Brigham and Women's Hospital
Founding Member, Mass General Brigham

INTERSTITIAL LUNG DISEASE

Hilary J. Goldberg, MD, MPH
Vice Chair of Quality, Assistant CMO, MGB AMC DOM
Pulmonary and Critical Care Medicine
Brigham and Women's Hospital
Associate Professor of Medicine
Harvard Medical School

Financial disclosures

- None

Objectives

- Review presentation, diagnostic approach to interstitial lung disease
- Distinguish between common forms of ILD in the clinical setting
- Understand current and emerging treatment options and natural history

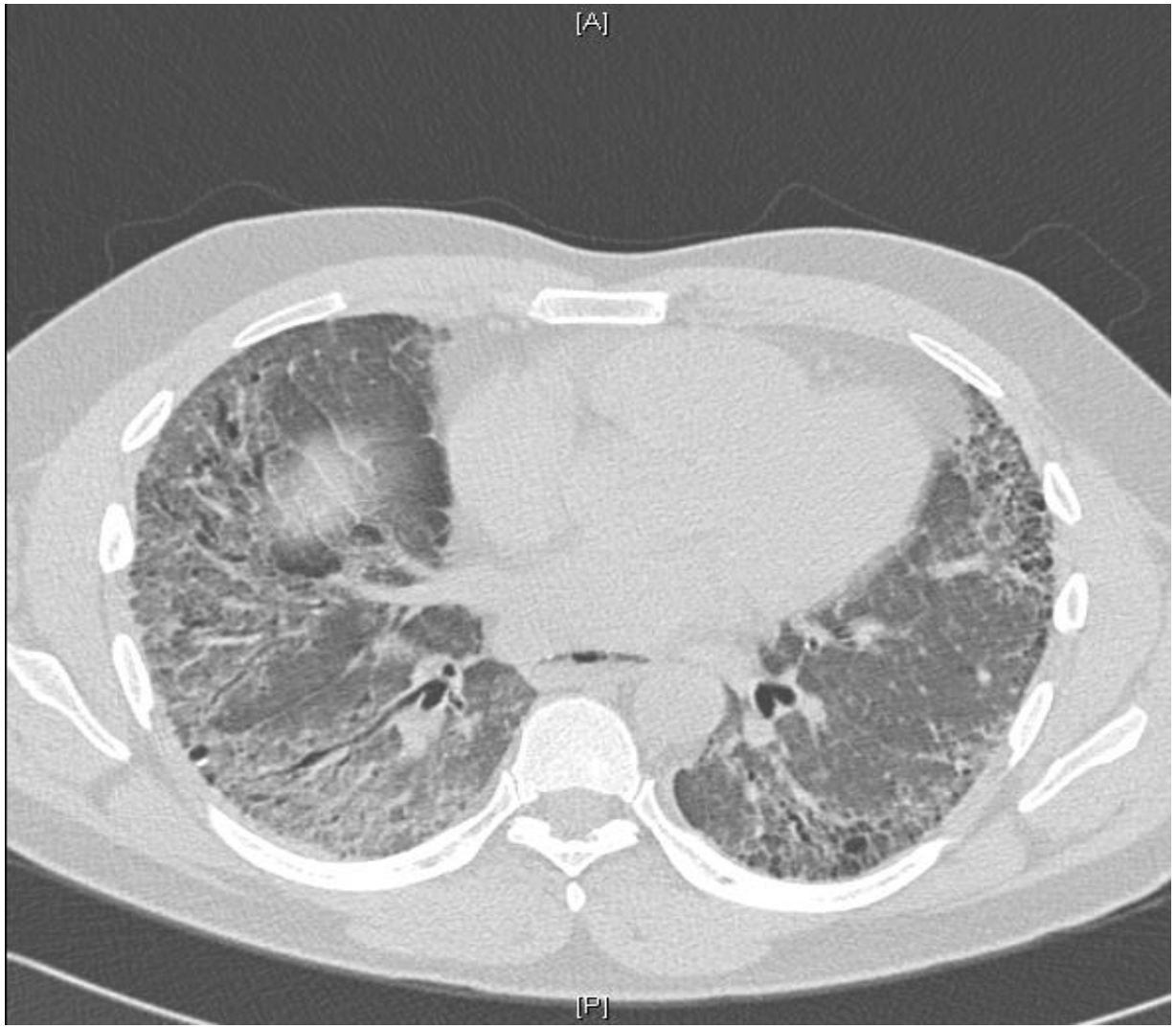
Presentation

- Presenting symptoms
  - SOB
  - Cough
  - Chest pain
  - Duration of symptoms
- Presenting physical signs
  - Hypoxia
  - Tachypnea
  - Inspiratory crackles
  - Clubbing
  - Cor pulmonale

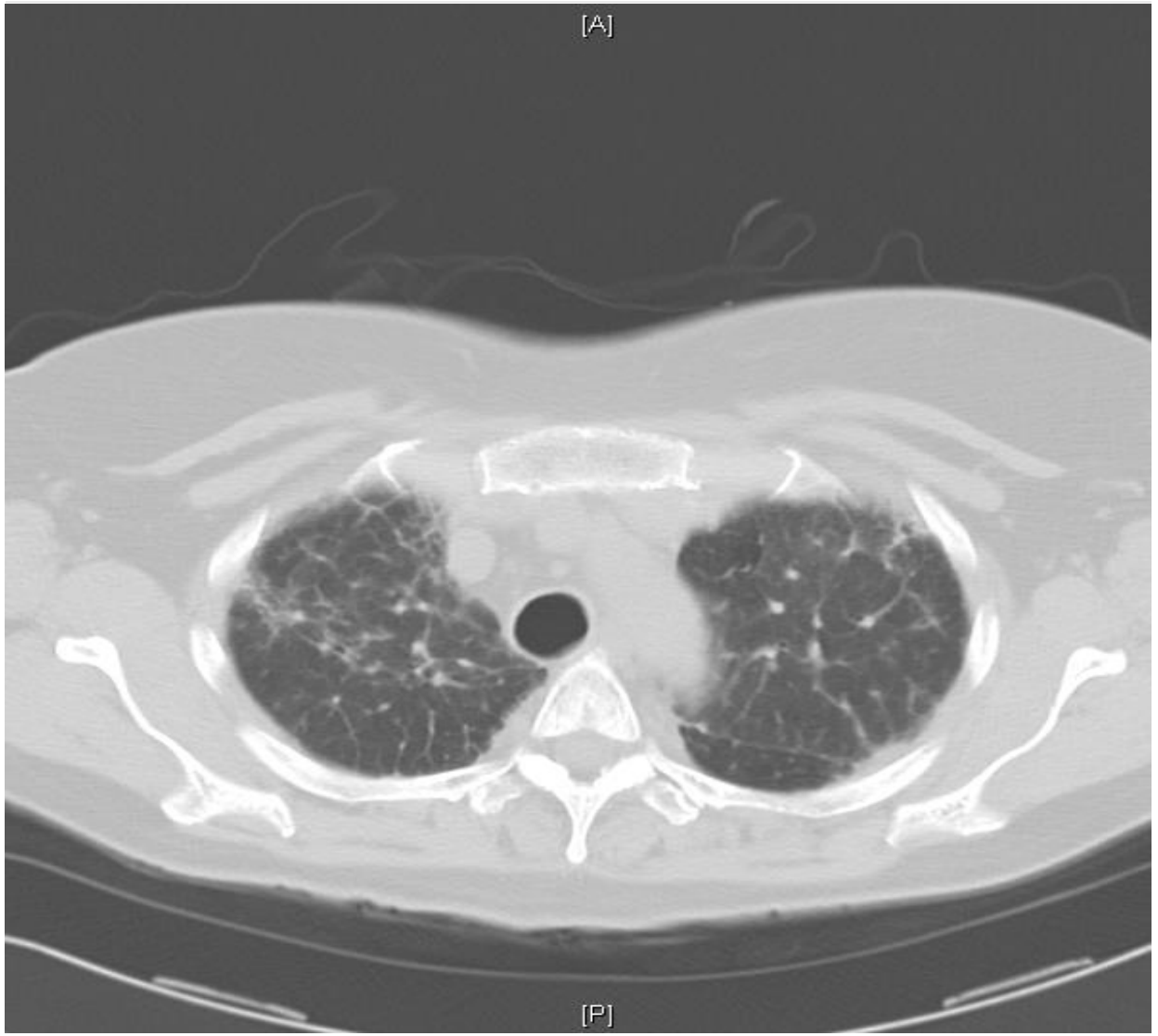
Imaging

- Radiographic features:
  - Pattern:
    - Reticular
    - Nodular
    - Combined: Reticulonodular
  - Location:
    - Upper lobe
    - Lower lobe
    - Homogenous vs. heterogenous

CT features



CT features



Pulmonary function testing

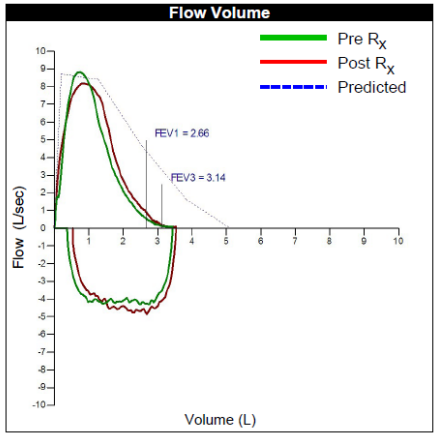
- Restrictive ventilatory defect:
  - Symmetric decrease in FEV1 and FVC
  - Decrease in TLC
  - Decreased diffusion capacity

- Mixed restriction and obstruction

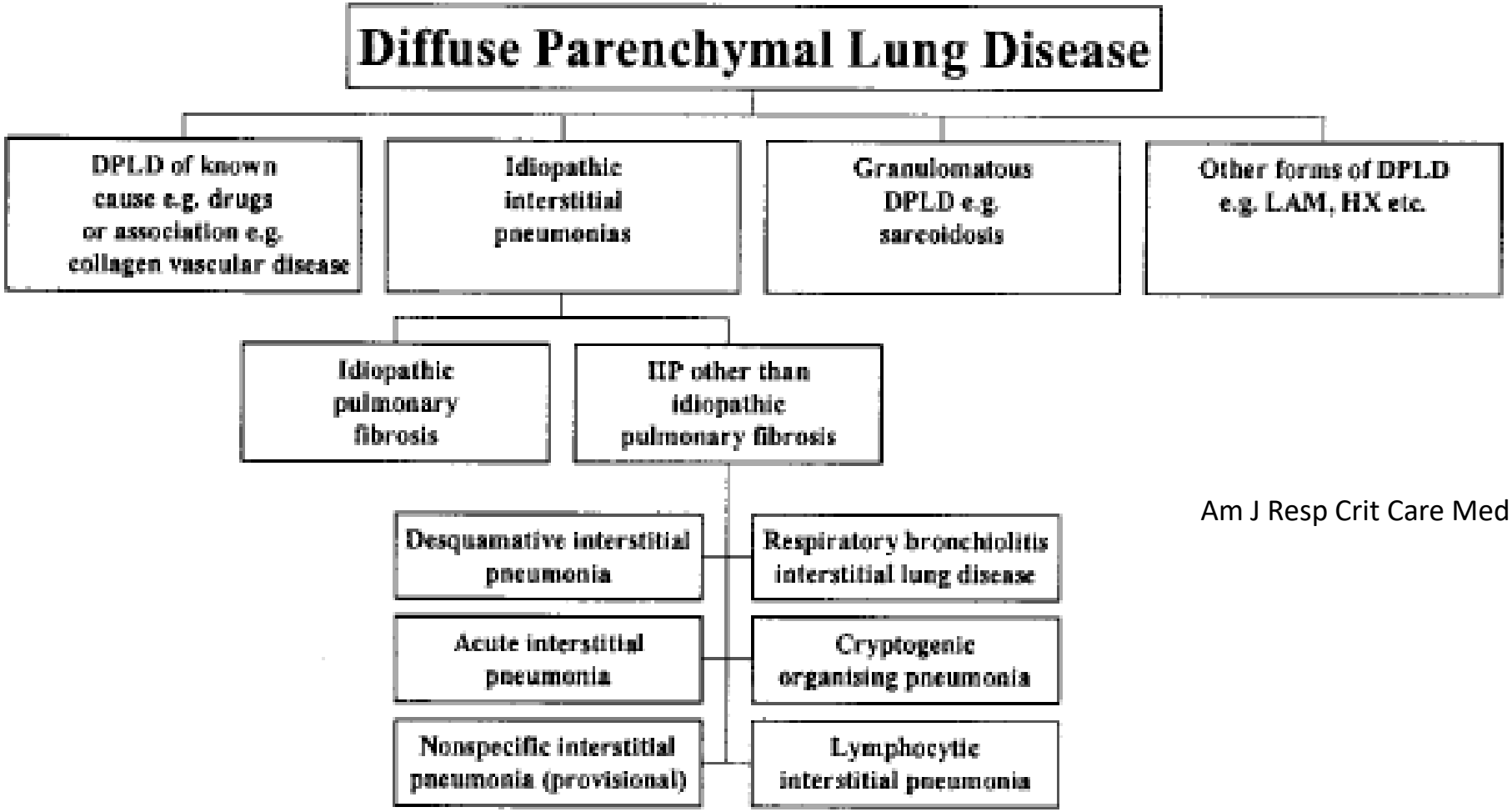
Spirometry (BTPS)		Predicted Range Mean	95%	Pre Bronchodilator Actual	% Pred
FEV_1	L	3.80	2.96	2.66	70
FVC	L	5.10	3.98	3.44	67
FEV_1 / FVC	%	74	66	77	104
FEV_6	L	4.71	3.67	3.40	72
FEV_1 / FEV_6	%	77	68	78	101
FEF_{25-75}	L/s	3.08	1.41	2.18	71
PEFR	L/s	8.72	6.07	8.82	101
FET	sec	----	----	6.69	----
MVV	L/m	136.2	79.4	----	----

Lung Volumes (Box)		Predicted Range Mean	95%	Pre Bronchodilator Actual	% Pred
TLC	L	7.96	6.35	4.46	56
FRC	L	4.37	2.91	2.61	60
IC	L	3.59	----	1.85	52
ERV	L	1.51	----	1.61	107
RV	L	2.86	2.10	1.00	35
RV/TLC	%	38	29	22	58
VC	L	5.10	3.98	3.46	68

Diffusion		Predicted Range Mean	95%	Pre Bronchodilator Actual	% Pred
DLCO	mL/min/mmHg	29.90	19.88	15.92	53
DLCO [Hb]	mL/min/mmHg	29.90	19.88	15.92	53
Hb	g/dl	14.6	12.0	----	----
VA [BTPS]	L	7.96	6.81	4.68	59
DLCO/VA	mL/min/mmHg/L	3.77	2.84	3.40	90



Classification of ILD



Am J Resp Crit Care Med 2002; 165: 277

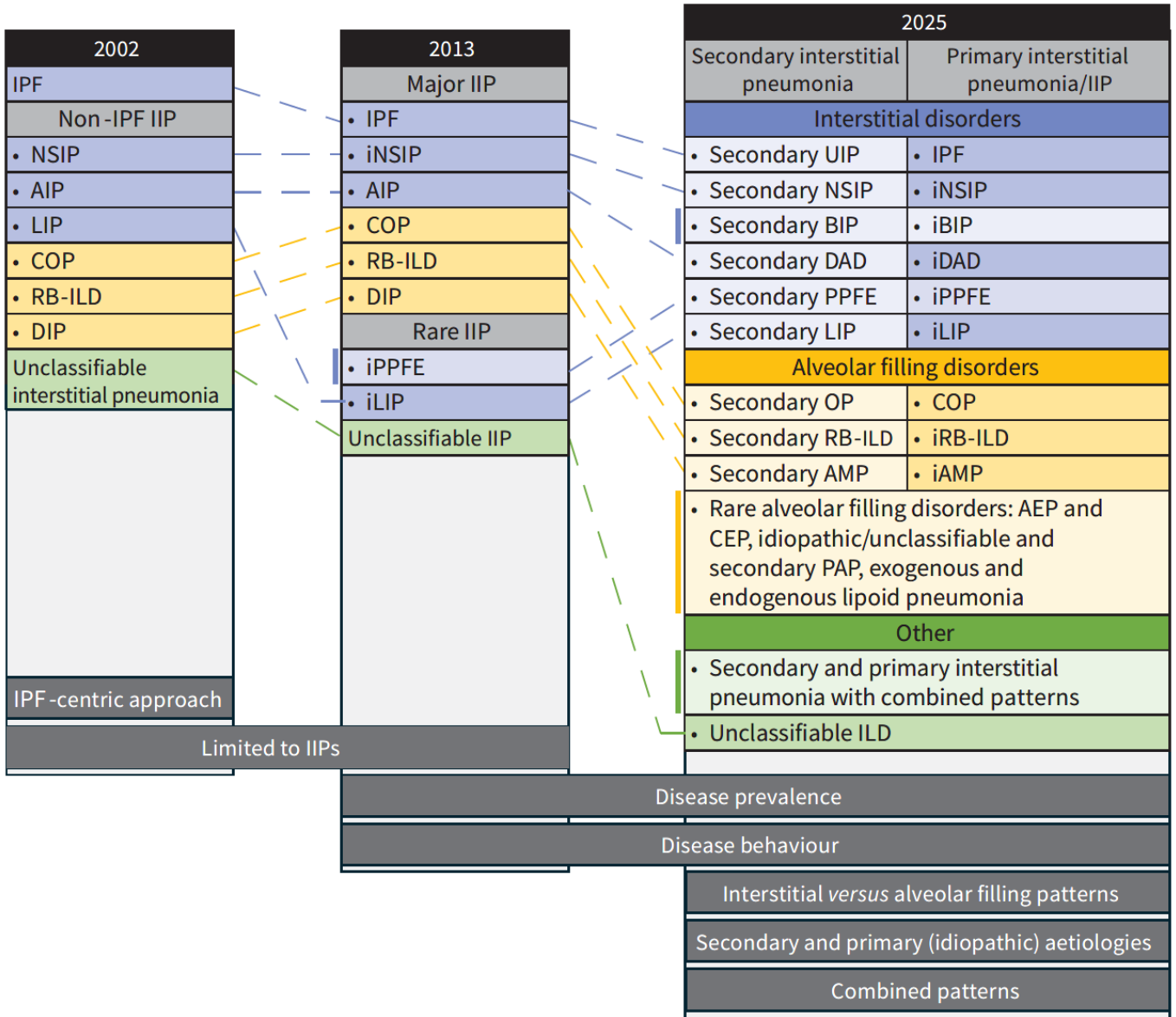
Updated classification of interstitial pneumonias

TABLE 1 Morphological patterns of interstitial and alveolar filling disorders and associated clinical-radiological-pathological diagnoses. Secondary aetiologies are listed before primary/idiopathic aetiologies to emphasise the importance of excluding an underlying cause before considering a diagnosis to be primary/idiopathic

Morphological patterns by pathology and imaging	Major clinical-radiological-pathological diagnoses	
	Secondary	Primary/idiopathic
Interstitial patterns		
UIP	Secondary UIP (*e.g.* CTD, HP, medications)	IPF (idiopathic UIP)
NSIP	Secondary NSIP (*e.g.* CTD >>> HP, medications)	Idiopathic NSIP
BIP[#]	Secondary BIP (*e.g.* HP >>> CTD, aspiration, inhalational exposures, medications)	Idiopathic BIP (provisional diagnosis[#])
DAD	Secondary DAD (multiple causes)	Idiopathic DAD (acute interstitial pneumonia)
PPFE	Secondary PPFE (*e.g.* IPF, CTD, HP, medications, radiation, transplant (restrictive allograft syndrome, pulmonary infection (post-tuberculosis), occupational)	Idiopathic PPFE
LIP	Secondary LIP (*e.g.* CTD, immune deficiency)	Idiopathic LIP
Alveolar filling patterns		
Organising pneumonia	Secondary organising pneumonia (*e.g.* CTD, post-infectious, medications, aspiration)	Cryptogenic organising pneumonia (idiopathic organising pneumonia)
RB-ILD	Secondary RB-ILD (*e.g.* smoking >>> CTD, medications, aspiration, hereditary)	Idiopathic RB-ILD
AMP[¶]	Secondary AMP (*e.g.* smoking >>> CTD, medications, aspiration, hereditary	Idiopathic AMP
Rare alveolar filling disorders	*e.g.* Acute and chronic eosinophilic pneumonia, pulmonary alveolar proteinosis, lipoid pneumonia (supplementary table S1)	
Other		
Combined pattern	Multiple combinations (*e.g.* NSIP + organising pneumonia, UIP + PPFE)	
Unclassifiable pattern	Unclassifiable ILD (multiple undefined patterns)	

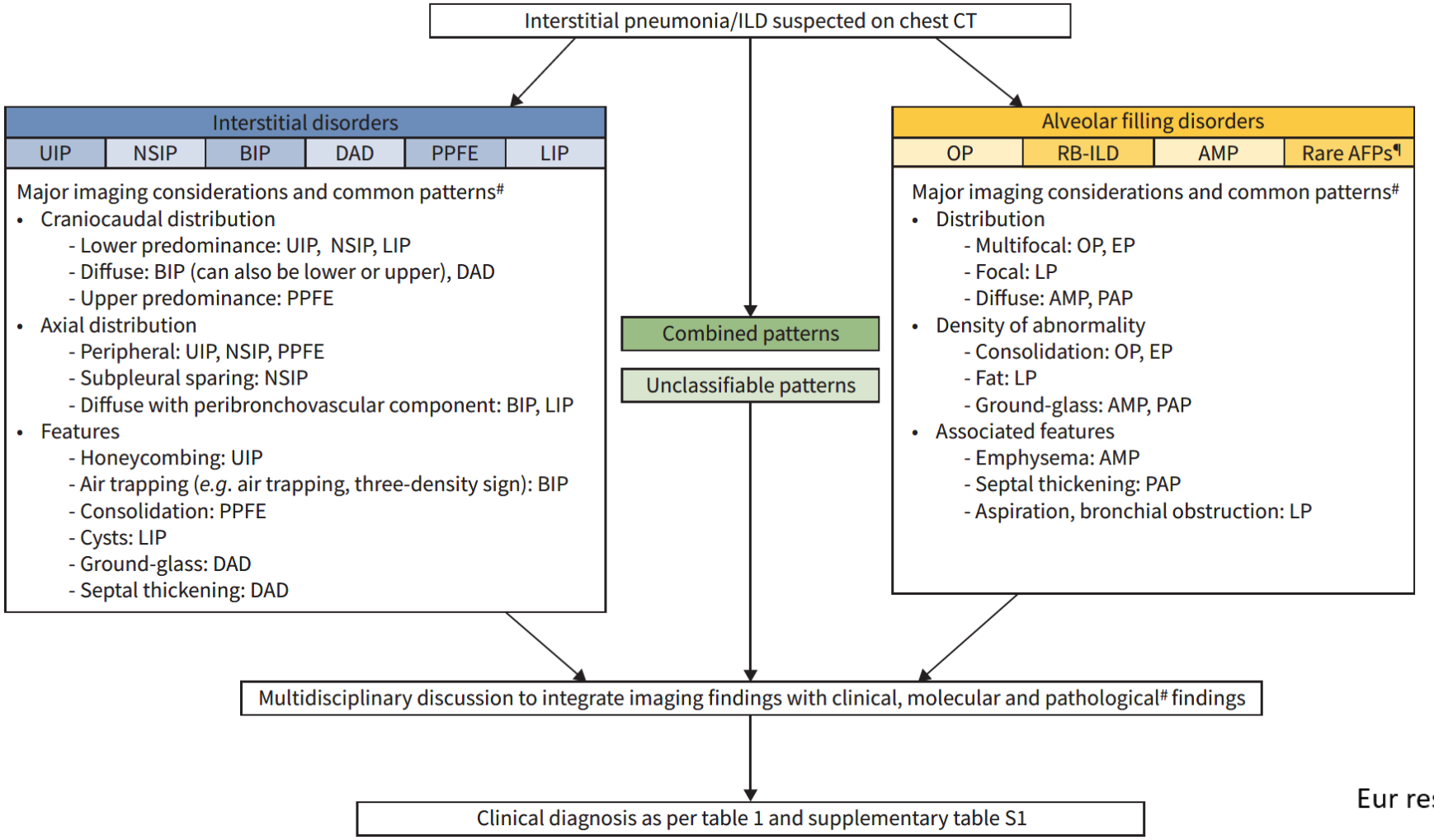
Eur resp J 2025; 66: 2500158

Updated classification of interstitial pneumonias



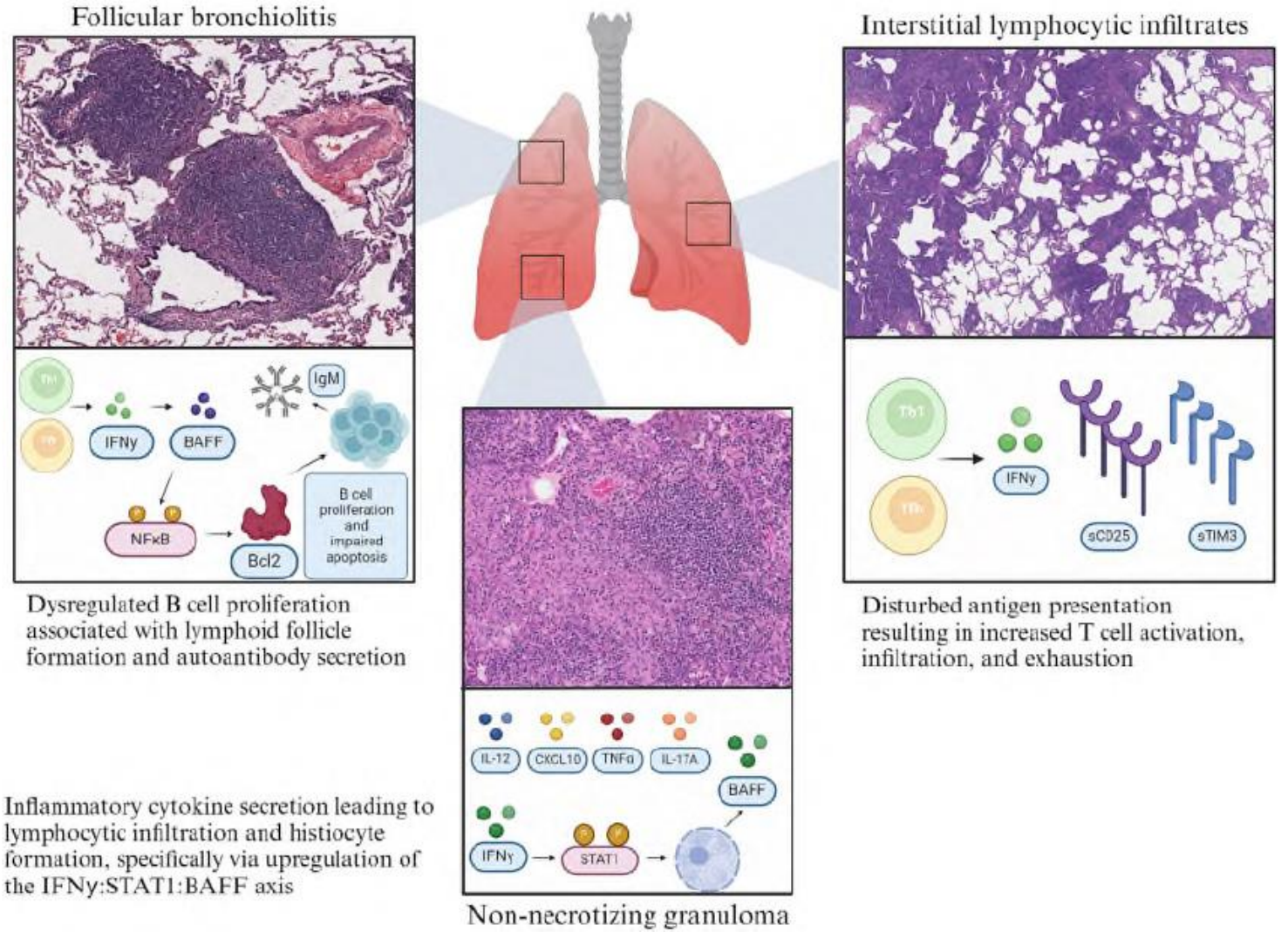
Eur resp J 2025; 66: 2500158

Updated classification of interstitial pneumonias



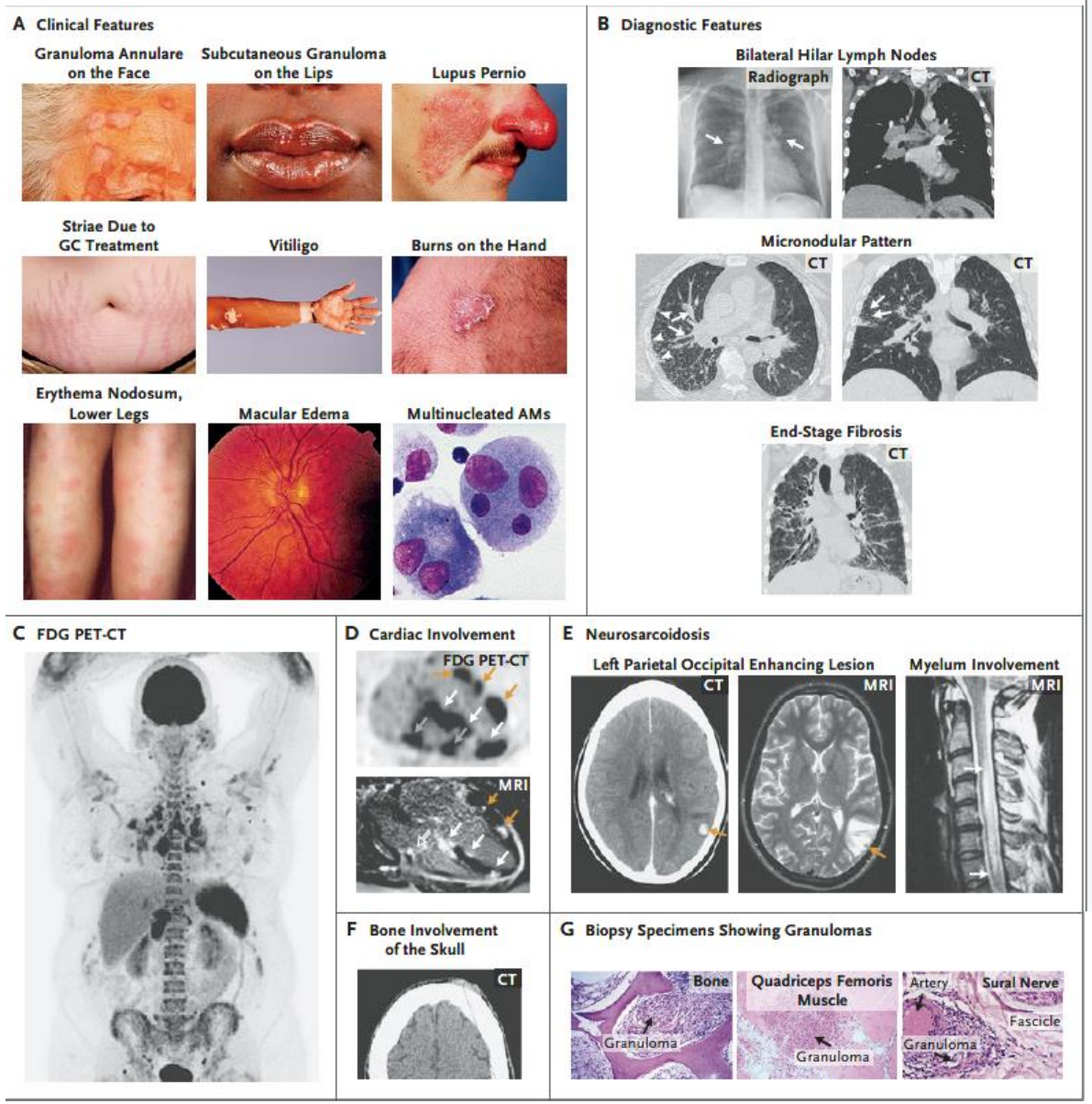
Eur resp J 2025; 66: 2500158

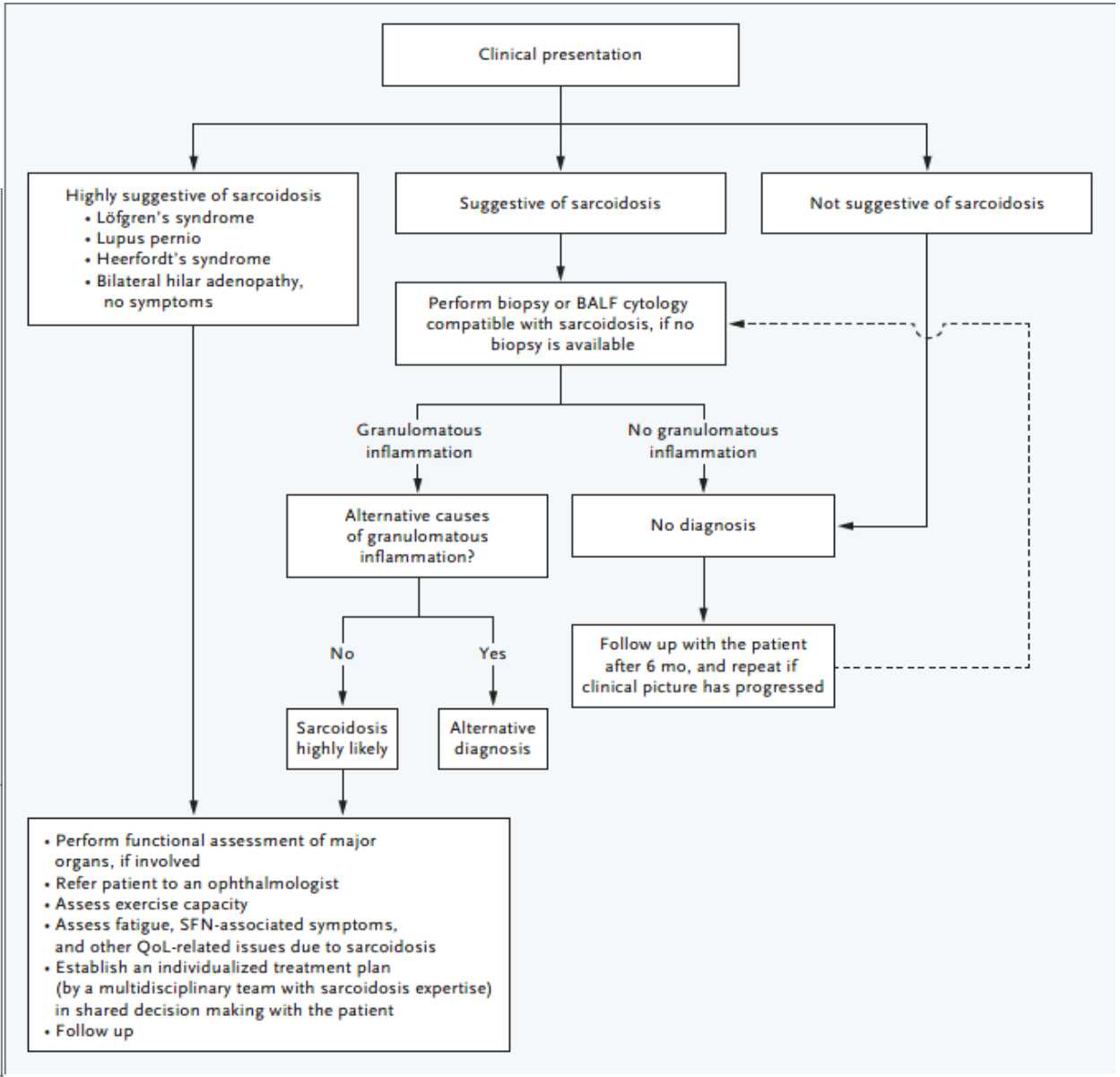
Granulomatous lung disease



The Lancet 2024; 75: 1

Sarcoidosis





New Eng J Med 2021; 385: 1018

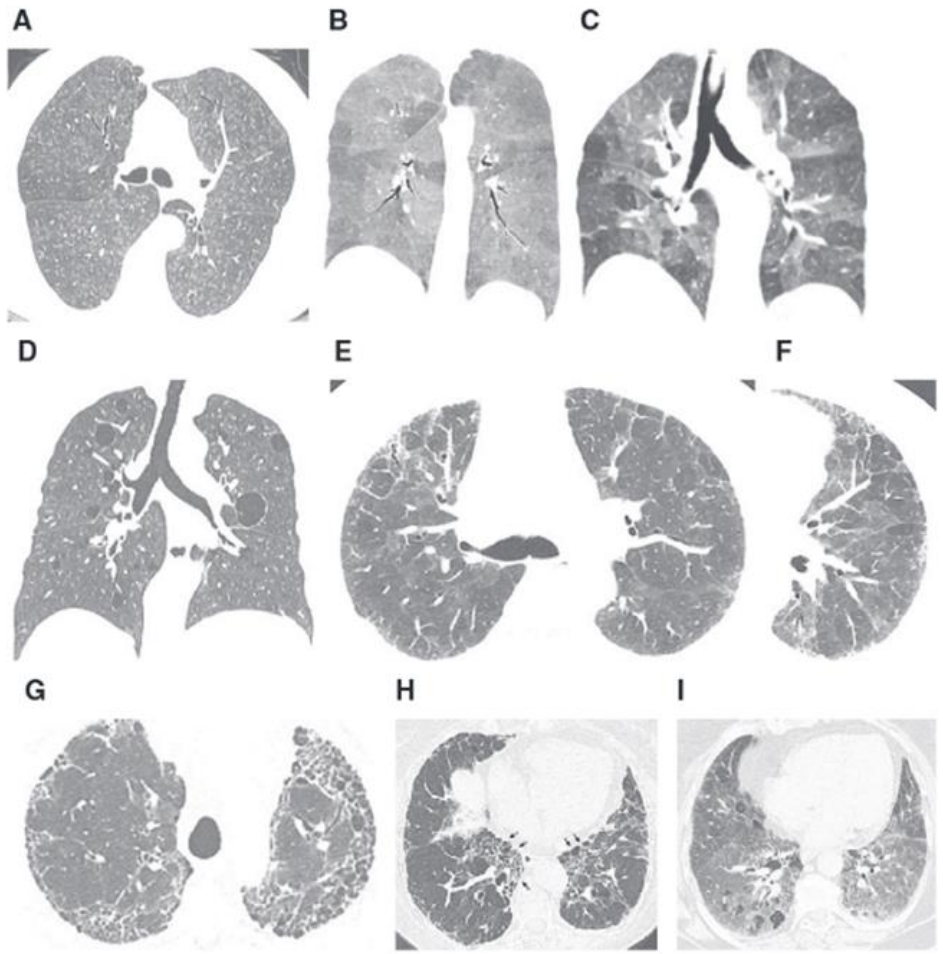
Hypersensitivity Pneumonitis

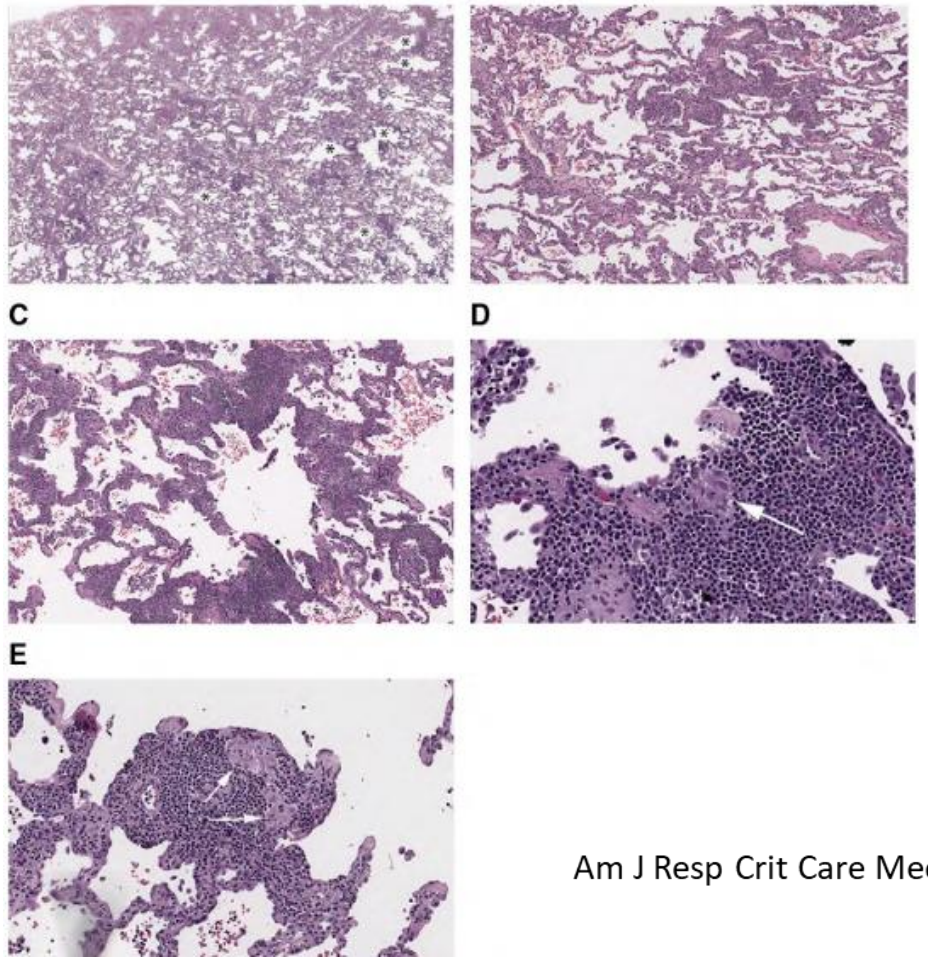
HRCT Pattern	Typical HP	Compatible with HP	Indeterminate for HP
Description	The "typical HP" pattern is suggestive of a diagnosis of HP. It requires *a*) at least one HRCT abnormality indicative of parenchymal infiltration and *b*) at least one HRCT abnormality indicative of small airway disease, both in a diffuse distribution	"Compatible-with-HP" patterns are nonspecific patterns that have been described in HP	N/A
Relevant radiological findings	HRCT abnormalities indicative of parenchymal infiltration: • GGOs • Mosaic attenuation* HRCT abnormalities indicative of small airway disease: • Ill-defined, centrilobular nodules • Air trapping Distribution of parenchymal abnormalities: • Craniocaudal: diffuse (with or without some basal sparing) • Axial: diffuse	Parenchymal abnormalities: • Uniform and subtle GGOs • Airspace consolidation • Lung cysts Distribution of parenchymal abnormalities: • Craniocaudal: diffuse (variant: lower lobe predominance) • Axial: diffuse (variant: peribronchovascular)	N/A

Am J Resp Crit Care Med 2020; 202: e36

HRCT Pattern	Typical HP	Compatible with HP	Indeterminate for HP
Description	The "typical HP" pattern is suggestive of a diagnosis of HP. It requires *a*) an HRCT pattern of lung fibrosis (as listed below) in one of the distributions and *b*) at least one abnormality that is indicative of small airway disease	"Compatible-with-HP" patterns exist when the HRCT pattern and/or distribution of lung fibrosis varies from that of the typical HP pattern; the variant fibrosis should be accompanied by signs of small airway disease	The "indeterminate-for-HP" pattern exists when the HRCT is neither suggestive nor compatible with a typical and probable HP pattern
Relevant radiological findings	HRCT abnormalities indicative of lung fibrosis are most commonly composed of irregular linear opacities/ coarse reticulation with lung distortion; traction bronchiectasis and honeycombing may be present but do not predominate The distribution of fibrosis may be: • Random both axially and craniocaudally or • Mid lung zone–predominant or • Relatively spared in the lower lung zones HRCT abnormalities indicative of small airway disease: • Ill-defined, centrilobular nodules and/or GGOs • Mosaic attenuation, three-density pattern,* and/or air trapping (*often in a lobular distribution*)	Variant patterns of lung fibrosis: • UIP pattern: basal and subpleural distribution of honeycombing with/without traction bronchiectasis (*per 2018 diagnosis of IPF guidelines* [20]) • Extensive GGOs with superimposed subtle features of lung fibrosis Variant (predominant) distributions of lung fibrosis: • Axial: peribronchovascular, subpleural areas • Craniocaudal: upper lung zones HRCT abnormalities indicative of small airway disease: • Ill-defined centrilobular nodules, or • Three-density pattern* and/ or air trapping	Lone patterns (i.e., not accompanied by other findings suggestive of HP) of: • UIP pattern (*as per 2018 IPF diagnosis guidelines* [20]) • Probable UIP pattern (*as per 2018 IPF diagnosis guidelines* [20]) • Indeterminate pattern for UIP (*as per 2018 IPF diagnosis guidelines* [20]) • Fibrotic NSIP pattern • Organizing pneumonia–like pattern • Truly indeterminate HRCT pattern

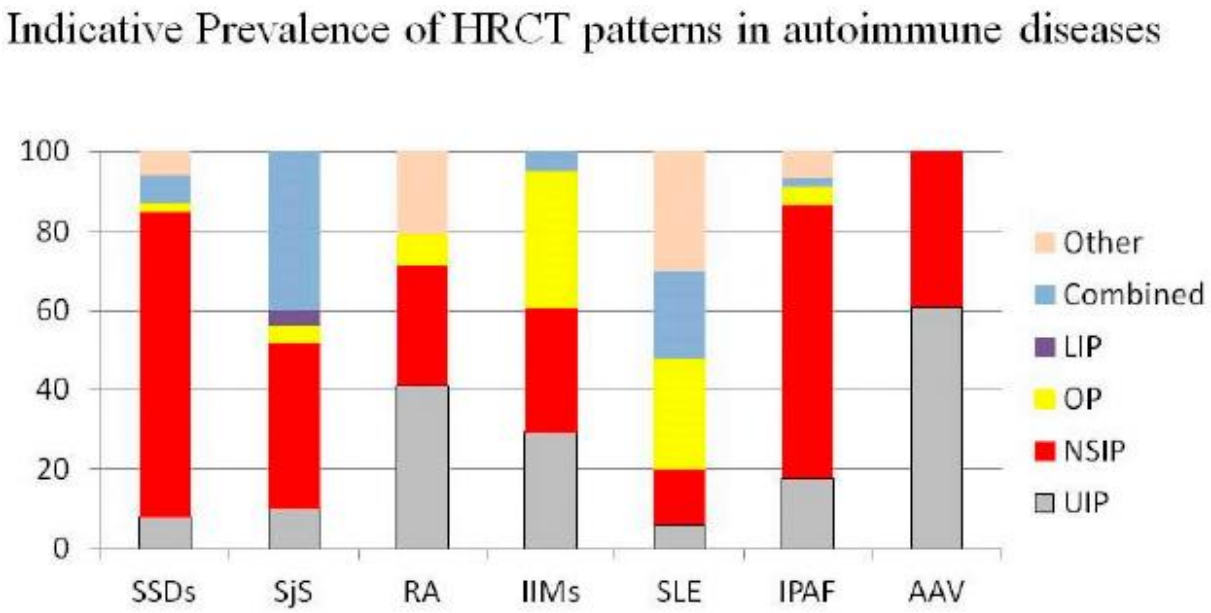
Hypersensitivity pneumonitis



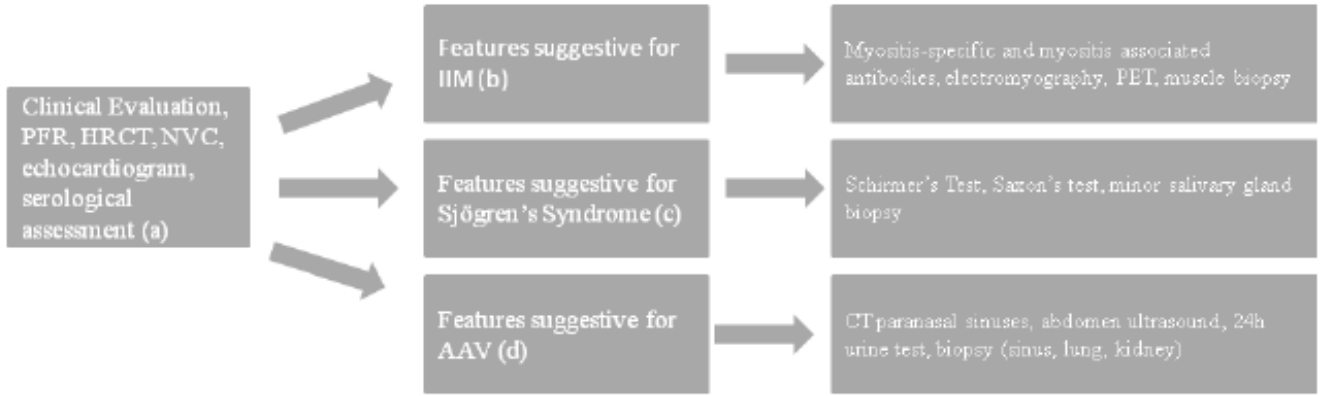


Am J Resp Crit Care Med 2020; 202: e36

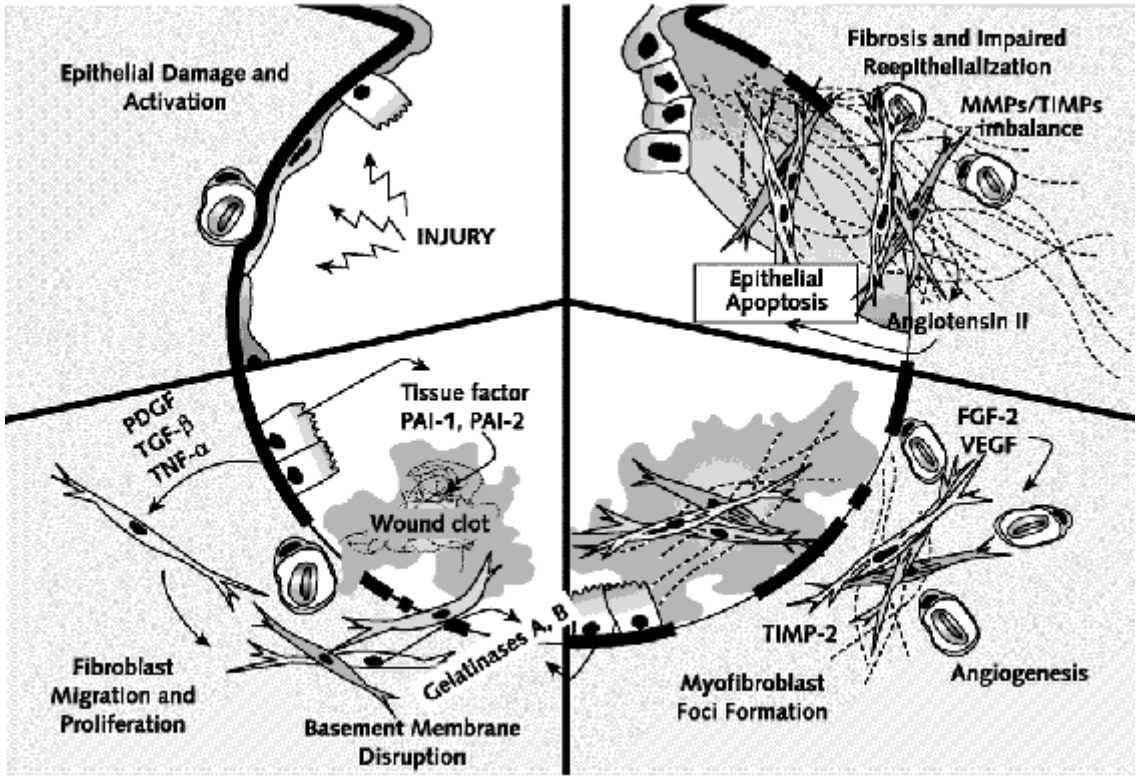
Autoimmune ILD

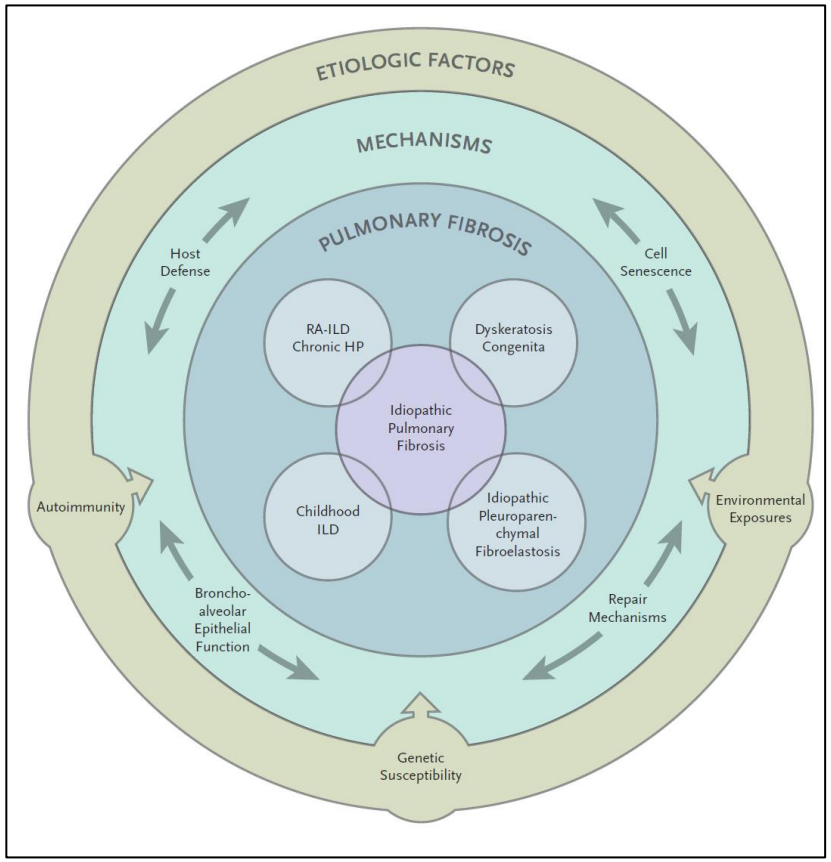


Diagnostics 2020; 10: 208



Pathophysiology of Idiopathic Pulmonary Fibrosis



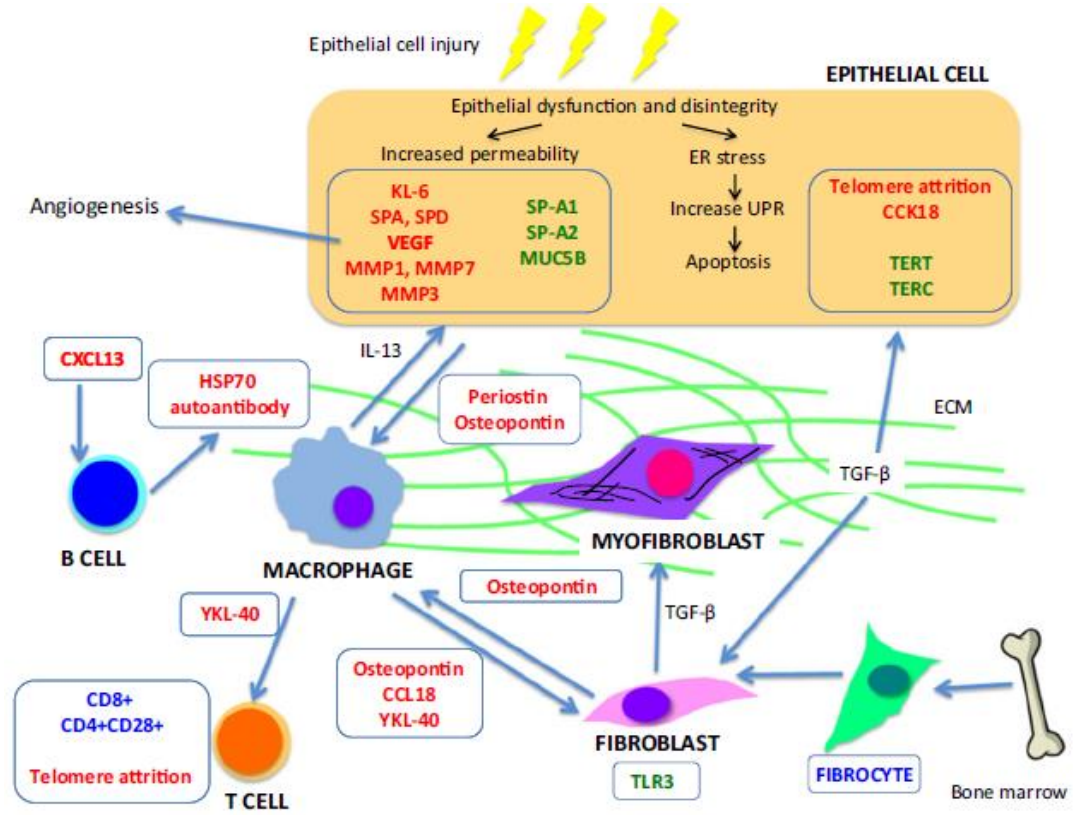


Annals of Internal Medicine, 2001, 134: 136

N Eng J Med 2019, 380: 94

Idiopathic Pulmonary Fibrosis – Potential Risk Factors

- Cigarette smoking
- Environmental
- Microbial agents
- GERD
- Genetic factors



Am J Resp Crit Care Med 2011; 183: 788

Respirology 2015; 20: 1010

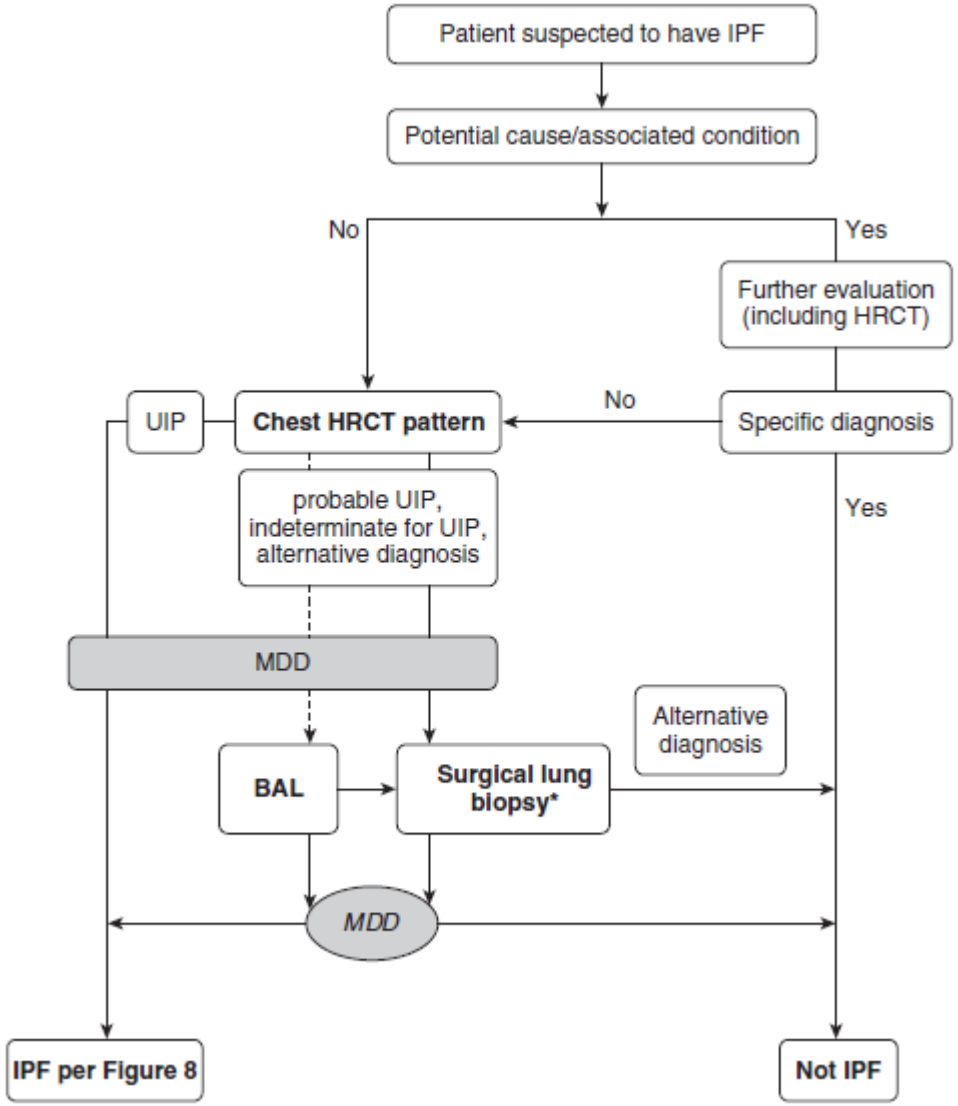
ILD – Genetic associations

TABLE 5 Molecular biomarkers in interstitial pneumonia

	Pathophysiology	Clinical accessibility	Clinical value		
			Diagnostic	Prognostic	Therapeutic
Genetic					
MUC5B rs35705950	Risk allele linked to increased pulmonary fibrosis susceptibility, but slower progression rate	Variably accessible	Unclear	Unclear	Unclear
Telomere-related genes (*TERT, TERC, RTEL1, PARN, DKC1, NAF1, ZCCHC8*)	Telomere-related gene variants linked to increased pulmonary fibrosis risk and rapid disease progression	Variably accessible	Potential value	Potential value	Unclear
Surfactant-related genes (*SFTPC, SFTPA1*, *SFTPA2*)	SRG variants linked to increased pulmonary fibrosis risk and to lung cancer	Variably accessible	Potential value	Unclear	Unclear
Other gene loci (including *DSP, KIF15, HLA-DRB1*)	Polymorphisms in these genes linked to increased pulmonary fibrosis risk	Variably accessible	Unclear	Unclear	Unclear
Short telomeres/telomeropathies					
Leukocyte telomere length	Leukocyte telomere length attrition associated with increased ILD susceptibility and rapid progression rate	Variably accessible	Potential value	Potential value	Emerging value in guiding post-lung transplant and ILD pharmacotherapy
Short telomere syndromes (including dyskeratosis congenita, Hoyeraal–Hreidarsson syndrome)	Clinical manifestation often at younger age, show Mendelian inheritance, have multiorgan involvement	Accessible	Potential value	Unclear	Unclear
Transcriptomic RNA signatures					
Lung biopsy-based Envisia Genomic Classifier	Integrates gene expression profiling with machine learning algorithms to recognise the genomic signature of a UIP pattern	Accessible in North America and Europe	Strengthens UIP diagnosis, but clinical utility unproven	Unclear	Unclear
Peripheral blood-based 52-gene RNA signature	Specific set of 52 genes whose combined expression pattern is indicative of IPF	Unclear	Unclear	Unclear	Unclear
Serum/plasma-based antibody panels					
Autoimmune serology (including ANA, dsDNA, anti-Sm, ACA, anti-Scl-70, anti-RNA polymerase III, anti-Jo-1, anti-MDA5, RF, anti-CCP, SS-A, SS-B, anti-RNP, ANCA, anti-U1 RNP, anti-PL-12 and anti-PL-7, anti-GM-CSF)	Identify the presence of discrete autoantibodies that target protein, nuclear or other cellular components which aid the diagnosis of specific autoimmune diseases	Accessible	Strengthens diagnosis of specific subtypes of CTD-ILD	Potential value	May guide choice of therapy
HP	Serum IgG testing against HP-associated antigens. Suboptimal sensitivity and specificity	Accessible	Positive test may support HP exposure	Unclear	Unclear
Other serum-/plasma-based protein markers					
Proteomics/specific proteins (including MMP-7, CCL18, SP-D, CA-125, CA19-9, KL-6, MMP-1, MMP-8, TGF-β, PDGF)	Tissue-derived glycoproteins, enzymes, and protein signatures linked to various pulmonary processes including innate immunity, tissue remodelling, extracellular matrix turnover and fibrosis	Variably accessible	Unclear	Unclear	Unclear
Inflammatory/immunological markers (CRP, ESR)	Acute-phase protein and proinflammatory markers that play pivotal roles in immune, autoimmune and inflammatory disorders	Globally accessible	Positive markers may support specific interstitial pneumonia diagnoses	Extent of positivity may predict outcomes (*e.g.* CRP)	May guide therapeutic response

Eur resp J 2025; 66: 2500158

Further evaluation

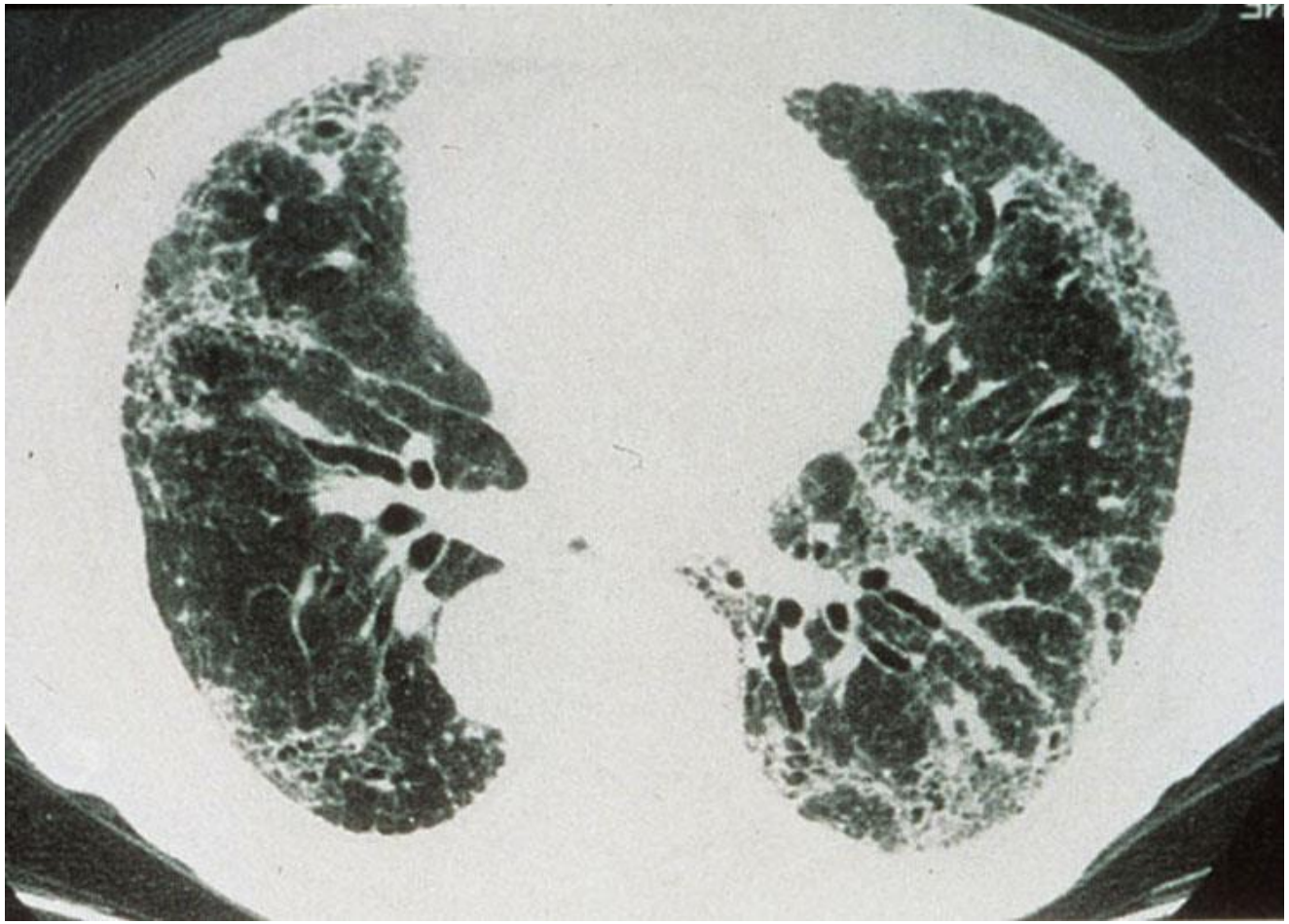


UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
• Dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing) • Predominant subpleural and/or paraseptal distribution of fibrosis • Patchy involvement of lung parenchyma by fibrosis • Fibroblast foci • Absence of features to suggest an alternate diagnosis	• Some histologic features from column 1 are present but to an extent that precludes a definite diagnosis of UIP/IPF *And* • Absence of features to suggest an alternative diagnosis *Or* • Honeycombing only	• Fibrosis with or without architectural distortion, with features favoring either a pattern other than UIP or features favoring UIP secondary to another cause* • Some histologic features from column 1, but with other features suggesting an alternative diagnosis†	• Features of other histologic patterns of IIPs (e.g., absence of fibroblast foci or loose fibrosis) in all biopsies • Histologic findings indicative of other diseases (e.g., hypersensitivity pneumonitis, Langerhans cell histiocytosis, sarcoidosis, LAM)

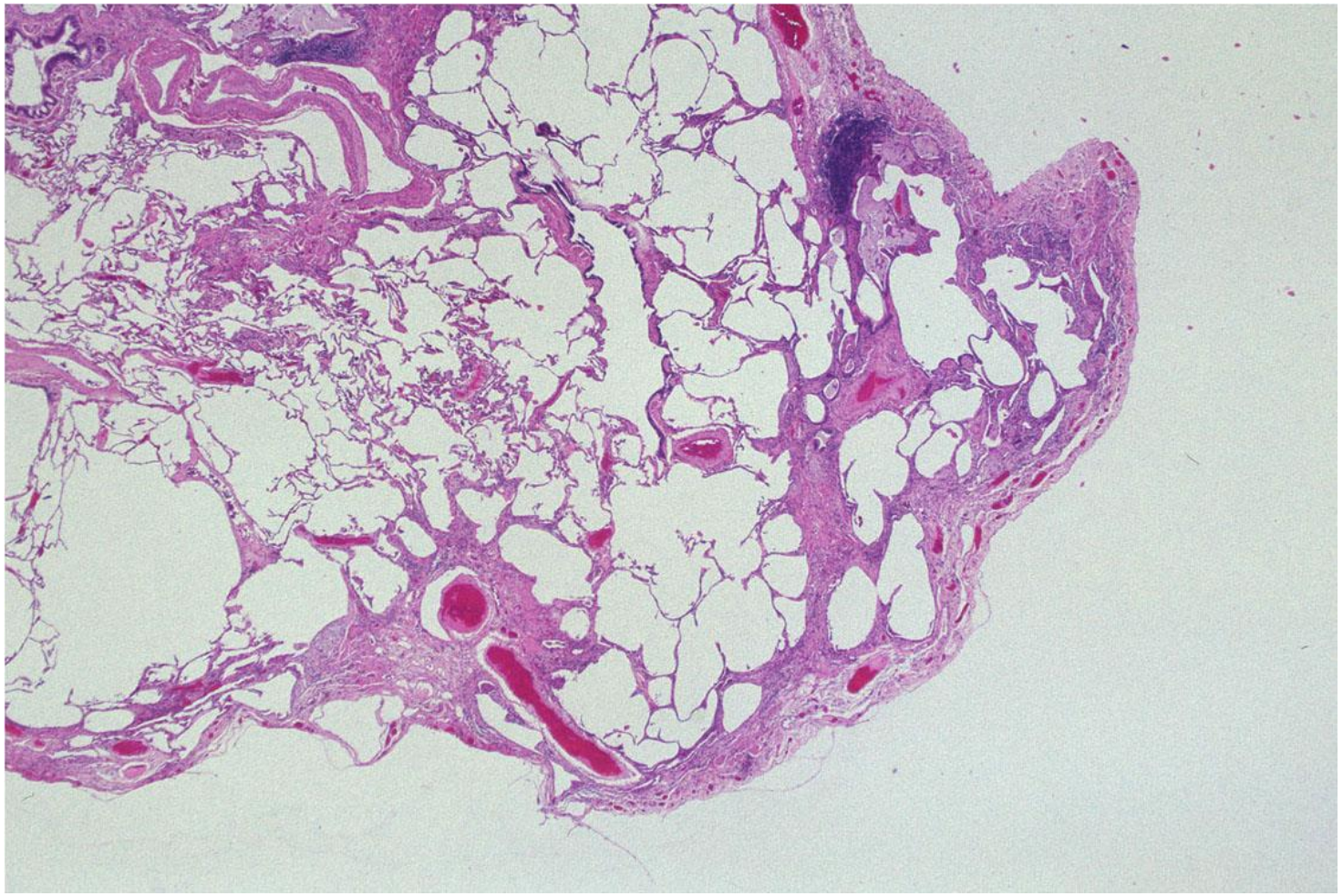
IPF suspected*		Histopathology pattern			
		UIP	Probable UIP	Indeterminate for UIP	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Probable UIP	IPF	IPF	IPF (Likely)**	Non-IPF dx
	Indeterminate for UIP	IPF	IPF (Likely)**	Indeterminate for IPF***	Non-IPF dx
	Alternative diagnosis	IPF (Likely)** /non-IPF dx	Non-IPF dx	Non-IPF dx	Non-IPF dx

Am J Resp Crit Care Med 2018; 198: e44

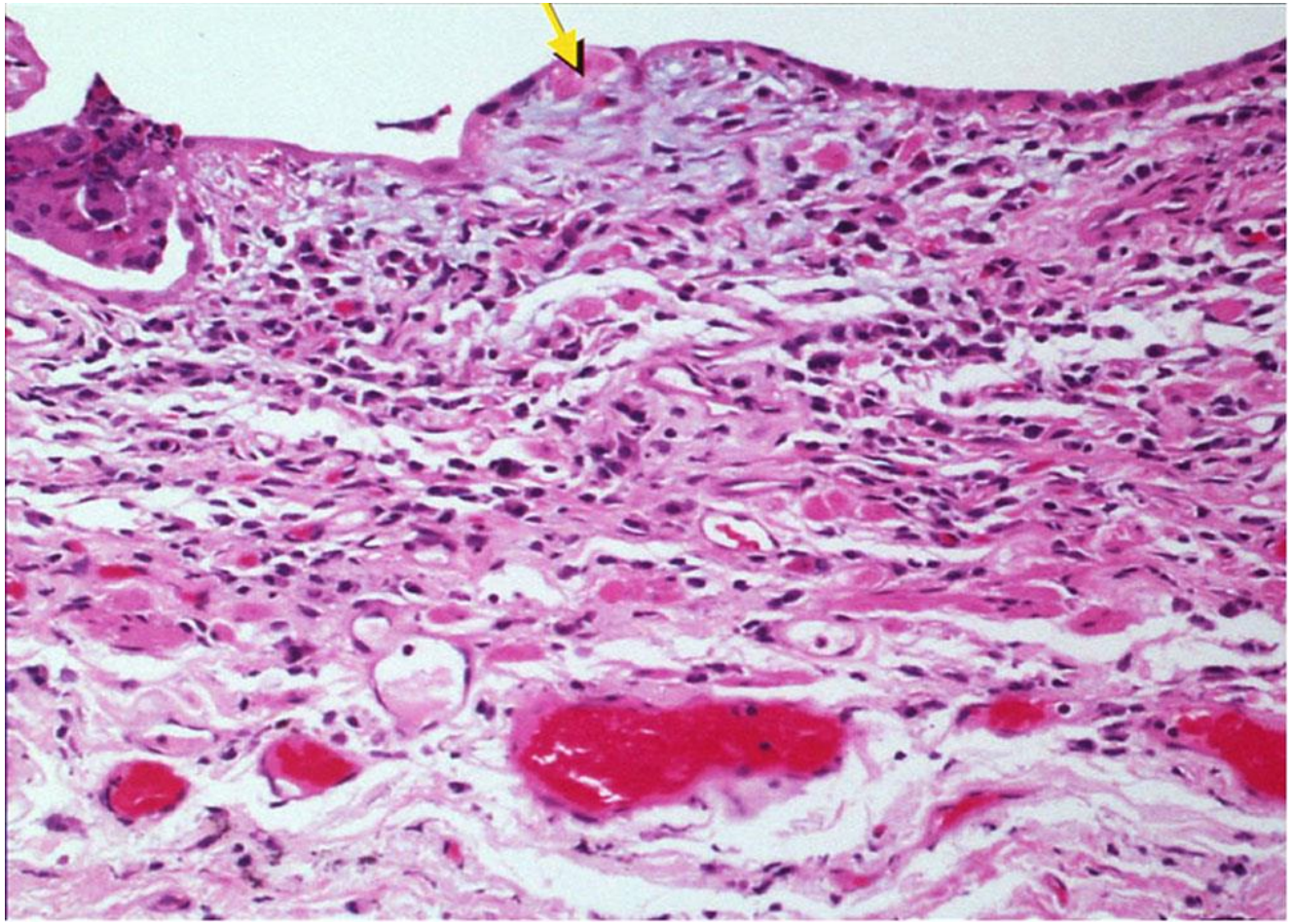
HRCT features of Idiopathic Pulmonary Fibrosis



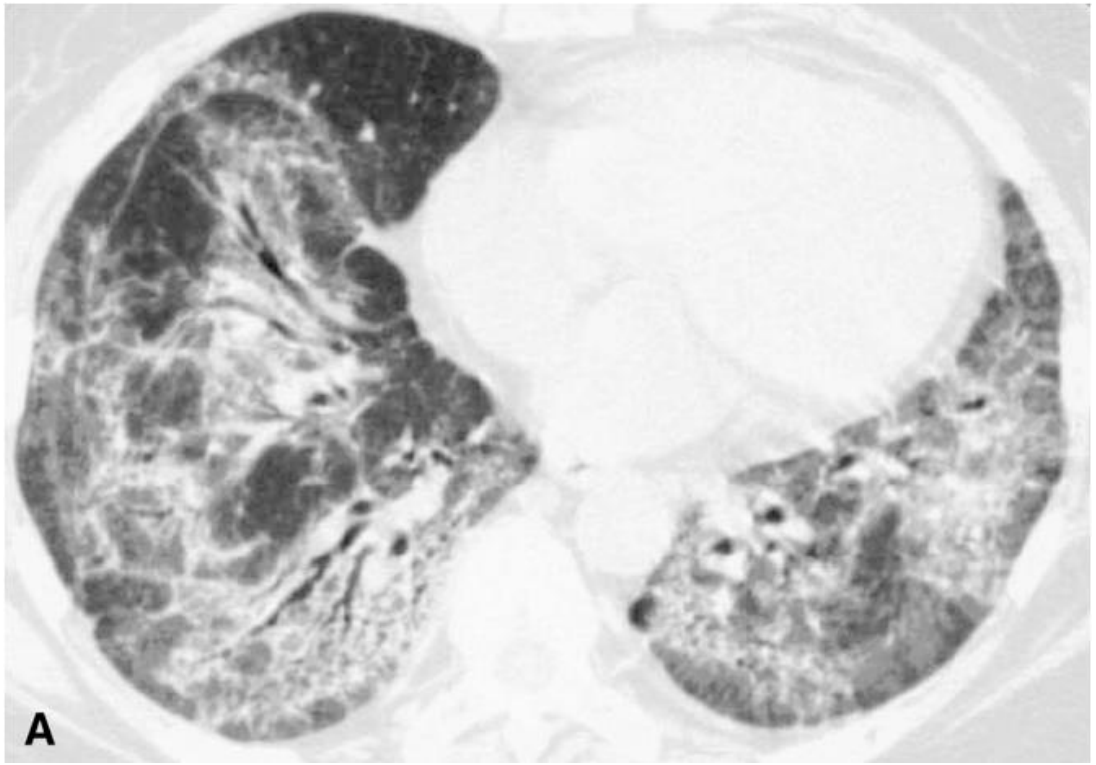
Histologic features of Usual Interstitial Pneumonia

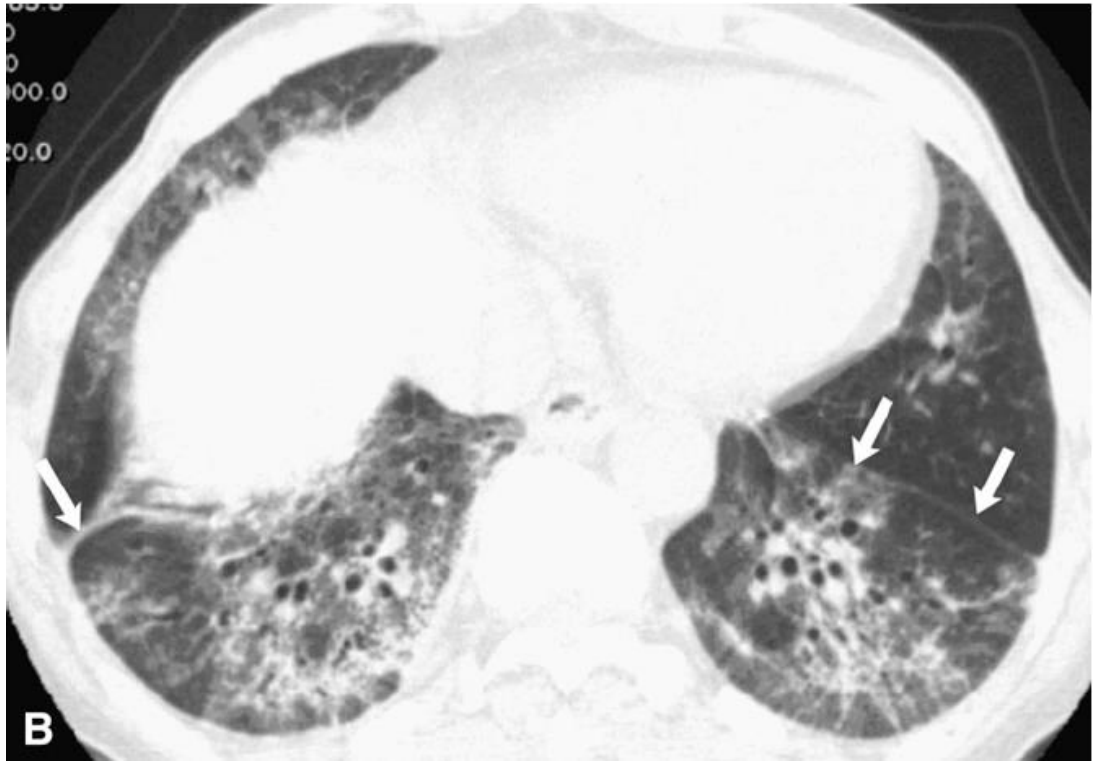


Histologic features of Usual interstitial Pneumonia



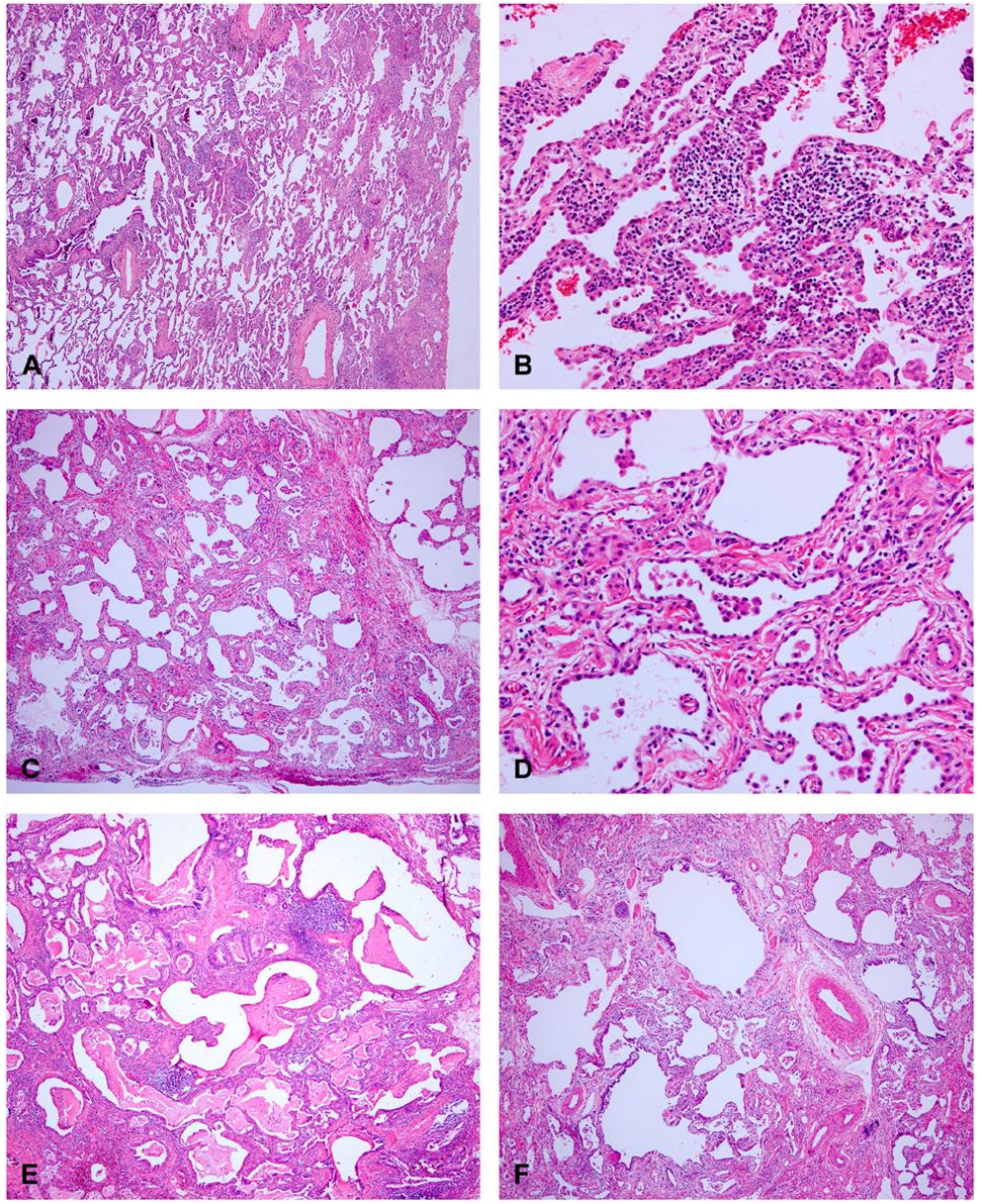
Features of NSIP





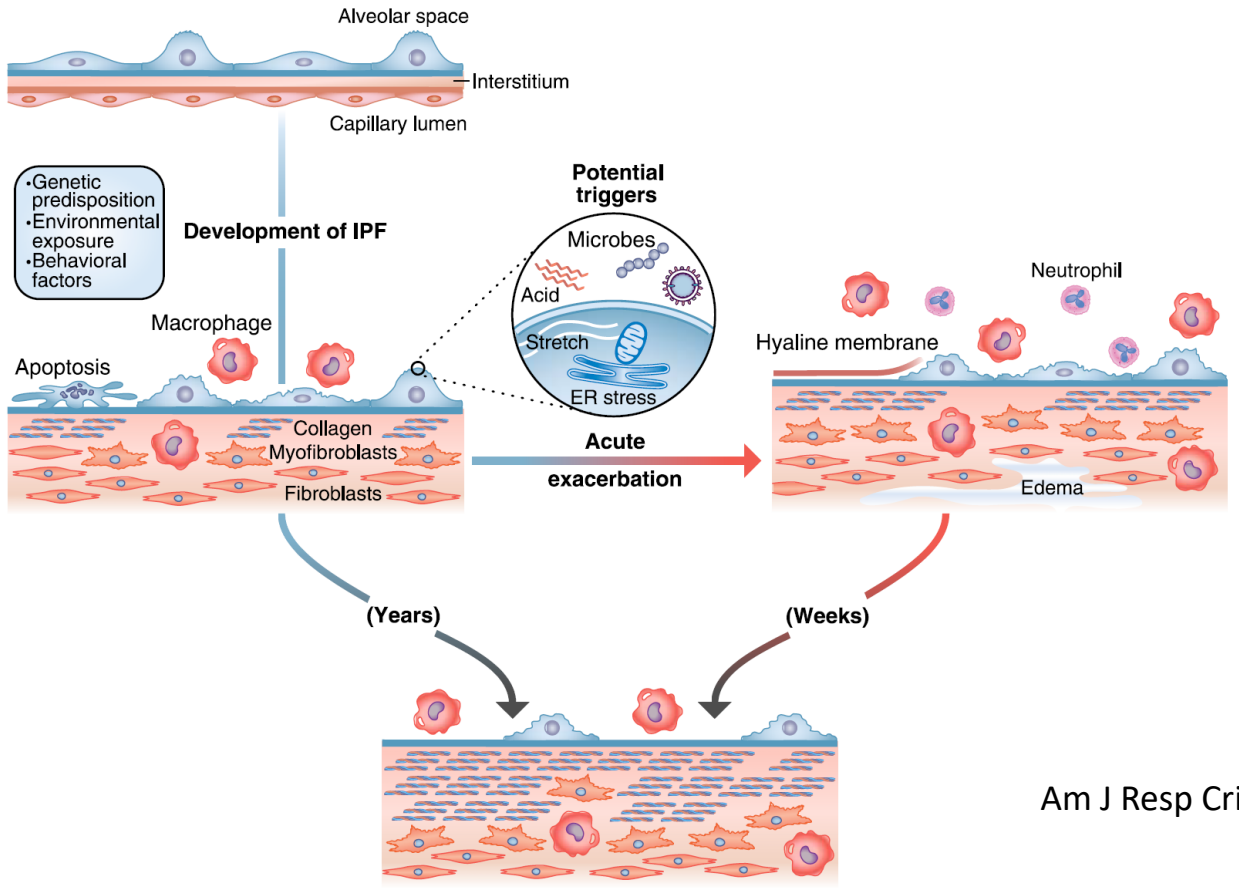
Am J Resp Crit Care Med 2008; 177: 1338

Pathology of NSIP



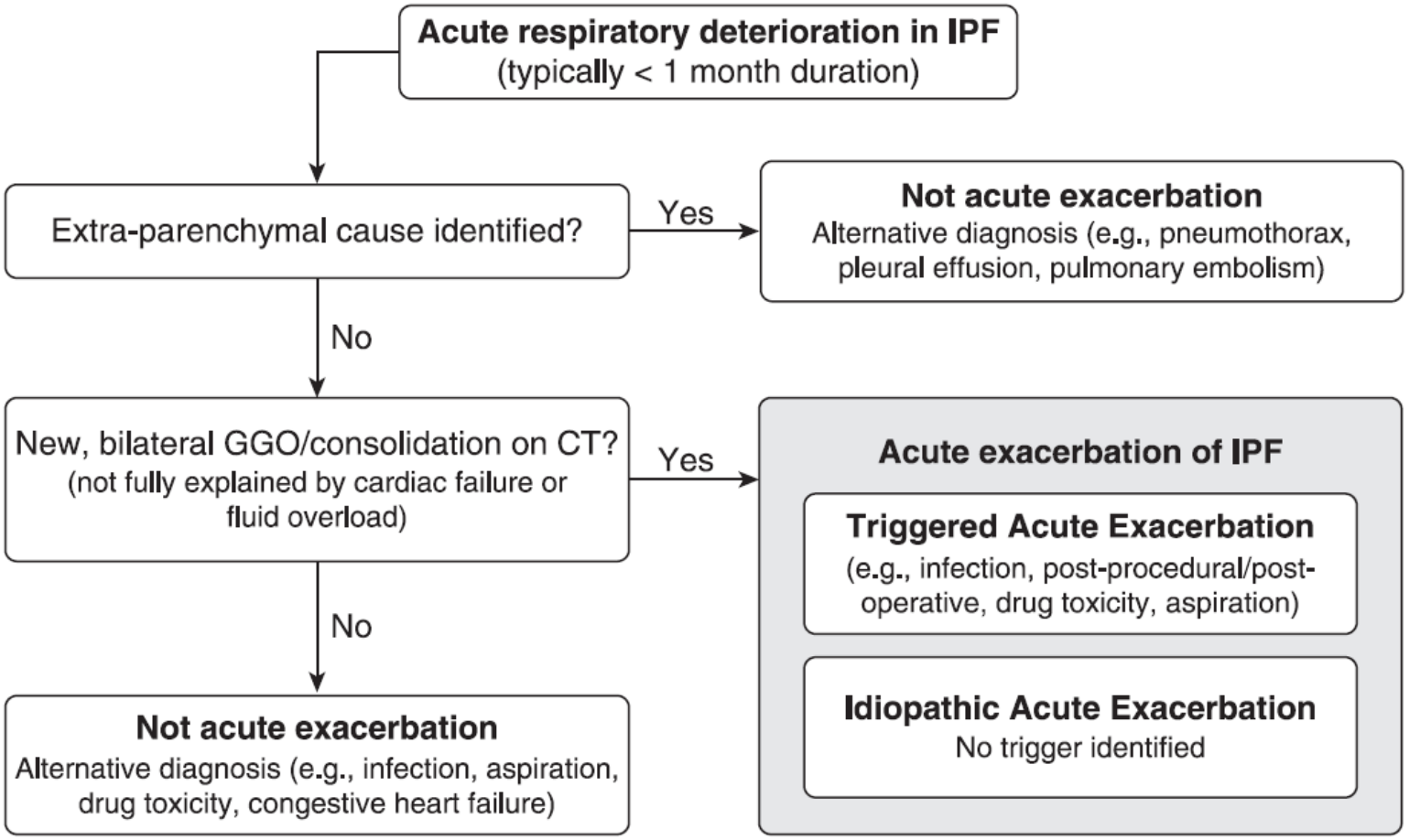
Am J Resp Crit Care Med 2008; 177: 1338

Acute exacerbation of interstitial lung disease



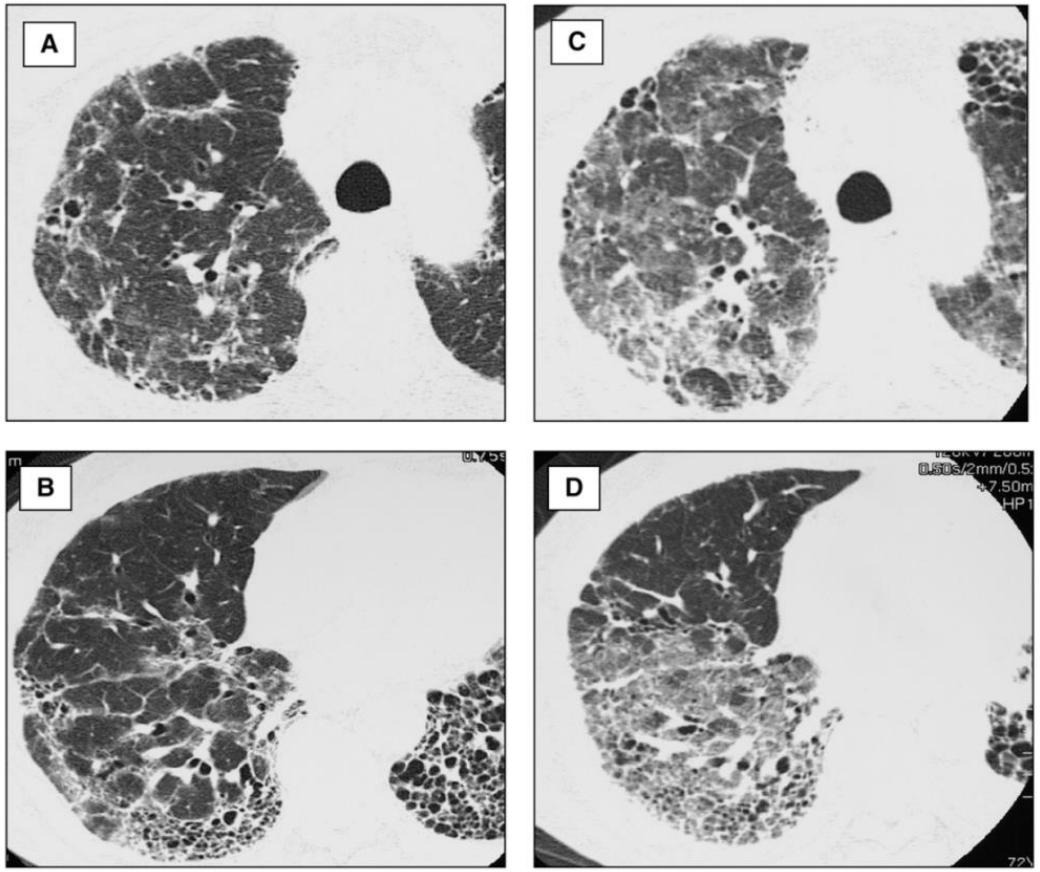
Am J Resp Crit Care Med 2016; 194: 265

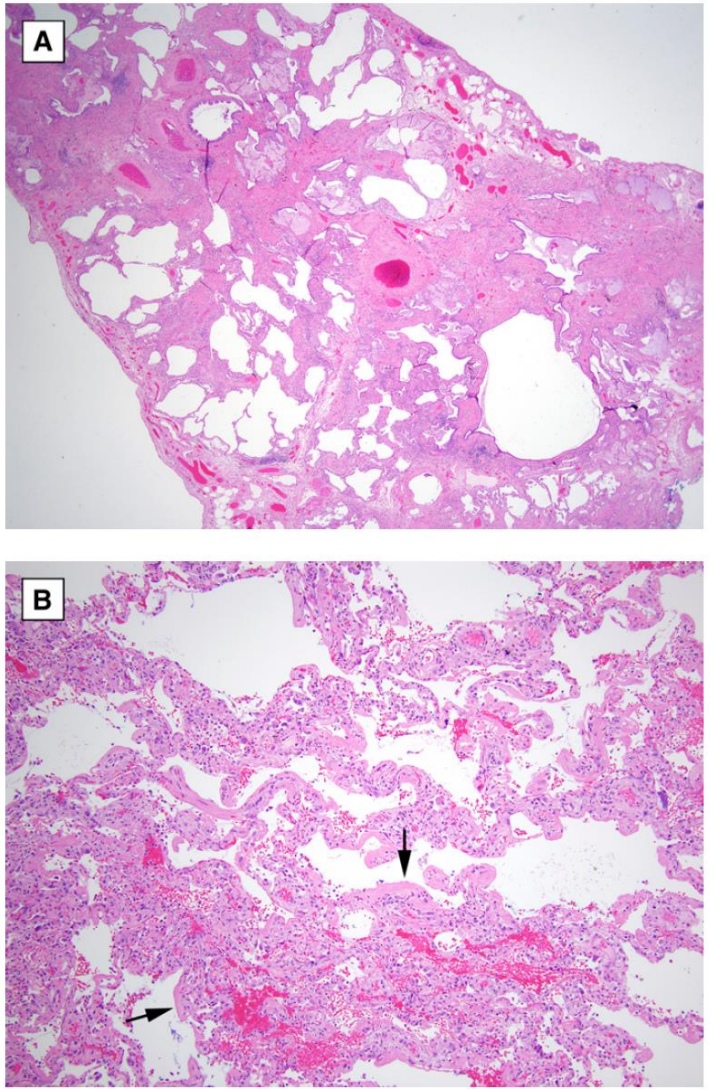
Acute exacerbation of interstitial lung disease



Am J Resp Crit Care Med 2016; 194: 265

Acute exacerbation of interstitial lung disease





Am J Respir Crit Care Med 2007; 176: 636

Idiopathic Pulmonary Fibrosis - Therapy

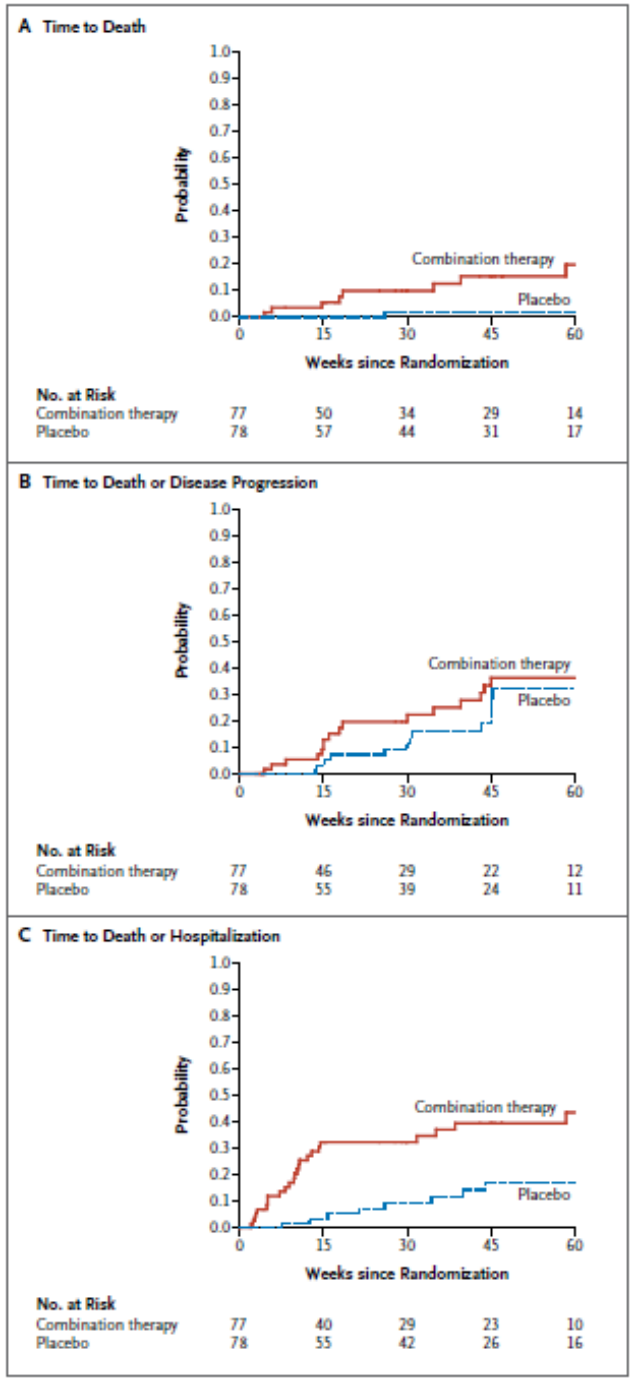
- Recommendation against the following:
  - Corticosteroid monotherapy
  - Colchicine
  - CSA
  - Combined corticosteroid and immune-modulator therapy
  - INF alpha
  - Bosentan
  - Etanercept

Am J Resp Crit Care Med 2011; 183: 788

Panther

- Prednisone/Azathioprine/NAC vs.NAC vs. placebo
- Triple therapy arm closed early:
  - Increased mortality (11% vs 1%)
  - Increased hospitalization (29% vs 8%)
  - More SAE's (31% vs. 9%)

Eur Respir J 2012; 39: 805
New Eng J Med 2012; 366: 1968



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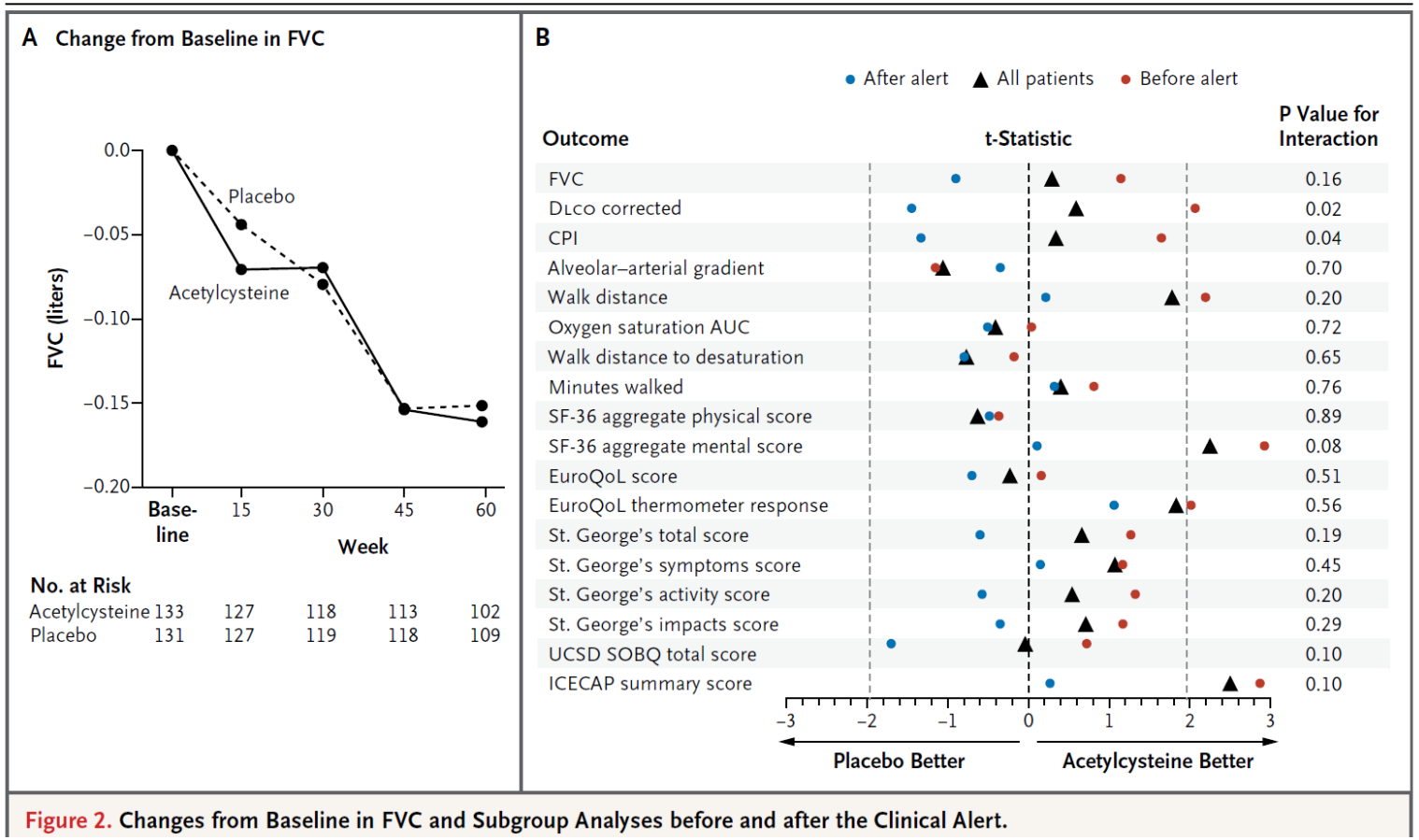


Figure 2. Changes from Baseline in FVC and Subgroup Analyses before and after the Clinical Alert.

N Eng J Med 2014; 370: 2093

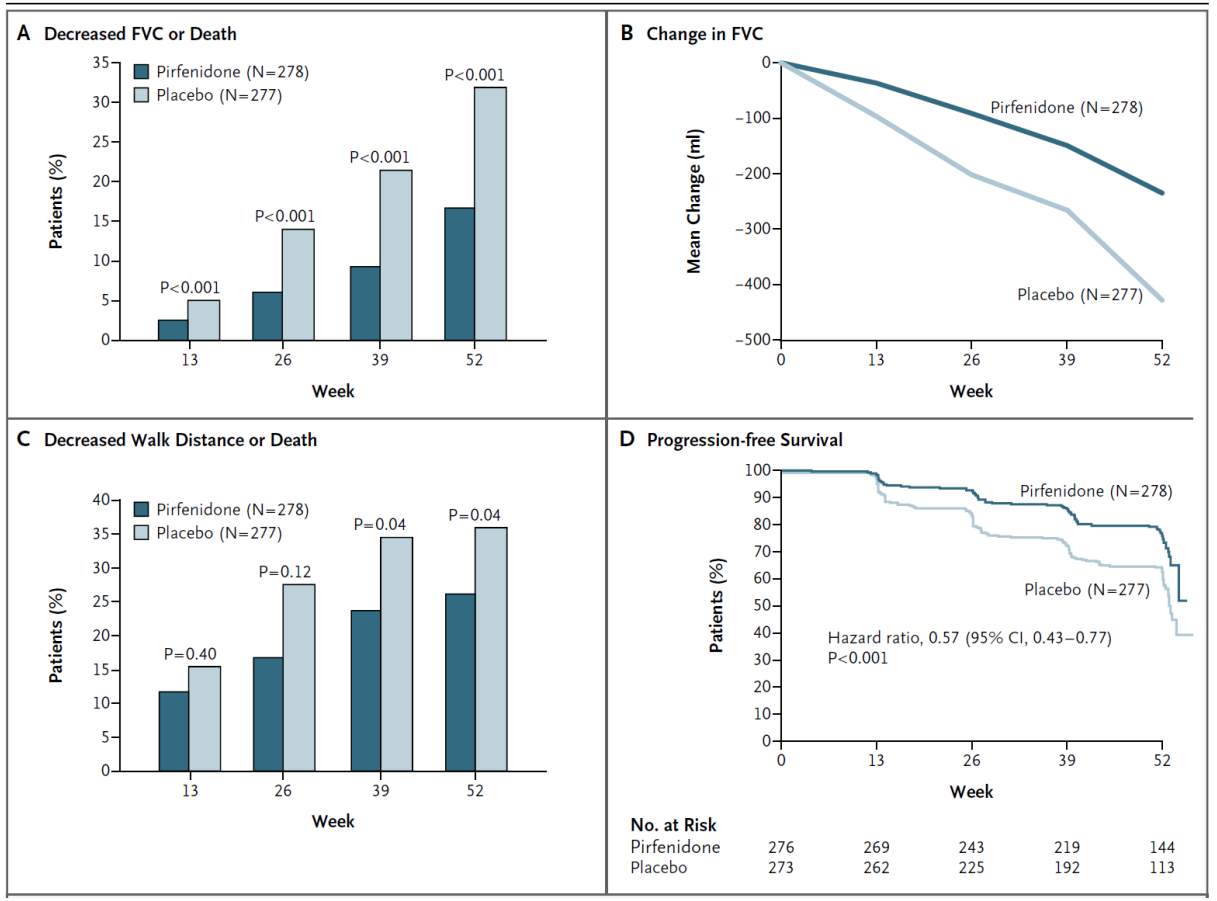
Pirfenidone

Anti-inflammatory and antifibrotic

Inhibits production and activity of TGF-beta

Animal studies:
Inhibits TGF-beta and pro-collagen/collagen gene and mRNA expression

Inhibits fibroblast mitogenesis



Expert Opin Investig Drugs. 2010 Feb; 19:275
N Eng J Med 2014; 370:2083

Impact of pirfenidone in setting of declining FVC

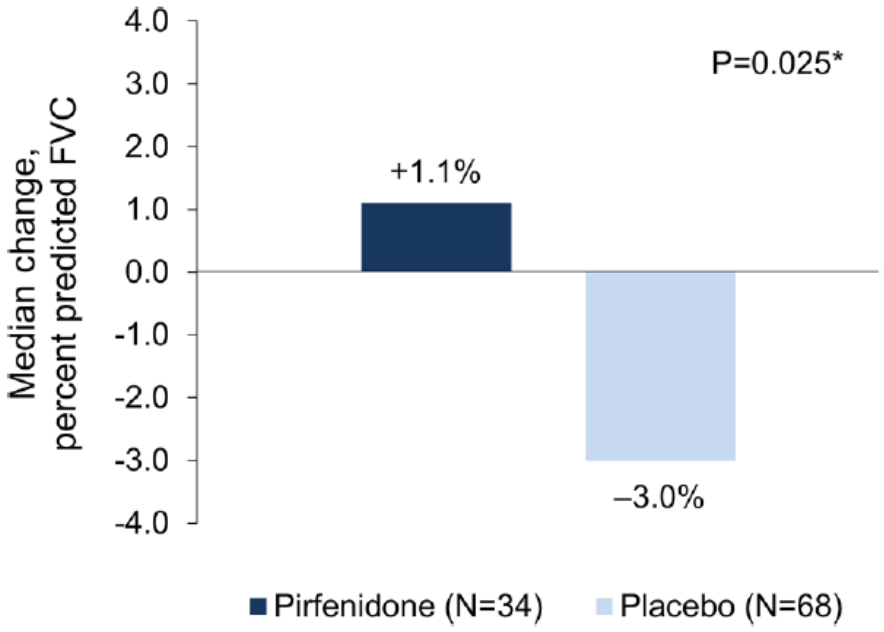


Table 3 Outcomes after 6 months of continued treatment following hospitalisation*

	Pirfenidone (N=44)	Placebo (N=49)	Relative difference (%)	p Value†
≥10% decline in FVC or death	4 (9.1%)	16 (32.7%)	−72.2	0.010
No further decline in FVC‡	15 (34.1%)	12 (24.5%)	39.2	0.364
Death	2 (4.5%)	14 (28.6%)	−84.3	0.002

*All-cause hospitalisation between baseline and month 6; treatment outcomes assessed during the 6-month interval beginning with the first study visit following the date of hospitalisation.
†Fisher's exact test.
‡Either no decline or increase in FVC.

Thorax 2016; 71: 429

Nintedanib

Competitive inhibitor of FGFR-1, VEGFR-2, PDGFR alpha and beta

Reduced proliferation, migration and survival of fibroblasts

Potentially also attenuates angiogenesis

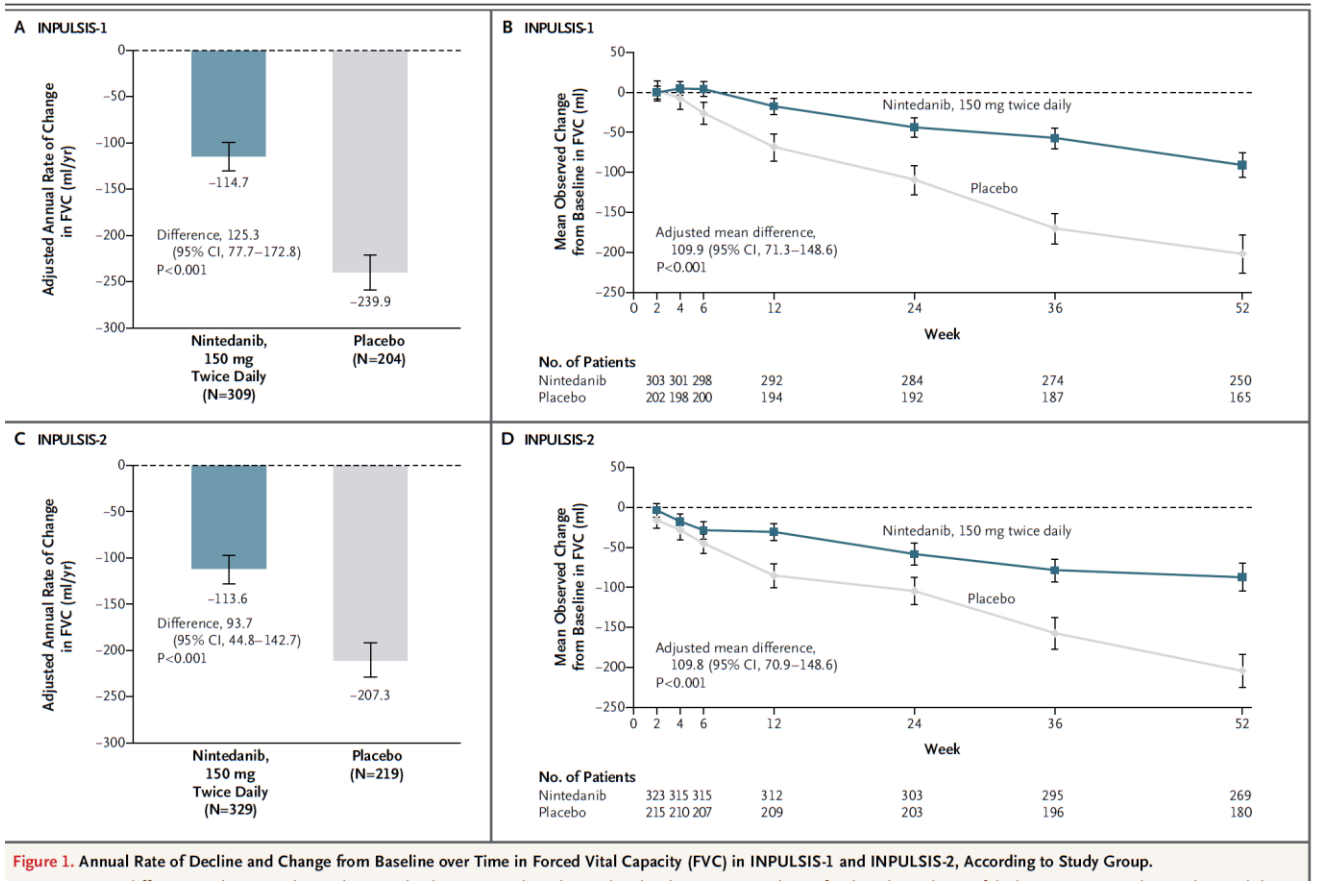


Figure 1. Annual Rate of Decline and Change from Baseline over Time in Forced Vital Capacity (FVC) in INPULSIS-1 and INPULSIS-2, According to Study Group.

Eur Resp J 2015; 45: 1434
N Eng J Med 2014; 370: 2071

Nintedanib

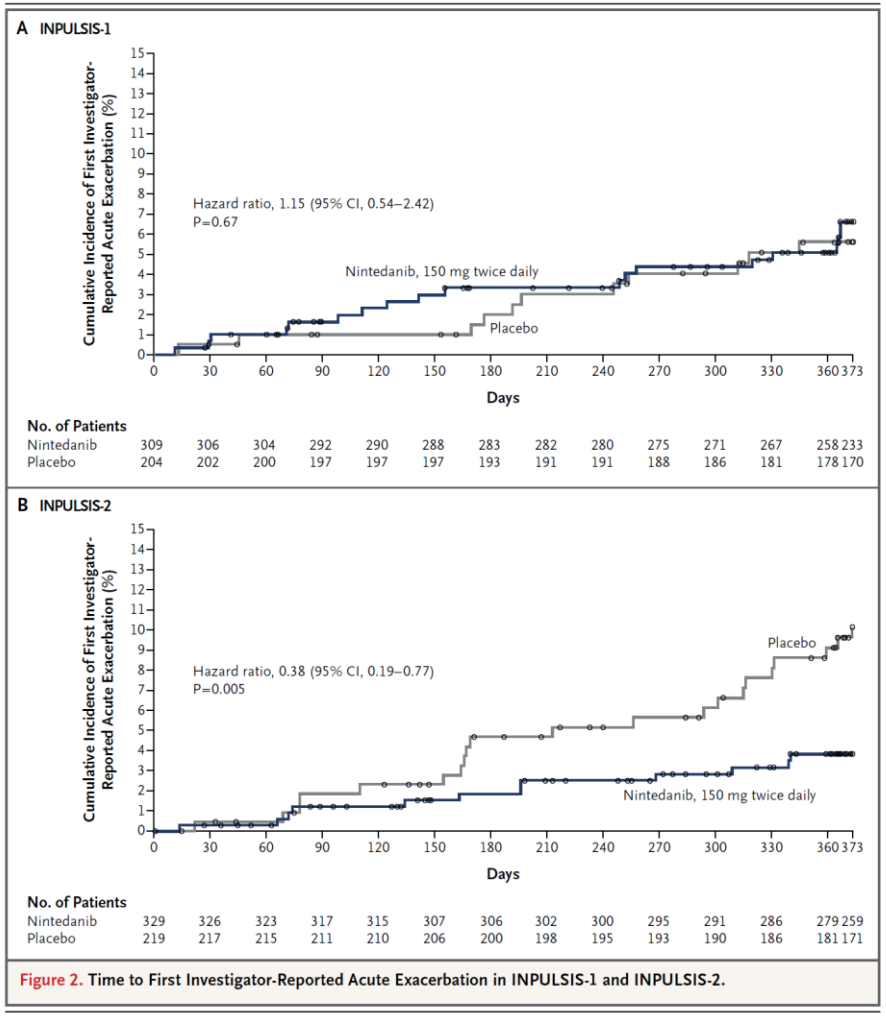
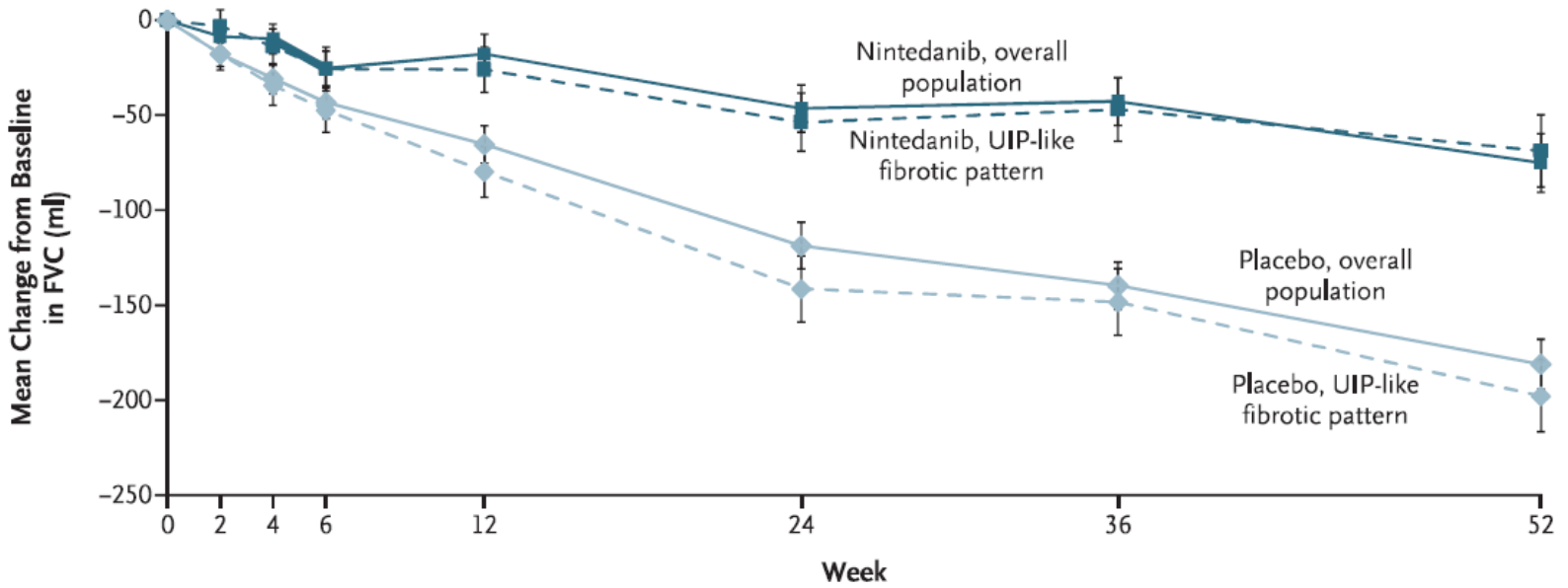


Figure 2. Time to First Investigator-Reported Acute Exacerbation in INPULSIS-1 and INPULSIS-2.

N Eng J Med 2014; 370: 2071

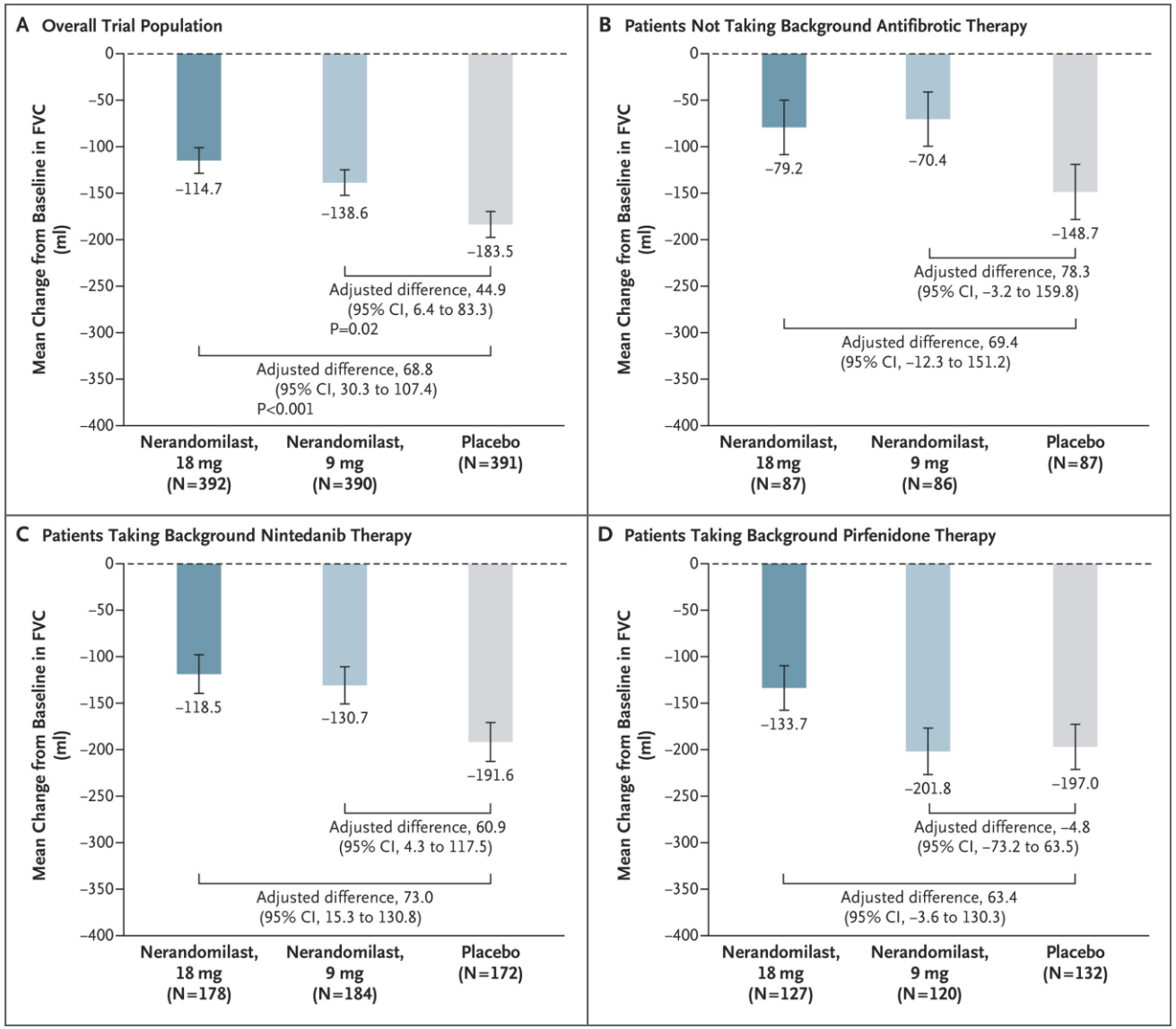
Nintedanib in progressive fibrosing interstitial lung disease



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

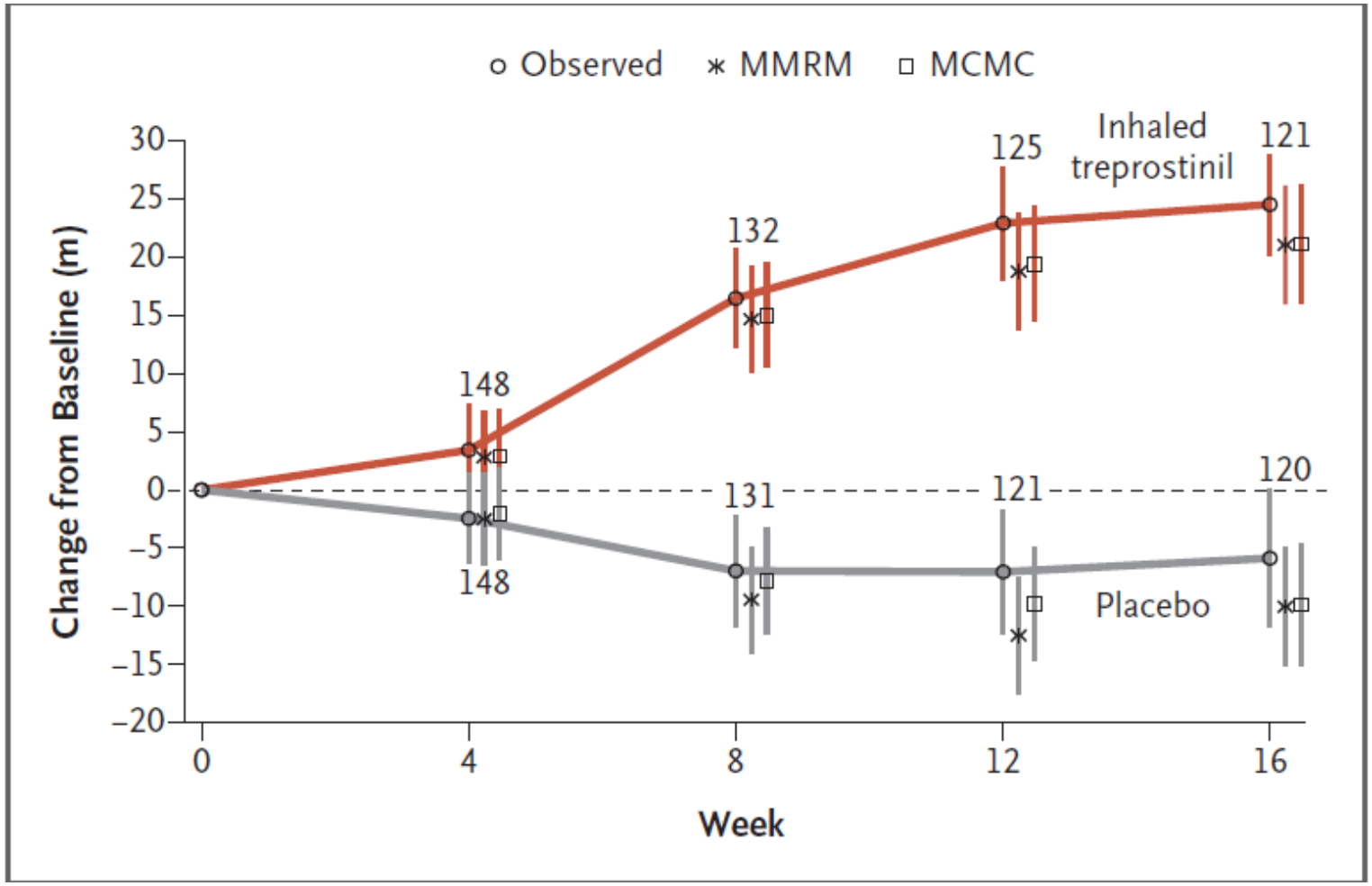
N Eng J Med 2019; 381: 18

Preferential Phosphodiesterase 4B inhibitor for IPF



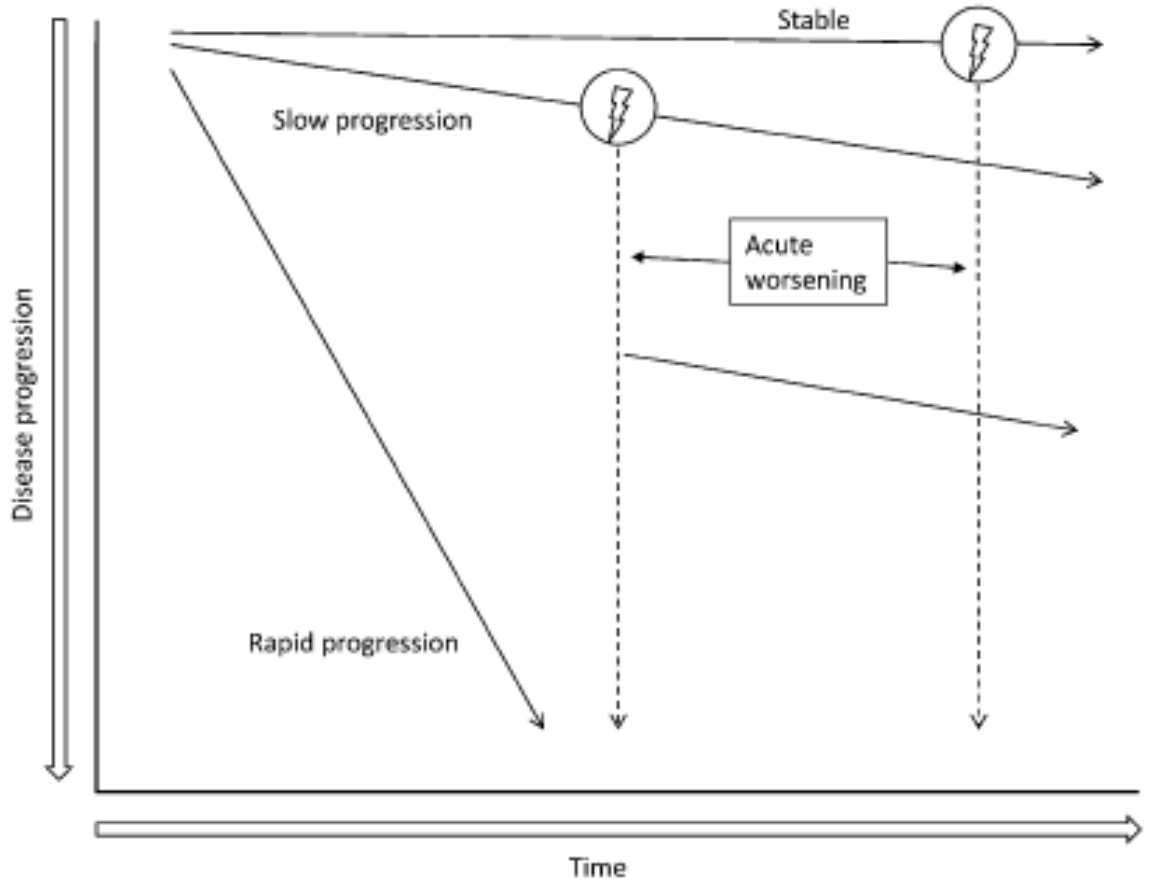
N Engl J Med 2025;392:2193

Inhaled Treprostenil for IPF associated pulmonary hypertension



N Engl J Med 2022; 386:23

Idiopathic Pulmonary Fibrosis – natural history



Am J Resp Crit Care Med 2011; 183: 788

Summary

- Confirm diagnosis of ILD and subtype
  - CXR, HRCT scan, Bronchoscopy, OLBx, “clinical picture”
- Assess function
  - PFTs, exercise oximetry testing, QOL tool (SF-36)
- Treatment plan
  - disease specific plus vaccines, exercise, nutrition, etc.

Question 1

- A 61 yo man with a 40 pack year smoking history as well as hyperlipidemia presents to his primary care physician with reports of progressive dyspnea on exertion and a dry cough for the past 2 years. Once an active man, able to walk an infinite distance on a flat surface, he now notes feeling short of breath with 3 flights of stairs and while playing with his grandchildren. His cough is non-productive and is not associated with various environmental exposures. He is a former banker. On exam, he is noted to have an oxygen saturation of 98% on room air and 97% after walking 200 yards. He has fine crackles at the bases of his lungs and no clinical evidence of volume overload. His basic lab values are normal. Pulmonary function tests show a reduced total lung capacity. A CT scan of the chest shows bibasilar, subpleural reticular findings without infiltrate or lymphadenopathy.

Question 1

- The most appropriate course of action at the present time is which of the following:
- A) Refer for lung biopsy as these findings represent an atypical presentation of an interstitial lung disease
- B) Start 40mg of prednisone a day
- C) After alternative diagnoses such as heart failure and indolent infection are ruled out, consider for lung transplant referral
- D) Refer the patient for pulmonary rehabilitation

Question 1

- The most appropriate course of action at the present time is which of the following:
- A) Refer for lung biopsy as these findings represent an atypical presentation of an interstitial lung disease
- B) Start 40mg of prednisone a day
- **C) After alternative diagnoses such as heart failure and indolent infection are ruled out, consider for lung transplant referral**
- D) Refer the patient for pulmonary rehabilitation

Consider appropriateness for pirfenidone/nintedanib and/or referral for lung transplant

Question 2

- A 51 yo woman with a history of Raynaud's Disease presents to her primary care physician with reports of progressive dyspnea on exertion and a dry cough for the past 6 months. Once able to walk an infinite distance on a flat surface, she now notes feeling short of breath with 3 flights of stairs and during exercise. Her cough is non-productive and is not associated with various environmental exposures. She works as a teacher. Weight is 60 kg. On exam, she is noted to have an oxygen saturation of 98% on room air and 92% after walking 200 yards. She has fine crackles at the bases of her lungs and no clinical evidence of volume overload. She is tender on palpation at the wrists and MCP joints. Her basic lab values are normal. Pulmonary function tests show a reduced total lung capacity. A CT scan of the chest shows bibasilar, subpleural reticular findings and diffuse ground glass.

Question 2

- The most appropriate course of action at the present time is which of the following:
- A) Refer for lung biopsy as these findings represent an atypical presentation of an interstitial lung disease
- B) Start 30mg of prednisone a day
- C) Start nintedanib 150 mg bid
- D) After alternative diagnoses such as heart failure and indolent infection are ruled out, consider for lung transplant referral

Question 2

- The most appropriate course of action at the present time is which of the following:
- A) Refer for lung biopsy as these findings represent an atypical presentation of an interstitial lung disease
- B) **Start 30mg of prednisone a day**
- C) Start nintedanib 150 mg bid
- D) After alternative diagnoses such as heart failure and indolent infection are ruled out, consider for lung transplant referral

Initiate immune modulation, with plan to add antifibrotic therapy if continued progression

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