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Mind the gap

Elucidating the spectrum of pulmonary fibrosis

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Disclosures

Currently receive grant support from the NIH.

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Case #1

- 59-year-old man with shortness of breath
- Dry cough and decreased exercise tolerance for 6 months
- 15 pack-year history (quit 20 years ago)
- Acid reflux, hypertension
- Preacher at church
- Family history: 2 older brothers with ILD, mother died of unknown lung disease at 63 years old
- CT scan: Subpleural reticulation, mild traction bronchiectasis

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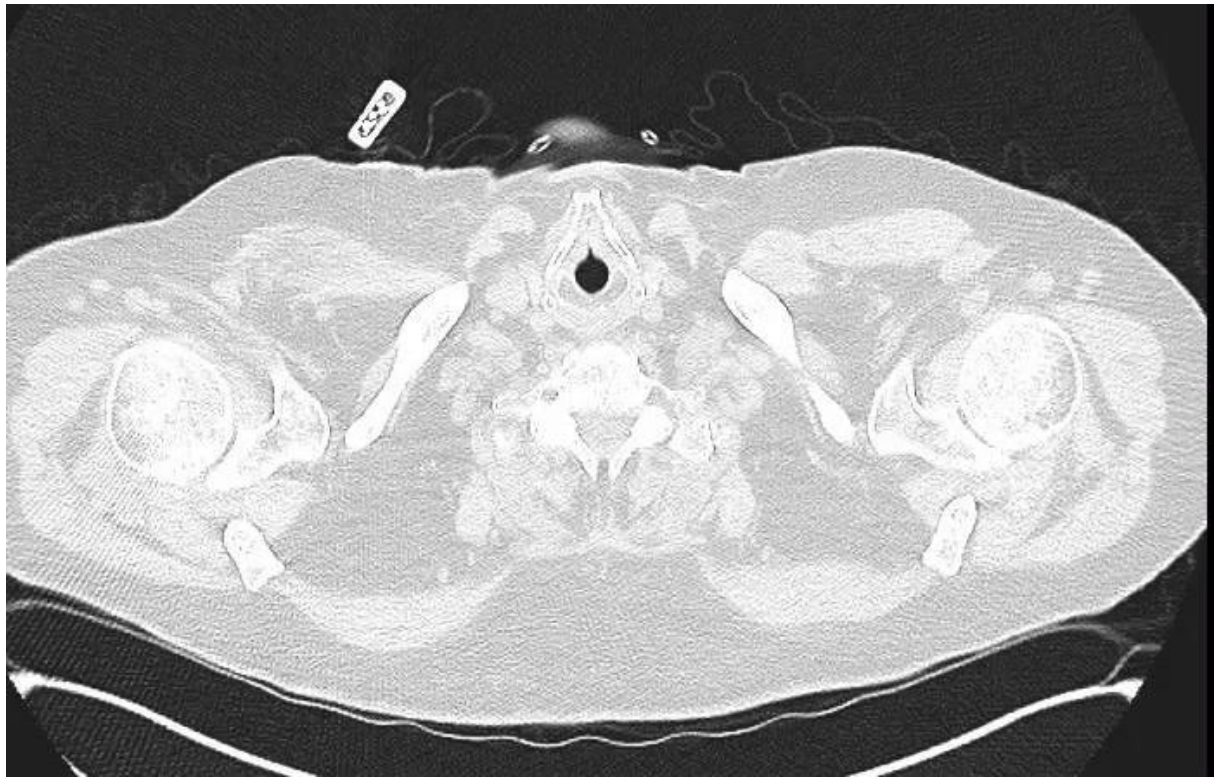
10 years later

- 8-10 liters of supplemental oxygen
- Older brother waitlisted for lung transplantation
- 3-vessel coronary artery disease
- Telomere length below 10th percentile



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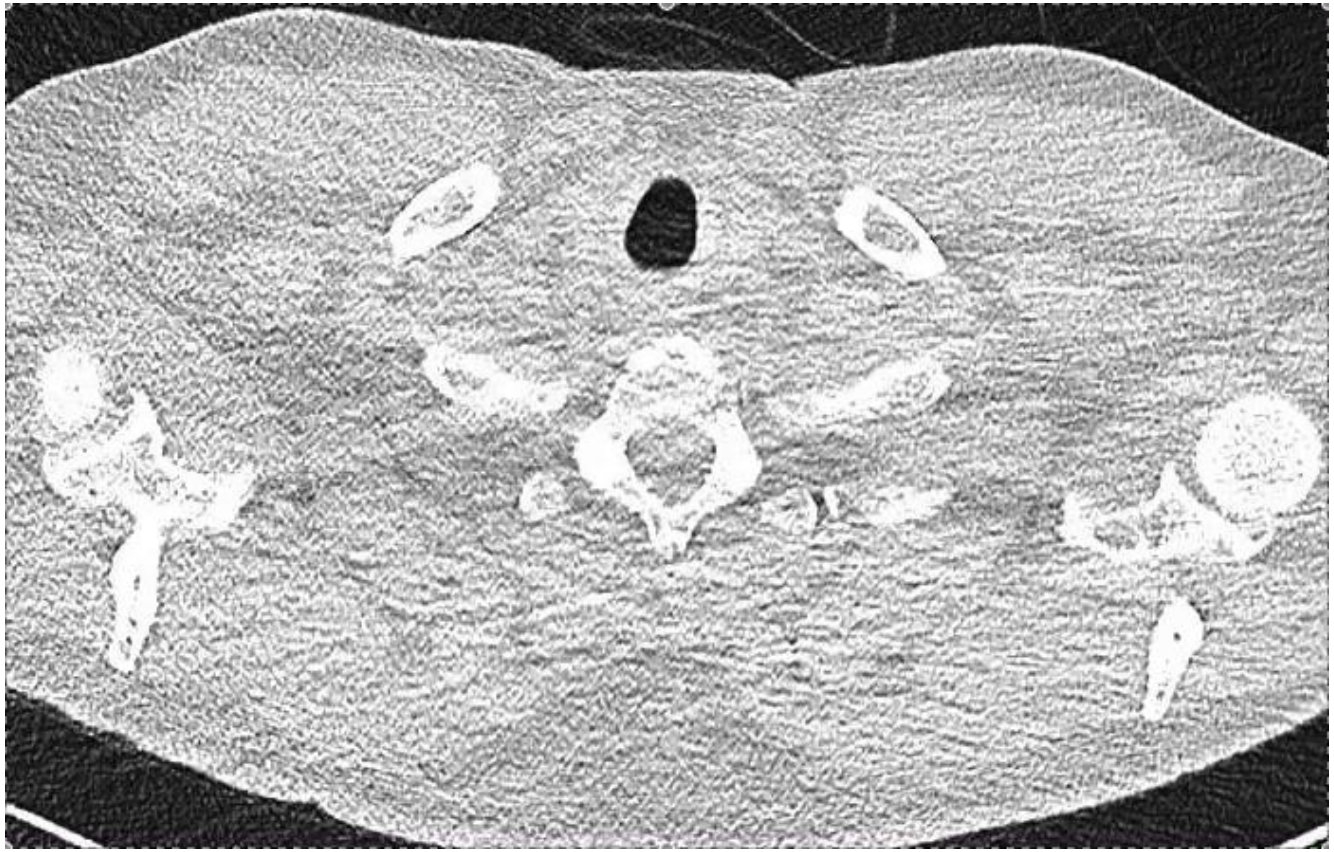
Case #2

- 59-year-old man with abnormal lung CT scan
- No respiratory symptoms, normal PFTs



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Questions

- Should Case #1 undergo screening for pulmonary fibrosis?
- Does Case #2 have ILD? How should we follow these individuals?
- Are there other tools to complement CT imaging to detect early stages of ILD?
- **Can we prevent pulmonary fibrosis?**

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Outline

- Early detection of lung fibrosis – why it matters
- Interstitial lung abnormalities
- Blood-based biomarkers

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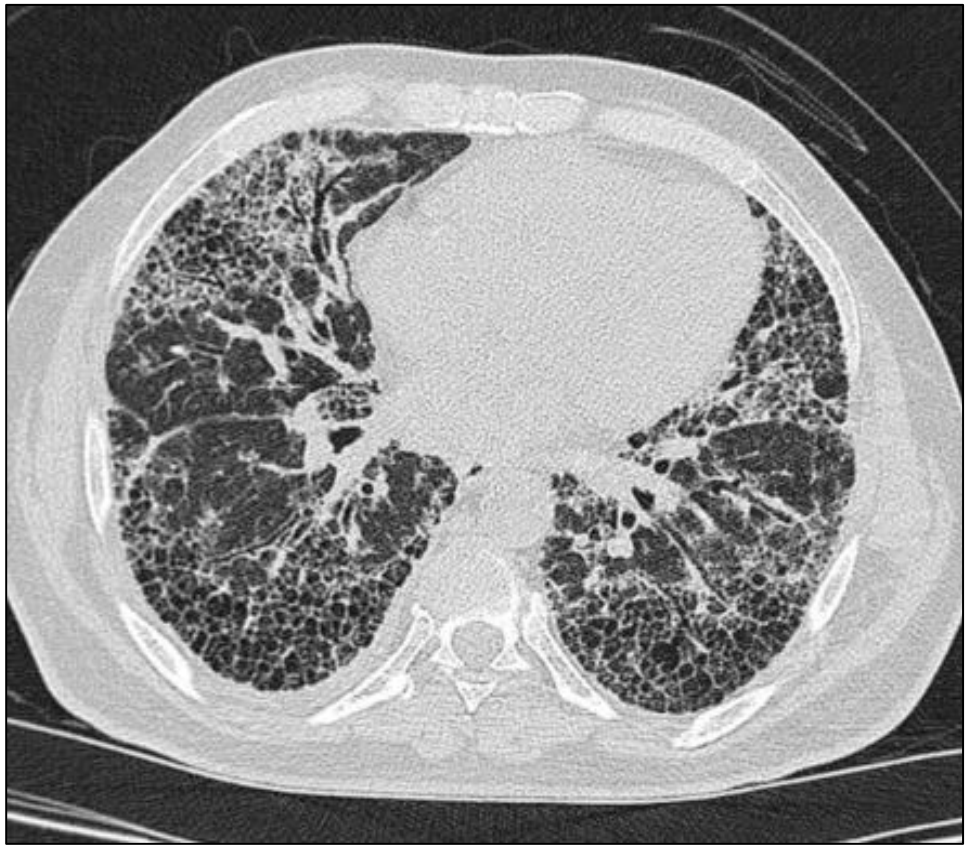
Pulmonary fibrosis

- Recurrent lung injury that can lead to fibrosis
- Strong genetic component (*MUC5B*, telomerase mutations)
- Common reason for lung transplantation (limited donor pool, ~50% 5-year survival)
- Current drugs slow progression but have side effects and often stopped



Lederer DJ, et al. New Engl J Med. 2018.
Wijsenbeek M, Vottin V. New Engl J Med. 2019.

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Onset of symptoms
Diagnosis by pulmonologist

Stable

Mild progressors

RAPID PROGRESSORS

Dise sion

Early Stage (Asymptomatic)

Late Stages (Symptomatic)

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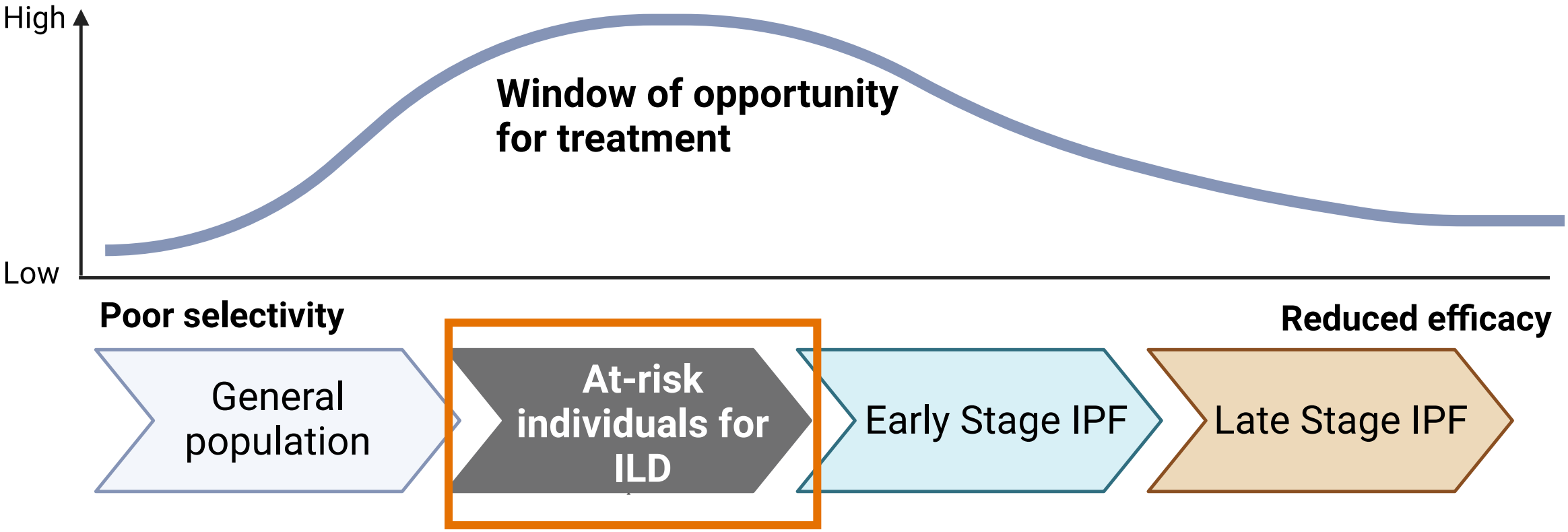
Optimal time to intervene in IPF



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“Establishing a diagnosis of pulmonary fibrosis in our traditional symptom-linked fashion is akin to diagnosing coronary artery disease only after a patient presents with a myocardial infarction…***A different approach is needed***, if we are to examine the biological events that underlie the early development of this disease.”

~David Lederer

Lederer DJ. Am J Resp Crit Care Med. 2012.

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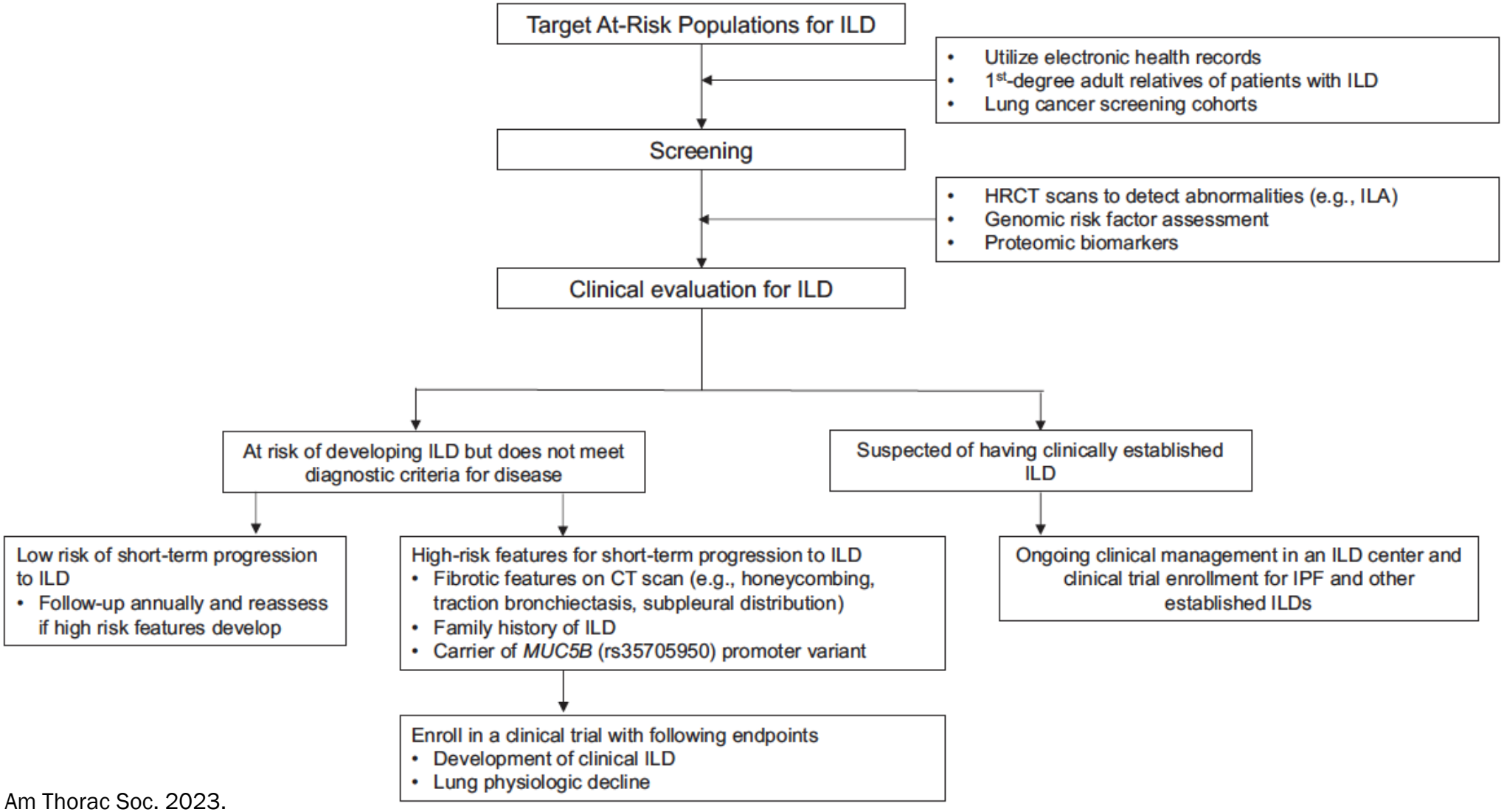
Approach to Clinical Trials for the Prevention of Pulmonary Fibrosis

John S. Kim[1,2], Sydney B. Montesi[3], Ayodeji Adegunsoye[5], Stephen M. Humphries[6], Margaret L. Salisbury[7], Lida P. Hariri[3,4], Jonathan A. Kropski[7], Luca Richeldi[8], Athol U. Wells[9,10], Simon Walsh[11], R. Gisli Jenkins[11], Ivan Rosas[12], Imre Noth[1], Gary M. Hunninghake[13], Fernando J. Martinez[14], and Anna J. Podolanczuk[14]



Kim JS, et al. Ann Am Thorac Soc. 2023.

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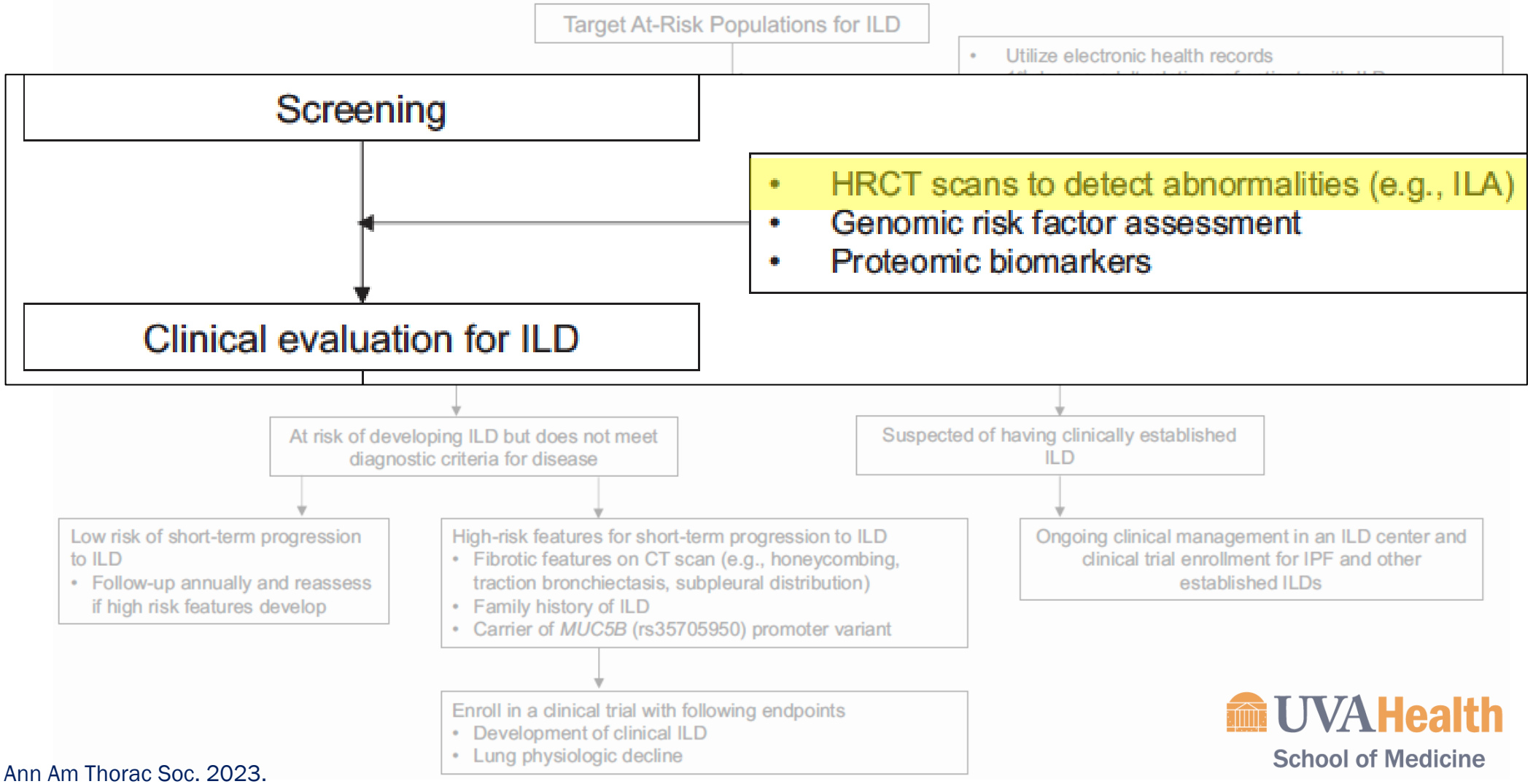

Kim JS, et al. Ann Am Thorac Soc. 2023.

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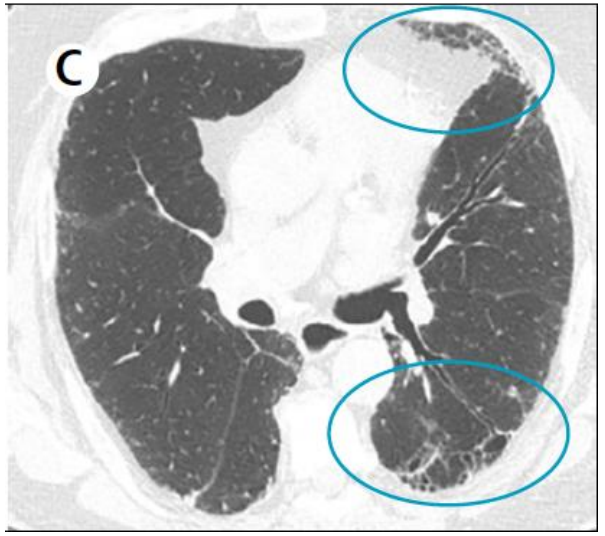
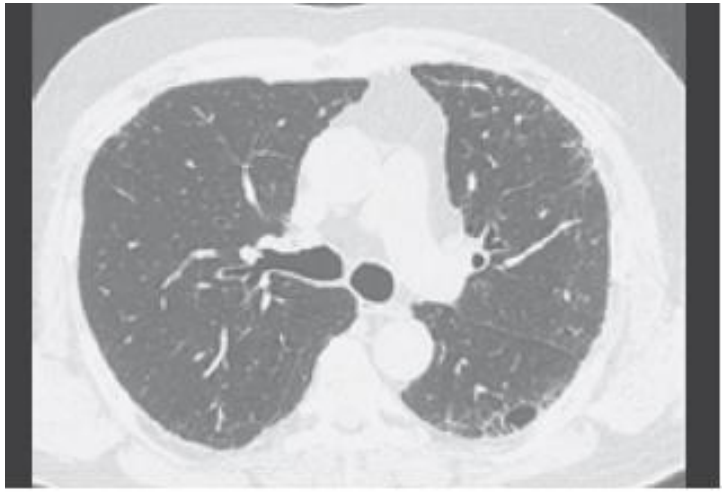
Interstitial lung abnormalities

- Qualitative assessment of ILD-related features
- Subjective
- Subpleural and fibrotic subtype most concerning
- Genomic variants related to IPF risk
- **Radiological phenotype**-not a clinical entity





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Hobbs BD, et al. Am J Resp Crit Care Med. 2019.
Hatabu H, et al. Lancet Resp Med. 2020.

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

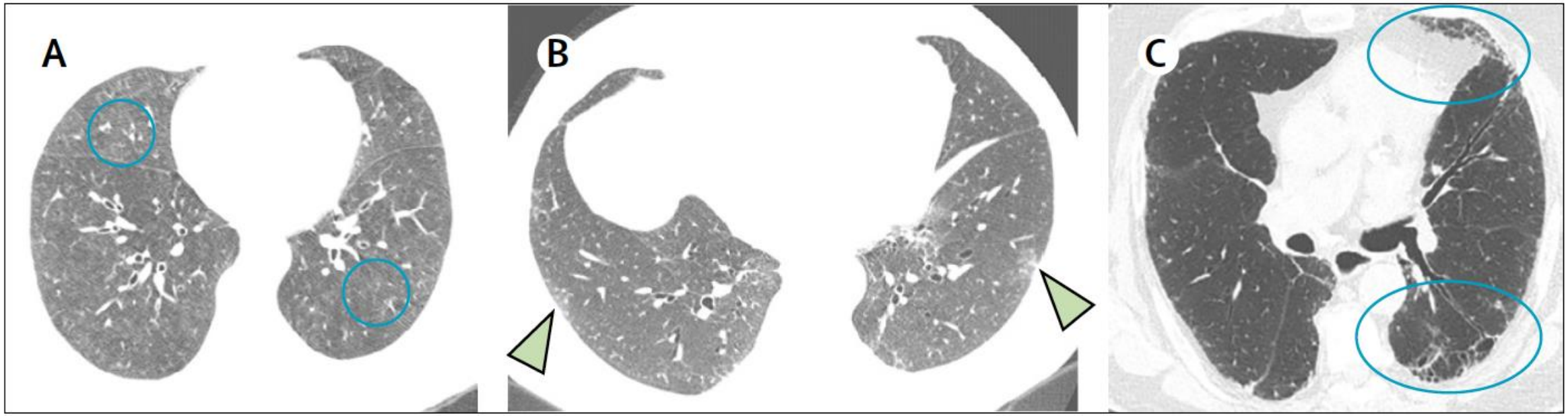
Hiroto Hatabu, Gary M Hunninghake, Luca Richeldi, Kevin K Brown, Athol U Wells, Martine Remy-Jardin, Johny Verschakelen, Andrew G Nicholson, Mary B Beasley, David C Christiani, Raúl San José Estépar, Joon Beom Seo, Takeshi Johkoh, Nicola Sverzellati, Christopher J Ryerson, R Graham Barr, Jin Mo Goo,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

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

Hatabu, H, et al. Lancet Resp Med. 2020.

Subtypes of ILA



Non-subpleural ILA

Subpleural non-fibrotic ILA

Subpleural fibrotic ILA

Hatabu, H, et al. Lancet Resp Med. 2020.

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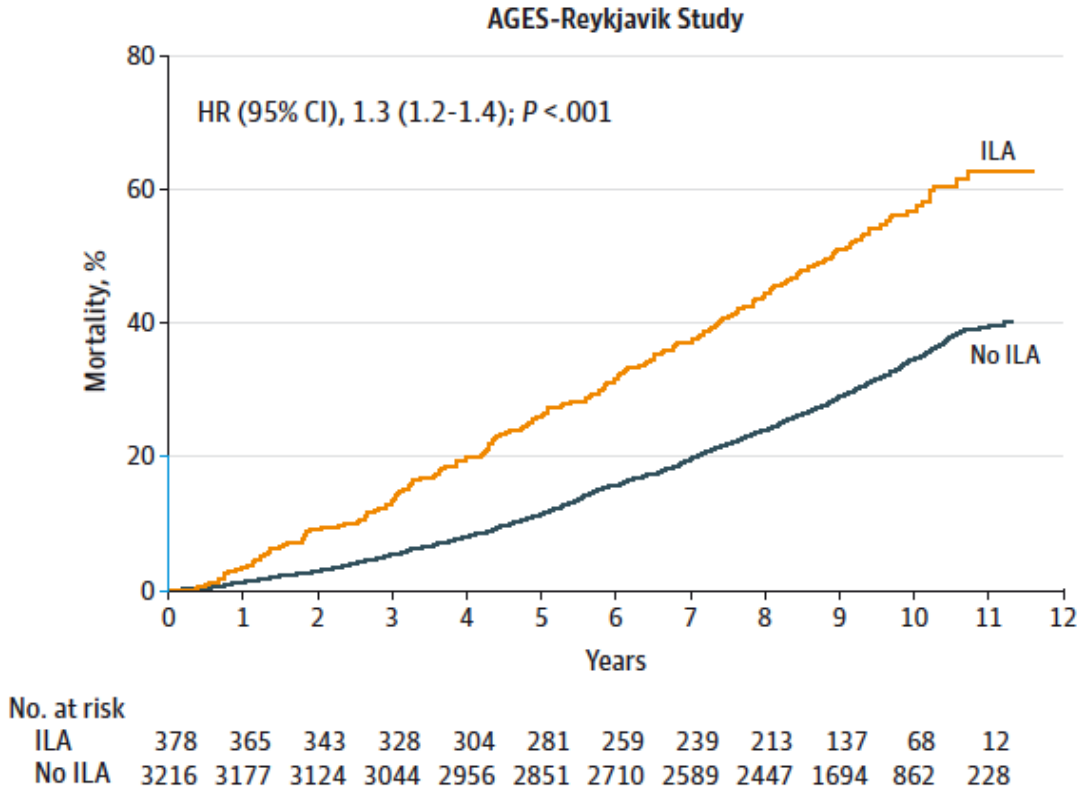
ILA is not trivial

- Higher risk of overall death
- Higher risk of respiratory-related mortality
- Correlate with lower lung function
- High risk of progression within 5-10 years
- Prevalent in 1st-degree relatives of patients with lung fibrosis



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Park S, et al. Am J Resp Crit Care Med. 2023.
Salisbury, ML, et al. Am J Resp Crit Care Med. 2020.
Hunninghake GM, et al. Am J Resp Crit Care Med. 2020.
Steele MP, et al. Am J Resp Crit Care Med. 2023.

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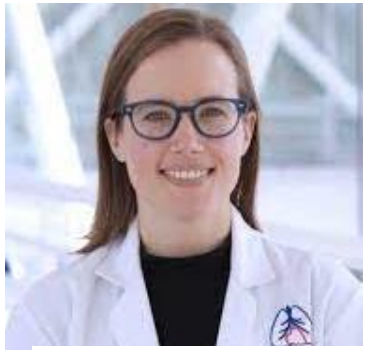
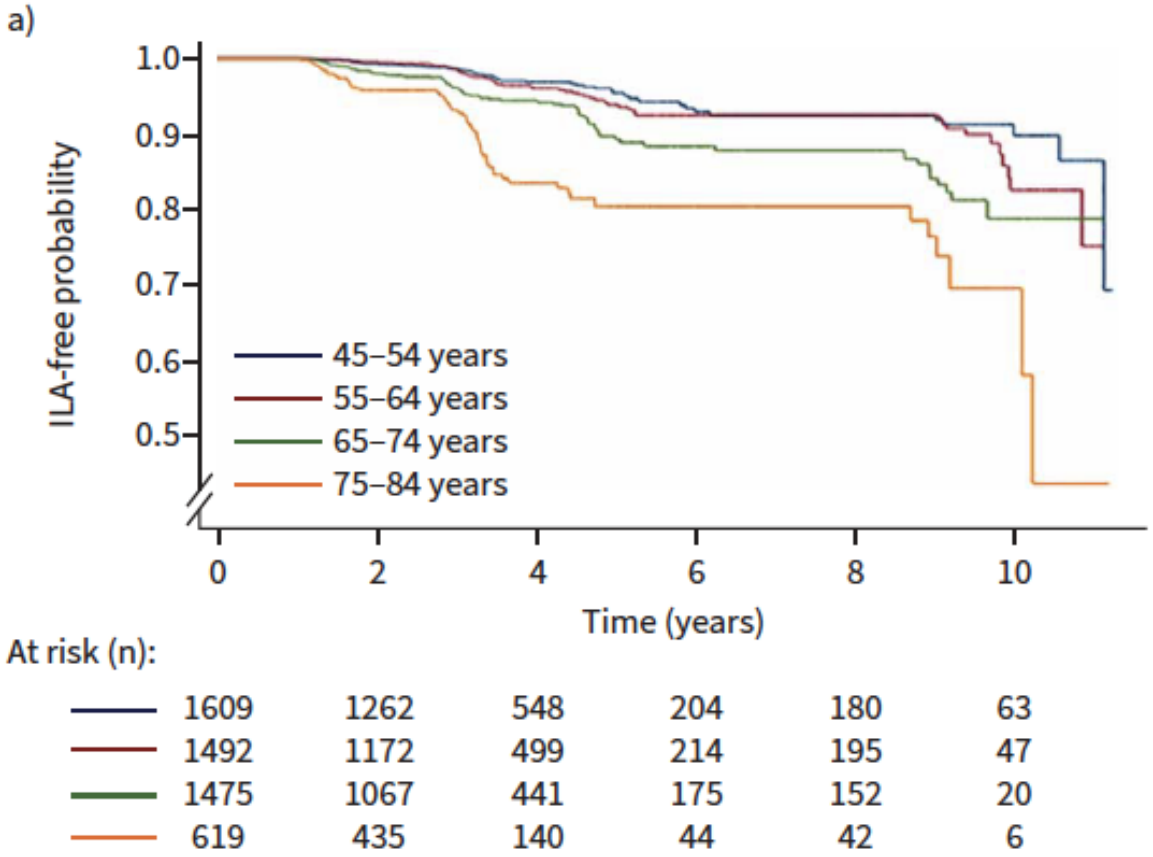
Incidence of interstitial lung abnormalities: the MESA Lung Study

Claire F. McGroder[1], Spencer Hansen[2], Karen Hinckley Stukovsky[2], David Zhang[1], P. Hrudaya Nath[3], Mary M. Salvatore[4], Sushilkumar K. Sonavane[5], Nina Terry[3], Justin T. Stowell[5], Belinda M. D'Souza[4], Jay S. Leb[4], Shifali Dumeer[4], Muhammad U. Aziz[3], Kiran Batra[6], Eric A. Hoffman[7], Elana J. Bernstein[1], John S. Kim[1,8], Anna J. Podolanczuk[1,9], Jerome I. Rotter[10], Ani W. Manichaikul[11,12], Stephen S. Rich[11,12], David J. Lederer[1,13], R. Graham Barr[1,14], Robyn L. McClelland[2] and Christine Kim Garcia[1,15,16]



Claire McGroder



Incidence (per 1000 person years)

- ILA: 13.1
- Fibrotic ILA: 3.5

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McGroder C, et al. Eur Resp J. 2023.

Long-Term Follow-Up of Interstitial Lung Abnormality: Implication in Follow-Up Strategy and Risk Thresholds

Sohee Park[1], Jooae Choe[1], Hye Jeon Hwang[1], Han Na Noh[2], Young Ju Jung[2], Jung-Bok Lee[3], Kyung-Hyun Do[1], Eun Jin Chae[1], and Joon Beom Seo[1]

- Adults over 50 years self-referred to health screening at Asan Medical Center
- 200 adults with ILA and follow-up lung CT
- *81% of patients* have progression (median time 3.2 years)
- *17% progress to UIP* (median time 11.8 years)
- Subpleural fibrotic subtype and fibrosis extent are independent predictors of progression

Park S, et al. Am J Resp Crit Care Med. 2023.

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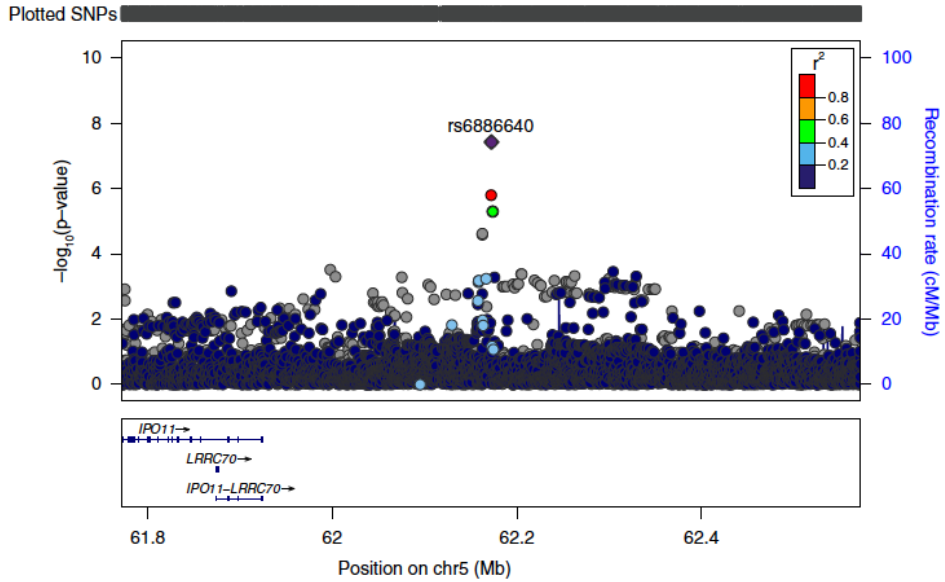
Genetics of ILA

- Overlapping genetic variants between ILA and IPF
- *MUC5B* (rs3575950) associates with ILA and subpleural-fibrotic ILA
- Unique variants associate with ILA only (*IPO11*, *FCF1P3*)
- ILA associates with shorter telomere length



Hunninghake GM, et al. New Engl J Med. 2013.
Hobbs BD, et al. Am J Resp Crit Care Med. 2019.
Salisbury ML, et al. Am J Resp Crit Care Med. 2020.
Putman RK, et al. Eur Resp J. 2022.

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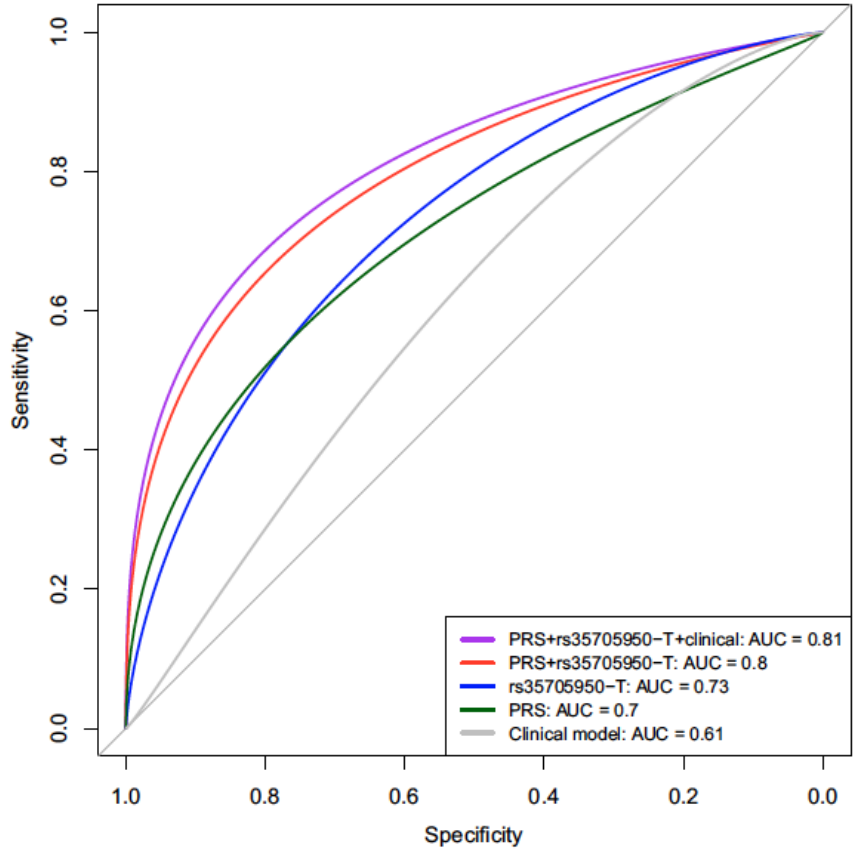
A Polygenic Risk Score for Idiopathic Pulmonary Fibrosis and Interstitial Lung Abnormalities

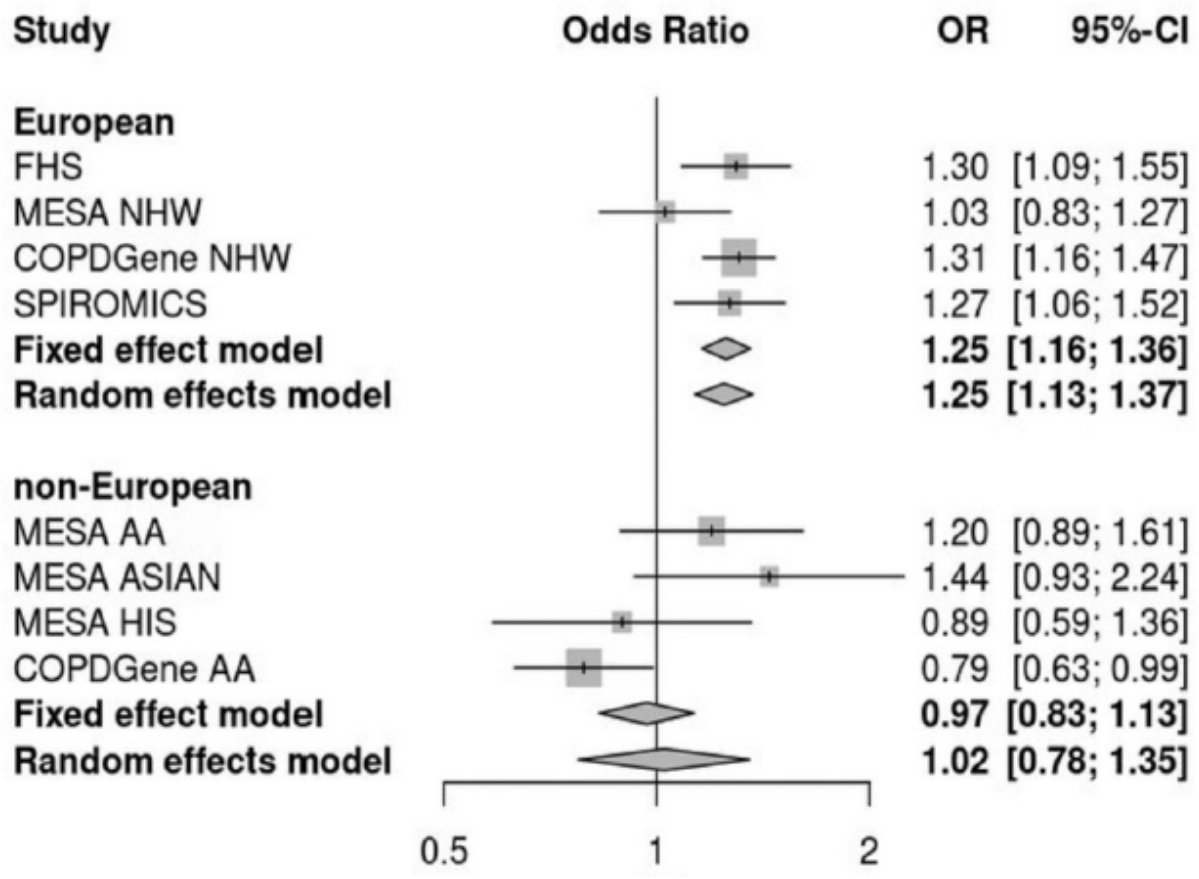
Matthew Moll[1,2*], Anna L. Peljto[6,7*], John S. Kim[8*], Hanfei Xu[9], Catherine L. Debban[10], Xianfeng Chen[11], Aravind Menon[1], Rachel K. Putman[1], Auyon J. Ghosh[12], Aabida Saferali[2], Mizuki Nishino[3], Hiroto Hatabu[3], Brian D. Hobbs[1,2], Julian Hecker[2], Gregory McDermott[13], Jeffrey A. Sparks[13], Louise V. Wain[14,15], Richard J. Allen[14,15], Martin D. Tobin[14,15], Benjamin A. Raby[2,4,5], Sung Chun[5], Edwin K. Silverman[1,2], Ana C. Zamora[11], Victor E. Ortega[11], Christine K. Garcia[16], R. Graham Barr[17,18], Eugene R. Bleecker[19], Deborah A. Meyers[19], Robert J. Kaner[20], Stephen S. Rich[10], Ani Manichaikul[10], Jerome I. Rotter[21], Josée Dupuis[9,22], George T. O'Connor[23], Tasha E. Fingerlin[24], Gary M. Hunninghake[1‡], David A. Schwartz[6,7‡], and Michael H. Cho[1,2‡]

Matthew Moll

IPF Risk

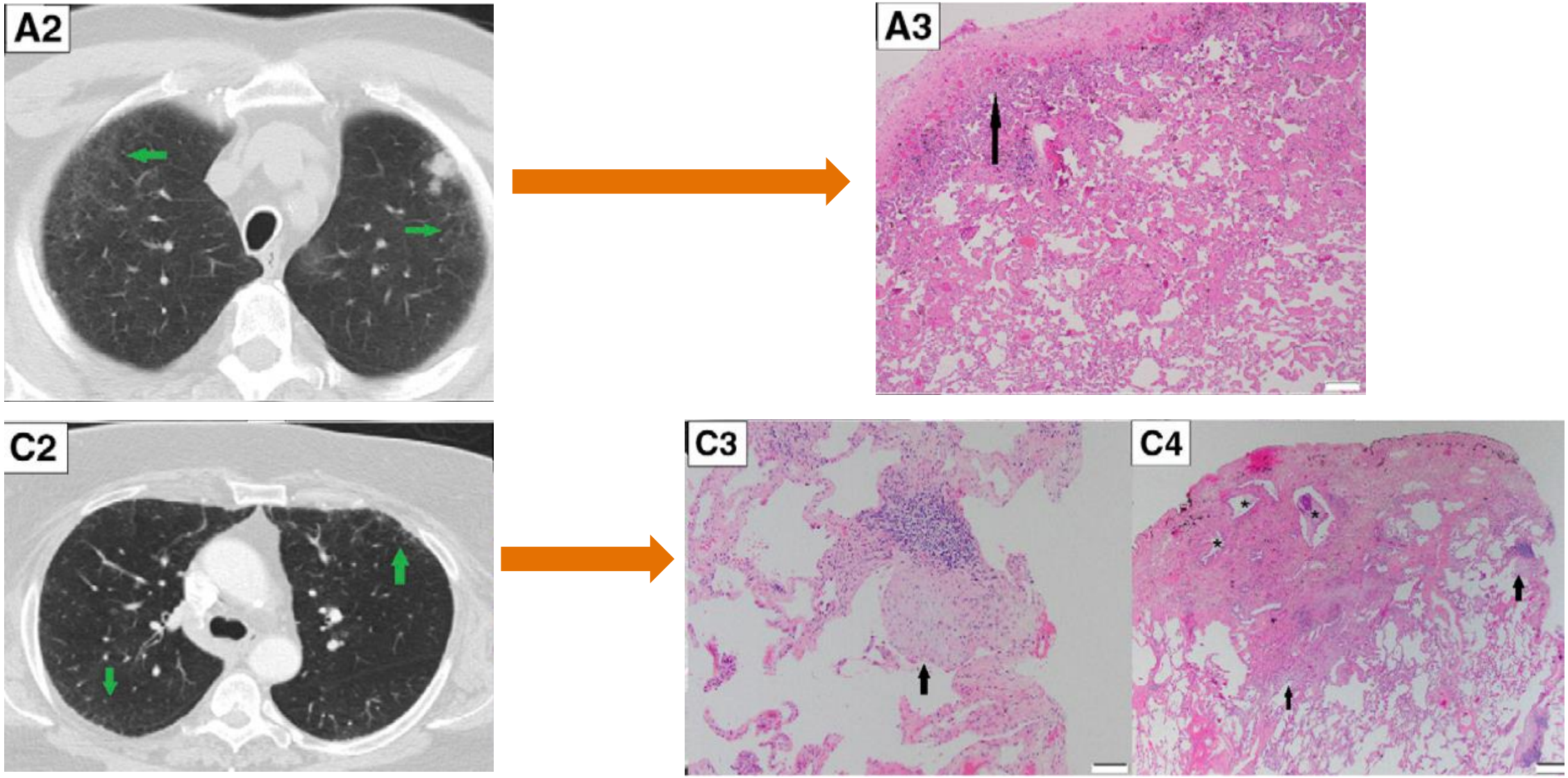


ILA Risk



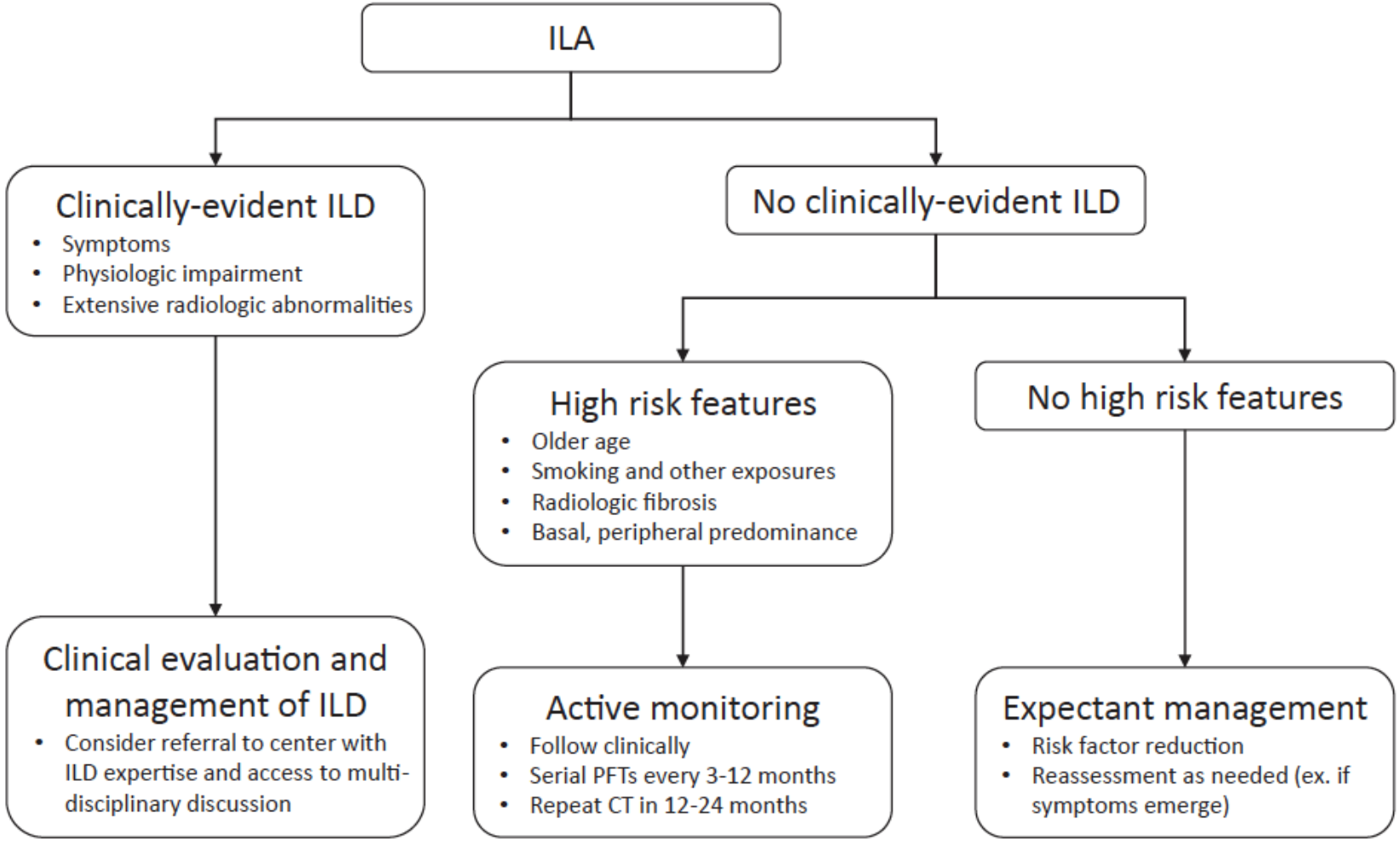
Moll M*, Peljto AL*, Kim JS*, et al. Am J Resp Crit Care Med. 2023.

Histopathology of ILA



Miller ER, et al. Am J Resp Crit Care Med. 2019.

Proposed management of ILA



Podolanczuk AJ, Putman RK. Clin Chest Med. 2021.

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ATS Clinical Statement on ILA

ATS
American Thoracic Society

- Guidance for clinicians and inform research objectives
- Led by Anna Podolanczuk, David Schwartz, Gary Matthew Hunninghake, and Christopher Ryerson
- Comprised of pulmonologists, radiologists, pathologists, and patients (Drs. Joon Beom Seo & Jin Woo Song)
- Voted on 11 questions about screening, follow-up, genetic testing

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Limitations of ILA

- Time consuming
- Subjective
- Heterogeneity in protocol

"Quantitative CT methods for evaluation of disease extent and determination of progress will need to be developed and validated…predicting significant physiological progression, the development of clinically significant disease, and mortality."

~Fleischner Position Paper (2020)

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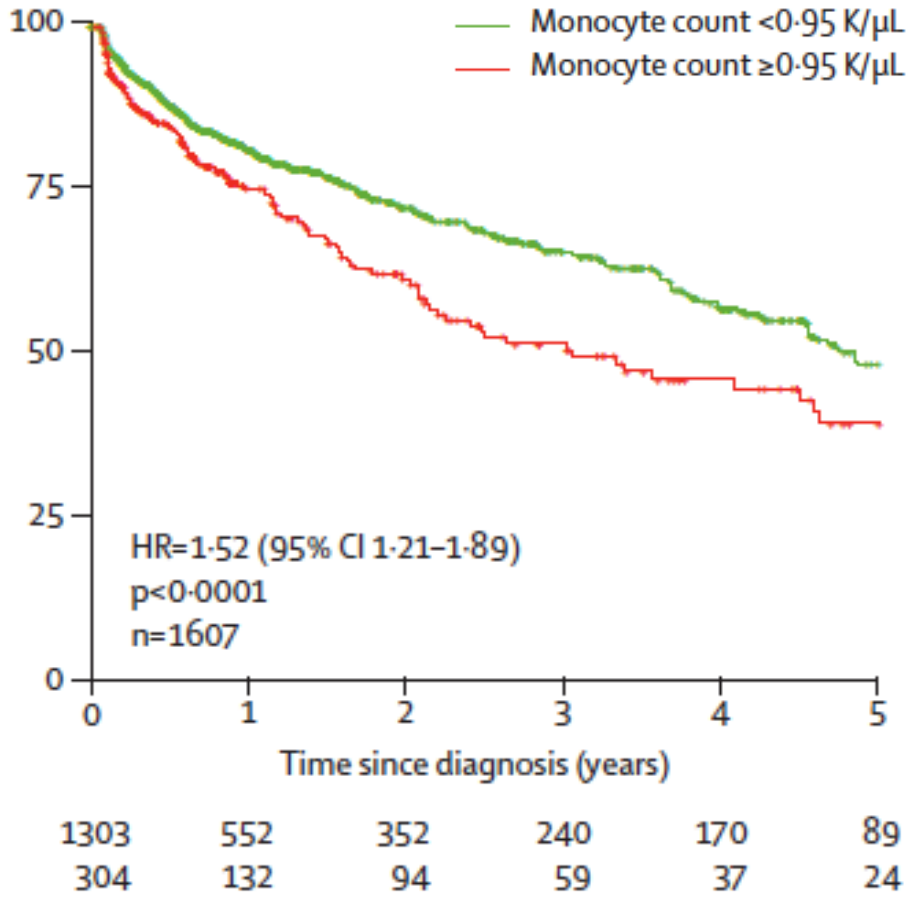
Monocytes predict survival in IPF

- Innate immune system implicated in IPF pathogenesis
- Monocyte-derived alveolar macrophages may drive lung fibrosis
- Monocyte count is an immunocellular biomarker in IPF
- Are higher blood monocyte levels associated with ILA?



Misharin AV, et al. J Exp Med. 2017.
Scott M, et al. Lancet Respir Med. 2019.
Kreuter M, et al. Am J Resp Crit Care Med. 2021.

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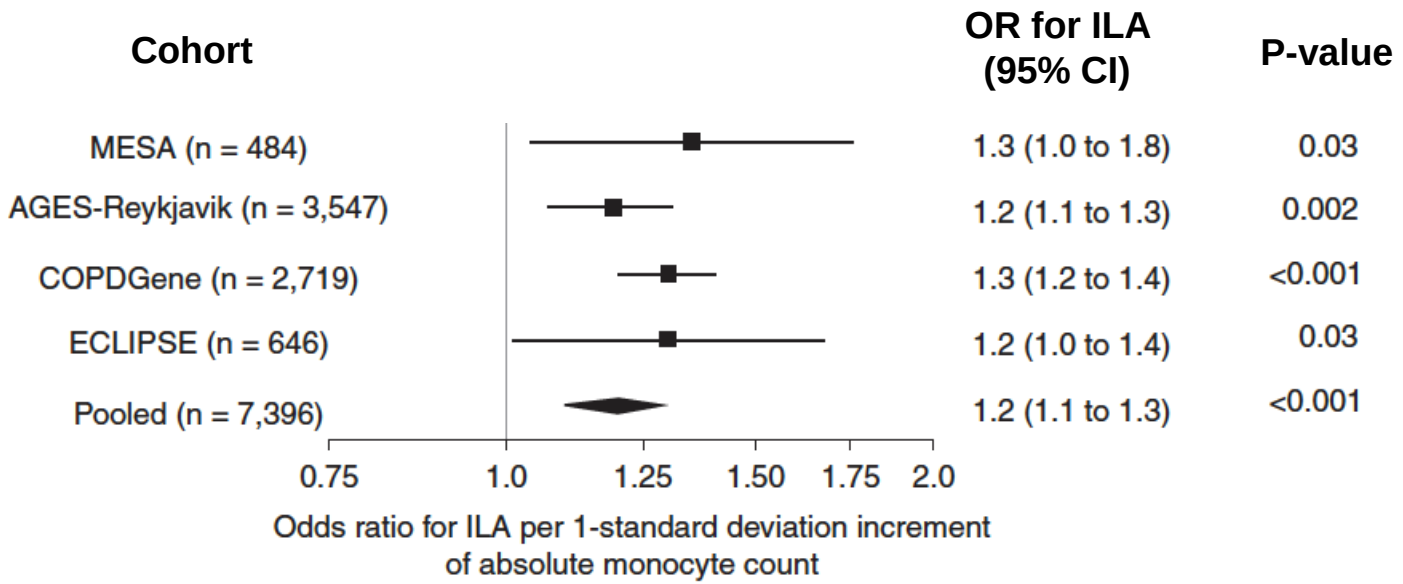
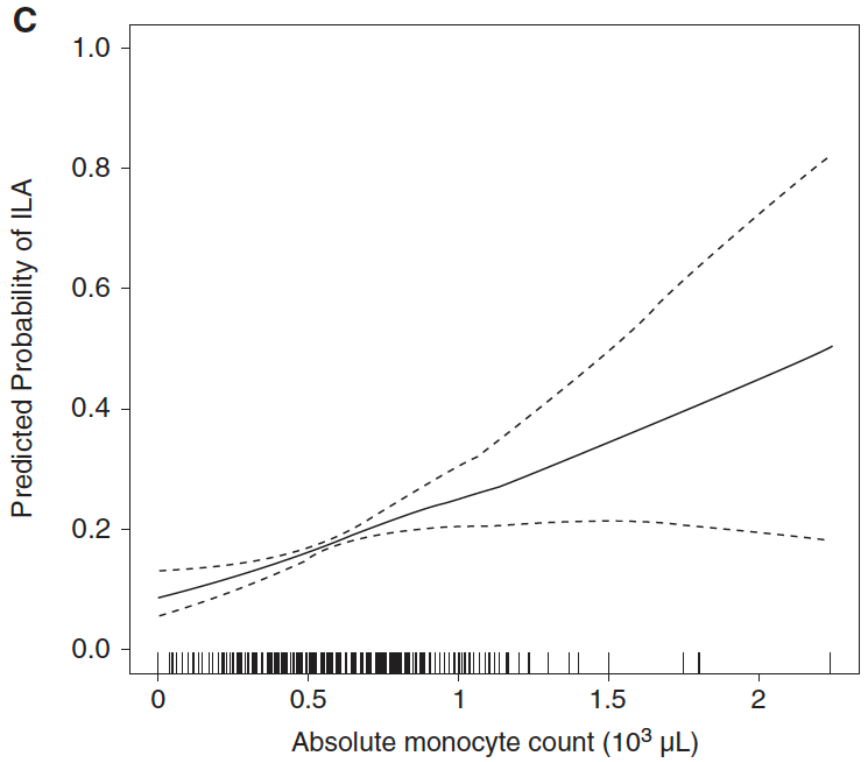
Associations of Monocyte Count and Other Immune Cell Types with Interstitial Lung Abnormalities

John S. Kim[1,2*], Gísli Thor Axelsson[3,4*], Matthew Moll[5,6*], Michaela R. Anderson[2], Elana J. Bernstein[2], Rachel K. Putman[5], Tomoyuki Hida[7,8], Hiroto Hatabu[7], Eric A. Hoffman[9,10,11], Ganesh Raghu[12], Steven M. Kawut[13,14], Margaret F. Doyle[15], Russell Tracy[15], Lenore J. Launer[16], Ani Manichaikul[17], Stephen S. Rich[17], David J. Lederer[18], Vilmundur Gudnason[3,4], Brian D. Hobbs[5,6], Michael H. Cho[5,6], Gary M. Hunninghake[5], Christine Kim Garcia[2], Gunnar Gudmundsson[3,19], R. Graham Barr[2,20], and Anna J. Podolanczuk[2,21]

Gísli Axelsson

Matthew Moll





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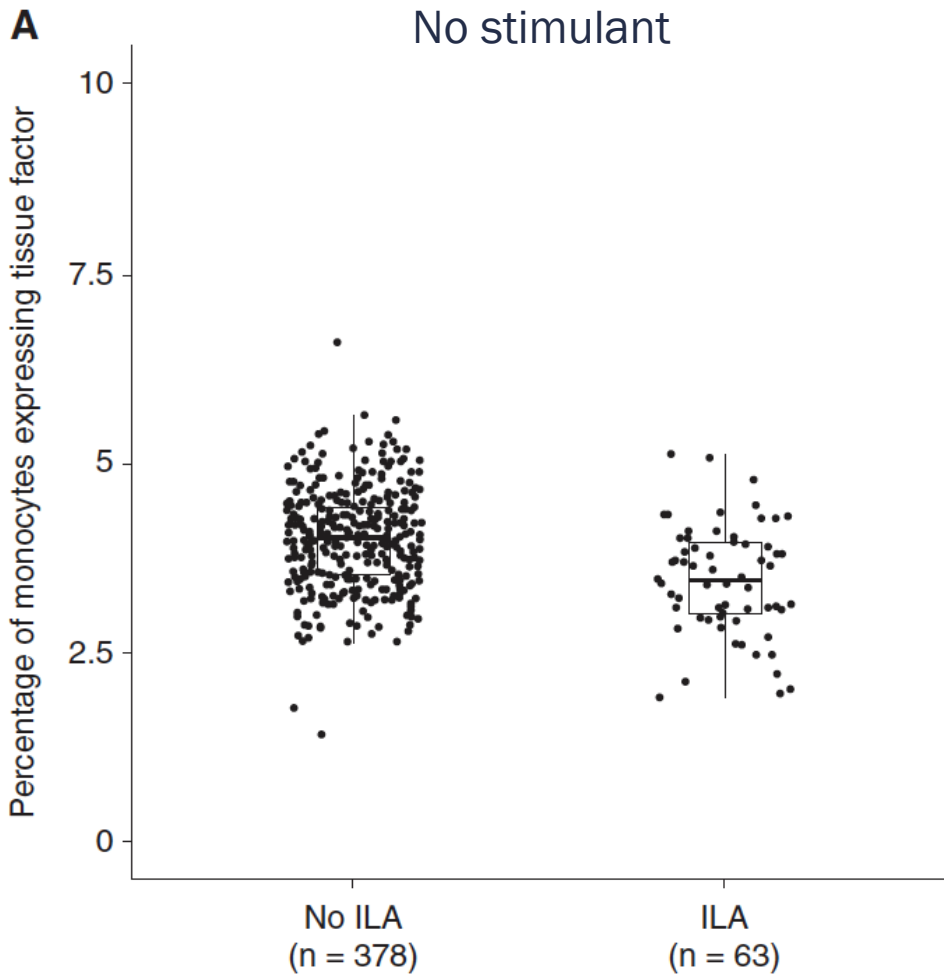
Kim JS*, Axelsson G*, Moll M*, et al. Am J Resp Crit Care Med. 2022.

Activated monocytes and ILA



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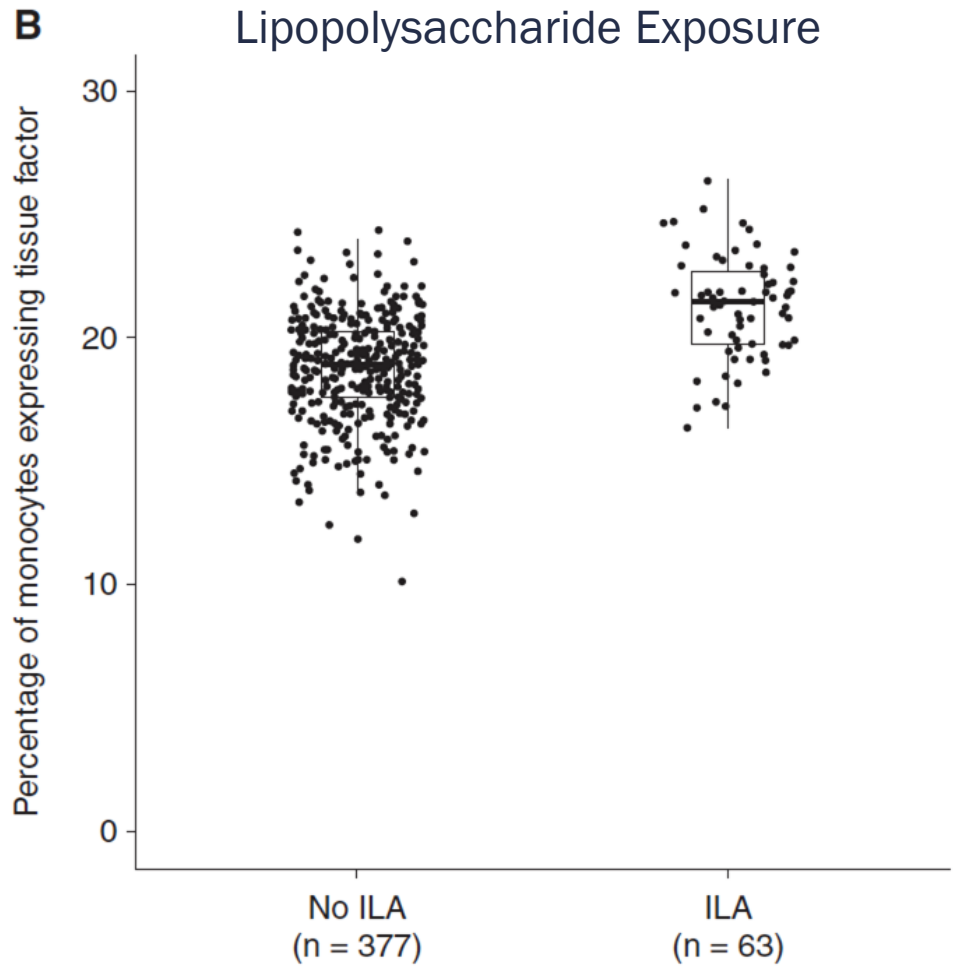
Activated monocytes and ILA



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Kim JS*, Axelsson G*, Moll M*, et al. Am J Resp Crit Care Med. 2022.

IPF blood monocytes have distinct functions


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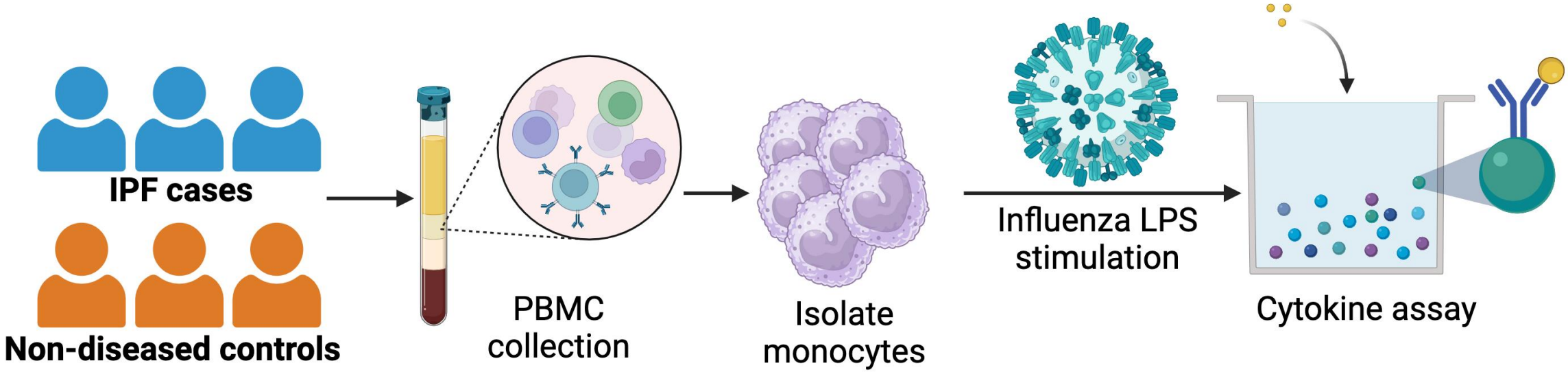

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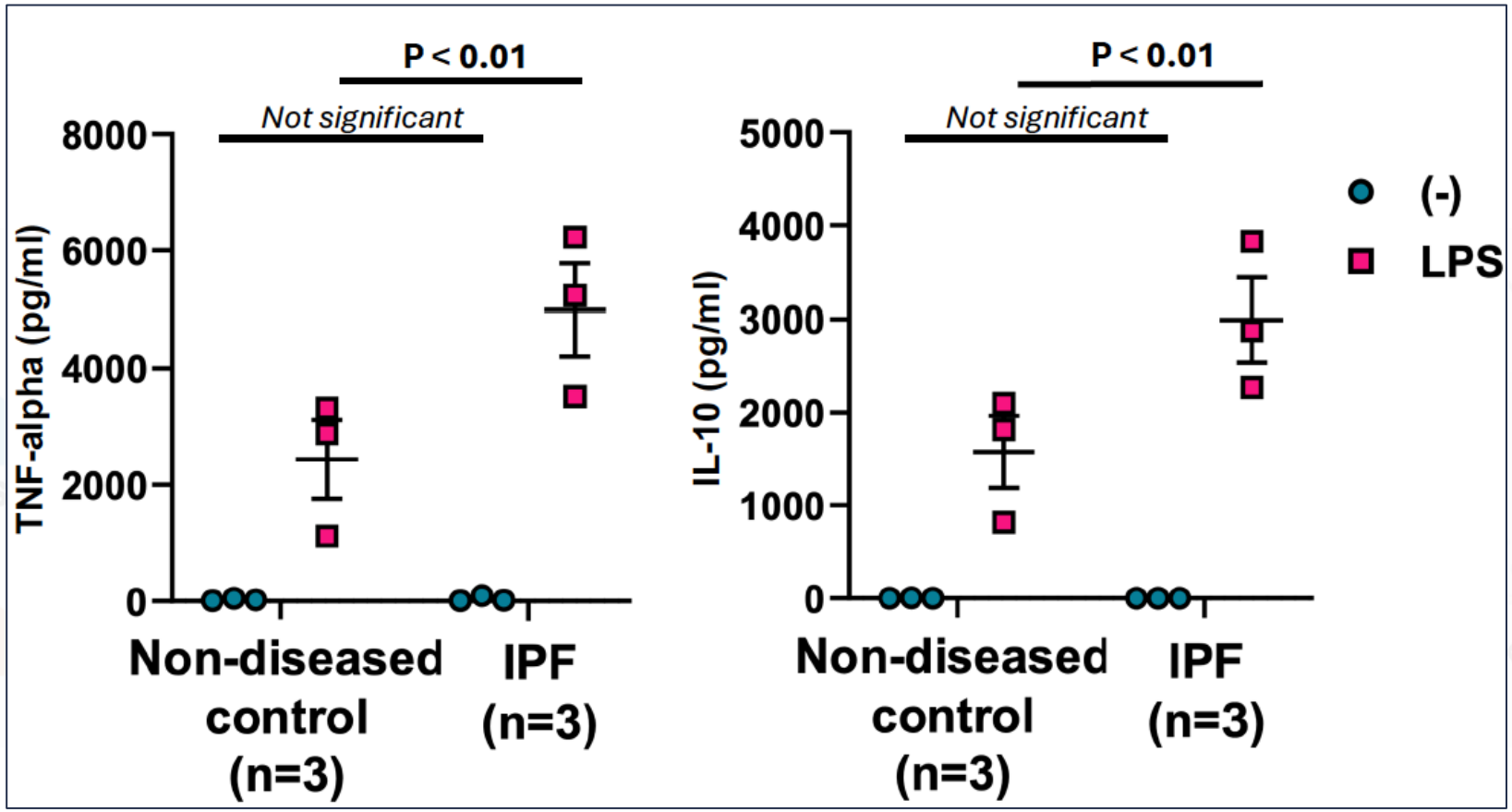
Unpublished.

IPF blood monocytes have distinct functions



Unpublished.

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Fatum Inexorabile: Do Monocytes Predict the Fate of Interstitial Lung Abnormalities?

There remains a major unmet need for simple, minimally invasive biomarkers that provide information regarding risk of development and/or progression of ILD and that measure treatment response in individuals at high risk of developing ILD

Kreuter M, Maher TM. Am J Resp Crit Care Med. 2022.

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Approach to Clinical Trials for the Prevention of Pulmonary Fibrosis

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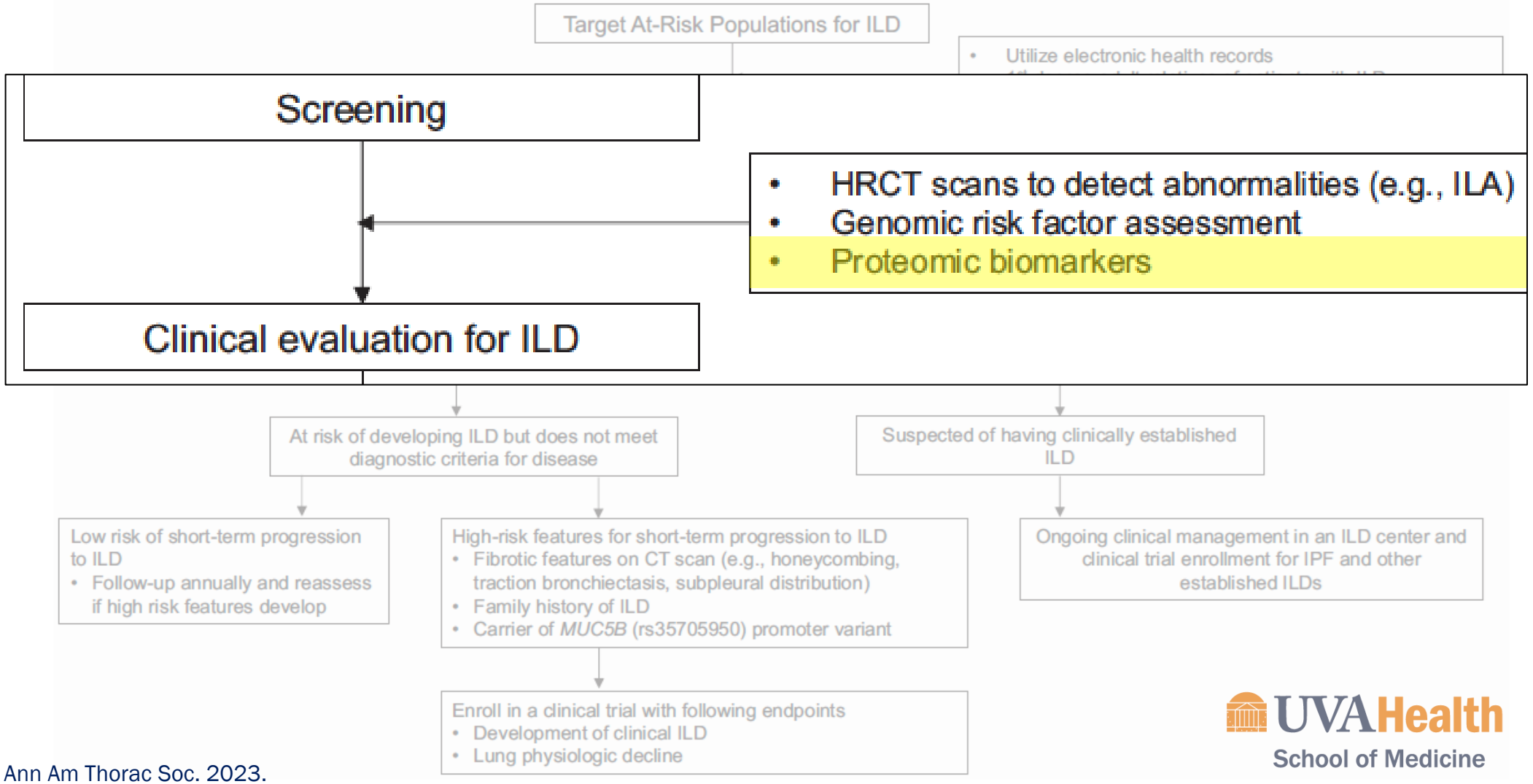

Kim JS, et al. Ann Am Thorac Soc. 2023.

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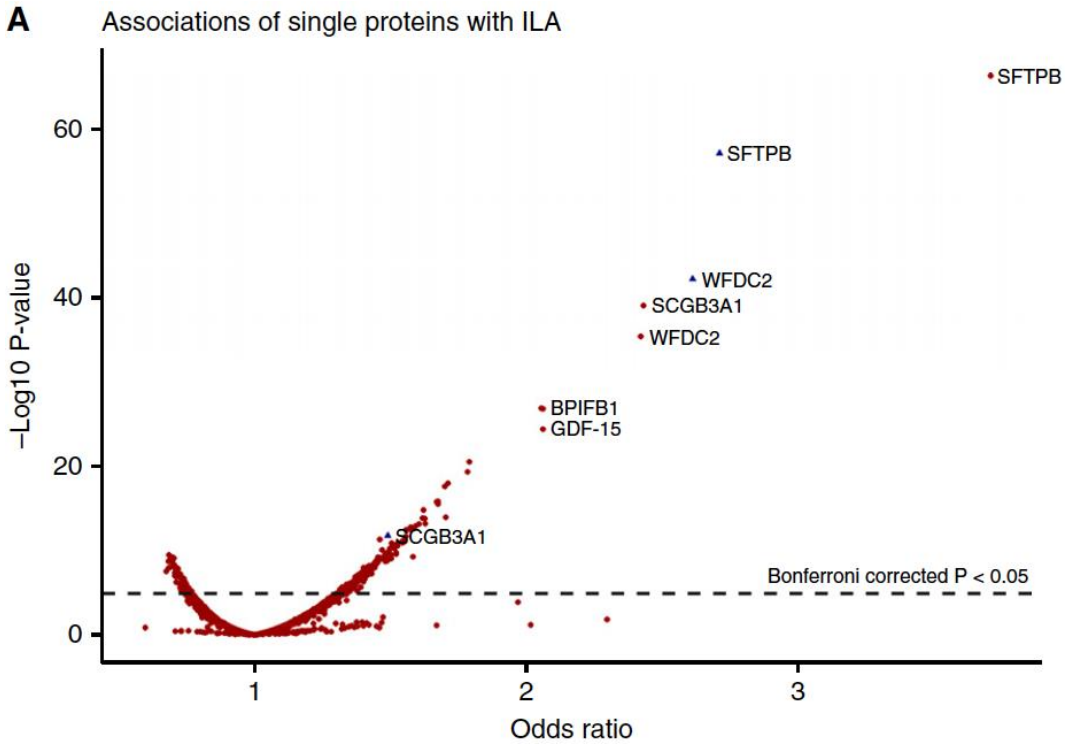
Blood-based protein biomarkers and ILA

- Prior studies have correlated protein biomarkers with ILA and quantitative assessments of interstitial abnormalities (e.g., QIA)
- GDF-15, surfactant proteins B and D, WFDC2
- Protein markers elevated in 1st-degree relatives of patients and correlate with ILA



Axelsson GT, et al. Am J Resp Crit Care Med. 2022.
Choi B, et al. Am J Resp Crit Care Med. 2024.
Rose JA, et al. Eur Resp J. 2025.

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Research questions

Are there plasma protein biomarkers that correlate with densiometric-based radiomic markers of lung injury and fibrosis?

Do these protein markers associate with new-onset lung fibrosis?

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High attenuation area (HAA)

- Automated densiometric based CT measurement
- Percentage of lungs with high attenuation areas (-600 to -250 Hounsfield units)
- Capture ground-glass/reticular abnormalities and exclude more dense areas (vessels, nodules)
- Confounding by artifact, adiposity

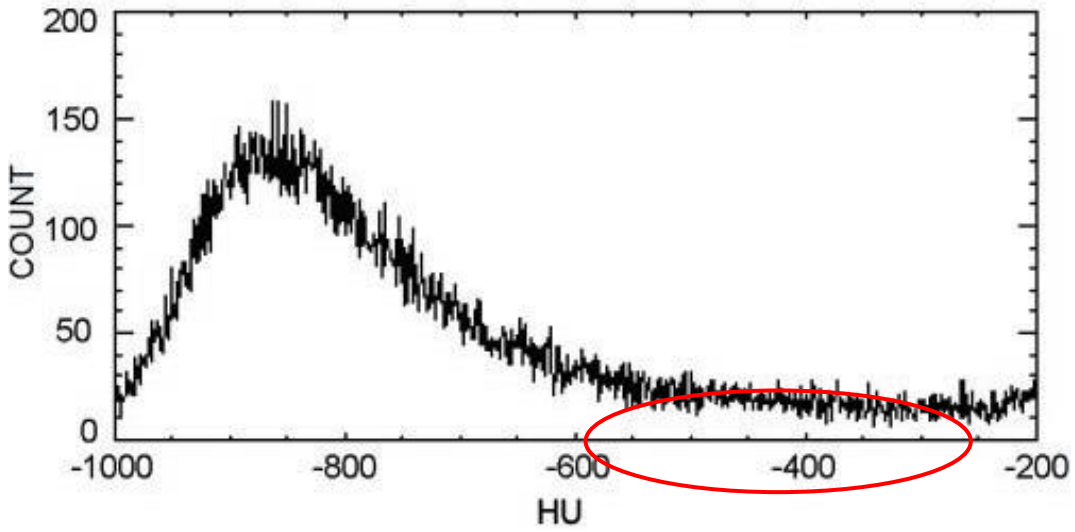


Figure 1A

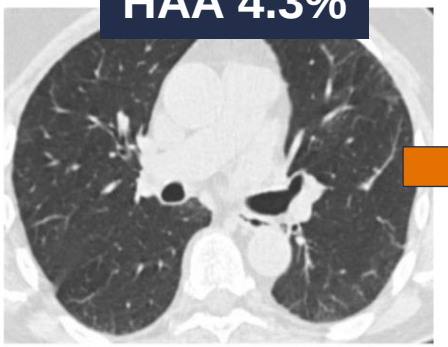
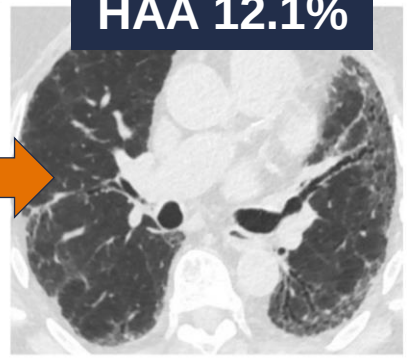


Figure 1B



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Lederer DJ, et al. Am J Resp Crit Care Med. 2009.
Kliment CA, et al. BMC Pulm Med. 2015.
Podolanczuk AJ, et al. Eur Resp J. 2016.
Kim JS, et al. Thorax. 2023.

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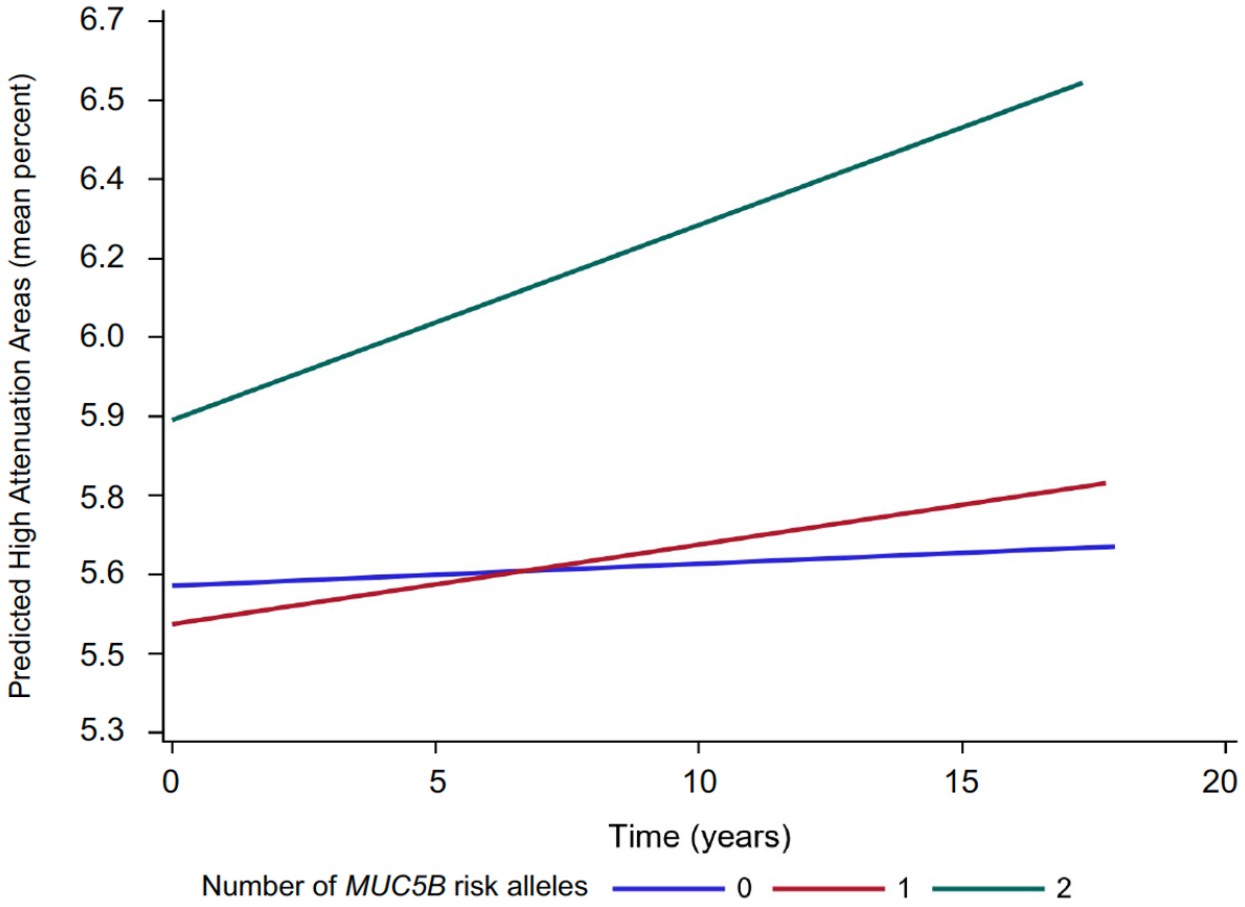
Original research

MUC5B, telomere length and longitudinal quantitative interstitial lung changes: the MESA Lung Study



1% HAA increment per year associated with:

- Overall death: HR of 1.07 (95%CI 1.02-1.12)
- ILD-related death and hospitalization: RR of 1.34 (95%CI 1.20-1.50)

Kim JS, et al. Thorax. 2023.

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Study design

1

Derive HAA-protein markers

MESA
Multi-Ethnic Study of Atherosclerosis

U.S. community-dwelling adults 45-84 years old
n=5486

SomaScan version 4.1 (6,401 protein analytes)

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Study design

1

Derive HAA-protein markers

MESA Multi-Ethnic Study of Atherosclerosis

U.S. community-dwelling adults 45-84 years old n=5486

2

Replicate HAA-protein markers

SPIROMICS

U.S. adult cigarette smokers n=1781

SomaScan version 4.1 (6,401 protein analytes)

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Study design

1 Derive HAA-protein markers

MESA Multi-Ethnic Study of Atherosclerosis

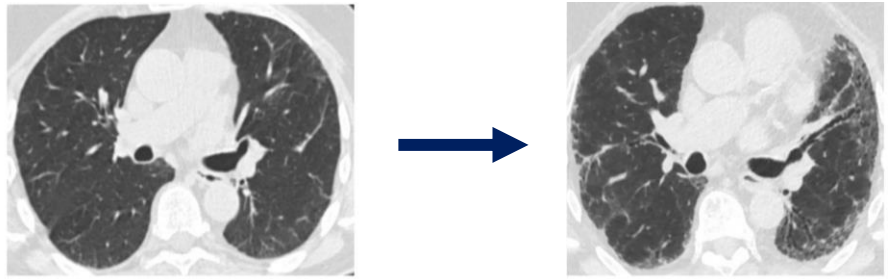
U.S. community-dwelling adults 45-84 years old n=5486

2 Replicate HAA-protein markers

SPIROMICS

U.S. adult cigarette smokers n=1781

3 Identify proteins that correlate with future fibrosis



SomaScan version 4.1 (6,401 protein analytes)

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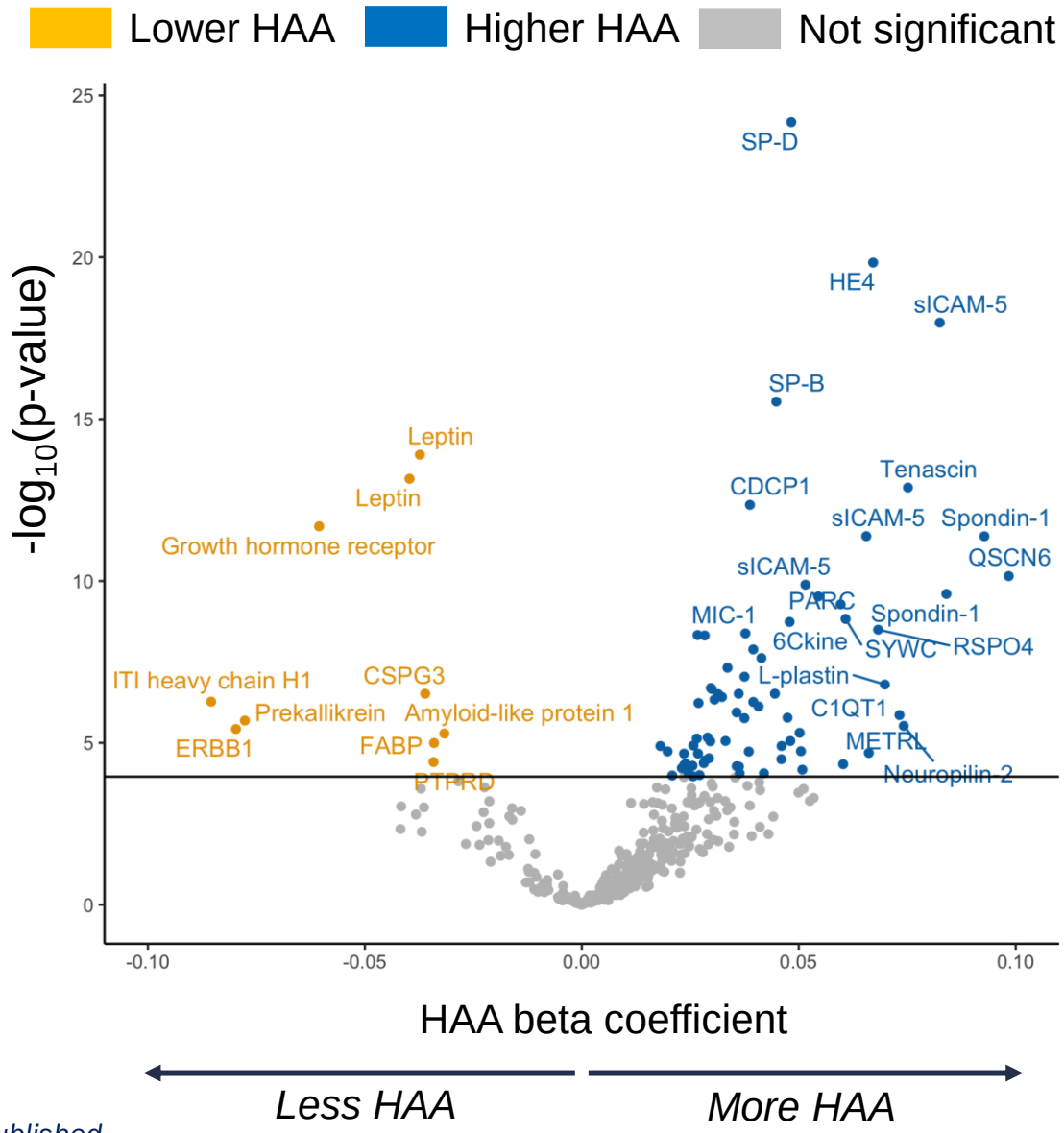
HAA-associated proteins



Unpublished.

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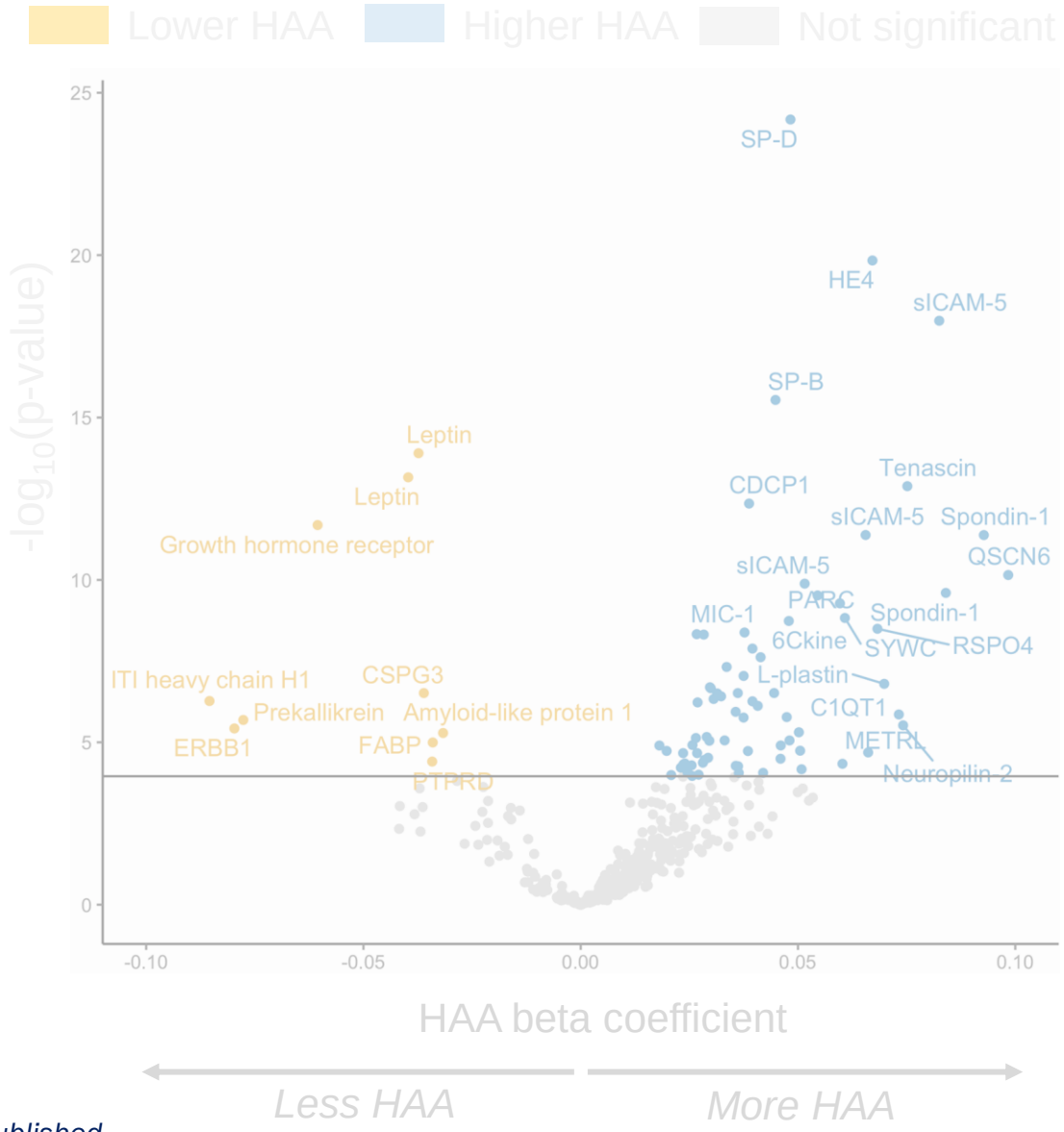
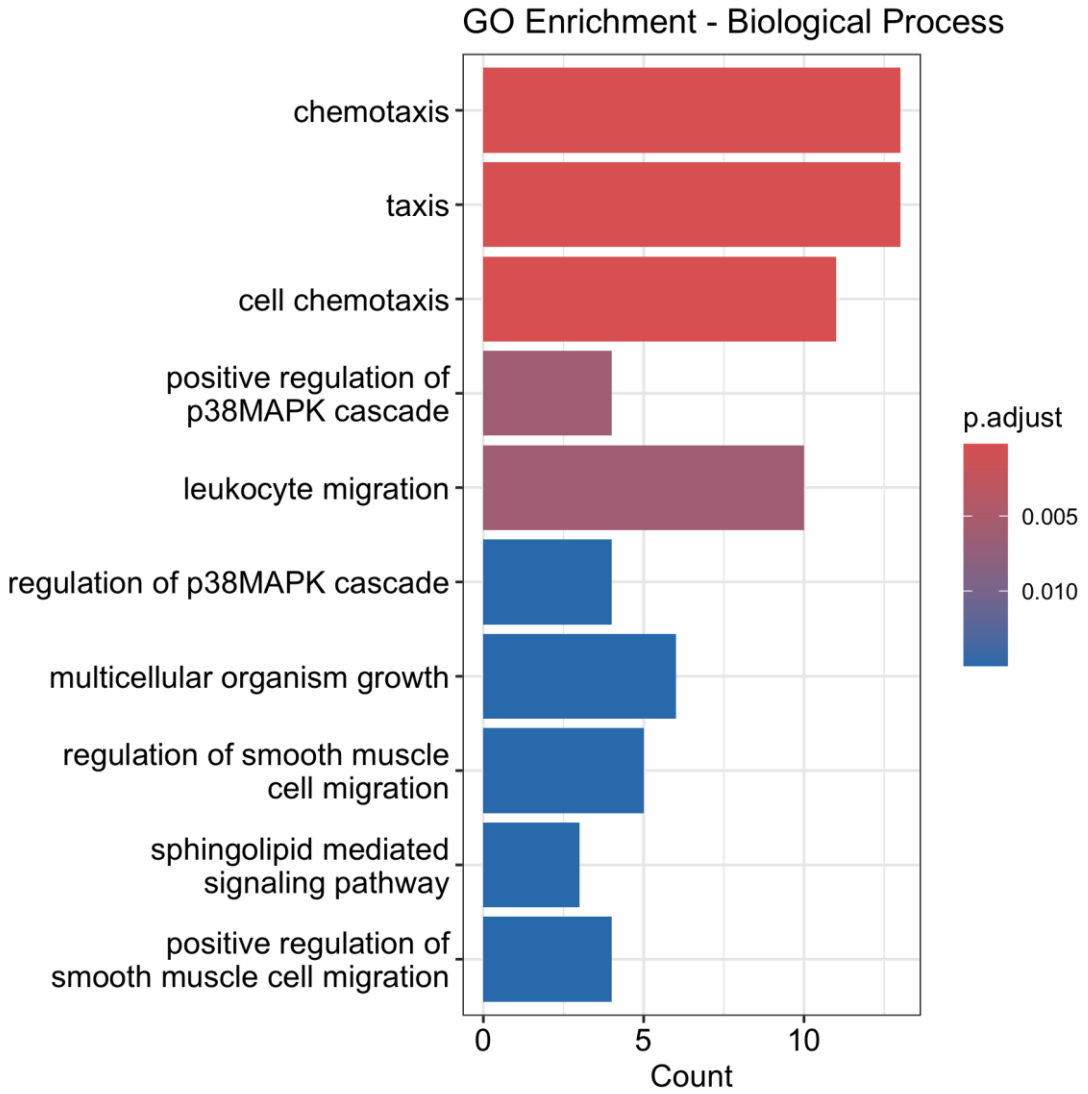
HAA-associated proteins





Unpublished.

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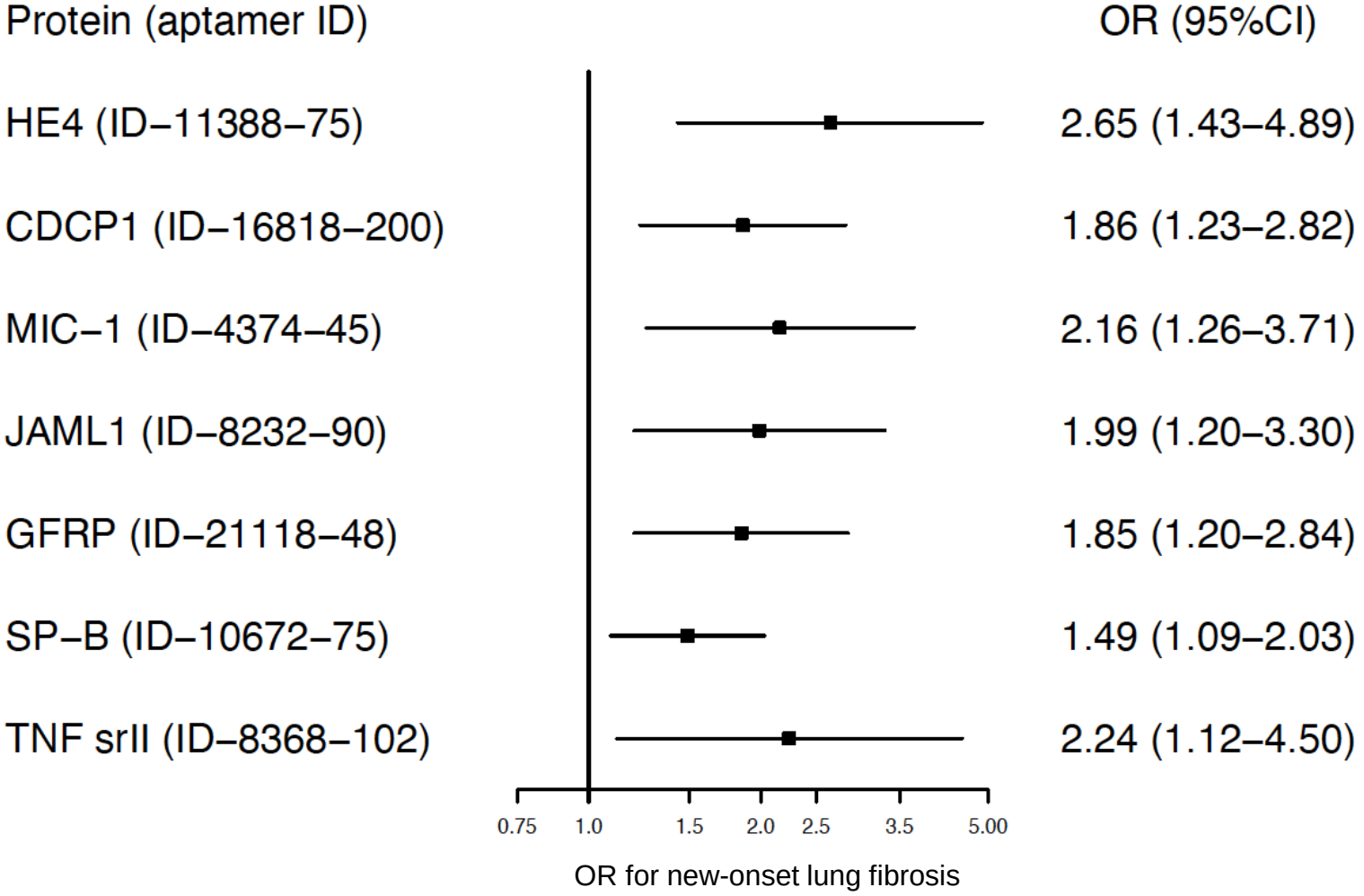
HAA-proteins and new-onset lung fibrosis



Logistic regression model adjusted for age, sex, smoking history, pack-years, height, weight, waist, eGFR, education, income, study site, PCA

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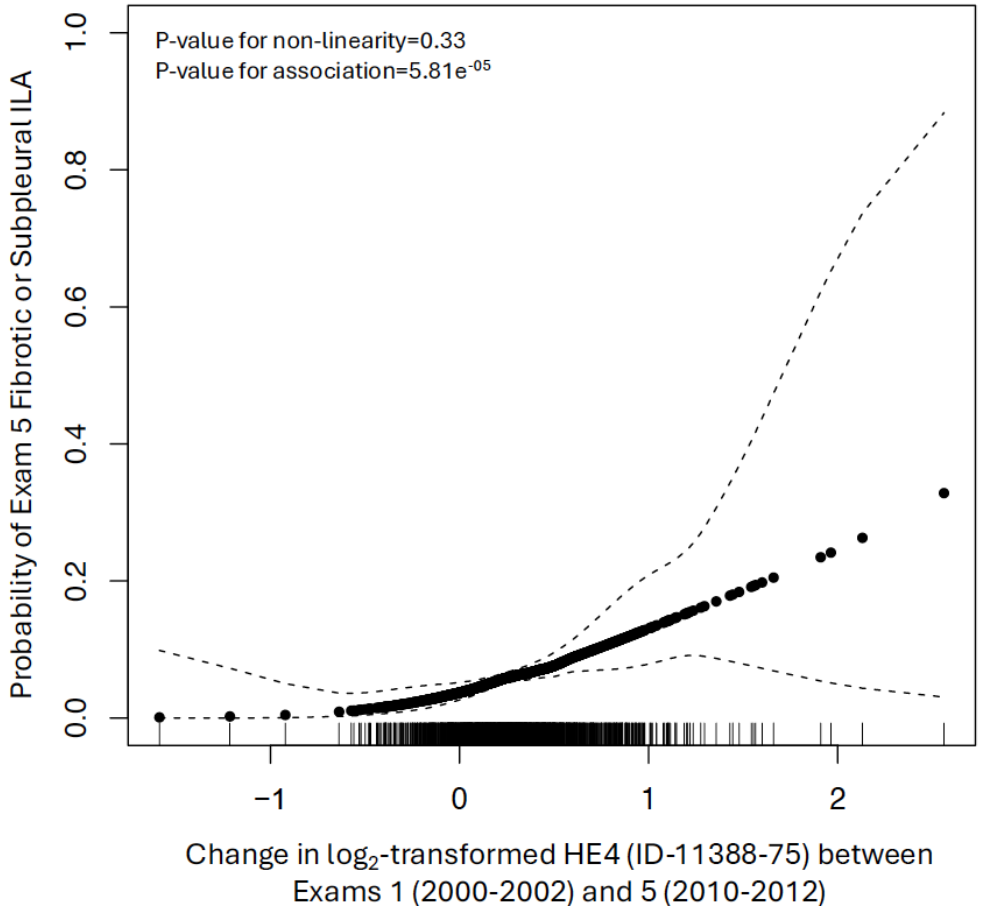
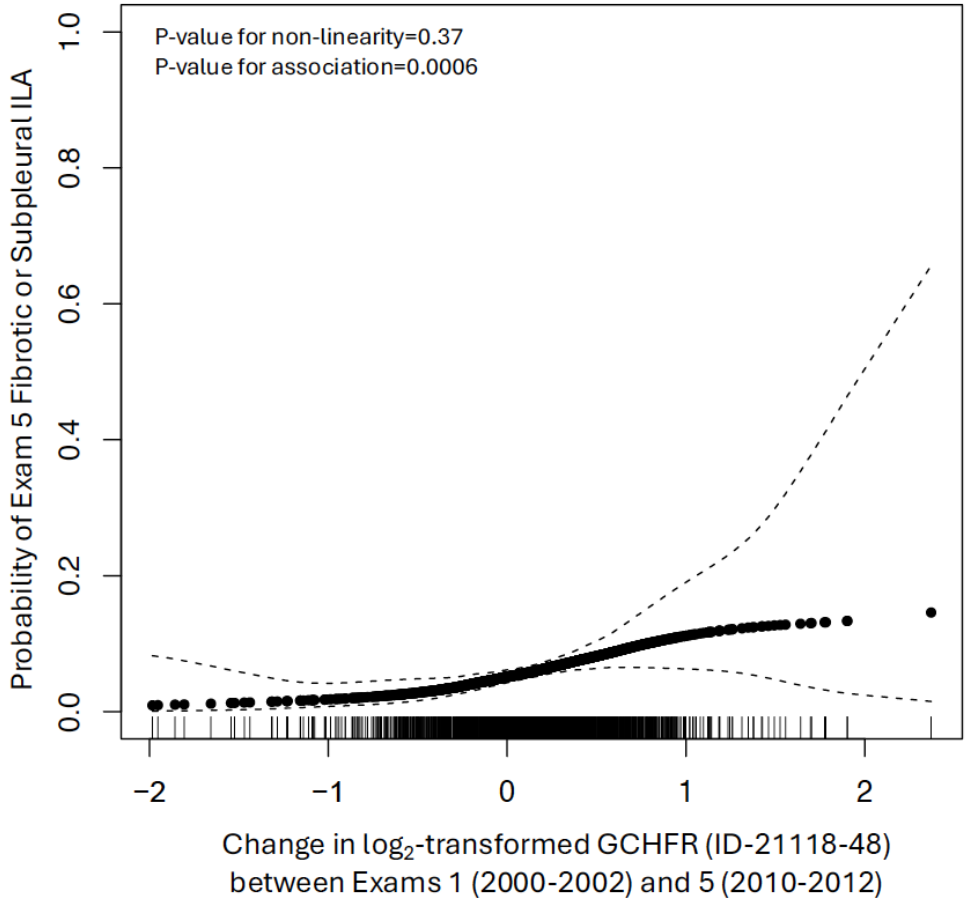
Unpublished.

Increases in HAA-derived proteins and new-onset lung fibrosis





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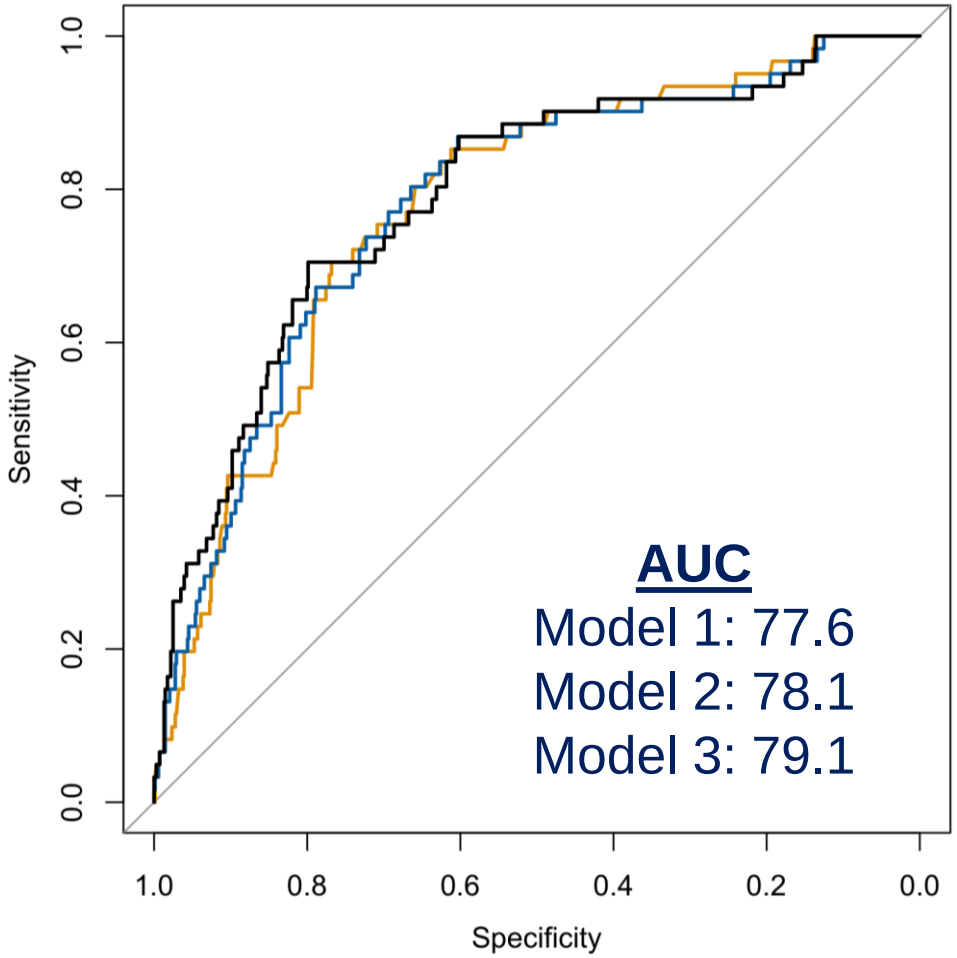
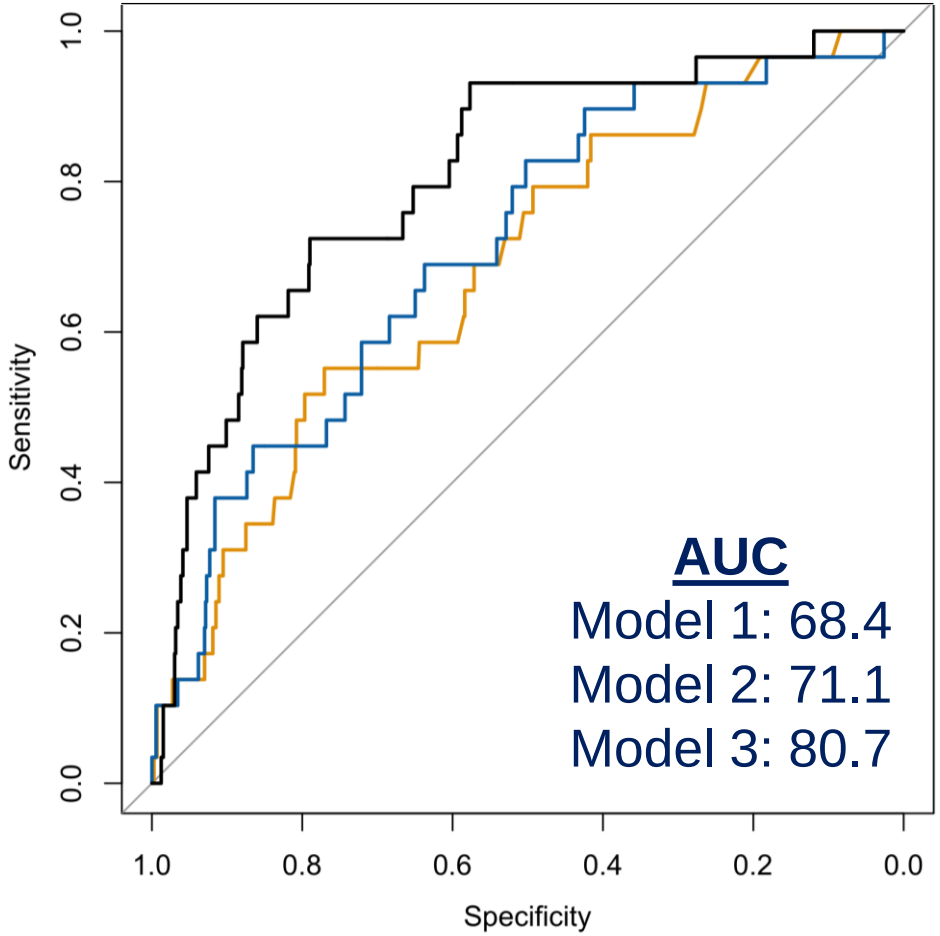
Unpublished.

HAA-proteins improve prediction

MESA NHW (n=747)



MESA non-NHW (n=757)



Model 1: Age, sex, smoking history, cigarette pack-years

Model 2: Model 1 + IPF polygenic risk score

Model 3: Model 2 + HAA-derived protein biomarkers

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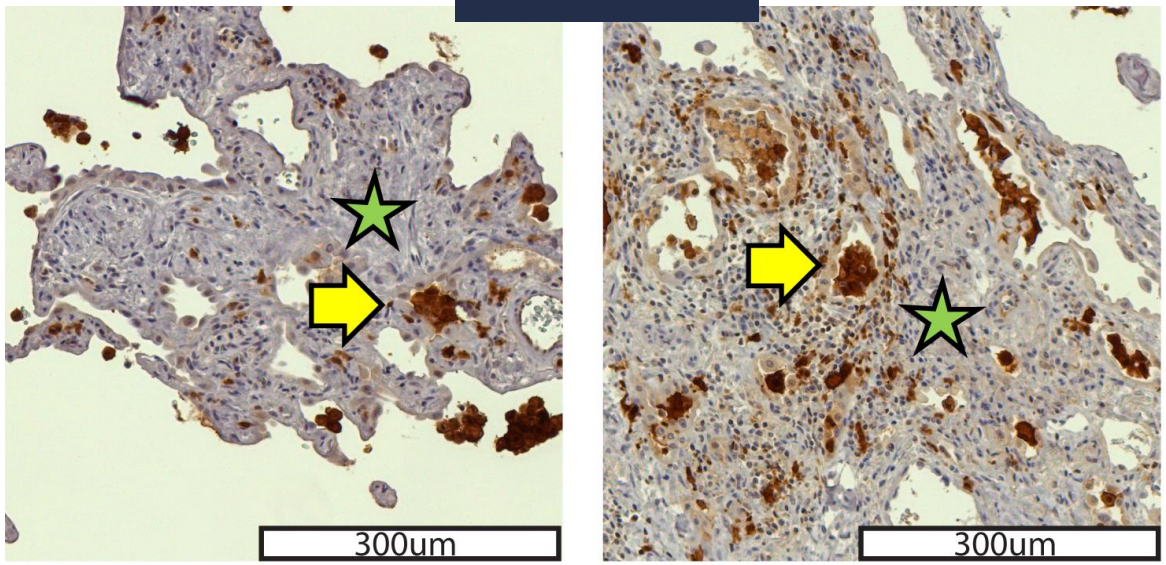
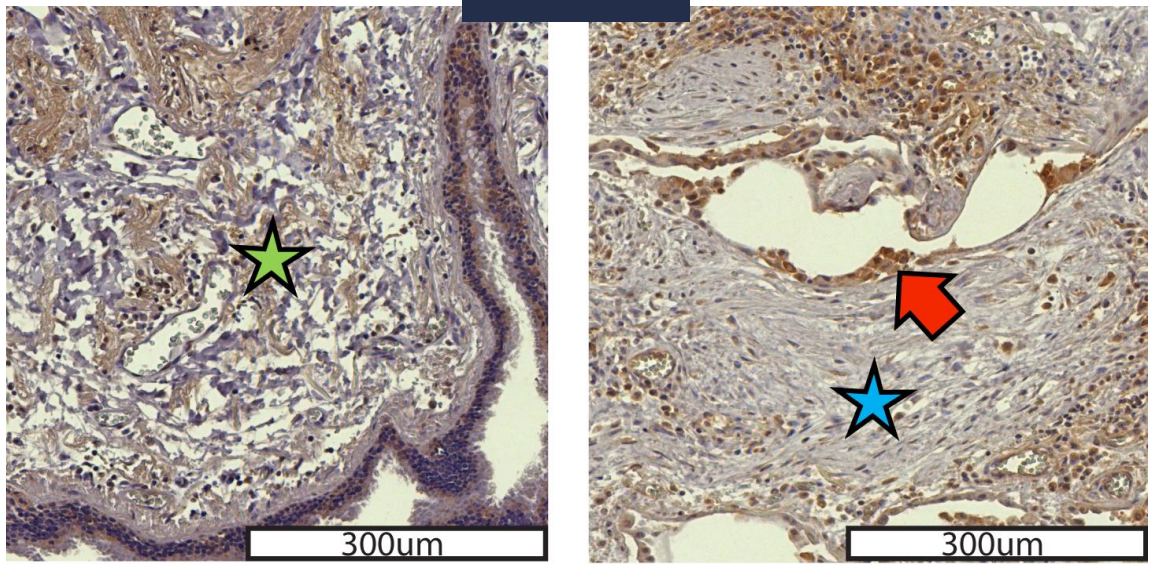
HAA-proteins stain IPF lung tissue

Riley Hannan

GCHFR



JAML



GCHFR stains intra-alveolar macrophages (yellow arrows) in areas of fibrosis (green star), typically lower lobes and subpleural.

JAML stains prominently in late fibrosis (green star) and staining of epithelium (red arrow) in early fibroblast foci (blue star).

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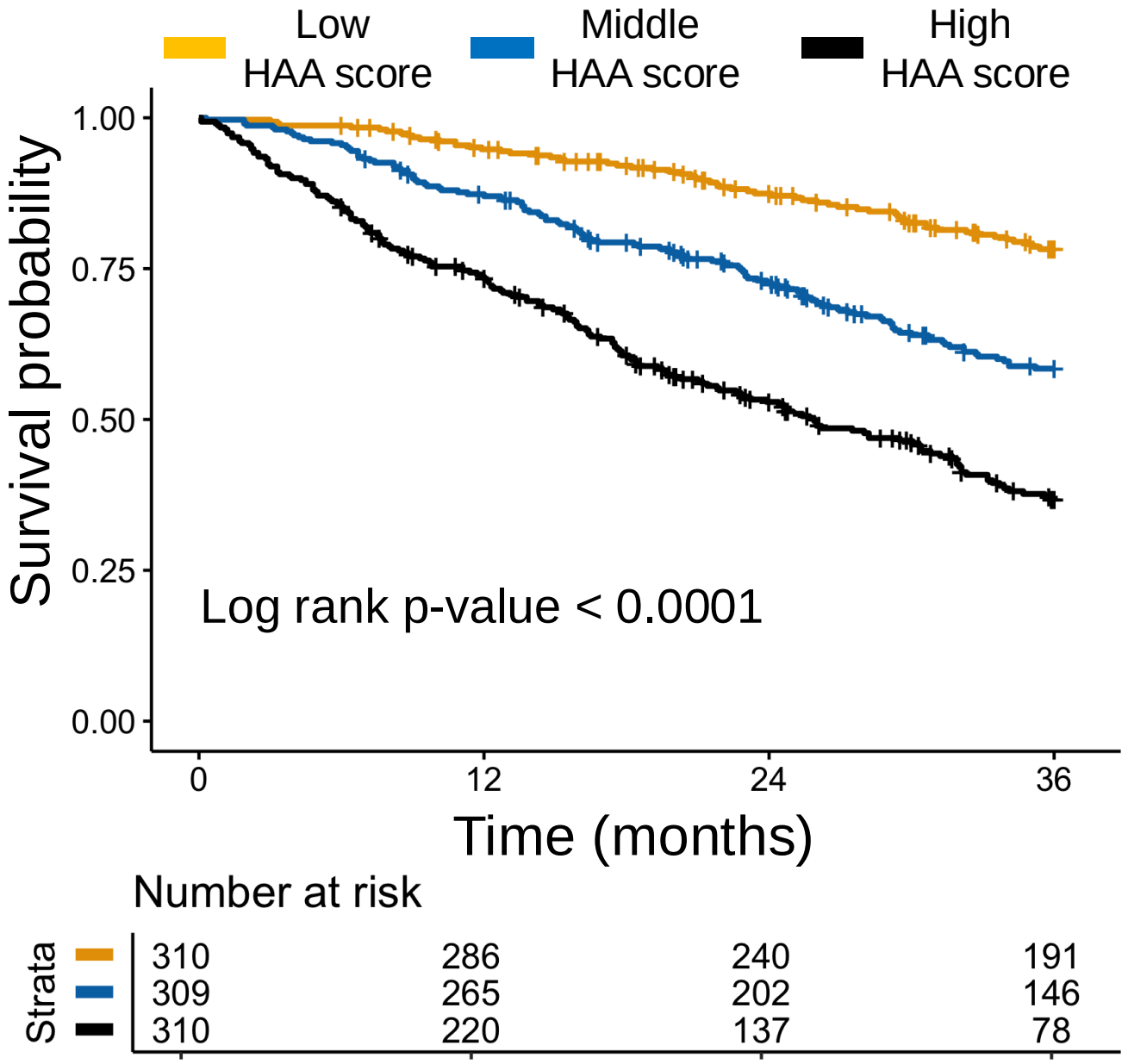
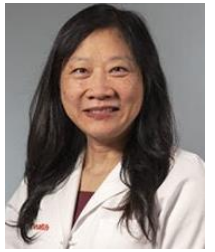
Unpublished.

HAA-proteins correlate with worse survival in IPF




Justin Oldham


Shwu-Fan Ma


Imre Noth

Pulmonary Fibrosis Foundation™

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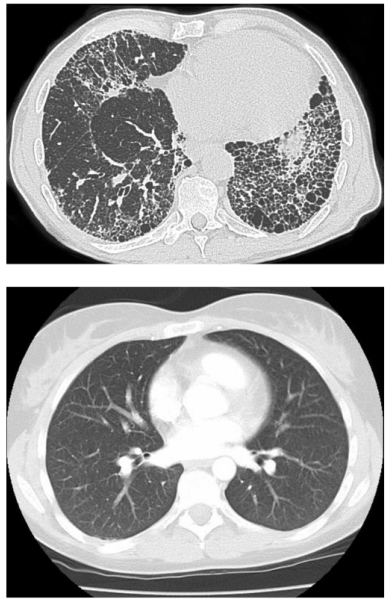
Unpublished.

Molecular correlates of DTA

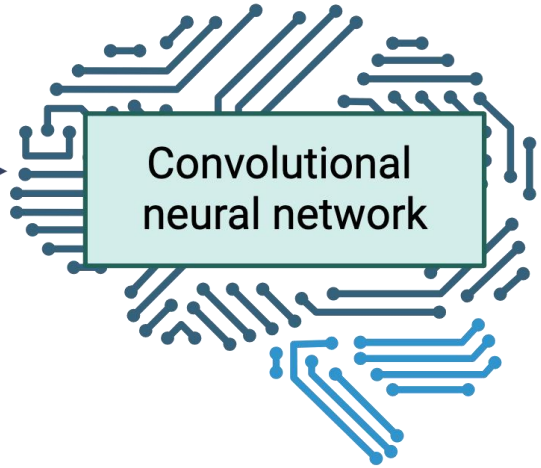

Stephen Humphries


David Lynch



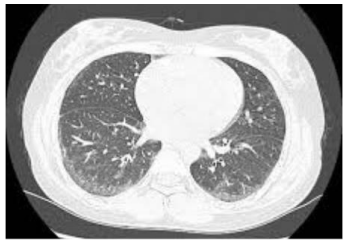
Representative UIP and normal CT lung images labeled by radiologist

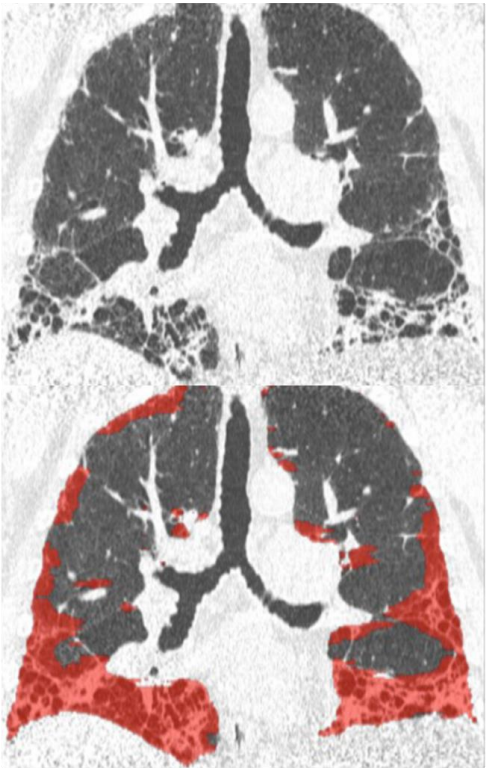
TRAINING



CNN #1
Lung segmentation

CNN #2
Label "normal" and "fibrotic"


Upload CT images



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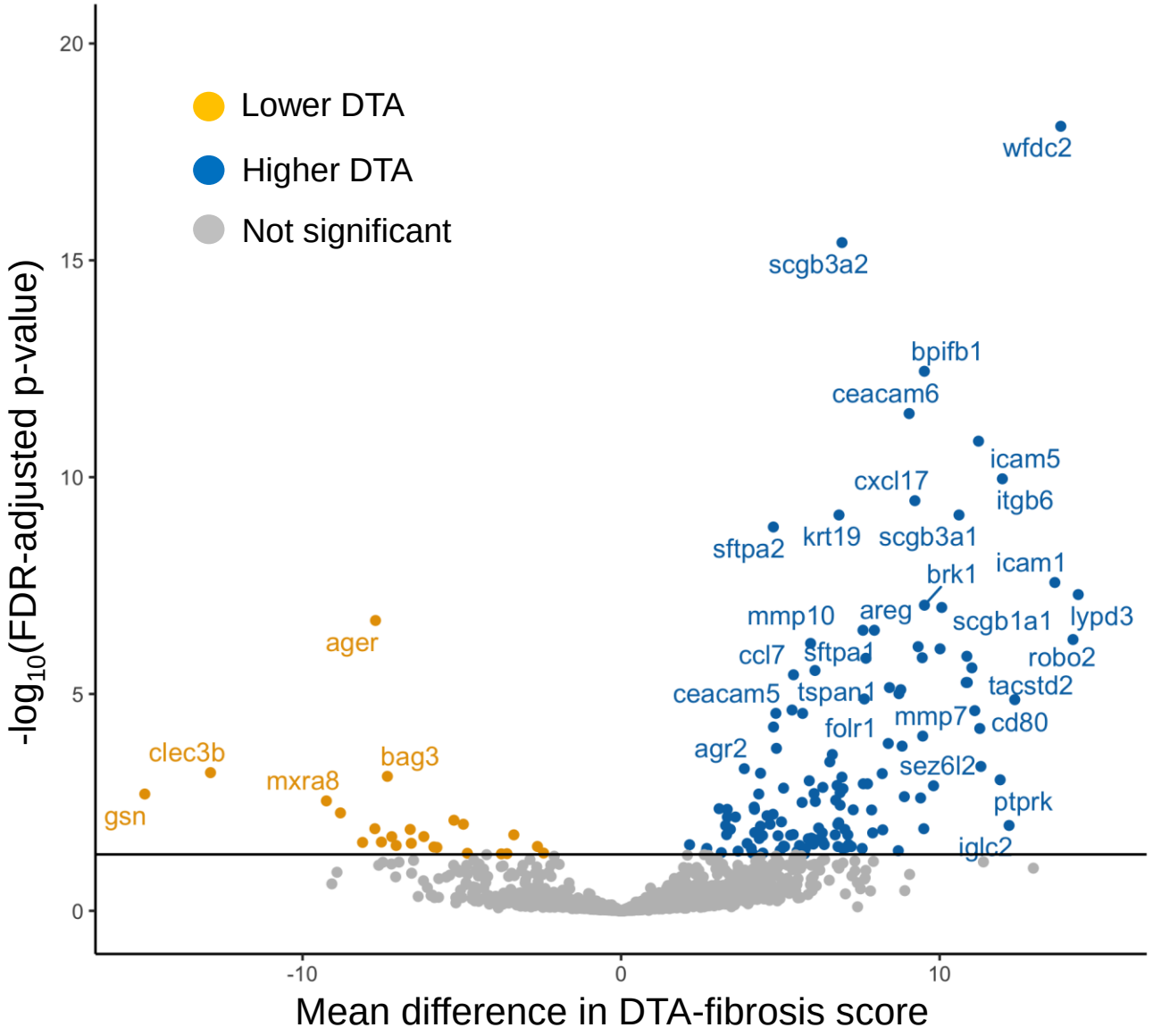
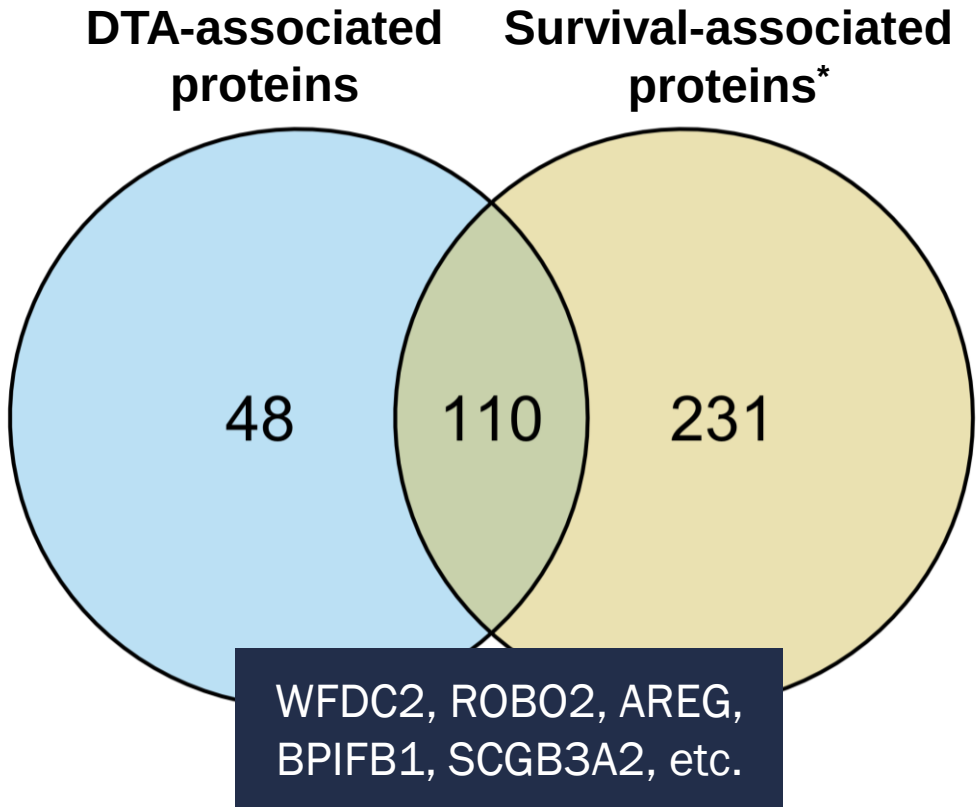
Humphries SM, et al. Respirology. 2022.

DTA-associated proteins



Pulmonary Fibrosis Foundation™



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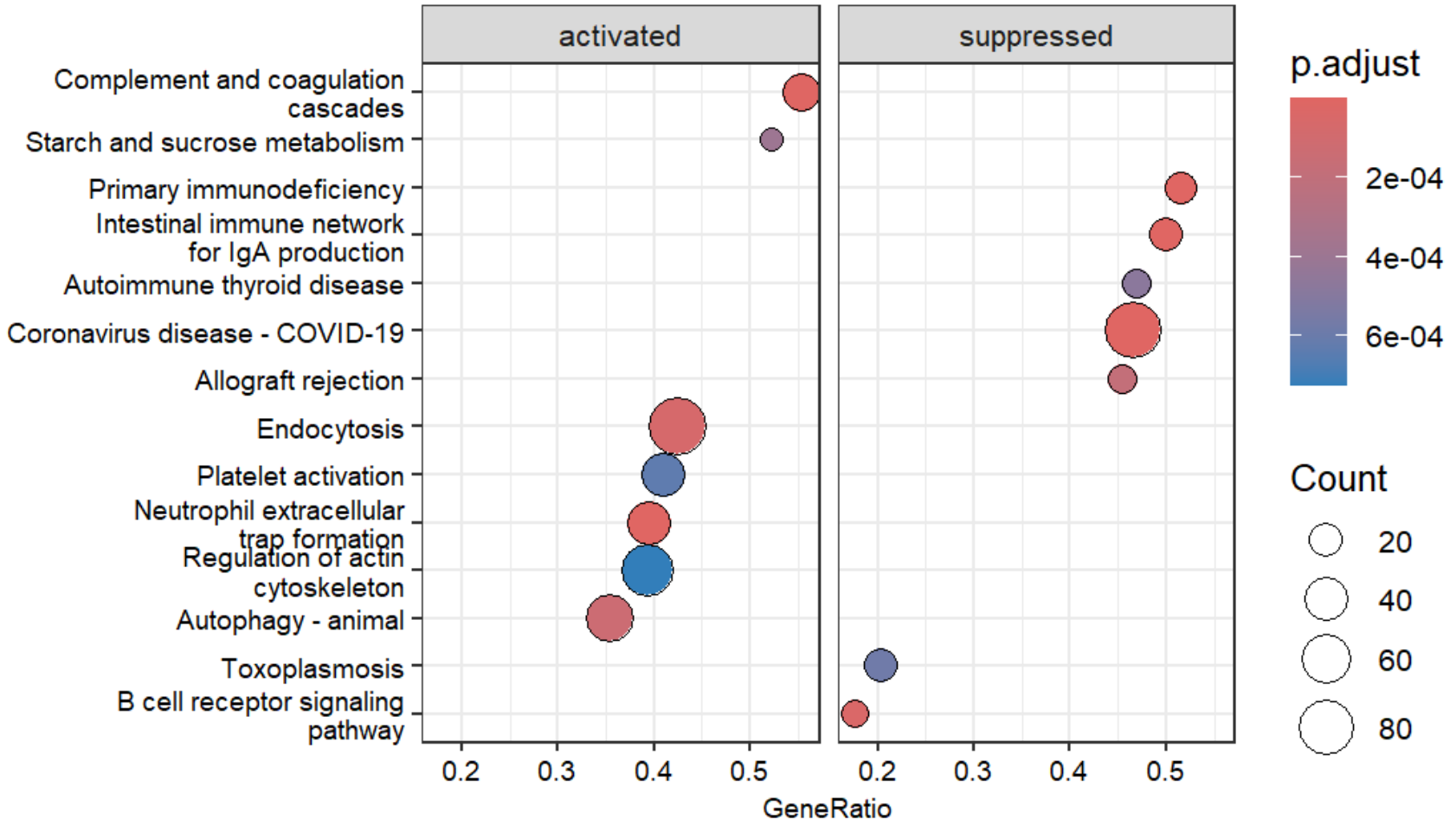
*Oldham JM, et al. Am J Resp Crit Care Med. 2024.

KEGG analysis of DTA



Unpublished.

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Future work

- Correlate with other semiquantitative proteomic assays (e.g., Olink)
- Fully quantify candidate protein biomarkers using ELISA assays, mass spectrometry
- Derive and validate prediction models (lung imaging + environmental exposure + genetics + biomarkers)
- Biologically validate protein biomarkers (multi-omic integration, lung tissue correlation)
- Awaiting approval of potential NIH R01 grant

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Summary

- Pulmonary fibrosis starts many years prior to diagnosis
- Current approach to testing therapies in patients with advanced disease is not sufficient
- Need to target earlier stages and develop treatments that target the subclinical phase of lung fibrosis
- Requires clinical trial enrichment (imaging, genomics, blood biomarkers)

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Collaborators

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- Julie Fanburg-Smith
- In Su Cheon
- Jie Sun

UMass Chan Medical School

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Weill Cornell Medical Center

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University of Michigan

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University of Iowa

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Columbia University

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- Mary Salvatore
- Christine Kim Garcia
- Clair McGroder

UCSF

- Peter Ganz

National Jewish Hospital

- Stephen Humphries
- David Lynch

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