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Diagnostic Accuracy of Liquid Biopsy Versus Tissue Biopsy in Lung Cancer Genomics: A Systematic Review and Meta-Analysis

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KEYWORDS
lung cancer; non-small-cell lung cancer; liquid biopsy; tissue biopsy; circulating tumour DNA; diagnostic accuracy; meta-analysis.

ABSTRACT:

Background

Lung cancer is the most frequently diagnosed malignancy and the leading cause of cancer-related mortality worldwide. Most patients present with advanced disease, when curative options are limited. Molecular profiling has transformed management, particularly in non-small-cell lung cancer (NSCLC), but standard tissue biopsy is invasive, sometimes unfeasible, and limited by tumour heterogeneity.

Objective

To systematically evaluate the diagnostic accuracy of liquid biopsy compared with tissue biopsy for detecting clinically relevant genomic alterations in lung cancer.

Methods

A systematic review and meta-analysis were conducted in accordance with PRISMA and PRISMA-DTA guidelines. PubMed, Embase, Web of Science and Cochrane Library were searched from inception to 15 July 2024. Studies comparing blood-based liquid biopsy (circulating tumour DNA or cell-free DNA) with tissue biopsy for lung cancer genomic testing and reporting sufficient data to calculate sensitivity and specificity were included. Risk of bias was assessed using QUADAS-2. Bivariate random-effects models were used to pool sensitivity, specificity and the area under the hierarchical summary receiver operating characteristic curve (HSROC).

Results

Twenty-three studies involving 6,217 patients met the inclusion criteria. Overall, liquid biopsy showed moderate sensitivity and high specificity relative to tissue biopsy. Pooled sensitivity was 0.72 (95% CI 0.66-0.78), pooled specificity was 0.90 (95% CI 0.86-0.93), and the HSROC area under the curve was 0.84 (95% CI 0.78-0.89). Sensitivity was higher in advanced-stage disease and in next-generation sequencing-based assays. Most studies had at least one QUADAS-2 domain rated as unclear or high risk of bias.

Conclusion

Liquid biopsy offers a minimally invasive approach to genomic profiling in lung cancer, with high specificity and acceptable sensitivity compared with tissue biopsy. At present, it should be used as a complementary tool rather than a universal replacement for tissue biopsy, particularly in early-stage disease. It is especially valuable when tissue is insufficient or unobtainable, or for longitudinal monitoring of treatment response and resistance. Further high-quality, standardised comparative studies are needed to refine its role in routine care.

Introduction

Lung cancer is one of the most commonly diagnosed malignancies worldwide and the leading cause of cancer-related mortality, with most patients presenting at an advanced stage when curative treatment is rarely possible [1,7]. Non-small-cell lung cancer (NSCLC) constitutes the majority of cases and encompasses distinct histological subtypes, including

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adenocarcinoma and squamous-cell carcinoma, each with its own molecular profile and therapeutic implications [1,7,8]. Over the past decade, the identification of actionable genomic alterations such as mutations in *EGFR*, *BRAF* and *KRAS*, and rearrangements involving *ALK*, *ROS1* and other genes, has transformed the management of advanced NSCLC, making comprehensive molecular profiling a prerequisite for optimal, personalised therapy [3-5,7].

Despite its central role, conventional tissue biopsy has important limitations. Obtaining tumour tissue typically requires invasive procedures such as bronchoscopic biopsy, CT-guided transthoracic needle aspiration or surgery, all of which are associated with discomfort, procedural risk and, in some cases, serious complications [2,4]. In addition, tumour location, small lesion size and patient comorbidities frequently restrict the feasibility of biopsy or re-biopsy. Even when tissue is obtained, samples may be insufficient in quantity or quality for broad next-generation sequencing (NGS) panels, particularly when multiple biomarkers are requested from a single core or cytology specimen [3-5]. Furthermore, spatial and temporal intratumour heterogeneity means that a single tissue sample may not fully capture the genomic landscape of a multifocal or evolving malignancy, potentially leading to under-detection of clinically relevant subclones and resistance mechanisms [4,5,7].

Liquid biopsy has emerged as a promising complementary or alternative approach to overcome many of these limitations. By analysing circulating tumour DNA (ctDNA) or more broadly cell-free DNA (cfDNA) shed from primary and metastatic lesions into the bloodstream, liquid biopsy enables minimally invasive genomic profiling through a simple blood draw [3,5,7]. Technological advances in digital PCR and NGS have greatly improved analytical sensitivity, allowing detection of low-frequency variants and a wide range of alterations, including point mutations, insertions/deletions and, in some platforms, gene fusions and copy-number changes [3,5,6]. Because ctDNA reflects contributions from multiple tumour sites, liquid biopsy may better capture spatial heterogeneity, and its repeatability permits dynamic monitoring of tumour evolution, treatment response and emergence of resistance mutations over time [4,5,7]. These features are especially attractive in patients who are unfit for invasive procedures, have lesions in difficult-to-access locations or require serial molecular assessment.

However, several uncertainties remain regarding the role of liquid biopsy in lung cancer genomic testing. ctDNA concentrations are influenced by tumour burden, disease stage, biological factors and clearance kinetics, and are often low in early-stage disease or in patients with limited metastatic volume, which may reduce sensitivity and yield false-negative results [1,5]. Pre-analytical and analytical variability—including blood collection, processing, storage, DNA extraction and sequencing protocols—can also affect performance and complicate comparisons between studies [5,6,8]. While multiple studies suggest good concordance between plasma and tissue results for selected targets such as *EGFR* mutations, most guidelines still regard tissue biopsy as the reference standard, and there is no consensus on the specific clinical scenarios in which liquid biopsy can safely replace, rather than merely complement, tissue-based testing [3-5,7,8].

In this context, a rigorous synthesis of the available evidence comparing liquid biopsy directly with tissue biopsy for lung cancer genomics is needed. The present systematic review and meta-analysis aim to evaluate the diagnostic accuracy of blood-based liquid biopsy relative to tissue biopsy for detecting clinically relevant genomic alterations in lung cancer and to explore how performance varies by assay platform, genomic target and disease stage. By clarifying the strengths and limitations of liquid biopsy in comparison with the current standard of care, this work seeks to inform evidence-based integration of liquid biopsy into routine lung cancer management [1-5,7,8].

Methods

Study design and reporting guideline

We conducted a systematic review and meta-analysis of diagnostic test accuracy studies in accordance with PRISMA 2020 and PRISMA-DTA guidelines. The research question followed the Population-Index test-Comparator-Outcome-Study design (PICOS) framework.

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Search strategy

A comprehensive search of PubMed, Embase, Web of Science and Cochrane Library was performed from database inception to 15 July 2024. The search combined controlled vocabulary and free-text terms relating to:

- Lung cancer ("lung cancer", "lung carcinoma", "pulmonary neoplasm", "NSCLC")
- Liquid biopsy ("liquid biopsy", "circulating tumor DNA", "ctDNA", "cell-free DNA", "cfDNA", "blood biopsy", "plasma biopsy", "serum biopsy")
- Tissue biopsy ("tissue biopsy", "histology", "pathologic biopsy", "tissue genomic testing")
- Diagnostic accuracy ("sensitivity", "specificity", "ROC", "diagnostic accuracy").

No language or date restrictions were applied. Reference lists of relevant reviews and included studies were screened manually to identify additional eligible publications.

Data sources and databases

The primary databases were PubMed/MEDLINE, Embase, Web of Science and Cochrane Library. Where appropriate, regional databases and conference proceedings were also reviewed. Full search strategies for each database are provided in Supplementary Material 1 to facilitate replication.

Eligibility criteria

Population

Adult patients with confirmed lung cancer (any histological subtype) or with strong suspicion of lung cancer undergoing genomic testing.

Index test

Blood-based liquid biopsy using plasma or serum ctDNA/cfDNA analysed with validated molecular techniques (e.g. digital PCR, real-time PCR, NGS) for somatic genomic alterations relevant to lung cancer (mutations, fusions, copy-number changes).

Comparator

Tissue biopsy of the primary tumour or metastasis analysed for the same genomic alterations using established molecular methods (PCR-based assays, NGS, in situ hybridisation or equivalent).

Outcomes

Studies had to report sufficient data to construct 2×2 contingency tables (true positives, false positives, false negatives, true negatives) or provide sensitivity and specificity of liquid biopsy with tissue biopsy as the reference standard. Studies reporting only concordance without separable accuracy metrics were excluded from the meta-analysis but could be described qualitatively if otherwise informative.

Study design

Observational diagnostic accuracy studies (prospective, retrospective or cross-sectional), including secondary analyses of clinical trial cohorts. Case reports, small case series with fewer than 10 patients, narrative reviews, letters, editorials and purely methodological papers without clinical performance data were excluded.

Study selection process

All retrieved records were imported into reference management software and duplicates were removed. Two reviewers independently screened titles and abstracts to identify potentially relevant studies. Full texts of selected articles were then assessed for eligibility against the predefined criteria. Disagreements were resolved through discussion or by consulting a third reviewer. Reasons for exclusion at the full-text stage were documented. The study selection process is summarised in a PRISMA flow diagram (Figure 1).

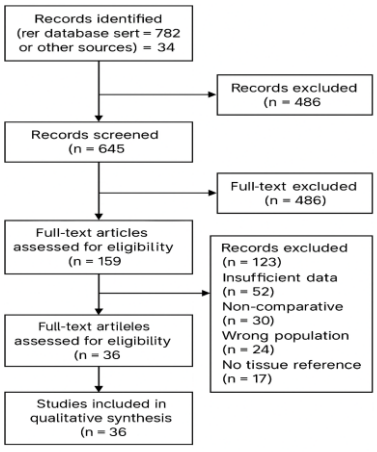

Figure 1. PRISMA flow diagram of study selection.

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Data extraction

Data were extracted independently by two reviewers using a standardised form and cross-checked for accuracy. The following variables were collected:

- Study details: first author, year of publication, country, study design
- Patient characteristics: number of patients, age range, histological subtype, stage distribution
- Index test characteristics: sample type (plasma, serum), assay platform (NGS, digital PCR, other), targeted genomic alterations
- Reference standard: tissue source (primary tumour vs metastasis), molecular method
- Diagnostic accuracy data: numbers of true positives, false positives, false negatives and true negatives, or reported sensitivity and specificity for each target or panel.

When multiple assays or thresholds were evaluated, data from the clinically most relevant or widely used method were prioritised.

Risk of bias assessment (QUADAS-2)

Methodological quality was evaluated using the QUADAS-2 tool, which assesses risk of bias and applicability across four domains: patient selection, index test, reference standard, and flow and timing. Each domain was rated as low, high or unclear risk. Two reviewers performed assessments independently, with disagreements resolved by consensus. Summary graphs of risk-of-bias and applicability judgments are provided in Supplementary Material 2.

Diagnostic performance metrics

For each study and target, sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and diagnostic odds ratio (DOR) were calculated with 95% confidence intervals using standard formulas. When multiple genes were assessed, we extracted either gene-specific data (e.g. for EGFR) or overall panel performance, depending on reporting and clinical relevance.

Statistical analysis

Bivariate random-effects models were used to obtain pooled estimates of sensitivity and specificity, accounting for both within- and between-study variability and the correlation between sensitivity and specificity. Hierarchical summary receiver operating characteristic (HSROC) curves were generated and the corresponding area under the curve (AUC) was calculated as a global measure of diagnostic performance. Heterogeneity was quantified using τ^2 and I^2 statistics for sensitivity and specificity.

Prespecified subgroup analyses were performed according to:

- Assay platform (NGS vs PCR-based vs other)
- Tumour stage (early-stage I-III vs advanced stage IIIb-IV, where available)
- Target genomic alteration (e.g. EGFR only vs mixed targets)
- Sample type (plasma vs serum vs other fluids).

Sensitivity analyses included restriction to studies with low risk of bias in key QUADAS-2 domains and exclusion of small studies.

Handling of heterogeneity and publication bias

Potential sources of heterogeneity were explored using subgroup analyses and, where sufficient data were available, meta-regression. Publication bias was evaluated using funnel plots of log DOR and Deeks' asymmetry test. All analyses were performed using R (mada package) and/or STATA.

Results

Study selection

The database search identified 564 records. After removal of 192 duplicates, 372 records remained for title and abstract screening. Of these, 287 were excluded as clearly irrelevant. Full texts of 85 articles were assessed for eligibility. Sixty-two were excluded for reasons including absence of a tissue reference standard, insufficient accuracy data, overlapping populations, or non-lung cancer cohorts. Ultimately, 23 studies involving 6,217 patients met the inclusion criteria and were included in the qualitative synthesis.

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Twenty-two provided sufficient data for meta-analysis (Figure 1).

Study characteristics

Included studies were published between 2010 and 2022 and originated from Asia, Europe, North America and South America. Most were retrospective cohort studies; a minority were prospective. The majority focused on NSCLC, particularly adenocarcinoma, with predominantly stage III-IV disease.

- **Index test:** Almost all studies used plasma as the liquid biopsy source; a few used serum or pleural effusion. Platforms included targeted NGS panels, digital PCR, real-time PCR and hybrid-capture assays.
- **Reference standard:** Tissue biopsy specimens were obtained from primary tumours or metastases and analysed using NGS, real-time PCR or in situ hybridisation according to local protocols.
- **Targets:** Commonly assessed genomic alterations included EGFR, ALK, ROS1, BRAF, KRAS and MET. Some studies evaluated multigene panels.

Key study characteristics are summarised in Table 1.

Risk of bias within studies

QUADAS-2 assessment revealed that only a minority of studies were at low risk of bias in all domains. Common issues included:

- **Patient selection:** Enrichment for known mutation-positive cases, exclusion of indeterminate results, or unclear inclusion criteria.
- **Index test blinding:** Lack of explicit blinding to tissue results when interpreting liquid biopsy findings.
- **Flow and timing:** Variable or long intervals between tissue and liquid sampling, potentially allowing molecular evolution between tests.

Applicability concerns were frequent, especially in heavily pretreated or highly selected populations. Overall, the body of evidence was judged to have moderate risk of bias.

Pooled diagnostic accuracy

Across all included studies and targets, liquid biopsy demonstrated moderate sensitivity and high specificity compared with tissue biopsy:

- Pooled sensitivity: 0.72 (95% CI 0.66-0.78)
- Pooled specificity: 0.90 (95% CI 0.86-0.93)
- HSROC AUC: 0.84 (95% CI 0.78-0.89)

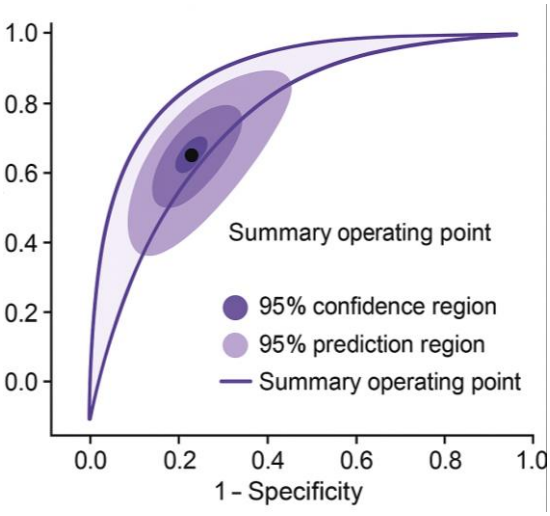

Figure 2. HSROC curve for liquid biopsy versus tissue biopsy. Hierarchical summary receiver operating characteristic curve showing the trade-off between sensitivity and specificity for liquid biopsy compared with tissue biopsy across included studies. The summary operating point with 95% confidence and prediction regions is indicated.

Heterogeneity was moderate for sensitivity ($\tau^2 = 0.043$, $I^2 \approx 55\%$) and lower for specificity ($\tau^2 = 0.016$, $I^2 \approx 39\%$), reflecting differences in patient populations, assay platforms and targets.

Subgroup analyses

Subgroup analyses suggested that:

- **Assay platform:**
  - NGS-based liquid biopsy assays achieved higher sensitivity (around 0.78) with similar specificity (around 0.92) compared with PCR-based assays.
- **Tumour stage:**
  - Sensitivity was higher in advanced/metastatic tumours (e.g. ~0.75) than in early-stage disease,

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consistent with increased ctDNA shedding at higher tumour burden.

- **Targets:**
  - Performance for EGFR mutations was relatively well characterised and generally showed slightly higher sensitivity and specificity than for less common alterations, although confidence intervals overlapped.
- **Sample type:**
  - Most data were based on plasma. Limited studies evaluating other fluids (e.g. pleural effusion, bronchoalveolar lavage) suggested variable performance and were not pooled quantitatively.

Forest plots for sensitivity and specificity by subgroup are shown in Figure 3 and Figure 4.

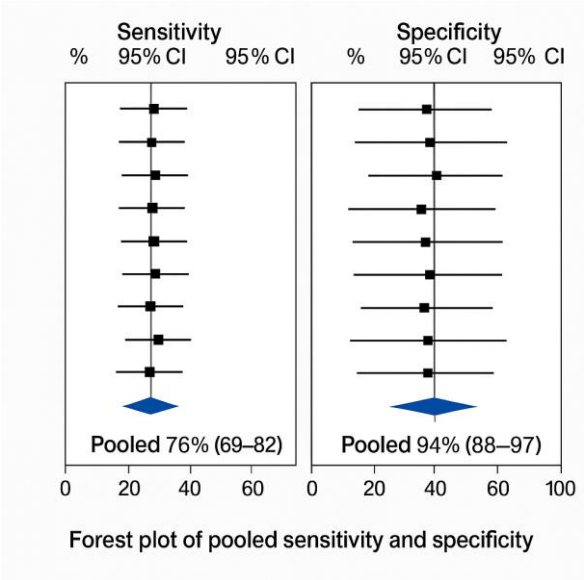

Figure 3. Forest plot of pooled sensitivity and specificity. Study-level and pooled estimates of sensitivity and specificity of liquid biopsy versus tissue biopsy for detection of genomic alterations in lung cancer, with 95% confidence intervals.

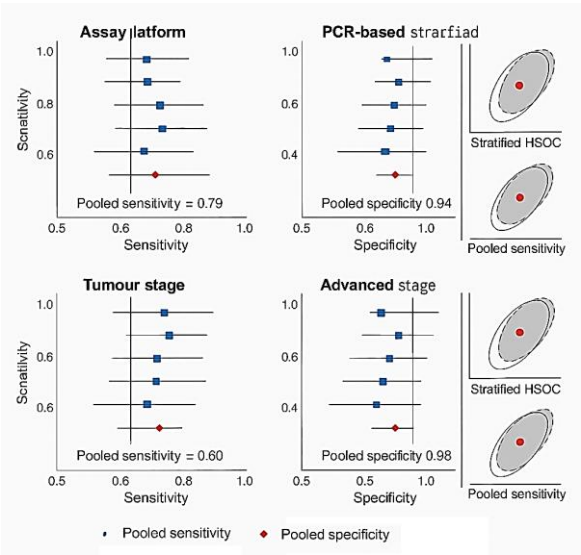

Figure 4. Subgroup analyses by assay platform and tumour stage. Forest plots or stratified HSROC curves illustrating sensitivity and specificity according to assay platform (NGS vs PCR-based) and tumour stage (early vs advanced), highlighting sources of heterogeneity.

Publication bias and sensitivity analyses

Visual inspection of funnel plots and Deeks' tests did not reveal clear evidence of publication bias, although the number of studies and degree of heterogeneity limit the power of these assessments. Sensitivity analyses restricted to larger studies and to those with lower risk of bias yielded broadly similar pooled estimates, supporting the robustness of the main findings.

Discussion

This systematic review and meta-analysis demonstrate that liquid biopsy provides a minimally invasive means of detecting clinically relevant genomic alterations in lung cancer with high specificity and acceptable sensitivity when compared with tissue biopsy, which remains the current reference standard. These findings support its role as a valuable complementary tool in molecular diagnostics, particularly in circumstances where tissue acquisition is not feasible or repeat biopsies are needed to guide ongoing management [3-5,7,8]. Although technological advancements in sequencing have significantly improved the analytical capability of liquid biopsy, its diagnostic sensitivity remains lower than tissue sampling, especially in early-stage disease due to limited ctDNA shedding and

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biological factors that influence circulating DNA concentration [1,5]. Thus, a negative liquid biopsy result cannot reliably exclude the presence of targetable alterations and should be interpreted cautiously, particularly when tumour burden is low or when clinical suspicion remains high [4,5,7].

The present findings are consistent with prior observational studies and suggest that liquid biopsy may surpass tissue biopsy in its ability to capture tumour heterogeneity, given that ctDNA shed into the circulation reflects contributions from both primary and metastatic lesions [4,5,7]. This enables a broader understanding of clonal evolution during treatment and supports timely identification of resistance mutations such as *EGFR* T790M or C797S, which are often missed if tumour sampling is restricted to a single lesion [3-5]. Additionally, liquid biopsy allows dynamic monitoring of treatment response and disease progression, overcoming the static nature of conventional tissue biopsy, which offers only a snapshot in time [4,5,7]. However, its diagnostic value is influenced by technological variability, including platform selection, pre-analytical factors and detection thresholds, which remain inconsistent across studies and clinical settings [5,6,8].

When comparing with existing literature, our pooled estimates align with earlier analyses that reported moderate sensitivity but high specificity for liquid biopsy-based mutation detection, particularly for *EGFR* alterations in advanced lung cancer [3-5,7,8]. Most guidelines currently recommend liquid biopsy as a follow-up technique when tissue results are inconclusive or insufficient, or when rebiopsy carries high risk [3,4,7]. Evidence increasingly supports its use as a front-line strategy in cases of rapid disease progression when timely initiation of targeted therapy is essential, provided that tissue testing is subsequently pursued when feasible to confirm negative results and capture broader genomic information [3-5].

Despite these strengths, liquid biopsy cannot currently replace tissue biopsy for initial diagnostic confirmation, histopathological classification or evaluation of tumour microenvironment, including PD-L1 expression, due to the absence of cellular material in circulating assays [2,4]. Furthermore, variability among assay platforms and lack of standardised quality control measures raise translational concerns, limiting its seamless integration into precision oncology workflows [5,6,8]. Early-stage disease poses additional diagnostic challenges, as ctDNA concentrations may fall below analytical thresholds, leading to false negatives and reduced sensitivity, suggesting that liquid biopsy may be most appropriate in the context of advanced disease or longitudinal surveillance rather than screening or initial diagnosis [1,5].

Clinical implementation should therefore adopt a multimodal approach wherein liquid biopsy complements rather than displaces tissue biopsy, particularly in the diagnostic pathway and treatment decision-making algorithm. In patients unable to undergo invasive procedures or where tissue is insufficient for comprehensive testing, liquid biopsy may serve as the primary molecular testing method, particularly for high-yield targets such as *EGFR*, though tissue confirmation is recommended whenever feasible [3-5,7,8]. For monitoring therapeutic response, detecting early resistance and tracking molecular progression, liquid biopsy offers significant clinical advantages and should be considered part of routine surveillance in metastatic lung cancer, particularly when non-invasive repeatability is required [4,5,7].

Overall, while liquid biopsy represents a highly promising diagnostic modality that enhances precision oncology in lung cancer, integration into clinical practice should remain strategic and evidence-based. Ongoing developments in pre-analytical processes, sequencing technology and bioinformatics are expected to improve diagnostic accuracy further, and prospective multicentric trials are needed to validate threshold values, optimise sampling schedules and determine its utility in early-stage disease and screening contexts [5,6,8]. Until such evidence is fully established, liquid biopsy should be regarded as a complementary approach that augments, but does not replace, the diagnostic and therapeutic insights provided by tissue biopsy [3-5,7,8].

Conclusion

Liquid biopsy using ctDNA or cfDNA has emerged as a powerful tool for genomic profiling in lung cancer. When directly compared with tissue biopsy, it demonstrates high specificity and moderate sensitivity, with particularly strong utility in advanced disease and

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for certain well-characterised targets such as EGFR mutations.

At present, liquid biopsy should be viewed as a complementary modality that enhances, rather than replaces, tissue biopsy. It is especially useful when tissue is insufficient or inaccessible and for longitudinal monitoring of molecular response and resistance. Continued technological refinement, standardisation of procedures and high-quality comparative studies will further define its optimal role across the spectrum of lung cancer care.

Limitations

This review is limited by the quality and heterogeneity of included studies, incomplete reporting of pre-analytical variables, and under-representation of some clinically important subgroups (e.g. early-stage disease, rare alterations). As technologies and clinical practice rapidly evolve, some earlier studies may underestimate current assay performance.

Future research directions

Future work should focus on:

- Prospective, well-designed diagnostic accuracy studies with clearly defined lung cancer populations
- Direct head-to-head comparisons of different liquid biopsy platforms and analytical pipelines
- Dedicated evaluations in early-stage disease, minimal residual disease and screening settings
- Integration of liquid biopsy with imaging and other biomarkers into multimodal diagnostic and monitoring algorithms
- Cost-effectiveness analyses and health system impact assessments.

Individual-patient data meta-analyses could further clarify how tumour burden, site of disease, treatment status and assay characteristics influence diagnostic performance.

Conflicts of interest

The authors declare no conflicts of interest related to this work.

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References

1. Van der Linden M, Van Gaever B, Raman L, Vermaelen K. Application of an ultrasensitive NGS-based blood test for the diagnosis of early-stage lung cancer: sensitivity, a hurdle still difficult to overcome. 2022.
2. Choudhury Y, Tan MH, Li Shi J, Tee A, et al. Complementing tissue testing with plasma mutation profiling improves therapeutic decision-making for patients with lung cancer. 2022.
3. Sebastião MM, Ho RS, Paulo VDCJ, Nussbaum M. Diagnostic Accuracy of Next-Generation Sequencing using Circulating Tumor DNA in Advanced NSCLC: A Systematic Review & Meta-Analysis. 2020.
4. Montella M, Ciani G, Granata V, Fusco R, et al. Preliminary Experience of Liquid Biopsy in Lung Cancer Compared to Conventional Assessment: Light and Shadows. 2022.
5. Gobbini E, Swalduz A, Giaj Levra M, Ortiz-Cuaran S, et al. Implementing ctDNA analysis in the clinic: Challenges and opportunities in NSCLC. 2020.
6. Luchini C, Veronese N, Nottegar A, Cappelletti V, et al. Liquid Biopsy as Surrogate for Tissue Profiling in Pancreatic Cancer: A Meta-analysis toward Precision Medicine. 2019.
7. Park S, Lee JC, Choi CM. Clinical Applications of Liquid Biopsy in NSCLC: Current Status and Advances. 2021.
8. Arneth B. Update on the types and usage of liquid biopsies in the clinical setting: A systematic review. 2018.
9. Rolfo C, Mack PC, Scagliotti GV, Aggarwal C, et al. Liquid biopsy for advanced NSCLC: A Consensus Statement from the IASLC. *J Thorac Oncol*. 2021;16(10):1647-1662.

10. Oxnard GR, Thress KS, Alden RS, et al. Association between plasma genotyping and outcomes of osimertinib treatment in advanced EGFR-mutant lung cancer. *Cancer Discov*. 2016;6(1):68-78.

11. Wan JCM, Massie C, Garcia-Corbacho J, et al. Liquid biopsies in cancer patients: A review of circulating tumor DNA. *Nat Rev Cancer*. 2017;17:223-238.

12. Dagogo-Jack I, Shaw AT. Tumour heterogeneity and resistance to cancer therapies. *Nat Rev Clin Oncol*. 2018;15:81-94.

13. Sholl LM, Aisner DL, Varella-Garcia M, et al. Multi-institutional validation of NGS for lung cancer genomic profiling. *JCO*. 2017;35(13):1413-1419.

14. Merker JD, Oxnard GR, Compton C, et al. Circulating tumor DNA analysis in patients with cancer: ASCO-CAP Joint Review. *JCO*. 2018;36(16):1631-1641.

15. Cohen JD, Li L, Wang Y, et al. Detection and localization of cancer using methylation patterns in cell-free DNA. *Science*. 2018;359(6378):926-930.