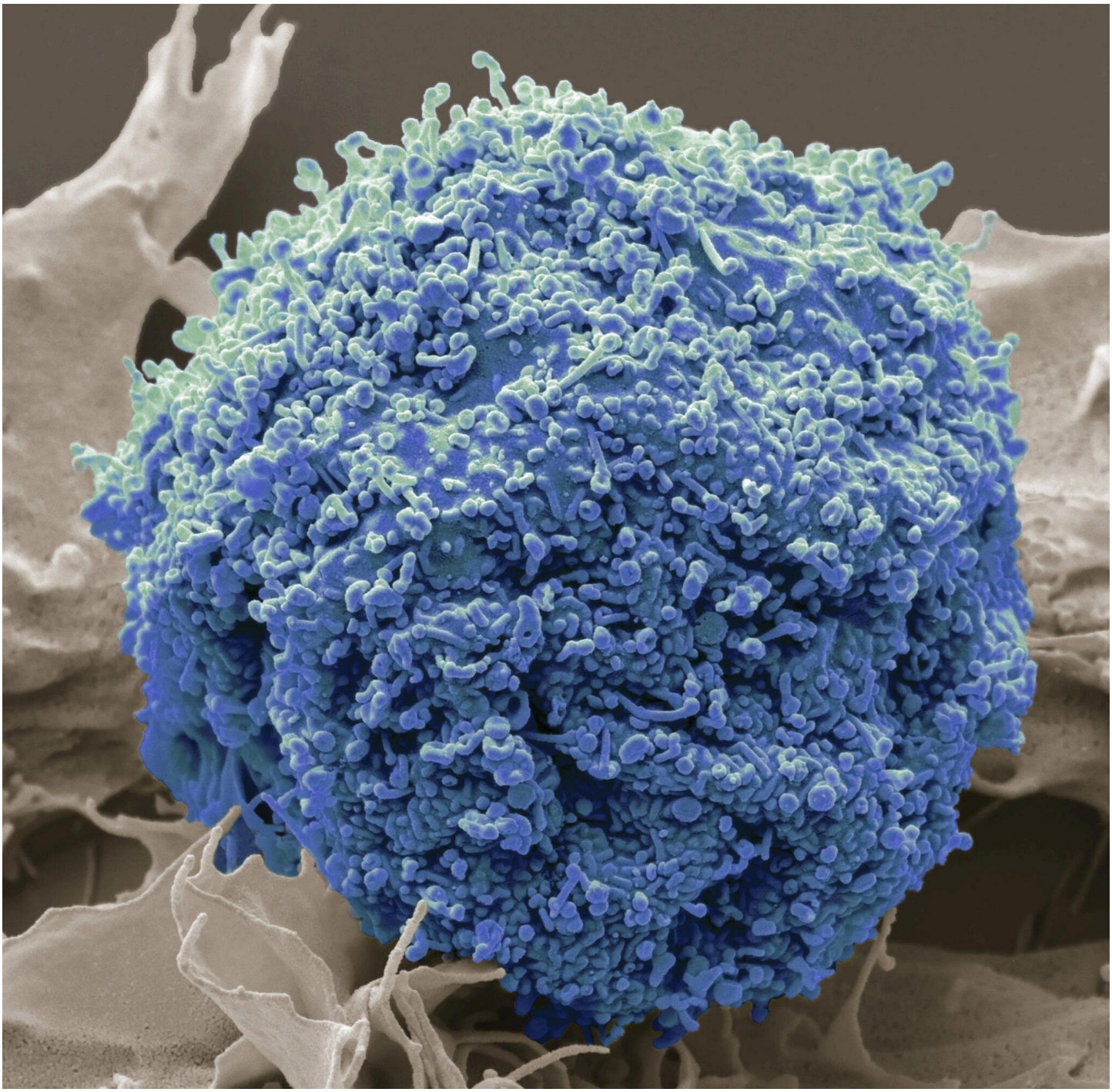

A cultured cell releasing large numbers of extracellular vesicles, which bud from the cell's surface. Science Photo Library

IN THE LAB

Cellular 'trash bins' might be a key to reviving multi-cancer early detection tests

Researchers study extracellular vesicles to improve cancer liquid biopsies

By Angus Chen and Marissa Russo July 29, 2025

Angus is STAT's cancer reporter. Marissa, when not working as an intern, studies extracellular vesicles in the brain in her Ph.D. research.

Catching cancer in its earliest stages is one of the most important factors in surviving it. Nipping a tumor in stage 1, before it's had time to claw its way through the body, is often the best way to give patients a chance at a cure. That's why dozens of companies have dived into blood-based screening technologies, with the hope of detecting multiple cancers by analyzing free-floating bits of tumor DNA.

The problem, at least so far, is that DNA-based liquid biopsies haven't lived up to their promise as an early-detection tool, experts told STAT, and many oncologists expressed doubt that they ever will. The tests on the market miss many cancers, and they're most likely to find tumors in more advanced stages. One major challenge is that the body rapidly degrades circulating tumor DNA in blood, and there is not a lot of cancer DNA in the blood at early disease stages.

That's leading researchers to turn to a new approach for early cancer detection, making use of nanoscale biological structures that our cells use to take out their garbage — and that are also believed to be important for certain types of cellular communication.

"Increasingly appreciated are extracellular vesicles. The pendulum has swung over the past decade or so of them being the trash bins of cellular processes to rich repositories of cellular cargo. Protein, DNA, RNA, lipids, et cetera," said Cesar Martin Castro, a cancer researcher at Harvard Medical School and Massachusetts General Hospital.

Along with other potential analytes encapsulated within these tiny bubbles, researchers told STAT, there's particular interest in DNA's single-stranded counterpart — RNA. That's partly because new methods have recently made the analysis of extracellular vesicles, and the RNA contained within, easier and more precise, experts said. "Technologies have gotten much more sophisticated to isolate them. They can isolate a cancer EV from a non-cancer EV. The content has gotten more secure; you don't need a large centrifuge anymore that leads to a loss of a lot of stuff," Castro said.

Over the last few years, several companies have been launched and deals have been struck around analyzing extracellular vesicles, and intriguing proof-of-concept papers have been published demonstrating the capacity to detect more than 90% of certain aggressive cancers. While the study of extracellular vesicles and analyzing them to

detect cancer is still in its infancy, Castro said, this recent activity is giving researchers a sense that this approach has some key advantages over cell-free DNA (ctDNA), as long as studies can be validated.

“I think the potential is higher than what ctDNA was at the same time of its trajectory or history,” Castro said. “It’s early, but there’s just more promise.”

DNA-based cancer liquid biopsies ‘will never work’

Ajay Goel is blunt when it comes to existing liquid biopsy cancer screening tests. “Multi-cancer early detection [tests], which are based on cell-free DNA, are garbage, for lack of a better word,” said Goel, a cancer researcher at City of Hope who formerly consulted for the DNA-based liquid biopsy company Grail and is now working on multiple approaches using extracellular vesicles. “It looks very attractive to have a blood test, but they have not worked, and they will never work.”

There are several DNA-based liquid biopsy early detection tests in development, with a few that are already commercially available. Grail sells the Galleri multicancer test to consumers for roughly a thousand dollars, and the colorectal cancer-specific Shield test from Guardant Health received approval from the Food and Drug Administration last year. These tests use DNA detected in blood and can find cancer, but they’re far less reliable in identifying early-stage cancers.

In a 2021 paper, Grail showed that Galleri has an overall sensitivity of 51.5%, a measurement of the likelihood that people with cancer will test positive. The sensitivity falls to 16.8% for stage 1 cancers, and 40.4% for stage 2 cancers. Grail declined to comment for this article.

Competitors don’t perform any better. Exact Sciences has been developing its own multi-cancer early detection tests. One was called CancerSEEK, which analyzes both DNA in the blood as well as cancer-specific protein markers and has been replaced by a newer test in development called Cancerguard. CancerSEEK achieved 27% sensitivity in a study called DETECT-A, Frank Diehl, the company’s MCED program lead, said in a presentation at the American Association for Cancer Research in 2024. The sensitivity was just 9% for stage 1 to 2 cancers, and 17% for stage 1 to 3. “Is 17% stage 1 to 3 sensitivity sufficient?” Diehl said in the presentation, adding that he believed the figure could be improved in the future. “What we thought is, it’s not enough.”

Oncologists STAT spoke with tended to agree, saying that they wanted to see higher performance from such tests before broadly recommending them to patients. “I would be hesitant, looking at the data, to use it,” said Aparna Parikh, a gastroenterologist and cancer researcher at Mass General, referring to multi-cancer early detection tests as a whole, including Grail’s.

There may be scenarios where certain existing tests are useful, Parikh said. For instance, Guardant’s Shield test performs poorly in detecting stage 1 and pre-cancerous polyps for colorectal cancer, but “where it’s useful is people who aren’t going to do stool tests and aren’t going to do colonoscopy,” she said. When it comes to colorectal cancer, especially, gastroenterologists have said these blood tests should not be considered replacements for colonoscopy.

Using these tests in conjunction with existing cancer screening methods may also be beneficial. Exact’s CancerSEEK test doubled the number of screen-detected cancers in a study, and in another study called ASCEND 2, the Cancerguard scored a 50% sensitivity for people known to be at higher risk for cancer by analyzing both methylation and protein status.

And tests that can help detect at least some cases of deadly cancers that currently have no screening method, like glioblastoma, pancreatic, or esophageal cancer, may also find a clinical role. Diagnosing some cancers at more advanced stages can still allow some patients to pursue curative-intent therapy that might not have worked at a later time, pointed out Tom Beer, Exact Sciences’ chief medical officer.

“I don’t think blood tests will replace best-in-class screening tests that are used for detecting early cancer and precancer,” he said. “We think the primary role will be expanding screening to the many cancers we don’t screen for today.”

How extracellular vesicles could advance early cancer detection

While shifting the diagnosis of some advanced cancers earlier is a worthy goal, it doesn’t fulfill the highest hopes and dreams of liquid biopsy cancer screening. For capturing cancer in its earliest stages, DNA-based liquid biopsy “doesn’t seem to work as well as we would like,” said Daniel Kim, a professor of biomolecular engineering and a cancer researcher at the University of California, Santa Cruz. “That might be because there

could be fundamental limitations in terms of the amount of DNA available in very early stages of cancer."

Cancer cells primarily shed DNA into the bloodstream when they die. "Most of that DNA will be degraded relatively rapidly. The only pieces that survive are short fragments," Kim said. That means, in the early stages of a cancer when there are fewer cells present in the body, far less tumor DNA is making it into the blood — which translates to a much smaller, harder to detect signal.

That's where extracellular vesicles might hold the edge. Cells expel large amounts of these vesicles while they're still alive, each one carrying a nano-sized sample of the molecules from the cell that birthed it. Because the contents are walled in by the vesicle's membrane, they're protected from enzymes that would eat away at long chains of DNA or RNA floating freely in the blood.

"Because EVs are removing things from their parental cells, that means their content is reflective of the parent cell," said Kenneth Witwer, president of the International Society for Extracellular Vesicles and a professor at Johns Hopkins University. "They reflect the content and presumably the state of health of the parental cell."

In theory, cancer cells might have a particularly strong extracellular vesicle signal, since malignant cells create more EVs than normal cells, and the material within should reflect the broad genomic changes that are characteristic of cancer.

It might also be easier to figure out the extracellular vesicle's tissue of origin compared to DNA, Witwer said, a crucial piece of information when trying to detect cancer. Finding a piece of tumor DNA is not of much use if "you don't really know where it came from," he said. In contrast, extracellular vesicles have genetic information tied to their tissue of origin. "EVs can be more specific precisely because of that return address that they have," Witwer added.

That's part of what makes the biology of extracellular vesicles "conducive to early cancer detection," said Pierre Arsène, CEO and founder of Mursla Bio. This biotech specializes in separating organ-specific extracellular vesicles from blood, and is working on a blood test for liver cancer called the EvoLiver test, which received FDA breakthrough device designation in April. The company's early results, presented at a conference last year, suggest the test might be able to detect early-stage liver cancer with 86% sensitivity and

88% specificity, over two times higher than current methods for detecting liver cancer among patients who are at high risk.

Other companies are jumping into the space as well. Pharus Diagnostics licensed a test developed by City of Hope's Goel, which analyzes microRNA — small molecules that regulate protein and gene expression — in extracellular vesicles. In an early trial comparing healthy controls to patients already diagnosed with cancer, the test detected 97% of pancreatic cancers in stage 1 or 2 when used in combination with CA19-9, a protein commonly used in diagnosing pancreatic cancer. (Goel holds several patents or has patents pending for tests using microRNAs to diagnose or detect different cancers, including this technology for pancreatic cancer.)

And extracellular vesicles may have yet untapped potential. In a preprint paper that UC Santa Cruz's Kim published, his team sequenced long non-coding regions of RNAs from extracellular vesicles, making use of recent technological advances from Oxford Nanopore. These long strands of RNA don't correspond to any protein-encoding gene, and have been difficult to study until recently, Kim said.

"Typically, with short-read technology, you just get like 150 base pairs of sequencing," Kim said. "But now we get the full RNA sequencing, and that helps us understand completely new biomarkers we'd never seen before in the blood."

When Kim studied the extracellular vesicles in a cohort of healthy patients and patients diagnosed with esophageal cancer, his group found over 250,000 novel long non-coding RNAs — a bounty of potential new indicators of health or disease. Then, Kim used a mathematical model to see if that data could help distinguish between the healthy patients and those with esophageal cancer.

"Definitely take this with a grain of salt, because it's just a training set. We have to validate it in a much larger, independent cohort," he said. "But it works perfectly. 100% classification of whether someone has cancer or not."

The model was also able to perfectly identify patients with Barrett's esophagus with high-grade dysplasia, a precursor to esophageal cancer, in the cohort of about 50 patients. For Kim, the study is a proof of principle that analyzing extracellular vesicles in this way could provide a rich new dataset that might aid early detection of cancers and, possibly, even pre-cancerous lesions — a holy grail in cancer screening.

"Anything that reliably broadens the detectable transcriptome is welcome," said Mass General's Castro. "This could be helpful in identifying new frontiers."

Castro cautioned against relying on the results of Kim's esophageal cancer study. "It's a preprint and hasn't been peer-reviewed," he said.

New cancer screening technologies are still in their infancy

If the life cycle of ctDNA liquid biopsy is any indication, cancer screening based on extracellular vesicles has a long trudge ahead. The field is only just getting on its feet, scientists told STAT. Technologies need to mature, and larger studies are sorely needed to validate extracellular vesicle approaches for early detection of cancer. If scientists are able to achieve that, then there would likely be years of engineering and optimization before the technology is at a point where it can be used commercially.

"There's a giant body of work occurring between an academic biomarker discovery and a robust, clinically available, proven, quality-controlled, scalable test you can deliver to human beings at a real turnaround time," said Exact's Beer.

There are also barriers fundamental to liquid biopsy in general that extracellular vesicle-based cancer screening may need to overcome. For one, the amount of extracellular vesicles produced by an early-stage cancer, or even from certain disease types, is still very low.

In the case of Mursla Bio's liver cancer test, there might be only tens of thousands of liver-specific extracellular vesicles of the potentially billions of EVs in a single milliliter of blood. In some disease types, there just might not be enough vesicles to reliably detect, said Hopkins' Witwer.

That's why many scientists told STAT they believe liquid biopsy screening tests will likely need to incorporate multiple biomarkers. That might include the contents of extracellular vesicles as well as serum proteins or other molecules in the blood, an approach that Exact Sciences told STAT is taking with its liquid biopsy tests.

"Everyone has their own lens on how they perceive their analyte of choice. The winner will be a multi-parametric approach," said Mass General's Castro. "It's foolhardy to say

ctDNA is going to give us all we need. There's no winner-take-all. It's just finding the right combinations."

Correction: An earlier version of this article stated Exact Sciences is developing a test called CancerSEEK. That test was the forerunner to Exact's current test called Cancerguard.