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REVIEW

Challenges in the diagnosis of idiopathic pulmonary fibrosis: the importance of a multidisciplinary approach

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ABSTRACT

Introduction: The diagnosis of Idiopathic pulmonary fibrosis (IPF) requires the careful exclusion of secondary causes of interstitial lung disease (ILD), and the collaboration among different specialists is considered paramount to establish a diagnosis with high diagnostic confidence. The multidisciplinary discussion (MDD) has assumed an increasing importance over the years in the different phases of the IPF diagnostic work-up.

Areas covered: The role of MDD in the diagnosis and management of IPF will be described. Practical insights will be provided into how and when to perform MDD based on the available scientific evidence. Current limitations and future perspectives will be discussed.

Expert opinion: In the absence of high diagnostic confidence, agreement between different specialists during MDD is recognized as a surrogate indicator of diagnostic accuracy. Often, despite a lengthy evaluation, the diagnosis remains unclassifiable in a significant percentage of patients. MDD therefore appears to be pivotal in attaining an accurate diagnosis of ILDs. The discussion among different specialists can also include other specialists, such as rheumatologists and thoracic surgeons, in addition to the core group of pulmonologists, radiologists, and pathologists. Such discussions can allow greater diagnostic accuracy and have important effects on management, pharmacologic therapies, and prognosis.

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1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive disease of unknown etiology, characterized by the relentless deposition of fibrotic tissue in the lung parenchyma, associated with significant mortality and poor prognosis despite available treatments [1]]. The diagnosis of IPF can be challenging it requires the careful exclusion of secondary causes of interstitial lung disease (ILD), and the collaboration among different specialists integrating clinical, radiological, and eventually histopathological data is considered paramount to establish diagnosis with high diagnostic confidence. Therefore, a multidisciplinary discussion (MDD) has been recommended at different stages of the IPF diagnostic work up, usually involving pulmonologists, chest radiologists, a pathologist with expertise in lung disease and a rheumatologist on a case-by-case basis. In this setting, MDD is pivotal to determine the need of further investigations such as bronchoalveolar lavage (BAL), transbronchial lung cryobiopsy (TBLC) or surgical lung biopsy (SLB), especially in more complex clinical cases, and to define the most appropriate therapeutic choice and the timing of follow up.

In this review, the role of MDD in the diagnosis and management of IPF will be described. Practical insights will be provided into how and when to perform MDD based on the available scientific evidence. Finally, current limitations and future perspectives of MDD will be discussed.

2. Diagnosis and therapeutic management

Over the last 10 years the perception of the multidisciplinary approach as key to diagnosis and management of IPF has changed, with increased emphasis on MDD as the gold standard of diagnosis.

Since 2002 the American Thoracic Society/European Respiratory Society (ATS/ERS) committee has emphasized the need for an integrated process in which clinicians, radiologists, and pathologists exchange data in the diagnostic work-up of idiopathic interstitial pneumonias [2]. This integrated approach has demonstrated increased physician agreement and diagnostic confidence for IPF [3].

The 2011 official ATS/ERS/JRS/ALAT guidelines for the diagnosis and management of IPF expressed a new concept of the diagnostic algorithm for IPF. The role of MDD was conceived as a discussion of clinical data among clinicians, radiologists, and pathologists [4], mostly for patients with a low suspicion of IPF due to radiological and clinical features suggestive of alternative diagnoses. According to the 2011 guidelines, patients with a 'possible usual interstitial pneumonia (UIP)' or 'inconsistent with UIP' pattern on HRCT should undergo surgical lung biopsy and subsequent multidisciplinary discussion to achieve a confident diagnosis, while a 'UIP pattern' on chest CT allows a more confident diagnosis of IPF in the appropriate clinical setting.

This recommendation was reaffirmed by the subsequent 2013 ATS/ERS update on idiopathic interstitial pneumonias classification

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Article highlights

- The role of MDD has changed over the years, becoming increasingly important and suggested at an earlier step in the IPF diagnostic algorithm.
- Clinical history with pulmonary function tests, HRCT images and autoimmune assessments have been identified as necessary data to achieve a consensus diagnosis and shared treatment and management choices.
- Experts in rheumatology, thoracic surgery, lung transplantation, genetics, palliative care, physiotherapy, and occupational medicine may play important roles in patient management and follow-up.
- A further role of MDD is to facilitate the access to clinical trials through an accurate pre-screening of candidate patients.
- Re-presentation of patient cases when the disease course or results of additional investigations are likely to result in a change of the diagnosis, or to discuss the management of ILDs with a progressive disease course represents an additional strength of MDDs.

[5]. The White Paper published in 2018 by the Fleischner Society suggested that SLB should be considered in cases of indeterminate radiological patterns and clinical features suggestive for alternative diagnosis, whereas can be avoided for 'probable UIP' patterns in the consistent clinical context [6]. Furthermore, with the 2018 guidelines [7], MDD was recommended at the beginning of the diagnostic process recognizing a greater benefit of MDD in cases of lower diagnostic confidence for 'probable UIP' or 'indeterminate for UIP' pattern or discordance among clinical, radiological and histological data. Indeed, several studies comparing patients undergoing single-disciplinary decision-making (SDD) with patients undergoing MDD, reported that SDD demonstrated suboptimal agreement (median, 70%; range, 47–87%) [8–12]. Therefore, MDD has been proposed as the gold standard in the diagnosis and management of ILDs. This suggestion has been welcomed by several experts, emphasizing the need for MDD to establish the benefits and risks of performing diagnostic investigations in an adequate clinical context and radiological pattern [13,14].

The next step comes from the latest 2022 guidelines update [15] in which the experts confirmed that it is possible to make a confident diagnosis of IPF during a multidisciplinary discussion even in patients with a 'probable UIP' pattern on HRCT with no need of other diagnostic procedures in the appropriate clinical context. Ultimately, the recommendations of the experts in recent years have led toward a common goal: to allow a timely diagnosis of IPF by avoiding invasive tests such as surgical lung biopsy through MDD. Often SLB confirms the identified HRCT pattern or is potentially harmful for patients at high risk [16–18]. It is therefore emphasized the discussion among different experts, also allowing the identification of non-IPF ILD cases at an early stage. The role of MDD in the diagnosis of IPF according to the guidelines is briefly described in Table 1.

It is widely acknowledged that the diagnostic work-up of IPF is complex due to nonspecific symptoms, generally dry cough and exertional dyspnea with chronic onset, requiring the exclusion of known causes of pulmonary fibrosis and collaboration among different specialists. The White Paper by the Fleischner Society underlined how MDD could reduce the diagnostic mistakes and imprecisions derived from a single specialist decision by integrating contributions from all the individuals involved. A similar level of experience among specialists involved in MDD is desirable to avoid the creation of a hierarchy of opinions and single-member dominance in the discussion.

Table 1. The role of MDD in the diagnosis of IPF according to the guidelines.

ATS/ERS/JRS/ALAT 2011 [5]	ATS/ERS/JRS/ALAT 2018 [10]	ATS/ERS/JRS/ALAT 2022 [17]
MDD should be performed after SLB	MDD should be performed once clinical and radiological data are available to determine the need for more invasive procedures (BAL, SLB)	MDD should be performed once clinical and radiological data are available to determine the need for more invasive tests (BAL, TBLC, SLB)

Abbreviations: ATS/ERS/JRS/ALAT: American Thoracic Society/European Thoracic Society/Japanese Respiratory Society/Asociatión LatinoAmericana de Tórax; MDD: multidisciplinary discussion, BAL: bronchoalveolar lavage; SLB: surgical lung biopsy; TBLC: transbronchial lung cryobiopsy.

There are still several limitations in the diagnostic process of ILD, attributable for example to the only moderate agreement among observers on the definition of the radiological pattern of UIP and to the lesser use of biopsy. Ryerson and coworkers discussed about the uncertainties arising from the terms 'probable', 'indeterminate' and 'alternative'. They proposed to define patients with a leading diagnosis that meets guideline criteria or with≥90% confidence as 'confident' diagnosis; while patients with a leading diagnosis with>50% confidence as 'provisional' diagnosis (with high or low confidence); and patients with no confident diagnosis as 'unclassifiable' [19].

3. When and how to perform MDD

Although MDD is strongly recommended by international guidelines [7,15] a consensus approach for the management of MDD is still lacking. A tentative standardization of MDD has been proposed with the publication of the position statement by the Thoracic Society of Australia and New Zealand and the Lung Foundation Australia [20].

The suggested toolkit addresses both the clinical information that needs to be provided during the discussion and the HRCT scanning protocol to be able to comment on high quality imaging. Experts suggest that not too many cases should be discussed (5 cases on average) in order to preserve performance and ensure recurrence of the meeting, an optimal duration could be 60 minutes. To increase attendance, meetings should be held regularly at the same time and place. Adopting a standardized list of potential ILD diagnoses with well-defined criteria, standardizing data presentation, and recommendations for initial management can be suggested.

Usually, MDD is held weekly to monthly, depending on the number of cases referred for discussion. MDD is performed at academic institutions and tertiary ILD centers and lasts around 30–60 minutes. In this regard, a Delphi survey involving the centers of the Care Centre Network promoted by the Pulmonary Fibrosis Foundation (PFF) highlighted how MDD is one of the three key elements in identifying an ideal ILD clinic [21]. A MDD can be carried out either 'face-to-face' or through web-based video conference platforms to facilitate each specialist's contribution. Virtual MDD

can be useful for challenging cases by allowing highly experienced specialists from different centers to collaborate and fostering collaboration between tertiary centers and other smaller institutions, enabling more patients to have a confident, high-level diagnosis without significant delays. A retrospective cross-sectional study described the impact of MDD on the diagnosis and management of ILD in two patient cohorts: internal patients, assessed in-person at an ILD clinic, and external patients, assessed by general pulmonologists and then presented at the MDD by an ILD pulmonologist after reviewing charts [22]. The latter approach has been shown to allow for easier and faster access to MDD experience without requiring all patients to be evaluated at an ILD clinic, and to ensure appropriate management for patients unable to travel to an ILD center. Fujisawa and colleagues recently conducted a retrospective study to evaluate the effectiveness of an online database in facilitating data sharing and MDD. 465 patients were evaluated during web-based MDDs with pulmonologists, radiologists and pathologists using the database and video conferencing. The authors demonstrated that web-based MDD changed the diagnosis in 47% of cases [23]. Beyond the diagnostic role of MDD, another important aim of multi-disciplinary discussion is to define disease progression. This aspect becomes crucial in the recently emerged concept of Progressive Pulmonary Fibrosis (PPF) [15,24]. Besides IPF, which is by definition a progressive chronic disease, the most recent ATS/ERS/JRS/ALAT Clinical Practice Guideline [15] define Progressive Pulmonary Fibrosis (PPF) as forms of non-IPF ILD of known or unknown etiology which demonstrate a progressive behavior despite standard treatments. Disease progression has been defined by at least two of the following criteria occurring within one year, without alternative explanation: worsening of respiratory symptoms; physiological evidence of disease progression, represented by an absolute decline in FVC of at least 5% or absolute decline in DLco at least of 10%; visually assessed radiological progression. Radiological criteria are described in Table 2. In this setting, the interaction between clinician and radiologist is essential to identify patients with signs of disease progression who could benefit from antifibrotic treatments [15,24]. MDD is a very useful tool especially in patients with multiple overlapping conditions such as pulmonary fibrosis combined with emphysema (CPFE). Indeed, it is not clear whether this entity represents a distinct disease phenotype or is simply the coincidence of two processes with a common etiology. Given the particularly poor prognosis, MDD may allow the identification of complications such as pulmonary hypertension and lung malignancy at an early stage and identify these patients as being at greater risk of rapid clinical deterioration [25] and foster discussion on the type of drug treatment to be adopted considering the predominance of fibrosis or emphysema [26].

A further role of MDD is to facilitate the access to clinical trials through an accurate pre-screening of candidate patients. Clinical trials are essential in the field of ILDs to explore new therapeutic options. In this perspective, the participation of a study coordinator to MDDs held in academic centers could be very useful. Furthermore, a significant aspect of the MDD is the patient's satisfaction with their diagnostic-therapeutic process when they learn that their case will be discussed collegially [27]. Increasing treatment compliance, making patients conscious of their disease, and gaining their trust are goals that physicians must achieve.

Furthermore, an MDD should be considered as a recurrent opportunity to study and rediscuss the patient's clinical case. Especially when it is not possible to ascribe a definite diagnosis right away. In this sense, it is crucial to investigate the clinical behavior of the disease during the MDD. The classification of disease behavior was initially proposed in 2013 [5], and distinguished five patterns: - reversible and self-limiting disease – potentially reversible disease but with risk of progression – stable disease over time – progressive but potentially curable disease – progressive disease despite treatment. A recent perspective from an international working group has integrated the observed pattern of disease behavior into the other key assessments (HRCT, histopathology and clinical probability of IPF) during the multidisciplinary discussion [28].

A future role of MDD could be explored in the field of Interstitial Lung Abnormalities (ILA) defined as incidental findings potentially compatible with early ILD in patients with no previous suspicion of ILD, detected on chest CT scans or abdominal CT scans encompassing the lower lung areas, and involving at least 5% of a lung zone (upper, middle or lower) [29]. ILAs include the following features: ground-glass or reticular abnormalities, lung distortion, traction bronchiectasis or bronchiolectasis, honeycombing, and non-emphysematous cysts. The distribution (subpleural or non-subpleural) and the presence of fibrosis define the potential progressive behavior and have a major impact on the prognosis [30]. To our knowledge, there are no studies investigating and validating the potential role of MDD in ILAs. However, considering the potential difficulties that both clinicians and radiologists may encounter in defining whether follow-up is needed and consequently the most appropriate follow-up timing, MDD could be a crucial tool to manage patients with ILAs in the near future.

Table 2. Radiological criteria of disease progression in Progressive Pulmonary Fibrosis (PPF).

Increased extent or severity of bronchiectasis or/and bronchiolectasis
New ground-glass areas with bronchiectasis
New reticulations
Increase extent or increase coarseness of preexisting reticulations
Evidence of new honeycombing or more extensive honeycombing
Volume loss

4. Members of MDD

Usually, the experts involved in MDDs are pulmonologists, thoracic radiologists, and pathologists. Other specialists such as rheumatologists, thoracic surgeons, palliative care specialists, nurses, respiratory therapists, physiotherapists, and dieticians may be required on a case-by-case basis. A detailed description of the role of each specialist in the MDD is reported below.

4.1. Pulmonologist

One or more pulmonologists firstly describe the clinical case providing information about the medical history, smoking status, environmental and/or occupational exposures, history of exposure to prescribed or illicit drugs, and family history as it pertains to ILD.

A key part of the diagnostic process includes a detailed assessment of medical history and in particular of any exposures to inhaled agents associated with specific ILDs. Chronic hypersensitivity pneumonitis (HP) develops in predisposed individuals after repeated exposure to one or more agents (e.g. fungi/molds, animal proteins, pelts, wild birds) [31] and the identification of a trigger antigen has been shown to be associated with improved survival [32]. Given the large diversity of exposures relevant to ILD, several questionnaires have been developed, commonly used to help clinicians to identify the cause of ILD [33]. The international guidelines advocate the need for further research in the identification of different questionnaires appropriate for different location and population as an important complement to patient care that can help physicians in clinical practice [34]. A recent study [35] aimed to assess the performance of the Chest Questionnaire [36] in 62 patients with ILD in a tertiary ILD center. The authors found that the Chest Questionnaire is a helpful tool for detecting potentially relevant exposures but cannot replace a detailed medical history taken by physicians.

Symptoms and signs should be accurately described, including the presence of exertional dyspnea, dry cough, inspiratory 'velcro-type' crackles on chest auscultations, digital clubbing, signs, or symptoms suggestive for autoimmune disease, such as puffy fingers, skin rash, Raynaud's phenomenon, arthralgias, myalgia, chronic dry mouth/eyes.

Parameters of pulmonary function tests (forced vital capacity – FVC, total lung capacity – TLC, forced expiratory volume during the first second/FVC ratio – FEV1/FVC) and of gas exchange (diffusing capacity of the lungs for carbon monoxide – DLco) and their changes during follow-up are essential information to understand severity of disease, progression, and prognosis and to suggest the therapeutic management.

Clinicians should also report available laboratory tests results, including autoimmune screening profile with autoantibodies (antinuclear antibodies – ANA, rheumatoid factor -RF, anti-cyclic citrullinated peptide ANTI-CCP, extractable nuclear antigen antibodies -ENA, etc). Table 3 summarizes information to be shared during MDD.

Table 3. Useful clinical information to share during multidisciplinary discussion.

General information (age, gender)
Respiratory signs and symptoms and their onset and evolution (exertional dyspnea, dry cough, digital clubbing, peripheral cyanosis, 'velcro-like' crackles)
Signs and symptoms of a systemic autoimmune disease (arthralgia, joint swollen, Raynaud's phenomenon, sclerodactyly, mechanics hands, muscle weakness, myalgia, sicca syndrome, rash)
Serological tests to exclude CTDs (CRP, ESR, RF, ACPA, ANA, CPK)
Pulmonary function tests (FVC, FEV1, TLC, DLco, 6MWT)
Smoking history
Occupational/environmental exposures (asbestos, metal or wood dust, birds, farming)
Drug history (consider use of medications known to cause pulmonary toxicity, such as chemotherapy agents, antiarrhythmic drugs, immunosuppressive drugs)
Family history of ILDs
HRCT features
Histological features, if available

Abbreviations: CTDs = Connective tissue disease; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor; ACPA anti-cyclic-citrullinated peptides antibodies; ANA = antinuclear antibodies; CPK = creatine phosphokinase; FVC = forced vital capacity; FEV1 = forced expiratory volume in one second; TLC = total lung capacity; DLco = diffusion capacity of the lung for carbon monoxide; 6MWT = six-minutes walking test; ILDs = Interstitial lung diseases; HRCT = high resolutions computed tomography.

4.2. Radiologist

After the clinical presentation, the chest HRCT examined and interpreted by a chest radiologist. The radiologic pattern should be classified according to which of the four patterns: UIP pattern, probable UIP pattern, indeterminate for UIP pattern, and pattern suggestive of an alternative diagnosis, as presented in the 2022 guidelines for the diagnosis of IPF [15].

The main feature of the UIP pattern is subpleural, lower lung-predominant honeycombing, defined as small cysts (measuring between 3 and 10 mm but up to 2.5 cm in size) with thick, well-defined walls, with or without traction bronchiectasis, often developed in several layers but also in a single layer of subpleural cysts. Of note, honeycombing must be distinguished from paraseptal emphysema and airspace enlargement with fibrosis. The UIP pattern usually develops with an apicobasal gradient and especially affects the dorsal lung regions [15]. However, the interobserver agreement for the UIP pattern identification has been shown to be only moderate between chest radiologists, even among experts [37]

When the patient's clinical and radiological features are not sufficient to make a confident diagnosis and the patient cannot undergo invasive diagnostic procedures, a 'working diagnosis' could be proposed. This approach demands a close clinical, radiological and laboratory follow-up and regular multidisciplinary re-discussion to review the diagnosis and the most appropriate disease management. To illustrate how important a strong collaboration between pulmonologists and radiologists is, Chung and Goldin [10]described the case of a 67-year-old woman with a working diagnosis of IPF. Although HRCT pattern was suggestive of a nonspecific interstitial pneumonia, her clinical history and physical examination were evocative of IPF. During the follow up, the patient developed arthralgia and her blood tests revealed positivity for anti-cyclic citrullinated peptide and rheumatoid factor; consequently, the working diagnosis of IPF was changed into rheumatoid arthritis associated with ILD. It therefore appears clear that a strong collaboration between the pulmonologist and radiologist in reaching a differential diagnosis is crucial, especially in the first phase of the clinical work-up, when it is essential to obtain a specific diagnosis, as it would imply different therapeutic options (e.g. immunosuppressive drugs, antifibrotics). On the other hand, once a progressive phenotype is developed, according to the specific PPF criteria [15] antifibrotics are suggested, regardless of the underlying diagnosis. A Delphi survey among ILD experts confirmed that the presence of at least one thoracic radiologist as well as the availability of a high-quality HRCT scan are essential to have an optimal MDD [38].

4.3. Pathologist

According to the diagnostic algorithm of the current guidelines for the diagnosis of IPF, those patients with 'indeterminate for UIP' pattern on HRCT should undergo further investigations, such as BAL, TBLC or SLB. Specifically, TBLC is considered an acceptable alternative to SLB in centers with high expertise. According to the expert committee, the diagnostic power of TBLC is 80% compared to 90% of SLB and it is highly probable that patients with non-diagnostic samples from TBLC have non-diagnostic samples from SLB too [15]. Additionally, histological examination has shown a significant impact on increasing diagnostic reliability in the multidisciplinary diagnosis of IPF [39]. COLDICE, a prospective and comparative study revealed high levels of diagnostic agreement between TBLC and SLB. Patients required a histological evaluation to reach a diagnosis, sequentially underwent both TBLC and SLB. At subsequent MDD, unidentified cases were discussed twice with either TBLC or SLB along with clinical and radiological data demonstrating high levels of diagnostic agreement between the two methods [40].

The pathologist's role can become crucial when HRCT does not show a UIP or a probable UIP pattern and the most appropriate procedure must be chosen to enhance diagnostic accuracy (i.e. BAL, TBLC or SLB). However, the main role of the pathologist is to classify histological features into one of the four identified patterns among UIP, probable UIP, indeterminate for UIP or alternative diagnosis, representing a critical step in formulating the final diagnosis [14,15].

The histopathological pattern of UIP includes a combination of patchy dense fibrosis with architectural distortion (i.e. destructive scarring and/or honeycombing); fibroblast foci with a predilection for subpleural and paraseptal lung parenchyma; and the absence of features suggesting an alternative diagnosis [7].

However, the histological classification of the disease is not always easy, especially considering the inter- and intralobar histological variability. A study published in 2004 highlighted that the overall kappa coefficient of agreement increased with multiple biopsies, supporting the practice of taking multiple biopsy specimens [41]. Furthermore, the presence of a UIP histopathological pattern, even if in a single area compared to multiple areas sampled by biopsy, is associated with a worse prognosis. Biopsy should be targeted to sample that area, suggested by HRCT, where a UIP pattern is most likely to be obtained [42].

4.4. Rheumatologist

Although the rheumatologist is not routinely involved in MDD, up to 20% of ILD are secondary to systemic autoimmune rheumatic diseases (SARDs). The ATS/ERS/ALAT/JRS guidelines underline the need to exclude known causes of interstitial lung disease, including connective tissue diseases (CTDs) which need to be investigated through a thorough clinical and serological screening. Typical manifestations of autoimmune involvement include arthropathy, muscle pain, changes in the distal extremities (Raynaud's phenomenon, joint deformities, sclerodactyly, onychodystrophy, skin rash). Physical evaluation is first performed during the initial patient's evaluation by the pulmonologist, who may however misinterpret clinical signs and serological results. In this regard, it is widely known that autoantibodies may be present in patients with non-rheumatic diseases and even in healthy people, so their interpretation should always be in the context of the clinical features. Moreover, many patients affected by ILDs have certain features that suggest an underlying autoimmune process but do not meet the standard diagnostic criteria for a specific SARDs [43,44]. These patients may have positive serology (auto-antibody profile) more or less specific for one or more conditions or negative serology but in the presence of familiarity or symptoms/signs suggestive of autoimmune disease. For this reason, during the multidisciplinary meeting, the clinician should provide all anamnestic and clinical information regarding systemic symptoms or serology compatible with connective tissue diseases. The presence of a rheumatologist could be therefore important to advise whether a further consultation is needed.

Lung involvement often occurs in confirmed cases of autoimmune disease, where treatment is easier to identify and quicker to start if recognized early. In other cases, such as myositis, respiratory symptoms and interstitial abnormalities may be the first clinical manifestation of the disease. In these often misdiagnosed cases, the presence of a rheumatologist during MDD could modify the diagnostic process and therefore have an important impact on the management, therapy and prognosis.

However, it may be difficult, especially non-academic institutions, to involve a rheumatologist with expertise in ILD. In a recent retrospective observational study, De Lorenzis et al. [25] have analyzed the agreement between pulmonologists and rheumatologists in identifying features suggestive of SARDs, defined as 'red flags' in a single center experience. Two different groups of patients were evaluated: the first one included subjects with a suspicion of ILD related to SARDs due to the detection of one or more red flags; the second consisted of patients with a definite autoimmune disease with uncertain progression of pulmonary involvement. After MDD with the active collaboration of a rheumatologist, fair to moderate agreement between the two specialists was detected. This finding reinforces the important role of rheumatologists in the MDD, as they could significantly contribute to diagnosis and therapeutic decisions.

4.5. Other helpful experts

In addition to the core MDD participants, other experts may provide important input that may facilitate the diagnosis and management of specific ILD cases. A thoracic surgeon could be involved in case of advanced disease to discuss the indication to lung transplantation. Although IPF is a chronic and progressive disease characterized by a poor prognosis, palliative care is rarely offered to these patients. Kalluri and coworkers [45] recently proposed a multidisciplinary collaborative care model as a useful approach to manage disease progression. An open question concerns the role of the palliative care in multidisciplinary discussions during the follow-up of

patients if there is evidence of disease progression. With the increasing availability of high-flow oxygen therapy devices outside the hospital, facilitating the end of life in more familiar patient environments should be a priority. In this setting, professionals as palliative specialists, psychologists, nurses, respiratory therapists, physiotherapists, and dieticians could contribute to the optimal management of patients with IPF.

5. Effects of COVID-19

The COVID-19 pandemic has had tremendous impacts on everyone's lives, the effects of which are still evident. Many jobs have been made 'smart' for reasons of epidemic containment, especially in the time before the development of vaccines in which social distancing was our only weapon available.

The consequences have been the interruption of the physician-patient relationship and the suspension of all those services normally guaranteed by the national health systems. With regards of the ILD centers, the multidisciplinary discussions have been radically changed, after an initial suspension due to the involvement of respiratory physicians in the emergency. This had serious effects on patients, especially in countries where access to antifibrotic therapies is allowed after diagnosis by a multidisciplinary team [46]. In some settings such as Australia, the ILD centers were already conducting multidisciplinary discussions in a hybrid mode (in-person and virtual) before the COVID-19 pandemic, and this continued during the initial phase of the pandemic [47]. Obviously, meetings held in this modality offered undoubted advantages such as the possibility of participation of a larger number of people as well as safety related to the risk of infection. Even for patients followed by hospitals far from the ILD centers, support can be given through online meetings. Sharing of data with other centers is crucial in this setting, considered the worst prognosis of patients furthest from the centers of reference [48]. An interesting future perspective has been proposed by a Japanese study, creating a single regional or national database that collects all the information needed to organize a remote multidisciplinary case discussion [23]. However, technological barriers, connectivity issues, or lack of experience with web applications are significant limitations. The results of various studies, including a survey involving physicians who deal with ILDs, have highlighted the need to invest in telemedicine, which is considered effective and convenient, also for the clinical monitoring of patients [49].

6. Scientific evidence of MDD: importance and limitations

An early and more confident diagnosis of IPF may increase survival because of early initiation of appropriate treatments (antifibrotic drugs) for the disease. Distinguishing IPF from the other ILDs, such as hypersensitivity pneumonitis (HP) or CTD-ILDs, is therefore crucial for the therapeutic implications, especially in the first phase of the disease. Indeed, as highlighted by Hambly and coauthors [50] HP, CTD-ILDs and other ILDs often share with IPF a progressive behavior, in particular the prevalence of progression seems to be similar between IPF and HP. Although an evidenced based algorithm for HP treatment is still not available, patients with fibrotic-HP, often characterized by a more probable progressive phenotype, should be discussed as candidates for an antifibrotic treatment, especially if a clinical and/or radiological progression is confirmed [51]. MDD is now considered a diagnostic gold standard in the field of ILD [7,15]. Several studies conducted in recent decades have supported how multidisciplinary discussion can radically change the improvement of diagnostic accuracy in a considerable number of cases and how it affects subsequent therapeutic management [3]. Flaherty and colleagues analyzed the change in the agreement rate among specialists in a total of 58 patients with interstitial lung disease admitted to the University of Michigan specialty center [3,52]. The study involved three clinicians, two radiologists and two pathologists who were presented with clinical data, radiological images and finally histological reports. Interestingly, the level of agreement among the participants improved after the multidisciplinary discussion. A consensus diagnosis was formulated in 80% of the cases examined and the level of agreement among pulmonologists also went from 'fair' ($k = 0.41$) to 'perfect' ($k = 0.86$) after multidisciplinary discussion. Physicians identified 75% of IPF cases and radiologists 48% of cases, before presentation of histopathologic information; while after discussion with the pathologists, the radiologists significantly modified their interpretations, and an excellent agreement was reached among the observers ($k > 0.8$). Thanks to the results obtained, the possibility of formulating a diagnosis of IPF in the absence of a biopsy when the pulmonologist and the radiologist agreed during MDD was advanced for the first time. Agreement rates were lower for patients with ILD other than IPF, in these cases MDD may be useful in deciding the subsequent diagnostic work-up [8]. In a subsequent study, Tominaga and coworkers [29] examined how the judgment of pulmonologists and radiologists on the diagnostic confidence level of IPF changed by providing additional information during the diagnostic process. Pulmonologists and radiologists were consulted on the diagnostic reliability of IPF in 95 patients diagnosed with IPF with a histological pattern consistent with UIP. The two involved groups of pulmonologists and radiologists were asked to assign a score from 1 to 5 reflecting their level of confidence in the diagnosis of IPF, first based on clinical information, then on chest CT images, and finally following MDD. The authors highlighted that with the increase of clinical and radiological information, the degree of certainty of the diagnosis decreased to a low or intermediate level in 41% of cases. Diagnoses of IPF were reassessed as 'unlikely for UIP' and alternative diagnoses such as HP, CTD-ILD, and nonspecific interstitial pneumonia (NSIP) were proposed [29]. A retrospective study retrieved the clinical-radiological information of 938 patients admitted to the University Hospitals Leuven (Belgium) between January 2005 and December 2015 [30]. These patients had been evaluated in the absence of a multidisciplinary discussion. 48.5% of cases were diagnosed by the referral center, the rest of the cases had not received a previous diagnosis. MDD led to a change in diagnosis in over 40% of patients and allowed a definite diagnosis in 384 patients who had no initial diagnosis (79.5% of patients without a pre-MDD diagnosis) [30].

Consistent results were obtained in a further study evaluating patients referred to two tertiary care centers in Australia after diagnosis of interstitial lung disease: over 50% of initial diagnoses were changed (even for more than 1 in 3 patients who had a pre-MDD diagnosis of IPF), while patients judged to have 'unclassifiable disease' received a specific diagnosis in over 70% of cases [11]. These studies underscore how MDD allows for diagnosis for cases that a single specialist decision-making process labeled as unclassifiable ILD. A retrospective analysis conducted by a UK specialist center also showed a major change in the number of unclassifiable ILD diagnoses. In 75% of the 76 cases proposed as unclassifiable, a diagnosis was identified as a result of MDD [9]. Identifying a diagnosis has an immediate repercussion in clinical practice on the prognosis, allowing access to therapies, or the possibility of participating in clinical trials in advanced clinical settings or in cases where standard treatments have failed [53]. Using the Flaherty model [3] a study published by Walsh and coworkers compared agreement among 7 different multidisciplinary teams (MDTs) responding to a cohort of 70 case reports [54]. This was probably the first study that exceeded important limitations of the previous studies described. The study evaluated the concordance rate not only among experts in a multidisciplinary team, but also between different multidisciplinary teams. The agreement rate between single MDTs and different MDTs for the diagnosis of IPF was good ($k = 0.60$) and similar (also valid for CTD-ILD with $k = 0.64$); while for other ILDs such as NSIP or HP the concordance rates were lower (fair for HP with $k = 0.29$ and fair/moderate for NSIP with $k = 0.42$). Certainly, the diagnostic criteria for the diagnosis of IPF were well defined at the time of this study, whereas this was not the case for other ILDs. This study showed a low level of inter-MDT agreement in the diagnosis of other ILDs, highlighting the need for updated guidelines. This was demonstrated by a recent survey which proposed 50 topics relating to how a multidisciplinary discussion should be conducted [38]. Of these, only 5 passed the consensus threshold among the 15 ILD experts interviewed and more than 100 ILD experts who answered the online questionnaire. This study showed the absence of a standardized methodology to conduct the meetings and a first attempt to solve the problem. The hot topics reported by the experts were: the quality of chest CT images; a standardized model for collecting patient data; the availability of adequate discussion spaces and a visual projection system. Finally, the experts also found it useful to have an annual benchmarking process aimed at having team members experienced in a minimum number of ILD cases/year [38]. Flaherty et al., using the same inter-observer agreement rate study design as the 2004 study, observed that there is significant disagreement regarding the diagnosis of idiopathic interstitial pneumonias (IIPs) among academic and community physicians [3]. Furthermore, the agreement among academic physicians was higher after MDD than physicians working outside the academic setting ($k = 0.71$ vs $k = 0.44$). Patients from non specialist medical centers were more often diagnosed with idiopathic pulmonary fibrosis. Another consideration is that the presence of more experienced physicians could influence the group and unintentionally produce diagnostic bias. This is especially true outside of centers where MDDs are performed on a regular basis. The diagnostic accuracy of MDD could be confirmed by looking at the mortality associated with the condition being diagnosed, considering that idiopathic pulmonary fibrosis is associated with higher mortality already in the first years after diagnosis [3].

A study by Walsh and colleagues used mortality data to assess the diagnostic accuracy for IPF in a large group of physicians with diverse experience and from different countries [55]. The study partially confirmed the improved accuracy of diagnosis by experienced university ('academic') professionals, but also highlighted the improvement in diagnostic accuracy in non-academic physicians who have regular access to MDDs. Finally, the complexity of making MDD a reproducible tool in different clinical centers is determined by the available resources. The duration, the number of clinical cases discussed, and the available specialists (such as pathologists) are strongly related to the work environment. A global survey carried out by Richeldi et al. revealed the absence of the pathologist in more than a third of the centers where MDDs are performed (and which also participated in the survey proposed to BRICC countries) [56], in contrast to what is recommended by the guidelines [6,15].

7. Future perspective

There are major challenges to be overcome in the field of interstitial lung disease, which are mainly addressed by the continued progress of research into the pathogenic aspect of these conditions.

The primary objective of the multidisciplinary discussion must always remain the achievement of a diagnosis of certainty by combining clinical, radiological, and histological features and the opinions of different specialists. Maintaining this approach in the multidisciplinary discussion allows for personalized treatment, always trying to keep the attention and discussion among experts on the diagnosis high, especially in the era of PPFs [24]. Additionally, MDD may play a pivotal role in facilitating the prescription of anti-fibrotic agents by providing information that satisfies guidelines adopted by regulatory agencies in different countries throughout the world.

The multidisciplinary discussion currently focuses on a panel of clinical and laboratory assessments that currently do not include biomarkers in clinical practice. Ideally, an experienced clinical pathologist or geneticist can help contextualize biomarkers during MDDs. Biomarkers, which can be based upon genomic or serologic findings, can provide information pertaining to ILD predisposition, a specific ILD diagnosis, how an ILD should be monitored, prognosis, and the likelihood of clinical response to specific therapies. In the context of genomic markers of susceptibility, the first to be described are mutations in genes encoding surfactant proteins (protein A2 gene and protein C gene), which are rare in sporadic IPF. Diagnostic serologic markers include protein A and D levels (SPA and SPD), which are more sensitive in detecting IPF than other ILDs [57]. However, their specificity is very low as blood levels of these proteins increase following any type 2 alveolar

cell damage, including bacterial pneumonia [58]. Some studies have hypothesized their role as predictive markers, observing a change in blood concentration levels following treatment with pirfenidone and nintedanib [59,60]. Another protein initially studied as a tumor marker of adenocarcinoma is KL-6. Its role remains to be defined but it has emerged as a possible monitoring marker, as compared to other markers its values are increased in acute exacerbations of IPF [61]. Furthermore, Bonella F. and colleagues [62] showed a change in serum KL-6 levels that could be used as a predictor of mid-term response to pirfenidone. Currently, the guidelines do not indicate the analysis of these serological markers, due to a low quality of evidence of the trials performed. However, approximately one out of four familial pulmonary fibrosis cases may have a known genetic alteration in surfactant constituents or telomere maintenance [63]. The identification of these alterations can predict prognosis (more than the histological subtype), possible extrapulmonary manifestations (i.e. occult cirrhosis in some forms related to short telomere syndrome) and therapeutic consideration (lung transplantation is recommended in patients with telomere syndrome for the progressive nature of the fibrosis). A family history of pulmonary fibrosis has been shown to be strongly associated with an increased risk of IPF [64]. Although not all these forms are exclusively genetic in origin, studies on these markers may help in screening of family members. In this context, geneticists could be very useful in the near future to integrate biomarkers during MDDs.

8. Expert opinion

The multidisciplinary discussion represents a fundamental step in the diagnostic process of patients with ILD as underlined in the latest guidelines [15]. Physicians in ILD academic centers were more likely to attend meetings compared to non-ILD academic centers or non-academic centers [56]. Its role is essential in patients who do not have a definite UIP pattern on HRCT that in the right clinical context allows physicians to achieve a confident diagnosis of IPF [6]. Given the significant clinical impact of reaching a correct diagnosis in terms of prognosis, integration of HRCT images and histological data when needed is fundamental, especially when the diagnostic confidence is low. In the absence of a high diagnostic confidence, agreement among several specialists during multidisciplinary meetings is recognized as a surrogate marker for diagnostic accuracy. Often, despite a lengthy evaluation, the diagnosis remains unclassifiable up to 10–20% of cases underlining how discussion among different specialists is decisive in ILD [65]. The integration of clinical, radiological and histological data has been emphasized also in the updated ATS/ERS classification of the idiopathic interstitial pneumonias (IIPs) [5]. Given the lack of standardization across MDDs, with potential impact on the diagnosis and prognosis, several studies have been conducted to define the 'optimal' characteristics of the MDD in ILD. From the recent international Delphi survey, ILD experts identified key themes and features of ILD MDD listing as highly desirable characteristics the presence of at least two pulmonologists, a radiologist, and at least one pathologist (when histopathological data are available), with one member with at least five years experience in ILD [38]. Clinical history with pulmonary function tests, HRCT images and autoimmune assessments have been identified as necessary data to achieve a consensus diagnosis and shared treatment and management choices. Other items defined as 'desirable' have been the presence of more specialties including experts in rheumatology, thoracic surgery, lung transplantation, ILD nurses, and occupational medicine to generate a more dynamic discussion; and evaluating the degree of confidence in the diagnosis by reporting a list of differential diagnoses in case a definitive diagnosis has not been achieved. Table 4 summarizes the essential and desirable features of MDDs. In particular, a standardized diagnostic ontology has been proposed for patients with ILD labeling as 'confident' diagnosis patients with a 90% or greater likelihood of a diagnosis on the basis of clinical judgment, 'provisional' diagnosis for patients who have a leading diagnosis (probability between 50% and 90%) underlining the diagnostic uncertainty and the need to discuss the clinical case again over time (e.g. collection of new data on the clinical or radiological progression, new laboratory tests), and 'unclassifiable' patients without a leading diagnosis [19]. This classification has recently been integrated by a committee group of experts using a Bayesian approach: 'pretest probability of IPF' (including HRCT pattern, histopathological pattern when available, clinical presentation and disease behavior) and 'posttest probability of IPF' providing a conceptual framework to assess the likelihood of a diagnosis of IPF, very useful in a real world setting [28]. As has already emerged from the recent literature, the committee has given particular attention to the much debated question of the need of surgical lung biopsy especially for patients with a high clinical probability of IPF or for patients with an increased operative risk. The experts concluded by confirming the importance of MDD in establishing the utility of SLB in patients whose confidence diagnosis is low or there is a high surgical risk and by reserving the procedure for patients with insufficient clinical and radiological information leading to a low-confidence diagnosis of IPF [28]. Geneticists are not usually present during MDD, but genomic assessments could be considered for patients with family history or atypical presentation of the disease. It could be very useful to discuss for these patients whether to consider lung transplantation or participation in clinical trials, and

Table 4. Essential features and desirable features of MDDs.

Essential features	Desirable features
Identification of clinical cases requiring MDD	Having more than one member from each discipline
Participation of at least one pulmonologist and chest radiologist. One pathologist and rheumatologist on a case-by-case basis.	Allowing the attendance of external physicians either in person or via videoconferencing
Clinical data and accurate medical history	Report the degree of confidence of the diagnosis
HRCT scan	List differential diagnosis if a confident diagnosis is not possible
Histological data, if available	Following a standardized protocol annually reviewed
Interaction among specialists involved	Identification of priority cases to discuss

Abbreviations: MDD: multidisciplinary discussion, HRCT: High Resolution Computed Tomography.

the implications for the screening of family members of patients with ILD.

In order to achieve a confident diagnosis of IPF, physicians have to exclude other causes of fibrosis including the presence of signs, symptoms or laboratory assessments suggestive of CTD. Despite this recommendation, the professional figure of rheumatologists is not mandatory among the experts usually involved in the MDD. The presence of a rheumatologist can be critical in identifying specific non pulmonary clinical manifestations that could not be easily recognized by traditional MDD members, especially in patients with a clinical context inconsistent with IPF. IPAF is a clinic entity in which clinical or serological abnormalities typical of CTD are present but insufficient to meet the classification criteria of a defined autoimmune disease [44]. The classification criteria share many characteristics with undifferentiated connective tissues and make it possible to identify as IPAF very different clinical entities including patients with very early SSc or other CTD such as myositis with a predominant pulmonary manifestation at the beginning. The presence of rheumatologists would lead to a more defined diagnostic framework avoiding a misclassification. If pulmonary involvement is the first manifestation, with CTD symptoms appearing later, discussion between pulmonologists and rheumatologists would lead to a definitive diagnosis more quickly. Although the involvement of several specialists during MDD could represent an unequivocal advantage in terms of diagnostic accuracy, in real life the participation of all these specialists is almost utopic especially from the time point of view. In this context, the use of hybrid methods, in-person and web-meetings, could streamline MDD participation. Additionally, a referral network around the MDD of palliative care, physicians, psychologists would be critical to ensure timely referral for patients.

Early guidelines recommended the use of MDD as a gold standard for diagnosing patients with IPF [2,4,7]. Recently, with the new concept of progressive pulmonary fibrosis, it has been proposed that patients should be grouped for treatment based on a shared disease behavior, regardless of the underlying specific diagnosis. This concept has been supported in the 2013 ATS/ERS classification, highlighting that management should be based on the most probable diagnosis after MDD and consideration of expected disease behavior. As the disease course is followed over time, MDD is no longer a key point only during the diagnostic process but has become a crucial time to discuss management options and evidence of ILD progression. In this context, the treating physician should consider re-presentation of patient cases when the disease course or results of additional investigations are likely to result in a change of the diagnosis, or to discuss the management of ILDs with a progressive disease course. As disease progression can be monitored using a variety of methods, MDDs may be considered as a very useful tool in the follow-up of patients with progressive ILDs.

Interstitial lung abnormalities (ILA) are incidental findings involving at least 5% of a lung zone (upper, middle or lower) potentially compatible with ILD in patients with no previous suspicion [66]. The prevalence of ILA is estimated around 4–9% in smokers and 2–7% in nonsmokers, but it will likely increase with more widespread use of HRCT. Although the diagnosis of ILA is radiological, clinicians have an important role in identifying those cases with a high probability of progression or with early stage ILD by establishing a follow-up timeline for all patients at high risk of progression. The correct timing of the clinical and radiological evaluation is currently unknown. In this regard, considering MDD as a moment of discussion of these issues could be absolutely helpful in the near future.

The recent coronavirus (COVID-19) pandemic has led to the rapid spread of video conferencing technologies in MDD ILDs. Telemedicine has been applied in MDDs even before the COVID-19 pandemic: Australia has used a hybrid virtual/in-person MDD approach in its clinical practice [20]. Telemedicine exploits the use of advanced and secure platforms for data sharing, also allowing greater collaboration between specialists and different centers and may help in the standardization of ILD-MDM in the near future [47]. Furthermore, an additional benefit of regular MDDs is to improve the skills of different specialists and train young specialists. In addition to the initial diagnosis, MDDs allow shared management of follow-up, even on complex issues such as end-of-life planning. Since there are currently no guidelines on how to organize MDDs, future studies also using telemedicine tools would be essential to define an effective and shared way for the management of IPF and ILDs.

In light of these aspects, further studies that collect data on the contribution of each expert in all the management phases (from diagnosis to treatment and follow-up), and on cooperation between the tertiary and local centers (e.g. making use of new technologies such as telemedicine and genetic and molecular biomarkers for personalized therapeutic approaches) would be needed. This would improve the role of MDD in clinical practice in order to identify an optimal and shared structure (still missing today) in different countries throughout the world.

Declaration of interest

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• **This paper describes Interstitial Lung Abnormalities including definition, risk factors, clinical outcomes, follow-up, and management.**