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REVIEW ARTICLE

Tumor-informed minimal residual disease testing in select solid tumors and hematologic malignancies: A narrative review

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Abstract

Tumor-informed circulating tumor DNA assays detect patient-specific cancer mutations in plasma and hold promise for detecting minimal residual disease (MRD) after or during definitive therapy. Recent large studies across solid tumors and hematologic malignancies suggest that tumor-informed MRD (TI-MRD) is strongly prognostic for relapse and survival. We reviewed disease evidence for these claims, as well as the potential utility in guiding therapeutic decisions. TI-MRD assays consistently achieved high analytical sensitivity. In solid tumors (colorectal cancer [CRC], non-small-cell lung cancer, breast cancer, and bladder cancer), multiple studies demonstrated that post-treatment MRD positivity conferred markedly worse recurrence-free and overall survival. TI-MRD positivity also often preceded clinical or radiological signs of relapse. Studies on hematologic malignancies, such as acute myelocytic leukemia (AML), diffuse large B-cell lymphoma, chronic lymphocytic leukemia (CLL), and multiple myeloma, also demonstrated prognostic power; however, TI-MRD also demonstrated effectiveness in guiding therapy escalation and de-escalation in AML and CLL studies. Ongoing trials in both solid tumors and hematologic malignancies are focused on further evaluating the utility of TI-MRD in guiding therapeutic decisions and enhancing patient survival. TI-MRD testing has matured into a broadly validated prognostic biomarker across multiple cancers supported by large prospective cohorts. Pending results of ongoing randomized trials will clarify its clinical utility in guiding adjuvant therapy. Key challenges remain, including low tumor shedding, assay cost, and standardization. We recommend cautious use of TI-MRD in practice where evidence is strongest (CRC and hematologic malignancies) while awaiting prospective validation in other settings.

Keywords: Tumor-informed minimal residual disease; Circulating tumor DNA; Non-small-cell lung cancer; Colorectal cancer; Breast cancer; Bladder cancer; Leukemia; Lymphoma

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1. Introduction

Circulating tumor DNA (ctDNA) refers to fragments of tumor-derived DNA molecules circulating in the blood, released through apoptosis, necrosis, or active secretion. These fragments carry tumor-specific genetic and epigenetic alterations, making ctDNA a particularly valuable biomarker for cancer detection and monitoring.[1] Following

curative intent therapy, ctDNA can indicate minimal residual disease (MRD) well before clinical or radiographic signs of relapse.[2] MRD refers to the clinical state of having residual malignant cells after therapy, while ctDNA is a biomarker used to assess MRD. MRD can be evaluated using tumor-agnostic or tumor-informed ctDNA assays. Tumor-agnostic MRD detection employs fixed ctDNA panels targeting common cancer-associated mutations or epigenetic signatures without prior knowledge of a specific patient's tumor genotype. It is broadly applicable and does not require tumor tissue. Tumor-informed MRD (TI-MRD) detection uses ctDNA assays that are personalized by first sequencing the patient's tumor to identify specific somatic mutations, which can then be detected in plasma.[3] TI-MRD detection is more sensitive and specific for identifying MRD after curative-intent therapy, whereas tumor-agnostic MRD detection is less sensitive but more broadly applicable.[4] Both approaches are prognostic for recurrence, but tumor-informed methods remain the preferred strategy when feasible. Contributing to the feasibility of TI-MRD is the role of tumor characteristics in determining ctDNA shedding rates, which directly influence TI-MRD detection sensitivity and reliability. Factors such as tumor size, stage, and cellular turnover can strongly affect the amount of ctDNA released into circulation. Larger, more necrotic tumors shed higher levels of DNA, whereas small or indolent lesions often remain below assay detection thresholds. Tumor vascularity and anatomic location can also influence the accessibility of ctDNA to the bloodstream. Well-vascularized and peripheral tumors are prone to shedding more readily than lesions confined to sanctuary sites such as the brain. These biological determinants set a "shedding floor" that even highly sensitive, patient-specific TI-MRD assays cannot overcome, underscoring the need to interpret negative TI-MRD results within the context of tumor biology.[5-7]

Recent prospective studies in diverse malignancies have shown that TI-MRD is a powerful prognostic marker. For example, in colorectal cancer (CRC), post-operative MRD positivity is associated with vastly increased risk of recurrence.[8,9] In resected lung and breast cancers, MRD positivity detected relapses months earlier than imaging.[2,10,11] In hematologic cancers, TI-MRD is highly efficacious for multiple myeloma,[12] large B-cell lymphoma,[13] chronic lymphocytic leukemia (CLL),[14] and acute myelocytic leukemia (AML),[15] and often outperforms conventional methods of detection.

In this narrative review, we review recent clinical trial data and results across studies assessing TI-MRD assays across solid tumors (CRC, non-small-cell lung cancers [NSCLC], breast, and urothelial) and hematologic malignancies (diffuse large B-cell lymphoma [DLBCL], Hodgkin lymphoma, AML, chronic myelogenous leukemia, and multiple myeloma). Table 1 presents common genetic mutations identified in TI-MDR specific to the malignant pathologies discussed in this review. We emphasize clinical trial data from 2015 to 2025, including large prospective cohorts and randomized controlled studies. We also summarize the key technical platforms, including their analytical limits of detection and performance. Table 2 summarizes notable trials on solid tumor MRD. We also address limitations of TI-MRD and offer recommendations for clinical integration and future trials.

2. Methods

We conducted a targeted narrative review (2015–2025) focusing on prospective multicenter cohorts, randomized or embedded biomarker trials, and analytical validation studies evaluating tumor-informed ctDNA (TI-ctDNA) assays. The search included PubMed/MEDLINE, major peer-reviewed journals (e.g., *New England Journal of Medicine*, *Nature Medicine*, *Annals of Oncology*, and *Clinical Cancer Research*), and ClinicalTrials.gov. Eligible studies met the following inclusion criteria: (i) evaluation of TI-MRD/ctDNA or error-suppressed sequencing methods (e.g., duplex sequencing, PhasED-Seq); (ii) enrollment of ≥50 participants or multicenter design; and (iii) reporting of analytical performance metrics (limit of detection [LoD], specificity, and reproducibility) and/or clinical validity endpoints (lead time vs. imaging, disease-free survival [DFS]/event-free survival [EFS]/OS, or validated prognostic associations). Exclusion criteria included single-patient case reports, animal studies, conference abstracts without peer-reviewed data, and studies lacking

Table 1. Common mutations used in TI-MDR specific to cancer type

Cancer type	Most common mutations used in TI-MRD panels
CRC	*APC*, *TP53*, *KRAS*, *PIK3CA*, *SMAD4*[31]
Breast cancer	*TP53*, *PIK3CA*[32]
NSCLC	*EGFR*, *KRAS*, *TP53*, *ALK*, *BRAF*[33]
Bladder cancer	*TP53*, *FGFR3*[34]
AML	*NPM1*, *FLT3*, *DNMT3A*, *IDH1*, *IDH2*, *TET2*, *RUNX1*[35,36]
DLBCL	*MYD88*, *CD79B*, *EZH2*, *BCL2*, *CREBBP*[37]
CLL	*NOTCH1*, *SF3B1*, *TP53*, *ATM*, *BIRC3*[38]
Multiple myeloma	*KRAS*, *NRAS*, *DIS3*, *BRAF*, *TP53*[39]

Abbreviations: AML: Acute myelocytic leukemia; CLL: Chronic lymphocytic leukemia; CRC: Colorectal cancer; DLBCL: Diffuse large B-cell lymphoma; NSCLC: Non-small-cell lung cancer; TI-MDR: Tumor-informed minimal residual disease.

Table 2. Notable solid tumor clinical trials and findings

Trial name	Cancer	Patients	Platform	Mean follow-up duration	Purpose/findings	Limitations
CIRCULATE/ GALAXY	CRC	2083	Signatera	23 months	Post-operative MRD positivity stratifies DFS risk, and MRD negativity across serial time points has high negative predictive value for recurrence. [42,43]	• Prospective study limits causal inferences. • Heterogeneity of participating centers and treatment pathways may affect generalizability. • Relatively short follow up duration to capture OS.
VEGA	CRC	1240	Signatera	Ongoing	Ongoing. Evaluation for de-escalation of therapy in MRD-negative patients. Early findings suggest a promising trend toward safe de-escalation. [46]	N/A
ALTAIR	CRC	240	Signatera	Ongoing	Ongoing. Evaluation for escalation of therapy in MRD-positive patients.	N/A
DYNAMIC	CRC	450	Safe-SeqS	60 months	MRD-guided adjuvant management in stage II disease reduced unnecessary chemotherapy exposure while maintaining RFS.[47]	Small sample size compared to traditional adjuvant therapy trials.
NIAGRA	Bladder cancer	1530	Signatera	65 months	Higher MRD clearance with adjuvant chemotherapy and immunotherapy treatment is associated with improved EFS and OS.[49]	ctDNA reporting is exploratory in nature. Prospective ctDNA-guided interventional data are warranted.
IMVIGOR010	Bladder cancer	809	Signatera	47 months	Phase III preliminary results demonstrate poorer survival outcomes when MRD is detected post-surgery.[50]	Post-hoc MRD+subgroup risk finding is exploratory in nature. Prospective TI-MRD guided studies required for possible prognostic use.
IMVIGOR011	Bladder cancer	760	Signatera	16.3 months	Initial results from phase III trial indicate post-cystectomy MRD-positive patients experienced improvements in DFS and OS with adjuvant atezolizumab therapy versus placebo. [52]	Post-hoc/Exploratory analyses suggest possible benefits in DFS and OS, and need further prospective studies to establish utility.
TRACERx	NSCLC	842	ECLIPSE™	60 months	Detection of MRD correlated with increased tumor size and necrosis. In addition, MRD positivity detected molecular relapse a median of 70 days before CT imaging could detect relapse.[11]	Complex treatment history and evolving standards introduce heterogeneity that complicates causal inference for treatment-outcome questions.
AEGEAN	NSCLC	802	Invitae Personalized Cancer Monitoring™	25.9 months	Early post-operative MRD clearance correlated with improved EFS.[56]	• Longer follow up is needed to assess OS. • Timing of perioperative TI-MRD testing is variable; unclear which timepoint best produces long term benefit.
MERMAID I	NSCLC	330	ArcherDX Personalized Cancer Monitoring™	Ongoing	Ongoing trial assessing whether post-operative MRD-positive patients have improved DFS with chemotherapy+immunotherapy adjuvant treatment.[58]	N/A
MERMAID II	NSCLC	284	ArcherDX Personalized Cancer Monitoring™	Ongoing	Ongoing trial assessing MRD-positive patients following adjuvant therapy, treated with immunotherapy versus MRD-negative patients on surveillance with DFS as the primary endpoint.	N/A

(*Cont'd...*)

Table 2. (*Continued*)

Trial name	Cancer	Patients	Platform	Mean follow-up duration	Purpose/findings	Limitations
c-TRAK-TN	Breast cancer	161	Thermo Fisher custom TaqMan Assay Design Tool™	18 months	Higher incidence of metastatic disease upon MRD detection in post-immunotherapy patients. [62]	• Small MRD+treatment cohorts limit power to assess treatment effect. • Unclear whether intervening on MRD+changed DFS/OS.
I-SPY 2	Breast cancer	712	Custom TI-MRD assay/Signatera	44 months	Lack of ctDNA clearance from pretreatment levels in post-chemotherapy patients was associated with a higher rate of metastatic recurrence. [59]	Heterogenous assay platforms and lack of standardization complicate ctDNA clearance results.

Abbreviations: CRC: Colorectal cancer; CT: Computed tomography; ctDNA: Circulating tumor DNA; DFS: Disease-free survival; EFS: Event-free survival; MRD: Minimal residual disease; NSCLC: Non-small-cell lung cancer; OS: Overall survival; RFS: Recurrence-free survival; TI-MDR: Tumor-informed minimal residual disease.

sufficient methodological transparency. We prioritized solid tumors (colorectal, non-small-cell lung, breast, and bladder/urothelial cancers) and lymphoid malignancies (DLBCL and classical Hodgkin lymphoma [cHL]) given the availability of prospective data and clinical relevance of MRD-guided strategies. Study selection was justified by relevance to current clinical utility and analytical validation thresholds necessary for regulatory and translational applications.

3. Technology landscape

TI-MRD assays require prior sequencing of the patient's tumor or hematologic malignancy to identify a panel of somatic variants.[16] Each assay then uses ultra-sensitive plasma DNA sequencing to query those variants in the sample.[17] Current key platforms include Signatera, which typically tracks around 16 patient-specific single-nucleotide variants through multiplex polymerase chain reaction (PCR), has a turnaround time of 3 weeks, and has been shown to detect two tumor variants among the 16 queried in the panel, with over 98% statistical sensitivity at ctDNA concentrations of 0.01–0.02%.[18] In this context, statistical sensitivity refers to the modeled probability of correctly identifying true ctDNA molecules at or above a given variant allele frequency after error suppression, rather than the clinical detection rate itself. Residual disease and recurrence (RaDaR) is another platform that interrogates up to 48 personalized variants through PCR-NGS to detect MRD in multiple tumor types. It has claimed a variant allele frequency detection rate of 0.001% and a turnaround time of 7 days from collection to reporting.[19] Other assays include the PhaseED-Seq, NeXT Personal, and Duplex Sequencing.[17] Each platform requires several milliliters of plasma, and some require a few hundred nanograms of tumor DNA. All assays aim for high specificity by requiring detection of multiple variants, and in practice, most require at least 2–3 mutated molecules to call a sample MRD-positive. For completeness, some assays incorporate epigenetic (methylation) signatures rather than variant sequencing. One such example is Guardant Reveal, which uses tumor-agnostic testing, a fixed panel, and plasma methylation profiles to detect MRD without tumor sequencing.[20]

Tumor-informed ctDNA MRD platforms now span two broad classes: (i) whole-genome sequencing (WGS)-derived personalized panels that track thousands of variants with model-level error modeling (e.g., NeXT Personal), achieving parts-per-million sensitivity with >99.9% analytical specificity; and (ii) targeted, personalized multi-variant assays (such as RaDaR and Signatera-style multiplex PCR-NGS) typically tracking 16–48 bespoke variants with stringent multi-molecule calling to preserve specificity.[17,21-24] Phased-variant enrichment (PhasED-Seq) further enhances detection by leveraging co-occurring mutations within single ctDNA fragments, enabling reliable MRD detection at ppm levels in lymphoma and solid tumors.[25] Error-corrected duplex sequencing reduces background error rates to ~10^{-9} per base, improving confidence at ultra-low variant allele frequencies and informing assay design and confirmation strategies.[26,27] Collectively, these innovations underlie the superior analytical sensitivity that favors TI-ctDNA for MRD after curative-intent therapy. At the same time, tumor-agnostic approaches (e.g., fixed panels ± methylation such as Reveal/xM) increasingly complement low-shedding diseases or tissue-infeasible cases.[9,28] In addition, the significant costs associated with the TI-MRD assays are important. They may pose substantial barriers to patient access. High out-of-pocket expenses may deter patients from opting for these tests, potentially delaying the detection of MRD and leading to missed opportunities for the early intervention. Even with insurance coverage, the financial burden can be considerable, especially

for uninsured or underinsured individuals.[29,30] Some companies offer financial assistance programs to alleviate these burdens, but eligibility criteria and application processes can be complex and time-consuming. The variability in test costs and reimbursement policies across different platforms further complicates decision-making for both patients and healthcare providers. Therefore, while these assays hold promise for improving patient outcomes through early detection, their accessibility remains a critical concern that needs to be addressed to ensure equitable healthcare delivery.

4. Solid tumors

4.1. CRC

CRC, one of the most common cancers worldwide, is considered the "lead disease" setting for TI-MRD monitoring. This is due to several favorable characteristics, including high levels of tumor DNA shedding, well-defined surgical windows, and a wealth of prospective research.[40] Multiple prospective cohorts and trials have demonstrated that post-operative MRD positivity predicts recurrence.

A landmark study of 96 stage III colon cancer patients found MRD in 21% of post-surgery samples, which corresponded to an inferior 3-year relapse-free rate. MRD was detectable in 17% of post-adjuvant chemotherapy patients, corresponding to a decreased recurrence-free interval (30% vs. 77% if ctDNA negative; hazard ratio [HR] = 3.8).[8] The results suggest that TI-MRD is a powerful post-operative and post-adjuvant prognostic marker in stage II colon cancer. The results also indicated that MRD post-adjuvant therapy can identify a subset of the patient population at very high risk of relapse, which supports investigations of additional or alternative adjuvant strategies in future trials. This result has also been supported by findings from Reinert *et al.*,[41] which demonstrated the utility of TI-MRD testing for tracking treatment effects and predicting relapse earlier than imaging.

The CIRCULATE-Japan GALAXY observational study has provided compelling evidence supporting the clinical utility of MRD. Recent data confirm that post-operative ctDNA positivity sharply stratifies DFS risk.[42,43] At the same time, persistent ctDNA negativity across serial time points carries an exceptionally high negative predictive value for recurrence. Notably, updated 2024 analyses showed that patients who achieved ctDNA clearance with adjuvant therapy experienced a nearly 50% relative reduction in mortality, linking MRD clearance directly to improved OS.[44] In the most recent analysis of the GALAXY cohort, ctDNA has emerged as the single most powerful prognostic factor for OS, even outperforming other traditional, well-established clinicopathological features. Importantly, ctDNA positivity was associated with significantly higher mortality compared with ctDNA negativity, regardless of recurrence site. These findings highlight the urgency of integrating TI-MRD-guided strategies into clinical practice and further validate the hypothesis that observation alone may be sufficient for MRD-negative patients.[9]

Serial MRD monitoring further adds prognostic information. A study by Henriksen *et al.*[45] followed 168 patients with stage III CRC. They found that post-operative ctDNA positivity was associated with an HR of 7 for recurrence and post-adjuvant ctDNA positivity with an HR of 51. Only patients who cleared ctDNA permanently during adjuvant chemotherapy did not relapse. The ctDNA growth rate was also discovered to be prognostic of survival. Patients who never cleared ctDNA invariably relapsed, and intermittent sampling achieved a median lead time of 9.8 months over computed tomography imaging. This study demonstrated that serial post-operative MRD testing had a substantial prognostic value and enabled the assessment of tumor growth rate. Therefore, MRD testing enabled earlier intervention.

Several companion randomized trials are underway, including VEGA, which is evaluating the de-escalation of therapy in MRD-negative patients, and ALTAIR, which is testing the escalation with trifluridine/tipiracil in MRD-positive patients. Early findings suggest promising trends toward safe de-escalation in stage II CRC.[46] In addition, the DYNAMIC trials have provided complementary evidence, showing that ctDNA-guided adjuvant management in stage II disease reduced unnecessary chemotherapy exposure while maintaining recurrence-free survival (RFS). Long-term follow-up has further confirmed and validated these outcomes.[47] These results demonstrate the utility of TI-MRD for guiding therapy, whether through escalation or de-escalation.

Finally, a 2024 analysis published in *Nature Medicine* reinforced these observations, demonstrating that TI-MRD is strongly associated with both recurrence and OS following curative resection. Collectively, these data establish TI-MRD as a clinically validated biomarker with immediate relevance for tailoring adjuvant therapy in CRC.[9] The accumulated CRC evidence has spurred clinical uptake, as Signatera has Medicare coverage for Stage II-III CRC MRD testing in the adjuvant and recurrence-monitoring settings. To summarize, TI-MRD is a prognostically powerful tool in CRC, and current research is exploring its utility for de-escalation and escalation for stage II/II disease and adjuvant decision-making. Notably, patient populations differ in tumor stage, molecular subtype, and treatment regimen, which can alter ctDNA shedding dynamics and MRD prevalence. Assay

performance is influenced by both biological and technical factors: different platforms vary in the number of tracked variants, sequencing depth, error-suppression strategies, and limits of detection, all of which affect sensitivity. Sampling time points, such as immediately post-surgery versus during adjuvant therapy or long-term surveillance, can also influence ctDNA detectability due to transient spikes from tumor cell death or clearance. Collectively, these variables mean that results from one platform, timepoint, or cohort may not be directly extrapolated to others, underscoring the need for careful interpretation and, ideally, cross-platform validation when applying TI-MRD findings to broader clinical settings.

4.2. Bladder: Muscle-invasive bladder cancer

Data on bladder cancers are an emerging field of study. Studies testing the utilization of TI-MRD for prognostic classification have shown promising results. A 2025 study studied MRD status in post-radical cystectomy patients and its association with disease recurrence.[48] Results indicated that patients with MRD-negative status post-surgery had significantly longer RFS than those with positive status. In addition, the MRD positivity reduced post-surgery, and those who converted to MRD negative status post-surgery showed more prolonged survival than those who remained MRD positive (36 months vs. 18 months). An exploratory ctDNA analysis from the NIAGARA trial corroborated these results, demonstrating significantly greater ctDNA clearance with perioperative durvalumab plus neoadjuvant chemotherapy compared with chemotherapy alone, with clearance strongly associated with improved EFS and OS.[49] Both studies showed a link between MRD-negative status and improved survival. MRD status has also demonstrated superiority to radiologic evidence of recurrence, with ctDNA positivity preceding radiologic presence by a median of 6 months.

In the phase III IMvigor010 trial, preliminary results among patients with urothelial carcinoma following surgery demonstrated poorer survival outcomes when tumor-derived DNA was detected in the bloodstream. Notably, ctDNA-positive patients derived a survival benefit from adjuvant atezolizumab compared with observation (OS HR = 0.59; 95% CI: 0.42–0.83).[50] Furthermore, the magnitude of ctDNA reduction with atezolizumab was associated with longer OS. These findings suggest that ctDNA positivity in muscle-invasive urothelial carcinoma identifies patients most likely to benefit from adjuvant immunotherapy. A prospective trial is ongoing to validate this strategy. In addition, initial results from the phase III IMvigor011 trial (NCT04660344) further strengthen this evidence. Using the Signatera MRD assay, patients with muscle-invasive bladder cancer who were MRD-positive after cystectomy experienced statistically significant and clinically meaningful improvements in both DFS and OS with adjuvant atezolizumab versus placebo.[51,52] Patients who tested MRD-positive but remained radiographically disease-free were randomized to atezolizumab or placebo, while persistently MRD-negative patients continued surveillance with serial ctDNA testing and imaging. The trial enrolled 760 high-risk patients, and results are anticipated to be presented within the year.

As of 2025, ctDNA-based MRD is clinically applied for surveillance and risk stratification, while therapeutic applications are actively being investigated in ongoing randomized trials.

4.3. Non-small-cell lung cancer

The TRACERx study[11] sequenced 100 resected NSCLCs using tumor-informed assays and detected >2 ctDNA variants preoperatively in 48% of patients who developed relapse, and demonstrated that MRD detection correlated with tumor size and necrosis. In addition, post-resection, phylogenetic MRD testing detected molecular relapse a median of 70 days before CT imaging could detect relapse. In 4/13 relapse cases, the lead time between molecular detection and imaging detection exceeded 6 months. In this cohort, ctDNA positivity post-treatment predicted eventual relapse and could identify subclonal sources of metastases. Similar findings have been reported in other studies,[53-55] which reiterate the utility of MRD as a means to stratify risk for earlier recurrence and worse RFS/OS.

The AEGEAN phase III trial demonstrated that perioperative durvalumab combined with chemotherapy significantly improved outcomes in patients with resectable stage IIA–IIIB NSCLC. Specifically, pathologic complete response rates were higher with durvalumab plus chemotherapy compared to chemotherapy alone (17.2% vs. 4.3%; $p<0.001$), and EFS was prolonged (HR = 0.68; 95% confidence interval: 0.53–0.88).[56] Subgroup analyses further suggested that ctDNA dynamics, such as early post-operative clearance, correlate with improved EFS, supporting ctDNA's role as a pharmacodynamic biomarker in a perioperative setting. The NADIM II trial also corroborated these results,[57] demonstrating that ctDNA clearance correlates with pathologic response and superior outcomes in patients undergoing neoadjuvant chemo-immunotherapy; however, it used tumor-agnostic MRD assays.

Furthermore, several ctDNA-guided randomized trials are currently underway. MERMAID-1 (NCT04385368) enrolls resected stage II–III NSCLC patients who are MRD-positive postoperatively, randomizing them to durvalumab plus chemotherapy or placebo plus chemotherapy, with DFS

as the primary endpoint.[58] MERMAID-2 (NCT04642469) focuses on MRD-positive patients following adjuvant therapy, comparing durvalumab with placebo, while MRD-negative patients continue surveillance. DFS remains the primary endpoint, and enrollment is ongoing.

Collectively, the data indicate that perioperative durvalumab plus chemotherapy improves pathologic complete response and EFS, and that ctDNA dynamics may serve as an early predictive biomarker. Ongoing trials will clarify the clinical utility of ctDNA-guided adjuvant interventions in NSCLC.

4.4. Breast cancer

Circulating ctDNA is detectable more frequently in high-risk subtypes (triple-negative and HER 2+) than in ER+ breast cancer.[59] A 2025 study in *Annals of Oncology* demonstrated that WGS-derived tumor-informed ctDNA detection in early breast cancer is feasible and can identify disease before imaging, with median lead times exceeding 6 months.[60] Similarly, another ultra-sensitive ctDNA platform detected ctDNA in all cases of recurrence, with a median lead time of approximately 417 days (range: 4–1,931 days). In addition, it demonstrated that early-on therapy persistence of ctDNA strongly predicted poor outcomes.[61] Limitations of these studies included low intervention uptake and modest sensitivity thresholds. Despite this, next-generation ultra-sensitive assays, particularly WGS-based platforms, hold promise for expanding detection windows, improving lead times, and enhancing both trial design and intervention efficacy.[60]

Promising results have also been observed using the Signatera assay in a study of 49 patients with high-risk stage I–III breast cancer within 3 years of treatment with surgery and adjuvant chemotherapy. Serial analysis with Signatera predicted 16/18 relapses with no false positives and demonstrated a median lead time of 8.9 months compared to clinically detected relapses.[2] Adjuvant-treated patients with MRD had dramatically inferior metastasis-free survival. A separate study using Signatera in 84 high-risk stage II–III breast cancer patients in the I-SPY 2 trial was able to demonstrate that the lack of ctDNA clearance from pretreatment levels in post-chemotherapy patients was associated with poor treatment response and ultimately a higher rate of metastatic recurrence.[59] The study also demonstrated that after completing neoadjuvant chemotherapy, 17/60 of the ctDNA pretreatment-positive patients who achieved a pathologic complete response were concordantly MRD-negative.[59]

The c-TRAK-TN trial, a phase II prospective study in early triple-negative breast cancer, employed ctDNA surveillance to trigger pembrolizumab therapy. The study revealed a high incidence of metastatic disease at the time of ctDNA detection. Notably, only a small subset of patients initiated pembrolizumab, and none achieved sustained ctDNA clearance.[62]

These findings and trials highlight the challenges of early intervention based on ctDNA alone and suggest that next-generation ultra-sensitive assays may improve early detection, patient selection, and therapeutic outcomes.

5. Clinical evidence in hematologic malignancies

5.1. DLBCL

DLBCL is curable; however, patients with residual disease after therapy invariably experience progression. Ultrasensitive methods for detecting MRD can improve the determination of remission and risk of relapse. The sequencing of immunoglobulin gene rearrangements or genome-wide mutations is typically used to assess TI-MRD testing in DLBCL. Results from a 2025 study analyzed ctDNA-MRD in 137 patients. They demonstrated that progression-free survival (PFS) for patients with positive versus negative MRD after completion of treatment was 29% versus 97%, respectively, with an HR = 28.7.[13] They demonstrated that MRD status at the end of therapy (EOT) had greater prognostic utility than conventional lymphoma response criteria based on positron emission tomography (PET) scans. Among PET-negative patients at the end of treatment, those with MRD still had a poor 2-year PFS (31%), whereas PET-positive but MRD-negative patients had a 93% 2-year PFS.[13] The prognostic value of TI-MRD testing was also demonstrated by Wang *et al.*[63] In this study, 150 patients with DLBCL were evaluated for MRD status at the EOT, with 76% MRD-negative and 24% MRD-positive. It was found that MRD-positive status significantly predicted inferior 2-year PFS (88% vs. 28%; HR = 9.7) and lower OS (97% vs. 50%; HR = 10.6). These results highlight the utility of TI-MRD for prognostic adjudication in DLBCL and the potential to identify patients who may benefit from consolidation therapy.

Aside from prognostic uses, recent studies are examining the use of MRD to guide therapeutic decisions. The SHORTEN-ctDNA trial is an ongoing trial testing de-escalation strategies. They are testing the feasibility and safety of shortening treatment based on early MRD clearance in patients (after three cycles).[64] The ALPHA-3 trial, on the other hand, is developing an escalation concept to determine whether MRD+ patients at the EOT benefit from consolidation therapy with cemacabtagene ansegedleucel (cema-cel) when compared with observation.[65] In terms of practical takeaways for clinicians, MRD testing can be performed at baseline, after

two cycles, and at the EOT to assess prognosis and relapse risk. A positive MRD should alert to a high risk, even if the PET is clean. Changing therapy based strictly on MRD results is not advised at present, as trials are ongoing.

5.2. Hodgkin lymphoma

cHL is a highly curable disease with the currently available therapeutics. However, patients with relapsed or refractory disease have lower survival rates, especially those after autologous bone marrow transplantation.[66] Therefore, accurate identification of patients at risk of relapse can help intensify therapy or de-escalate therapy in those at lower risk of relapse. A study examining 366 cHL patients utilized MRD to identify patients with very low relapse risk who might safely have less aggressive therapy. Researchers used pretreatment and on-treatment MRD levels to refine cHL risk prediction longitudinally and to detect radiographically occult MRD.[67] The study observed rapid molecular response with induction regimens, with MRD negativity rates rising to 38%, 85%, and 90% with each successive cycle of therapy. Accordingly, patients with higher MRD had inferior PFS at multiple timepoints. Recent studies and trials have also utilized TI-MRD as a prognostic marker in cHL. A 2024 pooled TI-MRD analysis demonstrated that across various cohorts, TI-MRD positivity during treatment and at the end of treatment was highly predictive of treatment failure[68] as MRD positive status remained strongly associated with worse PFS (HR = 9.9). Notably, patients who showed a complete response on PET scan but were ctDNA positive frequently relapsed. This highlights the complementary nature of TI-MRD testing alongside imaging. The NCI/CLARITY dataset demonstrated that undetectable ctDNA at the end of treatment predicted extremely low relapse risk and outperformed end-of-treatment PET/CT for PFS stratification; as many PET-positive findings proved to be false positives when TI-MRD was negative and biopsies were done.[69] To further reinforce the prognostic use of TI-MRD for cHL, a 2024 study examined the efficacy of pembrolizumab + AVD (doxorubicin, vinblastine, and dacarbazine). In a long-term follow-up, TI-MRD was assessed post-treatment, and it was observed that no patient who cleared ctDNA had relapsed to date; despite a notable rate of interim end-of-treatment PET positivity.[70]

Prospective trials are testing the use of TI-MRD to guide therapy choices in cHL. Trials such as PRECISE-HL are planning to study TI-MRD in relapsed/refractory cHL to steer de-escalation of chemotherapy in patients with the early deep molecular responses. The NCT06745076 trial also seeks to test personalized reduction of chemotherapy intensity for advanced cHL based on early clearance of ctDNA.

5.3. AML

In AML, peripheral blood ctDNA MRD assays are emerging as noninvasive alternatives to repeated bone marrow biopsies. The European Leukemia Net has recommended MRD testing for AML with specific genetic abnormalities.[71] Short *et al.*[72] demonstrated that ctDNA sequencing could detect new or persistent leukemia-associated mutations during remission that heralded overt relapse. Furthermore, they revealed that MRD could identify clinically relevant mutations that were not detectable in bone marrow and could help assess measurable residual disease.

Multiple trials have tested the prognostic value of MRD in AML. Among these are the pre-MEASURE trial and follow-ups. The study sought to assess whether MRD in remission patients before allogeneic hematopoietic cell transplant (HSCT) could identify those at increased risk of subsequent relapse and death. The study found that MRD-positive patients, particularly those with tumor cells with *FLT3* and *NPM1* mutations, were associated with a 47% increased risk of relapse; and a 24% difference in survival at 3 years compared to MRD-negative patients who underwent allogeneic HSCT.[73] However, relapse and worse survival were partially mitigated in younger patients who received high-intensity myeloablative conditioning, which could have consequences for conditioning choice and pre-HSCT intervention in AML patients. The prognostic value of MRD testing in AML was also demonstrated by Hirsch *et al.*[74] who found that MRD-positive patients with *DNMT3A*, *TET2*, and *ASXL1* mutations were associated with poorer prognosis, and that multiple co-existing mutations in complete remission were associated with a higher incidence of relapse, lower RFS, and lower OS. Another study, involving 76 *NPM1*-mutated AML patients, also sought to study the prognostic efficacy of MRD testing. They determined that MRD-negative patients have an overall 2-year survival of 84%, compared with 46% for MRD-positive patients.[75] Furthermore, 22/44 of the MRD-negative patients elected to stop therapy after a median of eight cycles and were found to have a 2-year treatment-free remission rate of 88%.

Trials have also been conducted to test the possibility of using MRD to guide therapy. The RELAZA2 trial assessed whether pre-emptive azacitidine for MRD-positive patients could prevent relapse. The authors demonstrated that at 6 months of treatment, 58% of MRD-positive patients were relapse-free; and at 12 months, relapse-free survival was 46%.[76] Thus, these findings prove that pre-emptive therapy with azacitidine can prevent or delay hematological relapse in MRD-positive AML patients who are at high risk of relapse. The GIMEMA AML1310 trial utilized MRD to classify post-treatment patients into

favorable, intermediate, and poor-risk groups. Favorable risk groups received autologous stem cell transplant (AuSCT), poor risk patients received allogeneic stem cell transplant (AlloSCT), and intermediate risk patients received either AuSCT or AlloSCT based on MRD levels. If MRD was positive, patients received the more aggressive AlloSCT, while MRD-negative patients received the less aggressive AuSCT. Results indicated that intermediate-risk patients assigned to AuSCT or AlloSCT had outcomes like those in the favorable-risk group.[77] The results support a personalized post-remission strategy that uses MRD to guide transplant intensity, which maintains efficacy while reducing unnecessary toxicity.

5.4. CLL

In CLL, TI-MRD complements marrow/flow MRD, reflecting total-body disease and clonal evolution under targeted agents. Early EOT ctDNA negativity after time-limited regimens (e.g., BTK inhibitor + BCL2 inhibitor) correlates with durable remissions; however, evolving subclones and low ctDNA levels necessitate broad variant panels and periodic sampling to avoid false negatives.[78,79] The MURANO trial aimed to investigate the prognostic value of TI-MRD for treatment efficacy in patients with refractory/relapsed CLL. Patients were given venetoclax + rituximab (VenR) versus bendamustine + rituximab (BR), and MRD was measured serially. Results indicated that VenR produced higher rates of undetectable MRD (uMRD), and higher uMRD rates at EOT predicted prolonged PFS.[80] In addition, MRD reappearance commonly preceded clinical progression by a median time of 25 months, thus giving a meaningful lead time window and highlighting TI-MRD as an early warning biomarker for relapse.[80] The CLL14 was another trial that aimed to explore the prognostic role of TI-MRD in CLL patients. They compared venetoclax + obinutuzumab (VenO) versus chlorambucil + obinutuzumab (ClbO) and utilized MRD as an endpoint. Results showed that high uMRD rates were associated with superior PFS and OS, supporting the use of VenO.[81] This validated TI-MRD as a prognostic endpoint for measuring efficacy in first-line CLL.

Trials have also explored TI-MRD as a therapy guiding option for CLL patients. The CAPTIVATE trial treated CLL patients with ibrutinib + venetoclax, and those who achieved uMRD were randomized to either treatment cessation or continuation of ibrutinib. DFS remained extremely high in both arms (95% placebo; 100% continuation), thus supporting the safety of fixed-duration/MRD-guided cessation of therapy in patients with uMRD.[82] The VISION trial also lent credence to the usage of TI-MRD in therapeutic de-escalation strategies. Refractory/relapsed CL patients received ibrutinib + venetoclax with a TI-MRD-guided stop/start rule; as patients who achieved uMRD could stop therapy while MRD reappearance triggered re-initiation. The trial demonstrated that MRD-guided cessation and reinitiation were safe, as high 1-year PFS and longer follow-up confirmed durable control in those who stopped treatment and effective responses on retreatment in those who required reinitiation.[83,84] Multiple other trials are ongoing, such as the MAJIC trial[85] and the CLL17 trial[86] to further explore this aspect of TI-MRD testing in CLL.

5.5. Multiple myeloma

Multiple myeloma has a 5-year OS of 48.5% for newly diagnosed multiple myeloma patients, and although therapy has improved survival rates, patients eventually relapse due to the presence of remnant tumor cells. Multiple myeloma is usually monitored by bone marrow MRD using flow cytometry but can also be monitored by ctDNA assays to track patient-specific mutations in myeloma, such as unique immunoglobulin rearrangements. Dhakal *et al.*[12] demonstrated that ctDNA MRD-positive patients had a median PFS of 31 months, compared to 84 months for MRD-negative patients. They also showed that TI-MRD assays had a higher positive predictive value for relapse than bone marrow flow cytometry (93% vs. 68%).[12] In addition, a study by Mithraprabhu *et al.*[87] demonstrated that MRD status and early molecular response to therapy, as defined by ctDNA reduction, improved risk stratification. Patients who achieved both ctDNA reduction and MRD negativity had significantly better outcomes than those who did not.

MRD is also being studied to adapt therapy in selected patients. The MASTER trial assessed MRD-adapted treatment in which patients received daratumumab + carfilzomib/lenalidomide/dexamethasone (Dara-Krd) ± AuSCT, and treatment duration was shortened for patients who achieved MRD negativity. Groups were also stratified based on the number of high-risk chromosomal abnormalities (HRCA). Results indicated that 3-year PFS rates were very favorable for patients with sustained MRD negativity who discontinued therapy early, and this held across risk groups. PFS was 88% in the low-risk groups, and 50% survival in patients with 2+ HRCA multiple myeloma.[88] This result provides proof for a pathway for treatment cessation in most patients with newly diagnosed multiple myeloma. The FORTE trial examined carfilzomib-lenalidomide-dexamethasone (KRd) strategies, specifically whether the addition of AuSCT affected MRD status. Results indicated that KRd + AuSCT produced more profound and sustained MRD negativity than KRd alone, and that MRD negativity strongly predicted longer PFS and OS.[89] This result reinforced the fact that MRD status can help inform post-induction strategy. Other trials, such as

the CASSIOPEIA trial, also yield similar results, showing that MRD status post-therapy or intra-therapy can inform therapeutic choices and contribute to prolonged PFS and OS, with decreased toxicity from unnecessary treatment.[90]

6. Limitations

While TI-MRD is emerging as an effective tool for stratifying risk and monitoring treatment response, certain limitations still exist that prevent its widespread use in the clinical setting. Future research should primarily focus on formulating standards and guidelines. A lack of guidelines for optimal ctDNA sampling time points is a significant concern. When is the ideal time to start sampling patients for MRD after EOT to predict relapse, and are there any changes in sensitivity at different timepoints? As mentioned, there are several platforms for detecting TI-MRD, such as PhasED-Seq, Signatera, and clonoSEQ. Each assay has a different LoD, error suppression methods, and reporting formats, which can lead to non-equivalent MRD results across labs. TI-MRD is also not 100% sensitive, as a minority of MRD-negative patients may still relapse. False-negative results may be due to low shedding, timing of sampling, or anatomic factors. Clonal hematopoiesis can yield false positives, and some tumors shed very little ctDNA, which can increase the risk of false negatives.[91,92] Therefore, the importance of serial sampling and complementary imaging remains critical for assessing for relapse/recurrence.[93]

There are also concerns regarding the lack of standardization in technical standards, including types of collection tubes and the number of centrifugation steps needed to process samples.[94,95] The studies demonstrate that storage temperature and centrifugation protocols affected ctDNA yield and analysis. Future research should focus on refining detection methods and establishing standardized protocols across diverse cancer populations. To date, trials have used different timepoints to assess MRD. For example, some tests are performed 4–8 weeks post-treatment, others at the EOT, and some prior to AuSCT.[96] Different action rules also make standardization difficult, such as escalating therapy at any presence of MRD versus requiring confirmed persistence. A lack of if-then algorithms reduces clinical confidence in the algorithm's utility. Cost is another barrier to widespread adoption, as tumor-informed assays and repeated serial testing are costly and require infrastructure that may not be readily available in all settings. In addition, variations in access and reimbursement can lead to equity concerns.[29,97]

7. Conclusion

TI-MRD testing has rapidly advanced from a proof of concept to clinical readiness in several cancers. The evidence is most mature in CRC among solid tumors, as trials such as CIRCULATE, DYNAMIC, and GALAXY have consistently demonstrated that TI-MRD stratifies recurrence risk and can guide adjuvant therapeutic decisions. In the other solid tumors, it is a rapidly maturing biomarker for recurrence/relapse surveillance. The strong HRs indicate that MRD detection identifies a very high risk of relapse, detectable before clinical or radiological signs appear. In some hematologic malignancies, it already informs clinical decisions in trials, such as TI-MRD-guided cessation or preemptive therapy in AML and multiple myeloma. It can adjudicate equivocal imaging in lymphomas, such as in DLBCL.[98,99] Having demonstrated the prognostic validity of TI-MRD in many cancers, the next step is to evaluate its predictive value by showing that acting on MRD status in patients leads to improved outcomes, as trials such as DYNAMIC in CRC are assessing. To maximize the clinical impact and standardize implementation, future research should focus on the following:

(i) Assay standardization, including consensus on the number and type of variants to track, sequencing depth, and error-suppression techniques.
(ii) Optimized sampling intervals, tailored to tumor type, treatment phase, and risk profile, to reliably capture MRD dynamics while balancing feasibility.
(iii) Integration with conventional modalities, such as imaging, pathology, and clinical assessment, to refine decision-making in equivocal cases and improve early relapse detection.
(iv) Cross-platform validation to ensure findings is generalizable across different TI-MRD assays and patient populations.

While awaiting therapy guidance results, we suggest using TI-MRD in conjunction with other modalities, such as imaging, pathology, and clinical features, when making decisions about patient care.

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The authors declare that they have no competing interests.

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