Idiopathic Pulmonary Fibrosis (IPF): Does the "I" Still Apply?

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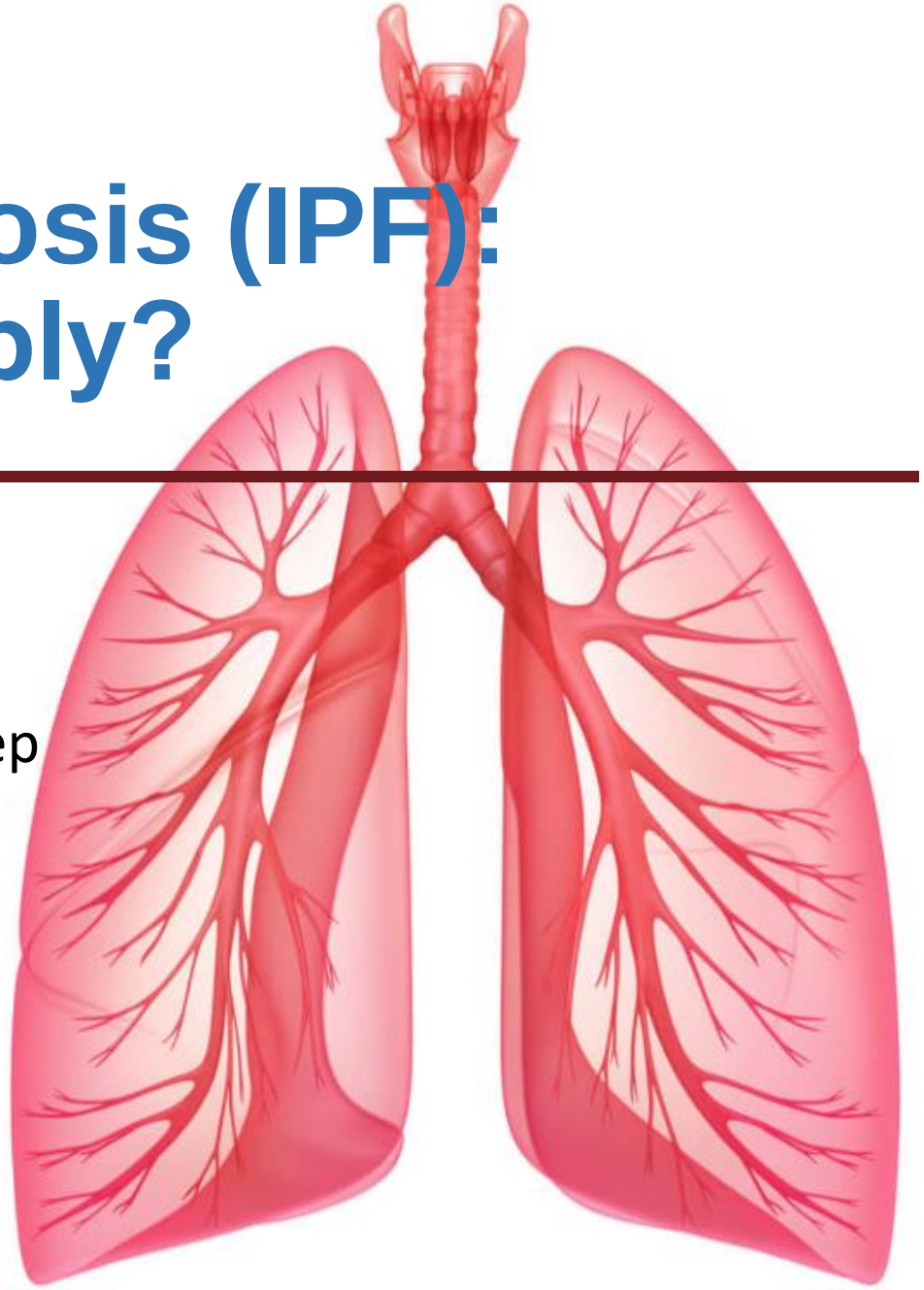

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Disclosures

Dr. Glassberg serves on the advisory board for Actelion, Bellerophon, Boehringer-Ingelheim, Bristol-Myers-Squibb, Genentech/Roche, and Red-X.

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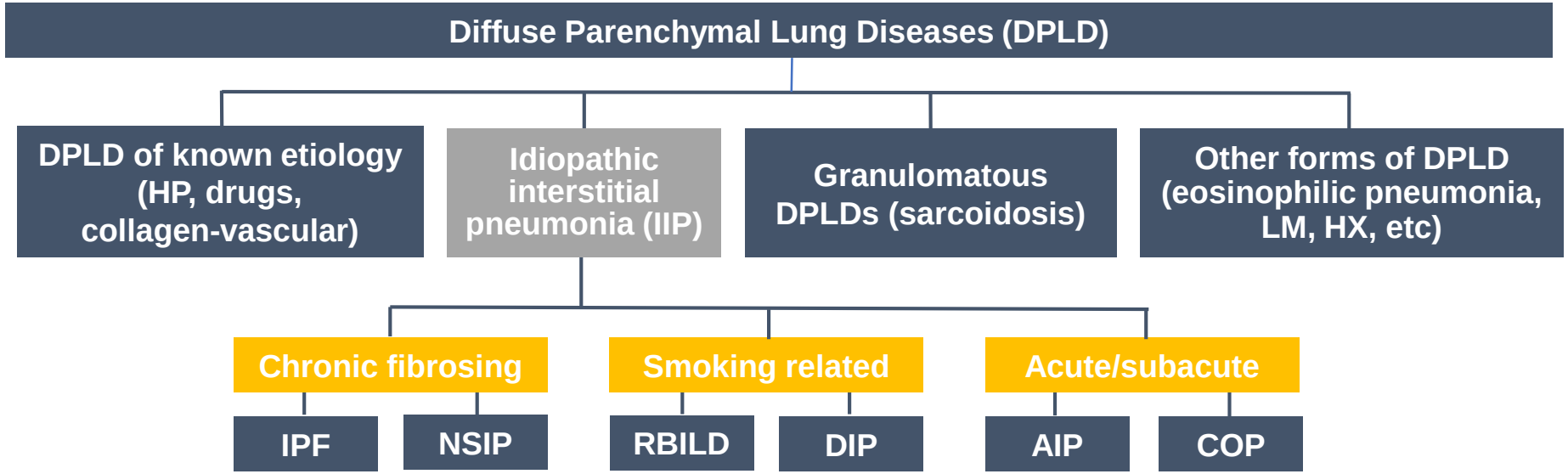
Learning Objectives

- Upon completion of this learning activity, participants should be able to describe risk factors associated with Idiopathic Pulmonary Fibrosis (IPF).
- Upon completion of this learning activity, participants should be able to review current ideas on pathogenesis of IPF and what the “I” could mean.

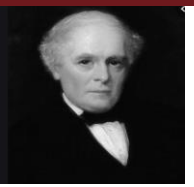
Diffuse Parenchymal (Interstitial) Lung Diseases



Very rare IIPs

- Idiopathic lymphocytic interstitial pneumonia (LIP)
- Idiopathic pleuroparenchymal fibroelastosis (PPFE)

The many names of Idiopathic Pulmonary Fibrosis



- 1838-1893: DJ Corrigan and cirrhosis of the lung

- 1893: William Osler and chronic interstitial pneumonia (subtitle cirrhosis of the lung)

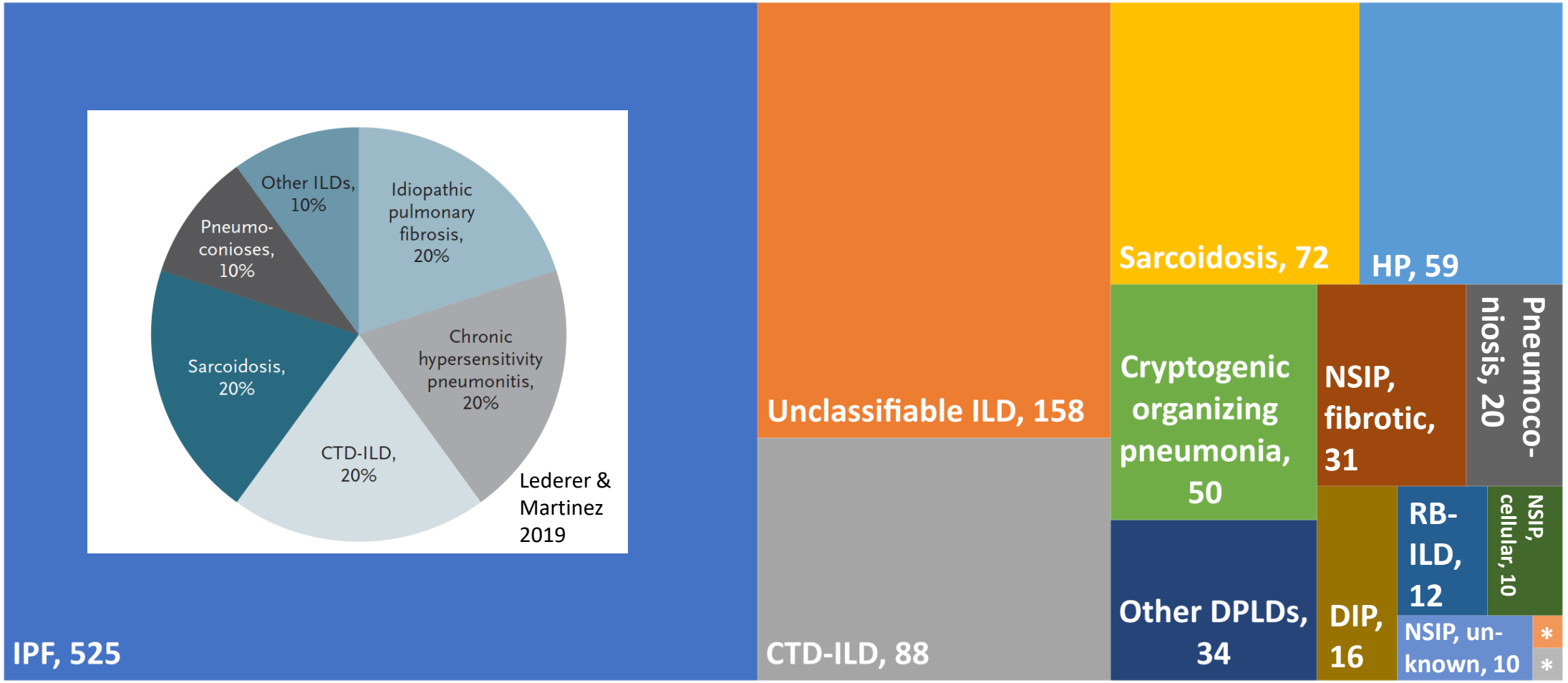
- 1948: Robbins noted no identifiable cause

- 1976: Crystal and colleagues popularized IPF

- 1998: Katzenstein recognized different lung pathologies with HRCT findings

- 2018: rename?

Number of patients with Interstitial lung disease (European IPF Registry 2009–2016)



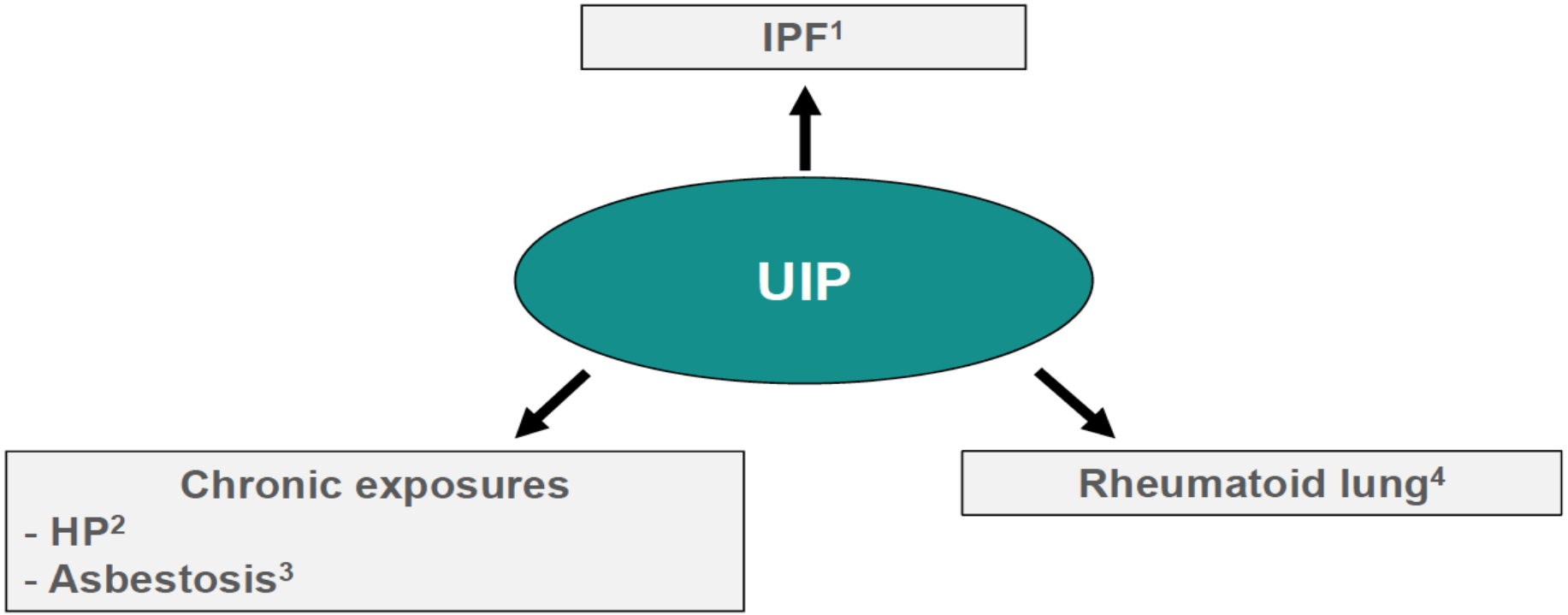
*Lymphocytic IP, 1; acute IP, 1.

CTD-ILD, connective tissue disease-associated interstitial lung disease; DIP, desquamative IP; DPLD, diffuse parenchymal lung disease; HP, hypersensitivity pneumonitis; IP, interstitial pneumonia; ILD, interstitial lung disease; NSIP, nonspecific IP; RB, respiratory bronchiolitis-associated interstitial lung disease.

Guenther A *et al. Respir Res* 2018;19:141.

UIP Is Not Always IPF[1]

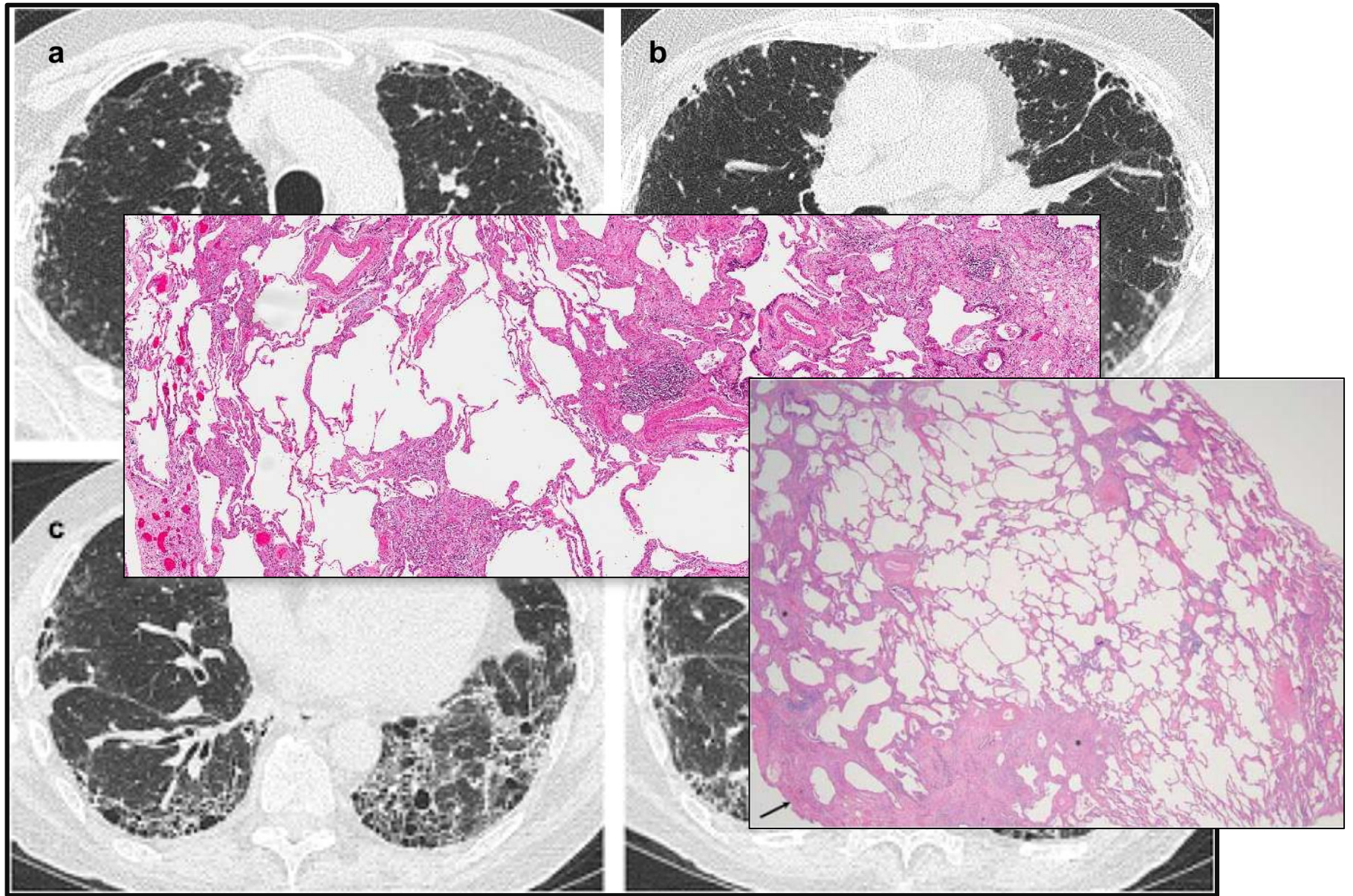
Putting the Pattern in Context



Distinct ILDs may appear very similar on HRCT and surgical lung biopsy, further complicating the process of diagnosis

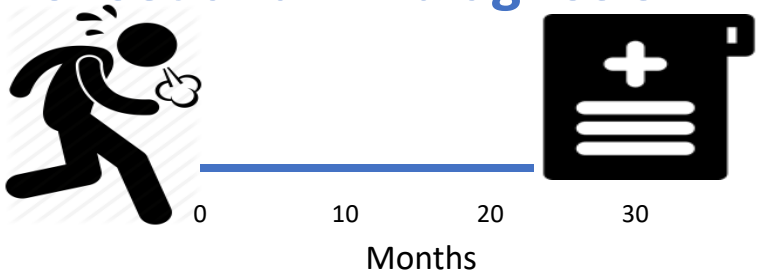
Raghu G et al. *Am J Respir Crit Care Med*. 2011;183:788-824. 2. Takemura T et al. *Histopathology*. 2012;61:1026-1035. 3. Glazer CS, Newman LS. *Clin Chest Med*. 04;25:467-478. 4. Kim EJ et al. *Chest*. 2009;136(5):1397-1405.

The Usual Interstitial Pneumonia (UIP) Pathology is not unique to the lungs of patients with IPF



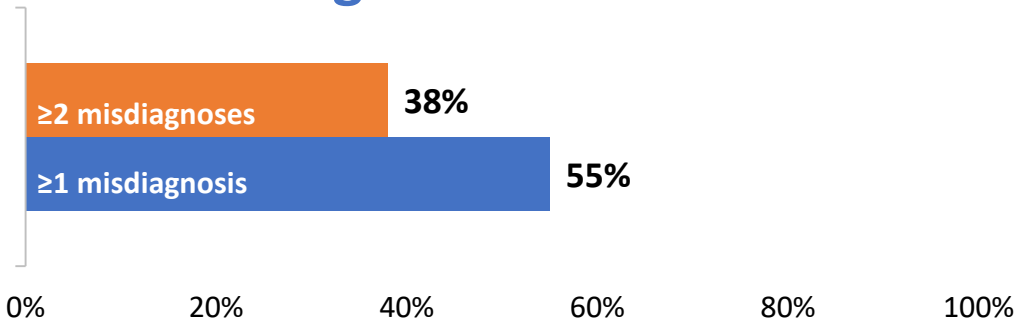
The delays in diagnosis/the misdiagnoses of IPF: Does the "I" matter?

1.9 y between symptom onset and IPF diagnosis



2-3 doctors seen before receiving IPF diagnosis

More Than Half of Patients Are Misdiagnosed *at Least* Once

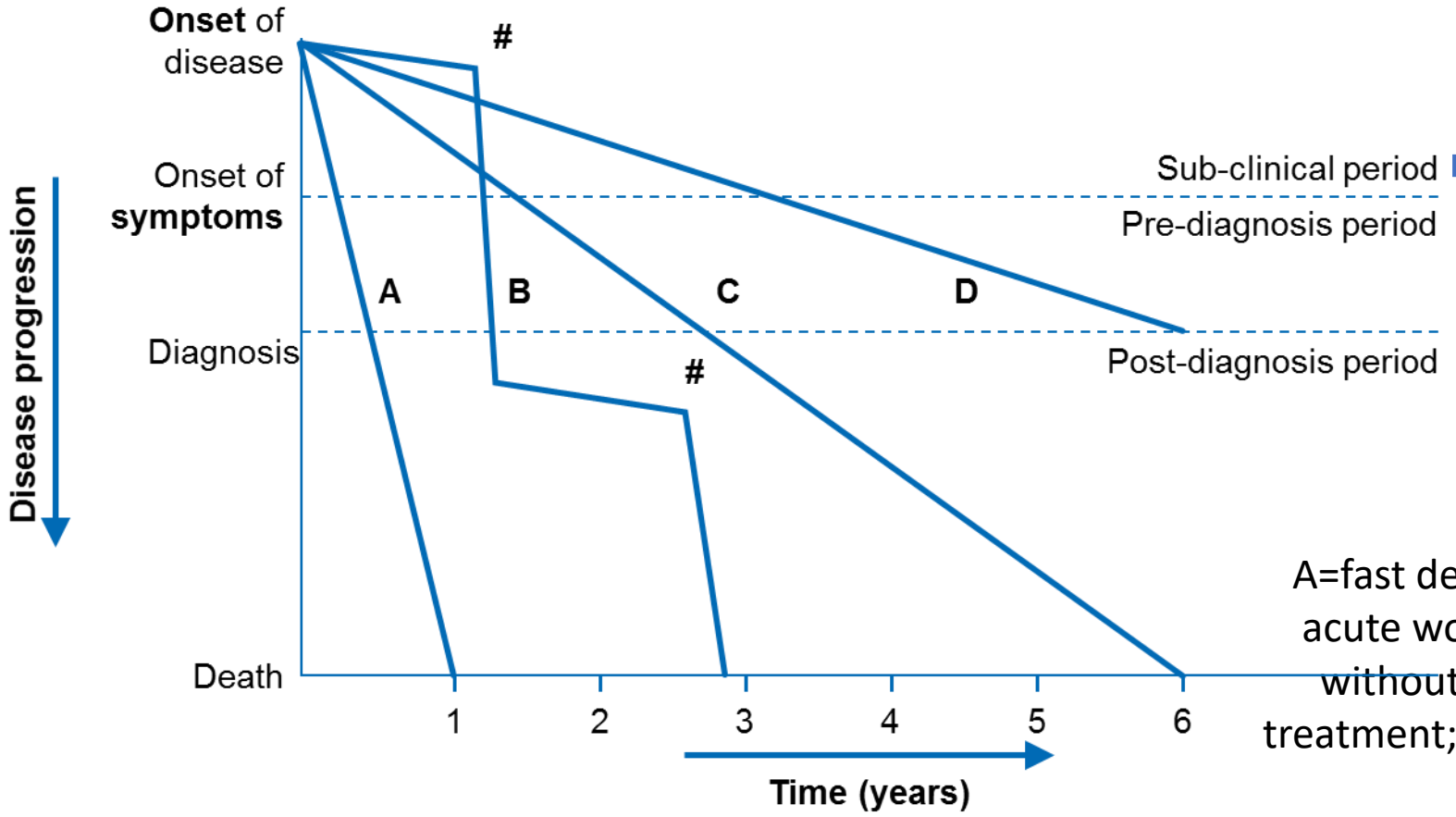


Common Misdiagnoses

Bronchitis (45%)
Allergies (34%)
COPD (34%)

Swigris JJ et al. *Chest*. 2015(suppl):1-8.; Cosgrove GP et al. *BMC Pulm Med*. 2018;8:9.

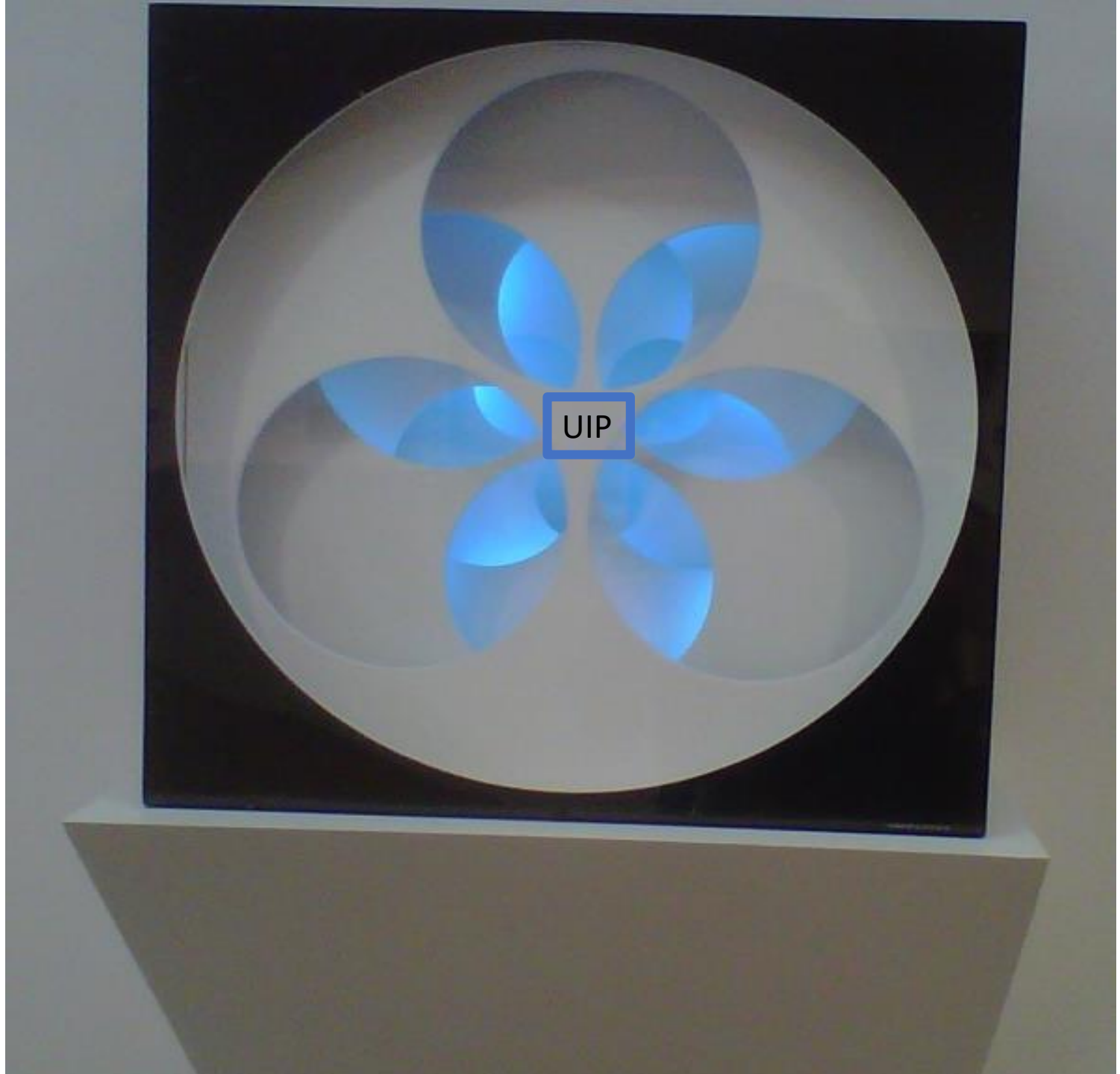
Natural evolution of IPF often seen in other ILDs

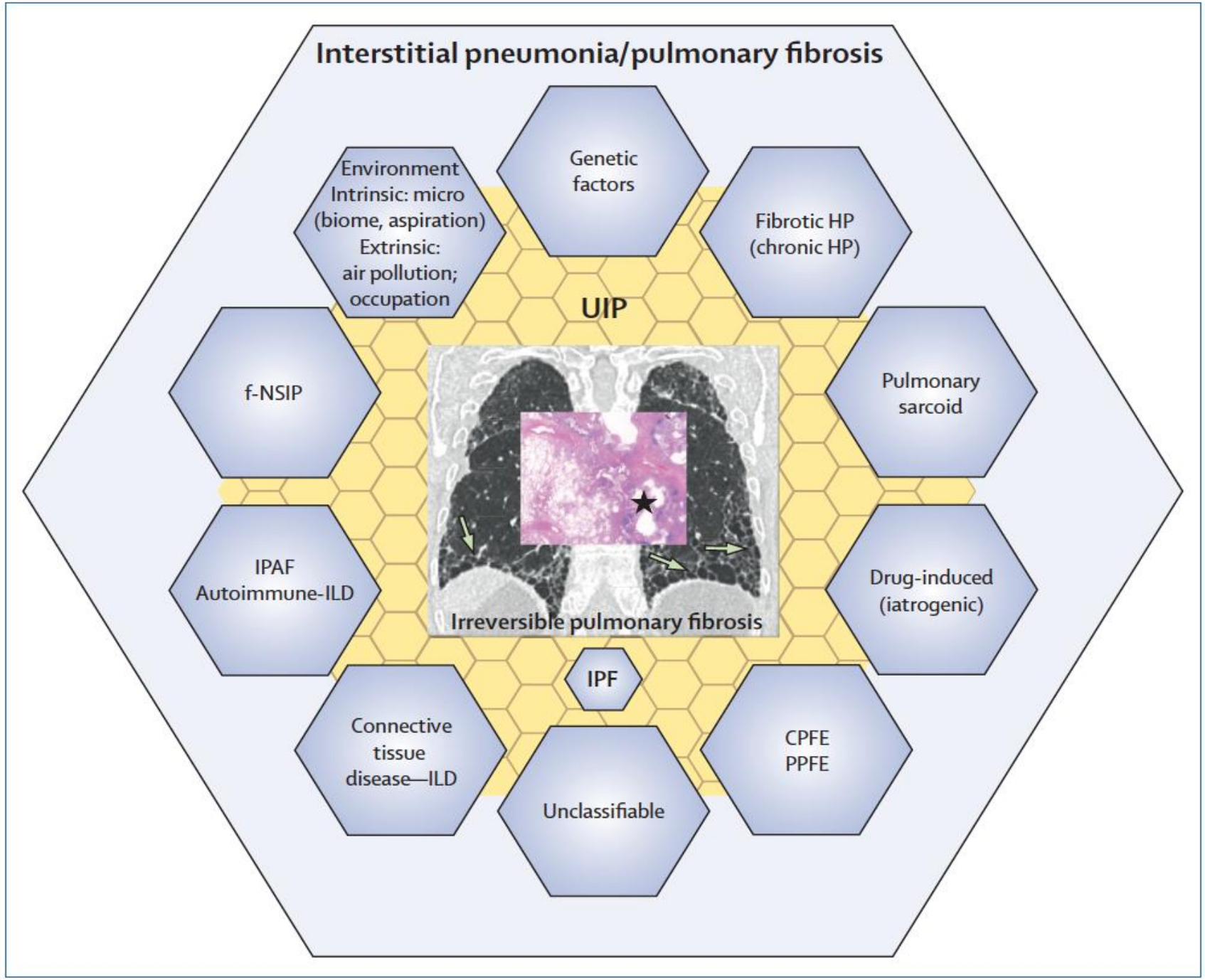


Sub-clinical disease
- Low-level symptoms
- Often denied
- Depending on exercise level of patient

A=fast decline without treatment; B=episodes of acute worsening; C=chronic progressive decline without treatment; D=slower decline without treatment; #=periods of relative stability interposed with periods of acute decline.

Ley B *et al. Am J Respir Crit Care Med* 2011;183:431–40; Cottin V *et al. Eur Respir Rev* 2014;23:106–10.


UIP

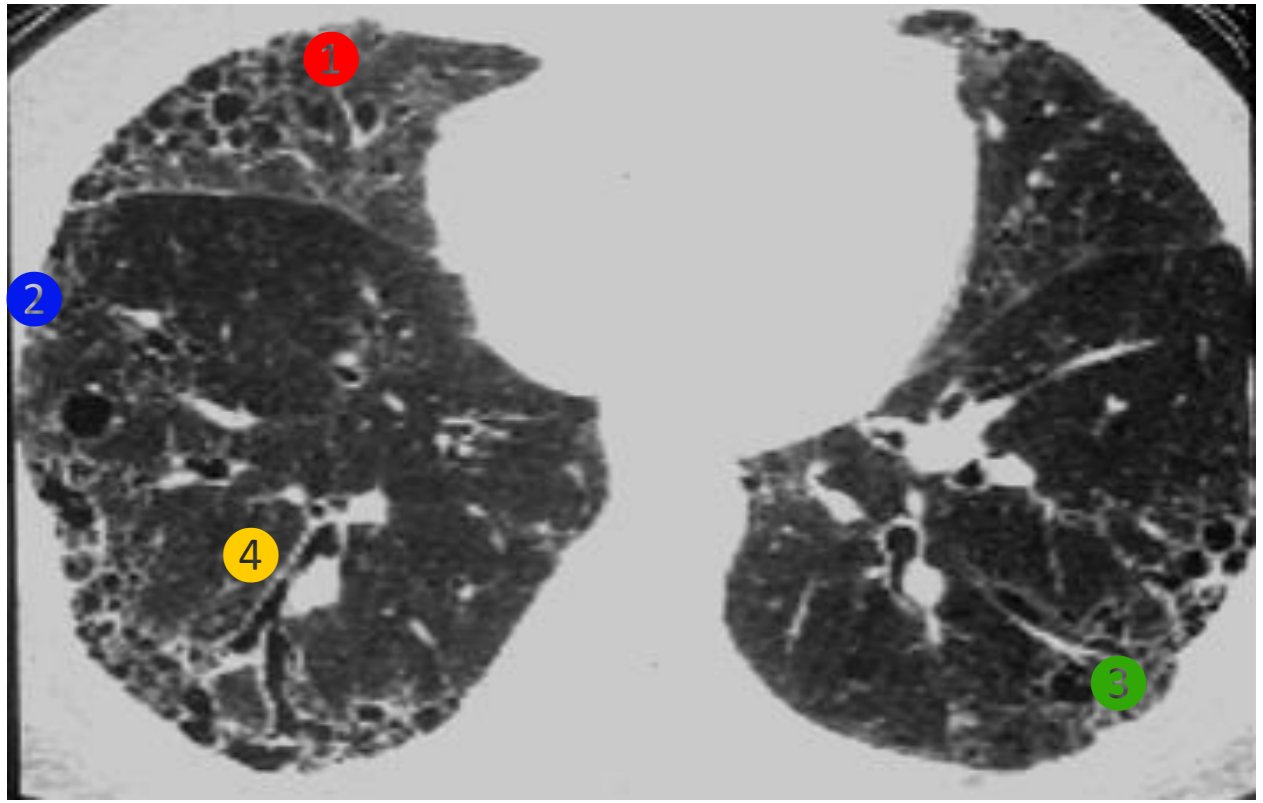


Raghu G. *Lancet Respir Med* 2019 Published Online September 14, 2019

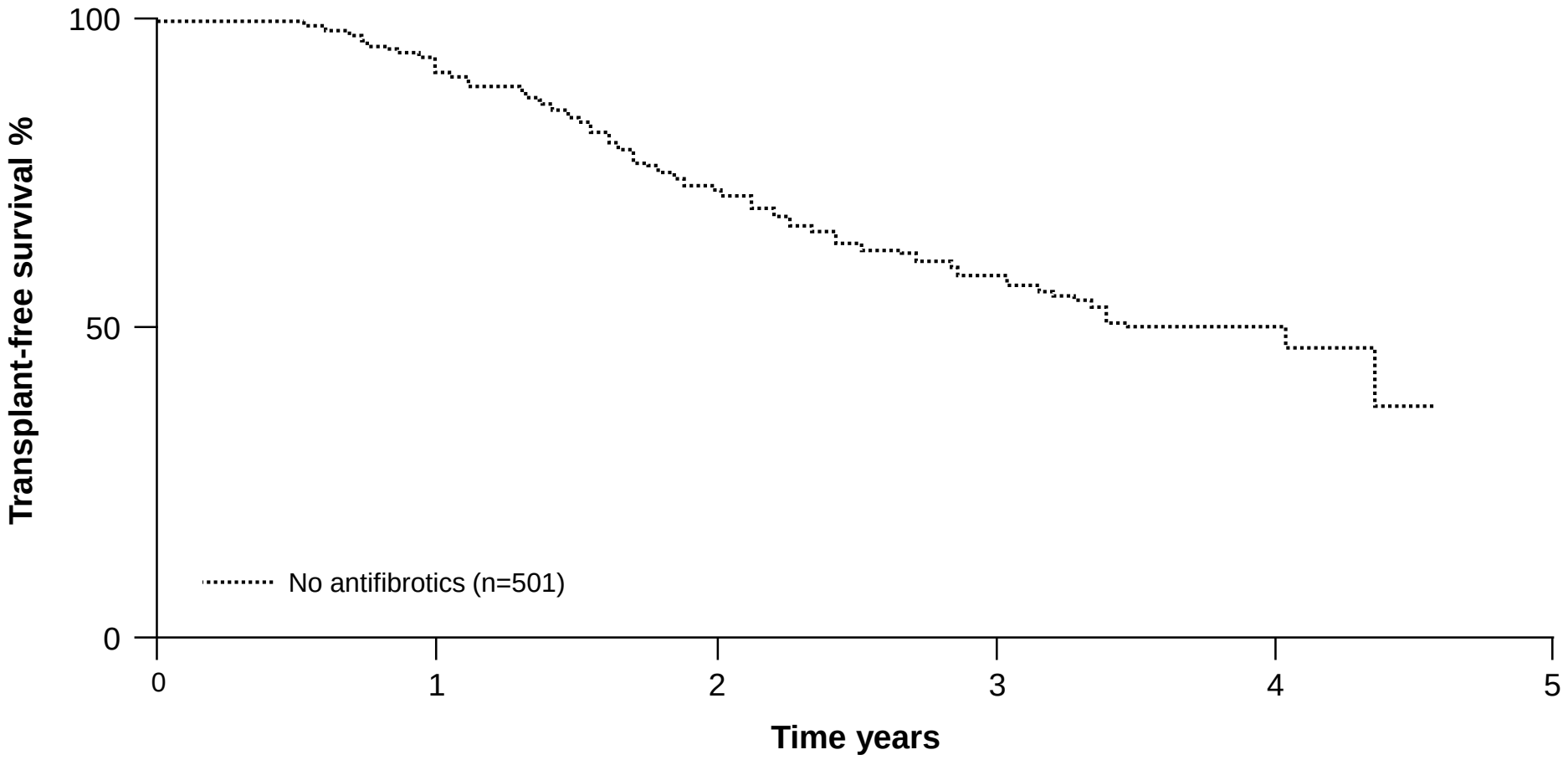
Definite UIP pattern imaging portends poor prognosis

1. Subpleural, basal predominance
2. Reticular abnormality
3. Honeycombing
4. Traction bronchiectasis

Absence of inconsistent features



Natural evolution of IPF



IPF, idiopathic pulmonary fibrosis.
Jo HE *et al. Eur Respir J* 2017;doi: 10.1183/13993003.01592-2016.

Although the clinical course is heterogeneous, the end result is the same…fibrosis

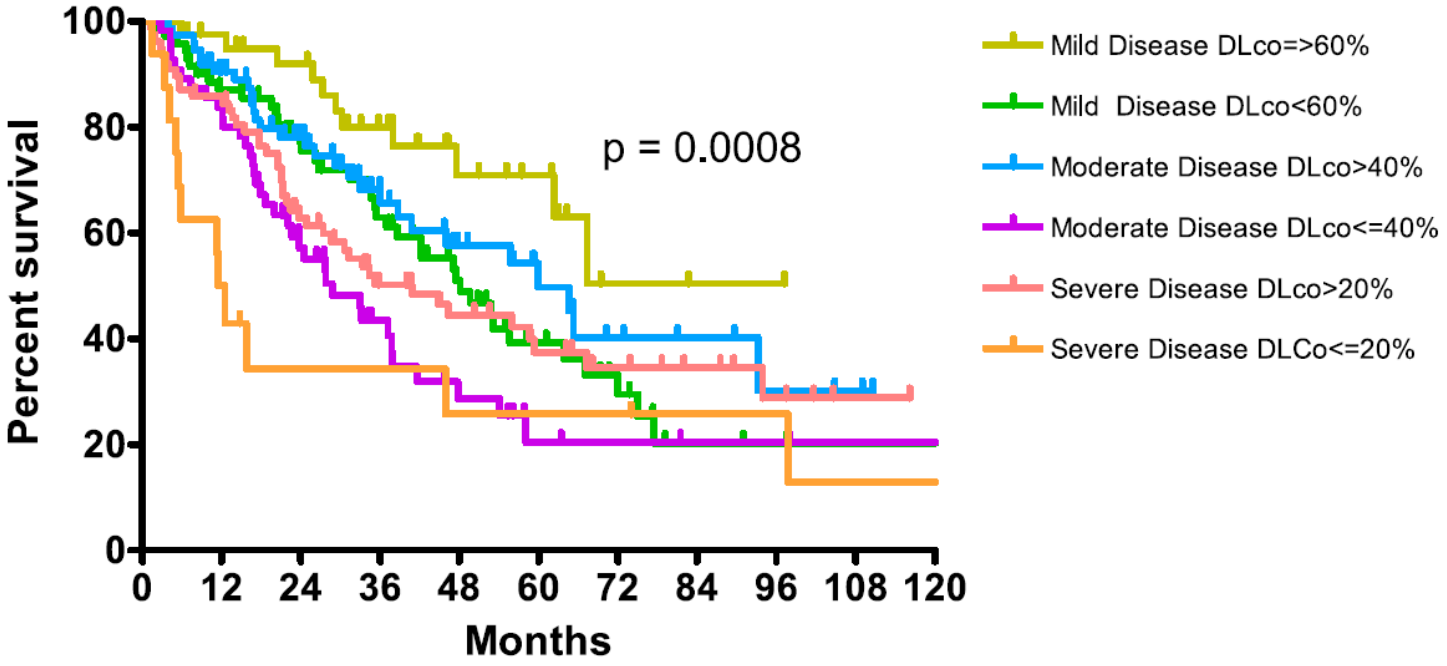


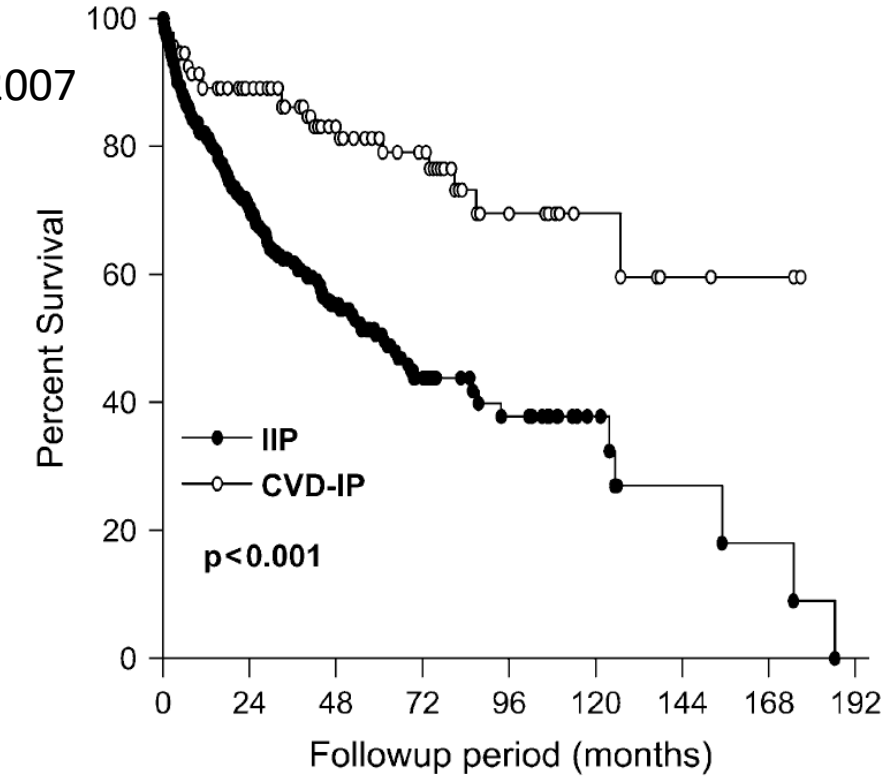
FIGURE 7. IPF survival stratified by the initial FVC % predicted (mild [≥70%], moderate [55%-69%], and severe [<55%] disease) and DLco % predicted. See Figure 2 legend for expansion of abbreviations.

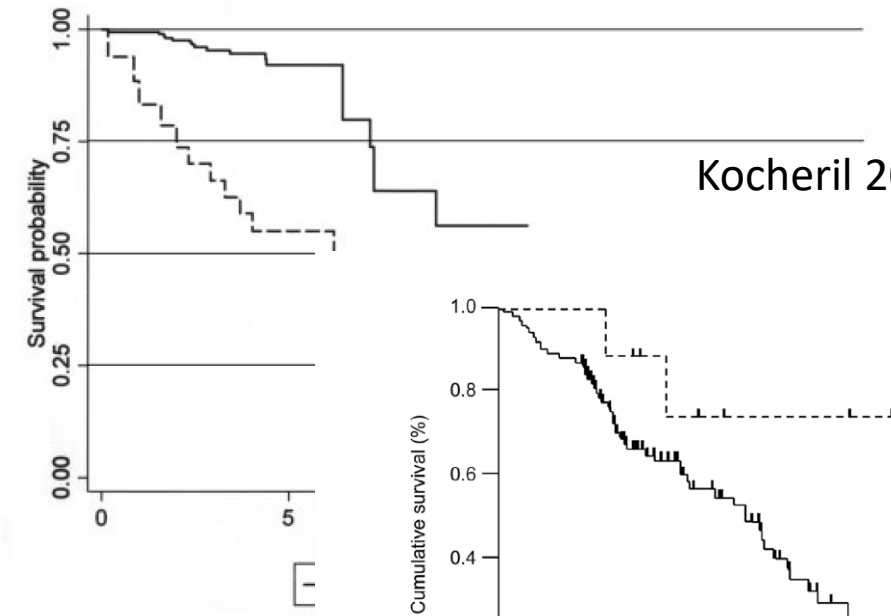
Nathan et *CHEST* 2011

What does better survival tell us?

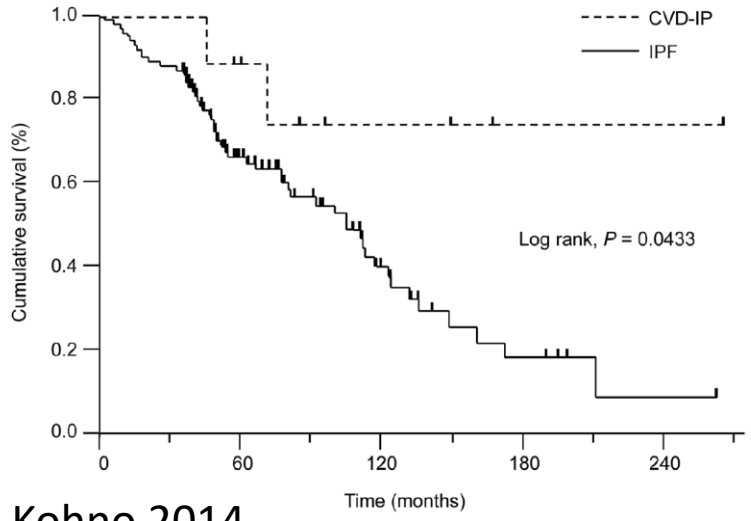
Park, Kim, Park, *et al.*: Prognosis of Fibrotic Interstitial Pneumonia

2007





Kocheril 2005



Kohno 2014

Are the Risk Factors for IPF Idiopathic?

- Age ≥60
- More extensive reticular densities
  - Probability of IPF: >80%
  - Specificity for IPF diagnosis: 96%
- White race
- Male sex
- American Indian descent
- Former smoker

Salisbury ML et al. *Respir Med*. 2016;118:88-95; Dove et al. Am Rev Respir Med 2019; Guenther A et al. *Respir Res*. 2018;19:141.

Comorbidities of patients with IPF: Are they unique?

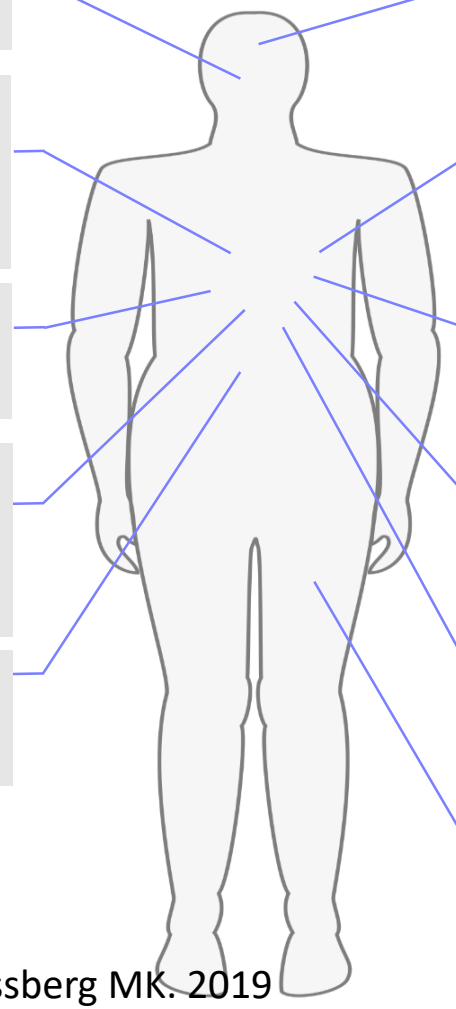
Obstructive sleep apnea
5.9%-91%

Gastroesophageal reflux disease
0%-94%

Pulmonary hypertension
3%-86%

Chronic obstructive pulmonary disease
6%-67%

Diabetes mellitus
10%-42%



Depression or anxiety
21%-49%

Pulmonary embolism
3%-6%

Congestive heart failure
4%-26%

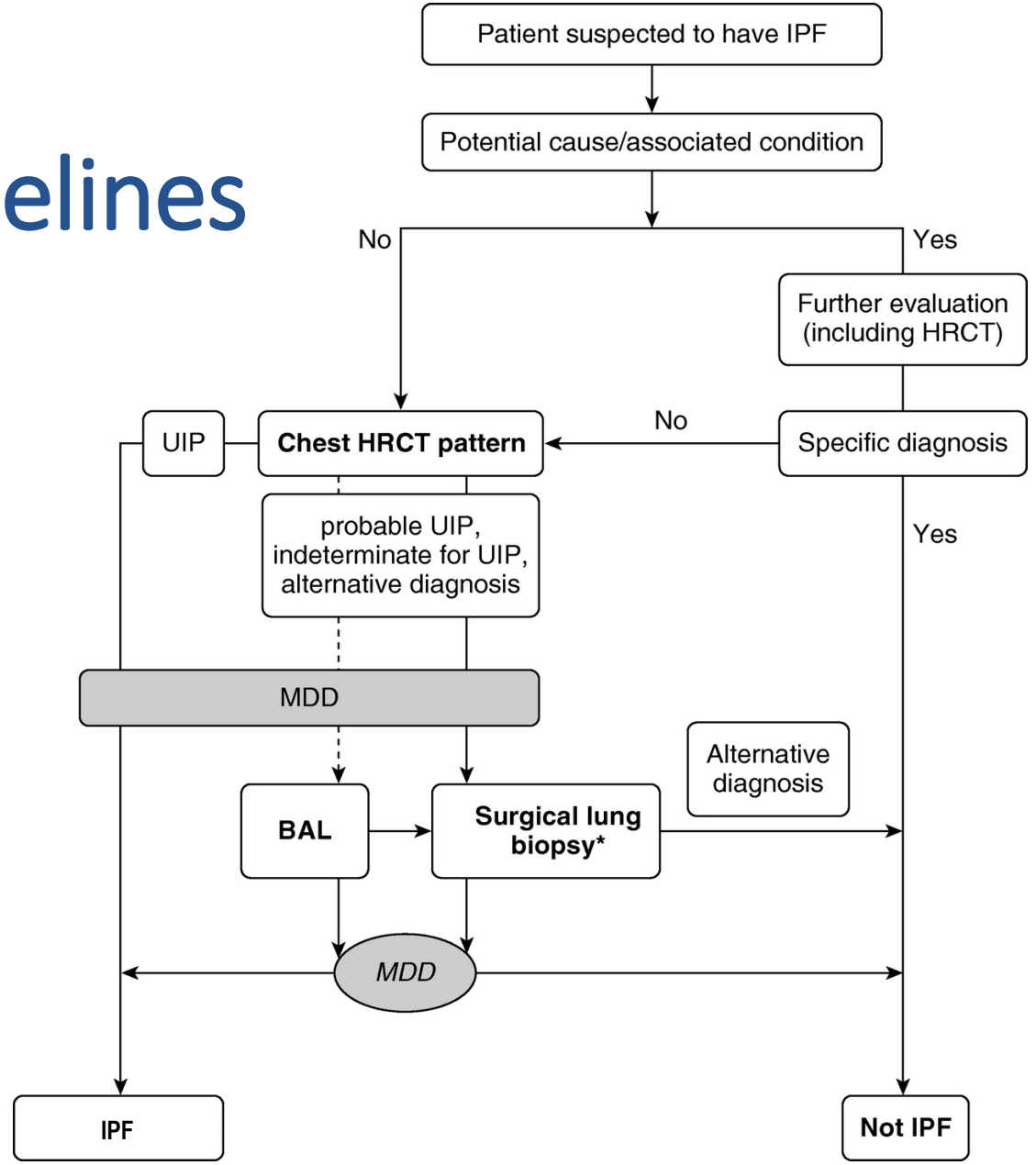
Coronary artery disease
3%-68%

Lung cancer
4%-23%

Sarcopenia prevalence poorly defined but common

King T, Nathan S. *Lancet Respir Med*. 2017;5:72-84.; Glassberg MK. 2019

IPF Diagnosis: ATS/Fleischner Guidelines 2019

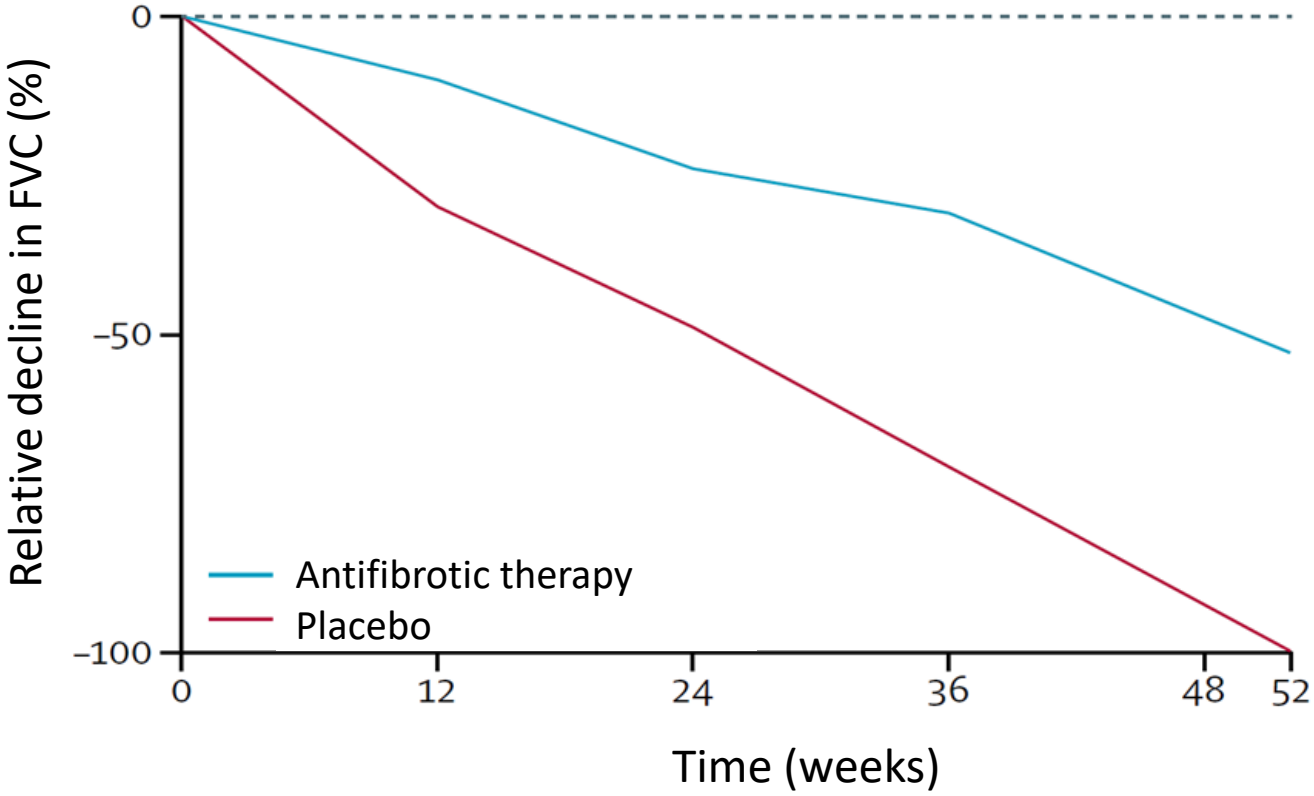


Raghu G et al. *Am J Respir Crit Care Med*. 2018;198(5):e44-e68.

Exclude known causes that eliminate the “I” in IPF

Category	Information needed
Autoimmune disease	History: joints, skin, dry eyes/mouth, Raynaud’s Exam: skin and joint changes Serologies: ANA, RF, anti-CCP, others
Chronic hypersensitivity pneumonitis	History: dampness, mold, water damage, humidifiers, hot tubs, birds, down bedding
Medications/radiation therapy	History: amiodarone, nitrofurantoin, chemotherapy, etc.
Pneumoconioses	Occupational history

Antifibrotics significantly reduce lung function decline in patients with fibrotic lung disease



IPF

Benefits are seen even in patients with more advanced disease at the time of antifibrotic initiation

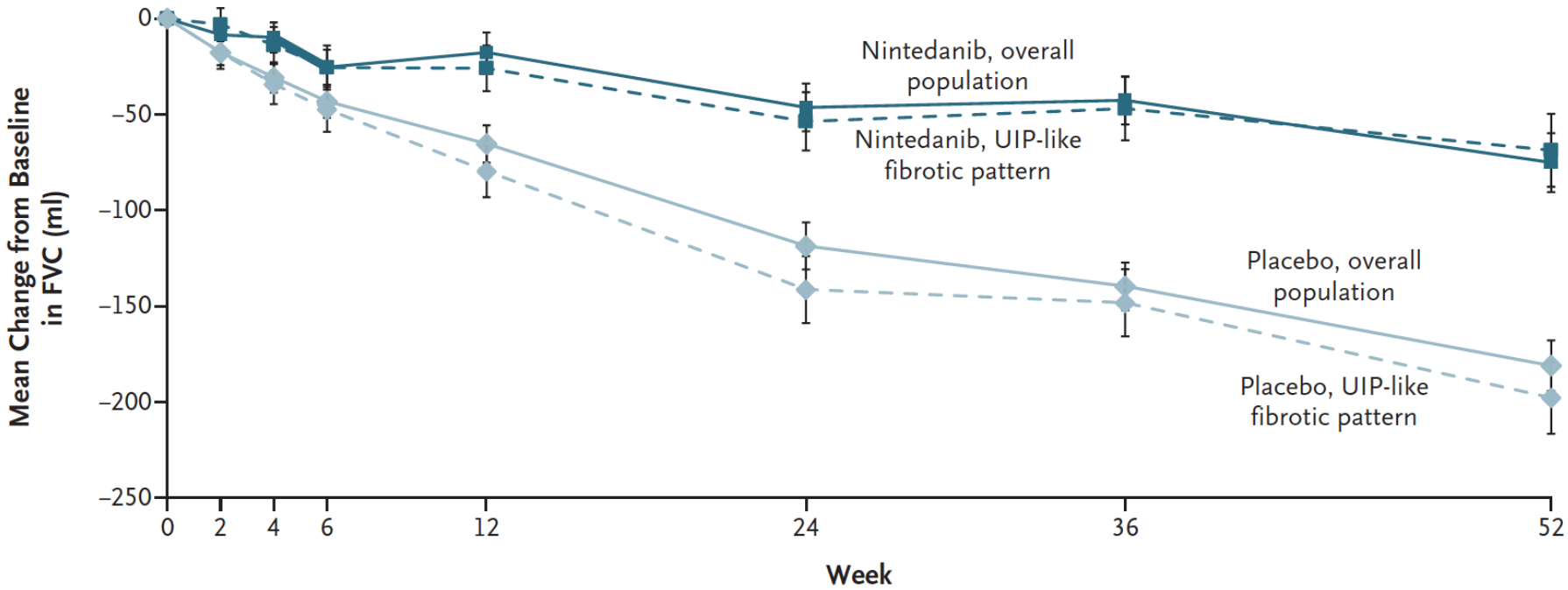
FVC, forced vital capacity.

Richeldi L *et al. Lancet* 2017;389:1941–52; Costabel U *et al. Respir Res* 2019;20:55.

Table 1. Characteristics of the Overall Population at Baseline.* InBUILD trial

Characteristic	Nintedanib (N=332)	Placebo (N=331)
Male sex — no. (%)	179 (53.9)	177 (53.5)
Age — yr	65.2±9.7	66.3±9.8
Former or current smoker — no. (%)	169 (50.9)	169 (51.1)
UIP-like fibrotic pattern on high-resolution CT — no. (%)	206 (62.0)	206 (62.2)
Criteria for disease progression in previous 24 mo — no. (%)		
Relative decline in FVC of ≥10% of predicted value	160 (48.2)	172 (52.0)
Relative decline in FVC of 5% to <10% of predicted value plus worsening of respiratory symptoms or increased extent of fibrosis on high-resolution CT	110 (33.1)	97 (29.3)
Worsening of respiratory symptoms and increased extent of fibrosis on high-resolution CT	62 (18.7)	61 (18.4)
FVC		
Mean value — ml	2340±740	2321±728
Percent of predicted value	68.7±16.0	69.3±15.2
Diffusing capacity for carbon monoxide†		
Mean value — mmol/min/kPa	3.5±1.2	3.7±1.3
Percent of predicted value	44.4±11.9	47.9±15.0
Total score on K-BILD questionnaire‡	52.5±11.0	52.3±9.8

Flaherty KR, et al. N Engl J Med 2019.



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

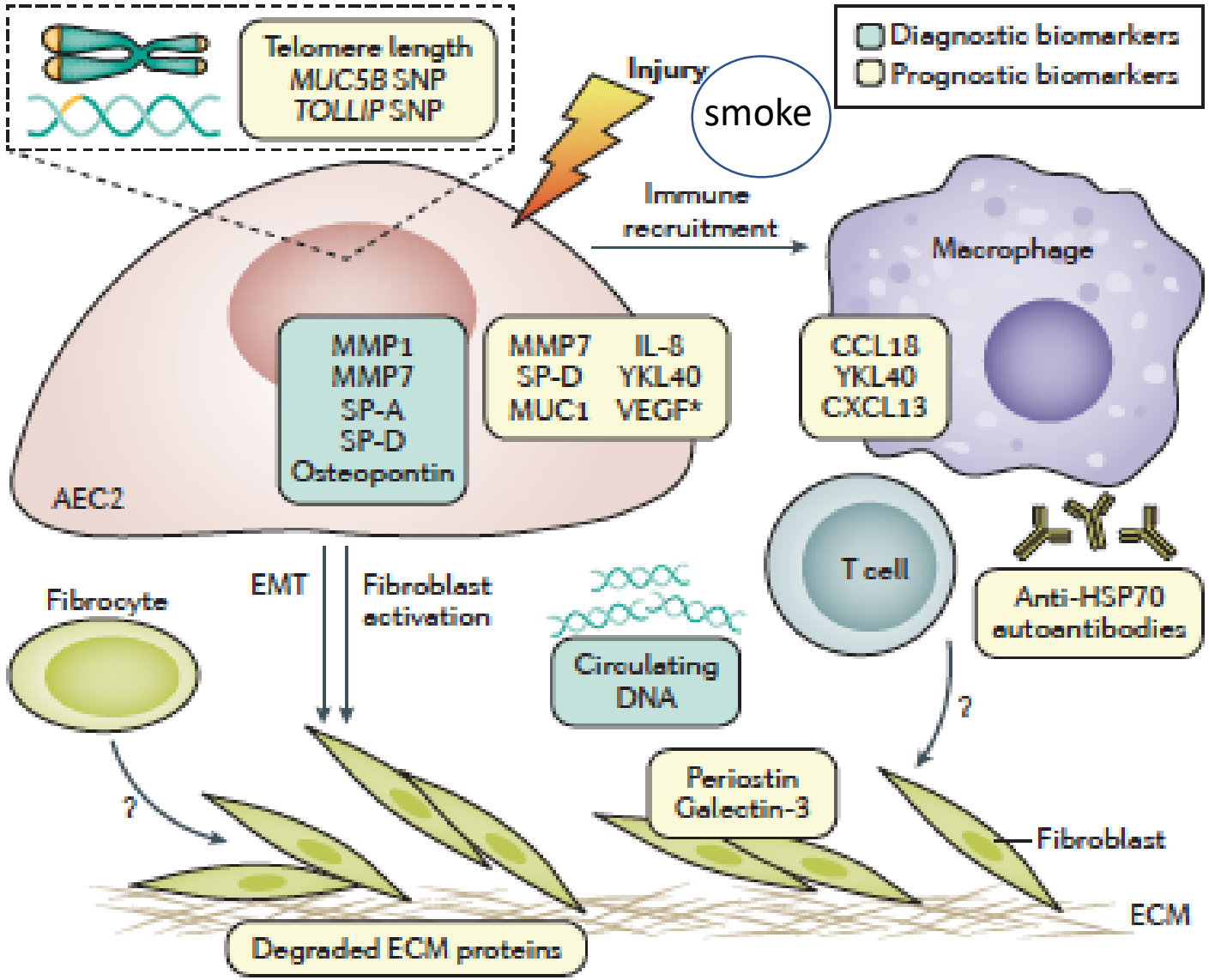
Figure 2. Decline from Baseline in Forced Vital Capacity (FVC).

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.

Maher T. et al. InJourney trial 2019

	Pirfenidone (n=127)	Placebo (n=126)
Age at screening, years	70·0 (61·0–76·0)	69·0 (63·0–74·0)
Sex		
Men	70 (55%)	69 (55%)
Women	57 (45%)	57 (45%)
Race		
White	120 (94%)	123 (98%)
Black	1 (1%)	2 (2%)
Asian	5 (4%)	0
Native American or Alaskan Native	1 (1%)	0
Other	0	1 (1%)
Body-mass index, kg/m^2	28·6 (26·5–32·9)	29·3 (26·2–32·7)
Previous surgical lung biopsy	40 (31%)	48 (38%)
Percent predicted FVC	71·0% (59·0–87·3)	71·5% (58·0–88·0)
Percent predicted DLco	44·6% (36·9–53·5)	48·0% (38·4–59·0)
Percent predicted FEV_1	75·0% (62·0–88·0)	76·0% (62·0–92·7)
FEV_1/FVC ratio	0·82 (0·78–0·86)	0·84 (0·78–0·87)
6MWD, m	372·0 (303·0–487·0)	395·0 (325·0–472·0)
Concomitant treatment with mycophenolate mofetil	23 (18%)	22 (17%)
IPAF diagnosis	15 (12%)	18 (14%)
Concomitant treatment with mycophenolate mofetil	6 (5%)	6 (5%)
Unclassifiable ILD diagnosis		
Low-confidence rheumatoid arthritis-ILD	0	0
Low-confidence systemic sclerosis-ILD	0	1 (1%)
Low-confidence undifferentiated connective tissue disease-ILD	3 (2%)	2 (2%)
Low-confidence chronic hypersensitivity pneumonitis-ILD	10 (8%)	9 (7%)
Low-confidence idiopathic non-specific interstitial pneumonia-ILD	4 (3%)	3 (2%)
Low-confidence sarcoidosis-ILD	0	0
Low-confidence myositis-ILD	0	0
Low-confidence other defined ILD	1 (1%)	0
Unclassifiable ILD	93 (73%)	93 (74%)

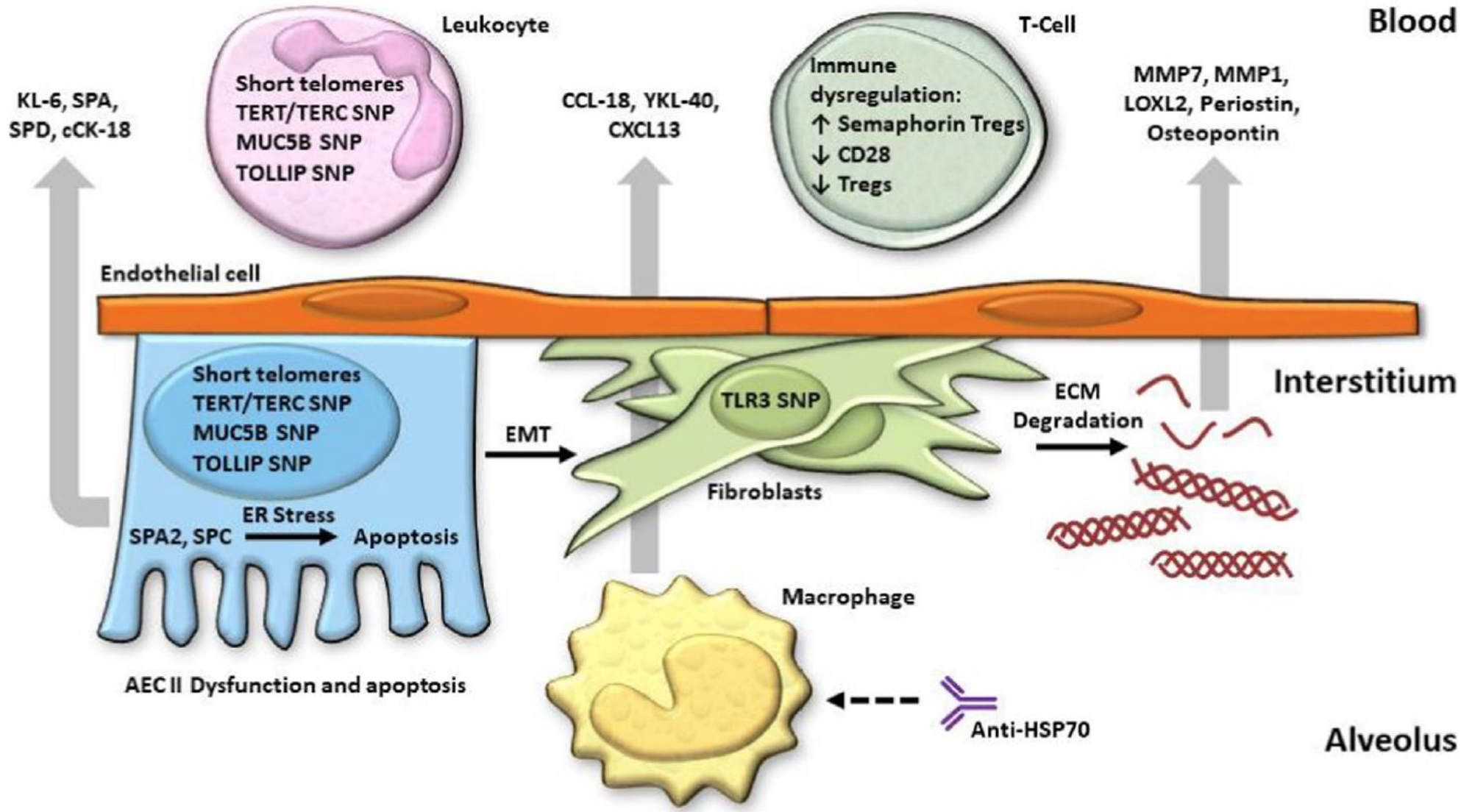
Common genes, common pathways for fibrotic lung disease



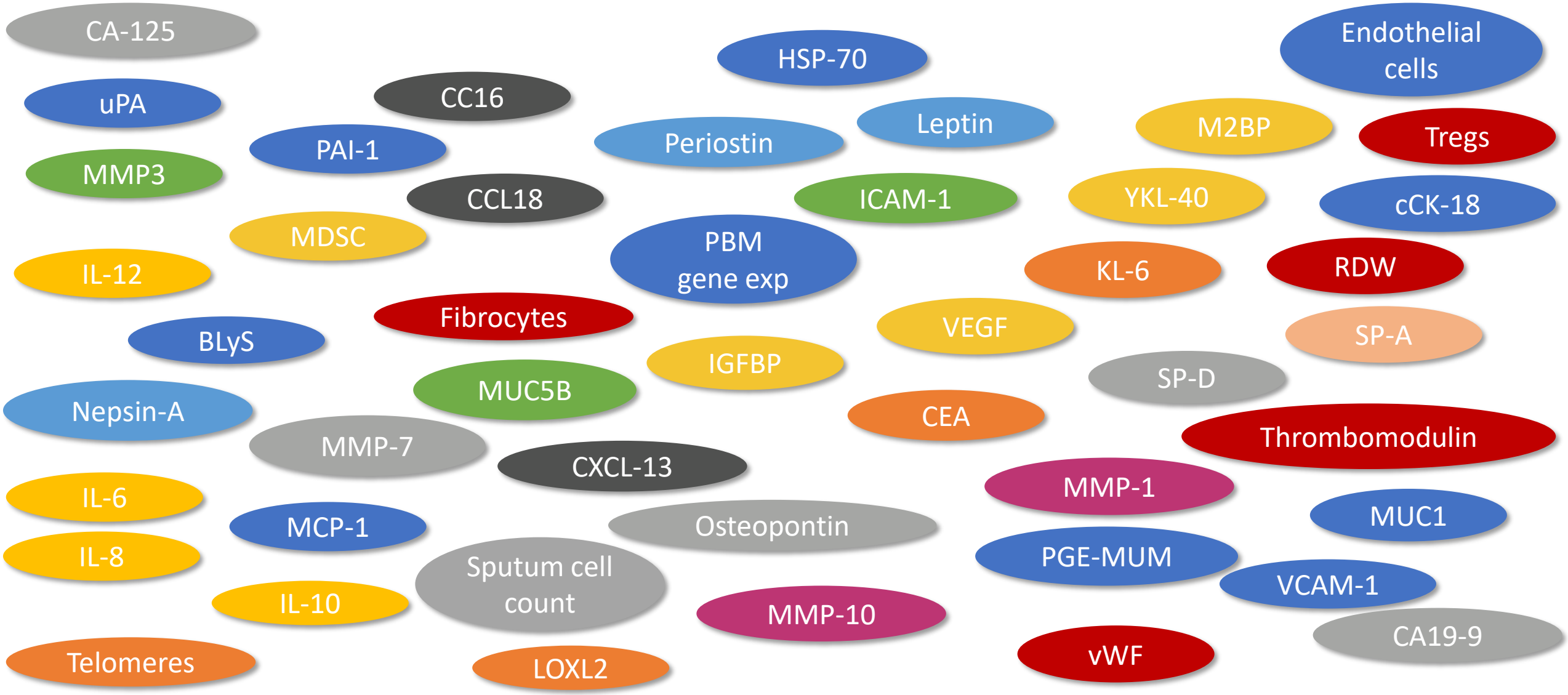
Martinez FJ et al. *Nat Rev Dis Primers*. 2017:3:1-19

Specific genetic risk factors associated with IPF

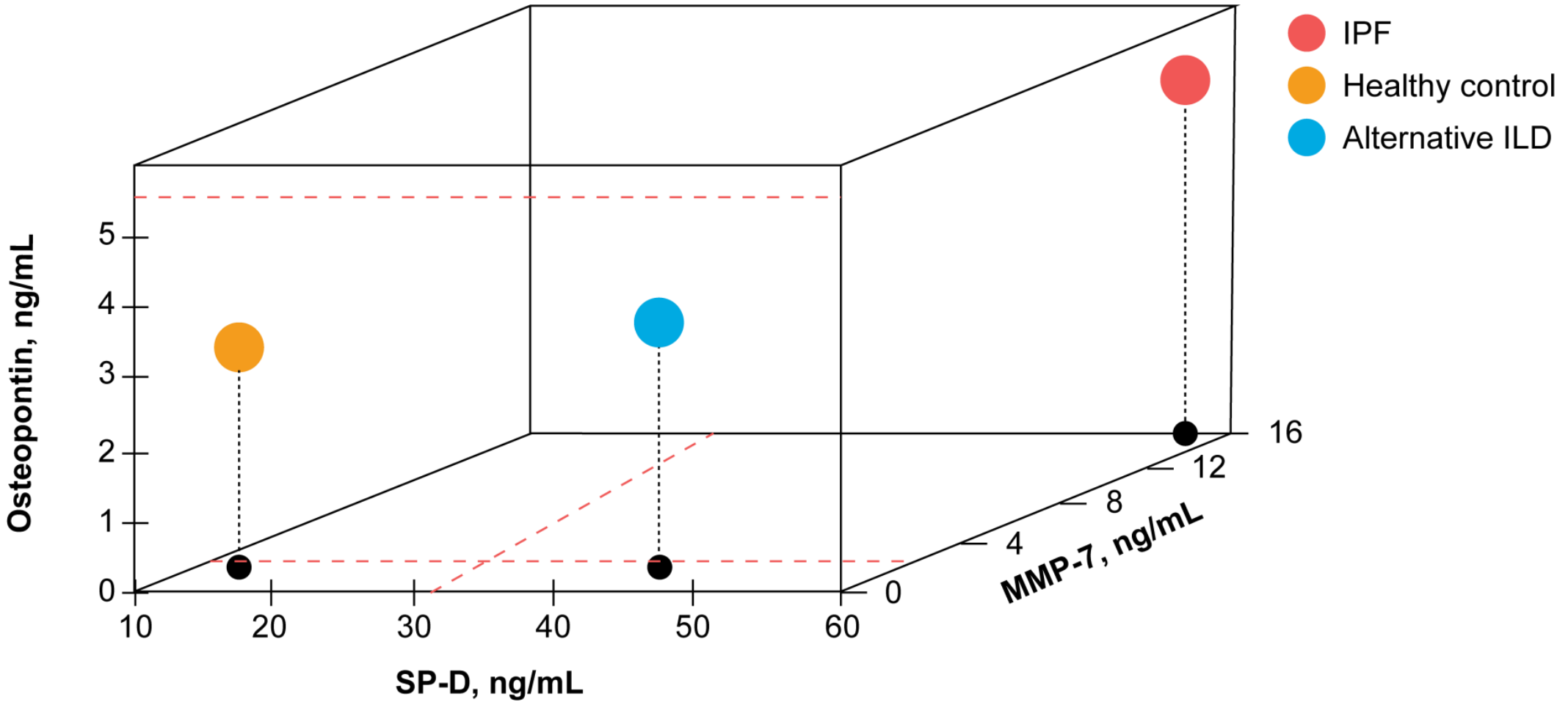
1) Mutations in *TERT, TERC, PARN, RTEL1* and others — genes involved in the maintenance of telomere length; there is aging of alveolar epithelial cells and fibroblasts with shortened telomeres (accelerated aging process)
2) Variations in some genes change cell adhesion, integrity, and cell to cell talk
3) Sequence variants in *MUC5B* may help identify individuals with early disease
5) Family history of more than one case of IPF in previous one or two generations (and biological siblings)


Blood
Leukocyte
Short telomeres
TERT/TERC SNP
MUC5B SNP
TOLLIP SNP
T-Cell
Immune
dysregulation:
↑ Semaphorin Tregs
↓ CD28
↓ Tregs
KL-6, SPA,
SPD, cCK-18
CCL-18, YKL-40,
CXCL13
MMP7, MMP1,
LOXL2, Periostin,
Osteopontin
Endothelial cell
Interstitium
Short telomeres
TERT/TERC SNP
MUC5B SNP
TOLLIP SNP
TLR3 SNP
EMT
ECM
Degradation
ER Stress
SPA2, SPC
Apoptosis
Fibroblasts
Macrophage
AEC II Dysfunction and apoptosis
Anti-HSP70
Alveolus

Biomarkers—It's a Zoo!

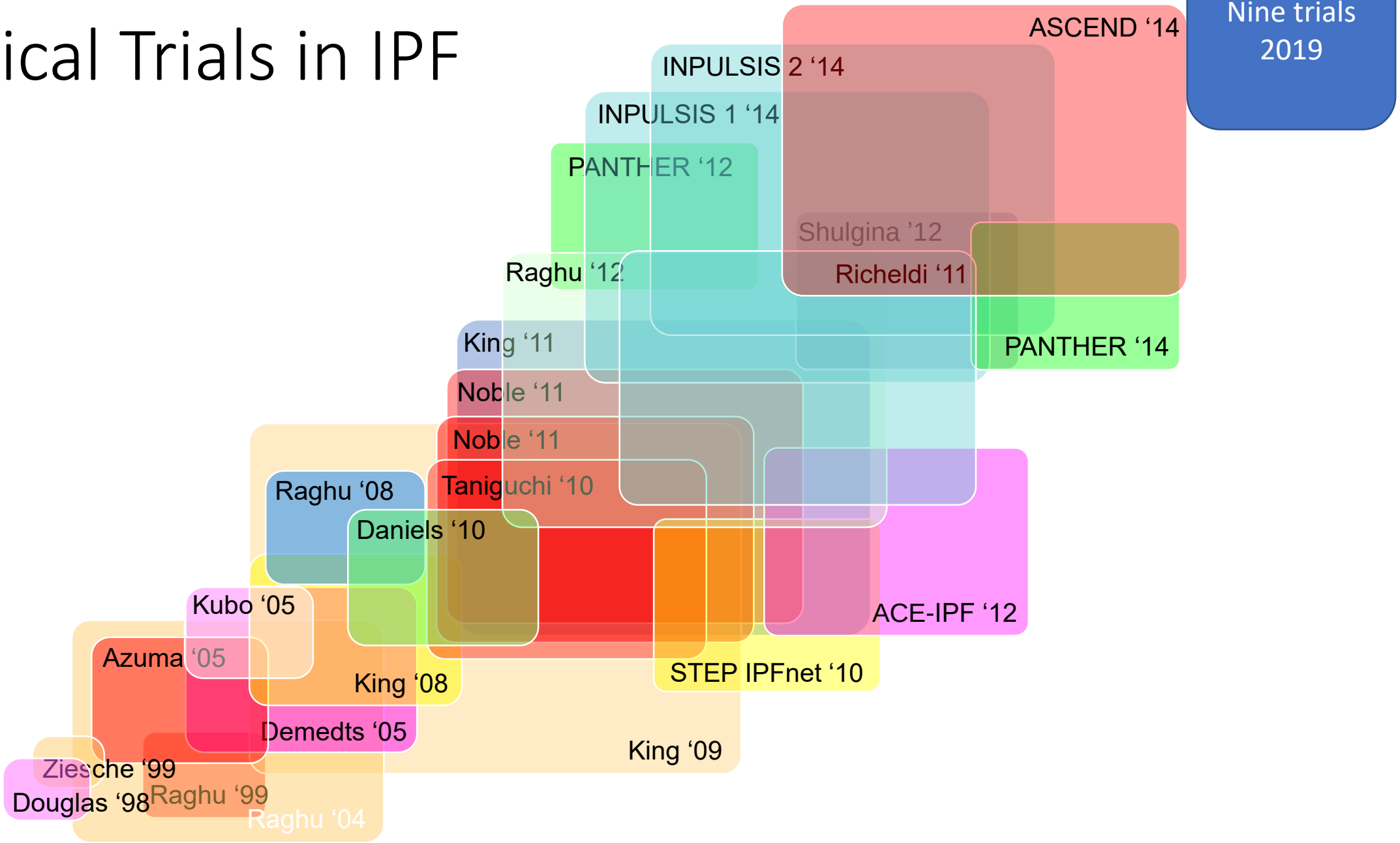


Biomarkers in the Diagnosis of IPF:
Use in Combination May Increase Accuracy, but not ready for prime time



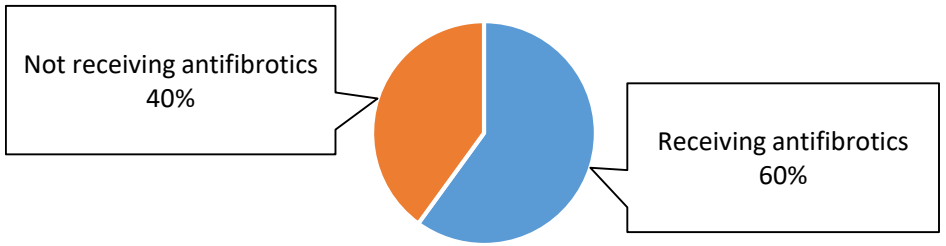
White ES et al. *Am J Respir Crit Care Med.* 2016;194 :1242-1251.

Clinical Trials in IPF

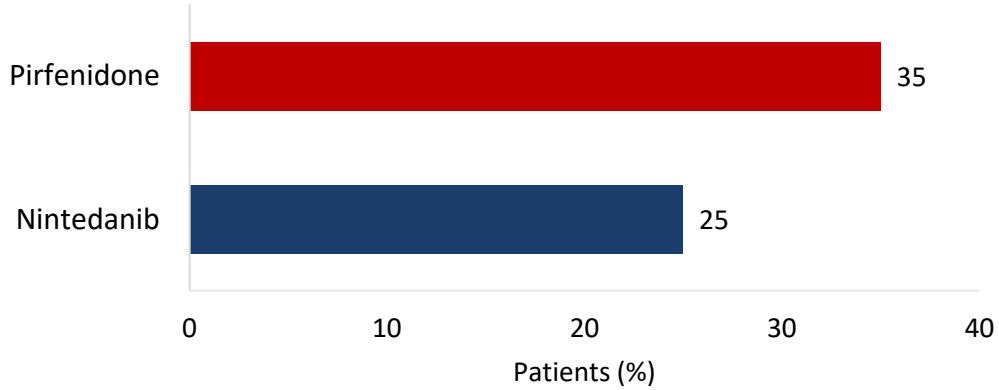


Numbers of patients currently on antifibrotic therapy

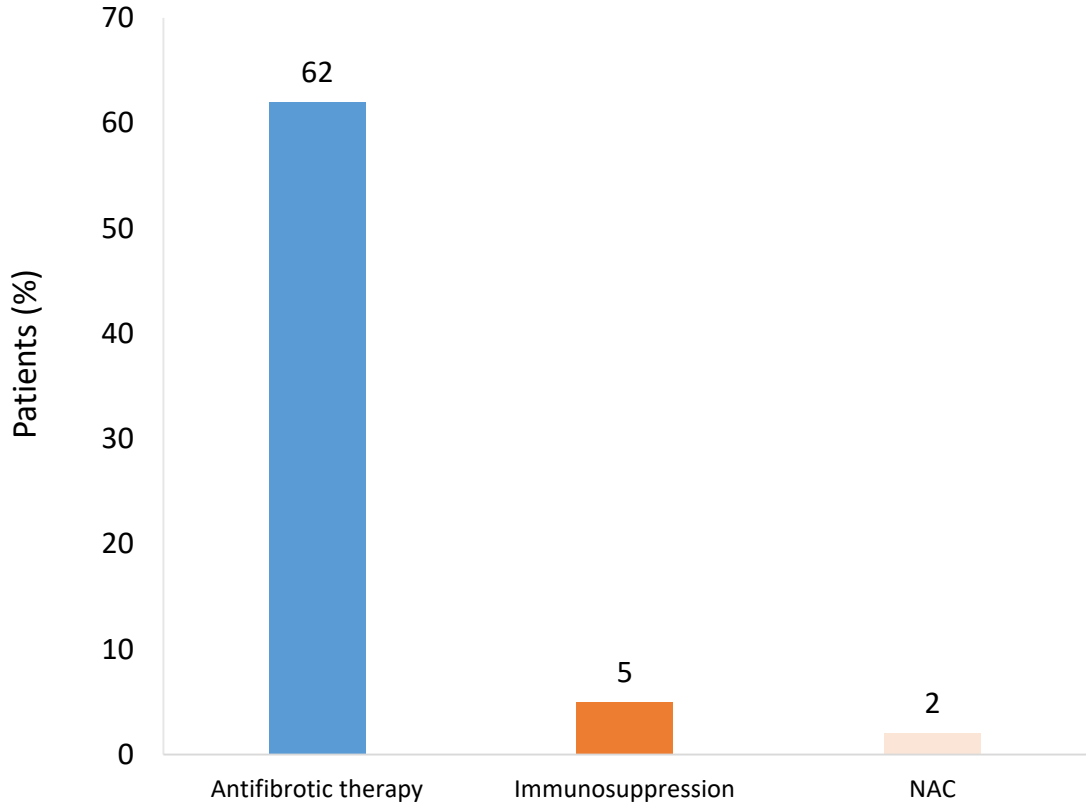
Medical therapy in patients with a confirmed IPF diagnosis in a chart review study across five European countries (n=1158)[1]



Antifibrotic usage before or at enrollment in the US IPF-PRO registry (n=662)[2]



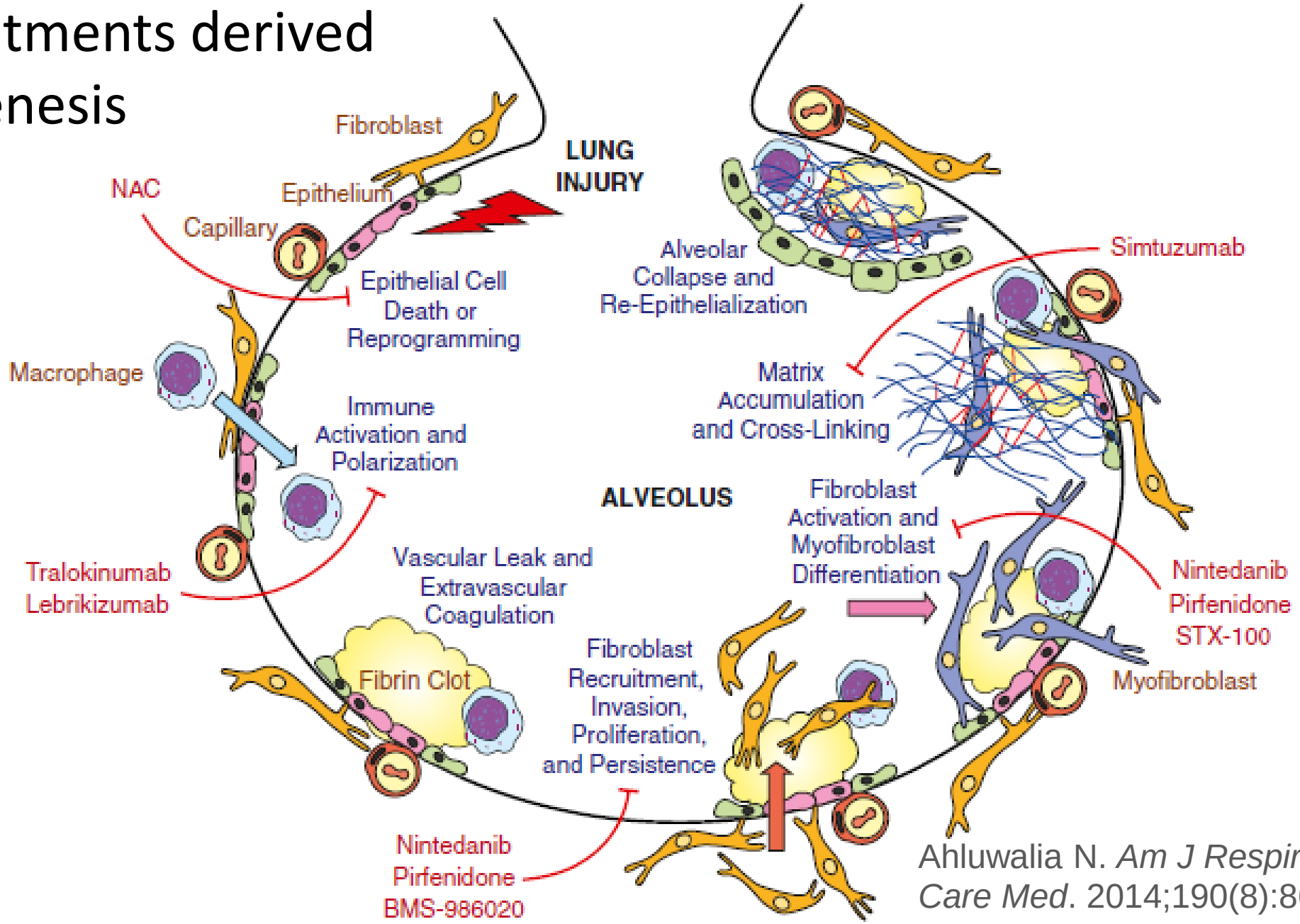
Baseline medical therapy of patients enrolled in the US PFF-PR (n=1461)[3]



IPF-PRO, Idiopathic Pulmonary Fibrosis Prospective Outcomes; NAC, N-acetylcysteine; PFF-PR, Pulmonary Fibrosis Foundation Patient Registry.

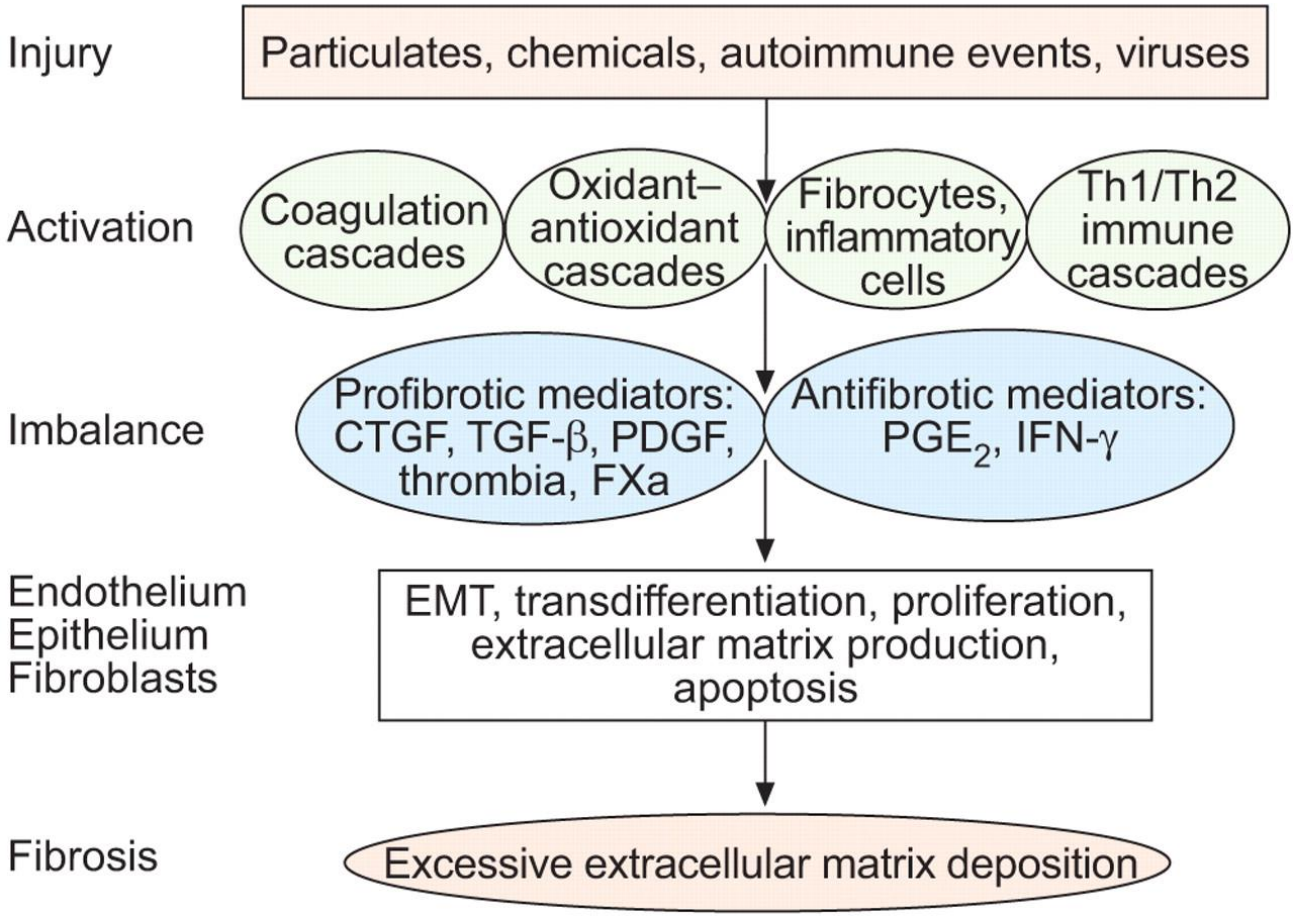
1. Maher T *et al*. *BMC Pulm Med* 2017;17:124; 2. Culver DA *et al*. Oral presentation at the CHEST Annual Meeting, San Antonio, Texas, US, October 6–10, 2018. Abstract 397A; 3. Flaherty K *et al*. *Eur Resp J* 2018;52:PA2199.

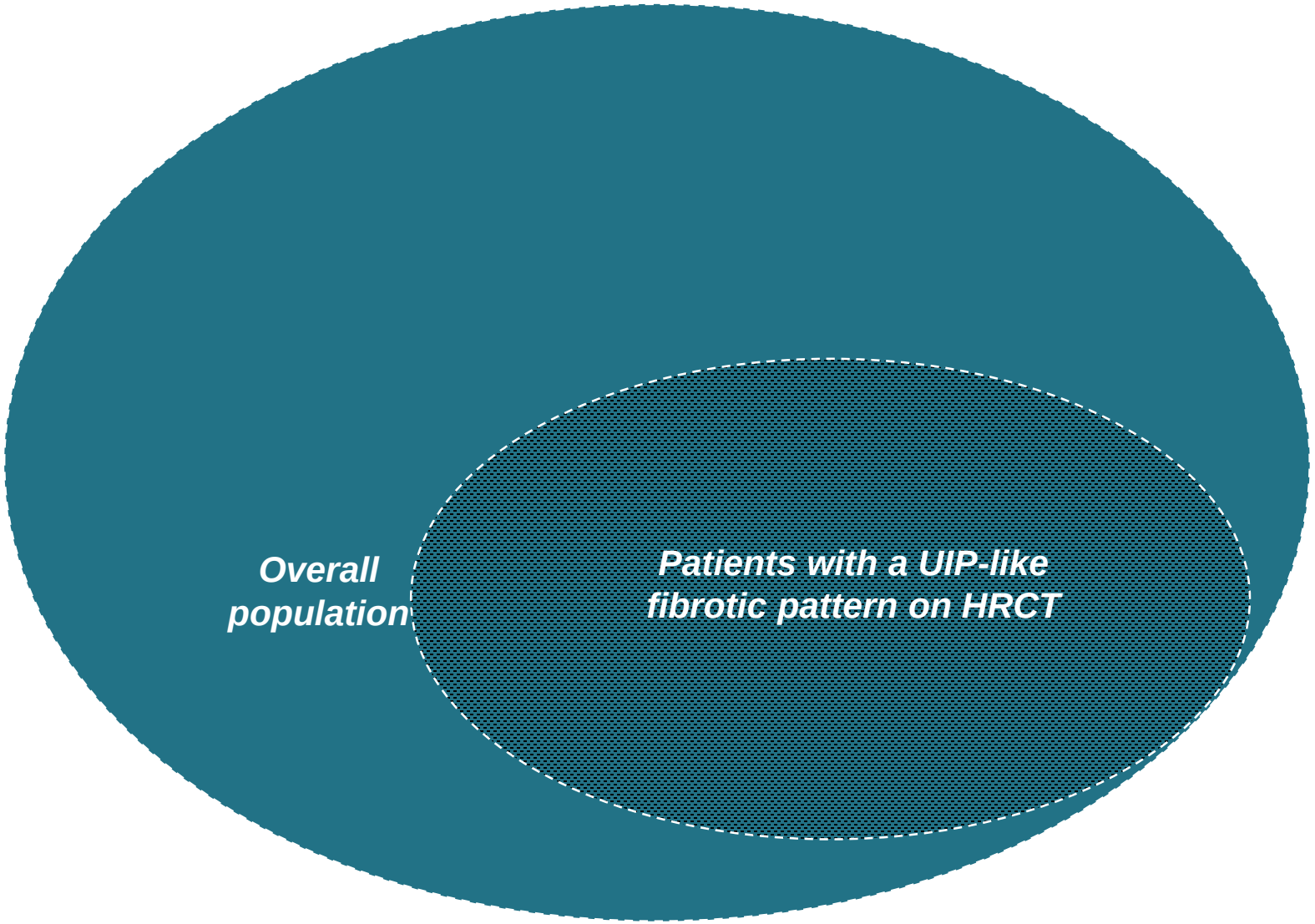
Potential treatments derived from pathogenesis



Ahluwalia N. *Am J Respir Crit Care Med*. 2014;190(8):867-878

Future targets for treatments for patients with fibrotic lung disease will forget the “I”?




Overall population
Patients with a UIP-like fibrotic pattern on HRCT

Redirect the “I” in Idiopathic

- Diligently **identify** causes of early **interstitial** lung abnormalities and not focus on a specific entity characterized by usual interstitial pneumonia of unknown cause
- Enhanced public awareness might prompt **at-risk individuals** to seek earlier medical attention for treatment of **irreversible** lung disease
- Approved drugs are safe and efficacious; they minimize/stabilize progression and **improve survival** from usual interstitial pneumonia


IT'S BREATHTAKING
PULMONARY FIBROSIS CURE RESEARCH
INVEST AND SUPPORT
VISIT: BREATHELIFE.LIFE
CHURCH annex
McDonald's
McDonald's


THE UNIVERSITY OF ARIZONA
COLLEGE OF MEDICINE PHOENIX