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Non-coding RNAs as non-invasive diagnostic biomarkers for lung cancer

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Abstract

Lung cancer stands as the second most prevalent cause of cancer-related mortality worldwide and is mainly influenced by delayed diagnosis, even with available therapeutic alternatives. The most recent studies indicate that non-coding RNAs (ncRNAs) are involved with maintaining homeostasis in cells, particularly in gene expression regulation. Hence dysregulation of these ncRNAs may develop cancer. ncRNAs in biofluids like blood, urine, saliva, serum, and plasma exosomes provide a non-invasive and less painful approach to detecting lung cancer progression. In this review novel studies for subclasses of ncRNAs such as long non-coding RNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (circRNA) have been summarized to determine the most Potential biomarkers for prognose lung cancer.

Keywords: Lung neoplasm, ncRNAs, lncRNA, miRNA, circRNA, Exosomes, Diagnosis

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1. Introduction

According to the statistics, lung cancer presents a high incidence, with an estimated 2.20 million new cases and 7.9 million mortalities annually worldwide (1). Lung cancer includes a variety of distinct tumor types. The primary cancer subtypes are non-small cell lung cancer (NSCLC), with 81% of prevalence categorized with lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUCC), large cell carcinoma (LCC), and small cell lung cancer (SCLC), with 14% of prevalence (2, 3). LUAD shows a higher incidence with less specific symptoms in women and individuals who smoke, and LUSC has more incidence in men and smokers with main symptoms like fever, coughing, and chest pain (4-6). One of the challenges in detecting lung cancer is that the early symptoms are subtle and fail to notice. Therefore most patients are commonly diagnosed at later stages. These reasons highlight the critical need for molecular biomarkers to facilitate accurate diagnosing and therapeutic interventions (7). Tissue biopsy, the gold standard for analyzing tumor mutational status has disadvantages. For instance, invasive collection with inadequate quality and difficulties in obtaining repetitive samples thereby limiting its molecular analysis effect (8, 9). However, liquid biopsy encompassing cell-free DNAs, cell-free RNAs, circulating tumor cells, exosomes, and circulating tumor DNA, operates as a valuable supplementary method by allowing the examination of various biomarkers present in blood samples (10-12). ncRNAs have vital roles in cellular processes. They can be categorized into two main groups: housekeeping ncRNAs and regulatory ncRNAs. The products of regulatory ncRNAs are essential for the maintenance of fundamental cellular activities like regulating gene expression, transcription, and post-transcription (13). For example, the regulation of gene expression through miRNAs is a major type of epigenetic control. One of the significant changes caused by epigenetic reprogramming is the alteration of these ncRNA profiles (14). The hypermethylation of specific miRNA promoters shows how ncRNA silencing through epigenetic mechanisms can lead to the dysregulation of essential signaling pathways in cancer development. The interactions between ncRNAs and DNA methylation are related to tumorigenesis and can be proposed as promising targeted therapies (15). The expression of certain miRNAs and lncRNAs has been correlated with the invasiveness and metastatic behavior of various types of tumor cancers, such as lung adenocarcinoma (16, 17). So, the dysregulation of ncRNAs is involved in the pathogenesis of lung cancer. Figure 1 illustrates the summary of ncRNAs in the pathogenesis of lung cancer with their irregular expression. The receiver operating characteristic (ROC) curve illustrates sensitivity versus specificity. It is widely used for evaluating the discriminatory power of diagnostic studies. Sensitivity refers to positive results in individuals with the disease, and specificity refers to negative results in individuals without the disease. Therefore, sensitivity and specificity show the accuracy of the test, and the most popular index for differentiating cancer from non-cancer classes is “The area under the ROC curve (AUC)” (18, 19). For instance, if the AUC of a diagnostic test is one, it indicates that the test perfectly distinguishes between patients and healthy individuals (20). This review investigates non-coding RNA utilization, extracted from biofluid samples in a minimally invasive procedure, as prospective diagnosis biomarkers for various lung cancer subtypes.

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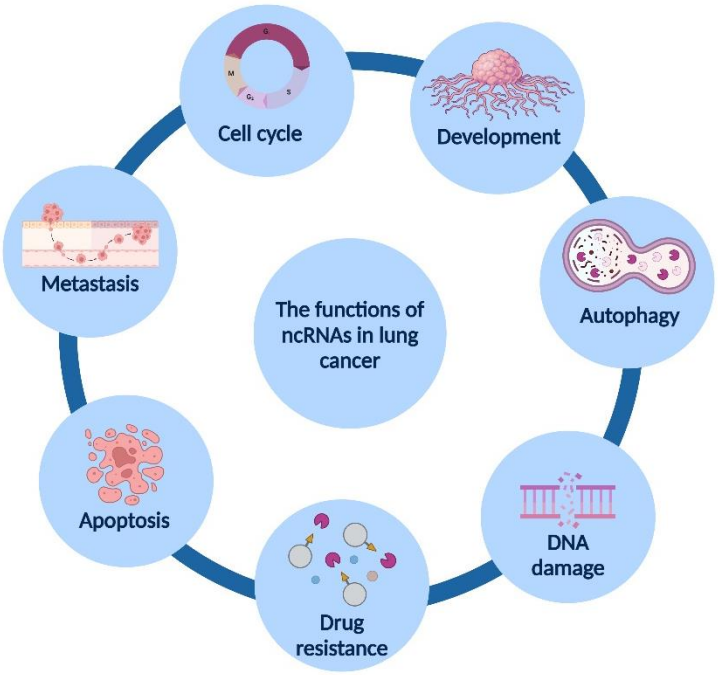


Figure 1. ncRNAs act as oncogenes or tumor suppressors by altering the biological processes of lung cancer. Created with biorender.com

2. Evidence acquisition

The Pubmed database was searched using the keywords: "lung cancer", lncRNA, miRNA, circRNA, biomarker, non-invasive, and blood/serum/plasma/exosome/urine/saliva to select the related research studies from 2020 to 2023.

3. Results

3.1. LncRNAs

LncRNAs are considered to be the largest molecule in subclasses of RNAs with a range of 200bp to 100kbp length (21). The engagement of lncRNAs in regulating gene expressions (22), modulating cell cycle, growth (23), cell migration, and invasion (24), correlates with their presence in cancers by their dysregulation from initiation stage to metastatic form of tumors (24, 25). LncRNAs are steady and can maintain themselves from deterioration, freezing, and thawing cycles (26). They can be transported by exosomes through their secondary structures. Therefore, lncRNAs in circulation are accessible non-invasive approaches for diagnosing cancer development and metastasis (27, 28). One of the exosomal lncRNA UFC1 evaluated by Zhang et al. (29), illustrated a decrease in PTEN expression, leading to metastasis and lung cancer cell proliferation. In two similar studies, lncRNAs RP11-397D12.4, ERICH1-AS1, AC007403.1 (30) with an AUC of 0.942 and lncRNAs NEAT1, ANRIL, SPRY4-IT1 (31) with an AUC of 0.876, were overexpressed in NSCLC cells compared to healthy controls and were stable even after three to five times of freeze-thaw cycles. LncRNAs can also show different expression profiles between positive and negative responses to a specific treatment. For example, wang et al. (32) found that patients demonstrated different responses to nivolumab immunotherapy, and showed upregulated expression patterns of exosomal lncRNAs, such as lnc-CENPH-1, lnc-CENPH-2, and lnc-ZFP3-3-TAF1-CCNB1, therefore they can predict the efficiency of immunotherapy. Tetik Vardarlı et al. used another non-invasive method, exhaled breath condensate (EBC), to collect lncRNAs HOTAIR, PVT1, NEAT1, MALAT1, and their investigation indicated significantly elevated expression levels compared to healthy controls, and showed their association with the development and progression of multiple malignancies like lung cancer (33). Table 1 collected the probability of lncRNAs as biomarkers for diagnosis.

3.2. circRNAs

circRNAs are closed-loop, formed by covalent bonds, resulting in a higher level of stability, and 10 times more abundant than their linear mRNAs, which makes them great options for diagnostic biomarkers and prognosis (44, 45). They are involved in regulation, transcription, translation, interaction with proteins, autophagy, and immunity and they act as miRNA sponges (46-49). They are also associated with drug resistance, progression, and development of cancers (50-52). Exosomal contents and circRNAs have been considered as potential biomarkers from liquid biopsy (53). One of the well-known functions of circRNAs is that they act as a sponge of miRNAs, impacting gene expression profiles and influencing signaling pathways. A study worked by zhu et al. showed that hsa_circ_0013958 acted as a sponge for miR-134 ($P < 0.001$), which leads to proliferation in LAC cells (54). Studies have shown that circRNAs can serve as a biomarker for drug resistance in the tumor. For example, wei et al. (52) found that circKIF20B was down-regulated in the exosomal serum of NSCLC cells which contributes to gefitinib resistance.

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Table 1. Novel lncRNAs as diagnosis biomarkers in lung cancer

LncRNAs	Subtype of cancer	Sample	Expression level	Method	Findings	Year	Reference
LINC00460	NSCLC	Plasma	Up	qRT-PCR	Correlated with osimertinib resistance In EGFR-Mutated Cells, an AUC value Of 0.722	2023	(34)
LINC02159	NSCLC	Serum	Up	RNA FISH	Involves In apoptosis and cell cycle arrest, and ALYREF/YAP1 signaling	2023	(35)
THRIL	LC	Serum	Up	qRT-PCR	Correlated with the expression of IGF1R By sponging Mir-99a, AUC=0.912, Sensitivity = 87.34%, Specificity = 83.78%	2023	(36)
nc-MLETA1	NSCLC	Plasma Exosome	Up	qRT-PCR	Related to the expression of EGFR By sponging Mir-186-5p leading to cell migration and Invasion	2023	(37)
MFI2-AS1	NSCLC	Plasma Exosome	Up	qRT-PCR	Known as an oncogene and is involved in tumor proliferation and metastasis	2023	(38)
Lnc- ABCA12-8	NSCLC	Blood	Up	qRT-PCR	Correlated with proliferation in cells, binds with ASF/SF2 protein leading to gefitinib-resistance	2022	(39)
RP5-977B1	NSCLC	Plasma Exosome	Up	qRT-PCR	AUC=0.8899 Sensitiv¬ity=82.86% Specificity =84.93% Associated with tumor stage and distant metastasis	2022	(40)
LINC00662	NSCLC	Plasma Exosome	Up	qRT-PCR	Promotes proliferation, and inhibits apoptosis	2021	(41)
ADAMTS9-AS2	NSCLC	Blood	Down	qRT-PCR	AUC=0.957 Sensitivity=95% Specificity =99.1%	2021	(42)
lnc-FRAT1-5, lnc-SRY-11, lnc-RNASE13-1 and lnc-RP11-80A15.1.1-2, lnc-ARL6IP6-4, lnc-DGKQ-1	NSCLC	Urine	The first three were up, The second three were down	qRT-PCR	Connected to proliferation apoptosis, showed a connection with PI3K/AKT, FOXO, and P53 signaling pathways	2021	(43)

Table 2. Selected circRNAs identified as diagnosis biomarkers in LC

circRNA	Subtype of cancer	Sample	Expression level	Method	Findings	Year	Reference
circVPS35L	NSCLC	Blood	Down	qRT-PCR	Correlated with tumor size and TNM stage	2023	(55)
circ-PDCD11	LLCC	Plasma	Up	qRT-PCR	Related to tumor metastasis	2023	(56)
hsa_circ_0023179	NSCLC	Serum	Up	qRT-PCR	Associated with TNM stage, migration in NSCLC	2023	(57)
hsa_circ_0000722	NSCLC	Plasma	Up	qRT-PCR	Sponges of mir-324-5p, mir-326, and mir-330-5p which are involved in several pathways and metabolism of cancer	2023	(58)
hsa_circ_0041150	SCLC	Serum	Up	qRT-PCR	Increases drug resistance in SCLC cells and correlated with proliferation, and	2023	(59)
EVs-circHIPK3	LC	Blood, plasma	Up	qRT-PCR	AUC=0.897,		
circ_0008717	NSCLC	Serum exosome	Up	qRT-PCR	Promoted cancer growth and had a role in the differentiation	2022	(60)
circVMP1	NSCLC	Blood	Up	qRT-PCR	Involved In Proliferation,	2022	(61)
FLI1 exonic circRNAs (FECR)	SCLC	Serum exosome	Up	RNA FISH and qRT-PCR	Correlated with metastasis	2019	(52)

3.3. miRNAs

miRNAs represent unique expression profiles in different tissues and cells that underlie their part in tumorigenesis through their interactions with specific cellular genes (62, 63). They are single-stranded, and have 21 to 23 nucleotide lengths (64). miRNAs are one of the richest in cells among RNAs. Within cellular systems, miRNAs modulate pivotal processes including cell proliferation, metastasis, chemoresistance, invasive behaviors, migration, and modulating apoptosis and autophagy pathways via miRNA-mRNA interaction networks (65). Tumors secrete these into various bodily fluids, including blood, urine, saliva, plasma, serum, and amniotic fluids which makes them highly effective biomarkers for cancers (66-68). Su et al. analyzed the expression of miR-21, miR-31, miR-210, and the methylation of 3 genes (RASSF1A, PRDM14, 3OST2) from the sputum of NSCLC patients at the early stage, and these miRNA biomarkers showed 81.5 % sensitivity and 85.9 % specificity but the combination of these two different types of circulating epigenetic biomarkers made a higher AUC of 0.93 (69). The AUC, sensitivity, and specificity have been categorized in Figure 2 for miRNAs obtained via liquid biopsy in different types of lung cancer (70-81). These findings suggest a promising prospect for miRNAs and their application as clinical biomarkers.

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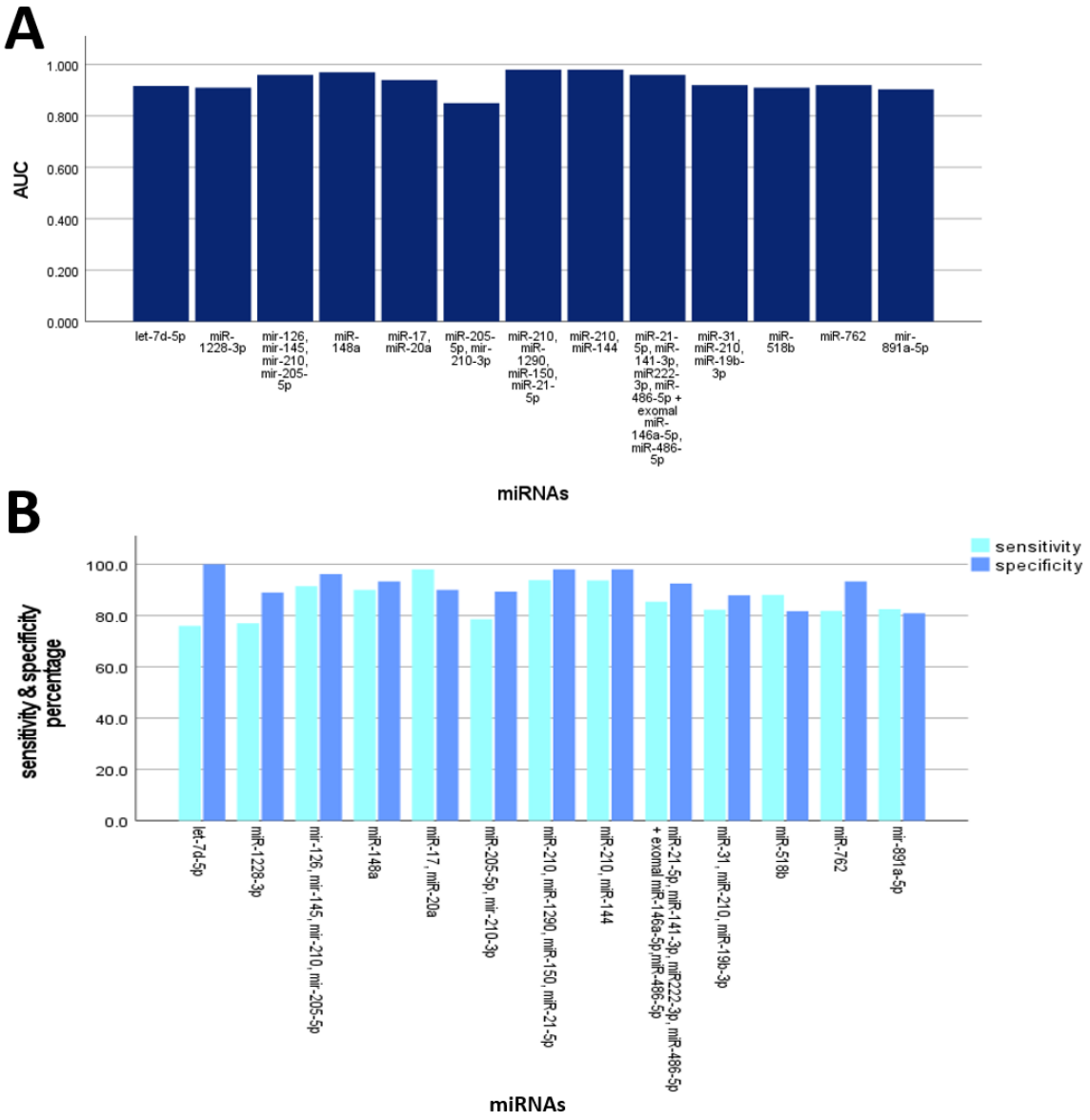


Figure 2. The comparison of miRNAs was collected in non-invasive ways. (A) miRNAs with an AUC value greater than 0.9. (B) High percentages of sensitivity and specificity, show their potential to be a diagnostic biomarker. Created with IBM SPSS Statistics 27 software

4. Conclusion

Ideal biomarkers are characterized by their non-invasive nature, ease of measurement, collection from different sources, high percentages of sensitivity and specificity, and the ability for early diagnosis (82). Numerous previous studies have indicated that certain ncRNAs have greater diagnostic accuracy with higher values of AUC, sensitivity, and specificity compared to conventional biomarkers such as carcinoembryonic antigen (CEA), cytokeratin-19 fragment (CYFRA21-1), squamous cell carcinoma antigen (SCCA), prolactin (PRL), and carbohydrate antigen 125(CA125) (83, 84). Some of the ncRNAs can differentiate the lung cancer subtypes, presenting an opportunity to enhance diagnosis and treatment effectiveness by using personalized medicine strategies (85, 86). Exosomes are extracellular vesicles that can protect their cargo from degeneration while transmitting their information between cells (87, 88). Tumor cells release more exosomes containing nucleic acids into body fluids than normal cells. Consequently, exosomes can be an ideal diagnosis tool (figure 3). Another study showed differentially expressed pseudogenes in plasma-derived exosomes such as LOC100129096, PTMAP2, CDC14C, LOC643634, FTH1P2, ARPC3P3, FTH1P11, and PTMAP5, from lung adenocarcinoma patients using RNA sequencing analysis that can be served as diagnostic biomarkers and for monitoring the treatments of patients (89). Pseudogenes can regulate oncogenes and tumor suppressors by interfering with the activity and function of critical protein-coding genes (90). Stasiak et al. reviewed many types of pseudogenes and classified them as predictor, inheritance, or prognostic biomarkers. They interact with various molecular levels, including RNA, DNA, and protein molecules. Some pseudogenes can also be detected in body fluid with a variety of detecting approaches. Despite many studies, the role of pseudogenes in organismal biology is still not fully clear and needs more investigation (91).

Methylated DNA, miRNA, and post-transcriptionally modified histones are known epigenetic signatures that indicate the essential cellular changes found at elevated levels in lung cancer patients. These epigenetic circulating signatures can serve as biomarkers and monitoring of

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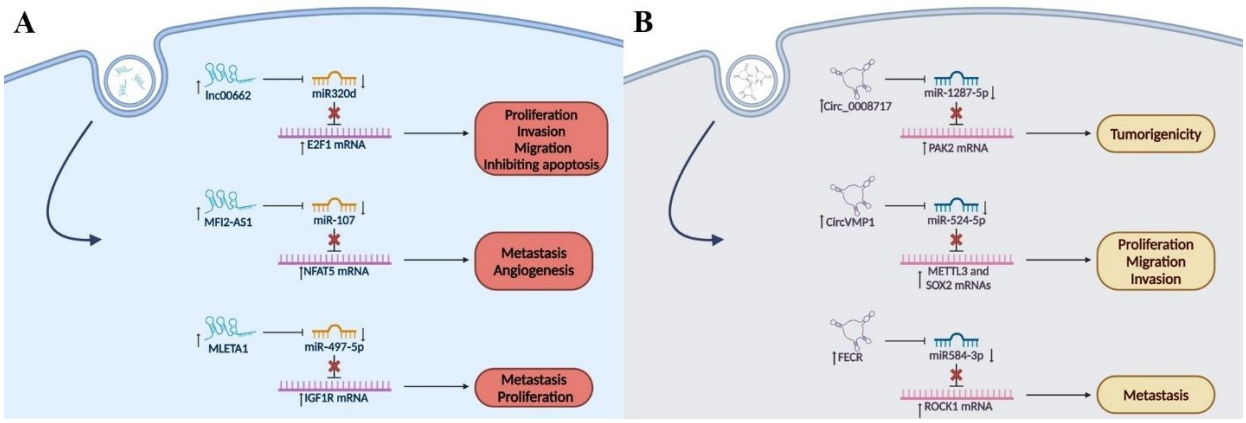


Figure 3. The involvement of exosomal ncRNAs in promoting lung cancer pathogenesis. (A) Exosomal lncRNAs prevent miRNAs from binding to their targets promoting metastasis and proliferation. (B) Exosomal circRNAs act as miRNA sponges to activate their mRNA targets leading to proliferation, migration, and invasion. Created with Biorender.com

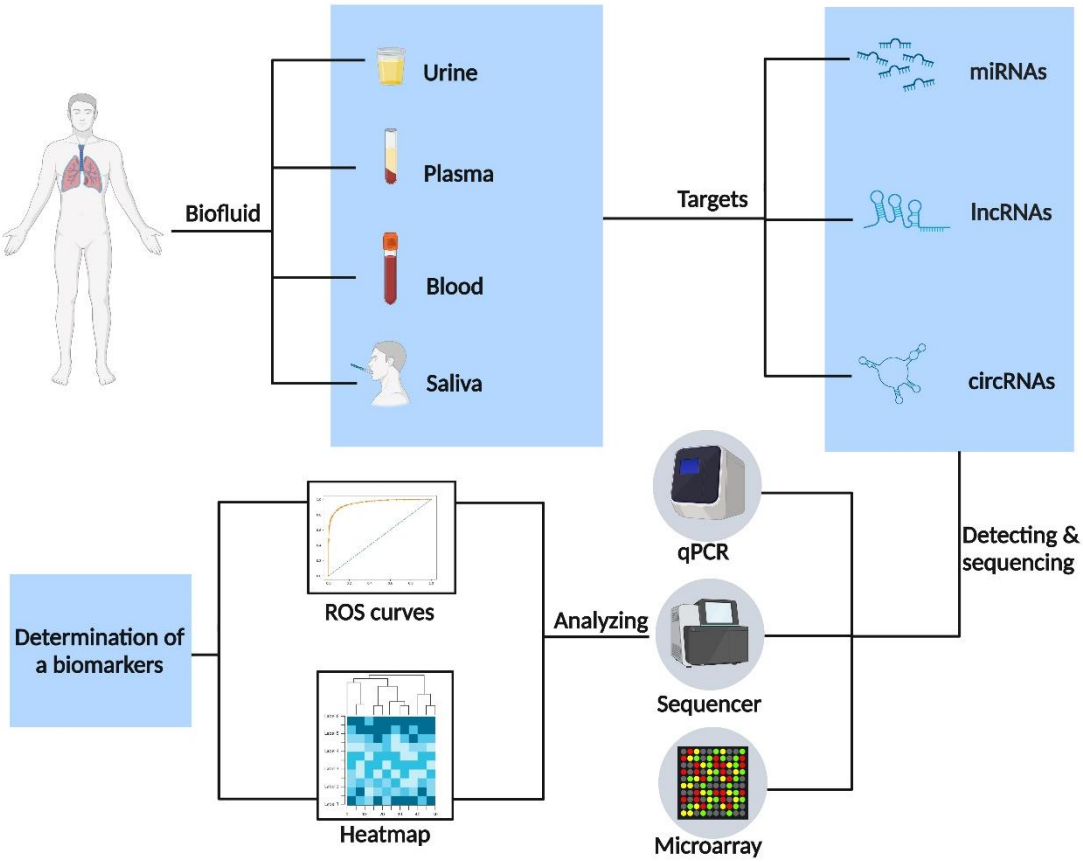


Figure 4. Determination of ncRNAs as novel biomarkers for lung cancer is a multistep process. ncRNAs isolated from liquid biopsies are followed by high-throughput sequencing, and finally statistical analysis to confirm them as a diagnostic biomarker. Created with biorender.com

treatment responses, as these processes are involved in the early stages of cancer progression (92). Belinsky reviewed the reprogramming of the epigenome in lung cancer, explaining the role of ncRNAs in gene silencing through cytosine DNA methylation and chromatin remodeling. This study emphasizes the reversible nature of epigenetic reprogramming and highlights how ncRNA-mediated hypermethylation targets can be developed (93). Chen et al. reviewed several lncRNAs such as HOTAIR, MALAT-1, and CCAT2 as potential epigenetic biomarkers for diagnosing NSCLC at early stages. The combination of epigenetic biomarkers with other early-detecting approaches could make diagnostic values significantly higher compared to using them individually. Hence, there will be a growing focus on these types of biomarkers for lung cancer diagnosis (17). Figure 4 offers a comprehensive overview, starting from collecting non-invasive samples to their identification as biomarkers. In conclusion, the utilization of non-coding RNAs (ncRNAs) presents an opportunity for the development of non-invasive diagnostic tools in lung cancer that can change early detection strategies.

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