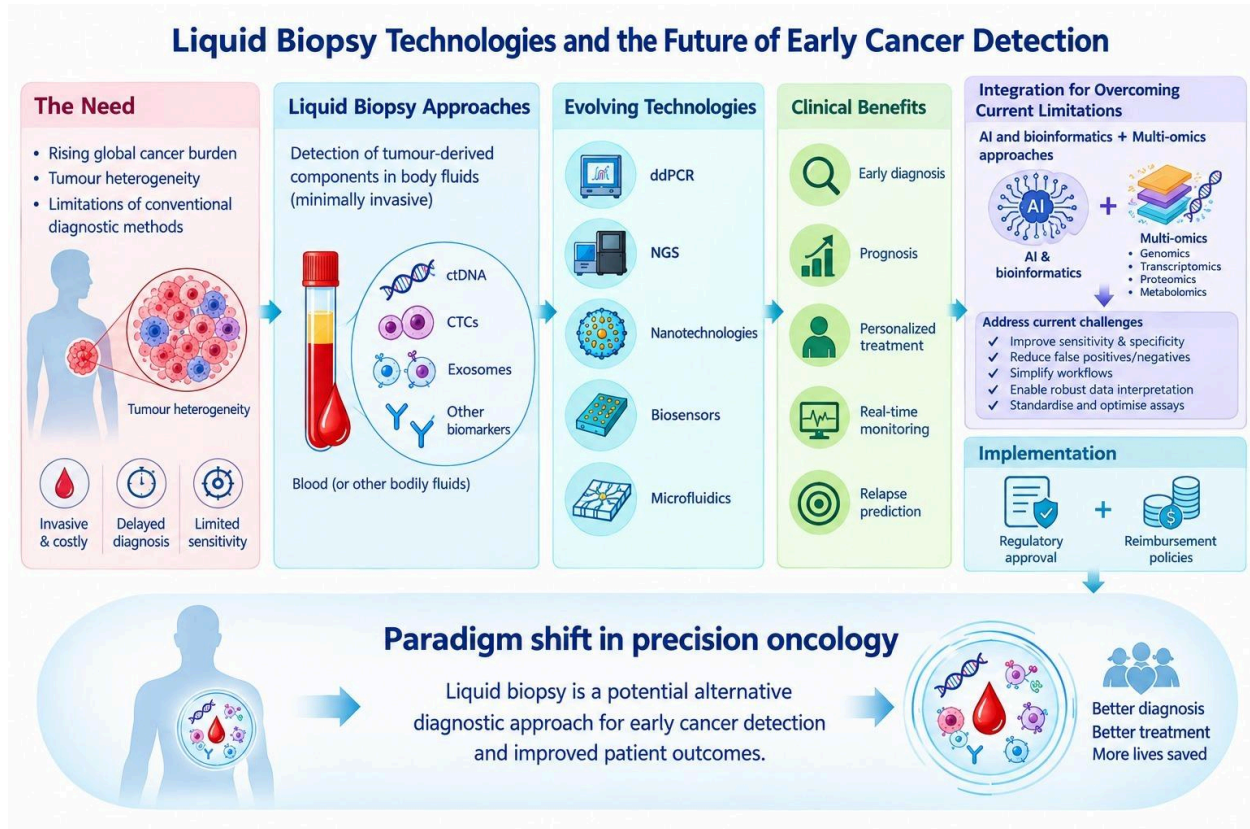


Liquid Biopsy Technologies and the Future of Early Cancer Detection



1. Introduction

- Why early cancer diagnosis remains one of healthcare's biggest challenges

Diagnosing cancer at an early stage can save lives by reducing treatment complexity. However, early detection remains challenging due to the biological and clinical complexity of cancer, as well as technical limitations. Some cancer types—such as lung, pancreatic, gastric, and ovarian cancers, often present symptoms only at an advanced stage. In contrast, other cancers may be asymptomatic or cause minor, vague, or nonspecific symptoms that are easily overlooked, leading to delayed diagnosis.

Existing techniques, such as imaging modalities including PET scans and MRI, are applicable to only a limited number of cancer types. Although they enable detailed visualization, they do not provide molecular-level information. They are also often unable to detect early-stage, small, or microscopic lesions because visible features may be ambiguous during the earliest phases of disease development. An efficient, reliable, rapid, and affordable routine screening tool for all cancer types is still lacking.

- The limitations of traditional tissue biopsies

In this context, tissue biopsy remains the clinical gold standard for determining malignancy and identifying the specific cancer type. However, it often relies on imaging to locate the exact position of the tumor, making it challenging to perform in early-stage disease.

Tissue biopsy also has several fundamental limitations. It is invasive and carries risks such as bleeding and infection; in some cases, surgery may be required to obtain a sample. These factors limit its suitability for patients with concurrent clinical complications. In addition, biopsy results can take several days to weeks, the procedure is costly, and it cannot fully capture the dynamic and evolving nature of malignancy. Consequently, repeated biopsies are often impractical for monitoring disease progression.

- The growing need for minimally invasive diagnostics

To address the limitations of tissue biopsy, minimally invasive approaches such as blood-based analysis and non-invasive approaches, such as urine or saliva testing, are gaining increasing attention. These methods offer several advantages: simpler, safer, and more convenient sampling can encourage regular screening, support early detection, and enable recurrence monitoring.

Minimally invasive or non-invasive approaches are particularly important for patients with inaccessible tumors or high medical complexity. They also hold potential for population-based

research, mass screening, and real-time tracking of disease progression. Liquid biopsy represents one such innovative and promising minimally invasive technique and could play a central role in the future of cancer management.

2. What Is a Liquid Biopsy?

- Understanding the science behind liquid biopsy technologies

Liquid biopsy (LB) refers to the analysis of circulating tumor-derived cellular or molecular components from bodily fluids such as blood (most commonly), saliva, urine, cerebrospinal fluid (CSF), pleural effusions and ascitic fluid. Therefore, it facilitates a comprehensive profiling of tumor genetic and biological characteristics at the molecular level. As these cancer-specific biomarkers are released into the body fluids long before the symptoms appear or tumors become clinically detectable, this enables early detection.

- Key biomarkers: ctDNA, CTCs, exosomes, and extracellular vesicles

Over the past few decades, a range of tumor-derived components recognised as potential key biomarkers for cancer-specific early-stage diagnosis are mentioned below. Of these, circulating tumor cells (**CTCs**), circulating cell-free tumor DNA (**ctDNA**), protein markers, and exosomes have been the most extensively investigated. While circulating cell-free tumor RNAs are receiving rapidly increasing interest, newer markers such as metabolites and tumor-educated platelets (**TEPs**) are also coming to the forefront.

- **CTCs** are cancer cells detached from the primary tumor and enter the bloodstream, the most common and important component responsible for malignancy progression. In 1860, Australian physician Thomas Ashworth reported CTCs in peripheral blood. Deep understanding of the biological characteristics of CTCs facilitates their application in screening, evaluating treatment efficacy and predicting disease recurrence.
- **ctDNA** is the fragmented DNA released from tumor cells to the circulatory system, and was first reported by Mandal and Metails in 1948. It holds the same genetic and epigenetic signature as the tumor it originated from.

- **Tumor-derived extracellular vesicles (tEVs)**, membrane-bound nanovesicles (30 and 10,000 nm) originating from cancerous cells, are classified into three different types based on diameter: exosomes (30–300nm), microvesicles (<1000 nm), and large oncosomes (1000 and 10,000 nm) circulate in various bodily fluids. Each subclass plays a different role. These are considered exceptionally stable biomarkers as internal moieties (oncogenic proteins, lipids, genetic material, metabolites) that carry crucial information regarding cancer and are protected inside it.
- **ctRNA** is tumour-derived fragmented RNA, which refers to various types of RNAs, including messenger RNAs (mRNAs), noncoding RNAs (long non-coding and microRNA), and, more recently, circular RNAs (circRNAs). Each of them provides unique regulatory and diagnostic insights. This distinct class of biomarker could be present in multiple forms, either freely or associated with ribonucleoprotein complexes or encapsulated within extracellular vesicles.
- **TEPs** are a new and unique class of biomarker originating from the alteration of the genetic profile of the platelets by the tumor during the interaction with the surrounding blood flow. Profiling the RNA of TEPs enables highly specific cancer detection and, under certain conditions, facilitates the identification of the primary tumor's anatomical origin.

- How tumors leave molecular traces in the bloodstream

Cancer cells undergo epithelial-mesenchymal transition (EMT), a process that reduces adhesiveness among neighbouring cells and makes them highly motile and invasive.

Tumour-associated macrophages (TAMs) mediate tumour cell invasion and migration toward nearby blood vessels. Once at the vessel, the process of intravasation occurs as the cancer cells utilize mechanical pressure and enzymatic activity to compromise the vascular wall, allowing them to penetrate the barrier and enter systemic circulation. When those cells die necrotically or apoptotically, they passively release their content, including nucleic acid components. In addition, nucleic acid components are released through active secretion within lipid-based structures and EVs.

3. Why Liquid Biopsies Are Gaining Momentum

Rapid, minimally invasive, or non-invasive diagnostic tools are essential for early cancer diagnosis, screening, and real-time monitoring of disease and therapy. Within this framework, LB is attracting attention as an alternative and complementary approach that can address the limitations of existing technologies. Its clinical utility has been explored over the past few decades, and the feasibility of using LB-based assays to analyze multiple cancer types by targeting several analytes simultaneously is becoming an increasingly important area of cancer research.

- Faster, less invasive diagnostic approaches

LB has evident clinical utility for early detection and screening in asymptomatic populations. The fundamental principle of LB is based on cancer biomarker detection from a simple blood/urine test, regardless of tumour accessibility and symptoms. Therefore, opt for a low-intervention procedure. It simply bypasses the risky process of tissue sample collection from an unreachable tumor in the internal organs, as in the case of tissue biopsy. Hence, LB has shown an easier, quicker and safer option by reducing the overall sample preprocedural time and streamlining the diagnosis process.

- Real-time monitoring of tumor evolution

Studies have shown that molecular traces of tumors can be detected in bodily fluids early in disease development, even before clinical signs appear. By tracking these biomarkers through frequent testing, LB enables early identification of disease progression, real-time assessment of tumor evolution, and estimation of tumor burden.

LB also shows potential for assessing a patient's response to treatment or the development of treatment resistance.

- The shift toward precision oncology and personalized medicine

When combined with advanced technologies such as next-generation sequencing (NGS) and polymerase chain reaction (PCR), LB offers a promising strategy for precision oncology and

personalized medicine. LB-based approaches provide molecular profiling of genetic and proteomic variations, tumor heterogeneity, and biological changes that occur during treatment. This information can help clinicians customize or optimize treatment over time for an individual patient's cancer. Overall, LB supports more informed treatment decisions based on a patient's genetic profile, lifestyle, and health-related characteristics.

4. Technologies Powering Modern Liquid Biopsies

The expansion of LB would not have been possible without advanced technologies. Several innovative technologies are used to isolate, enrich, detect, and analyze circulating biomarkers with high specificity and sensitivity. These advances have broadened the clinical applications of LB in oncology and personalized medicine.

Key technologies include molecular diagnostic methods, NGS, PCR, microfluidics, lab-on-chip systems, immunoassay-based platforms, spectroscopy-based approaches, nanotechnology, and point-of-care (POC) devices. More recently, artificial intelligence (AI) has been integrated to improve the interpretation of complex biological datasets. Modern LB is therefore evolving as an integrated combination of cutting-edge technologies.

4.1 Genomic Sequencing and Molecular Diagnostics

- Next-generation sequencing (NGS)

NGS is a robust genomic tool that offers several advantages by allowing sequencing of a comprehensive genomic profile and providing a wide range of information regarding genetic alteration. It is primarily focused on ctDNA and miRNA analysis and detects single-nucleotide variants, point mutations, deletions/insertions, copy number variants, and chromosomal rearrangements responsible for cancer. It can also potentially detect epigenetic modifications like aberrant DNA methylation, which is considered an early event of cancer development. To enhance sensitivity and specificity (>97%), several new NGS-based approaches, such as cancer personalized profiling by deep sequencing (CAPP-Seq) and tagged-amplicon deep sequencing

(Tam-Seq), have been developed. Though NGS possesses the unique capability to detect unknown gene targets with great sensitivity and specificity, it still has limitations, being expensive, requiring complex, sophisticated instrumentation for data analysis, and time-consuming.

- PCR-based technologies

PCR is another promising gold standard molecular diagnostic technique used for detecting, amplifying, and quantifying, especially circulating DNA and RNA fragments from the samples. Numerous PCR strategies are devised, such as quantitative PCR (qPCR), BEAMing, droplet digital PCR (ddPCR), allele-specific PCR (AS PCR), and methylation-specific PCR (MSP), to improve the sensitivity and specificity. The absolute quantification, along with genetic information regarding mutation, methylation and allele frequency, helps track tumor burden. It holds some technical shortcomings like false positive/negative results, risk of contamination, need for prior knowledge about the target sequence.

- Multi-omics integration

Relying on a single analyte alone couldn't be reliable or capture all the details, especially at an early stage and type of cancer that releases a low amount of the target analyte. Therefore, it may result in false positives or negatives that generate conflict and lead to an inconclusive interpretation. To overcome this issue, a new multi-omic approach has recently been adopted in LB, which targets the analysis of multiple analytes from a single sample. It is a combined investigation of genomic, epigenomic, proteomic, transcriptomic and metabolomic profiles. This comprehensive profiling tremendously improves the understanding of the underlying mechanism, diagnosis accuracy, personalized treatment.

4.2 Artificial Intelligence and Data Analytics

Integration of artificial intelligence (AI), the use of computational algorithms, is no doubt bringing a paradigm shift in oncology to acquire the promising capabilities of LB in clinical practice. The growing number of cancers day by day makes AI an essential tool in LB for handling vast, complex, high-dimensional datasets, finding hidden information, avoiding

inter-person error, and speeding up the multi-omics analysis. Specifically, the application of two subfields of AI, machine learning (ML) and deep learning (DL), is empowering and reshaping the future.

- AI-driven biomarker interpretation

One of the important contributions of AI models is finding biomarkers by assessing a massive multidimensional complex dataset. An unsupervised learning algorithm recognises relevant features and discovers cross-correlation between a variety of biological data, hence enabling the identification of a new biomarker subgroup. Promising results have been shown in AI-based biomarker discoveries across multiple cancer types, such as lung, colorectal, and breast cancer. AI's role is constantly progressing, focusing on confidence in clinical use.

- Pattern recognition in cancer diagnostics

AI with DL has shown an impressive ability to differentiate cancer-specific weak signals from background noise by interpreting the complicated, biologically variable, large-scale clinical dataset. Specifically, DL models such as the convolutional neural network (CNN) technique are excellent at extracting features and recognising disease-relevant patterns. Hence, it accelerates the diagnostic accuracy and sensitivity of LB-based techniques by reducing human error and time.

- Predictive analytics in oncology

AI integration in LB facilitates early diagnosis by capturing even faint biomarker signals. AI can monitor small changes in patient outcomes and enable prognosis. The prediction capability of AI models, for example, the CancerSEEK model, DNA evaluation of fragments for early interception (DELF), has demonstrated considerable improvement in survival rate for the patient in several studies. The application of AI has shown its efficacy in cancer type detection, classification and burden analysis.

4.3 Emerging Diagnostic Platforms

- Microfluidics and lab-on-chip systems

Microfluidic technologies or lab-on-chip systems have accelerated remarkable progress in LB-based cancer diagnosis in many ways. A single miniaturized device capable of integrating sampling, clinical-grade isolation, enrichment and detection using minimal sample and could be coupled with a suitable analytical tool (optical/electrochemical). Several microfluidic strategies that offer multiple uses have been explored over the past decade to achieve efficient and accurate detection of CTCs, EV, ctDNA/RNA, and protein markers with sensitivity at the single cell/ exosome/ nucleic acid level involved with numerous cancer types, such as brain, breast, cervical, colorectal, gastric, lung, ovarian and prostate. It offers enhanced sensitivity and specificity with multiplexing, and its isolation technique enables the recovery of samples without compromising sample integrity.

- Nanotechnology-enabled liquid biopsies

Another promising, effective, and impactful revolutionary translational technology for addressing the challenges of liquid biopsy is nanotechnology. Implementation of nanomaterials having nanodimensional structure with ease of synthesis, functionalization and bioconjugation, and their physiochemical properties, especially optical and electrical, offer high surface-to-volume ratio, improved sample separation, purification and enrichment, signal amplification, enhanced detection sensitivity and specificity of cancer signature markers. To date, numerous nanomaterials such as nanoparticles [gold nanoparticles (AuNPs), magnetic nanoparticles, carbon nanoparticles], quantum dots, nanofibers, nanorods, polymer nanoparticles, and metal-organic frameworks (MOFs) have demonstrated their effective incorporation in advancing the LB. Nanomaterial-integrated microfluidic chip, multi-omics and AI, nanobiosensors, nanopore sequencing coupled with nano-engineered devices, magnetic nanoparticle-based isolation, and nano-enhanced flow cytometry not only help in the clinical translation but also unlock the way for future directions towards scalability, rapid analysis, multiplexing, reproducibility and cost-effective POC development.

- Digital pathology integration

Digitalization of pathology refers to the analysis of tissue samples on glass slides in the form of digital images of high resolution, another growing field adding a level up to LB-based diagnosis. Recent developments exemplified by CTC-5, a new robust digital pathology approach for CTC isolation and characterization, transform traditional microscopy by creating high-quality multi-channel digital slides, demonstrating the proof-of-principle. It adds improved efficiency, accuracy, high-quality data with long-term storage, management, accessibility, scalability and sharing facilities. Further application of AI in digital pathology significantly enhances the precision, consistency and diagnostic reliability.

5. Clinical Applications in Early Cancer Detection

LB offers many potentially advantageous clinical applications, including minimal/non-invasive early diagnosis, cancer screening in asymptomatic populations, prognosis, assessment of minimal residual disease (MRD) and tumour burden, real-time progression and relapse monitoring, and tumour heterogeneity profiling. Though their clinical validity has been demonstrated in several platforms or technical settings, trials are still ongoing to prove their clinical utility. Discussion has been prioritized on cancer types such as lung, breast, colorectal, and pancreatic cancer due to their massive annual mortality and fatality worldwide. Hence, there is an urgency for early diagnosis before metastatic progression happens.

5.1 Lung Cancer Detection

- The importance of early-stage diagnosis

Lung cancer(LC), the leading threat of cancer incidence and deaths worldwide, with approximately 1.8 million deaths reported by the World Health Organisation (WHO) in 2022, remains undetected at the preliminary stage in current clinical settings. Among the two types of lung cancer, the less common and more aggressive is small cell (SCLC), and 85% of cases are accounted for by non-small cell lung cancer (NSCLC). Early detection is one of the biggest challenges in LC, as initially, patients don't have any symptoms to address. At the time symptoms present, it has mostly reached an advanced stage with a low five-year survival rate (10-60%). Therefore, to save and boost life expectancy, early diagnosis can help with the success of treatment.

- Liquid biopsy in high-risk patient screening

In this context, low-dose computed tomography (LDCT) is recommended for high-risk patients with a long-term smoking history within the age group of 50-74 years in current clinical practice. However, to overcome the limitations of LDCT, such as low specificity and risk of exposure to radiation, the LB emerged as an important less-invasive alternative for early-stage diagnosis that can improve overall treatment outcomes. Mostly blood-based biomarkers such as CTCs, mutation /methylation in ctDNA, mRNA, exosomes, proteins and tumour-educated platelets have been reported with successful clinical validation in detecting lung cancer at an early stage. The application of LB rapidly advanced after the approval of the first liquid biopsy test by ctDNA from blood samples, named the Cobas EGFR Mutation test v2, in 2016 by the United States Food and Drug Administration (FDA),

5.2 Breast and Colorectal Cancer

- Biomarker-driven detection strategies

Breast cancer (BC), a global threat among women, caused around 670,000 deaths in 2022. Studies suggest that BC is extremely heterogeneous, with six intrinsic subtypes, thereby justifying the integration of LB to track and overcome tumour heterogeneity and guide personalised treatment. Clinical investigation results of LB biomarker-based strategies, especially analysing ctDNA to detect BC mutations in key genes like BRCA1/2, ESR1, PIK3CA, TP53, and LB-based BC methylation assay, and CTCs for critical biomarker evaluation like HER2, validate their clinical significance and utility in asymptomatic early screening for BC. This fueled clinical research of early diagnosis where AI assistance and multi-omics strategies were explored to overcome technical challenges in clinical implementation for early-stage BC diagnosis.

According to the GLOBOCAN 2022 database, colorectal cancer (CRC) ranked 2nd in mortality among all types of cancers globally, underscoring the critical need for early diagnosis. Numerous LB-based analyses have demonstrated successful detection of CRC-specific early diagnostic markers like genetic mutations (APC, BRAF, KRAS), epigenetic signatures (hypermethylation in BMP3, SEPT9), carcinoembryonic antigen (CEA) and EV-packaged

miR-21 and miR-92. In 2016, Epi proColon (Septin 9) was the first and long-standing ctDNA blood test approved by the FDA for CRC screening. In 2024, the FDA approved Shield as a second blood-based screening alternative. Therefore, LB-biomarkers are broadening the scope of non-invasive early diagnosis.

- Monitoring recurrence and treatment response

These biomarkers are also promising in assessing recurrence risk and therapy or drug resistance by continuous monitoring. Technological advancements like ddPCR, sequencing, microfluidics, and biosensors enable comprehensive LB analysis that provides real-time assessment of treatment efficacy, thereby predicting relapse post-treatment or surgery. Several LB technologies are in clinical trials, and some LB strategies like Guardant360 CDx and FoundationOne Liquid CDx as companion diagnostics by analysing ctDNA mutations in PIK3CA or BRCA1/2, and the CellSearch® System to detect the number of CTCs for prognostic assessment in the management of BC, have been approved by the U.S. FDA. Several studies have confirmed the potential of ctDNA to predict recurrence in individuals who have undergone surgery for stage I-III localised CRC. Another study reported ctDNA's ability to predict recurrence with an average prediction of 9.4 months earlier than tomography imaging.

5.3 Pancreatic and Prostate Cancer

- Addressing hard-to-detect cancers

A silent and lethal type globally is pancreatic cancer (PC), of which 80-90% of cases are pancreatic ductal adenocarcinoma (PDAC). Prostate cancer (PCa), the most common type of cancer in men, grows very slowly and rarely causes any symptoms. Detection at the preliminary stage is a major challenge in healthcare for both types due to the lack of clinically significant specific symptoms. Around 80% of PC is diagnosed at an advanced stage when surgery is not possible. Unfortunately, among the 20% of patients diagnosed at a stage where surgery is possible, post-surgery recurrence rates are very high (80%). Because the pancreas resides deep behind the stomach, early-stage lesions cannot be felt physically and are easily missed by modern imaging scans. Furthermore, sampling these hidden tissues requires

invasive procedures that carry high risks of severe bleeding and acute pancreatitis. On the other hand, early identification is obstructed by the poor specificity of prostate-specific antigen (PSA) assays alongside physical exam constraints, which routinely fail to capture anterior prostatic lesions. Given these challenges, LB-based technologies present an ideal and effective solution.

- Opportunities for earlier intervention

Various LB strategies have been established and have shown clinical efficacy to date, which opens up avenues for early prevention, the only way to curative treatment. Multiple body fluids, including pancreatic juice, saliva, urine, and blood, have been examined for early detection of PC. Ongoing investigations revealed the clinical usefulness of mostly studied PC-biomarkers (CTC, ctDNA, EV, miRNA), involved in the detection of KRAS, CDKN2A, SMAD4 mutations, circulating epithelial cells (CECs), methylation status of ADAMTS1 and BNC1 and miRNAs (miR-34a-5p, miR-130a-3p, and miR-222-3p) for early intervention. However, innovative biomarkers identified for PCa diagnosis include urinary miRNAs such as miR-148a and miR-375, Prostate Cancer Antigen 3 (PCA3, also referred to as DD3), androgen receptor (AR) mutations, somatic *BRCA1/2* mutations in ctDNA.

6. Beyond Detection: Expanding Clinical Applications

- Monitoring treatment response in real time

Apart from early diagnosis, LB has enabled another significant clinical utility: continuous monitoring of patient outcomes in real time. Notable factors that make this feasible include short half-lives of the circulating biomarkers (for ctDNA, it typically ranges from a few minutes to a few hours) and technical advancements with nanotechnology integration, a mediated shift towards robust amplification-free, label-free biosensing, POC devices with direct readout, and multiplexed systems. As these biomarkers clear quickly, instantaneous changes in concentration by serial sampling provide insight into tumour burden and therapeutic response in real-time.

- Detecting minimal residual disease (MRD)

MRD, the presence of microscopic, trace amounts of tumor-derived molecular signatures after curative treatments, allows clinicians to predict treatment response or patient outcome. MRD tracking becomes possible due to refinement of LB technologies. Key biomarkers focused mostly on the detection of MRD in leukaemia, NSCLC, breast cancer, and colorectal cancer are ctDNA, CTC and recently EV. Still, there are no standardized guidelines ready for clinical implementation, as trials are ongoing, relying on CTC and ctDNA as MRD markers.

- Predicting recurrence before symptoms appear

Much literature has explored that tracking of tumor-derived LB markers (especially ctDNA and CTCs) before and after curative-intent steps can be a potential indicator of future recurrence or relapse during follow-up, even before symptoms appear. A significant correlation between CTC/ctDNA count and recurrence of disease has been reported, with widely varying lead time by assay sensitivity and cancer types that include breast, lung, colorectal and prostate. Overall, the fair and most reproducible recurrence signal has been observed in ctDNA lead time, i.e., months to years, whereas CTC lead time is less standardized. However, a miRNA-based LB assay that predicts gastric cancer recurrence from patients' blood has also recently been successfully established.

- Companion diagnostics and targeted therapies

LB is currently used as a companion diagnostic (CDx) in clinical practice to identify patients likely to benefit from therapy. CDx is helpful, especially in advanced cancer patients, in guiding treatment or therapy selection, real-time resistance monitoring and obtaining comprehensive genetic profiling. As of now, FDA-approved blood-based CDx include -

- PCR -based Cobas EGFR Mutation test v2 in first-line NSCLC patients to guide treatment.
- Therascreen PIK3CA RGQ PCR kit, another PCR-based CDx, received FDA approval to detect 11 PIK3CA mutations in patients with metastatic breast cancer.
- Guardant360® CDx: NGS-based, first approved LB for comprehensive genomic profiling in 2020 to detect EGFR mutations in NSCLC initially, then expanded to detect

EGFR exon 20 insertion (in 2021), then ESR1 mutation in breast cancer (in 2023) and in 2026 to target HER2 mutation in advanced NSCLC.

- FoundationOne Liquid CDx test approved in 2020 for advanced prostate and lung cancer, analyses over 324 cancer-related genes from ctDNA using NGS, later extended to ovarian cancer and breast cancer.

7. The Pharmaceutical and Commercial Opportunity

- The rise of precision oncology ecosystems

Continuous rapid improvement in LB technologies over the last decade has placed it as an essential tool in oncology. Its validated potential clinical applicability and trials support long-term impact on patient outcomes and management. Full molecular profiling enabled by minimally invasive access through biomarker interpretation even in real-time combines diagnosis, therapy selection or resistance assessment, prediction of clinical recurrence, accelerates decision-making, and personalised treatment feasibility, making LB the fundamental component in precision oncology. Further advancement is expected by progressive integration of LB with clinicopathological data, imaging tools, and AI.

- Diagnostic companies driving innovation

Driven by the growing need for minimally invasive, low-cost, fast procedures and tests, several molecular diagnostic companies such as Guardant Health, Bio-Rad Laboratories, GRAIL, Thermo Fisher Scientific, and Roche Molecular Diagnostics are leading efforts to translate LB clinical potential into real-world use. The global liquid biopsy market size is estimated to grow from USD 10.60 Billion in 2024 to USD 31.70 Billion by 2035, according to the market analysis report published by Spherical Insights & Consulting. Increasing global cancer burden demands scalable diagnostic platforms, creating scope for LB companies to enhance their service portfolio. They are commercialising multi-cancer detection (MCED) tests, exploring new strategies, designing assays, and expanding clinical impact. LB adoption is accelerating, driven by clinical validation, regulatory support, and rising provider interest. Technological advancement, collaborative business and investment from major firms and startups are

producing sensitive platforms, positioning LB as a core tool for a patient-centric healthcare ecosystem.

- Liquid biopsy as a strategic asset in drug development

Repeated sampling, real-time monitoring by tracking biomarkers LB techniques enable assessment of the effect of drugs, treatment response and patient outcomes, as mentioned above. It helps to evaluate whether the drug is effective or not. This is useful in tracking suitable patients by capturing molecular profiles and detecting resistance mutations. Thus, LB can guide drug development by optimizing clinical trial design and personalized therapy.

- Investment trends in oncology diagnostics

Investment in oncology diagnostics is expanding, with the strongest capital flow now inclined towards liquid biopsy. Key sources of capital, like pharmaceutical companies, reference laboratories, large firms, and instrument manufacturers, are investing in companies that have demonstrated clinical validation, regulatory progress, scalable laboratories, and reimbursement strategies. Advanced, ultra-sensitive, affordable, emerging technologies encompass NGS, AI-based analysis, multi-omics, fragmentomics, automation, and methylation profiling, which are also attracting capital and driving market growth. MRD and MCD testing are also considered high-growth investment opportunities.

8. Challenges Slowing Widespread Adoption

Despite holding great promise for onco-diagnostics advancement and management, clinical implementation of LB technologies is still pending. Several efforts are underway to resolve and address limitations associated with LB that retard its adoption in routine clinical settings.

- Sensitivity and specificity limitations

Among them, one major concern is sensitivity and specificity issue. Early-stage detection sometimes leads to false positives or negatives due to their extremely low level of presence. Sensitivity often are influenced due to variable shedding based on tumor biological subtype, anatomical location, assay sensitivity, cancer type, patient's age, heterogeneity, and pre-

analytical procedural causes. Specificity is compromised when some non-cancerous mutations and epigenetic changes cause false-positive results. Sometimes technical limitations, sequencing errors and sample contamination also cause specificity issues.

- False positives and diagnostic uncertainty

False positive results have serious consequences; turns diagnosis ambiguous and cause unnecessary delay. Therefore, limit the use of current LB methods in clinical settings. Proper clinical validation, assay design, optimization and standardization are mandatory before entering into routine practice.

- Standardization and clinical validation challenges

Current techniques face challenges in standardization and clinical validation that hinder their clinical implementation. Inconsistency in result observed due to lack of standardized protocol. Qualitative and quantitative differences between laboratories arise from following different pre-analytical procedures (including sample collection, processing, storage conditions and analyte separation, amplification). Adoption of diverse technical platforms (PCR, NGS, microfluidic, biosensor, etc.) and the absence of standard bioinformatic pipeline, variable result interpretation methods and reporting strategies reduce reproducibility and reliability. Large scale multicentered prospective trials are mandatory to establish reliable clinical performance. Inadequate of cancer-type specific assay, universally accepted references, standard protocols, and proper guidelines lead to inconsistent outcomes and retarding widespread clinical adoption.

- Regulatory approval pathways

The framework of LB test evaluation and approval by regulatory authorities is a prolonged and resource-demanding process that varies by country. After proving the technical accuracy, clinical relevance, and clinical utility, it goes for regulatory review. It gets approved by the regulatory agencies only after ensuring its safety and clinical benefits. Post-approval tracking of the test's safety and performance extensively adds regulatory burden. Collectively,

contrasting regulatory standards and approval pathways complicate the global integration of LB in clinical practice.

- Cost, accessibility, and reimbursement concerns

Economic barriers include expensive, sophisticated instruments, financial burden, complex procedures, limited accessibility and inadequate reimbursement policies, are major hurdles for LB integration. To make LB tests accessible and affordable to patients of all financial backgrounds, especially in low-income countries, economic barriers must be addressed by securing medical coverage and establishing effective reimbursement policies. In addition, educational programme initiatives should be considered to stimulate detailed understanding of LB test benefits and public awareness to guarantee informed decision-making. Also, securing the privacy of patients' genetic data is essential.

9. The Future of Cancer Detection

- Could liquid biopsy become part of routine health screening?

Liquid biopsy offers a practical approach for screening by facilitating the repeated non-invasive analysis of body fluids to identify disease-related biomarkers at an early stage. Investigations are ongoing to validate its general large-scale population screening. At present, it may work as an additional or complementary test. Improving the precision, affordability, sensitivity, specificity, and rapidity of these assays will soon make them an operational reality for routine screening.

- The convergence of AI, genomics, and diagnostics

The powerful synergy between AI, genomics, and advanced diagnostics is constantly evolving, providing the foundation needed to solve the shortcomings of bringing liquid biopsies into everyday clinical practice. Genomics provides deep insight into tumor profiling at the molecular level and strengthens the understanding of cancer biology. AI integration has demonstrated commendable diagnostic accuracy with high sensitivity, complex data analysis and promotes MRD, recurrence, and precision oncology. Combining genomics and AI with diagnostic platforms is transforming LB into a next-level multimodal platform.

- Moving from reactive oncology to predictive healthcare

Another important advantage of LB biomarkers is their prognostic ability, as several studies show this opens a new direction toward predictive healthcare. They capture real-time information about cancer stage, therapy response, patient outcomes, and recurrence before clinical symptoms appear, guiding clinicians to predict survival and treatment options. Therefore, LB is reshaping oncology by enabling prognostic evaluation and supporting a paradigm shift from reactive treatment to predictive, personalized healthcare.

10. Conclusion

Increased global cancer burden, tumour heterogeneity, and conventional technical limitations call for an urgent requirement of rapid, highly sensitive and affordable early diagnostic tools to reduce mortality and save lives. In this regard, in the last few decades, liquid biopsy, analysis of circulating tumor derived components from bodily fluids in minimal invasive manner, has emerged as a revolutionary approach supporting clinical utilities including early diagnosis, prognosis, personalized treatment, real-time progress monitoring and relapse prediction. Several robust techniques like ddPCR, NGS, nanotechnologies, biosensors and microfluidics are continuously evolving and subjected to clinical validation, empowering LB-based technologies. Obstacles like sensitivity, specificity, large procedural methods, false-positive or false-negative results, complex data interpretation, weak signal identification and amplification, and lack of standardised and optimised assays are also being actively investigated through integration of AI and multi-omics approaches. Appropriate regulatory approval and well-defined reimbursement policies are essential for implementing liquid biopsy into real-world applications. LB is a potential alternative diagnostic approach for shaping the future of oncology healthcare.