Medical News & Perspectives

Questions Swirl Around Screening for Multiple Cancers With a Single Blood Test

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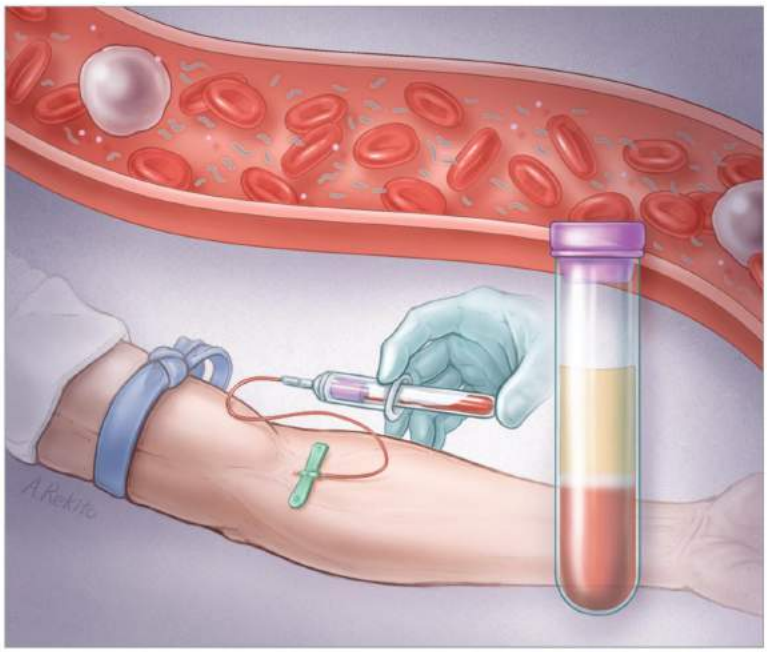
It sounds almost too good to be true: a single blood test that can detect 50 different cancers or more before any symptoms appear.

But this is not science fiction. At least 2 multicancer detection (MCD) blood tests, also called multicancer early detection tests, are already on the US market, and many more are in development.

Such tests are designed to detect circulating tumor cells, cell-free tumor DNA, proteins, and other biomarkers that suggest cancer might be present somewhere in the body. However, what the results of MCD tests mean and how they should be used is not yet clear.

Medical News website



Cancer is the leading cause of death worldwide and is second only to heart disease in the US. Only 5 cancers—colorectal, lung, breast, cervical, and prostate—have recommended screening methods, at least for some populations. Malignancies that lack population screening methods are expected to account for about half of new cancer diagnoses this year, according to the American Cancer Society.

Interest in a multicancer screening test that could detect many of the approximately 200 other types of malignancies at an early stage is booming among consumers, policymakers, lawmakers, physicians, and scientists.

"Like anything in medicine, there are a lot of unknowns, but I think this is incredibly exciting," gastroenterologist Anne Marie Lennon, MD, PhD, who recently became chair of medicine at the University of Pittsburgh Medical Center, said of MCD tests. Lennon previously was on the faculty at Johns Hopkins, where she codeveloped an MCD test that isn't yet on the market.

The assays are meant to complement available screening for common cancers, not replace it. And as their developers emphasize, MCD tests don't diagnose cancer. As with conventional cancer screening methods, a positive MCD test identifies individuals who need further evaluation to determine whether they have cancer, while a negative MCD test doesn't necessarily mean cancer isn't lurking somewhere.

"From the consumer perspective, these [MCD] tests are going to be very attractive," Robert Volk, PhD, a decision scientist at the MD Anderson Cancer Center, told *JAMA* in an interview. "It's a single blood test. It's easy to do."

Drawing a tube of blood may be easy. What comes after that is not.

"It's safe to say that the technology is not well enough developed to be marketed," Ruth Etzioni, PhD, a biostatistician at the Fred Hutchinson Cancer Center's Public Health Sciences Division, said in an interview.

In fact, the 2 tests that have been commercialized in the US have not yet been approved or cleared by the US Food and Drug Administration (FDA). They are marketed as laboratory developed tests (LDTs), a category over which the FDA has exercised enforcement discretion for nearly half a century. The agency hasn't enforced applicable regulatory requirements, specifically the demonstration of safety and effectiveness, for the majority of LDTs. Most laboratories that offer LDTs follow only the regulatory requirements of the Clinical Laboratory Improvement Amendments, which are intended to regulate their operations but not their tests.

"While these tests have the potential to improve care in selected indications, this must be proven, as they will add cost, complexity, and unintended adverse effects for patients," concluded a recent *JAMA Internal Medicine* review article about the use of tests to detect tumor DNA in a variety of situations, including MCD tests for population screening.

The Galleri MCD assay has not yet been greenlighted by the FDA, but more than 150 000 tests have been sold in the US and Canada since its commercial launch 2 years ago, according to Grail, the Menlo Park, California, company that developed and markets it. The company has also partnered with HCA Healthcare, the largest

US health system, which is providing the Grail MCD test at select physician practices. In addition, Grail has established a network of more than 9000 prescribers in private practice across the US.

"[T]his is an opportunity to be at the forefront of a new age of cancer screening," Chris Ott, MD, chief medical officer at HCA Healthcare Physician Services, said in a Grail press release last October.

However, there is still much uncertainty about the harms and benefits of MCD tests, suggesting that the forefront might not necessarily be the best place to be. Do MCD tests lead to improved cancer prognoses? Do they uncover tumors that were better left undetected? And do they cause unnecessary anxiety or provide false reassurance?

Setting the Stage

At least 3 MCD tests have a head start toward FDA approval or clearance.

The agency has designated the Grail test as well as MCD tests developed by Geneseeq, a Canadian company, and Burning Rock, based in Irving, California, as breakthrough devices, according to the companies. As the FDA puts it, breakthrough devices "provide for more effective treatments or diagnosis of life-threatening or irreversibly debilitating diseases or conditions," justifying priority review by the agency.

The Gaithersburg, Maryland, company, 20/20 GeneSystems, that makes OneTest, the other MCD test available to buy in the US market, does not plan to seek FDA approval until it collects real-world data about its accuracy in detecting cancer from a statistically significant number of people, according to its website.

Last November, the FDA convened a meeting of the Molecular and Clinical Genetics Panel of its Medical Devices Advisory Committee to make recommendations on the design of MCD tests, including what end points could help assess probable risks and benefits.

And MCD tests are a major focus of the new Cancer Screening Research Network launched by the National Cancer Institute (NCI) in January of this year.

"The Cancer Screening Research Network is geared toward studying a variety of different technologies for the purpose of cancer screening," oncologist Lori Minasian, MD, deputy director of the NCI's Division of Cancer Prevention, explained in an interview. "Not every cancer sheds into the blood. There are some cancers that could be detected better in urine or sputum or breathalyzers."

One of the first projects of the network, a central component of the Biden administration's Cancer Moonshot, is the Vanguard study. This year, the study will begin enrolling 24 000 people aged 45 to 70 years to test 2 MCD assays and help lay the groundwork for a much larger randomized trial.

Vanguard will not be comparing the tests with each other, Minasian noted. "We're not expecting a winner," she said. "We're expecting to better understand how to use these assays."

Minasian said she couldn't yet discuss which MCD assays will be tested in Vanguard. In interviews with *JAMA*, 20/20 GeneSystems Chief Executive Officer Jonathan Cohen said his company hopes that its test will be selected for Vanguard, while Grail President Joshua Ofman, MD, MSHS, said his company isn't interested in participating. "We have so much more data already," Ofman explained.

The 20/20 GeneSystems MCD test was developed using data from Taiwan, Chief Science Officer Michael Lebowitz, PhD, said in an interview. Physicians in that country have been offering tumor marker testing as part of annual physical examinations for a few years, Lebowitz said, and his company has had access to a database of information about the testing in 27 000 individuals.

Real-world data might not be enough to earn the FDA's blessings, though. At last November's FDA advisory committee meeting, panelists concluded that real-world data and evidence should be used to support clinical validation of MCD tests only in select situations, such as postmarket settings. Instead, the panelists advised that randomized trials be conducted to validate MCD tests.

At press time, the Grail test, which claims to detect more than 50 cancers, cost $949. The standard 20/20 GeneSystems test, which claims to detect more than 20 cancers, costs $189; a premium version, which tests for additional biomarkers, was available for $269; shipping for either 20/20 GeneSystems test was an additional $29.99.

Currently, neither public nor private insurance plans pay for MCD tests. Medicare covers screening tests only if the US Preventive Services Task Force recommends them with a grade "A" or grade "B," which isn't the case for either of the tests on the market. "Right now the evidence is nowhere near supporting a grade 'A' or grade 'B' recommendation" for MCD tests, Volk noted.

That issue might become moot. Legislation with broad bipartisan support has been introduced in the Senate and the House of Representatives that would give Medicare more leeway in covering MCD tests. The bills would authorize the federal insurance program for people aged 65 years or older to begin covering annual MCD tests as soon as the FDA approves or clears them, without waiting for the task force to deem them worthy.

Meanwhile, Grail announced last November that it is teaming with the Centers for Medicare & Medicaid Services to conduct a real-world study of the clinical impact of its test in as many as 50 000 Medicare beneficiaries. Medicare will cover the cost of the test and related and routine services for study participants, according to Grail. Trial participants will be compared with matched beneficiaries who received usual care but no testing.

Shifting the Stage

Research has shown that the recommended population cancer screening tests reduce mortality.

But no studies have been conducted to determine whether MCD tests lower cancer deaths. "We always have this mantra: it's got to show that it reduces cancer mortality," Etzioni, a member of the American Cancer Society's panel on cancer early detection, said of cancer screening.

Developers argue that clinical trials with a mortality end point would be impractical. Such studies would require 15 to 20 years and a million participants to answer that question, Grail's Ofman estimated. By the time such trials ended, he noted, the technology they evaluated would be obsolete.

That kind of thinking doesn't sit well with Philip Castle, PhD, MPH, director of the NCI's Division of Cancer Prevention and a member of the FDA's Medical Devices Advisory Committee.

After all, the reason to screen is to reduce cancer incidence or cancer-related mortality, Castle pointed out at last November's advisory committee meeting about MCD tests. "[W]e believe that mortality has to be the end point—cancer-specific mortality," he told his fellow panelists, who did not all agree. "And for many cancers, there is not

a proven surrogate end point that has been shown to correlate with mortality benefit."

Castle's colleague Minasian was more optimistic that questions about MCD tests' harms and benefits could be answered with shorter-term outcomes. "If we design the studies well...there will be an opportunity to look at markers that could be used for surrogates for mortality," she told *JAMA*.

Ofman and others have proposed that demonstrating MCD tests lead to earlier-stage cancer diagnoses is a reasonable surrogate for mortality. Earlier diagnosis alone benefits patients because it affords a better quality of life and less toxic therapies, Ofman said.

"Insisting on definitive proof of mortality benefit may have deadly consequences," 20/20 GeneSystems' Cohen said. "Many Americans may die unnecessarily."

In an August 2023 article, a group of authors with financial ties to Grail or other MCD test developers called for more efficient randomized trials. These trials would possibly have "alternative primary endpoints to complement cancer mortality...so that populations can benefit sooner if such tests are shown to be effective," they wrote.

Grail has organized and is funding a trial with the UK's National Health Service (NHS) to determine whether its test leads to earlier cancer diagnoses. Over just 10 months in 2021 and 2022, Ofman noted, the trial reached its goal of enrolling more than 140 000 people aged 50 to 77 years. Those randomized to screening will receive the Grail test annually for 3 consecutive years. Grail is supplying the tests, while the NHS is providing follow-up care when needed.

Results won't be known for a couple more years, at which point Grail will make its final submission to the FDA to support its application for approval, Ofman said. The NHS has said that it is committed to buying up to 1 million Grail tests if the initial trial results are promising. However, the health service hasn't explained how it would define promising results.

In the public hearing portion of the November FDA meeting, Etzioni noted that earlier detection doesn't always translate to reduced cancer mortality.

She pointed to the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), which enrolled approximately 202 000 postmenopausal women from the general population. Like previous ovarian cancer trials, UKCTOCS used a combination of the biomarker CA-125 in blood and transvaginal ultrasound. Participants were randomly assigned to annual CA-125 screening with transvaginal ultrasound as a second-line test, annual transvaginal ultrasound alone, or no screening.

After an average follow-up period of 11 years, no significant reduction in ovarian cancer mortality rates was seen in either of the screened groups compared with the no-screening group, the researchers reported in 2021.

"We need a screening strategy that can detect ovarian and tubal cancer in asymptomatic women even earlier in its course and in a larger proportion of women than the tests used in the trial," the authors concluded. "Meanwhile, our results emphasize the importance of having ovarian and tubal cancer mortality as the primary outcome in screening trials."

Experience is lacking in the use of downstaging—detecting cancers at an earlier stage—as an end point in screening trials, Etzioni said. "It's not known how much of a reduction in late-stage cancers is enough to make a difference in cancer mortality rates," she explained. In 2022, Etzioni coauthored a modeling study that concluded that stage shift appeared to be an unreliable predictor of mortality reduction for all the cancers that could be detected with MCD tests.

When Grail reports the findings of its UK trial, "there could be very positive headlines that there was a 10% reduction in advanced stage cancers," Etzioni noted. "We really don't know what that means. We don't even know whether to call that a success or not."

Positive or Negative—Now What?

Neither Grail nor 20/20 GeneSystems will ship their tests to consumers without a physician's order. However, both companies make it simple to get tested without ever stepping into a clinician's office.

They provide links on their websites to connect consumers to telemedicine prescribers and laboratories or urgent care centers where they can have blood drawn.

But a positive MCD test result "is the beginning, not the end," Minasian emphasized. "One of the questions that we have been thinking through is what do you do with that positive test?" No research on that question has bet been published, she noted.

The Grail test assesses methylation patterns in cell-free DNA with the use of machine learning. Cancer cells have different methylation patterns than normal cells. The result is presented as a simple yes or no: either a cancer signal was detected, or it wasn't. If a signal was detected, Grail has developed algorithms to narrow down its origin to a particular part of the body, such as the abdomen.

In a pilot study conducted in a US convenience sample of around 6700 people aged 50 years or older, the Grail test identified a cancer signal in 1.4% of participants, and 0.5%, or 1 in every 200 tested, were found to have cancer. The test's first or second cancer signal origin prediction was accurate 97% of the time. However, 52% of the cancers detected were stage III or stage IV, not the early-stage tumors that MCD tests aim to find.

The 20/20 GeneSystems test looks for a handful of older cancer biomarkers, including the prostate-specific antigen (PSA) and cancer antigen 125 (CA-125), which is not currently recommended for population screening. For $80, the test's premium version adds 5 more biomarkers, including C-reactive protein, which is typically used to monitor inflammation in such conditions as infections, asthma, and autoimmune diseases, and CA 15-3, most commonly used to monitor metastatic breast cancer during therapy. The 20/20 GeneSystems test results are presented as the risk of cancer in the next 12 months.

"The biggest challenge is that these assays are looking at multiple different kinds of cancers," Minasian pointed out. "You're not looking at apples and oranges. You're looking at apples, tomatoes, grapes, peas. They don't behave the same way."

And the tests alone can't precisely pinpoint where in the produce section a cancer might be located, if it's even present at all. That's one reason Etzioni worries that a positive test result could lead to "a diagnostic odyssey."

"My main concern is we might have an issue where the imaging test hasn't caught up to the cancer test," making it difficult to resolve the meaning of a positive result, Etzioni said. "If we're going to take on these tests, we also have to understand imaging better than we do."

CancerSEEK, an MCD test developed by Lennon and Johns Hopkins colleagues and acquired in 2021 by Exact Sciences Corporation, uses full-body positron emission tomography–computed tomography

(PET-CT) scans to follow up on positive test results. "You really need to know where the cancers are," Lennon said. "What is the quickest, least invasive, most cost-effective way of finding them?"

In 2020, she and her collaborators published the results of what they said was the first large prospective interventional clinical trial to evaluate an MCD test. The researchers incorporated an early version of their MCD test into the routine clinical care of 10 000 women with no history of cancer. In 26 of the women, 9 different types of cancer, including ovarian and uterine, were first detected by the MCD test. Fifteen of them underwent PET-CT imaging; the other 11 developed signs or symptoms that led to other types of imaging. Seventeen of the 26 had localized or regional disease.

The researchers extracted information from electronic medical records through November 2022 for an observational study of the longer-term health status of the 26 study participants with cancer first detected by the MCD test. After receiving treatment, half of them remained cancer free for an average of more than 4 years from their initial screening; 9 patients, all diagnosed at stage III or stage IV, were deceased, according to the study, presented last May in a poster session at the 2023 American Society of Clinical Oncology General Meeting.

Best to Let Sleeping Tumors Lie?

One concern is that MCD tests might detect slow-growing tumors that people would die with, not of, leading to unnecessary treatment and anxiety.

Neurosurgeon Daniel Orringer, of the New York University Grossman School of Medicine, compared the MCD tests with increasingly popular whole-body MRI scans, which can detect incidental cancers that never would have harmed a patient. Orringer coauthored a "discovery study" published last September about an MCD test that uses spectroscopy and machine learning algorithms to detect cancer. The test was developed by Dxcover, a company in Glasgow.

"Those whole-body MRI scans are detecting all kinds of lesions that are subclinical and asymptomatic," he explained in an interview. Such findings leave physicians and patients scratching their heads, Orringer said. "Okay, what do we do with it?"

Physicians should approach MCD test findings the same way they approach whole-body MRI findings, he noted. "Something that we teach our residents and medical students: we treat the patient and not the scan. We're going to treat the patient, and we're not going to treat the result from a mail away test."

Ofman, however, called the notion that MCD tests are likely to pick up tumors that never would have caused harm a misconception. "Slow-growing tumors that are unlikely to kill people are the same tumors that are not shedding into the blood," Ofman explained.

MCD tests are "tuned" to be highly specific to reduce the risk of false-positive results, Etzioni noted. But these do still occur.

What if the Grail test detects a cancer signal that it predicts is coming from the ovary but nothing is seen on imaging? "The doctor may say, 'It's a false-positive, come back next year for a repeat Galleri test,'" Ofman explained. Or, he said, the physician might recommend repeating the imaging in 3 months. A third option would be retesting in 3 to 6 months, which Grail will provide for free, Ofman said.

The tests' high specificity comes at a cost of sensitivity. "They are not informative if they're negative," Etzioni pointed out. "That's because the tests haven't been designed to rule out cancer. They've only been designed to rule in cancer." She cautioned that "if you have a negative test you may be falsely reassured."

Not Taught in Medical School

Physicians may be fielding questions from patients—perhaps after they saw a 20/20 GeneSystems ad in their Facebook feed—about whether they should get an MCD test.

"We are concerned that physicians don't fully understand how to use these tests," Minasian said. "Patients don't understand the risks and benefits because they haven't been systematically qualified."

Both Grail and 20/20 GeneSystems say they offer support to physicians. Grail Chief Executive Officer Bob Ragusa noted in a January blog post that his company offers clinicians access to a cohort of physicians with experience with its MCD test, including experts from NCI-Designated Cancer Centers. Grail also operates an "early cancer detection board" with third-party experts who can consult on challenging cases.

On its website, 20/20 GeneSystems offers to connect US physicians with questions about its test with physicians in East Asia who are more familiar with using biomarkers for cancer screening.

Still, at MD Anderson, "What I hear from my clinical colleagues is a great deal of concern," Volk said. "Who's appropriate for these tests? When should these tests be done? How often should they be done?"

Volk said he's particularly interested in the challenges that primary care physicians face when patients ask whether they should get an MCD test. He coauthored an article last April that detailed "core concepts for clinicians to share with patients," most of which emphasized all the unknowns about the tests.

"It's safe to assume that primary care clinicians are not ready to have those kinds of conversations," Volk said. And as for patients who are curious about taking an MCD test, "We just don't know at this time if this is a good idea or not." ■

Published Online: March 15, 2024. doi:10.1001/jama.2024.1018

Conflict of Interest Disclosures: Dr Lennon reported that under a license agreement between Exact Sciences and the Johns Hopkins University, she and the school are entitled to royalty distributions associated with CancerSEEK technology; she also reported serving as a consultant for Exact Science. Dr Volk reported receiving research funding from the American Cancer Society (ACS); the Cancer Prevention and Research Institute of Texas; the National Cancer Institute; the National Heart, Lung, and Blood Institute; and the Patient-Centered Outcomes Research Institute and serving as coleader of the ACS National Lung Cancer Roundtable Shared Decision-Making Task Group. Dr Etzioni reported owning stock in Seno Medical, a privately held medical imaging company, and serving on the American Urology Association's panel that issued the most recent prostate cancer screening guidelines. No other disclosures were reported.

Note: Source references are available through embedded hyperlinks in the article text online.