Section: General Surgery

Systematic Review

MINIMAL RESIDUAL DISEASE DETECTION USING CIRCULATING TUMOR DNA AFTER CURATIVE TREATMENT OF BREAST CANCER: A SYSTEMATIC REVIEW AND EVIDENCE UPDATE

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ABSTRACT

Background: Circulating tumor DNA (ctDNA) can identify molecular residual disease (MRD) after apparently curative treatment of early breast cancer and may anticipate recurrence before conventional clinical or radiological detection. Rapid assay development has strengthened prognostic validity, but whether ctDNA-directed management improves outcomes remains uncertain. **Objective:** To synthesize contemporary evidence on post-treatment ctDNA MRD in non-metastatic breast cancer, including diagnostic performance, prognostic value, molecular lead time, assay strategy, subtype-specific limitations, and clinical utility. **Materials and Methods:** A systematic evidence-update approach was used. Primary studies from recent comprehensive breast-cancer ctDNA systematic reviews and meta-analyses were reassessed against prespecified eligibility criteria, and a focused PubMed/MEDLINE update captured peer-reviewed evidence published after the latest prior diagnostic search through 28 August 2026. Eligible studies enrolled patients with stage I-III breast cancer treated with curative intent and measured ctDNA after neoadjuvant therapy, surgery, completion of systemic therapy, or during surveillance. Diagnostic studies were interpreted using QUADAS-2 domains and prognostic studies using QUIPS domains. Owing to substantial clinical and methodological heterogeneity, findings were synthesized narratively rather than re-pooled. **Results:** Post-treatment ctDNA positivity was consistently associated with substantially increased recurrence risk. A 2026 diagnostic meta-analysis reported pooled sensitivity/specificity of 0.40/0.95 for single-landmark testing and 0.79/0.98 for serial surveillance. A separate 2026 prognostic meta-analysis of 18 prospective studies (1,670 patients) found ctDNA positivity associated with shorter disease-free survival (pooled hazard ratio 6.92). Longitudinal tumor-informed studies commonly detected molecular relapse months before clinical recurrence. Recent 2025-2026 studies, including PRE-DICT and ALIENOR, further support the prognostic value of ultrasensitive postoperative and serial testing, while c-TRAK TN illustrates that molecular detection does not always create an actionable treatment window. **Conclusions:** ctDNA MRD after curative treatment has strong prognostic validity and high specificity, and serial testing improves sensitivity compared with a single landmark measurement. Clinical utility remains unproven: no definitive randomized evidence shows that systemic therapy initiated solely because of ctDNA positivity improves survival. ctDNA should therefore complement, not replace, standard surveillance and should preferentially be used in clinical trials or settings with an established evidence-based action.

INTRODUCTION

Breast cancer is a biologically heterogeneous disease for which modern surgery, radiotherapy, endocrine therapy, chemotherapy, anti-HER2 treatment, immunotherapy, and targeted agents cure a large proportion of patients with stage I-III disease. Nevertheless, recurrence remains a major cause of breast-cancer mortality. Conventional post-treatment assessment can document the absence of macroscopic disease but cannot directly determine whether microscopic malignant clones persist. Clinicopathologic variables and genomic-expression assays estimate recurrence probability at a population level; molecular residual disease testing seeks direct evidence of persisting tumor material in an individual patient.

Circulating tumor DNA is the tumor-derived fraction of cell-free DNA released into the bloodstream. Tumor-specific genomic alterations can be measured in plasma and used as individualized markers of residual malignancy. In the MRD setting, where tumor burden is extremely low, analytical sensitivity and specificity are particularly demanding; detectability varies with tumor biology, metastatic site, plasma volume, assay design, and sampling frequency. Early personalized mutation-tracking studies established that postoperative and surveillance ctDNA could anticipate metastatic relapse months before conventional detection.[1-3]

Subsequent evidence broadened clinical validity across residual triple-negative breast cancer (TNBC), ctDNA-triggered surveillance, and long-term postoperative monitoring.[4-6] Studies in neoadjuvant-treated disease, late hormone-receptor-positive/HER2-negative recurrence, and ultrasensitive postoperative testing further demonstrated subtype- and timing-dependent prognostic value.[7-9] More recent longitudinal and perioperative studies, including personalized monitoring, real-world tumor-informed testing, IMpassion031, and ALIENOR, have extended these observations.[10-13] In residual TNBC, ctDNA has also provided prognostic information alongside residual cancer burden and pathologic response.[14,15] Contemporary systematic reviews and meta-analyses now quantify the prognostic and diagnostic signal across diverse studies.[16-18]

The translational question, however, has changed. It is no longer sufficient to show that ctDNA predicts recurrence. A clinically useful MRD program must detect relapse early enough to create an actionable window, minimize false-negative and false-positive results, define what a positive or negative result means for each breast-cancer subtype, and, most importantly, link the result to an intervention that improves meaningful outcomes. Current ESMO and ASCO guidance emphasizes the distinction between clinical validity and proven clinical utility and does not support routine ctDNA-directed treatment or surveillance outside evidence-based settings.[19,20]

This systematic review and evidence update synthesizes post-treatment ctDNA MRD evidence after curative-intent treatment of breast cancer. It evaluates landmark versus serial strategies, tumor-informed versus plasma-only approaches, subtype- and site-specific performance, molecular lead time, prognostic associations, interventional evidence, and current professional guidance.

MATERIALS AND METHODS

2.1 Review design and reporting framework

This review was designed as a systematic evidence update and is reported with reference to applicable PRISMA 2020 principles. Because comprehensive breast-cancer ctDNA meta-analyses were published in 2024 and 2026, the historical evidence base was constructed by reassessing primary studies captured by those reviews and then extending the literature with a focused update through 28 August 2026. This approach avoids unnecessary duplication of recently completed multi-database searches while making the update method explicit. It should be distinguished from a fully de novo re-screening of every bibliographic database.

2.2 Eligibility criteria

Population: adults with stage I-III/non-metastatic invasive breast cancer receiving curative-intent treatment.

Index exposure/test: plasma ctDNA assessed after neoadjuvant therapy, after definitive surgery, after completion of adjuvant treatment, or longitudinally during post-treatment surveillance.

Eligible designs: prospective cohorts, retrospective biomarker analyses of prospectively collected samples, diagnostic-accuracy studies, clinical trials incorporating ctDNA MRD, and ctDNA-triggered intervention studies.

Outcomes: recurrence, distant recurrence, disease-free/relapse-free survival, distant disease-free survival, overall survival, sensitivity, specificity, positive/negative predictive value, and lead time from ctDNA detection to clinical or radiological recurrence.

Exclusions: metastatic-disease-only cohorts, baseline ctDNA without a post-treatment measurement, studies restricted to circulating tumor cells without ctDNA, non-human studies, single case reports, and non-peer-reviewed reports used as the sole evidence for a principal conclusion.

2.3 Information sources and search strategy

The historical evidence set was cross-checked against eligible primary studies reported in the 2024 systematic review/meta-analysis of operable breast cancer and the 2026 diagnostic and prognostic meta-analyses. These reviews searched combinations of PubMed/MEDLINE, Embase, CENTRAL/Cochrane, Scopus, Web of Science, Ovid MEDLINE, and related bibliographic sources over their respective search periods. A focused PubMed/MEDLINE update was then used to identify

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peer-reviewed reports published after the latest diagnostic-search cutoff (17 April 2025) through 28 August 2026. Search terms combined breast cancer with circulating tumor DNA/ctDNA and minimal or molecular residual disease, recurrence, relapse, postoperative, post-neoadjuvant, adjuvant, follow-up, and surveillance concepts. Reference lists of eligible new studies and major contemporary reviews were also checked. The reproducible PubMed update strategy is provided in Supplementary Appendix 1.

2.4 Study selection and data extraction

Primary-study reports were assessed against the prespecified criteria. Companion publications from the same cohort were linked to reduce double counting; the most mature or clinically informative report was prioritized for a given outcome, while companion reports were retained when they supplied distinct assay, treatment-response, or follow-up information. Extracted variables included study design, population and subtype, sample size, treatment setting, ctDNA assay, tumor-informed status, sampling time, recurrence events, sensitivity/specificity where reported, survival associations, lead time, and whether ctDNA results were used to direct treatment.

2.5 Risk of bias and applicability

Diagnostic-accuracy evidence was interpreted using QUADAS-2 domains (patient selection, index test, reference standard, and flow/timing), and prognostic-factor evidence using QUIPS domains (study participation, attrition, prognostic-factor measurement, outcome measurement, confounding, and analysis/reporting). Particular attention was paid to high-risk enrichment, retrospective biomarker analysis, assay threshold selection, incomplete longitudinal sampling, differential imaging after ctDNA detection, sparse events, short follow-up for hormone-receptor-positive disease, and overlapping cohorts. Formal numeric quality scores were not used; Table 3 summarizes study-level concerns qualitatively.

2.6 Evidence synthesis

A narrative synthesis was prespecified because assays, sampling schedules, disease subtypes, endpoint definitions, and treatment contexts varied substantially. No de novo pooled analysis was performed; contemporary meta-analytic estimates were used when they directly addressed diagnostic performance or prognosis, and newer primary studies were interpreted alongside those pooled estimates. Clinical utility was assessed separately from prognostic validity.

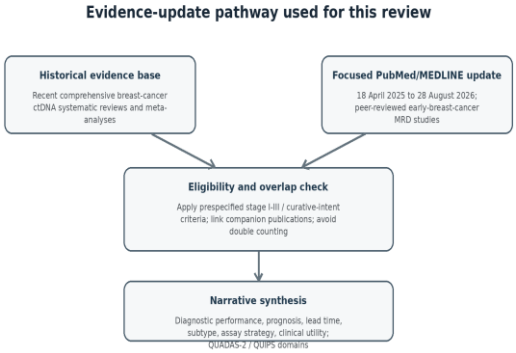

Figure 1: Evidence-update pathway. Because this review is anchored to recently completed systematic reviews and extends them with a focused update, the figure shows the evidence-update process rather than reconstructing a de novo record-level PRISMA flow for the historical literature

RESULTS

3.1 Characteristics of the evidence base

The evidence base spans early personalized digital-PCR studies, tumor-informed next-generation sequencing, whole-genome- and structural-variant-informed approaches, plasma-only assays, and longitudinal surveillance cohorts. The 2024 systematic review/meta-analysis included 57 studies (5,779 patients), while the 2026 diagnostic and prognostic meta-analyses included 17 and 18 studies, respectively. The focused update captured clinically important recent reports including long-term personalized monitoring, a real-world tumor-informed neoadjuvant cohort, the IMpassion031 ctDNA analysis, PRE-DICT, and the ALIENOR multicenter surveillance study. Most evidence remains observational or prospective-retrospective biomarker analysis rather than randomized ctDNA-guided intervention. Key primary studies are summarized in Table 1.

Table 1: Major primary studies informing post-treatment ctDNA MRD in early breast cancer

Study	Population	ctDNA strategy/timing	Principal finding	Interpretation
Garcia-Murillas et al., 2015	55 high-risk early BC	Personalized mutation tracking; postoperative and serial	Postsurgical ctDNA strongly predicted metastatic relapse; serial testing produced a median lead time of 7.9 months.	Proof of concept for molecular relapse.
Garcia-Murillas et al., 2019	101-patient prospective validation (144 combined)	Personalized dPCR; serial follow-up	Follow-up ctDNA strongly predicted relapse; median lead time 10.7 months; extracranial distant relapses were usually detected before clinical recurrence.	Validated prognostic value and site-specific limitations.
Coombes et al., 2019	49 treated primary BC	Personalized tumor-informed serial assay	16/18 relapses detected; sensitivity 89%, specificity	High specificity with clinically

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			100%; median lead time 8.9 months.	meaningful lead time.
Radovich et al., 2020	Residual TNBC after neoadjuvant chemotherapy	Post-neoadjuvant/postoperative plasma sequencing	ctDNA positivity was associated with inferior distant disease-free, disease-free, and overall survival.	Strong prognostic value in residual TNBC.
Magbanua et al., 2021	84 high-risk neoadjuvant-treated BC	Tumor-informed serial testing during and after NAC	All patients achieving pCR were ctDNA-negative after NAC; persistent ctDNA in non-pCR disease was associated with metastatic recurrence.	ctDNA dynamics complement pathologic response.
Lipsyc-Sharf et al., 2022	103 high-risk HR+/HER2- survivors >5 years from diagnosis	Tumor-informed testing every 6-12 months	All six distant recurrences were preceded by MRD positivity; median lead time 12.4 months.	Supports late molecular relapse detection in HR+ disease.
Turner et al., c-TRAK TN, 2023	161 entered TNBC surveillance	Prospective ctDNA-triggered intervention	ctDNA detected in 44 by 12 months; 72% of intervention-pathway patients with staging information already had metastases; only five started pembrolizumab.	Shows the gap between detection and actionable interception.
Stecklein et al., 2023	80 TNBC patients with residual disease	End-of-treatment ctDNA plus RCB	ctDNA positivity (33%) was independently associated with inferior 3-year EFS and OS.	ctDNA adds prognostic information beyond residual disease burden.
Shaw et al., 2024	156 primary BC; 34 relapses	Tumor-informed semiannual surveillance	30/34 relapses detected before clinical/radiological relapse; median lead time 10.5 months, up to 38 months.	Long-term serial surveillance has strong prognostic performance.
Garcia-Murillas et al., 2025	61 high-risk BC	Tumor-informed PCM assay; serial monitoring	Monitoring sensitivity 76.9% among relapsing patients; specificity and PPV 100%; median lead time 11.7 months.	Independent validation of personalized serial monitoring.
Elliott et al., 2025	114 patients receiving neoadjuvant therapy	Highly sensitive tumor-informed assay; longitudinal	Postoperative or follow-up ctDNA detection had 100% PPV for recurrence; median lead time 374 days.	Supports high-sensitivity longitudinal testing in real-world care.
Mittendorf et al., 2025	333 stage II/III TNBC in IMpassion031	Exploratory perioperative ctDNA analysis	Most patients cleared ctDNA by surgery; ctDNA positivity at surgery identified the poorest-prognosis subset among non-pCR patients.	ctDNA provides prognostic information beyond pCR.
Hunter et al., PRE-DICT, 2026	220 evaluable HER2-positive or TNBC	Ultrasensitive tumor-informed post-NAT and postoperative testing	Postoperative ctDNA strongly stratified invasive disease-free survival and was more prognostic than post-NAT response classification alone.	Supports ultrasensitive postoperative risk stratification.
Blaye et al., ALIENOR, 2026	83 patients after non-pCR to NAC; 473 plasma samples	Structural-variant-informed personalized ddPCR surveillance	25/27 recurrences were ctDNA-detected (sensitivity 92.6%); median lead time 13.9 months, with subtype-dependent lead time.	Multicenter evidence for ultrasensitive longitudinal surveillance.

Abbreviations: BC, breast cancer; ctDNA, circulating tumor DNA; dPCR, digital polymerase chain reaction; EFS, event-free survival; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor positive; MRD, molecular/minimal residual disease; NAC/NAT, neoadjuvant chemotherapy/therapy; pCR, pathologic complete response; PPV, positive predictive value; RCB, residual cancer burden; TNBC, triple-negative breast cancer.

3.2 Diagnostic performance: landmark versus serial surveillance

Timing is a major determinant of diagnostic performance. A single landmark sample after treatment can identify persistent molecular disease but may miss biologically present MRD when the number of tumor-derived molecules in the sampled plasma volume is below the assay detection threshold. Serial surveillance provides repeated opportunities for detection as residual disease expands.

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In the 2026 diagnostic meta-analysis by You and colleagues, 17 studies of postoperative MRD were included. Pooled sensitivity for landmark testing was 0.40 (95% CI 0.22-0.62) with specificity 0.95 (95% CI 0.81-0.99). For serial surveillance, pooled sensitivity increased to 0.79 (95% CI 0.71-0.85) while specificity remained very high at 0.98 (95% CI 0.92-0.99). The analysis therefore supports repeated surveillance as a more sensitive strategy than one-time landmark testing, while preserving high specificity.

The clinical implication is asymmetric. A positive postoperative result is usually highly informative, but a negative single-time-point result has limited ability to exclude residual disease. Serial negativity is more reassuring than a single negative result, although its meaning still depends on assay sensitivity, follow-up duration, disease subtype, and metastatic site.

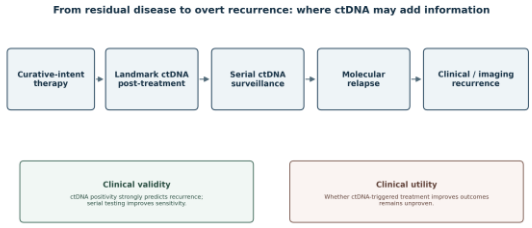

Figure 2: Conceptual position of ctDNA MRD testing after curative treatment. A molecular lead-time window may exist between completion of therapy and clinically evident recurrence. Clinical validity is well established; clinical utility requires proof that intervention within this window improves outcomes

3.3 Prognostic value

The prognostic association between post-treatment ctDNA and recurrence is among the most reproducible findings in the field. The 2024 systematic review and meta-analysis by Nader-Marta et al. included 57 studies (5,779 patients) and found worse disease-free and overall survival when ctDNA was detected, with stronger associations after treatment and with tumor-informed assays. Across included studies, recurrence-detection sensitivity varied widely, whereas specificity was generally high and the mean reported lead time was approximately 10.8 months.

A 2026 meta-analysis focused specifically on early breast-cancer prognosis and included 18 prospective studies comprising 1,670 patients. ctDNA positivity was associated with markedly shorter disease-free survival (pooled HR 6.92; 95% CI 3.64-13.13), although heterogeneity was substantial. More recent primary studies continue to show strong prognostic separation with postoperative or serial ctDNA, including personalized monitoring, highly sensitive real-world tumor-informed testing, PRE-DICT, and ALIENOR.

In TNBC, end-of-treatment ctDNA adds prognostic information to residual cancer burden and pathologic response. Stecklein et al. reported inferior 3-year EFS and OS among ctDNA-positive patients with residual TNBC, while the TBCRC 030 analysis linked end-of-neoadjuvant ctDNA clearance to lower residual cancer burden. IMpassion031 similarly found that ctDNA positivity at surgery identified a particularly poor-prognosis subset among non-pCR patients.

3.4 Molecular lead time and recurrence site

Lead time—the interval between first ctDNA positivity and conventional recurrence—is a major rationale for MRD surveillance. Foundational prospective studies reported median lead times of approximately 8-11 months. Shaw et al. reported a median lead time of 10.5 months, Garcia-Murillas et al. reported 11.7 months with a later personalized assay, Lipsyc-Sharf et al. reported 12.4 months in late HR+/HER2- recurrence, and ALIENOR reported a median of 13.9 months overall. Elliott et al. reported a median lead time of 374 days in a real-world tumor-informed cohort.

Long lead time does not necessarily imply better outcomes. Lead-time bias can make recurrence appear to be diagnosed earlier without changing the biological course unless an effective intervention is delivered during that interval. Moreover, a more sensitive assay or more frequent sampling can move the molecular-detection point earlier even when the date of clinical recurrence is unchanged.

Recurrence site affects sensitivity. In the 2019 validation cohort, 22 of 23 extracranial distant relapses were preceded by ctDNA detection, whereas only 1 of 6 brain-only recurrences was detected. Low-shedding locoregional recurrence may also be missed. ctDNA therefore cannot replace clinical assessment or site-appropriate imaging when symptoms or findings warrant evaluation.

3.5 Breast-cancer subtype

3.5.1 Triple-negative breast cancer

TNBC is attractive for molecular interception because relapse risk is front-loaded and post-neoadjuvant systemic options exist. Radovich et al. showed that ctDNA after neoadjuvant therapy/surgery in patients with residual TNBC was associated with inferior distant disease-free, disease-free, and overall survival. End-of-treatment ctDNA and residual cancer burden provide complementary prognostic information, and persistent ctDNA during neoadjuvant therapy is associated with poor response. IMpassion031 adds randomized-trial context by showing that surgical ctDNA status provides prognostic information beyond pCR. However, c-TRAK TN demonstrates that rapid disease kinetics can erode the intervention window because many ctDNA-positive patients already had radiologically detectable metastases when molecular relapse was identified.

3.5.2 Hormone receptor-positive/HER2-negative disease

HR+/HER2- breast cancer poses a different problem: recurrence can occur many years after primary therapy, and dormant low-volume disease may shed little ctDNA. Long-term surveillance studies show that molecular relapse can be detected well before

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clinical recurrence in some patients. In the late-adjuvant prospective cohort reported by Lipsyc-Sharf et al., all six distant recurrences were preceded by MRD positivity, with a median lead time of 12.4 months, but two MRD-positive patients had not recurred at last follow-up. ALIENOR reported a longer median lead time in ER-positive/HER2-negative disease than in TNBC, reinforcing the importance of subtype-specific disease kinetics.

3.5.3 HER2-positive disease

HER2-positive disease has high cure rates with contemporary HER2-directed therapy, making positive predictive value and overtreatment especially important. PRE-DICT included HER2-positive and TNBC populations and demonstrated that postoperative ctDNA was strongly prognostic, while post-neoadjuvant ctDNA alone was not an adequate surrogate for pathological complete response. ALIENOR also showed molecular lead time in HER2-positive disease, but clinical utility still requires prospective treatment-interception evidence.

3.6 Tumor-informed, whole-genome-informed, structural-variant, and plasma-only assays

Tumor-informed assays first characterize the patient's tumor and then track a personalized set of alterations in plasma. This improves specificity and can increase sensitivity by aggregating evidence across multiple private variants. Limitations include dependence on tissue, assay-development time, cost, and the possibility that the sampled primary tumor does not fully represent later clonal evolution.

Newer ultrasensitive approaches broaden the number or type of patient-specific markers. PRE-DICT illustrates high-sensitivity postoperative assessment, TBCRC 030 used a large personalized mutation set, and ALIENOR used structural-variant-informed digital PCR. Highly sensitive tumor-informed real-world testing also demonstrated 100% positive predictive value for postoperative/follow-up positivity in the Elliott cohort. These approaches require prospective evaluation under real-world clinical-use conditions because retrospective analysis of banked serial samples can overestimate completeness of sampling and follow-up.

Plasma-only strategies avoid the requirement for tumor tissue and may integrate sequence, methylation, fragmentation, or other molecular signals. They may improve scalability, but rigorous control of clonal hematopoiesis, technical error, and false-positive results is essential when expected tumor fraction is extremely low. At present, the most mature post-treatment breast-cancer MRD evidence remains concentrated in tumor-informed or highly personalized strategies.

3.7 Clinical utility and ctDNA-guided intervention

Clinical validity asks whether a biomarker predicts an outcome; clinical utility asks whether using that biomarker to make a decision improves patient outcomes compared with standard care. Most breast-cancer MRD evidence addresses the first question, not the second.

c-TRAK TN remains the clearest demonstration of the implementation challenge. Of 161 patients who entered surveillance, ctDNA was detected in 44 by 12 months. Among patients allocated to the intervention pathway with staging information, 72% already had radiologically detectable metastatic disease when molecular relapse was identified, and only five ultimately started pembrolizumab. The trial does not show that surveillance is intrinsically ineffective; it shows that assay sensitivity, sampling frequency, disease kinetics, staging procedures, and access to a rapidly deployable therapy jointly determine whether molecular relapse is actionable.

PRE-DICT, ALIENOR, IMpassion031, and recent longitudinal cohorts strengthen risk stratification but do not establish that ctDNA-triggered treatment improves survival. The decisive evidence will require randomized molecular-interception trials enrolling ctDNA-positive, imaging-negative patients and testing an effective intervention against an appropriate control, with clinically meaningful outcomes such as invasive disease-free or distant recurrence-free survival.

Table 2: Pooled evidence and current professional guidance

Source	Evidence base	Question	Key finding	Clinical meaning
Nader-Marta et al., 2024	57 studies; 5,779 patients	Operable BC prognosis	ctDNA detection associated with worse DFS and OS; associations stronger after treatment and with tumor-informed assays.	Strong prognostic validity with substantial heterogeneity.
You et al., 2026	17 diagnostic studies	Postoperative recurrence detection	Landmark sensitivity/specificity 0.40/0.95; surveillance 0.79/0.98.	Serial testing improves sensitivity while preserving high specificity.
Sisca et al., 2026	18 prospective studies; 1,670 patients	Prognosis in early BC	ctDNA positivity associated with shorter DFS; pooled HR 6.92 (95% CI 3.64-13.13).	Large adverse prognostic association; heterogeneity remains.
ESMO Precision Medicine Working Group, 2022	Expert recommendations	MRD/molecular relapse across cancers	High clinical validity acknowledged, but routine MRD-directed management not recommended without proven clinical utility.	Clinical validity is not equivalent to treatment utility.

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ASCO breast-cancer surveillance guideline, 2026	Evidence-based guideline / consensus	Follow-up after primary treatment	History, physical examination, and mammography remain core; ctDNA cannot be recommended generally for recurrence monitoring outside research.	ctDNA should not replace standard surveillance.

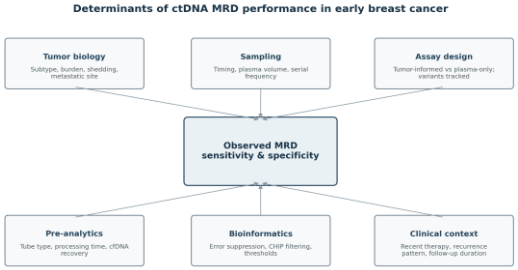

Figure 3: Major determinants of ctDNA MRD performance after curative breast-cancer treatment. Sensitivity and interpretation depend jointly on disease biology, sample characteristics, assay design, bioinformatics, and surveillance schedule

3.8 Risk-of-bias and applicability considerations

Across the key studies, the most common concerns were small event numbers, enrichment for high-risk disease, retrospective ctDNA analysis of prospectively collected samples, incomplete or variable serial sampling, and limited follow-up for late-recurrence phenotypes. Highly personalized assays generally reduced false-positive concern, but their dependence on tumor tissue and specialized workflows can limit applicability. Table 3 summarizes the principal study-level concerns using QUADAS-2/QUIPS concepts.

Table 3: Qualitative risk-of-bias and applicability considerations for key post-treatment studies

Study	Selection / applicability	Measurement / follow-up	Overall concern and main limitation
Garcia-Murillas 2015	Moderate: small, high-risk cohort	Low-moderate: personalized serial tracking	Moderate; proof-of-concept sample size and event count.
Garcia-Murillas 2019	Moderate: selected prospective cohort	Low-moderate: validated serial assay; site-specific false negatives	Moderate; brain-only recurrence sensitivity limited.
Coombes 2019	Moderate: small treated cohort	Low: personalized serial assay; long lead-time assessment	Moderate; limited sample and recurrence numbers.
Radovich 2020	Moderate: residual TNBC enrichment	Moderate: biomarker analysis within trial-derived cohort	Moderate; high-risk selected population limits generalizability.
Lipsyc-Sharf 2022	Moderate: high-risk HR+ survivors >5 years	Moderate: sparse recurrence events; serial testing	Moderate; small number of late metastatic recurrences.
c-TRAK TN 2023	Moderate: high-risk TNBC surveillance	Moderate: staging after ctDNA positivity affected implementation	Moderate; rapid disease kinetics and limited intervention exposure.
Shaw 2024	Moderate: selected long-term cohort	Moderate: retrospective assay of prospectively collected samples	Moderate; retrospective biomarker testing and subtype imbalance.
Garcia-Murillas 2025	Moderate: 61 high-risk patients	Low-moderate: tumor-informed serial PCM	Moderate; small relapse count and assay-specific applicability.
Elliott 2025	Moderate: real-world neoadjuvant cohort	Moderate: longitudinal high-sensitivity assay; follow-up still maturing	Moderate; nonrandomized and heterogeneous treatment context.
IMpassion031 ctDNA 2025	Low-moderate: randomized-trial population	Moderate: exploratory biomarker analysis	Moderate; ctDNA was exploratory and not used to guide therapy.
PRE-DICT 2026	Moderate: high-risk HER2+/TNBC	Low-moderate: ultrasensitive postoperative assay	Moderate; high-risk population and no ctDNA-guided intervention.
ALIENOR 2026	Moderate: non-pCR post-NAC population	Low-moderate: multicenter serial structural-variant assay	Moderate; enriched high-risk cohort and assay-specific workflow.

Note: These are qualitative domain-based judgments from published study characteristics, not numeric quality scores. No study was excluded solely on the basis of an overall qualitative concern.

DISCUSSION

4.1 Principal findings

This evidence update supports a progressive development from proof-of-concept molecular relapse detection to increasingly sensitive postoperative and longitudinal surveillance. Foundational personalized studies established that ctDNA can precede clinical recurrence by several months.[1-3] Subsequent work in residual TNBC, the c-TRAK TN intervention framework, and long-term serial surveillance confirmed strong prognostic validity while also exposing limits to actionable interception.[4-6]

Newer investigations have extended the evidence across neoadjuvant-treated disease, late hormone-receptor-positive/HER2-negative recurrence, and ultrasensitive postoperative assessment.[7-9] Recent 2025-2026 studies using personalized mutation panels, high-sensitivity tumor-informed assays, perioperative ctDNA analysis, and structural-variant tracking further support the value of longitudinal molecular monitoring.[10-13] In TNBC, end-of-treatment ctDNA and residual cancer burden provide

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complementary prognostic information, reinforcing the need to interpret ctDNA within pathologic response and disease context.[14,15]

These individual studies are consistent with contemporary pooled evidence: post-treatment ctDNA positivity is associated with substantially increased recurrence risk, serial surveillance improves sensitivity compared with a single landmark measurement, and the overall prognostic association remains strong despite substantial heterogeneity.[16-18] The central unresolved issue is therefore clinical utility rather than clinical validity.

4.2 How should a positive result be interpreted?

Because specificity is generally high, repeated detection of patient-specific ctDNA after curative treatment should be regarded as strong evidence of biologically active residual disease, particularly when multiple tumor-informed markers are used and pre-analytic quality is adequate. The clinical response, however, is not automatically "start systemic therapy." Confirmation, assessment for radiologically detectable disease, review of assay characteristics, and, where available, clinical-trial enrollment are appropriate. Therapeutic action should be supported by evidence for the relevant disease context rather than by prognostic information alone.

4.3 How should a negative result be interpreted?

A negative result means ctDNA was not detected in the analyzed plasma with the specific assay at that time; it does not prove the absence of residual malignant cells. A single negative landmark result is particularly limited because a one-time blood sample may miss very low-level molecular disease. Repeated negativity is more reassuring, but interpretation depends on follow-up duration, subtype, assay sensitivity, and recurrence site. This asymmetry - high confidence in many positive results but incomplete reassurance from a negative result - is central to safe clinical communication.

4.4 Current guideline position

ESMO recommendations distinguish the strong clinical validity of molecular residual disease/molecular relapse detection from the absence of proven clinical utility for routine MRD-directed treatment.[19] The 2026 ASCO breast-cancer surveillance guideline is similarly explicit: standard surveillance remains centered on history, physical examination, and mammography, and ctDNA testing cannot currently be recommended generally for recurrence monitoring outside clinical trials or research.[20]

Current professional guidance is therefore consistent with the evidence synthesized here: ctDNA MRD is highly promising and prognostically informative, but standard surveillance should not yet be replaced by molecular testing, and treatment decisions based solely on ctDNA positivity require prospective evidence of clinical benefit.

4.5 Implications for future trial design

Sampling should begin early enough after definitive treatment to identify molecular relapse before macroscopic disease becomes established, while avoiding perioperative periods in which high background cell-free DNA may reduce analytical sensitivity.

Surveillance frequency should reflect disease kinetics: rapidly relapsing TNBC may require shorter intervals than indolent hormone-receptor-positive disease, and subtype-specific lead-time data should inform schedules.

Assays should report plasma volume, number and type of variants tracked, analytical limit of detection, positivity rules, handling of clonal hematopoiesis, and treatment of indeterminate results.

Interventional trials should specify whether ctDNA positivity requires confirmation, how rapidly imaging and treatment are initiated, and whether ctDNA clearance is an exploratory pharmacodynamic endpoint rather than an assumed surrogate for survival.

Patient-reported outcomes should measure anxiety, reassurance, decisional conflict, and the burden of living with a molecular diagnosis before radiological disease is visible.

Health-economic analyses should account for repeated blood sampling, sequencing, confirmatory imaging, false-negative consequences, false-positive or unconfirmed signals, and downstream treatment.

4.6 Strengths and limitations

A strength of this review is its focus on the post-curative MRD question rather than combining early-disease surveillance with metastatic genotyping. It integrates foundational cohorts with 2025-2026 evidence, separates diagnostic performance from prognostic association, distinguishes clinical validity from clinical utility, and places the evidence within current ESMO and ASCO guidance.

Limitations arise from both the underlying literature and the review design. Primary studies are heterogeneous in assay platform, sampling timing, subtype, treatment exposure, positivity definition, recurrence endpoint, and follow-up duration. Several reports analyze archived specimens from prospective cohorts, some publications use overlapping patient sets, and high-risk enrichment may inflate positive predictive value compared with a general early-breast-cancer population. Very long follow-up is required to establish the meaning of persistent negativity in hormone-receptor-positive disease, while site-specific false negatives, particularly brain-only relapse, remain a concern.

This manuscript is a systematic evidence update anchored to recently completed comprehensive reviews plus a focused PubMed/MEDLINE update; it is not a completely de novo multi-database rerun performed by the present author group. Accordingly, a record-level PRISMA flow for the historical literature is not reconstructed. A future fully de novo update with a new multi-database search, duplicate independent screening, prospective protocol registration, and a complete record-level PRISMA flow would further strengthen methodological

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reporting and may be required by some target journals.

CONCLUSION

ctDNA-based MRD detection after curative treatment of breast cancer has progressed from proof of concept to robust clinical validity. Post-treatment positivity is consistently associated with a substantially increased risk of recurrence, and serial surveillance improves sensitivity compared with one-time landmark testing while maintaining very high specificity. Increasingly sensitive tumor-informed and structural-variant-informed approaches are extending the ability to detect molecular relapse before conventional recurrence.

The remaining barrier to routine use is not whether ctDNA can forecast relapse, but whether acting on molecular relapse improves outcomes. A lead-time window has value only if it enables a treatment that prevents or meaningfully delays overt metastatic disease. Until randomized molecular-interception trials establish that benefit, ctDNA should complement rather than replace standard surveillance, and treatment decisions based solely on MRD positivity should preferentially occur in clinical trials or settings with an evidence-based therapeutic action.

6. Declarations

6.1 Ethics approval

Not applicable. This review synthesizes published aggregate data and involved no new recruitment, intervention, or collection of identifiable patient information.

6.2 Data availability

All data discussed in this review are derived from the cited peer-reviewed publications. The reproducible focused PubMed/MEDLINE update strategy is provided in Supplementary Appendix 1.

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