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Liquid biopsies coming of age: biology, emerging technologies, and clinical translation- An introduction to the JITC expert opinion special review series on liquid biopsies

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ABSTRACT

Liquid biopsies are gaining momentum as minimally invasive means for cancer detection, characterization, monitoring, and interception. Composed of five expert-opinion review articles and five accompanying expert-physician viewpoints, this Journal for ImmunoTherapy of Cancer Special Review Series focuses on capturing and synthesizing the current state of science of liquid biopsies and their clinical relevance for cancer immunotherapy and beyond.

Our ability to generate and analyze genomic data has revolutionized our understanding of cancer biology and enabled precision medicine. Over the past decade, we have seen the emergence of minimally invasive blood-based next-generation sequencing technologies that allow for analyses of circulating tumor cells (CTCs), tumor-derived DNA fragments and particles shed in the bloodstream. These approaches, collectively called liquid biopsies, have been emerging as potentially powerful means for cancer detection, characterization, therapeutic response monitoring and interception. While analyses of tumor tissue are currently the gold standard for cancer diagnosis, staging, and prognosis, many real-world clinical challenges exist such as procedural complications and insufficient sampling, prolonged turnaround times, tumor tissue heterogeneity, and inability for longitudinal monitoring. Liquid biopsies hold promise to complement, and in some instances, overcome these shortfalls and assist in cancer diagnosis and minimal residual disease detection, improve the selection of personalized cancer treatment therapies and rapidly detect therapeutic response and resistance. The technologies and evidence are continuing to evolve, but liquid biopsies are already opening new opportunities for how patients receive care by minimizing the watch and wait approach, supporting treatment decisions through less-invasive blood sampling, and informing whether a treatment is effective earlier. Liquid biopsies are also gaining momentum in the field of cancer immunotherapy as a means to more accurately and rapidly predict therapeutic outcomes and monitor in real time tumor burden dynamics, tumor immunoediting, and evolution.

Capturing and synthesizing the current state of science of liquid biopsies is important to fully understand the potential of these approaches in the cancer care continuum and a crucial step toward mapping current evidentiary gaps and future opportunities. Comprised of several expert-opinion focused review articles, the scope of this Journal for ImmunoTherapy of Cancer Expert opinion Special Review Series is to provide insights into the biology of circulating tumor cells (CTCs) and circulating cell-free and tumor-derived DNA, critically discuss the technologies developed for CTC and cell-free tumor DNA detection and tracking, and understand the clinical applications of liquid biopsies as they become increasingly used for therapeutic decisions for cancer immunotherapy. Over the past decade, we have seen a growing number of regulatory approvals for

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 Anagnostouand 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 Leighl) 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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