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THE REGULATORY ROLE AND THERAPEUTICAL POTENTIAL OF NON-CODING RNAS IN LUNG CANCER- A REVIEW

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Abstract

Non-coding RNAs (ncRNAs), including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), have emerged as critical regulators of gene expression and key players in lung cancer pathogenesis. These molecules play pivotal roles in various aspects of lung cancer development, progression, metastasis, and resistance to therapy, presenting unprecedented opportunities for diagnostic and therapeutic innovation. This comprehensive review synthesizes current knowledge on the regulatory role and therapeutic potential of ncRNAs in lung cancer, with emphasis on molecular mechanisms, clinical applications, and future therapeutic strategies. A systematic analysis of the functional roles, molecular mechanisms, and clinical significance of ncRNAs in lung cancer was conducted, integrating evidence on miRNA biogenesis, lncRNA regulatory functions, and circRNA biological activities. The review examined dysregulated ncRNA signatures, their involvement in key oncogenic pathways, and emerging therapeutic approaches. Therapeutic strategies include miRNA mimics and inhibitors (antagomiRs), lncRNA-targeted therapies, and circRNA-modulating approaches. Early pre-clinical studies demonstrate that synthetic miRNA-based therapeutic molecules with protective coating approaches enable efficient delivery and anti-tumor activity. LncRNAs are highly stable in circulation, presenting opportunities for non-invasive early-stage cancer diagnostic tools. ncRNA profiling enables personalized medicine through patient stratification and treatment selection.

INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality worldwide, accounting for approximately 1.8 million deaths annually and representing roughly 18% of all cancer deaths. The disease is characterized by remarkable heterogeneity in histological subtypes, molecular profiles, and clinical presentations, making it one of the most challenging malignancies to treat. Non-small cell lung cancer (NSCLC) comprises approximately 85% of all lung cancer cases, while small cell lung cancer (SCLC) accounts for the remaining 15%. Despite advances in targeted therapies and immunotherapy, the five-year survival rate for lung cancer patients remains disappointingly low, ranging from 15-20% across all stages and subtypes.[1]

Recent advances in genomic and transcriptomic technologies have revealed the pivotal role of non-coding RNAs (ncRNAs) in lung cancer development, progression, and therapeutic resistance. Non-coding RNAs are functional RNA molecules that do not encode proteins but regulate gene expression at multiple levels,

including transcriptional, post-transcriptional, and epigenetic control. The most extensively studied classes of ncRNAs include microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), each possessing distinct biogenesis pathways, structural features, and regulatory mechanisms. The discovery that ncRNAs constitute more than 90% of the human transcriptome has fundamentally transformed our understanding of gene regulation and disease pathogenesis.[2]

The therapeutic potential of ncRNAs in lung cancer extends beyond their basic biological roles. miRNAs can function as either tumor suppressors or oncogenes, depending on their target genes and cellular context. lncRNAs have been demonstrated to regulate crucial oncogenic processes including epithelial-mesenchymal transition (EMT), metastasis, and chemotherapy resistance through various molecular mechanisms. circRNAs, with their unique structural properties including covalent closure and extraordinary stability, present novel opportunities for therapeutic intervention and serve as exceptional biomarkers for disease monitoring. These ncRNAs operate within complex regulatory networks, including competing endogenous RNA (ceRNA) networks, where they compete for miRNA binding and modulate the expression of cancer-related genes.[3]

The clinical significance of ncRNA research in lung cancer cannot be overstated. Dysregulated expression of specific ncRNAs has been associated with poor prognosis, advanced disease stage, and increased resistance to conventional treatments including chemotherapy, tyrosine kinase inhibitors (TKIs), and immunotherapy. Furthermore, ncRNAs exhibit remarkable tissue-specific and disease stage-specific expression patterns, making them potentially superior biomarkers compared to protein-based markers. The stability of circulating ncRNAs in body fluids such as serum and plasma has enabled the development of non-invasive liquid biopsy approaches for early detection, prognosis assessment, and real-time monitoring of treatment response.[4]

The delivery of RNA-based therapeutics remains the final frontier. Leveraging the technology behind mRNA vaccines, researchers are developing lung-targeted lipid nanoparticles (LNPs) and engineered exosomes to deliver therapeutic ncRNAs directly to the pulmonary system. While off-target effects and systemic stability remain hurdles, the high specificity of ncRNA interactions suggests a future where "undruggable" oncogenic drivers can finally be silenced. As our mapping of the non-coding genome becomes more granular, these molecules will likely transition from laboratory curiosities to the cornerstone of precision oncology in lung cancer.[5]

LITERATURE REVIEW

Suri et al., 2024, published a comprehensive review on non-coding RNAs as biomarkers in lung cancer, synthesizing evidence on the roles of miRNAs, lncRNAs, and circRNAs in cancer pathogenesis, particularly emphasizing their potential for early diagnosis, prognostication, and prediction of therapeutic response. The authors demonstrated that ncRNAs regulate critical biological processes including tumor initiation, progression, metastasis, and resistance to therapy. They highlighted recent advances in ncRNA-based diagnostic tools and therapeutic strategies, including miRNA mimics and inhibitors, lncRNA-targeted therapies, and circRNA-modulating approaches, offering promising avenues for personalized medicine in lung cancer management.[6]

Pan et al., 2021, examined epithelial-to-mesenchymal transition (EMT)-associated microRNAs and their roles in cancer stemness and drug resistance across multiple malignancies including lung cancer. The study comprehensively reviewed the relationship between EMT-associated miRNAs and cancer stemness/drug resistance, exploring various roles that specific miRNAs play in the stem-like nature of malignant cells. The authors identified critical interactions between EMT-associated miRNAs and drug-resistant complex signaling pathways in lung cancer, demonstrating that miRNA dysregulation not only drives EMT but also contributes substantially

to acquisition of cancer stem cell properties and therapy resistance.[7]

Qian et al., 2021, identified and characterized LCAT3, a novel m6A-regulated long non-coding RNA playing an oncogenic role in lung cancer through binding with FUBP1 to activate c-MYC. The investigators discovered that LCAT3 was upregulated in lung adenocarcinomas (LUAD) and that its overexpression was associated with poor prognosis. Mechanistically, they demonstrated that LCAT3 upregulation is attributable to N6-methyladenosine (m6A) modification mediated by METTL3, leading to LCAT3 stabilization. Loss-of-function assays revealed that LCAT3 knockdown significantly suppressed lung cancer cell proliferation, migration, and invasion, while the LCAT3-FUBP1-MYC axis was validated as a potential therapeutic target for LUAD.[8]

Abolfathi et al., 2023, conducted a literature review of microRNA and gene signaling pathways involved in the apoptosis pathway of lung cancer, identifying key miRNAs and target genes that could serve as diagnostic and prognostic biomarkers. Through comprehensive bioinformatics analysis and clinical study review, the authors identified miR-146b, miR-146a, miR-21, miR-23a, miR-135a, miR-30a, miR-202, and miR-181 as key microRNAs involved in apoptosis signaling pathways. They demonstrated that NF-κB, PI3K/AKT, and MAPK pathways play critical roles in regulation of apoptosis and identified specific miRNA-target gene pairs that abnormally regulate these pathways in lung cancer.[9]

Methadology:

This narrative literature review systematically collected and summarized published research on tumor suppressor genes in lung cancer, focusing on their molecular mechanisms, clinical significance, and therapeutic implications. Conducted in an academic setting over four months, the review used purposive sampling to select original research, systematic reviews, and meta-analyses published in English between 2022 and 2025 from databases including PubMed, Scopus, Web of Science, and Google Scholar. Keywords such as "TP53," "PTEN," "RB1," "therapy resistance," and "molecular mechanisms" were employed. Case reports, editorials, and duplicate or incomplete studies were excluded. No laboratory work was performed; literature was managed using reference management software.

MAIN BODY

1. Classification, Biogenesis, and Structural Characteristics of Non-Coding RNAs

1.1 Overview of Non-Coding RNA Classes in Lung Cancer

Non-coding RNAs comprise a heterogeneous group of functional RNA molecules with diverse structures, biogenesis pathways, and biological roles. The major classes relevant to lung cancer biology include microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), though other important classes such as small nucleolar RNAs (snoRNAs), small interfering RNAs (siRNAs), and piwi-interacting RNAs (piRNAs) also play important regulatory roles in malignant transformation. Understanding the distinct structural features, biogenesis mechanisms, and biological properties of each ncRNA class is fundamental to comprehending their roles in lung cancer and exploiting them for therapeutic purposes.[10]

Long non-coding RNAs are defined as transcribed RNA molecules exceeding 200 nucleotides in length that lack protein-coding capacity. Despite their large size, lncRNAs often function through mechanisms distinct from those utilized by miRNAs, including chromatin remodeling through interactions with histone-modifying complexes, competing for miRNA binding (ceRNA activity), direct protein interactions, and scaffolding of protein complexes. The structural diversity of lncRNAs, combined with their cell-type and tissue-specific expression patterns, makes them particularly valuable for understanding disease-specific molecular pathways.[11]

Circular RNAs are defined by their unique covalently closed loop structure, formed through backsplicing events in which a downstream exon is joined to an upstream exon. This distinctive structural feature confers multiple biological advantages over linear RNAs, including exceptional stability due to resistance to

exonuclease digestion, efficient nuclear export when marked with specific motifs, and the ability to function as competing endogenous RNAs and protein scaffolds. The discovery and characterization of circRNAs has opened new perspectives on post-transcriptional gene regulation and created novel opportunities for diagnostic and therapeutic applications.[12]

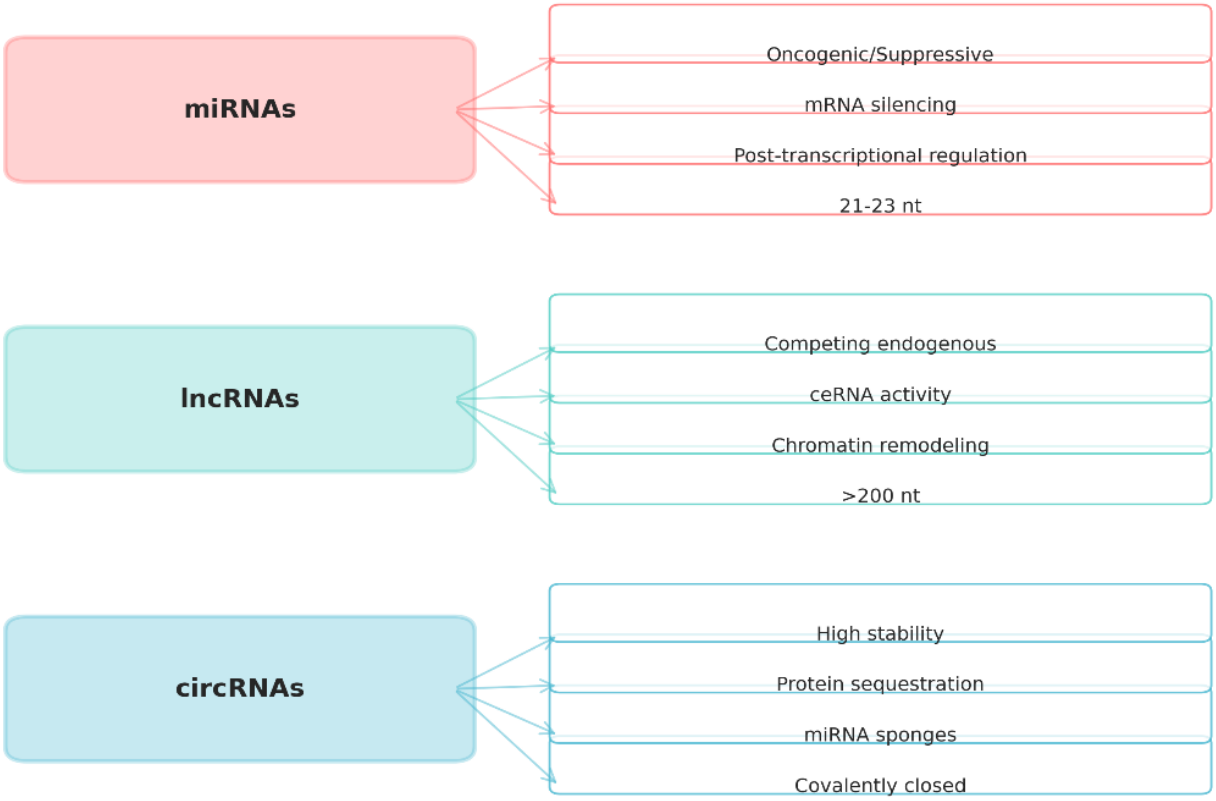

Figure 1: Classification and Biogenesis of Non-Coding RNAs in Lung Cancer

1.2 Biogenesis and Processing Pathways

1.2.1 miRNA Biogenesis and Maturation

The biogenesis of miRNAs occurs through a multi-step process beginning with transcription of primary miRNA transcripts (pri-miRNAs) by RNA polymerase II. Pri-miRNAs are typically several kilobases in length and contain 5' cap and 3' poly(A) tail structures characteristic of mRNA molecules, though they fold into characteristic stem-loop structures containing one or more miRNA sequences. In the nucleus, the RNAse III enzyme Drosha, in complex with its cofactor DiGeorge syndrome critical region 8 (DGCR8), cleaves pri-miRNA molecules to generate precursor miRNA (pre-miRNA) hairpins approximately 70 nucleotides in length.[13]

\Circular RNA biogenesis proceeds through alteRNAtive splicing mechanisms distinct from those generating canonical linear transcripts. The formation of circRNAs involves backsplicing, in which a splice donor site upstream of a given exon is joined to a splice acceptor site downstream of that exon, creating a closed circular structure. This backsplicing can occur between exons of a single pre-mRNA or, in some instances, between exons from different genes or chromosomal locations. The efficiency of circRNA formation is influenced by multiple factors including the length and sequence composition of introns flanking the circularized exons, the density and distribution of RNA-binding protein binding sites, and the expression levels of splicing machinery components.[14]

Table 1: Comparative Characteristics of Major Non-Coding RNA Classes

Feature	miRNA	lncRNA	circRNA
Size	21-23 nt	>200 nt	Variable (20 nt - >100 nt)
Structure	Linear duplex	Linear	Covalently closed loop
Biogenesis	Drosha/Dicer pathway	RNA Pol II	Backsplicing
Primary Function	mRNA targeting via RISC	Multiple (ceRNA, scaffold, chromatin)	miRNA sponging, protein sequestration
Stability	Moderate (half-life: hours)	Variable (hours to days)	Very high (resistant to exonucleases)
Nuclear Localization	~30%	~50-70%	Variable (20-80%)
Number in Genome	~2000 (known)	~20,000	~10,000+
Primary Therapeutic Target	antagomiRs, miRNA inhibitors	Knockdown, siRNA, ASOs	miRNA sponging competition

2: miRNA-Mediated Regulation in Lung Cancer

2.1 miRNA Dysregulation and Tumor Suppressive Functions

MicroRNAs exhibit profound dysregulation in lung cancer tissues compared to adjacent normal lung tissue, with characteristic patterns of upregulation and downregulation defining specific disease subtypes and molecular subtypes. Tumor suppressive miRNAs are frequently downregulated in lung cancer, and restoration of their expression has been shown to inhibit cancer cell growth, promote differentiation, and sensitize resistant cells to therapeutic agents. The let-7 family of miRNAs serves as a prototypical example of tumor-suppressive miRNAs in lung cancer, with decreased let-7 expression strongly correlating with poor prognosis and advanced disease stage.[15]

2.2 Oncogenic miRNAs in Lung Cancer

Conversely, numerous miRNAs exhibit elevated expression in lung cancer tissues and promote malignant phenotypes through suppression of tumor suppressor genes. miR-21 is among the most extensively studied oncogenic miRNAs in lung cancer and is consistently upregulated across multiple lung cancer histological subtypes. miR-21 targets multiple tumor suppressors including phosphatase and tensin homolog (PTEN), programmed cell death protein 4 (PDCD4), and tropomyosin 1 (TPM1).

PTEN phosphatase is particularly critical, as it negatively regulates the PI3K/AKT pathway, a central hub for growth and survival signaling. miR-21-mediated suppression of PTEN unleashes PI3K/AKT signaling, leading to enhanced cell survival and proliferation. Additionally, miR-21 directly targets PDCD4, a tumor suppressor that enhances apoptosis and inhibits translation of anti-apoptotic proteins. The combined effect of miR-21-mediated suppression of multiple tumor suppressors creates a powerful pro-tumorigenic signal that contributes substantially to lung cancer pathogenesis.[16]

miR-155 represents another consistently upregulated oncogenic miRNA in lung cancer, with elevated expression associated with poor prognosis and reduced survival. miR-155 targets the tumor suppressor gene TP53INP1 (tumor protein p53-inducible nuclear protein 1), a p53 target gene that promotes apoptosis and senescence. Additionally, miR-155 suppresses SOCS1 (suppressor of cytokine signaling 1), a negative regulator of JAK/STAT signaling, thereby promoting inflammatory signaling that supports tumor cell survival and immune evasion.

miR-372 and miR-373 are frequently upregulated in lung cancer and function through suppression of p21 and p27, cyclin-dependent kinase inhibitors that enforce G1/S phase checkpoint control. Loss of p21 and p27 expression permits uncontrolled cell cycle progression and is associated with aggressive tumors and poor prognosis. Furthermore, miR-372/373 target LATS2, a kinase involved in the Hippo pathway that normally antagonizes YAP/TAZ-driven proliferation.[17]

Table 2: Representative Oncogenic and Tumor-Suppressive miRNAs in Lung Cancer

miRNA	Type	Primary Targets	Functional Consequences	Clinical Association
miR-21	Oncogenic	PTEN, PDCD4, TPM1	↑ Proliferation, ↓ Apoptosis	Poor prognosis, drug resistance
miR-155	Oncogenic	TP53INP1, SOCS1	↑ Survival, ↑ Inflammation	Advanced stage, metastasis
miR-372/373	Oncogenic	p21, p27, LATS2	↑ Cell cycle, ↓ Apoptosis	Aggressive phenotype
let-7	Tumor suppressive	KRAS, HMGA2, MYC	↓ Proliferation	Poor prognosis when low
miR-200 family	Tumor suppressive	ZEB1, ZEB2	↓ EMT, ↓ Metastasis	Epithelial phenotype
miR-192/215	Tumor suppressive	ZEB1, PROM1	↓ Stemness	Survival advantage
miR-34	Tumor suppressive	NRAS, CDK4/6, SIRT1	↑ Apoptosis, ↓ Proliferation	Restored in therapy

3.1 MALAT1: A Paradigmatic lncRNA in Lung Cancer

MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) has emerged as one of the most extensively characterized and clinically relevant lncRNAs in lung cancer, with its expression levels correlating strongly with metastatic potential, poor prognosis, and therapeutic resistance. Discovered through the identification of a chromosomal translocation in early-stage lung adenocarcinoma patients who subsequently developed distant metastases, MALAT1 was initially designated as metastasis-associated, and subsequent studies have confirmed its role in promoting invasion and dissemination.

MALAT1 is an exceptionally abundant lncRNA in normal lung tissue, and its upregulation in lung cancer cells is associated with enhanced metastatic propensity. The lncRNA is primarily nuclear-localized and associates with nuclear speckles, subnuclear structures enriched in splicing factors and involved in regulation of gene expression. Mechanistically, MALAT1 functions through multiple distinct pathways, demonstrating the pleiotropic effects characteristic of many lncRNAs. MALAT1 regulates splicing of specific pre-mRNAs through interaction with serine/arginine-rich splicing factors (SR proteins), thereby influencing the production of specific mRNA isoforms with distinct functional properties.[18]

3.2 NEAT1 and Immune Evasion in Lung Cancer

NEAT1 (nuclear-enriched abundant transcript 1) represents another critical lncRNA with emerging importance in lung cancer biology, particularly regarding immune evasion and therapeutic resistance. NEAT1 is substantially upregulated in lung cancer tissues compared to adjacent normal tissue and plays a central role in the assembly and function of paraspeckles, nuclear foci distinct from nuclear speckles. These nuclear bodies have recently been implicated in regulation of innate immune responses and appear to sequester interferon-stimulated genes in their inactive state.[19]

3.3 H19 and Tumor Progression in Squamous Cell Carcinoma

H19 represents one of the oldest known lncRNAs, originally identified as an imprinted gene expressed during embryonic development, and subsequently recognized as dysregulated in multiple human cancers including lung squamous cell carcinoma. H19 is upregulated in lung squamous cell carcinomas compared to normal tissue or adenocarcinomas and expression levels correlate with poor prognosis and reduced survival. The lncRNA is primarily cytoplasmic and

functions through competing for miRNA binding, particularly members of the let-7 family.

H19 sequesters let-7 miRNAs, permitting elevated expression of let-7 target genes including HMGA2, a chromatin remodeling factor critical for EMT and metastatic capacity. HMGA2 is normally tightly suppressed by let-7 miRNAs in epithelial cells, but H19-mediated sequestration of let-7 allows HMGA2 overexpression in squamous cell carcinomas. HMGA2 drives EMT through multiple mechanisms including suppression of E-cadherin, reorganization of the actin cytoskeleton, and promotion of migratory and invasive gene expression programs.

3.4 Additional Functionally Important lncRNAs in Lung Cancer

Beyond MALAT1, NEAT1, and H19, numerous additional lncRNAs exhibit dysregulation and functional importance in lung cancer. LINC00152 is significantly upregulated in lung adenocarcinoma and promotes tumor progression through functioning as a ceRNA for miR-193a-3p and miR-200b, thereby de-repressing PD-L1 and ZEB1 respectively. LINC00152 dysregulation therefore links lncRNA pathways to immune evasion, a critical emerging area in lung cancer biology.

Table 3: Key Long Non-Coding RNAs in Lung Cancer

lncRNA	Expression	Primary Mechanisms	Key Targets	Clinical Significance
MALAT1	Upregulated	ceRNA, Splicing, Protein interaction	miR-204/217, CDK6, MMP2/9	Metastasis, TKI resistance
NEAT1	Upregulated	ceRNA, Nuclear structure	miR-193a-5p, PD-L1, EGFR	Immune evasion, TKI resistance
H19	Upregulated	ceRNA (let-7 sponging)	HMGA2, IL-6, KRAS	SCC progression, EMT
LINC00152	Upregulated	ceRNA	miR-193a-3p, miR-200b	Immune evasion, progression
PGM5-AS1	Upregulated	ceRNA	miR-25-3p, ZEB2	EMT, poor prognosis
LCAT3	Upregulated	ceRNA, protein interaction	miR-4686, EMT factors	Metastasis, stemness
TUG1	Upregulated	ceRNA, PRC2 recruitment	miR-143-3p, tumor suppressors	Drug resistance
FEZF1-AS1	Upregulated	ceRNA, Signaling	miR-133a-3p, FGFR1	Proliferation, invasion

6.1: CONCLUSION(S)

Non-coding RNAs represent a transformative frontier in lung cancer therapeutics, offering novel diagnostic and therapeutic options with significant potential to revolutionize patient management. Understanding the interplay between ncRNAs and protein-coding molecules in lung cancer should be explored further to open new avenues for treatment , and integrating ncRNA-related findings with epigenetic modifications and immunotherapy approaches will likely enhance therapeutic efficacy.

6.2: RECOMMENDATION(S)

Conducting large-scale validation studies to translate ncRNA biomarkers into clinical practice, investing in advanced delivery system development, particularly nanoparticle-based carriers approved by regulatory agencies, implementing multi-ncRNA profiling platforms for patient stratification and personalized treatment selection; and, initiating clinical trials combining ncRNA-based therapeutics with conventional chemotherapy and immunotherapy to evaluate synergistic effects.

6.3: LIMITATION(S)

However, significant limitations persist: current challenges include variable detection methods with differing sensitivity and specificity across platforms, incomplete understanding of off-target effects and mechanisms of miRNA-based therapeutics, insufficient long-term safety and efficacy data from human clinical trials, lack of standardized protocols for ncRNA quantification and biomarker validation, and the complexity of ncRNA-microenvironment interactions that require further elucidation. Despite these limitations, the emerging evidence strongly suggests that continued investigation of ncRNAs in addition to protein-coding genes will provide a holistic view of molecular mechanisms of cancer initiation, development, and progression , ultimately offering improved diagnostic accuracy, prognostic stratification, and therapeutic outcomes for lung cancer patients.

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