

Liquid Biopsy in Solid Tumour Follow-Up: Analytical Validity, Clinical Utility and the Gap Between Them

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Abstract

Circulating tumour DNA (ctDNA) liquid biopsy is increasingly proposed for solid tumour surveillance after curative-intent treatment, on the premise that molecular recurrence can be detected before it is radiologically or clinically apparent. We review the analytical validity evidence for tumour-informed and tumour-agnostic ctDNA assays separately, since the two approaches differ materially in sensitivity and applicability, and then examine the narrower and more recent evidence for clinical utility -- whether acting on a molecular recurrence signal actually improves outcome rather than simply advancing the date of diagnosis. Tumour-informed assays achieve materially higher sensitivity at low variant allele fractions than tumour-agnostic panels, and lead time to radiological recurrence across reviewed studies ranged from two to eleven months, but randomised evidence that intervening on a molecular-recurrence-only signal changes overall survival remains limited to a small number of tumour types. We set out where the evidence currently supports clinical adoption of ctDNA surveillance and where analytical validity has outpaced demonstrated clinical utility.

Keywords: Liquid biopsy; Circulating tumour DNA; Minimal residual disease; Molecular recurrence; Clinical utility

Introduction

Circulating tumour DNA shed into plasma by a solid tumour or its micrometastatic deposits can, in principle, be detected weeks to months before a recurrence becomes visible on cross-sectional imaging or produces a clinical symptom, and this lead time is the central rationale for proposing ctDNA-based surveillance after curative-intent treatment of a solid tumour.^[1] Two broadly different assay architectures dominate current clinical and research use: tumour-informed assays, which design a bespoke panel of variants identified from the patient's own resected tumour tissue, and tumour-agnostic panels, which screen a fixed set of genes or hotspots without reference to the individual tumour's own mutational profile.^[2]

These two architectures are not interchangeable in performance, and reviewing them together under a single 'ctDNA' label, as much early literature does, obscures a

meaningful difference in sensitivity at the low variant allele fractions typical of minimal residual disease. We review analytical validity separately for each architecture, then examine the clinical utility evidence -- considerably smaller and newer than the analytical validity literature -- for whether a positive molecular recurrence signal, once detected, changes management in a way that improves outcome.

The clinical appeal of ctDNA surveillance rests on a straightforward premise, that treating recurrence earlier produces a better outcome than treating it once it becomes clinically or radiologically apparent, but this premise does not automatically follow from lead time alone: for some tumour types and treatment settings, an earlier intervention window genuinely changes what treatment can achieve, while for others the available second-line or salvage treatments are no more effective when started several months earlier, meaning lead time without a

correspondingly more effective early intervention would simply advance the date of a diagnosis without changing the outcome it precedes.^[10]

This review therefore separates three distinct questions that are often conflated in discussions of ctDNA surveillance: can the assay detect molecular recurrence reliably (analytical validity); does detecting it earlier than imaging provide a meaningfully longer intervention window (lead time); and does acting on that earlier signal actually improve survival or another patient-relevant outcome (clinical utility). We address each in turn, since evidence quality and strength differ substantially across the three.

Analytical Validity

Tumour-informed assays, by designing a panel around variants already confirmed present in the patient's own tumour, achieve sensitivity at variant allele fractions below 0.01% in several validation studies, meaningfully lower than the detection floor typical of tumour-agnostic panels screening for variants without this prior information.^{[3][4]} This sensitivity advantage comes at the cost of requiring tumour tissue and a bespoke panel design turnaround before the assay can be used, making tumour-informed testing unsuitable for a patient without banked tumour tissue or for the very earliest post-operative surveillance window.

Tumour-agnostic panels, while less sensitive at very low variant allele fractions, do not require tumour tissue and can be deployed immediately, and several studies report acceptable sensitivity for larger-volume recurrences even though early micrometastatic disease is more likely to be missed.^[5] The choice between architectures is therefore not simply about which performs better in the abstract, but about which fits the clinical scenario -- tissue availability, turnaround requirement, and the disease burden threshold that matters for the specific tumour type under surveillance.

Clinical Utility

Lead time to radiological recurrence -- the interval between a positive ctDNA signal and subsequent imaging-confirmed recurrence -- has been reported across several tumour types and ranges from two to eleven months, a substantial window in principle for earlier intervention.^{[6][7]} Lead time alone, however, is not evidence of clinical utility: detecting recurrence earlier only improves outcome if an earlier intervention is available and effective, and this is the narrower question that randomised evidence has only recently begun to address.

A small number of randomised or prospective interventional studies have now tested whether acting on a molecular-recurrence-only signal -- in the absence of radiological or clinical recurrence -- changes overall survival, with encouraging but not yet conclusive results concentrated in a handful of tumour types, most prominently colorectal cancer in the adjuvant setting.^[8] For most other solid tumour types, clinical utility evidence remains limited to observational cohorts

reporting the association between ctDNA clearance or persistence and outcome, which is suggestive but does not establish that acting on the signal specifically, rather than the underlying disease biology it reflects, is what drives the association.^[9]

Discussion

The gap between analytical validity and clinical utility is not unique to ctDNA testing, but it is unusually wide here because the analytical performance literature has developed faster than the interventional trials needed to establish that early detection translates into improved survival, and clinical demand for the test has in several settings outpaced the evidence needed to support it.^[10] A laboratory considering ctDNA surveillance implementation should be explicit with referring oncologists about which of these two evidence bases -- analytical validity or clinical utility -- currently supports use in their specific tumour type, since the two are not interchangeable justifications for testing.

Reporting a positive molecular recurrence result to a clinician without an established intervention pathway for that specific tumour type risks generating anxiety and downstream investigation without a corresponding survival benefit, and several professional guidelines now explicitly restrict recommended ctDNA surveillance to the tumour types and clinical contexts where interventional evidence exists, rather than extending it broadly on the strength of analytical performance alone.

Why This Review's Framework Matters for Non-Specialist Laboratory Staff

Much of the preceding discussion assumes a reader already familiar with oncology trial design terminology, and it is worth restating the central distinction this review relies on in plainer terms for laboratory staff and trainees encountering ctDNA surveillance for the first time.

Analytical validity answers the question, does this test accurately measure what it claims to measure, in this case the presence of tumour-derived DNA fragments in a blood sample, independent of whether detecting that signal changes anything about the patient's care; this is the kind of validity question laboratory staff are most accustomed to addressing through standard analytical validation and quality assurance processes.^[3]

Clinical utility answers a different, further question, does using this test's result to guide a clinical decision actually produce a better outcome than not using it, a question that cannot be answered by analytical validation alone and that instead requires the kind of outcome-focused randomised or carefully controlled observational study this review has reviewed throughout.^[9]

Laboratory staff issuing ctDNA surveillance results, and the referring clinicians receiving them, benefit from keeping this distinction explicit, since a technically excellent, analytically

valid result does not, by itself, guarantee that acting on it will help the patient; that second guarantee depends on the separate, and currently much narrower, clinical utility evidence base this review has described.

Biological Basis for the Lead-Time Window

Understanding why ctDNA detection precedes radiological recurrence by a measurable interval, rather than being simply a more sensitive version of the same detection event, requires some discussion of the underlying tumour biology.

A recurrence must grow to a volume of roughly one centimetre in diameter, corresponding to on the order of a billion cells, before it becomes reliably visible on standard cross-sectional imaging, while shed ctDNA can in principle be detected from a substantially smaller burden of micrometastatic disease, since the detection event depends on the presence of circulating tumour-derived DNA fragments in plasma rather than on the tumour reaching a size visible to an imaging modality.^[1]

This difference in the biological threshold for detection, rather than any difference in how 'early' each method is tuned to look, is what produces the measured lead time, and it also explains why lead time varies across tumour types and even across individual patients: tumours that shed ctDNA more efficiently relative to their volume, or that recur in a pattern more readily detected on imaging at a given size, will show a different lead time than tumours with the opposite characteristics.^[2]

This biological variability is a further reason the two to eleven-month lead time range reported across studies should not be treated as a single fixed interval applicable uniformly across tumour types, but rather as reflecting genuine underlying variability in shedding biology and imaging detectability between the specific tumour types and clinical contexts studied.

Comparison with Previously Published Reviews

Several previous reviews have summarised the ctDNA surveillance literature, and it is worth situating this review's approach relative to that prior work.

Most previous reviews have organised the evidence by tumour type rather than by the three-question framework, analytical validity, lead time, and clinical utility, that we use here, an organisation that works well for a clinician seeking guidance on a specific tumour type but that can obscure the more general pattern, analytical validity substantially outpacing clinical utility evidence across nearly all tumour types studied, that we consider the more important message for laboratories and clinicians currently weighing whether to implement ctDNA surveillance broadly.^[10]

We believe this framework-based organisation, rather than a tumour-type-by-tumour-type catalogue, is more useful precisely because it transfers to tumour types not yet extensively studied: a laboratory considering ctDNA surveillance for a tumour type with limited published evidence can still ask the same three questions, is the assay analytically valid for this tumour type,

does it provide a meaningful lead time, and does an effective intervention exist to act on a positive signal, even where tumour-type-specific answers are not yet well established in the literature.

Staffing and Turnaround Considerations for Implementing Laboratories

Beyond the governance and evidence-review considerations discussed elsewhere in this review, practical staffing and turnaround factors also affect how successfully a laboratory can implement ctDNA surveillance testing day to day.

Tumour-informed panel design requires dedicated bioinformatics and molecular pathology staff time for each new patient entering surveillance, a workload that scales with the number of patients enrolled rather than being a fixed one-time cost, and laboratories should budget this ongoing staffing requirement explicitly rather than treating panel design as a one-off setup cost incurred only when the surveillance programme is first established.^[3]

Turnaround time from sample receipt to reported result also varies considerably between tumour-informed and tumour-agnostic approaches, and between in-house and send-away testing arrangements, and this turnaround should be communicated clearly to referring clinicians so that surveillance testing frequency and clinical follow-up scheduling can be planned around the realistic turnaround the local or referral laboratory can achieve, rather than around an assumed turnaround that may not match the actual service in place.^[4]

Governance Recommendations for Implementing Laboratories

Drawing together the preceding discussion, we propose the following governance framework for a laboratory considering whether and how to implement ctDNA surveillance testing.

Before offering ctDNA surveillance for a given tumour type, the laboratory should explicitly document, for its own internal governance records and for referring clinicians, the current state of evidence for that specific tumour type across all three questions: analytical validity, lead time, and clinical utility, rather than offering the test on the strength of general ctDNA literature that may not transfer to the specific tumour type in question.

Where clinical utility evidence remains observational only, the laboratory should work with referring oncology services to establish a clear local pathway for how a positive result will be acted on, ideally within the context of a clinical trial or a registry collecting prospective outcome data, rather than offering the test purely as a stand-alone surveillance tool outside any structured evidence-generating framework.

Finally, the laboratory should periodically review emerging randomised clinical utility evidence for each tumour type it offers surveillance for, since, as discussed under Future Directions above, several ongoing trials are likely to shift g

number of tumour types from observational-only to randomised-evidence status over the next several years, changing the balance of evidence underlying the laboratory's own testing offer.

Tumour Type	Clinical Utility Evidence	Guideline Status
Colorectal (adjuvant)	Randomised, strongest	Recommended selected settings
Breast (metastatic recurrence)	Observational, lead-time	Not yet routine
Urothelial (adjuvant)	Prospective, emerging	Context-specific
Most other solid tumours	Observational only	Not recommended

Table 1: Clinical Utility Evidence Strength and Guideline Status by Tumour Type.

Assay Platform and Pre-Analytical Considerations

Beyond the tumour-informed versus tumour-agnostic distinction discussed above, several pre-analytical and platform-level factors materially affect ctDNA assay performance in practice and deserve separate mention.

Plasma collection tube type and time to processing both affect ctDNA yield and the degree of background contamination from genomic DNA released by white blood cell lysis during sample transport; specialised cell-stabilising collection tubes are widely recommended for ctDNA testing specifically because standard EDTA tubes, if not processed within a few hours, allow leukocyte lysis that dilutes the tumour-derived signal with substantially larger quantities of non-tumour cell-free DNA.^[3]

Sequencing depth and bioinformatic variant-calling thresholds also vary meaningfully between commercial and laboratory-developed ctDNA assay platforms, and a laboratory evaluating or validating a given platform should not assume that a published sensitivity figure from one platform's validation study transfers directly to a different platform using different sequencing depth or variant-calling parameters, even where both platforms are nominally testing the same gene panel.^[4]

These pre-analytical and platform considerations are a further reason why direct comparison of sensitivity claims across different ctDNA assay platforms, raised earlier under Study Limitations, remains genuinely difficult, and why a laboratory's own validation data for its chosen platform, performed under its own pre-analytical conditions, is more informative than published sensitivity figures from a different laboratory's validation of the same or a similar platform.

Interaction with Other Surveillance Modalities

ctDNA surveillance does not typically replace existing surveillance modalities such as periodic cross-sectional imaging and tumour-marker blood tests, but is instead usually proposed as an addition to them, and the practical question of how to integrate ctDNA results with these existing modalities deserves separate comment.

Where a positive ctDNA result precedes radiological recurrence by the lead times discussed above, the practical question for a treating clinician becomes whether to intensify imaging surveillance in response to the positive molecular signal, in order to detect the anatomical site of recurrence as early as possible once it becomes radiologically visible, even before a specific intervention decision is made.^[7]

Several surveyed protocols adopt exactly this intensified-imaging response to a positive ctDNA result, reasoning that even where randomised evidence for a specific early intervention is not yet available, knowing the anatomical site of recurrence as early as possible is itself clinically useful for planning, a rationale distinct from, though related to, the direct survival-benefit question this review's clinical utility section addresses.

Comparison Across Molecular Recurrence Detection Technologies

ctDNA is not the only molecular technology proposed for detecting recurrence before it becomes clinically or radiologically apparent, and a brief comparison with other circulating-biomarker approaches is useful context for readers less familiar with this broader field.

Circulating tumour cells, intact cells rather than fragmented DNA shed from a tumour, have also been studied for recurrence surveillance, but generally show lower sensitivity than ctDNA at comparable disease burden, since intact cells are shed into circulation less abundantly than fragmented DNA and are technically more challenging to capture and enumerate reliably.^[1]

Circulating tumour-derived extracellular vesicles and specific protein biomarkers represent further candidate approaches under active investigation, generally at an earlier stage of analytical validation than ctDNA and without the same depth of either analytical validity or clinical utility evidence currently available, positioning them as potential future complements to, rather than near-term replacements for, ctDNA-based surveillance.^[2]

Methodological Features That Distinguish Strong from Weak Utility Evidence

Not all clinical utility studies in this literature carry equal weight, and it is worth being explicit about the methodological features that separate the small number of studies we regard as genuinely informative from the larger number that are merely suggestive.

The strongest design randomises patients with a positive molecular recurrence signal to an intervention arm versus a standard-surveillance or deferred-intervention arm, directly testing whether acting on the signal changes outcome; this design isolates the effect of the intervention from the effect of the underlying disease biology that produced the positive signal in the first place, a distinction observational designs cannot make.^[6]

A weaker, though still useful, design compares outcomes between patients who cleared ctDNA after an intervention and those who did not, without randomising who received the intervention; this design is vulnerable to confounding, since patients whose disease biology allows ctDNA clearance may have had a better prognosis regardless of the specific intervention received, and several widely cited observational studies in this space are of this weaker type.^[9]

The weakest design simply reports that ctDNA detection precedes radiological recurrence by a measured lead time, without any comparison of outcomes between an earlier-intervention group and a standard-timing group at all; this design establishes lead time but cannot, on its own, establish clinical utility, and should not be cited as utility evidence even though it is sometimes presented that way in secondary literature.

Equity and Access Considerations

Tumour-informed ctDNA testing's requirement for banked tumour tissue and a bespoke panel design turnaround raises equity considerations that are not always explicitly addressed in the clinical literature but that matter for implementation planning.

Patients treated at centres without routine tumour tissue banking infrastructure, or who are referred for surveillance some time after their original curative-intent treatment at a different institution, may not have accessible banked tissue available for tumour-informed panel design, effectively restricting them to the less sensitive tumour-agnostic approach regardless of their underlying tumour biology or clinical need.^[2]

This access disparity is worth making explicit to referring clinicians and patients, since it means the choice between tumour-informed and tumour-agnostic testing is, for a meaningful proportion of patients, not a genuine choice based on clinical characteristics but is instead determined by tissue availability and institutional banking practices that occurred, or did not occur, at the time of original treatment, well before surveillance testing was being considered.

Laboratories and health systems implementing ctDNA surveillance programmes should consider, where feasible, establishing routine tumour tissue banking at the time of initial curative-intent treatment specifically to preserve the option of tumour-informed testing for surveillance later, rather than only considering tissue banking needs once a surveillance programme is already being planned for a given patient.

Economic Considerations for ctDNA Surveillance Programmes

Implementing ctDNA surveillance carries a substantial recurring cost, serial testing over a multi-year surveillance period, that should be weighed explicitly against the strength of clinical utility evidence available for the specific tumour type under consideration.

For colorectal cancer in the adjuvant setting, where randomised clinical utility evidence is strongest, the economic case for serial ctDNA testing is comparatively straightforward to make, since the cost of testing can be weighed against a demonstrated survival benefit from the intervention it triggers.^[6]

For tumour types where clinical utility evidence remains observational only, the economic case is harder to make with confidence, since the cost of serial testing is incurred with certainty while the survival benefit of acting on a positive result remains unproven, and a laboratory or health system implementing surveillance in these settings should be transparent with funders and patients about this asymmetry between certain cost and uncertain benefit.^[9]

Regulatory and Professional Body Guidance

Professional society and regulatory guidance on ctDNA surveillance has evolved considerably over the period covered by this review's underlying literature, and summarising the current state of that guidance is useful for readers seeking an authoritative, consensus-based complement to this review's own evidence synthesis.

Major oncology professional societies have, in recent guidance updates, moved toward explicitly tumour-type-specific recommendations for ctDNA surveillance rather than blanket endorsement or rejection of the technology as a whole, a pattern consistent with this review's own framework-based conclusion that evidence strength varies substantially by tumour type rather than being uniform across ctDNA applications generally.^[10]

Regulatory approval status for specific ctDNA assay platforms also varies by jurisdiction and by whether the platform is marketed for a specific, labelled surveillance indication versus used as a laboratory-developed test under a broader regulatory pathway, a distinction that affects which analytical and clinical validation data a given platform is required to demonstrate before clinical use and that laboratories should verify explicitly for their chosen platform rather than assuming equivalent regulatory scrutiny across all commercially available ctDNA assays.

Patient Communication Considerations

Communicating a positive molecular recurrence result to a patient requires particular care given the gap between analytical validity and clinical utility described throughout this review.

A patient told that a blood test has detected molecular evidence of recurrence, in the absence of any visible disease on imaging and without a clearly established intervention pathway for their specific tumour type, faces a period of uncertainty and anxiety that may not be matched by any corresponding ability to act on the result differently than they otherwise would have.

We would recommend that any discussion of a positive ctDNA result with a patient explicitly address whether an evidence-based intervention exists for their specific tumour type and clinical context, rather than presenting the result as

inherently actionable simply because it was detected, since the clinical and emotional value of early detection depends entirely on there being something beneficial to do with the information.

Interpreting ctDNA Dynamics Rather Than a Single Result

Much of the clinical utility discussion in this review has, for simplicity, referred to a 'positive' or 'negative' ctDNA result, but in practice serial ctDNA surveillance generates a trajectory, a sequence of results over time, and the dynamics of that trajectory carry additional clinically relevant information beyond any single time point considered alone.

A rising ctDNA trajectory across successive surveillance time points, even where each individual measurement remains below a fixed positivity threshold, has in several studies shown stronger association with subsequent radiological recurrence than a single threshold-based positive or negative call, suggesting that trajectory-based interpretation may ultimately prove more clinically informative than single-time-point reporting as the field matures.^[6]

Conversely, a ctDNA result that briefly crosses a positivity threshold before returning to an undetectable level on a subsequent sample, sometimes described as a transient positive, has in some series not shown the same strength of association with recurrence as a persistently positive or rising trajectory, raising the possibility that a single isolated positive result should be interpreted with somewhat more caution than a sustained or rising pattern across multiple time points.^[8]

Laboratories reporting ctDNA surveillance results should consider presenting trajectory information, where multiple time points are available, alongside the individual result, to help referring clinicians interpret an isolated positive result in the context of the patient's own longitudinal pattern rather than in isolation.

Role of Multidisciplinary Tumour Board Discussion

Given the interpretive complexity discussed throughout this review, several surveyed implementation programmes route ctDNA surveillance results through multidisciplinary tumour board discussion rather than direct reporting to a single managing clinician, a practice worth describing as a further practical implementation consideration.

Multidisciplinary discussion allows the oncology, radiology, and laboratory perspectives on a given result, including the specific evidence strength for that tumour type discussed throughout this review, to be considered jointly before a management decision is communicated to the patient, reducing the risk that a positive result is acted on, or communicated, inconsistently with the evidence base actually available for that tumour type.^[9]

This practice also provides a natural forum for the laboratory to communicate the evidence-base caveats discussed throughout this review directly to the managing clinical team, rather than

relying on a written report alone to convey the distinction between analytical validity, lead time, and clinical utility that this review has argued is central to appropriate interpretation of a ctDNA surveillance result.

Study Limitations

This review synthesises a rapidly evolving literature, and several limitations of the underlying evidence base, rather than of this review's methodology specifically, should be borne in mind.

Most clinical utility studies to date have been conducted in a limited number of tumour types, predominantly colorectal cancer, and extrapolating conclusions from these tumour types to others with different biology, treatment options, and recurrence patterns should be done cautiously rather than assumed.

The analytical validity literature, while larger, is also heterogeneous in its reporting of variant allele fraction detection thresholds, with different studies using different reference standards and spike-in methodologies, complicating direct comparison of sensitivity claims across different tumour-informed and tumour-agnostic assay platforms.^[3]

Applicability Beyond Solid Tumour Follow-Up

Although this review has focused specifically on surveillance after curative-intent treatment of a solid tumour, ctDNA technology is also used in other oncology contexts, and briefly noting how those contexts differ from the surveillance setting helps clarify the scope of this review's conclusions.

ctDNA genotyping for treatment selection in metastatic disease, identifying an actionable mutation to guide targeted therapy choice, is a materially different application with its own, generally more mature, clinical utility evidence base, since the relevant outcome there is whether genotype-matched therapy improves response compared with unmatched therapy, a question several large trials have already addressed more definitively than the surveillance question this review has focused on.^[2]

ctDNA-based early cancer detection in asymptomatic, previously undiagnosed individuals is a third, distinct application, facing its own separate and, in several respects, even more demanding evidence requirements than recurrence surveillance, since a false-positive result in a previously healthy individual carries different consequences than a false-positive result in a patient already under active oncological follow-up; this application lies outside the scope of the present review entirely.^[1]

Future Directions

Several further randomised clinical utility trials are currently underway or recently completed in tumour types beyond colorectal cancer, and their results over the coming several years should substantially expand the number of tumour types for which guideline-endorsed ctDNA surveillance can be confidently recommended.

Standardisation of analytical validity reporting, particularly around variant allele fraction detection thresholds and reference standards, would also materially improve the ability of clinicians and laboratories to compare competing ctDNA assay platforms on a consistent basis, an improvement several professional bodies have begun to call for but that has not yet been widely adopted across the field.^[2]

Practical Checklist for Laboratories Considering Implementation

As a closing practical summary, we offer the following checklist for a laboratory director or oncology service lead assessing whether and how to implement ctDNA surveillance testing for a given tumour type.

Confirm the current evidence status for the specific tumour type under consideration across all three questions addressed in this review, analytical validity of the available assay platforms, demonstrated lead time, and clinical utility evidence strength, rather than relying on general impressions drawn from the broader ctDNA literature.

Establish, before offering the test clinically, an explicit local pathway for how a positive result will be acted on, including whether intensified imaging surveillance, a specific therapeutic intervention, or enrolment in a clinical trial or outcomes registry will follow a positive result, so that patients are not offered testing whose result the local service is not yet prepared to act on in any defined way.

Where feasible, participate in or establish a registry collecting prospective outcome data for patients undergoing ctDNA surveillance outside the context of a formal randomised trial, contributing further observational evidence that, while not equivalent to randomised clinical utility evidence, can help refine understanding of the technology's value in tumour types and settings not yet covered by randomised trials.

Conclusion

Tumour-informed ctDNA assays offer materially higher sensitivity than tumour-agnostic panels for minimal residual disease detection, and ctDNA surveillance can detect recurrence two to eleven months before radiological confirmation across the tumour types studied. Clinical utility evidence -- that acting on this earlier signal improves survival -- remains substantially narrower than the analytical validity evidence and is currently strongest in a small number of tumour types, and implementation should be guided by that narrower evidence base rather than by analytical performance alone.

References

1. Pantel K, Alix-Panabieres C. "Liquid biopsy and minimal residual disease -- latest advances and implications for cure". *Nat Rev Clin Oncol* 16(2019): 409-424.
2. Chin RI, Chen K, Usmani A, et al. "Detection of solid tumor molecular residual disease (MRD) using circulating tumor DNA (ctDNA)". *Mol Diagn Ther* 23(2019): 311-331.

3. Reinert T, Henriksen TV, Christensen E, et al. "Analysis of plasma cell-free DNA by ultradeep sequencing in patients with stages I to III colorectal cancer". *JAMA Oncol* 5(2019): 1124-1131.
4. Coombes RC, Page K, Salari R, et al. "Personalized detection of circulating tumor DNA antedates breast cancer metastatic recurrence". *Clin Cancer Res* 25(2019): 4255-4263.
5. Christensen E, Birkenkamp-Demtroder K, Sethi H, et al. "Early detection of metastatic relapse and monitoring of therapeutic efficacy by ultra-deep sequencing of plasma cell-free DNA in patients with urothelial bladder carcinoma". *J Clin Oncol* 37(2019): 1547-1557.
6. Tie J, Cohen JD, Lahouel K, et al. "Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer". *N Engl J Med* 386(2022): 2261-2272.
7. Parikh AR, Van Seventer EE, Siravegna G, et al. "Minimal residual disease detection using a plasma-only circulating tumor DNA assay in patients with colorectal cancer". *Clin Cancer Res* 27(2021): 5586-5594.
8. Kotani D, Oki E, Nakamura Y, et al. "Molecular residual disease and efficacy of adjuvant chemotherapy in patients with colorectal cancer". *Nat Med* 29(2023): 127-134.

9. Powles T, Assaf ZJ, Davarpanah N, et al. "ctDNA guiding adjuvant immunotherapy in urothelial carcinoma". *Nature* 595(2021): 432-437.
10. Dasari A, Grothey A, Kopetz S. "Circulating tumor DNA-defined minimal residual disease in solid tumors: opportunities and challenges". *J Clin Oncol* 36(2018): 1112-1114.

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