

ORIGINAL RESEARCH ARTICLE

Key contributors and trends in circulating tumor DNA research in lung cancer: A bibliometric analysis

Lin Su^{1,2†} , Xueli Bai^{1,2†} , Xiaohong Zhang^{1,2†} , Jiande Cheng^{1,2} , Jie Ding^{1,2} , Shuang Wei^{1,2} , Xiaochen Li², and Xiansheng Liu^{1,2*} 

¹Department of Respiratory and Critical Care Medicine, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan, Shanxi, China

²Department of Respiratory and Critical Care Medicine, Key Laboratory of Pulmonary Diseases of Health Ministry, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Abstract

Lung cancer is one of the leading causes of cancer-related mortality, and liquid biopsy, particularly the detection of circulating tumor DNA (ctDNA), offers a promising non-invasive alternative for diagnosis. Despite significant research on ctDNA in lung cancer, a comprehensive bibliometric analysis on this topic is lacking in the literature. This study systematically reviews ctDNA research trends in lung cancer using bibliometric methods to identify leading contributors, emerging themes, and underexplored areas for future research. We conducted a search of the Web of Science Core Collection database for ctDNA-related lung cancer publications up to 2023. The bibliometric analysis was performed using VOSviewers, CiteSpace, and the R package “bibliometrix.” The results revealed a total of 2862 publications on ctDNA in lung cancer, comprising 1998 articles and 864 reviews. Between 2021 and 2023, the number of publications stabilized, with an average of approximately 360 publications per year. The countries with the highest number of published papers were China and the United States. The University of Texas MD Anderson Cancer Center was the leading institution in terms of publication output. Among journals, *Cancers* published the highest number of papers, while *Clinical Cancer Research* had the highest citation impact. Lanman RB was the leading author by publication count, and Newman was the most co-cited author. Current research on ctDNA in lung cancer primarily focuses on areas such as minimal residual disease, prognosis and recurrence monitoring, adjuvant therapy decision-making, epidermal growth factor receptor and targeted therapy, and immunotherapy. This bibliometric analysis highlights the impact of ctDNA in lung cancer, revealing key contributors and emerging research trends.

Keywords: Circulating tumor DNA; Lung cancer; Bibliometric analysis; Research trends; Key contributors

†These authors contributed equally to this work.

***Corresponding author:**

Xiansheng Liu
(Doctorliu69@126.com)

Citation: Su L, Bai X, Zhang X, et al. Key contributors and trends in circulating tumor DNA research in lung cancer: A bibliometric analysis. *Cancer Plus*. 2025;7(1):11-27. doi: 10.36922/cp.5223

Received: October 19, 2024

Revised: January 10, 2025

Accepted: January 22, 2025

Published online: February 25, 2025

Copyright: © 2025 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Data from the International Agency for Research on Cancer, a subsidiary of the World Health Organization, revealed that in 2022, lung cancer accounted for approximately 2.5 million new cases and 1.8 million deaths worldwide, making it the leading cause of cancer-related morbidity and mortality globally.¹ Patient overall survival (OS) in lung cancer largely depends on three critical factors: disease stage, functional status, and the molecular characteristics of the cancer.² Significant advancements in molecular diagnostics and therapies have greatly improved survival rates, as molecular alterations, when identified, can be targeted with specific therapies.³ However, one challenge in molecular profiling is the limited availability of tumor samples. In approximately 23% of cases, difficulties in accessing tumor tissue noninvasively, or patient comorbidities, result in insufficient samples for molecular analysis.⁴ Furthermore, necrotic tumor cells can lower cellular density, potentially leading to the omission of actionable genetic alterations.⁵ Liquid biopsy has emerged as a practical alternative to traditional tissue biopsies, offering a new approach to lung cancer prevention, early diagnosis, and precise molecular analysis.⁶

Circulating tumor DNA (ctDNA) is the most extensively investigated biomarker in liquid biopsy. ctDNA consists of short DNA fragments, typically 120 – 160 base pairs in length, that are shed from tumor cells into the bloodstream. These fragments often reflect the genetic makeup of the primary tumor, including gene mutations, copy number variations, and methylation patterns. With a short half-life of <2 h, ctDNA provides real-time insights into the dynamic changes occurring within tumors.^{7,8} Advancements in the Cancer Genome Project and next-generation sequencing (NGS) have greatly improved the sensitivity and specificity of ctDNA screening. This has led to its growing recognition as a valuable biomarker for the accurate diagnosis, personalized treatment, and prognosis of lung cancer.⁹

Bibliometrics is a method used to quantitatively and qualitatively analyze literature within a specific research field,^{9,10} providing comprehensive insights into countries, organizations, journals, authors, references, and keywords. It allows for a deeper understanding of emerging research trends, collaborations, and scientific impact.

Despite extensive research on ctDNA in lung cancer, no comprehensive bibliometric analysis has been performed. This study systematically reviews ctDNA research trends in lung cancer using bibliometric methods to identify leading contributors, emerging themes, and underexplored areas for future research.

2. Methods

2.1. Search strategy

The literature search was conducted in the Web of Science Core Collection database (WoSCC) on June 15, 2024. The search criteria were as follows: (i) TS = (lung cancer); (ii) (TS = [ctDNA]) OR TS = (ctDNA); and (iii) #ii AND #i. This initial search resulted in 3,510 publications. To refine the results, we filtered the data by selecting only articles and reviews, restricting the language to English, and excluding publications from 2024. After applying these filters, 2862 publications remained.

2.2. Data analysis

VOSviewer (version 1.6.10) was used as a bibliometric analysis tool to create networks of co-authorship, co-occurrence, and co-citation. In VOSviewer visualizations, nodes represent entities such as countries, organizations, journals, or authors. The size and color of the nodes reflect the quantity and category of each element, while the thickness of the lines between nodes indicates the strength of collaboration or co-citation.¹¹ In this study, VOSviewer was used to analyze various factors, including countries, organizations, journals, co-cited journals, authors, co-cited authors, co-cited references, and co-occurring keywords. CiteSpace (version 6.3.R2), another software tool for bibliometric analysis and visualization, was also employed.¹² In CiteSpace, a “citation burst” refers to a set of references with high-frequency citations within a specific period. This feature was utilized to identify the references with the most frequent citation bursts. In addition, the R package “bibliometrix” (version 3.2.1) was used for keyword trend analysis and to construct a geographical distribution network for publications related to ctDNA in lung cancer.¹³ Figure 1 presents the flowchart of publication screening and data analysis.

3. Results

3.1. Analysis of annual publication trends

A total of 2862 publications were identified, comprising 1998 articles (69.81%) and 864 reviews (30.19%). Figure 2A illustrates the trends in annual publication output. From 2003 to 2014, the number of publications remained relatively low, gradually increasing from 15 to 46. However, a notable rise in annual output occurred between 2015 and 2020, with an average increase of approximately 51.33 publications per year, reaching 354 in 2020. Between 2021 and 2023, the number of publications stabilized, with an average of approximately 360 publications per year.

3.2. Analysis of countries and organizations

Table 1 ranks the top 10 countries and organizations by the number of publications.

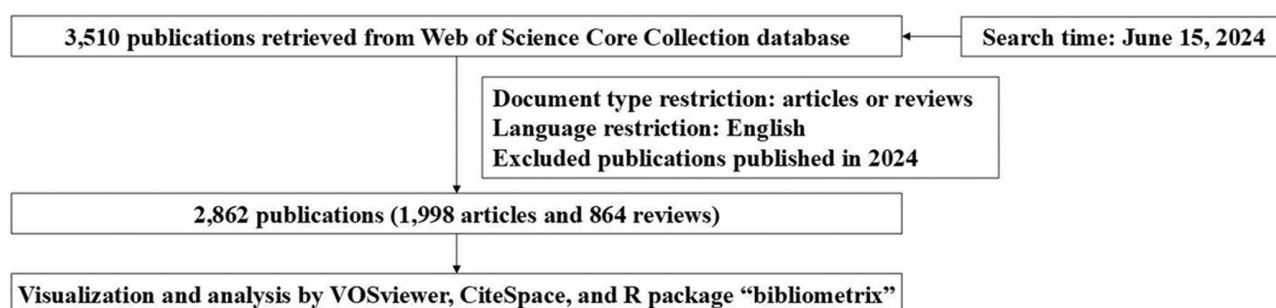


Figure 1. Flowchart of publication screening and data analysis

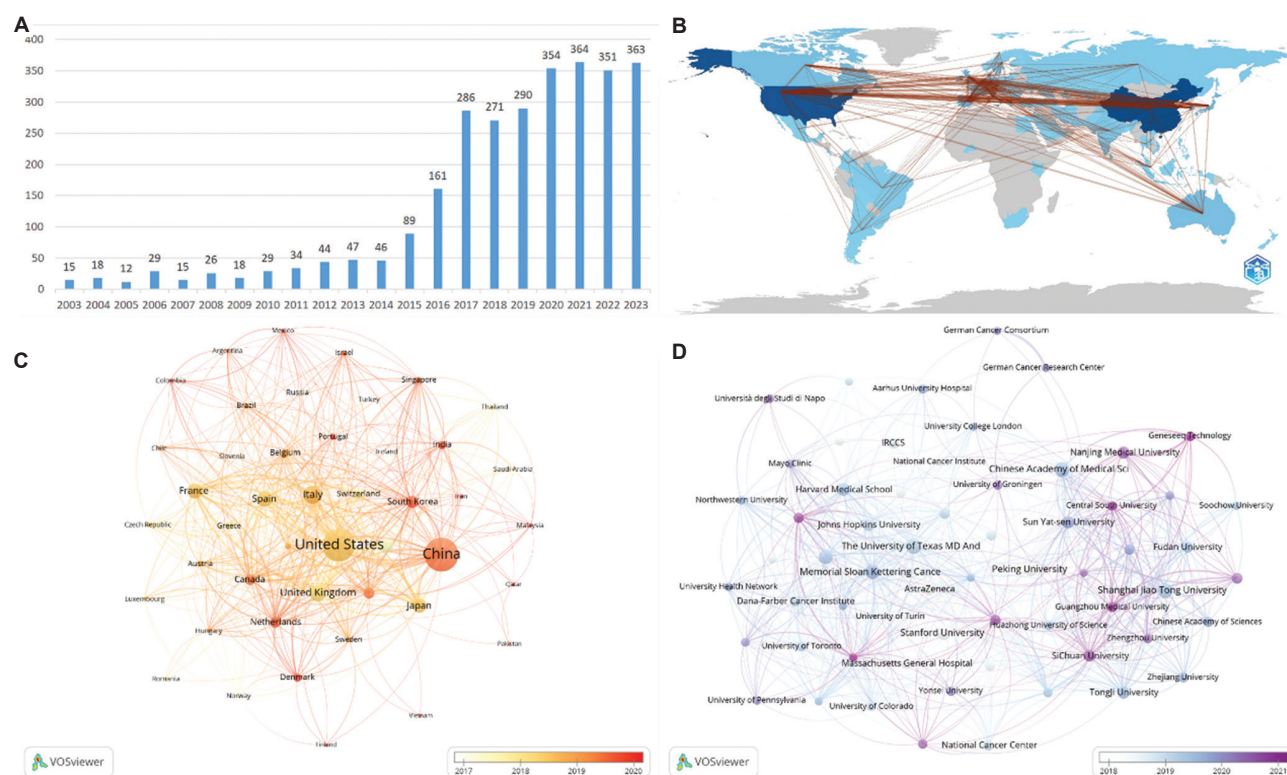


Figure 2. Distribution of publications. (A) Trends in annual publication output; (B) geographical distribution network for publications; (C) overlay visualization map of co-authorship analysis among countries; and (D) overlay visualization map of co-authorship analysis among institutions.

China led with 911 publications, followed by the United States with 817 and Italy with 272. In terms of citations, the United States ranked first with 64,216 citations, followed by China with 24,600 and the United Kingdom with 22,711. A geographical distribution network for publications on ctDNA in lung cancer was established (Figure 2B). An overlay visualization map of co-authorship among the 45 countries, each with at least five publications, was also created (Figure 2C). The United States and China exhibited the strongest bilateral cooperation, while the United States, the United Kingdom, and Italy also had close collaborative ties. Similarly, China, the United Kingdom, and Japan maintained cooperation. Although China produced the

most research, the United States (817) demonstrated a markedly higher number of collaborative links compared to China (435) and the United Kingdom (436).

The top 10 organizations included eight medical institutions and two pharmaceutical companies. The University of Texas MD Anderson Cancer Center led with 75 publications, followed by Shanghai Jiao Tong University (67 papers) and Chinese Academy of Medical Sciences (66 papers). In terms of citations, Memorial Sloan Kettering Cancer Center led with 9746 citations, followed by Stanford University (8938) and the University of Texas MD Anderson Cancer Center (8176). An overlay

visualization map of co-authorship among 62 institutions, each with at least 20 publications, was also constructed (Figure 2D). The University of Texas MD Anderson Cancer Center had the highest total link strength (155), with strong collaborative relationships with Memorial Sloan Kettering Cancer Center and Harvard Medical School.

3.3. Analysis of journals and co-cited journals

Table 2 presents the top 20 journals by publication count and the top 20 co-cited journals based on the number of

co-citations, along with their 2023 impact factors (IFs) from the 2023 Journal Citation Reports.

Cancers published the most papers (136), followed by *Lung Cancer* (96) and *Frontiers in Oncology* (91). A bibliographic coupling analysis of 64 journals with at least 10 publications was conducted, and an overlay visualization map was generated (Figure 3A). Active citation relationships were observed among *Cancers*, *Frontiers in Oncology*, and *Translational Lung Cancer Research*.

Table 1. Top 10 countries and organizations by the number of publications

Rank	Country	Counts	Citations	Total link strength	Organization	Counts	Citations	Total link strength
1	China	910	24,600	435	University of Texas MD Anderson Cancer Center	75	8,176	154
2	United States	850	64,216	817	Shanghai Jiao Tong University	67	1,295	86
3	Italy	272	18,712	425	Chinese Academy of Medical Sciences	66	1,829	88
4	United Kingdom	220	22,711	436	Guardant Health	62	3,786	84
5	Spain	191	10,092	349	Memorial Sloan Kettering Cancer Center	59	9,746	117
6	Germany	184	14,591	286	Stanford University	59	8,938	79
7	France	180	10,388	312	Peking University	57	2,535	91
8	Japan	170	6,719	262	Harvard Medical School	53	4,999	106
9	South Korea	122	7,366	185	AstraZeneca	52	5,293	104
10	Canada	103	6,254	178	Johns Hopkins University	48	5,797	68

Table 2. Top 20 journals and co-cited journals

Rank	Journal (IF)	Document count	Co-cited journal (IF)	Citations
1	Cancers (4.5)	136	Clinical Cancer Research (10)	9,746
2	Lung Cancer (4.5)	96	Journal of Clinical Oncology (42.1)	7,424
3	Frontiers in Oncology (3.5)	91	New England Journal of Medicine (96.2)	6,293
4	Translational Lung Cancer Research (4)	72	Journal of Thoracic Oncology (21)	5,439
5	Clinical Cancer Research (10)	69	Cancer Research (12.5)	4,616
6	Journal of Thoracic Oncology (21)	63	Annals of Oncology (56.7)	4,367
7	Oncotarget	57	Nature (50.5)	4,265
8	PLoS One (2.9)	50	Nature Medicine (58.7)	3,150
9	International Journal of Molecular Sciences (4.9)	44	PLoS One (2.9)	3,140
10	Journal of Thoracic Disease (2.1)	38	Lung Cancer (4.5)	3,077
11	Oncotargets and Therapy (2.7)	37	Oncotarget	3,013
12	Clinical Lung Cancer (3.3)	35	Proceedings of The National Academy of Sciences of The United States of America (9.4)	2,963
13	Annals of Oncology (56.7)	34	Clinical Chemistry (7.1)	2,669
14	Expert Review of Molecular Diagnostics (3.9)	33	Science Translational Medicine (15.8)	2,624
15	JCO Precision Oncology (5.3)	33	Lancet Oncology (41.6)	2,549
16	Scientific Reports (3.8)	32	Cancer Discovery (29.7)	2,466
17	BMC Cancer (3.4)	31	Science (44.7)	2,212
18	British Journal of Cancer (6.4)	31	British Journal of Cancer (6.4)	2,010
19	Molecular Oncology (5)	30	Scientific Reports (3.8)	1,904
20	Thoracic Cancer (2.3)	30	Nature Communications (14.7)	1,824

Abbreviation: IF: Impact factor.

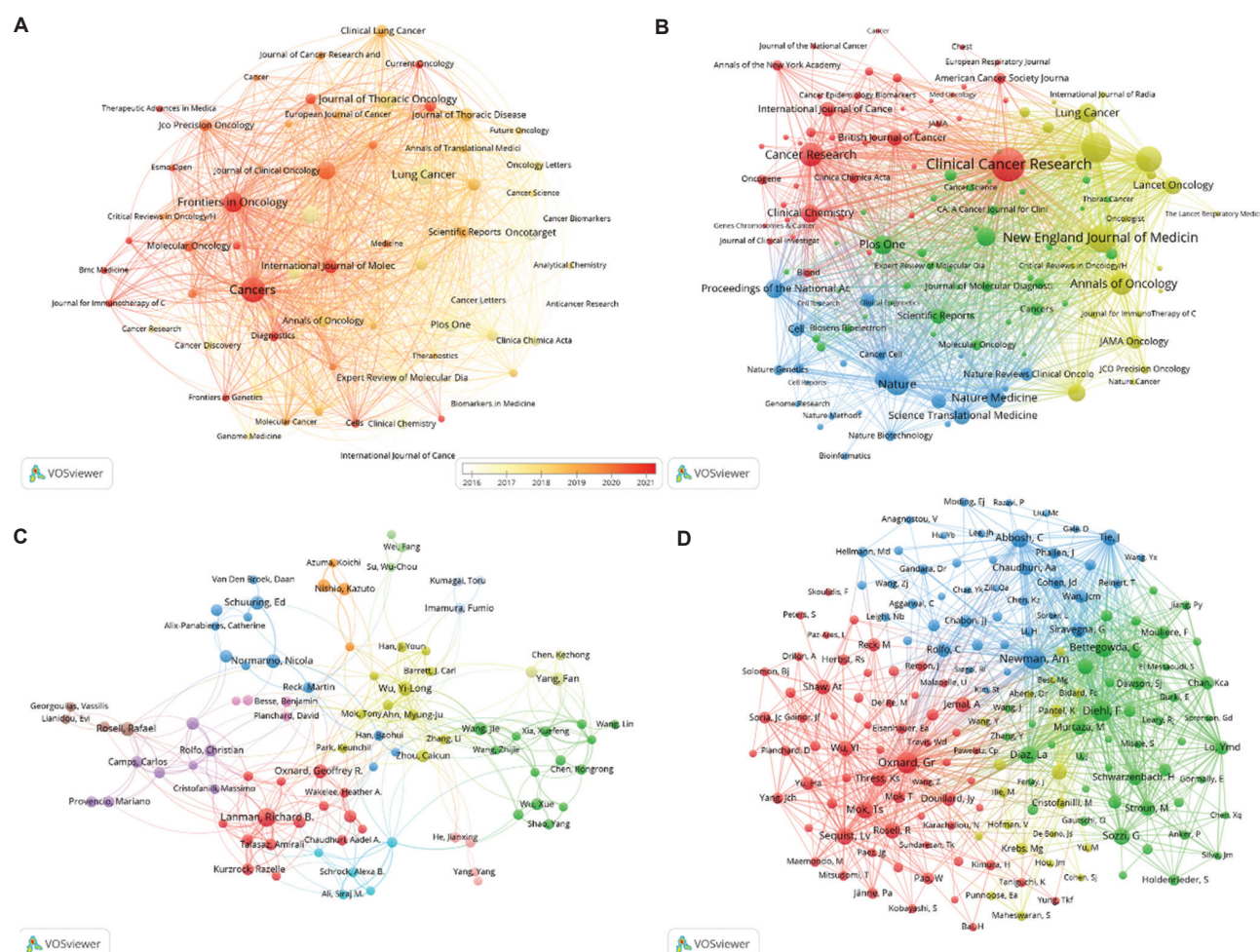


Figure 3. Sources and authors of publications. (A) Overlay visualization map of bibliographic coupling analysis of sources; (B) network visualization map of co-citation analysis of cited source; (C) network visualization map of co-authorship analysis of authors; and (D) network visualization map of co-citation analysis of cited authors.

The most frequently co-cited journal is *Clinical Cancer Research*, with 9746 co-citations, followed by *Journal of Clinical Oncology*, with 7424, and *New England Journal of Medicine*, with 6293. A co-citation analysis of 133 journals with at least 200 co-citations was also performed, and a network visualization map was created (Figure 3B). *Clinical Cancer Research* was frequently co-cited with *Journal of Clinical Oncology*, *New England Journal of Medicine*, and *Journal of Thoracic Oncology*.

3.4. Analysis of authors and co-cited authors

Table 3 lists the top 20 authors by publication count and the top 20 co-cited authors ranked by the frequency of co-citations.

Eight of the top 20 authors have published 20 or more papers on ctDNA in lung cancer, with Lanman RB, Wu YL, and Normanno N leading in terms of publication output.

A co-authorship network visualization map for authors with at least 10 publications was created (Figure 3C). Notably, Lanman RB, Richard B, and Raymond VM have extensively collaborated, whereas Yang F, Chen KZ, and Wang J have also demonstrated significant cooperation.

The most cited author was Newman A (803), followed by Oxnard GR (797) and Diehl F (767). A co-cited author network visualization map was generated for authors with at least 100 co-citations (Figure 3D), revealing active collaborations among Newman A, Diehl F, Bettgeowda C, Abbosh C, Oxnard GR, Mok TS, and Sequist LV.

3.5. Analysis of co-cited references

Table 4 lists the 20 most frequently co-cited references. A network visualization map for co-citation analysis was generated using references with at least 100 co-citations (Figure 4A). The reference “Bettgeowda *et al.*, 2014, Sci

Table 3. Top 20 authors and co-cited author

Rank	Author	Publication count	Co-cited author	Citations
1	Lanman RB	39	Newman A	803
2	Wu YL	24	Oxnard GR	797
3	Normanno N	22	Diehl F	767
4	Rosell R	22	Bettegowda C	590
5	Yang F	22	Abbosh C	572
6	Oxnard GR	21	Diaz LA	521
7	Schuuring E	21	Sequist LV	483
8	Wang J	20	Sozzi G	477
9	Diehn M	18	Mok TS	472
10	Hofman P	18	Tie J	447
11	Malapelle U	18	Rosell R	445
12	Nishio K	18	Heitzer E	429
13	Rolfo C	18	Siravegna G	428
14	Raymond VM	17	Schwarzenbach H	426
15	Sakai K	17	Thress KS	421
16	Zhou CC	17	Wu YL	418
17	Dive C	16	Jemal A	416
18	Holdenrieder S	16	Alix-PanabièresC	401
19	Kurzrock R	16	Stroun M	391
20	Meldgaard P	16	Murtaza M	365

Transl Med”¹⁷ exhibited strong co-citation links with “Newman *et al.*, 2014, Nat Med”¹⁸ and “Diehl *et al.*, 2008, Nat Med”¹⁹, among others.

3.6. References with citation bursts

CiteSpace identified 20 references that exhibited significant citation bursts (Figure 4B), with each bar representing a year and the red bar indicating strong citation burstiness.¹² These bursts occurred between 2012 and 2021, with strengths ranging from 41.24 to 89.59, and durations spanning from 3 to 6 years. The reference “Detection of Circulating Tumor DNA in Early- and Late-Stage Human Malignancies” by Bettegowda *et al.*¹⁷ exhibited the strongest citation burst (strength = 89.59) from 2015 to 2019. A summary of the key research findings from these 20 references is provided in Table 5.

3.7. Analysis of keywords

The co-occurrence analysis of keywords helped identify key research areas. Table 6 lists the top 20 most frequently used keywords in studies on ctDNA in lung cancer. A cluster analysis on keywords appearing more than 10 times was performed using VOSviewer (Figure 4C), with each cluster representing a distinct research focus.

Table 4. Top 20 most frequently co-cited references

Rank	Cited reference	Citations
1	Bettegowda <i>et al.</i> , 2014, Sci Transl Med, v6 ¹⁷	577
2	Newman <i>et al.</i> , 2014, Nat Med, v20, p552 ¹⁸	524
3	Diehl <i>et al.</i> , 2008, Nat Med, v14, p985 ¹⁹	475
4	Abbosh <i>et al.</i> , 2017, Nature, v545, p446 ²⁰	404
5	Diaz Jr and Bardelli, 2014, J Clin Oncol, v32, p579 ²¹	374
6	Dawson <i>et al.</i> , 2013, New Engl J Med, v368, p1199 ²²	320
7	Jahr <i>et al.</i> , 2001, Cancer Res, v61, p1659 ¹⁴	317
8	Chaudhuri <i>et al.</i> , 2017, Cancer Discov, v7, p1394 ¹⁵	307
9	Oxnard <i>et al.</i> , 2014, Clin Cancer Res, v20, p1698 ²³	290
10	Murtaza <i>et al.</i> , 2013, Nature, v497, p10 ²⁴	280
11	Wan <i>et al.</i> , 2017, Nat Rev Cancer, v17, p22 ⁷	279
12	Oxnard <i>et al.</i> , 2016, J Clin Oncol, v34, p3375 ²⁵	275
13	Leon <i>et al.</i> , 1977, Cancer Res, v37, p646 ²⁶	261
14	Mok <i>et al.</i> , 2009, New Engl J Med, v361, p947 ²⁷	261
15	Schwarzenbach <i>et al.</i> , 2011, Nat Rev Cancer, v11, p426 ²⁸	249
16	Mok <i>et al.</i> , 2015, Clin Cancer Res, v21, p3196 ²⁹	247
17	Forsheew <i>et al.</i> , 2012, Sci Transl Med, v4 ³⁰	245
18	Newman <i>et al.</i> , 2016, Nat Biotechnol, v34, p54 ³¹	245
19	Rosell <i>et al.</i> , 2012, Lancet Oncol, v13, p239 ³²	239
20	Crowley <i>et al.</i> , 2013, Nat Rev Clin Oncol, v10, p472 ³³	231

Figure 4D illustrates the keyword trend analysis, highlighting that “MRD,” “adjuvant therapy,” and “immunotherapy” have been prominent research areas over the past 3 years.

4. Discussion

Although tissue biopsy remains the gold standard for lung cancer diagnosis, non-invasive, real-time liquid biopsy has emerged as a valuable alternative. When combined with tissue biopsy, liquid biopsy serves as a crucial tool for predicting prognosis and guiding treatment decisions.^{6,16,34} At present, ctDNA detection has demonstrated significant clinical utility in various areas, including initial molecular typing, minimal residual disease (MRD) detection, prognosis, predicting treatment response, guiding therapeutic strategies, and identifying drug resistance mechanisms in lung cancer.³ Nonetheless, the broad clinical application of ctDNA is still limited by current detection technologies and tumor staging. To further expand its use, validation through prospective studies and real-world evidence is essential.

This study is the first to apply bibliometric analysis to ctDNA research in lung cancer. The WoSCC is widely

Table 5. Summary of the primary research content of the 20 references with the strongest citation bursts

Rank	Main research content
1	A review of the potential applications of circulating nucleic acids in cancer ²⁸
2	An article that presented a comparative analysis between ctDNA and other circulating biomarkers, as well as medical imaging, demonstrating that ctDNA serves as a highly sensitive, specific, and informative biomarker for metastatic breast cancer ²²
3	Using serial plasma samples to sequence cancer exomes, the article established proof-of-principle that exome-wide analysis of ctDNA can complement invasive biopsy approaches to identify mutations associated with acquired drug resistance in advanced cancers ²⁴
4	A method for tagged-amplicon deep sequencing was developed, confirming that the method can advance the idea of circulating DNA analysis as a non-invasive “liquid biopsy” for personalized cancer genomics ³⁰
5	A phase 3 trial, aimed to assess the safety and efficacy of erlotinib compared with standard chemotherapy for first-line treatment of European patients with advanced EGFR mutation-positive NSCLC ³²
6	A review that explored how tumor-associated mutations detectable in the blood can be used in the clinic after diagnosis ³³
7	Using digital polymerase chain reaction-based technologies, this study evaluated the ability of ctDNA to detect tumors, suggesting it is a sensitive, specific, and widely applicable biomarker ¹⁷
8	A study that presented CAPP-Seq as a new method for quantifying ctDNA and implemented CAPP-Seq for NSCLC ¹⁸
9	A review that summarized the applications of ctDNA, discussed its biology, and explored promising future applications to address unmet clinical needs ²¹
10	A study that utilized plasma from patients with advanced lung cancer or melanoma to create ddPCR tests, suggesting that non-invasive cell-free DNA (cfDNA) genotyping through ddPCR exhibits assay characteristics that could facilitate its successful application in clinical diagnostics ²³
11	A study that analyzed EGFR mutations in plasma-derived ctDNA, concluding that ctDNA can be used to assess the mutation status of EGFR ³⁵
12	Different technology platforms were tested for their ability to detect EGFR mutations, including threonine at amino acid position 790, in advanced NSCLC patients ³⁶
13	A study that investigated whether non-invasive genotyping of cfDNA is a useful biomarker for predicting the outcome of osimertinib ²⁵
14	A study that used a tumor-specific phylogenetic approach to profile the ctDNA of the study participants. The results showed that phylogenetic ctDNA profiling tracks the subclonal nature of lung cancer relapse and metastasis ²⁰
15	A review that explored the applications of ctDNA ⁷
16	A study that used massively parallel sequencing-based assays to evaluate the ability of ctDNA to detect MRD. The results showed that detection of ctDNA after resection for stage II colon cancer provides direct evidence of residual disease and identifies patients at very high risk of recurrence ³⁷
17	A study that described a novel, technically robust, blood-based assay to measure tumor mutation burden (bTMB) in plasma, showing that high bTMB is a clinically actionable biomarker for atezolizumab in NSCLC ³⁸
18	A study that applied CAPP-seq ctDNA analysis, and results showed that ctDNA analysis can robustly identify post-treatment MRD in patients with localized lung cancer ¹⁵
19	Clinical utility of comprehensive cfDNA analysis to identify genomic biomarkers in patients with newly diagnosed metastatic NSCLC ³⁹
20	A study that introduced improvements to CAPP-Seq to better facilitate lung cancer screening applications and establish the potential of cfDNA for lung cancer screening ⁴⁰

Abbreviation: ctDNA: Circulating tumor DNA; MRD: Minimal residual disease; CAPP-Seq: Cancer personalized profiling by deep sequencing; NSCLC: Non-small-cell lung cancer; ddPCR: Droplet digital polymerase chain reaction.

regarded as a comprehensive source of high-impact journals, providing robust citation data and standardized metadata. To ensure unbiased data analysis, we employed three distinct bibliometric tools. Compared to traditional review methods, bibliometric analysis provides a more thorough understanding of research trends and emerging topics in the field.

4.1. Current status of ctDNA research publications

To provide a more comprehensive understanding of the discussed methodologies and trends, this study included data spanning the past two decades, highlighting significant advancements in ctDNA research. The first

report on ctDNA in lung cancer was published in 2003, marking the beginning of research in this area, with just 15 papers published that year. By 2014, the number of publications had grown to 46, indicating that the field was still in its early stages. Between 2015 and 2020, the publication output increased rapidly, reflecting a growing interest in ctDNA among researchers. Between 2021 and 2023, the publication output stabilized, signaling continued academic engagement and monitoring of advancements in this field.

China and the United States are the leading contributors to ctDNA research in lung cancer, with the top eight medical institutions in this domain located within these

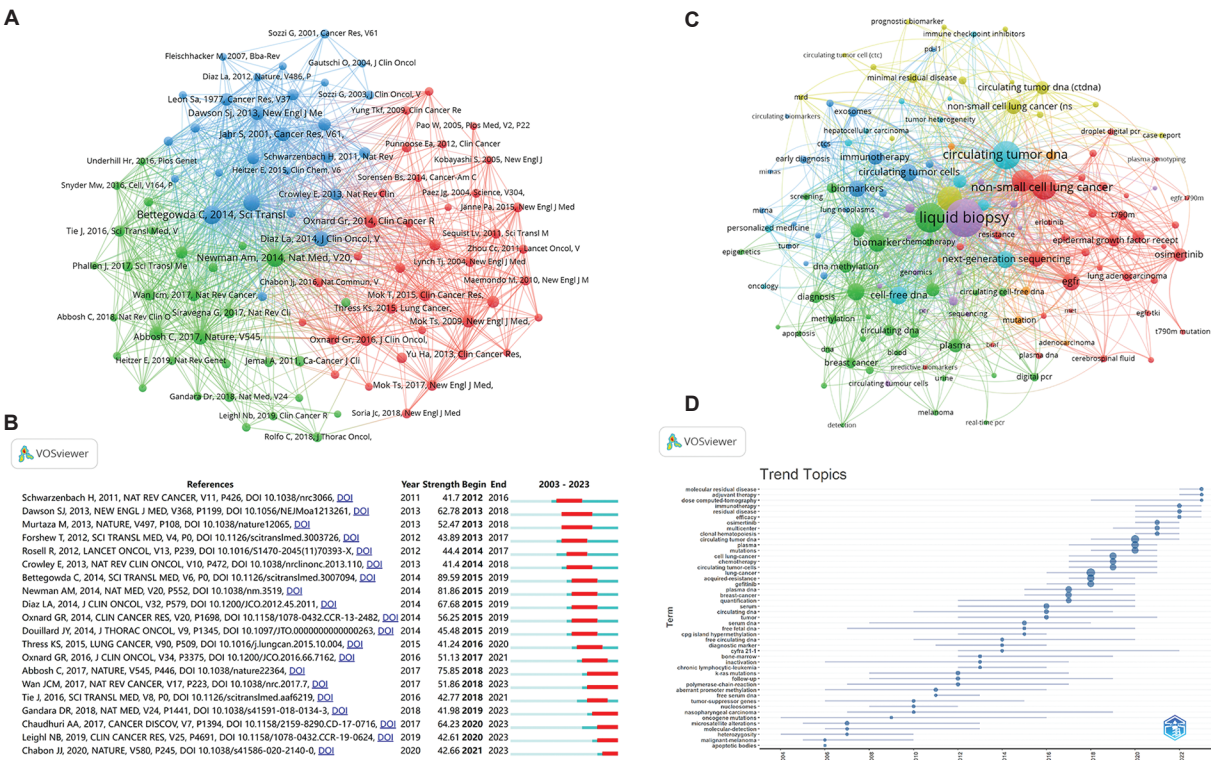


Figure 4. Citations and keywords of publications. (A) Network visualization map of co-citation analysis of cited references; (B) Top 20 references with the strongest citation bursts; (C) network visualization map of co-occurrence analysis of author keywords; and (D) keyword trend analysis.

Table 6. Top 20 co-occurring keywords

Rank	Keyword	Occurrences	Total link strength
1	Liquid biopsy	610	1713
2	Lung cancer	368	906
3	Circulating tumor DNA	345	894
4	NSCLC	269	647
5	ctDNA	253	749
6	NSCLC	200	580
7	Cell-free DNA	134	372
8	Circulating tumor cells	131	296
9	Cancer	130	359
10	EGFR	129	421
11	Next-generation sequencing	124	314
12	Biomarker	123	337
13	Biomarkers	120	352
14	NSCLC	102	207
15	Immunotherapy	99	251
16	NSCLC	96	219
17	Plasma	81	255
18	Prognosis	81	269
19	Targeted therapy	78	218
20	Osimertinib	77	218

Abbreviations: ctDNA: Circulating tumor DNA;
DNA: Deoxyribonucleic acid; EGFR: Epidermal growth factor receptor;
NSCLC: Non-small-cell lung cancer.

two nations. The dominance of these two countries may introduce potential biases in the dataset, such as an overrepresentation of research priorities, methodologies, and clinical practices prevalent in these countries. These biases underline the importance of fostering global collaborations. An overlay visualization map revealed that the United States, Italy, the United Kingdom, Spain, and Germany have actively contributed to the field over at least the past 5 years. Despite China's recent entry into the field, it has quickly become a leading contributor in terms of publication volume. There was a positive correlation between the ranking of organizations and the duration of their involvement in the field, as seen with institutions such as the University of Texas MD Anderson Cancer Center, Shanghai Jiao Tong University, Chinese Academy of Medical Sciences, and Memorial Sloan Kettering Cancer Center. Citation counts serve as a crucial measure of a country's or institution's influence in the field, and collaborating with other countries or organizations can significantly accelerate research advancements. The United States led in both total citations and link strength, followed by the United Kingdom and Italy. Although China had a higher publication count, its average citation per paper (27.03) is lower than that of the United Kingdom (103.23), Germany (79.30), and the United States (75.55). This observation highlights a significant discrepancy between

the quantity and quality of Chinese publications in this field. To address this, China should prioritize strengthening international collaboration as its research output continues to grow.

The journals *Cancers*, *Lung Cancer*, and *Frontiers in Oncology* have published the majority of studies related to ctDNA in lung cancer, making them the most influential sources in this field. Their focus on translational medicine and clinical oncology, particularly lung cancer, underscores the emphasis on the clinical applications of ctDNA in lung cancer. Most of the frequently co-cited journals possess high IFs, with each of the top eight journals exceeding an IF of 10. These prestigious international journals are essential in advancing ctDNA research in lung cancer.

While this study provides valuable insights into publication and citation metrics, it is important to acknowledge that variations in citation practices across disciplines could influence the analysis. For instance, clinical and translational research areas, such as ctDNA in lung cancer, often prioritize high-impact, practice-changing studies, which may lead to a concentration of citations in a few seminal publications. In contrast, basic science fields might distribute citations more evenly across a broader range of studies. These disciplinary differences could result in an overemphasis on high-output regions or journals specializing in translational oncology, potentially skewing the interpretation of research influence and trends. Future analyses could consider normalizing citation metrics or employing field-specific benchmarks to mitigate these biases.

Lanman RB, Wu YL, and Normanno N are the most prolific authors in this field, while Newman A, Oxnard GR, and Diehl F are the most frequently co-cited authors. In 2015, Lanman and his collaborators⁴¹ published a landmark paper, “Analytical and Clinical Validation of a Digital Sequencing Panel for Quantitative, Highly Accurate Evaluation of Cell-Free Circulating Tumor DNA,” which was the first comprehensive validation of the accuracy of ctDNA tumor profiling tests using NGS. Their findings indicated that for patients with advanced cancer, repeated invasive biopsies could potentially be avoided by sequencing plasma-derived DNA. Since then, Lanman and his team have made significant contributions to the development of ctDNA assays, establishing him as a leading expert in the field. In 2014, Newman *et al.*¹⁸ published the paper “An ultrasensitive method for quantitating ctDNA with broad patient coverage,” which has been co-cited 524 times. Using cancer personalized profiling by deep sequencing (CAPP-Seq) in non-small-cell lung cancer (NSCLC), they found a significant correlation between ctDNA levels and tumor size. This method allowed

for earlier response assessment compared to imaging techniques and enabled non-invasive tumor screening and genotyping. CAPP-Seq, which offers deeper sequencing than conventional panels, significantly improves detection sensitivity.¹⁸ The pioneering work of Newman A and his collaborator Diehl F has made CAPP-seq one of the most extensively investigated ctDNA detection technologies, evaluated across various tumor types.^{42,43}

4.2. Knowledge base, hotspots, and frontiers

A co-cited reference is defined as a source that is cited by multiple publications, forming the foundational research base of a particular field.^{10,44} Changes in co-cited references may signal shifts and advancements in research focus, while references exhibiting citation bursts are frequently cited by recent studies, indicating emerging trends.¹⁰ Co-occurrence analysis of keywords facilitates the rapid identification of the distribution and evolution of key topics within the field.

In this study, we identified the 10 most frequently co-cited references to determine the foundational research on ctDNA in lung cancer. In 2001, Jahr *et al.*¹⁴ published their research findings in *Cancer Research*, using advanced quantitative polymerase chain reaction techniques to analyze plasma samples from 30 cancer patients with diverse tumor types. They successfully determined the ratio of tumor-derived deoxyribonucleic acid (DNA) to non-tumor-derived DNA in circulation. This study laid the groundwork for future research on ctDNA in cancer. In 2008, Diehl *et al.*¹⁹ published the third most co-cited paper, introducing an innovative method called beads, emulsion, amplification, and magnetics (BEAMing) to quantify ctDNA in plasma samples from colorectal cancer patients. Their findings indicated that ctDNA measurements could be effectively used to monitor tumor dynamics in patients undergoing surgery or chemotherapy.

In 2013, Dawson *et al.*²² published a study in the *New England Journal of Medicine* comparing ctDNA levels with tumor imaging, cancer antigen 15-3, and circulating tumor cells (CTCs) in 30 women receiving systemic therapy for metastatic breast cancer. Personalized ctDNA assays showed a broader dynamic range and stronger correlation with tumor burden than CA 15-3 or CTCs. This paper exhibited a strong citation burst (62.78) from 2013 to 2018. The same year, Murtaza *et al.*,²⁴ published a study in *Nature* that tracked genetic alterations in metastatic cancers during therapy using serial blood samples from six patients with advanced breast, ovarian, and lung cancers (1 – 2 years follow-up). The study showed that exome-wide ctDNA analysis could complement invasive biopsy in identifying mutations associated with drug resistance. This article also

experienced a notable citation burst strength of 52.47 from 2013 to 2018. In 2014, Bettegowda *et al.*¹⁷ published the most co-cited study, which evaluated 640 cancer patients using digital polymerase chain reaction (dPCR) to detect tumors. Their findings suggested that ctDNA is a versatile, accurate, and reliable biomarker with broad clinical applications across different cancer types. This paper had the strongest citation burst (strength = 89.59) from 2015 to 2019. The paper by Newman *et al.*¹⁵ published in *Nature Medicine* in 2014, ranked as the second most co-cited reference. It had a citation burst strength of 81.86, also from 2015 to 2019, and has been discussed in a previous section. Oxnard *et al.*²³ published a 2014 paper in *Clinical Cancer Research* where they developed droplet digital PCR (ddPCR) tests to detect mutations in epidermal growth factor receptor (EGFR), Kirsten rat sarcoma virus (KRAS), and BRAF genes using plasma from patients with advanced lung cancer or melanoma. Their results showed that noninvasive cell-free DNA (cfDNA) genotyping using ddPCR could provide valuable insights into treatment response and resistance, detecting resistance mutations up to 16 weeks before radiographic progression. This paper had a citation burst strength of 56.25 from 2015 to 2019. Many of the early studies focused on ctDNA detection methods and its potential as a biomarker for various cancers. The surge in research since 2014 is largely due to advancements in digital genomic technologies, enabling the detection of rare mutant variants in complex DNA samples. In 2014, a review by Diaz *et al.*²¹ summarized ctDNA applications, its biology, and future potential to address unmet clinical needs (citation burst strength = 67.68, from 2015 to 2019). More recent research has continued to advance ctDNA detection technologies and clinical applications, especially in lung cancer. One of the most co-cited papers, published in *Nature* in 2017, employed a tumor-specific phylogenetic approach to analyze ctDNA from 100 participants in the TRACing Non-small-Cell Lung Cancer Evolution through Therapy (TRACERx) study. Their findings showed that phylogenetic analysis of ctDNA could effectively track subclonal traits of lung cancer proliferation and recurrence, introducing an innovative technique for ctDNA-based treatment research (citation burst strength of 75.85 from 2018 to 2023).²⁰ In 2017, Chaudhuri *et al.*¹⁵ published a paper in *Cancer Discovery* (citation burst strength of 64.23, from 2020 to 2023), analyzing ctDNA 255 samples, including 40 patients undergoing curative treatment for stages I – III lung cancer and 54 healthy individuals. Using the CAPP-seq ctDNA analysis method, the study found that ctDNA testing is more effective than traditional radiologic imaging at detecting residual or recurrent disease in patients with localized lung cancer. This approach could potentially enable personalized adjuvant treatment in

the early stages of the disease when the tumor burden is minimal. These two studies highlight the close relationship between ctDNA testing and both prognosis assessment and recurrence risk prediction, offering new hope for lung cancer patients. For these observations, it is evident that the early co-cited references primarily focused on ctDNA detection methods. However, most recent research has concentrated on ctDNA as a biomarker for lung cancer prognosis and recurrence risk prediction.

Based on the primary research themes of highly cited references, keyword clustering, and trending topic analysis, research on ctDNA in lung cancer from 2017 to 2023 has primarily focused on areas such as MRD, prognosis and recurrence monitoring, adjuvant therapy decision-making, EGFR mutations, targeted therapy, and immunotherapy.

4.2.1. MRD

MRD refers to cancer that persists in a patient after treatment but remains undetectable by current medical imaging techniques, representing a hidden stage of cancer progression. Assessing MRD status has become a standard criterion for evaluating the effectiveness of treatment in hematological malignancies and is closely linked to disease recurrence and prognosis.⁴⁵⁻⁴⁷ Liquid biopsy techniques, which can detect small numbers of CTCs or trace amounts of ctDNA, now enable the detection of MRD in patients with various malignancies. Monitoring CTCs and ctDNA during post-surgical follow-ups can detect disease recurrence months earlier than current radiological imaging methods. CTCs are tumor cells circulating in the blood, released either naturally or due to medical interventions, while ctDNA originates from CTCs or from the release of dead and apoptotic tumor cells from metastatic sites.⁴⁸ Extensive research has validated the reliability of both biomarkers.⁴⁹⁻⁵¹

Lung cancer is characterized by a complex landscape of driver genes, with nearly 70% of lung adenocarcinomas harboring at least one treatable driver gene mutation (e.g., EGFR, anaplastic lymphoma kinase [ALK], reactive oxygen species proto-oncogene 1 receptor tyrosine kinase, and cellular mesenchymal-epithelial transition factor). These mutations, which include point mutations, insertions/deletions, and fusions, have significantly distinct clinical implications.⁵²⁻⁵⁴ Given this complexity, heightened sensitivity is essential for MRD detection. A 2019 meta-analysis showed that ctDNA is as effective as CTCs in detecting EGFR and its subtypes, and is even superior in identifying KRAS and ALK mutations.⁵⁵ Although ctDNA is emerging as a more suitable marker for MRD in lung cancer, the high cost of ctDNA testing remains a significant challenge. Furthermore,

different gene phenotypes, such as tumor protein P53 and EGFR mutations, have been demonstrated to significantly improve the detection rate of ctDNA in lung cancer.⁵¹ Another important consideration is the potential interference from clonal hematopoiesis, as evidence suggests that over 50% of cfDNA mutations are associated with clonal hematopoiesis rather than tumor cell mutations.⁵⁶ Therefore, MRD assessment using ctDNA in lung cancer requires a nuanced approach that accounts for not only molecular events but also clinical treatment factors and specific analytical strategies, rather than relying on a simple binary evaluation.

4.2.2. Prognosis and recurrence warning

Historically, imaging has been the primary method for assessing the efficacy of lung cancer treatment, but its diagnostic accuracy is often limited by delays in detecting morphological changes. In contrast, ctDNA-MRD offers an advantage by identifying residual tumors at an early stage, even before such changes become visible through imaging. This feature enables early detection of recurrence and provides valuable, timely information for clinical decision-making.

In 2017, the TRACERx study tracked dynamic ctDNA levels in 24 post-surgery NSCLC patients. Among the 14 ctDNA-positive patients, 13 experienced disease recurrence, while only one ctDNA-positive patient remained disease-free. The median lead time for predicting recurrence through ctDNA was 70 days, highlighting ctDNA's potential as a reliable biomarker for predicting post-operative metastasis in NSCLC and facilitating early interventions.²⁰ In 2020, the TRACERx study expanded its analysis to 78 additional patients. Among the 45 patients who experienced recurrence, 37 tested positive for ctDNA, with a median lead time of 151 days, further emphasizing ctDNA's superior predictive power. In contrast, only one of 199 plasma samples from 23 non-recurrence patients tested positive for ctDNA, demonstrating the high specificity in the test.⁵⁷ By 2023, the TRACERx study shifted focus to the precise prediction of early lung cancer metastasis. Patients with negative pre-operative ctDNA had significantly better 2-year OS rates compared to those in the low ctDNA and high ctDNA groups (90% vs. 63% vs. 24%). Using multi-region transcriptomic analysis of samples from low-shedder patients (those with large tumor volumes but negative pre-operative ctDNA), the study revealed reduced gene activity related to the cell division cycle and DNA repair in ctDNA-negative patients. By integrating the bioinformatics tool ECLIPSE technology, the researchers predicted future metastatic subclones by detecting pre-operative subclonal amplification in plasma.⁵⁸

In 2017, Chaudhuri *et al.*¹⁵ applied the CAPP-seq ctDNA analysis and found that 94% of assessable patients with recurrence had detectable ctDNA in their first post-treatment blood sample. In 72% of cases, ctDNA presence preceded radiological detection of recurrence by a median lead time of 5.2 months, underscoring ctDNA's effectiveness in identifying MRD in patients with localized lung cancer.

In 2019, the Circulating Tumor DNA Analysis Informing Adjuvant Chemotherapy in Stage II Colon Cancer (DYNAMIC) study, led by Wang J, employed an NGS-based detection platform to monitor ctDNA levels in lung cancer patients who underwent surgery. The findings showed a rapid decline in ctDNA concentration after curative surgery, with a half-life of approximately 35 min. For patients testing positive for MRD, the ctDNA half-life was 103.2 min, while MRD-negative patients had a half-life of 29.7 min. This difference provides new biological markers for assessing post-operative recurrence risk, with ctDNA detecting tumor recurrence 165 days earlier than imaging.⁵⁹

In 2020, Zviran *et al.*⁶⁰ MRDetect study used whole-genome sequencing to develop a highly accurate MRDetect model. Among 22 post-operative patients with stages I – III NSCLC, five patients who relapsed were accurately identified as ctDNA-MRD positive, while 12 of the 17 non-relapse patients were correctly identified as ctDNA-MRD-negative, achieving a sensitivity of 100% and a specificity of 71%.

Despite differences in platforms and methodologies, these studies consistently underscore one critical finding: ctDNA serves as a faint but crucial signal in the blood of many lung cancer patients. This signal enhances our understanding of pretreatment prognosis and consistently demonstrates a strong correlation between ctDNA levels and tumor recurrence, providing an early warning of potential relapse risk after curative treatment.

4.2.3. Adjuvant therapy decision-making

At present, adjuvant therapy decisions for resectable stage II – III NSCLC patients are primarily based on staging and other clinical factors. These patients are considered high-risk and are typically recommended for adjuvant therapy; however, many still experience relapse despite receiving treatment. The “perioperative period” has become a focal point for the clinical application of ctDNA-MRD, with adjuvant therapy decision-making representing the most significant clinical benefit of ctDNA-MRD detection. A key area of research in MRD involves using ctDNA to guide adjuvant therapy decisions, enabling clinicians to identify and target the patients most likely to benefit from adjuvant therapy.

In 2021, Qiu *et al.*⁶¹ conducted the “CALIBRATE-NSCLC” study, which included 85 patients. The results

revealed that 18 patients had detectable ctDNA in their plasma within 1 month after surgery. Among these ctDNA-positive patients, those who received adjuvant therapy had a significantly lower risk of recurrence compared to those who did not receive adjuvant therapy. However, for patients with undetectable ctDNA after surgery, there was no apparent clinical benefit from receiving adjuvant therapy. These findings suggest that adjuvant therapy is beneficial for ctDNA-positive patients, but offers little advantage to ctDNA-negative patients.

In 2022, Xia *et al.*⁶² published the LUNGCA-1 study, which found that five out of 17 ctDNA-positive patients who received adjuvant therapy remained relapse-free, whereas all nine ctDNA-positive patients who did not receive adjuvant therapy relapsed. Even after adjusting for other clinicopathologic factors, adjuvant therapy independently predicted relapse-free survival in ctDNA-positive patients, but not in ctDNA-negative patients. These results further underscore the substantial benefit that ctDNA-positive patients gain from adjuvant therapy.

There is growing evidence that ctDNA testing can serve as a reliable marker for evaluating the effectiveness of post-operative adjuvant therapy in lung cancer. Both the TRACERx and DYNAMIC studies demonstrated that patients with continuously increasing ctDNA levels during adjuvant chemotherapy were more likely to relapse within a year after surgery. In contrast, patients whose elevated ctDNA levels returned to zero after adjuvant chemotherapy did not relapse.^{20,59}

4.2.4. EGFR and targeted therapy

Targeted therapy is currently the primary treatment for advanced lung cancer patients with positive driver gene mutations. While OS has significantly improved for these patients, treatment efficacy and prognosis vary among individuals. Incorporating biomarkers to monitor drug efficacy and predict disease progression during treatment could provide valuable insights. ctDNA, which mirrors the genetic profile of tumor tissue samples, is an ideal biomarker. Dynamic monitoring of ctDNA changes may help predict patient outcomes from targeted therapy and guide treatment adjustments to achieve better therapeutic results.

The FLAURA study, along with an exploratory endpoint analysis from the FLAURA2 study presented at the 2024 American Association Cancer Research Annual Meeting, utilized ddPCR to analyze dynamic EGFR mutations in ctDNA.^{63,64} The findings revealed that patients without detectable EGFR mutations in plasma ctDNA at baseline had comparable progression-free survival (PFS) benefits from osimertinib plus chemotherapy as those receiving

osimertinib monotherapy. However, for patients with detectable EGFR mutations in plasma ctDNA at baseline, combining osimertinib with chemotherapy extended median PFS from 13.9 months to 24.8 months and reduced the risk of disease progression or death by 40%. These findings suggest that combination therapy may be more effective for this subgroup of patients, and that baseline plasma ctDNA EGFR mutation status can serve as a prognostic indicator for treatment outcomes, with or without chemotherapy.

Targeted therapies are typically continued until disease progression occurs. However, this approach has limitations, as long-term medication use can affect quality of life and lead to drug resistance. Recently, the concept of “drug holidays” has gained attention, where patients temporarily discontinue medication after achieving satisfactory treatment results and enter an observation phase. A recent study published in *JAMA Oncology* by Dong *et al.*⁶⁵ first demonstrated that combining ctDNA with other tests to guide the use of targeted therapies in advanced NSCLC patients with positive driver genes can maintain survival benefits while reducing the treatment burden by allowing for a drug holiday.

4.2.5. Immunotherapy

Immunotherapy, particularly with programmed death 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) inhibitors, is widely used in the treatment of advanced lung cancer. However, not all patients respond effectively to this treatment, highlighting the need for reliable methods to promptly assess or predict patient responses and guide subsequent treatment strategies. As immunotherapy advances, challenges arise due to the heterogeneity of clinical responses and the limitations of imaging techniques in accurately and swiftly monitoring treatment effects. Furthermore, current biomarkers, such as PD-L1 expression or tumor mutational burden, do not consistently predict therapeutic outcomes. In this context, molecular response-based strategies, such as ctDNA, are urgently needed to interpret patient responses and inform treatment decisions. Research using ctDNA has demonstrated its potential to monitor changes in tumor burden during immune checkpoint inhibition, enabling the early identification of primary resistance and allowing patients to be redirected to alternative treatments.

The BR.36 phase 2 trial, which used ctDNA to guide molecular response-adaptive immuno-chemotherapy in lung cancer patients, reported a ctDNA response sensitivity of 82% and a specificity of 75% for Response Evaluation Criteria in Solid Tumors-defined responses. Patients with

molecular responses achieved longer PFS and OS. For patients classified with stable disease on imaging, dynamic ctDNA detection may offer a more effective, earlier, and convenient method to predict long-term clinical outcomes and guide personalized treatment.⁶⁶

A retrospective study examined the correlation between longitudinal ctDNA levels and clinical outcomes in first-line (1L) tislelizumab (anti-PD-1) plus chemotherapy-treated patients with non-squamous or squamous NSCLC from the RATIONALE-304 and 307 trials. The study found that ctDNA levels at the first response were significantly reduced compared to baseline levels and were associated with the clinical outcomes of 1L treatment with tislelizumab and chemotherapy. These findings suggest that ctDNA could serve as a surrogate biomarker for treatment effectiveness.⁶⁶⁻⁶⁹

4.3. Clinical implementation

It is worth noting that a growing number of studies have transitioned from experimental research to real-world applications. For example, ctDNA analysis has been integrated into health management systems in developed countries such as the United States, where regulatory approvals have facilitated its use in monitoring EGFR mutations and guiding immunotherapy for advanced lung cancer. However, global adoption remains uneven, with significant gaps in accessibility in low- and middle-income countries due to technological and financial barriers. Addressing these disparities is critical to maximizing the global clinical impact of ctDNA methodologies.

ctDNA technologies, including dPCR, ddPCR, NGS, and CAPP-Seq, demonstrate strong potential for funding and commercialization due to their clinical utility. dPCR and ddPCR are cost-effective and widely used for mutation detection. NGS offers comprehensive profiling, but cost-reduction innovations are necessary. CAPP-Seq excels in early detection, attracting both public and private sector partnerships.

4.4. Limitations

This study has certain limitations. It relies exclusively on data from the WoSCC database, which may have led to the omission of relevant research from other databases. In future research, we plan to incorporate cross-database validation, comparing WoSCC with Scopus and PubMed to ensure consistency and broader coverage. In addition, excluding non-English publications may have resulted in an underrepresentation of studies published in languages other than English. Moreover, publications from 2024 were excluded due to insufficient data availability.

5. Conclusion

Through bibliometric analysis, this study provides a comprehensive overview of ctDNA research in lung cancer and highlights emerging trends in the field. Researchers worldwide are increasingly focusing on ctDNA in lung cancer. Based on references with strong citation bursts, keyword clustering, and trend analysis, we found that ctDNA is a prominent biomarker for MRD in lung cancer, playing a critical role in predicting disease progression and guiding treatment decisions.

Acknowledgments

None.

Funding

This research was funded by the Science and Technology Innovation Project of Shanxi Universities (grant number 2022L160), the Fundamental Research Program of Shanxi Province (grant number 202303021221192), the Key Scientific Research Project for COVID-19 Infection Emergency Treatment at Shanxi Bethune Hospital (grant number 2023xg01), the COVID-19 Research Project of the Shanxi Provincial Health Commission (grant numbers 2023XG001 and 2023XG005), the Four “Batches” Innovation Project for Invigorating Medical through Science and Technology in Shanxi Province (grant number 2023XM003), the Cancer Special Fund Research Project of Shanxi Bethune Hospital (grant number 2020-ZL04), and the External Expert Workshop Fund Program of the Shanxi Provincial Health Commission (Proteomics Shanxi Studio for Professor Huang He).

Conflict of interest

Shuang Wei is an Editorial Board Member of this journal but was not involved, directly or indirectly, in the editorial or peer-review process of this paper. Separately, the other authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Author contributions

Conceptualization: Lin Su, Xiansheng Liu

Data curation: Lin Su

Funding acquisition: Lin Su, Shuang Wei, Xiansheng Liu

Methodology: Lin Su, Xueli Bai

Project administration: Xiansheng Liu

Resources: Shuang Wei, Xiaochen Li, Xiansheng Liu

Software: Lin Su, Xueli Bai, Xiaohong Zhang, Jiande Cheng, Jie Ding

Supervision: Xiaochen Li, Xiansheng Liu

Visualization: Lin Su, Xueli Bai

Writing – original draft: Lin Su

Writing – review & editing: Shuang Wei, Xiaochen Li, Xiansheng Liu

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Data used in this work are available from the corresponding author on reasonable request.

References

- Bray F, Laversanne M, Sung H, *et al.* Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74(3):229-263.
doi: 10.3322/caac.21834
- Campos-Balea B, de Castro Carpeño J, Massutí B, *et al.* Prognostic factors for survival in patients with metastatic lung adenocarcinoma: An analysis of the SEER database. *Thorac Cancer.* 2020;11(11):3357-3364.
doi: 10.1111/1759-7714.13681
- Reina C, Šabanović B, Lazzari C, Gregorc V, Heeschen C. Unlocking the future of cancer diagnosis - promises and challenges of ctDNA-based liquid biopsies in non-small cell lung cancer. *Transl Res.* 2024;272:41-53.
doi: 10.1016/j.trsl.2024.05.014
- Sundaresan TK, Sequist LV, Heymach JV, *et al.* Detection of T790M, the acquired resistance EGFR mutation, by tumor biopsy versus noninvasive blood-based analyses. *Clin Cancer Res.* 2016;22(5):1103-1110.
doi: 10.1158/1078-0432.CCR-15-1031
- Lazzari C, Bulotta A, Cangi MG, *et al.* Next generation sequencing in non-small cell lung cancer: Pitfalls and opportunities. *Diagnostics (Basel).* 2020;10(12):1092.
doi: 10.3390/diagnostics10121092
- Li W, Liu JB, Hou LK, *et al.* Liquid biopsy in lung cancer: Significance in diagnostics, prediction, and treatment monitoring. *Mol Cancer.* 2022;21(1):25.
doi: 10.1186/s12943-022-01505-z
- Wan JCM, Massie C, Garcia-Corbacho J, *et al.* Liquid biopsies come of age: Towards implementation of circulating tumour DNA. *Nat Rev Cancer.* 2017;17(4):223-238.
doi: 10.1038/nrc.2017.7
- Wen X, Pu H, Liu Q, Guo Z, Luo D. Circulating tumor DNA-A novel biomarker of tumor progression and its favorable detection techniques. *Cancers (Basel).* 2022;14(24):6025.
doi: 10.3390/cancers14246025
- Ji Z, Chen L, Yang Q, *et al.* Research trend of circulating tumor DNA associated with breast cancer from 2012 to 2021: A bibliometric analysis. *Front Oncol.* 2022;12:1090503.
doi: 10.3389/fonc.2022.1090503
- Wu F, Gao J, Kang J, *et al.* Knowledge mapping of exosomes in autoimmune diseases: A bibliometric analysis (2002-2021). *Front Immunol.* 2022;13:939433.
doi: 10.3389/fimmu.2022.939433
- van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. *Scientometrics.* 2010;84(2):523-538.
doi: 10.1007/s11192-009-0146-3
- Synnestvedt MB, Chen C, Holmes JH. CiteSpace II: Visualization and knowledge discovery in bibliographic databases. *AMIA Annu Symp Proc.* 2005;2005:724-728.
- Aria M, Cuccurullo C. Bibliometrix: An R-tool for comprehensive science mapping analysis. *J Informetrics.* 2017;11(4):959-975.
doi: 10.1016/j.joi.2017.08.007
- Jahr S, Hentze H, Englisch S, *et al.* DNA fragments in the blood plasma of cancer patients: quantitations and evidence for their origin from apoptotic and necrotic cells. *Cancer Res.* 2001;61(4):1659-1665.
- Chaudhuri AA, Chabon JJ, Lovejoy AF, *et al.* Early detection of molecular residual disease in localized lung cancer by circulating tumor DNA profiling. *Cancer Discov.* 2017;7(12):1394-1403.
doi: 10.1158/2159-8290.Cd-17-0716
- Wang H, Zhang Y, Zhang H, *et al.* Liquid biopsy for human cancer: Cancer screening, monitoring, and treatment. *MedComm (2020).* 2024;5(6):e564.
doi: 10.1002/mco2.564
- Bettegowda C, Sausen M, Leary RJ, *et al.* Detection of circulating tumor DNA in early- and late-stage human malignancies. *Sci Transl Med.* 2014;6(224):224ra224.
doi: 10.1126/scitranslmed.3007094
- Newman AM, Bratman SV, To J, *et al.* An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage. *Nat Med.* 2014;20(5):548-554.
doi: 10.1038/nm.3519
- Diehl F, Schmidt K, Choti MA, *et al.* Circulating mutant DNA to assess tumor dynamics. *Nat Med.* 2008;14(9):985-990.
doi: 10.1038/nm.1789
- Abbosh C, Birkbak NJ, Wilson GA, *et al.* Phylogenetic

- ctDNA analysis depicts early-stage lung cancer evolution. *Nature*. 2017;545(7655):446-451.
doi: 10.1038/nature22364
21. Diaz LA Jr., Bardelli A. Liquid biopsies: Genotyping circulating tumor DNA. *J Clin Oncol*. 2014;32(6):579-586.
doi: 10.1200/jco.2012.45.2011
 22. Dawson SJ, Tsui DW, Murtaza M, *et al*. Analysis of circulating tumor DNA to monitor metastatic breast cancer. *N Engl J Med*. 2013;368(13):1199-1209.
doi: 10.1056/NEJMoa1213261
 23. Oxnard GR, Paweletz CP, Kuang Y, *et al*. Noninvasive detection of response and resistance in EGFR-mutant lung cancer using quantitative next-generation genotyping of cell-free plasma DNA. *Clin Cancer Res*. 2014;20(6):1698-1705.
doi: 10.1158/1078-0432.Ccr-13-2482
 24. Murtaza M, Dawson SJ, Tsui DW, *et al*. Non-invasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA. *Nature*. 2013;497(7447):108-112.
doi: 10.1038/nature12065
 25. Oxnard GR, Thress KS, Alden RS, *et al*. Association between plasma genotyping and outcomes of treatment with osimertinib (AZD9291) in advanced non-small-cell lung cancer. *J Clin Oncol*. 2016;34(28):3375-3382.
doi: 10.1200/jco.2016.66.7162
 26. Leon SA, Shapiro B, Sklaroff DM, Yaros MJ. Free DNA in the serum of cancer patients and the effect of therapy. *Cancer Res*. 1977;37(3):646-650.
 27. Mok TS, Wu YL, Thongprasert S, *et al*. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361(10):947-957.
doi: 10.1056/NEJMoa0810699
 28. Schwarzenbach H, Hoon DS, Pantel K. Cell-free nucleic acids as biomarkers in cancer patients. *Nat Rev Cancer*. 2011;11(6):426-437.
doi: 10.1038/nrc3066
 29. Mok T, Wu YL, Lee JS, *et al*. Detection and dynamic changes of EGFR mutations from circulating tumor DNA as a predictor of survival outcomes in NSCLC patients treated with first-line intercalated erlotinib and chemotherapy. *Clin Cancer Res*. 2015;21(14):3196-3203.
doi: 10.1158/1078-0432.Ccr-14-2594
 30. Forshew T, Murtaza M, Parkinson C, *et al*. Noninvasive identification and monitoring of cancer mutations by targeted deep sequencing of plasma DNA. *Sci Transl Med*. 2012;4(136):136ra168.
doi: 10.1126/scitranslmed.3003726
 31. Newman AM, Lovejoy AF, Klass DM, *et al*. Integrated digital error suppression for improved detection of circulating tumor DNA. *Nat Biotechnol*. 2016;34(5):547-555.
doi: 10.1038/nbt.3520
 32. Rosell R, Carcereny E, Gervais R, *et al*. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13(3):239-246.
doi: 10.1016/s1470-2045(11)70393-x
 33. Crowley E, Di Nicolantonio F, Loupakis F, Bardelli A. Liquid biopsy: Monitoring cancer-genetics in the blood. *Nat Rev Clin Oncol*. 2013;10(8):472-484.
doi: 10.1038/nrclinonc.2013.110
 34. Galant N, Nicos M, Kuźnar-Kamińska B, Krawczyk P. Variant allele frequency analysis of circulating tumor DNA as a promising tool in assessing the effectiveness of treatment in non-small cell lung carcinoma patients. *Cancers (Basel)*. 2024;16(4):782.
doi: 10.3390/cancers16040782
 35. Douillard JY, Ostoros G, Cobo M, *et al*. Gefitinib treatment in EGFR mutated caucasian NSCLC: Circulating-free tumor DNA as a surrogate for determination of EGFR status. *J Thorac Oncol*. 2014;9(9):1345-1353.
doi: 10.1097/jto.0000000000000263
 36. Thress KS, Brant R, Carr TH, *et al*. EGFR mutation detection in ctDNA from NSCLC patient plasma: A cross-platform comparison of leading technologies to support the clinical development of AZD9291. *Lung Cancer*. 2015;90(3):509-515.
doi: 10.1016/j.lungcan.2015.10.004
 37. Tie J, Wang Y, Tomasetti C, *et al*. Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. *Sci Transl Med*. 2016;8(346):346ra392.
doi: 10.1126/scitranslmed.aaf6219
 38. Gandara DR, Paul SM, Kowanetz M, *et al*. Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab. *Nat Med*. 2018;24(9):1441-1448.
doi: 10.1038/s41591-018-0134-3
 39. Leighl NB, Page RD, Raymond VM, *et al*. Clinical utility of comprehensive cell-free DNA analysis to identify genomic biomarkers in patients with newly diagnosed metastatic non-small cell lung cancer. *Clin Cancer Res*. 2019;25(15):4691-4700.
doi: 10.1158/1078-0432.Ccr-19-0624
 40. Chabon JJ, Hamilton EG, Kurtz DM, *et al*. Integrating genomic features for non-invasive early lung cancer detection. *Nature*. 2020;580(7802):245-251.
doi: 10.1038/s41586-020-2140-0
 41. Lanman RB, Mortimer SA, Zill OA, *et al*. Analytical

- and clinical validation of a digital sequencing panel for quantitative, highly accurate evaluation of cell-free circulating tumor DNA. *PLoS One*. 2015;10(10):e0140712.
doi: 10.1371/journal.pone.0140712
42. Iwahashi N, Sakai K, Noguchi T, *et al*. Liquid biopsy-based comprehensive gene mutation profiling for gynecological cancer using CAnCER Personalized Profiling by deep Sequencing. *Sci Rep*. 2019;9(1):10426.
doi: 10.1038/s41598-019-47030-w
 43. Kaneko A, Kanemaru H, Kajihara I, *et al*. Liquid biopsy-based analysis by ddPCR and CAPP-Seq in melanoma patients. *J Dermatol Sci*. 2021;102(3):158-166.
doi: 10.1016/j.jdermsci.2021.04.006
 44. Chen C. CiteSpace II: Detecting and visualizing emerging trends and transient patterns in scientific literature. *J Assoc Inf Sci Technol*. 2006;57:359-377.
doi: 10.1002/asi.20317
 45. Kumar S, Paiva B, Anderson KC, *et al*. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol*. 2016;17(8):e328-e346.
doi: 10.1016/s1470-2045(16)30206-6
 46. Mohan M, Kendrick S, Szabo A, *et al*. Clinical implications of loss of bone marrow minimal residual disease negativity in multiple myeloma. *Blood Adv*. 2022;6(3):808-817.
doi: 10.1182/bloodadvances.2021005822
 47. Pierce E, Mautner B, Mort J, *et al*. MRD in ALL: Optimization and innovations. *Curr Hematol Malig Rep*. 2022;17(4):69-81.
doi: 10.1007/s11899-022-00664-6
 48. Xie W, Suryaprakash S, Wu C, Rodriguez A, Fraterman S. Trends in the use of liquid biopsy in oncology. *Nat Rev Drug Discov*. 2023;22(8):612-613.
doi: 10.1038/d41573-023-00111-y
 49. MRD may predict relapse in NSCLC. *Cancer Discov*. 2020;10(7):Of7.
doi: 10.1158/2159-8290.Cd-nd2020-010
 50. Kanayama M, Kuwata T, Mori M, *et al*. Prognostic impact of circulating tumor cells detected with the microfluidic “universal CTC-chip” for primary lung cancer. *Cancer Sci*. 2022;113(3):1028-1037.
doi: 10.1111/cas.15255
 51. Lam VK, Zhang J, Wu CC, *et al*. Genotype-specific differences in circulating tumor DNA levels in advanced NSCLC. *J Thorac Oncol*. 2021;16(4):601-609.
doi: 10.1016/j.jtho.2020.12.011
 52. Lawrence MS, Stojanov P, Polak P, *et al*. Mutational heterogeneity in cancer and the search for new cancer-associated genes. *Nature*. 2013;499(7457):214-218.
doi: 10.1038/nature12213
 53. Li T, Liu J, Zhou Y, *et al*. Clinical relevance of somatic mutations in Chinese lung adenocarcinoma and their prognostic implications for survival. *Cancer Med*. 2024;13(10):e7227.
doi: 10.1002/cam4.7227
 54. Zhong J, Bai H, Wang Z, *et al*. Treatment of advanced non-small cell lung cancer with driver mutations: current applications and future directions. *Front Med*. 2023;17(1):18-42.
doi: 10.1007/s11684-022-0976-4
 55. Lyu M, Zhou J, Ning K, Ying B. The diagnostic value of circulating tumor cells and ctDNA for gene mutations in lung cancer. *Onco Targets Ther*. 2019;12:2539-2552.
doi: 10.2147/ott.S195342
 56. Razavi P, Li BT, Brown DN, *et al*. High-intensity sequencing reveals the sources of plasma circulating cell-free DNA variants. *Nat Med*. 2019;25(12):1928-1937.
doi: 10.1038/s41591-019-0652-7
 57. Abbosh C, Frankell A, Garnett A, *et al*. Abstract CT023: Phylogenetic tracking and minimal residual disease detection using ctDNA in early-stage NSCLC: A lung TRACERx study. *Cancer Res*. 2020;80(16 Suppl):CT023-CT023.
doi: 10.1158/1538-7445.AM2020-CT023
 58. Abbosh C, Frankell AM, Harrison T, *et al*. Tracking early lung cancer metastatic dissemination in TRACERx using ctDNA. *Nature*. 2023;616(7957):553-562.
doi: 10.1038/s41586-023-05776-4
 59. Chen K, Zhao H, Shi Y, *et al*. Perioperative dynamic changes in circulating tumor DNA in patients with lung cancer (DYNAMIC). *Clin Cancer Res*. 2019;25(23):7058-7067.
doi: 10.1158/1078-0432.CCR-19-1213
 60. Zviran A, Schulman RC, Shah M, *et al*. Genome-wide cell-free DNA mutational integration enables ultra-sensitive cancer monitoring. *Nat Med*. 2020;26(7):1114-1124.
doi: 10.1038/s41591-020-0915-3
 61. Qiu B, Guo W, Zhang F, *et al*. Dynamic recurrence risk and adjuvant chemotherapy benefit prediction by ctDNA in resected NSCLC. *Nat Commun*. 2021;12(1):6770.
doi: 10.1038/s41467-021-27022-z
 62. Xia L, Mei J, Kang R, *et al*. Perioperative ctDNA-based molecular residual disease detection for non-small cell lung cancer: A prospective multicenter cohort study (LUNGCA-1). *Clin Cancer Res*. 2022;28(15):3308-3317.
doi: 10.1158/1078-0432.CCR-21-3044
 63. Jänne PA, Kobayashi K, Robichaux J, *et al*. Abstract CT017: FLAURA2: Exploratory analysis of baseline (BL) and

- on-treatment plasma EGFRm dynamics in patients (pts) with EGFRm advanced NSCLC treated with first-line (1L) osimertinib (osi)±platinum-pemetrexed. *Cancer Res.* 2024;84(7 Suppl):CT017.
doi: 10.1158/1538-7445.AM2024-CT017
64. Ramalingam SS, Vansteenkiste J, Planchard D, *et al.* Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med.* 2020;382(1):41-50.
doi: 10.1056/NEJMoa1913662
65. Dong S, Wang Z, Zhang JT, *et al.* Circulating tumor DNA-guided de-escalation targeted therapy for advanced non-small cell lung cancer: A nonrandomized controlled trial. *JAMA Oncol.* 2024;10(7):932-940.
doi: 10.1001/jamaoncol.2024.1779
66. Anagnostou V, Ho C, Nicholas G, *et al.* ctDNA response after pembrolizumab in non-small cell lung cancer: Phase 2 adaptive trial results. *Nat Med.* 2023;29(10):2559-2569.
doi: 10.1038/s41591-023-02598-9
67. Lu S, Wang J, Sun M, *et al.* Abstract LB289: Longitudinal ctDNA levels and clinical outcomes of first-line (1L) tislelizumab (TIS) + chemotherapy (chemo) treatment for advanced non-small cell lung cancer (NSCLC) in the RATIONALE-304 and 307 studies. *Cancer Res.* 2023;83(8 Suppl):LB289.
doi: 10.1158/1538-7445.AM2023-LB289
68. Lu S, Wang J, Yu Y, *et al.* Tislelizumab plus chemotherapy as first-line treatment for locally advanced or metastatic nonsquamous NSCLC (RATIONALE 304): A randomized phase 3 trial. *J Thorac Oncol.* 2021;16(9):1512-1522.
doi: 10.1016/j.jtho.2021.05.005
69. Wang J, Lu S, Yu X, *et al.* Tislelizumab plus chemotherapy vs chemotherapy alone as first-line treatment for advanced squamous non-small-cell lung cancer: A phase 3 randomized clinical trial. *JAMA Oncol.* 2021;7(5):709-717.
doi: 10.1001/jamaoncol.2021.0366