Where are we now: Clinical utility and challenges of circulating tumor DNA in breast cancer

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Circulating tumor DNA (ctDNA) is a minimally invasive biomarker providing real-time insights into breast cancer detection, treatment response and resistance. In early-stage disease, it shows promise for detecting minimal residual disease and predicting recurrence before clinical relapse, though further validation is needed. Its clinical utility is best established in metastatic breast cancer, guiding targeted therapies for actionable mutations with Food and Drug Administration-approved assays. The key challenges include assay variability, biological factors, cost and uncertain long-term benefits, which must be addressed before ctDNA becomes routine in clinical care.

Keywords

Circulating tumor DNA (ctDNA), early breast cancer, liquid biopsy, metastatic breast cancer, minimal residual disease , molecular marker, personalized oncology, resistance mutation, targeted therapy

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Circulating tumor DNA (ctDNA) has emerged as an innovative and minimally invasive tool in precision oncology. With a short half-life of 30–120 min, ctDNA provides real-time insight into tumor dynamics.[1] In early-stage breast cancer, there is growing evidence supporting its potential for minimal residual disease (MRD) detection and recurrence monitoring. In metastatic breast cancer (MBC), ctDNA has become an established biomarker for identifying genomic alterations and detecting resistance mechanisms.

Compared with tissue biopsy, ctDNA testing offers faster turnaround, easier access and broader representation of tumor heterogeneity. Concordance with tissue sequencing exceeds 90% when tumor fraction is above 1%.[2] Both the National Comprehensive Cancer Network and the European Society for Medical Oncology support the use of ctDNA testing in the metastatic setting for targeted therapy guidance when a tissue sample is unavailable or inappropriate (i.e. emerging *ESR1* mutations require a new tissue or liquid biopsy).[3] Multiple commercial assays, including FoundationOne® Liquid CDx (Foundation Medicine, Inc., Boston, MA, USA), Guardant360® CDx (Guardant Health, Inc., Redwood City, CA, USA) Caris Assure™ (Caris Life Sciences, Irving, TX, USA), OncoSELECT® (GenomOncology LLC, Cleveland, OH, USA), Oncodetect™ (Burning Rock Biotech, Guangzhou Guangdong, China) and Signatera™ (Natera, Inc., Austin, TX, USA) are clinically available, with FoundationOne® uniquely providing both tumor fraction quantification and molecular profiling.

ctDNA assays can be broadly categorized into tumor-agnostic and tumor-informed approaches (*Table 1*), which differ fundamentally in assay design, analytical sensitivity and clinical application. Tumor-agnostic assays analyse plasma cell-free DNA without requiring prior knowledge of tumor genomics, whereas tumor-informed assays use patient-specific somatic variants derived from tumor sequencing to enable highly sensitive detection of MRD.

Tumor-agnostic assays typically rely on a fixed gene panel or genome-wide approaches applied directly to plasma cfDNA without prior tumor sequencing. Broad mutation-based platforms such as FoundationOne® Liquid CDx and Guardant360® CDx utilize next-generation sequencing (NGS) and have demonstrated robust analytical performance in validation studies using tumor-derived DNA diluted into normal DNA, achieving >95% sensitivity for base substitutions and rearrangements at variant allele fractions of approximately 0.25–0.5%.[4] These assays have been shown to be reproducible and clinically validated in advanced breast cancers.

Alternatively, tumor-informed assays leverage tumor sequencing to develop personalized panels targeting patient-specific somatic variants, enabling substantially greater analytical sensitivity. Multiplex pathologic complete response (pCR)-based assays such as Signatera™ have been clinically validated in studies such as the Exploratory Breast Lead Interval Study (EBLIS), where ctDNA was detected prior to clinical and/or radiologic recurrence with a sensitivity of 89% and a median lead time of approximately 10 months prior to radiographic progression.[5] Whole-genome-informed platforms such as NeXT Personal® (Personalis, Inc., Fremont, CA, USA) extend this

Table 1: Types of circulating tumor DNA tests

	Types of ctDNA tests		
	Assay type	Assay	Utility
Early breast cancer	Tumor informed	Signatera	Minimal residual disease detection
		RaDar	
		Invitae Personalized Cancer Monitoring	
		Oncodetect	
		NeXT Personal	
	Tumor agnostic	Guardant Reveal	
Metastatic breast cancer	Tumor agnostic	Caris Assure	Mutation analysis and therapy guidance
		FoundationOne Liquid CDx	
		Guardant 360 CDx	
		OncoSELECT	
		Tempus xF	
		Neogenomics NeoLab	

approach by tracking hundreds to thousands of tumor-specific variants, achieving limits of detection in the parts-per-million (ppm) range (~3.45 ppm) and demonstrating 100% sensitivity and specificity in analytical validation studies.[6]

Considering the differences in technology, tumor-informed assays are particularly attractive for MRD detection at ultra-low ctDNA levels. In contrast, tumor-agnostic assays provide clinically validated detection of actionable genomic alterations at higher ctDNA fractions that can isolate specific biomarkers to guide therapeutic decisions in advanced disease. Combined tumor-agnostic genomic and epigenomic platforms such as Guardant Reveal™ have demonstrated enhanced analytical sensitivity, laying the groundwork for tumor-agnostic measures of MRD as well. In cohorts with breast cancer, these assays have demonstrated sensitivity of approximately 83% for recurrence detection and specificity approaching 99.5%, with persistent postsurgical ctDNA predicting shorter recurrence-free survival (hazard ratio [HR] 37.7; $P<0.0001$).[7–9]

Clinical utility of circulating tumor DNA in early breast cancer

ctDNA for early detection and screening

ctDNA testing is being studied as a complement to mammography for the detection of breast cancer. Current assays such as Galleri™ (GRAIL, Inc., Menlo Park, CA, USA) and CancerSEEK (Johns Hopkins University, Baltimore, MD, USA) demonstrate high specificity (>99%) but limited overall sensitivity (51–70%), with markedly lower detection rates for early-stage disease (as low as 2.6% for stage I breast cancer).[10,11] On-going large-scale trials aim to refine assay performance and validate ctDNA's role in population-level cancer screening.[12]

ctDNA for monitoring treatment response

After diagnosis, ctDNA quantification functions as a dynamic biomarker for therapeutic efficacy and disease burden. In the Pathologic Response Evaluation and Detection In Circulating Tumor-DNA (PREDICT-DNA)/TBCRC 040 study (NCT 002743910), patients with triple-negative breast cancer (TNBC) treated with neoadjuvant chemotherapy (NAC) with detectable ctDNA before surgery were 12.8 times more likely to recur, independent of pCR status.[13] In the I-SPY2 trial (NCT010423790), ctDNA negativity after NAC showed a significant association with improved distant recurrence-free survival irrespective of residual cancer burden status at surgery ($P<0.0001$).[14] Together, these findings suggest ctDNA surveillance during and after neoadjuvant therapy could outperform conventional pathologic markers of prognosis.

ctDNA for MRD surveillance

In the adjuvant setting, ctDNA enables an early identification of MRD, revealing microscopic tumor burden before clinical relapse. Tumor-informed assays such as Signatera™, RaDaR™ (Inivata Inc., Research Triangle Park, NC, USA), NeXT Personal® and Invitae Personalized Cancer Monitoring™ (Invitae Corporation, San Francisco, CA, USA) demonstrate 85–100% sensitivity and near-100% specificity for MRD detection.[6,15–17] Tumor-agnostic platforms such as Guardant Reveal™, which integrate methylation and mutation profiling, also show promise, achieving 71% sensitivity with a 5-month median lead time in early TNBC.[7]

The DARE trial (NCT04567420) evaluated the use of ctDNA to identify early molecular relapse and guide intervention in early-stage patients with hormone receptor-positive (HR+)/HER2- breast cancer on adjuvant endocrine therapy, randomizing patients with ctDNA-positive to switch to fulvestrant plus palbociclib or continue standard endocrine therapy. Interim American Society of Clinical Oncology (ASCO) 2025 results showed that among 507 patients screened, 99.5% of those with sustained ctDNA negativity remained recurrence-free at 27.4 months. Among 60 patients with ctDNA-positive, 73% had no radiographic disease, and 38 were randomized at analysis. Escalated therapy doubled ctDNA clearance at 3 months, with on-going follow-up to determine the impact on survival outcomes.[18]

Another important study to highlight is the ZEST trial (NCT04915755). Although the study was terminated early due to a lack of efficacy data and the final results have not yet been published, it remains a notable effort in this space. ZEST is a phase III double-blind trial evaluating the efficacy and safety of the poly (ADP-ribose) polymerase (PARP) inhibitor niraparib in patients with high-risk stage I–III triple-negative or BRCA-mutated/HER2-negative breast cancer who had undergone surgical resection and completed standard curative-intent therapy but were found to have detectable ctDNA in the absence of radiologic evidence of recurrence. A total of 1,901 evaluable patients underwent tumor-informed ctDNA testing (Signatera™) every 2–3 months. ctDNA positivity was identified in only a small proportion of patients (8%); notably, approximately 50% of ctDNA-positive cases already had radiologically confirmed metastases at the time of detection. Consequently, only 40 patients were ultimately randomized. Although actionable conclusions cannot be drawn at this time, this study represents an important investigation into MRD-directed therapy in early breast cancer, and final results are awaited.[19]

Clinical utility of ctDNA in metastatic breast cancer

Predictive role: guiding targeted therapy

In MBC, ctDNA is currently utilized to identify actionable mutations, notably within the PI3K/AKT/PTEN and ESR1 pathways, that guide targeted treatment decisions.

The SOLAR-1 trial (NCT02437318) established the efficacy of the PI3Kα inhibitor alpelisib and fulvestrant in *PIK3CA*-mutant HR+/HER2- MBC after first-line progression, extending median progression-free survival (PFS) to 11 months (compared to 5.7 months with placebo).[20] In this trial, ctDNA was used as a supplementary method for mutation detection, while tissue-based biomarker analysis was standard for patient selection. A 56% concordance rate was observed between plasma ctDNA and tumor

tissue testing, and the Food and Drug Administration (FDA) recommends confirming negative plasma-based *PIK3CA* mutation results with tissue testing when considering alpelisib.[20]

The CAPItello-291 study (NCT04305496) demonstrated that the AKT inhibitor capivasertib with fulvestrant nearly doubled PFS (7.3 versus 3.1 months) in tumors harboring *PIK3CA*/*AKT* or *PTEN* alterations (HR 0.50; *P*<0.001) after first-line progression.[21] Here, the presence of *PIK3CA*, *AKT* or *PTEN* alterations was evaluated with NGS on both tissue and plasma samples. Retrospective analysis demonstrated high concordance rates when detected ctDNA tumor fraction exceeded 1%, with rates of 92.5% at tumor fraction (TF) ≥10%, 97.1% at TF 1–10%, supporting the use of ctDNA as a minimally invasive alternative for identifying actionable mutations in such cases.[22] Discrepancies in concordance between SOLAR-1 and CAPItello-291 may relate to differences in assays (less sensitive PCR-based in SOLAR-1 compared to NGS) and clinical context of the tissue.

More recently, INAVO120 (NCT04191499) showed median PFS was 15 months with inavolisib plus fulvestrant and palbociclib versus 7.3 months with fulvestrant and palbociclib in first-line treatment of endocrine-resistant HR+/HER2– MBC harboring *PIK3CA* mutations.[23] The inavolisib arm has also shown a significant improvement in median OS – 34 months versus 27 months (HR 0.67; *P*=0.02).[24]

In *ESR1*-mutant tumors, the EMERALD and EMBER-3 trials established the superiority of oral selective estrogen receptor degraders over standard endocrine therapy in patients with HR+/HER2- MBC whose disease recurred or progressed on endocrine therapy, leading to recent FDA approvals of elacestrant and imlunestrant. In EMERALD (NCT03778931), patients receiving elacestrant achieved superior median PFS (HR 0.55 if *ESR1* mutation, *P*=0.0005).[25] In EMBER-3 (NCT04975308), patients receiving imlunestrant demonstrated a median PFS of 5.5 months versus 3.8 months with standard endocrine therapy (HR 0.62; *P*=0.0008) in *ESR1*-mutant tumors and an even greater effect when combined with abemaciclib (PFS 9.4 versus 5.5 months; HR 0.57; *P*<0.001).[26] Currently, however, both agents are approved in the USA for monotherapy use only.

Serial ctDNA surveillance may enable early detection of resistance mutations before radiologic progression, allowing timely treatment modification. The PADA-1 trial (NCT03079011) demonstrated that early switching to fulvestrant in *ESR1*-positive patients doubled PFS, extending from 5.7 to 11.9 months.[27] Similarly, in the SERENA-6 trial (NCT04964934), patients who proactively switched to camizestrant upon ctDNA-detected *ESR1* mutation achieved significantly longer PFS compared with those who continued standard of care therapy until clinical progression (16.0 versus 9.2 months; HR 0.44; *P*<0.0001) and delayed quality-of-life decline.[28] Of the 3,256 patients ctDNA-screened, 548 developed *ESR1* mutations over the study period, with a reported median time to detect an *ESR1* mutation of 22 months. The mutation was detected in roughly one of every six enrolled patients, and while the overall results are encouraging, these data points also underscore the potential challenges of implementing such surveillance strategies in routine clinical practice. On-going trials such as the FAIM trial (which is evaluating whether adding the AKT inhibitor ipatasertib to fulvestrant and palbociclib can improve PFS in patients with HR+/HER2- MBC with detectable ctDNA after 15 days of treatment) continue to explore ctDNA-guided therapy optimization.

Prognostic role: ctDNA burden and baseline mutations

Trends in ctDNA levels carry prognostic significance, with early declines correlating with radiographic response while rising levels often precede progression by weeks to months.[29–31] A cohort of the LIBERATE trial (NCT03702309) reported that ctDNA clearance on CDK4/6 inhibition was observed in 28% of patients and predicted dramatically improved time to treatment failure (HR 0.07) and OS (HR 0.07).[32]

Data remain sparse in metastatic TNBC and HER2+ disease and are limited to single-institution studies, but results suggest similar prognostic relevance. A study conducted in Asia that enrolled 70 women with refractory TNBC demonstrated that detectable ctDNA correlated with shorter PFS (5.16 versus 9.05 months, *P*=0.001), and higher ctDNA fraction further predicted poorer outcomes.[33] Another study that monitored serial ctDNA in 92 women with heavily pretreated HER2+ MBC reported that at a median follow-up of 12.7 months, a higher ctDNA fraction (>3.33% [median]) was associated with worse PFS (3.3 versus 5.9 months; HR 1.95; *P*=0.003) and poorer overall survival (OS; 12.6 versus 22.9 months; *P*=0.001).[34] Evaluation is also under way assessing ctDNA performance for predicting progression and the need for changes in therapy, in lieu of serial imaging. Our institution is currently assessing ctDNA in patients with MBC via low-pass whole-genome sequencing, every 6 weeks, for this purpose.

Where are we now? Challenges incorporating ctDNA into clinical practice

Findings from the DARE and SERENA-6 trials highlight ctDNA's potential to predict and delay disease progression across breast cancer stages. Yet, its clinical integration remains limited. Current ASCO guidelines do not recommend ctDNA monitoring or its use to guide therapy in early-stage disease, though multiple studies are investigating its utility.[35] Key issues include optimal testing intervals, clinical interpretation and insurance coverage. The clinical interpretation of ctDNA results is challenged by several issues, including assay sensitivity, risk of false-negative findings and uncertain actionability of positive results. In a subset analysis from the monarchE study enriched for invasive disease-free survival (IDFS) events, among the 910 patients with successful ctDNA assay testing, positive ctDNA detection was noted to be adversely prognostic. However, IDFS events were also noted in 15% patients who remained persistently ctDNA negative during the duration of the study, suggesting that ctDNA clearance does not fully prognosticate and risk-stratify patients.[36]

When ctDNA is detected, the optimal clinical and therapeutic intervention remains undefined. The prematurely terminated ZEST trial further highlights this consideration, with approximately 50% of ctDNA-positive patients having radiographic metastases at the time of detection.[37] It remains unclear if there is an opportunity to salvage in the setting of ctDNA positivity.

The on-going NSABP B64/EXActDNA-003 trial (NCT06401421) was designed to establish evidence-based guidelines for ctDNA surveillance in early breast cancer and is enrolling patients across breast cancer subtypes receiving neoadjuvant therapy to monitor ctDNA at defined intervals pretreatment, during treatment and posttreatment in surveillance for up to 5 years. Additional challenges include managing molecular recurrence without radiographic confirmation, raising concerns about over-surveillance, premature treatment escalation and heightened patient anxiety.

CtDNA utilization is best established and guideline-directed in the metastatic setting, where ctDNA monitoring can inform targeted therapy selection. However, it is not established how frequently ctDNA should be evaluated, which can be costly. In the SERENA-6 trial, ctDNA was analysed every 2–3 months with median *ESR1* mutation detection at

22 months (enrolling after 6 months of endocrine therapy). Considering the cost per test of $2,000–3,000, frequent monitoring is impractical in clinical practice.

Biological variability further complicates implementation since ctDNA shedding differs across subtypes and stages; early-stage and HR+ tumors often release minimal ctDNA, reducing detection rates and prognostic reliability. Tumor heterogeneity and clonal evolution further challenge longitudinal interpretation, particularly for surveillance and resistance monitoring. Emerging technologies such as methylation sequencing and fragmentomics may improve sensitivity but are not yet standard.[38–41]

In summary, while ctDNA represents an important tool for biomarker detection and disease monitoring, its widespread use, especially in early-stage breast cancer, remains constrained by cost, biological limitations and undefined testing intervals. Continued prospective studies and technological advances are needed to refine the potential for ctDNA in personalized breast cancer care. ❑

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