

REVIEW ARTICLE: THE EVOLVING LANDSCAPE OF CANCER BIOMARKERS FOR EARLY DETECTION

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ABSTRACT

Early detection remains the most critical strategy for improving patient survival and treatment efficacy across various malignancies. While traditional screening tools like mammography and colonoscopy have established benefits, they are often limited by invasiveness, low sensitivity, or a lack of multi-cancer detection capabilities. This review explores the transformative potential of liquid biopsy and advanced "omics" technologies in addressing these unmet clinical needs. We examine the role of circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and extracellular vesicles (exosomes) as non-invasive biomarkers that provide real-time insights into tumor biology and mutational profiles. Furthermore, the integration of multi-omics strategies—encompassing genomics, proteomics, and metabolomics—combined with artificial intelligence (AI) and machine learning is discussed as a powerful paradigm for identifying complex

disease patterns with unprecedented accuracy. While significant progress has been made in developing biomarkers for specific cancers such as breast, prostate, and colorectal, challenges regarding standardization, clinical validation, and global cost-effectiveness remain. Ultimately, the convergence of these technologies promises to shift oncology from reactive diagnosis to preemptive health management.

KEYWORDS: Cancer Biomarkers, Early Detection, Liquid Biopsy Circulating Tumor DNA (ctDNA), Multi-Omics, Artificial Intelligence (AI).

INTRODUCTION

Early detection of cancer is widely acknowledged as the most effective approach to improve patient outcomes, increase survival rates, and enhance the efficacy of treatment regimens.^[31, 32,57] A capability of detecting malignancies at the initial phases when they are localized and highly responsive to treatment can change a life-threatening tumor into a treatable one. Still, the existing screening tools—mammography, colonoscopy, and Pap smear tests—are, though efficient in identifying certain types of cancers, frequently limited by their intrusiveness, poor sensitivity, or inability to screen for several types of cancer at once.^[30,46] In extremely fatal types of cancer, including pancreatic and ovarian cancers, their diagnosis comes at advanced stages since they lack obvious early warning signs^[31,30] This urgent unmet clinical requirement has set in train a new research era committed to identifying and validating biomarkers—biologic molecules or markers indicating the presence of disease.^[2,45,47] The domain of cancer biomarkers for early detection is a swiftly advancing field within oncology, propelled by the advent of non-invasive liquid biopsies and advanced "omics" technologies that hold the promise of identifying malignancies long before clinical symptoms appear.^[29, 39, 9, 10, 15, 48]

The Liquid Biopsy Revolution: A Non-Invasive Frontier Liquid Biopsy

It is a new technique consisting of the analysis of body fluids like blood, urine, or saliva to detect cancer-associated biomarkers.^[33,11,4] It is a simple, non-painful, and reproducible technique compared to the traditional tissue biopsy, which is typically painful, invasive, and dangerous.^[10,44] The importance of the process is the analysis of several circulating factors from tumors.

- **Circulating Tumor DNA (ctDNA):** By far the most exciting part of liquid biopsy, ctDNA is made up of tiny fragments of DNA that the cancer cells shed into the bloodstream.^[4] Its potential as an early biomarker is enormous in the majority of cancers, including lung, colorectal, and pancreatic cancer.^[17,20,31,29,52] Compared to tissue biopsies, ctDNA provides an immediate snapshot of the tumor genome and its mutational profile along with a broad range of epigenetic alterations.^[7,56,49] Tumor burden is usually indicated by ctDNA amount and has a fast half-life that makes it an ideal marker for disease monitoring and treatment response.^[18,59] Low levels of ctDNA in the early-stage disease are a serious issue; however, advances in high-throughput sequencing and targeted amplification techniques are minimizing its detection threshold.^[52,58]

- **Circulating Tumor Cells (CTCs):** They are viable cancer cells that have broken away from the host tumor and are now in circulation. Although their very low count at the initial phase of the disease may render them nondetectable, analysis of them has a special benefit: it is capable of giving insights into the live tumor biology, i.e., morphology, protein composition, and metastatic potential.^[4,49] The capacity to culture CTCs from one blood sample would allow real-time chemosensitivity testing and individualized selection of treatment.^[4]
- **Extracellular Vesicles (EVs) and Exosomes:** Extracellular vesicles, like exosomes, are tiny lipid-bound particles secreted from almost all cells, including cancer cells. They function as "messengers" by transporting a load of biomolecules like proteins, lipids, and nucleic acids (including microRNAs and DNA) that indicate the status of their parent cell.^[6] The molecular load of exosomes has been found in studies to be helpful as an ideal source of biomarkers for early diagnosis.^[35,39,54,55] For instance, exosomal microRNAs were found to be of very high diagnostic utility for early ovarian and prostate cancers with a clear molecular signature more reliable in circulation than freely floating nucleic acids.^[28,35]
- **Proteins and Metabolites:** Protein and metabolite biomarkers in the blood have been the backbone of cancer screening over the last few decades, with some such examples including Prostate-Specific Antigen (PSA) and CA-125.^[26,34] But their imprecision has bred the quest for more precise panels of biomarkers. Improved proteomic and metabolomic platforms, enabled by mass spectrometry, can detect panels of tens of protein or metabolite biomarkers whose combined scrutiny can yield a stronger signal of incipient disease.^[13,19,22,54]

The Convergence of Technology: Multi-Omics and Artificial Intelligence

The most impressive recent cancer biomarker discovery breakthroughs have been the development of new technologies and multi-omics strategies. Integration of various "omics" layers-genomics, transcriptomics, proteomics, and metabolomics-leads to an all-encompassing picture of the biological alterations sculpted in the process of tumorigenesis.^[9, 60,53] For example, a multi-omics strategy may be able to quantify a patient's plasma for a panel of epigenetic markers (DNA methylation), circulating proteins, and metabolites in one step. The integration of these signals can provide much greater diagnostic specificity than for any of these biomarkers individually.^[9,57]

The quantity and complexity of data produced by these multi-omics investigations require the application of artificial intelligence (AI) and machine learning (ML).^[8,41,42,43,45,50] AI computer programs have the distinctive advantage of detecting weak, complicated patterns in extremely large datasets beyond any human capability to detect.^[8,50] AI programs can be learned from data from thousands of cancers and healthy patients to create record-breaking accuracy cancer risk or presence predictors.^[42,43,61] The use of AI is not only for analyzing data but rather to be utilized in furthering the performance of liquid biopsy technologies themselves, e.g., for directing sample processing and signal detection efficiency.^[41,42]

Cancer-Specific Biomarkers: Advances and Challenges

Distinguished advances have been achieved in the detection of biomarkers for certain cancer kinds, while sensitivity, specificity, and validation-related issues persist.^[2,12,1,10,46]

- **Breast Cancer:** Though mammography is the gold standard, fluid biopsy-adulting biomarkers such as miRNAs, cell circulations, and autoantibodies are also explored and proposed for use as adjunct tools, particularly for dense-breasted women in which mammography is not effective.^[10,11,13,14,50] Initial findings of ctDNA in breast cancer studies have been specifically encouraging potential for minimal residual disease detection following therapy, which may indicate high recurrence potential.^[51]
- **Prostate Cancer:** The widely popular PSA test is experiencing its shortcomings, which is why the establishment of novel biomarkers is sought.^[25,26,27] Urine-related markers, e.g., PCA3 mRNA, and exosomal miRNAs have been considered for enhancing the accuracy of diagnosis and minimizing avoidable biopsies, due to the high false-positive rate of the PSA test.^[27,28]
- **Colorectal Cancer:** In addition to the established stool-centered tests and colonoscopy, ctDNA and other non-invasive biomarkers are being crafted for enhancing screening rates and their performance in diagnosis.^[20,21,24] DNA-methylation-pattern-directed multi-cancer early detection (MCED) tests are an upsurge in potential, and clinical trials for their performance in diagnosing them in a mass population are in process.^[56]
- **Pancreatic and Liver Cancers:** For these highly aggressive malignancies, in which early diagnosis is essential, liquid biopsy presents an essential future.^[29,31,36,37,38,30,55] Hurdle is identifying the exponentially low levels of biomarkers in primary-stage disease. Efforts entail

perfecting ctDNA assays and the detection of new protein and exosome markers that have the potential to indicate the existence of a tumor when it is still resectable.^[31,55]

- **Other Cancers:** Its momentum continues in additional cancer forms too, such that in ovarian cancer, scientists are perfecting panels of serum and exosomal biomarkers to move beyond the shortcomings of CA-125.^[33,34,35,46] and in bladder cancer, urine-related markers continue to be tested as a non-invasive screening agent.^[40]

Clinical Translation and Future Outlook

Translating clinical research into practice will never be without challenges, starting from ensuring standardization in sample collection and analysis, conducting a rigorous clinical validation in large-scale prospective trials, and also attending to regulatory issues.^[1,47] A full investigation of the cost-effectiveness and accessibility of these new technologies within global healthcare systems also has to be considered to ensure an equitable introduction. Despite these challenges, there is no denying that the future of early detection of cancer is promising. The integration of liquid biopsy, multi-omics, and artificial intelligence is leading to the development of a new and powerful paradigm for cancer screening.^[43,60,61] Ongoing development from collaborative networks, such as the National Cancer Institute's Early Detection Research Network, is vital for translating these findings into a clinically useful test that saves lives.^[32,57] Ultimately, the best biomarkers of the future will allow for screening that is ground-breaking and patient-centered, moving the discipline from reactive diagnosis to preemptive health management.^[45]

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