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THE CLINICAL UTILITY OF CIRCULATING TUMOR DNA (CTDNA) IN BREAST CANCER: FROM DIAGNOSIS TO TREATMENT RESPONSE _A NARRATIVE REVIEW

Narrative Review

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ABSTRACT

Background: Breast cancer remains a leading cause of cancer-related morbidity and mortality among women worldwide, highlighting the urgent need for more accurate, minimally invasive diagnostic and monitoring tools. Circulating tumor DNA (ctDNA), derived from tumor cell apoptosis, necrosis, or active secretion, has emerged as a promising biomarker capable of providing real-time insights into tumor dynamics. Its use in oncology aligns with the growing shift toward precision medicine, offering the potential to overcome the limitations of conventional tissue biopsy and imaging techniques.

Objective: This narrative review aims to explore the clinical utility of ctDNA in breast cancer—from early detection and disease monitoring to prognostication and treatment response evaluation—while addressing current challenges and future directions in its clinical application.

Main Discussion Points: Recent advancements in ctDNA detection technologies, including digital PCR and next-generation sequencing (NGS), have enhanced analytical sensitivity and broadened clinical applicability. The review discusses ctDNA's role in detecting minimal residual disease (MRD), identifying resistance mutations, and tracking therapeutic efficacy across different breast cancer subtypes. Furthermore, it examines limitations such as biological variability, clonal hematopoiesis, assay standardization, and cost-effectiveness, emphasizing the need for robust validation and regulatory frameworks to support clinical integration.

Conclusion: CtDNA-based liquid biopsy represents a paradigm shift in breast cancer management, enabling personalized and dynamic patient care. However, its translation into routine practice demands multicenter validation, technological standardization, and equitable global accessibility to fully harness its potential in precision oncology.

Keywords: Circulating tumor DNA (ctDNA); Liquid biopsy; Breast cancer; Minimal residual disease (MRD); Precision oncology; Next-generation sequencing (NGS).

INTRODUCTION

Breast cancer remains the most frequently diagnosed malignancy worldwide and continues to be the leading cause of cancer-related mortality among women. According to GLOBOCAN 2020, more than 2.3 million new cases are reported annually, representing approximately 11.7% of all cancer diagnoses globally (1). Its burden is particularly pronounced in low- and middle-income countries, where disparities in healthcare infrastructure, delayed diagnosis, and limited access to advanced therapies result in poorer survival outcomes (2). From a molecular standpoint, breast cancer encompasses diverse subtypes—including hormone receptor-positive (HR+), human epidermal growth factor receptor 2-positive (HER2+), and triple-negative breast cancer (TNBC)—each characterized by unique genetic and clinical behaviors. This heterogeneity highlights the importance of precision medicine, as therapeutic responses and prognoses differ markedly among subtypes; for instance, HR+ tumors typically respond well to endocrine therapy, whereas TNBC often exhibits aggressive progression and lacks effective targeted treatment options (3). Despite remarkable advancements in diagnostic imaging, surgical interventions, and systemic therapies, early detection remains the cornerstone of favorable prognosis in breast cancer. Patients diagnosed at an early stage have a five-year survival rate exceeding 90%, whereas delayed detection drastically reduces survival due to metastatic spread (4). Even after successful initial treatment, recurrence remains a persistent concern, emphasizing the need for reliable and dynamic tools for disease surveillance. Conventional diagnostic approaches such as mammography, ultrasound, and MRI—though indispensable—possess notable limitations. These modalities often yield false-positive or false-negative results, particularly in individuals with dense breast tissue or small lesions, leading either to unnecessary procedures or delayed diagnosis (5). Similarly, tissue biopsy, while considered the gold standard for histopathological confirmation, is invasive, subject to sampling error, and unable to capture the spatial and temporal heterogeneity inherent in tumor evolution (6). Repeat biopsies are often clinically impractical and ethically challenging, especially in patients with metastatic disease. Serum biomarkers such as CA15-3 and carcinoembryonic antigen (CEA) have been utilized to monitor disease progression, yet their low sensitivity and specificity render them unreliable for early detection or real-time therapeutic monitoring (7).

Consequently, existing diagnostic strategies fail to provide continuous molecular insights into tumor dynamics, resistance mechanisms, and minimal residual disease (MRD) detection. This diagnostic gap underscores the urgent need for innovative, non-invasive technologies capable of longitudinally tracking tumor behavior with high sensitivity and precision. In this context, liquid biopsy has emerged as a transformative approach in oncology. By analyzing tumor-derived components circulating in peripheral blood—including exosomes, circulating tumor cells (CTCs), and particularly circulating tumor DNA (ctDNA)—it offers a minimally invasive window into the molecular landscape of cancer (8). Unlike tissue biopsies, which provide only a static snapshot, liquid biopsy allows real-time monitoring of tumor heterogeneity across both primary and metastatic sites, facilitating dynamic disease management (9). Among these biomarkers, ctDNA holds the greatest clinical promise. It consists of fragmented DNA released into the bloodstream through tumor cell apoptosis, necrosis, or active secretion, reflecting tumor-specific genetic and epigenetic alterations such as point mutations, copy number variations, and methylation changes (10). Recent technological advances in highly sensitive detection platforms, including digital polymerase chain reaction (dPCR) and next-generation sequencing (NGS), have enabled precise quantification of ctDNA even at extremely low concentrations (11). The clinical potential of ctDNA extends across multiple domains of breast cancer care—ranging from early diagnosis and prognosis to treatment response evaluation and detection of emerging resistance mutations. It provides a comprehensive molecular signature that can guide personalized therapeutic decisions and facilitate timely intervention (12). Given its non-invasive nature, reproducibility, and real-time utility, ctDNA-based liquid biopsy represents a paradigm shift toward precision oncology in breast cancer management. Therefore, the present study aims to explore the clinical utility of circulating tumor DNA in breast cancer, from diagnosis to treatment response. By evaluating its diagnostic accuracy, prognostic relevance, and monitoring potential, this research seeks to establish ctDNA as a reliable biomarker for individualized disease management and to bridge existing gaps in conventional diagnostic and follow-up strategies.

BIOLOGY AND ORIGIN OF CIRCULATING TUMOR DNA (CTDNA)

Mechanism of ctDNA Release: Circulating tumor DNA (ctDNA) originates primarily from necrotic and apoptotic processes within the tumor microenvironment. During apoptosis, endonuclease-mediated fragmentation of chromatin produces mono- and oligonucleosomal

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DNA segments, while necrosis results in longer, heterogeneous DNA fragments. Beyond these passive mechanisms, growing evidence suggests active secretion through exosomes and microvesicles that encapsulate tumor-derived nucleic acids and proteins for intercellular signaling (1). Factors such as tumor vascularization, hypoxia, and therapy-induced cytotoxicity influence both the rate and magnitude of ctDNA release, reflecting the dynamic interplay between tumor biology and host response (2). Consequently, ctDNA concentration and composition vary across disease stages and treatment contexts, providing an evolving molecular fingerprint of tumor burden and behavior (3).

Characteristics of ctDNA: CtDNA exhibits unique biochemical and molecular characteristics that distinguish it from other circulating nucleic acids. It typically consists of double-stranded DNA fragments averaging 166 base pairs in length—consistent with apoptotic nucleosomal fragmentation (4). What sets ctDNA apart is its tumor-specific genetic content, encompassing somatic mutations, copy number alterations, and epigenetic signatures such as aberrant promoter methylation (5). These molecular features enable ctDNA to function as a "liquid biopsy," offering real-time insights into tumor heterogeneity, clonal evolution, and treatment efficacy. The concentration of ctDNA in plasma correlates strongly with tumor size, vascular invasion, and metastatic dissemination, making it a valuable biomarker for assessing disease dynamics (6). Importantly, its transient nature allows near-instantaneous reflection of therapeutic effects, a capability that traditional imaging lacks.

Differences Between ctDNA and cfDNA: Cell-free DNA (cfDNA) encompasses all extracellular DNA fragments in the bloodstream, originating from both physiological cellular turnover and pathological conditions such as inflammation or trauma. CtDNA, by contrast, represents the tumor-derived fraction of cfDNA and carries cancer-specific molecular signatures, including somatic mutations and methylation patterns (7). Distinguishing ctDNA from the cfDNA background is essential for accurate cancer detection and monitoring, particularly in early-stage disease or minimal residual disease (MRD) assessment. Advanced sequencing and bioinformatics tools now differentiate ctDNA based on fragment size distribution, end motifs, and nucleosomal patterns, thereby improving analytical sensitivity and specificity (8).

METHODS OF CTDNA DETECTION AND ANALYSIS

PCR-Based Techniques

Digital PCR (dPCR): This technique allows for absolute quantification of mutant alleles with exceptional sensitivity, detecting variants present at frequencies as low as 0.01%. Its precision makes it particularly valuable for longitudinal monitoring of known mutations (9).

BEAMing (Beads, Emulsion, Amplification, and Magnetics): By combining emulsion PCR with flow cytometry, BEAMing enables single-molecule analysis of ctDNA, facilitating the detection of rare alleles in complex plasma samples (10).

ARMS-PCR (Amplification Refractory Mutation System): This method selectively amplifies known point mutations and is widely applied in targeted detection scenarios, although its sensitivity is moderate compared to digital PCR (11).

Next-Generation Sequencing (NGS) Techniques:

Targeted NGS Panels: These focus on clinically relevant oncogenic hotspots and allow multiplex mutation analysis across numerous genes in a single assay, balancing cost-effectiveness with high coverage (12).

Whole-Exome/Genome Sequencing: Broader in scope, these methods enable discovery of novel mutations and global genomic changes, though their sensitivity is lower and costs higher than targeted panels (13).

Duplex Sequencing: By sequencing both DNA strands, duplex sequencing drastically reduces sequencing errors, enhancing the detection of ultra-rare variants critical for MRD assessment (14).

Methylation-Specific Approaches:

Bisulfite Sequencing and Methylation Panels: These methods detect cancer-specific methylation changes in ctDNA and are being integrated into early detection assays, including commercial platforms such as the Galleri® test (15).

cfMeDIP-seq: Utilizing immunoprecipitation of methylated cfDNA followed by sequencing, cfMeDIP-seq offers a robust approach for identifying tissue-of-origin and epigenetic tumor signatures (16).

Single-Molecule and Ultrasensitive Technologies:

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CAPP-Seq (Cancer Personalized Profiling by deep Sequencing): This hybrid capture–based method provides sensitive and quantitative detection of mutations across individualized panels, making it ideal for patient-specific ctDNA tracking (17).

SiMSen-Seq: By incorporating unique molecular barcodes, SiMSen-Seq achieves high specificity for low-frequency variants, allowing precise quantification of minor tumor clones (18).

Nanopore-Based ctDNA Detection:

Oxford Nanopore Technologies (ONT): ONT enables real-time sequencing with direct methylation calling, offering a portable, label-free platform for ctDNA analysis (19).

CRISPR-Cas Biosensors: These emerging systems exploit CRISPR's sequence-specific cleavage to identify mutations rapidly and accurately without the need for PCR amplification (9,10).

Artificial Intelligence and Machine Learning in ctDNA Analysis:

Artificial intelligence (AI) and machine learning algorithms are increasingly being used to integrate multi-omic ctDNA data, recognizing complex methylation signatures, classifying mutation patterns, and predicting cancer presence or recurrence (11). Such computational tools enhance diagnostic precision and facilitate early intervention.

CLINICAL APPLICATIONS OF CIRCULATING TUMOR DNA (CTDNA) IN BREAST CANCER

Early Detection and Screening: CtDNA provides a promising avenue for early, non-invasive breast cancer detection. Studies have demonstrated that methylation markers such as NKX2-6, PER1, and SPAG6, as well as recurrent mutations in PIK3CA and TP53, can serve as early diagnostic indicators in plasma (12). The UK National Health Service has pioneered the integration of ctDNA-based liquid biopsy into clinical diagnostics for advanced breast cancer, enabling faster results compared with conventional biopsies. Additionally, exploratory research has identified ctDNA in breast milk and other non-blood fluids, expanding screening possibilities in pregnant or lactating women (13).

Prognostic and Predictive Value: In metastatic breast cancer, baseline ctDNA burden and mutation spectrum have shown strong prognostic value. Elevated ctDNA harboring mutations in ESR1, PIK3CA, or TP53 correlates with shorter progression-free and overall survival. Real-time detection of emergent ESR1 mutations allows clinicians to modify endocrine therapy before radiologic evidence of resistance appears, reflecting ctDNA's potential as an early warning biomarker (14,15).

Monitoring Treatment Response: Serial ctDNA measurements enable dynamic assessment of therapeutic response. Particularly in triple-negative breast cancer (TNBC), ctDNA clearance during neoadjuvant therapy correlates strongly with pathological complete response. Clinical trials such as PADA-1 and BOLERO2 have validated ctDNA monitoring as a decision-making tool for adjusting therapy in real time, particularly for mutations in ESR1, PIK3CA, and TP53 (16,17).

Detection of Minimal Residual Disease (MRD) and Recurrence: CtDNA has demonstrated exceptional sensitivity in detecting MRD well before clinical relapse. Tumor-informed assays, which rely on individualized mutation profiles, have detected recurrence up to a year prior to imaging findings. Technologies such as Clonesight have extended this led time to over five years in certain cases, underscoring ctDNA's potential for long-term surveillance (9,18). Tumor-agnostic panels, including methylation-based MRD tests, offer alternatives when tissue samples are unavailable.

Identification of Resistance Mutations: CtDNA enables early identification of molecular resistance mechanisms, including ESR1 mutations that precede endocrine therapy failure (19). Its use has been incorporated into routine NHS workflows in England to guide elacestrant therapy for ESR1-mutant breast cancers. Similarly, global trials have reported substantial benefits of ctDNA-guided administration of novel drugs like camizestrant, which delays disease progression in resistant cases (20).

CTDNA IN DIFFERENT SUBTYPES OF BREAST CANCER

ctDNA in HR+/HER2− Breast Cancer: As the most prevalent subtype, HR+/HER2− breast cancer benefits significantly from ctDNA-based monitoring due to its typically indolent course. Detection of ESR1 mutations through ctDNA provides early signals of endocrine resistance, allowing for timely therapeutic adjustments (21). Longitudinal profiling has also proven effective in identifying MRD and

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predicting relapse months before radiographic confirmation (13). The BioItaLEE trial emphasized ctDNA's prognostic importance in guiding personalized endocrine therapy.

ctDNA in HER2-Positive Breast Cancer: HER2-positive tumors, comprising 15–20% of breast cancers, exhibit aggressive clinical behavior but respond to HER2-targeted therapies. CtDNA analysis enables real-time evaluation of therapy response by quantifying changes in ERBB2 amplification or PIK3CA mutations (22). Early ctDNA reduction has been associated with higher pathological complete response rates, offering a less invasive strategy for treatment adaptation. Furthermore, emerging evidence links ctDNA-detected resistance mutations, such as TP53 and PIK3CA variants, to diminished trastuzumab efficacy, highlighting its potential in adaptive therapy planning (23).

ctDNA in Triple-Negative Breast Cancer (TNBC): TNBC represents the most aggressive and therapeutically challenging subtype. Given its high relapse rate and lack of targeted biomarkers, ctDNA serves as a crucial surveillance tool. Detection of recurrent TP53, BRCA1/2, and PIK3CA mutations in plasma precedes clinical recurrence by several months, providing opportunities for early intervention (24). Moreover, the dynamic reduction in ctDNA during neoadjuvant chemotherapy correlates with improved outcomes, positioning it as a valuable prognostic and therapeutic response marker (17).

Advantages of ctDNA Over Conventional Approaches: CtDNA-based assays offer several advantages over conventional tissue biopsies and imaging modalities. Being minimally invasive, they enable repeated sampling for continuous disease monitoring, reducing patient discomfort and procedural risks (18). Unlike single-site biopsies, ctDNA captures tumor heterogeneity across spatially distinct lesions, allowing comprehensive molecular profiling that reflects the evolving genomic landscape (9). Furthermore, ctDNA alterations often precede radiologic progression, providing an early warning system for recurrence or treatment failure (20). Operationally, ctDNA testing integrates seamlessly into precision oncology frameworks. High-throughput next-generation sequencing (NGS) platforms can concurrently assess hundreds of genes, enabling simultaneous evaluation of actionable mutations and resistance pathways (11). Tumor-informed MRD assays guide adjuvant therapy decisions and minimize sampling bias inherent to localized biopsies. Beyond mutation tracking, ctDNA is also being explored for monitoring therapeutic adherence, predicting thromboembolic risk, and supporting population-level cancer screening (22). Despite challenges in standardization and cost-effectiveness, ongoing prospective trials continue to refine its clinical implementation, positioning ctDNA as a cornerstone in the era of precision breast cancer care (23).

Figure 1 Advantages of ctDNA Over Conventional Approaches

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CRITICAL ANALYSIS AND LIMITATIONS

Technical and Analytical Limitations:

Assay sensitivity and standardization: The literature consistently shows that ctDNA constitutes a minute fraction of total cfDNA, rendering detection exquisitely sensitive to pre-analytical handling and platform choice. Comparative studies highlight variable limits of detection across digital PCR, BEAMing, and NGS, with non-uniform reporting of tube type, processing delays, centrifugation protocols, and extraction chemistries that undermines reproducibility and cross-study comparability (1). Multi-center evaluations seldom harmonize workflows end-to-end, and few reports include ring-trial data or external quality assessment, limiting confidence in pooled performance estimates (2).

Commercial complexity and methodological diversity: Rapid proliferation of proprietary kits, barcoding chemistries, capture panels, and error-suppression algorithms introduces heterogeneity that complicates meta-analysis and clinical translation. Head-to-head comparisons are rare, versioning is frequent, and analytical updates outpace peer-reviewed validation, creating moving targets for health-technology assessment and guideline panels (3).

Limits of detection in low-tumor-burden environments: Across early-stage disease and post-operative MRD contexts, tumor fraction often falls below conventional NGS sensitivity, leading to false negatives and widening confidence intervals around negative predictive value. Tumor-agnostic panels underperform when mutation burden is low, while tumor-informed assays improve sensitivity at the expense of cost and lead-time, and still risk sampling miss when spatial heterogeneity is high (3).

Thorough reporting is required: Many studies omit essential metadata—assay LoD, per-variant sensitivity, breadth of regions assayed, UMI depth, and estimated tumor fraction—blunting clinical interpretability and hindering evidence synthesis. Standardized minimal reporting sets and CONSORT-like extensions for liquid biopsy remain sporadically adopted (4).

BIOLOGICAL VARIABILITY

Clonal evolution and tumor heterogeneity: The reviewed body of work affirms that ctDNA integrates signals from primary and metastatic deposits, yet discordance with single-site tissue is common. Tumor-informed strategies may miss emergent subclones outside the indexed mutation list, whereas agnostic approaches dilute signal with background noise—both inflating heterogeneity-related misclassification risks (5).

Clonal hematopoiesis (CHIP): CHIP remains an under-addressed confounder. Without paired leukocyte sequencing, variants in TP53, DNMT3A, TET2, or KRAS may be misattributed to tumor, inflating false positives and leading to inappropriate therapy switches. Reported CHIP prevalence around diagnosis approaches 10–20% in breast cancer cohorts, with chemotherapy-associated expansion of TP53-mutant clones, yet many studies neither screen nor adjust for this source of bias (6).

Variability in ctDNA shedding and sampling noise: Shedding rates differ by subtype, size, vascularity, and site of metastasis, producing intra-patient volatility that can mimic biological response. Sparse or irregular sampling schedules amplify regression-to-the-mean and misinterpretation of transient rises or nadirs, particularly when action thresholds are not prospectively defined (5).

Interpretation and Clinical Integration

Ambiguity in useful conclusions: Several reports identify variants of uncertain significance or alterations in non-targetable genes (for example TP53, KRAS) without clear actionability frameworks, creating decision ambiguity and risk of overtreatment. Distinguishing passenger from driver events is inconsistently addressed, and few studies embed molecular tumor boards to adjudicate clinical significance prospectively (6).

Absence of evidence for improved outcomes in the future: Although ctDNA positivity correlates with recurrence and shorter PFS/OS, randomized evidence that ctDNA-triggered escalation or switch therapy improves survival remains limited. Many trials are single-arm or observational, with short follow-up and surrogate endpoints; consequently, guideline adoption for MRD-directed care is cautious pending phase III confirmation (7).

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COST-EFFECTIVENESS

EXPENSIVE INFRASTRUCTURE AND TECHNOLOGY REQUIREMENTS: IMPLEMENTATION REQUIRES SKILLED PERSONNEL, CURATED BIOINFORMATICS, AND PLATFORM MAINTENANCE. MANY STUDIES ARE CONDUCTED IN CENTRALIZED REFERENCE LABORATORIES, LIMITING EXTERNAL VALIDITY FOR DECENTRALIZED HEALTH SYSTEMS AND CREATING ACCESS INEQUITIES NOT CAPTURED IN TRIAL SETTINGS (21).

Mixed evidence on cost efficiency: Economic models show variable incremental cost-effectiveness ratios depending on assay type, action thresholds, and drug prices; some analyses approach common willingness-to-pay limits only under optimistic assumptions about reduction in futile therapy or earlier switch to effective agents (22). Real-world analyses citing system-level savings often benchmark against invasive tissue re-biopsy costs but may not fully account for longitudinal testing, confirmatory leukocyte sequencing for CHIP, or downstream imaging triggered by ctDNA signals (23).

Benefits of the health system's costs: Health-system pilots report faster access to targeted therapy and procedural cost offsets; however, these reports frequently lack controlled comparators, long-term outcomes, and comprehensive budget impact analyses that include false-positive workups and management of incidental findings (24).

Current Clinical Trials and Guidelines

Ongoing clinical studies: A large proportion of ongoing studies are single-arm cohorts evaluating associations between post-operative ctDNA positivity and recurrence. While they demonstrate feasibility and prognostic value, many are underpowered for treatment-effect estimates, use heterogeneous sampling cadences, and apply post-hoc thresholds. Neoadjuvant TNBC cohorts suggest concordance between ctDNA clearance and pCR, yet durability and utility for adaptive therapy remain to be proven in randomized designs with standardized imaging and mandated leukocyte controls to mitigate CHIP (1,7).

Regulatory perspectives: Regulatory clearances of liquid-biopsy CDx for specific variants enable therapy access, but these decisions typically rest on analytical validity and concordance with tissue—not on prospective survival benefit from ctDNA-guided management. Extensions to MRD use in early breast cancer are restrained pending robust trial data; consequently, labeling often circumscribes claims to detection rather than intervention guidance, reflecting the evidentiary gap between technical performance and clinical utility (25).

Role in precision medicine: The promise of ctDNA for resistance profiling and dynamic response assessment is well-illustrated in metastatic settings, yet the literature remains heterogeneous in defining actionable thresholds and timing for intervention. Subtype-specific differences in shedding and the prevalence of CHIP complicate generalization across HR+/HER2−, HER2-positive, and TNBC populations. Without harmonized endpoints, blinded adjudication, and protocolized management pathways, observed associations risk confounding by indication and surveillance intensity, limiting the translatability of encouraging signals into standardized care algorithms (25–27).

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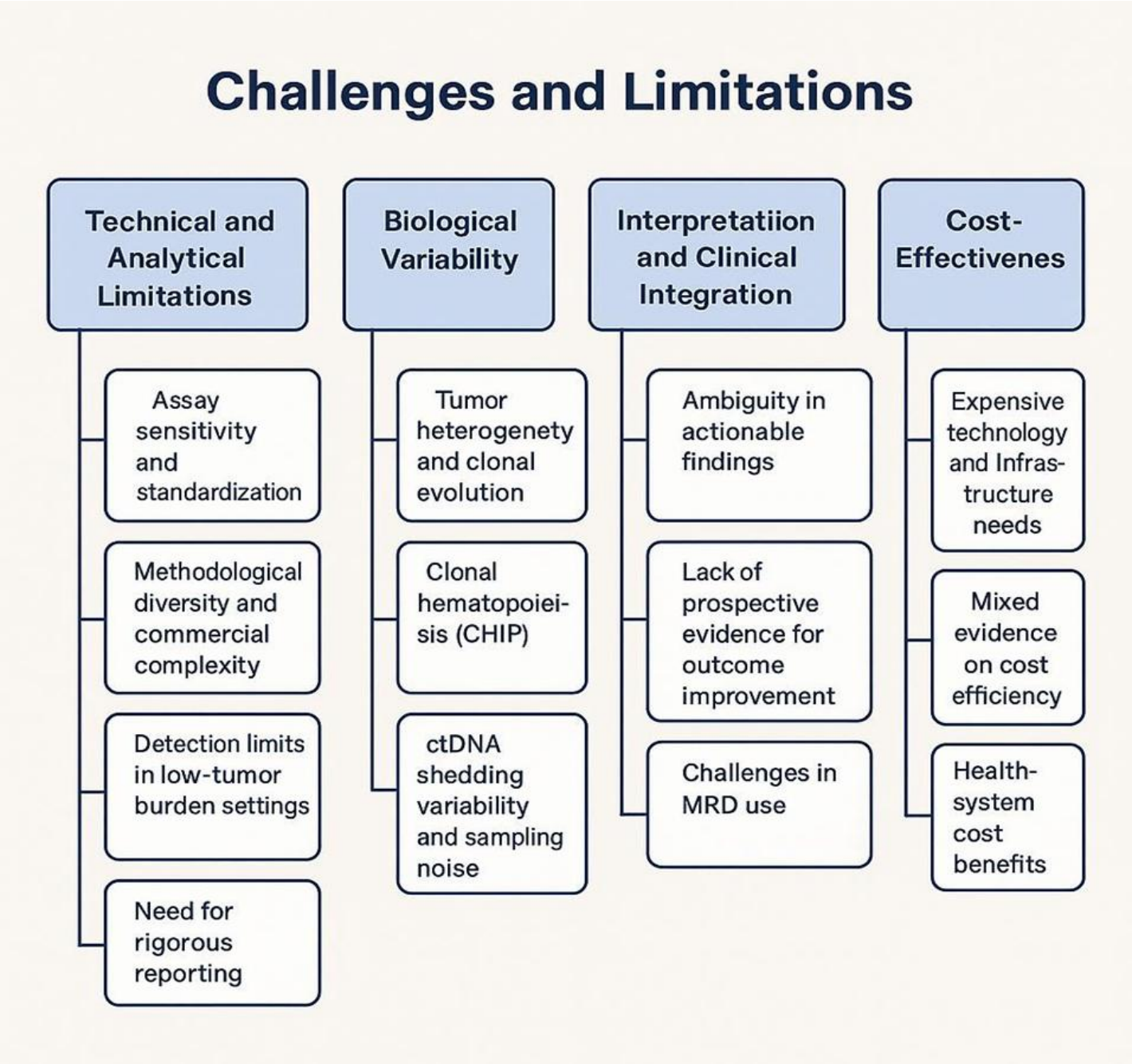

Figure 2 Challenges and Limitations

IMPLICATIONS AND FUTURE DIRECTIONS

The integration of multi-omic approaches represents a transformative direction for the future of breast cancer management, carrying profound implications for both clinical practice and translational research. Clinically, the convergence of ctDNA mutation profiling with proteomic, transcriptomic, and epigenomic data offers an avenue to surpass the sensitivity limits of single-modality assays, particularly in early detection and minimal residual disease (MRD) monitoring (21). Such composite molecular profiling enables more accurate disease classification, early relapse prediction, and real-time treatment tailoring, ultimately facilitating precision oncology that is responsive to each patient's evolving tumor biology. For oncologists, this means the potential to initiate therapy earlier, modify

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ineffective regimens in real time, and monitor outcomes with higher predictive value, thereby improving survival and quality of life. From a policy and guideline perspective, the growing body of evidence supporting multi-omics integration calls for formal inclusion of these technologies into standardized breast cancer diagnostic and surveillance pathways. Regulatory frameworks and institutional policies must evolve to accommodate assay validation, data harmonization, and ethical considerations related to multi-layered genomic data use (22). International oncology organizations may soon need to define consensus-based thresholds for ctDNA detection, multi-omic data integration, and their interpretive significance in guiding therapeutic interventions. However, several unanswered questions persist. The optimal combination of omic layers, frequency of testing, and bioinformatic models required to achieve maximal diagnostic yield remain to be defined. Longitudinal studies investigating how multi-omic ctDNA signatures correlate with treatment response, tumor microenvironment dynamics, and immune modulation are particularly lacking. There is also an urgent need to establish population-specific reference datasets to account for ethnic and biological diversity in molecular expression patterns, ensuring that findings are broadly generalizable. Future research should therefore focus on large-scale, prospective, multicenter trials employing standardized protocols and harmonized analytical pipelines. Randomized controlled designs integrating ctDNA-guided interventions with clinical endpoints such as progression-free and overall survival are needed to validate clinical utility. Furthermore, incorporating artificial intelligence and machine learning to synthesize multi-omic datasets could refine predictive modeling, reduce noise from biological variability, and improve clinical interpretability (26,28). Collectively, these advancements will not only enhance early detection and monitoring but will also pave the way for a new era of personalized medicine in breast cancer care—one where multi-omic ctDNA profiling becomes a clinical standard rather than a research frontier.

CONCLUSION

In conclusion, circulating tumor DNA (ctDNA) has emerged as a transformative biomarker with the potential to redefine breast cancer diagnosis, monitoring, and treatment personalization. The collective evidence demonstrates that ctDNA-based liquid biopsy can non-invasively capture tumor heterogeneity, detect minimal residual disease, identify emerging resistance mutations, and guide timely therapeutic interventions with remarkable precision. Although current findings are promising, the literature remains heterogeneous, with variations in analytical sensitivity, study design, and population diversity limiting universal applicability. The strength of evidence supports ctDNA's prognostic and predictive value, yet robust multicenter randomized trials are still needed to establish its direct impact on survival outcomes and treatment decisions. Clinicians are encouraged to integrate ctDNA testing as a complementary tool alongside imaging and histopathology, while researchers should focus on improving assay standardization, cost-effectiveness, and accessibility. Future research must prioritize large-scale validation and equitable implementation, ensuring that the benefits of ctDNA-guided precision medicine extend beyond specialized centers to become a global standard in breast cancer care.

AUTHOR CONTRIBUTION

Author	Contribution
Sidra Jabeen	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Asma Tariq	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Ayesha Kashif	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Huma Marwat	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published

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Sundas Ahmad	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Muhammad Saad Masood	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Ahmed Riaz	Contributed to study concept and Data collection Has given Final Approval of the version to be published
Arslan Shakeel	Writing - Review & Editing, Assistance with Data Curation
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