**INTRODUCTION AND OBJECTIVES:**
To identify a multiplexed panel of plasma biomarker assays for discriminating in former smokers between an Indeterminate Pulmonary Nodule (IPN) found to be clinically stable for at least one year and a pathologically established lung cancer diagnosis.

**METHODS:**
Plasma protein assays for the MagArray immunoassay platform were developed for biomarkers likely to provide discrimination between benign and malignant pulmonary nodules found on CT scan in former smokers. Retrospective plasma samples from a cohort of 217 subjects at high risk of lung cancer, collected at three medical centers across the US, were randomly assigned to a training set (n=73) and a testing set (n=144) for generalized linear modeling. The minimum set of protein biomarkers and clinical factors that provided the highest accuracy in classifying benign and malignant subjects were identified. Model performance was further evaluated by its ability to assign the correct risk classification for subjects with an intermediate risk nodule based on the Mayo Pre-Test Probability of Malignancy Model.

**RESULTS:**
A biomarker and clinical factor model consisting of TIMP1, ProSB, EGFR, CEA, and NAP2 protein biomarker levels, along with subject age, sex, nodule size, and nodule spiculated appearance provided an accuracy of 73% in the 144 testing subjects with a sensitivity of 76% and a specificity of 82%. The ROC curve AUC was 0.86 compared to the Mayo model AUC of 0.79 (Figure 1A). Within the 93 test subjects falling into the Mayo model intermediate risk range (0.05 to 0.65), the algorithm showed a ROC curve AUC of 0.82 compared to the Mayo model AUC of 0.64 (Figure 1B). Of those 93 subjects falling within the intermediate risk range, the algorithm correctly classified 70 of 93 samples (75%) as either benign or malignant.

**CONCLUSIONS:**
The multiplexed plasma protein and clinical factors assay correctly classified more former smokers with an indeterminate pulmonary nodule as being either benign or malignant than existing models (NRI = 51%). Former smokers with benign disease who are correctly classified as lower risk by the algorithm yet assigned an intermediate risk with the Mayo model may benefit the most from this algorithm by avoiding unnecessary lung biopsy and possible overtreatment. Likewise, those with cancer assigned an intermediate risk by the Mayo model and correctly reclassified by the algorithm as higher risk can be considered as candidates for more aggressive interventions.

**DISCLOSURES:**
MagArray, Inc., provided all financial support for the work reported.

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**Figure 1A:** Receiver operating characteristic (ROC) curves showing the model performance with the test set (A) and the Mayo model intermediate risk test set (B) with the area under the curve (AUC) and 95% confidence intervals.