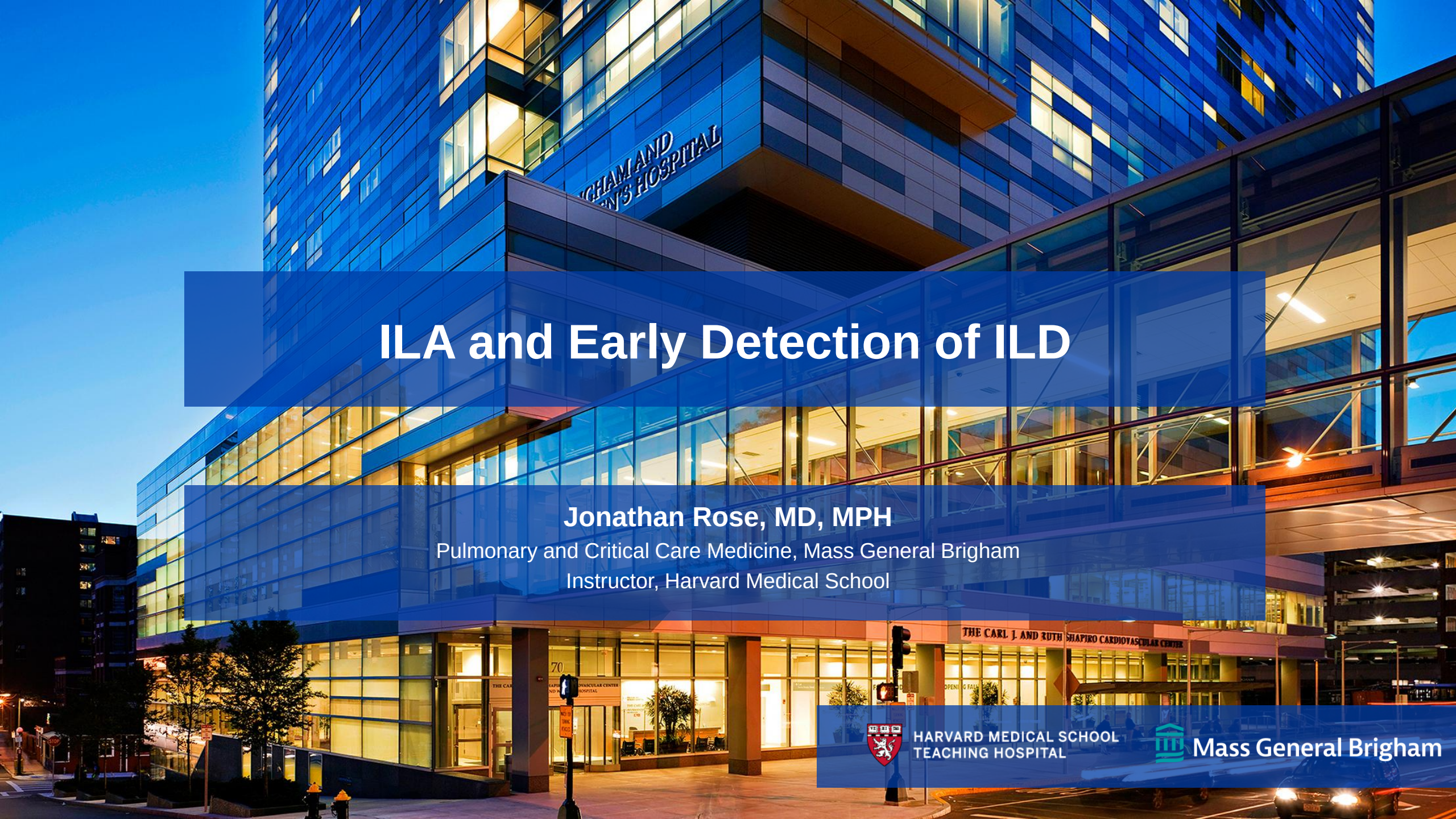


ILA and Early Detection of ILD

Jonathan Rose, MD, MPH

Pulmonary and Critical Care Medicine, Mass General Brigham

Instructor, Harvard Medical School

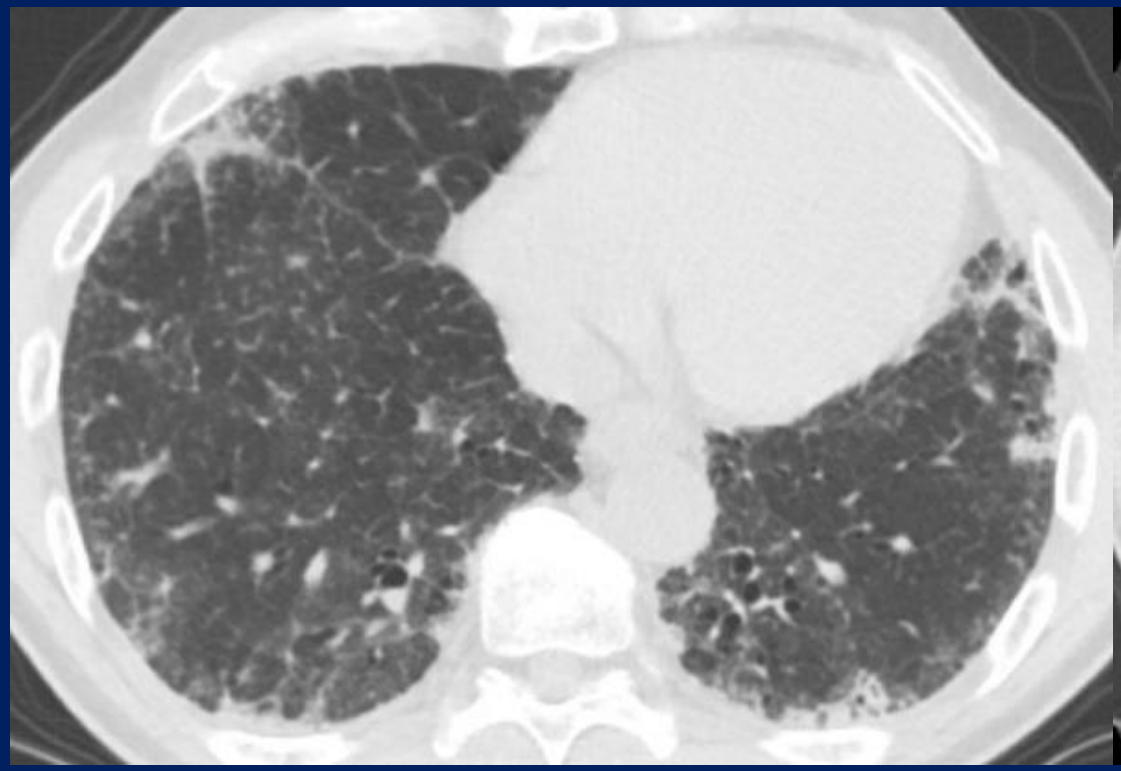
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

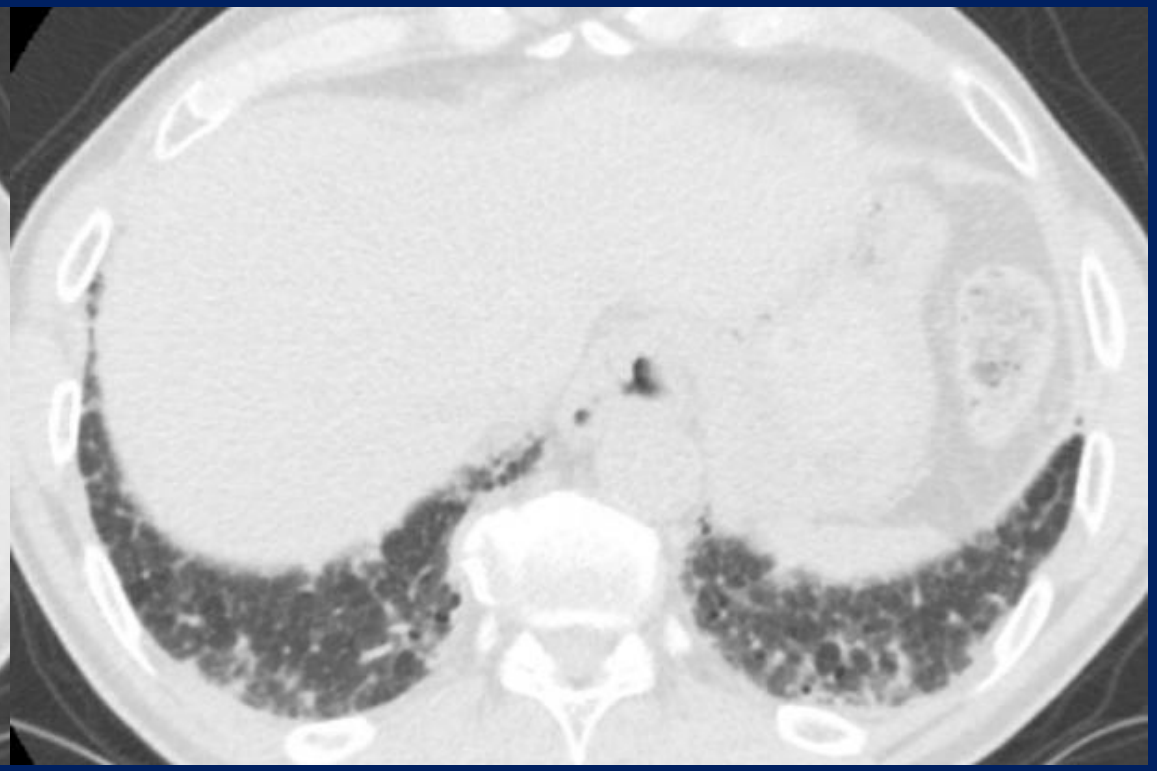
Mass General Brigham

Conflicts of Interest

None

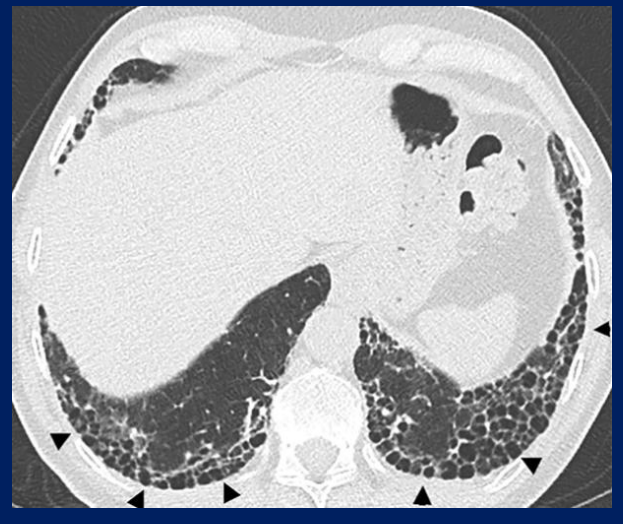
Case

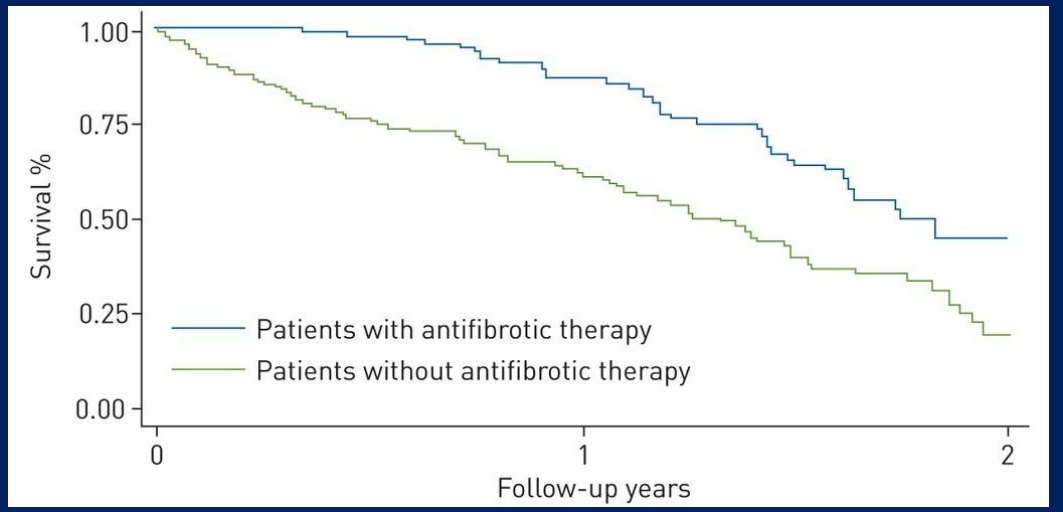


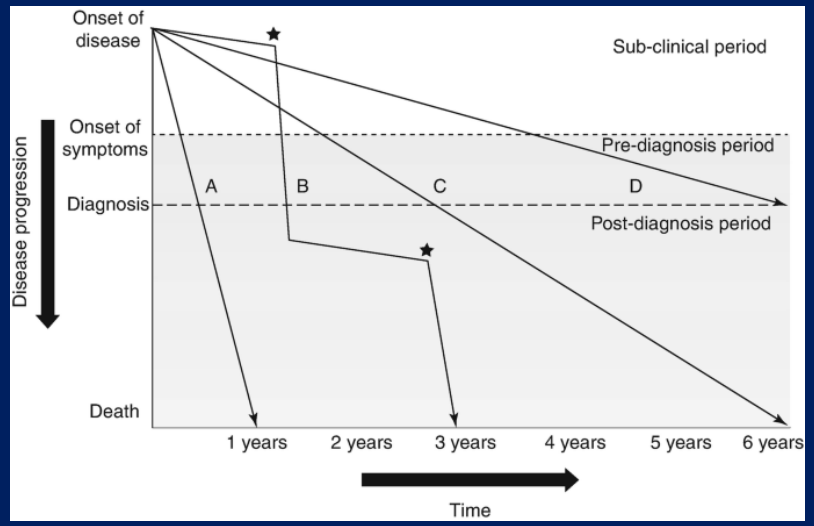


Case courtesy of Dr. Claire Cutting

Pulmonary Fibrosis







	By lung-function change category (based on relative change in FVC%)		
	Stable [A]	**Marginal [B]**	**Significant [C]**
	(*N* = 250)	**(*N* = 98)**	**(*N* = 142)**
Symptoms at IPF diagnosis, N (%)[b]			
Dyspnea/shortness of breath	209 (83.6 %)	88 (89.8 %)	132 (93.0 %)
Cough	175 (70.0 %)	71 (72.4 %)	110 (77.5 %)
Lung-function measures at IPF diagnosis, mean [median] (SD)			
FVC (liters)	2.6 (1.1)	2.4 (0.9)	2.4 (1.0)
FVC%	61.7 %(26.1 %)	58.5 % (24.0 %)	59.5 % (27.6 %)
FEV_1 (liters)	2.0 (0.9)	1.8 (0.7)	1.7 (0.6)
FEV_1/FVC	79.6 % (12.6 %)	79.9 % (11.8 %)	80.7 % (12.5 %)
DL_{CO} percent predicted	53.4 % (14.4 %)	51.2 % (16.1 %)	47.7 % (16.5 %)

Raghu G, et al. *Am J Respir Crit Care Med*. 2011; 183 (6): 788-824
Raghu G, et al. *Am J Respir Crit Care Med*. 2022; 205 (9): e18-e47

Behr J, et al. *Eur Respir J.* 2020; 56 (2): 1902279
Reichmann WM, et al. *BMC Pulm Med*. 2015; 15: 16

Early Detection in Pulmonary Fibrosis

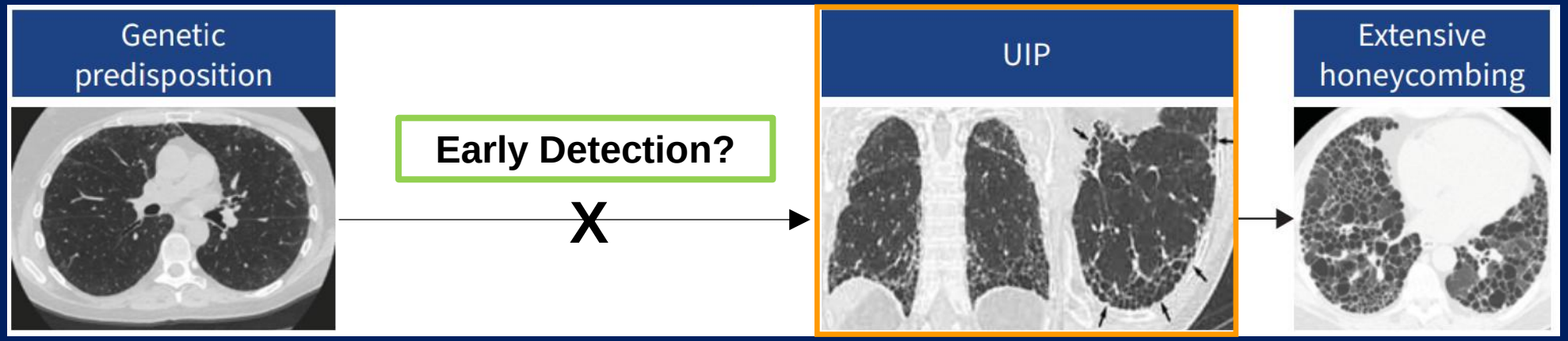
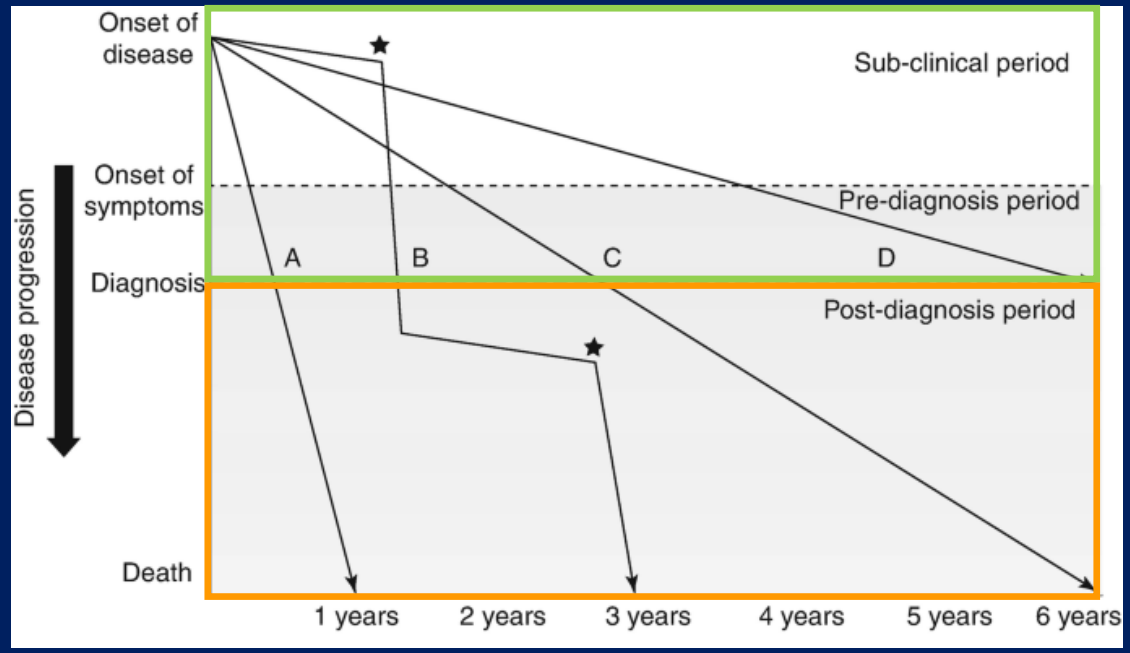
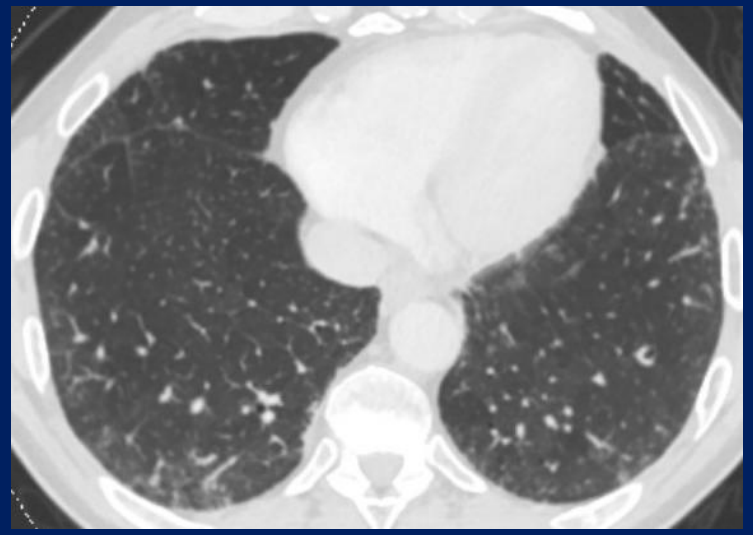
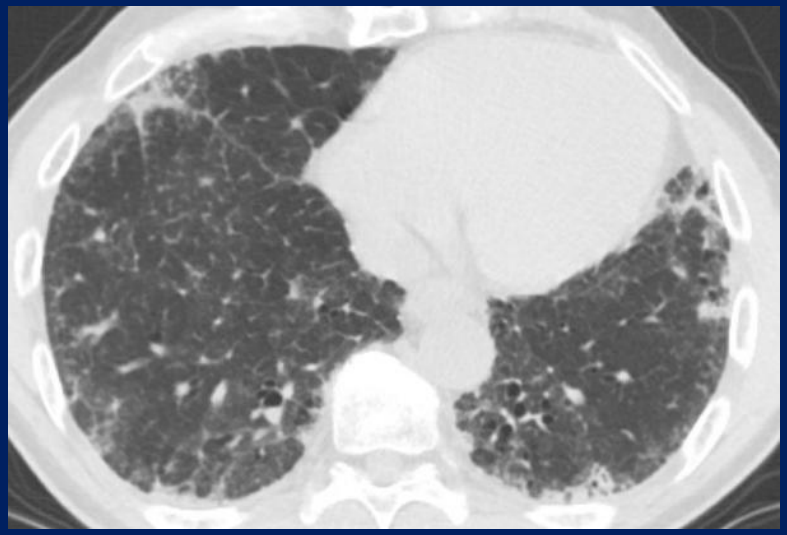
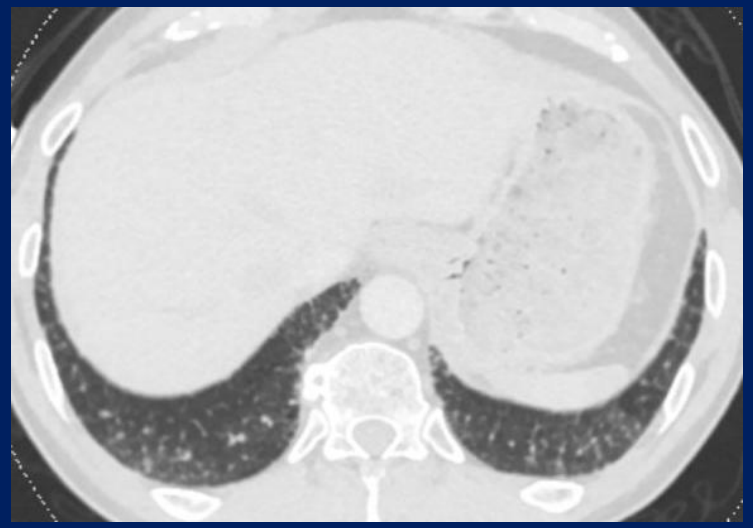
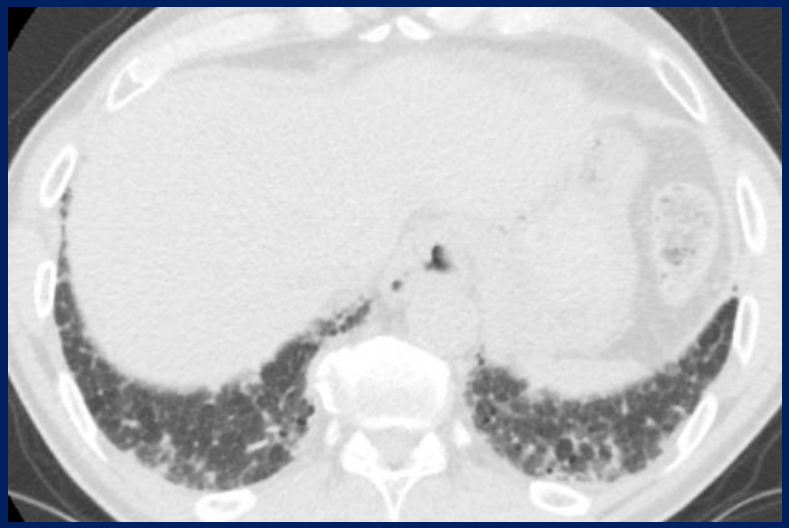


Figure modified from Podolanczuk A, et al. *Eur Respir J.* 2023; 61 (4): 2200957



Case

2019	2022	2025
		
		

Case courtesy of Dr. Claire Cutting

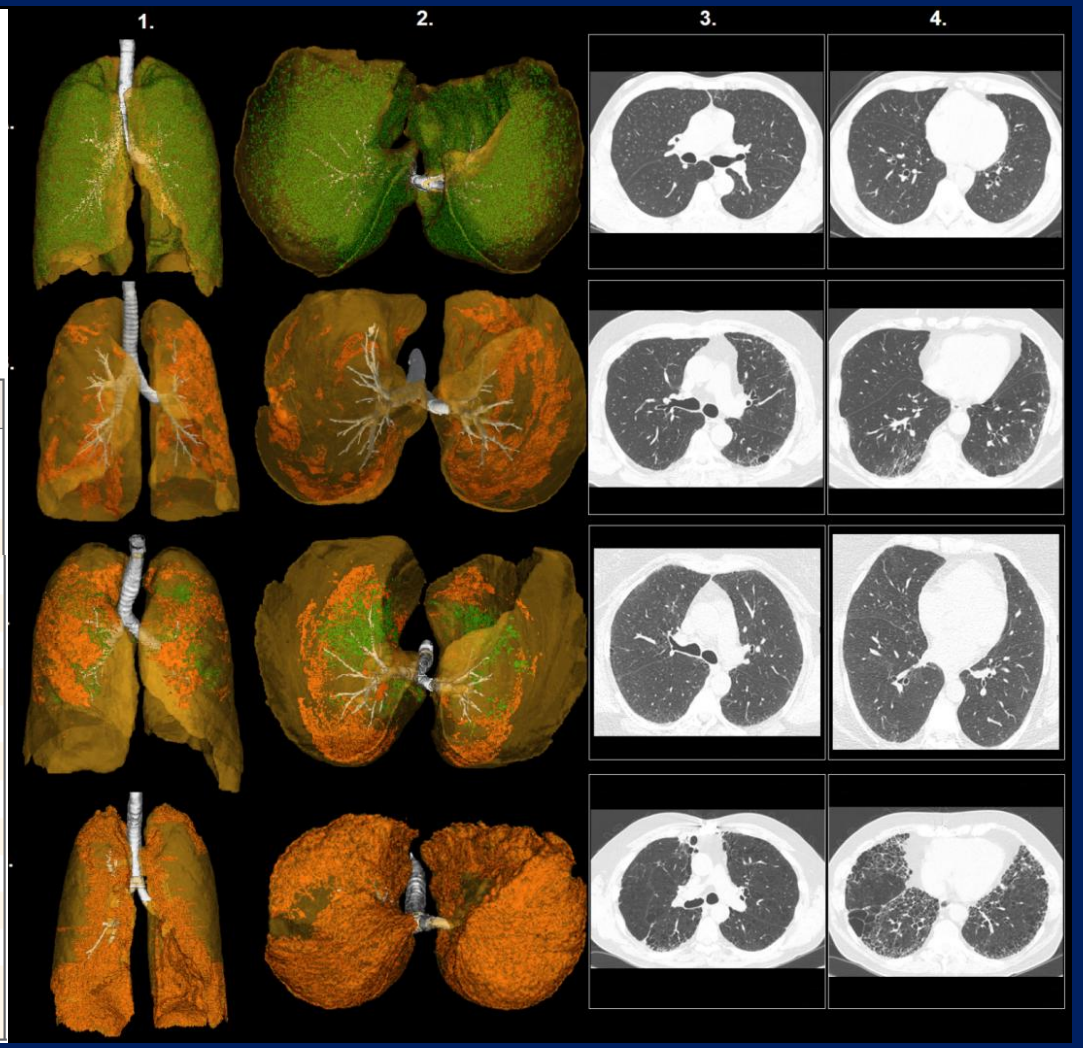
Interstitial Lung Abnormalities (ILA)

Lung Volumes and Emphysema in Smokers with Interstitial Lung Abnormalities

George R. Washko, M.D., M.M.Sc., Gary M. Hunninghake, M.D., M.P.H., Isis E. Fernandez, M.D., Mizuki Nishino, M.D., Yuka Okajima, M.D., Tsuneo Yamashiro, M.D., James C. Ross, M.S., Raúl San José Estépar, Ph.D., David A. Lynch, M.D., John M. Brehm, M.D., M.P.H., Katherine P. Andriole, Ph.D., Alejandro A. Diaz, M.D., Ramin Khorasani, Ph.D., Katherine D'Aco, M.S., Frank C. Sciurba, M.D., Edwin K. Silverman, M.D., Ph.D., Hiroto Hatabu, M.D., Ph.D., and Ivan O. Rosas, M.D., for the COPDGene Investigators*

Table 1. Baseline Characteristics of the Study Participants.*

Variable	Participants without ILA	P Value	Participants with Indeterminate HRCT Scans	P Value	Participants with ILA	P Value
Total — no. (%)	1361 (56)		861 (36)		194 (8)	
Median FVC — % of predicted‡	88 (75–100)	0.08	87 (74–99)	0.30	88 (77–98)	0.80
Median FEV_1:FVC %‡	70 (51–79)	0.04	68 (53–76)	0.01	71 (61–77)	0.32
Spirometric restriction — no. (%)§	414 (30)	0.82	266 (31)	0.004	81 (42)	0.002
Chest CT findings						
Median % emphysema¶						
–950 HU	4.1 (1.3–12.4)	<0.001	3.3 (0.9–9.7)	<0.001	2.2 (0.7–6.0)	<0.001
–910 HU	30 (15–47)	<0.001	23 (10–41)	<0.001	14 (7–29)	<0.001
Total lung capacity‖						
Median volume at full inspiration — liters	5.70 (4.80–6.78)	<0.001	5.21 (4.38–6.27)	0.08	5.02 (4.15–5.96)	<0.001
Median % of predicted value	107 (92–120)	<0.001	100 (84–112)	0.04	95 (81–109)	<0.001
<80% of predicted value — no. (%)	134 (10)	<0.001	169 (20)	0.77	40 (21)	<0.001
Median lung volume at relaxed exhalation — liters	3.13 (2.51–3.98)	0.06	3.04 (2.48–3.84)	<0.001	2.67 (2.23–3.44)	<0.001



Washko GR*, Hunninghake GM*, et al. *N Engl J Med*. 2011; 364 (10): 897-906

Interstitial Lung Abnormalities (ILA)

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, Johny 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†

AMERICAN THORACIC SOCIETY DOCUMENTS

Approach to the Evaluation and Management of Interstitial Lung Abnormalities

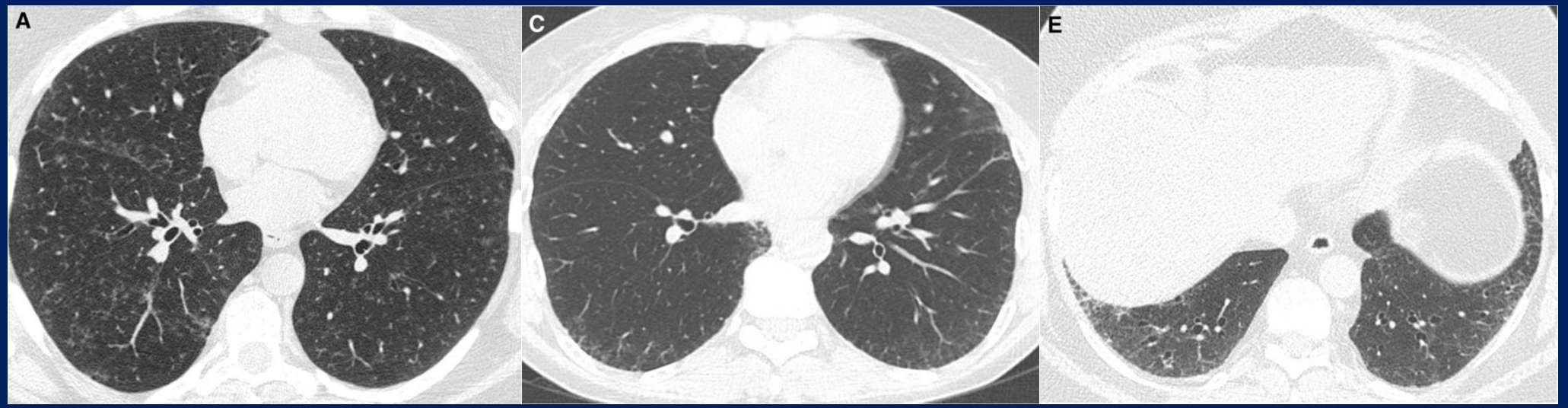
An Official American Thoracic Society Clinical Statement

Anna J. Podolanczuk*, Gary M. Hunninghake*, Kevin C. Wilson, Yet H. Khor, Fayez Kheir, Brandon Pang, Ayodeji Adegunsoye, Gretchen Cararie, Tamera J. Corte, Jim Flanagan, Gunnar Gudmundsson, Lida P. Hariri, Hiroto Hatabu, Stephen M. Humphries, Bhavika Kaul, John S. Kim, Melanie Konigshoff, Jonathan A. Kropski, Joyce S. Lee, Fengming Luo, David A. Lynch, Fernando J. Martinez, Sydney B. Montesi, Yuben Moodley, Justin M. Oldham, Sara Piciucchi, Rachel K. Putman, Luca Richeldi, Ivan O. Rosas, Margaret L. Salisbury, Mary M. Salvatore, Moises Selman, Joon Beom Seo, Jin Woo Song, Carey C. Thomson, Marina Vivero, Louise V. Wain, Marlies Wijsenbeek, David A. Schwartz‡, and Christopher J. Ryerson‡; on behalf of the American Thoracic Society Assembly on Clinical Problems

Hatabu H, et al. *Lancet Respir Med.* 2020; 8 (7): 726-737
Podolanczuk AJ*, Hunninghake GM*, et. *Am J Respir Crit Care Med.* 2025; 211 (7): 1132-1155

Interstitial Lung Abnormalities (ILA)

- Mild, often incidental, abnormalities on chest CT suggestive of ILD
- Non-focal, ≥ 5% of a lung zone, and include GGOs, reticulations, and traction bronchiectasis



Hatabu H, et al. *Lancet Respir Med.* 2020; 8 (7): 726-737
Podolanczuk AJ*, Hunninghake GM*, et. *Am J Respir Crit Care Med.* 2025; 211 (7): 1132-1155

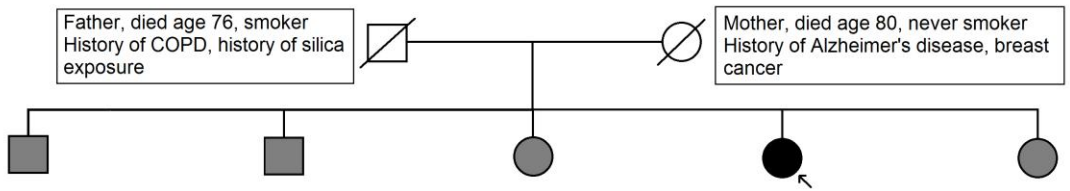
High Prevalence of ILA

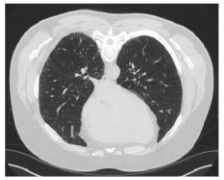
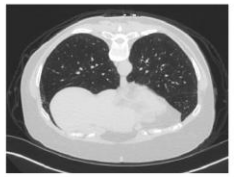
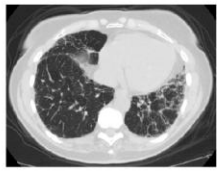
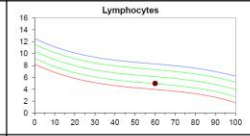
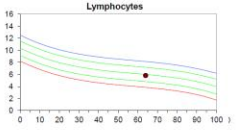
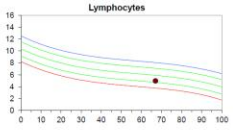
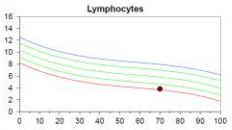
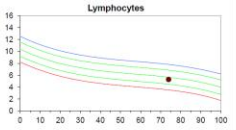
Present in 2-10% of population studies, higher in cohorts of smokers

	Population-based cohorts				Smoking and lung cancer screening cohorts				
	MESA[11,12,13,14]	Nagano, Japan*[15]	FHS[6,8,9]	AGES-Reykjavik[9]	ECLIPSE[9]	NLST[7,16]	COPDGene[4,9,17]	MILD[18]	DLCST[19]
Study characteristics									
Total number of chest CT scans evaluated	3137	3061	2633	5320	1670	884	9292	692	1990
Prevalence of ILAs	310 (10%)	80 (3%)	177 (7%)	377 (7%)	157 (9%)	86 (10%)	708 (8%)	28 (4%)	332 (17%)
Mean age of those with ILAs (years)	75	62	70	78	64	62	64	60	60

Hatabu H, et al. *Lancet Respir Med.* 2020; 8 (7): 726-737

Highest Risk in Relatives of Pts w/ PF



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					

Nashville FPF Cohort: ILA 23%, mean age 53

Salisbury ML, et al. *Am J Respir Crit Care Med.* 2020; 201: 1230-9

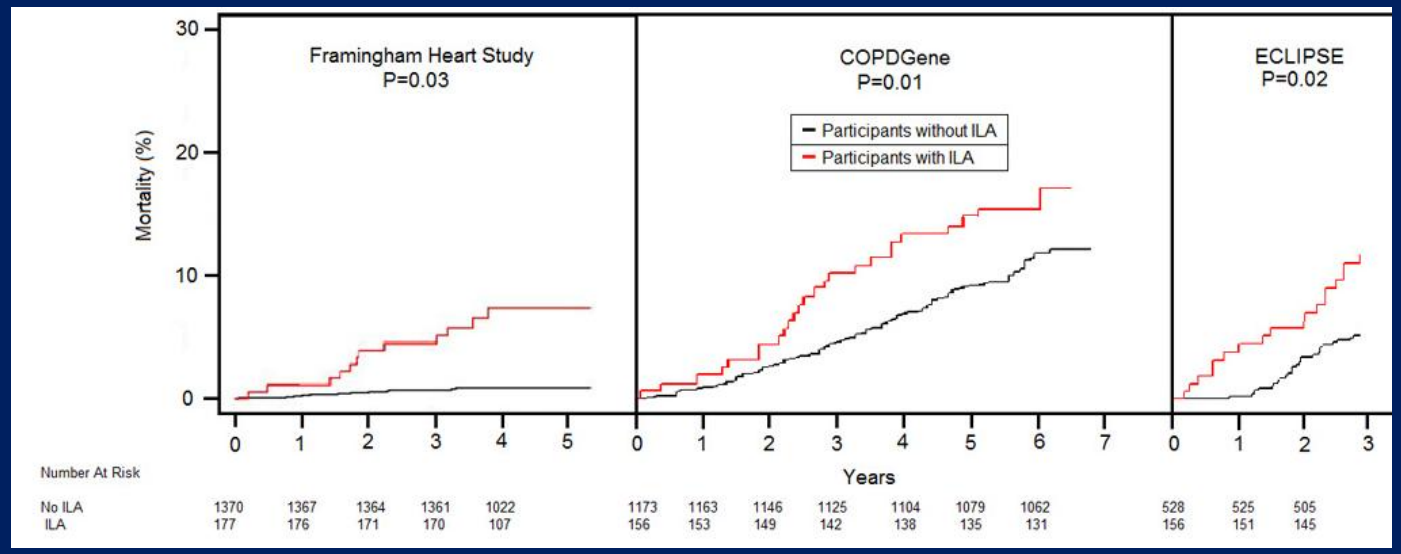
Boston PF Cohort: ILA 33%, mean age 59

Hunninghake GM, et al. *Am J Respir Crit Care Med.* 2020; 201: 1240-8

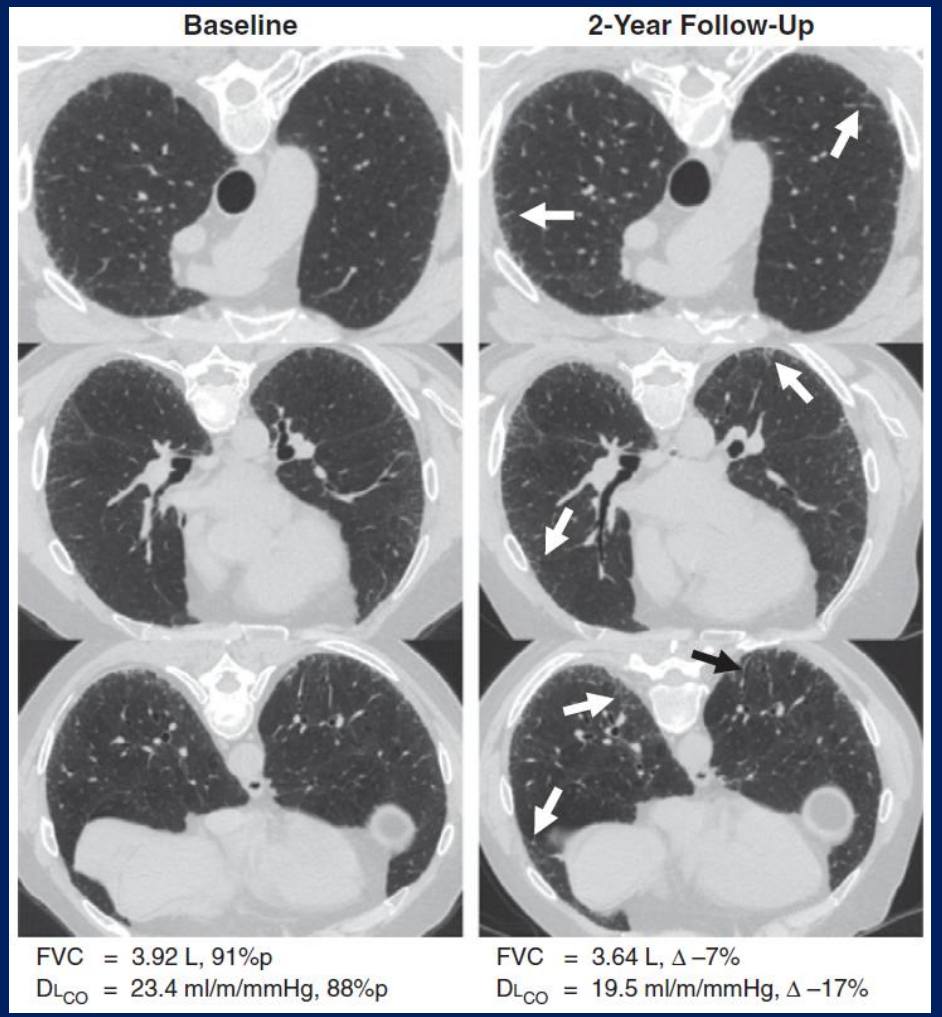
ILAs Associated with Poor Clinical Outcomes

Even mild, asymptomatic ILAs are associated with poor outcomes, such as progression and mortality

Increased Mortality



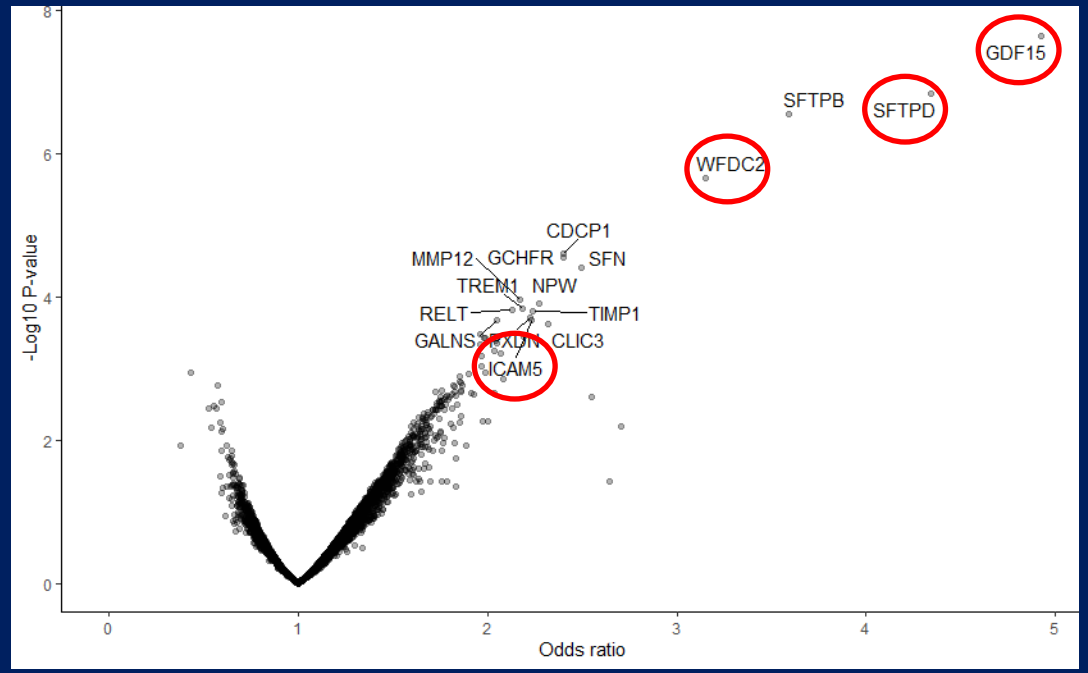
Progression



Putman RK, et al. *JAMA.* 2016; 315: 672–81
Rose JA, et al. *Am J Respir Crit Care Med.* 2023; 207 (2): 211-214

ILA and IPF Share Common Risk Factors and Molecular Markers

- Risk factors: age, smoking, *MUC5B*, and short telomeres
- Proteomic Markers:



Rose JA*, Steele MP*, et al. *Eur. Respir J.* 2025; 65 (6): 2401349

Table 2. Association between Interstitial Lung Abnormalities and *MUC5B* Genotype in the Framingham Heart Study.*

Status of Interstitial Lung Abnormalities	No. of Patients	*MUC5B* Genotype (rs35705950)			Adjusted Odds Ratio (95% CI)†	P Value	Adjusted Odds Ratio with Covariates (95% CI)‡	P Value
		G/G	G/T	T/T				
		no. of participants (%)						
Absence of interstitial lung abnormalities	1370	1113 (81)	247 (18)	10 (<1)	1.0		1.0	
Presence of interstitial lung abnormalities	177	115 (65)	56 (32)	6 (3)	2.3 (1.6–3.1)	<0.001	2.8 (2.0–3.9)	<0.001
Definite fibrosis§	47	26 (55)	20 (43)	1 (2)	3.0 (1.8–5.0)	<0.001	6.3 (3.1–12.7)	<0.001

Hunninghake GM, et al. *N Engl J Med.* 2013; 368 (23): 2192-200

qPCR‡ Measurement	Continuous Telomere Length		Shortest Quartile of Telomere Length (Q1) †	
	Odds Ratio§ 95% Confidence Interval	P-value	Odds Ratio 95% Confidence Interval	P-value
AGES-Reykjavik	15.4 (3.8-62.5)	0.0001	2.7 (1.4-5.1)	0.002
COPDGene	4.2 (2.1-8.5)	<0.0001	2.2 (1.5-3.4)	0.0001
Southern Blot Measurement	**Length Difference 95% Confidence Interval**	**P-value**		
Framingham Heart Study	767bp (76-1584)	0.03	--	--

Putman RK, et al. *Eur Respir J.* 2022; 60 (2): 2101814

Early Detection in Pulmonary Fibrosis

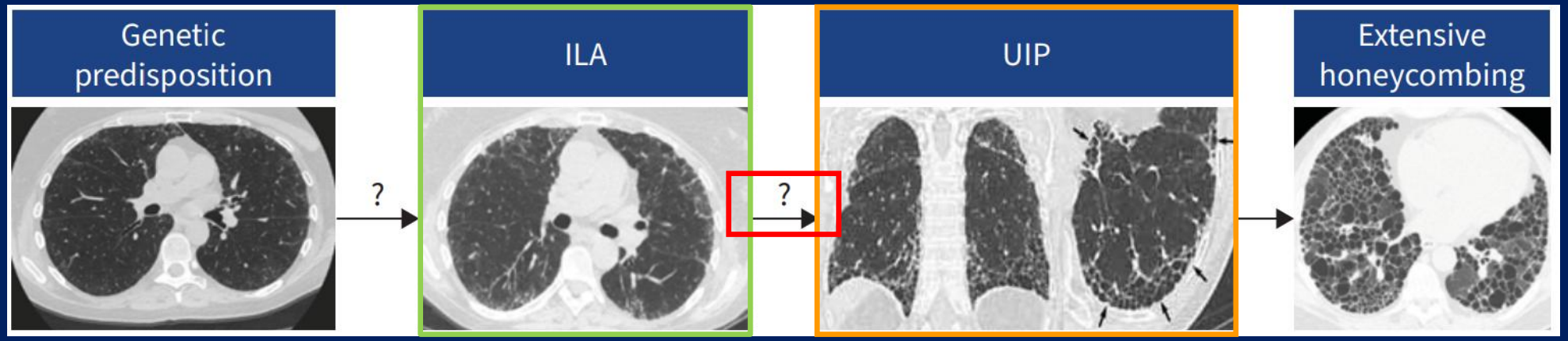
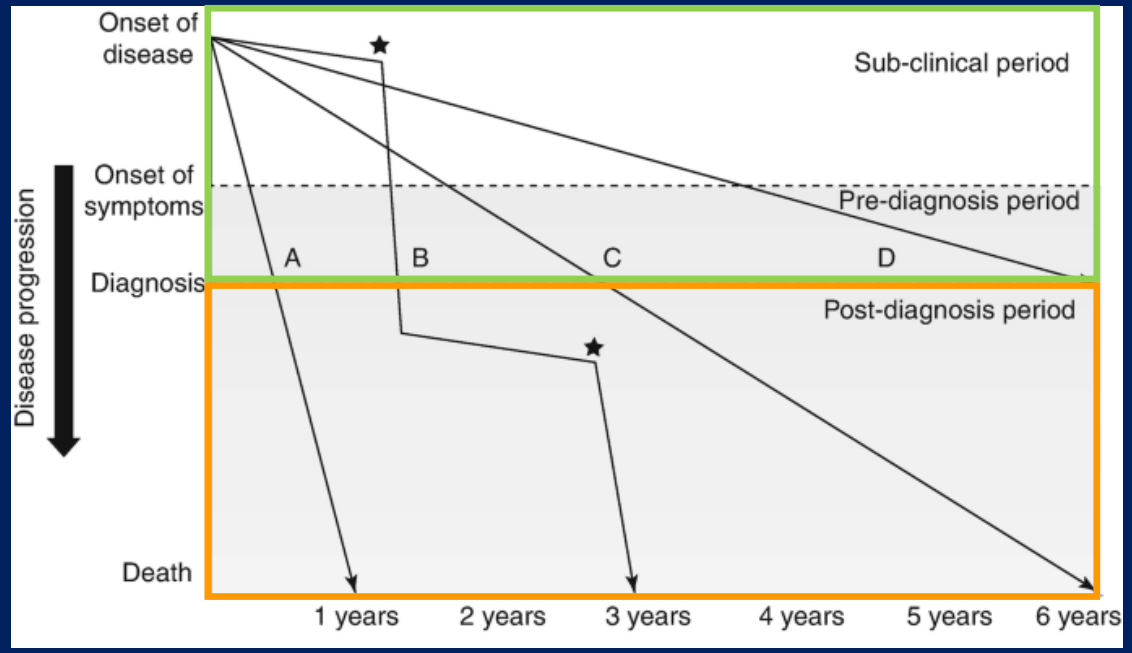


Figure modified from Podolanczuk A, et al. *Eur Respir J.* 2023; 61 (4): 2200957

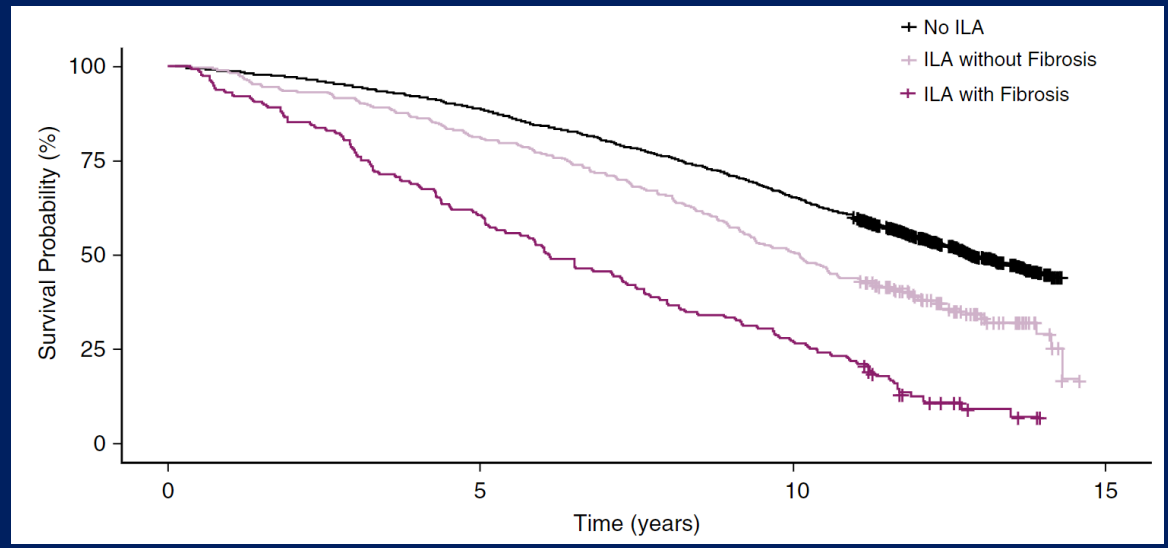


Radiologic Risk-Stratification of ILA

- In AGES-Reykjavik, imaging features/patterns associated with 5-year radiologic progression
- ILA with fibrosis had 8-fold more progression than ILA without fibrosis
- Fibrosis associated with increased mortality

Association between 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†	—	—	—	—
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‡	—	—	—	—

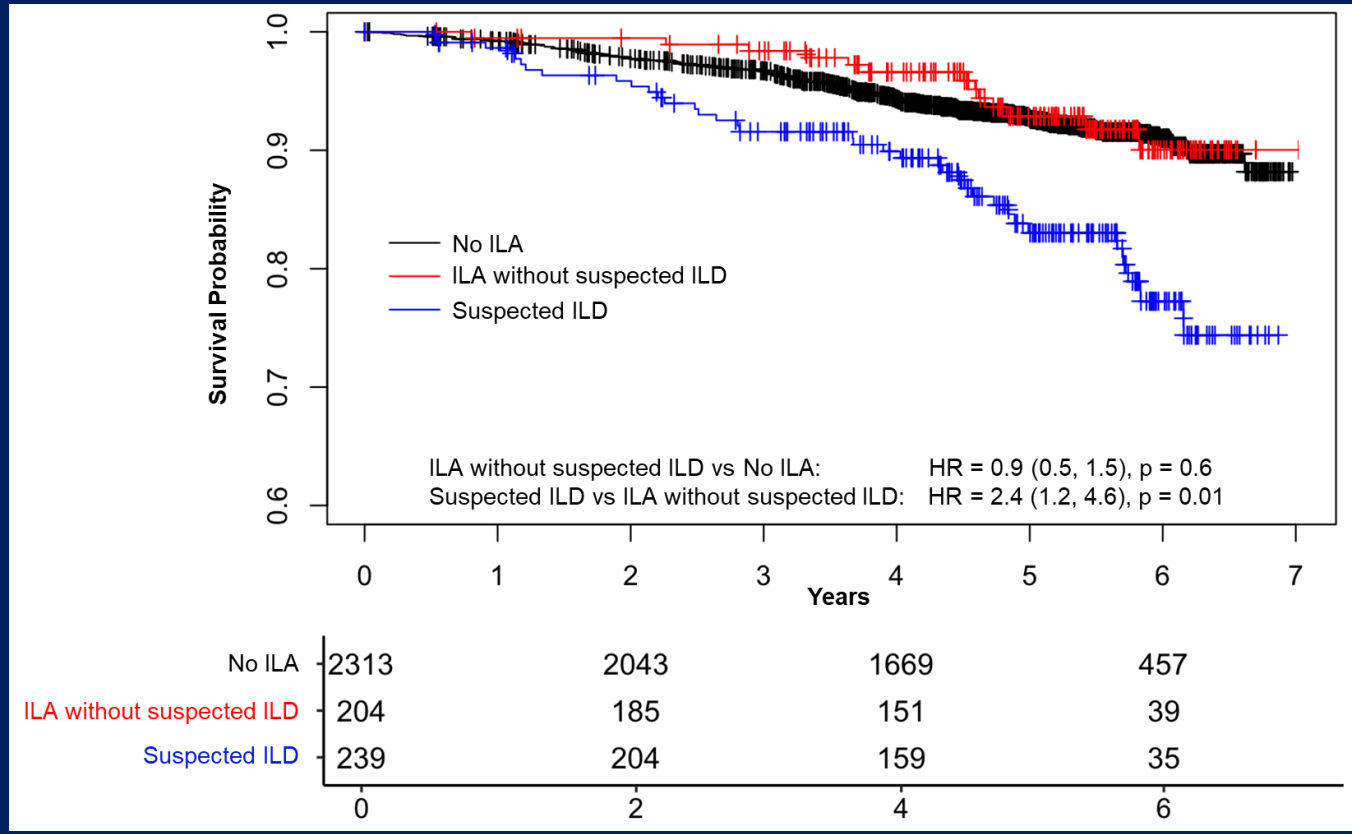


Putman RK, et al. *Am J Respir Crit Care Med.* 2019; 200 (2): 175-183

Risk Stratification of ILA using CT and PFTs

- Suspected ILD: ILA + one of the following:

1) Definite fibrosis on CT (mainly traction bronchiectasis)
2) FVC <80%
3) DLCO <70%



Rose JA, et al. *Am J Respir Crit Care Med.* 2023; 207 (1): 60-68

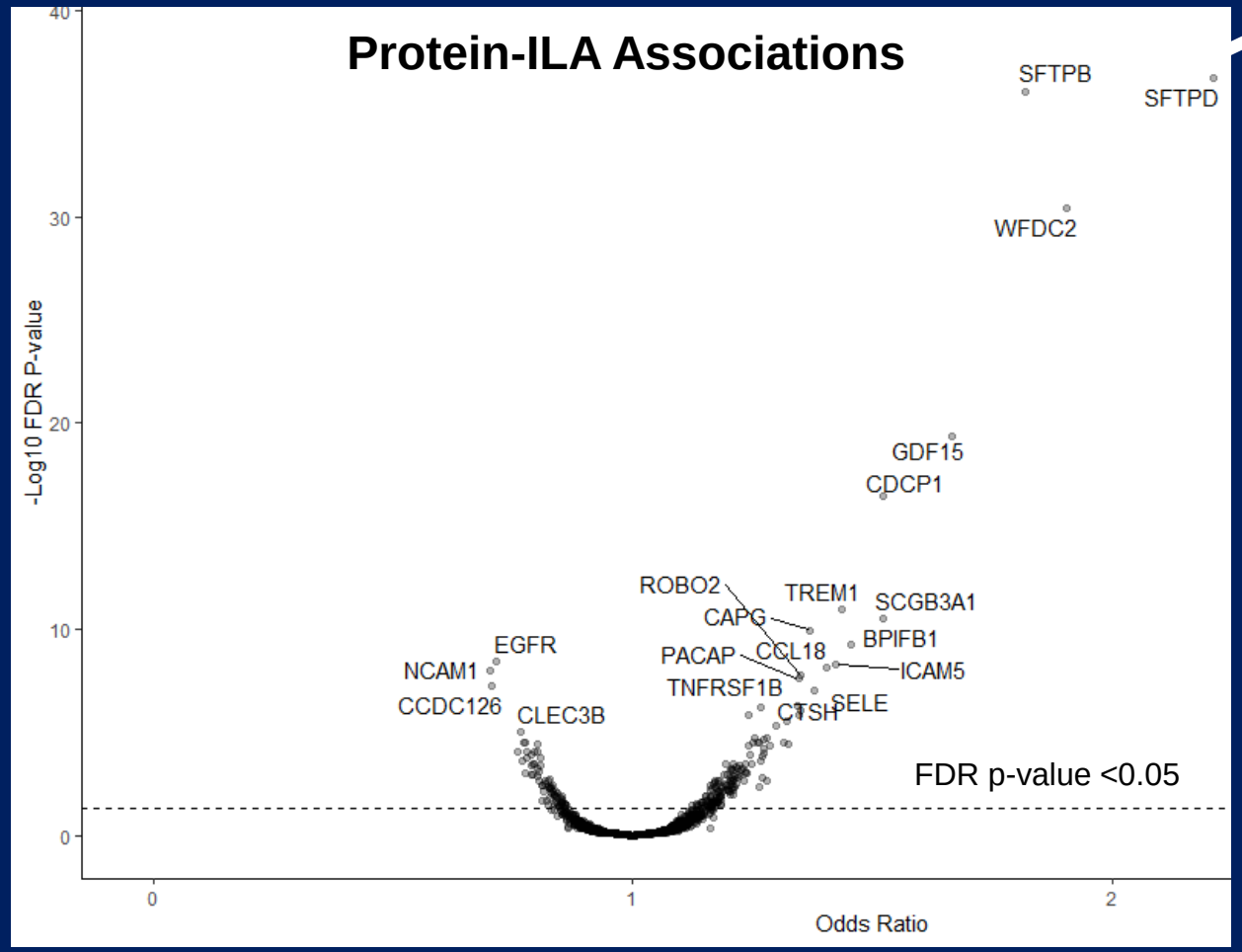
ILD Criteria May Be Effective at Excluding Low Risk ILA (with caveats)

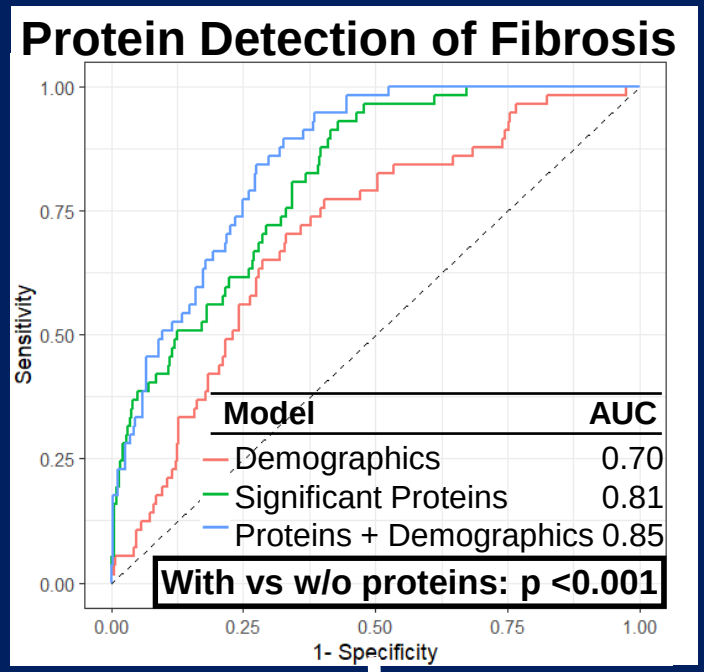
Outcome	No ILA (N=2313)	ILA without suspected ILD (N=204)	Adjusted Analysis	
			Effect Estimate	**P value**
			Mean Difference (95% CI)	
SGRQ—points, mean (SD)	19.4 (20.1)	18.5 (16.3)	2.2 (-0.2, 4.6)	0.1
6MWT—m, mean (SD)	421 (128)	415 (121)	-5.3 (-21.0, 10.5)	0.5
Exacerbation Frequency—no. per year, mean (SD)	0.26 (0.74)	0.16 (0.46)	-0.03 (-0.1, 0.07)	0.6
			Odds Ratio (95% CI)	
Supplemental Oxygen—no. (%)	214 (9.3%)	11 (5.4%)	0.9 (0.4, 1.8)	0.7
Severe Exacerbation—no. (%)	177 (7.7%)	6 (3.0%)	0.5 (0.2, 1.2)	0.1
			Hazard Ratio (95% CI)	
Mortality—no. (%)	161 (7.0%)	13 (6.4%)	0.9 (0.5, 1.5)	0.6

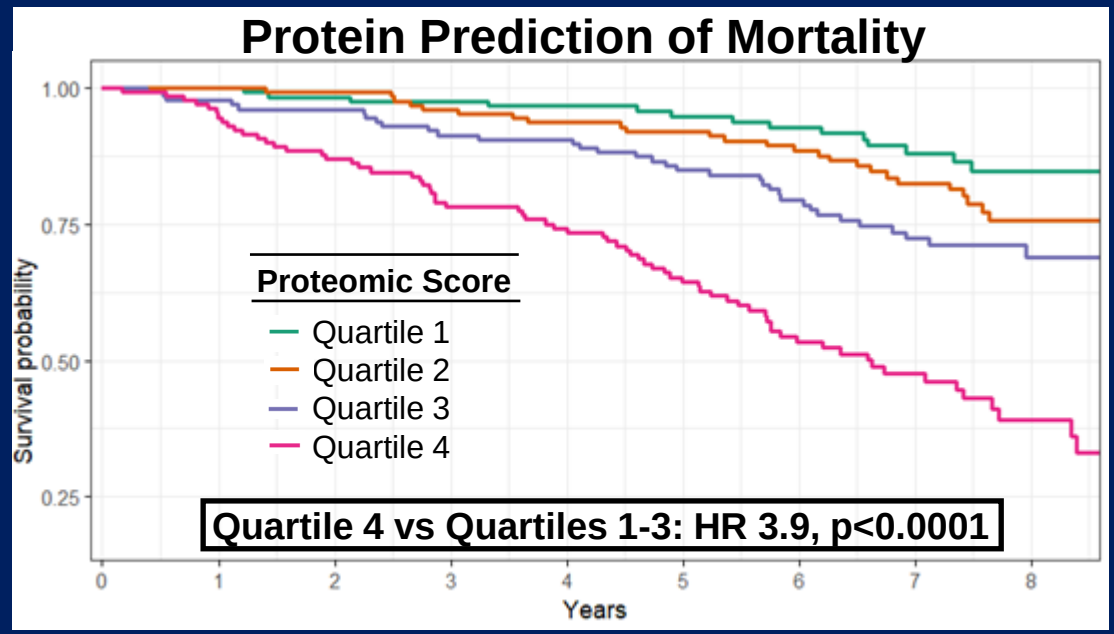
*Covariates included age, race, sex, BMI, pack-years smoking, current smoking status, and GOLD stage

Rose JA, et al. *Am J Respir Crit Care Med.* 2023; 207 (1): 60-68

Blood Biomarkers to Risk-Stratify ILA







Manuscript in preparation

ILA Recommendations for Clinical Practice

AMERICAN THORACIC SOCIETY DOCUMENTS

Approach to the Evaluation and Management of Interstitial Lung Abnormalities

An Official American Thoracic Society Clinical Statement

Anna J. Podolanczuk*, Gary M. Hunninghake*, Kevin C. Wilson, Yet H. Khor, Fayez Kheir, Brandon Pang, Ayodeji Adegunsoye, Gretchen Cararie, Tamera J. Corte, Jim Flanagan, Gunnar Gudmundsson, Lida P. Hariri, Hiroto Hatabu, Stephen M. Humphries, Bhavika Kaul, John S. Kim, Melanie Konigshoff, Jonathan A. Kropski, Joyce S. Lee, Fengming Luo, David A. Lynch, Fernando J. Martinez, Sydney B. Montesi, Yuben Moodley, Justin M. Oldham, Sara Piciucchi, Rachel K. Putman, Luca Richeldi, Ivan O. Rosas, Margaret L. Salisbury, Mary M. Salvatore, Moises Selman, Joon Beom Seo, Jin Woo Song, Carey C. Thomson, Marina Vivero, Louise V. Wain, Marlies Wijsenbeek, David A. Schwartz‡, and Christopher J. Ryerson‡; on behalf of the American Thoracic Society Assembly on Clinical Problems

THIS OFFICIAL CLINICAL STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS APPROVED APRIL 2025

Podolanczuk AJ*, Hunninghake GM*, et. *Am J Respir Crit Care Med.* 2025; 211 (7): 1132-1155

ILD Definition

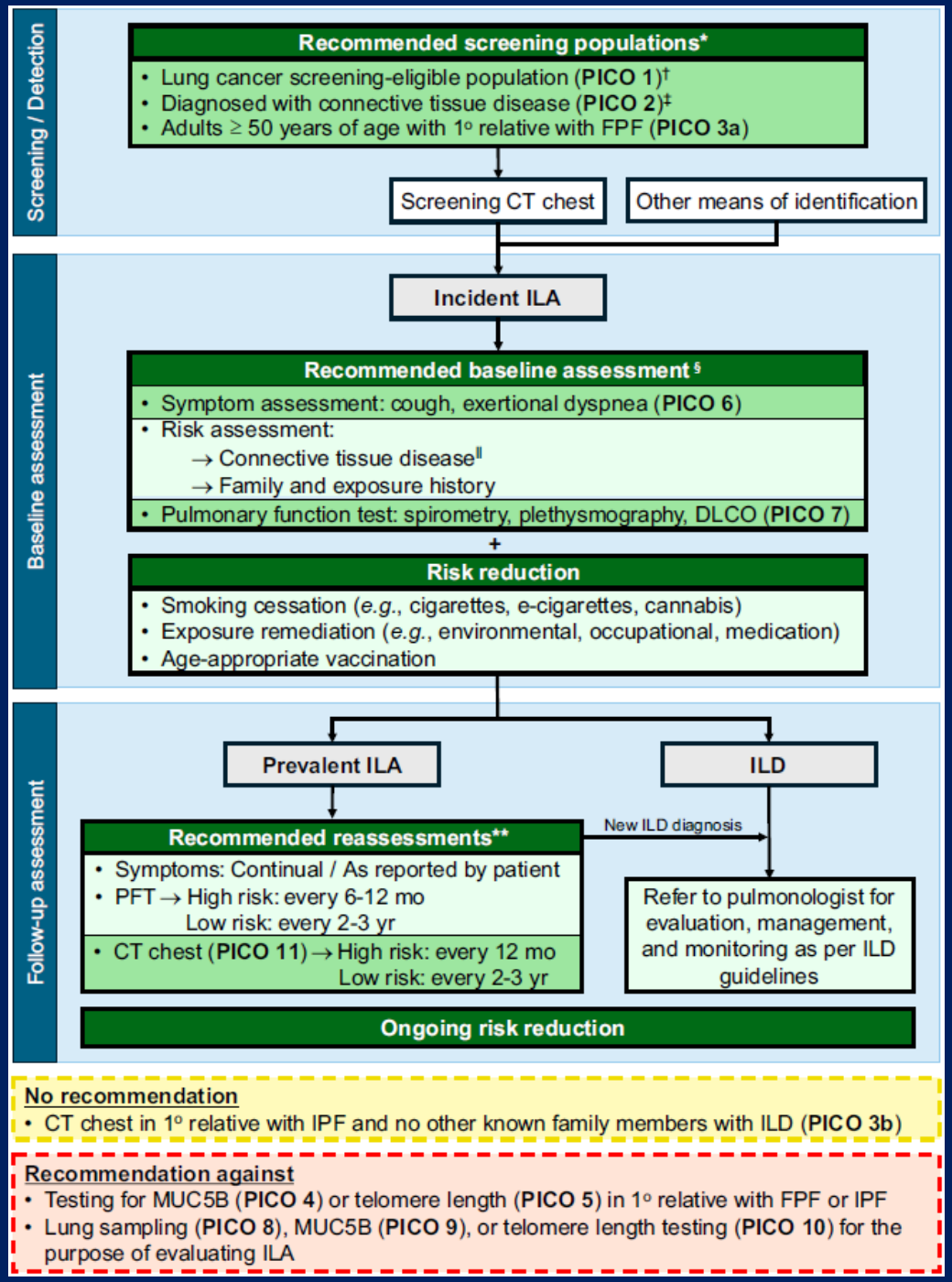
Table 3. Definition of ILD

Definition of interstitial lung disease for those with ILAs
In a person with CT features of ILAs, at least one of the following criteria must be present to define ILD*
• Symptoms: Any amount of dyspnea and/or cough that a clinician attributes to ILD
• Physiology (any of) ○ Any abnormality in FVC, TLC, or D_{LCO} that a clinician attributes to ILD (defined as a value or *z*-score below the lower limit of normal) ○ Satisfies physiologic criteria for progressive pulmonary fibrosis that a clinician attributes to ILD (9)
• Imaging (any of the following on chest CT) ○ Fibrotic abnormalities (honeycombing and/or reticulation with traction bronchiectasis) involving ⩾5% of total lung volume by visual estimate ○ Progressive fibrotic abnormality on serial chest CT ○ Presence of a major fibrotic ILD pattern on chest CT (i.e., UIP/probable UIP, fibrotic HP, or fibrotic NSIP)
• Pathology: Presence of a major fibrotic ILD pattern (i.e., UIP/probable UIP, fibrotic HP, or fibrotic NSIP)

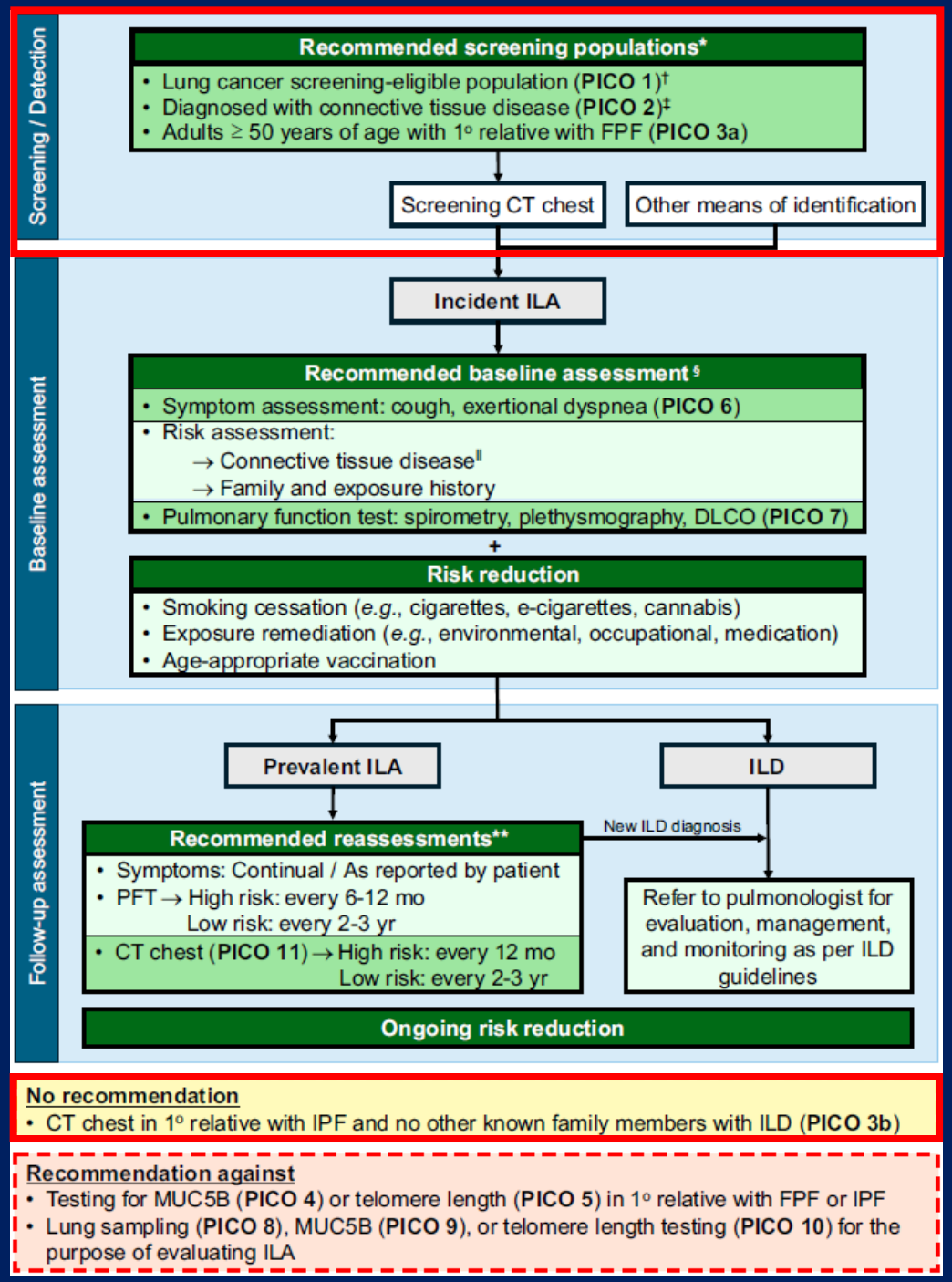
Definition of abbreviations: CT = computed tomography; HP = hypersensitivity pneumonitis; ILA = interstitial lung abnormality; ILD = interstitial lung disease; NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonitis.
*Further diagnostic workup may be needed to diagnose the specific ILD type. Diagnosis of nonfibrotic ILD requires integration of multiple domains.

Podolanczuk AJ*, Hunninghake GM*, et. *Am J Respir Crit Care Med.* 2025; 211 (7): 1132-1155

ILA Management



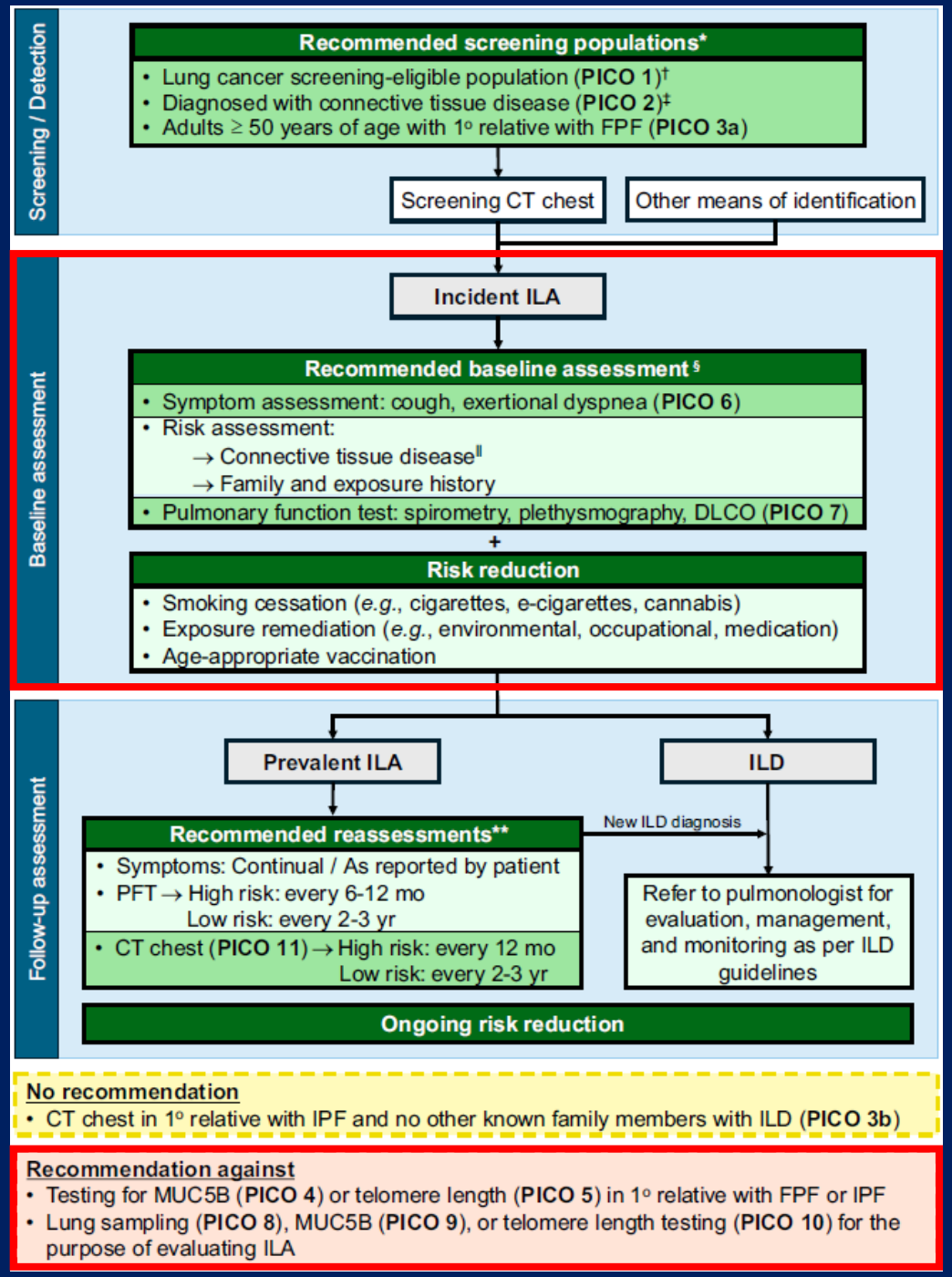
Podolanczuk AJ*, Hunninghake GM*, et. *Am J Respir Crit Care Med.* 2025; 211 (7): 1132-1155



ILA Management Screening

- Lung cancer screening CTs should be evaluated for ILA
- High-risk connective tissue disease (SSc, RA, MCTD, Sjogren's inflammatory myopathies)
- Adults >50 yo with a 1st degree relative with familial PF (ie someone with 2 relatives)

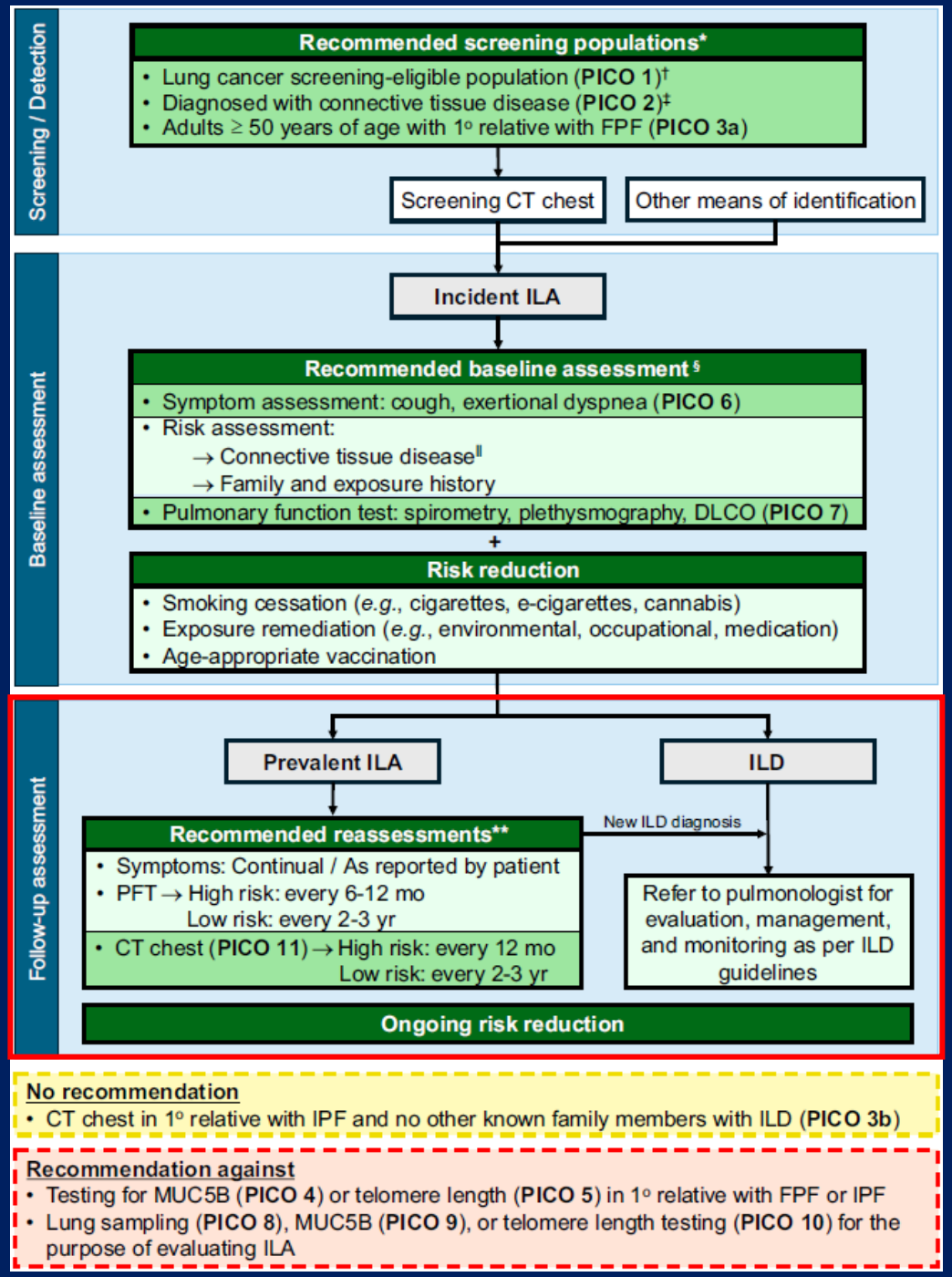
Podolanczuk AJ*, Hunninghake GM*, et. *Am J Respir Crit Care Med.* 2025; 211 (7): 1132-1155



ILA Management Evaluation

- Symptoms: dyspnea and cough
- Exposure history
- Family history
- CTD assessment:
  - Symptoms (e.g. arthritis, skin changes, dry eyes/dry mouth, weakness)
  - Exam
  - Serologies when clinically indicated
- Full PFTs
- HRCT (if not already obtained)

Podolanczuk AJ*, Hunninghake GM*, et. *Am J Respir Crit Care Med.* 2025; 211 (7): 1132-1155



ILA Management Follow-up

Based on risk assessment:

High-risk ILA features

Demographic and clinical factors
- Family history of pulmonary fibrosis
- Older age
- Smoking history
- Other inhaled exposures (e.g., occupational vapors, gases, dusts, and fumes; air pollution)
- Connective tissue disease

Genetic
- *MUC5B* promoter variant
- Leukocyte telomere length below age-adjusted 10th percentile

Imaging
- Definite fibrosis on CT (i.e., honeycombing, traction bronchiectasis or architectural distortion)
- Subpleural fibrotic and subpleural nonfibrotic subtypes
- Subpleural reticulation
- Greater extent of abnormalities (e.g., involvement of multiple lung zones)

Physiologic
- Abnormal or borderline FVC, TLC, and D_{LCO}

Podolanczuk AJ*, Hunninghake GM*, et. *Am J Respir Crit Care Med.* 2025; 211 (7): 1132-1155

Treatment Trial in Early ILD

DROP-FPF

A Study to Test Whether Nerandomilast Can Help Slow Down Changes in the Lung in People With a Family History of Pulmonary Fibrosis

ClinicalTrials.gov ID NCT07201922

Sponsor Boehringer Ingelheim

Information provided by Boehringer Ingelheim (Responsible Party)

Last Update Posted 2025-11-12

- Phase 3b double-blind, randomized, placebo-controlled exploratory trial
- Efficacy and safety of Nerandomilast over 2 years
- Participants >40 yo w/ ILA and 1st degree relative w/ PF; normal lung function
- Key Study Endpoints: change in quantitative CT and pulmonary function (FVC and DLCO)

Conclusions

- ILA are mild, often incidental, abnormalities on chest CT suggestive of ILD
- They are highly prevalent and highest in 1st degree relatives of patients with PF
- ILA may be the key to early detection of progressive fibrosis
- High risk populations like CTD and 1st degree relatives should be screened for ILA
- When detected, should have a thorough evaluation and be followed systematically to identify progression as soon as able

Thanks!

- Rob Hallowell
- Matt Hunninghake
- Rachel Putman, Ann Tukpah and Claire Cutting
- COPDGene, CGS-PF, UC, AGES-Reykjavik, SPIROMICS, FHS
- MGB PCCM
  - Bruce Levy
  - Hilary Goldberg
  - Eric Schmidt
  - George Washko
  - Mark Perella
  - Michael Cho
  - Benji Raby
- Funding:

NIH National Heart, Lung, and Blood Institute

FRANCIS FAMILY FOUNDATION
Brighter futures for all generations


Questions?
Comments?
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL
Mass General Brigham