

# **Management of ILA: Clinician's perspectives**

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Jin Woo Song

Univ. of Ulsan College of Medicine

Asan Medical Center, Seoul, Republic of Korea

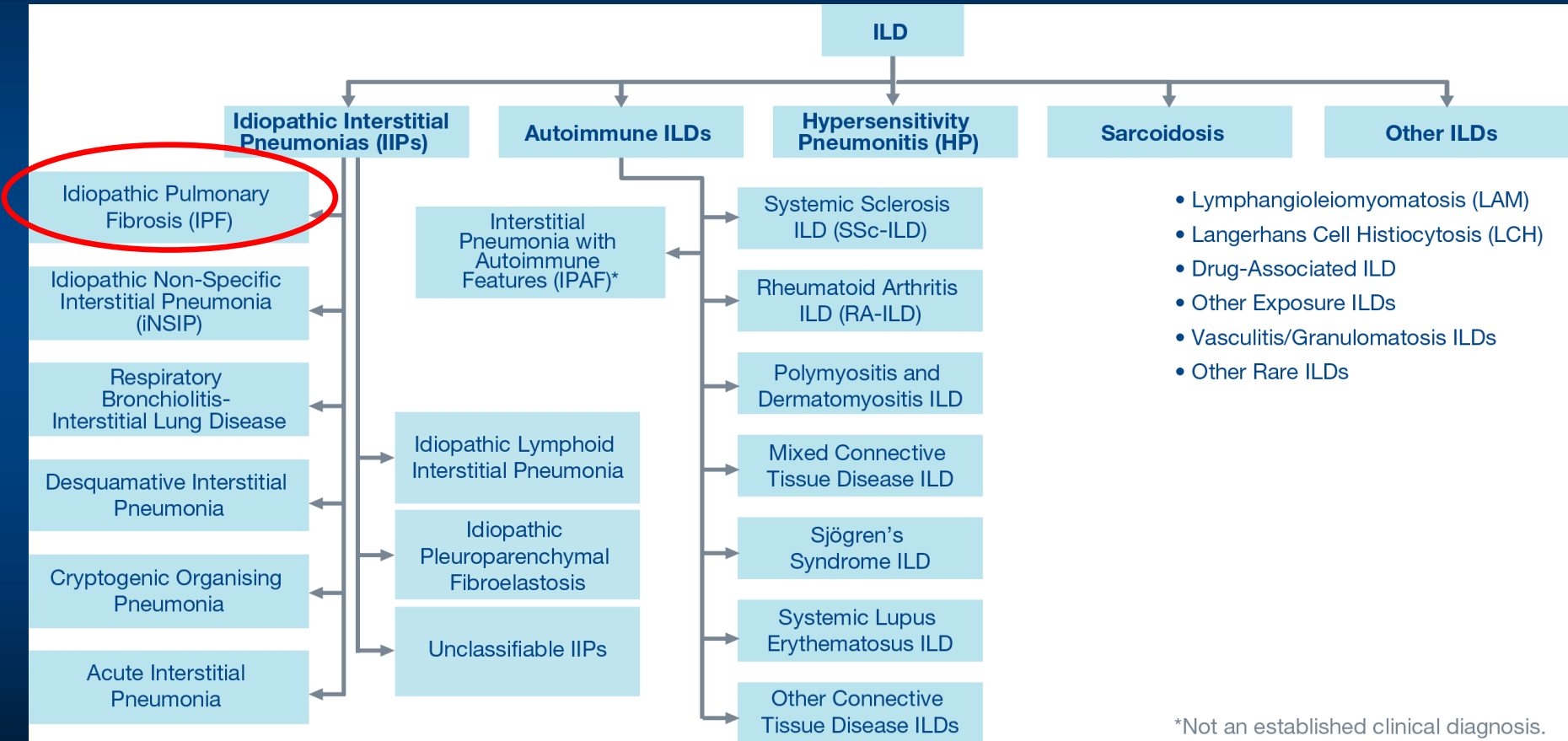
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- Interstitial lung abnormalities
  - Definition
  - Clinical implication
  - Risk factor for progression
  - Management

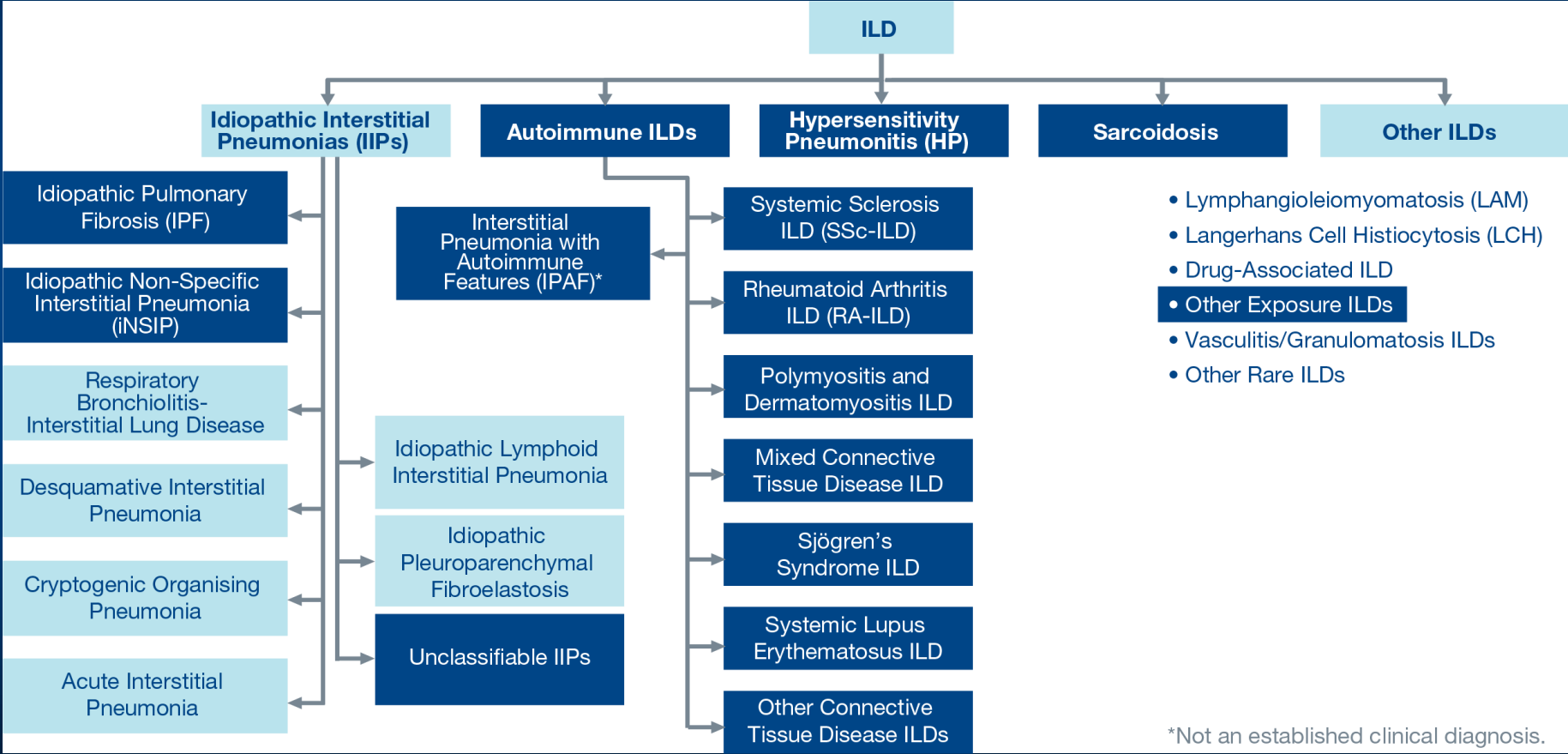
# Interstitial Lung Disease

- Diverse group of disorders that involve the distal pulmonary parenchyma
- Patients typically present with
  - Progressive dyspnea and cough
  - Abnormal pulmonary physiology
  - Abnormal CXR and/or HRCT
- Idiopathic or associated with systemic diseases (CTDs) or environmental exposures

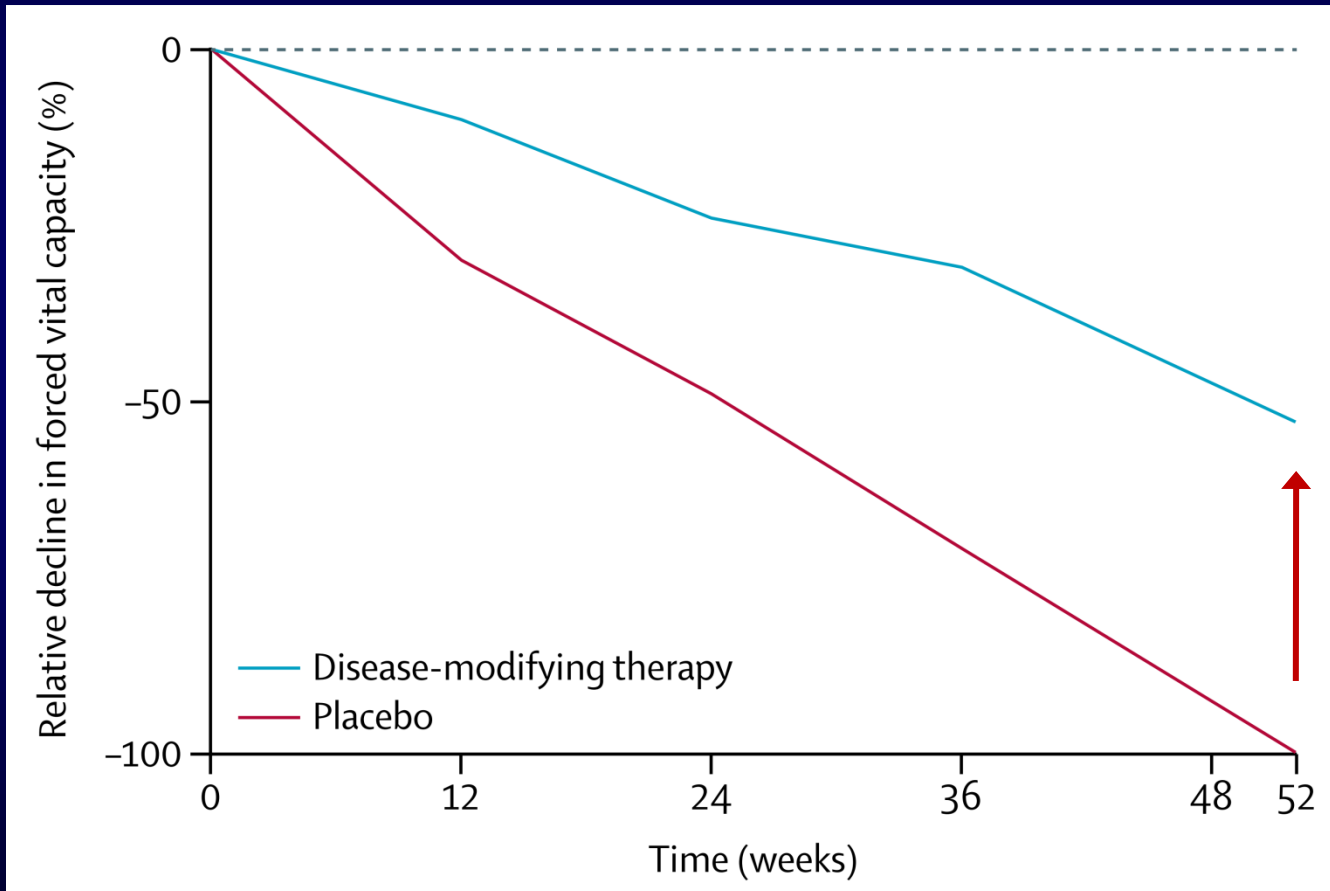
# ILD: classification



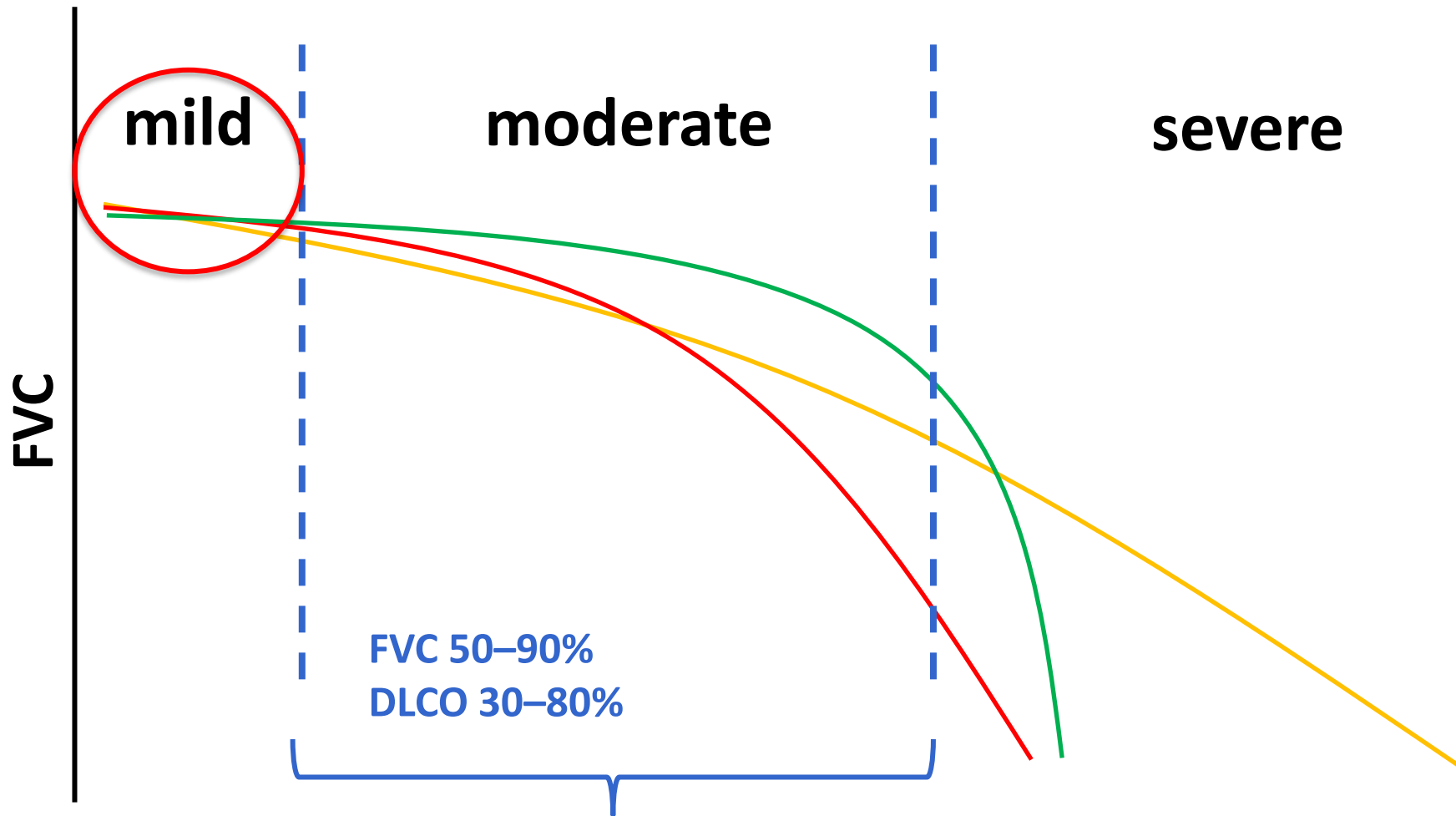
# Types of ILD likely to have a progressive fibrosing phenotype



# Effect of disease modifying therapy on lung function decline



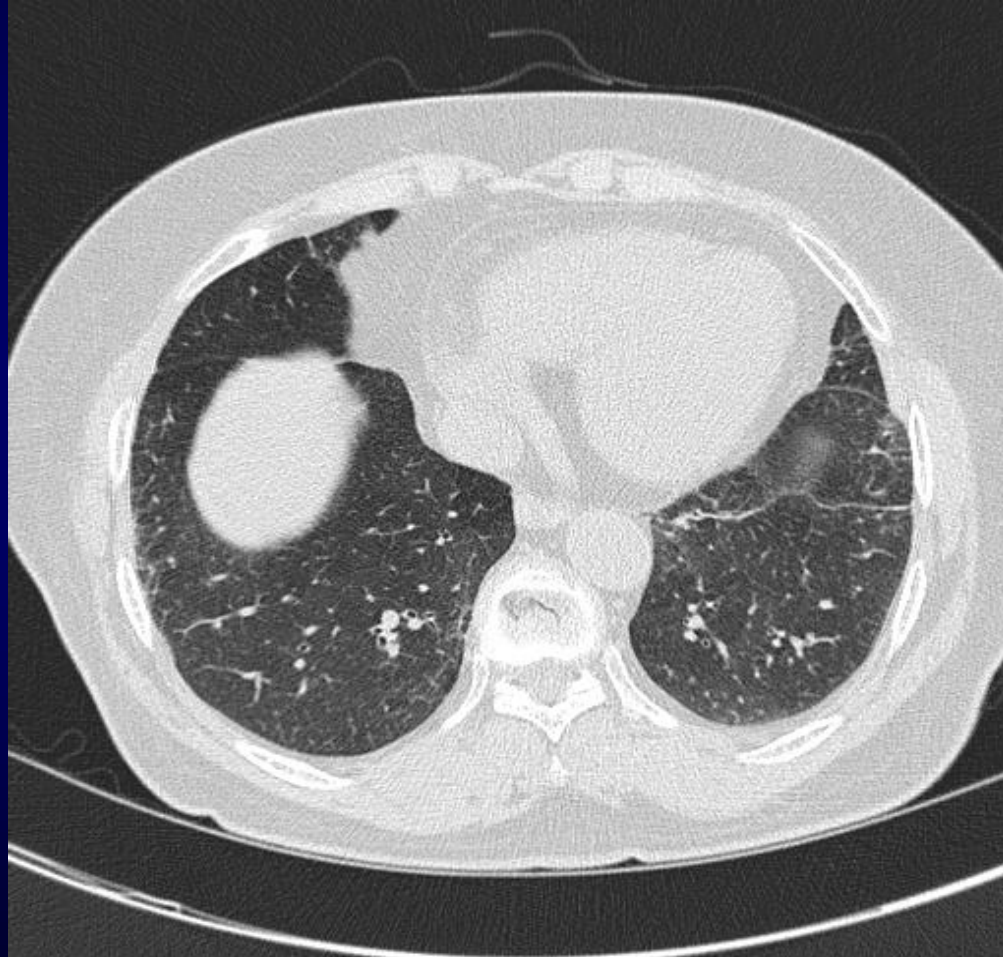
# Fibrosing ILD - clinical trial spectrum



Typical clinical trials spectrum  
Typical reimbursement spectrum

# Early ILD: visual assessment

Interstitial lung abnormalities (ILA)



Nondependent changes  $\geq$  5% of lung



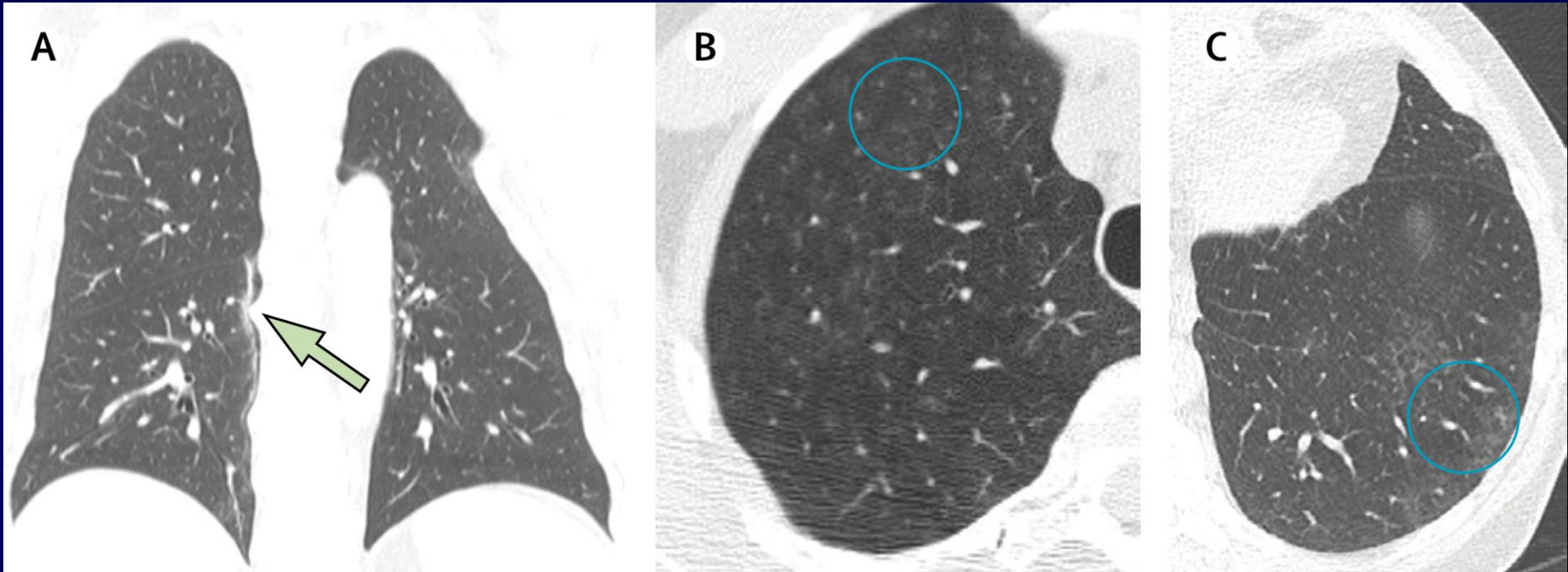
# Interstitial lung abnormalities detected incidentally on CT: a Position Paper from the Fleischner Society

*Hiroto Hatabu\*, Gary M Hunninghake, Luca Richeldi, Kevin K Brown, Athol U Wells, Martine Remy-Jardin, Johnny Verschakelen, Andrew G Nicholson, Mary B Beasley, David C Christiani, Raúl San José Estépar, Joon Beom Seo, Takeshi Johkoh, Nicola Sverzellati, Christopher J Ryerson, R Graham Barr, Jin Mo Goo, John H M Austin, Charles A Powell, Kyung Soo Lee, Yoshikazu Inoue, David A Lynch†*

## What are interstitial lung abnormalities (ILAs)?

- Incidental identification of non-dependent abnormalities, including ground-glass or reticular abnormalities, lung distortion, traction bronchiectasis, honeycombing, and non-emphysematous cysts
- Involving at least 5% of a lung zone (upper, middle, and lower lung zones are demarcated by the levels of the inferior aortic arch and right inferior pulmonary vein)
- In individuals in whom interstitial lung disease is not suspected

# What are not ILAs ?



Focal paraspinal fibrosis

Centrilobular nodularity

Unilateral

# What are not ILAs ?

## *Imaging findings restricted to:*

- Dependent lung atelectasis
- Focal paraspinal fibrosis in close contact with thoracic spine osteophytes (figure 2A)
- Smoking-related centrilobular nodularity in the absence of other findings (figure 2B)
- Mild focal or unilateral abnormality (figure 2C)
- Interstitial oedema (eg, in heart failure)
- Findings of aspiration (patchy ground-glass, tree in bud; figure 2C)

## *Preclinical and clinical identification:*

- Preclinical interstitial abnormalities identified during screening of high-risk individuals (eg, those with rheumatoid arthritis, scleroderma, occupational exposure, familial interstitial lung disease)
- Findings in patients with known clinical interstitial lung disease

# 간질성 폐이상(ILA) : 의의

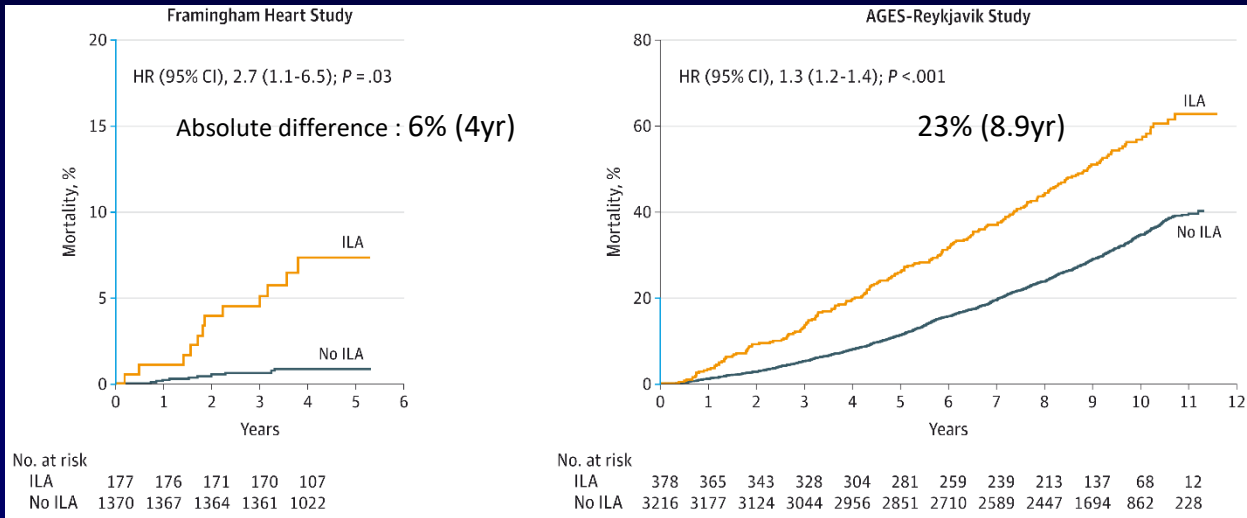
코호트	대상자	환자수	유병률	나이	진행	사망위험
COPDGene	흡연자	2416	8%	64	NA	1.8
MILD	흡연자	692	4%	60	20% (2yr)	NA
NLST	흡연자	884	10%	62	20% (2yr)	NA
ECLIPSE	흡연자	1670	9%	64	NA	1.4
DLCST	흡연자	1990	17%	60	NA	2.0

# Clinical impacts of ILA

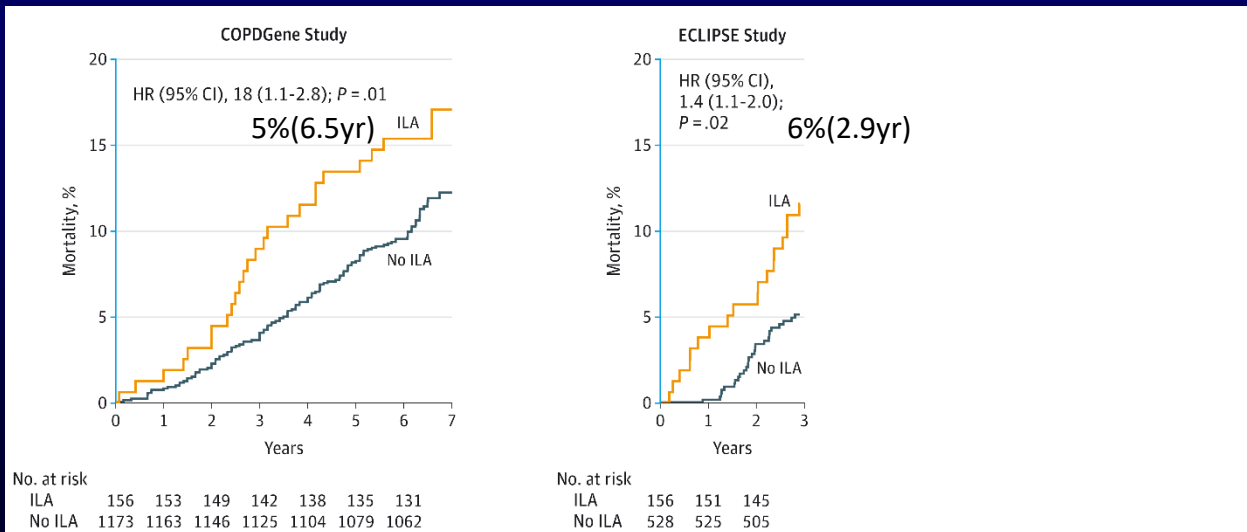
- More respiratory symptoms (Cough, SOB)
- More restrictive lung deficit (OR 2.3)
- Reduced 6MWD (OR 1.9)
- Worsening self-reported health and functional status (OR 0.66-0.72)
- Increased risk of development of clinical ILD/IPF
- Higher mortality (HR 1.3-2.7)

# Association Between Interstitial Lung Abnormalities and All-Cause Mortality

General population



Smokers



# Mortality, ILA, and cause of death for the AGES-Reykjavik Study

	No. (%) <sup>a</sup>			
	ILA	Indeterminate	No ILA	Overall
No. of participants	378	1726	3216	5320
Deaths				
Total	115 (100)	382 (100)	468 (100)	965
Cardiovascular <sup>b</sup>	48 (42)	161 (42)	204 (44)	413
Cancer <sup>c</sup>	29 (25)	111 (29)	151 (32)	291
Respiratory <sup>d</sup>	15 (13)	22 (6)	20 (4)	57
Pulmonary fibrosis	7	1	0	8
Other	8	21	20	49
Other <sup>e</sup>	23 (20)	88 (23)	93 (20)	204

# ILA in other respiratory disease

- Lung cancer: development and mortality
- ARDS: development and mortality
- COPD: AE and lung function

# Interstitial Lung Abnormalities and Lung Cancer Risk in the National Lung Screening Trial

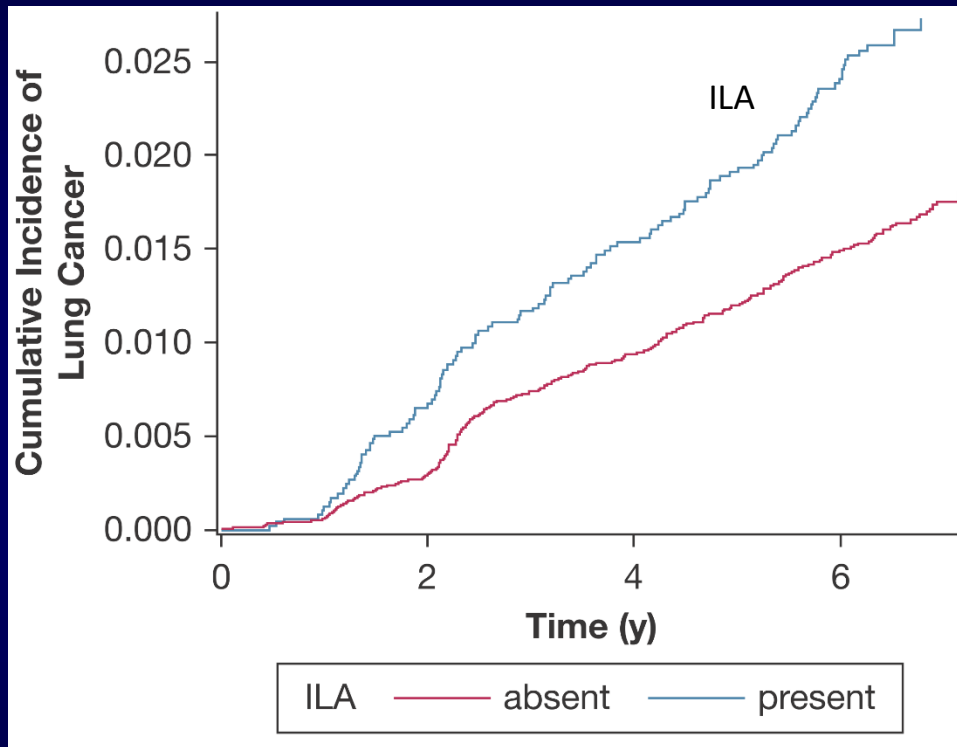


Stacey-Ann Whittaker Brown, MD, MPH; Maria Padilla, MD; Grace Mhango, MPH; Charles Powell, MD; Mary Salvatore, MD; Claudia Henschke, PhD, MD; David Yankelevitz, MD; Keith Sigel, MD, PhD; Juan P. de-Torres, MD; and Juan Wisnivesky, MD, DrPH

- NLST: 25,041 participants with CT images
- ILA in 20.2%
  - defined as evidences of reticular/reticulonodular op., honeycombing, fibrosis, or scarring on baseline CT

Characteristics	No ILA (n=19,988)	ILA (N=5,053)	P-value
Age, y	60 (57-64)	61 (58-66)	<0.01
Female	8,035 (40)	2,311 (46)	<0.01
Current smokers	9,503 (48)	2,505 (50)	0.01
Total pyrs	48 (39-66)	48 (39-66)	NS
FVC, % pred.	86 (75-97)	84 (71-96)	<0.01

# Cumulative lung cancer incidence based on the presence of ILAs on baseline CT scan



Study Arm	Model 1 Adjusted IRR (95% CI)	Model 2 Adjusted IRR (95% CI)	Model 3 Adjusted HR (95% CI)	Model 4 Adjusted HR (95% CI)
ILA vs no ILA	1.33 (1.07-1.65)	1.39 (1.11-1.74)	1.51 (1.13-2.03)	1.58 (1.17-2.15)

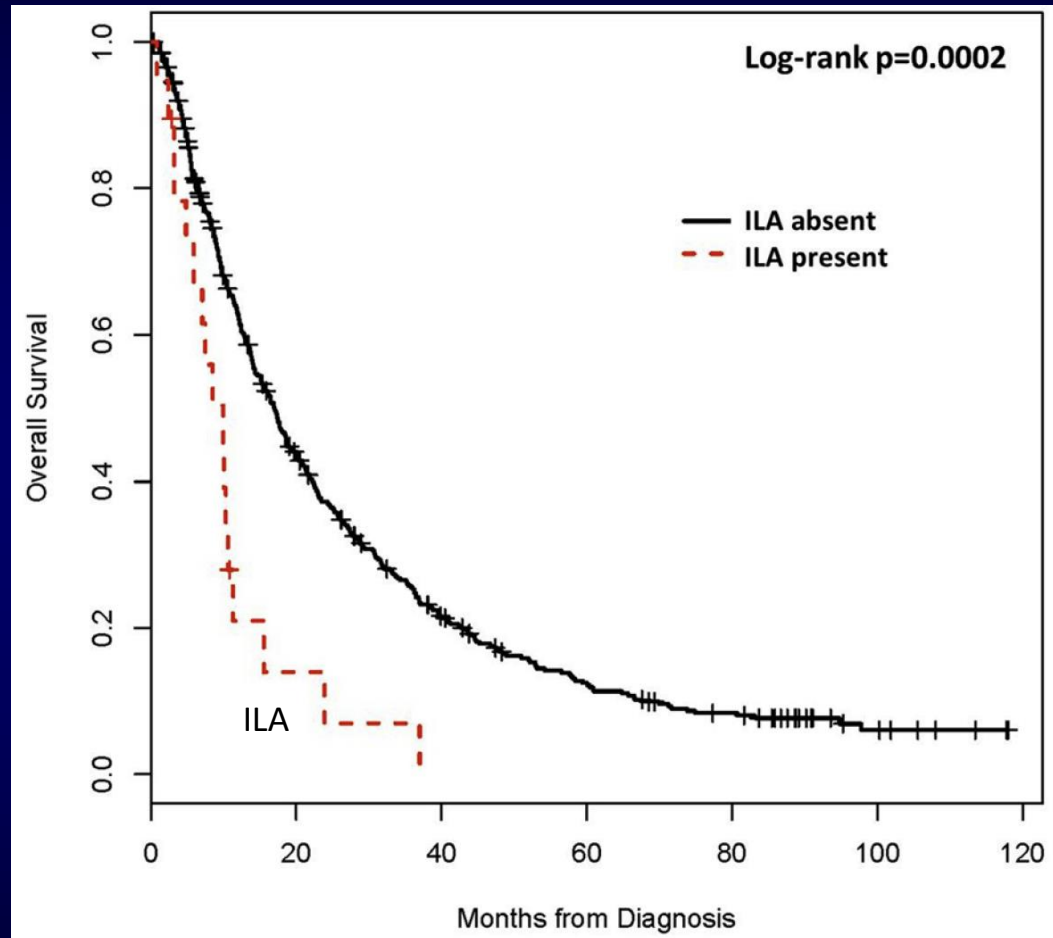
# Interstitial lung abnormality in stage IV non-small cell lung cancer: A validation study for the association with poor clinical outcome

Tetsuro Araki<sup>a,b,\*</sup>, Suzanne E. Dahlberg<sup>c</sup>, Tomoyuki Hida<sup>a</sup>, Christine A. Lydon<sup>d</sup>, Michael S. Rabin<sup>d</sup>, Hiroto Hatabu<sup>a</sup>, Bruce E. Johnson<sup>d</sup>, Mizuki Nishino<sup>a,b</sup>

- 484 patients with stage IV NSCLC
  - ILA in 3.9%

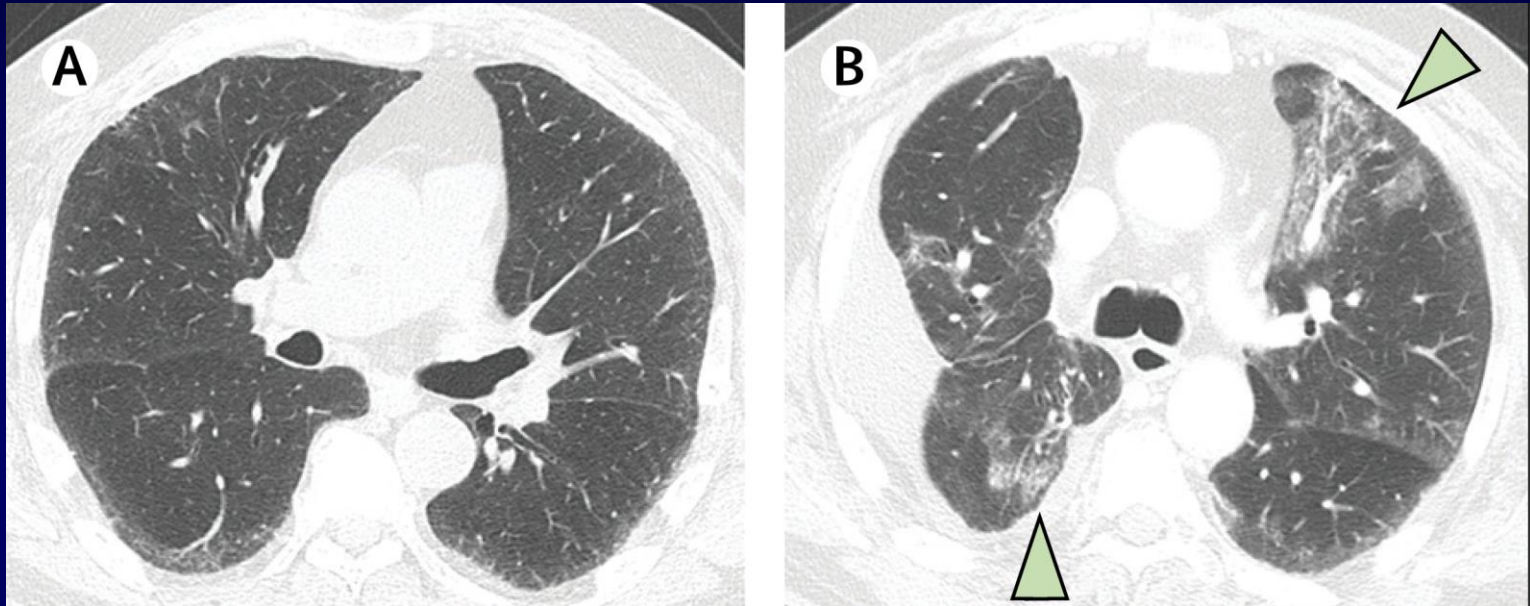
Characteristics	No ILA (n=465)	ILA (N=19)	P-value
Age, y	62 (23-90)	69 (39-95)	0.0008
Male	192 (41.2)	13 (68.4)	0.03
Ever-smoking	358 (77.0)	16 (84.2)	NS
Systemic Tx: none	63 (13.5)	0 (0)	NS
Chemotherapy	336 (72.3)	14 (73.7)	
TKI	66 (14.2)	5 (26.3)	

# Overall survival of patients with and without ILA



- Overall survival: 9.95 mo. (ILA) vs. 16.95 mo. (no ILA)
- Adjusted HR 2.09

# ILA in lung cancer treatment



- NSCLC patients treated with anti-PD-1 antibody (n=83)
  - development of interstitial pneumonitis: OR 6.64 [95% CI 1.78-24.76]
- Nonlung cancers patients treated with anti-PD-1 antibody (n=199)
  - development of interstitial pneumonitis: OR 6.29 [95% CI 2.34-16.92]

# Interstitial Lung Abnormalities Are Associated with Acute Respiratory Distress Syndrome

- Patients with sepsis/SIRS at BWH (n=460)
  - ARDS in 33 (14%)
- ILA in 19 (8%)
  - ARDS diagnosis: 74% vs. 15% (no ILA)
  - 28-day mortality: 37% vs. 21% (no ILA)

	Adjusted Comparison of ILA vs. No ILA	
	OR (95% CI)	P Value
ARDS	4.2 (2.1–8.2)	<0.0001
28-day mortality	2.3 (1.2–4.2)	0.01
28-day mortality (only patients with ARDS)	2.4 (0.9–6.5)	0.08

- Adjustments for age, and APACHE scores

# Interstitial Lung Abnormalities and the Clinical Course in Patients With COPD



Tae Seung Lee, MD; Kwang Nam Jin, MD, PhD; Hyun Woo Lee, MD; Seo-Young Yoon, MD; Tae Yun Park, MD; Eun Young Heo, MD; Deog Kyeom Kim, MD, PhD; Hee Soon Chung, MD, PhD; and Jung-Kyu Lee, MD

- 363 patients with COPD
  - ILA in 103 (28.4%)

Characteristics	No ILA (n=216)	Equivocal ILA (n=44)	ILA(n=103)	P-value
Age, y	64.6 (9.1)	65.9 (9.5)	68.6 (8.7)	0.003
Male	200 (92.6)	40 (90.9)	99 (96.1)	NS
Ever-smokers	195 (90.3)	39 (88.6)	91 (88.3)	NS
FEV <sub>1</sub> , L	1.6 (0.5)	1.5 (0.6)	1.5 (0.5)	0.025
FVC, L	3.2 (0.8)	2.9 (0.8)	3.0 (0.7)	0.032
Incidence of AE				
Mod to Severe	0.63 (0.96)	1.05 (1.39)	1.18 (1.45)	<0.001
Frequent AE	18 (8.3)	7 (15.9)	21 (20.4)	0.008

## Risk of AE in patients with COPD according to ILA status

Parameter	Moderate		Severe		Moderate to Severe	
	$\beta \pm SD$	<i>P</i> Value	$\beta \pm SD$	<i>P</i> Value	$\beta \pm SD$	<i>P</i> Value
ILA <sup>a</sup>	0.22 ± 0.08	.005	0.16 ± 0.08	.043	0.38 ± 0.12	.002
Age	-0.01 ± 0.01	.210	-0.00 ± 0.00	.586	-0.01 ± 0.01	.239
Male sex	0.02 ± 0.16	.884	0.34 ± 0.16	.034	0.36 ± 0.25	.142
Smoking intensity, pack-y	0.01 ± 0.00	< .001	0.00 ± 0.00	.456	0.01 ± 0.00	.005
Charlson Comorbidity Index	-0.03 ± 0.04	.431	0.05 ± 0.04	.146	0.02 ± 0.05	.672
Baseline FEV <sub>1</sub>	-0.34 ± 0.08	< .001	-0.47 ± 0.08	< .001	-0.81 ± 0.12	< .001
Positive bronchodilator response	-0.21 ± 0.11	.045	-0.23 ± 0.10	.028	-0.44 ± 0.16	.006

- ILA includes both equivocal and definite ILA.

# Annual decline in lung function according to longitudinal changes in ILA

Variables	Patients (n/N)	Univariate		Multivariate <sup>a</sup>	
		$\beta \pm SE$	P Value	$\beta \pm SE$	P Value
FEV <sub>1</sub> , mL/y	...	...	.056	...	<b>.016</b>
Improvement	59/307	-10.3 ± 6.5	...	-11.0 ± 6.2	...
No change	165/307	-24.2 ± 4.6	...	-25.7 ± 4.5	...
Progression	83/307	-34.2 ± 5.9	...	-38.3 ± 5.7	...
FVC, mL/y	...	...	.018	...	.006
Improvement	59/307	-8.3 ± 17.6	...	-9.6 ± 17.4	...
No change	165/307	-15.7 ± 6.7	...	-11.1 ± 6.6	...
Progression	83/307	-52.2 ± 11.1	...	-51.2 ± 10.7	...
FEV <sub>1</sub> -to-FVC ratio	...	...	.522	...	.440
Improvement	59/307	-0.08 ± 0.17	...	-0.11 ± 0.15	...
No change	165/307	-0.29 ± 0.10	...	-0.34 ± 0.09	...
Progression	83/307	-0.25 ± 0.17	...	-0.37 ± 0.17	...
DLCO, %/y	...	...	.799	...	.944
Improvement	59/307	-0.68 ± 0.57	...	-0.52 ± 0.55	...
No change	165/307	-0.45 ± 0.38	...	-0.39 ± 0.34	...
Progression	83/307	-0.83 ± 0.46	...	-0.64 ± 0.43	...

- Adjusted for age, sex, smoking intensity, and baseline lung function

# Risk factors of ILAs

- Advanced age: OR 2.2 (per 10 year increase)
- Male sex : OR 1.7
- Smoking: OR 1.8 (current-)
- Occupational exposure (vapours, gases, dusts, fumes)
- Air pollution (nitrogen oxides, elemental carbon)
- *MUC5B* promoter polymorphism: OR 2.8

# Overlap of Genetic Risk between Interstitial Lung Abnormalities and Idiopathic Pulmonary Fibrosis

- ILA assessed on CT in 6 cohort studies
  - ILA in 1,699 and 10,274 control subjects
  - GWAS of ILA in each cohort and combined the results
- Genome-Wide Significant Variants associated with ILA

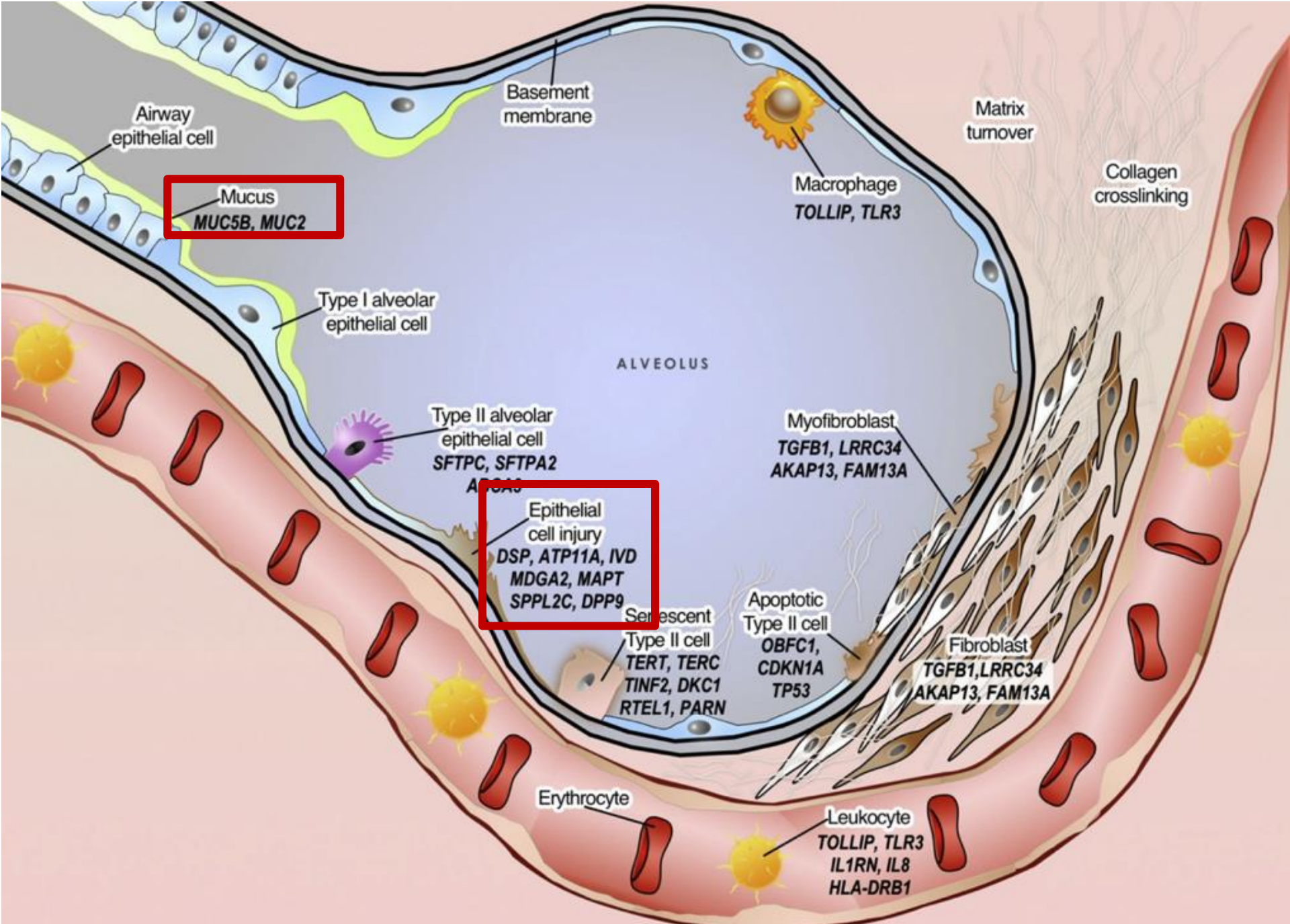
Chromosome/ Location	Position	rsID	Risk Allele	Risk Allele Frequency	Nearest Gene	ILA vs. No ILA		Subpleural ILA vs. No ILA		Replication in IPF Cohort	
						Odds Ratio* (95% CI)	P Value	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
3q13	106571023	rs73199442	T	0.06	<i>FCF1P3</i>	1.68 (1.39–2.02)	$5 \times 10^{-8}$	1.61 (1.31–1.99)	$7 \times 10^{-6}$	0.98 (0.85–1.12)	0.73
5q12	62172476	rs6886640	G	0.62	<i>IPO11</i>	1.28 (1.18–1.41)	$4 \times 10^{-8}$	1.27 (1.14–1.40)	$8 \times 10^{-6}$	1.06 (0.99–1.14)	0.11
6q15	87737841	rs7744971	G	0.28	<i>HTR1E</i>	1.26 (1.16–1.37)	$1 \times 10^{-7}$	1.32 (1.19–1.45)	$4 \times 10^{-8}$	1.01 (0.94–1.09)	0.75
11p15	1241221	rs35705950	T	0.11	<i>MUC5B</i>	1.97 (1.74–2.22)	$3 \times 10^{-27}$	2.22 (1.93–2.55)	$2 \times 10^{-29}$	4.84 (4.37–5.36)	$1 \times 10^{-203}$

# Overlap of Genetic Risk between Interstitial Lung Abnormalities and Idiopathic Pulmonary Fibrosis

- Association of 12 previously identified IPF genome-wide association loci with ILA

Chromosome/ Location	rsID	IPF Risk Allele	Nearest Gene	Studies	IPF Odds Ratio (95% CI)	ILA vs. No ILA		Subpleural ILA vs. No ILA		Direction of Effect Consistent with Prior Reports
						Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value	
4q22	rs2609255	G	<i>FAM13A</i>	(8)	1.29 (1.18–1.42)	1.18 (1.07–1.29)	$5 \times 10^{-4}$	1.22 (1.09–1.35)	$3 \times 10^{-4}$	Yes
6p24	rs2076295	G	<i>DSP</i>	(8, 11)	1.44 (1.35–1.54)	1.14 (1.05–1.2)	0.001	1.18 (1.08–1.29)	$3 \times 10^{-4}$	Yes
11p15	rs35705950	T	<i>MUC5B</i>	(8)	2.43 (2.13–2.77)	1.97 (1.74–2.22)	$3 \times 10^{-27}$	2.22 (1.93–2.55)	$2 \times 10^{-29}$	Yes
15q15	rs2034650	A	<i>IVD</i>	(8)	1.30 (1.19–1.41)	1.08 (0.99–1.17)	0.07	1.15 (1.05–1.26)	0.003	Yes
19p13	rs12610495	G	<i>DPP9</i>	(8)	1.29 (1.18–1.41)	1.14 (1.03–1.26)	0.01	1.23 (1.10–1.37)	$2 \times 10^{-4}$	Yes
3q26	rs6793295	C	<i>LRRC34</i>	(8)	1.30 (1.19–1.42)	1.06 (0.97–1.15)	0.20	1.12 (1.01–1.24)	0.03	Yes
17q21	rs1981997	G	<i>MAPT</i>	(8)	1.41 (1.28–1.56)	1.16 (1.03–1.30)	0.01	1.19 (1.05–1.36)	0.009	Yes
5p15	rs2736100	A	<i>TERT</i>	(7, 8)	2.11 (1.61–2.78)	1.03 (0.95–1.12)	0.44	1.06 (0.96–1.16)	0.23	Yes
10q24	rs11191865	A	<i>OBFC1</i>	(8)	1.25 (1.15–1.35)	1.03 (0.95–1.12)	0.46	1.03 (0.94–1.13)	0.56	Yes
13q34	rs1278769	G	<i>ATP11A</i>	(8)	1.27 (1.14–1.39)	1.04 (0.95–1.15)	0.37	1.04 (0.94–1.16)	0.45	Yes
15q25	rs62025270	A	<i>AKAP13</i>	(11)	1.27 (1.18–1.37)	1.09 (0.99–1.20)	0.08	1.07 (0.96–1.20)	0.23	Yes
7q22	rs4727443	C	<i>LOC100128334/ LOC105375423</i>	(8)	1.30 (1.19–1.41)	0.95 (0.87–1.03)	0.19	0.93 (0.84–1.02)	0.12	No

- Among 12 IPF GWAS loci, 11 showed directionally consistent associations with ILAs.



# Histopathology of Interstitial Lung Abnormalities in the Context of Lung Nodule Resections

- 424 patients who had undergone lung nodule resection (BWH)
  - ILA in 6%

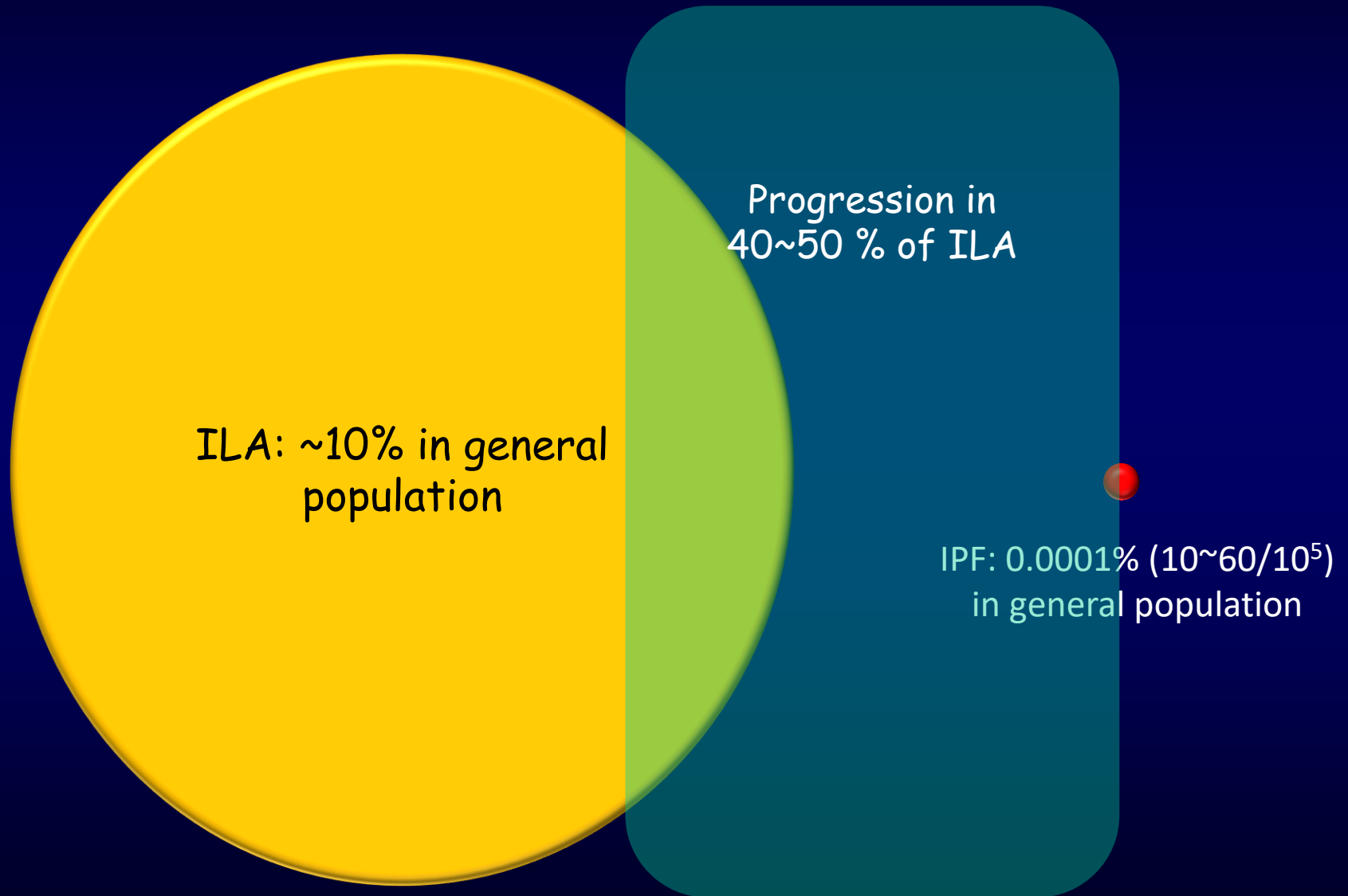
Characteristics	No ILA (n=257)	ILA (N=26)	P-value
Age, y	64 (57-7)	73 (63-80)	0.002
Male	148 (58)	18 (69)	NS
Current smoker	55 (22)	2 (8)	0.09
FVC, % pred	93 (76-106)	98 (89-106)	NS
Stage 2 or greater NSCLC	51 (20)	10 (38)	0.08

# ILA: histopathologic findings

Histopathologic features	No ILA (n=257, 61%)	ILA (n=26, 6%)	P-value
Fibrosis			
Any	133 (52)	19 (73)	0.04
Subpleural	43 (17)	12 (46)	0.001
Peribronchial	62 (24)	9 (35)	Ns
Interstitial	53 (21)	9 (35)	Ns
Emphysematous	39 (15)	4 (15)	Ns
Additional			
FBF	9 (4)	7 (28)	0.001
Honeycombing	0 (0)	2 (8)	0.008
UIP	0 (0)	2 (8)	0.008
RB	156 (67)	17 (71)	Ns
AAH	43 (17)	9 (35)	0.03

Number (percent)

# ILA and IPF: connecting the dots?



# Development and Progression of Interstitial Lung Abnormalities in the Framingham Heart Study

Tetsuro Araki<sup>1,2\*</sup>, Rachel K. Putman<sup>3\*</sup>, Hiroto Hatabu<sup>1,2</sup>, Wei Gao<sup>4,5</sup>, Josée Dupuis<sup>4,5</sup>, Jeanne C. Latourelle<sup>6,7</sup>, Mizuki Nishino<sup>2,8</sup>, Oscar E. Zazueta<sup>3</sup>, Sila Kurugol<sup>8</sup>, James C. Ross<sup>8,9</sup>, Raúl San José Estépar<sup>2,8</sup>, David A. Schwartz<sup>10</sup>, Ivan O. Rosas<sup>3</sup>, George R. Washko<sup>3</sup>, George T. O'Connor<sup>4,11</sup>, and Gary M. Hunninghake<sup>1,3</sup>

- 1867 participants who had serial chest CT scans 6 years apart
- ILA in 155 (8%) → progression in 118 (6%; 76% of ILA)

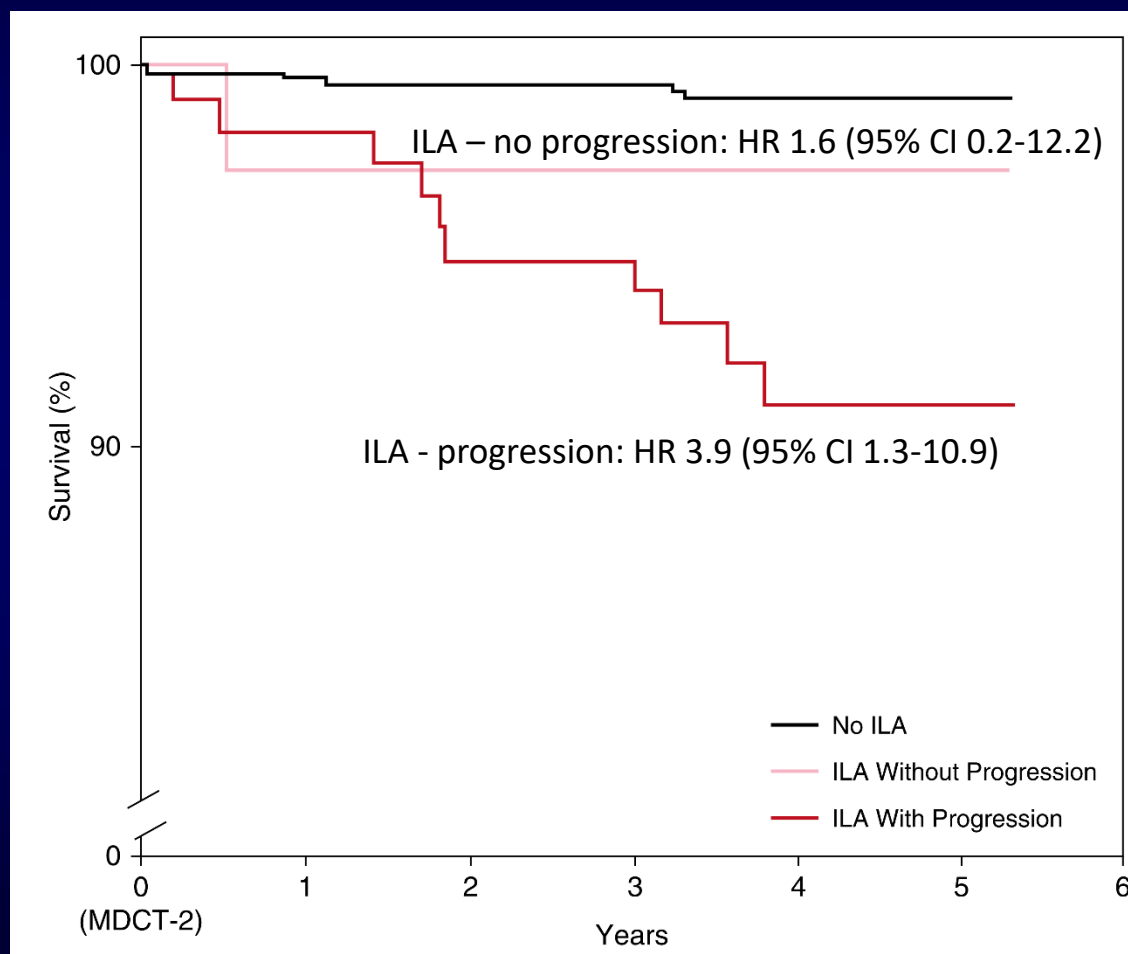
	No ILA (n = 660; 35%) (1)	ILA without Progression (n = 37; 2%) (2)	ILA with Progression (n = 118; 6%) (3)	P Values			
				All†	1 vs. 2‡	1 vs. 3§	2 vs. 3
Age, yr	49 ± 10	58 ± 11	65 ± 11	<0.0001	<0.0001	<0.0001	<0.0001
Sex, female, n (%)	296 (45)	20 (54)	53 (45)	0.6	0.3	0.96	0.3
Race, white, n (%)	660 (100)	37 (100)	118 (100)	—	—	—	—
Body mass index	28 ± 6	30 ± 6	28 ± 5	0.01	0.006	0.91	0.005
Pack-years smoking	16 ± 16	26 ± 19	24 ± 21	<0.0001	0.003	0.0001	0.7
Current smokers, n (%) <sup>¶</sup>	48 (7)	9 (25)	6 (5)	0.004	0.001	0.2	0.07
Former smokers, n (%)	263 (40)	14 (39)	61 (52)				
Never smokers, n (%)	349 (53)	13 (36)	51 (43)				
MUC5B genotype, n (%)							
G/G	529 (80)	27 (73)	78 (66)	0.0003	0.5	<0.0001	0.1
G/T	125 (19)	10 (27)	36 (31)				
T/T	6 (1)	0	4 (3)				

# Association of ILA progression with change in lung function

	ILA with Progression Compared with No ILA				ILA with Progression Compared with ILA without Progression			
	Unadjusted Analysis	P Value	Adjusted Analysis <sup>†</sup>	P Value	Unadjusted Analysis	P Value	Adjusted Analysis <sup>†</sup>	P Value
FEV <sub>1</sub> decline, ml/yr	13 ± 4	0.005	14 ± 5	0.005	9 ± 9	0.3	14 ± 10	0.2
FVC decline, ml/yr	29 ± 5	<0.0001	20 ± 6	0.0005	22 ± 11	0.04	25 ± 11	0.03
FEV <sub>1</sub> /FVC, change, %	-0.2 ± 0.07	0.004	-0.06 ± 0.07	0.4	-0.1 ± 0.1	0.3	-0.08 ± 0.16	0.6

- Additional adjustments for age, sex, body mass index, pack-years smoking, and current smoking status.
- Lung function decline (FVC):
  - No ILA: -35 ± 44 ml/year
  - ILA without progression: -40 ± 44ml/year
  - ILA with progression: -64 ± 51 ml/year

# Survival curves: no ILA, ILA ± progression



# Imaging Patterns Are Associated with Interstitial Lung Abnormality Progression and Mortality

Rachel K. Putman<sup>1</sup>, Gunnar Gudmundsson<sup>2,3</sup>, Gisli Thor Axelsson<sup>3,4</sup>, Tomoyuki Hida<sup>5,6</sup>, Osamu Honda<sup>7</sup>, Tetsuro Araki<sup>5,6</sup>, Masahiro Yanagawa<sup>7</sup>, Mizuki Nishino<sup>5,6</sup>, Ezra R. Miller<sup>1</sup>, Gudny Eiriksdottir<sup>4</sup>, Elías F. Gudmundsson<sup>4</sup>, Noriyuki Tomiyama<sup>7</sup>, Hiroshi Honda<sup>8</sup>, Ivan O. Rosas<sup>1</sup>, George R. Washko<sup>1,6</sup>, Michael H. Cho<sup>1,9</sup>, David A. Schwartz<sup>10</sup>, Vilmundur Gudnason<sup>4</sup>, Hiroto Hatabu<sup>5,6</sup>, and Gary M. Hunninghake<sup>1,6</sup>

- AGES-Reykjavik Study: progression assessed in 3,167
- Over 5 years, ILA in 327 (10%) – progressed in 238 (73% of ILA)

Covariate	Comparison of ILA with Progression with ILA without Progression		Comparison of ILA with Progression with No ILA	
	OR (95% CI)	P Value	OR (95% CI)	P Value
<i>MUC5B</i> genotype*	2.6 (1.5–4.4)	0.0004	2.9 (2.2–3.8)	<0.0001
Age <sup>†</sup>	1.08 (1.02–1.1)	0.01	1.08 (1.05–1.11)	<0.0001
Sex <sup>‡</sup>	0.6 (0.4–1.1)	0.1	0.6 (0.4–0.8)	0.0002
Body mass index <sup>§</sup>	1.05 (0.99–1.1)	0.1	1.06 (1.02–1.09)	0.001
Pack-years smoking <sup>  </sup>	0.99 (0.98–1.01)	0.3	1.01 (1.01–1.02)	<0.0001
Current smoking status <sup>¶</sup>	1.1 (0.5–2.4)	0.8	1.1 (0.7–1.8)	0.6

# Association bet. imaging features and ILA progression

	Unadjusted Analysis		Adjusted Analysis*	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Centrilobular nodules	0.2 (0.1–0.4)	<0.0001	0.2 (0.1–0.5)	0.0002
Ground glass <sup>†</sup>	—	—	—	—
Subpleural reticular markings	5.9 (2.3–15)	0.0002	6.6 (2.3–19)	0.0004
Nonemphysematous cysts	3.1 (1.6–5.9)	0.0005	2.5 (1.3–5.1)	0.009
Lower lobe predominant changes	5.2 (1.8–15)	0.002	6.7 (1.8–25)	0.004
Traction bronchiectasis	5.9 (2.3–14.9)	0.0002	6.6 (2.3–19)	0.0004
Honeycombing <sup>‡</sup>	—	—	—	—

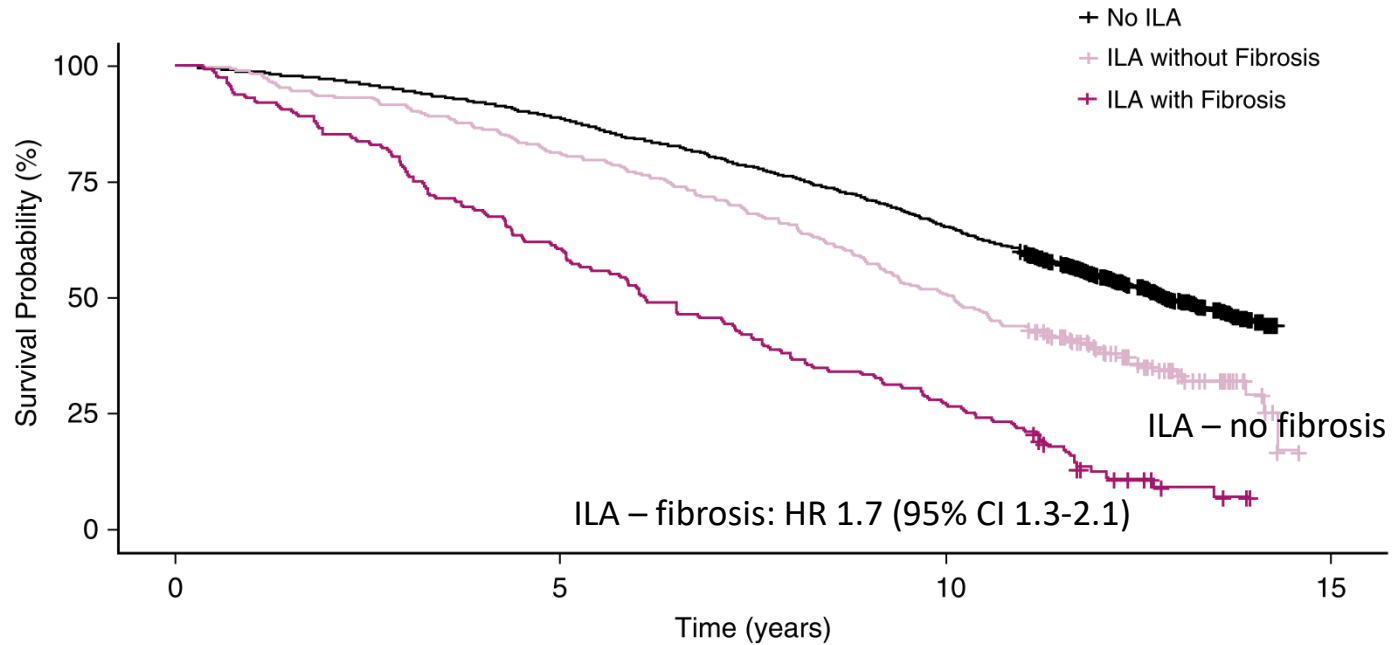
- Adjusted for age, sex, body mass index, pack-years smoking, current smoking status, and MUC5B genotype.

# Association bet. imaging features and mortality

	Unadjusted Analysis		Adjusted Analysis <sup>†</sup>	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Reticular markings	2.0 (1.3–3.1)	0.002	1.6 (1.0–2.5)	0.049
Centrilobular nodules	0.7 (0.6–0.9)	0.01	0.9 (0.7–1.1)	0.3
Nonemphysematous cysts	1.7 (1.3–2.2)	<0.0001	1.4 (1.1–1.8)	0.02
Traction bronchiectasis	2.0 (1.6–2.6)	<0.0001	1.6 (1.3–2.1)	0.0001
Lower lobe <sup>‡</sup> predominance	1.5 (0.95–2.5)	0.08	1.1 (0.6–1.7)	0.8
Subpleural location <sup>§</sup>	2.0 (1.3–3.2)	0.003	1.6 (1.0–2.7)	0.050
ILA without fibrosis	1.3 (1.2–1.4)	<0.0001	1.2 (1.1–1.3)	0.0004
Definite fibrosis	1.9 (1.7–2.1)	<0.0001	1.5 (1.3–1.6)	<0.0001
Indeterminate for UIP	1.6 (1.3–2.0)	<0.0001	1.2 (0.98–1.5)	0.07
Probable UIP pattern	3.3 (2.6–4.2)	<0.0001	1.9 (1.5–2.5)	<0.0001
UIP pattern	6.9 (4.2–11)	<0.0001	4.5 (2.8–7.2)	<0.0001

- Adjusted for age, sex, pack-years smoking, current smoking status, and body mass index

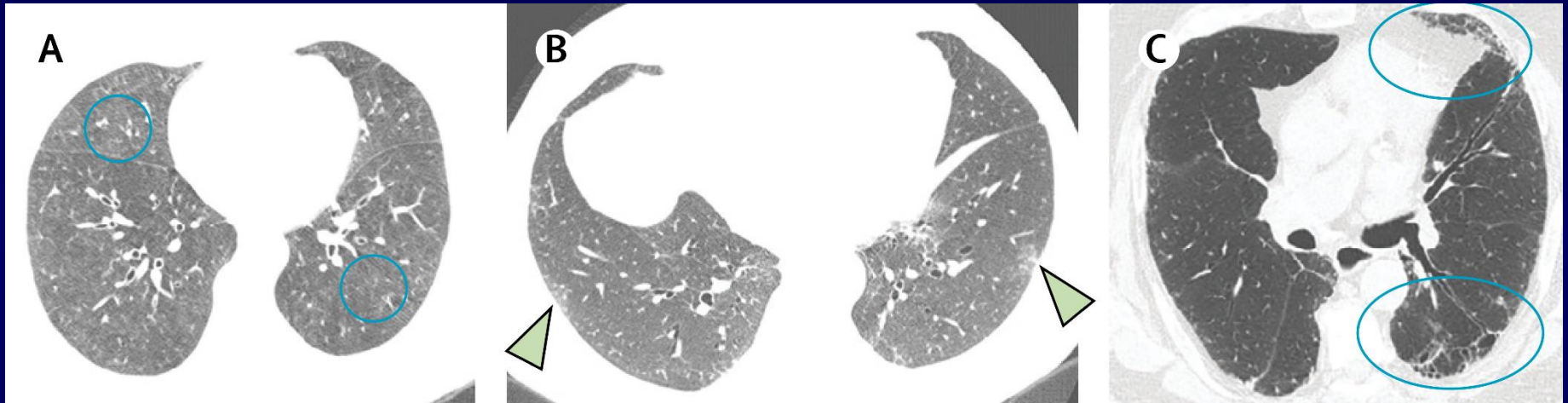
# Survival curve: no ILA, ILA ± fibrosis



Number at risk		0	5	10	15
No ILA		3,216	2,851	2,100	0
ILA without Fibrosis		249	202	126	0
ILA with Fibrosis		129	78	35	0

Time (years)

# Subcategories of ILAs



Non-subpleural

Subpleural  
- non-fibrotic

Subpleural  
- fibrotic

- Fibrosis: presence of architectural distortion (TBE or HC)

# Risk factors for progression of ILA

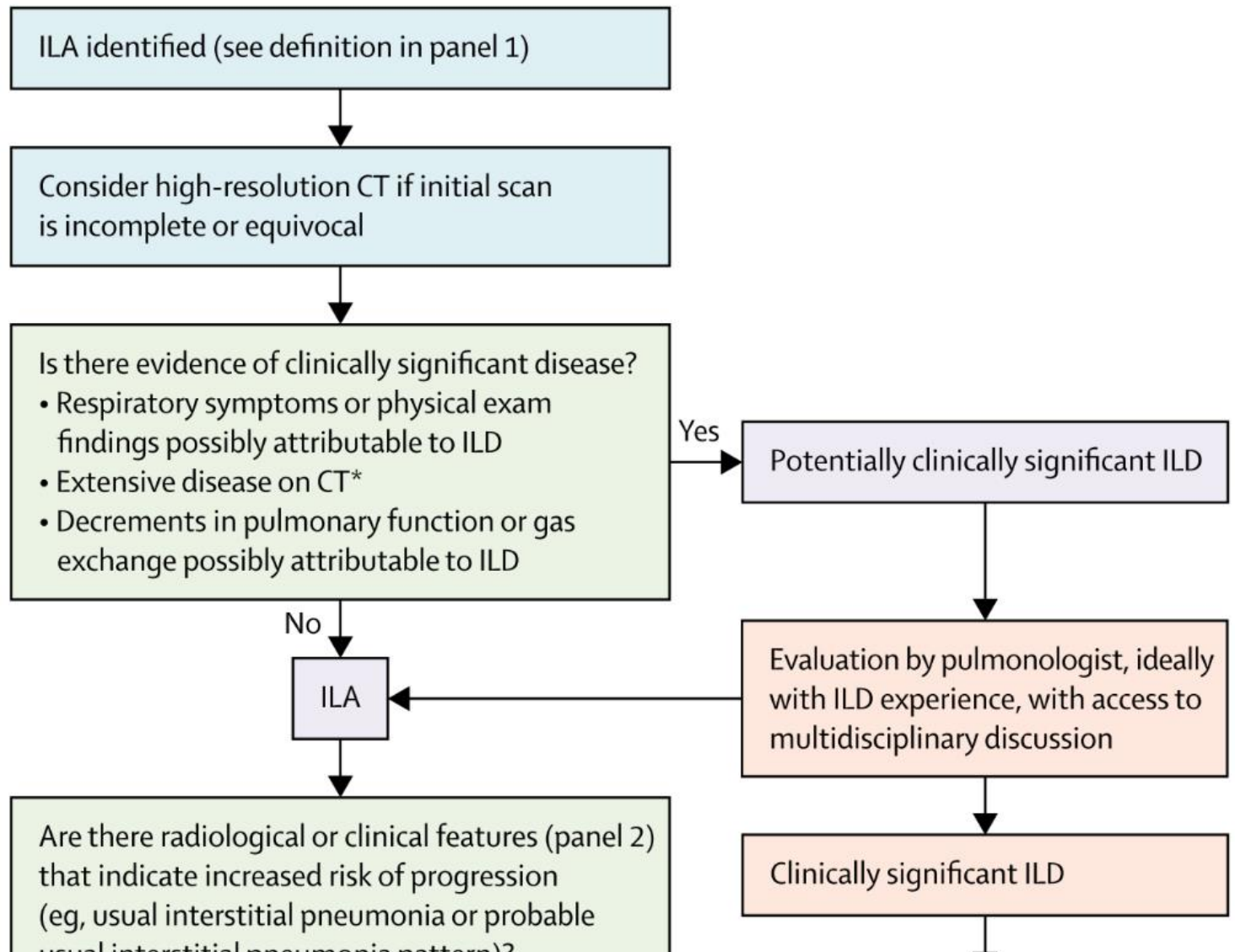
## Clinical risk factors

- Cigarette smoking
- Other inhalational exposures
- Medications (eg, chemotherapy, immune checkpoint inhibitors)
- Radiation therapy
- Thoracic surgery
- Physiological or gas exchange findings at lower limits of normal

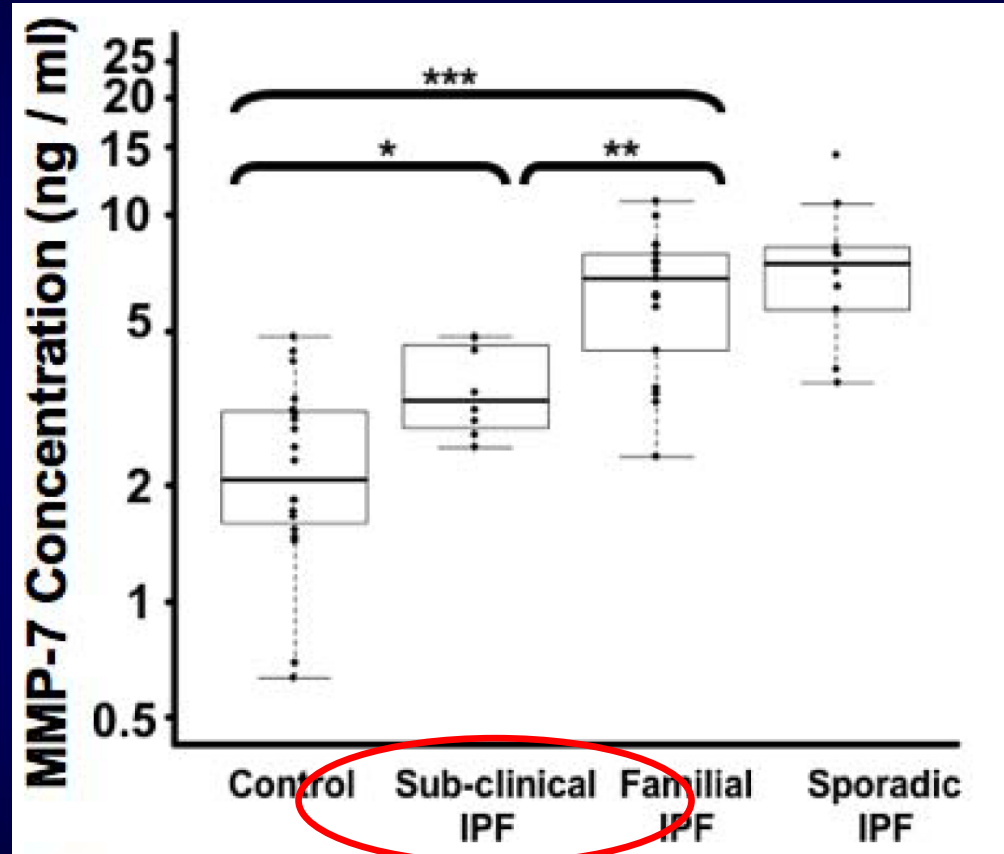
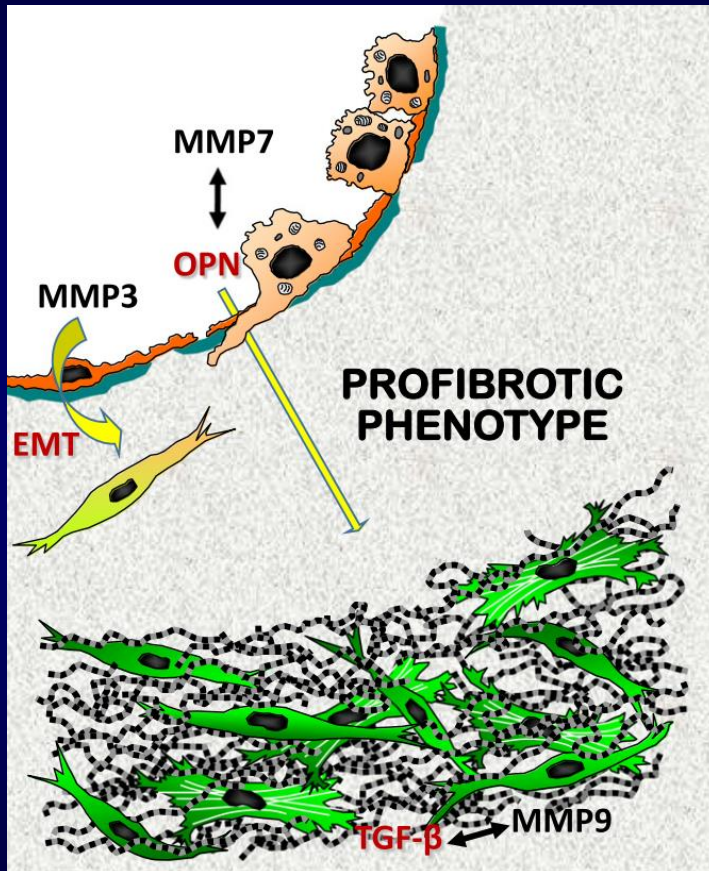
## Radiological risk factors

- Non-fibrotic interstitial lung abnormalities (ILAs) with basal and peripheral predominance
- Fibrotic ILAs with basal and peripheral predominance but without honeycombing (ILAs with probable usual interstitial pneumonia pattern)
- Fibrotic ILAs with basal and peripheral predominance and honeycombing (ILAs with usual interstitial pneumonia pattern)

# Management of ILA detected on CT

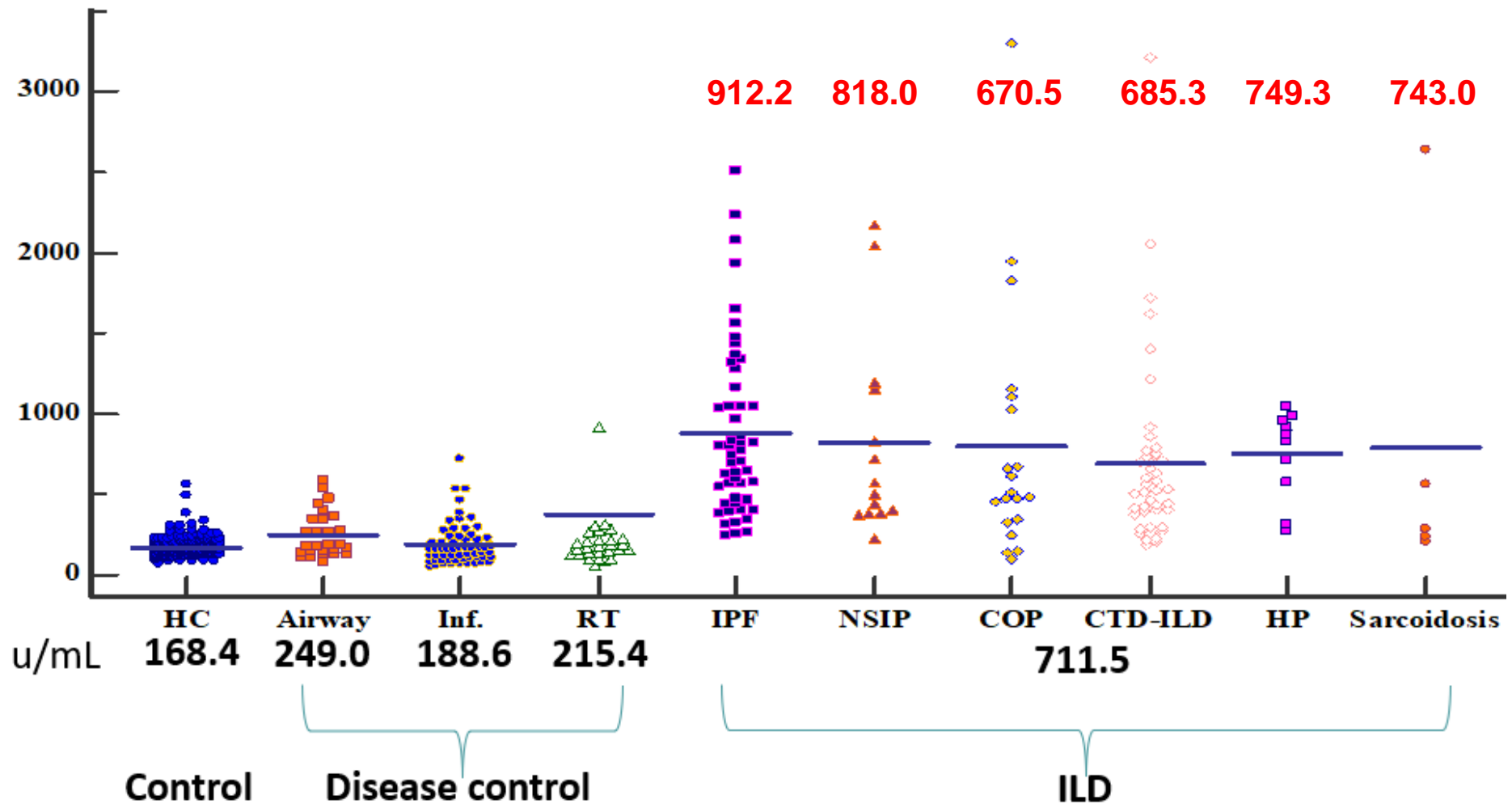


# Matrix metalloproteinase in IPF



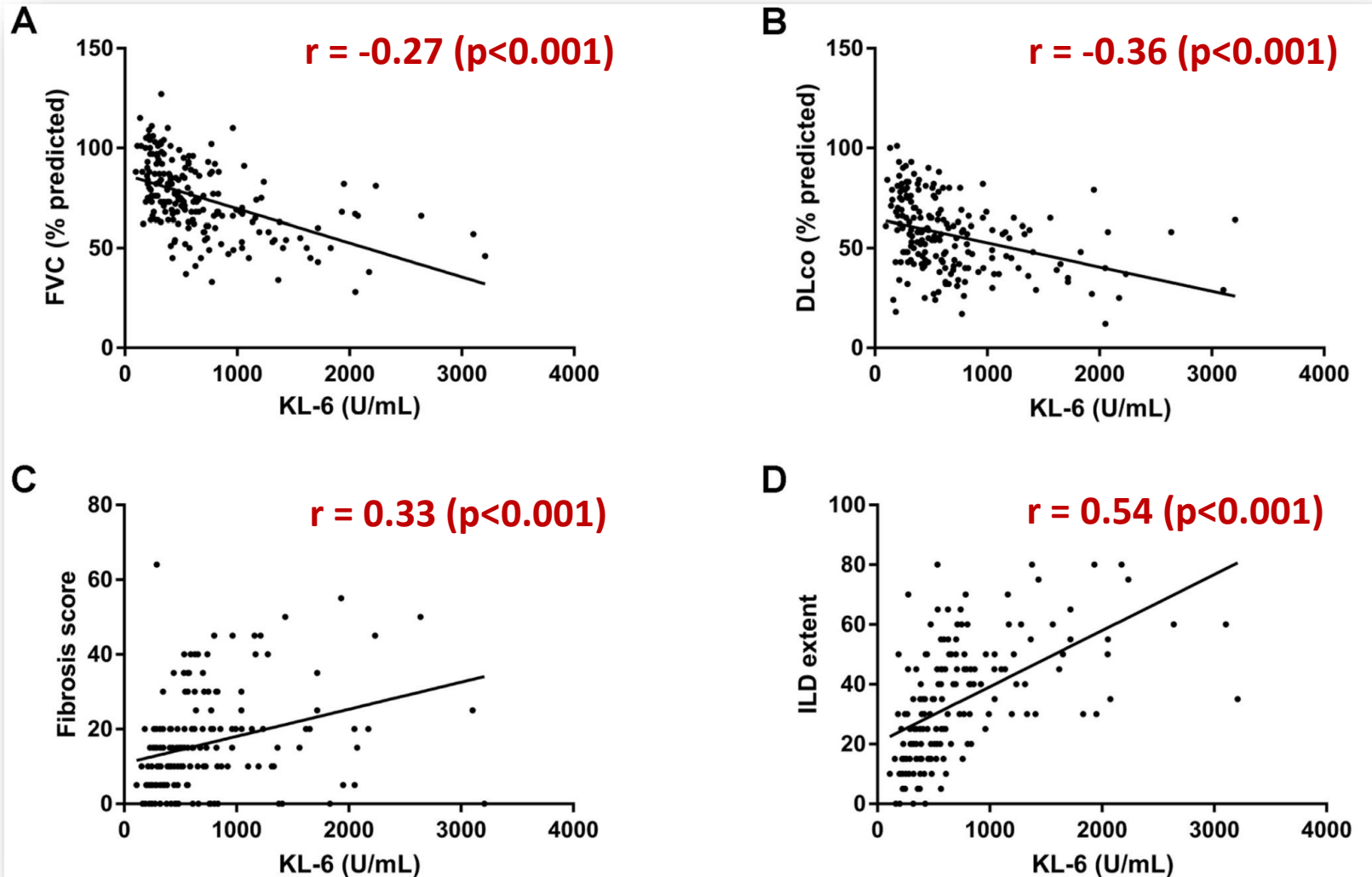
- ECM turnover regulation, activation and degradation of biological mediators

# Serum KL-6 differentiates between control and ILD groups

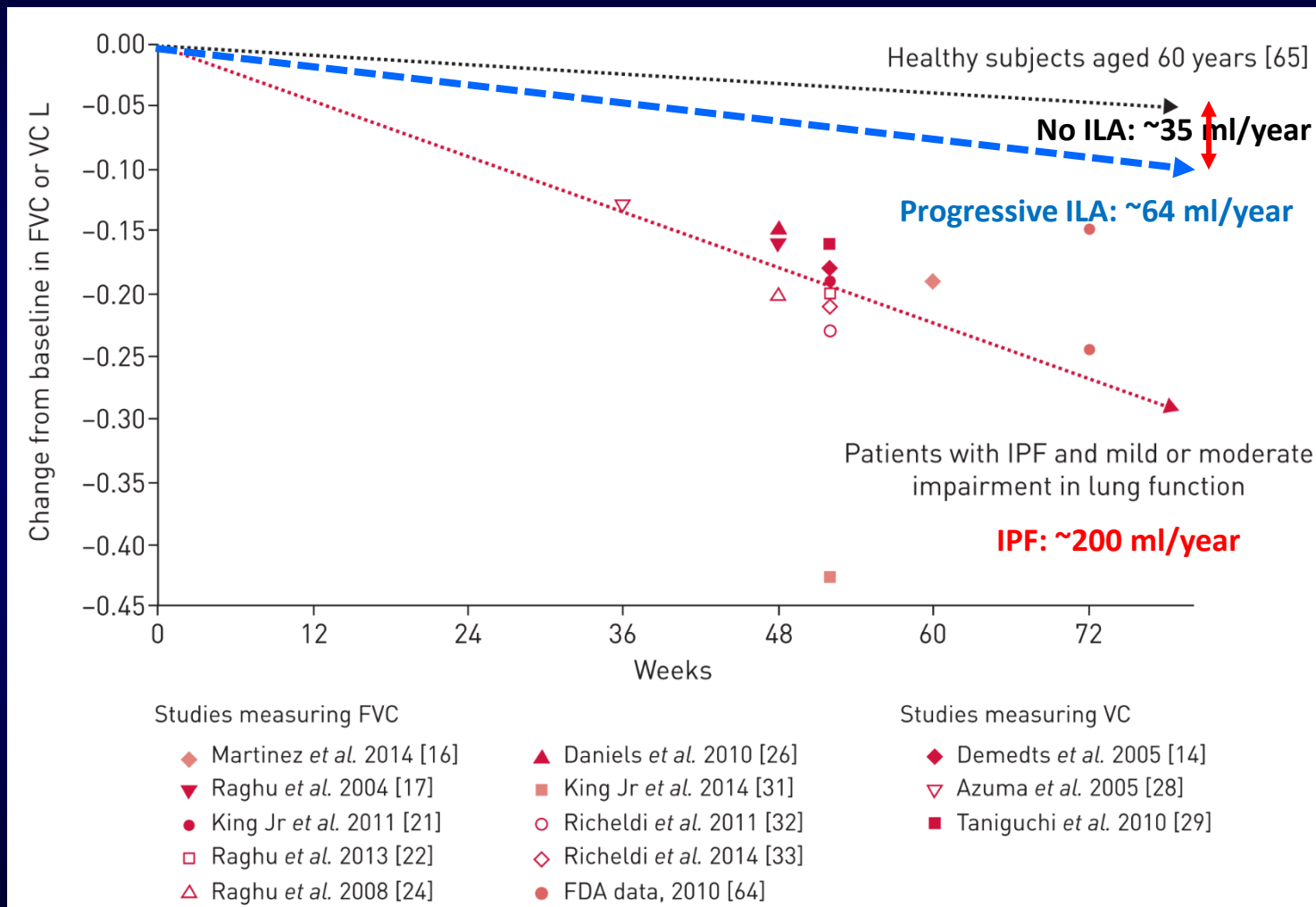


- Mean levels (U/mL)

# Correlation between KL-6 levels and disease severity

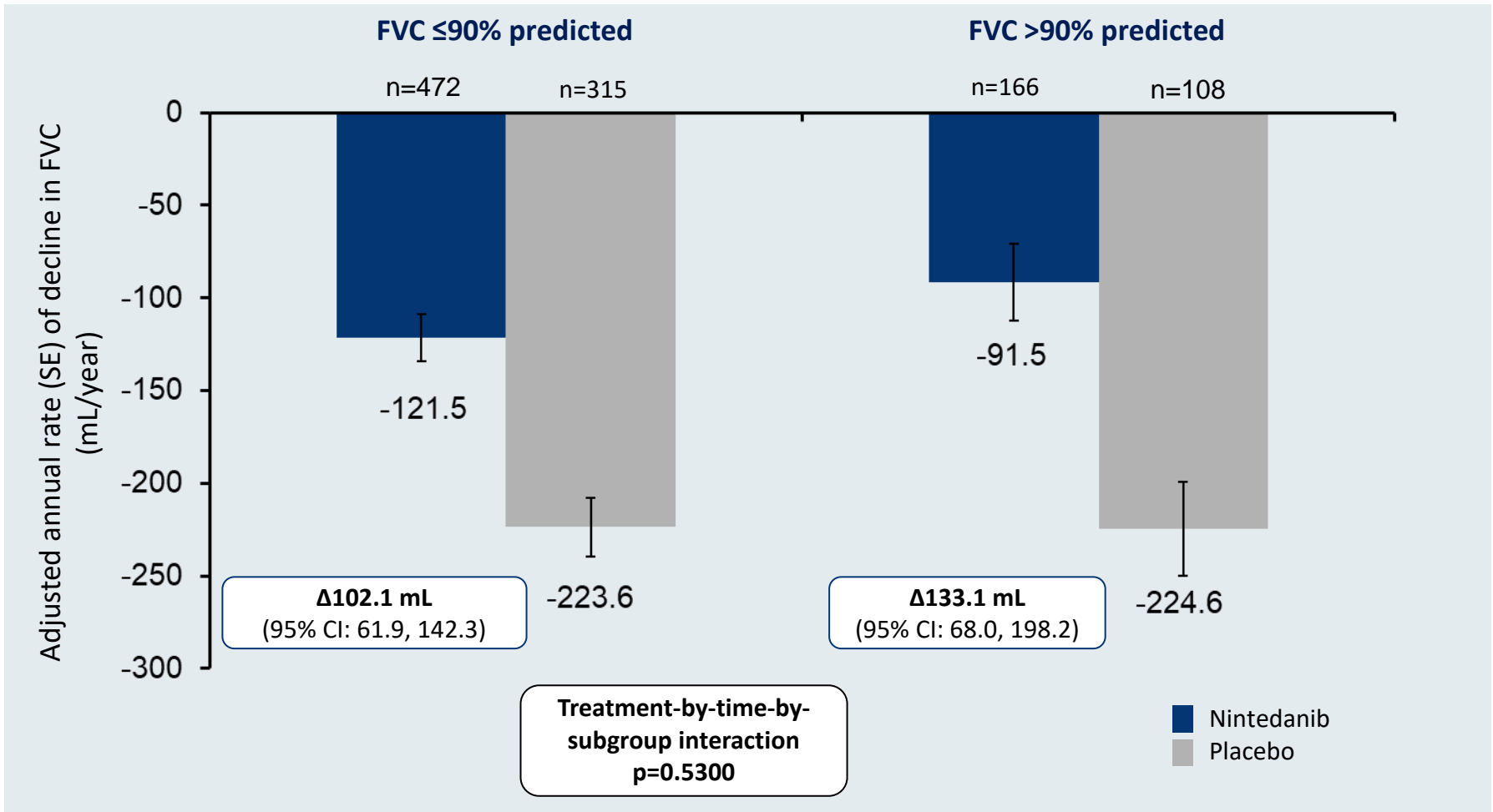


# Natural course of lung function decline in IPF/progressive ILA

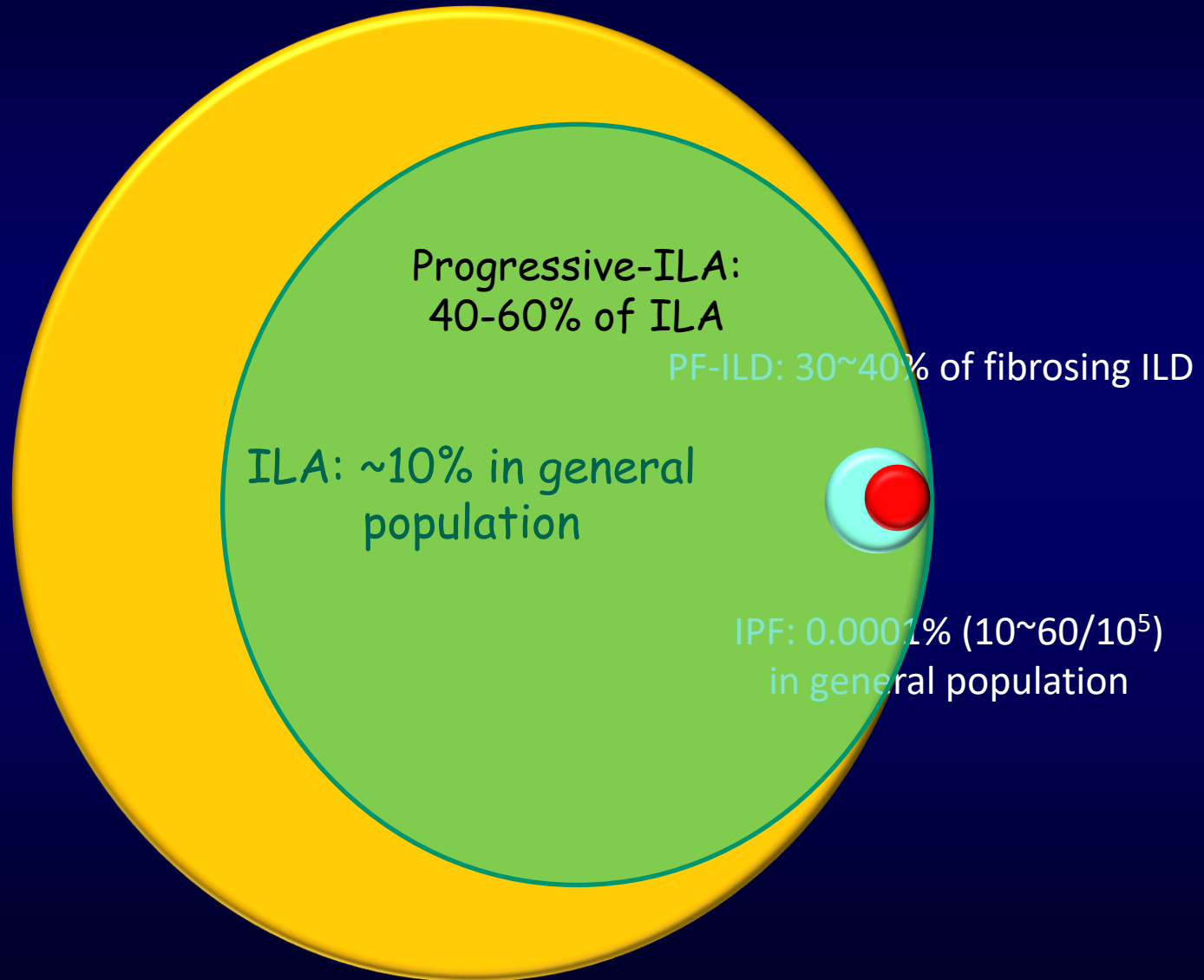


# Nintedanib in mild IPF

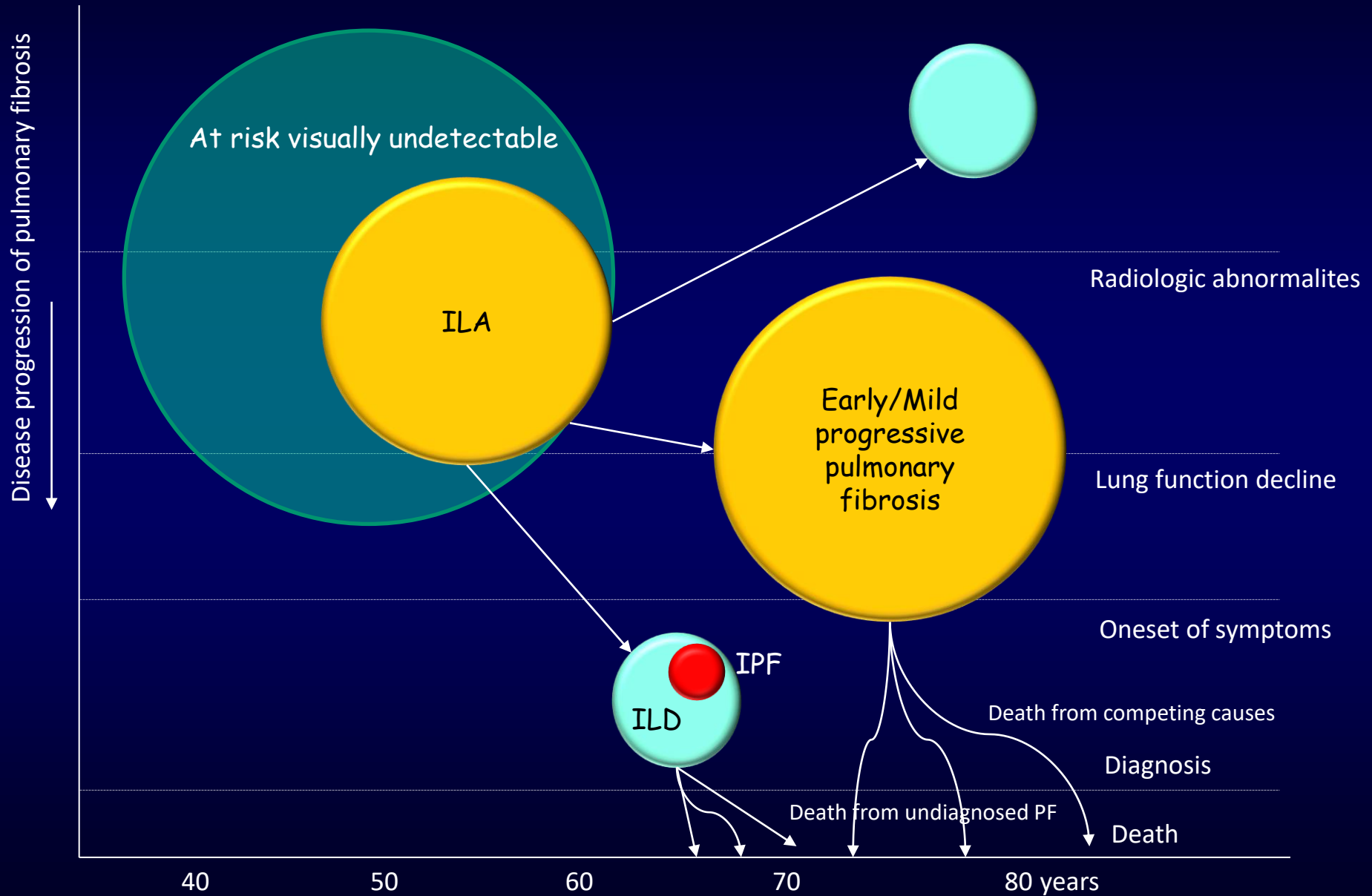
- Annual rate of decline in FVC



# Spectrum of fibrosing ILD with a progressive phenotype



# Progression of pulmonary fibrosis



# Summary

- Interstitial lung abnormalities
  - Prevalence: ~10%
  - clinical implication: impact on prognosis
  - progression: subpleural fibrotic ILA
  - Management: monitoring and treatment?

# ILA is early UIP ?

