J Human Gen Genom. 2023 Dec; 7(2): A-10-373-1 doi: 10.61186/jhgg.7.2.99
Published online 2024 September 18 **Review Article**

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

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Received 2023 December 14; **Accepted** 2024 September 17

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

[DOI: 10.61186/jhgg.7.2.99]

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.

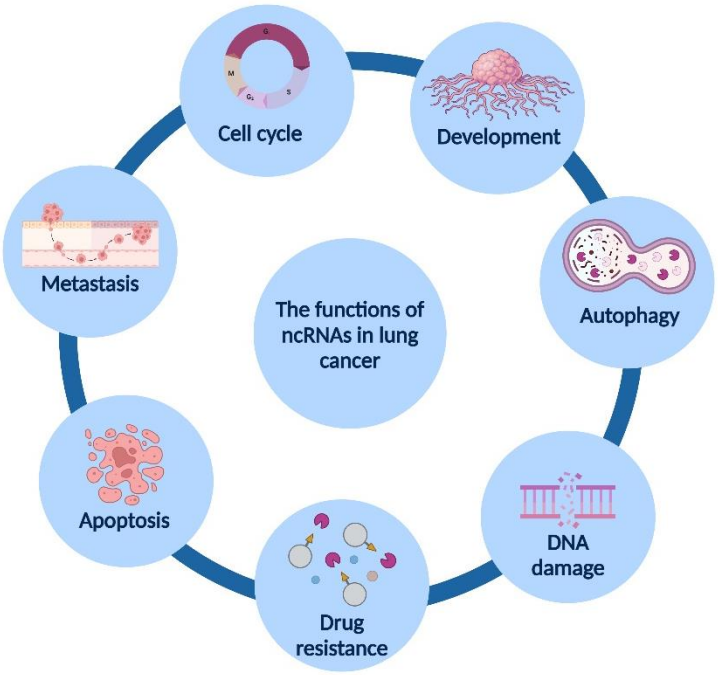

Figure 1. ncRNAs act as oncogenes or tumor suppressors by altering the biological processes of lung cancer. Created with biorender.com

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.

[DOI: 10.61186/jhgg.7.2.99]

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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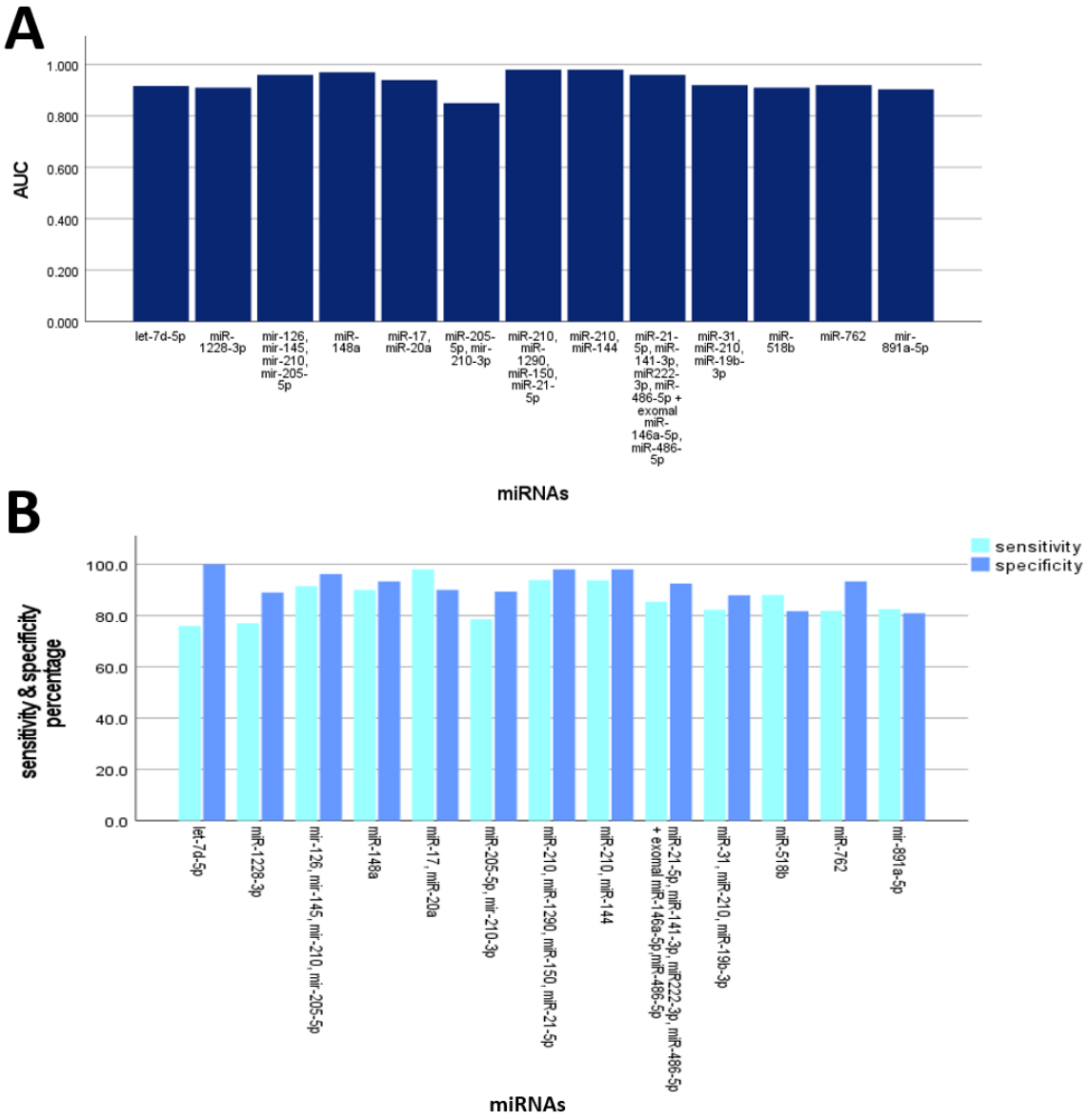

Figure 2. The comparison of miRNAs was collected in non-invasive ways. (A) miRNAs with an AUC value greater than 0.9. (B) High percentages of sensitivity and specificity, show their potential to be a diagnostic biomarker. Created with IBM SPSS Statistics 27 software

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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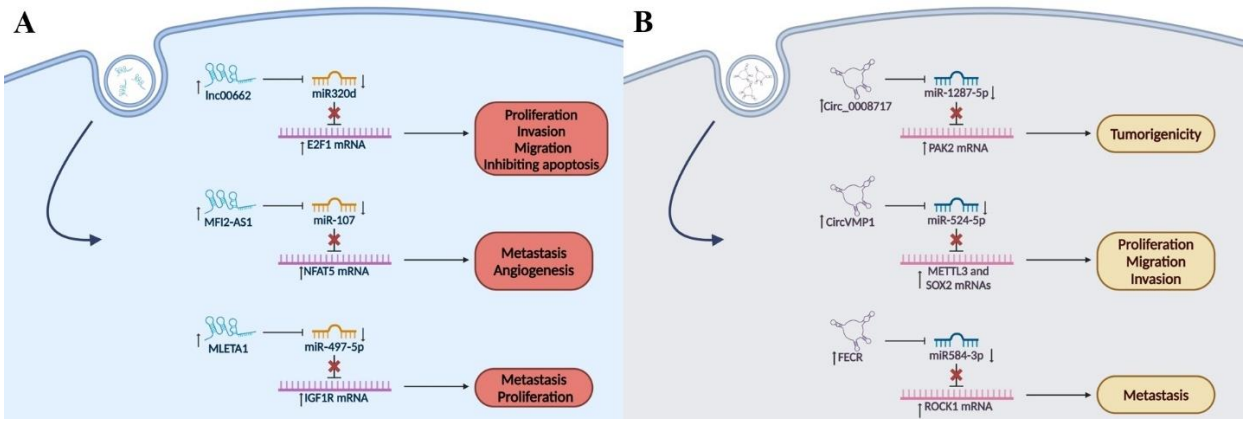

Figure 3. The involvement of exosomal ncRNAs in promoting lung cancer pathogenesis. (A) Exosomal lncRNAs prevent miRNAs from binding to their targets promoting metastasis and proliferation. (B) Exosomal circRNAs act as miRNA sponges to activate their mRNA targets leading to proliferation, migration,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

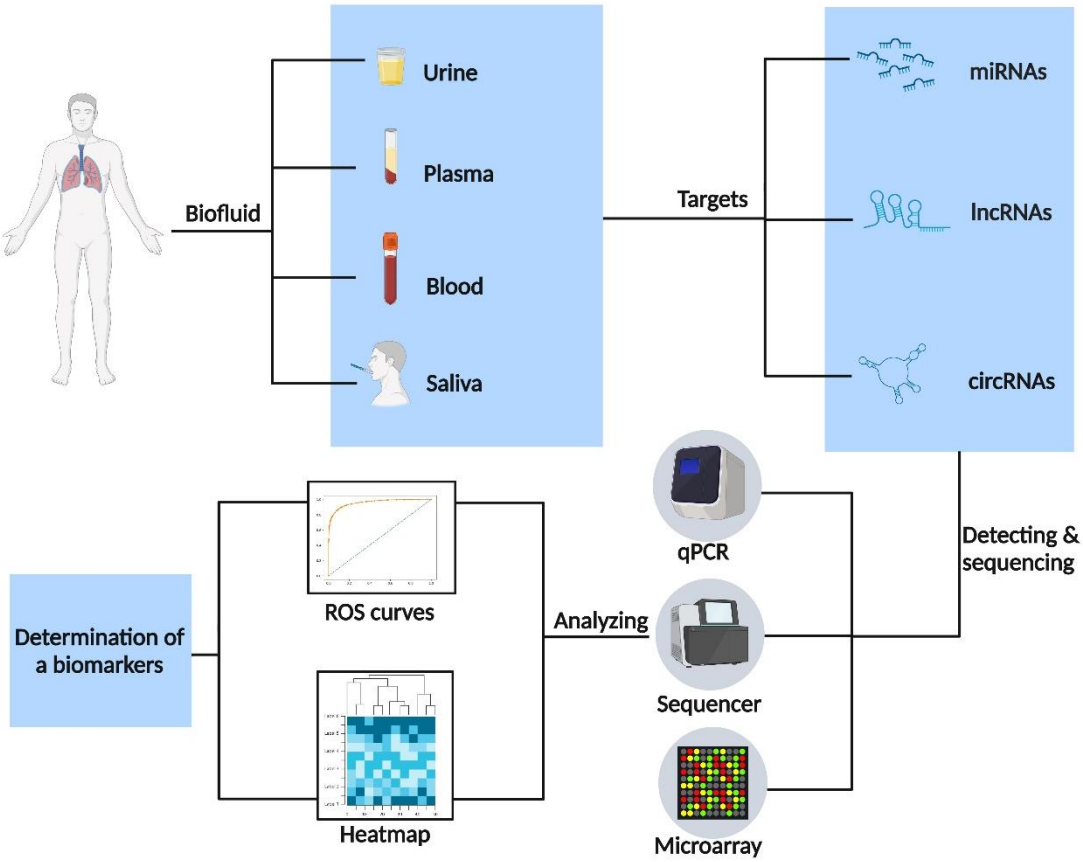

Figure 4. Determination of ncRNAs as novel biomarkers for lung cancer is a multistep process. ncRNAs isolated from liquid biopsies are followed by high-throughput sequencing, and finally statistical analysis to confirm them as a diagnostic biomarker. Created with biorender.com

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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References

1. Thai AA, Solomon BJ, Sequist LV, Gainor JF, Heist RS. Lung cancer. Lancet. 2021;398(10299):535-54.
2. Nicholson AG, Tsao MS, Beasley MB, Borczuk AC, Brambilla E, Cooper WA, et al. The 2021 WHO Classification of Lung Tumors: Impact of Advances Since 2015. J Thorac Oncol. 2022;17(3):362-87.
3. Wakelee HA, Chang ET, Gomez SL, Keegan TH, Feskanich D, Clarke CA, et al. Lung cancer incidence in never smokers. J Clin Oncol. 2007;25(5):472-8.
4. Kim L, Kim KH, Yoon YH, Ryu JS, Choi SJ, Park IS, et al. Clinicopathologic and molecular characteristics of lung adenocarcinoma arising in young patients. J Korean Med Sci. 2012;27(9):1027-36.
5. Zhao S, Guo X, Mizutani KI, Yamaguchi R, Yamada S, Gu C, Uramoto H. Overexpression of Teashirt Homolog 2 suppresses cell proliferation and predicts the favorable survival of Lung Adenocarcinoma. Int J Med Sci. 2021;18(9):1980-9.
6. Saito S, Espinoza-Mercado F, Liu H, Sata N, Cui X, Soukiasian HJ. Current status of research and treatment for non-small cell lung cancer in never-smoking females. Cancer Biol Ther. 2017;18(6):359-68.
7. Kang Y, You J, Gan Y, Chen Q, Huang C, Chen F, et al. Serum and Serum Exosomal CircRNAs hsa_circ_0001492, hsa_circ_0001439, and hsa_circ_0000896 as Diagnostic Biomarkers for Lung Adenocarcinoma. Front Oncol. 2022;12:912246.
8. Vanderlaan PA, Yamaguchi N, Folch E, Boucher DH, Kent MS, Gangadharan SP, et al. Success and failure rates of tumor genotyping techniques in routine pathological samples with non-small-cell lung cancer. Lung Cancer. 2014;84(1):39-44.
9. Alimirzaie S, Bagherzadeh M, Akbari MR. Liquid biopsy in breast cancer: A comprehensive review. Clinical Genetics. 2019;95(6):643-60.
10. Sorber L, Zwaenepoel K, Deschoolmeester V, Van Schil PE, Van Meerbeeck J, Lardon F, et al. Circulating cell-free nucleic acids and platelets as a liquid biopsy in the provision of personalized therapy for lung cancer patients. Lung Cancer. 2017;107:100-7.
11. Galarza Fortuna GM, Dvir K. Circulating tumor DNA: Where are we now? A mini review of the literature. World J Clin Oncol. 2020;11(9):723-31.
12. Peng Y, Mei W, Ma K, Zeng C. Circulating Tumor DNA and Minimal Residual Disease (MRD) in Solid Tumors: Current Horizons and Future Perspectives. Front Oncol. 2021;11:763790.
13. Leng S, Qu H, Lv X, Liu X. Role of ncRNA in multiple myeloma. Biomark Med. 2022;16(16):1181-91.
14. Lujambio A, Ropero S, Ballestar E, Fraga MF, Cerrato C, Setién F, et al. Genetic unmasking of an epigenetically silenced microRNA in human cancer cells. Cancer Res. 2007;67(4):1424-9.
15. Xu WW, Liao L, Dai W, Zheng CC, Tan XP, He Y, et al. Genome-wide CRISPR/Cas9 screening identifies a targetable MEST-PURA interaction in cancer metastasis. EBioMedicine. 2023;92:104587.
16. Bartels CL, Tsongalis GJ. [MicroRNAs: novel biomarkers for human cancer]. Ann Biol Clin (Paris). 2010;68(3):263-72.
17. Chen X, Yu S, Fan J. Epigenetic diagnostic biomarkers for non-small cell lung cancer: present and future perspectives. Translational Cancer Research. 2018;7(3):796-802.
18. Feng Y, Tian L. Issues and solutions in biomarker evaluation when subclasses are involved under binary classification. Statistical Methods in Medical Research. 2021;30(1):87-98.
19. Florkowski CM. Sensitivity, specificity, receiver-operating characteristic (ROC) curves and likelihood ratios: communicating the performance of diagnostic tests. Clin Biochem Rev. 2008;29 Suppl 1(Suppl 1):S83-7.
20. Hajian-Tilaki K. Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation. Caspian J Intern Med. 2013;4(2):627-35.
21. Li CH, Chen Y. Chapter Two - Insight Into the Role of Long Noncoding RNA in Cancer Development and Progression. In: Jeon KW, Galluzzi L, editors. International Review of Cell and Molecular Biology. 326: Academic Press; 2016. p. 33-65.
22. Obuse C, Hirose T. Functional domains of nuclear long noncoding RNAs: Insights into gene regulation and intracellular architecture. Curr Opin Cell Biol. 2023;85:102250.
23. Wapinski O, Chang HY. Long noncoding RNAs and human disease. Trends in Cell Biology. 2011;21(6):354-61.
24. Tsai MC, Spitale RC, Chang HY. Long intergenic noncoding RNAs: new links in cancer progression. Cancer Res. 2011;71(1):3-7.
25. Gutschner T, Diederichs S. The hallmarks of cancer: a long non-coding RNA point of view. RNA Biol. 2012;9(6):703-19.
26. Arita T, Ichikawa D, Konishi H, Komatsu S, Shiozaki A, Shoda K, et al. Circulating long non-coding RNAs in plasma of patients with gastric cancer. Anticancer Res. 2013;33(8):3185-93.
27. Badowski C, He B, Garmire LX. Blood-derived lncRNAs as biomarkers for cancer diagnosis: the Good, the Bad and the Beauty. NPJ Precis Oncol. 2022;6(1):40.
28. Fan T, Sun N, He J. Exosome-Derived LncRNAs in Lung Cancer. Front Oncol. 2020;10:1728.
29. Zang X, Gu J, Zhang J, Shi H, Hou S, Xu X, et al. Exosome-transmitted lncRNA UFC1 promotes non-small-cell lung cancer progression by EZH2-mediated epigenetic silencing of PTEN expression. Cell Death Dis. 2020;11(4):215.
30. Tang Q, Ni Z, Cheng Z, Xu J, Yu H, Yin P. Three circulating long non-coding RNAs act as biomarkers for predicting NSCLC. Cell Physiol Biochem. 2015;37(3):1002-9.
31. Hu X, Bao J, Wang Z, Zhang Z, Gu P, Tao F, et al. The plasma lncRNA acting as fingerprint in non-small-cell lung cancer. Tumour Biol. 2016;37(3):3497-504.
32. Wang Y, Cao S, Li J, Zhang Y, Ling X, Zhang L, et al. The predictive value of plasma exosomal lncRNAs/mRNAs in NSCLC patients receiving immunotherapy. Adv Med Sci. 2023;68(1):86-93.
33. Tetik Vardarli A, Ozgur S, Goksel T, Korba K, Karakus HS, Asik A, et al. Conversion of specific lncRNAs to biomarkers in exhaled breath condensate samples of patients with advanced stage non-small-cell lung cancer. Front Genet. 2023;14:1200262.
34. Nakano Y, Isobe K, Yoshizawa T, Urabe N, Homma S, Kishi K. Upregulation of long non-coding RNA LINC00460 in EGFR-mutant lung cancer indicates a poor prognosis in patients treated with osimertinib. Oncol Lett. 2023;26(3):380.
35. Yang Q, Wang M, Xu J, Yu D, Li Y, Chen Y, et al. LINC02159 promotes non-small cell lung cancer progression via ALYREF/YAP1 signaling. Mol Cancer. 2023;22(1):122.
36. Chen X, Zhu X, Yan W, Wang L, Xue D, Zhu S, et al. Serum lncRNA THRIL predicts benign and malignant pulmonary nodules and promotes the progression of pulmonary malignancies. BMC Cancer. 2023;23(1):755.
37. Hsu XR, Wu JE, Wu YY, Hsiao SY, Liang JL, Wu YJ, et al. Exosomal long noncoding RNA MLETA1 promotes tumor progression and metastasis by regulating the miR-186-5p/EGFR and miR-497-5p/IGF1R axes in non-small cell lung cancer. J Exp Clin Cancer Res. 2023;42(1):283.
38. Xu J, Wang H, Shi B, Li N, Xu G, Yan X, Xu L. Exosomal MFI2-AS1 sponge miR-107 promotes non-small cell lung cancer progression through NFAT5. Cancer Cell International. 2023;23(1):51.
39. He S, Shi J, Zhou H, Li Q, Wu L. Lnc-ABCA12-8 confers acquired resistance to gefitinib in non-small cell lung cancer by regulating the alternative splicing of fibronectin 1 in the IIICS region. Cancer Gene Ther. 2022;29(11):1686-96.
40. Min L, Zhu T, Lv B, An T, Zhang Q, Shang Y, et al. Exosomal LncRNA RP5-977B1 as a novel minimally invasive biomarker for diagnosis and prognosis in non-small cell lung cancer. International Journal of Clinical Oncology. 2022;27(6):1013-24.
41. Lv X, Lian Y, Liu Z, Xiao J, Zhang D, Yin X. Exosomal long non-coding RNA LINC00662 promotes non-small cell lung cancer progression by miR-320d/E2F1 axis. Aging (Albany NY). 2021;13(4):6010-24.
42. Abdul-Maksoud RS, Rashad NM, Elsayed WSH, Elsayed RS, Sherif MM, Abbas A, El Shabrawy M. The diagnostic significance of circulating lncRNA ADAMTS9-AS2 tumor biomarker in non-small cell lung cancer among the Egyptian population. J Gene Med. 2021;23(12):e3381.
43. Lin Q, Xie D, Pan L, Lou Y, Shi M. Urinary exosomal long noncoding RNAs serve as biomarkers for early detection of non-small cell lung cancer. Bioscience Reports. 2021;41(10).
44. Altesha MA, Ni T, Khan A, Liu K, Zheng X. Circular RNA in cardiovascular disease. J Cell Physiol. 2019;234(5):5588-600.
45. Zhu Y, Shen L, Xia Q, Tao H, Liu Z, Wang M, et al. Extracellular vesicle-derived circHIPK3: Novel diagnostic biomarker for lung cancer. Advances in Medical Sciences. 2023;68(2):426-32.
46. Tang Q, Hann SS. Biological Roles and Mechanisms of Circular RNA in Human Cancers. Onco Targets Ther. 2020;13:2067-92.
47. Gao W, Guo H, Niu M, Zheng X, Zhang Y, Xue X, et al. circPARD3 drives malignant progression and chemoresistance of laryngeal squamous cell carcinoma by inhibiting autophagy through the PRKCI-Akt-mTOR pathway. Mol Cancer. 2020;19(1):166.
48. Jian X, He H, Zhu J, Zhang Q, Zheng Z, Liang X, et al. Hsa_circ_001680 affects the proliferation and migration of CRC and mediates its chemoresistance by regulating BMI1 through miR-340. Mol Cancer. 2020;19(1):20.
49. Chen L-L. The expanding regulatory mechanisms and cellular

[DOI: 10.61186/jhgg.7.2.99]

functions of circular RNAs. Nature Reviews Molecular Cell Biology. 2020;21(8):475-90.
50. Chen Y, Wei S, Wang X, Zhu X, Han S. Progress in research on the role of circular RNAs in lung cancer. World J Surg Oncol. 2018;16(1):215.
51. Zhang Z, Yang T, Xiao J. Circular RNAs: Promising Biomarkers for Human Diseases. EBioMedicine. 2018;34:267-74.
52. Wei SL, Ye JJ, Sun L, Hu L, Wei YY, Zhang DW, et al. Exosome-derived circKIF20B suppresses gefitinib resistance and cell proliferation in non-small cell lung cancer. Cancer Cell Int. 2023;23(1):129.
53. Xian J, Su W, Liu L, Rao B, Lin M, Feng Y, et al. Identification of Three Circular RNA Cargoes in Serum Exosomes as Diagnostic Biomarkers of Non-Small-Cell Lung Cancer in the Chinese Population. J Mol Diagn. 2020;22(8):1096-108.
54. Zhu X, Wang X, Wei S, Chen Y, Chen Y, Fan X, et al. hsa_circ_0013958: a circular RNA and potential novel biomarker for lung adenocarcinoma. FEBS J. 2017;284(14):2170-82.
55. Liang N, Zhang X, Zhang L, Jiang M, Bai H, Ding C, et al. Peripheral Blood-Derived CircVPS35L as a Potential Diagnostic Biomarker for Non-Small Cell Lung Cancer. Oncology. 2023;101(8):527-36. (abstract)
56. Ma T, Miao H, Xiong Y, Ma Y, Dong Z. CircRNA circ-PDCD11 is highly expressed in lung large-cell carcinoma and predicts poor survival. Immunopharmacol Immunotoxicol. 2023;45(1):89-93. (abstract)
57. Zhang Q, Qin S, Peng C, Liu Y, Huang Y, Ju S. Circulating circular RNA hsa_circ_0023179 acts as a diagnostic biomarker for non-small-cell lung cancer detection. J Cancer Res Clin Oncol. 2023;149(7):3649-60.
58. Ni Y, Zhang W, Mu G, Gu Y, Wang H, Wei K, et al. Extracellular RNA profiles in non-small cell lung cancer plasma. J Thorac Dis. 2023;15(5):2742-53.
59. Zhang Y, Chao F, Lv L, Li M, Shen Z. Hsa_circ_0041150 serves as a novel biomarker for monitoring chemotherapy resistance in small cell lung cancer patients treated with a first-line chemotherapy regimen. J Cancer Res Clin Oncol. 2023;149(17):15365-82.
60. Wang H, Tang Z, Duan J, Zhou C, Xu K, Mu H. Cancer-released exosomal circular RNA circ_0008717 promotes cell tumorigenicity through microRNA-1287-5p/P21-activated kinase 2 (PAK2) axis in non-small cell lung cancer. Bioengineered. 2022;13(4):8937-49.
61. Xie H, Yao J, Wang Y, Ni B. Exosome-transmitted circVMP1 facilitates the progression and cisplatin resistance of non-small cell lung cancer by targeting miR-524-5p-METTL3/SOX2 axis. Drug Deliv. 2022;29(1):1257-71.
62. Mitchell PS, Parkin RK, Kroh EM, Fritz BR, Wyman SK, Pogosova-Agadjanyan EL, et al. Circulating microRNAs as stable blood-based markers for cancer detection. Proc Natl Acad Sci U S A. 2008;105(30):10513-8.
63. Pandey M, Mukhopadhyay A, Sharawat SK, Kumar S. Role of microRNAs in regulating cell proliferation, metastasis and chemoresistance and their applications as cancer biomarkers in small cell lung cancer. Biochim Biophys Acta Rev Cancer. 2021;1876(1):188552.
64. Perkel JM. Visiting "noncodarnia". Biotechniques. 2013;54(6):301, 3-4.
65. Pandey M, Mukhopadhyay A, Sharawat SK, Kumar S. Role of microRNAs in regulating cell proliferation, metastasis and chemoresistance and their applications as cancer biomarkers in small cell lung cancer. Biochimica et Biophysica Acta (BBA) - Reviews on Cancer. 2021;1876(1):188552.
66. Lagos-Quintana M, Rauhut R, Yalcin A, Meyer J, Lendeckel W, Tuschl T. Identification of tissue-specific microRNAs from mouse. Curr Biol. 2002;12(9):735-9.
67. Schwarzenbach H, Nishida N, Calin GA, Pantel K. Clinical relevance of circulating cell-free microRNAs in cancer. Nat Rev Clin Oncol. 2014;11(3):145-56.
68. Weber JA, Baxter DH, Zhang S, Huang DY, Huang KH, Lee MJ, et al. The microRNA spectrum in 12 body fluids. Clin Chem. 2010;56(11):1733-41.
69. Su Y, Fang H, Jiang F. Integrating DNA methylation and microRNA biomarkers in sputum for lung cancer detection. Clin Epigenetics. 2016;8:109.
70. Leng Q, Wang Y, Jiang F. A Direct Plasma miRNA Assay for Early Detection and Histological Classification of Lung Cancer. Translational Oncology. 2018;11(4):883-9.
71. Kumar S, Sharawat SK, Ali A, Gaur V, Malik PS, Kumar S, et al. Identification of differentially expressed circulating serum microRNA for the diagnosis and prognosis of Indian non-small cell lung cancer patients. Curr Probl Cancer. 2020;44(4):100540.
72. Yang C, Jia X, Zhou J, Sun Q, Ma Z. The MiR-17-92 Gene Cluster is a Blood-Based Marker for Cancer Detection in Non-Small-Cell Lung Cancer. Am J Med Sci. 2020;360(3):248-60.
73. Zhang X, Hu Y, Gong C, Zhang C. Overexpression of miR-518b in non-small cell lung cancer serves as a biomarker and facilitates tumor cell proliferation, migration and invasion. Oncol Lett. 2020;20(2):1213-20.
74. Wu Q, Yu L, Lin X, Zheng Q, Zhang S, Chen D, et al. Combination of Serum miRNAs with Serum Exosomal miRNAs in Early Diagnosis for Non-Small-Cell Lung Cancer. Cancer Manag Res. 2020;12:485-95.
75. Wan N, Zheng J. MicroRNA-891a-5p is a novel biomarker for non-small cell lung cancer and targets HOXA5 to regulate tumor cell biological function. Oncol Lett. 2021;22(1):507.
76. Xing L, Su J, Guarnera MA, Zhang H, Cai L, Zhou R, et al. Sputum microRNA biomarkers for identifying lung cancer in indeterminate solitary pulmonary nodules. Clin Cancer Res. 2015;21(2):484-9.
77. Jiang HG, Dai CH, Xu YP, Jiang Q, Xia XB, Shu Y, Li J. Four plasma miRNAs act as biomarkers for diagnosis and prognosis of non-small cell lung cancer. Oncol Lett. 2021;22(5):792.
78. Wu Y, Yin Q, Zhou YL, He L, Zou ZQ, Dai XY, Xia W. Evaluation of microRNAs as potential biomarkers in circulating HPV-DNA-positive non-small cell lung cancer patients. Cancer Biol Ther. 2021;22(2):136-48.
79. Wang X, Jiang X, Li J, Wang J, Binang H, Shi S, et al. Serum exosomal miR-1269a serves as a diagnostic marker and plays an oncogenic role in non-small cell lung cancer. Thorac Cancer. 2020;11(12):3436-47.
80. Chen L, Li Y, Lu J. Identification of Circulating miR-762 as a Novel Diagnostic and Prognostic Biomarker for Non-Small Cell Lung Cancer. Technol Cancer Res Treat. 2020;19:1533033820964222.
81. Elnaggar GN, El-Hifnawi NM, Ismail A, Yahia M, Elshimy RAA. Micro RNA-148a Targets Bcl-2 in Patients with Non-Small Cell Lung Cancer. Asian Pac J Cancer Prev. 2021;22(6):1949-55.
82. Atkinson AJ CW, DeGruttola VG, DeMets DL, Downing GJ, Hoth, DF ea. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69(3):89-95.
83. Fang R, Zhu Y, Khadka VS, Zhang F, Jiang B, Deng Y. The Evaluation of Serum Biomarkers for Non-small Cell Lung Cancer (NSCLC) Diagnosis. Front Physiol. 2018;9:1710.
84. Šutić M, Vukić A, Baranašić J, Försti A, Džubur F, Samaržija M, et al. Diagnostic, Predictive, and Prognostic Biomarkers in Non-Small Cell Lung Cancer (NSCLC) Management. J Pers Med. 2021;11(11).
85. Lebanony D, Benjamin H, Gilad S, Ezagouri M, Dov A, Ashkenazi K, et al. Diagnostic assay based on hsa-miR-205 expression distinguishes squamous from nonsquamous non-small-cell lung carcinoma. J Clin Oncol. 2009;27(12):2030-7.
86. Charkiewicz R, Sulewska A, Mroz R, Charkiewicz A, Naumnik W, Kraska M, et al. Serum Insights: Leveraging the Power of miRNA Profiling as an Early Diagnostic Tool for Non-Small Cell Lung Cancer. Cancers (Basel). 2023;15(20).
87. Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cell Biol. 2007;9(6):654-9.
88. Rabinowits G, Gerçel-Taylor C, Day JM, Taylor DD, Kloecker GH. Exosomal microRNA: a diagnostic marker for lung cancer. Clin Lung Cancer. 2009;10(1):42-6.
89. Liu XQ, Tufman A, Kiefl R, Li GF, Ma QL, Huber RM. Identification of lung adenocarcinoma-specific exosome RNAs in peripheral blood by RNA-Seq analysis. Eur Rev Med Pharmacol Sci. 2020;24(4):1877-86.
90. Sisu C. Pseudogenes as Biomarkers and Therapeutic Targets in Human Cancers. Methods Mol Biol. 2021;2324:319-37. (abstract)

[DOI: 10.61186/jhgg.7.2.99]

91. Stasiak M, Kolenda T, Kozłowska-Masłoń J, Sobocińska J, Poter P, Guglas K, et al. The World of Pseudogenes: New Diagnostic and Therapeutic Targets in Cancers or Still Mystery Molecules? Life (Basel). 2021;11(12).
92. Bhargava A, Bunkar N, Aglawe A, Pandey KC, Tiwari R, Chaudhury K, et al. Epigenetic Biomarkers for Risk Assessment of Particulate Matter Associated Lung Cancer. Curr Drug Targets. 2018;19(10):1127-47.
93. Belinsky SA. Unmasking the lung cancer epigenome. Annu Rev Physiol. 2015;77:453-74.

[DOI: 10.61186/jhgg.7.2.99]