Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper

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This Review provides an updated approach to the diagnosis of idiopathic pulmonary fibrosis (IPF), based on a systematic search of the medical literature and the expert opinion of members of the Fleischner Society. A checklist is provided for the clinical evaluation of patients with suspected usual interstitial pneumonia (UIP). The role of CT is expanded to permit diagnosis of IPF without surgical lung biopsy in select cases when CT shows a probable UIP pattern. Additional investigations, including surgical lung biopsy, should be considered in patients with either clinical or CT findings that are indeterminate for IPF. A multidisciplinary approach is particularly important when deciding to perform additional diagnostic assessments, integrating biopsy results with clinical and CT features, and establishing a working diagnosis of IPF if lung tissue is not available. A working diagnosis of IPF should be reviewed at regular intervals since the diagnosis might change. Criteria are presented to establish confident and working diagnoses of IPF.

Introduction

The approval of medical treatments for idiopathic pulmonary fibrosis (IPF) marks a new era in approaching this deadly disease: offering hope to patients and their physicians, a clearer path forward for companies interested in the development of new treatments, and the potential for new biological insights. This new era also offers clinicians the opportunity to review approaches to diagnosis. The diagnostic criteria for IPF published by the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) in 2011[1] have been crucial for defining entry criteria and ensuring appropriate recruitment for prospective clinical trials.[2–7] In turn, these trials, with large cohorts of well characterised patients, have provided considerable new clinically relevant information about disease presentation and its longitudinal behaviour.[8,9] The specific inclusion and exclusion criteria used in these studies have also highlighted the limitations of current diagnostic guidelines, and indicated opportunities for improvement.[9,10]

The diagnosis of IPF requires the collaboration of multiple specialists, the ability to interpret and communicate complex clinical data patterns, and to integrate uncertain or sometimes conflicting information. The clinician interprets the history and physical examination of the patient to develop a clinical context, the thoracic radiologist interprets the pattern present on high-resolution CT images of the chest and, if needed, the pathologist interprets the histopathological pattern seen on lung biopsy samples. All the information gained must then be shared in a common language to enable clinical decision making. Since so-called classic clinical stories and patterns are uncommon, some degree of clinical uncertainty is often present, and acknowledgment of this limitation and a clear plan to address it are essential.

For this Review, we identified specific questions pertaining to the diagnosis of IPF (panel 1), and did a search of the medical literature to identify evidence related to the topics identified and that had been published after the 2011 ATS/ERS/JRS/ALAT guidelines.[1] Using this research and the expert opinion of members of the Fleischner Society, we provide IPF diagnostic criteria that we believe will be useful for clinicians, clinical trialists, trial sponsors, and other interested groups.

Systematic review

An international multidisciplinary committee, including 17 members of the Fleischner Society with expertise in interstitial lung disease (ILD) and evidence-based medicine (eight pulmonologists, six radiologists, and three pathologists), and a medical librarian expert (SLK), developed the key questions believed to be important for the diagnosis of IPF (panel 1). Several face-to-face meetings were held, in addition to monthly conference calls. We did a literature search with the assistance of a medical librarian (search strategy and selection criteria and appendix). The committee was divided into subgroups assigned to specific

Key messages

- A confident diagnosis of IPF (idiopathic pulmonary fibrosis) can be made in the correct clinical context when CT imaging shows a pattern of typical or probable UIP (usual interstitial pneumonia)
- If the clinical context is indeterminate for IPF, or the CT pattern is not indicative of typical or probable UIP, biopsy should be considered to confirm the presence of a UIP histological pattern, and a confident diagnosis of IPF could then be made on the basis of a multidisciplinary evaluation
- If diagnostic tissue is not available, a working diagnosis of IPF could be made after a careful multidisciplinary evaluation
- All patients with an IPF diagnosis, particularly those with a working diagnosis, should have this diagnosis reviewed at regular intervals

sections and questions. Reviewers from each subgroup used a two-step screening process on the basis of article title and abstract, with predefined inclusion and exclusion criteria, to identify articles for inclusion in this Review. The subgroups reviewed the relevant literature and produced the first draft of their respective sections, which were compiled by the committee chair (DAL) and a complete first draft was created. This document was reviewed and edited by all committee members, and then circulated among all members of the Fleischner Society for comments, and appropriate revisions were made. The final Review was approved by all authors.

Clinical assessments

What specific clinical information is required to exclude other forms of ILD?

A diagnosis of IPF requires exclusion of alternative causes of fibrosing ILD, broadly grouped into systemic and exposure-related disorders. The clinical assessment requires an inquiring mind, a clear understanding of the differential diagnosis for IPF, and a comprehensive and structured approach to help exclude known causes and associations of fibrosing lung disease. A clear focus of a patient's clinical examination should be to establish the clinical probability of IPF, which is particularly increased when the patient is older than 60 years, male, and has a history of cigarette smoking.[11] Panel 2 lists some additional important clinical questions that need to be addressed when collecting the history of an individual with suspected IPF, and the specific clinical challenges of systemic autoimmune disease, chronic hypersensitivity pneumonitis, and familial pulmonary fibrosis are briefly discussed below.

A systematic assessment for connective tissue disease is necessary in patients who present with suspected IPF, and identification of a defined connective tissue disease (eg, rheumatoid arthritis) excludes IPF. Some patients with fibrosing lung disease have serological abnormalities or symptoms suggestive of an autoimmune disease, or both, but do not meet the criteria for a specific connective tissue disease (ie, interstitial pneumonia with autoimmune features).[3,12–17] A substantial proportion of patients with interstitial pneumonia with autoimmune features have imaging or pathological features of usual interstitial pneumonia (UIP),[18] and have similar survival to patients with IPF. The proposed criteria to identify interstitial pneumonia with autoimmune features have not been sufficiently validated to justify exclusion from a diagnosis of IPF, and these individuals should be considered to have IPF if they meet the diagnostic criteria outlined in this Review.

In every patient with fibrosing ILD, identification of exposure to antigens that might result in hypersensitivity pneumonitis is important, and lists of such antigens are available.[19] However, the clinical significance of such exposures can be difficult to establish, and no universally accepted criteria for chronic hypersensitivity pneumonitis exists. In general, antigen exposure is more likely to be clinically significant if the exposure coincides with or precedes the onset of symptoms, if symptoms fluctuate temporally in relation to the exposure, and if other imaging, histological, or laboratory features are suggestive of chronic hypersensitivity pneumonitis.[20] The clinical significance of histological findings suggesting hypersensitivity pneumonitis without known exposure (which accounts for as many as 50–60% of cases of histological chronic fibrotic hypersensitivity pneumonitis[21,22]) remains unclear; some of these cases are probably due to unrecognised antigens. The clinical usefulness of serum precipitins in the diagnosis of hypersensitivity pneumonitis is uncertain.[23] However, showing lymphocytosis on cellular analysis of bronchoalveolar lavage fluid can be helpful in supporting a diagnosis of hypersensitivity pneumonitis.[23–26] Some patients with a UIP pattern of pulmonary fibrosis have a history of occupational or medication exposures and these patients should be discussed at a multi-disciplinary conference to review the relevance of these exposures.[27–32]

Pulmonary fibrosis, including IPF, can cluster in families. Familial forms of IPF can be related to common genetic variants (eg, the rs35705950 promoter variant associated with increased *MUC5B* expression), or to rare variants (eg, in genes associated with telomere maintenance or surfactant metabolism).[33] The radiological presentation of familial IPF can differ from that of sporadic IPF, with a higher prevalence of diffuse or upper lung involvement,[34] and its pathology can also differ from that of non-familial IPF, with a higher prevalence of unclassifiable fibrosis on surgical lung biopsy.[35] Although some of these patients will not meet the strict definition of IPF because they fail to meet histological or imaging criteria, careful multidisciplinary consideration might result in a working diagnosis of IPF for some patients.

Imaging

CT plays a central role in the assessment of patients with ILD, and can be diagnostic in many situations.

***Panel 1*: Key questions to be addressed**

- What specific clinical information is required to exclude other forms of ILD?
- What are the key CT features for making a diagnosis of UIP?
- How can UIP or IPF be distinguished by CT from other fibrosing interstitial pneumonias?
- When is surgical or other biopsy indicated in the diagnosis of IPF?
- What are the crucial pathological features by which a diagnosis of UIP or IPF can be made?
- How can UIP or IPF be distinguished histologically from other fibrosing interstitial pneumonias?
- How should multidisciplinary diagnosis be performed in the diagnosis of IPF?
  - Who should be engaged in multidisciplinary diagnosis?
  - Which patients should undergo multidisciplinary diagnosis?
  - What are the limitations of multidisciplinary diagnosis?

ILD=interstitial lung disease. IPF=idiopathic pulmonary fibrosis. UIP=usual interstitial pneumonia.

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See **Online** for appendix

For **The Drug-Induced Respiratory Website** see http://pneumotox.com/

Panel 2: **Clinical checklist for alternative diagnoses**

General
- What are the severity, duration, and pace of the primary respiratory symptoms?

Systemic autoimmune disease
- Are symptoms or signs of a systemic autoimmune disorder present?
- Are serological findings suggestive of an autoimmune disorder? Eg, rheumatoid arthritis, systemic sclerosis, polymyositis and dermatomyositis, Steven-Johnson syndrome, or mixed-connective tissue disease.

Other systemic disease (sarcoid, immune-system abnormalities)
- Is there evidence of other organ involvement?

Hypersensitivity pneumonitis
- Does the patient have a clinically relevant exposure to an antigen, generally inhaled, known to result in the development of hypersensitivity pneumonitis?
- Do they have pets, including birds?
- What are they exposed to in their home or work environment? Is there water damage?
- Is the exposure clinically significant?
- Is the intensity clinically significant?
- Is there a temporal association between the exposure and symptom onset?

Occupational and environmental lung disease
- Does the patient work in an occupation known to be at risk for the development of lung disease?
- What do they do in their current job and previous jobs?
- What avocational exposures exist?

Drug-induced lung disease
- Does the patient use any medicines, herbs, vitamins, supplements, or recreational drugs that could account for the presence of lung disease?

Specific genetic syndromes
- Is there a family history of lung fibrosis?
- Is there evidence of premature graying, cryptogenic cirrhosis, aplastic anaemia, myelodysplasia, macrocytosis, or thrombocytopenia?

When IPF is considered in the differential diagnosis, the radiologist must indicate whether a UIP pattern is present and, if so, what their level of confidence is. Because of its importance, a systematic approach to CT of the chest in patients with suspected UIP is needed. This approach entails evaluation of image quality, precise assessment of specific disease features by use of standard terminology, and the determination of distribution and extent. This method should permit the radiologist to classify the CT pattern into one of four categories (table 1).

High-quality CT images are essential. Optimal quality CT requires thin sections (<2 mm) and high spatial resolution reconstruction.[36] Images should be obtained at full inspiration to total lung capacity. Inadequate inspiration increases lung attenuation, potentially leading to misinterpretation of key findings (eg, ground glass opacity and fine reticulation).[37] Volumetric CT acquisition is preferred to non-contiguous imaging because it improves the characterisation of patchy disease and delineation of disease extent, clarifies disease distribution, allows identification of ancillary findings, facilitates differentiation between honeycombing and traction bronchiectasis, and optimises comparison with follow-up images to assess progression or improvement.[38,39] Acceptable CT scans can be obtained with a reduced-dose technique by use of automatic tube current modulation, optimisation of tube potential, beam-shaping filters, or dynamic z-axis collimators.[40] Reduced-dose CT scans reconstructed with iterative algorithms can allow the detection of subtle interstitial abnormalities, and can be compared with standard-dose CT images.[41] Prone CT imaging is useful when disease is suspected in patients with normal or minimally abnormal chest radiographs, and particularly when dependent opacification is present on supine CT images.[42] Prone CT can also facilitate the diagnosis of honeycombing, reducing observer variation in diagnosing IPF.[43] Expiratory imaging is useful to identify air trapping, a feature that can suggest an alternative diagnosis such as chronic hypersensitivity pneumonitis or connective tissue disease.[44] Prone and expiratory acquisitions can be done with non-contiguous imaging and at lower doses than the inspiratory CT.[45]

What are the key CT features for making a diagnosis of UIP?

Honeycombing

Identification of honeycombing on chest CT is important for both diagnosis and prognosis in fibrotic ILD.[1,46–49] Honeycombing is a key characteristic of the UIP pattern, and is typically located in the dorsal, basal, and subpleural regions of the lung, but sometimes is seen only in the upper lungs in otherwise typical cases of UIP.

On CT, honeycombing is defined as clustered, thick-walled cystic spaces of similar diameters, generally measuring between 3 and 5 mm, but occasionally up to 25 mm in size (figure 1).[50] Although honeycombing can consist of several stacked layers of cysts, a single subpleural layer of two or three contiguous cysts is enough for a diagnosis of honeycombing (figure 1F).[51] Honeycomb cysts that are visually identified by CT are usually thought to correspond to cysts on gross pathological specimens,[39] but they can also correlate with foci of traction bronchiolectasis.[52] The much smaller cysts seen in histopathological specimens, called microscopic honeycombing, are beyond the spatial resolution of CT and often do not correlate with honeycombing on CT.[53] Micro-CT has shown that honeycombing develops at the periphery of the pulmonary lobule, in and around collapsed alveoli and connecting bronchioles.[54]

The identification of honeycombing on CT varies substantially between observers, most frequently because of the coexistence of other abnormalities—eg, emphysema and traction bronchiectasis. In a large study[55] in which observers were presented with single CT images, disagreement about the presence or absence of

	Typical UIP CT pattern	Probable UIP CT pattern	CT pattern indeterminate for UIP	CT features most consistent with non-IPF diagnosis
Distribution	Basal predominant (occasionally diffuse), and subpleural predominant; distribution is often heterogeneous	Basal and subpleural predominant; distribution is often heterogeneous	Variable or diffuse	Upper-lung or mid-lung predominant fibrosis; peribronchovascular predominance with subpleural sparing
Features	Honeycombing; reticular pattern with peripheral traction bronchiectasis or bronchiolectasis*; absence of features to suggest an alternative diagnosis	Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis*; honeycombing is absent; absence of features to suggest an alternative diagnosis	Evidence of fibrosis with some inconspicuous features suggestive of non-UIP pattern	Any of the following: predominant consolidation, extensive pure ground glass opacity (without acute exacerbation), extensive mosaic attenuation with extensive sharply defined lobular air trapping on expiration, diffuse nodules or cysts

UIP=usual interstitial pneumonia. IPF=idiopathic pulmonary fibrosis. *Reticular pattern is superimposed on ground glass opacity, and in these cases it is usually fibrotic. Pure ground glass opacity, however, would be against the diagnosis of UIP or IPF and would suggest acute exacerbation, hypersensitivity pneumonitis, or other conditions.

Table 1: **Diagnostic categories of UIP based on CT patterns**

honeycombing occurred in approximately a third of cases, particularly when this feature was mixed with traction bronchiectasis, large cysts, and superimposed paraseptal or centrilobular emphysema. Reviewing sequential multiplanar images is particularly important in such situations.

Reticular pattern

The reticular pattern is characterised by a network of fine lines. On CT scans from patients with UIP, reticulation is often irregularly spaced, with a mixture of thick and thin lines, in contrast to CT scans from those with non-specific interstitial pneumonia, in which spacing is more regular and lines are more homogeneous in thickness.

Traction bronchiectasis

Traction bronchiectasis and bronchiolectasis are a hallmark of lung fibrosis on chest imaging, and an important prognostic marker in UIP (figure 1).[56] This feature represents irregular bronchial and bronchiolar dilatation caused by retractile fibrosis in the surrounding lung parenchyma.[50] In the CT images of patients with UIP, traction bronchiectasis is predominantly seen in the periphery of the lungs, and affected airways typically have an irregular varicose appearance. This appearance, along with the background of lung fibrosis shown by reticulation and ground glass opacity, helps to distinguish traction bronchiectasis from freestanding bronchiectasis unrelated to fibrosis.[51] Traction bronchiectasis is also a salient feature in patients with fibrotic non-specific interstitial pneumonia, but the dilated bronchi seen in these patients are usually more central in the lung.[57] Although distinguishing honeycombing from traction bronchiectasis can be challenging, it is diagnostically important, since honeycombing increases the likelihood of UIP. Conglomerated peripheral traction bronchiectasis or bronchiolectasis can resemble honeycombing, particularly when it predominates at the lung bases. Viewing sequential, multiplanar CT images and post-processing reconstruction algorithms (eg, minimum intensity

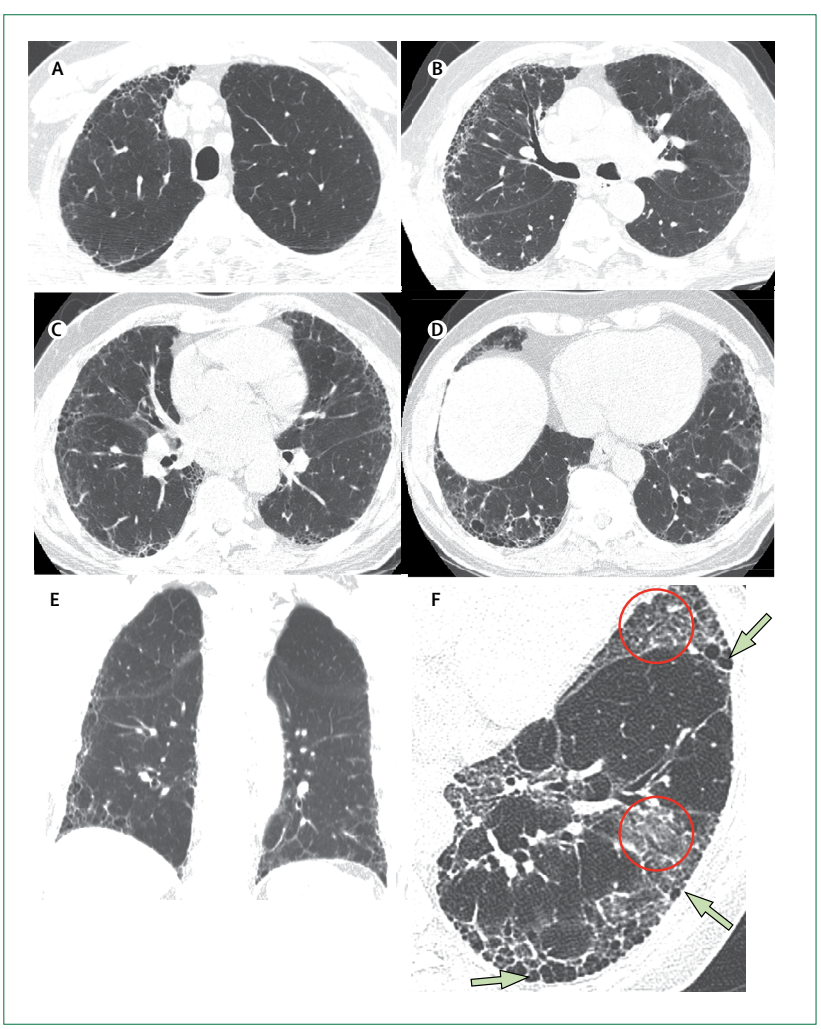

Figure 1: **Typical UIP CT pattern**

(A–F) Axial and coronal CT images for a patient with typical UIP show subpleural predominant reticular abnormality with traction bronchiectasis and honeycombing, with a clear craniocaudal gradient on coronal images (E). (F) A magnified view of a different patient shows areas of honeycombing occurring in single and multiple layers (arrows). Additionally, two areas of apparent ground glass abnormality (circles) are shown on closer inspection to contain dilated bronchi (traction bronchiectasis), and therefore likely to represent fibrosis. UIP=usual interstitial pneumonia.

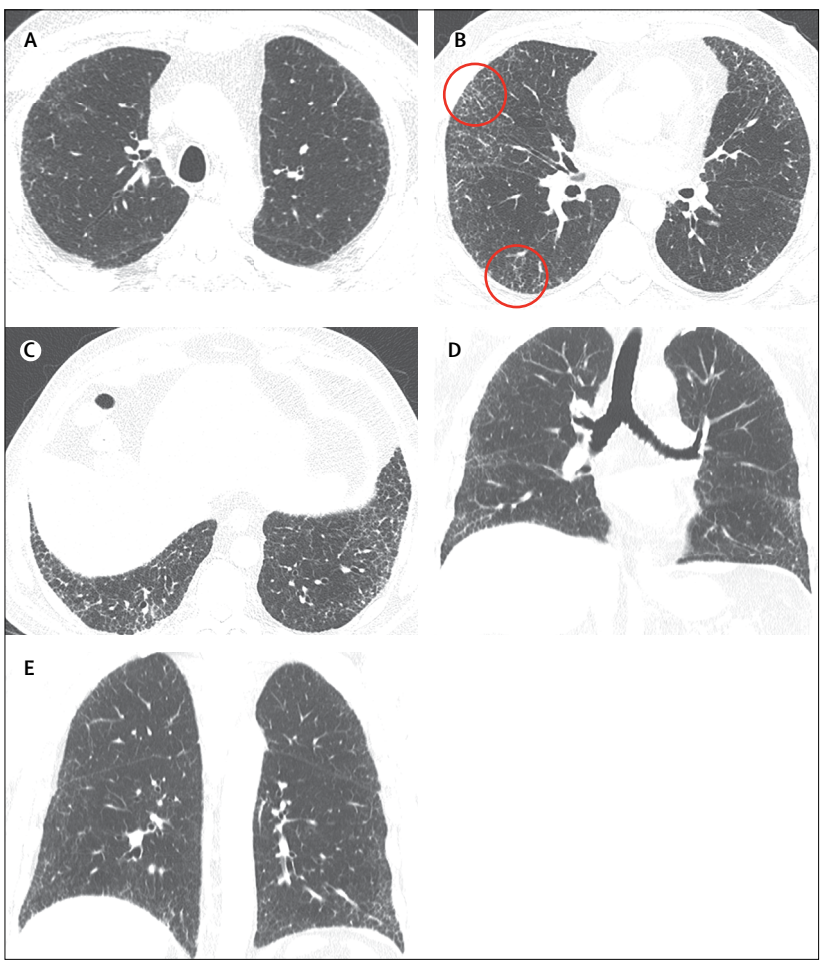

Figure 2: **Probable UIP CT pattern**
(A–E) CT images show basal predominant, subpleural predominant reticular abnormality, with peripheral traction bronchiectasis (circles in B) but no honeycombing. For this patient, UIP was proven with histology. UIP=usual interstitial pneumonia.

projection) can help differentiate honeycombing from traction bronchiectasis; however, honeycombing and traction bronchiectasis often coexist.[39] Indeed, some honeycomb cysts can contain bronchiolar markers and might therefore represent end-stage traction bronchiolectasis.[58] Overall, the identification of traction bronchiectasis appears to be associated with slightly less variation between observers than honeycombing, with moderate to good agreement reported for its presence or absence on CT.[48,56,59]

Ground glass opacity

Pure ground glass opacity is not usually a feature of UIP, although many patients with fibrotic lung disease have ground glass opacity admixed with reticular abnormality or traction bronchiectasis, or both (figure 1F). In this context, ground glass opacity should be regarded as part of the fibrotic process;[60] however, UIP is unlikely when pure ground glass opacity is present as an isolated finding of diffuse ILD. The presence of abundant pure ground glass opacity in a patient with fibrotic ILD, particularly in non-fibrotic areas of the lung, suggests acute exacerbation or infection.[61,62]

Other findings

Mild mediastinal lymph node enlargement is evident on CT in approximately 70% of patients with UIP.[63] Occasionally, fine linear or small nodular foci of calcification are observed within areas of fibrosis as a result of ossification,[64] and the prevalence of these calcifications is significantly higher in patients with UIP (28·5%), than in other diffuse fibrosing lung diseases (8·3%, p<0·001).[65] Some patients with otherwise typical UIP can also have some features of idiopathic pleuroparenchymal fibroelastosis (PPFE), with bilateral irregular pleuroparenchymal thickening in the upper and mid lungs.[66] Until the entity of overlapping UIP and PPFE can be further clarified, patients that otherwise meet the criteria for IPF should be considered to have IPF, whether or not an element of PPFE is present.

How can UIP be distinguished on CT from other fibrosing interstitial pneumonias?

A diagnosis of IPF cannot be established from CT scans alone. The UIP pattern seen in IPF is often radiologically indistinguishable from the UIP pattern seen in some cases of connective tissue disease, chronic hypersensitivity pneumonitis, and pneumoconiosis, and other diseases.[27,32,38,67] Also, very rarely sarcoidosis can present with CT features resembling a typical UIP pattern.[68]

The identification of a UIP pattern can be more challenging in smokers who have both lung fibrosis and emphysema—a disease combination observed in about a third of patients with IPF.[69,70] In a study[71] of 40 patients with lung fibrosis and concurrent emphysema, the radiological diagnosis was correct in only 30 (44%) of 68 readings, including 20 (50%) of 40 readings for UIP and 10 (36%) of 28 readings for non-specific interstitial pneumonia. Radiologists should describe the extent and relative severity of coexisting emphysema in patients with the UIP pattern, since the presence of emphysema influences patient management and prognosis.[72] The entity of airspace enlargement with fibrosis, which can be found in smokers, produces a cystic abnormality that resembles honeycomb cysts on CT.[73,74] However, airspace enlargement with fibrosis is usually predominant in the upper-to-mid lung, spares the most peripheral parts of the lung, and displays thinner walls than the cysts of honeycombing.[75] The CT features of airspace enlargement with fibrosis tend not to be associated with other CT signs of lung fibrosis, with the exception of combined pulmonary fibrosis and emphysema, which is characterised by the presence of emphysema, cysts, and a UIP pattern of fibrosis.[76]

It is important to differentiate the CT pattern of chronic hypersensitivity pneumonitis and connective tissue disease from UIP when possible. Features of hypersensitivity pneumonitis include an upper-lung or mid-lung

distribution of fibrotic abnormality (although about a third of cases have predominance in the lower lung),[77] profuse and poorly defined centrilobular nodules, and mosaic attenuation or air trapping. Mosaic attenuation and air trapping are helpful in distinguishing hypersensitivity pneumonitis from UIP,[77] particularly when present in a non-fibrotic area of lung, but they are frequently present within areas of advanced fibrosis in the lower lobes of the lungs of patients with IPF. Confidence in the identification of air trapping in the lungs decreases as the features of lung fibrosis become more extensive and coarse.[78] In a 2016 study,[10] mosaic attenuation or air trapping was the source of CT-pathological discordance in 51 (72%) of 71 patients who had a final diagnosis of IPF. Patients with connective tissue diseases, particularly rheumatoid arthritis, can also develop UIP. The presence on CT of pleural effusion, oesophageal dilation, or pericardial abnormality in a patient with a UIP pattern should highlight the possibility of an underlying connective tissue disease.[79]

In several studies,[10,48,80] up to 60% of patients that underwent biopsy and showed typical histological signs of UIP did not show a typical CT chest-imaging pattern. Thus, in the correct clinical setting, a diagnosis of IPF should not be excluded if the CT pattern is more suggestive of another ILD, such as non-specific interstitial pneumonia, chronic hypersensitivity pneumonitis, or sarcoidosis.[80] The CT pattern for UIP most frequently overlaps with that of fibrotic non-specific interstitial pneumonia. In a study[81] of 92 patients with an idiopathic interstitial pneumonia proven by surgical lung biopsy (including 20 with UIP, 16 with cellular non-specific interstitial pneumonia, and 16 with fibrosing non-specific interstitial pneumonia), radiologists made the correct chest imaging pattern diagnosis for 74 (80%) patients. Multivariate logistic regression analysis[81] showed that a UIP pattern could be independently predicted by the extent of honeycombing on CT. Also, subpleural sparing is a CT feature in up to 60% of patients with non-specific interstitial pneumonia, and it is not usually observed in patients with UIP.[77]

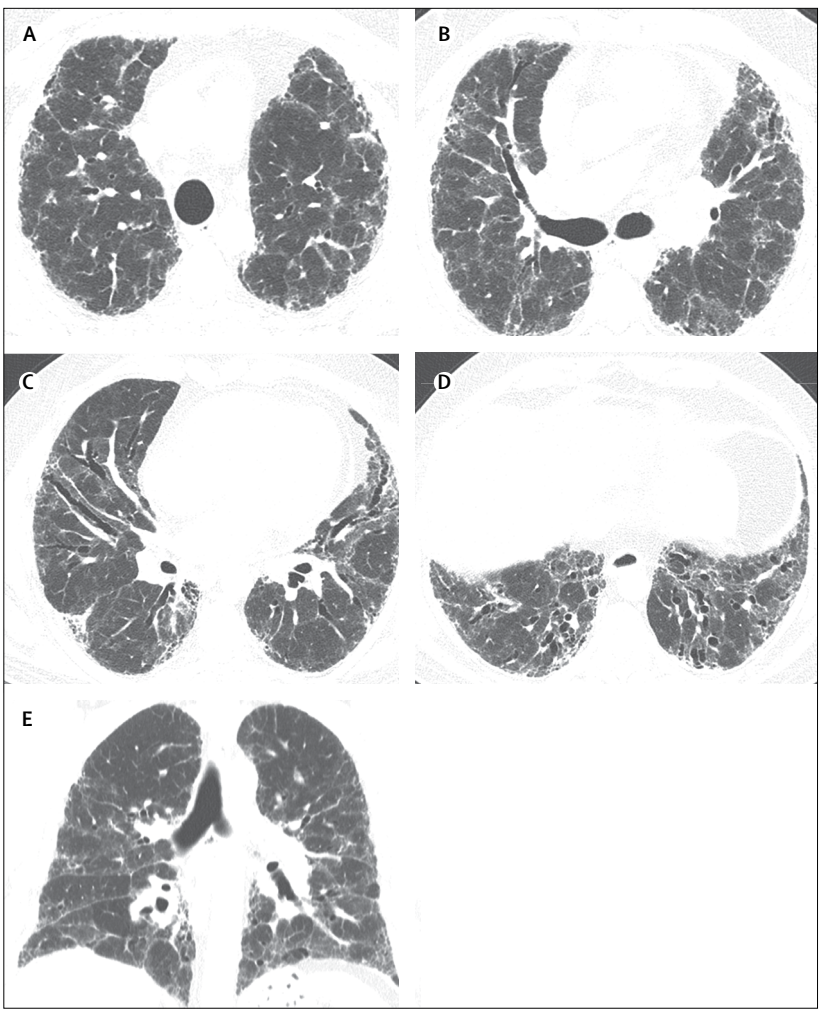

Figure 3: **CT pattern indeterminate for UIP**
(A–E) CT images show reticular abnormality with traction bronchiectasis, without honeycombing. Although the abnormality is lower-lung predominant, the findings are not typical for UIP because of peribronchovascular extension (C), patchy ground glass abnormality, and mosaic attenuation (E). For this patient, UIP was proven at biopsy. UIP=usual interstitial pneumonia.

Diagnostic categories of CT patterns

The 2011 guidelines on IPF[1] define three diagnostic categories based on CT appearance: UIP, possible UIP, and inconsistent with UIP (table 1). These classifications allowed some standardisation of diagnostic certainty and were shown to have some prognostic value in two studies;[82,83] however, a larger study[84] showed no difference in survival after statistical adjustments for the extent of fibrosis. In another large study,[85] interobserver agreement across these diagnostic categories was moderate both for fellows in training and thoracic radiologists.

In the appropriate clinical context, a typical UIP pattern by CT is sufficient to secure a diagnosis of IPF without the need to perform a surgical lung biopsy or other invasive tests.[86,87] The typical UIP pattern is characterised by reticular opacities with obligatory honeycombing, usually associated with traction bronchiectasis (figure 1). Ground glass opacity, if present, is usually admixed with reticular abnormality and honeycombing.[88] Such abnormalities are characteristically basal and peripheral, although they are often patchy.[89] Some degree of upper-lung involvement (including honeycombing) is normal,[86,89] and sometimes the craniocaudal distribution can be relatively uniform in patients with otherwise typical UIP. Up to 25% of patients with IPF have an asymmetric distribution of fibrosis.[90] The specificity of a confident diagnosis of the typical UIP pattern by CT has been reported to be 94–100% in most studies.[77,87,91] The sensitivity of diagnosis is lower, at 43–78%. The lower specificity is related to patients who either do not have honeycombing on CT or have atypical findings that impair the radiologist's ability to diagnose UIP on the basis of CT alone.[77,87,91] In an IPF clinical trial,[9] a typical

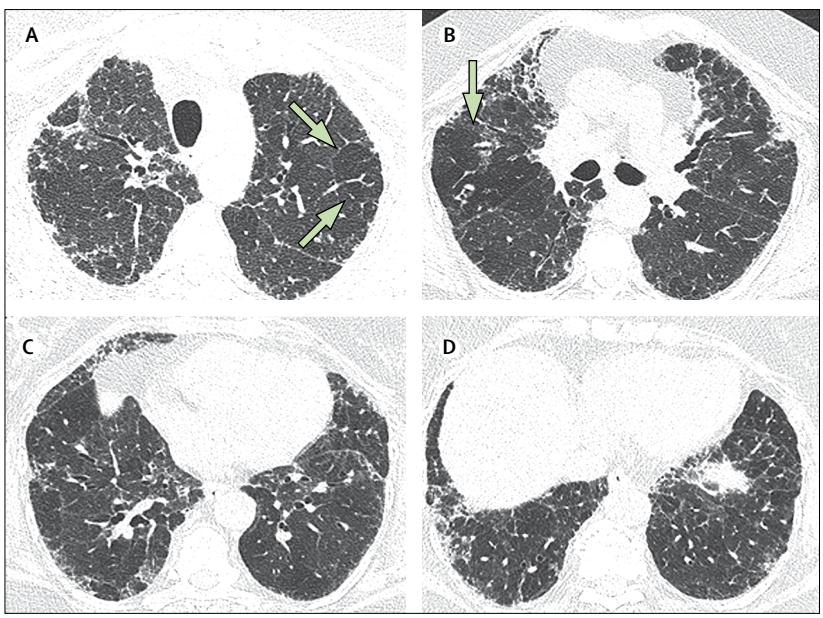

Figure 4: **CT pattern indeterminate for UIP**
(A–D) Inspiratory CT images show diffuse, peripheral predominant reticular opacities admixed with patchy areas of decreased (mosaic) attenuation (arrows). For this patient, UIP was proven at biopsy. UIP=usual interstitial pneumonia.

For examples of the **CT features of UIP** see http://get.pacsbin.com/fleischner/

UIP pattern was found by CT in only 567 (53%) of 1061 enrolled patients, and no difference in disease behaviour or treatment responsiveness was identified between patients with and without typical UIP.

The 2011 ATS/ERS/JRS/ALAT clinical practice guidelines[1] state that a biopsy is necessary to confirm the underlying histopathological pattern diagnosis of UIP in patients with possible UIP, which was defined as the presence of reticular abnormality and traction bronchiectasis with a subpleural and lower-zone predominance, and without honeycombing. However, studies[8,53] have shown that the absence of honeycombing should not exclude a diagnosis of UIP if all other features of UIP are present (particularly subpleural and basal predominance and traction bronchiectasis). These other CT findings can be regarded as showing a probable UIP pattern (figure 2), with 82–94% of these patients having a probable or definite UIP histopathological pattern on surgical lung biopsy.[8,53] In assessing the likelihood of UIP in these patients, it is helpful to incorporate an estimate of the clinical probability of IPF, which is increased in those who are older than 60 years, are current or former smokers, and have no history of other potential causes of fibrosis.[11,92]

A UIP pattern can still be found on histological testing of patients who do not have typical or probable UIP patterns (figure 3).[53] These patients, who might have been termed as "inconsistent with UIP" under the 2011 guidelines,[1] should be considered as indeterminate for UIP. In particular, in patients with biopsy-proven UIP, areas of decreased attenuation or mosaic attenuation were observed in 20 (43%) of 46 readings in one study[77] and in 51 (27%) of 188 patients in a different study (figure 4),[10] and therefore this finding cannot be used to exclude a diagnosis of IPF. However, the presence of mosaic attenuation or sharply defined lobular expiratory air trapping, or both, should always prompt clinical concern and multidisciplinary assessment for underlying hypersensitivity pneumonitis, particularly when these findings are extensive and present in non-fibrotic parts of the lung.

Many patients with fibrotic ILD have CT imaging features that clearly suggest a pattern other than that of UIP. Specifically, a clear upper-lobe predominance (figure 5), subpleural sparing, consolidation, predominant ground glass opacity (in a clinically stable setting), diffuse nodules, and cysts are only very rarely observed in patients with UIP.[48,77,80]

Examples of the CT features of UIP, with complete scrollable image datasets and corresponding histology, are available online.

Pathology

When is surgical or other biopsy indicated in the diagnosis of IPF?

The presence of a typical or probable UIP pattern on CT provides a diagnosis of IPF in the appropriate clinical context; no additional information is necessary, as discussed in the previous section. A surgical lung biopsy should be considered when the CT pattern is indeterminate or inconsistent with UIP, or when the clinical features suggest an alternative diagnosis (eg, exposures suggestive of hypersensitivity pneumonitis).

The current IPF guidelines[1] do not adequately address the diagnostic fate of patients who do not have a typical UIP pattern on CT and cannot, or choose not to, undergo a surgical lung biopsy. In this specific situation, bronchoscopy with transbronchial biopsy and bronchoscopic alveolar lavage could provide information to increase the likelihood of an IPF diagnosis or of an alternative diagnosis.[93,94] However, tissue obtained by transbronchial biopsy is usually inadequate for a confident diagnosis of UIP.[95] Histological identification of UIP requires specific microscopic findings that can generally only be fully appreciated in a surgical lung biopsy. Individual features of a UIP pattern, such as fibroblast foci, that can occasionally be seen on transbronchial biopsy, are not specific enough for a diagnosis of UIP. Although UIP features have been found in up to a third of transbronchial biopsy samples in patients with IPF,[96] there seem to be no prospective studies using an acceptable gold standard to show that a confident diagnosis of IPF can be made using transbronchial biopsy.

Despite advances in diagnosis by CT, surgical lung biopsy remains an important method for the diagnosis of IPF in a large subset of patients who cannot be diagnosed on the basis of clinical and imaging features alone.[10,80] Surgical lung biopsy is usually recommended for individuals with undiagnosed fibrosing ILD, unless

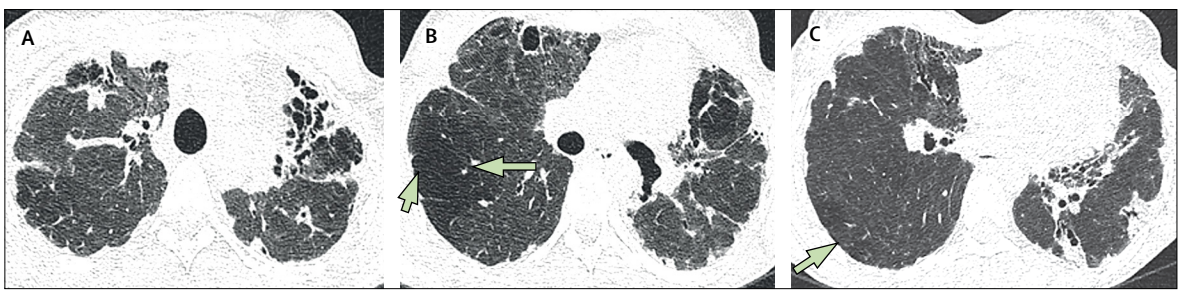

Figure 5: **CT pattern most consistent with non-IPF diagnosis**
(A–C) Inspiratory CT images show upper-lobe predominant peribronchovascular (bronchocentric) reticular opacities, architectural distortion, severe traction bronchiectasis, and areas of decreased attenuation (B and C; arrows). This CT pattern is consistent with the diagnosis of fibrotic hypersensitivity pneumonitis. IPF=idiopathic pulmonary fibrosis.

mitigating circumstances exist. Ideally, the biopsy samples should be taken from multiple lobes,[97,98] and should target areas of diseased but not end-stage lung. Each biopsy sample should measure at least 2–3 cm along the pleural margin and be 1–2 cm deep.[99] Biopsy samples measuring up to 4 cm in their greatest dimension are achievable.[100]

Morbidity and mortality are a concern with surgical lung biopsy. In a review[101] of 2820 surgical lung biopsies done for suspected ILD from 1997 to 2008 in the UK, 30-day mortality was 2·4% and 90-day mortality was 3·9%. In a US-based study of surgical lung biopsies done between 2000 and 2011,[102] in-hospital mortality was 1·7% for elective procedures but significantly higher, at 16%, for non-elective procedures.[102] Risk factors for mortality include being male, increasing age (particularly older than 65 years), comorbidities, open rather than thoracoscopic surgery, and a lung-diffusing capacity of less than 50% of predicted.[101,103] Notably, several of these risk factors substantially increase the clinical likelihood of IPF, and a provisional diagnosis of IPF before surgical lung biopsy was a risk factor for in-hospital mortality.[102] Complications of surgical lung biopsy include pneumothorax, pneumonia, protracted air leaks, acute exacerbations, and infections.[104,105] The decision to perform surgical lung biopsy to make a diagnosis of UIP should be individualised on the basis of these risk factors and discussion with the patient.

Transbronchial cryobiopsy has emerged as a possible alternative to surgical lung biopsy with potentially lower morbidity and mortality.[106–110] In this procedure, a cryoprobe that is cooled to –85 to –95°C is applied to the desired tissue. The resultant tissue sample is substantially larger than that of a transbronchial forceps biopsy. However, cryobiopsy samples are much smaller than surgical lung biopsy samples,[106] and this has implications in terms of the proportion of diagnoses successfully made: up to 80% for the cryobiopsy and higher than 95% for surgical lung biopsy.[109] Additionally, cryobiopsy samples are usually obtained from a more central site (away from pleural surface), and this could further reduce the diagnostic yield for IPF. Even if multiple samples are obtained, they are usually from the same site.[106] The diagnostic yield and complication rate

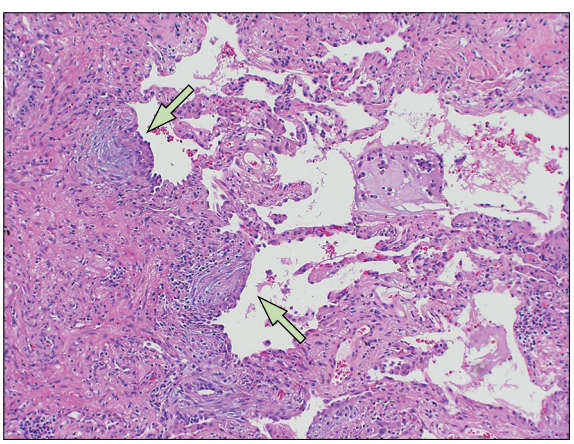

Figure 6: **Fibroblastic foci**
Fibroblast foci in UIP-IPF are sometimes highlighted by their basophilic appearance, reflective of increased mucopolysaccharide associated with young fibrous tissue. The fibroblast foci (arrows) show prominent basophilia and are rounded to a convex configuration and adjacent to dense scarring. UIP=usual interstitial pneumonia. IPF=idiopathic pulmonary fibrosis.

are variable and depend on the experience of the operator. At present, clinicians in Europe have more experience with this technique than those in the rest of the world. The role of transbronchial cryobiopsy in diagnosing fibrotic ILD remains unclear given the variable levels of clinical experience, and clearer standardisation of the technique and establishing a safety profile is needed that remains acceptable in less experienced hands. Surgical biopsy remains the gold standard for tissue diagnosis.

What are the key pathological features by which a diagnosis of UIP and IPF can be made?

IPF is pathologically characterised by a UIP pattern; however, UIP can also be seen in other settings including connective tissue disease, hypersensitivity pneumonitis, pneumoconiosis, and as a result of the toxic effects of drugs. For this reason, the term UIP-IPF is used in this Review to distinguish the UIP pattern in IPF from UIP occurring in other conditions. The major pathological features of UIP include: dense fibrosis, which causes

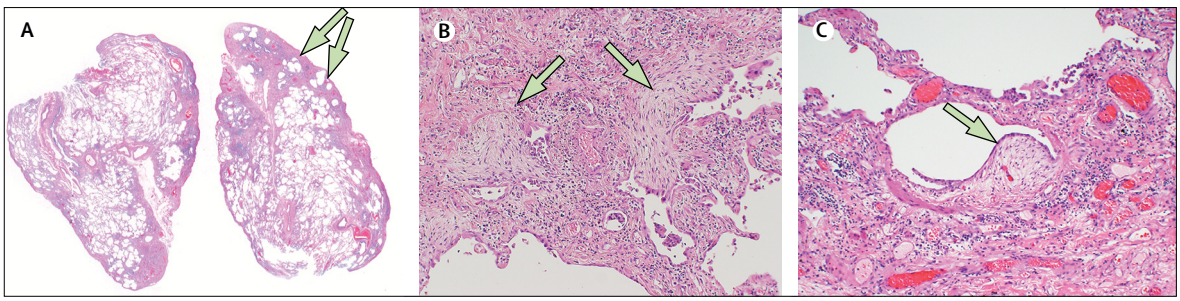

***Figure 7*: Definite UIP-IPF**
(A) Scanning power microscopy shows patchy subpleural and paraseptal scarring that includes some subpleural microscopic honeycombing (arrows). (B, C) Higher power evaluation from the same patient shows readily identifiable fibroblast foci (arrows). The fibroblast foci are pale and oedematous and somewhat convex or rounded in appearance and adjacent to scarring. Such a case fulfils the criteria for the diagnosis of definite UIP-IPF. UIP=usual interstitial pneumonia. IPF=idiopathic pulmonary fibrosis.

	Definite UIP-IPF	Probable UIP-IPF	Indeterminate for UIP-IPF	Features most consistent with an alternative diagnosis
General comments	Patients show features with all four criteria, and do not show features that might suggest an alternative diagnosis (eg, non-UIP)	Patients show either honeycomb fibrosis only, or a severe fibrosing process that falls short of showing all four criteria for definite UIP-IPF and do not show features that might suggest an alternative diagnosis	Patients show evidence of a fibrosing process but with features that are more in favour of either a non-UIP pattern, or UIP in a setting other than IPF	Patients show either a UIP pattern with ancillary features strongly suggesting an alternative diagnosis, or a non-UIP pattern (see cell below)
Specific criteria	Dense fibrosis causing architecture remodelling with frequent honeycombing; patchy lung involvement by fibrosis; subpleural or paraseptal distribution, or both; fibroblast foci at the edge of dense scars	Honeycomb fibrosis only or; dense fibrosis causing architecture remodelling with frequent honeycombing; patchy lung involvement by fibrosis; fibroblast foci at the edge of dense scars may or may not be present	Patients have less compelling histological changes than those classified by the final column (eg, occasional foci of centrilobular injury or scarring, rare granulomas or giant cells, only a minor degree of lymphoid hyperplasia or diffuse inflammation, or diffuse homogenous fibrosis favouring fibrotic non-specific interstitial pneumonia); these features, and the differential diagnoses they call to mind, become part of the multidisciplinary discussion and decision with regard to a multidisciplinary diagnosis of IPF, or not	Non-UIP pattern: patients with features of other fibrotic disorders—eg, fibrotic hypersensitivity pneumonitis, fibrotic non-specific interstitial pneumonia, fibrosing organising pneumonia, pleuroparenchymal fibroelastosis, pulmonary Langerhans cell histiocytosis, or smoking-related interstitial fibrosis; UIP pattern with ancillary features strongly suggesting an alternative diagnosis: eg, prominent diffuse alveolar damage or organising pneumonia (consider acute exacerbation of UIP), granulomas, (consider hypersensitivity pneumonitis, sarcoid, infection), marked interstitial inflammatory cell infiltrate away from areas of UIP (consider hypersensitivity pneumonitis)

UIP=usual interstitial pneumonia. IPF=idiopathic pulmonary fibrosis.

***Table 2*: Histopathological criteria for UIP in IPF (UIP-IPF)**

remodelling of lung architecture with frequent honeycomb fibrosis; fibroblast foci, which are typically scattered at the edges of dense scars (figure 6); patchy lung involvement; and frequent subpleural, paraseptal, and peripheral acinar distribution (figure 7, table 2). Specific pertinent findings should be absent, including diffuse alveolar damage, organising pneumonia, hypersensitivity pneumonitis, airway-centred processes, and granulomatous inflammation. One exception is in acute exacerbation of UIP-IPF, in which prominent hyaline membranes of diffuse alveolar damage and organising pneumonia can be superimposed on a UIP pattern.

Honeycombing (figure 8) is one of the key findings both pathologically and radiologically in IPF, although its presence is not required for the diagnosis. Both radiological and pathological honeycombing are defined by the presence of abnormal airspaces; however, the pathological definition applies to airspaces from microscopic honeycombing (beyond the resolution of CT) to cysts larger than a centimetre,[111] whereas the radiological definition applies to abnormal airspaces typically 3–5 mm in size.[50] Although these definitions overlap, radiological honeycombing should not be equated with pathological honeycombing.[53,67]

How can UIP-IPF be distinguished histologically from other fibrosing interstitial pneumonias?

The most common conditions that should be distinguished histologically from IPF include chronic hypersensitivity pneumonitis,[2,112–114] idiopathic non-specific interstitial pneumonia,[57,115] connective tissue disease, and PPFE.[66,116] Hypersensitivity pneumonitis typically shows bronchiolocentricity, cellular interstitial chronic inflammation, poorly formed granulomas, organising pneumonia, and, in more chronic disease, it can show fibrosis, including a UIP pattern (figure 9). Pathologically, non-specific interstitial pneumonia is characterised by uniform thickening of alveolar walls by fibrosis or chronic

inflammation, or both, without honeycombing. Fibroblast foci are either absent or inconspicuous. The fibrosis in PPFE is predominantly in the upper lobes and shows an intra-alveolar fibrosis with prominent elastosis in the alveolar interstitium, but can coexist with UIP and other patterns of interstitial fibrosis.[66,116] UIP associated with connective tissue disease can show coexistent features, including pleuritis, organising pneumonia, prominent interstitial chronic inflammation, and lymphoid hyperplasia including follicular bronchiolitis (figure 10).[67,117,118]

Most patients with IPF are either current or former cigarette smokers, and smoking-related changes can coexist with and complicate the histopathology of UIP in IPF. These changes include emphysema (sometimes associated with scarring), airspace enlargement with fibrosis,[119] respiratory bronchiolitis (which itself can be associated with fibrosis and ILD),[120–123] smoking-related intersitial fibrosis (with subpleural hyaline alveolar septal scarring that is sometimes stellate and centrilobular), desquamative interstitial pneumonia (DIP) with fibrosis, and a pattern that can be described as fibrotic non-specific interstitial pneumonia in a smoker (which resembles DIP fibrosis but without the airspace macrophages), that has also been called smoking-related idiopathic interstitial pneumonia.[124]

Histological diagnostic categories

A table in the 2011 ATS/ERS/JRS/ALAT IPF management guidelines[1] proposed criteria for "definite", "probable", "possible", and "definitely not" UIP that could be correlated with CT imaging as part of a diagnostic algorithm. However, these criteria do not take into account the increasing recognition of a UIP pattern occurring in diseases other than IPF, such as chronic hypersensitivity pneumonitis and connective tissue disease. We therefore propose a revised version of these guidelines in which criteria are more specifically related to UIP arising in patients with IPF (ie, UIP-IPF; table 2). In the indeterminate categories, it is important to provide a descriptive diagnosis, listing the various diagnostic considerations.

Guidance for multidisciplinary diagnosis

Multidisciplinary assessment of a patient with fibrotic ILD is important to establish the diagnosis and level of diagnostic confidence, determine the need for biopsy and other investigations, and help guide management. In the 2011 guidelines[1] for the diagnosis and management of IPF, a multidisciplinary diagnosis consisted of the integration of views from radiologists, pathologists, and pulmonary specialists, primarily on the basis of a formulaic tabulated approach. However, the process of multidisciplinary diagnosis is increasingly viewed as synonymous with diagnosis by interactive multidisciplinary discussion—an approach that has been shown to be effective in other disciplines—eg, diabetes, psychiatric conditions, and cancer.[125] Recommendations for how to conduct a multidisciplinary conference are listed in table 3. In fibrotic ILD, multiple studies[126,127] have shown that interobserver agreement among clinicians, radiologists, and pathologists increases substantially following multidisciplinary discussion, with an increase in diagnostic confidence and a change in the histological diagnosis in up to 20% of patients. In a single-centre

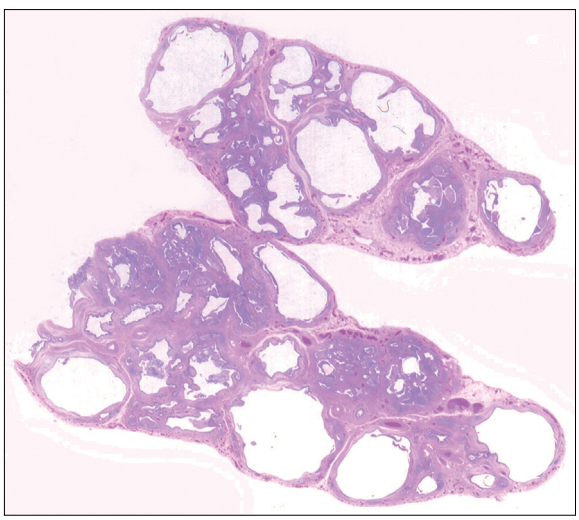

Figure 8: **Probable UIP-IPF**
Scanning power microscopy of a surgical biopsy sample shows that the lung is entirely replaced by honeycombing. Such a biopsy sample, in the appropriate clinical setting, is designated as probable UIP-IPF. UIP=usual interstitial pneumonia. IPF=idiopathic pulmonary fibrosis.

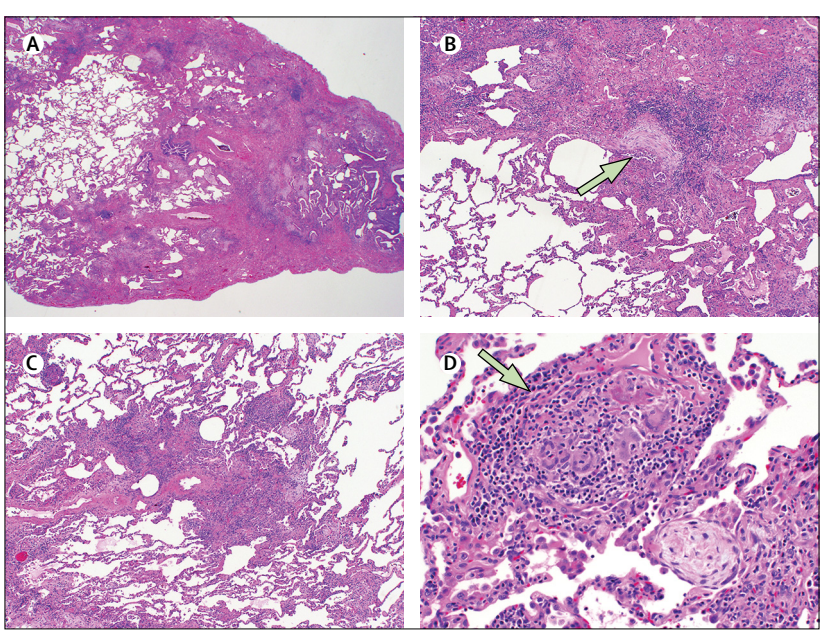

Figure 9: **Biopsy suggestive of an alternative diagnosis—chronic hypersensitivity pneumonitis**
In this surgical lung biopsy sample, some regions show the typical scanning-power appearance of UIP with peripheral and subpleural scarring (A) and readily identifiable fibroblast foci (B; arrow). Other microscopic fields in the same patient, however, show centrilobular injury (C) with associated organising pneumonia and small non-necrotising granulomas (D; arrow), characteristic of hypersensitivity pneumonitis.

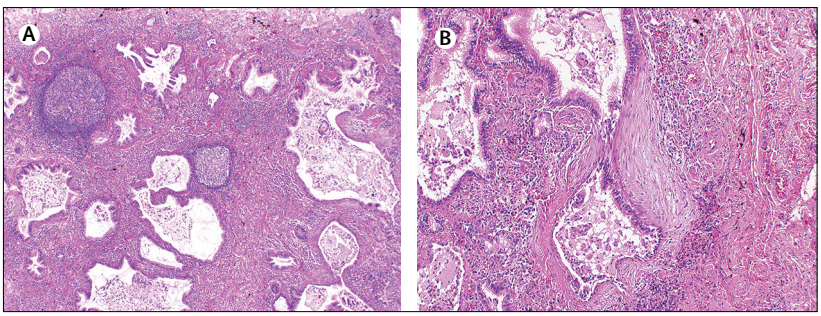

Figure 10: **UIP in connective tissue disease**
(A, B) This biopsy from a patient with rheumatoid arthritis and ILD shows honeycombing with prominent lymphoid hyperplasia with germinal centres; this hyperplasia is a clue to an underlying connective tissue disease. However, a few lymphoid follicles, including a rare germinal centre, are not uncommon in patients with UIP-IPF. Fibroblast foci were present in the regions of honeycombing in this case (B; centre). UIP=usual interstitial pneumonia. ILD=interstitial lung disease. IPF=idiopathic pulmonary fibrosis.

	Desirable features
Frequency	Weekly to monthly, depending on volume of patients
Patient selection	Focus on patients with disease that is not fully characterised, and those with suspicion of a non-IPF aetiology (eg, hypersensitivity pneumonitis, connective tissue disease); in experienced groups with a high volume of patients, those with typical features might not require review; selected patients might also be re-reviewed on follow-up
Nature of conference	Direct contact or telemedicine; pathology and radiology should be directly visualised
Participants	Clinician, radiologist, and pathologist with interest or experience in ILD; if not experienced, linkage to an experienced group is needed (eg, electronic transmission of images, review of slides, telephone or e-mail discussion of clinical aspects); a rheumatologist is often helpful
Goals of meeting	Diagnosis, management plan, review of disease progression
Documentation	First choice multidisciplinary diagnosis (including "unclassifiable disease"), realistic differential diagnoses, likely reversibility; recommendations on additional diagnostic tests
Communication	Final multidisciplinary diagnosis recorded in case notes and communicated in discharge statements; could also include list of conference participants, clinical, radiological, and pathological diagnoses, and management recommendations

IPF=idiopathic pulmonary fibrosis. ILD=interstitial lung disease.

Table 3: **Recommendations for multidisciplinary diagnosis conferences**

study,[128] for over 50% of patients a previous diagnosis of IPF was deemed inaccurate after multidisciplinary discussion. In a second study, multidisciplinary discussion resulted in a change in diagnosis for ten (37%) of 27 patients referred with a diagnosis of IPF, and seven patients referred with non-IPF diagnoses had their diagnosis changed to IPF.[129]

A major advantage of multidisciplinary diagnosis is that it reduces diagnostic imprecision due to recognised limitations in each of the three domains (ie, clinical, radiological, and pathological) by combining information from all three; however, the accuracy of each domain is heavily influenced by the individual experience of the clinician, radiologist, and pathologist involved. Uneven levels of experience within a multidisciplinary group might create a hierarchy of opinion, with the result that a single member could dominate the process to the detriment of interactive group discussion. Conversely, if a member of the group does not have sufficient experience with the condition, the diagnosis might be based on conclusions from a single domain, without interactive discussion. The multidisciplinary conference can facilitate weighting of data to provide clear diagnostic guidance on a case-by-case basis, minimising the uncertainty caused by clinical, radiological, or histological information that is difficult to classify. Although multidisciplinary diagnosis has multiple advantages and is widely regarded as the current diagnostic reference standard for IPF, it has not been formally validated. One major difficulty is that the multidisciplinary approach, by definition, integrates all available diagnostic information and therefore no independent diagnostic reference standard exists against which the multidisciplinary diagnosis can be validated.

Consistency of multidisciplinary diagnoses between expert groups requires an international consensus on the diagnostic criteria for IPF, which is conspicuously absent for many of the other causes of fibrosing interstitial pneumonia. In a study[130] in which seven expert multidisciplinary groups evaluated the same patient data, agreement on IPF as a first choice diagnosis was good (weighted $\kappa=0\cdot71$), but there was poor agreement on the diagnosis of chronic hypersensitivity pneumonitis ($\kappa=0\cdot24$) and idiopathic non-specific interstitial pneumonia ($\kappa=0\cdot25$). This discrepancy between the diagnoses probably reflects the international multidisciplinary work that has gone into establishing diagnostic criteria for IPF, and that no such initiatives have focused on hypersensitivity pneumonitis. Accepting this limitation, our consensus is that multidisciplinary diagnosis should be viewed as the appropriate method of IPF diagnosis in several specific contexts (panel 3).

The multidisciplinary diagnosis process should incorporate standardised data that are applicable to all patients. Additionally, the diagnosis should take into account atypical clinical, CT, or histological features, and non-standardised information that varies from patient to patient. For example, a confident IPF diagnosis requires the correct clinical context and the presence of a UIP pattern on CT; however, reconciling atypical features and integrating additional non-standard information is often necessary—eg, bronchoalveolar lavage findings (not performed at all centres), subtle clinical and serological features suggestive of immune dysregulation, and, perhaps most importantly, information on the natural history and treated course of disease (disease behaviour). For many patients, a definite diagnosis cannot be made, but a highly probable working diagnosis can be achieved. Thus, multidisciplinary diagnosis is essentially a process by which the existing evidence base is combined with clinical reasoning to increase the likelihood of an accurate diagnosis of IPF or of an alternative diagnosis. Specialists engaged in multidisciplinary diagnosis have

two important roles: to serve as expert representatives of their disciplines and, equally importantly, to scrutinise and debate the logic of clinical reasoning when this is required.

With this background, we identified the following key features of the multidisciplinary diagnosis process. Firstly, not all patients with IPF require multidisciplinary diagnosis. For example, discussion of patients with classic CT features of IPF in the correct clinical context is not needed if the patient has been reviewed by a single experienced radiologist and clinician. Multidisciplinary diagnosis exists to categorise patients who are not adequately characterised by the existing evidence base (panel 3). In patients with suspected IPF, the goal of multidisciplinary diagnosis is to establish or disprove the diagnosis with the highest level of confidence possible. Secondly, the minimum participants in the diagnosis group should consist of a clinician, radiologist, and pathologist with appropriate levels of experience in ILD diagnosis. The opinion of a rheumatologist with regard to the likelihood of connective tissue disease is often valuable. Other medical specialists (eg, occupational physicians, geneticists) could be helpful in specific cases. Although face-to-face discussion in a public forum is ideal, this is often impracticable for practitioners and patients not based or seen at expert centres. Telemedicine is an acceptable alternative. Finally, the diagnosis should be clearly communicated in the patient's medical record by indicating whether formal IPF diagnostic criteria were satisfied or whether clinical reasoning was required to produce a working diagnosis. The confidence of the working diagnosis should be declared as "confident" or "provisional with high or low confidence".[131]

***Panel 3*: Pathways to a confident working multidisciplinary diagnosis of IPF**

When can one make a confident diagnosis of IPF without biopsy?

- Clinical context of IPF*, with CT pattern of typical or probable UIP

When is a diagnostic biopsy necessary to make a confident diagnosis of IPF?

- Clinical context of IPF* with CT pattern either indeterminate or suggestive of an alternative diagnosis
- Clinical context indeterminate for IPF† with any CT pattern

When is multidisciplinary diagnosis necessary in the context of suspected IPF?

- When the clinical context or the CT pattern, or both, are indeterminate; the outcome of multidisciplinary discussion will be a decision whether to perform an additional clinical evaluation, bronchoalveolar lavage, or diagnostic biopsy, or some combination of these procedures
- After biopsy, to integrate the clinical, imaging, and histological features
- To re-review patients in whom the longitudinal course of disease is discordant with the previously established multidisciplinary diagnosis
- When diagnostic tissue is not available, to consider a working diagnosis of IPF

What should be done when diagnostic tissue is not available?

- Multidisciplinary diagnosis with consideration of the patient's age, sex, smoking status, findings on bronchoalveolar lavage, and longitudinal disease behaviour
- In this context, a working diagnosis of IPF can be made in the presence of a progressive fibrosing interstitial pneumonia, and in the absence of an alternative explanation; the level of diagnostic confidence of such a working diagnosis should be recorded, and the diagnosis should be reviewed at regular intervals, since it might change over time

IPF=idiopathic pulmonary fibrosis. UIP=usual interstitial pneumonia. *Clinical context of IPF includes all of the following: older than 60 years, absence of clinically significant environmental or medication exposure, no evidence of connective tissue disease. †Clinical context indeterminate for IPF includes any of the following: aged 60 years or younger, potentially significant environmental or medication exposure, or evidence of connective tissue disease.

Areas of uncertainty

The understanding of the diagnosis of IPF has many important gaps, and diagnostic guidelines will require regular revision. In this regard, several groups are working on combining imaging and clinical features to refine the assessment of the probability of IPF.[11,132] The clinical significance of atypical features on CT (eg, mosaic attenuation, apical pleuroparenchymal thickening) or by biopsy (eg, granulomas, PPFE) requires further clarification. More work is needed to understand the specificity of CT features that suggest a non-IPF alternative diagnosis (eg, upper-lobe predominance, subpleural sparing, consolidation, predominant ground glass opacity). Further studies of cryobiopsy and correlation with surgical biopsy and outcome should clarify the role of this technique in the diagnosis of IPF. We anticipate that molecular diagnosis with machine learning will play an increasing role in the diagnosis of IPF, particularly when combined with clinical and imaging features.[133,134] Finally, given the high prevalence of "early interstitial lung abnormality"[135] in CT scans of patients who have undergone imaging for other reasons,[136] and the clear association of these abnormalities with increased mortality,[137] the identification of clinical, radiological, and molecular predictors of IPF in this group will be crucial.

Conclusions and recommendations

The clinical, imaging, and histological criteria for diagnosis of IPF continue to evolve. Panel 3 provides some diagnostic parameters that can be followed for patients with suspected IPF based on the clinical diagnostic confidence and radiological and pathological categories discussed in this Review. A diagnosis of IPF can be confidently made in a patient with a typical clinical context of IPF, with a CT pattern of typical or probable UIP. In all other circumstances, multidisciplinary diagnosis is appropriate to inform the decision to proceed with biopsy or other diagnostic assessments. Multidisciplinary assessment can yield a working diagnosis of IPF in some situations where not all of the diagnostic criteria are met, particularly if diagnostic tissue is not available. However, such a diagnosis could change over time—eg, if a connective tissue disease becomes apparent, or a previously unrecognised exposure is identified. We hope that the scheme outlined in this Review will contribute to diagnostic clarity and help improve the management of patients with fibrotic lung diseases.

Search strategy and selection criteria

Because the 2011 American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association statement[1] was based on a systematic literature search that ended in May, 2010, for this Review we searched for publications from May 1, 2010, through to April 28, 2016, on the Ovid platform in MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Abstracts and Reviews of Effects, and Cochrane Database of Systematic Reviews, to identify new publications relevant to our key questions, assisted by a medical librarian experienced with literature searches for pulmonary diseases. An updated search was run later, up to April 20, 2017. A two-step screening process based on article title and abstract was done, with predefined inclusion and exclusion criteria. Articles were selected for inclusion if they were original scientific papers that dealt with one of our key questions, had a study population of more than ten patients, and had an English language abstract available.

Contributors

DAL and SLK developed and implemented the systematic search strategy. CJR advised on the systematic search. All authors participated in the literature search. DAL, NS, WDT, KKB, and AUW created the first draft of the Review. All authors critically reviewed the manuscript and approved the final version, taking accountability for the work.

Declaration of interests

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