.	Survey	Adults (> 18) without cancer diagnosis, and member of a family with verified	258 from 95 families	Questionnaire, interview

First Author Publication Year, Country of Origin[a]	Study Objectives	Study Design	Inclusion Criteria	Sample Size	Data Collection Methods
			HNPCC mutation or with a family history suggestive of hereditary cancer		
Cragun 2012, United States[184]	To explore differences between CRC survivors who did and did not express interest in having genetic testing for hereditary CRC if it were made available to them and to determine which factors most strongly correlate with interest in genetic testing.	Survey, secondary analysis	Patients with CRC	91	Questionnaire
de Leon 2004, Italy[189]	1) To evaluate how many high-risk individuals in each family underwent genetic testing for the search of constitutional mutations; 2) to ascertain whether mutation-positive unaffected individuals made proper use of the test (i.e., accepted endoscopic surveillance); and 3) to investigate the main findings of endoscopic surveillance in gene carriers.	Cross-sectional	Members of families with verified HNPCC germline mutation	164 from 32 families	Chart review
Dewanwala 2011, United States[210]	To examine the attitudes toward child-bearing and prenatal genetic testing among individuals undergoing genetic evaluation for LS.	Survey	Adults (≥ 18) with personal or family history suggestive of LS	161	Questionnaire
Esplen 2001, Canada and United States[174]	To systematically examine the attitudes and motivations associated with genetic testing for HNPCC, the current levels of psychosocial functioning of individuals engaged in the genetic testing process, and patterns of disclosure for receiving those results.	Survey	Adults (≥ 18) with personal or family history suggestive of HNPCC, and eligible for genetic testing	50	Questionnaire

First Author Publication Year, Country of Origin[a]	Study Objectives	Study Design	Inclusion Criteria	Sample Size	Data Collection Methods
Esplen 2003, Canada[203]	To describe current distress levels in a sample of high- and intermediate-risk CRC patients who have provided a blood sample for genetic testing, and explore the relationship between variables associated with current pre-test distress, and post-test distress.	Survey	Cases: Adults (> 20) with high or intermediate risk of CRC and cancer of the large bowel; FDR of cases and family history suggestive of hereditary cancer	220	Questionnaire
Esplen 2007, Canada[177]	To assess the psychosocial impact of genetic counselling and testing among individuals undergoing HNPCC genetic testing.	Survey	Adults (> 18) with CRC	314	Questionnaire
Esplen 2015, Canada[211]	To examine the longer-term psychosocial and behavioural impact on individuals undergoing genetic testing for LS in two Canadian familial CRC registries.	Survey	Adults (≥ 18) who were confirmed either mutation positive or negative	155	Questionnaire
Fantini 2007, France[206]	To characterize people who participate in a screening program for hereditary CRC, and to determine whether people at risk who test for inherited CRC are likely to develop a higher level of psychological distress than the norm.	Survey	Adults at risk for HNPCC, with or without cancer diagnosis	77	Questionnaire
Glanz 1999, United States[164]	To identify the sociodemographic, psychosocial, and social influence factors related to intentions to participate in genetic testing and genetic counselling for CRC risk among persons from 3 ethnic groups who are at increased family risk.	Survey	Cases: Adults (> 20) with cancer of the large bowel; FDR (> 18) of cases (excluding parents) without cancer diagnosis	426	Questionnaire
Graves 2014, United States[197]	To evaluate a telephone protocol for returning research results of MMR gene testing to identify LS.	Survey	Members of families with verified *hMSH2*, *hMLH1*, *hMSH6*, *hPMS2* mutation	Baseline: 107 6-month follow-up: 85	Questionnaire, interview

First Author Publication Year, Country of Origin[a]	Study Objectives	Study Design	Inclusion Criteria	Sample Size	Data Collection Methods
Gritz 1999, United States[226]	To examine the association between baseline measures of attitudes toward genetic testing and counselling for HNPCC and the affective state of patients who had given blood for a HNPCC genetic testing study.	Survey	Adults (≥ 18) HNPCC patients	269	Questionnaire
Palmquist 2010[165]	To explore the familial context of risk perception formation in 3 families with a documented genetic susceptibility to LS.	Qualitative description	Adults FDR (> 18) at 25% or 50% risk of dMMR mutation; member of a family with verified dMMR mutation or currently undergoing LS testing (including spouses)	26 from 3 families	Interview
Gritz 2005[225]	To examine the impact of HNPCC genetic test results on psychological outcomes among cancer-affected and -unaffected participants up to 1 year after results disclosure.	Survey	Cases: Diagnosed with CRC with a family history suggestive of hereditary cancer; relatives of HNPCC mutation-positive patients at 25% or 50% risk	155	Questionnaire
Pentz 2005[231]	To describe HNPCC family members' perceptions about who has a right to know about a genetic mutation in the family and who should disclose this information to family members, with a focus on the role that should be played by health professionals in disseminating this information.	Qualitative description	Members of families with verified HNPCC mutation, or undergoing testing, or family with at least 5 members at 50% risk	80 from 16 families	Interview

First Author Publication Year, Country of Origin[a]	Study Objectives	Study Design	Inclusion Criteria	Sample Size	Data Collection Methods
Koehly 2003[221]	1) To describe the composition of familial networks; 2) to characterize the patterns of family functioning and genetic counselling and testing discussions within the families; 3) to examine how the patterns, or the familial culture, were related to discussing genetic counselling and testing among family members; 4) to identify the characteristics of individuals with the most influence in the family.	Qualitative design, using Social Network methodology	Member of family with verified HNPCC mutation (including spouses)	36 from 5 families	Interview
Peterson 2003[166]	To describe how information about the identification of an HNPCC gene mutation was disseminated in 5 families, when and under what circumstances this information was shared, and how family members reacted to and acted on this information.	Qualitative description	Adults (≥ 18) from a family with a verified HNPCC mutation and at least 5 members at 50% risk	39 from 5 families	Interview
Vernon 1999[195]	To assess the association between intention to learn genetic test results and sociodemographic factors, medical history, psychosocial factors, attitudes, beliefs, and decisional considerations related to genetic testing.	Survey	Patients with CRC, and unknown mutation status	269	Questionnaire
Hadley 2003, United States[170]	To assess CRC screening behaviours of index cases with indeterminate HNPCC genetic test results and their at-risk FDRs, and what relational factors affect CRC screening in families in which the index case received indeterminate genetic test results.	Survey	Member of family with verified HNPCC mutation	104	Questionnaire
Eliezer 2014[230]	To explore how personal genetic test results and immediate and extended family members' test results for LS shape subsequent cancer distress, cancer worry, and depression.	Survey	Member of family with verified mutation	179 from 26 families	Questionnaire

First Author Publication Year, Country of Origin[a]	Study Objectives	Study Design	Inclusion Criteria	Sample Size	Data Collection Methods
Morris 2013[232]	To investigate relationships between spirituality (consisting of religious and existential well-being) and: 1) psychological factors (perceived cancer risk and worry, depressive symptoms, and cancer-related distress); 2) family network characteristics (social support and family communication regarding risk and genetic testing); and 3) screening practices for CRC.	Survey	Adults from families with verified HNPCC mutations	123 from 34 families	Questionnaire
Ersig 2011[257]	To examine the association of selected individual and relational characteristics with communication about HNPCC, and compare these associations between families with and without identified mutations.	Cross-sectional	Probands: mutation-positive status; FDR of probands	Index cases: 20 FDRs: 31	Interview
Ersig 2010[251]	To explore thoughts about and response to risk for HNPCC in the context of indeterminate genetic test results.	Qualitative description	Probands: indeterminate mutation status with HNPCC-associated cancer or met eligibility criteria for testing; FDR of probands	Index cases: 10 FDRs: 16 from 11 families	Interview
Hadley 2010[234]	To examine whether previous family experiences with genetic services for the inherited cancer susceptibility syndrome known as LS were associated with a decline or increase in baseline levels of depressive symptoms, disease worry, and genetic test–related distress among family members who receive genetic services at more distant time intervals.	Survey	Member of family with verified mutation	297 from 38 families	Questionnaire

First Author Publication Year, Country of Origin[a]	Study Objectives	Study Design	Inclusion Criteria	Sample Size	Data Collection Methods
Ashida 2009[236]	1) To investigate the associations between perceived family relationships before genetic testing as well as changes in perceptions 6 months after results disclosure and the changes in depression scores over a 12-month period after disclosure; and (2) To evaluate the moderating effect of family norms and discrepancy in worry about cancer on these associations.	Survey	Families with verified LS or at risk for inheriting a mutation	178 from 24 families	Questionnaire
Ersig 2009[214]	To examine CRC screening by endoscopy and disclosure of genetic test results among index cases at risk for HNPCC in the year after genetic test results were received. Of particular interest were the effects of mutation status (mutation-positive vs. inconclusive) and disclosure of the genetic test result to others on endoscopy completion.	Survey	Adults (≥ 18) with at least one HNPCC-associated cancer diagnosis, and a personal or family history suggestive of hereditary cancer	69	Questionnaire
Ersig 2009[209]	To compare colonoscopy screening, and the effect of relational factors on screening, between families with indeterminate and mutation-positive HNPCC genetic test results.	Survey	Individuals who underwent genetic testing and their adult children and siblings	46	Questionnaire, interview
Palmer 2005[245]	To describe how signal detection methods could be used to evaluate the impact of counselling and testing for susceptibility genes.	Survey	Members of a family with verified HNPCC mutation, without cancer diagnosis	56	Questionnaire
Hadley 2004[215]	To assess endoscopy use and predictors of adherence to endoscopy screening guidelines after the receipt of positive- and true negative HNPCC mutation results among asymptomatic individuals in families with known HNPCC mutation.	Survey	Adults (≥ 18) without a cancer diagnosis, at 50% risk of HNPCC mutation	56	Questionnaire
Halbert 2004, United States[212]	1) To assess whether genetic testing for HNPCC mutations and receipt of positive test results have an effect on the use of	Survey	Members of families with verified HNPCC	98	Interview, questionnaire

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	colonoscopy; 2) to identify factors associated with adherence to identify potential barriers to patient compliance.		mutation at 25% risk of inheriting mutation		
Ho 2003, China[182]	1) To study the decisional consideration process of Hong Kong Chinese toward genetic testing of CRC; and (b) to examine factors affecting decisional consideration of CRC genetic screening testing.	Survey	Individuals belonging to a Hereditary Gastrointestinal Cancer Registry	62 from 35 families	Questionnaire
Johnson 2002, United States[213]	To evaluate, in a clinic population, the impact of both genetic counselling and testing on subsequent CRC screening behaviour.	Cross-sectional	Patients without a cancer diagnosis, at risk of HNPCC	65	Chart review
Keller 2004, Germany[167]	To evaluate the uptake of genetic counselling in a nonselected sample of patients at risk for HNPCC.	Survey	Cases: adults (≥ 18), had surgery for CRC- or HNPCC-associated cancers with a family history suggestive of hereditary cancer; relatives of probands	25	Questionnaire
Keogh 2009, Australia[198]	To assess whether knowledge of insurance implications influenced uptake of genetic testing by participants in a research study of the causes of CRC.	Pre-post	Cases: CRC diagnosis before age of 45 years; FDR and SDR of probands	106 (47 from the original protocol; 59 in the modified protocol)	Chart review
Kidambi 2015, United States[199]	To examine 2 different IHC-based LS screening protocols at an urban, university hospital: selective screening based on criteria and universal screening of all CRC patients — in terms of number of LS cases identified.	Chart review	Patients with surgically resected CRC	392 (107 selective; 285 universal)	Chart review
Kinney 2000, United States[181]	To examine the level of interest in genetic testing for heritable CRC in African-American and white patients, and assess	Survey	Adults (≥ 18) with CRC	98	Structured Interview

First Author Publication Year, Country of Origin[a]	Study Objectives	Study Design	Inclusion Criteria	Sample Size	Data Collection Methods
	psychological factors and knowledge of the availability of genetic testing for CRC.				
Kinney 2000, United States[202]	To determine colorectal cancer screening behaviours, risk perceptions, and willingness to receive genetic testing to determine colorectal cancer susceptibility in FDRs of CRC patients.	Survey	FDR of persons with CRC	95	Structured interview
Kohut 2007, Canada[217]	To survey participants of the OFCCR regarding their duty to warn family members about a HNPCC-causing mutation.	Survey	High-risk individuals in patient registry; intermediate-risk individuals with personal or family history suggestive of hereditary cancer	105	Questionnaire
Kupperman 2013, United States[216]	To measure patient preferences (utilities) for scenarios entailing differing decisions regarding test use and risk-reducing surgeries and their associated outcomes among a group of individuals with a wide range of familiarity and experience with LS testing.	Cross-sectional	Individuals having undergone genetic testing and counselling for LS; NR for patients unknowledgeable about LS	70	Questionnaire, preference elicitation (time trade off)
Landsbergen 2011, Netherlands[223]	To investigate whether high levels of overall psychological distress are present during MSI testing and whether these levels are correlated with time since CRC diagnosis.	Survey	Patients with CRC, or eligible for MSI testing	89	Questionnaire
Landsbergen 2012[233]	To investigate general distress and cancer-specific distress in CRC patients during their treatment phase who meet criteria for MSI testing indicated by a pathologist.	Survey	Patients with CRC diagnosed before age 50 years, or second CRC diagnosed before 70 years (including partners)	CRC patients: 81 Partners: 50	Questionnaire
Landsbergen 2009, Netherlands[194]	To explore the reactions of patients to the offer of genetic testing in the period directly after surgical removal of the tumour.	Qualitative description	Patient with CRC and MSI-positive tumour	8	Interview, chart review

First Author Publication Year, Country of Origin[a]	Study Objectives	Study Design	Inclusion Criteria	Sample Size	Data Collection Methods
Leenan 2016, Netherlands[183]	1) To evaluate experiences and attitudes toward a family-mediated approach in an LS cohort; 2) to compare tested (mutation carriers and non-carriers) and non-tested individuals on demographic characteristics, anxiety, cancer worry, medical history, family communication, experiences and attitudes toward the family-mediated approach; and 3) to explore the motivations for uptake or decline of genetic testing for LS.	Survey	Individuals with a personal or family history of LS	129 from 33 families	Questionnaire
Lerman 1996, United States[175]	To explore how patients might react both to the availability of genetic testing for CRC susceptibility and to disclosure of genetic test results.	Survey	FDR of persons with CRC	45	Structured interview
Lindor 2004, United States[180]	To explore which patients opted to learn their results, to determine what reasons they had for deciding to learn results, to determine the effect of detail (an in-depth explanation of testing versus a brief overview), and to assess global psychological reactions to being offered and receiving these complex test results via a written communication.	Survey	Patients with CRC diagnosed before age 50 years; individuals with a family history suggestive of hereditary cancer	414	Questionnaire
Loader 2005, United States[169]	To assess the impact of a genetic evaluation for CRC genetic susceptibility including whether counselled individuals remember the information provided, change their behaviour, and alert their relatives to their potential risk.	Survey	Patients with CRC diagnosed before age 60 years with a FDR or SDR with CRC	37	Questionnaire, interview
Lynch 1999, United States[171]	To describe experiences with DNA-based genetic counselling with 7 HNPCC families, 5 of which showed *hMLH1* and two of which manifested *hMSH2* germline mutations.	Unclear	NR	199 from 7 families	Interviews, during counselling sessions

First Author Publication Year, Country of Origin[a]	Study Objectives	Study Design	Inclusion Criteria	Sample Size	Data Collection Methods
Manne 2007, United States[191]	1) To characterize the level of knowledge about the purpose and results of the MSI test among individuals considering this test, and to describe the level of previous exposure to information about the MSI test; 2) to characterize motivations for (perceived benefits) and against (perceived barriers) having the MSI test; 3) to examine the contribution of attitudinal and non-attitudinal variables to perceived benefits and barriers of MSI testing.	Cross-sectional data collected as part of an RCT	Individuals eligible for genetic testing (rBG criteria)	125	Questionnaire
McCann 2009, United States[186]	To explore the factors influencing family communication about genetic risk of CRC and colonoscopy among people who had a strong family history of CRC who were attending a genetic clinic with a view to having a genetic test for HNPCC.	Qualitative Description	Individuals with a strong family history of CRC	30 from 17 families	Interview
Meiser 2004, Australia[200]	To assess psychological impact and screening behaviours in both carriers and non-carriers of mutations pre-disposing to HNPCC, at baseline, 1 year, and 3 years after genetic testing.	Survey	Members of a family with verified HNPCC mutation	114	Questionnaire
Collins 2007[246]		Survey	Individuals undergoing predictive genetic testing, without a personal history of HNPCC-associated cancers or CRC	73	Questionnaire
Collins 2005[247]		Survey	Individuals undergoing predictive genetic testing, without a personal history of HNPCC-associated	98	Questionnaire

First Author Publication Year, Country of Origin[a]	Study Objectives	Study Design	Inclusion Criteria	Sample Size	Data Collection Methods
			cancers or CRC		
Mesters 2005, Netherlands[219]	To investigate people's perspective regarding informing one's biological family on the hereditary predisposition for HNPCC.	Qualitative description	Individuals with a family history suggestive of hereditary cancer	30	Interview
Murakami 2004, Japan[228]	To identify the prevalence and predictive factors of major and minor depression, acute stress disorder, PTSD, and post-traumatic stress symptoms after the disclosure of genetic test results for HNPCC in Japanese individuals, both in probands affected with cancer and in unaffected relatives.	Pre-post	Members of family (≥ 20) with verified *hMLH1*/*hMSH2* mutation	42	Interview, questionnaire
Petersen 1999, United States[207]	To examine the relationship between family history, risk perception, and interest in CRC gene testing.	Survey	Adults (> 18) without a cancer diagnosis, and at least one FDR with CRC	Surveys: 1,217 Interviews: 156	Questionnaire
Ramsey 2010, United States[235]	1) To determine how a hypothetical test for gene variants associated with a moderately increased CRC risk might influence individuals' health-related quality of life, cancer worry, health habits, and screening behavior; 2) to determine whether an individual's family history of CRC (and thus his/her current estimate of cancer risk) modified these issues.	Survey	Cases: Adults (> 18) with CRC; FDR of cases; population-based controls	Population-based controls: 170 FDRs: 310	Questionnaire
Ramsey 2003, United States[190]	1) To examine beliefs about and key issues related to testing for CRC susceptibility genes; and 2) to compare the relative importance of these issues and how they influence willingness to accept testing among the 3 groups (CRC patients, FDRs of CRC patients, and people with no personal or family history of CRC).	Qualitative description	Patients from registry, and their FDRs; population controls	CRC patients: 6 FDRs: 4 FDRs Controls: 5	Focus group
Reeve 2000, New Zealand[193]	To examine the impact of genetic testing for HNPCC by intensive study of the only group	Qualitative description	Individuals tested for HNPCC	7	Interview

First Author Publication Year, Country of Origin[a]	Study Objectives	Study Design	Inclusion Criteria	Sample Size	Data Collection Methods
	in New Zealand to have undergone genetic testing for HNPCC.				
Roygnan 2008, France[204]	To observe how probands deal with the transmission of the genetic information to their families; to let them talk freely about how they felt and how they told their relatives.	Qualitative description	Mutation-positive individuals	7	Interview
Shiloh 2008, United States[238]	1) To examine the distress and depression levels of individuals testing for HNPCC mutations prospectively from baseline (before testing) through 6 and 12 months after disclosure of test results; 2) to explore the modifying effects of mutation status and monitoring coping styles on distress and depression; and 3) to explore interactions between mutation status and monitoring coping style.	Survey	Cases: patients with CRC or endometrial cancer diagnosed before age 40 with tumours consistent with HNPCC, or with family history suggestive of HNPCC; family members of cases with identified mutations	253 (67 index cases and 186 family members at risk)	Questionnaire
Shipman 2013, United Kingdom[176]	To gain insight from those who have undergone MMR tumour testing and to assess the significance that testing holds for them. Of particular interest are the ways in which respondents “account” for testing via displays of knowledge and responsibility.	Qualitative description	Individuals consenting to MSI testing without prior genetic counselling	11	Interview
Stoffel 2008, United States[218]	To examine how genetic testing information is communicated in families at risk for LS, and to identify factors associated with disclosure of genetic test results to close and distant family members.	Survey	Adults (> 18) with a personal or family history suggestive of hereditary cancer (BG)	174	Questionnaire

First Author Publication Year, Country of Origin[a]	Study Objectives	Study Design	Inclusion Criteria	Sample Size	Data Collection Methods
Tomiak 2014, Canada[178]	1) To investigate the different factors affecting uptake of genetic counselling and testing in newly diagnosed CRC patients being seen in a Canadian academic hospital Cancer Assessment Clinic; 2) to examine the experience of individuals facing a choice about genetic counselling and/or testing in the context of newly diagnosed CRC, focusing on motivations and barriers encountered.	Qualitative description	Patients with CRC eligible for genetic testing	19	Interview
van Oostrom 2007, Netherlands[240]	To explore predictors for hereditary cancer distress 6 months after genetic susceptibility testing for a known familial *BRCA1/2* or HNPCC-related mutation, in order to gain insight into aspects relevant for the identification of individuals needing additional psychosocial support.	Survey	Adults at 50, 25, or 12.5% risk for known familial BRCA1/2 or HNPCC mutations	HNPCC: 96	Questionnaire
van Oostrom 2007[227]	To study differences between individuals opting for genetic cancer susceptibility testing of a known familial *BRCA1/2* and HNPCC-related germline mutation.	Survey	Adults at 50%, 25%, or 12.5% risk for known familial *BRCA1/2* or HNPCC mutations	HNPCC: 96	Questionnaire
van Oostrom 2007[241]	To examine prospectively the contribution of family functioning, differentiation to parents, family communication and support from relatives to psychological distress in individuals undergoing genetic susceptibility testing for a known familial pathogenic *BRCA1/2* or HNPCC-related mutation.	Survey	Adults (≥ 18) from a family with a verified HNPCC mutation or *BRCA1/2* mutation, with or without a personal history of cancer	HNPCC: 96	Questionnaire
van Oostrom 2006[242]	To explore the effect of age at the time of parental cancer diagnosis or death on psychological distress and cancer risk perception in individuals undergoing genetic testing for a specific cancer susceptibility.	Survey	Adults at 50%, 25%, or 12.5% risk for known familial *BRCA1/2* or HNPCC mutations	HNPCC: 96	Questionnaire

First Author Publication Year, Country of Origin[a]	Study Objectives	Study Design	Inclusion Criteria	Sample Size	Data Collection Methods
Vernon 1997, United States[249]	To describe the demographic and psychosocial correlates of 2 measures of psychologic distress (depression and anxiety) among 200 CRC patients undergoing genetic testing for HNPCC.	Cross-sectional	Patients with CRC with unknown mutation status	200	Questionnaire
Wagner 2005, Netherlands[201]	To evaluate the use of colonoscopy by proven HNPCC mutation carriers, and satisfaction with the counselling and screening procedures in the long term.	Survey	Individuals with known MMR gene mutations	70	Questionnaire
Wakefield 2007, Australia[168]	To describe the perceived pros and cons reported by individuals who have undergone at least one genetic counselling consultation, as well as having completed a genetic testing decision aid, before considering genetic testing for HBOC or HNPCC risk.	Qualitative description	Adults eligible for HBOC or HNPCC testing	22	Questionnaire, chart review
Walsh 2012, United States[185]	To establish key characteristics that patients, consumers, and health professionals consider in decision-making about being tested for hereditary LS.	Qualitative description	Patients with CRC, or at high risk for CRC; average-risk individuals; physicians; genetic counsellors	8	Focus group
Watkins 2011, Canada[208]	To explore how confirmed carriers experience disease management and view the quality of interactions with health care providers and the overall health care system.	Grounded theory	Member of family with known *MSH2* mutation	23	Interview
Yamashita 2008, Japan[239]	To investigate the psychological impact of disclosure of genetic test results and the factors associated with it, especially focusing on memory function, in participants who underwent genetic testing for HNPCC and were informed of the results.	Survey	Adults (> 20) with family history suggestive of HNPCC	46	Questionnaire

BG = Bethesda Guidelines; CRC = colorectal cancer; dMMR = deficient mismatch repair; FAP = familial adenomatous polyposis; FDR = first-degree relative; HBOC = hereditary breast–ovarian cancer syndrome; HNPCC = hereditary non-polyposis colorectal cancer; LS = Lynch syndrome; MMR = mismatch repair; MSI = microsatellite instability; NR = not reported; OFCCR = Ontario Familial Colon Cancer Registry; PTSD = post-traumatic stress disorder; rBG = revised Bethesda Guidelines; SDR = second-degree relative.
[a] Studies with a common (sub) sample of patients are grouped together, with the primary study left-justified in the cell and related studies right-justified in subsequent rows.

Appendix 54: Characteristics of Included Study Participants (Question 7)

First Author Publication Year, Country of Origin[a]	Sample Size	Sex (% Male; % Female; NR)	Mean Age in Years (SD)	Race[b]	Education[b]	Income	Relationship Status	% With Children	Mutation Status
Aktan-Collan 2011, Finland[196]	248	48.8% male 51.2% female	56.4 (9.0) Range 41 to 82	NR	12.0 years (mean) 3.8 years (SD)	NR	76% Married/ cohabiting	None: 0% 1: 24% 2: 40% 3: 25% 4: 11%	Mutation positive: 100%
Aktan-Collan 2000, Finland[172]	Baseline: 446 1-month follow-up: 299 1-year follow-up: 271	49% male 51% female	43 (NR) Range18 to 79	NR	33% Highest level of education is upper secondary or university 67% Highest level of education is primary or vocational education	NR	66% Married/ cohabiting	71%	Mutation positive: 30% Mutation negative: 70%
Aktan-Collan 2013[179]	208	42.3% male 57.7% female	44.3 (SD 13.1)	NR	11.3 years (mean) 3.5 years (SD)	NR	73.5% Married/ cohabiting	100%	Mutation positive: 30% Mutation negative: 70%
Aktan-Collan 2001[224]	271	43% male 57% female	43 (NR) Range 19 to 77	NR	62% Educated beyond primary level	NR	72% Married/cohabiting	73%	Mutation positive: 31%
Aktan-Collan 2001[248]	271	43% male 57% female	43 (SD) Range 19 to 77	NR	62% Educated beyond primary level	NR	72% Married/cohabiting	73%	Mutation positive: 31%
Aktan-Collan 2001[229]	271	Mutation negative: 41% male 59% female Mutation positive: 46% male 54% female	Mutation negative: 45.6 (12.9) Mutation positive: 37.8 (11.5)	NR	Mutation negative: 11.0 years (mean) 3.5 years (SD) Mutation positive: 12.1 years (mean) 3.2 years (SD)	NR	Mutation negative: 74% Married/ cohabiting Mutation positive: 68% Married/ cohabiting	Mutation Negative: 78% Mutation Positive: 64%	Mutation positive: 31% Mutation negative: 69%
Arver 2004, Sweden[188]	21	100% female	42.7 (15.5)	NR	NR	NR	NR	NR	Mutation positive: 33% Mutation negative: 77%

First Author Publication Year, Country of Origin[a]	Sample Size	Sex (% Male; % Female; NR)	Mean Age in Years (SD)	Race[b]	Education[b]	Income	Relationship Status	% With Children	Mutation Status
Balmana 2004, United States[243]	37	30% male 70% female	43.3 (12.9)	94% Caucasian 0% African-American 6% Latin 0% Asian-American	49% < College 51% > College	42.5% < $75,000 57.5% > $75,000	30% Single, divorced or widowed 70% Married/ cohabiting	76%	NR
Barrow 2015, United Kingdom[187]	591	NR	NR	NR	NR	NR	NR	NR	NR
Broderson 2004, United Kingdom[244]	437	31% male 69% female	NR	NR	NR	NR	NR	NR	NR
Bruwer 2013, South Africa[163]	80	31% male 69% female	40.8 (SD) Range 21-70	93% Mixed ancestry (Coloured population) and spoke Afrikaans 7% Caucasian with English as a first language	NR	NR	64% Married/ cohabiting	None: 12.5% 1: 21.3% 2: 28.8% 3: 27.5% 4: 7.5% 5: 2.5%	Mutation positive: 100%
Burton-Chase 2014, United States[222]	74	100% female	40 (8.7) Range 25 to 64	92% White	62% College or higher	NR	72% Married/ cohabiting	77%	Mutation positive: 78% Amsterdam II criteria: 22%
Carlsson 2007, Sweden[205]	19	Mutation carriers: 55% male 45% female Non-carriers: 37% male 63% female	Mutation carriers: 51 (Range 33 to 75) Non-carriers: 47 (Range 36 to 64)	NR	NR	NR	NR	NR	Mutation positive: 58% Mutation negative: 42%

First Author Publication Year, Country of Origin[a]	Sample Size	Sex (% Male; % Female; NR)	Mean Age in Years (SD)	Race[b]	Education[b]	Income	Relationship Status	% With Children	Mutation Status
Ceballos 2008, United States[237]	Cases: 45 Relatives: 102	Cases: 56% male 44% female Relatives: 44% male 56% female	Cases: 60 (12), Range 38 to 81 Relatives: 52 (15), Range 23 to 86	Cases: 89% Caucasian 11% other Relatives: 94% Caucasian 6% other	Cases: 4% < High school 20% High school 27% Some college 49% College/graduate degree Relatives: 10% < High school 21% High school 34% Some college 35% College/graduate degree	Cases: 16% < $30,000 38% $30,000 to $69,999 47% > $70,000 Relatives: 23% < $30,000 44% $30,000 to $69,999 33% > $70,000	NR	NR	NR
Claes 2004, Belgium[173]	Carriers: 19 Non-carriers: 21	Carriers: 58% male 42% female Non-carriers: 57% male = 43% female	Carriers: 40.7 (11.4), Range 22 to 60 Non-carriers: 42.7 (10.9), Range 19 to 64	NR	Carriers: 47% < High school 11% High school 42% > High school Non-Carriers: 29% < High school 19% High school 52% > High school	NR	Carriers: 21% Single 79% Stable relationship Non-carriers: 14% Single 86% Stable relationship	Carriers: 74% Non-carriers: 67%	Mutation positive: 48% Mutation negative: 52%
Claes 2005, Belgium[192]	Carriers: 36 Non-carriers: 36	Carriers: 67% male 33% female Non-carriers: 53% male 47% female	Carriers: 38.5 (10.0), Range 18 to 60 Non-carriers: 40.0 (11.8), Range 19 to 67	NR	Carriers: 50% < High school 8% High school 42% > High school Non-carriers: 31% < High school 14% High school 55% > High school	NR	Carriers: 19% No stable relationship 81% Stable relationship Non-carriers: 8% No stable relationship 92% Stable relationship	Carriers: 69% Non-carriers: 64%	Mutation positive: 50% Mutation negative: 50%

First Author Publication Year, Country of Origin[a]	Sample Size	Sex (% Male; % Female; NR)	Mean Age in Years (SD)	Race[b]	Education[b]	Income	Relationship Status	% With Children	Mutation Status
Codori 1999, United States[250]	Acceptors: 77 Decliners: 181 From 95 families	Acceptors: 45% male 55% female Decliners: 41% male 59% female	Acceptors: median = 44 (IQR = 23, range 19 to 70) Decliners: median = 50 (IQR = 22, range 22 to 83)	Acceptors: 96% Caucasian Decliners: 100% Caucasian	Acceptors: 16 years (median) 4 years (IQR) Decliners: 15 years (median) 6 years (IQR)	NR	Acceptors: 71% Married/ cohabiting Decliners: 75% Married/ cohabiting	NR	
Cragun 2012, United States[184]	91	59% male 41% female	65.0 (11.9) Range 35 to 93	94.4% White	65.5% At least some college	NR	69.2% Married/cohabiting	NR	NR
de Leon 2004, Italy[189]	164 from 32 families	NR	NR	NR	NR	NR	NR	NR	
Dewanwala 2011, United States[210]	161	29% male 71% female	46.1 (NR) Range 20 to 75	95% White	72% College graduate	79.8% < $50,000 20.2% ≥ $50,000	69.7% Married/ cohabiting 30.3% Not married/ cohabiting	68%	NR
Esplen 2001, Canada and United States[174]	Mutation positive: 23 Mutation negative: 7 Waiting for test result: 20	Mutation positive: 30% male 70% female Mutation negative: 43% male 57% female Waiting for test result: 40% male 60% female	Mutation positive: 44.3 (15.0) Mutation negative: 40.3 (6.8) Waiting for test result: 51.8 (14.8)	NR	NR	NR	NR	NR	NR

First Author Publication Year, Country of Origin[a]	Sample Size	Sex (% Male; % Female; NR)	Mean Age in Years (SD)	Race[b]	Education[b]	Income	Relationship Status	% With Children	Mutation Status
Esplen 2003, Canada[203]	220	48% male 52% female	63 (9.6)	NR	52% High school or less 48% Post-secondary	NR	79% Married/ cohabiting 21% Never married, divorced or widowed	NR	NR
Esplen 2007, Canada[177]	314	47% male 53% female	62.1 (9.7)	75% Anglo/North American 18% Anglo/European	52% High school or less 48% College or more	40% $21,000 to $50,000 28% $51,000 to $80,000 9% > $81,000	80% Married/ cohabiting 20% Single/divorced/ widowed	NR	NR
Esplen 2015, Canada[211]	155	Affected mutation positive: 47% male 52% female At-risk mutation positive: 37% male 63% female Mutation negative 40% male 60% female	Affected mutation positive: 56 (13), Range 26 to 78 At-risk mutation positive: 40 (11), Range 22 to 62 Mutation negative: 48 (12), Range 25 to 76	Affected mutation positive: 89% Anglo-Saxon At-risk mutation positive: 88% Anglo-Saxon Mutation negative: 95% Anglo-Saxon	Affected mutation positive: 46% High school or less 54% College or more At-risk mutation positive: 37% High school or less 63% College or more Mutation negative: 61% High school or less 39% College or more	NR	Affected mutation positive: 70% Married/ cohabiting 30% Single/divorced/ separated At-risk mutation positive: 82% Married/ cohabiting 18% single/divorced/ widowed Mutation negative: 86% Married/ cohabiting 14% single/divorced/ widowed	NR	NR
Fantini 2007, France[206]	77	49% male 51% female	44.27 (14.21)	NR	22% < High school 40% High school 37% University	NR	75% Married/ cohabiting 25% Non-married/divorced/ widowed	NR	NR

First Author Publication Year, Country of Origin[a]	Sample Size	Sex (% Male; % Female; NR)	Mean Age in Years (SD)	Race[b]	Education[b]	Income	Relationship Status	% With Children	Mutation Status
Glanz 1999, United States[164]	426	49% male 51% female	50.0 (16.4) Range 19 to 84	78.9% Japanese 11.7% Hawaiian or part-Hawaiian 9.4% Caucasian	35.7% High school or less 34.5% Some college 29.8% College graduate	NR	63.5% Married/ cohabiting 16.0% divorced, widowed or separated 20.5% never married	NR	NR
Graves 2014, United States[197]	Baseline: 107 6-month follow-up: 85	47% male 53% female	61.2 (14.9) Range 28 to 98	96.8% Caucasian 3.2% Non-Caucasian	23.8% High school or less 76.2% High school or higher	NR	NR	87.90%	Mutation positive: 41.1% Mutation negative: 58.9%
Gritz 1999, United States[226]	269	56% male 44% female	52% ≥50 years	88% White	32% High school or less				
Palmquist 2010[165]	26 from 3 families	42% male 58% female	Family A: 43 (NR), Range 21 to 63 Family B: 55 (NR), Range 23 to 82 Family C: 29 (NR), Range 21 to 56	1 Caucasian family 1 African-American family 1 Mexican-American family	NR	Family A: $46,000 (mean) Range $15,000 to $75,000 Family B: $34,000 (mean) Range $15,000 to $75,000) Family C: $32,000 (mean) Range < $15,000 to $75,000	NR	NR	NR
Gritz 2005[225]	155	Affected: 43% male 57% female Unaffected: 36% male 64% female	Affected: 47% ≥50 years Unaffected: :21% ≥50 years	Affected: 85% White Unaffected: 76% White	Affected: 32% ≤ High school 33% Some college 35% ≥ college Unaffected: 26% ≤ High school: 31% Some college 42% ≥ college	Affected: 59% ≤ $50,000 Unaffected: 54% ≤ $50,000	74% Married/ cohabiting	Affected: 80% Unaffected: 79%	Affected: Mutation positive: 37% Mutation negative: 63% Unaffected Mutation positive: 29% Mutation

First Author Publication Year, Country of Origin[a]	Sample Size	Sex (% Male; % Female; NR)	Mean Age in Years (SD)	Race[b]	Education[b]	Income	Relationship Status	% With Children	Mutation Status
									negative: 71%
Pentz 2005[231]	80 from 16 families	39% male 61% female	48 (NR) Range 21 to 81	85% White 10% Hispanic 5% African-American	18% ≤ High school 25% Some college 29% ≥ College graduate	43% ≤ $50,000 38% ≥ $50,000	71% Married/ cohabiting	84%	75% of families had a mutation
Koehly 2003[221]	36 from 5 families	42% male 58% female	49 (16.5) Range 21 to 82	NR	NR	NR	NR	NR	
Peterson 2003[166]	39 from 5 families	38% male 62% female	Family 1: 62 (NR), Range 23 to 81 Family 2: 39 (NR), Range 21 to 56 Family 3: 35 (NR), Range 28 to 45 Family 4: 63 (NR), Range 40 to 73 Family 5: 47 (NR), Range 21 to 63	4 Caucasian families 1 Hispanic family	Family 1: 4 of 10 completed college Family 2: 3 of 8 completed college Family 3: 6 of 7 completed college Family 4: 1 of 5 completed college Family 5: 0 of 9 completed college	Family 1: $59,000 (mean), $20,000 to $100,000 (range) Family 2: $32,000 (mean), < $15,000 to $75,000 (range) Family 3: $54,000 (mean), $20,000 to $100,000 (range) Family 4: $63, 000 (mean), $30,000 to 100,000 (range) Family 5: $34,000 (mean), $15,000 to $75,000 (range)	Number never married or divorced: Family 1: 1 of 10 Family 2: 3 of 8 Family 3: 4 of 7 Family 4: 0 of 5 Family 5: 1 of 9	NR	number personal history of HNPCC syndrome cancer family 1 (2 of 10); family 2 (3 of 8); family 3 (4 of 7); family 4 (1 of 5); family 5 (2 of 9)
Vernon 1999[195]	269	56% male 44% female	39% < 50 61% ≥ 50	88% White 12% Non-white	32% ≤ High school 67% > High school	33% ≤ $30,000 67% > $30,000	78% Married/ cohabiting 22% not married	84%	NR
Hadley 2003, United States[170]	104	43% male 57% female	43 (median) Range 18 to 83	87% White 7% African-American 3% Hispanic 2% Asian-American 1% Native-American	NR	48% < $50,000			

First Author Publication Year, Country of Origin[a]	Sample Size	Sex (% Male; % Female; NR)	Mean Age in Years (SD)	Race[b]	Education[b]	Income	Relationship Status	% With Children	Mutation Status
Eliezer 2014[230]	179 from 26 families	42% male 58% female	39 (NR) Range 18 to 72	97% White	NR	NR	60% Married/ cohabiting	NR	FDRs: Mutation positive: 60% Second and third degree relatives: Mutation positive: 45%
Morris 2013[232]	123 from 34 families	42% male 58% female	38.2 (12.75) Range 18 to 72	98.4% Caucasian	52.9% College/graduate degree	NR	56.9% Married/ cohabiting 29.3% Single	NR	NR
Ersig 2011[257]	Index cases: 20 FDRs: 31	Mutation positive: 16% male 84% female Indeterminate: 11% male 89% female	Mutation positive: 49.1 (15.0) Indeterminate: 48.6 (13.3)	100% Caucasian	Mutation positive: 52% College degree Indeterminate: 65% College degree	NR	Mutation positive: 72% Married/ cohabiting Indeterminate: Married/ cohabiting 65%	NR	NR
Ersig 2010[251]	Index cases: 10 FDRs: 16 from 11 families	Index cases: 20% male 80% female (n = 8) FDRs: 7% male 93% female	Index cases: 55.3 (8.3), Range 45 to 69 Children: 27.8 (7.3), Range 20 to 41 Siblings: 54.8 (5.3), Range 44 to 62	NR	NR	NR	NR	NR	NR
Hadley 2010[234]	297 from 38 families	41% male 59% female	42 (NR) Range 18 to 83	96% White	NR	NR	NR	NR	
Ashida 2009[236]	178 from 24 families	42% male 58% female	39.8 (14.8)	94.9% Caucasian 2.2% African-American	24.1% Graduate degree/training 52.8% College degree 22.2% High school diploma	NR	NR	NR	Mutation positive: 46.1%

First Author Publication Year, Country of Origin[a]	Sample Size	Sex (% Male; % Female; NR)	Mean Age in Years (SD)	Race[b]	Education[b]	Income	Relationship Status	% With Children	Mutation Status
Ersig 2009[214]	69	Mutation positive: 47% male 53% female Inconclusive: 32% male 68% female	Mutation positive: 47.1 (10.6) Inconclusive: 48.6 (11.6)	Mutation positive: 89.5% Caucasian Inconclusive: 93.5% Caucasian	NR	NR	Mutation positive: 78.9% Married/ cohabiting Inconclusive: 74.2% Married/ cohabiting	NR	Mutation positive: 55.1% Inconclusive: 44.9%
Ersig 2009[209]	46	11% male 89% female	54% > 50	100% Caucasian	Highest level of education completed = 3.70 (mean); 1.03 (SD) on a scale that includes 1= less than high school; 2 = high school graduate; 3 = vocational school/some college; 4 = college; 5= graduate school	NR	67% Married/ cohabiting	NR	Mutation positive: 50% Indeterminate: 50%
Palmer 2005[245]	56	Mutation negative: 28% male 72% female Mutation positive: 89% male 11% female	Mutation negative: 40.5 (13.4) Mutation positive: 32.6 (10.6)	Mutation negative: 94.9% White Mutation positive: 94.1% White	NR	Mutation negative: 61.5% < $50,000 Mutation positive: 29.4% < $50,000	NR	NR	Mutation positive: 30% Mutation negative: 70%
Hadley 2004[215]	56	Mutation negative: 28% male 72% female Mutation positive: 89% male 11% female	Mutation negative: 40.5 (13.4) Mutation positive: 32.6 (10.6)	Mutation negative: 94.9% White Mutation positive: 94.1% White	NR	Mutation negative: 61.5% < $50,000 Mutation positive: 29.4% < $50,000	NR	NR	Mutation positive: 30% Mutation negative: 70%
Halbert 2004, United States[212]	98	32% male 68% female	68% ≥ 40 32% < 40 years	NR	56% > High school 44% ≤ High school	NR	72% Married/cohabiting 28% Not married	NR	Mutation positive: 22% Mutation negative: 50%

First Author Publication Year, Country of Origin[a]	Sample Size	Sex (% Male; % Female; NR)	Mean Age in Years (SD)	Race[b]	Education[b]	Income	Relationship Status	% With Children	Mutation Status
									Decliners: 28%
Ho 2003, China[182]	62 from 35 families	61% male 39% female	42 (9.9) Range 18 to 68	NR	NR	NR	NR	NR	Mutation positive: 25.8% Mutation negative: 19.4% Awaiting test results: 32.3% Non-tested: 22.6%
Johnson 2002, United States[213]	65	49% male 51% male	26.2% < 50 73.8% ≥ 50	100% White	NR	NR	NR	NR	
Keller 2004, Germany[167]	Participated in information session: 25 Did not participate in information session: 48	Participants: 68% male 32% female Non-participants: 42% male 58% female	Participants: 24% < 40 years, 56% 41 to 60 years, 20% > 60 years Non-participants 19% < 40 years, 60% 41 to 60 years, 21% > 60 years	NR	Participants: 32% < 10 years 36% 10 to 12 years 32% > 12 years Non-participants: 35% < 10 years 27% 10 to 12 years 38% > 12 years	NR	NR	NR	NR
Keogh 2009, Australia[198]	Original ethics protocol: 47 Modified ethics protocol: 59	Original protocol: 53% male 47% female Modified protocol: 41% male 59% female	Original protocol: 46.8 (13.7) Modified protocol: 51.0 (13.9)	NR	Original protocol: 51% Higher education Modified protocol: 54% Higher education	NR	NR	NR	NR
Kidambi 2015, United States[199]	Selective screening: 107 Universal screening: 285	Selective screening: 39% male 61% female Universal screening: 50% male 50% female	Selective screening: 49.4 (15.0) Universal screening: 59.3 (13.9)	NR	NR	NR	NR	NR	Mutation positive: 9.9%

First Author Publication Year, Country of Origin[a]	Sample Size	Sex (% Male; % Female; NR)	Mean Age in Years (SD)	Race[b]	Education[b]	Income	Relationship Status	% With Children	Mutation Status
Kinney 2000, United States[181]	98	51% male 49% female	64 (13) Range 29 to 90	81% White 19% African-American	20% < High school 45% High school 35% College graduate	NR	71% Married/ cohabiting 29% Not married	NR	NR
Kinney 2000, United States[202]	95	36% male 64% female	44 (13) Range 18 to 72	80% Caucasian 10% African-American 2% Asian	37% ≤ High school 63% College	NR	62% Married/cohabiting 38% Not married	NR	
Kohut 2007, Canada[217]	105	NR	NR	NR	NR	NR	NR	NR	NR
Kupperman 2013, United States[216]	General practice: 49 CRC program: 21	General practice: 29% male 71% female CRC program: 62% male 38% female	52.3 (NR)	67% White	72% College degree	47% > $100,000	49% Married/cohabiting	54%	
Landsbergen 2011, Netherlands[223]	89	36% male 64% female	55 (median) Range 32 to 85	NR	NR	NR	83% Married/ cohabiting	88%	NR
Landsbergen 2012[233]	CRC patients: 81 Partners: 50	Mutation positive: 52% male 48% female Mutation negative: 50% male 50% female	Mutation positive: 48 (10) Mutation negative: 48 (12)	NR	Mutation positive: 61% > High school Mutation negative: 52% > High school	NR	Mutation positive: 100% Married/ cohabiting Mutation negative: 86% Married/ cohabiting	Mutation Positive: 91% Mutation Negative: 89%	
Landsbergen 2009, Netherlands[194]	8	NR	NR	NR	NR	NR	NR	NR	NR

First Author Publication Year, Country of Origin[a]	Sample Size	Sex (% Male; % Female; NR)	Mean Age in Years (SD)	Race[b]	Education[b]	Income	Relationship Status	% With Children	Mutation Status
Leenan 2016, Netherlands[183]	129 from 33 families who had been tested 16 who had not been tested	Mutation carriers: 44% male 56% female Mutation negative: 34% male 66% female Non-tested: 38% male 62% female	Mutation carriers: 52 (14) Mutation negative: 67 (13) Non-tested: 42 (17)	NR	Mutation carriers: 41% Higher education Non-carriers: 29% Higher education Non-tested: 38% Higher education	NR	Mutation carriers: 78% Married/ cohabiting 8% Single 12% Divorced/separated/ widowed Non-carriers: 76% Married/ cohabiting 10% Single 11% Divorced/separated/ widowed Non-tested: 56% Married/ cohabiting 19% Single 25% Divorced/separated/ widowed	Mutation carriers: 86% Non-carriers: 93% Non-tested: 56%	Mutation positive: 46% Mutation negative: 54%
Lerman 1996, United States[175]	45	44% male 56% female	47.8 (14.1)	83% White 17% African-American	73% > High school	NR	73% Married/ cohabiting	NR	NR
Lindor 2004, United States[180]	414	50% male 50% female	NR	98% Caucasian	NR	NR	NR	NR	MSI-H tumours: 22%
Loader 2005, United States[169]	37	39% male 61% female	59.9 (6.7)	NR	14.9 years (mean) 2.5 years (SD)	NR	69.4% Married/ cohabiting	97.2% Mean number of children: 2.7 SD in number of children: 1.1	Mutation positive: 18.9% Mutation negative: 81.1%
Lynch 1999, United States[171]	199 from 7 families	48% male 52% female	43.8 (NR) Range 18 to 92	NR	NR	NR	NR	NR	NR

First Author Publication Year, Country of Origin[a]	Sample Size	Sex (% Male; % Female; NR)	Mean Age in Years (SD)	Race[b]	Education[b]	Income	Relationship Status	% With Children	Mutation Status
Manne 2007, United States[191]	125	71% male 39% female	44.6 (6.1)	88% White 6.4% Black/African-American 1.6% Asian/Pacific Islander 1.6% Hispanic 2.4% Other	19.2% High school or less 44.8% Some college/trade school/business school 11.2% 4-year degree 2.4% Some graduate education 22.4% Graduate degree	$60,000 to $99,9999 (mean)	NR	NR	
McCann 2009, United States[186]	30 from 17 families	37% male 73% female	16.7% < 35 years	NR	NR	NR	80% Married/ cohabiting 3.3% Divorced 3.3% Widowed 13.3% Single	73.30%	NR
Meiser 2004, Australia[200]	114	39% male 61% female	Mutation positive: 36.8 (13.2) Mutation negative: 42.7 (12.6)	NR	33.6% No post-school 66.4% Post-school	NR	75.4% Married/ cohabiting 24.6% Not married	78.10%	Mutation positive: 28% Mutation negative: 72%
Collins 2007[246]	73	38% male 62% female	41 (median) Range 21 to 75	NR	Carriers: 78% Post-school education, including trade school Non-carriers: 70% Post-school education, including trade school	NR	Carriers: 63% Married/ cohabiting Non-carriers: 85% Married/ cohabiting	Carriers: 68% Non-carriers: 83%	Mutation positive: 26% Mutation negative: 74%
Collins 2005[247]	114	Carriers: 34% male 66% female Non-carriers: 41% male	Carriers: 36.8 (NR) Non-carriers: 43.1 (NR)	NR	Carriers: 71% post-school education Non-carriers: 65% post-school	NR	Carriers: 56% Married/ cohabiting Non-carriers: 83% Married/	Carriers: 66% Non-carriers: 83%	

First Author Publication Year, Country of Origin[a]	Sample Size	Sex (% Male; % Female; NR)	Mean Age in Years (SD)	Race[b]	Education[b]	Income	Relationship Status	% With Children	Mutation Status
		59% female			education		cohabiting		
Mesters 2005, Netherlands[219]	30	27% male 73% female	53 (12) Range 25 to 69	NR	NR	NR	NR	NR	Mutation positive: 37%
Murakami 2004, Japan[228]	42	48% male 52% female	50 (median) Range 21 to 69	NR	59.5% ≥ College		83.3% Married/ cohabiting 9.5% Living alone	78.60%	Mutation positive: 26% Mutation negative: 74%
Petersen 1999, United States[207]	Mail surveys: 1,217 Telephone survey: 156 From 650 families	Mail survey: 41% male 59% female Telephone survey: 47% male 53% female	Mail survey: 54.5 (14.7) Telephone survey: 55.1 (14.5)	Mail survey: 96.9% White Telephone survey: 91.9% White 3.4% Black 2.0% Hispanic 2.0% Asian	Mail survey: 28.4% Graduate degree 32.1% College graduate 25.7% Some college 10.5% High school graduate 1.5% No high school Telephone survey: NR	Mail survey: 37.5% > $75,000 24.4% $50,001 to $75,000 17.4% $35,001 to $50,000 13.3% $20,000 to $35,000 7.3% < $20,000 Telephone survey: 37.8% > $75,000 23.1% $50,00 to $75,000 14.0% $35,001 to $50,000 15.4% $20,000 to $35,000 9.8% < $20,000	NR	NR	NR
Ramsey 2010, United States[235]	Population-based controls: 170 FDRs: 310	Population-based controls: 39% male 61% female FDRs: 37% male 63% female	Male controls: 51.1 (NR) Male FDRs: 48.6 (NR) Female controls: 52.9 (NR) Female FDRs: 47.0 (NR)	NR	Controls: 2% < High school 8% High school 30% Some college 60% College graduate FDRs: < 1% < High school 13% High school 38% Some college 47% College graduate	NR	NR	NR	NR

First Author Publication Year, Country of Origin[a]	Sample Size	Sex (% Male; % Female; NR)	Mean Age in Years (SD)	Race[b]	Education[b]	Income	Relationship Status	% With Children	Mutation Status
Ramsey 2003, United States[190]	CRC patients: 6 FDRs: 4 Controls: 5	CRC patients: 17% male 83% female FDRs: 75% male 25% female Controls: 100% male	NR	CRC patients and FDRs: 100% White Controls: 80% White 20% Asian	CRC patients: 33.3% High school or less 66.7% Some college FDRs: 100% Some college Controls: 100% Some college	NR	CRC patients: 83.3% Married/ cohabiting 16.7% Divorced Relatives: 50% Married/ cohabiting 50% Divorced Controls: 100% Married/ cohabiting	NR	NR
Reeve 2000, New Zealand[193]	7	57% male 43% female	45 (NR) Range 34 to 64 years	NR	NR	NR	NR	NR	2 mutation-positive males 2 mutation-negative males 2 mutation-positive females 1 mutation-negative female
Roygnan 2008, France[204]	7	29% male 71% female	50 (NR) Range 38 to 65	NR	NR	NR	100% Married/ cohabiting	86%	Mutation positive: 100%
Shiloh 2008, United States[238]	Index cases: 67 At-risk family members: 186	50% male 50% female	42.4 (14.0)	95% White 2% African-American 2% Asian 2% Hispanic	NR	59% > $50,000	64% Married/ cohabiting	80%	Index cases: Mutation positive: 47.8% Indeterminate: 52.2%
Shipman 2013, United Kingdom[176]	11	54% male 46% female	NR	100% White British	NR	NR	NR	NR	NR
Stoffel 2008, United States[218]	174	30% male 70% female	46.7 (NR) Range 18 to 79	91% White	69% College graduate	NR	76% Married/cohabiting 21.8% Non-married 2.3% Unknown	NR	Mutation positive: 60% Mutation negative: 13% Indeterminate:

First Author Publication Year, Country of Origin[a]	Sample Size	Sex (% Male; % Female; NR)	Mean Age in Years (SD)	Race[b]	Education[b]	Income	Relationship Status	% With Children	Mutation Status
									27%
Tomiak 2014, Canada[178]	Acceptors: 12 Decliners: 7	Acceptors: 63% male 37% female Decliners: 71% male 29% female	Acceptors: 59 (median), Range 37 to 77 Decliners: 62 (median), Range 54 to 79	NR	Acceptors: 58% Post-secondary education Decliners: 57% Post-secondary education	NR	NR	Acceptors: 92% Decliners: 57%	NR
van Oostrom 2007, Netherlands[240]	96	33% male 67% female	41.0 (13.3)	NR	18.8% < High school 55.2% Some college 26% > College	NR	81.3% Married/ cohabiting 18.7%; Single, divorced, widowed	67.70%	Mutation positive: 29.3% Mutation negative: 70.7%
van Oostrom 2007[227]	96	33% male 67% female	41.0 (13.3)	NR	18.8% < High school 55.2% Some college 26% > College	NR	81.3% Married/ cohabiting 18.7%; Single, divorced, widowed	67.70%	Mutation positive: 29.3% Mutation negative: 70.7%
van Oostrom 2007[241]	96	33% male 67% female	41.0 (13.3)	NR	18.8% < High school 55.2% Some college 26% > College	NR	81.3% Married/ cohabiting 18.7%; Single, divorced, widowed	67.70%	Mutation positive: 29.3% Mutation negative: 70.7%
van Oostrom 2006[242]	96	33% male 67% female	41.0 (13.3)	NR	18.8% < High school 55.2% Some college 26% > College	NR	81.3% Married/ cohabiting 18.7%; Single, divorced, widowed	67.70%	Mutation positive: 29.3% Mutation negative: 70.7%
Vernon 1997, United States[249]	200	54% male 46% female	56.5 (NR)	90% White 10% African-American,	18.8% < High school 55.2% Some	NR	NR	NR	

First Author Publication Year, Country of Origin[a]	Sample Size	Sex (% Male; % Female; NR)	Mean Age in Years (SD)	Race[b]	Education[b]	Income	Relationship Status	% With Children	Mutation Status
				Hispanic, Asian and other	college 26% > College				
Wagner 2005, Netherlands[201]	70	34% male 66% female	51% 20 to 50 49% > 50	NR	NR	NR	NR	89%	Mutation positive: 100%
Wakefield 2007, Australia[168]	22	32% male 68% female	51.4 (NR)	NR	23% High school 36% Certificate or diploma 27% Undergraduate degree 14% Postgraduate degree	NR	77% Married/ cohabiting 9% never married 14% Separated or divorced 0% widowed	NR	NR
Walsh 2012, United States[185]	8	50% male 50% female	NR	63% Caucasian 25% Asian/Pacific Islander 13% Latino/Hispanic 13% other	38% Some college 38% College graduate 25% Graduate school	13% $0 to < $10,000 57% $30,000 to $75,000 50% > $75,000	63% Married/ cohabiting 13% never married 25% widowed	NR	NR
Watkins 2011, Canada[208]	23	39% male 61% female	48.9 (13.6) Range 26 to 78	NR	NR	NR	NR	NR	Mutation positive: 100%
Yamashita 2008, Japan[239]	46	48% male 52% female	49.5 (13.0)	NR	NR	NR	83% Married/cohabiting	80%	Mutation positive: 39.1% Mutation negative: 21.7% Indeterminate: 39.1%

CRC = colorectal cancer; FDR = first-degree relative; IQR = interquartile range; MSI-H = high microsatellite instability; NR = not reported; SD = standard deviation; SDR = second-degree relative.
[a] Studies with a common (sub) sample of patients are grouped together, with the primary study left-justified in the cell and related studies right-justified in subsequent rows.
[b] Descriptive results are presented according to categories reported in the primary studies.

Appendix 55: Acceptance of Genetic Testing

CRC Patients		
Hadley 2003[170]	People with HNPCC-associated cancer or a family history suggestive of HNPCC	81%
Kidambi 2015[199]	CRC patients participating in a selective screening process who participated in genetic counselling	77%[a]
Kidambi 2015[199]	CRC patients participating in a universal screening process who participated in genetic counselling	93%[b]
Relatives of Mutation Carriers or Suspected Mutation Carriers		
Aktan-Collan 2011[196]	First-born adult children of confirmed mutation carriers who had been told of their parents' mutation status	69%
Aktan-Collan 2000[172]	FDRs of people with a confirmed mutation and who are estimated to be at 50% risk of carrying a mutation. Identified through a Finnish registry, with an 85% participation rate	88%
Barrow 2015[187]	All asymptomatic FDRs of confirmed mutation carriers within a Manchester LS registry	56%
Bruwer 2013[163]	Siblings of confirmed mutation carriers[c]	97%
Bruwer 2013[163]	Children of confirmed mutation carriers[c]	74%
de Leon 2004[189]	FDRs of confirmed mutation carriers.[d]	34%
Hadley 2003[170]	All eligible FDRs of people with confirmed HNPCC mutation	51%
Keogh 2009[198]	All relatives of adults diagnosed with CRC before the age of 45 years who participated in a population-based case-control study to whom: - Insurance implications were stated in consent form - Insurance implications were not stated in consent form	 49% 81%
Peterson 2003[166]	FDRs of people with a confirmed mutation and who are estimated to be at 50% risk of carrying a mutation[e]	46% to 64%
Intention to Learn Test Results		
Lindor 2004[180]	CRC patients at risk for LS based on a young age at diagnosis or a family history of CRC who responded they wanted their MSI results	74%
Vernon 1999[195]	CRC patients who had blood drawn for testing	90%

CRC = colorectal cancer; FDR = first-degree relative; HNPCC = hereditary non-polyposis colorectal cancer; LS = Lynch syndrome; MSI = microsatellite instability.
[a] 86.7% of the sample agreed to receive genetic counselling, and of those, 77.0% underwent genetic testing.
[b] 58.3% of the sample agreed to receive genetic counselling, and of those, 92.9% underwent genetic testing.
[c] Total number of siblings, or children, was enumerated for each participant and the uptake rate was calculated based on the mutation carriers' description of who got testing, which was then confirmed with database records.
[d] All identified relatives of confirmed mutation carriers were included, and testing history was confirmed based on clinical records.
[e] Unclear whether reported proportions include all eligible FDRs, or only those who participated in the study.

Appendix 56: Medical Management and Screening Post-Test Result by Study

First Author, Year	Country	Study Design	Study Population	Result Summary
Aktan-Collan,[179] 2013	Finland	Survey	Adult members of family with verified LS mutation, without cancer diagnosis and at 50% risk of HNPCC	• All carriers (n = 62) had colonoscopies post-test • 83% of carriers followed screening recommendations (i.e., every 3 years or more) • 17% of carriers reported periods longer than 3 years
Barrow,[187] 2015	UK	Chart review/cross-sectional	Adults (> 18) FDR of MMR mutation carriers	• 97.2% of patients who had testing underwent colonoscopy vs. 34.9% of untested FDRs • 5.7% of carriers were late for their last colonoscopy (range: 3 to 13 months) • 11.8% of untested FDRs were late for their colonoscopy (range: 1 to 7 months) • 9/68 untested FDRs ceased screening altogether
Burton-Chase,[222] 2014	US	Qualitative description	Adults (≥ 25) females without a diagnosis of gynecologic cancer, who were LS mutation positive or met Amsterdam II criteria	• 24% colonoscopy non-adherent[a] • 26% colonoscopy adherent through research • 51% colonoscopy adherent through routine care
Claes,[192] 2005	Belgium	Survey	Members of families with verified dMMR mutation, without cancer diagnosis	• 100% of carriers were adherent (i.e., colonoscopy every 2 years) • No non-carriers had a colonoscopy 1 year post-test • 57% of non-carriers had no intention of screening or only when indicated
Claes,[173] 2004	Belgium	Survey	Members of families with verified HNPCC mutation, without cancer diagnosis	• 100% of carriers had intention to undergo colonoscopies • 3 carriers intended to have yearly colonoscopies; all other carriers intended to have colonoscopies as recommended

First Author, Year	Country	Study Design	Study Population	Result Summary
de Leon,[189] 2004	Italy	Cross-sectional, chart review	Members of families with verified HNPCC germline mutation	• 19/23 of unaffected carriers underwent pancolonoscopy within 1-2 years post-test • 4 unaffected carriers declined pancolonoscopy • Unaffected carriers mean age at first endoscopy = 33.1 years (SD = 8.7) • Mutation-negative controls mean age at first endoscopy = 38.5 years (SD = 13)
Ersig,[209] 2009	US	Cross-sectional	Individuals who underwent genetic testing and their adult children and siblings	• 53% had colonoscopy within past 2 years • 28.2% never had colonoscopy or had more than 3 years ago • 26.1% of participants from families with indeterminate mutations were not adherent • 13% of participants from mutation-positive families were not adherent • 19.6% of all participants at risk for HNPCC were not adherent
Ersig,[214] 2009	US	Survey	Adults (≥ 18) with at least one HNPCC-associated cancer diagnosis, and a personal or family history suggestive of hereditary cancer	• 69.6% of patients (n = 48, carriers = 30) had endoscopy within 1 year post-test • Indeterminate carriers were less likely than mutation positive to have endoscopy (OR = 0.19, *P* = 0.01)
Esplen,[174] 2001	Canada and US	Survey	Adults (≥ 18) with personal or family history suggestive of HNPCC, and eligible for genetic testing	• 11/16 individuals increased the frequency of their screening testing, including colonoscopy • 10/20 individuals want further information on screening • 9/20 individuals want to screen more often • 2/20 were confused about how often to screen

First Author, Year	Country	Study Design	Study Population	Result Summary
				• 12/20 want to be screened for other cancers than just CRC • All thought screening was important
Esplen,[211] 2015	Canada	Survey	Adults (≥ 18) who were members of a family with verified LS mutation, and were mutation positive or mutation negative	• Significantly more carriers had screening in past year compared with non-carriers
Graves,[197] 2014	US	Survey	Members of families with verified *hMSH2*, *hMLH1*, *hMSH6*, *hPMS2* mutation	• 64% of carriers had any cancer screening post-test • 51% of negative individuals had any cancer screening post-test
Hadley,[215] 2004	US	Survey	Adults (≥ 18) without a cancer diagnosis, at 50% risk of HNPCC mutation	• 30/56 had at least 1 colonoscopy pre-GCT (mutation status not a determinate) • 12/56 had at least 1 colonoscopy 1 year post-GCT • 9/17 carriers had colonoscopy 1 year post-GCT (6/17 not adherent – 3 were hypovigilant, and 3 were hypervigilant) • 3/39 mutation negative had colonoscopy 1 year post-GCT (5/39 not adherent – 2 were hypovigilant and 3 were hypervigilant)
Halbert,[212] 2004	US	Survey	Members of families with verified HNPCC mutation at 25% risk of inheriting mutation	• 16/22 carriers had colonoscopy 1 year post-test • 8/49 mutation negative had colonoscopy 1 year post-test • 6/27 decliners had colonoscopy • From baseline to follow-up there were no significant changes in colonoscopy use for mutation-negative individuals • From baseline to follow-up carriers reported increased colonoscopy use
Johnson,[213] 2002	US	Cross-sectional	Patients without a cancer diagnosis, undergoing CRC	• 50/65 had colonoscopy prior to testing

First Author, Year	Country	Study Design	Study Population	Result Summary
			exam or eligible for CRC exam	• 37/65 overdue for colonoscopy at time of testing • 15/65 overdue for colonoscopy at time of follow-up (mean 12.7 months post-visit) • 34/65 had colonoscopy post-visit; 5/65 were scheduled for colonoscopy; 11/65 were within recommended time interval • Carriers were significantly more likely to have colonoscopy compared with negative patient or decliners • Negative patients were significantly more likely to be overdue for screening compared to carriers or decliners
Loader,[169] 2005	US	Survey	Patients with CRC diagnosed before 60 years with a FDR or SDR with CRC	• Carriers had lower screening scores (based on frequency and time since last screening) compared with mutation-negative individuals
Lynch,[171] 1999	US	Unclear	NR	• 53/56 carriers would consider lifetime CRC screening • 37/56 carriers would consider prophylactic colectomy
Meiser,[200] 2004	Australia	Survey	Members of a family with verified HNPCC mutation	• At baseline, 3/12 of persons < 25 years had ever had colonoscopy vs. 74/101 of those > 25 years • Difference in colonoscopy use between baseline and 1-year follow-up was not different for carriers (16/21 at baseline vs. 15/21 at follow-up) • Non-carriers had significantly less colonoscopies between baseline and 1-year follow-up (48/65 at baseline, vs. 8/65 at follow-up) • All carriers had colonoscopy between 1-year and 3-year follow-up • 4 non-carriers had colonoscopy at time of 3-year follow-up

First Author, Year	Country	Study Design	Study Population	Result Summary
				• No carriers had prophylactic colectomy • 4/18 non-carriers > 51 years old had FOBT in previous 2 years at point of 3-year follow-up
Wagner,[201] 2005	Netherlands	Survey	Individuals with known MMR gene mutations	• 31% of unaffected carriers had regular colonoscopy before testing (62% every 2 years, 38% less frequent) • 88% of unaffected carriers had colonoscopy 1 to 2 years post-test
Watkins,[208] 2011	Canada	Grounded theory	Member of family with known *MSH2* mutation	• Only one carrier had not undergone screening post-test • Not all participants were adherent

CRC = colorectal cancer; dMMR = deficient mismatch repair; FDR = first-degree relative; FOBT = fecal occult blood test; GCT = genetic counselling and testing; HNPCC = hereditary non-polyposis colorectal cancer; LS = Lynch syndrome; MMR = mismatch repair; OR = odds ratio; SD = standard deviation; SDR = second-degree relative; vs. = versus.
[a] Adherence referred to whether patients had colonoscopies in accordance with recommendations based on status or risk profile, including whether participants had colonoscopies within the specified time frame (e.g., longer or shorter intervals than recommended)

Appendix 57: Critical Appraisal of the Included Studies: Cross-Sectional (Question 7)

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
Barrow 2015,[187] Chart review/cross-sectional, Chart review	• Research questions well suited to a chart review. • The chart review with data extraction was valid. • All eligible people in the database were included.	• Unclear if ethical approval was sought or obtained; it was not reported. • Unclear whether the target population was representative of the population for which the results could be generalized to or whether the sampled population was representative of the target population; no description of database coverage was provided and whether or not it includes a representative target area. • Part of the study included a discussion of a patient advisory group, but there was no mention of how the data were collected or analyzed. • There was no discussion of the limitations of the study in the publication.
Esplen 2015,[211] Survey, Questionnaire	• The target population is likely representative of the population to which the results will be generalized — a population-based registry was used. • A response rate of 70% was achieved and there were few differences between respondents and non-respondents. • A pilot was conducted and the questionnaires were both valid and reliable.	• No sample size calculation was provided. • Some discussion of limitations was done by the authors; however, there was no mention of the highly Anglo-Saxon population or the potential for recall bias.
Leenan 2016,[183] Survey, Questionnaire	• Research objectives and questions were clearly defined, as was the sampling strategy. • The research objectives were congruent with a survey design and the sampling strategy was congruent with the objectives. • Part of the questionnaire has face validity and appears reliable. • Data analysis strategies were appropriate for the type of data collected, and were planned	• It is unclear if the target population is representative of the general population, and whether the sample was obtained in a way that may introduce selection bias; it is unclear how the study families were identified and recruited from. • No sample size calculation was provided. • It is unclear whether a satisfactory response rate was achieved; response rate was high for tested individuals, but low for non-tested individuals.

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
	a priori. • The researchers have drawn an appropriate link between data and conclusions.	
Eliezer, 2014,[230] Survey, Questionnaire (Companion study to Hadley, 2003[170])	• Research questions were clearly stated and were suitable to the survey design. • Questionnaires were valid and reliable. • Analyses were planned a priori and authors drew appropriate links between the data and their conclusions.	• Sampling strategy not clearly defined in the current publication but was defined in a companion paper. • The sample likely primarily included those motivated to pursue testing. Was also a highly insured, white, employed population.
Kidambi 2015,[199] Retrospective, Chart review	• Research objectives clearly stated and were suitable for a chart review design. • Sampling strategy clearly described and, as they were aiming for the general CRC population, it is likely that the results are relevant to that population. • The data collection methods were valid and reliable. • Satisfactory response rate achieved. • Significant and non-significant results were reported. • Many potential biases were discussed by the authors, including potential changes in clinical practice and that it was a single centre design.	• Unclear if ethics approval as sought or approved. • Unclear if the CRC population at a large university hospital is completely representative of the larger CRC population.
Graves 2014,[197] Survey, Questionnaire, interview	• Research objectives clearly stated and are congruent with a survey design. • The sampling strategy is well defined and congruent with the objectives. • Analysis of results was planned a priori.	• Unclear if the target population is representative of the sample to which it will be generalized; if it is generalized those beyond CRC/LS (as the discussion implies that it might be), it is unclear if those at risk for other genetic mutations are similar to CRC mutations. • Sample size population not provided. • Questionnaires were neither valid nor reliable. • Unclear if a satisfactory response rate was achieved. 373 invited, 107 completed baseline, 85 completed the 6-month follow-up.

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
Kupperman 2013,[216] Cross-sectional, Questionnaire, preference elicitation (time trade off)	• Ethics approval was obtained. • Objectives were clearly stated and were suitable to the study design. • Questionnaire was reliable, valid, and a pilot test was conducted. • Data analysis strategies were appropriate.	• The sample was highly educated, and receiving care at a prestigious institution — suggestive of highly insured population. Income was also quite high. Therefore, the population may not be generalizable to a less-educated population with a lower income. • Sample size calculation not provided.
Morris 2013,[232] Cross-sectional, Questionnaire (Companion study to Hadley, 2003[170])	• The study objectives were clear and were suited to the cross-sectional design. • Most of the questionnaires used were validated and reliable instruments. • Many of the limitations and potential biases were discussed by the authors.	• The sample likely primarily included motivated individuals and was largely white, highly educated, and of a Christian faith. • It was unclear if there was a satisfactory response rate.
Dewanwala 2011,[210] Survey, Questionnaire	• If we assume the target population to be those who are eligible for genetic testing based on clinical criteria, it is representative of the population to which the results will be generalized. • A satisfactory response rate was achieved. • Data analysis was appropriate for the data collected and the conclusions were appropriate.	• The actual population who participated may not be representative of the target population; the population is from one centre, and the population is highly white. The Dana-Farber Cancer Center tends to serve those with good insurance, and therefore likely high incomes, education, etc. Further, as with most surveys, this one is likewise subject to participants who are highly motivated (e.g., 84% participation rate — the other 16% might have been very different). • The questionnaires were not piloted and were not valid or reliable; the questionnaires were developed at the institution and there was no mention of psychometrics.
Cragun 2012,[184] Survey, secondary analysis, Questionnaire	• Some of the questionnaires were valid and others were not. • The analysis techniques were appropriate for the data collected. • Authors discussed many of the limitations of the study.	• Unclear if ethics approval was sought or obtained. • Sampling strategy was not clearly defined. • It was unclear whether the target population representative of the population to which the results were be generalized and further unclear whether those who participated were systematically different from those who did not participate; 326 eligible participants, 128 could not be reached and no analysis is given regarding why or how they might differ from the total. Overall, 91 of a possible 326 participated. The final

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
		sample is largely white; with insurance; highly educated; and married.
Landsbergen, 2012,[223] Cross-sectional, Questionnaire	• Research objectives and questions were clearly defined, as was the sampling strategy. • The research objectives were congruent with a survey design and the sampling strategy was congruent with the objectives. • The study was pilot tested. • The study questionnaire was valid and reliable. • Data analysis strategies were appropriate for the type of data collected, and were planned a priori. • The researchers have drawn an appropriate link between data and conclusions.	• It is likely the way the sample was obtained could introduce selection bias; it is unclear how many participants were invited to the study and what the reasons for declining to participate were. There is some concern regarding channelling bias, as physicians recruited participants. • No sample size calculation was provided. • A satisfactory response rate was not achieved.
Aktan-Collan 2011,[196] Survey, Questionnaire	• A satisfactory response rate was achieved. • Qualitative results from open-ended questions were discussed. • Authors discussed the limitations and potential biases in their study with the exception of concerns regarding the validity, reliability, and piloting of the questionnaire.	• Unclear if the questionnaire was reliable or valid — no information was provided • Unclear if the questionnaire underwent a pilot study.
Landsbergen 2011,[233] Cross-sectional, Questionnaire	• Research objectives and questions were clearly defined, as was the sampling strategy. • The research objectives were congruent with a survey design and the sampling strategy was congruent with the objectives. • The study was pilot tested. • The study questionnaire was valid and reliable. • Data analysis strategies were appropriate for the type of data collected, and were planned a priori. • The researchers have drawn an appropriate link between data and conclusions.	• It is likely the way the sample was obtained could introduce selection bias; participants were recruited from one medical centre, and likely to include highly motivated individuals. • No sample size calculation was provided. • A satisfactory response rate was not achieved. • A full discussion and identification of the limitations and biases was lacking.

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
Hadley 2010,[234] Survey, Questionnaire	• The study objectives were clear and were suitable for the survey design. • Sampling strategy was clearly defined and was congruent with the study methods. • Questionnaires were valid and reliable.	• Sample likely primarily included those motivated to pursue testing. In addition, this was a highly insured, white, employed population. • Sample size calculation was not provided. • It was unclear if the questionnaires were pilot tested; however, this study is part of a larger "suite" of studies that used the same questionnaires.
Ramsey 2010,[235] Survey, Questionnaire	• Research objectives and questions were clearly defined, as was the sampling strategy. • The research objectives were congruent with a survey design and the sampling strategy was congruent with the objectives. • The target sample was representative of the population to which it will be generalized; they obtained a population-based sample of FDRs and matched controls. • The survey was pilot tested for clarity and ease of understanding. • The study questionnaire was valid and reliable. • Data analysis strategies were appropriate for the type of data collected, and were planned a priori. • Significant and non-significant results were reported. • The researchers have drawn an appropriate link between data and conclusions.	• The actual sample obtained is different from the target population; they were of higher socioeconomic status. • No sample size calculation was provided. • A satisfactory response rate was not achieved for either relatives or controls; males, persons of African-American race, and less-educated persons were less likely to respond to the survey.
Ashida, 2009,[236] Survey, Questionnaire	• The majority of the study questionnaires were valid and reliable. It was unclear whether the cancer worry questionnaire was reliable or valid, but scales used to assess depression and family relationships have been validated. • The data analysis strategy was appropriate for the type of data collected.	• The objectives were clearly stated; however, they seem like data dredging. • The sampling strategy was no clearly defined; participants in this study were recruited from among those in another study, but it is unclear how those participants were recruited.

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
		• It is unclear if the sampling strategy is focused on a representative sample, which would be ideal for this scenario. • The sample was primarily Caucasian and well educated. • Not clear if a satisfactory response rate was achieved; there was no description of how many families who were eligible participated in this sub-study, or of the response rate of the primary study. • Unclear if all significant and non-significant results were reported; this seems to be a post-hoc analysis.
Ersig 2009,[209] Cross-sectional, Questionnaire, interview	• The objectives and research questions were clear and suited to the cross-sectional questionnaire. • Although the questionnaires were developed by the investigators, they were fairly straightforward “yes” or “no” questions and were likely valid.	• The sample may not have been representative of the target population; respondents were primarily female, well educated, employed, older than 50, and partnered. All were Caucasian. Only 2 to 3 people per family participated, providing a limited picture of the social network. • Sample size calculation was not provided; matching was conducted to increase power in the analyses, but sample size was still small. • Some of the questions were prone to recall bias and may not be reliable. • Unclear if the response rate was satisfactory, but likely not; 61.5% of index cases, and 44% of first-degree relatives from the primary study.
Ersig 2009,[214] Survey, Questionnaire	• Objectives were clearly stated and suitable to the survey design. • Although the questionnaires were developed by the investigators, they were fairly straightforward “yes” or “no” questions and were likely valid. • Although the analyses were planned a priori, it was not clear that the questions were relevant to the screening behaviours and disclosure of test results.	• The sample was highly insured and primarily Caucasian. • The investigator-developed questions were likely not reliable — they were prone to recall bias. • It was unclear whether a satisfactory response rate was achieved. • Not all significant and non-significant data were reported.

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
	• The authors discussed the limitations and potential biases — most important is that the sample likely reflects motivated individuals and is highly skewed toward insured, employed individuals.	
Keogh 2009,[198] pre-post, Chart review	• Ethics approval obtained. • Sampling strategy congruent with the research objectives. • Data from all eligible people within the cohort were reviewed. • Questionnaires were reliable and valid. • A satisfactory response rate was achieved. • Researchers drew appropriate conclusions and were cognizant of the limitations of the study.	• Sample size calculation not provided. • A pilot test of the methods was not conducted. • This analysis was not planned a priori; this was planned post-hoc, to explore a hypothesis that arose mid-study.
Ceballos 2008,[237] Survey, Questionnaire	• Research questions were clearly stated and are appropriate for a survey design, though some details regarding the questionnaires may be missing. • Significant and non-significant results were reported. • There was an appropriate link drawn between results and conclusions; the conclusions seem based on the results from the survey, and supported by other literature; however, there were some flaws with this study, so the generalizability aspect seems a bit too generous on their part — it is uncertain whether participants outside of this study would behave in a similar manner.	• Sampling strategy not clearly defined in the citation; however, it was published elsewhere. • Unclear if the target population was representative of the population to which results may be generalized; patients in the registry and patients willing to participate may be fundamentally different from other CRC patients — additionally, relatives of cases identified and willing to participate may have a heightened interest in genetic testing, as opposed to relatives not participating. • Unclear if the questionnaires were valid; it is probably an accurate reflection of the questions that are being asked, but the survey might be flawed in that there was no "neutral" response for the truly ambivalent patient. It was also unclear if the questionnaire was reliable. • Unclear how many were approached to participate, and therefore unclear if there was a satisfactory response rate.

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
Shiloh 2008,[238] Survey, Questionnaire	• Research objectives and questions were clearly defined, as was the sampling strategy. • The research objectives were congruent with a survey design and the sampling strategy was congruent with the objectives. • The target sample was representative of the population to which it will be generalized; they aimed to have a representative sample and they recruited from across the US. • The study questionnaire was valid and reliable. • Data analysis strategies were appropriate for the type of data collected, and were planned a priori. • Significant and non-significant results were reported. • The researchers have drawn an appropriate link between data and conclusions.	• The actual sample is likely to contain participants who are highly motivated, educated, married with children, and white. • No sample size calculation was provided. • It is uncertain whether the questionnaire underwent any pilot testing. • It is unclear whether there was a satisfactory response rate, as participation was mediated through family members and no denominator is known.
Stoffel 2008,[218] Survey, Questionnaire	• Research objectives and questions were clearly defined, as was the sampling strategy. • The research objectives were congruent with a survey design and the sampling strategy was congruent with the objectives. • Data analysis strategies were appropriate for the type of data collected, and were planned a priori. • Significant and non-significant results were reported. • Authors have drawn an appropriate link between the data and conclusions.	• The population that was sampled is unlikely to be representative of the general population; the sample was predominantly female, white, and educated. • The sample was obtained from 4 large cancer centres which are likely to serve a largely white and educated population. • No sample size calculation was provided. • The questionnaire was researcher developed and its reliability and validity were uncertain, and it was uncertain whether the questionnaire underwent pilot testing. • Only 58% of eligible persons answered the questionnaire. • It is unclear whether the results of all open-ended questions were summarized and reported on.

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
Yamashita 2008,[239] Survey, Questionnaire	• Research objectives and questions were clearly defined. • The research objectives were congruent with a survey design. • Valid and reliable questionnaires were used, and supplemented with investigator questions to capture demographic information. • Data analysis strategies were appropriate for the type of data collected, and were planned a priori. • A satisfactory response rate was achieved. • Significant and non-significant results were reported. • The researchers have drawn an appropriate link between data and conclusions.	• The sampling strategy was not clearly defined and it is uncertain how they obtained their sample. • It is unclear whether the centre and physician from which the participants were recruited are representative of the target population. • No sample size calculation was provided.
Esplen 2007,[177] Survey, Questionnaire	• Research questions, objectives, and sampling strategies were clearly defined. • 65% response rate, and demographics seem representative of population. • Most of the questionnaires were validated and reliable; some questions were developed for this study based on the literature and prior work. • There was a good discussion of the limitations and strengths of the study.	• There was no sample size calculation provided.
Fantini 2007,[206] Survey	• Questionnaires were valid and reliable. • Data collection methods were congruent with the research questions and data analysis methods were appropriate for the type of data collected.	• Unclear if ethics approval was sought or obtained. • Unclear whether or not the target population was representative of those to whom the results will be generalized; unclear whether those who attend the clinic are different from the general CRC population. Additionally, those who agreed to participate may be more highly motivated, as many of those who attend the clinic self-refer for testing. • No sample size calculation was provided.

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
Kohut 2007,[217] Survey, Questionnaire	• Research objectives and questions were clearly defined, as was the sampling strategy. • The research objectives were congruent with a survey design and the sampling strategy was congruent with the objectives. • Data analysis strategies were appropriate for the type of data collected. • The researchers have drawn an appropriate link between data and conclusions.	• Ethics approval is not reported. • The population that was sampled is unlikely to be representative of the general population; the sample was small, of similar socioeconomic status, and most had not been identified as mutation carriers. • No sample size calculation was provided. • Questionnaire was not pilot tested, and has uncertain validity and reliability as it was researcher developed and not tested. • It is unclear if all data analysis was planned a priori, and it is unclear if all significant and non-significant results were reported. • A satisfactory response rate was not achieved. • It is uncertain whether all qualitative results were summarized and reported.
Manne 2007,[191] Cross-sectional data collected as part of an RCT, Questionnaire	• Research questions and objectives are suitable to a questionnaire as data collection. • The sampling piggybacked off an RCT, but is congruent with the objective to understand baseline knowledge of those undergoing testing. • Questionnaire was reliable and valid. • Seems that all significant and non-significant results were reported.	• It is unclear how people become "enrolled" at a cancer centre, or the community hospital, and whether this could introduce selection bias. It is possible that physicians only ask those people who have a better functional status or who they perceive to be more willing to participate. Further, among those who were invited to participate, the non-responders had a poorer functional status (ECOG) compared with responders. • Unclear if there was a sufficient sample size. • Data analysis strategy was not clearly described.
van Oostrom 2007 (3 publications)[227,240,241] and 2006 (1 publication),[242] Survey, Questionnaire	• Research objectives and questions were clearly defined, as was the sampling strategy. • The research objectives were congruent with a survey design and the sampling strategy was congruent with the objectives. • Data analysis strategies were appropriate for the type of data collected, and were planned a priori.	• The population that was sampled is unlikely to be representative of the general population; the sample was predominantly female and educated. • No sample size calculation was provided. • It is uncertain whether the questionnaire underwent any pilot testing. • The validity and reliability of the questionnaire was uncertain.

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
	• A satisfactory response rate was achieved. • Significant and non-significant results were reported. • The researchers have drawn an appropriate link between data and conclusions.	• Study limitations (i.e., validity and reliability of the questionnaire) were not discussed by the authors.
Claes 2005,[192] Survey Questionnaire, interview	• Research questions and data collection were suited to a survey — authors used Likert scale questions and reported on survey questions, not interviews. • The target population is likely representative of the population to which the results will be generalized as long as they are generalized to unaffected adult patients (from known HNPCC families) seeking predictive testing. • Data analysis strategies were appropriate and were justified in the text (though there was no mention that they were planned a priori). • Both significant and non-significant results were reported.	• Not clear that ethics approval was sought or obtained. • Unclear if the scales used were valid for cancer research. • Unclear how many people were approached to participate. • Sampling strategy was unclear; unclear how families with potential participants had been identified in the first place — how did the proband come to be known, and thus their unaffected adult relatives tested? • Sample size calculation was not provided. • The qualitative results were not reported; they stated they used interviews, but did not report on this.
Loader 2005,[169] Survey, Questionnaire	• A survey design was congruent with what could be gathered about their objectives. • The sampling strategy was clearly defined.	• It is unclear whether ethics approval was obtained, and the research questions stated are vague and unclear. • The target population was not representative of the population to which the results will be generalized; for some questions, this was more evident than for others. • There is the possibility for selection bias, as there was a low response rate at each step and few demographic characteristics were reported. • No sample size calculation was provided, and the questionnaire did not undergo pilot testing. • The validity and reliability of the questionnaire are unclear as little detail was reported.

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
		• It is unclear whether the data analysis was appropriate for the type of data collected, though it was mostly descriptive statistics. • It was also unclear whether analyses were planned a priori and if both significant and non-significant results were reported. • A satisfactory response rate was not achieved.
Wagner 2005,[201] Survey, Questionnaire	• Research objectives and questions were clearly defined, as was the sampling strategy. • The research objectives were congruent with a survey design and the sampling strategy was congruent with the objectives. • The questionnaire has face validity. • Data analysis strategies were appropriate for the type of data collected, and were planned a priori. • A satisfactory response rate was achieved. • Significant and non-significant results were reported. • Authors have drawn an appropriate link between the data and conclusions.	• Unclear if ethics approval was sought or obtained. • The population that was sampled is unlikely to be representative of the general population; the sample was predominantly female and likely to be highly motivated. • No sample size calculation was provided. • It is uncertain whether the questionnaire underwent any pilot testing. • The questionnaire relies on self-report and it is uncertain whether it is reliable.
Arver 2004,[188] Survey, Questionnaire	• Validated and reliable questionnaires were used (with the exception of questions regarding satisfaction with decision-making). • Response rates were high; 90% to 93%. • Qualitative responses were discussed.	• The target population was not likely representative of the population to which the results may be generalized; participants self-referred for testing. • It was unclear whether all significant and non-significant results were reported; unclear why only certain scales (e.g., 5 of the 8 SF-36 scales) were used or reported.
Balmana 2004,[243] Survey, Questionnaire	• Some construct validity was completed as part of the design of the questionnaire (however, the questionnaire was developed for the study). • Data analysis was planned a priori and was appropriate for the study design.	• Sampling strategy was not clearly defined; recruitment took place between March 1997 and August 2002, a 5-year period. 130 consented to participation but it is unclear how many people were invited and thus the participation rate. Unclear if everyone who was eligible was asked, if this was a consecutive sample,

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
	• Significant and non-significant results were reported.	or otherwise how people were approached. Further, it is unclear if the clinic serves a representative sample. • No mention of reliability of the questionnaire. • The authors did not discuss the impact of response rate, or lack of known validity or reliability of the author-developed questionnaire.
Broderson 2004,[244] Survey, Questionnaire	• Research questions were well suited to a survey. • A satisfactory response rate was achieved. • Both significant and non-significant results were reported.	• Sampling strategy not clearly defined; time period is unclear, whether all patients or a consecutive sample of patients, and how long they have been with the clinic was unclear. • Unclear if the target population is representative of the population to which the results will be generalized; the authors report there were more women who responded than men, which reflected the clinic population. Demographic and clinical details of participants were sparsely reported. • Questionnaires were developed by study authors for the study and were not validated or tested for reliability. There was no mention of pilot testing or preliminary psychometrics.
Claes 2004,[173] Survey, Questionnaire, interview	• Research questions and data collection were suited to a survey — authors used Likert scale questions and reported on survey questions, not interviews. • The target population is likely representative of the population to which the results will be generalized as long as they are generalized to unaffected adult patients (from known HNPCC families) seeking predictive testing. • Data analysis strategies were appropriate and were justified in the text (though there was no mention that they were planned a priori). • Both significant and non-significant results were reported. • 91% response rate; describes why some	• Not clear that ethics approval was sought or obtained. • Sampling strategy was unclear; unclear how families with potential participants had been identified in the first place — how did the proband come to be known, and thus their unaffected adult relatives tested? • Sample size calculation was not provided. • Validity and reliability of the questionnaires and scales are unclear — particularly the distress scale. • The qualitative results were not reported; they stated they used interviews, but did not report on this, although there was one verbatim quote.

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
	were non-responders in adequate detail. • Researchers drew appropriate conclusions, although their generalizations seemed a bit broad — results probably cannot stretch to all individuals wanting predictive testing, just those from known mutation families.	
de Leon 2004,[189] Cross-sectional, chart review, Chart review	• Research objectives and questions were clearly defined, as was the sampling strategy. • The research objectives were congruent with a survey design and the sampling strategy was congruent with the objectives. • The target population was likely representative of the population to which the results will be generalized. • Data analysis techniques were appropriate; data for relevant questions to this review are mainly descriptive, frequencies and proportions. • All significant and non-significant results were reported.	• Unclear whether ethics approval was sought or obtained. • It is unclear whether or not the way the sample was obtained could have contributed to bias; it is not reported whether all physicians from Rome and Aviano were referring suspected HNPCC patients to the study investigators. If so, then selection bias is unlikely. If not, it is a possibility. • Validity and reliability of the chart review or chart review methods are unclear. • Unclear if there was a satisfactory response rate. • The authors did not discuss study limitations or potential sources of bias.
Hadley, 2004,[215] and Palmer 2005[245]Survey, Questionnaire	• Research questions were clearly stated and were congruent with the survey design and the sampling strategy. • Researchers linked the data with the conclusions. • Limitations and potential biases were well discussed by the study authors — most importantly, the sample likely reflects motivated individuals and is highly skewed toward insured, employed individuals.	• The sample could have been prone to bias; likely included primarily those motivated to pursue testing as well as a highly insured, white, employed population. • No sample size calculation provided. • Questionnaires were likely not reliable; recall bias was possible.
Halbert 2004,[212] Survey, Questionnaire	• Research objectives and questions were clearly defined, as was the sampling strategy. • The research objectives were congruent with a survey design and the sampling strategy was	• It is unclear if the target population is representative of the population to which the results will be generalized; the representativeness of the families in the sample is uncertain.

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
	congruent with the objectives. • Data analysis strategies were appropriate for the type of data collected, and were planned a priori. • The researchers have drawn an appropriate link between data and conclusions. • Potential biases were identified and discussed.	• It is unclear whether how the sample was obtained could introduce selection bias, as little detail was given on how the participants were selected. • No sample size calculation was provided. • Questionnaire was not pilot tested, and has uncertain validity and reliability. • It is uncertain whether a satisfactory response rate was achieved.
Keller 2004,[167] Survey, Questionnaire	• Research objectives and questions were clearly defined, as was the sampling strategy. • The research objectives were congruent with a survey design and the sampling strategy was congruent with the objectives. • The target sample is likely to be representative of the population to which the results will be generalized; the sample was registry based. • Data analysis strategies were appropriate for the type of data collected, and were planned a priori. • All significant and non-significant results were reported. • The researchers have drawn an appropriate link between data and conclusions.	• Ethics approval is not reported. • It is unclear if how the sample was obtained could introduce selection bias; the response rate was quite low, and is likely to include highly motivated individuals. • No sample size calculation was provided. • Questionnaire was not pilot tested, and has uncertain validity and reliability as it was researcher developed and not tested.
Lindor 2004,[180] Survey, Questionnaire	• Research objectives and questions were clearly defined, as was the sampling strategy. • The research objectives were congruent with a survey design and the sampling strategy was congruent with the objectives. • Survey methods were pilot tested with up to 40 participants. • The questionnaires used were valid and reliable and appropriate for use in cancer patients.	• It is unclear whether the way the sample was obtained may introduce selection bias; participating individuals were likely to be highly motivated and interested in research. Included participants were not ethnically diverse and may not be representative of all colon cancer patients. • No sample size calculation was provided. • It is unclear if all data analysis was planned a priori as no plan was reported, and it is unclear whether all significant and non-significant results were reported.

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
	• A satisfactory response rate was achieved. • The researchers have drawn an appropriate link between data and conclusions.	• Reporting on demographic data was lacking.
Meiser 2004 (1 publication)[200] Collins 2005 (1 publication)[246] and 2007 (1 publication),[247] Survey, Questionnaire	• Research objectives and questions were clearly defined, as was the sampling strategy. • The research objectives were congruent with a survey design and the sampling strategy was congruent with the objectives. • The target sample was representative of the population to which it will be generalized. • Sample size calculation was provided. • Part of the study questionnaire was valid and reliable. • Data analysis strategies were appropriate for the type of data collected, and were planned a priori. • A satisfactory response rate was achieved, and all significant and non-significant results were reported. • The researchers have drawn an appropriate link between data and conclusions.	• It is unclear whether the way the sample was obtained may introduce selection bias, in that the actual sample may be highly motivated. • The survey did not undergo pilot testing, and contained some investigator-developed questionnaires.
Murakami 2004,[228] Pre-post, Interview, questionnaire	• Ethics approval sought and acquired. • Research objectives and questions seem well suited to the interview and questionnaire design. • Sampling strategy well defined. • Questionnaires used were valid and reliable; psychological outcomes assessed using DSM criteria, the personality using EPQ-R, and other demographic info via structured survey. The interrater reliability was tested. • There was a satisfactory response rate; 47 of 51 eligible people completed the baseline interview, and 42 of these completed the	• Although the sampling strategy was well defined and it seems likely that the sample obtained was representative of those asked to participate, the sample self-selected, thus is likely a highly motivated group. • No sample size calculation provided and methods were not pilot tested.

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
	1-month follow-up.	
Esplen 2003,[203] Survey, Questionnaire	• Research questions were clear and the sampling strategy was congruent with the objectives; the registry is an excellent source, but it is not clear how it was used. • The sample seems representative in terms of education, relationship status, sex, and other variables reported. • Most of the questionnaires were valid and reliable; however, some questions were developed for this study based on the literature and prior work.	• Sampling strategy was not clearly defined; the sample came from the Ontario registry, but it is unclear if it was all eligible people or how people were sampled from the registry. • No sample size calculation was provided and it was unclear whether or not a satisfactory response rate was achieved (as it was not reported).
Hadley, 2003,[170] Survey Questionnaire	• Objectives were suited to the survey design. • Sampling strategy was congruent with objectives. • Although the authors did not specifically state that the questionnaire was pilot tested, many questions were reused from prior research, which could mimic pilot testing. • While the authors did not specifically report the validity or reliability of the questionnaires, all questionnaires used were part of a package of questionnaires used for a consortium of related projects. • A satisfactory response rate was achieved among probands. • Authors provided a good discussion of the limitations and potential biases. The insurance-related risks could have been underestimated due to participants' belief that results are less accessible to insurers through this study format.	• The sample likely included primarily those motivated to pursue testing. Additionally, it was a highly insured, white, employed population. • A satisfactory response rate was not achieved among first-degree relatives.
Ho 2003,[182] Survey, Questionnaire	• Research objectives and questions were clearly defined, as was the sampling strategy.	• Ethics approval is not reported.

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
	• The research objectives were congruent with a survey design and the sampling strategy was congruent with the objectives. • Data analysis strategies were appropriate for the type of data collected, and were planned a priori. • The researchers have drawn an appropriate link between data and conclusions.	• The target population is unlikely to be representative of the population to which the results will be generalized; there is a limited number of families in the sample, and the relationship between the registry and the persons sampled is unclear. • It is unclear whether how the sample was obtained could introduce selection bias. • No sample size calculation was provided. • Questionnaire was not pilot tested, and has uncertain validity and reliability as it was researcher developed and not tested. • A satisfactory response rate was not achieved. • A full discussion, and identification, of the limitations and biases was lacking.
Johnson 2002,[213] Cross-sectional, Chart review	• Research objectives and questions were clearly stated and well suited to a cross-sectional design. • Data analysis was planned a priori and was appropriate for the type of data collected. • All eligible patient records were reviewed. • Significant and non-significant results were reported.	• Unclear if ethics approval was sought or obtained. • The results may not be generalizable beyond the setting of the particular clinic being examined. Sample was 100% Caucasian; additionally, three-quarters had previously participated in CRC screening — thus may be a highly motivated sample. • Unlikely that the questionnaire was valid or reliable.
Esplen 2001,[174] Survey, Questionnaire	• Unclear whether ethics approval was obtained, although participants had provided consent to have their blood drawn and genetic counselling on a previous occasion. • This was a pilot study prior to conducting larger studies. • Standardized measures and questionnaires were used. • Authors discussed potential biases and limitations of the study.	• The study population could represent a more motivated population, since they self-referred for testing, and then a proportion of those people participated in the survey. Unclear if the population is representative of a broad population who could be affected. • No sample size calculation was provided.
Aktan-Collan 2000,[172] 2001,[224,229,248] 2013,[179]	• Ethics approval was sought and obtained. • Research objectives and methods were	• Unclear whether the target population representative of the population to which the results will be

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
Survey, Questionnaire	clearly stated and were suitable to a survey design. • Sampling strategy was clearly defined and appropriate for the survey method.	generalized; unclear if the 36 families who participated were representative of the greater HNPCC population. • It is unclear whether the clinic served the greater HNPCC population. • Power calculation not provided; however, there was mention of lack of power for the "got cancer" portion of the sample that was subsequently excluded and the discussion mentions power — although no calculation was presented. • Validity of the questionnaires is unclear; some questions were developed for the study, others (State Trait Anxiety Inventory) were validated instruments. • Reliability of the questionnaires unclear — not reported.
Kinney 2000,[181] Survey, Interview (patients with CRC)	• Research objectives and questions were clearly defined, as was the sampling strategy. • The research objectives were congruent with a survey design and the sampling strategy was congruent with the objectives. • The target sample is likely to be representative of the population to which the results will be generalized; patients were recruited from a representative clinic and cancer support group. • Data analysis strategies were appropriate for the type of data collected, and were planned a priori. • The researchers have drawn an appropriate link between data and conclusions.	• It is unclear if how the sample was obtained could introduce selection bias; the sample was purposively selected to include African-Americans. • No sample size calculation was provided. • Questionnaire was not pilot tested, and has uncertain validity and reliability as it was researcher developed and not tested. • It is unclear whether a satisfactory response rate was achieved.
Kinney 2000,[202] Survey, Interview (FDR of patients with CRC)	• Research objectives and questions were clearly defined, as was the sampling strategy. • The research objectives were congruent with a survey design and the sampling strategy was congruent with the objectives.	• Ethics approval is not reported. • The target population is unlikely to be representative of the population to which the results will be generalized; the participants were white and well educated.

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
	• Data analysis strategies were appropriate for the type of data collected, and were planned a priori. • The researchers have drawn an appropriate link between data and conclusions.	• It is likely the way the sample was obtained could introduce selection bias; this sample was self-referred and referred by family members, and it is likely they are highly motivated. • No sample size calculation was provided. • Questionnaire was not pilot tested, and has uncertain validity and reliability as it was researcher developed and not tested. • It is unclear whether a satisfactory response rate was achieved. • It is unclear whether all significant and non-significant results were reported.
Codori 1999,[250] Survey	• Research objectives clearly stated and suitable for a survey design; they were looking for motivators for genetic testing, and reasons for declining testing. • Sampling strategy was congruent with the objectives and they were reasonably successful in tracking down individuals who declined testing. • Seems likely that a satisfactory response rate was achieved. • Exact *P* values were not reported but both significant and non-significant results were reported. • Authors addressed many of the limitations of their study; e.g., that study is not generalizable to clinical population as participants received free genetic counselling that did not influence their medical record.	• Sample size calculation not provided. • Unclear whether or not the questionnaires were reliable or valid. • There was no mention of methods a priori.
Glanz 1999,[164] Survey, Questionnaire	• Research objectives were clearly stated and were suitable to the survey study design. • Sampling strategy was clearly defined. • A pilot of the methods was conducted; they	• Unclear whether or not the target population was representative of the population for which the results will be generalized; unclear if those who live in Oahu are representative of the Hawaiian population. • Sample size population was not provided.

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
	describe conducting pre- and post-pilot tests after adding new elements to existing questionnaires. • Study questionnaires were partially valid; some sections were and some were not. They describe establishing face and content validity for new items, and other items were drawn from standardized questionnaires. • Study questionnaires were partially reliable; some sections were and some were not. They describe assessing using Cronbach's alpha. • A satisfactory response rate was achieved.	• Authors do not explore many limitations of their study.
Gritz 1999,[226] Vernon 1999,[195] Survey	• Ethics approval obtained. • Study objectives were clear and appropriate for a survey. • Sampling strategy was clearly defined and was congruent with the objectives. • Most sections of the questionnaire were validated instruments that were checked for reliability. • Response rate was 80%.	• Unclear whether the target population was representative of the population to which the results will be generalized; unclear the type of people or range of people seen at this one clinic, and how representative they are of a more general population. • Unclear if those who participated were particularly high or low distress patients. • The authors did not fully discuss potential biases; the study occurred in a single centre, the design was cross-sectional, the population was highly white, and perhaps a highly motivated population.
Petersen 1999,[207] Survey, Questionnaire	• Research objectives and questions were clearly defined, as was the sampling strategy. • The research objectives were congruent with a survey design and the sampling strategy was congruent with the objectives. • The target sample was representative of the population to which it will be generalized. • Sample size calculation was provided. • Data analysis strategies were appropriate for the type of data collected, and were planned a priori.	• The actual sample obtained was highly educated and white, and suggestive of selection bias. • The questionnaire was researcher developed and its reliability and validity were uncertain, and it was uncertain whether the questionnaire underwent pilot testing.

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
	• A relatively satisfactory response rate (> 50%) was achieved and interviews were conducted with survey non-responders. • Significant and non-significant results were reported. • The researchers have drawn an appropriate link between data and conclusions.	
Vernon 1997,[249] Cross-sectional, Questionnaire	• Research objectives and questions were clearly defined, as was the sampling strategy. • The research objectives were congruent with a survey design and the sampling strategy was congruent with the objectives. • The study questionnaire was valid and reliable. • Data analysis strategies were appropriate for the type of data collected, and were planned a priori. • A satisfactory response rate was achieved. • Significant and non-significant results were reported. • Authors have drawn an appropriate link between the data and conclusions.	• Unclear if ethics approval was sought or obtained. • The population that was sampled is unlikely to be representative of the general population; the sample was obtained from one cancer centre, and the population was younger, highly white, and at a later disease stage than the general CRC population. • The population consenting to participate could be more highly motivated and introduce self-selection bias. • No sample size calculation was provided. • It is uncertain whether the questionnaire underwent any pilot testing.
Lerman 1996,[175] Cross-sectional, Interview	• Research objectives and questions were clearly defined, as was the sampling strategy. • The research objectives were congruent with a survey design and the sampling strategy was congruent with the objectives. • Interview methods appear to have face validity and are from a previous study; they do not seem prone to recall bias. • A satisfactory response rate was achieved. • The researchers have drawn an appropriate link between data and conclusions.	• It is unclear whether ethics approval was obtained. • It is unclear whether the way the sample was obtained may introduce selection bias; recruitment occurred through only one cancer centre with a high proportion of African-American participants. • No sample size calculation was provided. • Appropriateness of the data analysis methods is unclear. • It is unclear if all data analysis was planned a priori as no plan was reported, and it is unclear whether all significant and non-significant results were reported.

First Author Year of Publication, Study Design, Data Collection Methods	Key Strengths	Key Limitations
		• A full discussion and identification of the limitations and biases was lacking.

CRC = colorectal cancer; DSM = Diagnostic and Statistical Manual of Mental Disorders; ECOG = Eastern Cooperative Oncology Group; EPQ-R = Eysenck Personality Questionnaire–Revised; HNPCC = hereditary non-polyposis colorectal cancer; LS = Lynch syndrome; RCT = randomized controlled trial; SF-36 = Short Form (36) Health Survey.

Appendix 58: Critical Appraisal of the Included Studies: Qualitative (Question 7)

First Author Year of Publication, Study Design, Data Collection Methods	Strengths	Limitations
Burton-Chase 2014,[222] Qualitative Description, Interview, Questionnaire	• Data collection strategies were well described, and congruent with the research questions. Interviews adequately addressed the need to seek patient perspectives, while questionnaire provided opportunity to gain demographic information and knowledge of cancer risk. • Data analysis strategies were well described. The two coders had a high level of agreement, and met to discuss discrepancies and emerging themes. Additionally, verbatim data to support the coding analysis was provided.	• The authors describe how eligible patients were identified, but it is unclear if participants were all participants in the registry, or only a subset. There is no description of when sampling stopped, and whether this was guided by data saturation, or convenience, for example. • Much of the qualitative data were enumerated, which is not appropriate given the sampling strategy. • It is clear that themes and concepts were rooted in the data; however, it is unclear if the full range of themes were reported. The analysis instead focused on identifying the number of participants who raised certain concepts, but it is unclear if the diversity within issues is covered. • There was little discussion of non-disclosure practices with reasons, which is relevant to the objectives and likely included in the data but not reported. • The role of the researcher is not described; nor have the researchers' assumptions and biases in particular relation to the research question been made explicit. • No techniques described to enhance dependability.
Tomiak 2014,[178] Qualitative description, Interview	• Study design and research questions clearly described and justified. • Reporting of verbatim data and independent analysis by more than one researcher used as techniques to enhance credibility of data and analysis.	• Unclear how study participants were selected from the target population. • Unclear whether data collection and sampling occurred until data saturation was reached. • Data collection strategy was poorly described. Unclear where data collection took place, what was included in the interview guide, how long the interviews lasted, and whether interviews were semi-structured or otherwise.

First Author Year of Publication, Study Design, Data Collection Methods	Strengths	Limitations
		• Unlikely that diversity in perspectives on the issue of uptake of genetic counselling and testing could be explored, given the small sample and underrepresentation of decliners. • The role of the researcher is not described; nor have the researchers' assumptions and biases in particular relation to the research question been made explicit. • No techniques reported to enhance dependability of data or the data analysis.
Bruwer 2013,[163] Qualitative description, Interview, Observation	• Data collection strategies are well described, and congruent with the research questions. • Analysis strategy is well described, and reported results are clearly supported by data, and from the perspective of participants. • Coding and theme development confirmed by two supervisors, although no description was provided of the process or results of this exercise. Additionally, verbatim data to support the coding analysis were provided.	• "Information-rich" participants were reported to be identified, although no description was provided of what is meant by "information-rich" in this context, or how people were identified. Ideally, participants would have reflected the range of potential emotional effects and familial communication patterns, although it is not clear if that is the case. • A thematic analysis is well described, although most of the reported data are in the form of frequency and counts. Frequency and counts, suggestive of generalizability or representativeness, are not appropriate for the sampling strategy, suggesting a high potential for biased estimates. • The role of the researcher is not described; nor have the researchers' assumptions and biases in particular relation to the research question been made explicit. • No techniques described to enhance dependability.
Shipman 2013,[176] Qualitative description, Interview	• Study design and research questions were clearly stated and justified. • Sampling strategy was well defined and congruent with research questions. • Data collection and analysis strategies were well described and congruent with research questions.	• Unclear if data collection and sampling continued until data saturation was reached.

First Author Year of Publication, Study Design, Data Collection Methods	Strengths	Limitations
	• Results are well rooted in participant perspectives and a diversity of perspectives was accounted for. • Limited description provided regarding co-construction of accounts of responsibility, between interviewer and participant. • Analysis by more than one researcher, and verbatim reporting of data used as strategies to enhance credibility. • Peer review as a strategy to enhance dependability.	
Walsh 2012,[185] Qualitative description, Focus group	• Study design and research questions clearly described and justified. • Data collection and analysis strategies are clearly reported and congruent with the research objectives. • Reporting of verbatim data and independent analysis by more than one researcher used as techniques to enhance credibility of data and analysis.	• Unclear whether a purposive sampling strategy was used, or how study participants were recruited and selected. • Unlikely that sampling and data collection occurred until data saturation was reached. • While it is likely that participant perspectives are reflected in the report, there is indication of the researcher's voice taking precedence over the patient's voice. • The role of the researcher is not described; nor have the researchers' assumptions and biases in particular relation to the research question been made explicit. • No techniques reported to enhance dependability.
Watkins 2011,[208] Grounded theory, Interview	• Study design and research questions were clearly stated and justified. • Sampling occurred until data saturation was reached. • Data collection and analysis strategies well described and congruent with research questions. • Results are well rooted in participant perspectives and a diversity of perspectives was represented.	• Sampling strategy is poorly reported, although it does seem that some sampling decisions were based on emerging theories, as is appropriate for a grounded theory approach. Participants were selected from a prior case-control study with no description of the purposive strategy used. Unclear how of 17 eligible families, 39 people could be included, but ultimately there were 23 participants.

First Author Year of Publication, Study Design, Data Collection Methods	Strengths	Limitations
	• Member checking and independent analysis by more than one researcher used as strategies to enhance credibility. • Peer review used as strategy to enhance dependability.	• The role of the researcher is not described; nor have the researchers' assumptions and biases in particular relation to the research question been made explicit.
Ersig 2010,[251] Qualitative description, Interview	• The study design is congruent with the research question, although no justification is reported.	• It appears that a representative sample was chosen, although a purposive sample would have been more appropriate for the research question. There was no mention of whether sampling continued until data saturation. • Data collection process is poorly described; for example, it is not reported who conducted the interviews or how long they lasted. • The role of the researcher is not described; nor have the researchers' assumptions and biases in particular relation to the research question been made explicit. • No techniques were reported to enhance the credibility or dependability of the results.
Palmquist 2010,[165] Qualitative description, Interview	• Purposive sampling strategy well described, and congruent with research questions. • Data collection and analysis strategies well described and congruent with research questions. • Results are consistent with data and rooted in participants' perspectives. • Credibility enhanced through independent analyses by more than one researcher and the reporting of verbatim data.	• Study design not clearly stated or justified. • Unclear if sampling and data collection continued until saturation. • Given that diversity in racial backgrounds drove sampling decisions, more cross-cultural comparisons would have been appropriate. • The role of the researcher is not described; nor have the researchers' assumptions and biases in particular relation to the research question been made explicit. • No strategies to enhance dependability were reported.
Landsbergen 2009,[194] Qualitative description, Interview, Chart Review	• Research questions were clearly stated and suited to qualitative inquiry • Data collection strategies are well described and congruent with research objectives.	• Study design not described nor justified. • Sampling strategy is clearly defined, but excludes people who are MSI negative whose perspectives would have been informative for the research question. Further, sampling did not continue until data saturation was reached.

First Author Year of Publication, Study Design, Data Collection Methods	Strengths	Limitations
		• Data analysis strategies are poorly described, and raise issues regarding congruence with the research questions, how themes were developed, and whether the diversity of perspectives were appropriately captured. • The role of the researcher is not described; nor have the researchers' assumptions and biases in particular relation to the research question been made explicit. • No techniques were reported to enhance credibility or dependability of the data or data analysis.
McCann 2009,[186] Qualitative description, Interview	• Study design and research questions clearly stated, justified, and congruent. • Data collection and data analysis strategies are well described. • Results are well rooted in participant perspectives, verbatim quotes are provided to support data analysis, and a diversity of perspectives are accounted for and reported. • Independent analysis of 4 transcripts by a separate researcher to enhance credibility.	• No techniques were reported to enhance the dependability of the results. • Sampling strategy is not well described and therefore unclear if strategy is congruent with research question. Medical records were used to determine eligibility, but no description was provided of how people were chosen from among the eligible individuals. • Unclear if sampling continued until data saturation, or how otherwise the sample size was determined. • The role of the researcher is not described; nor have the researchers' assumptions and biases in particular relation to the research question been made explicit.
Roygnan 2008,[204] Qualitative description, Interview	• Research questions were clearly stated and suited to qualitative inquiry. • Results are well rooted in participant perspectives, and a diversity of perspectives are accounted for and reported.	• Unclear whether ethics approval was obtained. • Sampling strategy is poorly described, in terms of sample size, selection criteria and recruitment. • Unlikely that sampling and data collection occurred until data saturation was reached. • Data collection and data analysis strategies are poorly reported, making critical appraisal difficult. • The role of the researcher is not described; nor have the researchers' assumptions and biases in particular relation to the research question been made explicit. • No techniques reported to enhance credibility or dependability of data or the data analysis.

First Author Year of Publication, Study Design, Data Collection Methods	Strengths	Limitations
Carlsson 2007,[205] Qualitative description, Interview	• Study design and data collection well justified and appropriate to evaluate experiences from and perceived impact on life after genetic testing. • Sampling strategy well described and justified, although no indication provided as to whether sampling continued until data saturation. • Data collection and analysis strategies well described and justified. • Themes and subthemes with supportive data outlined in a comprehensive table, suggesting data are rooted in participants' perspectives and diversity in perspectives has been explored.	• The role of the researcher is inadequately explored. Prior experience with the topic, and qualitative research, should have been outlined to explore assumptions and biases and the potential influence on data collection and analysis. • No techniques to enhance dependability were reported.
Wakefield 2007,[168] Qualitative description, Questionnaire, Chart review	• Study design and research questions clearly described and justified. • Data collection and analysis strategies are clearly reported and congruent with research objectives. • Results are rooted in participants' own perspectives, and diversity in perspectives was explored. • Reporting of verbatim data and independent analysis by more than one researcher used as techniques to enhance credibility of data and analysis. • Peer debriefing used as a technique to enhance dependability.	• Unclear whether ethics approval was obtained. • Unclear whether sampling and data collection occurred until data saturation was reached. • The role of the researcher is not described; nor have the researchers' assumptions and biases in particular relation to the research question been made explicit.
Mesters 2005,[219] Qualitative description, Interview	• Study design was well justified and congruent with research questions. • Data collection and analysis strategies are well described and congruent with research questions. • Results are well rooted in participant	• Unclear if ethics approval was obtained. • Sampling strategy is incongruent with the research question. A random sample was obtained, although it would have been more appropriate to select registry participants based on characteristics that could influence disclosure, such as age, children or no

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	perspectives, and a diversity of perspectives was explored in the analysis. • Credibility enhanced through independent analyses by more than one researcher and the reporting of verbatim data.	children, sex, psychological distress, social support, and ensure variation in these characteristics in the sample. Further, no rationale was provided for target sample size of 30, nor was a description provided regarding data saturation. • The role of the researcher is not described; nor have the researchers' assumptions and biases in particular relation to the research question been made explicit. • No strategies to enhance dependability were reported.
Pentz 2005,[231] Qualitative description, Interview	• Study design was well justified and congruent with research questions. • Results were rooted in participants' own perspectives and a diversity of perspectives was explored. • Credibility enhanced through independent analyses by more than one researcher and the reporting of verbatim data. • Peer review conducted to enhance dependability.	• Sample was recruited from another research study; therefore, not purposively developed to address this research question. • Limited detail was provided regarding data collection; for example, who conducted the interviews, how long they were, where they took place, or what questions were asked. • Unclear if data saturation was reached. • Limited detail was provided regarding data analysis; for example, how codes were developed and applied. • Qualitative data were quantified in the analysis, which resulted in lost meaning. • The role of the researcher is not described; nor have the researchers' assumptions and biases in particular relation to the research question been made explicit.
Koehly 2003,[221] Qualitative design using Social Network Methodology, Interview	• Study design and research questions clearly described and justified. • Sampling strategy clearly described and justified. • Data collection and analysis strategies were clearly described and justified.	• Recruitment was conducted through another research study, and therefore didn't allow for sampling until data saturation was reached. • Unclear whether diversity in perspectives related to familial discussions about genetic testing could be explored in 5 families and whether it is captured in the reported analysis. • The role of the researcher is not described; nor have the researchers' assumptions and biases in particular relation to the research question been made explicit.

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		• No techniques reported to enhance credibility or dependability of data or the data analysis.
Peterson 2003,[166] Qualitative description, Interview	• Study design was well justified and congruent with research questions. • Data collection and analysis strategies are well described and congruent with research objectives. • Results were rooted in participants' own perspectives. • Researcher assumptions and biases are described as they related to the research question. • Credibility enhanced through independent analyses by more than one researcher and the reporting of verbatim data. • Peer review conducted to enhance dependability.	• Sampling strategy was not well described. Participants were recruited from an ongoing clinical study, but it is unclear if all eligible families were included or a subset. If a subset, it is unclear how they were selected. • Unclear if data saturation was reached. • Unclear if diversity in perspectives were explored, as in most cases, results were described as if all families agreed.
Ramsey 2003,[190] Qualitative description, focus group	• Study design and data collection methods are well described and justified.	• Sampling strategy is not well described, as it is unclear how study participants were selected from those in the registry. • It is unlikely that a purposive sample was obtained. Matching by age and sex would likely not achieve diversity in perspectives. • Unlikely that data saturation was reached, given the sampling strategy and description of the approach. • Unlikely that participant concerns, versus researcher concerns, were adequately addressed. • Unclear how themes were developed, and whether initial impressions were subsequently verified against data. • The role of the researcher is not described; nor have the researchers' assumptions and biases in particular relation to the research question been made explicit. • No techniques to enhance dependability or credibility

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		of the data were reported.
Reeve 2000,[193] Qualitative description, Interview	• Study design and research questions were clearly stated and justified. • Sampling strategy well described, and congruent with the research questions. Sampling continued until data saturation was reached. • Data collection and analysis strategies were well described and congruent with the research question. • Results are well rooted in participant perspectives, and a diversity of perspectives was accounted for. • Member checking and independent analysis by more than one researcher conducted to enhance credibility.	• Unclear if ethics approval was obtained. • The role of the researcher is not described; nor have the researchers' assumptions and biases in particular relation to the research question been made explicit. • No techniques reported to enhance dependability.
Lynch 1999,[171] Unclear, Interview	• No major strengths identified.	• Study design and research questions are not described, nor justified. • No details are provided regarding how the 7 families in the sample were selected and recruited. • Data collection strategies are not well reported. Unclear when interviews took place — perhaps during clinical counselling sessions. • No details regarding the data analysis plan were provided, raising concerns regarding how themes were identified, whether results represent participant perspectives, and whether a diversity of perspectives have been explored. • The role of the researcher is not described; nor have the researchers' assumptions and biases in particular relation to the research question been made explicit. • No techniques reported to enhance credibility or dependability of data or the data analysis.

CRC = colorectal cancer; MSI = microsatellite instability.