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

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ABSTRACT

Background: Circulating tumor DNA (ctDNA) may guide adjuvant treatment after curative-intent therapy and support multicancer early detection (MCED), but prognostic accuracy and clinical utility are distinct.
Methods: PRISMA 2020 and PRISMA-S guided a narrative synthesis. MEDLINE/PubMed, Embase, Scopus, Web of Science, CENTRAL, trial registries and citation sources were searched to 31 January 2026. Two reviewers screened records and extracted data independently. Risk of bias and certainty of evidence were appraised descriptively, and no meta-analysis was performed because of heterogeneity in assays, designs and outcomes.
Results: Fifty-four unique records were screened; 29 reports (21 clinical/longitudinal and 8 analytical/diagnostic) were summarized. DYNAMIC reduced chemotherapy use in stage II colon cancer from 28% to 15% with similar five-year recurrence-free survival (88% vs 87%). IMvigor011 improved disease-free survival (hazard ratio 0.64) and overall survival (hazard ratio 0.59) in ctDNA-positive muscle-invasive bladder cancer. DETECT-A and PATHFINDER supported screening-pathway feasibility; SYMPLIFY and THUNDER supplied separate diagnostic context. Mortality benefit was not tested.
Conclusions: ctDNA has clinical utility in selected molecular-residual-disease settings when a prespecified result triggers effective treatment. In most settings it remains prognostic. MCED requires randomized net-benefit, mortality, and harm evaluations before population implementation.
Keywords: Circulating Tumor DNA; Liquid Biopsy; Molecular Residual Disease; Multicancer Early Detection; Cancer Prognosis.

INTRODUCTION

Liquid biopsy encompasses several analytically distinct approaches. Mutation tracking can identify tumor-associated variants (1, 2), while targeted sequencing and multi-analyte assays support cancer detection (3, 4). Longitudinal studies have examined postoperative or serial ctDNA in colorectal, bladder and breast cancer (5–7). Fragmentation, methylation and genome-wide integration provide additional analytical approaches (8–10). Prospective screening pathways and prediagnostic validation studies address early detection (11, 12), whereas TRACERx examined lung-cancer dissemination and relapse (13). These applications require separate evaluation of analytical performance and clinical benefit.

The clinical meaning of ctDNA cannot be reduced to detection of tumor-derived DNA in plasma. The central question is whether using a test changes management and improves outcomes or safely reduces unnecessary treatment. DYNAMIC directly evaluated a ctDNA-guided adjuvant strategy (14, 15). Classifier-validation studies establish diagnostic performance, but cannot by themselves establish clinical utility (16, 17).

A clinically credible ctDNA strategy must demonstrate more than an association with recurrence. Exploratory immunotherapy analyses and post-resection cohorts provide evidence of predictive or prognostic associations (18, 19). Neoadjuvant breast-cancer and colorectal cohorts examine response, residual disease and survival (20–22). Demonstrating that a test-triggered

intervention improves outcomes requires an appropriately designed interventional comparison.

Molecular residual disease detection and multicancer early detection address different clinical scenarios. MRD testing concerns patients with a known cancer diagnosis after curative-intent treatment. Studies in colorectal and bladder cancer examine persistent tumor burden and recurrence risk (5, 6). Its potential clinical value lies in selecting adjuvant treatment or adapting surveillance; this requires evidence specific to the disease, assay and intervention (14, 15).

MCED screening targets asymptomatic people, in whom cancer prevalence is lower than in symptomatic diagnostic cohorts. PATHFINDER examined diagnostic resolution after a positive result (23), and its companion analysis assessed psychosocial effects (24). False-positive results can lead to additional imaging, invasive procedures and distress. High specificity and accurate cancer-origin prediction alone do not establish net screening benefit: trials must also evaluate downstream harms, clinically meaningful outcomes and, ultimately, cancer mortality.

This review evaluates two domains separately: MRD after curative-intent treatment and MCED. MRD intervention studies illustrate both the limitations of ctDNA-triggered treatment (25, 26) and setting-specific benefit (27); feasibility studies and observational cohorts provide complementary evidence (28, 29). For MCED, symptomatic diagnostic evidence from SYMPLIFY (30), the ongoing Vanguard screening program (31), and THUNDER classifier validation (32) are distinguished from evidence that population screening improves outcomes.

METHODS

Protocol and eligibility criteria

This review uses PRISMA 2020 and PRISMA-S as reporting guides (33–34). It was not prospectively registered, and no public protocol is provided. Eligibility was organized separately for MRD after curative-intent treatment, longitudinal recurrence monitoring, and MCED in asymptomatic or screening-eligible populations. Limitations in search documentation and appraisal are disclosed below.

Eligible MRD studies were randomized trials, prospective interventional studies and longitudinal prognostic cohorts in solid tumors. In interventional studies, ctDNA results had to inform a prespecified management action, such as adjuvant-treatment allocation or intervention following molecular detection. Primary outcomes were recurrence-free survival, disease-free survival, overall survival, recurrence, treatment exposure and toxicity.

Prognostic studies related perioperative or serial ctDNA measurements to subsequent recurrence or survival. Neoadjuvant response cohorts were retained as supporting longitudinal evidence. Analytical and classifier-validation reports were treated as context, not as evidence that testing improves outcomes. Study-level citations and classifications are provided in Table S3.

Eligible MCED pathway studies enrolled asymptomatic or screening-eligible participants and reported diagnostic evaluation after a positive result, as in DETECT-A and PATHFINDER (11, 23). Psychosocial follow-up was considered separately (24). Case-control classifier studies were retained as diagnostic context (9, 16, 17), as were SYMPLIFY in symptomatic patients (30) and THUNDER validation studies (32). These sources were not interpreted as evidence of a mortality benefit from population screening.

Clinical-effectiveness synthesis excluded hematologic malignancies, case reports, purely technical studies, reviews, and reports without interpretable clinical outcomes. Selected analytical studies were retained only as context. Ongoing programs without results were described separately and were not assigned effectiveness ratings. Analytical and diagnostic reports were interpreted as context rather than effectiveness evidence.

Information sources and search strategy

Searches covered MEDLINE/PubMed, Embase, Scopus, Web of Science, CENTRAL and trial registries, with 31 January 2026 as the final search date. Source-level yields are reported in aggregate within the selection flow rather than platform by platform. Table S1 presents the search terms used for each source.

Search concepts combined ctDNA, cfDNA, liquid biopsy, residual disease, recurrence, surveillance, multicancer detection and solid tumors. The main search had no start-date restriction; language and human-study limits varied by source. Queries are reported at concept level in Table S1 rather than as verbatim platform exports. Analytical and diagnostic context reports are identified separately from clinical-effectiveness reports.

Study selection and data management

Records were deduplicated and linked using DOI, PMID, title, author, year and trial identifier. Registry records and publications are distinguished throughout the selection flow.

Supplementary Table S1 records the search terms for each source. PubMed field tags have been normalized editorially for presentation.

The post-deduplication set comprised 54 records: 42 bibliographic and 12 registry records. Two reviewers screened these records independently, with disagreements resolved by discussion or by a third reviewer; individual screening sheets are not included in the supplementary material.

Data extraction

Two reviewers independently extracted study design, population, assay, sampling, management algorithm, outcomes, numerical estimates and disclosures. Table S3 summarizes the study-level data, and Table S7 reproduces the extraction template used. Missing values were not imputed, and reported effect estimates were not recalculated.

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.

Risk of bias and certainty of evidence

Methodological appraisal was organized with reference to RoB 2, QUIPS, ROBINS-I and QUADAS-2 (35–38), applied descriptively rather than through completed signaling-question forms. Tables 3 and S4 therefore present appraisal considerations study by study rather than formal domain and overall ratings. Primary and exploratory analyses are considered separately.

Confidence was discussed by outcome using the GRADE domains of bias, inconsistency, indirectness, imprecision and publication bias (39), without formal upgrading or downgrading. Tables 4 and S5 accordingly describe the evidence and its interpretive limitations rather than assigning certainty grades. A negative trial result alone is not a reason to downgrade confidence in its estimate.

Data synthesis

A structured narrative synthesis separated MRD interventions, prognostic cohorts, MCED pathways, harms, and analytical context. Interpretation linked molecular detection to a management decision, a defined intervention, and patient-important outcomes. Heterogeneity in populations, assays, interventions, and endpoints precluded meta-analysis. Neither statistical nor narrative sensitivity analyses were performed. Potential publication bias was considered qualitatively and could not be reliably excluded.

The PRISMA reporting checklist in Table S6 identifies both available information and incompletely documented items.

RESULTS

Study selection

The selection flow comprised 54 unique records, 12 screening exclusions, 42 retrieved reports and 10 full-text exclusions, leaving 32 retained items. Table S3 summarizes 29 reports: 21 clinical, longitudinal or pathway reports and eight analytical or diagnostic context reports. Two further diagnostic reports, SYMPLIFY (30) and THUNDER (32), are discussed in the main text and appraisal tables, and Vanguard is an ongoing program (31). The 32 retained items therefore do not correspond to 32 independent completed studies, since several publications share cohorts.

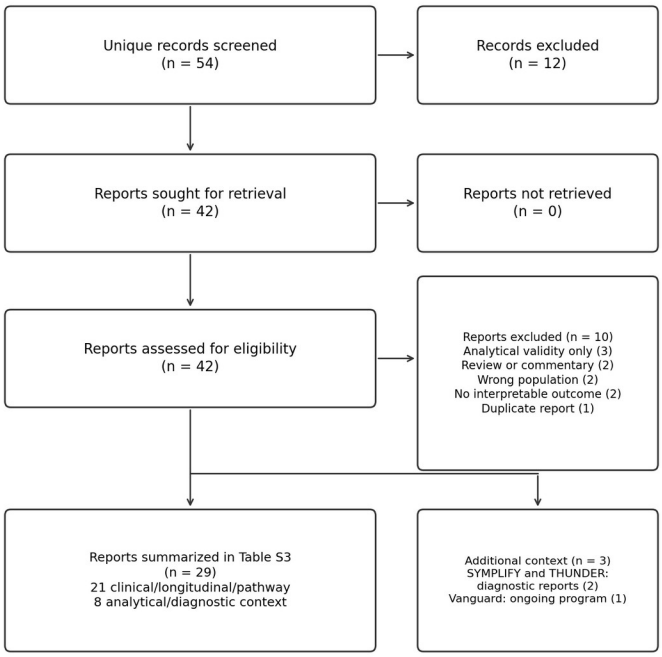

Figure 1. Study selection flow: 29 tabulated reports, two additional diagnostic context reports and one ongoing program.

Characteristics of included studies

The evidence comprises MRD intervention trials, longitudinal prognostic studies, MCED pathways, and a separate analytical/diagnostic context group. Table 1 summarizes selected reports; Table S3 lists study-level summaries. Linked follow-up reports are interpreted together, and participant counts must not be summed across overlapping cohorts.

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 reduced 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 the feasibility-stage OPTIMISE study illustrate why a ctDNA result does not automatically establish benefit from escalation or treatment at molecular recurrence (26, 28).

Table 1. Selected study characteristics and supporting diagnostic context

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.
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 2,240 (overlapping cohorts)	Prospective observational platform	MRD, DFS, OS, ACT interaction	Strong prognostic evidence; treatment interaction remains observational.
c-TRAK TN 2023 (25)	Early TNBC; 208 registered, 161 under surveillance	Prospective ctDNA surveillance with 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	De-escalation non-inferiority and escalation benefit were 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.
OPTIMISE 2023 (28)	Metastatic CRC after radical-intent treatment; n=32	Open-label randomized feasibility study	Feasibility of ctDNA-guided adjuvant treatment	32 enrolled; 14 standard-care and 16 ctDNA-guided participants reported; 19% ctDNA-positive in the guided arm
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 spans distinct settings. DETECT-A and PATHFINDER evaluated prospective diagnostic pathways in screening populations (11, 23), with additional psychosocial follow-up in PATHFINDER (24). CCGA and other classifier studies assessed diagnostic performance (9, 16, 17). SYMPLIFY enrolled symptomatic patients (30), while THUNDER provided development and validation data (32). These populations and designs should not be pooled as evidence of screening benefit.

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	De-escalation: 3-y RFS 85.3% vs 88.1%, non-inferiority not met; escalation: no benefit	Not a basis for universal escalation/de-escalation.
GALAXY (21, 29)	1,039 initial; 2,240 updated	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 registered; 161 monitored	ctDNA detection and pembrolizumab response	44/161 (27.3%) positive by 12 mo; metastases in 23/32 assigned intervention; 0/5 treated achieved sustained clearance	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.
OPTIMISE (28)	32 enrolled	Feasibility of a ctDNA-guided workflow	14 standard care; 16 ctDNA-guided; 19% positive in the guided arm	Feasibility evidence; not powered for efficacy
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.
THUNDER (32)	Prospective/validation cohorts	cfDNA methylation sequencing assay	Diagnostic performance and tissue-of-origin classification	Analytical/diagnostic context; not a mortality study.
SYMPLIFY (30)	Symptomatic adults; 5,461 evaluable	Prospective observational diagnostic cohort	Cancer-origin accuracy 85.2% among true-positive cases; diagnostic pathway outcomes	Supports diagnostic feasibility; not a population mortality trial.
Vanguard (31)	Active feasibility trial	Recruitment and diagnostic logistics	No effectiveness result available	Designed to inform a future definitive RCT.

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 included 968 evaluable patients with stage III colon cancer. De-escalation did not establish non-inferiority (3-year RFS 85.3% versus 88.1%), and escalation did not improve outcomes in ctDNA-positive patients (26). In the feasibility-stage OPTIMISE study, 32 patients were enrolled; 14 were assigned to standard care and 16 to ctDNA-guided treatment, with ctDNA detected in 19% of baseline samples in the guided arm. OPTIMISE supports feasibility of a prespecified workflow but was not powered to establish clinical benefit (28).

Prognostic and observational MRD evidence

Postoperative or serial ctDNA was associated with recurrence risk in colorectal cancer (5, 19, 21, 29), early-stage lung cancer (2, 13), and breast cancer (1, 7). Bladder-cancer studies also examined relapse and exploratory treatment interactions (6, 18). Neoadjuvant response monitoring (20) and tumor-agnostic MRD analysis (22) address related but distinct questions. Associations vary with assay, sampling, tumor shedding, treatment and endpoint.

Prognostic discrimination is not equivalent to clinical benefit. In c-TRAK TN, 208 patients registered and 161 entered ctDNA surveillance; 44/161 (27.3%) had ctDNA detected by 12 months. Of 32 assigned to intervention, 23 already had metastases on staging; none of the five starting pembrolizumab achieved sustained ctDNA clearance (25). A negative test cannot exclude all recurrences, particularly in low-shedding tumors.

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.

SYMPLIFY enrolled symptomatic patients referred for cancer investigation, not an asymptomatic screening population. Among 5,461 evaluable participants, 368 were diagnosed with cancer; cancer-origin prediction was correct in 85.2% of true-positive cases (30). This supports diagnostic evaluation in the studied setting. Vanguard was described as a feasibility program intended to inform a future definitive screening trial (31).

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 OPTIMISE show why the result cannot be generalized across tumors or interventions (25–26, 28).

For MCED, current evidence supports pathway feasibility and high specificity in selected cohorts but not mortality reduction. Implementation decisions must consider false-positive investigations, overdiagnosis, costs, diagnostic capacity, and equity of access.

Risk of bias

Randomized comparisons require outcome-level appraisal of allocation, deviations, missing data, measurement and selective reporting (35). Exploratory subgroup and observational findings additionally require careful consideration of selection and confounding (36, 37). Tables 3 and S4 identify relevant considerations, but complete tool-specific records are needed before formal ratings can be assigned.

Non-randomized evidence raises concerns about confounding, selection, assay timing, spectrum effects, and incomplete verification of negative tests (36–38). Lack of a randomized comparator limits causal utility claims but is not itself a flaw in a descriptive feasibility study. Tables 3 and S4 retain descriptive considerations and applicability notes; tool-specific ratings are not established.

Table 3. Descriptive appraisal considerations by study

Study/evidence group	Design / relevant framework	Assessment status	Descriptive consideration
DYNAMIC (14)	RCT; RoB 2	Descriptive appraisal	Open-label strategy but objective outcomes and prespecified analysis.
DYNAMIC 5-y follow-up (15)	Extended RCT follow-up; RoB 2	Descriptive appraisal	Primary follow-up and exploratory ctDNA-clearance analyses require separate appraisal.
DYNAMIC-III (26)	Randomized strategy trial; RoB 2	Descriptive appraisal	Primary strategy estimates and subgroup findings require separate outcome-level appraisal.
OPTIMISE (28)	Open-label randomized feasibility study; RoB 2	Descriptive appraisal	Small feasibility sample; not powered for a clinical outcome.
IMvigor011 (27)	Phase III RCT; RoB 2	Descriptive appraisal	Double-blind design and objective primary endpoint.
GALAXY (21, 29)	Prospective observational; QUIPS/ROBINS-I	Descriptive appraisal	Confounding in estimates of ACT benefit.
IMvigor010 ctDNA analysis (18)	Exploratory biomarker analysis; ROBINS-I	Descriptive appraisal	Post hoc subgroup and treatment interaction.

Study/evidence group	Design / relevant framework	Assessment status	Descriptive consideration
c-TRAK TN (25)	Prospective intervention cohort; ROBINS-I	Descriptive appraisal	Small treated subgroup and overt disease at ctDNA detection.
TRACERx (2, 13)	Prospective prognostic cohort; QUIPS	Descriptive appraisal	Selection and assay-timing limitations; no intervention test.
Breast MRD cohorts (1, 7, 20)	Prognostic cohorts; QUIPS	Descriptive appraisal	Small samples and heterogeneous timing.
DETECT-A (11)	Diagnostic pathway; QUADAS-2	Descriptive appraisal	Verification and pathway effects; no randomized outcome endpoint.
PATHFINDER (23–24)	Diagnostic pathway; QUADAS-2	Descriptive appraisal	No randomized control and incomplete long-term verification of negatives.
THUNDER (32)	Validation cohort; QUADAS-2	Descriptive appraisal	Analytical/diagnostic validation; no population-outcome endpoint.
SYMPLIFY (30)	Prospective observational diagnostic cohort; QUADAS-2	Descriptive appraisal	Symptomatic diagnostic setting; applicability to asymptomatic screening is indirect.
CCGA/Klein (9, 16)	Classifier validation; QUADAS-2	Descriptive appraisal	Spectrum and case-control applicability concerns.
Kim 2023 (17)	Classifier study; QUADAS-2	Descriptive appraisal	External intended-use population validation required.

Certainty of evidence

DYNAMIC provides randomized evidence on chemotherapy exposure and recurrence-free survival; the single-trial setting and non-inferiority margin constrain interpretation (14–15). IMvigor011 provides randomized DFS and OS estimates for a biomarker-selected population (27). Its result applies to the studied disease, assay and treatment combination. Formal outcome-level certainty has not been established.

For other MRD settings, the evidence remains heterogeneous. Colorectal cohorts show strong prognostic associations (21, 29), but intervention studies have not consistently demonstrated benefit from acting on a positive result (25, 26). OPTIMISE primarily assessed feasibility (28). Prognostic discrimination should therefore not be equated with proven treatment utility.

DETECT-A and PATHFINDER support the feasibility of screening pathways (11, 23); the companion PATHFINDER report addresses psychosocial outcomes (24). SYMPLIFY provides symptomatic diagnostic evidence (30), and THUNDER provides classifier validation (32). None of these reports establishes a mortality benefit from population screening. Tables 4 and S5 separate observed findings from benefits that remain unproven.

Table 4. Descriptive evidence profile and clinical interpretation

Finding	Evidence base	Certainty (narrative)	Interpretive limitations	Conclusion
ctDNA-guided de-escalation in stage II colon cancer (14–15)	RCT plus 5-y follow-up	Narrative	No serious inconsistency; some indirectness and imprecision from single strategy trial and non-inferiority margin	Reduced chemotherapy with non-inferior 2-y RFS and similar 5-y outcomes.
ctDNA-guided atezolizumab in ctDNA-positive MIBC (27)	Phase III RCT	Narrative	Randomized DFS and OS estimates; applicability limited to the studied disease, assay and treatment.	Improved DFS and OS.
ctDNA-guided strategy in stage III colon cancer (26)	Randomized strategy trial	Narrative	Complex intervention, phase 2 escalation component, imprecision	Prognostic value high; strategy benefit not established.
Treatment at molecular recurrence (25, 28)	Prospective intervention study plus randomized feasibility study	Narrative	Different interventions and small treated subgroups; assess each effect separately	Detection alone does not ensure benefit.
Post-treatment MRD prognosis across solid tumors (see Table S3)	Multiple prospective cohorts	Narrative	Consistent direction but heterogeneity and confounding	Strong prognostic value.

Finding	Evidence base	Certainty (narrative)	Interpretive limitations	Conclusion
MCED diagnostic-pathway feasibility (11, 23, 30, 32)	Prospective pathway and diagnostic validation reports	Narrative	No mortality endpoint; indirectness for population screening benefit	Feasibility and high specificity supported.
MCED population mortality benefit (11, 23, 30, 32)	Prospective diagnostic cohorts and validation studies	Narrative	No randomized mortality outcome in the included evidence	Broad implementation remains premature.

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 diagnostic pathways, but the evidentiary standard for population screening is not satisfied by specificity, positive predictive value, or stage distribution alone. Mature outcome follow-up, transparent assessment of harms, and replication independent of test manufacturers remain necessary.

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.

Limitations

Limitations include reliance on aggregate data, heterogeneous assays and outcomes, and the absence of prospective registration. The search was harmonized to a final date of 31 January 2026; per-source export files and screening sheets are not published, so the search cannot be reproduced record by record. Exclusions are reported by category rather than by citation, and the selection of context studies reflects editorial judgement. Appraisal is descriptive, without completed tool-specific forms or GRADE ratings. Overlapping cohorts and the limited volume of interventional evidence further constrain generalization.

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. DETECT-A, PATHFINDER, SYMPLIFY, and THUNDER support feasibility and selected diagnostic performance, but mortality benefit and net population benefit remain unknown. Future implementation requires randomized evidence of benefit, harms, and workable diagnostic pathways.

DECLARATIONS

Author contributions: Anel Ibrayeva: Conceptualization, Methodology, Investigation, Literature search, Data curation, Formal analysis, and Writing – original draft. Batyrbek Assembekov: Methodology, Investigation, Screening, Data extraction, Validation, and Writing – review and editing. Yulia Reshetnyak: Investigation, Data curation, Validation, Visualization, and Writing – review and editing. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

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Data availability statement: All data supporting this review are contained in the manuscript and in Tables S1–S7, which provide the search terms, exclusion categories, study-level summaries, descriptive appraisals and the reporting checklist. Record-level search exports, the citation-level exclusion log and completed appraisal forms are not deposited. Table S7 is provided as a reusable extraction template.

AI use statement: ChatGPT (OpenAI) supported English-language editing, consistency review, citation distribution and document layout. It did not reconstruct missing study records, run a new systematic search or grade the evidence. Scientific content and final verification remain the responsibility of the authors.

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Table S1. Search terms and sources

Source/platform	Search-date status	Coverage and limits	Reported terms / syntax
MEDLINE via PubMed	31 January 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	31 January 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	31 January 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	31 January 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	31 January 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	31 January 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	31 January 2026	All statuses	Equivalent combinations of ctDNA/cfDNA/liquid biopsy with MRD/recurrence/MCED terms, adapted to each interface

Note: 31 January 2026 is the final search date applied across sources. The strings below present the search logic at concept level and are not verbatim platform exports.

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

Table S3. Study-level evidence summaries

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
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

Report	Cancer/domain	Design	Sample	Assay	Endpoint	Main result	Evidence role
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	2,240; expanded overlapping cohort	Tumor-informed ctDNA	DFS/OS	MRD strongly associated with survival	Prognostic
Turner/c-TRAK TN 2023 (25)	TNBC	Prospective surveillance with intervention	208 registered; 161 monitored	Tumor-informed ctDNA	Detection and pembrolizumab	44/161 (27.3%) positive by 12 mo; 0/5 treated achieved sustained clearance	Actionability caution
Tie/DYNAMIC-III 2025 (26)	Stage III colon	Randomized strategy trial	968 evaluable	Tumor-informed ctDNA	Risk-adjusted ACT	De-escalation non-inferiority and escalation benefit not established	Actionability uncertain
Powles/IMvigor011 2025 (27)	MIBC	Phase III RCT	250 randomized	Tumor-informed ctDNA	DFS/OS	HR 0.64 and 0.59	Actionable
Callesen/OPTIMISE 2023 (28)	Metastatic CRC after radical-intent treatment	Open-label randomized feasibility study	32 enrolled; 14 standard care and 16 ctDNA-guided	Baseline ctDNA positive in 19% of guided arm	Feasibility	Not powered for efficacy	Workflow evidence
Martin-Arana 2025 (22)	Colon	Prospective diagnostic/prognostic	localized cohort	Tumor-agnostic plasma WES	MRD sensitivity	Promising; external validation needed	Prognostic/technical
Nadauld/ PATHFINDER psychosocial analysis 2025 (24)	MCED	Prospective cohort analysis	PATHFINDER cohort	Participant-reported outcomes	Psychosocial impact	Transient anxiety effects	Harms

Table S4. Descriptive appraisal and applicability considerations

Study or evidence group	Relevant framework	Descriptive appraisal consideration
DYNAMIC (14)	RoB 2	Setting-specific ctDNA-guided strategy
DYNAMIC 5-year follow-up (15)	RoB 2	Setting-specific; exploratory ctDNA-clearance analyses
DYNAMIC-III (26)	RoB 2	Complex escalation and de-escalation strategy
OPTIMISE (28)	RoB 2	Small feasibility sample; not powered for clinical outcome.
IMvigor011 (27)	RoB 2	Limited to biomarker-selected muscle-invasive bladder cancer and the evaluated assay-treatment combination
GALAXY/CIRCULATE-Japan (21, 29)	QUIPS and ROBINS-I	Observational estimates of adjuvant-treatment benefit
IMvigor010 ctDNA analysis (18)	ROBINS-I	Exploratory biomarker subgroup analysis not prospectively designed to establish treatment effectiveness
c-TRAK TN (25)	ROBINS-I	Small treated subgroup and frequent radiologically detectable disease at ctDNA detection
TRACERx (2, 13)	QUIPS	Research cohort with assay-timing and treatment-actionability limitations
Breast cancer MRD cohorts (1, 7, 20)	QUIPS	Small cohorts, heterogeneous sampling schedules and no randomized intervention test
DETECT-A (11)	QUADAS-2	Restricted population and non-randomized diagnostic pathway without mortality assessment
PATHFINDER (23–24)	QUADAS-2	No randomized comparator and incomplete long-term verification of participants with negative results
THUNDER (32)	QUADAS-2	Diagnostic validation context; no population-outcome endpoint.
SYMPLIFY (30)	QUADAS-2	Symptomatic diagnostic setting; applicability to asymptomatic screening is indirect.
CCGA/Klein validation studies (9, 16)	QUADAS-2	Case-control and spectrum effects limit applicability to an intended-use screening population
Kim 2023 (17)	QUADAS-2	Classifier-development evidence without adequate external validation in an intended-use screening population

Note: Entries are descriptive appraisals rather than formal, tool-specific ratings. The framework column identifies the instrument appropriate to each design, and applicability notes concern external validity rather than internal bias.

Table S5. Descriptive evidence profile

Outcome	Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty (narrative)
Reduced ACT without RFS loss in stage II colon (14–15)	1 RCT + follow-up	Descriptive appraisal	Single trial; no cross-study comparison	Setting-specific strategy	Non-inferiority margin affects interpretation	Not reliably assessable	Narrative
DFS/OS benefit in ctDNA-positive MIBC (27)	1 phase III RCT	Descriptive appraisal	Not applicable	Not serious for studied setting	Not graded	Not reliably assessable	Narrative
Stage III colon ctDNA-guided strategy (26)	1 randomized strategy trial	Descriptive appraisal	Not applicable	Not graded	Not graded	Not reliably assessable	Narrative
Treatment at molecular recurrence (25, 28)	2 intervention studies	Descriptive appraisal	Different interventions; no pooled estimate	Not graded	Not graded	Possible	Narrative
Post-treatment MRD prognosis (see Table S3)	Multiple cohorts	Descriptive appraisal	Not serious directionally	Not graded	Variable	Possible	Narrative
MCED diagnostic feasibility (11, 23–24, 32)	Prospective pathways	Descriptive appraisal	Not graded	Feasibility does not establish mortality benefit	Not serious for performance	Cannot exclude; sponsorship is not proof of bias	Narrative
MCED population benefit (see Tables 1–2)	Prospective pathways and diagnostic validation	Descriptive appraisal	Diagnostic performance does not establish mortality or net population benefit	Indirect for asymptomatic population screening	No pooled estimate	Not reliably assessable	Narrative

Table S6. PRISMA 2020 reporting 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	Methods – Protocol and eligibility criteria
6	Information sources	Databases, registries, and update search with dates	Methods and search supplement: databases and registers searched through 31 January 2026
7	Search strategy	Search terms reported by source	Table S1: search terms by source
8	Selection process	Independent screening and conflict resolution	Methods — Study selection: two reviewers, independent screening with third-reviewer adjudication
9	Data collection process	Independent extraction process	Methods — Data extraction: two reviewers, independent extraction
10a	Data items - outcomes	Outcome definitions	Methods – Data extraction
10b	Data items - other variables	Study and assay variables	Methods – Data extraction; Table S3
11	Risk of bias	Frameworks described; descriptive appraisal in place of completed tool-specific forms	Methods — Appraisal: descriptive appraisal (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	Methods – Data synthesis
13b	Data preparation	Narrative harmonization and no imputation	Methods – Data extraction and synthesis
13c	Presentation methods	Structured tables and narrative synthesis	Results; Tables 1-4
13d	Synthesis methods	Meta-analysis not performed because of heterogeneity	Methods – Data synthesis
13e	Heterogeneity exploration	Clinical sources discussed narratively	Results; Discussion
13f	Sensitivity analyses	Not performed; absence of meta-analysis does not preclude sensitivity analysis	Methods – Data synthesis: not performed
14	Reporting bias assessment	Considered qualitatively; no formal testing	Methods – Data synthesis; Table S5
15	Certainty assessment	Certainty described narratively, without GRADE ratings	Methods — Evidence confidence: certainty described narratively
16a	Study selection results	Flow counts and diagram	Results – Study selection; Figure 1 (reported counts)
16b	Excluded studies	Exclusions reported by category	Table S2: exclusion categories
17	Study characteristics	Characteristics and study summaries	Table 1; Table S3 (summaries, not full extraction forms)
18	Risk of bias results	Provisional shared-domain appraisal	Appraisal tables show descriptive considerations or documentation gaps; no verified formal risk-of-bias ratings.
19	Individual study results	Sample sizes and numerical estimates	Results; Tables 2 and S3
20a	Synthesis results - contributing studies	Studies grouped by clinical domain	Results – MRD interventions, prognosis and MCED
20b	Synthesis results - statistical synthesis	Not applicable; no meta-analysis	Methods – Data synthesis: no meta-analysis
20c	Synthesis results - heterogeneity	Narrative explanation	Results; Discussion
20d	Synthesis results - sensitivity	Not performed	Methods – Data synthesis: not performed
21	Reporting biases	Considered qualitatively; cannot reliably exclude	Methods – Data synthesis; Limitations
22	Certainty of evidence	Provisional outcome-level confidence	Evidence profile and Discussion; certainty described narratively
23a	Discussion - interpretation	Interpretation in relation to evidence	Discussion
23b	Discussion - evidence limitations	Risk of bias, indirectness, heterogeneity	Appraisal, confidence and Limitations
23c	Discussion - review limitations	Review-process limitations	Limitations; Methods – Information sources
23d	Discussion - implications	Practice and research implications	Discussion; Conclusions

Item	Topic	Requirement addressed	Location in manuscript
24a	Registration	Not prospectively registered	Methods – Protocol and eligibility criteria
24b	Protocol	Protocol not publicly deposited	Methods – Protocol and eligibility criteria
24c	Amendments	No registered amendment history	Methods — Information sources: final search date 31 January 2026
25	Support	Funding declaration provided	Declarations – Funding
26	Competing interests	Conflict-of-interest declaration provided	Declarations – Conflict of interest
27	Availability of data/materials	Available summaries and supplementary tables identified	Data availability; Tables S1–S7

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

Abbreviations: ACT, adjuvant chemotherapy; CI, confidence interval; CNV, copy-number variation; CRC, colorectal cancer; CSO, cancer signal origin; DFS, disease-free survival; HR, hazard ratio; MIBC, muscle-invasive bladder cancer; NSCLC, non-small cell lung cancer; OS, overall survival; PPV, positive predictive value; RCT, randomized controlled trial; RFS, recurrence-free survival; TNBC, triple-negative breast cancer; WES, whole-exome sequencing.