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Circulating and Serum Biomarkers in Non-Small Cell Lung Cancer

Diagnostic Value, Prognostic Stratification, Predictive Relevance, and Implications for Treatment Switching

Revaz Turmanidze[1], Alexandre Tavartkiladze[2, 3], Pati Revazishvili[2, 3], Thatia Potskhoraia[3], Maia Maisuradze[2, 3]

[1]New Vision University

[2]Tbilisi State Medical University

[3]Institute for Personalized Medicine

Abstract: ***Blood-based biomarkers have become central to the modern management of non-small cell lung cancer (NSCLC), but they do not all carry the same clinical weight. Circulating tumour DNA (ctDNA), interpreted within the broader cell-free DNA (cfDNA) compartment, is now the most actionable blood-based biomarker class because it can identify targetable drivers, acquired resistance mechanisms and, in selected settings, molecular residual disease (MRD). By contrast, circulating tumour cells (CTCs), classical serum tumour markers such as CYFRA 21-1, carcinoembryonic antigen (CEA) and squamous cell carcinoma antigen (SCC/SCCA), inflammatory mediators including interleukin-6 (IL-6) and serum amyloid A (SAA), and angiogenic or growth-factor markers such as VEGF, PDGF, FGF and EGF are currently strongest as tools for prognosis, response monitoring and biological risk stratification rather than as stand-alone determinants of drug switching. The practical challenge is therefore not merely whether a biomarker is abnormal, but whether convergent biomarker kinetics, clinical status and radiographic findings together justify repeat plasma testing, tissue re-biopsy, intensified surveillance or a true change in therapy. This review synthesizes current evidence across these biomarker classes, distinguishes validated actionability from promising but still exploratory signals, and proposes a pragmatic framework for integrating biomarker combinations into diagnostic work-up, prognostication and treatment-shift decisions in NSCLC. [1-6]***

Keywords: Non-small cell lung cancer; circulating tumor DNA; cell-free DNA; circulating tumor cells; liquid biopsy; CYFRA 21-1; carcinoembryonic antigen; squamous cell carcinoma antigen; interleukin-6; serum amyloid A; vascular endothelial growth factor; platelet-derived growth factor; fibroblast growth factor; biomarker-guided therapy; treatment resistance; precision oncology.

Key points

ctDNA is the most clinically actionable blood-based biomarker in NSCLC; most other circulating or serum markers are best used for risk stratification and dynamic monitoring. An isolated rise in a nonspecific serum marker should usually shorten the interval to imaging or trigger repeat plasma or tissue assessment, not independently mandate a drug change. The strongest rationale for switching treatment remains the combination of guideline-supported molecular findings, clear clinical or radiographic progression, or both. Postoperative ctDNA MRD positivity is a high-risk signal, but it is not yet a universal stand-alone trigger for escalation in all settings. [1-7]

1. Scope and Structure of this Review

This review is organized around four practical questions. First, which blood-based biomarkers genuinely alter treatment selection today? Second, which biomarkers mainly provide prognostic or monitoring value? Third, how should biomarker combinations be interpreted when disease control becomes uncertain? Fourth, at what point does a biomarker signal become strong enough to justify imaging, re-biopsy or therapy shift? Figures 1-3 summarize the evidence hierarchy and a pragmatic action pathway, while Tables 1-3 condense the evidence into clinic-facing tools. [1-6]

2. Introduction: the hierarchy of blood-based evidence in NSCLC

NSCLC is now managed in an era in which histology, stage and blood-based information intersect with tissue and plasma genomics. However, a clinically useful biomarker must be understood according to its dominant function: diagnostic, prognostic, predictive, or actionable. Diagnostic biomarkers help identify disease or support classification; prognostic biomarkers estimate risk independent of a specific therapy; predictive biomarkers indicate a higher probability of benefit from a given treatment; and actionable biomarkers can change what treatment is chosen or when it is changed. This hierarchy matters because the same biomarker may be informative without being decisive. [1-4]

Current guideline frameworks in advanced NSCLC give greatest practical authority to molecularly actionable findings, particularly when derived from next-generation sequencing of tumour tissue or plasma. CAP/IASLC/AMP recommendations support plasma genotyping when tissue is insufficient or unavailable, and contemporary NSCLC guidance increasingly recognizes liquid biopsy as an active component of front-line molecular work-up rather than a purely fallback test. That shift has major implications for how clinicians should interpret the broader blood-based biomarker landscape. [1-4]

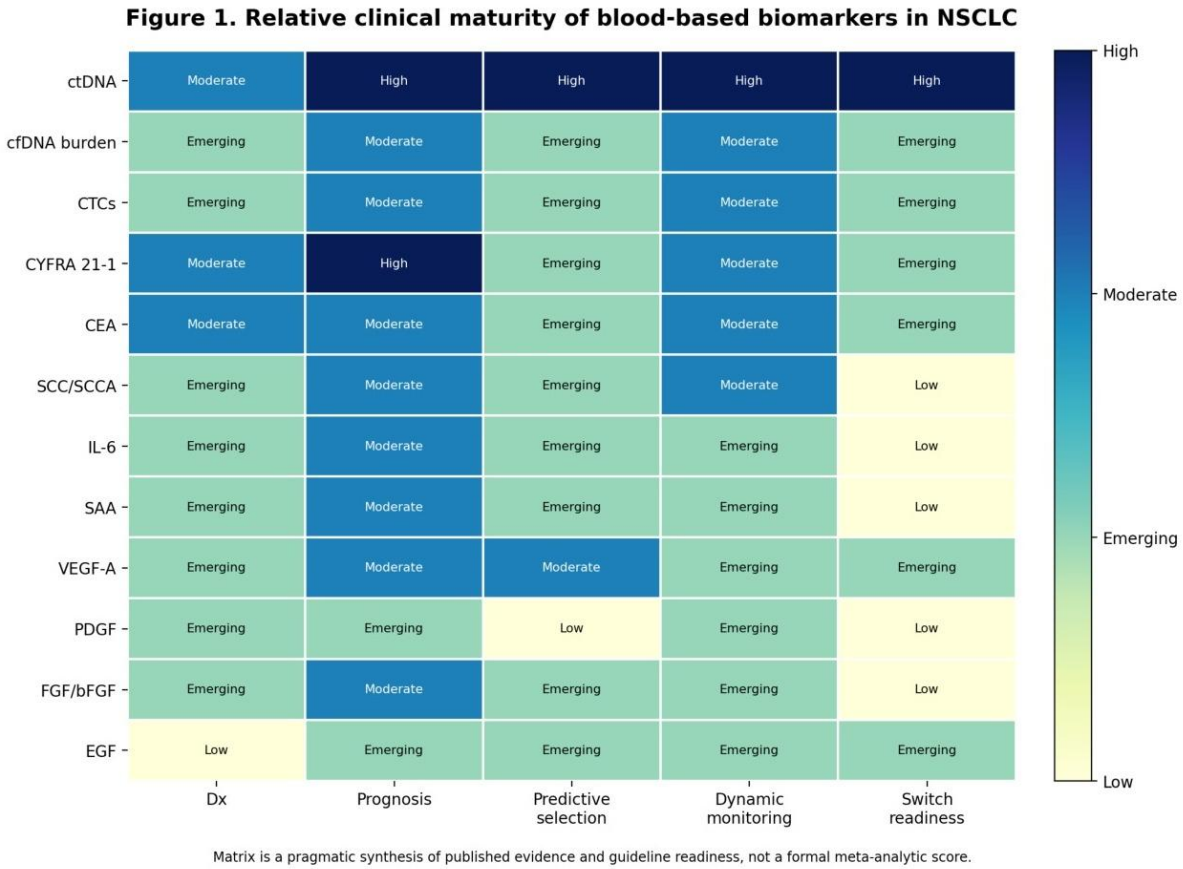

Figure 1: Relative maturity of major blood-based biomarker classes across diagnosis, prognosis, predictive selection, dynamic monitoring and readiness to support treatment switching in NSCLC. This synthesis figure was created for the present review and is intended as a conceptual map rather than a quantitative meta-analysis

What is truly actionable in current practice?

In routine NSCLC care, the most robust reason to alter systemic therapy on the basis of a blood test is the detection of a therapeutically relevant molecular event, for example an activating driver at baseline or an acquired resistance mechanism during progression. This is the domain in which ctDNA is strongest. By contrast, persistent CTCs, rising CYFRA 21-1, rising CEA, high IL-6 or rising SAA often indicate that disease biology is becoming more aggressive or less controlled, but they usually do not specify which next drug should be used. Their chief value is to prompt earlier reassessment. [1-6]

A useful practical distinction is therefore between biomarkers that can directly redirect therapy and biomarkers that accelerate clinical vigilance. The former include plasma or tissue genomic findings linked to approved targeted therapies or well-established resistance mechanisms. The latter include most protein-based markers and cell-based assays, which are best interpreted as signals that the clinician should scan sooner, repeat plasma testing, obtain tissue, or rethink surveillance intensity. [1-6]

Table 1: Blood-based biomarkers in NSCLC: specimen source, dominant role, strongest clinical setting, and treatment-switch readiness.

Biomarker	Specimen	Dominant role in practice	Best-validated setting	Can it independently justify a treatment switch?
ctDNA (genomic alterations)	Plasma	Actionable molecular profiling; resistance detection; MRD in selected settings	Advanced NSCLC for baseline genotyping or resistance work-up; postoperative MRD research/selected implementation	Yes, when a guideline-supported actionable alteration or resistance mechanism is identified
cfDNA burden/kinetics	Plasma	Dynamic monitoring; disease burden proxy	Advanced disease during systemic therapy	No; supportive only
CTCs	Whole blood	Prognostic stratification; early progression monitoring	Advanced disease; stage III monitoring in investigational workflows	No; supportive only
CYFRA 21-1	Serum	Prognosis; treatment monitoring	Advanced NSCLC; especially squamous-predominant biology and immunotherapy series	No
CEA	Serum	Prognosis; burden estimation; monitoring	Adenocarcinoma-enriched settings; EGFR-mutant TKI cohorts	No

Biomarker	Specimen	Dominant role in practice	Best-validated setting	Can it independently justify a treatment switch?
SCC/SCCA	Serum	Histology-linked prognosis; monitoring	Squamous NSCLC	No
IL-6	Serum/plasma	Inflammatory risk stratification	Checkpoint inhibitor or chemoimmunotherapy settings	No
SAA	Serum	Early risk stratification during immunotherapy	Anti-PD-1/PD-L1 treatment	No
VEGF-A	Serum/plasma	Emerging predictive/prognostic biomarker	Nonsquamous metastatic disease receiving chemo-immunotherapy ± bevacizumab	Not routinely; evidence still selective
PDGF	Serum/plasma	Exploratory biology/prognosis	Small observational series	No
FGF/bFGF	Serum/plasma	Exploratory prognosis	Operable or locally advanced NSCLC in selected studies	No
EGF	Serum/plasma	Exploratory or therapy-specific context	CIMAvax-EGF literature; not equivalent to EGFR genotyping	Not in routine global practice

ctDNA and cfDNA: the most clinically actionable blood-based biomarkers

Plasma-first profiling and baseline actionability

cfDNA describes the total pool of extracellular DNA fragments in circulation, whereas ctDNA denotes the tumour-derived fraction of that pool. This distinction is clinically important. Total cfDNA can reflect tumour burden, cell death and systemic injury, but ctDNA can reveal targetable alterations, copy-number changes, fusions and resistance clones that directly affect treatment selection. IASLC consensus statements and updated molecular testing guidelines therefore place liquid biopsy at the center of contemporary advanced NSCLC genotyping when tissue is limited, delayed or insufficient. [2-5]

The operational value of a plasma-first approach is speed. Studies comparing plasma comprehensive genomic profiling with standard-of-care tissue testing have shown that plasma can identify guideline-recommended biomarkers with clinically meaningful turnaround advantages, reducing the time to a matched therapeutic decision. The point is not that plasma replaces tissue in every case, but that plasma increasingly reduces the delay between diagnosis and biomarker-informed treatment. [4,5]

Acquired resistance and the logic of treatment switching

The clearest paradigm for blood-based treatment switching remains the identification of acquired resistance in patients already receiving a targeted agent. In EGFR-mutant disease, plasma detection of resistance mechanisms historically enabled rational movement across EGFR-TKI generations, and more broadly plasma genotyping now helps determine whether progression reflects target-dependent escape, off-target bypass signaling or the need for tissue re-biopsy because plasma is non-informative. In this sense, ctDNA is not merely prognostic; it can change the next line of therapy. [1-4]

Equally important is the negative result. A plasma assay that fails to detect a resistance mechanism does not exclude tumour evolution, especially when shedding is low. Guidelines therefore recommend tissue re-biopsy when plasma is negative but clinical suspicion for molecular progression remains high. This principle should govern the use of biomarker combinations more broadly: blood-based signals often refine timing and suspicion, but confirmatory molecular evidence still matters. [1-4]

Response kinetics, residual disease and early warning signals

Beyond baseline profiling and resistance detection, serial ctDNA and cfDNA measurements can provide a pharmacodynamic readout of treatment effectiveness. Declining ctDNA or cfDNA early during therapy has repeatedly been associated with improved outcomes, whereas persistence or re-emergence is associated with shorter progression-free intervals. Studies in EGFR-TKI-treated NSCLC also suggest that combining early ctDNA kinetics with cfDNA burden and CEA improves response monitoring. [8-10]

The postoperative setting adds another layer. Prospective perioperative studies such as LUNGCA-1, together with dynamic ctDNA analyses in resected NSCLC, have shown that postoperative ctDNA positivity marks a substantially higher risk of recurrence and can precede radiographic relapse by months. Emerging analyses in EGFR-mutant resected disease suggest that MRD frameworks may eventually inform adjuvant intensity or duration, but this remains an evolving area rather than a universal stand-alone switch trigger. [6,7,11-13]

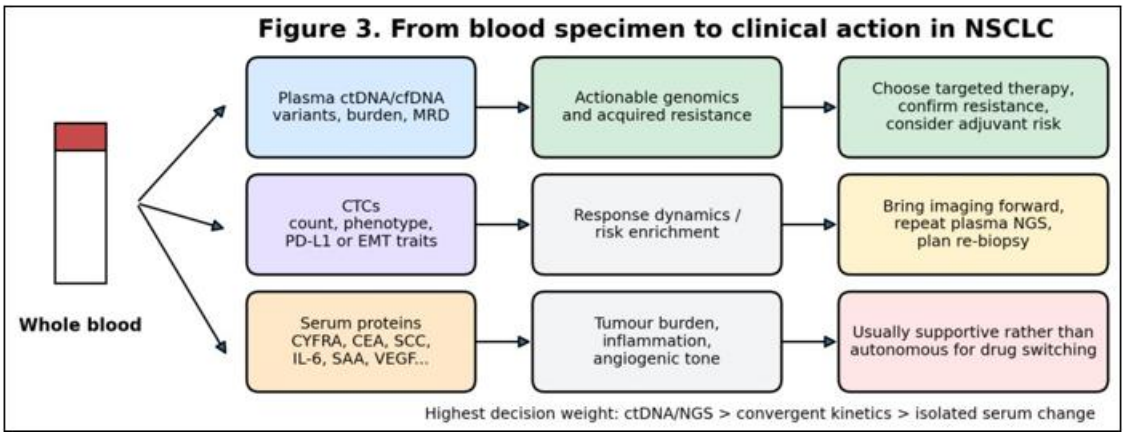

Figure 2: From specimen to clinical action in NSCLC: a pragmatic pathway linking blood draw, assay type, interpretation domain and downstream decision. This original synthesis figure emphasizes the different clinical roles of plasma genomic assays, serum protein markers and CTC-based approaches

Circulating tumour cells: biologically rich, clinically promising, not yet standardized enough for routine switching

CTCs are compelling because they are intact tumour cells rather than molecular fragments. In theory, they can inform on metastatic competence, epithelial-mesenchymal plasticity, PD-L1 expression and, with expanded phenotyping, even clonal evolution. In practice, however, CTC use in NSCLC remains constrained by platform heterogeneity, capture bias, assay sensitivity and the lack of harmonized cut-offs across laboratories. [14-16]

That limitation does not erase their clinical value. Prospective work in advanced NSCLC has shown that persistent or rising CTC counts during first-line platinum chemotherapy are associated with inferior outcomes and treatment resistance, whereas persistently negative CTC profiles correlate with more favorable progression-free and overall survival. Stage III studies combining chemoradiation and immunotherapy suggest that CTCs can flag progression risk before conventional imaging, and CTC dynamics during immune checkpoint blockade have also been linked to metabolic and clinical response. [14-16]

The appropriate role for CTCs today is therefore as an adjunctive high-risk signal. When CTCs persist or rise alongside other adverse markers, clinicians should consider shortening the interval to restaging or repeat molecular assessment. However, CTCs alone rarely specify which drug should follow, so routine switch algorithms based purely on CTC burden remain premature. [14-16]

Classical serum tumour markers: CYFRA 21-1, CEA and SCC/SCCA

Classical serum tumour markers retain considerable practical utility because they are inexpensive, widely available and easy to repeat serially. Their main limitations are imperfect specificity and modest mechanistic precision, but their strengths include burden estimation, response trending and, in some contexts, histology enrichment. CYFRA 21-1 often performs best as a broad NSCLC serum marker; CEA is particularly relevant in adenocarcinoma-predominant disease; and SCC/SCCA is most closely linked to squamous histology. [17-19]

Among these markers, CYFRA 21-1 has one of the most consistent prognostic signals. In prospective work it has correlated with survival, treatment benefit and the depth of response to systemic therapy. In the immune checkpoint era, both CYFRA 21-1 and CEA continue to stratify outcomes, and persistently elevated or rising values can mark patients who deserve closer interval assessment. Even so, a rise in CYFRA 21-1 does not tell the clinician whether to use a different targeted agent, chemotherapy backbone or immunotherapy strategy. [18-21]

CEA illustrates the same principle from another angle. In EGFR-mutant advanced NSCLC treated with EGFR-TKIs, lower baseline CEA has been associated with better response and survival. In resectable adenocarcinoma, the prognostic meaning of CEA and CYFRA 21-1 can differ according to EGFR mutation status, reinforcing the idea that serum markers are best interpreted in molecular context. SCC/SCCA appears most useful in squamous NSCLC, where it can complement CYFRA 21-1 in risk assessment and, in some reports, in treatment monitoring during radiotherapy-based management. [20-23]

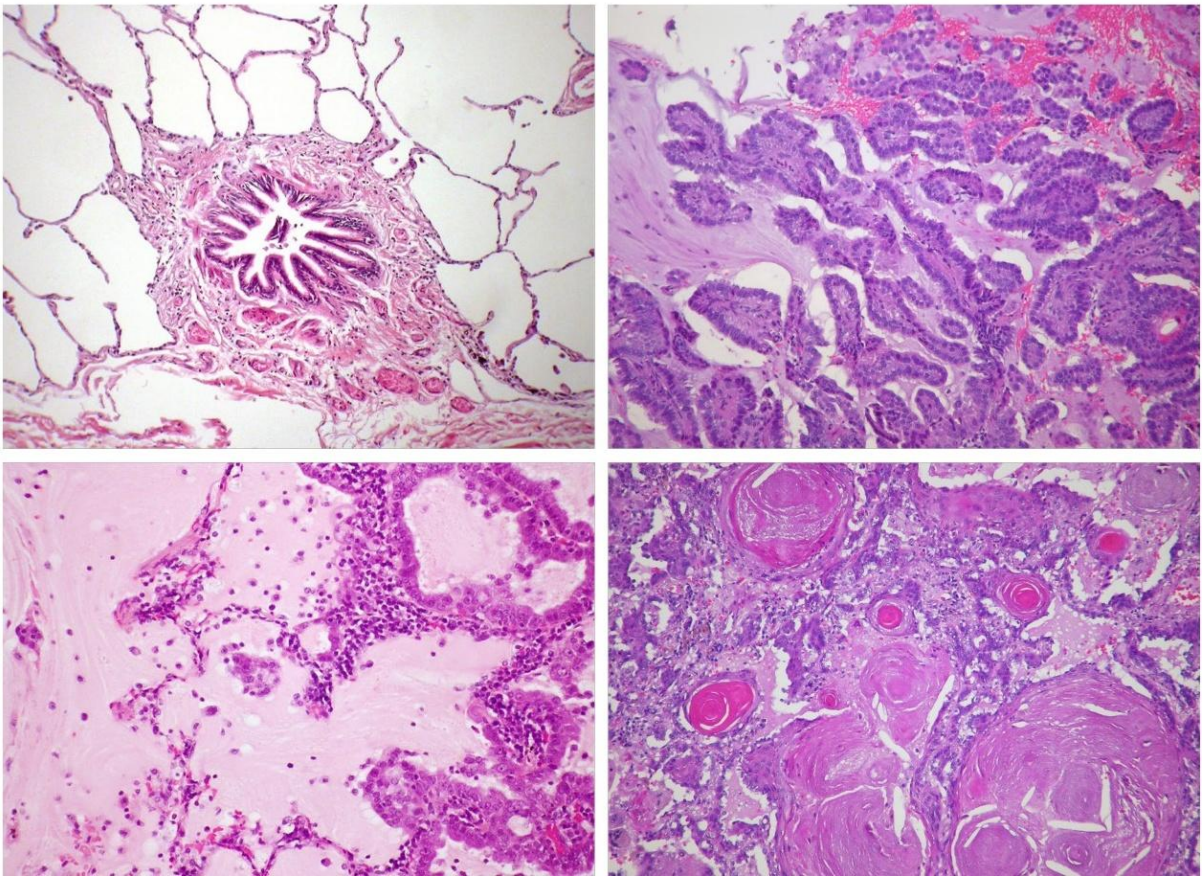

Figure 3: Representative histology montage illustrating normal lung and common malignant patterns relevant to NSCLC classification. Source image: "Lung cancer histology collection" by Ajpolino, derived from source material credited on Wikimedia Commons to Yale Rosen's Atlas of Pulmonary Pathology; used under CC BY-SA 4.0 after resizing for layout. This image is illustrative rather than a source of quantitative study data.

Inflammatory biomarkers: IL-6 and SAA as indicators of hostile tumour-host biology

IL-6 and SAA sit closer to the systemic inflammatory milieu than to tumour-specific molecular actionability, but in immunotherapy-treated NSCLC their importance has become difficult to ignore. High baseline IL-6 has been associated with poorer response and survival in patients receiving PD-1 or PD-L1 blockade, and cytokine-based models may refine risk assessment beyond PD-L1 alone in some cohorts. [24, 25]

SAA behaves similarly as an acute-phase reactant linked to poor outcomes in immune checkpoint inhibitor series. Both baseline values and early on-treatment changes have shown prognostic value, suggesting that the tempo of systemic inflammation may mirror a form of treatment resistance or immune-excluded disease biology. Yet neither IL-6 nor SAA currently dictates a specific treatment substitution. Their greatest clinical use is as a warning layer: if inflammatory markers worsen together with tumour-derived biomarkers or symptoms, the threshold for earlier imaging or molecular reassessment should fall. [24-26]

Angiogenic and growth-factor biomarkers: VEGF, PDGF, FGF and EGF

Serum or plasma angiogenic factors have long been studied in NSCLC because tumour vascular remodeling is tightly linked to growth, invasion and metastatic spread. Older literature associated higher circulating VEGF and, in some series, bFGF with worse prognosis. More recently, biomarker-enriched analyses have reopened the possibility that selected angiogenic markers may identify patients more likely to benefit from anti-VEGF strategies. [27-30]

Among the markers reviewed here, VEGF-A currently has the most plausible route toward selective predictive use, especially in nonsquamous metastatic NSCLC receiving chemo-immunotherapy with or without bevacizumab. By contrast, PDGF findings have been heterogeneous and sometimes counterintuitive, while FGF-family results remain mostly prognostic. EGF is a special case: circulating EGF should never be conflated with EGFR mutation testing. Therapeutic concepts such as CIMAvax-EGF belong to a distinct and geographically limited literature and are not substitutes for guideline-based EGFR molecular profiling. [28-32]

At present, these markers should be interpreted as emerging or context-dependent rather than routine decision tools. They may enrich biological understanding or refine trial selection, but they do not yet support a standard blood-based switch algorithm in the way ctDNA can. [27-32]

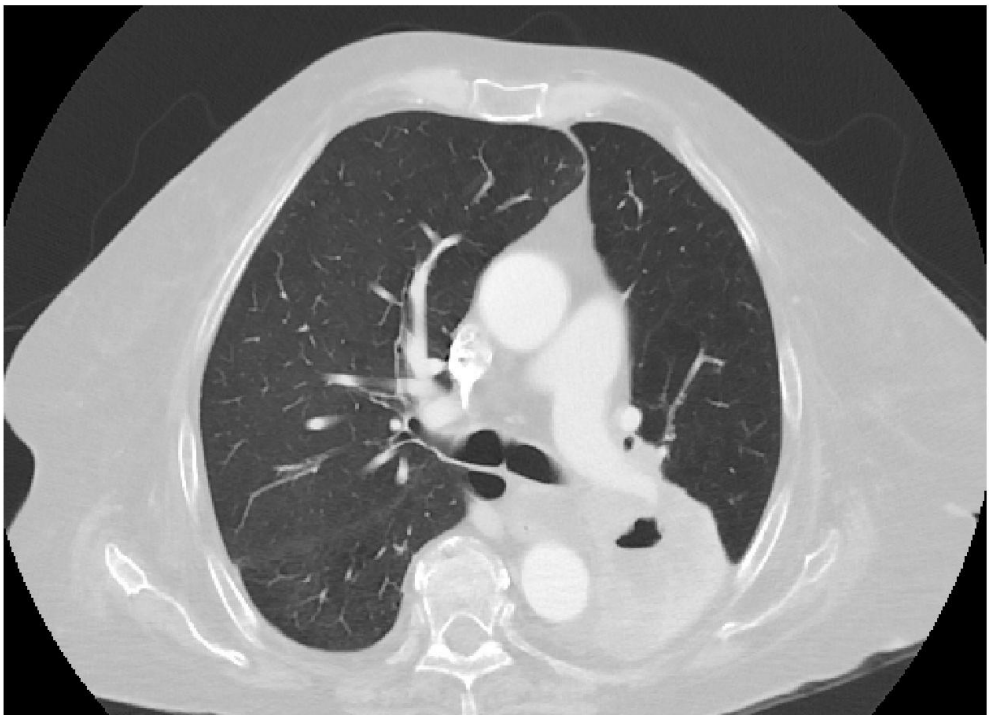

Figure 4: Representative thoracic CT image of lung cancer with cavitation. Source image: "CT scan of lung cancer with cavitation" by Jmarchn; Wikimedia Commons; CC0 1.0 public-domain dedication; resized for layout. Included as an illustrative clinical image.

When biomarker combinations should trigger imaging, re-biopsy or treatment shift

The question most relevant to clinical practice is not whether biomarker abnormalities occur, but what they should make the clinician do next. The strongest rationale for changing therapy remains a guideline-concordant actionable molecular result, unequivocal radiographic or clinical progression, or both. Most non-genomic biomarkers instead determine how urgently those confirmatory steps should occur. [1-5]

A convergent signal is more persuasive than an isolated one. For example, rising ctDNA burden together with increasing CYFRA 21-1 or CEA, persistent CTC positivity and worsening IL-6 or SAA suggests biologic progression well before a single marker alone would justify action. In such a situation, it is reasonable to accelerate imaging, repeat plasma genotyping or pursue tissue re-biopsy, especially if a matched next-line option might become available. By contrast, a solitary rise in one serum marker without corroboration should trigger confirmation and shorter interval follow-up, not an automatic switch. [8-10,14-16,24-26]

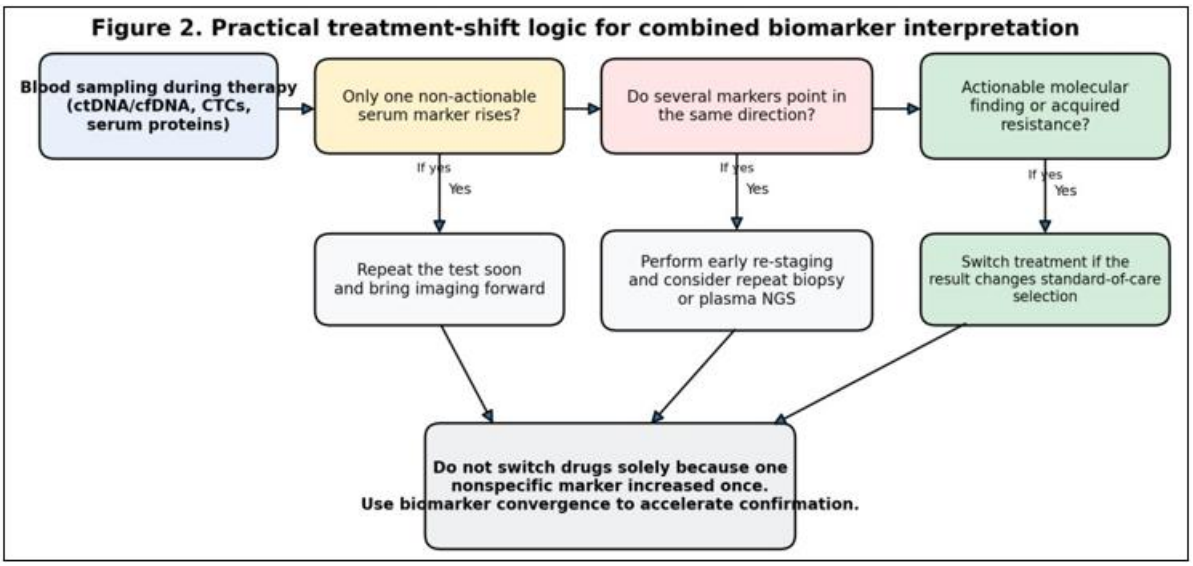

Figure 5: Pragmatic treatment-shift logic in NSCLC when circulating or serum biomarkers change during therapy. The figure distinguishes between actionable molecular events, multi-marker warning patterns and isolated nonspecific abnormalities. This figure was created for the present review.

Table 2: A practical interpretation framework for biomarker combinations and treatment-shift decisions in NSCLC.

Biomarker pattern	Most likely interpretation	Recommended next clinical step	Immediate switch justified?
Actionable ctDNA driver or resistance alteration detected	Therapeutically targetable biology identified	Align therapy with guideline-supported matched treatment; confirm context and prior exposure	Yes, if clinically appropriate and supported by current standards
Plasma negative but high clinical suspicion for molecular progression	Low shedding or incomplete capture remains possible	Obtain tissue re-biopsy if feasible or repeat broader testing	No, not on plasma negativity alone
Rising ctDNA plus rising CYFRA/CEA plus persistent CTCs	High suspicion for biologic progression	Short-interval imaging; repeat plasma NGS; consider tissue sampling	Usually not before confirmation
Isolated rise in CYFRA, CEA or SCC/SCCA	Possible burden change, assay noise or confounding	Repeat marker; review timing and non-malignant confounders; shorten scan interval	No
High baseline or rising IL-6/SAA on immunotherapy	Inflammatory poor-risk biology; possible resistance	Closer monitoring; integrate with symptoms, imaging and tumour-derived markers	No
Postoperative ctDNA MRD positivity	High recurrence risk	Intensify surveillance; multidisciplinary discussion; consider trial or context-specific adjuvant implications	Not universally
Low VEGF-A in a setting considering bevacizumab addition	Potentially enriched anti-VEGF sensitivity in selected cohorts	Contextual use only; consider disease subtype and study basis	Not routinely

3. Future Directions

The field is moving away from one-marker-at-a-time thinking toward multiplex, longitudinal models that integrate tumour-derived genomic fragments, host-response proteins, cell-based assays and imaging. This evolution is scientifically attractive but clinically demanding. The most urgent needs are assay standardization, prospective validation across treatment classes, and interventional trials showing that biomarker-guided changes actually improve outcomes rather than simply detect bad outcomes earlier. [3,4,11,12,30,32]

Two future trajectories are particularly important. First, ultrasensitive ctDNA platforms are likely to expand MRD-directed care in earlier-stage NSCLC, especially when linked to adjuvant personalization. Second, machine-learning frameworks that combine ctDNA kinetics with serum proteins and imaging features may eventually identify a subgroup in whom true pre-radiographic intervention is justified. Until then, the safest principle remains to use biomarkers to refine timing, probability and suspicion more often than to dictate an unconfirmed therapeutic change. [4,6,7,11-13]

Table 3: Landmark studies that shape current interpretation of blood-based biomarkers in NSCLC.

Study	Biomarker class	Clinical setting	Take-home message
Rolfo et al., 2021 [3]	Liquid biopsy consensus	Advanced NSCLC	Established plasma testing as a major component of contemporary NSCLC biomarker strategy
Page et al., 2022 [5]	Plasma CGP	Advanced NSCLC	Plasma comprehensive profiling can shorten time to biomarker-informed treatment
Chaudhuri et al., 2017 [6]	ctDNA MRD	Localized lung cancer	Early ctDNA detection can identify molecular residual disease before clinical relapse
Abbosh et al., 2017 [7]	ctDNA phylogenetics	Early-stage lung cancer	ctDNA can reflect tumour evolution and early relapse biology
Xia et al., 2022 [11]	Perioperative ctDNA	Resectable NSCLC	Perioperative ctDNA positivity stratifies MRD risk and recurrence
Qiu et al., 2021 [12]	Dynamic ctDNA	Resected NSCLC	Postsurgical and post-ACT ctDNA positivity predicts recurrence and ACT benefit patterns
Pellini et al., 2023 [10]	ctDNA monitoring	Chemo-immunotherapy	ctDNA persistence or lack of clearance identifies high-risk patients during induction treatment
Wang et al., 2023 [14]	CTC dynamics	First-line platinum chemotherapy	Persistent CTCs predict poorer response and survival
Edelman et al., 2012 [18]	CYFRA 21-1	Advanced NSCLC	CYFRA 21-1 is both prognostic and useful for treatment monitoring
Dall'Olio et al., 2020 [19]	CEA/CYFRA 21-1	ICI-treated advanced NSCLC	Serial serum markers can inform prognosis and early monitoring during immunotherapy
Kang et al., 2020 [24]	IL-6	PD-1/PD-L1 blockade	High baseline IL-6 marks inferior response and outcomes
Tanaka et al., 2025 [30]	VEGF-A	Metastatic NSCLC ± bevacizumab	Low VEGF-A may enrich benefit from adding bevacizumab in selected chemo-immunotherapy settings

Illustrative clinical and workflow images

The following images are included for editorial and educational context. They are not presented as data figures from the cited studies but as representative visuals of blood collection workflows, imaging context and pathology classification relevant to NSCLC biomarker practice.

Figure 6: Representative blood collection tubes relevant to plasma- and serum-based biomarker workflows. Source image: "Vacutainer blood bottles" uploaded by Tannim101 on Wikimedia Commons, with credit on the source page to photographer Tom Mallinson; used under CC BY 3.0 after resizing for layout.

4. Conclusions

The central message emerging from the current literature is not that blood-based biomarkers in non-small cell lung cancer derive their value only from formal guideline incorporation, but that their clinical utility exists along a spectrum of evidentiary strength and practical applicability. These biomarkers are not equivalent in function. Some primarily inform prognosis, some refine disease monitoring, some provide early warning of biological resistance, and a more limited subset—most notably actionable alterations identified through circulating tumor deoxyribonucleic acid analysis—can directly influence therapeutic selection and support treatment switching. Their relevance, therefore, lies not in uniformity, but in layered interpretation.

From a clinical perspective, the most compelling signals remain those that reveal actionable tumor biology. Such findings occupy the highest tier because they can identify a targetable driver, an acquired resistance mechanism, or a molecular rationale for therapeutic redirection. Beneath this level lies a second, clinically important tier composed of convergent biomarker change. Unfavorable dynamics in circulating tumor cells, cytokeratin-19 fragment, carcinoembryonic antigen, squamous cell carcinoma antigen, interleukin-6, serum amyloid A, and selected angiogenic mediators may collectively indicate increasing tumor activity, erosion of treatment control, or impending progression, in some cases before these changes are fully captured radiographically. By contrast, isolated and nonspecific biomarker abnormalities, although potentially biologically informative, rarely provide sufficient grounds on their own for altering treatment strategy. [1-5]

Thus, in routine practice, treatment switching in non-small cell lung cancer is most convincingly justified when blood-based biomarker evidence converges with molecularly actionable findings, radiographic progression, pathological reassessment, or unequivocal clinical deterioration. In this framework, guidelines should be viewed as an evidence-based scaffold rather than a substitute for physician judgment. Equally, biomarkers should not be regarded as mechanistic commands that dictate therapy in isolation. Their true value lies in sharpening clinical inference, improving temporal precision, and helping the treating physician recognize when biological change is maturing into clinical necessity.

The most realistic interpretation of the current blood-based biomarker landscape in non-small cell lung cancer is therefore neither reductionist nor dismissive. These biomarkers are best understood as instruments of precision oncology whose contribution may be decisive when they uncover actionable genomics, highly informative when they reveal coordinated signals of emerging resistance, and consistently meaningful when integrated into the broader clinical, radiographic, and pathological portrait of the patient. In that sense, biomarkers do not replace clinical judgment; they deepen it. [1-5,10,18,24,30]

References

[1] Riely GJ, Hanna NH, Aredo JV, et al. Non-Small Cell Lung Cancer, Version 4.2024, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2024;22(4):249-274.
[2] Lindeman NI, Cagle PT, Aisner DL, et al. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors. Arch Pathol Lab Med. 2018;142(3):321-346.
[3] Rolfo C, Mack P, Scagliotti GV, et al. Liquid Biopsy for Advanced NSCLC: A Consensus Statement From the International Association for the Study of Lung Cancer. J Thorac Oncol. 2021;16(10):1647-1662.
[4] Garcia-Pardo M, Czarnecka K, Law JH, et al. Plasma-first: accelerating lung cancer diagnosis and molecular profiling through liquid biopsy. Ther Adv Med Oncol. 2022;14:17588359221126151.
[5] Page RD, Drusbosky LM, Dada H, et al. Clinical Outcomes for Plasma-Based Comprehensive Genomic Profiling Versus Standard-of-Care Tissue Testing in Advanced Non-Small Cell Lung Cancer. Clin Lung Cancer. 2022;23(1):72-81.
[6] Chaudhuri AA, Chabon JJ, Lovejoy AF, et al. Early Detection of Molecular Residual Disease in Localized Lung Cancer by CAPP-Seq ctDNA Profiling. Cancer Discov. 2017;7(12):1394-1403.
[7] Abbosh C, Birkbak NJ, Wilson GA, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. Nature. 2017;545(7655):446-451.
[8] Zhou X, Zhang Y, Xu W, et al. Kinetics of plasma cell-free DNA predicts clinical response in non-small cell lung cancer patients. Sci Rep. 2021;11:7633.
[9] Zheng J, Wang X, Xu T, et al. Predictive value of early kinetics of ctDNA combined with cfDNA and serum CEA for EGFR-TKI treatment in advanced non-small cell lung cancer. Thorac Cancer. 2022;13(22):3162-3173.
[10] Pellini B, Szymanski J, Chin RI, et al. Circulating Tumor DNA Monitoring on Chemo-immunotherapy for Risk Stratification in Advanced Non-Small Cell Lung Cancer. Clin Cancer Res. 2023;29(22):4596-4605.
[11] 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.
[12] 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.
[13] Herbst RS, de Marinis F, Eberhardt WEE, et al. Molecular residual disease analysis of adjuvant osimertinib in resected EGFR-mutated stage IB-IIIA non-small-cell lung cancer. Nat Med. 2025;31(6):1958-1968.
[14] Wang Z, Wang Z, Yang X, et al. Circulating tumor cells dynamics during chemotherapy predict survival and response in advanced non-small-cell lung cancer patients. Ther Adv Med Oncol. 2023;15:17588359231167818.
[15] Purcell E, Niu Z, Owen S, et al. Circulating tumor cells reveal early predictors of disease progression in patients with stage III NSCLC undergoing chemoradiation and immunotherapy. Cell Rep. 2024;43(2):113687.
[16] Castello A, Carbone FG, Rossi S, et al. Circulating Tumor Cells and Metabolic Parameters in NSCLC Patients Treated with Checkpoint Inhibitors. Cancers (Basel). 2020;12(2):487.
[17] Molina R, Auge JM, Escudero JM, et al. Tumor markers (CEA, CA125, CYFRA 21-1, SCC and NSE) in patients with non-small-cell lung cancer as an aid in histological diagnosis and prognosis. Tumour Biol. 2003;24(4):209-218.
[18] Edelman MJ, Hodgson L, Rosenblatt PY, et al. CYFRA 21-1 as a prognostic and predictive marker in advanced non-small-cell lung cancer in a prospective trial: CALGB 150304. J Thorac Oncol. 2012;7(4):649-654.
[19] Dall'Olio FG, Abbati F, Facchinetti F, et al. CEA and CYFRA 21-1 as prognostic biomarker and as a tool for treatment monitoring in advanced NSCLC treated with immune checkpoint inhibitors. Ther Adv Med Oncol. 2020;12:1758835920952994.
[20] Miyadera K, Kaira K, Seki Y, et al. Serum CYFRA 21-1 as a Prognostic Marker in Non-Small-Cell Lung Cancer Patients Treated with Immune Checkpoint Inhibitors. Cancers (Basel). 2024;16:3712.
[21] Zhao XM, Yu Y, Hou M, et al. Prognostic and predictive value of serum carcinoembryonic antigen levels in advanced non-small cell lung cancer patients with EGFR-sensitive mutation and receiving tyrosine kinase inhibitors. Oncotarget. 2017;8(41):70865-70873.
[22] Jiang R, Wang X, Li K, et al. Predictive and prognostic value of preoperative serum tumor markers is EGFR mutation-specific in resectable non-small-cell lung cancer. Oncotarget. 2016;7(18):26823-26836.
[23] Chen F, Zhang D, Wu D, et al. Predictive value of serum SCCA and CYFRA21-1 levels on radiotherapy efficacy and prognosis in patients with non-small cell lung cancer. Biotechnol Genet Eng Rev. 2024;40(4):4205-4214.
[24] Kang DH, Park CK, Chung C, et al. Baseline Serum Interleukin-6 Levels Predict the Response of Patients with Advanced Non-small Cell Lung Cancer to PD-1/PD-L1 Inhibitors. Immune Netw. 2020;20(3):e27.
[25] Inoue Y, Yoshimura K, Mori K, et al. Cytokine profiling identifies circulating IL-6 and IL-15 as prognostic stratifiers in patients with non-small cell lung cancer receiving anti-PD-1/PD-L1 blockade therapy. Cancer Immunol Immunother. 2023;72(8):2717-2728.
[26] He LN, Yang XH, Li TT, et al. Baseline and early changes in circulating Serum Amyloid A predict survival outcomes in advanced non-small cell lung cancer patients treated with anti-PD-1/PD-L1 monotherapy. Lung Cancer. 2021;158:1-8.
[27] Kaya A, Ciledag A, Gulbay BE, et al. The prognostic significance of vascular endothelial growth factor levels in sera of non-small cell lung cancer patients. Respir Med. 2004;98(7):632-636.
[28] Brattstrom D, Bergqvist M, Hesselius P, et al. Serum VEGF and bFGF adds prognostic information in patients with normal platelet counts when sampled before, during and after treatment for locally advanced

non-small cell lung cancer. Lung Cancer. 2004;43(1):55-62.
[29] Hu MM, Hu Y, He JB, et al. Basic fibroblast growth factor shows prognostic impact on survival in operable non-small cell lung cancer patients. Thorac Cancer. 2015;6(4):450-457.
[30] Tanaka K, Kaira K, Naito T, et al. Serum VEGF-A as a biomarker for the addition of bevacizumab to chemo-immunotherapy in metastatic NSCLC. Nat Commun. 2025;16(1):2825.
[31] Ma R, Zhang Y, Xu J, et al. Serum Platelet-Derived Growth Factor Is Significantly Lower in Patients with Lung Cancer and Continued to Decrease After Platinum-Based Chemotherapy. Onco Targets Ther. 2020;13:1883-1892.
[32] Rodriguez PC, Rodriguez G, Gonzalez G, et al. A Phase III Clinical Trial of the Epidermal Growth Factor Vaccine CIMAvax-EGF as Switch Maintenance Therapy in Advanced Non-Small Cell Lung Cancer Patients. Clin Cancer Res. 2016;22(15):3782-3790.

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