physiology: part i: health and normal physiology. *J Extracell Vesicles* 2022;11:e12151.

8. Mohan A, Agarwal S, Clauss M, Britt NS, Dhillon NK. Extracellular vesicles: novel communicators in lung diseases. *Respir Res* 2020; 21:175.

9. Eckhardt CM, Gambazza S, Bloomquist TR, De Hoff P, Vuppala A, Vokonas PS, *et al.* Extracellular vesicle-encapsulated microRNAs as novel biomarkers of lung health. *Am J Respir Crit Care Med* 2023;207: 50–59.

10. Ahsan H, Chen Y, Parvez F, Argos M, Hussain AI, Momotaj H, *et al.* Health effects of arsenic longitudinal study (HEALS): description of a multidisciplinary epidemiologic investigation. *J Expo Sci Environ Epidemiol* 2006;16:191–205.

11. Nouws J, Wan F, Finnemore E, Roque W, Kim SJ, Bazan I, *et al.* MicroRNA miR-24-3p reduces DNA damage responses, apoptosis, and susceptibility to chronic obstructive pulmonary disease. *JCI Insight* 2021;6:e134218.

12. Slater SC, Jover E, Martello A, Mitić T, Rodriguez-Arabaolaza I, Vono R, *et al.* MicroRNA-532-5p regulates pericyte function by targeting the transcription regulator BACH1 and angiopoietin-1. *Mol Ther* 2018;26: 2823–2837.

13. Li C, Ni YQ, Xu H, Xiang QY, Zhao Y, Zhan JK, *et al.* Roles and mechanisms of exosomal non-coding RNAs in human health and diseases. *Signal Transduct Target Ther* 2021;6:383.

Check for updates

∂ Risk Stratifying Interstitial Lung Abnormalities to Guide Early Diagnosis of Interstitial Lung Diseases

Delayed diagnosis is common in interstitial lung diseases (ILDs) and is associated with decreased quality of life and a poor prognosis (1). Early diagnosis and initiation of appropriate management could improve patient outcomes (2–5). Studies in idiopathic pulmonary fibrosis (IPF) demonstrated that antifibrotic therapies also slow down disease progression in patients with more preserved lung function (3, 5).

Interstitial lung abnormalities (ILAs) found incidentally on computed tomography (CT) performed for other purposes, such as lung cancer screening or diagnostic cardiac CT, may facilitate early diagnosis of ILD, allowing for early treatment and removal of triggers that drive ILD progression. However, ILAs are relatively frequent, especially in older subjects (6). Systematic evaluation of population-based and lung cancer–screening cohorts showed a prevalence of ILAs of 4–9% in (former) smokers and 2–7% in never-smokers (7). With increasing use of CT scans, clinicians are confronted with the question, "what to do with this person with ILAs?" Risk stratification of ILAs is urgently needed to differentiate two subsets: *1*) ILAs with a high likelihood of progression to clinically relevant ILD; versus *2*) ILAs that pose no such risk and do not need further evaluation and follow-up.

In this issue of the *Journal*, Rose and colleagues (pp. 60–68) add another piece of evidence to the puzzle of risk stratification of ILAs (8). They investigated whether combining CT data and pulmonary function (spirometry and $D_{L_{CO}}$) could identify subjects with suspected ILD, associated with worse outcomes, within participants with ILAs in the Genetic Epidemiology of Chronic Obstructive Pulmonary Disease (COPDGene) cohort, a U.S.-based multicenter prospective cohort study of (current and former) smokers (9). People with known lung diseases other than COPD or asthma were excluded. CT scans were assessed for percentage of emphysema and ILAs, defined per criteria of the Fleischner Society (10). CT scans showing ILAs were scored on the presence of definite fibrosis. Importantly, $D_{L_{CO}}$ was corrected for the percentage of emphysema on CT. For suspected ILD, the authors used the following definition: presence of ILAs and at least one of the following three criteria: *1*) definite fibrosis on CT; *2*) post-bronchodilator FVC < 80% predicted; or *3*) $D_{L_{CO}}$ < 70% predicted after adjustment for emphysema.

Ten percent of participants (443 out of 4,360) had ILAs. Of those with ILAs, 239 (54%) met the criteria of suspected ILD; within this subset, 16% had definite fibrosis on CT, 57% had an FVC < 80%, and 67% had a $D_{L_{CO}}$ < 80% after adjustment for emphysema. The majority (62%) of participants with suspected ILD met only one criterium, 35% met two criteria, and 3% met all three criteria. Participants with suspected ILD were more likely to be of self-identified Black or African American race and had a higher pack-year smoking history. Compared with the ILA group, subjects with suspected ILD were more likely to have worse clinical endpoints (including quality of life, 6-minute-walk test, and respiratory exacerbations). Mortality rates were higher in the suspected ILD than in the ILA group (15% vs. 6%).

This study has several strengths, including the large, multicenter, prospective cohort design with longitudinal data collection. The authors take the important step of splitting ILAs in two separate subgroups with vastly different outcomes: ILAs versus suspected ILD. Although ILA is a CT-defined entity, suspected ILD is defined by a combination of radiological and physiological abnormalities and could be seen as a potential early phase in the evolutionary continuum of ILD (11). However, suspected ILD and even definite ILD is not a diagnosis but merely an umbrella term warranting further investigations, ideally in an experienced ILD center with a multidisciplinary team discussion (11, 12). Although it feels intuitively correct to refer subjects with suspected ILD for further work-up and follow-up, it is too early to conclude that people with ILAs without suspected ILD can be safely discharged from follow-up.

The study also has limitations. First, the COPDGene cohort studied only smokers, implicating the need to further validate and fine-tune the criteria of suspected ILD in broader populations. Second, although a $D_{L_{CO}} < 70\%$ predicted (after adjustment for emphysema) appeared to be the most important criterion in driving the associations with clinical endpoints, $D_{L_{CO}}$ was not measured at baseline but only in the second phase of COPDGene (5 years after enrollment). Replication of the lung function criteria (and their cut-offs) is warranted in independent cohorts with contemporaneous imaging, spirometry, and $D_{L_{CO}}$ data. Moreover, it is a concern that the single criterion of an often-variable measure such as $D_{L_{CO}}$ is sufficient to support labeling a person as having suspected ILD. Last, another potential caveat is the fact that the presence of subpleural reticulation was not included in the criteria for suspected ILD. This conforms to the Fleischner criteria, where the division is made in subpleural nonfibrotic ILA and subpleural fibrotic ILA (characterized by the presence of architectural distortion with traction bronchiectasis or honeycombing) (10). However, a recent population-based ILA study in China showed that subpleural reticulation in itself was an independent risk factor for progression (6).

Strikingly, the distribution of suspected ILD in COPDGene is equal in males and females, which is not reflecting the prevalence of IPF in registries and studies (13). Furthermore, there is a considerably lower death rate in subjects with suspected ILD than in patients with IPF. Besides a potential lead-time bias, this suggests that ILAs likely encompass the broad spectrum of ILDs. As the presence of connective tissue diseases or occupational exposures were not an exclusion criterium for participating in the COPDGene cohort, this may partially explain the survival and sex distribution, where the suspected ILD could be related to connective tissue disease or exposure. For this group, early detection of ILD may be most relevant, as immunosuppressive treatments and avoidance of disease triggers have the potential to reverse, stabilize, or slow down lung function decline (11). In the current study, self-identified Black race was a risk factor for suspected ILD. Previous studies have shown that women and people of Black ethnicity are less likely to receive a diagnosis of IPF and are underrepresented in registries and clinical trials (13, 14). Identifying suspected ILD in the group of ILAs—according to the approach by Rose and colleagues—may be a way to improve earlier diagnosis in broader and more diverse populations.

The results of this study underline that people with ILAs should undergo lung function testing, in line with previous expert recommendations (7, 10). The question remains, though, whether people with ILAs can be discharged from follow-up if lung function is normal and there are no signs of definite fibrosis on CT. Although several studies have identified blood biomarkers and genetic polymorphisms related to the presence of ILAs, limited data exist on biomarkers predictive of ILA progression (15, 16). It would be interesting to link the proposed suspected ILD classification with biomarkers and genetic data in COPDGene.

Taken together, the findings of Rose and colleagues support that it is time to complement the CT-based ILA classification with a clinical classification of suspected ILD, also incorporating lung function and potentially symptoms and blood biomarkers to identify patients as early as possible in the evolutionary continuum of the different ILDs. Such a holistic classification would pave the way for clinical trials investigating the long-term benefits of treating ILDs in the early phases, to improve outcomes for patients with often still poor prognoses. ∎

Marlies S. Wijsenbeek, M.D., Ph.D.
Department of Respiratory Medicine
Erasmus University Medical Center Rotterdam
Rotterdam, the Netherlands

Guy G. Brusselle, M.D., Ph.D.
Departments of Respiratory Medicine and Clinical Epidemiology
Erasmus University Medical Center Rotterdam
Rotterdam, the Netherlands
and
Department of Respiratory Medicine
Ghent University Hospital
Ghent, Belgium

ORCID ID: 0000-0002-4527-6962 (M.S.W.).

References

1. Spagnolo P, Ryerson CJ, Putman R, Oldham J, Salisbury M, Sverzellati N, *et al.* Early diagnosis of fibrotic interstitial lung disease: challenges and opportunities. *Lancet Respir Med* 2021;9:1065–1076.
2. Brereton CJ, Wallis T, Casey M, Fox L, Pontopiddan K, Laws D, *et al.* Time taken from primary care referral to a specialist centre diagnosis of idiopathic pulmonary fibrosis: an opportunity to improve patient outcomes? *ERJ Open Res* 2020;6:00120-2020.
3. Kolb M, Richeldi L, Behr J, Maher TM, Tang W, Stowasser S, *et al.* Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume. *Thorax* 2017;72:340–346.
4. Hewitt RJ, Bartlett EC, Ganatra R, Butt H, Kouranos V, Chua F, *et al.* Lung cancer screening provides an opportunity for early diagnosis and treatment of interstitial lung disease. *Thorax* 2022;77:1149–1151.
5. Albera C, Costabel U, Fagan EA, Glassberg MK, Gorina E, Lancaster L, *et al.* Efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis with more preserved lung function. *Eur Respir J* 2016;48: 843–851.
6. Zhang Y, Wan H, Richeldi L, Zhu M, Huang Y, Xiong X, *et al.* Reticulation is a risk factor of progressive subpleural nonfibrotic interstitial lung abnormalities. *Am J Respir Crit Care Med* 2022;206: 178–185.
7. Hata A, Schiebler ML, Lynch DA, Hatabu H. Interstitial lung abnormalities: state of the art. *Radiology* 2021;301:19–34.
8. Rose JA, Menon AA, Hino T, Hata A, Nishino M, Lynch DA, *et al.* Suspected interstitial lung disease in COPDGene. *Am J Respir Crit Care Med* 2023;207:60–68.
9. Regan EA, Hokanson JE, Murphy JR, Make B, Lynch DA, Beaty TH, *et al.* Genetic epidemiology of COPD (COPDGene) study design. *COPD* 2010; 7:32–43.
10. Hatabu H, Hunninghake GM, Richeldi L, Brown KK, Wells AU, Remy-Jardin M, *et al.* Interstitial lung abnormalities detected incidentally on CT: a position paper from the Fleischner Society. *Lancet Respir Med* 2020;8: 726–737.
11. Wijsenbeek M, Suzuki A, Maher TM. Interstitial lung diseases. *Lancet* 2022;400:769–786.

12. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, *et al.* Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2022;205:e18–e47.
13. Jalbert AC, Siafa L, Ramanakumar AV, Assayag D. Gender and racial equity in clinical research for idiopathic pulmonary fibrosis: a systematic review and meta-analysis. *Eur Respir J* 2022;59:2102969.
14. Assayag D, Morisset J, Johannson KA, Wells AU, Walsh SLF. Patient gender bias on the diagnosis of idiopathic pulmonary fibrosis. *Thorax* 2020;75:407–412.
15. Kim JS, Axelsson GT, Moll M, Anderson MR, Bernstein EJ, Putman RK, *et al.* Associations of monocyte count and other immune cell types with interstitial lung abnormalities. *Am J Respir Crit Care Med* 2022;205:795–805.
16. Maher TM. Biomarkers for interstitial lung abnormalities: a stepping-stone toward idiopathic pulmonary fibrosis prevention? *Am J Respir Crit Care Med* 2022;206:244–246.

🔄 Check for updates

∂ Criteria for Progressive Pulmonary Fibrosis: Getting the Horse Ready for the Cart

Progressive pulmonary fibrosis (PPF) (1), formerly progressive fibrosing interstitial lung disease (ILD) (2), designates a subset of fibrotic ILDs which share with untreated idiopathic pulmonary fibrosis (IPF) a natural course characterized by irreversible progression, causing worsening respiratory symptoms, a decline in lung function, and early mortality (3). Although each ILD is relatively rare, and a variable proportion of each develops a progressive phenotype (4), collectively, PPFs represent a devastating condition associated with a high humanistic and economic burden to patients, their caregivers, and society (5).

Generally, in medicine, potential therapy is envisaged, and clinical trials are designed long after a condition has been identified and its natural history characterized through observational studies. It is only after large trials have been conducted and experience has been acquired by specialized centers that guidelines are developed. With regard to PPF, a different and somewhat backward process was taken. In two early cohorts, including patients with both IPF or idiopathic nonspecific interstitial pneumonia, a decline in FVC over 6–12 months was associated with an increased risk of subsequent mortality, independently of the underlying ILD diagnosis (e.g., IPF vs. nonspecific interstitial pneumonia) (6, 7). A decline in lung function despite usual management, therefore, identified disease progression. An IPF-like disease behavior (8) was also identified in other non-IPF fibrotic ILDs (9, 10) and was strongly linked with mortality. The emergent concept of PPF (2) was then validated by a landmark clinical trial (INBUILD), designed and powered to provide evidence in PPF as a whole and not in specific diagnostic subgroups (11). Nintedanib decreased disease progression, as measured by FVC decline, in patients with PPF enrolled irrespective of the underlying ILD diagnosis (12).

Since then, studies have assessed the prevalence of PPF among non-IPF fibrotic ILDs and confirmed the impact of disease progression on subsequent mortality (13–16). Progression was generally defined using original or modified INBUILD criteria (11, 17). Recently, an international guideline statement proposed revised criteria for identifying PPF among fibrotic ILD (1). The criteria proposed include stand-alone measures of lung function decline and combinations of symptomatic, physiologic, and radiologic worsening, some being known to be associated with increased mortality in various fibrotic ILDs, and others being extrapolated from the IPF literature. With the exception of FVC decline, few of these criteria have been validated in non-IPF fibrotic ILDs. It was argued that clinical practice guidelines may have preceded the accumulation of evidence rather than incorporated it, "putting the cart before the horse" (18).

In this issue of the *Journal*, an article by Pugashetti and colleagues (pp. 69–76) and a letter by Khor and colleagues (pp. 102–105) explored whether different PPF criteria were associated with subsequent transplant-free survival (19, 20, respectively). Pugashetti and colleagues report the outcome of a large ($n = 1,341$) retrospective cohort from four centers. They confirmed that ≥10% relative FVC decline was the strongest predictor of subsequent reduced transplant-free survival, consistent with findings from the INBUILD study (21), and was the most consistent criterion irrespective of ILD subtype. Three additional stand-alone PPF criteria in the absence of ≥10% relative FVC decline (5–9% relative FVC decline, ≥15% relative $D_{L_{CO}}$ decline, and computed tomography progression of fibrosis), and three combinations of symptomatic, physiologic, and radiologic worsening, were also associated with reduced transplant-free survival in patients with non-IPF fibrotic ILD, in both the derivation and validation cohorts (19). Results were not affected by hospital site or immunosuppressive or antifibrotic therapy; however, the underlying ILD diagnosis and the PPF criteria met had an impact on subsequent survival.

The cohort was characterized by a high rate of disease progression, as half of the patients experienced a ≥10% relative FVC decline within 4 years. Clinicians should be aware that eventually, a majority of patients with fibrotic ILDs will experience disease progression, sometimes several years after the diagnosis; therefore, long-term follow-up is warranted. Compared with those with connective tissue disease-associated ILD, patients with fibrotic hypersensitivity pneumonitis and those with non-IPF idiopathic interstitial pneumonia more frequently experienced disease progression and had a greater risk of death after satisfying PPF criteria, paralleling previous studies (13–16). Thus, heterogeneity in disease course remains among ILD subtypes even after satisfying PPF criteria. In this study, PFF criteria were applied over a 4-year period to assess 5-year transplant-free survival (19). Disease progression was