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Approach to the Evaluation and Management of Interstitial Lung Abnormalities

An Official American Thoracic Society Clinical Statement

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Abstract

Background: There is growing interest in identifying early stages of interstitial lung disease (ILD) to improve patient outcomes. This document reviews updated evidence on interstitial lung abnormalities (ILAs); provides suggestions for screening, evaluation, and management; proposes criteria for distinguishing ILAs from ILD; and identifies research priorities.

Methods: A committee of clinical and methodology experts met by video conference to define ILAs and ILD by consensus and voted on 11 prespecified questions after reviewing synthesized evidence from a systematic literature search. Agreement of ⩾70% was required to approve each suggestion.

Results: ILA is defined as nondependent bilateral parenchymal abnormalities on computed tomography, including ground-glass opacities or reticulations, lung distortion, traction bronchiectasis, and/or honeycombing involving ⩾5% of a lung zone. The updated definition removes the prior exclusion of high-risk populations. ILD is distinguished from ILAs by symptoms (dyspnea/cough) attributable to an interstitial process, abnormal or declining lung function, fibrotic (honeycombing and/or reticulation with traction bronchiectasis involving ⩾5% of total lung volume) or progressive imaging abnormalities, and/or specific fibrotic ILD patterns on imaging or pathology. Suggestions include ILA/ILD assessment on imaging acquired for lung cancer screening, screening adults with connective tissue disease and first-degree relatives of patients with familial pulmonary fibrosis, assessing baseline symptoms and pulmonary function among those with ILAs, and monitoring ILAs with chest computed tomography every 2–3 years.

Conclusions: This document presents a comprehensive literature review of ILAs with updates to the Fleischner Society ILA definition, establishes a working ILD definition, and provides evidence-based suggestions for ILA evaluation and management.

Keywords: interstitial lung abnormalities (ILA); interstitial lung disease (ILD); pulmonary fibrosis; computed tomography; screening

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Summary of Recommendations

Screening

1. We suggest systematic assessment and documentation of the presence or absence of interstitial lung abnormalities (ILAs) and/or interstitial lung disease (ILD) in smokers who are undergoing lung cancer screening with a chest computed tomography (CT) scan. Vote: Approved by 38 of 38 (100%).
2. We suggest a baseline chest CT scan to screen for ILAs/ILD in adults with connective tissue diseases (CTDs) that are associated with an increased risk of ILD. Remarks: CTDs that are associated with an increased risk of ILD include rheumatoid arthritis, systemic sclerosis, polymyositis, dermatomyositis, antisynthetase syndrome, mixed CTD, Sjogren's disease, or overlap syndrome. Vote: Approved by 36 of 37 (97%).
3. (3a) We suggest chest CT screening for ILAs/ILD in adults ⩾50 years of age who have a first-degree relative with familial pulmonary fibrosis (FPF). Remarks: FPF is defined by at least two genetically related first- or second-degree relatives with fibrotic ILD. Vote: Approved by 34 of 36 (94%). (3b) We are neither in favor nor against chest CT screening for ILAs/ILD in adults ⩾50 years of age who have a first-degree relative with IPF and no other known family members with ILD. Remarks: The lack of a recommendation reflects a lack of consensus among the committee. Vote: Approved by 20 of 37 (54%), not approved by 17 of 37 (46%).
4. We suggest not performing *MUC5B* testing as an initial test before more definitive chest CT screening for ILAs/ILD in adults ⩾50 years of age who have a first-degree relative with pulmonary fibrosis (regardless of whether the first-degree relative has FPF or IPF and no other family members with ILD). Remarks: *MUC5B* testing refers to assessment of the *MUC5B* promoter variant (rs35705950). Vote: Approved by 37 of 37 (100%).
5. We suggest not performing telomere length measurement as an initial test before more definitive chest CT screening for ILAs/ILD in adults ⩾50 years of age who have a first-degree relative with pulmonary fibrosis (regardless of whether the first-degree relative has FPF or IPF and no other family members with ILD). Vote: Approved by 37 of 37 (100%).

Baseline Assessment

6. We suggest that patients with ILAs undergo baseline symptom assessment. Remarks: Symptom assessment is defined as inquiring about the presence of cough and dyspnea on exertion. This suggestion places high

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Artificial Intelligence Disclaimer: No artificial intelligence tools were used in writing this manuscript.

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value on noninvasive early identification of ILD and establishing a baseline for future comparison. Vote: Approved by 39 of 39 (100%).

7. We suggest that patients with ILAs undergo baseline pulmonary function testing (PFT). Remarks: PFT is defined as the measurement of FVC, TLC, and D_{LCO}. This suggestion places high value on noninvasive early identification of ILD and establishing a baseline for future comparison. Vote: Approved by 38 of 39 (97%).
8. We suggest that patients with ILAs not undergo baseline lung sampling for histopathological analysis. Remarks: This suggestion places high value on avoiding harm from an invasive procedure in the absence of robust evidence that the patient will benefit from the information obtained. Histopathologic sampling may be appropriate for some patients who meet criteria for ILD per existing ILD guidelines. Vote: Approved by 38 of 39 (97%).
9. We suggest that patients with ILAs not undergo baseline *MUC5B* testing. Remarks: *MUC5B* testing refers to assessment of the *MUC5B* promoter variant (rs35705950). This suggestion places a high value on avoiding the cost and burden of additional testing that is not universally available and may not contribute unique and clinically actionable information beyond what is gathered by other means. Vote: Approved by 38 of 39 (97%).
10. We suggest that patients with ILAs not undergo baseline telomere length measurement. Remarks: This suggestion places a high value on avoiding the cost and burden of additional testing that is not universally available and may not contribute unique and clinically actionable information beyond what is gathered by other means. Telomere length measurement and/or testing for specific telomeropathies (e.g., TERT, TERC) may be appropriate for some patients in whom family history or other clinical features suggest telomeropathy. Vote: Approved by 38 of 39 (97%).

Follow-up Assessment

11. We suggest that patients with ILAs undergo a follow-up chest CT scan 2–3 years after the baseline chest CT scan. Remarks: Earlier follow-up (12 mo) may be appropriate in some clinical contexts. The frequency of subsequent follow-up chest CT scans depends on multiple factors, including evidence of progression of the ILA on the initial follow-up chest CT scan. Vote: Approved by 34 of 36 (94%).

There is increasing interest in identifying early stages of ILD and pulmonary fibrosis, with the hope that these efforts will result in improved outcomes for patients with ILD. The term "ILA" was originally coined to describe chest CT imaging abnormalities suggestive of an underlying ILD in a person without a clinical diagnosis. In a position paper from the Fleischner Society, ILAs were defined as incidentally identified nondependent abnormalities, including ground-glass or reticular abnormalities, lung distortion, traction bronchiectasis, honeycombing, and nonemphysematous cysts involving ⩾5% of a lung zone (1). The primary objective of this document is to present an updated evidence-based review of the literature on ILA, to update its definition, and to provide expert opinion-based recommendations for its evaluation. A secondary objective is to propose criteria for distinguishing ILAs from more advanced abnormalities that are considered to represent ILD.

Methods

The methods are described in detail in the online supplement. A diverse committee was assembled that included clinical and methodology experts. The clinical statement included two patients who participated in the guideline panel and provided perspective on patient values and preferences. The co-chairs (A.J.P., G.M.H., D.A.S., and C.J.R.) drafted key clinical questions, which were subsequently discussed, modified, and approved by the full committee. While evidence syntheses were performed by a methodology team (F.K., Y.H.K., B.P., and K.C.W.) to inform each question, the co-chairs led the committee in defining ILA using consensus by discussion over a series of video conferences. The methodology team provided the committee with a video presentation summarizing the evidence synthesis for each population-intervention-control-outcome (PICO) question before a meeting of the full committee by video conference. Each meeting began with the opportunity to discuss the evidence synthesis, followed by the co-chairs sharing their opinion on each question, and then a full committee discussion about potential modifications to the suggestions. Following the video conference, the participants voted to accept or not accept the suggestions. Seventy percent agreement was needed to approve a suggestion. Failure to achieve 70% agreement resulted in no suggestion for or against the intervention. The clinical statement underwent anonymous peer review by four content experts. Following multiple cycles of review and revision, the guideline was reviewed and approved by a multidisciplinary board of directors. The clinical statement will be reviewed by the American Thoracic Society (ATS) 3 years after publication to determine if an update is necessary.

Definition of ILA and ILD

In developing this document, the committee identified several important underlying concepts: *1*) although normal lung, ILAs, and ILD likely represent a spectrum of changes, the development of specific criteria for ILAs and ILD would facilitate clinical recommendations for each category; *2*) the definitions of ILA and ILD should attempt to balance the sensitivity and specificity for disease progression and the need for treatment, recognizing that not all "disease" requires treatment; *3*) although ILA is often identified on routine chest CT scans, thin-section (<1.5 mm) CT is more sensitive than thicker sections; high-resolution CT (HRCT) with prone imaging can facilitate characterization and may be necessary if findings on supine imaging are equivocal; *4*) quantitative CT (QCT), which applies computer techniques for objective detection and measurement of specific radiologic features, holds promise for advancing ILA assessment but is still under investigation and not yet used routinely in clinical practice; *5*) we have made provisional recommendations when evidence was weak, with the intent that these recommendations will stimulate additional evidence generation; and, *6*) in conversations with patients (and consistent with published data), we prioritized early identification of disease and information sharing with patients over the potential burden of detecting findings of low or uncertain clinical significance, recognizing that all recommendations need to be personalized based on individual patient wishes and values (2).

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Table 1. Definition of ILA

Chest CT showing bilateral and nondependent ground-glass opacities, reticular abnormalities, lung distortion, traction bronchiectasis, and/or honeycombing involving ⩾5% of a lung zone*
• Nonemphysematous cysts, centrilobular nodularity, and features of pleuroparenchymal fibroelastosis can be present but do not contribute to the volume of affected lung needed to satisfy the definition of ILA • Bilaterality may not be necessary in some high-risk cases (i.e., with a family history of familial pulmonary fibrosis or known ILD-associated genetic variants) • The need for findings to be incidental and exclusion of high-risk populations has purposefully been removed from the definition • Mild abnormalities occurring exclusively in dependent locations on supine imaging should be confirmed to persist on prone imaging

Definition of abbreviations: CT = computed tomography; ILA = interstitial lung abnormality; ILD = interstitial lung disease.
*Upper, middle, and lower lung zones are demarcated by the levels of the inferior aortic arch and right inferior pulmonary vein, creating a total of six zones (three zones per lung).

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Definition of ILA

The definition of ILA presented in this document builds on what was previously described in the Fleischner Society Position Paper (1), incorporating recent evidence and evolving concepts. We define ILAs as nondependent bilateral parenchymal abnormalities detected on CT, including ground-glass or reticular abnormalities, lung distortion, traction bronchiectasis, and/or honeycombing involving ⩾5% of a lung zone by visual estimate (Tables 1 and 2), but without meeting the criteria for ILD defined below. "Nondependent" refers to parts of the lung that are less influenced by gravity during scan acquisition; this may include abnormalities that are present in dependent locations on supine imaging but persist on prone imaging. Examples are provided in Figure 1 and Figures E1 and E2 in the online supplement. Although the 5% threshold needs additional supporting data, there was insufficient evidence or rationale to suggest an alternative. We continue to recommend the demarcation of upper, middle, and lower lung zones by the levels of the inferior aortic arch and right inferior pulmonary vein. Nonemphysematous cysts, centrilobular nodularity, and features of pleuroparenchymal fibroelastosis can be present but do not contribute to the volume of affected lung needed to satisfy the definition of ILA. The clinical significance of these features requires further investigation.

The Fleischner Society definition of ILA required findings to be incidental and excluded high-risk populations. These features have been removed from the updated definition for multiple reasons. First, a definition of ILA that is independent of pretest probability is more practical for clinical use, particularly because radiologists frequently lack the necessary patient details to confirm whether these nonimaging criteria are met (3, 4). Second, ILAs can still be present in high-risk populations, and incorporating these groups within the definition of ILAs allows the committee to provide guidance for evaluation and management of these patients. Finally, in the absence of compelling data to suggest otherwise, it is simpler to create a relatively broad definition of ILA with consistent evaluation and management algorithms that can be applied to most clinical scenarios.

The committee discussed whether inclusion of high-risk populations in the definition of ILA should prompt reconsideration of the previous requirement for findings to be bilateral, with bilaterality retained in the definition of ILA for two main reasons. First, the need for abnormalities to be bilateral has been used in previous definitions, and maintaining consistency was desirable in the absence of compelling data to justify the change. Second, it was considered a priority to exclude patients at low risk with unilateral abnormalities that frequently stem from entities unlikely to represent progressive disease, such as postinfectious or aspiration-related abnormalities. Although the definition of ILA states that findings should be bilateral, there are some high-risk populations in which unilateral findings may have clinical relevance. Patients with a strong family history or known genetic variants who have unilateral findings may be at risk of future progression to ILD (5, 6), even though there may be a long interval between the initial identification of these abnormalities and the future diagnosis of ILD. Patients with CTD and/or occupational exposures may also present with unilateral abnormalities, but data on the risk of progression in such cases is limited, and findings often represent non-ILA etiologies (Table 2).

The Fleischner Society Position Paper identified three main subcategories of ILAs, including nonsubpleural ILAs (i.e., without

Table 2. Findings Not Considered an ILA

Category	Examples

Extent	• Mild/limited extent
	  ○ Mild focal abnormality (e.g., focal paraspinal ["friction"] fibrosis)
	  ○ Unilateral abnormality (note: unilateral abnormality may be sufficient to characterize as ILA in some populations, e.g., with a family history of familial pulmonary fibrosis)
	• Extensive abnormality that meets the definition of ILD per Table 3

Finding, pattern, etiology	• Dependent lung atelectasis • Unifocal or multifocal linear scarring • Nonemphysematous cysts, centrilobular nodularity, and/or features of pleuroparenchymal fibroelastosis, without other CT findings of lung disease • Findings of heart failure • Findings of aspiration (e.g., patchy ground-glass, opacities tree-in-bud nodularity)

Definition of abbreviations: CT = computed tomography; ILA = interstitial lung abnormality; ILD = interstitial lung disease.

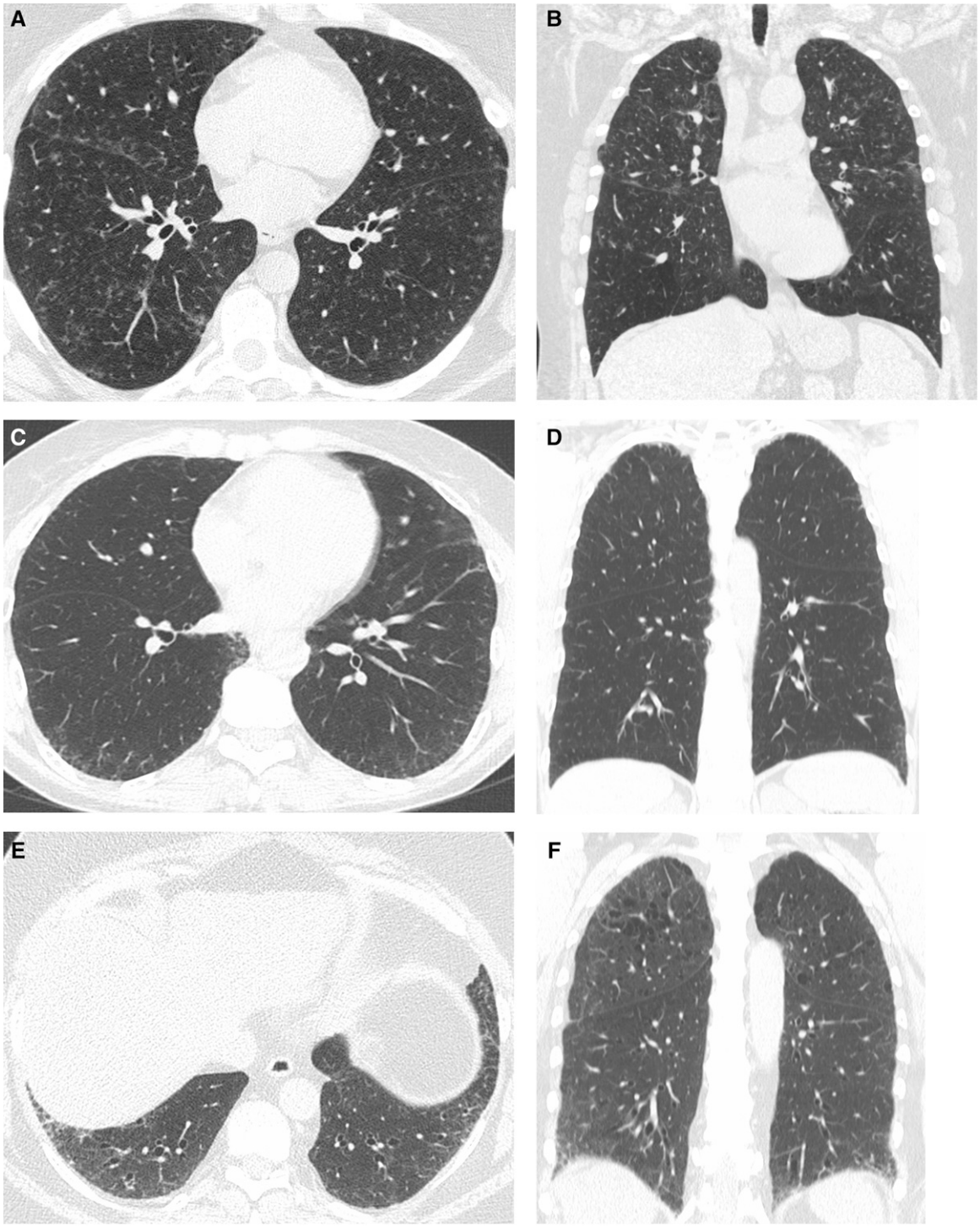

Figure 1. Interstitial lung abnormality (ILA) subtypes. (*A* and *B*) Nonsubpleural ILA. Axial (*A*) and coronal (*B*) images show patchy ground-glass and peribronchovascular opacities predominantly in the upper lung zones with minimal reticular opacities. (*C* and *D*) Subpleural nonfibrotic ILA. Axial (*C*) and coronal (*D*) computed tomography images show bilateral subpleural reticulations without traction bronchiectasis or honeycombing. (*E* and *F*) Fibrotic ILA. Axial (*E*) and coronal (*F*) images show bilateral subpleural reticulations with traction bronchiolectasis.

predominant subpleural localization), subpleural nonfibrotic ILAs (i.e., with predominant subpleural localization and without evidence of fibrosis), and subpleural fibrotic ILAs (i.e., with predominant subpleural localization and with evidence of pulmonary fibrosis). Fibrosis was defined by the presence of architectural distortion with traction bronchiectasis and/or honeycombing and applies to those ILAs that do not meet the extent or pattern criteria for ILD (*see* Figures E2C and E2D). The committee

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considered whether it is appropriate to more simply stratify ILAs only by the presence or absence of fibrosis, similar to the approach taken in major ILD patterns and diagnoses that are categorized as fibrotic and nonfibrotic (e.g., nonspecific interstitial pneumonia [NSIP] pattern, hypersensitivity pneumonitis [HP]); however, it was acknowledged that there is prognostic significance for each of the three previous categories (7–9), which the committee therefore chose to retain.

Definition of ILD

The committee identified the importance of distinguishing when an ILA would be more appropriately referred to as an ILD. We propose that an ILA should be defined as an ILD when it meets any criterion from any of the included domains described in Table 3. This definition is based on several core principles. First, the definition of ILD is intended to be simple and easily applied. We therefore intentionally avoided the need to integrate multiple features or domains, and we provide explicit and standardizable criteria where possible (e.g., specific thresholds for abnormality), highlighting the importance of quantifying these features in future studies to support the refinement of these criteria. Second, the committee acknowledged that progressive abnormalities are not a normal part of aging and any progression beyond the initial findings caused by an acute insult suffices to meet the definition of disease. Third, the presence of a major fibrotic ILD pattern implies the presence of a disease regardless of whether this is identified by imaging or pathology. Finally, the committee stressed that identifying the presence of a disease does not mandate the initiation of pharmacotherapy. The definition of ILD is therefore designed to capture patients who may benefit from intervention but stresses the need to approach management decisions on a case-by-case, patient-centered basis that considers the relative indications, benefits, and risks. It is also important to recognize that the above criteria are not intended to supersede clinical judgement and that ILD can be diagnosed in certain situations that do not meet the above criteria.

Abnormal symptoms and/or physiology are key criteria for ILD, as is progression as defined by the 2022 ATS/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association criteria (10). These criteria are purposefully broad, but with the requirement that clinical evaluation confirms that these abnormalities are related to an interstitial process rather than other etiologies (e.g., airway disease, anemia, heart disease). Dyspnea and cough are identified as key symptoms given their consistent association with prognosis in ILD (11, 12). Fatigue and exercise limitation were not specified in the definition of ILD; however, these descriptors may be used by some patients to describe the sensation of dyspnea and should be considered within their clinical context. Results from a single PFT can be used to meet the criteria for ILD; however, repeat testing may be appropriate if there are sufficient concerns about test quality. D_{LCO} is an important component of this testing because it is often the earliest physiologic abnormality of ILD (13–15). Abnormal oxygen saturation on exertion was considered but not included in the definition of ILD given the challenges with standardization and interpretation and the anticipated limited clinical utility beyond symptoms or other physiologic changes.

The key imaging criterion used to define ILD among those with ILAs is the presence of definite fibrosis on CT, defined by honeycombing and/or reticulation with traction bronchiectasis involving ⩾5% of the total lung volume (Figure 2). This criterion primarily applies to patients with significant abnormalities on chest imaging who have no symptoms and normal physiology. Symptoms may be absent in sedentary patients with ILD, and physiology in the normal range can still represent significant decline from baseline in patients who had high-normal or supranormal values before the development of ILD. Fibrotic abnormalities (Table 3) involving ⩾5% of total lung volume by visual estimate was decided as the most appropriate threshold, although this threshold needs additional supporting data. Isolated reticulation (i.e., without traction bronchiectasis) is a risk factor for radiological progression but was considered insufficiently specific for ILD unless there is documentation of progression (16). Bronchiolectasis (i.e., dilation of bronchioles within central portions of the secondary pulmonary lobule) is less prognostically informative and was therefore not included in the definition of ILD. The threshold of ⩾5% of total lung

Table 3. Definition of ILD

Definition of interstitial lung disease for those with ILAs
In a person with CT features of ILAs, at least one of the following criteria must be present to define ILD*
• Symptoms: Any amount of dyspnea and/or cough that a clinician attributes to ILD
• Physiology (any of) ○ Any abnormality in FVC, TLC, or D_{LCO} that a clinician attributes to ILD (defined as a value or *z*-score below the lower limit of normal) ○ Satisfies physiologic criteria for progressive pulmonary fibrosis that a clinician attributes to ILD (10)
• Imaging (any of the following on chest CT) ○ Fibrotic abnormalities (honeycombing and/or reticulation with traction bronchiectasis) involving ⩾5% of total lung volume by visual estimate ○ Progressive fibrotic abnormality on serial chest CT ○ Presence of a major fibrotic ILD pattern on chest CT (i.e., UIP/probable UIP, fibrotic HP, or fibrotic NSIP)
• Pathology: Presence of a major fibrotic ILD pattern (i.e., UIP/probable UIP, fibrotic HP, or fibrotic NSIP)

Definition of abbreviations: CT = computed tomography; HP = hypersensitivity pneumonitis; ILA = interstitial lung abnormality; ILD = interstitial lung disease; NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonitis.
*Further diagnostic workup may be needed to diagnose the specific ILD type. Diagnosis of nonfibrotic ILD requires integration of multiple domains.

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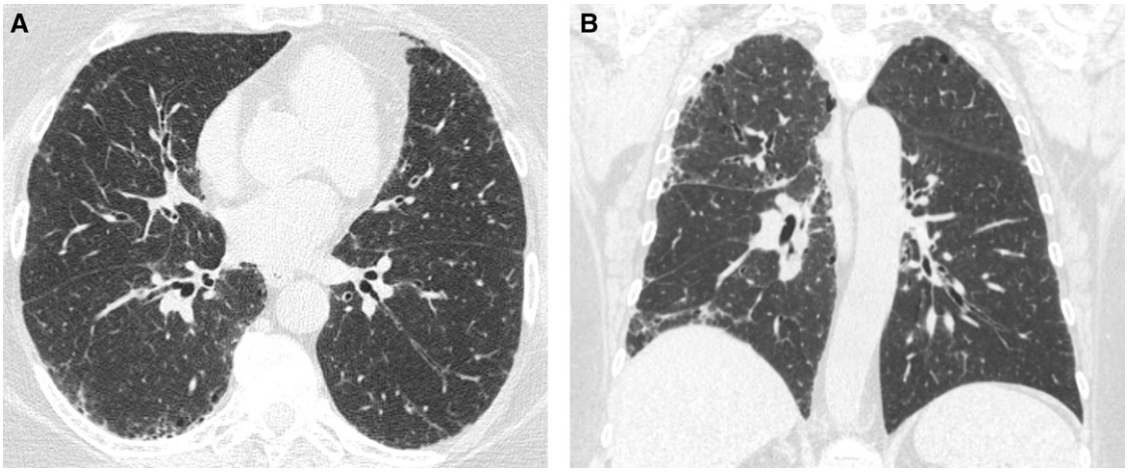

Figure 2. Example of interstitial lung disease. Axial (*A*) and coronal (*B*) images show bilateral predominantly subpleural reticular opacites with traction bronchiectasis and bronchiolectasis most apparent in the right lung base on the axial image.

volume to define ILD is distinguished from the use of ⩾5% of a lung zone to define ILAs to capture more diffuse involvement of ILD and enhance the specificity of the definition. Alternative approaches to estimating the severity of imaging abnormality were discussed (e.g., craniocaudal distance of abnormal lung, presence of abnormality in multiple locations), but these were considered too vague and challenging to implement in clinical practice. Finally, QCT may be useful; however, QCT estimates of fibrosis extent may differ from visual assessment. Further research is needed to determine what QCT features, measurement techniques, and thresholds are most appropriate to define ILD.

Additional imaging and pathology criteria used to define ILD among those with ILAs include the identification of a major fibrotic ILD pattern, including usual interstitial pneumonitis (UIP)/probable UIP, fibrotic HP, and fibrotic NSIP patterns. Though unusual, it is possible to meet imaging criteria for UIP based on guideline definitions even if the extent of fibrotic abnormalities is <5% based on previous guideline definitions (10). Other interstitial patterns (e.g., pleuroparenchymal fibroelastosis, lymphoid interstitial pneumonia, smoking-related interstitial fibrosis) were not included in the definition of ILD given the limited available data and the committee's impression that they typically have a lower likelihood of progression when found in isolation and in the absence of abnormal symptoms or physiology. The presence of a major fibrotic ILD pattern on histopathology was included to address the occasional scenario encountered in patients who had lung cancer resection; however, this criterion is not intended to provide justification for the performance of a lung biopsy in patients with ILAs. Although we included pathology patterns of fibrotic HP and fibrotic NSIP, these pathology patterns have a differential diagnosis, including non-ILD entities that should be considered in appropriate scenarios (e.g., localized changes related to tumor, postinfectious or postorganizing pneumonia fibrosis, postradiation changes, aspiration, right middle lobe syndrome, and smoking-related interstitial fibrosis). We did not consider molecular classifiers or endobronchial optical coherence tomography in the definition of ILD given the limited data on their utility in distinguishing ILAs from ILD. However, future studies may confirm the utility of these tools for this purpose.

Given the prognostic importance, imaging and pathology criteria for ILD in the context of ILAs focus on the presence of definite fibrosis; however, there are many other clinically relevant fibrotic and nonfibrotic ILDs. The committee noted that these patients typically have significant symptoms at presentation and would frequently meet the symptom and/or physiology criteria. There are additional interstitial patterns present on chest imaging and/or histopathology that would be considered to represent ILD even in the absence of symptoms or abnormal physiology (e.g., diffuse ground-glass abnormalities indicating cellular NSIP, centrilobular nodularity indicating nonfibrotic HP, features of sarcoidosis or organizing pneumonia). Integration of multiple domains is typically required to support a specific diagnosis in these scenarios.

Risk Factors for ILAs

Heritable factors greatly increase susceptibility for ILAs and ILD. Multiple common and rare genetic variants are associated with disease risk, and guidelines on the role of genetic counseling and testing have been published by several societies (17, 18). As many as 20% of patients with pulmonary fibrosis have FPF, defined by two or more genetically related individuals with fibrotic ILD (19). Although families with multiple cases of IPF represent a unique at-risk population (20), first-degree relatives of patients with sporadic IPF also have an increased risk of ILAs (13). In families with FPF or sporadic cases of IPF, between 15% and 30% of asymptomatic first-degree relatives have ILAs on chest CT (13, 21, 22), which is associated with older age, smoking, the gain-of-function *MUC5B* promoter variant, and reduced peripheral blood leukocyte telomere length (5, 13, 22–24). In multiple other studies, the *MUC5B* promoter variant is associated with the presence of ILAs (14). Recent evidence indicates that a polygenic risk score that includes the *MUC5B* promoter variant and other common IPF risk variants results in a substantial predictive power for the presence and progression of ILAs (25). In aggregate, those at risk of ILAs include first-degree relatives in families with FPF or sporadic cases of IPF, especially those >50 years of age with the *MUC5B* promoter variant

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and/or reduced telomere length. Additionally, factors associated with the development of ILAs in familial and sporadic cohorts include smoking, increased monocyte counts, and certain occupational and environmental exposures (e.g., mold, air pollution) (5, 26–30). The existing literature provides a robust evidence base for interactions between genetic susceptibility and environmental exposures as causative drivers of pulmonary fibrosis, providing a foundation for screening recommendations that incorporate patient education and shared decision-making with those at risk (17).

Clinical Relevance of ILAs

In the existing literature, ILAs are associated with increased respiratory symptoms, accelerated loss of lung function, radiologic progression of lung fibrosis, and increased all-cause (and respiratory-specific) mortality, particularly with advancing age (3, 24, 31–34). In meta-analyses, individuals with ILAs have a significantly higher risk of clinical symptoms compared with those without ILAs: chronic cough (four studies, 30.5% vs. 13.9%; risk ratio 1.59; 95% confidence interval [CI], 1.37–1.84) (14, 35–37) (Figure E3) and dyspnea on exertion (five studies, 37.1% vs. 18.4%; RR, 1.60; 95% CI, 1.37–1.88) (14, 22, 35–37) (Figure E4). More than half of individuals with ILAs experience progression of radiologic findings over 5 years, with associated clinical worsening, including onset of respiratory symptoms and reduction in exercise capacity (3, 4, 15). Approximately 10% progress to ILD annually, with some variation based on the at-risk population and definition of ILD used (3, 24, 33, 38). Lung function is also worse among patients with ILAs, regardless of whether measured as FVC (8, 39), TLC (8), or D_{LCO} (39, 40) (Table E2). ILAs predicted lung function decline measured as D_{LCO} in one study (41). FVC decline was less consistently associated with ILAs across studies, but ILAs that progressed radiologically were associated with a 64-ml annual decline in FVC, compared with a 35-ml decline in those without ILAs (32, 41–43) (Table E3). Multiple studies have demonstrated that individuals with ILAs have an increased risk of death (eight studies, 31.6% vs. 19.4%; RR, 1.66; 95% CI, 1.56–1.77; with seven additional studies showing an association between ILAs and mortality in adjusted multivariate analyses) (8, 31–33, 41, 43–50) (*see* Table E1 and Figure E5). The committee considered this clinical context when making suggestions for screening, evaluation, and management of ILAs and in the definition of ILD.

Evidence-based Suggestions for Screening

Question 1: Should Adult Smokers Undergo Chest CT Screening to Identify ILAs/ILD?

Suggestion.

- We suggest systematic assessment and documentation of the presence or absence of ILAs/ILD in smokers who are undergoing lung cancer screening with a chest CT scan. Vote: Approved by 38 of 38 (100%).

Evidence base. The evidence synthesis identified 24 studies that were enriched with current and former smokers and estimated prevalence of ILAs/ILD (15, 28, 37, 38, 42, 43, 47, 49, 51–66) (Figure E6). Many studies were conducted in the context of lung cancer screening (Table E4). When the studies were aggregated by meta-analysis, the estimated prevalence of ILAs/ILD was 8% (95% CI, 7–10%) (Figures E7 and E8).

Rationale. Identifying ILAs/ILD has desirable consequences (67, 68). It finds individuals who are at increased risk for respiratory symptoms, diminished lung function, and mortality. Offering follow-up imaging seems reasonable because many abnormalities will progress (*see* question 11), some to ILD, in which cases further diagnostic workup and therapy may be warranted to mitigate lung function decline (10). The evidence suggests that, for every 1,000 smokers who are screened by chest CT, 80 will be found to have ILAs/ILD (53). The committee acknowledged that the number needed to screen would not warrant screening in all adult smokers. However, in the context of lung cancer screening, the undesirable consequences of systematic assessment and documentation of ILAs/ILD are minimized, making the small prevalence of positive findings acceptable to the committee. The primary undesirable consequence of reporting ILAs/ILD is patient anxiety and the need for additional testing among those found to have abnormalities. Radiation exposure for those needing follow-up imaging is also a consideration. Cost and burden can be considerable but are mitigated in this setting because imaging is already being performed for lung cancer screening.

Additional considerations. Uptake of lung cancer screening has not been universal, even after several randomized controlled trials demonstrated that it reduces mortality from lung cancer (69, 70). Screening programs require considerable infrastructure and resources for follow-up and management of nodules and other incidental findings. There are no comparable data demonstrating a benefit of screening for ILAs/ILD on outcomes, and committee members agreed that a recommendation for screening of all smokers was not warranted at this time. Criteria for lung cancer screening vary from country to country (71). The U.S. Preventive Services Task Force recommends an annual low-dose CT scan for adults aged 50–80 years who have a 20–pack-year smoking history and currently smoke or have quit within the previous 15 years (72). Given the overlapping risk profile, the committee believed individuals undergoing CT screening for lung cancer should be assessed for ILAs/ILD. The committee did not address specific language that should be used for reporting of ILAs/ILD on CT scans, but, in general, descriptions should align with definitions established in this document and/or the Fleischner Society (1, 68). Clinical sites and radiology societies may wish to develop algorithms to standardize reporting as well as risk stratification and follow-up of findings, akin to what is done for lung nodules (73, 74). Serial follow-up with low-dose CT may be adequate to monitor ILAs, but evaluation of ILD requires HRCT. The committee acknowledges that these suggestions may increase the number of patients referred for evaluation of ILAs/ILD and cause strain on some providers and healthcare systems. Additional discussion of the potential for incidental findings may also be necessary as part of shared decision-making for lung cancer screening. This needs to be considered when implementing screening programs.

Question 2: Should Adults with CTD Undergo Chest CT Screening to Identify ILAs/ILD?

Suggestion.

- We suggest a baseline chest HRCT scan to screen for ILAs/ILD in adults with CTDs that are associated with an increased risk of ILD. Remarks: CTDs that are associated with an increased risk

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of ILD include rheumatoid arthritis, systemic sclerosis, polymyositis, dermatomyositis, antisynthetase syndrome, mixed CTD, Sjogren's disease, or overlap syndrome. Vote: Approved by 36 of 37 (97%).

Evidence base. The evidence synthesis found 52 studies that enrolled patients with CTDs who were not suspected of having ILD and estimated the prevalence of ILAs/ILD in those patients (75–126) (Figure E9). Patients with six different types of CTD were enrolled, including rheumatoid arthritis, systemic sclerosis, mixed CTD, Sjogren's syndrome, dermatomyositis/polymyositis, and systemic lupus erythematosus (SLE) (Table E5). When the studies were aggregated by meta-analysis, the estimated prevalence of ILAs/ILD was 40% (95% CI, 37–43%) (Figures E10 and E11). *A priori* subgroup analyses according to type of CTD demonstrated the following prevalences: rheumatoid arthritis (13 studies; prevalence, 23%; 95% CI, 17–29%) (81, 88, 96, 98, 100, 105, 106, 111, 120, 123–126) (Figure E12), systemic sclerosis (22 studies; prevalence, 45%; 95% CI, 42–49%) (75, 78, 79, 86, 89–95, 97, 103, 104, 108–110, 113–116, 118) (Figure E13), Sjogren's syndrome (5 studies; prevalence, 39%; 95% CI, 18–59%) (76, 82, 101, 119, 121) (Figure E14), and dermatomyositis/polymyositis (10 studies; prevalence, 44%; 95% CI, 37–52%) (77, 80, 83, 87, 92, 99, 107, 110, 112, 117) (Figure E15). The number of patients with SLE in the absence of overlap with another CTD was very small.

Rationale. The desirable consequences of identifying ILAs/ILD in patients with CTD are like those described in smokers (*see* question 1). However, there is an added benefit to identifying ILAs/ILD in patients with CTD. New pulmonary involvement in a patient with CTD may be an indication for the initiation or escalation of immunomodulatory therapy targeting the underlying CTD, and screening may identify such patients sooner than would occur without screening. The evidence suggests that, for every 1,000 patients with "high-risk" CTD (i.e., those listed above) who undergo chest CT screening, approximately 400 may be found to have ILAs/ILD. These patients may benefit from the desirable consequences of screening. The committee judged these desirable consequences as outweighing the undesirable consequences of patient anxiety, radiation exposure, and the costs and burdens of screening and subsequent diagnostic testing.

Additional considerations. The committee recommended baseline screening for ILD but did not reach a consensus on the frequency of follow-up if the initial screening result is negative. The risk of developing ILD is often highest in the early years after diagnosis, but this can vary depending on the underlying CTD (127, 128). Considerations for repeat screening should include the individual's risk profile based on factors such as antibody status, age, and other characteristics of the CTD. The prevalence of ILAs/ILD in SLE without overlap with other CTDs is low, and baseline screening was not recommended. Additionally, the increased risk of radiation from CT screening should be considered, particularly for individuals who are younger. Pulmonary function tests alone are not sensitive enough to detect ILD (129, 130), highlighting the need for CT screening. Although radiation exposure is a concern, modern techniques have significantly reduced the associated risks, and advancements like photon-counting CT may further decrease radiation exposure (130). The committee acknowledges that this suggestion may place additional strain on healthcare systems given the high prevalence of some of the included high-risk CTDs (e.g., rheumatoid arthritis).

Question 3: Should Adults with a First-Degree Relative with Pulmonary Fibrosis Who Are Not Suspected of Having ILD Undergo Chest CT Screening to Identify ILAs/ILD?

Suggestions.

- We suggest chest CT screening for ILAs/ILD in adults ⩾50 years of age who have a first-degree relative with FPF. Remarks: FPF is defined by at least two genetically related first- or second-degree relatives with fibrotic ILD. Vote: Approved by 34 of 36 (94%).
- We recommend neither for nor against chest CT screening for ILAs/ILD in adults ⩾50 years of age who have a first-degree relative with IPF and no other known family members with ILD. Remarks: The absence of a suggestion reflects a lack of consensus among the committee. Vote: Approved by 20 of 37 (54%), not approved by 17 of 37 (46%).

Evidence base. The evidence synthesis identified 11 studies that enrolled first-degree relatives of patients with pulmonary fibrosis (5, 13, 20–22, 24, 40, 41, 131–133) (Figure E16 and Table E6). Ten studies enrolled first-degree relatives of patients with FPF (at least two genetically related first- or second-degree relatives with fibrotic ILD) (13, 20, 22, 40, 41, 131, 132), and four studies enrolled first-degree relatives of patients with IPF and no other known family members with ILD (13, 41, 131, 133). When the first-degree relatives of patients with FPF were aggregated by meta-analysis, the estimated prevalence of ILAs/ILD after the removal of overlapping cohorts and outliers was 26% (95% CI, 18–34%) (Figure E17). When the first-degree relatives of patients with IPF and no other known family members with ILD were aggregated by meta-analysis, the estimated prevalence of ILAs/ILD after the removal of overlapping cohorts was 24% (95% CI, 13–38%) (Figure E18).

Rationale. The desirable consequences of identifying ILAs/ILD in adults with a first-degree relative with pulmonary fibrosis are akin to those described in smokers (*see* question 1). The evidence suggests that, for every 1,000 first-degree relatives of patients with pulmonary fibrosis who undergo chest CT screening (first-degree relatives of patients with FPF and first-degree relatives of patients with IPF and no other known family members with ILD), approximately 250 will be found to have ILAs/ILD and therefore may benefit from screening. For the first-degree relatives of patients with FPF, the committee judged the benefits of screening as outweighing the undesirable consequences of patient anxiety and the costs and burdens of screening and subsequent diagnostic testing. For the first-degree relatives of patients with IPF and no other known family members with ILD, however, there was disagreement about the balance of benefits versus potentially undesirable consequences. Approximately half of the committee concluded that such individuals should be managed like first-degree relatives of patients with FPF because the prevalence of ILAs/ILD is reported to be similar in the limited number of available studies. The other half of the committee concluded that the evidence informing potential benefits in this population was insufficient to justify the substantial additional cost and burden to the healthcare system given the larger number of patients for whom screening would be indicated. This concern was driven in large part by the smaller evidence base for estimation of the prevalence of ILAs/ILD in first-degree relatives of patients with IPF and no other known family members with ILD (172 total individuals) compared with first-degree

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relatives of patients with FPF (1,039 individuals), increasing the risk that selection and other bias might have influenced the estimate.

Additional considerations. The committee acknowledges that the definition of FPF varies by study, especially in terms of the degree of separation between the affected relatives and the types of pulmonary fibrosis included. The current definition was chosen by consensus based on best published evidence. Conditions like sarcoidosis and pleuroparenchymal fibroelastosis have been observed in FPF families, but it is not clear that these share the same genetic architecture as idiopathic interstitial pneumonias; in isolation, a family history of these conditions should not be considered sufficient to classify an individual as having FPF (6, 134). The age chosen to recommend screening is based on published data demonstrating increased prevalence in individuals older than the age of 50 years. Certain genetic variants or a young age at diagnosis for affected relatives may influence the age at which screening should begin; more data are needed for variant status–directed screening recommendations. Screening may be appropriate starting 5 years before the youngest age of diagnosis within the family.

The genetic architecture may differ between sporadic and familial cases of pulmonary fibrosis, impacting the decision to screen. However, family history may not always be known or accurately assessed, potentially underestimating the true prevalence of FPF. Most data on genetic risk come from populations of European genetic background, and risk may vary across different ancestries. Recommendations must balance individual patient considerations with population-level guidelines. Screening may be appropriate for individuals who request it because the information gained could be valuable. The availability of local resources will influence the feasibility of screening, and there are no current data on the cost effectiveness of such programs.

The committee did not vote on the intervals between screening CT scans for individuals whose initial scan does not suggest ILAs/ILD. In general, it was believed that the interval should be no more frequent than every 5 years to avoid overscreening. Subsequent screening or diagnostic evaluations may be done sooner if clinically indicated (e.g., if imaging abnormalities are detected during screening but do not meet the criteria to be classified as ILAs/ILD or if respiratory symptoms appear). Further research is needed to determine the optimal frequency.

Question 4: Should Adults with a First-Degree Relative with Pulmonary Fibrosis Who Are Not Suspected of Having ILD Undergo MUC5B Testing to Identify ILAs/ILD?

Suggestions.

- We suggest not performing *MUC5B* testing as an initial test before more definitive chest CT screening for ILAs/ILD in adults ⩾50 years of age who have a first-degree relative with pulmonary fibrosis (regardless of the first-degree relative has FPF or IPF and no other family members with ILD). Remarks: *MUC5B* testing refers to assessment of the *MUC5B* promoter variant (rs35705950). Vote: Approved by 37 of 37 (100%).

Evidence base. Seven relevant studies (5, 13, 20, 22, 41, 131, 132) were identified (Figure E19 and Table E7), and four of the studies were used to calculate estimates of interest to the committee (5, 13, 41, 132). In adults with a first-degree relative with pulmonary fibrosis, the prevalence of ILAs/ILD among those with the *MUC5B* promoter variant was 38% (95% CI, 24–52%) (Figure E20). The *MUC5B* promoter variant predicted ILAs/ILD with a sensitivity of 56% and a specificity of 60% (Figure E21).

Rationale. The committee considered *MUC5B* testing as an alternative to chest CT scanning to identify ILAs/ILD or as a preliminary test to identify patients who may benefit from chest CT scanning. In both contexts, even though the odds ratio for developing ILAs/ILD is quite high among individuals with the *MUC5B* variant, the committee considered that testing should not act as a gatekeeper to obtaining a CT scan. The committee concluded that the sensitivity and specificity of the test were insufficient to suggest *MUC5B* testing for screening. It is emphasized that the evidence base was small.

Additional considerations. *MUC5B* variant testing may not be routinely available in clinical practice and is associated with high cost, making screening with CT scans more precise and affordable. Moreover, genetic testing is relatively insensitive for detecting ILAs/ILD, and the utility of the test depends heavily on the population's prevalence. Ancestry plays a significant role, with the *MUC5B* variant being relatively common among individuals with European ancestry and rarer among those with African and Asian ancestry. Last, genetic testing for the *MUC5B* promoter variant may inform risk in other family members and may be considered when CT identifies the presence of ILAs/ILD (*see* question 9).

Question 5: Should Adults with a First-Degree Relative with Pulmonary Fibrosis Who Are Not Suspected of Having ILD Undergo Telomere Length Measurement to Identify ILAs/ILD?

Suggestions.

- We suggest not performing telomere length measurement as an initial test before more definitive chest CT screening for ILAs/ILD in adults ⩾50 years of age who have a first-degree relative with pulmonary fibrosis (regardless of whether the first-degree relative has FPF or IPF and no other family members with ILD). Vote: Approved by 37 of 37 (100%).

Evidence base. Three relevant studies were identified (Figure E22 and Table E8) (5, 13, 41). Only two studies reported data in a fashion that enabled calculations of outcomes of interest (13, 41), and those studies had overlapping cohorts, so only one study was used to inform the committee (13). In adults with a first-degree relative with pulmonary fibrosis, the prevalence of ILAs/ILD among those with a telomere length less than the 10th percentile for age was 44% (95% CI, 27–61%). A telomere length less than the 10th percentile for age predicted ILAs/ILD with a sensitivity of 50% and a specificity of 72%, although these estimates are based on only 105 individuals.

Rationale. The committee discussed telomere length measurement as an alternative to chest CT scanning to identify ILAs/ILD or as a preliminary test to identify patients who may benefit from chest CT scanning. In both situations, the committee concluded that the sensitivity and specificity were insufficient to suggest telomere length measurement in adults who have a first-degree relative with pulmonary fibrosis for the purposes of screening. The committee emphasized that the evidence was scarce for this specific question, which rendered the committee's confidence in the calculated test characteristics low.

Additional considerations. The considerations for telomere length testing are similar to those for *MUC5B* (*see* question 4). Results from studies in ILD populations

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further support the position that this test lacks sufficient sensitivity to serve as a screening test. However, some committee members thought that measuring telomere length may have additional utility beyond informing screening recommendations. Individuals with short telomeres often have other organ involvement, including liver disease and early bone marrow failure. Thus, measuring telomere length may prompt additional testing, such as a complete blood count and liver function tests. Genetic testing in individuals with short telomeres may also be indicated to identify inherited variants, which would inform risk in other family members. Thus, although telomere length testing should not act as a gatekeeper for screening CT scanning in appropriate individuals, it may be considered when CT identifies the presence of ILAs/ILD (*see* question 10).

Evidence-based Suggestions for Baseline Assessment

Question 6: Should Patients with ILAs Undergo Baseline Symptom Assessment?

Suggestion.

- We suggest that patients with ILAs undergo baseline symptom assessment. Remarks: Symptom assessment is defined as inquiring about the presence of cough and dyspnea on exertion. This suggestion places high value on noninvasive early identification of ILD and establishing a baseline for future comparison. Vote: Approved by 39 of 39 (100%).

Evidence base. Two studies were identified that performed symptom assessment in patients with ILAs and associated baseline symptoms with outcomes (5, 43) (Figure E23 and Table E9). One study performed an adjusted multivariable analysis and found that baseline dyspnea was associated with mortality in patients with ILAs (hazard ratio [HR], 1.1; 95% CI, 1.0–1.1) (43) (Table E10). Another study used a five-item questionnaire to derive a dyspnea score from 0 to 5; the study demonstrated that, although the average dyspnea score at baseline was similar among patients with or without ILAs, the annualized change in the dyspnea score during follow-up was numerically higher in those diagnosed with clinical disease or with subclinical progression of ILAs compared with those without progression (5).

Rationale. The committee concluded that, among persons with ILAs, the presence of cough or dyspnea can be a defining feature of ILD in the absence of clear alternative explanations for those symptoms and should be assessed at baseline. Lending construct validity that ILA is an early manifestation of ILD, persons with ILAs are more likely than those without ILAs to report cough and/or dyspnea (14, 34). In addition, the severity of self-rated dyspnea and the likelihood to report a regular cough are correlated with the severity (or extent) of ILAs, and progressive (i.e., worsening) ILAs correlate with progressive dyspnea during follow-up (6). Although there is insufficient evidence to recommend baseline symptom assessment in patients with ILAs for the purpose of predicting outcomes, symptom assessment can assist in distinguishing ILAs from ILD, establish a symptom burden at baseline against which changes can be assessed during future follow-up, and inform clinical assessment for other causes of abnormal CT findings that may require other specific management approaches.

Additional considerations. The committee discussed the idea that cough and dyspnea are relatively nonspecific and may have other causes (e.g., cardiac, asthma, postnasal drainage), particularly among individuals with relatively minor radiological abnormalities. It is important to evaluate for alternative explanations for these symptoms. Furthermore, ILAs and ILD may be associated with other symptoms (e.g., fatigue) (135, 136). However, cough and dyspnea were believed to be the most common. The committee did not have specific recommendations on how to measure symptoms. Studies have used various instruments, including visual analogue and numerical scales for cough and dyspnea assessment and more extensive questionnaires (6, 13, 14, 34). The committee acknowledges that the burden of symptom assessment in persons with ILAs may be borne by primary care providers. The type and extent of symptom assessment will depend on the local standard of care and availability of resources. The committee did not specifically address physical examination, but the presence or absence of inspiratory crackles on auscultation can aid in early identification of ILD and should ideally be documented alongside symptom assessment.

Question 7: Should Patients with ILA Undergo Baseline PFT?

Suggestion.

- We suggest that patients with ILAs undergo baseline PFT. Remarks: PFT is defined as the measurement of FVC, TLC, and D_{LCO}. This suggestion places high value on noninvasive early identification of ILD and establishing a baseline for future comparison. Vote: Approved by 38 of 39 (97%).

Evidence base. One study performed PFT in patients with ILAs and associated baseline pulmonary function with outcomes (32) (Figure E24). The study compared baseline FVC in patients with nonprogressive ILAs and progressive ILAs; it demonstrated that baseline FVC was not associated with radiologic progression (odds ratio [OR], 1.0; 95% CI, 0.9–1.0) (Table E11).

Rationale. Similar to question 6, abnormal lung function in an individual with ILAs was believed to be an important criterion to define ILD. Compared with persons without ILAs, those with ILAs have lower lung function, particularly lower TLC and D_{LCO} (14). In another study, first-degree relatives of patients with FPF who experienced development or progression of ILAs or were diagnosed with pulmonary fibrosis had lower TLC and D_{LCO} at baseline compared with individuals who did not experience that composite outcome (6). Although FVC was not different at baseline in persons with or without ILAs in several studies (6, 14), another study reported that individuals with progressive ILAs experience greater decreases in FVC during follow-up compared with those without ILAs and those with nonprogressive ILAs (32). Although there is insufficient evidence to recommend baseline PFT in patients with ILAs for the purpose of predicting outcomes, obtaining PFT is suggested to distinguish ILAs from ILD and to establish a baseline against which changes can be assessed during future follow-up.

Additional considerations. Similar to question 6, the committee acknowledges that uptake of this suggestion will depend on the availability of local resources. It may increase referrals to pulmonology.

Question 8: Should Patients with ILAs Undergo Baseline Lung Sampling for Histopathological Analysis?

Suggestion.

- We suggest that patients with ILAs not undergo baseline lung sampling for

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histopathological analysis. Remarks: This suggestion places high value on avoiding harm from an invasive procedure in the absence of robust evidence that the patient will benefit from the information obtained. Histopathologic sampling may be appropriate for some patients who meet criteria for ILD per existing ILD guidelines. Vote: Approved by 38 of 39 (97%).

Evidence base. There are no studies that assess the utility of histopathology in predicting ILA progression or in determining a diagnosis of ILD among those with ILAs. Evidence is limited to retrospective analyses of lung tissue obtained during nodule resections, which is inherently limited by sampling error (137) (Figure E25). One study included 26 patients with ILAs, 157 patients with indeterminate ILAs, and 257 patients without ILAs (Table E12). Compared with those without ILAs, those with radiologic ILAs were more likely to have histologic findings of subpleural fibrosis (OR, 2.1; 95% CI, 1.3–3.1), fibroblastic foci (OR, 4.2; 95% CI, 2.2–8.1), and atypical adenomatous hyperplasia (OR, 1.7; 95% CI, 1.1–2.6) (136) (Table E13).

Rationale. The committee concluded that there was insufficient evidence to justify routine baseline lung tissue sampling in patients with ILAs to predict outcomes or establish the presence of ILD, especially considering that lung sampling is an invasive test with potential harms. Few studies have performed invasive lung sampling for histologic characterization in these individuals (21). There is no evidence that biopsy findings, whether normal or abnormal, impact management in the absence of other ILD-defining features (i.e., symptoms, abnormal physiology, and/or definite fibrosis on CT). Given the limited data and potential harm from invasive procedures, the committee concluded that routine lung sampling is not warranted in this population.

Additional considerations. The committee emphasized that sampling may be appropriate in select patients whose baseline assessment suggests the presence of ILD, to secure a specific ILD diagnosis per existing guidelines, or if there is suspicion for infection or another pathology (10, 138, 139). Invasive lung sampling includes surgical lung biopsy and/or bronchoscopy with BAL for cellular analysis with or without transbronchial lung biopsy (including standard forceps or cryobiopsy) for microscopic, histopathologic, and/or genomic classifier evaluation. In ILA or ILD, if tissue is available because of procedures performed for other indications (e.g., lung nodule resection), it should be evaluated by histopathology, and abnormal interstitial findings should be reported. In the retrospective study of patients undergoing lung nodule resection, histologic interstitial fibrosis was found in more than half of those without ILAs on CT, but more specific features of fibrotic ILD (i.e., fibroblastic foci and honeycombing) were rare or absent; these features were present in a minority of those with ILAs (137). Individuals with a smoking history, especially those with prominent cystic abnormalities on CT, may have the more benign entity of smoking-related interstitial fibrosis, which should be distinguished from features of fibrotic ILD (i.e., UIP-like fibrosis) (140–144). The committee also discussed the use of a commercially available molecular classifier; among patients with ILD, this classifier has been reported to have a high specificity to detect histopathological UIP (145) but was not associated with differences in survival or PFT progression (146). This molecular classifier has not been studied in populations with or without ILAs, and therefore there is insufficient evidence to justify its use in this patient population.

Question 9: Should Patients with ILAs Undergo Baseline *MUC5B* Testing?

Suggestion.

- We suggest that patients with ILAs not undergo baseline *MUC5B* testing. Remarks: *MUC5B* testing refers to assessment of the *MUC5B* promoter variant (rs35705950). This suggestion places a high value on avoiding the cost and burden of additional testing that is not universally available and may not contribute unique and clinically actionable information beyond what is gathered by other means. Vote: Approved by 38 of 39 (97%).

Evidence base. Five studies performed *MUC5B* promoter variant testing in patients with ILAs and associated the *MUC5B* promoter variant (rs35705950) with outcomes (5, 24, 32, 33, 147) (Figure E26 and Table E14). When patients with stable ILAs were compared with patients with progressive ILAs, the *MUC5B* promoter variant was associated with radiologic progression (OR, 2.6; 95% CI, 1.5–4.4) in one study (33), but not in another study (OR, 1.5; 95% CI, 0.7–3.4) (32) (Table E15). The *MUC5B* promoter variant was not associated with mortality in three cohorts included in two studies (24, 147).

Rationale. Evidence pertaining to the *MUC5B* promoter variant as a predictor of radiologic progression was inconsistent. The committee concluded that testing that has a cost, is not currently universally available, and may not provide actionable information should not be suggested.

Additional considerations. The *MUC5B* variant has been shown to be strongly associated with the risk of IPF, but the data on its associations with prognosis on the individual level are less clear (148–151). Moreover, risk depends on population and ancestry. The committee considered whether the *MUC5B* result would change the type and frequency of follow-up monitoring, with a positive test prompting more frequent and extensive follow-up testing. The committee thought there were insufficient data at this time to recommend testing because it would not alter the clinical management of ILAs.

Question 10: Should Patients with ILAs Undergo Baseline Telomere Length Measurement?

Suggestion.

- We suggest that patients with ILAs not undergo baseline telomere length measurement. Remarks: This suggestion places a high value on avoiding the cost and burden of additional testing that is not universally available and may not contribute unique and clinically actionable information beyond what is gathered by other means. Telomere length measurement and/or testing for specific telomeropathies (e.g., TERT, TERC genetic variants) may be appropriate for some patients in whom family history or other clinical features suggest telomeropathy. Vote: Approved by 38 of 39 (97%).

Evidence base. Two studies performed telomere length measurement in patients with ILAs and associated short telomere length with outcomes (5, 152) (Figure E27 and Table E16). In one study that included two cohorts, the lowest 10th percentile of mean telomere length was associated with mortality in one cohort (HR, 2.0; 95% CI, 1.2–3.4) but not in the other cohort; the lowest quartile of mean telomere length was not associated with mortality in either cohort (152) (Table E17). In the other study, the radiologic progression cohort had mean telomere lengths of 6.17–6.26 kb, whereas the

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non–radiologic progression cohort had a mean telomere length of 6.47 kb (5).

Rationale. Evidence pertaining to telomere length as a predictor of mortality was inconsistent and as a predictor of radiologic progression was scarce. However, there are considerably more robust data from ILD literature linking telomere length to outcomes. Patients with telomere length below the 10th percentile may have an increased risk of disease progression (23, 153), and short telomere length may identify patients at the highest risk of death (154). The committee concluded that, given that testing has a cost, is not universally available, and may not provide actionable information, it should not be recommended. However, the committee emphasized that telomere length measurement may be appropriate for some patients whose family history or other clinical features suggest telomeropathy.

Additional considerations. The current standard for clinical measurement of leukocyte telomere length is by FlowFISH at a limited number of sites. However, there are multiple other methods, including quantitative PCR and extraction from whole-genome sequencing data, which have been used more commonly in research studies. The clinical implications of short telomeres measured using these different methods are not always consistent. The threshold for what constitutes short telomeres have also not been validated for these other methods. If telomere length testing is being considered, pretest probability should be evaluated, and is increased in the presence of features suggesting short telomere syndrome, including hair graying before age 30 years, cryptogenic liver cirrhosis, unexplained cytopenias, myelodysplastic syndrome, and acute myeloid leukemia (155).

Evidence-based Suggestions for Follow-up Assessment

Question 11: Should Patients with ILAs Undergo Longitudinal Follow-up with Serial Chest CT Scans?

Suggestion.

- We suggest that patients with ILAs undergo a follow-up chest CT scan 2–3 years after the baseline chest CT scan. Remarks: Earlier follow-up (12 mo) may be appropriate in some clinical contexts. The frequency of subsequent follow-up chest CT scans depends on multiple factors, including evidence for progression of the ILAs on the initial follow-up chest CT scan. Vote: Approved by 34 of 36 (94%).

Evidence base. Fifteen studies performed serial chest CT scans in patients with ILAs and associated radiologic progression with outcomes (5, 16, 32, 33, 37–39, 41–43, 46, 47, 156–158) (Figure E28). Frequency of repeat chest CT scanning ranged from 2 to 12 years, although most studies repeated imaging every 2–5 years (Table E18). All studies measured the prevalence of radiologic progression; after the elimination of outliers, the prevalence of radiologic progression was 46% (95% CI, 38–55%) (Figure E29). Two studies identified a positive association between radiologic progression and mortality (33, 157) (HR, 1.9; 95% CI, 1.3–2.8; and HR, 1.69; 95% CI, 1.21–2.34, respectively), whereas a third study found no association (32) (Table E19).

Rationale. For patients with ILAs, the primary purpose of follow-up imaging is to identify progression to ILD because further diagnostic workup may be warranted to inform management and therapeutic decisions and to mitigate lung function decline (10). The evidence suggests that, for every 1,000 patients with ILAs, 460 will experience progression, some to ILD, which the committee concluded warranted serial imaging. No study compared different frequencies of serial imaging; however, in a study of 305 individuals with ILAs, the median time to ILA progression was 3.2 years (156). Based on this, the committee suggests an initial follow-up chest CT scan 2–3 years after the initial detection of the ILA based on their collective clinical experience (159). Notably, the committee emphasized that earlier follow-up may be warranted in some situations.

Additional considerations. The average rate of progression of ILAs is slow, even in high-risk FPF cohorts, with most studies showing radiological progression over 5 years, and median times to progression to UIP as long as 11 years. However, some individuals can experience progression more rapidly (41). The committee weighed concerns for overtesting against the risk of loss to follow-up of individuals with clinically meaningful abnormalities and agreed that repeat HRCT at approximately 2–3 years may be appropriate for most individuals. However, some individuals with high-risk features may need earlier repeat imaging (12 mo). CT may be repeated sooner if there is clinical or physiologic evidence of progression. The committee did not vote on the frequency of follow-up with PFT and symptom assessment. However, most committee members thought follow-up annually with PFT would be appropriate to evaluate for progression to ILD. Some committee members expressed concern about the increased burden on the healthcare system. The committee acknowledges that the availability of local resources will impact the feasibility of follow-up testing. Patients should be appropriately informed about their findings and educated about symptoms that would prompt earlier evaluation and testing.

Approach to Evaluation and Management of ILAs

The suggested evaluation and management of ILAs are summarized in Figure 3, with additional details described in the remarks for each PICO question. The approach may need to be modified based on local resources and shared decision-making with patients. This approach was developed to prioritize the identification and appropriate management of ILAs at the highest risk of progression to ILD.

Detection of ILAs can occur through screening specific populations, including individuals already undergoing lung cancer screening, patients with a CTD, or adults ⩾50 years of age with a first-degree relative with FPF. In some situations, there may be utility in screening other at-risk populations, including individuals with a primary relative with IPF (committee consensus not achieved for this question) and some high-risk exposures (e.g., composite countertop cutting) (160). Some of these populations have a prevalence of ILD similar to other recommended screening populations; however, the limited available data were considered insufficient to support a recommendation for comprehensive screening in these subgroups. Beyond active screening, ILAs can also be detected through other means such as incidentally on a CT scan performed for an unrelated reason (e.g., cardiac CT), after which a dedicated HRCT examination is required for further characterization.

After the identification of an ILA and confirmation with HRCT, baseline assessment includes evaluation for potential causes, risk factors, and assessment of any functional impact, with specific recommendations for

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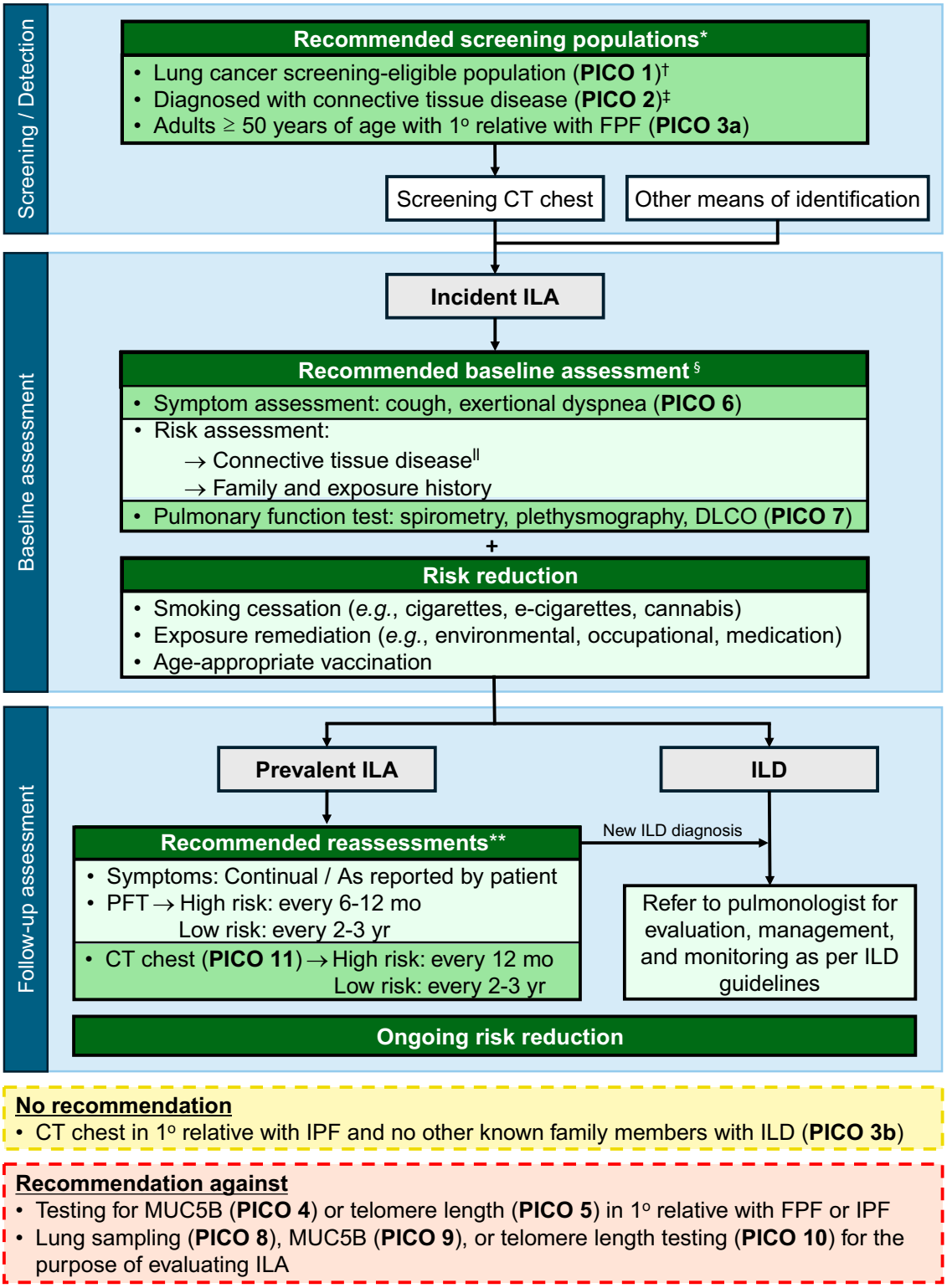

Figure 3. Evaluation and management of interstitial lung abnormality (ILA). Actions shown in darker green boxes indicate recommendations formulated based on prespecified population-intervention-control-outcome (PICO) questions, with the PICO question number shown in parentheses. Actions shown in lighter green boxes indicate additional suggestions that were not the subject of prespecified PICO questions. PICO questions that did not reach consensus are shown in dashed boxes at the bottom of the algorithm in yellow (no recommendation) and red (recommendation against). *Other high-risk populations may be appropriate for screening (e.g., high-risk occupations). †Patients at increased risk for lung cancer are recommended to undergo chest computed tomography (CT) screening for lung cancer. We further recommend systematic assessment and documentation of the presence or absence of ILAs/interstitial lung disease (ILD) in smokers who are undergoing lung cancer screening with a

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Table 4. Features Associated with Increased Risk of ILA Progression

High-risk ILA features
Demographic and clinical factors
• Family history of pulmonary fibrosis
• Older age
• Smoking history
• Other inhaled exposures (e.g., occupational vapors, gases, dusts, and fumes; air pollution)
• Connective tissue disease
Genetic
• *MUC5B* promoter variant
• Leukocyte telomere length below age-adjusted 10th percentile
Imaging
• Definite fibrosis on CT (i.e., honeycombing, traction bronchiectasis or architectural distortion)
• Subpleural fibrotic and subpleural nonfibrotic subtypes
• Subpleural reticulation
• Greater extent of abnormalities (e.g., involvement of multiple lung zones)
Physiologic
• Abnormal or borderline FVC, TLC, and D_{LCO}

Definition of abbreviations: CT = computed tomography; ILA = interstitial lung abnormality.

symptom assessment and PFT, including spirometry, plethysmography, and D_{LCO} measurement. Common causes of and risk factors for ILD should be considered, including features of CTD, family history, and environmental and occupational exposures. Patients with any concerning features on this evaluation should be referred to a pulmonologist, with earlier and potentially universal referral of all ILAs if local resources permit.

Individuals with prevalent ILAs and no high-risk features should have symptoms, PFT, and CT reevaluated every 2–3 years following the initial assessment until an individualized discussion suggests limited utility of further monitoring. Those in whom ILD develops or who have ILAs and high-risk features (Table 4) should be considered for earlier reassessment of symptoms, PFT, and/or repeat HRCT. This requires integration of clinical, genetic (when available), imaging, and physiologic data with shared decision-making. A multidisciplinary approach, as recommended by existing guidelines, is ideal, but implementation of this recommendation depends on local resources (10). Strategies should be taken throughout follow-up for harm minimization in all individuals with ILAs, including smoking cessation, exposure remediation and avoidance, and age-appropriate vaccination. It is crucial to share information with all those involved at each time point regarding the relative risks and benefits of testing to allow individuals at risk to actively participate in decision-making. A key priority is the development of adequate resources and educational materials to facilitate these conversations. There is currently no medical therapy for ILAs, which is a priority for future research.

Future Directions

There remain many unanswered questions about ILAs that represent priorities for future research (Table 5), with four the committee identified as critical.

1. Utility of screening first-degree relatives of patients with sporadic IPF. The committee voted 54% in favor of screening this population; however, this did not meet the prespecified consensus for approval. Although overlapping information obtained from genetic association (17) and screening studies (13, 131, 133) suggest that current definitions of FPF and sporadic IPF may not clearly define distinct groups, concern was raised about the sample sizes of existing studies and the broader implications that such an endeavor might have on health systems. Future work is needed to further validate these findings in larger and more diverse populations and to determine the impact of expanded screening recommendations on patient outcomes, healthcare costs, and healthcare resources.
2. Understanding the role of genetic testing and additional biomarker assessments in screening. Despite major recent advances in our understanding of genetic risk factors for pulmonary fibrosis (25, 161–163), the committee did not suggest testing for the *MUC5B* promoter variant or telomere length in those who have ILAs or in at-risk relatives (14, 152, 164, 165) as a result of modest test performance characteristics for discriminating ILAs. Although these findings highlight the need to identify scenarios in which genetic testing predicts clinically actionable outcomes in screening settings (166), including rare variant assessments, future assessments should consider how the total contribution of genetic variation could contribute to ILA risk across different populations and/or

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Figure 3. (*Continued*). chest CT scan. ‡Connective tissue diseases (CTDs) associated with an increased risk of ILD and that qualify for this recommendation include rheumatoid arthritis, systemic sclerosis, polymyositis, dermatomyositis, antisynthetase syndrome, mixed CTD, Sjogren's disease, undifferentiated CTD, or overlap syndrome. §Including high-resolution CT if not already performed. A multidisciplinary approach is ideal if local resources allow. ‖CTD assessment includes symptom assessment (e.g., skin changes, weakness, arthritis, dry eyes/dry mouth) and physical examination with autoimmune serologies considered when clinically indicated. **Frequency of reassessment depends on risk assessment per Table 4. High-risk features associated with ILA progression include family history of pulmonary fibrosis, older age, smoking history, other inhaled exposures (e.g., occupational vapors, gases, dusts and fumes; air pollution), CTD, presence of the *MUC5B* promoter variant, leukocyte telomere length below age-adjusted 10th percentile, presence of definite fibrosis on CT (i.e., honeycombing, traction bronchiectasis, or architectural distortion), subpleural fibrotic and subpleural nonfibrotic subtypes, subpleural reticulation, greater extent of imaging abnormalities, and abnormal or borderline FVC, TLC, and D_{LCO}. It may also be appropriate to reassess more frequently for other indications (e.g., lung cancer screening). Implementation depends on local resources. FPF = familial pulmonary fibrosis (defined as at least two genetically related first- or second-degree relatives with fibrotic ILD); IPF = idiopathic pulmonary fibrosis; PFT = pulmonary function test; prevalent ILA = ILA present on baseline and/or follow-up CT scan.

Table 5. Unresolved Questions and Future Research Needs in Those with or at Risk for ILAs

Unresolved Questions	PICO Questions Addressing	Specific Goals	Action Items
What is the role/value of screening in first-degree relatives of patients with IPF (i.e., without FPF)?	4	1) More accurately determine the prevalence of ILAs/ILD in first-degree relatives of patients with sporadic IPF 2) Determine the impact of expanded screening for ILAs on healthcare use	1) Replication of screening studies in sporadic IPF relatives in independent populations 2) Replication of screening studies in diverse racial/ethnic and international populations 3) Expanding the sample size of existing screening studies 4) Assessments of the downstream benefits of screening in this population 5) Assessments of the financial, insurance, and workforce allocation issues that such a recommendation might impact
Are there specific scenarios when biomarker assessments (e.g., clinical genetic testing, and telomere length testing) add value in screening for or assessment of those with or at risk for ILAs?	5, 6, 10, 11	1) Establish the role of genetic testing in ILA assessment 2) Determine the scenarios when telomere length testing improves clinical assessment 3) Determine the value of additional biomarkers (e.g., protein biomarkers, breath biomarkers) in ILA assessment	1) Determine the scenarios when rare-variant assessments in those with ILAs or in families are more likely to lead to clinically actionable results 2) Determine the scenarios when the combination of genetic tests (e.g., polygenic risk) help to better explain the genetic risk in families and when these tests can help to rule in, or rule out, disease risk 3) Genetic assessments of ILA in diverse racial/ethnic and international populations 4) Determine the scenarios in which telomere length testing might help to better understand disease burden beyond just the lung (e.g., liver disease, and bone marrow failure) 5) Assessments of biomarkers, not just with association, but in reference to their clinical value in specific populations
What is the role that QCT should play in the workup and management of those with ILAs?	NA	1) Determine which QCT metrics perform best in measuring disease extent, predicting outcomes and longitudinal follow-up 2) Determine which QCT metrics best measure disease progression	1) Compare QCT metrics for prediction of outcomes 2) Determine the clinical role for QCT metrics (e.g., risk-stratifying ILAs, tracking progression) 3) Assess the added clinical value of QCT compared with existing metrics 4) Assess the role of QCT in improving screening for ILAs and ILD
What is the role that alternative imaging techniques (PET-CT, endobronchial optical coherence tomography) should play in the workup and management of those with ILAs?	NA	1) Test the clinical utility of alternative imaging modalities	1) Assess the added clinical value of alternative metrics compared with existing metrics 2) Determine the role of alternate imaging modalities in improving diagnostic sensitivity and specificity 3) Assess the role of alternate imaging modalities for improving screening for ILAs and ILD 4) Determine the clinical utility of alternate imaging modalities for predicting progression
Can interventions in targeted populations with ILAs/ILD improve important clinical endpoints?	NA	1) Determine if pharmacologic interventions improve outcomes in those with ILAs/ILD 2) Determine if nonpharmacologic interventions improve outcomes in those with ILAs/ILD	1) Determine the populations most in need, and amenable to, future interventional studies 2) Determine the highest yield non-pharmacologic interventional efforts 3) Carefully consider the most relevant, and well-powered, clinical outcomes to measure in selected populations 4) Consider the most appropriate length of a clinical trial in selected populations

Definition of abbreviations: CT = computed tomography; FPF = familial pulmonary fibrosis; HP = hypersensitivity pneumonitis; ILA = interstitial lung abnormality; ILD = interstitial lung disease; NA = not applicable; NSIP = nonspecific interstitial pneumonia; PET = positron emission tomography; QCT = quantitative computed tomography; UIP = usual interstitial pneumonitis.

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genetic ancestries (25). Recent studies have also highlighted the potential for blood biomarkers to detect ILAs (167, 168) and predict outcomes (167–171). Although the roles of these biomarkers remain unclear, the development of biomarkers that accurately discriminate ILA presence and progression would be of high clinical value.

3. Role for QCT and alternate imaging modalities. QCT measures based on density metrics or machine-learning quantification of fibrosis potentially provide a more objective and reproducible metric of disease extent compared with visual assessment (5, 24, 126, 156, 172, 173). Longitudinal increases in QCT metrics have also been linked to lung function decline and survival (156, 173–175). Recently, multiple artificial intelligence–based diagnostic and QCT approaches for ILAs have been reported and may improve management of ILAs by enabling objective detection, risk stratification, and monitoring over time (176–178). However, how the specific QCT metrics and measurement techniques compare with each other and how dependent they are on CT scanner type and reconstruction algorithm are unknown. Additional imaging modalities (e.g., endobronchial optical coherence tomography, positron emission tomography imaging targeted to collagen or fibrin) show promise for screening (179–184), microscopic pathologic characterization (179, 180, 183–185), and predicting progression (179) in ILAs. Future studies are needed to provide further data on where these novel imaging methods may provide additional clinical value as a complement to existing modalities (e.g., chest CT and PFT).
4. Identification of treatments for ILAs. Screening for and monitoring those with ILAs would be more beneficial if there were interventions that improve relevant clinical outcomes (186). Future efforts to identify specific interventions should include study of nonpharmacologic interventions that likely have widespread benefit (e.g., smoking cessation, exposure avoidance), as well as pharmaceutical interventions that may be initially aimed at populations at the greatest risk for progression.

Conclusions

Tertiary prevention strategies that focus on established pulmonary fibrosis have had limited impact on the morbidity and mortality associated with ILD. Identifying individuals before the onset of clinically evident lung fibrosis (i.e., when findings qualify as ILA) provides an opportunity to intervene before the lung is extensively and irreversibly scarred (i.e., primary and secondary prevention) if effective and well-tolerated treatments can be identified (24, 33). This document presents a comprehensive literature review of ILAs that supports updates to the previous ILA definition made by the Fleischner Society (1), establishes a working definition of ILD, and provides evidence-based suggestions for the evaluation and management of ILAs. Together, these advances will improve clinical care and support future research by standardizing the approach to ILAs. In addition, this document highlights important unanswered questions, providing a direction for future initiatives, while emphasizing the need to identify treatment options for ILA. ■

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Hoffmann-La Roche, FibroGen, Nitto, Pliant, RespiVant, Zambon; received research support from Boehringer Ingelheim and Roche; received travel support from Boehringer Ingelheim and F. Hoffmann-La Roche. I.O.R. served on an advisory board for Avalyn Pharma, Boehringer Ingelheim, Genentech; received research support from Boehringer Ingelheim and Tvardi. M.L.S. served as a consultant for Boehringer Ingelheim, F. Hoffmann-La Roche, Orinove, Roche; received research support from Boehringer Ingelheim and NIH; received travel support from Boehringer Ingelheim. M.M.S. served on an advisory board for Boehringer Ingelheim; served as a consultant for AbbVie, Bioclinica, Lung Life AI; has intellectual property with Genentech; received honoraria from France Foundation and a peer review; received research support from Boehringer Ingelheim and Genentech; served as a reviewer for AbbVie and Bioclinica; served as a speaker for France Foundation. J.B.S. served as a fiduciary officer for Promedius; holds one pending and one issued Korean patent; holds stock in Anymedi Solution, Coreline, Promedius; received royalties from Corelinsoft, Promedius, Vuno. J.W.S. served on an advisory board for Boehringer Ingelheim, Daewoong, Taiho; received honoraria from Boehringer Ingelheim, Daewoong, Eisai, Savara, Spark Biopharma, Taiho; received research support

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from Korean Environment Industry and Technology Institute, Korean National Institute of Health, National Research Foundation of Korea. C.C.T. served as a consultant for Median Technologies and UpToDate; served as editor for Springer. M.V. served as a speaker for Oakstone. L.V.W. served on an advisory board for Medical Research Council; served as a consultant for Boehringer Ingelheim, Galapagos, GlaxoSmithKline; served as editor for European Respiratory Society; received research support from F. Hoffmann-La Roche, Genentech, Medical Research Council, Nordic Biosciences, Orion Pharma, Roche, Sysmex, Wellcome Trust; received travel support from Genentech. M.W. served on an advisory board for Boehringer Ingelheim and F. Hoffmann-La Roche; served as a consultant for Agomab, AstraZeneca, Avalyn Pharma, Bristol-Myers Squibb, Boehringer Ingelheim, Calluna, CLS Behring, F. Hoffmann-La Roche, Galapagos, Galecto, GlaxoSmithKline, Horizon, Kinevant, Molecure, Nerre, Novartis, Puretech, Thyron, Trevi, Vicore; received honoraria from Boehringer Ingelheim, CSL Behring, F. Hoffmann-La Roche, Novartis, Sanofi; served in a leadership role for Dutch Lung Fibrosis and Sarcoidosis Patient Associations; European Idiopathic Pulmonary Fibrosis and Related Disorders Federation, European Reference Network for Rare Lung Diseases; European Respiratory Society, Netherlands Respiratory Society; received research support from AstraZeneca, Boehringer Ingelheim, Daiichi, F. Hoffmann-La Roche, The Dutch Lung Foundation, The Dutch Pulmonary Fibrosis Organization, Sarcoidose.nl; served as a speaker for Boehringer Ingelheim, F. Hoffmann-La Roche, Novartis; received travel support from Boehringer Ingelheim, F. Hoffmann-La Roche; GlaxoSmithKline. D.A.S. served as a consultant for Vertex; served as a fiduciary officer for Eleven P15; holds multiple pending patents on the role of genetics and biomarkers in the early diagnosis of lung fibrosis; received research support from the NIH. C.J.R. served as a consultant for AstraZeneca, AbbVie, Avalyn, Boehringer Ingelheim, F. Hoffmann-La Roche, Pliant, Trevi, Veracyte; served as expert witness, received honoraria, and received research support from Boehringer Ingelheim; received travel support from Cipla and Boehringer Ingelheim. F.K., B.P., G.C., J.F., B.K., F.L., S.P., and M.S. reported no commercial or relevant non-commercial interests from ineligible companies.

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