

## Diagnosis of Idiopathic Pulmonary Fibrosis

### An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Executive Summary

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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 for UIP, 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 for UIP, or

an alternative diagnosis, conditional recommendations were made for performing BAL and surgical lung biopsy; due to 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 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), 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) 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 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 usual interstitial pneumonia (UIP), indeterminate for UIP, 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**

The American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Society (ALAT) collaborated to develop clinical practice guidelines for the diagnosis and management of IPF in 2011 (1). New evidence now enables us to improve the diagnostic criteria. The recommendations in this 2018 guideline are revisions of the diagnostic recommendations in the 2011

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

	2018 Guideline		2011 Guideline: Did Not Distinguish among Patients with Different HRCT Patterns
	HRCT Pattern of Probable UIP*, Indeterminate for UIP, and Alternative Diagnosis	HRCT Pattern of UIP*	
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

	<b>Strong Recommendation (“We recommend . . .”)</b>	<b>Conditional Recommendation (“We suggest . . .”)</b>
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.

guideline (1). 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 (see online supplement).

**Clinical Manifestations**

IPF is a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause. The typical patient with IPF is a male, older than 60 years of age, usually with a previous history of smoking tobacco, who presents with insidious onset of cough and/or exertional dyspnea, bibasilar inspiratory crackles, and radiologic evidence of fibrosis predominantly in the lower lobes without an apparent cause. 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) with a background of lower lobe fibrotic lung disease (2). Middle-aged adults (>40 yr and <60 yr), especially patients with risks for familial

pulmonary fibrosis and genetic predisposition factors for IPF, can rarely present with the otherwise same clinical scenario as the typical patient older than 60 years.

**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. Technical requirements of HRCT are described in Table 3 and Table E1 in the online supplement.

**HRCT Patterns**

We advocate the use of four diagnostic categories (Table 4) that incorporate the HRCT features described above. These categories include “UIP pattern” (Figure 1), “probable UIP pattern” (Figure 2), “indeterminate for UIP 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 (3, 4). Asymmetric disease may occur in up to 25% of cases (5). 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% (6–10); however, a significant minority of patients with histopathologic UIP do not fulfill HRCT criteria for UIP (7, 9–11).

Mediastinal lymphadenopathy may be present in patients with UIP (12). 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 (13). Patients with UIP may have features of pleuroparenchymal fibroelastosis at the lung apices (14, 15); 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” (1). Since 2011, several studies have reported that selected patients with a “possible UIP” pattern on HRCT

**Table 3.** High-Resolution Computed Tomography Scanning Parameters

Recommended Scanning Protocol	Advantages of Updated Recommendations
1. Noncontrast examination	—
2. Volumetric acquisition with selection of: <ul style="list-style-type: none"> <li>• Sub-millimetric collimation</li> <li>• Shortest rotation time</li> <li>• Highest pitch</li> <li>• Tube potential and tube current appropriate to patient size:                             <ul style="list-style-type: none"> <li>◦ Typically 120 kVp and <math>\leq 240</math> mAs</li> <li>◦ Lower tube potentials (e.g., 100 kVp) with adjustment of tube current encouraged for thin patients</li> </ul> </li> <li>• Use of techniques available to avoid unnecessary radiation exposure (e.g., tube current modulation)</li> </ul>	A. Acquisition covering the entire lung volume (vs. analysis of 10% of lung volume with sequential scanning) <ul style="list-style-type: none"> <li>• No risk of missing subtle infiltrative abnormalities</li> <li>• Possibility of multiplanar reformations, helpful for analysis of the ILD pattern and predominant distribution of lung changes</li> <li>• Possibility of post-processing to optimize detection of subtle hypoattenuated lesions (minimum intensity projection) and micronodular infiltration (maximum intensity projection)</li> <li>• 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)</li> <li>• Optimal to assess progression or improvement in patient's follow-up</li> </ul> B. Dramatic increase in temporal resolution and speed of data acquisition <ul style="list-style-type: none"> <li>• Motion-free images</li> </ul> C. Availability of numerous dose-reduction tools
3. Reconstruction of thin-section CT images ( $\leq 1.5$ mm): <ul style="list-style-type: none"> <li>• Contiguous or overlapping</li> <li>• Using a high-spatial-frequency algorithm</li> <li>• Iterative reconstruction algorithm if validated on the CT unit (if not, filtered back projection)</li> </ul>	—
4. Number of acquisitions: <ul style="list-style-type: none"> <li>• Supine: inspiratory (volumetric)</li> <li>• Supine: expiratory (can be volumetric or sequential)</li> <li>• Prone: only inspiratory scans (can be sequential or volumetric); optional (see text)</li> <li>• Inspiratory scans obtained at full inspiration</li> </ul>	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: <ul style="list-style-type: none"> <li>• 1–3 mSv (i.e., “reduced” dose)</li> <li>• Strong recommendation to avoid “ultralow-dose CT” (<math>&lt; 1</math> mSv)</li> </ul>	A. Considerable dose reduction compared to conventional scanning

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

according to the 2011 guidelines are highly likely to have histopathologic UIP despite the absence of radiologic honeycombing. Specifically, an HRCT pattern of possible UIP with peripheral traction bronchiectasis or bronchiolectasis in the correct clinical setting likely represents histopathologic UIP on biopsy (4, 16–18). 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 for UIP pattern.** It is now recognized that atypical HRCT features

frequently (i.e., about 30%) accompany a histopathologic pattern of UIP/IPF (19). Therefore, the category “indeterminate for UIP 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

**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: <ul style="list-style-type: none"> <li>• CT features:                             <ul style="list-style-type: none"> <li>◦ Cysts</li> <li>◦ Marked mosaic attenuation</li> <li>◦ Predominant GGO</li> <li>◦ Profuse micronodules</li> <li>◦ Centrilobular nodules</li> <li>◦ Nodules</li> <li>◦ Consolidation</li> </ul> </li> <li>• Predominant distribution:                             <ul style="list-style-type: none"> <li>◦ Peribronchovascular</li> <li>◦ Perilymphatic</li> <li>◦ Upper or mid-lung</li> </ul> </li> <li>• Other:                             <ul style="list-style-type: none"> <li>◦ Pleural plaques (consider asbestosis)</li> <li>◦ Dilated esophagus (consider CTD)</li> <li>◦ Distal clavicular erosions (consider RA)</li> <li>◦ Extensive lymph node enlargement (consider other etiologies)</li> <li>◦ Pleural effusions, pleural thickening (consider CTD/drugs)</li> </ul> </li> </ul>
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 for UIP”)	

*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.

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 suggests 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 for UIP 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.

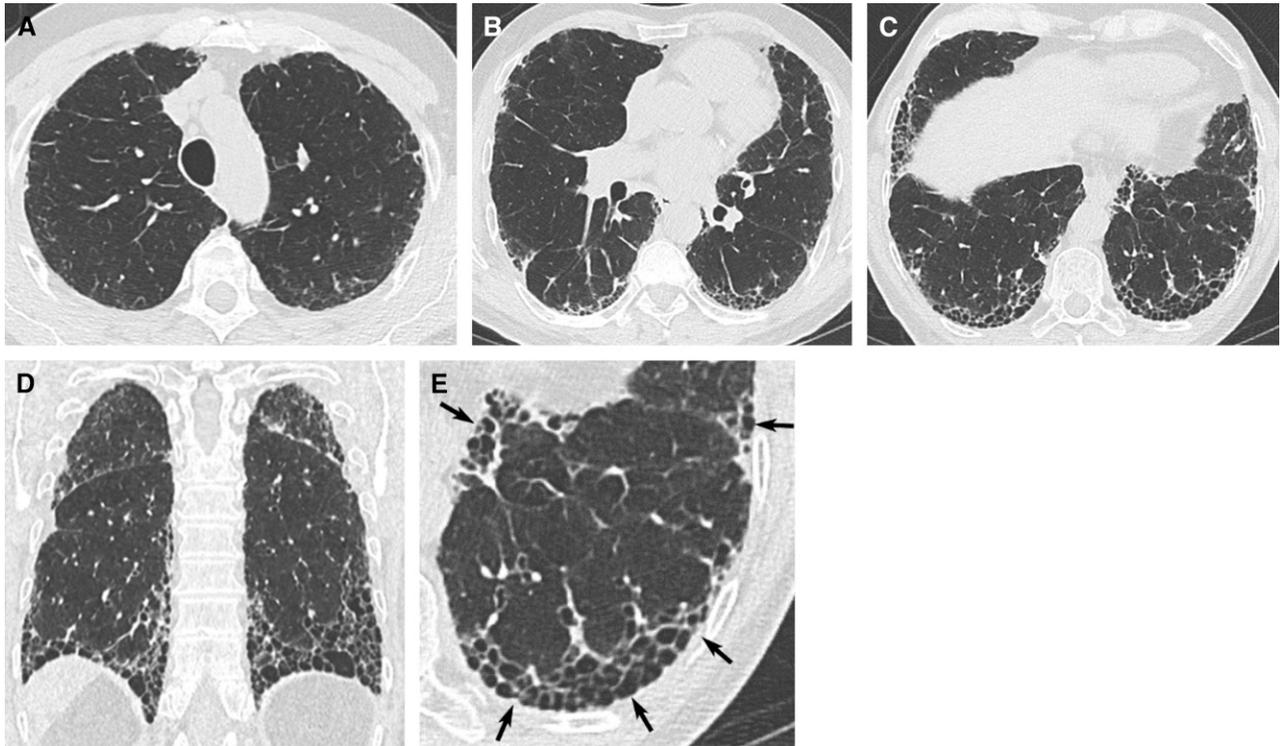
**SLB Technique**

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 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).

**Histopathology Patterns**

We recommend categorizing histopathologic findings of biopsies into “UIP” (Figure 7), “probable UIP,” “indeterminate for UIP,” and “alternative diagnosis” (Table 5). 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.



**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).

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, connective tissue disease [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

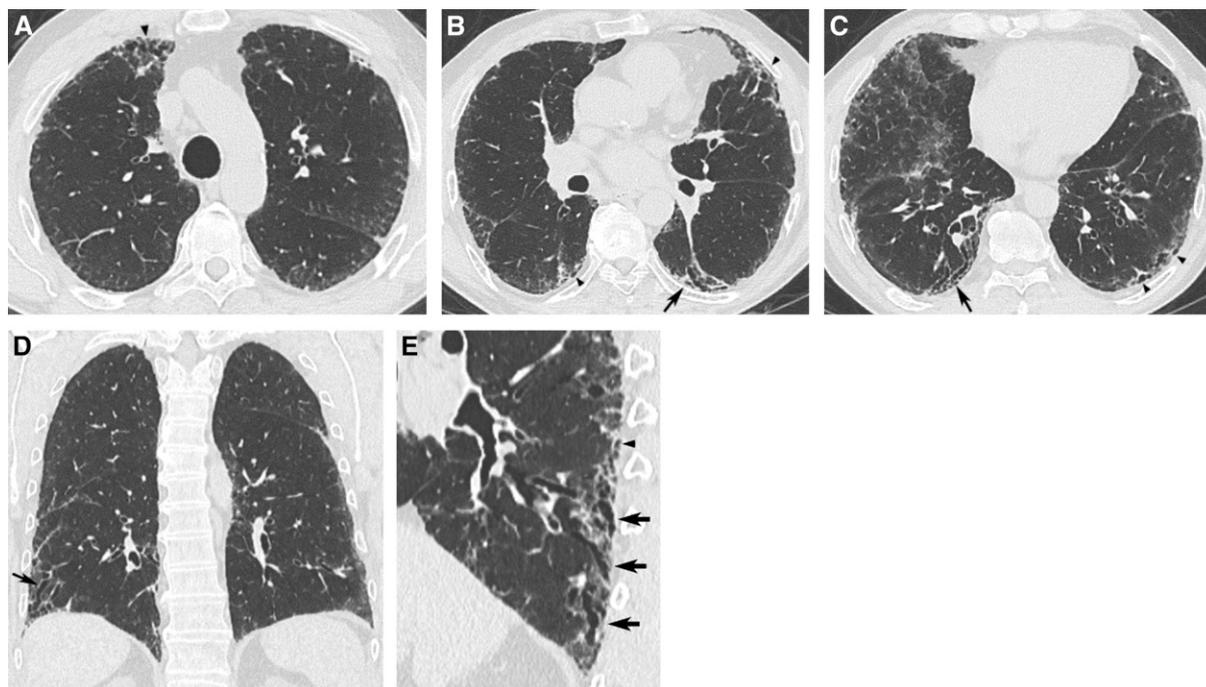
guidelines and the 2011 guidelines (1) and is similar to that suggested by a task force sponsored by the Fleischner Society (20).

## Diagnostic Interventions

The questions below are specifically intended for patients who are "clinically suspected of having IPF." This classically refers to patients with unexplained 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 (21). The panel's clinical experience is that identification and removal of potential



**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.

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 (21–23). 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 (24–30). 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.

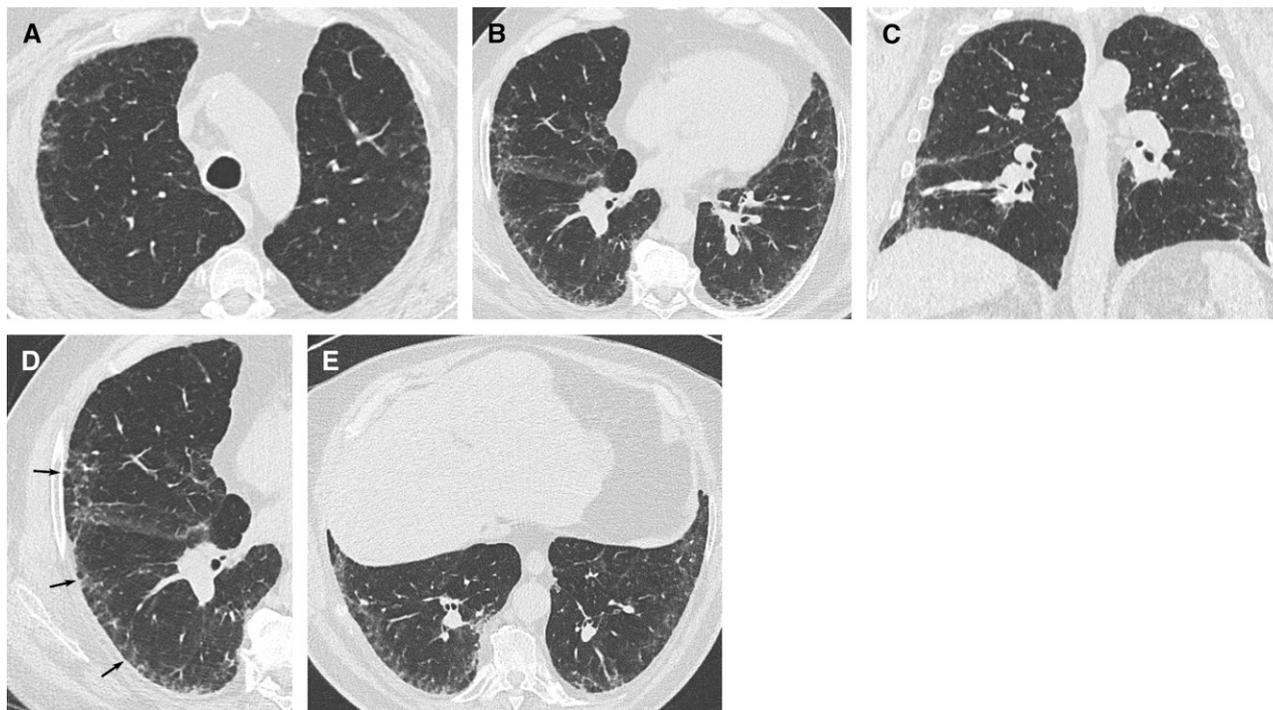
#### **ATS/ERS/JRS/ALAT recommendations.**

- **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).**

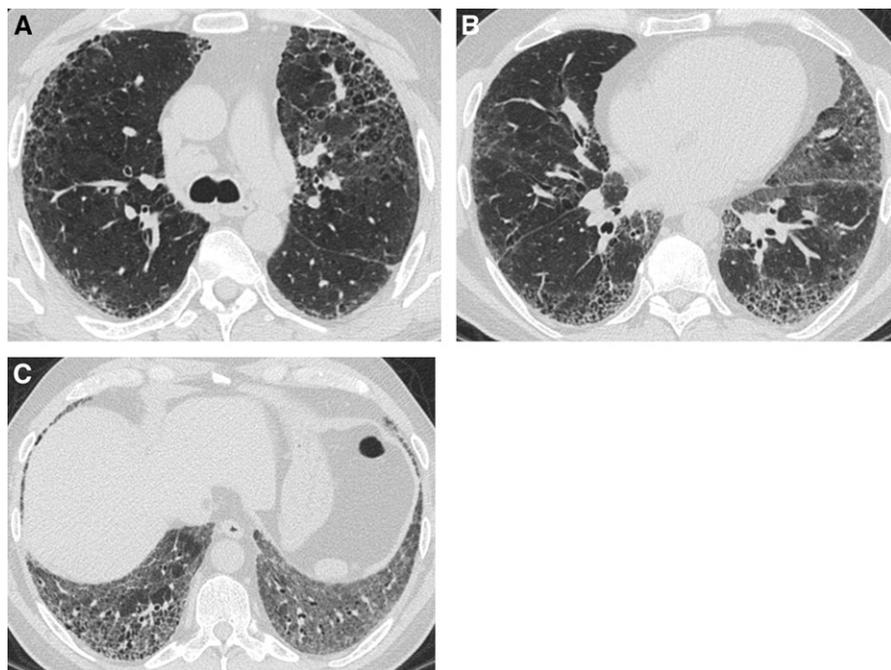
#### **Question 2: Should Patients with Newly Detected ILD of Unknown Cause Who Are Clinically Suspected of Having IPF Undergo Serological Testing to Exclude CTDs as Potential Causes of the ILD?**

**Discussion.** Diagnosis of IPF mandates exclusion of other causes of ILD, including CTD-related 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. These include muscle enzymes (creatinine phosphokinase, myoglobin, and 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- $\gamma$  (transcriptional intermediary factor 1- $\gamma$ ), 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/Sc175 (polymyositis/scleroderma 75), anti-PM/Sc100, and anti-Ku (31). 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.



**Figure 3.** Indeterminate for usual interstitial pneumonia (UIP) pattern (early 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.



**Figure 4.** Indeterminate for usual interstitial pneumonia 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.

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.

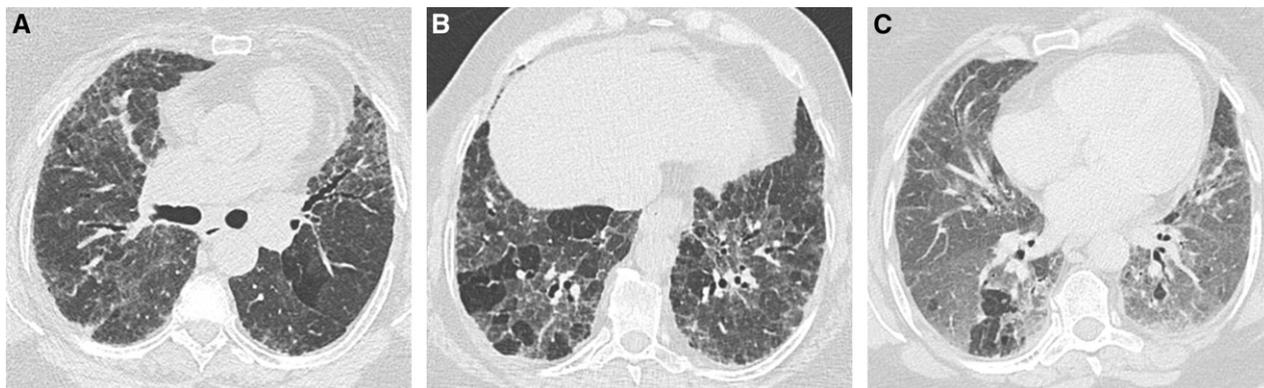
The guideline panelists do not refer all patients with new ILD to a rheumatologist; rather, referring only those with positive clinical manifestations, serologies, or other characteristics atypical for IPF (e.g., female, age <60 yr old). In many CTD-related ILDs, the lung disease is the first, dominant, or only feature of the CTD and, therefore, some patients will not fit standard rheumatologic diagnostic criteria at presentation.

**ATS/ERS/JRS/ALAT recommendations.**

- 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



**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.

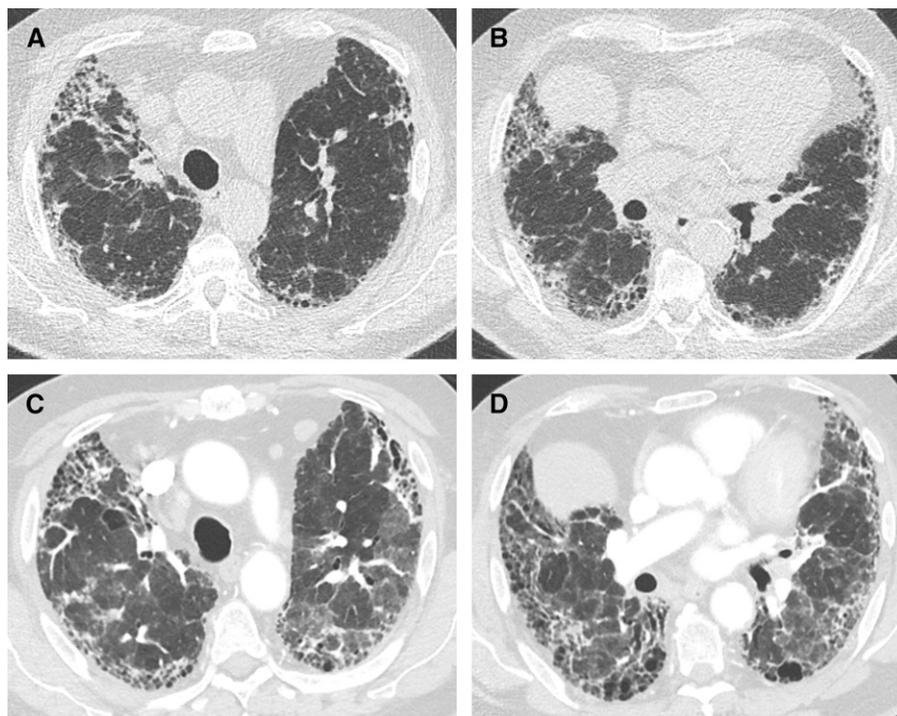
identify any studies that 1) compared clinical outcomes among patients who underwent BAL cellular analysis to those who did not undergo BAL cellular analysis, or 2) reported the test characteristics of BAL cellular analysis for distinguishing IPF from other ILDs. Therefore, we sought studies that compared BAL cell type proportions among patients with IPF to those among patients with other types of ILD. The full text of 14 articles was

reviewed, and 8 were selected for analysis (32–39) (Tables E7a–E7f).

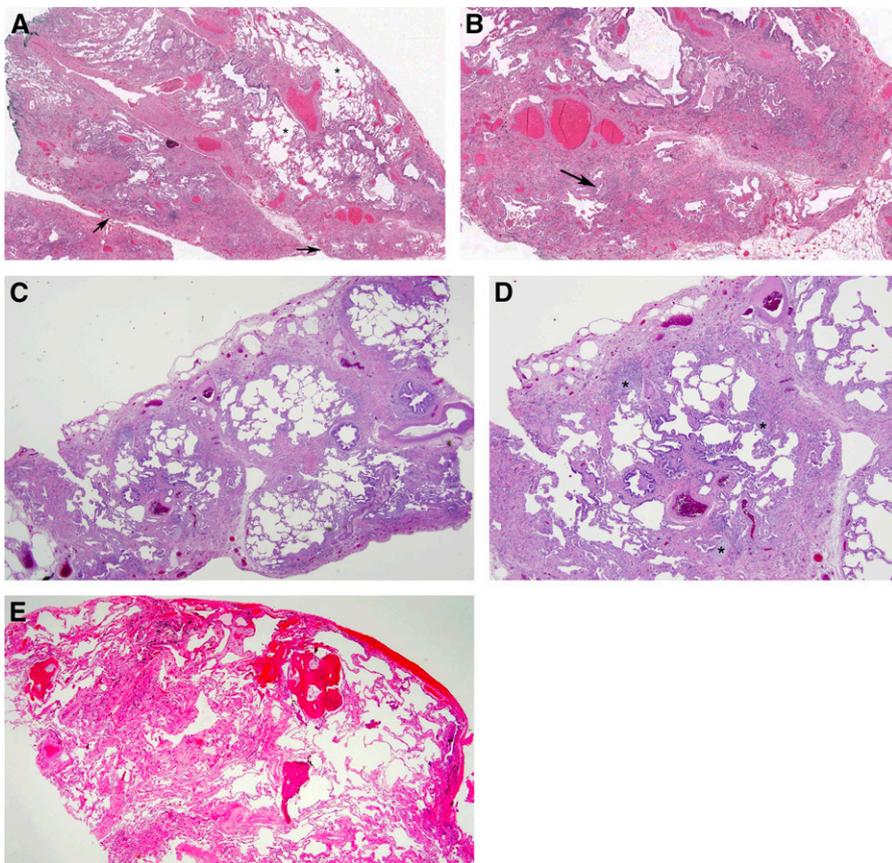
The eight studies enrolled patients with IPF, performed BAL, and measured components of the BAL fluid, including the percentage of neutrophils (32–37, 39), macrophages (32–36, 39), lymphocytes (32–39), and eosinophils (32, 34–37, 39), as well as the CD4/CD8 ratio (32, 34, 36, 37). The measurements were then compared with similar measurement from patients

with other types of ILD, including hypersensitivity pneumonitis (32, 33, 37), sarcoidosis (32, 36, 37), idiopathic NSIP (32, 34, 37–39), cryptogenic organizing pneumonia (previously called bronchiolitis obliterans organizing pneumonia) (32–34, 37), eosinophilic pneumonia (32), respiratory bronchiolitis-associated ILD (33), and lymphocytic interstitial pneumonia (33). Some BAL cell type proportions were markedly 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 individuals but a markedly lower proportion of eosinophils than patients with eosinophilic pneumonia; thus, patients with a markedly elevated proportion of eosinophils 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 individuals 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.

**Conclusions.** When the panel weighed the desirable consequences of BAL cellular analysis in patients who have an HRCT pattern of probable UIP, indeterminate for UIP, 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 was general agreement that



**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.



**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.

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 for UIP, or an alternative diagnosis, we suggest cellular analysis of their BAL fluid (conditional recommendation, very low quality of evidence).**

- 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).**

**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 a MDD as the diagnostic decision-maker. The full text of 54 articles was reviewed, and 26 were selected for analysis (40–65) (Table E8).

Pooling studies (unweighted) indicated that SLB obtained an adequate sample in all patients (11 studies; 918 of 918, 100%; 95% confidence interval [CI], 99–100%), although the panel acknowledged that this is not always the case in clinical practice. The proportion of SLBs 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, cryptogenic organizing pneumonia, 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%

**Table 5.** Histopathology Patterns and Features

UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
<ul style="list-style-type: none"> <li>• Dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing)</li> <li>• Predominant subpleural and/or paraseptal distribution of fibrosis</li> <li>• Patchy involvement of lung parenchyma by fibrosis</li> <li>• Fibroblast foci</li> <li>• Absence of features to suggest an alternate diagnosis</li> </ul>	<ul style="list-style-type: none"> <li>• Some histologic features from column 1 are present but to an extent that precludes a definite diagnosis of UIP/IPF</li> </ul> <p style="text-align: center;"><i>And</i></p> <ul style="list-style-type: none"> <li>• Absence of features to suggest an alternative diagnosis</li> </ul> <p style="text-align: center;"><i>Or</i></p> <ul style="list-style-type: none"> <li>• Honeycombing only</li> </ul>	<ul style="list-style-type: none"> <li>• Fibrosis with or without architectural distortion, with features favoring either a pattern other than UIP or features favoring UIP secondary to another cause*</li> <li>• Some histologic features from column 1, but with other features suggesting an alternative diagnosis†</li> </ul>	<ul style="list-style-type: none"> <li>• Features of other histologic patterns of IIPs (e.g., absence of fibroblast foci or loose fibrosis) in all biopsies</li> <li>• Histologic findings indicative of other diseases (e.g., hypersensitivity pneumonitis, Langerhans cell histiocytosis, sarcoidosis, LAM)</li> </ul>

*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.

CI, 1.6–12.5%), and delayed wound healing (4 studies; 14 of 430, 3.3%; 95% CI, 2.0–5.4%).

**Conclusions.** When the desirable consequences (adequate specimens in 100%, diagnosis made in 89%) were weighed against the undesirable consequences (surgical complications including mortality, exacerbations, respiratory infection, bleeding, prolonged air leak), 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 for UIP, 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. The panel emphasized that the decision to perform SLB should be made in the context of a 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.

**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 for UIP, or an alternative diagnosis, we suggest SLB (conditional recommendation, very low quality of evidence).**

- **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).**

**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 (65–71) (Table E9).

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%).

**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 for UIP, 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 for UIP, or an alternative diagnosis and lower among those with an HRCT pattern of UIP.

No consensus was reached on whether the desirable consequences of

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 for UIP	IPF	IPF (Likely)**	Indeterminate for IPF***	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 for IPF

- 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.

TBBx (adequate specimens in 78%, SLB avoided in 36%) outweigh the undesirable consequences (nondiagnostic in 64%, risk of procedural complications) in patients with an HRCT pattern of probable UIP, indeterminate for UIP, or an alternative diagnosis. The panel made no recommendation 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. In contrast, 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 (72, 73) but is not yet available in routine clinical practice, and further studies to validate this are pending.

**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 for UIP, or an alternative diagnosis, the panel made no recommendation for or against TBBx.**

- 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*).

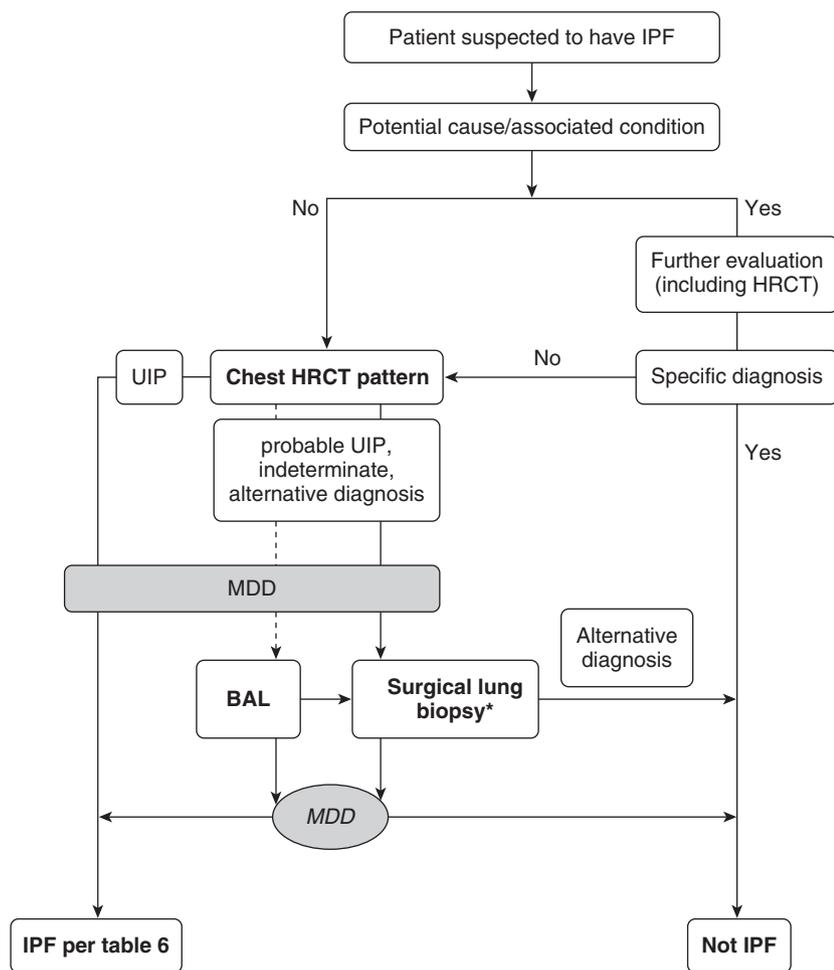
**Question 6: For Patients with Newly Detected ILD of Unknown Cause Who Are Clinically Suspected of Having IPF, Is Lung Cryobiopsy a Reasonable Alternative to SLB to Ascertain the Histopathology Diagnosis of UIP Pattern?**

**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 (63, 64, 69–71, 74–81) (Table E10).

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;



**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 85). 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.

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%).

**Conclusions.** Although the panel was enthusiastic about the desirable consequences of lung cryobiopsy (adequate

specimens in 96%, SLB avoided in 80%), this was offset by concern about the undesirable consequences (nondiagnostic in 20%, risk of procedural complications), lack of standardized procedure and approach, and the heterogeneous rates of adverse events noted in previous studies (82–84). 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? 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 for UIP, 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 for UIP, or an alternative diagnosis, the panel made no recommendation regarding 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 recommend NOT performing lung cryobiopsy (strong recommendation, very low quality of evidence).

**NOTE:** Recommendations for questions related to MDD and serum biomarkers are addressed in the full-text manuscript and online supplement (Tables E11 and E12).

## Conclusions

Evidence was discussed, diagnostic criteria for IPF were updated, and a committee of IPF experts formulated recommendations for individual diagnostic tests. A new feature of this guideline, compared with the prior version of the guideline (1), 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 for UIP, and alternative diagnosis). These recommendations should be reconsidered as new evidence becomes available.

Although the guideline panel recognized the need to refine and validate diagnostic approaches according to the HRCT patterns described above, the panel is

aware that other important issues exist that need to be addressed with future studies. These include studies of the utility of BAL and lung tissue specimens (regardless of whether obtained by TBBx, cryobiopsy, and/or SLB) for molecular diagnostic and machine learning tools, the impact of diagnosis on clinical outcomes, genetic testing, and the diagnostic utility of circulating biomarkers. ■

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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