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Title: Molecular signatures of non-small cell lung cancer (NSCLC) obtained from gene expression profiling of the benign bronchial mucosa of smokers with and without NSCLC

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Body: Background: Cigarette smoking accounts for 85-90% of lung cancers. Large-scale gene-expression profiling analyses have been undertaken to identify genes and pathways associated with lung carcinogenesis, and uncover lung cancer biomarkers. Tumor-distant, histologically normal bronchial biopsies have hitherto not been considered in such studies. Aims: In order to identify molecular signatures of smoking-related NSCLC, we have compared the gene expression profiles of histologically normal bronchial biopsies from current smokers with or without NCSCL, as well as non-smokers. Methods: RNA samples (97 biopsies) were used for hybridization with Affymetrix HG-U133 Plus 2.0 arrays. Differentially expressed genes were used to compare non-smokers (NS), smokers without cancer (SNC), and smokers with cancer (SC). Functional analysis was carried out using Ingenuity Pathway Analysis. Gene signatures of cigarette smoking and NSCLC were identified using the prediction analysis of microarray (PAM) method. Results: We identified 3 genes signatures that distinguished, respectively, SNC and NS (16 genes, 95.2% accuracy), SC and NS (8 genes, 100% accuracy), and SNC and SC (15 genes, 83% accuracy). This latter signature contains several genes that have been linked to lung disease/carcinogenesis, including genes encoding xenobiotic biotransformation proteins that protect the airway from the chemicals in cigarette smoke or contribute to lung carcinogenesis. Conclusions: Gene expression profiling of histologically normal bronchial biopsies resulted in a gene signature of NSCLC in smokers. Its potential as biomarker remains to

be tested.