



blood-based tests that are transforming precision cancer care for patients with early and advanced disease. Recent clinical readouts and U.S. Food & Drug Administration (FDA) approvals fuel momentum for clinical use of liquid biopsies as an alternative to traditional tissue biopsies. Given the established and emerging uses of liquid biopsies, it is critical to understand how best to leverage these technologies to support new breakthroughs and improve patient outcomes.

Liquid biopsy analytes include CTCs, circulating tumor DNA (ctDNA), which is the tumor-derived fraction of cell-free DNA (cfDNA), as well as cell-free RNAs (long non-coding RNAs and microRNAs), extracellular vesicles, tumor-educated platelets, proteins, and metabolites that can be interrogated to derive information about the overall tumor burden as well as the underlying biology as cancer cells undergo immunoediting and therapy-imposed evolutionary bottlenecks. To this end, we have engaged with liquid biopsy experts to synthesize and critically interpret the current state of liquid biopsies as these relate to ultrasensitive ctDNA detection (reviewed by Chaudhuri and colleagues), cfDNA biology and cancer interception by leveraging broad cfDNA analyses (reviewed by Velculescu and colleagues), the role of CTCs in understanding and capturing the metastatic cascade and biology of evolving tumors (reviewed by Pantel and Alix-Panabières), longitudinal ctDNA tracking to monitor tumor evolution, immunoediting and clinical response to cancer immunotherapy (reviewed by Anagnostou and colleagues) and regulatory ramifications of these approaches as they approach integration in clinical practice including the increasing number of patients receiving cancer immunotherapy (reviewed by Beaver and colleagues). The articles included in this Journal for ImmunoTherapy of Cancer Expert opinion Special Review Series outline the current state of the science, near term and future applications, and implications for clinical care and research by covering technological, biological and clinical aspects related to the use of liquid biopsies for early diagnosis, detection of minimal residual disease, and monitoring tumor evolution and therapeutic response. Authored by leading voices in cancer biology, technology development and immuno-oncology, these reviews explore minimally invasive cancer detection, ctDNA technologies and their calibration to the field of precision immuno-oncology; emerging technologies for CTCs and extracellular vesical detection in conjunction with their role in tumor evolution and tumor immune escape under the selective pressure of immunotherapies; minimally invasive approaches to capture outcomes with immunotherapy for patients with advanced/metastatic cancer; and a regulatory path for use of liquid biopsies in drug development including its value as an early endpoint for cancer immunotherapy.

Liquid biopsies have increasingly important implications for patients with cancer who have been treated or are seeking treatment with immunotherapies. Near-term

clinical applications of liquid biopsies likely include the systemic treatment of patients with early-stage cancers that relapse after curative-intent therapy as well as escalation or de-escalation systemic therapy strategies for individuals with metastatic disease guided by ctDNA detection or persistence. Despite the considerable enthusiasm, caution must be exercised in the routine use of liquid biopsy assays as important overarching questions remain: Do changes in ctDNA correlate with clinical benefit? Do treatment decisions triggered by the detection of ctDNA postcurative therapy lead to improved outcomes? Should changes in ctDNA for patients on active therapy inform additional treatment decisions? To bridge the technological advancements in liquid biopsies with clinical applications, we have invited precision oncology-focused clinicians to provide their insights and critical assessment of the state of implementation of liquid biopsies in clinical cancer care. Each main review article in this Journal for ImmunoTherapy of Cancer Expert opinion Special Review Series is accompanied by an expert clinician viewpoint focusing on clinical implementation of next-generation sequencing (discussed by Desai and Lovly), genome-wide and epigenetic cfDNA analyses (discussed by Rolfo and Russo), CTCs (discussed by Serrano and Malapelle), integration of ctDNA in clinical trial design (discussed by Aggarwal and Leigh) and next steps needed to translate liquid biopsies into approved diagnostics for patients with cancer (discussed by Normanno, Apostolidis, and Stewart). We hope that this 10-article series will serve as a valuable resource to support continued research and validation of the use of liquid biopsies to deliver the earliest best clinical care with precision.

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