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# Diagnostic approach of fibrosing interstitial lung diseases of unknown origin

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## **Abstract (287 words)**

Interstitial lung diseases encompass a broad range of numerous individual conditions, some of them characterized histologically by fibrosis, especially idiopathic pulmonary fibrosis, nonspecific interstitial pneumonia, chronic hypersensitivity pneumonia, interstitial lung disease associated with connective tissue diseases, and unclassifiable interstitial lung disease. The diagnostic approach relies mainly on the clinical evaluation, especially assessment of the patient's demographics, history, smoking habits, occupational or domestic exposures, use of drugs, and on interpretation of high-quality HRCT of the chest. Imaging is key to the initial diagnostic approach, and often can confirm a definite diagnosis, particularly a diagnosis of idiopathic pulmonary fibrosis when showing a pattern of usual interstitial pneumonia in the appropriate context. In other cases, chest HRCT may orientate toward an alternative diagnosis and appropriate investigations to confirm the suspected diagnosis. Autoimmune serology helps diagnosing connective disease. Indications for bronchoalveolar lavage and for lung biopsy progressively become more restrictive, with better considerations for their discriminate value, of the potential risk associated with the procedure, and of the anticipated impact on management. Innovative techniques and genetics are beginning to contribute to diagnosing interstitial lung disease and to be implemented routinely in the clinic. Multidisciplinary discussion, enabling interaction between pulmonologists, chest radiologists, pathologists and often other healthcare providers, allows integration of all information available. It increases the accuracy of diagnosis and prognosis prediction, proposes a first-choice diagnosis, may suggest additional investigations, and often informs the management. The concept of working diagnosis, which can be revised upon additional information being made available especially longitudinal disease behaviour, helps dealing with diagnostic uncertainty inherent to

interstitial lung diseases and facilitates management decisions. Above all, the clinical approach and how thoroughly the patient's history and possible exposures are assessed determine the possibility of an accurate diagnosis.

# 1 General approach to the diagnosis of fibrotic interstitial lung diseases

## 1.1 *Fibrotic interstitial lung diseases*

Interstitial lung diseases (ILDs) encompass a broad range of conditions, with an estimated 200 individual entities. These heterogeneous parenchymal lung disorders overlap in their clinical presentations and patterns of lung injury. Several diseases don't have an identified cause [1] and are labelled idiopathic or cryptogenic [2] including idiopathic pulmonary fibrosis (IPF) [3], and others are related to other diseases especially connective tissue diseases [4] or to environmental exposures such as hypersensitivity pneumonitis [5] or pneumoconioses.

Among ILDs, some are characterized histologically by fibrosis, i.e. by excessive extracellular matrix deposition especially collagen, associated with progressive destruction of the lung architecture and loss of physiologic properties of the lung. One of the most common types of fibrosing ILDs is IPF, a progressive disease characterised by decline in lung function and early mortality [6]. Patients with certain other types of chronic fibrosing ILD are also at risk of developing a progressive phenotype of fibrosis. These include idiopathic nonspecific interstitial pneumonia (NSIP) [7], unclassifiable idiopathic interstitial pneumonia [8, 9], autoimmune ILDs especially connective tissue diseases-ILDs [4], chronic hypersensitivity pneumonitis [5], and more rarely chronic sarcoidosis [10], and exposure-related diseases such as asbestosis and silicosis [11] (**Figure 1**).

Recently, it has been proposed that, for the purposes of clinical research and potentially treatment, various forms of fibrosing ILDs may be lumped together, because of similar

biological and clinical behaviours shared with IPF, i.e., self-sustaining fibrosis, progressive decline in lung function, and early mortality [12, 13]. The terminology “progressive fibrosing ILDs” has been coined to describe ILDs in patients who, independent of the etiologic classification, at some point in time exhibit a progressive fibrosing phenotype. This approach is reinforced by a common treatment approach for progressive fibrosing ILDs [14], and further illustrates that classification is likely to evolve in parallel with better understanding of pathogenesis and progress in the treatment approach.

Despite some common characteristics across fibrotic ILDs, it remains pivotal, however, that an accurate diagnosis be made in any patient, in order to guide management. In this article, we will review key elements that contribute to the diagnosis of ILDs, focusing on fibrotic ILDs.

## **1.2 Clinical evaluation**

A step-by-step evaluation is required to obtain a confident diagnosis of fibrotic ILDs (**Figure 2**). A detailed description is beyond the scope of the present article, however schematically, it is necessary to first suspect a first-choice diagnosis of one of the ILDs based on the clinical evaluation, epidemiologic data (probability of disease based on the known prevalence in the corresponding setting, and given age and sex), and the imaging features. The clinician is responsible for collecting all necessary information which will be discussed in multidisciplinary team and represents the basis for an accurate and synthetic diagnosis (**Table 1**).

Demographic features, especially age, are key to the diagnosis of ILDs. Indeed, IPF symptoms occur during the sixth and seventh decades, with a median age at diagnosis between 65 and 70 years. IPF is rare before the age of 50, and alternative diagnoses should be

first considered in younger individuals. Conversely, any idiopathic fibrotic ILD occurring after the age of 70 is likely to correspond to IPF. The majority of patients with IPF are men.

The familial occurrence of disease may contribute to the diagnosis [15], however the phenotype of fibrotic ILD may vary greatly between members of a given family with genetic pulmonary fibrosis, and therefore the individual approach to diagnosis is not influenced in a major way by the familial context. IPF resulting from telomerase-associated gene mutations (dyskeratosis congenita) may further be suggested by skin features, dyserythropoiesis, increased erythrocyte volume, or cryptogenic liver disease. Hermansky-Pudlack syndrome with albinism is exceedingly rare outside geographic nests (Puerto Rico).

Onset of disease may provide some clues to the diagnosis. While most forms of ILD have a chronic course and presentation, a more rapid development or worsening can occur, corresponding to acute exacerbations for IPF, occasionally in patients with early and previously unrecognized disease, or to acute or subacute flares of hypersensitivity pneumonitis.

Tobacco smoking is a risk factor for IPF, but also other rare ILDs especially desquamative ILD, which can have a progressive fibrotic course, Langerhans cell histiocytosis (which can be progressive but not fibrotic), and rheumatoid arthritis-associated ILD. Because at least two thirds of patients diagnosed with IPF are active or past cigarette smokers [16], a history of tobacco smoking can also orientate the diagnosis.

Clinical manifestations are most often nonspecific and consist of insidious respiratory symptoms, which may progressively worsen. The main symptom of IPF is progressive chronic dyspnoea on exertion. Paroxysmal cough refractory to antitussive agents is often present. Weight loss and fatigue may occur. On physical examination, basal “Velcro” crackles

are present early in the course of the disease; although not specific of IPF and possibly heard in other conditions (i.e. asbestosis, idiopathic nonspecific interstitial pneumonia, pulmonary fibrosis associated with connective tissue diseases), crackles at auscultation should alert the clinician of suspected IPF [7][17]. Finger clubbing is present in less than half of patients with IPF.

The physical examination also provides an opportunity to detect a variety of abnormalities which can be clues to the diagnosis of fibrotic ILD (**Table 2**). Particular attention must be paid to subtle skin manifestations supporting a diagnosis of idiopathic (autoimmune) inflammatory myopathy [18], systemic sclerosis [19], mixed connective tissue diseases, or rheumatoid arthritis. Occasionally, systemic manifestations of connective tissue diseases are limited, not fulfilling criteria for the diagnosis of an established connective tissue diseases, and ILD may then be classified as interstitial pneumonia with autoimmune features (IPAF) [20]. Upon examination, platythorax orientates to the diagnosis of pleural and parenchymal pulmonary fibroelastosis, especially in a young patient, with history of radiation therapy or chemotherapy.

Exclusion of known causes of chronic ILD is an essential step in the clinical approach to IPF and focuses on hypersensitivity pneumonitis, connective tissue diseases, and medication use. Domestic and occupational exposures are key to the diagnosis of hypersensitivity pneumonitis. Taking a comprehensive history of exposure is difficult and time consuming; it can be supported by the use of questionnaires ([www.chestnet.org](http://www.chestnet.org)) or websites ([www.hplung.com](http://www.hplung.com)). Patients must be thoroughly asked about systemic symptoms (especially rheumatologic, musculoskeletal, cutaneous, renal, and neurologic symptoms, muscle weakness, sicca syndrome, and Raynaud' phenomenon). One website dedicated to drug-induced ILD and regularly updated is useful for the differential diagnosis

([www.pneumotox.com](http://www.pneumotox.com)), although chronic fibrosing ILDs result rather rarely from drug intake, in contrast with more inflammatory, cellular ILDs.

### **1.3 Pulmonary function tests**

A restrictive ventilatory defect (reduced total lung capacity and forced vital capacity; normal or increased forced expiratory volume in one second : forced vital capacity ratio) with reduced diffusion capacity of carbon monoxide is typical of fibrotic ILDs. Although physiologic impairment can usually be observed from the onset of the disease, pulmonary function tests may be normal at an early stage even in IPF [21]. Diffusion capacity is reduced disproportionately to lung volumes in combined pulmonary fibrosis and emphysema [22, 23].

Characteristic arterial blood gas abnormalities include increased alveolar-arterial oxygen pressure difference, initially at exercise and eventually at rest. Hypoxemia at rest may occur earlier in the course of disease in case of concomitant emphysema or pulmonary hypertension. Disproportionate hypoxemia may occur in organising pneumonia due to right-to-left shunting through dilated vessels within lung consolidation [24].

Pulmonary function tests generally do not differentiate IPF from other chronic ILDs, although they may help in refining the differential diagnosis. Airflow obstruction may be found especially in lymphangioleiomyomatosis and in pulmonary Langerhans cell histiocytosis, however some obstructive ventilatory defect (disproportionate reduction in forced expiratory volume in one second, increase in total lung capacity, increase in residual volume : total lung capacity ratio) or a mixed ventilatory defect may be encountered in diseases with a component of airways involvement: sarcoidosis, hypersensitivity pneumonitis, rheumatoid lung, combined pulmonary fibrosis and emphysema, etc [25]. Such observation, however, is rarely useful in the diagnostic approach.

Pulmonary function tests are the most accurate means of quantifying the severity of diffuse lung disease, and of monitoring disease progression using serial measurements. Diffusion capacity best reflects morphologic severity and predicts mortality in fibrotic ILDs, whereas lung volumes and arterial oxygen levels correlate poorly with morphologic severity [25]. When detecting serial changes, one must distinguish between genuine changes and spurious change due to measurement variation [25]. A decline in forced vital capacity is considered significant when greater than an absolute or relative change of 10% from baseline values ; a decline in diffusion capacity greater than 15% from baseline values is considered significant. Smaller changes in forced vital capacity, such as a 5% change, may be significant or correspond to measurement variation, which is best adjudicated by further similar trends in following visits, or a concomitant decline in diffusion capacity or an increase in extent of ILD at imaging. Decline in lung volumes and especially serial trends in forced vital capacity predict mortality in IPF and in fibrotic ILDs in general [26-29].

#### ***1.4 Laboratory investigations***

Laboratory investigations contribute to rule out non-idiopathic ILDs. As a usual interstitial pneumonia (UIP) pattern can be the initial manifestation of a connective tissue disease, systematic serologic testing for autoantibodies and routine laboratory testing is recommended (**Table 3**) [3]. Of note, the prevalence of circulating antinuclear antibodies in the absence of clinical systemic manifestations is similar in patients with IPF and healthy controls with little or no impact on outcome [30, 31]. Referral to a rheumatologist may be beneficial when a systemic disease is suspected, especially when manifestations are subtle and IPAF is considered [20, 32].

Antigenic exposure, features of hypersensitivity pneumonitis at high resolution computed tomography (HRCT), or lymphocytosis at bronchoalveolar lavage (especially greater than 30%) [33], should lead to serologic testing for suspected antigens.

Even in the absence of family history, genetic testing should be considered in case of unexplained liver or blood cell abnormalities [15]. Unfortunately, there are no validated biomarkers in fibrotic ILDs, and current practice guidelines recommend against routine use of diagnostic blood biomarkers to separate IPF from other fibrotic ILDs, or for the monitoring of disease.

### ***1.5 Radiologic evaluation***

Chest imaging is key to the early detection of ILD, for the characterization of the ILD, and in most cases it guides the diagnostic approach. Together with demographic data and clinical evaluation including age, gender, tobacco smoking history, and presence of Velcro crackles at lung auscultation, the pattern of chest HRCT orientates toward the first-choice diagnosis. All patients with newly diagnosed ILD should undergo a chest HRCT. Careful attention to technique is required for the images to be interpreted (**Table 4**), and requires thin (1.5 mm or less) sections, and a reconstruction algorithm specific for lung parenchyma. Most centres now use volumetric acquisition, allowing coronal and sagittal reconstruction, which can be helpful to better appreciate distribution of disease.

If IPF is considered in the differential diagnosis, the HRCT should be interpreted in line with the international guidelines, which recognize four patterns and situations: UIP pattern, probable UIP pattern, indeterminate for UIP pattern, and suggesting an alternative diagnosis (**Table 5**) [3, 34]. The UIP pattern is defined by basal and subpleural predominance of reticular changes, associated with traction bronchiectasis and honeycombing, in the absence

of features suggesting an alternative diagnosis, especially profuse ground glass attenuation (**Figure 3**). Honeycombing consists in clustered subpleural cysts, 3-10 mm in diameter, with well-defined walls. Concurrent mild ground glass opacity is possible, especially if superimposed on fine reticular pattern. A uniform craniocaudal distribution of reticulation, or asymmetric disease [35], may be seen occasionally. Mediastinal lymphadenopathy may be encountered in IPF, in hypersensitivity pneumonitis and other ILDs, and is associated with long-term outcome [36]. Dilation of the pulmonary artery when present is associated with a poor prognosis (**Figure 4**) [37-39]. Calcified nodules corresponding to localized or dendriform ossification within the areas of fibrosis may be present especially in patients with a UIP pattern, although it may be observed also in NSIP or other fibrotic ILDs [40] (**Figure 5**). When present in the appropriate setting, the UIP pattern is highly predictive of a pathologic pattern of UIP, and therefore obviates the need for a lung biopsy [41, 42].

The probable UIP pattern on HRCT corresponds to reticular abnormalities, with basal and subpleural predominance, associated with traction bronchiectasis, and especially with peripheral, subpleural, traction bronchiolectasis, but without honeycombing [3, 34] (**Figure 6**). Although less definite than the UIP pattern, the probable UIP pattern is found in about 80% of patients who have a clinical presentation suggesting IPF, i.e. male older than 60 years, former smoker [43-45]. In contrast, a pathologic pattern of UIP would be found in about one third of patients with a HRCT pattern indeterminate for UIP. This subset includes patterns suggesting an early pattern of UIP (**Figure 7**), as well as patients with a truly indeterminate pattern, which is characterized by features or a distribution of fibrosis on HRCT that do not correspond to the subpleural and basal predominance of UIP, and which does not suggest another specific diagnosis either. An alternative diagnosis to UIP may be suggested by many features on CT (cysts, marked mosaicism, predominant ground glass attenuation, profuse

micronodules, centrilobular nodules, consolidation), by a predominantly peribronchovascular, perilymphatic, or upper or mid-lung distribution, or by the presence of other features not observed in idiopathic UIP (pleural plaques, dilated oesophagus, distal clavicular erosions, extensive lymph node enlargement, or pleural effusion or pleural thickening).

## **1.6 Bronchoalveolar lavage**

Bronchoalveolar lavage should be considered in most patients with ILD who do not have a UIP or probable UIP at HRCT, with the notable exception of patients in whom a decision has already been taken to pursue surgical lung biopsy. The bronchoalveolar lavage cellular analysis is especially useful for the diagnosis of eosinophilic pneumonia (> 25% eosinophils) [46], or in case of elevated percentage of lymphocytes (> 20%) suggesting sarcoidosis, hypersensitivity pneumonitis, nonspecific interstitial pneumonitis, or other conditions distinct from IPF.

Other scenarios in which bronchoalveolar lavage may play a central diagnostic role include alveolar proteinosis (stained with Periodic Acid Schiff), lipoid pneumonia (with staining for fat), acute eosinophilic pneumonia, malignancies (pulmonary lymphoma, lymphangitis carcinomatosa), diffuse alveolar hemorrhage (with red appearance of bronchoalveolar lavage fluid and hemosiderin-macrophages colored by Perls iron stain), opportunistic infections, smoking-related ILD (with tobacco-pigmented macrophages in respiratory bronchiolitis-associated ILD and in desquamative interstitial pneumonia), drug-induced ILD (possibility of alveolar eosinophilia, or foamy macrophages in amiodarone lung), and possibly pulmonary Langerhans cell histiocytosis (staining histiocytes with anti-CD1a antibodies). The lymphocyte CD4:CD8 ratio might be helpful when considering the diagnosis of sarcoidosis,

however its diagnostic value is generally poor, especially to differentiate IPF from hypersensitivity pneumonitis or from NSIP.

Of note, reactive type II pneumocytes (large cells with a dark-coloured nucleus and dark-coloured cytoplasm containing large vacuoles), normally not present in bronchoalveolar lavage fluid, can be seen in case of serious pulmonary damage, including diffuse alveolar damage, hypersensitivity pneumonitis, diffuse alveolar haemorrhage, eosinophilic pneumonia, *Pneumocystis jiroveci* infection or bacterial pneumonia. Reactive type II pneumocytes must be differentiated from malignant cells.

## **1.7 Lung biopsy**

Sampling lung tissue is far from being always necessary when diagnosing ILD, but can be obtained by a variety of histologic techniques. Cytologic examination of bronchoalveolar lavage can also provide a definitive diagnosis in some infectious or malignant ILDs.

Endobronchial and forceps transbronchial biopsies may be diagnostic in conditions in which the pathological features are characteristic or unique and can be appreciated in small specimens (**Table 6**). This is especially true for sarcoidosis and lymphangitic carcinoma which follow lymphatic routes of spreading. CT-guided transthoracic lung biopsy may be considered especially in case of airspace consolidation when organizing pneumonia or pneumonic-type lepidic carcinoma is considered [47, 48].

In other ILDs especially idiopathic interstitial pneumonias, where the lung architecture must be appreciated, transbronchial lung biopsies are insufficient for diagnosis, especially when a histopathologic pattern of UIP is considered. The current accepted standard practice for obtaining surgical lung biopsy is through video-assisted thoracoscopic, as traditional open lung biopsies are no longer recommended. The pattern of UIP is defined by distortion of the

lung architecture with subpleural and/or paraseptal fibrosis, patchy involvement with fibrotic lung alternating with areas of normal lung, histologic honeycombing (alveolar cell-lined cystic airspaces filled with mucus), and fibroblastic foci [3, 34, 44]. Careful search for histologic ancillary findings could be helpful in identifying conditions underlying the UIP pattern, as a UIP pattern can be associated with many diseases including IPF, chronic hypersensitivity pneumonitis, connective tissue diseases especially rheumatoid arthritis and anti-synthetase syndrome, asbestosis, chronic sarcoidosis, drug toxicity, familial pulmonary fibrosis, and immunoglobulin-4 syndrome [49].

Diagnostic yield using video-assisted thoracoscopic lung biopsy is excellent, sampling adequate lung sample in all cases, and contributing to diagnosis in about 90% of cases [3]. It is however associated with significant mortality, estimated to 1.7% for in-hospital mortality for elective procedures [44, 50, 51]. Non-elective procedures are associated with a greater risk and must be avoided, especially in subjects with rapidly progressive ILD or in case of suspicion of acute exacerbation of fibrotic ILD. Risk factors have been identified (**Table 7**), and it is likely that the risk of video-assisted thoracoscopic lung biopsy is now lower in the current era than what was previously published, if contra-indications and precautions are respected, and when the biopsy is performed by an experienced thoracic surgeon.

Recently, bronchoscopic transbronchial lung cryobiopsy, a minimally invasive technique, has been proposed as a novel technique for sampling lung tissue in ILD [52]. Although this technique was not assessed in recent guidelines due to insufficient evidence at that time [3], evidence is accumulating showing that transbronchial lung cryobiopsy may be a relatively safe procedure. It may have a diagnostic yield of approximately 80% [53], may contribute similarly to video-assisted surgical lung biopsy to the diagnostic approach of IPF obtained by multidisciplinary discussion [54], and might be accurate for the diagnosis of ILD [55],

although this is somewhat controversial [56]. The standardization of the procedure [57] and the publication of practice guidelines [53] may contribute to the more widespread use of transbronchial cryobiopsies. “Awake biopsy”, another minimally invasive uniportal, video-assisted thoracic surgery strategy under locoregional anesthesia in awake patients, is currently developed to optimize diagnostic assessment in patients with ILDs [58, 59].

## **1.8 Molecular biology**

Recently, genomic techniques based on next-generation RNA sequencing in samples obtained using transbronchial biopsy have demonstrated good-to-high sensitivity and specificity to predict UIP pattern at biopsy [60-62]. It is considered that such methods may help to identify idiopathic-UIP pattern in subjects with nondiagnostic HRCT, and to improve pathologist confidence in difficult to interpret biopsies [49]. Such molecular classifiers were developed to differentiate UIP from non-UIP in the idiopathic setting, however they have not been assessed for their ability to distinguish between idiopathic UIP (IPF) and secondary causes of UIP.

## **1.9 Genetics**

A growing proportion of cases with fibrotic ILD and especially IPF have familial aggregation of cases or occur in the context of a number of rare genetic disorders, indicating that genetic factors contribute significantly to the pathogenesis of these diseases. Several disease-associated genetic variants have been associated with both the occurrence and the outcome of familial and sporadic pulmonary fibrosis [15]. As the imaging and the histopathological pattern of familial disease are highly heterogeneous [63-65] and may differ among members of the same family, identification of the molecular variants only modestly contribute to the diagnostic approach of fibrotic ILD, with rare exceptions where genotype - phenotype correlations were established [15]. Currently, genetic testing should be especially considered

in individuals with ILD, either idiopathic or non-idiopathic, and in familial ILD, in idiopathic ILD occurring before the age of 50, or with a personal or familial history suggestive of telomerase gene mutations (bone marrow failure, thrombocytopenia, myelodysplastic syndrome, dyskeratosis congenita, or cryptogenic liver cirrhosis) [15]. In the future, a genotype-guided approach to diagnosis and treatment may represent the basis of precision medicine in fibrotic ILDs.

### ***1.10 Multidisciplinary discussion***

In IPF as in all ILDs, multidisciplinary discussion meeting has become the gold standard of diagnosis [3, 34]. Multidisciplinary discussion, enabling interaction between pulmonologists, chest radiologists, pathologists and often other healthcare providers (rheumatologist, thoracic surgeon, specialist nurse, palliative care specialist, etc), allows an active discussion of all clinical information available, facilitating the discussion of potential discrepancies [66, 67]. Heterogeneity exists across centres and countries with regards to how the multidisciplinary discussion is organised [68, 69]. Multidisciplinary discussion has been shown to increase the accuracy of diagnosis and prognosis prediction [66]. In experienced ILD centres, a change in the diagnosis between the referring diagnosis and that proposed by the multidisciplinary discussion is relatively common [70]. Even if the primary goal of the multidisciplinary discussion is focused on the diagnosis, its conclusions inform and impact the treatment decisions.

## **2 Diagnosis of interstitial lung diseases of unknown origin**

### ***2.1 Diagnosing idiopathic pulmonary fibrosis***

In patients in whom the diagnosis of IPF is suspected, the diagnostic algorithm has been recently updated [3]. The clinical evaluation is key to appreciate the clinical probability of diagnosis, especially based on age, gender, smoking history, crackles at lung auscultation, and often finger clubbing. In patients with a UIP pattern on chest HRCT, bronchoalveolar lavage and surgical lung biopsy are not required. When the imaging pattern is that of probable UIP, the clinical probability of disease needs to be considered [71, 72], as pathological confirmation of the diagnosis is often not necessary in the appropriate context and after multidisciplinary discussion. Specifically, a diagnosis of IPF can generally be made without lung biopsy in subjects older than 60 with a history of tobacco smoking and an HRCT pattern of probable UIP [43, 45]. In any case, the risks and benefit of a biopsy need be balanced if a biopsy is contemplated [72]. The approach to diagnosing IPF in a patient with a CT pattern of probable UIP must be nuanced, however, as there is some heterogeneity in this patient population [73]. In a patient with probable UIP on HRCT, the likelihood of a diagnosis of IPF is increased by the presence of a clinical context appropriate for IPF and by longitudinal disease behaviour suggesting IPF [73].

### ***2.2 Diagnosing nonspecific interstitial pneumonia***

First described in the setting of HIV infection, the histologic pattern of NSIP was identified as a “waste-basket pattern” of ILD which included those cases in whom appearances could not be sub-classified as one of the three main types of idiopathic interstitial pneumonia [74]. Histologic features were identified, including the presence of temporal and spatial

homogeneity within biopsy fields, in contrast to the marked heterogeneity seen in the UIP pattern [74], leading to the individualisation of NSIP as a pathologic pattern and of idiopathic NSIP as a clinical pathologic entity [1, 75]. Initially sub-categorised as cellular, fibrotic, or mixed, NSIP appearances have been since then described as “fibrotic NSIP” and “cellular NSIP”.

The pattern of NSIP is mostly associated with connective tissue diseases [76-80] except rheumatoid arthritis, a minority of patients with hypersensitivity pneumonitis [81-84] and prior acute lung injury or diffuse alveolar damage [74] or drug-induced disease [85], while idiopathic NSIP is rare. Patients with idiopathic NSIP have a better survival than those with a UIP pattern [86-90], although mortality is higher in idiopathic NSIP than in NSIP pattern associated with connective tissue diseases [91]. Furthermore, some heterogeneity exists within the pattern of NSIP [92], with some distinction made between isolated NSIP, typically chronic, as seen in systemic sclerosis, and NSIP/OP overlap, typically subacute in onset, as seen in idiopathic inflammatory (autoimmune) myositis. Management of NSIP is generally based on glucocorticoids and immunosuppressive therapy [93]; patients with a progressive fibrosing phenotype, who often exhibit poor response to immunomodulation, benefit from nintedanib [14].

Although distinguishing idiopathic NSIP (as a clinical pathologic entity) from the IPF has management and prognostic implications, it can be difficult, due to overlap of clinical and radiologic features of fibrotic NSIP with those of IPF, with a similar predominantly basal sub-pleural distribution but the absence of honeycombing [76, 94]. Bronchoalveolar lavage lymphocytosis can be present, however bronchoalveolar lavage cannot discriminate between NSIP and UIP [95]. At chest CT, the lower lung zones are predominantly involved, with a peripheral or diffuse distribution, and a combination of reticular pattern and traction

bronchiectasis [96] (**Figures 8, 9**). A recent meta-analysis of CT findings from patients with NSIP revealed significantly lower levels of the honeycombing pattern, less peripheral predominance and more subpleural sparing in NSIP than in UIP. [97]; patients with NSIP were also younger than those with UIP [97].

In an international study of ILD diagnosis among a large group of physicians, the unweighted and weighted kappa values for clinicians, radiologists, pathologists, and inter-multidisciplinary team meeting agreement on the diagnosis of NSIP were particularly low, and especially lower than for the diagnosis of IPF or connective tissue disease-ILD, and comparable to that of hypersensitivity pneumonitis [98]. A pattern suggesting NSIP on HRCT can correspond to a typical pathologic pattern of fibrotic NSIP on biopsy [96, 99].

Conversely, pathologic NSIP can present on imaging as the typical presentation of fibrotic NSIP, or can present with a pattern indeterminate for UIP or less frequently with a pattern of probable UIP. Therefore, a secure diagnosis of NSIP still requires pathologic confirmation.

### ***2.3 Diagnosing fibrotic chronic hypersensitivity pneumonitis***

The diagnosis of hypersensitivity is challenging and based on a combination of clinical, radiologic and pathologic features. Recent perspectives have summarized the available evidence on this topic [100, 101]. Although much knowledge has been accumulated, no consensus diagnostic criteria currently exist. The diagnosis of the *fibrotic* presentation of hypersensitivity pneumonitis is particularly challenging, with overlapping features with IPF, and with implications for prognosis [5, 102] and management. Similar to what was discussed above for NSIP, the reproducibility of the diagnosis of hypersensitivity pneumonitis is very low [98]. In a retrospective study of cases initially diagnosed as IPF, Morell and colleagues have retrospectively diagnosed chronic hypersensitivity pneumonitis in 43% of patients [103];

although these findings may not be applicable in every setting, they underscore the challenge to diagnose chronic fibrotic hypersensitivity pneumonitis and its possible overlap with IPF. In addition, patients with IPF may have been exposed to an antigen known to cause hypersensitivity pneumonitis including birds, in the absence of criteria for hypersensitivity pneumonitis, yet with an outcome intermediate between that of IPF and that of chronic hypersensitivity pneumonitis [104, 105].

In a Delphi survey, Morisset and colleagues identified key features contributing to the diagnosis of hypersensitivity pneumonitis, including identification of a causative antigen, lymphocytosis greater than 40% and a combination of mosaic attenuation and HRCT signs of fibrosis [106].

Patients with chronic hypersensitivity pneumonitis tend to be younger than those with IPF, with a greater proportion of females and of non-smokers [107], however this is not the case in all series [108]. Identification of the offending antigen is absolutely key to the diagnosis of hypersensitivity pneumonitis. When taking patient's history, the clinician should particularly target exposure to the most common fibrogenic factors in the domestic environment including birds, hot tubs, visible moulds such as those following domestic water damage, etc. When present, exposure to a known offending antigen increases the likelihood of hypersensitivity pneumonitis by a factor ~40 [109]. Serum precipitating immunoglobulin G antibodies are usually detectable in hypersensitivity pneumonitis. However, similar antibodies are present in 10-50% of exposed but asymptomatic individuals, therefore they are of questionable clinical relevance for diagnosis. Moreover, in many cases even typical of hypersensitivity pneumonitis, the offending antigen is not identified; this scenario occasionally labelled as "idiopathic hypersensitivity pneumonitis" justifies to include chronic hypersensitivity pneumonitis in the differential diagnosis of any patient with pulmonary fibrosis.

The presence of lymphocytosis greater than 15-20% at bronchoalveolar lavage increases the likelihood of hypersensitivity pneumonitis in patients with a HRCT pattern indeterminate for UIP [110]. Lymphocytosis at bronchoalveolar lavage greater than 30% may discriminate chronic hypersensitivity pneumonitis as compared to IPF [111], however NSIP and drug-induced ILD are also in the differential. A recent meta-analysis confirmed that lymphocyte count is higher in the bronchoalveolar lavage of chronic hypersensitivity pneumonitis compared to other fibrotic ILDs [112]. A lymphocyte threshold of 30% discriminated chronic hypersensitivity pneumonitis from IPF with a sensitivity of 55%, a specificity of 84%, a positive predictive value of 64%, and a negative predictive value of 78% [112].

On chest HRCT, chronic hypersensitivity pneumonitis is characterized by linear attenuation, emphysema, diffuse micronodules, and concurrent ground-glass attenuation, with or without honeycombing [113]. If fibrotic, chronic hypersensitivity pneumonitis is characterized by more extensive reticular pattern, traction bronchiectasis, honeycombing, and often a UIP pattern at HRCT [114-117]. The presence of lobular areas with decreased attenuation and vascularity, centrilobular nodules, and absence of lower zone predominance of abnormalities [108, 118] and especially the presence of mosaic attenuation [3, 6, 34, 119, 120] have been suggested to differentiate chronic fibrotic hypersensitivity pneumonitis from IPF (**Figure 10**). However, mosaic attenuation may lack specificity [107, 121], and the headcheese sign (with coexisting densities of normal lung, low attenuation due to air trapping, and ground glass attenuation) may be more discriminant [107].

If available, pathologic examination of the biopsy is suggestive of chronic fibrotic hypersensitivity pneumonitis if showing varying degrees of chronic bronchiolocentric inflammation, poorly formed non-necrotising granulomas, giant cells, airway-centred interstitial fibrosis, and absence of features suggestive an alternative diagnosis [106].

However, it should be emphasized that the pathologic patterns in hypersensitivity pneumonitis are diverse [122]; a UIP pattern can be seen, although generally with increase lymphocyte cellularity and poorly formed granulomas.

Taken together, not one criterion, but a combination of criteria differentiate chronic fibrotic hypersensitivity pneumonitis from IPF. Multidisciplinary discussion including thoracic radiologists is key.

## ***2.4 Idiopathic pneumonia with autoimmune features***

A significant proportion of patients with ILDs manifest autoimmune features, but do not fulfil the diagnostic criteria for a definite connective tissue disease [123]. In 2015, the European Respiratory Society (ERS) and American Thoracic Society (ATS) “Task Force on undifferentiated Forms of connective tissue disease-associated ILD” proposed classification criteria for a so-called research category of interstitial pneumonia with autoimmune features (IPAF) [20]. Criteria for IPAF are a combination of features from three domains: a clinical domain consisting of extra-thoracic features; a serologic domain with specific autoantibodies; and a morphologic domain with imaging patterns, histopathological findings or multi-compartment involvement [20].

By definition, the concept of IPAF implies that there can be an overlap between IPF and connective tissue disease-ILD. Patients meeting IPAF criteria tend to have a history of smoking similar to patients with IPF. The most frequent clinical and serological markers of autoimmune features are Raynaud' phenomenon and positive antinuclear antibodies, respectively [124-132]. NSIP is the predominant radiologic and histopathologic pattern, although patients meeting IPAF criteria through the clinical and serologic domains may also have a UIP pattern. Interestingly, autoimmune features may also be found in patients with

hypersensitivity pneumonitis [133]. A question that remains open is whether IPAF may also represent a clinical diagnosis. Further discussion on this topic can be found elsewhere [123].

### **3 Remaining challenges**

#### ***3.1 Unclassifiable interstitial lung disease***

Despite a thorough approach to diagnosis, some cases of ILD remain unclassifiable, which represents a hurdle for management. In addition, patients and their families consider it a priority to have an early and accurate diagnosis (this has been showed for IPF, but is likely for the diagnosis of any ILD) [134]. As discussed above, NSIP was initially described as a subgroup of interstitial pneumonias that could not be classified into one the three main categories of idiopathic interstitial pneumonias [74]; after commonalities were identified, NSIP was individualized as a diagnostic category. It is conceivable that in the future, newer diagnostic categories may be individualized. In addition, classification of ILDs may evolve to take into account pathogenesis and molecular markers, defining endotypes [135].

Unclassifiable ILD has been included in the classification of idiopathic interstitial pneumonias [1]. The main possible causes of ILD to remain unclassifiable include the lack of a lung biopsy in a patient with HRCT pattern indeterminate for UIP, whichever the reason: discrepancy between the HRCT pattern and the pathology pattern (**Figure 11**); lack of representativeness of the lung biopsy; or overlap between two pathology patterns [8, 136]. In a recent meta-analysis, unclassifiable ILD represented 11.9% of ILD cases [137]. A lower prevalence was found in centres that reported use of a formal multidisciplinary discussion of cases [137].

Patients with unclassifiable ILD tend to be younger than those with IPF, with a balanced proportion of men and women [8, 137]. In the landmark study by Ryerson et al., patients with unclassifiable ILD had significantly better survival than those with IPF and significantly worse survival than those with non-IPF idiopathic ILD [8]. The survival difference between unclassifiable ILD and IPF remained significant when adjusted for age and forced vital capacity [8]. Since then, several series have been published [9, 138, 139], and the imaging [140] and pathologic [141] features of this group of patients are beginning to be better described. Importantly, patients with progressive unclassifiable ILD benefit from pirfenidone [142] and from nintedanib [14].

### ***3.2 Managing uncertainty***

Because not all cases can be diagnosed accurately, there remains frequently a degree of uncertainty when diagnosing patients with chronic fibrotic ILD [72], which however is not a major hurdle to appropriate management. Multidisciplinary discussion especially when involving clinicians, radiologists and pathologists with expertise in ILD, reduces the number of cases with diagnostic uncertainty, and proposes additional investigations when appropriate [70].

#### **3.2.1 Concept of working diagnosis**

One important role of the multidisciplinary discussion is to manage the uncertainty in the diagnosis. Uncertainty in ILDs is frequent, is partly due to the lack of reproducibility of the clinician's and the radiologist' approach [66, 67], but is also inherent to ILDs. In case of diagnostic uncertainty, additional investigations may be proposed [65], a first-choice diagnosis is adjudicated, and the confidence in the diagnosis may be appreciated [68]. When a definitive diagnosis cannot be made despite thorough evaluation but the multidisciplinary

team has high confidence (greater than 70%) in the diagnosis proposed [69], such diagnosis may be referred to as a working diagnosis, implying that it may be refined especially upon additional information being made available. To propose a working diagnosis in cases that are difficult to diagnose is part of a pragmatic approach, in which management decision cannot await diagnostic certainty in all cases of ILD. The need to revisit the diagnosis, or to upgrade a working diagnosis into a definite diagnosis, may often come from monitoring of the patient and assessing longitudinal disease behaviour [1]. Specifically, the likelihood of a fibrotic idiopathic ILD heretofore considered unclassifiable to correspond to IPF increases when progressive disease occurs despite best supportive care and often empiric therapy. In IPF, it has been showed that patients with a working diagnosis of IPF had a similar outcome as compared to those diagnosed with IPF as per guidelines [143], validating the pragmatic concept of working diagnosis, and supporting the rationale for treatment initiation in these patients by expert multidisciplinary teams.

### **3.2.2 Disease behaviour**

The term “disease behaviour” is used to characterize the mode of disease progression, as natural course of disease and following drug therapy [1]. Disease behaviour can contribute to inform diagnosis, yet with some delay after initial presentation of disease. For example, relentless worsening of disease despite immunomodulation increases the likelihood of the fibrotic ILD to correspond to IPF over alternative diagnoses of idiopathic NSIP or unclassifiable fibrotic ILD. On the other hand, response to immunomodulation therapy increases the likelihood of NSIP versus IPF, and complete resolution of patchy infiltrates in the setting of autoimmune inflammatory myopathy increases the probability of NSIP/organizing pneumonia.

Recently, a number of different fibrosing ILDs were identified to share a common phenotype of progressive fibrosis characterised by self-sustaining fibrosis, decline in lung function, worsening quality of life, and early mortality [144, 145]. Commonalities exist in clinical behaviour and in the pathogenetic mechanisms that drive progressive fibrosis in the fibrotic ILDs with a progressive phenotype, which may be ‘lumped’ together for the purposes of clinical research and potentially treatment [13]. Hence, the progressive fibrosing phenotype of ILD is a disease behaviour category that contributes to the diagnostic approach.

Disease behaviour and how it is incorporated into management is likely to take a growing importance, as antifibrotic drugs have been demonstrated to reduce the rate of decline in lung function. Indeed, nintedanib reduces the decline in lung function in patients with progressive pulmonary fibrosis [14], and pirfenidone reduces lung function decline in patients with progressive unclassifiable pulmonary fibrosis [70]. On the other hand, one might consider that the need to precisely diagnose specific entities of fibrotic ILD may be reduced if antifibrotic therapy are approved in a broader range of conditions. In fact, making an accurate diagnosis will remain essential to guide management, as there are specificities of management in many ILDs even fibrotic, e.g. antigen eviction in hypersensitivity pneumonitis, or evidence-based use of immunosuppressive therapy in systemic sclerosis-associated ILD. In any case, assessing progression of disease once a diagnosis and a management plan have been agreed upon is key, and multidisciplinary discussion is expected to be the place to assess disease progression.

### **3.2.3 Innovative diagnostic techniques**

Innovative diagnostic techniques will likely contribute to classification and diagnosis in the future, and may contribute to reducing diagnostic uncertainty. These may include for example

HRCT analysis through machine learning algorithms [146], high-dimensional transcriptional data and molecular classifiers based on biopsy samples [61, 62, 147], breath analysis (« electronic nose ») [148, 149], in vivo probe-based confocal laser endomicroscopy [150], biomarkers [151], and others. Progress in characterization of genetic polymorphisms and mendelian mutations contributing to pulmonary fibrosis [15] will undoubtedly contribute to better diagnosis and classification of fibrotic ILDs [135], probably with personalized management consequences [151], although routine use of such concepts in the clinic still lies ahead. Biomarkers of disease activity (not only of disease classification) are eagerly awaited in fibrotic ILDs.

## **4 Conclusion**

The diagnosis of ILD is somewhat complex, because only with experience will the clinician promptly identify elements of diagnosis that are highly suggestive of a common diagnosis (e.g. IPF), or more unusual, atypical features that should suggest an alternative diagnosis. The diagnostic approach relies on interpretation of high-quality HRCT of the chest, which is the key of initial diagnostic approach, and often can confirm a definite diagnosis in the appropriate setting. Indications for bronchoalveolar lavage and for lung biopsy progressively are more restrictive, with better considerations for their discriminate value, the potential risk associated with the procedure, and the anticipated impact on management. Innovative techniques and genetics are beginning to contribute to diagnosing ILD in the clinic. However, above all, the clinical approach and how thoroughly the patient's history and possible exposures are assessed, determine the possibility of an accurate diagnosis.

## **Conflict of interest**

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**Table 1.** Clues from the initial evaluation that suggest specific types of fibrotic ILDs

<b>History</b>	<b>Manifestation</b>	<b>Frequently associated fibrotic ILD</b>
Age	Age < 60	CTD-ILD, sarcoidosis
	Age < 40	Genetic ILD associated to surfactant gene mutation
	Age > 70	IPF
Genetic syndromes	Pulmonary fibrosis in a family member Early hair greying Cytopenia, dysmyelopoiesis Unexplained liver disease	Genetic pulmonary fibrosis associated with telomeropathy
	Impaired vision, horizontal nystagmus Albinism (may be missing) Puerto Rico heritage	Hermansky-Pudlak syndrome
	Sarcoidosis in a family member	Familial sarcoidosis
Onset	Acute or subacute	Hypersensitivity pneumonitis Acute exacerbation of IPF Infection associated with fibrotic ILD Drug reaction Acute interstitial pneumonia Cryptogenic organizing pneumonia Dermatomyositis Systemic lupus erythematosus Diffuse alveolar hemorrhage complicating chronic ILD
Smoking	Active or past smoker	Respiratory bronchiolitis-ILD Desquamative interstitial pneumonia IPF Rheumatoid arthritis – associated ILD Combined pulmonary fibrosis and emphysema syndrome
Occupation	Foundry worker, coal miner, etc	Pneumoconiosis
Drug exposure	See <a href="http://www.pneumotox.com">www.pneumotox.com</a>	Drug-induced subacute ILD
	Bleomycin, nitrofurantoin, alkylating agents and other chemotherapy agents Radiation therapy	Drug- or radiation- induced chronic pulmonary fibrosis
Pleural effusion		Rheumatoid arthritis – associated ILD Lupus– associated ILD
Auscultation	Velcro crackles of lung bases	IPF NSIP Unclassifiable pulmonary fibrosis
	Wheezing, squeaks	Chronic hypersensitivity pneumonitis Bronchiolitis

The list is not exhaustive and is especially focused on fibrotic, chronic ILDs.

**Table 2.** Clues from the physical examination that suggest specific types of fibrotic ILDs.

<b>Organ</b>	<b>Manifestation</b>	<b>Frequently associated fibrotic ILD</b>
Eye	Uveitis	Sarcoidosis
	Scleritis	Systemic lupus erythematosus Systemic sclerosis Sarcoidosis Granulomatosis with polyangiitis
Eyes and salivary glands Lymphatic	Sicca syndrome Enlarged salivary glands Lymphadenopathies	Sjögren disease Sarcoidosis
Skin	Finger clubbing	IPF Asbestosis Genetic pulmonary fibrosis Desquamative interstitial pneumonia
	Erythema nodosum	Sarcoidosis
	Puffy fingers	Mixed connective tissue disease
	Sclerodactyly Raynaud' phenomenon Telangiectasia Subcutaneous calcinosis Digital ulcerations	Systemic sclerosis
	Heliotrope rash Gottron' papules or rash Periungueal rash Mechanics' hands	Dermatomyositis
	Photosensitivity Malar rash Mucosal ulcerations Alopecia	Systemic lupus erythematosus
	Liver and spleen	Hepatosplenomegaly
Skeletal muscle	Muscle weakness Myositis	Inflammatory myopathy Other connective tissue diseases Sarcoidosis
Joints	Synovitis Arthritis	Rheumatoid arthritis Other connective tissue diseases Sarcoidosis
Esophagus	Eosophageal dysmotility	Systemic sclerosis
Nervous system	Neurologic dysfunction	Sarcoidosis Connective tissue diseases Systemic vasculitides
Cardiovascular system	Pulmonary hypertension	Systemic sclerosis Systemic lupus erythematosus IPF Sarcoidosis

The list is not exhaustive and is especially focused on fibrotic, chronic ILDs.

**Table 3.** Main investigations useful at the time of diagnosis of fibrotic ILDs

Imaging	High-Resolution Computed Tomography Echocardiography
Pulmonary function tests	Forced Vital Capacity Diffusing capacity of carbon monoxide Total Lung Capacity Arterial blood gas analysis 6 minute walking test Maximal exercise testing
Cytology and pathology	Bronchoalveolar lavage Video assisted thoracoscopic lung biopsy Transbronchial cryobiopsy
Biology	Complete Blood Count C-reactive Protein Serum creatinine Liver function test Anti-nuclear antibody Rheumatoid factor, anti-cyclic citrullinated peptide Antisynthetase antibodies AntiSS-A, antiSS-B, antiScl-70, anticentromere antibodies Antineutrophil cytoplasmic antibodies Creatinine kinase, serum aldolase Precipitin antibodies (depending on exposure)
According to the context, or to be evaluated	Genetic tests Reflux evaluation (esophagoscopy, pH-metry) Polysomnography Right heart catheterisation Coronary artery investigations

**Table 4.** Summary of high-resolution computed tomography scanning parameters

Contrast	Noncontrast examination
Volumetric acquisition	<p>Sub-millimetric collimation</p> <p>Shortest rotation time</p> <p>Highest pitch</p> <p>Tube potential and tube current appropriate to patient size:</p> <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> <p>Use of techniques available to avoid unnecessary radiation exposure (e.g., tube current modulation)</p>
Reconstruction of images	<p>Reconstruction of thin-section CT images (<math>\leq 1.5</math> mm):</p> <p>Contiguous or overlapping</p> <p>Using a high-spatial-frequency algorithm</p> <p>Iterative reconstruction algorithm if validated on the CT unit (if not, filtered back projection)</p>
Acquisitions	<p>Supine: inspiratory (volumetric)</p> <p>Supine: expiratory (can be volumetric or sequential)</p> <p>Prone: only inspiratory scans (can be sequential or volumetric); optional</p> <p>Inspiratory scans obtained at full inspiration</p>
Radiation dose (for the inspiratory volumetric acquisition)	<p>1–3 mSv (i.e., “reduced” dose)</p> <p>Strong recommendation to avoid “ultralow-dose CT” (&lt;1 mSv)</p>

CT, computed tomography

**Table 5.** High-Resolution Computed Tomography scanning patterns according to reference [3] (*permission requested on March 29, 2020*).

UIP	Probable UIP	Indeterminate for UIP	Alternative diagnosis
<p>Subpleural and basal predominant; distribution is often heterogeneous*</p> <p>Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis†</p>	<p>Subpleural and basal predominant; distribution is often heterogeneous</p> <p>Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis</p> <p>May have mild GGO</p>	<p>Subpleural and basal predominant</p> <p>Subtle reticulation; may have mild GGO or distortion (“early UIP pattern”)</p> <p>CT features and/or distribution of lung fibrosis that do not suggest any specific etiology (“truly indeterminate for UIP”)</p>	<p>Findings suggestive of another diagnosis, including:</p> <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>

*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.

**Table 6.** Main conditions in which endobronchial or forceps transbronchial biopsies may be contributive.

	Endobronchial biopsies	Forceps transbronchial biopsies
Very useful	Sarcoidosis Lymphangitic carcinomatosis	Sarcoidosis Lymphangitic carcinomatosis Berylliosis Organising pneumonia Bronchiolo-alveolar carcinoma
Often or occasionally useful	Granulomatosis with polyangiitis Some infections	Diffuse alveolar damage Alveolar lipoproteinosis Eosinophilic pneumonia Lymphangioliomyomatosis Pulmonary Langerhans cell histiocytosis Silicosis Diffuse lymphoma Some infections Amyloidosis Hypersensitivity pneumonitis

**Table 7.** Main contra-indications to video-assisted thoracoscopic lung biopsy.

- Age (physiologic) > 75 years
- Rapid worsening or acute exacerbation (non-elective biopsy)
- Low pulmonary reserve (FVC <60-70%, DLco < 35-40% of predicted)
- Supplementary oxygen at rest
- Pulmonary hypertension
- Major comorbidities
- Immunodepression

FVC, forced vital capacity; DLco, diffusion capacity for carbon monoxide

## Figure Legends

**Figure 1.** Classification of interstitial lung diseases. Classification of idiopathic interstitial pneumonia is described in references [1, 75]. IPAF is not an established diagnosis.

**Figure 2.** Simplified algorithm for the diagnosis of interstitial lung diseases.

**Figure 3.** Axial chest HRCT demonstrating usual interstitial pneumonia (UIP) pattern in a patient with idiopathic pulmonary fibrosis, with lower lobe and peripheral predominance of reticulation, traction bronchiectasis, and honeycombing.

**Figure 4.** Axial chest HRCT (mediastinal window) demonstrating dilation of the main pulmonary artery in a patient with idiopathic pulmonary fibrosis. Diameter of the main pulmonary artery is greater than that of the ascending aorta.

**Figure 5.** Axial chest HRCT in the lower zones in a patient with idiopathic pulmonary fibrosis. The upper panel (parenchymal window) demonstrates a nodular pattern associated with reticulation. The lower panel (bone window, same slice) demonstrates that nodules are calcified, corresponding to dendriform ossification in the context of usual interstitial pneumonia pattern.

**Figure 6.** Axial chest HRCT demonstrating a pattern of probable usual interstitial pneumonia (UIP) in a patient with idiopathic pulmonary fibrosis, with lower lobe and peripheral predominance of reticulation. Honeycombing is not seen. Arrows indicate peripheral, subpleural traction bronchiolectases.

**Figure 7.** Axial chest HRCT demonstrating a pattern indeterminate for usual interstitial pneumonia (UIP), corresponding to early stage of idiopathic pulmonary fibrosis, with lower lobe and peripheral predominance of reticulation. Lung biopsy demonstrated a pathologic pattern of usual interstitial pneumonia.

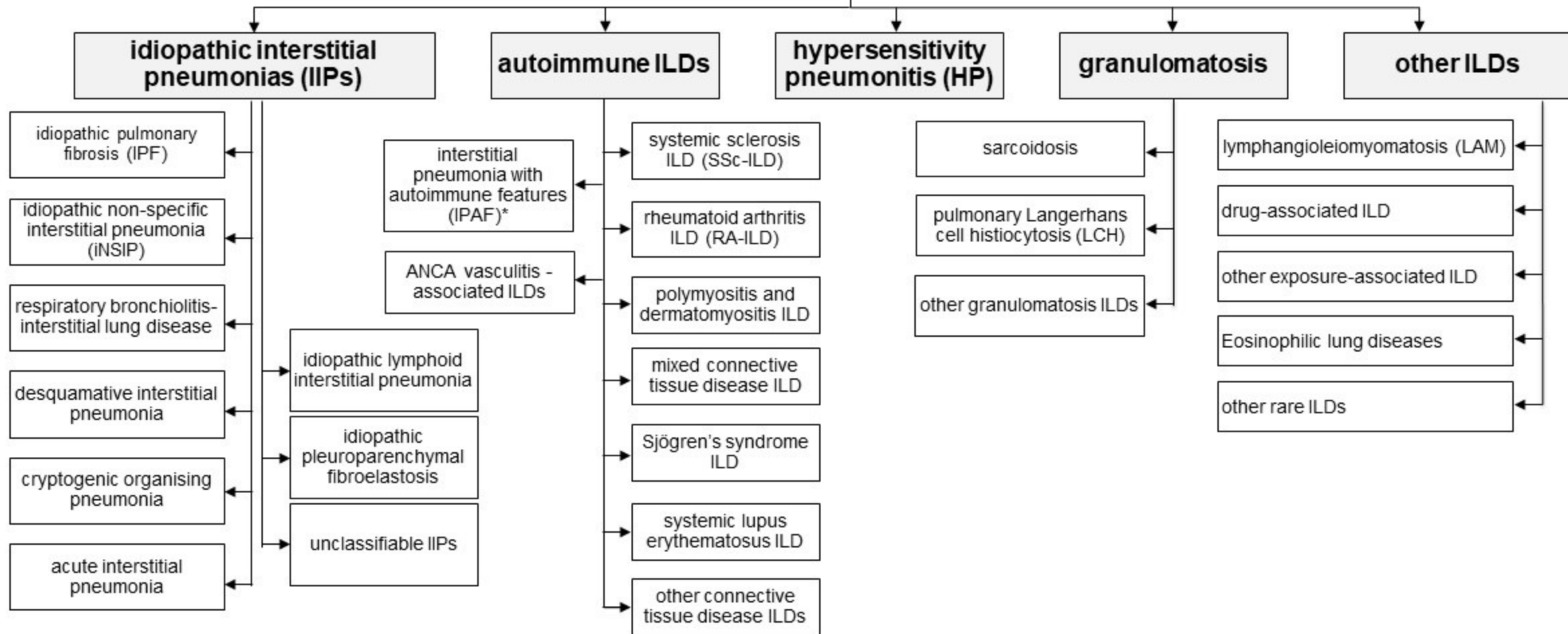
**Figure 8.** Axial chest HRCT demonstrating a pattern suggestive of nonspecific interstitial pneumonia (NSIP) in a patient with idiopathic pathologic NSIP. Lesions consist of diffuse ground glass attenuation admixed with fine reticulation, and traction bronchiectasis.

**Figure 9.** Axial chest HRCT in a patient with idiopathic, biopsy confirmed, nonspecific interstitial pneumonia (NSIP). Upper panel: at diagnosis, predominance of ground glass attenuation; lower panel: 8 years after diagnosis, lesions mostly consist of reticulation and traction bronchiectasis; with volume loss indicating fibrosis.

**Figure 10.** Axial chest HRCT (parenchymal window, inspiration acquisition) in a patient with chronic hypersensitivity pneumonitis (bird breeder's lung). Lesions predominate in the middle areas of the lung and consist of reticulation and mosaicism, with coexistence of lobular patterns of ground glass attenuation and lobular areas with decreased attenuation and air trapping.

**Figure 11.** Axial chest HRCT demonstrating areas of ground glass attenuation and traction bronchiectasis, suggesting nonspecific interstitial pneumonia at imaging. Pathologic examination of lung biopsy demonstrated a pattern of usual interstitial pneumonia. A diagnosis of unclassifiable fibrotic interstitial lung disease was made at multidisciplinary team meeting.

# Interstitial Lung Diseases



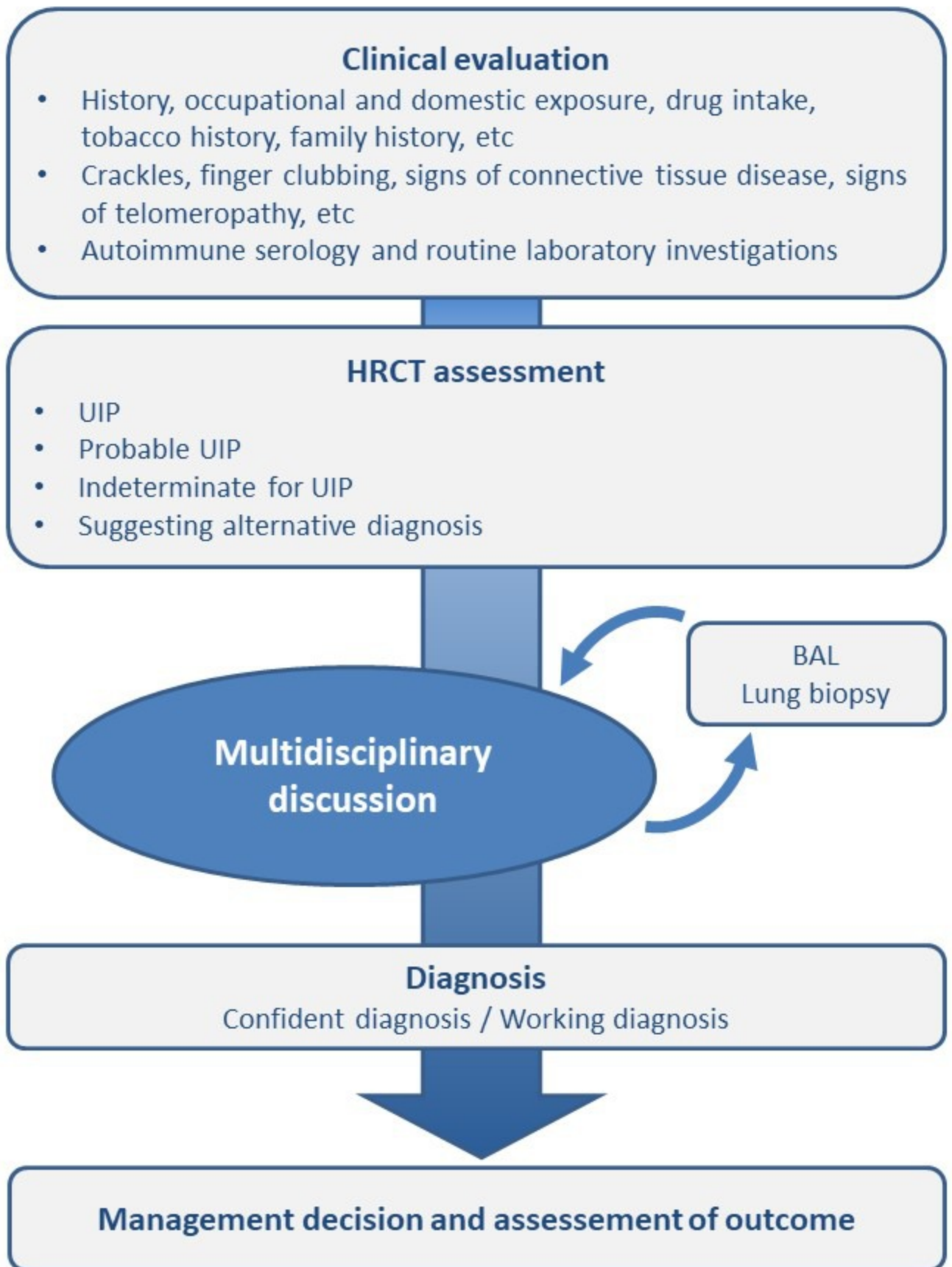


Figure 2

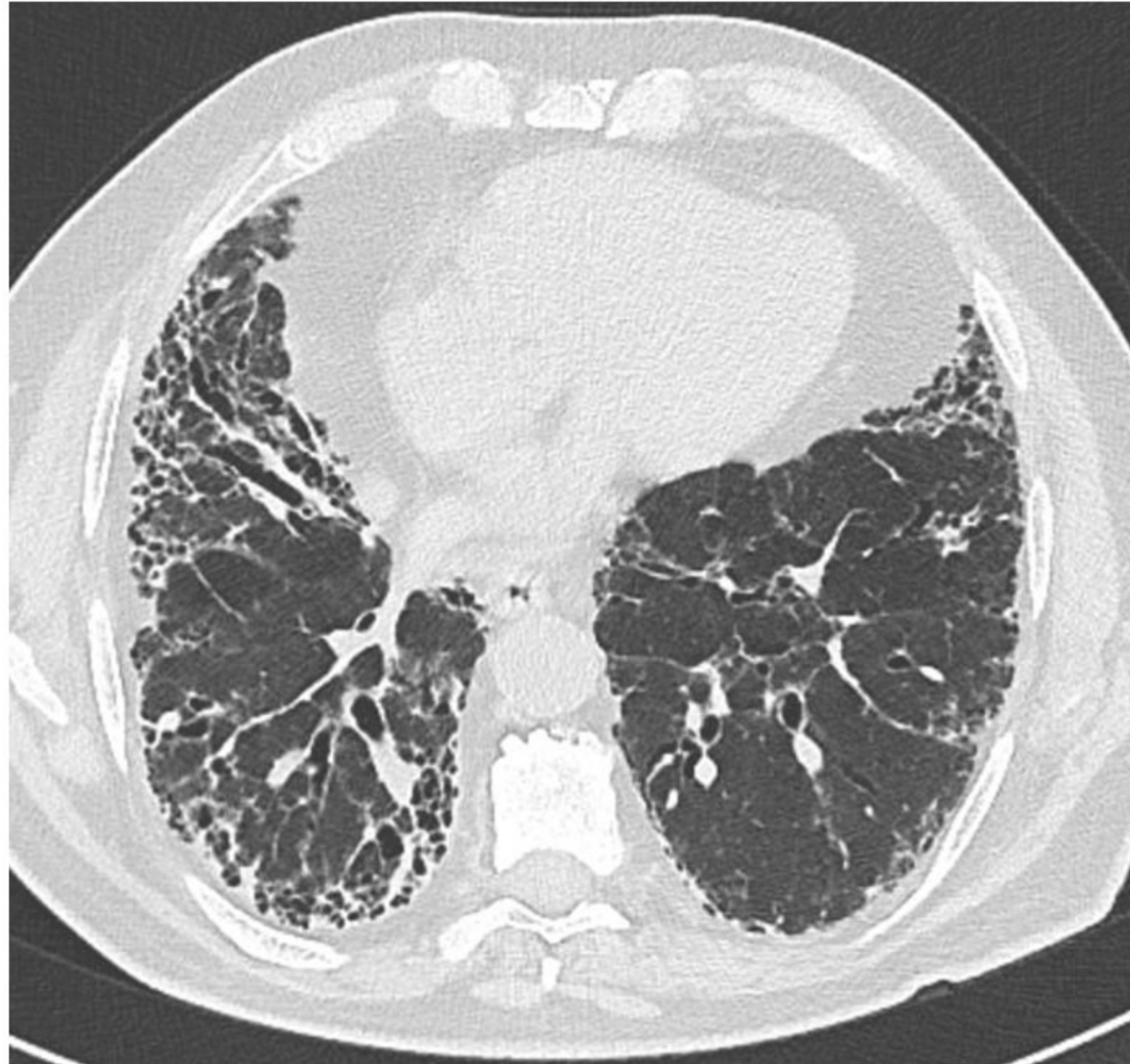


Figure 3

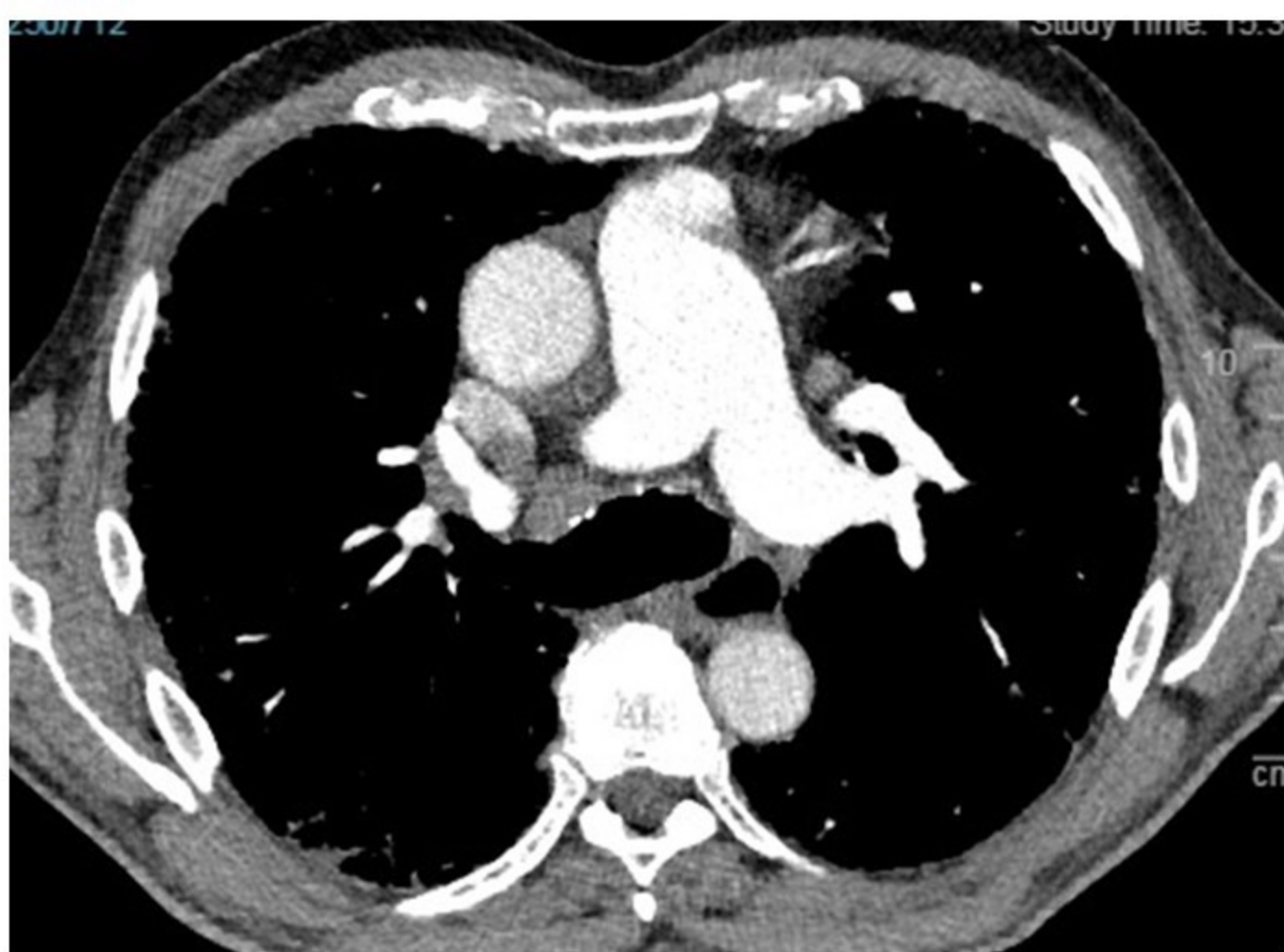


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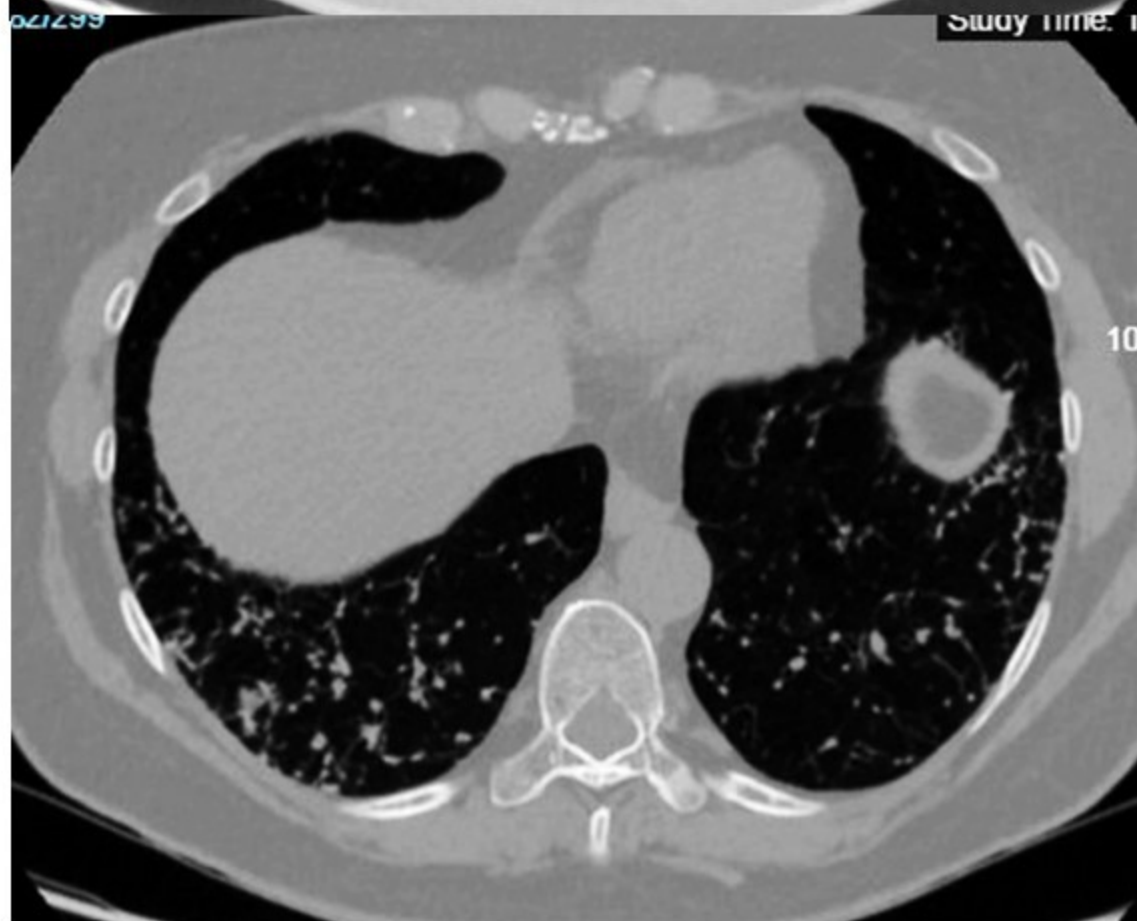


Figure 5

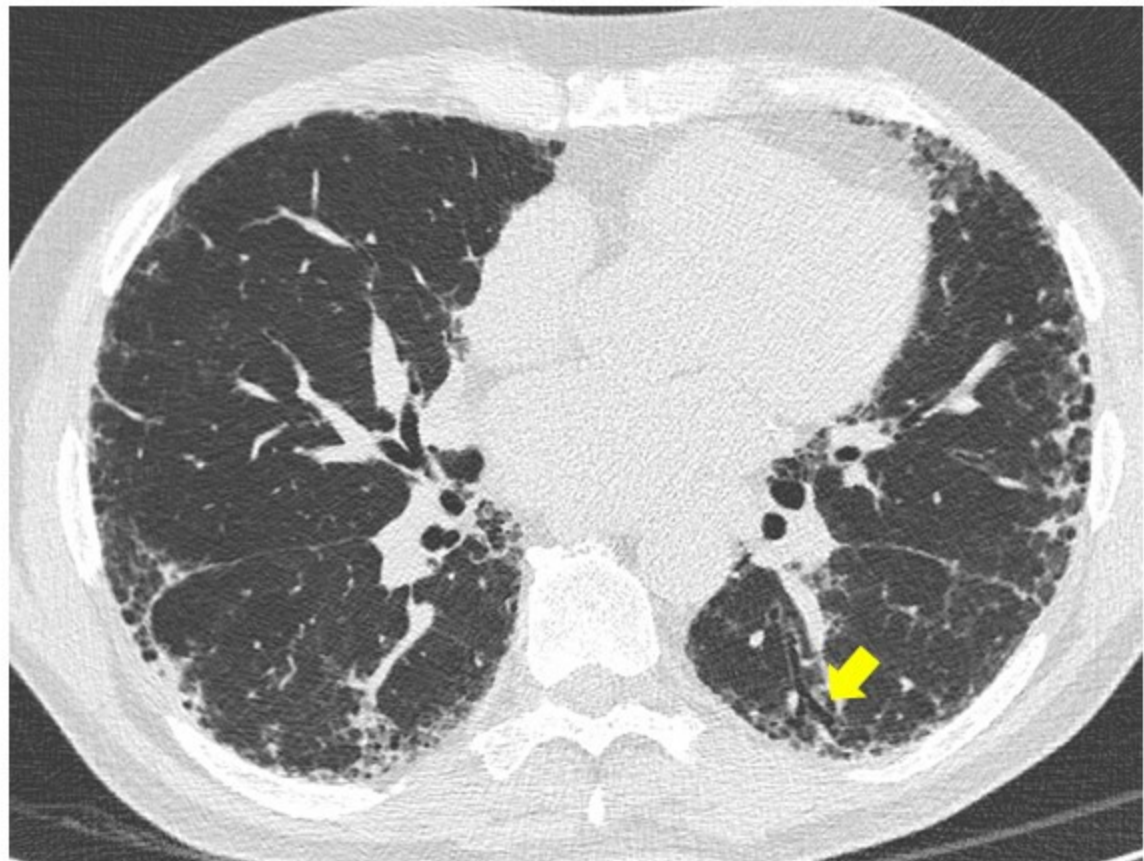
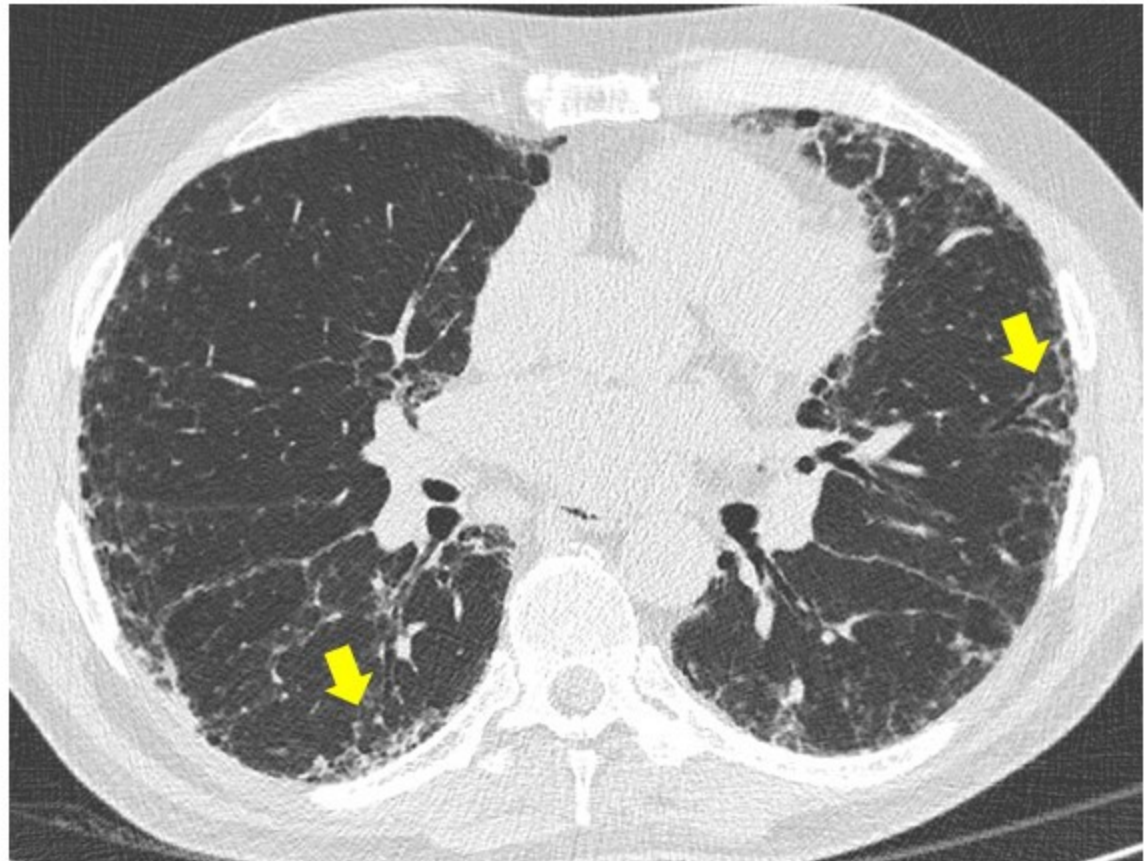


Figure 6

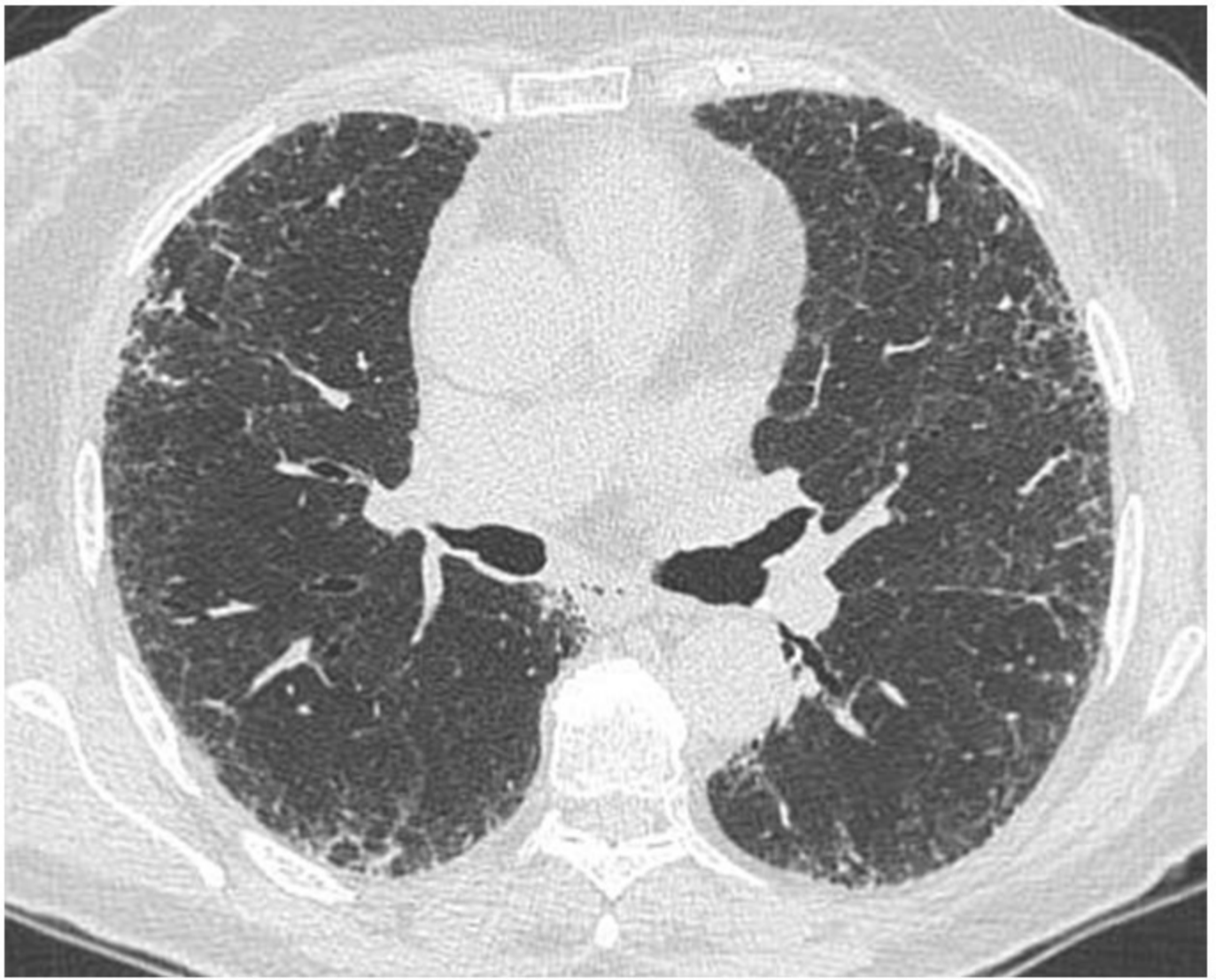


Figure 7

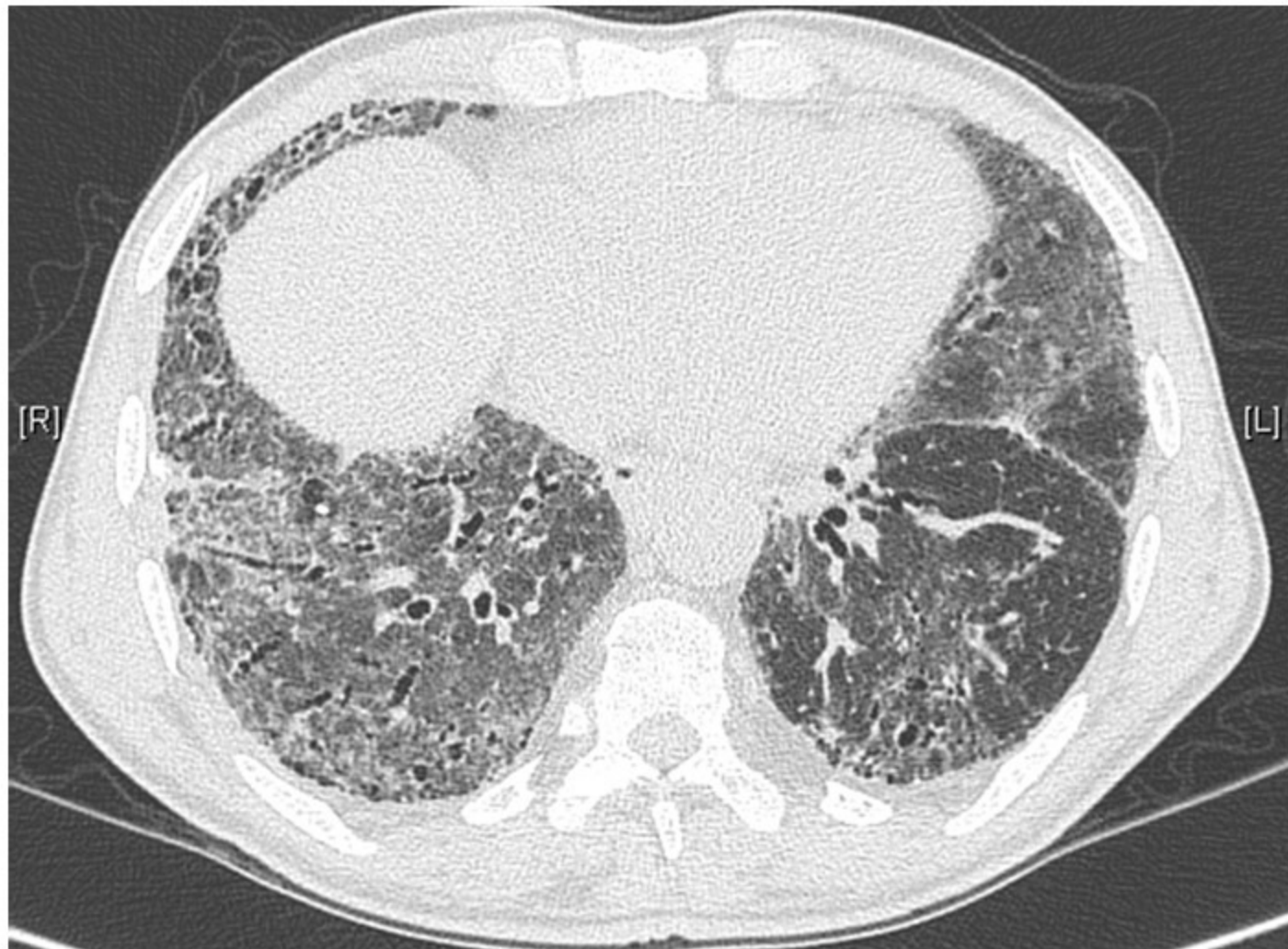


Figure 8

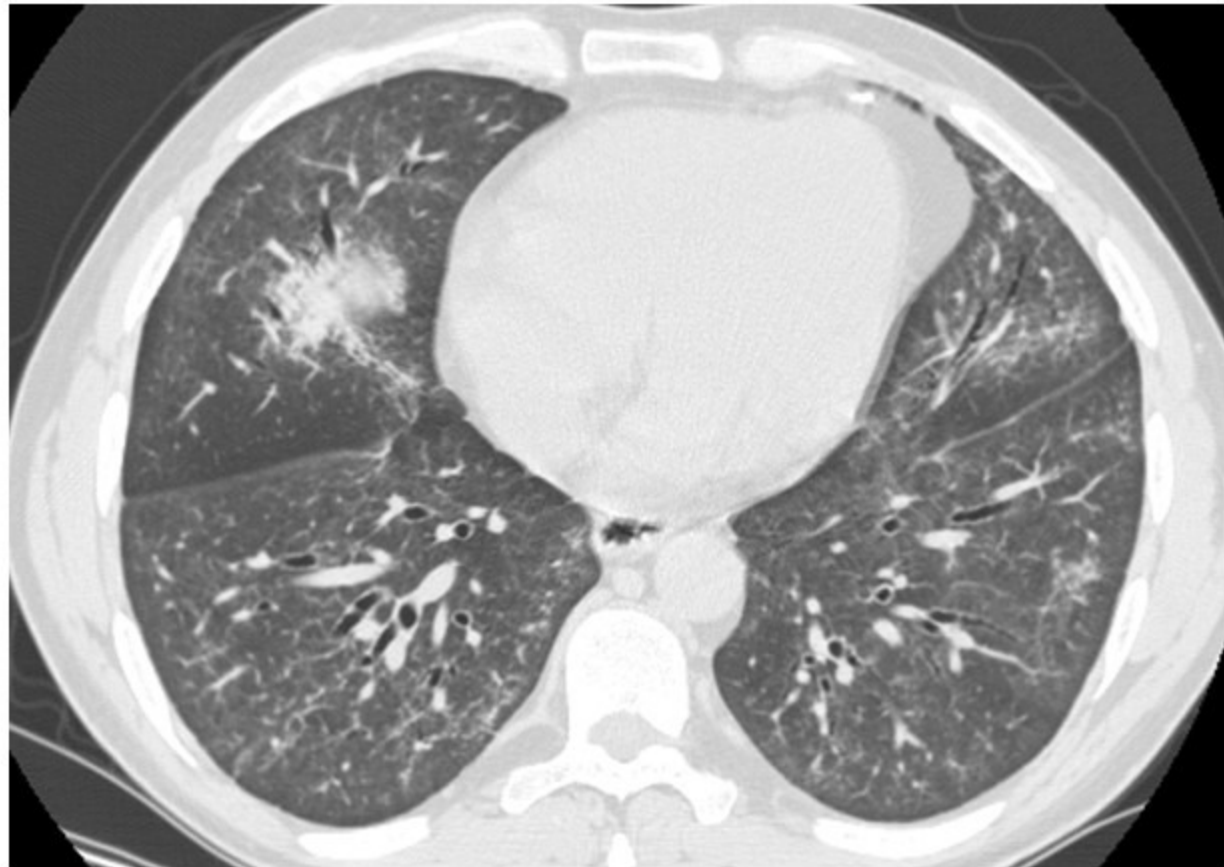


Figure 9

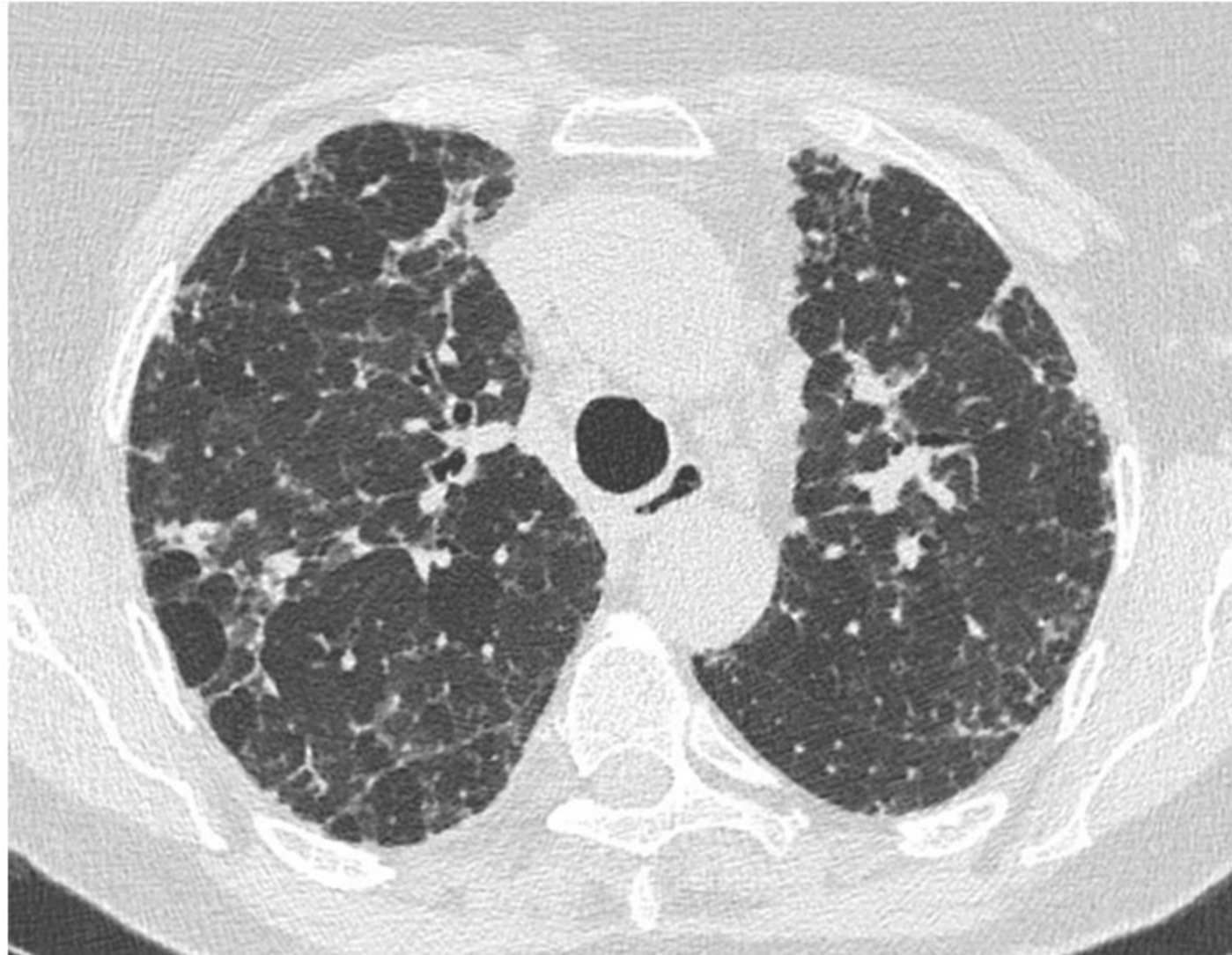


Figure 10



Figure 11