STAT

Thursday, December 2, 2021

## In The Lab

# Liquid biopsies could help screen for countless cancers. But who should get them?

**By Angus Chen**

By the time cancer is discovered, it's often too late to change its course. Close to half of cancers will already have spread, making death — whether within months, five years, or 10 years — a near certainty.

Mammograms, colonoscopies, and other cancer screenings may have caught some. But medicine doesn't screen for many cancers — though in the future, it's likely we will be able to with a simple blood draw.

Biotech companies are working to develop what are known as liquid biopsies, tests designed to detect dozens of different cancers. Studies suggest some of these tests can even find aggressive cancers when they're still constrained and likely curable, saving hundreds of thousands of lives. Two such tests — made by Grail and StageZero Life Sciences — are already available directly to patients as screening tools.

"These technologies work," said Viktor Adalsteinsson, a cancer researcher at the Broad Institute of MIT and Harvard who studies liquid biopsies. "There's room for improvement, certainly, but the studies done so far show convincingly they can detect cancer."

The bigger question, Adalsteinsson said, is whether they should be recommended for the general population. "That, I'm not yet convinced of," he said. It will hinge on whether the success of early data will hold in larger studies of liquid biopsy — confirming that they truly work as they're expected to — and how physicians and payers will integrate the new technology into medical practice.

"We're not waiting for the tests to get better. We're just waiting for trials to show that when you put them in the hands of physicians, outcomes get better," said Sana Raoof, a physician scientist at Memorial Sloan Kettering Cancer Center who has also worked as a consultant to Grail.

The tests being developed use different approaches to detect cancer, but the basic principle is the same. Cancer causes changes in the blood, and scientists can find those changes by analyzing the genetic material in a patient's sample.

The research that led to Grail's test happened, in a way, by accident. Researchers weren't looking at cancer, but at fetal DNA, which can sometimes wash into the blood of the mother without being encapsulated in a cell. A team of scientists began sequencing this "cell-free" DNA in the blood of 125,000 pregnant women, looking for aberrations that would indicate whether a fetus had a genetic disorder.

They found that was possible — "but they also found 10 or 12 women who had very abnormal looking DNA," said Josh Ofman, the chief medical officer of Grail. "They called all those women back, and guess what? Every one of them had an occult cancer," or signs of a tumor that was elsewhere in the body.

"That's when the light bulbs went off," Ofman said.

Illumina, now a DNA sequencing giant, was involved with the experiment and started Grail in 2015 shortly after that study, with a plan to develop a test that could screen for multiple cancers. (Illumina spun Grail out into its own business in 2016, only to merge with it again in 2021 in a $7.1 billion acquisition that quickly raised alarms among antitrust regulators.)

Grail's test, called Galleri, was granted a breakthrough designation in 2019 by the Food and Drug Administration, but hasn't yet been approved. Clinical trials of the test are ongoing. Physicians can, however, order the $949 test now for patients who have an elevated risk of cancer.

StageZero's cancer screen, called Aristotle, can also be ordered by physicians through a telehealth appointment for $1,500. The test is also not yet approved by the FDA. The test analyzes DNA from white blood cells to see if they've undergone any genetic changes that suggest the cells have quietly started to fight cancer. Other companies, like Exact Sciences and Guardant Health and Grail, have tests that look for free floating DNA shed by tumors into the blood as they grow. Those companies have their own analytical approaches to determine if the DNA is from cancer and where the tumor might be.

They all continue to refine their technologies, but the data so far suggest some of these multi-cancer blood screenings could offer more precise answers than the screening technology currently in use for lung, breast or other cancers, said Raoof. "I think the operating characteristics of these tests are already about an order of magnitude more impressive than currently approved screening tests," she said.

Take, for example, abnormal mammogram results, the vast majority of which don't turn out to be cancer. Something might look suspicious in an X-ray, but clinical follow-up finds real cancer only about 4% of the time. On the other hand, a trial done in over 6,000 people over the age of 50, some of whom had elevated risk for cancer, found that a positive Grail test

uncovered cancer about 45% of the time, Raoof said. In people who Grail determined didn't have any additional risks of cancer, that number drops to about 30%. Exact Science's test had a positive rate of about 19% when analyzing blood alone, and 41% when including follow-up imaging on a similar measure.

Given these results and the fact that drawing blood is far easier on a large scale than mammography, chest CTs, colonoscopies, and Pap smears, physicians like Raoof hope liquid biopsies will be used more widely soon. But the major obstacles between multi-cancer blood screenings and physician's offices is federal approval.

Physicians can order Grail's test now, but because the Food and Drug Administration hasn't approved it and the U.S Preventive Services Task Force hasn't recommended it, patients would have to pay for the test out-of-pocket. Large-scale trials, which are ongoing, will be needed for regulatory review and will take time.

"You know, half of Americans are diagnosed with some cancer in their lifetime. I wouldn't want some of my patients to get diagnosed with a late-stage cancer and die in the next 10 years because I was waiting for that trial to come out," Raoof said.

Other experts are less bullish on liquid biopsy. The Broad Institute's Adalsteinsson said those large clinical trials with hundreds of thousands of participants, like the one Grail is currently conducting in the U.K., are needed to confirm that the tests can reliably detect cancer at early stages and save lives in the general population. Then, he said, guidelines could be made recommending these tests on a large scale.

"You or I could think, 'well there's a test out there that could tell us now whether we have an underlying cancer that we aren't aware of," Adalsteinsson said. "And intervening early could save our lives. But there have been instances where that hasn't always been the case. So, it's a challenge thinking about when is the right time."

There are some cancers that grow so slowly that patients would die of other causes long before the cancer became a problem. Detecting these cancers might mean that a patient would go through surgery, chemotherapy, radiation or other onerous treatments that they might not have needed. While there's some evidence some blood tests, like the Galleri test, are better at catching aggressive cancers over indolent ones, Adalsteinsson says more research is still needed.

It's also true that traditional screening technologies doctors have been using for decades still work — and not nearly enough people use them, said Lecia Sequist, an oncologist at Massachusetts General Hospital and Harvard Medical School. For example, only 72% of women older than 50 had a mammogram in the last two years, and just an estimated 4% of eligible adults received lung cancer screening annually.

"And it's the number one cancer killer for both men and women, and we have a very effective cancer screening test," Sequist said.

Perhaps long-term clinical trials will show that multi-cancer blood tests can supplant tried and true screening methods, Sequist said. But even though she could order the tests for her patients today, like Adalsteinsson, she prefers to wait and see. "We have to read the entire book before jumping in with both feet," she said. "In the meantime, it's important not to lose sight of the fact that we can do better jobs with the cancer tests we have now, while we're developing the screening test of tomorrow."

---

*Angus Chen is a cancer reporter at STAT. angus.chen@statnews.com*