AMERICAN THORACIC SOCIETY DOCUMENTS

Diagnosis of Idiopathic Pulmonary Fibrosis

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

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This official clinical practice guideline of the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Society (ALAT) was approved by the ATS, JRS, and ALAT May 2018, and the ERS June 2018

Background: This document provides clinical recommendations for the diagnosis of idiopathic pulmonary fibrosis (IPF). It represents a collaborative effort between the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society.

Methods: The evidence syntheses were discussed and recommendations formulated by a multidisciplinary committee of IPF experts. The evidence was appraised and recommendations were formulated, written, and graded using the Grading of Recommendations, Assessment, Development, and Evaluation approach.

Results: The guideline panel updated the diagnostic criteria for IPF. Previously defined patterns of usual interstitial pneumonia (UIP) were refined to patterns of UIP, probable UIP, indeterminate, and alternate diagnosis. For patients with newly detected interstitial lung disease (ILD) who have a high-resolution computed tomography scan pattern of probable UIP, indeterminate, or an alternative diagnosis, conditional recommendations were made for performing BAL and surgical lung biopsy; because of lack of evidence, no recommendation was made for or against performing transbronchial lung biopsy or lung cryobiopsy. In contrast, for patients with newly detected ILD who have a high-resolution computed tomography scan pattern of UIP, strong recommendations were made against performing surgical lung biopsy, transbronchial lung biopsy, and lung cryobiopsy, and a conditional recommendation was made against performing BAL. Additional recommendations included a conditional recommendation for multidisciplinary discussion and a strong recommendation against measurement of serum biomarkers for the sole purpose of distinguishing IPF from other ILDs.

Conclusions: The guideline panel provided recommendations related to the diagnosis of IPF.

Keywords: idiopathic pulmonary fibrosis; interstitial lung disease; pulmonary fibrosis

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Summary of Recommendations

Adult patients with newly detected interstitial lung disease (ILD) of apparently unknown cause are clinically suspected of having idiopathic pulmonary fibrosis (IPF) if they have unexplained symptomatic or asymptomatic patterns of bilateral fibrosis on a chest radiograph or chest computed tomography (CT) scan, bibasilar inspiratory crackles, and an age typically older than 60 years. Rarely, middle-aged adults (>40 yr and <60 yr), especially those with risks for familial pulmonary fibrosis, may otherwise manifest the same clinical scenario as the typical patient older than 60 years. The recommendations in this guideline are for the patterns and distributions of images obtained by high-resolution CT (HRCT) imaging and, thus, require that patients be subjected to HRCT of the chest for evaluation.

For adult patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF:

- We recommend taking a detailed history of both medication use and environmental exposures at home, work, and other places the patient frequently visits to exclude potential causes of ILD (*motherhood statement*).
- We recommend serological testing to exclude connective tissue disease (CTD) as a potential cause of the ILD (*motherhood statement*).

For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF and have an HRCT pattern of probable UIP, indeterminate, or an alternative diagnosis:

- We suggest cellular analysis of their BAL fluid (*conditional recommendation, very low quality of evidence*).
- We suggest surgical lung biopsy (SLB) (*conditional recommendation, very low quality of evidence*).
- The panel made no recommendation for or against transbronchial lung biopsy (TBBx).
- The panel made no recommendation for or against lung cryobiopsy.

For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF and have an HRCT pattern of UIP:

- We suggest NOT performing cellular analysis of their BAL fluid (*conditional recommendation, very low quality of evidence*).
- We recommend NOT performing SLB (*strong recommendation, very low quality of evidence*).
- We recommend NOT performing TBBx (*strong recommendation, very low quality of evidence*).
- We recommend NOT performing lung cryobiopsy (*strong recommendation, very low quality of evidence*).

For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF:

- We suggest multidisciplinary discussion (MDD) for diagnostic decision-making (*conditional recommendation, very low quality of evidence*).
- We recommend NOT measuring serum MMP (matrix metalloproteinase)-7, SPD (surfactant protein D), CCL (chemokine ligand)-18, or KL (Krebs von den Lungen)-6 for the purpose of distinguishing IPF from other ILDs (*strong recommendation, very low quality of evidence*).

For comparison of the 2018 and 2011 diagnostic recommendations, see Table 1. For an explanation of strong and conditional recommendations, see Table 2.

Introduction

In 2000, IPF was defined as a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults and limited to the lungs (1). Usual interstitial pneumonia (UIP) is the histopathological pattern of IPF. IPF is characterized by progressive worsening of dyspnea and lung function and is associated with a poor prognosis.

In 2011, the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Society (ALAT) collaborated to develop a clinical practice guideline for the diagnosis and management of IPF (2). This evidence-based guideline provided diagnostic criteria for IPF on the basis of radiologic and histologic findings. However, the 2011 diagnostic criteria have since been shown to have important limitations in clinical practice (3–6). Numerous observational studies and randomized trials now enable us to improve on the 2011 diagnostic criteria.

The recommendations in this 2018 guideline are revisions of the diagnostic recommendations in the 2011 guideline (2). This guideline is intended to help clinicians make an accurate diagnosis of IPF and to empower them to implement recommended courses of action in the context of individual patient values and preferences, particularly decisions regarding which diagnostic interventions to pursue.

Methods

This guideline was developed in accordance with the policies and procedures of the ATS, ERS, JRS, and ALAT. Questions were selected according to their importance to clinical practice, as determined by the guideline panel, expert advisors, and a patient advocate. All recommendations were supported by a systematic review. We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to appraise the quality of evidence and to formulate, write, and grade most recommendations (Table 2) (7). We required 70% agreement on the direction of the recommendation (i.e., for or against) to make a recommendation; if such agreement was not achieved, no recommendation was made. "We recommend" indicates that the recommendation is strong and "we suggest" indicates that the recommendation is weak or conditional (Table 2). Definitions, technical "how to" recommendations, and recommendations for which there is no reasonable alternative to the recommended course of action (i.e., motherhood statements) were developed outside of the GRADE framework. The methods are described in detail within the online supplement.

Clinical Manifestations

IPF is a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause. It occurs primarily in older adults, is limited to the lungs, and is defined by the histopathologic and/or radiologic pattern of UIP. It should be considered in all adult patients with unexplained chronic exertional dyspnea, cough, bibasilar inspiratory crackles, and/or digital clubbing that occur without constitutional or other symptoms that suggest a multisystem disease.

The incidence of IPF increases with older age, with presentation typically consisting of insidious onset of dyspnea in the sixth and seventh decades (8, 9). Rarely, patients with IPF may present with an acute exacerbation as an initial manifestation (i.e., an unexplained worsening of dyspnea over a few weeks and new ground-glass opacification on HRCT scan with a background of lower lobe fibrotic lung disease) (10). Patients with IPF who are younger than 50 years old are rare; such patients may subsequently manifest features of an underlying CTD that was subclinical at the time IPF was diagnosed (11) or may have familial IPF (12). More men have been reported with IPF than women, and the majority of patients have a history of past cigarette smoking (13). Other risk factors associated with IPF include gastroesophageal reflux (14–17), chronic viral infections such as Epstein-Barr virus (18–26), hepatitis C (27–33), and a family history of ILD. Many patients with IPF also have other comorbid conditions that include emphysema (combined pulmonary fibrosis and emphysema), lung cancer, pulmonary hypertension, sleep apnea, and coronary artery disease (34). In some genetic forms, there is also extrapulmonary disease that manifests as bone marrow failure and liver disease (35, 36). In some patients, biological members of the family (primary relatives) also have IPF. At least 30% of patients who have sporadic or familial pulmonary fibrosis have genetic predisposing factors that are known to increase the risk of pulmonary fibrosis (37–39); however, the identified genetic factors in the telomerase and telomere pathways are also associated with other ILDs (40–43).

Diagnosis

HRCT Technique

The diagnostic approach to IPF is highly reliant on images of the lungs generated from volumetric scanning of the chest. This mode has essentially replaced sequential CT scanning, as it improves detection of all abnormalities, even if subtle or focal. It also ensures precise analysis of lesion characteristics and distribution on the basis of both cross-sectional images and multiplanar reformations. Technical requirements of HRCT include the following (Table 3 and Table E1 in the online supplement):

1. The thinnest collimation, shortest rotation time, and highest pitch that ensure creation of motion-free images. The kilovoltage and milliamperage selection should follow current recommendations for reduced-dose CT (44–47).
2. The number of acquisitions. The first acquisition is obtained in supine position at sustained end-inspiration (volumetric acquisition). The second acquisition is obtained in supine position over the entire thorax at sustained end-expiration, after a prolonged expiration (volumetric or sequential acquisition) (48, 49). The

Table 1. Comparison of ATS/ERS/JRS/ALAT Recommendations for the Diagnosis of IPF in the 2011 and 2018 Guidelines

	2018 Guideline		
	HRCT Pattern of Probable UIP*, Indeterminate, and Alternative Diagnosis	**HRCT Pattern of UIP***	**2011 Guideline: Did Not Distinguish among Patients with Different HRCT Patterns**
BAL cellular analysis	We suggest performing BAL cellular analysis (conditional)	We suggest *NOT* performing BAL cellular analysis (conditional)	"BAL cellular analysis should not be performed in the diagnostic evaluation of IPF in the majority of patients, but may be appropriate in a minority of patients."
Surgical lung biopsy	We suggest performing surgical lung biopsy (conditional)	We recommend *NOT* performing surgical lung biopsy (strong)	"Surgical lung biopsy is not required for patients with an HRCT pattern consistent with UIP."
Transbronchial lung biopsy	No recommendation was made either for or against transbronchial lung biopsy	We recommend *NOT* performing transbronchial lung biopsy (strong)	"Transbronchial biopsy should not be used in the evaluation of IPF in the majority of patients, but may be appropriate in a minority."
Lung cryobiopsy	No recommendation was made either for or against cryobiopsy	We recommend *NOT* performing cryobiopsy (strong)	Not addressed
Medical history of medication use and environmental exposures	We recommend taking a detailed history of both medication use and environmental exposures at home, work, and other places the patient frequently visits to exclude potential causes of ILD (motherhood statement)		"Diagnosis of IPF requires exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity)."
Serological testing to exclude connective tissue disease	We recommend serological testing to exclude connective tissue diseases as a potential cause of the ILD (motherhood statement)		"Diagnosis of IPF requires exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity)."
Multidisciplinary discussion	We suggest multidisciplinary discussion for decision-making (conditional)		"We recommend that a multidisciplinary discussion should be used in the evaluation of IPF."
Serum biomarkers	We recommend *NOT* measuring serum MMP-7, SPD, CCL-18, or KL-6 for the purpose of distinguishing IPF from other ILDs (strong)		Not addressed

Definition of abbreviations: ALAT = Latin American Thoracic Society; ATS = American Thoracic Society; CCL-18 = chemokine ligand 18; ERS = European Respiratory Society; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; JRS = Japanese Respiratory Society; KL-6 = Krebs von den Lungen-6; MMP-7 = matrix metalloproteinase 7; SPD = surfactant protein D; UIP = usual interstitial pneumonia.
The quality of evidence for all recommendations in the 2018 guideline was very low.
*The patterns of UIP have been refined in these 2018 guidelines, compared with the 2011 guidelines.

Table 2. Implications of Strong and Conditional Recommendations

	Strong Recommendation ("We recommend . . .")	Conditional Recommendation ("We suggest . . .")
For patients	The overwhelming majority of individuals in this situation would want the recommended course of action and only a small minority would not.	The majority of individuals in this situation would want the suggested course of action, but a sizeable minority would not.
For clinicians	The overwhelming majority of individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for different patients, and you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.
For policy makers	The recommendation can be adapted as policy in most situations, including for use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

third acquisition is aimed at clearing position-induced changes in the dependent lung of the first acquisition (50); it can be volumetric or sequential and can be limited to the lower lobes. It can also be systematic or optional, depending on the experience of the radiologist/technician interpreting the findings on supine inspiratory images once acquired. Instructions regarding the respiratory maneuver are necessary before each acquisition; direct command by the technologist's voice may be preferable to automatic patient instruction devices (51).

3. Scanning to evaluate acute respiratory worsening in a patient known to have ILD. Because acute pulmonary embolism should always be in the differential diagnosis of acute respiratory worsening, chest CT angiography should be obtained to detect pulmonary embolus, either alone or in addition to a noncontrast HRCT protocol, limited to supine acquisitions. A second major goal is to detect new ground-glass changes that raise the probability of acute exacerbation.

HRCT Features of the UIP Pattern

HRCT features frequently seen in UIP include honeycombing, traction bronchiectasis, and traction bronchiolectasis, which may be seen with the concurrent presence of ground-glass opacification and fine reticulation.

Honeycombing refers to clustered cystic airspaces of typically consistent diameter (3–10 mm, but occasionally larger) with thick, well-defined walls. It is usually accompanied by a reticular pattern containing traction bronchiectasis and bronchiolectasis (52). Honeycombing often presents as multiple layers of subpleural cysts on top of each other, but it may also present as a single layer. In these cases, distinction between honeycombing and paraseptal emphysema or traction bronchiolectasis may be difficult (53). Interobserver agreement for honeycombing is inconsistent (54–56), with disagreement most commonly due to subpleural pathology mimicking honeycombing (e.g., traction bronchiolectasis, paraseptal emphysema, and subpleural cysts) (55).

Traction bronchiectasis/bronchiolectasis is a key feature of pulmonary fibrosis that ranges from subtle irregularity and nontapering of the bronchial/bronchiolar wall to marked airway distortion and varicosity (57–60). It is usually peripheral/subpleural in UIP, often coexisting with honeycomb cysts, and may be best regarded as *peripheral traction bronchiolectasis*.

Ground-glass opacification is defined as hazy increased opacity of lung with preservation of the bronchial and vascular margins (52). An important distinction to make is "pure" ground-glass opacification versus ground-glass opacification superimposed on a fine *reticular pattern* (61). "Pure" ground-glass opacification is not a typical feature of UIP, and its presence in a patient with IPF should raise the possibility of an acute exacerbation (62, 63). In contrast, ground-glass opacification superimposed on a fine reticular pattern represents fibrosis and may be seen in patients with IPF. The presence of traction bronchiectasis/bronchiolectasis within the latter helps to distinguish between these two patterns (61).

HRCT Patterns

We advocate the use of four diagnostic categories that incorporate the HRCT features described above (Table 4). These categories include a "UIP pattern" (Figure 1), "probable UIP pattern" (Figure 2), "indeterminate pattern" (Figures 3 and 4), and "alternative diagnosis" (Figure 5).

UIP pattern. UIP is the hallmark radiologic pattern of IPF. Honeycombing is a distinguishing feature of UIP and must be present for a definite HRCT diagnosis of UIP to be made. It can be seen with or without peripheral traction bronchiectasis or bronchiolectasis. The typical distribution of UIP is subpleural with basal predominance, although some upper lobe involvement is common; in some cases, the craniocaudal distribution of UIP may be relatively uniform (64, 65). Asymmetric disease may occur in up to 25% of cases (66). Several studies have demonstrated that the positive predictive value of a radiologic diagnosis of UIP on HRCT for a pathologic diagnosis of UIP is between 90% and 100% (67–71); however, a

Table 3. High-Resolution Computed Tomography Scanning Parameters

Recommended Scanning Protocol	Advantages of Updated Recommendations
1. Noncontrast examination	—
2. Volumetric acquisition with selection of: • Sub-millimetric collimation • Shortest rotation time • Highest pitch • Tube potential and tube current appropriate to patient size: ° Typically 120 kVp and 9240 mAs ° Lower tube potentials (e.g., 100 kVp) with adjustment of tube current encouraged for thin patients • Use of techniques available to avoid unnecessary radiation exposure (e.g., tube current modulation)	A. Acquisition covering the entire lung volume (vs. analysis of 10% of lung volume with sequential scanning) • No risk of missing subtle infiltrative abnormalities • Possibility of multiplanar reformations, helpful for analysis of the ILD pattern and predominant distribution of lung changes • Possibility of post-processing to optimize detection of subtle hypoattenuated lesions (minimum intensity projection) and micronodular infiltration (maximum intensity projection) • Possibility of detection of additional lesions (e.g., incidental identification of lung nodule or focal consolidation in lung fibrosis that may correspond to lung carcinoma) • Optimal to assess progression or improvement in patient's follow-up B. Dramatic increase in temporal resolution and speed of data acquisition • Motion-free images C. Availability of numerous dose-reduction tools
3. Reconstruction of thin-section CT images (91.5 mm): • Contiguous or overlapping • Using a high-spatial-frequency algorithm • Iterative reconstruction algorithm if validated on the CT unit (if not, filtered back projection)	—
4. Number of acquisitions: • Supine: inspiratory (volumetric) • Supine: expiratory (can be volumetric or sequential) • Prone: only inspiratory scans (can be sequential or volumetric); optional (*see text*) • Inspiratory scans obtained at full inspiration	A. Expiratory scans useful to detect air trapping B. Prone scans allow analysis of peripheral lung changes without dependent lung atelectasis that may be mistaken for abnormal lung infiltration or mimic disease (e.g., pseudohoneycombing when combined with paraseptal emphysema) C. Inadequate inspiration increases lung attenuation (which should not be interpreted as ground-glass attenuation) and is responsible for dependent lung atelectasis (which may mimic abnormal lung infiltration or mask subtle abnormalities)
5. Recommended radiation dose for the inspiratory volumetric acquisition: • 1–3 mSv (i.e., "reduced" dose) • Strong recommendation to avoid "ultralow-dose CT" (<1 mSv)	A. Considerable dose reduction compared to sequential scanning

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

significant minority of patients with histopathologic UIP do not fulfill HRCT criteria for UIP (68, 70–72).

Mediastinal lymphadenopathy may be present in patients with UIP (73). Ground-glass opacification may be present, but it is not a dominant feature and is usually accompanied by a superimposed reticular pattern. Rarely, small ossified nodules within areas of fibrosis may be present, and these are more common (29%) in patients with UIP when compared with other fibrotic lung diseases (74). Patients with UIP may have features of pleuroparenchymal fibroelastosis at the lung apices (75, 76); however, there is no clear cut-off of the proportions of each pattern, and these cases should be regarded as UIP/IPF, if consistent with that diagnosis after MDD. UIP may present as an acute exacerbation (Figure 6) or coexist in patients with emphysema (Figure E1).

Probable UIP pattern. In the 2011 guideline, an HRCT pattern consisting of subpleural, basal-predominant reticular abnormalities without honeycombing was assigned the HRCT diagnosis category of "possible UIP" (2). Since 2011, several studies have reported that selected patients with a "possible UIP" pattern on HRCT according

Table 4. High-Resolution Computed Tomography Scanning Patterns

UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
Subpleural and basal predominant; distribution is often heterogeneous*	Subpleural and basal predominant; distribution is often heterogeneous	Subpleural and basal predominant	Findings suggestive of another diagnosis, including: • CT features: ° Cysts ° Marked mosaic attenuation ° Predominant GGO ° Profuse micronodules ° Centrilobular nodules ° Nodules ° Consolidation • Predominant distribution: ° Peribronchovascular ° Perilymphatic ° Upper or mid-lung • Other: ° Pleural plaques (consider asbestosis) ° Dilated esophagus (consider CTD) ° Distal clavicular erosions (consider RA) ° Extensive lymph node enlargement (consider other etiologies) ° Pleural effusions, pleural thickening (consider CTD/drugs)
Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis†	Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis May have mild GGO	Subtle reticulation; may have mild GGO or distortion ("early UIP pattern") CT features and/or distribution of lung fibrosis that do not suggest any specific etiology ("truly indeterminate")	

Definition of abbreviations: CT = computed tomography; CTD = connective tissue disease; GGO = ground-glass opacities; RA = rheumatoid arthritis; UIP = usual interstitial pneumonia.
*Variants of distribution: occasionally diffuse, may be asymmetrical.
†Superimposed CT features: mild GGO, reticular pattern, pulmonary ossification.

to the 2011 guidelines are highly likely to have histopathologic UIP, despite the absence of radiologic honeycombing (77). Specifically, an HRCT pattern of possible UIP with peripheral traction bronchiectasis or bronchiolectasis in the correct clinical setting likely represents histopathologic UIP on biopsy (65, 78–80). Therefore, subpleural, basal-predominant reticular abnormalities with peripheral traction bronchiectasis or bronchiolectasis should be regarded as "probable UIP." As with a UIP pattern, ground-glass opacification may be present in probable UIP, but it is not a dominant feature. Many patients with an HRCT pattern of probable UIP will be determined to have IPF once other factors such as histopathology are considered.

Indeterminate pattern. It is now recognized that atypical HRCT features frequently (i.e., about 30%) accompany a histopathologic pattern of UIP/IPF (81). Therefore, the category "indeterminate pattern" should be assigned when HRCT demonstrates features of fibrosis but does not meet UIP or probable UIP criteria and does not explicitly suggest an alternative diagnosis. This category includes a subset of patients with very limited subpleural ground-glass opacification or reticulation without obvious CT features of fibrosis, for whom there is a suspicion that early UIP or probable UIP is present. In such cases, it should be confirmed with prone inspiratory views that the subpleural opacities do not represent dependent atelectasis (Figure E2).

Alternative diagnosis. In some cases of fibrotic lung disease, there is clinical suspicion of IPF, but the HRCT pattern suggests an alternative diagnosis. Examples include bronchocentric fibrosis in the upper lobes or profuse mosaic attenuation that suggest hypersensitivity pneumonitis, posterior fibrotic retraction of the hila in sarcoidosis, or extensive ground-glass opacification with subpleural sparing in fibrotic nonspecific interstitial pneumonia (NSIP). Occasionally, the HRCT presentation may be that of a UIP, probable UIP, or indeterminate pattern, but ancillary findings suggest an alternative diagnosis. In such situations, an alternative diagnosis to IPF should be reconsidered.

CT findings in the presence of an acute exacerbation. Patients with an acute exacerbation of IPF have bilateral ground-glass opacification with or without consolidation on a background of lung fibrosis (Figure 6). In the absence of a previous HRCT study, bilateral ground-glass opacity and/or consolidation on a background of a UIP pattern is highly suggestive of an acute exacerbation and can be used to confirm an underlying IPF diagnosis in the appropriate clinical context.

SLB Technique

Video-assisted thoracoscopic surgery is the preferred approach to SLB for patients who can tolerate single-lung ventilation, rather than open thoracotomy. In patients with severe physiologic impairment or substantial comorbidity, the risks of SLB may outweigh

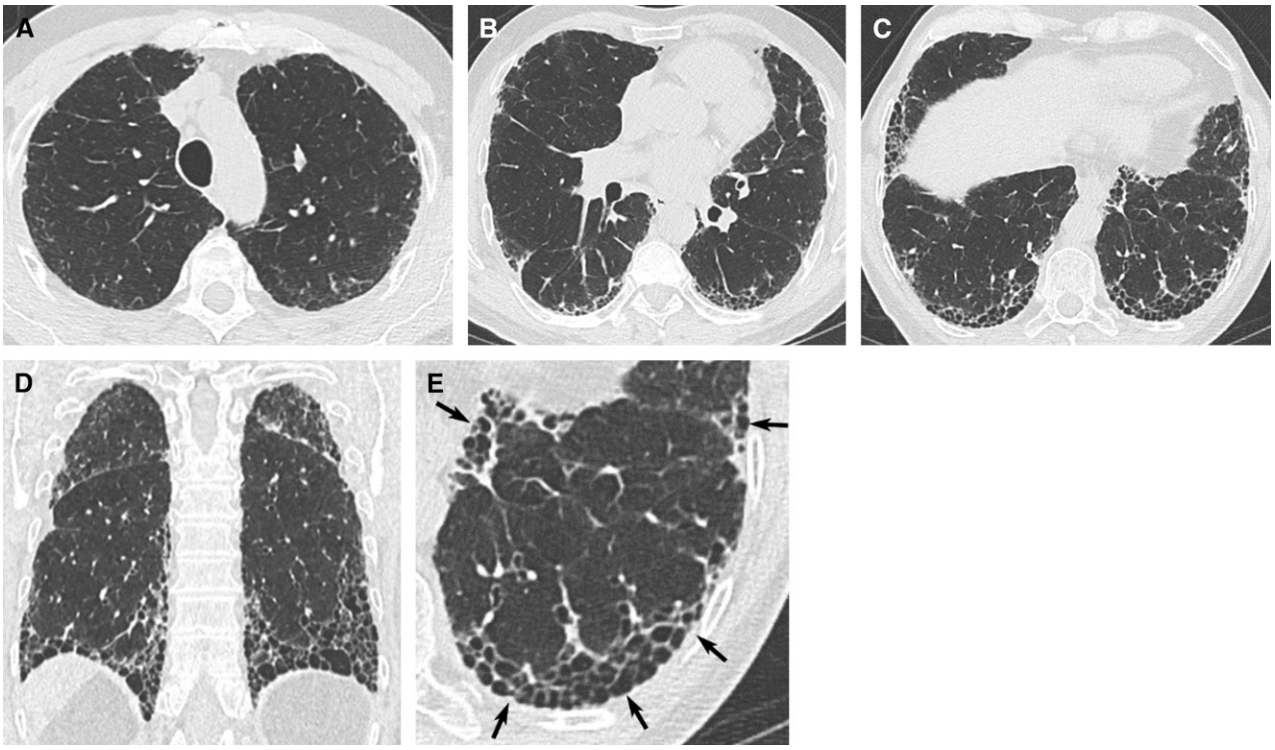

Figure 1. High-resolution computed tomography (CT) images demonstrating a usual interstitial pneumonia pattern. (*A–C*) Transverse CT section and (*D*) coronal reconstruction illustrating the presence of honeycombing with subpleural and basal predominance. Note the concurrent presence of mild ground-glass opacity. (*E*) Magnified view of the left lower lobe showing typical characteristics of honeycombing, consisting of clustered cystic airspaces with well-defined walls and variable diameters, seen in single or multiple layers (arrows).

the benefits of establishing a secure diagnosis of IPF; therefore, the final decision regarding whether or not to pursue a biopsy must be tailored to the clinical situation of the individual patient. Multiple biopsies should be obtained from two to three lobes, because the histologic patterns on SLB specimens obtained from different segments can be discordant (e.g., coexisting UIP pattern and fibrotic NSIP pattern from different lobes).

Methods for processing SLBs are variable and require careful handling of samples to avoid iatrogenic mechanical atelectasis and use of inflation techniques to preserve normal lung architecture. Special stains may be used in some patients, including iron stains to identify asbestos bodies in patients with incriminating exposure histories and elastic tissue stains for patients in whom vascular abnormalities differ from the secondary changes common in the UIP pattern. Connective tissue stains may also have value in distinguishing patterns of fibrosis but are of limited incremental value compared with biopsies processed with high-quality routine staining techniques like hematoxylin and eosin.

Histopathology Features of the UIP Pattern

The histopathologic hallmark and chief diagnostic criterion of UIP is a low magnification appearance of patchy dense fibrosis that *1*) is causing remodeling of lung architecture, *2*) often results in honeycomb change, and *3*) alternates with areas of less-affected parenchyma (Figure 7). These histopathologic changes typically affect the subpleural and paraseptal parenchyma most severely. Inflammation is usually mild and consists of a patchy interstitial infiltrate of lymphocytes and plasma cells associated with hyperplasia of type 2 pneumocytes and bronchiolar epithelium. The fibrotic zones are composed mainly of dense collagen, although scattered convex subepithelial foci of proliferating fibroblasts and myofibroblasts (so-called fibroblast foci) are a consistent finding. Microscopic honeycombing is characterized by cystic fibrotic airspaces that are frequently lined by bronchiolar epithelium and filled with mucus and inflammatory cells. Smooth muscle metaplasia in the interstitium is commonly seen in areas of fibrosis and honeycombing. A definitive pathologic diagnosis of the UIP pattern can be made when all of the above features are present, particularly when honeycombing is present. However, even in the absence of honeycombing, a definite diagnosis of a UIP pattern can still be made if all of the other typical features are present.

Key histologic features can be helpful in excluding alternate diagnoses, such as hypersensitivity pneumonitis (e.g., bronchiolocentric distribution with lymphocyte-rich bronchiolitis, extensive peribronchiolar metaplasia, poorly formed nonnecrotizing granulomas in peribronchiolar interstitium), acute exacerbation of IPF or acute interstitial pneumonia (i.e., hyaline membranes), cicatricial variants of cryptogenic organizing pneumonia with fibrosis (prominent organizing pneumonia), pneumoconiosis (e.g., asbestos bodies, prominent dust macules and/or silicotic nodules), sarcoidosis (prominent well-formed nonnecrotizing granulomas in a lymphatic distribution), smoking-related interstitial fibrosis (extensive respiratory bronchiolitis and exquisitely subpleural and/or peribronchiolar paucicellular densely

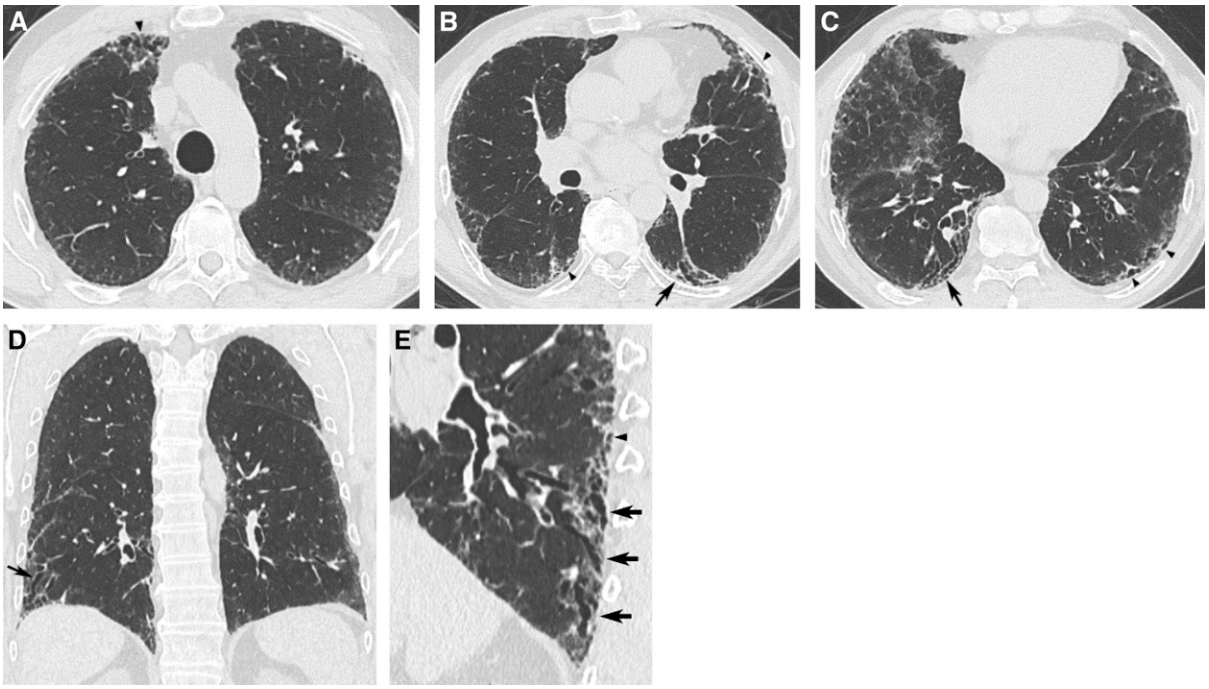

Figure 2. Probable usual interstitial pneumonia (UIP) pattern. (*A–C*) Transverse computed tomography (CT) section, (*D*) coronal reconstruction of both lungs, and (*E*) magnified sagittal view of the right lower lobe illustrating the presence of a reticular pattern with peripheral bronchiolectasis with subpleural and basal predominance. Depending on their orientation relative to the plane of the CT section, peripheral traction bronchiolectasis appear as tubular (arrows) or cystic (arrowheads) structures. Note the concurrent presence of mild ground-glass opacities in the subpleural areas of both lungs and the absence of honeycombing. UIP was proven at histology.

eosinophilic collagen without architectural distortion), and pleuroparenchymal fibroelastosis (prominent subpleural intraalveolar fibrosis and elastosis and visceral pleura fibrosis most marked in the upper lobes). The specificity of these findings is variable and ranges from only suggesting alternatives that will be resolved by correlation with other clinical, laboratory, and radiological findings in MDD, to others that establish an alternative diagnosis with greater certainty.

Histopathology Patterns

We recommend categorizing histopathologic findings of biopsies into "UIP," "probable UIP," "indeterminate for UIP," and "alternative diagnosis" (Table 5). Advantages of this approach are that this terminology is consistent with imaging categories (although the specificity of the "alternative diagnosis" categories differs) and it allows us to discuss the patterns in the context of other clinical data during an MDD. This facilitates making the most appropriate overall diagnosis for the patient, regardless of whether the diagnosis is IPF or not IPF. Biopsies designated as indeterminate for UIP demonstrate a pattern of fibrosis that does not meet criteria for UIP or any other histopathologic pattern of fibrotic interstitial pneumonia and, in some cases, may favor an alternative diagnosis while not categorically excluding the possibility of sampling bias in a patient who ultimately proves to have UIP. A subset of patients with previously occult IPF may present with an acute exacerbation, which is commonly characterized by a combination of a UIP pattern complicated by superimposed diffuse alveolar damage with or without associated hyaline membranes.

Diagnostic Criteria for IPF

Diagnosis of IPF requires the following:

1. Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, CTD, drug toxicity), and either #2 or #3:
2. The presence of the HRCT pattern of UIP (Table 4)
3. Specific combinations (Figure 8) of HRCT patterns (Table 4) and histopathology patterns (Table 5) in patients subjected to lung tissue sampling

The guideline panel's approach to diagnosis is summarized in Figures 8 and 9. It is based on these 2018 guidelines and the 2011 guidelines (2) and similar to that suggested by a task force sponsored by the Fleischner Society (82).

Patients with suspected IPF as described above are initially evaluated for identifiable causes of ILD, such as domestic and occupational environmental exposures, CTD, or drug toxicity. If a potential cause for ILD is identified, the patient undergoes a thorough evaluation to confirm or exclude hypersensitivity pneumonitis, CTD, pneumoconiosis, and iatrogenic causes (e.g., drug toxicity, radiation). If a specific diagnosis is not made or no potential cause for ILD is identified, then clinical findings and HRCT are considered during MDD to either ascertain or exclude the diagnosis of IPF (Figure 9) (83). IPF is diagnosed if the appropriate combination of HRCT patterns and histopathological patterns are present.

Diagnostic Interventions

The questions below are specifically intended for patients who are "clinically suspected of having IPF." This classically refers to patients with unexplained

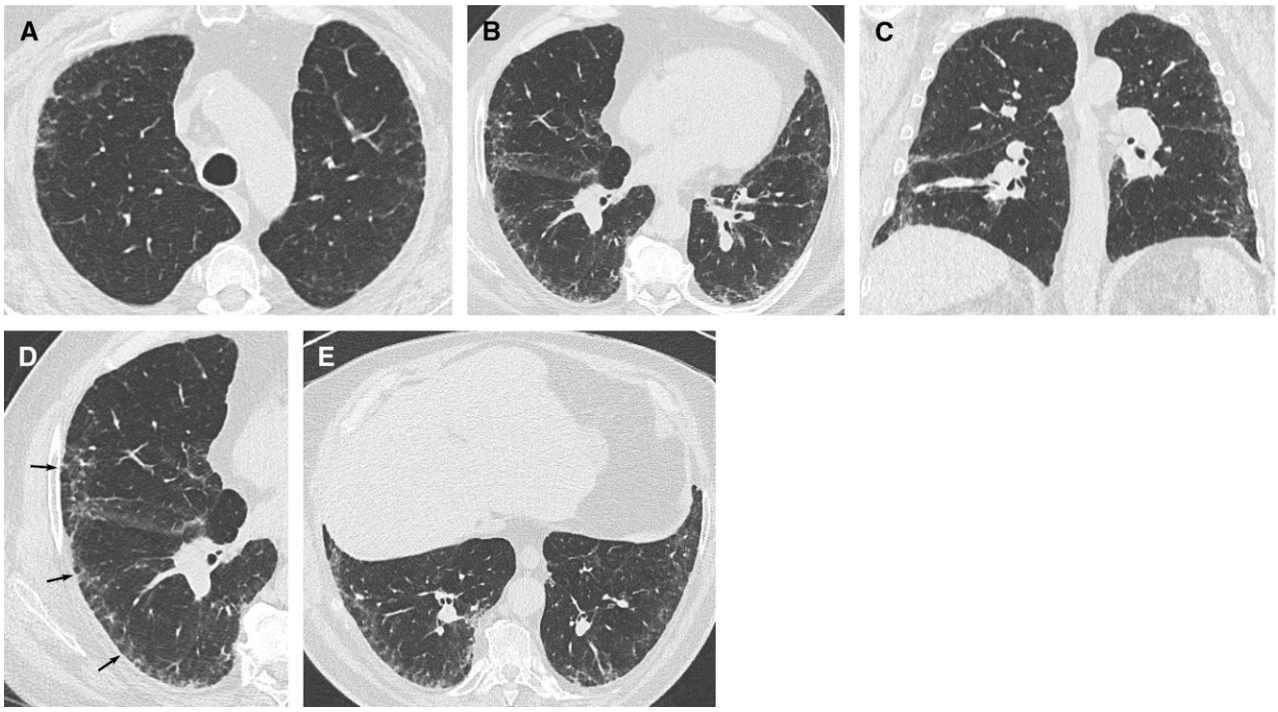

Figure 3. Indeterminate pattern (early usual interstitial pneumonia [UIP] pattern). (*A* and *B*) Transverse computed tomography (CT) section, (*C*) coronal reconstruction of both lungs, and (*D*) magnified view of the right lung in supine position showing ground-glass opacity and subtle reticulation in the subpleural areas (arrows) with a basal predominance. (*E*) Transverse CT section of the lower lung zones in prone position showing persistence of lung infiltration in nondependent areas, thus excluding gravitational abnormalities. UIP was proven at histology.

symptomatic or asymptomatic bilateral pulmonary fibrosis on a chest radiograph or chest CT scan, bibasilar inspiratory crackles, and an age typically older than 60 years. It must be recognized that the questions addressed are not restricted to patients older than 60 years, as middle-aged adults (>40 yr and <60 yr), especially patients with risks for familial pulmonary fibrosis, can rarely present with the otherwise same clinical scenario as the typical patient older than 60 years. The recommendations in this guideline are for the patterns and distributions of images obtained by HRCT and, thus, require that patients be subjected to HRCT of the chest for evaluation.

Question 1: Should Patients with Newly Detected ILD of Unknown Cause Who Are Clinically Suspected of Having IPF Undergo a Detailed, Prompted History of Medication Use and Environmental Exposures at Home, Work, and Other Places the Patient Frequently Visits to Exclude Potential Causes of the ILD?

Discussion. The guideline panel recognized there is no reasonable alternative to the proposed course of action, so a motherhood statement was made to take a detailed history of medication use and environmental exposures at home, work, and other places that the patient frequently visits, to identify or exclude potential causes of ILD (e.g., hypersensitivity pneumonitis, pneumoconiosis, drug toxicity). This is supported by an observational study that enrolled 1,084 patients with new-onset ILD of unknown cause reporting that 47% of the patients were identified as having hypersensitivity pneumonitis on detailed assessment, suggesting that a cause can be found in many patients who present with ILD (84). The panel's clinical experience is that identification and removal of potential causative environmental factors may result in improved clinical outcomes.

Many panelists use published questionnaires in their clinical practices to consider environmental exposures at home, work, and frequently visited places (84–86). Such questionnaires may be tailored to cultural habits and geographical differences. Examples of pertinent exposures include mold, birds, down feathers, animals, metal dusts (e.g., brass, lead, steel), wood dust (e.g., pine), vegetable dust, exposure to livestock, stone polishing and cutting, medications taken, current or recent occupations (e.g., hair dressing), and current or recent hobbies (27, 87–92). Although some panelists use the presence of antibody in serum against specific antigen to prompt further evaluation for hypersensitivity pneumonitis, the test is not standardized and the specificity and sensitivity for the diagnosis of hypersensitivity pneumonitis is unknown. The panelists who use serum antibody testing believe that such tests may identify an antigen that was not suspected by clinical history and, therefore, may prompt further investigations for the suspected etiology; also, if serum antibody testing is negative, the results reinforce the conclusion that the patient does not have hypersensitivity pneumonitis.

ATS/ERS/JRS/ALAT recommendation.

- **For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF, we recommend taking a detailed history of both medication use and environmental exposures at home, work, and other places the patient frequently visits to exclude potential causes of the ILD** (*motherhood statement*).

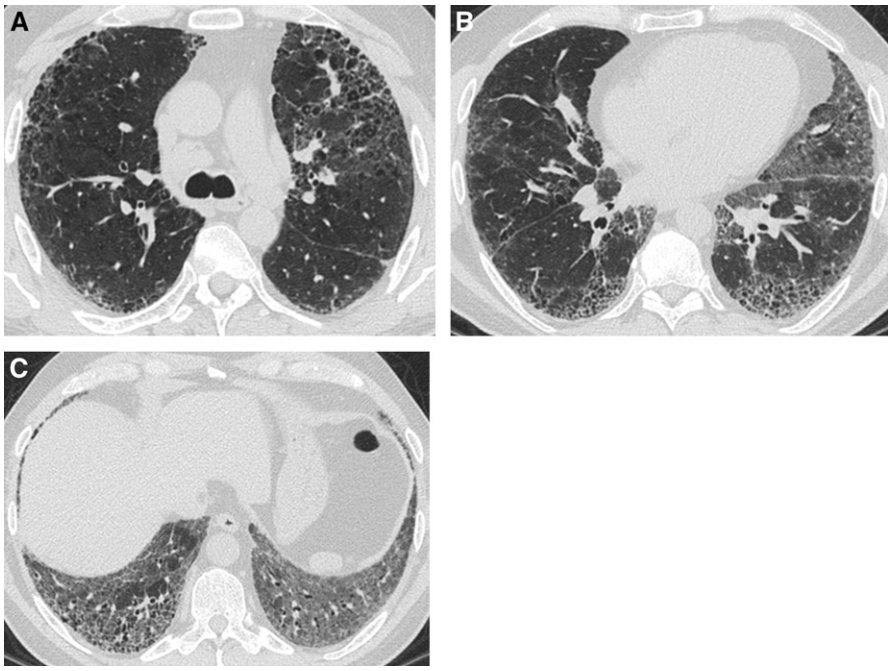

Figure 4. Indeterminate pattern. (*A–C*) Transverse computed tomography sections showing extensive lung infiltration combining honeycombing, mild to marked ground-glass opacity, asymmetrical distribution between both lungs, and no subpleural predominance.

Question 2: Should Patients with Newly Detected ILD of Unknown Cause Who Are Clinically Suspected of Having IPF Undergo Serological Testing to Exclude CTDs as Potential Causes of the ILD?

Discussion. Diagnosis of IPF mandates exclusion of other causes of ILD, including CTD-ILD (Table E2). The guideline panel concluded that foregoing serological testing was not a reasonable alternative. Therefore, a motherhood statement was made to perform routine serological testing in all patients with newly identified ILD. Although there was overwhelming agreement to perform serological testing, there was far less agreement about which serological tests to perform.

The majority of panelists acknowledged routinely testing for CRP (C-reactive protein), erythrocyte sedimentation rate, antinuclear antibodies (by immunofluorescence), rheumatoid factor, myositis panel, and anti–cyclic citrullinated peptide. Other detailed tests are performed on a case-by-case basis according to associated symptoms and signs. If myositis is suspected, additional tests include: creatinine phosphokinase, myoglobin, aldolase, antisynthetase antibodies (Jo-1 and others if available), anti–MDA5 (melanoma differentiation-associated protein 5), anti–Mi-2, anti-NXP2 (nuclear matrix protein 2), anti–TIF1-γ (transcriptional intermediary factor 1-γ), anti-SRP (signal recognition particle), anti-HMGCR (3-hydroxy-3-methylglutaryl-CoA reductase), anti-SAE (small ubiquitin-related modifier–activating enzyme), anti-U1RNP (U1 ribonucleoprotein), anti-PM/Scl75 (polymyositis/scleroderma 75), anti-PM/Scl100, and anti-Ku (93). If systemic sclerosis (i.e., scleroderma) is suspected, additional tests include: anti–Scl-70/topoisomerase-1, anti-centromere, anti-RNA polymerase III, anti-U1RNP, anti-Th/To, anti-PMScl, U3 RNP (fibrillarin), and anti-Ku. If Sjögren syndrome is suspected, additional tests include: anti-SSA/Ro (Sjögren-specific antibody A) and anti-SSB/La. If vasculitis is suspected, an additional test includes anti-cytoplasmic antibodies. A small minority of the panelists include all of the detailed tests listed above as an "ILD panel" at initial screening/baseline evaluation.

The guideline panelists do not refer all patients with new ILD to a rheumatologist; rather, referring only those with positive clinical manifestations, serologies, or other characteristics atypical for IPF (e.g., female, age <60 yr). In many CTD-ILDs, the lung disease is the first, dominant, or only feature of the CTD and, therefore, some patients will not fit standard rheumatologic diagnostic criteria at presentation. The term "interstitial pneumonia with autoimmune features" has been suggested to describe such patients; however, this is a research definition that requires validation (94).

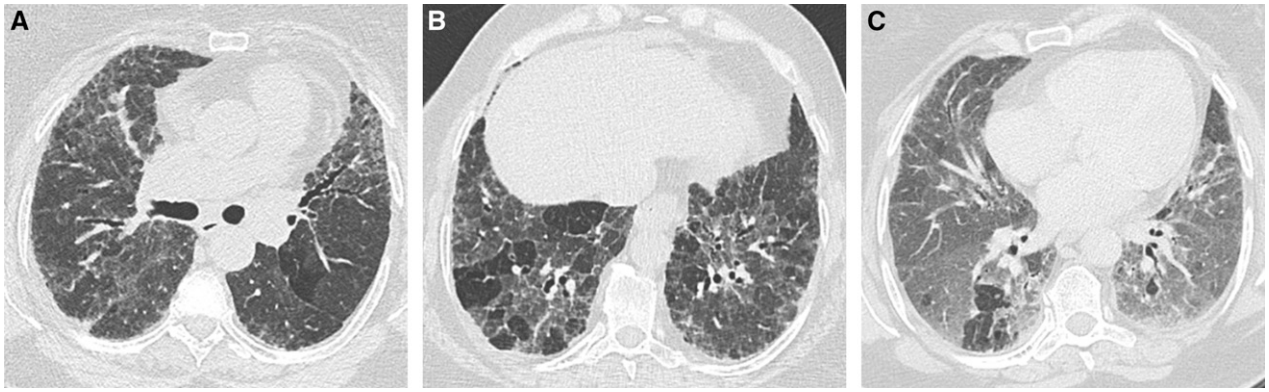

Figure 5. Computed tomography (CT) pattern suggestive of an alternative diagnosis for lung fibrosis. (*A* and *B*) Transverse CT sections obtained at deep inspiration showing disseminated lung infiltration, sparing some secondary pulmonary lobules in lung bases. (*C*) Transverse CT section obtained at expiration confirming lobular air trapping, all findings being highly suggestive of chronic hypersensitivity pneumonitis.

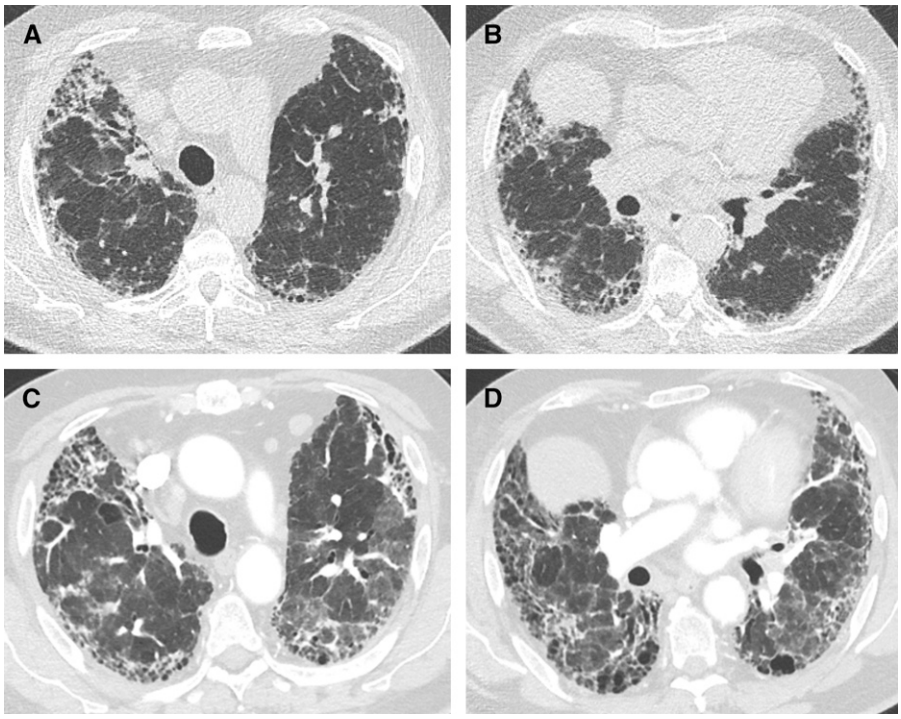

Figure 6. Acute exacerbation of idiopathic pulmonary fibrosis. (*A* and *B*) Transverse computed tomography sections obtained in the upper and mid lung zones and (*C* and *D*) during acute exacerbation showing newly developed, bilateral ground-glass opacification in both lungs on a background of usual interstitial pneumonia pattern.

ATS/ERS/JRS/ALAT recommendation.

- **For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF, we recommend serological testing to aid in the exclusion of CTDs as a potential cause of the ILD** (*motherhood statement*).

Question 3: Should Patients with Newly Detected ILD of Unknown Cause Who Are Clinically Suspected of Having IPF Undergo Cellular Analysis of Their BAL Fluid?

Evidence base. Our systematic literature search yielded 2,492 titles but did not identify any studies that *1*) compared clinical outcomes among patients who underwent BAL cellular analysis to those who did not undergo BAL cellular analysis, or *2*) reported the test characteristics of BAL cellular analysis for distinguishing IPF from other ILDs. Therefore, we sought studies that compared BAL cell type proportions across different ILDs. The full text of 14 articles was reviewed, and eight were selected for analysis (95–102) (Table E7a).

Studies enrolled patients with IPF, performed BAL, and measured components of the BAL fluid including the percentage of neutrophils (95–100, 102), macrophages (95–99, 102), lymphocytes (95–102), and eosinophils (95, 97–100, 102), as well as the CD4/CD8 ratio (95, 97, 99, 100). The measurements were then compared with those from patients with other types of ILD, including hypersensitivity pneumonitis (95, 96, 100), sarcoidosis (95, 99, 100), idiopathic NSIP (95, 97, 100–102), cryptogenic organizing pneumonia (COP, previously called bronchiolitis obliterans organizing pneumonia) (95–97, 100), eosinophilic pneumonia (95), respiratory bronchiolitis-associated ILD (RB-ILD) (96), and lymphocytic interstitial pneumonia (LIP) (96). Most studies reported mean cell type proportions, but some reported medians. Because the question was about using BAL to distinguish IPF from other types of ILD, we compared cell type measurements among patients with IPF to those among patients with other types of ILD using the mean difference (MD):

- *Neutrophil proportion*: Healthy individuals have ⩽3% neutrophils in their BAL fluid (23). Patients with IPF had a mean neutrophil percentage in their BAL that ranged from 5.9% to 22.08%, which was higher than patients with hypersensitivity pneumonitis (MD, +4.84%; 95% confidence interval [CI], +1.70% to +7.98%), cellular NSIP (MD, +3.40%; 95% CI, +0.33% to +6.47%), eosinophilic pneumonia (MD, +16.79%; 95% CI, +1.96% to +31.62%), RB-ILD (MD, +11.80%; 95% CI, +9.04% to +14.56%), and LIP (MD, +7.40%; 95% CI, +3.30% to +11.50%) (Table E7b). No differences were found when patients with IPF were compared with patients with fibrotic NSIP, COP, or sarcoidosis.
- *Macrophage proportion*: Healthy individuals have >85% alveolar macrophages in their BAL fluid (23). Patients with IPF had a mean alveolar macrophage percentage in their BAL that ranged from 49.18% to 83%, which was higher than patients with NSIP (MD, +23.07%; 95% CI, +7.55% to +38.59%), eosinophilic pneumonia (MD, +26.05%; 95% CI, +8.32% to +43.78%), and LIP (MD, +36.60%; 95% CI, +29.82% to +43.38%) (Table E7c). They had a lower percentage of macrophages in their BAL than patients with RB-ILD (MD, −15.50%; 95% CI, −19.06% to −11.94%). No differences were found when patients with IPF were compared with patients with hypersensitivity pneumonitis, COP, or sarcoidosis.
- *Eosinophil proportion*: Healthy individuals have ⩽1% eosinophils in their BAL fluid (23). Patients with IPF had a mean eosinophil percentage in their BAL that ranged from 2.39% to 7.5%, which was lower than patients with eosinophilic pneumonia (MD, −48.94%; 95% CI, −62.58% to −35.30%) (Table E7d). No differences were found when patients with IPF were compared with patients with NSIP, hypersensitivity pneumonitis, COP, sarcoidosis, RB-ILD, or LIP.
- *Lymphocyte proportion*: Healthy individuals have 10% to 15% lymphocytes in their BAL fluid (23). Patients with IPF had a mean lymphocyte percentage in their BAL fluid that ranged from 7.2% to 26.7%, which was lower than patients with NSIP (MD, −26.00%; 95% CI, −33.62% to −18.38%), sarcoidosis (MD, −14.87%; 95% CI, −25.09% to −4.65%), COP (MD, −31.43%; 95% CI, −38.78% to −24.08%), and LIP (MD, −43.20%; 95%

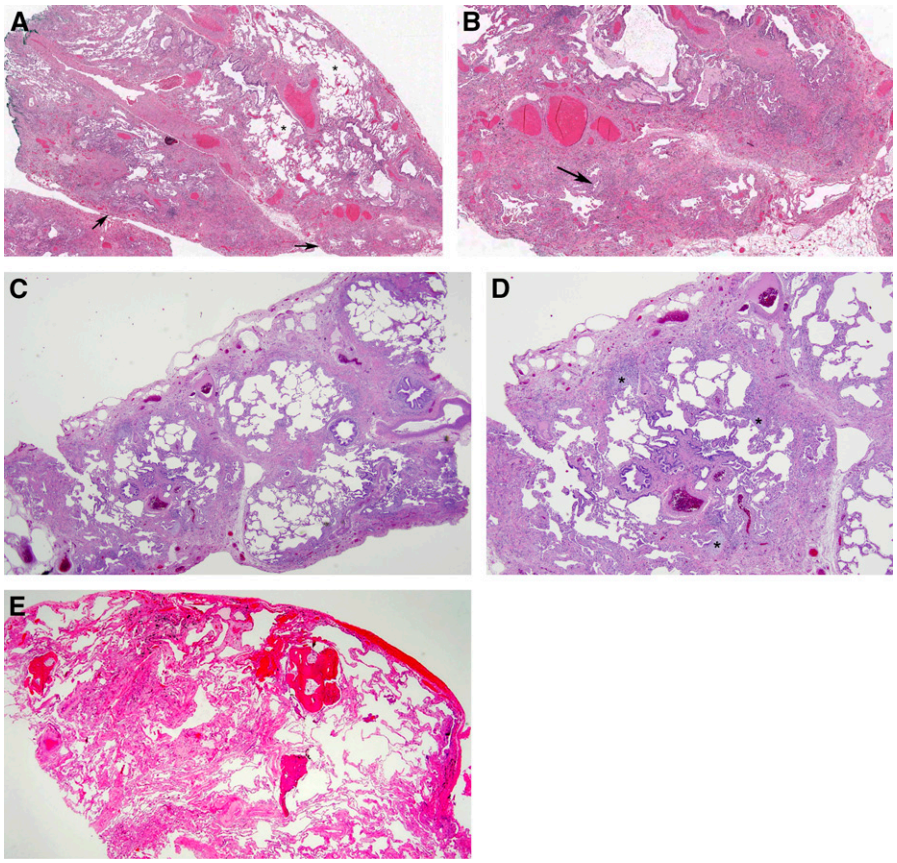

Figure 7. Histopathology demonstrating usual interstitial pneumonia (UIP). (*A*) Low-magnification photomicrograph showing classical UIP/idiopathic pulmonary fibrosis (IPF) pattern characterized by dense fibrosis with a predilection for subpleural and paraseptal parenchyma with associated architectural distortion in the form of microscopic honeycomb change (arrow) juxtaposed with relatively unaffected lung parenchyma (*). Visceral pleura is seen in the upper portion of the figure. (*B*) Higher-magnification photomicrograph showing subpleural scarring and honeycomb change with associated fibroblast foci (arrow). (*C*) Low-magnification photomicrograph showing probable UIP/IPF pattern characterized by subpleural and paraseptal predominant patchwork fibrosis that is less well developed and lacks the degree of associated architectural distortion in the form of either destructive scarring or honeycomb change illustrated in *A* and *B*. (*D*) Higher-magnification photomicrograph showing patchy fibrosis and fibroblast foci (*) but without the extent of scarring and honeycomb change illustrated in *A* and *B*. (*E*) Indeterminate for UIP/IPF pattern in which there is mild nonspecific fibrosis that lacks a well-developed patchy and predominantly subpleural/paraseptal distribution, architectural distortion, and fibroblast foci characteristic of classical UIP/IPF. There is associated osseous metaplasia, a common but nonspecific finding in UIP. Although these findings are not diagnostic, they do not preclude a diagnosis of UIP/IPF in a patient with supportive clinical and radiological findings.

CI, −48.83% to −37.57%) (Table E7e). They had a higher percentage of lymphocytes in their BAL than patients with RB-ILD (MD, +3.30%; 95% CI, +1.04% to +5.56%). No differences were found when patients with IPF were compared with patients with hypersensitivity pneumonitis or eosinophilic pneumonia.

- *CD4/CD8 ratio*: Healthy individuals have a CD4/CD8 ratio of 0.9 to 2.5 in their BAL fluid (23). Patients with IPF had a mean CD4/CD8 ratio of 1.4 to 7.2. Patients with IPF had a lower CD4/CD8 ratio in their BAL than patients with sarcoidosis (MD, −5.49; 95% CI, −8.45 to −2.53) and a higher ratio than patients with NSIP (MD, +0.95; 95% CI, +0.43 to +1.47) (Table E7f). No differences were found when patients with IPF were compared with patients with hypersensitivity pneumonitis, COP, eosinophilic pneumonia, Rb-ILD, or LIP.

The guideline panel had very low confidence in the estimated differences in the BAL fluid cellular composition of patients with IPF compared with patients with other ILDs. Its confidence was particularly diminished by the small number of studies and patients per study, as well as the wide range of proportions for each cell type across studies. In addition, the evidence was indirect (the question is about patients with ILD of unknown cause, but the patients studied all had confirmed causes of ILD), and there was a risk of selection bias due to lack of consecutive enrollment and detection bias due to measurements being performed in different laboratories and samples being obtained from different bronchopulmonary segments. The panel noted that many of the statistically significant differences were small and probably not clinically important.

Putting the evidence together. Some BAL cell type proportions were markedly (>10%) different in patients with IPF compared with patients with other ILDs (Figure E3). Patients with IPF had a slightly increased proportion of eosinophils compared with healthy patients but a markedly lower proportion of eosinophils than patients with eosinophilic pneumonia; thus, patients with a markedly elevated eosinophil count are more likely to have eosinophilic pneumonia than IPF. Patients with IPF had a similar to slightly higher proportion of lymphocytes and CD4/CD8 ratio in their BAL than healthy patients but a markedly lower proportion of lymphocytes and CD4/CD8 ratio in their BAL than patients with sarcoidosis; thus, patients with a markedly elevated proportion of lymphocytes and CD4/CD8 ratio are more likely to have sarcoidosis than IPF.

Desirable consequences. Cellular analysis of the BAL fluid may help distinguish IPF from some alternative ILDs, most notably eosinophilic pneumonia and sarcoidosis.

Undesirable consequences. Although none of the studies reported any complication from the BAL procedure, bronchoscopy is an invasive procedure that requires time and effort, has some risk of complications, and is uncomfortable to some patients.

Conclusions. Despite having very low confidence in the estimated effects described above, the panel believed that some of the differences were large enough that they were likely true, and those differences were consistent with the panel's collective clinical experience managing thousands of such patients. When the panel weighed the desirable consequences of BAL cellular analysis in patients who

Table 5. Histopathology Patterns and Features

UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
• Dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing) • Predominant subpleural and/or paraseptal distribution of fibrosis • Patchy involvement of lung parenchyma by fibrosis • Fibroblast foci • Absence of features to suggest an alternate diagnosis	• Some histologic features from column 1 are present but to an extent that precludes a definite diagnosis of UIP/IPF *And* • Absence of features to suggest an alternative diagnosis *Or* • Honeycombing only	• Fibrosis with or without architectural distortion, with features favoring either a pattern other than UIP or features favoring UIP secondary to another cause* • Some histologic features from column 1, but with other features suggesting an alternative diagnosis†	• Features of other histologic patterns of IIPs (e.g., absence of fibroblast foci or loose fibrosis) in all biopsies • Histologic findings indicative of other diseases (e.g., hypersensitivity pneumonitis, Langerhans cell histiocytosis, sarcoidosis, LAM)

Definition of abbreviations: IIP = idiopathic interstitial pneumonia; IPF = idiopathic pulmonary fibrosis; LAM = lymphangioleiomyomatosis; UIP = usual interstitial pneumonia.
*Granulomas, hyaline membranes (other than when associated with acute exacerbation of IPF, which may be the presenting manifestation in some patients), prominent airway-centered changes, areas of interstitial inflammation lacking associated fibrosis, marked chronic fibrous pleuritis, organizing pneumonia. Such features may not be overt or easily seen to the untrained eye and often need to be specifically sought.
†Features that should raise concerns about the likelihood of an alternative diagnosis include a cellular inflammatory infiltrate away from areas of honeycombing, prominent lymphoid hyperplasia including secondary germinal centers, and a distinctly bronchiolocentric distribution that could include extensive peribronchiolar metaplasia.

have an HRCT pattern of probable UIP, indeterminate, or an alternative diagnosis (i.e., identifying or excluding eosinophilic pneumonia, sarcoidosis, infection, and malignancy) versus the undesirable consequences (i.e., risk of a complication, burden, cost), the majority of the panel concluded that the upsides of the procedure outweigh the downsides in such patients. There were some strong dissenting opinions, but there was general agreement that BAL is appropriate when the radiologic differential diagnosis includes eosinophilic pneumonia, sarcoidosis, or infection. In contrast, the panel concluded that alternative diagnoses that can be excluded by BAL cellular analysis are sufficiently rare in patients who have an HRCT pattern of UIP that the downsides of the procedure typically outweigh the upsides in these patients.

ATS/ERS/JRS/ALAT recommendations.

- **For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF and have an HRCT pattern of probable UIP, indeterminate, or an alternative diagnosis, we suggest cellular analysis of their BAL fluid** (*conditional recommendation, very low quality of evidence*). *Remarks*: strong for, 1 vote; conditional for, 19 votes; conditional against, 4 votes; strong against, 0 votes. Agreement among the panelists was greatest for situations in which the differential diagnosis for the HRCT pattern includes eosinophilic pneumonia, COP, sarcoidosis, or infection.
- **For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF and have an HRCT pattern of UIP, we suggest NOT performing cellular analysis of their BAL fluid** (*conditional recommendation, very low quality of evidence*). *Remarks*: strong for, 0 votes; conditional for, 3 votes; conditional against, 20 votes; strong against, 1 vote.

Question 4: For Patients with Newly Detected ILD of Unknown Cause Who Are Clinically Suspected of Having IPF, Should SLB Be Performed to Ascertain the Histopathology Diagnosis of UIP Pattern?

Evidence base. Our systematic literature search yielded 945 titles but identified no studies that compared clinical outcomes among patients who underwent SLB to those who did not. Thus, we selected studies that measured diagnostic yield of SLB using an MDD as the diagnostic decision-maker. The full text of 54 articles was reviewed, and 26 were selected for analysis (103–128) (Table E8). All studies enrolled patients with ILD of unknown cause and did not exclude those with an HRCT pattern of UIP.

Pooling studies (unweighted) indicated that SLB obtained an adequate sample in all patients (11 studies; 918 of 918, 100%; 95% CI, 99–100%), although the panel acknowledged that this is not always the case in clinical practice. The proportion of SLB that resulted in a specific diagnosis (i.e., the diagnostic yield) was high (26 studies; 2,338 of 2,651, 88.2%; 95% CI, 86.9–89.4%), with a minority being deemed unclassifiable (26 studies; 313 of 2,651, 11.8%; 95% CI, 10.6–13.1%). Among final diagnoses, approximately one-third were IPF (24 studies; 752 of 2,360, 31.9%; 95% CI, 30.0–33.8%), and many others were potentially treatable etiologies like infection, sarcoidosis, hypersensitivity pneumonitis, eosinophilic pneumonia, lymphangioleiomyomatosis, COP, and vasculitis.

Overall mortality was low (23 studies; 79 of 2,268, 3.5%; 95% CI, 2.8–4.3%), but some of the deaths were probably disease related, because procedure-related mortality was lower (6 studies; 7 of 410, 1.7%; 95% CI, 0.8–3.5%). Many series reported no mortality, suggesting that lower procedural mortality is possible depending on center-specific variables such as patient selection. Additional complications included exacerbations (15 studies; 116 of 1,891, 6.1%; 95% CI, 5.1–7.3%), bleeding (7 studies; 6 of 756, 0.8%; 95% CI, 0.4–1.7%), severe bleeding (4 studies; 1 of 461, 0.2%; 95% CI, 0.04–1.2%), prolonged air leak (13 studies; 90 of 1,527, 5.9%; 95% CI, 4.8–7.2%), respiratory infection (9 studies; 32 of 496, 6.5%; 95% CI, 4.6–9.0%), neuropathic pain (1 study; 3 of 66, 4.5%; 95% CI, 1.6–12.5%),

IPF suspected*		Histopathology pattern			
		UIP	Probable UIP	Indeterminate for UIP	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Probable UIP	IPF	IPF	IPF (Likely)**	Non-IPF dx
	Indeterminate	IPF	IPF (Likely)**	Indeterminate***	Non-IPF dx
	Alternative diagnosis	IPF (Likely)** /non-IPF dx	Non-IPF dx	Non-IPF dx	Non-IPF dx

Figure 8. Idiopathic pulmonary fibrosis diagnosis based upon HRCT and biopsy patterns.
*"Clinically suspected of having IPF" = unexplained symptomatic or asymptomatic patterns of bilateral pulmonary fibrosis on a chest radiograph or chest computed tomography, bibasilar inspiratory crackles, and age greater than 60 years. (Middle-aged adults [>40 yr and <60 yr], especially patients with risks for familial pulmonary fibrosis, can rarely present with the otherwise same clinical scenario as the typical patient older than 60 years.)
**IPF is the likely diagnosis when any of the following features are present:

- Moderate-to-severe traction bronchiectasis/bronchiolectasis (defined as mild traction bronchiectasis/bronchiolectasis in four or more lobes including the lingual as a lobe, or moderate to severe traction bronchiectasis in two or more lobes) in a man over age 50 years or in a woman over age 60 years
- Extensive (>30%) reticulation on HRCT and an age >70 years
- Increased neutrophils and/or absence of lymphocytosis in BAL fluid
- Multidisciplinary discussion reaches a confident diagnosis of IPF.

***Indeterminate

- Without an adequate biopsy is unlikely to be IPF
- With an adequate biopsy may be reclassified to a more specific diagnosis after multidisciplinary discussion and/or additional consultation.

dx = diagnosis; HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis; UIP = usual interstitial pneumonia.

and delayed wound healing (4 studies; 14 of 430, 3.3%; 95% CI, 2.0–5.4%).

The guideline panel had very low confidence in the estimated effects of SLB on patient-important outcomes because of the study designs, inconsistent magnitudes of effect, and risk of selection bias due to lack of consecutive enrollment.

Putting the evidence together. Treatment of IPF was estimated in a prior iteration of this guideline to reduce 1-year mortality from roughly 8% to 5.5% and to increase the likelihood of slowed disease progression from 60.1% to 68% (129). These estimates, combined with those described above, suggest that for every 1,000 SLBs that are performed, 1,000 adequate specimens will be obtained, 882 specific diagnoses will be made, and 319 patients will be determined to have IPF. Assuming that all receive therapy, then for every 1,000 patients who undergo SLB, 1-year mortality will be reduced from 26 to 18 patients, and disease progression will be slowed in 217 patients instead of 192 patients. In addition, many patients will be determined to have an alternative cause of ILD that is potentially treatable. However, 17 patients will die as a result of the procedure, 61 patients will experience a perioperative exacerbation, and 65 patients will acquire a perioperative respiratory infection.

Desirable consequences. SLB obtains adequate specimens from 100% (95% CI, 99–100%) of patients, from which a definitive diagnosis can be made in 89% (95% CI, 88–90%). Potentially effective therapies exist for the roughly 30% of patients who will be diagnosed with IPF, as well as for many of the patients who will be determined to have an alternative diagnosis.

Undesirable consequences. SLB has potential complications, the most important of which is procedural mortality (1.7%; 95% CI, 0.8–3.5%) and the most common of which is respiratory infection (6.5%; 95% CI, 4.6–9.0%). Others include exacerbations, bleeding, prolonged air leak, neuropathic pain, and delayed wound healing, the most common of which occur in 6% of patients.

Conclusions. When the desirable consequences were weighed against the undesirable consequences, the guideline panel concluded that the upsides of SLB outweigh the downsides for most patients with newly detected ILD of uncertain etiology whose HRCT pattern is probable UIP, indeterminate, or an alternative diagnosis. The conclusion was strengthened by the panel's opinion that making a diagnosis provides additional unquantified benefits, such as more accurate estimates of prognosis, cessation of additional diagnostic testing, and the initiation of more specific treatment. However, it was mitigated by the panel's low confidence in the estimated effects of SLB. The panel emphasized that the decision to perform SLB should be made in the context of an MDD by experienced clinicians.

The opposite was true among patients whose HRCT pattern is UIP, for whom the panel was certain that the downsides of SLB outweigh the upsides. Because the likelihood of finding an etiology other than UIP is small in such patients, SLB is best considered confirmatory and, therefore, was judged by the panel to not be worth the risk of complications.

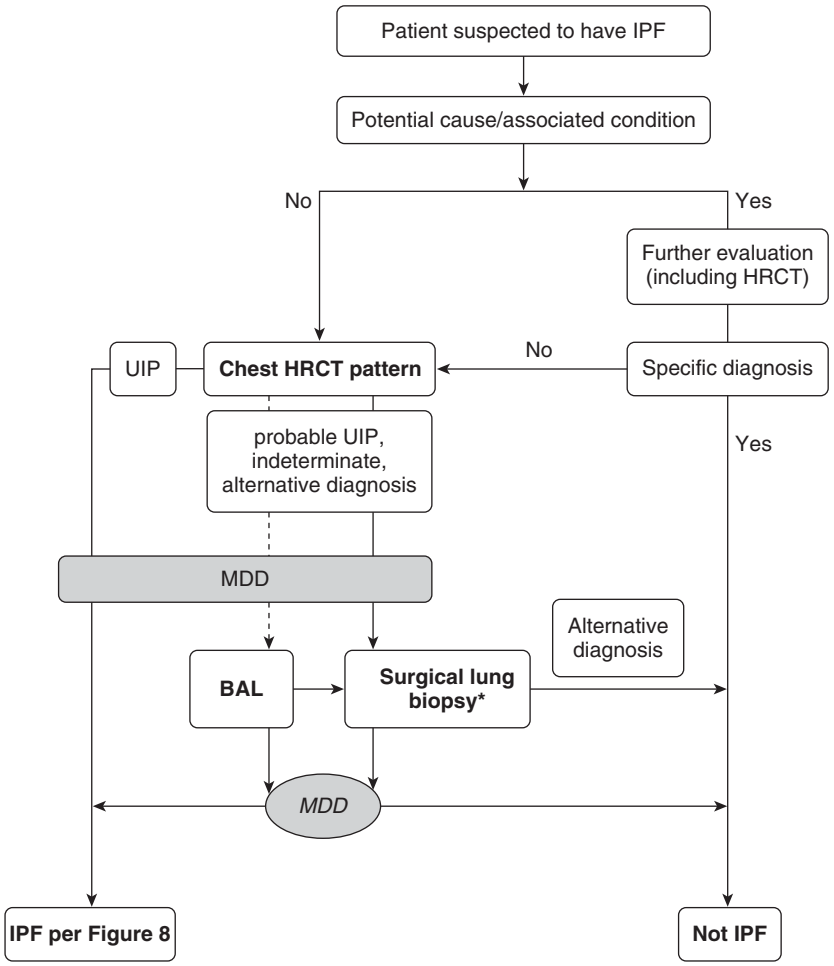

Figure 9. Diagnostic algorithm for idiopathic pulmonary fibrosis (IPF). Patients with suspected IPF (i.e., unexplained symptomatic or asymptomatic bilateral pulmonary infiltrates on a chest radiograph or chest computed tomography [CT] scan, bibasilar inspiratory crackles, and age older than 60 yr), unexplained dyspnea on exertion, and/or cough with evidence of interstitial lung disease (ILD) should be carefully evaluated for potential and/or identifiable causes of ILD, such as domestic and occupational environmental exposures, connective tissue disease (CTD), or drug toxicity. Middle-aged adults (>40 yr and <60 yr), especially patients with risks for familial pulmonary fibrosis, can rarely present with the otherwise same clinical scenario as the typical patient older than 60 years. If a potential cause for ILD is identified, the patient should undergo a thorough evaluation to confirm or exclude other known causes, such as hypersensitivity pneumonitis, CTD, pneumoconiosis, and iatrogenic causes (e.g., drug toxicity, irradiation). If a specific diagnosis is not made or no potential cause for ILD is identified, further evaluation is influenced by the patterns of high-resolution CT (HRCT) images of the chest and supportive clinical findings surfaced in the course of multidisciplinary discussion to ascertain or exclude the diagnosis of IPF. IPF is diagnosed if the appropriate combination of HRCT patterns and histopathological patterns are present. *Surgical lung biopsy is not indicated in patients at high risk for intra-, peri-, or postoperative complications (e.g., severe hypoxemia at rest and/or severe pulmonary hypertension with a diffusion capacity less than 25% after correction for hematocrit; *see* Reference 156). Surgical lung biopsy may be unnecessary in some familial cases. The panel has no recommendation for or against conventional transbronchial biopsy and/or cryobiopsy; however, if performed, histopathology may be sufficient in selected patients (*see* text of Questions 5 and 6). MDD = multidisciplinary discussion; UIP = usual interstitial pneumonia.

ATS/ERS/JRS/ALAT recommendations.

- **For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF and have an HRCT pattern of probable UIP, indeterminate, or an alternative diagnosis, we suggest SLB** (*conditional recommendation, very low quality of evidence*). *Remarks*: strong for, 0 votes; conditional for, 17 votes; conditional against, 4 votes; strong against, 0 votes.
- **For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF and have an HRCT pattern of UIP, we recommend NOT performing SLB** (*strong recommendation, very low quality of evidence*). *Remarks*: strong for, 0 votes; conditional for, 2 votes; conditional against, 1 vote; strong against, 18 votes.

Question 5: For Patients with Newly Detected ILD of Unknown Cause Who Are Clinically Suspected of Having IPF, Is TBBx a Reasonable Alternative to SLB to Ascertain the Histopathology Diagnosis of UIP Pattern?

Evidence base. Our systematic literature search yielded 945 titles but identified no studies that compared clinical outcomes among patients who underwent TBBx to those who did not. Thus, we selected studies that measured diagnostic yield of TBBx using an MDD as the diagnostic decision-maker. The full text of 16 articles was reviewed, and 7 were selected for analysis (128, 130–135) (Table E9). The studies enrolled patients with ILD of unknown cause and did not exclude those with an HRCT pattern of UIP.

Pooling studies (unweighted) indicated that TBBx obtained an adequate sample in roughly three-fourths of cases (five studies; 640 of 825, 77.6%; 95% CI, 74.6–80.3%). Among the adequate samples, a specific diagnosis was obtained from roughly half (seven studies; 409 of 948, 43.1%; 95% CI, 40.0–46.3%), with a slight majority deemed unclassifiable (seven studies; 539 of 948, 56.9%; 95% CI, 53.7–60.0%). Among all TBBx, only one-third yielded a specific diagnosis (i.e., the diagnostic yield) (seven studies; 409 of 1,133, 36.1%; 95% CI, 33.4–38.9%); however, it should be noted that there is uncertainty whether these specific diagnoses were actually correct, because the small samples are susceptible to sampling error and reduced ability to detect scattered histological features such as granulomas. There were no procedure-related deaths (one study; 0 of 49, 0%; 95% CI, 0–7.3%), with other complications including pneumothorax (one study; 5 of 49, 10.2%; 95% CI, 4.4–21.8%) and

prolonged air leak (one study; 3 of 49, 6.1%; 95% CI, 2.1–16.5%).

The guideline panel had very low confidence in the estimated effects of TBBx on patient-important outcomes because TBBx was not compared with SLB within the same population, there was inconsistency in the magnitude of effect, only one study reported complications with a small event rate in that study, and there was a risk of selection bias due to lack of consecutive enrollment.

Putting the evidence together. For every 1,000 TBBx performed, 780 adequate specimens will be obtained and 360 diagnoses will be made (i.e., SLB avoided). The remaining 640 patients will be undiagnosed after TBBx, many of whom will proceed to undergo SLB. No patients will die, but 102 will obtain a pneumothorax, with 61 having a prolonged air leak.

Desirable consequences. TBBx obtains adequate specimens from 77.6% (95% CI, 74.6–80.3%) of patients, from which a definitive diagnosis can be made and SLB avoided in 36.1% (95% CI, 33.4–38.9%).

Undesirable consequences. Approximately 64% (95% CI, 61–67%) of patients will remain undiagnosed after TBBx.

Conclusions. The panel believed that a major limitation of the evidence was that the studies did not stratify patients according to HRCT pattern. It was argued that patients whose HRCT pattern is probable UIP, indeterminate, or an alternative diagnosis are significantly more likely to have an etiology detectable by TBBx (e.g., sarcoidosis) than patients with an HRCT pattern of UIP. Thus, if patients had been stratified according to their HRCT pattern, the diagnostic yield and number of SLBs avoided would probably have been higher among those with an HRCT pattern of probable UIP, indeterminate, or an alternative diagnosis and lower among those with an HRCT pattern of UIP.

There was no consensus on whether avoiding 360 SLBs outweighed 640 patients remaining undiagnosed and having to undergo a second diagnostic procedure. As a result, there was no agreement about whether patients with an HRCT pattern of probable UIP, indeterminate, or an alternative diagnosis should routinely undergo TBBx. The panel made no recommend for or against TBBx as an alternative to SLB, meaning that until additional evidence becomes available, TBBx should be considered on a case-by-case basis. There was strong agreement that patients with an HRCT pattern of UIP should not undergo TBBx, because the likelihood of finding an etiology other than UIP is small and not worth the risk of complications in such patients.

Machine learning using molecular signatures is being developed to make a molecular diagnosis of UIP in TBBx specimens but is not yet available in routine clinical practice. The guideline panel acknowledges that recent studies about the utility of molecular diagnostic tools that involve machine learning using TBBx samples are promising (136, 137); further studies to validate this are pending. This recommendation will be revisited in future iterations of this guideline as related evidence accumulates.

ATS/ERS/JRS/ALAT recommendations.

- **For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF and have an HRCT pattern of probable UIP, indeterminate, or an alternative diagnosis, the panel made no recommendation for or against TBBx.** *Remarks*: strong for, 0 votes; conditional for, 10 votes; conditional against, 12 votes; strong against, 2 votes.
- **For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF and have an HRCT pattern of UIP, we recommend NOT performing TBBx** (*strong recommendation, very low quality of evidence*). *Remarks*: strong for, 0 votes; conditional for, 0 votes; conditional against, 6 votes; strong against, 18 votes.

Question 6: For Patients with Newly Detected ILD of Unknown Cause Who Are Clinically Suspected of Having IPF, Is Transbronchial Lung Cryobiopsy a Reasonable Alternative to SLB to Ascertain the Histopathology Diagnosis of UIP Pattern?

Evidence base. Our systematic literature search yielded 945 titles but identified no studies that compared clinical outcomes among patients who underwent lung cryobiopsy to those who did not. Thus, we selected studies that measured diagnostic yield of lung cryobiopsy using an MDD as the diagnostic decision-maker. The full text of 25 articles was reviewed, and 13 were selected for analysis (126, 127, 132, 135–146) (Table E10). The studies enrolled patients with ILD of unknown cause and did not exclude those with an HRCT pattern of UIP.

Pooling studies (unweighted) indicated that lung cryobiopsy obtained an adequate sample in the vast majority of cases (10 studies; 720 of 749, 96%; 95% CI, 94–97%). Among the adequate samples, a specific diagnosis was obtained in more than four-fifths of cases (13 studies; 692 of 833, 83%; 95% CI, 80–85%), with the remaining deemed unclassifiable (13 studies; 141 of 833, 17%; 95% CI, 15–20%). Among lung cryobiopsy procedures, the majority yielded a specific diagnosis (i.e., the diagnostic yield) (13 studies; 692 of 862, 80%; 95% CI, 77–83%).

Overall mortality was low (seven studies; 15 of 597, 2.7%; 95% CI, 1.7–4.3%), but some deaths were likely disease related, because procedure-related mortality was even lower (three studies; 1 of 427, 0.2%; 95% CI, 0.04–1.3%). Additional complications included exacerbations (three studies; 1 of 82, 1.2%; 95% CI, 0.2–6.6%), bleeding (six studies; 28 of 541, 5.2%; 95% CI, 3.6–7.4%), severe bleeding (eight studies; 5 of 674, 0.7%; 95% CI, 0.3–1.7%), prolonged air leak (two studies; 47 of 352, 13.4%; 95% CI, 10.2–17.3%), and respiratory infection (three studies; 3 of 409, 0.7%; 95% CI, 0.2–2.1%).

The guideline panel had very low confidence in the estimated effects of lung cryobiopsy on patient-important outcomes because lung cryobiopsy was not compared with SLB within the same population, there was inconsistency in the magnitude of effect, the complication event rate was low, and there was a risk of selection bias due to lack of consecutive enrollment.

Putting the evidence together. For every 1,000 lung cryobiopsies performed, 950 adequate specimens are obtained, and 790 diagnoses are made (i.e., SLB avoided). This means that 210 patients will remain undiagnosed after lung cryobiopsy, many of whom will proceed to SLB. Two patients will die from the procedure, and 12 patients will experience an exacerbation.

Desirable consequences. Lung cryobiopsy obtains adequate specimens

from 96% (95% CI, 94–97%) of patients, from which a definitive diagnosis can be made and SLB avoided in 80% (95% CI, 77–83%). Compared with SLB, lung cryobiopsy is associated with fewer respiratory infections and a trend toward less procedural mortality.

Undesirable consequences. Roughly 20% (95% CI, 17–23%) of patients will remain undiagnosed after lung cryobiopsy. Compared with SLB, patients who undergo lung cryobiopsy are more likely to have bleeding or a prolonged air leak.

Conclusions. Although the panel was enthusiastic about the desirable consequences of lung cryobiopsy, this was offset by concern about the lack of standardized procedure and approach and the heterogeneous rates of adverse events noted in previous studies (147–149). The panel identified many questions that need to be answered before recommending widespread use of cryobiopsy, including: How many specimens should be obtained to optimize diagnostic yield while minimizing complications? From which portion of the lung should they be obtained in relation to the microanatomy of the lung and diseased lung tissues? For how long should the probe be cooled?

The panel concluded that it is reasonable for experienced centers and experts with a track record of performing the procedure safely to continue performing lung cryobiopsy in patients whose HRCT pattern is probable UIP, indeterminate, or an alternative diagnosis. However, the panel believed very strongly and recommends that such experts work toward developing a standardized procedure that optimizes the balance between diagnostic yield and complications. Those who have not yet begun to perform cryobiopsy should wait until the procedure has been standardized before implementing this into clinical practice. In patients whose HRCT pattern is UIP, the panel believed that the downsides of lung cryobiopsy outweigh the upsides. Because the likelihood of finding an etiology other than UIP is small, lung cryobiopsy is best considered a confirmatory test and, therefore, was judged by the panel to not be worth the risk of complications.

ATS/ERS/JRS/ALAT recommendations.

- **For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF and have an HRCT pattern of probable UIP, indeterminate, or an alternative diagnosis, the panel made no recommendation regarding lung cryobiopsy.** *Remarks*: strong for, 1 vote; conditional for, 10 votes; conditional against, 8 votes; strong against, 3 votes.
- **For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF and have an HRCT pattern of UIP, we recommend NOT performing lung cryobiopsy** (*strong recommendation, very low quality of evidence*). *Remarks*: strong for, 0 votes; conditional for, 2 votes; conditional against, 1 vote; strong against, 19 votes.

Question 7: Should Patients with Newly Detected ILD of Unknown Cause Who Are Clinically Suspected of Having IPF Be the Subject of MDD for Decision-Making?

Evidence base. Our systematic literature search yielded 189 titles but identified no studies that *1*) compared clinical outcomes among patients who underwent single-discipline decision-making (SDD; either a single clinician or a group of clinicians from the same discipline) to those who underwent MDD, or *2*) reported the test characteristics of SDD using MDD as the reference standard. Therefore, we sought studies that measured agreement between SDD and MDD. The full text of 17 articles was reviewed, and 5 were selected for analysis (84, 150–153) (Table E11). Numerous studies measured agreement among individuals, but they were not selected for our analysis because they did not specifically compare SDD to MDD.

One study enrolled patients with an SDD diagnosis of IPF (84), and four studies enrolled patients with an SDD diagnosis of various types of ILD, including IPF (150–153). The studies subjected the patients to MDD and then compared the SDD diagnosis to the MDD diagnosis. In three studies, the SDD consisted of decision-making by a single respiratory clinician (84, 150, 151), in one study it consisted of either a single respiratory clinician or a single internist (152), and in one study it consisted of a group of pathologists (153). In three studies, the MDD consisted of decision-making by a respiratory clinician, radiologist, and pathologist (84, 150, 152); in one study it consisted of a radiologist and pathologist (84); and in one study it consisted of a respiratory clinician and a pathologist (153).

When measured as a proportion, median agreement between SDD and MDD was 70%, with a range from 47% to 87%. When measured using a Cohen's kappa score, agreement was moderate ($\kappa = 0.331$; 95% CI, 0.269–0.392). The guideline panel had very low confidence in this estimated agreement. Its confidence was diminished by the risk of bias conferred by not enrolling patients with true diagnostic uncertainty, not consecutively enrolling patients, the inconsistency of the estimates, the small study sizes, and possible indirectness (the question pertains to those for whom there is a suspicion of IPF, but this was not reported in the studies).

Putting the evidence together. For every 1,000 patients who undergo diagnostic decision-making, SDD and MDD will derive the same diagnosis in 700 patients and different diagnoses in 300 patients. If one accepts MDD as the reference standard, then as many as 300 patients will be potentially subject to incorrect therapy, delayed therapy, or unnecessary additional diagnostic testing.

Desirable consequences. SDD is more efficient for decision-making, given the increased time and effort required to obtain the opinion of colleagues in an MDD.

Undesirable consequences. If one accepts MDD as the reference standard for diagnostic decision-making, SDD demonstrated suboptimal agreement (median, 70%; range, 47–87%).

Conclusions. The guideline panel agreed that MDD is preferred, because the notion that as many as 300 patients may be subject to incorrect therapy, delayed therapy, or unnecessary additional diagnostic testing was deemed unacceptable. The panel believes the benefit of MDD is greatest when the HRCT pattern is probable UIP, indeterminate, or an alternative diagnosis, or when there exist discordant clinical, radiologic, and/or histologic data. There was substantial discussion on what MDD entails. Until further research is done to optimize MDD, the panel

concluded that it consists of an interaction between a pulmonologist (and rheumatologist on a case-by-case basis), radiologist, and pathologist. The modus operandi of the interaction is deferred to the confronted clinicians and could be face-to-face, by telephone, Internet/e-mail, text, and/or reading interpreted reports by experts via copies (printed, scanned, faxed). Face-to-face or voice-to-voice MDDs are encouraged when the formal clinical reports of the interpretation by experts in different disciplines are in discordance.

ATS/ERS/JRS/ALAT recommendation.

- **For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF, we suggest MDD for diagnostic decision-making** (*conditional recommendation, very low quality of evidence*). *Remarks*: strong for, 0 votes; conditional for, 23 votes; conditional against, 0 votes; strong against, 0 votes.

Question 8: Should Patients with Newly Detected ILD of Unknown Cause Who Are Clinically Suspected of Having IPF Undergo Serum Biomarker (MMP-7, SPD, CCL-18, KL-6) Measurement for the Purpose of Diagnosis?

Evidence base. Our systematic literature search yielded 429 articles but identified no studies that compared clinical outcomes among patients who underwent specific serum biomarker measurements to those who did not. The literature review on diagnostic accuracy studies was limited to four specific serum biomarkers on the basis of input from the committee.

MMP-7. We selected studies that measured the diagnostic accuracy of MMP-7 for distinguishing IPF from other types of ILD. We reviewed the full text of 12 articles and selected two studies (154, 155). One study evaluated the ability of serum MMP-7 to distinguish IPF from a heterogeneous mixture of alternative ILDs (154), and the other looked at the ability of serum MMP-7 to distinguish IPF from sarcoidosis, idiopathic NSIP, hypersensitivity pneumonitis, CTD-ILD, and drug-induced ILD (155). Serum MMP-7 levels distinguished IPF from other ILDs with a median sensitivity, specificity, accuracy, and diagnostic odds ratio of 71.7% (range, 71–72.3%), 64.4% (63–66.3%), 68.4% (68.3–68.5%), and 4.7 (4.2–5.1), respectively (Table E12a).

SPD. We selected studies that measured the diagnostic accuracy of SPD for distinguishing IPF from other types of ILD. We reviewed the full text of 16 articles and selected one study (154). The study evaluated the ability of serum SPD to distinguish IPF from a heterogeneous mixture of alternative ILDs. Serum SPD levels distinguished IPF from other ILDs with a sensitivity, specificity, accuracy, and diagnostic odds ratio of 70.0%, 65.0%, 68.5%, and 3.1, respectively (Table E12b).

CCL-18. We sought studies that reported the diagnostic accuracy of CCL-18 for distinguishing IPF from other types of ILD. We reviewed the full text of six articles and selected no studies.

KL-6. We sought studies that reported the diagnostic accuracy of KL-6 for distinguishing IPF from other types of ILD. We reviewed the full text of 55 articles and selected no studies.

The guideline panel had very low confidence in the estimated effects. Its confidence was diminished by the risk of bias conferred by not describing the reference standard, not stating whether the enrolled patients had true diagnostic uncertainty, and not consecutively enrolling patients. Moreover, the studies were small, and none of the studies were performed using Clinical Laboratory Improvement Amendments–approved assays.

Putting the evidence together. Assuming that 30% of patients with ILD have IPF, then for every 1,000 patients who undergo serum MMP-7 measurement for the purpose of distinguishing IPF from other ILDs, 672 patients will get a true-positive or true-negative result, whereas 338 patients will get a false result potentially leading to inappropriate therapy, delayed therapy, or unnecessary additional diagnostic testing. Similarly, for every 1,000 patients who undergo serum SPD measurement for the purpose of distinguishing IPF from other ILDs, 665 patients will get a true-positive or true-negative result, whereas 335 patients will get a false result potentially leading to inappropriate therapy, delayed therapy, or unnecessary additional diagnostic testing.

Desirable consequences. More than one-half of patients with ILD who undergo serum MMP-7 or SPD measurement will be correctly distinguished as having IPF or an alternative ILD. Samples for serum testing are easily obtained with few complications.

Undesirable consequences. More than one-third of results will be incorrect, leading to inappropriate therapy, delayed therapy, or unnecessary additional diagnostic testing, all of which may be associated with complications. In addition, testing for these biomarkers is costly and not widely available.

Conclusions. For the time being, the guideline panel dismissed serum biomarker measurement as an approach to distinguishing IPF from other ILDs because of the high false-positive and false-negative result rates.

ATS/ERS/JRS/ALAT recommendation.

- **For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF, we recommend NOT measuring serum MMP-7, SPD, CCL-18, or KL-6 for the purpose of distinguishing IPF from other ILDs** (*strong recommendation, very low quality of evidence*). *Remarks*: strong for, 0 votes; conditional for, 0 votes; conditional against, 6 votes; strong against, 15 votes.

Future Directions and Research Questions

The expert panel recognized that there is an urgent need to refine and validate diagnostic approaches in ILD. These needs can be roughly categorized as investigations into the roles of clinical observations, HRCT, bronchoscopy, histopathology, and biomarkers.

Clinical Observations

How should observed disease behavior be integrated into the IPF diagnostic algorithm? Should screening for comorbidities be part of the diagnostic evaluation for prognostic purposes? In patients with suspected IPF and a "probable UIP" pattern on HRCT, to what extent does observation of subsequent disease progression validate an initial IPF

diagnosis? Does therapy influence this observation or its diagnostic implication? In which patient populations is a "probable UIP" pattern on HRCT sufficient to provide a diagnosis of IPF without histopathologic confirmation? Waiting to assess disease behavior to make the diagnosis of IPF assumes that most patients with IPF progress in a predicted time; moreover, holding potentially effective medications for IPF until the disease progresses to ascertain the behavior pattern eliminates the possibility of obtaining treatment benefits early during the disease course. Future studies are needed to clarify these and other clinical situations.

HRCT

In patients with suspected IPF but no honeycombing on HRCT, what is the diagnostic importance of the severity and location of traction bronchiectasis? This includes the relative diagnostic significance of central bronchiectasis and peripheral bronchiolectasis. In patients with a fibrosing interstitial pneumonia, can the presence of mosaic attenuation separate chronic hypersensitivity pneumonitis from IPF? How can mosaic attenuation be quantified? Is standardized quantification of mosaic attenuation helpful in distinguishing the UIP seen in patients with IPF from UIP-like patterns seen in patients with chronic hypersensitivity pneumonitis? Can quality or quantity of ground-glass opacification be subcategorized according to the likelihood of IPF, either by subjective evaluation or automated methods? Does the craniocaudal distribution of fibrotic features alter the diagnostic likelihood of IPF? How is HRCT interpretation affected by the quality and quantity of available clinical information (e.g., age, concomitant illness, exposures)?

BAL and Transbronchial Lung Biopsy via Fiberoptic Bronchoscopy

How frequently do BAL cell type analysis, transbronchial lung tissue–derived histopathology, and/or transbronchial lung tissue–derived molecular profiles using machine learning (136, 137) provide added value to other clinically important information? This approach may include multidisciplinary formulation of diagnoses with and without bronchoscopic information, before SLB. Outcomes could include diagnostic agreement between clinicians, the prevalence of highly confident diagnoses, concordance with SLB data, therapeutic decisions, and subsequent disease behavior.

Lung Cryobiopsy

A standardized procedure for lung cryobiopsy that optimizes the balance between diagnostic yield and complications needs to be developed among experts currently engaged with the procedure.

Histopathology

How frequently does SLB alter the diagnosis for patients with each HRCT pattern, including UIP pattern? What impact does SLB have on pulmonary function indices or clinical endpoints at selected time points after biopsy? The same types of studies may be valuable for TBBx and lung cryobiopsy.

Empiric Therapy

Studies in patients diagnosed with "likely IPF" and treated with antifibrotic therapy at the time of the initial diagnosis without SLB are needed to enhance further understanding of the course of IPF in this cohort of patients with IPF.

Genetic Markers and Counseling

Is IPF truly an inherited disease? What are the genetic markers in patients manifesting IPF as "familial" IPF or "familial" interstitial pneumonia in whom a genetic marker or mutation in genes cannot be identified despite molecular genetic studies? What is the relationship between mutations or abnormal genetic markers and either intrinsic microenvironmental (e.g., microaspiration, lung microbiome, abnormal gastroesophageal reflux) or extrinsic exposures (i.e., ecogenetic factors)? Because IPF is predominantly a disease of the elderly, is there a role for genetic counseling for all patients with IPF? Although genetic variants account for part of the risk of developing sporadic IPF or familial forms of ILD (i.e., familial IPF, familial interstitial pneumonia), the clinical utility of these sequence variants will need to be determined in future studies.

Other Biomarkers

What is the optimal approach to excluding CTD and chronic hypersensitivity pneumonitis? Is there a role for measuring specific serum antibodies for either excluding chronic hypersensitivity pneumonitis or prompting clinicians to take a more detailed history of exposures? Studies of diagnostic molecular biomarkers are needed to *1*) evaluate the diagnostic accuracy of emerging molecular biomarkers, *2*) use machine learning tools to make a diagnosis of UIP, and *3*) integrate molecular markers with current diagnostic modalities in the multidisciplinary diagnosis of IPF. Novel biomarkers integrated into clinical diagnosis might include circulating markers or molecular signatures obtained from lung sampling, with a particular focus on less-invasive lung sampling (i.e., samples obtained by BAL, TBBx, or transbronchial lung cryobiopsy). What is the added diagnostic value of routine germline genetic testing in patients with suspected or known IPF?

Although beyond the scope of this guideline, the panel also emphasizes the need to refine prognostic approaches, identify risk factors for the development of IPF, and determine the impact and approach to the diagnosis of comorbid illness in the patient with IPF.

Conclusions

A comprehensive synthesis of all available evidence was performed to summarize data pertaining to key questions related to the diagnosis of IPF. The evidence was discussed, diagnostic criteria for IPF were updated, and a multidisciplinary committee of IPF experts formulated recommendations for individual diagnostic tests. The panel did not evaluate whether these diagnostic tests had utility for other reasons, such as determining prognosis, treatment response, etc. A new feature of this guideline, compared with the prior version of the guideline (2), is that a different approach is often recommended depending on whether the patient's HRCT pattern is UIP or something other than UIP (i.e., probable UIP, indeterminate, and alternative diagnosis). These recommendations should be reconsidered as new evidence becomes available. ■

This official clinical practice guideline was developed by an *ad hoc* subcommittee of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society.

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