Could a Simple Blood Test Replace the Invasive Tissue Biopsy?

Answer: It's complicated …

April 15, 2019 By Jake Siegel

For years, the idea seemed as far-fetched as a fairy tale.

Once upon a time, there was a tumor cell that died. Its innards spilled out into the bloodstream of the body where it had lived. The owner of that body went to a doctor and got a blood draw for a test, which identified the cell's floating DNA fragments as cancer. The doctor then drew up a personalized treatment plan based on those bits of DNA, and the patient lived happily ever after …

The appeal of a simple blood test to detect and analyze cancer is obvious. It could replace the necessary evil of tissue biopsies — invasive, often risky and painful procedures to collect tumor cells with a needle or through surgery. A vial of blood sounds like a better trade than a chunk of tissue.

Recently, the idea of these so-called "liquid biopsies" seems less like a fantasy. The U.S. Food and Drug Administration approved its first liquid biopsy test in 2016. It could detect mutations in a single gene in lung cancer patients.

Genetic sequencing technology has evolved rapidly since then. Today at the American Association of Cancer Research annual meeting, researchers presented results from a clinical trial that found a commercial blood test was as effective as tissue biopsies at detecting multiple genetic mutations in lung cancer patients. All of the mutations have targeted drugs available for them, meaning the liquid biopsy could help guide treatment.

Those results are incredibly exciting, said several experts at Fred Hutchinson Cancer Research Center. But they caution that a fairy-tale ending for liquid biopsies hasn't been written just yet. Their verdict: Don't expect blood tests to replace the oncologist's needle anytime soon.

"This latest trial shows that liquid biopsies are a reality," said Nancy Davidson, MD, senior vice president and director of the Clinical Research Division at Fred Hutch and president and executive director of its clinical-care partner, Seattle Cancer Care Alliance. "But the question is, how big of a reality can they be?"

Garbage in, gold out?

The term “liquid biopsy” is relatively new; it was coined in 2010. But the underlying principles have been around for decades.

There is an ocean of information sloshing around in your blood. And doctors dive in all the time, to check your cholesterol or glucose levels or white blood cell counts.

That ocean also contains a lot of cellular trash. Every day, cells in your body are dying. As they do, they shed bits of their DNA into the bloodstream.

When those fragments come from a cancer cell, they contain the same molecular defects as the tumor they came from, Davidson explained. Find the fragments, and you find a surrogate for the tumor.

Scientists are exploring several ways to use these blood tests.

Possible roles for liquid biopsies in the clinic

- Diagnosis — finding the telltale markers of cancer
- Guiding treatment — finding a tumor’s specific mutations that are druggable targets
- Tumor evolution — monitoring real-time changes that might suggest resistance to therapy
- Minimal residual disease — searching for the ghostly traces of cancer after treatment that might lead to relapse

Many challenges

The idea of a liquid biopsy sounds simple. In practice, it’s incredibly complex. The tests required to find those floating fragments must be exquisitely precise. The total amount of cellular DNA in a vial of blood is tiny; the amount of DNA that would come from a tumor is even more miniscule. Other proposed markers in the blood, like intact cells shed from a tumor, are even rarer.

Sequencing technology, while constantly improving and getting cheaper, has only just gotten to the point where it can detect circulating tumor DNA, said Kristy Lastwika, PhD, a postdoctoral research fellow at Fred Hutch. And the amount of DNA is related to how big the tumor is.

“The bigger the tumor, the more DNA it sheds,” Lastwika said. “So these tests are reliable at detecting larger, and therefore later-stage, tumors. But they’re not so great yet with smaller, earlier tumors.”

That raises the specter of false negatives — i.e., not detecting someone’s cancer, thus delaying diagnosis, even costing someone their life. Scientists just don’t know how early these tests could catch cancer, no matter how fine-tuned they become.

“A tiny little polyp in your colon that’s thinking about getting bigger is very unlikely to be causing any kind of circulating mutations that are detectable,” said Natasha Hunter, MD, an oncologist at SCCA and an affiliate member of Fred Hutch’s Clinical Research Division. “And if that DNA does exist, with the resolution of today’s tests we’re just not finding it.”

These tests don’t just have to prove they can detect miniscule amounts of genetic material. They also must reliably identify specific mutations. A concern with liquid biopsies (and all screening tests) is producing false positives: i.e., detecting cancer when it isn’t there. That causes unnecessary worry to patients, and expensive and even harmful follow-up procedures.

“You would need a test that’s almost perfect” to use liquid biopsies as a general screening tool, Lastwika said. A better use would be to focus on high-risk populations — say, older adults who have smoked for a certain number of years.

Which happens to be what Lastwika does. Together with her mentors, Fred Hutch’s Paul Lampe, PhD, and McGarry Houghton, MD, she is developing a blood test to help detect lung cancer in high-risk adults whose imaging scans are inconclusive. Those scans identify growths called pulmonary nodules, which can be cancerous but are often benign. Lastwika wants to create an alternative to submitting those patients to a painful, expensive and dangerous lung biopsy. But instead of tumor DNA, her test looks for autoantibodies — proteins produced by the immune system in response to disease or infection. Scientists think these proteins are produced long before tumor DNA would appear in the blood.

Will they help patients?

When Lastwika pursued her doctorate, people never even spoke about the possibility of liquid biopsies. Today, she thinks the technology is at an inflection point. In the not-too-distant future, she said, liquid biopsies could become the standard of care in certain clinical scenarios, like screening for high-risk populations.

Hunter agrees, but she expects progress to occur at different rates depending on tumor type, with no one-size-fits-all solution. Lung cancer has been a great test case for liquid biopsies because several targeted therapies exist to treat specific mutations, she said. “But in breast cancer it’s a little less of a straight line between the mutation that we see and the therapy that we can apply. There’s a real hunger for these tests in the clinic, and patients ask me about them all the time. But right now, for breast cancer patients, they just can’t replace a tissue biopsy.”

Davidson said a lot of work remains to show that liquid biopsies can make a difference for patients and their doctors.

“I only want to do a test if the result is going to be actionable, if it leads me and the patient to make a decision,” she said. “Right now, we’re in this limbo where we have increasing ability to do these tests. But we really need to know if they’re going to help patients.”

Hunter agreed that validation will be key. (She is involved with a clinical trial that aims to see

whether blood tests can predict a complete response to chemotherapy.) And while it's exciting to follow progress, it's important to not let hype obscure the many questions that remain.

"The liquid biopsy not going to fix everything or cure everything," she said. "It's not going to replace your need for a colonoscopy, at least not anytime soon. But it still has lots of applications that are exciting."

Davidson agreed, noting she's been following (and contributing to) liquid biopsy research for several years. Still, she said, "I'm pretty careful to suggest to patients that it's far from a panacea. And if I still really wanted to know what was going on in a patient with metastatic breast cancer, I'd do the biopsy. I would just hope there was an area for me that was easy to biopsy."

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