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Progressive Pulmonary Fibrosis and Interstitial Lung Abnormalities: *AJR* Expert Panel Narrative Review

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Progressive pulmonary fibrosis (PPF) and interstitial lung abnormalities (ILA) are relatively new concepts in interstitial lung disease (ILD) imaging and clinical management. Recognition of signs of PPF and identification and classification of ILA are important tasks during chest high-resolution CT interpretation to optimize management of patients with ILD and those at risk of developing ILD. However, in professional society guidance, the role of imaging surveillance remains unclear for stable patients with ILD, asymptomatic patients with ILA who are at risk of progression, and asymptomatic patients at risk of developing ILD without imaging abnormalities. In this *AJR* Expert Panel Narrative Review, we summarize the current knowledge regarding PPF and ILA and describe the range of clinical practice with respect to imaging patients with ILD, those with ILA, and those at risk of developing ILD. In addition, we offer suggestions to help guide surveillance imaging in areas with an absence of published guidelines, where such decisions are currently driven primarily by local pulmonologists' preference.

Fibrosing interstitial lung diseases (ILDs) encompass a diverse array of conditions such as idiopathic pulmonary fibrosis (IPF), connective tissue disease–related ILD (CTD-ILD), fibrotic hypersensitivity pneumonitis, and occupational lung disorders, among others. They are associated with varying degrees of morbidity and early mortality. The diagnosis relies on a combination of clinical evaluation; high-resolution CT (HRCT) of the chest; and, for some patients, additional evaluation such as bronchoalveolar lavage, tissue sampling, or both. Most importantly, multidisciplinary discussion remains essential when a confident diagnosis remains elusive [1].

An increasing number of scientific studies have also shed light on the importance of incidentally detected chest imaging abnormalities, specifically interstitial lung abnormalities (ILA). These abnormalities are associated with a variety of adverse health outcomes, including the development of fibrosing ILD and early mortality [2].

Guidelines standardizing the diagnosis of IPF were published in 2018 by both the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) [3] and the Fleischner Society [1]. With slight variations, both guidelines defined the associated clinical, radiologic, and pathologic features. In 2022, the ATS/ERS/JRS/ALAT guidelines were updated to refine the radiologic and clinical criteria and provide a definition of progressive pulmonary fibrosis (PPF) [4]. In 2020, the Fleischner Society published a position paper on ILA [2]. These guidelines have helped standardize the diagnosis of fibrosing ILD, particularly progressive fibrosing disorders, and have further highlighted the importance of ILA.

PPF and ILA are relatively new concepts in ILD imaging and clinical management, and recognition of signs of PPF and identification and classification of ILA are important tasks during chest HRCT interpretation to optimize management of patients with ILD

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TABLE 1: Summary of Suggested Imaging Follow-Up for ILD and ILA

Scenario	Suggested Imaging Follow-Up
Established ILD, clinically stable	Follow-up at 12–24 mo; however, some practitioners may choose not to perform follow-up imaging
Established ILD, new or worsening symptoms, or declining PFT results	Urgent or emergent HRCT, depending on acuity and severity
Newly diagnosed CTD with risk for ILD	Baseline HRCT to screen for ILD and ILA
Asymptomatic patient with CTD and no ILD or ILA on baseline CT	Follow-up at 24–48 mo
Asymptomatic patient with ILA at risk for progression	Follow-up at 12–24 mo
ILA with worsening signs or symptoms	Urgent or emergent HRCT, depending on acuity and severity
Acute dyspnea or hypoxia in patient with known or suspected ILD undergoing CTPA for PE	Unenhanced prone inspiratory HRCT before CTPA; outpatient HRCT after acute signs and symptoms have resolved

Note—ILD = interstitial lung disease, ILA = interstitial lung abnormalities, PFT = pulmonary function test, HRCT = high-resolution CT, CTD = connective tissue disease, CTPA = pulmonary CTA, PE = pulmonary embolism.

and those at risk of developing ILD. However, in the early professional society guidance, the role of follow-up imaging remains unclear in patients with stable ILD, asymptomatic patients with ILA, and asymptomatic patients without ILD or ILA but who are at risk of developing ILD. In this *AJR* Expert Panel Narrative Review, we summarize current knowledge regarding PPF and ILA and describe the range of clinical practice with respect to imaging patients with ILD, those with ILA, and those at risk of developing ILD. In addition, we offer suggestions to help guide surveillance imaging (Table 1) in areas with an absence of published guidelines, where such decisions are currently driven primarily by local pulmonologists' preference.

PPF

Definition

IPF is often regarded as the quintessential illustration of a progressive fibrotic ILD [5]. Several other fibrotic ILDs can progress such as sarcoidosis, hypersensitivity pneumonitis, and CTD-ILD. Although precise data on the percentage of patients with PPF among patients with non-IPF are lacking, estimates suggest that PPF affects approximately 13–60% of individuals with non-IPF ILD [4, 6, 7]. Originally defined as progressive fibrosing ILD [8], an ATS clinical practice guideline published in 2022 defined PPF as a non-IPF fibrosing ILD with the presence of two of the following three features occurring within 1 year of follow-up: deterioration in respiratory symptoms, demonstrable physiologic evidence of disease progression through pulmonary function tests (PFTs), and increased fibrosis on imaging [4] (Table 2). Importantly, PPF applies only to those patients whose fibrosis has progressed despite appropriate management tailored to the underlying ILD [9]. The diagnosis of PPF holds significant management implications regardless of the underlying cause of fibrosis. Antifibrotic medications, such as nintedanib and pirfenidone, have shown effectiveness in mitigating forced vital capacity (FVC) decline in patients with non-IPF with PPF who have not responded to conventional therapies targeting their primary condition [8, 10, 11].

High-resolution CT (HRCT) involves obtaining thin-section (≤ 1.25 mm) axial images through the chest. Prone and expiratory acquisitions are usually recommended for the initial HRCT examination, although repeating these acquisitions during follow-up examinations is typically unnecessary. Reticulation, characterized by a netlike appearance of interlacing lines typically located in the lung periphery, is the initial indication of fibrosis on HRCT. As fibrosis progresses, later manifestations include architectural distortion, which disrupts the normal secondary lobular anatomy, as well as traction bronchiectasis or traction bronchiolectasis, manifested as bronchial dilatation due to adjacent reticulation. Ultimately, advanced fibrosis may manifest with honeycombing, characterized by rows of cysts often stacked atop one another [12]. Increased extent of fibrosis on HRCT is usually determined visually, comparing

TABLE 2: Definition of Progressive Pulmonary Fibrosis

Category	Criteria
Clinical	Respiratory symptoms that have worsened
Physiologic	FVC predicted to show absolute decline of at least 5% within 1 y; or DL_{CO} (corrected for Hb) predicted to show absolute decline of at least 10% within 1 y
Radiologic	At least one of the following findings: Traction bronchiectasis and bronchiolectasis becoming more widespread or severe New GGO accompanied by traction bronchiectasis New fine reticulation Reticular abnormality becoming more widespread or more coarse New or increased honeycombing Increased lobar volume loss

Note—According to the description by Raghu et al. [7], at least two of the criteria in this table must have occurred within the preceding year with no alternate explanation available to satisfy the definition of progressive pulmonary fibrosis. FVC = forced vital capacity, DL_{CO} = diffusing capacity of the lung for carbon monoxide, Hb = hemoglobin, GGO = ground-glass opacity.

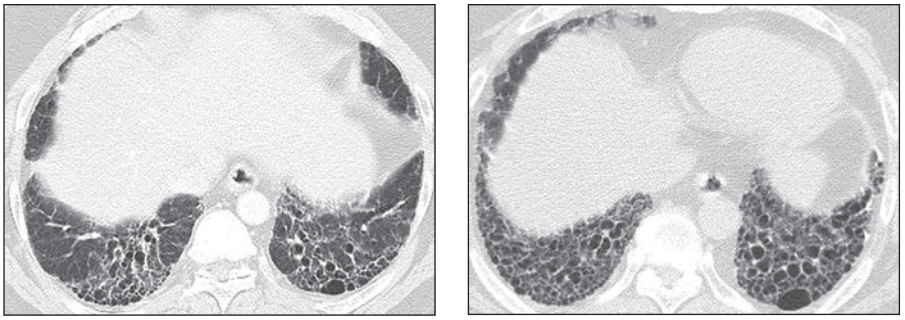

Fig. 1—64-year-old man with idiopathic pulmonary fibrosis and progressive disease.
A, Baseline axial high-resolution CT (HRCT) image shows peripheral and basal-predominant reticulation, architectural distortion, traction bronchiectasis, and subpleural honeycombing, consistent with usual interstitial pneumonia.
B, Axial HRCT image obtained 3 years later shows considerable progression of pulmonary fibrosis, manifesting with increasing extent of honeycombing as well as worsening traction bronchiectasis and reticulation.

the older examination with the current examination after review of axial, coronal, and sagittal reconstructions. Signs of progressive fibrosis on HRCT manifest as any of the following: new or worsening of traction bronchiectasis or traction bronchiolectasis, new reticulation or coarsening of reticulation, increased lobar volume loss, or the development or enlargement of honeycombing (Fig. 1). In many patients, fibrotic disease progression becomes more evident when comparing an HRCT examination with an HRCT examination performed at a distant point in time, rather than solely comparing it with the most recent examination.

When individuals with a fibrosing ILD experience new or worsening symptoms or a decline in pulmonary physiology, imaging is commonly used for further assessment. HRCT is preferred over radiography, as HRCT is better able to distinguish progression of underlying fibrosis from other causes of clinical deterioration, including infection, acute exacerbation of ILD (AE-ILD), pulmonary edema, or pulmonary thromboembolic disease [13–17] (Fig. 2). Patients with IPF are reported to be more than four times likely to have a prothrombotic state than control patients [18], and pulmonary embolism (PE) is more prevalent in outpatients with ILD than in those without ILD. In a retrospective cohort study that reported over 600,000 patient records from the Korean Health Insurance Review and Assessment Service, PE was found in 1746 per 100,000 persons with ILD compared with 113 per 100,000 persons in the general population [19]. For these reasons, patients with ILD in this acute clinical scenario usually undergo pulmonary CTA (CTPA) rather than being assumed to have AE-ILD or other diagnosis.

Evaluating the lungs on CTPA can be challenging, as patients with increased shortness of breath are usually not able to take a good inspiration, adding atelectasis on top of their known fibrotic ILD on these supine inspiratory images. Furthermore, respiratory motion and contrast medium artifacts may be present. Without the prone inspiratory images that are usually part of HRCT evaluation for ILD, it can be difficult to distinguish ILD progression and other diagnoses or superimposed atelectasis due to incomplete inspiration. Performing inspiratory prone HRCT in patients with fibrotic ILD before CTPA acquisition can help in the evaluation of these patients. Application of the most recent criteria from the IPF Clinical Research Network for AE-ILD can also help (Table 3). Some of the criteria for AE-ILD are based on CT findings including new bilateral ground-glass opacity (GGO), consolidation, or both, superimposed on a background usual interstitial pneumonia (UIP) pattern, that cannot be fully explained by heart failure, fluid overload, or extraparenchymal causes, such as pulmonary thromboembolism, pleural effusion, or pneumothorax, all of which have been excluded [20]. When diagnostic uncertainty remains, a dedicated unenhanced HRCT examination can be performed on an outpatient basis, after the acute symptoms have improved, to better evaluate the lungs.

Routine Follow-Up Imaging for Fibrotic ILD

The ideal interval for performing follow-up HRCT for patients with clinically stable ILD remains uncertain and is often individualized [9, 21]. Some health care providers choose to perform imaging studies only in patients with worsening symptoms or those with a decline in pulmonary physiology results. Limited evidence in patients with systemic sclerosis (SSc)-ILD indicates that a follow-up HRCT examination performed 12–24 months after the initial assessment facilitates early detection of disease progression and may influence prognosis [22]. Despite having minimal evidence, the American College of Radiology Appropriateness Criteria Thoracic Imaging Panel, through expert consensus, has affirmed that unenhanced chest HRCT is usually appropriate for the follow-up of patients with confirmed ILD who are not

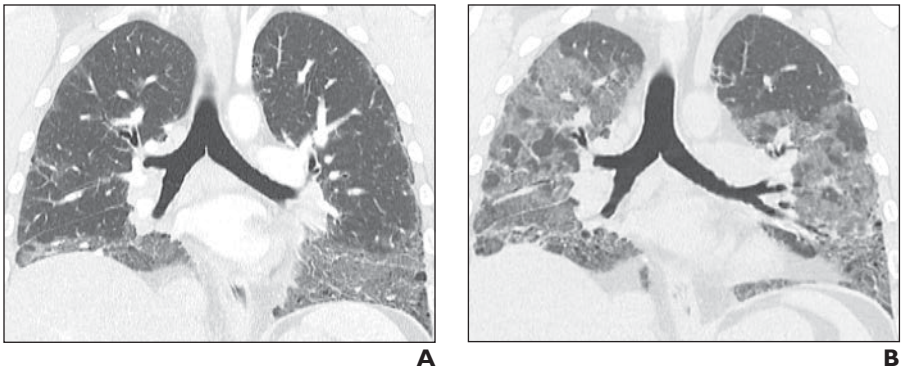

Fig. 2—34-year-old man with familial interstitial lung disease (ILD) and acute exacerbation. GGO = ground-glass opacity.
A, Baseline coronal reformatted high-resolution CT (HRCT) image shows basal-predominant GGOs with superimposed reticulation and some subpleural cysts.
B, Coronal reformatted HRCT image obtained 6 months later during acute exacerbation shows new and extensive bilateral GGOs. Patient was diagnosed with acute exacerbation of ILD after exclusion of infection and pulmonary edema.

TABLE 3: Diagnostic Criteria for Acute Exacerbation of IPF

Category	Criteria
Clinical	Prior or concurrent diagnosis of IPF Dyspnea that is new, typically less than 1 mo in duration, or is worsening Deterioration not fully explained by heart failure or fluid overload
Radiologic	UIP pattern of fibrosis New bilateral GGOs, consolidation, or both

Note—These criteria are further discussed by Collard et al. [20]. IPF = idiopathic pulmonary fibrosis, UIP = usual interstitial pneumonia, GGO = ground-glass opacity.

experiencing clinical deterioration, although the panel does not provide a specific time frame for follow-up [23].

Many pulmonologists opt for performing HRCT every 12–24 months for clinically stable patients with a fibrotic ILD, but this time frame is often individualized using clinical and physiologic data [24]. This approach helps in the timely detection of PPF, especially in patients with baseline HRCT findings such as honeycombing, traction bronchiectasis, and more extensive pulmonary fibrosis, as these features are indicative of a higher likelihood of fibrotic disease progression and are associated with early mortality [25–34]. Furthermore, PFTs are often insensitive for detecting disease progression, especially early in the disease course. A survey of over 500 pulmonologists and rheumatologists from the United States, Japan, and the European Union showed different practice patterns for imaging follow-up of ILD by region [35]. All surveyed pulmonologists from Japan performed chest radiography or HRCT at least every 12 months, often with an interval of between 3 and 6 months. Thirty percent of pulmonologists from the United States and European Union performed imaging only when the patient's condition worsened [35].

Some health care providers also use annual HRCT for the purpose of screening for complications associated with fibrotic ILD, with a specific focus on early detection of primary lung cancer [24]. The incidence of lung cancer in patients with ILD varies depending on several factors, including the underlying cause of fibrosis, the severity of fibrosis, and other individual risk factors such as smoking. A comprehensive meta-analysis comprising 35 studies, which examined the occurrence of lung cancer in individuals with IPF, revealed a prevalence rate of 13.5% [36]. This prevalence was higher among men and in individuals who smoke [36]. A meta-analysis investigating lung cancer in combined pulmonary fibrosis with emphysema (CPFE) found that patients with CPFE presented at a later stage and had a worse prognosis than those without CPFE [37] (Fig. 3). Diagnosing lung cancer in individuals with ILD poses challenges, as early malignancies are frequently misinterpreted as confluent fibrosis.

ILA

Definition, Prevalence, Risk Factors

ILA refer to incidental findings potentially reflective of unsuspected ILD on HRCT. The definition of ILA is imaging-based, and separation of ILA from ILD relies on clinical assessment including pulmonology evaluation and frequently PFTs [2, 38]. ILA are defined as nondependent abnormalities involving greater than 5% of any lung zone (upper, middle, or lower delineated by the levels of the inferior aortic arch and right inferior pulmonary vein) on partial or complete HRCT evaluation of the lungs. Given that fibrotic ILA are most commonly found predominantly or exclusively in the lower lobes, and together the lower lobes represent half of total lung volume on supine HRCT, 5% or more of each lower lobe translates to greater than 2.5% of total lung volume [39]. The arbitrary threshold of 5% is meant to exclude individuals with minimal abnormality. Findings, including GGO, reticulation, nonemphysematous cysts, honeycombing, traction bronchiectasis, and architectural distortion, are classified into one of three categories: nonsubpleural ILA, subpleural nonfibrotic ILA, or subpleural fibrotic ILA [2, 38] (Fig. 4). Fibrotic ILA are defined by the presence of honeycombing, traction bronchiectasis or bronchiolectasis, or architectural distortion and are categorized in accordance with current guidelines as typical, probable, or indeterminate for UIP [1, 3]. Reticulation, although a hallmark of pulmonary fibrosis, is not considered fibrotic ILA on its own because of the lower likelihood of progression and lower mortality in the absence of traction bronchiectasis or bronchiolectasis [40, 41].

ILA are common with a reported prevalence of up to 7% in individuals who never smoked and 10% in individuals older than 60 years with a history of smoking [2, 42]. Although ILA are underreported, they are increasingly recognized with the growing understanding of their clinical implications [43, 44]. ILA frequently exhibit radiologic progression and are associated with impaired pulmonary function, progression to fibrotic ILDs such as IPF, and increased morbidity and all-cause mortality [42, 45–48]. The increased risk of acute exacerbation of chronic obstructive pulmo-

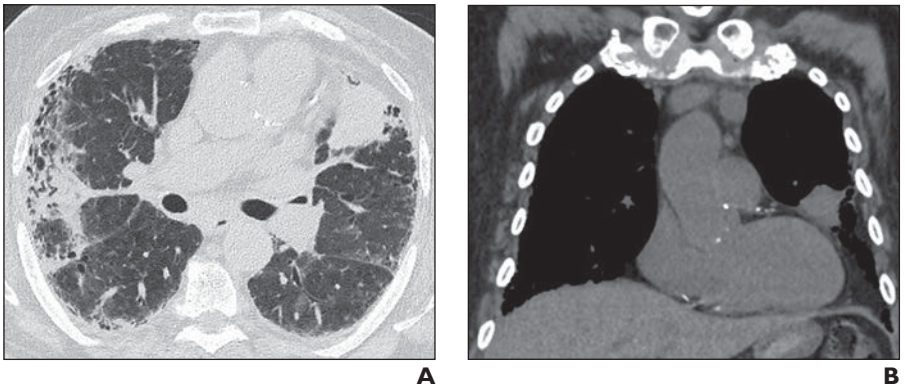

Fig. 3—67-year-old man with combined pulmonary fibrosis with emphysema (CPFE) and advanced primary lung cancer.
A, Axial high-resolution CT (HRCT) image shows left upper lobe mass, emphysema, and peripheral lung fibrosis.
B, Coronal reformatted HRCT image shows left upper lobe mass and metastatic ipsilateral mediastinal lymphadenopathy. Individuals diagnosed with CPFE frequently experience lung cancers that are diagnosed at more advanced stage compared with cancers in patients who do not have CPFE.

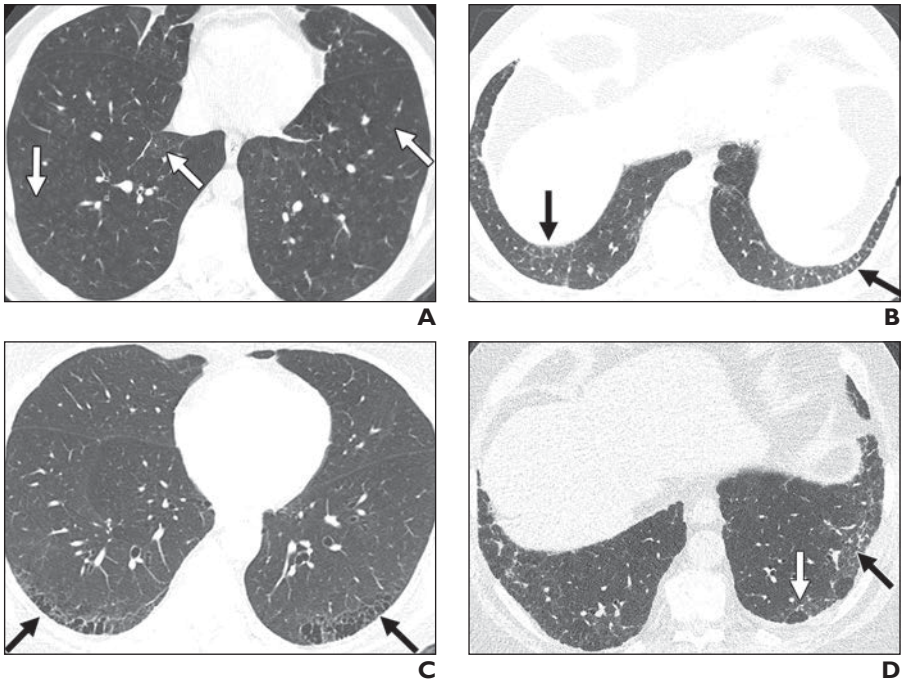

Fig. 4—Subtypes of interstitial lung abnormalities (ILA). GGO = ground-glass opacity.
A, Axial high-resolution CT (HRCT) image of 53-year-old man shows nonsubpleural ILA that are primarily nodular and are characterized by GGOs (*arrows*).
B, Axial HRCT image of 66-year-old woman shows subpleural nonfibrotic ILA characterized by reticulation (*arrows*) and GGOs.
C, Axial HRCT image of 58-year-old woman shows subpleural nonfibrotic ILA characterized by clustered cystic spaces (*arrows*).
D, Axial HRCT image of 72-year-old man shows subpleural fibrotic ILA characterized by GGOs, reticulation, and traction bronchiectasis (*arrows*).

nary disease (COPD) and lung cancer treatment-related complications is well recognized in patients with ILA [46, 49].

Several risk factors of ILA, including older age, smoking history, and the mucin 5B promoter polymorphism (variant rs35705950), are shared with IPF, suggestive of an overlap in some individuals [50–52]. Several aging-related biomarkers are also associated with an increased frequency of ILA, in particular growth differentiation factor 15, tumor necrosis factor–α, interleukin 6, and C-reactive protein (CRP) [53]. Male sex and additional newly described genetic loci not previously associated with IPF (variants rs6886640, rs73199442, and rs7744971) are also shown to increase the risk of developing ILA in some reports [50, 52]. Although the current ILA definition excludes individuals at increased risk of pulmonary fibrosis, emerging evidence supports the inclusion of such at-risk individuals [54, 55].

Progression Rates and Risk Factors for Progression

The rate of progression of ILA varies considerably across studies, reflecting the differences in patient cohorts studied with these abnormalities. From a single site where 884 patients were evaluated with CT in the National Lung Screening Trial, an older population with a cigarette smoking history of at least 30 pack-years, which was approximately 11% of individuals with nonfibrotic ILA and 37% of individuals with fibrotic ILA, experienced progression on CT over 2 years [51]. In contrast, the Age Gene/Environment Susceptibility (AGES)-Reykjavik study, a longitudinal birth cohort that includes individuals born in Reykjavik, Iceland, from 1907 to 1935, reported a substantially higher progression rate: 40% of patients with ILA showing definite progression and 32% of patients with showing probable progression over a 5-year period [45]. This wide range suggests that, although not all ILA progress, monitoring over longer follow-up periods is important to better estimate their natural history and clinical implications.

Specific radiologic characteristics have emerged as key indicators of progression. In a study by Putman et al. [45], patients with ILA characterized by subpleural reticulation, lower lobe predominance, or traction bronchiectasis had a sixfold increased likelihood of progression over a 5-year period, compared with individuals with ILA lacking these features [56]. ILA comprising honeycombing and ILA meeting the criteria for UIP, probable UIP, or both progressed in all cases [45]. These findings have been replicated in several subsequent studies [56, 57]. On this basis, the separation of fibrotic ILA from nonfibrotic ILA has emerged as the cardinal distinction when predicting likelihood of progression.

However, stratification of subpleural nonfibrotic ILA based on clinical risk is more challenging. This difficulty was addressed directly in a recent large study from China of 155,539 individuals undergoing a routine health check, with chest CT showing ILA in 2.1% of patients [58]. In nearly 44% of individuals with subpleural nonfibrotic ILA (198 of 454 patients), ILA progressed, with reticulation (96/272 [35.3%] individuals) being an independent predictor of progression in this subgroup (OR, 1.9 [95% CI, 1.2–3.0]; $p = .0040$). Importantly, there was no difference in radiologic progression between individuals with subpleural nonfibrotic ILA with extensive reticulation (defined by the number of lung zones involved rather than profusion of reticulation) compared with those with subpleural fibrotic ILA. ILA progression has been linked to increased mortality in the Framingham Heart Study (HR, 3.9 [95% CI, 1.3–10.9]; $p = .01$) and AGES-Reykjavik study (HR, 1.4 [95% CI, 1.3–1.5]; $p < .0001$) [45, 56]. These findings underscore the importance of identifying and reporting the specific CT features when assessing subpleural nonfibrotic ILA. The apparent differences between this study and others could be due to larger population size, differing definitions, or population differences. However, these findings suggest that the separation of fibrotic ILA from nonfibrotic ILA provided by the most recent ILA classification may be an

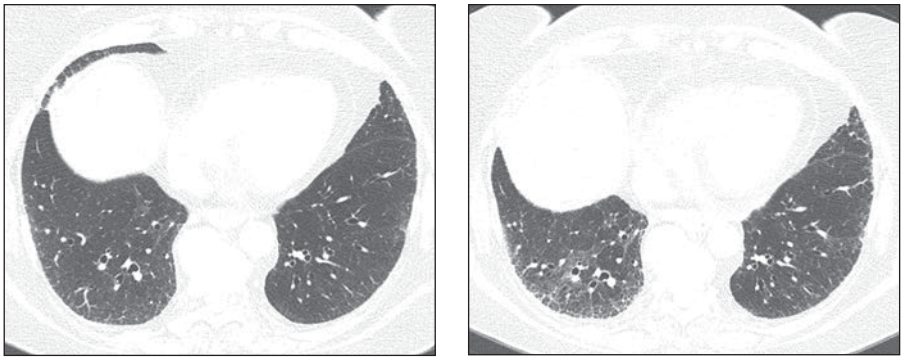

Fig. 5—77-year-old man with progression of nonfibrotic interstitial lung abnormalities (ILA) to fibrotic ILA. GGO = ground-glass opacity.
A, Baseline axial high-resolution CT (HRCT) image shows subpleural-predominant reticulation and mild GGOs without fibrotic features.
B, Axial HRCT image obtained 2 years later shows substantial progression with development of traction bronchiectasis and architectural distortion.

insensitive indicator of future progression, possibly due to the misclassification of reticular ILA, which can develop into definite fibrosis over time [2, 59, 60] (Fig. 5). This progression from nonfibrotic ILA to fibrotic ILA also highlights the need for continued surveillance, especially for individuals at higher risk.

The recognition of ILA holds significant management implications, as disease in many patients may progress to clinically significant ILD, prompting patients to pursue risk-reduction strategies, such as smoking cessation, limiting aspiration or reflux, and minimizing inhalational or medication exposures. The most effective management approach for progressive fibrotic ILA remains uncertain and is typically based on the patient's specific needs and circumstances [38].

Progressive ILA in Individuals at Increased Risk of Fibrosis

Although the initial definitions of ILA excluded findings in populations at increased risk of lung fibrosis, the HRCT findings and patterns of progression in these at-risk individuals are similar to those found in the general population. Examples of at-risk populations include individuals with a defined CTD, those exposed to fibrogenic materials such as asbestos, and biologic relatives of persons with familial pulmonary fibrosis.

CTDs

ILD is common in CTD. The prevalence of subclinical ILA has been best studied in SSc and rheumatoid arthritis (RA), although under the current definition, the term "ILA" would not apply to patients with CTD. However, older studies did not necessarily make this distinction; thus, this section uses the term "ILA" as it was used in those studies. The prevalence of CT abnormality at the time of SSc diagnosis is approximately 80% in patients with diffuse cutaneous scleroderma and 45% in those with limited SSc [54]. Because of this high prevalence, consensus documents recommend that all patients with SSc should be screened at time of diagnosis for ILD with PFTs and HRCT [61]. Early findings include subpleural GGOs, traction bronchiolectasis, traction bronchiectasis, and reticulation. The extent of abnormality increases slowly with time, and the severity of traction bronchiectasis also increases [55] (Fig. 6). In patients with abnormal findings on HRCT at the time of diagnosis, repeat HRCT may be performed every year or every other year. The value of repeated HRCT screening in those with initially normal HRCT findings is uncertain. The 2023 American College of Rheumatology guideline for screening and monitoring of ILD in people with systemic autoimmune rheumatic disease conditionally recommends screening for patients at increased risk of developing ILD and monitoring of known ILD in patients with a CTD diagnosis by PFTs, HRCT, or both but does not provide a recommendation for the frequency of monitoring [62]. Additionally, lung ultrasound might have a role in screening at-risk patients given emerging data showing its high sensitivity for detecting ILD [63, 64], which would allow HRCT to be reserved for patients with positive screening ultrasound and, thus, would reduce cumulative radiation exposure. Evaluating disease progression in patients with SSc-ILD or those with SSc and ILA necessitates using a range of techniques, which may include PFTs, HRCT examinations, symptom scoring, and assessments of desaturation during exercise [65].

ILD is also common in patients with RA, occurring in approximately 10% of patients [66], and ILA features are even more common. In a single-center study of patients with RA, ILA were present in approximately 45% of 91 individuals undergoing clinically indicated CT examinations [67]. A similar study from Brazil [68] showed a prevalence of 22%; in that study, sequential imaging over a mean

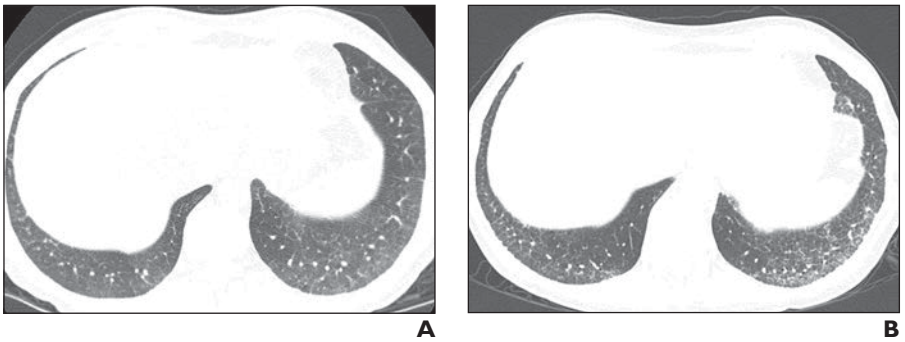

Fig. 6—49-year-old man with systemic sclerosis and progressive pulmonary fibrosis. GGO = ground-glass opacity.
A, Baseline axial high-resolution CT (HRCT) image shows mild subpleural GGOs (nonfibrotic).
B, Axial HRCT image obtained 4 years later shows evolution of GGOs to reticulation with traction bronchiolectasis.

interval of 4.4 years showed progression in 21 of 56 (38%) patients, with increasing extent and coarseness of reticulation. Progression was more common in those with greater extent of abnormality at baseline and in those with subpleural-predominant ILA.

Familial Pulmonary Fibrosis

In a study of first-degree relatives from families with two or more individuals having idiopathic interstitial pneumonia, 11 of 75 (14%) were found to have ILA on HRCT, and 25 of 71 (35%) had abnormal transbronchial biopsy results suggesting ILD [69]. The most common CT finding was reticulation; traction bronchiectasis, traction bronchiolectasis, and honeycombing were uncommon. Increasing age, smoking history, and short telomeres were significantly associated with CT abnormality. In a similar study, 77 of 494 (16%) relatives from families with familial interstitial pneumonia had evidence of fibrotic ILD [70]. Most recently, sequential evaluation of 296 screened relatives underwent follow-up after a median interval of 3.9 years [71]. Baseline CT findings of fibrotic ILA were associated with increased dyspnea on follow-up and with decreased survival. On quantitative CT (QCT) evaluation, 67 of 206 (33%) patients had an increase in fibrosis score, and 41 (20%) had a decrease in fibrosis score.

Surveillance Imaging for Asymptomatic Patients With CTD and No ILD or ILA

Several studies have shown that a significant portion of individuals with CTD and other autoimmune disorders develop ILD, with ILD rates reaching up to 40–50% of individuals with certain conditions [72, 73]. Autoimmune-associated ILD contributes significantly to patient morbidity and early mortality, and screening is often performed at the time of the initial CTD diagnosis. Among patients who develop CTD-ILD, it is estimated that 13–40% exhibit the PPF phenotype [74].

A critical unanswered question is whether patients without ILD or ILA on chest HRCT at the time of CTD diagnosis should undergo subsequent screening and, if so, at what intervals, especially when asymptomatic. CT is not the only diagnostic test to screen patients for ILD; referring clinicians typically rely on PFTs and the 6-minute walk test (6MWT) if patients are asymptomatic. The results of this testing often determine whether follow-up HRCT is needed. However, PFTs may be unreliable in certain situations, including in patients with combined obstruction and restriction, as seen in conditions such as CPFE. Additionally, if the reduced FVC stems from a non-ILD cause, such as severe obesity, chronic pleural effusion, or exaggerated kyphosis, then identification of concurrent pulmonary fibrosis will require additional investigation such as repeat HRCT [75].

Assuming that PFTs and 6MWT are either normal or cannot be reliably performed, at what time interval should referring clinicians rescreen patients with CTD for ILD? No standard consensus guidelines answer this question; therefore, the decision to rescreen depends largely on the perceived risk of developing ILD. In a large comprehensive meta-analysis of patients across all CTD subtypes, the presence of positive rheumatologic serologies as well as higher inflammatory markers such as erythrocyte sedimentation rate (ESR) and CRP increased the risk for development of ILD, suggesting a lower threshold to screen asymptomatic patients with elevated laboratory markers [76]. That study also concluded that CTD cannot be considered as a single entity when determining whether to screen patients given the variability for development of ILD among the various subtypes of CTD. Therefore, studies assessing a specific CTD subtype when evaluating the ILD risk are important [13]. In one study of patients with SSc, the presence of positive antitopoisomerase I/anti-Scl-70 antibodies was the only baseline variable found to adequately predict decline in FVC over 3 years, suggesting that yearly screening may be beneficial in this patient subset. In patients with known RA-ILD, the presence of high titers of anticyclic citrullinated peptide antibodies predicted progression of ILD, suggesting that routine screening of patients with high titer antibodies should be performed [77].

Although there are consensus guidelines on the need to perform HRCT screening for ILD in certain CTD subtypes such as SSc [65], the routine rescreen interval has not been established [78]. According to an online survey of 486 physicians who manage patients with progressive fibrotic ILD, most referring clinicians perform HRCT every 6–12 months in patients with established ILD [6]. Therefore, the interval for asymptomatic patients without established ILD should be longer and is likely between 24 and 48 months, depending on risk factors, age, and perceived risk of ILD development.

QCT for Identifying PPF and Progressive ILA

Identification of PPF on visual comparison of CT scans is challenging and subjective, requiring accurate alignment of anatomically comparable images. Quantitative evaluation is potentially more precise and more sensitive to subtle change (Fig. 7). Precision in QCT and reproducibility of QCT necessitate meticulous attention to both patient and technical factors. This aim involves optimizing patient conditions to ensure motion-free images and consistent inspiration as well as fine-tuning technical variables, such as scanning and reconstruction parameters, dose, slice thickness, and the CT scanner's manufacturer, model, and reconstruction kernel [79]. Multiple QCT biomarkers based on machine learning have been developed and applied to examinations of individuals with fibrotic lung disease, as summarized in a recent publication [80]. In multiple fibrotic lung diseases, the extent of fibrosis on QCT correlates with symptoms and pulmonary function impairment and is an independent predictor of physiologic progression and mortality [81–85]. Serial change in QCT measurement of fibrosis is also an independent predictor of mortality [86]. Serial change in QCT measurement at 24 weeks can predict subsequent change in FVC at 48 weeks [87]. The minimum clinically important difference in QCT fibrosis extent has been calculated to be 4–5% [84]. QCT has also been applied to individuals with early ILA [71]; in a study of 4450 patients enrolled in the Genetic Epidemiology of COPD (COPDGene) Study, progression of fibrosis by more than 0.58% at 5 years was associated with increased mortality [88].

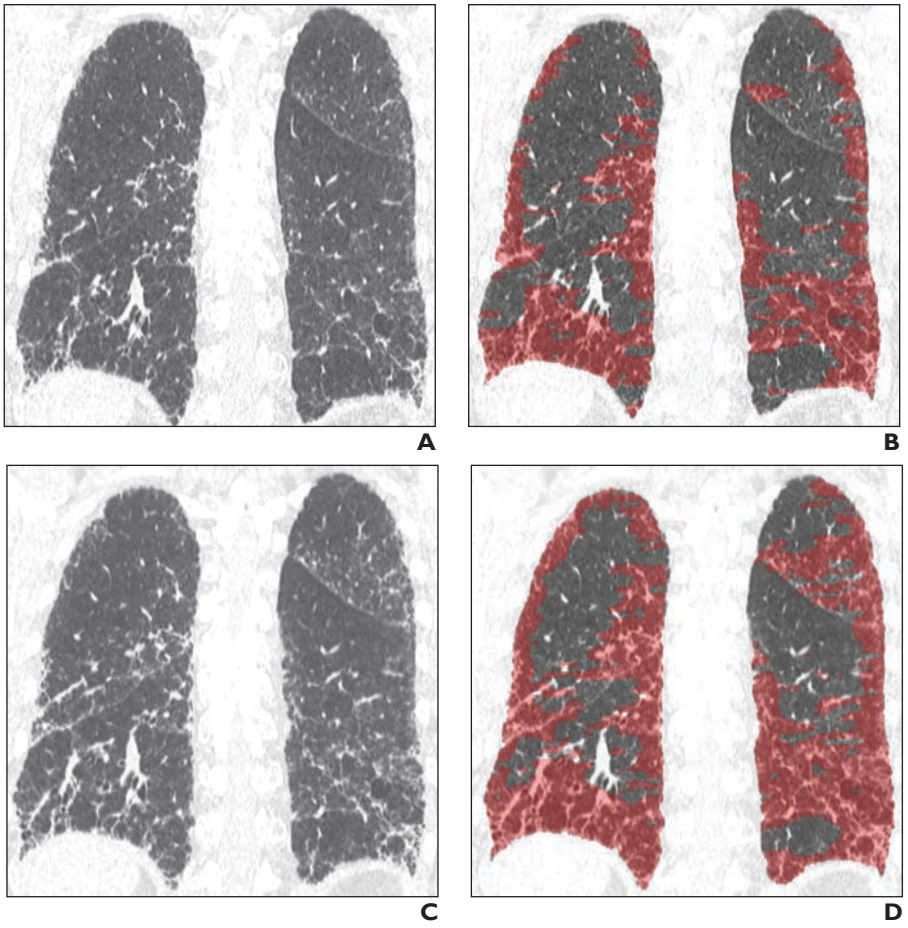

Fig. 7—68-year-old woman with interstitial pulmonary fibrosis. (Courtesy of Humphries S, Quantitative Imaging Laboratory, National Jewish Health, Denver, CO)
A, Coronal reformatted high-resolution CT (HRCT) image shows moderately extensive lung fibrosis.
B, Data-driven textural analysis (DTA) image shows that 29% of lung volume is occupied by fibrosis (*red*).
C, Coronal reformatted HRCT image obtained 14 months later shows increase in extent of fibrosis.
D, Corresponding DTA image confirms progression with 38% fibrosis (*red*).

Consensus Statements

- HRCT of the chest is the established imaging test for diagnosing patients suspected of having fibrotic ILD and for evaluating patients with worsening respiratory signs and symptoms that suggest disease progression.
- ILA are increasingly recognized as risk factors for the development of fibrotic ILD and have been shown across many large studies to be independent risk factors for mortality.
- Radiologists play an important part in identifying patients with ILA and PPF.
- Just as accurate classification of ILD on chest HRCT is important to patient diagnosis and management, correctly identifying and classifying ILA can help identify patients at risk of developing ILD and help guide management. Furthermore, recognizing HRCT findings of PPF can assist pulmonologists in optimizing treatment.
- For patients with ILD or ILA, changes in signs and symptoms, decline in pulmonary function, or both are strong indications for HRCT of the chest. However, the frequency, if any, of repeat imaging has not been determined for patients with clinically stable ILD, asymptomatic patients with ILA, and asymptomatic patients without ILD or ILA but who are at risk of developing ILD.
- Although imaging surveillance is mostly driven by local pulmonologists' preference, this article has offered relevant guidance.
- Future studies are needed to address these questions to improve patient outcomes while also being good stewards of available health care resources.

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