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Circulating Tumor Cells and Cell-Free DNA/RNA Liquid Biopsies vs. Traditional Tissue Biopsy to Improve Cancer Screening: A Scoping Review

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Abstract

Introduction: The goal of cancer screening is to maximize the likelihood of successful treatment outcomes for affected patients and prevent cancer development in the general public. Delays in diagnosis or barriers to accessing care are associated with lower survival rates, increased treatment-related complications, and higher healthcare costs. Liquid biopsies, particularly blood-based cell-free DNA/RNA and CTC liquid biopsies, offer a promising, less invasive alternative to traditional tissue biopsies, supporting cancer diagnostics, disease monitoring, and informing treatment decisions by providing comprehensive blood-based genetic data and early detection capabilities.

Methods: A literature search was conducted on the use of cfDNA/cfRNA and CTCs in liquid biopsies for cancer detection, recent advancements, and their efficacy compared to traditional cancer screening methods, such as tissue biopsies.

Results: Traditional screening techniques like mammography, colonoscopy, CT scans, and tissue biopsies are often invasive or limited to isolated tumors, while liquid biopsies offer a minimally invasive method to detect one or more cancer types from a single blood draw, providing real-time cancer characterization and continuous monitoring. Despite their potential advantages, liquid biopsies are not yet widely accepted as replacements for tissue biopsies, which remain the standard for initial tumor diagnosis and staging, and are limited in sensitivity for detecting certain cancers that do not shed sufficient genetic material into the bloodstream.

Discussion: Liquid biopsies offer significant advancements in personalized medicine by providing detailed molecular profiles of tumors, guiding targeted therapies, and enabling precise, individualized treatment plans. Additionally, point-of-care liquid biopsy tests have the potential to make cancer screening more accessible and convenient, especially in low-resource settings, by allowing rapid, on-site analysis with reduced healthcare costs.

Conclusion: CTC and cfDNA/cfRNA liquid biopsies offer a transformative approach to cancer screening by detecting blood-based cancer biomarkers. They provide a non-invasive, real-time snapshot of tumor heterogeneity, aiding in early cancer detection, continuous monitoring, and informing treatment response, though further research and technological advancements in liquid biopsy sensitivity are needed for full clinical integration.

Keywords: cancer screening; circulating tumor cells; CTCs; cell-free DNA; cfDNA; cell-free RNA; cfRNA; liquid biopsy; multi-cancer detection

Introduction

Cancer treatments are often highly invasive and costly, typically involving surgery, chemotherapy, radiotherapy, or hormonal therapy, all of which carry great risks to patient mortality and survivorship. Despite advances in immunotherapy and precision medicine, cancer is still among the top causes of death around the world, highlighting several key issues: the absence of a definitive cure, the impossibility of direct prevention, and the challenges of early detection [1]. These issues emphasize the need for advancements in cancer screening technology, which are crucial for supporting cancer treatment workflows and improving diagnostic accuracy. Improved cancer screening strategies can lead to more effective interventions for high-risk populations while reducing healthcare costs for the general public.

Cancer screening aims to detect cancer at an early and more treatable stage. Cancer screening workflows rely on various tests and procedures, including both traditional and emerging biopsy techniques. The traditional approach, tissue biopsy, involves examining tumor tissue obtained through invasive procedures. The difference between invasive and minimally invasive procedures lies in the extent of tissue disruption; invasive procedures require larger incisions or significant body entry, while minimally invasive techniques use smaller incisions to minimize tissue damage and recovery time. Tissue biopsy is

associated with discomfort, substantial costs, and occasionally, is ineffective due to its inability to capture tumor heterogeneity [2]. In contrast, emerging methods such as liquid biopsies, specifically blood-based circulating tumor cell (CTC) and cell-free (cf) liquid biopsies, offer less invasive alternatives that involve analyzing CTC's, cell-free DNA (cfDNA), or cell-free RNA (cfRNA) and other cancer biomarkers present in the blood or plasma, as opposed to surgically obtained tumor samples. cfDNA and cfRNA are derived from the natural process of cell death, where circulating DNA and RNA fragments are shed into the bloodstream. This includes DNA and RNA from tumor cells, providing a cancer "fingerprint" that can be used to identify specific cancer types [3]. Similarly, CTCs are shed from solid tumors that enter the bloodstream directly through the endothelium or indirectly through the lymphatic system. CTCs are considered a primary mechanism for distant metastasis, and as such their presence in peripheral blood allows for a convenient liquid biopsy of cancer [4].

The advantage of using liquid biopsy over traditional tissue biopsy lies in its minimally invasive nature and its potential to efficiently reflect the entire genetic composition of the tumor, which supports faster and more informed cancer diagnosis and treatment decisions [5].

Since the U.S. Food and Drug Administration approved the first liquid biopsy test for cancer monitoring and blood-based genetic testing in the 2010s, liquid biopsies have played an important role in providing new approaches to cancer diagnostics, disease monitoring, and clinical decision-making through the analysis of CTCs and cfDNA/cfRNA [6, 7]. Compared to traditional tissue biopsies, blood-based liquid biopsies can allow for the detection of cancer at earlier stages when it is more treatable and provide further insights into disease progression and resistance mechanisms [2]. The Galleri Test, for example, is able to detect signals from multiple cancer types from cfDNA in the blood, significantly expanding the scope of early detection [8, 9]. However, challenges remain, including the sensitivity and specificity of tests, interpretation of results, high costs of screening, and integration of liquid biopsy into existing screening protocols [10]. Despite these challenges, blood-based liquid biopsies continue to hold clinical promise, particularly in supporting cancer diagnostics and understanding intratumoral heterogeneity and dynamics, and as a result, have the potential to play a key role in comprehensive cancer management [2].

This paper evaluates CTC and cell-free liquid biopsies across various use cases, specifically in cancer detection, to determine their optimal application in clinical settings compared to traditional screening methods. It explores the basic functions of CTC and cf liquid biopsies, current innovations, and future research directions. Further, this review examines how CTC and cf liquid biopsies can be integrated with other screening methods to improve cancer diagnosis and treatment strategies, ultimately aiming to reduce the global burden of cancer.

Methods

The literature search for this study was conducted for peer-reviewed articles that describe the use of CTCs and cfDNA/cfRNA in the context of liquid biopsies for cancer detection, current methodologies and recent advancements in the field of liquid biopsies, and the efficacy of liquid biopsies compared to traditional cancer screening methods. Several databases, including PubMed, BioMed Central, SciDirect, and Wiley, were used to ensure a broad and thorough review of the current research on CTC and cfDNA/cfRNA liquid biopsies. The search strategy employed a combination of keywords and phrases to capture all relevant studies. The primary keywords used were "cancer screening," "circulating tumor cells," "CTCs," "cell-free DNA," "cfDNA," "cfRNA," "liquid biopsy," and "multi-cancer detection." The literature considered in this review spanned from March 2004 to January 2024.

Results

Biological Basis of Liquid Biopsies

The mechanisms of CTC and cell-free nucleic acid release into circulation, differences between tumor-derived and normal cell-derived nucleic acids, and factors affecting CTC and cfDNA/cfRNA concentrations in blood, collectively form the biological basis for minimally invasive blood-based cancer detection and monitoring through liquid biopsies.

cfDNA and cfRNA are released into the bloodstream primarily through apoptosis and necrosis of cells, including tumor cells [11, 12]. Apoptosis results in the release of DNA fragments of approximately 167 base pairs, corresponding to the length of DNA wrapped around a nucleosome. On the other hand, necrosis produces larger DNA fragments due to the more "chaotic" breakdown of cellular structures [11]. In cancer screening, this is especially important because these larger fragments are less frequently detected in plasma samples, whereas in the process of apoptosis, which is the main mechanism of cfDNA generation, smaller, more uniform fragments that are more readily analyzed are produced, thereby making cfDNA read length a crucial quality control metric in the cancer screening workflow [11, 13]. Additionally, active secretion via extracellular vesicles from viable cells also contributes to the presence of cfDNA and cfRNA in circulation. Along with cf nucleic acid release mechanisms, differences between tumor-derived and normal cell-derived nucleic acids are important to consider in understanding liquid biopsies. Tumor-derived cfDNA, otherwise known as circulating tumor DNA (ctDNA), and cfRNA, or circulating tumor RNA (ctRNA), exhibit distinct characteristics compared to their normal cell-derived counterparts. ctDNA is shorter than cfDNA from non-cancer cells due to cancer-

related hypomethylation, making it more susceptible to nuclease cleavage [13]. Further, ctDNA contains tumor-specific genetic alterations, such as mutations, copy number variations, and methylation patterns, which can serve as highly specific markers for cancer detection. On the other hand, CTCs are tumor cells shed from the primary tumor and carried through the circulatory or lymphatic systems. While most research has focused on CTCs in the bloodstream, these cells are distinct from primary tumor cells, possessing unique properties that aid in detaching from the tumor, intravasating into the blood, and forming clusters with more metastatic potential. Isolating CTCs, as well as cfDNA/RNA from other blood-based biomarkers, has been a challenge, but recent advancements have enabled research into CTC biology and their use in cancer screening [14]. Finally, understanding the biological basis of liquid biopsies requires considering several factors that influence the concentrations of CTCs and cfDNA/cfRNA in the blood. Namely, high tumor burden significantly correlates with increased levels of CTCs, ctDNA, and ctRNA, while low tumor burden results in lower concentrations, highlighting the need for improved sensitivity in liquid biopsies for full clinical integration. Additionally, factors such as the rate of cell turnover, the efficiency of DNA and RNA clearance from the bloodstream, and the presence of RNases that degrade RNA molecules also play crucial roles [12, 13].

Overview of Different Liquid Biopsy Technologies

Liquid biopsy technologies that detect CTCs and cfDNA/cfRNA include various use cases. The Epithelial ImmunoSPOT (EPISPOT) assay analyzes CTCs and has shown success in patients with breast, colon, and prostate cancer [15]. It uses antibodies that attach to the EpCAM gene or CD326 on tumor cells which allows these cells to be cultured both in living organisms and in lab conditions. The CellSearch system also detects antibodies to isolate CTCs with epithelial markers like EpCAM and has shown a correlation between CTC counts and patient survival in prostate cancer. Specifically, the CellSearch system uses immunomagnetic separation to capture CTCs and identifies them through fluorescent staining based on cytokeratin, DAPI, and CD45 markers [16]. Droplet digital PCR (ddPCR), on the other hand, detects ctDNA which is released into the bloodstream from dying cancer cells. By amplifying and analyzing ctDNA thorough polymerase chain reaction (PCR), ddPCR identifies tumor-specific mutations, which allows for more effective monitoring of cancer progression and treatment response. As such, the ability to detect and quantify ctDNA with high precision makes ddPCR a valuable technology in the field of personalized oncology [42]. The cobas® EGFR Mutation Test v2 similarly uses PCR to amplify target EGFR sequences, making it highly sensitive to low levels of mutant DNA. It is cfDNA-based and detects mutations in the epidermal growth factor receptor (EGFR) gene, such as exon 19 deletions, exon 21 L858R substitutions, and exon 20 T790M resistance mutations, by using cfDNA collected from a patient's plasma [47]. The Quantidex qPCR BCR-ABL IS Kit, however, is a cfRNA-based test used to screen for chronic myeloid leukemia (CML) through PCR quantification of BCR-ABL1 transcripts. BCR-ABL1 transcripts result from the fusion of the BCR and ABL1 genes, which produces an abnormal tyrosine kinase that commonly causes CML, making it a key CML biomarker. By providing a minimally invasive and effective way of measuring BCR-ABL1 transcript levels, which can be used to evaluate treatment response to tyrosine kinase inhibitor therapy, Quantidex qPCR BCR-ABL IS allows for more accurate treatment and disease monitoring in CML patients [50]. As evidenced in Table 1, the wide range of sensitivity in various blood-based liquid biopsy tests reflects differences in sequencing approaches, depth of coverage, and other factors across different studies and clinical settings, emphasizing the need for standardization in the laboratory.

Table 1. Comparison of commonly used liquid biopsy techniques. The table provides a detailed comparison of various liquid biopsy analytes (CTCs, ctDNA, cfDNA, cfRNA) and their associated tumor types, detection technologies, sensitivity limits, and basis of detection.

Liquid Biopsy	Cancer	Technology	Sensitivity	Detection	Ref
CTCs	Breast	Celsee systems	94%	Size differences, deformability	[34]
	Breast	ApoStream™	2 CTCs/7.5 mL	Surface charge, polarizability	[35]
	Breast	CTC-Chip	5-1; 281 CTCs/mL	Tumor specific antigens	[36, 37]
	Breast	RosetteSep	2 CTCs/mL	CD4, DGC	[38]
	Breast, Prostate, Colon	EPISPOT/S100-EPISPOT	48%; 22 CTCs	EpCAM/CD326	[39]
	Prostate	AdnaTest	2 CTCs	EpCAM, PSA, PSMA PCR	[40]
	Prostate	CellSearch system	73% for CTCs ≥ 2; 69% for CTCs ≥ 5 per 7.5 mL	EpCAM	[41]
ctDNA	Breast, Prostate, Colorectal	Droplet digital PCR	MAF detection < 0.1%	N/A	[42]
	Breast, Prostate, Colorectal	BEAMing	MAF detection ~ 0.02%	N/A	[43]
	Colorectal, Breast	PARE	ctDNA detection < 0.001%	N/A	[44]
	Ovarian, Breast	TAm-Seq/eTAm-Seq	MAF detection ~ 2%; MAF detection ~ 0.25%	N/A	[45]
	Lung	CAPP-Seq	MAF detection ~ 0.02%	N/A	[46]
cfDNA	Lung	cobas® EGFR Mutation Test v2	73%	EGFR Exon 19 deletions	[47]
	Colorectal	Epi proColon®	68.2%	4.7 pg/mL	[48]
	Colorectal	Shield™	91%	N/A	[49]
cfRNA	Blood	Quantidex qPCR BCR-ABL IS Kit	MR4 (1 in 10,000 cells)	BCR-ABL1 and ABL1	[50]
	Blood	QXDx BCR-ABL %IS Kit for use on the QXDx Auto DG ddPCR System	MR4.5 to MR5 (1 in 100,000 to 1,000,000 cells)	BCR-ABL1 and ABL1	[51]
	Blood	MRDx BCR-ABL Test, MRDx BCR-ABL Test	MR4.5 (1 in 100,000 cells).	BCR-ABL1 and ABL1	[52]

CTCs: Circulating tumor cells, ctDNA: Circulating tumor DNA, EPISPOT: Epithelial ImmunoSPOT, DGC: Density gradient centrifugation, PARE: Personalized analysis of rearranged ends, MAF: Mutant allele fraction. MR: Molecular Response, MR4: 4-log reduction, meaning a 10,000-fold decrease in BCR-ABL levels, MR4.5: 4.5-log, MR5: 5-log reduction.

Clinical Applications and Case Studies

Liquid biopsies have emerged as a promising tool for improving cancer detection and management, demonstrating potential across various clinical applications. They can offer clinical value by identifying biomarkers, such as ctDNA which can correlate with disease progression, that ultimately helps predict responses to specific therapies. In the realm of early cancer detection, the CancerSEEK test [17], which analyzes ctDNA and protein biomarkers, has shown significant promise. A study involving 1,005 patients with non-metastatic cancers reported a median sensitivity of 70% across eight cancer types, with high sensitivity for ovarian (98%) and liver (100%) cancers [17]. Further, liquid biopsies have been applied in detecting minimal residual disease, potentially predicting cancer recurrence. A study of 130 stage II colon cancer patients found that ctDNA detection after surgery identified all patients who later relapsed, with a median time of 167 days before recurrence [19]. In the context of treatment selection, a study of 323 Non-Small Cell Lung Cancer (NSCLC**)** patients showed that ctDNA analysis detected Epidermal Growth Factor Receptor (EGFR) mutations in 72% of cases, comparable to tissue biopsy results [18]. The potential of liquid biopsies for multi-cancer early detection has been demonstrated by the Galleri test, which analyzes cell-free DNA. In a study of 6,689 individuals aged 50 and older, the test detected 29 cancers across 13 types not typically screened for, with a 38.7% true positive rate and 99.3% specificity [17]. Studies like those on the Galleri Test have demonstrated the potential of liquid biopsies to detect multiple cancer types from a single blood sample, significantly expanding the scope of early detection.

Along the same lines, the QuantideX qPCR BCR-ABL IS Kit is a FDA approved cfRNA liquid biopsy test for cancer screening, and has undergone rigorous clinical trials to validate its performance as a monitoring tool for CML. Key findings from these trials highlight the kit's sensitivity, with a limit of detection of 0.002% International Scale or MR4, which allows for the detection of very low levels of BCR-ABL transcripts [20]. The test demonstrated a linear relationship from MR0.3 to MR4.7, highlighting its effectiveness for continuous disease monitoring. Additional studies reported a maximum standard deviation of 0.13 MR within the MR0.7-MR3.7 range, based on over 7,300 data points from RNA extracted from human peripheral blood, demonstrating reproducible results across various testing environments [20, 21]. As the first FDA-cleared cfRNA liquid biopsy screening test for BCR-ABL1 transcripts in CML patients, the QuantideX kit sets a new standard in molecular monitoring; these studies suggest that it is a highly sensitive, reliable, and reproducible tool that enhances monitoring capabilities, enabling clinicians to make timely treatment decisions that could support cancer screening workflows and improve patient outcomes. With its high sensitivity and rapid turnaround time (~4 hours), the QuantideX qPCR BCR-ABL IS Kit allows healthcare providers to monitor treatment responses closely, supporting personalized treatment strategies based on real-time data [20, 22].

Liquid Biopsies vs. Conventional Screening Methods

While conventional screening techniques like mammography, colonoscopy, CT scans, and tissue biopsies as a whole are limited to isolated tumors and often invasive, liquid biopsies provide a minimally invasive approach that can potentially detect multiple cancer types from a single blood draw [37]. Conventional methods typically offer a snapshot of the tumor at a specific time, whereas liquid biopsies can provide real time characterization of cancers, allowing for continuous monitoring of disease progression and treatment response [12]. Additionally, liquid biopsies can overcome the limitations of tumor heterogeneity by sampling ctDNA, ctRNA, or other cell types that characterize the entire tumor, unlike traditional tissue biopsies that may miss certain mutations due to localized sampling [10]. Liquid biopsies have the potential to be more cost-effective, efficient, and less invasive compared to conventional tissue biopsies, but despite their potential, liquid biopsies are not yet widely accepted as a replacement for tissue biopsies in clinical practice [5]. Tissue biopsies remain the gold standard for initial tumor diagnosis and histological evaluation, which are essential for accurate staging and treatment planning [23]. Liquid biopsies are currently seen as complementary tools rather than standalone diagnostic methods. Further, the sensitivity of liquid biopsies is also limited for detecting certain types of cancers, particularly those that do not follow a hematogenous spread pattern. For example, cancers that primarily spread through lymphatic routes or remain localized may not shed sufficient ctDNA into the bloodstream for detection by liquid biopsies [23].

Table 2. Comparison of Conventional Tissue Biopsy and Liquid Biopsy

Liquid Biopsy	Tissue Biopsy
Minimally invasive	Invasive
Shorter time	Longer time
Highly sensitive	Lower sensitivity
Reveals tumor heterogeneity	Does not reveal tumor heterogeneity
Lower cost of specimen collection	Higher cost of specimen collection
Continuous tumor monitoring	Tumor snapshots
Real time drug response monitoring	No real time monitoring of drug response
Repeated specimen collection	Repeated surgeries not feasible

Discussion

Current State of Liquid Biopsy Technology

The field of liquid biopsies has evolved significantly, particularly with the emergence of fragmentomics, an innovative approach that focuses on analyzing cfDNA fragment characteristics in plasma. The study by Qi et al. (2023) highlights that cfDNA carries vital epigenetic information reflective of its tissue of origin, making it a promising tool for minimally invasive tumor diagnostics [24]. One significant challenge in fully integrating cfDNA liquid biopsies in the clinic is the low yield of measurable cfDNA in blood samples, which include fragments from various cell sources. Fragmentomics addresses this by characterizing cfDNA fragments based on fragment length, end motifs, and fragmentation patterns, among others. Qi et al. (2023) demonstrated that these characteristics differ significantly for individuals with cancer. For example, ctDNA is associated with shorter fragment lengths compared to normal-cell-derived cfDNA, at approximately 143 bp for cancer patients compared to 167 bp for healthy individuals [24]. Further, fragmentomics can allow clinicians to identify specific tumors in the body by tracing epigenetic markers within cfDNA fragments. These unique patterns, such as preferred end coordinates and nucleosome footprints, is particularly valuable in oncology, where distinguishing between normal and ctDNA can improve early screening and monitoring of cancer progression [24]. However, despite its promise, the field faces challenges related to preexisting sensitivity limits in current screening technology, which prevents library construction for sequencing and ultimately reduces diagnostic accuracy [24].

Challenges of Clinical Integration

The integration of cfDNA and cfRNA liquid biopsies into standard cancer screening workflows face several challenges. Sensitivity and specificity remain significant hurdles, particularly in the detection of early-stage cancers where tumor-derived genetic material may be present at very low concentrations in the blood [25, 26]. More studies are needed to assess the accuracy of liquid biopsies and their ability to identify various tumor types effectively [4]. For example, nanopore sequencing and AI-assisted analysis could allow for the detection of even smaller quantities of tumor-derived genetic material which shows promise for improving the sensitivity and specificity of liquid biopsies [26, 27]. On the other hand, there is variability in the performance of different liquid biopsy technologies, which can lead to inconsistent results across studies [27]. These limitations reveal the need for further technological advancements and standardization in liquid biopsy methodologies. This includes larger, multicenter trials, standardized protocols, and comprehensive data reporting. Collaboration among researchers, healthcare workers, and industry stakeholders will be central to overcoming existing challenges and realizing the full potential of liquid biopsies in cancer screening and management [10, 11].

Regulatory and ethical considerations further complicate the integration of liquid biopsies into the clinic, as ensuring patient safety and protecting health data while validating new diagnostic methods requires stringent oversight and clear ethical guidelines that are not yet in place [28]. For example, the comprehensive data provided by liquid biopsies raises concerns regarding overdiagnosis and the resulting psychological impact on patients. The increased sensitivity of these tests may lead to the detection of cancers that may not develop or cause harm, resulting in unnecessary treatments and psychological stress for patients. It is important to balance the benefits of early detection with the risks of overdiagnosis and to offer appropriate counseling and support to patients [29]. Further, the cost-effectiveness of liquid biopsies varies greatly depending on the healthcare setting and the specific use

case. For colorectal cancer screening in the United States, conventional colonoscopy still remains the most cost-effective method, with an incremental cost-effectiveness ratio (ICER) of $28,071 per year of life gained. While liquid biopsies offer a non-invasive alternative and can increase adherence to screening, they are not yet fully cost-effective when used as the primary screening method. For example, the ICER for a colonoscopy-liquid biopsy hybrid approach was significantly higher at $377,538 per year of life gained, indicating that the cost still outweighs the benefits at this stage [30].

Implications for Cancer Screening and Management

Liquid biopsies have the potential to provide significant advancements in the field of personalized medicine by providing detailed molecular profiles of tumors, which can guide the selection of targeted therapies. This approach allows for more precise treatment plans tailored to the genetic makeup of an individual's cancer, potentially increasing the efficacy of treatment and reducing adverse effects [31]. Similarly, multi-modal screening approaches that combine liquid biopsies with other molecular or imaging biomarkers could enhance the accuracy and reliability of cancer detection and monitoring [32].

The development of point-of-care liquid biopsy tests could make cancer screening more accessible and convenient, particularly in low-resource settings. These tests would allow for rapid, on-site analysis of biofluids, providing immediate results and facilitating timely clinical decision-making [31, 32]. As a result, liquid biopsies have the potential to significantly reduce health inequities in cancer screening by addressing several barriers that underserved populations face. Traditional cancer screening methods often require invasive procedures and access to specialized medical facilities, which can be problematic for individuals with limited resources. Liquid biopsies offer a minimally invasive, cost-effective, and accessible alternative that have the potential to be integrated into routine healthcare visits, thereby increasing adherence to screening guidelines among populations that are typically underrepresented in cancer screening programs. Additionally, liquid biopsies can facilitate early detection of multiple cancer types simultaneously, which is particularly beneficial for communities exposed to environmental carcinogens or those with higher cancer incidence rates due to socioeconomic factors [32]. By simplifying the screening process and making it more accessible, liquid biopsies can help bridge the gap in cancer care, ensuring that all individuals, regardless of their socioeconomic status, have the opportunity for early detection and timely treatment of cancer [33].

Conclusions

cfDNA and cfRNA liquid biopsies represent a new transformative approach in cancer screening, leveraging the biological basis of circulating nucleic acids released from tumor cells into the bloodstream. Clinically, liquid biopsies have demonstrated potential in early cancer detection, monitoring disease progression, and assessing treatment response, and compared to conventional screening methods, offer a non-invasive, real-time, and comprehensive snapshot of tumor heterogeneity. While liquid biopsies hold significant promise for improving cancer detection and management, further research and technological advancements are needed to address current limitations and fully integrate these tools into clinical practice. Nevertheless, the implications of liquid biopsies for cancer screening and management are profound, potentially enabling earlier detection, personalized treatment strategies, and improved accessibility, emphasizing the importance of continued investment in this rapidly evolving field.

List of Abbreviations Used

cell-free: cf
cell-free DNA: cfDNA
cell-free RNA: cfRNA
CML: chronic myeloid leukemia
CT: computed tomography
ctDNA: circulating tumor DNA
ctRNA: circulating tumor RNA
ddPCR: droplet digital PCR
DGC: density gradient centrifugation
EPISPOT: EPithelial ImmunoSPOT
CTCs: circulating tumor cells
EGFR: epidermal growth factor receptor
ICER: incremental cost-effectiveness ratio
MR: molecular response
NSCL: non-small cell lung cancer

Conflicts of Interest

The author declares that they have no conflict of interest.

Ethics Approval and/or Participant Consent

The study required no ethics approval or participant consent.

Authors' Contributions

DWR: contributed to the design of the study, the review of literature and collection of data, interpretation and analysis of the data, revised the manuscript, and gave final approval of the version to be published.

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References

[1] Upadhyay A. Cancer: An unknown territory; rethinking before going ahead. Genes & Diseases. 2021 Sep;8(5):655–61. https://doi.org/10.1016/j.gendis.2020.09.002

[2] Hirahata T, Ul Quraish R, Quraish AU, Ul Quraish S, Naz M, Razzaq MA. Liquid Biopsy: A Distinctive Approach to the Diagnosis and Prognosis of Cancer. Cancer Inform. 2022 Jan;21:117693512210760. https://doi.org/10.1177%2F11769351221076062

[3] Shegekar T, Vodithala S, Juganavar A. The Emerging Role of Liquid Biopsies in Revolutionising Cancer Diagnosis and Therapy. Cureus. 2023 Aug 17;15(8):e43650. https://doi.org/10.7759/cureus.43650

[4] Edd JF, Mishra A, Smith KC, Kapur R, Maheswaran S, Haber DA, et al. Isolation of circulating tumor cells. iScience. 2022 Aug;25(8):104696. https://doi.org/10.1016%2Fj.isci.2022.104696

[5] Adhit KK, Wanjari A, Menon S, K S. Liquid Biopsy: An Evolving Paradigm for Non-invasive Disease Diagnosis and Monitoring in Medicine. Cureus. 2023 Dec 8;15(12):e50176. https://doi.org/10.7759/cureus.50176

[6] Caputo V, Ciardiello F, Della Corte CM, Martini G, Troiani T, Napolitano S. Diagnostic value of liquid biopsy in the era of precision medicine: 10 years of clinical evidence in cancer. Exploration of Targeted Anti-tumor Therapy. 2023 Feb 28;102–38. https://doi.org/10.37349%2Fetat.2023.00125

[7] Kwapisz D. The first liquid biopsy test approved. Is it a new era of mutation testing for non-small cell lung cancer? Ann Transl Med. 2017 Feb;5(3):46–46. https://doi.org/10.21037/atm.2017.01.32

[8] Turnbull C, Wald N, Sullivan R, Pharoah P, Houlston RS, Aggarwal A, et al. GRAIL-Galleri: why the special treatment? The Lancet. 2024 Jan;403(10425):431-432. https://doi.org/10.1016/s0140-6736(23)02830-1

[9] Neal RD, Johnson P, Clarke CA, Hamilton SA, Zhang N, Kumar H, et al. Cell-Free DNA–Based Multi-Cancer Early Detection Test in an Asymptomatic Screening Population (NHS-Galleri): Design of a Pragmatic, Prospective Randomised Controlled Trial. Cancers. 2022 Oct 1;14(19):4818. https://doi.org/10.3390/cancers14194818

[10] Anitha K, Posinasetty B, Naveen Kumari K, Chenchula S, Padmavathi R, Prakash S, et al. Liquid biopsy for precision diagnostics and therapeutics. Clinica Chimica Acta. 2024 Feb;554:117746. https://doi.org/10.1016/j.cca.2023.117746

[11] Heitzer E, Auinger L, Speicher MR. Cell-Free DNA and Apoptosis: How Dead Cells Inform About the Living. Trends in Molecular Medicine. 2020 May;26(5):519–28. https://doi.org/10.1016/j.molmed.2020.01.012

[12] Connal S, Cameron JM, Sala A, Brennan PM, Palmer DS, Palmer JD, et al. Liquid biopsies: the future of cancer early detection. J Transl Med. 2023 Feb 11;21(1):118. https://doi.org/10.1186/s12967-023-03960-8

[13] Stejskal P, Goodarzi H, Srovnal J, Hajdúch M, Van 'T Veer LJ, Magbanua MJM. Circulating tumor nucleic acids: biology, release mechanisms, and clinical relevance. Mol Cancer. 2023 Jan 21;22(1):15. https://doi.org/10.1186/s12943-022-01710-w

[14] Lin D, Shen L, Luo M, Zhang K, Li J, Yang Q, et al. Circulating tumor cells: biology and clinical significance. Sig Transduct Target Ther. 2021 Nov 22;6(1):404. https://doi.org/10.1038/s41392-021-00817-8

[15] Alix-Panabières, C., & Pantel, K. Liquid biopsy in cancer patients: advances in capturing viable CTCs for functional studies using the EPISPOT assay. Expert Review of Molecular Diagnostics. 2015 Sep 21;15(11):1411–1417. https://doi.org/10.1586/14737159.2015.1091729

[16] De Bono JS, Scher HI, Montgomery RB, Parker C, Miller MC, Tissing H, et al. Circulating Tumor Cells Predict Survival Benefit from Treatment in Metastatic Castration-Resistant Prostate Cancer. Clinical Cancer Research. 2008 Oct 1;14(19):6302–9. https://doi.org/10.1158/1078-0432.ccr-08-0872

[17] Cohen JD, Li L, Wang Y, Thoburn C, Afsari B, Danilova L, et al. Detection and localization of surgically resectable cancers with a multi-analyte blood test. Science. 2018 Feb 23;359(6378):926–30. https://doi.org/10.1126/science.aar3247

[18] Wang W, He Y, Yang F, Chen K. Current and emerging applications of liquid biopsy in pan-cancer. Translational Oncology. 2023 Aug;34:101720. https://doi.org/10.1016%2Fj.tranon.2023.101720

[19] Page RD, Drusbosky LM, Dada H, Raymond VM, Daniel DB, Divers SG, et al. Clinical Outcomes for Plasma-Based Comprehensive Genomic Profiling Versus Standard-of-Care Tissue Testing in Advanced Non–Small Cell Lung Cancer. Clinical Lung Cancer. 2022 Jan;23(1):72–81. https://doi.org/10.1016/j.cllc.2021.10.001

[20] Brown JT, Beldorth IJ, Laosinchai-Wolf W, Fahey ME, Jefferson KL, Ruskin AK, et al. Analytical Validation of a Highly Sensitive, Multiplexed Chronic Myeloid Leukemia Monitoring System Targeting BCR-ABL1 RNA. The Journal of Molecular Diagnostics. 2019 Jul;21(4):718–33. https://doi.org/10.1016/j.jmoldx.2019.03.002

[21] Kim JC, Chan-Seng-Yue M, Ge S, Zeng AGX, Ng K, Gan OI, et al. Transcriptomic classes of BCR-ABL1 lymphoblastic leukemia. Nat Genet. 2023 Jul;55(7):1186–97. https://doi.org/10.1038/s41588-023-01429-4

[22] Shelton DN, Bhagavatula P, Sepulveda N, Beppu L, Gandhi S, Qin D, et al. Performance characteristics of the first Food and Drug Administration (FDA)-cleared digital droplet PCR (ddPCR) assay for BCR::ABL1 monitoring in chronic myelogenous leukemia. Eşkazan AE, editor. PLoS ONE. 2022 Mar 17;17(3):e0265278. https://doi.org/10.1371/journal.pone.0265278

[23] Lone SN, Nisar S, Masoodi T, Singh M, Rizwan A, Hashem S, et al. Liquid biopsy: a step closer to transform diagnosis, prognosis and future of cancer treatments. Mol Cancer. 2022 Mar 18;21(1):79. https://doi.org/10.1186/s12943-022-01543-7

[24] Qi T, Pan M, Shi H, Wang L, Bai Y, Ge Q. Cell-Free DNA Fragmentomics: The Novel Promising Bio marker. IJMS. 2023 Jan 12;24(2):1503. https://doi.org/10.3390%2Fijms24021503

[25] Batool SM, Yekula A, Khanna P, Hsia T, Gamblin AS, Ekanayake E, et al. The Liquid Biopsy Consortium: Challenges and opportunities for early cancer detection and monitoring. Cell Reports Medicine. 2023 Oct;4(10): 101198. https://doi.org/10.1016/j.xcrm.2023.101198

[26] Boukovala M, Westphalen CB, Probst V. Liquid biopsy into the clinics: Current evidence and future perspectives. The Journal of Liquid Biopsy. 2024 Jun;4(8):100146. http://dx.doi.org/10.1016/j.jlb.2024.100146

[27] Febbo PG, Allo M, Alme EB, Cuyun Carter G, Dumanois R, Essig A, et al. Recommendations for the Equitable and Widespread Implementation of Liquid Biopsy for Cancer Care. JCO Precis Oncol. 2024 Feb; (8):e2300382. https://doi.org/10.1200/po.23.00382

[28] Levit LA, Peppercorn JM, Tam AL, Marron JM, Mathews DJH, Levit K, et al. Ethical Framework for Including Research Biopsies in Oncology Clinical Trials: American Society of Clinical Oncology Research Statement. JCO. 2019 Sep 10;37(26):2368–77. https://doi.org/10.1200/jco.19.01479

[29] Alimirzaie S, Bagherzadeh M, Akbari MR. Liquid biopsy in breast cancer: A comprehensive review. Clinical Genetics. 2019 Jun;95(6):643–60. https://doi.org/10.1111/cge.13514

[30] Aziz Z, Wagner S, Agyekum A, Pumpalova YS, Prest M, Lim F, et al. Cost-Effectiveness of Liquid Biopsy for Colorectal Cancer Screening in Patients Who Are Unscreened. JAMA Netw Open. 2023 Nov 16;6(11): e2343392. https://doi.org/10.1001/jamanetworkopen.2023.43392

[31] Siravegna G, Marsoni S, Siena S, Bardelli A. Integrating liquid biopsies into the management of cancer. Nat Rev Clin Oncol. 2017 Sep;14(9):531–48. https://doi.org/10.1038/nrclinonc.2017.14

[32] Heitzer E, Haque IS, Roberts CES, Speicher MR. Current and future perspectives of liquid biopsies in genomics-driven oncology. Nat Rev Genet. 2019 Feb;20(2):71–88. https://doi.org/10.1038/s41576-018-0071-5

[33] Pink RC, Beaman EM, Samuel P, Brooks SA, Carter DRF. Utilising extracellular vesicles for early cancer diagnostics: benefits, challenges and recommendations for the future. Br J Cancer. 2022 Feb 1;126(3):323–30. https://doi.org/10.1038/s41416-021-01668-4

[34] Gogoi P, Sepehri S, Zhou Y, Gorin MA, Paolillo C, Capoluongo E, et al. Development of an Automated and Sensitive Microfluidic Device for Capturing and Characterizing Circulating Tumor Cells (CTCs) from Clinical Blood Samples. Chalmers J, editor. PLoS ONE. 2016 Jan 25;11(1):e0147400. https://doi.org/10.1371/journal.pone.0147400

[35] Gupta V, Jafferji I, Garza M, Melnikova VO, Hasegawa DK, Pethig R, et al. ApoStreamTM, a new dielectrophoretic device for antibody independent isolation and recovery of viable cancer cells from blood. Biomicrofluidics. 2012 Jun 1;6(2):024133. https://doi.org/10.1063/1.4731647

[36] Cristofanilli M, Stopeck A, Reuben JM. Circulating Tumor Cells, Disease Progression, and Survival in Metastatic Breast Cancer. The New England Journal of Medicine. 2004 Aug 19;351(8):781-91. https://doi.org/10.1056/nejmoa040766

[37] Sequist LV, Nagrath S, Toner M, Haber DA, Lynch TJ. The CTC-Chip: An Exciting New Tool to Detect Circulating Tumor Cells in Lung Cancer Patients. Journal of Thoracic Oncology. 2009 Mar;4(3):281–3. https://doi.org/10.1097/jto.0b013e3181989565

[38] Zuccolo J, Unruh TL, Deans JP. Efficient isolation of highly purified tonsil B lymphocytes using RosetteSep with allogeneic human red blood cells. BMC Immunol. 2009 Dec;10(1):30. https://doi.org/10.1186%2F1471-2172-10-30

[39] Alix-Panabières C, Pantel K. Liquid biopsy in cancer patients: advances in capturing viable CTCs for functional studies using the EPISPOT assay. Expert Review of Molecular Diagnostics. 2015 Nov 2;15(11): 1411–7. https://doi.org/10.1586/14737159.2015.1091729

[40] Cayrefourcq L, De Roeck A, Garcia C, Stoebner PE, Fichel F, Garima F, et al. S100-EPISPOT: A New Tool to Detect Viable Circulating Melanoma Cells. Cells. 2019 Jul 20;8(7):755. https://doi.org/10.3390%2Fcells8070755

[41] De Bono JS, Scher HI, Montgomery RB, Parker C, Miller MC, Tissing H, et al. Circulating Tumor Cells Predict Survival Benefit from Treatment in Metastatic Castration-Resistant Prostate Cancer. Clinical Cancer Research. 2008 Oct 1;14(19):6302–9. https://doi.org/10.1158/1078-0432.ccr-08-0872

[42] Ballehaninna UK, Chamberlain RS. Serum CA 19-9 as a Biomarker for Pancreatic Cancer—A Comprehensive Review. Indian J Surg Oncol. 2011 Jun;2(2):88–100.

[43] Chen M, Zhao H. Next-generation sequencing in liquid biopsy: cancer screening and early detection. Hum Genomics. 2019 Dec;13(1):34. https://doi.org/10.1007/s13193-011-0042-1
[44] Wang TL, Diaz LA, Romans K, Bardelli A, Saha S, Galizia G, et al. Digital karyotyping identifies thymidylate synthase amplification as a mechanism of resistance to 5-fluorouracil in metastatic colorectal cancer patients. Proc Natl Acad Sci USA. 2004 Mar 2;101(9):3089–94. https://doi.org/10.1073/pnas.0308716101
[45] Gormally E, Caboux E, Vineis P, Hainaut P. Circulating free DNA in plasma or serum as biomarker of carcinogenesis: Practical aspects and biological significance. Mutation Research/Reviews in Mutation Research. 2007 May;635(2–3):105–17. https://doi.org/10.1016/j.mrrev.2006.11.002
[46] Taniguchi K, Uchida J, Nishino K, Kumagai T, Okuyama T, Okami J, et al. Quantitative Detection of EGFR Mutations in Circulating Tumor DNA Derived from Lung Adenocarcinomas. Clinical Cancer Research. 2011 Dec 15;17(24):7808–15. https://doi.org/10.1158/1078-0432.ccr-11-1712
[47] Jenkins S, Yang JCH, Ramalingam SS, Yu K, Patel S, Weston S, et al. Plasma ctDNA Analysis for Detection of the EGFR T790M Mutation in Patients with Advanced Non–Small Cell Lung Cancer. Journal of Thoracic Oncology. 2017 Jul;12(7):1061–70. https://doi.org/10.1016/j.jtho.2017.04.003
[48] Shirley, M. Epi proColon® for Colorectal Cancer Screening: A Profile of Its Use in the USA. Mol Diagn Ther. 2020 Aug;24(4):497-503. https://doi.org/10.1007/s40291-020-00473-8
[49] Coronado GD, Jenkins CL, Shuster E, Johnson C, Amy D, Cook J, et al. Blood-based colorectal cancer screening in an integrated health system: a randomised trial of patient adherence. Gut. 2024 Mar 7;73(4):622-628. https://doi.org/10.1136/gutjnl-2023-330980
[50] Leung B, Aung H, Nandini A, Abdulrasool G, Lau C, Seymour L. Analytical Validation of a 37-Gene Next-Generation Sequencing Panel for Myeloid Malignancies and Review of Initial Findings Incorporating Updated 2022 Diagnostic and Prognostic Guidelines. The Journal of Molecular Diagnostics. 2024 May;26(5):399–412. https://doi.org/10.1016/j.jmoldx.2024.01.010
[51] Chung HJ, Hur M, Yoon S, Hwang K, Lim HS, Kim H, et al. Performance Evaluation of the QXDx BCR-ABL %IS Droplet Digital PCR Assay. Ann Lab Med. 2020 Jan 1;40(1):72–5. https://doi.org/10.3343%2Falm.2020.40.1.72
[52] Ross DM, Masszi T, Gómez Casares MT, Hellmann A, Stentoft J, Conneally E, et al. Durable treatment-free remission in patients with chronic myeloid leukemia in chronic phase following frontline nilotinib: 96-week update of the ENEST freedom study. J Cancer Res Clin Oncol. 2018 May;144(5):945–54. https://doi.org/10.1007/s00432-018-2604-x

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