A standard blood sample, like the one seen here at Memorial Sloan Kettering Cancer Center in New York, can reveal invaluable information about a patient's cancer and how to treat it through a liquid biopsy.
PHOTOGRAPH BY STEPHAN ELLERINGMANN, LAIF/REDUX

SCIENCE

How liquid biopsies have made it easier to treat cancer

The tests detect traces of disease in a patient's blood. Here's how they're used—and why scientists hope they're the future of cancer screening.

BY **ALLIE YANG**

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A traditional tissue biopsy comes with risks and challenges—the target area can be hard to reach and bleeding and pain can last up to a month afterward. Patients can expect steep medical bills and up to a four-week wait to get results. That's a problem when a patient is dealing with an aggressive cancer.

In the past two decades, scientists have developed an alternative: liquid biopsies. These use body fluids, usually blood, to screen for cancer. The advantage of blood over tissue sampling is that it can easily—and repeatedly—be collected. A standard 7.5-10 milliliter sample of "peripheral blood," often taken from the arm, can be collected from a cancer patient and test results returned in about a week, potentially moving up the treatment timeline, says Jeffrey Campbell Thompson, assistant professor of medicine at the Perelman School of Medicine.

Right now, liquid biopsies are not reliable enough to detect new cancers, but they can be useful for monitoring ongoing treatments in patients who have been diagnosed, says Amir Goldkorn, a professor at the USC Keck School of Medicine and founder of the Liquid Biopsy Core at USC Norris Comprehensive Cancer Center.

Nevertheless, experts say research to develop better liquid biopsies is progressing quickly, and they're hopeful this tool will soon be able to identify cancer at all stages.

A universe in a vial of blood

To understand how liquid biopsies work, it's important to know what doctors are looking for in a blood sample, and what they can do with that information. When blood is spun in a centrifuge, it separates into two main parts—a lighter, transparent plasma that's mostly water, and a denser, red portion that contains various cells.

In a cancer patient, this denser portion of the blood may also contain loose, live cancer cells—called circulating tumor cells, or CTCs—that came from a tumor. This happens when a tumor grows large enough that some cells are pushed out and into the blood stream, says Erica Carpenter, assistant professor of medicine and director of the Liquid Biopsy Laboratory at the University of Pennsylvania.

(*Cancer vaccines are showing promise*.)

Though most cancer cells die in the bloodstream, some may seed a new tumor elsewhere, a process called metastasis. CTCs are identified by extracting and analyzing their DNA or by finding certain proteins on the outer surface of the cell, Goldkorn says. These markers can provide clues as to where the cell came from. Elevated levels of the protein THBS2, for example, may indicate pancreatic cancer. Higher THBS2 levels are associated with a lower chance of survival.

Circulating tumor DNA (ctDNA) from cancerous cells can be found in the plasma portion of a blood sample. CtDNA makes up only a tiny percentage of total DNA in a sample. But by sequencing the ctDNA and comparing it with DNA from healthy cells, researchers can identify mutations that help point to a certain cancer.

How liquid biopsies are being used today

Currently, liquid biopsies are overwhelmingly used to help determine treatment for cancer patients who have already been diagnosed. Thompson says at his hospital, patients get a liquid biopsy at their very first oncology appointment. That test can return crucial information within a week, but test results with actionable information on their cancer is not guaranteed.

Liquid biopsies have shown success with cancers in the lung (the kind these tests are most frequently used on, Carpenter says), pancreas, prostate, digestive system, kidney, skin, and breast. Because liquid biopsies can be easily performed, cancer patients can also be closely monitored throughout their treatment to determine whether it is having an effect.

(*How sleeping cycles affect the spread of breast cancer*.)

Still, finding traces of cancer in the blood is like finding a needle in a haystack, experts say. Circulating tumor cells are exceedingly rare compared to all other cells found in the blood. “A standard 7.5 milliliter sample of blood may have about 40 billion red blood cells in it. The average number of CTCs that you might find is maybe five,” says Goldkorn. Generally, the more CTCs found in the blood, the lower the chance of survival.

Because CTCs are intact cells, biomarkers like hormone receptors can still be found on the outer surface. For example, if CTCs from a breast cancer patient appear with estrogen receptors but not progesterone receptors, this may indicate the cancer is using estrogen to grow—so a doctor can prescribe a medicine that lowers estrogen levels or stops estrogen from acting on the cancer cells.

The ctDNA can also help doctors decide between immunotherapy (activating the immune system to fight the cancer) and a targeted medication that limits damage to normal cells, Carpenter says.

(*Cancer looks different in every body*.)

If a mutation in the epidermal growth factor receptor *(EGFR)* gene is detected in the ctDNA, doctors will know the patient is unlikely to respond to immunotherapy but may be a candidate for a targeted medication like erlotinib, which inhibits EGFR protein activity, slowing or stopping cancer growth, Carpenter says.

Timely DNA sequencing is especially important because starting a patient on immunotherapy after diagnosis and then switching to targeted therapy later if a specific mutation is found can be toxic and harm healthy parts of the body, Thompson says.

How liquid biopsies will be used in the future

The greatest limitation of liquid biopsies right now is their low sensitivity for cancer detection. If the cancer disease timeline is separated into three parts: diagnosis, treatment, and post-treatment, liquid biopsies are currently most useful in the middle stage, where traces of cancer are most prevalent, Goldkorn explains.

Scientists are working hard to increase sensitivity. In the future, liquid biopsies might allow us to screen for cancer in routine blood tests—before a patient gets sick. They also may help physicians monitor a patient for remaining traces of cancer.

Carpenter is also hopeful we'll develop liquid biopsies that can help detect brain cancers, as these seem to elude traditional liquid biopsy detection in peripheral blood.

Less than a decade ago, researchers were in a similar place with using liquid biopsies on lung cancer—and now there are several institutions routinely using it for advanced lung cancer care, Carpenter says. She hopes that work to increase liquid biopsy's sensitivity will allow the diagnostic to be used everywhere, within our lifetimes.

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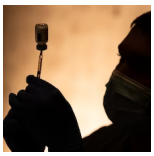

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