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MICROBIOME-GUIDED PRECISION ONCOLOGY IN NON-SMALL CELL LUNG CANCER (NSCLC): BIOMARKERS AND MODIFIABLE TARGETS

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ABSTRACT – Non-small cell lung cancer (NSCLC) remains the most frequently diagnosed malignancy and the leading cause of cancer-related death worldwide. Although targeted therapies for actionable alterations and immune checkpoint inhibitors (ICIs) have improved outcomes, clinical benefit is highly heterogeneous, with frequent primary non-response and early acquired resistance. This unmet need has intensified the search for robust prognostic factors and predictive biomarkers. The human microbiota has emerged as a relevant candidate within this landscape, given its central role in immune modulation, systemic inflammation, epithelial barrier integrity, and the production of bioactive metabolites. Increasing evidence supports a gut-lung axis in NSCLC, with dysregulated intestinal and airway microbial profiles associated with aggressive phenotypes, metastatic patterns, and survival endpoints. Mechanistically, dysbiosis may influence tumor progression and therapy response through microbe-associated molecular pattern signaling and metabolite-driven effects on antigen presentation, interferon pathways, and regulatory T-cell balance, ultimately reshaping the tumor microenvironment. In immunotherapy, baseline gut microbiome features and iatrogenic perturbations have been linked to reduced ICI efficacy, while microbiota-restoring strategies such as fecal microbiota transplantation can rescue anti-PD-1 activity in translational models. Importantly, emerging data extend the relevance of the microbiome to oncogene-addicted NSCLC: baseline fecal signatures have been associated with the efficacy and gastrointestinal toxicity of Epidermal Growth Factor Receptor-tyrosine kinase inhibitors (EGFR-TKIs), and experimental microbiota perturbation can suppress EGFR-TKIs' antitumor effects, whereas microbiota-supporting interventions may enhance response. Despite promising signals, inter-study variability and confounding exposures limit comparability. This narrative short review is based on a non-systematic search of PubMed/MEDLINE, Embase, and Scopus focused on NSCLC microbiome/gut-lung axis and outcomes with ICIs and EGFR-TKIs. Prospective, well-controlled multi-omics studies integrating microbiome, metabolome, immune profiling, and rigorous clinical annotation are needed to validate actionable signatures and define microbiota-informed strategies to optimize NSCLC treatment.

KEYWORDS: Microbiota, Non-small cell lung cancer, Target therapy, Immunotherapy.

INTRODUCTION

Non-small cell lung cancer (NSCLC) still holds a sobering record worldwide, remaining the most frequently diagnosed malignancy and the leading cause of cancer-related death, with nearly 2.5 million new cases reported in 2022[1]. Over the last decade, major therapeutic advances have reshaped the management of this disease[2]. In particular, the identification of actionable genomic alterations, such as Epidermal Growth Factor Receptor (EGFR) mutations and Anaplastic Lymphoma Kinase (ALK) or ROS1 rearrangements, has enabled the use of targeted therapies that have substantially improved survival outcomes[3,4]. In parallel, immunotherapy, especially immune checkpoint inhibition, has revolutionized the treatment of several solid tumors, including NSCLC[5,6]. Despite these successes, however, clinical benefit remains heterogeneous: a significant proportion of patients fail to respond, and many who initially respond develop early resistance[7]. This reality highlights an urgent and growing unmet need, one that has expanded alongside the progress of targeted therapy and immunotherapy, to define robust prognostic factors and, above all, reliable predictive biomarkers[8]. In this context, the microbiota is increasingly being considered as a meaningful contributor to the biomarker landscape. This vast ecosystem, with which the human body coexists and continuously interacts, has been recognized for decades; only more recently, however, has attention focused on its role in systemic and severe diseases, including cancer[9-11]. The human microbiota comprises a complex community of microorganisms, predominantly bacteria, but also viruses and fungi, distributed throughout the body in a near-ubiquitous manner. The gastrointestinal tract represents the largest and most densely populated microbial niche[12]. Notably, specific members of the gut microbiota (e.g., *Fusobacterium nucleatum*) can act as pathobionts: organisms that are typically commensal but, under stress-inducing conditions such as oxidative stress or inflammation, may acquire pathogenic traits that favor tumor initiation and progression[13]. The microbiota contributes to host homeostasis through multiple, interconnected mechanisms, including immune modulation and the production of bioactive metabolites[14]. Given this extensive host-microbe crosstalk, it has been hypothesized that disruption of a healthy microbial ecosystem, commonly referred to as dysbiosis, may contribute to primary resistance and acquired resistance to cancer therapies, including both targeted agents and immunotherapy[15]. Understanding these interactions and identifying microbiota- and metabolite-based signatures associated with response could therefore open new avenues for biomarker development and, potentially, therapeutic personalization in NSCLC. This article is a short narrative review aimed at summarizing and conceptually integrating current evidence on the role of the gut and lung microbiota in NSCLC biology and in treatment outcomes. A non-systematic literature search was performed in PubMed/MEDLINE, Embase, and Scopus using combinations of keywords including "non-small cell lung cancer", "NSCLC", "microbiome", "microbiota", "gut-lung axis", "lung microbiota", "immune checkpoint inhibitors", "EGFR", and "tyrosine kinase inhibitors". Studies were prioritized based on relevance to: (1) NSCLC patient cohorts linking microbiome features with prognosis or response/toxicity to ICIs or EGFR-TKIs; (2) translational and mechanistic studies supporting causal pathways (immune modulation, metabolites, barrier integrity); and (3) reports addressing airway/lung microbiota signatures in NSCLC.

ROLE OF MICROBIOTA IN NSCLC

Evidence[16] has established that specific members of the gut microbiota can actively contribute to carcinogenesis, particularly in gastrointestinal tract tumors. Increasing evidence now suggests that a gut-lung axis may also be relevant in lung cancer, although this relationship is complex, multifactorial, and influenced by host factors[17], tumor biology, and treatment exposure[18]. In particular, several host-related factors can markedly shape microbiome composition and, if not carefully accounted for, may blur or even inflate the observed associations with prognosis or treatment outcomes in NSCLC. Smoking history is a major example: beyond the simple distinction between current, former, or never smokers, cumulative exposure (pack-years) can influence both oral-airway and gut microbial communities[19]. Diet represents another key driver, since habitual patterns, such as fiber intake, fat quality and quantity, and alcohol consumption, can directly affect microbial metabolism, including short-chain fatty acid production and downstream metabolic signaling[20,21]. Likewise, body mass index (BMI) and overall metabolic status (for instance, obesity or insulin resistance) can shift inflammatory tone and microbial ecology, potentially acting as hidden modifiers of microbiome-outcome relationships[22]. Systemic corticosteroids are also relevant because they can alter immune activation and, in turn, microbial diversity and stability[23]. In real-world oncology practice, prior treatment lines and the broader therapeutic history (chemotherapy, radiotherapy, earlier ICIs or TKIs), together with cumulative exposure to supportive medications, may further perturb the microbiota and complicate cross-study comparisons[24]. Finally, geographic variation should not be underestimated: population-level differences in base-

line microbiome structure, driven by diet, environment, and lifestyle, can substantially affect reproducibility across cohorts from different regions[25]. In patients with lung cancer, compositional shifts have been reported in both pulmonary and intestinal microbial communities, including increased relative abundances of *Bacteroidetes*, *Fusobacteria*, *Cyanobacteria*, and *Spirochaetes*, alongside a reduction in *Firmicutes*. Importantly, analyses of both gut and respiratory tract microbiota indicate a measurable dysregulation in NSCLC, and some studies have linked these alterations to more aggressive phenotypes, including an association with distant metastasis[26-30]. Mechanistically, the pathogenic contribution of the gut microbiome to NSCLC is thought to arise primarily through modulation of chronic inflammation and immune dysfunction, mediated not only by microbial components but also by microbiota-derived metabolites[31]. Microbe-associated molecular patterns (MAMPs) can engage pattern-recognition receptors (e.g., TLRs and NOD-like receptors) on epithelial and immune cells, promoting cytokine release and shaping systemic inflammatory tone. In parallel, microbial metabolites, including short-chain fatty acids (SCFAs), secondary bile acids, and tryptophan-derived compounds, can influence epithelial barrier integrity, antigen presentation, and the differentiation and function of immune subsets (e.g., regulatory T cells, Th1/Th17 polarization, and cytotoxic CD8+ T-cell activity). Dysbiosis may therefore foster a pro-tumorigenic milieu by enhancing myeloid-driven immunosuppression, skewing macrophage polarization toward tumor-promoting phenotypes, increasing systemic inflammatory cytokines, and impairing effective T-cell priming and trafficking, ultimately reshaping the tumor microenvironment in ways that favor progression and dissemination[32]. A multi-omics study integrating serum metabolomics with fecal microbiome profiling identified candidate biomarkers in early-stage NSCLC, supporting the translational relevance of these pathways[33]. Given the intimate interplay between the gut microbiota and the immune system, it has been hypothesized that microbiome composition may also influence response to immunotherapy, particularly immune checkpoint inhibitors (ICIs), which represent a cornerstone of NSCLC treatment[34]. Proposed mechanisms include microbiota-driven enhancement (or impairment) of dendritic cell maturation and antigen presentation, regulation of interferon signaling, modulation of effector-to-regulatory T-cell balance, and metabolite-mediated tuning of T-cell fitness and exhaustion states[35]. Nonetheless, the molecular details of these host-microbe interactions are not yet fully elucidated, and inter-study variability remains substantial. In this evolving field, several Gut Onco-Microbiome Signatures (GOMS) have been proposed as potential prognostic and predictive markers across cancer types. Preliminary evidence suggests that patients more likely to benefit from ICIs often exhibit a gut microbiota profile closer to a "healthy-like" GOMS[36]; however, the biological and clinical implications of this association require rigorous validation in larger, well-controlled cohorts. Consistent with a functional role for dysbiosis in treatment outcomes, multiple studies[15,37] have reported that concomitant medications known to perturb microbiota, most notably antibiotics and proton pump inhibitors (PPIs), may be associated with reduced immunotherapy efficacy, including evidence emerging from meta-analytic evaluations of PPIs exposure. Importantly, emerging evidence[38,39] suggests that gut microbiota may play a role both in mutant EGFR-driven lung carcinogenesis and in shaping treatment outcomes in oncogene-addicted NSCLC treated with targeted therapy. Preclinical data[38] supports the idea that mutant EGFR-driven lung carcinogenesis itself can be accompanied by reproducible gut dysbiosis. In a lung-specific conditional EGFR-mutant transgenic mouse model, serial stool sampling before tamoxifen (baseline), after induction of mutant EGFR expression, and at lung tumor appearance showed that microbiota diversity increased as tumors emerged[38]. Taxonomically, the tumor stage was characterized by significant increases in families such as *Lachnospiraceae* and *Ruminococcaceae*, alongside significant decreases in *Lactobacillaceae*; notably, *Lactobacillus spp.* were relatively abundant at baseline but were depleted with lung tumor occurrence[38]. In a recent study[39], baseline fecal profiling in treatment-naïve patients with EGFR-mutant NSCLC receiving first-line EGFR-tyrosine kinase inhibitors (EGFR-TKIs) suggested associations with both tolerability and efficacy. Higher α-diversity was observed in patients with no/mild diarrhea *vs.* those with more severe diarrhea, β-diversity differed according to best overall response, and *Ruminococcus* was enriched among responders, supporting gut microbiota features as candidate biomarkers of EGFR-TKI activity and toxicity[39]. In parallel to gut dysbiosis, the lung microbiota itself appears highly heterogeneous and spatially structured, with distinct community compositions across different lung regions within the same individual. In this context, Liu et al[40] compared microbiota profiles across healthy lung tissue, non-tumor lung tissue on the same side as the cancer, and healthy lung tissue on the contralateral side in patients with lung cancer, reporting a stepwise decline in α-diversity across these compartments. Notably, taxa such as *Staphylococcus* and *Dialister* were most abundant in healthy lung tissue and progressively decreased in contralateral healthy tissue and then in ipsilateral lung tissue adjacent to the tumor, suggesting that disruption of the local microbial ecological balance may accompany, and potentially contribute to, lung cancer development and progression. Beyond spatial gradients, microbial composition has also been linked to prognosis and metastatic patterns: patients with advanced lung cancer showed a relatively higher abundance of *Thermus*, while *Legionella* was more abundant

in patients with metastatic disease[40]. Additional evidence indicates that specific airway taxa may mark organ-specific dissemination; for example, increased *Pseudomonas* abundance has been reported in patients with lung cancer and brain metastasis[41]. Consistent with these observations, Peters et al[42] performed 16S rRNA gene sequencing on paired lung tumor and distal normal tissue samples from patients with NSCLC and found prognostically relevant differences within the "normal" compartment. A higher abundance of *Koribacteraceae* in distal normal lung tissue was associated with improved recurrence-free survival (RFS) and disease-free survival (DFS), whereas greater abundances of *Bacteroidaceae, Lachnospiraceae*, and *Ruminococcaceae* correlated with poorer RFS and DFS[42]. Collectively, these findings support the concept that airway and lung microbiota signatures may function as prognostic indicators in lung cancer, complementing gut-based biomarkers and underscoring a multi-compartment host-microbe interplay along the gut-lung axis (Table 1).

Table 1. Microbiome-related evidence in NSCLC treated with ICIs or EGFR-TKIs.

Type of therapy	Study	Compartment	Microbiome exposure/ signal	Association with outcomes
ICIs	Boesch, 2021[28]	Local/tumor lung	Tumor-associated microbial signatures	Linked to response to checkpoint blockade (predictive signal from local lung compartment).
	Ciappina, 2025[16]	Indirect (PPI exposure)	PPIs as microbiome-perturbing co-medication	PPI exposure associated with worse PFS/OS in ICI-treated cancer cohorts
	Crespin, 2023[45]	Indirect (antibiotics exposure)	Antibiotics as microbiome-perturbing co-medication	Antibiotic exposure associated with worse clinical outcomesunder ICIs
	Thomas, 2023[38]	Gut	GOMS (community-level signatures)	Proposes signature-based biomarkers for ICI benefit; emphasizes validation/ portability requirements.
EGFR-TKIs	Kim, 2026[40]	Gut	Dysbiosis emerging with EGFR-driven tumor development (↑ Lachnospiraceae/ Ruminococcaceae; ↓ Lactobacillaceae; diversity changes)	Supports a tumor–microbiome couplingin EGFR-driven carcinogenesis (biological plausibility for microbiome relevance in EGFR-addicted NSCLC).
	Tabe, 2025[41]	Gut	Baseline diversity/taxa (e.g., Ruminococcus in responders)	Baseline microbiome features associated with EGFR-TKI efficacy (best overall response) and GI toxicity (diarrhea severity).

EGFR-TKIs, Epidermal Growth Factor Receptor- tyrosine kinase inhibitors; GI, gastrointestinal; GOMS, Gut Onco-Microbiome Signatures; ICIs, immune checkpoint inhibitors; NSCLC, non-small-cell lung cancer; PPIs, proton pump inhibitors. ↑ Higher; ↓ Lower.

MICROBIOTA MODULATION TO IMPROVE RESPONSE RATES

Given the growing link between gut dysbiosis and clinical outcomes in NSCLC, microbiota modulation is increasingly explored as a strategy to enhance treatment efficacy and mitigate toxicity along the gut-lung axis. Mechanistically, both gut and airway microbial ecosystems can shape tumor biology and anti-tumor immunity by calibrating inflammatory tone, cytokine networks, antigen presentation, interferon signaling, effector T-cell fitness, and checkpoint activity. In the immunotherapy setting, seminal clinical evidence showed that baseline gut microbiome composition and prior antibiotic exposure correlate with poorer outcomes to PD-1 blockade, while enrichment in "beneficial" taxa and restoration of eubiosis can rescue anti–PD-1 activity in preclinical models. Notably, fecal microbiota transplantation

(FMT) from clinical responders reinstated sensitivity to PD-1 blockade, supporting a causal role for the microbiome in ICI efficacy[43,44]. Accordingly, proposed interventions span multiple layers: (1) avoidance of iatrogenic dysbiosis (e.g., minimizing unnecessary antibiotics and carefully evaluating PPIs); (2) dietary optimization (higher fiber intake to favor SCFA-producing taxa, strengthen epithelial barrier function, and improve systemic immune homeostasis); (3) prebiotics/probiotics/synbiotics aimed at restoring eubiosis and attenuating pro-tumor inflammation; and (4) FMT to re-establish a "responder-like" microbial ecosystem, an approach conceptually supported by ICI translational studies[43-45]. Beyond diet, lifestyle modifiers are increasingly viewed as biologically plausible co-adjuvants: geographic provenance and habitual dietary patterns shape microbiome composition; high meat/fat intake has been correlated with increased lung cancer risk, while lipid-derived metabolites may exert divergent effects (ω6 polyunsaturated fatty acids promoting pro-inflammatory phenotypes *vs.* ω3 fatty acids showing anti-proliferative/pro-apoptotic activity in lung cancer models via redox/autophagy pathways), and physical activity may enhance microbiome diversity, reduce gut permeability, and dampen inflammation/oxidative stress, processes relevant to carcinogenesis and treatment tolerance[45]. For EGFR-targeted therapy, preclinical longitudinal evidence in lung adenocarcinoma models shows that altering the gut microbiota can causally influence EGFR-TKI activity: in PC-9 tumor-bearing mice, antibiotic perturbation suppressed gefitinib antitumor efficacy, whereas combining gefitinib with probiotics or Traditional Chinese Medicine improved outcomes (tumor burden and related readouts), with mediation analyses identifying microbiome features that regulate gefitinib's antitumor effect[46].

CONCLUSIONS

Available data[32] supports a clinically meaningful interplay between gut microbiota, systemic immunity, and lung cancer biology. In NSCLC, dysbiosis has been associated with aggressive phenotypes, inflammatory signatures, and differential responses to immune checkpoint blockade. Emerging evidence[39] now extends this concept to oncogene-addicted disease: clinical fecal profiling suggests that baseline community structure may correlate with EGFR-TKI efficacy and gastrointestinal toxicity. These findings position the gut microbiota as both a potential biomarker and a modifiable factor that could be leveraged to improve outcomes. However, the field remains limited by inter-study variability, confounding exposures (diet, antibiotics, PPIs), and incomplete mechanistic resolution. The next step is the execution of well-controlled, prospective, multi-omics trials integrating microbiome, metabolome, host immune profiling, and rigorous clinical annotation to determine whether microbiota signatures are causal, predictive, and actionable. If validated, microbiota-informed treatment algorithms could become a practical component of precision oncology, complementing genomic profiling to optimize both efficacy and tolerability of ICIs and targeted therapies.

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