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Interstitial Lung Disease for the Rheumatologist

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Disclosures

- None relevant to this talk

Outline

- Initial presentation of ILD
  - Idiopathic pneumonia with Autoimmune Features (IPAF).
  - Established Rheumatologic Disease
- Considerations in CTD-ILD
  - Disease-specific
  - Progressive Pulmonary Fibrosis

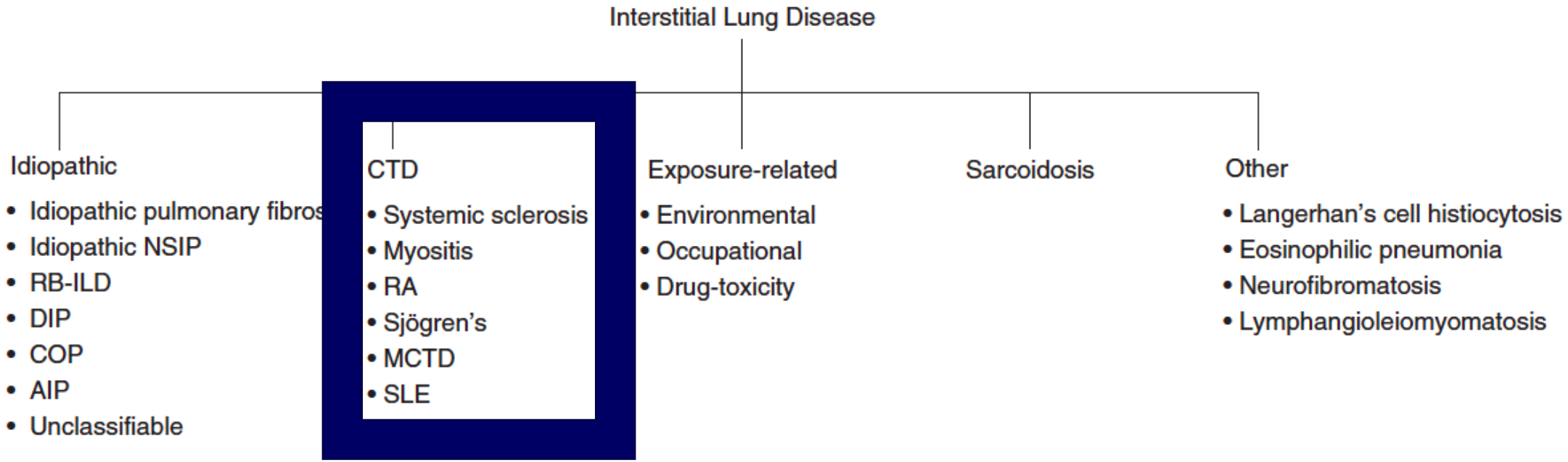
Common Pulmonary Manifestations of Connective Tissue Disease

	ILD	Airways	Pleural	Vascular	DAH
Systemic sclerosis	+++	–	–	+++	–
Rheumatoid arthritis	++	++	++	+	–
Primary Sjögren's syndrome	++	++	+	+	–
Mixed CTD	++	+	+	++	–
Polymyositis/ dermatomyositis	+++	–	–	+	–
Systemic lupus erythematosus	+	+	+++	+	++

The signs show prevalence of each manifestation (–=no prevalence; +=low prevalence; ++=medium prevalence; +++=high prevalence). ILD=interstitial lung disease. DAH=diffuse alveolar haemorrhage. CTD=connective tissue disease.

Fischer and DuBois, *Lancet* 2012; 380: 689–98

Connective Tissue Related Interstitial Lung Disease



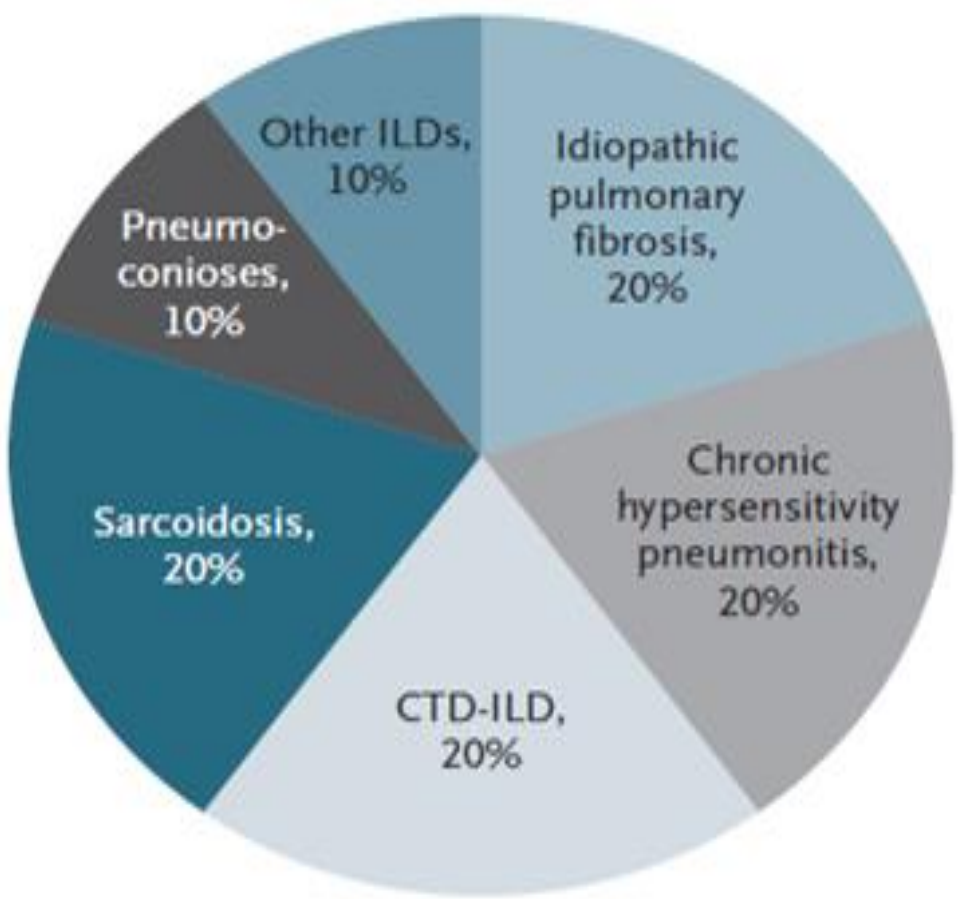
Idiopathic diagnosis is based on exclusion of autoimmune disease- and exposure-related disease using history, physical, imaging patterns and multidisciplinary discussion

Graney and Fischer, AnnalsATS May 2019

Estimates of ILD Diagnoses Prevalence

CTD

- Systemic sclerosis
- Myositis
- RA
- Sjögren's
- MCTD
- SLE



Henry Ford Hospital ILD Program 2021

350 New Evaluations

700 Established Patients

>30% CTD-ILD

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Graney and Fischer, AnnalsATS May 2019

Workup of Connective Tissue Disease on Presentation for ILD

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Case 1

- 61 yo M with progressive dyspnea, cough and pleuritic pain for 1 year presents for second opinion of interstitial lung disease after surgical lung biopsy showed ‘nonclassifiable fibrosis’

. Positive ANA on serologic workup without a known systemic disease.

- Pulmonary Function Tests

  FVC 3.38(69%)

  FEV1 2.69 (73%)

  FEV1/FVC 79%

  FET 100% 7.90 sec

  DLCO 12.3(43%)

  DLCOadj 12.3 (43%)

  IVC 3.18

- Six Minute Walk Test: Desaturation to 94% on room air

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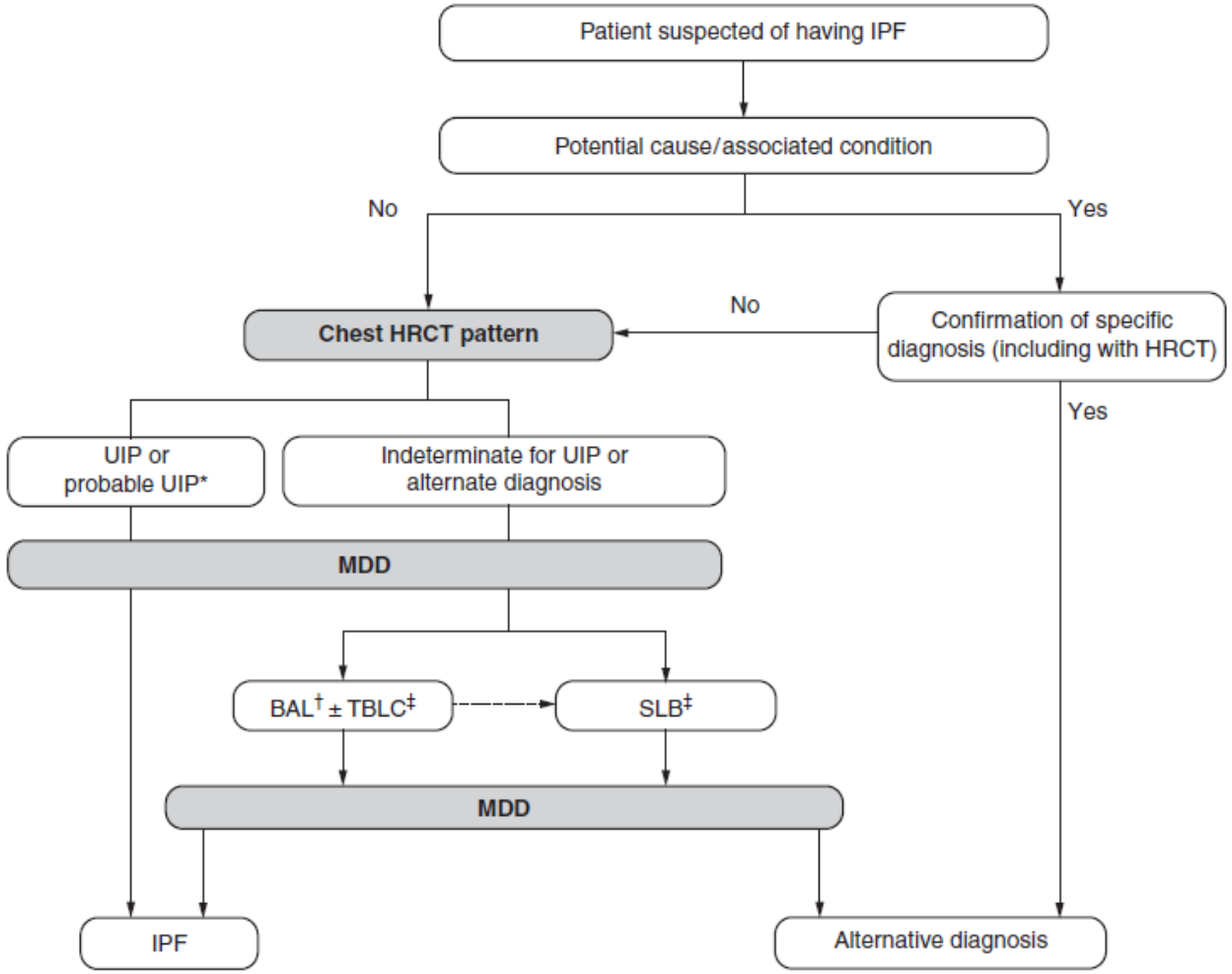
Kamiya H. BMJ Open 2019;9:e031444.

Radiograph

- High resolution chest CT
  - Inspiratory hold images
  - Prone imaging (inspiratory hold) to ensure that changes are not secondary to atelectasis
  - Expiratory images to evaluate for air-trapping or to distinguish air-trapping from pulmonary vascular disease (mosaic attenuation)
- Radiographic pattern + distribution of findings are helpful along with history in narrowing the differential

Diagnostic Algorithm



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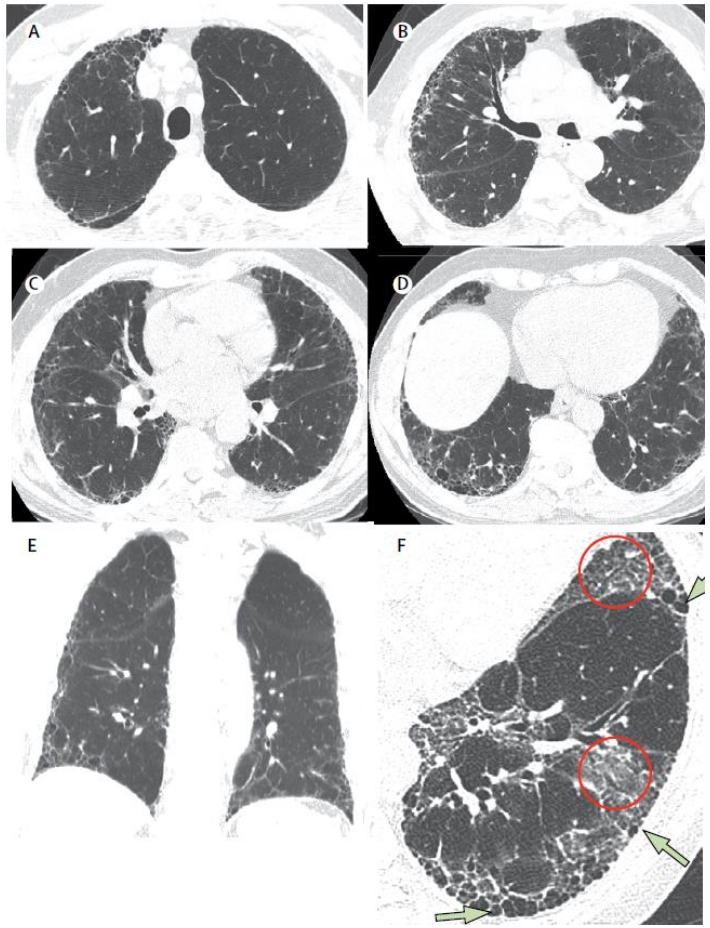
Raghu et al, AJRCCM 2022; 205(9): e18-47.

Typical Usual Interstitial Pneumonia



- Basilar predominant
- Subpleural reticulation
- Traction bronchiectasis
- Honeycombing
- ABSENCE of inconsistent features
  - Ground glass
  - Diffuse mosaic attenuation with air-trapping
  - Consolidation
  - Cysts

Lynch et al, *Lancet Respir Med* 2018; 6: 138–53

Radiographic Features to Predict the Presence of CTD-ILD (over Idiopathic)

TABLE 3: Performance of Specific CT Signs in Differentiation of Connective Tissue Disease–Associated Interstitial Lung Disease (CTD-ILD) From Idiopathic Pulmonary Fibrosis (IPF) in Patients With Usual Interstitial Pneumonia CT Pattern

CT Sign	Percentage of Patients With IPF With CT Sign ($n = 133$)	Percentage of Patients With CTD-ILD With CT Sign ($n = 63$)	Sensitivity (%)	Specificit (%)	Positive Likelihood Ratio	Negative Likelihood Ratio	p
Anterior upper lobe	12.8 (17)	25.4 (16)	25.4	87.2	1.99	0.86	0.028[a]
Exuberant honeycombing	6.0 (8)	22.2 (14)	22.2	94.0	3.69	0.83	< 0.001[a]
Straight edge	6.0 (8)	25.4 (16)	25.4	94.0	4.22	0.79	< 0.001[a]
More than one sign	4.5 (6)	23.8 (15)	23.8	95.5	5.28	0.80	< 0.001[a]
Any CT sign	19.5 (26)	42.9 (27)	42.9	80.5	2.19	0.71	< 0.001

Note—Values in parentheses are number of subjects.
[a]Statistically significant.

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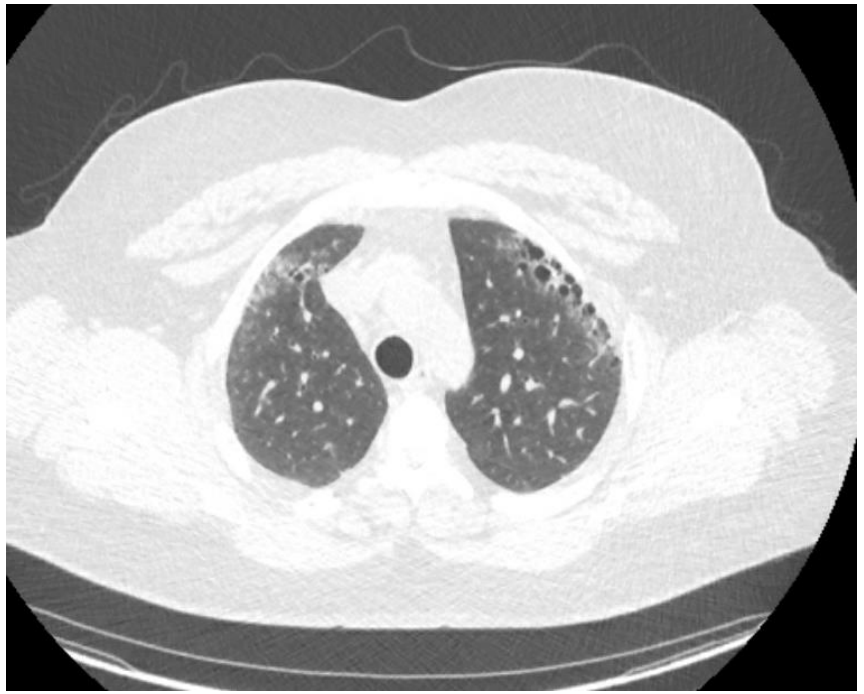
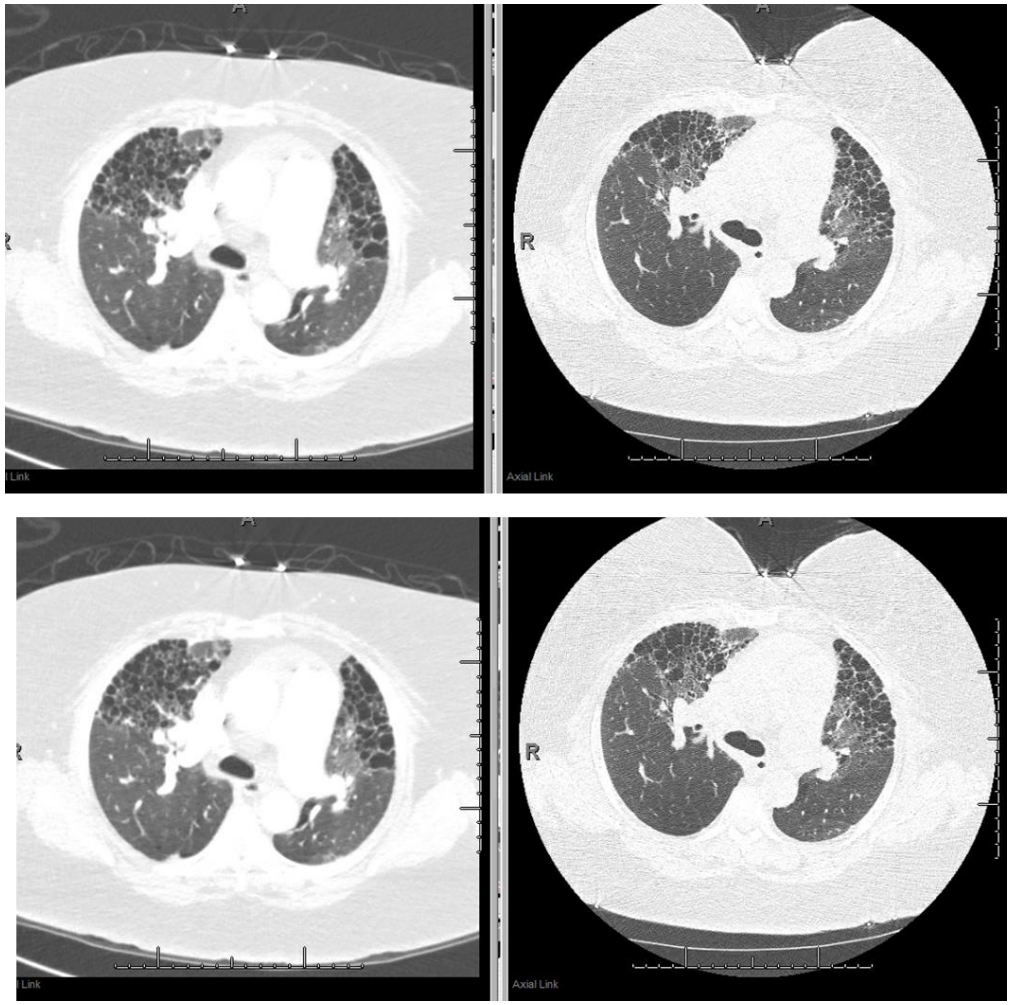
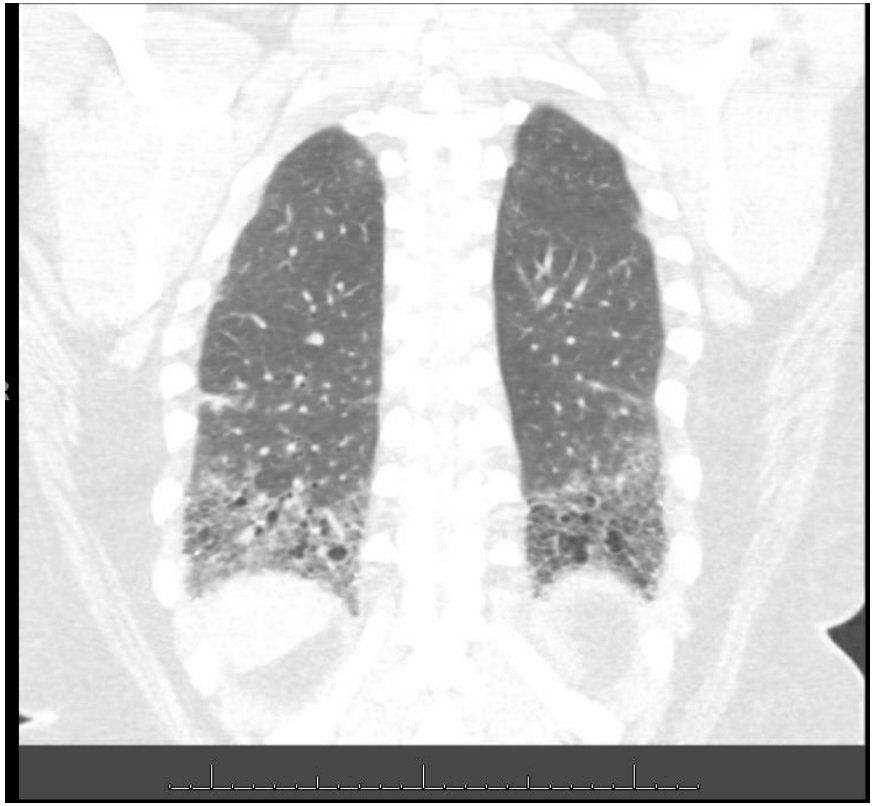
Chung et al, 2018 Feb;210(2):307-313

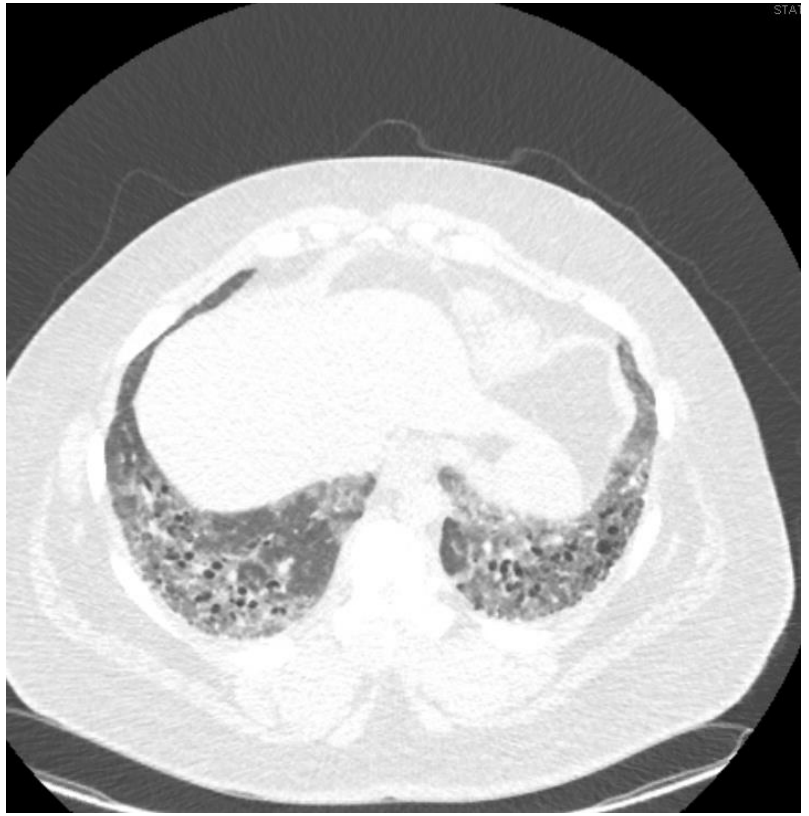
anterior upper lobe sign



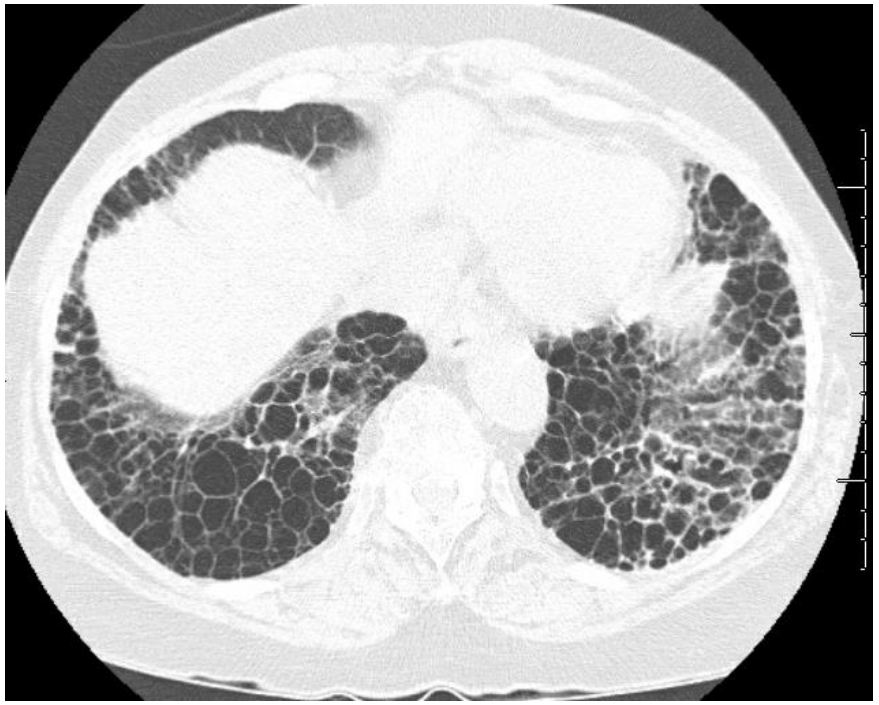


Straight edge sign

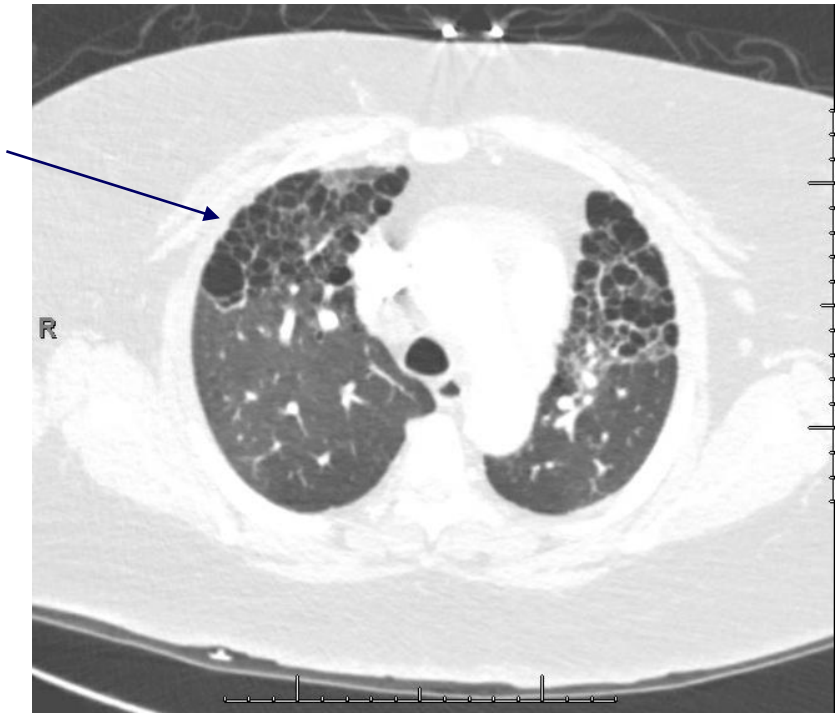


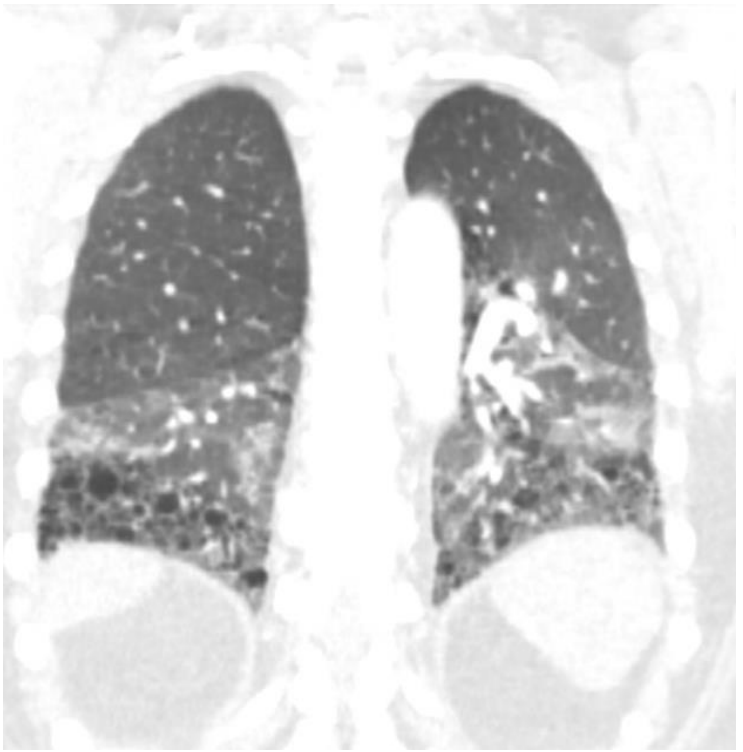


Exuberant Honeycombing

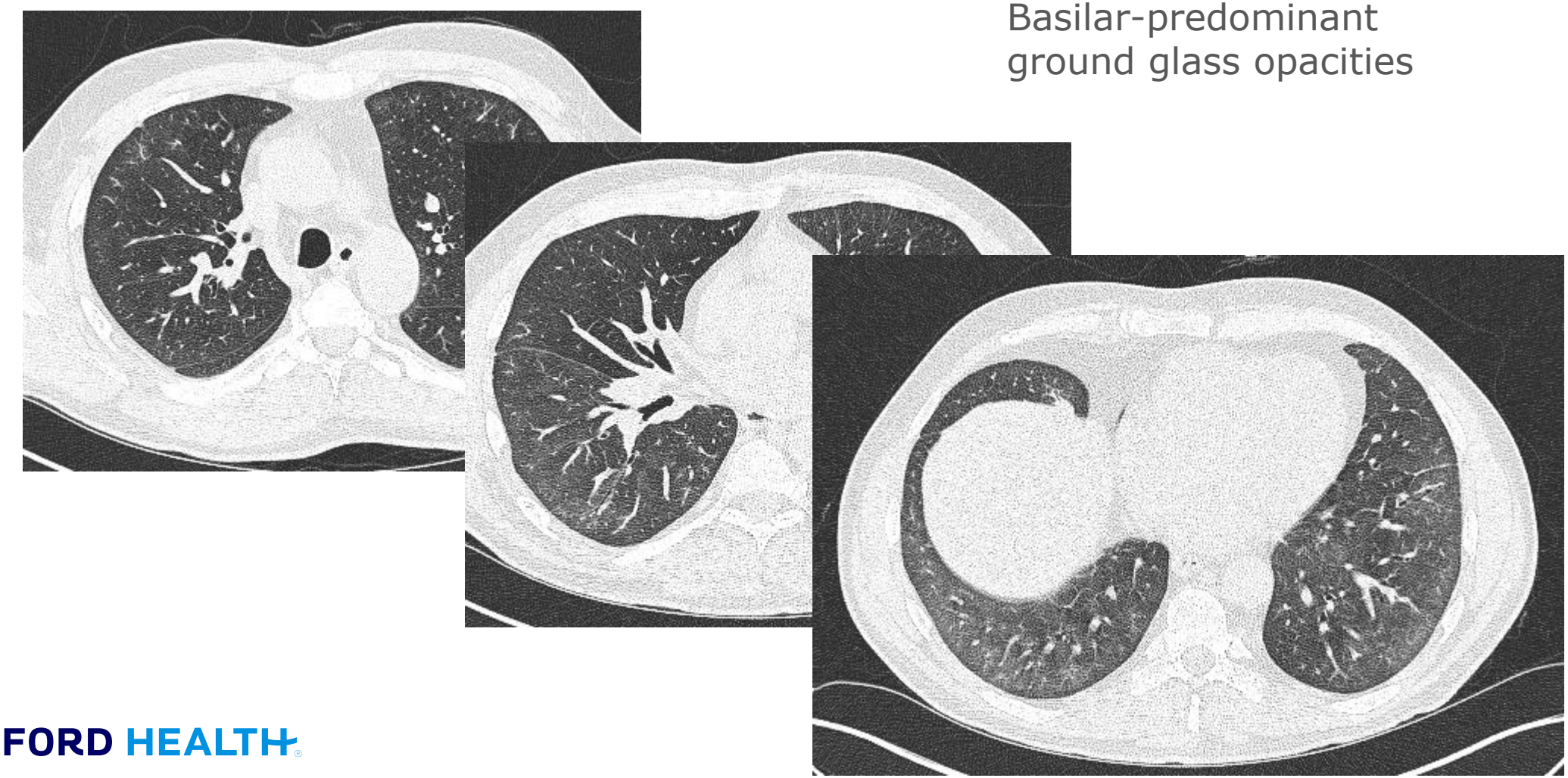


All three signs



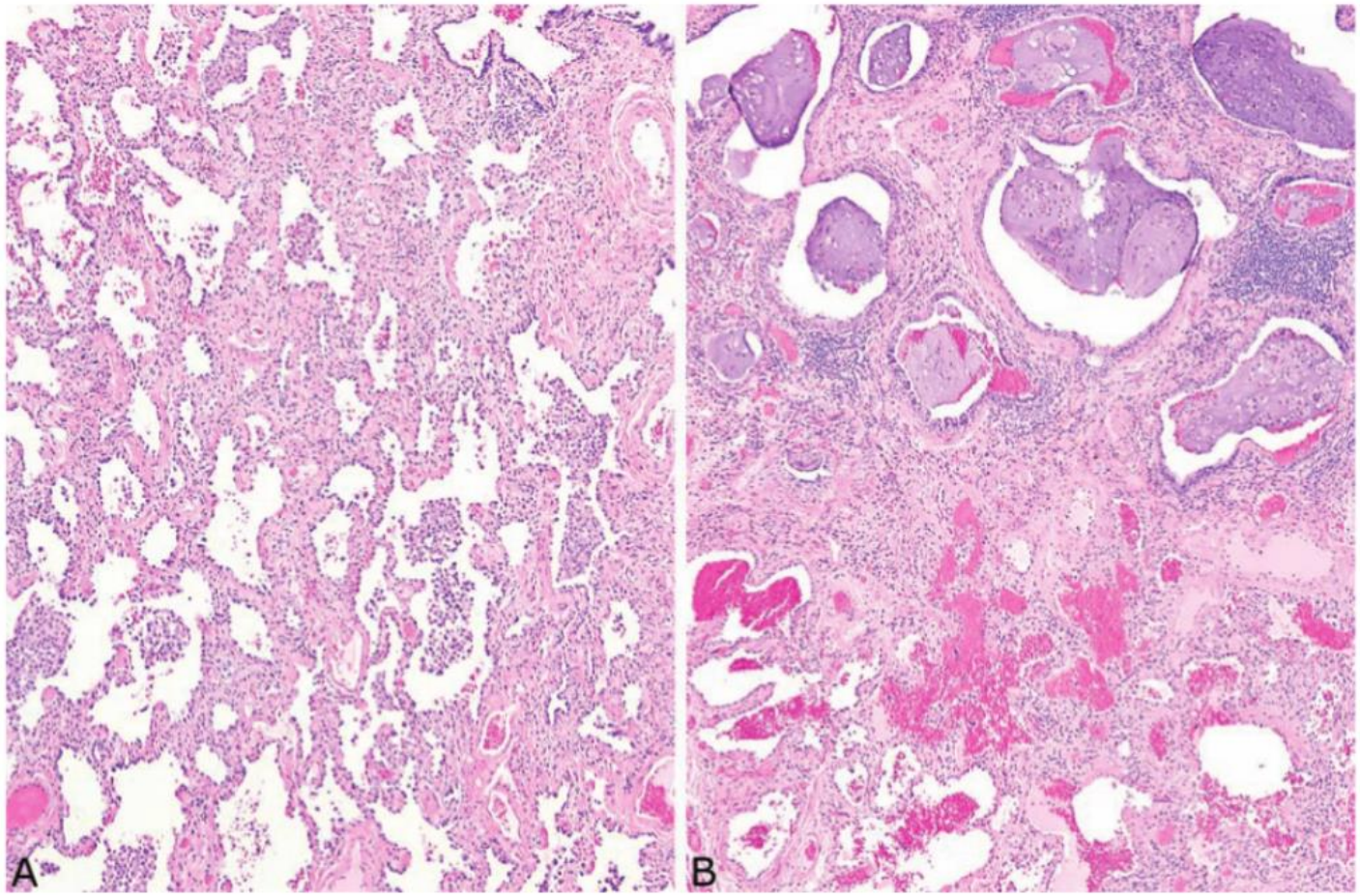


Back to our case



Basilar-predominant
ground glass opacities

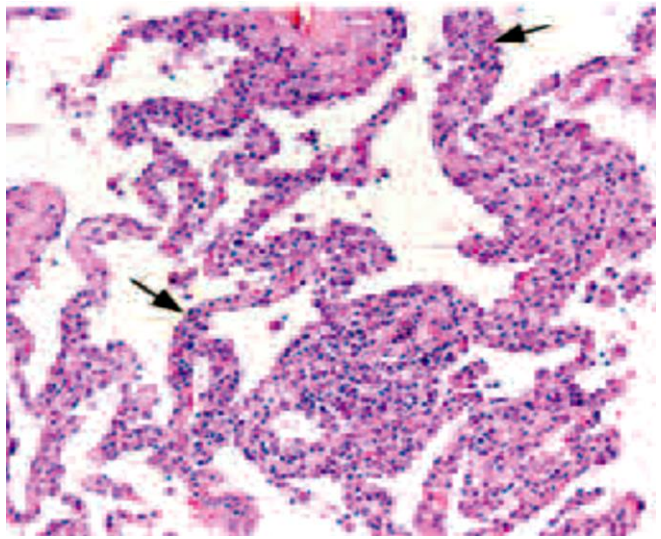
Nonclassifiable Fibrosis



Nonspecific Interstitial Pneumonia

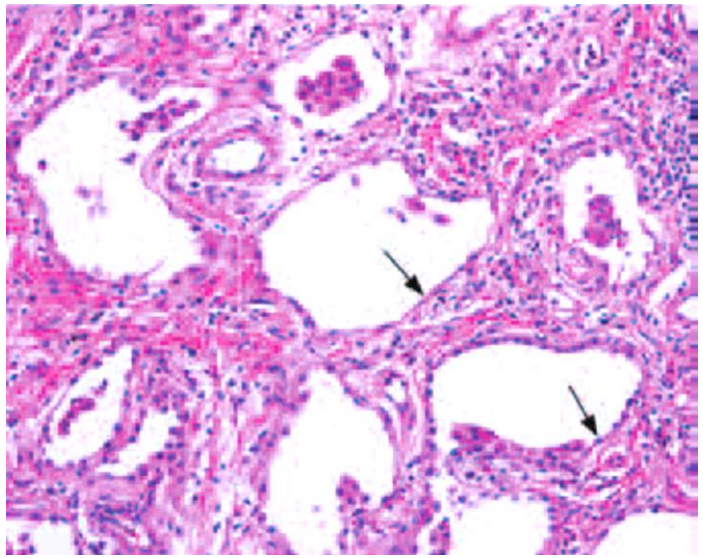
Cellular

- Mild to moderate chronic inflammation
- Type II pneumocyte hyperplasia in areas of inflammation



Fibrosing

- Dense or loose interstitial fibrosis lacking temporal heterogeneity/ patchy features of UIP
- Mild or moderate interstitial chronic inflammation
- Preserved lung architecture



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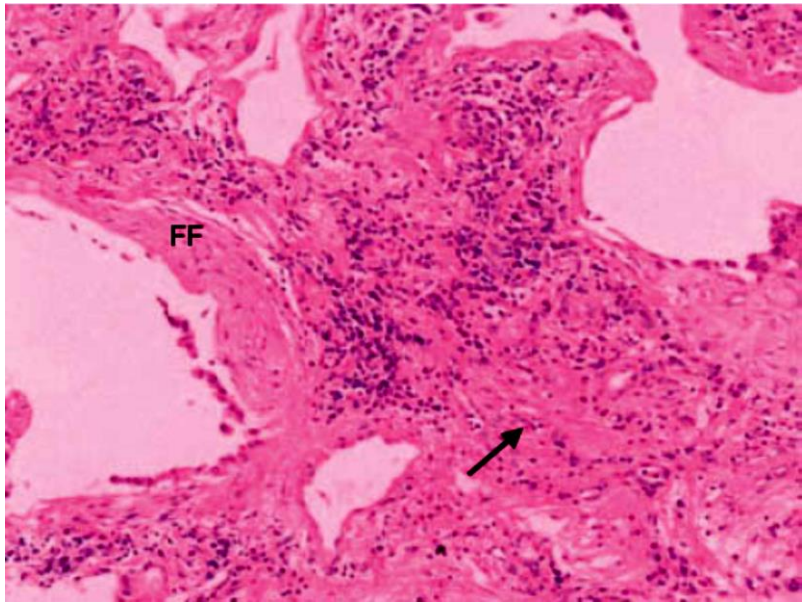
AJRCCM 2002; 165: 277-304.

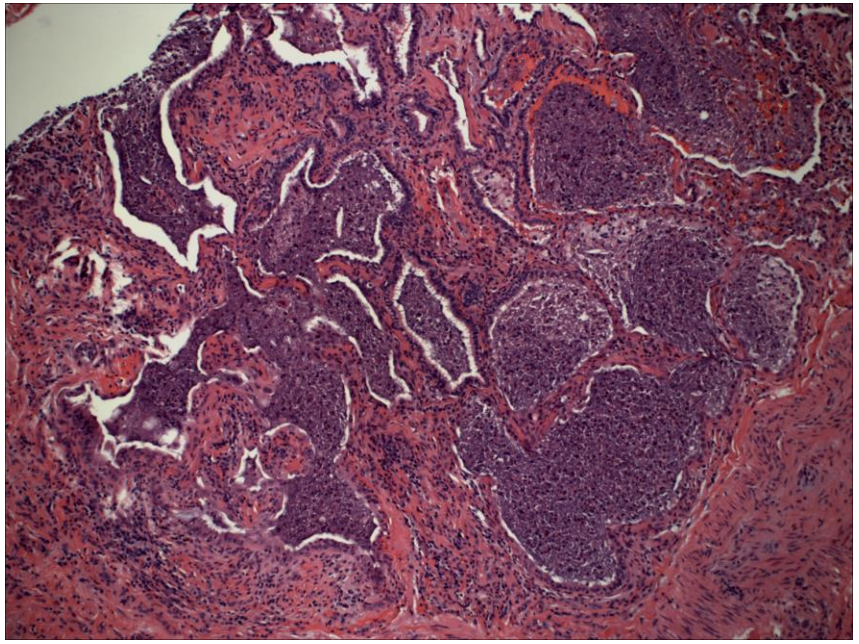
Usual Interstitial Pneumonia – Pathology



Honeycombing:

- Enlarged cystic spaces
- Bronchiolization
- Goblet cell hyperplasia

- Fibroblastic Foci
- Smooth Muscle Hyperplasia



Case 1

- **Smoking:** Never
- **Occupational history:** sales (works out of basement for years)
- **Exposures:** no known mold or water damage, no birds
- **Autoimmune :**
  - Review of systems: Raynaud, dysphagia, arthralgias, early bilateral foot neuropathy, pleuritic chest pain and hair loss in the year prior to presentation.
  - Exam notable for puffy digits, mild ankle tenderness bilateral. Abnormal nailfold capillary microscopy.

    NO sclerodactyly, telangectasias, fingertip ulcers
  - ANA 1:640 (homogenous and speckled), Scl70 100, RNA polymerase negative

Case 1

- Diagnosed with systemic sclerosis with extensive degree of ILD
- Echocardiogram unremarkable
- Mycophenolate Mofetil prescribed
- Enrolled for Scleroderma Lung Study (SLS) III trial consideration

New Presentation of ILD- Suggested Attention to CTD

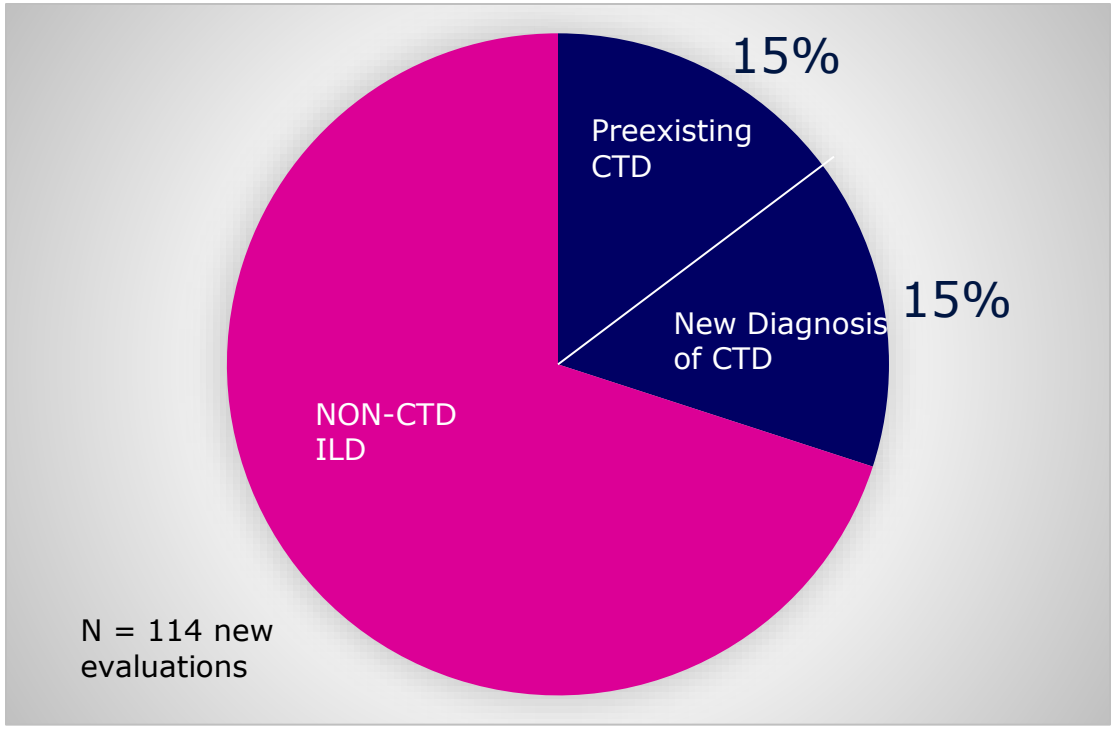
- History of colitis, thrombocytopenia, response to systemic steroids, female, <40 years old
- Autoimmune review of systems
  - Raynaud/joint/dermatologic/GI/myalgias/weakness/neuropathy
- Examination
  - Look for joint deformity/ skin changes

New Presentation of ILD- Suggested Attention to CTD

- Laboratory workup
  - Recommended screening in suspected idiopathic pulmonary fibrosis: ANA w/ titer, RF, Anti-CCP, SSA/SAB, Anti-SCL 70, CPK, aldolase +/- ANCA
  - More comprehensive in patients with suspected extrapulmonary disease

Connective Tissue Disease is Common in New ILD Evaluations

Johns Hopkins ILD Clinic



New CTD diagnosis in patients was associated with ANA ≥ 1:640, elevated CPK or elevated aldolase

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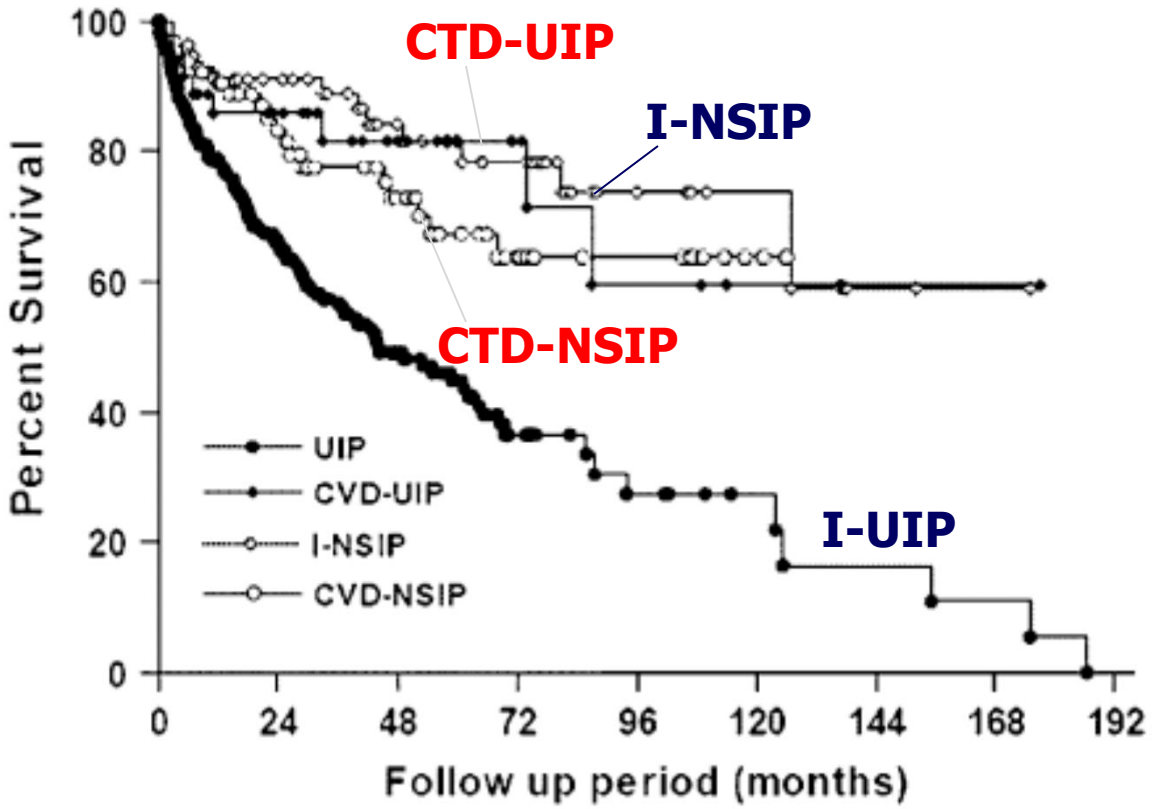
Mittoo et al, *Respir Med* 2009; 103 (8): 1152-8.

Pathologic Pattern in Established Connective Tissue Disease Does NOT Change Prognosis



5-Year Survival

CTD-NSIP - 81.5%

I-NSIP – 67.4%

CTD-UIP – 81.6%

I-UIP – 44.8%

p<0.001

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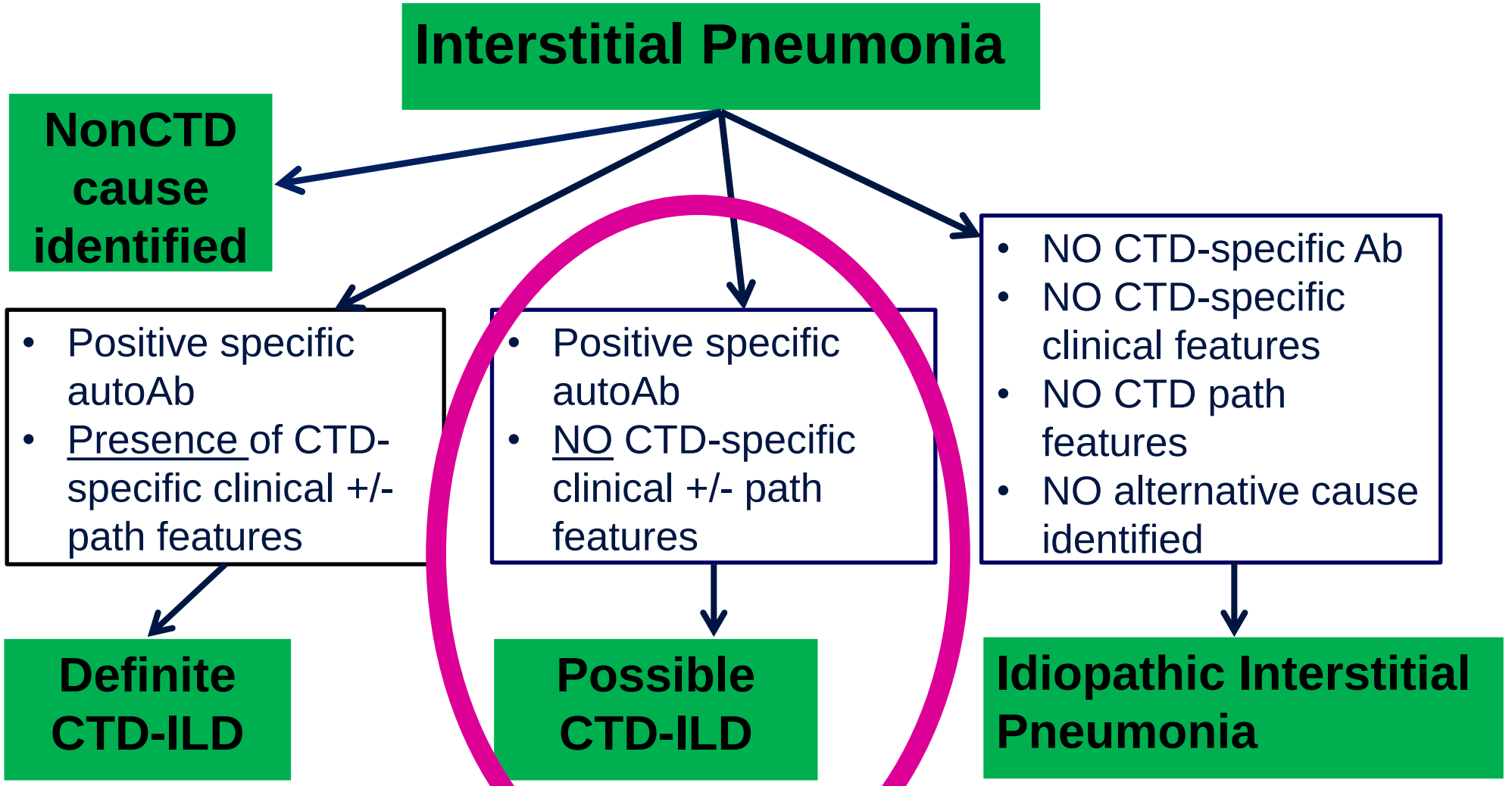
Park et al, *AJRCCM* 2007; 175: 705-711.

Diagnostic Algorithm



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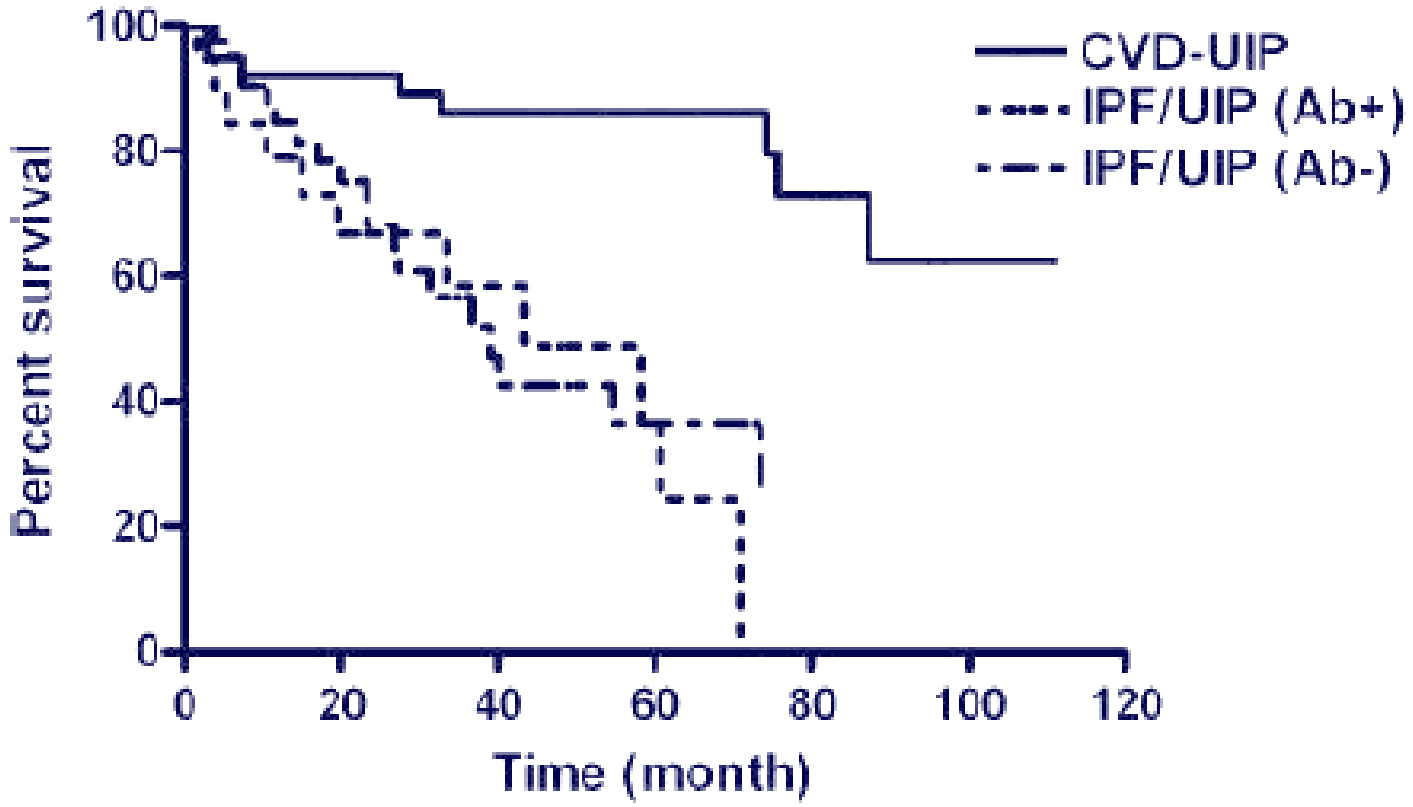
Adapted from Fischer and DuBois, *Lancet* 2012; 380: 689–98.

Positive Autoantibodies in IPF Do NOT Improve Prognosis



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Song et al, *CHEST* 2009; 136:23-30.

Interstitial Pneumonia with Autoimmune Features

1. Presence of an interstitial pneumonia by HRCT or SLB *and*
2. Exclusion of alternative etiologies *and*
3. Does not meet criteria for a defined CTD *and*
4. At least one feature from at least two of the following domains:

A. Clinical domain

1. Distal digital fissuring (i.e., "mechanic hands")
2. Distal digital tip ulceration
3. Inflammatory arthritis *or* polyarticular morning joint stiffness ⩾60 min
4. Palmar telangiectasia
5. Raynaud phenomenon
6. Unexplained digital edema
7. Unexplained fixed rash on the digital extensor surfaces (Gottron sign)

B. Serologic domain

1. ANA ⩾ 1:320 titer, diffuse, speckled, homogeneous patterns *or*
   a. ANA nucleolar pattern (any titer) *or*
   b. ANA centromere pattern (any titer)
2. Rheumatoid factor ⩾2 × upper limit of normal
3. Anti-CCP
4. Anti-dsDNA
5. Anti-Ro (SS-A)
6. Anti-La (SS-B)
7. Anti-ribonucleoprotein
8. Anti-Smith
9. Anti-topoisomerase (Scl-70)
10. Anti-tRNA synthetase (e.g., Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS)
11. Anti–PM-Scl
12. Anti–MDA-5

C. Morphologic domain

1. Suggestive radiology patterns by HRCT:
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
2. Histopathology patterns or features by surgical lung biopsy:
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
   e. Interstitial lymphoid aggregates with germinal centers
   f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)
3. Multicompartment involvement (in addition to interstitial pneumonia):
   a. Unexplained pleural effusion or thickening
   b. Unexplained pericardial effusion or thickening
   c. Unexplained intrinsic airways disease* (by PFT, imaging or pathology)
   d. Unexplained pulmonary vasculopathy

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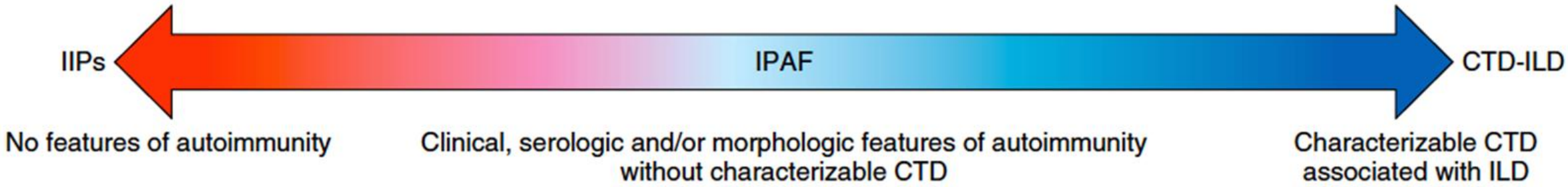
ERS/ATS Task Force on Undifferentiated Forms of CTD-ILD, *Eur Respir J* 2015; 46: 976–987.

Idiopathic Pneumonia with Autoimmune Features (IPAF)



Features associated with worse prognosis

- Increasing age
- Ever smoker
- Usual interstitial pneumonia pattern (vs nonUIP pattern)
- Lower DLCO

(Gender & %predicted FVC were not predictive)

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Bridget A. Graney and Aryeh Fischer, AnnalsATS May 2019

Workup of ILD in Established CTD

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Case 2 – Rheumatology-ILD clinic visit

68 year old man with history of Rheumatoid Arthritis (+RF, +CCP) referred with increasing shortness of breath and cough over the past 2 months

Joint symptoms are well-controlled. Denies chest discomfort and lower extremity edema

Medications: Methotrexate, Etanercept

Social history: 20 pack-year cigarette smoking, quit 15 years ago, recently laid off from a bank

Physical exam: 99.5, 128/72, 98, 18, 94% on room air; s1s2 regular, fair air movement with bibasilar crackles; no peripheral edema

Case 2 - Differential

- Chronic obstructive pulmonary disease exacerbation
- Congestive heart failure
- Infection – viral, bacterial, mycobacterial, fungal
- Manifestation of Rheumatoid Arthritis: bronchiolitis obliterans, bronchiectasis, interstitial lung disease, pulmonary hypertension, pleural effusions
- Drug side effect: Methotrexate and/or Etanercept

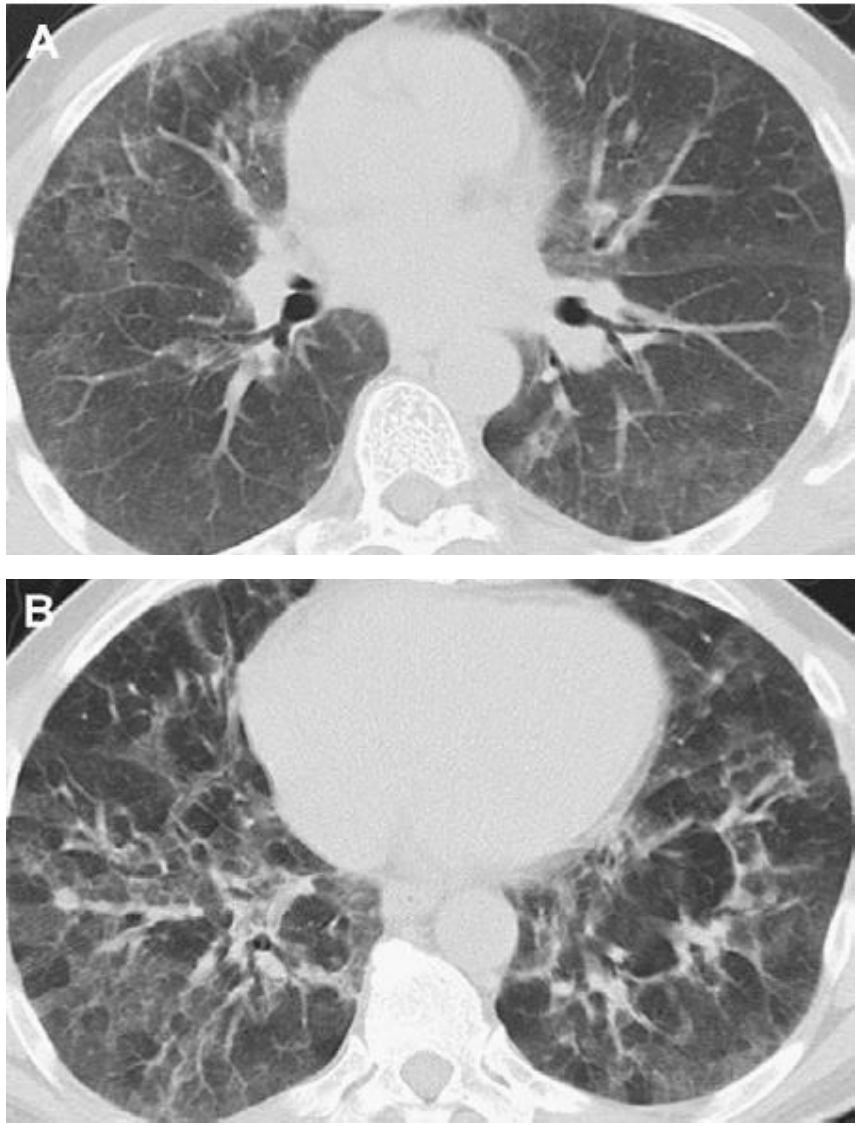
Criteria for Drug-Induced Lung Disease

Criteria	
Correct identification	History – current and remote drugs, OTC, herbal, illicit, radiation
Singularity	Likelihood of the drug causing adverse pulmonary event
Temporal eligibility	Comparison to films prior to drug exposure, dechallenge and rechallenge response
Characteristic features	Clinical, imaging, BAL, pathologic pattern
Exclusion of other causes of ILD	Infection, pulmonary edema, pulmonary involvement from the background condition

Camus, *Respir* 2004; 71: 301-26.

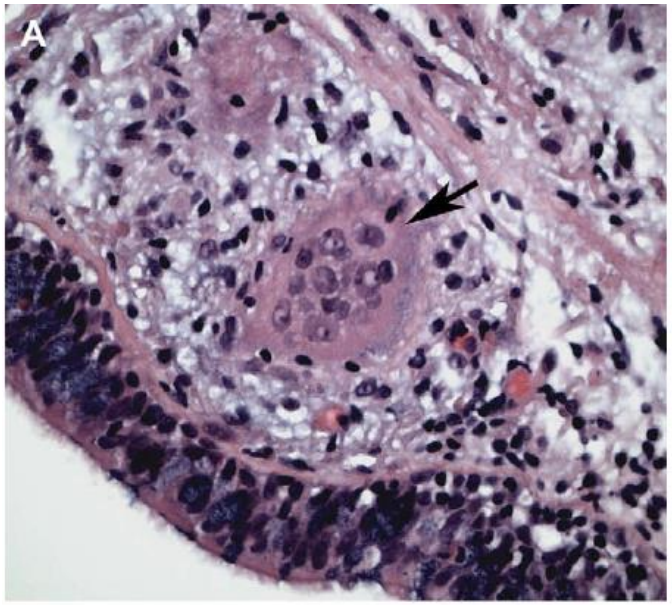
Case – Workup

- Pulmonary Function Testing
- Chest imaging (Chest x-ray, High resolution chest CT)
- Considerations:
  - Bronchoscopy with bronchoalveolar lavage +/- transbronchial biopsy
  - Surgical lung biopsy
  - Repeat serology (Rheumatoid Factor, CCP)
  - Verify prior PPD status (risk of reactivation)



Ground glass opacities with mosaic attenuation

Respiratory mucosa with rare multinucleated giant cell (arrow).



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Thavarajah et al, *Resp Med* 2009; 103: 661-9.

Patients with CTD in Need of Pulmonary Evaluation

- Symptoms: dyspnea (workup with complete PFTs, HRCT, consideration of echocardiogram)
- Abnormal PFTs and/or HRCT
- Based on PFT and HRCT screening & disease state: systemic sclerosis, amyopathic dermatomyositis
- Incidental findings of ILD (symptom correlation with degree of ILD involvement may be poor in CTD-ILD)

Disease Specific Considerations in ILD

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ILD in Rheumatoid Arthritis

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ILD in Rheumatoid Arthritis

TABLE 1 Prevalence and clinical features of rheumatoid arthritis (RA)-associated lung diseases

Disease phenotype	Clinical features	Prevalence
Parenchymal lung disease		
UIP pattern	Radiographic pattern: subpleural, basal predominant reticular opacities, honeycombing, minimal ground-glass opacity, architectural distortion with traction bronchiectasis Associated with worse outcomes compared to other disease patterns in RA	8–66%
NSIP pattern	Extensive ground-glass opacity, traction bronchiectasis, subpleural sparing Lower risk of disease progression and better treatment response compared with UIP	19–57%
Organising pneumonia	Focal ground-glass opacities, consolidations, reversed halo sign	0–11%
Other (*e.g.* LIP or DIP)	Thin-walled cysts, centrilobular nodules, ground-glass attenuation, peribronchovascular septal thickening, upper-lobe predominant	Rare
Rheumatoid nodules	May be single or multiple and range in size, typically asymptomatic unless they cavitate or rupture, in which case infection, pleural effusion or bronchopleural fistula may occur	<1% radiographically, 30% on autopsy specimens
Caplan's syndrome	Complication that occurs in those with pneumoconiosis from occupational exposure to coal, silica or asbestos Sudden development of multiple nodules, from 0.5 to several centimetres in diameter, distributed throughout the lungs but predominantly at the lung periphery	<1% in the USA by autopsy
Airway disease		
Upper airway		
Cricoarytenoiditis	Arthritis of the cricoarytenoid joint leading to mid-line adduction of vocal cords with resultant hoarseness and/or stridor	32–75% *via* laryngoscopy 54–72% on CT scans
Lower airway		
Bronchiectasis	Associated with chronic infection	Present on HRCT in ~30%, though many cases clinically silent
Bronchiolitis (constrictive or follicular)	Female sex, high RF titre and long disease duration	By pulmonary function testing or radiographic pattern: 8–30%
Pleural disease		
Pleural effusion	Middle-aged males with positive RF and rheumatoid nodules Rheumatoid effusion: classically sterile, exudative fluid with low pH (<7.3), glucose <60, and elevated LDH	Symptomatic in 3–5%, though present in up to 70% in autopsy studies

- Lung Involvement in 60% of patients
- Typically occurs following articular manifestations

- Complex relationship between:

  Genetics: Twins, MUCB5 gene

  Environmental: smoking

  Autoimmune factors

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Kadura, EUROPEAN RESPIRATORY REVIEW, 2021

Prevalence and Prognosis of RA-ILD

- A Cohort of 1460 pt
- ILD in 3.6%
- Onset of ILD within 3 yrs
- Median Survival 3yrs

- RA-ILD vs RA-UIP

- Male Predominance

- UIP is the most common pathologic finding

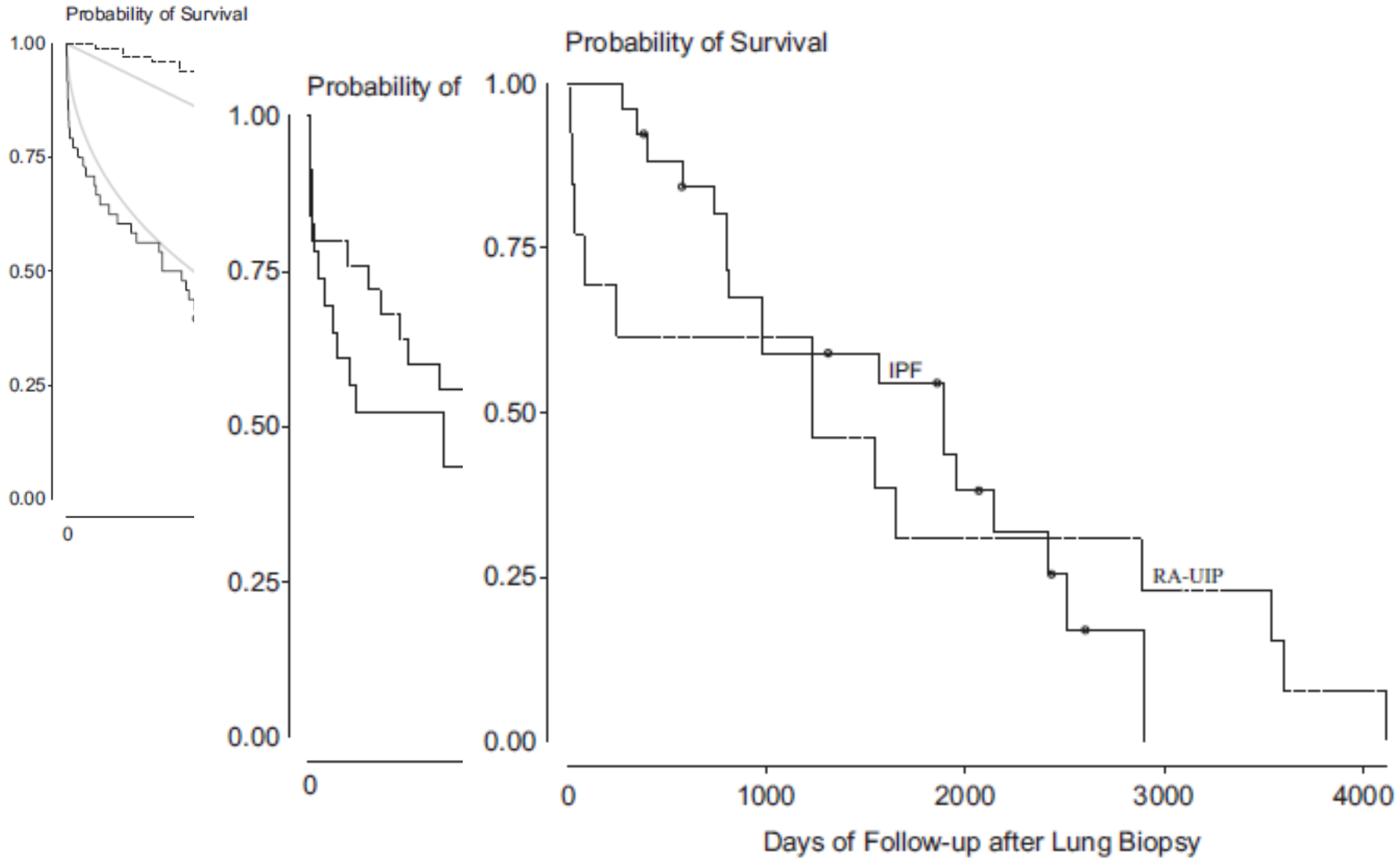
	UIP	non-UIP	Comments and references
Age	Older	Younger	Trend towards older age in RA-UIP[39, 41]
Gender	M>F	F>M	[21, 30, 41]
Smoking	More smoking	Less smoking	[40, 42]
RA Disease duration	Unrelated	Unrelated	[23, 42]
RA severity	Unknown	Unknown	
Anti-CCP antibodies	Lower	Higher	Trend towards lower CCP in one study[66]
Baseline PFT	Restrictive	Restrictive	No difference in severity of restriction and diffusion abnormalities[41, 43]
Response to treatment	Poor	Better	Anecdotal evidence and subgroup analysis data[56]
Acute exacerbations	Reported	Not reported	Case reports and observational study[62, 63, 67]
Survival	Worse	Better	Better in some studies[41, 43, 63] but not in others[40]

Koduri et al, *Rheum* 2010; 49 (8): 1483-9.

Iqbal et al, Ther Adv Musculoskel Disease 2015

Assayag et al, *MEDICINA* (Buenos Aires) 2014; 72: 158-165

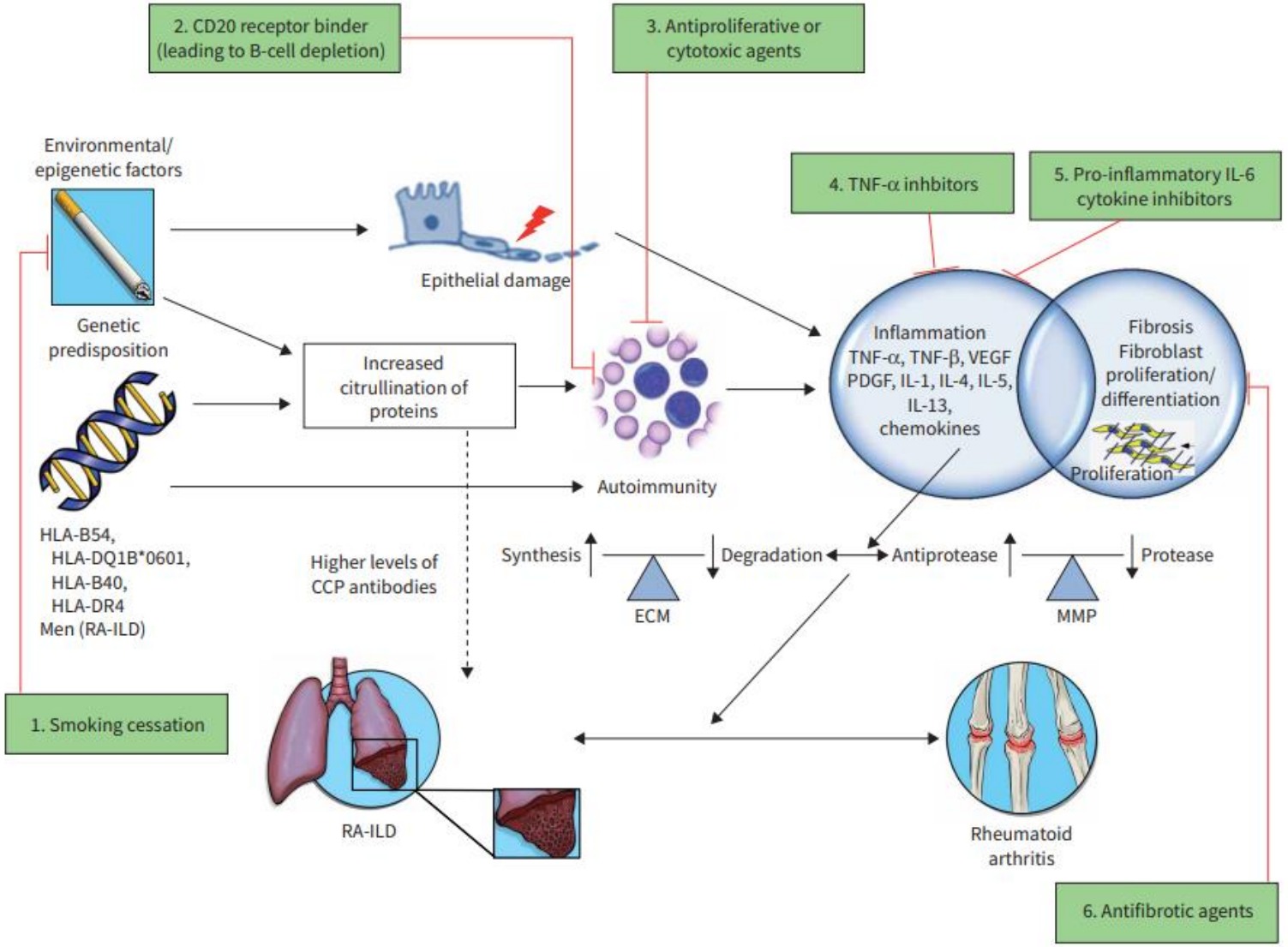
RA - Fibrotic Interstitial Pneumonia is Associated with Worse Survival



Solomon et al, *Respiratory Medicine* 2013, 107: 1247-1252.

RA-ILD THERAPY

- No RCTs comparing medications efficacy.
- DMARDs, Biologic agents and potential for pulmonary toxicity ??
- Therapeutic alternatives
- Antifibrotics
- Transplant referral



Myositis-related ILD

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Myositis

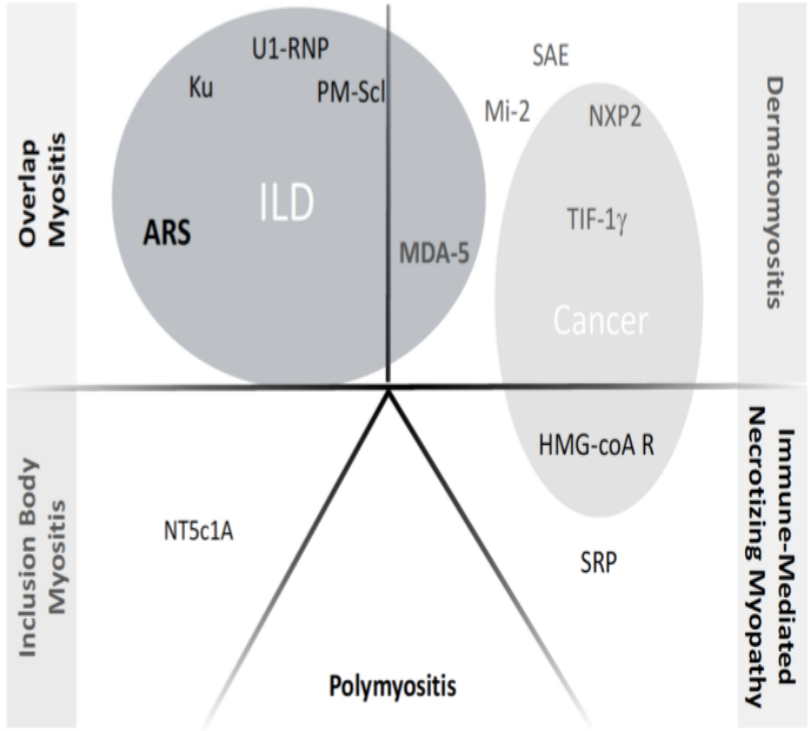

FIGURE 1 | Current classification of inflammatory myopathies and the respective autoantibodies. ILD, Interstitial Lung Disease; ARS, anti-tRNA-antisynthetase autoantidodies, including anti-Jo-1, PL7, PL12, OJ, EJ, Zo, KS, YRS. NXP2: example of myositis specific autoantibody or myositis associated autoantibody; when appearing inside gray circles, the autoantibodies have been shown to correlate with occurrence of either ILD or Cancer, respectively.

TABLE 1 | Prevalence of ILD in the context of Inflammatory-myopathy.

Diseases	Autoantibodies	Prevalence of the ILD	References
	Myositis-specific autoantibodies		
Dermatomyositis	MDA-5	90%	(15–17)
Antisynthetase syndrome	All ARS	80%	(18, 19)
	Jo-1	70%	
	Non-Jo-1	85%	
	Myositis-associated autoantibodies		
Overlap myositis	RNP	50%	(20)
	PM-Scl	25%	(21, 22)
	Ku	35%	(23)

ARS, anti-ARNt synthetase auto-antibodies; ILD, Interstitial Lung Disease.

Risk factors for ILD: older age at diagnosis, elevated ESR, elevated CRP, fever, arthralgia/arthritis

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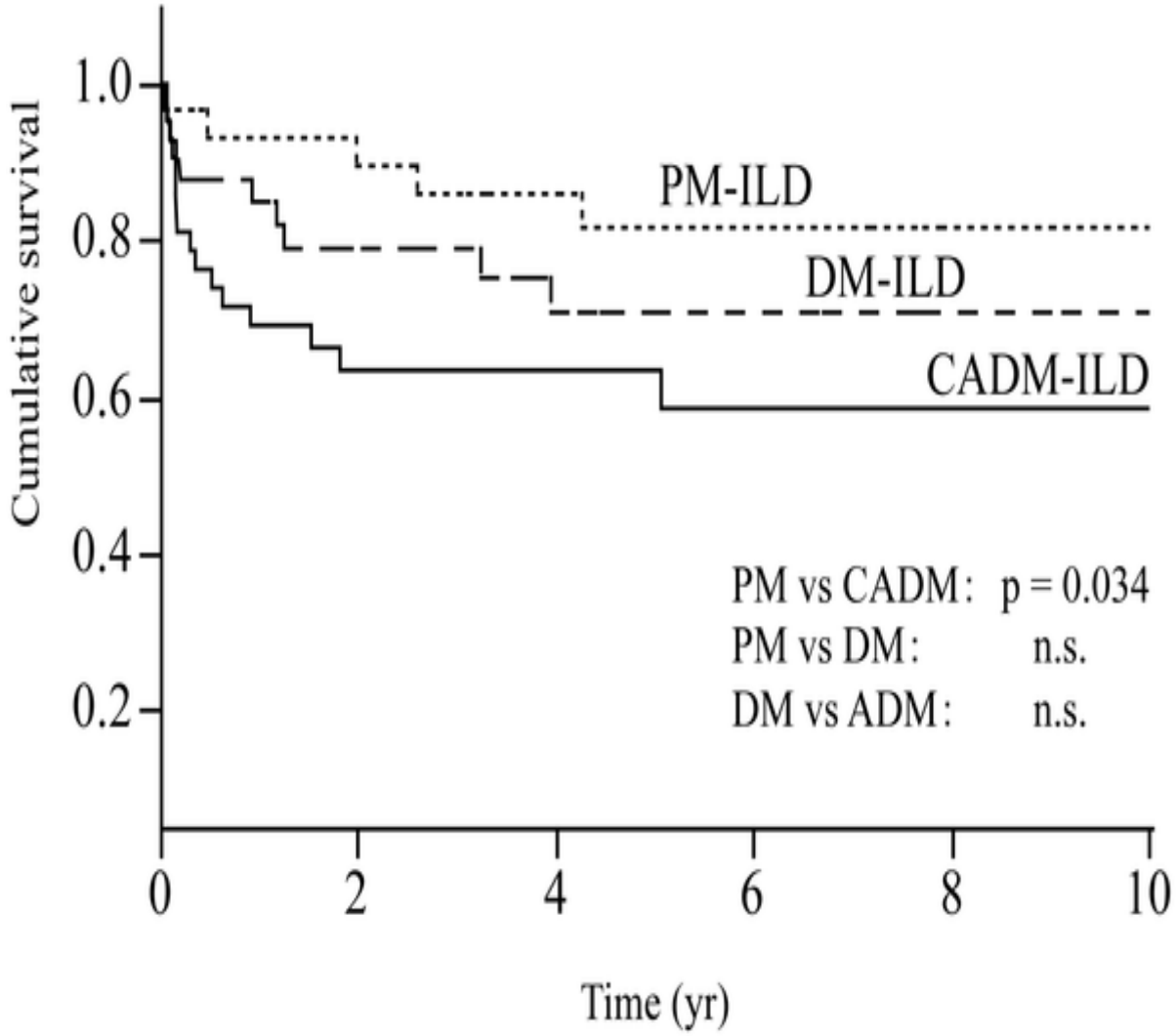
Hashimoto D, et al. (2014)
Hervier B Med. 6:326. doi: 10.3389/fmed.2019.00326

Prognosis of Autoimmune Myositis



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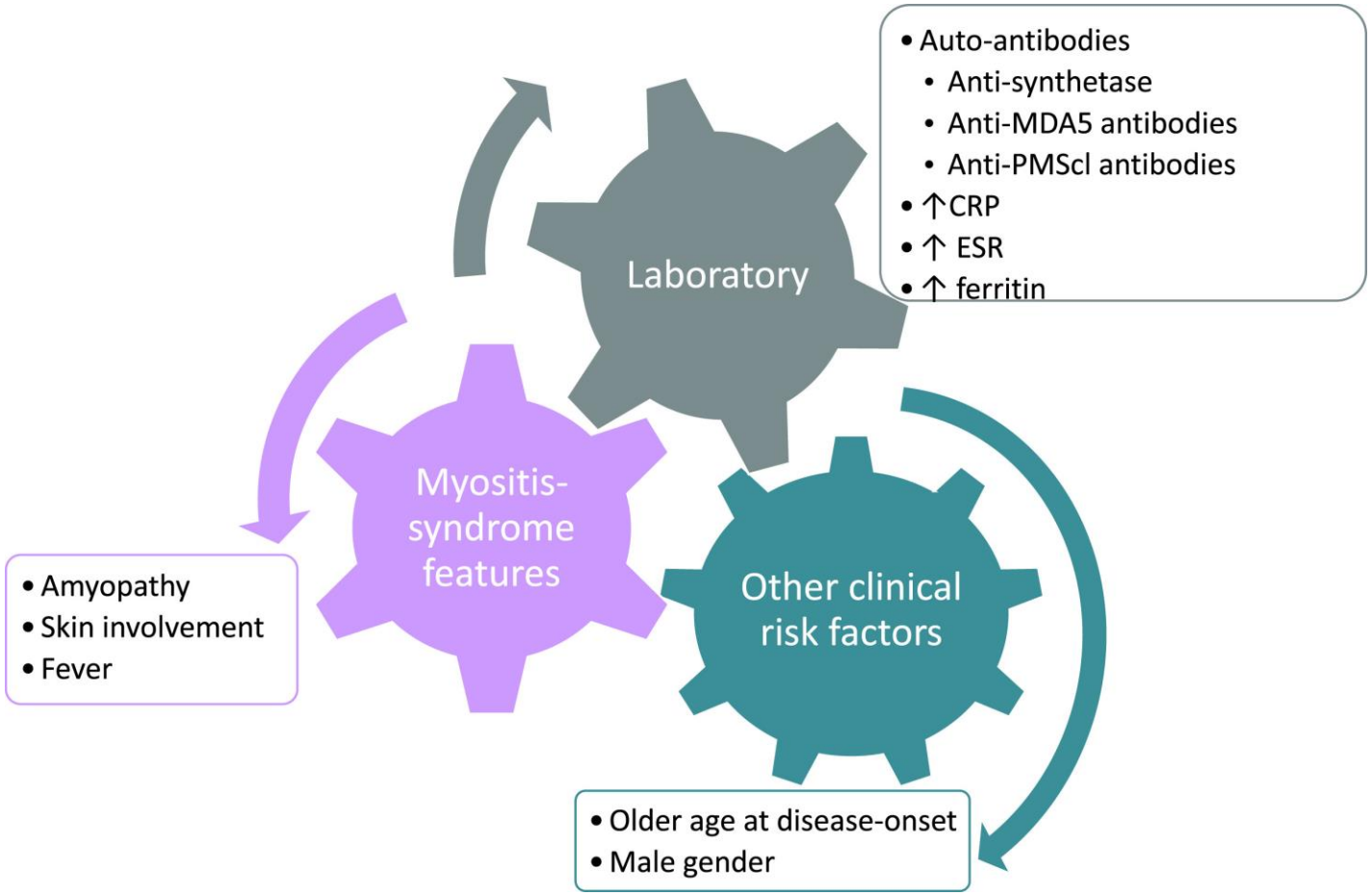
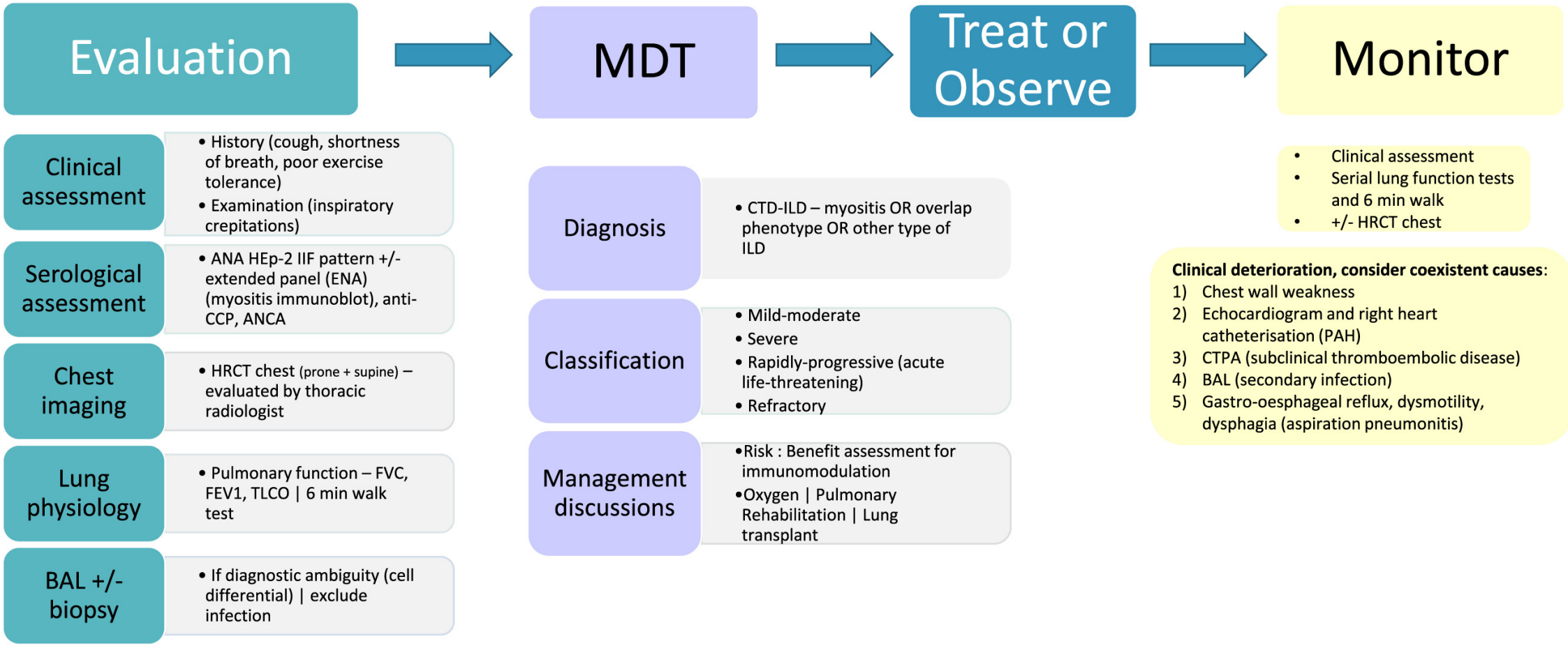
Hashimoto D, et al. (2014)
Hervier B Med. 6:326. doi: 10.3389/fmed.2019.00326

Risk Factors for Myositis-related ILD Development



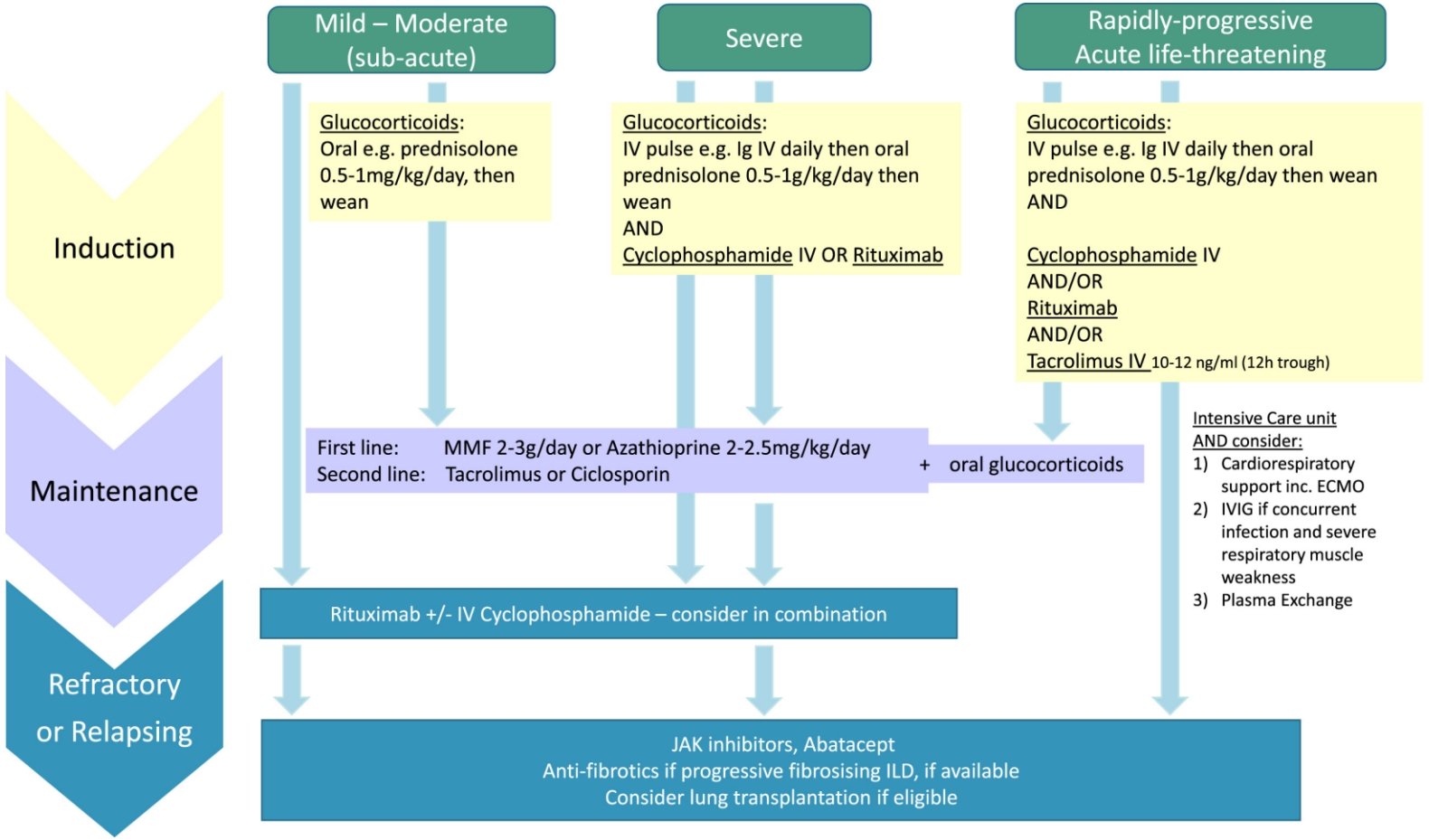
Mehta et al,Best Pract & Clin Res Rheum; 2022: 101769

Evaluation and Management of Myositis-ILD



Mehta et al,Best Pract & Clin Res Rheum; 2022: 101769

Evaluation and Management of Myositis-ILD



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Mehta et al,Best Pract & Clin Res Rheum; 2022: 101769

ILD in Systemic Sclerosis

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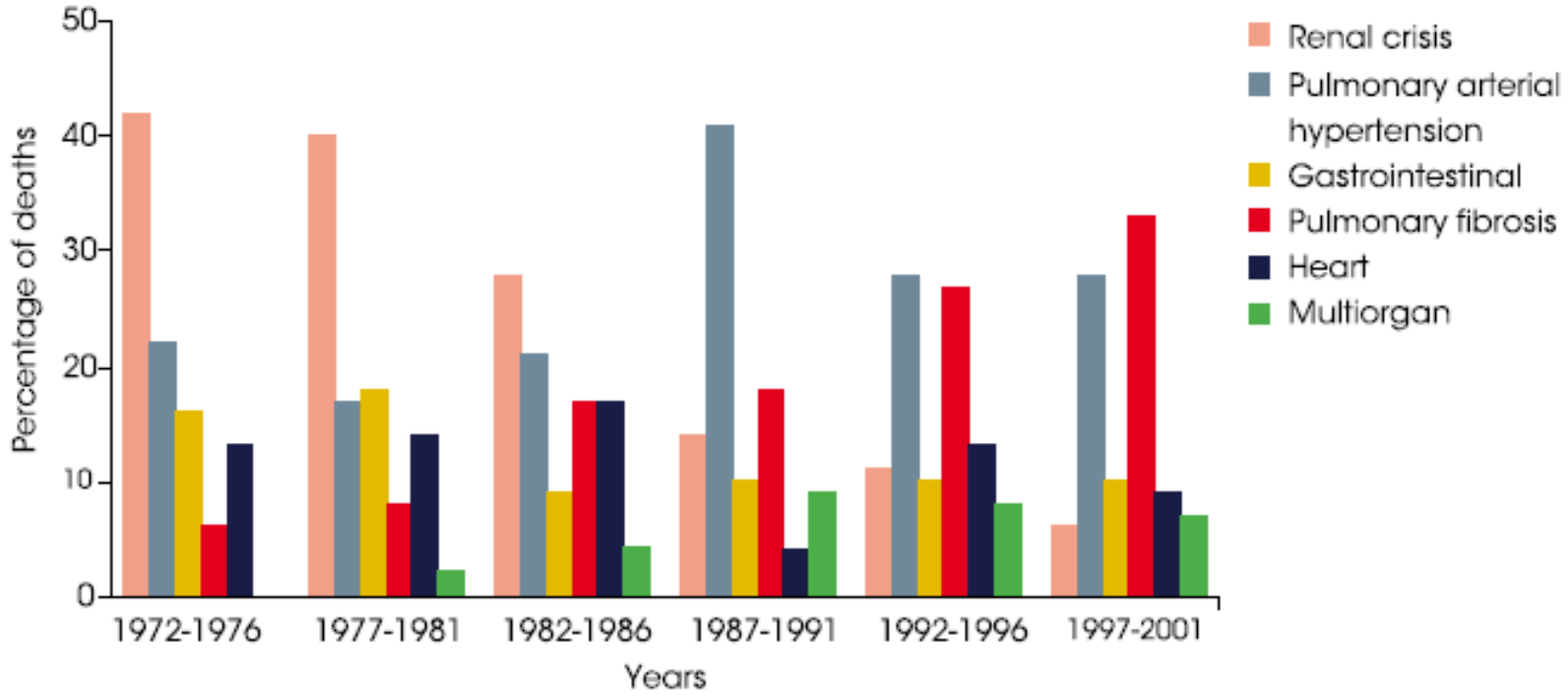
Systemic Sclerosis; Prognosis



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.

Ann Rheum Dis, Steen VD and Medsger TA, 2007

ILD in Systemic Sclerosis

- Up to 70-80% with ILD on autopsy (not necessarily symptomatic)
- Estimated Mortality is 3.7/1.000.000 in USA
- PFTs are not sufficient to rule out the presence of ILD (NEED HRCT)

- Risk factors for progressive Fibrotic ILD:
  - **Diffuse Disease**, Race (AA), Older age at the presentation
  - Early course of the disease (first 5 yrs)
  - Scl-70 Ab, absence of anticentromere antibody.

Bouros et al, *AJRCCM* 2002; 165: 1581-6.

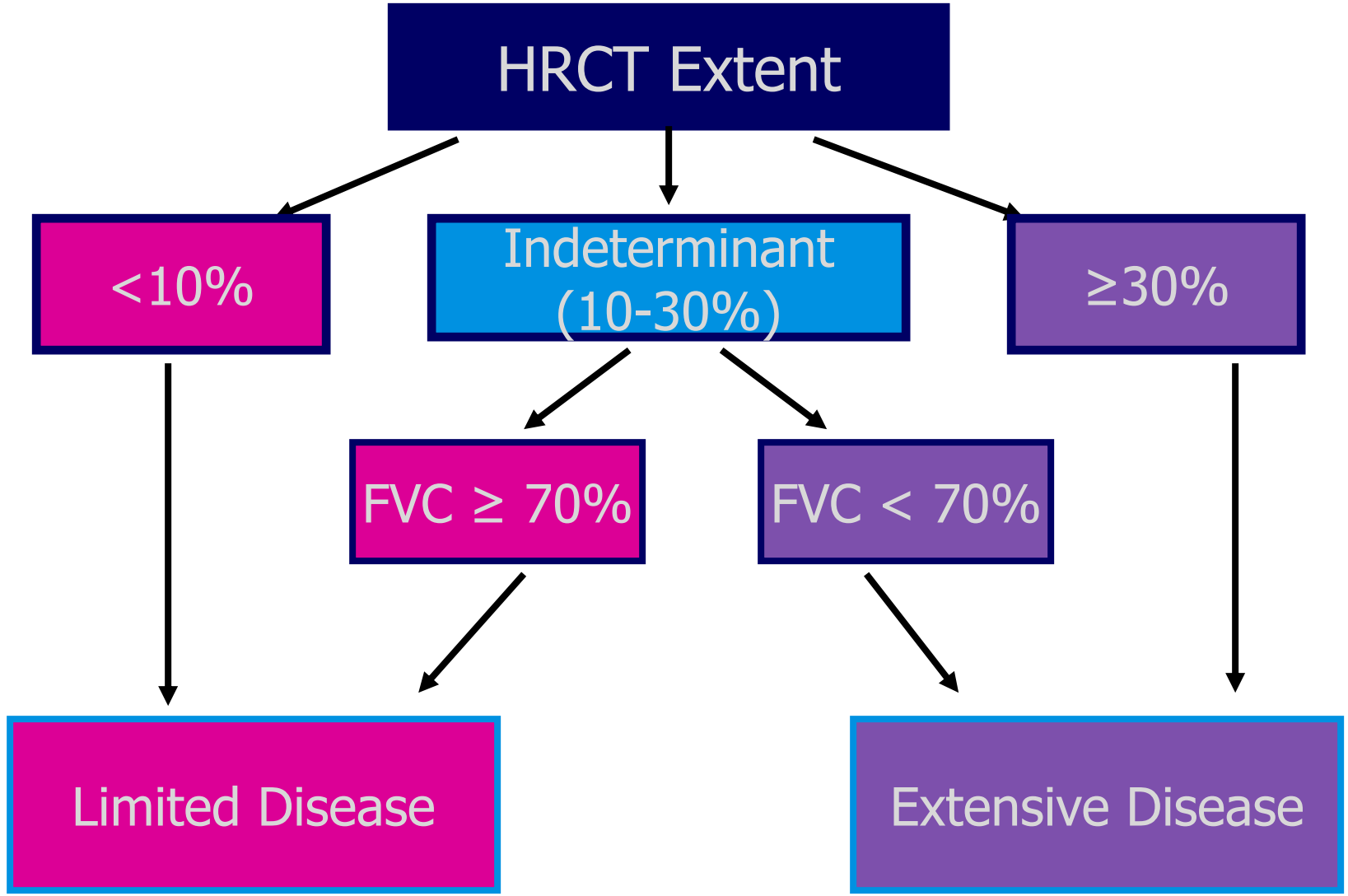
Desai et al, *Radiology* 2004; 232: 560-7.

Wells, *Rheum* 2008; 47: v59-v61

Launay et al, *J Rheumatol* 2006; 33:1789-801.

Suliman et al, Arthritis & Rheum, 2015; 67(12): 3256-3261.

Staging of ILD in Systemic Sclerosis



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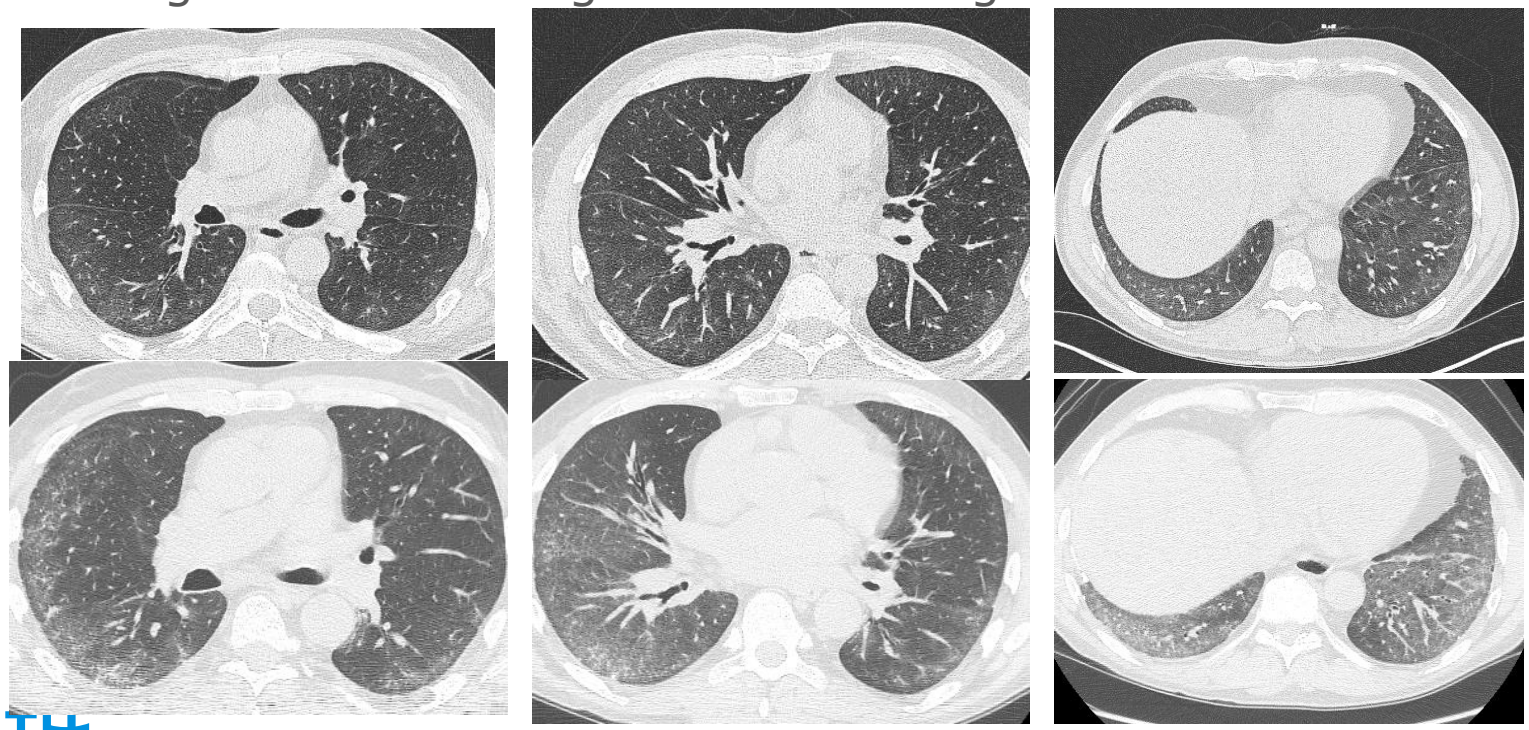
Adapted from Goh et al, *AJRCCM* 2008; 177: 1248-54.

Systemic Sclerosis; Treatment

Steroids – Scleroderma renal crisis	SLS 1	SLS 1 – follow up study extended to 2 years	Mycophenolate in SScILD	SLS 2
FAST	SENSCIS	SENSCIS subgroup analysis on Mycophenolate	Rituximab	Tocilizumab
HSCT	Lung transplant	Pirfenidone	Abituzumab	Other general treatment

Case 1 Revisited

- Patient completes SLS III trial
- Continues MMF 1.5 gm bid
- Repeat chest CT 2 years later shows progression in ground glass opacities
- Offered Nintedanib for Progressive Fibrosing Interstitial Lung Disease



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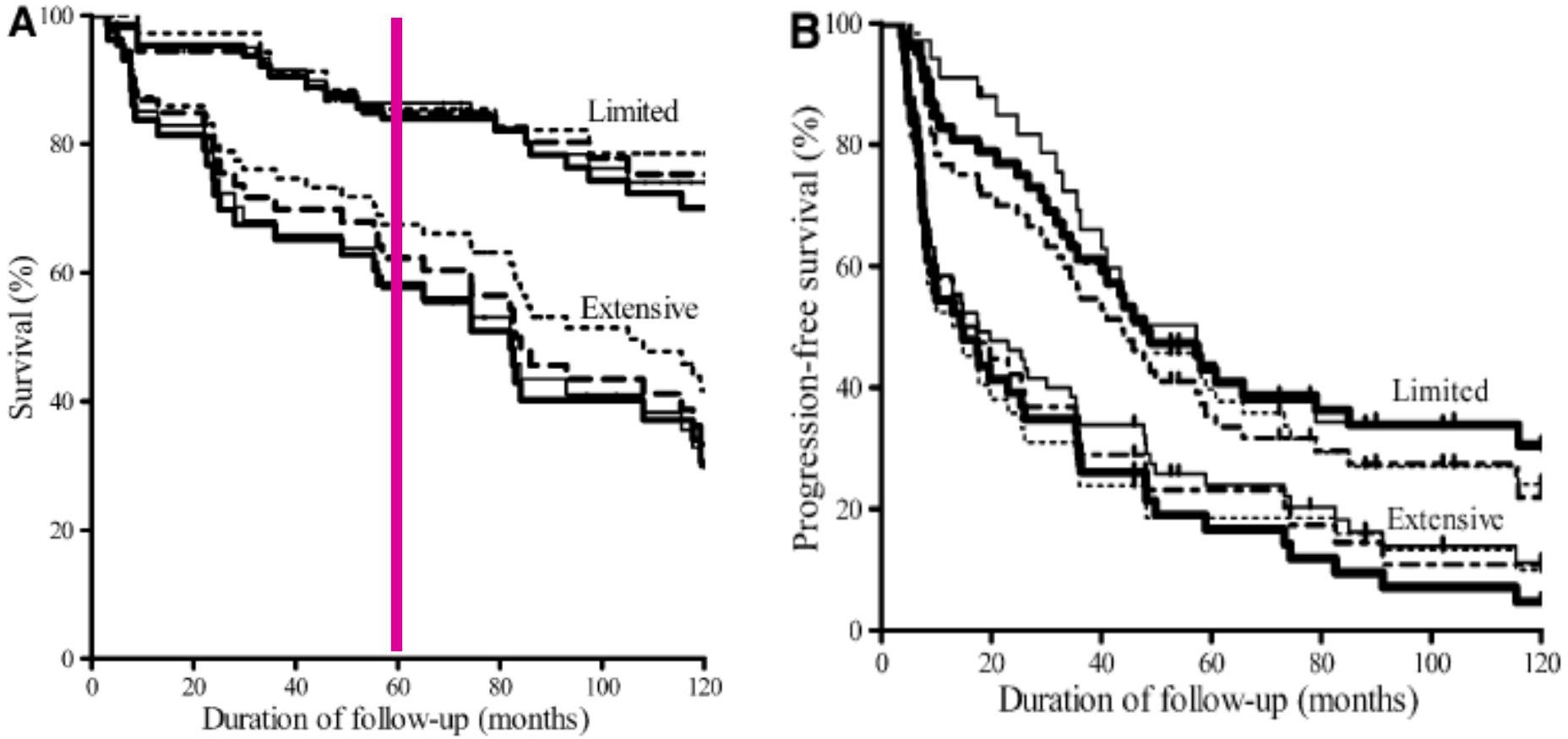
Staging of ILD in Systemic Sclerosis



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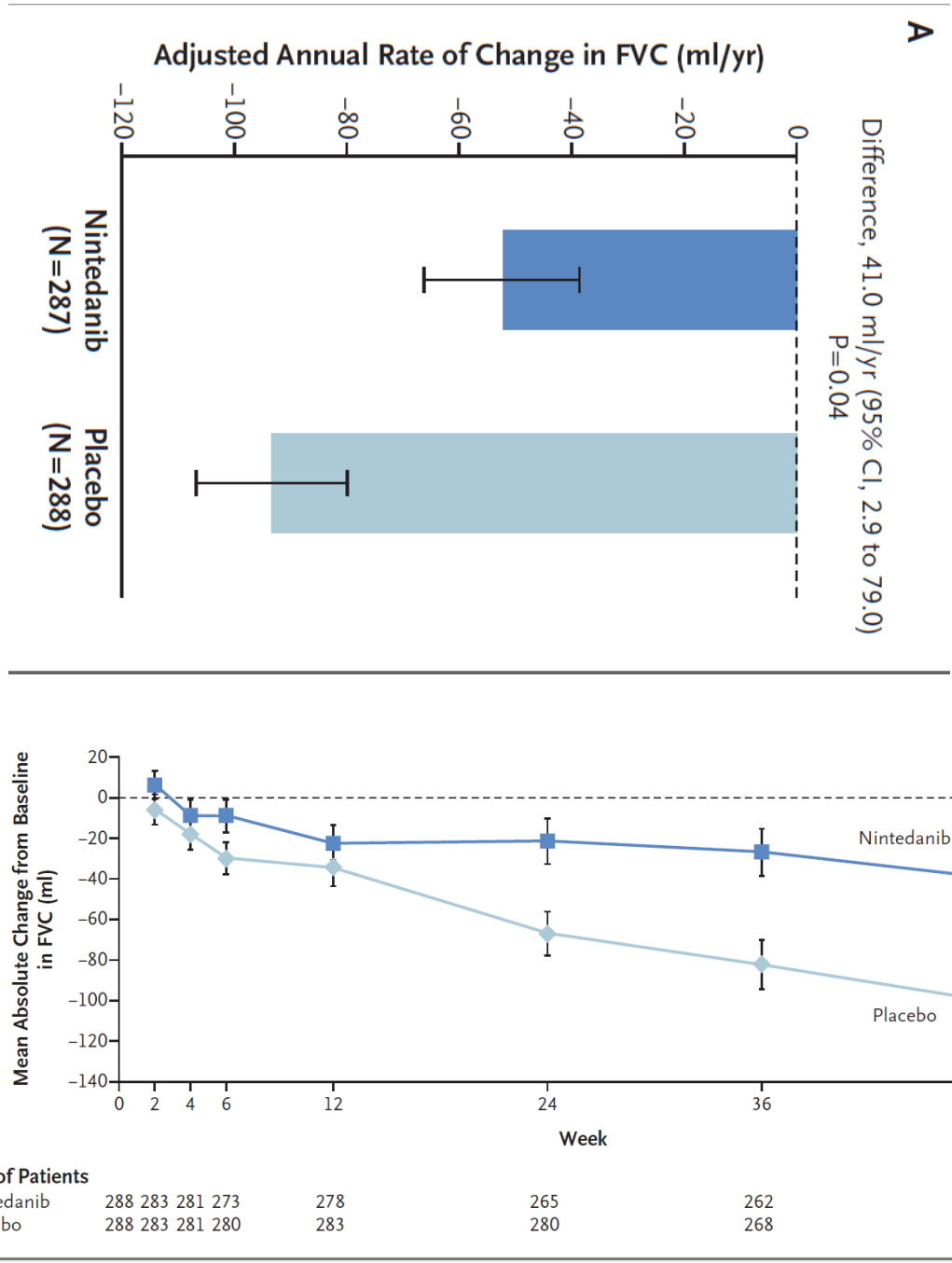
Goh et al, *AJRCCM* 2008; 177: 1248-54.

Treatment- SENSCIS

- The annual rate of change in FVC over a 52-week period was lower in the Nintedanib group than in the placebo group (−52.4 ml per year vs. −93.3 ml per year; difference, 41.0 ml per year; 95% confidence interval [CI], 2.9 to 79.0; P = 0.04)



Progressive Pulmonary Fibrosis

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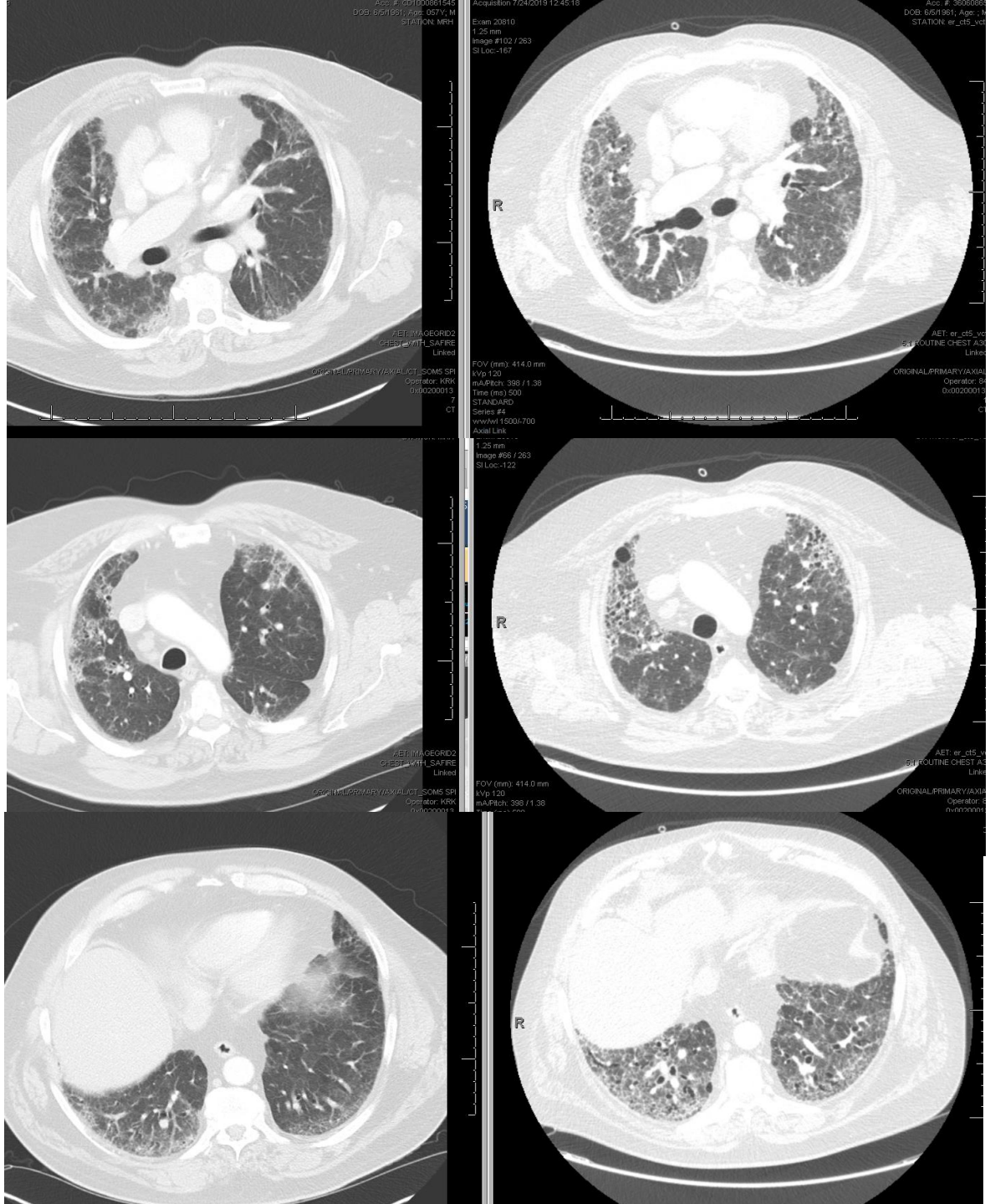
Changes in 3 months



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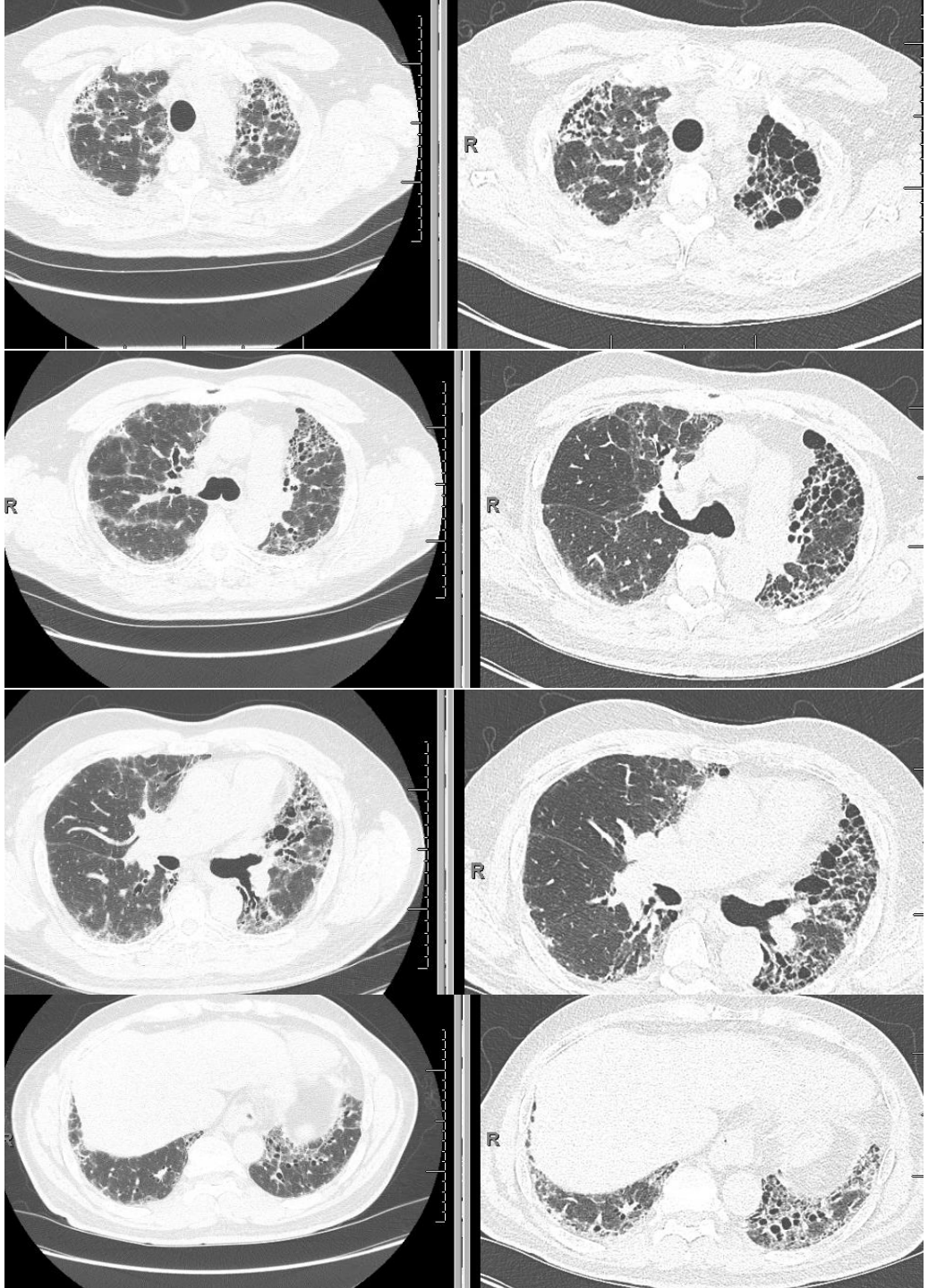
Changes in 1 year



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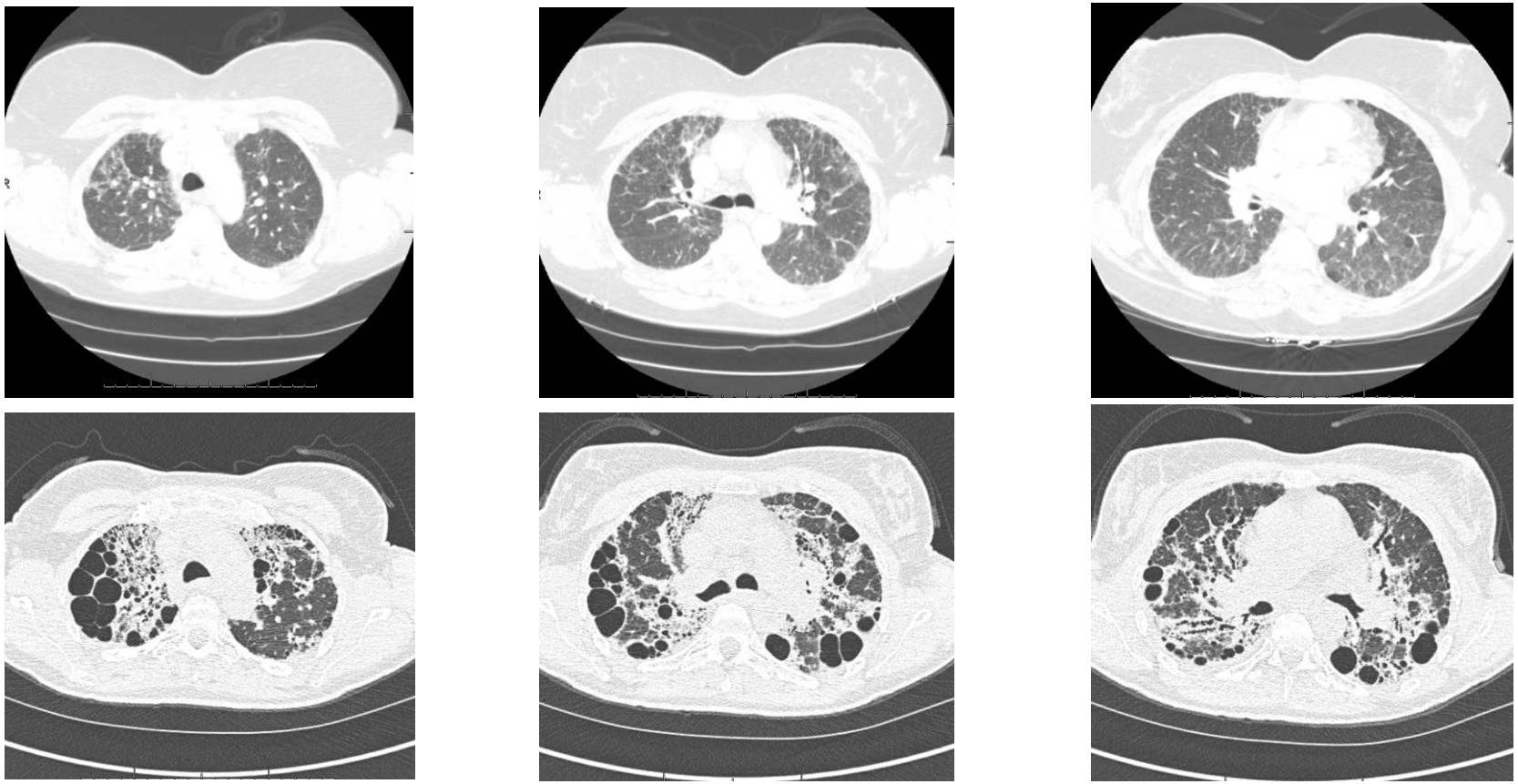
A Change in 3 years



Definition & Diagnostic Criteria

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults
An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

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

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Raghu G et al Am J Respir Crit Care Med Vol 205, Iss 9, pp e18–e47, May 1, 2022

Historical Perspective

Lumpers v/s splitters – Historically, we likely grouped all ILDs into a general category of pulmonary fibrosis

- **Lumping** – Lots of heterogeneity and hence difficult to study & response to treatment differs
  Ex – old retrospective data looking at corticosteroid use and survival - patients who responded to steroids were younger, females with biopsy showing more cellular than fibrotic disease – likely had NSIP
- **Splitting -** emphasis on diagnosis to determine therapy and prognosis.
  - Likely helped in success of IPF clinical trials
  - Fails to account for subsequent disease behavior

The Presence of Honeycombing in CTD-ILD is Associated with a Worse Prognosis

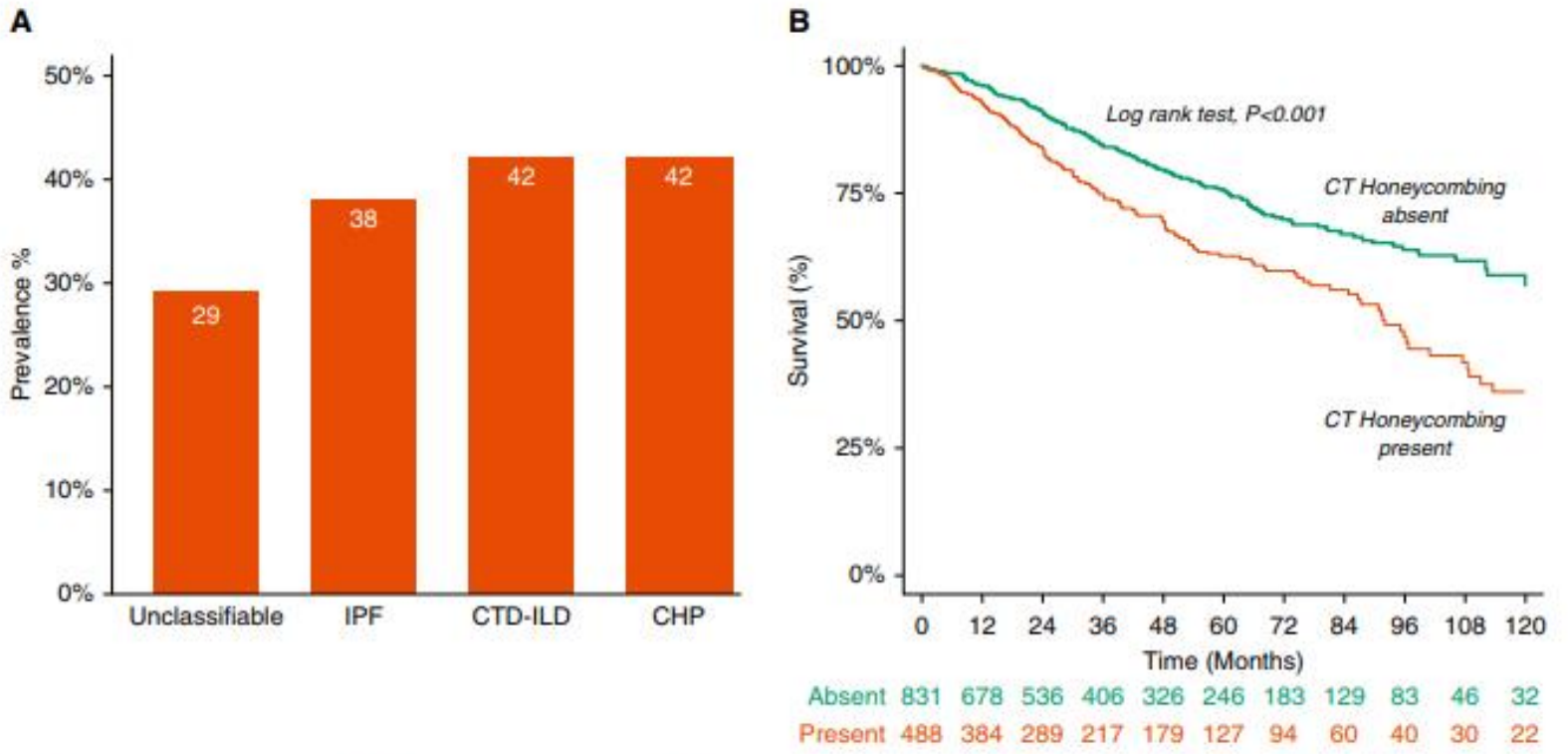
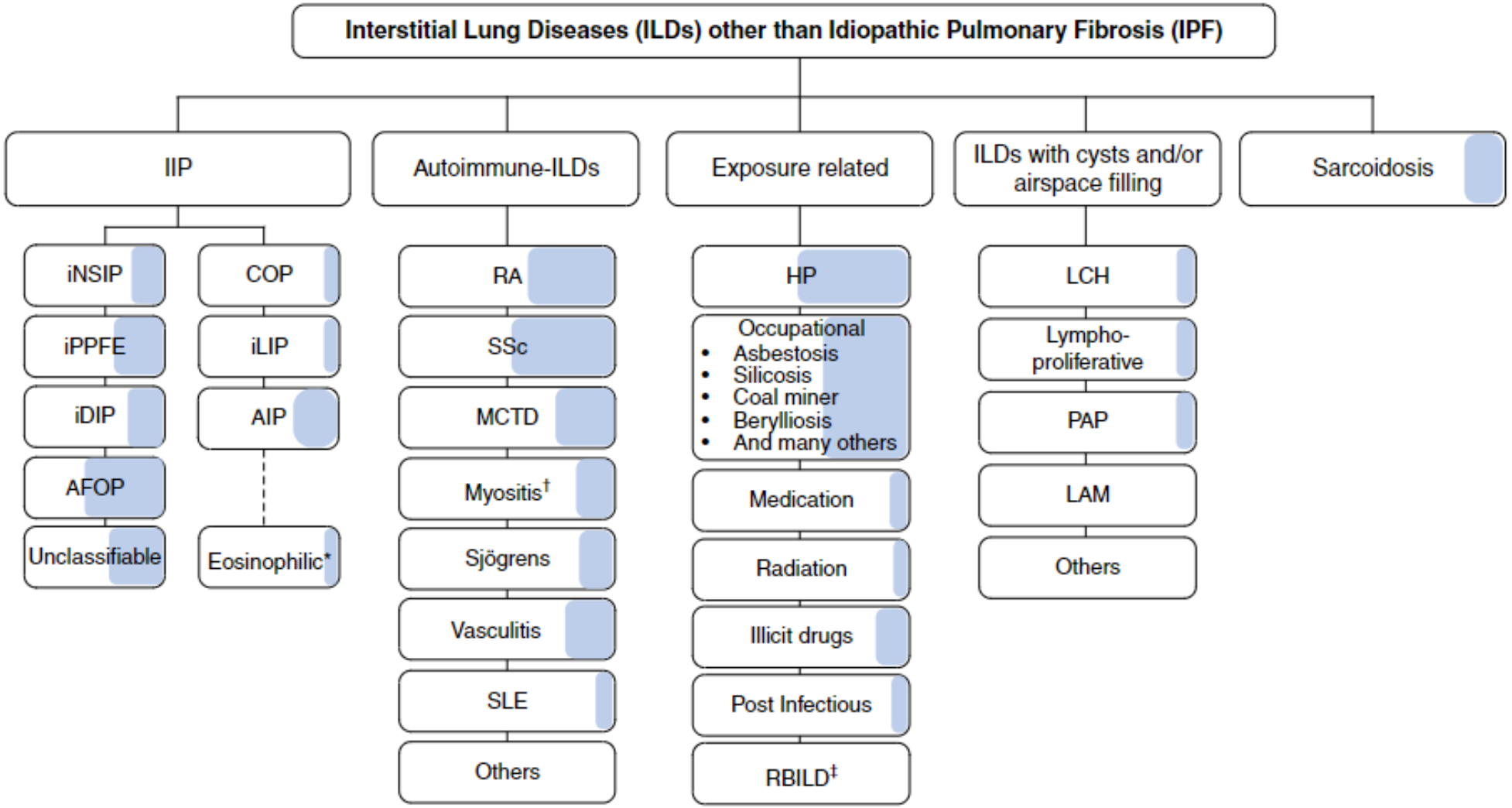


Figure 1. (*A*) Computed tomography (CT) honeycombing is prevalent across diverse interstitial lung disease (ILD) subtypes; (*B*) Kaplan-Meier analysis demonstrates worsened 10-year survival in participants with ILD and CT honeycombing. CHP = chronic hypersensitivity pneumonitis; CTD-ILD = connective tissue disease–associated ILD; IPF = idiopathic pulmonary fibrosis.

Adegunsoye et al: CT Honeycombing: a PF-ILD Phenotype Annals ATS **May 2019**

ILD Manifesting as Progressive Pulmonary Fibrosis



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Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. Cottin et al. Eur Respir Rev 2018;27:180076

Raghu G et al Am J Respir Crit Care Med Vol 205, Iss 9, pp e18–e47, May 1, 2022

Clinical Trial Enrollment Criteria

Clinical trial	Design	Criteria for disease progression				Study duration	Outcomes
		Time frame	Pulmonary function	Symptoms	HRCT		
Nintedanib in non-IPF PF-ILD [4▪▪]	Phase 3, double-blinded, placebo, RCT	24 months	FVC ≥10% decline (relative) or two of these: FVC 5–10% decline (relative)	Worsening symptoms	Increased extent of fibrosis	52 weeks	Annual rate of decline in FVC at 52 weeks: between-group difference 107.0–ml (95% CI 65.4–148.5)
Pirfenidone in progressive unclassifiable ILD [5▪]	Phase 2, double-blinded, placebo, RCT	6 months	FVC > 5% decline (absolute)	Worsening symptoms		24 weeks	Predicted mean change in FVC over 24 weeks[a]: between-group difference 95.3–ml (95% CI 35.9–154.6]
Pirfenidone in non-IPF PF-ILD (RELIEF) [41]	Phase 2, double-blinded, placebo, RCT	12 months	FVC ≥5% decline (absolute)			48 weeks	Absolute change in percentage predicted FVC over 48 weeks: favored pirfenidone[b]
Pirfenidone in patients with RA-ILD (TRAIL1) [42]	Phase 2, double-blinded, placebo, RCT	12 months	FVC ≥10% decline (relative) or FVC 5–10% decline (relative) and DLCO ≥15% decline (relative)			52 weeks	The composite endpoint of decline in percentage predicted FVC of at least 10% or death: not completed

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Progressive fibrosing interstitial lung disease: treatable traits and therapeutic strategies. Wongkarnjana et al, Curr Opin Pulm Med 2020

Clinical characteristics of ILDs manifesting as PPF

Condition	% of ILD patients	Prognosis	Progressive Fibrosing Phenotype
IPF	12	Median survival 3-4 years	90-100
SSc-ILD	9	40% 10 year mortality	40
RA-ILD	8	UIP pattern: Median survival 3 year (longer)	32
Sarcoid(fibrotic)	45	10-year mortality: 10%	13
Fibrotic HP	3	5 year survival: 50-80%	21
Unclassifiable	8	5 year survival: 45-70%	53

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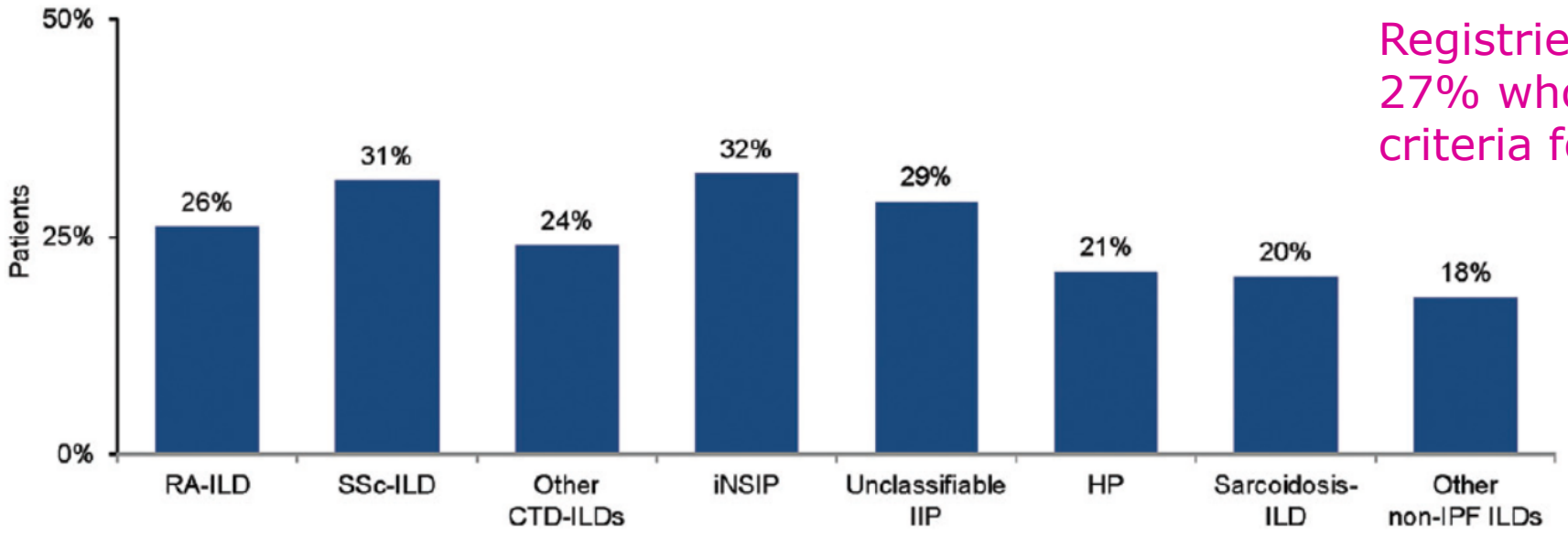
Spectrum of fibroitic lung diseases. Wijsenbeek M and Cottin V. N EnglJ Med 2020;383:958–68

Epidemiology

- Survey of 243 pulmonologists, 203 rheumatologists, 40 internists
- **13-40% of non IPF ILDs have a progressive fibrosing phenotype**



Registries report 14-27% who meet criteria for PPF

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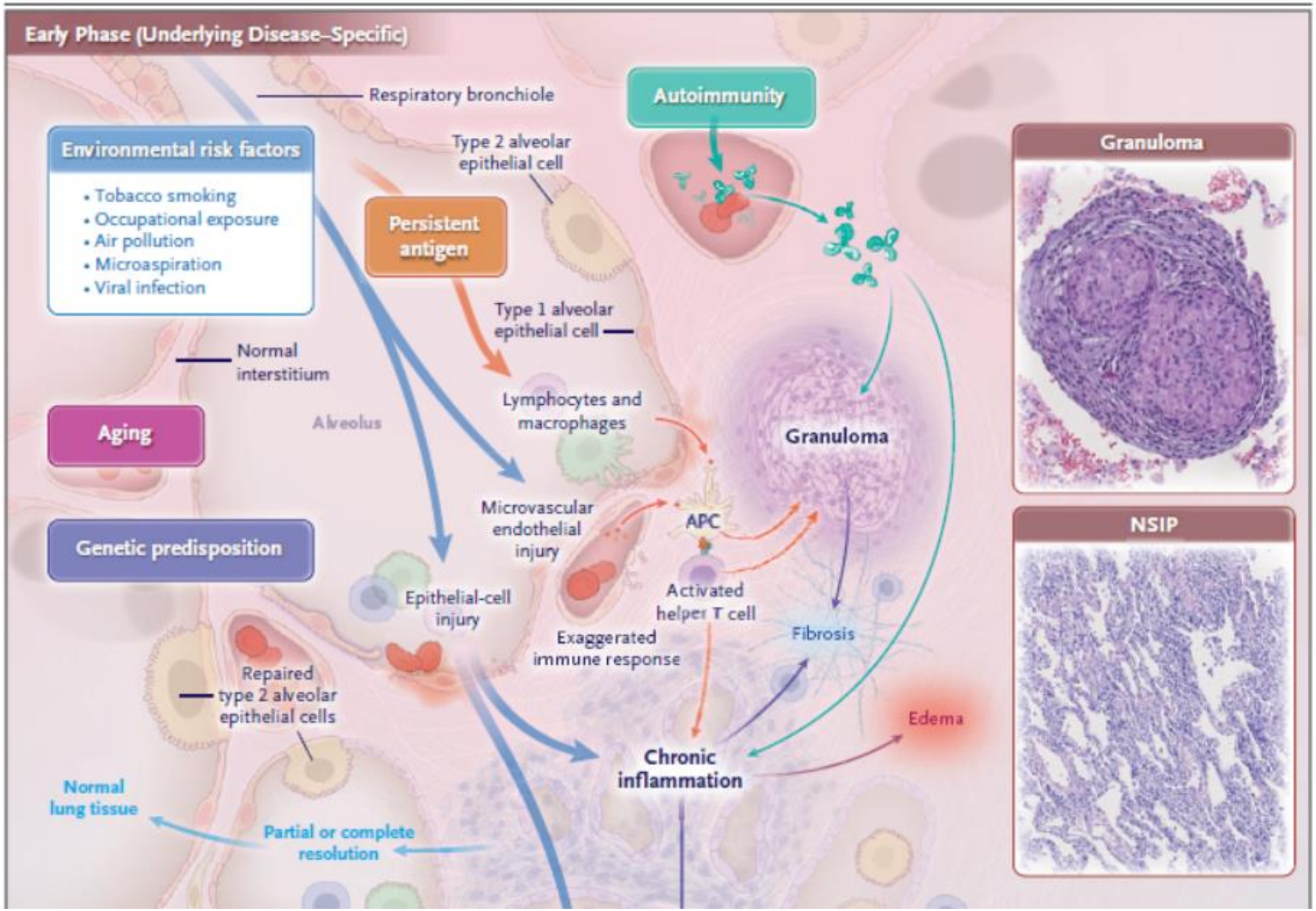
Progressive fibrosing interstitial lung diseases: current practice in diagnosis and management. Wijsenbeek M et al. CurrMed Res Opin2019;5:2015–24

Pathogenesis Early phase

Early phase: various inflammatory responses may lead to a profibrotic environment



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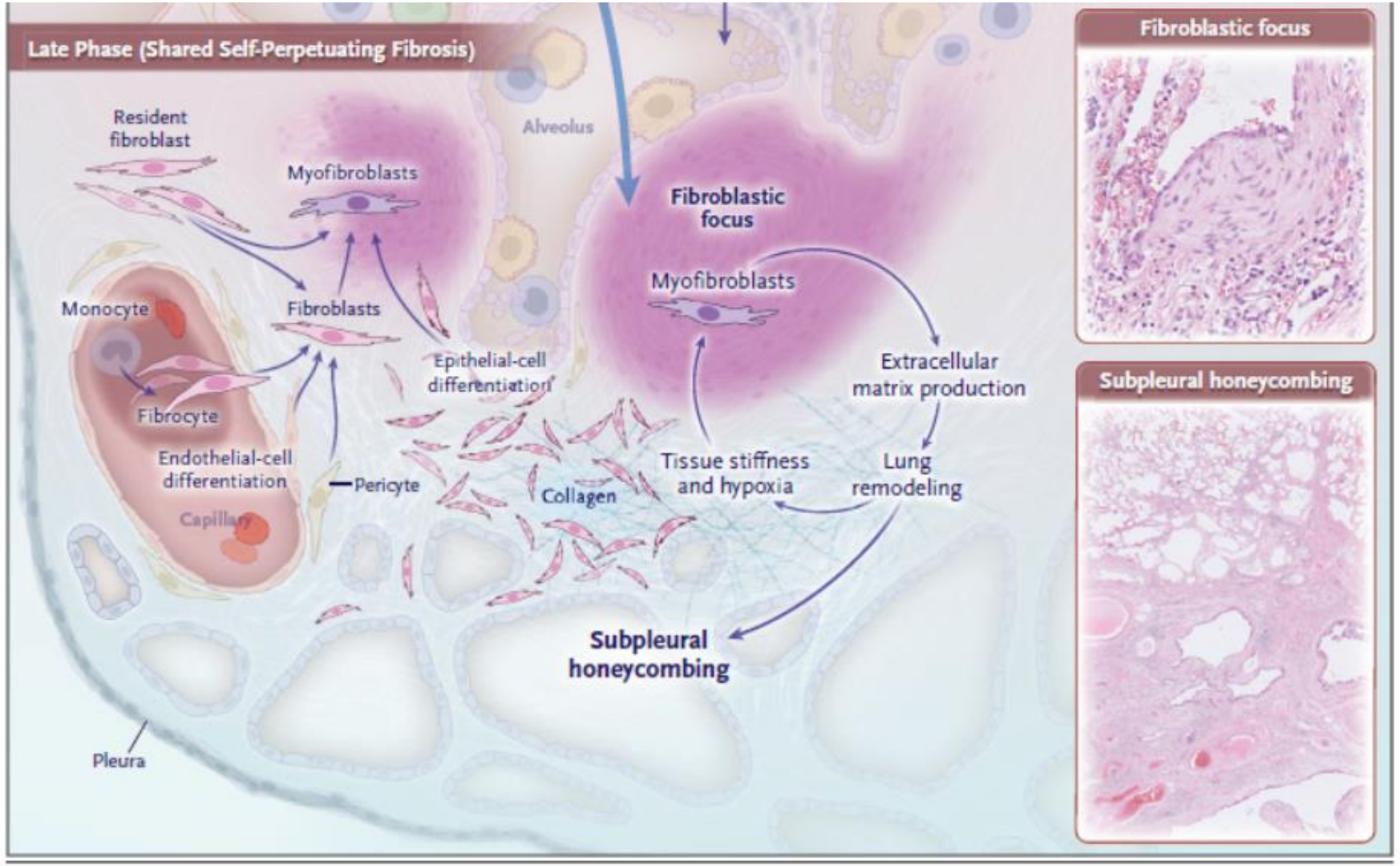
Spectrum of fibroitic lung diseases. Wijsenbeek M and Cottin V. N EnglJ Med 2020;383:958–68

Pathogenesis Late phase

Late phase: the current concept is that there are more shared mechanisms of self-perpetuating fibrosis



Spectrum of fibroitic lung diseases. Wijsenbeek M and Cottin V. N EnglJ Med 2020;383:958–68

Pathogenesis – genetic susceptibility

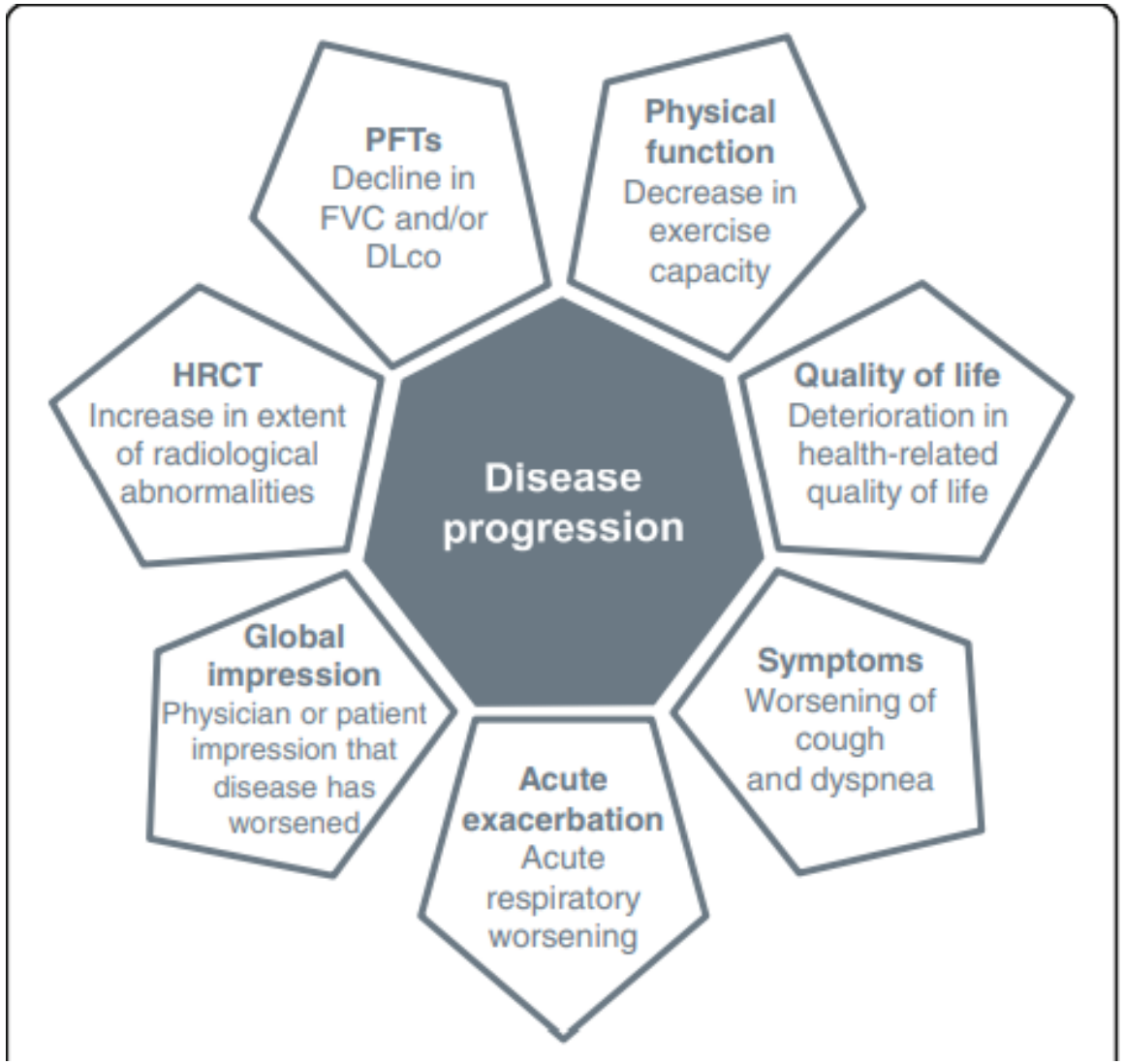
- **MUC5B** (involved in airway clearance and bacterial host defense) &
- **Telomere shortening and telomere related gene mutations** (*TERT, TERC, RTEL1*, and *PARN*)

- Associated with increased risks of -
- **IPF**
- **RA–ILD**
- **Chronic HP**

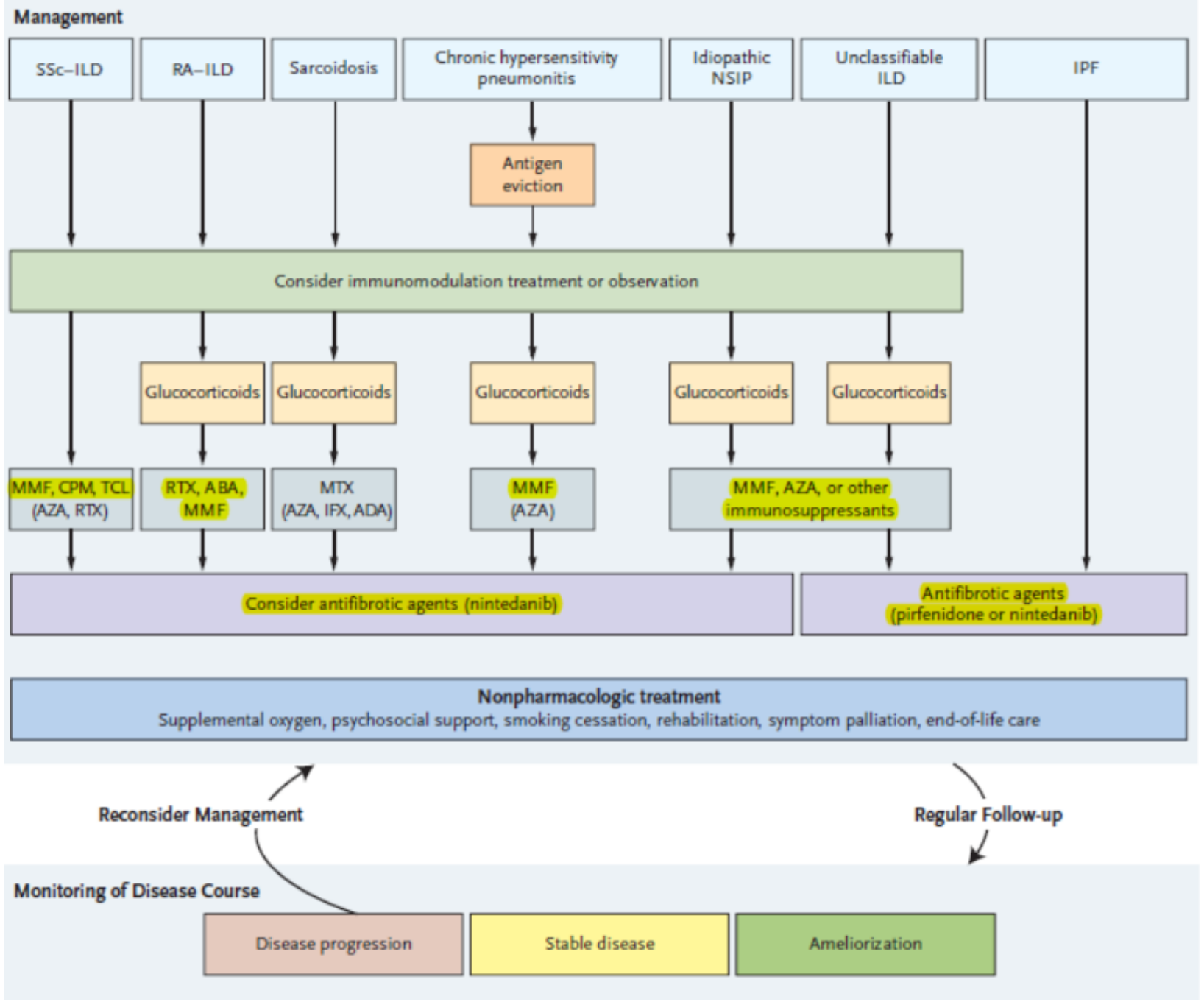
- but not SSc–ILD, sarcoidosis, or antisynthetase syndrome

Spectrum of fibroitic lung diseases. Wijsenbeek M and Cottin V. N EnglJ Med 2020;383:958–68

Multimodal assessment of disease progression



Pharmacological Management in Progressive Pulmonary Fibrosis



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Spectrum of fibroitic lung diseases. Wijsenbeek M and Cottin V. N EnglJ Med 2020;383:958–68

INBUILD trial

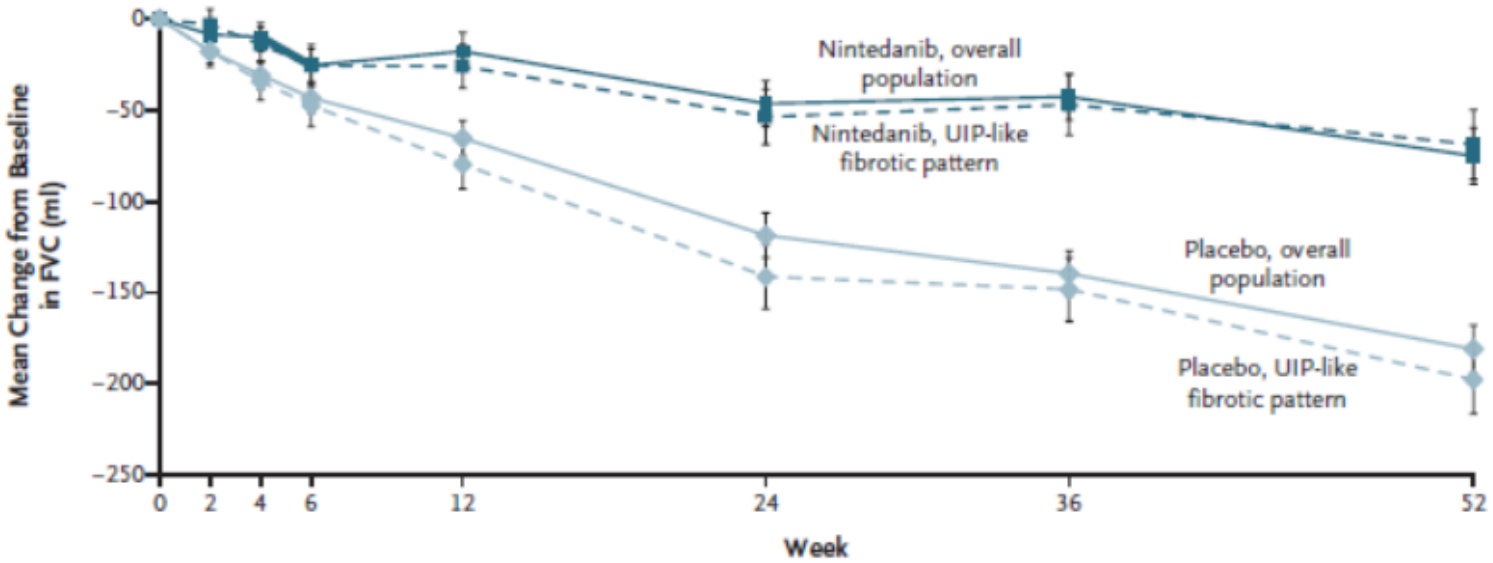
- Double-blind, randomized, placebo-controlled, phase 3 trial in 15 countries - Nintedanib 150mg twice a day v/s Placebo
- Primary endpoint – Annual rate of FVC decline at 52 weeks
- FVC decline rate in
- **80.8 ml/yr** in the Nintedanib compared to **187.8 ml/yr** in the placebo group (between-group difference, 107.0 ml; 95%CI, 65.4 to 148.5; P<0.001)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, S.L.F. Walsh, Y. Inoue, L. Richeldi, M. Kolb, K. Tetzlaff, S. Stowasser, C. Coeck, E. Clerisme-Beaty, B. Rosenstock, M. Quaresma, T. Haeufel, R.-G. Goeldner, R. Schlenker-Herceg, and K.K. Brown, for the INBUILD Trial Investigators*



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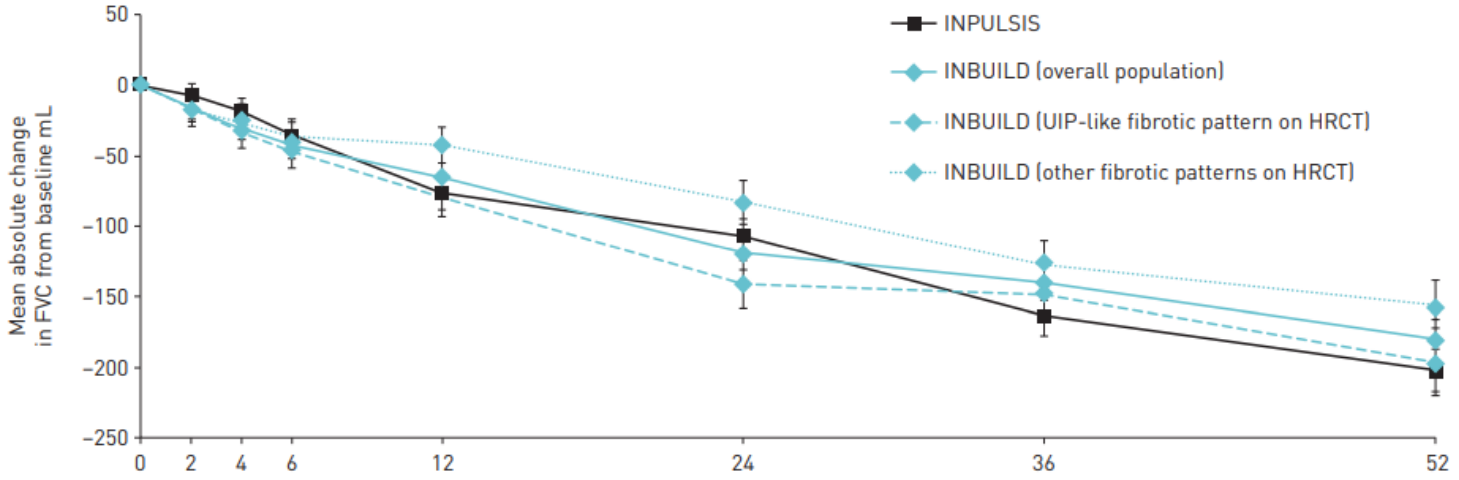
Flaherty KR et al. N Engl J Med. 2019 Sep 29. doi: 10.1056/NEJMoa1908681.

FVC decline in the placebo groups in IPF compared to PF-ILD



Number of subjects							
INPULSIS	417	408	407	403	395	383	345
INBUILD (overall population)	325	326	325	320	311	296	274
INBUILD (UIP-like fibrotic pattern)	202	202	201	197	190	176	162
INBUILD (other fibrotic patterns)	123	124	124	123	121	120	112

FIGURE 2 Observed change in forced vital capacity (FVC) from baseline (mean (SE)) over 52 weeks in the placebo groups of the INPULSIS and INBUILD trials. HRCT: high-resolution computed tomography; UIP: usual interstitial pneumonia.

- Beyond exploring the effects of Nintedanib, the INBUILD trial provided insights into the **natural history of PPF**
- Similar annual rates of decline in the FVC in placebo group and in patients with a UIP-like fibrotic pattern to those seen in pooled data from the INPULSIS trials in patients who met a case definition for IPF

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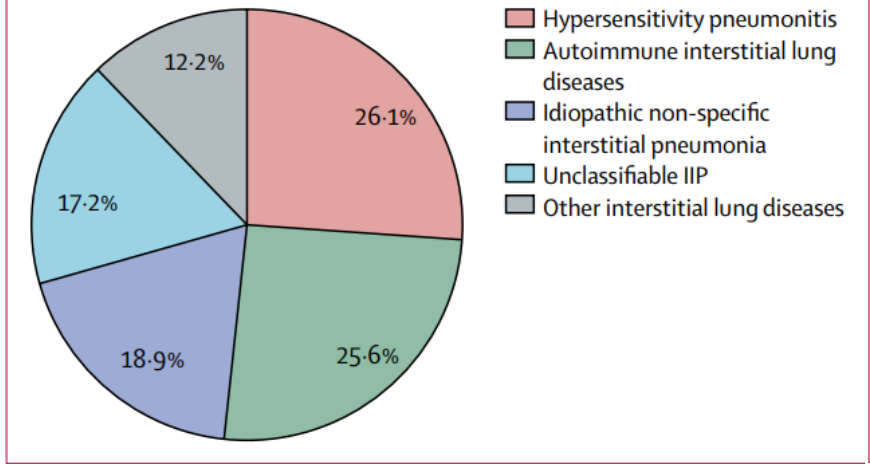
Brown KK, Martinez FJ, Walsh SLF, et al. Eur Respir J. 2020;55(6):2000085.

Subgroup analysis of INBUILD

Nintedanib in patients with progressive fibrosing interstitial lung diseases—subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial

*Athol U Wells, Kevin R Flaherty, Kevin K Brown, Yoshikazu Inoue, Anand Devaraj, Luca Richeldi, Teng Moua, Bruno Crestani, Wim A Wuyts, Susanne Stowasser, Manuel Quaresma, Rainer-Georg Goeldner, Rozsa Schlenker-Herceg, Martin Kolb on behalf of the INBUILD trial investigators**



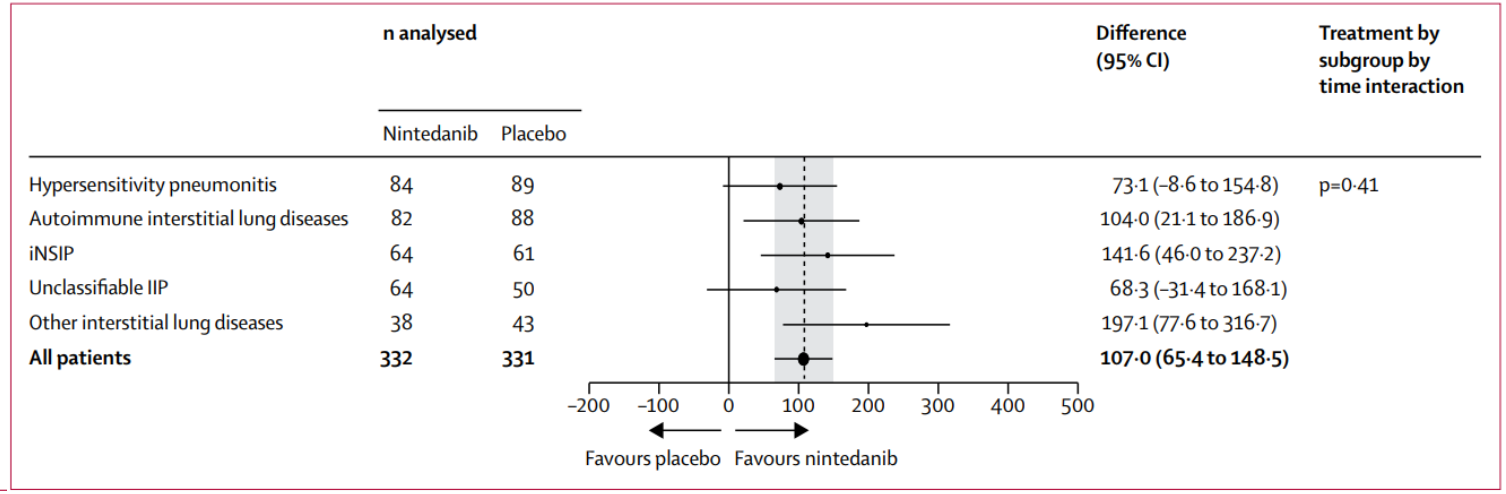


Figure 2: **Annual rate of decline in forced vital capacity (mL/year) in five groups by interstitial lung disease diagnosis (overall population)**
iNSIP=idiopathic non-specific interstitial pneumonia. IIP=idiopathic interstitial pneumonia. Other interstitial lung diseases (ILDs)=sarcoidosis, exposure-related ILDs and other terms in the other fibrosing ILDs category.

- The effect of Nintedanib versus placebo on reducing the rate of FVC decline <u>was consistent across the five subgroups by ILD diagnosis</u>

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Wells et al, Lancet Respir Med 2020; 8: 453–60

Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial

Toby M Maher, Tamera J Corte, Aryeh Fischer, Michael Kreuter, David J Lederer, Maria Molina-Molina, Judit Axmann, Klaus-Uwe Kirchgaessler, Katerina Samara, Frank Gilberg, Vincent Cottin

- Double-blind, randomized, placebo-controlled, phase 2 trial in 70 centers with Unclassifiable PFILD - 2403 mg oral pirfenidone daily or placebo

- Primary endpoint was mean predicted FVC change over 24 weeks, measured by daily home spirometry.

	Pirfenidone (n=127)	Placebo (n=126)	Pirfenidone vs placebo	p value*
Predicted FVC change from baseline measured by site spirometry, mL				
Mean (95% CI)	−17·8† (−62·6 to 27·0)	−113·0‡ (−152·5 to −73·6)	95·3 (35·9 to 154·6)	0·002
Median (Q1–Q3)	−7·5 (−185·4 to 112·3)	−125·8 (−238·2 to 2·2)	118·3	..
FVC change from baseline measured by site spirometry, % predicted				
Rank analysis of covariance	..	..	..	0·038
Patients with >5% decline in FVC	47 (37%)	74 (59%)	0·42 (0·25 to 0·69)§	0·001
Patients with >10% decline in FVC	18 (14%)	34 (27%)	0·44 (0·23 to 0·84)§	0·011
DLco change from baseline, % predicted				
Rank analysis of covariance	..	..	..	0·09
Patients with >15% decline in DLco¶	3 (2%)	11 (9%)	0·25 (0·07 to 0·93)§	0·039
6MWD change from baseline, m				
Rank analysis of covariance	..	..	..	0·040
Patients with >50 m decline in 6MWD¶	36 (28%)	35 (28%)	1·03 (0·59 to 1·78)§	0·92

- Predicted mean change in FVC measured by site spirometry was lower in patients given pirfenidone than placebo (**treatment difference 95·3 mL** [95% CI 35·9 to 154·6], p=0·002)

HENRY FORD HEALTH®

Maher TM et al. Lancet Respir Med2020 Feb;8(2):147-157

RELIEF trial Behr et al

Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial

- Double-blind, randomized, placebo-controlled, phase 2b trial in 17 centers in Germany with PFILD - oral pirfenidone (267 mg TID in week 1, 534 mg TID in week 2, and 801 mg TID thereafter) v/s placebo
- Primary endpoint – Change in FVC decline at 48 weeks
- The study was **prematurely terminated** on the basis of an interim analysis for futility triggered by **slow recruitment**

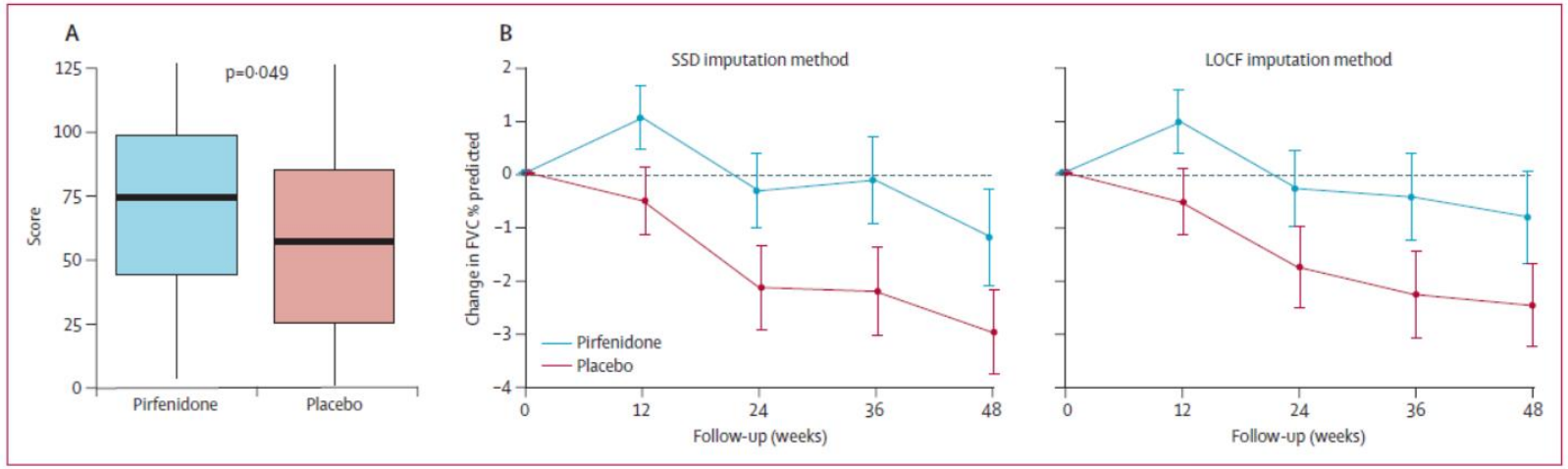

Figure 2: **Absolute change in percentage of predicted FVC and time course for mean change in percentage of predicted FVC from baseline to week 48**
(A) Distribution of Wilcoxon scores (from Mann-Whitney *U* test) for the absolute change in percentage of predicted FVC (FVC % predicted) from baseline to week 48 in the intention-to-treat population (n=127) for the pirfenidone and placebo groups (using the prespecified SSD imputation method for missing data, with deaths ranked worst). (B) Mean changes from baseline in FVC % predicted (SE) over the 48-week trial period in the pirfenidone and placebo groups after imputation of missing values (including those of deceased patients) according to the prespecified SSD method or, alternatively, the post-hoc LOCF imputation method. FVC=forced vital capacity. LOCF=last observation carried forward. SSD=sum of squared differences.

Multiple statistical imputations were conducted for missing data with the primary analysis **favoring the pirfenidone arm**

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Behr et al.Lancet Respir Med 2021; 9: 476–86

Antifibrotics in PPF – 2022 guideline recommendations

- **Nintedanib**
- Suggest **nintedanib** for the treatment of PPF in patients who have failed standard management for fibrotic ILD, other than IPF (conditional recommendation, low quality evidence).
- Standard management will differ from patient to patient
- Recommend research into the efficacy, effectiveness, and safety of nintedanib in specific types of non-IPF ILD manifesting PPF

- **Pirfenidone**
- Recommend further research into the efficacy, effectiveness, and safety of pirfenidone in both
- 1) non-IPF ILD manifesting PPF in general and
- 2) specific types of non-IPF ILD manifesting PPF.

Raghu G et al Am J Respir Crit Care Med Vol 205, Iss 9, pp e18–e47, May 1, 2022

Henry Ford Hospital ILD Program Experience

- Combined immunosuppression and antifibrotics
  - 14 patients active
  - 3 discontinued (GI side effects)
  - Monitoring
    - ILD pharmacy team to address timely labs

Comprehensive care in PPF

ATS PRIMER ON PROGRESSIVE FIBROSING INTERSTITIAL LUNG DISEASES

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Summary

- **Rheumatologic evaluation in the initial evaluation of**
- **Pulmonary involvement** in Multidisciplinary diagnosis and management of CTD-ILD
- **Progressive pulmonary fibrosis** represents a phenotype that may occur in many cases of ILD.
- Many **factors** likely determine the **course of ILD progression** including inciting injurious mechanisms and underlying genetic predisposition.
- **Anti-fibrotic therapies targeting the shared aspects of fibrosis across ILDs** have proven a viable treatment option.
- **Standard ILD therapies** remain a cornerstone despite the more rapid course of disease supporting regular monitoring and interventions as appropriate.

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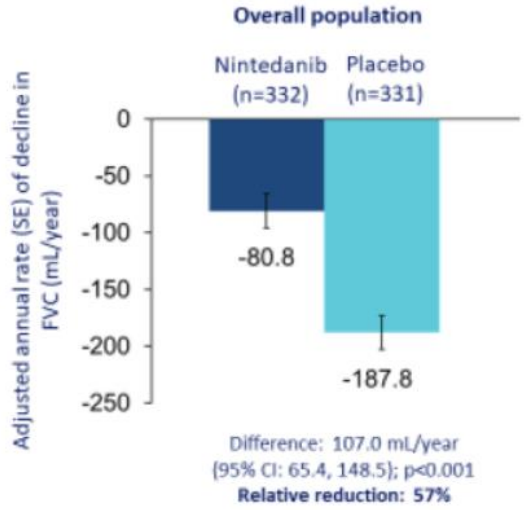
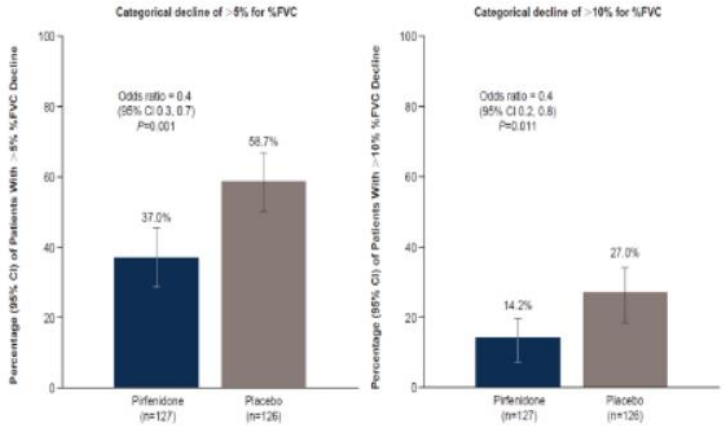
Thank you!

Flaherty et al (2019)[49]	663 patients with non-IPF progressive fibrosing ILD	Nintedanib 150 mg twice daily *vs* placebo for 52 weeks	Mean annual rate of FVC decline at 52 weeks	Nintedanib –80·8 mL/year *vs* placebo –187·8 mL/ year; difference of 107 mL/year (95% CI 65·4 to 148·5)	Presence of at least one of the following within 2 years before screening: relative FVC decline of ≥10% of predicted value; relative FVC decline of 5% to <10% of predicted value and worsening respiratory symptoms or increased fibrosis on HRCT; worsening respiratory symptoms and increased fibrosis on HRCT	Findings consistent when stratified by HRCT pattern (usual interstitial pneumonia *vs* non-usual interstitial pneumonia)
Maher et al (2020)[50]	253 patients with progressive fibrosing unclassifiable ILD	Pirfenidone 801 mg three times daily *vs* placebo for 48 weeks	Mean change in FVC% predicted at 24 weeks, measured by daily home spirometry	Median change: pirfenidone –87·7 mL *vs* placebo –157·1 mL	Decline in FVC of >5% or clinically significant symptomatic worsening; extent of fibrosis >10% on HRCT	Secondary outcome (laboratory-based spirometry) treatment difference between pirfenidone *vs* placebo was 95·3 mL (95% CI 35·9–154·6)
Behr et al (2021)[51]	127 patients with non-IPF progressive fibrosing ILD	Pirfenidone 801 mg three times daily *vs* placebo for 48 weeks	Mean absolute change in FVC% predicted at 48 weeks	Mean difference between pirfenidone *vs* placebo was 1·69% (95% CI 0·65 to 4·03)	Progressive disease documented by at least three pulmonary function tests obtained 6–24 months before enrolment, with an annual decline in FVC% predicted of ≥5%	Trial terminated prematurely; multiple statistical approaches presented

INBUILD



U-ILD



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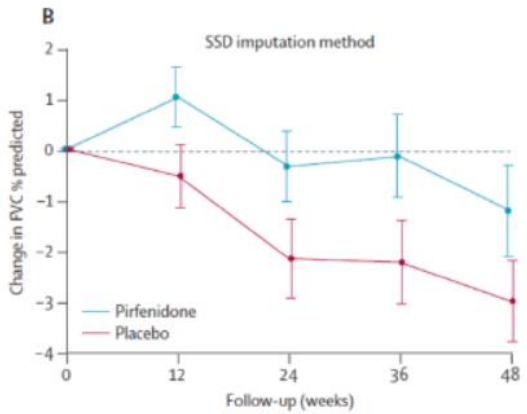

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