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On behalf of Lung Foundation Australia and the Thoracic Society of Australia and New Zealand

THE INTERSTITIAL LUNG DISEASE MULTIDISCIPLINARY MEETING

FROM THE THORACIC SOCIETY OF AUSTRALIA AND NEW ZEALAND AND THE LUNG FOUNDATION AUSTRALIA*

POSITION STATEMENT

OCTOBER 2017

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Pneumonitis; HR, high resolution; HSF, high spatial frequency; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPAF, interstitial pneumonia with autoimmune feature; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; LFA, Lung Foundation Australia; MDM, multidisciplinary meeting; NSIP, nonspecific interstitial pneumonia; SLB, surgical lung biopsy; TSANZ, Thoracic Society of Australia and New Zealand; uILD, unclassifiable ILD.

ABSTRACT

Interstitial lung diseases (ILD) are a diverse group of pulmonary diseases for which accurate diagnosis is critical for optimal treatment outcomes. Diagnosis of ILD can be challenging and a multidisciplinary approach is recommended in international guidelines. The purpose of this position paper is to review the evidence for the use of the multidisciplinary meeting (MDM) in ILD and suggest an approach to its governance and constitution, in an attempt to provide a standard methodology that could be applied across Australia and New Zealand. This position paper is endorsed by the Thoracic Society of Australia and New Zealand (TSANZ) and the Lung Foundation Australia (LFA).

KEY WORDS

clinical respiratory medicine, interstitial lung disease, multidisciplinary meeting, pulmonary fibrosis, rare lung diseases.

ABBREVIATIONS

6MWT, 6-min walk test; ATS/ERS, American Thoracic Society/European Respiratory Society; BAL, bronchoalveolar lavage; CCP, cyclic citrullinated peptide; CT, computed tomography; CTD, connective tissue disease; CTD-ILD, CTD-related ILD; DLCO, diffusion capacity of the lung for carbon monoxide; FOV, field of view; HP, hypersensitivity

CONTENTS

INTRODUCTION

Interstitial lung diseases (ILD) are a diverse group of conditions that distort the lung interstitium with varying degrees of inflammation and fibrosis. Although they frequently display similar clinical, radiological and histological features, each form of ILD may display a distinctly different natural history, response to treatment and burden upon the individual's life.[1,2] It is therefore critical to correctly diagnose the specific ILD so that management can be tailored accordingly.[3–5]

Beyond their homogeneous presentations, there are a number of other features of ILD that make their diagnosis difficult. Consensus diagnostic criteria are available for only a small proportion of ILD. Even where detailed diagnostic criteria exists, as for idiopathic pulmonary fibrosis (IPF), the application of those criteria is prone to variation[1,6]; among subjects referred to the Australia IPF Registry, 23% do not meet consensus diagnostic criteria at multidisciplinary review.[7] Finally, as ILD guidelines are updated, there may be a delay between such changes and their implementations by clinicians.[8] In recognition of these difficulties, the use of the multidisciplinary meeting (MDM) in the diagnosis of ILD has been advocated in multiple recent consensus statements.[9–11] Such MDM aim to provide access to clinicians with expertise in ILD and through multidisciplinary interaction, improve diagnostic accuracy.[12,13]

Accurate ILD diagnosis has become especially important following two significant therapeutic findings in the last decade. First, the combination of azathioprine, prednisolone and N-acetylcysteine (NAC) is associated with inferior outcomes in IPF, making the distinction of IPF from other ILD for which immune suppression may be indicated critical.[14,15] Second, two anti-fibrotic agents—pirfenidone and nintedanib—have demonstrated efficacy in decreasing disease progression of IPF by approximately 50% and are now standard of care for mild-moderate IPF.[16–20] Their efficacies for other types of ILD have not yet been demonstrated and inappropriate use may be associated with a lack of effect, side effects and significant cost. Prescription of anti-fibrotic agents for IPF in Australia requires that the diagnosis has been confirmed at an MDM while in New Zealand, although an MDM consensus diagnosis is not required, only respiratory specialists are able to prescribe pirfenidone.[20]

There has been only one previous paper published setting out the practical aspects of running an ILD-specific MDM.[1] Variation in ILD diagnostic technique may lead to diversity in final diagnosis and it is therefore important that the MDM is standardized where possible.[19,21] This position paper reviews the evidence for the use of the MDM in ILD and suggests an approach to its governance and constitution, in an attempt to provide a standard methodology that could be applied across Australia and New Zealand. Where there is limited published literature, the panel of authors with expertise in ILD have provided their considered opinion.

The expert panel was comprised of six respiratory physicians, one pathologist, one radiologist and one rheumatologist with ILD expertise. Authors were assigned specific sections of the position paper for completion which included comprehensive literature review for their allocated section. The articles for inclusion were determined by the assigned author and were not systematically reviewed. All sections, including the referenced articles, were then reviewed and discussed at subsequent meetings with opportunity for all authors to contribute to all sections. After completion of the specific sections by the assigned authors, two authors (J.D.P. and I.N.G.) compiled and edited the manuscript. All authors reviewed and approved the final manuscript.

The purpose of this position paper is to highlight important aspects of the ILD MDM as it applies to Australia and New Zealand and does not represent a guideline. This position paper is endorsed by the Thoracic Society of Australia and New Zealand (TSANZ) and the Lung Foundation Australia (LFA) and will be disseminated through publication in Respirology and the LFA and TSANZ websites. The clinical relevance of this paper will be reviewed after a maximum of 5 years from the date of publication.

CURRENT UNDERSTANDING OF THE ROLE OF MDM IN ILD DIAGNOSIS

Gauging the accuracy of diagnosis in ILD is difficult due to the absence of a reference gold standard. Instead, it typically has been assessed using inter-observer agreement, expressed as the kappa coefficient, either within or between attending specialty groups. The kappa coefficient describes agreement between measurements and is scored between −1 and 1; a higher kappa coefficient reflects greater agreement. Diagnostic confidence has also been used as an end point. While each is suggestive of an increased likelihood of an accurate diagnosis and are the current best endpoints available, it is unclear how closely they approach true accuracy of diagnosis.

Several studies point to the need for a multidisciplinary approach to ILD diagnosis, due to insufficient levels of agreement between expert diagnostic groups working in isolation. In a study involving a 10-member panel of expert pathologists who examined 96 biopsy specimens to provide one of a range of 15 diagnoses, the level of agreement was only fair, with a kappa value of 0.38.[22] A study of 11 radiologists reviewing imaging from 131 patients demonstrated similar findings, with only moderate agreement being achieved (kappa = 0.48).[23] In both studies, for conditions with easily characterized appearances, and when diagnostic confidence was high, the level of agreement was higher.[22,23]

The improvements in diagnostic performance brought by multidisciplinary discussion have been demonstrated using methodology that has come to be termed the Flaherty model, based on the landmark study of MDM in ILD by Flaherty et al. in 2004.[12] In this model, diagnostic material is provided to clinicians, who initially examine that data in isolation to provide a diagnosis, and then re-examine the data in discussion with other specialty groups to provide a post-discussion diagnosis, with the impact upon inter-observer agreement examined. Flaherty et al.'s study included 58 patients with suspected idiopathic interstitial pneumonia (IIP). Among the three expert clinicians, the kappa value after examination of clinical material and the high-resolution computed tomography (HRCT) was 0.41 (95% CI: 0.29–0.52). Agreement improved to kappa values of 0.67 (95% CI: 0.54–0.79) after multidisciplinary radiological discussion. With the addition of histological data and group discussion between clinicians, radiologists and pathologists, kappa values improved further to excellent levels of 0.86 (95% CI: 0.76–0.95). Total agreement was reached between all participating clinicians, radiologists and pathologists on a final diagnosis in 47 of the 58 cases (81%). Discussion amongst the different specialty groups led to changes in the diagnosis and improved confidence with the assigned diagnosis. This study[12] and those described above exploring single specialty group diagnoses[22,23] highlight the importance of ensuring that the multidisciplinary team consists of clinicians, radiologists and pathologists, and also implies the meeting should be governed in such a manner that ensures that each specialty group contributes to discussion.

International guidelines emphasize the importance of diagnosticians having specific expertise in ILD.[9] Inter-observer agreement in a multidisciplinary context appears improved by expertise, based on a further study by Flaherty et al.[13] In that study, experts were gathered in an 'academic' group, characterized by extensive tertiary centre involvement in the management of ILD patients, and two non-expert 'community' groups. Academic clinicians consistently demonstrated greater inter-observer agreement than the community clinicians, with a kappa value after multidisciplinary discussion of 0.71 (SE: 0.03), compared with community physicians whose agreement was moderate with a kappa value of 0.44 (SE: 0.07). Additionally, major differences between academic and community physicians were apparent with regards to final diagnosis, with inter-clinician kappa values sitting between 0.20 and 0.56. Finally, community-based physicians reached a relatively smaller range of diagnoses, and were much more likely to focus on IPF.

The impact of ILD expertise has been demonstrated more recently. Walsh et al. in 2017 used a web-based cohort of 60 cases to evaluate diagnostic performance of a panel of 34 expert ILD physicians in comparison to 370 other participating physicians.[24] The expert ILD physician group was made up of respiratory physicians working in specialist ILD clinics with a track record of publication in the field. The highest levels of agreement for the diagnosis of IPF was observed in the expert group, with a weighted kappa value of 0.65 (interquartile

range (IQR): 0.53–0.72), while physicians without access to an MDM had the lowest levels of agreement at 0.46 (IQR: 0.33–0.58). The expert group made diagnoses of IPF more frequently and with greater confidence than those physicians working in non-university affiliated institutions and their diagnoses were more likely to be prognostically significant (85.2% vs 66.4%; P = 0.02) compared with non-IPF diagnoses than those made by other physicians. The academic status, duration of experience and attendance at an MDM were independently associated with greater prognostic accuracy of the diagnosis of IPF.[24] Despite these findings pointing to the importance of ILD expertise, no process currently exists through which such expertise might be benchmarked. However, physicians in practice for a duration >20 years and attached to an academic institution, or attending a weekly MDM, demonstrated similar diagnostic performance to that of the expert panel, providing guidance on what an expert's attributes might represent.

The extent to which MDM agree with one another has also been examined by Walsh et al.[6] Seven international centres were provided with diagnostic material for 70 cases, which was examined using the Flaherty model. Agreement between MDM with respect to their first-choice diagnosis and differential diagnoses for the four most frequent diagnoses was examined using an unweighted and weighted kappa, respectively. Overall inter-meeting agreement for first-choice diagnosis was moderate at 0.50, increasing somewhat for IPF at 0.60 and connective tissue disease-related ILD (CTD-ILD) at 0.64. When diagnostic outputs were examined more broadly to allow inclusion of the differential diagnosis, agreement was greater, with the weighted kappa value for IPF being 0.71 (IQR: 0.64–0.77) and CTD-ILD being 0.73 (IQR: 0.68–0.78). Agreement for hypersensitivity pneumonitis (HP) diagnoses was only fair at 0.29 (IQR: 0.27–0.40) and at a low-moderate level of 0.42 (IQR: 0.37–0.49) for nonspecific interstitial pneumonia (NSIP). In summary, it appeared that concordance between MDM was high for conditions such as IPF where diagnostic guidelines exist, and for easily recognized conditions, such as CTD-ILD. For conditions where diagnostic features remain less certain, agreement between MDM is at best moderate but still better than outside the MDM.

A key consideration with regards to the utility of an MDM for ILD is whether it leads to a change in diagnosis and subsequent management. To explore this, Jo et al. prospectively examined 90 cases who were referred to two Australian multidisciplinary teams.[7] Of those, 48 (53%) had their referral diagnosis altered. Changes of statistical significance included a reduced frequency of unclassifiable ILD (uILD), decreasing from 42% of cases to 12% and increases in the diagnosis of CTD-ILD (moving from 10% to 21% of cases) and HP (moving from 3% to 16% of cases). Whilst there was no significant change in the overall frequency of diagnosis of IPF, referred cases of IPF were reclassified in 10 of 27 cases and an additional 7 unclassifiable cases were diagnosed with IPF. Overall, the MDM demonstrated significant utility in defining a diagnosis and, for those referred with IPF, providing an alternative diagnosis in over one-third of cases.

Summary

Many current consensus statements advocate the use of expert multidisciplinary discussion for the diagnosis of ILD including IPF. The available evidence demonstrates that MDM improves inter-observer agreement, increases the proportion of high confidence diagnoses and reduces the frequency of unclassifiable diagnoses. Whilst a confident expert clinician diagnosis of IPF also carries high inter-observer agreement, when IPF cases are considered by a multidisciplinary team, their diagnoses are frequently changed and such diagnoses have greater prognostic significance, suggesting that the MDM should be the method used for confirmation of an IPF diagnosis. For other non-IPF diagnoses, inter-observer agreement is relatively lower, in particular for those conditions lacking hallmark features or consensus criteria for their diagnosis, suggesting the need for improved diagnostic techniques and criteria, in addition to an MDM approach, in those conditions.

PRACTICAL CONSIDERATIONS IN RUNNING AN MDM FOR ILD

MDM standardization

No consensus currently exists on the structure of an MDM. Jo et al. surveyed 10 expert centres and demonstrated common properties among their ILD MDM, allowing suggestions to be made for core requirements that could provide a model for standardization (Table 1).[25] These suggestions should be viewed with an understanding of the primary role of the ILD MDM, which is to provide as accurate and confident ILD diagnosis as possible. A collaborative approach with the treating physician can be taken, with the MDM used to provide a consensus diagnosis and recommendations for further investigations and initial treatment. Subsequent management can then be undertaken by the treating physician and their patient, so as to maximize continuity and convenience (Fig. 1).

Data presentation (input to the MDM)
Diagnostic material

In the setting of the large overlap in clinical, radiologial and pathological features across ILD presentations, subtle features within only one of these domains may be all that is available to point to a particular condition and by extension, guide treatment. A detailed and systematic consideration of all diagnostic material is therefore essential to maximize the diagnostic confidence of the ILD MDM.[12] Where there is variability in the approach to presentation of clinical material or a lack of standardization of key radiological and histopathological tools, biases in data analysis by the MDM may occur which potentially reduce accuracy and concordance in MDM diagnosis and recommendations.[1,12,24] While there are no data to suggest the best presentation format (e.g. audio-visual template or less formal oral presentation), a minimum set of core clinical data and investigations of adequate quality for diagnostic review should be available for discussion (Table 2).

Clinical data

A comprehensive patient history is an invaluable tool in the evaluation of a patient with an ILD and there are a number of key features that should be routinely presented. These include the dynamic time course of disease (acute, subacute and chronic), the potential causes of disease (known or unknown) and the context of the disease (presence of extrapulmonary or systemic features).[26]

Table 1 Suggested core components of an interstitial lung disease multidisciplinary meeting

Structure of ILD MDM
1. Dedicated to the exclusive discussion of ILD cases 2. An adequate caseload to enable regular meetings Membership 3. Minimum attendance by two or more respiratory physicians, a radiologist and a histopathologist 4. Presentation of data ideally by the treating respiratory physician 5. Attendance by a respiratory physician with expertise in ILD
Data input
6. Presentation of a comprehensive set of key clinical data and adequate investigations of sufficient quality (Table 2) 7. Presentation of data in a standardized format†

...continued overleaf

Governance
8. A consensus approach to diagnosis formulation, involving discussion between all professional groups 9. Use of a standardized list of potential ILD diagnoses with well-defined terms and current definitions† Data output 10. Provision of a consensus diagnosis, degree of diagnostic confidence (definite, provisional and unclassifiable) and differential diagnoses 11. A suggested initial management plan, including provision to rediscuss with further diagnostic material, if appropriate 12. A standardized and comprehensive means of communication of MDM outcomes with the referring physician and other healthcare providers

†These items will be provided as part of the LFA/TSANZ MDM position statement toolkit.
ILD, interstitial lung disease; LFA, Lung Foundation Australia; MDM, multidisciplinary meeting; TSANZ, Thoracic Society of Australia and New Zealand.

Figure 1 The role of the MDM in clinical care: flow diagram. ILD, interstitial lung disease; MDM, multidisciplinary meeting.

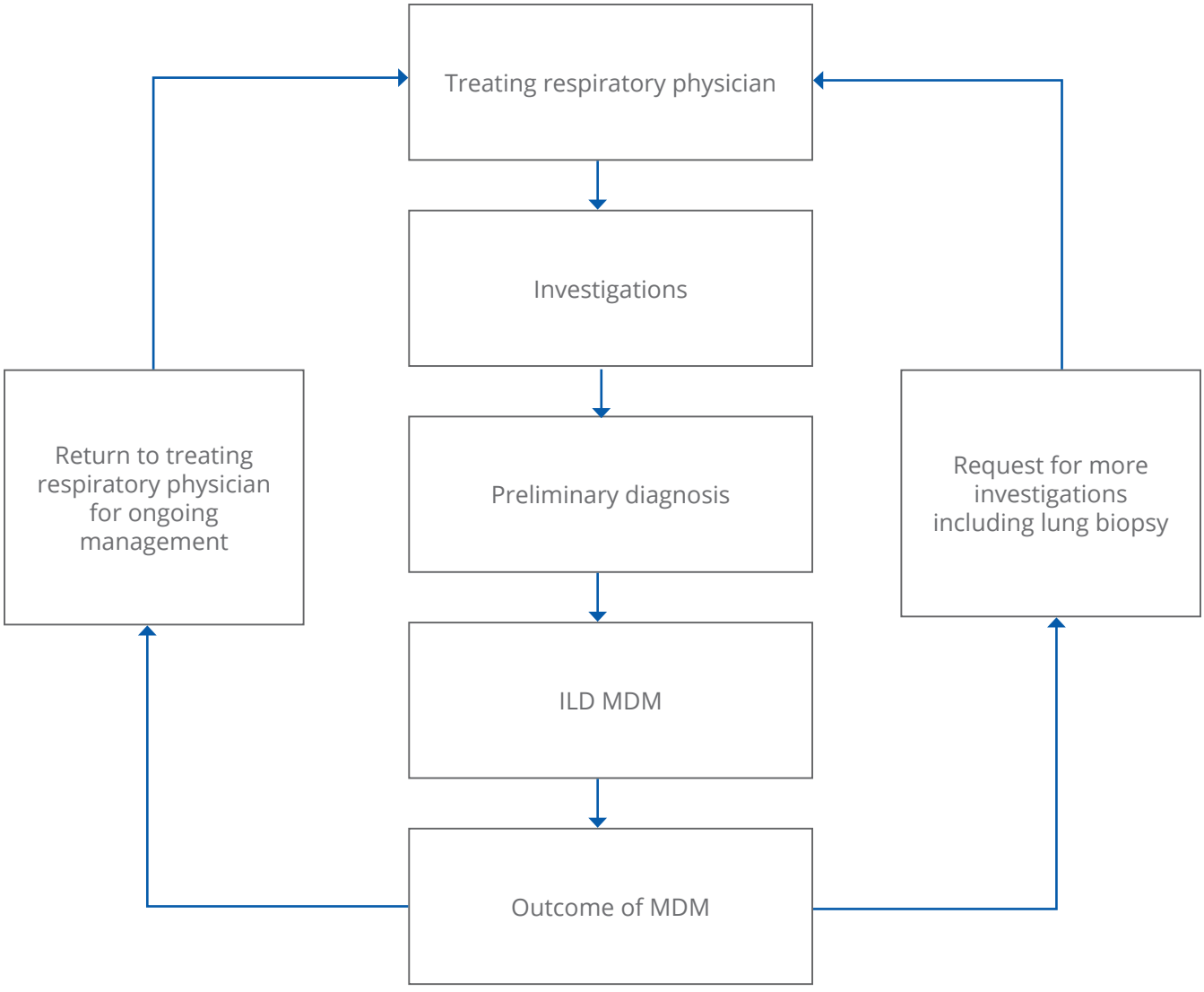

Table 2 Core and ancillary data to be presented in a standardized format at the interstitial lung disease multidisciplinary meeting

Core data (to be presented in every case)	**Ancillary data** (to be presented when performed)
Clinical history Age, gender History of presenting and current symptomatology, temporal pattern and response to therapy Exposures (tobacco and other smoking history, occupational and environmental exposures such as to birds and mould, medications, including non-prescription items) Relevant family history Co-morbidities Symptoms of connective tissue disease Treatment	
Clinical examination BMI SpO2 at rest Cardiorespiratory examination Rheumatology/immunological examination findings	Investigations Histopathology 6MWT Bronchoscopy and BAL Echocardiography Exercise testing Extended myositis screen Polysomnography Other (e.g. right heart catheter and hypersensitivity precipitins)
Investigations (serial if available) Pulmonary function tests HRCT Serology	

6MWT, 6-min walk test; BAL, bronchoalveolar lavage; SpO2, oxygen saturation.

Dyspnoea, one of the principal ILD symptoms, should be described in detail. Its evolution may differentiate an inflammatory process, typically present over a brief or relapsing period, from a fibrotic process, when an insidious course is usually present. The degree and pace of progression of dyspnoea in ILD should be described, given the link with disease severity and prognosis, especially in IPF.[27]

Other symptoms should also be described. Establishing the predominant symptom can assist in the diagnostic process: for example, a predominance of cough, whilst a common symptom in IPF presentations, may suggest bronchocentric processes such as sarcoidosis or HP; the presence of pleuritic pain or effusions may suggest CTD-ILD, drug-induced lung disease or asbestosis.[28] Prominent non-respiratory symptoms such as myalgia, arthralgia, Raynaud's phenomenon and sicca symptoms may also be suggestive of an underlying CTD.[26]

A comprehensive description of risk factors and exposures is vital in establishing the cause of ILD. Smoking history should explore beyond tobacco use.[29] The occupational history should sequentially review all employments and explore the specific duties of the patient, along with types and duration of exposure. Non-occupational exposures, including hobbies and the home environment, should be carefully considered. The therapeutic history should include prescribed medication, over the counter therapies, supplements and illicit drug use. Family history should consider conditions beyond the specific ILD exhibited by the patient.[30] Relevant co-morbidities, such as gastrooesophageal reflux disease, pulmonary hypertension, cardiovascular history, metabolic syndrome and sleep apnoea, should be presented as they have prognostic and therapeutic implications.[31]

Serology and other blood tests

The detection of autoantibodies can assist in changing the diagnosis of IIP to CTD-ILD in up to 19% of cases in ILD clinics.[32–35] Guidelines from the American Thoracic Society and European Respiratory Society (ATS/ERS) recommend testing for antinuclear antibody (ANA), anti-cyclic citrullinated peptide (anti-CCP) and rheumatoid factor (RF) in all patients with suspected ILD.[36] Because the diagnosis of CTD-ILD has implications for treatment and prognosis, if there is any suggestion of CTD symptoms, a more detailed autoimmune screen can be performed (Table 3) and review by a rheumatologist or immunologist is advisable. Although blood tests alone are rarely diagnostic of a specific ILD, certain autoantibodies are more specific for CTD such as anti-CCP for rheumatoid arthritis; dsDNA and anti-Smith antibodies for systemic lupus erythematosus; and antitopoisomerase (Scl-70) for systemic sclerosis (scleroderma).[37] It should also be emphasized that amongst the clinical syndromes associated with myositis specific antibodies, lung manifestations can dominate in the absence of clinical myositis or rash.[38,39]

Table 3 Standard and extended panel collagen vascular disease serological testing

Collagen vascular disease serological testing
Rheumatoid factor (RF)
Cyclic citrullinated polypeptide antibody (CCP Ab)
Antinuclear antibody (ANA)
Antibodies to extractable nuclear antigens (ENA)† Double-stranded DNA antibody (dsDNA Ab) Anti-neutrophil cytoplasmic antibody (ANCA)
PR3/MPO
Creatinine kinase ‡

†Will differ based on the laboratory conducting the test.
‡May be required in selected cases based on clinical suspicion. PR3/MPO, proteinase 3/myeloperoxidase.

Table 4 Genetic mutations in pulmonary fibrosis

Genetic mutations in pulmonary fibrosis
Telomerase components (25–30%)
TERT (15%)/TERC (5%)
RTEL1 (8%)
PARN (4%)
Surfactant and other syndromes (5–10%)
TIFN2, DKC1, STING, SFTPC, SFTPA 1, 2, ABCA 3 (recessive)
MUC5B promoter risk allele

Genetic testing is not currently available in Australia and New Zealand unless undertaken as part of a clinical trial or in selected lung transplant units.

ABCA, ATP-Binding Cassette, Subfamily A; TERT, Telomerase Reverse Transcriptase; DKC1: Dyskerin; MUC5B: Mucin 5, Subtype B, Tracheobronchial; PARN, Polyadenylate-specific Ribonuclease; RTEL1, Regulator of Telomerase Elongation Helicase 1; SFTPA 1,2, Surfactant Pulmonary Associated Protein A1, 2; SFTPC, Surfactant Pulmonary Associated Protein C; STING, Stimulator of type I IFN gene; TERC, Telomerase RNA Component; TIFN2, Tellomeric repeat binding factor 2 - interacting protein.

Understanding the genetic basis of disease and useful biomarkers are subjects of ongoing research and may compliment the diagnostic process. Genetic abnormalities (Table 4) have been identified, particularly in familial ILD, and when present, may impact on therapeutic decisions.[40] Although genetic testing for IPF is not widely available nor suggested as part of a routine ILD MDM presentation, it may be appropriate in some circumstances. For example, patients with premature greying, liver fibrosis and haematological disorders may have a telomeropathy. Its recognition is significant given the impact of these disorders on post-transplant outcomes.[41] Diagnostic and prognostic efficacy of a vast array of specific biomarkers including Krebs von der Lungen 6 (KL6), surfactant proteins A and D and matrix metalloproteinases (MMP) 7 and 1 are being evaluated in IPF but are not currently part of routine clinical practice.[42–44]

Lung function tests

Complete assessment of pulmonary physiology is recommended for patients with ILD.[45,46] Patients with suspected ILD should perform spirometry, diffusion capacity of the lung for carbon monoxide (DL_{CO})[47] and total lung volumes, completed to the specifications of the ATS/ERS Task Force Standardisation of Lung Function Testing, to ensure accuracy and repeatability of testing.[48] At MDM, the forced vital capacity (FVC) and DL_{CO} should be presented as a minimum requirement. Both the baseline values and pattern of change in sequential testing are highly useful, assisting diagnostically and in the estimation of prognosis in IPF and other conditions.[49,50]

In addition, the 6-min walk test (6MWT) performed to the specifications of the ERS/ATS technical standard for field walking tests[51] is a reliable and practical measure of exercise capacity which complements assessment of physiological limitation and has greater prognostic implications in certain types of ILD than spirometric data.[52] The outcome parameters of the 6MWT are walk distance, the baseline and end of test oxygen saturation and the Borg dyspnoea and fatigue score. In IPF, the walk distance achieved has been shown to be significantly lower in patients with the poorest functional status while a change in the walk distance over serial measures is highly predictive of mortality, with a minimal clinically important distance of between 24 and 45 m.[53,54] Similarly, oxygen desaturation has been shown to be predictive of mortality.[55,56]

Radiology

HRCT imaging is integral in the detection and characterization of the various subtypes of ILD as well as assessing for disease progression and treatment response.[9] The diagnostic quality of the available images should be assessed by the ILD MDM radiologist and discussion may need to be deferred if imaging is substandard. Usually a non-contrast CT is performed unless concurrent evaluation of mediastinal lymph nodes and vascular structures is clinically indicated. The HRCT scans should include, at minimum, contiguous or non-contiguous axial scans with thin sections reconstructed at ≤10 mm intervals with slice collimation ≤1.25 mm, using a high-resolution reconstruction algorithm.[57] Multidetector CT (MDCT) scanners enable a large volume of data to be obtained in a single breath hold enabling both rapid scanning and reducing the potential for motion artefacts. Scans should be obtained on full inspiration without respiratory motion, and prone scans are useful to assess details that on supine scan may have been obscured or augmented by dependent density, such as subtle basal reticulation. Expiratory scans are helpful to demonstrate lobular gas trapping suggestive of HP.[58] A standardized protocol that encompasses the features described above (Table 5) is suggested to enhance comparability of studies performed at different centres and to avoid insufficient or uninterpretable material.[57]

Table 5 HRCT chest protocol (Based on the recommendations of Kazerooni et al[57] and scanning protocols from three Australian tertiary referral centres.)

HRCT chest protocol		
Position Supine, arms raised		
Acquisition types Supine, inspiration series: helical Supine, expiration series: axial Prone, inspiration series: axial	**Scan range** Lung apices to lung bases 1 cm below lung apices to 1 cm above lung bases	**Spacing (mm)** 10 20
Reconstruction algorithm	HSF	20

Suggested image reconstructions				
Reformat	**Format**	**Thickness (mm)**	**Spacing**	**Algorithm**
Lung	Axial	≤5	≤5	Lung
	Coronal	≤5	≤5	Lung
	Sagittal	≤5	≤5	Lung
	Supine inspiration	≤1.25	≤10	Bone
	Supine expiration†	≤1.25	≤20	Bone
	Prone inspiration†	≤1.25	≤20	Bone
	Axial	≤5	≤5	Soft tissue
	Coronal	≤5	≤5	Soft tissue

Equipment specifications: the CT scanner should meet or exceed the following: (i) MDCT acquisition with axial mode available; (ii) Scan rotation time < 1 s; (iii) Acquired slice thickness <1.5 mm; (iv) Images should be available on PACS workstation for review by a radiologist; and (v) Provide a radiation dose report in the radiological record. Technical specifications: These include: (i) Radiation: tube potential and tube current selected should be appropriate to the patient's size; (ii) Collimation: regulate these images to encompass patient's size. For HR images of the pulmonary parenchyma, reconstruct a small FOV. Widen the FOV for standard chest images; (iii) Expiratory and prone images: acquire in axial (incremental) mode not helical (volumetric) to reduce cumulative dose;

(iv) Reconstruction algorithm: HR images should be reconstructed <1.5 mm (not thicker). Algorithm must be of HSF and the name of the algorithm depends on the vendor; (v) Intravenous (i.v.) contrast: avoid when primary aim is evaluating the lung parenchyma as subtle findings may be obscured by intrapulmonary i.v. contrast.

†These images are not necessary in all patients. Where not specifically requested, these images may be part of a default protocol when imaging is not readily available for radiological review at the time of patient attendance.

CT, computed tomography; FOV, field of view; HR, high resolution; HSF, high spatial frequency; MDCT, multidetector CT; PACS, Picture archiving and communication system.

Bronchoalveolar lavage

While the utility of bronchoalveolar lavage (BAL) cellular analysis in the diagnosis and management of patients with ILD is controversial, it has gained acceptance as a source of diagnostic information that when obtained in the appropriate clinical context and paired with other clinical information including adequate chest imaging is useful.[59,60] Pulmonary infections can cause a subacute diffuse parenchymal infiltrate or may coexist with an ILD. Where an infectious aetiology is suspected, a BAL should be screened for viral, bacterial and fungal pathogens.[61] A BAL cellular analysis may be helpful in patients without a confident usual interstitial pneumonia (UIP) pattern of fibrosis on HRCT, keeping in mind that a BAL in ILD patients may display a normal cell count and differential, and coexistent airway pathology such as bronchitis may influence the composition of the BAL. Through a BAL cellular analysis, recognition of an inflammatory cellular pattern may narrow down the differential diagnosis but may not add prognostic value or predict response to treatment.[60] A lymphocytosis may be suggestive of a granulomatous process such as sarcoidosis, drug toxicity or in cases of extreme elevation such as >50% may be suggestive of exposure to antigen-causing HP.[62] Similarly, a cell differential displaying an elevated eosinophil count is suggestive of eosinophilic lung disease. The appearance of the BAL may also assist in diagnosis such as in the case of diffuse alveolar haemorrhage where successive aliquots do not show decrease in the amount of bloody discolouration of the BAL.[63] It may be both a diagnostic tool and means of treatment for conditions such as pulmonary alveolar proteinosis (PAP).[59]

Histology

Interpretation of histopathological data is an integral aspect of diagnosis in ILD. As for imaging, the quality of the available material should be assessed by the ILD MDM histopathologist. For the majority of ILD, surgical lung biopsy (SLB) is the recommended standard of tissue acquisition.[9] Ideally, two biopsies from separate lobes targeting areas of involved lung tissue but avoiding normal lung and end stage disease should be obtained. Planning of biopsy site by preoperative consultation with the thoracic radiologist and/or respiratory physician is likely to improve diagnostic yield. Jo et al. (2016) demonstrated that MDM discussions can guide selection of patients for SLB, while reducing the need for SLB in cases where a confident diagnosis can be established without histopathology.[7] Alternatively, the consensus recommendation may be to defer diagnosis and recommend biopsy, where clinical and radiological material is inconclusive and the patient has sufficient physiological reserve. Transbronchial forceps biopsy may be useful in the assessment of processes with a lymphangitic distribution (e.g. sarcoidosis or silicosis) or bronchiolocentric distribution (e.g. HP) or in those with pathognomonic histological features (e.g. Langerhans' cell histiocytosis and organizing pneumonia). Consensus guidelines, however, do not recommend transbronchial forceps biopsy in IPF diagnosis due to the low diagnostic yield of this approach.[9] The role of bronchoscopic lung cryobiopsy is evolving, and at this stage protocols are lacking defining the size, number and sampling locations to achieve the best diagnostic accuracy.[64] Whilst there is encouraging data with respect to the impact of transbronchial lung cryobiopsy (TBLC) on MDM diagnostic confidence, its comparative accuracy to SLB remains the subject of research.[65]

Summary

To avoid bias produced by variation in data input at the MDM, we suggest that a standardized approach to data presentation is taken, that the clinical material is presented in a comprehensive manner, and that imaging, histology and other diagnostic material are of sufficient quality, as outlined above. Baseline and, where available, sequential pulmonary physiology and radiology can aid in diagnosis and provide prognostic information. If there is clinical suspicion of a CTD, detailed autoimmune serology and specialist rheumatological consultation should be obtained. Histology is an important adjunct to diagnosis and should be presented whenever available.

MDM constitution

The positive effect of multidisciplinary discussion, and the impact of expertise on inter-observer agreement and diagnostic confidence has been highlighted above. In our opinion, such considerations are broadly reflected in the constitution of MDM among ILD centres worldwide. In the survey by Jo et al. (2016) of expert centres, each held an ILD-specific MDM every 1–2 weeks, with a caseload of at least six cases and lasting

an hour, providing a format and workload that is likely to maintain expertise.[7,25] Our experience is that it is difficult to incorporate such discussion within a more general respiratory MDM such as a general respiratory radiology meeting, due to the intricacies of ILD diagnosis and the very detailed input by the core specialties required for an adequate discussion.

There is an absence of data within the current literature that precisely validates the ideal MDM constitution. Personnel attending the MDM in Jo et al.'s survey universally included a thoracic physician, radiologist and histopathologist, whilst junior doctors and nursing staff also frequently attended, and some meetings included a rheumatologist, immunologist, transplant physician and thoracic surgeon.[25] The increase in rate of CTD-ILD cases post ILD MDM discussion from 10% to 21% may suggest that rheumatology attendance at the MDM is useful.[7] The impact of input from other disciplines on MDM diagnosis is unknown. It is our experience that having at least one respiratory physician aside from the treating respiratory physician allows for more robust discussion of the consensus diagnosis and stronger diagnostic confidence.

Summary

We suggest that ILD diagnosis takes place in a dedicated ILD MDM. Because ILD presentations require comprehensive review of diagnostic material presented in a standardized manner, diagnosis within a general respiratory radiology meeting is unlikely to allow adequate depth of discussion. A core group of essential attendees include respiratory physicians, radiologists and histopathologists. It is preferable that each MDM is attended by at least two respiratory physicians including the treating respiratory physician, and that the core group has specific ILD expertise. Where available, rheumatologist participation can help to refine ILD diagnosis.

MDM governance

It is important that broad participation is facilitated, so that collective thinking and expertise sharing within the meeting occur, and that clinical decision-making is not dominated by one specialty group.[6] Jo et al.'s survey in 2016 found that between MDM in international ILD centres, differences in governance were apparent with respect to the quantity of data presented and the manner of presentation.[25] Differences were also apparent with respect to the manner of discussion to provide a final diagnosis. A consensus approach was not necessarily used uniformly, with some meetings leaving the final diagnosis to the treating physician. Flaherty et al.'s data make clear that meetings should be governed in a manner where discussion involves all professional groups, and that a consensus approach to diagnosis should be used if inter-observer agreement is to be maximized.[12] All clinicians involved in the MDM process should adhere to current guideline recommendations for diagnosis to enable standardization across individual MDM. On occasion, a consensus diagnosis is not achieved despite discussion and, as outlined below, in those cases a diagnosis of uILD may be needed.[66]

Summary

We suggest that meetings are governed in a manner where input from all applicable diagnosticians is enabled and the final diagnosis is provided upon achieving a consensus. Where significant disparity of opinion remains following discussion, the diagnostic confidence of the MDM consensus diagnosis is likely to require adjustment.

MDM outputs

The principal output from an ILD MDM is the consensus ILD diagnosis, and a series of differential diagnoses. In Jo et al.'s survey, all MDM provided this information.[25] ILD centre MDM generally attempted to quantify their diagnostic certainty, although no validated approach currently exists with regards to such a measure. We support the use of nomenclature for diagnostic confidence of 'definite', 'provisional' and 'uILD' provided by Ryerson et al.,[66] with more precise percentages of confidence reserved for use in a research setting. Where the MDM reaches a consensus diagnosis of uILD, recommending differential diagnoses may aid in clinical decision-making for the patient. Further sub-categorization of uILD based on the adequacy of diagnostic material may assist in improvement of the limited understanding of disease behaviour in this category of ILD.[66]

The recent ATS/ERS consensus statement on ILD recommends that for conditions where a range of disease behaviours are possible, or where the ILD remains unclassifiable, a prediction of disease behaviour is provided.[11] However, while there are a number of well-established predictors of survival in IPF, such predictors are less well validated in other forms of ILD. Even in IPF, the most extensively studied of the ILD, no model has been established that adequately predicts progression outside of mortality, such as physiological or symptomatic decline.[67]

Treatment goals and management recommendations are also frequently provided by the MDM.[9] Whilst the inclusion of these secondary outputs at MDM may be useful, their value will depend greatly on the constitution of the individual MDM. Frequently, a multimodality approach is needed in the management of those with ILD, especially when that disease is advanced or part of a systemic or autoimmune condition that affects multiple organs. An in-depth understanding of the patient's psychosocial circumstances and co-morbidities is often needed, given that many potential therapies may be side-effect laden or taxing in other ways. In the absence of professional groups that may contribute to treatment, such as a rheumatologist, palliative care physician or transplant physician, or those who have firsthand experience of patient factors that may modify those treatment plans, management recommendations may need to be limited.

Finally, a record should be kept of MDM discussions and the key features that led to a consensus diagnosis. Accurate secure recording of such information is suggested for audit activities. Information from the MDM regarding consensus diagnosis should be communicated with the patient's referring clinician and general practitioner in a standardized manner that provides easy interpretation of findings.

Summary

We suggest that the consensus diagnosis, differential diagnoses and level of diagnostic certainty are reported in all cases. In the absence of a consensus, the group may term the case unclassifiable and suggest further investigations (such as lung biopsy) and repeat presentation if necessary. Findings should be documented to allow benchmarking and audit of the MDM. A prediction of disease behaviour may also be provided, but the lack of validation of such an approach should be explicitly stated. Treatment recommendations may be provided, but may need to be limited if additional professional groups need to be consulted or patient-specific factors could not be discussed. Adequate communication with the referring physician should occur.

Common diagnostic dilemmas

For the purposes of standardization and compatibility across MDM, defined diagnostic features of ILD beyond those currently included in consensus statements would be highly valuable. Until such statements become available, it is useful to consider those diagnoses that most commonly form dilemmas in the ILD MDM.

Probable and possible IPF

The ATS/ERS guidelines for IPF diagnosis subdivide patients considered to have IPF into those with definite, probable and possible IPF, and those with features inconsistent with IPF.[9] Whilst the utility of these guidelines has been clearly demonstrated, especially with regard to standardization of patients for recruitment into clinical trials, there is potential for variation in the interpretation of when to consider patients to have probable/possible IPF. By definition, patients without the full complement of the established criteria for definite IPF may have other differential diagnoses. Which condition forms the most likely of those differential diagnoses for the particular patient should be discussed at the MDM and take into account clinical information beyond that outlined in the consensus statement, such as demographics and pattern of progression, that contribute to diagnostic probability.[11] It is upon that discussion that the final diagnosis should be made and subsequent management decisions, including the need for biopsy and the use of antifibrotic or other therapy, placed. Other differential diagnoses are then listed as alternatives and might be reconsidered once the response to initial management can be assessed.

Hypersensitivity pneumonitis

While conditions such as IPF are well defined using international guidelines, the diagnosis of HP is highly variable due to a lack of specific diagnostic criteria.[12] Radiological features can be highly suggestive of this condition but are, as yet, unvalidated. Histopathological findings may overlap with IPF, NSIP and CTD-ILD, and supportive tests such as precipitins and BAL lymphocytosis have an undefined positive predictive value. Due to a lack of defined diagnostic criteria, there is low inter-observer agreement in assigning HP as a diagnosis.[12] One study has identified a significant increase in the number of diagnoses of HP in patients otherwise considered to have idiopathic disease, when more specific diagnostic criteria for chronic hypersensitivity are used.[68] However, until improved diagnostic methodology exists, clinical judgement that takes into account clinical features such as disease behaviour, treatment responsiveness, the likelihood of antigen exposure and the relative likelihood of alternative conditions should be used.

Unclassifiable ILD

It is also crucial that a standard definition of uILD, which occurs in 10–25% of patients presented at the ILD MDM, be utilized, as different interpretations of this term may lead to very different outcomes between MDM.[66] The main concern in this regard is that the diagnosis of uILD may be given without consideration of a core data set. Ideally, the label of uILD would be reserved for patients who remain unclassifiable despite MDM discussion of a full set of core data, with the provisional nature of this diagnosis stated where data are missing or cannot be obtained.[66] Another issue is the diagnostic label applied to patients with a low diagnostic certainty: clearly, there is a threshold whereby patients move from a low diagnostic certainty to being truly unclassifiable. As discussed earlier, this threshold is difficult to standardize, but a recent international working party has suggested that patients with a diagnostic certainty below 50% be considered unclassifiable.[66] Due to the uncertainty inherent in this diagnostic label, repeat presentation of patients at a future date with assessment of disease trajectory, repeat interval imaging and further MDM discussion is of value.

Interstitial pneumonia with autoimmune features

Interstitial pneumonia with autoimmune features (IPAF) was developed as a research term to enable further study of this emerging patient group with what appears to be an IIP and clinical, serological or histopathological features of CTD insufficient to meet the established diagnostic criteria. By definition, patients who fit the IPAF criteria will also be otherwise considered to have either a working diagnosis for therapeutic purposes of an IIP or suspected CTD-ILD by their treating physicians.[36] We suggest the latter terms continue to be used for such presentations, given the current lack of added validated impact of the term IPAF upon therapeutic and prognostic discussion. IPAF remains an important area of research and documenting each patient who meets the IPAF classification to improve the understanding of the implications of this classification is useful.

PRACTICAL APPROACHES TO RUNNING MULTIDISCIPLINARY TEAMS IN AUSTRALIA AND NEW ZEALAND

How might the MDM be run?

In planning the ILD MDM, provision of adequate infrastructure including venue and telecommunications equipment is vital. Meetings should be held at the same time and place at regular intervals to maximize attendance. The duration of meetings, whilst dependent on the number of cases for presentation, should ideally be limited to 45–90 min. It is our experience that between six and eight cases can be discussed in a 60-min period. A weekly to fortnightly format enables discussion of cases within a relatively short time frame from referral. Incentives for participants to attend the meeting are useful, such as providing an educational focus to the case presentations and clearly articulating the benefits to patient care through audit incentives.

As the MDM is complex in its governance and number of attendees, it is highly beneficial to its smooth running that a meeting coordinator is used. Coordination of the meeting includes ensuring attendance at the meeting of the required professional groups, the gathering of data for patients referred to the meeting so that it is available at discussion, recording inputs to discussions, documenting the consensus diagnosis and other meeting outputs, ensuring the treating clinician is informed of meeting outcomes, and maintaining records for audit and research purposes. Who coordinates the meeting will depend on local institutional factors and roles could be assigned to junior medical staff, allied health staff or nursing staff with appropriate administrative support.

Approaches to maximizing access

In Australia and New Zealand, the location of the ILD MDM may have a bias to be held in larger, tertiary hospital institutions where all of the core members from various professional groups are more likely to be co-located. Whilst this suggests a centralization of the MDM process, this need not be the case. Outer metropolitan and regional areas with significant expertise in ILD management and familiarity may exist, although not necessarily in all core disciplines, such that some cases could be definitively discussed at those institutions where no additional expert input was required. There is evolving evidence to suggest that, through early access to specialist centres with specific ILD expertise, improved clinical outcomes occur, with earlier disease recognition and prescription of appropriate therapy.[69] So as to avoid delayed diagnosis, referral networks to the central MDM by regional centres need to be easily accessible. The use of tele/video conferencing is an invaluable interactive tool in overcoming the geographical separation of ILD experts and in enabling more remote areas to refer patients for consensus diagnosis. Similar principles apply to those patients cared for in the private health sector, whereby clinicians may access videoconferencing to minimize impact on clinical practice and maximize time efficiency. All case discussants should be aware of the meeting day and time and should be invited in advance if their input on specific cases is required.

As discussed below, the successful coordination of such a service may be time- and labour intensive with infrastructure and funding implications.

Approaches to maximizing expert input

Systems that allow the exchange of knowledge and expertise between MDM centres within Australia and New Zealand carry a number of benefits as such an approach is more likely to lead to standardization

of assessments and broader agreement in otherwise difficult to characterize cases, including uILD and some presentations of HP and NSIP. To achieve collaboration, a standardized format or pro forma of the documentation generated by individual MDM is required. Australia and New Zealand already benefit from existing networks between experts in ILD, such as the Australian IPF Registry through LFA and the Orphan Lung Disease, Lung Transplant, Interstitial Lung Disease and Pulmonary Vascular Disease (OLIV) Special Interest Group of the TSANZ. Although not without some logistical challenges, these networks could be used to facilitate such a process. Potential formats for collaborative inputs include quarterly meetings utilizing tele/video conferencing of contentious cases nominated by individual MDM, or a panel of reference cases to allow inter MDM bench-marking. Finally, all MDM irrespective of size are encouraged to perform an annual audit that includes the overall relative frequency of specific ILD diagnoses including unclassifiable cases as a further means of comparison with other regional MDM.

KEY IMPLICATIONS FOR PRACTICE

The incorporation of the MDM in the diagnostic process for patients presenting with an ILD has become standard of care. In Australia, this standard has been recognized in the pharmaceutical benefits scheme (PBS) criteria required to be fulfilled prior to prescription of anti-fibrotic therapy for IPF. However, while the Australian medical benefit schedule provides specific funding for other forms of MDM, a hurdle to the implementation of the ILD MDM within routine ILD practice in Australia and New Zealand is its lack of clearly designated government funding. The advocacy of institutional and professional bodies may need to be sought to clarify funding arrangements with government.

Whilst there is no doubt that the ILD MDM does increase the administrative burden on staff and resources, its advantages in terms of improving diagnostic accuracy, minimizing exposure to unnecessary and/or potentially harmful diagnostic or treatment modalities, improving clinical outcomes and broadening opportunities for education, training and research mean that this burden should not be seen as a barrier to participation. For clinicians currently considering how best to ensure that their patients have access to an ILD MDM, there are a number of options. For those working in centres where there is already respiratory, radiological and histopathological expertise in ILD, it is likely that establishment of an ILD MDM will be most suitable. In some cases, for those working in proximity to an existing centre, it will be most appropriate to form a linkage with that ILD MDM. For others in more remote locations, participation via video link may be most appropriate. Participation in an existing ILD MDM in this way can act as a springboard for the establishment of other ILD MDM once appropriate expertise is attained. It should be emphasized however that the quality of outputs from the ILD MDM is heavily dependent on the quality and standardization of data inputs and on the expertise of participants, as highlighted in this position statement. To facilitate the implementation and standardization of the MDM, national bodies such as the TSANZ and LFA will provide an online 'toolkit', containing useful protocols and other clinical documents.

Despite the potential hurdles and barriers, the positive impact of the ILD MDM extends beyond improved ILD diagnosis. Within teaching hospitals, the concentrated discussion of a wide range of ILD provides an opportunity for education of medical, nursing and allied health staff that can be integrated into under-graduate and postgraduate training programmes. The peer discussion component of the MDM provides an opportunity for audit and continuing medical education for all professional groups involved, and the case-load discussed at the ILD MDM acts as an obvious focal point for ILD research and clinical trials.

CONCLUSION

The accurate diagnosis of ILD is of critical importance given the positive outcomes that the correct use of specific therapies now provide. Improving diagnostic techniques remains an area of unmet need in ILD, and is an area of intense research and development. In recognition of this, this document will require updating as new evidence becomes available. In the meantime, the authors hope that this TSANZ position statement provides a useful foundation for those involved in the establishment and governance of ILD MDM.

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Disclosure statement

The authors' disclosure statement is available in Appendix S1 (Supplementary Information).

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SUPPLEMENTARY INFORMATION

Additional supplementary information can be accessed via the html version of this article at the publisher's website.

APPENDIX

S1 Disclosure statement.

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