JOURNAL OF AMERICAN MEDICAL SCIENCE & RESEARCH

Review Article
ISSN: 3041-5578
Journal homepage: https://medical.researchfloor.org/

Unveiling the Timeline of Liquid Biopsy Analytes Release: Review of the Implications for Early Cancer Detection

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ABSTRACT

Background: *Liquid biopsy has revolutionized cancer diagnostics by providing a minimally invasive means of capturing tumor-derived biomarkers from body fluids. Unlike conventional tissue biopsy, it enables real-time monitoring of tumor heterogeneity and evolution. Circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), exosomes, and microRNAs (miRNAs) represent the most clinically relevant analytes, each with distinct mechanisms and timing of release into circulation.*

Methods: *This review synthesizes recent global, Sub-Saharan African, and Nigerian literature published within the last decade. Emphasis is placed on comparative mechanisms of analyte release, timing in the cancer continuum, and translational applications in detection, monitoring, and therapeutic stratification. Key advances and challenges in clinical utility, especially in resource-limited settings, are highlighted.*

Results: *ctDNA offers high sensitivity for early detection and mutational profiling, while CTCs provide insights into metastatic potential and treatment resistance. Exosomes and miRNAs act as stable carriers of genetic and proteomic information, expanding diagnostic and prognostic possibilities. Integration of multi-analyte approaches enhances sensitivity and specificity across cancer types. However, significant barriers including infrastructural limitations, cost, and lack of standardized protocols—hamper adoption in low- and middle-income countries.*

Conclusion: *Liquid biopsy represents a paradigm shift in oncology, enabling early diagnosis, personalized treatment, and dynamic disease monitoring. Future directions include multi-analyte platforms combined with artificial intelligence, standardized assays, and equitable global access. Region-specific validation in Sub-Saharan Africa and Nigeria remains essential to ensure its translation into clinical practice and maximize impact.*

Keywords: *circulating tumor DNA, Circulating Tumor Cells, Early cancer detection, EXOSOMEs, Liquid biopsy, microRNAs, Precision oncology,Tumor heterogeneity.*

Citation: Umobong EO, Gbaa ZL, Anenga RN, Ugwu I, Tsegha LJ, Ojo BA, Gbaa FA and Otene, SA (2025). Unveiling the Timeline of Liquid Biopsy Analytes Release: Review of the Implications for Early Cancer Detection. *Journal of American Medical Science and Research.* *DOI: https://doi.org/10.51470/AMSR.2025.04.01.63*

Received 28 April 2025
Revised 24 May 2025
Accepted 25June 2025

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Introduction

Cancer remains one of the leading global causes of morbidity and mortality, with an estimated 19.3 million new cases and 10 million deaths reported in 2020 alone [1]. Despite advances in therapeutics, survival outcomes are largely determined by the stage at diagnosis, highlighting the critical importance of early detection. Conventional diagnostic approaches, such as tissue biopsy and imaging, though invaluable, are limited by invasiveness, sampling bias, tumor heterogeneity, and an inability to provide dynamic, real-time insights into tumor evolution [2]. These limitations have catalyzed the emergence of liquid biopsy(LB)as a transformative diagnostic tool in oncology.

Liquid biopsy refers to the analysis of circulating tumor-derived materials in body fluids such as blood, urine, or saliva [3]. These analytes include circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), exosomes and extracellular vesicles (EVs), microRNAs (miRNAs), proteins, and metabolites. Each analyte provides complementary insights into tumor biology, ranging from genetic and epigenetic alterations to phenotypic characteristics and intercellular signaling [4]. Liquid biopsy is minimally invasive, repeatable, and capable of capturing tumor heterogeneity across primary and metastatic sites, making it particularly attractive for early detection, prognostication, treatment monitoring, and surveillance [5].

A central but underexplored dimension of liquid biopsy is the timeline of analyte release into the circulation. Understanding when specific biomarkers appear during carcinogenesis is crucial for determining their utility in early detection and risk stratification. For example, ctDNA can be detected in circulation during pre-invasive lesions, providing a window for earlier diagnosis than imaging might allow[6]. In contrast, CTCs typically emerge later, associated with vascular invasion and metastatic spread[7]. Exosomes and EVs are secreted continuously, including at pre-malignant stages, and may therefore represent among the earliest markers of tumor initiation[8]. Similarly, dysregulated circulating miRNAs are stable in body fluids and detectable in early carcinogenesis, while tumor-associated proteins and

DOI: https://doi.org/10.51470/AMSR.2025.04.01.63

metabolites often appear early but may lack specificity [9].

Emerging evidence suggests a progressive timeline: Exosomes and miRNAs appear earliest, followed by ctDNA reflecting real-time tumor dynamics, while CTCs arise predominantlyduring invasive stages. This chronology has profound implications for clinical practice. If validated, it could enable the integration of liquid biopsy into cancer screening algorithms, particularly in settings where resource constraints and late-stage presentation remain significant barriers to improving outcomes [10].

Despite these advances, challenges persist. Technical issues such as sensitivity, assay standardization, and biological variability hinder broad implementation. Moreover, most available data are derived from high-income countries, with limited studies from Sub-Saharan Africa and Nigeria, where late diagnosis and limited access to molecular diagnostics remain pervasive [11]. Addressing these gaps is essential to ensure that the promise of liquid biopsy is equitably realized.

This review synthesizes current evidence on the timing of tumor analyte release in liquid biopsy, critically evaluating their role in early cancer detection. It highlights biological mechanisms, comparative analyte kinetics, clinical applications, limitations, and future perspectives, with a view to guiding precision oncology and advancing early detection strategies across diverse healthcare contexts. (Table1)

Table 1: Comparative Timeline of Biomarker Analyte Release in Cancer Progression

Analyte	Earliest Stage of Release	Source/Origin	Detection Window	Key Clinical Applications	Representative References
Circulating Tumor DNA (ctDNA)	Very early (precancerous lesions, early tumorigenesis)	Apoptosis, necrosis, active secretion by tumour cells	Persistent throughout cancer progression; increases with tumor burden	Early detection, MRD monitoring, recurrence detection, genomic profiling	[6,7].
Circulating Tumor Cells (CTCs)	Early invasive stage; often detectable before metastasis	Tumour cell intravasation into bloodstream	Intermittent; correlates with tumor vascularity and aggressiveness	Prognosis, therapy response, metastatic risk assessment	[5,8]
Exosomes / Extracellular Vesicles	Early premalignant changes; tumour microenvironment remodeling	Secreted by tumour and stromal cells	Stable; persistent in circulation even in early disease	Liquid biopsy for molecular cargo (RNA, DNA, proteins), tumour communication	[2,5]
MicroRNAs (miRNAs)	Early dysplasia; reflect epigenetic changes	Tumour-derived exosomes, apoptotic bodies	Highly stable, detectable in plasma/serum early	Non-invasive biomarker for early diagnosis and subtype classification	[7,10]
Proteins (e.g., tumour markers)	Late premalignant to invasive stage	Secretory activity of tumour cells	Widely used clinically; sensitivity varies by tumour type	Traditional screening (CEA, AFP, CA19-9), treatment monitoring	[9,11]

***Key insights from this table**: **ctDNA** appears earliest and persists, making it ideal for early detection and MRD. CTCs typically emerge later, tied to invasion and metastasis, aiding prognosis. Exosomes and miRNAs appear early and offer functional insight into tumour biology. Proteins remain clinically important but lag in sensitivity vs. nucleic acid biomarkers.*

Biology of Analyte Release

The entry of tumor-derived materials into the circulation is governed by a complex interplay of cellular processes, tumor microenvironment dynamics, and systemic factors. Each analyte,ctDNA, CTCs, exosomes, miRNAs, proteins, and metabolites, has distinct mechanisms of release, influencing its timing, abundance, and clinical detectability. Understanding these biological underpinnings is essential for interpreting liquid biopsy results and optimizing their use in early detection.

Apoptosis: Programmed cell death generates small, fragmented nucleic acids and cellular debris, which are phagocytosed or released into circulation. ctDNA fragments (typically ~160–180 bp, corresponding to nucleosomal DNA) are predominantly released through apoptosis [12]. Apoptotic release occurs throughout tumorigenesis, including in pre-malignant stages, contributing to the early detectability of ctDNA.

Necrosis: Rapidly proliferating tumours often outgrow their vascular supply, leading to hypoxia and necrosis. This process generates larger, irregular DNA fragments and proteins that enter the bloodstream [13]. Necrosis is more prominent in advanced tumours, correlating with higher concentrations of ctDNA and tumor-derived proteins in later disease stages.

Active Secretion: Tumour cells actively secrete exosomes and extracellular vesicles (EVs) containing DNA, RNA, miRNAs, proteins, and metabolites. This process is not limited to malignant cells but is upregulated in cancer, enabling intercellular communication, immune evasion, and pre-metastatic niche formation.Exosomal release is continuous and occurs early in tumourigenesis, even in pre-malignant lesions, making exosomes potential early biomarkers. The cargo within exosomes is selectively packaged, reflecting the tumor's molecular profile more faithfully than random cell death products [14].

Tumor Invasion and Vascular Dissemination: Circulating tumor cells (CTCs) arise when malignant cells detach from the primary tumour and intravasate into blood or lymphatic vessels [15]. This requires epithelial-mesenchymal transition (EMT), degradation of the extracellular matrix, and angiogenesis. Consequently, CTC release generally occurs later in the cancer timeline, correlating with invasive and metastatic potential rather than pre-malignant states. However, rare studies have reported CTCs in some early-stage breast and prostate cancers[16]. (Figure 1)

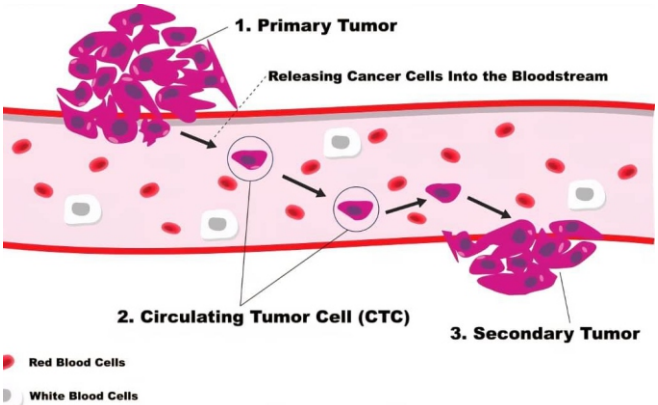

Figure1: The metastatic cascade: Circulating tumor cell dissemination and secondary tumor formation

DOI: https://doi.org/10.51470/AMSR.2025.04.01.63

can be detected in plasma even at preclinical stages of tumor development. Studies have shown ctDNA to be present in the circulation months to years before clinical diagnosis, particularly in cancers with high proliferative indices such as lung and colorectal malignancies. The release dynamics of ctDNA are influenced by several factors, including tumor burden, cellular turnover rate, hypoxia (low oxygen conditions), and exposure to treatment. The levels of ctDNA in the blood often correlate with the stage and progression of the disease. This makes ctDNA a valuable biomarker for monitoring disease progression and treatment response [19-24].

In contrast, circulating tumor cells (CTCs) are intact, viable malignant cells that are shed into the bloodstream during the process of invasion and intravasation (entry into the bloodstream). Their release tends to occur at later stages of cancer evolution when local invasion and metastatic dissemination are established. While CTCs provide valuable insights into tumor heterogeneity and metastatic potential, they are rarely detected in early lesions, which limits their utility as a primary early biomarker. Their presence often signifies a more advanced disease state [25-28].

Exosomes and other extracellular vesicles (EVs) are secreted via regulated cellular pathways and are released continuously by both normal and malignant cells. Tumor-derived exosomes carry a variety of cargo, including proteins, nucleic acids, and lipids, which are reflective of their parent cells. They can be detected even in the early stages of tumor development. Their role in intercellular communication and in preparing the pre-metastatic niche makes them an important analyte for both early detection and disease monitoring. Exosomes are particularly stable in biofluids, and their contents can provide a snapshot of the tumor's molecular landscape [29-31].

MicroRNAs (miRNAs), which are small non-coding RNAs, are released either within exosomes or bound to circulating proteins. They are remarkably stable in biofluids and can be detected in early tumor stages. miRNAs have shown promise in differentiating malignant from benign conditions and in tracking therapeutic response. Similarly, circulating proteins and metabolites are also released, often reflecting systemic effects of tumor metabolism. However, these analytes frequently lack the tumor specificity found in nucleic acid-based biomarkers. Their levels can be influenced by a wide range of non-cancer-related conditions, making them less specific for early-stage tumor detection compared to ctDNA or exosomal miRNAs [32-38].

Collectively, ctDNA and exosomal miRNAs emerge as the earliest detectable analytes, often preceding radiologic evidence of malignancy. In contrast, CTCs and many circulating proteins appear later in tumor evolution. Understanding these release kinetics provides a crucial framework for designing multimodal liquid biopsy strategies tailored for both early detection and longitudinal disease monitoring. This approach leverages the strengths of each analyte to create a more comprehensive and sensitive diagnostic tool. Here is the list of references in Vancouver style, based on the citations provided in the original text.

Comparative Insights:

The different tumor-derived analytes detectable through liquid biopsy are released into circulation along a temporal spectrum, and their relative sensitivity and specificity vary by cancer type and disease stage. Comparative evaluation of these biomarkers underscores their complementary roles in the continuum of cancer detection and monitoring.

Exosomes and extracellular vesicles (EVs) appear to be among the earliest analytes shed into circulation. Their secretion is an active process occurring even in pre-malignant lesions, and their cargo,including DNA, RNA, and miRNAs, reflects the molecular alterations of tumor cells. Several studies have reported elevated exosomal miRNA profiles in patients with stage 0 and stage I breast and lung cancers, suggesting a role in early carcinogenesis [39,40]. Because exosomal contents are selectively packaged, they provide a more specific signature of tumor biology compared to proteins or metabolites, which may be elevated in benign conditions.

MicroRNAs (miRNAs), either free or exosome-encapsulated, are similarly detectable in early stages of cancer development. Their high stability in circulation makes them robust biomarkers. Dysregulated miRNA signatures, such as overexpression of miR-21 and miR-155, have been identified in early breast and colorectal cancers [41,42]. Importantly, these markers can be detected before imaging abnormalities, suggesting their potential integration into screening pathways for high-risk populations.

Circulating tumor DNA (ctDNA), while not universally present in pre-invasive disease, can be identified in early-stage cancers. It was demonstrated that ctDNA was detectable in over 50% of patients with stage I malignancies across multiple cancer types [43]. Its short half-life allows it to serve as a real-time biomarker, capturing tumor dynamics during treatment or recurrence. However, sensitivity in very early disease remains lower compared to advanced cancers, largely due to the small fraction of ctDNA relative to background cell-free DNA from normal tissues [44].

Circulating tumor cells (CTCs) emerge later in the disease timeline, correlating with the acquisition of invasive and metastatic potential. Although isolated reports describe their presence in early breast and prostate cancers, large-scale analyses indicate that CTCs are more reliably detected in advanced disease [45,46]. Their rarity in circulation poses technical challenges, but their intact cellular structure provides unique opportunities for phenotypic and functional analysis, including drug sensitivity profiling and characterization of epithelial-mesenchymal transition states [47].

Proteins and metabolites, while historically the first tumor biomarkers to be clinically applied, have limitations due to poor specificity. For example, prostate-specific antigen (PSA) can be elevated in benign prostatic hyperplasia, while carbohydrate antigen 125 (CA-125) may rise in non-malignant gynecological disorders [48]. Nevertheless, when used in conjunction with nucleic acid-based biomarkers, these analytes may enhance diagnostic accuracy, particularly in resource-limited settings where access to advanced molecular platforms remains a challenge [49].

Taken together, the comparative evidence highlights a progressive timeline of analyte release. Exosomes and miRNAs are often detectable at the earliest stages, ctDNA appears soon after malignant transformation, while CTCs emerge predominantly during invasive and metastatic phases. Proteins and metabolites may provide early but less specific signals. This chronology underscores the need for multi-analyte liquid biopsy approaches, which leverage the strengths of each analyte to maximize sensitivity and specificity across the cancer continuum [50].

DOI: https://doi.org/10.51470/AMSR.2025.04.01.63

Clinical Implications:

The translation of liquid biopsy from bench to bedside has significantly influenced cancer management across the diagnostic and therapeutic continuum. Its impact is particularly evident in early detection, prognostication, real-time monitoring, and guiding therapeutic decision-making.

One of the most promising clinical applications is in early cancer detection. The ability to detect tumor-derived nucleic acids, proteins, and vesicles in circulation prior to radiologic evidence offers the potential for non-invasive screening. For instance, multi-analyte tests such as *CancerSEEK* have demonstrated sensitivities above 70% for early-stage malignancies in colorectal, ovarian, and pancreatic cancers [51]. In Nigeria and other Sub-Saharan African countries, where late-stage presentation remains the norm due to weak screening programs, liquid biopsy could provide an accessible alternative to imaging-heavy modalities [52].

Liquid biopsy also plays an expanding role in prognostication. Higher baseline levels of ctDNA and CTCs have been correlated with poor survival outcomes in breast, colorectal, and prostate cancers[53,54]. In Sub-Saharan Africa, where pathological staging is often unavailable due to infrastructural limitations, molecular staging through liquid biopsy could refine prognostic stratification and influence therapeutic intensity [55].

In the monitoring of treatment response, liquid biopsy provides dynamic, real-time insights that conventional imaging or serum biomarkers cannot. The decline in ctDNA burden has been shown to precede radiologic tumor shrinkage, making it a reliable early marker of therapeutic efficacy [56]. Conversely, ctDNA persistence after surgery or chemotherapy predicts minimal residual disease (MRD) and heralds recurrence months before clinical detection [57]. This utility could be transformative in Nigeria, where follow-up systems are often suboptimal, enabling clinicians to detect recurrence earlier with simple blood draws [58].

Beyond monitoring, liquid biopsy is shaping therapeutic guidance and resistance profiling. Genomic alterations identified in ctDNA allow for the non-invasive selection of targeted therapies, such as EGFR inhibitors in non-small cell lung cancer (NSCLC) [59]. Moreover, serial profiling can detect emerging resistance mutations, allowing treatment adaptation without repeat tissue biopsy[60]. Such precision-guided therapy has been reported in African cancer cohorts, though uptake remains slow due to cost and infrastructural barriers [61].

Another critical implication is the potential role of liquid biopsy in screening high-risk populations. Individuals with hereditary cancer syndromes, such as BRCA1/2 mutation carriers, or populations with endemic exposures, such as aflatoxin-associated hepatocellular carcinoma in West Africa, may benefit from routine liquid biopsy surveillance [62]. Such strategies could bridge the gap in preventive oncology in regions where access to endoscopy, colonoscopy, or mammography remains limited.

Importantly, the integration of liquid biopsy into clinical workflows in resource-limited settings must be carefully contextualized. While its potential is vast, challenges related to affordability, assay standardization, and infrastructural readiness persist [63]. Nonetheless, with falling sequencing costs and the increasing miniaturization of diagnostic platforms, liquid biopsy is poised to redefine cancer care in both high-income and low-resource settings alike.

Technological Platforms and Methodologies:

The performance of liquid biopsy hinges on the precision of technologies used to capture and characterize tumor-derived biomarkers. These methodologies have evolved rapidly, enabling high sensitivity and specificity across diagnostic, prognostic, and therapeutic contexts.

ctDNA Analysis: Detecting ctDNA—particularly in early-stage cancers where concentrations are minimal—relies on exceptionally sensitive molecular platforms. Digital PCR (dPCR) and its derivative droplet digital PCR (ddPCR) offer cost-efficient, high-precision quantification of known hotspot mutations (e.g., EGFR, KRAS), making them ideal for minimal residual disease monitoring [64]. In contrast, next-generation sequencing (NGS) enables broader profiling—detecting SNVs, gene fusions, and copy number changes—through targeted panels like Guardant360 and comprehensive exome approaches, which have proven clinically valuable in NSCLC, colorectal, and breast cancers [65,66].

Circulating Tumor Cells (CTCs): Due to their rarity in circulation (1–10 cells per 10 mL), CTC detection requires sophisticated enrichment technologies. The FDA-approved CellSearch® system relies on EpCAM-based immunoaffinity capture and is extensively used in breast, prostate, and colorectal cancer monitoring [67,68]. Label-free techniques—including size-based microfluidics and dielectrophoresis—circumvent marker limitations and improve detection of mesenchymal-like CTCs. Further, single-cell sequencing of captured CTCs provides rich insights into tumor heterogeneity and therapy resistance mechanisms [69].

Exosome and Extracellular Vesicle Analysis: Exosomes carry rich molecular cargo—from DNA and RNA to proteins—reflecting their tumor origin. Conventional isolation via ultracentrifugation ensures high purity, though newer methods like size-exclusion chromatography and immunoaffinity capture are enhancing efficiency and yield. Downstream proteomic and transcriptomic analyses of exosomal contents, such as PD-L1, are revealing resistance and metastasis markers in melanoma and lung cancer models [70].

MicroRNAs (miRNAs) and Other Non-Coding RNAs: Circulating miRNAs remain stable in biofluids—whether within exosomes or bound to proteins—and offer practical, sensitive biomarkers. Detection by qPCR and sequencing-based methods has shown that miRNA panels can reliably differentiate cancers in breast and gastric settings. In Sub-Saharan contexts, their simplicity and lower cost make them promising alternatives to sequencing-intensive techniques[71].

Fragmentomics and Methylation Profiling: Novel research is focusing on cfDNA fragmentation patterns—shortened lengths and unique end motifs—as early indicators of cancer presence and ctDNA dynamics. Meanwhile, methylation profiling (e.g., multi-cancer Galleri assays) achieves high specificity (>85%) in identifying tissue origin across diverse tumor types [72].

Multi-Analyte Integration: Emerging platforms are combining multiple analytes—ctDNA, CTCs, exosomes, miRNAs—to improve detection sensitivity, especially in cancers with poor ctDNA shedding such as gliomas or pancreatic malignancies. This integrative method leverages molecular and cellular signals for a more comprehensive tumor census [73,74].

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Regional Feasibility and Accessibility: In regions like Nigeria and broader Sub-Saharan Africa, infrastructure and cost limitations impede the uptake of advanced liquid biopsy platforms. However, affordable methods like ddPCR and targeted PCR panels present practical entry points. As sequencing costs decline, broader adoption of NGS-based assays in regional oncology centers becomes increasingly viable [75].

Challenges and Limitations:

Despite the transformative potential of liquid biopsy (LB) in cancer diagnostics, multiple challenges hinder its integration into standard clinical workflows, particularly in resource-limited settings. One of the primary concerns is analytical sensitivity—detecting low-frequency tumor-derived signals (ctDNA, CTCs, exosomes) against a high background of normal cell-free nucleic acids remains technically demanding [76,77]. Early-stage tumors may shed minimal analyte quantities, resulting in false negatives, while biological variability between patients further complicates interpretation [78].

Another key limitation is pre-analytical variability. Factors such as sample collection tubes, storage temperature, processing delays, and centrifugation protocols significantly impact analyte stability and concentration. Even minor variations in plasma handling can lead to substantial differences in ctDNA yield or exosome integrity, limiting reproducibility across studies and institutions [79].

Cost and infrastructure barriers also impede large-scale adoption, particularly in low- and middle-income countries (LMICs). High-throughput sequencing, digital PCR, and other next-generation LB platforms require specialized laboratory equipment, bioinformatics support, and trained personnel, making widespread deployment challenging [80,81]. Moreover, the lack of standardized regulatory guidelines, clinical validation studies, and consensus on cut-off thresholds for positivity restricts the use of LB as a definitive diagnostic tool rather than an adjunct [82].

Tumor heterogeneity introduces further complexity. Although LB offers a dynamic snapshot of tumor evolution, the heterogeneous shedding of analytes between metastatic sites can lead to underrepresentation of certain clones. Furthermore, distinguishing tumor-derived signals from age-related or benign somatic mutations (clonal hematopoiesis) remains an ongoing bioinformatics challenge [83].

Addressing these limitations requires harmonization of LB workflows, robust multi-center validation studies, and scalable, cost-effective assays tailored to regional healthcare systems. Developing AI-driven bioinformatics tools for signal-to-noise optimization, implementing pre-analytical SOPs, and increasing access to sequencing technologies in LMICs will be critical to maximizing LB's impact in oncology [84,85].

Future Perspectives:

The future of liquid biopsy research lies in advancing its clinical precision, scalability, and accessibility, particularly in the context of early analyte release detection. Several transformative directions are emerging:

First, multi-omics integrationis gaining prominence, combining ctDNA, CTCs, exosomal RNA, miRNAs, methylation markers, and proteomic signatures to provide a comprehensive molecular fingerprint of tumors. This approach overcomes the limitations of single-analyte assays and captures tumor heterogeneity more effectively, enhancing diagnostic accuracy even at minimal disease burden stages [86].

Second, ultra-sensitive analytical technologies, such assingle-molecule sequencing, microfluidics-based rare analyte enrichment, and artificial intelligence (AI)-driven pattern recognition, are expected to revolutionize early cancer detection. These innovations promise ctDNA detection in picogram quantities, high-throughput CTC phenotyping, and advanced bioinformatics to distinguish tumor-derived signals from background noise [87,88].

Third, longitudinal liquid biopsy monitoring will become integral to precision oncology. Serial sampling may detect clonal evolution and treatment resistance months before imaging, allowing earlier therapeutic interventions [89]. This approach is already transforming clinical trials, where liquid biopsies are incorporated as surrogate endpoints for minimal residual disease (MRD) and therapeutic response prediction [90].

Additionally, global access and implementation remain critical challenges. While liquid biopsy adoption accelerates in high-income countries, low- and middle-income countries (LMICs) face barriers such as infrastructural deficits, high costs, and limited expertise. Research collaborations, portable diagnostic devices, and AI-driven data interpretation may help democratize access to this technology [91].

Finally, regulatory standardization and clinical validation will shape the field's trajectory. Initiatives such as the Blood Profiling Atlas Consortium (BloodPAC) and large multicenter trials are working toward harmonizing assay methodologies, pre-analytical workflows, and reporting standards, which will be pivotal for routine clinical integration [92].

In summary, future liquid biopsy research will increasingly emphasize integrated analytics, extreme sensitivity, longitudinal monitoring, and global equity, positioning these tools as central to next-generation precision oncology.

Conclusion:

Liquid biopsy is revolutionizing cancer diagnostics by providing a minimally invasive, real-time tool for early detection, tumor monitoring, and personalized therapy through analytes such as ctDNA, CTCs, exosomes, and miRNAs. While advancements are improving assay performance and clinical integration, challenges in standardization, sensitivity, cost, and accessibility persist, particularly in low- and middle-income countries. Ongoing research and global collaboration are essential to fully realize its potential as a complement and possible alternative to traditional tissue biopsy, fostering more precise and patient-centered cancer care.

Recommendations:

Future efforts should focus on standardizing liquid biopsy assays with unified protocols for collection, processing, and interpretation to ensure reproducibility and clinical reliability. Integrating liquid biopsy into multidisciplinary cancer care should be prioritized for early detection, treatment monitoring, and minimal residual disease assessment. Innovation is needed to develop multi-analyte platforms combining ctDNA, CTCs, exosomes, and miRNAs to enhance diagnostic accuracy. Cost reduction, accessibility improvements—especially in low- and middle-income countries—large-scale validation, and supportive regulatory frameworks are essential for clinical adoption. Leveraging AI and advanced bioinformatics will strengthen data integration, while improved infrastructure, workforce training, and global collaboration will be key to realizing liquid biopsy's potential in precision oncology.

DOI: https://doi.org/10.51470/AMSR.2025.04.01.63

Conflicts of interest: none

Sources of funding: we received no grants or funding for this review work.

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