



Circulating Tumor DNA as a Prognostic Marker in Early-Stage Breast Cancer

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Abstract

Circulating tumor DNA (ctDNA) -- the tumor-derived fraction of cell-free DNA shed into blood plasma -- has emerged as a candidate biomarker for detecting molecular residual disease after curative-intent treatment for early-stage breast cancer, at a point when standard pathological and imaging-based staging cannot distinguish patients who are truly disease-free from those harboring undetectable micrometastatic disease. This article synthesizes the literature establishing ctDNA's prognostic value in this setting, from the foundational demonstrations that tumor-derived mutations are detectable and quantifiable in plasma, through personalized tumor-informed assays that track patient-specific mutation panels across serial postoperative and neoadjuvant blood draws, to a recent meta-analysis of 42 pooled studies reporting that ctDNA positivity carries a multivariate hazard ratio for disease-free survival rising from roughly 2.5 at pre-treatment baseline to more than 7 during postoperative surveillance, with detection preceding clinical relapse by a mean lead time exceeding ten months. We give particular weight to the assay-design and analytical-validity literature, since reported sensitivity varies by nearly an order of magnitude across studies depending on whether a personalized multiplex panel or a tumor-agnostic platform is used, and to the smaller but essential body of interventional trial evidence, exemplified by the c-TRAK TN trial, that tests whether acting on a positive ctDNA result actually improves outcomes rather than merely moving the diagnosis of an already-determined recurrence earlier in time. Read together, the evidence supports ctDNA as a genuine, reproducible, independent prognostic marker for recurrence in early breast cancer, while leaving demonstrated clinical utility, cross-platform assay standardization, and a fuller biological account of inter-patient shedding variability as the field's central open problems.

Keywords: circulating tumor DNA; breast cancer; minimal residual disease; liquid biopsy; prognostic biomarker

1. Introduction

Early-stage breast cancer is, by the standard measures used to counsel patients, a curable disease for the large majority of women who present with it: five-year relative survival for localized and regional disease now exceeds 90% in most high-income health systems, and adjuvant systemic therapy — chemotherapy, endocrine therapy, HER2-targeted agents, or some combination — has been refined over four decades specifically to convert a meaningful minority of those women, the ones whose disease will otherwise recur, into long-term survivors. The persistent clinical problem is that nobody can currently say, at the point surgery ends and adjuvant therapy begins, which women are in that minority. Pathological stage, grade, receptor status, and multigene expression assays such as Oncotype DX and MammaPrint all stratify risk at a population level, but none of them directly measures whether a given patient's tumor has, in fact, been eradicated. A patient can complete every recommended line of therapy and still harbor a handful of malignant cells that will, months or years later, seed a metastatic recurrence that no imaging study can see coming until it is large enough to produce symptoms or a visible lesion.

Circulating tumor DNA (ctDNA) — the fraction of cell-free DNA in blood plasma that carries tumor-specific somatic alterations, shed by dying or actively secreting tumor cells — has emerged over the past decade as a candidate solution to exactly this problem. Its clinical plausibility in breast cancer specifically was first demonstrated in the metastatic setting, where Dawson and colleagues showed that serial ctDNA measurement tracked tumor burden and treatment response more sensitively than either the conventional serum protein biomarker CA 15-3 or enumeration of circulating tumor cells, establishing that ctDNA dynamics carry real-time information about disease trajectory in breast cancer before any early-stage application had been tested [1]. The core observation, established in landmark work by Bettegowda and colleagues across more than 640 patients with fourteen tumor types, is that ctDNA is detectable in the large majority of patients with metastatic disease and in a meaningful fraction of patients with localized disease, that its concentration in plasma tracks tumor burden, and that its mutant allele fraction can fall to the limit of detection or below in patients who respond to treatment [2]. Applied to breast cancer specifically, this

observation raises a direct and clinically consequential question: if a patient's own tumor has been genomically fingerprinted, can serial blood draws after curative-intent surgery detect the presence of residual disease before it becomes radiologically or clinically apparent, and does that detection carry independent prognostic weight beyond what pathology and standard biomarkers already provide?

This article synthesizes the literature bearing on that question, restricted specifically to early-stage (non-metastatic, potentially curable) breast cancer. We are not attempting to cover the parallel and much larger literature on ctDNA in metastatic breast cancer, where the technology is used chiefly for genotyping and treatment selection rather than for detecting occult disease, except where a metastatic-setting study establishes a technical or biological point that the early-stage literature depends on. Nor is this a technical assay-validation paper; we did not generate new data. What follows is an attempt to trace the field from its foundational demonstrations that tumor-derived DNA is detectable and trackable in plasma at all, through the specific prospective and retrospective cohorts that established ctDNA's prognostic value for recurrence in early breast cancer, to the interventional trials that have begun testing whether acting on a positive ctDNA result actually changes outcomes, and finally to the assay-design and analytical-validity literature that determines whether any given study's claimed sensitivity is trustworthy in the first place.

It is worth stating the scope of the claim precisely at the outset, because "prognostic marker" is doing real work in this article's title. The evidence reviewed here supports ctDNA detection after primary treatment, and ctDNA persistence during neoadjuvant therapy, as strong, reproducible, independent predictors of subsequent relapse — a genuinely prognostic association. It does not yet, on the evidence synthesized here, establish that intervening on a positive ctDNA result — starting additional therapy before radiological relapse — improves survival; that is a predictive-utility question that only randomized interventional trials can answer, and as of this writing those trials are still largely in progress or have reported feasibility rather than definitive survival benefit. We try to keep that distinction visible throughout rather than letting a strong prognostic signal read as an established clinical practice.

2. Biology and Detection of Circulating Tumor DNA

Cell-free DNA circulates in the blood of both healthy individuals and patients with cancer, released continuously by apoptotic and necrotic cells throughout the body; in cancer patients, a variable fraction of that cell-free DNA — typically well under 1% in early-stage disease, and sometimes below one part in ten thousand — carries the somatic mutations, copy-number changes, or methylation marks that mark it as tumor-derived rather than originating from normal hematopoietic or other turnover [2]. Detecting that minority fraction reliably, against a background of wild-type cell-free DNA and the sequencing errors that any polymerase or sequencer introduces, is fundamentally a signal-to-noise problem, and the methodological history of ctDNA detection is largely a history of pushing the achievable limit of detection down by orders of magnitude through increasingly clever error suppression.

Two broad detection strategies have dominated the early-stage breast cancer literature, and the distinction between them matters for interpreting almost every result discussed later in this article. Tumor-informed assays first sequence the patient's own resected tumor (and often a matched normal sample) to identify a personalized panel of somatic variants — anywhere from a handful to several thousand, depending on the platform — and then design a plasma assay, typically digital PCR or targeted deep sequencing, to track exactly those variants in serial blood draws. Because the assay is told in advance which mutations to look for, it can apply extremely aggressive error suppression and achieve variant allele fraction (VAF) detection limits in the range of 0.01% to 0.03%, an order of magnitude or more below what a tumor-naïve, genome-wide approach can typically achieve with comparable specificity [3,4]. Tumor-agnostic (or tumor-naïve) assays, by contrast, do not require prior tumor sequencing; they apply a fixed panel or genome-wide sequencing approach directly to plasma, trading some analytical sensitivity for the practical advantage of not needing archival tumor tissue or a lead time to design a personalized panel, which matters when a clinical decision cannot wait for panel design [5].

The foundational demonstration that either approach could work at all rests on a small number of papers that are worth treating as the field's common ancestors.

Diehl and colleagues showed, in colorectal cancer, that digital PCR-based tracking of a single dominant somatic mutation in serial plasma samples could quantify tumor burden dynamically enough to detect surgical response and early recurrence, establishing digital PCR as a viable quantitative readout for circulating mutant DNA years before next-generation sequencing panels became standard [6]. Newman and colleagues' CAPP-Seq (CANcer Personalized Profiling by deep Sequencing) method, developed initially in non-small-cell lung cancer, demonstrated that a carefully designed, hybrid-capture-based sequencing panel combined with computational error suppression could achieve broad patient coverage — detecting ctDNA in the large majority of patients across cancer stages — while reaching sensitivity down to roughly 0.02% mutant allele fraction, establishing the sequencing-based (as opposed to single-locus digital PCR) branch of the field [7]. Bettegowda and colleagues' cross-tumor-type survey, already introduced above, remains the standard reference for the claim that ctDNA detectability scales with disease burden and stage, and that it falls toward and below assay limits of detection in patients who respond to treatment [2]. Phallen and colleagues extended targeted error-correction sequencing specifically toward the harder problem of early-stage, localized disease detection across breast, lung, ovarian, and colorectal cancer, reporting that a broad but fixed 58-gene panel could detect ctDNA in a majority of stage I and II patients across those tumor types when combined with their CancerSEEK-style error-suppression pipeline — an important precedent for tumor-agnostic detection in exactly the disease-stage range this article is concerned with [8].

Applied specifically to lung cancer but methodologically foundational for how the breast cancer field would later structure its own trials, Abbosh and colleagues' TRACERx phylogenetic ctDNA analysis demonstrated that tracking a patient-specific panel of clonal mutations, derived from multi-region tumor sequencing, through serial postoperative plasma samples could detect molecular residual disease with a lead time of a full year or more before radiological relapse in a substantial fraction of patients who went on to recur [9]. That "phylogenetically informed, personalized panel, serial postoperative sampling" design template — sequence the tumor once, then track its private mutations in blood indefinitely — is

essentially the design every major early-stage breast cancer ctDNA study reviewed in the following sections adopted, with variations mainly in panel size, sequencing depth, and sampling interval.

3. ctDNA as a Prognostic Marker After Curative-Intent Treatment

The single most influential study establishing ctDNA's prognostic value specifically in early breast cancer is Garcia-Murillas and colleagues' mutation-tracking study, which followed 55 patients with early breast cancer after surgery using a personalized digital PCR assay tracking one or two somatic mutations identified from each patient's primary tumor. ctDNA detected in a postoperative "landmark" sample, or emerging during serial follow-up, was strongly associated with subsequent clinical relapse, and detection in serial samples preceded clinical or radiological relapse by a median lead time reported in months, establishing that molecular relapse is, in most patients who go on to recur, detectable well before symptomatic or imaging-confirmed relapse [10]. The study's central contribution was less the specific lead time number, which subsequent studies would replicate with variation, than the demonstration that a single or dual-mutation, personalized, serial-sampling design was sufficient to achieve strong prognostic discrimination in a disease, early breast cancer, where absolute ctDNA shedding is often lower than in the metastatic setting the earlier foundational papers had mostly studied.

Coombes and colleagues extended this personalized-panel design considerably in scale and analytical rigor, applying a bespoke, multiplex-PCR-based, patient-specific panel of 16 somatic mutations per patient (the assay that would later be commercialized as Signatera) to serial plasma from 49 women with early breast cancer, reporting that this deeper personalized panel could detect ctDNA in patients who went on to relapse with high sensitivity and very high specificity (93 to 100% sensitivity depending on the mutant allele fraction threshold applied, and specificity above 99.8%), and that ctDNA detection anteceded clinical detection of metastatic recurrence, again by a lead time measured in months [3]. McDonald and colleagues, applying their own personalized targeted digital sequencing assay (TARDIS) tracking a median of sixteen variants per patient, reported comparable sample-level sensitivity (87.5% at a 0.03%

mutant allele fraction threshold) with perfect specificity on unmutated controls, and specifically demonstrated the assay's ability to detect residual disease in the postoperative, pre-adjuvant-therapy window — the point at which a positive result would carry the most direct implication for escalating systemic therapy [4].

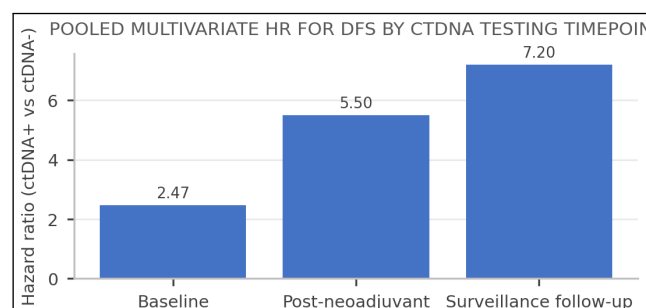


Figure 1: Pooled multivariate hazard ratio for disease-free survival in ctDNA-positive versus ctDNA-negative patients with operable breast cancer, by testing timepoint, from Nader-Marta et al.'s systematic review and meta-analysis of 42 quantitatively pooled studies (4,729 patients) [11]. The prognostic association sharpens markedly as testing moves from pre-treatment baseline to post-neoadjuvant and postoperative surveillance timepoints.

Beyond these individual cohort studies, the accumulated evidence has now been formally pooled. Nader-Marta and colleagues' systematic review and meta-analysis, synthesizing 57 studies (42 of them contributing to quantitative pooling, spanning 4,729 patients in the meta-analytic subset) of ctDNA for predicting recurrence in operable breast cancer, reported that ctDNA positivity carried a multivariate hazard ratio for disease-free survival of 2.47 at baseline (before any systemic therapy), rising to 5.50 when measured after completion of neoadjuvant therapy, and rising further to 7.20 when detected during postoperative surveillance follow-up — a pattern indicating that ctDNA's prognostic discrimination sharpens considerably as the measurement moves later in the treatment course, closer to the point where a positive result reflects genuine minimal residual disease rather than pre-treatment tumor burden [11]. The same meta-analysis reported a mean lead time across the pooled diagnostic-accuracy studies of 10.81 months between ctDNA detection and clinical relapse, with a wide range (0 to 58.9 months) reflecting genuine heterogeneity across assay platforms, sampling intervals, and molecular subtypes rather than a single fixed biological quantity. Diagnostic sensitivity across the pooled studies ranged widely, from 0.31 to 1.0, and specificity from 0.70 to 1.0 — a spread that itself is an important finding, because it means that "ctDNA detects recurrence" is not a single, assay-independent fact but a

claim whose accuracy depends heavily on which assay, panel size, and sampling schedule a given study used, a point we return to in the section on analytical validity below.

Longer-term follow-up cohorts have extended this evidence beyond the immediate postoperative window. Serial postoperative monitoring studies with extended follow-up have reported that ctDNA detected years after initial surgery — well beyond the conventional high-risk recurrence window for hormone-receptor-positive disease — retains strong prognostic value, consistent with the biological reality that hormone-receptor-positive breast cancer has a well-documented tendency to recur late, sometimes more than a decade after diagnosis, a pattern that imaging-based surveillance is poorly suited to anticipate and that a molecular marker capable of detecting minimal residual disease is, in principle, well suited to address.

4. ctDNA and Response to Neoadjuvant Therapy

A second, related application tracks ctDNA dynamics during neoadjuvant (preoperative) systemic therapy rather than after surgery, with two distinct goals: predicting pathological response before surgery, and, separately, using post-neoadjuvant, pre-surgical ctDNA status as an early readout of residual disease risk. Magbanua and colleagues, studying a cohort of patients with high-risk HER2-negative early breast cancer receiving neoadjuvant chemotherapy, found that ctDNA detectable at baseline or during treatment was strongly associated with subsequent recurrence and death, that ctDNA clearance during neoadjuvant therapy was associated with better outcomes than persistent detectability, and that ctDNA status measured after the completion of neoadjuvant therapy but before surgery carried independent prognostic information beyond pathological complete response status itself — meaning ctDNA and pathology are not simply redundant readouts of the same underlying biology, but each contribute distinct prognostic information [12].

The triple-negative subtype, which lacks the estrogen-receptor, progesterone-receptor, and HER2-targeted maintenance therapies available for other subtypes and where recurrence risk is disproportionately concentrated in the first few years after diagnosis, has attracted particular attention because it is the subtype where an early, actionable

signal of residual disease would most directly inform an escalation decision. Radovich and colleagues' preplanned secondary analysis of the BRE12-158 randomized trial found that detectable ctDNA, and separately detectable circulating tumor cells, after completion of neoadjuvant chemotherapy were each independently associated with markedly worse disease-free and overall survival in patients with residual triple-negative disease, and that the combination of both positive markers identified a subgroup at particularly high recurrence risk — a finding directly relevant to how such patients might eventually be triaged for escalated or experimental adjuvant therapy [13]. Riva and colleagues, using patient-specific digital PCR tracking during neoadjuvant chemotherapy specifically in triple-negative disease, reported that persistent ctDNA detectability during treatment, rather than only its presence or absence at a single timepoint, tracked closely with eventual pathological response, reinforcing that the trajectory of ctDNA levels over the treatment course, not merely a single measurement, carries clinically relevant information [14]. A related, mutation-agnostic readout of the same underlying biology comes from the metastatic triple-negative setting, where Stover and colleagues showed that the overall tumor fraction of cell-free DNA, estimated genome-wide from shallow whole-genome sequencing of copy-number alterations rather than from tracking specific point mutations, was itself independently associated with survival — a finding that anticipates why, in the early-stage setting discussed here, an aggregate shedding-based signal can sometimes provide prognostic information even before or alongside a patient-specific mutation panel is available [15].

It is worth noting that the neoadjuvant setting introduces a methodological wrinkle relative to the postoperative setting: because the primary tumor is often still present (or only recently removed) during at least part of the sampling window, a positive ctDNA result during neoadjuvant therapy reflects some mixture of persistent primary tumor shedding and, potentially, micrometastatic disease, whereas a positive result well after complete surgical resection is more unambiguously interpretable as residual or metastatic disease. Studies in this section have generally been careful to draw this distinction, typically emphasizing the post-neoadjuvant, pre-surgical or post-surgical timepoint as the one with the cleanest prognostic interpretation, but it is a

distinction a reader synthesizing across studies needs to keep in mind rather than treating every reported "ctDNA positive" result as biologically equivalent.

5. Molecular Residual Disease and Interventional Trials

The studies discussed so far are overwhelmingly observational: ctDNA is measured, outcomes are subsequently observed, and an association (often a strong one) is reported. That is sufficient to establish prognostic value but not, by itself, sufficient to establish that acting on a positive ctDNA result changes a patient's outcome for the better — the intervention could, in principle, be ineffective, harmful, or simply too late even when started earlier than a radiological relapse would have been detected. Interventional trials that randomize or otherwise prospectively act on ctDNA status are therefore a distinct and smaller body of evidence, and one that the field has been careful, in its more recent guideline documents, to keep conceptually separate from the observational prognostic literature [16].

The c-TRAK TN trial, conducted in the UK specifically in moderate- and high-risk early-stage triple-negative breast cancer, is the most mature such study in this disease setting. Turner and colleagues used serial ctDNA mutation tracking after completion of standard curative-intent treatment to identify patients with molecular residual disease and, in patients who tested ctDNA-positive, offered pembrolizumab as an intervention aimed at eradicating minimal residual disease before it became clinically apparent, comparing outcomes against a ctDNA-positive but untreated (surveillance-only) comparison group drawn from the trial's broader screened population [17]. The trial confirmed that ctDNA surveillance was logistically feasible at the scale needed for a national trial and that ctDNA-positive patients had, as expected, markedly worse outcomes than ctDNA-negative patients, but it also illustrated the practical difficulty of this kind of trial: molecular relapse in triple-negative disease can progress rapidly to radiological relapse, meaning the intervention window between a positive ctDNA result and clinically apparent disease is sometimes too narrow for an experimental therapy to be started and to have a meaningful chance of altering the disease course, a candid limitation the trial investigators themselves emphasized in their published results. The c-TRAK TN

experience is, in that sense, as valuable for what it revealed about trial design constraints — turnaround time from blood draw to actionable result, the pace of triple-negative disease progression once molecular relapse begins, and the practical challenge of offering a meaningfully different therapy at the point of molecular rather than radiological relapse — as for its direct efficacy findings.

The ASCO and College of American Pathologists' joint review of circulating tumor DNA analysis in patients with cancer, published by Merker and colleagues, remains a useful frame for exactly this distinction between analytical validity, clinical validity (the prognostic associations reviewed in the preceding two sections), and clinical utility (evidence that acting on ctDNA improves outcomes), and it explicitly cautioned, based on the evidence available at the time of its publication, that clinical utility for most ctDNA applications, including molecular residual disease monitoring in early breast cancer, remained to be established through prospective interventional trials rather than assumed from strong observational prognostic associations alone [16]. That caution remains, in our reading of the more recent literature synthesized in this article, substantially still warranted: the prognostic evidence has become considerably stronger and more consistently reproduced across independent cohorts and assay platforms since 2018, but the interventional evidence, of which c-TRAK TN is the most complete example in early breast cancer specifically, is still limited in scale and has not yet produced an unambiguous survival benefit that would justify ctDNA-guided treatment escalation as a standard-of-care recommendation outside a clinical trial.

6. Analytical Validity, Assay Design, and Cross-Platform Comparison

Every prognostic and predictive claim reviewed above rests on an assay's ability to reliably call a true positive apart from background noise, and the assays used across the studies synthesized in this article differ substantially in their reported analytical sensitivity and specificity, differences that are not merely a technical footnote but a direct determinant of how comparable any two studies' reported sensitivities and lead times actually are. Panet and colleagues' review of analytical validity in early breast cancer ctDNA assays compiled reported limits of

detection and specificity across the major platforms used in the field, and Table 1 reproduces a representative subset of that comparison [5]. Personalized, tumor-informed panels tracking on the order of sixteen or more patient-specific variants — the Coombes and McDonald assays discussed above are directly comparable examples — achieve sample-level sensitivity in the high 80s to 100% range at mutant allele fractions as low as 0.01% to 0.03%, with specificity above 99.8%, considerably outperforming assays built around a single or a small handful of tracked mutations, which remain useful (as in Garcia-Murillas and colleagues' original digital PCR design) but trade some sensitivity for simplicity and cost [3,4,10].

Table 1: Reported analytical sensitivity and specificity of representative circulating tumor DNA detection assays used in early-stage breast cancer studies, illustrating how detection limit and panel design vary across the personalized (tumor-informed) and tumor-agnostic assay families discussed in this article [3,4,7,5].

Assay	Panel design	Limit (VAF)	Sensitivity	Spec.
Coombes 16-gene	Patient-specific multiplex PCR	0.01-0.03%	93-100%	>99.8%
McDonald TARDIS	Patient-specific digital seq., 16 variants	0.03%	87.5%	100%
Newman CAPP-Seq	Hybrid-capture seq., broad coverage	~0.02%	Most stage II-IV cases	96%
Garcia-Murillas	Patient-specific, 1-2 mutations	Higher than multiplex	Lower than multiplex	High

This heterogeneity in analytical performance has direct consequences for interpreting the pooled sensitivity range (0.31 to 1.0) reported in the Nader-Marta meta-analysis discussed earlier [11]: a substantial part of that range is very plausibly explained by which generation and design of assay a given contributing study used, rather than by a single underlying biological sensitivity of ctDNA detection in early breast cancer. Cescon and colleagues' broader review of circulating tumor DNA and liquid biopsy across oncology makes a parallel point at the level of the whole field, not just breast cancer: as sequencing depth, panel design, and computational error-suppression methods have matured across the decade since Newman and colleagues' original CAPP-Seq paper, the achievable limit of detection has fallen by roughly two orders of magnitude, and comparisons between an early 2010s study and a 2020s study using nominally the same clinical endpoint can therefore reflect assay-generation differences as much as biological ones [18,7].

A separate strand of the analytical-validity literature has focused specifically on what property of cell-free DNA, beyond the presence or absence of a specific tracked mutation, correlates with prognosis. Lamminaho and colleagues reported that cell-free DNA integrity — the ratio of longer to shorter cell-free DNA fragments, which shifts in the presence of tumor-derived DNA relative to the shorter fragments typical of normally apoptotic cell turnover — was itself independently associated with poorer breast cancer survival, a finding that complements mutation-tracking approaches by suggesting that even mutation-agnostic, purely physical properties of the circulating DNA pool carry prognostic signal, a potentially useful fallback or complementary readout in patients for whom no tumor-specific mutation panel has been designed [19]. Olsson and colleagues' earlier serial monitoring study, using both digital PCR of tumor-specific mutations and analysis of chromosomal copy-number changes in plasma, similarly demonstrated that occult metastatic disease could be detected substantially ahead of clinical relapse using either readout, with the two approaches showing considerable but imperfect concordance — a reminder that "ctDNA positive" can mean somewhat different things depending on whether an assay is tracking point mutations, structural rearrangements, or copy-number profiles [20].

Recent systematic reviews focused specifically on hormone-receptor-positive, HER2-negative early breast cancer — the molecular subtype with the largest absolute number of patients and the longest recurrence tail — have reached a broadly consistent conclusion: ctDNA detectability is prognostic within this subtype specifically, not merely as an average effect diluted across all molecular subtypes pooled together, though the absolute sensitivity achieved in the lower-shedding luminal subtypes tends to run somewhat below what is reported in triple-negative or HER2-positive disease, where somatic mutation burden and shedding rates tend to be higher [21]. Nguyen and colleagues' more recent personalized mutation-tracking study in high-risk early breast cancer reinforces this picture with a contemporary assay design, reporting that ctDNA recurrence prediction remained robust in a cohort enriched for exactly the higher-risk, node-positive and larger-tumor-size patients for whom a prognostic biomarker capable of triaging adjuvant treatment intensity would have the most direct clinical value [22].

7. Open Challenges

Several limitations recur across the literature synthesized here clearly enough to be worth stating plainly rather than leaving implicit. First, and most fundamentally, is the clinical-utility gap already discussed in the interventional-trials section: strong, consistent, independently replicated prognostic association is not the same evidentiary standard as a demonstrated survival benefit from acting on that association, and the c-TRAK TN experience shows this gap is not merely theoretical — the trial's own investigators reported genuine difficulty translating a positive molecular signal into a timely, effective intervention in triple-negative disease specifically [17]. Closing this gap requires more, and larger, randomized interventional trials, ideally across molecular subtypes with different typical shedding rates and different recurrence kinetics, and those trials are expensive, slow, and only just beginning to mature.

Second, assay heterogeneity, discussed at length in the preceding section, remains a genuine obstacle to synthesizing the field's evidence cleanly. A sensitivity of 31% in one pooled study and 100% in another are not really measuring the same thing when the underlying assays differ by two orders of magnitude in analytical limit of detection [11,5]. Cross-platform comparison studies, standardized reference materials, and consistent reporting of assay-level analytical validity alongside clinical results — the kind of reporting standard the ASCO/CAP joint review explicitly called for — would materially improve the field's ability to compare across studies, and adoption of that standard has been inconsistent [16].

Third, the biological determinants of ctDNA shedding itself remain incompletely understood. Not all tumors, even at comparable size and stage, shed detectable ctDNA into plasma at comparable rates, and the molecular-subtype-dependent sensitivity differences noted above (lower apparent sensitivity in luminal, hormone-receptor-positive disease relative to triple-negative or HER2-positive disease) likely reflect real biological differences in shedding rate rather than purely an assay artifact, though disentangling the two explanations cleanly within any single study is difficult [21]. A patient whose tumor simply does not shed appreciable ctDNA will test ctDNA-negative regardless of true disease status, a false-reassurance failure mode

that is conceptually distinct from, and arguably more clinically dangerous than, ordinary assay noise.

Fourth, cost, turnaround time, and equitable access remain practical barriers to translating even a well-validated assay into routine surveillance. Personalized, tumor-informed panels require access to archival tumor tissue, a sequencing and panel-design lead time typically measured in weeks, and a cost structure that, at least as of the studies reviewed here, has not been evaluated in a way that supports confident statements about population-level cost-effectiveness for routine postoperative surveillance in early breast cancer, as opposed to the higher-risk, higher-shedding disease settings (later-stage disease, or triple-negative subtype) where the pretest probability of a clinically meaningful positive result is higher.

Fifth, lead time itself, while consistently reported as substantial (a pooled mean above ten months in the Nader-Marta meta-analysis), is heterogeneous enough — ranging from essentially zero to nearly five years across pooled studies — that a single "ctDNA detects relapse X months early" headline number obscures more than it reveals about any individual patient's likely experience, and better characterization of which clinical and molecular features predict a longer versus shorter lead time would materially improve how useful a positive result is for treatment-timing decisions [11].

8. Conclusion

The literature reviewed here supports a specific and, we think, defensible claim: circulating tumor DNA, detected through either personalized tumor-informed panels or, with somewhat reduced sensitivity, tumor-agnostic assays, is a genuine, reproducible, independent prognostic marker for recurrence in early-stage breast cancer, with hazard ratios for disease-free survival that strengthen from roughly 2 to 3 at baseline to 5 to 7 when measured after neoadjuvant therapy or during postoperative surveillance, and with detection typically preceding clinical or radiological relapse by a lead time measured in months across a wide but genuine range [11]. This prognostic signal has now been demonstrated across multiple independent cohorts, assay platforms, and molecular subtypes, from the foundational single-mutation digital PCR work of Garcia-Murillas and colleagues through the deeper personalized panels of Coombes and McDonald and their colleagues, to the more recent, larger contemporary cohorts represented

by Nguyen and colleagues' work, and it holds specifically within the hormone-receptor-positive population that dominates the disease's overall incidence as well as within the higher-shedding triple-negative subtype where intervention trials have so far concentrated [10,3,4,22,21].

What the literature does not yet establish, and what genuinely separates ctDNA's current status from a validated clinical practice, is clinical utility: proof that identifying molecular residual disease early and acting on it — escalating, changing, or restarting systemic therapy before radiological relapse — actually improves survival rather than simply moving the diagnosis of an already-determined outcome earlier in time. The c-TRAK TN trial represents the field's most mature attempt to test that question directly in early breast cancer, and its experience, more cautionary than triumphant, is a useful corrective against overstating where the field currently stands [17,16]. Making ctDNA surveillance a genuinely actionable clinical tool, rather than an elegant but still largely observational prognostic marker, will depend on larger and more numerous interventional trials, on continued standardization of assay analytical validity and reporting so that results are comparable across platforms and institutions, and on a clearer biological account of why shedding rates differ so substantially across patients and molecular subtypes. None of these are reasons to discount the strength of the prognostic evidence accumulated so far; they are, read together, the honest remaining distance between a well-evidenced biomarker and a standard of care.

9. References

1. Dawson, S.J., Tsui, D.W., Murtaza, M., Biggs, H., Rueda, O.M., Chin, S.F., et al. (2013) Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer. *New England Journal of Medicine*, 368(13): 1199-1209. DOI: [10.1056/NEJMoa1213261](https://doi.org/10.1056/NEJMoa1213261)
2. Bettegowda, C., Sausen, M., Leary, R.J., Kinde, I., Wang, Y., Agrawal, N., et al. (2014) Detection of Circulating Tumor DNA in Early- and Late-Stage Human Malignancies. *Science Translational Medicine*, 6(224): 224ra24. DOI: [10.1126/scitranslmed.3007094](https://doi.org/10.1126/scitranslmed.3007094)
3. Coombes, R.C., Page, K., Salari, R., Hastings, R.K., Armstrong, A.C., Ahmed, S., et al. (2019) Personalized Detection of Circulating Tumor DNA Antedates Breast Cancer Metastatic Recurrence. *Clinical Cancer Research*, 25(14): 4255-4263. DOI: [10.1158/1078-0432.CCR-18-3663](https://doi.org/10.1158/1078-0432.CCR-18-3663)
4. McDonald, B.R., Contente-Cuomo, T., Sammut, S.J.,

Odenheimer-Bergman, A., Ernst, B., Perdigones, N., et al. (2019) Personalized Circulating Tumor DNA Analysis to Detect Residual Disease After Neoadjuvant Therapy in Breast Cancer. *Science Translational Medicine*, 11(504): eaax7392. DOI: [10.1126/scitranslmed.aax7392](https://doi.org/10.1126/scitranslmed.aax7392)

5. Panet, F., Papakonstantinou, A., Borrell, M., Vivancos, J., Vivancos, A., Oliveira, M. (2024) Use of ctDNA in Early Breast Cancer: Analytical Validity and Clinical Potential. *npj Breast Cancer*, 10: 50. DOI: [10.1038/s41523-024-00653-3](https://doi.org/10.1038/s41523-024-00653-3)
6. Diehl, F., Schmidt, K., Choti, M.A., Romans, K., Goodman, S., Li, M., et al. (2008) Circulating Mutant DNA to Assess Tumor Dynamics. *Nature Medicine*, 14(9): 985-990. DOI: [10.1038/nm.1789](https://doi.org/10.1038/nm.1789)
7. Newman, A.M., Bratman, S.V., To, J., Wynne, J.F., Eclow, N.C.W., Modlin, L.A., et al. (2014) An Ultrasensitive Method for Quantitating Circulating Tumor DNA with Broad Patient Coverage. *Nature Medicine*, 20(5): 548-554. DOI: [10.1038/nm.3519](https://doi.org/10.1038/nm.3519)
8. Phallen, J., Sausen, M., Adleff, V., Leal, A., Hruban, C., White, J., et al. (2017) Direct Detection of Early-Stage Cancers Using Circulating Tumor DNA. *Science Translational Medicine*, 9(403): eaan2415. DOI: [10.1126/scitranslmed.aan2415](https://doi.org/10.1126/scitranslmed.aan2415)
9. Abbosh, C., Birkbak, N.J., Wilson, G.A., Jamal-Hanjani, M., Constantin, T., Salari, R., et al. (2017) Phylogenetic ctDNA Analysis Depicts Early-Stage Lung Cancer Evolution. *Nature*, 545(7655): 446-451. DOI: [10.1038/nature22364](https://doi.org/10.1038/nature22364)
10. Garcia-Murillas, I., Schiavon, G., Weigelt, B., Ng, C., Hrebien, S., Cutts, R.J., et al. (2015) Mutation Tracking in Circulating Tumor DNA Predicts Relapse in Early Breast Cancer. *Science Translational Medicine*, 7(302): 302ra133. DOI: [10.1126/scitranslmed.aab0021](https://doi.org/10.1126/scitranslmed.aab0021)
11. Nader-Marta, G., Monteforte, M., Agostinetti, E., Cinquini, M., Martins-Branco, D., Langouo, M., et al. (2024) Circulating Tumor DNA for Predicting Recurrence in Patients With Operable Breast Cancer: A Systematic Review and Meta-Analysis. *ESMO Open*, 9(3): 102390. DOI: [10.1016/j.esmoop.2024.102390](https://doi.org/10.1016/j.esmoop.2024.102390)
12. Magbanua, M.J.M., Swigart, L.B., Wu, H.T., Hirst, G.L., Yau, C., Wolf, D.M., et al. (2021) Circulating Tumor DNA in Neoadjuvant-Treated Breast Cancer Reflects Response and Survival. *Annals of Oncology*, 32(2): 229-239. DOI: [10.1016/j.annonc.2020.11.007](https://doi.org/10.1016/j.annonc.2020.11.007)
13. Radovich, M., Jiang, G., Hancock, B.A., Chitambar, C., Nanda, R., Falkson, C., et al. (2020) Association of Circulating Tumor DNA and Circulating Tumor Cells After Neoadjuvant Chemotherapy With Disease Recurrence in Patients With Triple-Negative Breast Cancer. *JAMA Oncology*, 6(9): 1410-1415. DOI: [10.1001/jamaoncol.2020.2295](https://doi.org/10.1001/jamaoncol.2020.2295)
14. Riva, F., Bidard, F.C., Houy, A., Saliou, A., Madic, J., Rampanou, A., et al. (2017) Patient-Specific Circulating Tumor DNA Detection During Neoadjuvant Chemotherapy in Triple-Negative Breast Cancer. *Clinical Chemistry*, 63(3): 691-699. DOI: [10.1373/clinchem.2016.262337](https://doi.org/10.1373/clinchem.2016.262337)
15. Stover, D.G., Parsons, H.A., Ha, G., Freeman, S.S., Barry, W.T., Guo, H., et al. (2018) Association of Cell-Free DNA Tumor Fraction and Somatic Copy Number Alterations With Survival in Metastatic Triple-Negative Breast Cancer. *Journal of Clinical Oncology*, 36(6): 543-553. DOI: [10.1200/JCO.2017.76.0033](https://doi.org/10.1200/JCO.2017.76.0033)
16. Merker, J.D., Oxnard, G.R., Compton, C., Diehn, M., Hurley, P., Lazar, A.J., et al. (2018) Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. *Journal of Clinical Oncology*, 36(16): 1631-1641. DOI: [10.1200/JCO.2017.76.8671](https://doi.org/10.1200/JCO.2017.76.8671)
17. Turner, N.C., Swift, C., Jenkins, B., Kilburn, L., Coakley, M., Beaney, M., et al. (2023) Results of the c-TRAK TN Trial: A Clinical Trial Utilising ctDNA Mutation Tracking to Detect Molecular Residual Disease and Trigger Intervention in Patients With Moderate- and High-Risk Early-Stage Triple-Negative Breast Cancer. *Annals of Oncology*, 34(2): 200-211. DOI: [10.1016/j.annonc.2022.11.005](https://doi.org/10.1016/j.annonc.2022.11.005)
18. Cescon, D.W., Bratman, S.V., Chan, S.M., Siu, L.L. (2020) Circulating Tumor DNA and Liquid Biopsy in Oncology. *Nature Cancer*, 1(3): 276-290. DOI: [10.1038/s43018-020-0043-5](https://doi.org/10.1038/s43018-020-0043-5)
19. Lamminaho, M., Kujala, J., Peltonen, H., Tengstrom, M., Kosma, V.M., Mannermaa, A. (2021) High Cell-Free DNA Integrity Is Associated with Poor Breast Cancer Survival. *Cancers*, 13(18): 4679. DOI: [10.3390/cancers13184679](https://doi.org/10.3390/cancers13184679)
20. Olsson, E., Winter, C., George, A., Chen, Y., Howlin, J., Tang, M.E., et al. (2015) Serial Monitoring of Circulating Tumor DNA in Patients With Primary Breast Cancer for Detection of Occult Metastatic Disease. *EMBO Molecular Medicine*, 7(8): 1034-1047. DOI: [10.15252/emmm.201404913](https://doi.org/10.15252/emmm.201404913)
21. Ajjawi, I., Rozenblit, M., Rios-Hoyo, A., Lustberg, M.B. (2025) Prognostic Value of Circulating Tumor DNA in HR+/HER2-Stage I-III Breast Cancer: A Systematic Review. *Cancers*, 17(17): 2831. DOI: [10.3390/cancers17172831](https://doi.org/10.3390/cancers17172831)
22. Nguyen, S.T., Nguyen Hoang, V.A., Nguyen Trieu, V., Pham, T.H., Dinh, T.C., Pham, D.H., et al. (2025) Personalized Mutation Tracking in Circulating-Tumor DNA Predicts Recurrence in Patients With High-Risk Early Breast Cancer. *npj Breast Cancer*, 11(1): 58. DOI: [10.1038/s41523-025-00778-z](https://doi.org/10.1038/s41523-025-00778-z)

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The authors declare that they have no competing

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Ethical Approval

Not applicable. This review did not involve human participants, animal subjects, or the collection or analysis of primary patient data.

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