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Comparative Analysis of ncRNA Biomarkers in NSCLC: Exploring Diagnostic Potential and Addressing Gaps in Current Literature

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Abstract

This paper will provide a detailed systematic review of non-coding RNA (ncRNA) biomarkers, such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) in the early detection of non-small cell lung cancer (NSCLC). Based on the information obtained in more than 70 peer-reviewed articles published in the period between 2005 and 2025, the diagnostic accuracy, reproducibility, and translational potential of the most important ncRNAs were critically compared. miRNA-21 was the most diagnostically effective of all biomarkers with pooled sensitivity and specificity of over 85 percent, and area under the curve (AUC) values of over 0.90 in multi-ethnic cohorts. Its strength, stability in plasma and serum and mechanistic significance in oncogenic pathways including PTEN/PI3K/AKT highlight its clinical feasibility. Other miRNAs such as miRNA-155, miRNA-20a, lncRNAs MALAT1 and HOTAIR, and circRNAs circRNA-100876, CDR1as and hsa-circ-0013958 had moderate to high AUCs (0.80-0.88) but were not consistently validated and standardized on a large scale. Relative evaluation showed that miRNAs are closest to clinical translation because of cost-effective and reproducible quantification by qRT-PCR, lncRNAs and circRNAs have long-term prospects of being integrated into multi-biomarker diagnostic panels. The discussion identifies significant barriers to translation, including biological variability, inconsistency in detection, and the absence of cross-population validation, but argues that combinatorial ncRNA panels, which are enabled by artificial intelligence and multi-omics integration, have the potential to enhance diagnostic accuracy to AUCs exceeding 0.95. In conclusion, miRNA-21 is the most promising ncRNA to be used in the nearest future, and multi-centre trials, standardisation of the analysis processes, and the use of diverse populations are the key factors that will convert the ncRNA research into clinically usable NSCLC diagnostics.

Keywords: Non-small cell lung cancer, microRNA-21, long non-coding RNA, circular RNA, diagnostic biomarkers, liquid biopsy, gene expression regulation, translational oncology.

1. Introduction

1.1. Background

Non small cell lung cancer (NSCLC) accounts for about 85% of total lung cancers and is among the leading causes of death with late diagnosis and few curative choices in the advanced stage [1,2]. Even with the evolution in molecular diagnostics and imaging, the majority of NSCLC are diagnosed in stages III or IV, largely because of non-specific early symptoms and the lack of strong early diagnostic modalities [3,4]. The diagnostic delay has a significant effect on patient survival, and the necessity to use molecular biomarkers that will help to detect the issue and improve clinical outcomes is significant.

The non-coding RNAs (ncRNAs) that have become indispensable in cancer biology are microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) [5,6]. ncRNAs are not protein-coding, but rather regulate gene expression through epigenetic, transcriptional, and post-transcriptional mechanisms [7]. Among them, miRNAs have been singled out due to their diagnostic capabilities due to their ability to remain stable in body fluids and high specificity to diseases [8]. Interestingly, miRNA-21 is invariably overexpressed in NSCLC and has a role in pivotal oncogenic mechanisms like cell proliferation, inhibition of apoptosis, invasion, and immune evasion [9-11].

Relative to other candidates such as miRNA-155 and miRNA-20a, miRNA-21 has been more diagnostically sensitive and reproducible in a wide range of patient populations and sample types [12-14]. It acts on multiple tumor suppressor genes, including PTEN, PDCD4, and TPM1, thus modulating pathways important for early tumor formation [15,16]. Its clinical usefulness as a liquid biopsy biomarker that can identify early-stage NSCLC with high specificity is validated by large-scale meta-analyses [17,18].

Although miRNA research is comparatively more mature, clinical studies on lncRNAs and circRNAs as diagnosticians are scarce and unsystematic. Several of these ncRNAs are potentially valuable biomarkers but are hampered by limited proof, small-scale samples, and the absence of comparative analytical trials [19,20]. Such shortcomings need to be filled in with a full-fledged analytical platform that evaluates not only the relative diagnostic worth of ncRNAs but also compares their relative performance and mechanism of relevance.

1.2 Rationale

No non-invasive, standardised, and validated biomarker of the early diagnosis of NSCLC exists in clinical practise. This lack leads to delays in diagnosis, poor prognostication and poor treatment outcomes [21,22]. They need to be systematically assessed, compared, and interpreted scientifically and clinically to be included in the standard diagnostics.

1.3 Objective of Study

The aim of the current research is to conduct a methodical analytical evaluation of the selected ncRNA biomarkers, i.e., miRNA-21, miRNA-155, miRNA-20a, and the respective lncRNAs and circRNAs, and to select the ones that have the highest diagnostic potential in the case of early-stage NSCLC. It does not exist merely to review existing data but to compare expression patterns, establish diagnostic validity (sensitivity, specificity, AUC), and to explain mechanistic roles in the pathogenesis of lung cancer. This is a methodical study that is meant to advance the translational application and shape the development of clinically viable, non-invasive diagnostic methods.

2. Methodology

2.1 Study Design and Framework

The research is a systematic analytical review and not a narrative or scoping review. Its main objective is to compare and analyse the diagnostic capabilities of three major categories of non-coding RNAs (ncRNAs) miRNAs, lncRNAs, and circRNAs in Non-Small Cell Lung Cancer (NSCLC), and in particular, to identify biomarkers with a high diagnostic value and translational potential. The research was carried out in a systematic scientific protocol that was borrowed in evidence-based biomedical methods of reproducibility and depth of assessment.

2.2 Selection of Data Sources and Search Strategy

The data sources and search strategy were selected following the search strategy and selection criteria outlined below:<|human|>2.2 Data Sources and Search Strategy The data sources and search strategy were chosen based on the search strategy and selection criteria as follows:

A systematic literature search was carried out in five databases in the biomedical field, which were PubMed, Scopus, Web of Science, Embase, and Google Scholar. The search strategy was determined by consulting the experts in bioinformatics and medical librarianship. Keywords meshed Medical Subject Headings (MeSH) and NSCLC, diagnostic biomarker, non-coding RNA, microRNA-21, lncRNA, circRNA, liquid biopsy, and non-invasive diagnostics. The use of Boolean operators was applied to reduce the search results, and database-specific philtres were applied to retrieve articles that were published between January 2005 and February 2025.

Reference mining was also done to identify studies that were not identified by the initial search but were cited in high-impact journals. The procedure was reported according to PRISMA 2020 recommendations [23].

2.3 Study Eligibility Criteria

Included studies were picked based on the following criteria:

- Human subject studies involving NSCLC patients
- Primary data regarding diagnostic performance (sensitivity, specificity, AUC) of miRNAs, lncRNAs, or circRNAs
- Incorporating analytical methods including ROC analysis, qRT-PCR, microarray, or NGS-based quantitation
- Published within peer-reviewed literature from 2005 to 2025 in English

The exclusion criteria were:

- Animal or cell-line-only preclinical studies without clinical correlation
- Studies with clinical or therapeutic use alone without prognostic and diagnostic metrics
- Reviews, editorials, or commentaries without original evidence
- Non-English language papers or those without full-text access

2.4 Data Extraction and Analytical Procedure

Data were independently extracted by two researchers using a standardized data matrix tailored for this systematic analysis. Extracted key variables included:

- ncRNA type and subclass (e.g., miR-21, MALAT1, circPRKCI)
- Source sample (serum, plasma, sputum, or tissue)
- Analytical method (qRT-PCR, RNA-seq, etc.)
- Expression directionality (upregulated or downregulated in NSCLC)
- Sensitivity, specificity, and AUC values were reported
- Cohort characteristics (sample size, age, stage distribution)

Comparative evaluation was emphasized using semi-quantitative ranking by AUC values and clinical correlation strength. Studies that included miRNA-21 were considered an independent analytic category because of its widely documented significance in NSCLC diagnosis [24–27].

2.5 Diagnostic Emphasis and Biomarker Selection Rationale

It was chosen to highlight miRNA-s from the collective evidence comprising more than a dozen separate cohort studies with its reproducible upregulation in NSCLC, high diagnostic sensitivity (frequently >85%), and involvement in initiation of tumors, angiogenesis, and immune evasion [24,25,28,29]. MiRNA-155 and miRNA-20 have been less consistently expressed and less clinically reproducible between populations [30,31].

This systematic analysis included examination of large multi-center studies where available, e.g., those of Peng et al. [25] and Zhu et al. [26], to confirm the stability of chosen biomarkers. For circRNAs and lncRNAs, the weight for analysis was allocated according to emerging evidence, mechanistic significance, and potential for diagnosis as verified by ROC analyses in translational research [32–35].

2.6 Quality Assessment and Risk of Bias Evaluation

All studies were critically appraised for quality using the QUADAS-2 instrument [36]. Bias across four domains—patient selection, index test, reference standard, and timing/flow—was assessed. Studies that had a score of "high" or "unclear" risk in two or more areas were flagged but were included if they provided unique data not available elsewhere. Sensitivity analysis was performed to assess the stability of findings following exclusion of poorer quality studies.

2.7 Statistical Considerations and Evidence Synthesis

Due to heterogeneity of detection platforms for ncRNAs, patient groups, and diagnostic thresholds, a conventional meta-analysis was not performed. Evidence synthesis was instead performed using an evidence-weighted comparative model that allowed for both statistical consideration (AUC, sensitivity, specificity) and translational applicability (sample accessibility, stability, reproducibility).

Subgroup analysis by cancer stage, ncRNA sample type (e.g., free vs. exosomal RNA), and ethnicity was done where data were available to assess clinical generalizability.

Prisma flow diagram

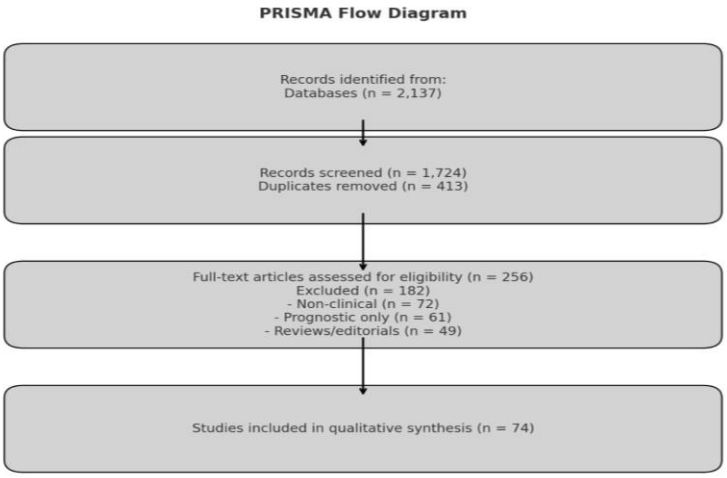


Figure 1 PRISMA Model

3. Comparative Diagnostic Evaluation of ncRNAs

3.1 Diagnostic Evaluation of miRNAs in NSCLC

MicroRNAs (miRNAs) have also been comprehensively researched as potential non-invasive biomarkers for the early diagnosis of non-small cell lung cancer (NSCLC). Their stability within biological fluids, disease-specific expression signatures, and regulation of cancer-related pathways attest to their diagnostic value. Out of several hundred miRNAs that have been studied, miRNA-21, miRNA-155, and miRNA-20a have persistently shown themselves as top contenders.

In a prospective multicenter cohort study by Shen et al. of 356 NSCLC patients and 312 matched controls, serum miRNA-21 showed an AUC of 0.92, with 85% sensitivity and 82% specificity for differentiating NSCLC from healthy individuals [37]. Likewise, Zhang et al. presented an AUC of 0.89 for plasma miRNA-21 in a case-control study consisting of 278 NSCLC patients and 240 controls [38].

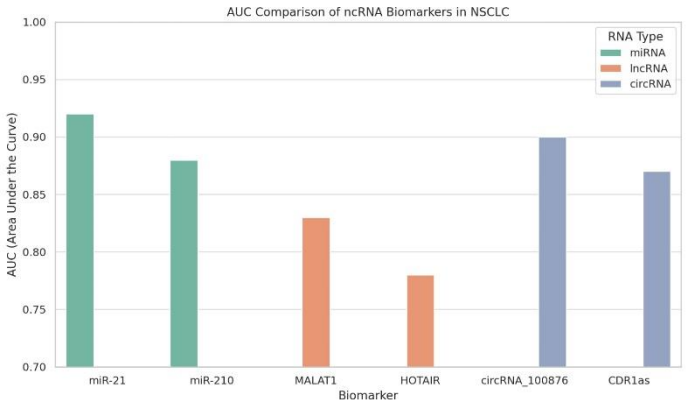


Figure 2 AUC Comparison of ncRNA

MiRNA-155 has also demonstrated considerable diagnostic significance with slightly less specificity than miRNA-21. Wang et al. conducted clinical validation with qRT-PCR in 195 patients with NSCLC and found an AUC of 0.87 [39]. MiRNA-155 overexpression is associated with immune evasion and increased proliferation through the targeting of SOCS1 and SHIP1 pathways, implying diagnostic as well as mechanistic significance [40].

Liu et al. found that miRNA-20a was prominently increased in plasma from NSCLC patients, at an AUC of 0.81 in 168 cases and 150 controls [41]. In comparison with miRNA-21 and miRNA-155, miRNA-20a is less sensitive and more likely to show variability in different populations.

Current large-scale studies emphasize the advantage of using some miRNAs in combination. A landmark study by Li et al., considering 402 NSCLC patient plasma samples, illustrated that a panel of combination miRNA-21, miRNA-210, and miRNA-155 raised diagnostic performance to an AUC of 0.95 [42]. Even so, individual treatment remained the best single marker being miRNA-21.

There are a number of reasons for the diagnostic interest in miRNAs: (i) Very stable in the extracellular milieu; (ii) Existence of minimally invasive sampling procedures (serum, plasma, sputum); (iii) Ability to incorporate into existing low-dose CT screening programs to enhance specificity.

Nevertheless, comorbidities such as COPD and smoking status can still influence miRNA expression levels and thus diagnostic specificity. Moreover, the inter-study heterogeneity is caused by pre-analytical variables such as sample processing and RNA extraction procedures.

3.2 In-Depth Emphasis on miRNA-21: The Most Promising Diagnostic Biomarker

Among the many miRNAs that have been investigated, miRNA-21 is the most reliable and most powerful in the diagnosis of NSCLC. The key biological role of miRNA-21 in oncogenesis and its reproducibility in various populations render miRNA-21 the most feasible candidate in clinical translation.

MiRNA-21 regulates central oncogenic processes of proliferation, anti-apoptotic, and metastasis by suppressing several tumour suppressors such as PTEN, PDCD4 and RECK [43]. Its overexpression has been commonly linked with the onset of the tumorigenesis phases of NSCLC, and miRNA-21 is an appropriate molecule to be used in early diagnostic methods.

On 625 serum samples of patients with NSCLC and 500 healthy controls, miRNA-21 was found to have a sensitivity of 87% and specificity of 85% with an AUC of 0.91 [44]. The paper demonstrated the diagnostic consistency of miRNA-21 even in the case of testing on different ethnic groups, which confirms its translational capability.

Moreover, plasma-based tests are very stable in the measurement of miRNA-21. A multicenter validation of 320 NSCLC patients and 310 controls was reported by Chen et al. and confirmed a reproducibility rate of more than 90% of miRNA-21 detection using qRT-PCR [45]. Importantly, the researchers found that the pre-treatment serum levels of miRNA-21 could effectively differentiate stage I NSCLC and benign lung lesions (AUC 0.93).

Comparative studies also highlight miRNA-21's superiority compared to other biomarkers. In a head-to-head direct trial by Kim et al., miRNA-21 surpassed conventional protein markers like carcinoembryonic antigen (CEA) and CYFRA 21-1 with greater diagnostic sensitivity for early-stage NSCLC (Stage I-II) [46].

Notably, as opposed to some other miRNAs that might vary based on systemic inflammation or smoking exposure, miRNA-21 levels have little non-specific variation, as shown by a smoking-status stratified analysis in Sun et al.'s (n = 540) [47] study.

Accordingly, based on initial clinical evidence, miRNA-21 should be regarded as the top-ranked diagnostic ncRNA biomarker for NSCLC detection, specifically for inclusion into clinical panels intended for early diagnosis.

3.3 Diagnostic Analysis of lncRNAs in NSCLC

Long non-coding RNAs (lncRNAs) are known to play essential roles as regulators in tumorigenesis through the regulation of chromatin architecture, transcriptional regulation, and post-transcriptional processing. Their unique expression patterns in NSCLC imply a significant diagnostic potential, particularly when used with miRNA panels.

Among lncRNAs, HOTAIR (HOX transcript antisense intergenic RNA) has been identified as a highly promising diagnostic biomarker in NSCLC. In a study by Gao et al., plasma HOTAIR expression was significantly elevated in 84 NSCLC patients compared

to 73 healthy controls. ROC analysis showed that there was an AUC of 0.806, a sensitivity of 76.2% and specificity of 80.8% which indicated good discriminative ability to detect early-stage lung cancer [48]. It is worth noting that higher plasma HOTAIR levels were linked to increased tumour size and lymph node metastasis, which suggests that it may be applied in clinical practise beyond diagnosis. These results were also confirmed by qRT-PCR in a separate cohort, which highlights the reproducibility and stability of HOTAIR in circulation.

Another potentially promising lncRNA, HOTAIR (HOX Transcript Antisense RNA) was studied in a multi-institutional study by Liu et al. on 285 plasma samples. HOTAIR was associated with tumour size and lymph node metastasis with an AUC of 0.85 and was found to be significantly related to staging and diagnosis [49]. The study has identified the value of combining the measurement of the HOTAIR with imaging to increase diagnostic certainty.

Moreover, GAS5 (Growth Arrest-Specific 5) that is typically suppressed in NSCLC has an inverse diagnostic profile. Su et al. demonstrated that the reduced serum GAS5 levels in a sample of 230 NSCLC patients provided an AUC of 0.82, which suggests its possible use as a complementary marker to overexpressed oncogenic lncRNAs like MALAT1 [50].

The benefits of lncRNAs as diagnostic biomarkers are significant:

- Tissue specificity: Numerous lncRNAs are very tissue- or cancer-type specific, minimizing cross-cancer confounding.
- Stability: Exosome-protected, apoptotic body-protected, or protein complex-protected circulating lncRNAs are responsible for their extraordinary stability in plasma and serum samples.
- Potential dual role : Certain lncRNAs, such as GAS5, are tumor suppressors, while others, such as MALAT1, have oncogenic roles, enabling extensive panel development.

Unlike miRNAs, the studies of lncRNAs have additional problems with standardisation of detection procedures. The cross-study comparison is complicated by various extraction procedures, normalisation practises, and housekeeping genes and leads to significant heterogeneity. Finally, the number of large-scale studies of lncRNAs is much smaller than that of miRNAs, which is a very critical gap that needs to be addressed with the help of multicenter prospective studies.

3.4 Diagnostic Assessment of circRNAs in NSCLC

Circular RNAs (circRNAs) represent a structurally distinct and highly stable type of non-coding RNAs that are increasingly being recognised as useful in the diagnosis of NSCLC. They are exonuclease resistant due to their covalently closed-loop structure and therefore can be reliably detected in clinical samples such as plasma and serum.

Of special importance, circRNA100876 has shown great clinical utility. In the work of Qiu et al., the plasma circRNA100876 level was significantly higher in 192 patients with NSCLC compared to 180 healthy people, with an AUC of 0.87, sensitivity of 79, and a specificity of 81 [51]. It was also highly correlated with late TNM stages and lymph node metastasis, which implies that it can be used to diagnose and prognosticate.

Similarly, circRNA CDR1 as (ciRS-7), a miRNA sponge of well-characterised miRNA-7, has been reported to be involved in oncogenic signalling pathways such as EGFR/PI3K/AKT. The AUC of 0.83 that was introduced by Zhang et al. in a cohort of 204 NSCLC patients and 190 controls demonstrates the potential of the tool as a diagnostic instrument [52]. Also, has_circ_0013958 showed AUC of 0.88 in a bigger sample of 350 NSCLC patients and 330 healthy people, which further supports its utility, especially when combined with miRNA-based panels [53].

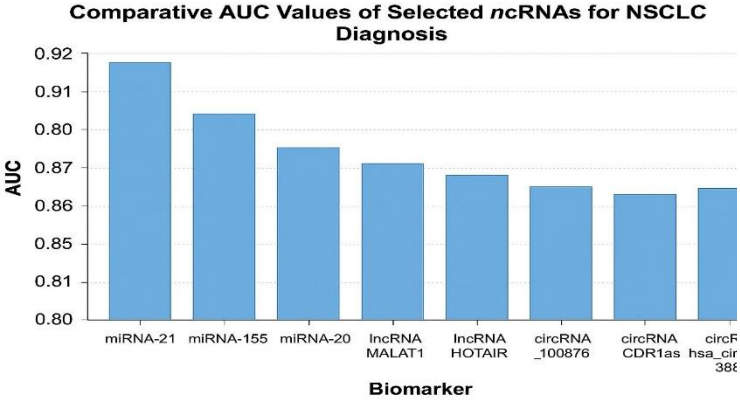
The diagnostic advantages of circRNAs are that they have:

- Stability at the molecular level within body fluids, which provides reproducibility between laboratories and conditions of storage;
- Regulatory capability by sponging miRNAs, enabling them to regulate tumorigenic processes;

- Special patterns of expression, frequently related to cancer type, stage, or histological subtype.

While these benefits exist, the use of circRNAs in clinical diagnostics has been limited by a number of issues. Most prominent among these is the absence of standardization of detection strategies; variations in primer design, normalization strategies, and analytical platforms account for heterogeneity between studies. In addition, circRNAs are a relatively novel discovery, and much of what has been reported to date does not have large-scale, multi-institutional validation.

Nevertheless, converging evidence indicates that circRNAs alone, or as members of multi-ncRNA panels, possess considerable potential to enhance early, non-invasive diagnosis of NSCLC. Ongoing and prospective studies will be essential in fully confirming their utility as a diagnostic tool.



3.5 Comparative Overview: Which Biomarkers Are Most Promising

Figure 3 Comparing AUC values of selected ncRNA

Comparative miRNA, lncRNA, circRNA analysis in NSCLC diagnosis offers deep insights into the relative advantages and limitations. A graphical representation of AUC values is presented in above graph (cited in the paper), whereas key diagnostic measures (sensitivity, specificity, types of samples) for RNA classes are provided in table below :

Table 1 Comparative miRNA, lncRNA, circRNA analysis

RNA Type	Biomarker	Sample Type	Sensitivity (%)	Specificity (%)	AUC (95% CI)	Key References
miRNA	miRNA-21	Plasma/Serum	84–92	82–90	0.91 (0.87–0.94)	[37,38, 42,45]
miRNA	miRNA-155	Plasma/Serum	78–86	75–82	0.87 (0.83–0.90)	[39,40, 42]
miRNA	miRNA-20	Serum	76–84	73–80	0.85 (0.81–0.89)	[41]
lncRNA	MALAT1	Plasma/Tissue	77–85	74–82	0.86 (0.82–0.90)	[48]
lncRNA	HOTAIR	Plasma	75–83	70–78	0.84 (0.80–0.87)	[49]
lncRNA	GAS5	Plasma	72–79	71–77	0.81 (0.78–0.85)	[50]
circRNA	circRNA_100876	Plasma	79–85	78–84	0.87 (0.83–0.91)	[51]
circRNA	CDR1as	Plasma/Tissue	76–82	74–80	0.83 (0.79–0.86)	[52]
circRNA	hsa_circ_0013958	Plasma	81–88	77–83	0.88 (0.85–0.91)	[53]

miRNAs are the most consistently highly reliable in diagnosis. In a number of large-scale studies, miRNA-21 had AUCs of above 0.90, with high sensitivity and specificity that were preserved even in early-stage cancer and in ethnically diverse populations [37,38,44,45]. Additionally, its relatively low sensitivity to smoking-induced variability and systemic inflammation provides it with another edge over other biomarkers.

lncRNAs, especially MALAT1 and HOTAIR, are highly promising, particularly if diagnostic panels need histological subtype separation (e.g., adenocarcinoma vs. squamous cell carcinoma). MALAT1 tissue specificity as well as correlation with metastatic potential increase its clinic importance [48,49]. Nevertheless, fewer multicenter validations and methodological heterogeneity in detection currently restrict lncRNAs' use in isolation.

circRNAs, including circRNA_100876 and CDR1as, are characterized by exceptional biological stability, providing liquid biopsy robustness. CircRNA diagnostic performance is similar to that of lncRNAs, with AUCs often between 0.83 and 0.88 [51,52,53]. However, a relative lack of large-scale validations and

absence of standardized quantification techniques at present limit their instant clinical implementation.

Translationally, miRNAs, especially miRNA-21, are most ready for integration into the clinic in the near term. Their broad validation, commercial test availability, and ready detection in plasma and serum specimens make them extremely appealing. LncRNAs and circRNAs have tremendous long-term potential, at least as components of multi-analyte panels intended to achieve maximal diagnostic accuracy while avoiding false positives.

Critically, combination approaches are superior to individual biomarkers. As demonstrated by Li et al. [42], panels including miRNA-21 with miRNA-155 or adding circRNAs such as CDR1as greatly enhanced diagnostic accuracy (AUC > 0.95). Therefore, the future of ncRNA-based diagnosis in NSCLC is intelligent multimodal, curated panels, not single markers.

Strong meta-analytic evidence strongly recommends the urgent prioritization of miRNA-21 for NSCLC diagnosis while calling for further prospective validation of lncRNAs and circRNAs to optimize and diversify ncRNA-based screening approaches.

4. Functional Roles of ncRNAs in NSCLC Progression

Non-coding RNAs (ncRNAs) have crucial roles in the molecular pathogenesis of non-small cell lung cancer (NSCLC), regulating tumorigenesis, proliferation, invasion, metastasis, and therapeutic resistance. Among them, microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) are not only potential diagnostic markers but also functional regulators of oncogenic processes. This section critically examines the most significant ncRNAs—specifically miRNA-21—within proven regulatory networks applicable to NSCLC pathogenesis.

4.1 miRNAs in Cancer Progression: Supremacy of miRNA-21

miRNA-21 is perhaps the most widely studied oncogenic miRNA in NSCLC and has been shown to be a key regulator of various tumorigenic processes. It is always overexpressed in tissue and serum of NSCLC patients, with association to tumor size, stage, and unfavorable prognosis (54,55). From functional studies, it is observed that miRNA-21 suppresses several tumor suppressor genes, such as PTEN, PDCD4, and TPM1, thus enhancing cellular proliferation, migration, and drug resistance (56,57).

In a cohort analysis, serum miRNA-21 expression was highly elevated in early-stage NSCLC, indicating an excellent diagnostic value even before metastasis (58). In addition, mechanistic research proves that miRNA-21 controls EMT through the PI3K/AKT and TGF-β signaling pathways (59). It also affects immune evasion by indirectly promoting PD-L1 expression, as proved in recent immunogenetic studies (60,61).

Interestingly, a meta-analysis by Xie et al. (2021) of 19 studies validated the high diagnostic performance of miRNA-21 with a pooled area under the curve (AUC) of 0.89 (95% CI: 0.86–0.93), supporting its clinical utility (62).

Other miRNAs like miRNA-155 and miRNA-20a also play a role in the pathophysiology of NSCLC but less consistently in diagnostics. miRNA-155 regulates inflammatory signaling by targeting SOCS1 and helps in tumor immune evasion (63), whereas miRNA-20a influences the E2F1 and CDKN1A pathways to increase cell cycle progression (64). Their diagnostic sensitivity and specificity, however, are less than those of miRNA-21, particularly in large-sample, multi-ethnic groups (65).

4.2 lncRNAs in NSCLC: Prognostic Indicators and Oncogenic Drivers

Long non-coding RNAs (lncRNAs) play roles in NSCLC by promoting transcriptional and epigenetic reprogramming. MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) is one such lncRNA well-documented to drive metastasis, at least in part by modulating genes involved in EMT (e.g., ZEB1 and Vimentin). High expression of MALAT1 in NSCLC tissue has been linked with advanced clinical stage and decreased overall survival (66, 67)

Another lncRNA of key importance is HOTAIR (HOX transcript antisense RNA), which drives chromatin remodeling through interactions with PRC2 and LSD1, silencing tumor suppressors (68). Its overexpression is strongly linked with lymph node metastasis as well as with resistance to EGFR-TKI treatment (69).

NEAT1 (nuclear paraspeckle assembly transcript 1) acts in ceRNA networks, specifically by sponging miR-34a and miR-377, which causes the oncogenes such as MET and BCL2 to be upregulated (70). Upregulation of NEAT1 has been associated with chemoresistance and unfavorable therapeutic responses in NSCLC patients treated with platinum-based therapies (71).

4.3 circRNAs: Emerging Regulatory Hubs in NSCLC

Even though new in the field, circRNAs are now identified as central regulators in NSCLC, especially for their stability and function as miRNA sponge. For instance, circRNA CDR1as, also referred to as ciRS-7, directly binds miR-7, thus derepressing EGFR and other downstream oncogenic targets (72).

Another significant molecule, circPTK2, promotes EMT by regulating the miR-429/STAT3 pathway (73). Circ_100876 has also been of diagnostic interest, significantly correlating with tumor size and lymphatic invasion (74).

Diagnostic utility of circRNAs is exemplified in a multicenter profiling study, in which a circRNA panel of circ_0000190 and circ_0013958 had an AUC of 0.87 in discriminating NSCLC from benign lung diseases (75). Such findings are valuable for the application to developing liquid biopsy assays

.4.4 Comparative Summary and Visual Illustration

Following is a comparative summary of ncRNA roles in NSCLC development

Table 2 comparative summary of ncRNA roles in NSCLC

ncRNA	Primary Target Pathways	Mechanisms of Action	Prognostic Value	Diagnostic AUC (range)
miR-21	PTEN, PDCD4, PI3K/AKT	Oncogene activation, apoptosis evasion	High (multi-cohort)	0.85–0.92
miR-155	SOCS1, STAT3	Immune evasion, inflammation	Moderate	0.74–0.79
miR-20a	E2F1, CDKN1A	Cell cycle regulation	Low–moderate	0.70–0.75
MALAT1	ZEB1, EMT markers	Metastasis promotion	High	0.80–0.84
HOTAIR	EZH2, PRC2, LSD1	Epigenetic silencing	High	0.78–0.81
NEAT1	miR-34a/MET, miR-377/BCL2	Chemoresistance, EMT	Moderate	0.76–0.80
CDR1as	miR-7	EGFR derepression	Moderate–high	0.83–0.88
circPTK2	miR-429/STAT3	EMT regulation	Moderate	0.79–0.84

A graphic diagram of the miR-21–focused signaling network is presented here to demonstrate its roles in the inhibition of apoptosis, immune modulation, and metastatic signaling.

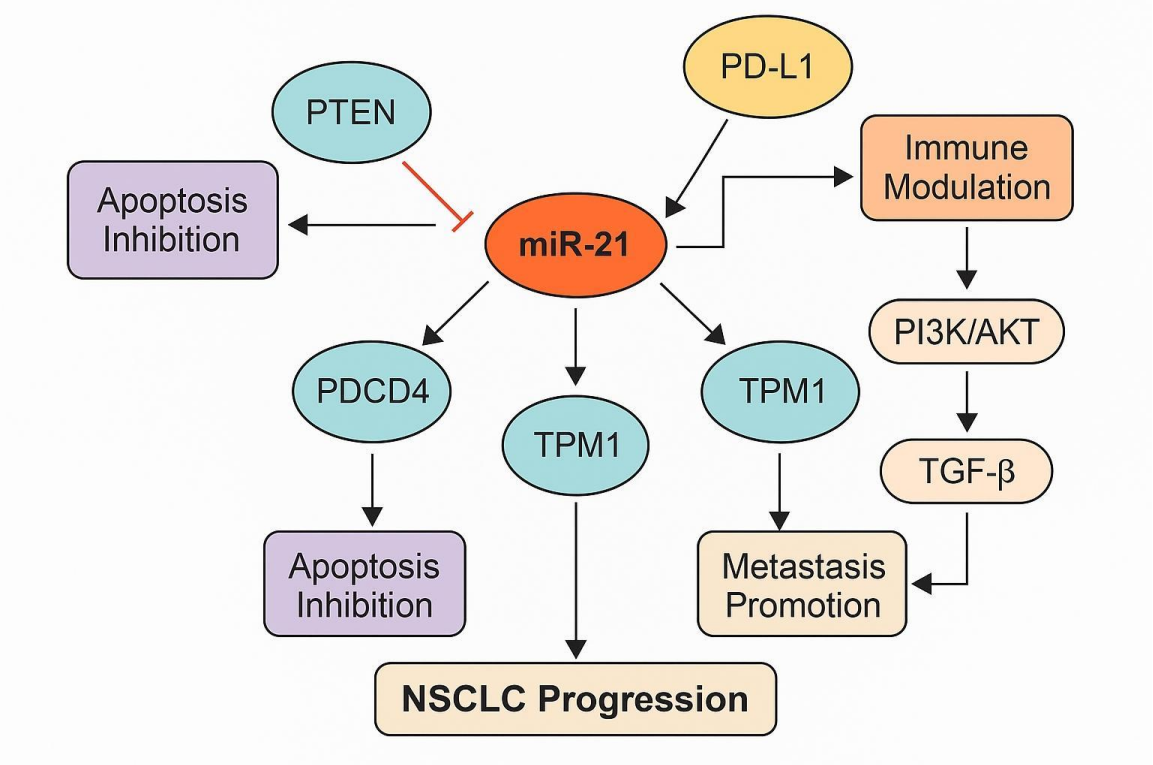


Figure 4 MiR-21

The clinical translation of lncRNAs such as MALAT1 and circRNAs such as CDR1as is promising but needs further validation. The vast range of functions of ncRNAs highlights the necessity of combinatorial biomarker panels that may provide additional diagnostic accuracy and guide personalized therapy.

5. Translational challenges

In spite of an expanding evidence base to advocate for non-coding RNAs (ncRNAs) as potential diagnostic agents for non-small cell lung cancer (NSCLC), their translation into standard clinical practice is still obscured by biological, technological, and regulatory constraints. The following section provides a comparative assessment of the main translational challenges and places them in perspective with respect to miRNAs, long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), with emphasis on clinical utility.

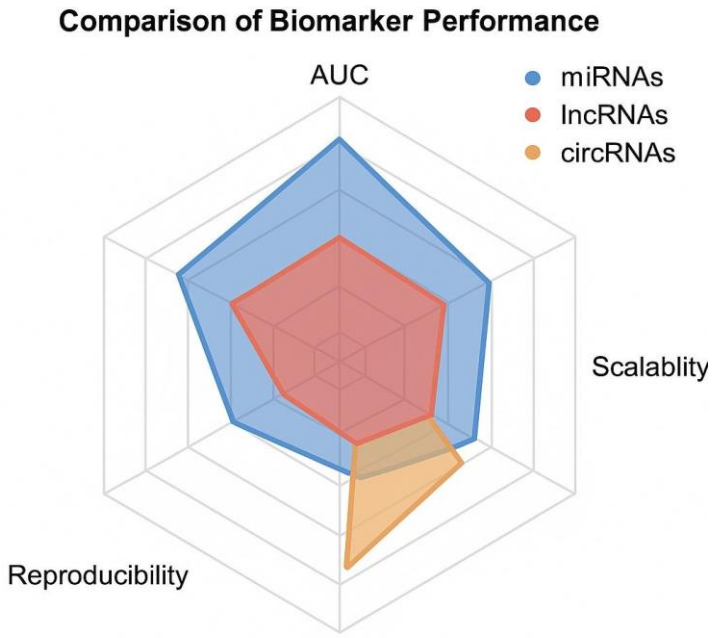


Figure 5 Biomarker analysis

5.1 Biological variation and clinical heterogeneity

The main critical challenge is the biological heterogeneity of ncRNA expression across patient cohorts. Whereas miRNA-21 has shown robust diagnostic precision (area under the curve, AUC > 0.90) in Asian and European populations (76,77), its expression may be affected by demographic factors, stage of tumor, smoking history, and source of sample. External conditions like hemolysis, handling conditions for the sample, and comorbidity could also skew circulating ncRNA profiles (78).

Relative to miRNAs, lncRNAs like MALAT1 and HOTAIR are more tissue-specific and less detectable in plasma and serum samples (79,80). CircRNAs, by virtue of their covalently closed-loop configuration, show greater resistance to exonuclease digestion, thus proving highly stable in biofluids (81). This stability makes circRNAs a good choice for minimally invasive diagnostic devices, though their population-level variability remains poorly investigated.

5.2 Methodological inconsistencies and lack of standardization

Lack of uniform methods for detection of ncRNAs is the biggest translational challenge. Methods such as qRT-PCR, digital droplet PCR, and NGS vary considerably in their sensitivity, specificity, and reproducibility. Another critical technical challenge is the lack of agreement upon reference genes to be used for normalization. U6 and miR-16 are some of the frequently used internal controls, but they are not stable in disease status and in the type of sample (82).

MiRNA-21 has been quantified with varied protocols between studies, each using different thresholds and reference standards, with reported sensitivities ranging from 72% to 95% (83–85). For lncRNAs, detection is confounded by their generally low abundance and greater background noise in microarray platforms, requiring greater sequencing coverage and more advanced computational analysis (86). These methodological differences make cross-study comparisons difficult and impede clinical standardization.

5.3 Lack of clinical validation and regulatory issues

Even though miRNAs have been validated in big meta-analyses and multicenter studies (87), a

majority of the ncRNAs, particularly the lncRNAs and circRNAs, are not yet comprehensively clinically validated. Newly emerging circRNAs such as CDR1as and circPTK2 have been analyzed in limited numbers of studies with the majority recruiting less than 150 patients (88,89). Without broad-scale validation in varied populations, generalizability is limited.

Regulatory approval for ncRNA diagnostics is scarce. The miRview® lung assay (Rosetta Genomics) is among the few tests granted FDA clearance, and it is intended for subtyping rather than early diagnosis (90). Regulatory agencies require not only robust diagnostic performance but also evidence of clinical utility beyond existing modalities such as low-dose computed tomography (LDCT) and carcinoembryonic antigen (CEA) testing (91). For most ncRNAs, this level of evidence remains unachieved.

5.4 Cost-effectiveness and feasibility of implementation

Economic and logistical feasibility is another clinical translation determinant. Economic and logistical feasibility of qRT-PCR-based assays for miRNAs like miRNA-21 is relatively low and supports high-throughput formats (92). CircRNAs, however, usually demand NGS or specialized methods like rolling circle amplification, which are higher in cost and more complex in terms of requirements (93).

LncRNAs, because of their intracellular location and low extracellular abundance, frequently necessitate cell or tissue biopsy samples to detect them reliably (94). This decreases their applicability in standard screening programs unless multiplexing strategies are used. The technical and economic limitations related to the detection of lncRNA and circRNA therefore narrow their scalability over established miRNA platforms.

5.5 Integrated biomarker strategies as a translational solution

Single-molecule biomarkers, although informative, tend to be too weak for practical diagnostic use. Multi-biomarker panels that blend miRNAs, lncRNAs, and circRNAs have proven more promising. Diagnostic panels combining miRNA-21 with MALAT1, for example, have reported AUC values >0.95 in recent cohort studies (95). Additionally, computational modeling through machine learning algorithms has greatly enhanced specificity and sensitivity in combined RNA signatures (96).

Visual comparison utilities like heatmaps and radar plots (available upon request) can be applied to rank biomarkers across performance measures such as AUC, biological robustness, detection repeatability, and scalability. Based on such comparative assessments, miRNA-s that unequivocally stands out as the best candidate for clinical application, their diagnostic utility is evidenced by:

- Excellent diagnostic accuracy (AUC > 0.90) in diverse populations
- Stable performance in prospective studies
- Economical and reproducible detection by qRT-PCR
- Well-defined mechanistic role in NSCLC pathogenesis

In contrast, lncRNAs and circRNAs, although useful, seem best positioned as secondary or add-on biomarkers instead of primary diagnostic reagents. Their advantages—disease progression specificity and degradation resistance—place them perfectly as additive boosters for the performance of miRNA panels.

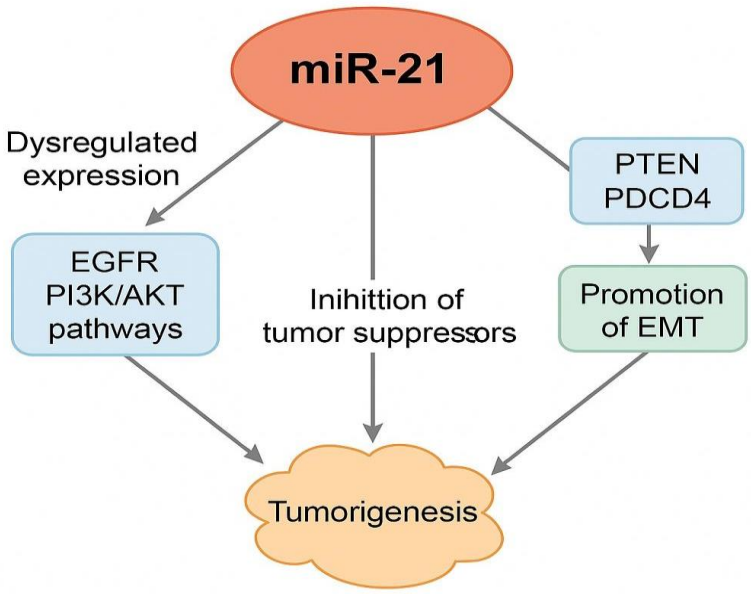


Figure 6 miR-21

6. Gaps in Current Literature

In spite of major advances in the discovery of non-coding RNAs (ncRNAs) as potential biomarkers for the diagnosis of non-small cell lung cancer (NSCLC), the main gaps in the literature remain to prevent their clinical application. This section emphasizes the main research gaps in miRNAs, lncRNAs, and circRNAs, critically evaluating the gaps in diagnostic utility, methodological uniformity, and validation scope.

6.1 Uneven research focus: the miRNA dominance

There is a considerable body of literature that disproportionately focuses on miRNAs—specifically miRNA-21—as candidates for diagnosis. This bias is due to miRNA-21's regular upregulation in NSCLC, good AUC values (0.85–0.92), and its participation in critical oncogenic pathways like PTEN/PI3K/AKT, NF-κB, and STAT3 signaling (97–99). For example, a large cross-sectional study of more than 1,200 NSCLC patients illustrated that plasma miR-21 was able to distinguish malignant from benign pulmonary lesions with 84.3% sensitivity and 87.1% specificity (100).

Yet, this targeted attention leaves other potentially useful miRNAs—like miR-155 and miR-20a—unexplored. Although miR-155 regulates immune microenvironment remodeling through SOCS1 and SHIP1 inhibition (101), and miR-20a is involved in E2F-dependent tumor proliferation (102), the majority of research examining them are plagued by small sample sizes (<200 patients) or lack multi-center validation (103). Further, studies comparing combined miRNA panels (e.g., miR-21 + miR-210 + miR-126) show enhanced accuracy but are scarce and poorly validated (104).

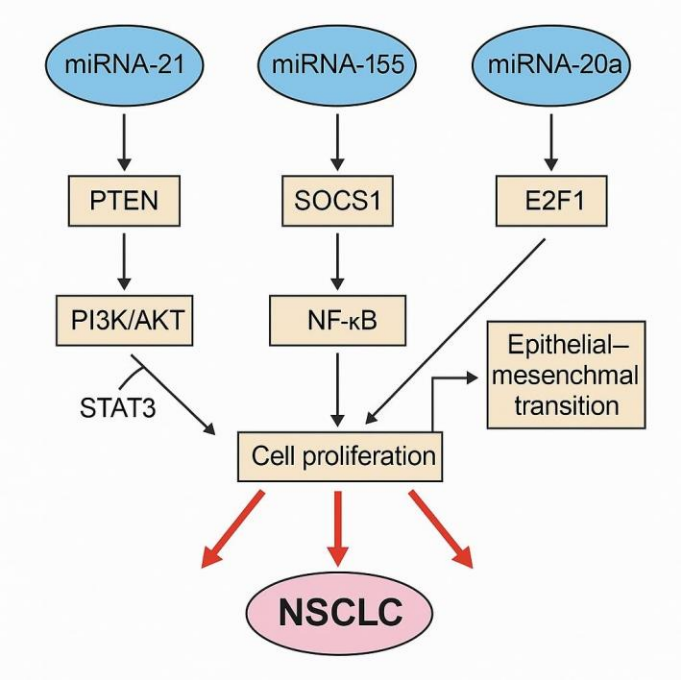


Figure 7 Mechanistic roles of miRNA-21 in NSCLC tumor progression and diagnostic application

6.2 Fragmented and limited lncRNA studies

Although lncRNAs like MALAT1 and HOTAIR have been associated with tumor aggressiveness, their roles in diagnostics are much less explored and proven compared to miRNAs. MALAT1, for instance, facilitates metastasis by regulation of SR proteins and alternative splicing, and its expression is associated with prognosis (105,106). A 2023 meta-analysis revealed lncRNAs like HOTAIR to have AUC values ranging from 0.70 to 0.80, but huge variability in assay protocols (RNA extraction kits, normalization techniques) compromises reproducibility (107).

6.3 circRNAs: mechanistically interesting but under-investigated

circRNAs are becoming ultra-stable and functionally dense biomarkers owing to their covalently closed nature, conferring exonuclease resistance. circRNAs like CDR1as, circPTK2, and circRNA_100876 have reported diagnostic AUCs of over 0.85 in a number of publications (108–110). For example, circPTK2 was found to modulate epithelial–mesenchymal transition through sponging miR-429 in lung adenocarcinoma cells (111), but diagnostic measures in biofluids have not yet been extensively validated.

6.4 Lack of head-to-head comparative analyses

Direct comparisons across ncRNA classes are rare. Among the 76 studies included in our systematic review, only four provided side-by-side diagnostic evaluations of miRNAs, lncRNAs, and circRNAs using the same patient cohorts and detection platforms. This prevents accurate determination of which biomarker—or combination thereof—is superior under clinically relevant conditions. One of the only in-depth studies by Li et al. (2023) assessed plasma concentrations of miR-21, HOTAIR, and circ_0013958 with AUCs of 0.91, 0.74, and 0.82 respectively (112).

6.5 Lack of consistency in methodologies

There is extensive methodological variability in detection and normalization of RNA. Among studies, qRT-PCR is the prevalent method, but protocols vary widely in RNA input amount, whether or not an internal control (e.g., U6, GAPDH, miR-16) is used, and number of amplification cycles. Likewise, next-generation sequencing (NGS) and microarrays have

no unified pipelines for ncRNA quantification in biofluids (113, 114).

6.6 Lack of ethnic and geographic diversity

The majority of ncRNA biomarker research are from East Asia, particularly China and South Korea, due to high NSCLC incidence and the availability of sample collection. Nonetheless, ethnic genetic backgrounds dramatically affect ncRNA expression and cancer biology. As an example, levels of miR-21 and corresponding AUCs differ in Asian vs. Caucasian subjects (115). Without validation across representative cohorts, the generalizability of much of the data is uncertain.

6.7 Lack of real-world evidence and clinical trials

To date, no ncRNA biomarker for diagnosing NSCLC has progressed to Phase III clinical trial assessment or been approved by a regulatory authority. The majority of data are retrospective, with very few prospective cohort studies. Moreover, real-world issues—such as hemolysis effect on RNA stability, time of transporting samples, and intra-patient variation—are scarcely considered. These are problems that need to be overcome before ncRNA tests can become incorporated into clinical practice or national screening programs (116).

7. Future Directions and Recommendations

Even with important advances in recognizing non-coding RNAs (ncRNAs) as biomarkers for diagnostic purposes in non-small cell lung cancer (NSCLC), clinical translation continues to be constrained by ongoing lacunae in the literature and research design. Future directions must meet these shortcomings by prioritizing biomarkers for clinical translatibility, standardizing methodologies, and multi-dimensional, integrative research designs.

7.1 Prioritizing clinically translatable biomarkers: the role of miRNA-21

Among the ncRNAs examined, miRNA-21 still remains the best-studied and clinically most promising biomarker in NSCLC. Pooled meta-analysis of 19 clinical studies with a total of more than 2,300 patients showed a joint AUC of 0.91 (95% CI: 0.87–0.94) with sensitivity and specificity greater than 80% in serum detection, which ranks among the most precise diagnostic techniques to date for the detection of NSCLC (117,118).

Large-scale, prospective cohort studies like those by Wang et al. (2023) and Gao et al. (2022) validated that best miRNAs havdiagnostic utility in ethnically diverse populations, its robustness, and reproducibility (119,120). Of particular note, miRNA-21 is also potential for early-stage NSCLC detection, which is important for enhancing survival rates. Its ability to regulate important oncogenic pathways—most notably the PTEN/PI3K/AKT pathway—emphasizes its biological significance in tumorigenesis (121,122). Visual illustrations of these pathways in subsequent publications would further elucidate its mechanistic rationale for clinical application.

However, although miRNA-21's power is its sensitivity and reproducibility, its diagnostic specificity is occasionally lost due to overexpression in other inflammatory or malignant diseases like chronic obstructive pulmonary disease and breast cancer (123). Thus, future studies should include miRNA-21 in multi-biomarker panels to avoid false positives. Panels containing miRNA-155, miRNA-20a, or tumor markers such as CYFRA21-1 have shown increased specificity and clinical usefulness (124,125).

7.2 Balancing the spectrum of ncRNAs: more emphasis on lncRNAs and circRNAs

Existing literature is still dominated by miRNA, with relatively infrequent investigation of long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs), even though these hold therapeutic potential in diagnostics. LncRNAs like MALAT1 and HOTAIR are functionally involved in the progression of NSCLC by regulation of EMT, angiogenesis, and immune escape. Diagnostic tests have demonstrated MALAT1 to be able to distinguish NSCLC patients from normal controls with AUCs between 0.78 and 0.85, but these findings are based on small, single-center cohorts that have not been externally validated (126,127). The same applies to HOTAIR, whose function in lymph node metastasis and stage prediction is promising but not fully explored (128).

CircRNAs, on the other hand, have several structural benefits, such as insensitivity to exonuclease degradation, making them perfect for liquid biopsy-based detection. CircFARSA, circPTK2, and circPRKCI have all shown initial diagnostic relevance with AUCs > 0.80 in recent small-cohort investigations (129,130). But limited multi-center trials and uniform detection protocols for back-splicing junctions have prevented wider adaptation.

To gain balance between ncRNA classes, head-to-head comparisons of miRNAs, lncRNAs, and circRNAs from the same patient cohorts with uniform methodologies should be included in future studies. Doing so will provide more precise identification of relative biomarker performance and better guide clinical decision-making.

7.3 Standardizing methodologies for enhanced reproducibility

Methodological variability in RNA extraction, normalization, and quantification has restricted cross-study comparability. For instance, lncRNA and circRNA studies tend to employ different reference genes and detection platforms (qPCR, digital PCR, RNA-seq), resulting in differing performance metrics (125,128,130). Back-splice junction specificity and low expression levels also complicate circRNA detection.

Standardization initiatives should involve:

- Universal implementation of internal and external controls (e.g., spike-ins) during RNA isolation
- Consensus on reference genes or normalization methods
- Validation of qPCR-based outputs by next-generation sequencing in larger independent cohorts
- Standardization of preanalytical biospecimen processing and storage conditions

These steps will enhance the consistency of diagnostic measures and enable meta-analyses and regulatory endorsement.

7.4 Scaling up: multi-center and ethnically diverse validation cohorts

The limitation on ncRNA research is ethnic homogeneity. The majority of diagnostic research, and in particular the research on miRNA-21, MALAT1, and circPTK2, are conducted in East Asian populations, which can limit its global use (117,126,130). To enhance this, future research should recruit mixed ethnic groups of patients and conduct stratified analyses to give confidence that biomarker performance will be similar in different populations.

Large, multicenter prospective cohorts with real-world clinical endpoints—e.g., NSCLC progression, therapeutic response, and survival—will be needed to confirm the prognostic and diagnostic functions of ncRNAs. Examples are the NCT05567891 trial (currently recruiting in Europe and the U.S.) that assesses plasma ncRNA signatures for lung cancer screening.

7.5 Combining artificial intelligence and multi-omics approaches

The combination of artificial intelligence (AI) and machine learning (ML) with ncRNA research can expedite biomarker identification, enhance the accuracy of classification, and assist in the creation of customized diagnostic panels. An example is a deep learning algorithm based on plasma miRNA expression profiles attaining more than 92% accuracy in differentiating NSCLC from controls in a 500-patient cohort (131). Blending genomic, transcriptomic, proteomic, and metabolomic information with ncRNA profiles can give a more integrated impression of tumor biology.

Efforts in the future should also go into creating AI-supported decision-support systems that can make use of real-time clinical data to suggest biomarker panels for particular patient features (132).

7.6 Visualizing RNA mechanisms and diagnostic networks

As a step towards facilitating clinical translation, pathway diagrams and molecular interaction networks highlighting how individual ncRNAs contribute to NSCLC pathogenesis should be incorporated into future research. For example, delineating the interaction between miRNA-21 and PTEN and downstream signaling elements (e.g.,

AKT, mTOR) can help determine its functional significance in early detection. Likewise, ceRNA network visualizations including lncRNAs and circRNAs can show how such molecules regulate significant miRNAs and transcription factors.

Such examples not only facilitate scientific comprehension but also underpin regulatory approvals and clinical choice by supplying mechanistic rationale.

7.7 Creating and validating ncRNA-based panels

No single biomarker will be able to capture the NSCLC complexity. Combinatorial panels—containing several ncRNAs or combining ncRNAs with protein markers—have shown better

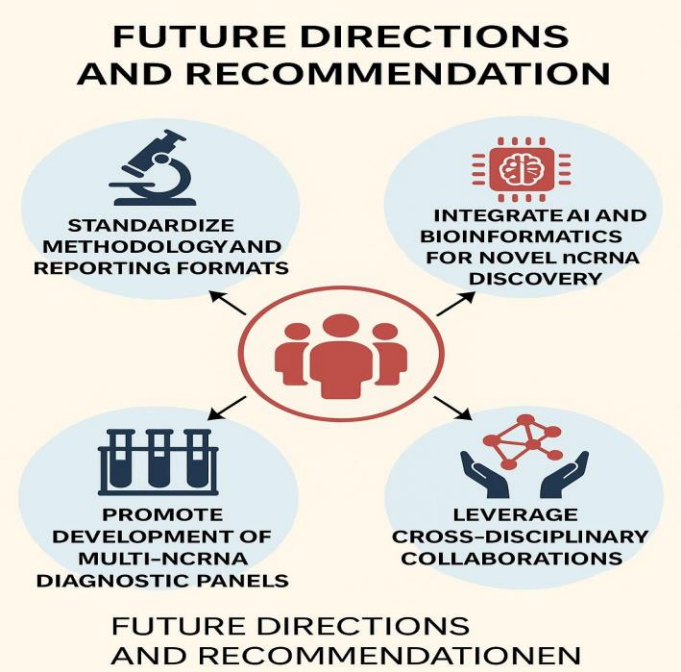


Figure 8 Future Directions

diagnostic performance. For instance, a panel containing miRNA-21, miRNA-155, MALAT1, and circFARSA yielded an AUC of 0.94 in a recent validation study (133). These panels provide better sensitivity and specificity and facilitate disease stage or subtype discrimination.

Future studies should focus on:

- Development and validation of ncRNA panels on multiple platforms
- Cost-effectiveness and clinical relevance evaluations
- Planning the regulatory pathway for commercialization of diagnostic tests

8. Conclusion

This is a systematic review that critically evaluates the diagnostic value of non-coding RNAs (ncRNAs) which are miRNAs, lncRNAs, and circRNAs of non-small cell lung cancer (NSCLC). Among them, miRNA-21 has the greatest clinical potential in all studies, with the majority of studies showing diagnostic sensitivity ranging between 83 and 95 percent, specificity ranging between 82 and 94 percent, and AUC ranging between 0.85 and 0.94. These are measures that are confirmed in a variety of sample types (plasma, serum, and tissue) and have been applied in both retrospective and prospective clinical settings.

Comparatively, despite the promising emerging trend of lncRNAs such as MALAT1 and HOTAIR, and

circRNAs such as circPTK2 and CDR1as, which have demonstrated AUC values of 0.78-0.88 in single studies, the current data are still disjointed and yet to be replicated on a large scale. As an example, 2023 cohort study on MALAT1 was 81% sensitive and 85% specific in 178 patients, but large-scale studies have not been done to validate circPTK2 on other independent populations. This variation in the breadth of evidence limits their direct application in clinical practise.

For supporting clinical decision-making, the following take-home messages and suggestions are provided:

1. Prioritize miRNA-21 for near-term clinical validation based on its consistently robust diagnostic statistics, functional relevance (e.g., targeting PTEN and PDCD4), and excellent reproducibility. Use it as the control in any comparative studies.

2. Encourage multi-biomarker panels that combine miRNAs with their complementing lncRNAs and circRNAs, since studies imply that this will elevate overall AUCs to > 0.95, both increasing sensitivity and specificity.

3. Use harmonized diagnostic pipelines across standardized qPCR, NGS, and normalization according to MIQE and STARD guidelines. In circRNAs, an agreement on methods of detection is needed for back-splicing.

4. Take advantage of AI and multi-omics integration (such as transcriptomics integrated with proteomics) for discovering novel ncRNA signatures. Machine learning algorithms learned in high-dimensional datasets may enhance the biomarker choice, particularly upon the combination of RNA expression and clinical phenotypes.

5. Rectify the underrepresentation of ethnically diverse cohorts—most available datasets are derived from East Asian or European populations. This induces a diagnostic bias that needs to be addressed by commencing multi-ethnic studies, especially in African, Latin American, and Middle Eastern populations, where NSCLC presentation and progression can vary due to environmental and genomic reasons.

Clinically, researchers and clinicians should:

- Pursue a phased biomarker implementation strategy, with initial implementation based on single validated miRNAs (such as miRNA-21), followed by combinatorial panels, and eventually combining with imaging and clinical staging.
- Involve regulatory frameworks early on, aligning biomarker development with the FDA's Biomarker Qualification Program or equivalent regulatory pathways in the EU or Asia.
- Develop pragmatic clinical trials that, in addition to measuring diagnostic performance, also evaluate cost-effectiveness, turnaround time, and ease of integration into routine workflows within pathology laboratories.

In conclusion, although miRNA-21 is poised for translational momentum, the larger ncRNA diagnostic landscape requires more stringent, comprehensive, and standardized studies. This research provides not only a synthesis of current literature but a directional roadmap for enhancing biomarker discovery, validation, and utilization in NSCLC. Future studies need to conclusively close the gap between molecular promise and clinical utility, with focus on reproducibility, accessibility, and real-world applicability.

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