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Early View

Invited review

ERS International Congress 2021: highlights from the Interstitial Lung Diseases Assembly

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Please cite this article as: Guler SA, Cuevas-Ocaña S, Nasser M, *et al*. ERS International Congress 2021: highlights from the Interstitial Lung Diseases Assembly. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00640-2021).

ERS International Congress 2021: highlights from the Interstitial Lung Diseases Assembly

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Abstract

This article provides an overview of scientific highlights in the field of interstitial lung disease (ILD), presented at the virtual European Respiratory Society Congress 2021. A broad range of topics was discussed this year, ranging from translational and genetic aspects to novel innovations with the potential to improve the patient pathway. Early Career Members summarize a selection of interesting findings from different congress sessions, together with the leadership of Assembly 12 – Interstitial Lung Disease.

Introduction

The field of interstitial lung diseases (ILDs) has rapidly evolved in the past years, with exciting new developments. During the European Respiratory Society (ERS) congress 2021 many oral presentation and e-poster sessions were dedicated to ILD. The program also included interesting expert view, guideline, state-of-the art and "hot topic" sessions on the new guidelines for sarcoidosis, holistic care in ILD, post-COVID ILD, biomarkers, pulmonary hypertension in ILD, the association between lung cancer and fibrotic ILD, and rare lung diseases.

This year's oral presentation sessions included genetic and translational aspects, new innovations and treatment options, better understanding of pathogenesis and disease course, novel approaches to diagnosis, and prognostic challenges in ILD, as well as epidemiology and outcomes in rare lung diseases.

This article summarizes the authors' personal scientific highlights across all four groups of Assembly 12: group 12.01 "Idiopathic interstitial pneumonias", group 12.02 "ILDs/diffuse parenchymal lung diseases (DPLDs) of known origin", group 12.03 "Sarcoidosis and other granulomatous ILDs/DPLDs" and group 12.04 "Rare ILDs/DPLDs".

Idiopathic Interstitial Pneumonias

Many challenges and opportunities in the field of idiopathic interstitial pneumonias were vividly discussed during this year's ERS congress, including diagnostic challenges, the need for better treatment options, and the impact of comorbidities. Furthermore, prediction and early identification of disease progression in patients with pulmonary fibrosis were important discussion topics.

Several studies evaluated potential non-invasive and simple solutions for ILD diagnosis. Qiu *et al*. identified a differentially expressed immune-related gene panel from bronchoalveolar lavage (BAL) samples of IPF patients and healthy individuals, from which *CXCL14*, *SLC40A1*, *RNASE3*, *CCR3*, *RORA* were used to build a prognostic signature for survival. This 5-gene-based signature differentiated significantly between high and low-risk patient groups (AUC=0.837) [1]. At a protein level, a novel inverse association between pro-fibrotic cytokines and antimicrobial peptides (AMPs) in BAL was identified [2]. The different AMP profiles in BAL of patients with IPF and other fibrotic ILDs compared with non-fibrotic patients might open up new possibilities for early diagnosis of patients at risk. At cellular levels, *in vitro* and *in vivo* studies showed an accumulation of senescent cells and demonstrated a reduction of NK cells in the IPF lung due to a deficient lung recruitment capacity resulting in an increase of NK cells in the blood [3]. Of interest, at a clinical level, Nishikiori *et al.* developed an artificial intelligent (AI) software to detect interstitial pneumonias from chest radiographs. This refined AI algorithm was able to distinguish chest radiographs of patients with progressive fibrosing ILD versus other abnormal findings with 87% accuracy, and fibrosing ILDs versus normal chest radiographs with 95% accuracy [4]. This highlights the potential of AI to assist in the identification and monitoring of ILDs.

Given the frequently prolonged time from symptoms to diagnosis, it is important to assess disease behavior early during the peri-diagnostic period in patients with suspected ILD. The STARLINER study found that during this period IPF patients had accelerated worsening of some patient-reported outcomes (PRO) compared to non-IPF ILD patients. Thus, PRO results can potentially facilitate the diagnosis of IPF in the early stages of disease [5]. In addition, a multicenter registry study identified that patients with suspected familiar IPF presented with similar lung function decline and prognosis compared to patients with sporadic IPF, further emphasizing the importance of early referral [6].

Since currently available antifibrotic treatments do not stop lung function decline, more studies are urgently needed to identify new therapeutic compounds. Tzouvelekis *et al.* developed two biosynthetic thyroid receptor beta agonists (thyromimetics), which showed therapeutic activity against bleomycin-induced lung injury *in vivo*. Thus, thyromimetics may be a potential new therapy for pulmonary fibrosis in the future [7]. The multinational phase 2 PINTA study assessed the efficacy and safety of GLPG1205 in IPF versus placebo. GLPG1205 is a selective G-protein-coupled receptor 84 antagonist, which inhibits monocyte and neutrophil migration and activation. The use of GLPG1205 resulted in numerically but not significantly smaller decline in FVC (-34 mL vs -76 mL) after 26 weeks. No relevant safety signals were observed for GLPG1205 alone or with pirfenidone, but higher rates of early discontinuation were observed for the combination of GLPG1205 and nintedanib [8]. Despite these results, further development of GLPG1205 has been discontinued.

Current treatments are often associated with adverse events, sometimes leading to reduced dosage or treatment breaks. Importantly, Porse *et al.*, showed that patients receiving reduced nintedanib or pirfenidone treatment had a similar survival compared to patients receiving full treatment doses, with all treated participants experiencing an increased survival compared to the no treatment group [9]. A French multicenter phase 2 randomized controlled trial evaluated the efficacy and safety of cyclophosphamide added to glucocorticoids in 120 patients with acute exacerbation of IPF. The 3-month all-cause mortality was 45% in patients treated with cyclophosphamide versus 31% in the placebo group (p=0.1). These data provide evidence against the use of cyclophosphamide for acute exacerbations of IPF [10].

In addition to genetic predisposition and aging, environmental factors, such as long-term exposure to air pollution, constitute risk factors for acute exacerbations and disease progression in IPF. Tomos *et al.* reported that increased concentrations of traffic-related air pollutants (e.g. O_3) were associated with changes in IL-4, IL-13 and osteopontin inflammatory mediators involved in lung repair mechanisms [11]. A retrospective, multicenter study including 3178 patients with IPF found that 1 in 10 patients with IPF developed lung cancer. IPF patients with lung cancer had a significantly worse prognosis than those without this comorbidity [12]. Aligned with these results, a bioinformatic analysis by Li *et al.* identified that several differentially expressed genes between IPF and healthy BAL samples shared PD-L1 expression and PD-1 checkpoint pathways with cancer. These results further support lung cancer screening in IPF patients, and vice versa, and might help uncover potentially new treatments for these patients. Further studies identifying personalized approaches to the diagnosis and management of patients with IPF and lung cancer are urgently needed [13].

Although IPF patients have the worst survival, all ILDs can develop progressive fibrosis (PF-ILD). According to the EXCITING registry PF-ILDs are characterized by a reduced likelihood of survival compared with stable-ILDs [14]. Therefore, finding biomarkers that identify patients at higher risk of progressive fibrosis is a huge unmet need. Circulating pneumoproteins like KL-6 seem to be promising in stratifying ILD patients at risk of developing progression at one year, according to the preliminary results of the multicenter international VAMOS study [15]. Peripheral monocytes, easy to obtain, have been also investigated in a subgroup analysis of the INBUILD trial and show a good correlation with survival and disease progression [16]. An association between the TERT_rs2736100 polymorphism and PF-ILD was identified by Dos-Reis-Estrella *et al*. in patients with familial interstitial pneumonia [17].

Another interesting study suggested that telomere-related mutations may cause pulmonary fibrosis indirectly via altering the heritable trait telomere length. Thus, it was suggested that first-degree family members with short telomere syndromes could be screened despite having no mutations [18]. During an exciting discussion, the need to incorporate genetic data into ILD clinical practice to better predict individual disease progression was emphasized.

ILDs/DPLDs of known origin

Many interesting presentations focused on ILDs of known origin, with the majority presenting findings on connective tissue disease (CTD)-associated ILDs.

With the aim to improve the diagnosis of ILD in systemic sclerosis (SSc), a panel of serum biomarkers was investigated in two Australian SSc centres. Of the 28 analysed biomarkers, SP-D, Ca15-3, and ICAM-1 were kept in the models. After adjustment for age, sex, smoking status, and forced vital capacity (FVC) %-predicted, the combination of these markers was associated with a high likelihood for ILD, and the severity of ILD [19]. Another group confirmed the prognostic significance of the serum biomarker CCL18 in SSc-ILD. The CCL18 SNP rs2015086 was associated with CCL18 serum levels, but not with mortality in their population[20]. A Norwegian group investigated the progression of subclinical CTD-ILD, which was defined as ILD without respiratory symptoms, FVC >80% predicted, and a semi-quantitative radiological ILD extent <5%. The progression of the subclinical (n=67) and clinical (n=231) ILD subgroups were compared; over a median observation time of 4.5 years 51% of the clinical, but also 38% of the subclinical CTD-ILD patients showed progression. These findings challenge the typical “watchful waiting” management approach in the subclinical CTD-ILD population [21]. The need for standardization of HRCT scans in SSc-ILD was emphasized by a Swedish group who showed different extents of ground glass depending on whether scans were performed in prone position, supine position, or after 10 breaths with a positive expiratory pressure device [22].

A variety of research questions were also studied in patients with rheumatoid arthritis (RA) and other CTD-ILDs. A cohort of 83 CTD-ILD patients in Sri Lanka included 53% with RA-ILD of whom 56% were women and 73% had a radiological NSIP pattern, unlike the typical male RA-ILD and UIP predominance in other RA-ILD cohorts [23]. RA-ILD incidence trends were analyzed in Olmsted County (USA), where 1248 RA-ILD cases in two time periods (1955-1994 and 1999-2014) were identified. Unlike the previously reported declining incidence of other extra-articular RA manifestations, the incidence of RA-ILD did not decline over these 6 decades. Nevertheless, we should keep in mind a potential impact of the more frequent use of chest CT scans and likely more sensitive detection of RA-ILD over time[24]. Radiological quantification of RA-ILD (reticulations and traction bronchiectasis) for prognostication was evaluated by a Korean group. Patients with and without ≥12% lung fibrosis on CT had a 5-year mortality of 50% and 17%, respectively [25]. A Belgian group reported 89 out of 1500 RA patients to have ILD, with 3.8% of the total RA and 29% of the RA-ILD population presenting with a progressive phenotype [26]. Progressive pulmonary fibrosis was also investigated retrospectively in a French cohort of 73 patients with Sjögren’s syndrome associated ILD. Despite immunosuppressive therapy, 43% of the patients were reported to have an FVC decline ≥10% at follow-up, with survival rates of 80% at 5 years and 62% at 10 years. However, given the nature of this clinical cohort a selection bias of patients with a progressive disease course is possible [27].

Two Portuguese groups reported prognostic factors in hypersensitivity pneumonitis (HP): In a cohort of 14 patients with chronic HP, a radiological UIP pattern and a higher GAP index were associated with a higher mortality risk [28]. In 86 multidisciplinary discussion diagnosed HP cases with a radiological UIP pattern, one third had a progressive disease behaviour despite immunosuppressive therapy. In this progressive subgroup the proportion of patients without an identified antigen was higher, with lower FVC %-predicted, and more advanced fibrosis on CT scan compared to the non-progressive subgroup. This study nicely describes that there is significant heterogeneity in disease behaviour in fibrotic HP patients, even when a UIP pattern is present [29].

To facilitate the diagnosis of asbestosis, a Dutch group created an AI supported system that integrates information from chest CT scans and pulmonary function tests. In a training set (311 patients) and a test set (88 patients) its diagnostic accuracy against the reference standard (3/3 pulmonologists agreeing on asbestosis) was tested. Besides a remarkable performance of the AI algorithm (AUC 0.87), diffusion capacity of the lungs for carbon monoxide (DLCO) alone also had a similarly good diagnostic performance (AUC 0.85). The validation and incremental benefit of the AI system is still work in progress [30].

A very relevant topic during this COVID-19 era, is the impact of COVID-19 on patients with ILD. The EUSTAR registry reported 90 SSc-ILD patients with COVID-19, of whom 19% were deceased and an additional 10% needed mechanical ventilation or ECMO after a median follow-up of 5.5 weeks, emphasizing the potential severity of COVID-19 in patients with SSc-ILD [31]. A Japanese group compared COVID-19 patients with (n=26) and without (n=52, age- and sex-matched) preexisting ILD, and found that non-invasive ventilation (31% vs 2% of cases), and tocilizumab treatment (27% vs 8% of cases) were used more frequently in ILD patients, without differences in other management approaches. Mortality rate was higher in ILD compared to the control group (11.5% versus 3.8%) [32].

In a pro-con debate Prof. Bruno Crestani and Prof. Sara Tomassetti discussed the timely topic of post COVID ILD syndrome. Both experts agreed that severe COVID-19 pneumonia can induce a pro-fibrotic condition and development of lung fibrosis in some cases. Prof. Crestani talked about common biological pathways and similarities in aging-associated risk factors for post COVID fibrosis and IPF. Consequently, he argued that similar management approaches should be considered. Prof. Tomassetti proposed 5 different phenotypes of post-COVID ILD, with the most common presenting with NSIP/OP patterns and a likely underlying auto-inflammatory pathogenesis. Both speakers emphasized that with the currently unknown significance and risk for progression more research is needed before advocating specific pharmacological treatment for post-COVID ILD.

Sarcoidosis and other granulomatous ILDs/DPLDs

A whole session of the conference was dedicated to the new ERS guideline on management and treatment of sarcoidosis, published in 2021 [33]. Besides the specific recommendations for treatment of pulmonary, skin, cardiac and neurologic sarcoidosis, an important part of the discussion was dedicated to treatment indication. Treatment should only be introduced if there is a danger of death, permanent disability, or an unacceptable loss of quality of life. Predictors of mortality include presence of pulmonary hypertension, >20% fibrosis on HRCT, composite physiological index >40 or DLCO <40%, or dilatation of the pulmonary artery. The risk of under treatment versus overtreatment should always be carefully evaluated.

Most presentations in this group focused on better understanding of sarcoidosis. A few studies aimed to gain better insights in disease pathogenesis and identify new therapeutic targets. One study demonstrated that neuropilin-2 (NRP2) is a promising new therapeutic target in pulmonary sarcoidosis [34]. NRP2 plays an important role in the regulation of inflammatory responses and is highly expressed in granulomas found in the lungs of sarcoidosis patients, especially on alveolar macrophages and CD4+ T cells. The immunomodulatory protein ATYR1923 selectively binds to NRP2and reduced the number of alveolar macrophages and CD4+ cells in two different mouse lung inflammatory models. Moreover, ATYR1930, which contains the same immunomodulatory domain as ATYR1923, reduced granuloma formation in an *in vitro* model [34]. Results of a phase 1/2 clinical trial in patients with pulmonary sarcoidosis are expected soon (NCT03824392).

A Dutch group investigated the role of the mechanistic target of rapamycin 1 (MTORC1) signaling pathway in granuloma formation in sarcoidosis and other granulomatous disorders. Tissue of 74 sarcoidosis patients, 19 patients with hypersensitivity pneumonitis, and 7 patients with granulomatosis with polyangiitis (GPA) were collected. 32 (43%) of the sarcoidosis patients had an active MTORC1 signaling pathway, versus 31% in other ILDs (p=0.63). MTORC1 activation was not associated with disease behavior but could potentially be a therapeutic target in a subset of patients [35].

Multiple antigens have been proposed as potential trigger for sarcoidosis, including different environmental factors. The French RespiRare network evaluated the association between mineral dust exposure and pediatric sarcoidosis. Parents of patients with pediatric sarcoidosis (n=36), healthy controls (n=36), and sickle-cell disease controls (n=21) completed an environmental questionnaire on direct and indirect exposures. The indirect exposure scores (i.e. parents' occupational exposure) were higher in patients with sarcoidosis than in both control groups, particularly exposure to metal dust, talc or abrasive agents, and cleaning with scouring products. The authors conclude that there may be a role of early exposures in the pathophysiology of sarcoidosis [36]. An interesting question is whether different exposures are related to specific organ involvement. In a retrospective study, the medical records of 238 patients with sarcoidosis were screened to collect data on exposures. Patients with sarcoidosis limited to the lungs were more frequently exposed to inorganic dust (e.g. silica, metal). Interestingly, patients with liver and spleen involvement were more likely to have contact with livestock or jobs with close human contacts, suggesting an antigen that disseminates systemically. Finally, patients with eye involvement were more likely to be active smokers. These results suggest that different exposures may lead to different sarcoidosis phenotypes, although the clinical implications still need to be addressed in future studies [37].

Besides environmental exposures, a modified microbiome could also be involved in sarcoidosis disease pathogenesis. One study focused on the differences in bacterial and fungal microbiome between patients with sarcoidosis (n=35) and healthy controls (n=35). The bacterial taxonomic distribution in both oral wash and BAL fluid was similar in both study groups, but bacterial diversity was lower in sarcoidosis patients. Notably, fungal taxonomic distribution was significantly different between the groups. For example, aspergillus was the most dominating genus in BAL samples of sarcoidosis patients, but undetectable in controls. Whether the microbiome is associated with disease course, and could be a novel treatment target for sarcoidosis, still needs to be elucidated [38].

Besides identification of new therapeutic targets, there is also a major need to optimize first-line treatment and tapering regimes, as these are currently largely based on expert opinion. A multi-center prospective observational study assessed the long-term response to prednisone treatment in newly treated patients with pulmonary sarcoidosis. Prednisone was initiated at 40 mg and tapered to 10 mg at week 10. In this study cohort (n=25), FVC and DLCO improved significantly between baseline and month 1 (change in FVC %-predicted: +11.5%+-8.5, p<0.001, change in DLCO %-predicted: +12.5%+-7.8, p<0.001). After month 1, lung function parameters remained stable up until 12 months. The same trends were found for dyspnea, fatigue, and quality of life measured with the King's Sarcoidosis Questionnaire. Importantly, mean weight increase during one year was 8.2kg (SD 6.2). These results might guide future trial design and optimize treatment schedules [39].

A frequently used third-line treatment option for sarcoidosis is infliximab, a TNF-alpha inhibitor. A retrospective study (n=95) evaluated the effects of infliximab treatment on symptoms of small fiber neuropathy (SFN), using the SFN screening list. In patients with improved and stable SFN symptoms, inflammatory activity on FDG-PET scan significantly decreased, whereas inflammation did not decrease in patients with worsened SFN symptoms. This implicates that persistent inflammation may be related to SFN symptoms [40]. Improving treatment options for this debilitating symptom is an important field for future study, especially since the current sarcoidosis guidelines cannot provide a recommendation for treatment of SFN symptoms due to a lack of evidence [33].

Finally, a study in 200 sarcoidosis patients focused on factors influencing cough, measured with the Leicester Cough Questionnaire. A higher Body Mass Index (BMI) and lower Forced expiratory Volume in 1 second (FEV1) was associated with worse cough, indicating that targeting airway obstruction and weight may potentially improve cough symptoms in sarcoidosis [41].

Rare ILDs/DPLDs

This year's congress programme on rare ILDs and DPLDs primarily encompassed clinical research, providing new insights into clinical and radiological manifestations, as well as phenotyping underrecognized entities.

An Italian retrospective cohort in patients with pulmonary alveolar proteinosis (PAP) aimed to identify predictors for fibrotic evolution. Out of 64 patients included, 12 developed pulmonary fibrosis within 8 years of follow up. Distinct clinical and therapeutic modalities have been identified among patients with fibrotic and non-fibrotic groups. The fibrotic group had a slightly female predominance (58.3%), with a mean age at diagnosis of 46 years. Two third of patients underwent at least 1 session of whole lung lavage (WLL). 44% had more than 1 session and in 50% of cases WLL was followed by inhaled granulocyte-macrophage colony stimulating factor (GM-CSF). In contrast, the non-fibrotic group had a male predominance (73%) and younger age at diagnosis (41 years). Around 73% had received one session of WLL and 40 % had received more sessions. In only 23% of cases, WLL was followed by inhaled GM-CSF. In a multivariate regression analysis, DLCO (p=0.002) and partial pressure of oxygen (p=0.011) at diagnosis were significantly associated with fibrosis development [42].

In a small single-center Spanish retrospective cohort of lymphangioleimyomatosis (sporadic-LAM [n=10 patients] and associated with tuberous sclerosis complex [TSC-LAM; n=8 patients]), S-LAM patients were older at diagnosis (55 vs 34 years old), with 44% of patients having obstructive lung physiology with mean FEV1 of 69% of predicted. The mean annual FEV1 and DLCO decline was 1.4% and 2.4 %, respectively. MTOR inhibitors were used in 61%. S-LAM had worse prognosis: 1 patient underwent lung transplantation and 2 other patients died during a mean follow-up of 15 years [43]. Another small retrospective Portuguese cohort of 12 patients with LAM evaluated medium-term tolerance of m-TOR inhibitors. They found a maintained positive effect of sirolimus at 1 and 2 years of follow-up in treated patients (n=8), with good drug tolerance and no side-effects. These results support long-term use of sirolimus in patients with LAM [44].

A British case series of 10 patients with nitrofurantoin induced ILD aimed to describe this neglected entity of drug-induced ILD. The median age of women receiving nitrofurantoin for recurrent urinary tract infection was 80 years. The mean duration between nitrofurantoin initiation and ILD diagnosis was 17 months. The mean blood eosinophils' count was 0.19 10^9/L with mean FVC at presentation of 80% predicted. The HRCT showed peribronchovascular ground glass and septal thickening in the majority of patients, while isolated consolidations and usual interstitial pneumonia pattern was less commonly observed. Nitrofurantoin discontinuation led to improvement in 60% of cases. Glucocorticoids were used in 4 patients because of persisting ILD despite nitrofurantoin discontinuation [45].

The OrphaLung Network in France for rare pulmonary diseases presented a large retrospective cohort on chronic idiopathic bronchiolitis (CIB), a rare form of chronic and irreversible bronchiolitis in adults. A total of 71 cases with CIB were identified using radiological and histological criteria for evidence of bronchiolitis. Patients were included if they had direct signs of bronchiolitis on HRCT of the chest (tree in bud, branched V- or Y-shaped infiltrates, centrilobular micronodules) or, if available, when lung biopsy showed idiopathic bronchiolitis. The mean age at diagnosis was 52 (± 14) years with a female predominance (71%). Only 41% of patients had history of previous smoking. Obstructive lung physiology (FEV1/FVC < 0.7) was present in 69% of cases. Direct HRCT signs were present in 81% of patients. Evidence of bronchiolitis was seen in all but one biopsied patient (27 patients, lymphocytic [8], follicular [7], constrictive [7], granulomatous [3]). Long-acting beta2 agonists and inhaled corticosteroids were used in 77% and 73%, respectively. Half of patients were treated with macrolides at one point during their follow-up. Macrolide use was not associated with better outcome. Oral steroids and other immunosuppressive medication were only used in 45% and 12%, respectively. The mean duration of follow-up was 5.1 (±4.4) years. During follow-up 13 patients developed chronic respiratory failure, 1 patient received lung transplantation and 5 patients died [46].

In parallel, the same network reported the largest series until now on patients with pulmonary light chain deposition disease (LCDD), an extremely rare and underrecognized cause of cystic lung disease and bronchiectasis. 31 patients were included in the analysis, 68% were female, and 67% were (former) smokers. The mean age at first presentation was 43.5 (±11.4) years and 50 (±10.7) years at diagnosis. Dyspnea (93%) and cough (80%) were the most common symptoms. Hemoptysis was reported by 30% of patients. Obstructive lung physiology (FEV1/FVC< 0.7) was present in 45% with a mean FEV1 of 86% (±26%) of predicted. DLCO was reduced in 90% of cases. Plasma kappa light chains were increased in 87%, while no patients had increased lambda light chains. The diagnosis was obtained by surgical lung biopsy (36%), post lung transplantation (32%), and bronchial biopsy (26%). The majority of patients had mixed cystic and bronchiectatic forms. The mean annual FEV 1 decline was 127 mL/year. Different chemotherapeutic strategies were used aiming at reducing secretion of light chains. Unfortunately, there was no apparent efficacy. At the end of study period, 15 patients underwent bilateral lung transplantation and 3 patients died. The median transplantation-free survival was 9 years [47].

Concluding remarks

This article highlights scientific advances in the field of ILD presented at ERS 2021. The meeting provided the community with valuable new insights into disease pathophysiology, potential therapeutic targets, and disease course of different ILDs. Moreover, this year's congress showed that novel approaches to enhance early diagnosis and improve care for patients with ILD are emerging. We welcome everyone to join and contribute to next year's ERS congress.

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