Protocol: Targeted screening for Lynch syndrome in people with colorectal cancer and their relatives

Review group:	Corinna Clark Samantha Johnson Chris Stinton Karoline Freeman On behalf of WeBS-ESG
Correspondence to:	Karoline Freeman Warwick Screening Warwick Applied Health Warwick Medical School University of Warwick Coventry CV4 7AL
Tel:	02476 574026
Email:	k.freeman@warwick.ac.uk

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Abbreviations

CRC	Colorectal cancer
DARE	Database of abstracts of reviews of effects
EEA	European Economic Area
EPCAM	Epithelial cellular adhesion molecule
IHC	Immunohistochemistry
LS	Lynch Syndrome
MMR	Mismatch repair
MSI	Microsatellite instability
MSI-H	High microsatellite instability
NICE	National Institute for Health and Care Excellence
PPI	Patient and public involvement

1 Background

1.1 Condition

Lynch syndrome (LS) is a rare genetic condition that increases the risk of developing certain types of cancer.[1] It is caused by a germline pathogenic variant in mismatch repair (MMR) genes (MLH1, MSH2, MSH6, and PMS2) or in the epithelial cellular adhesion molecule (EPCAM) gene (responsible for silencing MSH2 expression). MMR is a system that recognises and repairs errors in DNA that arise during replication and recombination. Pathogenic variants in MMR genes lead to deficiency in MMR proteins and the accumulation of errors in DNA regions called microsatellites, leading to microsatellite instability (MSI)[2] and an increased risk of cancer.[1] LS is the most common hereditary cause of colorectal cancer (CRC), accounting for an estimated 3% of CRC cases.[3 4] Individuals with LS have a lifetime CRC risk reported to be between 10% and 80% depending on the gene variant,[4 5] as well as a greater risk of developing other cancers (e.g. endometrial, ovarian, pancreatic, gastric, biliary tract, urothelial, sebaceous gland adenomas, keratoacanthomas, and brain cancers).[4 1] In the UK, it is estimated that approximately 1 in 500 people have LS,[6 7] with only 5% being diagnosed.[8]

1.2 Testing for Lynch Syndrome

Prior to 2017, referral for LS testing was based on criteria related to a family history of cancer and early age of cancer onset (Amsterdam Criteria and Revised Bethesda Guidelines). Given the population prevalence, improved patient outcomes from surveillance and intervention or treatment pathways,[9] and other considerations (such as screening technology advances), the National Institute for Health and Care Excellence (NICE) DG27 Guidelines[10] expanded eligibility for LS testing criteria to include all people with CRC.[8]

The NICE DG27 diagnostic Guideline recommends (1) immunohistochemistry (IHC) testing for the absence of any mismatch repair proteins (MLH1, MSH2, MSH6 and PMS2), or (2) microsatellite instability (MSI) testing. If MSI testing is positive or the MLH1 result is abnormal, testing for BRAF V600E and MLH1 promoter hypermethylation (to exclude sporadic or non-LS cancers) should follow. If MSH2, MSH6 or PMS2 are abnormal or BRAF V600E and MLH1 promoter hypermethylation are negative, then germline DNA testing should be implemented to confirm a LS diagnosis.

1.3 Current Targeted Screening Proposal for LS in CRC Patients

As LS is inherited in an autosomal dominant pattern, and so first-degree relatives have a 50% chance of also having LS, current NICE diagnostic guidelines (DG27) highlight the potential benefit to cascade screening 'at risk' family members following an LS diagnosis in patients with CRC or endometrial cancer[11] and cascade screening forms part of the NHS England pathway for implementing Lynch syndrome testing and surveillance.[11] Given the 50% risk to first degree relatives of also having LS, screening immediate family members (children, parents, siblings) of CRC- LS patients (and cascading through families as needed) could provide a route to increase diagnoses and improve prognoses through prevention, surveillance and treatment strategies. For example, in a Finnish cohort study, regular surveillance reduced the risk of CRC by 62% and reduced mortality by 65%.[12] The current NHS England LS diagnostic pathway[11] advises that at risk family members are given letters to take to their GP as a route

to obtain a referral to a genetics service; however, cascade testing that relies on patients communicating their LS diagnosis to family members and family members subsequently initiating testing can have low uptake rates.[13] [14] Reported barriers include interpersonal /family dynamics, psychosocial issues (e.g. anxiety, stigma concerns), lack of understanding, and organisational and environmental barriers,[13] which can disproportionally affect underserved populations such as minority groups, people with disabilities, and people from lower socioeconomic backgrounds.[15] A recent report from Bowel Cancer UK, suggested that only half of UK health authorities provide letters for the family members of LS patients to enable them to access genetic testing.[16] Issues have also been highlighted with the implementation of the DG27 guidelines, with lower than predicted numbers of CRC patients being assessed for LS.[7] Concerns about service-level delivery of LS diagnoses have led to calls for better national and local infrastructure to implement CRC index case LS diagnosis and cascade testing for family members.[7]

This evidence map aims to summarise the volume of evidence on existing testing pathways for Lynch syndrome in CRC patients and their asymptomatic relatives and testing strategies for targeted screening for LS in asymptomatic relatives of CRC patients.

2 Research question and overall approach

2.1 Research question

The overall research question is:

What is the volume and type of evidence relevant to targeted screening for LS in asymptomatic relatives of CRC – LS patients.

2.2 Overall approach

The review will be undertaken using the UK NSC assessment approach for an Evidence Map.

3 Methods

3.1 Decision questions

Key questions for the evidence map are:

Question 1. Are there any national or international guidelines or recommendations for targeted screening of LS in CRC patients and/or their asymptomatic relatives?

Question 2. What is the volume and type of evidence available on screening tests used to detect LS in asymptomatic relatives of CRC patients with LS mutations?

Question 3. What is the volume and type of evidence available on the penetrance of CRC among people who have mismatched repair gene mutations or EPCAM gene deletions?

3.2 Identification and selection of studies

3.2.1 Search strategy

Systematic literature searches will be undertaken using terms for the condition which will identify evidence for all review questions. The search strategies were developed in MEDLINE (Ovid) using terms relating to Lynch syndrome and colorectal cancer. The search conducted by Exeter PenTAG [17] was used as a starting point.

The search will be adapted for EMBASE (Ovid) and supplemented with searches for guidelines using the two websites Dimensions and TRIP. An example of the search strategy that may be used in the major databases is provided in Appendix 1.

The search strategy will comprise the following elements:

1) Searching of electronic bibliographic databases,
2) Searching the websites Dimensions and TRIP for guidelines
3) A Google search for guidelines (considering the first 5 pages)

In addition, the papers referenced in the original open call submission will be assessed against the review eligibility criteria.

3.2.2 Study eligibility criteria

Studies that satisfy the following criteria listed in Table 3.2 will be included:

Table 3.1 Question 1 - Are there any national or international guidelines or recommendations for targeted screening of LS in CRC patients and/or their asymptomatic relatives?

	Inclusion criteria	Exclusion criteria
Population	Colorectal cancer (CRC) patients and/or their asymptomatic relatives	Patients with non-CR cancers
Target condition	Lynch syndrome	Lynch-like syndrome Lynch syndrome detected via a different route than through CRC patients

Intervention / exposure	Any national and/or international guidelines/recommendations (can include recommendations in academic publications) on targeted screening for Lynch syndrome in CRC patients and/or cascade testing of their asymptomatic relatives. Any national and/or international guidelines/ recommendations on non-targeted testing such as ad hoc diagnosis with or without management of LS in CRC patients.	Papers not clearly stating in the title or abstract that they are guidelines, or recommendations on targeted screening / testing for LS in CRC and/or their asymptomatic relatives Guidelines and recommendations on management/surveillance only
Comparator	N/A	N/A
Outcomes	N/A	N/A
Study designs	Any	N/A

Table 3.2 Question 2. What is the volume and type of evidence available on screening tests used to detect LS in asymptomatic relatives of CRC patients with LS mutations?

	Inclusion criteria	Exclusion criteria
Population	Asymptomatic relatives of CRC patients with LS	CRC patients Relatives of LS patients with other cancers (e.g. endometrial)
Target condition	Lynch syndrome	Lynch-like syndrome
Intervention / exposure	Any germline genetic test	LS criteria, tumour based biochemical and genetic tests
Reference standard	Any (e.g. a genetic test different to index test or follow-up to CRC)	N/A
Comparator	Any/None	N/A
Outcomes	Sensitivity Specificity Positive and negative predictive values Likelihood ratios Area under the curve Any other test accuracy/validity outcomes	N/A

Study designs	Studies in randomly sampled or consecutively enrolled populations and systematic reviews* (priority) Single gate studies Two-gate studies if none/few of above Studies of test analytical and clinical validity	Case studies

*Systematic reviews will be defined as per Centre for Reviews and Dissemination (CDR) Database of Abstract of Reviews of Effects (DARE) criteria[18]

Table 3.3 Question 3. What is the volume and type of evidence available on the penetrance of CRC among people who have mismatched repair gene mutations or EPCAM gene deletions?

	Inclusion criteria	Exclusion criteria
Population	Asymptomatic individuals with LS with confirmed MMR and EPCAM genetic variants	Patients with previous cancer diagnosis and LS Individuals with CRC or other cancer diagnosis LS not confirmed through germline testing (e.g. high MSI levels/MSI status, or on basis of criteria such as Amsterdam criteria) Lynch-like syndrome Variants/groups of variants where it is not clearly stated that they are classed as LS
Target condition	CRC	Extra-colonic tumours Adenomas
Exposure	Confirmed MMR and EPCAM genetic variants	No MMR and EPCAM genetic variants
Comparator	Any/None	N/A
Outcomes	CRC diagnosis in individuals with LS Cumulative penetrance estimates Any other measure reported that captures the penetrance of CRC among individuals with LS	Proportions of genes/ variants detected without subsequent case ascertainment
Study designs	Prospective cohort studies and systematic reviews* (priority) Retrospective cohort studies Cross-sectional studies	Case studies

*Systematic reviews will be defined as per Centre for Reviews and Dissemination (CDR) Database of Abstract of Reviews of Effects (DARE) criteria[18]

In addition to the exclusions specified for the three review questions in tables 3.1-3.2, papers that fulfil the following criteria will be excluded:

Qualitative studies, studies reporting outcomes not listed in our inclusion criteria, studies where outcomes of interest could be calculated from the data reported but are not explicitly stated (e.g. papers that report true positives and false negatives but not sensitivity), studies where more than 10% of the sample do not meet our inclusion criteria and are not reported separately, articles not available in the English language, articles published prior to 2015, single case studies (one patient or one family), letters, reviews, editorials, communications, commentaries, conference abstracts, and other grey literature.

3.3 Review strategy

Titles and abstracts of records identified by the searches will be assessed against the inclusion/exclusion criteria by one reviewer.

We will note the number of unclear studies by question following title and abstract assessment and decide in collaboration with the UK NSC partners whether a full text assessment is required based on volume of included studies for each of the three review questions. The purpose of the evidence map is to aid discussion on whether there is sufficient published evidence to support a more in-depth review.

If full text review of unclear studies is agreed on, full text articles will be assessed by one reviewer. If full text assessment is not required, we will report the number of unclear records as potential additional studies.

3.4 Data extraction strategy

Data will be extracted by a single reviewer. For each question, data will only be extracted from the highest priority studies (see section 3.6). Non-prioritised studies will not undergo data extraction. Numbers of deprioritised studies will be reported for each review question.

3.5 Assessment of study quality

No assessment of study quality will be undertaken.

3.6 Methods for reporting

We will employ an order of priority approach to reporting of the studies. For prioritised studies we will report type of study, study objectives, study PICO and reported outcomes as per our inclusion criteria above. We will report number of non-prioritised studies. The prioritisation for the three review questions will be as follows:

Question 1:

We will prioritise documents from the UK and studies from 1) Northwest Europe and 2) other G7 countries (Canada, France, Germany, Italy, Japan, the United States, and the EEA (27 EU member countries plus Iceland, Liechtenstein, Norway and Switzerland)) as well as Australia, New Zealand and China over any other countries. We will report studies from the UK separately and before any other studies.

Question 2:

We will first prioritise studies from the UK and studies from 1) Northwest Europe and 2) other G7 countries (Canada, France, Germany, Italy, Japan, the United States, and the EEA (27 EU member countries plus Iceland, Liechtenstein, Norway and Switzerland)) as well as Australia, New Zealand and China over any other countries. We will report studies from the UK separately and before any other studies.

We will then prioritise studies in randomly assigned or consecutively enrolled populations and systematic reviews over other single gate studies. If none or few of the aforementioned are available, we will consider two-gate studies. We will define SR using the DARE criteria.[18]

In addition, we will count studies on new tests without any evidence on test accuracy where studies only report the analytical and/or clinical validity of the test.

Question 3:

We will first prioritise studies from the UK and studies from 1) Northwest Europe and 2) other G7 countries (Canada, France, Germany, Italy, Japan, the United States, and the EEA (27 EU member countries plus Iceland, Liechtenstein, Norway and Switzerland)) as well as Australia, New Zealand and China over any other countries. We will report studies from the UK separately and before any other studies.

We will then prioritise prospective cohort studies and SRs over other study designs (e.g. retrospective studies and cross-sectional studies).

4 Patient and Public Involvement

No PPI activity will be undertaken as part of this evidence map.

5 Timescale

Table 5.1 Project timeline

Protocol sign off	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8
Searches and deduplication								
Sifting ~2000 titles and abstracts								
Full text retrieval of studies								
Prioritisation of included studies								
Data extraction for 15 studies								
Write up								
References								

6 Research team's contributions

Name: Dr Corinna Clark
Job title: Assistant Professor
Address: Warwick Screening, Warwick Medical School, University of Warwick, Coventry, CV4 7AL
Email: Corinna.Clark@warwick.ac.uk
Contribution: Protocol development, sifting, data extraction, report writing

Name: Dr Chris Stinton
Job title: Senior Research Fellow
Address: Warwick Screening, Warwick Medical School, University of Warwick, Coventry, CV4 7AL
Email: C.Stinton@warwick.ac.uk
Contribution: Protocol development, project oversight

Name: Mrs Samantha Johnson
Job title: Information Specialist
Address: Warwick Screening, Warwick Medical School, University of Warwick, Coventry, CV4 7AL
Email: Samantha.A.Johnson@warwick.ac.uk
Contribution: Development of search strategies, undertaking searches, reference management

Name: Dr Karoline Freeman
Job title: Associate Professor
Address: Warwick Screening, Warwick Medical School, University of Warwick, Coventry, CV4 7AL
Email: k.freeman@warwick.ac.uk
Contribution: Project lead, protocol development, report writing

7 Competing interest of authors

None of the authors declared any competing interests for the project.

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9 Appendices

Appendix 1: Search strategies

Searches run: 05 June 2025

Ovid MEDLINE(R) ALL <1946 to June 04, 2025>

1	(lynch adj3 syndrome*).mp.		5012
2	(lynch adj3 (famil* or relative* or relation* or carrier*)).mp.	659	
3	1 or 2		5031
4	(colon* or colorectal* or crc).mp.		869963
5	exp Colorectal Neoplasms/		256652
6	4 or 5		909112
7	3 and 6		4154
8	limit 7 to yr="2015 -Current"		2687
9	limit 8 to english language		2559
10	exp animals/ not humans.sh.		5345204
11	9 not 10		2545

Embase Classic+Embase <1947 to June 04 2025 >

1	(lynch adj3 syndrome*).mp.		9679
2	(lynch adj3 (famil* or relative* or relation* or carrier*)).mp.	1182	
3	1 or 2		9720
4	(colon* or colorectal* or crc).mp.		1429317
5	exp colorectal cancer/		442754
6	4 or 5		1468952
7	3 and 6		9220
8	limit 7 to (article or article in press)		3876
9	limit 8 to yr="2015 -Current"		2677
10	limit 9 to english language		2517
11	(exp animal/ or exp invertebrate/ or nonhuman/ or animal experiment/ or animal tissue/ or animal model/ or exp plant/ or exp fungus/) not (exp human/ or human tissue/)		9343968
12	10 not 11		2492