York Evidence Synthesis Group

MULTI-CANCER EARLY DETECTION TESTS FOR SCREENING

NIHR Reference No. NIHR161758

Final amended version 28/09/23

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Date completed	22/09/2023

PROSPERO registration number: CRD42023467901

This review is funded by the NIHR Evidence Synthesis Programme

PLAIN ENGLISH SUMMARY

Cancer screening is available for certain cancers in the NHS, such as cervical, breast and bowel cancer. Other types of cancer are usually found after patients develop symptoms, therefore, they are diagnosed at a more advanced stage and are more difficult to treat. Blood tests to detect cancer signals at a very early stage are currently being developed; these tests could help identify a range of different cancers before symptoms develop, when they are easier to treat. These 'multi-cancer early detection' tests are recommended for screening people with a higher risk of cancer, such as those aged 50 or older. However, there is a risk that screening healthy people for such a wide range of cancers will cause anxiety, lead to unnecessary follow up tests and potentially diagnose cancers at such an early stage that they may never have advanced enough to need treatment.

The aim of this project is to systematically review studies that have assessed the effectiveness of blood-based multi-cancer early detection tests. A systematic review is a research method where all relevant studies assessing a specific question are found and summarised. We will search for all relevant studies of multi-cancer early detection blood tests (e.g., Galleri, PanSEER, CancerSEEK). The target population is adults 50-79 years old without symptoms of cancer or a diagnosis of cancer within the previous three years. However, if we do not find enough studies in the target population, then we will include studies where patients known to have cancer are compared against people who are not suspected of having cancer ('case-control' studies) and we will also consider including people younger than 50 and/or older than 79 years old. We will assess the reported data to determine whether these technologies are clinically effective (i.e., they are accurate and acceptable to people being screened). If appropriate, we will combine the results of the included studies using statistical methods, although we expect that we will have to combine results narratively (not using statistics) for most outcomes.

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1 DECISION PROBLEM

1.1 Purpose of the decision to be made

Population-based cancer screening in the NHS is currently limited to selected cancers (cervical, breast, bowel).[1] Additionally, some people at a high risk of developing lung cancer can receive a lung health check.[2] Other cancers are often detected after presentation of symptoms, many of which will be diagnosed at stages 3 and 4, where treatment options may be limited. Breast, prostate, lung, and bowel cancers together account for just over half of all new cancers diagnosed.[3]

The Galleri® test (developed by GRAIL) is a multi-cancer early detection (MCED) blood test that uses genetic sequencing to detect potential signals of cancer.[4] The assay is combined with a machine learning based classification algorithm that identifies patterns predictive of cancer and indicative of potential cancer site of origin. Results from an early case-control study indicate that it could identify more than 50 types of cancer before symptoms occur, including cancers that are typically difficult to identify early (e.g. head and neck, bowel, ovarian, pancreatic, lung).[5] The test detects circulating cell-free DNA (cfDNA) and is able to predict the most likely site, or sites, within the body that the signal is coming from (the 'Cancer Signal Origin'), allowing for confirmatory follow up tests. Galleri predicts up to two Cancer Signal Origins by comparing the methylation pattern to the patterns of 21 possible Cancer Signal Origin predictions. Predicting the origin of the cancer signal helps healthcare providers select the appropriate follow-up diagnostic tests. Cancer Signal Origins can be either an anatomic site (e.g., colorectal) or a cellular lineage (e.g., lymphoid).[REF] The Galleri® test is recommended for use in adults with an elevated risk for cancer, such as those aged 50 or older.[6] The clinical utility of the Galleri test for population screening in the UK is currently being assessed by a randomised controlled trial, the NHS-Galleri research trial.[7] Other blood-based MCED tests include PanSEER and CancerSEEK, which have also reached advanced stages of development.[8]

The NHS Long Term Plan ambition seeks to diagnose 75% of cancers at stage 1 or 2, to enable more effective treatment.[9] A MCED test embedded within a national screening programme, and in addition to existing cancer screening programmes, may increase the number of cancers diagnosed at an earlier stage. However, there is a potential risk that screening healthy people for such a wide range of cancers will create anxiety, lead to unnecessary follow up tests, and also overdiagnosis of cancers at such an early stage that they might never have advanced enough to require treatment. In addition, cancers with no effective treatments may be identified.[10]

The aim of this assessment is to synthesise clinical effectiveness evidence on blood-based MCED tests for population-based screening. Although technologies are also being developed to detect cancer

signals in other bodily fluids, such as urine, we will only focus on blood-based tests in this assessment.

1.2 Interventions

This assessment will evaluate blood-based multi-cancer early detection tests for cancer screening.

1.3 Populations and relevant subgroups

The population of interest is individuals aged 50-79 years without clinical suspicion of cancer and who have not been diagnosed with cancer or received treatment for cancer within the last three years.

The subgroups relevant to this appraisal will be individuals at elevated risk of cancer (e.g. smoking history, genetic predisposition, family history or personal history of malignancy), and patients with different cancer types detected (i.e. primary site) and cancer stages, where diagnostic accuracy may differ. Where possible, we will also record and take account of different ethnic and socio-economic groups.

1.4 Place of the intervention in the treatment pathway

As a screening test, the setting is community, including primary care, as part of a national screening programme.

1.5 Relevant comparators

The comparator is no multi-cancer early detection test for cancer screening (individuals should still be offered relevant existing screening programmes and clinical follow-up of symptoms).

1.6 Key outcomes to be addressed

Key outcomes include accuracy of the test for detecting cancer (including sensitivity, specificity, positive and negative predictive values by site and stage); accuracy of the 'Cancer Signal Origin', i.e. the cancer type that is most likely, and the second most likely, to be present; number of cancers detected (by site and stage); time to diagnosis (or exclusion of cancer); incidental findings; additional tests and procedures (depending on cancer type suspected); mortality; potential harms; health-related quality of life; acceptability to individuals screened; satisfaction of individuals screened.

1.7 Objectives

The aim of this project is to assess the accuracy and clinical effectiveness, acceptability and feasibility of the use of blood-based multi-cancer early detection tests for screening individuals aged 50-79 years without clinical suspicion of cancer and who have not been diagnosed with cancer or received treatment for cancer within the last three years.

The objective is to conduct a systematic literature review of the clinical effectiveness evidence on blood-based multi-cancer early detection tests for screening. Cost data and NHS efficiency outcomes will not be collected as part of this review, but will be evaluated as part of other ongoing work. However, a range of stakeholders are supporting protocol development and will help with understanding and interpreting the findings of the review within the broader context, taking account of the feasibility of blood-based multi-cancer early detection tests within the NHS Screening Programme, as well as the upcoming randomised controlled NHS-Galleri trial.[11, 12]

2 METHODS FOR SYNTHESISING EVIDENCE ON CLINICAL EFFECTIVENESS

The systematic review will be conducted following the general principles recommended in CRD's guidance and reported in accordance with the PRISMA statement.[13, 14]

2.1 Search strategy

The aim of the search is to systematically identify published and unpublished studies of MCED tests used for the purposes of population screening. Comprehensive searches of electronic databases, trial registers, examination of relevant websites and reference checking of included studies and reviews will be undertaken.

A search strategy for MEDLINE (Ovid) is included in Appendix 1. The strategy combines terms for: 1. cancer, with 2. liquid biopsy or blood tests, and 3. screening or early detection. Specific phrases for the tests such as multi-cancer early detection tests will also be included in the strategy as well as the brand names of individual tests (e.g. Galleri, PanSEER, CancerSEEK). The search is limited to publications from 2010 onwards to reflect the recent development of these technologies. Study design or publication type limits will not be used.

The following databases will be searched: MEDLINE ALL (Ovid), Embase (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL, Wiley), the Science Citation Index (Web of Science), Cochrane Database of Systematic Reviews (CDSR, Wiley), Database of Abstract of Reviews of Effects (DARE), KSR Evidence (Ovid).

Unpublished, ongoing or grey literature will be identified through searching the HTA database, International HTA database (INAHTA), websites of international HTA organisations, Conference Proceedings Citation index – Science (Web of Science), ClinicalTrials.gov, WHO trials register, and PROSPERO. All search results will be imported into EndNote 20 reference management software and deduplicated.

After screening, the websites of MCED test manufacturers will be examined to identify any further references. The reference lists of included studies and relevant reviews will also be checked for any relevant references.

2.2 Study selection

All references identified by the electronic searches will be uploaded into EPPI-Reviewer. The machine learning and text mining tool in EPPI-Reviewer will be used to prioritise titles and abstracts for screening.[15] Prioritised titles and abstracts will be assessed by one reviewer with the first 10% of records assessed by two reviewers to ensure consistency; disagreements will be resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be assessed independently by two reviewers, using the same process for resolution of disagreements as outlined above. Studies published as conference abstracts will be eligible for inclusion. Foreign language publications will be eligible for inclusion and will be translated for data extraction where possible, depending on resource limitations. Where translation is not possible, potentially eligible foreign language publications will be listed as requiring further assessment. Eligible ongoing studies without relevant outcome data reported at the time of data extraction will be listed as 'Ongoing Studies'.

2.3 Inclusion criteria

Population

The target population is individuals aged 50-79 years without clinical suspicion of cancer and who have not been diagnosed with cancer or received treatment for cancer within the last three years. However, if insufficient relevant studies are identified, then studies including patients known to have cancer (i.e. case-control studies) will be considered for inclusion. Studies that include individuals with a wider age range than 50-79 years will also be considered for inclusion.

Subgroups of interest are individuals at elevated risk of cancer (e.g. smoking history, genetic predisposition or personal history of malignancy), patients diagnosed with different cancer types (i.e. primary site) and at different cancer stages, where diagnostic accuracy may differ.

Interventions

This assessment will evaluate blood-based multi-cancer early detection tests for cancer screening, such as Galleri, PanSEER, CancerSEEK and similar technologies aiming to detect multiple cancers at an early stage.

Studies assessing blood-based tests for assessing prognosis (e.g. risk-stratification, tumour staging and genotyping) or therapeutic decision-making (e.g. guiding precision therapy or monitoring response to treatment) in patients known to have cancer will not be eligible for inclusion.

Comparators

Not applicable; uncontrolled studies are eligible for inclusion.

Outcomes

Outcomes of interest include accuracy of the test (including sensitivity, specificity, positive and negative predictive values, reference standard test used to diagnose true disease status (if any)); number of cancers detected (by site and stage); time to diagnosis (or exclusion of cancer); incidental findings; additional tests and procedures; mortality; potential harms; health-related quality of life, acceptability to individuals screened; satisfaction of individuals screened.

Relevance and validity of the different outcomes will depend on whether a reference standard test is used to diagnose true disease status when a cancer signal is detected, and what additional tests are conducted on individuals without a cancer signal detected. The reference standard will depend on the cancer site being investigated.

Study designs

Prospective clinical trials (including randomised and other controlled trials) and cohort studies will be sought. If insufficient relevant trials and prospective cohort studies are identified, case-control studies including patients known to have cancer will be considered for inclusion if relevant outcome data are reported.

For case-control studies, only the following outcomes will be considered relevant: accuracy of the test (including sensitivity, specificity, positive and negative predictive values) (by site and stage); accuracy of the 'Cancer Signal Origin' (by site and stage); number of cancers detected (by site and stage); acceptability to individuals screened; satisfaction of individuals screened.

2.4 Data extraction

A standardised data extraction form will be developed and piloted. Data on the intervention(s), patient characteristics, setting, study design, reference standard test(s) used, and relevant outcomes will be extracted from included studies by one reviewer and independently checked by a second reviewer.

2.5 Quality assessment

Risk of bias will be assessed using a checklist appropriate to the study design. Relevance of the included studies to the review question will also be assessed, since it may be necessary to include

studies with a wider patient population than the target population for MCED test-based cancer screening. Assessment of risk of bias and relevance will be undertaken by one reviewer and independently checked by a second reviewer.

2.6 Methods of analysis/synthesis

In the initial synthesis, the results of data extraction will be presented in structured tables and as a narrative summary, grouped by population and MCED test characteristics. Where sufficient clinically and statistically homogenous data are available, data will be pooled using appropriate meta-analytic techniques, as described below. If case-control studies reporting relevant outcome data are included, studies of different designs will not be pooled and separate meta-analyses of prospectively designed studies and case-control studies will be conducted. However, it is anticipated that a narrative approach to synthesis will be required for most outcomes.

Validity of the test accuracy measures will be dependent on the reference standard (e.g., routine screening for specific cancer types and clinical investigation when symptoms present) and length of follow-up in prospective studies. Sensitivity of the test may be subject to bias where only individuals with a positive result of the MCED test undergo further diagnostic investigations during the study, and those with a negative result of the MCED test do not undergo further diagnostic investigations during the study. In this case, false negatives of the MCED test might be missed, unless detected at future routine screening or clinical investigation after presentation with symptoms, which may not occur for all individuals during the follow-up period of the study. In other words, all negative results of an MCED test are assumed to be 'true' negative results which will result in estimate of sensitivity that are higher than they would be if a perfect reference standard was used.

Additionally, within studies that include patients known to have cancer (i.e., case-control studies), estimates of sensitivity will also be higher than they would be for the target population. Estimates of positive and negative predictive values within studies including patients known to have cancer will also not be reflective of the target population.

Bivariate meta-analyses of sensitivity and specificity will only be performed where true positive (TP), false positive (FP), true negative (TN) and false negative (FN) results of an MCED test are reported and verified according to a reference standard during the follow-up of the prospective studies. If possible, sensitivity and specificity will be plotted in forest plots with 95% confidence intervals and bivariate meta-analyses of sensitivity and specificity will be performed using R Shiny application metaDTA v.2.0.5.[16, 17] Where TP, FP, TN and FN values of the MCED test are not reported and cannot be calculated or cannot be verified according to a reference standard during the follow-up of the study or for studies including patients known to have cancer, pooling of specificity values and 95% confidence intervals (Cis) using random-effects meta-analysis will be considered. If only a few

studies (less than 5) are included, a Bayesian random effects meta-analysis will be considered, using a semi-informative prior distribution for the between-study heterogeneity.[18]

For other clinical outcomes where sufficient homogenous data are reported, results will be synthesised using Bayesian fixed and random-effects meta-analyses using a semi-informative prior distribution for the between-study heterogeneity if less than five studies are included.[18]

Where data are insufficient for meta-analysis a narrative synthesis will be performed, by comparing the tabulated results across studies to identify broad evidence of accuracy and clinical effectiveness of blood-based MCED tests for population-based screening.

2.6.1 Investigation of heterogeneity and subgroup analyses

For outcomes where meta-analyses are performed and a sufficient number of studies is available, heterogeneity will be assessed visually and by examining between-study heterogeneity estimates, such as I^2 statistic and the between-study standard deviation, and if feasible, by performing separate meta-analyses in different subgroups of participants.

3 STAKEHOLDER INVOLVEMENT

We will to ensure that relevant perspectives are properly considered during protocol development and as part of the process of understanding, interpretating and contextualising the findings of this review. We will work with a range of content experts involved in the cancer screening and care pathway, including general practitioners and cancer screening and diagnostic experts, as well as representatives from the National Screening Committee. We will also seek additional clinical input and input from patients and members of the public (via the TRANSFORM platform,[19] the Humber and North Yorkshire Cancer Alliance, Cancer Research UK and HealthWatch).

4 COMPETING INTERESTS OF AUTHORS

None.

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17. Patel A, Cooper N, Freeman S, Sutton A. Graphical enhancements to summary receiver operating characteristic plots to facilitate the analysis and reporting of meta-analysis of diagnostic test accuracy data. *Research Synthesis Methods* 2021;**12**:34-44.

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APPENDICES

APPENDIX 1: LITERATURE SEARCH STRATEGIES

Database: Ovid MEDLINE(R) ALL <1946 to September 13, 2023>
Search Strategy:
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1 Neoplasms/ (504101)
2 ((cancer$ or neoplas$ or tumour$ or tumor$ or carcinoma$ or oncolog$ or malignan$ or precancer$) adj6 (multiple$ or many or several or numerous or various or varied or miscellaneous or mixed or diverse or different)).ti,ab. (481091)
3 (multicancer$ or multi-cancer$ or multitumo?r$ or multi-tumo?r$ or pan-cancer$ or pancancer$ or pan-tumo?r$ or pantumo?r$ or cross-cancer$ or crosscancer$ or cross-tumo?r$ or crosstumo?r$).ti,ab. (4793)
4 ((cancer$ or neoplas$ or tumour$ or tumor$ or carcinoma$ or oncolog$ or malignan$ or precancer$) adj3 (type or types)).ti,ab. (174370)
5 1 or 2 or 3 or 4 (993603)
6 Liquid Biopsy/ (2716)
7 ((liquid$ or fluid$ or biofluid$ or bio-fluid$) adj3 biops$).ti,ab. (8392)
8 6 or 7 (8976)
9 Biopsy/ or Biopsy, Fine-Needle/ (203652)
10 exp Blood/ (1196437)
11 9 and 10 (9122)
12 ((blood or h?ematolog$ or plasma or serum) adj3 biops$).ti,ab. (5561)
13 11 or 12 (14504)
14 Hematologic Tests/ (10175)
15 ((blood or h?ematolog$ or plasma or serum) adj2 (test or tests or testing or tested or assay$)).ti,ab. (79621)
16 14 or 15 (88397)
17 Multiomics/ (822)
18 ((multiomic$ or multi-omic$ or panomic$ or pan-omic$ or integrative omic$) adj4 (test or tests or tested or testing or assay$ or biops$)).ti,ab. (114)
19 17 or 18 (924)
20 ((Multi-analyte$ or multianalyte$) adj4 (detect$ or screen$ or test or tests or tested or testing or assay$ or biops$)).ti,ab. (571)
21 8 or 13 or 16 or 19 or 20 (112181)
22 5 and 21 (5730)
23 Mass Screening/ (116511)
24 Diagnostic Screening Programs/ (156)
25 early diagnosis/ (30350)
26 "Early Detection of Cancer"/ (38071)
27 (screen$ or detect$).ti. (656777)
28 ((early or earlystage or earli$ or first or initial or timely) adj3 (screen$ or detect$ or diagnos$ or test or tests or testing or tested)).ti,ab. (434798)
29 (screen$ adj3 (test$ or tool$ or method$ or strateg$ or modalit$ or technolog$ or program$ or service$ or policy or policies or guideline$ or population$)).ti,ab. (201334)
30 23 or 24 or 25 or 26 or 27 or 28 or 29 (1188487)
31 22 and 30 (1886)
32 ((cancer$ or neoplas$ or tumour$ or tumor$ or carcinoma$ or oncolog$ or malignan$ or precancer$) adj6 (multiple$ or many or several or numerous or various or varied or miscellaneous or mixed or diverse or different) adj6 (screen$ or detect$)).ti,ab. (12043)
33 ((cancer$ or neoplas$ or tumour$ or tumor$ or carcinoma$ or oncolog$ or malignan$ or precancer$) adj6 (type or types) adj6 (screen$ or detect$)).ti,ab. (4420)

34 32 or 33 (15191)
35 21 and 34 (606)
36 31 or 35 (2018)
37 (((multi-cancer$ or multicancer$ or multi-tumo?r$ or multitumo?r$) adj6 (detect$ or screen$ or test or tests or tested or testing or assay$)) or MCED or MCDBT).ti,ab. (155)
38 ((multiple cancer$ or multiple tumo?r$) adj6 (detect$ or screen$ or test or tests or tested or testing or assay$)).ti,ab. (523)
39 ((pan-cancer$ or pancancer$ or pan-tumo?r$ or pantumo?r$) adj6 (detect$ or screen$ or test or tests or tested or testing or assay$)).ti,ab. (202)
40 ((cross-cancer$ or crosscancer$ or cross-tumo?r$ or crosstumo?r$) adj6 (detect$ or screen$ or test or tests or tested or testing or assay$)).ti,ab. (5)
41 ((multi-class cancer$ or multiclass cancer$ or multi-class tumo?r$ or multiclass tumo?r$) adj6 (detect$ or screen$ or test or tests or tested or testing or assay$)).ti,ab. (6)
42 37 or 38 or 39 or 40 or 41 (869)
43 (Galleri or GalleriTM).mp. (7)
44 PanSEER$.mp. (3)
45 CancerSEEK$.mp. (7)
46 CancerEMC$.mp. (1)
47 (PanTum or PanTumDetect).mp. (3)
48 Epitope-detection in monocytes.mp. (12)
49 CancerRadar$.mp. (0)
50 (IvyGene$ or IvyGeneCORE$).mp. (0)
51 CancerLocator$.mp. (1)
52 CancerDetector$.mp. (1)
53 (EpiPanGI Dx$ or EpiPanGIDx$).mp. (1)
54 OverC.mp. (2)
55 DEEPGEN.mp. (6)
56 Dxcover$.mp. (1)
57 trucheck$.mp. (0)
58 Elypta$.mp. (0)
59 MiRXES$.mp. (6)
60 Freenome$.mp. (1)
61 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 (47)
62 DELFI$.mp. (693)
63 Omni1$.mp. (24)
64 Signal-X$.mp. (48)
65 Harbinger$.mp. (2098)
66 EDIM$.mp. (180)
67 LUNAR$.mp. (4523)
68 MERCURY$.mp. (55377)
69 62 or 63 or 64 or 65 or 66 or 67 or 68 (62897)
70 22 and 69 (5)
71 36 or 42 or 61 or 70 (2835)
72 exp animals/ not humans.sh. (5154669)
73 71 not 72 (2804)
74 limit 73 to yr="2010 -Current" (2280)