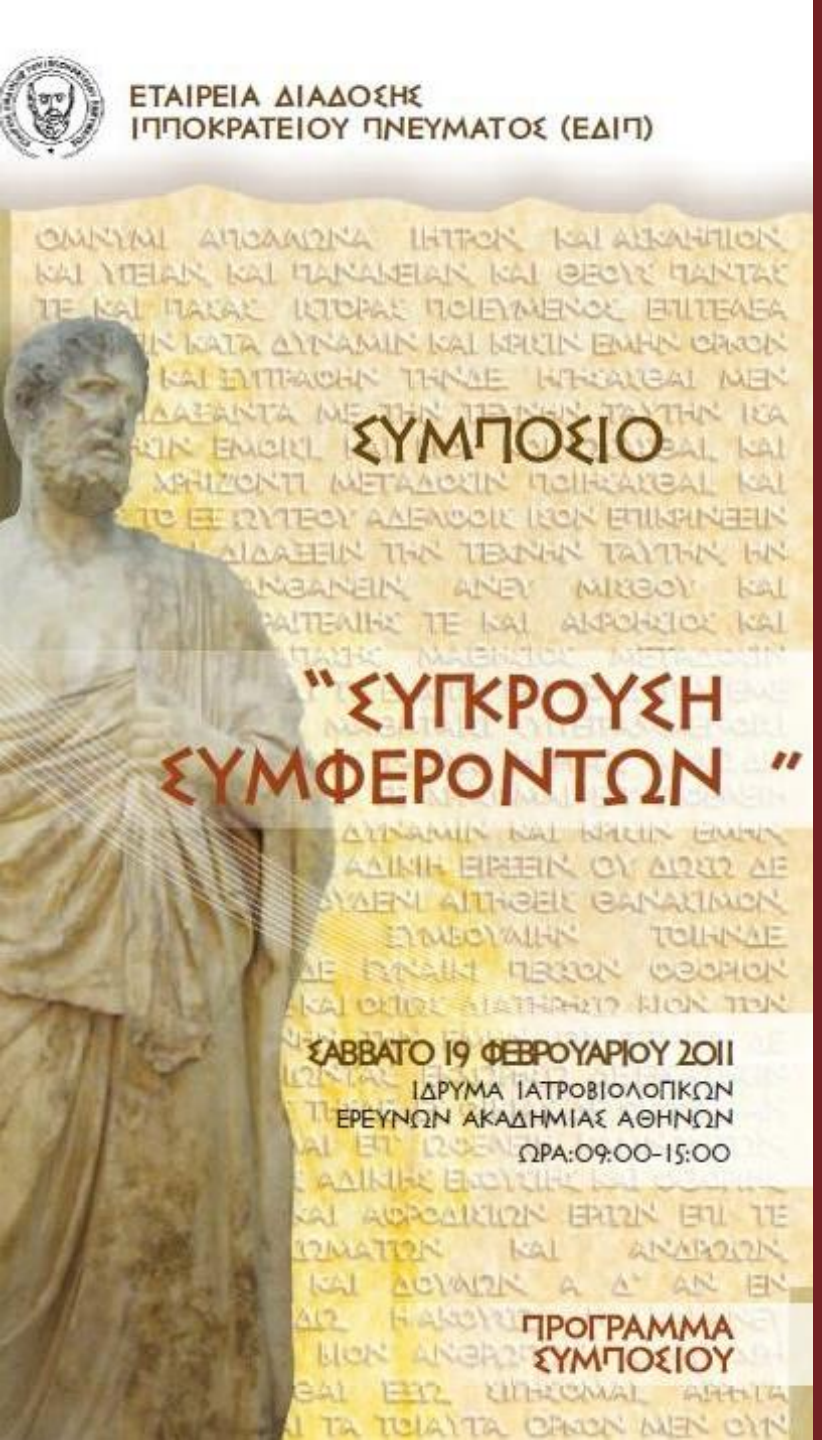
ΠΝΕΥΜΟΝΙΚΉ ΊΝΩΣΗ ΣΤΑ ΣΥΣΤΗΜΑΤΙΚΆ ΡΕΥΜΑΤΙΚΆ ΝΟΣΉΜΑΤΑ: ΚΛΙΝΙΚΉ ΥΠΟΨΊΑ – SCREENING - ΘΕΡΑΠΕΥΤΙΚΟΊ ΧΕΙΡΙΣΜΟΊ

Ανδρέας Γ. Μπούνας

ΡΕΥΜΑΤΟΛΟΓΟΣ

ΠΑΤΡΑ



CONFLICT OF INTEREST

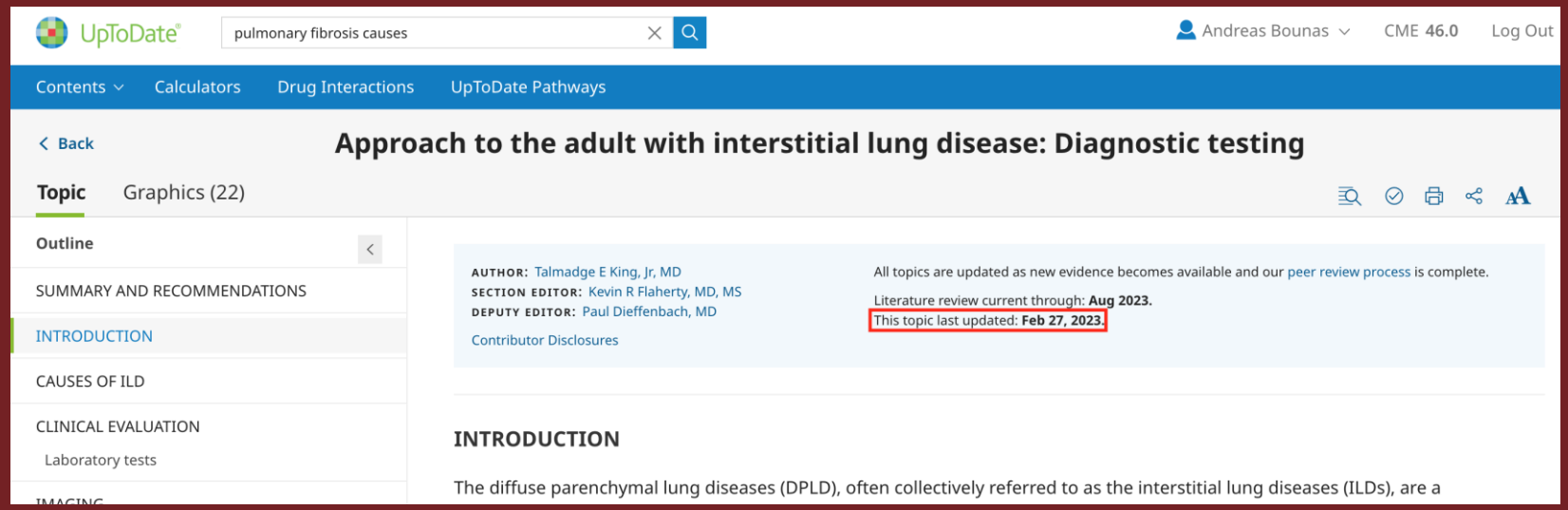
Προβλέπεται Honorarium για την συγκεκριμένη παρουσίαση

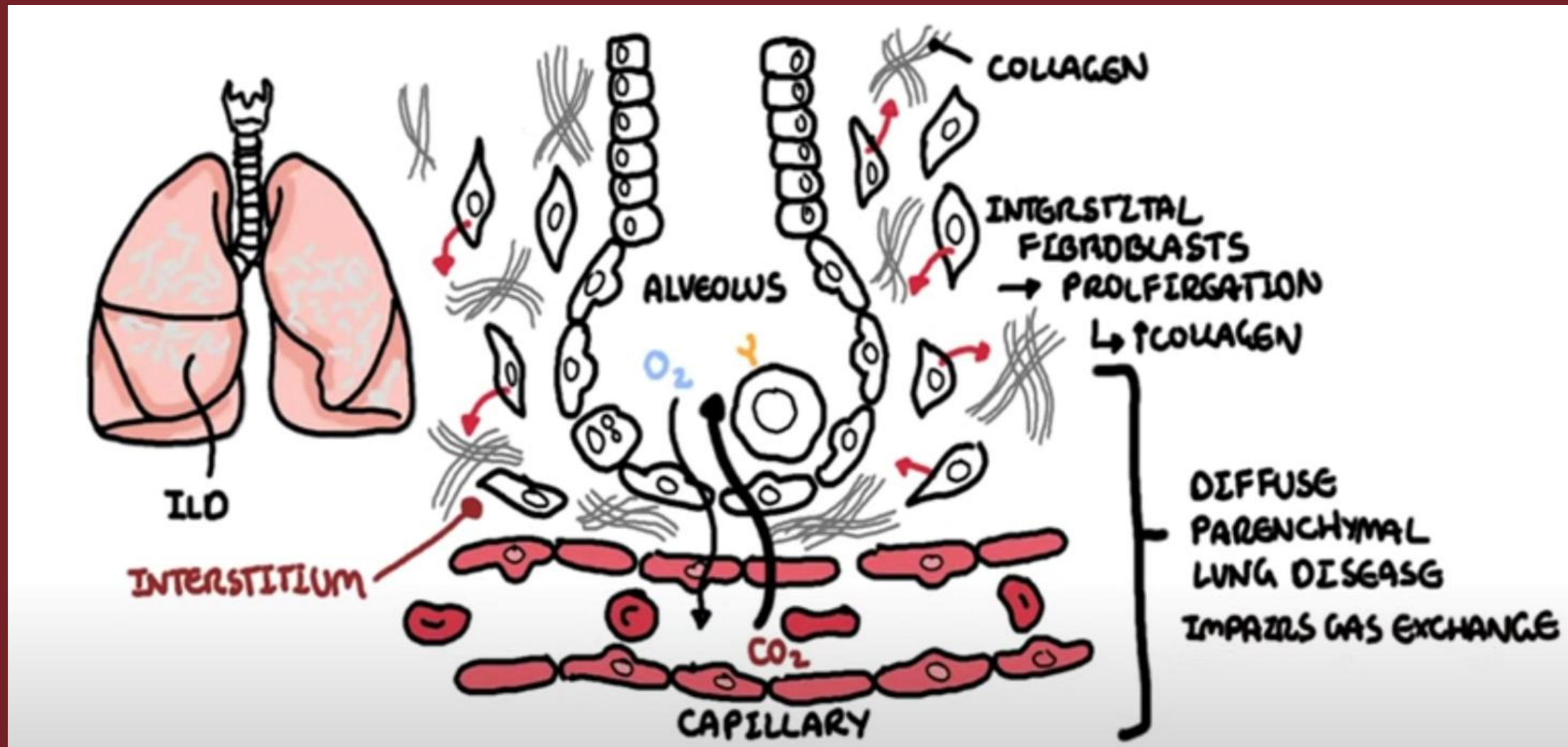
ΣΧΕΔΙΟ ΟΜΙΛΙΑΣ

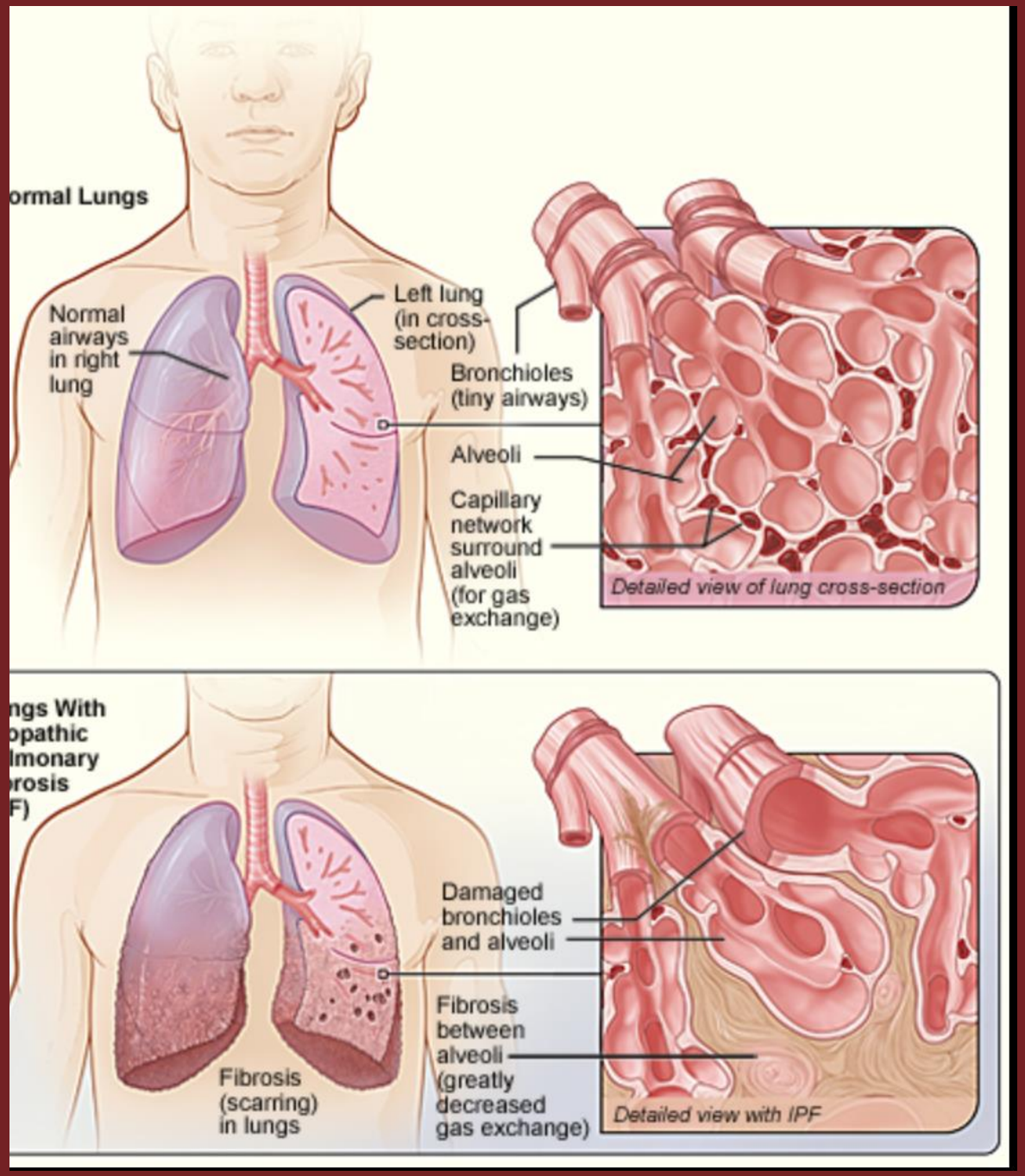
- Εισαγωγή
- Κλινική υποψία, Screening και Διάγνωση ILD
- Progressive Pulmonary Fibrosis (PPF)
- Θεραπευτικοί χειρισμοί
- Συμπεράσματα

ΕΙΣΑΓΩΓΗ

- diffuse parenchymal lung diseases (DPLD)
- interstitial lung diseases (ILDs)
- Interstitium



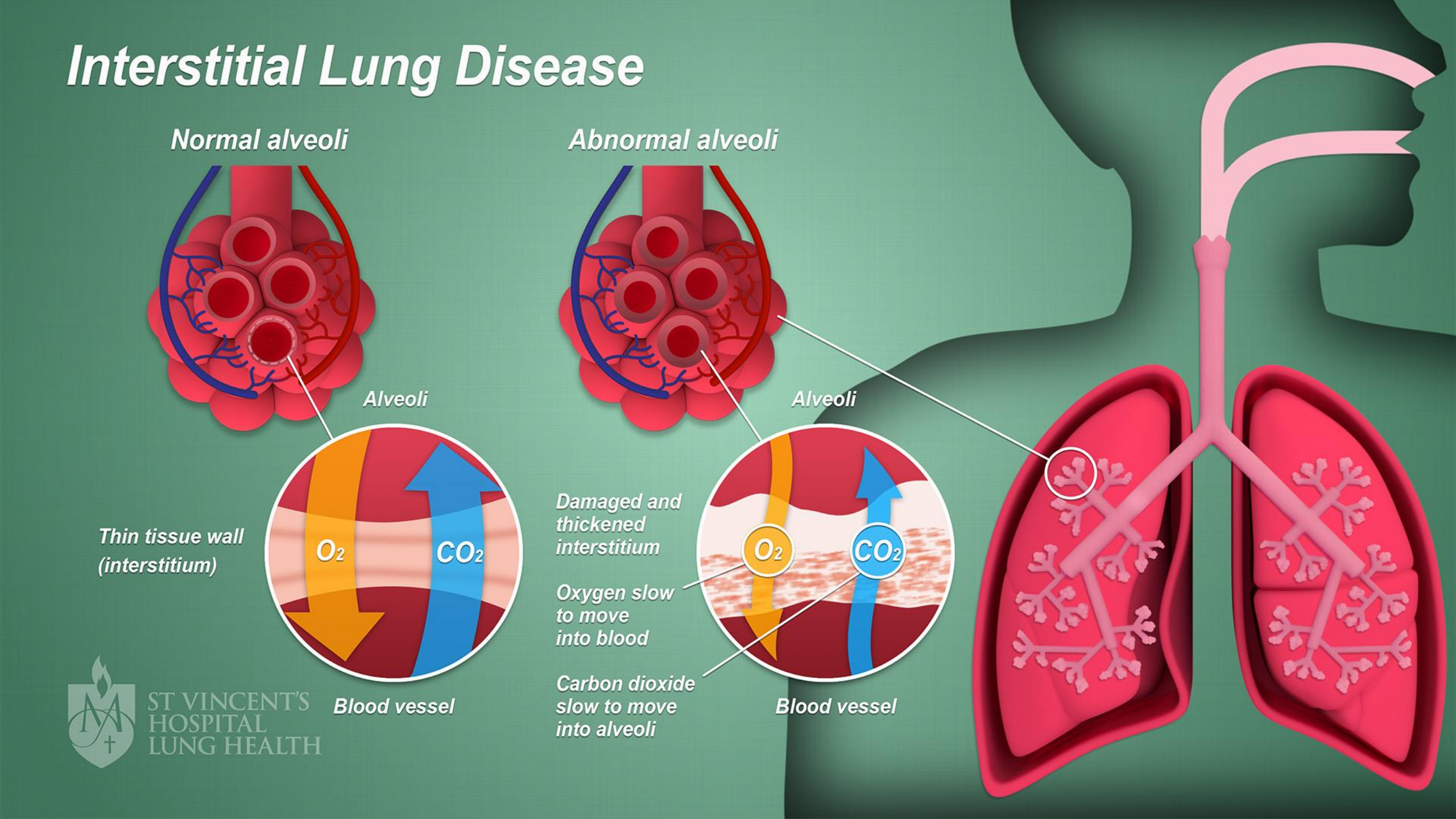

COLLAGEN
INTERSTITIAL FIBROBLASTS
→ PROLIFERATION
↳ ↑COLLAGEN
ALVEOLUS
O_2
CO_2
ILD
INTERSTITIUM
CAPILLARY
DIFFUSE PARENCHYMAL LUNG DISEASE
IMPAIRS GAS EXCHANGE



ILD

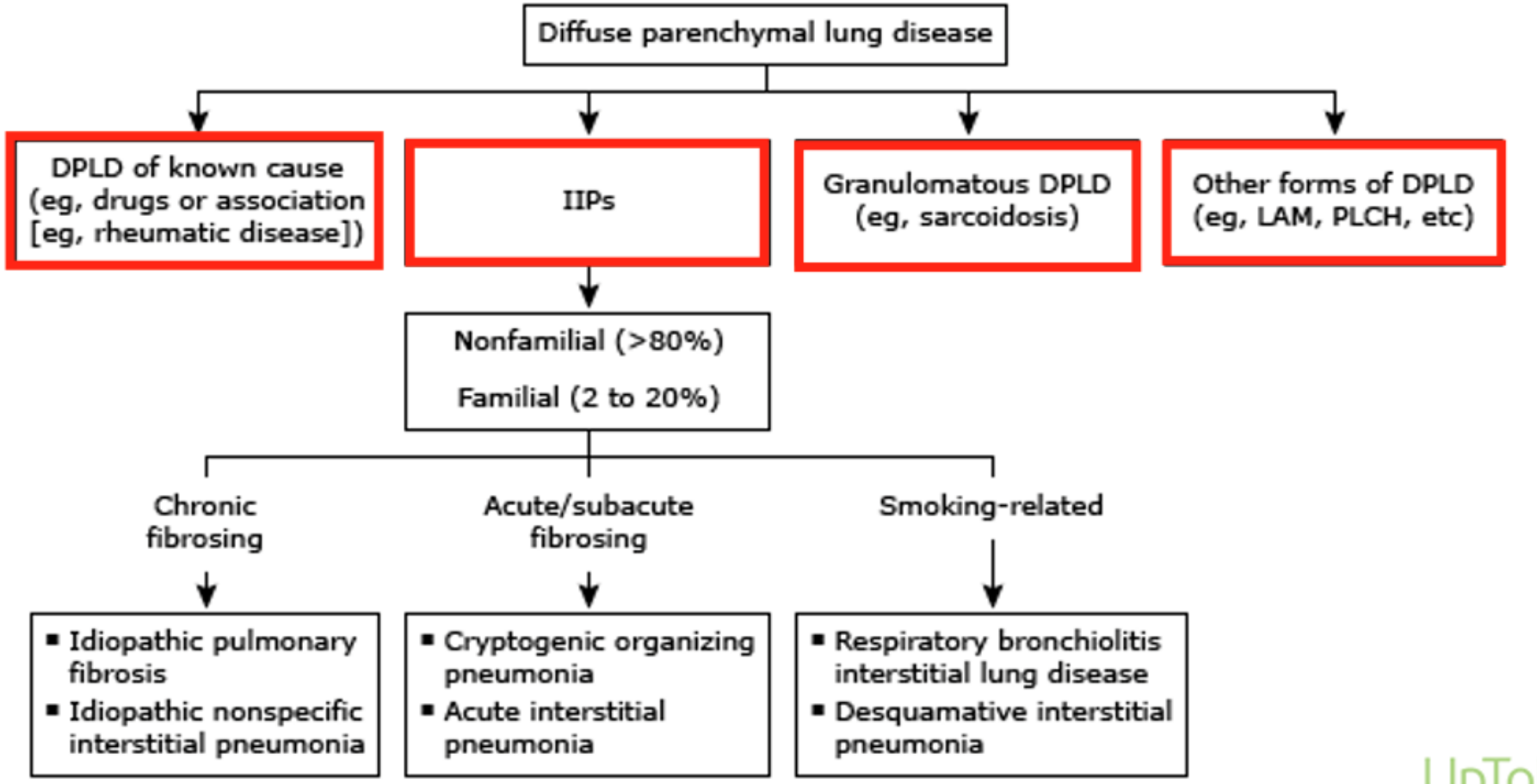
FIBROSIS

Interstitial Lung Disease



ST VINCENT'S HOSPITAL LUNG HEALTH

Diffuse parenchymal lung diseases



UpToDate®

ILD-CTD

- Συχνή και σοβαρή επιπλοκή σε πλείστες CTDs

Atzeni F, Gerardi MC, Barilaro G, et al. Interstitial lung disease in systemic autoimmune rheumatic diseases: a comprehensive review. Expert Rev Clin Immunol. 2018 Jan;14(1):69–82.

- Υψηλότερος επιπολασμός σε SSc και RA

Perelas A, Silver RM, Arrossi AV, et al. Systemic sclerosis-associated interstitial lung disease. Lancet Respir Med. 2020 Mar;8(3):304–320.

Kadura S, Raghu G. Rheumatoid arthritis-interstitial lung disease: manifestations and current concepts in pathogenesis and management. Eur Respir Rev. 2021 Jun;30;30(160):210011.

Cottin and Brown *Respiratory Research* (2019) 20:13
https://doi.org/10.1186/s12931-019-0980-7

Respiratory Research

REVIEW Open Access

Interstitial lung disease associated with systemic sclerosis (SSc-ILD)

Vincent Cottin[1*] and Kevin K. Brown[2]

Abstract

Background: Systemic sclerosis (SSc) is a rare connective tissue disease with a heterogeneous clinical course. Interstitial lung disease (ILD) is a common manifestation of SSc and a leading cause of death.

- 30-60% ILD σε SSc

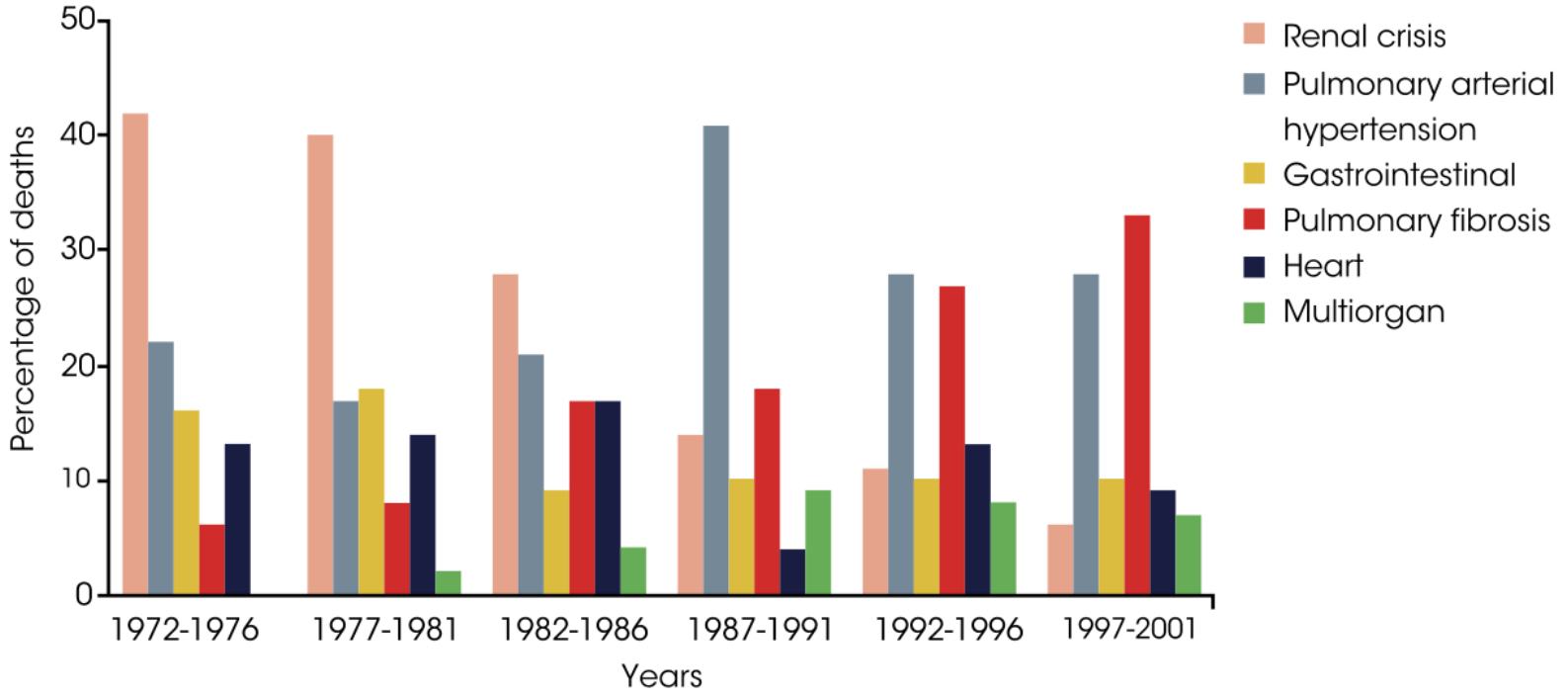
Cottin and Brown *Respiratory Research* (2019) 20:13
https://doi.org/10.1186/s12931-019-0980-7

Respiratory Research

REVIEW Open Access

Interstitial lung disease associated with systemic sclerosis (SSc-ILD)

Vincent Cottin[1*] and Kevin K. Brown[2]



p<0.001 for changes in frequency of death due to renal crisis and pulmonary fibrosis from 1972-1976 to 1997-2001.

Fig. 2 Causes of SSc-related deaths between 1972 and 2001 (Adapted from [21]). Reproduced from Ann Rheum Dis, Steen VD and Medsger TA, Volume 66, Pages 940–44, 2007, with permission from BMJ Publishing Group Ltd.

EUROPEAN RESPIRATORY REVIEW
REVIEW
S. KADURA AND G. RAGHU

Rheumatoid arthritis-interstitial lung disease: manifestations and current concepts in pathogenesis and management

Suha Kadura and Ganesh Raghu

Dept of Medicine, Center for Interstitial Lung Diseases, University of Washington, Seattle, WA, USA.

Corresponding author: Ganesh Raghu (graghu@uw.edu)

Check for updates

Shareable abstract (@ERSpublications)
Rheumatoid arthritis (RA) is a systemic inflammatory disorder, with the most common extra-articular manifestation of RA being lung involvement. RA-ILD is a leading cause of death in RA patients and is associated with significant morbidity and mortality. https://bit.ly/3w6oY4i

Cite this article as: Kadura S, Raghu G. Rheumatoid arthritis-interstitial lung disease: manifestations and current concepts in pathogenesis and management. *Eur Respir Rev* 2021; 30: 210011 [DOI: 10.1183/16000617.0011-2021].

Abstract

Rheumatoid arthritis (RA) is a systemic inflammatory disorder, with the most common extra-articular

- Σε RA 10-29% ILD με συμπτώματα και ευρήματα σε HRCT
- 2η αιτία θανάτου

Kadura S, Raghu G. Rheumatoid arthritis-interstitial lung disease: manifestations and current concepts in pathogenesis and management. Eur Respir Rev. 2021 Jun;30;30(160):210011.

Spagnolo P, Lee JS, Sverzellati N, et al. The lung in rheumatoid arthritis: focus on interstitial lung disease. Arthritis Rheumatol. 2018 Oct;70(10):1544–1554.

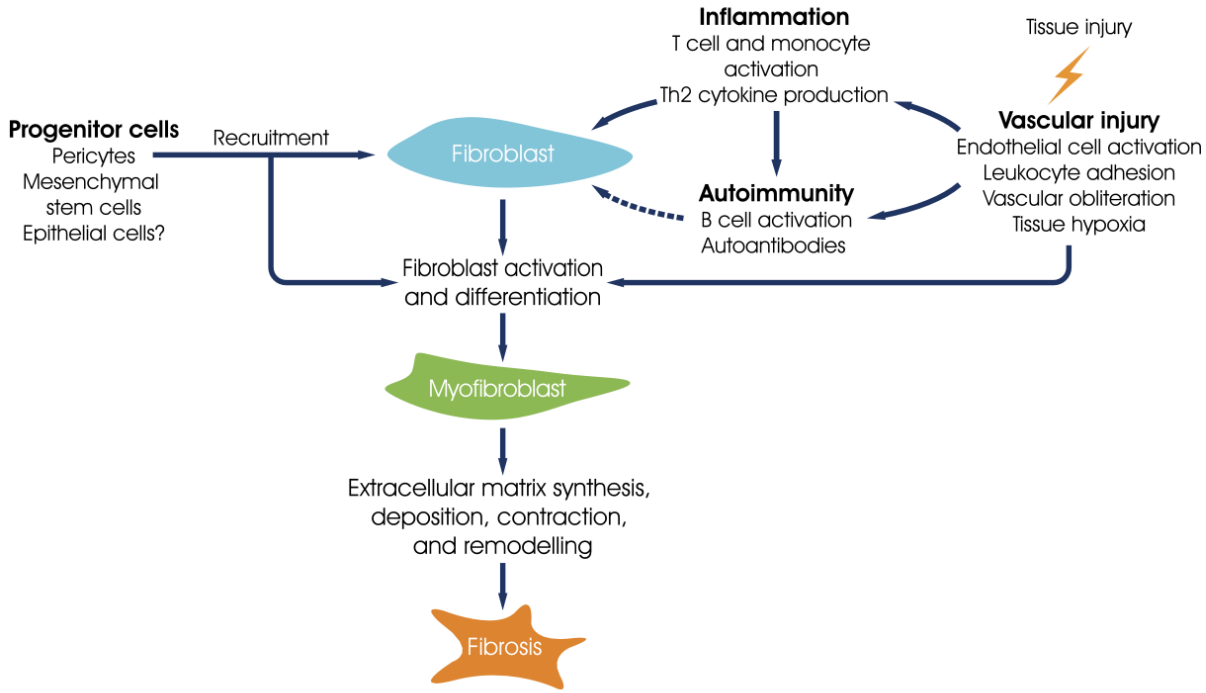


Fig. 1 The pathogenesis of SSc (Adapted from [2]). SSc is initiated by microvascular injury, inducing inflammation, an autoimmune response, and fibroblast activation and differentiation. Activated myofibroblasts perform a series of functions, culminating in excess deposition of extracellular matrix and the development of fibrosis. Republished with permission of The Journal of Clinical Investigation, from Systemic sclerosis: a prototypic multisystem fibrotic disorder, Varga J and Abraham D, Volume No. 117, Edition No. 3, 2007; permission conveyed through Copyright Clearance Center, Inc.

to SSc, and validated with a group of SSc experts. The new criteria were shown to have a sensitivity of 91% and a specificity of 92% for detecting SSc. Skin thickening of

SSc-ILD is defined by the identification of fibrotic features on chest HRCT or standard chest x-ray, generally most pronounced in the lung bases, and/or when

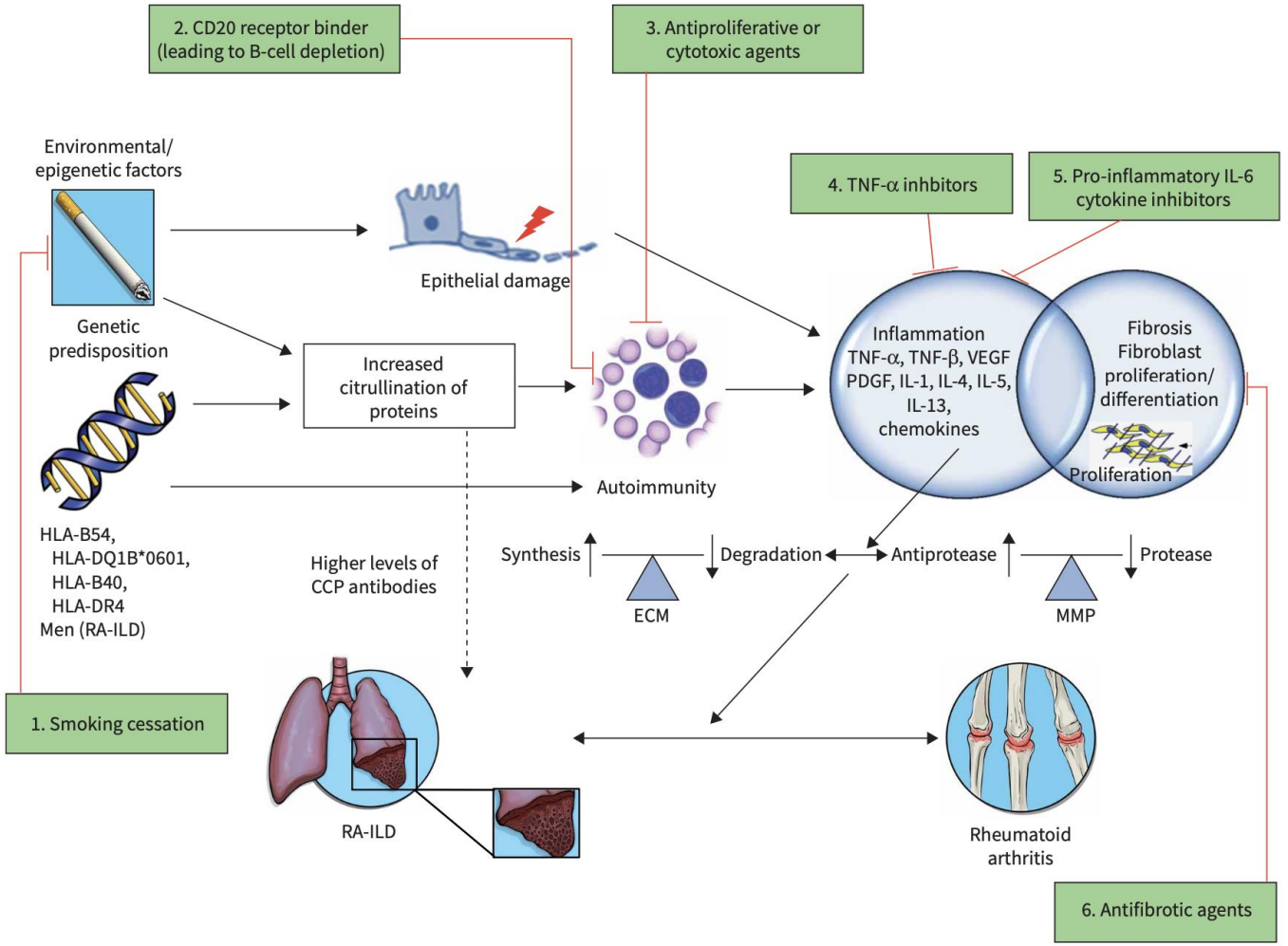


FIGURE 3 Schematic illustration of the concepts in the pathogenesis of rheumatoid arthritis (RA)-associated interstitial lung disease (ILD) with various therapeutic targets. The pathogenesis of RA is thought to involve an interplay between various risk factors (including smoking history, male

ILD-CTD

- Ποικίλη πορεία…
- …➔ Ίνωση → PPF → αναπνευστική ανεπάρκεια → θάνατος

Spagnolo P, Distler O, Ryerson CJ, et al. Mechanisms of progressive fibrosis in connective tissue disease (CTD)-associated interstitial lung diseases (ILDs). Ann Rheum Dis. 2021 Feb;80(2):143–150.

ILD-CTD

- Σημαντική η έγκαιρη διάγνωση
- Ιδίως στην FIBROTIC CTD-ILD & PPF
- Πολύπλοκη ωστόσο
- multidisciplinary approach

Wells A, Devaraj A, Renzoni EA, et al. Multidisciplinary evaluation in patients with lung disease associated with connective tissue disease. Semin Respir Crit Care Med. 2019 Apr;40(2):184–193.

Cottin V, Hirani NA, Hotchkin DL, et al. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. Eur Respir Rev. 2018 Dec 31;27(150):180076.

ILD-CTD

- Εξατομικευμένη,ολοκληρωμένη και έγκαιρη θεραπεία
- Έλεγχος αυτοανοσίας και φλεγμονής
- Πρόληψη εξέλιξης της ίνωσης

Cottin V, Hirani NA, Hotchkin DL, et al. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. Eur Respir Rev. 2018 Dec 31;27(150):180076.

Wells A, Devaraj A, Renzoni EA, et al. Multidisciplinary evaluation in patients with lung disease associated with connective tissue disease. Semin Respir Crit Care Med. 2019 Apr;40(2):184–193.

ΚΛΙΝΙΚΉ ΥΠΟΨΙΑ

SCREENING

ΔΙΆΓΝΩΣΗ FIBROTIC CTD-ILD

- ILD…επιπλοκή μιας CTD ή
- ILD…αρχική εκδήλωση
- Υποκλινική για έτη (παρότι προχωρημένη) ιδίως στην RA !!!
- In patients with new-onset ILD, multidisciplinary assessment allows a specific diagnosis to be established in up to 80.5% of cases

Sebastiani M, Faverio P, Manfredi A, et al. Interstitial pneumonia with autoimmune features: why rheumatologist-pulmonologist collaboration is essential. Biomedicines. 2020 Dec 26;9(1):17.

Kadura S, Raghu G. Rheumatoid arthritis-interstitial lung disease: manifestations and current concepts in pathogenesis and management. Eur Respir Rev. 2021 Jun;30;30(160):210011.

Wells A, Devaraj A, Renzoni EA, et al. Multidisciplinary evaluation in patients with lung disease associated with connective tissue disease. Semin Respir Crit Care Med. 2019 Apr;40(2):184–193.

ΣΗΜΕΙΑ & ΣΥΜΠΤΩΜΑΤΑ

- Ξηρός μη παραγωγικός βήχας
- Δύσπνοια «προσπάθειας» &
- Τρίζοντες βάσεων («Velcro-type» crackles)
- (Συσχετίζονται με ίνωση)

Kondoh Y, Makino S, Ogura T, et al. 2020 guide for the diagnosis and treatment of interstitial lung disease associated with connective tissue disease. Respir Investig. 2021 Nov;59(6):709–740.

ILD-CTD

(Επί υποψίας…)

- Α/α θώρακος
- **PFTs** (TLC,FVC,DLCO)
- **HRCT θώρακος**

Kondoh Y, Makino S, Ogura T, et al. 2020 guide for the diagnosis and treatment of interstitial lung disease associated with connective tissue disease. Respir Investig. 2021 Nov;59(6):709–740.

HRCT ΘΩΡΑΚΟΣ & CTD-ILD

- Επιβεβαιώνει την διάγνωση
- (Συνήθως περιττή η βιοψία ή το BAL)
- Ποσοτικοποιεί τις βλάβες
- Τις ταυτοποιεί (UIP vs non-UIP)
- Εξέλιξη της νόσου (follow up)

Giménez Palleiro A, Franquet T. Radiological patterns in interstitial lung disease. Semin Fund Esp Reumatol. 2013;14(4):97–105.

Table 2. Radiological patterns and signs of fibrosis on chest HRCT [40].

Radiological patterns	Radiological signs
Linear-reticular pattern	• Thickening of the intralobular septa: produces linear images of several centimeters in length. • Intralobular interstitial thickening: presence of a fine reticular meshwork extending from the peribronchovascular structures of the center of the lobule to the interlobular septa, with a 'spider web' morphology.
Nodular pattern	• Small nodules: > 2 mm • Miliary nodules: 1–2 mm
Ground-glass pattern	• Faint increase in lung density often geographically distributed, which does not obliterate adjacent vascular structures
Cystic pattern	• Thin-walled rounded images (generally 1 to 3 mm thick), well-defined and with air inside them
Condensation or consolidation pattern	• Increased pulmonary attenuation associated with blurring of adjacent vessel contours
Usual interstitial pneumonia (UIP)	• Subpleural, basal and symmetrical localization; occasionally diffuse • Apico-basal progression' • Ground-glass' (minimal)Reticulation, bronchiectasis and traction bronchiectasis' • Honeycombing' pattern
Nonspecific interstitial pneumonia (NSIP) Nonspecific interstitial pneumonia (NSIP) fibrotic*	• Variable involvement (central and peripheral) • Preference in inferior lobes • Patchy 'ground-glass' opacities associated with linear, reticular and micronodular images • Traction bronchiectasis/bronchilectasis* • Infrequent 'honeycombing' pattern

*Traction bronchiectasis/bronchilectasis refers to NSIP fibrotic.

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*Traction bronchiectasis/bronchilectasis refers to NSIP fibrotic.

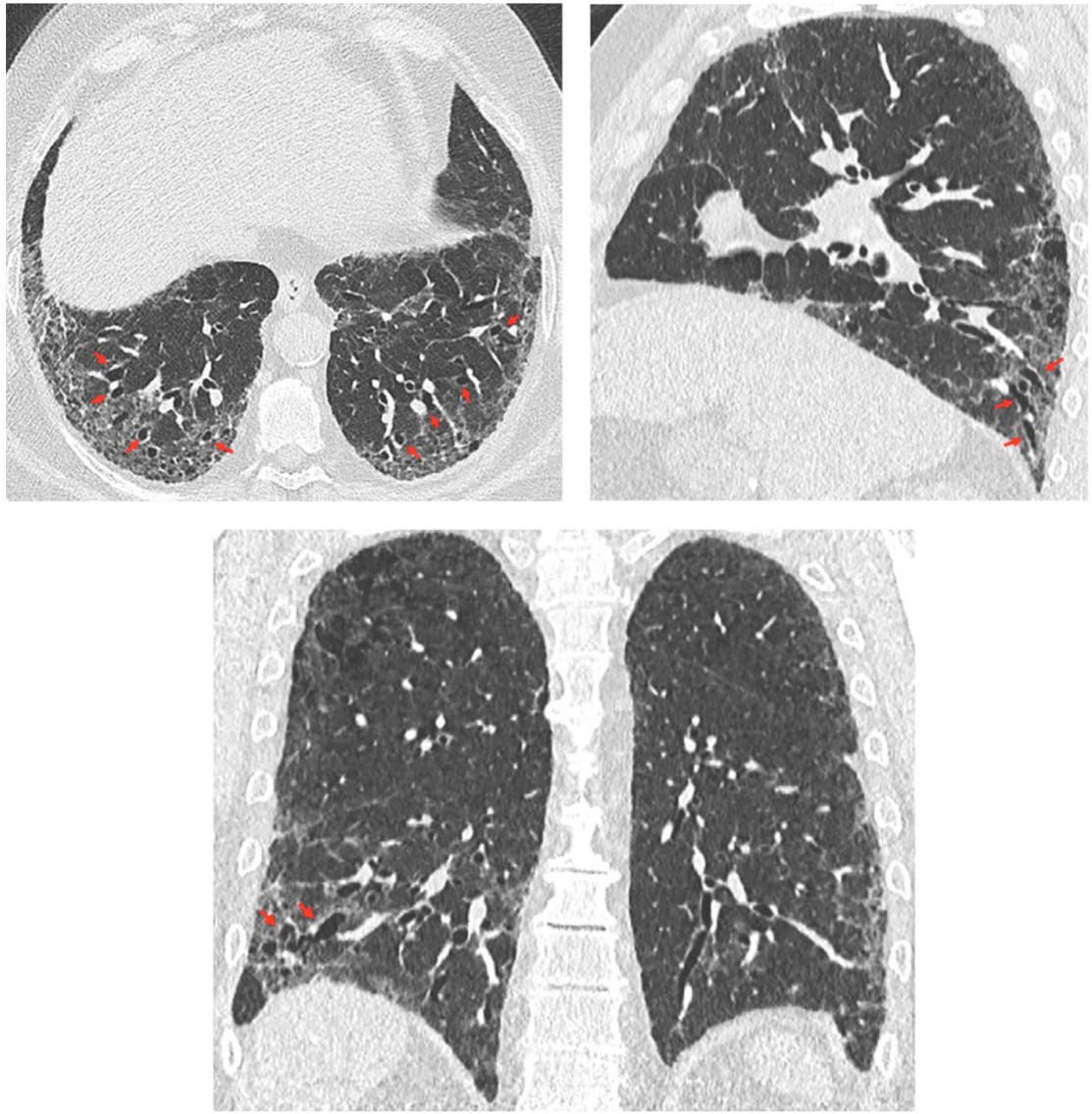
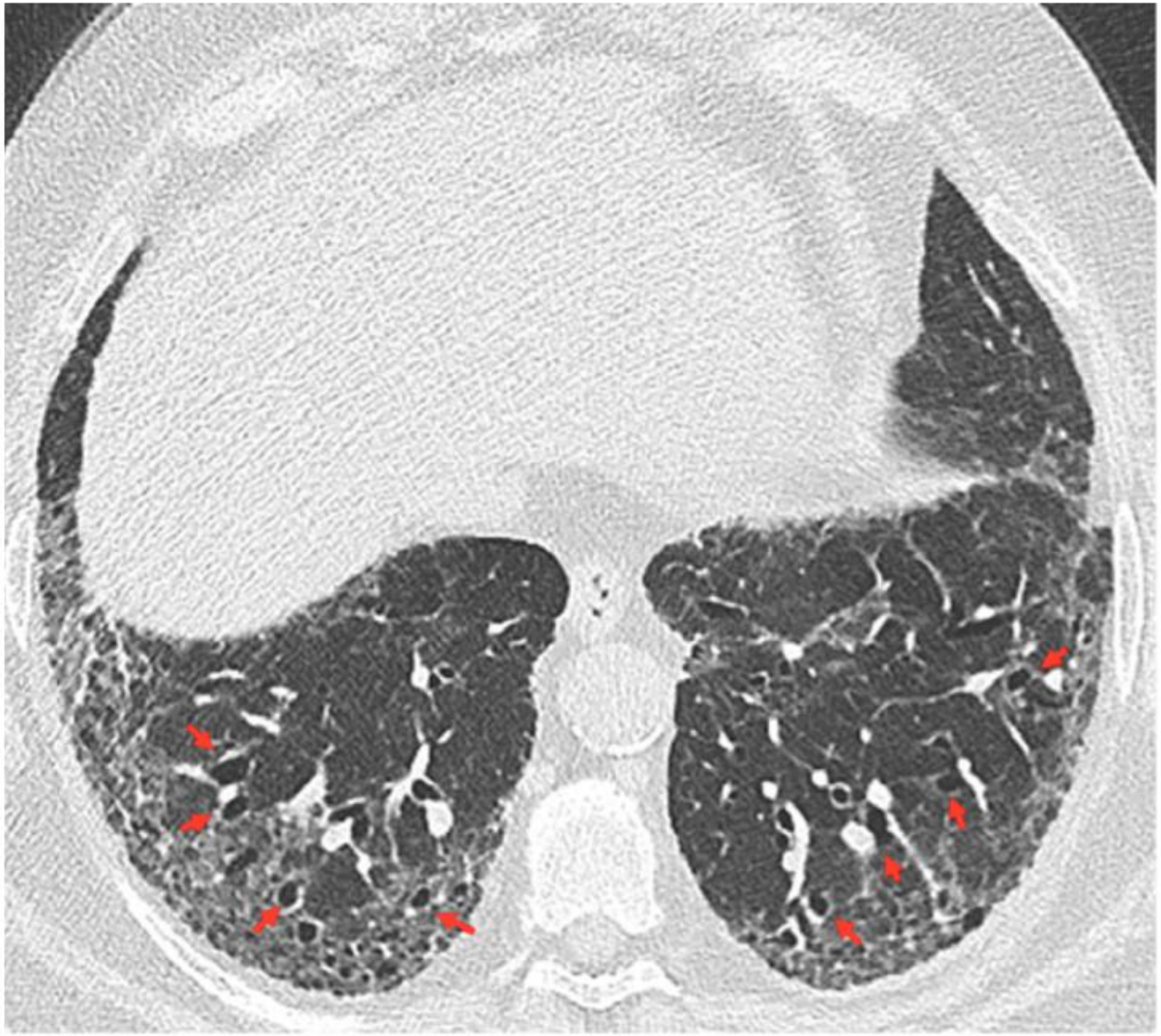
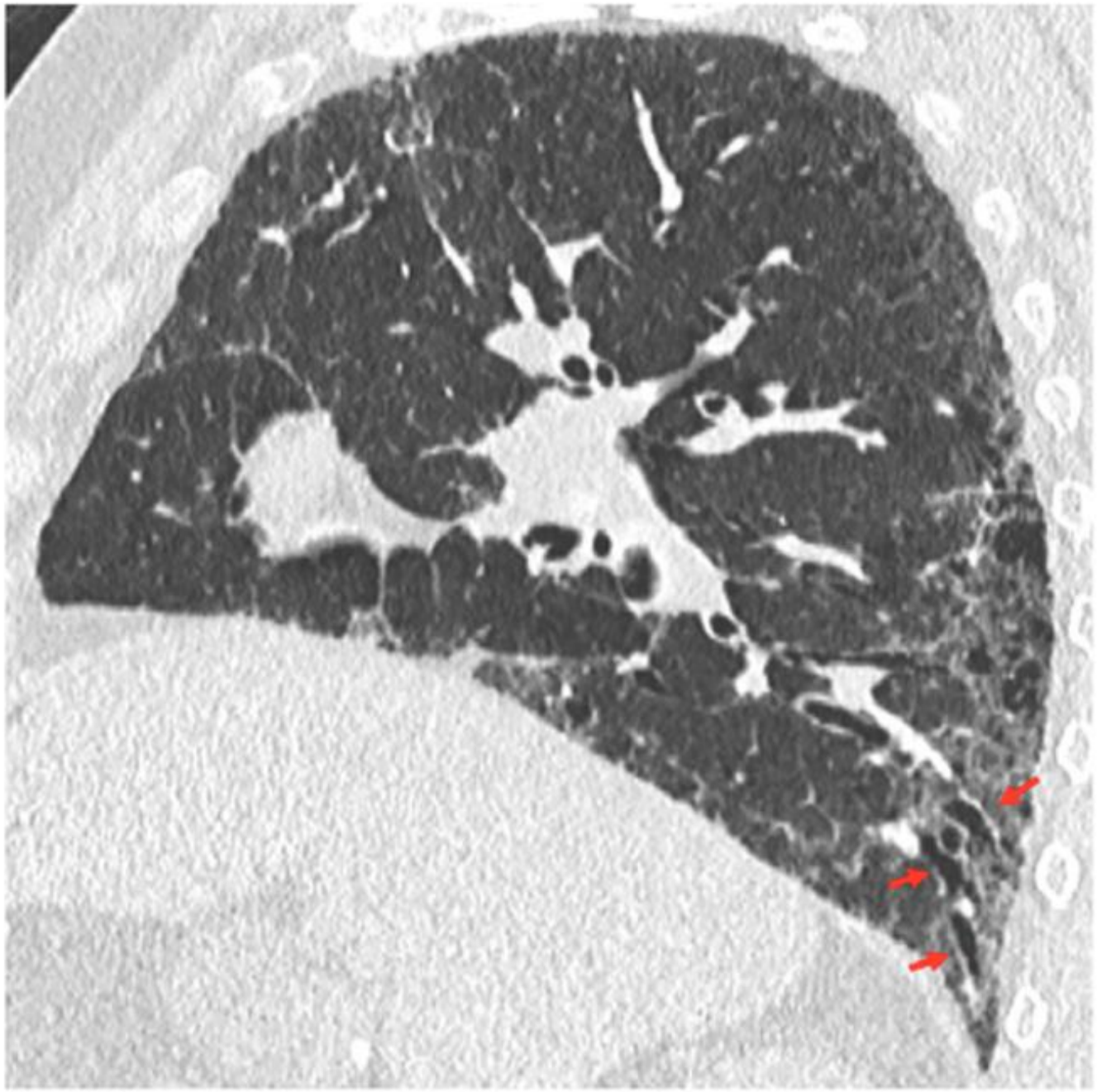
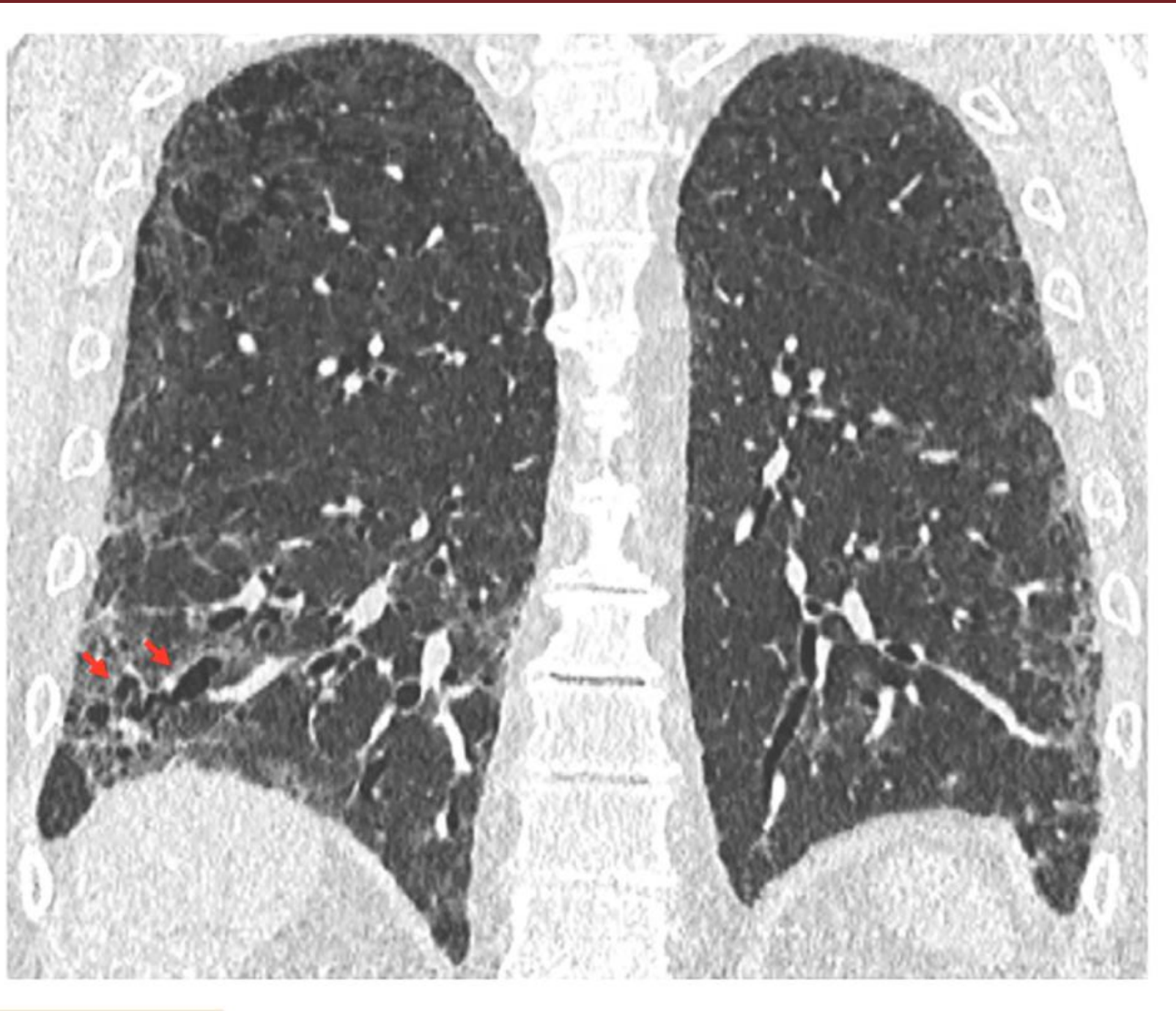


Figure 1. Traction bronchiectasis/bronchiolectasis. Axial, sagittal, and coronal computed tomography images show subpleural-predominant, lower lung–predominant reticular abnormality with traction bronchiectasis (arrows). Traction bronchiectasis/bronchiolectasis represents irregular bronchial and/or bronchiolar dilatation caused by surrounding retractile fibrosis; distorted airways are thus identified in a background of reticulation and/or ground-glass attenuation. On contiguous high-resolution computed tomography sections, the dilated bronchi or bronchioles can be tracked back toward more central bronchi. The pattern in this patient represents the probable usual interstitial pneumonia pattern.







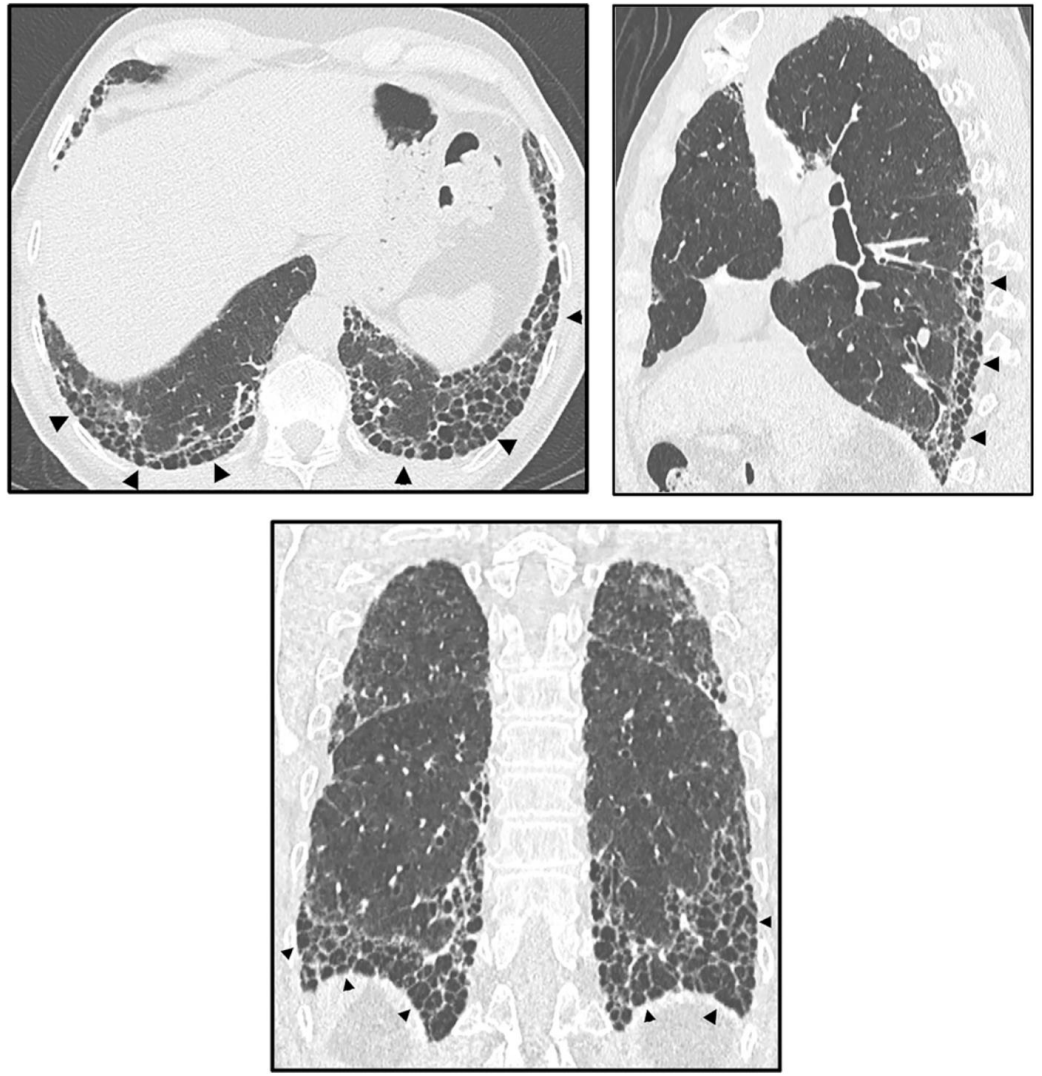
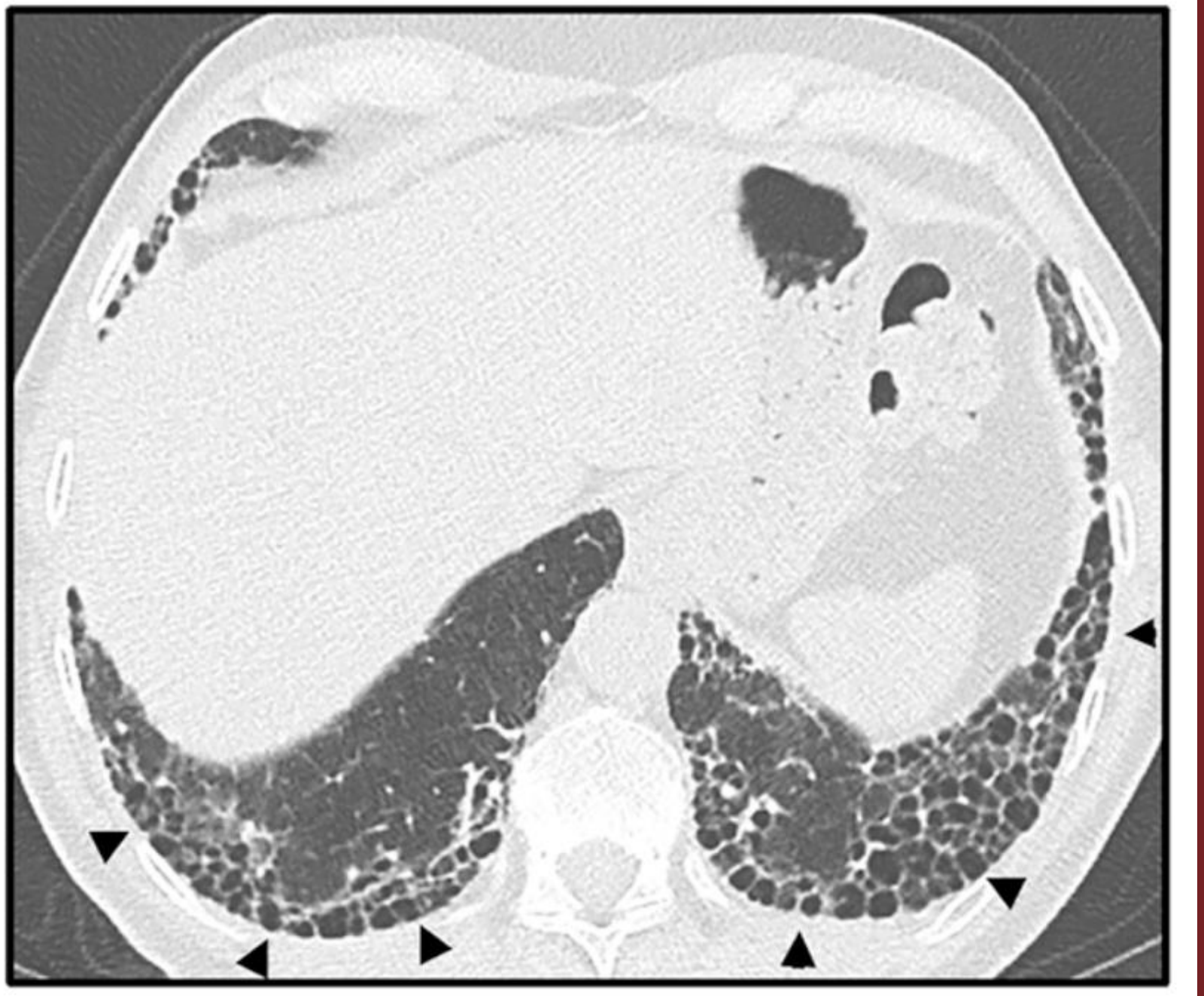
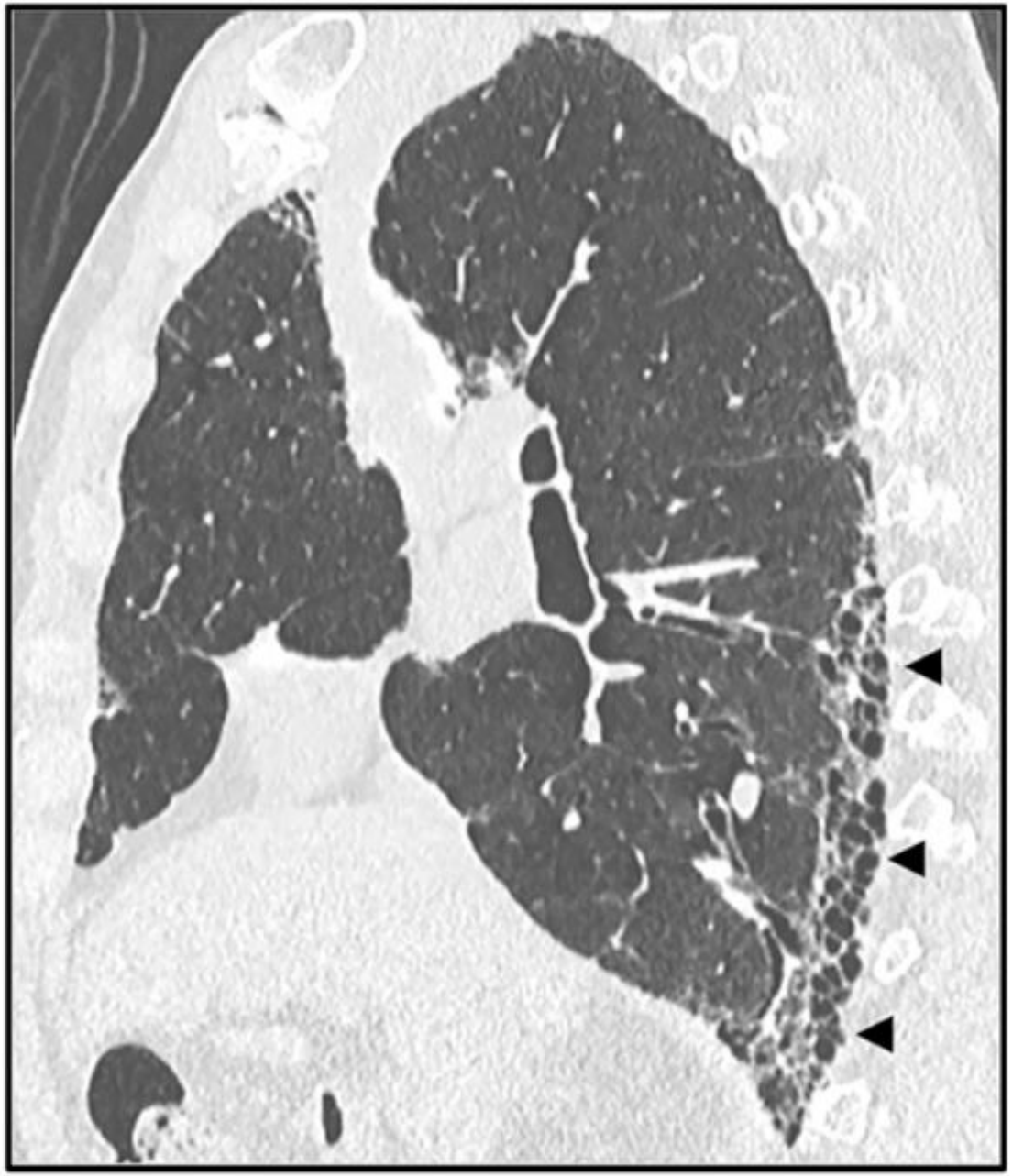
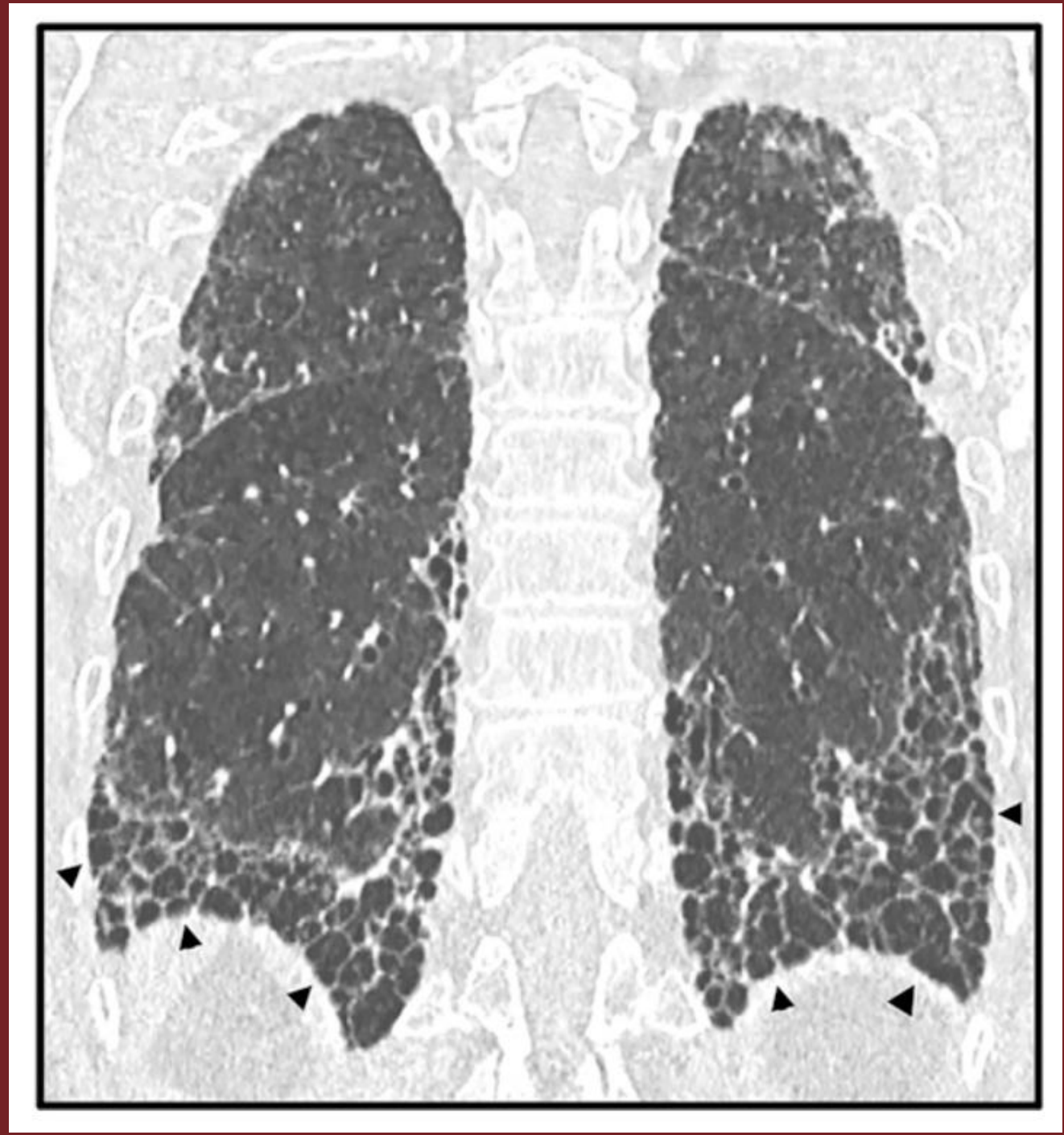


Figure 2. Honeycombing. Axial, sagittal, and coronal computed tomography images show subpleural-predominant, lower lung–predominant reticular abnormality with honeycombing (arrowheads). Honeycombing is defined by clustered, thick-walled, cystic spaces of similar diameters, measuring between 3 and 10 mm but up to 2.5 cm in size. The size and number of cysts often increase as the disease progresses. Often described in the literature as being layered, a single layer of subpleural cysts is also a manifestation of honeycombing. Honeycombing is an essential computed tomography criterion for typical ("definite") usual interstitial pneumonia–idiopathic pulmonary fibrosis pattern when seen with a basal and peripheral predominance. In this pattern, honeycombing is usually associated with traction bronchiolectasis and a varying degree of ground-glass attenuation.







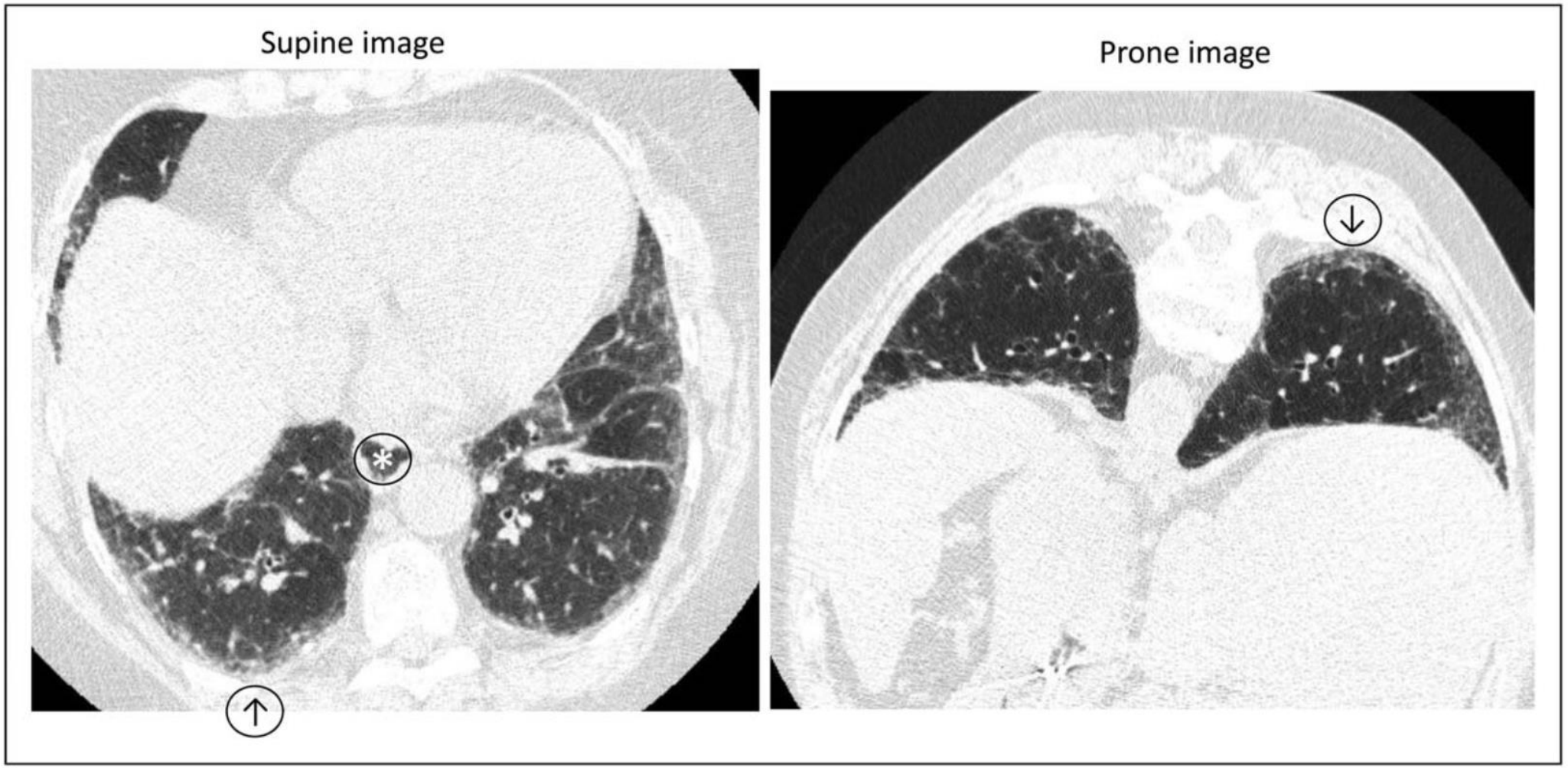


FIGURE 1. High-resolution CT in systemic sclerosis-interstitial lung disease. Inspiratory and prone HRCT demonstrating minimal reticulation, subpleural ground glass opacity (↑) that persists on prone imaging (↓) suggestive of interstitial lung abnormalities and an early fibrotic lung disease. No honeycombing or traction bronchiectasis. *Note slightly dilated esophagus. CT, computed tomography; HRCT, high-resolution CT.

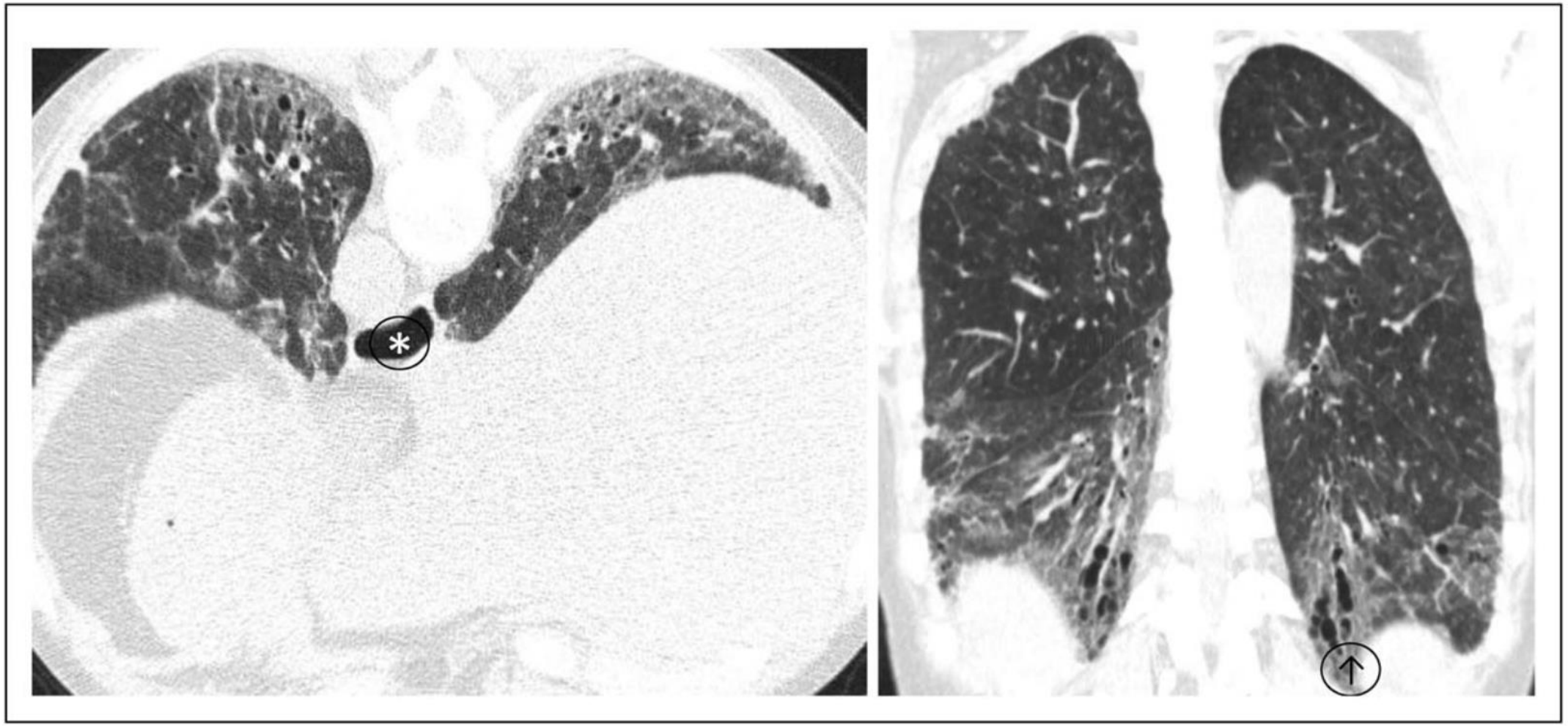


FIGURE 3. Nonspecific interstitial pneumonitis pattern. Lower lung predominant homogeneously distributed ground glass opacity, reticulation, traction bronchiectasis (↑) and dilated esophagus (*) without honeycombing. Appearances are compatible with scleroderma-related interstitial lung disease (NSIP pattern).

CTD-ILD MONITORING

- PFTs
- 6MWT
- QoL
- …HRCT
- …U/S καρδίας (doppler)

Atzeni F, Gerardi MC, Barilaro G, et al. Interstitial lung disease in systemic autoimmune rheumatic diseases: a comprehensive review. Expert Rev Clin Immunol. 2018 Jan;14(1):69–82.

SSc-ILD

- 30-60% Pts με SSC
- PPF κύρια αιτία θανάτου
- κυρίως NSIP

Perelas A, Silver RM, Arrossi AV, et al. Systemic sclerosis-associated interstitial lung disease. Lancet Respir Med. 2020 Mar;8(3):304–320.

Castelino FV, Dellaripa PF. Recent progress in systemic sclerosis-interstitial lung disease. Curr Opin Rheumatol. 2018 Nov;30(6):570–575.

SSc-ILD screening

- HRCT (άμα τη διαγνώσει!!! και ετησίως!!!)
- PFTs (αρχικά…ίσως false negative)
- PFTs (κάθε 3-6 μήνες)

Hoffmann-Vold AM, 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 Feb;80(2):219–227.

Suliman YA, Dobrota R, Huscher D, et al. Brief report: pulmonary function tests: high rate of false-negative results in the early detection and screening of scleroderma-related interstitial lung disease. Arthritis Rheumatol. 2015 Dec;67(12):3256–3261.

RA-ILD

- 10-29% Pts με RA
- 2η αιτία θανάτου
- Κυρίως UIP

. Kadura S, Raghu G. Rheumatoid arthritis-interstitial lung disease: manifestations and current concepts in pathogenesis and management. Eur Respir Rev. 2021 Jun;30;30(160):210011.

RA-ILD screening ?

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Expert Review of Respiratory Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierx20

Management of progressive pulmonary fibrosis associated with connective tissue disease

María Molina-Molina, Iván Castellví, Claudia Valenzuela, José Ramirez, José Antonio Rodríguez Portal, Tomás Franquet & Javier Narváez

To cite this article: María Molina-Molina, Iván Castellví, Claudia Valenzuela, José Ramirez, José Antonio Rodríguez Portal, Tomás Franquet & Javier Narváez (2022) Management of progressive pulmonary fibrosis associated with connective tissue disease, Expert Review of Respiratory Medicine, 16:7, 765-774, DOI: 10.1080/17476348.2022.2107508

To link to this article: https://doi.org/10.1080/17476348.2022.2107508

Published online: 05 Aug 2022.

RA-ILD screening

40].

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bular septa,

Table 3. SER-SEPAR proposed screening criteria for diffuse interstitial lung disease in patients diagnosed with rheumatoid arthritis [44].

The following 3 clinical situations are to be screened for ILD:

(1) Patients with respiratory symptoms (cough and/or dyspnea) of more than 3 months of evolution.

(2) Patients in whom velcro-type crackles are detected in respiratory auscultation, even if they are asymptomatic.

(3) In patients without respiratory symptoms and with normal respiratory auscultation, screening will be done according to the score obtained based on the number of risk factors present for the development of this complication.

Any patient scoring ≥ 5 points will be considered eligible for screening:

Set of variables and proposed score for each of the overall score	**Score**
• Age ≥ 60 years	2
• Male sex	1
• History of smoking (active smoker or former smoker)	
◦ ≤ 20 packs/year: 2 points	2
◦ > 20 packs/year: 3 points	3
• Duration of disease > 5 years	1
• Persistently moderately-high activity: Average DAS28-VSG > 3.2 since disease diagnosis in baseline RA (time since diagnosis ≤ 12 months) or DAS28-VSG > 3.2 for a minimum of 6 months in established RA	1
• Serology (only the criterion with the highest weighting is counted toward the total score)	
◦ RF positive > 3 times above ULN	1
◦ ACPA positive ≤ 3 times the ULN	2
◦ ACPA positive > 3 times the ULN	3
• Family history of ILD	1

ACPA: anti-cyclic citrullinated peptide antibodies; ILD: interstitial lung disease; RA: rheumatoid arthritis; RF: rheumatoid factor; SEPAR: Spanish Society of Pneumology and Thoracic Surgery; SER: Spanish Society of Rheumatology; ULN: upper limit of normal.

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2023 American College of Rheumatology (ACR) Guideline for the Screening and Monitoring of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Disease

Guideline Summary

This guideline was developed to provide recommendations for the screening of Interstitial Lung Disease (ILD) in people with Systemic Autoimmune Rheumatic Diseases (SARDs) [Rheumatoid Arthritis (RA), Systemic Sclerosis (SSc), Idiopathic Inflammatory Myositis (IIM including polymyositis, dermatomyositis, antisynthetase syndrome, immune-mediated necrotizing myopathy), Mixed Connective Tissue Disease (MCTD), and Sjögren's Disease (SjD)] associated with the greatest risk of ILD, and for monitoring for ILD progression. These recommendations facilitate rheumatologists' identification of ILD among people with SARDs and will assist in optimizing the co-management of people with SARDs-associated ILD by rheumatologists and pulmonologists.

This summary was approved by the ACR Board of Directors on 12 August 2023. These recommendations are included in a full manuscript, pending peer review, which was submitted for publication in Arthritis & Rheumatology and Arthritis Care and Research.

Table 1. Summary of recommendations for screening of SARD-ILD

Summary of recommendations
For people with SARDs at increased risk of developing ILD, we **conditionally** recommend screening with PFTs.
For people with SARDs at increased risk of developing ILD, we **conditionally** recommend screening with HRCT of the chest.
For people with SARDs at increased risk of developing ILD, we **conditionally** recommend screening with HRCT chest and PFTs over PFTs alone.
For people with SARDs at increased risk of developing ILD, we **conditionally** recommend *against* screening with 6MWD.
For people with SARDs at increased risk of developing ILD, we **conditionally** recommend *against* screening with chest radiography.
For people with SARDs at increased risk of developing ILD, we **conditionally** recommend *against* screening with ambulatory desaturation testing.
For people with SARDs at increased risk of developing ILD, we **conditionally** recommend *against* screening with bronchoscopy.
For people with SARDs at increased risk of developing ILD, we **strongly** recommend *against* screening with surgical lung biopsy.

Table 2. Summary of Recommendations for Monitoring for ILD Progression

Summary of recommendations
For people with SARDs-ILD, we **conditionally** recommend monitoring with PFTs.
For people with SARDs-ILD, we **conditionally** recommend monitoring with HRCT chest.
For people with SARDs-ILD, we **conditionally** recommend monitoring with PFTs and HRCT chest over PFTs alone.
For people with SARDs-ILD, we **conditionally** recommend monitoring with ambulatory desaturation testing.
For people with SARDs-ILD, we **conditionally** recommend *against* monitoring with chest radiography.
For people with SARDs-ILD, we **conditionally** recommend *against* monitoring with 6MWD.
For people with SARDs-ILD, we **conditionally** recommend *against* monitoring with bronchoscopy.
For people with IIM-ILD and SSc-ILD, we suggest PFTs for monitoring every 3-6 months rather than either shorter or longer intervals, for the first year, then less frequently once stable.
For people with RA-ILD, SjD-ILD, and MCTD-ILD, we suggest PFTs for monitoring every 3-12 months rather than shorter or longer intervals, for the first year, then less frequently once stable.
For people with SARDs-ILD, we do not provide guidance about frequency of routine HRCT chest for monitoring ILD but suggest HRCT when clinically indicated.
For people with SARDs-ILD, we suggest assessment for ambulatory desaturation every 3-12 months rather than at shorter or longer intervals.

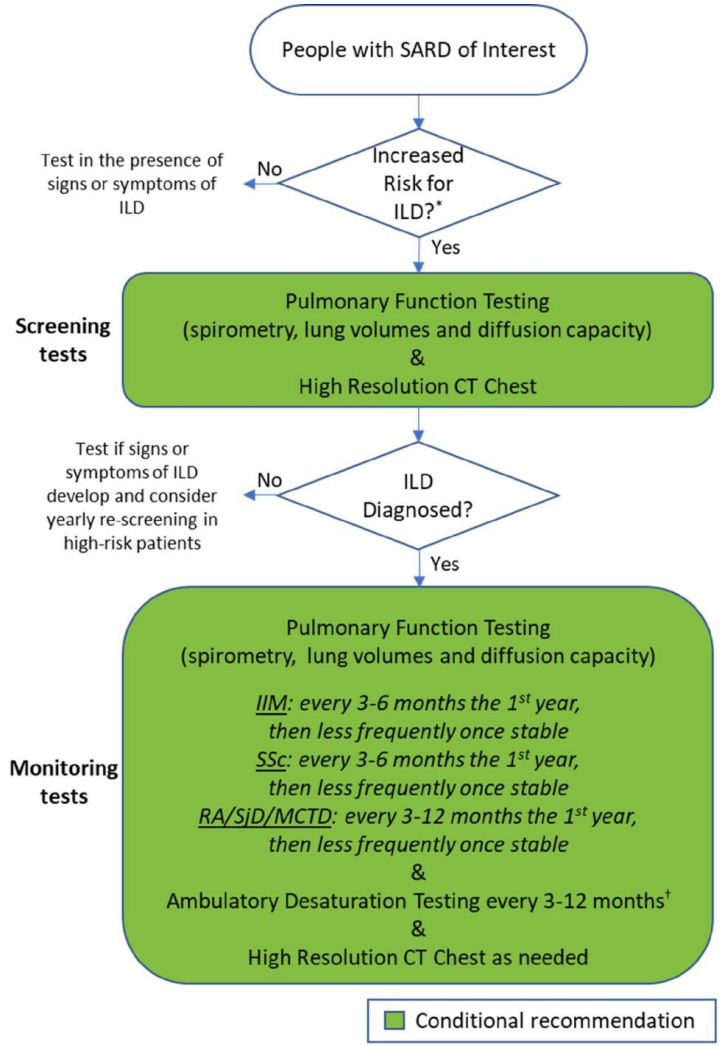


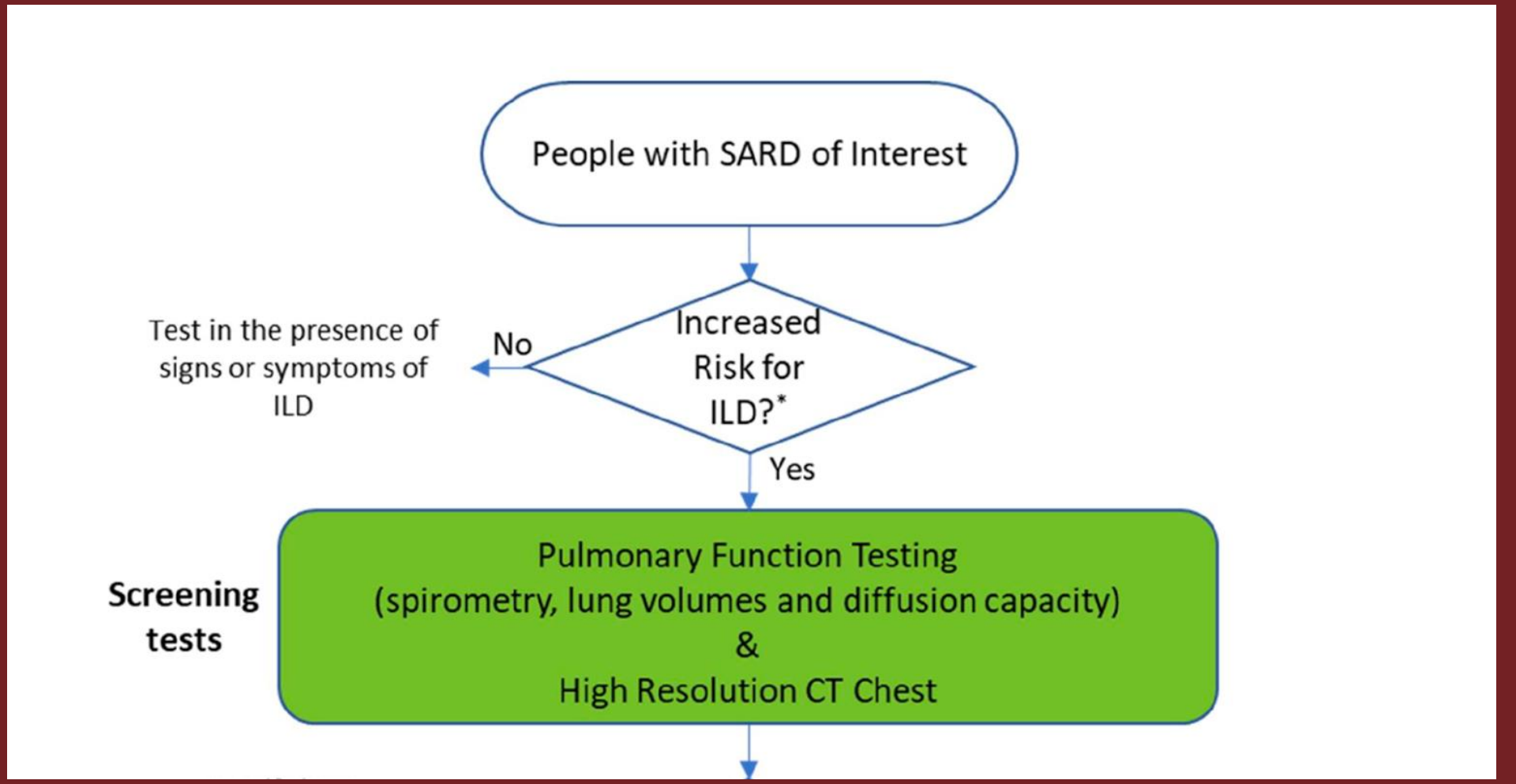
Figure 1: Recommendations for ILD Screening and Monitoring

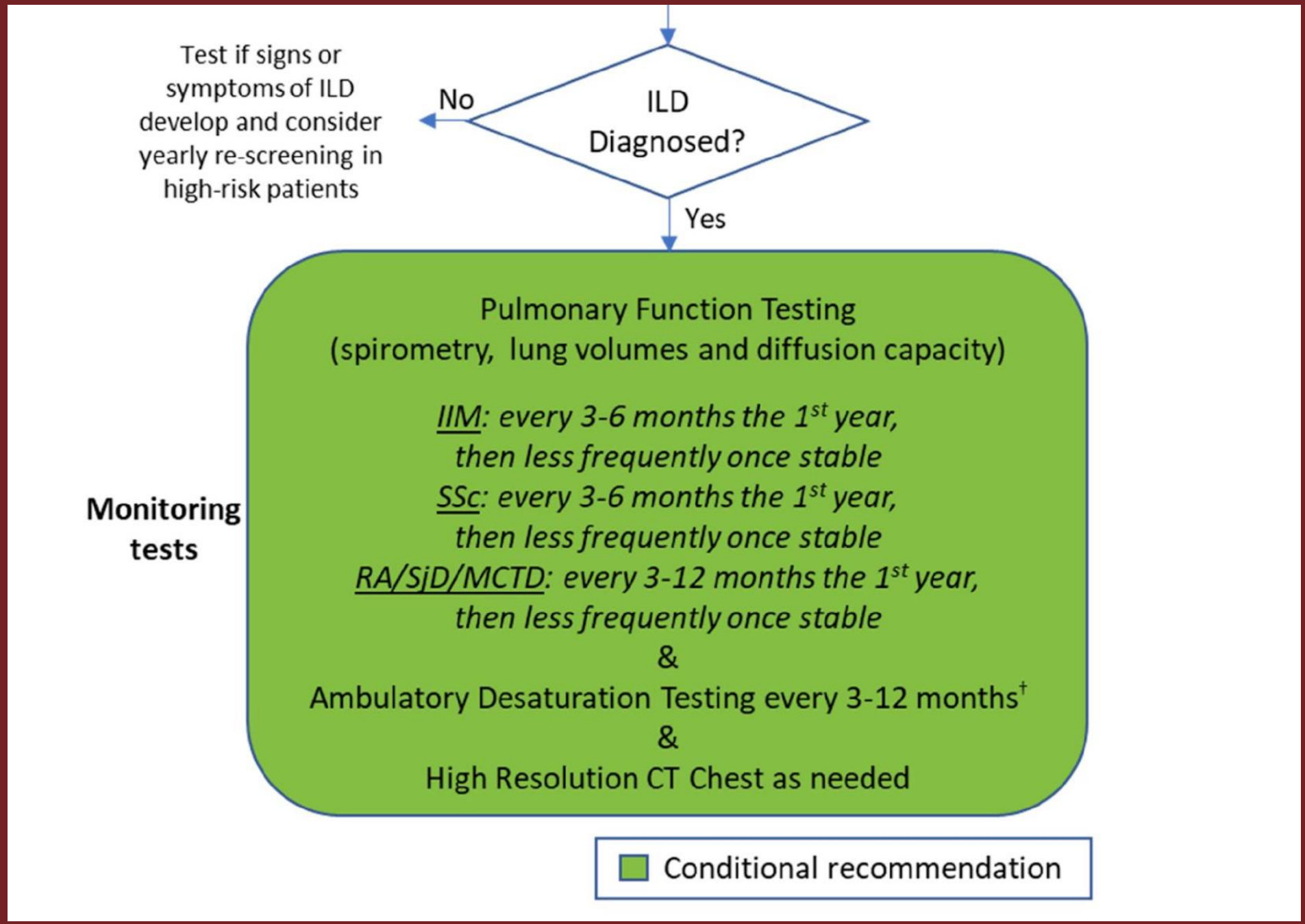
* See Table 1 for risk factors for interstitial lung disease

† Ambulatory desaturation can be done during a routine office visit or as part of 6-minute walk testing

SARD = systemic autoimmune rheumatic disease; ILD = interstitial lung disease; CT = computed tomography; IIM = idiopathic inflammatory myopathy; SSc = systemic sclerosis; RA = rheumatoid arthritis; SjS = Sjögren's disease, MCTD = mixed connective tissue disease

Note. Frequency of monitoring in italics are suggestions to assist application of the recommendations.


People with SARD of Interest
Increased Risk for ILD?*
No
Test in the presence of signs or symptoms of ILD
Yes
Screening tests
Pulmonary Function Testing
(spirometry, lung volumes and diffusion capacity)
&
High Resolution CT Chest


Test if signs or symptoms of ILD develop and consider yearly re-screening in high-risk patients
No
ILD Diagnosed?
Yes
Monitoring tests
Pulmonary Function Testing
(spirometry, lung volumes and diffusion capacity)
IIM: every 3-6 months the 1st year, then less frequently once stable
SSc: every 3-6 months the 1st year, then less frequently once stable
RA/SjD/MCTD: every 3-12 months the 1st year, then less frequently once stable
&
Ambulatory Desaturation Testing every 3-12 months†
&
High Resolution CT Chest as needed
Conditional recommendation

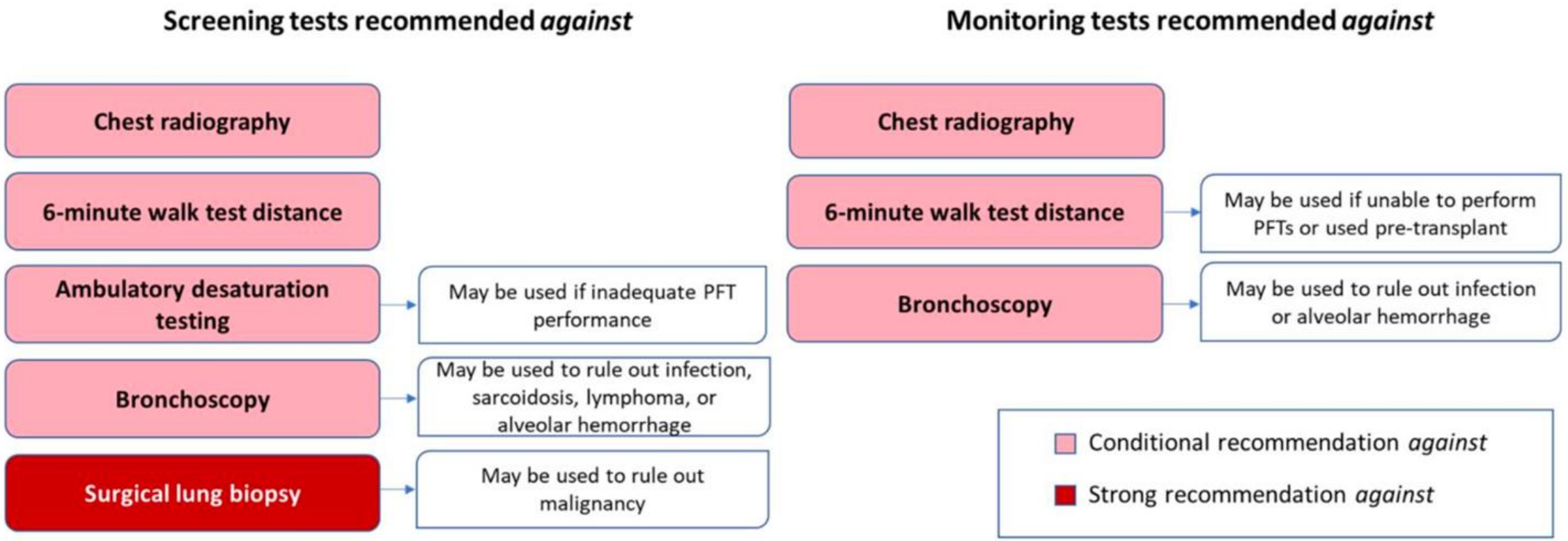


Figure 2: Interstitial lung disease screening and monitoring tests recommended *against*. Tests shown are recommended against for routine use, although examples are provided when these tests may have utility for assessing patients or ruling out other conditions.
PFT = pulmonary function test

- ILD πρώτη εκδήλωση σε CTDς
- 10-14% (στην RA)
- Περιοδικές επανεκτιμήσεις
- Κλινικά & εργαστηριακά

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 Oct;76 (10):1700–1706.

Table 5. Panel of antibodies to be requested in the evaluation of an ILD to assess its possible association with a CTD.

In the initial evaluation of all patients

- Antinuclear antibodies (detection by indirect immunofluorescence)
- Rheumatoid factor and anti-cyclic citrullinated peptide antibodies (ACPA)

If rheumatoid arthritis is suspected

- Anti-citrullinated peptide antibody (ACPA)
- Rheumatoid factor

If systemic sclerosis is suspected

- Anti-Scl70/topoisomerase I
- Anti-centromere
- Anti-RNA polymerase III
- Anti-U1RNP
- Anti-NOR 90
- Anti-U3RNP (anti-fibrillarin)
- Anti-Th/To
- Anti-PM/Scl
- Anti-Ku

If inflammatory myopathy is suspected

- Anti-synthetase (Jo-1, PL-7, PL-12, EJ, OJ and KS)
- Anti-MDA5
- Anti-Mi-2
- Anti-NXP2
- Anti-TIF1-γ
- Anti-SRP
- Anti-HMG-CoA reductase
- Anti-SAE
- Anti-U1RNP
- Anti-PM/Scl75
- Anti-PM/Scl100
- Anti-Ku

If primary Sjögren's syndrome is suspected

- Anti-SSA/Ro60
- Anti-TRIM21/Ro52
- Anti-SSB/La
- Rheumatoid factor

If ANCA vasculitis is suspected*

- Anti-neutrophil cytoplasm antibody (ANCA)

- approximately 10–25% of cases that are initially idiopathic evolve into a CTD by clinical onset
- or autoimmunity positivity (although there is no consensus on what should be the frequency of serial testing for CTD)

Hu Y, Wang LS, Wei YR, et al. Clinical characteristics of connective tissue disease-associated interstitial lung disease in 1,044 Chinese patients. Chest. 2016 Jan;149(1):201–208.

Kagiyama N, Takayanagi N, Kanauchi T, et al. Antineutrophil cytoplasmic antibody-positive conversion and microscopic polyangiitis development in patients with idiopathic pulmonary fibrosis. BMJ Open Respir Res. 2015;2(1):e000058.

PROGRESSIVE

PULMONARY

FIBROSIS

(PPF)

Κατάσταση !!! Όχι νόσος !!!

REVIEW
PROGRESSIVE-FIBROSING ILD

Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases

Vincent Cottin[1,11], Nikhil A. Hirani[2], David L. Hotchkin[3], Anoop M. Nambiar[4], Takashi Ogura[5], María Otaola[6], Dirk Skowasch[7], Jong Sun Park[8], Hataya K. Poonyagariyagorn[3], Wim Wuyts[9] and Athol U. Wells[10,11]

Affiliations: [1]Louis Pradel Hospital, Reference Center for Rare Pulmonary Diseases, Hospices Civils de Lyon, UMR 754, Université Claude Bernard Lyon 1, Lyon, France. [2]Edinburgh Lung Fibrosis Clinic and MRC Centre for Inflammation Research, The Queen's Medical Research Centre, The University of Edinburgh, Edinburgh, UK. [3]Division of Pulmonary and Critical Care Medicine, Oregon Clinic, Portland, OR, USA. [4]Division of Pulmonary and Critical Care Medicine, Dept of Medicine, University of Texas Health Science Center San Antonio and the South Texas Veterans Health Care System, San Antonio, TX, USA. [5]Kanagawa Cardiovascular and Respiratory Center, Kanagawa, Japan. [6]Fundación FUNEF, Instituto de Rehabilitacion Psicofísica (IREP Hospital), Buenos Aires, Argentina. [7]Dept of Internal Medicine II, Cardiology, Pneumology and Angiology, University Hospital Bonn, Bonn, Germany. [8]Division of Pulmonary and Critical Care Medicine, Dept of Internal Medicine and Lung Institute of Medical Research Center, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea. [9]Unit for Interstitial Lung Diseases, University Hospitals Leuven, Leuven, Belgium. [10]Interstitial Lung Disease Unit, Royal Brompton Hospital, London, UK. [11]Co-lead authors of this paper.

Correspondence: Athol U. Wells, Interstitial Lung Disease Unit, Emmanuel Kaye Building, Manresa Road, London, SW3 6LR, UK. E-mail: athol.wells@rbht.nhs.uk

@ERSpublications
Other chronic ILDs with a progressive-fibrosing phenotype may have a clinical course similar to IPF. Although challenging, identification of these patients is crucial, and requires a multidisciplinary approach, to ensure optimal diagnosis and management. http://ow.ly/8q8M30mGDsQ

Cite this article as: Cottin V, Hirani NA, Hotchkin DL, *et al.* Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. *Eur Respir Rev* 2018; 27: 180076 [https://doi.org/10.1183/16000617.0076-2018].

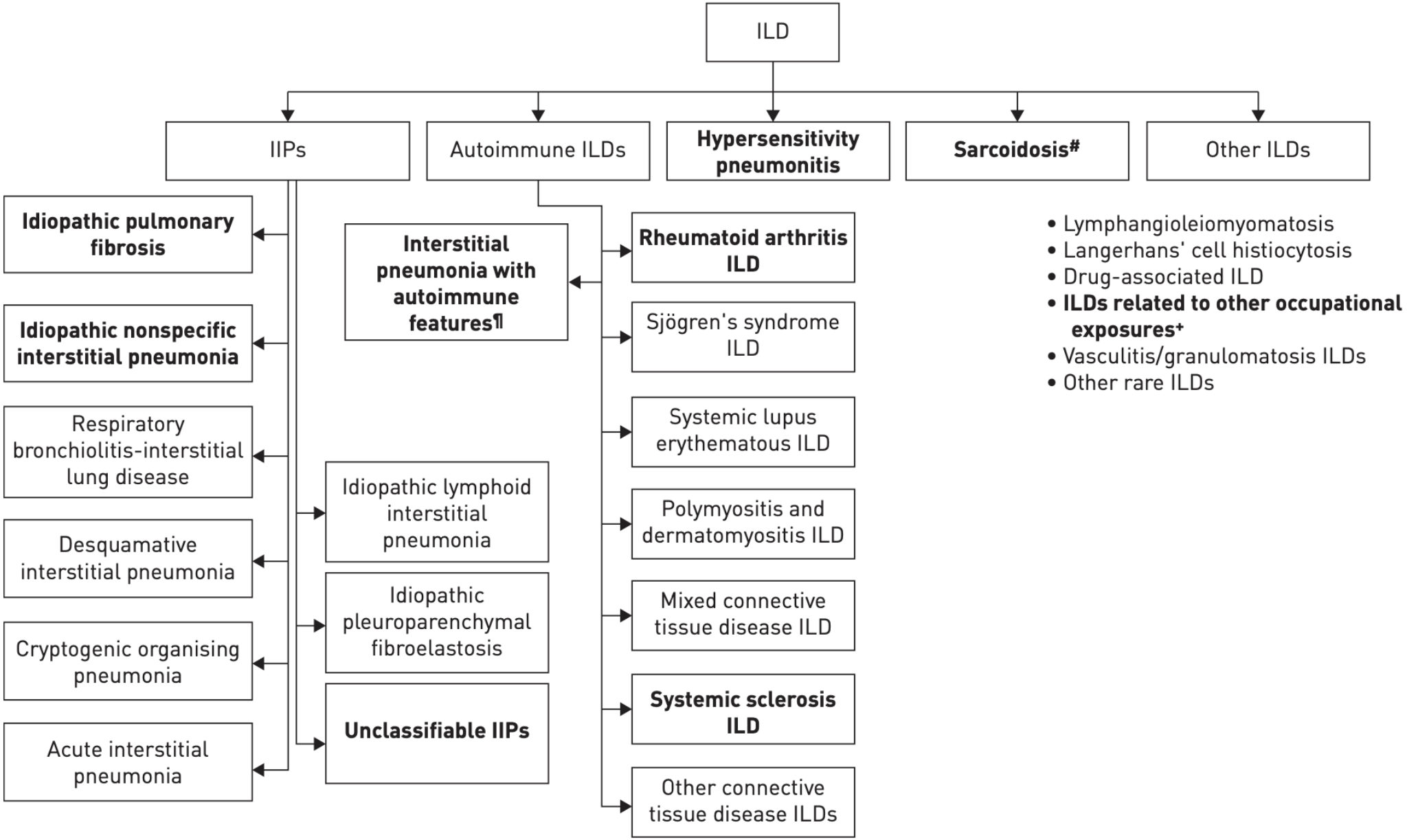


FIGURE 1 Types of interstitial lung disease (ILD) most likely to have a progressive-fibrosing phenotype (indicated in bold). IIPs: idiopathic interstitial pneumonias. #: stage IV sarcoidosis only; ¶: not an established clinical diagnosis; +: *e.g.* asbestosis, silicosis.

AMERICAN THORACIC SOCIETY DOCUMENTS

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

Ganesh Raghu, Martine Remy-Jardin, Luca Richeldi, Carey C. Thomson, Yoshikazu Inoue, Takeshi Johkoh, Michael Kreuter, David A. Lynch, Toby M. Maher, Fernando J. Martinez, Maria Molina-Molina, Jeffrey L. Myers, Andrew G. Nicholson, Christopher J. Ryerson, Mary E. Strek, Lauren K. Troy, Marlies Wijsenbeek, Manoj J. Mammen, Tanzib Hossain, Brittany D. Bissell, Derrick D. Herman, Stephanie M. Hon, Fayez Kheir, Yet H. Khor, Madalina Macrea, Katerina M. Antoniou, Demosthenes Bouros, Ivette Buendia-Roldan, Fabian Caro, Bruno Crestani, Lawrence Ho, Julie Morisset, Amy L. Olson, Anna Podolanczuk, Venerino Poletti, Moisés Selman, Thomas Ewing, Stephen Jones, Shandra L. Knight, Marya Ghazipura, and Kevin C. Wilson; on behalf of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax

This official clinical practice guideline was approved by the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax February 2022

Abstract

with evidence-based recommendations using the GRADE approach.

Table 4. Definition of Progressive Pulmonary Fibrosis

Definition of PPF
In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation*:
1 Worsening respiratory symptoms
2 Physiological evidence of disease progression (either of the following): a. Absolute decline in FVC ⩾5% predicted within 1 yr of follow-up b. Absolute decline in D_{LCO} (corrected for Hb) ⩾10% predicted within 1 yr of follow-up
3 Radiological evidence of disease progression (one or more of the following): a. Increased extent or severity of traction bronchiectasis and bronchiolectasis b. New ground-glass opacity with traction bronchiectasis c. New fine reticulation d. Increased extent or increased coarseness of reticular abnormality e. New or increased honeycombing f. Increased lobar volume loss

Definition of abbreviations: ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; PPF = progressive pulmonary fibrosis.

*Although it is critical to exclude alternative explanations of worsening features for all patients with suspected progression, this is particularly important in patients with worsening respiratory symptoms and/or decline in D_{LCO} given the lower specificity of these features for PPF compared with FVC and chest computed tomography.

(Figure 13
traction br
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pattern, in
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disease pr
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IPF (136).
the pattern
may inclu
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to honeyc
traction br

CTD) [49–51].

3. Progressive pulmonary fibrosis associated with CTD

Different definitions of progressive pulmonary fibrosis have been used, based on expert consensus, definitions used in clinical trials, and recently the definition published in the recent international guide, based on functional, clinical, and radiological parameters [52]. The INBUILD randomized clinical trial [53] used the following criteria to define progression in patients with fibrosing ILD: 1) a decrease in baseline FVC >10%; 2) a decrease in FVC between 5–10% with evidence of fibrosing progression on HRCT of the chest; 3) a decrease in FVC between 5–10% with worsening respiratory symptoms (dyspnea and dry cough); or 4) worsening dyspnea with progression of fibrosis on HRCT in the previous 24 months despite treatment. As a definition of progression, some experts also

high doses, is an independent ris
scleroderma renal crisis [64]. The
fibrotic patterns (UIP and fibrosin
contrary, there is accumulating e
effect of steroids as treatment of

Cytotoxic immunosuppressiv
used to treat CTD and CTD-IL
mycophenolate, azathioprine, ca
in ILD associated with inflamma
mide (in RA). Despite their use
only been demonstrated in RCT
mide and mycophenolate for th
with none of them having a the

Methotrexate has classically
with RA-ILD because of the risk
However, the literature confirm
induced pneumonitis is very lo
confirmation that methotrexate
ing ILD in patients with RA, but

Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med. 2019 Oct 31;381(18):1718–1727.

PPF in SSc-ILD

- 67% of patients → in 5years → pulmonary progression
- Of these 32-37% → have PPF

Hoffmann-Vold AM, 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 Feb;80(2):219–227.

Vonk MC, Walker UA, Volkmann ER, et al. Natural variability in the disease course of SSc-ILD: implications for treatment. Eur Respir Rev. 2021 Mar 31;30(159):200340.

Table 4. Main risk factors for ILD development in SSc and RA, and prognostic factors for mortality and progression of ILD.

Systemic sclerosis

Risk factors for ILD development

- Male gender
- African-American or Asian ethnicity
- Diffuse skin involvement
- Cardiac involvement
- Anti-Scl 70 or topoisomerase I and anti-Th/To positivity

Variables associated with an increased risk of ILD progression

Demographic	• Male sex • Older age • African-American ethnicity • Smoking
Clinical	• Diffuse skin involvement with elevated Rodnan index scores at diagnosis of ILD • Poorly controlled gastroesophageal reflux disease • Presence of arthritis • Time of disease evolution (first 3 years)
Laboratory	• Elevated C-reactive protein • Anti-Scl 70 antibody positivity • Anti-RNA polymerase III antibody positivity • Elevated KL-6 levels
Pulmonary function tests	• Low basal FVC (< 70%) • Low basal DLCO not due to other causes (mainly pulmonary arterial hypertension) • Deterioration of FVC ≥ 10% during follow-up or fall in its values between 5% and 9% with a deterioration of DLCO ≥ 15%
HRCT	• Extent of fibrotic changes > 20%

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Expert Review of Respiratory Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierx20

Management of progressive pulmonary fibrosis associated with connective tissue disease

María Molina-Molina, Iván Castellví, Claudia Valenzuela, José Ramirez, José Antonio Rodríguez Portal, Tomás Franquet & Javier Narváez

Published online: 05 Aug 2022.

PPF in RA-ILD

- 53% of patients → in 5years → pulmonary progression
- Of these 40% → have PPF

Olson A, Hartmann N, Patnaik P, et al. Estimation of the prevalence of progressive fibrosing interstitial lung diseases: systematic literature review and data from a physician survey. Adv Ther. 2021 Feb;38(2):854–867.

Spagnolo P, Distler O, Ryerson CJ, et al. Mechanisms of progressive fibrosis in connective tissue disease (CTD)-associated interstitial lung diseases (ILDs). Ann Rheum Dis. 2021 Feb;80(2):143–150.

Rheumatoid arthritis

Risk factors for ILD development

- Male sex
- Advanced age
- Late onset of the disease
- Duration of RA
- Smoking
- Moderate or high sustained RA activity according to DAS28 scores
- RF positive
- ACPA positive
- Antibodies directed against carbamylated proteins (anti-CarP)
- *MUC5B* gene mutations
- Mutations of telomerase genes leading to accelerated telomere shortening

Taylor & Francis
Taylor & Francis Group

Expert Review of Respiratory Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierx20

Management of progressive pulmonary fibrosis associated with connective tissue disease

María Molina-Molina, Iván Castellví, Claudia Valenzuela, José Ramirez, José Antonio Rodríguez Portal, Tomás Franquet & Javier Narváez

Published online: 05 Aug 2022.

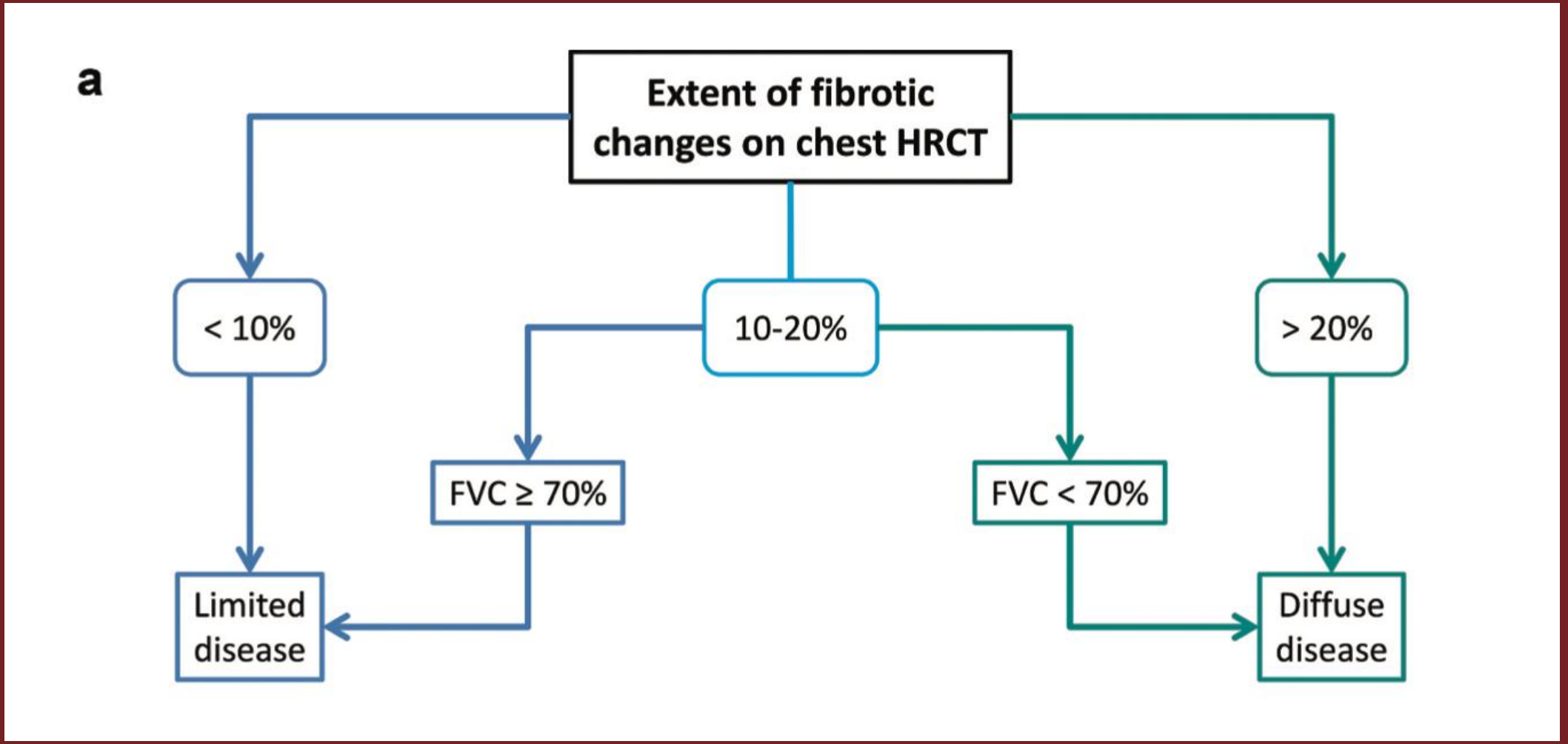
Prognostic factors

Variables associated with ILD progression

- Radiologic pattern of UIP
- Elevated ACPA titers
- Degree of baseline DLCO deterioration (having been demonstrated with two cutoff points: DLCO < 45% and, in those patients with a progressive fibrosing phenotype, DLCO < 54%), decrease ≥ 10% in FVC during follow-up
- Extensive pulmonary involvement on HRCT of the chest
- Elevated serum levels of IL-6 and KL-6

Prognostic factors for mortality

- Advanced age at the time of diagnosis of ILD (> 60-65 years)
- Male sex
- Duration of RA (the longer the duration of disease at the time of ILD diagnosis, the higher the mortality)
- Moderate or high disease activity as assessed by the DAS28-VSG index
- UIP pattern*
- FVC and/or low baseline DLCO
- Decrease in FVC >10% or DLCO >15% during follow-up
- Extensive lung involvement on HRCT of the chest (>20-30%)
- Elevated serum levels of KL-6



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 Jun 1;177(11):1248–1254.

b

Sat O_2 in the 6' walk test

≤ 94% → 1 point

> 94% → 0 points

+

Arthritis

Yes/sometimes → 1 point

No → 0 points

=

SPAR model

Score 0-2

Predictions

Score SPAR 0: 6% cases with ILD progression

SPAR 1: 36% cases with ILD progression

SPAR 2: 86% cases with ILD progression

Wu W, Jordan S, Becker MO, et al. Prediction of progression of interstitial lung disease in patients with systemic sclerosis: the SPAR model. Ann Rheum Dis. 2018 Sep;77(9):1326–1332.

ILD-CTD

ΘΕΡΑΠΕΙΑ

ILD-CTD

ΘΕΡΑΠΕΙΑ

- Εξατομικευμένη & ολοκληρωμένη
- (Υποκείμενη νόσος - CTD)
- (Συννοσηρότητες)
- (Εξωπνευμονικές εκδηλώσεις)
- (Safety-effectiveness)

GCs

- Μέρος της αρχικής αγωγής (low-dose)
- Οχι RCTs για CTD-ILD
- Μεσαίες και μεγάλες δόσεις →SSc renal crisis
- Σε UIP –NSIP ?
- Σε PPF ??? → detrimental !!!

Papiris SA, Kolilekas L, Kagouridis K, et al. ipf-acute exacerbations: advances and future perspectives. Front Pharmacol. 2022;13:836553.

Papiris SA, Kagouridis K, Papadaki G, et al. Treating CTDs related fibrotic ILDs by immunosuppressants: "facts and faults". Lung. 2014 Apr;192(2):221–223.

ΑΝΟΣΟΚΑΤΑΣΤΑΛΤΙΚΑ στην CTD-ILD

- Κυκλοφωσφαμίδη (CP) & MMF
- RCTs... Ναί !!!
- Κανένα θεραπευτική ένδειξη !

Tashkin DP, Roth MD, Clements PJ, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med. 2016 Sep;4(9):708–719.

Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med. 2006 Jun 22;354(25):2655–2666.

Μεθοτρεξάτη (MTX)

- RA-ILD…acute pneumonitis?
- However, the literature confirms that the actual risk of drug-induced pneumonitis is very low (0.3%)

Solomon DH, Glynn RJ, Karlson EW, et al. Adverse effects of low-dose methotrexate: a randomized trial. Ann Intern Med. 2020 Mar 17;172(6):369–380.

Ridker PM, Everett BM, Pradhan A, et al. Low-dose methotrexate for the prevention of atherosclerotic events. N Engl J Med. 2019 Feb 21;380(8):752–762.

Sparks JA, Dellaripa PF, Glynn RJ, et al. Pulmonary adverse events in patients receiving low-dose methotrexate in the randomized, double-blind, placebo-controlled cardiovascular inflammation reduction trial. Arthritis Rheumatol. 2020 Dec;72(12):2065–2071.

MTX

- There is no confirmation that methotrexate increases the risk of developing ILD in patients with RA, but recent studies suggest that …
- …RA control achieved with this drug is associated with a delay in the onset of ILD and a better prognosis

Ibfelt EH, Jacobsen RK, Kopp TI, et al. Methotrexate and risk of interstitial lung disease and respiratory failure in rheumatoid arthritis: a nationwide population-based study. Rheumatology (Oxford). 2021 Jan 5;60(1):346–352.

Juge PA, Lee JS, Lau J, et al. Methotrexate and rheumatoid arthritis associated interstitial lung disease. Eur Respir J. 2021 Feb;57(2):2000337.

Kiely P, Busby AD, Nikiphorou E, et al. Is incident rheumatoid arthritis interstitial lung disease associated with methotrexate treatment? Results from a multivariate analysis in the ERAS and ERAN inception cohorts. BMJ Open. 2019 May 5;9(5):e028466.

Επί επιδείνωσης της ILD…

- Rescue therapy με βιολογικά
- Αντιινωτικά
- HSCT

ΒΙΟΛΟΓΙΚΑ σε CTD-ILD

- Μόνο το TCZ έχει μελέτες για SSc-ILD
- FDA approved για SSc-ILD

Roofeh D, Lin CJF, Goldin J, et al. Tocilizumab prevents progression of early systemic sclerosis-associated interstitial lung disease. Arthritis Rheumatol. 2021 July;73(7):1301–1310.

Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2020 Oct;8(10):963–974.

- RTX & ABT
- Real-life μελέτες παρατήρησης
- On going RCTs (σε SSc-ILD – RA-ILD)

Saunders P, Tsipouri V, Keir GJ, et al. Rituximab versus cyclophosphamide for the treatment of connective tissue disease-associated interstitial lung disease (RECITAL): study protocol for a randomised controlled trial. Trials. 2017 Jun 15;18(1):275.

Evaluation of efficacy and safety of rituximab with mycophenolate mofetil in patients with interstitial lung disease (EvER-ILD) [cited 2022 24 enero]. Available from: https://clinicaltrials.gov/ct2/show/NCT02990286

Vicente-Rabaneda EF, Atienza-Mateo B, Blanco R, et al. Efficacy and safety of abatacept in interstitial lung disease of rheumatoid arthritis: a systematic literature review. Autoimmun Rev. 2021 Jun;20(6):102830.

ΑΝΤΙΙΝΩΤΙΚΑ

- 2 φάρμακα στην αγορά για ILD
- NINTEDANIB
- PIRFENIDONE

Μόνο το NINTEDANIB FDA & EMA APPROVED

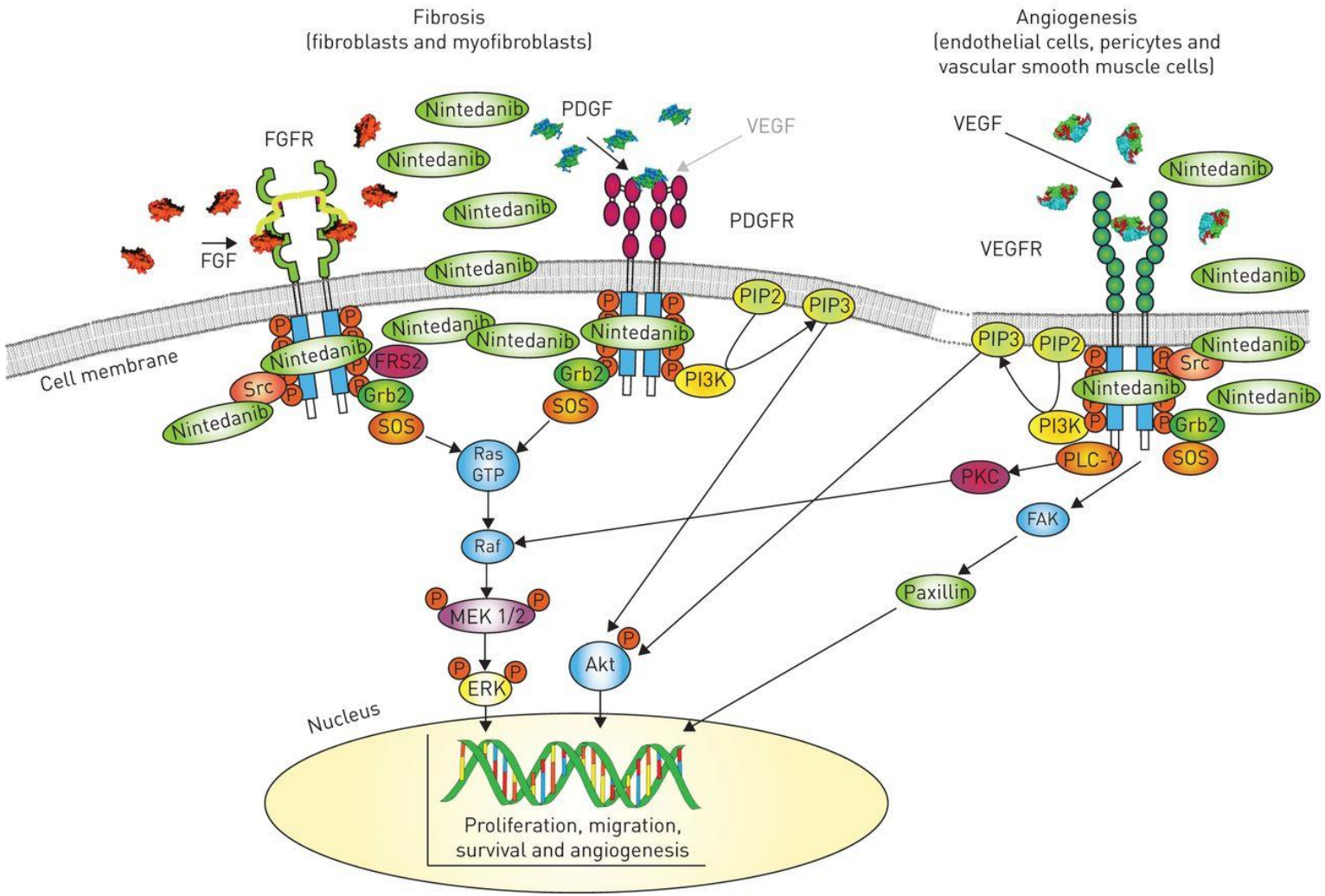
1. for the treatment of fibrosing SSc-ILD, (based on data from the phase III RCT SENSCIS)

2. for other progressive fibrosing ILD, including CTD- ILD, (based on results from the phase III RCT INBUILD)

Distler O, Highland KB, Gahlemann M, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med. 2019 Jun 27;380(26):2518–2528.

Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med. 2019 Oct 31;381 (18):1718–1727.

Polypharmacology of nintedanib and the downstream signalling pathways.



Lutz Wollin et al. Eur Respir J 2015;45:1434-1445

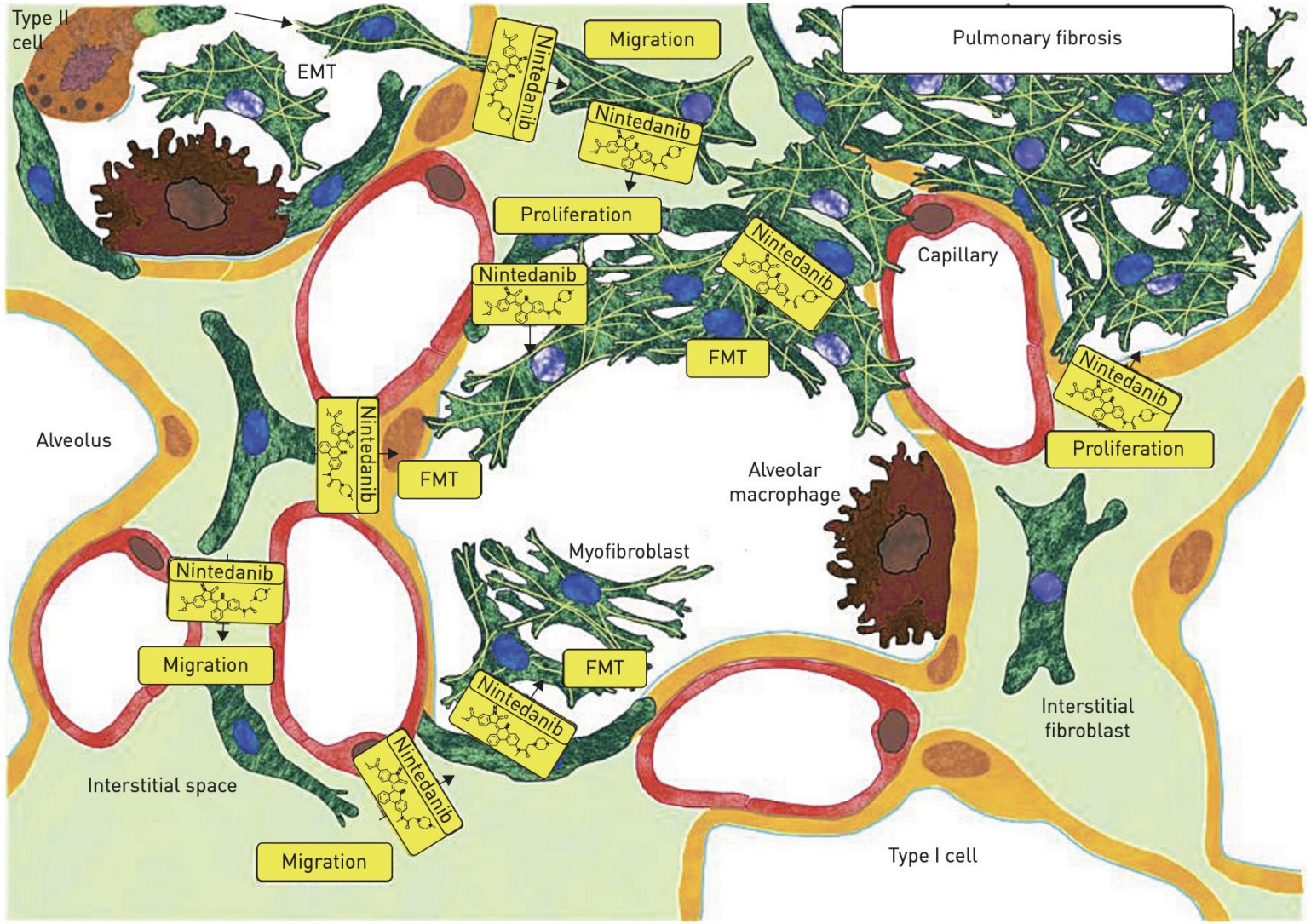
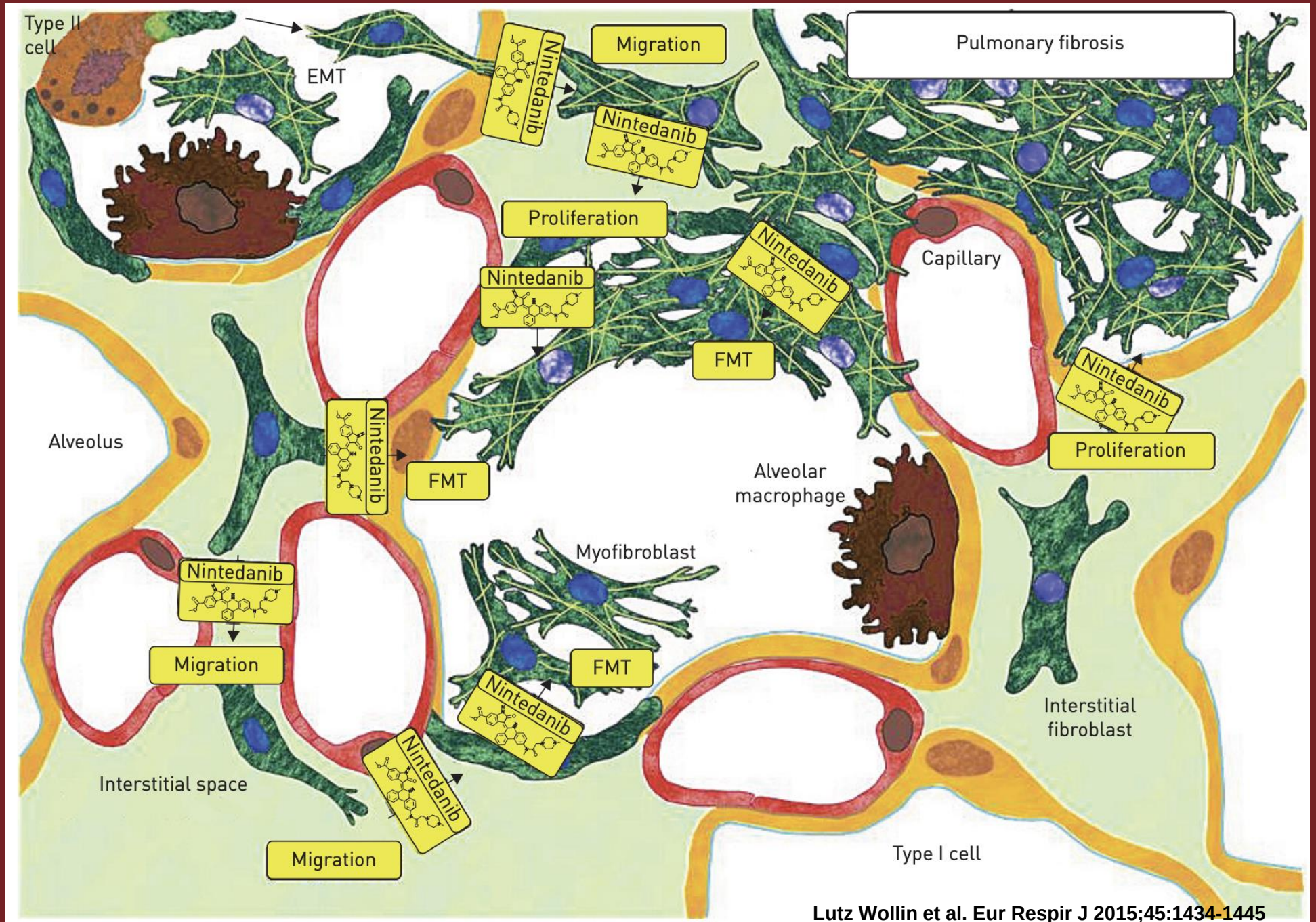


FIGURE 4 Current understanding of the mode of action of nintedanib in fibrotic lung diseases. The scheme reflects ongoing processes in the pathology of idiopathic pulmonary fibrosis (IPF). As a result of epithelial damage, alveolar epithelial cells undergo apoptosis and epithelial type II cells transform into myofibroblasts (epithelial–mesenchymal transition (EMT)) to provide mesenchymal cells for the initial repair process. Residual lung fibroblasts in the interstitium start to proliferate and migrate to the site of injury. Excessive fibroblast proliferation, migration and transformation to myofibroblasts (fibroblast to myofibroblast transformation (FMT)), and synthesis and deposition of extracellular matrix (ECM) are hallmarks of the fibrotic pathology in IPF. Nintedanib (yellow molecules) interferes with fibroblast/myofibroblast proliferation, FMT and migration. By limiting the number of fibroblasts/myofibroblasts, the synthesis and deposition of ECM are reduced. Nintedanib was found to have no effect on EMT. The effects of nintedanib on fibrocytes and other structural cells of the lung need further exploration. The inhibitory activities of nintedanib are shown in yellow.

Lutz Wollin et al. Eur Respir J 2015;45:1434-1445



Lutz Wollin et al. Eur Respir J 2015;45:1434-1445

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease

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ABSTRACT

BACKGROUND

Interstitial lung disease (ILD) is a common manifestation of systemic sclerosis and a leading cause of systemic sclerosis–related death. Nintedanib, a tyrosine kinase inhibitor, has been shown to have antifibrotic and antiinflammatory effects in preclinical models of systemic sclerosis and ILD.

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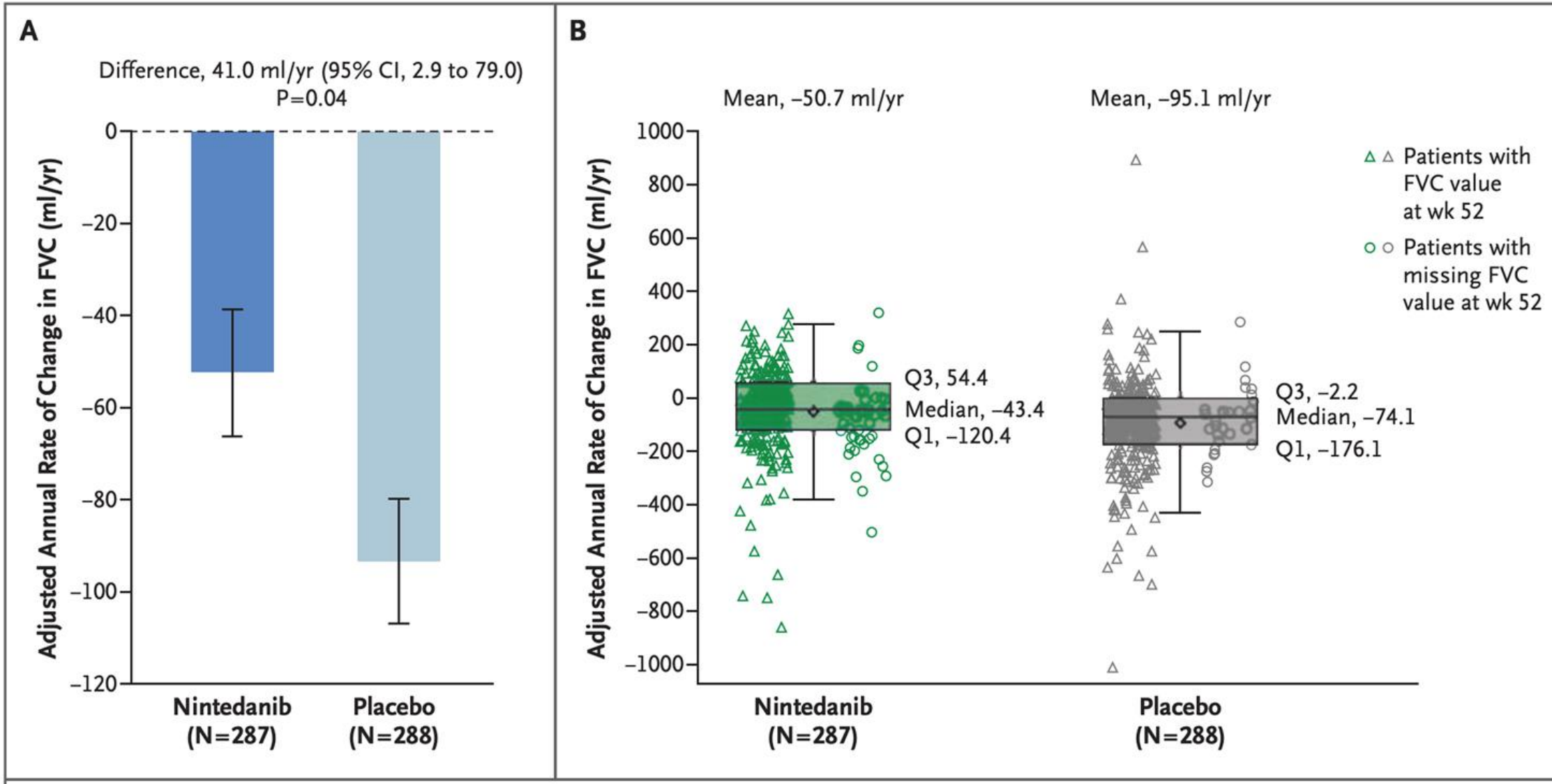
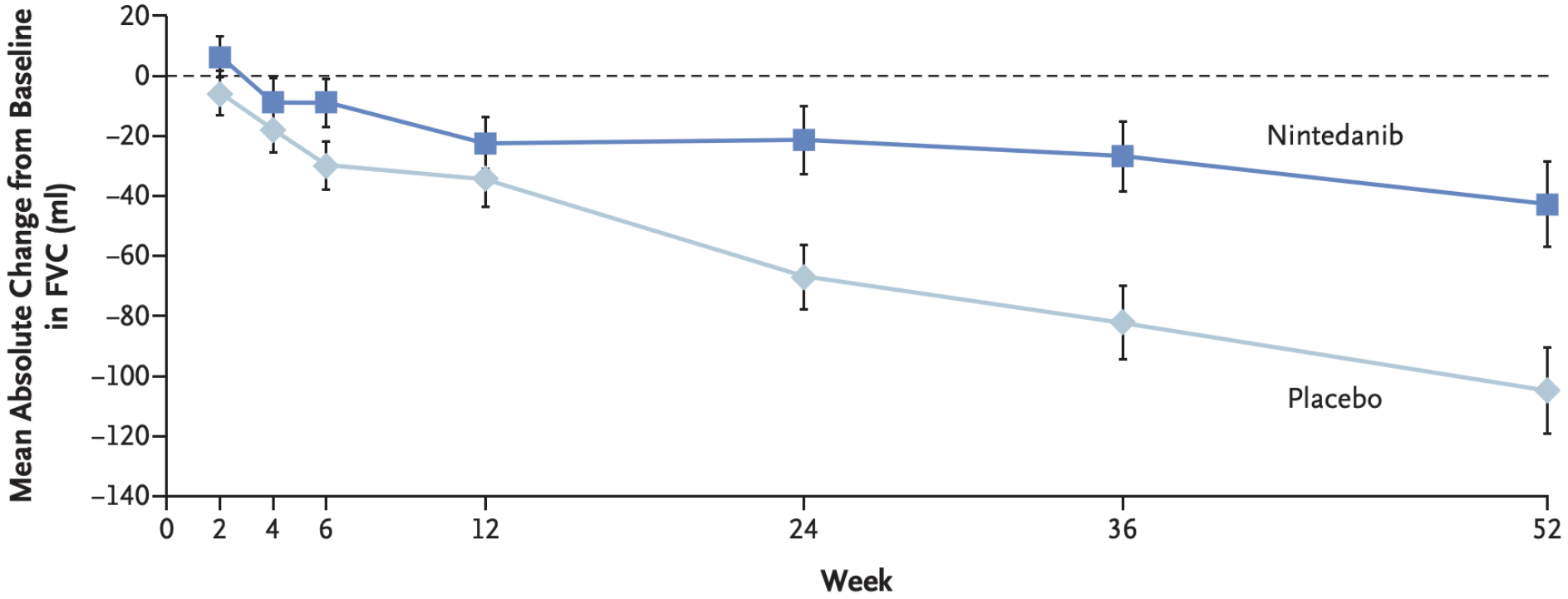

A
Difference, 41.0 ml/yr (95% CI, 2.9 to 79.0)
P=0.04
Adjusted Annual Rate of Change in FVC (ml/yr)
0
−20
−40
−60
−80
−100
−120
Nintedanib (N=287)
Placebo (N=288)
B
Mean, −50.7 ml/yr
Mean, −95.1 ml/yr
Adjusted Annual Rate of Change in FVC (ml/yr)
1000
800
600
400
200
0
−200
−400
−600
−800
−1000
Patients with FVC value at wk 52
Patients with missing FVC value at wk 52
Q3, 54.4
Median, −43.4
Q1, −120.4
Q3, −2.2
Median, −74.1
Q1, −176.1
Nintedanib (N=287)
Placebo (N=288)

C



No. of Patients							
Nintedanib	288	283	281	273	278	265	262	241
Placebo	288	283	281	280	283	280	268	257

Figure 2. Decline in Forced Vital Capacity.

Arthritis & Rheumatology
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American College of Rheumatology
Empowering Rheumatology Professionals

Nintedanib in Patients With Autoimmune Disease–Related Progressive Fibrosing Interstitial Lung Diseases: Subgroup Analysis of the INBUILD Trial

Eric L. Matteson,[1] Clive Kelly,[2] Jörg H. W. Distler,[3] Anna-Maria Hoffmann-Vold,[4] James R. Seibold,[5] Shikha Mittoo,[6] Paul F. Dellaripa,[7] Martin Aringer,[8] Janet Pope,[9] Oliver Distler,[10] Alexandra James,[11] Rozsa Schlenker-Herceg,[12] Susanne Stowasser,[13] Manuel Quaresma,[13] and Kevin R. Flaherty,[14] on behalf of the INBUILD Trial Investigators

Objective. To analyze the efficacy and safety of nintedanib in patients with fibrosing autoimmune disease–related interstitial lung diseases (ILDs) with a progressive phenotype.

Methods. The INBUILD trial enrolled patients with a fibrosing ILD other than idiopathic pulmonary fibrosis, with diffuse fibrosing lung disease of >10% extent on high-resolution computed tomography, forced vital capacity percent predicted (FVC%) ≥45%, and diffusing capacity of the lungs for carbon monoxide percent predicted ≥30% to <80%. Patients fulfilled protocol-defined criteria for progression of ILD within the 24 months before screening, despite management deemed appropriate in clinical practice. Subjects were randomized to receive nintedanib or placebo. We assessed the rate of decline in FVC (ml/year) and adverse events (AEs) over 52 weeks in the subgroup with autoimmune disease–related ILDs.

appropriate in clinical practice. Subjects were randomized to receive nintedanib or placebo. We assessed the rate of decline in FVC (ml/year) and adverse events (AEs) over 52 weeks in the subgroup with autoimmune disease–related ILDs.

Results. Among 170 patients with autoimmune disease–related ILDs, the rate of decline in FVC over 52 weeks was −75.9 ml/year with nintedanib versus −178.6 ml/year with placebo (difference 102.7 ml/year [95% confidence interval 23.2, 182.2]; nominal $P = 0.012$). No heterogeneity was detected in the effect of nintedanib versus placebo across subgroups based on ILD diagnosis ($P = 0.91$). The most frequent AE was diarrhea, reported in 63.4% and 27.3% of subjects in the nintedanib and placebo groups, respectively. AEs led to permanent discontinuation of trial drug in 17.1% and 10.2% of subjects in the nintedanib and placebo groups, respectively.

Conclusion. In the INBUILD trial, nintedanib slowed the rate of decline in FVC in patients with progressive fibrosing autoimmune disease–related ILDs, with AEs that were manageable for most patients.

INTRODUCTION

Interstitial lung disease (ILD) is a common manifestation of systemic autoimmune diseases including rheumatoid arthritis (RA) (1), systemic sclerosis (SSc) (2), and mixed connective tissue disease (MCTD) (3). Some patients with autoimmune disease–related ILD develop a progressive fibrosing phenotype characterized by increasing lung fibrosis on high-resolution computed tomography (HRCT), decline in lung function, worsening symptoms and quality of life, and early mortality, despite immunomodulatory therapy (2–9). Decline in forced vital capacity percent predicted (FVC%) is a predictor of mortality in patients with autoimmune disease–associated ILDs (2,10,11).

Immunosuppressants and disease-modifying antirheumatic drugs (DMARDs) are the standard of care for systemic autoimmune diseases, but their efficacy in slowing the progression of ILD

A video abstract of this article can be found at https://players.brightcove.net/3806881048001/default_default/index.html?videoId=6295457676001

The INBUILD Trial was funded by Boehringer Ingelheim International

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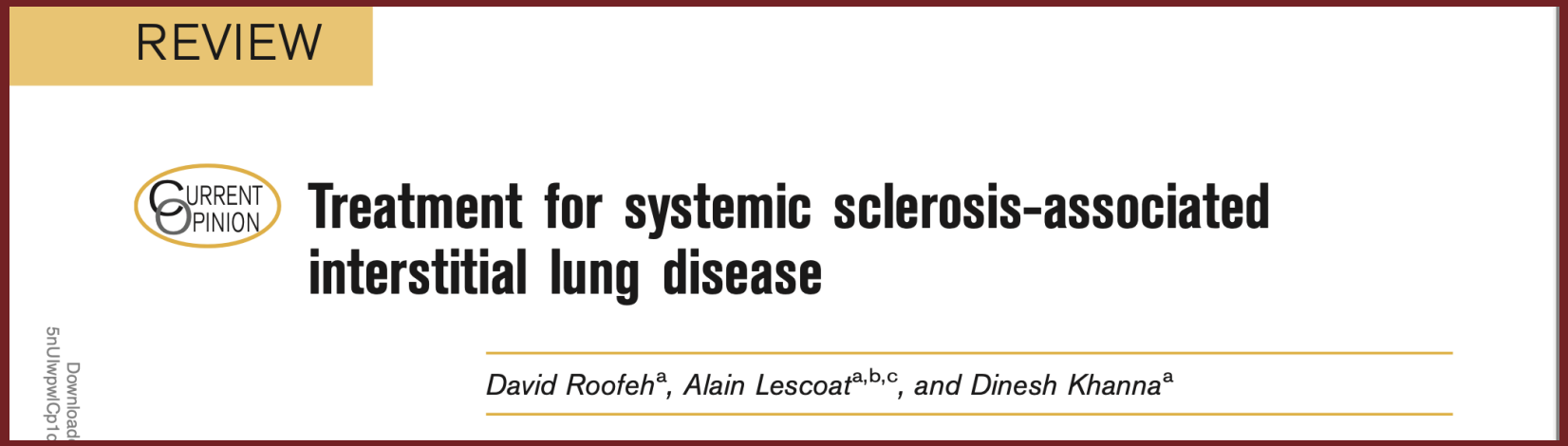

REVIEW

CURRENT OPINION

Treatment for systemic sclerosis-associated interstitial lung disease

David Roofeh[a], Alain Lescoat[a,b,c], and Dinesh Khanna[a]

Curr Opin Rheumatol 2021, 33:240 – 248

(A)HSCT

- In the last decade, three key trials have examined the use of autologous hematopoietic stem cell transplantation (ASCT) for treatment of SSc-ILD: Autologous Stem Cell Systemic Sclerosis Immune Suppression Trial (ASSIST), Autologous Stem Cell Transplantation International Scleroderma (ASTIS), and Scleroderma Cyclophosphamide or Transplantation (SCOT) studies
- In the ASTIS trial, despite early treatment- related mortality (10.1%) and an increase in serious adverse events, the transplant arm demonstrated a long-term survival benefit at year 1, year 2, and year 4.

REVIEW

Treatment for systemic sclerosis-associated interstitial lung disease

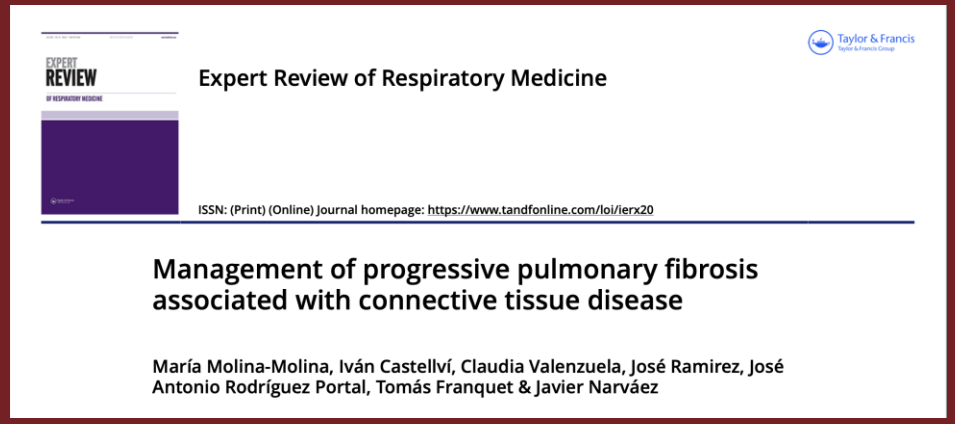
David Roofeh[a], Alain Lescoat[a,b,c], and Dinesh Khanna[a]

Curr Opin Rheumatol 2021, 33:240 – 24

- In the SCOT trial, survival at 54 months posttreatment showed 91% of transplant patients were alive, compared with 77% of the comparator arm of monthly CYC.
- More patients receiving ASCT improved in FVC than those in the CYC group at 54 months: 36% of the ASCT patients improved (relative increase of FVC by 10%) compared with 23% of the CYC patients.
- The per- centage of patients who had an adverse event of grade 3 or more was higher in the ASCT group than in the CYC group suggesting that careful patient selection and monitoring is needed for ASCT.

LUNG TRANSPLANTATION

- When PPF does not show stabilization, despite the measures taken, lung transplantation should always be considered in candi- date patients and the case should be referred to Lung Transplant Units before reaching an advanced stage of respiratory involvement.



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Management of progressive pulmonary fibrosis associated with connective tissue disease

María Molina-Molina, Iván Castellví, Claudia Valenzuela, José Ramirez, José Antonio Rodríguez Portal, Tomás Franquet & Javier Narváez

Published online: 05 Aug 2022.

EXPERT OPINION

Ανεκπλήρωτες ανάγκες στην PPF-CTD

- Αξιόπιστοι προγνωστικοί βιοδείκτες
- Εργαλεία καθοδήγησης για κατάλληλες θεραπείες
- Άλλες απεικονιστικές μέθοδοι
- Για εξατομικευμένη Ιατρική
- Νεώτερα φάρμακα (JAK αναστολείς, pentraxin 2, κλπ)

5. Conclusion

CTD-ILD especially those with progressive pulmonary fibrosis have a high morbidity and mortality rate. In order to reverse this situation and improve the prognosis and QoL of patients, a multidisciplinary diagnostic and therapeutic approach is necessary as the best model of care to guarantee early diagnosis and comprehensive and individualized treatment. Antifibrotic drugs are considered for those presenting progressive pulmonary fibrosis.

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Expert Review of Respiratory Medicine

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THANK
YOU