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# Practical guidance for the early recognition and follow-up of patients with connective tissue disease-related interstitial lung disease

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ABSTRACT

*Background:* The early detection and management of (progressive) interstitial lung disease in patients with connective tissue diseases requires the attention and skills of a multidisciplinary team. However, there are currently no well-established standards to guide the daily practice of physicians treating this heterogenous group of diseases.
*Research question:* This paper aimed to identify gaps in scientific knowledge along the journey of patients with connective tissue disease-related interstitial lung disease and to provide tools for earlier identification of interstitial lung disease and progressive disease.
*Study Design and Methods:* The opinions of an international expert panel, which consisted of pulmonologists and rheumatologists were collected and interpreted in the light of peer-reviewed data.
*Results:* Interstitial lung disease is a common complication of connective tissue diseases, but prevalence estimates vary by subtype. Screening and monitoring by means of clinical examination, chest radiography, pulmonary function testing, and disease-specific biomarkers provide insight into the disease activity of patients presenting with connective tissue diseases in a routine setting. Multiple phenotypic and genotypic characteristics have been identified as predictors of the development and progression of interstitial lung disease. However, these risk factors differ between subtypes. To ensure earlier diagnosis of rapidly progressive phenotypes, a risk-based method is necessary for determining the need for HRCT and additional testing.
*Interpretation:* To reduce the underdiagnosis of CTD-ILDs in clinical practice, a standardized and systematic multidisciplinary risk-based approach is suggested. Collaboration across disciplines is essential for the management of CTD-ILD.

*Abbreviations:* AS, antisynthetase syndrome; CTD, connective tissue disease; CTD-ILD, connective tissue disease-associated interstitial lung disease; dcSSc, diffuse cutaneous SSc; DLCO, diffusion capacity of the lungs for carbon oxide; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IIM, idiopathic inflammatory myopathy; IMM-ILD, idiopathic inflammatory myopathy-related ILD; ILD, interstitial lung disease; IOS, impulse oscillometry; lcSSc, limited cutaneous SSc; MDT, multidisciplinary team; MUC5B, mucin 5B; NSIP, non-specific interstitial pneumonia; PFT, pulmonary function test; PPF, progressive pulmonary fibrosis; RA, rheumatoid arthritis; RA-ILD, rheumatoid arthritis-related ILD; RF, rheumatoid factor; ScL-70, anti-topoisomerase; SSc, systemic sclerosis; SSc-ILD, systemic sclerosis-related ILD; UIP, usual interstitial pneumonia.

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## 1. Introduction

Interstitial lung diseases (ILDs) are a diverse group of disorders with a wide range of causes, clinical manifestations, and outcomes [1]. The estimated prevalence ranges between 72.1 and 164.2 cases per 100,000 Europeans [2]. ILDs associated with connective tissue diseases (CTD-ILDs) represent a substantial subset accounting for almost 20% of all ILDs [1]. Systemic sclerosis-related ILD (SSc-ILD) and rheumatoid arthritis-related ILD (RA-ILD) account for approximately 31% and 39% of these CTD-ILDs [1]. Other autoimmune rheumatic diseases associated with ILDs include idiopathic inflammatory myopathy (IIM-ILD, dermatomyositis, polymyositis, antisynthetase syndrome(AS)), primary Sjögren's syndrome, systemic lupus erythematosus and mixed connective tissue disease [3].

The presentation and clinical course of CTD-ILDs vary considerably [3]. A proportion of patients with CTD-ILDs develop progressive pulmonary fibrosis (PPF) that causes irreversible lung damage, morbidity and increased mortality [2]. In particular, PPF represents the primary cause of death for patients with CTDs along with cardiovascular comorbidities [4]. Maintaining a high level of suspicion for ILD is important as early but irreversible lung function loss can occur asymptomatically, while other patients present with nonspecific symptoms such as fatigue, cough or dyspnoea on exertion that may hide behind other organ involvement or associated comorbidities (eg, myopathy, cardiac disease) [3].

Due to the variety of CTD-ILD subtypes, each with its own unique characteristics, the paucity of high-quality research, and the absence of international guidelines, early identification and management of ILD continue to be challenging today. This results in disparate approaches to clinical care and therapy, as well as delays in the identification of ILDs, whereas early recognition can be important to stabilize or slow irreversible lung function loss immediately. Moreover, to ensure optimal coordination and quality of patient care, it is necessary to consider CTD-ILDs from both pulmonary and rheumatological perspectives simultaneously. Recently, new guidelines for the treatment of ILD in people with systemic auto-immune rheumatic diseases have been proposed by the American College of Rheumatology [5,6]. In order to help clinicians applying those recommendations we aimed to bring those recommendations together with the reality of the multidisciplinary approach integrating disease evaluation, patient follow-up to propose the best treatment strategy.

This article was developed based on the collective experience and the discussions held at a meeting attended by the authors, who are all - rheumatologists or pulmonologists - experts in CTD-ILD and supplemented with scientific literature. The focus was on the difficulties encountered along the pathway for patients with CTD-ILDs and the need for holistic care through a multidisciplinary approach, as is required for rare diseases and diseases associated with multiple comorbidities [7]. The objective was to gain a better understanding of the scientific knowledge gaps and educational needs of healthcare professionals who work with these patients and to develop practical advice for risk- and symptom-based early ILD detection.

In November 2021 eight European rheumatologists and pulmonologists with acknowledged interest and expertise in the management of CTD-ILD gathered online for a workshop on the multidisciplinary challenges in the CTD-ILD patients' pathway and care. The panel discussed the challenges in the early recognition of progressive CTD-ILD, the need for collaboration between rheumatologists and pulmonologists, and the scientific knowledge gaps in CTD-ILD patient care for various health care providers in order to advance the knowledge and to provide practical guidance for daily practice.

Following a series of state-of-the-art presentations, predefined questions were used to structure in-depth discussion of expert opinions and summarize the relevant evidence.

This report represents the opinion of the expert panel, based on reliable peer-reviewed data.

## 2. Results

### 2.1. Characteristics of CTD patients susceptible to ILD

ILD is a frequent manifestation of CTDs, with prevalence estimates varying depending on the subtype of CTD, the population studied, and the research methodology used [8]. It is currently not fully comprehended why some patients with CTD develop ILD while others do not. Nonetheless, several phenotypic and genotypic characteristics have been identified as predictors of ILD development and risk of progression. Among these are demographic factors, clinical signs and symptoms, and serological markers, some of which are only accessible through clinical trials and other with limited validation in clinics [9]. Although all CTDs carry the risk of ILD, it is more frequent in SSc and IIM [1]. Due to the large number of patients in this group, the authors emphasized the need for rheumatologists and pulmonologists to have clear levers i.e. useful insights, education and tools to timely recognize the pulmonary symptoms and to identify patients with ILD and those at risk for progression. This brings up the requirement for specific recommendations.

#### 2.1.1. Systemic sclerosis

SSc is an orphan disease with a heterogenous expression, characterized by fibrosis of the skin, typically starting at the extremities, generalized vasculopathy witnessed by the Raynaud's phenomenon, and the presence of SSc specific antibodies (anti-centromere, anti-topoisomerase (ScL-70), and anti-RNA polymerase antibodies) [10]. Depending on the detection method and the extent of cutaneous disease, the estimated frequency of CTD-ILD varies largely around 50% of patients with SSc. ILD usually develops in the first five years of the disease course, often within two years of non-pulmonary symptom onset. Interestingly, the leading cause of death in SSc has evolved over the past three decades, from scleroderma renal crisis to pulmonary arterial hypertension (PAH) and lung fibrosis (LF). Today, both PAH and LF are recognized to be a major source of morbidity in SSc. Table 1 represents the primary risk factors for the development of SSc-ILD [11–13]. ILD occurs in dcSSc as well as in lcSSc. In a multicentre study with 772 patients with SSc in Flanders (60% with limited cutaneous involvement (lcSSc), 20% with diffuse cutaneous involvement (dcSSc) and 20% with precursor, "early" systemic sclerosis according to LeRoy), the prevalence of SSc-ILD was assessed at baseline and during follow-up by high-resolution computed tomography (HRCT) [14]. ILD was present at baseline in 35% of lcSSc and 56% of patients with dcSSc. At five years of follow-up, more than half of the patients with baseline ILD, had progressed according to the above mentioned study [14]. The prognosis correlates with the extent of lung fibrosis at baseline HCRT, with standard mortality rates increasing 2.2 times in patients with no fibrosis to 8.0 times in patients with >25% fibrosis [15]. The European Scleroderma Trials and Research Group (EUSTAR) database showed that over the course of five years, approximately one-third of patients with SSc-ILD advanced each year, while 70% remained stable [9]. Predictors for progressive ILD and mortality are listed in Table 1 [1,16].

#### 2.1.2. Rheumatoid arthritis

The prevalence of RA-ILD is not well established, with estimates ranging from 4 to 68% depending on the assessment method [17–19]. In a cross-sectional study of community based patients with joint disease of less than two year duration, Gabbay et al. found abnormalities consistent with ILD on HRCT in 33% of patients, but only 14% of cases were considered clinically significant [20]. Even though patients with RA are less likely than patients with SSc to develop ILD, the absolute number of patients with RA who have ILD is substantial. RA is a highly prevalent disease, with a global prevalence of 0.24%; consequently, it is improbable that all patients with RA will be screened [21].

The identification of risk factors allows for stratifying patients with RA who are at increased risk for ILD (Table 1) [22–25]. Known risk factors for progression or death are represented in Table 1 [1,26,27].

**Table 1**
Risk factors for CTD-ILDs and PPF (features of most common CTD-ILDs).

| | | Rheumatoid arthritis 1,22,25,27 | Systemic Sclerosis [1,11–13,15,16,69,71–73] | Idiopathic inflammatory myopathy [32–35] |
|---|---|---|---|---|
| EARLY RECOGNITION OF ILD | Risk factors for the development of ILD | male sex;<br>obesity;<br>current smoking;<br>older age at disease onset;<br>longer disease duration;<br>higher disease activity;<br>rheumatoid nodules;<br>CCP antibodies;<br>increased RF level;<br>elevated ESR;<br>MUC5B variant | male sex;<br>black race;<br>smoking history;<br>older age at disease onset;<br>diffuse cutaneous lesions;<br>topoisomerase antibodies;<br>absence of centromere antibodies | older age at disease onset;<br>arthritis/arthralgia, fever;<br>Jo-1 antibodies;<br>MDA-5 antibodies;<br>elevated ESR |
| | Recommendations for early detection | Use of risk-based screening tools (eg, Juge et al.) [24,58] | HRCT in all patients at baseline and close monitoring for the first 3–5 years | HRCT in all patients at baseline and PFT yearly monitoring for high-risk patients |
| PROGRESSIVE PULMONARY FIBROSIS | Predictors for progressive pulmonary fibrosis and mortality | male sex;<br>older age;<br>FVC < 70% predicted;<br>> 20% disease extent on HRCT;<br>honeycombing or UIP pattern on HRCT | male sex;<br>black race;<br>disease duration of <7 years;<br>diffuse cutaneous lesions;<br>reduced FVC;<br>reduced DLCO;<br>>20% disease extent on HRCT;<br>topoisomerase antibodies | Myositis subtype with more severe phenotypes with bad clinical response (ie,<br>MDA-5 antibodies,<br>Jo-1 antibodies) |
| | Recommendations | PFT at baseline; HRCT in suspected ILD or high-risk and yearly follow up for PFT | PFT and HRCT in all and yearly PFT (if high risk every 3–6 months) | PFT at baseline; HRCT in suspected ILD or high-risk (Jo-1, MDA-5) with yearly PFT |

Mortality was higher in patients with RA-ILD compared to matched patients with RA without ILD (10-year mortality of 60.1% vs. 34.5% respectively) [4].

### *2.1.3. Idiopathic inflammatory myopathies*

The IIMs, also referred to as myositis, are a rare and heterogeneous group of autoimmune disorders, with varying organ manifestations, prognoses and therapeutic responses [28,29]. The main representatives of this group are polymyositis, dermatomyositis and AS). Although IIM subtypes affect different tissues, they are commonly characterized by muscle weakness, skin rash and myositis-specific autoantibodies [28].

ILD has been detected in patients with IIM at prevalence estimates of 30% on average, varying from 6% in juvenile dermatomyositis to 71% in AS [29,30]. Both in AS and amyopathic MDA-5 dermato-pulmonary syndromes, extra-pulmonary manifestations may be lacking, highlighting the need for a multidisciplinary approach. A retrospective French multicentric study described the clinical presentation and outcome of 47 patients admitted to the intensive care unit for acute respiratory failure revealing AS or anti-MDA-5 antibodies [31]. In 13–38% of patients, ILD can be the first manifestation and precede the diagnosis of autoimmune disease by several years [32]. Suggested risk factors are listed in Table 1 [33–35]. In some idiopathic ILDs, the presence of autoantibodies in the absence of a CTD may help identify distinct phenotypes and outcomes that resemble associated CTD-ILDs. For instance, when myositis-specific autoantibodies are found in idiopathic ILD, the outcomes are similar to IIM-ILD and the ILD management could be similar for both groups [36].

Literature on (*epi*)genetics is limited today, with some preliminary data in SSc-ILD [37]. A meta-analysis of 28 studies found no significant link between the mucin 5B (MUC5B) rs35705950 mutation and the risk of SSc-ILD, but interestingly it may predict for susceptibility to idiopathic and familial interstitial pneumonia, as well as RA-ILD, suggesting a pathogenetic connection [23,38].

Due to the complexity described above, screening tools are required to aid in early case detection, and these screening tools must be CTD-specific, guided by the assessment of risk factors discussed above. Until recently, no formal guidelines existed on systematic screening for CTD-ILD except for SSc-ILD. Today, new recommendations have been proposed through ACR guidelines [5,6]. Indeed, it is nowadays recommended to screen patients (and to consider yearly re-screening for high-risk population) with pulmonary function test and high-resolution CT scan. In the particular context of RA, interesting screening tools for RA-ILD, based on risk factors, have been developed. Through our expert discussion, we confirm the need for a validated easy to use risk score [24,39–44]. Juge et al. have recently developed and validated a risk score for detecting subclinical RA-ILD, which may allow identification before the onset of respiratory symptoms (Table 2) [24]. Healthcare professionals who are involved in daily practice should be aware of the potential ILDs complicating the disease course of CTD patients and practical advice for risk- and symptom-based early ILD detection should be widely available to guide decision making for pulmonary screening.

It is important to specifically assess the possibility of ILD in CTD patients, although there is still a great heterogeneity in the exploration of this comorbidity. In general, a careful symptomatic and clinical evaluation allows the identification of advanced pathologies where the early forms are difficult to identify. In patient subgroups recognized as being at high-risk to develop ILDs, it is appropriate to carry out other investigations based on respiratory functional evaluation and imaging.

**Table 2**
Risk scores associated with the risk of subclinical RA-ILD. Risk matrix model was stratified by the presence or absence of each independent risk factor for subclinical RA-ILD (age at RA onset, DAS28-ESR disease activity scores, and sex; model without MUC5B rs35705950 genetic testing); †High risk level for RA-ILD; ‡ Higher level of risk for RA-ILD; §Highest level of risk for RA-ILD.

| | DAS28-ESR <2.9 | | DAS28-ESR 2.9–4.3 | | DAS28-ESR >4.3 | |
|---|---|---|---|---|---|---|
| Risk matrix variable | Female | Male | Female | Male | Female | Male |
| ≤49 years | 3.6 (0.8, 7.1) | 11.9 (3.3, 24.7) | 8.6 (2.3, 17.6) | 25.6 (7.2, 53.7)† | 17.5 (4.0, 40.4) | 43.6 (9.7, 81.8)† |
| 50–58 year | 9.1 (2.2, 20.3) | 26.6 (8.8, 53.5)† | 20.2 (7.9, 35.8) | 48.0 (21.7, 73.8)† | 36.3 (10.1, 66.2)† | 67.4 (22.0, 91.5)‡ |
| >58 years | 24.6 (8.0, 51.2) | 54.4 (26.8, 79.3)‡ | 45.4 (20.2, 71,9)† | 75.2 (45.2, 93.7)§ | 65.1 (35.3, 91.1)‡ | 87.2 (59.1, 98.3)§ |

Adapted from Juge et al. [24]

For example, in SSc, baseline screening with HRCT is recommended because of the high prevalence of SSc-ILD, but no consensus exists for baseline screening in other CTD-ILDs [45]. The use of biomarkers can also be useful for a prognostic approach in expert centres used to interpret the results. In addition to the diagnosis, it is also important to ensure a systematic follow-up in order to early identify PPF.

### 2.2. Diagnosis and monitoring of CTD-ILD

Signs and symptom assessments, lung function tests and HRCT are currently used to diagnose and monitor CTD-ILD patients.

#### 2.2.1. High Resolution Computed Tomography

HRCT is sensitive and specific in its ability to detect ILD, making it the golden standard for the diagnosis of ILD. Honeycombing, reticulation, traction bronchiectasis and/or ground glass opacities with superimposed fibrotic features are fibrotic features on HRCT [46]. The most common radiological patterns of CTD-ILDs are usual interstitial pneumonia (UIP), particularly in RA, and non-specific interstitial pneumonia (NSIP) or organising pneumonia in most other CTDs such as IIM. UIP shows more reticulation, bronchiectasis, and honeycombing and is associated with poorer survival in RA, similar to idiopathic pulmonary fibrosis, whereas NSIP exhibits more ground glass opacities with or without reticulations [26,47]. A retrospective single-center cohort in the Netherlands revealed that 22% of outpatients with CTD-ILD had fibrotic patterns at baseline HRCT (fibrotic NSIP, UIP, and other) [48].

The interpretation of radiological findings may become more meaningful if clinical considerations are taken into account. Therefore, consultation between the radiologist and clinician is essential. In addition, due to the sensitivity for ILD, HRCT can detect subclinical abnormalities that may not progress into ILD with clinical significance. In the upcoming years, eyes are geared towards new artificial intelligence-based tools which may in the future aid clinicians (based on deep learning methods or Radiomics) in the qualification and quantification of ILD, as well as serve in daily practice. Close collaboration, such as the Open-Source Imaging Consortium (https://repository.osicild.org), is required.

Even if baseline HRCT does not detect ILD, the patients at high risk for ILD should be followed for new respiratory symptoms and pulmonary function must still be monitored. In certain countries, HRCT may be difficult to obtain, causing delays in the diagnosis. In this context, chest ultrasound can be useful on top of chest examination in order to advance the screening while waiting for imaging to be carried out. Nevertheless, this cannot be to our opinion a way to systematically screen patients as thoracic ultrasonography is experience dependent and needs a specific training [49].

#### 2.2.2. Pulmonary function tests

Pulmonary function tests can reveal restrictive lung physiology (decreased total lung capacity or TLC) or impaired gas exchange (DLCO). These test are very useful for monitoring the progression of ILD, but they are not specific enough to be used as diagnostic tools [18]. In SSc, there is consensus that baseline pulmonary function tests should be administered in addition to HRCT and auscultation in all patients in order to provide baseline values and to be repeated regularly [11]. Spirometry is a simple and low-cost method for identifying signs of ILD-related pulmonary restriction. In case of suspected restriction, the diagnosis has to be confirmed by measuring total lung capacity (TLC). Regular spirometry and measurement of diffusion capacity are recommended for the monitoring of ILD to detect signs of disease progression. For instance, the current definition of progressive pulmonary fibrosis (PPF) necessitates the presence of at least two of the three following criteria within the past year without an alternative explanation: 1) worsening respiratory symptoms 2) physiological evidence of progression as measured by spirometry and diffusion and 3) radiological evidence of PPF on chest CT [50]. Of interest, impulse oscillometry (IOS) has also been identified as an easy alternative to HRCT for detecting early pulmonary involvement in patients with SSc and RA, but still has to be validated in large multicentric prospective studies [51,52].

#### 2.2.3. Signs & symptoms

Symptom assessments lack sensitivity for the detection of ILD. In a series of patients with RA-ILD confirmed on HRCT (ground glass opacification, septal thickening, reticulation, traction bronchiectasis and/or honeycombing), 90% did not have dyspnoea or cough [53]. It may be difficult to reliably detect early pulmonary symptoms or to elicit a history of dyspnoea on exertion in patients with CTDs, as they frequently adapt their lifestyles to their condition or lead sedentary lives [45]. The auscultatory detection of fine crackles during a clinical examination has a moderate sensitivity for the early identification of ILD [54]; a holistic approach to the diagnosis of ILD is needed.

#### 2.2.4. Multidisciplinary collaboration

Consequently, multidisciplinary collaboration is considered the method of choice for ILD diagnosis and severity evaluation integrating HRCT, PFT and symptom evaluation and pulmonary, rheumatology and radiology expertise [3]. The multidisciplinary approach may also be beneficial in the follow-up of patients with minimal ILD on HRCT. Cooperation and alignment on diagnostic evidence increases the level of care and is especially beneficial in complex patient cases. While it is still unclear when and how multidisciplinary teams (MDTs) are needed, as well as how they should be standardized, Cottin et al. have recently summarized current perspectives [5].

#### 2.2.5. Guidelines

Starting from the guidelines for the identification and follow-up of fibrotic interstitial lung disease, many position statements and consensus work have been published to guide clinical practice for CTD-ILDs, including the recent guideline on PPF [55]. However, practical guidance specific for clinical management of CTD-ILDs is missing. Concerning SSc-ILD a panel of 27 European pulmonologists, rheumatologists, and internists has now developed evidence-based consensus statements for the identification and management of SSc-ILD [11]. Agreement was reached that HRCT is the primary tool for diagnosing ILD in patients with SSc, with pulmonary function testing and clinical assessment of respiratory symptoms serving as supporting diagnostic tools (dyspnoea, exercise-induced oxygen desaturation via the 6-min walking test (6MWT), and quality of life). The ACR guidelines stated that screening tests have to be considered in the presence of signs or symptoms of ILD. They propose a yearly re-screening in high-risk patients that has to be identified by clinicians in order to propose an adequate management. Screening tools in patients with RA are being developed, such as the Juge et al. risk score to detect subclinical RA-ILD (Table 2) [24]. Our multidisciplinary panel stated that even though 6MWT is not recommended, it allows clinician to easily identify significant lung disease. Moreover, 6MWT allow to evaluate both pulmonary and muscular capacity in combination that can help in order to propose a holistic integrated evaluation. The multidisciplinary panel agreed on the potential of PFT for early detection of ILD that can also be suspected through a longitudinal follow-up, whereas HRCT needs to be performed as gold standard in order to confirm the ILD diagnosis considering the low added value of chest radiography. Bronchoscopy, surgical lung biopsy or cryobiopsy are also not recommended by the expert panel accordingly to the stated recommendation in ACR guidelines for diagnostic of CTD-ILDs.

#### 2.2.6. In practice

As illustrated in Fig. 1, due to the high prevalence of ILD in systemic sclerosis and its status as the leading cause of death, HRCT screening should be performed even in the absence of symptoms, whereas lung function tests (FVC and DLCO), in combination with the clinical history of symptoms are useful for assessing progression over time.

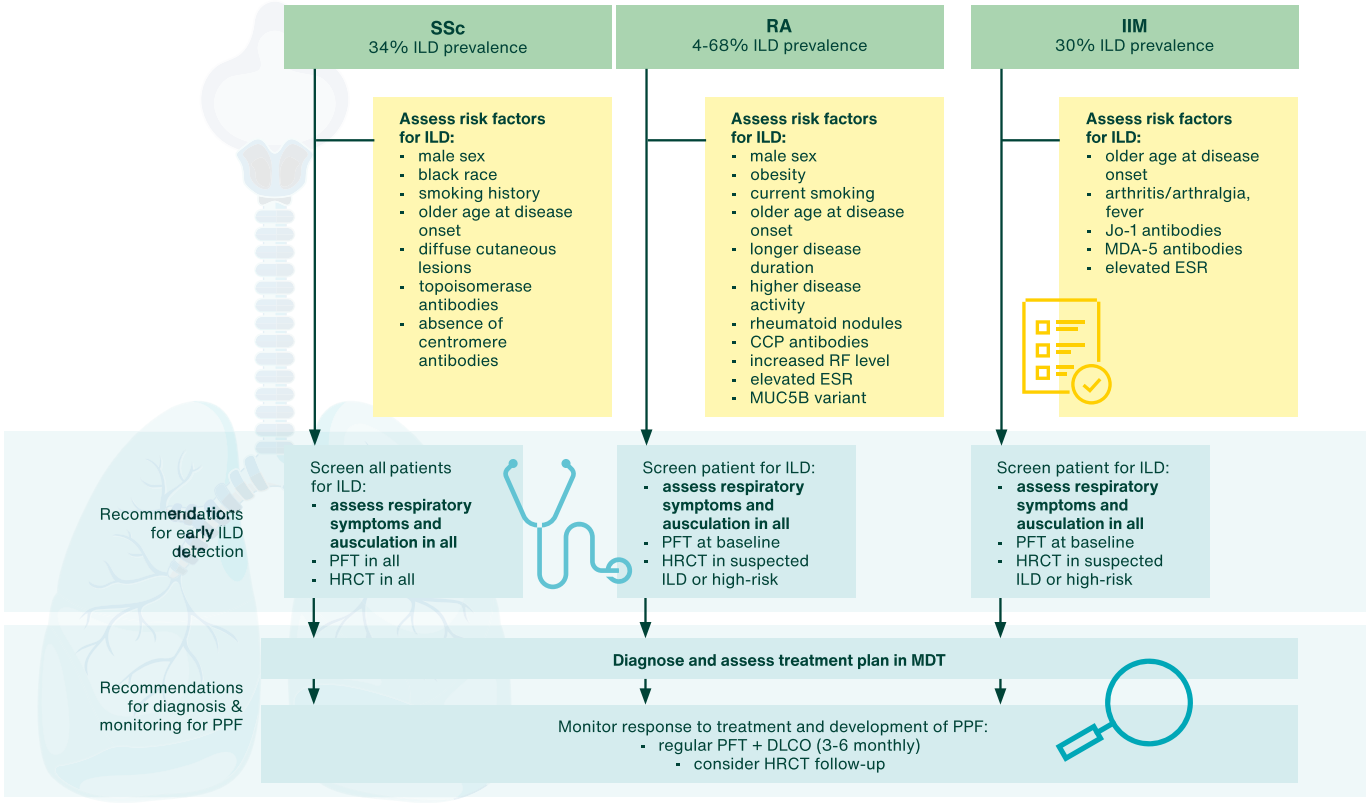


**Fig. 1.** CTD-ILD patient algorithm in SSc [73], RA [17–20], and IIM [29,30]

HRCT as a screening tool in patients with RA is impractical due to the high prevalence of RA and the relatively low proportion of patients with RA-ILD. However, RA-ILD is substantially underdiagnosed. The high absolute number of RA patients with ILD necessitates vigilant monitoring in order to detect at the earliest stages the occurrence of ILD with a dedicated strategy integrating risk factors [56,57]. The clinical examination with auscultation are useful options for detecting Velcro-crackles. In addition, risk factors must be considered to determine which patients are more likely to develop ILD (male gender, smoking history, disease duration and severity, high titre of RF or CCP) [24,25]. Although no formal risk screening tool exists, several have recently been proposed [24,58]. Furthermore, many RA patients have a history of smoking, and spirometry should be recommended.

The 2023 ACR Guidelines proposed a preferred ILD therapy for each underlying condition. Nevertheless, disease evaluation is complex and needs to be carefully addressed through a multidisciplinary team for an individualized approach. The early identification of progressive pulmonary fibrosis has to be considered as a medical need for an early specific anti-fibrotic therapy as recommended in the recent PPF guidelines [55]. To date, RA-ILD management is still debated. While the potential of biologic therapy to reduce RA-ILD evolution is still unclear, it has been proven that nintedanib was able to slow down disease progress over the time [59–61], whereas the evidence for pirfenidone is not sufficient due to the early termination of the TRAIL1 study [62]. The 2023 ACR guidelines conditionally recommend adding the antifibrotic treatment nintedanib or pirfenidone as therapeutic options for the management of progressive RA-ILD despite first line treatment. The expert panel suggests to evaluate the balance between the inflammatory and the fibrotic ILD process in order to adapt the anti-inflammatory and anti-fibrotic treatment over time [63]. Of importance, usual interstitial pneumonia (UIP) pattern in RA-ILD is known to be associated with a poor prognosis and needs to be carefully evaluated [64]. The approach in expert centers is traditionally integrated and multidisciplinary. Even if ACR guidelines propose preferred immunomodulatory treatment, there is no RCTs comparing medication for the treatment of RA-ILD. In addition, some disease-modifying anti-rheumatic drugs (DMARDs) have been recognized to be associated with an increased risk of lung toxicity which should not discourage to use them, as the benefit/risk ratio is largely in favour of using them. Therefore, clinicians have to carefully evaluate those patients in order to exclude this specific complication during patient follow-up (albeit rare). Treatment with immunosuppressive agents is generally used regardless of the pattern of fibrosis. Patients are typically evaluated concurrently in a pulmonary and rheumatology consultation, resulting in an integrated and holistic view of the disease situation. This allows all anamnestic, clinical and pulmonary factors to be considered. During the initial evaluation of patients with CTD-ILD, short-term PFTs (within 3 months) and HRCT (within 6 months) should be considered to determine the rate of progression. In mild CTD-ILD (FVC $\geq$70% and $<$ 20% fibrosis extent on HRCT [65]), PFTs should be scheduled every 6 months for the first 1 to 2 years. Patients with moderate-to-severe ILD at baseline or progressive disease must have more frequent PFTs (every 3–6 months). During the first 3 years after a patient's diagnosis, a HRCT is repeated to identify patients who may have progressive disease. PPF in its earliest stages is important for determining which patients may benefit from antifibrotic therapies, which patients should be considered for participation in clinical trials, and which patients should be referred to an expert center. HRCT and PFT should be repeated within 3–6 months to 1 year, depending on the underlying disease, the ILD pattern and the extent, in order to determine the response to treatment and to allow for early identification of progression of inflammation or PPF.

### 2.3. *Need for multidisciplinary collaboration*

Recent research has shown that a consensus-based multidisciplinary approach to the care of patients with CTD-ILDs improves diagnostic accuracy and is likely to improve patient outcomes [5,66,67]. Typically, pulmonologist, rheumatologists, immunologists, thoracic radiologists

and pathologists work together to diagnose, make initial treatment decisions and monitor complex cases. Interestingly, the virtual organization of these meetings has enabled rheumatologists and pulmonologists without access to a multidisciplinary team to discuss the cases they refer.

Multidisciplinary teams also promote networking within and between hospitals and raise awareness of ILD. Expert institutions are establishing regular, easily accessible online forums for discussing patient cases. However, there are differences between countries. In some countries, like Belgium, expert centers participating in the European Reference Network for Rare Connective Tissue and Musculoskeletal Diseases, as well as Lung are well-known and, concerning systemic sclerosis a multidisciplinary consensus has been published [68,69]. Within the European Respiratory Society, the PROFILE.net initiative connects clinicians, scientists and experts in progressive fibrosing ILD and in artificial intelligence to redefine typical ILD patterns and to develop clinical decision supports systems, as needed in the evaluation of ILDs (https://www.ersnet.org/science-and-research/clinical-research-collaboration-application-programme/profile-net-progressive-fibrosing-lung-diseases-network/) [70].

Interestingly, while specific rheumatology and pulmonology reference centers existed in the past, these now start to overlap or to collaborate. Multidisciplinary experts in rare rheumatic diseases from across the Netherlands regularly convene in an online MDT (Arthritis Research and Collaboration Hub, ARCH) to evaluate patient cases in a secure setting. Pulmonology expert and treatment centers for ILD have been established in the Netherlands which collaborate through networks and shared MDTs. As a result, improvements in patient care are brought to the same level nationwide. In Sweden, it is possible for hospitals to send HRCTs for evaluation weekly to the specialized center, while in most countries, hospitals have assembled MDTs to discuss cases and to determine access to management. In Greece, the specialized facilities are not as well-known yet, which may lead to a disconnect between rheumatologists in small hospitals or the private sector and the expert centers and, as a result, referral delays.

The key to the management of these patients appears to be the multidisciplinary approach to follow-up and coordinated management. Multidisciplinary discussions continue to be imperative in order to optimally direct the patient follow-up based on the knowledge of the various experts present at the meeting. In addition, these meetings enable the anticipation of complex situations that do not respond to conventional therapeutic strategies, while putting into perspective the possibility of enrolling patients in clinical studies in order to provide them with the highest quality individualized treatment.

### *2.4. Interpretation*

This manuscript brings together multidisciplinary perspectives in order to propose practical guidance for the early recognition and follow-up of patients with connective tissue disease-related interstitial lung disease for clinicians. The authors suggest that a systematic and standardized approach is the best way to reduce the risk of underdiagnosis of CTD-ILDs in clinical practice. Risk-based screening allows for the earlier diagnosis of rapidly evolving phenotypes. HRCT is not routinely recommended at diagnosis in all CTDs but essential in patients with suspected ILD. Clinical examination, chest radiography, pulmonary function abnormalities, and disease-specific biomarkers can predict disease activity and indicate the need for additional testing. In contrast, the risk of developing ILD in SSc is so high that it is generally accepted that all patients, regardless of their risk factors, should be screened at diagnosis with HRCT and regularly monitored [11].

The multidisciplinary approach is the best way to ensure that rheumatologists and pulmonologists are taking care of CTD-ILDs as systemic diseases.

## Declaration of competing interest

**JG** reports personal fees for advisory board, work and lectures from Boehringer Ingelheim, Janssen, SMB, GSK, Roche, AstraZeneca, Aquilon, Volition, Oncoradiomics, and Chiesi, non-financial support for meeting attendance from AstraZeneca, Chiesi, MSD, Roche, Boehringer Ingelheim and Janssen. He is in the permanent SAB of Radiomics (Oncoradiomics SA) for the SALMON trial without any specific consultancy fee for this work. He is co-inventor of one issued patent on radiomics licensed to Radiomics (Oncoradiomics SA). He confirms that none of the above entities or funding was involved in the preparation of this work.**JM** has received grant/research support to the institution from the Erasmus Research innovation grants and sarcoidosis patients support group sarcoidosis.nl, and reports consulting fees and lecture honoraria from Boehringer Ingelheim and personal fees from Hoffmann la Roche and Novartis.**AC** has received speaker fees from Boehringer Ingelheim**JdVB** has received grant/research support to her institution from ReumaNederland (Dutch patient Society for Rheumatology), Nationale Vereniging voor mensen met lupus, APS, sclerodermie en MCTD (Dutch patient society), ARCH (Autoimmune Research and Collaboration Hub; Dutch interdisciplinary society for patients and caregivers), Janssen-Cilag, and Boehringer Ingelheim; consulting fees from Boehringer Ingelheim, Jansen-Cilag and Abbvie (payments made to institution); speaker fees from Dutch Society (payments made to institution), Boehringer Ingelheim (payments made to institution), Janssen-Cilag (payments made to institution).**TD** reports consultancy fees, speaker fees, honoraria, advisory boards from Abbvie, Amgen, Boehringer Ingelheim, GSK, Genesis Pharma, Janssen, Lilly, SOBI, UCB and Pfizer, non-financial support for meeting attendance from Abbvie, Genesis Pharma, Janssen, Elpen, Enorasis, UCB and Pfizer.**KS** has received fees for speaking and/or consulting fees from Boehringer Ingelheim; Travel expenses from UCB, Boehringer Ingelheim; research grants to Aarhus University Hospital from Danish Rheumatism Association; and has been primary investigator in trials by GSK and Boehringer Ingelheim**AT** has received grant/research support to his institution for Scientific Research in Interstitial Lung Diseases from Boehringer Ingelheim and Roche; consulting fees from Boehringer Ingelheim, Roche, Chiesi, GlaxoSmithKline, Astra Zeneca and Elpen (payments made to self and institution); speaker fees from Boehringer Ingelheim, Roche, Chiesi, GlaxoSmithKline, Astra Zeneca and Elpen; support for attending meetings and/or travel from Boehringer Ingelheim, Chiesi, Roche, Menarini, Elpen and AstraZeneca.**VS** has received grant/research support to her institution from the Research Foundation Flanders, Belgian Fund for Scientific Research in Rheumatic Diseases, Janssen-Cilag, Boehringer Ingelheim and Vlaeynatie; consulting fees from Boehringer Ingelheim (payments made to self and institution) and Janssen-Cilag (payments made to institution); speaker fees from UCB (payments made to institution), Boehringer Ingelheim (payments made to self and institution), Janssen-Cilag (payments made to institution); support for attending meetings and/or travel from Boehringer Ingelheim (payments made to institution).

## Data availability

No data was used for the research described in the article.

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## References

[1] Wijsenbeek M, Cottin V. Spectrum of fibrotic lung diseases. N Engl J Med 2020;383(10):958–68.
[2] Hilberg O, Hoffmann-Vold AM, Smith V, et al. Epidemiology of interstitial lung diseases and their progressive-fibrosing behaviour in six European countries. ERJ Open Research 2022;8:00597–2021.
[3] Jeganathan N, Sathananthan M. Connective tissue disease-related interstitial lung disease: prevalence, patterns, predictors, prognosis, and treatment. Lung 2020;198(5):735–59.
[4] Hyldgaard C, Hilberg O, Pedersen AB, et al. A population-based cohort study of rheumatoid arthritis-associated interstitial lung disease: comorbidity and mortality. Ann Rheum Dis 2017;76(10):1700–6.
[5] 2023 American College of Rheumatology (ACR) Guidelines for the treatment of intertstitial lung disease in People with systemic autoimmune rheumatic disease. 2023.
[6] 2023 American College of Rheumatology (ACR) Guidelines for the Screening and Monitoring of intertstitial lung disease in People with systemic autoimmune rheumatic disease. 2023.
[7] Cottin V, Martinez FJ, Smith V, Walsh SLF. Multidisciplinary teams in the clinical care of fibrotic interstitial lung disease: current perspectives. Eur Respir Rev 2022;31(165):220003.
[8] Fischer A, Distler J. Progressive fibrosing interstitial lung disease associated with systemic autoimmune diseases. Clin Rheumatol 2019;38(10):2673–81.
[9] Hoffmann-Vold A-M, Allanore Y, Alves M, et al. Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. Ann Rheum Dis 2021;80(2):219–27.
[10] Volkmann ER, Andréasson K, Smith V. Systemic sclerosis. Lancet (London, England) 2023;401(10373):304–18.
[11] Hoffmann-Vold A-M, Maher TM, Philpot EE, et al. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. The Lancet Rheumatology 2020;2(2):e71–83.
[12] Distler O, Assassi S, Cottin V, et al. Predictors of progression in systemic sclerosis patients with interstitial lung disease. Eur Respir J 2020;55(5):1902026.
[13] Nihtyanova SI, Schreiber BE, Ong VH, et al. Prediction of pulmonary complications and long-term survival in systemic sclerosis. Arthritis & rheumatology (Hoboken, NJ) 2014;66(6):1625–35.
[14] Vandecasteele E, Melsens K, Vanhaecke A, et al. Incidence, prevalence and long-term progression of Goh algorithm rated interstitial lung disease in systemic sclerosis in two independent cohorts in flanders: a retrospective cohort study. Semin Arthritis Rheum 2021;51(5):969–76.
[15] Hoffmann-Vold AM, Fretheim H, Halse AK, et al. Tracking impact of interstitial lung disease in systemic sclerosis in a complete Nationwide cohort. Am J Respir Crit Care Med 2019;200(10):1258–66.
[16] Guler SA, Winstone TA, Murphy D, et al. Does systemic sclerosis-associated interstitial lung disease burn out? Specific phenotypes of disease progression. Ann Am Thorac Soc 2018;15(12):1427–33.
[17] Shaw M, Collins BF, Ho LA, Raghu G. Rheumatoid arthritis-associated lung disease. European respiratory review : an official journal of the European Respiratory Society 2015;24(135):1–16.
[18] Wallace B, Vummidi D, Khanna D. Management of connective tissue diseases associated interstitial lung disease: a review of the published literature. Curr Opin Rheumatol 2016;28(3):236–45.
[19] Denis A, Henket M, Ernst M, et al. Progressive fibrosing interstitial lung disease in rheumatoid arthritis: a retrospective study. Front Med (Lausanne) 2022;9:1024298.
[20] Gabbay E, Tarala R, Will R, et al. Interstitial lung disease in recent onset rheumatoid arthritis. Am J Respir Crit Care Med 1997;156(2 Pt 1):528–35.
[21] Cross M, Smith E, Hoy D, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014;73(7):1316–22.
[22] Palomäki A, Palotie A, Koskela J, et al. Lifetime risk of rheumatoid arthritis-associated interstitial lung disease in MUC5B mutation carriers. Ann Rheum Dis 2021;80(12):1530–6.
[23] Juge PA, Lee JS, Ebstein E, et al. MUC5B promoter variant and rheumatoid arthritis with interstitial lung disease. N Engl J Med 2018;379(23):2209–19.
[24] Juge PA, Granger B, Debray MP, et al. A risk score to detect subclinical rheumatoid arthritis-associated interstitial lung disease. Arthritis & rheumatology (Hoboken, NJ) 2022;74(11):1755–65.
[25] Kelly C, Emery P, Dieudé P. Current issues in rheumatoid arthritis-associated interstitial lung disease. The Lancet Rheumatology 2021;3(11):e798–807.
[26] Kim EJ, Elicker BM, Maldonado F, et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 2010;35(6):1322–8.
[27] Jacob J, Hirani N, van Moorsel CHM, et al. Predicting outcomes in rheumatoid arthritis related interstitial lung disease. Eur Respir J 2019;53(1):1800869.
[28] Lundberg IE, Fujimoto M, Vencovsky J, et al. Idiopathic inflammatory myopathies. Nat Rev Dis Primers 2021;7(1):86.
[29] Lilleker JB, Vencovsky J, Wang G, et al. The EuroMyositis registry: an international collaborative tool to facilitate myositis research. Ann Rheum Dis 2018;77(1):30–9.
[30] Maloir Q, Laurence S, Christian VF, Fanny G, Renaud L, Julien G. Clinical experience in anti-synthetase syndrome: a monocentric retrospective analytical study. Acta Clin Belg 2022;77(3):624–30.
[31] Vuillard C, Pineton de Chambrun M, de Prost N, et al. Clinical features and outcome of patients with acute respiratory failure revealing anti-synthetase or anti-MDA-5 dermato-pulmonary syndrome: a French multicenter retrospective study. Ann Intensive Care 2018;8(1):87.
[32] Shappley C, Paik JJ, Saketkoo LA. Myositis-related interstitial lung diseases: diagnostic features, treatment, and complications. Current Treatment Options in Rheumatology 2019;5(1):56–83.
[33] Zhang L, Wu G, Gao D, et al. Factors associated with interstitial lung disease in patients with polymyositis and dermatomyositis: a systematic review and Meta-analysis. PloS One 2016;11(5):e0155381.
[34] Sato S, Masui K, Nishina N, et al. Initial predictors of poor survival in myositis-associated interstitial lung disease: a multicentre cohort of 497 patients. Rheumatology (Oxford) 2018;57(7):1212–21.
[35] Charrow A, Vleugels RA. Cutaneous ulcerations in anti-MDA5 dermatomyositis. N Engl J Med 2019;381(5):465.
[36] Graham J, Bauer Ventura I, Newton CA, et al. Myositis-specific antibodies identify a distinct interstitial pneumonia with autoimmune features phenotype. Eur Respir J 2020;2001205.
[37] Guiot J, Henket M, Andre B, et al. A new nucleosomic-based model to identify and diagnose SSc-ILD. Clin Epigenetics 2020;12(1):124.
[38] Lou HQ, Huang CX, Li GY, et al. The association between MUC5B Rs35705950 and risks of idiopathic interstitial pneumonia, systemic sclerosis interstitial lung disease, and familial interstitial pneumonia: a Meta-analysis. Iran J Public Health 2020;49(12):2240–50.
[39] Bendstrup E, Møller J, Kronborg-White S, et al. Interstitial lung dis-ease in rheumatoid arthritis remains a challenge for clinicians. J ClinMed 2019;8:203.
[40] Solomon JJ, Swigris JJ, Kreuter M, et al. The attitudes and practices of physicians caring for patients with rheumatoid arthritis-interstitial lung disease: an international survey. Rheumatology (Oxford) 2022;61:1459–67.
[41] Manfredi A, Cassone G, Cerri S, et al. Diagnostic accuracy of a Velcro sound detector (VECTOR) for interstitial lung disease in rheumatoid arthritis patients: the InSPIRAtE validation study (INterStitial pneumonia in rheumatoid ArThritis with an electronic device). BMC Pulm Med 2019;19:111.
[42] Paulin F, Doyle TJ, Mercado JF, et al. Development of a risk indicator score for the identification of interstitial lung disease in patients with rheumatoid arthritis. Reumatol Clin (Engl Ed) 2021;17:207–11.
[43] Xue J, Hu W, Wu S, et al. Development of a risk nomogram model for identifying interstitial lung disease in patients with rheumatoid arthritis. Front Immunol 2022;13:823669.
[44] Narvaez J, Aburto M, Seoane-Mato D, et al. Screening criteria for interstitial lung disease associated to rheumatoid arthritis: expert proposal based on Delphi methodology. Reumatol Clin (Engl Ed) 2023;19:74–81.
[45] Wijsenbeek M, Suzuki A, Maher TM. Interstitial lung diseases. Lancet (London, England) 2022;400(10354):769–86.
[46] Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner society: glossary of terms for thoracic imaging. Radiology 2008;246(3):697–722.
[47] Yunt ZX, Chung JH, Hobbs S, et al. High resolution computed tomography pattern of usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease: relationship to survival. Respir Med 2017;126:100–4.
[48] Chiu YH, Spierings J, de Jong PA, et al. Predictors for progressive fibrosis in patients with connective tissue disease associated interstitial lung diseases. Respir Med 2021;187:106579.
[49] Gutierrez M, Ruta S, Clavijo-Cornejo D, et al. The emerging role of ultrasound in detecting interstitial lung disease in patients with rheumatoid arthritis. Joint Bone Spine 022 2024;89:105407.
[50] Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 2022;205(9):e18–47.
[51] Panagopoulos PK, Goules AV, Georgakopoulou VE, et al. Small airways dysfunction in patients with systemic sclerosis and interstitial lung disease. Front Med (Lausanne) 2022;9:1016898.
[52] Cheng WC, Chang SH, Chen WC, et al. Application of impulse oscillometry to detect interstitial lung disease and airway disease in adults with rheumatoid arthritis. BMC Pulm Med 2023;23(1):331.
[53] Chen J, Shi Y, Wang X, Huang H, Ascherman D. Asymptomatic preclinical rheumatoid arthritis-associated interstitial lung disease. Clin Dev Immunol 2013;2013:406927.
[54] Moran-Mendoza O, Ritchie T, Aldhaheri S. Fine crackles on chest auscultation in the early diagnosis of idiopathic pulmonary fibrosis: a prospective cohort study. BMJ Open Respir Res 2021;8(1):e000815.
[55] Rajan SK, Cottin V, Dhar R, et al. Progressive pulmonary fibrosis: an expert group consensus statement. Eur Respir J 2023;61(3):2103187.

[56] Nieto MA, Rodriguez-Nieto MJ, Sanchez-Pernaute O, et al. Mortality rate in rheumatoid arthritis-related interstitial lung disease: the role of radiographic patterns. BMC Pulm Med 2021;21(1):205.
[57] Chen J, Chen Y, Liu D, et al. Predictors of long-term prognosis in rheumatoid arthritis-related interstitial lung disease. Sci Rep 2022;12(1):9469.
[58] Narváez J, Aburto M, Seoane-Mato D, et al. Screening criteria for interstitial lung disease associated to rheumatoid arthritis: expert proposal based on Delphi methodology. Reumatol Clin (Engl Ed) 2023;19(2):74–81.
[59] Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med 2019;381:1718–27.
[60] Wells AU, Flaherty KR, Brown KK, et al. Nintedanib in patients withprogressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Respir Med 2020;8:453–60.
[61] Matteson EL, Aringer M, Burmester GR, et al. Effect of nintedanib in patients with progressive pulmonary fibrosis associated with rheumatoid arthritis: data from the INBUILD trial. Clin Rheumatol 2023;42:2311–9.
[62] Solomon JJ, Danoff SK, Woodhead FA, et al. Safety, tolerability, and efficacy of pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease: a randomised, double-blind, placebo-controlled, phase 2 study. Lancet Respir Med 2023;11:87–96.
[63] Raghu G, Montes, SB, Silver RM, et al. Treatment of Systemic Sclerosis–associated Interstitial Lung Disease: Evidence-based Recommendations. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med, 209(2), 137–152.
[64] Kim EJ, Elicker BM, Maldonado F, et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 2010;35: 1322–8.
[65] Goh NS, Desai SR, Veeraraghavan S, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med 2008;177(11): 1248–54.
[66] Fisher JH, Cottin V. Care delivery models and interstitial lung disease: the role of the specialized center. Clin Chest Med 2021;42(2):347–55.
[67] Graney BA, He C, Marll M, et al. Essential components of an interstitial lung disease clinic: results from a Delphi survey and patient focus group analysis. Chest 2021; 159(4):1517–30.
[68] Talarico R, Aguilera S, Alexander T, et al. The added value of a European reference network on rare and complex connective tissue and musculoskeletal diseases: insights after the first 5 years of the ERN ReCONNET. Clin Exp Rheumatol 2022;40 Suppl 134(5):3–11.
[69] Piette Y, Van den Bossche F, Aerts N et al. Flemish network on rare connective tissues diseases (CTD): patient pathways in systemic sclerosis. First steps taken. Acta Clin Belg, 79:1, 26–33.
[70] Guiot J, Walsh S. The ERS PROFILE.net clinical research collaboration is dedicated to the set-up of an academic network to enhance imaging-based management of progressive pulmonary fibrosis. Eur Respir J 2023;62(3):2300577. Sep 9.
[71] Jaeger VK, Wirz EG, Allanore Y, et al. Incidences and risk factors of organ manifestations in the early course of systemic sclerosis: a longitudinal EUSTAR study. PloS One 2016;11(10):e0163894.
[72] McNearney TA, Reveille JD, Fischbach M, et al. Pulmonary involvement in systemic sclerosis: associations with genetic, serologic, sociodemographic, and behavioral factors. Arthritis Rheum 2007;57(2):318–26.
[73] Vandecasteele E, Melsens K, Vanhaecke A, et al. Incidence, prevalence and long-term progression of Goh algorithm rated interstitial lung disease in systemic sclerosis in two independent cohorts in flanders: a retrospective cohort study. Semin Arthritis Rheum 2021;51(5):969–76.