

New approach in liquid biopsies makes it easier to detect circulating tumor DNA in blood samples

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Tumors constantly shed DNA from dying cells, which briefly circulates in the patient's bloodstream before it is quickly broken down. Many

companies have created blood tests that can pick out this tumor DNA, potentially helping doctors diagnose or monitor cancer or choose a treatment.

The amount of [tumor](#) DNA circulating at any given time, however, is extremely small, so it has been challenging to develop tests sensitive enough to pick up that tiny signal. A team of researchers from MIT and the Broad Institute of MIT and Harvard has now come up with a way to significantly boost that signal, by temporarily slowing the clearance of tumor DNA circulating in the bloodstream.

The researchers developed two different types of injectable molecules that they call "priming agents," which can transiently interfere with the body's ability to remove circulating tumor DNA from the bloodstream. In a study of mice, they showed that these agents could boost DNA levels enough that the percentage of detectable early-stage lung metastases leapt from less than 10% to above 75%.

This approach could enable not only earlier diagnosis of [cancer](#), but also more sensitive detection of tumor mutations that could be used to guide treatment. It could also help improve detection of cancer recurrence.

"You can give one of these agents an hour before the [blood](#) draw, and it makes things visible that previously wouldn't have been. The implication is that we should be able to give everybody who's doing liquid biopsies, for any purpose, more molecules to work with," says Sangeeta Bhatia, the John and Dorothy Wilson Professor of Health Sciences and Technology and of Electrical Engineering and Computer Science at MIT, and a member of MIT's Koch Institute for Integrative Cancer Research and the Institute for Medical Engineering and Science.

Bhatia is one of the senior authors of the new study, along with J. Christopher Love, the Raymond A. and Helen E. St. Laurent Professor

of Chemical Engineering at MIT and a member of the Koch Institute and the Ragon Institute of MGH, MIT, and Harvard and Viktor Adalsteinsson, director of the Gerstner Center for Cancer Diagnostics at the Broad Institute.

Carmen Martin-Alonso Ph.D. '23, MIT and Broad Institute postdoc Shervin Tabrizi, and Broad Institute scientist Kan Xiong are the lead authors of the [paper](#), which appears in *Science*.

Better biopsies

Liquid biopsies, which enable detection of small quantities of DNA in [blood samples](#), are now used in many cancer patients to identify mutations that could help guide treatment. With greater sensitivity, however, these tests could become useful for far more patients. Most efforts to improve the sensitivity of liquid biopsies have focused on developing new sequencing technologies to use after the blood is drawn.

While brainstorming ways to make liquid biopsies more informative, Bhatia, Love, Adalsteinsson, and their trainees came up with the idea of trying to increase the amount of DNA in a patient's bloodstream before the sample is taken.

"A tumor is always creating new cell-free DNA, and that's the signal that we're attempting to detect in the blood draw. Existing liquid biopsy technologies, however, are limited by the amount of material you collect in the tube of blood," Love says. "Where this work intercedes is thinking about how to inject something beforehand that would help boost or enhance the amount of signal that is available to collect in the same small sample."

The body uses two primary strategies to remove circulating DNA from the bloodstream. Enzymes called DNases circulate in the blood and

break down DNA that they encounter, while [immune cells](#) known as macrophages take up cell-free DNA as blood is filtered through the liver.

The researchers decided to target each of these processes separately. To prevent DNases from breaking down DNA, they designed a monoclonal antibody that binds to circulating DNA and protects it from the enzymes.

"Antibodies are well-established biopharmaceutical modalities, and they're safe in a number of different disease contexts, including cancer and autoimmune treatments," Love says. "The idea was, could we use this kind of antibody to help shield the DNA temporarily from degradation by the nucleases that are in circulation? And by doing so, we shift the balance to where the tumor is generating DNA slightly faster than is being degraded, increasing the concentration in a blood draw."

The other priming agent they developed is a nanoparticle designed to block macrophages from taking up cell-free DNA. These cells have a well-known tendency to eat up synthetic nanoparticles.

"DNA is a biological nanoparticle, and it made sense that immune cells in the liver were probably taking this up just like they do synthetic nanoparticles. And if that were the case, which it turned out to be, then we could use a safe dummy nanoparticle to distract those immune cells and leave the circulating DNA alone so that it could be at a higher concentration," Bhatia says.

Earlier tumor detection

The researchers tested their priming agents in mice that received transplants of cancer cells that tend to form tumors in the lungs. Two weeks after the cells were transplanted, the researchers showed that these priming agents could boost the amount of circulating tumor DNA

recovered in a blood sample by up to 60-fold.

Once the blood sample is taken, it can be run through the same kinds of sequencing tests now used on liquid biopsy samples. These tests can pick out tumor DNA, including specific sequences used to determine the type of tumor and potentially what kinds of treatments would work best.

Early detection of cancer is another promising application for these priming agents. The researchers found that when mice were given the nanoparticle priming agent before blood was drawn, it allowed them to detect circulating tumor DNA in blood of 75% of the mice with low cancer burden, while none were detectable without this boost.

"One of the greatest hurdles for cancer liquid biopsy testing has been the scarcity of circulating tumor DNA in a blood sample," Adalsteinsson says. "It's thus been encouraging to see the magnitude of the effect we've been able to achieve so far and to envision what impact this could have for patients."

After either of the priming agents are injected, it takes an hour or two for the DNA levels to increase in the bloodstream, and then they return to normal within about 24 hours.

"The ability to get peak activity of these agents within a couple of hours, followed by their rapid clearance, means that someone could go into a doctor's office, receive an agent like this, and then give their blood for the test itself, all within one visit," Love says. "This feature bodes well for the potential to translate this concept into [clinical use](#)."

The researchers have launched a company called Amplifyer Bio that plans to further develop the technology, in hopes of advancing to clinical trials.

"A tube of blood is a much more accessible diagnostic than colonoscopy screening or even mammography," Bhatia says. "Ultimately, if these tools really are predictive, then we should be able to get many more patients into the system who could benefit from cancer interception or better therapy."

More information: Carmen Martin-Alonso et al, Priming agents transiently reduce the clearance of cell-free DNA to improve liquid biopsies, *Science* (2024). [DOI: 10.1126/science.adf2341](https://doi.org/10.1126/science.adf2341).
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