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BMJ INVESTIGATION

Galleri promises to detect multiple cancers—but new evidence casts doubt on this much hyped blood test

A blood test being trialled in large numbers of people in England is facing mounting evidence against its implementation as a screening tool for early cancer. Margaret McCartney and Deborah Cohen investigate

Margaret McCartney, [1] Deborah Cohen[2]

Big promises have been made for the Galleri blood test, which its maker, the Californian biotechnology company Grail, says is capable of detecting more than 50 types of cancer. Harpal Kumar, president of Grail Europe, has hailed the test as a "groundbreaking and potentially life-saving advance that could have a tremendous human and economic benefit."

Video 1 Deborah Cohn explains why politicians should be wary of bypassing NHS evaluations

The NHS is currently running a £150m trial of the test, involving more than 100 000 participants in England. Depending on the results, the plan is to roll out a further pilot involving up to one million tests.[1 2] If effective, the test would help the NHS meet its target to diagnose 75% of cancers at an early stage by 2028. Trial success would also hand Grail a lucrative deal; although contract details remain confidential, a single test in the US currently retails for $950 (£750; €880).

Multicancer early detection tests such as Galleri are touted as a game changer. Instead of screening for one disease at a time, as the NHS does for breast, bowel, and cervical cancer, for example, technology now exists that has the potential to test for dozens of cancers from a single blood sample.

But experts believe that Galleri has been overhyped and that the current trial is unethical. Concern is mounting over why this particular new screening test has been selected, how it is being evaluated, and whether the bar to success has been set too low.

New evidence

Documents leaked to *The BMJ* indicate that the criteria being used, unpublished until now, are unsuitable to justify a new national screening programme aimed at saving lives.

They show that even Mike Richards, the chair of the independent UK National Screening Committee, has privately voiced "serious concerns" to Amanda Pritchard, NHS England's chief executive, about the trial and its ability to provide sufficient evidence "on whether the benefits of testing outweigh any potential harms and at reasonable cost."

Other documents obtained by *The BMJ* detail the deal between the NHS and Grail, raising questions about whether it is too industry friendly. As well as agreeing to buy one million tests after satisfactory completion of the first stage of the trial,[1] the NHS has committed itself to buying five million more tests by 2030 if the test fulfils certain criteria, show documents seen by *The BMJ*. In return, Grail would build a "new state-of-the-art test processing and sequencing facility in the UK once the NHS commits to purchasing minimum annual volumes, keeping the UK at the global forefront of clinical application of genomics."[3]

Richard Sullivan, director of the Institute of Cancer Policy at King's College London, says that the Grail deal is a "clear cut case of public risk and private profit." He says, "It is following a pattern established in this country over the past decade where the regulatory or evidential bar is being set lower and lower in favour of the private sector, with the public sector (that is, our taxes) taking all the risk."

Added to these concerns, it emerged in June that Grail is facing a class action lawsuit in the US.[4] Embittered investors, faced with steep losses, claim that the company exaggerated Galleri's effectiveness to increase its share price. The plaintiffs claim it was "false and misleading" that the rollout would "save tens of thousands of lives." A Grail spokesperson told *The BMJ* that they "don't comment on ongoing litigation."

NHS trial: a mistake?

Experts also say it is unclear why an NHS trial is being done of a test that showed so little promise in earlier trials.

The test is one of several multicancer detection blood tests, or "liquid biopsies," on the market and uses sequencing technology to analyse DNA fragments circulating in the blood, also known as cell free DNA (cfDNA). These cfDNA fragments from cancer cells have specific "methylation patterns." Grail says that Galleri checks over a million methylation sites in DNA, using machine learning and artificial intelligence to detect whether someone is harbouring a cancer.

NHS England claims that the test can identify many cancers that "are difficult to diagnose early," such as head and neck, ovarian, and pancreatic cancers.

But some eight months before the NHS Galleri trial was announced in 2020, Grail published data showing that in patients already known to have cancer the test detected only 43.9% of stage I-III cancers.[5]

In 2021 another Grail funded study in *Annals of Oncology* found that the test sensitivity for stage I cancers was only 16.8%.[6] Many of the authors declared fees, patents, or stock holdings with the company.

These results are "strikingly low," says Clare Turnbull, professor of cancer genetics at the Institute of Cancer Research in London. "A good screening test would typically be anticipated to have high sensitivity for early stage cancers, as these are usually the cancers for which surgery would offer the patient a high likelihood of cure (or long term remission)," she adds.

Paul Pharoah, professor of cancer epidemiology at the Cedars-Sinai Medical Center, Los Angeles, agrees: "I do not think that the evidence was sufficiently strong to warrant the trial," he says. "With a sensitivity for stage I disease of less than 20% overall and only 44% for all stage I-III cancers diagnosed through other tests, I do not think a trial is ethical." He says it was unclear why "a trial of a test with such little promise" was done.

Some clues can be seen in emails obtained by *The BMJ* through freedom of information requests. On 15 October 2020 Illumina, the then parent company of Grail, emailed Nadhim Zahawi, a minister in the Department for Business, Energy and Industrial Strategy, requesting a meeting to discuss "this revolutionary technology" that could have "an incredibly positive impact on UK patients and for the UK economy."

The email referred to links that Grail and Illumina already had in the UK. Illumina's "world leading sequencing technology was invented in the UK," and Grail had a significant clinical trial programme with centres in London, it said.

It added, "We will continue to build on that foundation, and our other collaborations with the NHS, Genomics England, industry and academia to help realise the promise of the UK's recently published genomic strategy."

A government aide suggested that a meeting should be granted as "they are a big company that makes machines, it ticks the industry box." The deal, with a press release signalling the launch, occurred just six weeks later.

Sullivan says, "The oven ready alignment with the genomics community and the wider NHS England push in this area blinded [the government] to the wider considerations of whether this technology was in the public interest."

NHS England didn't respond to questions about why it didn't put a contract out to tender. Instead, a spokesperson said, "At the time of the agreement in 2020, Galleri was the only test for which a company was in a position to do a trial at sufficiently large scale."

Behind closed doors

The £150m NHS trial began screening participants in mid-2022, but its details have been marked by secrecy. It is generally considered good practice to have the trial protocol available for scrutiny before a trial starts and is publicly registered, with full details of how the trial is to be conducted and the outcome measures.

Clinicaltrials.gov records the start date of the trial as August 2021, but trial details were not uploaded until more than a year later, in October 2022. Funded by Grail, this prospective randomised controlled trial aimed to recruit 140 000 asymptomatic patients between 2021 and 2026. Participants make three visits to a mobile clinic over two years, with half having a Galleri test and half in the control group. The primary outcome measure was the absolute numbers of stage III and IV cancers diagnosed.[7]

Interim results of the trial were published in an NHS England blog at the end of May,[8] saying that NHS England "did not find them compelling enough" to proceed directly to the planned large scale pilot programme in July 2024.[9] Full details were not published. Instead, NHS England will wait for the final trial results, expected in 2026, before making any further rollout decision.

Documents obtained by *The BMJ* outline for the first time what the "success criteria" are that the trial needs to meet. The NHS has committed to buying a million tests if the Galleri test produces a positive predictive value (the proportion that gives true positives) of over 30%, a 30% reduction in stage IV cancers in the intervention arm, compared with the control arm, and a 75% higher number of cancers detected by Grail than in the control group.

Would these criteria mean "success" for patients? Turnbull says that just demonstrating a shift in the distribution or proportion of cancers presenting at different stages does not tell us whether or not this multicancer early detection tool is improving survival in patients with those cancers. She cites a recent meta-analysis across screening studies for various cancers showing that stage distribution largely does not predict survival.[10]

She adds, "Galleri's own data have shown that survival stage-for-stage is poorer for cancers detected by the Galleri-MCED [multicancer early detection] than for those not detected."[11] This is crucial, she says, because it may be that the supposedly early stage cancers that are detected by Galleri are ones that have already metastasised—and that the technology is demonstrating that it is better than imaging at detecting early metastasis.

Pharoah agrees. "There is the whole question of what would be the appropriate endpoint. With a multicancer detection test (multi-harm opportunity from overtreatment) I cannot see that anything other than all cause mortality is sufficient." When such a large section of the population is exposed to screening, even a small proportion of false positive testing can have a large effect on demand for imaging and diagnostic investigations, costs, and waiting lists, he adds.

There are other warnings that the Galleri test might fail to deliver on its promises. A 2023 *Lancet* study suggests that the test's sensitivity is even lower in a screening population than in previous trial populations.[11 12] In the Pathfinder study, conducted on asymptomatic patients in North America, 1.4% had a positive test, but 62% of these results turned out to be false positives.[12]

Box: NHS decision making over Grail's test

As the NHS Galleri trial continues, there are concerns over the close relationship between key government figures and its manufacturer, Grail.

In 2021, as president of Grail Europe, Harpal Kumar issued a summary of the partnership between Grail and NHS England.[3] This said that with "pivotal help from NHSE senior leadership, influential individuals/KOLs [key opinion leaders] and the AAC [accelerated access collaboration], we were able to persuade Grail leadership that the NHS is the best system globally in which to conduct such studies," with the promise of building a new facility and an "opportunity for UK plc."

Kumar is also a Grail shareholder and was knighted in 2016 while David Cameron was prime minister.

In 2018 Cameron was a paid adviser to Illumina, which spun off Grail in 2016 before finalising the reacquisition of it in 2020.

Freedom of information requests from *The BMJ* have shown that Cameron and Illumina staff met Nadhim Zahawi, then undersecretary of state for business and industry, in March 2021. Cameron is minuted as saying that in the NHS "our customers do not leave and join a new insurance business every couple of years. This means the data gained is invaluable, as you can look at a patient's data over their whole lifetime. This is a selling point of the UK which NZ [Nadhim Zahawi] may wish to

emphasise." At the same meeting, it was planned that "Illumina will keep NZ involved in UK investment in R+D so they can be part of the UK life science success stories."

Disquiet

Usually, decisions on what constitutes cost effective NHS screening are made by the independent UK National Screening Committee. Freedom of information requests by *The BMJ* have revealed major disquiet expressed between UK NSC and NHS England regarding Grail.

In September 2023 UK NSC members wrote to NHS England saying that they would recommend evaluating how well the test worked outside a trial only when there was "a fair degree of confidence that the major screening questions (eg test accuracy, diagnosis, treatment, acceptability, ethics) are answered or there is strong reason to believe they would meet the criteria. The Grail test is well short of most of these, so the UK NSC would have been very unlikely to recommend large scale programmatic evaluation without more basic research."

In February 2024 Mike Richards, chair of UK NSC, wrote to Amanda Pritchard, chief executive of NHS England, with "serious concerns." He said that if the trial led to a rollout of a "million tests" the committee recommended the need for a control group, with research ethics approval, but "unfortunately, those responsible within NHSE for this phase of the programme have declined to take our advice on this."

As a result of all these failings, Richards said, the UK NSC might be unable to make a recommendation about the rollout of Galleri at the end of the project.

An NHS England spokesperson, however, says that they believed that Grail was "now being subjected to one of the largest and most rigorous investigations done in any healthcare system worldwide," that no decision had been made, and no further details were available.[8]

By contrast, an NHS England source speaking to *The BMJ* under the condition of anonymity said, "The clinical or scientific data doesn't stack up, but that should have come first. This is not the way to do a trial—it should be done transparently. It's not been thought through at all."

Open door to industry

Concern over the decision making process around Grail serves as a timely reminder to the new health and social care secretary, Wes Streeting, who recently stated his aim is to make the UK a "life sciences and medical technology powerhouse." He said, "By ensuring the NHS works hand in hand with life sciences research institutions and medical technology companies, the government will drive the development of new treatments and help grow the industries."[13]

But while an open door policy to industry might be one thing, it does not mean open standards, says Richard Sullivan, director of the Institute of Cancer Policy at King's College London. "The new government needs a more rigorous and transparent way of reviewing med tech clinical research, especially when it involves such widespread access to NHS resources," he says. "They also need to change their language. It's all promissory science and hype. This serves no public good whatsoever."

Competing interests: MM was on the steering committee for the Evidence Based Early Diagnosis conference in 2024 at the University of St Andrews.

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