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SPECIAL ARTICLE

Proceedings of the American College of Rheumatology/ Association of Physicians of Great Britain and Ireland Connective Tissue Disease–Associated Interstitial Lung Disease Summit: A Multidisciplinary Approach to Address Challenges and Opportunities

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INTRODUCTION

Interstitial lung disease (ILD), a group of diffuse parenchymal lung disorders classified together based on specific clinical, radiologic, and histopathologic features, is often associated with significant morbidity and mortality and is a common manifestation in connective tissue disease (CTD) (1). ILD often arises within the context of a specific exposure or is associated with an underlying CTD. The CTDs are a spectrum of systemic autoimmune disorders with significant clinical heterogeneity characterized by immune-mediated organ dysfunction, and the lung is a frequent target. All CTD patients are at risk of developing ILD, and those with systemic sclerosis (SSc), polymyositis/dermatomyositis (PM/DM), and rheumatoid arthritis (RA) are at particularly high risk (1,2). ILD may develop at any point in the natural history of CTD, is most frequently identified in the setting of an established CTD, and may also be the first clinically apparent manifestation of occult CTD. Determining whether a patient has a diagnosis of CTD-associated ILD is important, as this knowledge may impact treatment decisions, guide surveillance for other concomitant clinical features, and help with assessment of prognosis (3).

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The intersection of CTD with ILD is complex and fraught with areas of controversy and uncertainty. There are numerous gaps in our understanding of why certain CTD populations are more likely to develop ILD, but certain phenotypic risk factors have been identified. In RA, these include older age, cigarette smoking, male sex, rheumatoid factor positivity, anti–citrullinated protein antibody (ACPA) positivity, and more severe articular disease (4–6). In SSc, autoantibodies are the most reliable predictor of ILD, with anti–Scl-70 being one of the strongest (7). In PM/DM, autoantibody profiles also are useful predictors of ILD, especially antisynthetase antibodies (e.g., Jo-1, PL-7, PL-12), anti-PM/Scl antibody, and anti–melanoma differentiation–associated protein 5 antibody (8–10). Knowledge of reliable risk factors for ILD development in other CTDs is lacking. Since the advent of computed tomography (CT), it has been possible to characterize ILD with greater precision than previously (11,12), yet significant gaps remain with respect to reliable determinants of the prevalence of ILD among patients with CTD, and there is controversy surrounding whether to implement early detection strategies in these patients.

Perhaps the greatest unmet needs for ILD in CTD are in the realm of therapeutics. Few effective therapies exist, most decisions about management are based on experience rather than evidence, and there remains a desperate need for well-designed multicenter clinical trials of both existing and novel agents (13).

With a desire to highlight key areas needing scientific and therapeutic focus in CTD-associated ILD, in 2017 the Association of Physicians of Great Britain and Ireland and the American College of Rheumatology supported a multidisciplinary panel of international clinician-scientists from pulmonology, rheumatology, thoracic radiology, and lung pathology specialties with interests and expertise in ILD to convene a 1-day summit on CTD-associated ILD. The goals of the summit were to highlight key clinical and research aspects of CTD-associated ILD, identify unmet needs, and outline future research goals in this complex intersection of diseases. In this report we detail the proceedings of this summit, which were anchored around 5 domains: 1) clinical, 2) biomarkers, 3) diagnostic imaging and histopathology, 4) treatment and clinical trials design and outcome measures, and 5) translational research.

Clinical domain

Statement of the problem and current understanding. ILD is among the leading causes of morbidity and mortality in patients with CTD (1,2). Our understanding of ILD in the setting of CTD is challenged by a combination of factors including the systemic nature of the patients' rheumatologic disease. Patients with CTD-associated ILD, compared to those with idiopathic pulmonary fibrosis (IPF), present with a greater degree of heterogeneity and marked variability in natural history. IPF is a devastating progressive fibrosing ILD associated with a high burden of morbidity and mortality (14). A clinical diagnosis of IPF is made only after careful interpretation of integrated clinical, radiologic, and often lung histopathologic data. Classification of IPF is restricted to those individuals with a lung injury pattern of usual interstitial pneumonia (UIP) based on high-resolution CT (HRCT) scanning or surgical lung biopsy, after all known etiologies for UIP—such as underlying CTD—have been evaluated and excluded (14). Patients with CTD may have a mix of inflammatory and fibrotic ILD along with multicompartment lung involvement including airways, pleural, and pulmonary vascular disease, which may confound determination of the etiology of their respiratory impairment and potential responses to therapy. Furthermore, the ability to predict progression of ILD in CTD is challenging as some patients develop ILD that is mild and nonprogressive, while others have a more progressive course with unrelenting decline in function as seen in IPF.

Optimal care of patients with CTD-associated ILD requires collaboration and close interaction by the rheumatology and pulmonology communities. Rheumatologists have begun to improve their surveillance for lung involvement in patients with CTD, though clear guidelines (and training) have been lacking. Pulmonologists evaluating patients with ILD have become more attuned to the demographic, historical, and phenotypic features that may suggest an underlying CTD, though their level of expertise with that evaluation varies widely. Our understanding of natural history has been limited mostly to prospective observational studies and retrospective analyses, but clinical, pulmonary physiologic, and radiologic data emerging from prospective trials may identify those patients at highest risk for developing ILD and those who are candidates for treatment and participation in clinical trials (15). While there has been greater emphasis on a multidisciplinary approach to patient care and education of physicians, effective collaboration between pulmonologists and rheumatologists still falls short due to practical reasons including interest, limited expertise in this area, and availability of and access to ancillary resources. Collective experience and a recent study demonstrate that collaborative efforts can be effective in enhancing patient care (16,17).

Challenges and unmet needs. One of the challenges in CTD-associated ILD is that the prevalence of ILD among different groups of patients with CTD varies so widely (Table 1), with the highest estimated prevalence rates noted among patients with SSc and those with PM/DM (1,2,18). Severity of disease is most notable in patients in whom ILD is predominantly fibrotic such as patients with UIP as is seen in RA, with mortality rates comparable to those of IPF (6,19,20). While prevalence may define the frequency of ILD in any given CTD, focusing on the severity of disease based on features identified by chest imaging, with pathologic correlation when histologic data are available, may offer greater insight into prognosis compared to a focus on any specific CTD, and may thus guide decision-making with regard to treatment and inclusion in clinical trials.

Table 1. Connective tissue disease–associated interstitial lung disease: estimated prevalence rates, lung injury patterns, and clinical presentation*

CTD	Estimated prevalence of ILD†	ILD pattern	Frequency CTD is occult
Polymyositis, dermatomyositis, antisynthetase syndrome	40%	NSIP with OP, NSIP, OP, UIP	Often
Rheumatoid arthritis	10% clinical, 30% subclinical	UIP, NSIP, OP	Less often
Sjögren's syndrome	40%	NSIP, UIP, LIP	Less often
Systemic sclerosis	30–40% clinical, 80% subclinical	NSIP, UIP	Less often
Systemic lupus erythematosus	8–12%	DAH, NSIP	ILD is infrequent
Interstitial pneumonia with autoimmune features	100%	NSIP, OP, NSIP with OP, UIP, LIP	Always

* CTD = connective tissue disease; ILD = interstitial lung disease; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; UIP = usual interstitial pneumonia; LIP = lymphocytic interstitial pneumonia; DAH = diffuse alveolar hemorrhage.
† From refs. 1, 2, 6, 18, 45, 76, and 77.

Efforts to identify CTD patients with ILD or those who are at risk of developing ILD require an approach to screening that has the dual objectives of identifying early-stage disease and more specifically identifying those at greatest risk for progression and functional decline. Our present approaches do not allow us to fulfill either of those screening goals effectively, though emerging evidence suggests a framework for screening. In RA for example, as highlighted in a recent high-level review (6), the pattern of UIP predominates in most series (6,20,21), and certain phenotypic features (older age, male sex, history of smoking, and ACPA positivity) that may predict a higher risk for ILD have been identified in retrospectively studied cohorts. However, prospective data are only now being gathered to test and validate predictive models that may allow selective and targeted screening efforts (22–26). In RA there is a suggestion that pulmonary physiologic data can predict decline, though it is unclear whether this can serve as the sole screening strategy (27). In SSc and PM/DM, retrospective studies have identified phenotypic, autoantibody, radiologic, and pulmonary physiologic data that identify patients at increased risk for ILD and for mortality (28–30). Such understanding has led to the development of algorithms utilizing a combination of HRCT and pulmonary physiologic data to assess severity of disease and offers insights into assessment of prognosis (28–30). Screening strategies that identify ILD are important in view of evidence indicating that immunosuppressive treatment produces modest benefits. Data on utilization of antifibrotic drugs approved for use in IPF are not available, but these agents are being investigated in ongoing prospective trials.

Proposed future directions. A clearer understanding of long-term historical data will require multicenter cooperation using prospective databases that encompass phenotypic, pulmonary physiologic, radiologic, genomic, and proteomic data that may help elucidate factors that can best predict which patients are at risk for ILD and for progressive disease. Heightened awareness and recognition that lung disease is common among patients with CTD should lead to creative and sustained efforts to improve education of rheumatologists regarding clinical features of lung disease and utilization of pulmonary physiologic data to facilitate prompt and appropriate referral, and to forge closer collaborations with pulmonology colleagues. For the pulmonologist, dedicated education and training is needed to aid in recognizing important clinical and historical features that indicate a diagnosis of a CTD and to gain better understanding of autoimmune serologies in the evaluation in patients with ILD. Much of this can be accomplished by greater cooperation between the academic societies of the two disciplines, utilizing existing educational opportunities but also creating additional learning modalities such as case-based online educational modules. Finally, enhanced fellowship training in both disciplines with elective rotations in one another's specialty during fellowship, and encouragement of collaborative pulmonary and rheumatology fellowship opportunities, will also enhance recognition of these disorders and will hopefully improve the care of patients with CTD-associated ILD.

Biomarker domain

Current understanding and unmet needs. Biomarkers refer to a category of objective medical signs that correlate with certain aspects of normality or abnormality and may be defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (31). Given the heterogeneity of ILD complicating CTD, the identification of biomarkers is an important endeavor. However, to date there are no validated biomarkers for CTD-associated ILD.

Diagnosis of CTD-associated ILD is currently limited to the use of clinical data including history, physical examination, pulmonary function testing, and data from lung imaging and histopathologic studies. In order for biomarkers to become important tools for clinical practice, the specific measures should be accessible, reproducible, accurate, and clinically useful. Obtaining samples must be feasible, and the risk acceptable. While

biomarkers in ILD studies may be obtained from lung tissue and bronchoalveolar lavage (BAL) fluid, biomarkers obtained from peripheral blood would be far better given ease of access, convenience, and cost factors. At the same time, analysis of tissue or BAL fluid from the site of pathophysiologic activity in the lungs is a potentially more promising route for discovering ILD-relevant biomarkers than analysis of the blood. This is especially the case when other organ involvement in a systemic disease contributes to the overall heterogeneity of measured signals in the blood, thereby potentially confounding or limiting interpretation of a serologic finding (e.g., rheumatoid factor, antinuclear antibody, erythrocyte sedimentation rate).

Several challenges need to be met before the acquisition of valid biomarkers for CTD-associated ILD can become a reality. A systematic review using an NCBI search strategy with the terms "interstitial lung disease," "connective tissue disease," and "biomarker" was used in preparation for this summit. Case reports, case series, studies with inappropriate design or patient populations, pediatric studies, and studies with <20 cases were excluded from the analysis. The Outcome Measures in Rheumatology (OMERACT) filter was applied to evaluate articles for truthfulness, feasibility, and discriminatory ability (32,33). Articles were also subjected to analysis of whether the proposed biomarker measured an appropriate target domain (34). There were only 23 articles that passed these initial stages.

Candidate biomarkers have been identified in a number of the studies fulfilling the search criteria and passing the OMERACT filter. Chen and colleagues reported a strong association between the presence of ILD in RA patients and elevated peripheral blood levels of matrix metalloproteinase 7 (MMP-7) and interferon-γ–inducible protein 10 (CXCL10) as measured by multiplex enzyme-linked immunosorbent assay (ELISA). This association was confirmed in 2 independent Chinese RA cohorts. The authors subsequently validated their findings using a different quantitative platform (sandwich ELISA) in a separate cohort of RA patients from the US (22). Further work by Doyle and colleagues demonstrated that a regression model composed of several clinical variables could be used to identify both clinically evident ILD and subclinical ILD in 2 independent RA cohorts (25). This association was significantly improved with the addition of the peripheral blood biomarkers MMP-7, surfactant protein D (SP-D), and activation regulated chemokine/CCL18. In the Scleroderma Lung Study (SLS I), analysis of serum Krebs von den Lungen 6 and SP-D in peripheral blood demonstrated significant associations with parenchymal lung disease in SSc patients with ILD (35).

BAL also has proven utility in the assessment of alveolitis in SSc. Schmidt et al compared the levels of alveolar cytokines in 32 SSc patients, by multiplex ELISA (36). They found higher levels of interleukin-7 (IL-7), IL-4, IL-6, IL-8, and CCL2 in BAL fluid from patients who had ILD. However, their observations were limited by the small sample size of the cohort. Though potential biomarkers for CTD-associated ILD from different sources including peripheral blood and BAL have been studied in patient cohorts, to date the use of these biomarkers has not been adopted in everyday practice. Further prospective studies are clearly needed.

Overall, the current evidence in support of specific candidate biomarkers consists predominantly of results obtained from relatively small retrospective or cross-sectional studies with limited power. Most published studies have been conducted at single-center academic institutions and results may not be broadly applicable. Furthermore, given the clinical heterogeneity of CTD-associated ILD, it is likely that no single biomarker will have utility in diagnosis and prognosis, or act as a measure of disease progression and response to therapy.

Proposed future directions. A number of future directions are proposed to address these unmet needs and challenges in CTD-associated ILD biomarker development (Figure 1). Ideally, biomarkers will be used to achieve a number of specific aims in CTD-associated ILD. They may facilitate screening or diagnosis to identify individuals at high risk of developing ILD, or alternatively to identify those with early, preclinical disease. In addition, biomarkers may be used to risk-stratify patients at baseline and assess prognosis. They may provide data on disease progression and/or response to therapy. Furthermore, they may serve as surrogate markers for use as clinical trial end points or as tools to provide mechanistic pathophysiologic insight. Biomarker studies in other forms of ILD, namely IPF, have led to significant ongoing improvements in our understanding of the pathophysiology of pulmonary fibrosis (37–39), and these data exemplify the types of studies that may be considered in future investigations addressing CTD-associated ILD.

In conclusion, the development of accurate and practical biomarkers for diagnosis, prognosis assessment, analysis of disease progression, and evaluation of treatment response in CTD-associated ILD is an important research endeavor with considerable implications related to clinical trials and clinical practice. Further deliberations by multidisciplinary stakeholders are needed to determine the best course for the future development of CTD-associated ILD biomarkers.

Diagnostic imaging/histopathology domain

Imaging. *Current understanding*. CT imaging of the chest plays a critical role in identifying and characterizing CTD-associated ILD and in longitudinal follow-up when ILD is present. Its use must also be balanced against longer-term risk associated with radiation exposure. In addition to ILD, clinically important findings that may be identified on CT include features that indicate airways, pulmonary vascular, or pleural disease. Any pattern of ILD may occur in any of the CTDs, and the estimated prevalence of specific patterns varies by disease (40–42) (Table 1). CT

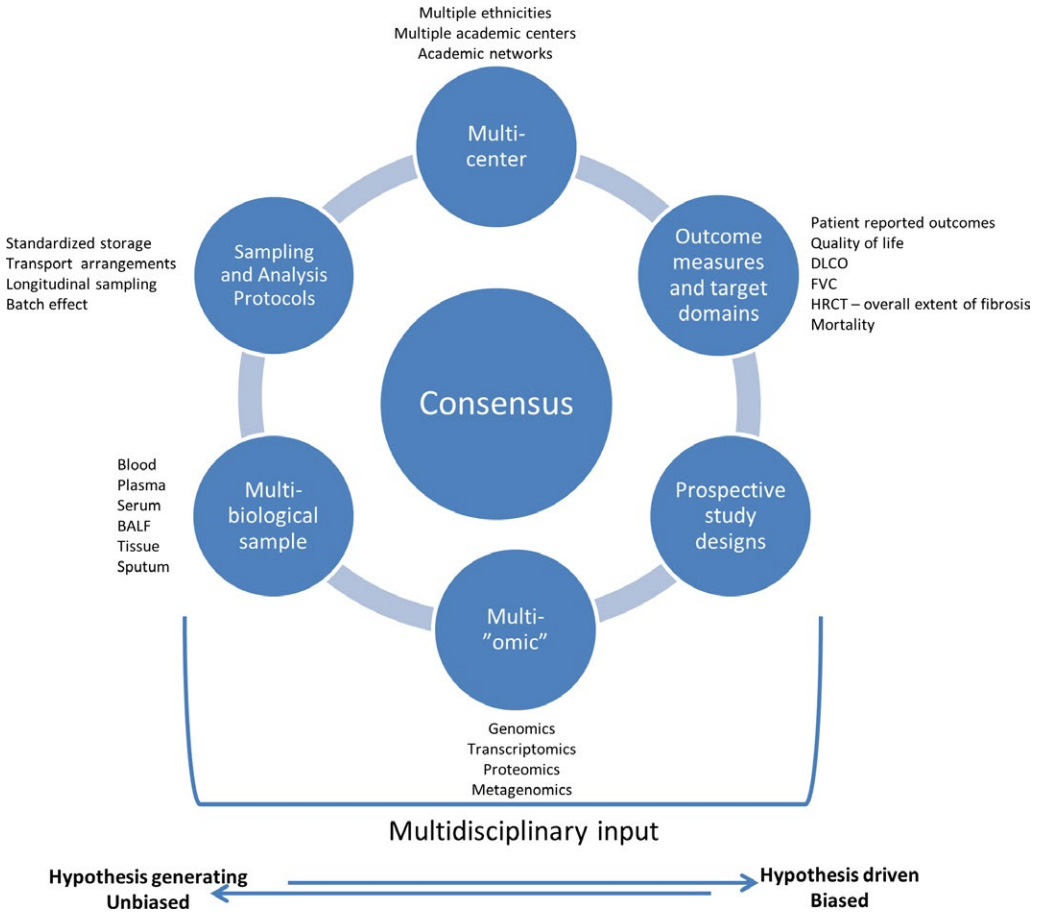

Figure 1. Proposed future investigative directions for the development of connective tissue disease–associated interstitial lung disease biomarkers. DL_{CO} = diffusing capacity for carbon monoxide; FVC = forced vital capacity; HRCT = high-resolution computed tomography; BALF = bronchoalveolar lavage fluid.

can reveal asymptomatic lung disease in a substantial proportion of patients with CTD, and these changes may progress slowly over time (Figure 2).

Unmet needs. The utility of CT in screening for early CTD–associated ILD is unknown. If ILD is present, we do not know how to identify patients in whom it is likely to progress, and optimal follow-up and treatment of patients with early changes remains unclear. Quantitative methods are increasingly being used for determining the extent of disease evidenced on CT, and have been used to document decreases in the extent of CTD-associated ILD in clinical trials (43,44). However, a standardized quantitative approach has not yet been developed, and the sensitivity of these techniques in identifying short-term longitudinal change is unknown.

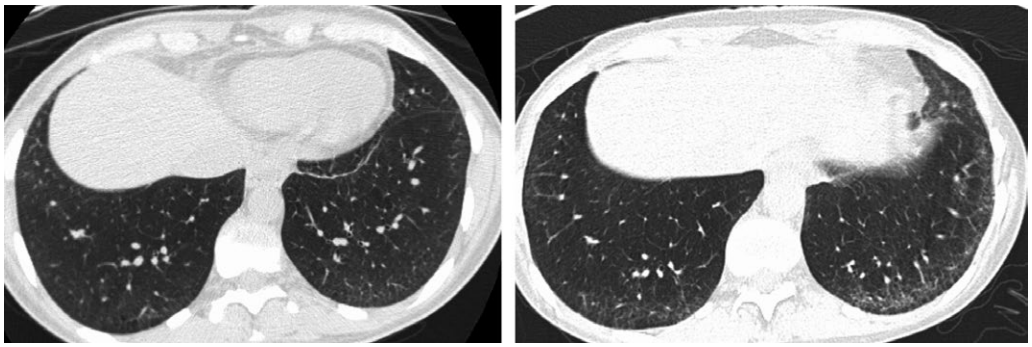

Figure 2. Progression of interstitial lung abnormalities in a patient with systemic sclerosis, as demonstrated by computed tomography. The image on the right was obtained 3 years after the image on the left.

Proposed future directions. There is a critical need for assembly of prospective cohorts of well-characterized patients with SSc, RA, and PM/DM/antisynthetase syndrome who would undergo CT at enrollment, with follow-up scanning at specific intervals. This could be achieved through a multi-institutional network, and perhaps by collaboration with industry to share CT scans performed in the context of clinical trials. Specifically, achievement of the following could yield valuable insights: 1) elucidation of the relationship between CT-determined phenotype (UIP, nonspecific interstitial pneumonia [NSIP], organizing pneumonia, lymphocytic interstitial pneumonia) and progression of CTD-associated ILD or response to treatment, 2) elucidation of the relationship between baseline extent of abnormality on quantitative CT and both short-term and medium-term outcome (death, progression, improvement), and 3) development and validation of techniques for phenotyping and quantifying CTD-associated ILD.

Histopathology. *Current understanding*. The decision on whether histologic examination of the lung would be useful in cases of CTD requires an analysis of potential benefit versus risk of an invasive procedure. Microscopic examination of surgical lung biopsy specimens from patients with CTDs often shows histologic clues indicating that the etiology is of an autoimmune nature (Table 2) as opposed to the findings being idiopathic or the result of other disease (45–47). Some of these histologic features (e.g., fibrosis) have been shown to be related to prognosis, but none have been influential in determining treatment decisions (48–50). These cases often do not fit into a single histologic category when using the criteria for idiopathic interstitial pneumonia (IIP), and instead show overlapping features of 2 or more entities (51). The risk of mortality from surgical lung biopsy was recently evaluated. In 2 large series in the US and the UK (52,53), the 30-day mortality rate with elective surgical lung biopsies was 1.5% and 1.0%, respectively. However, in the US series, the risk of death was 6.0% in patients with CTDs. The odds ratio for 90-day mortality in patients with CTD was similar to that in the overall cohort in the UK study. The risk of mortality was increased in patients who were being treated with glucocorticoids.

Table 2. Histologic features associated with underlying connective tissue disease

Prominent lymphoid aggregates with germinal center formation
Increased lymphocytic inflammation with plasma cell infiltrates
Overlapping features of peripheral honeycombing with central fibrosis
Involvement of multiple pulmonary compartments (interstitial disease with additional small airway, vascular, or pleural disease)
Nonspecific interstitial pneumonia pattern with additional organizing pneumonia

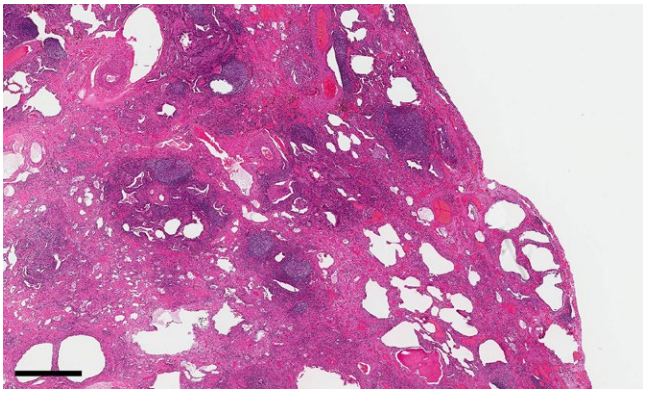

Figure 3. Surgical lung biopsy specimen from a patient with known connective tissue disease–associated interstitial lung disease (ILD) in whom the ILD was progressing typically, showing a mixed pattern of subpleural and centrilobular fibrosis with prominent lymphoid aggregates. Bar = 1 mm.

Whether to obtain a surgical lung biopsy depends on the clinical situation, and several frequently encountered scenarios were considered, and consensus reached, by the summit participants: 1) A patient has known CTD, has been shown clinically and/or radiologically to have ILD, and the ILD is progressing typically (Figure 3). In this case, the participants recommended not obtaining a biopsy because the results would not alter the treatment strategy. 2) A patient has certain clinical or serologic features suggesting possible CTD-associated ILD but does not meet established criteria for a CTD. In this case, the consensus was that a biopsy may be performed to assess whether specific histologic features support the presence of an autoimmune ILD (e.g., "interstitial pneumonia with autoimmune features") that might impact treatment strategies. 3) A patient has a known CTD but has an atypical clinical picture suggesting hypersensitivity pneumonitis, has drug-induced lung toxicity, or has an atypical radiologic pattern. In this case, the participants agreed that biopsy may be indicated

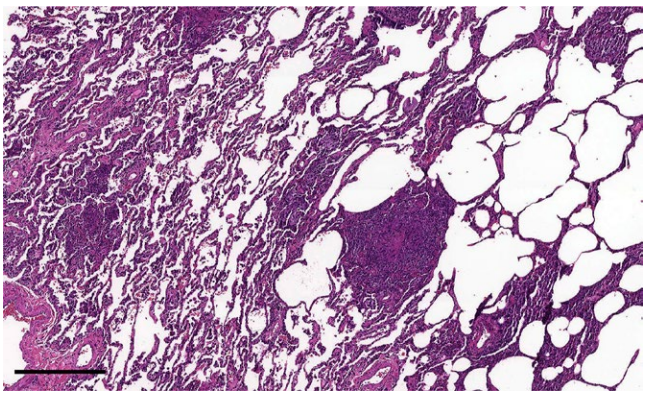

Figure 4. Surgical lung biopsy specimen from a patient with rheumatoid arthritis treated with biologic agents who developed nodular ground-glass opacities seen on computed tomography. The biopsy demonstrates granulomatous *Pneumocystis pneumonia*. Bar = 400 μm.

in order to differentiate between hypersensitivity pneumonitis, drug toxicity, or an infectious etiology (Figure 4) rather than CTD-associated ILD.

The availability of antifibrotic therapies raises the question of whether a biopsy may reveal certain histologic features that would guide therapy (e.g., whether a CTD patient with a UIP pattern of fibrosis should be offered antifibrotic therapy). However, there are currently no available data to answer this question.

Proposed future directions. The recent advances with the technique of cryobiopsy (54)—and wider application of this innovative procedure—may provide valuable insights into lung histopathology in CTD-associated ILD. However, as recently emphasized by an international cryobiopsy working group (55), the technique has not yet been standardized, and its place in the diagnostic algorithm of ILD remains to be defined. In part, this reflects concerns over the diagnostic yield and safety of the procedure, along with the rapid spread of the technique without safety or competency standards (55). Another limitation and concern regarding cryobiopsy is the substantial procedural variability among centers and interventional pulmonologists (55). Usual practice is not to perform a surgical lung biopsy in "typical" scenarios as discussed above, but the advent of cryobiopsy may change this paradigm by providing a safer and easier approach to obtaining parenchymal lung tissue. It remains to be seen whether cryobiopsy will become a common procedure in the evaluation of ILD, but if it does, we would anticipate that access to far greater numbers of histopathologic samples in CTD-associated ILD will allow for a greater understanding of the correlations between lung injury patterns on HRCT and histopathology. Cryobiopsy might also lead to insights into whether specific autoimmune histopathology features are more predictive of underlying CTD and could help with refining of the histopathologic criteria for interstitial pneumonia with autoimmune features (45). We anticipate a need for approaches based on imaging or histopathology to optimize treatment strategies, i.e., antiinflammatory versus antifibrotic therapies—and having more access to lung tissue should enhance such approaches as histopathologic findings remain the gold standard to define presence of fibrosis.

Treatment/clinical trials domain

Statement of the problem and current understanding. The clinical management of CTD-associated ILD is challenging, as 1) the natural history remains poorly understood though with significant recognized disease and individual patient heterogeneity, 2) there are no approved therapies, and 3) with the exception of recent clinical trials in SSc-associated ILD (44,56,57), there has been a paucity of interventional clinical trials. A similar dilemma existed in IPF, but over the last decade the performance of multiple large multicenter clinical trials in IPF led to a much better understanding of the disease trajectory, and to the availability of approved antifibrotic therapy. There are significant challenges to embarking on large clinical trials in CTD-associated ILD, but the substantial unmet need, especially in RA-associated and SSc-associated ILD, is a powerful incentive for overcoming these obstacles.

Phenotypic heterogeneity and natural history diversity. In clinical trials the goal is to recruit subjects with diseases of uniform pathobiology and natural history (i.e., homogeneity). However, the CTD-associated ILDs have complex systemic manifestations, multicompartment pulmonary disease, and a highly variable natural history. Their interstitial component can be classified according to the recognized pathologic patterns of the IIPs (58). The most common histologic patterns associated with CTD are NSIP and UIP, but any of the pathologic patterns can occur. Given that the systemic disease in CTD is immune driven, there is a rationale to believe that humoral and T cell–directed inflammatory processes contribute to the lung injury. However, many patients with CTD-associated ILD develop progressive ILD despite treatment with a variety of immunomodulatory agents that control the underlying disease.

Some CTD patients have clear symptoms of lung disease at the time of ILD diagnosis. Others have "subclinical" disease, i.e., radiologic findings suggestive of ILD in the absence of symptoms, and some have no evidence of lung disease at the time of the CTD diagnosis, but are at risk of developing ILD. There are no consensus guidelines that define either subclinical or clinically overt ILD in this context. Any potential definition would have to include subjective reports (symptom scores), chest imaging with qualitative and quantitative HRCT scoring, and pulmonary physiology assessment. For instance, subclinical CTD-associated ILD could be defined according to a threshold in extent and pattern of abnormality on HRCT in the setting of normal pulmonary physiology and the absence of respiratory symptoms. Clinically overt CTD-associated ILD could be defined as HRCT-detected abnormality plus lung function impairment or decline and/or respiratory symptoms. This potentially offers a unique opportunity to initiate clinical trials for all "stages" of disease and therein generate much-needed natural history data.

Proposed future directions. One option to improve study subject homogeneity is to pool subjects based on the underlying pathologic pattern of the ILD rather than the specific CTD (e.g., grouping patients with a UIP pattern of disease regardless of the underlying CTD). A limitation to this approach is that biopsy is infrequently performed in CTD-associated ILD, so the pathologic pattern cannot always be confirmed. Even when a biopsy is performed, a "classic" UIP histologic pattern is relatively uncommon, and "mixed" patterns are frequent. The radiologic pattern seen on HRCT of the chest is often used as a surrogate for lung biopsy, and thereby to classify the type of CTD-associated ILD. This is common practice in the IIPs based on consensus criteria, and it seems intuitively attractive to extrapolate this HRCT classification

to CTD-associated ILD. However, HRCT patterns have not been as robustly correlated with pathology in CTD-associated ILD. The relationship between HRCT patterns and disease progression is reasonably well established in idiopathic disease (e.g., a UIP pattern is associated with a worse outcome than a non-UIP pattern), but comparative studies in CTD-associated ILD are scarce. There is a pressing need for longitudinal HRCT-based studies in CTD-associated ILD. Presently, it may be more practical to perform trials according to the underlying CTD and subsequently stratify according to HRCT pattern.

With regard to natural history diversity, an attractive investigational model would be to enroll unselected patients with CTD into a multicenter longitudinal observational cohort, in which both incident and prevalent cases at all stages could be studied (Figure 5). In isolation, unbiased observational cohort studies, though informative, can be difficult to perform and fund. A therapeutic intervention study is more likely to be attractive and is easy to justify in clinically overt CTD-associated ILD, but in patients who have subclinical ILD or are at risk for ILD the justification is more nuanced. A number of these at-risk patients will develop ILD, but the proportion and time scale are uncertain. Moreover, some of these patients are likely to already be receiving treatment for extrapulmonary features of their CTD. Such a trial design was, however, recently applied in a phase III study of anti–IL-6 antagonist treatment of patients with early SSc and elevated acute-phase reactant levels (59). Treatment, in the context of a trial, could only be justified if the intervention is known to have low risk of harm. Mycophenolate mofetil (MMF) is a commonly used immunosuppressant in various CTD-associated ILDs. In early diffuse SSc, it is used for management of skin fibrosis, although there are differences among practices. Consideration can be given to case–control or longitudinal observational cohorts to assess the incident cases of ILD in patients who have been treated with MMF versus those who have not, accounting for covariates such as duration of disease, ethnicity, autoantibody status, and geographic distribution. The safety profile is good, and a randomized controlled trial of MMF for primary prevention of ILD in at-risk patents with CTD may be ethically justifiable.

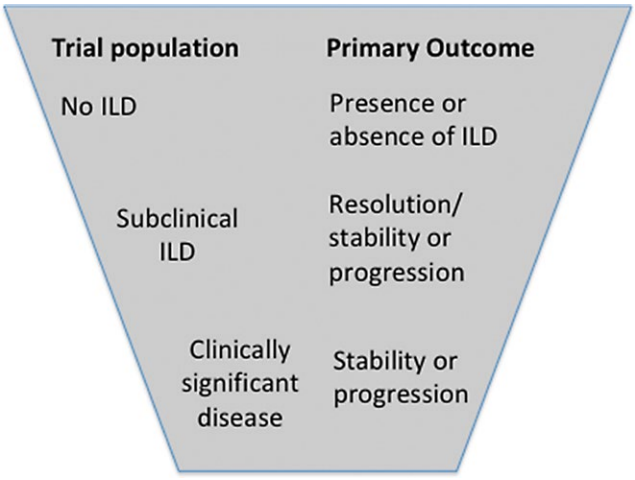

Figure 5. Suggested disease population stratification, and corresponding primary trial outcome, for interstitial lung disease (ILD) clinical trials in patients with connective tissue disease.

Addressing systemic manifestations. Well-executed clinical trials demand a defined standard of care. For subjects at risk for developing CTD-associated ILD and those with subclinical ILD, this would be "no-treatment" for the underlying ILD. While there are currently no approved drugs for CTD-associated ILD, there are ongoing late-phase trials with pirfenidone and nintedanib, drugs currently approved for IPF, that include patients with clinically significant CTD-associated ILD. Many clinicians prescribe glucocorticoids and/or other immunomodulatory drugs, commonly cyclophosphamide (CYC), MMF, or azathioprine, for CTD-associated ILD. In rapidly progressing CTD-associated ILD, which can occur in DM, for example, these and other agents are accepted as appropriate therapy. A similar case may be made for SSc-associated ILD, in which there is some prospective trial evidence of efficacy of CYC and MMF (44,57), especially in specific subgroups. Thus, while placebo-controlled studies may still be ethically viable for patients with CTD-associated ILD, the fact that routine care often includes immunomodulatory therapies makes such trial design more difficult to successfully recruit patients for and implement. Trial stratification methodology could be utilized to ensure the veracity of results.

End points for clinical trials in CTD-associated ILD. Trial end points are often dependent on the phase of study and study aims. For subjects recruited into a trial for CTD patients at risk for ILD, the end point would be the development of subclinical or clinically overt ILD, as defined a priori. There have been few efficacy trials in the setting of clinically overt CTD-associated ILD, and primary end points are not well established. In IPF, mortality, while clinically relevant, does not appear to be a feasible primary end point (60). Because the association between decline in forced vital capacity (FVC) and subsequent death is high, change in FVC is now the established primary end point in IPF efficacy trials and has been recognized by regulatory agencies as a surrogate for mortality. In contrast to IPF, our understanding of the behavior of CTD-associated ILD within a trial setting, in terms of change in lung function, hospitalization, and mortality, is very limited. It is unlikely that studies in CTD-associated ILD powered on a mortality end point could be practically performed. There are data to confirm that change in FVC correlates with mortality in CTD-associated ILD as it does in IPF (27,61), but hospitalization rates are unknown. Tools, such as blood biomarkers and/or risk scores to improve the ability to determine "predicted events" during the period of observation, would be invaluable.

In the absence of an established relevant single end point, a composite "event-driven" end point may be a tempting solution, comprising, for example, ≥10% decline in FVC, ≥15% decline in diffusing capacity for carbon monoxide, hospitalization, and/or death (62,63). However, the use of composite end points presents its own difficulties that may limit interpretation of the data (64). Finally, patient-reported outcomes (PROs), including dyspnea, cough, or quality of life, should be considered in all efficacy trials. The OMERACT group recently provided consensus-based domains and PROs for use in clinical trials. Although some PRO-related instruments, such as the Mahler dyspnea index and St. George's Respiratory Questionnaire, have been validated via clinical trials (SLS-I and II) (65) and observational cohort studies, many have not. Therefore, ongoing and future trials should proactively validate outcome measures. Table 3 summarizes ongoing clinical studies in CTD-associated ILD that have been submitted to ClinicalTrials.gov.

In conclusion, the unmet need for therapy in CTD-associated ILD, combined with a plethora of potential antifibrotic drugs in industry pipelines, demands a new age of clinical trials. Lessons learned from studies in IPF suggest that recruitment of patients into well-designed studies can both increase understanding of the natural history of disease and lead to the discovery of effective treatments. Recruitment of CTD patients from the full spectrum of disease, i.e., from those at risk for ILD to those with clinically overt CTD-associated ILD, is ambitious and would require multicenter cooperation, but offers the potential for dramatically increasing our knowledge in these understudied disorders.

Translational research domain

The purview of translational research in CTD-associated ILD is exceptionally broad. In this section we focus on several themes identified by summit participants as being of particular relevance due to high levels of future promise, as well as addressable barriers to progress. The discussion will be divided into 1) databases and bioregistries, 2) technology for precision medicine, 3) quality of life outcome measures, and 4) animal models.

Databases and bioregistries. *Statement of the problem*. While randomized controlled trials remain the gold standard for hypothesis-driven clinical research questions on treatment efficacy, the information contained in clinical registries and biorepositories offers unique opportunities for advancing our understanding of CTD-associated ILD. Particularly in the context of rare diseases such as CTD-associated ILD, maximizing the use of existing registries and biorepositories will be necessary to form the groundwork for targeted clinical trials.

Current understanding. The accumulation of real-world registry data over time provides a more dynamic and evolving picture of disease course, which is more generalizable and relevant to the real-world patient population (66). Targeted biologic sample repositories, particularly when aligned to clinical registry information, may be used with maximal effect both to specifically inquire into the connected contributions of genetic susceptibility, environmental, and lifestyle factors in influencing disease pathogenesis and to develop a future individualized precision medicine approach.

Challenges and unmet needs. There are significant barriers to data sharing when clinical and biologic registries are designed within disconnected, institutional "silos of information" or when there is no available technological platform for data sharing between institutions at a national or international level. Differences in defining the terms of reference of diseases for inclusion into disease registries, or in the precise domains of clinical information stored, prevent clinical equivalence between registry data sets, which in turn prevents the merging of information between research groups. For biologic samples, variations in sample collection and processing can lead to variations in the quality of available biobanked material and may affect their suitability for sample collaboration between groups. This is of particular importance with rare diseases, for which larger populations are needed to enable sufficient collection of relevant material.

Proposed future directions. A more collaborative approach from the research community is needed to maximize scientific output, with an emphasis on improved sharing of available data and on the standardization of future data collection through the formation of national and/or international disease registries. One such effort has been recently launched by the Pulmonary Fibrosis Foundation (PFF) with the creation of a large network of PFF Care Centers around the US. Within the PFF Care Network a collaborative PFF Registry was established, which now includes >2,000 patients with diverse forms of ILD. High-quality clinical data are being collected, there is an accompanying biorepository, and a potentially valuable research database will be available for access by independent investigators (https://www.pulmonaryfibrosis.org/medical-community/pff-patient-registry).

Technology for precision medicine. *Statement of the problem and current understanding*. In the pursuit of truly personalized medicine, the capacity to monitor individuals in their unique environments should be paramount. While a number of technologies have emerged to assess physiology (e.g., heart rate, blood pressure), mobility (accelerometry), and even to measure PROs on a daily basis, this technology has not adequately evolved to include outcomes relevant in CTD-associated ILD, nor has it been adopted in CTD-associated ILD research. The thoughtful proactive development and implementation of technology will provide a powerful new tool for research, including the assessment of therapy and potentially direct therapeutic interventions for CTD-associated ILD.

Table 3. Pending or currently recruiting clinical trials in CTD-associated ILD (as of September 2018)*

Trial name	ClinicalTrials.gov identifier	Study type	Disease entity	Participants (target or estimated)	End point
Abatacept in RA-ILD (APRIL)	NCT03084419	Interventional (phase II open label)	RA-ILD	30	No. of participants without significant decrease (≥10%) in FVC following abatacept treatment
Phase II Study of Pirfenidone in Patients With RA-ILD	NCT02808871	Interventional (phase II)	RA-ILD	270	Incidence of the composite end point of decline in FVC (% of predicted) of ≥10% or death
BI 1199.247: Efficacy and Safety of Nintedanib in Patients With Progressive Fibrosing Interstitial Lung Disease	NCT02999178	Interventional (phase III)	Progressive fibrosing ILD including CTD-ILD	600	Annual rate of decline in FVC (in ml) over 52 weeks
BI 1199.214: A Trial to Compare Nintedanib With Placebo for Patients With Scleroderma Related Lung Fibrosis	NCT02597933	Interventional (phase III)	SSc-ILD	520	Annual rate of decline in FVC (in ml)
Scleroderma Lung Study III: Combining Pirfenidone With Mycophenolate	NCT03221257	Interventional (phase II)	SSc-ILD	150	Change from baseline, measured at 3-month intervals, in the mean FVC
Study to Compare the Efficacy of Mycophenolate Mofetil in Systemic Sclerosis Related Early Interstitial Lung Disease	NCT02896205	Interventional (phase III)	SSc-ILD	60	Change from baseline in FVC at 6 months, after treatment with oral mycophenolate mofetil or placebo
Abituzumab in SSc-ILD	NCT02745145	Interventional (phase II)	SSc-ILD	22	Annual rate of absolute FVC change in volume (in ml)
Abatacept for Myositis-ILD	NCT03215927	Interventional/ pilot study	Antisynthetase syndrome–ILD	20	Primary outcome criterion for efficacy will be the % change in FVC from baseline visit to week 24 between the 2 treatment arms (standard of care/ placebo vs. standard of care/abatacept)
Rituximab Versus Cyclophosphamide in Connective Tissue Disease–ILD (RECITAL)	NCT01862926	Interventional	CTD-ILD	116	Absolute change in FVC (time frame 48 weeks)

* CTD-associated ILD = connective tissue disease–associated interstitial lung disease; RA-ILD = rheumatoid arthritis–associated ILD; FVC = forced vital capacity; SSc-ILD = systemic sclerosis–associated ILD.

Challenges and unmet needs. There are technological barriers to progress. The pace of technological advancement in information systems, including mobile technologies, has outstripped the rate of progress seen in health care information sharing. The academic health care community runs the risk of losing opportunities to improve and shape the quality and quantity of data

platforms that may be used to further enrich the information available for research.

Proposed future directions. Significant opportunities exist for the research community to influence the development of research technology, including mobile technologies, to enhance the type and quality of data collection. This could be achieved through partnership with biotechnology and engineering research communities, and through engagement with patient-centered organizations to ensure that both the research community and the patients themselves benefit from future partnerships.

Quality of life outcome measures. *Statement of the problem and current understanding*. Little is understood about the impact of CTD-associated ILD on daily living, including quality of life (QoL). Challenges to studying and understanding the effects of CTD-associated ILD on health-related QoL include the differing organ manifestations and effects of specific CTDs and elucidation of the pulmonary and extrapulmonary contributions to QoL. Nonetheless, it is critical to understand how patients experience disease as we assess the impact of treatments and other interventions. PRO questionnaires are designed to assess the influence of disease on patient function and individual subjective life experience. They remain an important outcome measure, due to both their reproducibility in quantifying the impact of disease severity and their sensitivity to change.

Challenges and unmet needs. The evaluation of how a specific disease impacts QoL for patients with simultaneously overlapping symptoms of ILD and systemic disease manifestations presents clear challenges. While some rheumatic disease–specific QoL instruments, including the Systemic Sclerosis QOL questionnaire (67), contain domains that are specific for respiratory manifestations of disease, others, including the Rheumatoid Arthritis Quality of Life questionnaire (68), which was validated using RA patients without ILD, have not been designed to determine the specific impact of RA-associated ILD on health-related QoL. Although efforts have been made to validate lung-specific QoL measures such as the King's brief ILD questionnaire for ILD other than IPF, other measures, including the St. George's Respiratory Questionnaire, which was initially designed for patients with chronic obstructive pulmonary disease, have been subsequently validated for patients with IPF but not those with CTD-associated ILD (69,70).

Proposed future directions. Future work is needed to determine whether a new QoL tool should be designed, tested, and validated in collaboration with CTD-associated ILD patients to fully reflect all disease-specific impacts on QoL. Alternatively, consideration should be given to whether an existing generic, and/or symptom-specific tool that has previously been validated in IPF or a CTD can be tested and validated in the CTD-associated ILD population. The establishment of a QoL outcome measure working group is needed in order to obtain consensus on whether such instruments should be symptom specific, disease specific, or generic (such as the Short Form 36 QoL questionnaire) (71). Validation testing of candidate QoL outcome measures, with engagement of patient-centered organizations, should be performed to assess their accuracy in determining association with disease severity and sensitivity to change.

Table 4. Summary of proposed future directions in connective tissue disease–associated interstitial lung disease (CTD-associated ILD)

Standardized international criteria for the classification of CTD-ILD
Deliver international guidelines that standardize clinical, radiologic, histopathologic, and biologic parameters for the diagnosis and classification of CTD-ILD
Defining the natural history of CTD-ILD
Deliver multicenter global clinical networks of well-defined disease groups, encompassing longitudinal integrated collections of phenotypic, physiologic, radiologic, genomic, and biologic data
Clinical care
Deliver multidisciplinary clinics for rheumatology, pulmonology, and allied health care professionals to enhance patient care
Cross-disciplinary clinical training
Deliver cross-disciplinary fellowship clinical training opportunities for medical graduates
Biomarker development
Deliver precision medicine–based biomarker platforms to guide the optimal therapies to the individual patient
Early screening strategies for ILD
Develop and utilize early detection strategies that identify ILD earlier and ultimately predict those at highest risk for disease progression
Integration of imaging and histopathology
Generate ILD imaging repositories across the spectrum of CTD-associated ILD that correlate with histopathologic specimens
Refine cryobiopsy techniques to enrich the availability of parenchymal lung tissue specimens
Clinical trials of future interventions in CTD-ILD
Validate CTD-specific trial end points
Incorporate novel technologies to validate quality of life end points and patient-reported outcome measures
Develop and incorporate composite end points specific to CTD-ILD
Develop an integrated clinical, radiologic, laboratory, and biologic database solution that aligns large data sets and allows maximum interrogation
Translational research
Form shared national/international registries with biologic repositories
Create new, and optimize existing, quality of life measures in CTD-ILD
Develop animal models of CTD-ILD

Animal models. *Statement of the problem, current understanding, and unmet needs*. Animal models provide a critical tool in identifying relevant biologic pathways in disease as well as providing a model to test therapeutic agents. To better understand the pathogenesis of fibrotic lung diseases, a number of animal models have been developed. Recent advances have allowed for the development of models to study targeted injuries of type II alveolar epithelial cells, fibroblastic autonomous effects, and targeted genetic defects (72). However, there are few models of CTD-associated ILD. Although a model of RA-associated ILD in SKG mice has been described (73), other animal models for CTD, including in tight-skinned mice, either have not been characterized for lung disease or do not manifest lung disease (74). It remains uncertain whether murine models of fibrotic lung disease, which include bleomycin-induced, radiation-induced, or adoptive cell transfer models of lung fibrosis (72), are sufficiently similar to human CTD-associated ILD to be of use in identifying molecular targets for drug development (75).

Proposed future directions. An inventory of currently existing animal models of ILD, documenting their disease equivalence to specific manifestations of human CTD-associated ILD as well as any known overlap of the recognized molecular mechanisms of human and murine disease, is needed. Where adequate animal models do not currently exist, funding and research efforts will be needed to develop better animal models of CTD-associated ILD that more closely reflect the human condition and are therefore relevant for disease pathway evaluation and drug development in preclinical studies.

Summary

This document summarizes the proceedings of a recent summit on CTD-associated ILD attended by a multidisciplinary panel of international clinician-scientists with expertise in CTD-associated ILD. Key clinical aspects are outlined, and a variety of research initiatives are proposed (Table 4) with the aim of addressing the many unmet needs and challenges within the complex intersection between CTD and ILD. Our hope is that further multidisciplinary collaboration around the research into and care of patients with CTD-associated ILD will lead to greater disease awareness, earlier disease detection and diagnosis, implementation of interdisciplinary treatment approaches with novel therapeutic agents, and, ultimately, improved quality of life and outcomes for those who are affected by these diseases.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Fischer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Fischer, Strek, Cottin, Dellaripa, Bernstein, Brown, Danoff, Distler, Hirani, Jones, Khanna, Lee, Lynch, Maher, Millar, Raghu, Silver, Steen, Volkmann, Mullan, O'Dwyer, Donnelly.

Acquisition of data. Fischer, Strek, Cottin, Dellaripa, Bernstein, Brown, Danoff, Distler, Hirani, Jones, Khanna, Lee, Lynch, Maher, Millar, Raghu, Silver, Steen, Volkmann, Mullan, O'Dwyer, Donnelly.

Analysis and interpretation of data. Fischer, Strek, Cottin, Dellaripa, Bernstein, Brown, Danoff, Distler, Hirani, Jones, Khanna, Lee, Lynch, Maher, Millar, Raghu, Silver, Steen, Volkmann, Mullan, O'Dwyer, Donnelly.

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