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**Title:** Lepidic and non-lepidic adenocarcinomas have distinct gene expression signatures that correlate with aggressiveness

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**Body:** Method: A total of 103 lung adenocarcinomas from 57 never smokers and 56 ever smokers were studied using gene expression arrays. Results: Unsupervised hierarchical clustering analysis revealed two groups of patients. In the first group, the tumor gene expression profile resembled that of normal lung. In the second group, there were two distinctive gene clusters, which were not seen in the first group. Gene Ontology terms associated with these two distinctive gene clusters were "cell proliferation" and "invasion", respectively. The classification was associated with smoking status (p-value 0.01), lepidic component (p-value 0.0005) and EGFR (p-value 0.0002) or KRAS (p-value 0.02) mutation status.

Table 1. Characteristics associated with gene expression profiles

		Group 1	Group 2	
Gene expression		Ressembles normal	"Proliferative" and "invasive" gene	
profile		lung	clusters	
				p-value
Smoking status				0.01
	Never smoker	35 (61%)	28 (50%)	
	Ever smoker	22	28	
Lepidic component				0.00005
	Yes	31 (54%)	12 (21%)	
	No	26	34	
EGFR mutation				0.0002
	Yes	32 (56%)	16 (30%)	
	No	25	38	

KRAS mutation				0.02
	Yes	4 (7%)	14 (25%)	
	No	53	41	

Conclusion: Lung adenocarcinomas have gene expression profiles that correspond to their clinical and histological presentation. Our study confirms the greater aggressiveness of non-lepidic versus lepidic adenocarcinomas and offers new opportunities to uncover genetic alterations that drive clinical evolution.