SCLC is a rapidly progressive form of lung cancer with early hematogenous spread that claims more than 20,000 lives per year in the United States alone. Although first-line platinum-based therapy (with or without immune checkpoint inhibition)\(^1\)\(^2\) is often effective, upon progression, the disease is highly resistant and often rapidly fatal. Topotecan is approved as second-line therapy, but enrollment in clinical trials is often the most appealing option. In the past 5 to 10 years, we have seen the emergence of a wide range of targeted and immune therapies across multiple cancer types, such that SCLC now has promising drugs in clinical trials. However, given the often rapidly progressive nature of SCLC, some patients get only one chance at a next-line therapy before clinical decline prevents eligibility for other treatment options.

Could a blood-based biomarker improve outcomes in SCLC through facilitating precision therapy? Such an approach is particularly appealing in SCLC owing to early hematogenous spread with high circulating tumor cell (CTC) shed and frequently limited evaluable tissue sample after biopsy. CTC testing has been an ongoing area of study for years—CTC number at baseline portends worse prognosis, and significant decrease in detectable CTCs after one cycle of chemotherapy correlates with clinical responses.\(^3\) More recently, circulating tumor DNA (ctDNA) testing has been adopted widely as a strategy for genotyping of advanced NSCLC.\(^4\) Although ctDNA testing is widely used to screen for targetable genomic alterations, studies also suggest that ctDNA provides effective prognostication as an early marker for response or progression in both NSCLC and SCLC.\(^5\)\(^-\)\(^7\) Concordance between ctDNA and SCLC tumor DNA at baseline has suggested reliability of ctDNA results with the added opportunity for detecting genomic intratumor heterogeneity not captured in a single-site tumor tissue biopsy.\(^8\)

In this issue of the *Journal of Thoracic Oncology*, Mohan et al.\(^9\) report results from their analysis of ctDNA and CTC in 69 patients with SCLC, 39 with limited-stage (LS) and 30 with extensive-stage (ES) disease. They used whole genome sequencing of plasma DNA for copy number analysis and targeted next-generation sequencing (NGS) of 110 SCLC-related genes for mutation analysis. Parallel blood samples were collected to enumerate CTCs. Tumor-related genomic changes were noted by ctDNA in 94% of LS samples and 100% of ES samples. CTC analysis increased detection to 95% in LS samples. Although the focus of the reported study is ctDNA testing, the simultaneous collection of CTC samples provides a unique opportunity for considering each method as a means to evaluate patients with SCLC. This study effectively demonstrates excellent sensitivity of ctDNA detection in ES-SCLC, which could allow for disease monitoring and evaluation. Even in LS-SCLC, most samples have detectable ctDNA. Although the investigators describe CTCs as providing “differing yet overlapping information” with ctDNA, the input provided by CTCs seems to only minimally affect the results. Reviewing the ctDNA and CTC correlation across 48 cases with results for both (Fig. 1, adapted from Supplementary Fig. 5 by Mohan et al.\(^9\)), one can see many cases with high content of ctDNA but only low levels of CTCs. Furthermore, more sensitive ctDNA assays are
available with capacity for reliable mutation detection below 2.5% allelic fraction, and these could further increase the sensitivity of ctDNA analysis in SCLC.

Since the inception of CTC and ctDNA assays, there have been two areas of significant clinical impact considered. The first, detection of targetable genomic alterations, is an area of widespread ctDNA utilization but one which is less relevant in SCLC, given the lack of established genomic targets. The second, and perhaps the true opportunity in SCLC, is monitoring of the state of disease. Although various data sets have been presented supporting this, it is not an area of clinical utilization outside of a trial setting. Why is this? Have the right clinical scenarios not been defined for monitoring disease burden? This is an area ripe for specific clinical trial attention. Detection of a resistance mutation in the setting of NSCLC leads many clinicians to adjust treatment as indicated. Similarly, detection of increasing disease burden by ctDNA levels may indicate resistance even without identifying a particular mechanism. Moreover, it is disease resistance and portends a poor prognosis—a clinical study to determine if early intervention can impact outcomes is a logical next step.

The widespread availability of ctDNA assays suggests that this should be the focus of clinical development going forward, but which ctDNA assay is best suited for studying SCLC? Targeted NGS panels specifically built for optimal coverage of SCLC genes exist and have shown promise for ctDNA monitoring. One challenge is that copy number loss (such as loss of RB1) is difficult to detect in plasma when ctDNA levels are low. Now, the emergence of large-targeted NGS panels for ctDNA sequencing, many spanning hundreds of genes, may create increased opportunities for plasma-based monitoring of SCLC. The tools are available; now all that is needed is the perfect clinical application, and SCLC may be just that.

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