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From Blood to Bedside: A Review of Liquid Biopsy for Minimal Residual Disease and Recurrence Prediction in Early-Stage Breast Cancer

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Abstract:

- ***Background***

Early-stage breast cancer carries a significant risk of recurrence due to undetectable minimal residual disease (MRD). Conventional surveillance lacks sensitivity for early relapse detection. Liquid biopsy, particularly circulating tumor DNA (ctDNA), offers a promising non-invasive strategy to detect MRD and predict recurrence.

- ***Methods***

This review synthesizes recent evidence on liquid biopsy applications in early-stage breast cancer, with emphasis on MRD detection and recurrence monitoring. We evaluate key assay platforms—including digital droplet PCR (ddPCR), next-generation sequencing (NGS), and cancer personalized profiling by deep sequencing (CAPP-Seq)—and examine their clinical integration.

- ***Results***

Liquid biopsy demonstrates high sensitivity and specificity in detecting ctDNA at subclinical levels, enabling earlier relapse prediction compared to imaging or serum markers. ddPCR offers affordability and precision for targeted mutations, while NGS and CAPP-Seq provide broader genomic coverage and adaptability. Integration into clinical pathways enables dynamic monitoring from diagnosis through treatment and surveillance. However, challenges remain, including assay standardization, cost, and validation across diverse populations.

- ***Conclusion***

Liquid biopsy represents a paradigm shift in early-stage breast cancer management, enabling proactive monitoring and individualized treatment. Future priorities include global assay harmonization, large-scale validation trials, and in tegration of multi-omic and AI-based approaches to enhance predictive accuracy and clinical adoption.

Keywords: *Blood To Bedside, Breast Cancer, Liquid Biopsy, Minimal Residual Disease, Recurrence Prediction.*

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I. INTRODUCTION

Breast cancer remains the most frequently diagnosed malignancy and the leading cause of cancer-related deaths among women globally, with an estimated 2.3 million new cases and 685,000 deaths reported in 2020 [1]. Advances in screening, surgery, systemic therapy, and targeted interventions have significantly improved survival in early-stage breast cancer; however, disease recurrence remains a major challenge [2]. Traditional Clinicopathological parameters and imaging modalities are limited in their ability to detect minimal residual disease (MRD) or predict recurrence at a molecular level [3]. The concept of MRD refers to microscopic or molecular disease persisting after curative-intent treatment, which may eventually manifest as overt relapse [4]. Detecting MRD early provides an opportunity for timely therapeutic intervention, potentially improving outcomes. Conventional monitoring strategies such as tumour markers (CA15-3, CEA), radiological imaging, and clinical follow-up lack sensitivity and specificity, often identifying relapse only after substantial tumour burden develops [5].

II. CONCEPT OF LIQUID BIOPSY

Liquid biopsy refers to the analysis of tumor-derived materials in biological fluids, primarily blood, to provide molecular insights into cancer biology [8]. Liquid biopsy is a minimally invasive technique based on the analysis of tumour-derived materials in blood or other body fluids, has emerged as a transformative tool in oncology. It enables dynamic monitoring of tumour evolution through circulating tumour DNA (ctDNA), circulating tumour cells (CTCs), and other analytes [6]. In early-stage breast cancer, liquid biopsy shows promise in detecting MRD and predicting recurrence months before clinical or radiological evidence of relapse [7]. This ability to provide real-time molecular insights bridges the gap between curative treatment and relapse surveillance, making liquid biopsy a powerful candidate for bedside application.

Unlike tissue biopsy, which is invasive and limited by sampling bias, liquid biopsy allows for non-invasive, real-time monitoring of tumor dynamics, capturing intra- and intertumoural heterogeneity [9].

The main analytes studied include:

- Circulating tumor DNA (ctDNA)**:** fragmented DNA released into the bloodstream from apoptotic or necrotic tumor cells, carrying tumor-specific mutations, copy number variations, and methylation patterns [10].
- Circulating tumor cells (CTCs): intact tumor cells shed from primary or metastatic sites, which provide information on tumor aggressiveness and metastatic potential [11].
- Extracellular vesicles (EVs) and exosomes**:** vesicles containing nucleic acids, proteins, and metabolites reflecting tumor biology [12].
- Other biomarkers**:** such as tumor-derived RNA, proteins, and methylation signatures [13].

The analytical approaches include next-generation sequencing (NGS), digital droplet PCR (ddPCR), and other ultrasensitive methods that enable the detection of rare tumor-derived fragments in plasma [14]. In breast cancer, liquid biopsy has been extensively studied in both metastatic and early-stage settings. While CTCs have prognostic significance in advanced disease, ctDNA is increasingly being recognized as the most sensitive marker for minimal residual disease (MRD) and recurrence prediction [15]. By providing a dynamic and longitudinal assessment of tumor evolution, liquid biopsy serves as a powerful adjunct to conventional diagnostics and surveillance.

➢ *Liquid Biopsy in MRD Detection*

Minimal residual disease (MRD) represents subclinical levels of tumor burden that persist following curative-intent therapy and often precede clinical relapse [16]. In early-stage breast cancer, MRD is the critical link between apparent remission and eventual recurrence. Conventional approaches such as imaging and serum tumor markers lack the sensitivity to detect MRD until disease burden is significant [17]. Circulating tumor DNA (ctDNA) has emerged as the most sensitive biomarker for MRD detection. It reflects tumor-specific genomic alterations and can be identified in plasma months to years before radiological relapse [18]. Garcia-Murillas et al. demonstrated that ctDNA positivity after curative treatment was strongly predictive of relapse in early breast cancer, with a median lead time of ~7.9 months before clinical detection [19]. Similarly, Olsson et al. showed that ctDNA detected recurrence with high accuracy, outperforming conventional surveillance strategies [20].

In hormone receptor–positive (HR+) disease, ctDNA detection has been particularly effective in identifying patients at risk of late recurrence [21]. In triple-negative breast cancer (TNBC), which has aggressive biology and a higher relapse rate, ctDNA monitoring allows for early detection of progression and may guide timely therapeutic escalation [22]. Circulating tumor cells (CTCs) have also been studied in MRD, with trials such as SUCCESS highlighting their prognostic significance in early-stage breast cancer [23]. However, CTC detection is less sensitive compared to ctDNA, making ctDNA the preferred modality for MRD surveillance. Collectively, liquid biopsy provides a powerful tool for early detection of MRD, enabling a potential paradigm shift from reactive to proactive management in breast cancer surveillance.

➢ *Recurrence Prediction in Early-Stage Breast Cancer*

Recurrence remains a major clinical challenge in early-stage breast cancer, occurring in up to 20–30% of patients despite apparently curative treatment [24]. Conventional prognostic tools, including tumor size, nodal status, and molecular subtype, offer risk stratification but do not reliably identify individuals at imminent risk of relapse [25]. Liquid

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biopsy, particularly circulating tumor DNA (ctDNA), has emerged as a sensitive tool to predict recurrence before it becomes clinically or radiologically evident. Several studies have demonstrated the prognostic significance of ctDNA detection in early breast cancer. It has been reported that ctDNA positivity after completion of therapy strongly correlated with relapse risk, with hazard ratios exceeding 20 for recurrence [26]. It has been shown that patient-specific ctDNA detection preceded clinical relapse by a median of 11 months, highlighting its lead-time advantage over standard surveillance [27].

Subtype-specific variations in recurrence prediction have also been observed. In hormone receptor–positive (HR+) cancers, ctDNA is particularly valuable in detecting late recurrences, which may occur beyond 5 years' post-treatment [28]. In HER2-positive disease, ctDNA monitoring complements existing biomarkers such as HER2 amplification status, allowing for earlier intervention in high-risk patients [29]. For triple-negative breast cancer (TNBC), ctDNA has demonstrated predictive power for both early relapse and treatment resistance [30].

Clinical trials have begun integrating ctDNA-based MRD detection into interventional strategies. For instance, the c-TRAK TN trial investigated ctDNA-guided therapy escalation in TNBC, providing proof-of-principle for personalized surveillance [31]. Commercial assays such as Signatera and Guardant Reveal have also been developed for individualized recurrence monitoring [32]. Thus, liquid biopsy holds significant potential for recurrence prediction in early-stage breast cancer, offering clinicians an opportunity to intervene preemptively and personalize follow-up care.

➢ *Clinical Translation and Bedside Application*

The clinical utility of liquid biopsy in early-stage breast cancer lies in its potential to transform follow-up and adjuvant treatment strategies from population-based to individualized care [33]. By detecting ctDNA-defined minimal residual disease (MRD) or molecular relapse, clinicians can identify patients who may benefit from therapy escalation while sparing low-risk patients from unnecessary treatment [34].

- *Integration into Follow-up Protocols*

Traditional follow-up relies on scheduled imaging and clinical examination, which often detect recurrence only after significant tumor burden has developed [35]. Liquid biopsy allows for dynamic surveillance through serial blood sampling, providing a non-invasive, real-time assessment of disease status [36].

- *Guiding Adjuvant Therapy Decisions:*

ctDNA positivity after primary therapy may justify intensification of systemic treatment, such as extended endocrine therapy in HR+ disease or additional chemotherapy in high-risk TNBC [37]. Conversely, persistently negative ctDNA could support treatment de-escalation strategies, reducing toxicity without compromising outcomes [38].

- *Personalized Surveillance Strategies*

Several clinical studies are pioneering ctDNA-guided interventions. The c-TRAK TN trial tested whether immunotherapy could be initiated upon ctDNA detection in TNBC patients [31]. Similarly, the Signatera assay has demonstrated feasibility in guiding post-treatment monitoring, detecting relapse up to a year earlier than imaging [32].

- *Broader Clinical Impact*

Beyond recurrence prediction, liquid biopsy may also guide re-biopsy avoidance, track emerging resistance mutations, and facilitate real-time therapy adaptation [39]. For example, HER2 amplification or ESR1 mutations detected in ctDNA can inform targeted therapeutic adjustments [40]. Collectively, the transition "from blood to bedside" illustrates the capacity of liquid biopsy to complement existing protocols, ushering in a new paradigm of precision surveillance and therapy in early breast cancer.

III. CURRENT LIMITATIONS AND CHALLENGES

Despite promising results, liquid biopsy for MRD detection and recurrence prediction in early-stage breast cancer faces several barriers to widespread clinical implementation. These challenges span technical, biological, clinical, and economic domains.

➢ *Technical Challenges*

The sensitivity of liquid biopsy assays remains a major limitation. ctDNA is often present at very low levels in early-stage disease or during remission, making detection prone to false negatives [41]. While ultra-deep sequencing and digital PCR have improved detection limits, assay variability and lack of standardization across laboratories hinder reproducibility [42]. Furthermore, pre-analytical variables (blood collection, storage, and processing) significantly impact assay reliability [43].

➢ *Biological Challenges*

Not all tumors shed ctDNA at detectable levels. Tumor biology, size, vascularization, and metastatic potential influence ctDNA release [44]. Certain breast cancer subtypes, such as indolent luminal A tumours, may shed less ctDNA than aggressive TNBC or HER2-positive tumors [45]. Moreover, clonal hematopoiesis of indeterminate potential (CHIP) can contribute non-tumor DNA mutations to plasma, confounding interpretation [46].

➢ *Clinical Challenges*

Although ctDNA positivity correlates strongly with relapse risk, clinical protocols for how to act upon this information are not yet standardized. Whether treatment escalation based solely on ctDNA detection improves survival

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remains under investigation [47]. In addition, regulatory approvals for ctDNA-guided interventions are still limited to research or select commercial assays [48].

IV. ECONOMIC AND ETHICAL CHALLENGES

The high cost of sequencing-based assays limits accessibility, especially in low- and middle-income countries [49]. Insurance coverage and reimbursement policies are inconsistent, further impeding equitable adoption. Ethically, acting on ctDNA detection without radiologic confirmation raises concerns about overtreatment and patient anxiety [50]. Thus, while liquid biopsy holds immense promise, these limitations underscore the need for further technological refinement, standardization, cost-effectiveness studies, and prospective clinical validation before it can be universally integrated into early breast cancer management.

V. OTHER CHALLENGES AND LIMITATIONS

Despite its promise, the integration of liquid biopsy into early-stage breast cancer management faces several challenges:

- *Analytical Sensitivity and Specificity*

While techniques such as ddPCR and NGS have improved sensitivity, ctDNA and CTC detection may still yield false negatives in patients with extremely low tumor burden, especially during remission [51, 52]. Background "clonal hematopoiesis" mutations may confound interpretation of ctDNA results [53].

- *Standardization of Methodologies:*

Lack of consensus on pre-analytical (sample collection, storage), analytical (assay platforms), and post-analytical (bioinformatics pipelines) procedures reduces reproducibility across studies [54, 55]. There is no universally accepted cut-off values exist for defining MRD positivity.

- *Cost and Accessibility*

High-throughput sequencing and advanced assays remain expensive and limited to specialized centers, making large-scale clinical implementation difficult in low- and middle-income countries [56].

- *Clinical Interpretation and Validation*

While liquid biopsy positivity has been correlated with recurrence risk, standardized guidelines for clinical decision-making (e.g., when to escalate or de-escalate therapy) are still evolving [57,58]. Large, prospective, randomized trials are needed to validate clinical utility in guiding treatment.

- *Tumor Heterogeneity:*

Spatial and temporal heterogeneity may limit the representativeness of circulating biomarkers, as ctDNA may not fully capture resistant subclones or micro-metastatic disease [59].

- *Regulatory and Ethical Considerations:*

Regulatory approval pathways remain uncertain, as most assays are validated in research but not yet fully standardized for routine clinical use [60]. Ethical issues regarding predictive recurrence testing and patient anxiety require careful counseling strategies.

VI. CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Liquid biopsy for minimal residual disease (MRD) and recurrence prediction in early-stage breast cancer is steadily moving from proof-of-concept into clinical integration. Prospective trials such as c-TRAK-TN and BRE12-158 are actively evaluating whether ctDNA positivity can be used to guide earlier therapeutic interventions, including escalation with immunotherapy or PARP inhibitors in high-risk patients [61, 62]. Tumor-informed assays also show promise in enhancing post-surgical surveillance, complementing standard imaging and clinical follow-up.

Importantly, MRD detection provides an opportunity to personalize adjuvant therapy: ctDNA-negative patients may avoid unnecessary toxicity through de-escalation, while ctDNA-positive patients could benefit from earlier treatment intensification before overt relapse [63; 64]. Furthermore, the incorporation of multi-omic strategies—such as methylation profiling, fragmentomics, transcriptomics, and proteomics combined with artificial intelligence and machine learning tools may significantly improve sensitivity and predictive accuracy, particularly in low-shedding tumors [65].

Serial ctDNA monitoring has already demonstrated the ability to detect molecular relapse several months before clinical or radiological evidence, opening a window for preemptive therapeutic intervention that could improve survival outcomes [66, 67]. However, for liquid biopsy to transition into routine practice, standardized assay protocols, harmonized cut-off thresholds for MRD positivity, and regulatory approval frameworks are urgently required [68].

In low- and middle-income countries, simplified and cost-effective technologies such as droplet digital PCR (ddPCR) could provide feasible entry points for MRD testing, although infrastructural limitations and workforce training remain challenges [69]. Finally, ethical and psychosocial considerations including the impact of communicating a "molecular relapse" without available interventions necessitate careful patient education and shared decision-making to avoid undue distress while maintaining transparency in clinical care.

VII. CONCLUSION

Liquid biopsy using ctDNA and CTCs offers a powerful tool for early-stage breast cancer by detecting minimal residual disease and predicting recurrence ahead of imaging, enabling personalized surveillance and treatment. Despite its strong

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prognostic value, routine use is limited by technical and infrastructural barriers. Advances in tumour-informed assays, methylation and fragmentomic approaches, and AI-driven analytics, alongside standardization, cost reduction, and regulatory approval, are expected to drive clinical adoption. Ultimately, liquid biopsy could transform care by guiding therapy decisions, minimizing unnecessary toxicity, and improving outcomes through earlier intervention.

RECOMMENDATIONS

Implementing risk-adapted, multi-modal screening that combines stool and blood biomarkers with imaging requires robust global standardization and large-scale validation studies. The integration of artificial intelligence and machine learning offers opportunities to merge clinical, biomarker, and imaging data, while strategies must also prioritize cost-effective adoption within healthcare systems, especially in resource-limited settings. Expanding research into emerging biomarkers, including exosomal RNA, microRNAs, and metabolomics, will further strengthen applications for recurrence detection and minimal residual disease monitoring. Equally important are efforts to enhance clinician and public awareness, supported by strong partnerships among policymakers, researchers, and industry to ensure effective translation and widespread scalability.

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