Letter to the Editor

Biomarkers: a new frontier in lung cancer detection

Jehron Pura-Bryant[1#], Justin A. Olivera[1#^], Mara B. Antonoff[2]

[1]Albert Einstein College of Medicine, Bronx, NY, USA; [2]Thoracic and Cardiovascular Surgery Department, UT MD Anderson Cancer Center, Houston, TX, USA

[#]These authors contributed equally to this work as co-first authors.

Correspondence to: Mara B. Antonoff, MD. Thoracic and Cardiovascular Surgery Department, UT MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 1489, Houston, TX 77030, USA. Email: mbantonoff@mdanderson.org.

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In the October 2023 issue of *Translational Lung Cancer Research*, Stephens and colleagues published a narrative review of current literature highlighting potential biomarkers to supplement lung cancer screening (LCS) and aid in detection of lung cancer in never-smokers (LCINS) (1). We applaud the authors on their contribution, which clearly underscores the rapid expansion of progress in lung cancer biomarkers while emphasizing ongoing knowledge gaps in this area. The authors have called attention to the important point that the current level of evidence is not yet robust enough to translate biomarker-based detection to everyday clinical practice. The investigators conclude with forward-facing recommendations for thoracic oncologic clinicians and researchers to direct efforts and resources to validating existing biomarker candidates to enable rapid incorporation into practice sooner.

This review identified several key observations. First, there is a clear, important distinction between biomarkers that aid in enhanced LCS versus those that can inform detection of LCINS. Because LCS guidelines are contingent upon smoking history, nonsmokers routinely fall through the early-detection net despite LCINS making up an increasingly large portion of the overall disease prevalence. In the context of biomarkers, LCINS requires distinct categorization on the basis of being "*molecularly*, *histologically*, *and pathologically distinct from tobacco smoking-related cancers*" (1). It is notable that all of the biomarkers identified in this review were sourced from blood or sputum, consistent with an overall push in the field to identify a reliable method of liquid biopsy for lung cancer detection (2). Moreover, the authors noted that the preponderance of evidence supports that metabolites [specifically L-(+)-glucose, cysteinyl-glutamine, phosphatidylethanolamine, and threonine-glutamine] carry the highest sensitivity and specificity for LCS compared to healthy controls, but low overall specificity for lung cancer because the abnormal metabolites can also be indicative of other systemic pathologies. The authors cited recent evidence to suggest microRNA (miRNA) panels have the greatest potential for widespread LCS, while conceding that current detection models lack clinical validation. Lipid panels have the highest sensitivity and specificity for detecting LCINS, but have a similar issue of low overall specificity confounded by other systemic pathologies. In sum of all of these findings, the authors conclude that nucleic acids (especially miRNA-155) will likely be the most applicable biomarker for LCINS once large trials are able to validate it.

We applaud the authors on their extensive narrative review, and we believe that its findings are in-line with another recent publication by Deboever and colleagues (3). Here, the authors cite excessive underutilization of low-dose computed tomography (LDCT) screening among eligible patients (less than 6% of eligible American patients were screened in 2021) and very high false-positive rates as factors that necessitate the adoption of screening adjuncts,

^ ORCID: 0009-0003-1528-1028.

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namely peripheral biomarkers. Both papers cite cell-free DNA (cfDNA) as a useful biomarker for the detection of early-stage lung cancer, but Deboever and colleagues additionally concluded circulating tumor DNA (ctDNA) has potential as a biomarker for detection of late-stage (> T2b) cancer. Stephens and Deboever both mention the potential role of autoantibodies as high-specificity adjuncts to LDCT, with Stephens and colleagues discussing the EarlyCDT-Lung test's detection of stage I–II lung cancers. Deboever and colleagues added that antibody arrays could potentially be combined to create comprehensive panels with higher sensitivity and specificity, while Stephens and colleagues remind us that higher-level evidence is needed to validate autoantibody assays for LCS.

While we applaud the summative value of the publication by Stephens and colleagues, their findings led us to an additional conclusion: the widespread adoption of biomarkers for LCS and LCIS will address several disparities related to the current detection paradigm, making screening and treatment more equitable. In a review of disparities in lung cancer incidence, risk, and diagnosis via screening, Raman and colleagues made several observations relevant to this paper (4). They recognized racioethnic minorities had higher rates of lung cancer after adjusting for race, smoking status, and observational exposure, and found Black women who never smoked had significantly higher incidence rates compared to women with European ancestry. This disparity extended to risk, with Black patients with lung cancer diagnoses found to have smoked fewer cigarettes and later in life at the time of diagnosis than White patients. They also highlighted several factors at the systemic and provider level that contribute to disparities.

Developing LCS programs requires staff and resources that smaller centers do not have, contributing to geographic disparities in access. Economic disparities extend to patients, with patients with government insurance and lower income significantly less likely to complete LCS. Providers also exhibit bias that impacts both their ability and willingness to provide equitable care, with higher provider implicit bias scores associated with shorter visit times and perceived lack of informative communication, support, and partnering among Black patients. Copeland and colleagues found the adoption of a multidisciplinary care model that considered critical social determinants of health specific to lung cancer resulted in reduced time to diagnosis in patients at high-risk for treatment delay (5). As multidisciplinary care becomes more common in lung cancer and leads to better treatment outcomes, widespread adoption of biomarkers for lung cancer detection will allow for earlier collaboration between medical, surgical, and radiation oncologists. In a computer-based model assessing LCS methods, Kong and colleagues discovered that integrating biomarkers into screenings could be more cost-effective compared to the current standard-of-care (6). This finding is encouraging as we strive to bridge the gap in LCS and care for vulnerable communities. A simulated biomarker-based screening program demonstrated economic efficiency, offering patients access to screenings they might otherwise be denied under the criteria set by the US Preventive Services Task Force or the Centers for Medicare & Medicaid Services. This model holds promise in reducing disparities in lung cancer management among vulnerable populations who are financially disadvantaged. We encourage Stephens and colleagues to consider these perspectives as they engage in additional ongoing and highly needed projects. Nonetheless, we congratulate them on their superb paper and look forward to more work from this group.

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Footnote

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