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High specificity lung cancer test to rule out cancer in non-malignant lung nodules found at LDCT.

Tung-Ming Tsai, Dorian Pamart, Nathalie Hardat, Marielle Herzog, Jin-Shing Chen; National Taiwan University Hospital, Tapei, Taiwan; Belgian Volition SRL, Isnes, Belgium; National Taiwan University Hospital, Taipei, Taiwan

Background: Lung Cancer (LC) is the leading cause of cancer death worldwide and smoking is the leading risk factor. Only 15% of patients with LC are still alive 5 years after diagnosis due to advanced diseases stage at diagnosis. Low-Dose Computed Tomography (LDCT) is the widely accepted standard for screening of individuals at high risk of lung cancer. However, LDCT has several limitations including the high prevalence of non-malignant pulmonary nodules detected leading to overdiagnosis, the potential harms of cumulative radiation dose and poor adherence to recommended follow-up. Therefore, novel blood-based tests could offer a simple follow confirmation approach and this test is designed to find those patients who DO NOT have cancer. **Methods:** We measured levels of nucleosomes, CEA and CYFRA21-1in a cohort of 912 subjects and report data relating to 184 smoker subjects referred for CT scan at National Taiwan University Hospital. The smoker patients were later confirmed to have either a LC (n = 129, including 59 patients at early stage (stage 0-I), 15 at stage II, 47 at late stage (III and IV) and 8 with unknown stage), or non-malignant nodules (n = 41), or control with no-nodules (n = 14). Whole blood was collected in EDTA plasma tubes for analysis by six different Nu.Q chemiluminescent magnetic microparticle immunoassays (Belgian Volition, Belgium) targeting H3.1-nucleosomes or different histone modifications (H3K9Me3-, H3K27Me3-, H3K36Me3-, H3K9Ac-, H3K14Ac-nucleosomes). CEA was analyzed on the Abbott ARCHITECT analyzer. CYFRA21-1 was analyzed on the Roche Cobas E411 analyzer. We evaluated each biomarker levels individually and in a combinatorial approach by logistic regression for their performance in discriminating subject with a LC vs non-malignant nodules. **Results:** Among the eight individual markers evaluated, the best area under the curve (AUC) in discriminating LC vs non-malignant nodule were observed for CEA, H3K9Ac-nucleosomes and CYFRA21-1 with an AUC of 0.68, 0.69 and 0.74, respectively and a specificity at 95% sensitivity of 9.5%, 7.3% and 21.4%, respectively. A logistic regression approach defined H3K9Ac-nucleosomes, CEA and CYFRA21-1 as the best panel of biomarkers tested to improve the discrimination between LC and non-malignant nodules relatives to the markers alone, achieving a specificity of 34.1% at 95% sensitivity and an AUC of 0.80. 55 out of the 59 stage 0-I, 25/26 stage III and 20/21 stage IV LC were detected by this combination of markers while 34.1 % of the patients with benign nodules are found negative and not sent to unnecessary biopsy to ascertain the nodule status. **Conclusions:** Results of our proof-of-concept study indicate that a blood test combining H3K9Ac-nucleosome levels with CEA and CYFRA21-1 levels could help to rule-out patients with a non-malignant nodule offering a non-invasive tool as an aid to the decision-making process of the malignancy status of nodules detected by LDCT. Research Sponsor: Belgian Volition SRL.

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