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Extended Research Article

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

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Scientific summary

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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) from multiple cancers in the blood.

The use of a MCED test as a screening tool in a 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. A 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 offer no improvement in mortality or health-related quality of life (HRQoL). In addition, screening of healthy people for 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Published and unpublished prospective clinical trials and cohort studies of blood-based MCED tests for screening were sought.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 tests for assessing prognosis or therapeutic decision-making in patients with cancer were not eligible for inclusion.

The target population was individuals aged 50–79 years without clinical suspicion of cancer and who had not been diagnosed with, or received treatment for, cancer within the last 3 years. As insufficient 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 for study characteristics was developed and piloted. Data on the intervention(s), participant characteristics, setting, study design, reference standard test(s) used and relevant outcomes were extracted by one reviewer and independently checked by a second. Accuracy data were extracted on a case-by-case basis due to reporting differences. Risk of bias and applicability were assessed using the quality assessment of diagnostic accuracy studies (QUADAS-2) 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 8069 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 13 MCED tests or technologies, met the inclusion criteria: 1 ongoing randomised controlled trial (RCT), 13 completed cohort studies, 17 completed case-control studies, 4 ongoing cohort studies and 1 ongoing case-control study. Studies assessed the following MCED tests: Galleri® (GRAIL, Menlo Park, CA, USA), CancerSEEK (Exact Sciences, Madison, WI, USA), SPOT-MAS™ (Gene Solutions, Ho Chi Minh City, Vietnam), Trucheck™ (Datar Cancer Genetics, Bayreuth, Germany), CDA (Cancer Differentiation Analysis; AnPac Bio, Shanghai, China) and AICS® (AminoIndex Cancer Screening; Ajinomoto, Tokyo, Japan). MCED technologies that were at an unclear stage of development and did not appear to be available for use were also included: Aristotle® (StageZero Life Sciences, Richmond, Ontario), CancerenD24 (unknown), OncoSeek® (SeekIn Inc., San Diego, CA, USA), SeekInCare® (SeekIn Inc., San Diego, CA, USA), OverC™ (Burning Rock Biotech, Guangzhou, China), Carcimun test (Carcimun Biotech, Garmisch-Partenkirchen, Germany) and SpecGastro (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 3 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 multi-cancer early detection tests available for use

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 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 tests in participants with a negative MCED (index) test result.

Only one study was undertaken in the UK, in individuals with suspected cancer, so not reflective of the target 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 were not well reported. There were also concerns about the applicability of CancerSEEK, which has since been modified (now called Cancerguard™) and is undergoing further assessment. The applicability of Screening for the Presence Of Tumour by Methylation And Size (SPOT-MAS), Trucheck, CDA and AICS 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 reported below [95% confidence interval (CI) shown in brackets] are not directly comparable across different MCED tests, owing to differences in the number of cancer types each test can detect:

Galleri (three 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 (two 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 (two 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 (one study)
Sensitivity: 90.0% (55.5% to 99.7%)
Specificity: 96.4% (95.9% to 96.8%)
CDA (one study)
Sensitivity: 40.0% (12.2% to 73.8%)
Specificity: 97.6% (96.8% to 98.2%)

AminoIndex Cancer Screenings for individual cancers separately; sensitivity ranged from 16.7% (3.0% to 56.4%) for ovary/uterus cancer to 51.7% (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 (stages I–II) compared with later stage cancers (stages III–IV). Among the Galleri studies, sensitivity for detecting stages I–II cancer ranged from 27.5% (25.3% to 29.8%) to 37.3% (29.8% to 45.4%) and sensitivity for detecting stages 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 stages I–II cancer of 12.7% (6.6% to 23.1%) and sensitivity for detecting stages III–IV cancer of 53.1% (36.4% to 69.1%).

One Galleri study 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 available 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 CDA, where sensitivity for detecting cancers without a current screening programme available was lower than for cancers with a current screening programme in the UK. One study of Galleri had high sensitivity for detecting lung cancer, leading to opposing findings depending on whether lung cancer was considered to be covered by existing available screening programmes or not.

Subgroup results by participant demographic characteristics

One study each of Galleri and CancerSEEK reported MCED test performance by pre-specified subgroups of interest (age, sex and ethnicity). For CancerSEEK, sensitivity was slightly lower for participants under 50 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 lowest (43%) for the small number of participants classified as 'Other' ethnicity. 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; sensitivity of 100%). One study using an earlier version of the Galleri test reported results by age and sex for a subset of 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. For an earlier version of the GRAIL test, the time to diagnostic resolution was shorter for those with a true positive result compared to false-positive results.

Studies of multi-cancer early detection technologies at an unclear stage of development

Risk-of-bias assessment identified substantial concerns. Most studies were case-control, 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.

Comments on the draft report noted that important details about the potential benefits, harms and 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 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. Balancing test accuracy and cost with the likelihood of improving outcomes for NHS patients was considered critical. Focusing MCED screening only on high-risk groups, or on cancers with genuine treatment and prognosis improvement potential, particularly those not currently covered by existing screening programmes was discussed.

Conclusions

Limited evidence is available on the potential for early detection of treatable cancers, and the consequences of introducing screening with a 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, 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 a MCED test is to correctly classify people without 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 (stages I–II). Sensitivity also appeared to vary substantially for different cancer sites, although results are limited by small patient numbers for some cancers. The sensitivity of most 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. While some differences were observed by ethnicity, these results should be interpreted with caution as most participants recruited were white and the 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, had a high risk of bias and high or unclear applicability concerns.

No meaningful results were reported relating to patient-relevant outcomes, such as mortality, potential harms, HRQoL, acceptability or satisfaction. Time to diagnostic resolution was long, particularly for patients with false-positive results, which can lead to substantial burden on healthcare resources as well as psychological burden on individuals.

Recommendations for research

Randomised controlled trials 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 overtreatment and cost-effectiveness of implementing MCED tests for screening in the UK.

Study registration

This study is registered as PROSPERO CRD42023467901.

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