Protocol for an evidence map: Investigating a programme modification to the NHS Bowel Cancer Screening Programme (NHS BCSP) to incorporate blood-based liquid biopsy triage tests for patients who screen positive on a faecal immunochemical test (FIT)

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1 Plain English Summary: Exploring the use of a blood test when people need further action after a bowel cancer screening test

1.1 How does the NHS screen for bowel cancer in the UK?

Bowel cancer is common in the UK. Older people are more likely to get bowel cancer and have lower chances of successful treatment, especially if the cancer is detected at an advanced stage. The UK National Screening Committee (UK NSC) recommends that everyone aged 50 to 74 is offered screening for bowel cancer every two years. People in this age group are sent a home testing kit in the post. They send a small amount of poo to a testing lab. The lab tests the poo for traces of blood, which can be a sign of bowel cancer.

Most people hear that their test result is normal, and no further action is needed. Some people are told that their poo had some traces of blood in it. They will be offered a further test called a colonoscopy to find out what is causing the blood. A specialist uses a thin, flexible tube with a camera to look inside the bowel. Colonoscopy is very effective at diagnosing bowel problems. But there are some downsides: some people find it embarrassing or uncomfortable, and the preparation – drinking a special solution the day before to completely empty the bowel – can be unpleasant and disruptive. Complications can also occasionally occur. Colonoscopy is also expensive to the NHS because it needs a specialist team.

1.2 What are we trying to find out?

The UK NSC wants to explore if they could improve the screening programme. They want to know if people who need further action after the poo test should have a special blood test done to look for signs of cancer. Only the people whose blood test also shows these signs of cancer would then be invited to have a colonoscopy. Avoiding an unnecessary colonoscopy could be better for patients and reduce the workload and costs for the NHS. But this would only be worthwhile if the blood test results are reliable and the benefits outweigh any potential harms.

The UK NSC wants to check if there is enough evidence for it to be worth exploring this idea in more depth. We'll search for how many studies and what types of studies have looked at:

- How accurate these blood tests are in the relevant people (those who needed further action after the poo test).
- Whether people think it's acceptable to have one of these special blood tests when further action is needed after the poo test, and to use the results to decide if someone should have a colonoscopy.
- What the overall effect on people's health would be of using these special blood tests to decide who should have a colonoscopy, and the overall value for money for the NHS.

2 Background

2.1 Bowel Cancer

Bowel cancer, also known as colorectal cancer, develops in the lining of the large bowel (colon) and rectum.(1) It is the fourth most common type of cancer in the UK, with an incidence of 44,100 new diagnosed cases per year, and accounted for 11% of all new cancer cases diagnosed between 2017-2019.(2) Data from Cancer Research UK indicate that incidence rates are highest and ten-year survival rates lowest in older people. Approximately 16,800 deaths were attributed to bowel cancer between 2017-2019.(2)

Screening programmes aim to detect bowel cancer and potentially pre-cancerous lesions of the bowel before symptoms appear (secondary prevention) with the aim of improving treatment options and outcomes for those diagnosed with the disease.

2.2 Current NHS Bowel Cancer Screening Programme (NHS BCSP)

The UK National Screening Committee (NSC) currently recommends screening for bowel cancer in adults aged between 50-74 years living in the UK, and screening is offered biennially.(3) In 2006, the Department of Health and Social Care in England agreed funding for a national screening programme which achieved a full national roll out in England and Wales in 2010.(4) A national bowel cancer screening programme was also introduced in Scotland in 2007,(5) and in Northern Ireland in 2010.(6)

Since its inception, the NHS BCSP in England has undergone several modifications. These include a change in the initial screening test used to detect blood in the stool from guaiac faecal occult blood test (gFOBT) to faecal immunochemical test (FIT) for haemoglobin,(7) and an expansion of the age range of people invited for screening from 60-69 years to 50-74 years.(3)

Currently, people aged 50-74 years who are registered with a General Practitioner (GP) and live in England are invited biennially for screening through the NHS BCSP. All eligible individuals receive a bowel cancer screening home test kit (FIT kit) through the post and are asked to provide a stool sample. Samples are sent to a local laboratory for testing, using prepaid packaging which is provided with the kit. Results are sent to individuals within two weeks, in binary form. If traces of blood were detected in the stool sample, the individual is invited for a colonoscopy, to investigate the bowel visually using a camera, while if no traces of blood are detected then no further action is taken.(8) This bowel cancer screening approach is also replicated nationally in Scotland,(9, 10) Northern Ireland,(6) and Wales.(11)

The number of people eligible for the NHS BCSP and uptake rates have both consistently increased, year-on-year, since 2014. The number of people screened in the 30 months prior to March 2014 was 4,562,303, rising to 6,764,895 in the 30 months prior to March 2024, resulting in an increasing demand for diagnostic

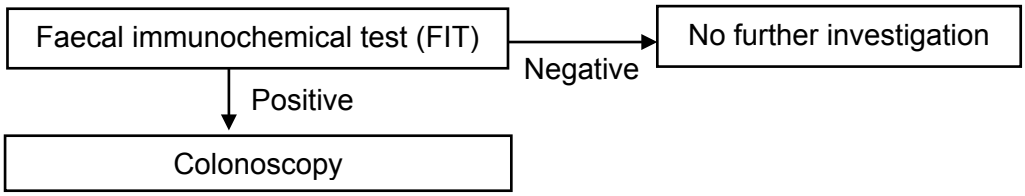
(endoscopic and radiological) services. During the year 2023-2024, the programme also carried out a total of 92,755 diagnostic tests (endoscopic and radiological) from both screening and surveillance episodes, resulting in 5,320 cancer diagnoses and the placing of a further 6,567 people into surveillance.(12) During 2021-22, a false positive rate of 9% was reported, based on the number of people (6,231) who received a 'nothing abnormal detected' result following diagnostic investigation. A further 34,763 people received an episode result of 'low-risk adenoma' or another finding and were returned to routine recall.(13)

2.3 Proposed programme modification

During the 2024 'Open Call for New Topics', the UK NSC received a proposal for a programme modification to the current NHS BCSP. The proposal is for the introduction of a blood-based liquid biopsy as a second tier or triage test, to be offered to patients with a positive FIT result (i.e., those currently invited for a colonoscopy following the detection of blood in their stool sample).

This evidence map will consider evidence regarding introducing any blood-based liquid biopsy as a triage test in FIT-positive individuals, as a means of determining who should undergo colonoscopy. Figure 1 shows the proposed modification to the current NHS BCSP.

Current NHS Bowel Cancer Screening Programme:



Modification under consideration:

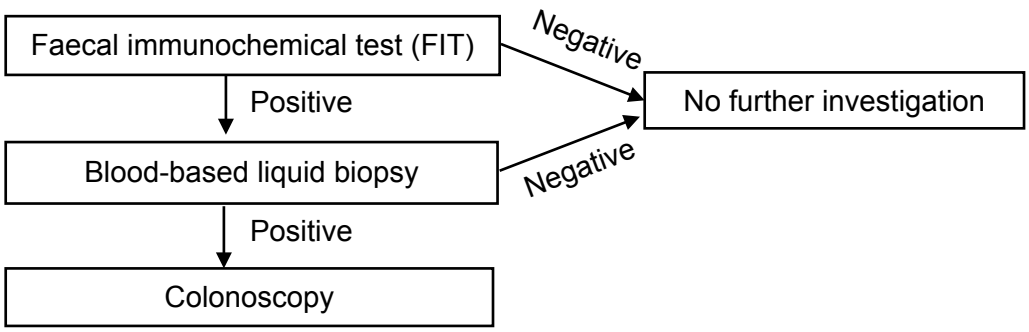


Figure 1: Flow chart comparing current screening programme and modification under consideration

2.6 Liquid Biopsy as Bowel Cancer Triage Test

Blood-based liquid biopsy tests are used to screen for cancer by measuring the following primary analytes individually or in combination: cell-free DNA (cfDNA) of a freely floating tumour cell; circulating tumour cells (CTC) that have detached from a tumour; circulating tumour DNA (ctDNA) or circulating tumour ribonucleic acid; methylation markers; extracellular vesicles; known proteins, antibodies or exosomes associated with cancer.(14)

Multi-cancer early detection (MCED) tests such as the NHS-Galleri test,(15) PanSeer,(16) CancerSEEK,(17) and the Dxcover® Cancer Liquid Biopsy platform (Dxcover, UK),(18) examine the presence of such biomarkers to simultaneously detect diverse cancers. This evidence map will not consider use of MCEDs, but will instead focus on potential use of blood-based liquid biopsy tests that solely target bowel cancer. In the UK, there are currently no such tests offered within the NHS BCSP. However, a number of these tests are available in the UK, including ColonAiQ (Breakthrough Genomics), Colox (Novigenix) and Shield (Guardant Health).

2.7 Importance of evaluating potential modifications to screening programmes

Before modifying any screening programme, it is important to understand whether the proposed modification leads to better overall outcomes, at a reasonable cost, compared with the current approach. There are many important considerations, including the overall impact on accuracy, patient experience, timeliness, cost and resource use. The UK NSC used a structured, evidence-based process to ensure that any recommended modifications are safe, effective and acceptable to the population.

3 Aims of the evidence map

Evidence maps are rapid evidence products which aim to gauge the volume and type of evidence relating to a specific topic. They enable assessment of whether sufficient evidence exists to justify commissioning a more sustained review.

This evidence map aims to evaluate the volume and type of evidence on key issues related to modification of the NHS BCSP, to include the use of blood-based liquid biopsy tests as triage tests for people who test positive on a FIT within the screening programme.

This evidence map will consider the following questions:

1. What is the volume and type of evidence available on the accuracy of blood-based liquid biopsy tests used to triage people who screen positive on a FIT for bowel cancer?
2. What is the volume and type of evidence available on the acceptability of blood-based liquid biopsy tests used to triage people who screen positive on a FIT for bowel cancer?
3. What is the volume and type of evidence available on the clinical and cost-effectiveness of blood-based liquid biopsy tests used to triage people who screen positive on a FIT for bowel cancer?

The findings of this evidence map will provide the basis for discussion to support UK NSC decision making on whether there is sufficient evidence to justify the commissioning of further work on this topic.

4 Methods for the evidence map

An evidence map will be prepared, in accordance with UK NSC process guidance.(19) Titles and abstracts will be assessed for inclusion and included articles will be reviewed at the abstract level, with full text articles examined only where key information is not clear from the abstract. Separate inclusion criteria have been developed for each key question.

4.1 Inclusion and exclusion criteria

Evidence for all questions will be restricted to full reports available in English, reported since 2015. Conference abstracts, commentaries and editorials will not be included.

Systematic reviews identified through the search will be treated as a source of eligible studies, unless they fulfil all inclusion criteria for a particular question. In this case, they will be considered as the primary source of evidence for that question and supplemented by primary studies published since the last search date for the systematic review.

4.1.1 Question 1: What is the volume and type of evidence available on the accuracy of blood-based liquid biopsy tests used to triage people who screen positive on a FIT for bowel cancer?

Table 1 describes the inclusion criteria for this question.

Table 1 Inclusion criteria for question 1

Population	Symptomless adults who screen positive on a FIT for bowel cancer. Studies conducted in a general (rather than FIT-positive) symptomless adult population will also be included if these could provide data restricted to the FIT positive group.
Index test	Any blood-based liquid biopsy test that solely targets bowel cancer. Studies of multi-cancer early detection (MCED) tests will be excluded.

Target condition	Bowel cancer
Reference standard	Any reported reference standard
Outcomes	Any measure of accuracy (e.g. sensitivity, specificity, positive predictive values, negative predictive values, likelihood ratios)
Study designs	Single gate (cohort/cross-sectional) or two gate (case-control) test accuracy studies.

4.1.2 Question 2: What is the volume and type of evidence available on the acceptability of blood-based liquid biopsy tests used to triage people who screen positive on a FIT for bowel cancer?

Table 2 describes the inclusion criteria for this question.

Table 2 Inclusion criteria for question 2

Population	Symptomless adults who screen positive on a FIT for bowel cancer. If no studies are identified which were conducted in this population, studies conducted in a general screening-eligible, symptomless population will be included.
Intervention	Any blood-based liquid biopsy test that solely targets bowel cancer. Studies of multi-cancer early detection (MCED) tests will be excluded.
Outcomes	Any outcome related to acceptability of blood-based liquid biopsy tests, including screening uptake.
Study designs	RCTs, observational studies, qualitative studies, and surveys or questionnaire studies.

4.1.3 Question 3: What is the volume and type of evidence available on the clinical and cost-effectiveness of blood-based liquid biopsy tests used to triage people who screen positive on a FIT for bowel cancer?

Table 3 describes the inclusion criteria for this question.

Table 3 Inclusion criteria for question 3

Population	Symptomless adults undergoing screening for bowel cancer
Intervention	Screening strategy involving an initial FIT, followed by any blood-based liquid biopsy that solely targets bowel cancer in those that test positive on the initial FIT, followed by confirmatory testing. Studies of multi-cancer early detection (MCED) tests will be excluded.
Comparator	Screening strategy based only on FIT followed by confirmatory testing.
Outcomes	Mortality, number of cases of bowel cancer detected, number of colonoscopies, any cost-effectiveness outcome.
Study designs	RCTs, non-randomised studies of interventions, economic evaluations (including economic models)

4.2 Study identification

Studies will be identified using bibliographic search methods following the UK NSC guidelines for evidence maps.

4.2.1 Bibliographic searching

The following databases will be searched:

- MEDLINE (Ovid SP)
- Embase (Ovid SP)
- Web of Science (Clarivate)

A sensitive search strategy based on a combination of relevant controlled vocabulary headings and free-text terms for ‘colorectal cancer’, ‘liquid biopsy’ and ‘screening’ will be used. Search limits will be applied to retrieve only English language studies. Additionally, a publication type limit will be applied to the Embase search to exclude conference abstracts and conference papers.

In order to maintain relevance to current clinical practice, a date limit to identify papers published between 2015 and 2025 will also be applied to the search. An example draft search strategy for the MEDLINE database is reported in the Appendix.

4.2.2 Managing the searches

Search results will be exported to EndNote 21 for deduplication using the default deduplication settings. Search results will be imported into Nested Knowledge® (nested-knowledge.com) for further de-duplication and screening.

4.3 Review strategy

Review processes will be undertaken in Nested Knowledge®, systematic review software.

All titles and abstracts identified by the searches will be screened by one reviewer. A random sample of 20% of records will be independently screened by a second reviewer with the remaining 80% checked using ‘Robot Reviewer’, the AI second reviewer in Nested Knowledge®. Where there is a disagreement between the human reviewers, disagreements will be resolved through discussion. Where there is disagreement between the human reviewer and the robot reviewer, the human reviewer will re-consider the abstract and make a final decision on inclusion.

Full data extraction and risk of bias assessment is not part of the evidence map process. The following 'top level’ information will be extracted from each included study:

- For review question 1: objectives, population (screen positive on a FIT or general screening-eligible, symptomless population), study design (one or two gate), number of participants, index test evaluated, reference standard, measure(s) of diagnostic accuracy reported, country of study, conclusions
- For review question 2: objectives, population (screen positive on a FIT or general screening-eligible, symptomless population), study design, number of

participants, index test evaluated, acceptability outcomes reported, country of study, conclusions
- For review question 3: objectives, study design, country of study, intervention, comparator, outcome(s) reported, number of participants (where relevant), conclusions

This simplified data extraction process will be undertaken by one reviewer and checked by a second reviewer. Full texts will be examined, as necessary, to clarify information that is unclear from the abstract.

4.4 Synthesis methods

A summary of the volume and type of available evidence will be provided for each key question, highlighting where evidence relates to a UK setting. This summary will include an indication of whether the current evidence base is likely to be adequate to justify further assessment.

In addition, a brief description of each included study will be provided (based on the 'top level' data extraction described above). This study level information will also be summarised in tables and figures, which will be designed to facilitate rapid visualisation of the volume and type of available evidence.

The UK NSC evidence map template will be used, following the document formatting guidelines provided in the specification document.

5 Competing interests of authors

None of the authors have any competing interests.

6 Timetable/milestones

Tasks	Target dates
Start	7 May 2025
Protocol	16 May 2025
First evidence map draft	20 June 2025
BESS Group responding to the feedback from UK NSC Evidence team	Send an amended version to the UK NSC Evidence team ~ 1 or 2 weeks after receiving feedback
Reference group meeting	Feedback from reference group to be sought ASAP, once the draft is ready (via email if necessary)
ESGs responding to the feedback from reference group	Updated version to be ready 1 or 2 weeks after receiving feedback
Public consultation	Currently 3-month public consultation, but this can change
UK NSC meeting	Feedback from UK NSC to be sought at earliest opportunity

ESGs responding to the feedback from the UK NSC	Final document to be ready ASAP after the UK NSC meeting□□

7 References

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Appendix: Literature search strategy

Draft MEDLINE Search

Database, version and platform

MEDLINE(R) ALL 1946 to May 13, 2025 via OvidSP. Please note that this date (13 May 2025) reflects the version of the database at the search development date and not the exact version of the database when the search will be conducted.

#	Search terms
1	exp Colorectal Neoplasms/
2	((bowel or colorectal or colorectum or colon or colonic or rectal or rectum) adj1 (cancer$ or carcinoma$ or neoplas$ or tumor$ or tumour$ or malignan$ or metastas$)).ti,ab,kw.
3	1 or 2
4	Liquid Biopsy/
5	((liquid or plasma) adj2 (biops$ or "biopsy-based")).ti,ab,kw.
6	(("blood-based" or blood or plasma) adj4 (biomarker$ or "biological marker$" or test$ or assay$ or sample$ or triage or triaging or screen$ or detect$)).ti,ab,kw.
7	("ColonAiQ" or "LUNAR-2" or "Shield™" or "Shield" or "Colox" or "Colox R" or "Epi proColon" or "Epi proColon R" or "Epi proColon®" or "Freenome test" or "Freenome's test" or “Raman test”).ti,ab,kw.
8	or/4-7
9	Mass Screening/ or Early Detection of Cancer/
10	(screen$ or detect$).ti,ab,kf.
11	9 or 10
12	3 and 8 and 11
13	english.lg.
14	12 and 13
15	limit 14 to yr="2015-2025"