Nadine Al-Naamani, M.D., M.S.
Steven M. Kawut, M.D., M.S.
University of Pennsylvania
Philadelphia, Pennsylvania

ORCID ID: 0000-0001-7864-6096 (J. Minhas).

*Corresponding author (e-mail: jasleen.minhas@pennmedicine.upenn.edu).

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Integrated Biomarkers for Indeterminate Pulmonary Nodules: Is 2-Year Imaging Follow-Up Enough for Suspected Benign Lesions?

To the Editor:

We read with great interest the study by Kammer and colleagues (1) concerning the diagnostic performance of a combined model (CBM), incorporating a serum biomarker, the Mayo risk score, and radiomics features, for indeterminate pulmonary nodules (IPNs). The study revealed that the novel CBM could act as a noninvasive and more accurate method for the diagnosis of IPNs than the current clinical assessment tool. However, we have some concerns.

With the widespread use of low-dose computed tomography for screening, IPNs, especially those manifesting as subsolid nodules (SSNs), are being increasingly detected. The most recommended strategy for SSNs is close follow-up until the appearance of increased nodule size or new solid component. In their study, Kammer and colleagues noted that disease outcomes of nodules might be identified during 2-year longitudinal imaging follow-up showing no signs of growth of benign nodules. However, to our best knowledge, the recommended appropriate follow-up period for SSNs is a minimum of 3 years of surveillance (2), as persistent SSNs frequently represent peripheral adenocarcinoma, with a volume-doubling time of more than 400 days (3). Furthermore, recent studies have indicated that interval growth could occur even after 5 years of stability in a small fraction of SSNs, and a longer follow-up period is required to confirm subsequent growth of SSNs (4, 5). Thus, we wonder how many SSNs were included in Kammer and colleagues' study and whether short 2-year follow-up was enough to enable their differentiation. Is it possible that some indolent SSNs included in the study were invasive but were misjudged as benign nodules because of insufficient follow-up? In addition, is the diagnostic performance of the CBM valuable for different nodule types, given that SSNs show obviously different clinicopathologic features from those of pure solid nodules (6)?

To sum up, we would like the authors to provide the proportions of SSNs in different cohorts and to identify more accurate outcomes of SSNs by pathological examination or prolonging the follow-up period before analysis. Furthermore, to improve the credibility of this integrated biomarker, investigating the diagnostic performance of the CBM in different nodule types is also important before using it in clinical practice. ■

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Mengmeng Zhao, M.D.
Yunlang She, M.D.
Chang Chen, Ph.D., M.D.*
Tongji University
Shanghai, People's Republic of China

*Corresponding author (e-mail: changchenc@tongji.edu.cn).

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Reply to Zhao *et al.*

From the Authors:

We appreciate the response by Zhao and colleagues and their interest in our work, and we welcome the opportunity to present some additional details about our data (1). To begin, we wish to echo their concerns that 2-year follow-up may not be sufficient for subsolid nodules (SSNs). In fact, a closer examination of our data reveals that clinical practice at Vanderbilt University Medical Center is even more aggressive than this.

Zhao and colleagues correctly point out that our methods section states that "two-year longitudinal imaging follow-up showing no signs of growth for benign nodules" is sufficient to establish benign disease. We admit that this general criterion is likely insufficient for SSNs, but many of our patients were in fact either diagnosed via invasive procedures or followed for much longer than 2 years, including several who were followed for up to 5 years before showing signs of growth necessitating invasive diagnoses. Among the 170 patients from Vanderbilt University Medical Center, 18 (10%) had SSNs (7 pure ground-glass opacities), and 14 of those 18 (78%) received diagnoses of cancer (11 adenocarcinoma, 2 squamous cell carcinoma, and 1 small-cell lung cancer). Of the 18 SSNs, half were suspicious enough on their first computed tomography scans to trigger diagnostic bronchoscopy, leading to cancer diagnoses in 8 patients and a benign diagnosis in 1 patient. The benign nodule had a pretest Mayo Clinic Model probability of cancer of 74% and a combined biomarker model risk of 57%, so although the combined biomarker model did provide a decrease in risk, it would not have delayed the diagnostic procedure. The other 3 benign SSNs were followed for 280, 748, and 1,887 days. Only the patient followed for 1,887 days was finally marked "benign" after only surveillance; the patient followed for 280 days received a diagnosis of histoplasmosis infection by fungal serology, and diagnosis was made on bronchoscopy in the patient followed for 748 days. These lengthy surveillance timelines did not affect our reported clinical outcomes of time to diagnosis among cancers and number of procedures among those with benign disease.

The limitation to this analysis is that our role as a tertiary care center generates some selection bias within our sample population; many less suspicious SSNs that are stable over time likely are never referred to us. In addition, clinical practice in our region is likely more aggressive, with disposition toward tissue diagnosis among pulmonary nodules, including SSNs, considering the prevalence of histoplasmosis infections. ■

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Michael N. Kammer, Ph.D.*
Fabien Maldonado, M.D.
Steve A. Deppen, Ph.D.
Vanderbilt University
Nashville, Tennessee

Anna Baron, Ph.D.
University of Colorado
Aurora, Colorado

Eric L. Grogan, M.D.
Vanderbilt University
Nashville, Tennessee

ORCID IDs: 0000-0001-7912-8450 (M.N.K.); 0000-0002-3661-662X (S.A.D.); 0000-0002-3886-9399 (E.L.G.).

*Corresponding author (e-mail: michael.kammer@vumc.org).

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Contribution of Chronic Obstructive Pulmonary Disease as a Mediator for the Association Between Air Pollution and Lung Cancer

To the Editor:

We read with interest the recent article by Huang and colleagues (1), its accompanying editorial (2), and correspondence (3, 4). The long-term impact of air pollution on lung diseases, particularly chronic obstructive pulmonary disease (COPD) and lung cancer, has drawn substantial research interest in the context of worsening air pollution

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