more rational and targeted use of ILE, with this combination potentially resulting in high success rates of treatment. The authors should again be congratulated on achieving this in a relatively rare disease, speaking to their expertise and experience in the management of chylothorax, from which the clinical community can learn valuable lessons. However, it should be noted that this is a retrospective study with a relatively small sample size, a mixed pediatric and adult population, and no comparator group. This is not a criticism, as such cases are complex and difficult to study because of their rare nature, but the cost and resource implications, as well as the 14.6% complication rate overall from multiple procedures, should be noted. Nevertheless, resolution of symptoms in 9.5 days after intervention in this selected study group, compared with total duration of debilitating symptoms in these patients of average 283 days at the time of recruitment into study, highlights the importance of timely targeted intervention. The required use of intranodal lymphangiography in three patients who were unable to undergo DCMRL also highlighted the need for flexible approaches and a multiskilled radiologist and physician team to approach this complex disease. This is reinforced by the fact that 94% of patients had failed conservative treatment for chylothorax before inclusion in the study, including nonfat diets, total parenteral nutrition, or octreotide, which highlights the need to pursue such treatment before consideration of this image-based approach.

How then should clinicians approach chylothorax cases in light of this evidence? This study has highlighted the potential for better phenotyping of patients who present with chyle in the wrong place using imaging to delineate the precise anatomical abnormality, and as such is a very welcome step forward in assessment and management of this often difficult-to-manage condition. Accepting that a clinical assessment of etiology, excluding common causes with specific treatment (e.g., lymphoma, trauma), and simple treatments (diet, octreotide) are still required, image-based phenotyping is very appealing as the next step in achieving clinical treatment success, especially for those patients who do not respond to standard treatment approaches. However, comparative data are now required to define the most efficacious and safest interventions in anatomically defined chylothorax. This study has provided the tools to conduct such studies, which, given the rare nature of chylothorax, are likely to need multicenter collaboration. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 Schild HH, Strassburg CP, Welz A, Kalff J. Treatment options in patients with chylothorax. *Dtsch Arztebl Int* 2013;110:819–826.
2 McGrath EE, Blades Z, Anderson PB. Chylothorax: aetiology, diagnosis and therapeutic options. *Respir Med* 2010;104:1–8.
3 Cope C, Salem R, Kaiser LR. Management of chylothorax by percutaneous catheterization and embolization of the thoracic duct: prospective trial. *J Vasc Interv Radiol* 1999;10:1248–1254.
4 Nadolski GJ, Itkin M. Thoracic duct embolization for nontraumatic chylous effusion: experience in 34 patients. *Chest* 2013;143:158–163.
5 Schwartz FR, James O, Kuo PH, Witte MH, Koweek LM, Pabon-Ramos WM. Lymphatic imaging: current noninvasive and invasive techniques. *Semin Intervent Radiol* 2020;37:237–249.
6 Gurevich A, Nadolski GJ, Itkin M. Novel lymphatic imaging and percutaneous treatment of chyluria. *Cardiovasc Intervent Radiol* 2018;41:1968–1971.
7 Itkin M. Lymphatic intervention techniques: look beyond thoracic duct embolization. *J Vasc Interv Radiol* 2016;27:1187–1188.
8 Gurevich A, Hur S, Singhal S, DiBardino D, Haas AR, Hansen-Flaschen JH, *et al.* Nontraumatic chylothorax and chylopericardium: diagnosis and treatment using an algorithmic approach based on novel lymphatic imaging. *Ann Am Thorac Soc* 2022;19:756–762.

Air Pollution and Child Lung Health: Critical Thresholds at Critical Times

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In September 2021, the World Health Organization (WHO) released updated global air quality guidelines (AQGs) for the first time since 2005. Incorporating a wealth of interim evidence demonstrating the adverse health effects of air pollution, the WHO tightened recommendations for target air pollution concentrations, including lowering the AQG for fine particulate matter (particulate matter ≤2.5 μm in aerodynamic diameter [$PM_{2.5}$]) from 10 μg/m^3 to 5 μg/m^3 (1). These updated guidelines not only emphasize the global urgency of improving air quality to prevent illness and death but also send the message that harmful effects occur even at lower concentrations of air pollution.

On the heels of these more stringent recommendations, in this issue of

AnnalsATS, Takebayashi and colleagues (pp. 763–772) investigated the association

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between concurrent exposure to low concentrations of $PM_{2.5}$ and lung function growth over 4 years in a large cohort of 1,466 pre- and early adolescent school children across 10 cities in Japan (2). Exposure measurements captured continuous ambient $PM_{2.5}$, ozone (O_3), and nitrogen dioxide (NO_2) concentrations at or near each school and were characterized by relatively low overall annual mean $PM_{2.5}$ concentrations of 13.5 $\mu g/m^3$. Perhaps counter to the sense that air pollution—even at lower thresholds—is harmful to lung health, the authors found no significant associations between $PM_{2.5}$ at these concentrations and lung function growth over the study period in models adjusted for confounders and copollutants.

These results are in contrast to previous literature demonstrating adverse effects of higher $PM_{2.5}$ concentrations (>20 $\mu g/m^3$) on longitudinal childhood lung function trajectories (3), as well as corresponding improvements in lung function with reduced exposure to air pollution during adolescence (4).

Despite its null findings, this study highlights an important paradigm of how environmental insults may alter the trajectory of human health and increase risk for future disease depending on the dose and timing of such exposures. Prior evidence for the presence of critical windows of susceptibility supports that, as early as the prenatal period, ambient air pollution exposures at specific weeks of gestation (with corresponding developmental milestones) have differential effects on lung function and respiratory disease risk during childhood (5–8). These and other data highlight the importance of examining the influence of environmental exposures on lung function trajectories during uniquely vulnerable points across the life course. In line with this concept, Takebayashi and colleagues present a unique snapshot of the impact of air pollutant exposures experienced at the verge of the accelerated lung growth of adolescence that ultimately contributes to the attainment of peak individual lung function in early adulthood. This inquiry is motivated by epidemiologic data from other cohorts that have linked environmental risk factors present at the preadolescent life stage to the development of chronic lung disease in middle age (9), emphasizing the importance of examining air pollutant exposures during critical windows of development that could have far-reaching consequences on lung health later in life. It remains to be seen what associations may exist between preadolescent low-dose $PM_{2.5}$ exposures and the attainment of peak lung health in extended follow-up periods of this cohort.

Apart from its overall contribution to this framework, the study has several strengths. The authors enrolled a large number of participants over a broad geographic area, allowing for generalizability of findings across Japan. In addition, high spirometry completion rates captured lung function at repeated points along the growth curve within the pre/early adolescent life stage. Another strength of the study is the inclusion of other air pollutants (O_3 and NO_2) in multipollutant models and multiple other sensitivity analyses resulting in consistent findings. However, as the authors gathered exposure data contemporaneous to lung function measurements, one gap in our ability to interpret a lack of relationship lies in the absence of exposure data before preadolescence. In effect, early-life exposures not captured by the current study may have already "set the course" toward an altered lung health trajectory. Looking forward to future trajectories, we must also consider that lung function values at time of study entry are a function of the cumulative effects of exposures experienced before that point in childhood, contributing to the phenomenon described by Peto in 1981 as the horse-racing effect (10).

Given the study findings, is it safe to say, then, that lower concentrations of $PM_{2.5}$ exposure during pre/early adolescence are benign for lifelong lung health? It is a comfort that we likely cannot take in good conscience, especially in the current environmental climate. Rather, a singular focus on physiologic measurements as the prime indicator of lung health is a gross overestimation and, more importantly, may miss opportunities for early intervention to preempt progression to disease. Instead, a greater focus on evaluating intermediate phenotypes of impaired lung health, such as respiratory symptoms and early changes on lung imaging, may help to identify altered respiratory status among individuals without established disease (11). For example, persistent respiratory symptoms in "healthy" young adult populations predict risk of future chronic lung disease, including accelerated lung function decline (12). Furthermore, detectable changes on chest computed tomography using objective analytic tools in otherwise visually normal-appearing lung have been associated with increased morbidity and mortality from chronic lung disease (13). This emerging evidence suggests that early markers of impaired lung health beyond spirometry may help to more precisely evaluate the harm associated with toxic exposures.

Until there is further evidence, the revised WHO AQGs serve as an impetus to continue to push the agenda for cleaner air. In these efforts, it is imperative to consider the unique vulnerability of developing children to the short- and long-term health effects of air pollution. ■

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References

1 World Health Organization. WHO global air quality guidelines: particulate matter ($PM_{2.5}$ and PM_{10}), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. Geneva: World Health Organization; 2021.

2 Takebayashi T, Taguri M, Odajima H, Hasegawa S, Asakura K, Milojevic A, *et al.* Exposure to $PM_{2.5}$ and lung function growth in pre- and early-adolescent schoolchildren: a longitudinal study involving repeated lung function measurements in Japan. *Ann Am Thorac Soc* 2022;19: 763–772.

3 Gauderman WJ, Vora H, McConnell R, Berhane K, Gilliland F, Thomas D, *et al.* Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. *Lancet* 2007;369:571–577.

4 Gauderman WJ, Urman R, Avol E, Berhane K, McConnell R, Rappaport E, *et al.* Association of improved air quality with lung development in children. *N Engl J Med* 2015;372:905–913.

5 Bose S, Rosa MJ, Mathilda Chiu YH, Leon Hsu HH, Di Q, Lee A, *et al.* Prenatal nitrate air pollution exposure and reduced child lung function: timing and fetal sex effects. *Environ Res* 2018;167: 591–597.

6 Bose S, Chiu YM, Hsu HL, Di Q, Rosa MJ, Lee A, *et al.* Prenatal nitrate exposure and childhood asthma. influence of maternal prenatal stress and fetal sex. *Am J Respir Crit Care Med* 2017; 196:1396–1403.

7 Lee A, Leon Hsu HH, Mathilda Chiu YH, Bose S, Rosa MJ, Kloog I, *et al.* Prenatal fine particulate exposure and early childhood asthma:

effect of maternal stress and fetal sex. *J Allergy Clin Immunol* 2018; 141:1880–1886.
8 Rosa MJ, Just AC, Kloog I, Pantic I, Schnaas L, Lee A, *et al.* Prenatal particulate matter exposure and wheeze in Mexican children: effect modification by prenatal psychosocial stress. *Ann Allergy Asthma Immunol* 2017;119:232–237.e1.
9 Bui DS, Walters HE, Burgess JA, Perret JL, Bui MQ, Bowatte G, *et al.* Childhood respiratory risk factor profiles and middle-age lung function: a prospective cohort study from the first to sixth decade. *Ann Am Thorac Soc* 2018;15:1057–1066.
10 Peto R. The horse-racing effect. *Lancet* 1981;2:467–468.
11 Liu GY, Kalhan R. Impaired respiratory health and life course transitions from health to chronic lung disease. Chest 2021;160:879–889.
12 Kalhan R, Dransfield MT, Colangelo LA, Cuttica MJ, Jacobs DR Jr, Thyagarajan B, *et al.* Respiratory symptoms in young adults and future lung disease: the CARDIA lung study. *Am J Respir Crit Care Med* 2018;197:1616–1624.
13 Harmouche R, Ash SY, Putman RK, Hunninghake GM, San Jose Estepar R, Martinez FJ, *et al.* Objectively measured chronic lung injury on chest CT. *Chest* 2019;156:1149–1159.

The Genomic Classifier and Our Quest for Diagnostic Certainty in Interstitial Lung Disease

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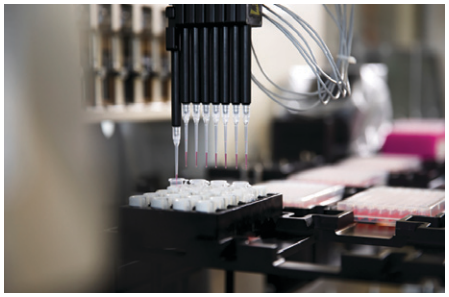

Interstitial lung diseases (ILDs) are a collection of complex and heterogeneous diseases that can be challenging to diagnose. Multidisciplinary discussions (MDDs) involve the dynamic exchange of information between chest radiologists, ILD clinicians, and lung pathologists and are currently the gold standard for ILD diagnosis (1). In particular, the addition of histopathologic data increases the diagnostic confidence of clinical radiologic diagnoses (2). Surgical lung biopsies (SLB) have traditionally been the preferred method to obtain tissue as they provide larger samples to better assess morphology; however, the associated risks may preclude patients from undergoing the procedure (3–5). As a result, a patient may be left with a low-confidence ILD diagnosis (i.e., unclassifiable ILD). Such a scenario is not uncommon, with 10–24% of ILD cases being unclassifiable (6, 7).

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive ILD with a poor prognosis comparable to aggressive cancers (8). An accurate diagnosis of IPF is important as it has therapeutic implications (e.g., early initiation of an antifibrotic) and informs discussions around prognosis. IPF can be diagnosed without a biopsy when there is high clinical suspicion and a definite or probable usual interstitial pneumonia (UIP) pattern on high-resolution computed tomographic (HRCT) imaging. Otherwise, a biopsy may be required to determine histopathological features to either support or refute an IPF diagnosis.

The Envisia Genomic Classifier (GC) was developed with the intent to identify a UIP pattern on transbronchial forceps biopsies (TBBx) and thus potentially avoid the need for more invasive procedures such as SLB for ILD diagnosis (9). Using machine learning, an algorithm based on genomic data from SLBs was used to identify a molecular signature for a UIP pattern (9). The RNA sequence of lung tissue obtained by TBBx is first determined, and then, using the classifier, its pattern of gene expression is classified as UIP or not UIP.

In this issue of *AnnalsATS*, Kheir and colleagues (pp. 827–832) conducted a systematic review on the use of GC testing in ILD diagnosis that will be used to inform updates to the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society clinical practice guideline for IPF (10). Studies were eligible if they included patients with an undiagnosed ILD, evaluated the use of the GC, and reported diagnostic test characteristics, agreement, and/or diagnostic confidence. There were four studies included that evaluated diagnostic test characteristics with a sensitivity of 68% and specificity of 92% based on pooled estimates. There were only two studies included that assessed diagnostic agreement, with moderate kappas (0.64 and 0.75) when comparing GC results to reference standards (MDD or histopathology alone). Both studies demonstrated improved diagnostic confidence when the GC was integrated into MDD review, although agreement between the GC and MDD diagnosis was more likely for cases with a probable HRCT pattern than indeterminate.

The use of a GC to aid accurate ILD diagnosis is an attractive concept. In theory, a GC decreases the subjectivity and interobserver variability of histopathology interpretation and increases the yield of less invasive testing. However, barriers to its widespread use remain. It likely best serves specific clinical scenarios (e.g., patients with a probable UIP pattern on imaging and/or those without access to an ILD center). It is unable to determine the specific ILD subtype

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