

Validation of Airway Epithelial Cell TP53 Biomarker for Lung Cancer Risk

Daniel J. Craig, MD¹, Erin L. Crawford², Heidi Chen, Eric L. Grogan, Steven A. Deppen, Thomas Morrison, Sanja L. Antic, Pierre P. Massion, James C. Willey³

¹Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

²College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

³Division of Hematology and Oncology, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: daniel.craig@rockets.utoledo.edu

Keywords: Molecular Oncology, Biomarker, Lung Cancer

Published: 14 December 2023

Background: There is a need for biomarkers that reliably detect those at highest risk for developing lung cancer, thereby enabling more effective screening by annual low-dose CT. We previously discovered a biomarker for lung cancer risk characterized by an increased prevalence of TP53 somatic mutations in airway epithelial cells (AEC)¹. Here we present results from a blinded retrospective case-control validation study.

Methods: AEC genomic (g)DNA specimens were collected at Vanderbilt University in collaboration with the National Cancer Institute (NCI) Early Detection Risk Network (EDRN) according to a University of Toledo IRB-approved protocol. Synthetic DNA internal standards (IS) were prepared for 3 exons in TP53 spanning 193 base pairs and mixed with each AEC genomic DNA specimen prior to competitive multiplex PCR amplicon NGS library preparation. These competitive IS molecules enable the determination of site-specific sequencing error and thus lower the limit of detection for detecting somatic mutations (1,2).

Results: TP53 mutation prevalence was significantly associated with cancer status. The lung cancer detection receiver operator characteristic (ROC) area under the curve (AUC) for the TP53 biomarker was 0.845 (0.749-0.942) with sensitivity: 60.0%, and specificity: 96.7%. In contrast, TP53 mutation prevalence was not significantly associated with age or smoking status among non-cancer subjects. The combination of TP53 mutation prevalence and Brock Risk Score significantly improved the association with lung cancer compared with either factor alone.

Conclusion: These results support the validity of the TP53 mutation prevalence biomarker and justify taking additional steps to assess this biomarker in AEC specimens from a prospective cohort and in matched nasal brushing specimens as a potential non-invasive surrogate specimen.

References:

1. Craig DJ, Morrison T, Khuder SA, Crawford EL, Wu L, Xu J, Blomquist TM, Willey JC. *Technical advance in targeted NGS analysis enables identification of lung cancer risk-associated low frequency TP53, PIK3CA, and BRAF mutations in airway epithelial cells*. BMC Cancer, 2019. **19**(1): p 1081.
2. Blomquist T, Crawford EL, Yeo J, Zhang X, Willey JC. *Control for stochastic sampling variation and qualitative sequencing error in next generation sequencing*. Biomol Detect Quantif, 2015. **5**: pp. 30-37.