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The Role of cfDNA in Early Diagnosis and Treatment Management of Breast Cancer: Implementation Challenges and Opportunities in Southeast Asia

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Abstract

Background: Breast cancer is the most common malignancy among women worldwide and a growing public-health challenge in Southeast Asia. Mammography has reduced sensitivity in many Asian populations because of a high prevalence of dense breast tissue and an earlier peak age of onset. Circulating cell-free DNA (cfDNA) and circulating tumour DNA (ctDNA) have emerged as non-invasive biomarkers for detection, monitoring and precision management. **Objective:** To synthesise current evidence on cfDNA applications across the breast-cancer care continuum, and to appraise opportunities and implementation challenges in Southeast Asia, while distinguishing analytical validity, diagnostic accuracy and clinical utility. **Methods:** We conducted a non-systematic narrative review of English-language literature (2010-2025) from PubMed/MEDLINE, Scopus, Web of Science and Google Scholar, supplemented by regional reports, using terms combining cfDNA/ctDNA/liquid biopsy with breast cancer and Southeast Asian country names. Evidence was organised using the analytical validity-clinical validity-clinical utility framework,

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and breast-specific findings were separated from multi-cancer assay results. **Results:** Multi-omics cfDNA assays integrating genomic, epigenetic and fragmentomic features show high specificity and promising, stage-dependent sensitivity for early detection; several key performance estimates, however, derive from multi-cancer rather than breast-specific cohorts. ctDNA supports response monitoring, minimal-residual-disease detection and resistance identification, but most regional evidence is prognostic rather than interventional, and outcome benefit from acting earlier remains largely unproven. Regional evidence is concentrated in Vietnam and Thailand. Clonal haematopoiesis, low ctDNA shedding in early disease and pre-analytical variation remain important error sources. **Conclusion:** cfDNA-based liquid biopsy is a promising adjunct that should currently complement, not replace, established breast-imaging pathways. Realising its potential in Southeast Asia will require locally generated evidence and coordinated action on cost, infrastructure, regulation and equity.

Subject Areas

Oncology, Molecular Diagnostics, Public Health

Keywords

Breast Cancer, Circulating Cell-Free DNA, Circulating Tumour DNA, Liquid Biopsy, Precision Oncology, Early Detection, Southeast Asia

1. Introduction

1.1. cfDNA and ctDNA as Liquid-Biopsy Biomarkers

Circulating cell-free DNA (cfDNA) refers to fragmented DNA released into the bloodstream through apoptosis, necrosis and active secretion. In patients with cancer, a fraction of cfDNA derives from tumour cells and is termed circulating tumour DNA (ctDNA). ctDNA carries the genetic and epigenetic signatures of the tumour, providing a non-invasive "liquid biopsy" that can reflect tumour dynamics, heterogeneity and treatment response without repeated tissue sampling [1].

cfDNA circulates as free fragments, as DNA bound to proteins or nucleosomes, and within extracellular vesicles. ctDNA analysis typically targets tumour-specific alterations such as single-nucleotide variants, copy-number alterations and epigenetic modifications, including aberrant DNA methylation, which is often tissue-specific and therefore valuable for diagnosis and prognosis [1]. Across the care continuum, cfDNA has been explored for early detection, primary-tumour characterisation, minimal-residual-disease (MRD) assessment, treatment-response monitoring and early recurrence detection; ctDNA levels can track tumour burden more closely than protein biomarkers such as CA 15-3 [2].

1.2. Breast Cancer Burden in Southeast Asia: Epidemiology and Regional Challenges

Breast cancer is the most common cancer among women in Southeast Asia, but incidence, risk factors and health-system capacity vary widely across countries [3]. Reported patterns include comprehensive registry data and rapid urbanisation in Singapore, heterogeneous incidence and access in Thailand, likely under-representation of rural burden in the Philippines and Indonesia, and emerging real-world ctDNA experience in Vietnam [3] [4]. Region-specific challenges include a high prevalence of radiologically dense breast tissue, an earlier peak incidence (often in the 40s), frequent late-stage presentation, and resource limitations affecting screening infrastructure and specimen quality [3] [5] [6].

1.3. Limitations of Conventional Screening in Asian Populations

Mammographic sensitivity is markedly reduced in dense breasts. Reported sensitivity was 47.4% in asymptomatic Japanese women in their 40s in the J-START study and 54% - 67% for Korean women aged 45 - 49 [5]. Supplemental ultrasound and MRI can improve detection but are constrained by cost, availability and interpretive expertise, particularly in rural areas [3] [5]. These limitations motivate complementary, blood-based approaches; importantly, the mammography evidence cited here derives from East Asian (Japanese and Korean) cohorts rather than from Southeast Asia specifically, a distinction we maintain throughout (Section 5).

1.4. Rationale and Objectives

The convergence of dense breast tissue, earlier onset and imaging limitations creates a clear rationale for cfDNA-based approaches, which are independent of breast density [7]. This review synthesises evidence on cfDNA in early detection, treatment monitoring and precision management of breast cancer, with emphasis on Southeast Asia. Throughout, we (i) separate analytical validity, diagnostic accuracy and clinical utility; (ii) distinguish breast-specific from multi-cancer evidence; (iii) qualify outcome claims; and (iv) distinguish Southeast Asian from other Asian and global data. We frame cfDNA assays as complements to, not replacements for, established breast-imaging pathways.

2. Methods

This is a non-systematic narrative review; it was not registered and did not follow PRISMA, and no formal risk-of-bias or meta-analysis was undertaken. It is therefore susceptible to selection bias, and findings should be read as an interpretive synthesis rather than a pooled estimate.

Data sources and search terms

We searched PubMed/MEDLINE, Scopus, Web of Science and Google Scholar for English-language records published between January 2010 and December 2025, supplemented by manufacturer white papers, registry pages and regional

news releases identified by hand-searching and citation tracking. Search strings combined biomarker terms ("cell-free DNA", "cfDNA", "circulating tumor DNA", "ctDNA", "liquid biopsy", "methylation", "fragmentomics", "minimal residual disease") with disease terms ("breast cancer", "breast neoplasm") and regional terms ("Southeast Asia", "ASEAN", "Vietnam", "Thailand", "Malaysia", "Singapore", "Philippines", "Indonesia"), using Boolean operators and, where available, MeSH headings.

Eligibility criteria

We prioritised primary studies reporting analytical validation, diagnostic accuracy, or clinical outcomes of cfDNA/ctDNA in breast cancer; region-relevant epidemiological and health-systems literature; and multi-cancer early-detection (MCED) studies where breast-cancer performance could be identified. We excluded non-English records, conference abstracts without extractable performance data, and sources whose methodology could not be appraised. Grey-literature and commercial sources were retained only for context and are flagged as such.

Approach to selection and synthesis

One reviewer screened titles/abstracts and full texts; ambiguous inclusions were resolved by discussion among authors. Evidence was organised using the established evaluation hierarchy of analytical validity, clinical validity (diagnostic accuracy) and clinical utility (the ACCE framework). For every diagnostic-performance estimate we sought to record the cancer population, disease stage, comparator group, and whether the cohort was a screening or a clinically symptomatic population. Findings were synthesised qualitatively; because study designs and endpoints were heterogeneous, results are presented descriptively and no quantitative pooling was performed.

3. cfDNA in Early Detection: Analytical Validity, Diagnostic Accuracy and Clinical Utility

Below we separate the three evidence domains rather than reporting them together, because a test can be analytically robust yet lack demonstrated clinical utility.

3.1. Analytical Validity

Analytical validity concerns whether an assay accurately and reproducibly measures the analyte it targets. Multi-omics platforms such as SPOT-MAS (Screening for the Presence of Tumour by Methylation and Size) integrate next-generation sequencing (NGS) and machine learning to interrogate genetic, fragmentomic and epigenetic features of ctDNA [8] [9]. An analytical-validation study reported a cancer-signal sensitivity of 73.9% and specificity of 95.9% across 285 patients with five cancer types versus 222 healthy individuals [10]. This is a multi-cancer analytical-validation estimate in a case-control design, not a breast-specific screening result, and case-control designs are known to overstate accuracy relative to intended-use populations.

3.2. Diagnostic Accuracy (Clinical Validity)

Diagnostic accuracy concerns whether assay results correspond to disease status in the intended population. Here it is essential to separate breast-specific from multi-cancer evidence, and to note stage, comparator and cohort type. The large prospective K-DETEK cohort (9024 asymptomatic participants in Vietnam) reported an overall sensitivity of 70.8% for cancer and a specificity of 99.7% with a negative predictive value of 99.92%, but these are aggregate multi-cancer figures across all screened cancers, not breast-specific, and should not be read as breast-cancer screening performance [8]. Breast-specific classifiers report an area under the curve (AUC) of about 0.90 for distinguishing breast cancer from non-cancer, with stage-dependent sensitivity (62.3% Stage I, 73.9% Stage II, 88.3% Stage IIIA), reflecting the difficulty of detecting early, low-shedding disease [11]. **Table 1** disaggregates the principal estimates by test type, population and stage, comparator and cohort type.

Table 1. Principal cfDNA early-detection performance estimates, disaggregated by assay type (breast-specific vs. multi-cancer), population and stage, comparator, and cohort type (screening vs. clinically ascertained).

Assay (test type)	Population and stage	Comparator	Cohort type	Reported performance
SPOT-MAS (multi-cancer, MCED)	285 patients with 5 cancer types; mixed stage	222 healthy individuals	Case-control (analytical validation)	Sensitivity 73.9%, specificity 95.9% for a cancer signal across all cancers combined [10]
SPOT-MAS (multi-cancer, MCED); K-DETEK	9024 asymptomatic participants; screening population	Follow-up/clinical confirmation	Prospective screening cohort	Overall sensitivity 70.8% (all cancers); specificity 99.7%; NPV 99.92% not breast-specific [8]
Multimodal cfDNA classifier (breast-specific)	Breast cancer vs comparators; stage I - III	Non-cancer, benign lesions, healthy	Case-control (clinically ascertained)	AUC 0.90 vs non-cancer, 0.88 vs benign, 0.92 vs healthy [11]
Multimodal cfDNA classifier (breast-specific)	Breast cancer by stage	Within-assay across stages	Case series (clinically ascertained)	Sensitivity 62.3% (Stage I), 73.9% (Stage II), 88.3% (Stage IIIA) [11]
cfMeDIP-seq methylation (breast-specific)	Pre-diagnosis samples; asymptomatic, up to 6 - 7 yr before diagnosis	Matched cancer-free controls	Nested case-control (pre-diagnostic)	AUC 0.930 in an independent test set [12]
Tumour-informed ctDNA (breast-specific)	Early-stage breast cancer; recurrence surveillance	Clinical/radiological recurrence	Prospective cohort (Vietnam)	Recurrence sensitivity 80.0%, specificity 96.3%; lead time up to 11.0 mo [4]

3.3. Clinical Utility

Clinical utility concerns whether using the test improves patient-relevant outcomes. This is the least mature domain: no breast-cancer cfDNA screening assay has yet demonstrated, in prospective controlled studies, that its use reduces late-stage diagnosis or mortality relative to standard pathways. Accordingly, early-detection cfDNA assays should currently be regarded as complementary to, rather than replacements for, established breast-imaging pathways. In practice, this

means a cfDNA signal should trigger, not bypass, confirmatory imaging (mammography with ultrasound or MRI as indicated) and tissue biopsy, and a negative cfDNA result should not be used to defer guideline-recommended screening.

3.4. Methylation and Fragmentomics

Aberrant DNA methylation is a hallmark of cancer, and cfDNA methylation signatures can be detected before clinical diagnosis. Using cfDNA methylation immunoprecipitation sequencing (cfMeDIP-seq) on pre-diagnosis samples, one study identified signatures predicting breast cancer up to six years before clinical detection, with an AUC of 0.930 in an independent test set [12]; this is a nested pre-diagnostic case-control result requiring prospective validation before clinical use. Fragmentomics fragment size, distribution and end motifs adds orthogonal information; cytosine-starting 4-mer end motifs (e.g., CGCC, CCCC) are enriched and certain guanine-starting motifs depleted in breast-cancer cfDNA, and these features improve machine-learning classifiers [11].

3.5. Sources of False-Positive and False-Negative Results

Interpreting the estimates above requires attention to well-recognised error sources that are especially consequential in screening, where disease prevalence is low.

- **Clonal haematopoiesis (CH/CHIP).** Somatic mutations arising in expanded haematopoietic clones are shed into plasma and are a major cause of false-positive ctDNA calls, particularly for larger panels covering genes such as TP53; in one high-intensity sequencing study a majority of plasma variants in cancer patients had features consistent with clonal haematopoiesis [13] [14]. Sequencing paired white-blood-cell DNA is the standard mitigation and should be built into screening assays [14] [15].
- **Low ctDNA shedding in early-stage disease.** ctDNA constitutes only a small fraction of total cfDNA, and this fraction is lowest in early-stage and minimal-residual settings; limited plasma genome-equivalents cap the detectable variant-allele frequency and drive false negatives, and some tumours shed little ctDNA even when advanced [15]. This biological floor explains the stage-dependent sensitivity in **Table 1** and cautions against over-interpreting a negative result.
- **Pre-analytical variation.** Blood-collection tube type, draw-to-processing interval, temperature, centrifugation and extraction method all affect cfDNA yield, integrity and background from leukocyte lysis, producing both false negatives and spurious signals; without harmonised pre-analytical protocols, cross-study performance is not directly comparable [16] [17].

4. cfDNA in Treatment Monitoring and Precision Oncology

cfDNA offers minimally invasive monitoring of response, MRD and resistance. We report the regional evidence and then qualify the extent to which it establishes

benefit.

4.1. Treatment-Response and Neoadjuvant Monitoring

Plasma cfDNA methylation/promoter profiles can predict pathological complete response (pCR) to neoadjuvant chemotherapy; a Random Forest model achieved an AUC of 0.980 with 95.3% accuracy for predicting pCR [18]. Serial ctDNA can track tumour burden during therapy and, in metastatic disease, correlates with response more dynamically than CA 15-3, including earlier detection of progression and emerging resistance during CDK4/6-inhibitor therapy [2]. These are predictive/prognostic associations; whether acting on them improves outcomes is addressed in Section 4.4.

4.2. Minimal Residual Disease and Recurrence Detection

In Southeast Asian cohorts, tumour-informed ctDNA assays show high prognostic accuracy. For 110 early-stage patients, the K-TRACK assay predicted recurrence with 80.0% sensitivity and 98.3% specificity, with lead times up to 11.0 months before clinical or radiological recurrence [19]. A higher tumour fraction (e.g., >10%) is associated with worse survival and a low fraction (<1%) with better real-world overall survival, including in bone-only metastatic disease [2]. Lead time and prognostic separation are consistently demonstrated; a demonstrated survival benefit from earlier, ctDNA-triggered intervention is not (Section 4.4).

4.3. Resistance Detection and Therapy Guidance

Liquid biopsy can detect resistance-conferring alterations before clinical progression. Rising *ESR1* mutations can be tracked in ER-positive metastatic disease on aromatase inhibitors; the PADA-1 trial, one of the few interventional data sets in this area, showed that switching therapy upon *ESR1* detection improved progression-free survival [2]. In a Southeast Asian real-world study, *ESR1* mutations were found in 12.5% of metastatic ER-positive patients (variants including Y537N, Y538G) [19]. *ERBB2* (HER2) amplification in ctDNA has been associated with high response rates to anti-HER2 therapy when tissue is unavailable [20]. Beyond PADA-1, most therapy-guidance evidence remains associative.

4.4. Interpreting Outcome Claims: Prognostic versus Predictive Evidence

A central caveat applies to Sections 4.1 - 4.3: earlier molecular detection and prognostic association do not, by themselves, establish that earlier treatment changes improve outcomes. Lead-time and length biases can make earlier detection appear beneficial even when it is not, and a biomarker that stratifies prognosis need not identify patients who benefit from acting sooner. Establishing clinical utility requires interventional evidence randomised or well-controlled studies showing that ctDNA-guided decisions improve survival, quality of life, or other patient-relevant endpoints without net harm. PADA-1 provides such a signal for *ESR1*-

guided switching; for MRD-guided escalation and for most monitoring applications, confirmatory interventional trials are still awaited. Claims of outcome benefit in this review should be read with this limitation in mind.

5. Regional Provenance of the Evidence: Southeast Asia versus Other Populations

Because assay performance and genetics are population-dependent, we make explicit where the evidence originates and caution against generalising narrow regional data to all of Southeast Asia.

Evidence generated in Southeast Asian cohorts

The most directly applicable Southeast Asian evidence is concentrated in Vietnam and Thailand. Vietnamese work includes the SPOT-MAS/K-DETEK MCED programme, the tumour-informed and hybrid K-TRACK ctDNA assays, and real-world utilisation and recurrence-monitoring studies [4] [8] [10] [19]. Thailand's Genomics Thailand Initiative provides population-specific germline and tumour data, reporting a higher frequency of pathogenic germline variants (23% - 24%) and a different *BRCA*1:*BRCA*2 ratio than Western cohorts [6]. Access-focused evidence includes Philippine data on disparities in breast-cancer surgical care [21] and a Southeast Asia-wide scoping review of screening barriers [22].

Evidence from other Asian and global populations

Several frequently cited figures are not Southeast Asian. The mammography-sensitivity data are from Japan and Korea (East Asia) [5]; several fragmentomic and methylation early-detection studies were conducted in Chinese or mixed international cohorts [11] [12]; and market and technical-standardisation sources describe Asia-Pacific or global contexts [15]-[17] [23] [24]. Foundational error-source evidence on clonal haematopoiesis and pre-analytical variation is likewise global [13] [14] [16].

Caveat on generalisation

Consequently, broad "Southeast Asian" conclusions currently rest heavily on data from a small number of countries chiefly Vietnam and Thailand with limited primary evidence from Indonesia, the Philippines, Malaysia, Myanmar, Cambodia, Laos and Brunei. Extrapolation across the region should be cautious until locally generated validation data become available for the specific populations and health systems in question.

6. Implementation Challenges in Southeast Asian Healthcare Systems

6.1. Economic and Cost Barriers

High costs are a primary obstacle. NGS-based multi-omics assays impose financial burdens often prohibitive for public systems and individual patients, and reimbursement varies widely, leaving many patients with substantial out-of-pocket expense [23] [25]. Affordable, high-sensitivity assays aligned with price-sensitive markets are needed [23].

6.2. Infrastructure and Technical Limitations

Laboratory capacity is uneven. While Singapore, Thailand and Malaysia have more advanced molecular infrastructure, others are still building capacity. Real-world Vietnamese experience highlights low DNA quality in FFPE tissue and white-blood-cell lysis in plasma affecting reliability [4]; Genomics Thailand notes that only about 10% of tumour tests reveal immediately actionable targets [6]. Sustained investment in laboratory networks, training and quality assurance is required.

6.3. Regulatory and Reimbursement Complexities

The regulatory landscape is fragmented and evolving, with a lack of standardised pathways, inconsistent coverage and country-specific approval processes creating uncertainty and delaying access [24]. Progressive frameworks and expanding reimbursement in some countries are reducing barriers unevenly [23].

6.4. Accessibility and Socioeconomic Disparities

Geographic and socioeconomic disparities limit equitable access [22]. In the Philippines, access to cancer care is constrained by few specialised providers and geographic and socioeconomic barriers despite insurance coverage [21]. Vietnamese utilisation data show ctDNA tests were often ordered only once for breast cancer, likely for cost reasons, unlike lung or liver cancer [4]. Community-based interventions can improve screening participation in low-income settings [26].

7. Future Directions and Regional Integration Strategies

7.1. Technological Innovation and Artificial Intelligence

Multi-omics analysis combined with AI can improve sensitivity for early-stage disease and may reduce long-term costs through automation, provided algorithms are trained on region-specific data such as that from the Genomics Thailand Initiative [6] [8]. MCED platforms that screen several cancers from one draw may add value where multiple malignancies are prevalent, but breast-cancer performance must be reported and validated separately [10].

7.2. Regional Collaboration and Partnership Models

Public-private partnerships and regional knowledge-sharing can subsidise costs, build infrastructure, harmonise pre-analytical and analytical protocols, and share validation data. Academic-industry collaboration, as in the development of SPOTMAS in Vietnam, illustrates a model for technology transfer suited to regional needs [10].

7.3. A Proposed Tiered Testing Pathway

Given the region's economic diversity, a tiered model is more realistic than a uniform one. Crucially, each tier should enter routine care only against a defined clin-

ical indication, a specified confirmatory diagnostic pathway, and a stated minimum evidence threshold (Table 2). Across all tiers, cfDNA is positioned as an adjunct: a positive result triggers standard imaging and tissue confirmation, and no cfDNA result alone diagnoses or excludes breast cancer.

Table 2. Proposed tiered cfDNA testing pathway, specifying for each tier the clinical indication and target population, the confirmatory diagnostic pathway, and the minimum evidence required before routine implementation.

Tier	Clinical indication and target population	Technology focus	Confirmatory diagnostic pathway	Minimum evidence required before routine care
Comprehensive	Therapy selection and resistance profiling in known metastatic or high-risk disease (e.g., strong family history, pathogenic-variant carriers)	Multi-omics/ tumour-informed ctDNA	Tissue genomic profiling and standard staging imaging; positive findings actioned within a molecular tumour board	Analytical validation in local samples plus prospective evidence that assay-guided decisions change management with acceptable outcomes (ideally interventional)
Intermediate	Adjunctive early detection or post-treatment monitoring in eligible screening-age groups already within an imaging pathway	Targeted cfDNA panels/ methylation	Mandatory imaging (mammography ± ultrasound/MRI) and tissue biopsy to confirm any positive signal before intervention	Prospective diagnostic-accuracy data in the intended breast-cancer screening population, with defined PPV/NPV and a validated confirmatory algorithm
Basic	Initial triage and risk-stratification in resource-limited settings to prioritise referral for imaging	cfDNA quantification/ focused mutation panels	Referral to standard imaging and clinical assessment; cfDNA result never used alone to diagnose or exclude cancer	Demonstrated reproducibility, cost-effectiveness and evidence that triage improves timely referral without net harm from false results

7.4. Policy Frameworks and Regulatory Harmonisation

Regional harmonisation potentially through ASEAN frameworks could support mutual recognition of approvals, standardised evidence requirements that account for regional data, and expedited pathways for well-validated technologies [23]. A phased reimbursement approach is prudent: begin with established uses (e.g., response monitoring in metastatic disease), then adjuvant-therapy guidance, and finally early detection in defined high-risk groups as evidence ideally interventional solidifies. Workforce development in liquid-biopsy interpretation, bioinformatics and genetic counselling is essential.

7.5. Addressing Regional Specificities and Health Equity

Strategies should reflect the region's dense-breast prevalence and distinct molecular profile, including differing triple-negative frequency and *BRCA* patterns, necessitating locally tailored panels and interpretation [5] [6]. Higher cfDNA levels reported in triple-negative disease may have subtype-specific prognostic value [27]. Equity measures mobile units, simplified collection, telemedicine and trained community health workers should be built in from the outset, alongside local validation, cost-effectiveness analyses and implementation-science research.

8. Conclusion

cfDNA-based liquid biopsy is a promising, non-invasive adjunct across the breast-cancer care continuum and is particularly attractive where mammography is limited by dense breast tissue. The current evidence, however, is strongest for analytical validity and prognostic/diagnostic association, and weakest for demonstrated clinical utility: early-detection assays should complement, not replace, established imaging pathways; many key figures derive from multi-cancer rather than breast-specific cohorts; outcome benefit from earlier, ctDNA-guided action is largely unproven outside selected settings such as *ESR*1-guided switching; and regional conclusions rest mainly on Vietnamese and Thai data. Clonal haematopoiesis, low early-stage shedding and pre-analytical variation must be managed to control false results. Realising cfDNA's potential in Southeast Asia will depend on locally generated, appropriately controlled evidence and on coordinated action across cost, infrastructure, regulation and equity.

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Author Contributions

Saidunnessa and Sufi Sumsul Yeaman contributed equally as co-first authors; they conceptualised and designed the review, developed the search strategy and performed the literature search and screening. Saidunnessa, Sufi Sumsul Yeaman and Jannatul Shamia carried out data extraction, evidence appraisal and interpretation. Sufi Sumsul Yeaman and Jannatul Shamia drafted the original manuscript. Md Mohasin Uddin and Tahsin Sarara Anmol critically revised the manuscript for important intellectual content and contributed to the discussion of clinical and regional implications. Sufi Sumsul Yeaman supervised the work and, as corresponding author, coordinated revisions. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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