

Case for liquid biopsies builds in advanced lung cancer

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Lung CA seen on CXR. Credit: [CC BY-SA 4.0](#) James Heilman, MD/Wikipedia

For patients with advanced lung cancer, a non-invasive liquid biopsy may be a more effective and suitable alternative to the gold standard tissue biopsy to detect clinically relevant mutations and help guide their course of treatment, suggests a new study published this week in the journal *Clinical Cancer Research* from researchers at the Abramson Cancer Center at the University of Pennsylvania (ACC).

In patients with advanced non-small cell lung cancer (NSCLC) treated at Penn's ACC, mutations detected from liquid biopsies (cell-free circulating tumor DNA (ctDNA) captured from blood) closely paralleled the mutations from [tissue](#) biopsies identified in next generation sequencing tests: EGFR, TP53, and ALK, to name a few. What's more, in several cases, liquid biopsies captured clinically relevant mutations not found in tissue biopsies as patients' disease progressed.

These data add to the growing evidence supporting the use of liquid biopsies, particularly when tissue samples are nonexistent or hard to obtain, as is often the case with lung cancer and other cancers that have metastasized throughout the body. About half of the 102 patients in this study did not have sequenceable biopsy tissue, so researchers relied on blood tests to detect mutations. In addition, clinicians are now seeing the emergence of targetable resistance mutations in advanced NSCLC as the disease progresses and therapies change. Keeping up with such an evolution is not as feasible with traditional tissue biopsies, the authors said, but much more plausible with serial blood samples.

"This represents a bit of a paradigm shift," said senior author Erica L. Carpenter, PhD, MBA, director of the Circulating Tumor Material Laboratory and research assistant professor at the Perelman School of Medicine at the University of Pennsylvania. "The [tissue biopsy](#) sequencing result has been considered the gold standard against which one compares the ctDNA result. Our work suggests that one can act on a ctDNA result, even in the absence of the so-called gold standard, and get

a clinical response in these patients. It also offers the advantage of testing without discomfort to the patient and possible risks associated with invasive biopsies."

Importantly, the study addresses an urgent, unmet need articulated in the recently released "Cancer Moonshot Blue Ribbon Panel Report 2016" that called for more efforts toward the development of non-invasive tests for markers, including ctDNA, to accelerate the ability to detect the emergence of drug-resistant disease. "Being able to accurately predict when a patient may develop drug resistance could have profound implications for selecting appropriate cancer therapies for individual patients," states the report, which notes 10 key recommendations put forth by members of the Blue Ribbon Panel, including Chi Van Dang, MD, PhD, director of the ACC.

In the study, researchers enrolled 102 consecutive patients with advanced NSCLC treated at Penn between February 2015 and March 2016 who had blood samples sent for ctDNA testing as part of their routine clinical care. Most were women (68 percent) with adenocarcinoma (81 percent) and stage IV disease (96 percent), all with different courses of treatment.

Liquid biopsy samples were collected in all 102 patients and sent to Guardant Health in California for genomic analysis; the 70 gene Guardant360 panel was utilized. Tissue samples were only able to be collected in 50 patients and subsequently analyzed at Penn's Center for Personalized Diagnostics with a 47-gene panel.

Among the 50 patients, 41 mutations were detected by both methods, while 24 therapeutically targetable driver EGFR mutations (a known driver of lung disease) were detected in tissue samples and 19 in ctDNA samples. Importantly, concordance between the two tests was nearly 100 percent when the samples were obtained concurrently, with discordance increasing when the blood samples were collected at longer intervals

after the tissue sample. One explanation for this may be that the blood test can detect new mutations that have evolved to resist treatment and may not have been detectable at time of the initial tissue test. The EGFR T790M resistance mutation was identified in eight liquid samples and only four tissue samples.

Serial liquid biopsies were also performed on six patients as part of disease surveillance, and in all six cases, the results helped guide clinical decision making, either by identifying a driver or resistance mutation amenable to targeted therapy, or by confirming that chemotherapy was likely the best course of action when a tissue sample was not possible.

The researchers also described the clinical history of three of these patients for whom ctDNA detected the emergence of therapeutically targetable variants over the course of their therapy. One patient presented with metastatic disease at diagnosis, with a tissue biopsy detecting no variants in EGFR, ALK, or ROS1. Upon referral to Penn, ctDNA testing revealed an EML4-ALK translocation and a TP53 mutation, and the patient started on crizotinib monotherapy with significant improvement in symptoms. Two months following therapy, a repeat ctDNA test showed a decrease in EML4-ALK, and the TP53 mutation was undetectable, which correlated with symptomatic and radiographic improvement. The other two patients had similar success stories.

To further understand the potential clinical actionability of ctDNA next generation sequencing, all detected mutations were also cross-referenced against available U.S. Food and Drug Administration (FDA)-approved, off-label, or investigational therapies. The majority of patients (70 percent) were determined to have a relevant clinical trial available, 56 (55 percent) patients had an off-label targeted therapy that could potentially be used, and 32 (31 percent) patients had an FDA-approved therapy available to them to target the detected mutation.

Taken together, these data suggest that liquid biopsies for NSCLC patients can yield results with high clinical relevance, including detection of therapeutically targetable mutations in EGFR, ALK, and other genes.

According to the authors, this is the largest study of its kind to use a clinical assay to monitor NSCLC patients. It also demonstrates for the first time the clinical utility of the non-invasive blood tests in patients for whom tissue analysis is not possible.

The next step is to evaluate the [liquid biopsy](#)'s utility at diagnosis as a complement to tissue testing, and in the context of genetically heterogeneous metastatic disease. Here, the researchers reported on serial ctDNA testing for six patients, but indicated that larger scale studies will be required to further evaluate ctDNA monitoring for treatment selection, including patients for whom no therapeutically targetable mutations are detected and who may be candidates for checkpoint inhibitors.

"The ever-expanding number of targeted therapies for lung cancer patients has been accompanied by a need for diagnostics with real-time detection of therapeutically targetable mutations," said co-author Corey J. Langer, MD, a professor of Hematology/Oncology and director of the Thoracic Oncology Program in Penn's Abramson Cancer Center, and a treating physician on the trial. "More and more, liquid biopsies are proving to help fill this need. While [tissue samples](#) will likely remain a major part of the initial diagnostic process, this non-invasive approach appears to be another powerful tool in our toolbox to help determine the best course of treatment for [lung cancer patients](#)."

Provided by Perelman School of Medicine at the University of Pennsylvania

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