benefit. The results of one study conducted in rural Guatemala suggest that reduced exposure to HAP through the use of a chimney stove intervention could improve lung function as measured by spirometry later in childhood (11).

Poverty is inextricably intertwined with exposure to HAP as drivers of early-childhood respiratory illnesses that put children on a lower lung function growth trajectory and at increased risk of developing an adult respiratory illness (12). As the economies of LMICs develop, increased emissions from traffic and power generation will contribute to the cumulative exposure to air pollution. A great challenge for public health officials in these countries will be to prevent increased exposures of children to air pollution while the necessary economic development is being pursued. Distributed energy generation from solar-power microgrids is one potential solution, but the search for low-cost, feasible, clean cooking solutions must continue so that this public health problem can be addressed sooner rather than later. ■

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John R. Balmes, M.D.*
Department of Medicine
University of California, San Francisco
San Francisco, California

and

School of Public Health
University of California, Berkeley
Berkeley, California

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ORCID ID: 0000-0002-2246-7002 (J.R.B.).

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Mediastinal Lymphadenopathy in Interstitial Lung Disease
Time to Be Counted

The history of digital biomarker research based on computed tomography (CT) in interstitial lung disease (ILD) is long, spanning more than 20 years. Early studies involved radiologists visually quantifying the extent of parenchymal disease and investigating its prognostic effect, mainly in the setting of fibrotic lung disease. This research has mostly provided consistent results: that with increasing fibrosis, honeycombing or severity of traction bronchiectasis comes with an increased risk for mortality (1, 2). Attempts have also been made to construct multidimensional staging systems for different ILDs designed to provide an objective score that maps to an evidence-based management strategy, much in the same way that lung cancer is staged (3, 4).

Despite these efforts, CT-based biomarkers and staging tools have largely failed to translate from research to routine clinical practice for a number of reasons. First, visual quantification of

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ILD on CT is a matter of fine judgement, liable to significant interobserver variability and, as a continuous variable, is not easily applied to management decisions in an individual patient (5). Perhaps most important, concerns remain regarding the reproducibility of visual CT scoring, even in the hands of expert radiologists (6). These shortcomings have spurred a groundswell of interest in objective computer-based quantitative CT (QCT), beginning with simple measures of lung density, followed by more sophisticated textural analysis capable of quantifying the extent and distribution of specific parenchymal patterns such as honeycombing and ground glass opacification (7, 8). Recent innovations in computer-based ILD evaluation include the discovery of a new computer-derived CT parameter, so-called vascular-related structures, which provides sharper prognostic discrimination than traditional CT markers of disease severity in several fibrotic lung diseases, as well as the application of deep learning to QCT in idiopathic pulmonary fibrosis (9, 10).

Common to most of this research is that it has focused on the lung parenchyma, whereas in contrast, the mediastinum has been relatively ignored. This shortcoming is surprising, given that ILD radiologists all over the world know very well that mediastinal node enlargement frequently occurs in patients with ILD. It is also remarkable when one considers the importance of evaluating mediastinal lymph nodes in other pulmonary diseases such as lung cancer and sarcoidosis. And yet the importance of mediastinal lymph node enlargement in ILD is a poorly understood and underrated phenomenon. Too often I have myself been guilty of reporting "enlarged mediastinal lymph nodes consistent with the presence of ILD" merely to highlight that I have not missed this finding, rather than to convey its significance.

In this issue of the *Journal*, Adegunsoye and colleagues (pp. 747–759) make a strong argument for systematic radiologic evaluation of mediastinal lymph node (MLN) enlargement, as well as the distribution of mediastinal lymphadenopathy in patients with ILD (11). The purpose of their study was to test whether outcome distinctions exist between patients with ILD with and without enlarged MLNs. Their primary outcome measure was all transplant-free survival with all-cause and respiratory hospitalizations, lung function, and plasma cytokine concentrations as secondary outcomes. The authors left very little room for error in their study design, which followed a robust discovery-validation protocol using three cohorts from separate institutions with different referral patterns to verify the generalizability of their findings. MLN measurements were made at stations 1–9 (as designated by the International Association for the Study of Lung Cancer) by two thoracic radiologists who underwent hands-on training before the study to ensure consistency in their analyses. It is noteworthy (and of practical relevance) that the agreement between the two radiologists on lymph node enlargement, the total number of enlarged nodes, and the site of largest lymph nodes was remarkably good ($k = 0.64–0.69$). This result refreshingly contrasts the reported reproducibility of semiquantitative scoring of CT patterns such as honeycombing, which, as mentioned earlier, is inconsistent at best (5, 12).

MLN enlargement analyses of the paratracheal and lower mediastinal nodes (stations 1–7 and 8–9, respectively) were made using a binary $\geq$10 mm or $<$10 mm in short axis dimension categorization. Compared with those without enlarged MLNs, older, male patients with increasing smoking exposure and, therefore, not surprisingly, patients with IPF, more commonly had MLN enlargement. Interestingly, although MLN enlargement was more common than not in patients with interstitial pneumonia with autoimmune features it was proportionately less frequent in patients with connective tissue disease-related ILD and chronic hypersensitivity pneumonitis. The primary finding comes from the survival analysis, which demonstrated an increased risk for mortality associated with MLN enlargement in the all-comers ILD discovery cohort, which was then replicated in all three validation cohorts, with lower mediastinal lymphadenopathy consistently conferring a higher mortality risk than paratracheal lymphadenopathy. These survival differences were independent of radiologic honeycombing or an enlarged pulmonary artery (which may be a marker of pulmonary hypertension), and on subgroup analysis, the greatest prognostic separation between those with and without enlarged MLNs was in patients with IPAF and unclassifiable ILD. Because these ILD subtypes incorporate disorders that range from being intrinsically stable to being inexorably progressive, these results suggest that MLN enlargement may be a novel CT biomarker of progressive disease behavior. Given the growing research focus on the progressive fibrotic phenotype, this finding may be of great practical importance for several reasons (13). First, in a proportion of patients with IPF, baseline investigations may be insufficient to guide initial management decisions, but knowledge of likely short-term disease behavior may increase confidence sufficiently to allow a working diagnosis of IPF to be made (14). Second, if the eagerly anticipated results of the INBUILD study are positive, then accurate prediction of progressive fibrotic ILD at presentation would allow initiation of antifibrotic therapy without delay (15). Last, early identification of patients who will develop progressive fibrotic ILD would enable early initiation of quality of life–improving measures and facilitate planning for the future. The authors also evaluated relationships between more than 40 circulating cytokines and MLN enlargement, as well as their associations with outcome. Specifically, elevated levels of the anti-inflammatory cytokine IL-10 (an essential regulator of proinflammatory responses in pulmonary fibrosis) were associated with increased mortality in patients with and without enlarged MLNs. Taking these findings together, it is likely that the most predictive models of future progressive fibrotic ILD will come from a combination of CT and serum biomarkers of disease progression.

Being able to identify how ILD will progress in a specific patient will allow clinicians to initiate patients on appropriate treatment at the earliest opportunity, as well as disease progression. This remains one of the most urgent challenges for effective management for patients with progressive ILD. Until now, CT biomarker research in ILD has focused on baseline and longitudinal changes based on the extent of disease in the lung parenchyma. In this issue of the *Journal*, Adegunsoye and colleagues provided compelling evidence that the mediastinum can no longer be overlooked. I will adjust my CT reports accordingly. ■

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Simon L. F. Walsh, M.D.
National Heart and Lung Institute
Imperial College
London, United Kingdom

ORCID ID: 0000-0003-0497-5297 (S.L.F.W.).

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Ceramides, Autophagy, and Apoptosis Mechanisms of Ventilator-induced Lung Injury and Potential Therapeutic Targets

Before the introduction of mechanical ventilation in the 1950s, preterm infants often died after birth from severe respiratory failure due to lung immaturity, surfactant deficiency, and the lack of suitable ventilators to support small infants. Survival of preterm infants dramatically improved with the introduction of continuous positive airway pressure (1), recognition of the importance of surfactant insufficiency in the pathobiology and treatment of neonatal respiratory distress syndrome (2), and the use of antenatal steroids (3). Although mechanical ventilation allowed an increasing number of preterm infants to survive, it was soon recognized that lung injury due in part to ventilator-induced lung injury led to persistent mortality and late morbidities including chronic lung disease, or bronchopulmonary dysplasia (BPD), as originally described by Northway and colleagues (4). Overall, advances in respiratory care over the past several decades, including improved strategies for mechanical ventilation, have led to dramatic advances in neonatal care and have been lifesaving for countless babies.

Despite these achievements, the adverse effects of mechanical ventilation on short- and long-term respiratory outcomes after preterm birth persist. Data from the Neonatal Research Network in 2015 showed that 87% of extremely preterm infants (gestational age, 22–28 wk) who survived more than 12 hours were treated with some form of mechanical ventilation (5). Although mechanical ventilation is lifesaving and often unavoidable, its use is associated with the development of BPD (6). Animal models show that even a short duration of mechanical ventilation to a preterm lung injures the lung and reduces the response to surfactant therapy (7). The many efforts to limit lung injury include improving ventilator strategies (8–10) such as volume-controlled ventilation (11, 12), antenatal steroids (13), and surfactant (14). These strategies have allowed many babies to avoid aggressive mechanical ventilation and to even decrease the use of early mechanical ventilation. In fact, rates of mechanical ventilation have dropped in the past 15 years (5). However, these advances have led to the survival of infants at lower gestational ages and birthweights with continued need for mechanical ventilation to survive. Hence, the rates of BPD remain fixed at 40% (5). In addition, despite substantial increases in the use of less-invasive ventilation after birth, there was no significant decline in oxygen dependence at 36 weeks and no

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