Unclassifiable interstitial lung disease: from phenotyping to possible treatments

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Purpose of review
Accurate diagnosis of interstitial lung diseases (ILDs) can be challenging, and a substantial percentage of ILD patients remain unclassifiable even after thorough assessment by an experienced multidisciplinary team. In this review, we summarize the recent literature on the definition, prevalence, diagnosis, treatment, and prognosis of unclassifiable ILD, and also discuss important current issues and provide future perspectives on the classification of ILD.

Recent findings
Approximately 12% of patients with ILD are considered unclassifiable, with large variability across previous studies that is in part secondary to inconsistent definitions of unclassifiable ILD and other ILD subtypes. A recent International Working Group suggested that unclassifiable ILD should be defined by the absence of a leading diagnosis that is considered more likely than not after multidisciplinary discussion of all available information. Clinical features and outcomes of unclassifiable ILD are intermediate between idiopathic pulmonary fibrosis and nonidiopathic pulmonary fibrosis ILD cohorts, and choices for pharmacotherapy should be considered on a case-by-case basis.

Summary
Recent studies have provided additional data on the clinical features and prognosis of unclassifiable ILD, but also highlight the many uncertainties that still exist in ILD diagnosis and classification. New tools are needed to more accurately characterize patients with unclassifiable ILD.

Keywords
classification, diagnosis, idiopathic pulmonary fibrosis, interstitial lung disease, management

INTRODUCTION

Interstitial lung diseases (ILDs) are a large group of inflammatory and fibrotic disorders that damage the lung parenchyma [1]. Despite many similarities in symptoms and physiology at presentation, the underlying biology, prognosis, and recommended treatment approaches differ substantially across ILD subtypes [1–3]. For example, idiopathic pulmonary fibrosis (IPF), which is characterized by a radiological and pathological usual interstitial pneumonia (UIP) pattern, is more frequent in older men, current or former smokers, and patients with gastroesophageal reflux [3]. In contrast, connective tissue disease (CTD)-associated ILDs occur more frequently in younger women [4], while patients with hypersensitivity pneumonitis are less likely to be smokers [5]. There are antifibrotic therapies that can slow progression of IPF [6,7], while immunosuppressive pharmacotherapies are commonly used for non-IPF ILDs [8,9].

Distinguishing among ILD subtypes is frequently challenging, and accurate diagnosis often requires a multidisciplinary effort by a team of experienced ILD clinicians, chest radiologists, and lung pathologists [10▪]. Even after a comprehensive evaluation by a group of experts, a substantial percentage of ILD patients cannot be provided with a specific diagnosis and are labeled with 'unclassifiable ILD' [11–13]. In this review, we summarize the evolving literature on the definition, prevalence, diagnosis, treatment, and prognosis of unclassifiable ILD, and we discuss potential approaches to its phenotyping and management.

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KEY POINTS

- A large percentage of patients with ILD are unclassifiable, even after a comprehensive review of all clinical, radiological, and pathological information by a group of experts.
- Choices for pharmacotherapy of unclassifiable ILD require a case-by-case consideration of the relative likelihoods of the differential diagnosis, the anticipated disease behavior and response to therapy, and potential medication adverse effects and tolerability.
- A more precise definition, novel diagnostic tools, guidance on how to approach specific clinical scenarios are needed to advance our understanding of unclassifiable ILD.

DEFINITION AND TERMINOLOGY

Clinicians and researchers have used several terms to indicate that a patient with ILD cannot be provided with a specific diagnosis, including unclassifiable ILD, unclassified ILD, undefined ILD, and undetermined ILD [11,14–16]. The most common definition of unclassifiable ILD is the absence of a specific diagnosis following a multidisciplinary discussion and review of available clinical, radiological, and pathological information [11,12▪], but the threshold for considering an ILD patient unclassifiable has been inconsistently applied and is not clearly defined in previous consensus statements [1,17]. An International Working Group perspective recently suggested that unclassifiable ILD be defined by the absence of a leading diagnosis that is considered more likely than not (i.e., no single diagnosis that is thought to be at least 51% likely after multidisciplinary discussion), with a provisional and confident diagnosis applying to patients with 51–89% diagnostic confidence and at least 90% confidence, respectively [18▪]. This group recommended that unclassifiable ILD be further subclassified according to whether an adequate surgical lung biopsy was available, and further that a differential diagnosis should be provided and most notably whether IPF was considered a likely possibility (Fig. 1) [18▪]. Previous studies have described many reasons for not being able to confidently diagnose a patient with ILD. These can be broadly categorized into three common scenarios, including an incomplete evaluation, the presence of overlapping findings that are common to multiple distinct ILD subtypes, and nonspecific findings that are not characteristic of any single ILD subtype. Examples for each of these possibilities are presented in Table 1.

PREVALENCE

Estimates for the prevalence of specific ILD subtypes vary substantially. Studies on ILD epidemiology are frequently based on International Classification of

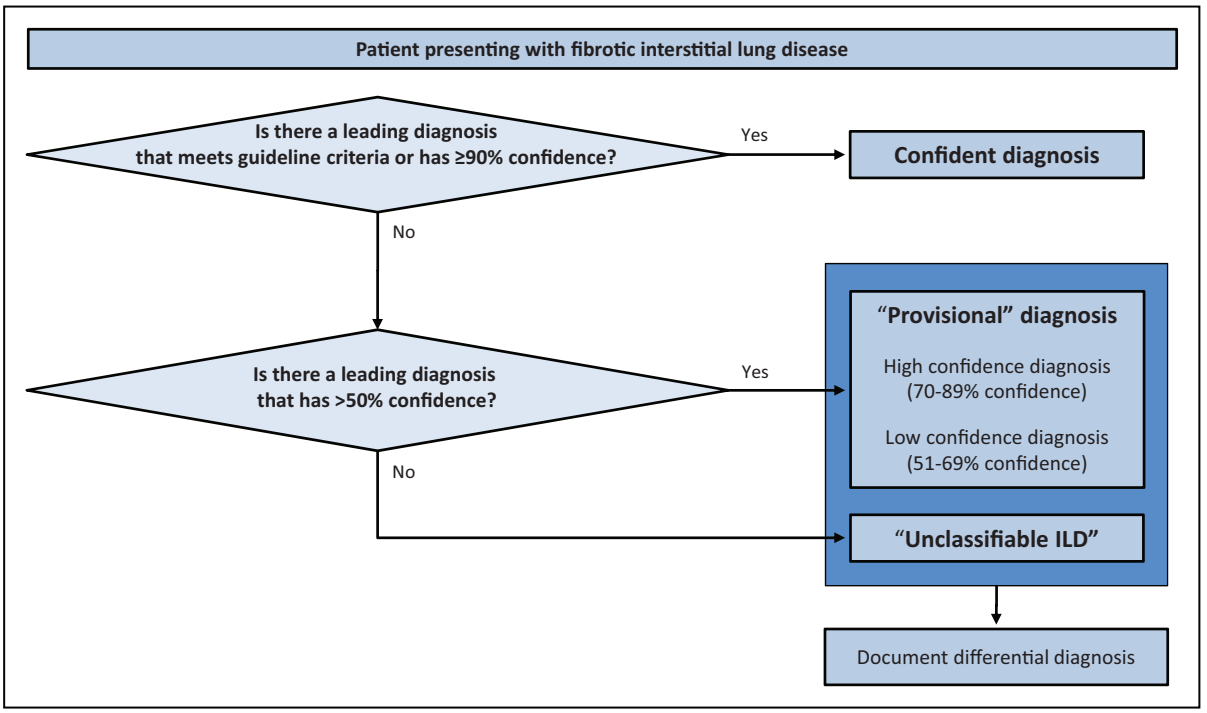

FIGURE 1. Proposed approach to the classification of fibrotic interstitial lung disease. Reprinted with permission [18▪] of the American Thoracic Society. ©2018 American Thoracic Society. ILD, interstitial lung disease.

Table 1. Reasons for unclassifiable interstitial lung disease

	Clinical [11,12▪]	Radiological [19▪]	Pathological [20▪]	Multidisciplinary discussion [11,12▪,21]
Incomplete evaluation	Unable to obtain adequate history (e.g., exposures)	Not available	No biopsy performed (e.g., unfavorable risk–benefit ratio, patient preference)	Not available
		HRCT quality insufficient	Insufficient biopsy quality (too small, damaged, nonoptimal sampling location)	Difficult interpretation of poor quality diagnostic material
Overlapping findings	Multiple risk factors predisposing for different specific ILDs	Overlap with non-ILD features (e.g., cardiac failure, infection)	Overlapping histological features	Discrepant clinical, radiological, and pathological features
		Acute exacerbation		Discrepant interpretation of information by members
		Features of different specific ILDs		
Nonspecific findings	Stable disease, mild symptoms	Indeterminate for UIP	Only advanced interstitial fibrosis	Poorly classifiable findings
		Prior treatment (e.g., corticosteroids)	Prior treatment (e.g., corticosteroids)	

HRCT, high-resolution computed tomography; ILD, interstitial lung disease; UIP, usual interstitial pneumonia.

Diseases codes that have significant limitations compared with contemporary ILD classification [22–24]. Other studies have been based on cohorts recruited from ILD referral centers, and are thus not representative of the general population. Within these specialized ILD clinics, the prevalence of unclassifiable ILD is estimated to be approximately 12%, but with substantial variability between studies likely due to heterogeneous study designs and diagnostic approaches [13]. The proportion of ILD patients who remain unclassifiable may be lower in cohorts that have undergone a multidisciplinary discussion [13], and is particularly high (up to 45%) in an elderly ILD population [25].

CLINICAL FEATURES AND INVESTIGATIONS

The clinical features of unclassifiable ILD are similar to other common fibrotic ILD subtypes for two main reasons. First, a relatively consistent burden of dyspnea, cough, and functional limitation prompts patients to seek medical attention, regardless of the underlying cause, and thus patients have similar ILD severity at the time of diagnosis. Second, unclassifiable ILD likely includes a heterogeneous mixture of patients, and thus consists of patients with clinical features that are intermediate between the different diagnostic possibilities.

Symptoms of unclassifiable ILD are nonspecific, including dyspnea, cough, chest discomfort, reduced exercise capacity, and fatigue. Patients often have exertional hypoxemia that eventually can occur at rest, crackles on lung auscultation, and occasionally digital clubbing [12▪]. The mean age in previous cohorts ranges from 58 to 65 years, and about 50% of patients have a history of cigarette smoking [2,12▪,26–30]. Some studies report a balanced sex distribution [2,26], and others either a male [12▪,27,28], or female predominance [29▪,30]. At diagnosis, patients have mild reduction in forced vital capacity (FVC) and moderate reduction in diffusion capacity of the lung for carbon monoxide (DLCO) (66–79% and 41–55%, respectively) [2,12▪,26–30]. A subgroup of patients with unclassifiable ILD have autoimmune features but cannot be assigned a specific CTD diagnosis, with a proposal that these patients be labeled as having interstitial pneumonia with autoimmune features [31]. Future studies are needed to demonstrate the clinical validity of this grouping, and to evaluate its potential treatment implications.

The diagnosis and classification of ILDs requires high-quality, thin section, preferably contiguous high-resolution computed tomography (HRCT) imaging. Few studies report HRCT findings of patients with unclassifiable ILD, and patterns are either nonspecific or difficult to classify. Two studies have reported radiological patterns of patients with unclassifiable ILD, with definite UIP reported in 6–17% and possible UIP in 26–50% of patients [11,29▪]. Other commonly reported radiological patterns include nonspecific interstitial pneumonia, desquamative interstitial pneumonia, and features suggested of chronic hypersensitivity pneumonitis [12▪].

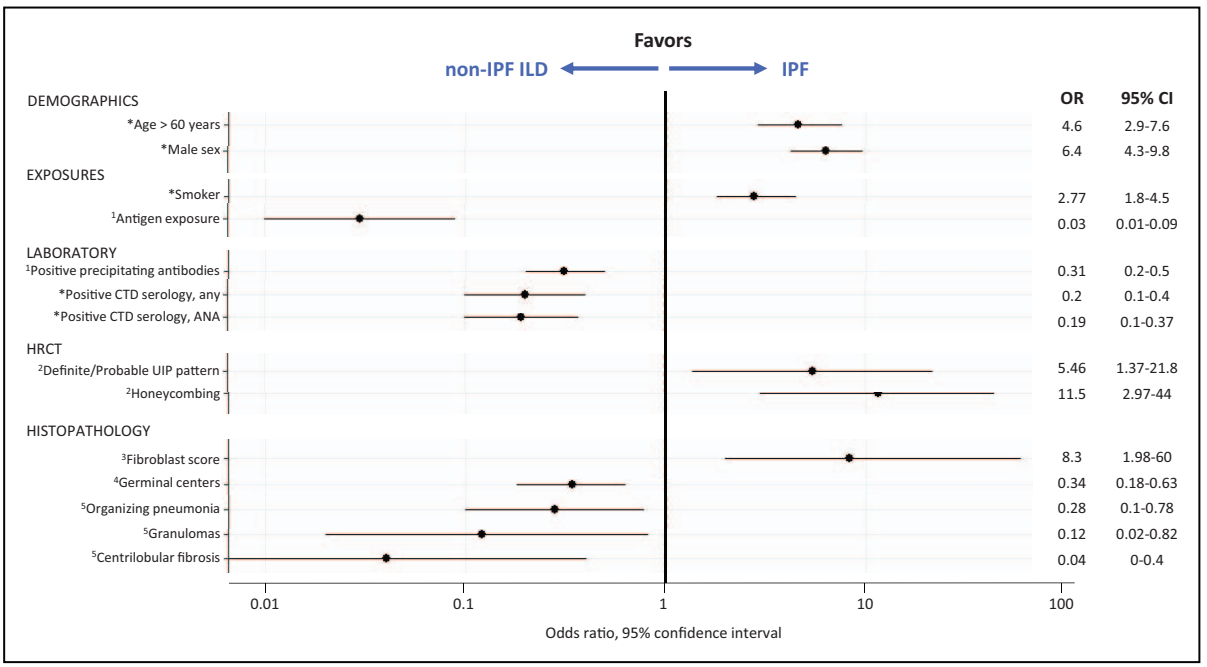

FIGURE 2. Selected features that increase or decrease the odds of idiopathic pulmonary fibrosis. Data from the St. Paul's Hospital (Vancouver, Canada) interstitial lung disease database of 882 patients; 1. Lacasse *et al.* (2003) [5], 2. Hunninghake *et al.* (2003) [38], 3. Flaherty *et al.* (2003) [39], 4. Song *et al.* (2009) [40], and 5. Takemura *et al.* (2012) [41]. 95% CI, 95% confidence interval; ANA, antinuclear antibody; CTD, connective tissue disease; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; OR, odds ratio; UIP, usual interstitial pneumonia.

The largest studies of patients with unclassifiable ILD report only 22–28% of patients underwent a surgical lung biopsy [11,12▪,29▪], with the majority of these patients having overlapping histological patterns [29▪]. Surgical lung biopsy was not performed in the remaining patients for a variety of reasons, largely driven by the uncertain risk–benefit ratio in some situations. Specifically, the estimated in-hospital mortality of 1.7% for elective procedures and 16% for nonelective biopsies can be difficult to justify in patients with mild and potentially nonprogressive disease and in patients with advanced ILD that is associated with greater risk of complication [32▪,33▪]. Furthermore, surgical lung biopsy does not always yield a specific ILD diagnosis, with approximately 10% of cases still remaining unclassifiable following biopsy [12▪,34]. Consequently, the risk of biopsy should be weighed against the potential benefit on an individual basis including consideration of patient preference.

Bronchoalveolar lavage cellular analysis is usually nonspecific in patients with unclassifiable ILD [15,28]. Transbronchial lung cryobiopsy has a higher diagnostic yield compared with conventional transbronchial biopsy and might allow pathological phenotyping in a population of unclassifiable ILD patients that does not qualify for surgical lung biopsy [35▪,36▪]; however, the safety and yield of cryobiopsy have not been clearly established in comparison with surgical lung biopsy [35▪]. Additional data are needed to clarify the role of bronchoscopic studies in patients with fibrotic ILD.

The above features are best considered in the context of a multidisciplinary discussion of experts, typically defined as a dynamic face-to-face review of all available clinical, radiological, and pathological data. Multidisciplinary discussion has replaced the previous pathological reference standard for ILD diagnosis [17], and is strongly recommended in recent guidelines for patients with fibrotic ILD [1,3]. Multidisciplinary teams should particularly consider the many factors that can alter the likelihood of an IPF or a non-IPF ILD diagnosis (Fig. 2). This process improves diagnostic confidence [10▪,37], and may decrease the percentage of patients who are considered unclassifiable [13].

MANAGEMENT

Many nonpharmacological therapies for patients with fibrotic ILD are nonspecific and should routinely be considered for patients with unclassifiable ILD. These include smoking cessation, avoidance of potentially harmful exposures, pneumococcal and influenza vaccinations, pulmonary rehabilitation,

long-term oxygen therapy, and management of comorbidities. Lung transplantation is an option for some patients with unclassifiable ILD, while others might benefit more from a more palliative approach that places greater emphasis on symptom management.

Antifibrotic medications (pirfenidone and nintedanib) are only approved for the treatment of IPF, with most regions funding these therapies exclusively in patients who meet IPF diagnostic criteria from established clinical practice guidelines [6,7]. Subgroup analyses suggest that nintedanib may be beneficial in patients with suspected IPF who did not meet guideline criteria [42▪]; however, additional studies are needed to better define this subgroup of potential responders and to replicate this finding prospectively. Randomized controlled trials are currently evaluating this question by testing the safety and efficacy of pirfenidone and nintedanib in patients with unclassifiable ILD (Table 2) [43,44]. Immunosuppressive medications may be a treatment option for unclassifiable ILD when there is a low likelihood of IPF and a primary differential diagnosis of chronic hypersensitivity pneumonitis [9], CTD-ILD [45], or other non-IPF ILDs [46]. The decision to initiate a trial of immunosuppressive therapy in this situation must be balanced against the previously demonstrated detrimental effects of immunosuppressive therapy in patients with IPF [47].

PROGNOSIS

The survival of patients with unclassifiable ILD appears to be intermediate between the survival of IPF and non-IPF ILD patients, with 2-year survival rates ranging from 70 to 76% [11,12▪,28,29▪]. This is again expected considering the heterogeneous population of unclassifiable ILD that includes patients with mild disease in which biopsy is not considered necessary and other patients with severe disease that prohibits performance of a surgical lung biopsy. Independent risk factors for mortality in patients with unclassifiable ILD include older age, lower FVC, and crackles on lung auscultation [12▪], with lower DLCO%-predicted and higher fibrosis score on HRCT independently predicting both mortality and disease progression in another study [11]. Traction bronchiectasis on HRCT, increased pulmonary artery diameter, and higher Composite Physiologic Index have also been reported as mortality risk factors [29▪].

DISCUSSION

Our understanding of ILD diagnosis and classification continues to evolve. Recent publications have provided a framework for a more consistent approach to ILD diagnosis, and the future study of these patients. Despite these advances, there remain several important questions related to unclassifiable ILD.

Is unclassifiable interstitial lung disease a useful category?

The main potential downside to designation of unclassifiable ILD as a disease category is that it is a heterogeneous and poorly defined collection of patients, and that providing a label for these patients might be used as justification to refrain from further pursuit of an underlying cause [49]. It is critical, however, that this label should instead prompt a regular re-evaluation and search for new information that might increase the confidence in a specific ILD diagnosis. It is unknown what

Table 2. Ongoing randomized controlled trials in patients with unclassifiable interstitial lung disease

Study	Patients, *n*	Study design	Key inclusion criteria	Primary outcome	Treatment/ duration	Expected date of results
Pirfenidone in patients with unclassifiable progressive fibrosing ILD [43]	250	Phase II, double-blind, randomized, placebo-controlled	Rate of decline in FVC > 5% or symptomatic worsening over the last 6 months	Rate of decline in FVC	Pirfenidone titrated up to 2403 mg/ day for 24 weeks	Early 2020
Efficacy and safety of nintedanib over 52 weeks in patients with progressive fibrosing interstitial lung disease [44,48]	600	Phase III, double-blind, randomized, placebo-controlled	Rate of decline in FVC > 10 or >5% and symptomatic or radiological worsening over the last 24 months	Rate of decline in FVC	Nintedanib 150 mg twice daily for 52 weeks	Late 2019

FVC, forced vital capacity; ILD, interstitial lung disease; *n*, number.

percentage of unclassifiable ILD cases can be assigned a confident diagnosis at re-evaluation and how frequently cases should be revisited. The most practical approach is to conduct this reassessment on an ad hoc basis, with a likely role to perform some tests more regularly (e.g., serologies or computed tomography every 1–2 years). Regardless, there remain a large number of ILD patients that cannot be assigned a specific diagnosis. Having a label for these patients is necessary to facilitate studies of these patients, including identification of its biological and clinical phenotypes as well as enrolment of patients in clinical trials. For clinical purposes, the integration of available data into a 'working diagnosis' can facilitate pragmatic management decisions; however, it is important to recognize the need to reassess the diagnosis of these patients during long-term follow-up.

How should unclassifiable interstitial lung disease be defined and subcategorized?

An International Working Group recently proposed that unclassifiable ILD be defined by the absence of a leading diagnosis that is considered more likely than not (Fig. 1) [18▪]; however, this is a highly subjective definition that is significantly impacted by the thoroughness of the diagnostic evaluation. Some studies have required a surgical lung biopsy prior to categorization of an ILD patient as unclassifiable; however, this working group instead suggested both biopsied and nonbiopsied patients be considered in the same category, but with subgrouping according to the presence or absence of a biopsy. Similarly, some studies have required a multidisciplinary discussion for these patients; however, this resource is not available in many regions and has other incompletely understood limitations that prohibit its routine requirement in the ILD diagnostic process. Currently, it remains unclear how unclassifiable ILD should be defined, which diagnostic steps should be compulsory before calling a case unclassifiable, and how unclassifiable ILD should be subcategorized. Advances in molecular phenotyping with transcriptomics [50,51], proteomics [52,53], metabolomics [54,55], and epigenetics [56] may eventually allow an accurate ILD diagnosis in many patients who are currently considered unclassifiable.

What pharmacotherapies should be considered for patients with unclassifiable interstitial lung disease?

Choices for pharmacotherapy of unclassifiable ILD are challenging and require a case-by-case consideration of the relative likelihoods of the differential diagnosis, the anticipated disease behavior and response to therapy, and potential medication adverse effects and tolerability. Potential treatment options for patients with unclassifiable ILD include short-term immunosuppressive therapy with reassessment of the initial treatment response, long-term immunosuppressive therapy, antifibrotic therapy, and observation without pharmacotherapy. Determining whether a given treatment strategy has been effective in an individual patient is limited by the heterogeneous disease progression. For this reason, disease progression despite therapy is often interpreted as a failure of therapy; however, disease stability while on a given treatment is of less certain significance. Given the absence of proven benefit for any pharmacotherapy in unclassifiable ILD, observation without therapy should be considered in patients with mild and stable disease, or in frail patients who might be more prone to clinically significant adverse effects.

Clinical trials are currently ongoing in unclassifiable ILD; however, design of these studies and their translation into clinical practice is a major challenge for several reasons. First, unclassifiable ILD is inconsistently defined in the previous literature, and attempts to standardize the nomenclature and definition for this group of patients remains highly subjective [18▪]. Second, large patient numbers and careful selection of trial endpoints are required to overcome the 'noise' that arises from the variable rates of progression for the heterogeneous population of patients with unclassifiable ILD. Third, the heterogeneous biology of unclassifiable ILD indicates that targeted therapies may be unlikely to work except in small and more consistently defined subgroups. Despite these limitations, there is much insight to be gained from the testing of potential pharmacological interventions in these patients, and specifically evaluation of biological predictors of response to therapy.

CONCLUSION

Unclassifiable ILD is a common, but heterogeneous and poorly defined subgroup of ILD. Recent studies have provided additional data on the clinical features and prognosis of unclassifiable ILD, but also highlight the many uncertainties that still exist in ILD diagnosis and classification. Novel approaches to ILD diagnosis and classification are needed to advance our understanding of unclassifiable ILD, reduce the proportion of unclassifiable cases, and support development of evidence-based treatment approaches for specific biological phenotypes.

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Conflicts of interest

C.J.R. has received research funding, grant support, and speaking honoraria from Boehringer Ingelheim and Hoffmann-La Roche. S.A.G. reports no conflicts of interest.

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- ■■ of outstanding interest

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The Fleischner Society White Paper summarizes recent advances in IPF diagnosis and suggests new IPF diagnostic criteria. The newly proposed high-resolution computed tomography (HRCT) and pathological categories for assessing the usual interstitial pneumonia (UIP) pattern include typical UIP, probable UIP, indeterminate for UIP, and most consistent with a non-IPF diagnosis. Additional recommendations on how to perform a multidisciplinary conference and a checklist of questions that point to a non-IPF diagnosis are provided.

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The study used a secondary care dataset and mortality statistics from England to estimate the mortality rate associated with surgical lung biopsy in patients with ILD. The authors report an in-hospital mortality of 1.7%, a 30-day mortality of 2.4%, and 90-day mortality of 3.9%. Risk factors for mortality included male sex, older age, higher number of comorbidities, and an open (compared with thoracoscopic) procedure.

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