DEVELOPMENTAL MEDICO-LIFE-SCIENCES

ISSN (P): 3007-2786, (E): 3007-2794 DOI: https://doi.org/10.69750/dmls.03.08.0225

EDITORIAL Open Access

Liquid Biopsy and Circulating Biomarkers: The Future of Early Cancer Detection

Naveed Shuja [1]

1- Professor of Biochemistry, Continental Medical College (CMC), Lahore, Pakistan.

Corresponding Author: Naveed Shuja, **Email:** rananaveedshuja@gmail.com, **Cell:** +92-3334205687

Keywords: Liquid Biopsy; Biomarkers, Tumor; Early Detection of Cancer; Cell-Free Nucleic Acids; Circulating Tumor Cells; MicroRNAs.

Received: 17/04/2026
Revised: 15/07/2026
Accepted: 19/08/2026
Published: 31/08/2026

The greatest opportunity in oncology may not lie in discovering another drug, but in diagnosing cancer before treatment becomes difficult [1]. While there have been significant advances in imaging, molecular pathology, and targeted therapies, many malignancies are still identified when symptoms have developed or when metastasis has occurred. Liquid biopsy has thus raised tremendous interest as a possible way to change the paradigm of cancer diagnosis from anatomical identification of established disease to molecular detection of cancer at the earliest stages [2].

It's an intriguing idea. Tumours constantly shed biological material into the bloodstream such as circulating tumour DNA (ctDNA), circulating tumour cells, extracellular vesicles, microRNAs, proteins, metabolites and other molecular signals. Increasingly, these signals can be detected and interpreted from a routine blood sample: modern sequencing and computational technologies. Cancer might be detected before it is visible radiographically in theory, which may allow for a window of opportunity for potentially curative intervention missed on traditional pathways of diagnosis.

Of the circulating biomarkers, ctDNA has proven to be the most intensively studied. The DNA fragments derived from a tumour may carry abnormalities such as mutations, methylation, copy number changes and specific patterns of DNA fragmentation. However, no one molecular signal is likely to suffice for universal cancer screening. The field is now multi-modal; genomic, epigenomic, proteomic and fragmentomic data are now combined with other clinical factors and machine-learning algorithms. The most ambitious example of this approach is multi-cancer early detection platforms, which seek to not just detect cancer, but to guess what tissue the cancer is arising from [4,5].

This technological advancement is impressive; however, analytical sophistication does not equal clinical utility. In the early stages of the disease, tumours may release very small amounts of DNA into the bloodstream, and sensitivity can vary widely depending on the biology of the tumour, its vascularity, anatomic site, and disease burden [6]. The signals given off by some aggressive cancers may be detectable early, while others may not give off molecular signals until relatively advanced stages. In contrast, genomic changes that are similar to those found in tumours may be the result of non-cancerous biological events such as clonal haematopoiesis. The impact of false-positive results in asymptomatic populations may be significant, with repeated imaging, invasive procedures, anxiety and unnecessary health care costs [7].

The main question is not, then, whether the liquid biopsy can detect cancer, but whether meaningful patient outcomes are improved [8]. Reduction in the number of molecular abnormalities should not be the endpoint of screening programmes reduction in the number of cases of advanced stage disease or cancer-specific mortality should be. Stage shifting is a biologically desirable phenomenon, but does not necessarily translate to lives saved. Uncontrolled lead-time bias, overdiagnosis and

identification of indolent tumors are still potential concerns and need to be addressed in prospective, sufficiently powered trials [9].

One additional problem is what occurs after a positive test. The discovery of a cancer-associated signal in the circulation and failure to obtain a reliable identification of tissue of origin might trigger a lengthy and costly diagnostic process [10]. Clinical pathways thus need to change as the assays change. In isolation, blood-based screening cannot achieve its purpose, but must be backed by a clear confirmatory pathway that includes specific imaging, endoscopy, sampling, molecular pathology, and multidisciplinary decision-making. Much like the test, architecture around the test will also play a key role in the success of liquid biopsy [11].

AI will probably play a key role in this architecture. The information about cancer in circulation is multi-dimensional and often subtle. Thousands of genomic, epigenetic, proteomic and fragmentomic features can be incorporated into machine-learning models that would be too many to manually interpret [12]. These techniques might be used to better distinguish between malignant and non-malignant signals and to better determine where a tumour originated. But algorithmic complexity brings with it extra responsibilities, which are external validation, calibration between populations, transparency, reproducibility and ongoing evaluation for demographic or biological bias [13].

These implications go beyond screening. The idea of monitoring disease is already changing with the use of circulating biomarkers. If treatment is apparently curative, identification of molecular residual disease might be a way to identify patients at risk of recurrence months before conventional imaging. Repeat ctDNA measurements can also be used to give an early indication of response, resistance or relapse. This capability of repeatedly questioning the tumour biology without the need for invasive tissue sampling could revolutionize cancer management from a series of static diagnostic snapshots into continuous molecular surveillance [14,15].

However, the future of liquid biopsy shouldn't be reserved for a few technologically advanced health systems. The death toll from cancer is also rapidly shifting to low and middle-income countries where access to pathology, imaging and specialist oncology services is already poor [16]. Cancer inequalities could be exacerbated by a diagnostic revolution that demands expensive sequencing machines, sophisticated computing systems and the need to repeatedly validate initial investigations. Scalable assays, pre-analytical standards and cost-effective laboratory procedures, and validation in diverse ethnological and geographical populations must therefore become the focus of the field [17].

More maturity will be needed in regulation too. Commercial enthusiasm is outpacing the level of evidence for population-level screening. Biomarker sensitivity and specificity determined in a case-control or high-risk study setting do not necessarily extrapolate to a low prevalence population of asymptomatic individuals in which PPV may be significantly reduced. Independent prospective validation should precede widespread implementation, and claims of clinical benefit should be separated clearly from evidence of analytical performance [18,19].

Liquid biopsy cannot and should not be presented as an alternative to imaging, pathobiology or tissue biopsy. Its future is most likely an integrated one. Molecular signals in the blood could help identify who needs imaging; imaging could be used to localise any suspicious disease; tissue could be used to make a definitive diagnosis; and serial circulating biomarkers could then be used to monitor remaining disease and response to therapy. Such an integrated diagnostic ecosystem could make cancer detection earlier, more precise, and less invasive [20].

The responsibility, as well as the promise, is therefore great. Liquid biopsy could be one of the hallmark technologies of modern oncology, but it may be so if oncologists do not fall into the trap of celebrating the achievements of molecular detection for clinical benefit in the past. The next step should go beyond ever more sophisticated assays, and to proof that these technologies lead to changes in outcomes relevant to the patient [15,16].

When cancer is diagnosed, the most important change may not only be the manner in which, but beyond that. Oncology might shift from the point of tumour detection, which is generally after it becomes anatomically apparent, to the point of malignancy recognition, which could be during its very first molecular evolution. The potential future for cancer detection could thus start not in the scan room, or with a biopsy needle, but with a signal that travels quietly in the blood [17-20].

Conflict of Interest: The author declares no conflict of interest.

Funding: This work received no external funding.

Author's Contribution: N.S. conceptualized the article, conducted the literature review, drafted the manuscript, critically revised its intellectual content, and approved the final version.

REFERENCES

1. Ma L, Guo H, Zhao Y, Liu Z, Wang C, Bu J, et al. Liquid biopsy in cancer: current status, challenges and future prospects. *Signal Transduct Target Ther.* 2024;9(1):336. doi: 10.1038/s41392-024-02021-w.
2. Fu SW, Tang C, Tan X, Srivastava S. Liquid biopsy for early cancer detection: technological revolutions and clinical dilemma. *Expert Rev Mol Diagn.* 2024;24(10):937-955. doi: 10.1080/14737159.2024.2408744.
3. Zhang Q, Zhang X, Xie P, Zhang W. Liquid biopsy: an arsenal for tumour screening and early diagnosis. *Cancer Treat Rev.* 2024;129:102774. doi: 10.1016/j.ctrv.202 4.102774.
4. Mishra M, Ahmed R, Das DK, Das Pramanik D, Dash SK, Pramanik A. Recent advancements in the application of circulating tumor DNA as biomarkers for early detection of cancers. *ACS Biomater Sci Eng.* 2024;10(8):4740-4756. doi: 10.1021/acsbiomat erials.4c00606.

5. Metcalf GAD. MicroRNAs: circulating biomarkers for the early detection of imperceptible cancers via biosensor and machine-learning advances. *Oncogene.* 2024;43(28):2135-2142. doi: 10.1038/s41388-024-03076-3.
6. Rayamajhi S, Sipes J, Tetlow AL, Saha S, Bansal A, Godwin AK. Extracellular vesicles as liquid biopsy biomarkers across the cancer journey: from early detection to recurrence. *Clin Chem.* 2024;70(1):206-219. doi: 10.1093/clinchem/hvad176.
7. Lee Van E, Pinsky P. Predictive performance of cell-free nucleic acid-based multi-cancer early detection tests: a systematic review. *Clin Chem.* 2024;70(1):90-101. doi: 10.1093/clinchem/hvad134.
8. Guerra CE, Sharma PV, Castillo BS. Multi-cancer early detection: the new frontier in cancer early detection. *Annu Rev Med.* 2024;75:67-81. doi: 10.1146/annurev-med-050522-033624.
9. Zhang K, Fu R, Liu R, Su Z. Circulating cell-free DNA-based multi-cancer early detection. *Trends Cancer.* 2024;10(2):161-174. doi: 10.1016/j.trecan.2023.08.010.
10. Wang X, Wang L, Lin H, Zhu Y, Huang D, Lai M, et al. Research progress of CTC, ctDNA, and EVs in cancer liquid biopsy. *Front Oncol.* 2024;14:1303335. doi: 10.3389/fonc.2024.1303335.
11. Ge Q, Zhang ZY, Li SN, Ma JQ. Liquid biopsy: comprehensive overview of circulating tumor DNA. *Oncol Lett.* 2024;28(5):548. doi: 10.3892/ol.2024.14681.
12. Febbo PG, Allo M, Alme EB, Carter GC, Dumanois R, Essig A, et al. Recommendations for the equitable and widespread implementation of liquid biopsy for cancer care. *JCO Precis Oncol.* 2024;8. doi: 10.1200/PO.23.00382.
13. Bao H, Yang S, Chen X, Dong G, Mao Y, Wu S, et al. Early detection of multiple cancer types using multidimensional cell-free DNA fragmentomics. *Nat Med.* 2025;31(8):2737-2745. doi: 10.1038/s41591-025-03735-2.
14. Nguyen VTC, Nguyen TH, Doan NNT, Pham TMQ, Nguyen GTH, Nguyen TD, et al. Multimodal analysis of methylomics and fragmentomics in plasma cell-free DNA for multi-cancer early detection and localization. *eLife.* 2023;12. doi: 10.7554/eLife.89083.
15. Alexander GE, Lin W, Ortega FE, Ramaiah M, Jung B, Ji L, et al. Analytical validation of a multi-cancer early detection test with cancer signal origin using a cell-free DNA-based targeted methylation assay. *PLoS One.* 2023;18(4). doi: 10.1371/journal.pone.0283001.
16. Schrag D, Beer TM, McDonnell CH 3rd, Nadauld L, Dilaveri CA, Reid R, et al. Blood-based tests for multicancer early detection (PATHFINDER): a prospective cohort study. *Lancet.* 2023;402(10409):1251-1260. doi: 10.1016/S0140-6736(23)01700-2.
17. Jamshidi A, Liu MC, Klein EA, Venn O, Hubbell E, Beausang JF, et al. Evaluation of cell-free DNA approaches for multi-cancer early detection. *Cancer Cell.* 2022;40(12):1537-1549.e12. doi: 10.1016/j.ccell.2022.10.022.
18. Liu MC, Oxnard GR, Klein EA, Swanton C, Seiden MV; CCGA Consortium. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. *Ann Oncol.* 2020;31(6):745-759. doi: 10.1016/j.annonc.2020.02.011.
19. Lennon AM, Buchanan AH, Kinde I, Warren A, Honushefsky A, Cohain AT, et al. Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention. *Science.* 2020;369(6499). doi: 10.1126/science.abb9601.
20. Cristiano S, Leal A, Phallen J, Fiksel J, Adleff V, Bruhm DC, et al. Genome-wide cell-free DNA fragmentation in patients with cancer. *Nature.* 2019;570(7761):385-389. doi: 10.1038/s41586-019-1272-6.

This Article May be cited as: Shuja N. Liquid biopsy and circulating biomarkers: the future of early cancer detection. *Dev. Med. Life Sci.* 2026;3(8).1-3. doi:10.69750/dmls.03.08.0225.