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Circulating tumor DNA clearance as a trial-level early efficacy signal in solid tumors: a protocol for a systematic review and meta-analysis of randomized trials

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ADMINISTRATIVE INFORMATION**Support** - No funding support.**Review Stage at time of this submission** - Data analysis.**Conflicts of interest** - The authors declare no conflicts of interest.**INPLASY registration number:** INPLASY2025120021

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 6 December 2025 and was last updated on 3 October 2026.

*Sirui Tang, Yujie Chen, and Zhonghou Wang contributed equally.

INTRODUCTION

Review question / Objective To explore the trial-level association between treatment effects on circulating tumor DNA (ctDNA) clearance and treatment effects on overall survival (OS), progression-free survival (PFS), and recurrence-related outcomes, including recurrence-free survival (RFS), disease-free survival (DFS), and event-free survival (EFS), in randomized controlled trials of systemic anticancer therapy for solid tumors. ctDNA clearance is evaluated among patients with detectable ctDNA at baseline. A secondary objective is to assess the prognostic association between post-treatment ctDNA status and clinical outcomes. This evaluation is exploratory and hypothesis-generating; formal surrogate endpoint validation remains beyond its scope.

Rationale ctDNA dynamics can reflect residual disease and treatment activity, but prognostic associations alone do not establish trial-level surrogacy. Randomized evidence linking treatment effects on ctDNA clearance to treatment effects on clinical outcomes remains limited and heterogeneous across tumor types, treatments, clinical settings, assays, and sampling schedules. This review examines these associations using comparative treatment effects across randomized trials, with particular attention to uncertainty, cross-validated performance, and the influence of clinical setting and study design.

Condition being studied Solid tumors treated with systemic anticancer therapy in neoadjuvant/perioperative, adjuvant/postneoadjuvant, or palliative/metastatic settings. The review focuses on ctDNA clearance and post-treatment ctDNA status as biomarkers of molecular response or

residual disease, and their associations with survival and recurrence-related clinical outcomes.

METHODS

Search strategy PubMed, Embase, the Cochrane Library, and Web of Science were searched from database inception to April 15, 2026. The search combined controlled vocabulary and free-text terms relating to circulating tumor DNA or molecular residual disease, ctDNA clearance or longitudinal molecular response, randomized trials, solid tumors, and survival or recurrence outcomes. No restrictions were imposed on tumor type or treatment modality. Reference lists of eligible publications and relevant reviews were also screened.

Participant or population Patients with solid tumors enrolled in randomized controlled trials of systemic anticancer therapy in neoadjuvant/perioperative, adjuvant/postneoadjuvant, or palliative/metastatic settings. Analyses of ctDNA clearance were restricted to patients with detectable ctDNA at baseline and an eligible post-intervention ctDNA assessment.

Intervention Systemic anticancer treatments evaluated in the experimental arms of eligible randomized controlled trials. Treatment modalities were not restricted, provided that the trials supplied interpretable ctDNA measurements and sufficient data to estimate comparative treatment effects on ctDNA clearance and clinical outcomes.

Comparator The corresponding randomized control arms of eligible trials. Experimental and control arms were required to provide sufficient data for estimating between-arm treatment effects on ctDNA clearance and at least one eligible clinical outcome. Within each trial, clearance definitions and assessment time points were consistent between arms.

Study designs to be included Randomized controlled trials with experimental and control arms reporting interpretable ctDNA measurements and sufficient data to estimate comparative treatment effects on ctDNA clearance and at least one eligible clinical endpoint.

Eligibility criteria Eligible studies were randomized controlled trials of systemic anticancer therapy for solid tumors that reported ctDNA measurements and at least one of OS, PFS, RFS, DFS, or EFS, with sufficient arm-level data to extract or derive treatment-effect estimates.

Exclusion criteria comprised single-arm, non-randomized, or observational studies; reviews, meta-analyses, editorials, letters, and case reports; conference abstracts without extractable trial-level data; unclear ctDNA assessment timing, undefined clearance criteria, or absent baseline assessment; insufficient data to estimate treatment effects on both ctDNA and clinical outcomes; and duplicate reports or secondary analyses without additional relevant data.

Information sources Information was obtained from PubMed, Embase, the Cochrane Library, and Web of Science, covering database inception to April 15, 2026. Reference lists of eligible articles and relevant reviews were screened for additional studies.

Main outcome(s) The main outcomes were exploratory trial-level associations between treatment effects on ctDNA clearance and treatment effects on OS, PFS, and recurrence-related outcomes.

ctDNA clearance was defined as conversion from detectable ctDNA at baseline to undetectable ctDNA at the earliest eligible protocol-defined post-intervention assessment among baseline ctDNA-positive patients. Treatment effects were expressed as log relative risks for ctDNA clearance and log hazard ratios for clinical outcomes. PFS was analyzed separately; RFS, DFS, and EFS were grouped as recurrence-related outcomes while retaining their original trial-specific definitions. Leave-one-out cross-validated R^2 was prioritized when interpreting out-of-sample performance.

Additional outcome(s) Additional outcomes included the prognostic association between post-treatment ctDNA status, classified as positive versus negative, and OS, PFS, or recurrence-related outcomes. ctDNA status at the earliest post-treatment assessment and median time to ctDNA clearance were extracted when reported.

Data management Two reviewers independently extracted trial-level data using a standardized form. Extracted variables included trial characteristics, registration numbers, sample sizes, tumor types, treatment regimens, ctDNA assessment timing, follow-up duration, baseline ctDNA-positive denominators, arm-specific clearance counts and proportions, and clinical-outcome hazard ratios with 95% confidence intervals.

The earliest eligible protocol-defined post-intervention assessment was selected within each trial. Hazard ratios and confidence intervals were converted to the logarithmic scale to derive

standard errors when necessary. Discrepancies were resolved through consensus. Data management and statistical analyses were conducted in R.

Quality assessment / Risk of bias analysis Risk of bias in the included randomized trials was assessed using the Cochrane RoB 2.0 tool across its five domains. Publication bias was evaluated using Egger's regression test, Begg's rank-correlation test, and the trim-and-fill method. Certainty of evidence for each clinical endpoint was assessed using GRADE, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias. Evidence from randomized trials was initially rated as high certainty and downgraded when concerns were identified. Final certainty ratings were determined through consensus.

Strategy of data synthesis All analyses were exploratory and conducted at the trial level. Weighted linear regression related log relative risks for ctDNA clearance to log hazard ratios for clinical outcomes, using the inverse variance of the clinical-outcome estimate as the weight. Slopes, apparent R^2 with 95% confidence intervals, adjusted R^2 , and leave-one-out cross-validated R^2 were estimated.

Gaussian copula correlation and Kendall's tau provided complementary measures of dependence. Bayesian hierarchical models were used for complementary OS and PFS analyses, reporting posterior slopes, credible intervals, predictive intervals, and residual between-trial heterogeneity.

Prognostic hazard ratios comparing post-treatment ctDNA-positive and ctDNA-negative patients were pooled using random-effects models. Heterogeneity was assessed using I^2 and Cochran's Q. Analyses were conducted in R using meta, metafor, rstan, and rstanarm. Findings were interpreted as exploratory associations.

Subgroup analysis Exploratory subgroup analyses examined cancer type, treatment modality, disease status, ctDNA marker selection strategy, analytical platform, and treatment setting. Treatment settings were classified as neoadjuvant/perioperative curative-intent, adjuvant/postneoadjuvant curative-intent, or palliative/metastatic.

Regression estimates were not calculated when fewer than three trials were available for an endpoint-setting stratum. Assessment timing and follow-up duration were summarized descriptively. Universal 8-week assessment-time and 3-year follow-up dichotomies were removed because their clinical meaning differed across treatment settings.

Sensitivity analysis Leave-one-out analyses assessed the influence of individual trials on trial-level associations and prognostic pooled estimates. A design-based sensitivity analysis excluded DYNAMIC-III because treatment assignment was guided by ctDNA status.

Recurrence-outcome analyses also examined DFS-only and EFS-only data and grouped analyses excluding EFS or RFS. RFS-only regression was not estimated because only two trials were available. Sensitivity findings were interpreted alongside cross-validated R^2 and the uncertainty of the estimates.

Language restriction The original protocol permitted reports in any language, with translation where necessary.

Country(ies) involved China.

Other relevant information

This is a post-publication amendment to INPLASY2025120021, originally registered on December 6, 2025. The recorded review stage at initial registration was "Data analysis." The completed review was published online on July 30, 2026, in Translational Cancer Research.

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The revised text describes methods reported in the completed review. It does not establish that all methodological details were specified before analysis.

Keywords circulating tumor DNA (ctDNA), surrogate endpoints, clearance, trial-level surrogacy, early treatment response.

Contributions of each author

Author 1 - Sirui Tang.

Author 2 - Yujie Chen.

Author 3 - Zhonghou Wang.

Author 4 - Huiran Zang.

All authors contributed to conception and design, data analysis and interpretation, manuscript writing, and final approval. Sirui Tang, Yujie Chen, and Zhonghou Wang collected and assembled the data. Huiran Zang provided administrative support.