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Screening for many types of cancer with a single blood sample – too good to be true?

PERSPECTIVES

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Better cancer screening is important for public health, but the enthusiasm surrounding multicancer early detection (MCED) tests should be tempered.

The prognosis for many cancer patients has improved considerably in the last few years, in part as a result of better prevention and early detection. Nevertheless, cancer still accounts for over 20 % of deaths in many Western countries, including Norway (1).

Norway has population-based breast cancer and cervical cancer screening programmes for women. A bowel cancer screening programme has recently commenced for both women and men (2), and the introduction of lung cancer screening for smokers is also under consideration (3). All current screening tests (mammography for breast cancer, pap smear for cervical cancer, stool test for bowel cancer and low-dose CT for lung cancer in smokers) are designed to find cancer in one organ. Together, these four types of cancer make up approximately 50 % of all cases of cancer in Norway (4). There are as yet no good screening tests for the remaining 50 %.

A revolution in cancer screening?

A new approach to cancer screening has recently been introduced, multi-cancer early detection (MCED) testing. MCED tests simultaneously screen for cancer in multiple organs with a single sample of peripheral blood. Several companies in the US, Europe and Asia are working to develop MCED tests, and there are high hopes for the technology (5). Billions of investment funds are contributing to an expectation that MCED tests will revolutionise cancer screening. It is hoped that this testing can be easily integrated into primary healthcare, increase participation in cancer screening and perhaps lead to prevention of all deaths from cancer.

A recent study of 6,700 women in the US showed that a new MCED test had a specificity of 99 % for cancer in various organs (6). However, the test only had a sensitivity of 18 % for stage I tumours and 43 % for stage II tumours. Patients with a positive MCED test result had to undergo extensive investigations, including PET scans, to find possible tumours and their location in the body. The patients were followed up for one year after MCED testing. Of 96 cancers incident during the follow-up period, only 26 were found in the MCED testing, with the rest being diagnosed on the basis of clinical symptoms or routine screening tests.

Another recent study with 7,000 patients aged 50 years or older also demonstrated specificity of over 99 % for a different MCED test (7), but the positive predictive value was only 38 %. The MCED test only detected 35 of the 121 diagnosed cancers, and conventional screening tests would have detected 29 of these 35.

Criticism from international journals

The Galleri test, made by the company Grail in California, is already commercially available in the US. It is sold online directly to anyone who wants it for NOK 12,000 [GBP 888] per test. The company recommends repeating the test each year, although the basis for this recommendation is unclear (7). Like some other MCED tests, it detects circulating cell-free DNA (cfDNA) from tumours in peripheral blood (8). When a cancer signal is detected, the test should be able to say which organ is the most likely origin of the cancer, and

thus should be able to facilitate targeted investigation to locate the tumour. Exactly how the tests do this is protected by patents, and publicly available information is limited (8). There is still a lack of clarity about the best follow-up for patients who receive a positive result for the 50 types of cancer covered by the test.

An ongoing trial with the Galleri test from the market leader Grail has received much attention in the international scientific literature and media (9–11). The trial was lauded as a game-changing collaboration between the National Health Service (NHS) in the UK and the manufacturer Grail, and has enrolled more than 140,000 healthy volunteers in England (9). Patients were randomised to either MCED testing or cancer screening with current methods. The trial's primary outcome measure is not cancer mortality, but stage distribution of newly diagnosed cancers as a surrogate outcome measure. The hypothesis is that more tumours in the MCED group will be diagnosed at an earlier stage. The trial is estimated to cost over NOK 2 billion [GBP 150 million], which is being financed by Grail. Provisional results were expected to be available last year, but have not been published yet. Neither the NHS nor the company has clarified the status of the trial. This has drawn criticism in The Lancet and BMJ (10, 11).

It recently became known that the directors of Grail have been accused of manipulating share prices and forcing out critics of the test (11). Donald Berry, a leading US expert on cancer screening, was asked to leave Grail's expert panel and told the journal Cancer Letter: 'It was like a cult, with sceptics banned. They arranged to talk to and to listen to people who had drunk the Kool-Aid.' (12) The Norwegian oil fund is a part owner of Grail, but has not made a statement about the matter (13).

Six times higher rate of detection

The premise for MCED testing is appealing. Detecting multiple types of cancer with a single blood sample is almost too good to be true. One modelling study has estimated that MCED testing can increase early detection rates of cancer in the US from 100,000 to 600,000 cases per year (14). But there are many reasons for scepticism.

> ***«Detecting multiple types of cancer with a single blood sample is almost too good to be true»***

MCED tests are less sensitive for early-stage cancer than many of the current screening tests. Population screening for cancer is effective because it detects cancer at an early stage, and even detects precursors of some types of cancer. However, MCED tests are very poor at detecting precursors to cancer, such as polyps in the colon or cell changes in the cervix. Recent studies have produced disappointing results for cancer testing in peripheral blood compared with current methods of bowel cancer screening (15). It is not known whether the same applies for MCED testing.

«The increased sensitivity of MCED tests will lead to more overdiagnosis and cause more harm than the present screening tests»

More overdiagnosis?

We are concerned that MCED screening will lead to increased overdiagnosis of cancer. Overdiagnosis occurs when a screening test detects cancer that would not have caused disease or death in patients without screening (16). It is estimated that 25 % of breast cancer detected in mammography and 50–60 % of prostate cancer detected in prostate-specific antigen (PSA) screening is already overdiagnosed with the current tests. The increased sensitivity of MCED tests and the need for extensive radiological investigations following a positive test result will lead to more overdiagnosis and cause more harm than the present screening tests.

The ideal screening test has high sensitivity and specificity. High sensitivity maximises detection of patients with cancer, while high specificity means that there are few false positive results. However, test performance and pre-test probability of disease must be considered together. The incidence of cancer in a 60-year-old person in Norway is approximately 1.5 %. This means that 98.5 % of men aged 60 years do not have cancer when screened. Even though an MCED test can detect most types of cancer, with almost perfect specificity it will give false positive results in 50 % of individuals. The costs, side effects and complications associated with the extensive follow-up of positive MCED tests are high, which will cause considerable concerns for patients and relatives.

Good decisions are based on good knowledge

The early MCED studies illustrate complex issues regarding study outcome measures, duration and conflicts of interest. The industry-financed NHS trial selected change in cancer stage as the primary outcome measure, and it was argued that earlier detection of the same type of cancer tends to result in a better prognosis. However, this assumption does not apply to all types of cancer, for example liver or pancreatic cancer. Patients in the NHS trial are only followed up for 1–2 years. Better outcome measures would have been cancer incidence and mortality over a 10-year period, which are required for other screening tests. We believe it is worthwhile conducting good studies. The potential drawbacks are too great to take shortcuts (17). To date, no randomised trials have been conducted to investigate whether MCED testing leads to reduced mortality from cancer.

Unanswered questions

There are many unanswered questions about MCED tests, and some scepticism is warranted. We do not know whether these tests will replace or supplement current screening tests. It is unknown how often they should be repeated and who might need to be screened. It is unclear what follow-up patients with positive MCED test results require, and what to do about those patients who test positive but in whom no cancer is found. It is also not known how much more overdiagnosis MCED screening will lead to.

MCED tests are attractive, and there is a great deal of enthusiasm for the new opportunities offered by liquid biopsy technology. Yet we should be cautious until randomised trials with cancer incidence and mortality as outcome measures are available.

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