blood plasma contains a few thousand copies of DNA fragments, less than 10% of which on average are derived from the tumor, depending on a patient’s stage of the disease (1). To achieve greater sensitivity and specificity, researchers have developed various molecular technologies to capture these DNA fragments, ranging from locus-specific assays to targeted whole-exome or whole-genome massively parallel sequencing.

ctDNA has a few biological properties that make it a promising biomarker for cancer monitoring. These fragments of DNA are thought to be by-products of apoptosis and necrosis released in blood during cancer development (2). The blood circulation is able to accumulate signals coming from different parts of the cancer, and when the cancer spreads, from different lesions in the body. In this way, analysis of ctDNA in blood plasma presents conceptual advantages over tumor tissue biopsies, as it poses less risk to patients and is less limited by spatial heterogeneity. For example, Forshew, et al. detected an unexpected EGFR mutation in the plasma of high-grade serous ovarian cancer patients at relapse that was only present at a low level in biopsies—1 out of 8 lesions archived from the tissue bank (3).

A study also reported that the concentrations of ctDNA decrease shortly after surgery, making it a very dynamic tool for rapid analysis of tumor mass changes and showing promise for assessing prognosis after surgery (4). Notably, somatic (i.e., tumor-specific) alterations on ctDNA are intrinsically specific to changes in tumors. Taking these two properties together, ctDNA has potential to track tumor progression and monitor treatment efficiency. In the same study, Diehl, et al. tracked ctDNA dynamics in 18 advanced colorectal cancer (CRC) patients and showed that ctDNA provides higher sensitivity than carcinoembryonic antigen, the standard biomarker for tracking tumor responses and prognosis in CRC patients (4). In another study, Dawson, et al. studied a group of metastatic breast cancer patients (n=52) and showed that the dynamics of ctDNA provided the earliest indication of responses compared with circulating tumor cells and serum marker CA 15-3 compared with CT imaging (5).

Because of its noninvasive nature, ctDNA analysis also facilitates more regular longitudinal follow-up, offering great opportunities for identifying treatment resistance early on. For example, studies have shown that in non-small cell lung cancer and CRC patients, known resistance-conferring mutations could be detected in plasma in good concordance with tumor biopsy data (6-8). Beyond known resistance mechanisms, ctDNA also offers the possibility of identifying previously unknown genetic alterations associated with resistance (9). Identifying early the molecular-based mechanisms of acquired resistance to targeted drugs helps clinicians adapt new therapeutic approaches with the aim of suppressing expansion of the resistance-conferring clones. Furthermore, ctDNA analysis holds the potential to provide genomic data that would enable physicians to implement alternative therapies before resistance manifests clinically.