



Liquid Biopsy in Oncology: A Review of Global Perspectives, Sub-Saharan African Realities, and Future Innovations

Otene, SA¹, Ugwu, IV², Umobong, EO³, Gbaa, ZL^{*4}, Onyewuchi, AJ⁵, Anenga, RN⁶, Ojo, BA⁷ and Gbaa, Af⁸

¹Radiology Department, Federal University of Health Sciences, Otukpo (FUHSO), Benue State, Nigeria

²Department of Anatomic Pathology, Federal University of Health Sciences, Otukpo, Nigeria

³Histoconsult Laboratory, Abuja, Nigeria

⁴Department of Surgery, College of Health Sciences, Benue State University, Makurdi, Nigeria

⁵Department of Surgery, Federal University of Health Sciences, Otukpo, Nigeria

⁶Department of Anatomical Pathology, Benue State University Teaching Hospital, Makurdi, Nigeria

⁷Department of Histopathology, Benue State University Teaching Hospital, Makurdi, Nigeria

⁸College of Health Sciences, Benue State University, Makurdi, Nigeria

ABSTRACT

Background: Liquid biopsy is a minimally invasive diagnostic method that analyses circulating tumor-derived analytes, such as circulating tumour DNA (ctDNA), circulating tumour cells (CTCs), exosomes, and extracellular vesicles (EVs), to provide real-time information about tumour biology. It has become a key tool for early detection, prognosis, treatment monitoring, and assessment of minimal residual disease (MRD) in oncology.

Objective: To have a comprehensive overview of liquid biopsy technologies, their clinical applications, global adoption patterns, insights from Sub-Saharan Africa (SSA), and recent advancements, while highlighting implementation challenges and future directions.

Methods: A narrative review was conducted using literature from PubMed, Scopus, and Web of Science (2015–2025), focusing on global, Sub-Saharan African, and Nigerian studies. The research was evaluated for its relevance to technical innovations, biomarker utility, epidemiological data, and clinical integration.

Results: Liquid biopsy demonstrates enhanced sensitivity and specificity for cancer detection, with next-generation sequencing (NGS) and digital PCR enabling precise mutation characterisation. Circulating tumour DNA (ctDNA) is the most thoroughly studied biomarker, while circulating tumour cells (CTCs)

and extracellular vesicles (EVs) provide further insights into cancer heterogeneity. Adoption is high in rich countries, while Sub-Saharan Africa has problems like poor infrastructure, high costs, and a lack of technical skills. New systems that combine multi-omics, AI-driven analytics, and point-of-care devices are going to make clinical value better.

Conclusion: Liquid biopsy represents a revolutionary progression in oncology diagnostics, offering non-invasive, real-time molecular characterisation. To achieve fair global adoption, it is necessary to reduce economic, infrastructure, and legal barriers, especially in areas with limited resources.

Keywords: Cancer diagnostics; circulating tumour cells; circulating tumour DNA; Extracellular vesicles; Exosomes; Liquid biopsy; Next-generation sequencing; Precision oncology; sub-Saharan Africa.

Introduction

Cancer is a leading cause of morbidity and mortality worldwide, with almost 20 million new cases and 9.7 million deaths documented in 2022, signifying a continual rise in occurrence in both wealthy and impoverished areas [1]. Conventional tissue biopsy has proven essential for cancer diagnosis and molecular characterisation; nevertheless, it is inherently invasive, time-consuming, and may not sufficiently capture tumour heterogeneity [2]. Additionally, recurrent tissue collection is often impractical in advanced disease, limiting opportunities for longitudinal cancer monitoring [3]. The limitations have generated interest in liquid biopsy, a minimally invasive diagnostic technique that analyses tumor-derived analytes—such as circulating tumour DNA (ctDNA), circulating tumour cells (CTCs), exosomes, extracellular vesicles (EVs), and additional biomarkers—obtained from blood or other bodily fluids [4–6].

Liquid biopsy has various clinical advantages, including early detection, real-time disease monitoring, therapeutic guidance, and the identification of minimal residual disease (MRD), all of which are crucial for precision oncology [7]. Next-generation sequencing (NGS), digital droplet PCR (ddPCR), and single-cell profiling have all made liquid biopsy procedures much more sensitive and selective. This has made it easier to use them in clinical practice [8]. Regulatory approvals, such as the U.S. FDA's endorsement of the Guardant360® CDx and Foundation One® Liquid CDx tests, underscore the therapeutic importance of liquid biopsy in guiding targeted therapies [9]. The global adoption of liquid biopsy is increasing, with substantial research contributions from high-income countries (HICs). However, imbalances persist in low- and middle-income countries (LMICs), particularly in Sub-Saharan Africa, where implementation is hindered by high costs, inadequate technical ability, and limited comprehension of precision tools [10]. Integrating liquid biopsy into African oncology care could

Citation: Otene, SA, Ugwu, IV, Umobong, EO, Gbaa, ZL, Onyewuchi, AJ, Anenga, RN, Ojo, BA and Gbaa, AF (2025). Liquid Biopsy in Oncology: A Review of Global Perspectives, Sub-Saharan African Realities, and Future Innovations.

Journal of American Medical Science and Research.

DOI: <https://doi.org/10.51470/AMSR.2025.04.01.72>

Received 30 April 2025

Revised 26 May 2025

Accepted 28 June 2025

Corresponding Author: **Gbaa LZ**

Email Address: zulumbaa@gmail.com

Copyright: © The Author(s) 2025. This article is Open Access under a Creative Commons Attribution 4.0 International License, allowing use, sharing, adaptation, and distribution with appropriate credit. License details: <http://creativecommons.org/licenses/by/4.0/>.

Data is under the CC0 Public Domain Dedication (<http://creativecommons.org/publicdomain/zero/1.0/>) unless otherwise stated.

enhance cancer outcomes by providing scalable alternatives to resource-intensive tissue diagnostics.

This paper provides a comprehensive analysis of liquid biopsy principles, technology, and applications, focusing on global and Sub-Saharan African perspectives. We emphasise recent accomplishments, challenges in clinical translation, and future directions, highlighting the importance of augmenting research capacity to guarantee equitable access to liquid biopsy-guided oncology therapy worldwide.

Fundamentals of Liquid Biopsy

Liquid biopsy is a sophisticated diagnostic and monitoring technique that identifies tumor-derived analytes in biological fluids, notably blood, as well as urine, saliva, cerebrospinal fluid (CSF), and pleural effusions. In contrast to conventional tissue biopsy, which is invasive, spatially limited, and time-intensive, liquid biopsy provides a minimally invasive and dynamic approach to capture tumour heterogeneity and real-time genetic evolution [11-13].

Biological Foundation: Tumour cells experience apoptosis, necrosis, and active secretion, discharging nucleic acids, proteins, and extracellular vesicles into the bloodstream. Principal analytes comprise: Circulating Tumour DNA (ctDNA): Minuscule DNA fragments originating from tumour cells, identifiable at low allelic frequencies, indicative of tumour mutational profile and clonal evolution [14-15].

Circulating Tumour Cells (CTCs): Intact neoplastic cells released into the bloodstream, utilised for phenotypic and genotypic analysis, prognostic evaluation, and assessment of medication resistance [16].

Extracellular Vesicles (EVs) are nano-sized lipid bilayer particles, including exosomes, that transport DNA, RNA, and proteins, offering insights into the tumour microenvironment and intercellular signaling [17].

Other biomarkers, including circulating microRNAs, tumor-associated proteins, and methylation markers, provide multi-omics integration to improve diagnostic accuracy [18,19].

Benefits when Compared to Conventional Biopsy:

Non-Invasiveness: Frequent sampling diminishes patient pain and danger, facilitating longitudinal observation. **Real-Time Tumour Evolution Monitoring:** Records clonal evolution, newly developed resistance mutations, and minimal residual disease (MRD) [20].

Comprehensive Tumour Profiling: Captures geographical and temporal heterogeneity, mitigating the sampling bias associated with single-site samples [21,22].

Expedited Turnaround and Scalability: Facilitates accelerated clinical decision-making, particularly with high-throughput sequencing technology [23].

Analytical Sensitivity and Specificity: Liquid biopsy assays, specifically next-generation sequencing (NGS) and droplet digital PCR (ddPCR), demonstrate high sensitivity, identifying mutant alleles at frequencies as low as 0.01%. Molecular barcoding, error suppression algorithms, and orthogonal validation methods enhance specificity [24,25].

Categories of Liquid Biopsy Assays: PCR-based approaches, such as ddPCR and BEAMing, offer cost-effectiveness and high sensitivity, though they are restricted to targeted mutation panels²⁶. NGS-based panels facilitate extensive mutation profiling, including gene fusions, copy number variations, and methylation alterations²⁷.

Epigenomic profiling through DNA methylation and histone modification signatures enhances the sensitivity of early cancer detection [28].

Multi-Omics Integration: The integration of genomics, transcriptomics, proteomics, and metabolomics improves the discovery of biomarkers [29].

Liquid biopsy signifies a significant transition from reactive to proactive oncology, allowing for early detection, informing precision medicine, and supporting adaptive treatment strategies [30,31].

Analytical Sensitivity and Specificity: Liquid biopsy assays, particularly next-generation sequencing (NGS) and droplet digital PCR (ddPCR), achieve remarkable sensitivity, detecting mutant alleles at frequencies as low as 0.01% [23]. Specificity is enhanced through molecular barcoding, error suppression algorithms, and orthogonal validation methods [24,25].

Technological platforms and technical analysis: Liquid biopsy technology utilises sophisticated molecular and cellular methods to identify and analyse rare tumor-derived biomarkers within a predominant background of normal nucleic acids and proteins. The evolution of these platforms over the past decade has been significant, influenced by advancements in sensitivity, specificity, and cost-effectiveness. The primary technological categories encompass polymerase chain reaction (PCR)-based techniques, next-generation sequencing (NGS) platforms, and single-cell methodologies, enhanced by developing multi-omics pipelines that integrate genomic, epigenomic, proteomic, and metabolomic data to provide a comprehensive understanding of tumour biology.

PCR Methods: Digital PCR (dPCR) and droplet digital PCR (ddPCR) are essential PCR-based methodologies for the quantification of low-frequency mutations and copy number variations in circulating tumour DNA (ctDNA). ddPCR attains single-molecule resolution through the partitioning of DNA samples into numerous droplets, facilitating the absolute quantification of mutant alleles with detection limits under 0.1% [32]. PCR-based assays exhibit high sensitivity and cost-effectiveness; however, their application is confined to targeted hotspot mutation analysis, which limits their effectiveness in identifying novel alterations.

Next-Generation Sequencing (NGS) offers high-throughput and scalable analysis of ctDNA, CTCs, and EV-associated nucleic acids, facilitating comprehensive genomic profiling of hundreds of genes concurrently [33]. Hybrid-capture and amplicon-based panels are extensively utilised for the identification of point mutations, insertions, and deletions (indels), structural rearrangements, and epigenomic signatures. Advancements in error-correction techniques and the implementation of unique molecular identifiers (UMIs) have enhanced the accuracy of next-generation sequencing (NGS), enabling the identification of mutations at variant allele frequencies (VAF) as low as 0.01% [34].

BEAMing and Additional Digital Platforms: BEAMing (Beads, Emulsion, Amplification, and Magnetics) integrates emulsion PCR with flow cytometry for the detection of single-base mutations in ctDNA [35]. This highly sensitive technology is particularly suited for MRD detection and therapy monitoring, but is labor-intensive and less scalable than NGS. Safe-SeqS and other error-corrected sequencing methods similarly mitigate PCR errors, thereby enhancing sensitivity for the detection of ultra-rare mutations.

CTC isolation and single-cell platforms utilise technologies like CellSearch, which is FDA-approved and employs immunomagnetic enrichment. Additionally, emerging microfluidic devices facilitate high-throughput CTC capture based on parameters such as size, deformability, or surface markers [36]. Single-cell RNA sequencing (scRNA-seq) of circulating tumour cells (CTCs) offers significant insights into tumour heterogeneity, epithelial-mesenchymal transition (EMT), and resistance to therapy [37].

Extracellular vesicle (EV) profiling encompasses nanoparticle tracking analysis (NTA), tunable resistive pulse sensing (TRPS), and advanced mass spectrometry for proteomic analysis. EV-based multi-omics platforms offer reliable sources for biomarkers, particularly in the detection of RNA and proteins [38].

Integration of Multi-Omics Data and AI-Driven Analytical Approaches: Artificial intelligence and machine learning improve the analysis of extensive liquid biopsy datasets, facilitating the identification of multi-omic signatures that predict treatment response and survival outcomes. The integration of ctDNA, CTC, EV, and proteomic profiles generates a detailed tumour map, enhancing precision oncology and early detection initiatives [39].

Clinical Applications and Biomarker Landscape:

Liquid biopsy has transitioned from an investigational method to a significant complement to traditional diagnostics, facilitating earlier detection, enhanced disease monitoring, and tailored treatment selection across various cancer types. The utility of this approach is its capacity to capture tumour heterogeneity and offer dynamic insights into tumour evolution in real time, thus informing therapeutic strategies and enhancing patient outcomes.

Early Cancer Detection and Screening: Early detection is fundamental to enhancing cancer survival rates, and liquid biopsy provides a minimally invasive method for identifying the disease at a preclinical stage. Multi-analyte assays, including the CancerSEEK and Galleri tests, utilise integrated ctDNA methylation patterns and protein biomarkers to attain elevated sensitivity and specificity in the detection of various cancers [40,41]. Furthermore, ctDNA detection demonstrates potential in population-level screening programs; however, challenges related to technical sensitivity and cost-effectiveness hinder routine implementation [42].

Detection of Minimal Residual Disease (MRD) and monitoring of recurrence: ctDNA-based MRD detection represents a significant application of liquid biopsy. Research, including the TRACERx and CAPP-Seq trials, has shown that ctDNA can identify recurrence several months prior to imaging, thereby offering an opportunity for early intervention [53,44]. Personalised, tumor-informed assays are being validated to customise surveillance protocols.

Targeted Therapy and Precision Oncology: Liquid biopsy enables noninvasive genomic profiling for therapy selection, particularly in cases where tissue biopsies are inaccessible or impractical. FDA-approved assays, including Guardant360 CDx and FoundationOne Liquid CDx, identify actionable mutations in genes such as EGFR, ALK, and KRAS, facilitating targeted therapies for lung and colorectal cancers [45,46]. Liquid biopsy facilitates the swift identification of emerging resistance mutations, thereby permitting prompt modifications to therapy [47]. **Tracking Biomarkers in Immuno-Oncology:** In addition to genomic profiling, liquid biopsy platforms are progressively

integrating immune-related biomarkers, including tumour mutational burden (TMB) and PD-L1 status, to forecast responses to checkpoint inhibitors [48]. Single-cell sequencing is enhancing the biomarker landscape by enabling the phenotyping of circulating immune cells and profiling of cytokines. **Surveillance of Metastatic Disease and Tumour Evolution:** Serial monitoring of ctDNA, CTCs, and exosomal content demonstrates clonal evolution and metastatic potential, facilitating precision treatment adjustments over time[49]. Liquid biopsy is essential for monitoring the dynamic tumour profiles in cancers such as triple-negative breast cancer (TNBC) and pancreatic adenocarcinoma. (Figure 1)

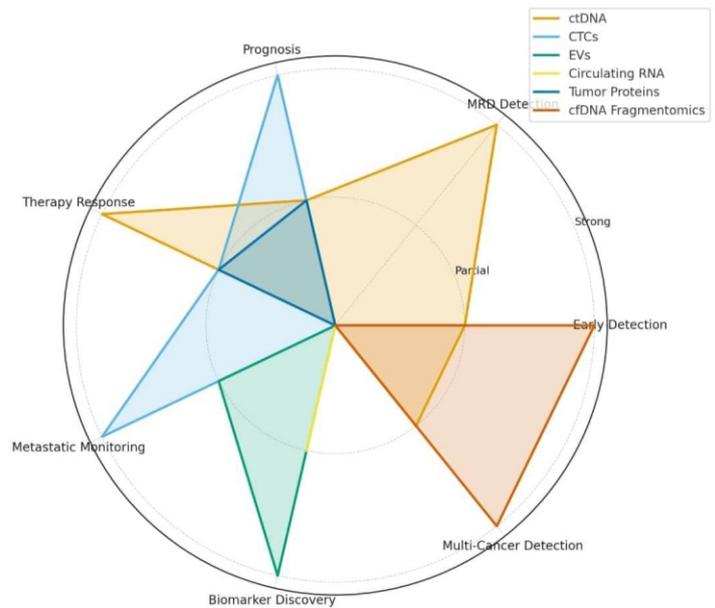


Figure 1: Clinical Biomarkers in Liquid Biopsy and Their Applications

Liquid biopsy is thus emerging as a central tool in cancer management, extending beyond genomics to integrate proteomics, transcriptomics, and epigenomics. This multi-layered biomarker approach accelerates the shift toward individualized oncology, enabling clinicians to anticipate tumor evolution and improve therapeutic precision.

The global epidemiology of liquid biopsy in oncology.

The adoption of liquid biopsy has increased significantly globally in the last decade, propelled by advancements in sequencing technologies, validation through clinical trials, and regulatory approvals. The global liquid biopsy market was valued at approximately 6.5 billion USD in 2023 and is projected to surpass 20 billion USD by 2030, indicating an annual growth rate of 20–25% [50,51]. The growth is primarily due to rising cancer incidence, the demand for minimally invasive diagnostics, and the incorporation of precision oncology into clinical practice.

In high-income countries, including North America, Europe, and certain areas of the Asia-Pacific, liquid biopsy is progressively integrated into standard care protocols for early cancer detection, companion diagnostics, and monitoring of minimal residual disease (MRD). The U.S. Food and Drug Administration (FDA) has approved the Guardant360 CDx and FoundationOne Liquid CDx assays for tumour mutation profiling in non-small cell lung cancer (NSCLC) and other solid tumours [52,53]. In the United States, over 40% of patients with advanced NSCLC are estimated to undergo ctDNA-based testing as part of their treatment planning [54].

In Europe, the European Society for Medical Oncology (ESMO) guidelines support the use of liquid biopsy across various tumour types, especially for the detection of resistance mutations and the adaptation of treatment [55].

The Asia-Pacific region represents a significant and expanding market for liquid biopsy research and its clinical application. China has led large-scale screening trials that incorporate ctDNA and methylation profiling, exemplified by the CCGA (Circulating Cell-free Genome Atlas) trial and the LUNG-CA study [56,57]. Regulatory agencies in Japan have authorised NGS-based liquid biopsy tests, while South Korea and Singapore are allocating resources towards population-scale genomic screening initiatives [58,59].

The global burden of cancer is a catalyst for innovation. In 2022, the global cancer burden was 20 million new cases and 9.7 million deaths, with projections indicating 35 million new cases by 2050 [60]. The increasing prevalence highlights the necessity for early detection methods, especially among asymptomatic groups. Multi-cancer early detection (MCED) blood tests, exemplified by Galleri (GRAIL), which identify over 50 cancer types with high specificity, are currently undergoing extensive validation and have the potential to transform cancer screening methodologies [61,62].

The landscape of clinical trials related to liquid biopsy has expanded significantly, with more than 1,400 trials registered globally as of 2025 [63]. The United States and China dominate in trial volume, with growing involvement from Europe and emerging economies. The trials examine various indications, including early detection, minimal residual disease tracking, and monitoring responses to immunotherapy, with circulating tumour DNA as a central biomarker [64].

Obstacles to Global Standardisation: Despite extensive implementation, significant global disparities remain. Regulatory harmonisation, assay standardisation, and data sharing present substantial challenges to attaining equitable access. Furthermore, although liquid biopsy is prevalent in tertiary care facilities in high-income countries, its accessibility in low- and middle-income countries is limited, thereby sustaining diagnostic disparities [65]. (Figure 1)

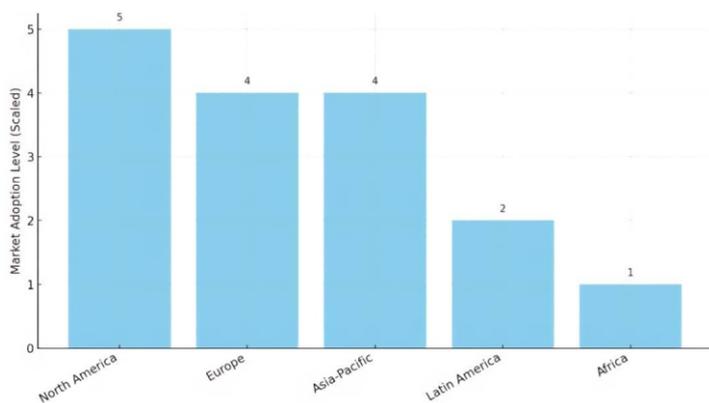


Figure 1: Global Trends in Liquid Biopsy Research and Implementation

Highlights: Liquid biopsy adoption is strongest in North America, Europe, and parts of Asia-Pacific, with growing investment in population-scale screening. Regulatory approvals are concentrated in high-income countries, emphasizing the need for harmonized guidelines and improved infrastructure in LMICs. The proliferation of clinical trials and MCED assays highlights the liquid biopsy's role in next-generation cancer screening and personalized medicine.

Perspectives on Liquid Biopsy in Oncology from Sub-Saharan Africa and Nigeria Liquid biopsy presents a minimally invasive,

real-time method for cancer diagnosis and monitoring, garnering significant global interest. However, its implementation in Sub-Saharan Africa (SSA) and Nigeria is constrained by systemic issues related to healthcare infrastructure, research capacity, and funding. Cancer incidence in Sub-Saharan Africa is increasing as a result of population growth, ageing, urbanisation, and changes in lifestyle [66,67]. Cancer accounts for approximately 10 million deaths worldwide each year, with over 70% of these fatalities occurring in low- and middle-income countries (LMICs), including numerous African nations. Cancer in Nigeria results in over 100,000 new cases and 70,000 deaths each year, highlighting considerable disparities in screening, diagnosis, and access to treatment [68,69].

Restricted Availability of Molecular Diagnostics: Molecular oncology services, encompassing advanced genomics platforms, are underdeveloped throughout Sub-Saharan Africa due to high costs and insufficiently trained personnel. Liquid biopsy technologies, while potentially transformative, remain largely absent from standard oncology practice. In Nigeria, only a limited number of tertiary hospitals possess next-generation sequencing (NGS) or droplet digital PCR (ddPCR) platforms, thereby limiting access to precision medicine methodologies [70,71]. Current cancer diagnosis predominantly relies on histopathology, which, although essential, is less effective in capturing tumour heterogeneity and evolution compared to liquid biopsy [72].

Investigating Research Capacity in Regional Studies: Interest in cancer genomics research in Sub-Saharan Africa is increasing, with institutions like the African Cancer Genomics Consortium (ACGC) starting to characterise tumour mutational landscapes in breast, cervical, and prostate cancers [73,74]. Nonetheless, literature regarding liquid biopsy applications is limited, with the majority of African studies concentrating on proof-of-concept assessments of circulating tumour DNA (ctDNA) or cell-free DNA (cfDNA) detection in breast, cervical, and hepatocellular carcinomas [75,76]. Nigerian studies are predominantly constrained to small pilot projects, frequently affected by limited sample sizes and the absence of validation cohorts [77].

Obstacles to Execution: The implementation of liquid biopsy in Sub-Saharan Africa encounters several obstacles: **Economic limitations:** The substantial initial expenses associated with sequencing and bioinformatics infrastructure restrict clinical implementation.

Healthcare disparities: Restricted insurance coverage and out-of-pocket payment systems further limit patient access to advanced diagnostics [78].

Challenges in the supply chain: The importation of reagents, servicing of equipment, and logistics of sample preservation continue to pose challenges, resulting in delays in molecular testing [79].

Identified deficiencies in training: The deficiency of molecular pathologists, oncologists, and bioinformaticians obstructs the integration of emerging research into clinical workflows [80].

Opportunities and Emerging Initiatives:

Despite these challenges, SSA offers distinct prospects for the adoption of liquid biopsy.

The potential of population genomics. The African continent exhibits the highest levels of human genetic diversity, providing a unique opportunity to investigate novel cancer mutations and biomarkers relevant to global oncology [81].

Regional consortia, including H3Africa and the African Pathology and Oncology Network (APON), are establishing infrastructure for genomic medicine research and molecular diagnostics [82].

Telemedicine and digital pathology: These advancements may enable centralised expertise, remote consultation, and training, potentially addressing geographical barriers [83]. Cost-effective technologies, including portable and low-cost molecular platforms like CRISPR-based diagnostics and targeted sequencing, are under evaluation for their applicability in low- and middle-income country settings [84].

Nigerian Case Analysis

Nigeria, characterised by a rapidly increasing cancer burden and a diverse demographic, is a priority nation for the implementation of liquid biopsy techniques. The elevated prevalence of breast, cervical, prostate, and liver cancers, frequently identified at advanced stages, highlights the critical necessity for non-invasive, early detection techniques [85]. Pilot studies conducted in Nigerian tertiary hospitals have shown the feasibility of cfDNA quantification for breast cancer staging and ctDNA detection for hepatocellular carcinoma prognosis [86,87]. Nationwide adoption necessitates policy reform, funding, local manufacturing of consumables, and robust partnerships among academia, government, and industry.

Prospective Pathways and Novel Advancements

Liquid biopsy (LB) is transitioning from a research tool to a fundamental component of precision oncology. Its future is characterised by multidisciplinary integration, the advancement of assay development, and increased accessibility. Recent innovations emphasise enhancing assay sensitivity, refining standardisation, and broadening applications to include screening, treatment optimisation, and real-time disease monitoring beyond advanced cancers.

Integration of Multi-Omics and Systems Biology Methodologies: The integration of multi-omics platforms, such as genomics, transcriptomics, proteomics, and metabolomics, has the potential to significantly enhance the diagnostic yield of liquid biopsy. The integration of circulating tumour DNA (ctDNA), circulating tumour cells (CTCs), extracellular vesicles (EVs), microRNAs (miRNAs), and methylation signatures provides a comprehensive characterisation of tumour biology [90,91]. Multi-omics approaches have demonstrated potential in the identification of early-stage malignancies, the prediction of therapeutic resistance, and the characterisation of tumour heterogeneity [92,93]. Artificial intelligence (AI)-driven computational frameworks and machine learning algorithms are progressively utilised to integrate various data modalities for effective predictive modelling [94].

Highly Sensitive Detection Technologies: Novel detection modalities, including advanced next-generation sequencing (NGS) platforms, CRISPR-based diagnostics, and single-molecule sequencing technologies, seek to reduce detection thresholds for ctDNA and other analytes, thereby facilitating the screening of early-stage or minimal residual disease (MRD) states [95,96]. Emerging technologies such as nanopore sequencing, plasmonic nanotechnology biosensors, and advancements in digital droplet PCR (ddPCR) are facilitating innovation in cost-effective, high-precision assays [97,98]. The absence of globally standardised protocols for pre-analytical handling, assay validation, and clinical interpretation has impeded the implementation of LB.

Future initiatives prioritise standardised workflows and the establishment of international consensus guidelines⁹⁹. Regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are progressively assessing LB-based companion diagnostics, facilitating expedited clinical adoption [100].

Early cancer detection and population screening are being transformed by commercially available multi-cancer early detection (MCED) tests, such as Galleri® and CancerSEEK®. These advancements are broadening the application of liquid biopsy from targeted cancer monitoring to comprehensive screening [101,102]. These platforms utilise ctDNA methylation profiling, fragmentomics, and multi-omics biomarkers to detect cancer signals from various tissue origins with enhanced sensitivity [103]. The extensive implementation of these tests has the potential to transform cancer screening, especially in low- and middle-income countries, provided that cost and infrastructural challenges are resolved.

Liquid biopsy is emerging as a significant biomarker in immunoncology, facilitating the prediction of immunotherapy responses, the identification of resistance mechanisms, and the monitoring of changes in the tumour microenvironment [104,105]. Analyses of ctDNA-based tumour mutational burden (TMB), microsatellite instability (MSI), and neoantigen load may inform Personalised immunotherapy strategies [106]. Continuous monitoring of ctDNA dynamics enables real-time evaluation of treatment effectiveness, facilitating early therapeutic adjustments by clinicians.

Point-of-Care Platforms and Innovations in Global Health in low- and middle-income countries, innovation is increasingly directed towards the development of cost-effective, portable LB devices. Microfluidics platforms and lab-on-a-chip devices present opportunities for decentralised cancer diagnostics [107]. When integrated with mobile health technologies and cloud-based AI analytics, these platforms have the potential to enhance access in underserved regions substantially.

Directions for Future Research

Fragmentomics and Epigenomics: Analysing DNA fragment size distributions and methylation patterns for the purposes of early detection and tissue-of-origin identification [108].

Advancements in single-cell sequencing of circulating tumour cells (CTCs) will enhance understanding of intra-tumoural heterogeneity and the evolution of resistance [109].

Liquid biopsy applications are broadening to include autoimmune conditions, infectious diseases, and monitoring of organ transplantation [110].

Personalised cancer vaccines can benefit from the integration of LB-derived neoantigen data, potentially guiding the development of next-generation therapies [111].

The future of liquid biopsy lies in multidisciplinary innovation, where multi-omics, advanced sequencing, and AI-driven analytics converge to create an integrated diagnostic ecosystem. Emphasis on affordability, scalability, and regulatory alignment is essential for global equity in cancer diagnostics, especially in Sub-Saharan Africa and other resource-constrained regions.

Conclusion: Liquid biopsy is transforming oncology by providing a minimally invasive, real-time tool for cancer diagnosis, prognostication, and treatment monitoring through analytes such as ctDNA, CTCs, and EVs. Advances in NGS, dPCR, and microfluidics have improved its accuracy, supporting its integration into precision oncology for early detection, MRD assessment, and therapy guidance.

While widely adopted in high-income countries, implementation in LMICs, especially Sub-Saharan Africa, remains limited due to infrastructural, financial, and expertise gaps, underscoring the need for investment and early diagnostic integration to improve cancer outcomes.

Recommendations:

Invest in diagnostic infrastructure (molecular pathology and genomics labs).

Promote local manufacturing of reagents and sequencing platforms.

Strengthen workforce capacity through training in molecular diagnostics and bioinformatics.

Create regional reference centers for cancer genomics and quality control.

Conduct context-specific research and clinical trials in Sub-Saharan Africa.

Integrate liquid biopsy into national policies and insurance coverage.

Leverage AI and digital health for data interpretation and specialist support.

Foster global collaboration for technology transfer and innovation sharing.

Conflicts of interest: There are no conflicts of interest.

Funding sources: For this review article, we did not receive any grants or funding.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74(3):229–263. doi:10.3322/caac.21834 ([PubMed](#))
2. Mandel P, Metais P. Les acides nucléiques du plasma sanguin chez l'homme. *C R Seances Soc Biol Fil.* 1948;142(3-4):241–243. (No DOI available) ([PubMed](#))
3. Wan JCM, Massie C, Garcia-Corbacho J, Mouliere F, Brenton JD, Caldas C, et al. Liquid biopsies come of age: towards implementation of circulating tumour DNA. *Nat Rev Cancer.* 2017;17(4):223–238. doi:10.1038/nrc.2017.7
4. Heitzer E, Haque IS, Roberts CES, Speicher MR, et al. Current and future perspectives of liquid biopsies in genomics-driven oncology. *Nat Rev Genet.* 2019;20(2):71–88. doi:10.1038/s41576-018-0071-5
5. Alix-Panabières C, Pantel K. Clinical applications of circulating tumor cells and circulating tumor DNA as liquid biopsy. *Cancer Discov.* 2016;6(5):479–491. doi:10.1158/2159-8290.CD-15-1483
6. Ignatiadis M, Sledge GW Jr, Jeffrey SS. Liquid biopsy enters the clinic—implementation issues and future challenges. *Nat Rev Clin Oncol.* 2021;18(5):297–312. doi:10.1038/s41571-020-00457-x

7. Siravegna G, Marsoni S, Siena S, Bardelli A. Integrating liquid biopsies into the management of cancer. *Nat Rev Clin Oncol.* 2017;14(9):531–548. doi:10.1038/nrclinonc.2017.14
8. Mouliere F, Chandrananda D, Piskorz AM, Moore EK, Morris J, Ahlborn LB, et al. Enhanced detection of circulating tumor DNA by fragment size analysis. *Sci Transl Med.* 2018;10(466):eaat4921. doi:10.1126/scitranslmed.aat4921
9. U.S. Food and Drug Administration. FDA approves liquid biopsy companion diagnostic test for multiple cancers. FDA Press Release. 2020. Available from: <https://www.fda.gov/news-events>
10. Atanda AT, Adeloye D, Uwizeye D, Gyedu A, Otu A, Adesunkanmi AR, et al. Oncology in Africa: current and future prospects. *Ecancermedicalscience.* 2022;16:ed115. doi:10.3332/ecancer.2022.ed115
11. Siravegna G, Marsoni S, Siena S, Bardelli A. Integrating liquid biopsies into the management of cancer. *Nat Rev Clin Oncol.* 2017;14(9):531–548. doi:10.1038/nrclinonc.2017.14 ([PubMed](#), [Nature](#))
12. Heitzer E, Haque IS, Roberts CES, Speicher MR. Current and future perspectives of liquid biopsies in genomics-driven oncology. *Nat Rev Genet.* 2019;20(2):71–88. doi:10.1038/s41576-018-0071-5
13. Wan JCM, Massie C, Garcia-Corbacho J, Mouliere F, Brenton JD, Caldas C, et al. Liquid biopsies come of age: towards implementation of circulating tumour DNA. *Nat Rev Cancer.* 2017;17(4):223–238. doi:10.1038/nrc.2017.7
14. Bettegowda C, Sausen M, Leary RJ, Kinde I, Wang Y, Agrawal N, et al. Detection of circulating tumor DNA in early- and late-stage human malignancies. *Sci Transl Med.* 2014;6(224):224ra24. doi:10.1126/scitranslmed.3007094
15. Abbosh C, Birkbak NJ, Wilson GA, Jamal-Hanjani M, Constantin T, Salari R, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature.* 2017;545(7655):446–451. doi:10.1038/nature22364 ([Pure OAI](#), [Orca](#))
16. Alix-Panabières C, Pantel K. Clinical applications of circulating tumor cells and circulating tumor DNA as liquid biopsy. *Cancer Discov.* 2016;6(5):479–491. doi:10.1158/2159-8290.CD-15-1483
17. Thakur BK, Zhang H, Becker A, Matei I, Huang Y, Costa-Silva B, et al. Double-stranded DNA in exosomes: a novel biomarker in cancer detection. *Cell Res.* 2014;24(6):766–769. doi:10.1038/cr.2014.44
18. Schwarzenbach H, Nishida N, Calin GA, Pantel K. Clinical relevance of circulating cell-free microRNAs in cancer. *Nat Rev Clin Oncol.* 2014;11(3):145–156. doi:10.1038/nrclinonc.2014.5

19. Moss J, Magenheim J, Neiman D, Zemmour H, Loyfer N, Korach A, et al. Comprehensive human cell-type methylation atlas reveals origins of circulating cell-free DNA in health and disease. *Nat Commun.* 2018;9(1):5068. doi:10.1038/s41467-018-07466-6
20. Garcia-Murillas I, Schiavon G, Weigelt B, Ng C, Hrebien S, Cutts RJ, et al. Mutation tracking in circulating tumor DNA predicts relapse in early breast cancer. *SciTransl Med.* 2015;7(302):302ra133. doi:10.1126/scitranslmed.aab0021
21. Murtaza M, Dawson SJ, Pogrebniak K, Rueda OM, Provenzano E, Grant J, et al. Multifocal clonal evolution characterized using circulating tumour DNA in a case of metastatic breast cancer. *Nat Commun.*2015; 6:8760. doi:10.1038/ncomms9760
22. Gerlinger M, Rowan AJ, Horswell S, Math M, Larkin J, Endesfelder D, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med.* 2012;366(10):883–892. doi:10.1056/NEJMoa1113205
23. Hindson BJ, Ness KD, Masquelier DA, Belgrader P, Heredia NJ, Makarewicz AJ, et al. High-throughput droplet digital PCR system for absolute quantitation of DNA copy number. *Anal Chem.* 2011;83(22):8604–8610. doi:10.1021/ac202028g
24. Newman AM, Bratman SV, Stehr H, Lee LJ, Liu CL, Diehn M, et al. FACTERA: a practical method for the discovery of genomic rearrangements at breakpoint resolution. *Bioinformatics.* 2014;30(23):3390–3393. doi:10.1093/bioinformatics/btu549
25. Schmitt MW, Kennedy SR, Salk JJ, Fox EJ, Hiatt JB, Loeb LA. Detection of ultra-rare mutations by next-generation sequencing. *Proc Natl AcadSci USA.* 2012;109(36):14508–14513. doi:10.1073/pnas.1208715109
26. Dressman D, Yan H, Traverso G, Kinzler KW, Vogelstein B. Transforming single DNA molecules into fluorescent magnetic particles for detection and enumeration of genetic variations. *Proc Natl AcadSci USA.* 2003;100(15):8817–8822. doi:10.1073/pnas.1133470100
27. Adalsteinsson VA, Ha G, Freeman SS, Choudhury AD, Stover DG, Parsons HA, et al. Scalable whole-exome sequencing of cell-free DNA reveals high concordance with metastatic tumors. *Nat Commun.*2017; 8:1324. doi:10.1038/s41467-017-00965-y
28. Shen SY, Singhanian R, Fehringer G, Chakravarthy A, Roehrl MHA, Chadwick D, et al. Sensitive tumour detection and classification using plasma cell-free DNA methylomes. *Nature.* 2018;563(7732):579–583. doi:10.1038/s41586-018-0703-0
29. Hasin Y, Seldin M, Lusis A. Multi-omics approaches to disease. *Genome Biol.* 2017;18(1):83. doi:10.1186/s13059-017-1215-1
30. Crowley E, Di Nicolantonio F, Loupakis F, Bardelli A. Liquid biopsy: monitoring cancer-genetics in the blood. *Nat Rev ClinOncol.* 2013;10(8):472–484. doi:10.1038/nrclinonc.2013.110
31. Alix-Panabières C, Pantel K. Liquid biopsy: from discovery to clinical application. *Cancer Discov.* 2021;11(4):858–873. doi:10.1158/2159-8290.CD-20-131A
32. Diehl F, Schmidt K, ChotiMA, Romans K, Goodman S, Li M, et al. Circulating mutant DNA to assess tumor dynamics. *Nat Med.* 2008;14(9):985–990. doi:10.1038/nm.1789
33. Burnham P, Kim MS, Agbor-EnohS, LuikartH, ValentineHA, KhushKK, et al. Single-stranded DNA library preparation uncovers the origin and diversity of ultrashort cell-free DNA in plasma. *Sci Rep.* 2016; 6:27859. doi:10.1038/srep27859
34. Newman AM, BratmanSV, StehrH, Lee LJ, Liu CL, DiehnM, et al. FACTERA: A practical method for the discovery of genomic rearrangements at breakpoint resolution. *Bioinformatics.* 2014;30(23):3390–3393. doi:10.1093/bioinformatics/btu549
35. Wang D, Shen Y, Qian H, Jiang J, Xu W. Emerging advanced approaches for liquid biopsy: in situ nucleic acid assays of extracellular vesicles. *Theranostics.* 2024;14(19):7309–7332. doi:10.7150/thno.102437
36. BoguslawskiH, SzemielAM, Johnson SM, et al. Extracellular vesicle-based liquid biopsy biomarkers and their emerging roles in cancer. *Biomarker Res.* 2023;11(1):73. doi:10.1186/s40364-023-00540-2
37. Di SarioG, RossellaV, FamulariES, Maurizio A, Lazarevic D, GianneseF, et al. Enhancing clinical potential of liquid biopsy through a multi-omic approach: A systematic review. *Front Genet.* 2023; 14:1152470. doi:10.3389/fgene.2023.1152470
38. Kim SY, JeongS, Lee W, Jeon Y, Kim YJ, Park S, et al. Cancer signature ensemble integrating cfDNA methylation, copy number, and fragmentation facilitates multi-cancer early detection. *ExpMol Med.* 2023;55(11):2445–2460. doi:10.1038/s12276-023-01119-5
39. Chabon JJ, HornburgMI, AnagnostouV, et al. Machine learning yields lung cancer test—Lung-CLiP for plasma ctDNA. *Cancer Discov.* 2020;10(6):753–767. doi:10.1158/2159-8290.CD-19-1482.
40. Lennon AM, Buchanan AH, Kinde I, Warren A, Honushefsky A, CohainAT, et al. Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention. *Science.* 2020;369(6499): eabb9601. doi:10.1126/science.abb9601 ([PubMed](#))

41. Klein EA, Richards D, Cohn A, Tummala M, Lapham R, Cosgrove D, et al. Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. *Ann Oncol.* 2021;32(9):1167–1177. doi:10.1016/j.annonc.2021.05.806 ([PubMed](#))
42. Wan JCM, Massie C, Garcia-Corbacho J, Mouliere F, Brenton JD, Caldas C, et al. Liquid biopsies come of age: towards implementation of circulating tumour DNA. *Nat Rev Cancer.* 2017;17(4):223–238. doi:10.1038/nrc.2017.7
43. Abbosh C, Birkbak NJ, Wilson GA, Jamal-Hanjani M, Constantin T, Salari R, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature.* 2017;545(7655):446–451. doi:10.1038/nature22364
44. Newman AM, Bratman SV, To J, Wynne JF, Eclov NC, Modlin LA, et al. An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage. *Nat Med.* 2014;20(5):548–554. doi:10.1038/nm.3519
45. Marcus L, Subramaniam S, Cheng J, Shum E, Fashoyin-Aje L, Lemery S, et al. FDA approval summary: Pembrolizumab for the treatment of tumor mutational burden-high solid tumors. *Clin Cancer Res.* 2021;27(17):4685–4689. doi: 10.1158/1078-0432.CCR-21-0335
46. Clark TA, Beroukhi R, Liang WS, Walsh AM, Lee JH, Lawrence MS, et al. Clinical utility of comprehensive genomic profiling in advanced cancer. *JCO Precis Oncol.* 2022;6: ePO2100617. doi:10.1200/PO.21.00617
47. McCoach CE, Blakely CM, Banks KC, Levy B, Chue BM, Raymond VM, et al. Clinical utility of cell-free DNA for molecular profiling in advanced NSCLC. *JCO Precis Oncol.* 2019;3:PO.18.00269. doi:10.1200/PO.18.00269
48. Gandara DR, Paul SM, Kowanetz M, Schleifman E, Zou W, Li Y, et al. Blood-based tumor mutational burden as a predictor of clinical benefit in NSCLC patients treated with atezolizumab. *Nat Med.* 2018;24(9):1441–1448. doi:10.1038/s41591-018-0134-3
49. Ignatiadis M, Sledge GW Jr, Jeffrey SS. Liquid biopsy enters the clinic implementation issues and future challenges. *Nat Rev Clin Oncol.* 2021;18(5):297–312. doi:10.1038/s41571-020-00457-x.
50. Grand View Research. Liquid biopsy market size & share report, 2024–2030. San Francisco: Grand View Research; 2024.
51. MarketsandMarkets. Liquid biopsy market by product, biomarker, application, and region. 2023.
52. U.S. Food and Drug Administration. FDA approves the liquid biopsy next-generation sequencing-based FoundationOne Liquid CDx test as a companion diagnostic. Silver Spring (MD): FDA; 26 August 2020.
53. Foundation Medicine. FoundationOne® Liquid CDx: FDA-approved blood-based companion diagnostic for solid tumors. Cambridge (MA): Foundation Medicine; 2020. ([Corporate press release]; no DOI).
54. Merker JD, Oxnard GR, Compton C, Diehn M, Hurley P, Lazar AJ, et al. Circulating tumor DNA analysis in patients with cancer: ASCO–CAP joint review. *J Clin Oncol.* 2018;36(16):1631–41. doi:10.1200/JCO.2017.76.8671
55. Pascual J, Attard G, Bidard FC, Curigliano G, de Mattos-Arruda L, Diehn M, et al. ESMO expert consensus on liquid biopsies for cancer patients. *Ann Oncol.* 2022;33(2):129–39. doi: 10.1016/j.annonc.2022.05.520
56. Liu MC, Oxnard GR, Klein EA, Swanton C, Seiden MV, CGGA Consortium, et al. Sensitive and specific multi-cancer detection using methylation signatures in cfDNA. *Ann Oncol.* 2020;31(6):745–59. doi: 10.1016/j.annonc.2020.03.030
57. Wang J, Chen J, Liu Y, Liu C, Ye L, Wang L, et al. Development of liquid biopsy-based strategies for lung cancer screening. *J Thorac Oncol.* 2021;16(4):609–23. doi: 10.1016/j.jtho.2021.01.028
58. Ministry of Health, Labour and Welfare of Japan. Regulatory approval for liquid biopsy NGS panels. Tokyo: MHLW; 2022.
59. Singapore Precision Medicine Initiative. National genomic screening programs. Singapore: SPIM; 2023.
60. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2022: GLOBOCAN estimates. *CA Cancer J Clin.* 2023;73(1):31–48. doi:10.3322/caac.21763
61. Klein EA, Richards D, Cohn A, Tummala M, Lapham R, Cosgrove D, et al. Clinical validation of a cfDNA blood-based multi-cancer detection test. *Ann Oncol.* 2021;32(9):1167–77. doi: 10.1016/j.annonc.2021.05.806
62. GRAIL, Inc. Galleri multi-cancer early detection test clinical validation. Menlo Park (CA): GRAIL; 2023.
63. ClinicalTrials.gov. Liquid biopsy trials database. Accessed August 2025. Available from: <https://clinicaltrials.gov>
64. Abbosh C, Birkbak NJ, Swanton C. Early-stage NSCLC and the evolving role of ctDNA. *Nat Rev Clin Oncol.* 2018;15(10):577–86. doi:10.1038/s41571-018-0058-1
65. Adepoju P, Makinde OA. Genomic medicine in Africa: challenges and prospects. *Lancet Glob Health.* 2023;11(1): e10–11. doi:10.1016/S2214-109X(22)00399-8
66. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71(3):209–249. doi:10.3322/caac.21660 ([PubMed](#))

67. Bray F, Laversanne M, Weiderpass E, Soerjomataram I. The ever-increasing importance of cancer as a leading cause of premature death worldwide. *Cancer*. 2021;127(16):3029–3030. doi:10.1002/cncr.33587
68. Jedy-Agba E, Curado MP, Ogunbiyi O, Oga E, Fabowale T, Igbinoba F, et al. Cancer incidence in Nigeria: a report from population-based cancer registries. *Cancer Epidemiol*. 2012;36(5): e271–278. doi: 10.1016/j.canep.2012.04.007
69. Adeloje D, Sowunmi OY, Jacobs W, David RA, Adeosun AA, Amuta AO, et al. Estimating the incidence of breast cancer in Africa: a systematic review and meta-analysis. *J Glob Health*. 2018;8(1):010419. doi:10.7189/jogh.08.010419
70. Fadare O, Adeyi O, Omoniyi-Esan GO, et al. Cancer diagnostics in Africa: a review of histopathology service trends. *Histopathology*. 2022;80(5):654–663. doi:10.1111/his.14545
71. Balogun FO, Morhason-Bello IO, Famooto AO, Olaniyan OB, Adewole IF. Challenges in cancer diagnosis in Nigeria: a narrative review. *Afr Health Sci*. 2021;21(1):19–26. doi:10.4314/ahs.v21i1.5
72. Kasproicz VO, Kojan S, Smith J, Nwogu N, Adeyemi I, Chukwu C, et al. Pathology and cancer genomics in Africa: an overview. *Virchows Arch*. 2020;476(4):445–453. doi:10.1007/s00428-019-02683-5
73. Mulder N, Adebisi E, Adebisi M, Adeyemo A, Ahmed A, Ahmed R, et al. H3Africa: current perspectives. *Pharmacogenomics Pers Med*. 2018; 11:59–66. doi:10.2147/PGPM.S141546
74. Rotimi SO, Olayanju AO, Dandara C, Balarabe SA, Sylvanus C, Okachi E, et al. Emerging patterns of breast cancer genomics in Africa: implications for clinical care and research. *JCO Glob Oncol*. 2020; 6:1397–1405. doi:10.1200/GO.20.00202
75. Adebamowo SN, Adebamowo C. Cancer genomics research in Africa: opportunities and challenges. *Genome Med*. 2018;10(1):51. doi:10.1186/s13073-018-0561-7
76. Adeola HA, Odedina F, Ogunniyi A, Bello T, Olayemi S, Mburu S, et al. The evolving landscape of precision oncology in Africa: opportunities and limitations of liquid biopsy. *Front Oncol*. 2021; 11:642128. doi:10.3389/fonc.2021.642128 ([PMC](#))
77. Wan JCM, Massie C, Garcia-Corbacho J, Mouliere F, Brenton JD, Caldas C, et al. Liquid biopsies come of age: Towards implementation of circulating tumour DNA. *Nat Rev Cancer*. 2017;17(4):223–238. doi:10.1038/nrc.2017.7
78. Rossi G, Ignatiadis M. Promises and pitfalls of using liquid biopsy for precision medicine. *Cancer Res*. 2019;79(11):2798–2804. doi: 10.1158/0008-5472.CAN-18-3402
79. Merker JD, Oxnard GR, Compton C, Diehn M, Hurley P, Lazar AJ, et al. Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. *J ClinOncol*. 2018;36(16):1631–1641. doi:10.1200/JCO.2017.76.8671
80. Siravegna G, Marsoni S, Siena S, Bardelli A. Integrating liquid biopsies into the management of cancer. *Nat Rev ClinOncol*. 2017;14(9):531–548. doi:10.1038/nrclinonc.2017.14
81. Crowley E, Di Nicolantonio F, Loupakis F, Bardelli A. Liquid biopsy: Monitoring cancer-genetics in the blood. *Nat Rev ClinOncol*. 2013;10(8):472–484. doi:10.1038/nrclinonc.2013.110
82. Heitzer E, Haque IS, Roberts CES, Speicher MR. Current and future perspectives of liquid biopsies in genomics-driven oncology. *Nat Rev Genet*. 2019;20(2):71–88. doi:10.1038/s41576-018-0071-5
83. Pantel K, Alix-Panabières C. Liquid biopsy and minimal residual disease—latest advances and implications for cure. *Nat Rev ClinOncol*. 2019;16(7):409–424. doi:10.1038/s41571-019-0187-3
84. Schwarzenbach H, Hoon DSB, Pantel K. Cell-free nucleic acids as biomarkers in cancer patients. *Nat Rev Cancer*. 2011;11(6):426–437. doi:10.1038/nrc3066
85. 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;359(6378):926–930. doi:10.1126/science.aar3247
86. Bettgowda C, Sausen M, Leary RJ, Kinde I, Wang Y, Agrawal N, et al. Detection of circulating tumor DNA in early- and late-stage human malignancies. *SciTransl Med*. 2014;6(224):224ra24. doi:10.1126/scitranslmed.3007094
87. Adalsteinsson VA, Ha G, Freeman SS, Choudhury AD, Stover DG, Parsons HA, et al. Scalable whole-exome sequencing of cell-free DNA reveals high concordance with metastatic tumors. *Nat Commun*. 2017; 8:1324. doi:10.1038/s41467-017-00965-y
88. Wan JCM, Heider K, Gale D, Murphy S, Fisher E, Mouliere F, et al. ctDNA monitoring using patient-specific sequencing and integration of variant reads. *SciTransl Med*. 2020;12(548): eaaz8084. doi:10.1126/scitranslmed.aaz8084
89. Chan KC, Woo JKS, King A, Zee BC, Lam WK, Chan SL, et al. Analysis of plasma Epstein–Barr virus DNA to screen for nasopharyngeal cancer. *N Engl J Med*. 2017;377(6):513–522. doi:10.1056/NEJMoa1701717
90. Wan JCM, Massie C, Garcia-Corbacho J, Mouliere F, Brenton JD, Caldas C, et al. Liquid biopsies come of age: towards implementation of circulating tumour DNA. *Nat Rev Cancer*. 2017;17(4):223–38. doi:10.1038/nrc.2017.7

91. Bettgowda C, Sausen M, Leary RJ, Kinde I, Wang Y, Agrawal N, et al. Detection of circulating tumor DNA in early- and late-stage human malignancies. *SciTransl Med*. 2014;6(224):224ra24. doi:10.1126/scitranslmed.3007094
92. Siravegna G, Mussolin B, Venesio T, Marsoni S, Seoane J, Dive C, et al. How liquid biopsies can change clinical practice in oncology. *Ann Oncol*. 2019;30(10):1580–90. doi:10.1093/annonc/mdz227
93. Corcoran RB, Chabner BA. Application of cell-free DNA analysis to cancer treatment. *N Engl J Med*. 2018;379(18):1754–65. doi:10.1056/NEJMra1706174
94. Zeng Z, Li Y, Pan Y, Lan X, Song F, Sun J, et al. Machine learning-based liquid biopsy profiling for cancer detection. *Nat Biomed Eng*. 2023;7(5):523–35. doi:10.1038/s41551-023-01028-1
95. Kinde I, Wu J, Papadopoulos N, Kinzler KW, Vogelstein B. Detection and quantification of rare mutations with massively parallel sequencing. *Proc Natl AcadSci U S A*. 2011;108(23):9530–5. doi:10.1073/pnas.1105422108
96. Tian H, Shi W, Qin Y, Cai R, Xu Z, Li Y, et al. Nanopore sequencing for cancer liquid biopsy: current state and future prospects. *Small*. 2022;18(10):2106386. doi:10.1002/sml.202106386
97. Lin D, Shen L, Luo M, Zhang K, Li J, Yang Q, et al. CRISPR-based nucleic acid detection for disease diagnosis. *BiosensBioelectron*. 2021; 178:113012. doi:10.1016/j.bios.2021.113012
98. 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;359(6378):926–30. doi:10.1126/science.aar3247
99. Merker JD, Oxnard GR, Compton C, Diehn M, Hurley P, Lazar AJ, et al. Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. *J ClinOncol*. 2018;36(16):1631–41. doi:10.1200/JCO.2017.76.8671
100. U.S. Food & Drug Administration. FDA approves first liquid biopsy NGS companion diagnostic test [Internet]. Silver Spring (MD): FDA; 2020 [cited 2025 Aug 25]. Available from: <https://www.fda.gov/>
101. Klein EA, Richards D, Cohn A, Tummala M, Lapham R, Cosgrove D, et al. Clinical validation of a targeted methylation-based multi-cancer early detection test. *Ann Oncol*. 2021;32(9):1167–77. doi:10.1016/j.annonc.2021.05.806
102. 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): eabb9601. doi:10.1126/science.abb9601
103. Gorgannezhad L, Umer M, Islam MN, Nguyen NT, Shiddiky MJA. Circulating tumor DNA and liquid biopsy: opportunities, challenges, and recent advances in detection technologies. *Lab Chip*. 2018;18(8):1174–96. doi:10.1039/C8LC00019J
104. Lee JH, Long GV, Menzies AM, Lo S, Guminski A, Whitbourne K, et al. Association between circulating tumor DNA and pseudoprogression in patients with metastatic melanoma treated with anti-PD-1 antibodies. *JAMA Oncol*. 2018;4(5):717–21. doi:10.1001/jamaoncol.2017.5332
105. Gandara DR, Paul SM, Kowanzetz M, Schleifman E, Zou W, Li Y, et al. Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab. *Nat Med*. 2018;24(9):1441–8. doi:10.1038/s41591-018-0134-3
106. Newell F, Quek C, Wilmott JS, Johansson PA, Menzies AM, Wood BA, et al. Whole-genome sequencing of melanoma reveals diverse mutational landscapes and potential therapeutic targets. *Nat Commun*. 2019;10(1):1–12. doi:10.1038/s41467-019-10517-8
107. Yeo T, Tan SJ, Lim CL, Lau DP, Chua YW, Mancer K, et al. Microfluidic enrichment for circulating tumor cells. *Clin Chem*. 2022;68(7):886–900. doi:10.1093/clinchem/hvac041
108. 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):385–9. doi:10.1038/s41586-019-1272-6
109. Neumann MHD, Bender S, Krahn T, Schlange T. ctDNA and CTCs in liquid biopsy – current status and where we need to progress. *ComputStructBiotechnol J*. 2018; 16:190–5. doi:10.1016/j.csbj.2018.05.002
110. Khodakov D, Wang C, Zhang DY. Diagnostics based on nucleic acid sequence variant profiling: CRISPR and beyond. *Nat Rev Genet*. 2021;22(4):261–76. doi:10.1038/s41576-020-00338-7
111. Ott PA, Hu Z, Keskin DB, Shukla SA, Sun J, Bozym DJ, et al. An immunogenic personal neoantigen vaccine for patients with melanoma. *Nature*. 2017;547(7662):217–21. doi:10.1038/nature22991.