Interdisciplinary Approach to Interstitial Lung Disease

Advances in the Practice of Pulmonary and Critical Care Medicine
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Division of Pulmonary and Critical Care Medicine
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Disclosures to Audience

- Financial Relationships with Relevant Commercial Interest:

  I have served on scientific advisory boards for Boehringer-Ingelheim and have performed consulting work for the Gerson Lehrman Group, and I have worked on a modified-delphi project related to early pulmonary fibrosis detection funded by Boehringer-Ingelheim in the three years preceding this presentation.

Primary Learning Objectives

- Evaluation and Diagnosis of Interstitial Lung Disease (focus on the Idiopathic Interstitial Pneumonias)
- PF Clinical Trials
- The Future of Early Detection for Pulmonary Fibrosis

Classification of Interstitial Lung Disease (ILD)

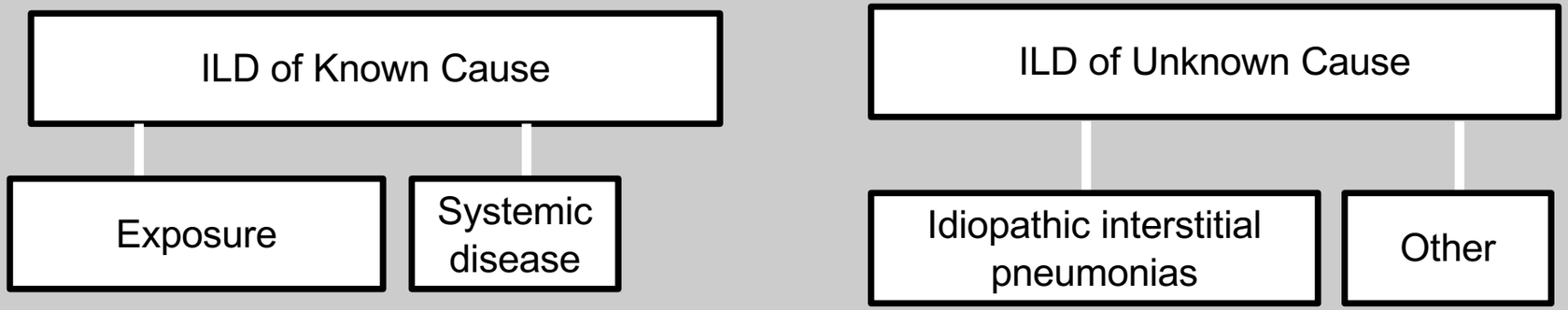
Hunninghake GM, Rosas IO. Interstitial Lung Diseases. In: Jameson JL, Fauci AS, Kasper DK, Hauser SL, Longo DL, Loscalzo J (Eds.). Harrison's Principles of Internal Medicine. 20th Edition. 2018; ch297. New York: McGraw-Hill Education.

Classification of Interstitial Lung Disease (ILD)

ILD of Known Cause

ILD of Unknown Cause

Classification of Interstitial Lung Disease (ILD)



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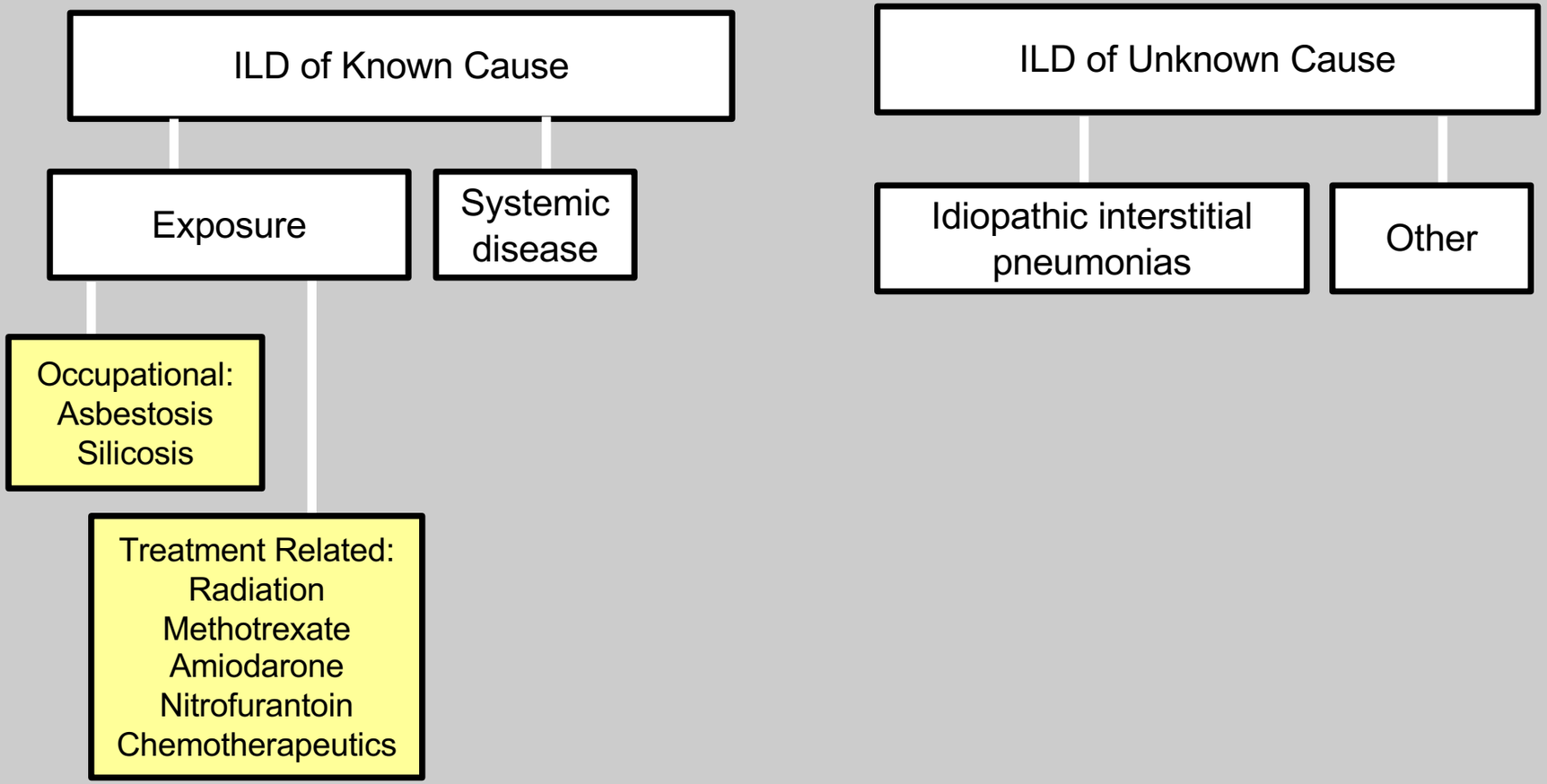

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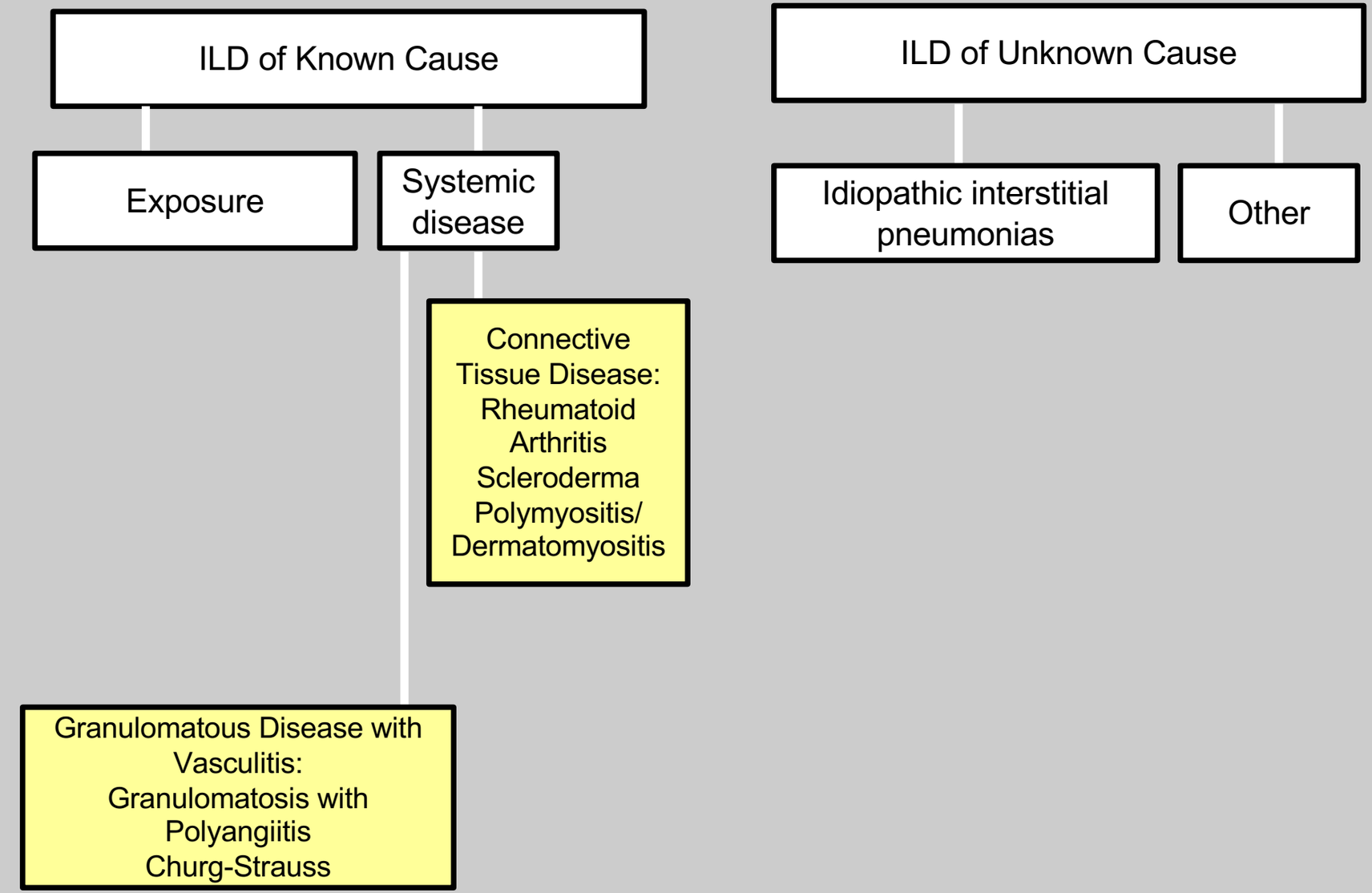

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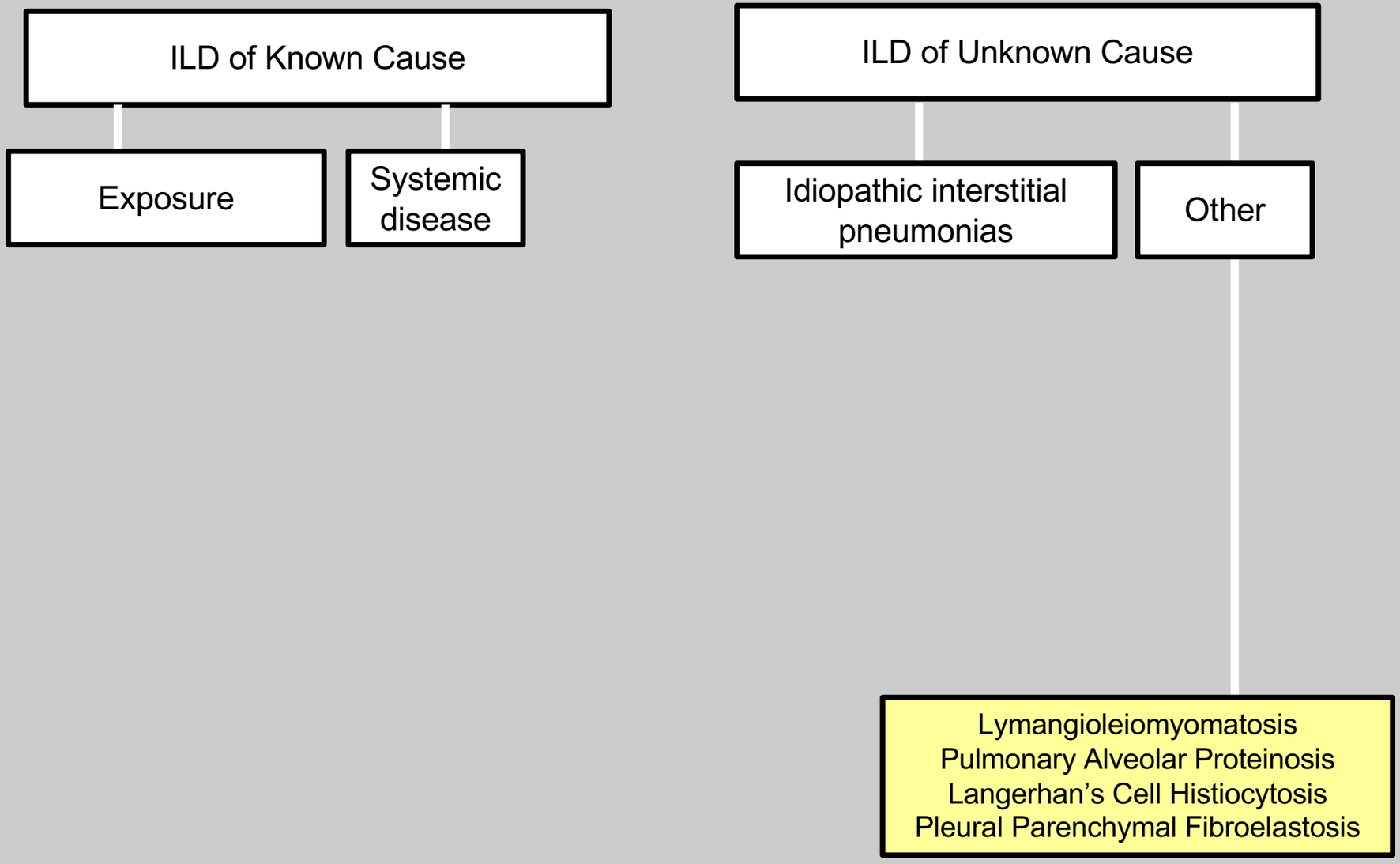

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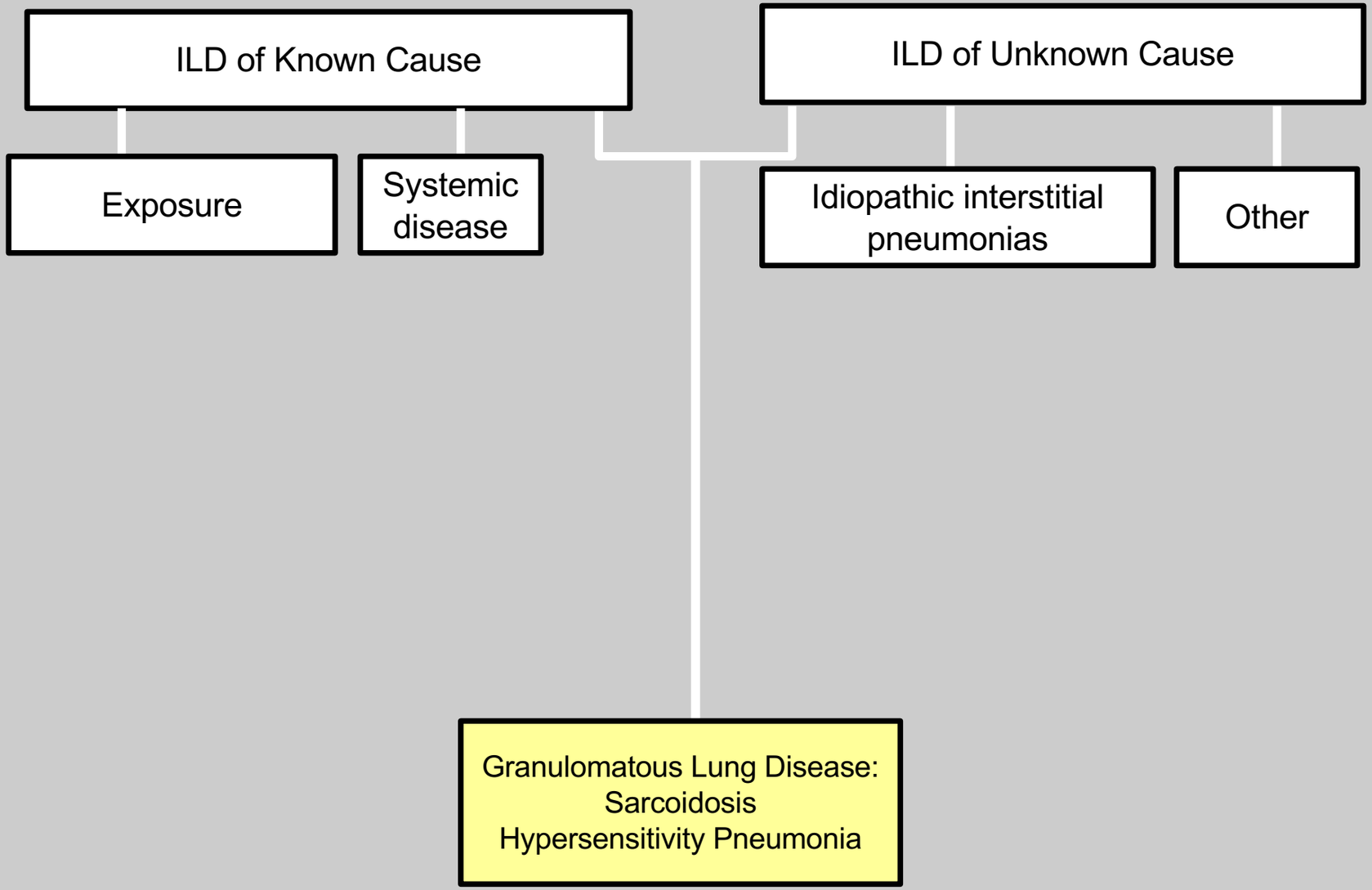
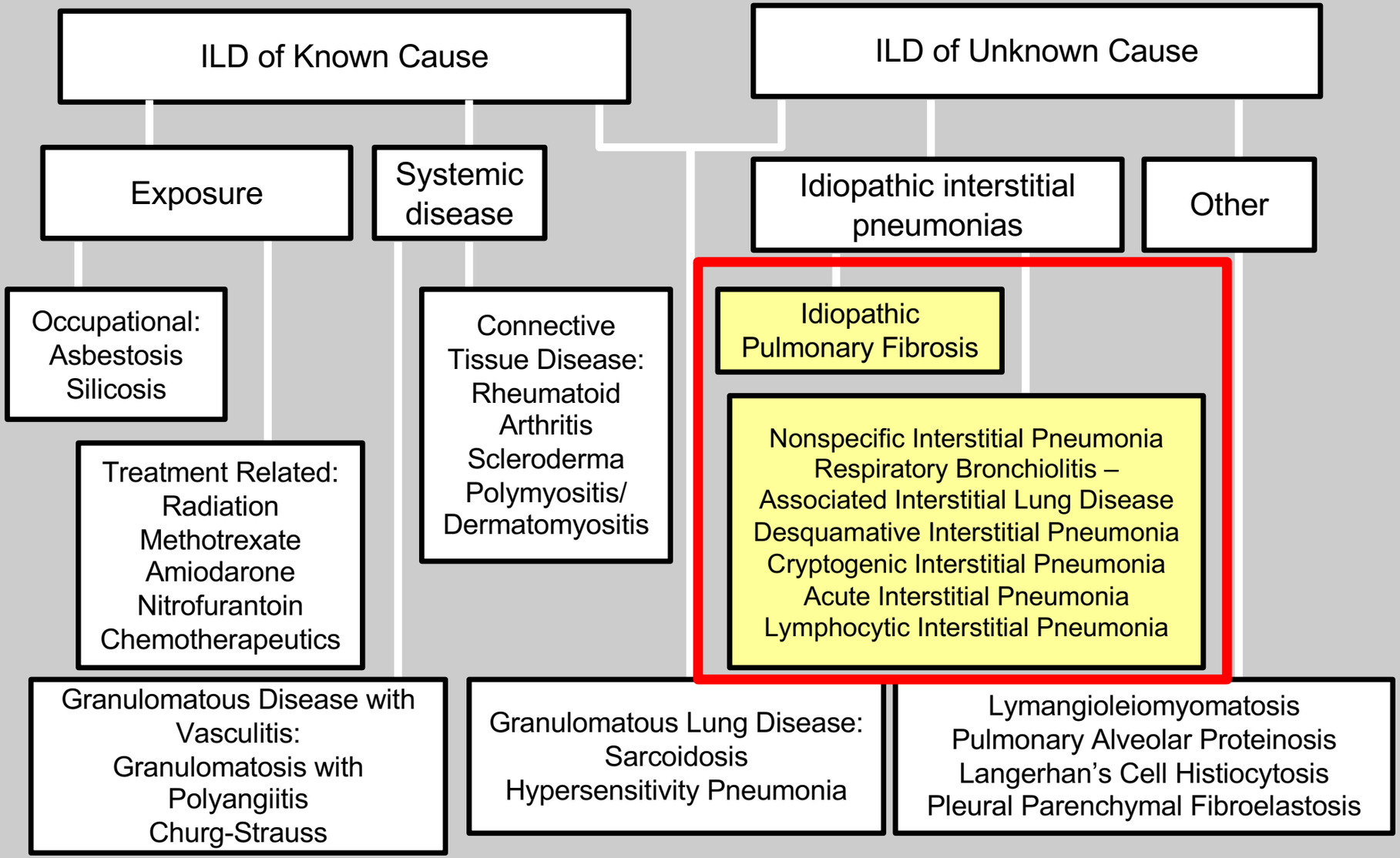
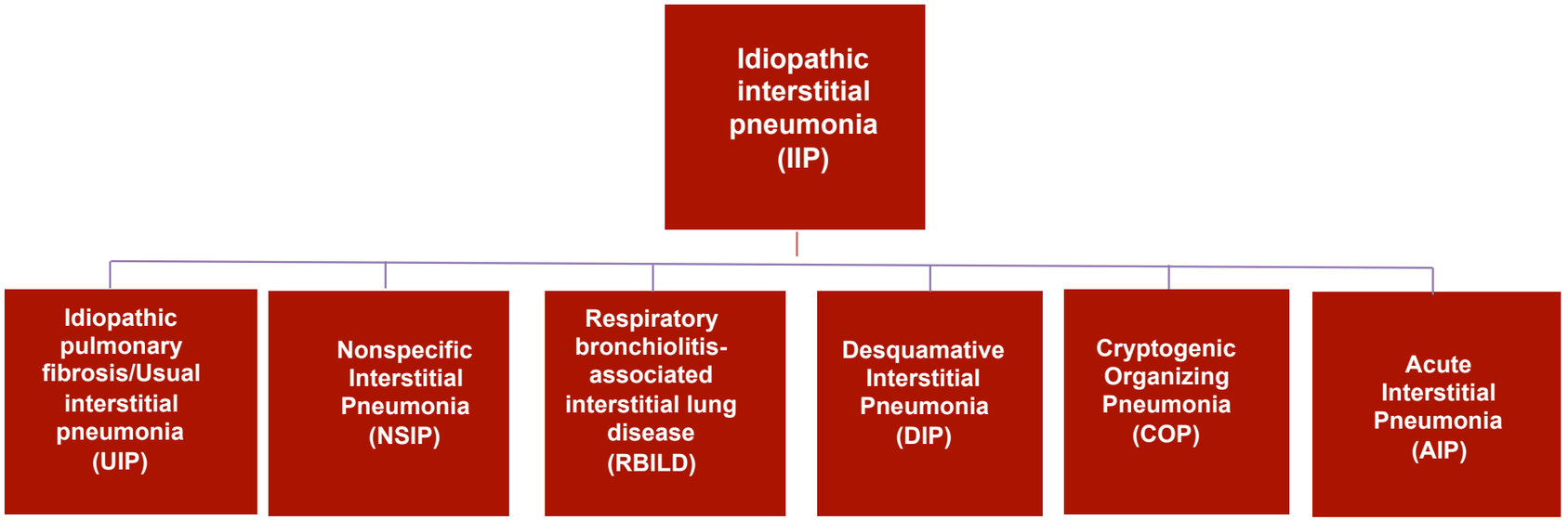


Classification of Interstitial Lung Disease (ILD)

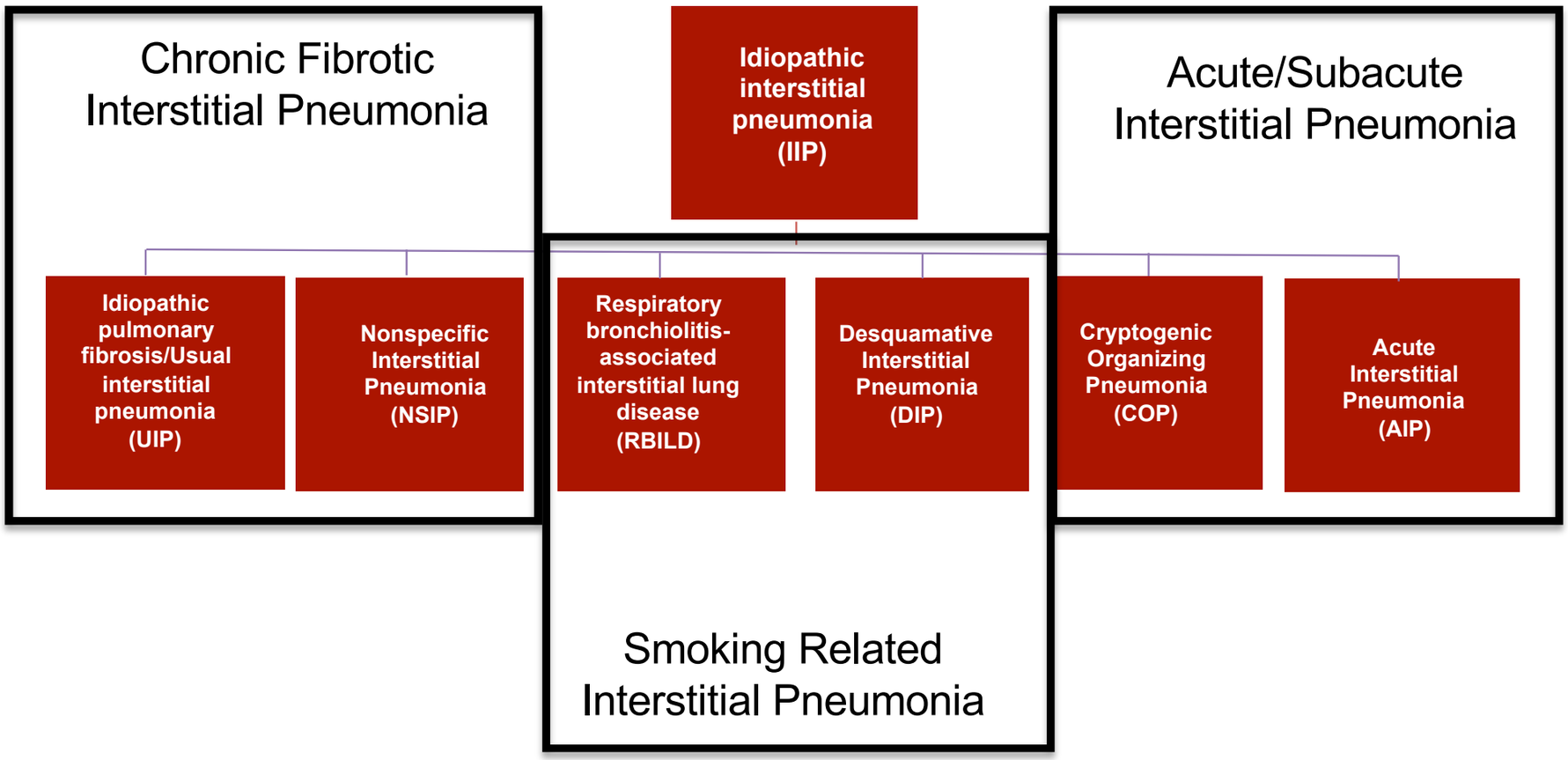


Idiopathic Interstitial Pneumonias



Adapted from ATS/ERS *AJRCCM* 2000 and 2013

Idiopathic Interstitial Pneumonias

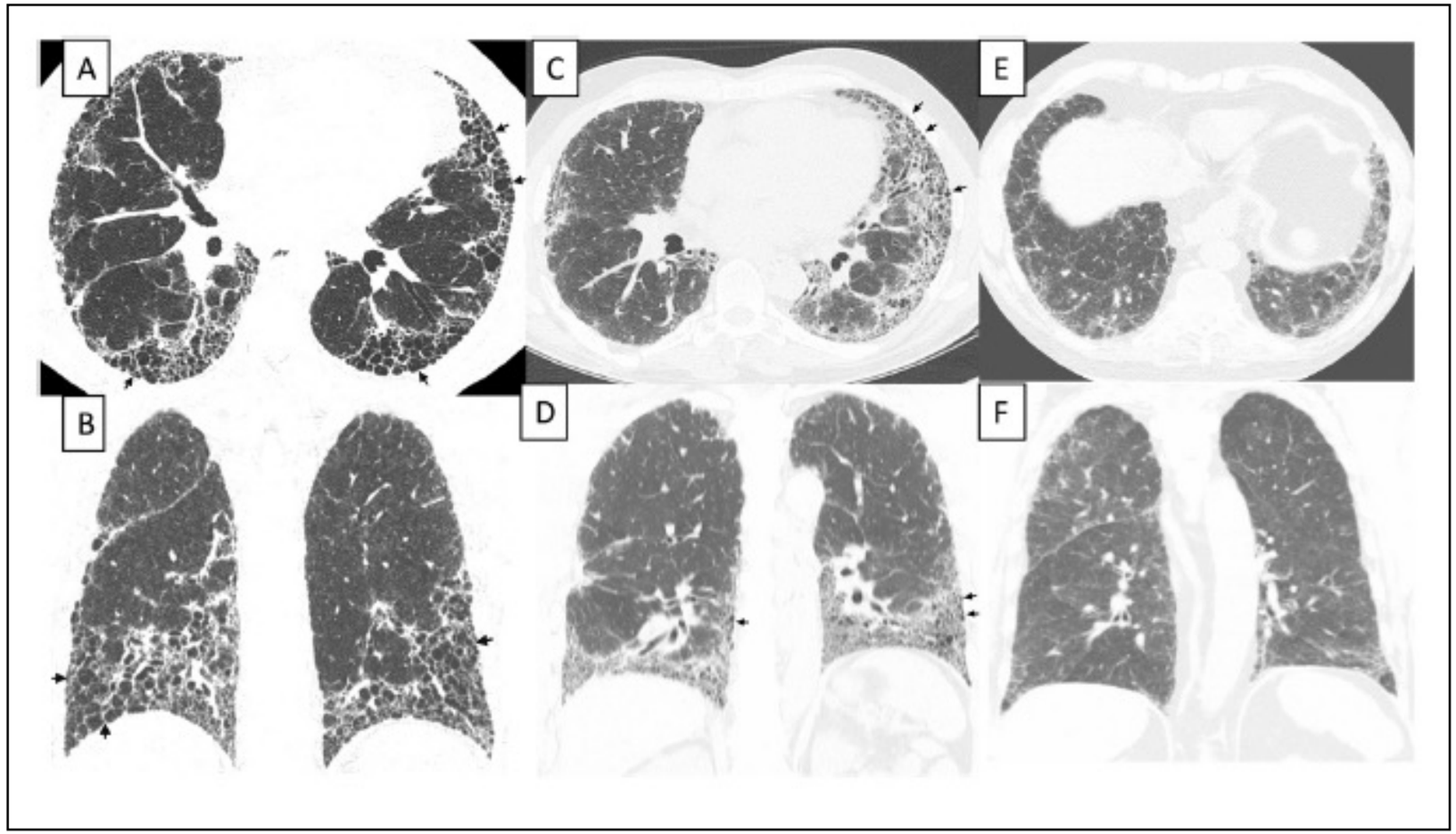


Adapted from ATS/ERS *AJRCCM* 2000 and 2013

Idiopathic Pulmonary Fibrosis

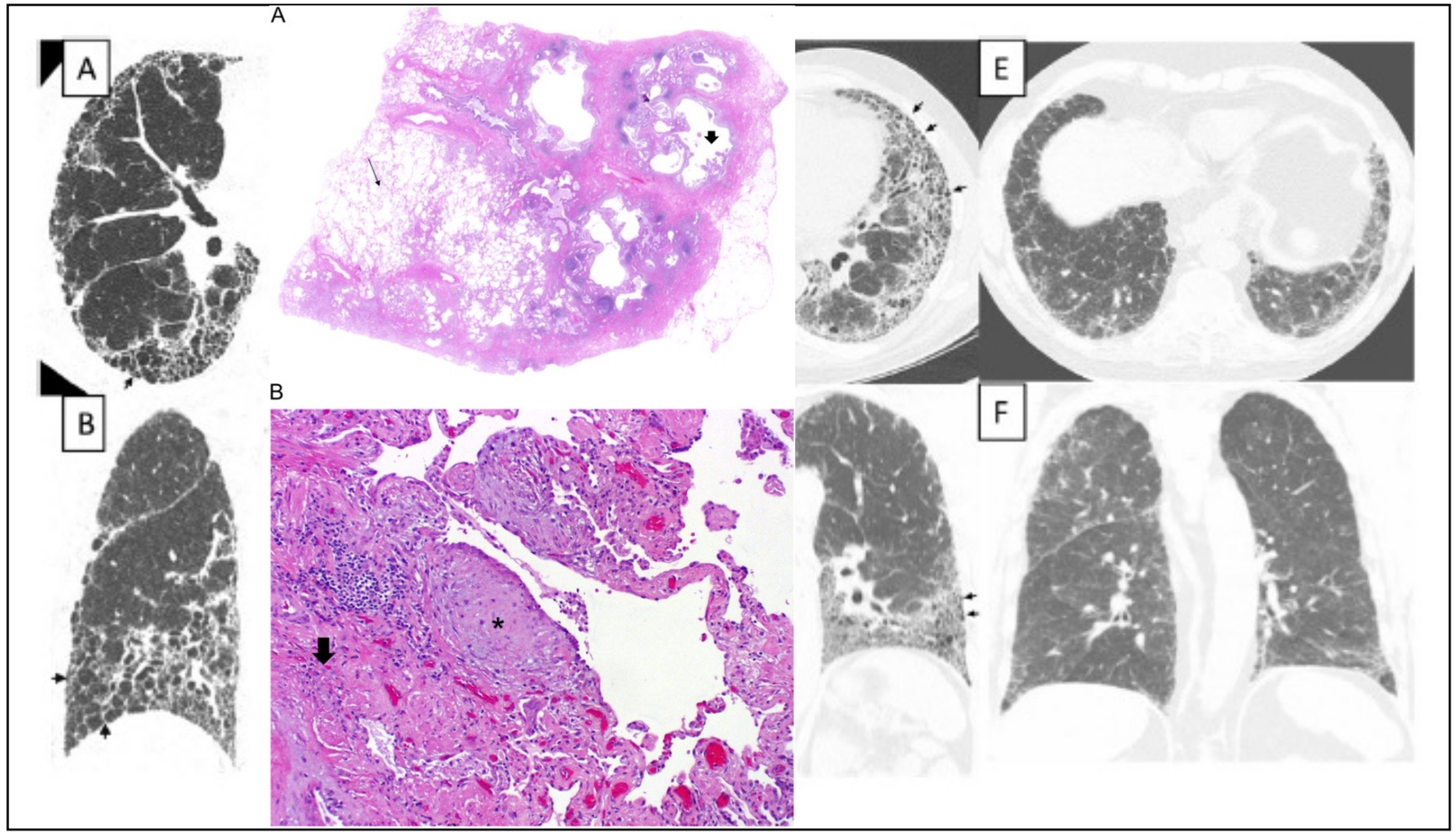
- Definition: Most common diffuse interstitial pneumonia of unknown cause (although genetics appears to play a strong role).
- Epidemiology: Prevalence 50-200:100,000; men>women, age>60, history of smoking is relatively common
- Diagnosis: Clinical presentation, exclude known causes, imaging and diagnostic lung biopsy (UIP), serology and biomarkers
- Prognosis: Survival 3-5 years ~ 50%
- Treatment: Antifibrotics, transplant, physical therapy, palliative management

IPF: HRCT Characteristics



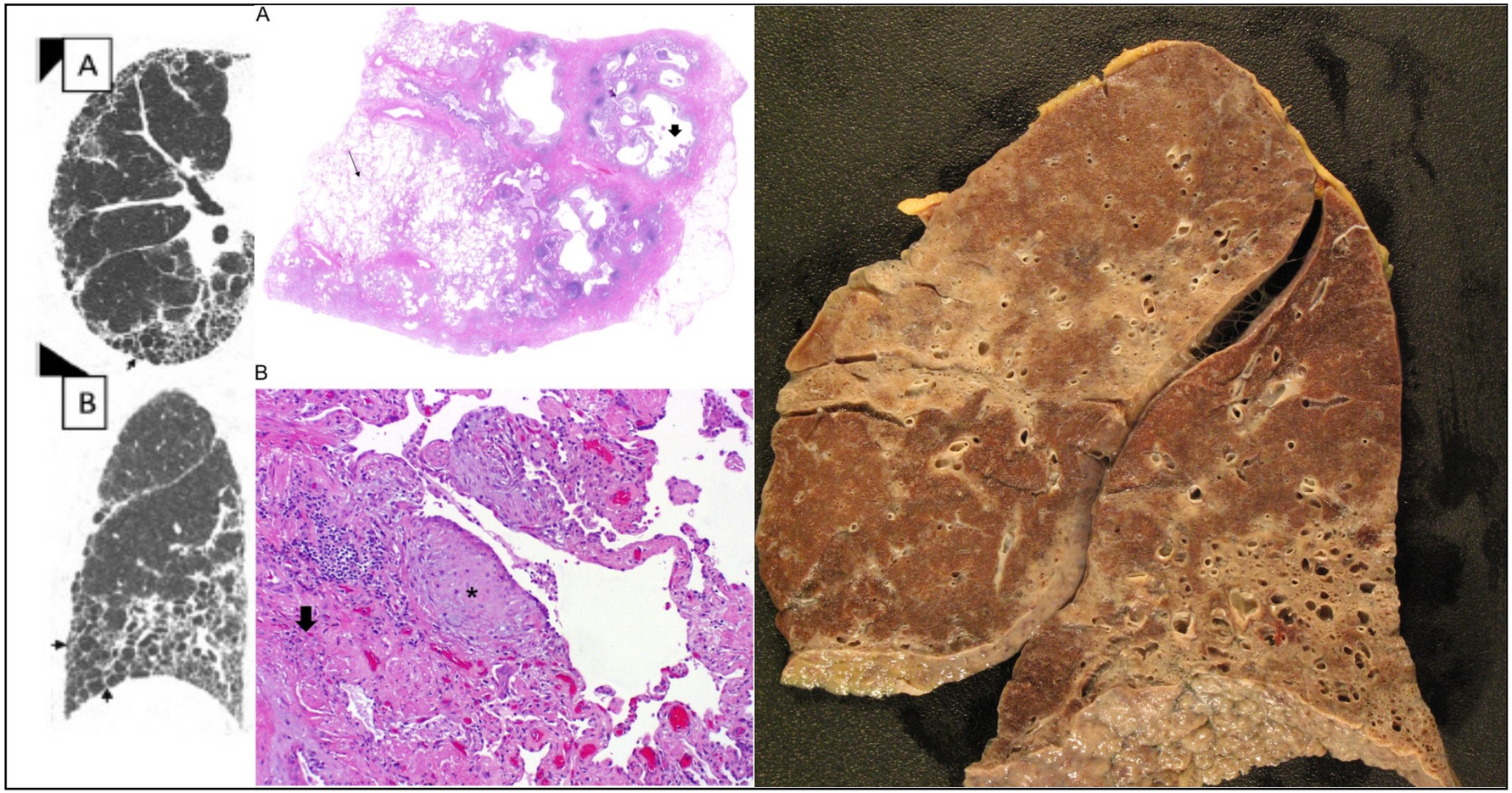
Raghu, AJRCCM, 2011
Raghu, AJRCCM, 2018

IPF: Histopathologic Characteristics

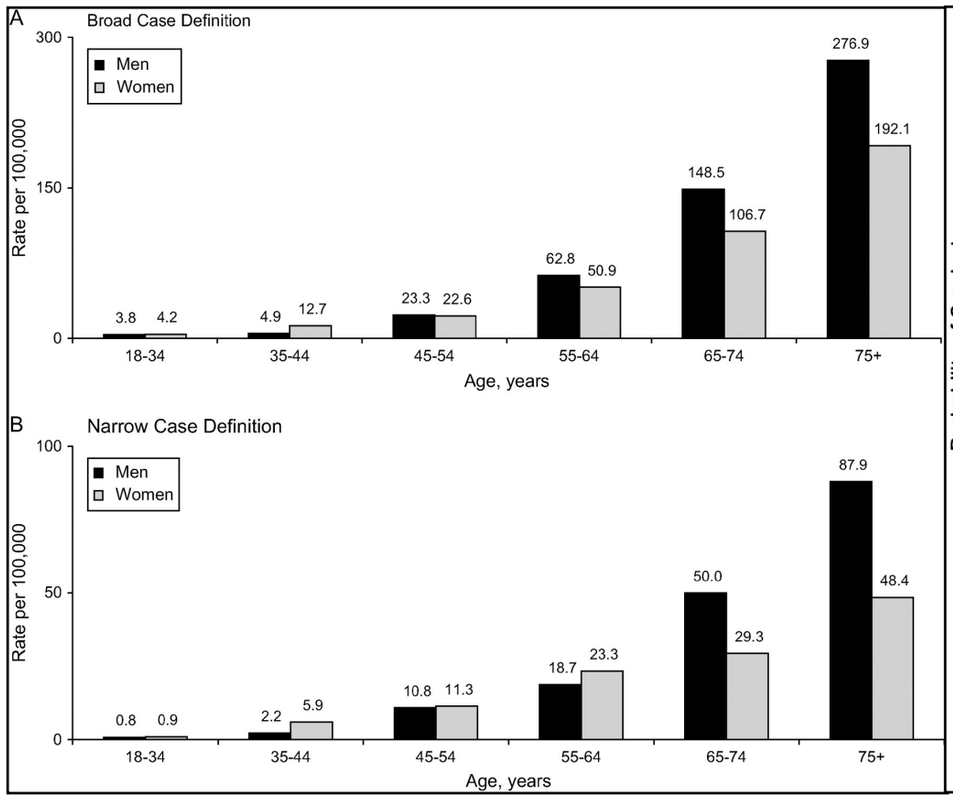


Raghu, AJRCCM, 2011
Raghu, AJRCCM, 2018

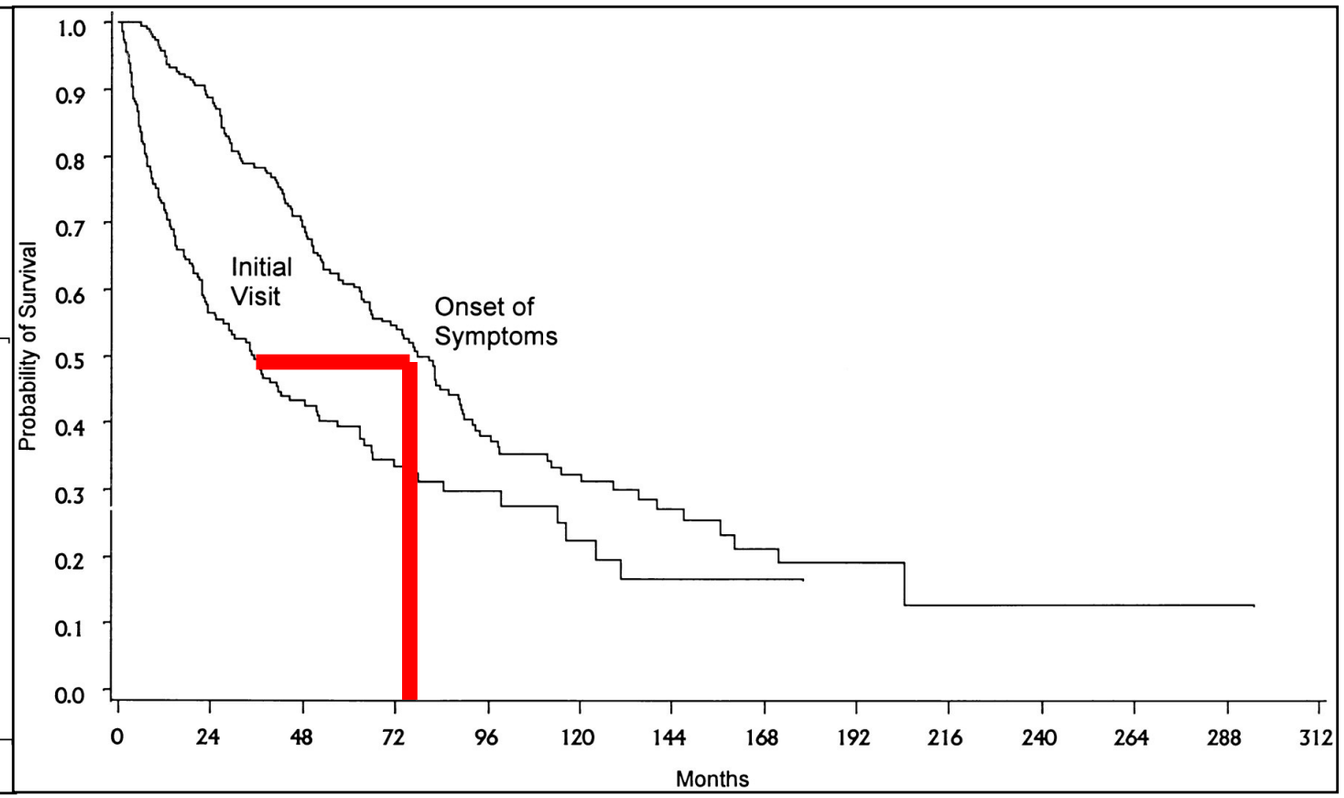
IPF: Autopsy Characteristics



Idiopathic Pulmonary Fibrosis: Prevalence and Prognosis

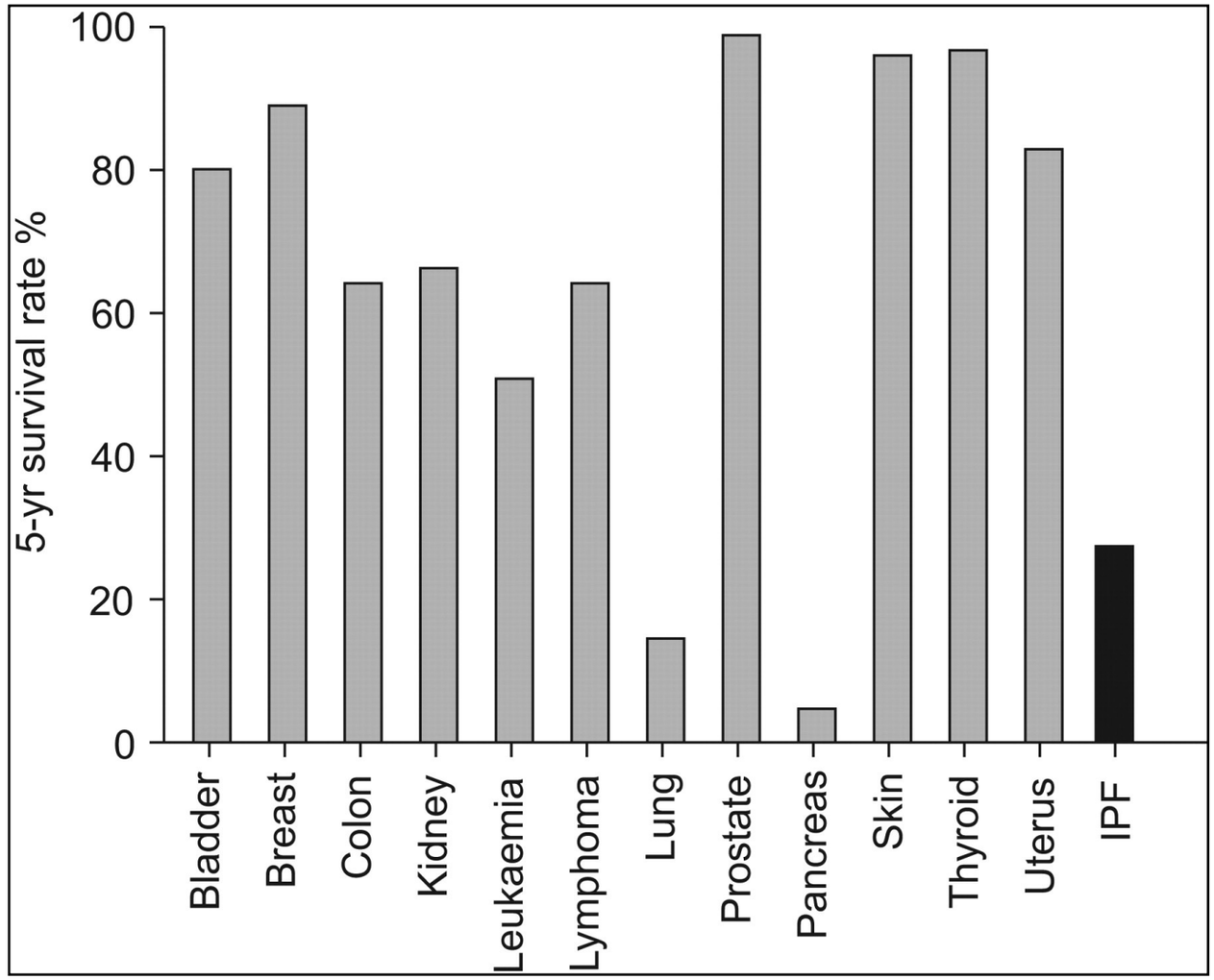


Raghu, AJRCCM, 2006



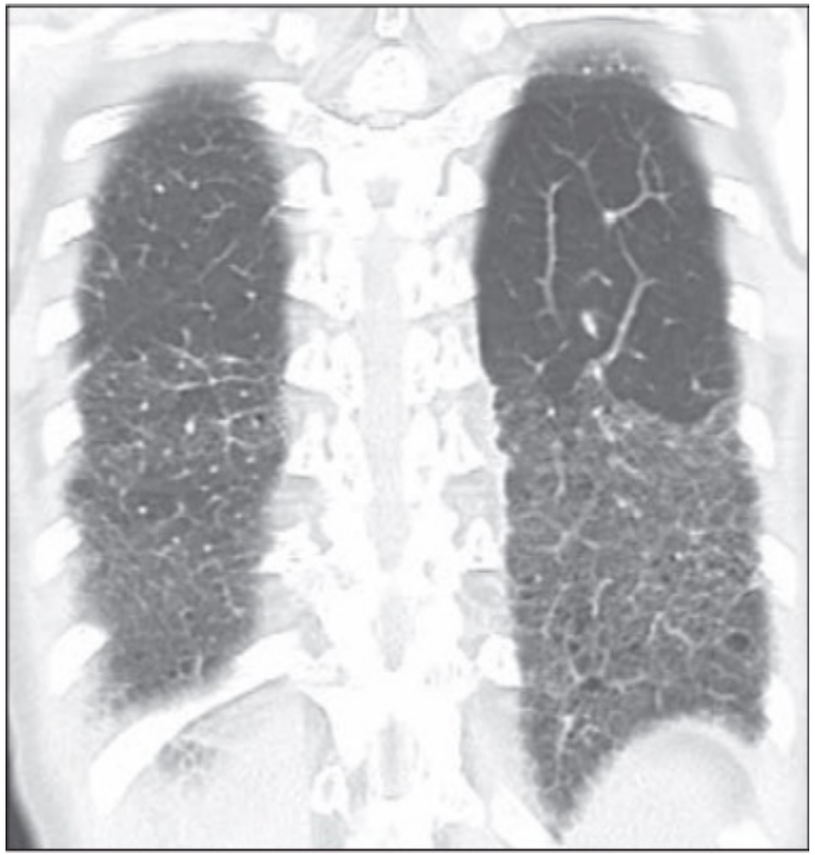
King, AJRCCM, 2001

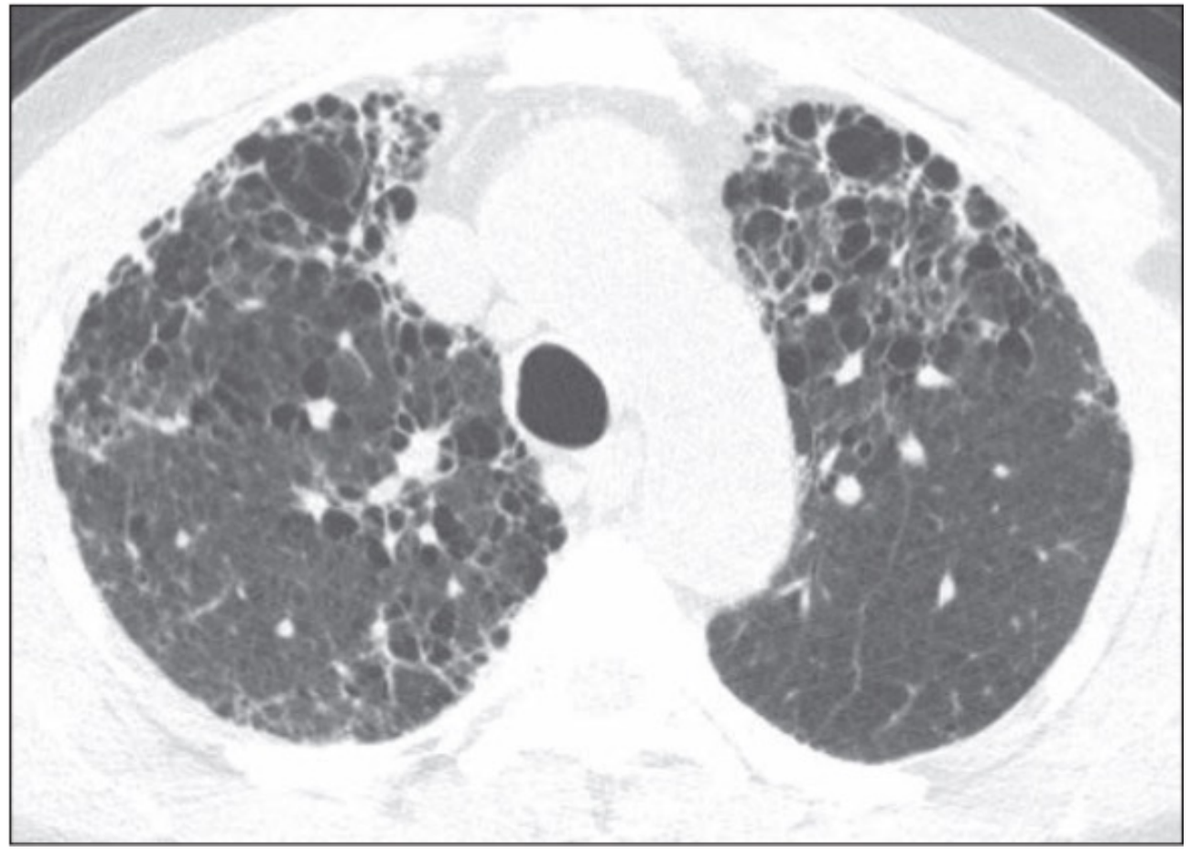
Idiopathic Pulmonary Fibrosis: Comparison to Cancer



Vancheri, Eur Resp J, 2010

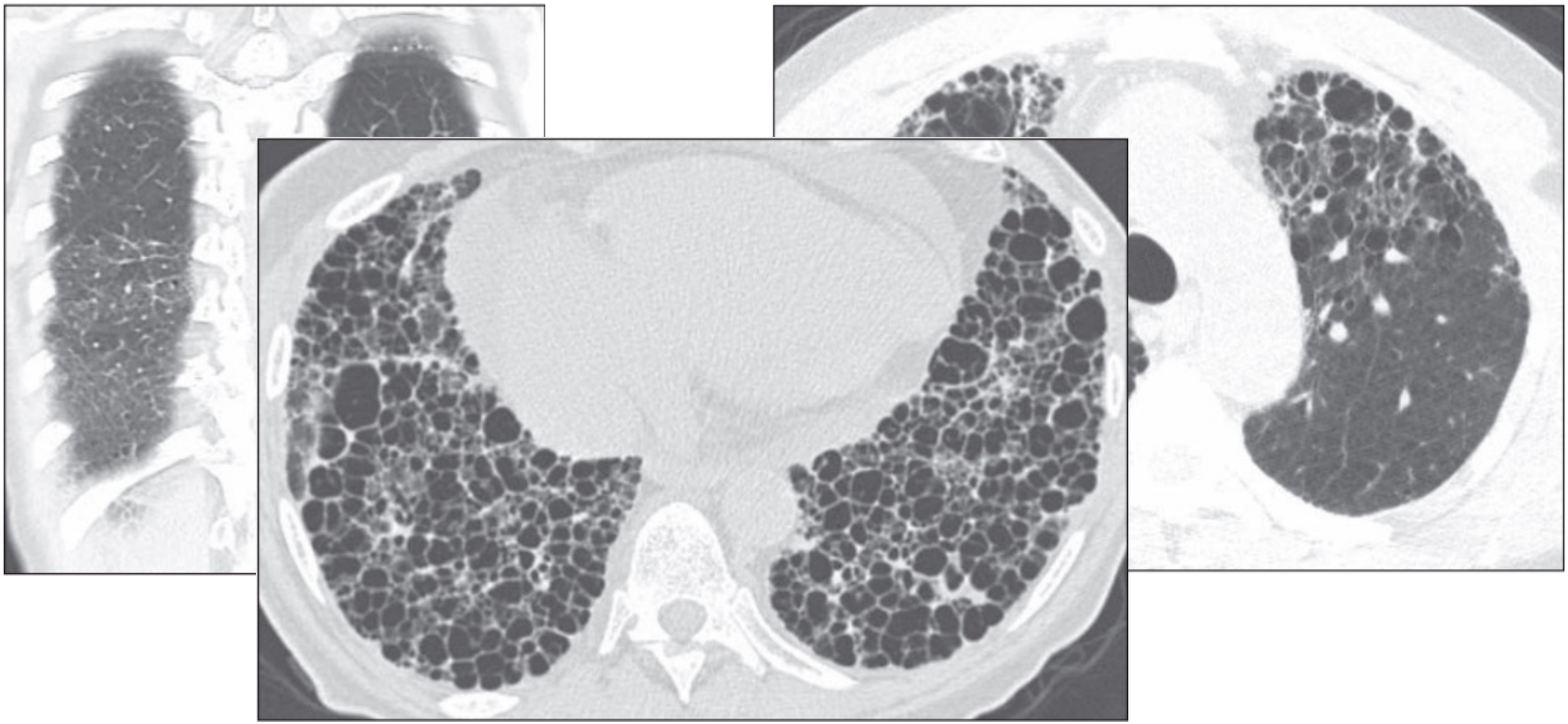
Imaging Characteristics Suggesting Alternate Diagnoses





AJR 2018; 210:307–313

Imaging Characteristics Suggesting Alternate Diagnoses

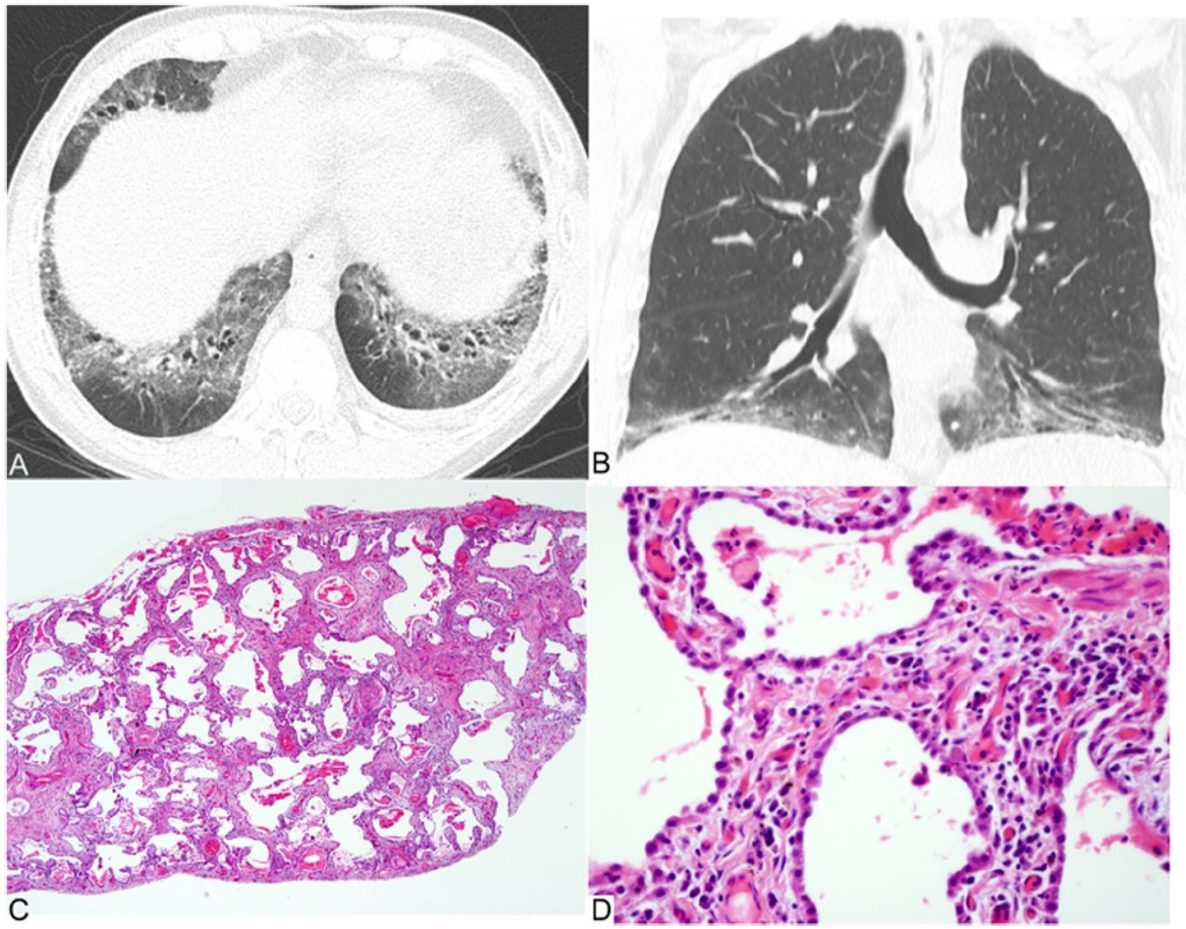


AJR 2018; 210:307–313

Non Specific Interstitial Pneumonia

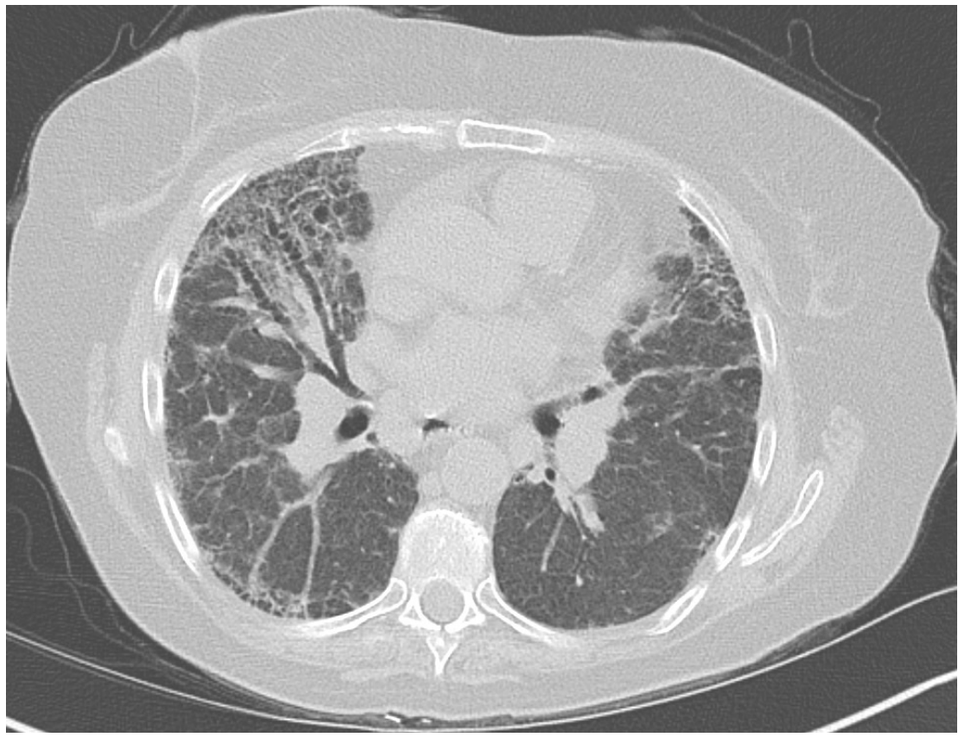
- Definition: Diffuse interstitial pneumonia, primary or secondary
- Epidemiology: Prevalence is not well established, similar men and women, age<60 is not uncommon, history of smoking is common
- Diagnosis: Clinical presentation, imaging and lung biopsy (cellular and fibrotic NSIP), serologies and biomarkers
- Prognosis: Survival 5-10 years in greater than 80%
- Treatment: Immune modulators (for cellular NSIP), antifibrotics?, transplant, physical therapy, palliative management.

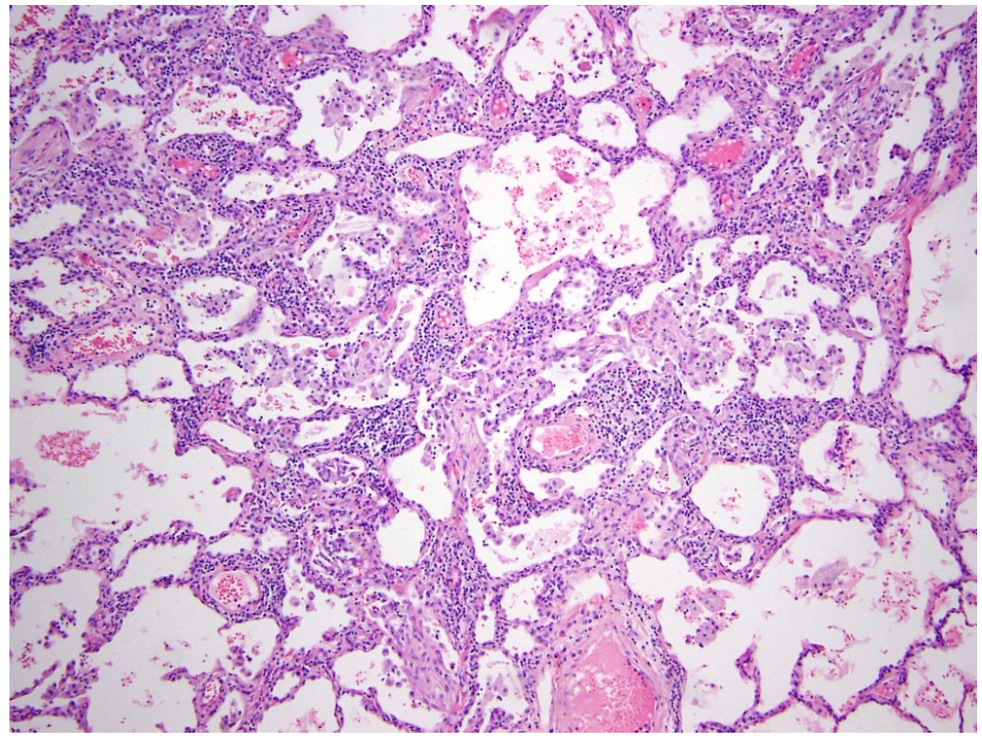
NSIP



Travis AJRCCM 2013

NSIP



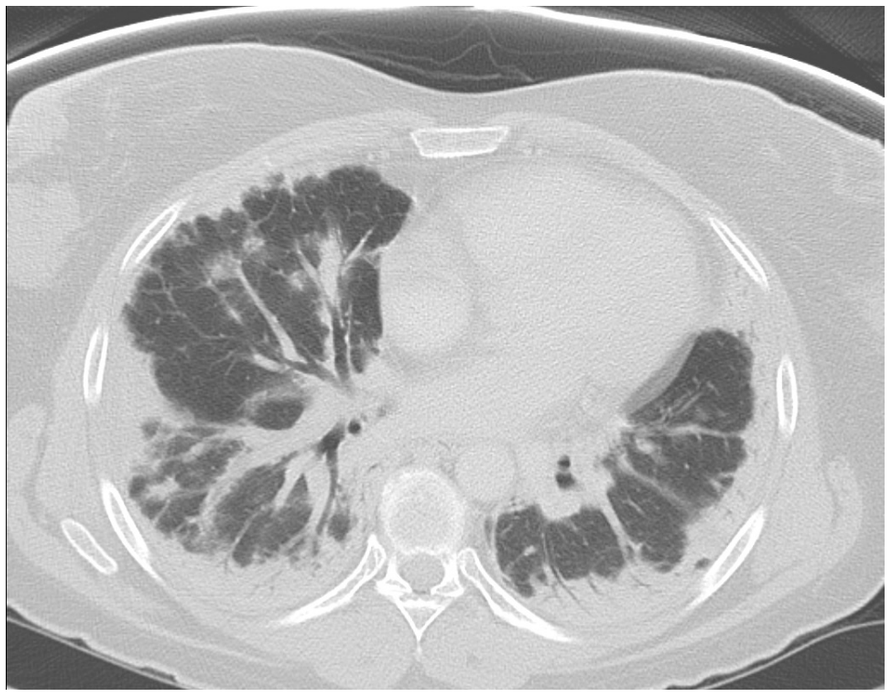


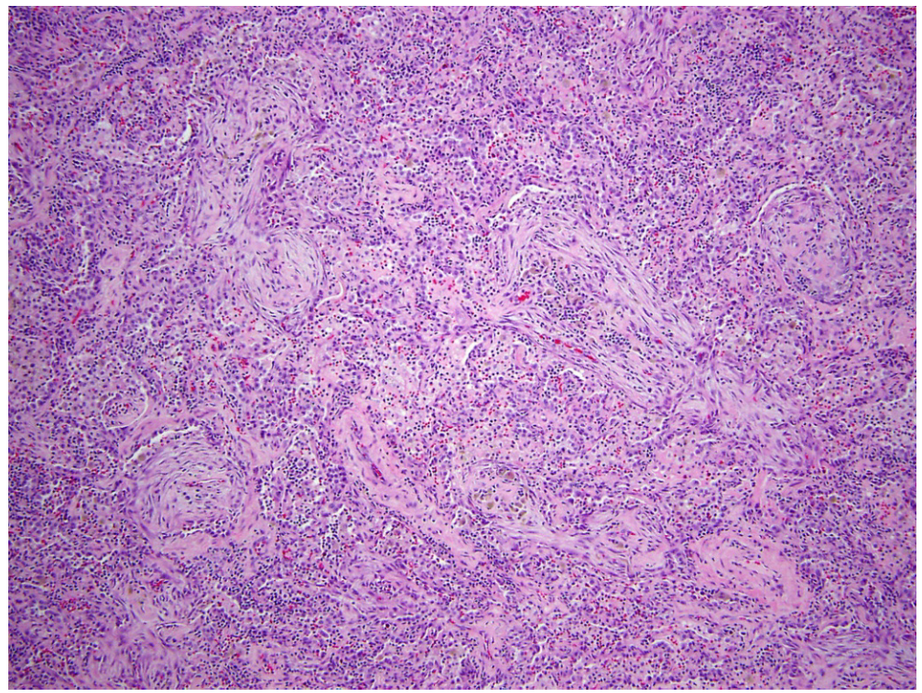
Hunninghake GM, Rosas IO. Interstitial Lung Diseases. In: Jameson JL, Fauci AS, Kasper DK, Hauser SL, Longo DL, Loscalzo J (Eds.). Harrison's Principles of Internal Medicine. 20th Edition. 2018; ch297. New York: McGraw-Hill Education.

Cryptogenic Organizing Pneumonia

- Definition: Unusually acute or subacute illness, often includes patchy or migratory consolidative opacities. Can be primary or secondary (often seen in dermato/myositis)
- Epidemiology: Prevalence is not well established, average age 50-60, can occur in isolation or coincident with other diseases.
- Diagnosis: Clinical presentation (can prevent with flu-like prodrome), imaging, lung biopsy (COP), and serologies.
- Prognosis: Usually good but can have a variant of rapid progression to fibrosis.
- Treatment: Immune modulators, steroids (we use MMF, Rituxan).

COP





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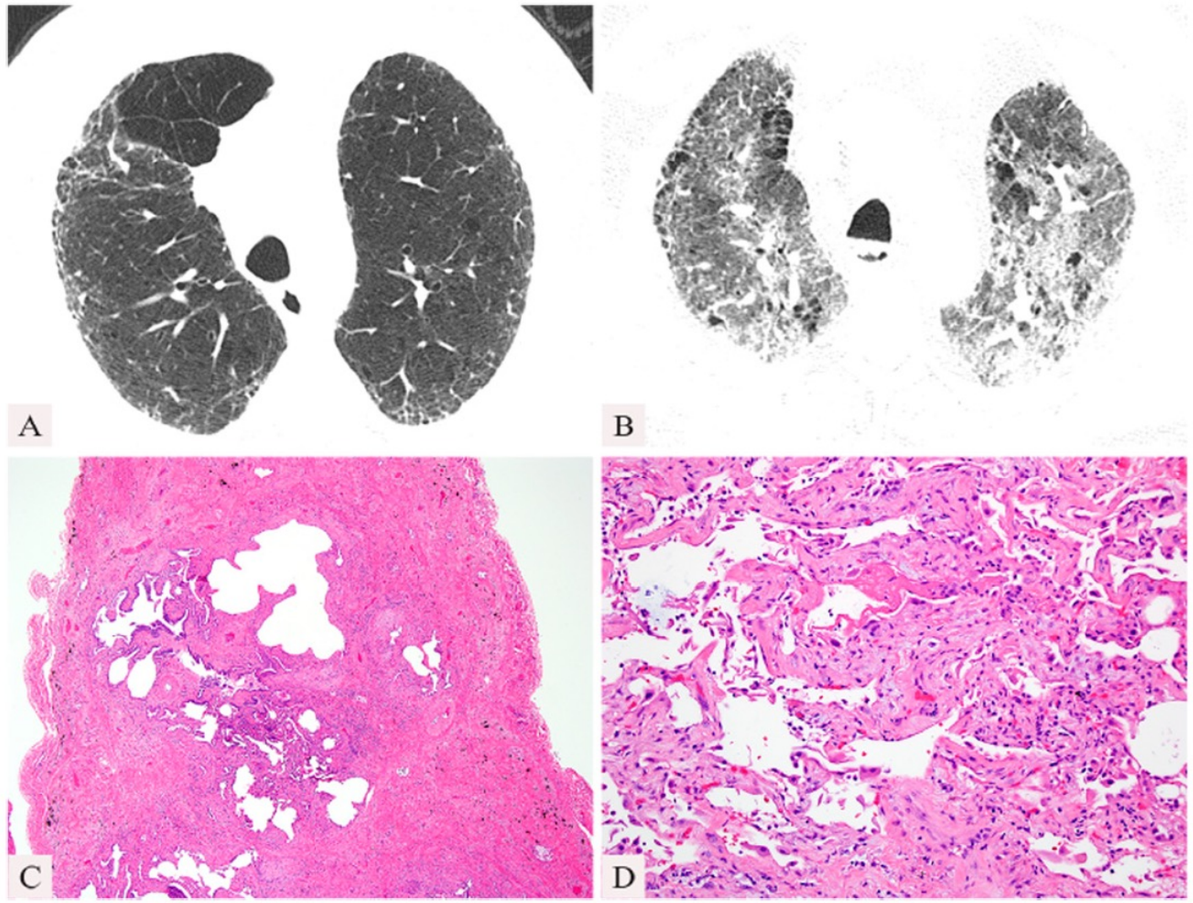
Acute Exacerbation of Interstitial Pneumonia

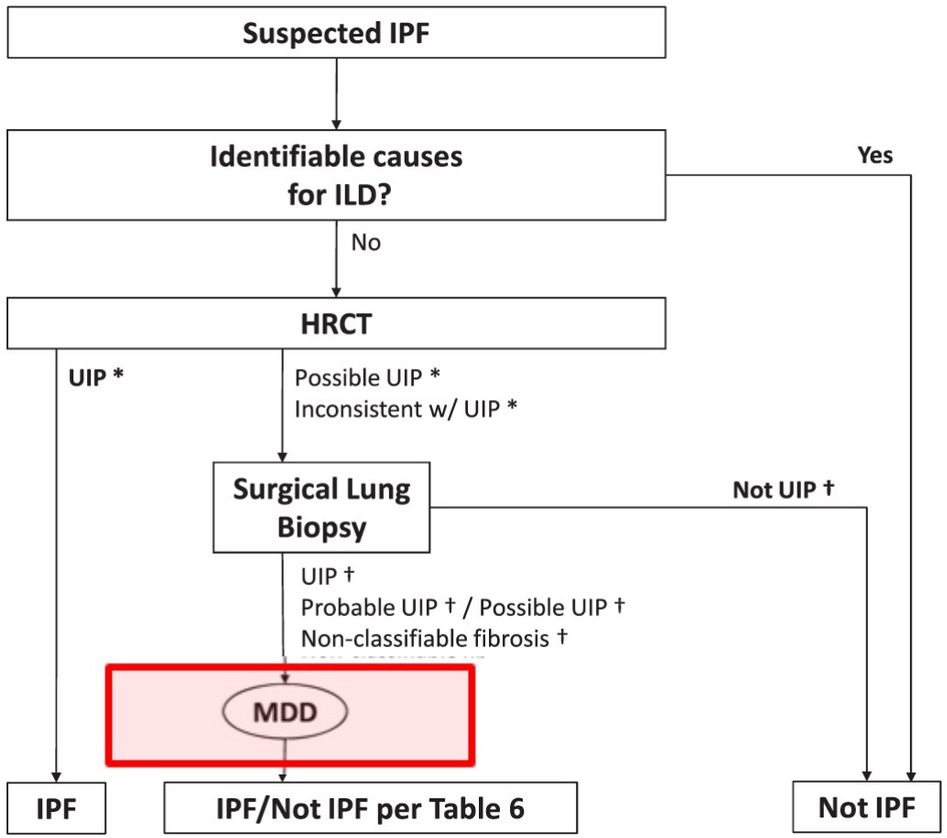
- Definition: Acute or subacute disease progression in a patient with pre-existing diagnosis of interstitial pneumonia
- Epidemiology: In IPF, 20% of subjects have acute exacerbations. Important to remember this can occur in all fibrotic lung diseases.
- Diagnosis: Clinical presentation, lung biopsy is rarely performed- can exacerbate condition
- Prognosis: One year survival less than 50%
- Treatment: Unknown

Acute Exacerbation of Interstitial Pneumonia



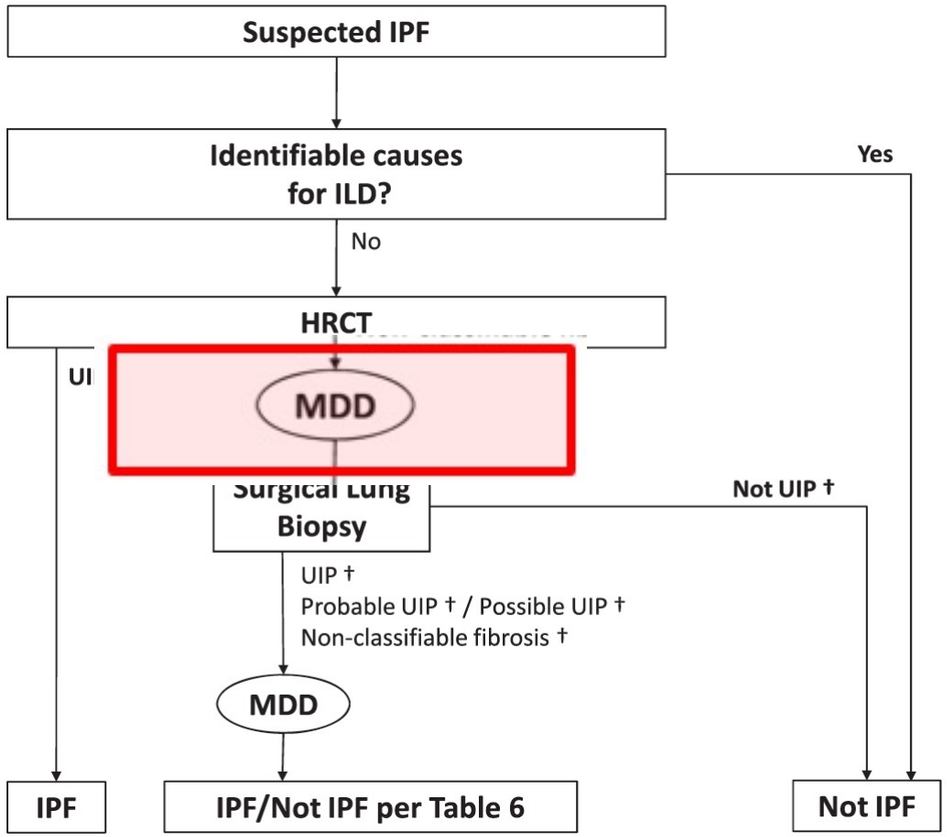
Travis AJRCCM 2013

IPF Multi Disciplinary Diagnosis



Raghu AJRCCM 2011

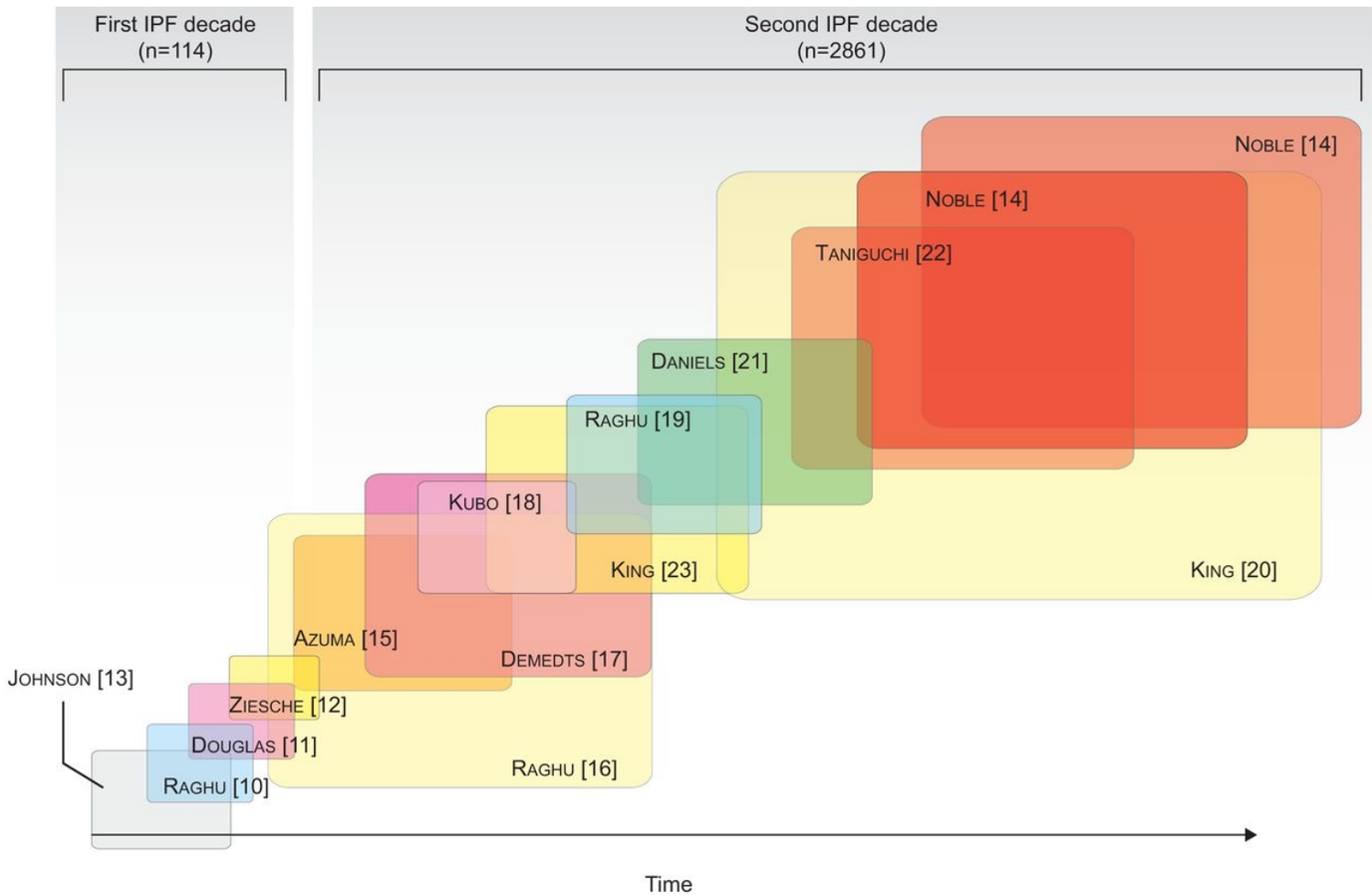
ILD Multi Disciplinary Diagnosis



Summary of the Evaluation of ILD

- A multidisciplinary approach is favored to establish a diagnosis and plan of care
- IPF is a progressive fibrotic lung disease that generally has a poor survival
- Other IIP's can be associated with progressive fibrotic lung disease but also can have more variable clinical courses and survival.
- Until recently immune suppression and transplant were standard of care of progressive fibrotic lung disease

Update on Clinical Trials in Pulmonary Fibrosis



Richeldi, European Respiratory Review 2013; 22: 103-5.

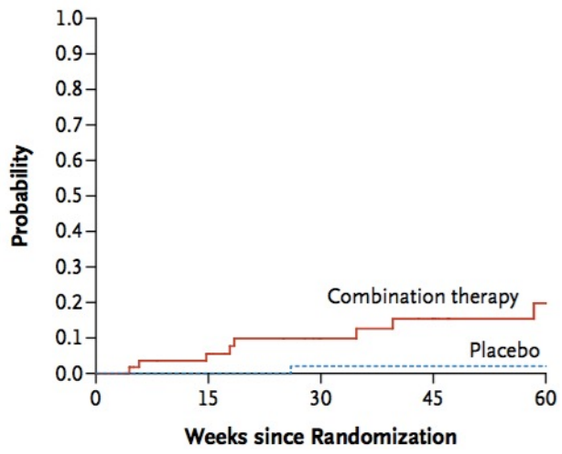
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prednisone, Azathioprine, and *N*-Acetylcysteine for Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

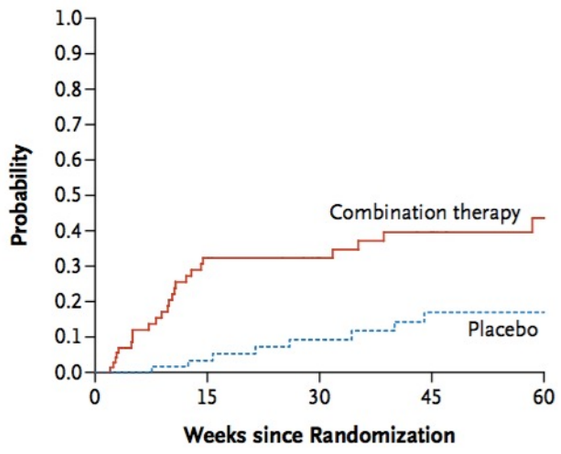
Time to Death



No. at Risk

Combination therapy	77	50	34	29	14
Placebo	78	57	44	31	17

Time to Death or Hospitalization



No. at Risk

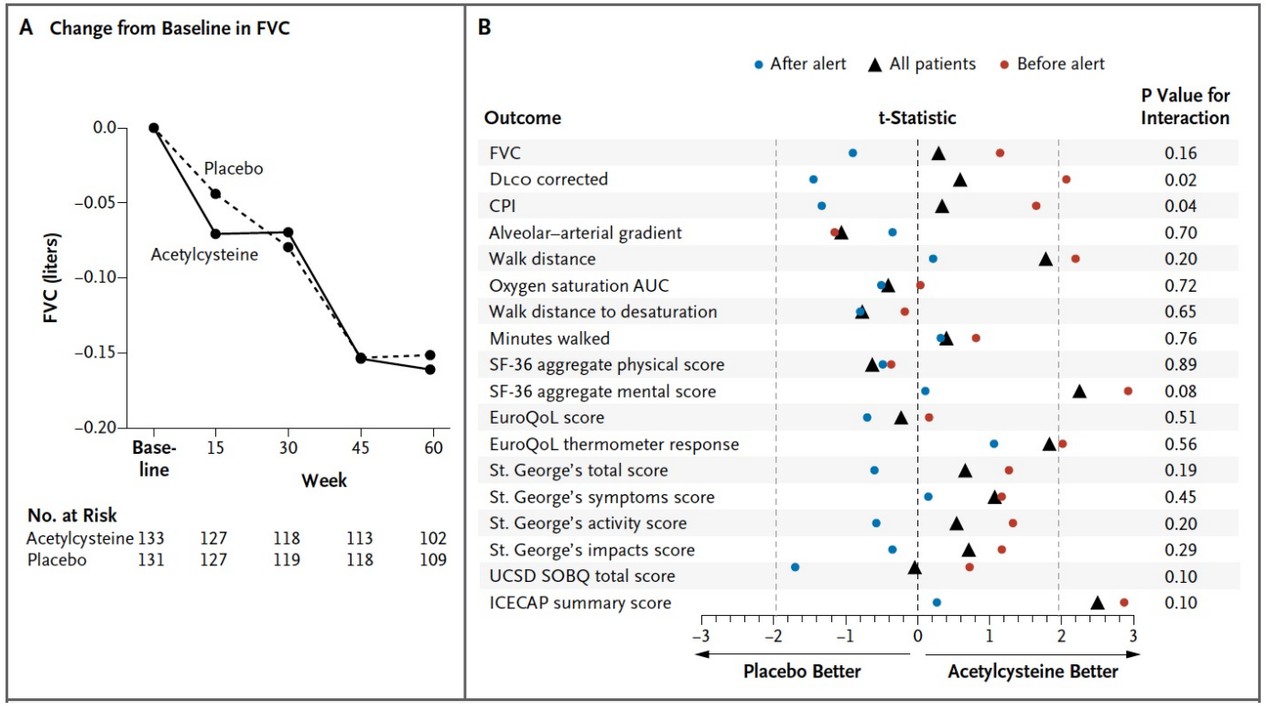
Combination therapy	77	40	29	23	10
Placebo	78	55	42	26	16

Raghu NEJM 2012

ORIGINAL ARTICLE

Randomized Trial of Acetylcysteine in Idiopathic Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*



Raghu NEJM 2012

ORIGINAL ARTICLE

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

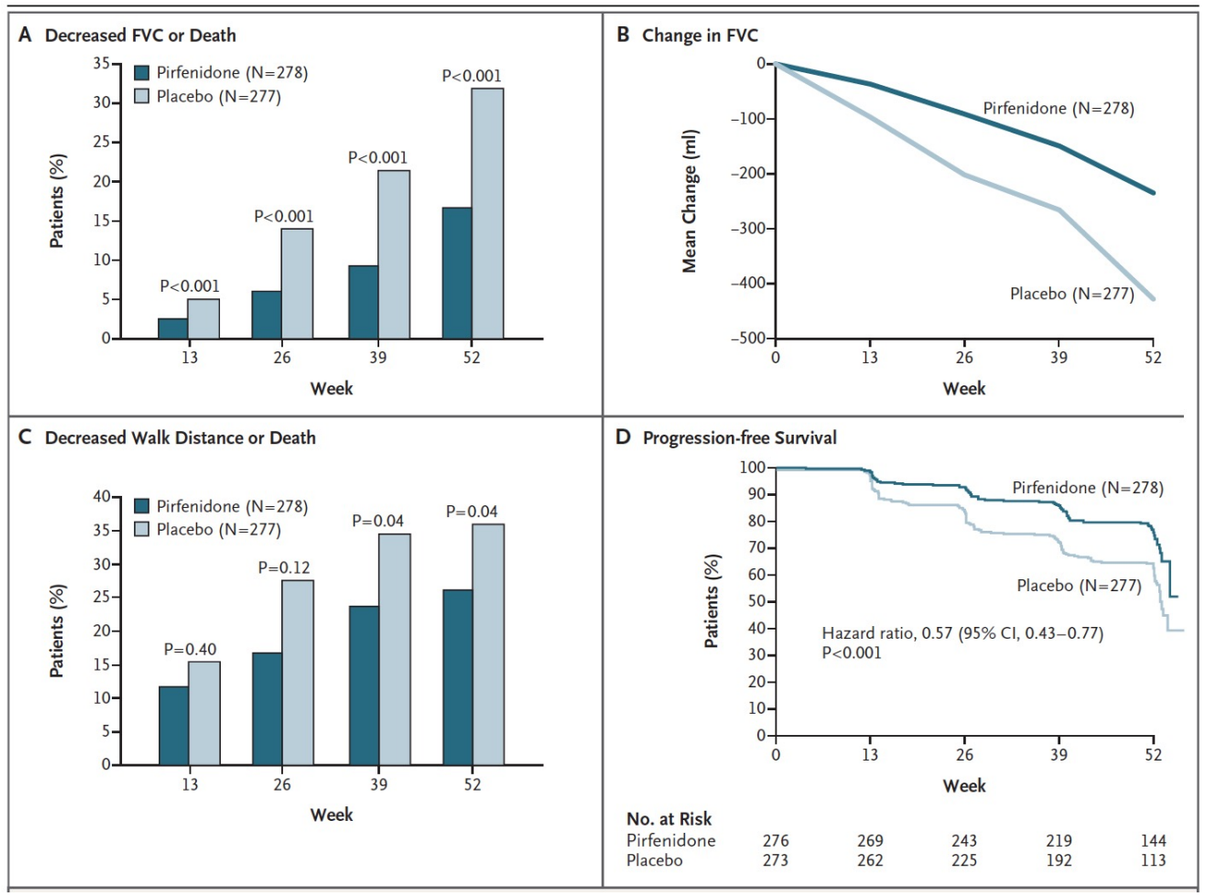
Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D., Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D., Ian Glaspole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D., Peter M. Hopkins, M.D., David Kardatzke, Ph.D., Lisa Lancaster, M.D., David J. Lederer, M.D., Steven D. Nathan, M.D., Carlos A. Pereira, M.D., Steven A. Sahn, M.D., Robert Sussman, M.D., Jeffrey J. Swigris, D.O., and Paul W. Noble, M.D., for the ASCEND Study Group*

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Pirfenidone (N=278)	Placebo (N=277)
Age — yr	68.4±6.7	67.8±7.3
Male sex — no. (%)	222 (79.9)	213 (76.9)
U.S. enrollment — no. (%)	187 (67.3)	184 (66.4)
Former smoker — no. (%)	184 (66.2)	169 (61.0)
Lung physiological features		
FVC — % of predicted value	67.8±11.2	68.6±10.9
FEV_1:FVC	0.84±0.03	0.84±0.04
Carbon monoxide diffusing capacity — % of predicted value	43.7±10.5	44.2±12.5
Dyspnea score†	34.0±21.9	36.6±21.7
Distance on 6-min walk test — m	415.0±98.5	420.7±98.1
Use of supplemental oxygen — no. (%)	78 (28.1)	76 (27.4)
Time since diagnosis — yr	1.7±1.1	1.7±1.1
Diagnostic finding on high-resolution computed tomography — no. (%)		
Definite pattern of usual interstitial pneumonia	266 (95.7)	262 (94.6)
Possible pattern of usual interstitial pneumonia‡	12 (4.3)	15 (5.4)
Surgical lung biopsy — no. (%)	86 (30.9)	79 (28.5)

King NEJM 2014

Primary and Key Secondary Efficacy Outcomes



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Adverse Events

Table 3. Adverse Events.*

Adverse Event	Pirfenidone (N=278)	Placebo (N=277)
	no. of patients (%)	
Cough	70 (25.2)	82 (29.6)
Nausea	100 (36.0)	37 (13.4)
Headache	72 (25.9)	64 (23.1)
Diarrhea	62 (22.3)	60 (21.7)
Upper respiratory tract infection	61 (21.9)	56 (20.2)
Fatigue	58 (20.9)	48 (17.3)
Rash	78 (28.1)	24 (8.7)
Dyspnea	41 (14.7)	49 (17.7)
Dizziness	49 (17.6)	36 (13.0)
Idiopathic pulmonary fibrosis†	26 (9.4)	50 (18.1)
Bronchitis	39 (14.0)	36 (13.0)
Constipation	32 (11.5)	38 (13.7)
Back pain	30 (10.8)	37 (13.4)
Dyspepsia	49 (17.6)	17 (6.1)
Nasopharyngitis	33 (11.9)	30 (10.8)
Anorexia	44 (15.8)	18 (6.5)
Vomiting	36 (12.9)	24 (8.7)
Decrease in weight	35 (12.6)	22 (7.9)
Gastroesophageal reflux	33 (11.9)	18 (6.5)
Insomnia	31 (11.2)	18 (6.5)

King NEJM 2014

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ESTABLISHED IN 1812 MAY 29, 2014 VOL. 370 NO. 22

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

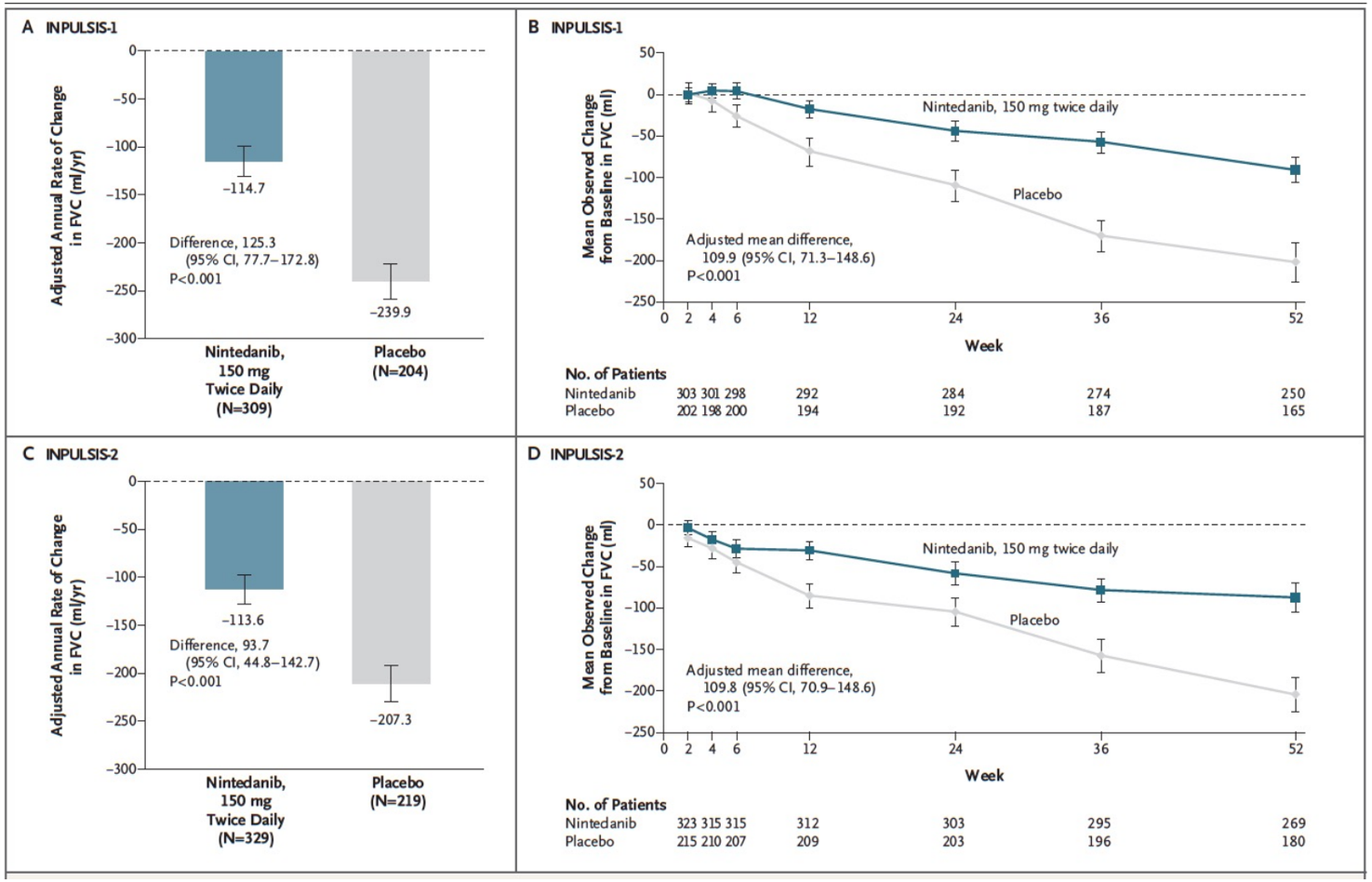
Luca Richeldi, M.D., Ph.D., Roland M. du Bois, M.D., Ganesh Raghu, M.D., Arata Azuma, M.D., Ph.D., Kevin K. Brown, M.D., Ulrich Costabel, M.D., Vincent Cottin, M.D., Ph.D., Kevin R. Flaherty, M.D., David M. Hansell, M.D., Yoshikazu Inoue, M.D., Ph.D., Dong Soon Kim, M.D., Martin Kolb, M.D., Ph.D., Andrew G. Nicholson, D.M., Paul W. Noble, M.D., Moisés Selman, M.D., Hiroyuki Taniguchi, M.D., Ph.D., Michèle Brun, M.Sc., Florence Le Maulf, M.Sc., Mannaïg Girard, M.Sc., Susanne Stowasser, M.D., Rozsa Schlenker-Herceg, M.D., Bernd Disse, M.D., Ph.D., and Harold R. Collard, M.D., for the INPULSIS Trial Investigators*

Table 1. Baseline Characteristics of Patients in INPULSIS-1 and INPULSIS-2.*

Characteristic	INPULSIS-1		INPULSIS-2	
	Nintedanib (N=309)	Placebo (N=204)	Nintedanib (N=329)	Placebo (N=219)
Male sex — no. (%)	251 (81.2)	163 (79.9)	256 (77.8)	171 (78.1)
Age — yr	66.9±8.4	66.9±8.2	66.4±7.9	67.1±7.5
Weight — kg	82.0±16.8	81.2±16.3	76.6±15.9	76.3±16.5
Body-mass index†	28.6±4.5	28.1±4.6	27.6±4.6	27.2±4.5
Smoking status — no. (%)				
Never smoked	71 (23.0)	51 (25.0)	103 (31.3)	71 (32.4)
Former smoker	217 (70.2)	144 (70.6)	218 (66.3)	139 (63.5)
Current smoker	21 (6.8)	9 (4.4)	8 (2.4)	9 (4.1)
Time since diagnosis of idiopathic pulmonary fibrosis — yr	1.7±1.4	1.6±1.4	1.6±1.3	1.6±1.3
Specimen from surgical lung biopsy available — no. (%)	60 (19.4)	33 (16.2)	84 (25.5)	52 (23.7)
Systemic corticosteroid therapy — no. (%)‡	68 (22.0)	43 (21.1)	68 (20.7)	46 (21.0)
FVC				
Mean — ml	2757±735	2845±820	2673±776	2619±787
Median — ml	2700	2721	2615	2591
Percentage of predicted value	79.5±17.0	80.5±17.3	80.0±18.1	78.1±19.0
FEV_1:FVC (%)	81.5±5.4	80.8±6.1	81.8±6.3	82.4±5.7
DLCO				
mmol/min/kPa	4.0±1.2	4.0±1.1	3.8±1.2	3.7±1.3
Percentage of predicted value§	47.8±12.3	47.5±11.7	47.0±14.5	46.4±14.8
SpO_2 — %	95.9±2.0	95.9±1.9	95.8±2.6	95.7±2.1
Total SGRQ score¶	39.6±17.6	39.8±18.5	39.5±20.5	39.4±18.7

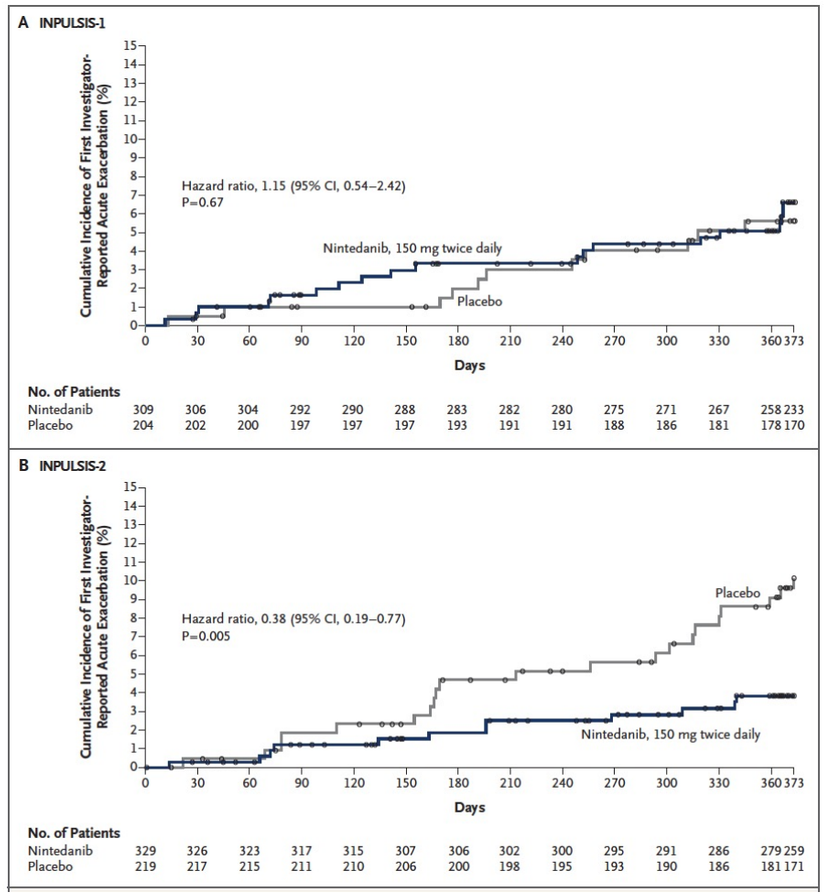
Richeldi NEJM 2014

Annual rate of decline in lung function



Richeldi NEJM 2014

Reduction in rate of acute exacerbations



Richeldi NEJM 2014

Adverse Events

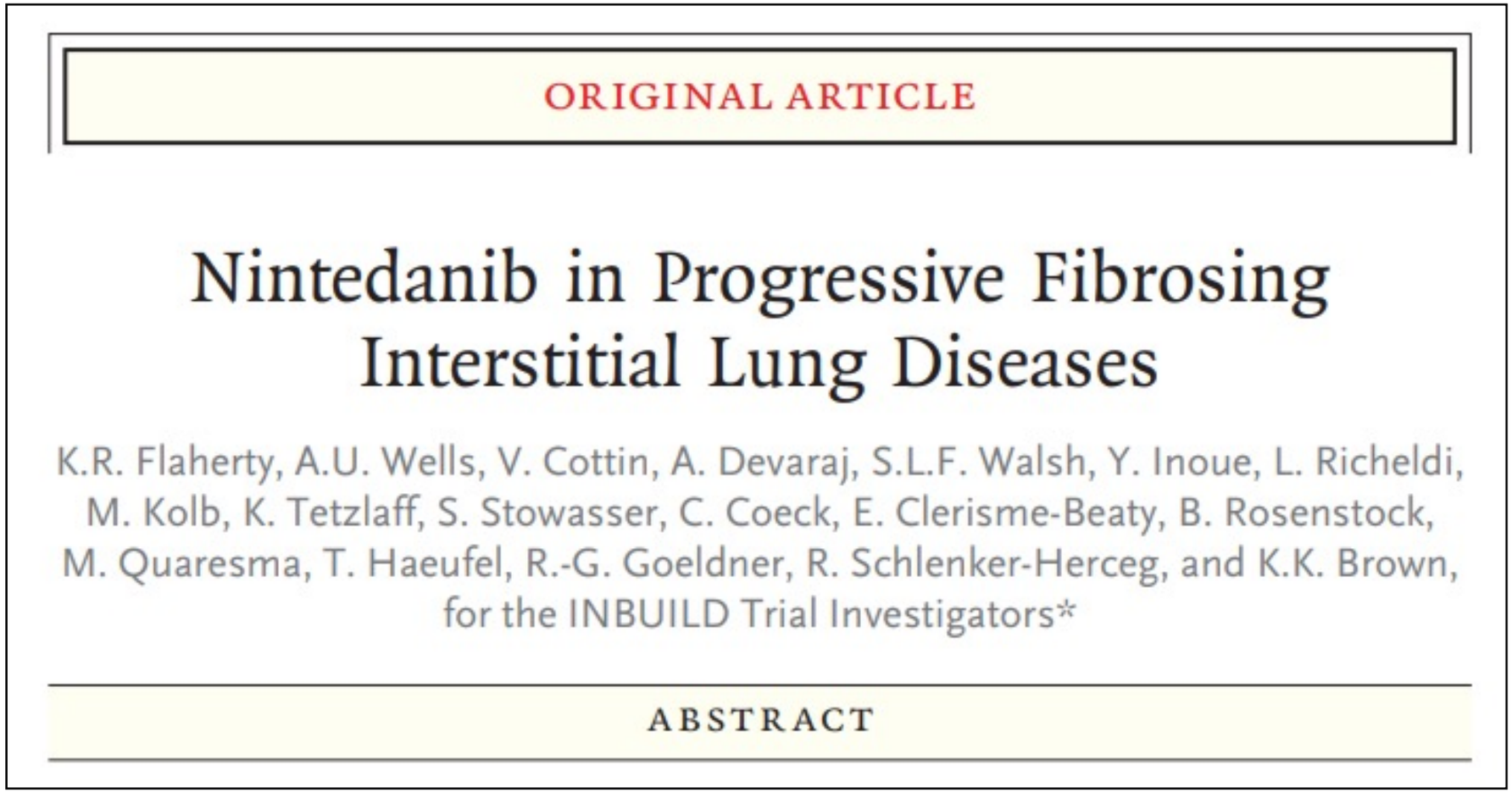
Table 3. Adverse Events.

Event	INPULSIS-1		INPULSIS-2	
	Nintedanib (N=309)	Placebo (N=204)	Nintedanib (N=329)	Placebo (N=219)
	number of patients (percent)			
Any adverse event	298 (96.4)	181 (88.7)	311 (94.5)	198 (90.4)
Any adverse event, excluding progression of idiopathic pulmonary fibrosis*	296 (95.8)	179 (87.7)	311 (94.5)	197 (90.0)
Most frequent adverse events†				
Diarrhea	190 (61.5)	38 (18.6)	208 (63.2)	40 (18.3)
Nausea	70 (22.7)	12 (5.9)	86 (26.1)	16 (7.3)
Nasopharyngitis	39 (12.6)	34 (16.7)	48 (14.6)	34 (15.5)
Cough	47 (15.2)	26 (12.7)	38 (11.6)	31 (14.2)
Progression of idiopathic pulmonary fibrosis*	31 (10.0)	21 (10.3)	33 (10.0)	40 (18.3)
Bronchitis	36 (11.7)	28 (13.7)	31 (9.4)	17 (7.8)
Upper respiratory tract infection	28 (9.1)	18 (8.8)	30 (9.1)	24 (11.0)
Dyspnea	22 (7.1)	23 (11.3)	27 (8.2)	25 (11.4)
Decreased appetite	26 (8.4)	14 (6.9)	42 (12.8)	10 (4.6)
Vomiting	40 (12.9)	4 (2.0)	34 (10.3)	7 (3.2)
Weight loss	25 (8.1)	13 (6.4)	37 (11.2)	2 (0.9)
Severe adverse events‡	81 (26.2)	37 (18.1)	93 (28.3)	62 (28.3)
Serious adverse events‡	96 (31.1)	55 (27.0)	98 (29.8)	72 (32.9)
Fatal adverse events	12 (3.9)	10 (4.9)	25 (7.6)	21 (9.6)
Adverse events leading to treatment discontinuation§	65 (21.0)	22 (10.8)	58 (17.6)	33 (15.1)
Gastrointestinal disorders	26 (8.4)	3 (1.5)	21 (6.4)	2 (0.9)
Respiratory, thoracic, and mediastinal disorders	12 (3.9)	10 (4.9)	8 (2.4)	18 (8.2)
Investigation results¶	10 (3.2)	1 (0.5)	8 (2.4)	1 (0.5)
Cardiac disorders	5 (1.6)	4 (2.0)	2 (0.6)	3 (1.4)
General disorders and conditions involving site of study-drug administration‖	8 (2.6)	3 (1.5)	2 (0.6)	1 (0.5)

Richeldi NEJM 2014

Update on Clinical Trials in Pulmonary Fibrosis

Update on Clinical Trials in Pulmonary Fibrosis



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*

ABSTRACT

Flaherty NEJM 2019

Included ILDs

	Nintedanib (n=332)	Placebo (n=331)
Hypersensitivity pneumonitis	84 (25.3)	89 (26.9)
Autoimmune ILDs	82 (24.7)	88 (26.6)
Rheumatoid arthritis-associated ILD	42 (12.7)	47 (14.2)
Systemic sclerosis-associated ILD	23 (6.9)	16 (4.8)
Mixed connective tissue disease-associated ILD	7 (2.1)	12 (3.6)
Other autoimmune ILDs	10 (3.0)	13 (3.9)
Idiopathic non-specific interstitial pneumonia	64 (19.3)	61 (18.4)
Unclassifiable idiopathic interstitial pneumonia	64 (19.3)	50 (15.1)
Other ILDs*	38 (11.4)	43 (13.0)

Data are no (%) of patients.

*Included sarcoidosis, exposure-related ILDs and selected other terms in "Other fibrosing ILDs".

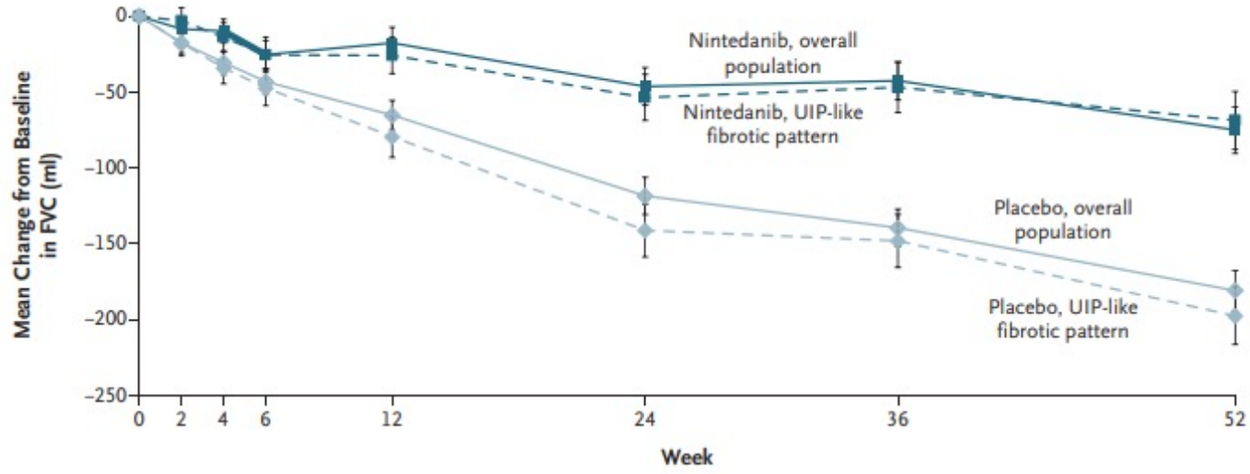
Flaherty NEJM 2019

Progressive Pulmonary Fibrosis

- Definition of progressive pulmonary fibrosis (over 24 months)
  - Decline in FVC >10%
  - Decline in FVC 5-10%
    - With increased respiratory symptoms
    - Increased extent of fibrosis on chest CT
  - Worsening Respiratory Symptoms and increased extent of fibrosis of chest CT.

Flaherty NEJM 2019

Primary Efficacy Outcome



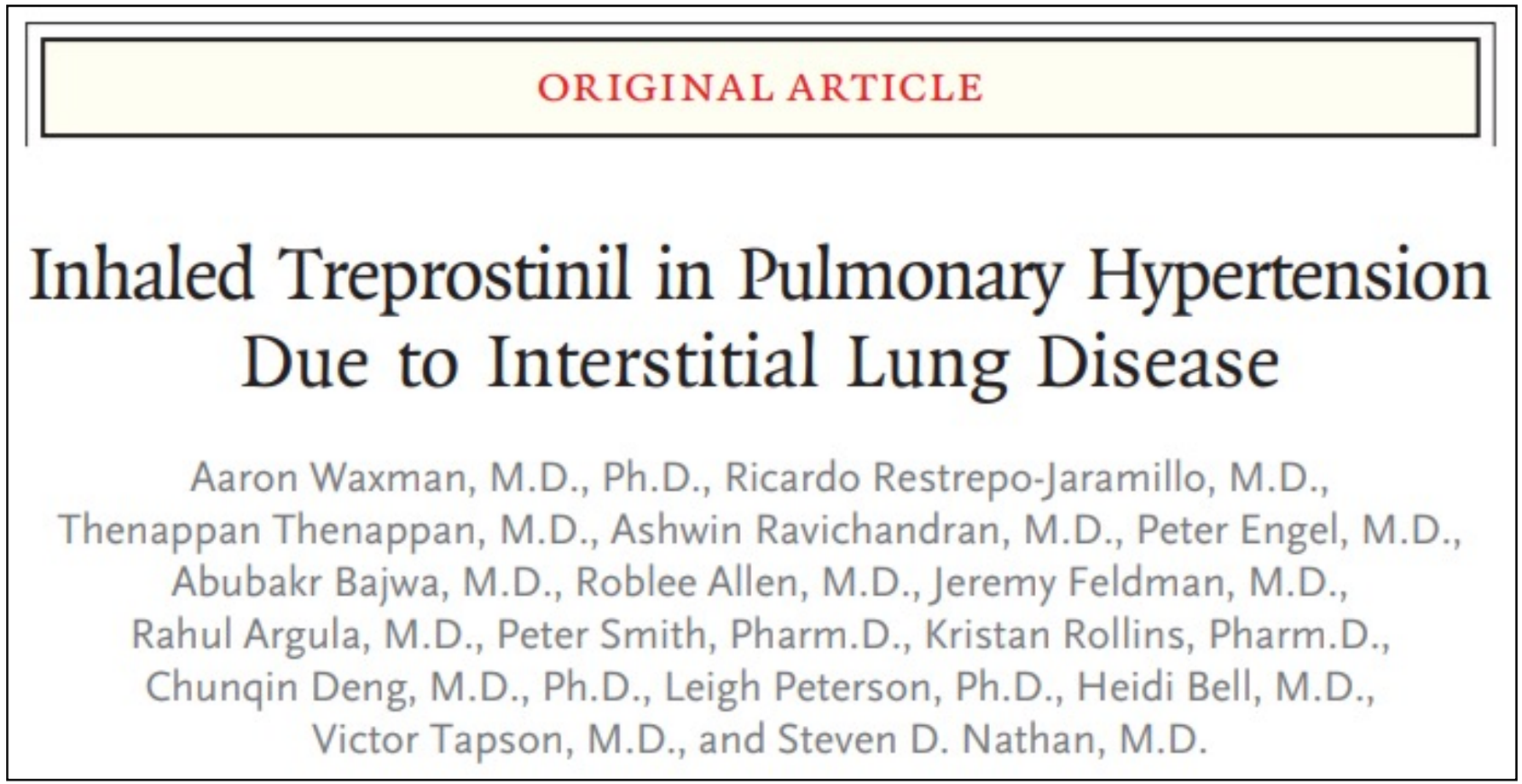
No. of Patients								
Overall population								
Nintedanib	332	326	320	322	314	298	285	265
Placebo	331	325	326	325	320	311	296	274
Patients with UIP-like fibrotic pattern								
Nintedanib	206	203	200	199	193	180	171	160
Placebo	206	202	202	201	197	190	176	162

Figure 2. Decline from Baseline in Forced Vital Capacity (FVC).

Shown is the observed mean change from baseline in FVC over the 52-week trial period in the overall population and in patients with an imaging pattern of usual interstitial pneumonia (UIP) on high-resolution computed tomography in the nintedanib group and the placebo group. The I bars indicate the standard error.

Flaherty NEJM 2019

Update on Clinical Trials in Pulmonary Fibrosis



ORIGINAL ARTICLE

Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

Aaron Waxman, M.D., Ph.D., Ricardo Restrepo-Jaramillo, M.D., Thenappan Thenappan, M.D., Ashwin Ravichandran, M.D., Peter Engel, M.D., Abubakr Bajwa, M.D., Roblee Allen, M.D., Jeremy Feldman, M.D., Rahul Argula, M.D., Peter Smith, Pharm.D., Kristan Rollins, Pharm.D., Chunqin Deng, M.D., Ph.D., Leigh Peterson, Ph.D., Heidi Bell, M.D., Victor Tapson, M.D., and Steven D. Nathan, M.D.

Waxman NEJM 2021

Definition of Group III Pa HTN

- ILD and Group III Pulmonary Hypertension (by right heart cath)
  - PVR > 3 Woods units
  - PCWP < 15 mm Hg
  - Mean PA pressure > 25 mm Hg

Flaherty NEJM 2019

Primary and Key Secondary Efficacy Outcomes

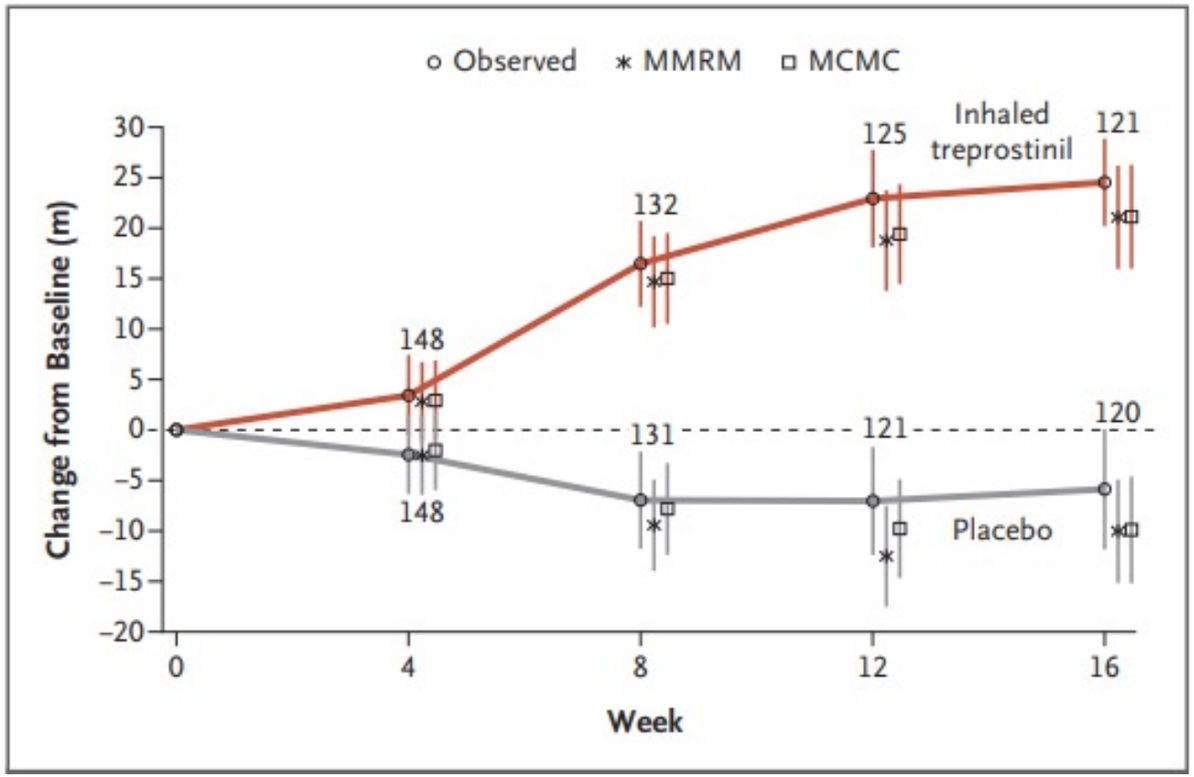
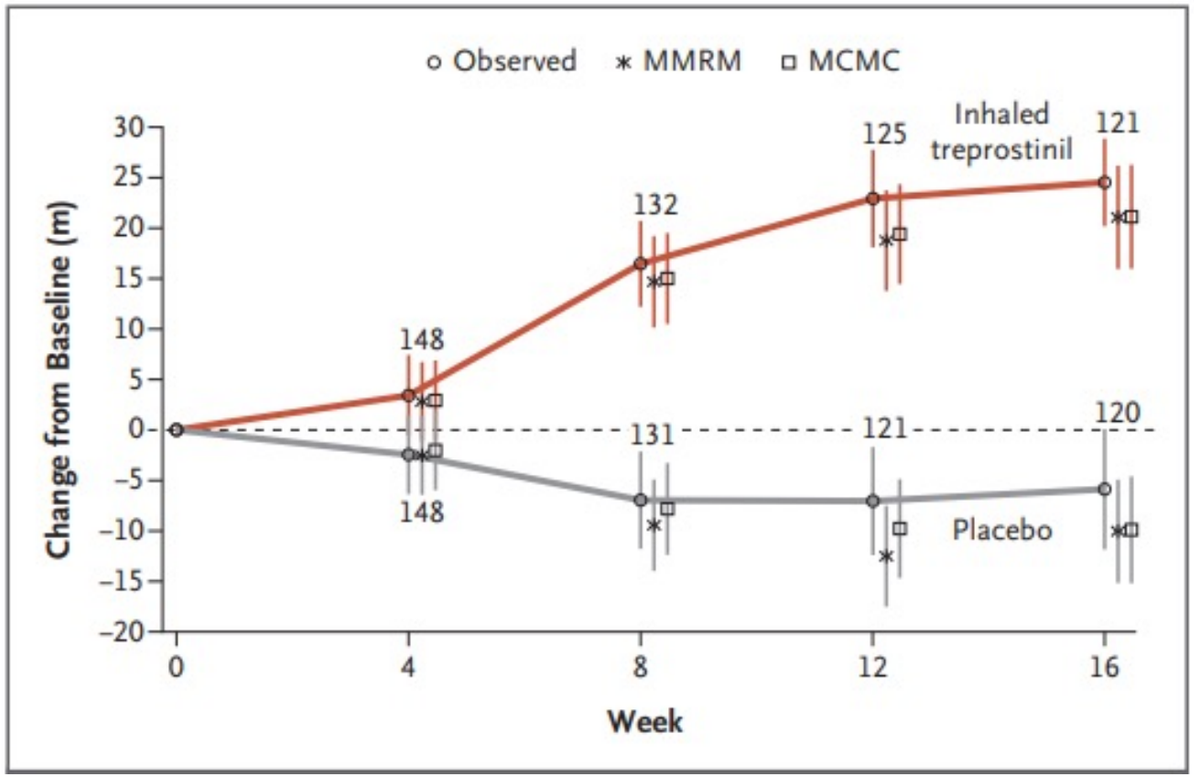


Table 2. Summary of Primary and Secondary End Points.*

End Point	Inhaled Treprostinil (N=163)	Placebo (N=163)	Treatment Effect (95% CI)	P Value
Primary end point				
Change in peak 6-minute walk distance from baseline to wk 16 — m†	21.08±5.12	−10.04±5.12	31.12±7.25 (16.85 to 45.39)‡	<0.001
Secondary end points§				
Change in plasma concentration of NT-proBNP from baseline to wk 16¶				
Mean (±SD) change — pg/ml	−396.35±1904.90	1453.95±7296.20		
Median — pg/ml	−22.65	20.65		
Range — pg/ml	−11,433.0 to 5373.1	−5483.3 to 87,148.3		
Ratio to baseline	0.85±0.06	1.46±0.11	0.58±0.06 (0.47 to 0.72)‖	<0.001
Occurrence of clinical worsening — no. (%)			0.61 (0.4 to 0.92)**	0.04
Any event	37 (22.7)	54 (33.1)		
Hospitalization for cardiopulmonary indication	18 (11.0)	24 (14.7)		
Decrease in 6-minute walk distance of >15% from baseline	13 (8.0)	26 (16.0)		
Death from any cause	4 (2.5)	4 (2.5)		
Lung transplantation	2 (1.2)	0		
Least-squares mean change in peak 6-minute walk distance from baseline to wk 12 — m†	18.77±4.99	−12.52±5.01	31.29±7.07 (17.37 to 45.21)‡	<0.001
Least-squares mean change in trough 6-minute walk distance from baseline to wk 15 — m	9.3±5.5	−12.7±5.5	21.99±7.7 (6.85 to 37.14)‡	0.005††

Waxman NEJM 2021

Primary and Key Secondary Efficacy Outcomes



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Least-squares mean change in trough 6-minute walk distance from baseline to wk 15 — m	9.3±5.5	−12.7±5.5	21.99±7.7 (6.85 to 37.14)‡	0.005††

Waxman NEJM 2021

Adverse Events

Table 3. Summary of Adverse Events.

Variable	Inhaled Treprostinil (N=163)	Placebo (N=163)	P Value*
Total no. of adverse events	890	793	
Patients with ≥1 adverse event — no. (%)	152 (93.3)	149 (91.4)	0.68
Total no. of serious adverse events†	53	89	
Patients with ≥1 serious adverse event — no. (%)	38 (23.3)	42 (25.8)	0.70
Total no. of adverse events leading to withdrawal of treprostinil or placebo	47	38	
Most frequently occurring adverse events — no. of patients (%)‡			
Cough	71 (43.6)	54 (33.1)	0.07
Headache	45 (27.6)	32 (19.6)	0.12
Dyspnea	41 (25.2)	51 (31.3)	0.27
Dizziness	30 (18.4)	23 (14.1)	0.37
Nausea	25 (15.3)	26 (16.0)	>0.99
Fatigue	23 (14.1)	23 (14.1)	>0.99
Diarrhea	22 (13.5)	19 (11.7)	0.74
Throat irritation	20 (12.3)	6 (3.7)	0.007
Oropharyngeal pain	18 (11.0)	4 (2.5)	0.003
NT-proBNP increased	9 (5.5)	25 (15.3)	0.006

Low BP
Bleeding problems
Facial flushing

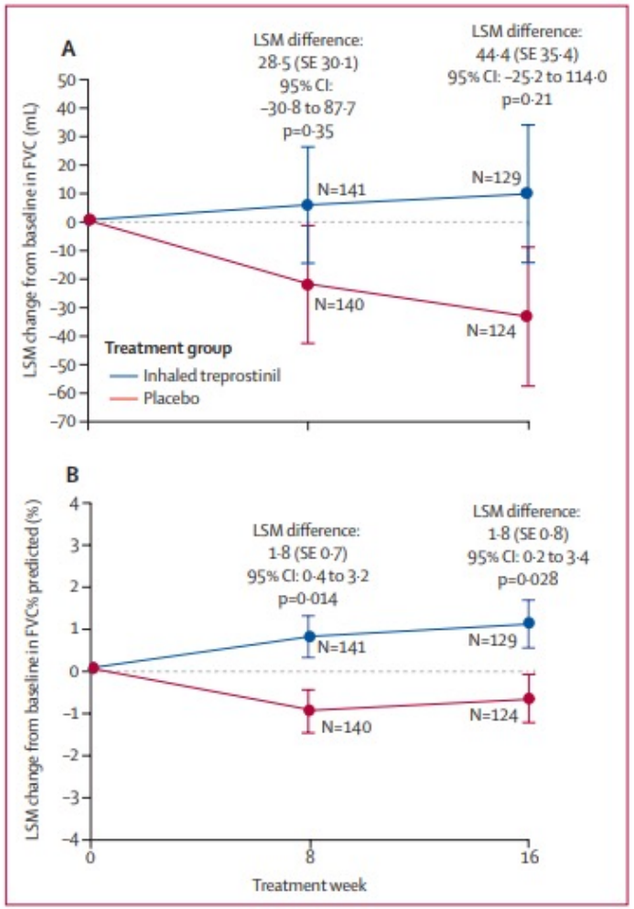
Prior authorization generally requires right heart catheterization documenting Group 3 PaHTN

Waxman NEJM 2021

Important Secondary Efficacy Outcome

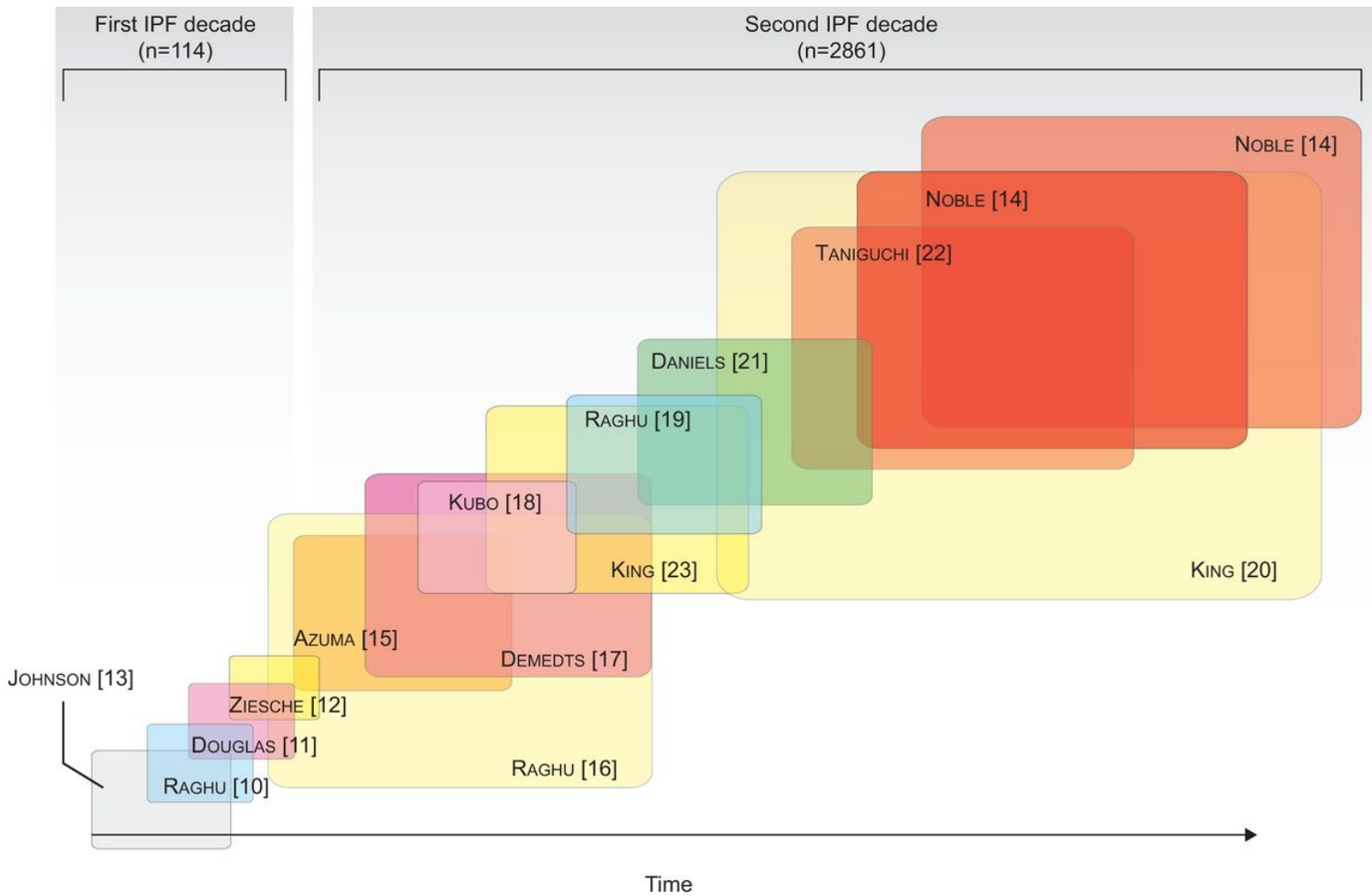
Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: a post-hoc analysis of the INCREASE study

Steven D Nathan, Aaron Waxman, Sudarshan Rajagopal, Amy Case, Shilpa Johri, Hilary DuBrock, David J De La Zerda, Sandeep Sahay, Christopher King, Lana Melendres-Groves, Peter Smith, Eric Shen, Lisa D Edwards, Andrew Nelsen, Victor F Tapson



Nathan Lancet Resp Med 2021

Update on Clinical Trials in Pulmonary Fibrosis



Current Clinical Trials at BWH

- Pliant – phase 2a double-blind, randomized, placebo-controlled study of avB6/avB1 inhibitor.
- (more to come)

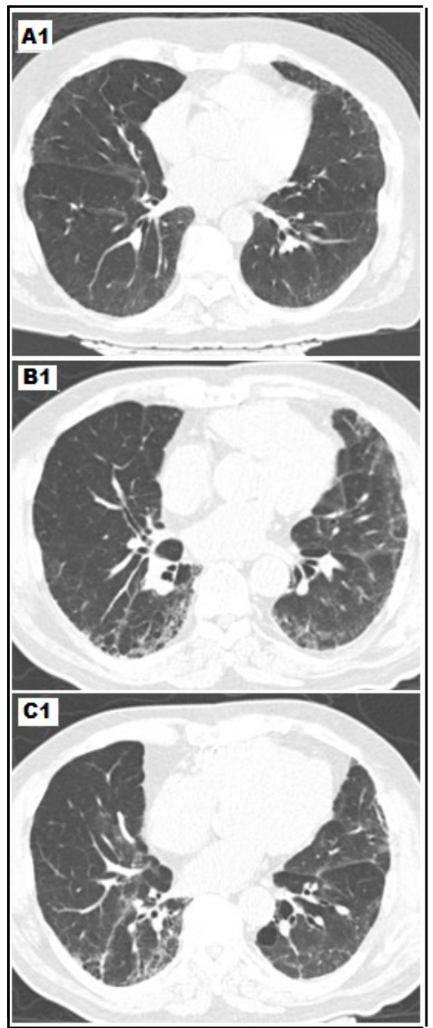
Richeldi, European Respiratory Review 2013; 22: 103-5.

Summary of Clinical Trials of IPF (PF)

- Immune suppression may be harmful in IPF patients
- Antifibrotics reduce rate of decline in lung function in IPF patients (even those with less severe disease), in patients with progressive pulmonary fibrosis (including systemic sclerosis and other forms of pulmonary fibrosis) and there is some evidence that antifibrotic therapy may improve survival.
- Antifibrotics are associated with significant side effects that lead to discontinuation of therapy, no evidence of improvement in QoL associated with therapy.
- Inhaled treprostinil may improve 6MWD in patient with pulmonary fibrosis and Group III pulmonary hypertension.
- Studies for other forms of PF, combination therapies, and many new compounds are ongoing.

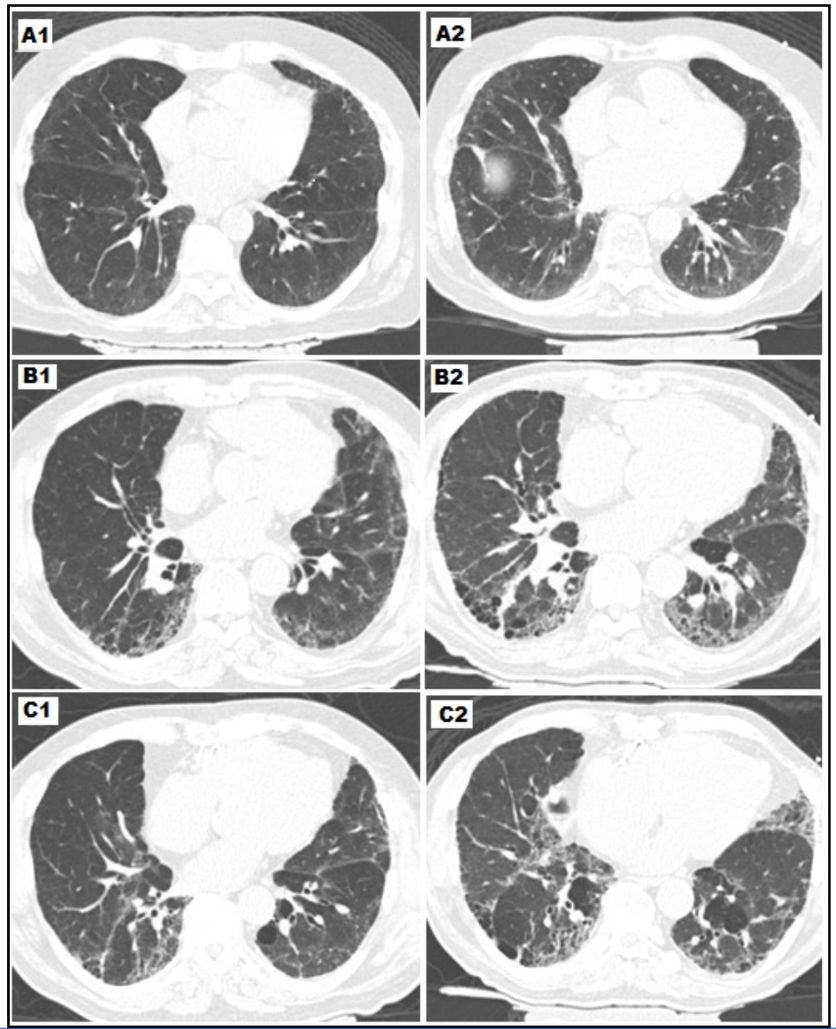
The Future of Early Detection for Pulmonary Fibrosis

- Goal: Prevent early but detectable stages of pulmonary fibrosis from progressing



The Future of Early Detection for Pulmonary Fibrosis

- Goal: Prevent early but detectable stages of pulmonary fibrosis from progressing to the more advanced stages of pulmonary fibrosis that help to diagnose disease.



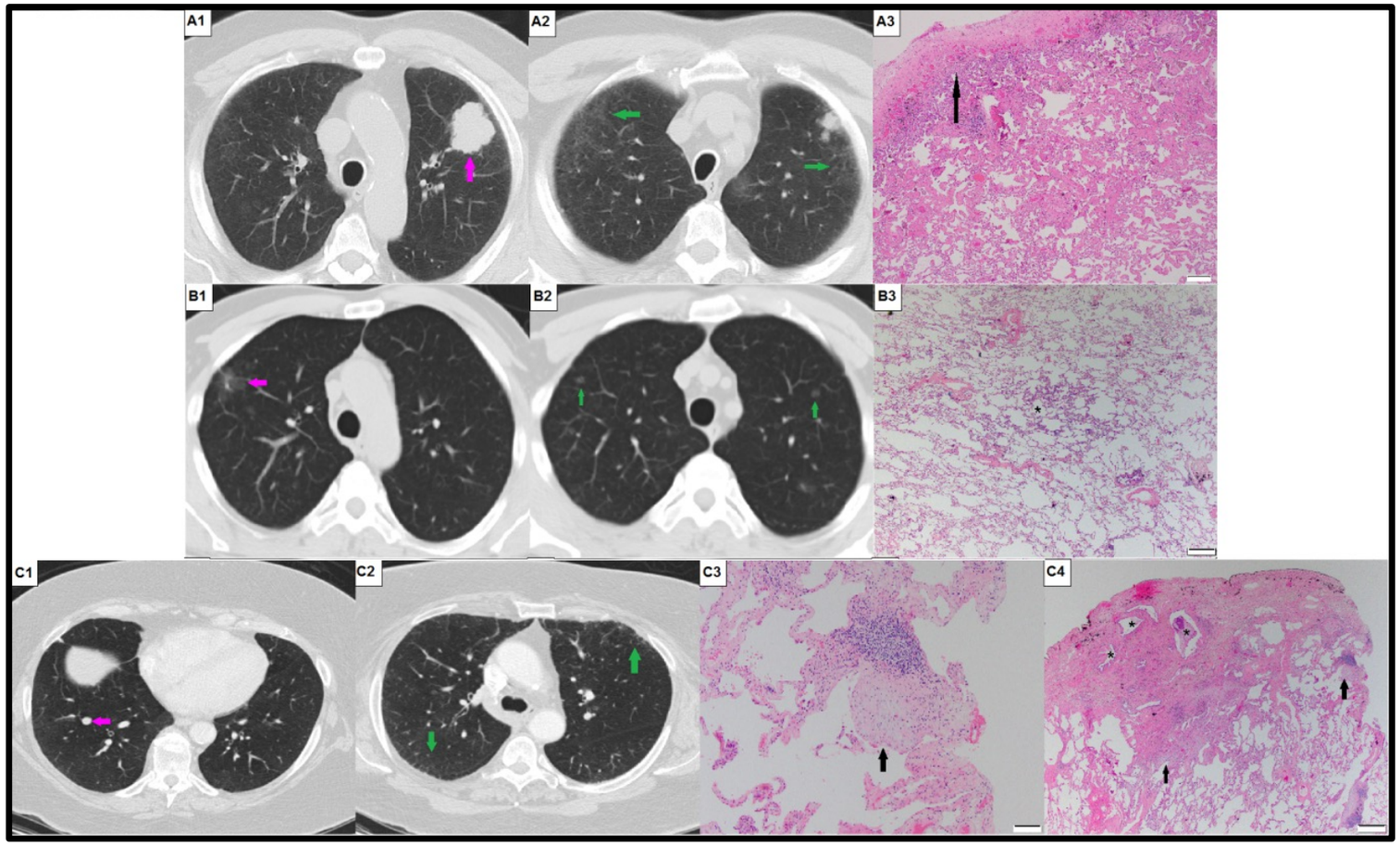
What Do We Know About Research Participants With Interstitial Lung Abnormalities (ILAs)?

- ILAs are relatively common among older persons
- Compared to those without ILA, those with ILA
  - Are more likely to report respiratory symptoms
  - Have reduced measures of TLC
  - Have reduced exercise capacity (6MWD/VO_2 max/participate in physical activity)
  - Have reduced DLCO

Am J Respir Crit Care Med. 2009; 180(5): 407-414.
Respir Med. 2010; 104(11):1712-21.
N Engl J Med. 2011; 364(10): 897-906.
Am J Respir Crit Care Med. 2012; 185(7):756-762.
Radiology. 2013; 268(2): 563-71.
N Engl J Med. 2013; 368(23):2192-200.
Eur Respir J. 2016;48(5):1442-1452.
Thorax. 2018; 73(9): 884-6.

What Do We Know About Research Participants With Interstitial Lung Abnormalities (ILAs)?

- BWH path cohort (undergoing lung nodule resection) – 424 samples with histopathology and chest CT
  - ILA associated with:
    - Subpleural fibrosis (OR 2.1, *P*=0.0009)
    - Fibroblastic foci (OR 4.2, *P*<0.0001)



Am J Respir Crit Care Med. 2018; 197(7):955-8.

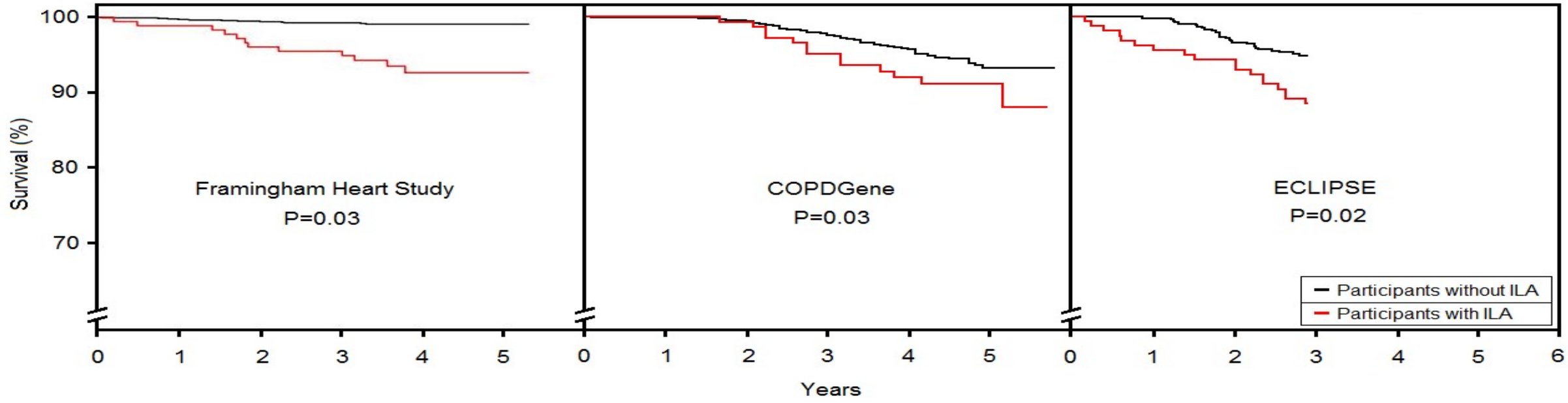
What Do We Know About the Progression of Interstitial Lung Abnormalities?

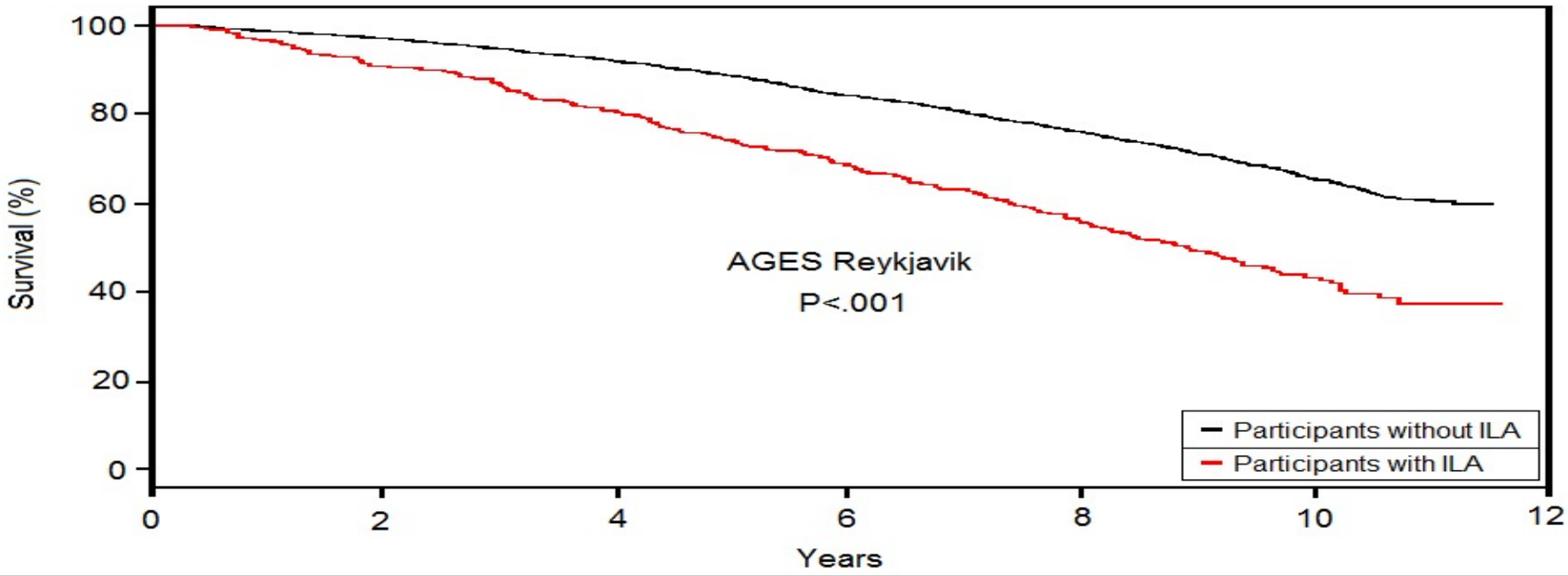
Table 2. Association of ILA Progression with Change in Spirometry

	ILA with Progression compared to No ILA				ILA with Progression compared to ILA without Progression			
	Unadjusted Analysis	P-value	Adjusted Analysis†	P-value	Unadjusted Analysis	P-value	Adjusted Analysis†	P-value
FEV1‡ Decline (mL/year)	179 ± 26	<.0001	24 ± 23	0.3	104 ± 44	0.02	29 ± 33	0.4
FVC§ Decline (mL/year)	31 ± 5	<.0001	22 ± 6	0.0001	24 ± 11	0.03	30 ± 12	0.01
FEV1/FVC Change (%)	23 ± 7	0.0006	9 ± 7	0.2	16 ± 15	0.3	15 ± 16	0.4

* P-values for all analyses, both adjusted and unadjusted are calculated using general linear models to account for familial relationships in the FHS.
± values are linear regression coefficients ± standard error
†Adjusted analyses include additional adjustments for age, sex, BMI, pack years smoking and current smoking status
‡ FEV1 is forced expiratory volume in one second
§FVC is forced vital capacity

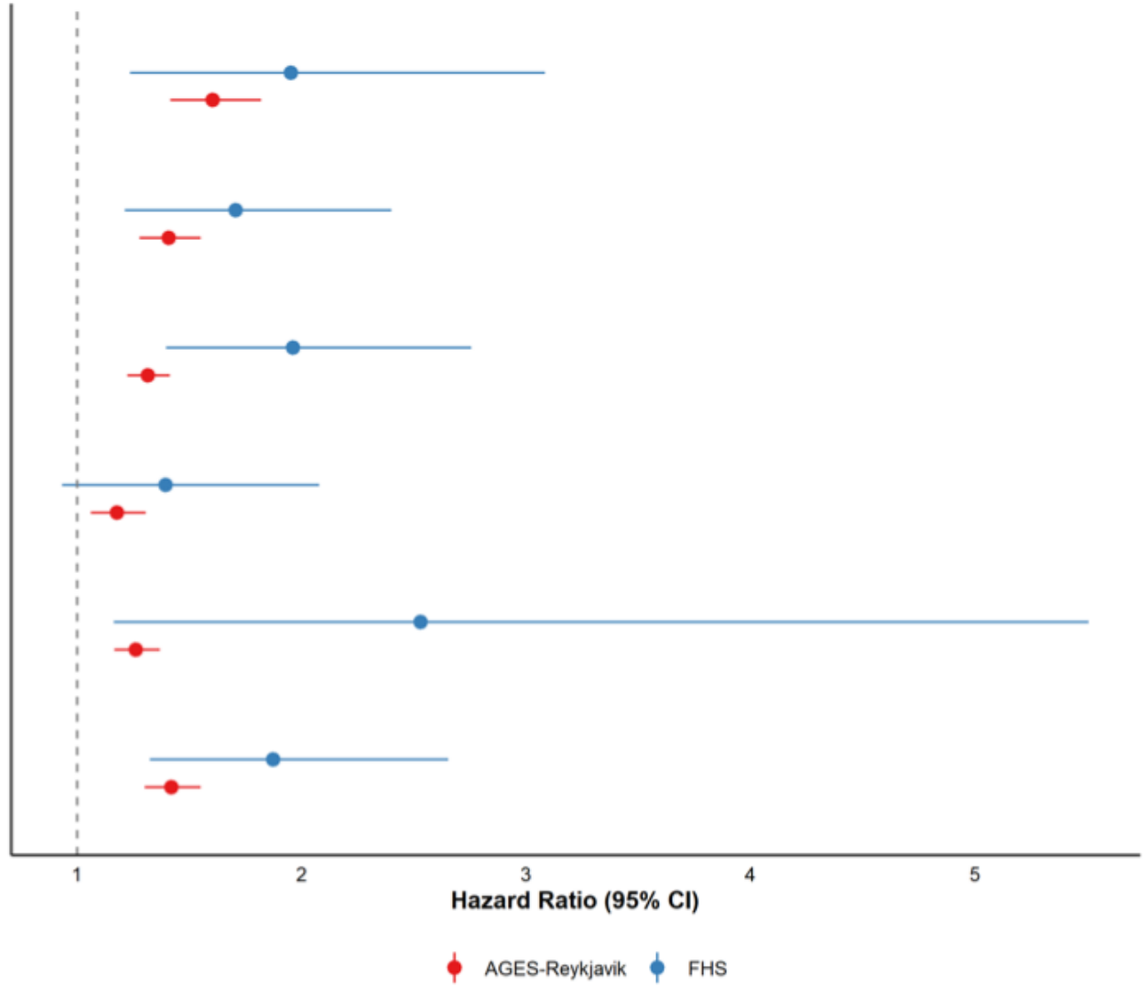
Respir Med. 2010; 104(11):1712-21.
Eur Respir J. 2011; 38(2):392-400.
Radiology. 2013; 268(2): 563-71.
Am J Respir Crit Care Med. 2016; 194(12):1514-22.



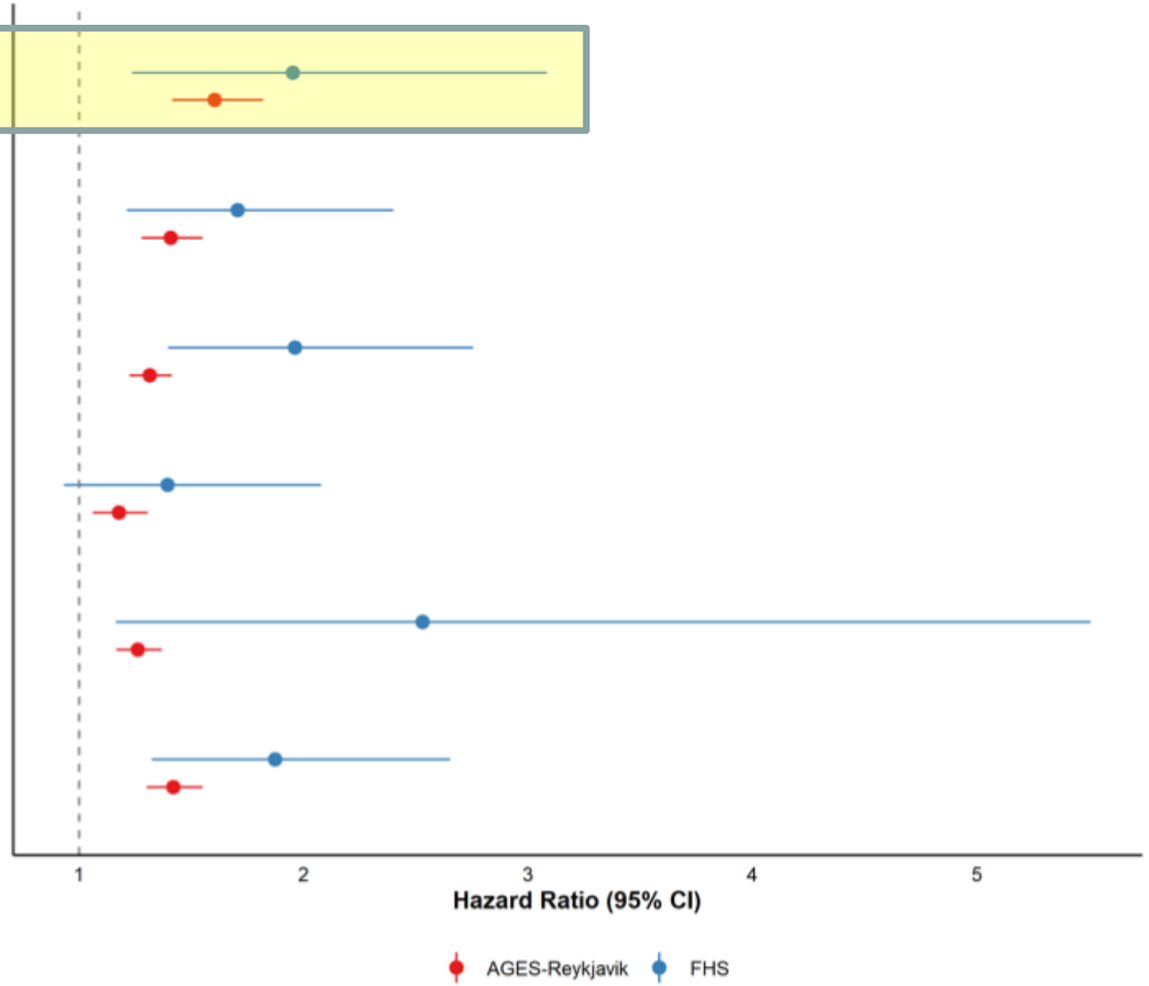


JAMA. 2016;315(7):672-81.
AJRCCM. 2016;194(12):1514-22.
Eur Respir J. 2016;48(5):1442-1452.
AJRCCM. 2017;195(1):138-41.
Eur Respir J. 2017; 49(4).
Resp Med 2018; 136:77-82.

	AGES-Reykjavik			FHS		
	HR	95% CI	N	HR	95% CI	N
ILA	1.60	1.41-1.82	5180	1.95	1.23-3.08	2449
DM	1.41	1.28-1.55	5180	1.70	1.21-2.40	2449
CVD	1.31	1.22-1.41	5180	1.96	1.40-2.76	2449
COPD	1.18	1.06-1.31	5180	1.39	0.93-2.08	2449
CKD	1.26	1.16-1.37	5180	2.53	1.16-5.51	2449
Cancer	1.42	1.30-1.55	5180	1.87	1.32-2.65	2449



	AGES-Reykjavik			FHS		
	HR	95% CI	N	HR	95% CI	N
ILA	1.60	1.41-1.82	5180	1.95	1.23-3.08	2449
DM	1.41	1.28-1.55	5180	1.70	1.21-2.40	2449
CVD	1.31	1.22-1.41	5180	1.96	1.40-2.76	2449
COPD	1.18	1.06-1.31	5180	1.39	0.93-2.08	2449
CKD	1.26	1.16-1.37	5180	2.53	1.16-5.51	2449
Cancer	1.42	1.30-1.55	5180	1.87	1.32-2.65	2449

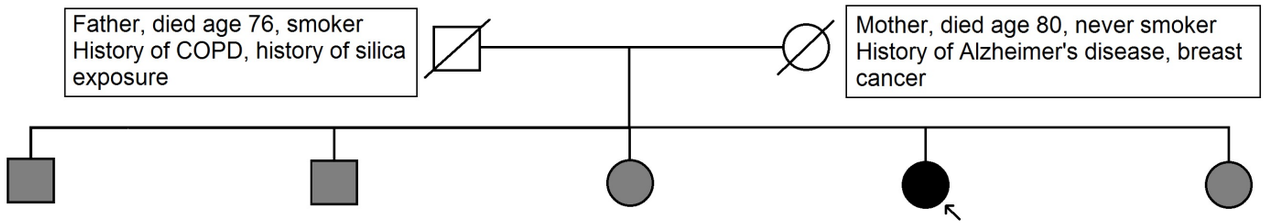


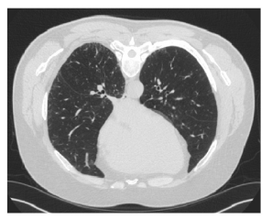
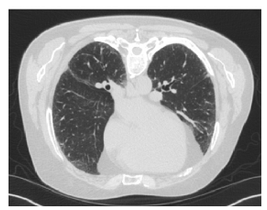
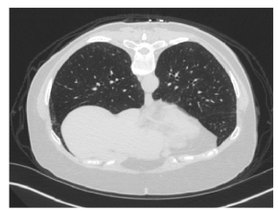
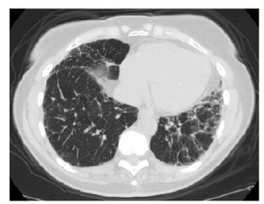
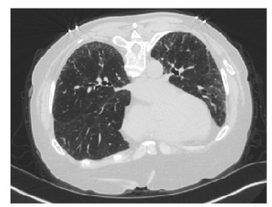
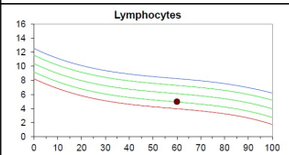
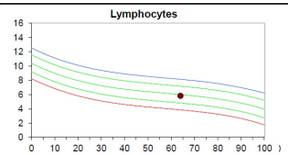
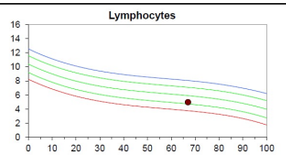
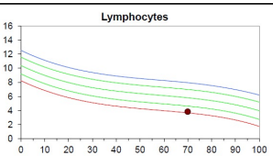
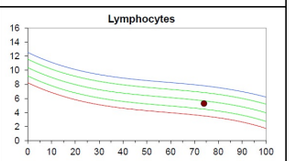
Screening first-degree relatives of patients with pulmonary fibrosis

- CGS-PF study important findings
  - In 105 first-degree relatives of patients with FPF/IPF (median age ~60)
    - 31% had ILA
    - 18% ILD
    - No major differences in the rates of ILA or ILD between relatives recruited from a proband with known FPF or one with “sporadic” pulmonary fibrosis.

Hunninghake GM, et al. Am J Respir Crit Care Med. 2020; 201(10): 1240-1248.

Screening first-degree relatives of patients with pulmonary fibrosis



Age	Age = 60	Age = 64	Age = 67	Age = 70	Age = 74
History of Smoking	Never Smoker	Former Smoker	Never Smoker	Never Smoker	Never Smoker
Diagnosis	ILD	ILD	ILA	IPF	ILD
Pulmonary Function Tests	FVC = 4.98L 109% TLC = 6.52L 96% DLCO = 25.57 90%	FVC = 4.10L 83% TLC = 5.70L 77% DLCO = 18.65 62%	FVC = 3.18L 121% TLC = 4.68L 101% DLCO = 18.49 92%	FVC = 1.82L 70% TLC = 3.07L 66% DLCO = 12.00 61%	FVC = 2.75L 95% TLC = 4.21L 80% DLCO = 12.52 59%
Chest CT image					
Lymphocyte Telomere Lengths					
MUC5B promoter genotype					

Hunninghake GM, et al. Am J Respir Crit Care Med. 2020; 201(10): 1240-1248.

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Case:

- HPI: 51 y/o previously healthy man presented with a persistent cough x 2-3 years, CXR done by his PCP was abnormal, so a chest CT was obtained. Dyspnea with multiple flights of stairs x 1 year. +Raynaud's on right hand x 2 years.
- PMH: Thrombocytopenia
- All: None
- Meds: Omeprazole

Case:

- FHx:

Father – died from pulmonary fibrosis at 67

Maternal GM – died of unknown lung disease

Brother – abnormal LFTs

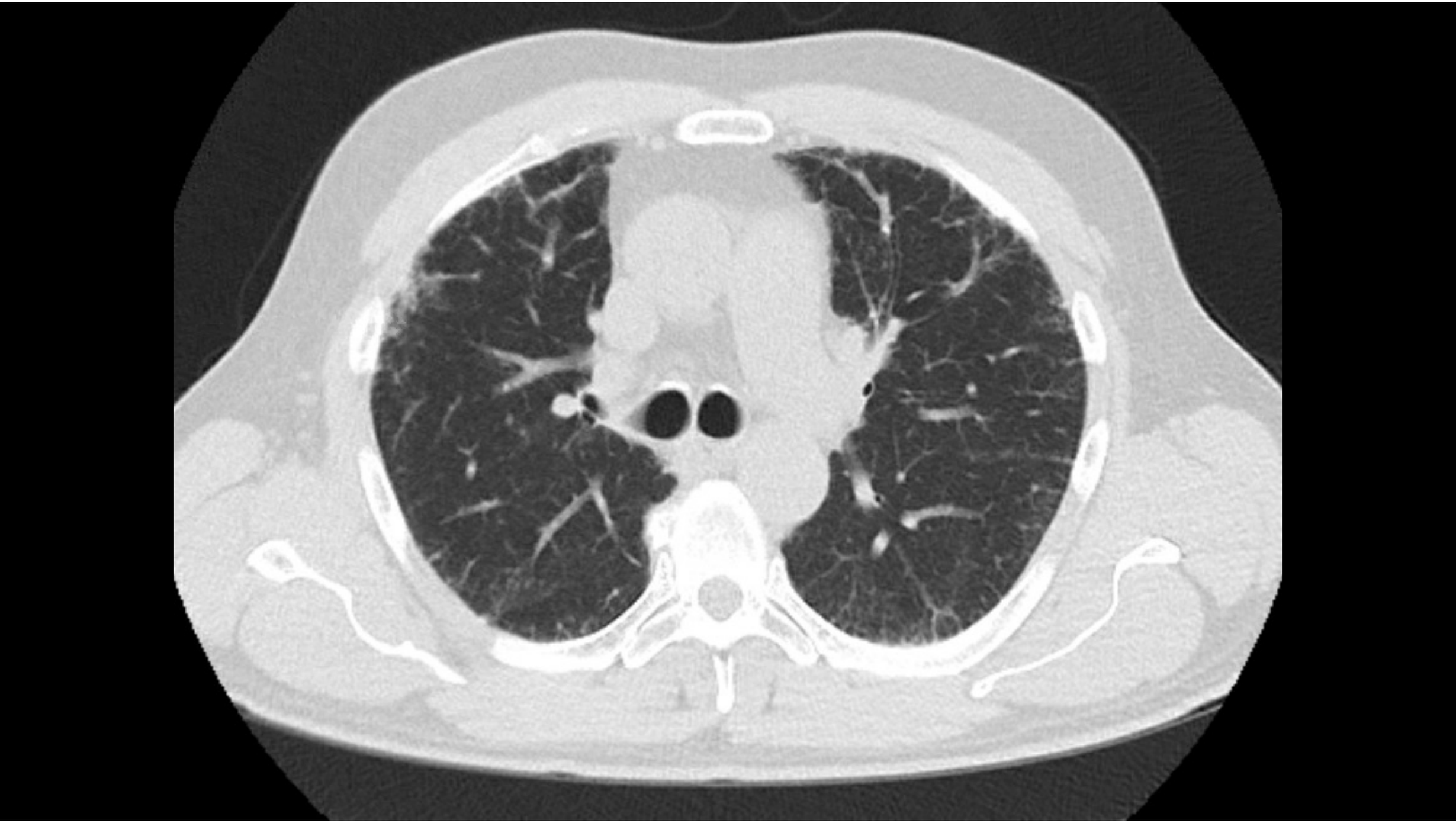
- SHx: Never smoker, rare EtOH, no drugs. Self employed in construction, owns a company with his brother, no current exposures but previously dust (plaster, concrete), horse hair plaster

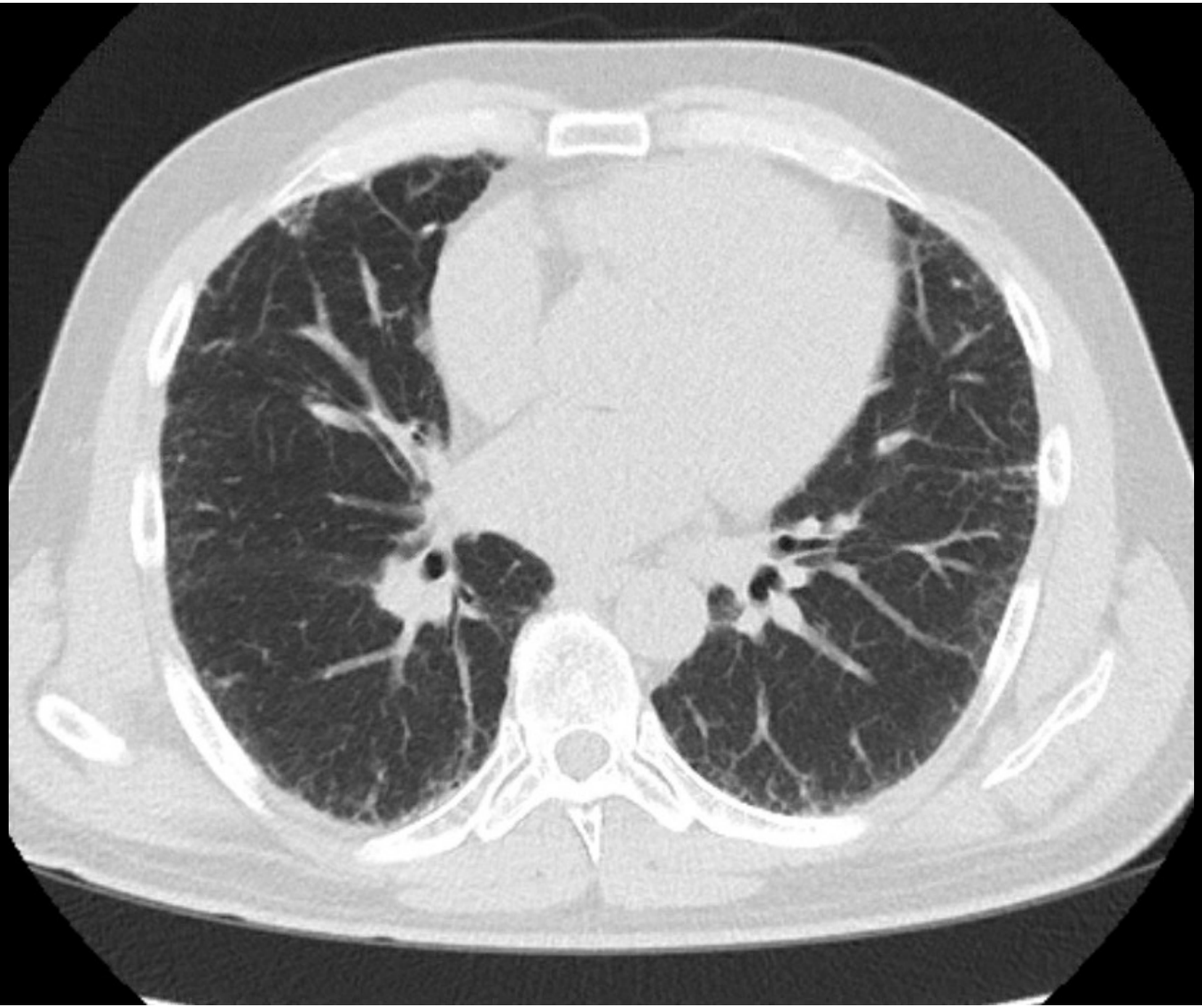
Case:

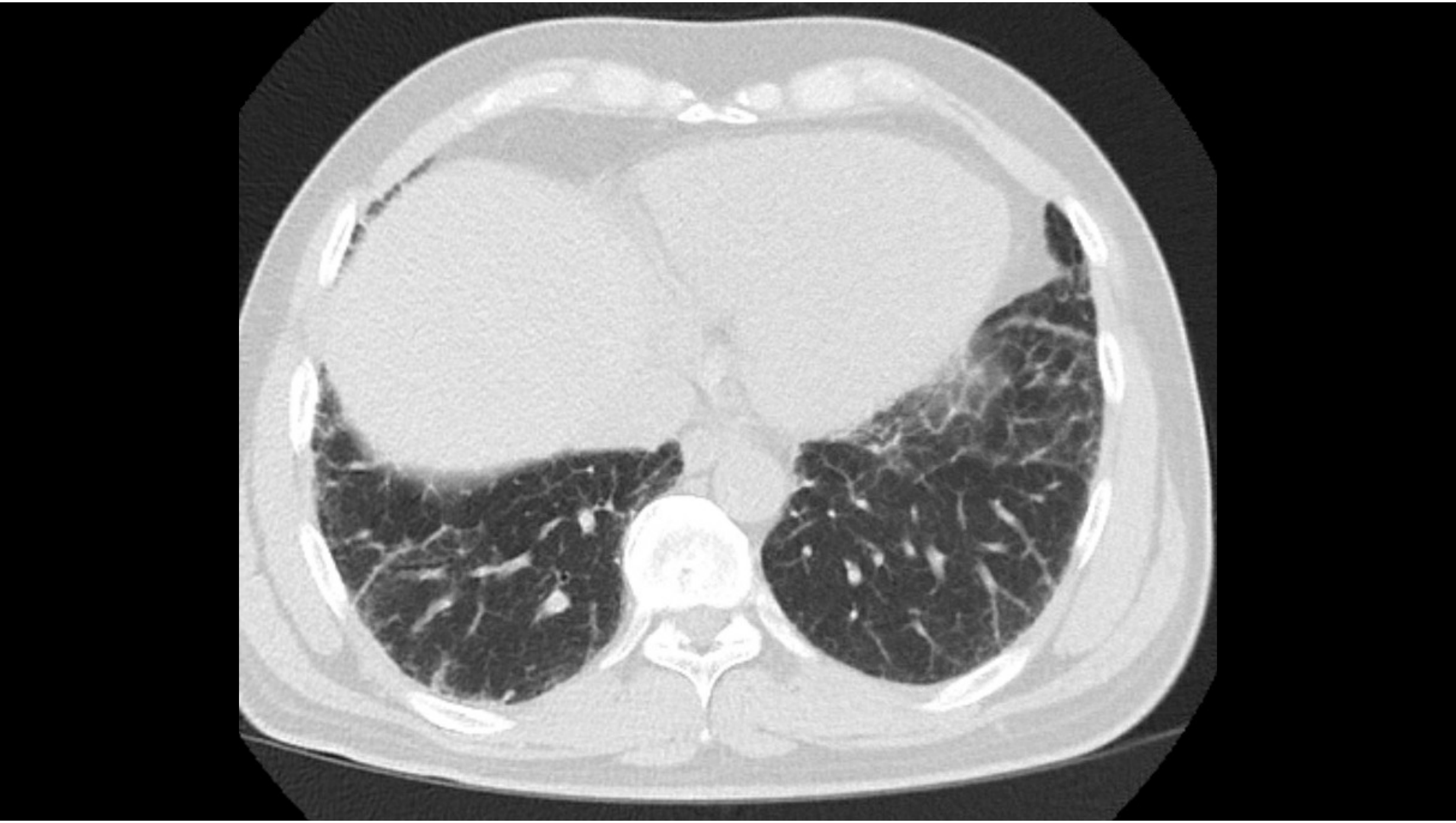
- PE:
  - VSS – SpO2 99% on RA
  - Gen: NAD
  - CV: RRR, no murmurs, rubs, or gallops
  - Pulm: bibasilar crackles
  - Ext: normal capillary microscopic exam

Case:

- Pulmonary Function Testing
  - FEV1 – 2.35L – 64% predicted
  - FVC – 3.12L – 69% predicted
  - FEV1/FVC – 75
  - TLC – 4.31L – 66% predicted
  - DLCO – 18.3 – 70% predicted







Case:

- Serologic evaluation sent for connective tissue disease

Case:

- Connective Tissue Disease Labs
  - ANA – trace
  - Anti-centromere – negative
  - Anti-La < 3
  - Anti RO 52 < 2
  - Anti RO 60 < 5
  - Anti-Sm <3
  - RNP<4
  - SCL-70 <1
  - CCP – 2.2 (negative)
  - Extended Myositis Antibody Panel – all negative

What would be the next best step in management?

Surgical lung biopsy	**A**
Repeat chest CT and PFTs	**B**
Presentation at Multidisciplinary Team Meeting	**C**
Bronchoscopy with BAL and cryobiopsy	**D**

Case:

- What would be the next best step in management?

A. Surgical lung biopsy
B. Repeat Chest CT and PFTs
C. Presentation at Multidisciplinary Team Meeting
D. Bronchoscopy with BAL and cryobiopsy