

Molecular advances in early-stage and locally advanced non-small cell lung carcinoma: Shaping the future of precision oncology-systematic review

Science Progress

2025, Vol. 108(3) 1–32

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DOI: 10.1177/00368504251383055

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Abstract

Objective: To synthesize recent molecular advances that inform diagnosis, risk-stratification, and perioperative treatment in early-stage and locally advanced non-small cell lung carcinoma (NSCLC), with emphasis on comprehensive genomic profiling, minimal residual disease (MRD) detection by circulating tumor DNA (ctDNA), and the translation of biomarkers into targeted and immunotherapy strategies.

Methods: Systematic review registered in PROSPERO (CRD420251076423). Searches of PubMed, Scopus, Web of Science, and Embase (January 2015–April 2025) followed PRISMA 2020/PRISMA-S. From 4640 records, 890 duplicates were removed; 3750 titles/abstracts were screened; 150 full texts were assessed; 75 studies met inclusion criteria. Risk of bias used Newcastle–Ottawa Scale (NOS) for observational studies and Cochrane RoB 2 tool for randomized controlled trials; certainty was summarized with GRADE where applicable.

Results: Actionable alterations (e.g. EGFR, ALK, KRAS, MET, RET, BRAF, NTRK) are prevalent in early-stage NSCLC and comparable to advanced disease, supporting routine comprehensive genomic profiling in curative-intent settings. Next-generation

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sequencing (NGS) and ctDNA enable the detection of MRD, earlier relapse prediction, and dynamic treatment monitoring. Perioperative strategies integrating targeted therapy and immunotherapy (e.g. adjuvant EGFR-TKI, neoadjuvant chemo-immunotherapy) improve pathological and disease-free outcomes in selected biomarker-defined populations. Evidence profiles generally show low-to-moderate risk of bias and moderate-to-high certainty for key outcomes related to profiling and MRD, with heterogeneity across platforms and endpoints.

Conclusions: Molecular advances—particularly broad NGS and ctDNA-based MRD—are reshaping the perioperative management of early and locally advanced NSCLC, enabling precision selection for targeted and immunotherapy approaches. Standardization of testing workflows and reporting, and cost-effective implementation are priorities for equitable adoption and for future trials that combine NGS, MRD, and multi-omic/AI-driven risk stratification.

Keywords

Non-small cell lung carcinoma, genomic profiling, next-generation sequencing (NGS), circulating tumor DNA, minimal residual disease, precision oncology, precision oncology, targeted therapy

Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer diagnoses and remains the leading cause of cancer-related mortality worldwide.¹ Although advances in targeted therapies and immune checkpoint inhibitors have significantly improved outcomes in metastatic disease, early-stage and locally advanced NSCLC continue to exhibit high relapse rates—up to 70% within five years post-resection—underscoring the need for more effective, personalized treatment strategies.²

The advent of comprehensive genomic profiling has revolutionized the landscape of NSCLC, uncovering a diverse array of molecular subtypes driven by specific genomic alterations. Actionable mutations in genes such as *EGFR*, *ALK*, *ROS1*, *KRAS*, *MET*, *RET*, *BRAF*, and *NTRK* have enabled the implementation of precision medicine approaches across disease stages.^{3,4} Notably, studies have revealed that the prevalence of actionable genomic alterations in early-stage NSCLC is comparable to that in advanced disease, positioning genomic analysis as a cornerstone for risk stratification and therapeutic decision-making even in potentially curable settings.^{5,6}

Beyond primary oncogenic drivers, genomic profiling facilitates the detection of co-mutations with significant prognostic and predictive implications. For instance, co-alterations in *TP53*, present in nearly half of NSCLC cases, are linked to poor survival in *EGFR*-mutant tumors.^{7,8} Similarly, mutations in *KEAP1* and *STK11* have been associated with resistance to immunotherapy and altered responses to immune checkpoint blockade, highlighting the complexity of tumor-immune interactions and the need for individualized therapeutic strategies.⁹

Recent landmark trials have further underscored the importance of integrating molecular profiling into clinical decision-making for early-stage NSCLC. The NeoADAURA trial demonstrated that neoadjuvant osimertinib, combined with chemotherapy, significantly improved major pathological response rates compared to chemotherapy alone, setting a new benchmark for targeted neoadjuvant therapy. Similarly, KEYNOTE-671 and CheckMate-816 highlighted the clinical benefit of combining immunotherapy with chemotherapy in the perioperative setting, with substantial improvements in event-free survival and pathological complete response rates. These studies confirm that biomarker-driven treatment strategies are no longer confined to advanced disease but are reshaping the curative-intent management of early-stage NSCLC. In this context, next-generation sequencing (NGS) is not only a diagnostic tool but also a cornerstone of precision oncology, enabling individualized therapeutic strategies from the earliest stages of disease.^{10,11,12}

In parallel, the emergence of liquid biopsy technologies—particularly circulating tumor DNA (ctDNA)—offers a non-invasive method to detect minimal residual disease (MRD), predict recurrence, and dynamically monitor treatment response. These innovations have opened new avenues for tailoring therapy intensity and duration in real time, thereby enhancing the precision and personalization of early-stage NSCLC management.¹³

These advances in next-generation sequencing and liquid biopsy technologies are central to the realization of precision oncology. By enabling comprehensive genomic characterization, early identification of actionable drivers, and non-invasive monitoring of minimal residual disease (MRD), they facilitate truly individualized treatment selection and dynamic therapy adaptation. Collectively, these approaches bridge the gap between molecular insights and clinical decision-making, ensuring that therapeutic strategies are both biologically informed and patient-centered.^{10,13}

This systematic review aims to comprehensively analyze the current state of molecular advances in early-stage and locally advanced NSCLC, examining the evidence supporting molecular profiling, targeted therapies, immunotherapy approaches, and liquid biopsy applications. By synthesizing data from recent clinical trials, molecular studies, and translational research, this review seeks to provide a comprehensive framework for understanding how precision oncology approaches are transforming treatment paradigms and improving patient outcomes in these disease stages. The ultimate goal is to inform clinical practice and guide future research directions in the rapidly evolving field of molecular oncology for early-stage and locally advanced NSCLC.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) and PRISMA-S guidelines, ensuring methodological transparency and reproducibility. The review protocol was prospectively registered with PROSPERO (CRD420251076423). The aim was to evaluate recent molecular advances in early-stage and locally advanced non-small cell lung cancer

(NSCLC), with a focus on genomic profiling, resistance mechanisms, and targeted therapy integration.

Study selection

A comprehensive literature search was conducted across four databases: PubMed, Scopus, Web of Science, and Embase, covering publications from January 2015 to April 2025. The search terms used included: “early-stage NSCLC,” “molecular profiling,” “genomic alterations,” “targeted therapy,” “ctDNA,” “liquid biopsy,” “resistance mechanisms,” and “precision oncology.” Boolean operators (AND, OR) were used to refine search results. Reference lists of relevant studies were manually screened for additional articles. Full search strategies for each database, including search terms and Boolean operators, are provided in Appendix A. The search yielded 1340 articles from PubMed, 970 from Scopus, 1100 from Web of Science, and 1250 from Embase. A total of 4640 articles were retrieved. After removing 890 duplicates, 3750 articles were screened by title and abstract, and 150 were assessed in full text. Finally, 75 articles were included. A PRISMA 2020 flow diagram (Figure 1) summarizes this process.

Eligibility criteria

Inclusion criteria were: (1) original research articles or clinical trials published in English; (2) studies investigating molecular characterization or targeted therapies in early-stage or locally advanced NSCLC; (3) papers reporting outcomes of genomic profiling, ctDNA-based monitoring, or resistance to therapy. Exclusion criteria included: (1) reviews, editorials, and conference abstracts; (2) studies focused exclusively on metastatic NSCLC; (3) preclinical studies without clinical correlation.

Data extraction

Data extraction was conducted using a standardized form developed for this review. Key variables extracted include: study characteristics (authors, year, country, design), patient population (stage, histological subtype), molecular alterations (e.g. EGFR, ALK, KRAS, MET), type of molecular testing (tissue vs. liquid biopsy), intervention details (targeted therapy or immunotherapy), and reported clinical outcomes (e.g. disease-free survival, overall survival, recurrence rates, resistance mechanisms).

In addition to electronic database searches, the reference lists of all included articles were manually screened to identify additional eligible studies. Citation tracking (“snowballing”) was performed using tools such as Google Scholar and Scopus to identify newer studies that cite the included papers. Conference abstracts and proceedings from major oncology meetings (e.g. ASCO, ESMO, WCLC) were reviewed for relevant unpublished data. Where necessary, study authors were contacted for clarification or to obtain missing information.

For observational cohort studies, we used the Newcastle–Ottawa Scale (NOS), which is widely adopted for non-randomized designs. Studies scoring 7 or higher were

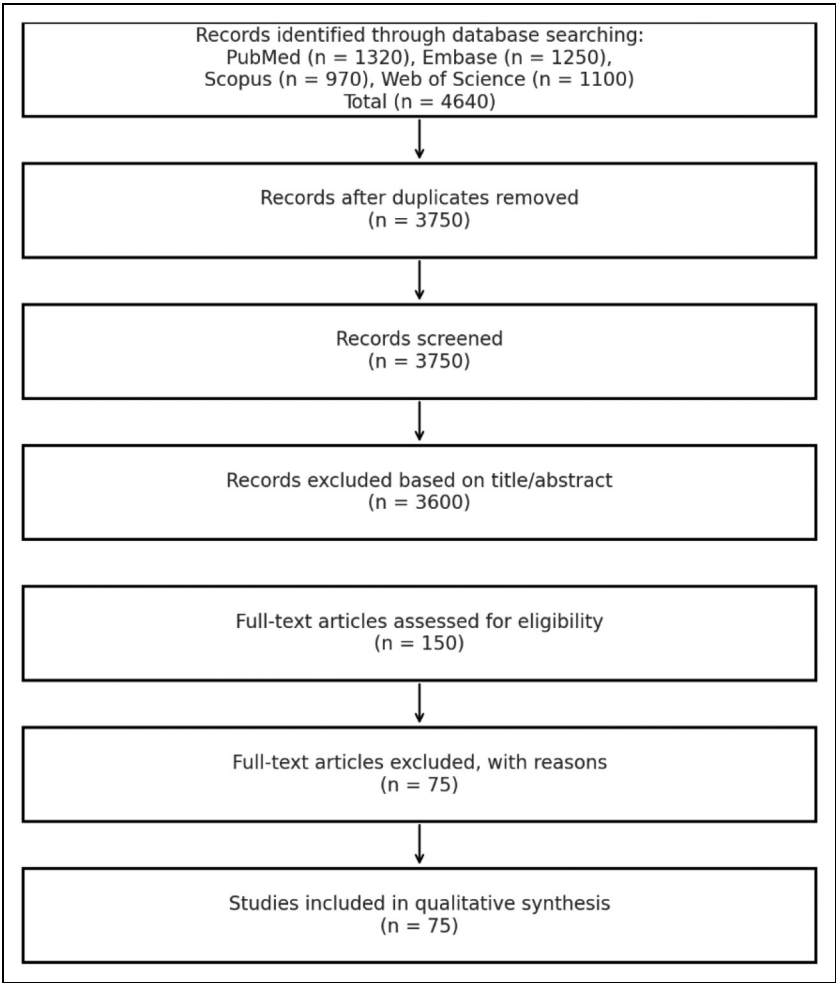


Figure 1. PRISMA 2020 flow diagram for study search.

considered high quality. For randomized controlled trials, we applied the Cochrane RoB 2 tool to better assess randomization, allocation concealment, and blinding. This dual-tool approach allowed tailored quality assessment according to study design.

All search results were imported into reference management software (EndNote X9, Clarivate Analytics; 2013. Philadelphia, PA, USA.) for duplicate removal. Screening of titles and abstracts, followed by full-text eligibility assessment, was conducted independently by two reviewers (WA and AA) as well as any risk of bias. Discrepancies were resolved through discussion or third-party adjudication (SA). In addition, the potential for selective outcome reporting and publication bias was evaluated by reviewing study protocols (if available), trial registries, and comparing registered outcomes with

reported results. For randomized trials, discrepancies between prespecified and published outcomes were noted. Moreover, the overall certainty of the evidence was evaluated using the GRADE approach, where applicable. We assessed the body of evidence for each key outcome across studies based on risk of bias, consistency, directness, precision, and potential publication bias. The certainty was categorized as high, moderate, low, or very low.

Outcomes

The primary outcomes were the prevalence and prognostic implications of actionable molecular alterations in early-stage and locally advanced NSCLC. Secondary outcomes included the impact of genomic profiling and ctDNA analysis on treatment decisions, resistance mechanisms, and patient survival.

Review

Molecular profiling in early stage and locally advanced NSCLC

The implementation of comprehensive genomic profiling (CGP) in early-stage NSCLC has emerged as a critical tool for identifying actionable driver mutations and accelerating treatment decisions at disease recurrence.³ Studies analyzing over 6697 patients with lung adenocarcinoma (LUAD) who underwent surgery between 2011 and 2021 demonstrated that broad genomic testing leads to faster rates of targeted treatment at recurrence with metastatic disease.¹⁴ This approach proves particularly valuable given that up to 55% of patients with NSCLC face disease recurrence after resection,¹⁵ yet currently only one in five patients with early disease receive the benefits of comprehensive molecular testing,¹⁶ proving a critical gap in precision of molecular oncology implementation.

Insights from recent genomic studies. Recent advances in the genomic profiling of NSCLC have provided critical insights into the mutational landscape and its clinical implications. In a landmark study,¹⁷ comprehensive analysis of 74 early-stage NSCLC patients revealed a diverse array of 285 mutations across both tissue DNA and circulating tumor DNA (ctDNA) samples. The most frequently mutated genes included EGFR, TP53, KMT2B, BRAF, PIK3CA, CDKN2A, and KRAS. Importantly, EGFR mutations were detected in 42.9% of tissue samples but only 12.8% of ctDNA, underscoring the limitations of plasma-based genotyping in early-stage disease. The clinical relevance of EGFR mutations was further supported by the ADAURA trial,¹⁸ where adjuvant Osimertinib significantly improved disease-free survival (DFS) in patients with resected EGFR-mutated NSCLC. Moreover, a recent study¹⁹ employing next-generation sequencing (NGS) of a 1021-gene panel in 36 Chinese NSCLC patients revealed distinct mutation profiles between tumor subtypes and metastatic status. CTNNB1 mutations were exclusively detected in non-metastatic lung adenocarcinoma (LUAD), while ARID1A mutations were significantly associated with non-metastatic lung squamous cell carcinoma (LUSC), highlighting subtype- and stage-specific genetic alterations. These findings

highlight the critical need for integrating tissue and liquid biopsy-based genomic assessments to enhance precision oncology by guiding targeted therapies, monitoring disease evolution, and adapting treatment strategies in real time. This approach is particularly vital in early-stage NSCLC, where matching patients to therapies like osimertinib based on dynamic molecular profiles can significantly improve clinical outcomes.

Comparative analysis of early- vs. late-stage NSCLC. McGuire et al. (2022)² conducted a detailed comparative study to identify clinically actionable molecular alterations in early-stage versus late-stage NSCLC, utilizing an age- and sex-matched pair analysis approach. Their findings demonstrate that key actionable mutations—such as **KRAS**, **EGFR**, **ALK**, **ROS1**, **RET**, and **MET exon 14 skipping**—occur at comparable frequencies in both early and late-stage disease. While *KRAS mutations* were more common in late-stage cases, *EGFR mutations* appeared more frequently in early-stage tumors, particularly among never-smokers, though differences were not statistically significant after adjustment. Notably, *RET rearrangements* were only found in early-stage cases, and both stages exhibited similar frequencies of EGFR mutations in exon 20 insertions, all of which are now targetable with approved therapies. These results support implementing broad-panel molecular testing at initial resection to preemptively guide future treatment decisions and reduce delays at recurrence.

In early-stage NSCLC, the distribution of actionable genetic alterations varies by molecular subtype. Muthusamy et al. (2024)²⁰ reported mutation frequencies of 16.1% for **EGFR**, 41.7% for **KRAS**, 1.5% for **BRAF V600E**, 3.1% for **MET exon 14 skipping**, 1.8% for **ALK rearrangements**, 1.1% for **RET fusions**, and 0.6% for **ROS1 rearrangements**. Certain alterations show stage-specific patterns; **MET exon 14 skipping** is enriched in early-stage tumors, while **BRAF V600E** is more prevalent in advanced disease. Additionally, **TP53** mutations are associated with early-onset NSCLC, whereas **ATM** mutations correlate with late-onset cases and elevated **PD-L1** expression, potentially indicating increased responsiveness to immunotherapy.²¹ These findings highlight the clinical importance of comprehensive molecular profiling in early-stage NSCLC for guiding precision treatment strategies.

Moreover, Yokochi et al. (2025)²² conducted a retrospective database analysis assessing the prevalence and characteristics of druggable mutations detected by cancer gene panel (CGPa) testing among patients with NSCLC in Japan. The study included 1425 adult NSCLC patients without prior known actionable mutations. Results demonstrated that 44.6% of patients harbored druggable mutations, predominantly involving *EGFR* and *NTRK* genes, particularly among LUAD and LUSC subtypes respectively. These mutations were frequently detected late, with a median interval of 701 days from initial therapy to identification. Following CGPa testing, only 23.0% of patients subsequently received targeted therapy. The authors concluded that earlier implementation of comprehensive genomic profiling is crucial, as timely identification of actionable mutations could significantly improve therapeutic decisions and patient outcomes by enabling earlier use of targeted therapies. Table 1 provides a comprehensive comparative overview of key molecular biomarkers in NSCLC, integrating prevalence patterns in early-stage

Table 1. Comparative overview of actionable biomarkers in NSCLC: prevalence across stages, therapeutic implications, and representative clinical trials.
45,47,49,51,54,55,57,60,67,68,69,70,71,72,73,74,76,79,80

Biomarker	Early-stage prevalence (%)	Advanced-stage prevalence (%)	Approved / emerging therapies	Therapeutic implications (early vs advanced)	Representative trials
EGFR (ex19del/ L858R)	10–20%	Comparable	EGFR-TKIs (osimertinib, erlotinib, gefitinib, afatinib, dacomitinib)	Early: adjuvant osimertinib improves DFS. Advanced: 1L/ 2L EGFR-TKIs	ADAURA; AENEAS
ALK fusions	5–8%	Comparable	ALK-TKIs (alectinib, brigatinib, lorlatinib, crizotinib)	Early: adjuvant alectinib (DFS benefit). Advanced: ALK-TKIs standard of care	ALINA; NAUTIKAI
KRAS (including G12C)	15–40%	25–40%	KRAS G12C inhibitors (sotorasib, adagrasib)	Early: perioperative trials emerging. Advanced: KRAS inhibitors approved	CodeBreak 200; KRYSTAL-1
BRAF V600E	1–2%	2–4%	Dabrafenib + trametinib	Early: limited perioperative data. Advanced: approved in metastatic NSCLC	NCI-MATCH
MET exon 14 skipping	3–4%	4–6%	MET inhibitors (capmatinib, tepotinib, savolitinib)	Early: perioperative trials ongoing. Advanced: approved 1L/2L	GEOMETRY mono-1;
RET fusions	1–3%	Comparable	RET inhibitors (selpercatinib, pralsetinib)	Early: Adjuvant therapy. Advanced: Approved	LIBRETTO-431/432
ROS1 / NTRK fusions	ROS1: <1% NTRK: <1%	Comparable	ROS1/NTRK inhibitors (Crizotinib, entrectinib)	Early: limited data. Advanced: approved	STARTRK-1/2
HER2 (ERBB2)	2–3%	Comparable	HER2-directed trastuzumab deruxtecan (T-DXd)	Early: limited data. Advanced: Activity in HER2-mutant NSCLC	DESTINY-Lung01

(continued)

Table 1. Continued.

Biomarker	Early-stage prevalence (%)		Advanced-stage prevalence (%)	Approved / emerging therapies	Therapeutic implications (early vs advanced)	Representative trials
	Variable	Variable				
PD-L1 (expression biomarker)	Variable	Variable	Variable	Immune checkpoint inhibitors (atezolizumab, pembrolizumab, nivolumab, durvalumab)	Early: adjuvant/neoadj-uvant. Advanced: immune checkpoint inhibitor ± chemo standard in PD-L1 + disease	PACIFIC

Abbreviations: NSCLC; non-small cell lung carcinoma

versus advanced disease, associated therapeutic implications, and representative clinical trial evidence.

Prognostic significance of actionable oncogenic drivers

The prognostic and predictive implications of actionable biomarkers differ substantially between early and advanced stages of NSCLC. For example, *EGFR mutations*, which confer sensitivity to tyrosine kinase inhibitors, are associated with improved disease-free survival in resected tumors, although their impact on overall survival remains controversial. Conversely, *KRAS mutations* appear less prognostic in early-stage disease but predict poor response in advanced cases, particularly when co-occurring with STK11 or KEAP1 alterations. Similarly, *ALK and RET rearrangements*, though less frequent in early stages, identify subgroups likely to benefit from early integration of targeted therapies such as alectinib. PD-L1 expression has emerged as an important immunotherapy biomarker, with perioperative trials confirming its predictive role in guiding the use of checkpoint blockade. By contrast, multivariate analysis of patients with stages I-IIIb NSCLC revealed that *TP53 mutations* are associated with a significantly increased rate of developing distant metastases.²⁶ This finding has profound implications for treatment planning and surveillance strategies in early-stage patients, as TP53-mutated tumors may require more aggressive adjuvant approaches or closer monitoring protocols.^{23,24,25,26}

Development of combination targeted therapies

The integration of comprehensive genomic profiling in EGFR-mutant NSCLC has revealed that co-occurring actionable mutations—such as de novo MET amplification and ERBB2 alterations—are associated with significantly shorter progression-free survival when treated with first-generation EGFR TKIs, underscoring their adverse prognostic impact.²⁷ These findings emphasize the need for thorough molecular characterization prior to initiating targeted therapy. Additionally, recent evidence from the ADAURA trial has confirmed the clinical benefit of adjuvant osimertinib in patients with resected EGFR-mutant NSCLC, particularly those harboring exon 19 deletions or L858R mutations, demonstrating improved outcomes and establishing adjuvant targeted therapy as a new standard of care in early-stage disease.¹⁸ Moreover, a recent comprehensive synthesis demonstrated that molecularly selected patients with early-stage NSCLC derive substantial benefit from adjuvant and perioperative targeted therapies, showing significant and durable improvements in disease-free survival (DFS), particularly in EGFR- and ALK-altered cohorts, thereby reinforcing the integration of biomarker-driven strategies into curative treatment pathways.²⁷ Collectively, these insights highlight the critical role of molecular profiling in guiding both initial and adjuvant treatment strategies in EGFR-driven NSCLC.

Emerging evidence suggests that *KRAS mutation* status, while well-established as a prognostic factor in advanced NSCLC, may have limited prognostic impact in early-stage disease when combined with tumor size parameters.²⁸ However, the development of *KRAS G12C mutation* inhibitors has opened new therapeutic avenues, with sotorasib

showing encouraging efficacy in heavily pretreated patients harboring KRAS G12C mutations.²⁹

Resistance mechanisms to single-agent and combination therapies

The introduction of targeted therapies against oncogenic drivers, such as EGFR, ALK, ROS1, RET, MET, BRAF, and KRAS, has revolutionized NSCLC management. However, resistance to these agents remains a major clinical challenge.

Resistance to EGFR tyrosine kinase inhibitors. Resistance to EGFR TKIs in NSCLC can be broadly categorized into EGFR-dependent and EGFR-independent molecular mechanisms, each posing distinct therapeutic challenges. Primary resistance, observed in approximately 20–30% of cases, is defined by a poor initial response to TKIs and is frequently attributed to pre-existing *de novo* mechanisms such as co-occurring genetic alterations or alternative pathway activations that bypass EGFR inhibition.²⁹ This finding underscores the necessity of extensive pre-treatment molecular profiling in advanced NSCLC to identify inherently TKI-resistant cases and to inform the development of combinatorial targeted therapies aimed at overcoming intrinsic resistance.

The *T790 M mutation in EGFR exon 20* represents the most prevalent acquired resistance mechanism to first- and second-generation EGFR TKIs, occurring in 50–63% of post-treatment tumor samples. This mutation restores ATP affinity to near wildtype levels and creates steric hindrance that prevents drug binding to the kinase pocket.³⁰ This leads to the development of third-generation inhibitors like Osimertinib, which is currently indicated as first-line therapy in patients with NSCLC and sensitizing EGFR mutations; as second-line therapy in patients who present the resistance-associated mutation T790 M after treatment with previous EGFR-TKIs; and as adjuvant therapy for patients with early stage, resected NSCLC, harboring EGFR mutations. Osimertinib irreversibly binds to mutant EGFR via its acrylamide group that forms a covalent bond with the Cys797 residue located in the ATP-binding site of mutant EGFR.³¹

However, resistance to osimertinib emerges and involves multiple mechanisms, with *T790 M loss and C797S mutations* representing the most common on-target resistance occurring in approximately 65% of patients. The spatial relationship of C797S and T790 M mutations determines therapeutic options: when occurring in *cis* (same allele), tumors are resistant to all EGFR inhibitor generations, while *trans* mutations (different alleles) retain sensitivity to combination approaches.³¹ Novel fourth-generation EGFR inhibitors (e.g. BLU-945, BBT-176) targeting C797S are in early-phase clinical trials and have shown preclinical efficacy against *cis*- and *trans*-resistance patterns.³²

Additional resistance mutations include *G796R/S*, *L792H*, *L718Q*, and *G724S substitutions*, each presenting distinct therapeutic challenges.³³ In addition, there are other off-target EGFR independent mechanisms that convey resistance, such as MET amplification, HER2 amplification, PIK3CA amplification and BRAF mutation (V600E).³³ Moreover, the emergence of *drug-tolerant persister cells* represents a particularly complex resistance mechanism, characterized by altered chromatin states, epigenetic modifications, and metabolic reprogramming.³⁴

Resistance to ALK inhibitors. For ALK-rearranged NSCLC, resistance often arises through secondary mutations in the ALK kinase domain (e.g. L1196 M and G1202R) or amplification of the ALK gene itself, which sustain downstream signaling despite TKI treatment.³⁵ Additionally, bypass signaling pathways—such as EGFR or KRAS activation—can compensate for ALK inhibition, enabling tumor survival.³⁶ These adaptive changes highlight the tumor's ability to exploit parallel signaling networks when primary oncogenic drivers are suppressed.

Resistance to ROS1 inhibitors. ROS1 rearrangements, while relatively rare (0.6% in early-stage disease), represent highly actionable alterations with approved targeted therapies.³⁷ The identification of these fusions through comprehensive genomic profiling has enabled access to effective treatments such as crizotinib and subsequent-generation ROS1 inhibitors.³⁷ Resistance in ROS1-rearranged NSCLC frequently involves mutations in the ROS1 kinase domain (e.g. G2032R), as well as activation of bypass pathways such as MET amplification and KRAS mutations.³⁷

Resistance to MET inhibitors. In MET-driven NSCLC, particularly those with MET exon 14 skipping mutations or amplification, resistance to MET inhibitors (e.g. capmatinib, tepotinib) arises via several mechanisms. These include secondary MET mutations (e.g. D1228N, Y1230C), which interfere with drug binding, and activation of alternative pathways like KRAS amplification or EGFR upregulation, allowing tumors to bypass MET inhibition.³⁸

A recent case report in *Frontiers in Oncology* demonstrated that even low-level MET gene copy gain in an EGFR-mutant, TKI-resistant metastatic NSCLC patient yielded a meaningful therapeutic response—specifically, a 7-month progression-free survival—when treated with combined osimertinib and savolitinib, underscoring the potential utility of targeted therapy against MET-mediated resistance even at sub-threshold amplification levels.³⁹

Resistance to BRAF inhibitors. Similarly, resistance to BRAF-targeted therapies in patients with BRAF V600E mutations, such as dabrafenib and trametinib, may occur through MAPK pathway reactivation via NRAS mutations or upregulation of CRAF and MEK, highlighting the need for combination strategies to delay resistance.⁴⁰ These findings underscore the complexity of tumor adaptation and the importance of longitudinal molecular monitoring.

Resistance to KRAS inhibitors. Recent advances in KRAS-targeted therapy, particularly with KRAS G12C inhibitors like sotorasib and adagrasib, have demonstrated promising initial responses in NSCLC patients. Nonetheless, resistance can develop through multiple routes, including secondary KRAS mutations (e.g. Y96D), amplification of KRAS G12C, or activation of compensatory pathways such as EGFR, HER2, or PI3K-AKT signaling.^{40,41}

Other resistance mechanisms. The complexity of therapeutic resistance in NSCLC is further intensified by histological transformation and epigenetic reprogramming. A subset of tumors undergo *epithelial-to-mesenchymal transition (EMT)* or *transform into small cell lung cancer (SCLC)*, both of which confer more aggressive phenotypes with enhanced capacity to evade targeted therapies.⁴¹ Additionally, *alterations in cell cycle regulatory pathways*—such as CDK4/6 amplifications or loss of the tumor suppressor CDKN2A—facilitate unchecked proliferation, undermining the efficacy of kinase inhibitors.⁴² These adaptive changes underscore the critical importance of integrating dynamic molecular profiling and rational combination strategies to anticipate and counteract resistance mechanisms in NSCLC.

Impact of molecular advances on patient outcomes and survival improvements

Beyond targeted gene panels, emerging comprehensive sequencing technologies are increasingly applied in early-stage NSCLC. Whole-exome sequencing (WES) provides detailed information on mutational burden and novel driver events, while RNA sequencing enables the detection of gene fusions, alternative splicing, and expression-based signatures with therapeutic implications.^{19,20} Furthermore, liquid biopsy-based NGS platforms are now being investigated for minimal residual disease (MRD) detection, offering the ability to non-invasively monitor recurrence risk and treatment response. Collectively, these technologies expand the scope of precision oncology by integrating genomic, transcriptomic, and dynamic molecular data into therapeutic decision-making.

Integration of comprehensive genomic profiling (CGP). Real-world evidence from comprehensive genomic profiling studies shows that patients who receive CGP have improved detection of actionable biomarkers (53% versus 14%) and greater use of matched therapies compared to single-gene testing approaches.⁴³ A 2023 multicenter cohort study investigating the timing of CGP in metastatic solid tumors demonstrated a pronounced survival benefit for patients with lung cancer who underwent earlier CGP. Specifically, patients who received CGP in the second and third tertiles after metastatic diagnosis experienced significantly higher mortality risks compared to those tested in the first tertile.⁴⁴ These findings underscore the critical importance of early integration of CGP in the management of metastatic lung cancer, as delayed testing may limit the clinical benefit of targeted therapies and adversely impact patient outcomes.

Moreover, trials such as LC-SCRUM (Lung Cancer Genomic Screening Project for Individualized Medicine) and BATTLE (Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination) have demonstrated the feasibility and clinical utility of molecular profiling in real-time decision-making. The BATTLE trial, a pioneering study in adaptive randomization based on biomarker profiles, showed that tailoring therapy to individual tumor genomics improves disease control rates, particularly in previously treated NSCLC patients.⁴⁵ Similarly, the LC-SCRUM-Japan initiative established a nationwide genomic screening platform for lung cancer, facilitating early identification of rare but targetable alterations like ALK, ROS1, and RET fusions, which expanded therapeutic options and enrollment in matched clinical trials.⁴⁶ Moreover, the

NCI-MATCH trial (Molecular Analysis for Therapy Choice) included NSCLC among various solid tumors and emphasized that assigning therapies based on specific molecular alterations, regardless of tumor origin, can lead to clinically meaningful responses.⁴⁷ These studies collectively underscore that early and comprehensive genomic analysis should be an integral part of NSCLC management to personalize treatment, avoid ineffective therapies, and enhance long-term survival.

The economic implications of routine CGP in early-stage NSCLC are increasingly recognized. In a recent U.S.-based cost-effectiveness analysis, **Muthusamy et al. (2023)**²⁰ demonstrated that CGP-guided therapy improves quality-adjusted life years (QALYs) and can be cost-effective compared with limited gene testing when integrated early in the treatment pathway. These findings reinforce that CGP implementation should be considered not only from a clinical but also from an economic standpoint, particularly as the cost of sequencing continues to decrease and targeted therapies expand into earlier disease settings.

Table 2 summarizes the most recent clinical trials highlighting the importance of molecular diagnosis in early-stage and locally advanced NSCLC.

Integration of circulating tumor DNA. The integration of ctDNA-based MRD monitoring has emerged as a transformative tool in NSCLC, enabling early detection of recurrence, stratification of relapse risk, and refinement of post-treatment surveillance strategies. It represents a promising approach for early-stage disease monitoring with significant clinical potential.

ctDNA-based MRD detection strategies can be broadly divided into *tumor-informed* and *tumor-agnostic* approaches. Tumor-informed assays, such as Signatera, require prior knowledge of patient-specific tumor mutations and enable highly sensitive detection of recurrence risk. Tumor-agnostic approaches, in contrast, use predefined gene panels without prior tumor sequencing, offering faster turnaround but generally lower sensitivity in early-stage disease.⁴⁸

In early-stage NSCLC, these approaches have been evaluated in landmark adjuvant and neoadjuvant immunotherapy trials. For example, ctDNA analyses in IMpower010 (atezolizumab), CheckMate-816 (nivolumab), AEGEAN (durvalumab), and NADIM (nivolumab + chemotherapy) have demonstrated prognostic value, with ctDNA clearance after surgery or neoadjuvant treatment correlating with improved disease-free survival.^{49,50,51} The integration of ctDNA into escalation/de-escalation strategies is an area of active investigation, aiming to tailor adjuvant therapy intensity based on MRD status rather than stage alone. Ongoing phase III trials, such as MERMAID-1 and MERMAID-2, are prospectively evaluating ctDNA-guided therapeutic strategies, highlighting the potential of this approach to optimize treatment selection in early-stage and locally advanced lung cancer.⁵⁰

In comparison with tissue-based next-generation sequencing (NGS), liquid biopsy has faster turnaround and facilitates longitudinal sampling, yet its sensitivity is reduced in early-stage disease due to low ctDNA burden. Comparative workflow analyses suggest that tissue NGS is more effective for baseline comprehensive profiling, whereas liquid biopsy is particularly valuable for serial monitoring, detecting MRD, and overcoming

Table 2. Summary for the recent key clinical trials (2019–2024) on molecular advances in early-stage and locally advanced NSCLC.

Trial/Target	Molecular Target	Phase/ Study	Patient Population	Key Findings	Recommendations
ADAURA ⁶⁵	EGFR (ex19del/ L858R)	III	Resected stage IB–IIIA NSCLC, EGFR-mut.	Osimertinib improved DFS benefit.	FDA-approved adjuvant osimertinib for EGFR-mut. NSCLC; routine EGFR testing.
AENEAS2 ⁶⁶	EGFR (ex19del/ L858R)	III	Locally advanced/metastatic NSCLC, EGFR-mutant	PFS: 19.3 months (aumolertinib), 9.9 months (gefitinib), toxicity higher with gefitinib	Aumolertinib is a well-tolerated third-generation EGFR TKI that could serve as a treatment option for EGFR-mut. NSCLC in the first line setting.
ALINA ⁶⁷	ALK fusion	III	Resected stage IB–IIIA, ALK + NSCLC	Adjuvant alectinib improved DFS	Alectinib recommended as adjuvant therapy for ALK + NSCLC.
P2.01-06 NAUTIKA1 ⁶⁸	ALK + NSCLC	II	Stage IB–III ALK + NSCLC	Neoadjuvant alectinib for 8 weeks, followed by surgery; they then received up to 4 cycles of platinum-based chemotherapy	Neoadjuvant alectinib demonstrated major pathological response and was well tolerated
LIBRETTO-431 ⁶⁹	RET fusion	III	RET Fusion + advanced NSCLC.	Selpercatinib vs. Platinum-based chemotherapy ± pembrolizumab. Selpercatinib significantly prolonged PFS with higher ORR	May establish selpercatinib as first-line treatment for RET fusion-positive NSCLC.

(continued)

Table 2. Continued.

Trial/Target	Molecular Target	Phase/ Study	Patient Population	Key Findings	Recommendations
LIBRETTO-432 ⁷⁰ (NCT04819100)	RET fusion	III	RET + NSCLC	Ongoing trial evaluating adjuvant selpercatinib.	Await results; potential adjuvant use for RET + NSCLC.
SWORD-I ⁷¹ (NCT04161391)	RET altered	I/II	RET-altered NSCLC, both treatment-naïve and those previously treated with RET TKI	Tumor regressions were observed in both TKI-naïve and pretreated patients	
GEOMETRY mono-1 ⁷²	MET exon 14	II	MET-altered NSCLC.	Neoadjuvant/adjuvant capmatinib under investigation.	Capmatinib may expand to early-stage MET-driven NSCLC pending trial outcomes.
CodeBreak 200 ⁷³	KRAS G12C	III	Locally unresectable or metastatic KRAS G12C mut. NSCLC following progression on at least one systemic therapy, including platinum-based chemotherapy and immune checkpoint inhibitor	Sotorasib	FDA-approved sotorasib as a new standard of care option for patients with advanced stage KRAS G12C mut. NSCLC who have progressed after 1 st -line therapy.
KRYSTAL-I ⁷⁴	KRAS G12C	II/III	KRAS G12C-mutated solid tumors, including NSCLC.	Adagrasib achieved favorable objective response rate. Phase III trial is ongoing to evaluate adagrasib monotherapy vs. docetaxel in previously treated patients with KRAS G12C-mut. NSCLC.	FDA-approved adagrasib in previously treated, KRAS G12C-mutated, advanced/metastatic NSCLC.

(continued)

Table 2. Continued.

Trial/Target	Molecular Target	Phase/ Study	Patient Population	Key Findings	Recommendations
STARTRK-1 (NCT02097810)	ROS1/NTRK	II	ROS1+ NSCLC	Entrectinib improved PROs	FDA-approved for ROS1+ NSCLC; effective in brain mets.
STARTRK-2 (NCT02568267) ⁷⁵	HER2 mut.	II	Unresectable or metastatic non-squamous NSCLC who had relapsed following or were refractory to standard treatment	Trastuzumab deruxtecan (T-DXd) demonstrated clinically significant antitumor activity: progression- PFS: 8.2 months, OS: 17.8 months	T-DXd represents a potential targeted therapy for HER2 mut. NSCLC, although pulmonary toxicity warrants close monitoring
DESTINY-Lung01 ⁷⁶					
BRF113928 ^{77,78}	BRAFV600E mut.	II	BRAF V600E-mut. metastatic NSCLC	Dabrafenib and trametinib achieve ORR of 68.4% in previously treated patients and 63.9% in treatment-naïve patients and OS of 18.2 months for previously treated and 17.3 months for treatment-naïve patients.	The most frequent adverse events were pyrexia and epistaxis

(continued)

Table 2. Continued.

Trial/Target	Molecular Target	Phase/ Study	Patient Population	Key Findings	Recommendations
PACIFIC ^{79,80}	-	III	Unresectable Stage III NSCLC who had not progressed following concurrent chemoradiotherapy	Durvalumab (Imfinzi), a PD-L1 inhibitor, as consolidation therapy significantly improves both PFS and OS	While PD-L1 was not required for inclusion in the PACIFIC trial, PD-L1 expression emerged as a potentially predictive biomarker for benefit from durvalumab. FDA approved durvalumab for all eligible patients regardless of PD-L1 expression.

Abbreviations: NSCLC; non-small cell lung carcinoma, mut.; mutant, DFS; disease-free survival, PFS; progression-free survival, EGFR; epidermal growth factor receptor, TKI; tyrosine kinase inhibitor, mets; metastasis, PRO; Patient-reported outcomes, ORR; overall response rate, OS; overall survival.

spatial heterogeneity. Thus, the two approaches are complementary rather than competitive, and their integration offers the most robust strategy for precision oncology in both early-stage and advanced NSCLC.^{42,48}

Economic impact and the promise of targeted-immunotherapy synergy. The integration of comprehensive molecular profiling in NSCLC has demonstrated both clinical and economic value. By identifying patients with genomic alterations unlikely to benefit from immunotherapy, such profiling enables the avoidance of ineffective treatments and associated toxicities, leading to significant cost savings compared to limited approaches like EGFR-only testing. Furthermore, the combination of targeted therapies with immunotherapy is emerging as a promising strategy to enhance outcomes, particularly in subgroups with lower monotherapy efficacy—such as EGFR-mutant tumors. In adjuvant immunotherapy, the IMpower010 trial demonstrated that atezolizumab significantly improved DFS versus best supportive care after adjuvant chemotherapy in patients with stage II–IIIA NSCLC, particularly those with PD-L1 $\geq 1\%$, leading to its FDA approval. Similarly, PEARLS/KEYNOTE-091 evaluated pembrolizumab in the adjuvant setting and showed a DFS benefit irrespective of PD-L1 status, expanding applicability to a broader patient population.^{51,52}

Emerging biomarkers and novel therapeutic targets

The landscape of biomarker discovery in NSCLC continues to expand beyond traditional driver mutations, with NGS revealing previously unrecognized therapeutic targets and prognostic markers.

Fanconi anemia pathway. Innovative projects implementing NGS in early-stage NSCLC have identified novel genetic alterations with potential roles as biomarkers of tumor evolution and patient monitoring. Analysis of 15 surgical samples using comprehensive cancer gene panels revealed that 39.36% of genes presented frequent mutations, with significant representation of Fanconi anemia pathway mutations in 80% of analyzed patients.⁵³

NOTCH signaling pathway. Notch signaling pathway alterations have emerged as a significant area of investigation, with NOTCH3 mutations identified among the genes with highest mutation frequencies in ctDNA from early-stage patients.^{54,55} The Notch pathway's role in lung cancer development and its potential as a therapeutic target continues to be explored through ongoing clinical investigations.

NTRK gene fusions. NTRK gene fusions, though rare, represent clinically actionable oncogenic drivers that enable targeted therapy with tropomyosin receptor kinase (TRK) inhibitors when identified through comprehensive molecular profiling.⁵⁶ These fusions result from chromosomal rearrangements involving NTRK1, or NTRK3 genes, leading to constitutively activated TRK fusion proteins that promote tumorigenesis in various NSCLC histologies, including LUAD, LUSC, and neuroendocrine carcinoma,

without restriction to specific clinical features such as age, sex, or smoking history.⁵⁶ The identification of NTRK fusions in NSCLC has direct therapeutic implications, as first-generation tropomyosin receptor kinase (TRK) inhibitors—larotrectinib and entrectinib—have demonstrated high response rates and durable disease control, including in patients with central nervous system metastases.⁵⁷ These agents are now recommended as first-line treatment options for patients with advanced or metastatic NSCLC harboring NTRK fusions, offering a histology-agnostic approach to targeted therapy. Given the low frequency but high therapeutic relevance of NTRK fusions, broad molecular profiling—preferably with RNA-based NGS—is advocated for all NSCLC patients, particularly those lacking other actionable drivers.⁵⁸ This approach ensures that eligible patients are identified for precision therapy with TRK inhibitors, which can significantly improve outcomes in this otherwise challenging subset of lung cancer.

Homologous recombination repair pathway. The characterization of homologous recombination repair pathway alterations has revealed new therapeutic opportunities in NSCLC. Comprehensive genomic profiling has identified alterations in the HRR pathway, including somatic BRCA1/2 mutations in advanced NSCLC, providing treatment options with platinum agents or PARP inhibitors.⁵⁹ This represents an expansion of precision medicine approaches beyond traditional lung cancer targets.

Microsatellite instability. Tumor mutational burden (TMB) and microsatellite instability (MSI) have emerged as pivotal tumor-agnostic biomarkers guiding immunotherapy decisions in NSCLC. High TMB and MSI-high (MSI-H) status are associated with increased neoantigen load and immune responsiveness, correlating with improved outcomes to immune checkpoint inhibitors. Studies indicate that up to 16% of NSCLC patients harbor such immunotherapy-predictive genomic alterations.⁶⁰ CGP enables simultaneous assessment of these biomarkers alongside actionable driver mutations, allowing for a more nuanced understanding of each tumor's molecular landscape.⁶⁰ This integrated approach enhances patient stratification and optimizes personalized immunotherapy strategies.

The certainty of evidence across key clinical and molecular outcomes was assessed using the GRADE approach, and the findings were summarized in Table 3.

Bridging the gap—what are we still missing?

Stage-specific genomic differences. Despite recent advances in genomic profiling that revealed the molecular landscape of NSCLC, it shows that this cancer varies significantly between early-stage (operable) and stage IIIA (locally advanced) disease. There is a significant molecular difference between early-stage (I–II) and stage IIIA NSCLC. Early-stage tumors often harbor higher frequencies of KRAS and MET exon 14 skipping mutations, whereas EGFR, ALK rearrangements, and BRAF V600E mutations are more frequently observed in advanced stages.^{2,20,21} In non-metastatic subtypes, CTNNB1 mutations are enriched in LUAD, while ARID1A alterations are more common in LUSC. Stage IIIA tumors demonstrate increased TP53, KEAP1, and STK11

Table 3. GRADE evidence profile of molecular advances in NSCLC.

Outcome	Number of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Certainty	Key Reference
Detection of actionable mutations via NGS	8	Observational & RCTs	Low	Low	Low	Moderate	Unclear	Moderate	19–26
Impact of molecular profiling on DFS	10	RCTs	Low	Low	Low	Low	Low	High	32,44,47,59,62,64,69,70,76
Effectiveness of ctDNA for MRD detection	4	Prospective cohorts	Moderate	Moderate	Low	Moderate	Low	Moderate	48–50,55
Targeted therapy vs. standard care for EGFR-mut NSCLC	4	RCTs	Low	Low	Low	Low	Low	High	10, 18,62,63
Risk of resistance emergence with EGFR TKIs	7	Observational studies	Moderate	High	Low	Moderate	Unclear	Low	31,32,33,35,36,40,42

Abbreviations: GRADE; Grading of Recommendations, Assessment, Development and Evaluation, NSCLC; non-small cell lung carcinoma, NGS; next generation sequencing, DFS; disease free survival, RCT; randomized control trials, ctDNA; circulating tumor DNA, MRD; minimal residual disease, mut.; mutant, TKIs; tyrosine kinase inhibitors.

co-mutations, which are linked to immunotherapy resistance.^{7,8,26} These patterns highlight the need for stage-specific molecular profiling to guide therapeutic strategies.

Importantly, several of these alterations are already being explored in early-stage and locally advanced NSCLC clinical trials. For instance, ADAURA (NCT02511106) established the benefit of adjuvant osimertinib in resected EGFR-mutant NSCLC, while the ALINA trial (NCT03456076) demonstrated the efficacy of alectinib in ALK-positive resected tumors. Similarly, BRAF V600E-mutant NSCLC is under investigation in early-stage adjuvant settings using dabrafenib–trametinib combinations.^{27,28,31} These studies highlight that molecular profiling is not only descriptive but also directly informs trial-based therapeutic strategies in operable NSCLC.

Tumor microenvironment barriers. The tumor microenvironment (TME) significantly influences therapeutic efficacy in NSCLC, particularly in stage IIIA disease. Activated fibroblasts and elevated TGF- β levels impair the delivery and activity of EGFR TKIs. Additionally, immune exclusion, characterized by reduced CD8+ T-cell infiltration, diminishes response to checkpoint inhibitors. Hypoxia-induced resistance, mediated by HIF-1 α , further compromises the effect of agents like Osimertinib.^{31,32,33} Targeting both tumor-intrinsic and TME-mediated resistance mechanisms is therefore essential for optimizing treatment outcomes.

Recent perioperative immunotherapy trials, including CheckMate 816 (NCT02998528), have shown improved pathological response rates when immune checkpoint inhibitors are used in resectable NSCL. However, resistance patterns associated with STK11, KEAP1, and TP53 co-mutations^{7,26} underscore the importance of integrating molecular context into trial design and patient stratification.

Liquid biopsy limitations. Liquid biopsy, particularly circulating tumor DNA (ctDNA) analysis, has emerged as a promising tool for monitoring minimal residual disease (MRD) and predicting recurrence in NSCLC. However, its sensitivity is substantially reduced in early-stage disease due to lower tumor burden.^{17,18} For instance, the detection rate of EGFR mutations in plasma is significantly lower than in tissue samples, with only a minority of stage I patients exhibiting detectable ctDNA. This limitation is primarily attributable to the low fraction of tumor-derived DNA in circulation at early stages. To overcome this challenge, combining ctDNA analysis with circulating tumor cell (CTC) enumeration has been shown to enhance sensitivity. Moreover, serial ctDNA monitoring can improve the prediction of recurrence, enabling more timely therapeutic interventions.^{48,49,50} Despite these advances, the clinical utility of ctDNA in early-stage NSCLC remains constrained by technical limitations, and further research is needed to optimize its application in this setting.

Prospective studies such as TRACERx and ongoing MERMAID-1 and -2 trials (NCT04642469, NCT04642492) are evaluating ctDNA-guided adjuvant strategies, demonstrating how molecular monitoring is increasingly embedded into early-stage trial frameworks.

Limitations of molecular profiling. Despite its transformative potential, molecular profiling in early-stage NSCLC faces several limitations. Tissue sampling in small tumors often results in inadequate DNA yield, and intratumoral heterogeneity may lead to sampling bias that underestimates genomic complexity.^{17,19} Also, liquid biopsy approaches have reduced sensitivity in early disease due to the low ctDNA fraction.^{48,49,50} NGS technologies present logistical challenges, including turnaround time, interpretation of variants of uncertain significance, and disparities in access across healthcare systems.^{19,20,22} Moreover, the cost-effectiveness of universal NGS in early-stage NSCLC remains debated, particularly in low- and middle-income countries with limited infrastructure. These limitations underscore the importance of combining molecular assays with clinical and pathological risk factors to ensure accurate patient stratification.

Ongoing MERMAID trials (NCT04385368)⁶¹ are evaluating ctDNA-guided adjuvant strategies, demonstrating how molecular monitoring is increasingly embedded into early-stage trial frameworks.

Global implementation challenges. Comprehensive genomic profiling (CGP) demonstrates cost-effectiveness in high-income settings by improving quality-adjusted life years through personalized therapy. However, resource-limited regions face challenges including high cost, limited NGS infrastructure, and poor adherence to testing guidelines. These disparities necessitate strategic investment in diagnostics, capacity building, and policy reforms to achieve equitable implementation of precision oncology.

Recent advances in artificial intelligence (AI) and digital pathology are reshaping the landscape of precision oncology in NSCLC. AI-driven models trained on multi-omics data and radiogenomic features have demonstrated high accuracy in stratifying early-stage disease and predicting recurrence, complementing traditional clinicopathological risk factors.⁶² Moreover, digital pathology platforms applying spatial transcriptomics and multiplex immunohistochemistry provide unprecedented resolution of tumor heterogeneity, allowing integration of molecular and morphological biomarkers. These innovations enhance patient stratification, refine minimal residual disease (MRD) monitoring, and inform perioperative therapeutic decisions, thereby addressing critical gaps highlighted in earlier targeted therapy and immunotherapy trials.

Moreover, a recent work demonstrates that radiogenomic machine learning algorithms, combining imaging features with molecular profiling, reliably predict key oncogenic mutations and recurrence risk in early-stage NSCLC with high accuracy—highlighting their potential as non-invasive, dynamic profiling tools that complement tissue and liquid biopsy approaches.⁶³

Future directions. Emerging innovations such as spatial transcriptomics and AI-powered digital pathology offer insights into intratumoral heterogeneity and molecular subtyping.^{53,54} These tools, combined with advanced MRD monitoring^{49,50} and novel targeted agents,^{56,57,59} are poised to enhance NSCLC personalization. Ongoing translational research is crucial to overcoming therapeutic resistance and realizing the full potential of molecular strategies in early and locally advanced NSCLC.

Emerging therapeutic approaches are poised to further transform the early-stage NSCLC landscape. mRNA-based cancer vaccines, designed to elicit robust antitumor immune responses against patient-specific neoantigens, have demonstrated promising results in early-phase clinical trials.⁶⁰ Similarly, recombination-based therapies, including engineered T-cell receptor (TCR) and CAR-T strategies, are being explored for their ability to target tumor-specific mutations and neoantigens.⁶⁴ These novel modalities complement ongoing efforts to integrate multi-omic profiling, spatial transcriptomics, and artificial intelligence into clinical workflows, offering unprecedented opportunities to refine patient selection and improve outcomes. Their incorporation into perioperative settings could represent the next frontier in curative-intent precision oncology.

Collectively, the integration of targeted therapies (ADAURA, ALINA), perioperative immunotherapy (CheckMate 816), and MRD-directed strategies (TRACERx, MERMAID) provides a clinically relevant roadmap. Future studies combining NGS-based detection, spatial transcriptomics, and AI-driven risk stratification will be critical for refining precision oncology in early and locally advanced NSCLC.^{53,65,66}

In addition to molecular and technical considerations, the psychosocial dimensions of precision oncology warrant greater emphasis. Emerging survivorship studies demonstrate that genomic testing and precision-guided treatment may impose significant emotional, informational, and financial burdens on patients and families.⁶⁴ Anxiety surrounding genomic risk, expectations of targeted therapies, and uncertainty in test interpretation can exacerbate distress, particularly in resource-limited settings where access to novel agents remains inequitable. Incorporating psychosocial support, patient education, and culturally sensitive counseling into precision oncology pathways is therefore essential.

Summary and conclusion

In conclusion, the findings of this review highlight not only the expanding molecular understanding of NSCLC but also its direct translation into practical clinical algorithms for early and locally advanced disease. By linking genomic alterations and resistance mechanisms with perioperative trial evidence, the narrative underscores how molecular biology insights are increasingly shaping real-world treatment pathways for oncology practitioners. Advances in genomic and transcriptomic technologies, combined with liquid biopsy applications, have enabled the early detection of actionable alterations, the identification of resistance mechanisms, and the optimization of perioperative therapeutic strategies. Integration of biomarkers such as EGFR, ALK, KRAS, and PD-L1 into clinical practice has already reshaped standard care, while novel approaches—including mRNA vaccines, recombination therapies, and multi-omic platforms—are expanding the horizon of precision oncology. Nevertheless, challenges related to tissue sampling, heterogeneity, cost-effectiveness, and global accessibility remain. Continued translational research and equitable implementation are essential to realize the full potential of molecular advances in achieving durable cures for patients with early-stage and locally advanced NSCLC.

This review is limited by heterogeneity in included studies, differences in patient selection criteria for early-stage NSCLC, and underrepresentation of negative or

unpublished studies. Variations in molecular testing methods and reporting standards may also introduce bias. As this is a narrative synthesis rather than a meta-analysis, effect estimates were not pooled.

Acknowledgements

The author thanks Dr Ahmed Ali (AA) and Dr Sara Ahmad (SA) for assistance with literature screening, study selection, and risk-of-bias assessment. AI-assisted tools were used only for language refinement/formatting; all scientific content was developed by the author.

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Ethical considerations

This work is a systematic narrative review conducted in accordance with PRISMA guidelines and did not involve any new studies with human participants or animals performed by the authors. Hence, ethical approval was not required.

Author contributions

WA (Wael Abdo Hassan) conceived and designed the study; developed and registered the protocol; performed database searches, screening, eligibility assessment, and data extraction; conducted the qualitative synthesis and GRADE assessment; drafted and critically revised the manuscript; and approved the final version.

Declaration of conflicting interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

Data availability statement

All data generated or analyzed in this study are included in the article and its supplementary materials.

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Appendix A

Full Search Strategies by Database

Database	Search Strategy
PubMed	(("non-small cell lung cancer"[MeSH Terms] OR "NSCLC"[Title/Abstract] OR "non-small cell lung carcinoma"[Title/Abstract]) AND ("early stage"[Title/Abstract] OR "stage I"[Title/Abstract] OR "stage II"[Title/Abstract] OR "stage IIIA"[Title/Abstract] OR "locally advanced"[Title/Abstract]) AND ("molecular profiling"[Title/Abstract] OR "genomic alterations"[Title/Abstract] OR "next-generation sequencing"[Title/Abstract] OR "targeted therapy"[Title/Abstract] OR "ctDNA"[Title/Abstract] OR "liquid biopsy"[Title/Abstract] OR "precision oncology"[Title/Abstract] OR "molecular residual disease"[Title/Abstract])

(continued)

Continued.

Database	Search Strategy
Embase	AND ("2015/01/01"[Date - Publication] : "2025/04/30"[Date - Publication]) ('non small cell lung cancer'/exp OR 'non small cell lung carcinoma':ab,ti OR NSCLC:ab,ti) AND ('early stage':ab,ti OR 'stage I':ab,ti OR 'stage II':ab,ti OR 'stage IIIA':ab,ti OR 'locally advanced':ab,ti) AND ('molecular profiling':ab,ti OR 'genomic alterations':ab,ti OR 'next generation sequencing':ab,ti OR 'targeted therapy':ab,ti OR 'circulating tumor DNA':ab,ti OR 'liquid biopsy':ab,ti OR 'precision oncology':ab,ti OR 'molecular residual disease':ab,ti) AND [2015–2025]/py
Scopus	TITLE-ABS-KEY("non-small cell lung cancer" OR NSCLC OR "non-small cell lung carcinoma") AND TITLE-ABS-KEY("early stage" OR "stage I" OR "stage II" OR "stage IIIA" OR "locally advanced") AND TITLE-ABS-KEY("molecular profiling" OR "genomic alterations" OR "next-generation sequencing" OR "targeted therapy" OR "ctDNA" OR "liquid biopsy" OR "precision oncology" OR "molecular residual disease") AND PUBYEAR > 2014 AND PUBYEAR < 2026
Web of Science	TS = ("non-small cell lung cancer" OR "non-small cell lung carcinoma" OR NSCLC) AND TS = ("early stage" OR "stage I" OR "stage II" OR "stage IIIA" OR "locally advanced") AND TS = ("molecular profiling" OR "genomic alterations" OR "next-generation sequencing" OR "targeted therapy" OR "ctDNA" OR "liquid biopsy" OR "precision oncology" OR "molecular residual disease") Timespan: 2015–2025 Indexes: SCI-EXPANDED, SSCI, ESCI