Pulmonary Perspective

Subclinical Interstitial Lung Disease

Why You Should Care

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The widespread use of high-resolution computed tomography in clinical and research settings has increased the detection of interstitial lung abnormalities (ILA) in asymptomatic and undiagnosed individuals. We reported that in smokers, ILA were present in about 1 of every 12 high-resolution computed tomographic scans; however, the long-term significance of these subclinical changes remains unclear. Studies in families affected with pulmonary fibrosis, smokers with chronic obstructive pulmonary disease, and patients with inflammatory lung disease have shown that asymptomatic and undiagnosed individuals with ILA have reductions in lung volume, functional limitations, increased pulmonary symptoms, histopathologic changes, and molecular profiles similar to those observed in patients with clinically significant interstitial lung disease (ILD). These findings suggest that, in select at-risk populations, ILA may represent early stages of pulmonary fibrosis or subclinical ILD. The growing interest surrounding this topic is motivated by our poor understanding of the inciting events and natural history of ILD, coupled with a lack of effective therapies. In this perspective, we outline past and current research focused on validating radiologic, physiological, and molecular methods to detect subclinical ILD. We discuss the limitations of the available cross-sectional studies and the need for future longitudinal studies to determine the prognostic and therapeutic implications of subclinical ILD in populations at risk of developing clinically significant ILD.

Keywords: interstitial lung disease; interstitial lung abnormalities; familial pulmonary fibrosis; rheumatoid arthritis; smoking

There is growing awareness that some forms of interstitial lung disease (ILD) transition from asymptomatic or “subclinical” stages (1–5) before an eventual clinical diagnosis. Most broadly defined, subclinical ILD encompasses groups of individuals who have specific radiologic, physiological, and in some cases histopathologic abnormalities but are either asymptomatic or have symptoms that have not been attributed to ILD. However, more generally we refer to subclinical ILD in undiagnosed individuals who have interstitial lung abnormalities (ILA) defined by chest computed tomography (CT) scans (3), which are consistent with, but more subtle than, those observed in patients with

established clinical ILD. Herein we use the term *subclinical ILD* in its most general sense.

Subclinical ILD was first described more than two decades ago in families affected with interstitial pneumonia (6). Moreover, one of the earliest descriptions of familial pulmonary fibrosis (FPF), compiled a century ago, suggests that chest X-ray abnormalities were present in two first-degree relatives decades before the anatomic–pathologic confirmation of noninfectious interstitial pneumonia (7). More recent studies demonstrate that screening affected FPF kindreds with high-resolution computed tomography (HRCT) scans leads to detection of subclinical ILD in asymptomatic relatives (8, 9). This suggests that some individuals at risk for ILD (e.g., members of families affected with pulmonary fibrosis, smokers, and individuals with connective tissue diseases) have mild radiologic changes on CT scan, and a subset of these patients over time could develop ILD (10, 11).

Subjects with subclinical ILD have histopathologic changes (Table 1) and genetic/genomic profiles found in patients with clinically significant ILD. These radiologic, physiological, functional, pathologic, and molecular similarities suggest that in some patients, subclinical ILD precedes the development of ILD. Given the natural history of the idiopathic interstitial pneumonias, and the lack of effective therapies for advanced fibrotic remodeling, research studies that enhance our understanding of the natural history of ILD could improve therapeutic approaches and clinical outcomes (12–14). Furthermore, a better understanding of subclinical ILD may lead to the discovery of molecular pathways involved in the pathogenesis of pulmonary fibrosis and provide insight into disease mechanisms (12–14).

Given the widespread use of HRCT in clinical and research settings, we anticipate that an increasing number of primary care providers and pulmonary specialists will evaluate and treat subjects with subclinical ILD and will therefore be tasked with determining the diagnostic and prognostic significance of these radiologic abnormalities (Table 2). In this perspective we discuss the available methods to assess subclinical ILD and the clinical and prognostic implications of detecting subclinical ILD in populations at risk of developing pulmonary fibrosis. Last, we make recommendations regarding diagnostic approaches and follow-up of individuals with subclinical ILD (Figure 1).

DETECTION AND ASSESSMENT OF SUBCLINICAL ILD

Visual and Automated Methods to Detect Subclinical ILD

HRCT scanning is the radiologic standard in the evaluation of ILD and presently the preferred method to detect subclinical ILD in the research setting (2, 15). The HRCT visual inspection method used to detect subclinical ILD in our research studies was initially developed by Avila and colleagues to identify subclinical ILD in patients with Hermansky-Pudlak syndrome (16). We have validated this semiquantitative inspection method in

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TABLE 1. PATHOLOGIC AND RADIOLOGIC CHARACTERISTICS OF SELECT POPULATIONS WITH SUBCLINICAL INTERSTITIAL LUNG DISEASE

Population	Pathologic Features		Radiologic Features	References
	BAL	Lung		
Familial pulmonary fibrosis	Neutrophil accumulation, macrophage activation, increased CD4 ⁺ T cells expressing activation markers	UIP, HP, NSIP, and cellular interstitial and OP	Positive gallium-67 scan	6, 10
Connective tissue disease	Elevation of PDGF-AB and PDGF-BB		Septal lines, reticulation, traction bronchiectasis, cyst formation, ground-glass attenuation	17
Smokers		Airspace enlargement with fibrosis, UIP, respiratory bronchiolitis, Langerhans cell histiocytosis, and nondescript interstitial changes	Nondependent ground-glass reticular abnormalities, centrilobular nodules, nonemphysematous cysts, traction bronchiectasis, honeycombing	1, 3, 5, 46, 47, 60
Postoperative		Subpleural fibrotic lesions	Honeycombing, reticular shadow, ground-glass opacities	58, 59

Definition of abbreviations: BAL = bronchoalveolar lavage; HP = hypersensitivity pneumonia; ILD = interstitial lung disease; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; PDGF = platelet-derived growth factor; UIP = usual interstitial pneumonia.

other cohorts at risk of developing pulmonary fibrosis including FPF (10) and rheumatoid arthritis (17), and smokers (15). In these studies HRCT abnormalities were defined as nondependent visual changes affecting more than 5% of the lung parenchyma. The most common radiologic changes include ground-glass and reticular abnormalities, diffuse centrilobular nodularity, honeycombing, traction bronchiectasis, and nonemphysematous cysts (Table 1).

Using visual inspection we observed that subclinical ILD in smokers is geographically distributed in four distinct patterns: (1) centrilobular-predominant centrilobular and/or peribronchial ground-glass opacities sparing the peripheral lung parenchyma, (2) subpleural-reticular/nodular and/or ground-glass opacities in a predominantly subpleural distribution, (3) mixed-mixed centrilobular and subpleural abnormalities, and (4) radiologic ILD—extensive radiologic changes consistent with firm radiologic evidence of ILD based on American Thoracic Society guidelines (15, 18). Although radiologic progression has been demonstrated in small numbers of subjects with subclinical rheumatoid arthritis and ILD (RA-ILD) (17) and smokers (~50 and 25–44%, respectively) (5, 19), it is important to note that the clinical significance of radiologic subtypes is unclear and that progression of subclinical ILD to clinically significant

ILD has been demonstrated only in a small number of studies (5, 11). Longitudinal studies will be required to identify which radiologic abnormalities most commonly precede the development of ILD in at-risk populations.

Visual inspection of subclinical ILD is based on conventional imaging interpretation and has been proven to be an effective method to quantify subclinical ILD (3); however, in the research setting, automated methods that objectively measure HRCT scan features are desirable as they are more efficient and may improve the consistency of subclinical ILD characterization across studies. High-attenuation areas, defined as more than 10% of lung parenchyma with CT attenuation values between –600 and –250 Hounsfield units (HU), were used to identify subclinical ILD in the Multi-Ethnic Study of Atherosclerosis (MESA)-Lung Study (1). As reported by these authors, this automated method detected ground-glass opacities, reticular abnormalities, and pulmonary fibrosis when compared with visual inspection, but additional radiologic abnormalities not consistent with ILD, such as atelectasis, were also reported. Over the last three decades automated decision-making algorithms have been combined with digitalized image texture analysis to predict or classify radiologic features on chest CT. Our research group and others have shown that automated assessment of HRCT scans

TABLE 2. PREVALENCE OF SUBCLINICAL INTERSTITIAL LUNG DISEASE IN SELECT POPULATIONS

Population	Number with Subclinical Disease Based on Pathology (%) (Ref.)	Number with Subclinical Disease Based on Radiology (%) (Ref.)	Cumulative Percentage (Range)
Familial pulmonary fibrosis	8/17 (47%) (6)	4/17 (24%) (6) 33/417 (8%) (8) 31/143 (22%) (10)	35% (8–47%)
Connective tissue disease		21/64 (33%) (17) 16/36 (44%) (51) 50/90 (56%) (55) 4/7 (57%) (57)	46% (33–57%)
Smokers		80/3079 (3%) (5) 194/2416 (8%) (3)	5% (3–8%)
Postoperative*	7/15 (50%) (59) 56/487 (11%) (60)	11/91 (12%) (58)	15% (11–50%)

* The ratios in this row represent the percentage of people with subclinical findings who developed acute interstitial pneumonia.

Figure 1. Diagnostic algorithm and recommended follow-up of individuals with subclinical interstitial lung disease (ILD). CT = computed tomography; DL_{CO} = carbon monoxide diffusing capacity; HRCT = high-resolution computed tomography; ILA = interstitial lung abnormalities; PCP = primary care physician; PFTs = pulmonary function tests.

using texture analyses may be able to detect and quantify subclinical ILD in FPF and in patients with RA-ILD (20, 21).

Several technical limitations of both the visual and automated methods need to be addressed. When assessing the presence of subclinical ILD in at-risk individuals outside of the research setting, it is important to consider atelectasis and the impact of interference and scatter from obesity and rib shadows as common sources of false-positive chest CT interpretations (22). These limitations can be readily addressed in follow-up studies with simple approaches such as prone imaging. Furthermore, comparison studies will be required to determine the most effective and cost-efficient method to assess subclinical ILD, as uniformity will enable reproducible interstudy comparisons. Although the long-term benefits, risks, and costs associated with implementing chest CT screening remain to be determined, in the future these findings could lead to a broader use of chest CT scans to detect subclinical ILD in smokers and other populations at risk of developing pulmonary fibrosis.

Physiological and Functional Assessments

To determine the impact of subclinical ILD on lung function, our group and others have assessed changes in pulmonary function tests, 6-minute walk tests, and cardiopulmonary exercise tests in subjects affected with rheumatoid arthritis, kindreds of individuals affected with FPF, as well as large cohorts of smokers (1, 3, 10, 17).

There is evidence that subclinical ILD in smokers is associated with reductions in lung volumes. In a population-based study Lederer and colleagues showed that subclinical ILD defined by high-attenuation areas is associated with spirometric restriction (1). This finding is consistent with other large population-based studies, which have demonstrated that smoking is a risk factor for the development of spirometric restriction (23). We demonstrated that subclinical ILD is associated with both reductions in total lung capacity and lesser amounts of emphysema in smokers (3). It is important to note that restrictive and obstructive lung diseases can have opposing effects on

lung volumes and can confound the interpretation of spirometry. Therefore the fact that ever-smokers had reductions in lung volumes (mean reduction, 0.44 L) and were less likely to meet the diagnostic criteria for chronic obstructive pulmonary disease (COPD) strongly suggests that subclinical ILD is associated with a restrictive physiology. In contrast to these findings, there is no evidence of lung restriction in FPF studies despite radiologic and physiological evidence of parenchymal lung abnormalities, which may be the result of detection at an early disease stage, radiologic changes that translate into low fibrosis burden, or underpowered studies.

In subjects affected with rheumatoid arthritis or kindreds of individuals affected with FPF, subjects with subclinical ILD had subtle but statistically significant reductions in carbon monoxide diffusing capacity (DL_{CO}) compared with subjects without subclinical ILD, effects that were more apparent among smokers (10, 17). Diaz de Leon and colleagues studied a cohort with FPF with confirmed telomerase (TERT) mutations and radiologic evidence of subclinical ILD (24). The authors found significant reductions in DL_{CO} at rest and during exercise in subjects with subclinical ILD compared with those without subclinical ILD (24). Comparable findings were present in a Japanese lung cancer screening study, which demonstrated that subclinical ILD was associated with a significant decline in DL_{CO} (25). Similarly, the cardiopulmonary exercise tests of FPF kindreds with subclinical ILD, compared with those without subclinical ILD, had reductions in dead space ventilation at peak exercise and exercise-induced abnormalities in gas exchange (10).

We have recently shown that subclinical ILD is associated with functional decrements of clinical significance as measured by 6-minute walk tests. In the COPDGene Study, the mean 6-minute walk distance (6MWD) in smokers with subclinical ILD is 386 m, comparable to the 6MWD of patients with idiopathic pulmonary fibrosis (IPF) in clinical trials (373–392 m) (26, 27). This study also demonstrated that 19% of subjects with subclinical ILD had a 6MWD less than 250 m (28), a cutoff shown in IPF patients to impart a 2.65-fold increase in the risk of death over 1 year (26).

The available evidence demonstrates that subclinical ILD is frequently associated with significant physiological and functional abnormalities in at-risk populations. However, these studies suggest that spirometry alone may be an inadequate screening tool for subclinical ILD, as spirometric restriction is not uniformly present and isolated decreases in FVC can reflect restrictive and/or obstructive physiology under the new American Thoracic Society/European Respiratory Society guidelines (29). Hence a more comprehensive picture of the degrees of impairment experienced by subjects with early radiologic changes could be achieved with a complete set of pulmonary function tests with lung volumes and DL_{CO} to establish a baseline for further follow-up.

Genetic and Genomic Associations

Research studies suggest that genetic and genomic similarities exist between subjects with subclinical ILD and patients with pulmonary fibrosis. In families affected with pulmonary fibrosis, we have shown that matrix metalloproteinase-7 (MMP7) peripheral blood concentrations are significantly increased in subclinical ILD and that MMP7 levels correlate with disease severity in FPF (30). Although one study suggests that MMP7 concentrations predict disease progression and mortality in patients with IPF (31), additional longitudinal studies will be required to determine whether the predictive value of MMP7 in subjects with subclinical ILD is also associated with progressive disease. Other studies have shown that subclinical ILD is associated with increased levels of surfactant protein (SP)-A, SP-D, and Krebs von den Lungen (KL)-6. Interestingly, SP-D and KL-6 were significantly higher in subjects with progressive radiologic changes (5, 25). Additional biomarkers of interest include serum CC-chemokine ligand 18, which has been shown to have predictive value in IPF (32), as well as CXCL9 and CXCL10, which have been shown to differentiate anti-Jo-1 antibody-positive ILD from IPF (33).

Several studies have identified subclinical ILD in subjects with genetic mutations demonstrated to be associated with IPF and FPF (11, 24, 34, 35). Diaz de Leon and colleagues assessed a variety of pulmonary, blood, skin, and bone parameters in 20 asymptomatic subjects with heterozygous TERT mutations and radiologic evidence of subclinical ILD (24). The authors concluded that subclinical ILD, bone marrow dysfunction, and premature graying are clinical features of asymptomatic TERT mutation carriers. El-Chemaly and colleagues reported the natural history of pulmonary fibrosis in two subjects with the same telomerase mutation. The authors found that subclinical alveolar inflammation is associated with telomerase insufficiency and that it can progress to pulmonary fibrosis over 2–3 decades (11). Crossno and colleagues assessed the presence of subclinical ILD in the daughter of a patient with a known *SFTPC* (I73T) mutation. Both father and daughter were found to have an additional heterozygous mutation in ATP-binding cassette A3 (*ABCA3*) (D123N). Remarkably, although the daughter's chest CT scan showed only mild focal subpleural septal thickening, her transbronchial biopsies showed evidence of interstitial fibrotic remodeling (35).

SUBCLINICAL ILD IN POPULATIONS AT RISK OF DEVELOPING PULMONARY FIBROSIS

Familial Pulmonary Fibrosis

The presence of subclinical ILD in families was first shown by Bitterman and colleagues (6). Under the premise that inflammation may precede fibrosis, pathologic and radiologic features were used to determine that approximately 50% of asymptomatic family members had evidence of alveolar inflammation. More recently, Steele and colleagues evaluated 111 families with interstitial pneumonia, finding a high risk for ILD among

asymptomatic family members and estimating that approximately 8% of self-reported unaffected family members have subclinical ILD (8).

These studies strongly suggested that characterization of subclinical ILD in at-risk subjects was feasible. To determine clinical, radiologic, and pathologic features of subclinical ILD in patients at risk of developing IPF, we studied 143 asymptomatic subjects from 18 kindreds affected with FPF (10). Using HRCT, we identified subclinical ILD in 22% of unaffected relatives; these subjects were on average 20 years younger than their relatives with established disease. A history of smoking was significantly increased in both subjects with subclinical ILD and relatives with established disease when compared with unaffected relatives. In addition, we performed video-assisted thoracoscopic lung biopsies in a subset of patients with subclinical ILD, and noted that subclinical ILD was associated with diverse histologic subtypes observed in ILD (Figure 2).

These studies demonstrate that detection of subclinical ILD in genetically susceptible individuals can be both feasible and informative. In addition, these studies suggest that research studies in populations at risk of developing pulmonary fibrosis may increase our understanding of the natural history of ILD in general. Although we lack the ability at this time to identify which individuals will go on to develop clinically significant ILD, the future availability of genetic testing may enhance the predictive value of subclinical ILD in FPF.

Smokers

An estimated 94 million U.S. adults who are current or former smokers have an increased risk of developing lung cancer or parenchymal lung diseases (i.e., ILD and COPD) (36). In the general population, older age, male sex, and a history of chronic tobacco smoke exposure are important risk factors for the development

Figure 2. Subclinical interstitial lung disease in familial pulmonary fibrosis (FPF). High-resolution computed tomography (HRCT) prone images (A and B) and lung histology (C and D; video-assisted thoracic surgery lung biopsies) were obtained in two asymptomatic brothers with first-degree relatives affected with FPF. The younger brother was asymptomatic; his HRCT shows mild subpleural fibrosis (A), whereas his biopsy demonstrated patchy, temporally uniform interstitial fibrosis with focal organizing pneumonia (C). The older brother did not have a diagnosis of FPF but did have a history of mild exertional dyspnea and abnormal pulmonary function tests; he had an HRCT that showed moderate subpleural fibrosis with minimal honeycombing (B) and a lung biopsy that demonstrated the geographic heterogeneity of usual interstitial pneumonia (D, arrowhead indicates fibroblast foci).

of ILD, including IPF (37). It has also been demonstrated that a significantly higher percentages of subjects with subclinical ILD and FPF are current or former smokers, suggesting that gene-environment interactions play a key role in the pathogenesis of lung fibrosis (8, 10, 38, 39). On the basis of these observations our research group and others have demonstrated that subclinical ILD is present in a significant proportion of smokers screened for the development of COPD (3, 15), cardiovascular disease (1), or lung cancer (5, 19). A spectrum of chest CT abnormalities classically observed in smokers was first described by Remy-Jardin and colleagues (40). The most common radiologic findings include micronodules, ground-glass attenuation, patchy hypoattenuation, and emphysema. Pathologically, these radiologic findings seem to correspond to areas of macrophage accumulation in the alveoli and fibrosis adjacent to the terminal respiratory bronchioles (41). Similar chest CT findings have been described in smokers with subclinical ILD; however, in the COPD Gene Study (3) subclinical ILD with a subpleural distribution (*see above*) was more common than the “RB-ILD-like” changes described by Remy-Jardin and colleagues. These findings suggest that subclinical ILD represents a heterogeneous group of diffuse parenchymal lung diseases previously associated with smoking (14, 19, 42–45).

Katzenstein and colleagues described the presence of interstitial fibrosis in lobectomy specimens excised for neoplasms in cigarette smokers with no clinical evidence of ILD (46). These subjects demonstrated pathologic evidence of smoking-related ILD and usual interstitial pneumonia. Pathologic changes seen in the lungs of asymptomatic smokers have also included airspace enlargement with fibrosis, respiratory bronchiolitis, Langerhans cell histiocytosis, and nondescript interstitial changes (Table 1) (47).

In summary, multiple studies have demonstrated that subclinical ILD observed in the chest radiographs or CT scans of smokers represents a heterogeneous group of parenchymal lung diseases. Although these studies demonstrate that the radiologic changes in population-based studies resemble those found in family-based studies, the long-term clinical significance of subclinical ILD in smokers remains unclear and follow-up in the research setting will be required. In the meantime, clinicians should continue to emphasize smoking prevention and cessation.

Connective Tissue Diseases

Several autoimmune diseases, such as rheumatoid arthritis (RA), scleroderma, polymyositis/dermatomyositis, lupus, and Sjögren's syndrome, have a high prevalence of ILD with variable therapeutic responses and clinical outcomes (48). In RA studies in which open lung biopsies or chest CT scans were performed, 5–40% of the study population had evidence of parenchymal lung disease (49–52). These findings could be clinically relevant as one prospective study demonstrated that 34% of RA patients with ILD had radiologic evidence of disease progression (9). Furthermore, the presence of interstitial pneumonia, particularly biopsy-proven usual interstitial pneumonia, is associated with a poor prognosis (53). We have previously shown that 33% of RA patients without dyspnea or cough have subclinical ILD identified on chest HRCT (17). In this study we observed progression of radiologic abnormalities and increased transforming growth factor- β_1 bronchoalveolar lavage concentrations in a subset of RA subjects with subclinical ILD, suggesting these subjects may be at higher risk of developing clinically significant ILD. As observed in other populations at risk of developing pulmonary fibrosis, a history of smoking in patients with RA is associated with the presence of subclinical ILD.

Chest CT scans have been used to identify occult ILD in patients with scleroderma as pulmonary complications are an important cause of morbidity and mortality (54–56). In a study of

scleroderma patients with normal lung volumes, 56% of subjects had HRCT abnormalities suggesting fibrosing alveolitis (55). Similarly, in a study of patients affected with Sjögren's syndrome, four of seven subjects with normal pulmonary function tests had radiologic evidence of interstitial abnormalities on chest CT scans (57).

In light of the strong associations between systemic inflammation in autoimmune diseases, smoke-induced lung injury, and cardiopulmonary disease, we anticipate that early detection of lung disease will continue to be an area of active research in connective tissue diseases. As we anticipate that only a subset of these patients with subclinical ILD will develop clinically significant ILD, further longitudinal studies are required to identify subjects with subclinical ILD who could benefit from early intervention and how in turn these decisions can improve patient outcomes.

Postoperative Acute Lung Injury

Studies have identified subclinical ILD in preoperative CT scans of patients who developed postoperative respiratory failure. In a retrospective analysis of 15 subjects who developed postoperative acute respiratory distress syndrome (ARDS), 11 patients had evidence of interstitial pneumonia on preoperative CT scan (58). In a similar study, 50% (7 of 14) of individuals who developed postoperative acute interstitial pneumonia (AIP, or Hamman-Rich syndrome) had evidence of subpleural fibrosis on postmortem histologic examination (59). Of note, AIP is a rare idiopathic interstitial pneumonia that is pathologically indistinguishable from ARDS. Another study of 917 patients demonstrated a 6–11% incidence of respiratory failure after lobectomy in patients with foci resembling usual interstitial pneumonia with or without airspace enlargement with fibrosis (Table 1) (60). Although the findings detailed above are preliminary, they suggest that subclinical ILD may increase the risk for postoperative ARDS and/or death.

SUGGESTED CLINICAL ALGORITHM FOR SUBCLINICAL ILD

At present there are important limitations to proposing a clinical algorithm for the management of subclinical ILD. First, we emphasize that further longitudinal studies are required to determine the subset of patients with subclinical ILD who will go on to develop clinically significant ILD. Second, there is no evidence that early detection or interventions will improve clinical outcomes in patients with subclinical ILD. However, we believe it is reasonable to consider follow-up in select subjects at risk of developing ILD, particularly in clinical scenarios where removing an environmental exposure could lead to improved outcomes as compared with waiting for the patient to develop respiratory symptoms or physiological abnormalities. For example, an asymptomatic subject with declining measures of pulmonary function and radiologic ILA on chest CT who is exposed to birds may have early stages of hypersensitivity pneumonitis (61). Similarly, we have shown that smoking is associated with subclinical ILD in genetically susceptible individuals (familial pulmonary fibrosis) and patients with connective tissue diseases (rheumatoid arthritis), suggesting that smoking cessation may reduce the risk of developing clinically significant disease. With the above in mind and based on the published literature reviewed in this perspective, we propose a clinical algorithm to prioritize follow-up studies in subjects with subclinical ILD (Figure 1). The algorithm integrates several factors including the presence or absence of symptoms, physiological abnormalities, and other pertinent clinical tests used to rule out extrapulmonary disease.

CONCLUSIONS

The increased use of chest CT scans to screen subjects at risk of developing lung cancer, cardiovascular disease, and pulmonary disease will lead to the detection of ILA that may represent early stages of ILD. Even when unrecognized by a patient or physician, subclinical ILD can be associated with physiological and functional decrements, ILD histopathologies, and less frequently poor clinical outcomes (i.e., preoperative risk for ARDS). Although uncertainty still remains regarding the long-term prognostic implications of subclinical ILD, in select populations at risk of developing ILD, subclinical ILD may represent an early disease stage for a subset of individuals who will progress to clinically significant ILD.

Although one may question the need to detect subclinical ILD in the absence of effective therapies for pulmonary fibrosis, it is possible that novel therapies for pulmonary fibrosis will prove most effective at earlier disease stages. Longitudinal studies are required to better define the natural history of subclinical ILD; this will allow us to identify which patients will go on to develop clinically significant ILD, and to conclusively demonstrate that subclinical ILD indeed precedes the development of pulmonary fibrosis in at-risk populations. In addition, more sensitive noninvasive metrics to assess subclinical ILD (biomarkers and genetic assays) will be necessary to make these findings relevant to every-day clinical practice.

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