throughout without major complications. Just under 7% had minor side effects, such as wheezing, dyspnea, cough, bronchospasm, epistaxis, dizziness, bleeding, and nausea, that required an intervention. Pre- and post-bronchoscopy spirometry was performed, and although 13% had a fall to less than 90% of their baseline, this was not thought to be clinically significant in most instances. Patient characteristics associated with adverse events after bronchoscopy included female sex, lower preprocedure forced expiratory volume in 1 second (FEV₁), bronchodilator reversibility, asthma, and the visualization of secretions and friability during the procedure. Greater caution should therefore be taken when enrolling patients with these features into a bronchoscopy protocol. As well, it should be noted that patients with FEV₁ less than 30% predicted were deliberately excluded from the study for safety reasons. Altogether, though, research bronchoscopies appear to be safe in patients with mild to moderate COPD, an

observation that parallels our own recent experience.

What remains to be determined is whether this protocol, for all its exacting detail, actually results in consistent sampling technique across sites. In-person training sessions for bronchoscopists were provided before the start of the study, but the possibility of significant interindividual and center variation during specimen collection should be considered. Technical inconsistencies could have profound confounding effects. This is particularly true for microbiome profiling: even the simple act of suctioning through the bronchoscope before sample collection or whether a nasal or oral route is preferentially chosen (which the authors acknowledge was not rigorously defined in the protocol) could introduce degrees of contamination that might obscure true biological signals. A central processing site as is used in SPIROMICS can certainly help to mitigate further sources of contamination. In the authors' favor, at least previous multisite

microbiome studies in airway diseases such as the Lung HIV Microbiome Project have demonstrated neither segregation of the data by center (7–9) nor that biological signals change even after accounting for center (5).

The hope regarding protocols such as the one put forth by Wells and colleagues is that the expansion of research bronchoscopies around the world will help to generate enough lung samples to properly understand COPD phenotypes, their underlying pathophysiology, and novel therapies that can counteract the progression of disease. It goes without saying, though, that none of this is possible without the continued generosity of the COPD patient population who appear willing to sacrifice a bit of their own comfort and time for no greater motivation than the betterment of their fellow patients. And for this, we thank them. ■

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

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Looking at the Airway to Understand Interstitial Lung Disease

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Disease prevention represents the Holy Grail in the practice of medicine. Primary prevention aims to avoid disease onset,

whereas secondary prevention intervenes at an early stage to prevent progression or recurrence, and tertiary prevention seeks to reduce morbidity in those with established or advanced disease (1). At

present, interstitial lung disease (ILD) management operates largely within the realm of tertiary prevention. A few notable exceptions exist: the removal of the causative antigen in early hypersensitivity

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pneumonitis and smoking cessation for those with smoking-related ILD are examples of secondary prevention. But the majority of patients with ILD already have significant physiologic limitation at the time of presentation, leaving tertiary prevention as the only viable option.

This grim reality stems in part from significant delays that often occur in patients with ILD (2), which are likely compounded by the nonspecific nature of ILD symptoms and low prevalence relative to other lung diseases. Early disease recognition is critical to begin moving the goal post from tertiary prevention to proximal preventative spaces. The recent characterization on chest computed tomography (CT) of preclinical interstitial lung abnormalities (ILAs) (3, 4) and closely related high attenuation areas (5) provides hope that such an endeavor is possible. Along with valuable epidemiologic data, nearly a decade of research in this arena has provided evidence that most ILAs will progress (6) and that individuals with these radiographic findings are at increased risk for physiologic limitation, hospitalization, and death (4, 7, 8). As a consequence, ILA is, by every metric, synonymous with early ILD. This recognition represents perhaps our best opportunity to begin pivoting to secondary prevention in this population.

And yet, secondary prevention still falls short of our ultimate goal. To move toward primary prevention, we must understand what constitutes an at-risk individual. We know that cumulative cigarette smoke exposure increases the risk for ILAs (5), as does presence of the *MUC5B* promoter polymorphism (3). In this issue of the *AnnalsATS*, Miller and colleagues (pp. 447–454) add to this body of literature by identifying airway abnormalities as another potentially important contributor to the development of ILAs (9). These authors show that individuals with ILAs have increased airway wall thickness (AWT) on chest computed tomography across several cohorts, including patients with chronic obstructive pulmonary disease and community-dwelling adults, when compared with those without ILA. This association was largely maintained across confounders such as age, sex, smoking

history, and lung function. AWT was assessed by Pi10, a composite measure of wall thickness and luminal narrowing, which has been linked to clinically relevant endpoints in chronic obstructive pulmonary disease (10).

In addition to the link between AWT and the presence of ILAs, Miller and colleagues showed that AWT is inversely proportional to total lung capacity and forced vital capacity in those with ILAs (9). Although the strength of association between AWT and lung function varies considerably across cohorts and after adjustment for relevant confounders, these findings further support that increased AWT may be an early indicator of clinically significant ILD. Notably, gas transfer was not assessed in this population, but would provide additional valuable information in assessing the significance of these findings. Although smoking history may have influenced the relationship between AWT and lung function metrics, this exposure did not appear to influence the overall relationship between AWT and ILA presence.

The relevance of these findings was supported by an even more striking increase in AWT observed in a cohort of patients with IPF. On average, airway walls were >50% thicker in those with IPF compared with those with and without ILAs. Interestingly, ILA cases with radiographic features suggestive of IPF did not have markedly increased AWT when compared with those with findings suggestive of an alternative ILD. This observation, along with the absent correlation between AWT and lung function in this IPF cohort raises the question of whether AWT would serve as a relevant biomarker beyond early ILD.

These findings by Miller and colleagues also reinforce the work of others who have shown that airway abnormalities may play a role in the development of ILD (9). Conti and colleagues demonstrated increased levels of mucin *MUC5B* staining cells in the distal airways of patients with IPF (11), whereas Molyneaux and colleagues showed that lung microbial burden may influence both susceptibility and outcomes in IPF (12). Such findings are not limited to IPF, as Guerrero Zúñiga and colleagues recently demonstrated functional airway abnormalities in

patients with chronic hypersensitivity pneumonitis (13).

We cannot ascertain whether AWT is a true ILA risk factor, given the cross-sectional nature of this investigation, but the longitudinal data contained in the various cohorts used in this investigation will almost certainly provide some insight into this question in the coming years. If increased AWT is confirmed to be an ILA risk factor, the next question is how to identify this finding in an efficient manner. The manual selection and measurement of AWT is unrealistic in clinical practice. But with the rapid expansion of quantitative imaging and machine learning applications in ILD (14, 15), AWT determination may eventually be a mouse click away for anyone undergoing chest computed tomography.

In conclusion, Miller and colleagues have identified an exciting new layer to the complex tapestry that is early ILD (9). Given the significant morbidity and mortality that results from progressive ILDs, it is critical that we begin to place as much emphasis on preventing early ILD progression (secondary prevention) as we do treating established, and often advanced, ILD (tertiary prevention). This will not be easy, as the reporting of ILAs by radiologists remains a problem, as does the referral of patients with ILA to a pulmonologist (16). But once we begin to reliably identify these individuals, prospective studies will allow for the identification of new modifiable risk factors and further characterization of known potential risk factors, such as AWT. It is then that we will move closer to that holy grail of primary prevention in patients with ILD. ■

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Diagnosis from Afar: Is Remote Multidisciplinary Discussion Appropriate for Interstitial Lung Disease Care?

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Assigning a definitive diagnosis with high confidence in cases of interstitial lung disease (ILD) remains challenging for many cases because of the substantial overlap of clinical, radiologic, and histopathologic features among this heterogeneous group of pulmonary diseases. Erroneous diagnoses have real implications for patients, such as the administration of steroids or immunosuppressive agents in a disease where these drugs have been shown to be harmful, or the inappropriate initiation of

antifibrotic agents for diseases where the safety and efficacy are unknown. The wrong diagnosis may also affect the entire ILD community at large by enrolling the wrong patients into randomized clinical trials. As consensus diagnostic criteria exist for only some ILDs, multidisciplinary discussion (MDD) has been recommended as a key part of diagnostic decision-making for idiopathic pulmonary fibrosis and the other idiopathic interstitial pneumonias (1, 2). Although the specific composition and format of MDD varies by center, most consist of a pulmonologist, radiologist, and pathologist; meet at least weekly; involve data presentation by the clinician directly caring for the patient; and use a consensus

approach to diagnosis (3). Although studies have examined interobserver agreement in ILD diagnosis among individual clinicians (4–6), as well as concordance between MDDs from different international centers (7), the utility of MDD for remote

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