

Table SI. Relative plasma levels of 12 miRNAs chosen from earlier reports of NSCLC studies in training set.

miRNA	Supplementary references	Healthy control (n=20)	NSCLC (n=40)	Fold change	P-value
miR-210	(1,2,4,5,14)	0.95	3.65	3.84	<0.0001 ^b
miR-1290	(3,7,18)	1.12	5.76	5.14	<0.0001 ^b
miR-150	(6,23,24)	0.82	8.14	9.93	<0.0001 ^b
miR-21-5p	(3,5,25)	1.63	4.86	4.86	<0.0001 ^b
miR-25	(10,11,22)	0.52	0.98	1.88	0.001 ^a
miR-190b	(15,20)	2.64	1.52	1.74	0.001 ^a
miR-29c	(12,13)	0.76	1.48	1.95	0.001 ^a
miR-22	(8,9)	0.94	1.64	1.74	0.001 ^a
miR-939	(19,26)	1.18	1.79	1.52	0.003 ^a
miR-1246	(21,18)	1.35	2.15	1.59	0.003 ^a
miR-214	(16,22)	0.98	1.36	1.39	0.005 ^a
miR-1254	(17)	2.45	3.61	1.47	0.005 ^a

^aP<0.01; ^bP<0.0001. miRNA/miR, microRNA; NSCLC, non-small cell lung cancer.

Table SII. Diagnostic Performance of the four miRNAs and CEA in distinguishing NSCLC from health control by the ROC curve analyses.

Group	Parameter	AUC	95% CI	P-value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Training set (n=60)	miR-210	0.75	0.69-0.89	0.006	75	75	86	50	75
	miR-1290	0.88	0.67-0.95	0.001	88	85	81	68	87
	miR-150	0.91	0.80-1.04	<0.001	90	85	84	71	88
	miR-21-5p	0.77	0.62-0.87	0.003	78	75	70	52	77
	Combined miRNA	0.96	0.82-1.10	<0.001	95	95	93	86	95
	CEA	0.69	0.51-0.79	0.012	68	0.65	57	40	67
	Combined miRNA and CEA	0.95	0.79-1.12	<0.001	93	95	90	83	93
Testing set (n=128)	miR-210	0.71	0.60-0.88	0.006	70	70	62	42	70
	miR-1290	0.82	0.68-0.94	0.001	82	80	75	57	81
	miR-150	0.85	0.76-1.08	<0.001	85	85	80	64	85
	miR-21-5p	0.75	0.58-0.86	0.005	75	75	67	48	75
	Combined miRNA	0.93	0.78-1.08	<0.001	93	90	89	78	92
	CEA	0.67	0.53-0.82	0.012	66	65	57	37	66
	Combined miRNA and CEA	0.92	0.81-1.09	<0.001	93	88	88	76	91

CEA, carcinoembryonic antigenic; ROC, receiver operating characteristic; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value.

Table SIII. Diagnostic Performance of the four miRNAs and CEA in distinguishing NSCLC from BLD by the ROC curve analyses.

Group	Parameter	AUC	95% CI	P-value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Training set (n=60)	miR-210	0.73	0.68-0.86	0.006	73	70	63	45	72
	miR-1290	0.83	0.68-0.95	0.001	83	80	75	59	82
	miR-150	0.91	0.72-1.08	<0.001	90	85	84	71	88
	miR-21-5p	0.74	0.58-0.86	0.005	73	75	64	48	73
	Combined miRNA	0.96	0.80-1.05	<0.001	95	90	90	82	93
	CEA	0.68	0.47-0.76	0.028	68	60	56	36	65
	Combined miRNA and CEA	0.93	0.78-1.08	<0.001	93	85	86	74	90
Testing set (n=138)	miR-210	0.71	0.58-0.87	0.014	72	70	61	47	72
	miR-1290	0.80	0.64-0.92	0.004	80	80	71	59	80
	miR-150	0.89	0.76-1.09	<0.001	90	86	83	73	88
	miR-21-5p	0.78	0.64-0.85	0.006	77	76	68	54	77
	Combined miRNA	0.94	0.81-1.12	<0.001	94	94	90	85	94
	CEA	0.65	0.56-0.82	0.010	64	60	74	66	62
	Combined miRNA and CEA	0.91	0.79-1.10	<0.001	91	90	86	78	91

CEA, carcinoembryonic antigenic; BLD, benign lung disease; ROC, receiver operating characteristic; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value.

Table SIV. Univariate and multivariate logistic regression analyses of parameters associated with non-small cell lung cancer in the two sets combined.

Parameter	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age, years (<60 vs. ≥60)	1.56	1.20-1.69	0.15	-	-	0.48
Sex (Male vs. female)	1.32	0.27-2.48	0.43	-	-	0.89
Smoking status (Ever and current vs. never)	1.84	1.15-2.54	0.11	-	-	0.56
miR-210 expression (Low vs. high)	4.63	2.24-6.62	0.009 ^b	2.05	0.83-3.85	0.095
miR-1290 expression (Low vs. high)	8.32	5.44-13.76	0.002 ^b	4.13	2.12-6.89	0.011 ^a
miR-150 expression (Low vs. high)	14.75	11.32-19.47	<0.001 ^c	11.42	8.25-14.53	0.001 ^b
miR-21-5p expression (Low vs. high)	6.94	4.25-9.05	0.004 ^b	3.92	1.58-6.16	0.018 ^a
CEA expression (Low vs. high)	2.40	1.13-4.38	0.025 ^a	-	-	0.260

^aP<0.05; ^bP<0.01; ^cP<0.001. CEA, carcinoembryonic antigen; OR, odds ratio; CI, confidence interval; miR, microRNA.

Supplementary References

1. Tan X, Qin W, Zhang L, Hang J, Li B, Zhang C, Wan J, Zhou F, Shao K, Sun Y, et al: A 5-microRNA signature for lung squamous cell carcinoma diagnosis and hsa-miR-31 for prognosis. *Clin Cancer Res* 17: 6802-6811, 2011.
2. Guan P, Yin Z, Li X, Wu W and Zhou B: Meta-analysis of human lung cancer microRNA expression profiling studies comparing cancer tissue with normal tissue. *J Exp Clin Cancer Res* 31: 54, 2012.
3. Yang C, Sun C, Liang X, Xie S, Huang J and Li D: Integrative analysis of microRNA and mRNA expression profiles in non-small-cell lung cancer. *Cancer Gene Ther* 23: 90-97, 2016.
4. Eilertsen M, Andersen S, Al-Saad S, Richardsen E, Stenvold H, Hald SM, Al-Shibli K, Donnem T, Busund LT and Bremnes RM: Positive prognostic impact of miR-210 in non-small cell lung cancer. *Lung Cancer* 83: 272-278, 2014.
5. Duncavage E, Goodgame B, Sezhiyan A, Govindan R and Pfeifer J: Use of microRNA expression levels to predict outcomes in resected stage I non-small cell lung cancer. *J Thorac Oncol* 5: 1755-1760, 2010.
6. Cao M, Hou D, Liang H, Gong F, Wang Y, Yan X, Jiang X, Wang C, Zhang J, Zen K, et al: MiR-150 promotes the proliferation and migration of lung cancer cells by targeting SRC kinase signalling inhibitor 1. *Eur J Cancer* 50: 1013-1024, 2014.
7. Mo D, Gu B, Gong X, Wu L, Wang H, Jiang Y, Zhang B, Zhang M, Zhang Y, Xu J and Pan S: MiR-1290 is a potential prognostic biomarker in non-small cell lung cancer. *J Thorac Dis* 7: 1570-1579, 2015.
8. Liang B, Wang GX, Long G, Qiu JH and Hu ZL: Tumor suppressor miR-22 suppresses lung cancer cell progression through post-transcriptional regulation of ErbB3. *J Cancer Res Clin Oncol* 138: 1355-1361, 2012.
9. Shin YM, Yun J, Lee OJ, Han HS, Lim SN, An JY, Lee KH, Lee KM and Choe KH: Diagnostic value of circulating extracellular miR-134, miR-183, and miR-22 levels in lung adenocarcinoma-associated malignant pleural effusion. *Cancer Res Treat* 46: 178-185, 2014.
10. Wu T, Chen W, Kong D, Li X, Lu H, Liu S, Wang J, Du L, Kong Q, Huang X and Lu Z: MiR-25 targets the modulator of apoptosis 1 gene in lung cancer. *Carcinogenesis* 36: 925-935, 2015.
11. Wang P, Yang D, Zhang H, Wei X, Ma T, Cheng Z, Hong Q, Hu J, Zhuo H, Song Y, et al: Early detection of lung cancer in serum by a panel of microRNA biomarkers. *Clin Lung Cancer* 16: 313-319.e1, 2015.
12. Heegaard NH, Schetter AJ, Welsh JA, Yoneda M, Bowman ED and Harris CC: Circulating miRNA expression profiles in early stage nonsmall cell lung cancer. *Int J Cancer* 130: 1378-1386, 2012.
13. Zhu W, He J, Chen D, Zhang B, Xu L, Ma H, Liu X, Zhang Y and Le H: Expression of miR-29c, miR-93, and miR-429 as potential biomarkers for detection of early stage non-small lung cancer. *PLoS One* 9: e87780, 2014.
14. Boeri M, Verri C, Conta D, Roz L, Modena P, Facchinetto F, Calabro E, Croce CM, Pastorino U and Sozzi G: MicroRNA signatures in tissues and plasma predict development and prognosis of computed tomography detected lung cancer. *Proc Natl Acad Sci USA* 108: 3713-3718, 2011.
15. Patnaik SK, Yendumuri S, Kannisto E, Kucharczuk JC, Singhal S and Vachani A: MicroRNA expression profiles of whole blood in lung adenocarcinoma. *PLoS One* 7: e46045, 2012.
16. Long H, Wang Z, Chen J, Xiang T, Li Q, Diao X and Zhu B: MicroRNA-214 promotes epithelial-mesenchymal transition and metastasis in lung adenocarcinoma by targeting the suppressor-of-fused protein (Sufu). *Oncotarget* 6: 38705-38718, 2015.
17. Foss KM, Sima C, Ugolini D, Neri M, Allen KE and Weiss GJ: MiR-1254 and miR-574-5p: Serum-based microRNA biomarkers for early-stage non-small cell lung cancer. *J Thorac Oncol* 6: 482-488, 2011.
18. Kim G, An HJ, Lee MJ, Song JY, Jeong JY, Lee JH and Jeong HC: Hsa-miR-1246 and hsa-miR-1290 are associated with stemness and invasiveness of non-small cell lung cancer. *Lung Cancer* 91: 15-22, 2016.
19. Rani S, Gately K, Crown J, O'Byrne K and O'Driscoll L: Global analysis of serum microRNAs as potential biomarkers for lung adenocarcinoma. *Cancer Bol Ther* 14: 1104-1112, 2013.
20. Lu S, Kong H, Hou Y, Ge D, Huang W, Ou J, Yang D, Zhang L, Wu G, Song Y, et al: Two plasma microRNA panels for diagnosis and subtype discrimination of lung cancer. *Lung Cancer* 123: 44-51, 2018.
21. Huang W, Li H and Luo R: The microRNA-1246 promotes metastasis in non-small cell lung cancer by targeting cytoplasmic polyadenylation element-binding protein 4. *Diagn Pathol* 10: 127, 2015.
22. Wang C, Ding M, Xia M, Chen S, Van Le A, Soto-Gil R, Shen Y, Wang N, Wang J, Gu W, et al: A five-miRNA panel identified from a multicentric case-control study serves as a novel diagnostic tool for ethnically diverse non-small cell lung cancer patients. *EBioMedicine* 2: 1377-1385, 2015.
23. Zhang N, Wei X and Xu L: MiR-150 promotes the proliferation of lung cancer cells by targeting P53. *FEBS Lett* 587: 2346-2351, 2013.
24. Yin QW, Sun XF, Yang GT, Li XB, Wu MS and Zhao J: Increased expression of microRNA-150 is associated with poor prognosis in non-small cell lung cancer. *Int J Clin Exp Pathol* 8: 842-846, 2015.
25. Tian F, Li R, Chen Z, Shen Y, Lu J, Xie X and Ge Q: Differentially expressed miRNAs in tumor, adjacent, and normal tissues of lung adenocarcinoma. *Biomed Res Int* 2016: 1428271, 2016.
26. Ma R, Wang C, Wang J, Wang D and Xu J: MiRNA-mRNA interaction network in non-small cell lung cancer. *Interdiscip Sci* 8: 209-219, 2016.