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Circulating Tumor DNA in Early Breast Cancer
A Review

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IMPORTANCE Circulating tumor DNA (ctDNA) has emerged as a noninvasive biomarker with the potential to detect minimal residual disease (MRD), monitor treatment response, and identify recurrence (eg, molecular relapse) earlier than conventional clinical or imaging approaches. Although ctDNA-based MRD assays have demonstrated prognostic value in early breast cancer, their optimal clinical utility remains uncertain.

OBSERVATIONS This review summarizes the current data on ctDNA MRD assays in early breast cancer. Although these assays have established analytical and clinical validity, their clinical utility remains uncertain. Dynamics of ctDNA during neoadjuvant therapy are associated with pathologic complete response and long-term outcomes. Following completion of curative-intent therapy, ctDNA positivity (eg, presence of MRD) is strongly associated with future distant recurrence. Similarly, the emergence of ctDNA during surveillance precedes the clinical diagnosis of overt metastatic disease. Although observational studies and meta-analyses have supported ctDNA as a complementary biomarker for established risk-stratification tools, evidence that demonstrates improved outcomes with ctDNA-guided management remains limited. Furthermore, the optimal timing and frequency of testing remain unknown, and studies comparing assays are lacking. Multiple ongoing prospective interventional trials are evaluating whether ctDNA-guided treatment escalation or de-escalation can improve patient outcomes and support the routine implementation of ctDNA assays in clinical practice.

CONCLUSIONS AND RELEVANCE ctDNA-based MRD assays hold promise for refining risk stratification, enabling earlier detection of recurrence, and informing treatment decisions in patients with early breast cancer, but clinical utility has not yet been demonstrated. Prospective trials are essential to determine whether ctDNA-guided interventions improve outcomes beyond standard management. Clinicians should understand the strengths, limitations, and evolving evidence base of ctDNA assays, as well as patient preferences, prior to incorporating them into patient care.

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Many patients with early-stage breast cancer experience relapse, while others receive unnecessary therapy and experience associated toxic effects.[1-3] These challenges highlight the need for biomarkers to precisely assess risk and guide personalized clinical decision-making. Circulating tumor DNA (ctDNA) is a promising, minimally invasive biomarker.[4] Because ctDNA represents only a fraction of cell-free DNA (cfDNA), most of which is derived from normal cellular turnover, its quantity is often reported as the tumor fraction. The term *minimal residual disease* (MRD) refers to the presence of microscopic disease that is not detected by traditional imaging.[5-7] The development of highly sensitive ctDNA assays has made this analyte the most promising for MRD detection in patients with solid tumors.

Quantitatively, ctDNA serves as a sensitive gauge for the presence of MRD in the bloodstream and can provide a dynamic readout of response when tracked longitudinally.[8] Qualitatively, ctDNA can reflect the underlying tumor biology from multiple angles and be assessed over time to capture tumor evolution under selective pressure during treatment.[9-11]

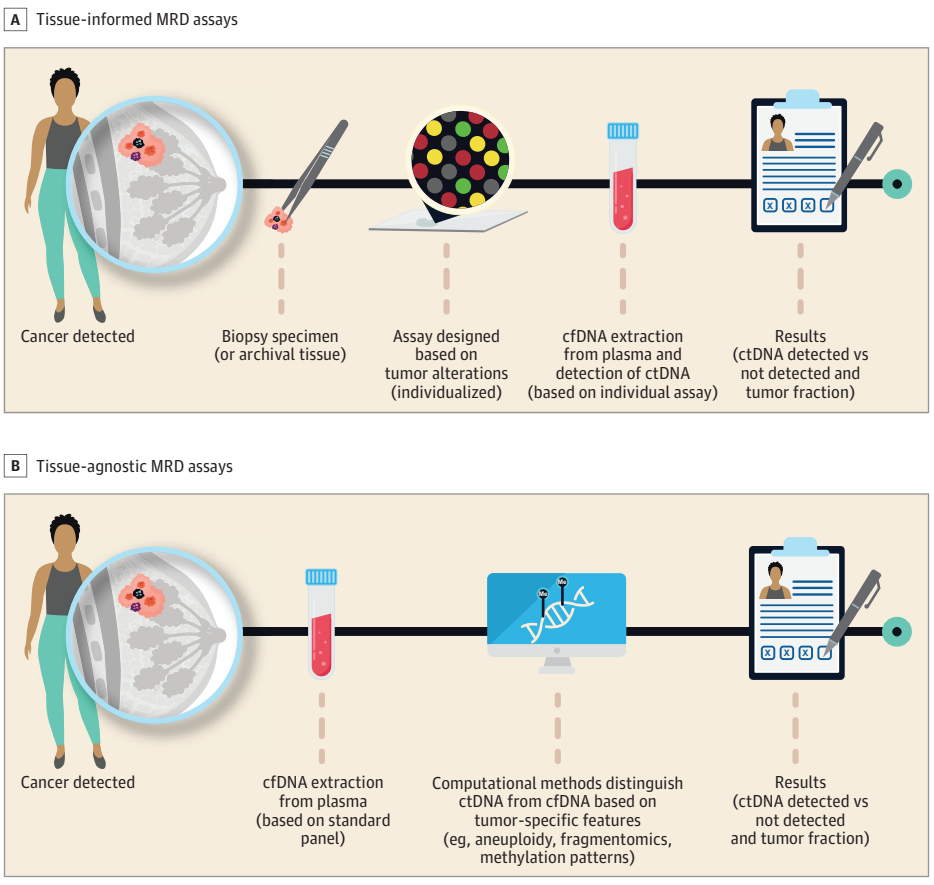
ctDNA-based MRD assays are increasingly used in clinical practice given their established prognostic value and growing commercial availability. However, these assays are not currently endorsed for routine use by clinical guidelines, as evidence demonstrating clinical utility (namely, that ctDNA-guided interventions are associated with improved patient outcomes) has yet to be proven.

This review focuses on ctDNA assays that were developed to detect and track MRD and describes their characteristics, current evidence, and the steps required to support their clinical implementation in patients with early breast cancer.

Approaches to ctDNA Analysis for MRD Detection

MRD assays are classified as tumor informed (ie, bespoke) or tumor agnostic. For tumor-informed assays (**Figure 1**A), DNA from

Figure 1. Illustration of Tissue-Informed vs Tissue-Agnostic Circulating Tumor DNA (ctDNA) Assays for Minimal Residual Disease (MRD) Detection



cfDNA indicates cell-free DNA.

tumor tissue is first sequenced to identify tumor-specific variants, which are then tracked in plasma through individualized assays.[12] This approach distinguishes ctDNA from cfDNA by identifying a specific genomic fingerprint and filtering out germline variants and clonal hematopoiesis via sequencing normal DNA, maximizing specificity.[12] However, sensitivity in early-stage disease is limited by the low ctDNA concentration compared with normal cfDNA, as the alterations of interest may not be present in the small plasma volume sampled (sampling bias).[7] To address this, novel assays track an increasing number of alterations (from digital polymerase chain reaction [PCR]–based assays tracking 1-2 variants, to whole-exome [WES]–based and whole-genome sequencing [WGS]–based tests tracking dozens to thousands of alterations).[13,14] These improvements have produced highly sensitive assays with limits of detection (LOD) in the 1- to 3-parts-per-million range (**Table 1**[15-22]). The major limitations of this approach are the reliance on tumor tissue, as approximately 20% of patients may be ineligible for analysis due to insufficient tissue, longer turnaround times (because a bespoke assay is developed for each patient), and the inability to detect new and acquired alterations present in the metastasis but not the primary tumor.

Tumor-agnostic assays (Figure 1B) do not require tissue, offer a faster turnaround, and can be less costly.[23] Instead of evaluating genomic variants, they identify features unique to tumor-derived DNA, such as aneuploidy, fragment length, and methylation patterns, often combined via machine-learning approaches to achieve greater sensitivity.[24-26] To further characterize tumor biology, some tumor-agnostic assays also include sequencing of common cancer gene variants via WES or targeted next-generation sequencing panels,[27,28] similar to comprehensive genomic profiling assays used in the metastatic setting to identify actionable genomic variants.[11,23,29,30] However, the sensitivity and specificity of available tumor-agnostic assays are substantially lower than bespoke approaches, as the latter can rely on true-positive variants identified by tissue sequencing to filter out variants associated with sequencing errors or clonal hematopoiesis and optimize the signal-to-noise ratio.

Clinical Evidence on ctDNA Detection and Tracking in Early Breast Cancer

Monitoring ctDNA Dynamics in the Neoadjuvant Setting

In the neoadjuvant setting, the prevalence and dynamics of ctDNA are highly prognostic. **Table 2**[8,18,31-50] summarizes prior studies using ctDNA MRD assays. At baseline, detection of ctDNA depends on assay sensitivity and tumor biology: more than 90% of triple-negative and *ERBB2*-positive (*ERBB2*$^{+}$) tumors are ctDNA-positive before neoadjuvant therapy (NAT) using highly sensitive MRD assays, while the proportion decreases for luminal tumors, which is consistent with the different replication rate and tumor shedding of these subtypes.[33,35] Within tumor subtypes,

Table 1. Circulating Tumor DNA (ctDNA) Assays for Minimal Residual Disease (MRD) Detection in Early Breast Cancer With Analytical Validation Data

ctDNA MRD assay[a]	Type of assay	Targets/panel	Limit of detection	CMS reimbursement indication in early breast cancer (as of March 16, 2026)[b]
Tissue agnostic				
Guardant Reveal[15]	Plasma-only, epigenomic-based assay	Approximately 4 Mb of epigenomic regions differentially methylated between ctDNA and normal cfDNA	LOD95: 0.01%	NA
Tissue informed				
NeXT Personal (Personalis)[16]	WGS-based, personalized NGS panel	Up to 1800 somatic variants	LOD95: 3.45 ppm	Stage II-III breast cancer for recurrence monitoring in the surveillance setting for up to 6 y, all subtypes
RaDaR (NeoGenomics)[17]	WES-based, personalized multiplex PCR-NGS assay	Up to 48 somatic variants	LOD95: 0.0011% VAF	High-risk, stage II/III HR-positive/*ERBB2*-negative breast cancer, 5 or more y from diagnosis who presently do not have evidence of disease
Pathlight (SAGA)[18]	WGS-based, personalized digital PCR assay	Up to 16 patient-specific structural variants	LOD95: 5 ppm (0.005%)	Stage II-III breast cancer for recurrence monitoring in the surveillance setting for up to 6 y, all subtypes
Signatera Exome[19]	WES-based, personalized multiplex PCR-NGS assay	16 Patient-specific clonal variants	0.01% VAF	Stage II-III breast cancer in the neoadjuvant setting, all subtypes; stage IIb-III breast cancer in the adjuvant and recurrence monitoring settings, all subtypes
Signatera Genome[20]	WGS-based, personalized multiplex PCR-NGS assay	64 Patient-specific clonal variants	LOD95: 5-9 ppm (0.0005%-0.009%)	Stage II-III breast cancer in the neoadjuvant setting, all subtypes; stage IIb-III breast cancer in the adjuvant and recurrence monitoring settings, all subtypes
FoundationOne Tracker[21]	CGP-based, personalized multiplex PCR-NGS assay	2-16 Patient-specific clonal variants	Analytical sensitivity of >97.3% at ≥5 MTM/mL	NA
Exact Sciences (Oncodetect)[22]	WES-based, personalized hybrid capture NGS	50-200 Patient-specific clonal variants	LOD: 5 ppm (0.005%)	NA

Abbreviations: cfDNA, cell-free DNA; CMS, US Centers for Medicare & Medicaid Services; CGP, comprehensive genomic profiling; HR, hormone receptor; LOD, limit of detection; MTM, mean tumor molecules; NA, not applicable; NGS, next-generation sequencing; PCR, polymerase chain reaction; ppm, parts per million; VAF, variant allele frequency; WES, whole-exome sequencing; WGS, whole-genome sequencing.

[a] The included assays were selected based on relevance to MRD detection in breast cancer and the availability of published analytical validation data.

[b] Some ctDNA MRD assays are reimbursed by CMS for the indications reported in the table, although none are approved by the US Food and Drug Administration nor endorsed by clinical guidelines.

and with sufficiently sensitive assays, tumor fraction also increases with the disease burden and is associated with nodal status and tumor stage.[35,51]

More relevant than baseline ctDNA detection is on-treatment dynamics, which are significantly associated with outcomes.[18,33,35] In a retrospective cohort from the Princess Margaret Hospital (Toronto, Ontario, Canada), clearance of ctDNA before cycle 2 of NAT with a tumor-informed, WGS-based assay was significantly associated with longer relapse-free interval, and all patients who cleared ctDNA remained progression free[18] at a median follow-up of 4.7 years. In the I-SPY2 study, clearance at the preoperative time point or ctDNA persistence with a WES-based assay was associated with shorter distant relapse–free survival even after adjusting for known prognostic factors (HR of 6.88 for late clearance and HR of 16.50 for no clearance vs persistent negative).[35] Among patients with a residual cancer burden (RCB) score of II/III, 3-year distant recurrence-free survival (DRFS) was 98% for persistently ctDNA-negative patients, 91% for clearance at week 3, 92% for week 12, 63% before surgery, and only 35% for patients with no clearance, showing how ctDNA clearance provides further risk stratification beyond the absence of pathologic complete response (pCR) after NAT.[35] Consistent results were observed in other studies that used WGS-based assays.[33,52] In the TBCRC-040 study, patients with triple-negative breast cancer (TNBC) or *ERBB2*$^+$ tumors and residual disease after NAT had a 3-year relapse-free survival of 94% if they were ctDNA-negative before surgery, compared with 54% if they were ctDNA-positive with a WGS-based assay.[37]

Data on the association between ctDNA clearance and surgical response (eg, pCR and RCB) have been less consistent and highly dependent on the timing of assessment and tumor subtype. In I-SPY2, most patients were positive at baseline (92% with TNBC, 77% with *ERBB2*$^+$ disease, and 76% with hormone receptor [HR]–positive [HR$^+$]/*ERBB2*-negative [*ERBB2*$^-$] tumors), but only a few remained ctDNA-positive before surgery (16% with TNBC, 3% with *ERBB2*$^+$ disease, and 8% with HR$^+$/*ERBB2*$^-$ tumors). As most patients cleared ctDNA, the negative predictive value (NPV) of ctDNA clearance after NAT for response (eg, RCB-0/I) was limited (65% for TNBC, 66% for *ERBB2*$^+$ disease, and 32% for HR$^+$/*ERBB2*$^-$), although all patients with response had ctDNA clearance (specificity, 96%-100%). However, rapid ctDNA clearance was associated with response: 82% of patients with either TNBC or *ERBB2*$^+$ disease and clearance by week 3 had RCB-0/I at surgery, although the prognostic value was limited for HR$^+$/*ERBB2*$^-$ disease, as only 42% of patients who cleared ctDNA had RCB-0/I.[35] Similarly, in the TBCRC-030 study, 7 of 8 patients with TNBC who cleared ctDNA early (eg, at week 3) using a tissue-informed, WGS-based assay demonstrated a response (eg, RCB 0/1) compared with 7 of 11 at week 12.[36] In the TBCRC-040 (PREDICT-DNA) study, which assessed only late clearance before surgery and used a different WGS-based assay, the NPV of a negative

Table 2. Selected Studies Investigating the Prognostic Role of Circulating Tumor DNA (ctDNA) Minimal Residual Disease (MRD) Assays in Early-Stage Breast Cancer[a]

Source	Study design	Population; sample size	Assay	Time points	Objectives/end points	Results
ctDNA dynamics during neoadjuvant therapy and association with response and outcomes						
Elliot et al,[18] 2025	Retrospective analysis	Early-stage breast cancer treated with neoadjuvant therapy (any subtype); 100 patients; 568 plasma samples	Pathlight	Baseline (pre-NAT) and serial during neoadjuvant therapy (including C2); postoperative surveillance samples	ctDNA dynamics during NAT; lead time to clinical recurrence; association between ctDNA status and RCB; association between ctDNA status and distant recurrence	Baseline ctDNA was detected in 91 of 95 cases (96%) with a median VAF of 0.15% (range, 0.0011%-38.7%). ctDNA positivity at C2 was associated with higher risk of distant recurrence and better RCB discrimination. ctDNA was detected before recurrence in all cases. Median lead time to recurrence, 417 d (range, 4-1931)
HUNT-TNBC (Yoo et al,[31] 2026)	Retrospective analysis	TNBC receiving neoadjuvant therapy; 80 patients; 444 plasma samples	Pathlight	Baseline, 4-7 wk after initiating preoperative systemic therapy (T1), preoperatively (T2), within 3 mo after surgery (T3), and every 6 mo during follow-up	Prevalence and clearance of ctDNA during neoadjuvant therapy; NPV of ctDNA clearance for pCR; association between ctDNA clearance and RFS	Baseline ctDNA was detected in 93.4% of patients. Most patients cleared ctDNA during treatment (61% at T1; 70% at T2); NPV of MRD clearance for pCR was 79.5% at T1 and 71.4% at T2; seven of 8 patients who had ctDNA after surgery experienced recurrence (median lead time, 10.9 mo)
Garcia-Murillas et al,[32] 2025	Retrospective analysis	High-risk early breast cancer treated with NAT; 61 patients; median of 8 (range 2-12) samples per patient	Invitae (50 patient-specific variants)	Baseline, during neoadjuvant therapy, postsurgery, and during surveillance	Baseline ctDNA status, association with relapse risk	Baseline prevalence, 67.8%; ctDNA was detected in 10 of 13 patients who experienced relapse (76.9% sensitivity, 100% specificity, 100% PPV); detection of ctDNA during monitoring was associated with high risk of relapse (hazard ratio, 37.2; 95% CI, 10.5-131.9). Median lead time to relapse was 11.7 mo
Garcia-Murillas et al,[33] 2025	Retrospective analysis	Stage I-III breast cancer; 78 patients (23 TNBC, 35 *ERBB2*-positive, 18 HR-positive, and 2 unknown); 617 plasma samples	NeXT Personal	Baseline, cycle 2 of neoadjuvant therapy, postsurgery, every 3 mo for 1 y and every 6 mo thereafter	ctDNA dynamics during NAT; lead time to clinical recurrence	Baseline ctDNA prevalence, 98%; 5-y RFS of 100% among ctDNA and 41.7% among ctDNA-positive patients considering any time point during follow-up; median lead time from ctDNA detection to clinical relapse, 15 mo. No recurrences were observed among patients with ctDNA undetected
NeoN (Loi et al,[34] 2026)	Correlative analysis from a phase 2 trial in which patients received nivolumab, carboplatin, and paclitaxel for 12 wk	Stage I-III TNBC; 108 patients; 86 plasma samples	Pathlight	Baseline, after 2 cycles of treatment (T1), and after surgery (T2)	ctDNA dynamics; association between EFS and ctDNA status	Baseline prevalence 91%; clearance from baseline to T1 (74%): pCR rate, 63%; 3-y EFS, 90.6%; no clearance from baseline to T2 (18%): pCR rate. 0%; 3-y EFS, 45.5%
I-SPY2 (Magbanua et al,[35] 2023)	Correlative analysis from phase 2 adaptive clinical trial (chemotherapy with or without novel therapies)	Stage II-III HR-positive or TNBC; 283 patients; 1024 plasma samples	Signatera Exome	Baseline (T0), 3 wk (T1), 12 wk (T2), presurgery (T3)	ctDNA prevalence at different points and dynamics, association with RCB and DRFS	Early ctDNA clearance at T1 predicted response to NAT in TNBC (OR, 13) not in HR-positive/*ERBB2*-negative (OR, 1.2); ctDNA^{+} at T3 was associated with worse DRFS (HR of 6.79 in HR-positive/*ERBB2*-negative; hazard ratio, 5.40 in TNBC)
TBCRC-030 (Parsons et al,[36] 2023)	Case-control, correlative analysis from a phase I2 trial of 12 wk of paclitaxel vs cisplatin in TNBC	Stage II-III TNBC; 38 patients; 114 plasma samples	MAESTRO	Baseline, 3 wk, 12 wk (EOT)	ctDNA dynamics and association with response	ctDNA detectable in 100% at baseline, 79% at wk 3, and 55% at wk 12; tumor fraction decreased 285-fold from baseline to wk 3 in responders vs 24-fold in nonresponders; 12-wk ctDNA clearance strongly correlated with RCB (cleared in 10 of 11 patients with RCB-0; none in RCB-3)

(continued)

Table 2. Selected Studies Investigating the Prognostic Role of Circulating Tumor DNA (ctDNA) Minimal Residual Disease (MRD) Assays in Early-Stage Breast Cancer[a] (continued)

Source	Study design	Population; sample size	Assay	Time points	Objectives/end points	Results
I-SPY2 (Magbanua et al,[8] 2025)	Correlative analysis from a phase 2 adaptive clinical trial (chemo-therapy with or without novel agents)	Stage II-III breast cancer; 723 patients; 2607 plasma samples	Signatera Exome	Baseline (T0), 3 wk (T1), 12 wk (T2), presurgery (T3)	ctDNA prevalence at different points and dynamics; association between ctDNA status and dynamics with RCB; association between ctDNA status and dynamics with DRFS; clonal evolution and percentage of conservation of ctDNA assays variants in tumor	Average prevalence: 81% at T0, 42% at T1, 20% at T2, 9% at T3; positive association between ctDNA status at T3 and DRFS among patients with residual disease: 3-y DRFS of 88% for RCB-II/ctDNA negativity, 57% for RCB-II/ctDNA-positive, 83% for RCB-III/ctDNA-negative, and 22% for RCB-III/ctDNA-positive; clearance at T1 was associated with higher likelihood of pCR/RCB-I compared with no clearance at T2 response across subtypes (OR, 5.8-15.0); Cox models incorporating RCB score and ctDNA dynamics had the highest C-index for predicting DRFS (C-index, 0.84); 94%-97% of ctDNA assay variants were conserved in the primary vs on-treatment or post-NAT tissue samples
PREDICT-DNA (Hunter et al,[37] 2026)	Prospective cohort study	Stage II-III *ERBB2*-positive or TNBC; n = 184	NeXT Personal	Baseline, post-NAT/ presurgery	NPV of ctDNA for pCR post-NAT	165 of 178 Patients were ctDNA-positive at baseline; NPV, 60% (95% CI, 0.50-0.69); RFS hazard ratio, 9.6 (95% CI, 2.6-35; *P* = .001) for ctDNA-positive vs ctDNA-negative at the preoperative point
NSABP B-59/GBG-96-GeparDouze (Balic et al,[38] 2025)	Correlative analysis from phase 2 clinical trial	Stage II-III TNBC; n = 212 (ctDNA cohort)	Oncodetect	Baseline, post-NAT/ presurgery, postsurgery	Association between postsurgery ctDNA result and DRFI	154 of 160 (96%) Were ctDNA-positive at baseline; post-NAT ctDNA detection: 21% among patients with residual disease, 2% among patients with pCR; DRFI hazard ratio, 30.3 (95% CI, 10.4-88.7) for ctDNA-positive vs ctDNA-negative at the postoperative point
Molecular relapse during surveillance and association with clinical recurrence and outcomes						
Parsons et al,[39] 2020	Retrospective analysis	Metastatic breast cancer: 16 ER-positive/*ERBB2*-negative patients, 16 plasma samples; early-stage: 142 patients and 271 plasma samples	WES-based assay	MBC: ≤6 mo from metastatic breast cancer diagnosis; early stage: after surgery, 1 y from surgery, 4 y from surgery	Association between ctDNA detection and distant recurrence	ctDNA detection: 81% in new metastatic breast cancer; 23% after surgery; and 19% at 1 y; ctDNA-positive at 1 y strongly associated with recurrence (hazard ratio, 20.8); median lead time to recurrence, 18.9 mo
EBLIS (Shaw et al,[40] 2024)	Retrospective analysis	Early breast cancer; 156 patients (any subtype); 1136 plasma samples	Signatera Exome	During follow-up, every 6 mo	Sensitivity of ctDNA for molecular relapse detection; lead time to clinical recurrence; association with RFS and OS	ctDNA^{+} before relapse in 30 of 34 patients (patient-level sensitivity, 88.2%); 4 false-negative cases had HR-positive/*ERBB2*-negative tumors; median lead time to relapse, 10.5 mo (range, 0-38); ctDNA positivity was associated with worse RFS and OS
CHiRP (Lipsyc-Sharf et al,[42] 2022; Yoo et al,[41] 2025)	Prospective observational cohort study, retrospective ctDNA analysis	Stage II-III HR-positive/*ERBB2*-negative >5 y postdiagnosis; n = 83	RaDaR	Every 6-12 mo	ctDNA detection, RFS by ctDNA detection, predictive value	ctDNA positivity in 9.6% of patients at any point. All ctDNA positivity relapsed (median lead time, 1.39; range, 0.01-4.24 y). NPV of ctDNA negativity test of being recurrence-free 3 y after testing: 96.6%
Garcia-Murillas et al,[43] 2019	Prospective cohort study, restrospective ctDNA analysis	Early breast cancer, all subtypes; n = 101	Tumor-informed, ddPCR	Every 3 mo for 1 y, then every 6 mo for 5 y	RFS stratified by ctDNA status	Time-dependent HR for RFS, 25.2; median lead time between ctDNA detection and relapse, 10.7 mo (95% CI, 8.1-19.1)

(continued)

Table 2. Selected Studies Investigating the Prognostic Role of Circulating Tumor DNA (ctDNA) Minimal Residual Disease (MRD) Assays in Early-Stage Breast Cancer[a] (continued)

Source	Study design	Population; sample size	Assay	Time points	Objectives/end points	Results
monarchE (Loi et al,[44] 2024)	Correlative analysis of a phase 3 randomized clinical trial; abemaciclib + ET vs ET alone	HR-positive/*ERBB2*-negative, node-positive, high risk; n = 910 (ctDNA cohort)	Signatera Exome	Baseline (preabemaciclib), at 3, 6, and 24 mo	ctDNA detection; iDFS stratified by ctDNA status	Baseline ctDNA detection 8%; ctDNA emergence: 10%; ctDNA clearance: 41%; 4-y iDFS rate of 79% for ctDNA-negative vs 20% for ctDNA positivity
PALLAS (Parsons et al,[45] 2025)	Correlative analysis of a phase 3 randomized clinical trial; palbociclib + ET vs ET alone	HR-positive/*ERBB2*-negative, node-positive, high risk; n = 420 (ctDNA cohort), 1012 plasma samples	Signatera Genome	Postsurgery (C1D1); after 6 mo; after 2 y (EOT)	Correlation between MRD positivity and recurrence	ctDNA positivity of 8% on C1D1 of palbociclib (some patients were receiving ET); ctDNA status was associated with DRFI at C1D1 (5-y DRFI of 93% for ctDNA-negative vs 28% for ctDNA-positive patients) and EOT (5-y DRFI of 95.4% for ctDNA-negative vs 31.6% for ctDNA-positive patients)
TRAK-TN (Turner et al,[46] 2023)	Phase 2 prospective trial with ctDNA surveillance and intervention for ctDNA-positive cases	Early-stage TNBC, high risk, posttreatment; 208 registered, 45 randomized/allocated	ddPCR	Every 3 mo for 2 y	12-mo and 24-mo ctDNA detection rate sustained ctDNA clearance with receipt of pembrolizumab	12-mo ctDNA positivity: 27.3%; 72% of ctDNA-positive patients allocated to intervention had metastases. No durable ctDNA clearance with receipt of pembrolizumab (0%)
ZEST (Turner et al,[47] 2025)	Phase 3 randomized clinical trial of niraparib vs placebo for ctDNA-positive patients	Stage I-III, TNBC or *BRCA1*-variant HR-positive breast cancer; 2746 prescreened, 147(ctDNA-positive, 40 randomized	Signatera Exome	Every 2-3 mo (within 16 wk of EODT for TNBC and 5 y of EODT for HR-positive)	DFS (changed to safety and tolerability of niraparib when enrollment stopped)	Discontinued early due to low ctDNA-positive detection rate. Niraparib showed modest benefit (relapse-free interval hazard ratio, 0.66; 95% CI, 0.66-1.36).
DARE (Pusztai et al,[48] 2025)	Ongoing phase 2 randomized clinical trial of palbociclib + fulvestrant vs continuation of ET for ctDNA-positive patients	High-risk stage II-III HR-positive/*ERBB2*-negative while receiving ET 6 mo to 7 y; n = 585; 38 randomized (as of April 2025)	Signatera Exome	Every 6 mo	Longitudinal ctDNA detection; RFS and MRFS in the ctDNA-negative cohort; ctDNA dynamics and clearance rates; RFS by ctDNA dynamics	12% ctDNA-positive during surveillance; of 32 randomized: clearance of 56.3% with palbociclib + fulvestrant vs 25% with continuation of ET; RFS rate of 99% at 36 mo in ctDNA-negative patients
LEADER (Spring et al,[49] 2025; Medford et al,[49,50] 2026)	Phase 2 trial of addition of ribociclib to adjuvant ET for ctDNA-positive patients	Stage I-III HR-positive/*ERBB2*-negative while receiving ET; 161 prescreening, 15 ctDNA-positive, 10 enrolled	Signatera Exome	3, 6, and 12 mo	Molecular response	12-mo NPV for RFS 99% for ctDNA-negative patients; DRFS by ctDNA response: 5.4 mo (2 nonresponders), 18.6 mo (5 responders)

Abbreviations: C1D1, cycle 1, day 1; ddPCR, droplet digital polymerase chain reaction; DFS, disease-free survial; DRFI, distant recurrence-free interval; DRFS, distant recurrence–free survival; EFS, event-free survival; EODT, end of day therapy; EOT, end of therapy; ET, endocrine therapy; HR, hormone receptor; iDFS, invasive disease-free survival; MRD, minimal residual disease; MRFS, molecular relapse–free survival; NAT, neoadjuvant therapy; NPV, negative predictive value; OR, odds ratio; OS, overall survival; pCR, pathologic complete response; PPV, positive predictive value; RCB, residual cancer burden; RFS, recurrence-free survival; TNBC, triple-negative breast cancer; VAF, variant allele frequency; WES, whole-exome sequencing.

[a] Studies included were selected based on relevance to ctDNA monitoring in early-stage breast cancer, sample size (≥50 patients), or study design (ctDNA-guided prospective clinical trial).

test result after NAT for pCR was 60%.[37] Although early clearance is more predictive than late clearance, when early clearance should be assessed is unknown, as to our knowledge no study compared clearance at multiple time early points.[37] Furthermore, assays with different LOD have different clearance rates. Because pCR rates vary with patient populations and treatment regimens, the proportion of patients clearing at each time point varies, even with the same assay at the same time point. Finally, pCR provides rapid information and has been used as a surrogate end point for recurrence and survival, which remain the criterion standard. This should be considered when designing and interpreting studies that compare new technologies, such as ctDNA, with end points that are not the criterion standard.

Few studies have used tumor-agnostic ctDNA assays in the neoadjuvant setting. Baseline ctDNA positivity has generally been lower across all subtypes compared with tissue-informed assays, likely reflecting the lower sensitivity of tumor-agnostic approaches in breast cancer.[28,53] In the PELOPS study, 40% of patients with node-positive, HR$^+$/*ERBB2*$^-$ breast tumors were ctDNA-positive before NAT.[53] In PHERGAIN, which used the same tumor-agnostic assay, baseline prevalence was 67.5% for patients with *ERBB2*$^+$ breast cancer.[54]

While these studies have demonstrated the clinical validity of ctDNA dynamics during NAT, prospective clinical trials with ctDNA-guided interventions are needed to prove clinical utility before implementing ctDNA testing in clinical care. Trials could be designed to

test if a treatment switch to novel agents in this setting could cure MRD and spare patients from developing metastatic recurrence. Findings from the association between early clearance, high pCR rates, and excellent long-term outcomes support de-escalation trials with shorter NAT durations.

Detection of MRD After NAT

Detection of MRD in the perioperative setting is also associated with long-term outcomes. In I-SPY2, post-NAT ctDNA status was a poor predictor of response at surgery but remained associated with the risk of recurrence and further refined prognosis among patients with residual disease. Patients with undetectable ctDNA after NAT had improved 3-year DRFS rates compared with ctDNA-positive patients for RCB-II (88% vs 57%; adjusted hazard ratio, 0.29) and RCB-III (83% vs 22%; adjusted hazard ratio, 0.14). However, extensive residual disease remained associated with a poor prognosis.[8]

In the EBLIS study, which assessed ctDNA status after surgery, the risk of recurrence was 30-fold higher across subtypes among MRD-positive vs MRD-negative patients at the first postsurgical time point with a WES-based assay.[40] In monarchE, the 4-year invasive disease-free survival (iDFS) rate was 20% for MRD-positive patients compared with 79% for MRD-negative patients at baseline with the same assay. In the PALLAS trial, the 5-year distant relapse–free interval was 27.8% for MRD-positive patients, compared with 93% for MRD-negative patients at baseline, using a WGS-based assay.[55]

The most accurate prediction of outcomes by MRD status is with repeated testing, during which patients with any positive result are classified as MRD-positive and those with all negative results as MRD-negative. In EBLIS, the risk of recurrence for MRD-positive vs MRD-negative was almost doubled by serial testing (hazard ratio, 53) compared with the single postoperativepoint (hazard ratio, 30).[40] In monarchE, 10% of ctDNA-negative patients at baseline developed positive results during follow-up, and 41% of ctDNA-positive patients cleared ctDNA. Patients with ctDNA detected during follow-up had worse outcomes compared with ctDNA-negative patients, although the risk of recurrence was higher for patients with ctDNA clearance compared with always negative patients (4-year iDFS, 0%, 11%, 58.3%, and 87.5% among persistently positive, negative to positive, positive to negative, and persistently negative disease, respectively). This suggests that although ctDNA clearance may not fully mitigate the risk of recurrence for some patients, it could indicate eradication of micrometastatic disease for others.[44]

However, serial analyses are subject to immortal time bias, as patients must remain alive and progression free to undergo repeated testing; therefore, they are less informative for decision-making at specific time points. Comparisons with a single–time point landmark analyses have suggested that the favorable outcomes observed in MRD-negative patients are largely associated with repeated negative MRD tests, as more than 80% of recurrences occur in patients with an initial negative MRD test result.[40,44]

The poor prognosis of MRD-positive patients after surgery has informed the design of clinical trials for treatment escalation. In the ASPRIA trial (NCT04434040), patients with TNBC and residual disease after NAT who are ctDNA positive are treated with 6 cycles of sacituzumab govitecan plus atezolizumab. Similarly, KAN-HER2 (NCT05388149) is testing the addition of neratinib to trastuzumab emtansine for *ERBB2*$^+$ breast cancer in patients with residual disease who are MRD-positive. **Table 3**[56] summarizes ongoing studies using ctDNA MRD status as an integral biomarker (as of March 2026).

One major challenge of these studies is the high number needed to screen, given the good prognosis of most patients with early breast cancer and low prevalence of MRD in the perioperative setting. In PALLAS and monarchE, only 8% of patients were MRD-positive at baseline.[44] Among patients with TNBC and residual disease after NAT, prevalence of MRD at the postoperative time point ranged between 3.6% and 34% across different populations and assays.[57] In the DAPHNE study, 4.7% of patients with *ERBB2*$^+$ disease and residual disease after NAT were MRD-positive after surgery.[58] MRD results might be considered as an additional prognostic factor for the low-risk population for whom treatment de-escalation could be considered. The ongoing Safe-De (NCT05058183) study is enrolling patients with stage I, TNBC, or *ERBB2*$^+$ breast cancer and omitting chemotherapy for patients who are MRD-negative at 2 and 4 weeks postoperatively, who instead undergo molecular surveillance and are treated on detection of MRD. Similarly, the SIGNAL-ER 101 study (NCT07214532) is evaluating whether ctDNA can help select patients with intermediate-risk HR$^+$/*ERBB2*$^-$ disease for treatment with adjuvant CDK4/6 inhibitors (CDK4/6i). In the study, only participants who are ctDNA-positive at baseline initiate CDK4/6i therapy; ctDNA-negative patients receive endocrine therapy alone, with ctDNA testing every 3 months and delayed initiation of CDK4/6i until the time of MRD detection.

Diagnosis of Molecular Relapse During Surveillance

In the surveillance setting (after completion of systemic therapies other than endocrine therapy), serial ctDNA testing allows for the detection of MRD months to years before clinical relapse, and almost all patients who develop MRD experience distant recurrence with sufficient follow-up.[41,42] The lead time between MRD detection and recurrence is highly variable and depends on the frequency and timing of time points, as well as the assay used, with a median of 10 to 15 months across studies but a very broad range (0 to 63.5 months) that differs across subtypes.[18,33,35] Although few cross-assay comparisons are available, higher sensitivity is associated with improvement in detection rates and lead times. In cTRAK-TN, MRD during surveillance for TNBC was first detected by a WES-informed assay in 47.9% of patients, by digital PCR testing in 0%, and with both assays simultaneously in 52.1% of patients; the median lead time increased from 3.9 months with droplet digital PCR to 6.1 months[46,59] with a WES-based assay. In chemoNEAR, pre-NAT detection rates (100% with WGS-based vs 84% with WES-based vs 76% with digital PCR) and lead times (median of 10.2 months with WES-based vs 15.6 months with WGS-based assays) improved with higher sensitivity.[33] A major limitation of lead time bias estimations from retrospective studies is the lack of concurrent scans that are not routinely performed during follow-up. Thus, the lead time between MRD detection and relapse at imaging is impossible to infer, and likely shorter than what is reported between molecular and clinical recurrence.

A critical unknown at this time is whether intervening on molecular relapse can be curative or substantially delay recurrence, as the only 2 randomized studies to date have failed to demonstrate clinical utility. cTRAK-TN was a phase 2 study for patients with TNBC and either residual disease after NAT or stage II to III disease after surgery who were first followed up with MRD monitoring every

Table 3. Ongoing Clinical Trials Investigating the Clinical utility of Circulating Tumor DNA (ctDNA) in Early-Stage Breast Cancer

Study	Study design (sample size)	Setting	Population	MRD assay	Intervention	Primary end point
ASPRIA (NCT04434040)	Phase 2, single arm (n = 40)	Postneoadjuvant (ctDNA testing 2-12 wk postoperative if no RT, ≥1 wk post RT if RT administered)	TNBC with residual disease, MRD-positive	Signatera Exome	Sacituzumab govitecan + atezolizumab	18-wk ctDNA clearance
KAN-HER2 (NCT05388149)	Phase 2, single arm (n = 15)	Postneoadjuvant (ctDNA testing after 2-6 cycles of T-DM1)	*ERBB2*-positive with residual disease, MRD-positive	RaDaR	Neratinib added to T-DM1	12-wk ctDNA clearance
Artemis (NCT04803539)	Phase 2, randomized (n = 260)	Postoperatory and postadjuvant therapy	Stage II-III TNBC, MRD-positive	Next-generation sequencing	Capecitabine vs capecitabine and camrelizumab and apatinib	iDFS
Cupcake (NCT06225505)	Phase 2, randomized (n = 450)	Patients with high-risk TNBC (those at high risk for recurrence undergo ctDNA testing every 4 mo for 2 y)	Any patient with TNBC and residual disease after neoadjuvant therapy or stage IIB-III TNBC or local recurrence	FoundationOne Tracker	To determine if the combination of ctDNA and PET imaging can help detect metastases limited in size and No. of sites. Those who are ctDNA-positive will be randomized to interventional arms using the trials within cohorts approach	OS
PERSEVERE (NCT04849364)	Phase 2, umbrella trial (planned number, 197; actual number, 52)	Postneoadjuvant	TNBC with residual disease	Foundation medicine	Patients with residual TNBC were assigned to talazoparib and capecitabine or pembrolizumab and capecitabine or inavolisib and capecitabine with or without standard of care pembrolizumab or talazoparib and capecitabine with or without standard of care pembrolizumab	2-y DFS
Safe-De (NCT05058183)	Phase 2, single arm (n = 400)	Adjuvant (ctDNA testing 2-4 wk after surgery)	Stage I TNBC or *ERBB2*-positive	Signatera Exome	Chemotherapy omitted in MRD-negative patients; molecular surveillance and delayed treatment in case of ctDNA emergence	iDFS and DRFS in MRD-negative patients
SIGNAL-ER 202 study (NCT07214532)	Phase 2, single arm (n = 725)	Adjuvant setting, ctDNA testing every 3 mo for up to 4 y	High-risk HR-positive and *ERBB2*-negative	Signatera Genome	Patients initiate ET and CDK4/6i if MRD-positive and ET alone if MRD-negative, with continued surveillance and delayed CDK4/6i initiation in case of molecular relapse	iDFS (compared with historical controls from NATALEE[56])
DARE (NCT04567420)	Phase 2, randomized (n = 100 for the intervention part)	Surveillance (ctDNA testing every 6 mo)	High-risk HR-positive/*ERBB2*-negative, 6 mo to 7 y receiving adjuvant ET	Signatera Exome	Randomization to fulvestrant-palbociclib or continuation of standard ET for 2 y	RFS
LEADER (part 2) (NCT03285412)	Phase 2, single-arm (n = 30 for the intervention part)	Surveillance (ctDNA testing at baseline, 6 mo, and 12 mo during surveillance at 3 mo, 6 mo, and 12 mo during intervention)	High-risk; HR-positive/*ERBB2*-negative, ≥1 y of adjuvant ET remaining	Signatera Exome	Addition of ribociclib to ongoing ET for 1 y	12-mo ctDNA clearance
MIRaDoR (NCT05708235)	Phase 2, multiarm, noncomparative (n = 1260 surveillance, n = 40 for each arm)	Surveillance (ctDNA testing every 3 mo for 1 y, then every 6 mo during surveillance; every 3 mo during intervention)	High-risk HR-positive/*ERBB2*-negative, receiving adjuvant ET for 2-4 y	Signatera Exome	Continuation of ET; giredestrant; giredestrant + abemaciclib; giredestrant + inavolisib	3-mo ctDNA decrease or clearance in each arm
TRAK-ER (NCT04985266)	Phase 2, randomized (n = 1100 surveillance, n = 132 randomized)	Surveillance (ctDNA testing every 3 mo during surveillance)	High-risk HR-positive/*ERBB2*-negative, up to 7 y receiving adjuvant ET	Invitae personalized cancer monitoring	Standard ET or palbociclib-fulvestrant for 24 mo	RFS
TREAT-ctDNA (NCT05512364)	Phase 3, randomized (n = 1960 surveillance; n = 220 intervention)	Surveillance (ctDNA testing every 6 mo during surveillance; at wk 4, wk 16, and every 4 mo during treatment)	High-risk, HR-positive/*ERBB2*-negative, 4.5 to 7 y receiving ET	Signatera Exome	Standard ET or elacestrant for 24 mo	Distant metastases-free survival

(continued)

3 months up to 1 year and then randomized to receive pembrolizumab or observation on detection of MRD using a tumor-informed digital PCR assay that tracked 1 to 2 variants.[46] The MRD detection rate by 12 months was 27% (44 of 161). Of the 32 MRD-

Table 3. Ongoing Clinical Trials Investigating the Clinical utility of Circulating Tumor DNA (ctDNA) in Early-Stage Breast Cancer (continued)

Study	Study design (sample size)	Setting	Population	MRD assay	Intervention	Primary end point
CATE (NCT06923527)	Phase 2, single-arm (n = 50)	Surveillance (ctDNA testing at screening and every 3 mo during intervention)	High-risk, HR-positive/*ERBB2*-negative, ≥5 y from diagnosis after completing adjuvant ET	NeXT Personal	Elacestrant for 1 y	ctDNA clearance
SURVIVE HERoes (NCT06643585)	Phase 2, randomized (n = 180)	Surveillance (ctDNA testing every 3 mo during intervention)	*ERBB2*-positive or *ERBB2*-low, MRD-positive (from the SURVIVE study)	RaDaR assay	Trastuzumab deruxtecan with or without ET or standard of care (ET with or without CDK4/6i or neratinib) for 12 mo	12-mo ctDNA clearance
SURVIVE (NCT05658172)	Phase 3, randomized, double-blinded (n = 3500)	Surveillance (ctDNA testing every 3 mo for the first 3 y, every 6 mo for the consecutive 2 y)	Intermediate-risk to high-risk breast cancer	RaDaR assay	Liquid biopsy specimen–based follow-up (ctDNA, CTCs, tumor markers) vs standard surveillance	OS; overall lead-time effect

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CTC, circulating tumor cells; DFS, disease-free survival; DRFS, distant recurrence-free survival; ET, endocrine therapy; HR, hormone receptor; iDFS, invasive disease-free survival; MRD, minimal residual disease; OS, overall survival; PET, positron emission tomography; RFS, recurrence-free survival; RT, radiotherapy; T-DM1, trastuzumab emtansine; TNBC, triple-negative breast cancer.

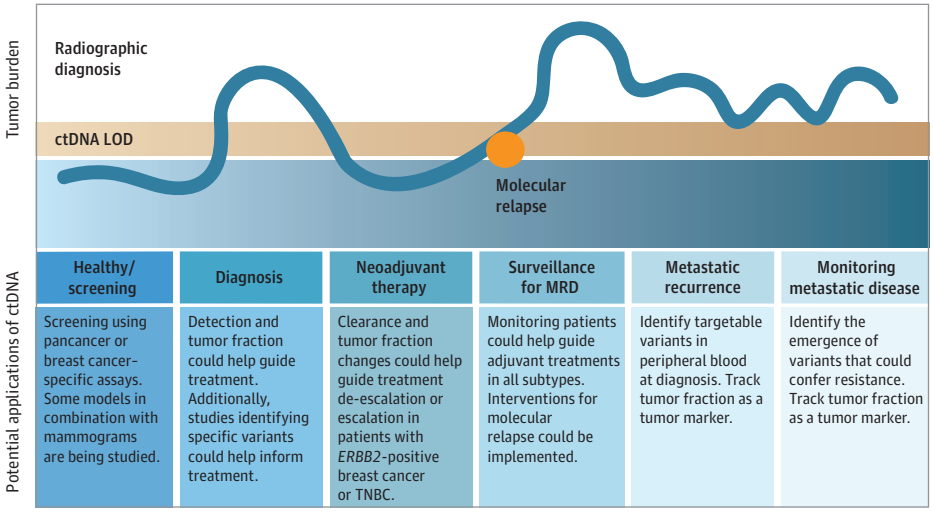
positive patients who were randomized to the intervention, 23 (72%) had imaging-confirmed metastatic disease at the time of MRD detection. Among patients without radiographic recurrence, 4 declined treatment with pembrolizumab and only 5 initiated treatment, none of whom achieved sustained MRD clearance. Given the few treated patients, the trial was ultimately noninformative for the efficacy end point.[46] However, cTRAK-TN highlighted several key challenges in MRD-guided trials that informed future studies, including the need for highly sensitive assays to maximize the lead time between molecular and clinical recurrence, importance of initiating MRD monitoring early in high-risk populations, and need to evaluate interventions with established activity in the adjuvant setting.

With a similar design, ZEST included a lower-risk population of patients with stage I to III TNBC or *BRCA1/2* pathogenic/likely pathogenic variant carriers with HR$^+$/*ERBB2*$^-$ tumors who were enrolled between 16 weeks and 5 years from the end of definitive therapy for TNBC and *BRCA1/2* carriers, respectively.[47] Participants underwent MRD surveillance with a tumor-informed assay every 2 to 3 months and were randomized 1:1 to treatment with niraparib or placebo on MRD detection. The trial was terminated early due to feasibility challenges, including a low ctDNA detection rate and a high rate of metastatic disease at the time of MRD detection. Of the 2746 prescreened patients, 147 (8%) were MRD-positive, and 49% already had radiographic recurrence at the time of ctDNA detection, leaving only 40 patients eligible for randomization.[47] Most of the MRD-positive results were detected at the earliest time point (≤6 months from the end of definitive therapy; 59.2% of cases), underscoring the importance of early testing. Furthermore, the high number needed to screen brought attention to the difficulty of conducting these trials in lower-risk populations. Although the low number of randomized patients limited the interpretation of efficacy, a numerical trend toward longer recurrence-free survival was observed with niraparib compared with placebo (median recurrence, 11.4 vs 5.4 months; hazard ratio, 0.64; 95% CI, 0.30-1.39). These findings underscore the importance of early MRD testing and logistical challenges of conducting MRD-guided intervention trials but suggest that this strategy might still be successful in preventing or delaying recurrences.[47]

Many other interventional studies of MRD tracking during surveillance are ongoing. Most of them include patients with HR$^+$/*ERBB2*$^-$ disease and test treatment intervention with CDK4/6i and/or novel endocrine agents (Table 2). In LEADER, which completed accrual, patients receiving adjuvant endocrine therapy underwent WES-informed MRD testing and, if positive, received ribociclib and an aromatase inhibitor for 12 months. Of the 162 patients who underwent screening, 140 had successful assay design, 15 tested positive (10.7%), and 10 initiated treatment. Of the 9 patients with available 3-month clearance data, 6 had molecular response, and 3 of them cleared. The median time to recurrence was longer for patients with MRD clearance (18.6 months) than patients with no clearance (7.2 months); additional follow-up is ongoing. In DARE, which includes MRD testing every 6 months, MRD-positive patients are randomized to receive treatment with fulvestrant plus palbociclib vs continuation of adjuvant therapy placebo for 2 years. Initial results showed an MRD detection rate of 8.9%, and 71% of positive patients had no evidence of metastatic disease. The last study update reported a higher 3-month clearance rate in the experimental arm (56.3%) compared with the control arm (25%). One of 9 patients with MRD clearance experienced relapse compared with 6 of 10 patients with MRD increase.[48] The 29% rate of metastatic relapse at the time of ctDNA detection reported by DARE was substantially lower than the 50% reported with the same assay by the ZEST study, in which 90% of patients had TNBC. This aligns with the different biology of luminallike and TNBC and highlights how the window for intervention is likely longer for more indolent tumors, whereas for more aggressive subtypes it is unclear whether molecular-only relapse could be successfully treated.

Another way to establish the clinical utility of MRD surveillance is to test its implementation in follow-up beyond specific interventions. In the large phase 3 SURVIVE study (NCT05658172), 3500 patients with intermediate-risk to high-risk breast cancer are randomized to standard follow-up or a liquid biopsy specimen–based follow-up tracking ctDNA via WES-based test, circulating tumor cells, and tumor markers. The primary end point is overall survival. If positive, this study will establish the clinical utility of MRD tracking during surveillance, regardless of specific treatment interventions prompted by MRD detection.

Figure 2. Schema for Potential Applications of Circulating Tumor DNA (ctDNA) Testing in Breast Cancer



LOD indicates limit of detection; MRD, minimal residual disease; TNBC, triple-negative breast cancer.

Conclusions

The use of ctDNA MRD assays for patients with early breast cancer remains investigational, but accumulating evidence suggests that they may complement standard care by refining risk stratification, monitoring response, and detecting molecular relapse before clinical recurrence. Potential applications of MRD testing are shown in Figure 2.

Across studies, MRD status is a strong and consistent prognostic marker, but clinical utility must be established before routine use. In the neoadjuvant setting, ctDNA clearance is associated with long-term outcomes across subtypes and pCR in TNBC. Among patients with residual disease after NAT, MRD further refines recurrence risk. These data support trials testing ctDNA-guided escalation or de-escalation strategies, although ctDNA clearance has not yet been prospectively validated as a surrogate end point. Such studies should include robust time-to-event outcomes. Postoperatively, MRD positivity identifies a population at high risk of recurrence and represents a rational target for escalation trials. In the surveillance setting, the promise of early detection of molecular relapse is tempered by high numbers needed to screen, uncertain lead-time benefit, and unanswered questions about optimal timing, overlap with scan-detectable metastatic disease, frequency, and the potential harm of early intervention.

Although ctDNA MRD assays are available in the US, several caveats should be considered before use in routine practice. Liquid biopsies introduce additional costs and potential out-of-pocket expenses for patients. Positive results may lead to additional testing, patient anxiety, and potential exposure to unnecessary therapies. Early initiation of treatment in asymptomatic patients may not only negatively affect quality of life but also limit future treatment options and potentially lead to clonal selection of aggressive, treatment-resistant clones with a detrimental association with survival.

Across all settings, education of patients and clinicians is essential, as assays differ in performance and should not be used interchangeably. Until clinical utility is proven, ctDNA testing for MRD detection should be reserved for prospective registries and well-designed clinical trials, with clear, predefined interventions based on positive or negative results. Careful attention to patient understanding and preferences, psychological effects, and downstream consequences is crucial. With continued work, ctDNA has the potential to meaningfully advance personalized care in early breast cancer.

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