EDRN Lung Team Project #2 validation of molecular biomarkers for the early detection of lung cancer in the setting of indeterminate pulmonary nodules

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Abstract:

Background: The goal of the Early Detection Research Network (EDRN) Lung Team Project #2 (LTP-2) is to establish a cohort (n= 300) of high-risk people with indeterminate pulmonary nodules (6mm-30mm) to clinically validate the diagnostic accuracy of existing molecular and imaging biomarkers discovered and analytically validated through the EDRN program. These biomarkers comprise signals measured in serum (glycan or cytokine), plasma (protein, miRNA, RNA, or methylated circulating tumor DNA), airway epithelial cells (RNA or DNA), nasal brush cells (RNA or DNA), and/or chest CT images. **Methods**: Eligible participants had an indeterminate nodule discovered incidentally or through low-dose CT screening within 14 months prior to enrollment and were aged 45–90 years, with 20 pack-years or more cigarette smoking history, free of lung cancer, and willing to provide blood, nasal brushing, and optionally bronchoscopic brush biopsy specimens. Baseline medical and demographic data were collected from each subject. Baseline and years 1 and 2 follow-up CT images were obtained. Each specimen at each respective site was labeled with a 2-D barcode provided by the DMCC and specimen information was entered into the Validation Study Information Management System (VSIMS) developed by the EDRN Data Management and Coordinating Center (DMCC). Aliquots of blinded specimens from selected cases and controls will be dispensed to each EDRN site for biomarker analysis. Analysis plan: Primary endpoint: The positive diagnostic likelihood ratio (DLR+) will be used to measure biomarker performance within values of DLR+ >= 2 or DLR- <= 0.5, a range considered clinically useful for any patients with indeterminate lung nodules. The sample size calculation targeted >80% power to test the null hypotheses that a) a positive biomarker does not alter risk across a range of specificities, and b) a negative biomarker does not alter risk across a range of sensitivities. The EDRN Data Management and Coordinating Center (DMCC) will unblind and complete analysis and report results. Exploratory endpoint: The diagnostic accuracy of combined biomarkers will be calculated using a logistic regression model with flexible functional forms. **Results and Discussion**: More than 300 subjects were enrolled into the LTP2 cohort including a sufficient number of cases and controls (cohort size n>300) to reach power according to calculated estimates. Chest CT images were collected and are in the process of transfer to a central database. Plasma specimens have been distributed to test sites. RNA and DNA extraction from NBC and AEC is in process and based on results thus far the specimen quality and quantity is more than sufficient from the number of subjects needed to reach power for the primary endpoint and to conduct the planned exploratory analyses.