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ARTICLE

The Clinical and Operational Value of Early Comprehensive NGS in Non-Small Cell Lung Cancer

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Abstract

Lung cancer remains the leading cause of cancer-related mortality worldwide, and non-small cell lung cancer (NSCLC) accounts for most cases. Advances in targeted therapies and immunotherapy have improved outcomes, but their benefit depends on timely molecular characterization. Early next-generation sequencing (NGS), performed at or near diagnosis, is increasingly used to identify actionable alterations and inform first-line and perioperative treatment planning. In this review, we examine the clinical, operational, and economic rationale for early comprehensive NGS in NSCLC. Upfront sequencing can improve diagnostic yield, preserve limited tissue, reduce turnaround time, and help avoid non-matched systemic therapy. Practical implementation strategies include Molecular Tumor Boards, low-input assays, liquid biopsy integration, and selected artificial intelligence-supported workflow tools, as well as emerging applications such as minimal residual disease monitoring. Improving access to testing and integrating it more consistently into routine care will be important to extend the benefits of comprehensive genomic profiling to a broader range of patients with NSCLC.

Keywords: non-small cell lung cancer; next-generation sequencing; comprehensive genomic profiling; circulating tumor DNA; healthcare economics; molecular tumor board; artificial intelligence; minimal residual disease.

1. INTRODUCTION

Lung cancer comprises a biologically diverse group of malignancies with distinct therapeutic vulnerabilities [1,2]. Non-small cell lung cancer (NSCLC) accounts for approximately 80% to 85% of cases [1]. Outcomes remain poor at the population level, largely because many patients present with advanced disease [1,2]. Over the past decade, molecular profiling has identified multiple oncogenic drivers that now inform treatment selection across NSCLC subtypes [5,9,10]. Broad-panel next-generation sequencing (NGS) enables simultaneous assessment of DNA and RNA and can detect point mutations, gene fusions, copy-number alterations, and selected complex variants from limited tissue samples [3,4,11]. Compared with sequential single-gene testing, comprehensive profiling improves diagnostic yield and is better suited to small biopsy specimens, where limited tissue and delayed results can compromise treatment planning [3,4,11,29].

As biomarker-matched treatment options expand in both advanced and perioperative NSCLC, molecular results are increasingly needed early in the care pathway [3,4,34,41]. When comprehensive profiling is initiated at or near diagnosis, it is more likely to inform first-line therapy, adjuvant planning, and clinical trial eligibility before treatment decisions are finalized [3,4,11,41,48]. Despite these advantages, biomarker workups remain inconsistent across practice settings, and reflex testing is still underused in many

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regions [8]. In this review, we examine the clinical, operational, and economic rationale for performing comprehensive NGS early in NSCLC, with particular attention to treatment selection, tissue stewardship, turnaround time, and implementation across diverse health systems.

2. SEARCH STRATEGY AND SELECTION CRITERIA

This narrative review used a structured literature search to evaluate the clinical, operational, and economic impact of early comprehensive genomic profiling in NSCLC. PubMed and ClinicalTrials.gov were searched for English-language publications from database inception through February 2026 using combinations of Medical Subject Headings (MeSH) and free-text terms, including "NSCLC," "lung cancer," "next-generation sequencing," "comprehensive genomic profiling," "liquid biopsy," "ctDNA," "minimal residual disease," "reflex testing," "mortality," and "cost." Priority was given to randomized trials, pivotal single-arm studies, real-world observational cohorts, implementation studies reporting operational metrics, health economic analyses, and major professional guideline statements. Preclinical studies, purely mechanistic reports, and articles focused exclusively on sequential single-gene testing without meaningful relevance to broader NGS-based strategies were excluded. The final reference set was selected on the basis of relevance to the review's central themes: early biomarker capture, treatment selection, tissue stewardship, turnaround time, and health-system impact.

3. THE CLINICAL RATIONALE: BIOMARKER CAPTURE AND PERIOPERATIVE MANAGEMENT

Early comprehensive genomic profiling does more than refine tumor classification; it can directly influence systemic therapy selection from the outset of care [3,4,11]. The clinical importance of molecular selection in advanced NSCLC has been recognized since early first-line studies showing that EGFR-mutated tumors derive greater benefit from EGFR-targeted therapy, whereas EGFR-wild-type disease fares better with chemotherapy [18]. Its relevance now extends beyond metastatic disease to resectable NSCLC, where targetable alterations remain clinically important and may affect adjuvant planning, clinical trial eligibility, and, in selected settings, neoadjuvant decision-making [41]. This broader relevance also reflects the biologic complexity of apparently localized disease. Even in resectable NSCLC, substantial intratumor heterogeneity and copy-number complexity have been linked to recurrence risk, reinforcing the limitations of relying on stage alone for postoperative risk assessment [12]. In particular, early molecular characterization is essential when considering biomarker-directed perioperative strategies such as adjuvant osimertinib in EGFR-mutated disease [3,4,34,41]. More broadly, timely profiling helps ensure that actionable alterations are identified before treatment choices are finalized [3,4,11,41]. Table 1 summarizes the diagnostic limitations of conventional testing and the practical advantages of comprehensive DNA- and RNA-based profiling.

Table 1. The Diagnostic and Clinical Impact of Comprehensive NGS versus PCR / Small Panels in NSCLC

Biomarker Category / Target	Diagnostic Gap (What PCR & Small Panels Miss)	Value of Comprehensive DNA/RNA NGS	Guideline-Matched Therapy & Key Clinical Outcome	Economic & Operational Relevance
Gene Fusions (ALK, ROS1, RET, NTRK1/2/3)	DNA-based assays or targeted PCR may miss novel fusion partners and rearrangements with complex intronic breakpoints.	RNA-based or combined DNA/RNA NGS improves detection of expressed fusions across diverse partners and breakpoint	**ALK:** Alectinib (median PFS 34.8 vs 10.9 mo; 5-year OS 62.5% vs 45.5%) [32]. **RET:** Selpercatinib (median PFS 24.8 vs 11.2 mo) [22].	Broader fusion detection may reduce missed opportunities for matched therapy; modeling studies suggest benefit from earlier CGP-

Biomarker Category / Target	Diagnostic Gap (What PCR & Small Panels Miss)	Value of Comprehensive DNA/RNA NGS	Guideline-Matched Therapy & Key Clinical Outcome	Economic & Operational Relevance
		architectures [49,50].	**ROS1:** Entrectinib (ORR 77%; median duration of response 24.6 mo) [31].	guided treatment selection [44].
Complex Mutations (EGFR ex20ins, MET ex14 skipping)	Hotspot PCR panels may miss heterogeneous EGFR exon 20 insertion variants and diverse MET exon 14 splice-site alterations [51,52].	Medium-sized or comprehensive NGS captures a broader spectrum of EGFR exon 20 and MET exon 14 alterations in one assay [51,52].	**EGFR ex20ins:** Amivantamab plus chemotherapy (median PFS 11.4 vs 6.7 mo) [16]. **MET ex14:** Capmatinib (ORR 68% in previously untreated disease) [20].	Broad upfront testing may reduce sequential retesting, repeat biopsy burden, and delays associated with stepwise workups [37,44].
Prognostic Co-mutations (STK11, KEAP1, TP53)	Small, targeted assays often focus on actionable oncogenes and may omit co-mutations relevant to prognosis or treatment response.	Broad profiling characterizes co-mutation patterns that may refine prognosis and anticipated benefit from standard immunotherapy [41].	No directly matched targeted therapy; primary value is prognostic stratification and treatment-context interpretation.	Avoiding ineffective immunotherapy in resistant molecular subsets may reduce downstream cost and unnecessary treatment exposure [44].
Emerging & Rare Targets (HER2/ERBB2, KRAS G12C, BRAF V600E)	Sequential single-gene testing across multiple low-frequency targets can exhaust limited tissue and prolong time to complete molecular characterization.	Multiplex low-input profiling allows parallel testing from restricted specimens, including small biopsies and cytology-derived material [45].	Supports identification of less common actionable alterations and eligibility for biomarker-directed clinical trials and approved targeted therapies when applicable [4,10].	Comprehensive profiling combined with Molecular Tumor Board review was associated with higher targeted-therapy eligibility in one NSCLC analysis [38].

Abbreviations: *CGP, comprehensive genomic profiling; DNA, deoxyribonucleic acid; NGS, next-generation sequencing; ORR, objective response rate; OS, overall survival; PCR, polymerase chain reaction; PFS, progression-free survival; RNA, ribonucleic acid.*

The diagnostic advantages summarized in Table 1 are clinically most apparent in driver classes that are structurally complex or highly heterogeneous, where delayed or sequential testing may miss opportunities for early biomarker-matched therapy [49-52]. Early broad DNA/RNA next-generation sequencing (NGS) is therefore particularly important in NSCLC because several clinically actionable alterations are incompletely captured by sequential single-gene testing approaches [48-52]. In real-world advanced NSCLC, obtaining comprehensive genomic profiling before first-line treatment increased matched targeted therapy use and decreased ineffective immune checkpoint inhibitor exposure in driver-positive disease, supporting the importance of having complete molecular results available before treatment selection is made [48]. Beyond its role in guiding initial therapy, the ultimate survival impact of broader genomic testing in advanced NSCLC remains an area of active debate. Real-world and prospective observational studies suggest that

comprehensive genomic profiling may be associated with improved overall survival, particularly when broader testing increases detection of actionable biomarkers and receipt of matched therapy [17,27]. However, other propensity-matched cohorts comparing NGS with routine EGFR/ALK testing have not shown a significant median overall survival advantage overall, despite signals for improved short-term survival [7]. Taken together, current evidence suggests that any survival benefit from NGS is likely mediated by earlier identification of actionable alterations and access to matched therapy, rather than by the testing platform alone [7,17,27]. This broader diagnostic yield can also expand treatment options beyond routine local testing; in the ATLAS study, centralized comprehensive NGS increased detection of druggable alterations from 7.9% to 25.9% and identified additional clinical trial opportunities in advanced NSCLC [25]. Beyond the more common drivers discussed above, comprehensive profiling can also identify less frequent actionable alterations such as HER2 mutations, KRAS G12C, and BRAF V600E, for which agents such as trastuzumab deruxtecan, sotorasib or adagrasib, and dabrafenib plus trametinib have demonstrated clinically meaningful activity in metastatic NSCLC [19,23,24,26]. This distinction is important because the clearest clinical value of early NGS lies in driver classes for which broader testing improves detection and directly influences treatment selection. For ALK, ROS1, and RET fusions, multiplex NGS is advantageous because current practice increasingly favors RNA-based or combined DNA/RNA approaches, which provide broader detection across fusion partners and breakpoint architectures than narrower single-analyte strategies [49]. This limitation is clinically relevant even in cytology-based specimens, where RNA-based NGS identified actionable EML4::ALK and SLC34A2::ROS1 fusions that were not detected by the corresponding FISH assays, directly illustrating what sequential or orthogonal single-target testing can miss [50].

A similar argument applies to EGFR exon 20 insertions and MET exon 14 skipping, both of which comprise highly diverse alteration classes that are not reliably captured by narrow hotspot-based approaches alone [51,52]. In a pooled analysis of 636 NSCLC cases with EGFR exon 20 insertions, 104 unique variants were identified, and currently available PCR assays would have detected only 11.8% to 58.9% of cases, indicating that a substantial proportion of patients may be missed without broader NGS-based testing [51]. MET exon 14 alterations are likewise diverse, with Frampton et al identifying 221 cases containing 126 distinct sequence variants and concluding that this diversity necessitates comprehensive genomic profiling for clinical detection [52]. Early identification is clinically consequential because matched therapy yields substantial benefit once these drivers are recognized, including median progression-free survival of 34.8 versus 10.9 months and a 5-year overall survival rate of 62.5% versus 45.5% with first-line alectinib versus crizotinib in ALK-positive NSCLC, an objective response rate of 77% with median duration of response of 24.6 months with entrectinib in ROS1 fusion-positive disease, median progression-free survival of 24.8 versus 11.2 months with selpercatinib in RET fusion-positive NSCLC, median progression-free survival of 11.4 versus 6.7 months with amivantamab plus chemotherapy in EGFR exon 20 insertion-positive disease, and an objective response rate of 68% in previously untreated patients with capmatinib in MET exon 14-altered NSCLC [16, 20, 22, 31, 32]. Collectively, these findings support performing broad NGS at diagnosis rather than waiting for sequential negative testing, because delayed or incomplete profiling may postpone recognition of alterations for which biomarker-matched therapy offers substantial clinical benefit [48-52].

4. EVOLVING DIAGNOSTIC MODALITIES: TISSUE STEWARDSHIP AND LIQUID BIOPSY

The clinical value of comprehensive profiling depends in part on the quality and quantity of diagnostic material available for testing [29, 33, 45]. In advanced NSCLC, many diagnoses are established from fine-needle aspirates or small core biopsies, which increases the risk of quantity-not-sufficient errors when tissue is consumed by sequential testing [29,45]. Delaying broad profiling until after multiple single-gene assays can increase sample exhaustion, assay failure, and the need for repeat procedures [29]. More recent low-input platforms suggest that small cytology and biopsy specimens do not necessarily preclude comprehensive testing, with multiplex DNA/RNA assays now feasible using very limited material [45]. Real-world data from Japan also suggest that increasing use of multiplex panel testing may shorten time to treatment in routine practice, with time to treatment decreasing over time after implementation of an NGS-based companion

diagnostic panel [28]. By shortening turnaround time and preserving limited samples, these approaches allow residual cytology specimens, including FNA rinses and pleural effusions, to be used as primary molecular material rather than reserve tissue [45].

Plasma-based NGS provides an important complementary option when tissue is limited, unsafe to obtain, or unavailable within a clinically acceptable timeframe [34,35,39]. In addition to improving feasibility in such settings, liquid biopsy can identify spatial heterogeneity and emergent resistance mechanisms that may not be fully represented in a single tissue sample [36,41]. ctDNA-based approaches are also being explored in earlier-stage disease, including postoperative minimal residual disease monitoring and relapse-risk assessment, where tumor-informed phylogenetic profiling has identified relapse before conventional imaging in some patients [13,41]. However, plasma testing depends on tumor shedding, and false-negative results remain a recognized limitation in patients with low-volume or early-stage disease [37,41]. For patients with limited tissue or urgent treatment needs, plasma NGS can help accelerate molecular characterization [6,34,39]. However, negative plasma results should be interpreted cautiously and followed by tissue-based testing when clinically feasible [37,45]. This complementary role is clinically relevant because actionable alterations such as MET exon 14 skipping can be identified through either liquid- or tissue-based testing and still inform matched therapy selection [21].

5. HEALTH ECONOMICS: TURNAROUND TIME, PAYER VALUE, AND GLOBAL HETEROGENEITY

While comprehensive NGS offers clear clinical advantages, its upfront cost remains a major barrier to implementation, particularly in resource-constrained settings and health systems with limited reimbursement support [46,47]. On a per-test basis, single-gene PCR assays are less expensive. However, evaluating diagnostic costs in isolation can underestimate the broader economic consequences of sequential testing, including delayed treatment decisions, repeat biopsies, and additional workflow inefficiencies [14,37,44]. In this context, the relevant comparison is not simply assay price, but the total downstream cost of the diagnostic and treatment pathway [37,44]. A microsimulation analysis from the Netherlands similarly found that parallel DNA/RNA NGS was diagnostically superior to sequential single-gene testing, detected additional actionable aberrations, and remained cost-effective after inclusion of treatment costs and long-term outcomes [15]. A recent global micro-costing study likewise found that NGS became less costly than single-gene testing when the number of biomarkers tested was sufficiently high, with cost savings emerging at approximately 10 to 12 biomarkers in standardized models of advanced nonsquamous NSCLC [43].

The economic value of early NGS also depends on its effect on treatment selection. By identifying actionable driver alterations upfront, comprehensive profiling can reduce the use of non-matched systemic therapy and may help avoid ineffective first-line immune checkpoint inhibitor treatment in molecular subsets less likely to benefit, such as tumors with certain driver alterations or resistance-associated co-mutations [41]. Cost-utility analyses suggest that upfront medium-sized or comprehensive NGS strategies can be economically favorable within the first year of care, with savings driven by fewer sequential assays, reduced re-biopsy requirements, and more appropriate use of targeted therapy pathways [15,37,44,46]. These findings support a broader view of diagnostic value that extends beyond initial assay acquisition costs. However, cost-effectiveness is not uniform across health systems; for example, a Thai cost-utility analysis found that sequential NGS identified more biomarker-positive patients and improved survival outcomes but was not cost-effective compared with single EGFR testing at the local willingness-to-pay threshold [42]. This variability may be especially relevant when designing reimbursement policies and resource-stratified implementation models across diverse health systems [42,46,47].

6. SYSTEMIC IMPLEMENTATION: MOLECULAR TUMOR BOARDS AND AI-SUPPORTED WORKFLOW

Translating complex genomic results into treatment decisions requires supporting clinical infrastructure,

not just assay availability. Molecular Tumor Boards (MTBs) can help interpret uncommon alterations, prioritize off-label options, and identify relevant clinical trials when routine reporting alone is insufficient [30,38]. Despite concerns about the resource intensity of these multidisciplinary discussions, observational data indicate that the direct cost of MTB review represents only a small fraction of the overall diagnostic pathway, accounting for approximately 2% to 3% of total diagnostic journey cost in one analysis [38]. In NSCLC, comprehensive panels followed by MTB discussion have been associated with higher rates of targeted therapy eligibility than smaller targeted panels, while also supporting referral to off-label treatments and clinical trials [38,41].

At the same time, routine NGS generates a growing documentation burden, including biomarker extraction, terminology standardization, and longitudinal tracking across pathology reports and clinical records. In this setting, artificial intelligence (AI) may serve as a workflow support tool rather than a substitute for expert review [40,41]. Early pilot data show that large language model-based systems can extract and standardize biomarker information from unstructured pathology reports with high accuracy [40]. In one independent Dutch NSCLC cohort of more than 4,000 patients, a fine-tuned model achieved a micro F1 score of 0.95 and correctly standardized 98.7% of KRAS mutation notation [40]. These tools may improve audit capacity and reporting consistency, but their clinical role still depends on prospective validation, local oversight, and integration into existing multidisciplinary workflows [40,41].

7. CONCLUSION

The expanding use of biomarker-matched therapies in NSCLC has made timely molecular testing increasingly important. Compared with sequential single-gene approaches, upfront comprehensive NGS is better positioned to identify actionable drivers early enough to influence first-line and perioperative treatment planning. Tissue-based and plasma-based assays should be viewed as complementary rather than competing strategies, with the optimal approach determined by disease stage, tissue availability, and clinical urgency. Successful implementation, however, depends not only on assay performance but also on the surrounding infrastructure, including access to Molecular Tumor Boards, efficient reporting systems, and reimbursement pathways that support timely profiling. Taken together, the available evidence supports early comprehensive NGS as an increasingly important component of contemporary NSCLC care, while highlighting the need for broader access and context-specific implementation across diverse health systems.

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