Multi-cancer early detection tests for general population screening: a systematic literature review

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ABSTRACT

Background: General population cancer screening in the UK is limited to selected cancers. Blood-based multi-cancer early detection (MCED) tests aim to detect potential cancer signals from multiple cancers in the blood. The use of an MCED test for population screening requires a high specificity and a reasonable sensitivity to detect early-stage disease, so that the benefits of earlier diagnosis and treatment can be realised.

Objective: To undertake a systematic literature review of the clinical effectiveness evidence on blood-based MCED tests for screening.

Methods: Comprehensive searches of electronic databases (including MEDLINE and Embase) and trial registers were undertaken in September 2023 to identify published and unpublished studies of MCED tests. Test manufacturer websites and reference lists of included studies and pertinent reviews were checked for additional studies. The target population was individuals aged 50 to 79 years without clinical suspicion of cancer. Outcomes of interest included test accuracy, number and proportion of cancers detected (by site and stage), time to diagnostic resolution, mortality, potential harms, health-related quality of life (HRQoL), acceptability and satisfaction. Risk of bias was assessed using the QUADAS-2 checklist. Results were summarised using narrative synthesis. Stakeholders contributed to protocol development, report drafting, and interpretation of review findings.

Results: Over 8000 records were identified. Thirty-six studies met the inclusion criteria: one ongoing randomised controlled trial (RCT), 13 completed cohort studies, 17 completed case-control studies and five ongoing cohort or case-control studies. Individual tests claimed to detect from three to over 50 different types of cancer. Diagnostic accuracy of currently available MCED tests varied substantially: Galleri® (GRAIL) sensitivity 20.8% to 66.3%, specificity 98.4% to 99.5% (3 studies); CancerSEEK (Exact Sciences) sensitivity 27.1% to 62.3%, specificity 98.9% to 99.1% (2 studies); SPOT-MAS™ (Gene Solutions) sensitivity 72.4% to 100%, specificity 97.0% to 99.9% (2 studies); TruCheck™ (Datar Cancer Genetics) sensitivity 90.0%, specificity 96.4% (1 study); CDA (AnPac Bio) sensitivity 40.0%, specificity 97.6% (1 study). AICS® (Ajinomoto) screens for individual cancers separately, so no overall test performance statistics are available. Where reported, sensitivity was lower for detecting earlier stage cancers (Stage I-II) compared with later stage cancers (Stage III-IV). Studies of seven other MCED tests at an unclear stage of development were also summarised.

Limitations: Study selection was complex; it was often difficult to determine the stage of development of MCED tests. The evidence was limited; there were no completed RCTs and most included studies had a high overall risk of bias, primarily owing to limited follow-up of participants with negative test

results. Only one study of Galleri recruited asymptomatic individuals aged over 50 in the USA, however, study results may not be representative of the UK general screening population. No meaningful results were reported relating to patient relevant outcomes, such as mortality, potential harms, HRQoL, acceptability or satisfaction.

Conclusions: All currently available MCED tests reported high specificity (>96%). Sensitivity was highly variable and influenced by study design, population, reference standard test used and length of follow-up.

Future work: Further research should report patient relevant outcome and consider patient and service impacts.

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Abbreviations

AICS	AminoIndex Cancer Screening
CA125	Cancer antigen 125
CAP	Cluster Randomized Trial of PSA Testing for Prostate Cancer
CCGA	Circulating Cell-free Genome Atlas
CDA	Cancer Differentiation Analysis
CDSR	Cochrane Database of Systematic Reviews
cfDNA	Cell-free DNA
CI	Confidence interval
CSO	Cancer Signal Origin
CT	Computed tomography
CTC	Circulating tumour cells
ctDNA	Circulating tumour DNA
DARE	Database of Abstracts of Reviews of Effects
DELFI	DNA Evaluation of Fragments for Early Interception
DNA	Deoxyribonucleic acid
EDI	Equality, Diversity and Inclusion
FN	False negative
FP	False positive
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
INAHTA	International Health Technology Assessment database
MCED	Multi-cancer early detection
NA	Not applicable
NHS	National Health Service
NPV	Negative predictive value
PET-CT	Positron emission tomography-computed tomography
PPCS	Prospective Population-based Cohort Study
PPV	Positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROMIS	Patient-Reported Outcomes Measurement Information System
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	Randomised controlled trial
SPOT-MAS	Screening for the Presence Of Tumour by Methylation And Size
TN	True negative
TP	True positive
UKCTOCS	UK Collaborative Trial of Ovarian Cancer Screening

PLAIN LANGUAGE SUMMARY

Cancer screening is only available for some cancers. New tests that look for signs of cancer in blood (blood-based multi-cancer early detection tests) are being developed; they aim to detect multiple different cancers at an early stage, when they are potentially more treatable. Taking account of stakeholder feedback, we reviewed all studies assessing the effectiveness of blood-based multi-cancer early detection tests for cancer screening. We thoroughly searched for relevant studies and found over 8000 records. We included 30 completed studies and six ongoing studies of 13 different tests. None of the studies were good quality, mainly because they didn't properly check whether the test result might have been incorrect and participants with a negative test result actually had cancer. Most studies included participants who are different from the general UK population that would be likely to have this type test for cancer screening. None of the studies reported meaningful results for patient-relevant outcomes, such as death, potential harms, quality of life and acceptability. We found 14 completed studies assessing six tests that are currently available: Galleri® (GRAIL), CancerSEEK (Exact Sciences), SPOT-MAS™ (Gene Solutions), TruCheck™ (Datar Cancer Genetics), CDA (AnPac Bio) and AICS® (Ajinomoto). All of the tests were quite good at ruling out cancer, but their accuracy for finding cancer varied a lot, mostly because of differences in the study methods and characteristics of the included participants. The tests were better at finding more advanced cancers, which are potentially less curable than early cancers, so more research is needed to know whether tests would actually save lives. Better designed studies including participants similar to those who might get the test in the real world, and which report on patient-relevant outcomes and properly consider patient experience and impact on services, are needed. Several new studies are planned or underway.

Word count: 298

SCIENTIFIC SUMMARY

Background

General population cancer screening in the UK is limited to selected cancers (cervical, breast, bowel and, for some high-risk individuals, lung). Most other cancers are detected after presentation of symptoms, when the disease tends to be at a more advanced stage and treatment options may be more limited. Blood-based multi-cancer early detection (MCED) tests aim to detect potential cancer signals (such as circulating cell-free deoxyribonucleic acid [cfDNA]) from multiple cancers in the blood.

The use of an MCED test as a screening tool in a generally healthy, asymptomatic population, requires a high specificity and a reasonable sensitivity to detect early-stage disease, so that the benefits of earlier diagnosis and treatment can be realised. An MCED test embedded within a national population-based screening programme, in addition to existing cancer screening programmes, may increase the number of cancers diagnosed at an earlier stage. However, identification of cancers with no effective treatments, even at an early stage, may have no improvement on mortality or health-related quality of life (HRQoL). In addition, early screening of healthy people for such a wide range of cancers, and the expected lengthy time to diagnostic confirmation, may create anxiety and lead to unnecessary follow-up tests, when false positive test results occur.

Objectives

The aim of this project was to conduct a systematic review to assess the accuracy and clinical effectiveness, acceptability and feasibility of blood-based MCED tests for population-based screening.

Methods

Comprehensive searches of electronic databases (including MEDLINE and Embase) and trial registers were undertaken in September 2023. Test manufacturer websites and reference lists of included studies and pertinent reviews were checked for additional relevant studies.

Published and unpublished prospective clinical trials and cohort studies of blood-based MCED tests for screening were sought. Studies assessing blood-based tests for assessing prognosis or therapeutic decision-making in patients with cancer were not eligible for inclusion.

The target population was individuals aged 50 to 79 years without clinical suspicion of cancer and who had not been diagnosed with, or received treatment for, cancer within the last three years. As insufficient relevant studies were identified within the target population, studies that included patients known to have cancer (i.e., case-control studies) and studies that included individuals with a different age range were included.

Outcomes of interest were test accuracy (including sensitivity, specificity, positive and negative predictive values), number and proportion of cancers detected (by site and stage), mortality, time to diagnostic resolution, incidental findings, additional tests and procedures, potential harms, HRQoL, acceptability and satisfaction.

A standardised data extraction form was developed and piloted. Data on the intervention(s), participant characteristics, setting, study design, reference standard test(s) used, and relevant outcomes were extracted from included studies by one reviewer and independently checked by a second reviewer. Risk of bias and applicability were assessed using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) checklist by one reviewer and independently checked by a second. Disagreements were resolved through discussion. Results were summarised using narrative synthesis.

Stakeholders contributed to protocol development, report drafting, and interpretation of review findings.

Results

The electronic searches identified 8,069 records; 228 full texts were further reviewed. Eleven additional records were identified from searching MCED test manufacturer websites. Study selection was complex; it was often difficult to determine whether studies assessed technologies at an early stage of development, or the final or near-final version of the test.

Thirty-six studies, evaluating thirteen MCED tests or technologies, met the review inclusion criteria: one ongoing randomised controlled trial (RCT), 13 completed cohort studies, 17 completed case-control studies, four ongoing cohort studies and one ongoing case-control study. Studies assessed the following MCED tests: Galleri® test (GRAIL, Menlo Park, California), CancerSEEK (Exact Sciences, Madison, Wisconsin), SPOT-MAS™ (Gene Solutions, Ho Chi Minh City, Vietnam), TruCheck™ (Datar Cancer Genetics, Beyreuth, Germany), CDA (Cancer Differentiation Analysis; AnPac Bio, Shanghai, China) and AICS® test (AminoIndex Cancer Screening; Ajinomoto, Tokyo, Japan). Other MCED technologies included in the review, that were at an unclear stage of development and did not appear to be available for use, were: Aristotle® (StageZero Life Sciences, Richmond, Ontario), CancerenD24 (manufacturer unknown), OncoSeek® (SeekIn Inc, San Diego, California), SeekInCare® (SeekIn Inc, San Diego, California), OverC™ (Burning Rock Biotech, Guangzhou, China), Carcimun-test (Carcimun Biotech, Garmisch-Partenkirchen, Germany) and SpecGastro test (manufacturer unknown). Technologies that appeared to be at a very early stage of development did not meet the inclusion criteria for the review.

Individual MCED tests and technologies claimed to detect from three to over 50 different types of cancer. Owing to the differences in the number of cancer types detected, study design and populations, statistical pooling of results was not considered appropriate.

Studies of MCED tests available for use

The risk of bias assessment identified substantial concerns with the included studies. Case-control studies have a high risk of bias in the QUADAS-2 'patient selection' domain. Almost all of the studies had a high risk of bias in the 'flow and timing' domain, however, this is difficult to avoid when the reference standard for positive test results involves invasive testing, as it is not practical or ethical to undertake such invasive tests in participants with a negative MCED (index) test result.

Only one study was undertaken in the UK, although this was in individuals in whom cancer was suspected, so not reflective of the general cancer screening population. Cancer risk and the availability of general population cancer screening programmes differ worldwide, which will impact the applicability of results of the included studies to the UK. Ethnicity and socioeconomic status of included participants was not well reported in the included studies. There were also concerns about the applicability of the CancerSEEK test, which has since been modified (now called Cancerguard™) and is undergoing further assessment. The applicability of the SPOT-MAS, Trucheck, CDA and AICS tests assessed in the included studies was unclear.

Outcomes relating to MCED test performance (i.e., test accuracy and number of cancers detected by site and/or stage) were reported in most studies. Overall test sensitivity and specificity are not directly comparable across different MCED tests, owing to the differences in the number of cancer types each test claims to detect. Diagnostic accuracy varied substantially (95% confidence interval [CI] shown in brackets):

Galleri (3 studies)

Sensitivity: 20.8% (14.0 to 29.2) to 66.3% (61.2 to 71.1)

Specificity: 98.4% (98.1 to 98.8) to 99.5% (99.0 to 99.8)

CancerSEEK (2 studies)

Sensitivity: 27.1% (18.5 to 37.1) to 62.3% (59.3 to 65.3)

Specificity: 98.9% (98.7 to 99.1) to 99.1% (98.5 to 99.8)

SPOT-MAS (2 studies)

Sensitivity: 72.4% (66.3 to 78.0) to 100% (54.1 to 100)

Specificity: 97.0% (95.1 to 98.4) to 99.9% (99.6 to 100)

TruCheck (1 study)

Sensitivity: 90.0% (55.5 to 99.7)

Specificity: 96.4% (95.9 to 96.8)

CDA (1 study)

Sensitivity: 40.0% (95% CI 12.2 to 73.8)

Specificity: 97.6% (95% CI 96.8 to 98.2)

AICS screens for individual cancers separately; sensitivity ranged from 16.7% (95% CI 3.0 to 56.4) for ovary/uterus cancer to 51.7% (95% CI 34.4 to 68.6) for gastric cancer.

Sensitivity by cancer stage was only reported in some studies of Galleri and CancerSEEK. Sensitivity was considerably lower for detecting earlier stage cancers (Stage I-II) compared with later stage cancers (Stage III-IV). Amongst the Galleri studies, sensitivity for detecting Stage I-II cancer ranged from 27.5% (25.3 to 29.8) to 37.3% (29.8 to 45.4) and sensitivity for detecting Stage III-IV cancer ranged from 83.9% (81.7 to 85.9) to 89.7% (84.5 to 93.6). The CancerSEEK cohort study reported sensitivity for detecting Stage I-II cancer of 12.7% (95% CI 6.6 to 23.1) and sensitivity for detecting Stage III-IV cancer of 53.1% (95% CI 36.4 to 69.1).

One study of Galleri found that sensitivity was higher in an 'elevated risk' cohort (23.4%, 95% CI 14.5 to 34.4) than a 'non-elevated risk' cohort (16.3%, 95% CI 6.8 to 30.7).

Studies of Galleri, CancerSEEK, SPOT-MAS, CDA and AICS reported sensitivity by cancer site and found that it varied substantially, although the total number of participants diagnosed with certain types of cancer was low, so results are difficult to interpret.

Screening programme availability:

The sensitivity of the MCED tests to detect solid tumour cancers without a current screening programme in the UK was generally higher than the sensitivity to detect cancers with a current screening programme in the UK (breast, cervical and colorectal). However, this was not the case in one study of Galleri and the study of the CDA test, where sensitivity for detecting solid tumour cancers without a current screening programme was lower than for cancers with a current screening programme in the UK.

Subgroup results by participant demographic characteristics:

One study each of Galleri and CancerSEEK reported MCED test performance by pre-specified subgroups of interest (i.e., age, sex and ethnicity). For CancerSEEK, sensitivity was slightly lower for

participants less than 50 years of age, compared to participants aged 50 or over, while for Galleri sensitivity was very similar across the age categories presented. The sensitivity of Galleri was highest for Hispanic participants (63%), and it was lowest (43%) for the small number of participants classified as 'Other' ethnicity in the study. Sensitivity of CancerSEEK ranged from 50% in participants with unknown ethnicities to 70.4% in Asian participants (and cancer was correctly detected by the CancerSEEK test in one Hispanic participant resulting in a sensitivity of 100%). One study using an earlier version of the Galleri test reported results by age and sex for a subset of study participants; cancer signal detection rate was similar in males and females and increased with age for both sexes, however, few details were given on the subset of participants analysed. Only one study of Galleri reported data for participants with a low socioeconomic status.

Patient relevant outcomes

Only limited results relating to patient relevant outcomes, such as mortality, potential harms, HRQoL, acceptability and satisfaction of individuals screened, were reported in some studies of Galleri, CancerSEEK and AICS.

Studies of MCED technologies at an unclear stage of development

The risk of bias assessment identified substantial concerns. Most studies were case-control studies so had a high risk of bias in the 'patient selection' domain of QUADAS-2. Most studies also had a high risk of bias in the 'index test' and/or 'flow and timing' domains. All studies were considered to have high or unclear concerns relating to the applicability of study participants, index tests and reference standard tests.

Outcomes relating to MCED test performance were reported in most studies. OncoSeek reported the lowest overall sensitivity across all cancer types (47.4%), and CancerenD24 reported the lowest sensitivity in detecting bladder cancer (38.0%). By stage, OverC and SeekInCare reported a sensitivity of 35.4% and 50.3%, respectively, for stage I cancer. The highest sensitivity overall came from the Carcimun-test (88.8%), however, the exclusion of individuals with inflammation is noted as a disadvantage. The SpecGastro test was only developed to detect three types of gastrointestinal cancer (colorectal, gastric, and oesophageal).

Stakeholder engagement

At the protocol stage, stakeholders highlighted issues with the implementation of MCED tests, including resource use, impact on existing diagnostic services and wider care pathways, the need to balance benefits with potential risks, and consideration of factors likely to affect test uptake. Stakeholders also reinforced the importance of patient relevant outcomes.

Stakeholders commenting on the draft report noted that important details about the potential benefits, harms, and possible unintended consequences of implementing MCED tests in the UK were poorly reported, limiting the relevance of the available evidence for policy decision-making. Other feedback fell into six broad areas: poor applicability and generalisability of available evidence; limitations of the current evidence base; the potential impact of MCED tests on existing screening, diagnostic and treatment pathways; opportunities to enhance services to improve outcomes; acceptability and potential impact on populations offered and/or receiving screening, and; targeting specific groups to support early identification and improve outcomes.

Conclusions

Limited evidence is available on the potential for early detection of treatable cancers, and the consequences of introducing screening with an MCED test in a UK population. There were no completed RCTs identified for any of the MCED tests and most included studies had a high overall risk of bias, primarily owing to limited follow-up of participants with negative test results. There were concerns about the applicability of the participants in most studies. Only one study of Galleri recruited asymptomatic individuals aged over 50 years but it was conducted in the USA, therefore, study participants and results may not be representative of a UK screening population.

All currently available MCED tests (Galleri, CancerSEEK, SPOT-MAS, TruCheck, CDA and AICS) reported high specificity (>96%) which is essential if an MCED test is to correctly classify people who do not have cancer. Sensitivity was variable and influenced by study design, population, reference standard test used and length of follow-up. Sensitivity also varied by cancer stage; where reported, MCED tests had considerably lower sensitivity to detect earlier stage cancers (Stage I-II). Sensitivity also appeared to vary substantially for different cancer sites, although results are limited by small patient numbers for some cancer sites. The sensitivity of most of the MCED tests to detect solid tumour cancers without a current screening programme in the UK was higher than their sensitivity to detect cancers with a screening programme in the UK (breast, cervical and colorectal). Where reported, differences in test accuracy by age and sex were small. Whilst some differences were observed by ethnicity, these results should be interpreted with caution as the majority of participants recruited to studies were White and numbers of participants from other ethnic groups were small.

Evidence on seven MCED technologies which were at an unclear stage of development and did not appear to be available for use were briefly summarised; most were evaluated in case-control studies and had a high risk of bias, all studies had high or unclear applicability concerns.

No meaningful results were reported relating to patient relevant outcomes, such as mortality, potential harms, HRQoL, acceptability or satisfaction.

Recommendations for research

RCTs with sufficiently long follow-up, reporting outcomes that are directly relevant to patients, such as mortality/morbidity, safety, and HRQoL, are needed and some are planned or underway.

Research is also needed on the resource implications of MCED tests on NHS services, risk of over-treatment and cost-effectiveness of implementing MCED tests for screening in the UK.

Word count: 2354

Study registration

This study is registered as PROSPERO CRD42023467901.

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1 BACKGROUND

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

The Galleri® test (GRAIL, Menlo Park, California) is a multi-cancer early detection (MCED) blood test that uses genetic sequencing to detect potential signals of cancer and is currently recommended by the manufacturer for use in adults with an elevated risk of cancer, such as those aged 50 years or older.[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. The test detects circulating cell-free deoxyribonucleic acid (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 (CSO) by comparing the methylation pattern to the patterns of 21 possible CSO predictions. Predicting the origin of the cancer signal helps healthcare providers select the appropriate follow-up diagnostic tests. The CSO can be either an anatomic site (e.g., colorectal) or a cellular lineage (e.g., lymphoid).[5]

Another blood-based MCED test which detects cfDNA and protein biomarkers (such as cancer antigen 125, CA125) is CancerSEEK (Exact Sciences, Madison, Wisconsin).[6] MCED tests based on detecting other cancer-related biomarkers in the blood are also available.[7] For example, SPOT-MAS™ (Gene Solutions, Ho Chi Minh City, Vietnam) detects circulating tumour DNA (ctDNA) – a type of cfDNA – and applies machine learning algorithms to detect five types of cancer.[8] TruCheck™ (Datar Cancer Genetics, Beyreuth, Germany) detects the presence of circulating tumour cells (CTCs) and their clusters, which are causatively associated with malignant tumours and are rare among asymptomatic populations.[9] CDA (Cancer Differentiation Analysis; AnPac Bio, Shanghai, China) detects and analyses electrical biophysical signatures in whole blood samples and generates a CDA value (with higher values indicating higher cancer risk), rather than focusing on specific cells.[10] The AICS® test (AminoIndex Cancer Screening; Ajinomoto, Tokyo, Japan) uses plasma-free amino acid profiles as biomarkers for six different types of cancer, but rather than giving an overall prediction, the test ranks participants on the probability of having each of the cancers tested (grouped into A, B, or C, with C as the high-risk group).[11] A recent review summarised these different MCED technologies and provides an overview of the type of biomarkers (e.g., cfDNA, CTC, protein or metabolites) that can be used to differentiate a variety of cancers.[12]

The NHS Long Term Plan ambition seeks to diagnose 75% of cancers at stage I or II, to enable more effective treatment.[13] An MCED test embedded within a national population-based screening programme, in addition to existing cancer screening programmes, may increase the number of cancers diagnosed at an earlier stage, potentially improving the likelihood of treatment success and consequent survival rates. However, the identification of cancers with no effective treatments even at an early stage may have no improvement on mortality or health-related quality of life (HRQoL). It is also unclear whether detecting some cancers earlier impacts cancer-specific mortality since they might still have been detected and successfully treated using existing screening and referral pathways, without MCED testing.[14]

In addition, early screening of healthy people for such a wide range of cancers, and the expected lengthy time to diagnostic resolution, may create anxiety and lead to unnecessary follow-up tests, when false positives occur.[15, 16] The potential for overdiagnosis of cancers at such an early stage that they might never have advanced enough to require treatment, may also lead to unintended harms.[17] Communication of a negative MCED test result might also lead to false reassurance and reduce uptake to other existing screening programmes or lead to delays in individuals presenting to their GP with symptoms, even though it is recommended that regular screening is continued regardless of MCED test result.[18]

The aim of this project was to assess the accuracy and clinical effectiveness, acceptability and feasibility of blood-based MCED tests for population-based screening of individuals aged 50 to 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 was to conduct a systematic literature review of the clinical effectiveness evidence on blood-based MCED tests for screening.

2 METHODS

The systematic review was conducted following the general principles recommended in the Centre for Reviews and Dissemination's guidance and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Appendix 1, Table 9 and Table 10).[19, 20] The systematic review was registered with PROSPERO, registration number CRD42023467901.

2.1 Inclusion criteria

2.1.1 Population

The target population was individuals aged 50 to 79 years without clinical suspicion of cancer and who had not been diagnosed with cancer or received treatment for cancer within the last three years. As insufficient relevant studies were identified within the target population, studies including patients known to have cancer (i.e., case-control studies) and studies that included individuals with a wider age range than 50 to 79 years were considered for inclusion.

Subgroups of interest were individuals at elevated risk of cancer (e.g., smoking history, genetic predisposition or personal history of malignancy), and patients diagnosed with different cancer types (i.e., primary site) and at different cancer stages, where diagnostic accuracy may differ. Where possible, we also planned to examine differences in demographic characteristics such as age and sex, as well as potentially important characteristics associated with health inequalities, such as ethnic group and socio-economic status.

2.1.2 Interventions

This review included blood-based MCED tests for cancer screening, where these tests aim to detect multiple types of cancer. 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 were not eligible for inclusion.

Technologies are also being developed to detect cancer signals in other bodily fluids, such as urine.[12] However, such technologies are in a much earlier stage of development than blood-based tests so we only focused on blood-based MCED tests in this review.

2.1.3 Comparators

The comparator was no MCED test but individuals should still be offered relevant existing screening programmes and clinical follow-up of symptoms. Uncontrolled studies were also eligible for inclusion if relevant outcome data were provided.

2.1.4 Outcomes

Outcomes of interest related to test performance were

- accuracy of the test; including sensitivity, specificity, positive and negative predictive values, and reference standard test used to determine true disease status, if any
- accuracy of the CSO

- number and proportion of cancers detected (by site and stage), including the proportion of cancers targeted by the test which were detected

Patient-relevant outcomes of interest were:

- mortality (all-cause and disease-specific);
- time to diagnosis (or exclusion) of cancer;
- incidental findings;
- additional tests and procedures;
- potential harms;
- HRQoL;
- acceptability to individuals screened
- satisfaction of individuals screened.

2.1.5 Study designs

Prospective clinical trials (including randomised and other controlled trials) and cohort studies were sought. As insufficient relevant trials and prospective cohort studies were identified, we included case-control studies, including patients known to have cancer, if relevant outcome data were reported.

For case-control studies, only the following outcomes were relevant: accuracy of the test (sensitivity and specificity); accuracy of the CSO; number of cancers detected (by site and stage); acceptability to individuals tested; and satisfaction of individuals tested.

Early development studies (e.g., pre-clinical studies using biobank samples, studies training, evaluating or refining algorithms) which did not recruit participants with the aim of assessing diagnostic accuracy or clinical effectiveness of the tests were not eligible for inclusion.

2.2 Search strategy for identification of studies

The aim of the search was 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 systematic reviews was undertaken.

A search strategy was designed in Ovid MEDLINE by an Information Specialist (MH) in consultation with the review team. The strategy combined terms for multiple cancer, terms for liquid biopsy or blood tests, and terms for screening or early detection. Searches of the title and abstract fields of database records along with relevant subject headings were included in the strategy. Specific phrases for the tests such as “multi-cancer early detection tests” were also included in the strategy as well as

the brand names of individual tests (e.g., Galleri, PanSEER, and CancerSEEK). The search was limited to records published from 2010 onwards to reflect the recent development of these technologies. No further limits were applied. The MEDLINE strategy was peer reviewed by a second Information Specialist and any necessary adjustments or corrections made. The strategy was then adapted for use in all other databases and resources searched.

The following databases were searched in September 2023: 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), and KSR Evidence (Ovid).

Unpublished, ongoing or grey literature was identified through searching the health technology assessment (HTA) database, International HTA database (INAHTA), websites of international HTA organisations, Conference Proceedings Citation index – Science (Web of Science), ClinicalTrials.gov, WHO International Clinical Trials Registry portal, and PROSPERO. All search results were imported into EndNote 20 reference management software and deduplicated.

After screening records identified by electronic searches, manufacturers of MCED tests were identified from the included studies and their websites examined to identify further references published from 2020 onwards. The reference lists of included studies and relevant systematic reviews were also checked for any relevant references.

The full search strategies can be found in Appendix 2.

2.3 Study selection

All references identified by the electronic searches were uploaded into EPPI-Reviewer. The machine learning and text mining tool in EPPI-Reviewer (priority screening) was used to prioritise titles and abstracts for screening.[21] All titles and abstracts were assessed by one reviewer (CK, GR, RW, SD, SN or YL) with the first 10% of prioritised records assessed by two reviewers to ensure consistency; disagreements were resolved by discussion or, if necessary, a third independent reviewer. The full texts of potentially eligible studies were assessed independently by two reviewers (CK, GR, RW, SD, SN or YL), using the same process for resolution of disagreements as outlined above. Studies published as pre-prints or conference abstracts reporting relevant outcome data were eligible for inclusion. Foreign-language publications were eligible for inclusion and translated for data extraction, if applicable. Eligible ongoing studies (e.g., reported in protocols and trial registers) without relevant outcome data reported at the time of data extraction were included.

2.4 Data extraction

A standardised data extraction form was developed and piloted. Data on the intervention(s), patient characteristics, setting, study design, reference standard test(s) used, and relevant outcomes were extracted from included studies by one reviewer (RW, SN or YL) and independently checked by a second reviewer (CK, GR, RW, SN or YL). Disagreements were resolved through discussion.

The following values were extracted or calculated for each MCED test:

- the number of true positives (TP) which is the number of people with a positive cancer signal (i.e., a positive result of the MCED test) who do have cancer, i.e., the number of people correctly identified by the MCED test as having cancer
- the number of false positives (FP) which is the number of people with a positive cancer signal who do not have cancer, i.e., the number of people incorrectly identified by the MCED test as having cancer
- the number of true negatives (TN) which is the number of people with a negative cancer signal (i.e., a negative result of the MCED test) who do not have cancer, i.e., the number of people correctly identified by the MCED test as not having cancer
- the number of false negatives (FN) which is the number of people with a negative cancer signal who do have cancer, i.e., the number of people incorrectly identified by the MCED test as not having cancer

Measures of test accuracy are as follows:

- Sensitivity = TP / (TP + FN)

This is the true positive rate which is the probability that an individual with cancer receives a positive MCED test result; in other words, the ability of a test to correctly classify a person with cancer.

- Specificity = TN / (TN + FP)

This is the true negative rate which is the probability that an individual without cancer receives a negative MCED test result; in other words, the ability of a test to correctly classify a person without cancer.

- Positive predictive value (PPV) = TP / (TP + FP)

This is the probability that a person who receives a positive MCED test result has cancer.

- Negative predictive value (NPV) = TN / (TN + FN)

This is the probability that a person who receives a negative MCED test result does not have cancer.

These test accuracy measures were extracted or, where not directly reported, calculated from other reported data using package epiR[22] in RStudio version 4.3.1,[23] where appropriate. Calculated measures, as opposed to directly reported measures, are identified as such in all results tables. Sensitivity was also extracted or calculated where possible by cancer site and stage. Specificity was not presented by site and stage as it is important that a test correctly classifies that a person does not have cancer of any type or stage.

2.5 Critical appraisal

Risk of bias and applicability were assessed using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) checklist[24] by one reviewer (RW or YL) and independently checked by a second reviewer (CK, GR, RW or YL). Disagreements were resolved through discussion.

2.6 Data synthesis and investigation of heterogeneity

Data were not suitable for pooling in a meta-analysis due to the difference in study designs, populations, and interventions. The results of data extraction are presented in a series of structured tables grouped by MCED test and visualised using the R package "ggplot2"[25] where appropriate. Narrative summaries of differences in study designs, populations and MCED tests as well as narrative summaries of MCED test performance and patient relevant outcomes by MCED test and across MCED tests are presented, where appropriate.

Certainty in the body of evidence was considered in terms of the study design (e.g., cohort vs case-control), the type of reference standard test used, the extent and length of follow-up for true and false negatives, and the relevance of the population (e.g., asymptomatic vs symptomatic population).

2.6.1 Subgroup analyses

A narrative summary of results relevant to subgroups of interest (individuals at elevated risk of cancer, diagnosed with different cancer types, age groups, ethnic group and sex) and differences in accuracy by CSO is presented, where available.

Results by cancer types with and without current screening in the UK are also presented. Although this was not a pre-specified subgroup of interest in the protocol,[26] stakeholders commented that this was a useful summary of the available evidence.

2.7 Stakeholder involvement

We ensured that relevant perspectives were properly considered during protocol development and as part of the process of understanding, interpreting and contextualising the findings of this review. In developing the protocol, we worked with a range of content experts involved in the cancer screening and care pathway, including general practitioners and cancer screening and diagnostic research and implementation experts, as well as representatives from the UK National Screening Committee. We also worked with the manager at Healthwatch York[27] to ensure that issues raised by patients and public communities were considered at an early stage.

Upon completion of the review, a draft copy of the final report was shared with a selected group of stakeholders (as outlined in the Acknowledgements). Comments and feedback from these stakeholders were incorporated into the final draft of the report.

Several further consultation exercises were then undertaken to explore the broader views of patients and the public about the use of MCEDs as part of a general population screening programme. These open discussions (one group involving 11 participants, and two individual consultations with separate informants) took place remotely via Zoom, to maximise opportunities for involvement, and lasted between 1 and 1.5 hours. The group discussion was led by one of the co-authors (RC) and our Healthwatch York partner, whilst the individual consultations were undertaken by our Healthwatch partner alone. At the start of each discussion, participants were given some brief context about MCEDs and an outline of the purpose of the session (based on the information provided in the invitation – see Appendix 3). A brief verbal description of the review undertaken, based on the Plain Language Summary, was also provided. With the support of several organisations, including Healthwatch York, the TRANSFORM platform and Involve Hull,[28] the Humber and North Yorkshire Cancer Alliance,[29] we were able to involve people from across the UK with lived experience of a cancer diagnosis, carers, as well as people who would meet the inclusion criteria for general population screening using MCEDs in this review.

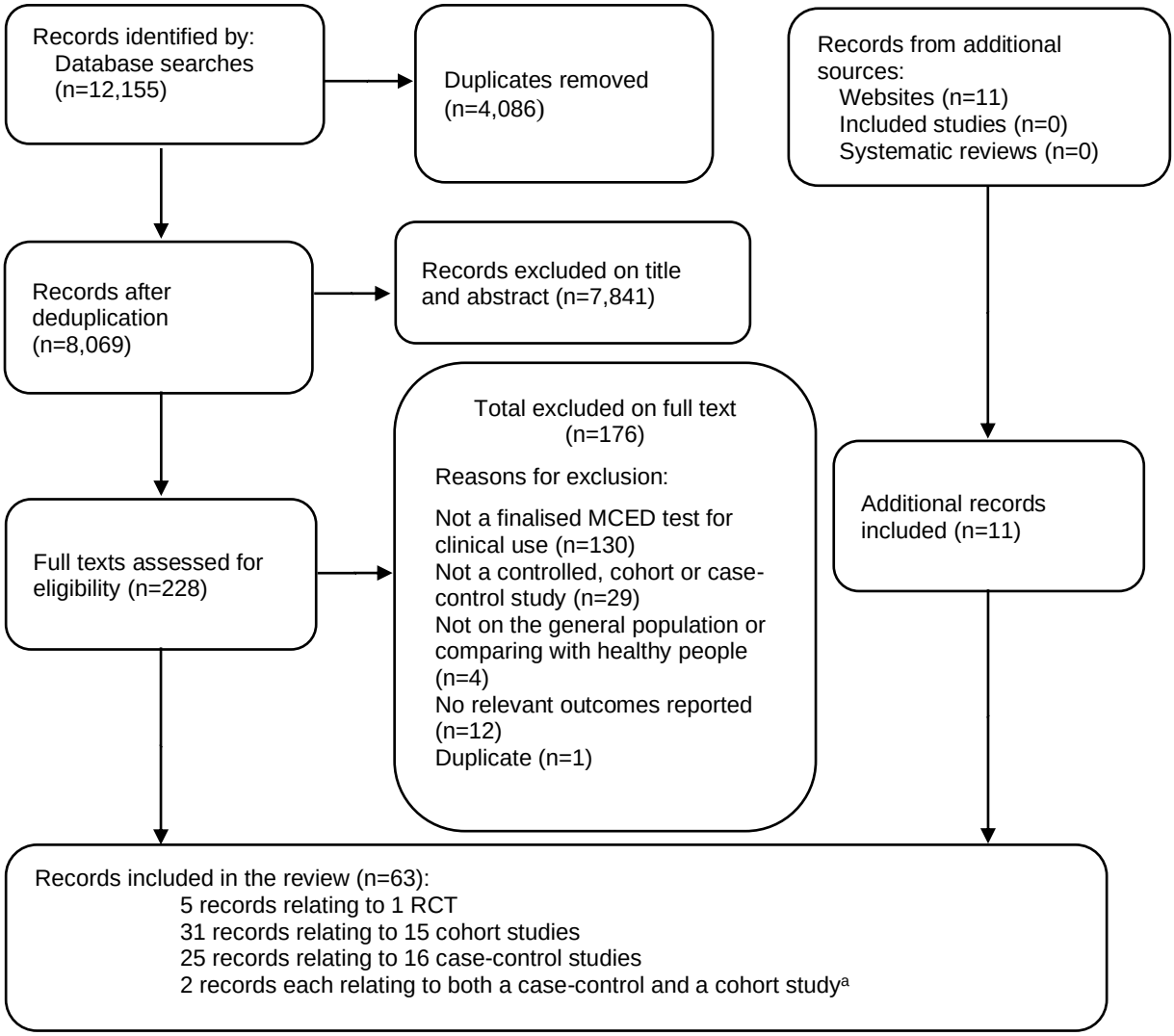
3 RESULTS

3.1 Studies included in the review

The electronic searches identified a total of 8,069 records after deduplication between databases. The full texts of 228 records were ordered for further review; 176 were excluded at full paper stage and are listed in Appendix 4, along with the reasons for their exclusion. No additional records were identified from screening reference lists of included studies and relevant systematic reviews. Eleven additional records were identified from searching MCED test manufacturer websites.

Sixty-three records reporting results from 36 individual studies, evaluating 13 tests or technologies met the review inclusion criteria. There was a considerable amount of duplicate reporting in e.g., multiple conference abstracts and posters, in addition to the main journal article describing a study. One ongoing randomised controlled trial (RCT), 13 completed cohort studies, 17 completed case-control studies, four ongoing cohort studies and one ongoing case-control study were included. Figure 1 presents the flow of records through the selection process.

Figure 1 Flow diagram of the study selection process



RCT = randomised controlled trial; MCED = multi-cancer early detection
Some records described more than one study, as well as some studies being reported in more than one record
[a] Four studies reported (two case-control, two cohort) in two records

Study selection was complex. In particular, it was often difficult at full-text screening to determine whether studies were reporting results for technologies at an early stage of development, or whether studies were assessing the final or near-final version of the test.

Where known, we only included studies that appeared to assess tests that were in the final stages of development, e.g., for the GRAIL MCED test, we only included studies that assessed the "refined MCED test" (Galleri), i.e., the PATHFINDER study[30] and the Circulating Cell-free Genome Atlas (CCGA) substudy 3,[31] but not CCGA sub studies 1 and 2 that assessed an earlier version of the test.[32] For CancerSEEK, completed studies assessed what appears to be an earlier version of the test.[6, 33] A modified version of the test, now called Cancerguard™ is undergoing further assessment but no completed eligible studies were found.[34] Studies were also included reporting data on SPOT-MAS,[35] Trucheck,[36] CDA,[37] and AICS[38] which are blood-based MCED tests currently available for use, according to the manufacturer's websites.

Studies of other MCED technologies at an unclear stage of development, which do not seem to be available for use at the date of submission of this report, were also included in this review: Aristotle® (StageZero Life Sciences, Richmond, Ontario), CancerenD24 (manufacturer unknown), OncoSeek® (SeekIn Inc, San Diego, California), SeekInCare® (SeekIn Inc, San Diego, California), OverC™ (Burning Rock Biotech, Guangzhou, China), Carcimun-test (Carcimun Biotech, Garmisch-Partenkirchen, Germany) and SpecGastro test (manufacturer unknown).

Technologies that appeared to be at a very early stage of development and, therefore, not meeting the inclusion criteria for the review are described in Section 3.6.

The main references for completed and ongoing studies included for each test or technology are summarised in Table 1, along with the number of cancer types detected or targeted by each test. Additional records reporting supplementary information for studies in Table 2,[39-57] are detailed in Appendix 5, Table 11.

Table 1 Completed and ongoing studies available for each test and number of cancers detected or targeted by each test

		Completed prospective studies			Ongoing prospective studies			Number of cancers[a]
Manufacturer	**Test name**	**RCT**	**Cohort**	**Case-control**	**RCT**	**Cohort**	**Case-control**	
Available MCED tests								
GRAIL	Galleri (Refined MCED test)	-	PATHFINDER[30] SYMPLIFY[58] Cance, 2023[59]	CCGA substudy 3[31]	NHS-Galleri[60]	PATHFINDER2[61] REFLECTION[62] SUMMIT[63]	-	50[5 b]
ExactSciences	CancerSEEK	-	DETECT-A[6]	Cohen, 2018[33]	-	-	-	15
Gene Solutions	SPOT-MAS	-	K-DETEK[8]	Nguyen, 2023[64]	-	-	-	5
Datar Cancer Genetics	Trucheck	-	RESOLUTE[9] TrueBlood[9]	-	-	-	-	4 [c]
AnPac Bio	CDA	-	PPCS[10 d]	-	-	-	-	26 [e]
Ajinomoto Group	AICS	-	Mikami, 2019[11] AICS Follow-up study[65] Suzuki, 2014[66 f]	-	-	-	-	6 [g]
MCED technologies at unclear stage of development								
StageZero Life Sciences	Aristotle	-	-	Dempsey, 2020[67]	-	-	-	9 [h]
Manufacturer unknown	CancerenD24	-	-	Arber, 2017[68] Massarwi, 2019[69] Shapira, 2020[70] Shapira, 2021[71] Madah, 2023[72]	-	-	-	5-21 [i]
SeekIn	OncoSeek	-	-	Luan, 2023[73] Mao, 2023[74]	-	-	-	9[74]
SeekIn	SeekInCare	-	Mao, 2023[75 j] SeekIn Inc[76 j]	Mao, 2023[75 j] SeekIn Inc[76 j]	-	-	-	27[76]
Buring Rock Biotech	OverC	-	-	THUNDER[77] THUNDER-II[78]	-	PREVENT[79]	PREDICT[80]	
Carcimun biotech	Carcimun-test	-	-	Salat, 2022[81]	-	-	-	17[81]
Manufacturer unknown	SpecGastro test	-	-	Ma, 2022[82]	-	-	-	3[82]

Abbreviations: MCED = multi cancer early detection; RCT = randomised controlled trial.

[a] cancers detected or targeted by the test, where cancer types detected are listed, that number is reported, otherwise, number of cancer types detected in included studies is reported; [b] some cancer sites are combined so in total more than 50 cancer types are claimed to be detectable; [c] cancer types disclosed by participants during follow-up in in the RESOLUTE study only (2 refused to disclose cancer types); [d] data for a cross-sectional (non-interventional) study were also reported; [e] 26 reported from the website (cancer site details not provided) but only 13 listed in Xie 2022[10]; [f] cohort of women tested for breast cancer only; [g] developed to test for 7 cancers but pancreatic cancer was excluded from the study because it was not commercially available; [h] 9 reported from the website but 11 reported in Dempsey 2020; [i] number of cancers reported differed for each study; [j] reported both a case-control and real world cohort.

3.2 Characteristics of the included studies

Table 2 summarises study characteristics for each of the MCED tests currently available for use. Further details of each study and technology are presented in Appendix 5, Table 11.

There were no completed prospective RCTs identified for any of the MCED tests. All studies were either prospective cohort studies or case-control studies. Only one study (SYMPLIFY[58]) was undertaken in the UK (sites in England and Wales), although this was in individuals in whom cancer was suspected. Cancer risk and the availability of general population cancer screening programmes differ worldwide, which will impact the applicability of results of the included studies to the UK. Most of the prospective cohort studies and control groups in all case control studies recruited participants without any known history of cancer. The 'elevated-risk' cohort of the PATHFINDER study included 1622 participants (41%) who had a history of invasive or haematological malignancy with treatment completed >3 years prior to enrolment (Appendix 5, Table 11). Participants with a cancer history with treatment completed >3 years prior were also eligible for enrolment into the SYMPLIFY[58] study, but the number of recruited participants with a history of cancer was not reported.

Ethnicity of included participants was not well reported across the included studies and socioeconomic status was reported in only one study of Galleri that recruited individuals with low socioeconomic status. Only the three Galleri studies,[30, 31, 58] and the two CancerSEEK studies[6, 33] reported on participants' ethnic backgrounds (Appendix 5, Table 11). The majority of participants included in these studies were from White Caucasian background (81.2% to 91.7% in three studies of Galleri[30, 31] and 55.4% to 94.9% in the two studies of CancerSEEK).[6, 33] The case-control CancerSEEK study further included 17.8% of participants of Asian ethnicity,[33] compared with DETECT-A which only included 0.4%,[6] and the Galleri studies (PATHFINDER: 1.9%, SYMPLIFY: 4.2% [including South Asian and Chinese], CCGA substudy 3: 1.8%).[30, 31, 58]

Outcomes relating to the MCED test performance (i.e., accuracy of the test, accuracy of CSO and number of cancers detected by site and/or stage) were reported in most studies. Very limited patient relevant outcomes, such as mortality, potential harms (e.g., relating to adverse effects of additional tests and procedures undertaken), HRQoL (e.g., anxiety), acceptability and satisfaction of individuals screened were reported only in studies of Galleri and CancerSEEK.

Table 2 Summary of the included studies for each MCED test

Study details	Participant information	Review outcomes assessed	QUADAS-2 overall result
GRAIL Galleri			

Study details	Participant information	Review outcomes assessed	QUADAS-2 overall result
PATHFINDER[30] Prospective cohort study, USA	Adults aged ≥50 Cohort 1: elevated risk group (n=3655) Cohort 2: non-elevated risk group (n=2923) Ethnicity: 91.7% White	Accuracy of the test Accuracy of CSO Number of cancers detected by site and stage Acceptability to individuals screened Health-related quality of life (anxiety)	Risk of bias: High Applicability concerns: Unclear
SYMPLIFY[58] Prospective cohort study, England and Wales	Adults aged ≥18 referred for urgent investigation for possible cancer or with non-specific symptoms that might be due to cancer (n=5851) Ethnicity: 90.4% White	Accuracy of the test Accuracy of CSO Number and proportion of cancers detected by site and stage	Risk of bias: High Applicability concerns: High
CCGA substudy 3[31] Prospective case-control study, North America	Adults aged ≥20 Cancer arm (n=2823) Non-cancer arm (n=1254) Ethnicity:81.2% White	Accuracy of the test Accuracy of CSO Number and proportion of cancers detected by site and stage	Risk of bias: High Applicability concerns: High
Employer-based implementation study[59] Prospective cohort study, USA	Industrial-based workers from three US companies (n=812) Ethnicity not reported	Acceptability and satisfaction of individuals screened	Risk of bias: High Applicability concerns: High
CancerSEEK			
DETECT-A[6] Prospective cohort study, USA	Women aged 65 to 75 (n=9911) Ethnicity: 94.9% White	Accuracy of the test Number and proportion of cancers detected by site and stage Mortality Potential harms	Risk of bias: High Applicability concerns: High
Earlier proof of concept case-control study[33] Case-control study, USA	Patients diagnosed with cancer (n=1005) Control (n=812) Ethnicity :55.4% White	Accuracy of the test Accuracy of CSO Number and proportion of cancers detected by site and stage	Risk of bias: High Applicability concerns: High
SPOT-MAS			
K-DETEK[8] Prospective cohort study, Vietnam	Individuals aged ≥40 attending outpatient clinics for follow-up of chronic conditions or undergoing annual routine check-ups (n=2795) Ethnicity not reported	Accuracy of the test Accuracy of CSO Number of cancers detected by site	Risk of bias: High Applicability concerns: Unclear
Nguyen et al., 2023[64] Case-control study, Vietnam	Patients diagnosed with cancer stages I-IIIA (n=738) Control (n=1550) Ethnicity not reported	Accuracy of the test Accuracy of CSO Number and proportion of cancers detected by site	Risk of bias: High Applicability concerns: High
Trucheck			
RESOLUTE[9] Prospective cohort study, India	Asymptomatic adults (n=10625) Ethnicity not reported	Accuracy of the test Number of cancers detected by site	Risk of bias: High Applicability concerns: High

Study details	Participant information	Review outcomes assessed	QUADAS-2 overall result
TrueBlood[9] Prospective cohort study, India	Symptomatic adults and those with prior diagnosis of cancer (n=5509, with an additional 4743 individuals suspected of cancer enrolled) Ethnicity not reported	Accuracy of the test Number and proportion of cancers detected	Risk of bias: High Applicability concerns: High
CDA			
Prospective Population-based Cohort Study (PPCS)[10] Prospective cohort study, China	Adults aged >40 with no history of cancer (n=1957) Ethnicity not reported	Accuracy of the test Number and proportion of cancers detected by site	Risk of bias: Unclear Applicability concerns: High
AICS			
Mikami et al., 2019[11] Prospective cohort study, Japan	Adults who underwent AICS at three hospital sites (total n=10245) Ethnicity not reported	Accuracy of the test by site Number and proportion of cancers detected by site	Risk of bias: High Applicability concerns: High
AICS Follow-up study[65] Prospective cohort study, Japan	Adults who underwent AICS (n=5490) Ethnicity not reported	Number of cancers detected	Risk of bias: High Applicability concerns: Unclear
Suzuki et al., 2014[66] Prospective cohort study, Japan	Healthy women (two publications with n=115 and n=83) Ethnicity not reported	Number of cancers detected	Risk of bias: Unclear Applicability concerns: High

Abbreviations: CSO = Cancer Signal Origin; MCED = multi-cancer early detection; PET-CT = positron emission tomography-computed tomography.

MCED technologies that appear to be at an earlier stage of development and for which it is unclear whether the finalised test version is being evaluated, or if they may still undergo further modification (i.e., Aristotle, CancerenD24, OncoSeek, SeekInCare, OverC, Carcimun-test and SpecGastro test), are presented in Section 3.4.3 with study characteristics presented in Appendix 6, Table 12.

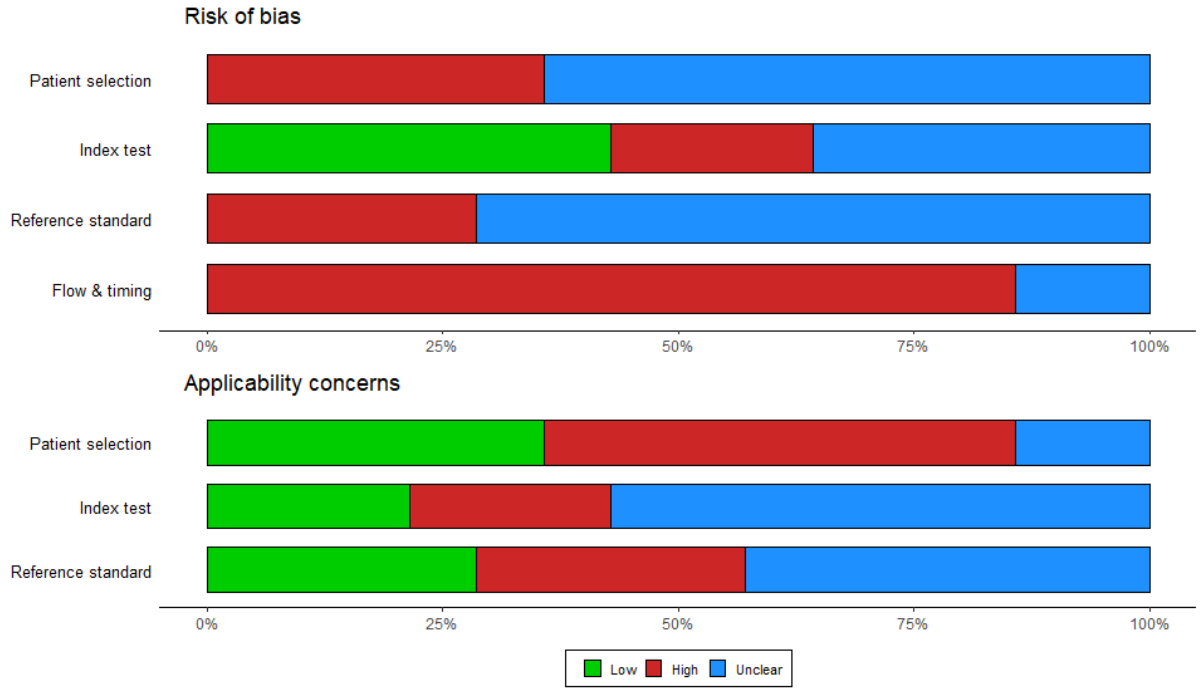
3.3 Quality of the included studies

3.3.1 Available MCED tests

An overall summary of QUADAS-2 assessments of the studies of MCED tests currently available for use is presented in Figure 2 (using the R packages "robvis"[83] and "ggplot2"[25]). The risk of bias assessment identified substantial concerns with the included studies. Patient selection and the reference standard were poorly reported in most of the studies, resulting in an 'unclear' risk of bias and/or applicability judgement. Almost all the included studies had a high risk of bias in the 'flow and timing' domain of QUADAS-2. However, this is difficult to avoid in studies where the reference standard for positive test results involves invasive testing, as it would not be practical or ethical to undertake such invasive tests in participants with a negative MCED (index) test result.

There was a high applicability concern relating to the 'patient selection' domain of QUADAS-2 for several studies as the included participants did not reflect the target population of interest for this review. The index test was also poorly reported across several studies, resulting in an "unclear" applicability concern in this domain.

Figure 2 QUADAS-2 overall summary



QUADAS-2 assessments for each study of MCED tests currently available for use are summarised in Table 3. One study of each of Galleri,[31] CancerSEEK,[33] and SPOT-MAS[64] were case-control studies, which are considered to have a high risk of bias in the 'patient selection' domain of the QUADAS-2 checklist.[24] There was a high concern regarding the applicability of the index test for the studies evaluating CancerSEEK, as this test has been modified (now called Cancerguard™) and is undergoing further assessment.[34]

Table 3 QUADAS-2 assessment results for studies of each MCED test

Study	Risk of Bias				Applicability Concern		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
GRAIL Galleri							
PATHFINDER[30]	High	Unclear	Unclear	High	Low	Low	Unclear
SYMPLIFY[58]	Unclear	Low	Unclear	High	High	Low	Low
CCGA substudy 3[31]	High	Unclear	Unclear	High	High	Low	Unclear
Employer-based implementation study[59]	Unclear	High	High	High	High	High	Unclear
CancerSEEK							

Study	Risk of Bias				Applicability Concern		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
DETECT-A[6]	High	Unclear	Unclear	High	Low	High	High
Earlier proof of concept case-control study[33]	High	Unclear	Unclear	High	High	High	Unclear
SPOT-MAS							
K-DETEK[8]	Unclear	Low	High	High	Low	Unclear	Low
Nguyen et al., 2023[64]	High	High	Unclear	High	High	Unclear	Unclear
Trucheck							
RESOLUTE[9]	Unclear	Low	Unclear	High	Low	Unclear	High
TrueBlood[9]	Unclear	High	Unclear	High	High	Unclear	Unclear
CDA							
PPCS[10]	Unclear	Low	Unclear	Unclear	Low	Unclear	High
AICS							
Mikami et al., 2019[11]	Unclear	Low	High	High	Unclear	Unclear	High
AICS Follow-up study[65]	Unclear	Low	High	High	Unclear	Unclear	Low
Suzuki et al., 2014[66]	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low

3.3.2 MCED technologies at an unclear stage of development

The QUADAS-2 assessment of the studies of MCED technologies at an unclear stage of development is summarised in Appendix 6, Table 13. All of the studies had a high risk of bias and/or applicability concerns; most were case-control studies, and there were also concerns regarding whether the index test was the finalised version of the MCED test, as well as the lack of follow-up reported for healthy controls in some studies.

3.4 Outcomes reported in the included studies

No completed RCTs were found for any of the included MCED tests. The Galleri test has an RCT ongoing (see Section 3.5), which plans to report interim results at one year of follow-up. However, no data are currently available for this RCT, so data were extracted from prospective cohort and case-control studies evaluating the refined GRAIL MCED test (Galleri). For other MCED tests, no planned RCTs were identified and only data from prospective cohort and case-control studies were extracted, where available (see Table 1).

Due to the substantial differences in the number of cancers detected by the included tests, study design and populations, statistical pooling of results was not considered appropriate. Results for all MCED tests are presented within tables, described, and compared, where appropriate.

Relevance, validity and comparability of the different outcomes depends upon study design, whether a reference standard test was used to diagnose true disease status when a cancer signal was detected

(i.e., positive MCED test result returned), and which additional tests, if any, were conducted on study participants without a cancer signal detected (negative MCED test result returned), to determine true disease status. The most appropriate reference standard test, or combination of tests, is also dependent on the cancer site being investigated and these may differ in their diagnostic accuracy. In addition, overall test sensitivity and specificity are not directly comparable across different MCED tests as the number of cancers each test claims to detect are different (see Table 1, and Appendix 7, Table 14).

Another key issue is that accurate classification of true and false negatives will depend on the extent and length of follow-up in prospective studies. A short follow-up will result in estimates of sensitivity that are higher than they would be if a perfect reference standard test was used to rule out cancer in all study participants with a negative test result. Sensitivity of the MCED test will therefore be subject to bias when only participants with a positive MCED test result undergo further diagnostic investigations during the study. In such cases, FN test results might be missed, unless detected at future routine screening, or clinical investigation after presentation with symptoms, which may not occur for all participants during the follow-up period of the study. In other words, negative results of an MCED test may incorrectly be assumed to be 'true' negative results, due to a lack of further testing and a short follow-up time.

Additionally, within studies that include patients known to have cancer (i.e., case-control studies) or who have been referred due to a suspicion of cancer (e.g., symptomatic individuals), estimates of sensitivity will be higher than they would be for the target population of asymptomatic individuals. Estimates of PPV and NPV in these studies will not be reflective of an asymptomatic screening context and are therefore not directly relevant to our target population.

Comparability and relevance of test accuracy measures collected from different studies will therefore be dependent on:

- Which reference standard test (or combination of tests) was used to diagnose cancer in individuals with a positive MCED test result, and the accuracy of that reference standard test (classification of TP and FP).
- Whether further investigations, beyond follow-up, were carried out to rule out cancer in individuals with a negative MCED test result (classification of TN and FN).
- Whether length of follow-up of individuals with a negative MCED test result would be sufficient to detect cancers present at the time of MCED test (classification of TN and FN).
- The prevalence of cancer in the study population in relation to the target population for screening (interpretation of PPV and NPV).
- The location of the studies affects the generalisability of results to UK clinical practice for most of the technologies. Differences in participants' ethnicity, cancer risk factors, and

characteristics of the healthcare system (including existing screening programmes and referral pathways) can impact the prevalence of different cancers.

These issues should be kept in mind when interpreting and comparing the results presented in this section.

3.4.1 Test performance in the included studies

Accuracy of the test and accuracy of the CSO of the Galleri, CancerSEEK, SPOT-MAS, TruCheck and CDA tests is presented in Table 4. Test performance for AICS is not included in Table 4, as each cancer is tested for separately, so no overall results are available. Accuracy of first or second CSO was measured only in the PATHFINDER[30] and SYMPLIFY[58] cohort studies of Galleri and in the Cohen 2018[33] case-control study of CancerSEEK. Where measured, other studies only assessed the accuracy of the first CSO.

Number of cancers detected by the MCED tests by stage is reported in Table 5. Cancer stage was reported for Galleri and CancerSEEK only and total cancers detected by cancer stage were not reported in the PATHFINDER study for the refined MCED test (Galleri). Sensitivity of Galleri and CancerSEEK by cancer stage, where reported, is shown in Figure 3.

Table 4 Test performance and accuracy of the tests

	Test (Manufacturer)								
	Galleri			CancerSEEK		SPOT-MAS		TruCheck	CDA
Study	**CCGA substudy 3[31]**	**PATHFINDER[30]**	**SYMPLIFY[58]**	**Cohen 2018[33]**	**DETECT-A[6]**	**Nyugen 2023[64]**	**K-DETEK[8]**	**RESOLUTE[9]**	**Xie 2022[10]**
Design	**Case-control[b]**	**Cohort**	**Cohort**	**Case-control[b]**	**Cohort**	**Case-Control[b]**	**Cohort**	**Cohort**	**Cohort**
Number analysed[a]	4077	6369	5461	1817	9911	713	2792	6884	1957
Total cancers (n)	2823	120	368	1005	96	239	6	10	10
TP (n)	1453	25	244	626	26	173[c]	6	9	4
FP (n)	6	33	79	7	108	14[c]	4	250	47
FN (n)	1370	95	124	379	70	66[c]	0[d]	1	6
TN (n)	1248	6216	5014	805	9707	460[c]	2782	6624	1900
Accuracy of the test, % (95% CI)									
Sensitivity	51.5 (49.6 to 53.3)	20.8 (14.0 to 29.2)[c]	66.3 (61.2 to 71.1)	62.3 (59.3 to 65.3)	27.1 (18.5 to 37.1)	72.4 (66.3 to 78.0)[c]	100 (54.1 to 100)[c]	90.0 (55.5 to 99.7)[c]	40.0 (12.2 to 73.8)[c]
Specificity	99.5 (99.0 to 99.8)	99.5 (99.3 to 99.6)	98.4 (98.1 to 98.8)	99.1 (98.5 to 99.8)	98.9 (98.7 to 99.1)	97.0 (95.1 to 98.4)[c]	99.9 (99.6 to 100)[c]	96.4 (95.9 to 96.8)[c]	97.6 (96.8 to 98.2)[c]
PPV	NA	43.1 (31.2 to 55.9)	75.5 (70.5 to 80.1)	NA	19.4 (13.1 to 27.1)	NA	60.0 (26.2 to 87.8)[c]	3.5 (1.6 to 6.5)[c]	7.8 (2.2 to 18.9)[c]
NPV	NA	98.5 (98.2 to 98.8)	97.6 (97.1 to 98.0)	NA	99.3 (99.1 to 99.4)	NA	100 (99.9 to 100)[c]	100 (99.9 to 100)[c]	99.7 (99.3 to 99.9)[c]
First CSO correct	88.7 (87.0 to 90.2)	84.0 (65.3 to 93.6)	85.2 (79.8 to 89.3)	67.7 (64.0 to 71.3)[c]	Not reported	median 0.70 (range 0.55-0.78)	83.3 (43.6 to 97)[c]	Not reported	Not reported
First or second CSO correct	Not reported	88.0 (70.0 to 95.8)	90.7 (86.0 to 93.9)	85.6 (82.7 to 88.2)	Not reported	Not reported	Not reported	Not reported	Not reported

Abbreviations: CCGA = Circulating Cell-free Genome Atlas; CI = confidence interval; CSO = cancer signal origin; FN = false negatives; FP = false positives; MCED = multi cancer early detection; NA = not applicable; NPV = negative predictive value; PPV = positive predictive value; TN = true negatives; TP = true positives.

[a] Number analysed is those who received the MCED test, with follow-up information and/or diagnostic resolution; [b] PPV and NPV statistics are not applicable for case-control studies including people known to have cancer; [c] values calculated from other reported data; [d] only people with a positive signal on the SPOT-MAS test were followed-up so all negative signals are assumed to be true negatives.

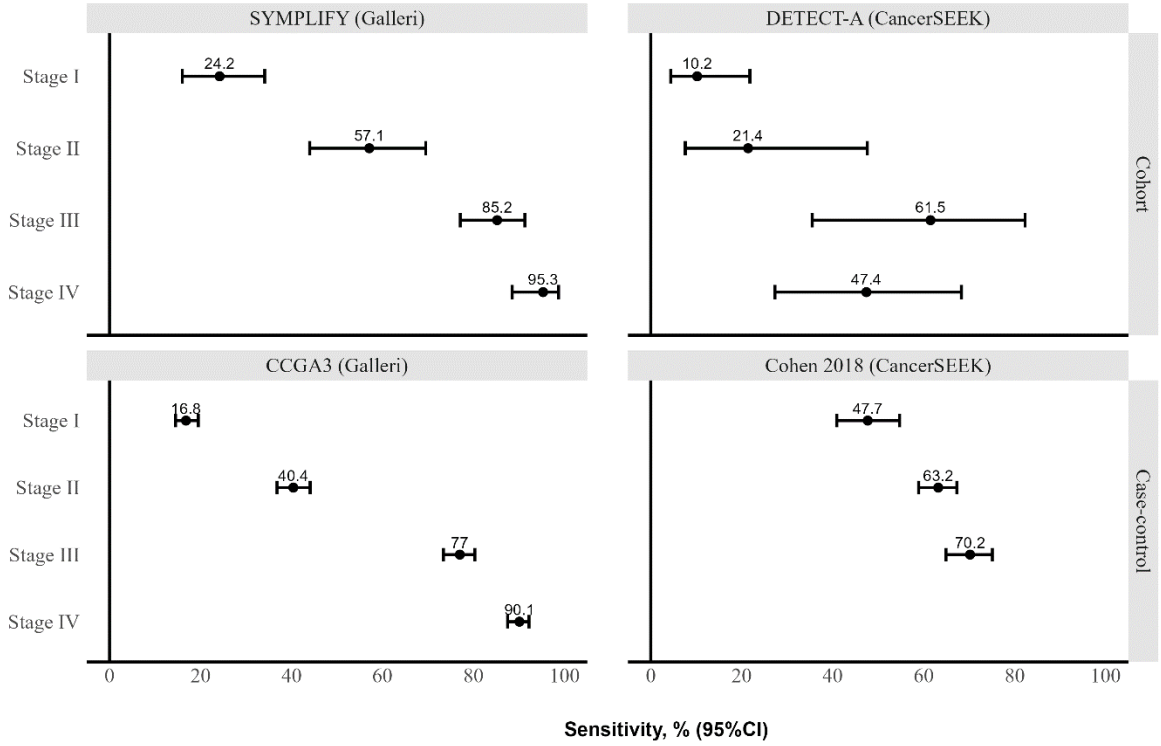
Table 5 Number and proportion of cancers detected by the MCED tests by stage

	Galleri									CancerSEEK					
Study	**CCGA substudy 3 (case-control)[31]**			**PATHFINDER (cohort)[30]**			**SYMPLIFY (cohort)[58]**			**Cohen 2018 (case-control)[33]**			**DETECT-A (cohort)[6]**		
Test accuracy[a]	**MCED test (+)**	**Total cancers**	**Sensitivity**	**MCED test (+)**	**Total cancers**	**Sensitivity**	**MCED test (+)**	**Total cancers**	**Sensitivity**	**MCED test (+)**	**Total cancers**	**Sensitivity**	**MCED test (+)**	**Total cancers**	**Sensitivity**
Overall	1453	2823	51.5 (49.6 to 53.3)	26	120	20.8 (14.0 to 29.2)	244	368	66.3 (61.2 to 71.1)	626	1005	62.3 (59.3 to 65.3)	26	96	27.1 (18.5 to 37.1)
I	143	849	16.8 (14.5 to 19.5)	4	Not reported		23	95	24.2 (16 to 34.1)	95	199	47.7 (40.9 to 54.7)	5	49	10.2 (4.4 to 21.8)
II	284	703	40.4 (36.8 to 44.1)	4	Not reported		36	63	57.1 (44 to 69.5)	314	497	63.2 (58.9 to 67.3)	3	14	21.4 (7.6 to 47.6)
III	436	566	77 (73.4 to 80.3)	6	Not reported		92	108	85.2 (77.1 to 91.3)	217	309	70.2 (64.9 to 75.1)	8	13	61.5 (35.5 to 82.3)
IV	557	618	90.1 (87.5 to 92.2)	4	Not reported		82	86	95.3 (88.5 to 98.7)	NA[b]	NA[b]	NA[b]	9	19	47.4 (27.3 to 68.3)
I-II	427	1552	27.5 (25.3 to 29.8)	8	Not reported		59	158	37.3 (29.8 to 45.4)	409	696	58.8 (55.1 to 62.4)	8	63	12.7 (6.6 to 23.1)
III-IV	993	1184	83.9 (81.7 to 85.9)	10	Not reported		174	194	89.7 (84.5 to 93.6)	NA[b]	NA[b]	NA[b]	17	32	53.1 (36.4 to 69.1)
Not staged / uncertain	23	67	34.3 (24.1 to 46.3)	3	Not reported		11	16	68.8 (41.3 to 89)	NA	NA	NA	1	1	100 (20.7 to 100)
Missing	10	20	50 (29.9 to 70.1)	0	Not reported		Not reported			Not reported			Not reported		
Recurrent	Not reported			5	Not reported		Not reported			Not reported			Not reported		

Abbreviations: MCED = multi cancer early detection; NA = not applicable.

[a] Number of people with a true positive (+) MCED test and total number of people diagnosed with cancer in the study (i.e., true positives and false negatives of the MCED test), sensitivity is % and 95% confidence interval calculated from other reported data; [b] only people with Stage I-III cancers recruited.

Figure 3 Performance (sensitivity) of MCED tests by cancer stage*.



*Cancer stage reported for solid tumours only, not for haematological malignancies.

3.4.1.1 Galleri

PATHFINDER[30] recruited two cohorts: one included participants considered at elevated risk of cancer (n=3655) and another included participants without an elevated cancer risk (n=2923). The primary aim of this study was to assess the accuracy of an old version of the MCED test produced by GRAIL. However, analysis of blood specimens with the refined MCED test (Galleri) was also carried out. The refined MCED test results were not returned to physicians or participants and did not influence diagnostic evaluation. The number of positive cancer signals detected on both the old and refined versions of the MCED test was 41 out of 92 (44.0%, 95% CI 34.2 to 54.2%). The refined MCED test detected fewer positive signals overall and most discordant negatives (42/51; 82.4%) had a haematological MCED cancer signal CSO prediction. The old and refined test versions agreed on 99.7% (95% CI 98.7% to 99.2%) of negative signals (Figure S4 in Schrag et al.[30]). Although carried out in the USA, the participants recruited to this study are reflective of our target population in terms of age and recruited participants are broadly representative of a screening population (i.e., asymptomatic) with some individuals expected to be at higher or lower risk of cancer. However, it is unclear whether the proportions of individuals with and without additional cancer risk factors recruited to the PATHFINDER study are reflective of the UK target screening population.

Table 4 presents results for the refined MCED test (Galleri). Only 120 cancers were detected in 6369 analysed participants (a cancer detection rate of 1.9%), reflecting the asymptomatic population recruited to this study. Sensitivity was low (20.8%, 95% confidence interval [CI] 14.0% to 29.2%) although the first CSO was correct in 84.0% of cancers detected (95% CI 65.3% to 93.6%) increasing to 88.0% (95% CI 70.0% to 95.8%) for first or second CSO. The PPV was 43.1% (95% CI 99.3% to 99.6%). Specificity was high (99.5%, 95% CI 99.3% to 99.6%) and the NPV was also high (98.5%, 95% CI 98.2% to 98.8%), although a short follow-up and lack of reference standard testing on participants with a negative MCED test limits the interpretation of these results.

Fifteen different cancer types were identified. The number of participants with each cancer type are presented in Appendix 7, Table 15 and the number of cancers identified by the MCED test by stage are presented in Table 5. However, the total number of cancers diagnosed (including FN of the MCED test) for each cancer type and at each stage was not reported so these results are difficult to interpret and the sensitivity of the MCED test by different cancer types and stages is unknown.

Performance of the refined MCED test in the elevated and non-elevated risk cohorts are presented in Appendix 8, Table 19. In the elevated risk cohort, 77 cancers were detected in 3532 participants (2.2%); in the non-elevated risk cohort 43 cancers were detected in 2837 participants (1.5%). Sensitivity was lower for the non-elevated risk cohort (16.3%, 95% CI 6.8% to 30.7%) than for the elevated risk cohort (23.4%, 95% CI 14.5% to 34.4%) but specificity remained high for both groups. The proportions of correct first, and first or second CSO, and PPV were lowest for participants without additional cancer risk but specificity and NPV were similar across groups (Appendix 8, Table 19).

Included patients in the SYMPLIFY study[58] were symptomatic, so not reflective of the target population of interest for this review. Participants were investigated according to current NHS practice and without knowledge of the MCED test results, which were not returned to clinicians or study participants. Results for 5,461 participants with an evaluable MCED test and diagnostic test results are presented in Table 4, of which 368 (6.7%) had a cancer diagnosis. A sensitivity of 66.3% (95% CI 61.2% to 71.1%) and specificity of 98.4% (95% CI 98.1% to 98.8%) were reported, with first CSO correct in 85.2% (79.8% to 89.3%) of cases, rising to 90.7% (86.0% to 93.9%) for first and second CSO.

Sensitivity of the MCED test increased with cancer stage, 37.3% (95% CI 29.8% to 45.4%) for stages I-II and 89.7% (95% CI 84.5% to 93.6%) for stages III-IV (full results by stage are presented in Table 5 and Figure 3). Sensitivity, specificity, and accuracy of CSO also varied by cancer site. Although specificity remained high for all cancer sites (ranging from 96.2% to 100%[58]), sensitivity varied substantially by cancer site although the total number of participants diagnosed with certain types of

cancer was low, so results are difficult to interpret (Appendix 7, Table 15). SYMPLIFY also reported sensitivity of the MCED test by cancer site and stage (Supplementary material, page 8 of Nicholson et al.[58]) and shows that sensitivity of the CSO increases by cancer stage for all cancer sites, although there are very small numbers is some categories making results difficult to interpret. The accuracy of the first CSO was higher for stages III-IV and lower for stages I-II (Supplementary material, page 21[58]).

CCGA substudy 3[31] was a case-control study recruiting 4077 participants where 2823 were known to have cancer (cases, 69%) and 1254 were confirmed not to have cancer at one year follow-up (controls, 31%). Test performance is presented in Table 4. Specificity was high (99.5%, 95% CI 99.0% to 99.8%) with 51.5% sensitivity (95% CI 49.6% to 53.3%) and the first CSO was correct in 88.7% of cases (95% CI 87.0% to 90.2%). Sensitivity of the MCED test increased with cancer stage, being relatively low 27.5% (95% CI 25.3% to 29.8%) for stages I-II but higher for stages III-IV (83.9%, 95% CI 81.7% to 85.9%; full results by stage are presented in Table 5 and Figure 3). Sensitivity also varied by cancer site although the total number of participants diagnosed with certain types of cancer was low, so results are difficult to interpret (Appendix 7, Table 15). Sensitivity of the MCED test by cancer site and stage is also reported in CCGA substudy 3 (Supplementary Table S5 of Klein et al.[31]) and shows that sensitivity of the CSO increases by cancer stage for all cancer sites, although there are very small numbers is some categories, making results difficult to interpret. The accuracy of the first CSO is also reported by cancer type and shows great variability (from 0% to 87%, Supplementary Table S7 of Klein et al.[31]).

3.4.1.2 CancerSEEK

DETECT-A[6] was a prospective cohort study in the USA, which recruited 9911 women who were followed up for 12 months. In total, 96 women (0.97%) were diagnosed with cancer during the study, 26 of which were first detected by the CancerSEEK test (sensitivity 27.1%, 95% CI 18.5% to 37.1%, Table 4). Specificity was 98.9% (95% CI 98.7% to 99.1%; PPV 19.4%, 95% CI 13.1% to 27.1%; Table 4). The accuracy of the CSO was not reported. The majority of the cancers (65.6%) diagnosed during the DETECT-A[6] study were Stage I-II (Table 5), however the sensitivity of the CancerSEEK test to detect Stage I-II cancers was lower (12.7%, 95% CI 6.6% to 23.1%) than the sensitivity to detect Stage III-IV cancers (53.1%, 95% CI 36.4% to 69.1%) (full results by stage are presented in Table 5 and Figure 3).

A case-control study of CancerSEEK recruited 1005 patients diagnosed with stage I-III cancers (see Appendix 7, Table 16 for the cancer types among recruited patients) and 812 healthy controls.[33] Specificity was high (99.1%, 95% CI 98.5 to 99.8%) with only 7 out of 812 (0.9%) healthy controls receiving FP test results (Table 4). However, 379 out of 1005 cancers were not detected by the test (sensitivity 62.3%, 59.3% to 65.3%, Table 4) and first CSO was correct in 67.7% of positive tests

across all cancer types, with first CSO correct in less than 50% of cases for liver, lung, and upper gastrointestinal cancers (Table S8 and S10 of Cohen et al., 2018[33]). The proportion of first or second CSO being correct was higher, 85.6% across all cancer types (Table 4). Sensitivity of the CancerSEEK test increased with advancing cancer stage (Figure 3).

The number and proportion of each cancer type detected by the CancerSEEK test is provided in Appendix 7, Table 16. Sensitivity of the CancerSEEK test was highest to detect ovarian cancer and lowest to detect breast cancer in both studies.[6, 33]

The participants included in the DETECT-A study[6] are closer to the target population of interest in this review (asymptomatic screening 50 to 79 years old), than the participants in Cohen 2018,[33] although DETECT-A was limited to women aged 65 to 75 years.

3.4.1.3 Other MCED tests

The SPOT-MAS test was evaluated in the K-DETEK[8] cohort study which recruited 2792 participants over the age of 40 without clinical suspicion of cancer or history of cancer from outpatient clinics in Vietnam. Only the 10 participants (0.36%) who had a positive signal on the SPOT-MAS test were followed-up (for six months) for further diagnostic investigations. Therefore, all negative signals of the SPOT-MAS test were assumed to be TN in the K-DETEK[8] study. Sensitivity and NPV of the SPOT-MAS test are calculated as 100% (Table 4), although this is unlikely to reflect true test performance. Out of the 10 positive signals, six were confirmed to be cancer (PPV, 60%, 95% CI 26.2% to 87.8%) and four were FP (specificity 99.9%, 95% CI 99.6% to 100%; Table 4). First CSO was correct for 83.3% (five out of six) of the cancers; the types of cancer detected by the SPOT-MAS test in the K-DETEK[8] study are presented in Appendix 7, Table 17. A case-control study[64] recruited 239 patients diagnosed with Stage I-IIIA cancers (see Appendix 7, Table 17 for the cancer types among recruited patients) and 474 healthy controls as a validation cohort for the SPOT-MAS test. Specificity of the SPOT-MAS test was high (97.0, 95% CI 95.1% to 98.4%) with only 14 out of the 474 healthy controls with FP results. Sensitivity was 72.43% (95% CI 66.3% to 78.0%) and first CSO was correct for a median of 70% of cancers across all cancer types (Table 4).

Two studies, RESOLUTE and TrueBlood, evaluated the performance of the TruCheck test.[9] In total, 10 participants out of 6884 (0.15%) were diagnosed with cancer during the RESOLUTE study,[9] 9 of which were detected by the TruCheck test (sensitivity 90%, 95% CI 55.5% to 99.7%; Table 4; see Appendix 7, Table 18 for the types of cancer detected by the TruCheck test). An FP signal was also returned in 250 participants who were found not to have cancer (specificity 96.4%, 95% CI 95.9% to 96.8%; PPV 3.5%, 95% CI 1.6% to 6.5%; Table 4). In the TrueBlood study,[9] the sensitivity of the TruCheck test was 93%, correctly detecting cancer in 9224 out of 9920 participants with known or suspected (later confirmed) cancer.

The CDA test was evaluated in the Prospective Population-based Cohort Study (PPCS)[10] where 1957 were followed-up for a median duration of 15 months (range 12 to 20 months). In total, 10 participants (0.51%) were diagnosed with cancer, 4 of which were detected by the CDA test (sensitivity 40%, 95% CI 12.2% to 73.8%; see Appendix 7, Table 18 for the types of cancer detected by the CDA test). An FP signal was also returned in 47 participants who were found not to have cancer (specificity 97.6%, 95% CI 96.8% to 98.2%; PPV 7.8%, 95% CI 2.2% to 18.9%, Table 4).

The AICS test was evaluated in a cohort study[11] which followed participants for up to 6.2 years. Sensitivity by cancer type is presented in Appendix 7, Table 18. AICS was also evaluated in the AICS follow-up study[65] Out of 622 participants with a Rank C (high risk for cancer on the AICS test) who had received a detailed examination in an interim analysis, two cases of prostate cancer and one case of each of lung, colorectal and breast cancer were detected. In another study,[66] up to 115 healthy women were tested for breast cancer using AICS in Japan, and the authors recommended that where rank B or C is returned from the AICS test, further inspection with mammography should be carried out.

The number of cancers detected by the SPOT-MAS, TruCheck, CDA and AICS tests and the total number of cancers diagnosed in cohort studies was very low due to limited follow-up investigations and/or short follow-up periods (Appendix 7, Table 17 and Table 18). Therefore, sensitivity of these tests and any differences in the sensitivity of the tests by specific cancer types and stages are difficult to interpret. Furthermore, stage of cancer detected was not reported for any of the SPOT-MAS, TruCheck, CDA and AICS studies, and accuracy of CSO was not reported for the TruCheck, CDA or AICS tests.

3.4.1.4 MCED test performance for cancers with and without a current screening programme

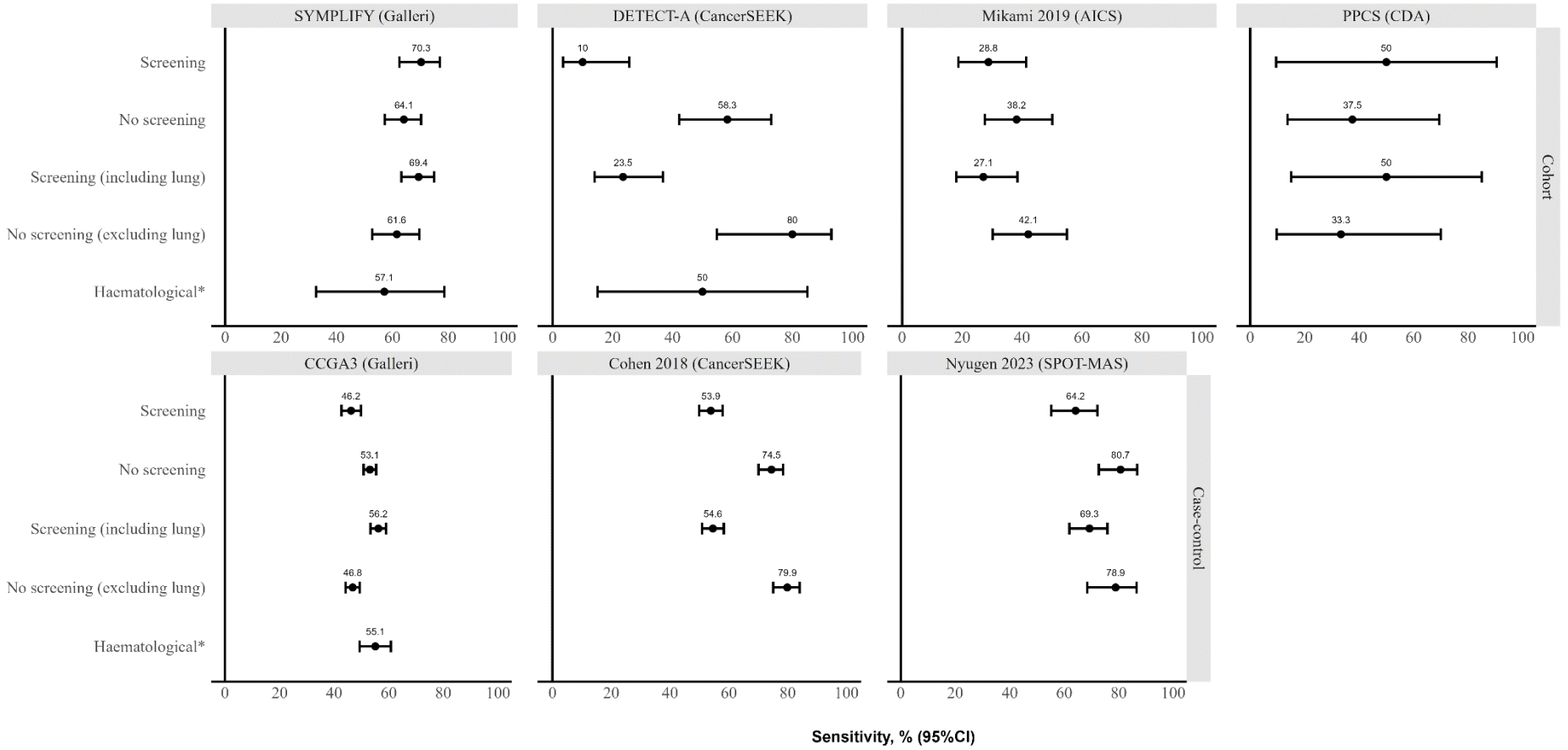
The number and proportion of cancer types with and without a current screening programme in the UK detected by the tests are reported in Table 6 and Figure 4, where they could be extracted or calculated. The numbers and proportions of each specific cancer type detected by each MCED test are presented in Appendix 7, Table 15 to Table 18.

In one of the studies of Galleri (CCGA substudy 3[31]) and both studies of CancerSEEK, sensitivity of the tests to detect solid tumour cancers without a current screening programme in the UK was higher than their sensitivity to detect cancers with a current screening programme (breast, cervical and colorectal) in the UK (Table 6, Figure 4). However, when lung cancer is considered covered by existing screening programmes, sensitivity of the Galleri test is higher for solid tumour cancers with a current screening programme in both CCGA substudy 3[31] and SYMPLIFY[58] (Table 6, Figure 4), which can be explained by the relatively high sensitivity of the Galleri test to detect lung cancer, compared to its overall sensitivity (Appendix 7, Table 15).

The sensitivity of the SPOT-MAS and AICS tests to detect solid tumour cancers without a current screening programme in the UK was higher than the sensitivity of these MCED tests to detect cancers with a current screening programme in the UK, but the sensitivity for solid tumour cancers without a current screening programme was lower for the CDA test (Table 6, Figure 4).

Haematological malignancies were diagnosed for two studies of Galleri and one study of CancerSEEK (Figure 4). In CCGA substudy 3[31] and SYMPLIFY[58] sensitivity of the Galleri test for detecting haematological malignancies was similar to its overall sensitivity. Four haematological malignancies were diagnosed during the DETECT-A study, two of which were detected by the CancerSEEK test (sensitivity 50%, 95% CI 15% to 85%) which is higher that its overall sensitivity (Table 6). No haematological malignancies were diagnosed during the studies of the SPOT-MAS, AICS and CDA tests (Figure 4), although neither the SPOT-MAS nor the AICS test claim to be able to detect these cancers (Appendix 7, Table 14).

Figure 4 Performance (sensitivity) of MCED tests by the availability of screening programme in the UK



*Screening programme considered for solid tumours only, not for haematological malignancies.

Table 6 Number and proportion of cancers detected by MCED tests by cancer types with and without a current screening programme in the UK

Test (Manufacturer)	Galleri						CancerSEEK					
Study	CCGA substudy 3 (case-control)[31]			SYMPLIFY (cohort)[58]			Cohen 2018 (case-control)[33]			DETECT-A (cohort)[6]		
Test accuracy[a]	MCED test (+)	Total cancers	Sensitivity	MCED test (+)	Total cancers	Sensitivity	MCED test (+)	Total cancers	Sensitivity	MCED test (+)	Total cancers	Sensitivity
Overall	1453	2823	51.5 (49.6 to 53.3)	244	368	66.3 (61.2 to 71.1)	626	1005	62.3 (59.3 to 65.3)	26	96	27.1 (18.5 to 37.1)
Screening programme: Breast, cervix, colorectal	349	755	46.2 (42.7 to 49.8)	104	148	70.3 (62.5 to 77.0)	322	597	53.9 (49.9 to 57.9)	3	30	10.0 (3.5 to 25.6)
No screening programme[b]	948	1785	53.1 (50.8 to 55.4)	132	206	64.1 (57.3 to 70.3)	304	408	74.5 (70.1 to 78.5)	21	36	58.3 (42.2 to 72.9)
Screening programme: Breast, cervix, colorectal, lung	651	1159	56.2 (53.3 to 59.0)	159	229	69.4 (63.2 to 75.0)	383	701	54.6 (50.9 to 58.3)	12	51	23.5 (14 to 36.8)
No screening programme[c]	646	1381	46.8 (44.2 to 49.4)	77	125	61.6 (52.8 to 69.7)	243	304	79.9 (75.1 to 84.1)	12	15	80.0 (54.8 to 93.0)
Haematological malignancies	156	283	55.1 (49.3 to 60.8)	8	14	57.1 (32.6 to 78.6)	0	0	NA	2	4	50.0 (15.0 to 85.0)

Test (Manufacturer)	SPOT-MAS			AICS			CDA		
Study	Nyugen 2023 (case-control)[64]			Mikami 2019 (cohort study)[11]			Xie 2022 (PPCS cohort study)[10]		
Test accuracy[a]	MCED test (+)	Total cancers	Sensitivity	MCED test (+)	Total cancers	Sensitivity	MCED test (+)	Total cancers	Sensitivity
Overall	173	239	72.4 (66.3 to 78.0)	NA[d]	NA[d]	NA[d]	4	10	40.0 (12.2 to 73.8)
Screening programme: Breast, cervix, colorectal	77	120	64.2 (55.3 to 72.2)	17	59	28.8 (18.8 to 41.4)	1	2	50.0 (9.5 to 90.5)
No screening programme[b]	96	119	80.7 (72.7 to 86.8)	26	68	38.2 (27.6 to 50.1)	3	8	37.5 (13.7 to 69.4)
Screening programme: Breast, cervix, colorectal, lung	113	163	69.3 (61.9 to 75.9)	19	70	27.1 (18.1 to 38.5)	2	4	50.0 (15.0 to 85.0)
No screening programme[c]	60	76	78.9 (68.5 to 86.6)	24	57	42.1 (30.2 to 55.0)	2	6	33.3 (9.7 to 70.0)
Haematological malignancies	0	0	NA	0	0	NA	0	0	NA

Abbreviations: CCGA = Circulating Cell-free Genome Atlas; MCED = multi cancer early detection; NA = not applicable; PPCS = Prospective Population-based Cohort Study.

[a] Number of people with a true positive (+) MCED test and total number of people diagnosed with cancer in the study (i.e., true positives and false negatives of the MCED test), sensitivity is % and 95% confidence interval calculated from other reported data; [b] assumes there is no screening programme for lung cancer in the UK; [c] assumes there is a screening programme for lung cancer in the UK; [d] overall test performance statistics are not available for AICS test as each cancer targeted by the test is tested for separately.

3.4.1.5 MCED test performance by subgroups

MCED test performance by pre-specified subgroups of interest (i.e., age, sex, and ethnicity) was reported in or could be calculated from studies of Galleri and CancerSEEK. Subgroup results by socioeconomic status were not reported in any of the included studies.

Test performance results (sensitivity, specificity and first CSO accuracy, where available) by age and ethnicity subgroups from the CCGA substudy 3[31] of Galleri and the CancerSEEK case-control study[33] are presented in Appendix 8, Table 20. Specificity was high for all age and ethnicity subgroups in both studies. For CancerSEEK, sensitivity and CSO accuracy were slightly lower for participants less than 50 years of age compared to participants aged 50 years or above while for Galleri, sensitivity and CSO accuracy were very similar across the age categories presented.

Sensitivity of Galleri was highest for Hispanic participants (63%), although with a slightly lower specificity than for other ethnic groups (98% compared to 99 to 100%), and it was lowest (43%) for the small number of participants classified as 'Other' in the study. Sensitivity of CancerSEEK ranged from 50% in participants with unknown ethnicities to 70.4% in Asian participants (and cancer was correctly detected by the CancerSEEK test in one Hispanic participant resulting in a sensitivity of 100%). However, any differences in the sensitivity of the Galleri or CancerSEEK test by ethnicity should be carefully interpreted as the majority of participants recruited to studies were White and other ethnic subgroups have much smaller numbers of participants.

A poster presentation reported the number of signals for cancers detected by age categories and sex (male/female, as defined in the publication) as well as the CSO distribution and prediction of accuracy by sex for a subset of the PATHFINDER participants, using the earlier version of the GRAIL MCED test.[84] Reported data showed that the cancer signal detection rate was similar in males and females and increased with age for both, however few details were given on the subset of participants analysed and a now superseded version of the MCED test was used, so these findings should be interpreted with caution. No subgroup data by ethnicity were reported and no subgroup data were available for the refined MCED test.

3.4.2 Other outcomes reported in included studies

Additional outcomes relevant to this review were reported in studies of Galleri and CancerSEEK, including mortality, potential harms, acceptability, and satisfaction of individuals screened. One study of the AICS test also reported very limited information on survival.

3.4.2.1 Mortality

The DETECT-A study reported mortality outcomes among individuals who received a positive CancerSEEK test result, 4.3 years after the initial study.[85, 86] Among the 26 participants with a true

positive test result, half were in remission; sixteen (62%) were alive (5 at stage I, 4 at stage II, 5 at stage III and 2 at stage IV), of which seven had cancers where no standard screening options are currently available.[86] All deceased participants had stage III (n=3) or IV cancer (n=7) at the time of diagnosis. Among participants with FP test results, only two developed cancer: one was diagnosed with stage I breast cancer 2.7 years after the test, and one with stage III ovarian cancer 2.9 years after the test.[85]

Information on mortality was reported for the PATHFINDER study for only two participants who were followed-up for more than one year after diagnosis.[87] One had stage I renal cell carcinoma and stage II head and neck cancer, and after a combination of treatments, was alive and cancer free at ≥502 days after diagnosis.[87] One had stage IIIB lung cancer, and was alive at ≥683 days post-diagnosis, but metastatic disease had developed.[87]

Survival information for four participants who had the AICS test in the AICS follow-up study[65] and were diagnosed with cancer (two detected by AICS and two not detected by AICS) was obtained from a cancer registry. All participants were alive at the time the information was obtained and were undergoing treatment.

3.4.2.2 Potential harms and impact on healthcare systems

In the PATHFINDER study, results reported for the earlier version of the GRAIL MCED test showed diagnostic resolution was achieved after initial evaluations in 82% (32 out of 39) of participants with a positive test result, and additional testing was only required for individuals with a cancer history and negative initial evaluation or an equivocal initial evaluation. Whole body imaging was required in 69% cases (27 out of 39), but only contributed to diagnosis in under half of cancer cases (49%), and was only useful when detecting the presence of non-localised cancer.[88] The median time to diagnostic resolution was 57 days (IQR 33 to 143 days) for TP results and 162 days (IQR 44 to 248 days) for FP results.[30] Overall, 52% (17/33) participants with a TP test result had at least one clinic visit (average number 0.9 among the 33 participants), compared to 32% (18/57) participants with a FP result (average number 1 among the 57 participants); 79% (26/33) of participants with TP results had at least one lab test (average number of tests 3.7), compared to 88% (50/57) with FP results (average number 4); and 91% (30/33) individuals with TP results had imaging tests (average number 1.5), compared to 93% (53/57) of those with FP results (average number 1.9).[30] More participants with TP test results had surgical and non-surgical procedures compared to those with FP results (82% vs 30%).[30] Similar findings might be expected for participants testing positive with the refined version of the GRAIL MCED test (Galleri). In the SYMPLIFY study, median time to diagnosis was 35 days (lower quartile 20, upper quartile 57 days, Supplementary material, page 21 in Nicholson et al.[58]). However, this outcome is not directly relevant to the asymptomatic screening population considered

in this review, since included patients had already been referred, and investigations were not triggered by positive MCED test and CSO results.

In the DETECT-A study, no adverse events were reported from the CancerSEEK test directly. 101 participants with a positive MCED test result underwent confirmatory positron emission tomography-computed tomography (PET-CT), a form of CT with radiation exposure more than twice as high as the exposure from standard CT; 62% required no further follow-up, while 16% had non-invasive procedures, 19% had minimally invasive procedures, and 3% (3 cases) required surgery.[6] Another potential source of harm may come from decreased adherence to standard of care screening following a negative result. However, no differences in the proportion of participants who had a mammogram before and after enrolment in the study were found.[6]

3.4.2.3 Acceptability and satisfaction

Both Galleri and CancerSEEK were reported as being generally acceptable to participants, with 97.1% and 95.0% of participants reporting high satisfaction with MCED testing or with participating in the study, respectively.[6, 89] Among DETECT-A participants who received false results on the CancerSEEK test (false positives/negatives), 0.8% reported dissatisfaction and 1.7% would not participate in the study again, compared to 0.2% and 1% of those who received the correct results (true positives/negatives).[6] Similarly, in the PATHFINDER study, 17.6% of participants who had a FP result reported dissatisfaction with MCED testing, compared to 8.0% of those with a TP result, and 2.8% of those with a negative result on the Galleri test.[89]

The PATHFINDER study additionally reported changes in anxiety levels of participants receiving the GRAIL MCED test, across different stages of the study (at pre-test, return of results, diagnostic resolution, and end of study).[89] Although the overall mean levels of anxiety did not change substantially, the proportion of participants who reported increased anxiety (defined as scoring 3 points or more on the PROMIS [Patient-Reported Outcomes Measurement Information System] anxiety scale) changed between different stages of the study. However, the study did not examine anxiety levels whilst participants were waiting for test results, only after they had received the results. When participants received results of the MCED test, around half of those who received a positive result reported increased anxiety (57.9% for TP, 46.4% for FP).[89]After diagnostic resolution, the proportion with increased anxiety levels halved for the FP group (24.2%), and was similar to those with a negative test result (27.4%), while the proportion remained the same for the TP group (56.0%).[89]

A study to evaluate the implementation of the Galleri test as an employee benefit among individuals with low socioeconomic status, identified a number of factors that were important for test uptake, including: the test being an on-site event; having trusted long-term employees on site that spoke the

same language and helped with any translations as necessary; the test results being explained in their native language; and the ability to administer the test without computer or digital equipment.[59] However, this evaluation relied on employer insight, employee feedback and observations of GRAIL staff, so there is a potential for considerable bias in these results.

3.4.3 MCED technologies at an unclear stage of development

The type of outcomes reported for MCED technologies at an unclear stage of development varied across studies and were not directly comparable with one another. Therefore, a short summary is provided below, and further details on study characteristics as well as any results reported can be found in Appendix 6, Table 12.

All studies were case-control studies, except for two publications from SeekInCare[75, 76] which reported both case-control and prospective cohort studies including 'real-world' cohorts. A case-control study of CancerenD24,[70] reported that cancer patients and healthy controls were matched on ethnicity but did not include a description of the different ethnic groups. Ethnicity was not reported in any other study. All studies reported on the accuracy of the MCED technology, including sensitivity and specificity, and some studies also reported these for each stage/type of cancer detected. OncoSeek reported the lowest overall sensitivity across all cancer types (47.4%),[73] and CancerenD24 reported the lowest sensitivity in detecting bladder cancer (38.0%).[70] By stage, OverC and SeekInCare reported a sensitivity of 35.4% and 50.3%,[75, 77] respectively, for stage I cancer. The highest sensitivity overall came from the Carcimun-test (88.8%),[81] however, the exclusion of individuals with inflammation is noted as a disadvantage of the technology as a screening tool in the general population. The SpecGastro test was only developed to detect three types of gastrointestinal cancer (colorectal, gastric, and oesophageal).[82]

3.5 Ongoing studies of included technologies

The NHS-Galleri trial[60] is the only ongoing RCT identified. An interim analysis of NHS-Galleri at one-year post-randomisation is planned for late 2023/early 2024,[90] which is expected to report on the number of stage IV cancers detected in each study arm. NHS-Galleri and PATHFINDER2 both plan to recruit healthy volunteers over 50 years of age (up to age 77 in NHS-Galleri), which is reflective of the target screening population for this review.[60, 61] A list of ongoing studies identified for the included technologies is presented in Table 7.

Table 7 Summary of ongoing studies for included technologies

Study details	Participant information	Intervention	Outcomes
GRAIL Galleri			
NHS-Galleri[60] Clinical trial identifier: ISRCTN91431511 NCT05611632 Randomised controlled trial Estimated completion date: 28/02/26	Healthy volunteers aged 50 to 77	Blood collection and Galleri (MCED) test Comparator: blood collection and storage for potential future evaluation	Incidence rate of stage III and IV cancers adjusted by the follow-up time in the intervention arm compared with the control arm; test performance; safety; impact on healthcare resource utilisation; cancer-specific mortality; potential impact of overdiagnosis
PATHFINDER2[61] Clinical trial identifier: NCT05155605 Prospective single-arm trial Estimated completion date: 30/07/26	Individuals aged ≥50	GRAIL MCED blood test	Safety; test performance; anxiety; participant-reported intention to follow guideline recommended cancer screening procedures; cancer detection rate of PET-CT; number and type of diagnostic evaluations; radiation exposure; accuracy amongst subgroups; perceptions of the MCED test
REFLECTION[62] Clinical trial identifier: NCT05205967 Prospective cohort study Estimated completion date: 23/08/26	Individuals aged ≥22 who have opted to be screened with Galleri MCED test	Galleri blood based MCED test	Signal detection and cancer detection among participants; feasibility and acceptability; healthcare resource utilisation associated with cancer diagnostic workups for participants with signal detected
SUMMIT[63] Clinical trial identifier: NCT03934866 Prospective cohort study Estimated completion date: August 2030	Individuals aged 55 to 77 who are at high risk for lung cancer due to a significant smoking history	GRAIL blood test and low dose CT scan at the same visit	Test performance of GRAIL blood test and of delivering a low-dose CT screening service
OverC – Burning Rock Biotech			
PREVENT[79] Clinical trial identifier: NCT05227534 Prospective cohort study Estimated completion date: 31/12/28	Asymptomatic participants with cancer risk, aged 40-75	OverC multi-cancer detection blood test	Accuracy of the test after 1, 3 and 5 years; health-related quality of life; acceptability (satisfaction with the test)

Study details	Participant information	Intervention	Outcomes
PREDICT[80] Clinical trial identifier: NCT04817306 Prospective case-control study Estimated completion date: 31/03/23	Cancer patients, those with benign diseases, and healthy controls aged 40-75	OverC multi-cancer detection blood test	Accuracy of the test; accuracy of CSO

Abbreviations: CT = computed tomography; MCED = multi-cancer early detection; PET-CT = positron emission tomography-computed tomography.

3.6 Technologies excluded from the review

As discussed in Section 3.2, full-text screening identified several blood-based MCED technologies currently at an early stage of development and not ready to be implemented, which did not meet the inclusion criteria for this review. Given the fast-moving pace of research in this area, some of these may become available in the near future. We therefore provide a brief, non-exhaustive summary of some of these technologies below including: DELFI (DNA evaluation of fragments for early interception) developed by DELFI Diagnostics (Baltimore, Maryland), with two ongoing clinical trials evaluating its use in detecting lung cancer;[91, 92] Aurora (AnchorDx, Guangzhou, China), which detects five types of cancer and has a planned clinical trial in asymptomatic populations;[93, 94] PanTum (Zygnum AG, Darmstadt, Germany), with two ongoing clinical trials in China[95] and India;[96] LUNAR-2 (Guardant Health, Palo Alto, California), with an ongoing trial in individuals at high-risk of cancer;[97-99] and HarbingerHx (Harbinger Health, Cambridge, Massachusetts), with an ongoing case-control study and expected product launch date in 2025.[100] Further details can be found in Table 8.

Table 8 Summary of technologies excluded from the review

Technology	Manufacturer	Description	Completed/ongoing studies
Adela's MCED tests	Adela Bio (Foster City, California)	A genome-wide methylome enrichment platform that combines cfDNA with machine learning.	Ongoing: CAMPERR[101] is an ongoing case-control study to evaluate the test across 20 types of cancer.
Aurora	AnchorDx (Guangzhou, China)	A targeted methylation profiling platform capturing cancer-specific DNA methylation signatures across five cancer types (lung, breast, colorectal, gastric, esophageal)	Completed: Pre-clinical studies used plasma samples in a training/validation cohort.[93, 94] A large prospective clinical trial is planned in asymptomatic populations.
CAPP-Seq	Diehn Lab at Stanford (Stanford, California)	Cancer personalised profiling by deep sequencing – a method for quantifying circulating tumour DNA (ctDNA).	Completed: Initially implemented for non-small cell lung cancer.[102] Generalisable to other tumour types and work is ongoing to establish its clinical utility as an early detection tool for cancer.
DELFI	Delfi Diagnostics (Baltimore, Maryland)	DNA evaluation of fragments for early interception. Uses a machine learning algorithm to detect abnormalities of cfDNA across the genome.	Completed: Pre-clinical study using plasma samples to detect 7 types of cancer.[91, 92] Ongoing: Two ongoing clinical trials on lung cancer: DELFI-L101[103] and DELFI-L201[104] (also known as CASCADE-LUNG), and one ongoing clinical trial (DETECT study,[105] past completion date) to detect cancer in liver transplant recipients.
Dxcover	Dxcover Limited (Glasgow, United Kingdom)	A blood-based test using infrared spectroscopy combined with machine learning to screen for eight types of cancer (brain, breast, colorectal, kidney, lung, ovarian, pancreatic, and prostate)	Completed: Discovery stage study using biobank samples to differentiate non cancer symptomatic from cancer patients.[106]
Elypta's MCED test	Elypta (Solna, Sweden)	A metabolism-based liquid biopsy using profiles of human glycosaminoglycans (GAGome).	Ongoing: An ongoing study[107] is assessing the performance of the test measured in plasma, in urine, or both in a prospective cohort of firefighters.
HarbingerHx	Harbinger Health (Cambridge, Massachusetts)	A platform that combines ctDNA with machine learning for early detection of cancer. Expected to launch in 2025.[108]	Ongoing: CORE-HH[100] is an ongoing case-control study to assess the performance of the platform in detecting cancer.
LUNAR-2	Guardant Health (Palo Alto, California)	A blood-based test initially designed to detect colorectal cancer, but ongoing trials are evaluating its use in other types of cancer.	Ongoing: SHIELD[97-99] is an ongoing study of individuals at high-risk of cancer (first cohort will be focused on lung cancer).

Technology	Manufacturer	Description	Completed/ongoing studies
MERCURY	Geneseeq Technology (Toronto, Canada)	A blood-based test using cfDNA features for multi-cancer early detection.	Completed: Evaluated in a case-control study of 3 types of cancer (liver, colorectal, lung).[109] Ongoing: The Jinling cohort[110] is an ongoing prospective cohort study evaluating the use of MERCURY test in an average risk population.
MNALDI	Not reported	Multiplexed nanomaterial-assisted laser desorption/ionization for cancer identification	Completed: Pre-clinical study using plasma samples from two hospitals in China to detect six different cancers (liver, lung, pancreatic, colorectal, stomach, thyroid).[111]
PanSeerX	Singlera Genomics (San Diego, California)	A blood-based cancer screening test based on cancer-specific methylation signatures.	Ongoing: The FuSion Programme[112-114] is an ongoing prospective cohort study of asymptomatic individuals to evaluate the performance of the PanSeer assay.
PanTum	Zygnum AG (Darmstadt, Germany)	EDIM (Epitope detection in monocytes) technology focuses on the detection of two biomarkers (Apo10 and TKTL1) in monocytes, tested in 8 different types of cancer.[115]	Completed: Early case-control study evaluating its use in 3 types of cancer (bile duct, colorectal, pancreatic).[116] Ongoing: Two ongoing clinical trials in China[95] and India.[96]
Raman Spectroscopy	Epigeneres Biotech (Mumbai, India)	Identifies cancer using biochemical fingerprints of Raman Spectroscopy and expression patterns of polymerase chain reaction.	Ongoing: An ongoing clinical trial[117] to assess the feasibility of Raman Spectroscopy as a screening tool for cancer detection in India.
TEC-Seq	Not reported	Targeted error correction sequencing of cfDNA from 58 genes, based on four types of cancer (colorectal, lung, ovarian, and breast).	Completed: Initial validation was done using plasma samples of patients and healthy controls.[118]
YiDiXue	Shenzhen Keruida health technology (Shenzhen, China)	A blood-based multi-cancer early detection test.	Ongoing: SZ-PILOT Study[119] is an ongoing case-control study to evaluate the clinical efficacy of the YiDiXue test.

4 STAKEHOLDER ENGAGEMENT

At the protocol stage, early discussion with stakeholder representatives acknowledged the potential value of early diagnosis where this might result in improved treatment outcomes and survival rates, but this consultation also highlighted the importance of taking account of issues with the possible implementation of these tests including:

- Resource use and potential impact on existing diagnostic services (including any resulting need for further investigation/confirmation and waiting times between diagnosis and treatment, as well as planned frequency of testing)
- Impact on wider care pathways (including primary care)
- The need to balance any benefits with potential risks to patients and the public (including anxiety, the risks associated with both false positive and false negative test results, the potential active identification of cancers that might otherwise prove unproblematic for screened individuals, and the possible lack of effective treatment)
- Consideration of factors likely to affect test uptake (including possible health inequalities, such as ethnic group and socio-economic status).

Comments received at protocol stage also reinforced the importance of patient relevant outcomes, resulting in the inclusion of outcomes related to potential harms, HRQoL, acceptability to individuals screened, and satisfaction of individuals screened.

The initial stakeholder group (as listed in the Acknowledgements) were also invited to comment on a draft version of the final report, particularly to check technical descriptions, handling of available tests and tests in development, and presentation of study details for each test. All agreed these were appropriate, particularly in view of the early stage of development of these technologies and the rapidly growing evidence base. Those consulted also noted that important details about the potential benefits, harms, and possible unintended consequences of implementing these tests in the UK were often not reported, limiting the relevance of available evidence for policy decision-making. Concerns were expressed about the limitations of the current evidence base and the need for improved understanding of the natural history of, and treatment outcomes for, early-stage cancers detected by MCED tests in healthy individuals at different ages, particularly older people. Several stakeholders also expressed concerns at the high risk of bias ratings for all of the studies, and commented on the wide variation in the nature of the MCED tests as well as variability in the study findings, noting inherent difficulties in distinguishing between the quality of the study, the context in which it was undertaken, and the value of the test itself. Other feedback fell into three broad areas relating to the poor applicability and generalisability of the available evidence, the potential impact of MCED

screening on existing screening, diagnostic and treatment pathways and the acceptability and potential impact on populations offered and/or receiving screening.

Following conclusion of the systematic literature review work, additional PPI consultation explored the broader views of patients and the public about the use of MCED tests as part of a general population screening programme.

Feedback from all stakeholder engagement is summarised below under six main themes

1. **Poor applicability and generalisability of available evidence**

- *Population of interest:* Where reported, substantial differences between study participant characteristics and the target population for this review (the anticipated UK screened population), including population age range, ethnicity and cancer stage and type, were noted.
- *Relevance to UK context:* Given that the review only identified one UK based study, and that substantial differences in the organisation and resourcing of services exist across the different healthcare environments in which studies were undertaken, the applicability of the current evidence base was questioned.

2. **Limitations of the current evidence base**

- *Effectiveness of MCED tests in identifying cancers.* Whilst recognising the early stage of this research, contributors wanted reassurance that MCED tests actually worked, and that high quality evidence was available to decision-makers before general population screening programmes were considered. Several PPI contributors queried whether tests claiming to identify a very broad spectrum of cancers might actually be less appropriate to the NHS than tests that claim to identify fewer, treatable, cancers with a good prognosis and higher likelihood of recovery (especially where these were not already covered by an existing screening programme). They also raised concerns about how test effectiveness was being measured and whether an appropriate spectrum of outcomes is being considered.
- *Balancing effectiveness and cost-effectiveness.* PPI contributors wanted much more detailed information about the variety of tests available, their respective cost, and accompanying claims about the numbers and types of cancers targeted, expressing concerns about both the commercial sector support for existing research and the cost-effectiveness of MCED tests for the NHS. They highlighted the need for better quality information and evidence from future independently conducted research and evaluation.

3. **Potential impact of MCED screening on existing screening, diagnostic and treatment pathways**

- *Unknown effect on existing screening programmes*. Concerns were raised about the lack of evidence around implementation of MCED screening alongside existing, potentially duplicative, cancer-specific screening programmes. In the event of a negative MCED result,

the potential to reduce participation in already established and demonstrably effective screening programmes (particularly where the screening process might be less appealing to patients) was highlighted. This could actually result in a reduction in the detection of early stage disease and the potential for increased mortality.

- *Likely increased pressure on existing screening and diagnostic services.* Although little is known about plans for the implementation of an MCED screening programme in the UK, many issues were raised around the possible impact on already stretched blood testing services and diagnostic pathways. It was also noted that the current evidence base provides little to guide decisions about the appropriate frequency of MCED screening and optimal length of follow-up, especially in the context of existing cancer-specific screening programmes and taking account of patient characteristics, such as increasing age.
- *Likely increased pressure on existing treatment and support services and resources.* The possible impact on primary, secondary and tertiary care was raised; the consequences of screening a large proportion of the healthy population should not be underestimated given the potential increase in NHS/healthcare system costs.
- *Implications for general practice.* The practical implications for general practice were of particular concern, especially given current appointment difficulties and limited consultation time. All stakeholders noted that many cancer symptoms are also common in benign conditions, making them difficult to discriminate and potentially resulting in missed opportunities for early diagnosis, and that there may already sometimes be a lack of consistency in screening and referral decisions by GPs. PPI contributors suggested that clear guidance could be formulated to clarify the circumstance in which GPs should be able to refer patients for MCED screening, particularly if the introduction of these tests results in patients becoming less willing to report symptoms to GPs in case they might become ineligible for screening.
- *Timely and appropriate communication of results.* PPI contributors, in particular, highlighted the considerable anxiety experienced by both patients and families awaiting test results, but also the importance of good support when results are communicated. Concerns were raised about the variety of ways that MCED test results might be shared with screened individuals, and the potentially damaging impact of some of these regardless of outcome. Furthermore, the likely need for increased anxiety management and support required after a positive result, especially in the case of a false positive finding, was acknowledged. The importance of evaluating and establishing resulting effects on general practice workload was considered a priority, especially in view of current pressures.

4. Opportunities to enhance services to improve outcomes

- *Implementation of decision support tools and improved education for GPs.* Having better support systems in place for GPs was considered critical. One content expert cited experience

with other screening programmes where challenges had been experienced in separating out use of tests for screening in asymptomatic populations and in populations with symptoms. Additional training on the appropriate use of MCED tests on the diagnostic testing pathway might also be required, especially if GPs were able to make referrals for screening tests. The value of clear and properly applied decision support systems in this context was highlighted.

- *Appropriate health service design and resourcing.* Contributors acknowledged that the proposed implementation of an effective MCED test as part of a general population screening programme could, in theory, improve existing services if properly integrated, but that this would inevitably result in increased NHS costs, bringing more people into the system, resulting in the need for further testing, and placing additional burden on an already stretched system. PPI contributors noted the potential to improve efficiency, patient experience and screening uptake, were screening programmes to be integrated, perhaps via dedicated and suitably located community screening and diagnostic hubs to maximise opportunities for access. Additionally, the involvement of nurses, physician associates, and community pharmacists to support accurately and clearly communicating screening test results, potentially alongside general health checks and advice, was strongly favoured. It was acknowledged that the effectiveness, cost-effectiveness and acceptability of any accompanying service design changes would need to be properly evaluated in future research.
- *Integrating general population screening with targeted health checks.* PPI contributors noted the positive impact that contact with cancer services has on lifestyle behaviours, and that implementing a general population cancer screening programme of this sort could also provide an excellent opportunity for prevention initiatives, for example, through undertaking general health checks and providing lifestyle advice and information. This might be especially important in the case of a negative test result.

5. Acceptability and potential impact on populations offered and/or receiving screening

- *Acceptability of the MCED screening test.* All stakeholders agreed that acceptability was paramount, and that, whilst the acceptability of a simple blood test might be quite high, little evidence is available to confirm this. The likelihood that acceptability and uptake would not be distributed evenly across the population eligible for screening and the associated potential for exacerbating existing health inequalities was noted. PPI contributors also noted that regular MCED testing might, in some groups, actually reduce uptake of other possibly less acceptable screening tests. The need to properly demonstrate improved outcomes as a result of MCED screening across all populations was considered a priority.
- *Acceptability of MCED test outcomes.* Stakeholders repeatedly observed the possibility that MCED tests could have the potential to detect early-stage cancers that, for many, might never result in symptoms or significant morbidity, particularly in older people. Consideration of the

impact of unnecessary distress and potentially invasive intervention is currently absent from the existing evidence base.

- *The effects of false positives on those screened.* Although the information provided to those invited for screening might be critical to uptake, concerns were expressed about the possible impact of a false positive test result, both in terms of unnecessary anxiety and distress caused, and also on subsequent confidence in screening programmes and diagnostic services. The need to better understand the impact on MCED screened individuals and their families was noted.
- *The effect of a negative MCED test outcome on those screened.* The potential for undue reassurance and changes in other health-related behaviours (including routine screening uptake) following a negative MCED test result was noted, with the possible impact greater in some groups; again, the need to better understand the wider effects of different MCED test outcomes was highlighted.
- *Poorly reported or missing patient relevant outcomes.* The need for improved collection of patient relevant outcomes in future research was emphasized by all stakeholders, but especially given their importance in cost-effectiveness assessments. In particular, the vital need to assess the performance of MCED screening using mortality endpoints was emphasised, not only due to its importance for patients, but also because of known inaccuracies in existing staging investigations at diagnosis, and the possibility that MCED tests might exacerbate these problems due to their mechanism of action (detection of evidence of cancer in the circulating blood).

6. Targeting specific groups to support early identification and improve outcomes

PPI contributors highlighted a number of considerations around the adoption of MCED testing, noting the need to balance test accuracy and cost with the likelihood of improving outcomes for NHS patients. In particular they were interested in exploring options for a more focused approach to MCED screening, for example, use of MCED tests that targeted:

- cancers not currently covered by existing cancer screening programmes (even if these tests identified fewer cancers)
- cancers that are treatable/stageable where outcomes might be improved (even if these tests identified fewer cancers)
- groups recognised as being at high risk of certain cancers (rather than in the general population)
- groups less likely to engage with health services (to facilitate earlier identification)
- younger age groups of 30-40 years or younger (to facilitate earlier identification)
- people in remission following successful cancer treatment (where appropriate/feasible)

5 PATIENT AND PUBLIC INVOLVEMENT

As part of this study, we aimed to include the perspectives of patients and the public (along with other stakeholders) in both our protocol development and to help us better understand, interpret and contextualise the findings from the review.

We used a range of methods to achieve this, including inviting and receiving comments on the draft protocol prior to undertaking the review, incorporating limited feedback and observations on the draft final report, and hosting both group and individual discussions with representatives from the wider community, including people with lived experience of a cancer diagnosis, carers and those potentially eligible for screening.

Feedback at protocol stage resulted in the inclusion of additional patient relevant outcomes (including potential harms, HRQoL, acceptability to individuals screened, and satisfaction of individuals screened). It also highlighted the importance of broader issues of consideration to the implementation of such a screening programme. Subsequent PPI consultation was designed to further explore the issues identified through earlier stakeholder feedback, including resource use and potential impact on existing services, the need to balance any benefits with potential risks to patients and the public, and consideration of factors likely to affect test uptake.

The group PPI session provided an opportunity for a more reflective discussion on the issues raised, offering a more nuanced interpretation of these, as well as raising several additional themes, including limitations in the current evidence base, accompanying opportunities to enhance services to improve outcomes, and the potential for a more targeted population approach for MCED screening.

The nature of the evidence synthesis brief necessitated a focus on the existing evidence base to support future decision-making, primarily in terms of developing subsequent research. The short timeframe allowed for this work impacted the feasibility of stakeholder involvement generally and patient and public involvement in particular. We had an opportunity to involve PPI contributors at the conclusion of this work, and designed a process in collaboration with our partner organisation, Healthwatch York, to maximise involvement as we were able to give potential contributors only short notice to join a group discussion. We targeted a number of different organisations and individuals in our network (as listed, with grateful thanks, in our Acknowledgements), many of whom provided exceptional support with recruiting potential participants. Using Zoom, we were able to involve people from a range of backgrounds and geographical locations, and with a wide variety of experiences. All PPI contributors actively engaged in the discussions, enriching our understanding of

considerations around the implementation of these tests as part of a general population screening programme.

The findings of this review raised many questions for stakeholders, and the PPI consultation emphasised the vital importance of good communication with patients and the public about our understanding of the current evidence base for these tests. Our project engagement work to date has provided a strong foundation for effective dissemination through existing PPI contributors, as well as strengthening and fostering relationships with key organisations via our Healthwatch channels and cancer related PPI groups.

In line with University of York Policy (Payment of Individuals for Involvement with and Contribution to Research), all PPI contributors were offered honoraria in the form of a gift voucher to acknowledge their time and contribution. By agreement, all PPI contributors were also either acknowledged by name or in association with the organisations with which they were affiliated.

The reporting of our patient and public involvement is aligned with the Guidance for Reporting Involvement of Patients and the Public Short Form (GRIPP2)[120] as detailed in Appendix 9.

6 EQUALITY, DIVERSITY AND INCLUSION (EDI)

The independent research team for this project comprised a range of experience and expertise, and included both junior and senior methodologists. This review was designed to inform decisions about future research on the use of MCED tests as part of a general population screening programme, specifically focusing on people without cancer symptoms aged 50-79 years. As such, we took a pragmatic approach to stakeholder engagement, inviting protocol and report feedback from content experts with specific knowledge of equity and diversity considerations in screening, as well as inviting contributions and input from people meeting the population criteria for the review and people and carers with lived experience of a cancer diagnosis. Comments, views and feedback from organisations and people across the UK representing these populations were included in the review.

The available evidence has limited generalisability to the population of interest in this review and no directly applicable evidence was available to indicate the impact of an MCED screening programme on different groups. However, all stakeholders emphasised the potential, without appropriate mitigations, for an MCED based screening programme to exacerbate existing health inequalities. The concerns raised reflected recognised differences in motivation, willingness and practical difficulties in taking up the offer of screening amongst different groups (for example, working mothers or those with childcare responsibilities who may not prioritise their own health, those without a permanent address or who are homeless and therefore not registered with a GP, and those in particular types of employment where flexibility is limited). Likely differences in uptake and outcomes amongst

different ethnic and socio-economic groups were also emphasised. Finally, the importance of considering overall patient burden was noted, particularly in terms of convenience of access to screening and any subsequent diagnostic testing (especially in remote areas), and the necessary travel time and associated cost (in both urban and rural areas) associated with this. All these observations mirror the evidence for differential access and uptake in other cancer screening programmes.[121-125] From the evidence reviewed and the accompanying stakeholder feedback, it is clear that the feasibility, accessibility and impact of such a screening programme on a broad range of different groups requires detailed evaluation and mitigations may be required.[126-128]

The evidence in this field can be complex and difficult to understand, but every effort was made to ensure the language and terminology used in our report was accessible and understandable. The report was edited in response to feedback about terminology or concepts necessary to understand the evidence base and, where necessary, more detailed explanation was incorporated in the text. Additionally, several visual representations were incorporated to simplify presentation of some complex results and findings.

Acknowledging the tight timetable for delivery of this project, to maximise opportunities for engagement and reduce burden on PPI contributors, we circulated invitations to participate in a meeting without any expectation of preparation. We instead provided a platform for remote participation and open discussion, whilst offering compensation for time and contribution. Due to the short notice provided, or for reasons of digital exclusion, it is possible that some groups might not have been able to participate. However, the report will be shared with all participants (subsequent to the necessary permissions), and further co-production work is planned with patients, the public and third sector advocacy groups to support ongoing communication to a wider audience about the current evidence base for MCED tests.

7 IMPACT AND LEARNING

This systematic review has highlighted significant gaps in the evidence for MCED tests as they might be applied in a UK context. We have identified and reported on a wide variety of research needs, some of which are likely to be addressed in UK projects that are already planned or underway. The relationships fostered as part of our review and consultation work, with both stakeholder organisations and patients and the public, have also yielded opportunities for involvement in all future UK research projects of which we are currently aware.

This review has already had direct impact on three planned or early stage MCED test research projects. It is directly informing a project supported by the UK National Screening Committee (UK NSC) which has recently commissioned an evidence review of MCEDs (led by Bethany Shinkins,

University of Warwick and Jason Oke, University of Oxford). These findings will be incorporated into the UK NCS evidence review and supplemented by a review of the methodological literature, with the overarching aim of identifying issues uniquely related to MCEDs and developing criteria for the UK NSC to use in the evaluation of MCEDs tests in a screening context. Members of the research team for this project will contribute to this work wherever possible and appropriate. This review is also being used as foundation work to underpin a project being led by the Centre for Health Economics (CHE) in partnership with the Centre for Reviews and Dissemination, University of York, that will support the understanding of the economic impacts of these tests and technologies. Finally, it has already contributed to planning and is informing the design of an HTA project NHS-Galleri RCT[60].

To proactively communicate the findings of this review, we are now beginning to work with partners Healthwatch,[27] Involve Hull,[28] Yorkshire and Humber Cancer Alliance[29] and our combined wider networks, to co-produce and develop dissemination resources explaining the current state of the evidence in a form accessible for target audiences

Finally, in view of the rapidly developing evidence in this field, enabling prompt public access to the findings of this review will maximise its impact, particularly for non-UK based projects. For example, the review could be valuable in informing the USA National Cancer Institute Vanguard Study on Multi-Cancer Detection study[129, 130] which is due to begin a pilot study in 2024.

8 DISCUSSION

In terms of accuracy, the use of an MCED test as a screening tool in a generally healthy, asymptomatic population, alongside existing cancer screening programmes, requires a high specificity and high accuracy of the predicted CSO. It also requires reasonable sensitivity to detect early-stage disease so that the benefits of earlier diagnosis, where treatment options exist, can be realised, compared with a later-stage diagnosis where symptoms may be present and treatment options may be more limited. A potential advantage of MCED tests would be if they are able to detect cancer earlier, with test results used to intervene with therapies with intent to cure, thus positively impacting on mortality and HRQoL.

Limited evidence is available on the potential for early detection of treatable cancers, and the consequences of introducing screening with an MCED test in a UK population. In particular there is some concern that MCED tests may tend to identify cancers with an increased risk of late recurrence, meaning that even if a patient is initially diagnosed as having early stage cancer and treated, the disease may later recur leading to no improvement in survival.[18, 131, 132]

However, there is ongoing debate about whether detecting cancer at an earlier stage always leads to an improvement in mortality. The recent UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) trial,[133] which randomised women aged 50 to 74 years to annual multimodal screening or transvaginal ultrasound screening or no screening, found a significant reduction in the incidence of late-stage ovarian cancer with screening, but no benefit in terms of mortality. This is not an isolated case; the Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) trial[134] made the same observation for prostate cancer and this has been discussed widely in the literature.[14, 18, 132]

8.1 Summary of findings

This review summarised existing evidence on MCED test performance and patient-relevant outcomes. We included 36 studies evaluating 13 technologies that reported relevant outcomes for this review, and risk of bias assessment identified substantial concerns with the included studies. We found no completed RCTs or prospective cohort studies carried out in a UK asymptomatic population reporting accuracy measures, morbidity or mortality outcomes. Limited evidence on acceptability to patients and the potential impact on health services was found, although none in a UK setting. Ongoing studies may provide relevant evidence within the target screening population once their findings are published.

Of the 30 completed studies reporting results, only SYMPLIFY[58] (evaluating the Galleri test) was conducted in the UK (England and Wales), although participants recruited had been referred for urgent investigation of possible cancer and are therefore not reflective of the population of asymptomatic individuals aged 50 to 79 years, which was the target population of this review. Prospective cohort studies that recruited asymptomatic individuals outside the UK included PATHFINDER[30] (Galleri test, USA), DETECT-A[6] (CancerSEEK, USA), K-DETEK[8] (SPOT-MAS, Vietnam), RESOLUTE[9] (TruCheck, India), PPCS[10] (CDA, China), and Suzuki et al.[66] (AICS, Japan) (see Appendix 5 for further study details). Of these, studies recruiting participants deemed to be most similar to the target population for this review (in terms of age and sex) were PATHFINDER,[30] K-DETEK[8] and PPCS,[10] although the studies' location affects generalisability of results to UK clinical practice due to potential differences in cancer prevalence, healthcare systems and population ethnicity.

Test accuracy and number of overall cancers detected will be different if included participants are at high risk of cancer (e.g., in a population already being investigated due to symptoms), asymptomatic with or without risk factors for cancer, or whether they are already known to have cancer (such as in case-control studies). The length of prospective follow-up and extent of further diagnostic investigations conducted for all participants, with or without a positive signal on the MCED test, will also impact on the total number of cancers diagnosed. Prospective follow-up within the included

cohort studies ranged from six months to six years, and total numbers of cancers diagnosed were relatively low, impacting on MCED test accuracy estimates.

All currently available MCED tests had high specificity (>96%), an essential requirement of an MCED test to correctly classify people who do not have cancer. Diagnostic test sensitivity is inversely proportional to specificity, therefore an MCED tests with high specificity may have lower sensitivity. Sensitivity of the MCED tests was variable and influenced by study population, study design, reference standard test used and length of follow-up. Sensitivity also varied by cancer stage; generally, MCED tests had lower sensitivity to detect earlier stage cancers (Stage I-II) compared with later stage cancers (Stage III-IV). Where reported, accuracy of CSO was variable, ranging from 67.7% to 70% in case-control studies of CancerSEEK and SPOT-MAS to 85% to 90% in cohort studies of Galleri (Table 4).

The sensitivity of most of the MCED tests to detect solid tumour cancers without a current screening programme in the UK (excluding lung cancer) was higher than their sensitivity to detect cancers with a current screening programme in the UK, except for CDA and in one of the Galleri studies (Table 6). Similar results were found when lung cancer is considered to be covered by existing screening programmes; except for the Galleri test, since the sensitivity of the Galleri test to detect lung cancer is higher than its overall sensitivity. The sensitivity of the MCED tests to detect haematological malignancies was around 50%, although not all of the MCED tests claim to be able to detect these cancers.

The probability that an individual who receives a positive cancer signal has cancer (PPV) from the three cohort studies recruiting asymptomatic participants with ages similar to the target population of this review (and not focusing exclusively on women) ranged from 7.8% for CDA,[10] to 60.0% for SPOT-MAS[8] although 95% CIs were wide, so there is considerable uncertainty in these estimates (Table 4). The probability that an individual who receives a negative test result does not have cancer (NPV) ranged from 98.5% for Galleri[30] to 100% for SPOT-MAS[8] (Table 4). However, PPV and NPV values are directly related to the prevalence of the disease in the population being tested; PPV will increase and NPV will decrease with increasing prevalence. Prevalence of different cancers is variable across countries (due to ethnicity, risk factors, and healthcare system differences, among others) meaning these results are unlikely to be directly relevant to the UK screening population. The lack of a perfect reference test for all types of cancer may have led to some FP being inaccurately classified (e.g., if tumour too small to be detected by imaging), which may also bias PPV results.The lack of a reference standard test that can be applied to all study participants with negative test results, further limits interpretation.

No important differences in test accuracy by age, sex or ethnicity were observed for Galleri or CancerSEEK; however, studies of these tests recruited a majority of participants from White backgrounds, so results may not be applicable to other ethnic subgroups. No subgroup results were available for the SPOT-MAS, TruCheck, CDA and AICS tests and no subgroup results were available by socio-economic status for any of the MCED tests included in the review.

Limited results for patient relevant outcomes were reported for Galleri and CancerSEEK, and these are unlikely to reflect the target population of asymptomatic individuals aged 50 to 79 years old in a UK setting. Mortality data were available for a very small number of participants, mostly from case reports with follow-up of up to four years post cancer diagnosis. No adverse events were reported for either test; however, for the earlier version of the GRAIL MCED test, time to diagnostic resolution was shorter for those with a TP result compared to a FP result and over 90% of participants with FP results required further imaging tests.

No increase in anxiety levels across participants was reported at different stages of the PATHFINDER study (Galleri test).[30] This does not, however, rule out that individual participants may have experienced substantial increases in anxiety whilst awaiting test results, and while awaiting diagnostic resolution particularly for those with a positive signal on the MCED test, as anxiety was not measured at these key times. .

An additional seven MCED technologies which were at an unclear stage of development and did not appear to be currently available for use were included in the review. Most were evaluated in case-control studies and did not report relevant outcome data for the target population of interest. Many other blood-based MCED technologies which appeared to be at an early stage of development were identified but excluded from the review. These MCED tests and technologies may undergo further development and modification and become available for use in the future.

8.2 Strengths and limitations

The literature review was undertaken using systematic methods, reducing the potential for errors and bias. Comprehensive searches were undertaken to identify relevant evidence, including searches of manufacturers' websites, which identified recent emerging findings from the included studies in conference posters and presentations; this was an important process in such a fast-moving field. The inclusion criteria were clearly defined in advance and full texts were assessed against the inclusion criteria by at least two experienced reviewers. The validity and applicability of the included studies were assessed using an appropriate quality assessment tool for diagnostic accuracy studies. A data extraction tool was developed and piloted; data extraction and validity assessment processes were independently checked for accuracy.

The systematic review was conducted by an independent team of experienced reviewers, statisticians, and information specialists, who were free of potential conflicts of interest. The project benefited from stakeholder input from a range of independent content experts, healthcare professionals, and patient and public representatives, which strengthened the protocol, and the presentation and interpretation of findings in the final report.

The review was limited by weaknesses in the evidence base. There were no completed RCTs identified for any of the MCED tests. Only one study[30] (of the Galleri test), recruited individuals aged over 50 years without a clinical suspicion of cancer. However, this study was conducted in the USA, therefore, participants and results may not be representative of the UK screening population of interest in this review. Most studies were considered to have a high overall risk of bias, in addition to concerns regarding applicability. The variability in test specifications, study designs and included populations meant that meta-analysis was not appropriate.

The aim of this project was to identify available MCED tests for population-based screening, rather than to review all MCED technologies. However, reporting of many of the identified studies and technologies was limited, adding to the complexity of the study selection process; it was often difficult to determine the stage of development of technologies and whether studies were reporting results for tests at an early stage of development, or assessing a final or near-final version of the test that could be used for screening. In addition, the limited reporting made it difficult to assess the risk of bias and applicability of some of the included studies.

In addition to our review of blood-based MCED tests that are currently available for use, we have included evidence on technologies for which it is unclear whether they are fully developed tests, and presented a non-exhaustive list of technologies at a very early stage of development.

A recent review[135] (published after our pre-specified search date) of MCED technologies identified 20 studies across various phases of development including four studies not identified by our search strategy. As these four studies all described tests at an early stage of development, which would not have been eligible for inclusion in our review, this serves as reassurance that our search terms were sufficiently broad to capture the most relevant records.

8.3 Implications for future research

It is important that the principles that underpin existing disease screening programmes in the NHS are also applied to MCED tests. It is essential that appropriately designed studies assess the natural history of early-stage cancers detected by MCED tests in healthy individuals at different ages, before MCED tests are introduced into a screening programme. Such studies should be designed to enable

the development of decision models to direct clinical treatment towards those asymptomatic patients most likely to benefit from, and least likely to be harmed by, treatments.

The most promising and studied blood-based MCED tests are based on detecting cancer-related alterations in cfDNA. However, concentrations of cfDNA are relatively low at early cancer stages so it is unclear whether a simple blood draw would ever contain cfDNA in sufficient amounts to detect very small tumours.[7, 136] Data collection from large RCTs is needed to evaluate the ability of currently available MCED tests to detect early stage cancers and whether acting on a positive MCED test improves mortality.[14] The NHS-Galleri RCT[60] is being conducted in an asymptomatic UK population aged 50 to 77, but its primary objective is to evaluate whether there is a significant reduction in incidence of advanced stage cancer (stages III-IV) in the intervention arm compared to control, three years post-randomisation. Mortality outcomes will also be collected as secondary outcomes. Sampling of participants for the NHS-Galleri RCT aims to ensure that the recruited sample is representative of the wider population in terms of age and socioeconomic status, and that sufficient numbers are recruited from groups typically under-represented in clinical trials, such as those from ethnic minority backgrounds.[137] As such, when fully reported, data from this trial may provide high quality, direct evidence on the efficacy of this MCED test in a UK screening context.

However, the impact of MCED tests on NHS services including the practicalities of implementing MCED tests is currently unknown, but likely to be substantial. Further research is needed on the resource implications, risk of over-treatment and cost-effectiveness of implementing MCED tests for screening in the NHS.

The National Cancer Institute (USA) is launching the Vanguard Study on Multi-Cancer Detection which will begin enrolling healthy people aged 45 to 70 in a four-year pilot study from 2024 to assess the feasibility of a study to evaluate MCED tests.[129, 130] Conclusions from the pilot study will inform the decision of whether to launch a longer term RCT, which may compare more than one MCED test with standard of care screening. Should this RCT go ahead with mortality and HRQoL outcomes, as well as assessment of the number and type of diagnostic workups needed after a positive test, and potential harms arising from the workups themselves, this would provide important information on the comparability of different tests. However, this study would be carried out in a US context, which has key differences to the UK (e.g., different population characteristics, cancer prevalence, health care system, and existing screening programmes) so its potential generalisability to the NHS is unclear.

Studies that capture patient-relevant outcomes are also required. A longitudinal observational design with a nested qualitative study to evaluate the psychological impact of the Galleri test (sIG(n)al)[138] is embedded in the NHS-Galleri trial. Participants who have a cancer signal detected (expected number approximately 700) will be sent questionnaires at various timepoints to evaluate outcomes including

anxiety, the psychological consequences of screening, reassurance/concern about the test result, understanding of results and help/health-seeking behaviour. Depending on response rates this may provide valuable insight into these important outcomes, although data will be collected within the context of a clinical trial and no translation of questionnaires will be available, which may lead to fewer responses from participants from diverse backgrounds. In addition, participants with a negative MCED test result will not be studied, which may limit the applicability of findings to the target UK screening population. Studies including participants representative of the UK screening population and with sufficiently long follow-up should be carried out to better understand the potential psychological and behavioural impacts of MCED tests in practice, both in those with positive and negative test results.

The setting up of a registry to collect and evaluate real-world evidence on MCED tests, to record the diagnostic pathway and patterns of care following a test and impact on relevant patient outcomes such as mortality, morbidity, adverse events and HRQoL, has also been suggested.[16]

As more MCED tests become available, it is important that appropriate studies are carried out and reported in sufficient detail for their diagnostic accuracy, feasibility and acceptability to be evaluated. Given the large variability in the number of cancers detected by different MCED tests, and the differences in accuracy for different cancers and stages within and between tests, comparison of the accuracy, costs and benefits of the different MCED tests against each other in a UK screening context would be valuable.

9 CONCLUSIONS

This comprehensive review summarised the existing evidence on 13 tests and technologies that aim to detect multiple cancers for screening of healthy populations. Although current available evidence does not support strong conclusions, studies reported promising accuracy evidence despite limitations. Additional studies are ongoing or planned which will address some current limitations.

RCTs with sufficiently long follow-up, reporting outcomes that are directly relevant to patients, such as mortality/morbidity, safety, HRQoL and impact of (true and false) positive and (false) negative results on the health system, are needed and some are planned or underway. Given the potential false reassurance of a false negative test result, studies with sufficiently long follow-up for detection of emerging cancers in those testing negative, and evaluating the impacts of a negative test on compliance with existing screening programmes, are essential for the proper assessment of the possible negative impacts of each test.

Given the limitations of current treatment strategies for some cancers, even if detected early, an MCED test that more accurately detects fewer, but more treatable cancers, and for which there is

currently no national screening programme, may have greater overall benefits than the use of a test that detects many cancers with no effective treatment, or those already covered by existing screening programmes. No completed or ongoing study was found comparing the potential benefits to individuals or healthcare systems of different MCED tests against each other.

Decisions on implementation of MCED tests for screening in an asymptomatic population need to be underpinned by solid evidence, preferably RCTs carried out in a relevant population, setting, and with an appropriate length follow-up, so that an evidence-based evaluation can be carried out. At the moment, this evidence is lacking for all the tests evaluated in this report. Careful consideration is needed of which, if any, of the MCED tests currently available should be used, taking account of the current paucity of high-quality, relevant evidence on their accuracy, acceptability, cost/utility benefits and impact on the NHS.

ADDITIONAL INFORMATION

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Melissa Harden contributed to the protocol, developed search strategies, conducted a range of searches to locate studies and wrote sections of the report.

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All authors read and approved the final version of the report.

Data Sharing agreement

This study did not generate any new data as it used existing sources, and all data is contained within the manuscript. Any queries should be addressed to the corresponding author.

Ethics statement

This review did not involve the collection or analysis of any data that was not included in previously published research in the public domain. Therefore, no ethical approval was required.

Information Governance Statement

This is a systematic literature review and therefore, the current research did not handle any personal information.

Disclaimer

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APPENDICES

APPENDIX 1. PRISMA CHECKLIST

Table 9 PRISMA 2020 abstract checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

Table 10 PRISMA 2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	4-5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	19
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	19
METHODS 4-			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	19-21
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	21-22
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	21-22, Appendix 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	22
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	22-24
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	23-24
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	22-23
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	24
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	23
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	24
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics,	23-24

Section and Topic	Item #	Checklist item	Location where item is reported
		or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	24
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	24
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	24
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A (no meta-analysis was done)
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	24
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	25-27, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	27, 52-53, Table 8, Appendix 2
Study characteristics	17	Cite each included study and present its characteristics.	30-32, Tables 1-2, Appendix 4 Table 10
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	32-34, Figure 2, Table 3, Appendix 4 Table 11
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Tables 4-6, Figures 3-4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table 2, Appendix 4 Table 10
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A (no meta-analysis was done,

Section and Topic	Item #	Checklist item	Location where item is reported
			narrative synthesis results can be found on pages 34-44)
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	47 (subgroup analyses), Appendix 5 Tables 13-16, Appendix 6 Tables 17-18
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A (no meta-analysis was done)
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	34-36, 67
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	63-66
	23b	Discuss any limitations of the evidence included in the review.	67
	23c	Discuss any limitations of the review processes used.	67
	23d	Discuss implications of the results for practice, policy, and future research.	67-69
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A (The protocol was prepared but not published).
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	24 (Additional analyses from stakeholder), 55-61 (additional

Section and Topic	Item #	Checklist item	Location where item is reported
			stakeholder engagement after protocol stage)
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	2-3, 5
Competing interests	26	Declare any competing interests of review authors.	2
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	All data extracted are provided in Tables 4-6, and Appendices 3-6

APPENDIX 2. SEARCH STRATEGIES

1. Database searches

MEDLINE ALL

via Ovid http://ovidsp.ovid.com/

Date range: 1946 to September 13, 2023

Date searched: 14th September 2023

Records retrieved: 2280

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)

Key:
/ = subject heading (MeSH heading)
sh = subject heading (MeSH heading)
exp = exploded subject heading (MeSH heading)
$ = truncation
? = optional wildcard – one or no characters
ti,ab = terms in title or abstract fields
mp = multi-purpose field search – searches several fields including title, original title, abstract, keyword, subject heading word
adj3 = terms within three words of each other (any order)

Embase

via Ovid http://ovidsp.ovid.com/

Date range: 1974 to 2023 September 13

Date searched: 14th September 2023

Records retrieved: 5318

1 neoplasm/ (444533)
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. (676542)
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$).ti,ab. (7553)
4 ((cancer$ or neoplas$ or tumour$ or tumor$ or carcinoma$ or oncolog$ or malignan$ or precancer$) adj3 (type or types)).ti,ab. (253298)
5 1 or 2 or 3 or 4 (1167319)
6 liquid biopsy/ (11133)
7 ((liquid$ or fluid$ or biofluid$ or bio-fluid$) adj3 biops$).ti,ab. (14049)
8 6 or 7 (16738)
9 biopsy/ (178541)
10 exp blood/ (2566272)
11 9 and 10 (29880)
12 ((blood or h?ematolog$ or plasma or serum) adj3 biops$).ti,ab. (10439)
13 11 or 12 (38994)
14 blood examination/ (18548)
15 ((blood or h?ematolog$ or plasma or serum) adj2 (test or tests or testing or tested or assay$)).ti,ab. (127454)
16 14 or 15 (142450)
17 ((multiomic$ or multi-omic$ or panomic$ or pan-omic$ or integrative omic$) adj4 (test or tests or tested or testing or assay$ or biops$)).ti,ab. (220)
18 ((Multi-analyte$ or multianalyte$) adj4 (detect$ or screen$ or test or tests or tested or testing or assay$ or biops$)).ti,ab. (777)
19 8 or 13 or 16 or 17 or 18 (195146)
20 5 and 19 (14344)
21 mass screening/ (61673)
22 cancer screening/ (97647)
23 early cancer diagnosis/ (13662)
24 (screen$ or detect$).ti. (792212)

25 ((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. (638156)
26 (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$)).ti,ab. (294581)
27 22 or 23 or 24 or 25 or 26 (1533346)
28 20 and 27 (4213)
29 ((cancer$ 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$)).ti,ab. (17272)
30 ((cancer$ or neoplas$ or tumour$ or tumor$ or carcinoma$ or oncolog$ or malignan$ or precancer$) adj6 (type or types) adj6 (screen$ or detect$)).ti,ab. (6375)
31 29 or 30 (21840)
32 19 and 31 (1075)
33 28 or 32 (4496)
34 (((multi-cancer$ or multicancer$ or multi-tumo?r$ or multitumo?r$) adj6 (detect$ or screen$ or test or tests or tested or testing or assay$)) or MCED or MCDBT).ti,ab. (339)
35 ((multiple cancer$ or multiple tumo?r$) adj6 (detect$ or screen$ or test or tests or tested or testing or assay$)).ti,ab. (849)
36 ((pan-cancer$ or pancancer$ or pan-tumo?r$ or pantumo?r$) adj6 (detect$ or screen$ or test or tests or tested or testing or assay$)).ti,ab. (463)
37 ((cross-cancer$ or crosscancer$ or cross-tumo?r$ or crosstumo?r$) adj6 (detect$ or screen$ or test or tests or tested or testing or assay$)).ti,ab. (10)
38 ((multi-class cancer$ 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$)).ti,ab. (10)
39 34 or 35 or 36 or 37 or 38 (1587)
40 (Galleri or GalleriTM).mp. (28)
41 PanSEER$.mp. (7)
42 CancerSEEK$.mp. (17)
43 CancerEMC$.mp. (1)
44 (PanTum or PanTumDetect).mp. (6)
45 Epitope-detection in monocytes.mp. (18)
46 CancerRadar$.mp. (1)
47 (IvyGene$ or IvyGeneCORE$).mp. (7)
48 CancerLocator$.mp. (1)
49 CancerDetector$.mp. (1)
50 (EpiPanGI Dx$ or EpiPanGIDx$).mp. (2)
51 OverC.mp. (1)
52 DEEPGEN.mp. (13)
53 Dxcover$.mp. (9)
54 trucheck$.mp. (4)
55 Elypta$.mp. (1)
56 MiRXES$.mp. (42)
57 Freenome$.mp. (60)
58 40 or 41 or 42 or 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 (205)
59 DELFI$.mp. (1238)
60 Omni1$.mp. (135)
61 Signal-X$.mp. (1058)
62 Harbinger$.mp. (2991)
63 EDIM$.mp. (265)
64 LUNAR$.mp. (8154)
65 MERCURY$.mp. (72070)
66 59 or 60 or 61 or 62 or 63 or 64 or 65 (85868)
67 20 and 66 (21)
68 33 or 39 or 58 or 67 (6044)

69 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (6811834)
70 68 not 69 (5933)
71 limit 70 to yr="2010 -Current" (5318)

Key:
/ = subject heading (Emtree heading)
exp = exploded subject heading (Emtree heading)
$ = truncation
? = optional wildcard – one or no characters
ti,ab = terms in title or abstract fields
mp = multi-purpose field search – searches several fields including title, original title, abstract, keyword, subject heading word, candidate terms, device trade name, device manufacturer.
adj3 = terms within three words of each other (any order)

Cochrane Library

via Wiley http://onlinelibrary.wiley.com/

Cochrane Central Register of Controlled Trials (CENTRAL): Issue 8 of 12, Aug 2023

Records retrieved: 147

Cochrane Database of Systematic Reviews (CDSR): Issue 9 of 12, Sep 2023

Records retrieved: 5

Date searched: 14th September 2023

#1 MeSH descriptor: [Neoplasms] this term only 8947
#2 ((cancer* or neoplas* or tumour* or tumor* or carcinoma* or oncolog* or malignan* or precancer*) near/6 (multiple* or many or several or numerous or various or varied or miscellaneous or mixed or diverse or different)):ti,ab,kw 13359
#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,kw 112
#4 ((cancer* or neoplas* or tumour* or tumor* or carcinoma* or oncolog* or malignan* or precancer*) near/3 (type or types)):ti,ab,kw 5978
#5 #1 or #2 or #3 or #4 25636
#6 MeSH descriptor: [Liquid Biopsy] this term only 29
#7 ((liquid* or fluid* or biofluid* or bio-fluid*) near/3 biops*):ti,ab,kw 344
#8 MeSH descriptor: [Biopsy] this term only 5028
#9 MeSH descriptor: [Biopsy, Fine-Needle] this term only 149
#10 #8 or #9 5175
#11 MeSH descriptor: [Blood] explode all trees 24865
#12 #10 and #11 365
#13 ((blood or h?ematolog* or plasma or serum) near/3 biops*):ti,ab,kw 1245
#14 MeSH descriptor: [Hematologic Tests] this term only 236
#15 ((blood or h?ematolog* or plasma or serum) near/2 (test or tests or testing or tested or assay*)):ti,ab,kw 19859
#16 MeSH descriptor: [Multiomics] this term only 4
#17 ((multiomic* or multi-omic* or panomic* or pan-omic* or integrative omic*) near/4 (test or tests or tested or testing or assay* or biops*)):ti,ab,kw 59

#18 ((Multi-analyte* or multianalyte*) near/4 (detect* or screen* or test or tests or tested or testing or assay* or biops*)):ti,ab,kw 19
#19 #6 or #7 or #12 or #13 or #14 or #15 or #16 or #17 or #18 21691
#20 #5 and #19 462
#21 MeSH descriptor: [Mass Screening] this term only 4556
#22 MeSH descriptor: [Diagnostic Screening Programs] this term only 4
#23 MeSH descriptor: [Early Diagnosis] this term only 806
#24 MeSH descriptor: [Early Detection of Cancer] this term only 2044
#25 (screen* or detect*):ti 20977
#26 ((early or earlystage or earli* or first or initial or timely) near/3 (screen* or detect* or diagnos* or test or tests or testing or tested)):ti,ab,kw 24204
#27 (screen* near/3 (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,kw 17601
#28 #21 or #22 or #23 or #24 or #25 or #26 or #27 51044
#29 #20 and #28 156
#30 ((cancer* or neoplas* or tumour* or tumor* or carcinoma* or oncolog* or malignan* or precancer*) near/6 (multiple* or many or several or numerous or various or varied or miscellaneous or mixed or diverse or different) near/6 (screen* or detect*)):ti,ab,kw 469
#31 ((cancer* or neoplas* or tumour* or tumor* or carcinoma* or oncolog* or malignan* or precancer*) near/6 (type or types) near/6 (screen* or detect*)):ti,ab,kw 148
#32 #30 or #31 588
#33 #19 and #32 86
#34 #29 or #33 162
#35 (((multi-cancer* or multicancer* or multi-tumo?r* or multitumo?r*) near/6 (detect* or screen* or test or tests or tested or testing or assay*)) or MCED or MCDBT):ti,ab,kw 19
#36 ((multiple next cancer* or multiple next tumo?r*) near/6 (detect* or screen* or test or tests or tested or testing or assay*)):ti,ab,kw 18
#37 ((pan-cancer* or pancancer* or pan-tumo?r* or pantumo?r*) near/6 (detect* or screen* or test or tests or tested or testing or assay*)):ti,ab,kw 9
#38 ((cross-cancer* or crosscancer* or cross-tumo?r* or crosstumo?r*) near/6 (detect* or screen* or test or tests or tested or testing or assay*)):ti,ab,kw 0
#39 ((multi-class next cancer* or multiclass next cancer* or multi-class tumo?r* or multiclass next tumo?r*) near/6 (detect* or screen* or test or tests or tested or testing or assay*)):ti,ab,kw 1
#40 #35 or #36 or #37 or #38 or #39 44
#41 (Galleri or GalleriTM):ti,ab,kw 7
#42 PanSEER*:ti,ab,kw 0
#43 CancerSEEK*:ti,ab,kw 1
#44 CancerEMC*:ti,ab,kw 0
#45 (PanTum or PanTumDetect):ti,ab,kw 0
#46 "Epitope-detection in monocytes":ti,ab,kw 0
#47 CancerRadar*:ti,ab,kw 0
#48 (IvyGene* or IvyGeneCORE*):ti,ab,kw 2
#49 CancerLocator*:ti,ab,kw 0
#50 CancerDetector*:ti,ab,kw 0
#51 (EpiPanGI next Dx* or EpiPanGIDx*):ti,ab,kw 0
#52 OverC:ti,ab,kw 0
#53 DEEPGEN:ti,ab,kw 0
#54 Dxcover*:ti,ab,kw 0
#55 trucheck*:ti,ab,kw 0
#56 Elypta*:ti,ab,kw 1
#57 MiRXES*:ti,ab,kw 6
#58 Freenome*:ti,ab,kw 4
#59 #41 or #42 or #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 21
#60 DELFI*:ti,ab,kw 58

#61 Omni1*:ti,ab,kw 10
#62 Signal-X*:ti,ab,kw 2
#63 Harbinger*:ti,ab,kw 54
#64 EDIM*:ti,ab,kw 16
#65 LUNAR*:ti,ab,kw 340
#66 MERCURY*:ti,ab,kw 1367
#67 #60 or #61 or #62 or #63 or #64 or #65 or #66 1846
#68 #20 and #67 0
#69 #34 or #40 or #59 or #68 with Cochrane Library publication date Between Jan 2010 and Dec 2023, in Cochrane Reviews, Cochrane Protocols 5
#70 #34 or #40 or #59 or #68 with Publication Year from 2010 to 2023, in Trials 147

Key:
MeSH descriptor = subject heading (MeSH heading)
* = truncation
? = wildcard - zero or one characters
ti,ab,kw = terms in title, abstract or keyword fields
near/3 = terms within three words of each other (any order)
next = terms are next to each other

Science Citation Index (SCI)

Conference Proceedings Citation Index – Science (CP-SCI)

via Web of Science, Clarivate Analytics https://clarivate.com/

Date searched: 14th September 2023

Date range SCI: 1900 - present

Date range CP-SCI: 1990 - present

Records retrieved: 3635

1: TS=((cancer* or neoplas* or tumour* or tumor* or carcinoma* or oncolog* or malignan* or precancer*) NEAR/6 (multiple* or many or several or numerous or various or varied or miscellaneous or mixed or diverse or different)) Editions: WOS.SCI,WOS.ISTP Results: 723028
2: TS=(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*) Editions: WOS.SCI,WOS.ISTP Results: 5387
3: TS=((cancer* or neoplas* or tumour* or tumor* or carcinoma* or oncolog* or malignan* or precancer*) NEAR/3 (type or types)) Editions: WOS.SCI,WOS.ISTP Results: 173814
4: #1 OR #2 OR #3 Editions: WOS.SCI,WOS.ISTP Results: 791026
5: TS=((liquid* or fluid* or biofluid* or bio-fluid*) NEAR/3 biops*) Editions: WOS.SCI,WOS.ISTP Results: 11933
6: TS=((blood or hematolog* or haematolog* or plasma or serum) NEAR/3 biops*) Editions: WOS.SCI,WOS.ISTP Results: 7076
7: TS=((blood or hematolog* or haematolog* or plasma or serum) NEAR/2 (test or tests or testing or tested or assay*)) Editions: WOS.SCI,WOS.ISTP Results: 102865
8: TS=((multiomic* or multi-omic* or panomic* or pan-omic* or "integrative omic*") NEAR/4 (test or tests or tested or testing or assay* or biops*)) Editions: WOS.SCI,WOS.ISTP Results: 150
9: TS=((Multi-analyte* or multianalyte*) NEAR/4 (detect* or screen* or test or tests or tested or testing or assay* or biops*)) Editions: WOS.SCI,WOS.ISTP Results: 934

10: #5 OR #6 OR #7 OR #8 OR #9 Editions: WOS.SCI,WOS.ISTP Results: 121323
11: #4 AND #10 Editions: WOS.SCI,WOS.ISTP Results: 7226
12: TI=(screen* or detect*) Editions: WOS.SCI,WOS.ISTP Results: 1352372
13: TS=((early or earlystage or earli* or first or initial or timely) NEAR/3 (screen* or detect* or diagnos* or test or tests or testing or tested)) Editions: WOS.SCI,WOS.ISTP Results: 496428
14: TS=(screen* NEAR/3 (test* or tool* or method* or strateg* or modalit* or technolog* or program* or service* or policy or policies or guideline* or population*)) Editions: WOS.SCI,WOS.ISTP Results: 226626
15: #12 OR #13 OR #14Editions: WOS.SCI,WOS.ISTP Results: 1868737
16: #15 AND #11 Editions: WOS.SCI,WOS.ISTP Results: 3024
17: TS=((cancer* or neoplas* or tumour* or tumor* or carcinoma* or oncolog* or malignan* or precancer*) NEAR/6 (multiple* or many or several or numerous or various or varied or miscellaneous or mixed or diverse or different) NEAR/6 (screen* or detect*)) Editions: WOS.SCI,WOS.ISTP Results: 25546
18: TS=((cancer* or neoplas* or tumour* or tumor* or carcinoma* or oncolog* or malignan* or precancer*) NEAR/6 (type or types) NEAR/6 (screen* or detect*)) Editions: WOS.SCI,WOS.ISTP Results: 5218
19: #17 OR #18 Editions: WOS.SCI,WOS.ISTP Results: 28735
20: #19 AND #10 Editions: WOS.SCI,WOS.ISTP Results: 1380
21: #20 OR #16 Editions: WOS.SCI,WOS.ISTP Results: 3330
22: TS=(((multi-cancer* or multicancer* or multi-tumo$r* or multitumo$r*) NEAR/6 (detect* or screen* or test or tests or tested or testing or assay*)) or MCED or MCDBT) Editions: WOS.SCI,WOS.ISTP Results: 263
23: TS=(("multiple cancer*" or "multiple tumor*" or "multiple tumour*") NEAR/6 (detect* or screen* or test or tests or tested or testing or assay*)) Editions: WOS.SCI,WOS.ISTP Results: 591
24: TS=((pan-cancer* or pancancer* or pan-tumo$r* or pantumo$r*) NEAR/6 (detect* or screen* or test or tests or tested or testing or assay*)) Editions: WOS.SCI,WOS.ISTP Results: 275
25: TS=((cross-cancer* or crosscancer* or cross-tumo$r* or crosstumo$r*) NEAR/6 (detect* or screen* or test or tests or tested or testing or assay*)) Editions: WOS.SCI,WOS.ISTP Results: 5
26: TS=(("multi-class cancer*" or "multiclass cancer*" or "multi-class tumor*" or "multi-class tumour*" or "multiclass tumor*" or "multiclass tumour*") NEAR/6 (detect* or screen* or test or tests or tested or testing or assay*)) Editions: WOS.SCI,WOS.ISTP Results: 9
27: #22 OR #23 OR #24 OR #25 OR #26 Editions: WOS.SCI,WOS.ISTP Results: 1120
28: TS=(Galleri or GalleriTM) Editions: WOS.SCI,WOS.ISTP Results: 9
29: TS=(PanSEER* or CancerSEEK* or CancerEMC* or PanTum or PanTumDetect or "Epitope-detection in monocytes" or CancerRadar* or IvyGene* or IvyGeneCORE* or CancerLocator* or CancerDetector* or "EpiPanGI Dx*" or EpiPanGIDx* or OverC or DEEPGEN or Dxcover* or trucheck* or Elypta* or MiRXES* or Freenome*) Editions: WOS.SCI,WOS.ISTP Results: 56
30: TS=(DELFI* or Omni1* or Signal-X* or Harbinger* or EDIM* or LUNAR* or MERCURY*) Editions: WOS.SCI,WOS.ISTP Results: 160412
31: #30 AND #11 Editions: WOS.SCI,WOS.ISTP Results: 8
32: #31 OR #29 OR #28 OR #27 OR #21 Editions: WOS.SCI,WOS.ISTP Results: 4367
33: #31 OR #29 OR #28 OR #27 OR #21 Editions: WOS.SCI,WOS.ISTP Timespan: 2010-01-01 to 2023-12-31 Results: 3660
34: TI=(animal or animals or rat or rats or mouse or mice or rodent or rodents or porcine or murine or sheep or lamb or lambs or ewe or ewes or pig or pigs or piglet or piglets or sow or sows or minipig or minipigs or rabbit or rabbits or kitten or kittens or dog or dogs or puppy or puppies or monkey or monkeys or horse or horses or foal or foals or equine or calf or calves or cattle or heifer or heifers or hamster or hamsters or chicken or chickens or livestock) Editions: WOS.SCI,WOS.ISTP Results: 3210270
35: #33 not #34 Editions: WOS.SCI,WOS.ISTP Results: 3635

Key:
TS = topic tag; searches in title, abstract, author keywords and keywords plus fields
TI = search in title field
* = truncation
$ = represents zero or one character
NEAR/3 = terms within three words of each other (any order)

EB Health - KSR Evidence

via Ovid http://ovidsp.ovid.com/

Date range: 2015 to 2023 Week 37

Date searched: 14th September 2023

Records retrieved: 45

1 ((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)).af. (5847)
2 (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$).af. (44)
3 ((cancer$ or neoplas$ or tumour$ or tumor$ or carcinoma$ or oncolog$ or malignan$ or precancer$) adj3 (type or types)).af. (3123)
4 1 or 2 or 3 (7502)
5 ((liquid$ or fluid$ or biofluid$ or bio-fluid$) adj3 biops$).af. (143)
6 ((blood or h?ematolog$ or plasma or serum) adj3 biops$).af. (29)
7 ((blood or h?ematolog$ or plasma or serum) adj2 (test or tests or testing or tested or assay$)).af. (579)
8 ((multiomic$ or multi-omic$ or panomic$ or pan-omic$ or integrative omic$) adj4 (test or tests or tested or testing or assay$ or biops$)).af. (1)
9 ((Multi-analyte$ or multianalyte$) adj4 (detect$ or screen$ or test or tests or tested or testing or assay$ or biops$)).af. (1)
10 5 or 6 or 7 or 8 or 9 (735)
11 4 and 10 (52)
12 (screen$ or detect$).af. (53046)
13 ((early or earlystage or earli$ or first or initial or timely) adj3 (screen$ or detect$ or diagnos$ or test or tests or testing or tested)).af. (5713)
14 (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$)).af. (4258)
15 12 or 13 or 14 (54744)
16 11 and 15 (38)
17 ((cancer$ 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$)).af. (196)
18 ((cancer$ or neoplas$ or tumour$ or tumor$ or carcinoma$ or oncolog$ or malignan$ or precancer$) adj6 (type or types) adj6 (screen$ or detect$)).af. (102)
19 17 or 18 (277)
20 10 and 19 (16)
21 16 or 20 (39)
22 (((multi-cancer$ 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).af. (2)

23 ((multiple cancer$ or multiple tumo?r$) adj6 (detect$ or screen$ or test or tests or tested or testing or assay$)).af. (8)
24 ((pan-cancer$ or pancancer$ or pan-tumo?r$ or pantumo?r$) adj6 (detect$ or screen$ or test or tests or tested or testing or assay$)).af. (0)
25 ((cross-cancer$ or crosscancer$ or cross-tumo?r$ or crosstumo?r$) adj6 (detect$ or screen$ or test or tests or tested or testing or assay$)).af. (0)
26 ((multi-class cancer$ 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$)).af. (0)
27 22 or 23 or 24 or 25 or 26 (8)
28 (Galleri or GalleriTM).af. (0)
29 PanSEER$.af. (0)
30 CancerSEEK$.af. (0)
31 CancerEMC$.af. (0)
32 (PanTum or PanTumDetect).af. (0)
33 "Epitope-detection in monocytes".af. (0)
34 CancerRadar$.af. (0)
35 (IvyGene$ or IvyGeneCORE$).af. (0)
36 CancerLocator$.af. (0)
37 CancerDetector$.af. (0)
38 (EpiPanGI Dx$ or EpiPanGIDx$).af. (0)
39 OverC.af. (0)
40 DEEPGEN.af. (0)
41 Dxcover$.af. (0)
42 trucheck$.af. (0)
43 Elypta$.af. (0)
44 MiRXES$.af. (0)
45 Freenome$.af. (0)
46 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 (0)
47 DELFI$.af. (12)
48 Omni1$.af. (0)
49 Signal-X$.af. (0)
50 Harbinger$.af. (18)
51 EDIM$.af. (6)
52 LUNAR$.af. (19)
53 MERCURY$.af. (136)
54 47 or 48 or 49 or 50 or 51 or 52 or 53 (191)
55 11 and 54 (0)
56 21 or 27 or 46 or 55 (45)
57 limit 56 to yr="2010 -Current" (45)

Key:
$ = truncation
? = optional wildcard – one or no characters
af = terms in any field
adj3 = terms within three words of each other (any order)

Database of Abstracts of Reviews of Effects (DARE)

Health Technology Assessment (HTA) database

via http://www.crd.york.ac.uk/CRDWeb/

Date range DARE: Inception – 31st March 2015

Date range HTA database: Inception – 31st March 2018

Date searched: 14th September 2023

Records retrieved: 5

1 MeSH DESCRIPTOR neoplasms IN DARE,HTA 1187
2 ((cancer* or neoplas* or tumour* or tumor* or carcinoma* or oncolog* or malignan* or precancer*) NEAR6 (multiple* or many or several or numerous or various or varied or miscellaneous or mixed or diverse or different)) IN DARE, HTA 434
3 ((multicancer* or multi-cancer* or multitumor* or multitumour* or multi-tumor* or multi-tumour* or pan-cancer* or pancancer* or pan-tumor* or pan-tumour* or pantumor* or pantumour* or cross-cancer* or crosscancer* or cross-tumor* or cross-tumour* or crosstumor* or crosstumour*)) IN DARE, HTA 0
4 (((cancer* or neoplas* or tumour* or tumor* or carcinoma* or oncolog* or malignan* or precancer*) NEAR3 (type or types))) IN DARE, HTA 231
5 #1 OR #2 OR #3 OR #4 1646
6 MeSH DESCRIPTOR Liquid Biopsy IN DARE,HTA 1
7 (((liquid* or fluid* or biofluid* or bio-fluid*) NEAR3 biops*)) IN DARE, HTA 4
8 MeSH DESCRIPTOR Biopsy IN DARE,HTA 122
9 MeSH DESCRIPTOR Biopsy, Fine-Needle IN DARE,HTA 49
10 #8 OR #9 171
11 MeSH DESCRIPTOR blood EXPLODE ALL TREES IN DARE,HTA 266
12 #10 AND #11 1
13 (((blood or hematolog* or haematolog* or plasma or serum) NEAR3 biops*)) IN DARE, HTA 8
14 MeSH DESCRIPTOR Hematologic Tests IN DARE,HTA 21
15 (((blood or hematolog* or haematolog* or plasma or serum) NEAR2 (test or tests or testing or tested or assay*))) IN DARE, HTA 260
16 (((multiomic* or multi-omic* or panomic* or pan-omic* or “integrative omic” or “Integrative omics”) NEAR4 (test or tests or tested or testing or assay* or biops*))) IN DARE, HTA 0
17 (((Multi-analyte* or multianalyte*) NEAR4 (detect* or screen* or test or tests or tested or testing or assay* or biops*))) IN DARE, HTA 2
18 MeSH DESCRIPTOR Mass Screening IN DARE,HTA 998
19 MeSH DESCRIPTOR Diagnostic Screening Programs IN DARE,HTA 0
20 MeSH DESCRIPTOR early diagnosis IN DARE,HTA 80
21 MeSH DESCRIPTOR Early Detection of Cancer IN DARE,HTA 129
22 ((screen* or detect*)) IN DARE, HTA 8752
23 (((early or earlystage or earli* or first or initial or timely) NEAR3 (screen* or detect* or diagnos* or test or tests or testing or tested))) IN DARE, HTA 820
24 ((screen* NEAR3 (test* or tool* or method* or strateg* or modalit* or technolog* or program* or service* or policy or policies or guideline* or population*))) IN DARE, HTA 1163
25 #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 8921
26 #6 OR #7 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 274
27 #5 AND #25 AND #26 7
28 (((cancer* or neoplas* or tumour* or tumor* or carcinoma* or oncolog* or malignan* or precancer*) NEAR6 (multiple* or many or several or numerous or various or varied or miscellaneous or mixed or diverse or different) NEAR6 (screen* or detect*))) IN DARE, HTA 5
29 (((cancer* or neoplas* or tumour* or tumor* or carcinoma* or oncolog* or malignan* or precancer*) NEAR6 (type or types) NEAR6 (screen* or detect*))) IN DARE, HTA 3
30 #28 OR #29 8
31 #26 AND #30 1
32 #27 OR #31 8

33 (((multicancer* or multi-cancer* or multitumor* or multitumour* or multi-tumor* or multi-tumour*) NEAR6 (detect* or screen* or test or tests or tested or testing or assay*))) IN DARE, HTA 0
34 (MCED or MCDBT) IN DARE, HTA 0
35 ((("multiple cancer" or "multiple cancers"or "multiple tumor" or "multiple tumours") NEAR6 (detect* or screen* or test or tests or tested or testing or assay*))) IN DARE, HTA 0
36 (((pan-cancer* or pancancer* or pan-tumor* or pan-tumour* or pantumor* or pantumour*) NEAR6 (detect* or screen* or test or tests or tested or testing or assay*))) IN DARE, HTA 0
37 (((cross-cancer* or crosscancer* or cross-tumor* or cross-tumour* or crosstumor* or crosstumour*) NEAR6 (detect* or screen* or test or tests or tested or testing or assay*))) IN DARE, HTA 0 3
38 ((("multi-class cancer" or "multi-class cancers" or "multiclass cancer" or "multiclass cancers" or "multi-class tumor" or "multi-class tumors" or "multi-class tumour" or "multi-class tumours" or "multiclass tumor" or "multiclass tumors" or "multiclass tumour" or "multiclass tumours") NEAR6 (detect* or screen* or test or tests or tested or testing or assay*))) IN DARE, HTA 0
39 #33 OR #34 OR #35 OR #36 OR #37 OR #38 0
40 (Galleri*) IN DARE, HTA 0
41 ((PanSEER* or CancerSEEK* or CancerEMC* or PanTum or PanTumDetect or "Epitope-detection in monocytes" or CancerRadar* or IvyGene* or IvyGeneCORE* or CancerLocator* or CancerDetector* or "EpiPanGI Dx" or EpiPanGIDx* or OverC or DEEPGEN or Dxcover* or trucheck* or Elypta* or MiRXES* or Freenome*)) IN DARE, HTA 0
42 ((DELFI* or Omni1* or Signal-X* or Harbinger* or EDIM* or LUNAR* or MERCURY*)) IN DARE, HTA 31
43 #5 AND #26 AND #42 0
44 #32 OR #39 OR #43 8
45 (*) IN DARE, HTA FROM 2010 TO 2023 36791
46 #44 AND #45 5

Key:
MeSH DESCRIPTOR = subject heading (MeSH heading)
* = truncation
adj3 = terms within three words of each other (order specified)

International Health Technology Assessment (HTA) database

via https://database.inahta.org/

Date range: Inception – 14th September 2023

Date searched: 15th September 2023

Records retrieved: 46

1. ((((screen* or detect* or diagnos* or test or tests or testing or tested)[Title] OR (screen* or detect* or diagnos* or test or tests or testing or tested)[abs] OR (screen* or detect* or diagnos* or test or tests or testing or tested)[Keywords]) AND ((early or earlystage or earli* or first or initial or timely)[Title] OR (early or earlystage or earli* or first or initial or timely)[abs] OR (early or earlystage or earli* or first or initial or timely)[Keywords])) OR (((test* or tool* or method* or strateg* or modalit* or technolog* or program* or service* or policy or policies or guideline* or population*)[Title] OR (test* or tool* or method* or strateg* or modalit* or technolog* or program* or service* or policy or policies or guideline* or population*)[abs] OR (test* or tool* or method* or strateg* or modalit* or technolog* or program* or service* or policy or policies or guideline* or population*)[Keywords]) AND ((screen*)[Title] OR (screen*)[abs] OR (screen*)[Keywords])) OR ((screen* or detect*)[Title]) OR ("Early Detection of Cancer"[mh]) OR ("Early Diagnosis"[mh]) OR ("Diagnostic Screening

Programs"[mh]) OR ("Mass Screening"[mh])) AND ((((((Multi-analyte* or multianalyte*)[Title] OR (Multi-analyte* or multianalyte*)[abs] OR (Multi-analyte* or multianalyte*)[Keywords]) OR ((multiomic* or multi-omic* or panomic* or pan-omic* or "integrative omic" or "Integrative omics")[Title] OR (multiomic* or multi-omic* or panomic* or pan-omic* or "integrative omic" or "Integrative omics")[abs] OR (multiomic* or multi-omic* or panomic* or pan-omic* or "integrative omic" or "Integrative omics")[Keywords]) OR ("Multiomics"[mh])) AND ((biops* or test or tests or testing or tested or assay*)[Title] OR (biops* or test or tests or testing or tested or assay*)[abs] OR (biops* or test or tests or testing or tested or assay*)[Keywords])) OR ("Hematologic Tests"[mh]) OR (((biops* or test or tests or testing or tested or assay*)[Title] OR (biops* or test or tests or testing or tested or assay*)[abs] OR (biops* or test or tests or testing or tested or assay*)[Keywords]) AND ((blood or hematolog* or haematolog* or plasma or serum)[Title] OR (blood or hematolog* or haematolog* or plasma or serum)[abs] OR (blood or hematolog* or haematolog* or plasma or serum)[Keywords])) OR (("Blood"[mhe]) AND (("Biopsy, Fine-Needle"[mh]) OR ("Biopsy"[mh]))) OR (((biops*)[Title] OR (biops*)[abs] OR (biops*)[Keywords]) AND ((liquid* or fluid* or biofluid* or bio-fluid*)[Title] OR (liquid* or fluid* or biofluid* or bio-fluid*)[abs] OR (liquid* or fluid* or biofluid* or bio-fluid*)[Keywords])) OR ("Liquid Biopsy"[mh])) AND (((multicancer* or multi-cancer* or multitumor* or multitumour* or multi-tumor* or multi-tumour* or pan-cancer* or pancancer* or pan-tumor* or pan-tumour* or pantumor* or pantumour* or cross-cancer* or crosscancer* or cross-tumor* or cross-tumour* or crosstumor* or crosstumour*)[Title] OR (multicancer* or multi-cancer* or multitumor* or multitumour* or multi-tumor* or multi-tumour* or pan-cancer* or pancancer* or pan-tumor* or pan-tumour* or pantumor* or pantumour* or cross-cancer* or crosscancer* or cross-tumor* or cross-tumour* or crosstumor* or crosstumour*)[abs] OR (multicancer* or multi-cancer* or multitumor* or multitumour* or multi-tumor* or multi-tumour* or pan-cancer* or pancancer* or pan-tumor* or pan-tumour* or pantumor* or pantumour* or cross-cancer* or crosscancer* or cross-tumor* or cross-tumour* or crosstumor* or crosstumour*)[Keywords]) OR ((((type or types)[Title] OR (type or types)[abs] OR (type or types)[Keywords]) OR ((multiple* or many or several or numerous or various or varied or miscellaneous or mixed or diverse or different)[Title] OR (multiple* or many or several or numerous or various or varied or miscellaneous or mixed or diverse or different)[abs] OR (multiple* or many or several or numerous or various or varied or miscellaneous or mixed or diverse or different)[Keywords])) AND ((cancer* or neoplas* or tumour* or tumor* or carcinoma* or oncolog* or malignan* or precancer*)[Title] OR (cancer* or neoplas* or tumour* or tumor* or carcinoma* or oncolog* or malignan* or precancer*)[abs] OR (cancer* or neoplas* or tumour* or tumor* or carcinoma* or oncolog* or malignan* or precancer*)[Keywords])) OR ("Neoplasms"[mh]))) limit: 2010 to 2023, 44 hits

2. (Galleri or GalleriTM or PanSEER* or CancerSEEK* or CancerEMC* or PanTum or PanTumDetect or "Epitope-detection in monocytes" or CancerRadar* or IvyGene* or IvyGeneCORE* or CancerLocator* or CancerDetector* or "EpiPanGI Dx" or EpiPanGIDx* or OverC or DEEPGEN or Dxcover* or trucheck* or Elypta* or MiRXES* or Freenome*)[Title] OR (Galleri or GalleriTM or PanSEER* or CancerSEEK* or CancerEMC* or PanTum or PanTumDetect or "Epitope-detection in monocytes" or CancerRadar* or IvyGene* or IvyGeneCORE* or CancerLocator* or CancerDetector* or "EpiPanGI Dx" or EpiPanGIDx* or OverC or DEEPGEN or Dxcover* or trucheck* or Elypta* or MiRXES* or Freenome*)[abs] OR (Galleri or GalleriTM or PanSEER* or CancerSEEK* or CancerEMC* or PanTum or PanTumDetect or "Epitope-detection in monocytes" or CancerRadar* or IvyGene* or IvyGeneCORE* or CancerLocator* or CancerDetector* or "EpiPanGI Dx" or EpiPanGIDx* or OverC or DEEPGEN or Dxcover* or trucheck* or Elypta* or MiRXES* or Freenome*)[Keywords] limit: 2010 to 2023, 2 hits

3. ((DELFI* or Omni1* or Signal-X* or Harbinger* or EDIM* or LUNAR* or MERCURY*)[Title] OR (DELFI* or Omni1* or Signal-X* or Harbinger* or EDIM* or LUNAR* or MERCURY*)[abs] OR (DELFI* or Omni1* or Signal-X* or Harbinger* or EDIM* or LUNAR* or MERCURY*)[Keywords]) AND ((((((Multi-analyte* or multianalyte*)[Title] OR (Multi-analyte* or multianalyte*)[abs] OR (Multi-analyte* or multianalyte*)[Keywords]) OR ((multiomic* or multi-omic* or panomic* or pan-omic* or "integrative omic" or "Integrative omics")[Title] OR (multiomic*

or multi-omic* or panomic* or pan-omic* or "integrative omic" or "Integrative omics")[abs] OR (multiomic* or multi-omic* or panomic* or pan-omic* or "integrative omic" or "Integrative omics")[Keywords]) OR ("Multiomics"[mh])) AND ((biops* or test or tests or testing or tested or assay*)[Title] OR (biops* or test or tests or testing or tested or assay*)[abs] OR (biops* or test or tests or testing or tested or assay*)[Keywords])) OR ("Hematologic Tests"[mh]) OR (((biops* or test or tests or testing or tested or assay*)[Title] OR (biops* or test or tests or testing or tested or assay*)[abs] OR (biops* or test or tests or testing or tested or assay*)[Keywords]) AND ((blood or hematolog* or haematolog* or plasma or serum)[Title] OR (blood or hematolog* or haematolog* or plasma or serum)[abs] OR (blood or hematolog* or haematolog* or plasma or serum)[Keywords])) OR (("Blood"[mhe]) AND (("Biopsy, Fine-Needle"[mh]) OR ("Biopsy"[mh]))) OR (((biops*)[Title] OR (biops*)[abs] OR (biops*)[Keywords]) AND ((liquid* or fluid* or biofluid* or bio-fluid*)[Title] OR (liquid* or fluid* or biofluid* or bio-fluid*)[abs] OR (liquid* or fluid* or biofluid* or bio-fluid*)[Keywords])) OR ("Liquid Biopsy"[mh])) AND (((multicancer* or multi-cancer* or multitumor* or multitumour* or multi-tumor* or multi-tumour* or pan-cancer* or pancancer* or pan-tumor* or pan-tumour* or pantumor* or pantumour* or cross-cancer* or crosscancer* or cross-tumor* or cross-tumour* or crosstumor* or crosstumour*)[Title] OR (multicancer* or multi-cancer* or multitumor* or multitumour* or multi-tumor* or multi-tumour* or pan-cancer* or pancancer* or pan-tumor* or pan-tumour* or pantumor* or pantumour* or cross-cancer* or crosscancer* or cross-tumor* or cross-tumour* or crosstumor* or crosstumour*)[abs] OR (multicancer* or multi-cancer* or multitumor* or multitumour* or multi-tumor* or multi-tumour* or pan-cancer* or pancancer* or pan-tumor* or pan-tumour* or pantumor* or pantumour* or cross-cancer* or crosscancer* or cross-tumor* or cross-tumour* or crosstumor* or crosstumour*)[Keywords]) OR ((((type or types)[Title] OR (type or types)[abs] OR (type or types)[Keywords]) OR ((multiple* or many or several or numerous or various or varied or miscellaneous or mixed or diverse or different)[Title] OR (multiple* or many or several or numerous or various or varied or miscellaneous or mixed or diverse or different)[abs] OR (multiple* or many or several or numerous or various or varied or miscellaneous or mixed or diverse or different)[Keywords])) AND ((cancer* or neoplas* or tumour* or tumor* or carcinoma* or oncolog* or malignan* or precancer*)[Title] OR (cancer* or neoplas* or tumour* or tumor* or carcinoma* or oncolog* or malignan* or precancer*)[abs] OR (cancer* or neoplas* or tumour* or tumor* or carcinoma* or oncolog* or malignan* or precancer*)[Keywords])) OR ("Neoplasms"[mh]))) 0 hits

Key:
[Keywords] = search of keywords field
[abs] = search of abstract field
[Title] = search of title field
[mh] = subject heading search

* = truncation

PROSPERO

via https://www.crd.york.ac.uk/prospero/

Date searched: 15th September 2023

Records retrieved: 71

#1 MeSH DESCRIPTOR Neoplasms 1947
#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) 3573

#3 multicancer* or multi-cancer* or multitumor* or multitumour* or multi-tumor* or multi-tumour* or pan-cancer* or pancancer* or pan-tumor* or pan-tumour* or pantumor* or pantumour* or cross-cancer* or crosscancer* or cross-tumor* or cross-tumour* or crosstumor* or crosstumour* 33
#4 (cancer* or neoplas* or tumour* or tumor* or carcinoma* or oncolog* or malignan* or precancer*) adj3 (type or types) 4942
#5 #1 OR #2 OR #3 OR #4 8700
#6 MeSH DESCRIPTOR Liquid Biopsy 7
#7 (liquid* or fluid* or biofluid* or bio-fluid*) adj3 biops* 134
#8 MeSH DESCRIPTOR Biopsy 103
#9 MeSH DESCRIPTOR Biopsy, Fine-Needle 29
#10 MeSH DESCRIPTOR Blood EXPLODE ALL TREES 816
#11 #8 OR #9 132
#12 #10 AND #11 0
#13 (blood or hematolog* or haematolog* or plasma or serum) adj3 biops* 71
#14 MeSH DESCRIPTOR Hematologic Tests 38
#15 (blood or hematolog* or haematolog* or plasma or serum) adj2 (test or tests or testing or tested or assay*) 1199
#16 (multiomic* or multi-omic* or panomic* or pan-omic* or "integrative omic" or "Integrative omics") adj4 (test or tests or tested or testing or assay* or biops*)1
#17 (Multi-analyte* or multianalyte*) adj4 (detect* or screen* or test or tests or tested or testing or assay* or biops*) 0
#18 #6 OR #7 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 1397
#19 #18 AND #5 112
#20 MeSH DESCRIPTOR Mass Screening 371
#21 MeSH DESCRIPTOR Diagnostic Screening Programs 37
#22 MeSH DESCRIPTOR early diagnosis 161
#23 MeSH DESCRIPTOR Early Detection of Cancer 397
#24 (screen* or detect*):TI,KW,RQ 6490
#25 ((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,KW,RQ 818
#26 (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) 15154
#27 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*) 5839
#28 #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 23489
#29 #19 AND #28 63
#30 ((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*)) 43
#31 ((cancer* or neoplas* or tumour* or tumor* or carcinoma* or oncolog* or malignan* or precancer*) adj6 (type or types) adj6 (screen* or detect*)) 107
#32 #30 OR #31 146
#33 #18 AND #32 7
#34 #29 OR #33 64
#35 (multicancer* or multi-cancer* or multitumor* or multitumour* or multi-tumor* or multi-tumour*) adj6 (detect* or screen* or test or tests or tested or testing or assay*) 7
#36 MCED or MCDBT 2
#37 ("multiple cancer" or "multiple cancers" or "multiple tumor" or "multiple tumours") adj6 (detect* or screen* or test or tests or tested or testing or assay*) 0
#38 (pan-cancer* or pancancer* or pan-tumor* or pan-tumour* or pantumor* or pantumour*) adj6 (detect* or screen* or test or tests or tested or testing or assay*) 0
#39 (cross-cancer* or crosscancer* or cross-tumor* or cross-tumour* or crosstumor* or crosstumour*) adj6 (detect* or screen* or test or tests or tested or testing or assay*) 0
#40 ("multi-class cancer" or "multi-class cancers" or "multiclass cancer" or "multiclass cancers" or "multi-class tumor" or "multi-class tumors" or "multi-class tumour" or "multi-class tumours" or

"multiclass tumor" or "multiclass tumors" or "multiclass tumour" or "multiclass tumours") adj6 (detect* or screen* or test or tests or tested or testing or assay*) 0
#41 #35 OR #36 OR #37 OR #38 OR #39 OR #40 7
#42 (PanSEER* or CancerSEEK* or CancerEMC* or PanTum or PanTumDetect or "Epitope-detection in monocytes" or CancerRadar* or IvyGene* or IvyGeneCORE* or CancerLocator* or CancerDetector* or "EpiPanGI Dx" or EpiPanGIDx* or OverC or DEEPGEN or Dxcover* or trucheck* or Elypta* or MiRXES* or Freenome*) 3
#43 DELFI* or Omni1* or Signal-X* or Harbinger* or EDIM* or LUNAR* or MERCURY* 326
#44 #43 AND #19 0
#45 #44 OR #42 OR #41 OR #34 69
#46 Galleri or GalleriTM 3
#47 #45 or #46 71

Key:
MeSH DESCRIPTOR = subject heading (MeSH heading)
* = truncation
TI,KW,RQ = terms in title, keyword or research question field
adj3 = terms within 3 words of each other (order specified)

ClinicalTrials.gov

https://clinicaltrials.gov/ct2/

Date searched: 15th September 2023

Records retrieved: 325
1. 208 Studies found for: ("liquid biopsy" OR "blood test" OR "haematological test" OR "hematological test" OR "plasma test" OR "serum test") AND (screen OR screened OR screening OR detect OR detection) | (cancer OR neoplasm OR tumour OR tumor) AND (multiple OR many OR several OR numerous OR various OR varied OR miscellaneous OR mixed OR diverse OR different)
2. 2 Studies found for: ("liquid biopsy" OR "blood test" OR "haematological test" OR "hematological test" OR "plasma test" OR "serum test") AND (screen OR screened OR screening OR detect OR detection) | ("cancer type" OR "cancer types" OR "tumour type" OR "tumour types" OR "tumor type" OR "tumor types")
3. 12 Studies found for: (multiomic OR multi-omic OR multianalyte OR multi-analyte) AND (test OR tests OR tested OR testing OR assay OR biopsy) | (cancer OR neoplasm OR tumour OR tumor) AND (multiple OR many OR several OR numerous OR various OR varied OR miscellaneous OR mixed OR diverse OR different)
4. No Studies found for: (multiomic OR multi-omic OR multianalyte OR multi-analyte) AND (test OR tests OR tested OR testing OR assay OR biopsy) | ("cancer type" OR "cancer types" OR "tumour type" OR "tumour types" OR "tumor type" OR "tumor types")
5. 26 Studies found for: (detect OR detection OR screen OR screened OR screening OR test OR assay) | (multicancer OR multi-cancer OR multitumor OR multitumour OR multi-tumor OR multi-tumour)
6. 5 Studies found for: MCED OR MCDBT
7. 13 Studies found for: (detect OR detection OR screen OR screened OR screening OR test OR assay) | (pan-cancer OR pancancer OR pan-tumor OR pan-tumour OR pantumor OR pantumour)
8. 11 Studies found for: (detect OR detection OR screen OR screened OR screening OR test OR assay) | ("multiple cancer" OR "multiple cancers" OR "multiple tumor" OR "multiple tumors" OR "multiple tumour" OR "multiple tumours")
9. 5 Studies found for: (Galleri OR GalleriTM OR PanSEER OR CancerSEEK OR CancerEMC OR PanTum OR PanTumDetect OR "Epitope-detection in monocytes" OR CancerRadar OR IvyGene OR IvyGeneCORE OR CancerLocator OR CancerDetector OR "EpiPanGI Dx" OR EpiPanGIDx OR OverC OR DEEPGEN)

10. 17 Studies found for: Dxcover OR trucheck OR Elypta OR MiRXES OR Freenome OR "Harbinger health test" OR EDIM OR "MERCURY test"
11. 26 Studies found for: (DELFI OR Omni1 OR Signal-X OR LUNAR) AND (detect OR detection OR screen OR screened OR screening OR test OR assay or biopsy) | (cancer OR neoplasm OR tumour OR tumor)

WHO International Clinical Trials Registry Platform (ICTRP)

https://trialsearch.who.int/Default.aspx

Date searched: 18th September 2023

Records retrieved: 266

Basic search interface used. No date limits available in basic search interface, therefore results from all years downloaded and records pre-2010 removed in EndNote.

1. 12 records for 12 trials found for: (cancer* OR neoplas* OR tumour* OR tumor*) AND (multiple* OR many OR several OR numerous OR various OR varied OR miscellaneous OR mixed OR diverse OR different) AND (liquid biops*)
2. 23 records for 17 trials found for: (cancer* OR neoplas* OR tumour* OR tumor*) AND (type OR types) AND (liquid biops*)
3. 212 records for 204 trials found for: (cancer* OR neoplas* OR tumour* OR tumor*) AND (multiple* OR many OR several OR numerous OR various OR varied OR miscellaneous OR mixed OR diverse OR different) AND (blood OR haematolog* OR hematolog* OR plasma OR serum) AND (screen* OR detect* OR test* OR assay*)
4. 2 records for 2 trials found for: (cancer* OR neoplas* OR tumour* OR tumor*) AND (multiple* OR many OR several OR numerous OR various OR varied OR miscellaneous OR mixed OR diverse OR different) AND (multiomic* OR multi-omic* OR multianalyte* OR multi-analyte*)
5. 29 records for 29 trials found for: (multicancer* OR multi-cancer* OR multitumor* OR multitumour* OR multi-tumor* OR multi-tumour*) AND (detect* OR screen* OR test OR tests OR tested OR testing OR assay*)
6. 9 records for 9 trials found for: ("multiple cancer" OR "multiple cancers" OR "multiple tumor" OR "multiple tumors" OR "multiple tumour" OR "multiple tumours") AND (detect* OR screen* OR test OR tests OR tested OR testing OR assay*)
7. 9 records for 9 trials found for: (pan-cancer* OR pancancer* OR pan-tumor* OR pan-tumour* OR pantumor* OR pantumour*) AND (detect* OR screen* OR test OR tests OR tested OR testing OR assay*)
8. No results were found for: (cross-cancer* OR crosscancer* OR cross-tumor* OR cross-tumour* OR crosstumor* OR crosstumour*) AND (detect* OR screen* OR test OR tests OR tested OR testing OR assay*)
9. 9 records for 9 trials found for: (Galleri OR GalleriTM OR PanSEER OR CancerSEEK OR CancerEMC OR PanTum OR PanTumDetect OR Epitope-detection in monocytes OR CancerRadar OR IvyGene OR IvyGeneCORE OR CancerLocator OR CancerDetector OR “EpiPanGI Dx” OR EpiPanGIDx OR OverC OR DEEPGEN)
10. 12 records for 12 trials found for: Dxcover OR trucheck OR Elypta OR MiRXES OR Freenome OR “Harbinger health test” OR EDIM OR “MERCURY test”
11. 10 records for 10 trials found for: (DELFI OR Omni1 OR Signal-X OR LUNAR) AND (cancer* OR neoplas* OR tumour* OR tumor*)
12. No Studies found for: (multiomic OR multi-omic OR multianalyte OR multi-analyte) AND (test OR tests OR tested OR testing OR assay OR biopsy) | ("cancer type" OR "cancer types" OR "tumour type" OR "tumour types" OR "tumor type" OR "tumor types")

2. Website searches

HTA Agencies
Date searched: 19th September 2023
Records retrieved: 12

Browsed or searched the following HTA Agency websites to check for additional reports not found through database searches. A date limit of 2010 was applied.

Agency for Healthcare Research and Quality (AHRQ), USA
1. https://www.ahrq.gov/research/findings/ta/index.html
Browsed list of technology assessments, topic refinements and archive of technology assessments – 3 relevant reports found
2. https://www.ahrq.gov/research/findings/evidence-based-reports/search.html
Filtered list to cancer and browsed 133 results – 1 relevant report found

Adelaide Health Technology Assessment (AHTA), AUSTRALIA
https://health.adelaide.edu.au/adelaide-health-technology-assessment/research-services/publications/
Browsed following lists (2010 onwards):
reports and monographs – none relevant
protocols – none relevant
Technology Briefs and Prioritising summaries – 2 relevant reports found
Presentations and abstracts – none relevant

Agency for Care Effectiveness – Singapore
https://www.ace-hta.gov.sg/
Browsed lists of technology guidance, horizon scanning reports, scientific publications – 1 relevant report found

Austrian Institute for Health Technology Assessment
https://eprints.aihta.at/
Search terms used:
1. liquid biopsy – 24 results browsed, none relevant
2. multicancer – 0
3. multi-cancer – 0
4. cancer screening – 69 results browsed, none relevant

Canadian Agency for Drugs and Technologies in Health (CADTH), CANADA
https://www.cadth.ca/
General search https://www.cadth.ca/search?s=&facets_query=&page=0
1. liquid biopsy – 52 results, 4 potentially relevant
2. multi-cancer early detection - 3 results, all duplicates with 1.
3. MCED – 3 results, all duplicates with 1.
Browsed projects in progress page and topics under consideration page – none relevant

Health Information and Quality Authority, IRELAND HIQA

https://www.hiqa.ie/reports-and-publications/health-technology-assessments
Browsed all 126 health technology assessments – none relevant

Scottish Health Technologies Group
https://shtg.scot/our-advice/
Browsed all publications 2010-2023 – 1 relevant report found
in progress: https://shtg.scot/what-we-do/work-programme/
Browsed all publications – none relevant

Health Technology Wales
https://healthtechnology.wales/reports-guidance/
1. liquid biopsy – 4 results – none relevant
2. multi-cancer early detection – 52 results – none relevant
Browsed all 251 reports – none relevant

National Institute for Health and Care Excellence
https://www.nice.org.uk/
General search box:
1. "liquid biopsy" – 2 results, none relevant.
2. "multicancer" – 0 results.
3. "multi-cancer" – 0 results.
4. https://www.nice.org.uk/guidance/published Searched for cancer, limited to 2010 to current, filtered to Diagnostic guidance – 11 results browsed for relevance, none relevant
in development – 4 results browsed for relevance, none relevant
awaiting development – 101 results browsed for relevance, none relevant
5. https://www.nice.org.uk/guidance/published Searched for cancer, limited to 2010 to current, filtered to Medtech innovation briefings – 24 results browsed for relevance, none relevant

National Institute for Health Research Journals Library
https://www.journalslibrary.nihr.ac.uk/search/#/
1. liquid biopsy – 79 results browsed, none relevant
2. muticancer – 0
3. multi-cancer – 0
4. cancer screening, limited to HTA assessments – 363 results browsed, 1 relevant
https://www.journalslibrary.nihr.ac.uk/hta/hta24660/#/abstract

Belgian Health Care Knowledge Centre
https://www.kce.fgov.be/en/all-reports-0
1. cancer - Filtered to HTA reports – browsed 19 reports – none relevant

Test manufacturer website searches

After screening, the included studies were examined to produce a list of company names and their tests. The website of each company (where available) was located and browsed to find further relevant references relating to multi-cancer early detection tests used for screening published from 2020 onwards.

1. Company: Adela
Test: No name
https://www.adelabio.com/
Date searched: 11th October 2023

2. Company: Ajinomoto Group
Test: AminoIndex Cancer Screening (AICS)
https://www.ajinomoto.com/innovation/action/aminoindex
Date searched: 10th October 2023

3 Company: AnPac Bio-Medical Science
Test: No name
https://www.anpacbio.com/
Date searched: 10th October2023

4. Company: AVRT
Test: Aristotle
https://avrtnow.com/aristotle/
Date searched: 10th October 2023

5. Company: Burning Rock DX
Test: OverC
https://us.brbiotech.com/
Date searched: 10th October 2023

6. Company: Datar Cancer Genetics
Tests: TruCheck, Trueblood, EasyCheck
https://datarpgx.com/
Date searched: 10th October 2023

7. Company: Elypta
Test: No name
https://www.elypta.com/
Date searched: 10th October 2023

8. Company: Exact Sciences
Test: CancerSEEK
https://www.exactsciences.com/
Date searched: 10th October 2023

9. Company**:** Gene Solutions
Test: SPOT-MAS
https://genesolutions.vn/en/product/spot-mas/
Date searched: 10th October 2023

10. Company: GenePlus Bejing
Test: No name
https://en.geneplus.cn/home
Date searched: 10th October 2023

11. Company: Geneseeq
Test: Mercury
https://na.geneseeq.com/
Date searched: 11th October 2023

12. Company: GRAIL
Test: Galleri
https://grail.com/
https://www.galleri.com/
Date searched: 11th October 2023

13. Company: Guardant
Test: Guardant LUNAR-2 (also known as Shield)
https://guardanthealth.com/
Date searched: 10th October 2023

14. Company: Harbinger Health
Test: Harbinger Health Test
https://www.harbinger-health.com/
Date searched: 11th October 2023

15. Company: RMDM Group
Test: PanTum test
https://rmdm.group/
Date searched: 11th October 2023

16. Company: SeekIn
Test: OncoSeek
https://www.seekincancer.com/
Date searched: 10th October 2023

17. Company: Singlera Genomics
Test: PanSeerX
https://singleraoncology.com/
Date searched: 10th October 2023

Websites could not be located for the following companies: Nanjing Shihe Jiyin, Carcimun Biotech, and Shenzhen Kerida Health Technology. In addition, the names of companies producing the following tests could not be found: SpecGastro test and CancerD24.

APPENDIX 3. PPI INVITE

Multi-cancer early detection tests for general population screening

General population cancer screening is only available for some cancers (cervical, breast, bowel). Additionally, in some areas of England and Wales people at high risk of developing lung cancer can receive a lung health check. Breast, prostate, lung, and bowel cancers together account for just over half of all new cancers diagnosed. Most other cancers are detected after presentation of symptoms. Many of these will be diagnosed at stages III and IV. This means treatment options may be more limited.

New tests that look for signs of cancer in blood (blood-based multi-cancer early detection tests - MCEDs) are being developed; they aim to detect multiple different cancers at an early stage, when they are potentially more treatable. The NHS Long Term Plan ambition seeks to diagnose 75% of cancers at stage I or II, to enable more effective treatment. An MCED test embedded within a national population-based screening programme, in addition to existing cancer screening programmes, may increase the number of cancers diagnosed at an earlier stage. This could potentially improve the likelihood of successful treatment and increase survival rates.

The possible introduction of such a tests raises a number of questions. Several research projects have been commissioned to explore the impact of these tests within the context of a general population screening programme. We would like to explore some of these questions with patients and the public, particularly those who might be eligible for this type of screening and those with lived experience of a cancer diagnosis.

We are planning an online focus group involving a number of organisations to discuss these on **Friday 17th November between 1 and 2.30pm**.

Some of the things that we want to explore on this call are:

- How willing people are to take up MCED screening opportunities
- What impact this might have on other screening programmes
- What concerns people have about false negative and false positive results
- How people feel about universal versus targeted use of screening tools

APPENDIX 4. LIST OF EXCLUDED STUDIES WITH RATIONALE

Excluded on Intervention (n=130)

1. cfDNA Assay Prospective Observational Validation for Early Cancer Detection and Minimal Residual Disease.
2. Collecting Blood Samples From Patients With and Without Cancer to Evaluate Tests for Early Cancer Detection.
3. Development and Validation of Harbinger Health Test for Early Cancer Detection.
4. Multi-Cancer Early Detection (MCED) of Firefighters.
5. PAN-study: Pan-Cancer Early Detection Study (PAN).
6. PERformance of Multi-Cancer Early-detectIon Based on Various Biomarkers in fEmale Cancers, PERCEIVEII.
7. PERformance of Multi-Cancer Early-detectIon Based on Various Biomarkers in fEmale Cancers, PERCEIVE-I.
8. PRediction Of Five Usual Tumors Using Blood Test for Risk Assessment and Early Detection.
9. Prospective Screening and Differentiating Common Cancers Using Peripheral Blood Cell-Free DNA Sequencing.
10. Screening for High Frequency Malignant Disease.
11. The FuSion Program: A Prospective and Multicenter Cohort Study of Pan-Cancer Screening in Chinese Population.
12. The Jinling Cohort.
13. The PREDICT Study: Prospective Early Detection In a Population at High-risk for Common Malignant Tumor.
14. The STRIVE Study: Development of a Blood Test for Early Detection of Multiple Cancer Types.
15. Clinical Study of Pan-cancer DNA Methylation Test in Plasma.
16. LEVANTIS-0087A: GAGomes for Multi-Cancer Early Detection in Asymptomatic Adults (LEV87A).
17. LEVANTIS-0093A: GAGomes for Multi-Cancer Early Detection in High-Risk Adults (LEV93A).
18. Non-invasive Liquid Biopsy Analysis of Epigenomics Signatures in Multiple Cancer Types.
19. Pan-canceR Early DetectIon projeCT.
20. Pan-canceR Early-Stage deteCtion by lIquid Biopsy tEchNique projecT.
21. Project CADENCE (CAncer Detected Early caN be CurEd).
22. The Sanderson Study: A Case Control Study for the Development of Multiomics Blood Tests for Cancer Screening.
23. Akolkar D, Patil D, Crook T, et al. Circulating ensembles of tumor-associated cells: A redoubtable new systemic hallmark of cancer. International Journal of Cancer 2020;146:3485-94. doi: https://dx.doi.org/10.1002/ijc.32815
24. Alexander G, Lin W, Ramaiah M, et al. Analytical validation of a multi-cancer early detection test with tissue localization using a cell-free DNA-based targeted methylation assay. Cancer Research Conference: American Association for Cancer Research Annual Meeting, AACR 2020;80 doi: https://dx.doi.org/10.1158/1538-7445.AM2020-721
25. Alexander GE, Jung B, Ji L, et al. Analytical performance of a cfDNA-based targeted methylation multi-cancer early detection test for population-scale screening. Cancer Research Conference: AACR Annual Meeting 2021;81 doi: https://dx.doi.org/10.1158/1538-7445.AM2021-112
26. Antonowicz S, Kumar S, Wiggins T, et al. Diagnostic metabolomic blood tests for endoluminal gastrointestinal cancer - a systematic review and assessment of quality. Cancer Epidemiol Biomarkers Prev 2016;25:6-15. doi: http://dx.doi.org/10.1158/1055-9965.EPI-15-0524
27. Baker M, Cameron JM, Sala A, et al. Multicancer early detection with a spectroscopic liquid biopsy platform. Journal of Clinical Oncology Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO 2022;40 doi: https://dx.doi.org/10.1200/JCO.2022.40.16_suppl.3034

28. Bao H, Wang Z, Ma X, et al. Letter to the Editor: An ultra-sensitive assay using cell-free DNA fragmentomics for multi-cancer early detection. Molecular Cancer 2022;21:129. doi: https://dx.doi.org/10.1186/s12943-022-01594-w
29. Bergamaschi A, Collins F, Ellison C, et al. Changes in DNA hydroxymethylation for the detection of multiple cancers in plasma cellfree DNA. Journal of Clinical Oncology Conference 2019;37 doi: https://dx.doi.org/10.1200/JCO.2019.37.15_suppl.3058
30. Best M, Sol N, Kooi I, et al. Allowance of tumor-educated platelets for multiclass liquid biopsy-based diagnosis of cancer. Journal of Clinical Oncology Conference 2015;33
31. Bratulic S, Limeta A, Dabestani S, et al. Noninvasive detection of any-stage cancer using free glycosaminoglycans. Proceedings of the National Academy of Sciences of the United States of America 2022;119:e2115328119. doi: https://dx.doi.org/10.1073/pnas.2115328119
32. Bryce AH, Liu MC, Seiden MV, et al. Performance of a cell-free DNA-based multi-cancer detection test as a tool for diagnostic resolution of symptomatic cancers. Cancer Research Conference: AACR Annual Meeting 2021;81 doi: https://dx.doi.org/10.1158/1538-7445.AM2021-LB058
33. Budnik B, Amirkhani H, Forouzanfar MH, et al. A novel proteomics-based plasma test for early detection of multiple cancers in the general population. medRxiv 2023;08 doi: https://dx.doi.org/10.1101/2023.05.06.23289613
34. Cameron JM, Antoniou G, Brennan PM, et al. Early colorectal cancer detection with a spectroscopic liquid biopsy. Cancer Research Conference: American Association for Cancer Research Annual Meeting, ACCR 2023;83 doi: https://dx.doi.org/10.1158/1538-7445.AM2023-6506
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36. Carey J, Leal A, Chesnick B, et al. Detecting cancer using genome-wide cfDNA nucleosomal fragmentation in a prospective multi cancer cohort. Cancer Research Conference: AACR Annual Meeting 2021;81 doi: https://dx.doi.org/10.1158/1538-7445.AM2021-570
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38. Chen J, Yang Y, Wang Z, et al. A Multicancer Malignant Pleural Effusion Diagnostic Test Using Hexokinase 2 and Single-Cell Sequencing. Clinical Chemistry 2022;68:680-90. doi: https://dx.doi.org/10.1093/clinchem/hvac003
39. Chen X, Dong Z, Hubbell E, et al. Prognostic Significance of Blood-Based Multi-cancer Detection in Plasma Cell-Free DNA. Clinical Cancer Research 2021;27:4221-29. doi: https://dx.doi.org/10.1158/1078-0432.CCR-21-0417
40. Chen X, Gole J, Gore A, et al. Non-invasive early detection of cancer four years before conventional diagnosis using a blood test. Nature communications 2020;11:3475. doi: https://dx.doi.org/10.1038/s41467-020-17316-z
41. ChiCtr. PanTum technique for the detection of peripheral blood APO10 and TKTL1 in the diagnosis of high incidence of malignant tumors in Chinese population, 2020.
42. ChiCtr. A prospective, multicenter cohort study of pan-cancer screening in Chinese population, 2021.
43. ChiCtr. SZ-PILOT Study: Prospective observational study of the YiDiXueTM multi-cancer early detection Kit in multi-cancer early screening in normal people, 2022.
44. Constancio V, Nunes SP, Moreira-Barbosa C, et al. Early detection of the major male cancer types in blood-based liquid biopsies using a DNA methylation panel. Clinical Epigenetics 2019;11:175. doi: https://dx.doi.org/10.1186/s13148-019-0779-x
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Excluded on population (n=4)

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Excluded on outcomes (n=12)

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APPENDIX 5. DETAILS OF THE INCLUDED STUDIES

Table 11 Characteristics of the included studies for each MCED test

Study details	Participant information	Intervention	Outcomes	Methodological details
GRAIL Galleri				
Study name: PATHFINDER Clinical trial identifier: NCT04241796 Study design: Prospective cohort study Location: USA (outpatient clinics at seven US health networks) Funding source: GRAIL, LLC Author/year: Schrag, 2023[30] (full journal article & appendices) Author/year: Schrag, 2022[89] (conference abstract reporting anxiety, distress and satisfaction results) Associated publications (with no additional relevant data for extraction): Author/year: Klein, 2023[88] (conference poster comparing 'refined test' and early test) Author/year: Westgate, 2023[84] (conference poster comparing 'real-world experience' with PATHFINDER; does not report data for extraction as some patients still under review) Author/year: Schrag, 2022[39] (conference abstract, no additional results reported) Author/year: Beer, 2021[40]	6578 of 6662 (98.7%) participants recruited for the main study (between 12/12/19 and 4/12/20) had analysable results for the refined MCED test. Cohort 1: elevated risk group (n=3655 adults aged 50 or older meeting at least one of the following criteria: history of smoking ≥100 cigarettes in lifetime, documented genetic cancer predisposition, or personal history of invasive or haematological malignancy with treatment completed >3 years prior to enrolment). 1622 (41%) of cohort 1 had a previous cancer history. Cohort 2: non-elevated risk group (n=2923 adults aged 50 or older with none of the conditions listed in the elevated risk group). See table S11 in Schrag, 2023 appendices for participant demographics	Refined MCED test.	Main study (old version of the test): Extent of diagnostic testing (time to achieve diagnostic resolution, number of clinic visits, number of lab tests, number of imaging tests, number of procedures). Secondary: Accuracy of the test (including PPV, NPV, specificity). Accuracy of Cancer Signal Origin. Refined MCED test results extracted (reported in Schrag, 2023 appendices). Acceptability and health-related quality of life (anxiety): Participants' reported outcomes and perceptions of the MCED test. Only reported for the main study, however, participants' experience of the test is not altered by re-analysis of blood tests using refined test	Main study (old version of MCED test): If a cancer signal was detected, participants had diagnostic assessment coordinated by, and at the discretion of, their doctor. Doctors determined when the diagnostic work-up was considered complete. End-of-study assessment done 12 months post-enrolment: review of electronic health records (supplemented with telephone contact as needed). Status assessment was considered complete if a cancer diagnosis was reported during the follow-up period or no cancer diagnosis was recorded at the end-of-study 12 month assessment. Participants with no MCED cancer signal detected but who had a confirmed cancer diagnosis within 12 months were classified as false negative. Sensitivity was not included in performance outcomes due to the lack of a 'gold-standard' to establish cancer status of all participants at time of blood draw. A cancer diagnosis was established by pathological, laboratory or radiographic confirmation; 113/122 (93%) cancers were pathologically confirmed. Refined MCED test: Analysis of PATHFINDER blood specimens with the refined MCED test was added to the statistical analysis plan on 14/12/20. The refined MCED test results were not returned to physicians or participants and did not influence diagnostic evaluation. **QUADAS-2** Domain 1: Patient selection RoB: High. Concerns regarding applicability: Low. Domain 2: Index test RoB: Unclear. Concerns regarding applicability: Low.

Study details	Participant information	Intervention	Outcomes	Methodological details
(ASCO meeting abstract and poster, interim analysis of new test, but incomplete data) Author/year: Beer, 2021[40, 41] (ASCO meeting abstract, interim analysis of old test) Author/year: McDonnell, 2022[87] (conference abstract describing diagnostic workup of 2 (non-GI) cancer patients from interim dataset). Author/year: Klein, 2023[42] (conference abstract, old test) Author/year: Nadauld, 2020[43] (conference abstract, old test) Author/year: Nadauld, 2021[44] (protocol only, no results) Author/year: GRAIL LLC, 2020[45] (clinical trial register record, no results)	and baseline characteristics. Ethnicity: Non-Hispanic White (n=6071; 91.7%) Hispanic (n=132; 2.0%) Non-Hispanic Black (n-90; 1.4%) Asian (n=129; 1.9%) Other (n=66; 1.0%) Not reported (n=131; 2.0%)		(results were not returned to physicians or participants).	Domain 3: Reference standard RoB: Unclear. Concerns regarding applicability: Unclear. Domain 4: Flow and timing RoB: High.
Study name: SYMPLIFY Clinical trial identifier: ISRCTN10226380 Study design: Prospective cohort study Location: England and Wales Funding source: Grail Bio UK Author/year: Nicholson, 2023[58] Author/year: University of Oxford, 2021 (clinical trial register record)[46]	6238 participants (5851 clinically evaluable participants). Adults aged 18 years or over referred for urgent investigation for a possible gynaecological, lung, lower GI or upper GI cancer or to a rapid diagnostic centre with non-specific symptoms that might be due to cancer. Exclusion criteria: history of cancer within the previous 3 years. The number of participants	MCED test (Galleri). Blood sample during one visit to hospital. After that participants will have no further direct involvement, all follow-up is through collection of data.	Accuracy of the test (sensitivity, specificity, PPV, NPV). Accuracy of the test (sensitivity, specificity, PPV, NPV) within each referral pathway (gynaecological, lower gastrointestinal, lung, rapid diagnostic centre, upper gastrointestinal). Accuracy of Cancer Signal Origin. yield for the MCED test.	All patients were eligible for recruitment if they were referred for urgent investigation of possible cancer or with non-specific symptoms that might be cancer. All patients were followed up until diagnostic resolution (standard of care investigations provided by hospital staff) within 3 months of enrolment, or 9 months if investigations were not complete. Sites were also asked to report any delayed and subsequent cancer diagnoses after diagnostic resolution was reached for initial investigations. Variations in standard of care across sites was mitigated by recruiting from established, protocolised 2-week wait pathways that followed national standards. The MCED test was run without knowledge of the clinical outcomes. No results were returned to the participant or their clinicians.

Study details	Participant information	Intervention	Outcomes	Methodological details
	with a history of cancer was not reported Ethnicity: White (n=4938; 90.4%) Mixed (n=62; 1.1%) South Asian (n=200; 3.7%) Chinese (n=26; 0.5%) African or Caribbean (n=171; 3.1%) Other (n=64; 1.2%)			**QUADAS-2** Domain 1: Patient selection RoB: Unclear. Concerns regarding applicability: High. Domain 2: Index test RoB: Low. Concerns regarding applicability: Low. Domain 3: Reference standard RoB: Unclear. Concerns regarding applicability: Low. Domain 4: Flow and timing RoB: High.
Study name: Circulating Cell-free Genome Atlas (CCGA) substudy 3 Study website: https://grail.com/clinical-studies/ccga-study/ Clinical trial identifier: NCT02889978 Study design: Prospective case-control Location: North America (142 sites for all CCGA substudies) Funding source: GRAIL Author/year: Klein, 2021[31] Author/year: Tang, 2023[47] (test performance across racial and ethnic groups) Author/year: Bryce, 2023[48] (test performance within a subgroup of participants with symptoms suspicious for cancer) Author/year: Shao, 2023[49] (post-hoc analysis of participants with cancer split into three subgroups: solid screened	Adults aged 20 years or older. Cancer arm: individuals diagnosed with cancer and/or scheduled to undergo biopsy and/or surgical resection for known or highly suspected malignancy. Exclusion: individuals who received chemotherapy, radiotherapy, definitive local therapy or surgery before blood draw. Non-cancer arm: non-cancer participants. Total 5,309 participants enrolled in CCGA substudy 3 between August 2016 and February 2019 (cancer = 3,237, noncancer = 2,069). 4,077 were included in the Confirmed	Blood collection and multi-cancer early detection test (developed by GRAIL).	Accuracy of Cancer Signal Origin (sensitivity and specificity); cancer signal origin prediction (overall accuracy); and both combined. Accuracy by age group. Accuracy of Cancer Signal Origin by method of cancer diagnosis (screening test or clinical presentation). Accuracy of Cancer Signal Origin in a pre-specified group of 12 cancer classes.	The MCED test results were not returned to participants or health care providers. Clinical, pathology and radiology data were collected from participant questionnaires and abstracted from medical records, including reports of adverse events from the study blood draw. Participant follow up for clinical information was carried out annually (within ±2 months from anniversary of enrolment) from a search of medical records or direct contact with participants. **QUADAS-2** Domain 1: Patient selection RoB: High. Concerns regarding applicability: High. Domain 2: Index test RoB: Unclear. Concerns regarding applicability: Low. Domain 3: Reference standard RoB: Unclear. Concerns regarding applicability: Unclear. Domain 4: Flow and timing RoB: High.

Study details	Participant information	Intervention	Outcomes	Methodological details
tumours, solid unscreened tumours and haematological malignancies) Associated publications (with no additional relevant data for extraction): Author/year: Rossi, 2022[50] (commentary on Klein) Author/year: Klein, 2021[51] (conference abstract only – same as Klein, 2021 paper[31]) Author/year: Klein, 2021[52] (conference poster - same as Klein 2021 and Tang 2023 papers). Author/year: Venn, 2023[53] (conference poster - test performance across racial and ethnic groups) Author/year: Tang, 2021[54] (conference abstract - test performance across racial and ethnic groups) Author/year: Yimer, 2021[55] (conference poster - exploratory analysis to evaluate test positive rate on cancer classification and cancer subtypes)	Status analysis set (cancer = 2,823, noncancer = 1,254). The most common reasons for exclusion were incomplete year-one follow-up for non-cancer participants, presence of non-malignant conditions and enrolment, and unconfirmed cancer or treatment status at blood draw. See table 1 in Klein, 2021 for participant demographics and baseline characteristics. Ethnicity: Non-Hispanic White (n=3312; 81.2%) Hispanic (n=295; 7.2%) Non-Hispanic Black (n=278; 6.8%) Asian, Native Hawaiian or Pacific Islander (n=75; 1.8%) American Indian or Alaska native (n=15; 0.4%) Other (n=102; 2.5%)			
Author/year: Cance, 2023[59] (conference poster reporting employer-based implementation of Galleri®) Clinical trial identifier: Not reported Study design: Prospective cohort study Location: USA (industrial-based workers from three companies)	812 industrial-based workers from three US companies (employed in manufacturing jobs that did not require a college degree). Ethnicity was not reported in this study.	Galleri® MCED test.	Number of cancers detected (MCED test results). Acceptability (factors important for MCED test uptake in the employer setting).	No follow-up of participants with no cancer signal detected (n=808). Of those with a cancer signal detected (n=4); 2 were lost to follow-up, 1 is undergoing follow-up, 1 had a diagnosis of breast cancer at the time of taking the test. Factors that were important for MCED test uptake in the employer setting were derived from employer insight into the employee population, employee feedback, and observations of GRAIL staff at on-site events.

Study details	Participant information	Intervention	Outcomes	Methodological details
Funding source: GRAIL, LLC				**QUADAS-2** Domain 1: Patient selection RoB: Unclear. Concerns regarding applicability: High. Domain 2: Index test RoB: High. Concerns regarding applicability: High. Domain 3: Reference standard RoB: High. Concerns regarding applicability: Unclear. Domain 4: Flow and timing RoB: High.
CancerSEEK				
Study name: DETECT-A Clinical trial identifier: Not reported Study design: Prospective cohort study Location: USA Funding source: The Marcus Foundation; Lustgarten Foundation for Pancreatic Cancer Research; The Virginia and D. K. Ludwig Fund for Cancer Research; The Sol Goldman Center for Pancreatic Cancer Research; Susan Wojcicki and Dennis Troper; the Rolfe Foundation; The Commonwealth Fund; The Conrad R. Hilton Foundation; The John Templeton Foundation; Benjamin Baker; and Burroughs Wellcome Career Award for Medical Scientists Author/year: Lennon, 2020[6] Author/year: Papadopoulos, 2020[56] (conference abstract) Follow-up of true positives over 4.3 years: Author/year: Buchanan, 2023[86] Follow-up of false positives over 4.3 years:	10,006 participants (9911 participants assessed after withdrawals, exclusions, etc). Women aged 65 to 75 years not previously known to have cancer (recruited between September 2017 and May 2019). See supplementary table 4 for participant demographics. Ethnicity: Non-Hispanic White (n=9406; 94.9%) African American (n=63; 0.6%) Asian (n=41; 0.4%) Other (n=350; 3.5%) Not reported (n=51; 0.5%)	Multicancer blood testing with PET-CT/other imaging for diagnostic resolution.	Potential harms (feasibility and safety). Accuracy of the test (sensitivity, specificity, PPV, NPV).	Used an earlier version of the test with two biomarkers (mutations and proteins). The latest version has 4 markers (aneuploidy, methylation, mutations, proteins). Enrolled only women aged 65-75 with no personal history of cancer from a population with high adherence to standard of care (SOC) screening. 10,006 participants enrolled through the Geisinger Health System (health service organisation) which allowed access to electronic medical records. Of these, 9911 individuals participated in the study, and followed-up for 12 months. Used a two-step approach by taking two blood samples: first blood sample was evaluated with the test, and individuals with abnormal values were invited back to provide a second blood sample, which served as a confirmation blood test, to determine whether consistently abnormal biomarkers were detected and to exclude mutations due to clonal haematopoiesis of indeterminate potential (CHIP). If the second blood sample was also positive, then participants were considered to have a positive test. Multidisciplinary Review Committee reviewed these results to rule out any non-cancer related cause, and invited those where no such cause was found to undergo a full-body diagnostic positron emission tomography-computed tomography (PET-CT) scan to confirm the results of the blood test (7 were not

Study details	Participant information	Intervention	Outcomes	Methodological details
Author/year: Lennon, 2023[85]				recommended for PET-CT due to various health conditions). Some participants with a positive result who developed symptoms during this period were referred back to their physicians for management (and so did not have PET-CT). Geisinger Healthcare System electronic medical records were reviewed to assess cancer status 12 months after enrolment and the Tumor Registry was queried for any DETECT-A participants. Compared the number of positive cases of cancer detected using the test, vs those detected from standard of care screening, or via other methods (e.g., first onset of symptoms). 26 cases detected by the test, 24 by SOC, and 46 by other methods. QUADAS2: Domain 1: Patient selection RoB: High. Concerns regarding applicability: Low Domain 2: Index test RoB: Unclear. Concerns regarding applicability: High Domain 3: Reference standard RoB: Unclear. Concerns regarding applicability: High Domain 4: Flow and timing RoB: High
Earlier proof of concept case-control study: Study name: Not reported Clinical trial identifier: Not reported Study design: case-control Location: USA Author/year: Cohen, 2018[33]	1005 patients diagnosed with cancer and 812 controls in a case-control study. Ethnicity: Caucasian (n=1007; 55.4%) Asian (n=323; 17.8%) Black (n=168; 9.2%) Black/Hispanic (n=14; 0.8%)	Multicancer blood testing.	Accuracy of the test (sensitivity, specificity, and identification of cancer type). Accuracy of Cancer Signal Origin (sensitivity, specificity, and identification of cancer type).	QUADAS2: Domain 1: Patient selection RoB: High. Concerns regarding applicability: High Domain 2: Index test RoB: Unclear. Concerns regarding applicability: High Domain 3: Reference standard RoB: Unclear. Concerns regarding applicability: Unclear Domain 4: Flow and timing RoB: High

Study details	Participant information	Intervention	Outcomes	Methodological details
	Caucasian/Hispanic (n=30%1.7) Hispanic (n=77; 4.2%) Other (n=5; 0.3%) Not reported (n=193; 10.6%)			
SPOT-MAS				
Study name: K-DETEK Clinical trial identifier: NCT05227261 Study design: Prospective cohort study Location: Vietnam Funding source: Gene Solutions Author/year: Nguyen, 2023[8] (Interim report 6 months from initiation)	Individuals aged 40 or older presenting at outpatient clinics for follow-up of chronic conditions (e.g., hypertension, diabetes) or for routine annual health check-ups, with neither clinical suspicion of cancer nor history of confirmed cancer. Estimated enrolment: 3000. Interim analysis included 2795 participants, enrolled from 13 major hospitals and 1 research institute in Vietnam in April 2022 to July 2022. Ethnicity was not reported in this study.	SPOT-MAS (Screening for the Presence Of Tumor by Methylation And Size) blood test.	Accuracy of the test: true-positive values, false-positive values, cases without current diagnostic resolution, number of negative cases and PPV. Accuracy of Cancer Signal Origin: 'Tissue-of-origin' predictions were also reported, shown by its return rate and overall prediction accuracy.	Study participants were scheduled for follow-up visits at 6 and 12 months after enrolment. This study reported interim results at 6 months. Test results sent to participants within 30 days of their next check-up appointment at the hospital. Diagnostic resolution: Test results were explained by physicians. Those with cancer signal detected had consultations with physicians regarding the appropriate diagnostic tests relating to the five cancer types (liver, lung, breast, colorectal, gastric), depending on the cancer signal of origin prediction (e.g., lung cancer – chest CT scan). For cancer types not covered by the SPOT-MAS test, reported as "other cancers", participants were advised to undergo a health check-up with a full body CT scan as recommended by their physicians. If no abnormal results returned from imaging, participants were recommended to take SPOT-MAS at 6 months to re-confirm. Participants with no cancer signal detected were followed up at 6 months to confirm non cancer status. 13 participants had cancer signal detected, of which 6 were true positives, 4 false positives, and 3 did not have diagnostic confirmation test (excluded by the study when estimating PPV). QUADAS-2: Domain 1: Patient selection RoB: Unclear. Concerns regarding applicability: Low Domain 2: Index test RoB: Low. Concerns regarding applicability: Unclear Domain 3: Reference standard

Study details	Participant information	Intervention	Outcomes	Methodological details
				RoB: High. Concerns regarding applicability: Low Domain 4: Flow and timing RoB: High
Study name: Not reported Clinical trial identifier: Not reported Study design: Case-control Location: Vietnam Funding source: Gene Solutions Author/year: Nguyen, 2023[64]	738 cancer patients (stages I-IIIA) and 1,550 healthy controls. Discovery cohort: 499 cancer patients and 1076 healthy controls. Validation cohort: 239 cancer patients and 474 healthy controls. Enrolment between May 2019 and December 2022. Ethnicity was not reported in this study.	SPOT-MAS.	Accuracy of the test: sensitivity and specificity. Accuracy of Cancer Signal Origin: accuracy of tumour of origin reported.	All cancer patients were confirmed to have one of the five cancers analysed in the study (breast, colorectal, liver, lung, gastric) by imaging and subsequent tissue biopsy. Healthy subjects were confirmed to have no history of cancer at time of enrolment and followed-up for 6 months and 1 year to confirm. QUADAS-2: Domain 1: Patient selection RoB: High. Concerns regarding applicability: High Domain 2: Index test RoB: High. Concerns regarding applicability: Unclear Domain 3: Reference standard RoB: Unclear. Concerns regarding applicability: Unclear Domain 4: Flow and timing RoB: High
Trucheck				
Study name: RESOLUTE and TrueBlood Clinical trial identifier: CTRI/2019/01/017219 and CTRI/2019/03/017918 Study design: Prospective cohort studies (re-analysis of samples) Location: India Funding source: Datar Cancer Genetics Author/year: Ranade, 2021[9]	RESOLUTE: asymptomatic adults with only age-associated elevated risk of cancer and no prior diagnosis of cancer (n=10,625). Enrolment between 14 February 2019 and 30 June 2019. TrueBlood: symptomatic adults and those with prior diagnosis of cancer (n=5,509 cancer patients, subsequently enrolled an additional 4,743	Blood test for identification of circulating tumour cells (CTCs) and their clusters (circulating ensembles of tumor-associated cells; C-ETACs). Participants were blinded to the status of C-ETACs in their blood.	Accuracy of the test: number of cases with a positive/negative test result and PPV.	This was a re-analysis and one year follow up of the RESOLUTE study, and re-analysis of the TrueBlood study with additional enrolled cohort. Asymptomatic individuals had blood collected before screening, and symptomatic individuals had blood taken before biopsy. Re-analysis of RESOLUTE study using different assay, which led to additional 78 samples being identified as positive. Also re-analysed TrueBlood study, which led to an additional 179 positive samples detected. Study participants from RESOLUTE were followed up telephonically (median duration 379 days) to enquire about cancer status. 211/470 (44.9%) of C-ETAC positive and 3,530/10155 (38.7%) of C-ETAC negative individuals were

Study details	Participant information	Intervention	Outcomes	Methodological details
	individuals suspected of cancer) Ethnicity was not reported in this study.			lost to follow-up. Stage and grade of cancer was not ascertainable. QUADAS-2 (RESOLUTE): Domain 1: Patient selection RoB: Unclear. Concerns regarding applicability: Low Domain 2: Index test RoB: Low. Concerns regarding applicability: Unclear Domain 3: Reference standard RoB: Unclear. Concerns regarding applicability: High Domain 4: Flow and timing RoB: High QUADAS-2 (TrueBlood): Domain 1: Patient selection RoB: Unclear. Concerns regarding applicability: High Domain 2: Index test RoB: High. Concerns regarding applicability: Unclear Domain 3: Reference standard RoB: Unclear. Concerns regarding applicability: Unclear Domain 4: Flow and timing RoB: High
CDA				
Study name: Prospective Population-based Cohort Study (PPCS) Clinical trial identifier: Not reported Study design: Prospective cohort study Location: China Funding source: National Natural Science Foundation of China, Science and Technology	PPCS: >40 years without confirmed history of cancer at enrolment (n=1,957). Enrolment between 1/1/19 and 31/12/19. Ethnicity was not reported in this study.	CDA test – chip technology that can detect electrical based biophysical signals in blood samples. CDA values were categorised	Accuracy of the test: sensitivity and specificity.	Also included a cross-section study (RHCS) but this did not meet our inclusion criteria, therefore only PPCS is reported here. In PPCS, new diagnoses of cancer since study enrolment were identified through record linkage with the cancer registry. These cancer patients did not know their CDA results when they were diagnosed. Median duration of follow-up was 15 months (12-20 months). QUADAS-2: Domain 1: Patient selection

Study details	Participant information	Intervention	Outcomes	Methodological details
Commission of Shanghai Municipality, Shanghai Municipal Health Commission Author/year: Xie, 2022[10]		into "normal", "needs attention", and "high-risk".		RoB: Unclear. Concerns regarding applicability: Low Domain 2: Index test Rob: Low. Concerns regarding applicability: Unclear Domain 3: Reference standard Rob: Unclear. Concerns regarding applicability: High Domain 4: Flow and timing RoB: Unclear
AICS				
Study name: Not reported Clinical trial identifier: Not reported Study design: Prospective cohort study Location: Japan Funding source: Grants-in-Aid for Scientific Research for Priority Areas of Cancer and Innovative Areas, Japanese Ministry of Education, Culture, Sports, Science and Technology, and Ajinomoto Co., Inc. Author/year: Mikami, 2019[11]	Adults who underwent AICS from three hospital sites: Chiba Cancer Center (N=2,886), Mitsui Memorial Hospital (N=4,967) and Saihaku Hospital (N=2,392). Total N=10,245. Enrolment between Jan 2010 and Dec 2015. Ethnicity was not reported in this study.	AminoIndex Cancer Screening (AICS) test. A single blood test which calculates the probability of each cancer, and classifies into ranks A, B or C (high-risk).	Accuracy of the test: sensitivity and PPV by each cancer type.	Chiba Cancer Center: cancer incidence was reported from the regional cancer registry. Mitsui Memorial Hospital and Saihaku Hospital: detailed examinations were performed for individuals who were ranked as C (high-risk). Individuals recruited from Saihaku Hospital were further tracked based on regional follow-up surveillance. For participants in ranks A and B, information on cancer incidence was collected from health check-up records. The maximum follow-up period was 6.2 years. QUADAS-2: Domain 1: Patient selection RoB: Unclear. Concerns regarding applicability: Unclear Domain 2: Index test Rob: Low. Concerns regarding applicability: Unclear Domain 3: Reference standard Rob: High. Concerns regarding applicability: High Domain 4: Flow and timing RoB: High
Study name: AICS Follow-up study Clinical trial identifier: Not reported	Adults who underwent AICS (n=5,490). Enrolment between June 2013 and January 2017.	AICS.	Accuracy of the test: number of confirmed cancer cases.	This was an interim analysis of 5,490 participants who were tested with AICS.

Study details	Participant information	Intervention	Outcomes	Methodological details
Study design: Prospective cohort study Location: Japan Funding source: Ajinomoto Co., Inc. Author/year: Maeda, 2017[65]	Ethnicity was not reported in this study.			Those with rank C (high-risk) underwent detailed examination depending on the cancer type; examinations included endoscopy, CT, colonoscopy, echo, MRI, mammography, cervical cytology. Cancer registry data were also collected (for all ranks A, B, or C). Of the 2,346 participants who were ranked as C, detailed examination was carried out in 622 participants. Of the 5,490 participants overall, cancer registry data were collected for 650 participants enrolled between 2013 and 2014. QUADAS-2: Domain 1: Patient selection RoB: Unclear. Concerns regarding applicability: Unclear Domain 2: Index test Rob: Low. Concerns regarding applicability: Unclear Domain 3: Reference standard Rob: High. Concerns regarding applicability: Low Domain 4: Flow and timing RoB: High

Study details	Participant information	Intervention	Outcomes	Methodological details
Study name: Not reported Clinical trial identifier: Not reported Study design: Prospective cohort study Location: Japan Funding source: Not reported Author/year: Suzuki, 2014[66] (conference abstract) Author/year: Suzuki, 2015[57] (conference abstract)	Healthy women tested for breast cancer: one conference abstract reported 115 women (enrolment dates not reported) and one reported 83 women (enrolled July 2012 to September 2013). Ethnicity was not reported in this study.	AICS for breast cancer screening.	Accuracy of the test: number of confirmed cancer cases.	Women were tested with both AICS and mammography to detect breast cancer. QUADAS-2: Domain 1: Patient selection RoB: Unclear. Concerns regarding applicability: High Domain 2: Index test Rob: Unclear. Concerns regarding applicability: Unclear Domain 3: Reference standard Rob: Unclear. Concerns regarding applicability: Low Domain 4: Flow and timing RoB: Unclear

Abbreviations: AICS = AminoIndex Cancer Screening; ASCO = American Society of Clinical Oncology; CCGA = Circulating Cell-free Genome Atlas; CDA = Cancer Differentiation Analysis; CT = computed tomography; MCED = multi-cancer early detection; MRI = magnetic resonance imaging; NPV = negative predictive values; PET-CT = positron emission tomography – computed tomography; PPCS = Prospective Population-based Cohort Study; PPV = positive predictive values; RESOLUTE = Realtime Enrichment Screen for Outright detection of Latent Undiagnosed malignant Tumors in asymptomatic individuals Efficiently; RHCS = Routine Health Checkup Study; SOC = standard of care; SPOT-MAS = Screening for the Presence Of Tumour by Methylation And Size.

APPENDIX 6. INCLUDED STUDIES OF MCED TECHNOLOGIES AT AN UNCLEAR STAGE OF DEVELOPMENT

Table 12 Characteristics of the included studies of MCED technologies at an unclear stage of development

Study details	Participant information	Review outcomes assessed/results	QUADAS-2 overall result
Aristotle - StageZero Life Sciences			
Case-control (Dempsey, 2020),[67] United States	Cancer arm (n=1013) Non-cancer arm (n=1832; including 1042 healthy controls and 790 with other health conditions) Ethnicity was not reported in this study.	Accuracy of the test (sensitivity, PPV and NPV across 11 types of cancer): Sensitivity: cervical, nasopharynx and stomach cancer reported highest sensitivity at 100%, lowest reported for colon at 55.6%; PPV ranged from 5.6% for liver to 77.7% for breast; NPV ranged from 96.7% for colon polyps to 100% for bladder, cervical, endometrial, liver, nasopharynx, ovarian and stomach.	Risk of bias: High Applicability concerns: High
CancerenD24 – manufacturer unknown			
Case-control (Arber, 2017),[68] Israel	Not reported Ethnicity was not reported in this study (cancer patients and healthy controls were matched on ethnicity).	Accuracy of the test (across 7 types of cancer): For colorectal cancer: sensitivity: 79.2%, specificity: 74.7%, PPV: 38%, NPV: 94.8% For pancreatic cancer: sensitivity: 70%, specificity: 75.9%, PPV: 17.1%, NPV: 97.3% Other outcomes reported: Sensitivity and specificity for haematological malignancies were also statistically significant (but not reported). The test was unable to discriminate patients with cervical, stomach and lung cancer and healthy subjects.	Risk of bias: High Applicability concerns: High

Study details	Participant information	Review outcomes assessed/results	QUADAS-2 overall result
Case-control (Massarwi, 2019),[69] Israel	Not reported Ethnicity was not reported in this study.	Accuracy of the test: sensitivity (across 5 types of cancer): 94% for all cancers (bladder: 100%, pancreas: 89%, colorectal: 100%, colon adenoma: 87%, stomach: 100%); specificity: 84% (healthy subjects), 74% (healthy subjects with family history), 95% (healthy subjects without family history); NPV also reported (ranged from 93% to 100% depending on cancer type and whether there is family history).	Risk of bias: High Applicability concerns: High
Case-control (Shapira, 2020),[70] Israel	Cancer arm (n=222) Non-cancer arm (n=745) Ethnicity was not reported in this study.	Accuracy of the test: specificity (across 17 types of cancer): 68.6%, sensitivity and NPV reported for each type of cancer (sensitivity ranged from 38.0% [bladder] to 100% [oesophageal, Squamous cell carcinoma, and stomach]).	Risk of bias: High Applicability concerns: High
Case-control (Shapira, 2021),[71] Israel	Cancer arm (n=552) Non-cancer arm (n=724) Ethnicity was not reported in this study.	Accuracy of the test: sensitivity (across 8 cancer types): 84% (haematological), 80% (lung), 73% (breast), 71% (head and neck and GI cancers)	Risk of bias: High Applicability concerns: High
Case-control (Madah, 2023),[72] Israel	Cancer arm (n=464) Non-cancer arm (n=1138; matched on age, gender and medical history) Ethnicity was not reported in this study.	Accuracy of the test (across 21 major cancer types): sensitivity: 87%, specificity: 87%	Risk of bias: High Applicability concerns: High

Study details	Participant information	Review outcomes assessed/results	QUADAS-2 overall result
OncoSeek – SeekIn Inc			
Case-control (Luan, 2023),[73] China	Two independent validation cohorts: Cohort 1: Cancer arm (n=363) Non-cancer arm (n=5556) Nov 2012 to May 2022 Cohort 2 (same data as Cohen 2018, CancerSEEK): Cancer arm (n=1005) Non-cancer arm (n=812) Ethnicity was not reported in cohort 1, and cohort 2 examined the same participants as Cohen 2018.	Accuracy of the test (supplements table S3): In cohort 1: sensitivity: 47.4% (42.1%-52.7%), specificity: 90.0% (89.2%-90.8%), PPV: 23.7% (20.6%-26.9%), NPV: 96.3% (95.8%-96.8%) In cohort 2: sensitivity: 49.3% (46.1%-52.4%), specificity: 90.1% (87.9%-92.1%), PPV: 86.1% (83.0%-88.8%), NPV: 58.9% (56.1%-61.7%)	Risk of bias: High Applicability concerns: High
Case-control (Mao, 2023),[74] China	Cancer arm (n=1959) Non-cancer arm: (n=7423) Divided into one training and two independent validation cohorts Ethnicity was not reported in this study.	Note: results were not provided separately for training and validation cohorts, only that it was consistent between them. Accuracy of the test (across 9 common cancer types): sensitivity: 51.7% (49.4%-53.9%), sensitivity for pancreatic cancer: 77.6% (69.3%-84.6%). Sensitivity ranged from 37.1% to 77.6% across breast, colorectal, liver, lung, lymphoma, oesophagus, ovary, pancreas and stomach cancers. Specificity: 92.9% (95% CI 92.3 to 93.5) Accuracy of CSO: 66.8% (within true positives)	Risk of bias: High Applicability concerns: High
SeekInCare – SeekIn Inc			

Study details	Participant information	Review outcomes assessed/results	QUADAS-2 overall result
Case-control and prospective cohort study (Mao 2023),[75] China	Case-control: Cancer arm (n=615; stage I-IV, 8 common cancers, 19 uncommon cancers) Non-cancer arm (n=898) Real-world cohort: 1212 subjects (median follow-up time: 753 days [range 78-1669 days]) Ethnicity was not reported in this study.	Accuracy of the test: Case-control: sensitivity: 69.4% (stage I: 50.3%, stage II: 64%, stage III: 73.8%, stage IV: 86.2%), specificity: 98.0%, sensitivity by each type of cancer (breast: 45.1%, stomach: 50.0%, lung: 63.4%, colorectum: 69.4%, lymphoma: 70.5%, liver: 81.4%, pancreas: 82.4%, leukemia: 90.9%) Real-world cohort: sensitivity: 72.2%, specificity: 96.1%, PPV: 22.0%, NPV: 99.6%	Case-control: Risk of bias: High Applicability concerns: High Cohort study: Risk of bias: High Applicability concerns: Unclear
SeekIn Inc news article: case-control and prospective cohort study (SeekIn Inc, 2022),[76] location not reported	Case-control: Cancer arm (n=616; stage I-IV 8 common cancers, 19 other types) Non-cancer arm (n=898) Real-world cohort: 604 subjects (median follow-up time: 404 days) Ethnicity was not reported in this study.	Accuracy of the test: Case-control: sensitivity: 68.0% (stage I: 49.0%, stage II: 61.3%, stage III: 72.5%, stage IV: 85.4%), specificity: 98.0% Real-world cohort (detected 12 cancer cases): sensitivity: 92.3%, specificity: 97.7%, PPV: 57.1%, NPV: 99.7%	Case-control: Risk of bias: High Applicability concerns: High Cohort study: Risk of bias: Unclear Applicability concerns: Unclear
OverC – Burning Rock Biotech			
THUNDER (Gao, 2023)[77] Case-control, China	Independent validation sample (age-matched): Cancer arm (n=473) Non-cancer arm (n=473). Apr 2021 to Nov 2021 Ethnicity was not reported in this study.	Accuracy of the test: sensitivity: 69.1% (64.8%-73.3%), specificity: 98.9% (97.6%-99.7%); sensitivity by stage: stage I 35.4% (26.6%-45.0%), stage II 54.5% (43.6%-65.2%), stage III 82.4% (75.1%-88.3%), stage IV 93.8% (88.2%-97.3%). Accuracy of CSO: first CSO correct: 83.2% (78.7%-87.1%), first or second CSO correct: 91.7% (88.2%-94.5%) Subgroup analysis by age and sex.	Risk of bias: High Applicability concerns: High

Study details	Participant information	Review outcomes assessed/results	QUADAS-2 overall result
THUNDER-II (Gao, 2021)[78] Case-control, China	Independent validation sample: Cancer arm (n=202) Non-cancer arm (n=158; including 76 healthy controls and 82 high-risk individuals) Ethnicity was not reported in this study.	Accuracy of the test: sensitivity: 74.8% (68.1%-80.5%), specificity: 98.1% (94.1%-99.5%); sensitivity by stage: Stage I 53.0% (40.4%-76.3%), stage II 73.3% (57.8%-84.9%), stage III 90.4% (78.2%-96.4%), stage IV 92.3% (78.0%-98.0%). Accuracy of CSO: 80.8% (73.4%-86.6%)	Risk of bias: High Applicability concerns: High
Carcimun-test – Carcimun Biotech			
Case-control (Salat, 2022),[81] Austria	Cancer patients (across 17 cancer types, undergoing surgery) and healthy controls Cancer arm (n=170); Non-cancer arm (n=137) Ethnicity was not reported in this study.	Accuracy of the test: accuracy: 90.0%, sensitivity: 88.8%, specificity: 91.2%, PPV: 92.0%, NPV: 87.0% Mortality: 5-year all-cause mortality was similar among cancer patients who were true positives and false negatives, suggesting the test had missed clinically relevant cancers. Potential harms: no adverse effects observed for the blood withdrawal.	Risk of bias: High Applicability concerns: High
SpecGastro test – manufacturer unknown			
Case-control (Ma, 2022),[82] China	Gastrointestinal cancer patients (n=282; 98 colorectal cancer, 136 gastric cancer, 48 oesophageal cancer) and 195 controls Ethnicity was not reported in this study.	Accuracy of the test: sensitivity: 76.6% (71.1%-81.3%), specificity: 89.2% (83.8%-93.1%). Sensitivity by each cancer type: colorectal (87.8% [79.2%-93.2%]), gastric (69.9% [61.3%-77.3%]), oesophageal (72.9% [57.9%-84.3%])	Risk of bias: High Applicability concerns: High

Abbreviations: CSO = Cancer Signal Origin; GI = gastrointestinal; NPV = negative predictive values; PPV = positive predictive values; THUNDER = The Unintrusive Detection of Early-stage cancers.

Table 13 QUADAS-2 assessment results for the included studies of MCED technologies at an unclear stage of development

Study	Risk of Bias				Applicability Concern		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Aristotle – StageZero Life Sciences							
Case-control (Dempsey, 2020)[67]	High	High	Unclear	Unclear	High	Unclear	Unclear
CancerenD24 – manufacturer unknown							
Case-control (Arber, 2017)[68]	High	High	Unclear	High	High	Unclear	Unclear
Case-control (Massarwi, 2019)[69]	High	High	Unclear	High	High	Unclear	Unclear
Case-control (Shapira, 2020)[70]	High	High	Unclear	High	High	Unclear	Unclear
Case-control (Shapira, 2021)[71]	High	High	Unclear	High	High	Unclear	Unclear
Case-control (Madah, 2023)[72]	High	High	Unclear	High	High	Unclear	Unclear
OncoSeek – SeekIn Inc							
Case-control (Luan, 2023)[73]	High	High	Low	High	High	Unclear	Unclear
Case-control (Mao, 2023b)[74]	High	Unclear	Unclear	Unclear	High	Unclear	Unclear
SeekInCare – SeekIn Inc							
Case-control study (Mao 2023a)[75]	High	High	Unclear	Unclear	High	Unclear	Unclear
Prospective cohort study (Mao 2023a)[75]	High	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
SeekIn Inc news article: case-control study (SeekIn Inc, 2022)[76]	High	High	Unclear	Unclear	High	Unclear	Unclear
SeekIn Inc news article: Prospective cohort study (SeekIn Inc, 2022)[76]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
OverC – Burning Rock Biotech							
THUNDER (Gao, 2023)[77]	High	Low	Unclear	High	High	Unclear	Unclear
THUNDER-II (Gao, 2021)[78]	High	Low	Unclear	Unclear	High	Unclear	Unclear
Carcimun-test – Carcimun Biotech							
Case-control (Salat, 2022)[81]	High	Low	Unclear	High	High	High	Unclear
SpecGastro test – manufacturer unknown							
Case-control (Ma, 2022)[82]	High	Unclear	Unclear	Unclear	High	High	High

Abbreviations: MCED = multi-cancer early detection; THUNDER = The Unintrusive Detection of Early-stage cancers.

APPENDIX 7. CANCER TYPES DETECTED BY INCLUDED TESTS

Table 14 List of cancer types detected by included tests

	Galleri[30, 31, 58 a]	CancerSEEK[6]	SPOT-MAS[35, 64]	TruCheck[9]	CDA[10 b]	AICS[11]
1	Adrenal	Appendix	Breast	Breast	Breast	Breast
2	Ampulla of vater	Bile duct	Colorectal	Colon	Cervical	Colorectal
3	Anus	Bladder	Gastric	Esophageal	Colorectal	Gastric
4	Bladder	Breast	Liver	Ovarian	Liver	Lung
5	Bone/soft tissue	Colorectal	Lung		Lung	Prostate
6	Brain	Kidney			Lymphoma	Uterine/Ovarian
7	Breast	Liver			Multiple Myeloma	
8	Cervix	Lung			Other	
9	Choriocarcinoma	Lymphoma			Prostate	
10	CNS	Ovary			Pancreatic	
11	Colorectal	Pancreatic Neuroendocrine			Stomach	
12	Gallbladder	Sarcoma			Thyroid	
13	Head and neck	Stomach			Uterine	
14	Kidney	Thyroid				
15	Liver/bile duct	Uterine				
16	Lung					
17	Lymphoid leukaemia					
18	Lymphoma					
19	Malignant immunoproliferative disease					
20	Melanoma					
21	Mesothelioma					
22	Myeloid neoplasm					
23	Non-melanoma non BCC/SCC skin cancer					
24	Oesophago-gastric					
25	Ovary					
26	Pancreas					
27	Penis					
28	Plasma cell neoplasm					
29	Prostate					

30	Sarcoma
31	Small intestine
32	Stomach
33	Testis
34	Thymus
35	Thyroid
36	Urothelial tract
37	Uterus
38	Vagina
39	Vulva
40	Waldenstrom macroglobulinemia
41	Multiple primaries, Other/unspecified or Unknown primary

Abbreviations: AICS = AminoIndex Cancer Screening; CDA = Cancer Differentiation Analysis; SPOT-MAS = Screening for the Presence Of Tumour by Methylation And Size.
[a] website reports over 50 cancers detected;[5] [b] website reports 26 cancers detected but no details are given[37]

Table 15 Number and proportion of cancers detected by the GRAIL MCED test (Galleri) for different cancer types

Study	CCGA substudy 3 (case-control)[31]			PATHFINDER (cohort)[30]			SYMPLIFY (cohort)[58]		
Test accuracy[a]	MCED test (+)	Total cancers	Sensitivity	MCED test (+)	Total cancers	Sensitivity	MCED test (+)	Total cancers	Sensitivity
Overall	1453	2823	51.5 (49.6 to 53.3)	26	120	20.8 (14.0 to 29.2)	244	368	66.3 (61.2 to 71.1)
Anus	18	22	81.8 (61.5 to 92.7)[b]	None detected			5	5	100 (56.6 to 100)
Bladder	8	23	34.8 (18.8 to 55.1)[b]	None detected			3	5[e]	37.5 (13.7 to 69.4)
Urothelial Tract	8	10	80.0 (49.0 to 94.3)	None detected					
Breast	160	524	30.5 (26.7 to 34.6)	5	Not reported		4	7	57.1 (25 to 84.2)
Cervix	20	25	80.0 (60.9 to 91.1)	None detected			3	4	75.0 (30.1 to 95.4)
Colon/Rectum	169	206	82.0 (76.2 to 86.7)[b]	2	Not reported		97	137	70.8 (62.4 to 78.3)
Gallbladder	12	17	70.6 (46.9 to 86.7)	None detected			1	1	100 (20.7 to 100)
Oesophagus	85	100	85.0 (76.7 to 90.7)[b]	None detected			21	22[f]	95.5 (77.2 to 99.9)
Stomach	20	30	66.7 (48.8 to 80.8)[b]	1[c]	Not reported				
Lymphoid Leukaemia	21	51	41.2 (28.8 to 54.8)	1	Not reported		None detected		
Lymphoma	98	174	56.3 (48.9 to 63.5)[b]	5[d]	Not reported		8	14	57.1 (28.9 to 82.3)
Myeloid Neoplasm	2	10	20.0 (5.7 to 51.0)	None detected			None detected		
Plasma Cell Neoplasm	34	47	72.3 (58.2 to 83.1)[b]	1	Not reported		None detected		
Head and Neck	90	105	85.7 (77.8 to 91.1)[b]	2	Not reported		0	1	0.0 (0.0 to 79.0)
Kidney	18	99	18.2 (11.8 to 26.9)	None detected			1	5	20 (3.6 to 62.4)
Liver/Bile-duct	43	46	93.5 (82.5 to 97.8)[b]	2	Not reported		4	4	100 (51 to 100)
Lung	302	404	74.8 (70.3 to 78.7)[b]	1	Not reported		55	81	67.9 (56.6 to 77.8)
Melanoma	6	13	46.2 (23.2 to 70.9)	None detected			None detected		
Ovary	54	65	83.1 (72.2 to 90.3)[b]	2	Not reported		9	14	64.3 (35.1 to 87.2)
Uterus	44	157	28.0 (21.6 to 35.5)	1	Not reported		12	30	40 (22.7 to 59.4)
Pancreas	113	135	83.7 (76.6 to 89.0)[b]	1	Not reported		11	12	91.7 (61.6 to 99.8)
Prostate	47	420	11.2 (8.5 to 14.6)	1	Not reported		1	11	9.1 (0.2 to 41.3)
Sarcoma	18	30	60.0 (42.3 to 75.4)	1	Not reported		None detected		
Thyroid	0	14	0.0 (0.0 to 21.5)	None detected			0	1	0.0 (0.0 to 79)
Other	30	59[g]	50.8 (38.4 to 63.2)	None detected			7	11[h]	63.6 (35.4 to 84.8)
Multiple Primaries	16	19	84.2 (62.4 to 94.5)	None detected			None detected		
Unknown Primary	17	18	94.4 (74.2 to 99.7)	None detected			2	3	66.7 (20.8 to 93.9)

Abbreviations: CCGA = Circulating Cell-free Genome Atlas; MCED = multi-cancer early detection.
[a] Number of people with a true positive (+) MCED test and total number of people diagnosed with cancer in the study (i.e., true positives and false negatives of the MCED test), sensitivity is % and 95% confidence interval calculated from other reported data; [b] prespecified cancer types in CCGA substudy 3; [c] cancer of the small intestine; [d] including one case of Waldenstrom macroglobulinemia; [e] bladder and urothelial cancers reported together; [f] oesophagogastric cancers; [g] other cancer types were adrenal (n=1), ampulla of vater (n=1), brain (n=6), choriocarcinoma (n=1), mesothelioma (n=7), non-melanoma non-BCC/SCC skin cancer (n=2), other/unspecified (n=10), penis (n=1), small intestine (n=13), testis (n=6), thymus (n=2), vagina (n=2), vulva (n=7); [h] other cancer types were mesothelioma (n=6), vaginal (n=2), bone and soft tissue (n=1), CNS (n=1) and malignant immunoproliferative disease (n=1).

Table 16 Number and proportion of cancers detected by the CancerSEEK test

Study	**Cohen 2018 (case-control)[33]**			**DETECT-A (cohort)[6]**		
Test accuracy[a]	**MCED test (+)**	**Total cancers**	**Sensitivity**	**MCED test (+)**	**Total cancers**	**Sensitivity**
Overall	626	1005	62.3 (59.3 to 65.3)	26	70	27.1 (18.5 to 37.1)
Bladder	None detected			0	1	0.0 (0.0 to 79)
Breast	70	209	33.5 (27.4 to 40.1)	1	27	3.7 (0.7 to 18.3)
Colon/Rectum	252	388	64.9 (60.1 to 69.5)	2	3	66.7 (20.8 to 93.9)
Oesophagus	31	45	68.9 (54.3 to 80.5)	None detected		
Stomach	49	68	72.1 (60.4 to 81.3)	0	3	0.0 (0.0 to 56)
Lymphoma	None detected			2	4	50.0 (15 to 85)
Kidney	None detected			1	2	50.0 (9.5 to 90.5)
Liver/Bile-duct	43	44	97.7 (88.2 to 99.6)	0	2	0.0 (0.0 to 65.8)
Lung	61	104	58.7 (49 to 67.6)	9	21	42.9 (24.5 to 63.5)
Ovary	53	54	98.1 (90.2 to 99.7)	6	7	85.7 (48.7 to 97.4)
Uterus	None detected			2	15	13 (3.7 to 37.9)
Pancreas	67	93	72.0 (62.2 to 80.1)	0	2	0.0 (0.0 to 65.8)
Sarcoma	None detected			0	2	0.0 (0.0 to 65.8)
Thyroid	None detected			1	5	20 (3.6 to 62.4)
Other	None detected			2	2[b]	100 (34.2 to 100)

Abbreviations: MCED = multi-cancer early detection.
[a] Number of people with a true positive (+) MCED test and total number of people diagnosed with cancer in the study (i.e., true positives and false negatives of the MCED test), sensitivity is % and 95% confidence interval calculated from other reported data; [b] other cancer types were appendix (n=1) and unknown carcinoma (n=1).

Table 17 Number and proportion of cancers detected by the SPOT-MAS test

Study	Nyugen 2023 (case-control)[64]			K-DETEK (cohort)[8]		
Test accuracy[a]	**MCED test (+)**	**Total cancers**	**Sensitivity**	**MCED test (+)**	**Total cancers**	**Sensitivity**
Overall	173	239	72.4 (66.3 to 78.0)	6	6	100 (54.1 to 100)
Breast	33	67	49.3 (37.7 to 60.9)	1	Not reported	
Colon/Rectum	44	53	83.0 (70.8 to 90.8)	None detected		
Gastric	19	31	61.3 (43.8 to 76.3)	1	Not reported	
Liver/Bile-duct	83	91	91.2 (83.6 to 95.5)	3	Not reported	
Lung	36	43	83.7 (70.0 to 91.9)	None detected		
Other	None detected			1[b]	Not reported	

Abbreviations: MCED = multi-cancer early detection.
[a] Number of people with a true positive (+) MCED test and total number of people diagnosed with cancer in the study (i.e., true positives and false negatives of the MCED test), sensitivity is % and 95% confidence interval calculated from other reported data; [b] other cancer type was endometrial (n=1).

Table 18 Number and proportion of cancers detected by the TruCheck, CDA and AICS tests

Test / Study	TruCheck (Ranade 2021 [cohort study])[9]			CDA (Xie 2022 [PPCS cohort study])[10]			AICS (Mikami 2019 [cohort study])[11]		
Test accuracy[a]	**MCED test (+)**	**Total cancers**	**Sensitivity**	**MCED test (+)**	**Total cancers**	**Sensitivity**	**MCED test (+)**	**Total cancers**	**Sensitivity**
Overall	9	10	90.0 (55.5 to 99.7)	4	10	40.0 (12.2 to 73.8)	NA[b]	NA[b]	NA[b]
Breast	4	Not reported		0	1	0.0 (0.0 to 79.0)	9	31	29.0 (16.1 to 46.6)
Colon/Rectum	1	Not reported		1	1	100 (20.7 to 100)	8	28	28.6 (15.3 to 47.1)
Gallbladder	None detected			0	1	0.0 (0.0 to 79.0)	None detected		
Oesophagus	1	Not reported		None detected			15	29[c]	51.7 (34.4 to 68.6)
Stomach	None detected			1	2	50.0 (9.5 to 90.5)			
Kidney	None detected			0	1	0.0 (0.0 to 79.0)	None detected		
Lung	None detected			1	2	50.0 (9.5 to 90.5)	2	11	18.2 (5.1 to 47.7)
Ovary	1	Not reported		None detected			1	6[d]	16.7 (3.0 to 56.4)
Uterus				None detected					
Prostate	None detected			1	2	50.0 (9.5 to 90.5)	8	22	36.4 (10.3 to 57)
Unknown Primary	3	Not reported		None detected			None detected		

Abbreviations: AICS = AminoIndex Cancer Screening; MCED = multi-cancer early detection; NA = not available; PPCS = Prospective Population-based Cohort Study.
[a] Number of people with a true positive (+) MCED test and total number of people diagnosed with cancer in the study (i.e., true positives and false negatives of the MCED test), sensitivity is % and 95% confidence interval calculated from other reported data; [b] overall test performance statistics are not available for AICS test as each cancer targeted by the test is tested for separately; [c] gastric cancer; [d] ovarian / uterine cancer reported together.

APPENDIX 8. TEST PERFORMANCE OF GRAIL MCED TEST AND CANCERSEEK BY SUBGROUPS

Table 19 Test performance statistics of the refined MCED test (Galleri) in the PATHFINDER study by risk cohorts

	All patients	≥50 y With Additional Risk	≥50 y Without Additional Risk
Number analysed[a]	6369	3532	2837
Total cancers (n)	120	77	43
TP (n)	25	18	7
FP (n)	33	22	11
FN (n)	95	59	36
TN (n)	6216	3433	2783
Accuracy of the test, % (95% confidence interval)			
Sensitivity	20.8 (14.0 to 29.2)[b]	23.4 (14.5 to 34.4)[b]	16.3 (6.8 to 30.7)[b]
Specificity	99.5 (99.3 to 99.6)	99.4 (99.0 to 99.6)	99.6 (99.3 to 99.8)
PPV	43.1 (31.2 to 55.9)	45.0 (30.7 to 60.2)	38.9 (20.3 to 61.4)
NPV	98.5 (98.2 to 98.8)	98.3 (97.8 to 98.7)	98.7 (98.2 to 99.1)
First CSO correct	84.0 (65.3 to 93.6)	88.9 (67.2 to 96.9)	71.4 (35.9 to 91.8)
First or second CSO correct	88.0 (70.0 to 95.8)	88.9 (67.2 to 96.9)	85.7 (48.7 to 99.3)

Abbreviations: CSO = cancer signal origin; FN = false negatives; FP = false positives; MCED = multi cancer early detection; NPV = negative predictive value; PPV = positive predictive value; TN = true negatives; TP = true positives.

[a] Complete analysis set, those who received the MCED test, with follow-up information and/or diagnostic resolution, [b] values calculated from other reported data.

Table 20 Test performance by age and ethnicity in the CCGA substudy 3 of GRAIL MCED test and Cohen 2018 study of CancerSEEK

Test performance % (95% CI)[a]	CCGA substudy 3 (case-control)[31]					Cohen 2018 (case-control)[33]				
	MCED tests (+)	Total cancers	Sensitivity	Specificity	First CSO accuracy	MCED tests (+)	Total cancers	Sensitivity	Specificity	First CSO accuracy
Overall	1453	2823	51.5 (49.6 to 53.3)	99.5 (99.0 to 99.8)	88.7 (87.0 to 90.2)	626	1005	62.3 (59.3 to 65.3)	99.1 (98.5 to 99.8)	67.7 (64.0 to 71.3)
< 50 years	21	385	55.1 (50.1 to 60.0)	99.8 (98.6 to 100.0)	87.1 (81.9 to 91.0)	85	152	55.9 (48.0 to 63.6)	99.7 (98.3 to 99.9)	63.5 (52.9 to 73.0)
≥ 50 years	1241	2438	50.9 (48.9 to 52.9)	99.4 (98.6 to 99.7)	89.0 (87.1 to 90.6)	541	853	63.4 (60.1 to 66.6)	98.7 (97.3 to 99.4)	68.4 (64.4 to 72.2)
≥ 65 years	725	1331	54.5 (51.9 to 57.2)	99.4 (97.9 to 99.8)	88.5 (86.0 to 90.7)	299	475	62.9 (58.5 to 67.2)	98.6 (95.9 to 99.5)	66.6 (61.0 to 71.7)
50 – 79 years	Not reported					494	775	63.7 (60.3 to 67.1)	99.1 (97.7 to 99.7)	66.8 (62.5 to 70.8)
White[b]	1193	2316	50.5 (48.4 to 52.5)	99.6 (99.0 to 99.8)	Not reported	365	675	54.1 (50.3 to 57.8)	98.5 (96.5 to 99.4)	72.6 (67.8 to 76.9)
Hispanic (all races)	121	192	63.0 (56.0 to 69.5)	98.1 (93.2 to 99.5)	Not reported	1	1	100 (20.7 to 100)	100 (96.9 to 100)	100 (20.7 to 100)
Black[b]	104	193	53.9 (46.8 to 60.8)	100 (95.7 to 100)	Not reported	11	14	78.6 (52.4 to 92.4)	98.7 (95.4 to 99.6)	63.6 (35.4 to 84.8)
Unknown	34	65	52.3 (40.4 to 64.0)	100 (89.6 to 100)	Not reported	7	14	50 (26.8 to 73.2)	100 (98 to 100)	71.4 (35.9 to 91.8)
Other	25	57[c]	43.9 (31.8 to 56.7)	100 (89.6 to 100)	Not reported	239	323[d]	70.4 (68.9 to 78.5)	100 (85.1 to 100)	60.3 (53.9 to 66.2)

Abbreviations: CCGA = Circulating Cell-free Genome Atlas; CI = confidence interval; CSO = cancer signal origin.

[a] Number of people with a true positive (+) MCED test and total number of people diagnosed with cancer in the study (i.e., true positives and false negatives of the MCED test), sensitivity, specificity and first CSO accuracy are % and 95% CI, calculated from other reported data in Klein 2021,[31] Tang 2023 (CCGA substudy)[47] and Cohen 2018 (Table S4 and S10)[33]. Some categories of ethnicity combined compared to those reported in the original study reports, to align subgroups across the two tests, [b] non-Hispanic; [c] includes American Indian or Alaska native, Asian, native Hawaiian or Pacific islander; [d] Asian.

APPENDIX 9. GRIPP2 SHORT FORM TABLE

Section and topic	Item	Reported on page No
1: Aim	Report the aim of PPI in the study	24-25 – Stakeholder involvement
2: Methods	Provide a clear description of the methods used for PPI in the study	24-25 – Stakeholder involvement
3: Study results	Outcomes - Report the results of PPI in the study, including both positive and negative outcomes	55-59 – Stakeholder Engagement 60-61 – Patient and Public Involvement
4: Discussion and conclusions	Outcomes - Comment on the extent to which PPI influenced the study overall. Describe positive and negative effects	4 – Abstract 10 - Plain language summary 11-12, 15-16 - Scientific summary 24-25 – Stakeholder involvement 55-59 - Stakeholder Engagement 63, 67 – Discussion 69-70 - Conclusion
5: Reflections/critical perspective	Comment critically on PPI input in the study, reflecting on the things that went well and those that did not, so others can learn from this experience	60-61 - Patient and Public Involvement