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Systematic review

CIRCULATING TUMOR DNA FOR MOLECULAR RESIDUAL DISEASE DETECTION AND MULTICANCER EARLY DETECTION: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Circulating tumor DNA (ctDNA) is one of the most clinically advanced liquid biopsy technologies in oncology, but its value differs between molecular residual disease (MRD) assessment after curative-intent treatment and multicancer early detection (MCED) in asymptomatic populations.

Objective: To evaluate the clinical effectiveness, actionability, and certainty of evidence for ctDNA-based MRD strategies and cfDNA- or ctDNA-based MCED pathways.

Methods: The review followed PRISMA 2020 and PRISMA-S. Bibliographic databases and trial registries were searched through July 9, 2026, with a targeted evidence update on July 15, 2026. Two reviewers independently screened records, extracted data, and assessed risk of bias using RoB 2, QUIPS, ROBINS-I, or QUADAS-2 according to study design. Certainty was evaluated using GRADE. Meta-analysis was not undertaken because of substantial clinical and methodological heterogeneity.

Results: Fifty-four unique records were screened. Twenty-nine completed reports representing 25 study programs were included in the narrative synthesis, and three ongoing or incompletely published programs were described separately. In the randomized DYNAMIC trial, ctDNA-guided management reduced adjuvant chemotherapy use in stage II colon cancer from 28% to 15%; five-year recurrence-free survival was 88% versus 87%. In IMvigor011, atezolizumab improved disease-free survival in ctDNA-positive muscle-invasive bladder cancer (hazard ratio 0.64, 95% confidence interval 0.47-0.87) and overall survival (hazard ratio 0.59, 95% confidence interval 0.39-0.90). For MCED, PATHFINDER 2 reported 60.3% positive predictive value and 99.6% specificity in a conference abstract, whereas NHS-Galleri did not meet its primary endpoint for reducing stage III-IV cancers.

Conclusions: ctDNA has demonstrated clinical utility in selected MRD settings when a prespecified test result is linked to an effective treatment decision. In many other tumors it remains primarily prognostic. MCED testing has shown feasibility and high specificity, but mortality benefit and net population-level benefit remain unproven; broad implementation is therefore premature.

Keywords: circulating tumor DNA, ctDNA, liquid biopsy, molecular residual disease, minimal residual disease, multicancer early detection, MCED, systematic review

1. Introduction

Liquid biopsy has moved in recent years from a largely experimental concept into the domain of clinically meaningful tools in personalized oncology [1-12]. One of its most extensively studied components is the analysis of circulating tumor DNA, which may reflect the presence of a tumor clone, its molecular features, and disease dynamics [1-2,5-8,10,13]. ctDNA is being evaluated across several clinical uses, including detection of molecular residual disease after curative-intent treatment, early detection of molecular relapse, monitoring of treatment response, and development of blood-based approaches for multicancer early detection [1-24].

The clinical meaning of ctDNA cannot be reduced to the ability to detect tumor-derived DNA fragments in plasma. The more important question is whether test results lead to changes in medical management that improve outcomes or safely reduce unnecessary treatment [14-15,25-28]. This distinction is fundamental in oncology. An analytically sensitive assay may detect a molecular signal accurately, yet still lack demonstrated clinical utility [3-4,9,16-17].

For a ctDNA-guided strategy to be clinically credible, it must show more than an association between a positive result and recurrence risk [1-2,5-8,13,18-22,29]. It must also show an effective downstream action, such as initiation, omission, intensification, or de-escalation of treatment, modification of surveillance, or early therapeutic intervention [14-15,25-28].

Molecular residual disease detection and multicancer early detection represent different clinical scenarios and should not be judged by identical standards. MRD testing is performed in patients with a known cancer diagnosis after treatment given with curative intent [1,5-7,14-15,18-22,26-29]. In this setting, pre-test recurrence risk remains clinically important, and ctDNA detection may serve as a marker of persistent microscopic tumor burden [1-2,5-8,13,18-22,29]. Its potential value lies in improved selection for adjuvant therapy, reduction of treatment intensity in patients at lower risk, escalation of therapy in patients at high molecular risk, or earlier intervention when molecular relapse is detected [14-15,25-28].

Multicancer early detection requires a different evidentiary logic. Unlike MRD testing, MCED is intended for

asymptomatic people or screening-eligible populations [4,9,11,16,23]. Cancer prevalence is substantially lower in this setting. Even high specificity may therefore produce a clinically meaningful number of false-positive results [11,23-24]. Such results may initiate additional diagnostic cascades, including repeat laboratory testing, imaging, invasive procedures, emotional distress, and potential overdiagnosis [11,23-24]. For MCED, it is insufficient to demonstrate detection of a cancer signal or prediction of the tissue of origin [4,9,16-17]. The test must identify clinically meaningful cancers at earlier stages without creating excessive harm, and should ultimately reduce mortality or produce a substantial and durable shift in population-stage distribution [30-31].

This systematic review therefore evaluates ctDNA-based strategies separately for two key domains. The first domain is molecular residual disease detection after potentially curative treatment [1,5-7,14-15,18-22,25-29]. The second is multicancer early detection [4,9,11,16,23-24,30-32]. This separation avoids methodological mixing of distinct clinical tasks and allows a more precise assessment of where ctDNA can already be considered a tool for clinical decision-making and where further testing is required in randomized trials, diagnostic pathway studies, and implementation studies that assess accuracy, outcomes, safety, and health-system feasibility [14-15,27,30-31].

2. Methods

2.1. Protocol and eligibility criteria

This systematic review was conducted in accordance with PRISMA 2020 and PRISMA-S reporting principles [33-34]. The protocol was not prospectively registered. Eligibility criteria were structured separately for MRD after curative-intent treatment, post-treatment recurrence monitoring, and MCED in asymptomatic or screening-eligible populations.

Eligible MRD studies were randomized trials, prospective interventional studies, and longitudinal prognostic cohorts in solid tumors. For intervention studies, the ctDNA result had to be linked to a prespecified management action, including administration, omission, escalation, or de-escalation of systemic therapy, modification of surveillance, or initiation of treatment at molecular relapse [14-15,21,25-28]. Primary outcomes were recurrence-free survival, disease-free survival, overall survival, recurrence, treatment exposure, and toxicity.

For prognostic MRD studies, ctDNA had to be measured after completion of curative-intent treatment or during serial follow-up and related to subsequent clinical or radiological recurrence [1-2,5-7,13,18-22,29]. Cross-sectional analytical studies without longitudinal clinical outcomes were used only as technological context and were not graded as evidence of clinical effectiveness.

Eligible MCED studies included prospective screening or diagnostic-pathway studies in asymptomatic or screening-eligible participants with reported diagnostic resolution after a positive result [11,23-24,30,32]. Case-control classifier-development studies and biobank-only validation studies were retained as supporting evidence for analytical or diagnostic validity but were not treated as independent evidence of population screening benefit [3-4,8-10,12,16-17].

Exclusion criteria were hematologic malignancies, single case reports, technical reports without clinically interpretable outcomes, commercial or news materials, reviews without original data, and publications without transparent methods. Ongoing programs without any effectiveness or diagnostic-performance results were described separately and were excluded from risk-of-bias and GRADE assessments. Conference abstracts reporting outcome data were appraised provisionally using the information available at the review cutoff, with limitations related to incomplete reporting incorporated into risk-of-bias and certainty judgments

2.2. Information sources and search strategy

The main search was conducted from database inception to July 9, 2026 in MEDLINE via PubMed, Embase via Elsevier, Scopus, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials. Trial searches covered ClinicalTrials.gov, WHO ICTRP, ISRCTN, and jRCT. A targeted update search on July 15, 2026 was undertaken to identify newly published reports and major 2026 conference abstracts, including ALTAIR, PATHFINDER 2, and NHS-Galleri. Complete source-specific strategies are provided in Supplementary Table S1.

Search concepts combined circulating tumor DNA, cell-free DNA, liquid biopsy, molecular or minimal residual disease, recurrence or surveillance, multicancer early detection, solid tumors, and cancer. No date restriction was applied in the main search. English-language and human-study limits were applied where supported by the platform. Conference abstracts were retained only when they represented the most recent report of a major ongoing program and were clearly identified as non-peer-reviewed evidence.

2.3. Study selection and data management

Records were managed in a reference-management workspace. Deduplication used DOI, PMID, normalized title, first author, publication year, and trial registration identifier. Registry entries were linked to publications but retained as separate records when they supplied current recruitment or reporting status.

The complete executable search strategies are reported in Supplementary Table S1 rather than repeated in the main text.

After deduplication, 54 unique records were available for screening, comprising 42 bibliographic records and 12 trial-registry records. Screening was performed independently by two reviewers, with disagreements resolved by discussion and, when necessary, adjudication by a third reviewer.

2.4. Data extraction

Two reviewers independently extracted bibliographic details, tumor type and stage, study design, sample size, assay type, tumor-informed or tumor-agnostic approach, sampling time, clinical decision algorithm, comparator, endpoint definitions, numerical effect estimates with confidence intervals, follow-up, publication status, funding, and conflicts of interest. The completed study-level extraction table is provided in Supplementary Table S3, and the reusable extraction template is provided in Supplementary Table S7.

MRD outcomes included recurrence-free survival, disease-free survival, overall survival, molecular clearance, treatment exposure, and toxicity. MCED outcomes included cancer signal detection rate, sensitivity, specificity, positive predictive value, cancer signal origin accuracy, diagnostic resolution, false-positive investigations, invasive procedures, psychosocial outcomes, and stage distribution.

2.5. Risk of bias and certainty of evidence

Randomized trials were assessed with RoB 2 and classified as low risk, some concerns, or high risk [35]. Prognostic factor studies were assessed with QUIPS [36]. Non-randomized studies estimating effects of interventions were assessed with ROBINS-I [37]. Diagnostic accuracy and diagnostic-pathway studies were assessed with QUADAS-2 [38]. Domain-level judgments are reported in Supplementary Table S4.

Certainty of evidence was evaluated by outcome using GRADE domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias [39]. Because several questions were informed by a single randomized trial or by heterogeneous observational cohorts, certainty ratings were not inferred directly from study design. The evidence profile is reported in Supplementary Table S5.

2.6. Data synthesis

A structured narrative synthesis was performed. MRD-guided interventional studies, prognostic and observational MRD evidence, MCED diagnostic pathway studies, and studies of harm, economic consequences, and implementation were evaluated separately. Interpretation prioritized not only analytical or diagnostic accuracy, but also the presence of a complete clinical chain. This chain required detection of a molecular signal, change in clinical decision-making, delivery of a defined intervention, and impact on outcomes or potential harm.

The completed PRISMA 2020 checklist is provided in Supplementary Table S6.

3. Results

3.1. Study selection

A total of 54 unique records entered title, abstract, or registry screening. Twelve records were excluded at this stage, leaving 42 reports that were sought and retrieved for full-text assessment. Ten reports were excluded after full-text review. Twenty-nine completed reports representing 25 study programs were included in the narrative synthesis, while three ongoing or incompletely published programs were described separately. The study-selection process is shown in Figure 1. Full-text exclusion categories are provided in Supplementary Table S2.

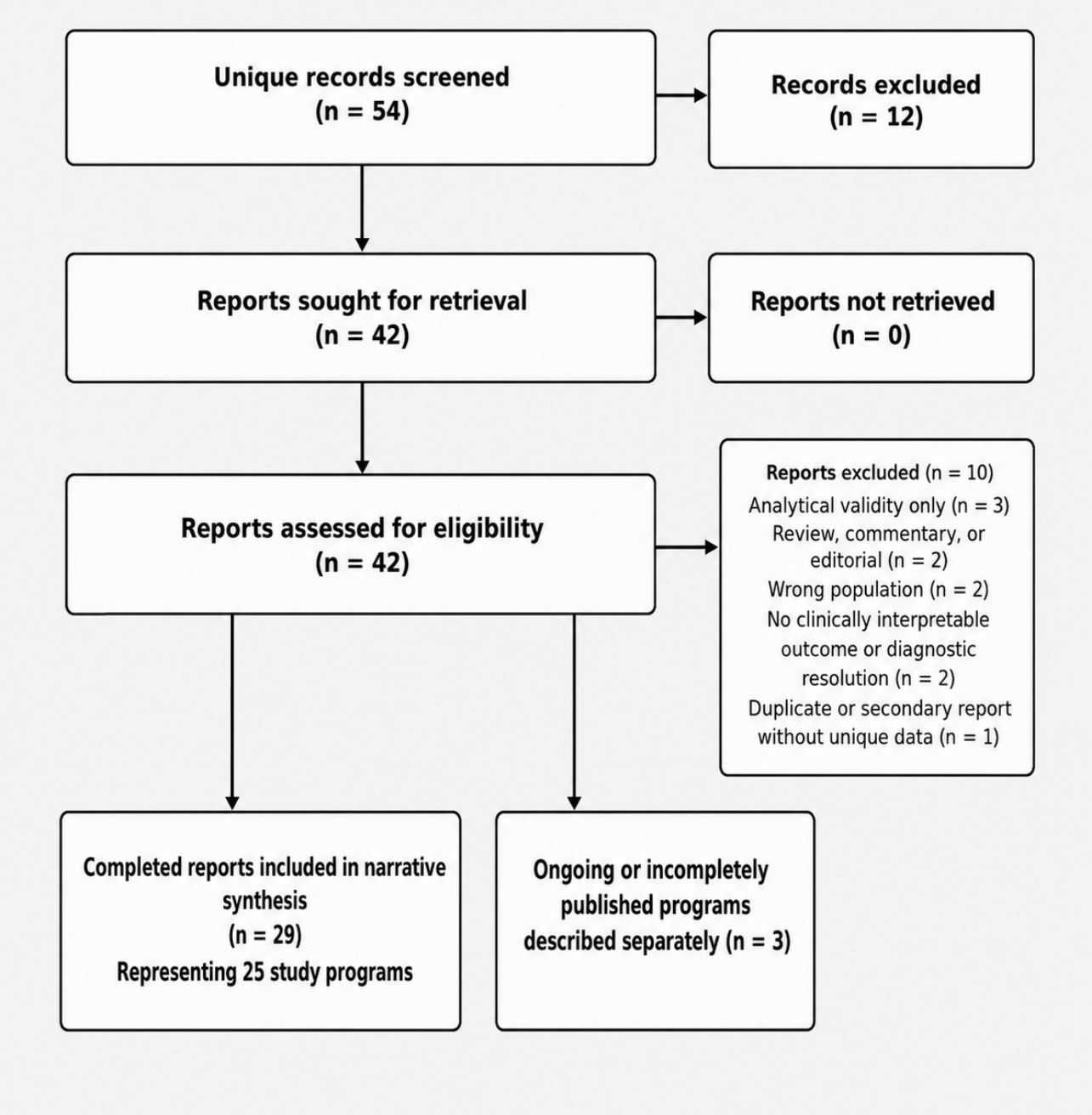

Figure 1. PRISMA 2020 flow diagram

3.2. Characteristics of included studies

The completed evidence was divided into MRD-guided intervention studies, longitudinal prognostic MRD studies, MCED diagnostic-pathway studies, and analytical or classifier-validation studies used as supporting context. Key characteristics are summarized in Table 1, and full extraction is provided in Supplementary Table S3.

The most clinically actionable evidence came from DYNAMIC in stage II colon cancer and IMvigor011 in ctDNA-positive muscle-invasive bladder cancer [14-15,27]. DYNAMIC demonstrated a reduction in chemotherapy exposure without an apparent loss of recurrence-free survival, whereas IMvigor011 demonstrated improved disease-free and overall survival with biomarker-selected adjuvant atezolizumab. DYNAMIC-III and ALTAIR showed that detection of molecular residual disease does not guarantee benefit from escalation or treatment at molecular recurrence [26,28].

Table 1. Selected key characteristics of completed studies included in the clinical synthesis

Study	Population/sample	Design and assay	Endpoint	Interpretation
Garcia-Murillas 2015 [1]	Early breast cancer; n=55	Prospective tumor-informed cohort	Molecular relapse	ctDNA anticipated clinical relapse and established prognostic validity.

Study	Population/sample	Design and assay	Endpoint	Interpretation
TRACERx 2017/2023 [2,13]	Early NSCLC; prospective cohort	Tumor-informed phylogenetic ctDNA	Relapse and dissemination	Strong biological and prognostic evidence; treatment actionability not tested.
Reinert 2019 [5]	Stage I-III CRC; n=130	Prospective ultradeep sequencing	Postsurgical recurrence	Postoperative ctDNA strongly stratified recurrence risk.
Christensen 2019 [6]	Bladder cancer; n=68	Longitudinal tumor-informed cfDNA	Metastatic relapse	Molecular relapse preceded clinical progression in many patients.
Coombes 2019 [7]	Early breast cancer; n=49	Personalized serial ctDNA	Metastatic recurrence	ctDNA frequently preceded metastatic recurrence.
IMvigor010 biomarker analysis 2021 [18]	Resected MIBC; randomized-trial biospecimens	Exploratory ctDNA subgroup analysis	Adjuvant atezolizumab interaction	Hypothesis-generating predictive signal; prospective confirmation required.
Loupakis 2021 [19]	CRC after metastasectomy; n=112	Personalized ctDNA cohort	MRD and recurrence	Post-resection ctDNA associated with high recurrence risk.
Magbanua 2021 [20]	Neoadjuvant-treated breast cancer; n=84	Prospective serial ctDNA	Response and survival	ctDNA dynamics reflected response and prognosis.
DYNAMIC 2022/2025 [14-15]	Stage II colon cancer; n=455	Randomized ctDNA-guided strategy	Chemotherapy use and RFS	Reduced chemotherapy exposure with comparable 2- and 5-year RFS.
GALAXY/CIRCULATE-Japan 2023/2024 [21,29]	Resectable CRC; n=1,039 and expanded cohort	Prospective observational platform	MRD, DFS, OS, ACT interaction	Strong prognostic evidence; treatment interaction remains observational.
c-TRAK TN 2023 [25]	High-risk early TNBC; n=208	Prospective surveillance/intervention	ctDNA-triggered pembrolizumab	Illustrated limitations of late molecular detection and weak intervention uptake.
DYNAMIC-III 2025 [26]	Stage III colon cancer; n=968 evaluable	Randomized strategy trial	Risk-adjusted adjuvant therapy	Prognostic separation was strong; escalation benefit was not established.
IMvigor011 2025 [27]	ctDNA-positive MIBC; n=250 randomized	Phase III double-blind RCT	DFS and OS	Atezolizumab improved DFS and OS versus placebo.
ALTAIR 2026 [28]	ctDNA-positive resected CRC; n=243	Phase III double-blind RCT	DFS after molecular recurrence	Primary DFS endpoint not met; toxicity substantial.
Martin-Arana 2025 [22]	Localized stage II-III colon cancer	Tumor-agnostic plasma WES	MRD sensitivity and relapse biology	Promising detection method; external clinical validation required.
DETECT-A 2020 [11]	Asymptomatic women; n=10,006	Prospective blood test plus PET-CT pathway	Feasibility and diagnostic resolution	Feasible pathway without mortality endpoint.
PATHFINDER 2023/2025 [23-24]	Screening-eligible adults; n=6,662	Prospective MCED return-of-results cohort	Diagnostic resolution and psychosocial outcomes	Feasible pathway; false-positive work-up and anxiety remain relevant.
CCGA validation 2020/2021 [9,16]	Multiple cancers and controls	Targeted methylation classifier validation	Sensitivity, specificity, tissue of origin	Diagnostic validation, not population outcomes evidence.

MCED evidence included DETECT-A, PATHFINDER, PATHFINDER 2, NHS-Galleri, CCGA validation studies, and related diagnostic-pathway or psychosocial analyses [9,11,16,23-24,30,32]. These studies support feasibility, high specificity, and targeted diagnostic routing, but they differ in design and endpoint. PATHFINDER 2 and NHS-Galleri were available as 2026 conference abstracts and were therefore treated as preliminary evidence pending full peer-reviewed reports [30,32]. Key numerical findings and their clinical interpretation are summarized in Table 2.

Table 2. Key numerical results and clinical conclusions

Study/program	Sample size	Primary endpoint	Main numerical result	Clinical conclusion
DYNAMIC [14-15]	455 randomized	Chemotherapy use; RFS	Chemotherapy 15% vs 28%; 2-y RFS 93.5% vs 92.4%; 5-y RFS 88% vs 87%	Supports de-escalation in stage II colon cancer.
DYNAMIC-III [26]	968 evaluable	3-y RFS in ctDNA-negative; 2-y RFS in ctDNA-positive	72.5% were ctDNA-negative; strong prognostic separation; escalation superiority not established	Not a basis for universal escalation/de-escalation.
GALAXY [21,29]	1,039 initial; expanded cohort	DFS/OS and ACT interaction	Postoperative ctDNA strongly associated with recurrence; treatment interaction observational	High prognostic value; causal treatment inference limited.
c-TRAK TN [25]	208 enrolled	ctDNA detection and pembrolizumab response	ctDNA detected in 27.3%; many had radiographic metastases; no ctDNA clearance in treated subgroup	Cautionary actionability evidence.
IMvigor011 [27]	761 monitored; 250 randomized	DFS and OS	DFS 9.9 vs 4.8 mo, HR 0.64 (0.47-0.87); OS 32.8 vs 21.1 mo, HR 0.59 (0.39-0.90)	Direct evidence of MRD-guided treatment benefit.
ALTAIR [28]	243 randomized	DFS	Median DFS 9.30 vs 5.55 mo; HR 0.79 (0.60-1.05); P=0.107	Primary endpoint not met.
DETECT-A [11]	10,006	Cancer detection pathway	Prospective blood test plus PET-CT pathway; mortality not assessed	Feasibility only.
PATHFINDER [23]	6,662	Diagnostic resolution	Median resolution 79 d; true-positive 57 d; false-positive 162 d	Feasibility with substantial downstream testing.
PATHFINDER 2 [32]	35,878 enrolled; 32,007 performance set	PPV, specificity, sensitivity, resolution	PPV 60.3%; specificity 99.6%; all-cancer sensitivity 39.3%; median resolution 48 d	Conference-level performance evidence; no mortality endpoint.
NHS-Galleri [30]	142,924 randomized	Stage III-IV cancer incidence	Primary endpoint not met: 706 vs 688 events; IRR 1.03; stage IV reduction secondary	No definitive population implementation conclusion.
Vanguard [31]	Active feasibility trial	Recruitment and diagnostic logistics	No effectiveness result available	Designed to inform a future definitive RCT.

3.3. Evidence for MRD-guided interventions

In DYNAMIC, 455 patients with stage II colon cancer were randomized. Chemotherapy was administered to 15% of the ctDNA-guided group and 28% of the standard-management group. Two-year recurrence-free survival was 93.5% versus 92.4%, and at a median follow-up of 59.7 months five-year recurrence-free survival was 88% versus 87% [14-15]. The clinical contribution of the strategy was therefore reduced treatment exposure without an apparent survival penalty, rather than improved survival.

In IMvigor011, 761 patients entered serial ctDNA surveillance and 250 ctDNA-positive patients were randomized to atezolizumab or placebo. Median disease-free survival was 9.9 versus 4.8 months (hazard ratio 0.64, 95% confidence interval 0.47-0.87), and median overall survival was 32.8 versus 21.1 months (hazard ratio 0.59, 95% confidence interval 0.39-0.90) [27]. This provides direct evidence that an MRD result can select a population in which a defined intervention improves outcomes.

DYNAMIC-III enrolled 968 evaluable patients with stage III colon cancer and confirmed marked prognostic separation by postoperative ctDNA status, but the ctDNA-guided escalation component did not establish superior recurrence-free survival [26]. In ALTAIR, 243 ctDNA-positive patients were randomized after curative-intent treatment; trifluridine-tipiracil did not significantly improve the primary disease-free survival endpoint compared with placebo (median 9.30 versus 5.55 months; hazard ratio 0.79, 95% confidence interval 0.60-1.05) and produced substantial grade 3 or higher toxicity [28].

3.4. Prognostic and observational MRD evidence

Across colorectal cancer, early-stage non-small cell lung cancer, breast cancer, and bladder cancer, postoperative ctDNA positivity was consistently associated with increased recurrence risk and often preceded clinical or radiological progression [1-2,5-7,13,18-22,29]. The magnitude of association varied by assay, sampling time, tumor shedding, treatment exposure, and endpoint definition.

Prognostic discrimination is not equivalent to clinical benefit. c-TRAK TN illustrated this distinction: ctDNA was detected in 27.3% of 208 enrolled patients, but many already had radiologically detectable metastatic disease at molecular detection and pembrolizumab did not produce ctDNA clearance in the small treated group [25]. Negative ctDNA also cannot fully exclude recurrence, particularly in low-shedding tumors or sanctuary sites.

3.5. Evidence on MCED

DETECT-A enrolled 10,006 women and demonstrated that a multi-analyte blood test followed by PET-CT could be incorporated into a prospective diagnostic pathway [11]. PATHFINDER enrolled 6,662 participants; among participants with a cancer signal detected result, median time to diagnostic resolution was 79 days, and false-positive participants underwent substantial laboratory and imaging

evaluation [23]. These studies established feasibility but were not designed to demonstrate mortality reduction.

PATHFINDER 2 enrolled 35,878 participants; the 2026 ASCO abstract reported 287 positive tests among 32,007 participants with 12-month cancer assessment, 173 confirmed cancers, positive predictive value of 60.3%, specificity of 99.6%, and median diagnostic resolution of 48 days [32]. NHS-Galleri randomized 142,924 participants. Its primary endpoint - a statistically significant reduction in stage III-IV cancers across 12 prespecified cancers - was not met (706 versus 688 events; incidence rate ratio 1.03), although reductions in stage IV disease and increases in stage I-II diagnoses were reported as secondary findings [30]. The NCI Vanguard Study remains an active feasibility study for a future definitive randomized trial [31].

3.6. Clinical applicability of ctDNA and cfDNA

Clinical applicability requires a complete chain from molecular detection to a valid decision, an effective intervention, and improved patient-important outcomes. DYNAMIC and IMvigor011 satisfy this chain in defined settings [14-15,27]. DYNAMIC-III, c-TRAK TN, and ALTAIR show why the result cannot be generalized across tumors or interventions [25-26,28].

For MCED, current evidence supports pathway feasibility and high specificity but not mortality reduction. Conference-level results from PATHFINDER 2 improve estimates of diagnostic performance, while NHS-Galleri provides randomized evidence that the prespecified late-stage primary endpoint was not met [30,32]. Implementation decisions must therefore consider false-positive investigations, overdiagnosis, costs, capacity for confirmatory diagnostics, and equity of access.

4. Risk of bias

RoB 2 judgments were low risk or some concerns for the principal randomized trials [35]. DYNAMIC and IMvigor011 had low overall risk for their primary endpoints [14,27]. DYNAMIC-III and ALTAIR were judged as some concerns because interpretation depended on complex strategy algorithms, incomplete maturity for some endpoints, or reliance on exploratory subgroup and sensitivity analyses [26,28].

QUIPS, ROBINS-I, and QUADAS-2 assessments identified moderate or serious limitations in many non-randomized studies, particularly confounding, heterogeneous sampling schedules, selective analysis, spectrum effects, verification bias, and incomplete assessment of false-negative participants [36-38]. Table 3 summarizes overall judgments; domain-level assessments are provided in Supplementary Table S4.

Table 3. Risk of bias

Study/evidence group	Design and tool	Overall judgment	Main concern
DYNAMIC [14]	RCT; RoB 2	Low risk	Open-label strategy but objective outcomes and prespecified analysis.
DYNAMIC 5-y follow-up [15]	Extended RCT follow-up; RoB 2	Some concerns	Some post hoc ctDNA-clearance analyses.
DYNAMIC-III [26]	Randomized strategy trial; RoB 2	Some concerns	Complex prespecified escalation/de-escalation algorithms and subgroup interpretation.
ALTAIR [28]	Phase III RCT; RoB 2	Some concerns	Primary endpoint negative; central review and subgroup findings exploratory.
IMvigor011 [27]	Phase III RCT; RoB 2	Low risk	Double-blind design and objective primary endpoint.
GALAXY [21,29]	Prospective observational; QUIPS/ROBINS-I	Moderate to serious	Confounding in estimates of ACT benefit.
IMvigor010 ctDNA analysis [18]	Exploratory biomarker analysis; ROBINS-I	Serious	Post hoc subgroup and treatment interaction.
c-TRAK TN [25]	Prospective intervention cohort; ROBINS-I	Serious	Small treated subgroup and overt disease at ctDNA detection.
TRACERx [2,13]	Prospective prognostic cohort; QUIPS	Moderate	Selection and assay-timing limitations; no intervention test.
Breast MRD cohorts [1,7,20]	Prognostic cohorts; QUIPS	Moderate	Small samples and heterogeneous timing.
DETECT-A [11]	Diagnostic pathway; QUADAS-2	Moderate	Verification and pathway effects; no randomized outcome endpoint.
PATHFINDER [23-24]	Diagnostic pathway; QUADAS-2	Moderate	No randomized control and incomplete long-term verification of negatives.
PATHFINDER 2 [32]	Conference abstract; QUADAS-2 framework	Some concerns	Incomplete peer-reviewed reporting at cutoff.
NHS-Galleri [30]	Randomized screening trial; RoB 2 preliminary	Some concerns	Conference-level reporting and immature mortality follow-up.
CCGA/Klein [9,16]	Classifier validation; QUADAS-2	Moderate	Spectrum and case-control applicability concerns.

Study/evidence group	Design and tool	Overall judgment	Main concern
Kim 2023 [17]	Classifier study; QUADAS-2	High risk	External intended-use population validation required.

5. Certainty of evidence

Certainty was moderate for ctDNA-guided de-escalation in stage II colon cancer because the evidence is based primarily on one randomized strategy trial with a relatively wide non-inferiority margin, despite consistent five-year follow-up [14-15]. Certainty was high for the relative disease-free and overall survival effects of atezolizumab among ctDNA-positive patients in IMvigor011, but applicability remains limited to the studied disease, assay, and treatment context [27].

For other MRD settings, certainty was low to moderate. Prognostic associations were consistent, but direct evidence that a ctDNA-triggered intervention improves patient-important outcomes was limited or negative [1-2,5-7,13,18-22,25-26,28-29].

For MCED, certainty was moderate for diagnostic-pathway feasibility and low or very low for reduction in late-stage disease or mortality. PATHFINDER 2 and NHS-Galleri were conference reports at the review cutoff, and the NHS-Galleri primary endpoint was not met [30,32]. The complete GRADE profile is provided in Supplementary Table S5. Outcome-level certainty ratings are summarized in Table 4.

Table 4. Certainty of evidence

Finding	Evidence base	Certainty	GRADE rationale	Conclusion
ctDNA-guided de-escalation in stage II colon cancer [14-15]	RCT plus 5-y follow-up	Moderate	No serious inconsistency; some indirectness and imprecision from single strategy trial and non-inferiority margin	Reduced chemotherapy without apparent RFS/OS loss.
ctDNA-guided atezolizumab in ctDNA-positive MIBC [27]	Phase III RCT	High	Low risk of bias; precise DFS and OS effects; limited setting-specific applicability	Improved DFS and OS.
ctDNA-guided strategy in stage III colon cancer [26]	Randomized strategy trial	Low to moderate	Complex intervention, phase 2 escalation component, imprecision	Prognostic value high; strategy benefit not established.
Treatment at molecular recurrence [25,28]	Prospective intervention study plus phase III RCT	Low	Inconsistent interventions, imprecision, negative primary endpoint	Detection alone does not ensure benefit.
Post-treatment MRD prognosis across solid tumors [1-2,5-7,13,18-22,29]	Multiple prospective cohorts	Moderate	Consistent direction but heterogeneity and confounding	Strong prognostic value.
MCED diagnostic-pathway feasibility [11,23-24,32]	Prospective pathway studies; one conference report	Moderate	No mortality endpoint; indirectness for screening benefit	Feasibility and high specificity supported.
MCED reduction in late-stage cancer or mortality [30]	One large randomized trial reported in conference abstract form	Very low to low	Primary endpoint not met; mortality immature; incomplete reporting	Broad implementation remains premature.

6. Discussion

This review separates analytical validity, prognostic validity, and clinical utility. ctDNA is clinically actionable only when the test identifies a population for whom a defined management strategy produces net benefit. DYNAMIC and IMvigor011 are the clearest examples, but they support setting-specific decisions rather than universal ctDNA-guided oncology [14-15,27].

MCED evidence has advanced from retrospective classifier validation to prospective pathways and a large randomized trial [11,23,30,32]. Nevertheless, the evidentiary standard for population screening is not satisfied by specificity, positive predictive value, or stage distribution alone. The failure of NHS-Galleri to meet its primary stage III-IV endpoint strengthens the need for mature mortality follow-up, transparent assessment of harms, and replication independent of test manufacturers [30].

The practical implication is that ctDNA and cfDNA tests provide clinical information rather than treatment. Their value depends on timing, assay sensitivity, tumor biology, availability of effective interventions, and the capacity of the health system to resolve positive findings without disproportionate harm.

7. Limitations

First, the review was based on aggregate published data and did not have access to individual participant data. Second, clinical and methodological heterogeneity precluded a defensible meta-analysis. Third, several 2026 findings were available only as conference abstracts and should be updated when full peer-reviewed reports appear. Fourth, certainty judgments remain sensitive to the choice of outcome and to the distinction between prognostic performance and treatment effect.

8. Conclusions

ctDNA has demonstrated clinical utility in selected solid-tumor MRD settings. The strongest evidence supports reduced chemotherapy exposure in stage II colon cancer without an apparent loss of recurrence-free survival and improved disease-free and overall survival with

atezolizumab in ctDNA-positive muscle-invasive bladder cancer [14-15,27]. In most other settings, ctDNA remains a powerful prognostic biomarker whose optimal treatment response has not been established.

MCED should not be described as an established population screening method. Prospective studies support feasibility and high specificity, but NHS-Galleri did not meet its prespecified primary late-stage endpoint, and mortality benefit remains unknown [11,23,30-32]. Future implementation requires randomized evidence of net benefit, mature mortality outcomes, acceptable false-positive and overdiagnosis burdens, and feasible diagnostic pathways.

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Conflicts of interest

The source manuscript did not include a completed conflict-of-interest declaration.

Data availability

All study-level data used in the narrative synthesis, search strategies, exclusion categories, risk-of-bias judgments, GRADE assessments, and the completed PRISMA checklist are provided in the manuscript and Supplementary Tables S1-S7.

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Supplementary material

Supplementary Table S1. Complete search strategies

Source/platform	Search date	Coverage and limits	Executable strategy
MEDLINE via PubMed	9 Jul 2026; update 15 Jul 2026	Inception to search date; humans; English at screening	(("circulating tumor DNA"[tiab] OR "circulating tumour DNA"[tiab] OR ctDNA[tiab] OR "cell-free DNA"[tiab] OR cfDNA[tiab] OR "liquid biopsy"[tiab]) AND ("molecular residual disease"[tiab] OR "minimal residual disease"[tiab] OR recurrence[tiab] OR relapse[tiab] OR surveillance[tiab] OR "multi-cancer early detection"[tiab] OR multicancer[tiab]) AND (cancer*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR neoplasm*[tiab])) NOT (leukemia[tiab] OR lymphoma[tiab] OR myeloma[tiab])
Embase via Elsevier	9 Jul 2026	Inception to search date; humans; English at screening	('circulating tumor DNA'/exp OR 'cell free DNA'/exp OR 'liquid biopsy'/exp OR ctdna:ti,ab,kw OR cfdna:ti,ab,kw) AND ('molecular residual disease':ti,ab,kw OR 'minimal residual disease'/exp OR recurrence:ti,ab,kw OR relapse:ti,ab,kw OR surveillance:ti,ab,kw OR 'multi-cancer early detection':ti,ab,kw OR multicancer:ti,ab,kw) AND 'neoplasm'/exp NOT ('leukemia'/exp OR 'lymphoma'/exp OR 'multiple myeloma'/exp)
Scopus	9 Jul 2026	Inception to search date; article or conference paper; English	TITLE-ABS-KEY((ctdna OR "circulating tumor DNA" OR "circulating tumour DNA" OR cfdna OR "cell-free DNA" OR "liquid biopsy") AND ("molecular residual disease" OR "minimal residual disease" OR recurrence OR relapse OR surveillance OR "multi-cancer early detection" OR multicancer) AND (cancer OR tumor OR tumour OR neoplasm)) AND NOT TITLE-ABS-KEY(leukemia OR lymphoma OR myeloma)
Web of Science Core Collection	9 Jul 2026	Inception to search date; English	TS=((ctDNA OR "circulating tumor DNA" OR "circulating tumour DNA" OR cfDNA OR "cell-free DNA" OR "liquid biopsy") AND ("molecular residual disease" OR "minimal residual disease" OR recurrence OR relapse OR surveillance OR "multi-cancer early detection" OR multicancer) AND (cancer OR tumor OR tumour OR neoplasm)) NOT TS=(leukemia OR lymphoma OR myeloma)
Cochrane CENTRAL	9 Jul 2026	Inception to search date	(ctDNA OR "circulating tumor DNA" OR cfDNA OR "cell-free DNA" OR "liquid biopsy") AND ("molecular residual disease" OR "minimal residual disease" OR recurrence OR relapse OR "multi-cancer early detection" OR multicancer) AND (cancer OR tumor OR neoplasm)
ClinicalTrials.gov	9 Jul 2026; status update 15 Jul 2026	All study types and statuses	("circulating tumor DNA" OR ctDNA OR "cell-free DNA" OR cfDNA OR "liquid biopsy") AND ("molecular residual disease" OR "minimal residual disease" OR recurrence OR relapse OR "multi-cancer early detection" OR multicancer)
WHO ICTRP, ISRCTN, jRCT	9 Jul 2026	All statuses	Equivalent combinations of ctDNA/cfDNA/liquid biopsy with MRD/recurrence/MCED terms, adapted to each interface

Supplementary Table S2. Full-text exclusion categories

Reason for exclusion	Number of reports
Analytical validity or classifier development without longitudinal clinical outcome	3
Review, commentary, or editorial without original eligible data	2
Wrong population, including hematologic malignancy or non-screening population	2
No clinically interpretable outcome or no diagnostic resolution	2
Duplicate or secondary report without unique extractable data	1

A citation-level exclusion log should be retained with the review archive.

Supplementary Table S3. Study-level data extraction

Report	Cancer/ domain	Design	Sample	Assay	Endpoint	Main result	Evidence role
Garcia-Murillas 2015 [1]	Breast	Prospective cohort	55	Tumor-informed mutation tracking	Relapse prediction	ctDNA anticipated relapse	Prognostic
Abbosh 2017 [2]	NSCLC	Prospective translational cohort	100	Tumor-informed phylogenetic assay	Relapse dynamics	ctDNA tracked tumor evolution	Prognostic
Phallen 2017 [3]	Pan-cancer	Validation cohort	200+	Targeted ctDNA sequencing	Early detection	Technical feasibility	Analytical context
Cohen 2018 [4]	Eight cancers	Case-control validation	1,005	CancerSEEK multi-analyte	Detection/localization	Feasibility; no outcomes	Diagnostic context
Reinert 2019 [5]	CRC	Prospective cohort	130	Ultradeep tumor-informed sequencing	Postsurgical recurrence	Strong prognostic association	Prognostic
Christensen 2019 [6]	Bladder	Prospective cohort	68	Tumor-informed cfDNA	Metastatic relapse	Molecular lead time	Prognostic
Coombes 2019 [7]	Breast	Prospective cohort	49	Personalized ctDNA	Metastatic recurrence	ctDNA antedated recurrence	Prognostic
Cristiano 2019 [8]	Pan-cancer	Classifier validation	236 cancers plus controls	Fragmentomics	Cancer detection	Technical validation	Analytical context
Liu/CCGA 2020 [9]	Pan-cancer	Validation study	6,689	Targeted methylation	Sensitivity/specificity/ CSO	High specificity; stage-dependent sensitivity	Diagnostic context
Zviran 2020 [10]	Pan-cancer	Method validation	multiple cohorts	Genome-wide cfDNA integration	Ultrasensitive monitoring	Technical performance	Analytical context
Lennon/DETECT-A 2020 [11]	MCED	Prospective interventional	10,006	Multi-analyte test plus PET-CT	Diagnostic pathway	Feasible; mortality not assessed	Pathway
Chen 2020 [12]	Pan-cancer	Nested case-control	605 samples	Methylation blood test	Prediagnostic detection	Signal before diagnosis; design indirect	Analytical context
Powles/IMvigor010 2021 [18]	MIBC	Exploratory RCT biomarker analysis	581 biomarker-evaluable	Tumor-informed ctDNA	Treatment interaction	Hypothesis-generating benefit in ctDNA-positive	Predictive exploratory
Loupakis 2021 [19]	Metastatic CRC resection	Prospective cohort	112	Personalized ctDNA	MRD and recurrence	Strong recurrence stratification	Prognostic
Magbanua 2021 [20]	Breast	Prospective cohort	84	Tumor-informed ctDNA	Response/survival	ctDNA dynamics prognostic	Prognostic

Report	Cancer/ domain	Design	Sample	Assay	Endpoint	Main result	Evidence role
Tie/DYNAMIC 2022 [14]	Stage II colon	Randomized strategy trial	455	Tumor-informed ctDNA	Chemotherapy use; RFS	15% vs 28% chemotherapy; noninferior 2-y RFS	Actionable
Tie/DYNAMIC follow-up 2025 [15]	Stage II colon	Extended RCT follow-up	455	Tumor-informed ctDNA	5-y RFS/OS	RFS 88% vs 87%; OS 93.8% vs 93.3%	Actionable
Kotani/GALAXY 2023 [21]	Resectable CRC	Prospective observational	1,039	Tumor-informed ctDNA	MRD; ACT interaction	Strong prognostic association	Prognostic/ predictive exploratory
Klein 2021 [16]	Pan-cancer	Independent validation	4,077	Targeted methylation	Sensitivity/specificity/ CSO	High specificity; no outcome benefit	Diagnostic context
Schrag/ PATHFINDER 2023 [23]	MCED	Prospective pathway cohort	6,662	Targeted methylation MCED	Diagnostic resolution	Median 79 d	Pathway
Abbosh/TRACERx 2023 [13]	NSCLC	Prospective translational cohort	421	Tumor-informed ctDNA	Dissemination/relapse	Strong prognostic evidence	Prognostic
Kim 2023 [17]	Pan-cancer	Classifier study	multiple cohorts	Methylation/CNV/ fragmentation	Detection/CSO	Improved classifier performance	Analytical context
Nakamura/GALAXY 2024 [29]	Resectable CRC	Prospective observational	expanded cohort	Tumor-informed ctDNA	DFS/OS	MRD strongly associated with survival	Prognostic
Turner/c-TRAK TN 2023 [25]	TNBC	Prospective surveillance/intervention	208	Tumor-informed ctDNA	Detection and pembrolizumab	27.3% positive; limited intervention signal	Actionability caution
Tie/DYNAMIC-III 2025 [26]	Stage III colon	Randomized strategy trial	968 evaluable	Tumor-informed ctDNA	Risk-adjusted ACT	Prognostic separation; escalation not superior	Actionability uncertain
Powles/IMvigor011 2025 [27]	MIBC	Phase III RCT	250 randomized	Tumor-informed ctDNA	DFS/OS	HR 0.64 and 0.59	Actionable
Bando/ALTAIR 2026 [28]	Resected CRC	Phase III RCT	243	Tumor-informed ctDNA	DFS	HR 0.79; primary endpoint negative	Negative actionability
Martin-Arana 2025 [22]	Colon	Prospective diagnostic/prognostic	localized cohort	Tumor-agnostic plasma WES	MRD sensitivity	Promising; external validation needed	Prognostic/ technical
Nadauld/ PATHFINDER 2025 [24]	MCED	Prospective cohort analysis	PATHFINDER cohort	Participant-reported outcomes	Psychosocial impact	Transient anxiety effects	Harms

Supplementary Table S4. Domain-level risk-of-bias and applicability assessment

Study or evidence group	Tool	Selection or randomization	Deviations or confounding	Missing data	Outcome or index test	Selective reporting	Applicability	Overall judgment
DYNAMIC [14]	RoB 2	Low	Low	Low	Low	Low	Setting-specific ctDNA-guided strategy	**Low risk**
DYNAMIC 5-year follow-up [15]	RoB 2	Low	Low	Some concerns	Low	Some concerns	Setting-specific; exploratory ctDNA-clearance analyses	**Some concerns**
DYNAMIC-III [26]	RoB 2	Low	Some concerns	Low	Low	Some concerns	Complex escalation and de-escalation strategy	**Some concerns**
ALTAIR [28]	RoB 2	Low	Low	Low	Low	Some concerns	Heterogeneous disease stages and ctDNA-assessment windows	**Some concerns**
IMvigor011 [27]	RoB 2	Low	Low	Low	Low	Low	Limited to biomarker-selected muscle-invasive bladder cancer and the evaluated assay-treatment combination	**Low risk**
GALAXY/CIRCULATE-Japan [21,29]	QUIPS and ROBINS-I	Moderate	Serious confounding	Moderate	Low	Moderate	Observational estimates of adjuvant-treatment benefit	**Moderate to serious**
IMvigor010 ctDNA analysis [18]	ROBINS-I	Moderate	Serious	Moderate	Low	Serious	Exploratory biomarker subgroup analysis not prospectively designed to establish treatment effectiveness	**Serious**
c-TRAK TN [25]	ROBINS-I	Moderate	Serious	Moderate	Low	Moderate	Small treated subgroup and frequent radiologically detectable disease at ctDNA detection	**Serious**
TRACERx [2,13]	QUIPS	Moderate	Moderate	Moderate	Low	Moderate	Research cohort with assay-timing and treatment-actionability limitations	**Moderate**
Breast cancer MRD cohorts [1,7,20]	QUIPS	Moderate	Moderate	Moderate	Low	Moderate	Small cohorts, heterogeneous sampling schedules and no randomized intervention test	**Moderate**
DETECT-A [11]	QUADAS-2	Low	Not applicable	Moderate	Moderate verification concerns	Moderate	Restricted population and non-randomized diagnostic pathway without mortality assessment	**Moderate**
PATHFINDER [23-24]	QUADAS-2	Low	Not applicable	Moderate	Moderate verification concerns	Moderate	No randomized comparator and incomplete long-term verification of participants with negative results	**Moderate**
PATHFINDER 2 [32]	QUADAS-2	Unclear	Not applicable	Unclear	Low for reported diagnostic-performance measures	Unclear	Conference abstract with incomplete peer-reviewed methodological reporting	**Some concerns**
NHS-Galleri [30]	Preliminary RoB 2	Low	Low	Unclear	Low	Unclear	Conference-level reporting and immature mortality follow-up	**Some concerns**
CCGA/Klein validation studies [9,16]	QUADAS-2	Moderate	Not applicable	Low	Low	Moderate	Case-control and spectrum effects limit applicability to an intended-use screening population	**Moderate**
Kim 2023 [17]	QUADAS-2	High	Not applicable	Unclear	Moderate	Moderate	Classifier-development evidence without adequate external validation in an intended-use screening population	**High risk**

Supplementary Table S5. GRADE evidence profile

Outcome	Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty
Reduced ACT without RFS loss in stage II colon [14-15]	1 RCT + follow-up	Not serious	Not applicable	Serious: single setting/strategy	Serious: non-inferiority margin	Undetected	Moderate
DFS/OS benefit in ctDNA-positive MIBC [27]	1 phase III RCT	Not serious	Not applicable	Not serious for studied setting	Not serious	Undetected	High
Stage III colon ctDNA-guided strategy [26]	1 randomized strategy trial	Some concerns	Not applicable	Serious	Serious	Undetected	Low-moderate
Treatment at molecular recurrence [25,28]	2 intervention studies	Serious	Serious	Serious	Serious	Possible	Low
Post-treatment MRD prognosis [1-2,5-7,13,18-22,29]	Multiple cohorts	Moderate	Not serious directionally	Moderate	Variable	Possible	Moderate
MCED diagnostic feasibility [11,23-24,32]	Prospective pathways	Moderate	Moderate	Serious for mortality benefit	Not serious for performance	Possible industry sponsorship	Moderate for feasibility
MCED late-stage/mortality benefit [30-31]	1 RCT abstract + ongoing trial	Some concerns	Not applicable	Serious	Serious	Possible	Very low-low

Supplementary Table S6. Completed PRISMA 2020 checklist

Item	Topic	Requirement addressed	Location in manuscript
1	Title	Identifies the report as a systematic review	Title page
2	Abstract	Structured summary with objectives, methods, results, and conclusions	Abstract
3	Rationale	Rationale in context of existing knowledge	Introduction
4	Objectives	Explicit review objective and domains	Introduction
5	Eligibility criteria	Inclusion/exclusion criteria and grouping for synthesis	Section 2.1
6	Information sources	Databases, registries, and update search with dates	Section 2.2; Table S1
7	Search strategy	Full strategies for all sources	Table S1
8	Selection process	Independent screening and conflict resolution	Section 2.3
9	Data collection process	Independent extraction process	Section 2.4
10a	Data items - outcomes	Outcome definitions	Section 2.4
10b	Data items - other variables	Study and assay variables	Section 2.4; Table S3
11	Risk of bias	Tools and process by design	Section 2.5; Table S4
12	Effect measures	HR, RR, proportions, medians, and CIs	Tables 2 and S3
13a	Synthesis eligibility	Separate MRD, prognosis, MCED, and harms groups	Section 2.6
13b	Data preparation	Narrative harmonization and no imputation	Section 2.6
13c	Presentation methods	Structured tables and narrative synthesis	Results; Tables 1-4
13d	Synthesis methods	Meta-analysis not performed because of heterogeneity	Section 2.6
13e	Heterogeneity exploration	Clinical sources discussed narratively	Results; Discussion
13f	Sensitivity analyses	Not performed; not applicable without meta-analysis	Section 2.6
14	Reporting bias assessment	Considered in GRADE	Section 2.5; Table S5
15	Certainty assessment	GRADE domains and outcome-level ratings	Section 2.5; Table S5
16a	Study selection results	Flow counts and diagram	Section 3.1; Figure 1
16b	Excluded studies	Category-level reasons; citation log to archive	Table S2
17	Study characteristics	Characteristics and full extraction	Table 1; Table S3
18	Risk of bias results	Overall and domain-level judgments	Table 3; Table S4

Item	Topic	Requirement addressed	Location in manuscript
19	Individual study results	Sample sizes and numerical estimates	Table 2; Table S3
20a	Synthesis results - contributing studies	Studies grouped by clinical domain	Sections 3.3-3.6
20b	Synthesis results - statistical synthesis	Not applicable; no meta-analysis	Section 2.6
20c	Synthesis results - heterogeneity	Narrative explanation	Results; Discussion
20d	Synthesis results - sensitivity	Not applicable	Section 2.6
21	Reporting biases	Considered qualitatively and in GRADE	Section 5; Table S5
22	Certainty of evidence	Outcome-level certainty ratings	Section 5; Tables 4 and S5
23a	Discussion - interpretation	Interpretation in relation to evidence	Section 6
23b	Discussion - evidence limitations	Risk of bias, indirectness, heterogeneity	Sections 5-7
23c	Discussion - review limitations	Review-process limitations	Section 7
23d	Discussion - implications	Practice and research implications	Sections 6 and 8
24a	Registration	Not prospectively registered	Section 2.1
24b	Protocol	No public protocol available	Section 2.1
24c	Amendments	No protocol amendments reported	Section 2.1
25	Support	Funding information was not provided in the source manuscript.	Funding
26	Competing interests	Conflict-of-interest information was not provided in the source manuscript.	Conflicts of interest
27	Availability of data/materials	Study-level data and supplementary materials provided	Data availability; Tables S1-S7

Supplementary Table S7. Data extraction template

Domain	Variables	Instructions
Identification	Author, year, journal, DOI, PMID, registry identifier	Record exactly as reported
Population	Cancer type, stage, setting, age, inclusion/exclusion criteria, sample size	Separate screened, enrolled, randomized, and analyzed populations
Study design	RCT, intervention cohort, prognostic cohort, diagnostic pathway, classifier validation	Specify prospective/retrospective and single-/multicenter
Assay	ctDNA/cfDNA target, tumor-informed vs tumor-agnostic, platform, threshold, blinding	Record version and timing of assay
Sampling	Postoperative window, serial schedule, preanalytical handling	Record time from treatment to blood draw
Clinical algorithm	Action after positive/negative test, comparator, confirmatory work-up	Required for actionability assessment
Outcomes	RFS, DFS, OS, recurrence, treatment exposure, toxicity, PPV, specificity, sensitivity, resolution, harms	Use study definitions and time horizons
Effect estimates	Events, proportions, HR/RR/OR, 95% CI, P value	Extract adjusted and unadjusted estimates separately
Risk of bias	Tool, domain judgments, support for judgment	RoB 2, QUIPS, ROBINS-I, or QUADAS-2
Certainty and applicability	GRADE domains, clinical applicability, funding, conflicts	Separate prognostic validity from clinical utility