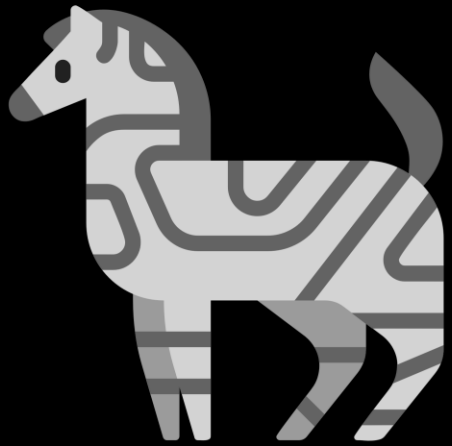
Miscellanea

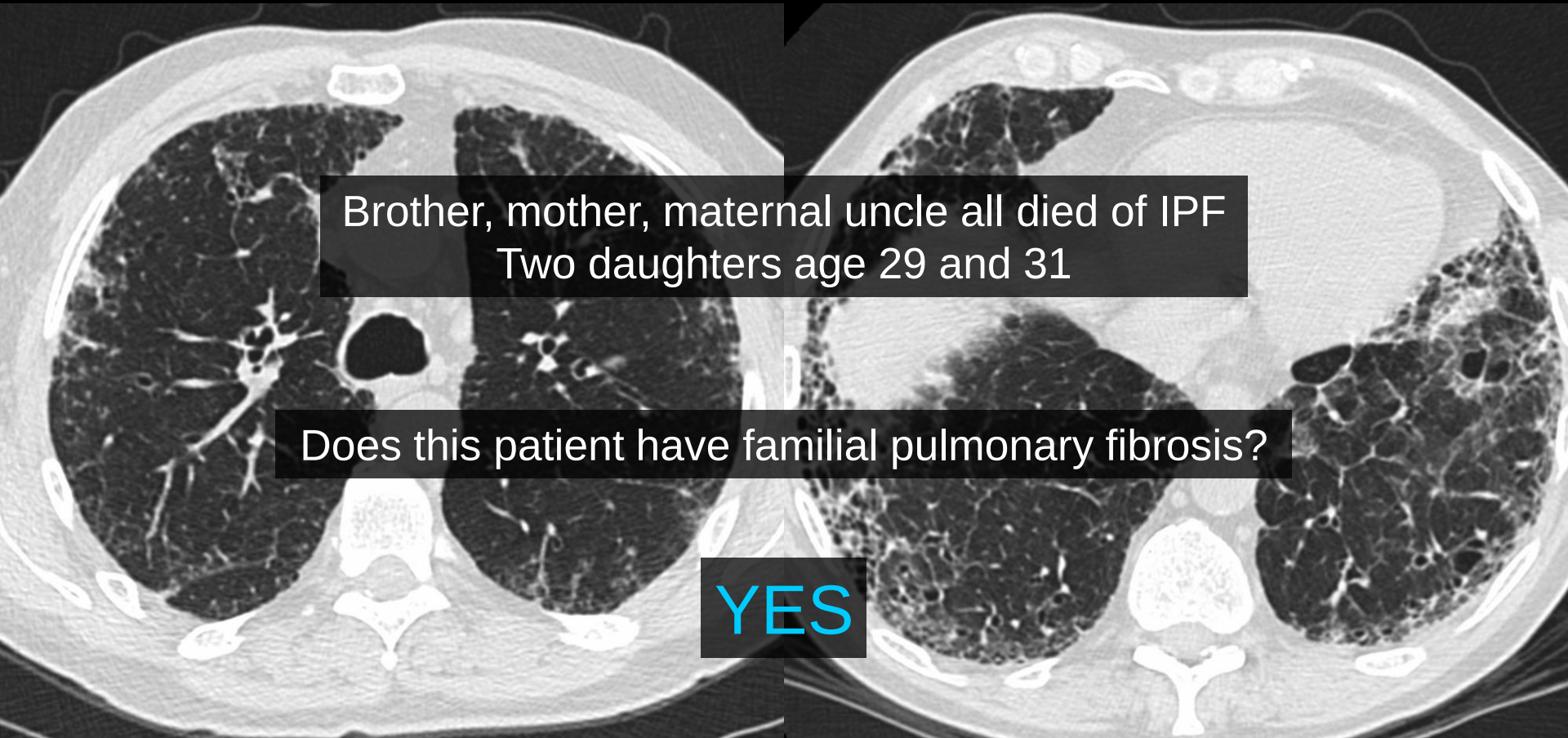
We Have No Relevant Disclosures



Outline

- Familial Fibrosis and Unclassifiable ILD
- Progressive Pulmonary Fibrosis
- Acute Exacerbation of UIP
- Interstitial Lung Abnormality
- Pleuroparenchymal Fibroelastosis
- Pulmonary Alveolar Proteinosis
- Exogenous Lipoid Pneumonia
- Meningotheliomatosis

68-year-old male, dyspnea while golfing



Brother, mother, maternal uncle all died of IPF
Two daughters age 29 and 31

Does this patient have familial pulmonary fibrosis?

YES

Familial Pulmonary Fibrosis

Fibrosis in at least 2 first degree relatives

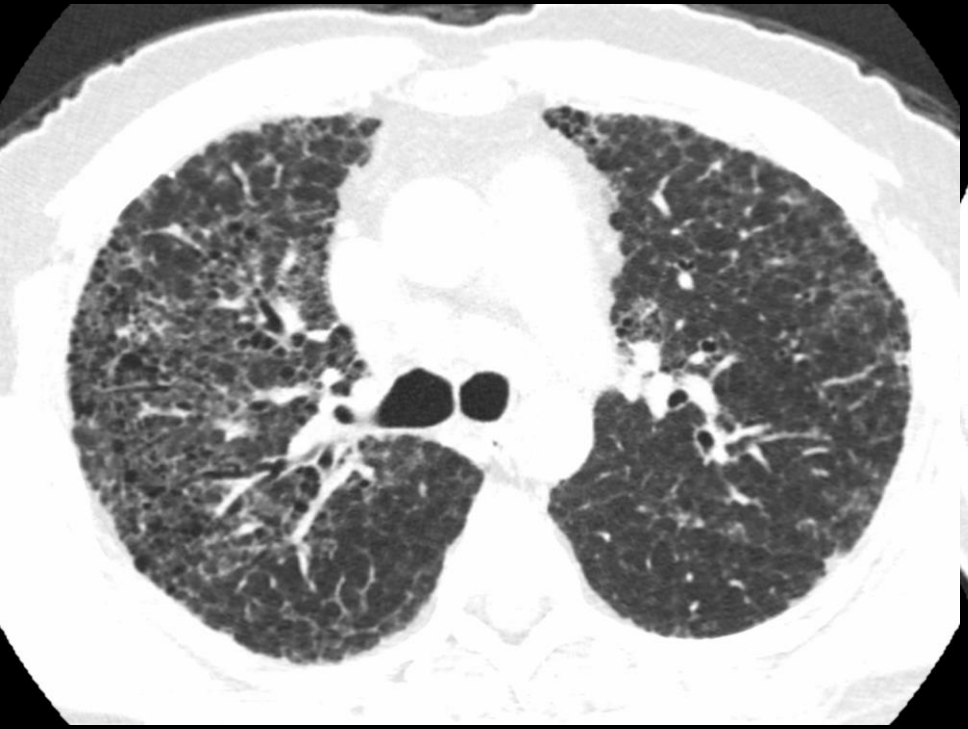
Aka:

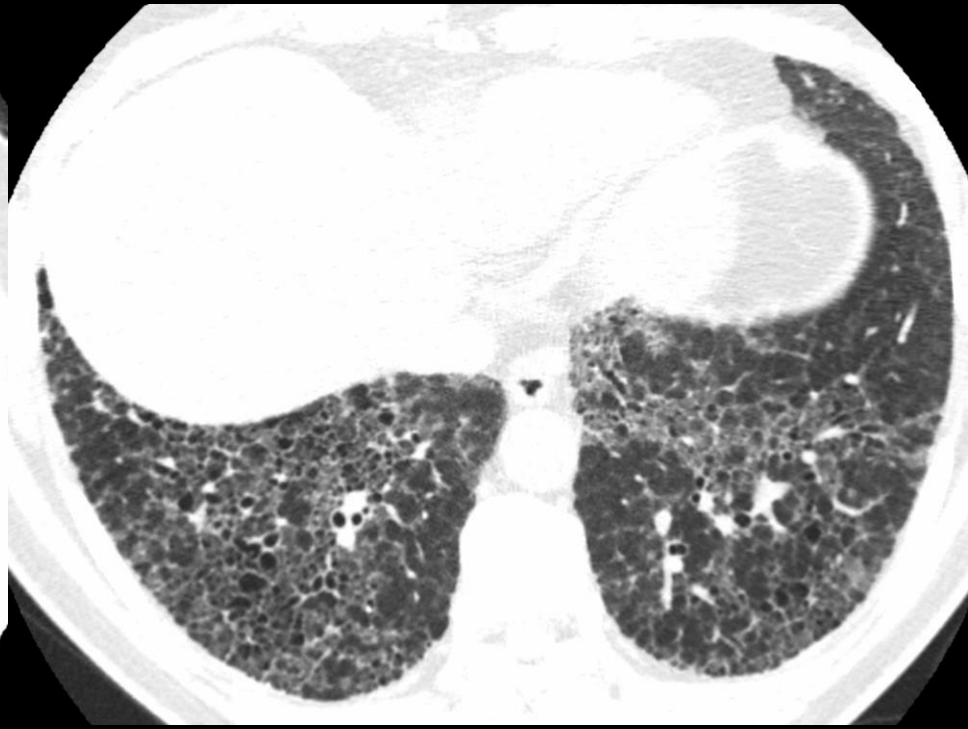
- Familial Interstitial Pneumonia (FIP)
- Familial IPF

Often occur at earlier ages than other IIP

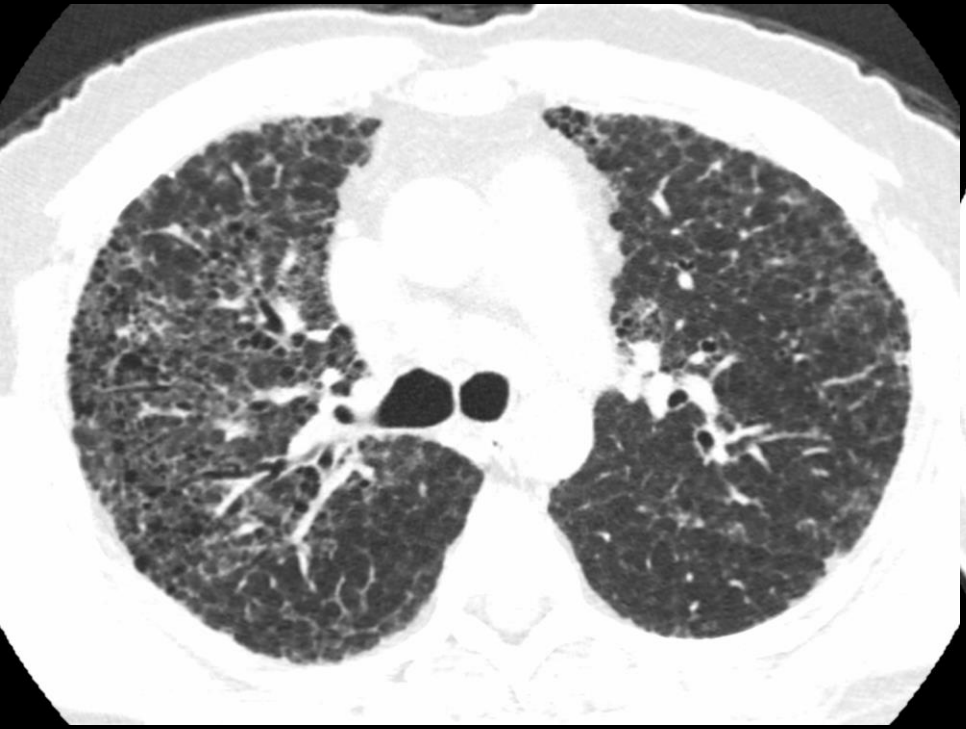
Significant phenotypic variability

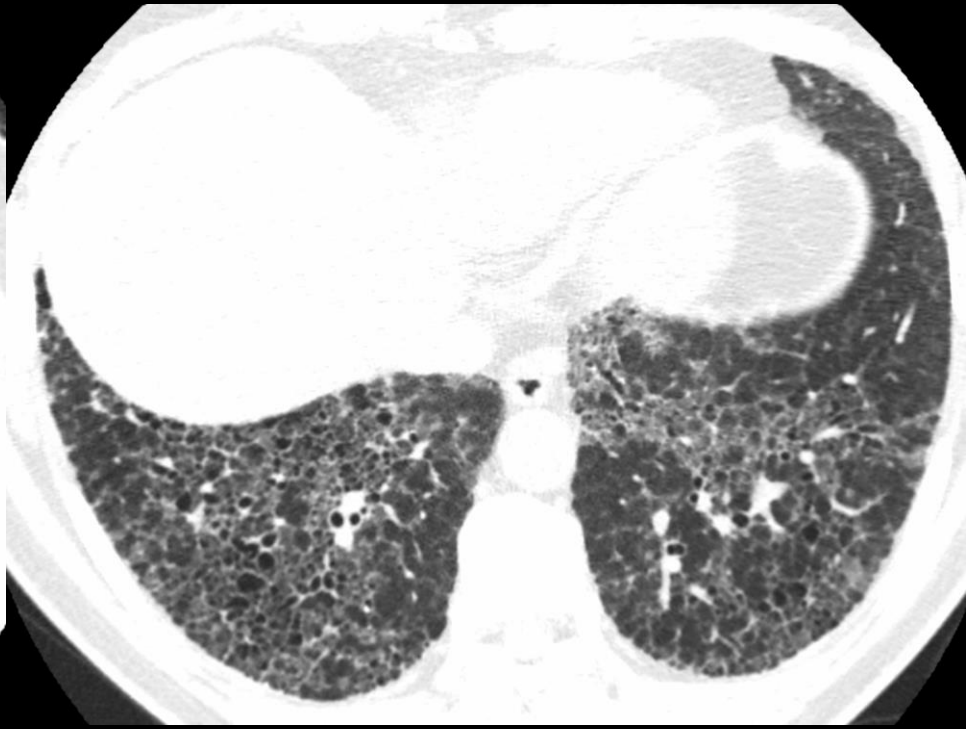
45-year-old – how would you classify?





Unclassifiable – son with SFTPC





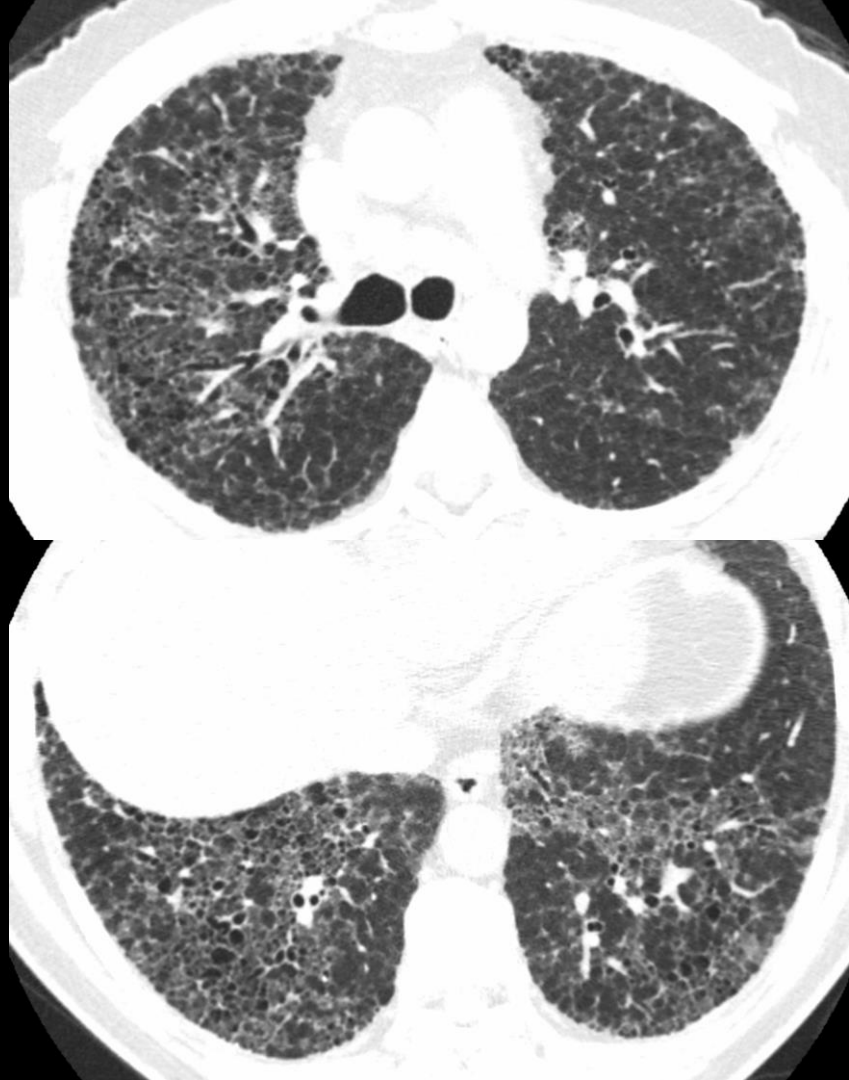
Genetic testing instead of biopsy → Confirmed SFTPC Mutation

Many patients with FPF are difficult to classify on imaging and/or pathology

Genes Known to Cause FPF

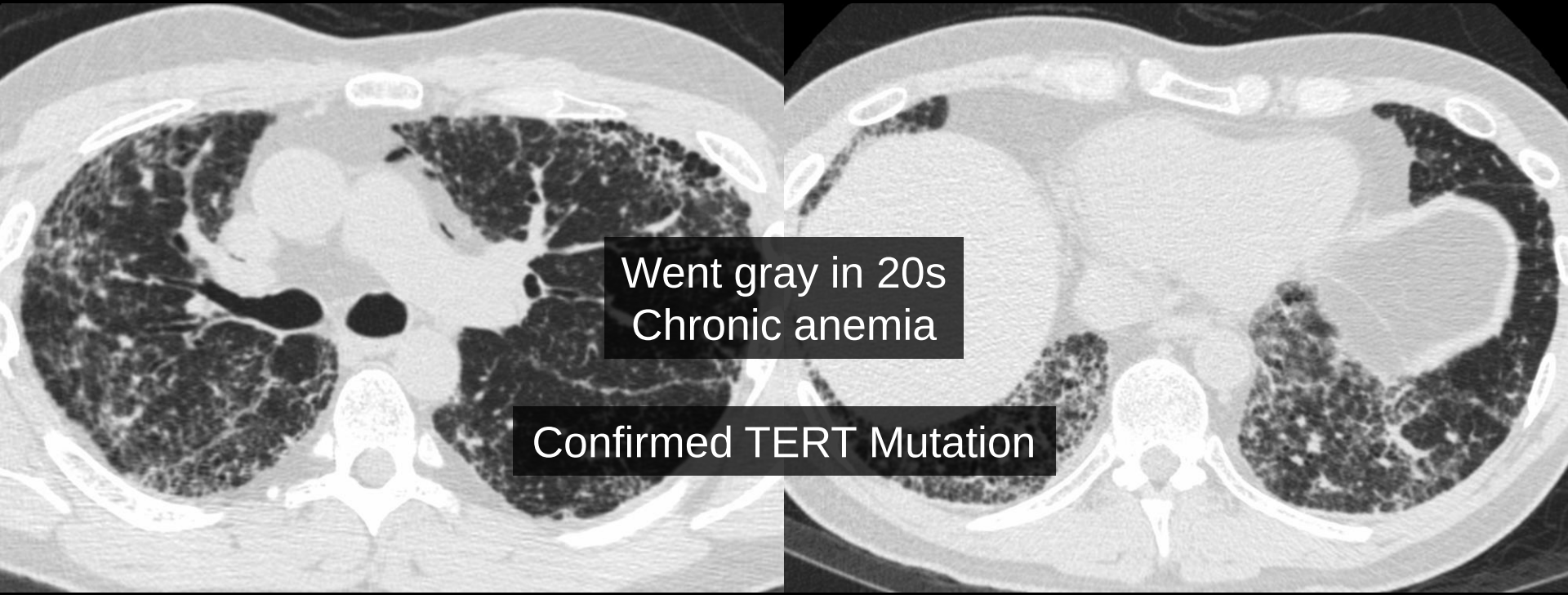
Surfactant	Telomeropathy	Other
• SFTPC • SFTPA2 • ABCA3	• TERT • TERC • DKC1 • RTEL1 • PARN	• Host Defense (MUC5B; TOLLIP) • Autoimmune (COPA)

- Surfactant mutations:
  - ~20% of adult FPF cases
  - HRCT often unclassifiable
  - Histology → UIP
- Genetic anticipation



48-year-old with “IPF”

Brother recently died of ILD

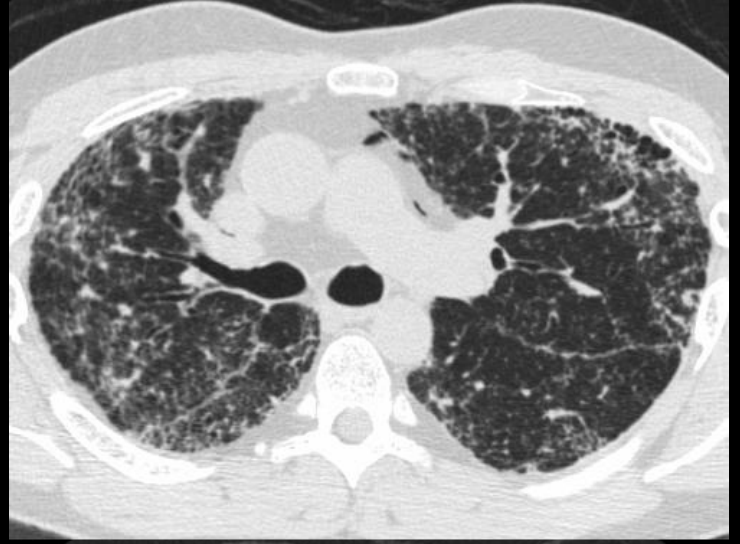


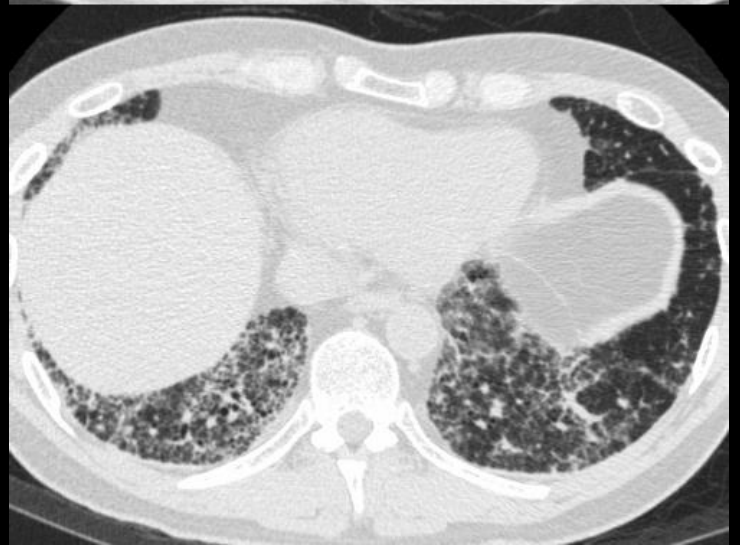
Telomeres

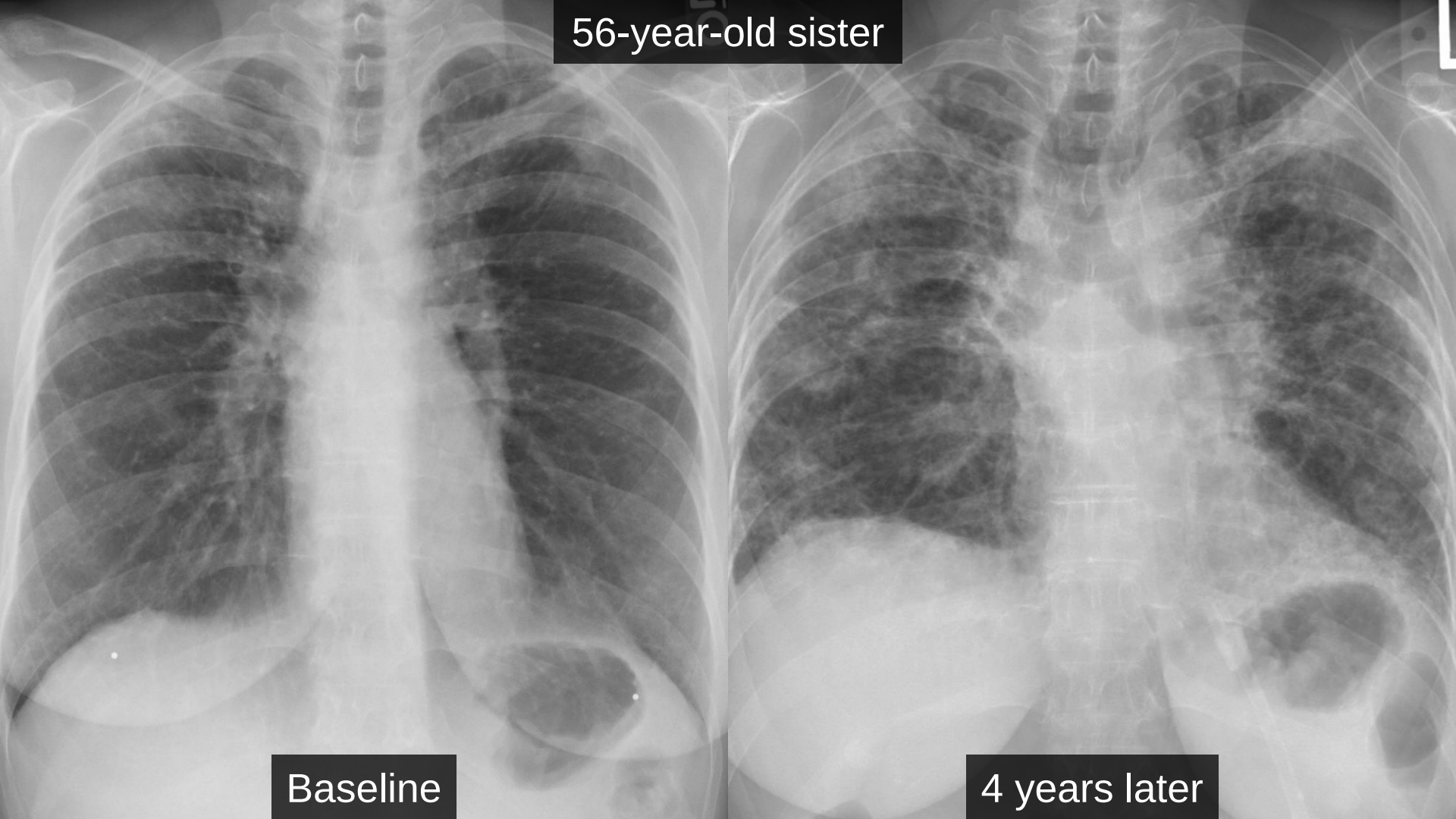
- TTAGGG repeats added to chromosomes during replication
- Telomere shortening → cell death → premature aging

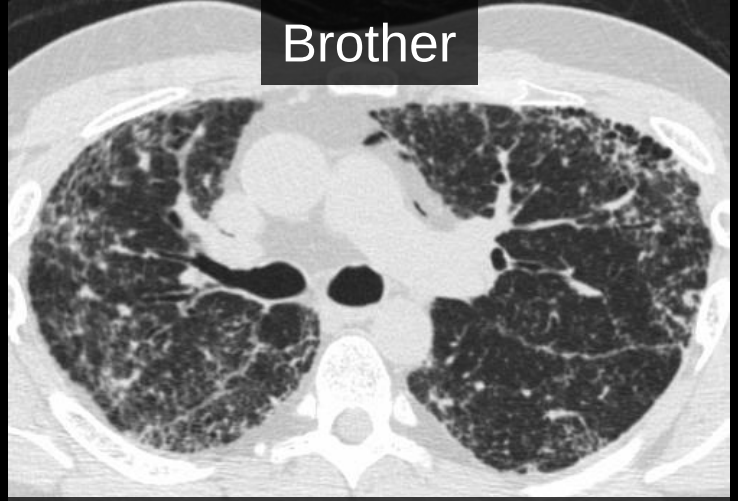
Telomeropathy:

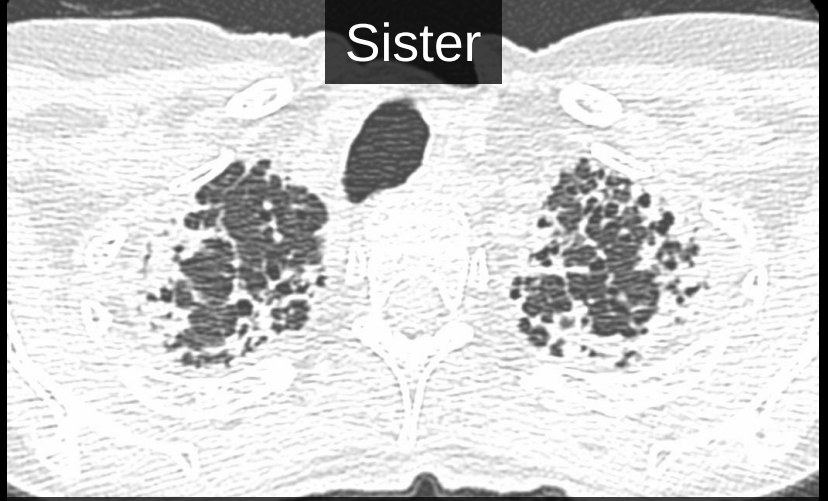
- Pulmonary fibrosis
- Premature graying
- Cryptogenic cirrhosis
- Bone marrow failure



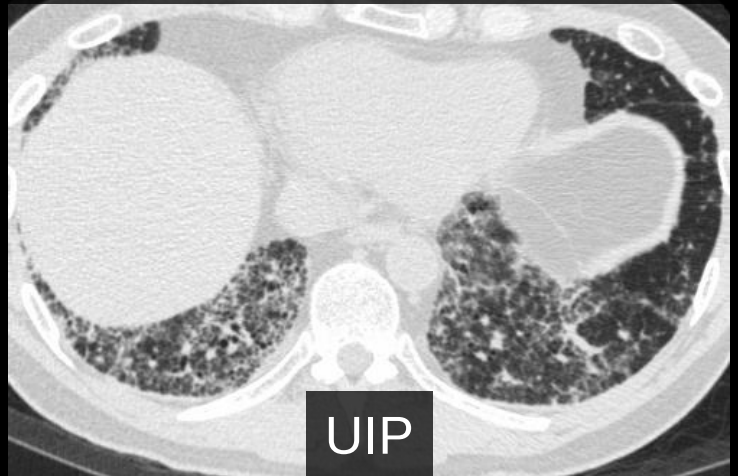


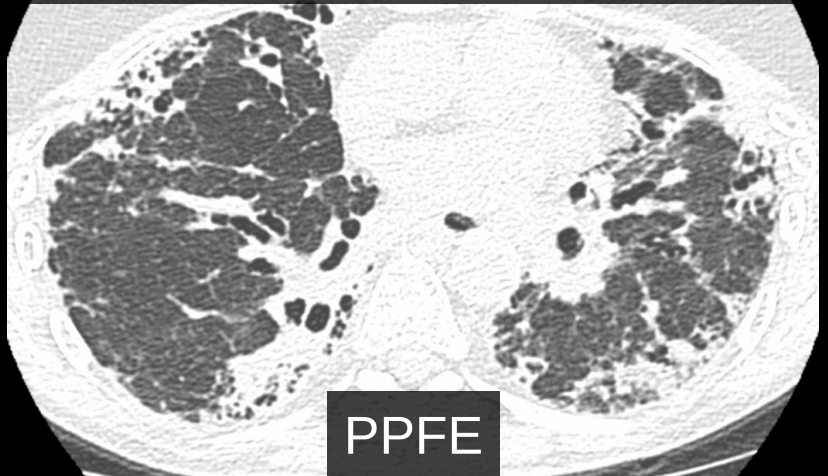

56-year-old sister
Baseline
4 years later





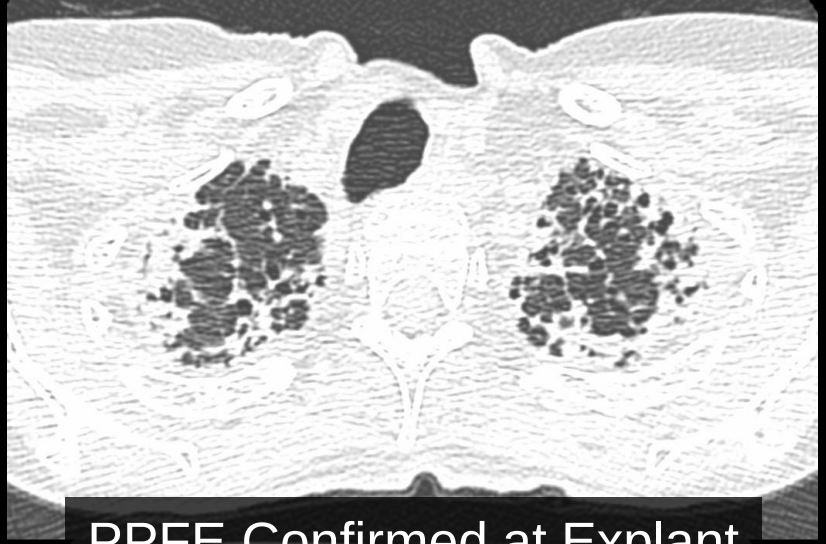
Patients in Same Families Often Have Different Patterns!

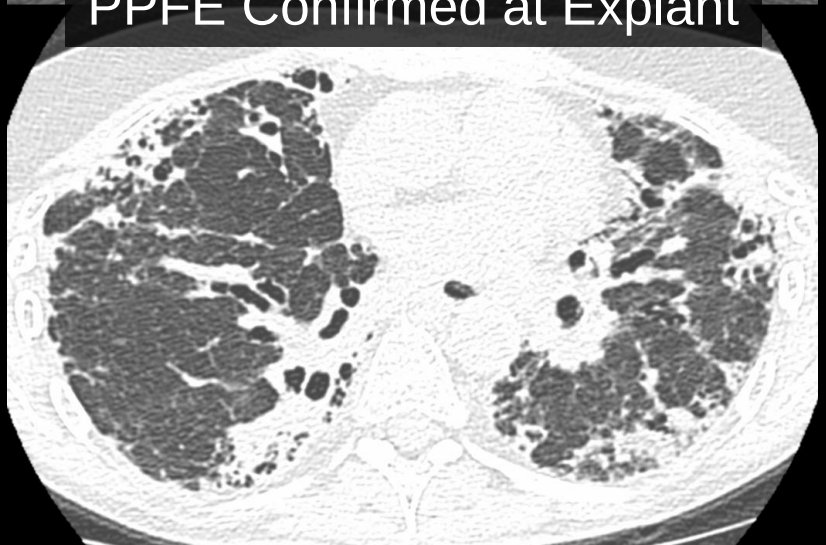




Radiologic Patterns in Telomeropathies:

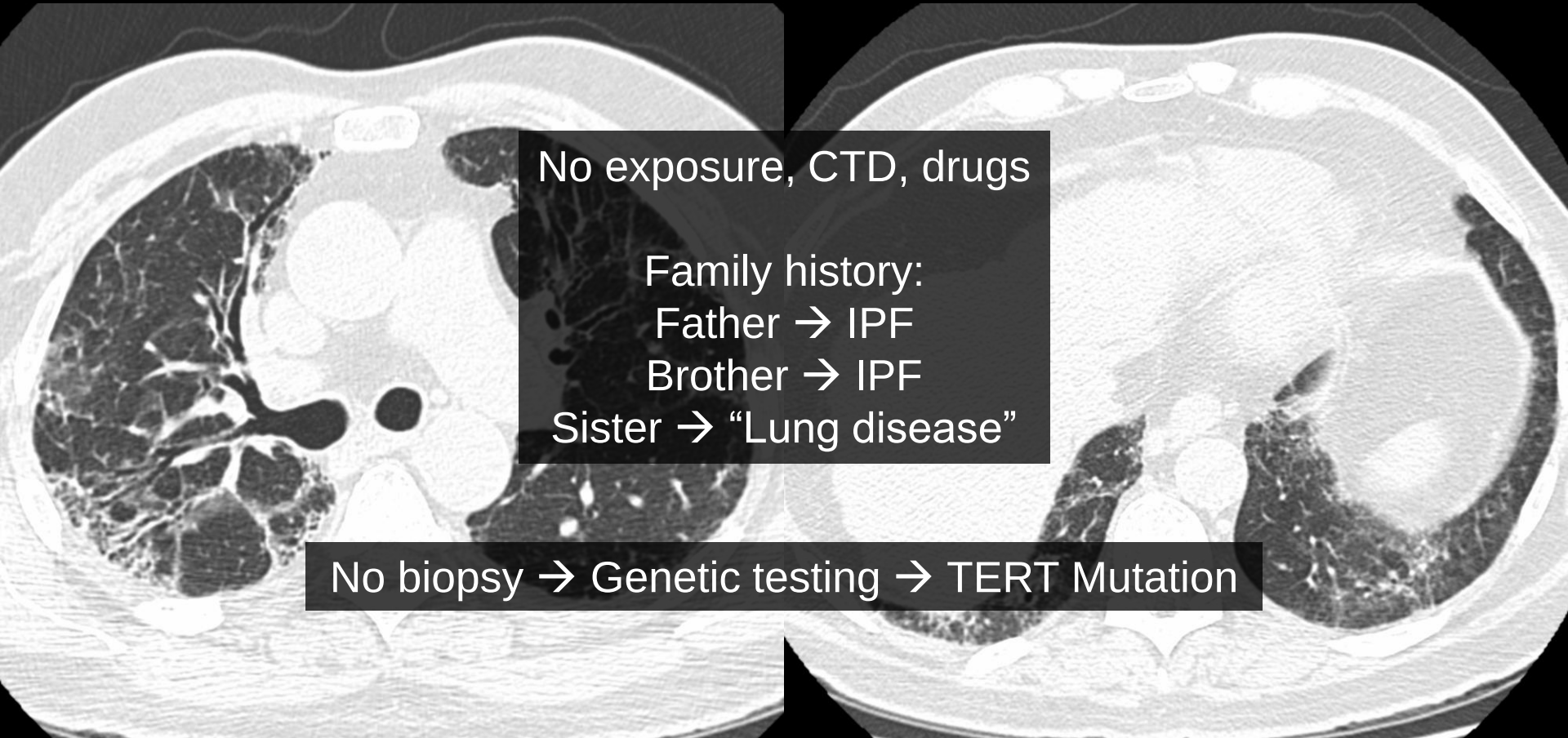
- UIP (50%)
- Unclassifiable (20%)
- Chronic HP
- PPFE
- NSIP
- IPAF





PPFE Confirmed at Explant

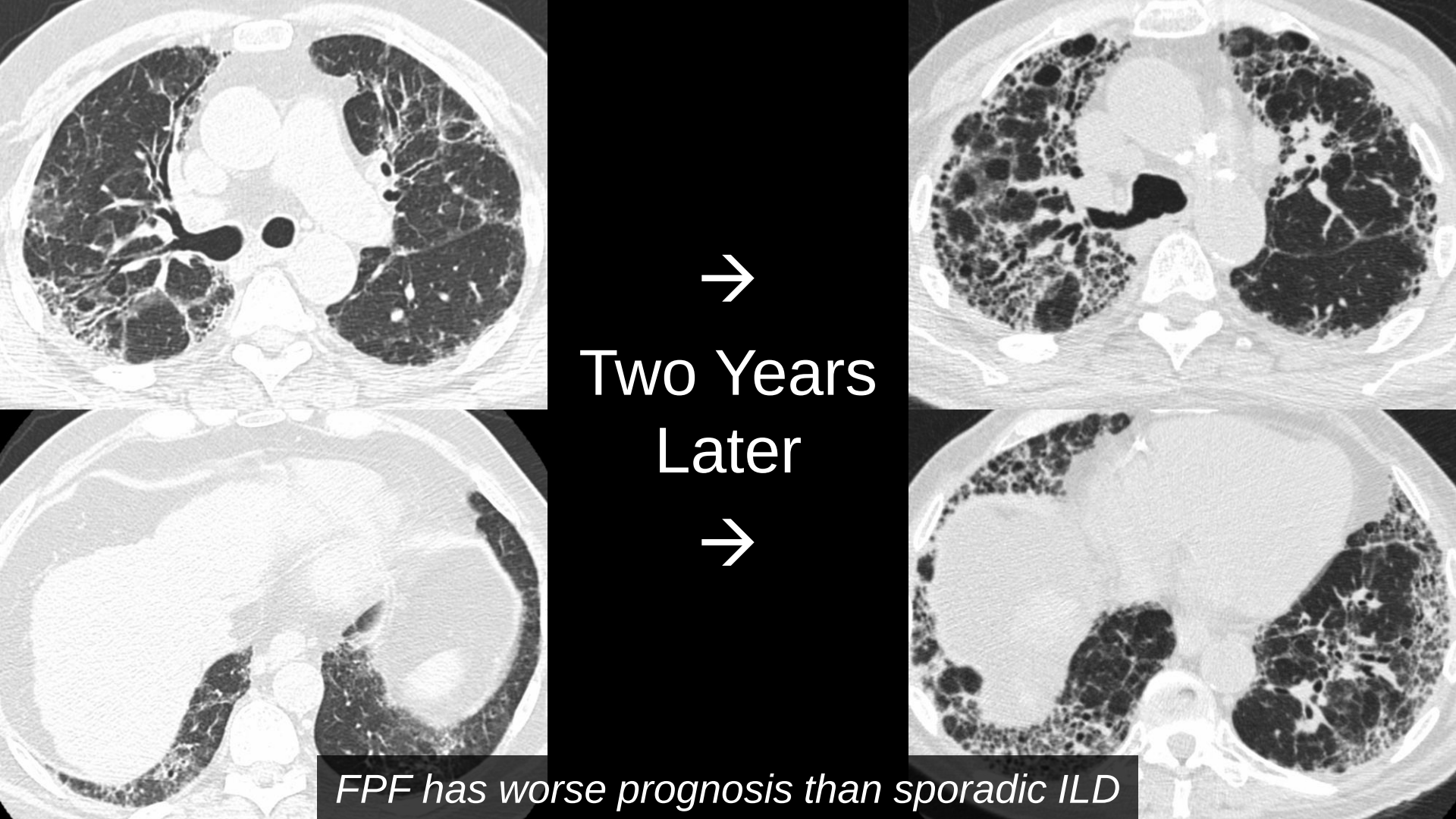
63-year-old male – dyspnea x 1 year



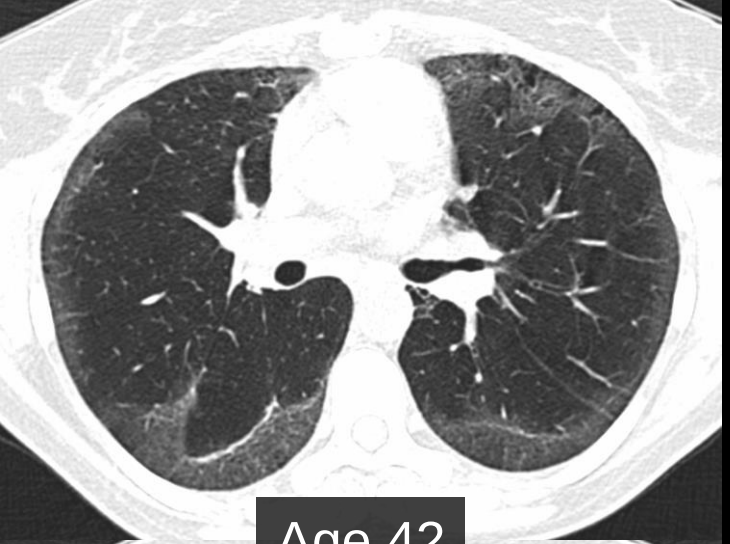
No exposure, CTD, drugs

Family history:
Father → IPF
Brother → IPF
Sister → “Lung disease”

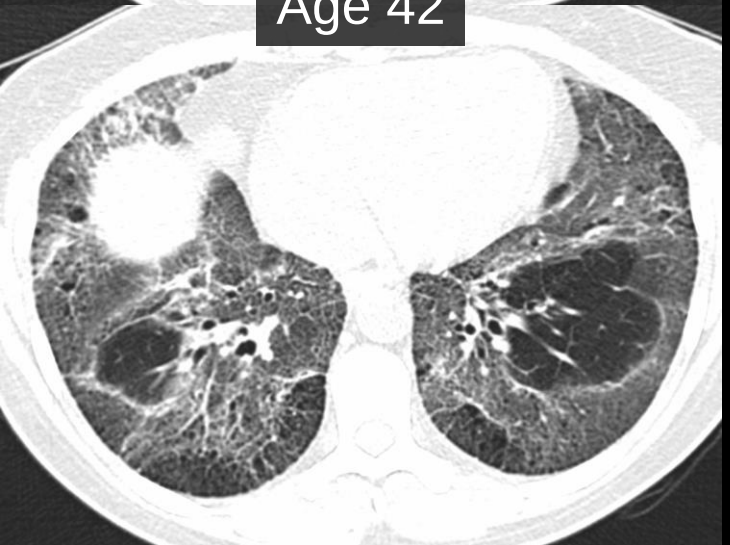
No biopsy → Genetic testing → TERT Mutation



FPF has worse prognosis than sporadic ILD



Age 42

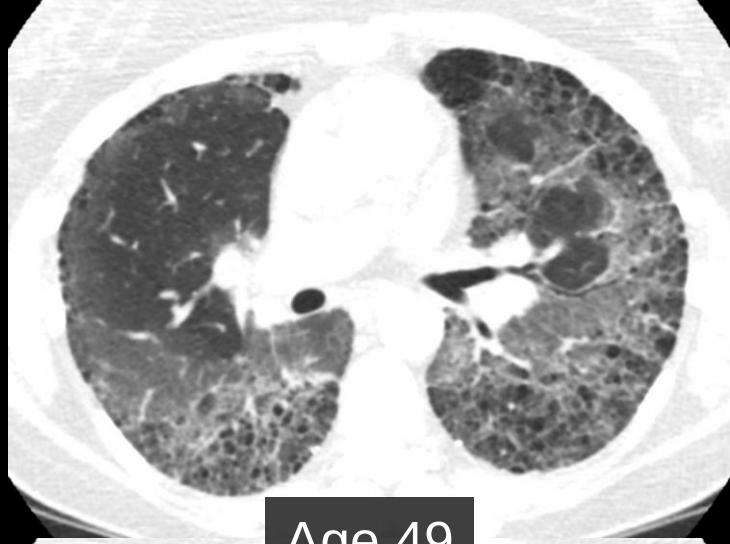


Twin A

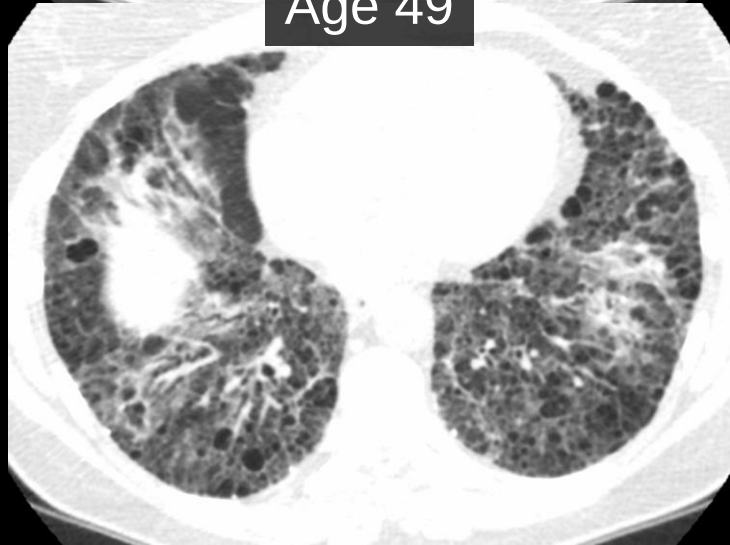
Gray hair @18

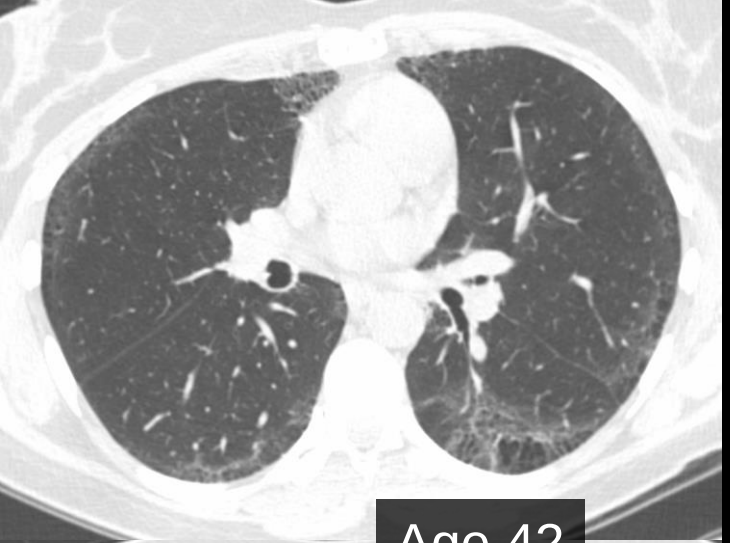
Explant:

NSIP + UIP

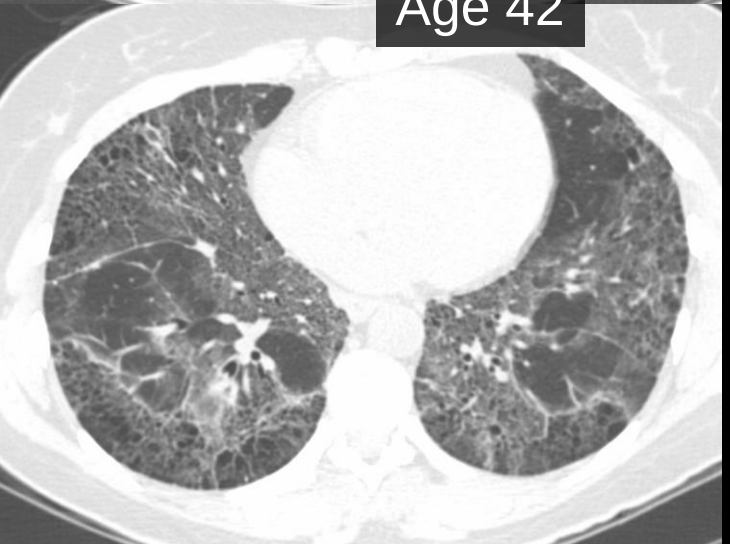


Age 49





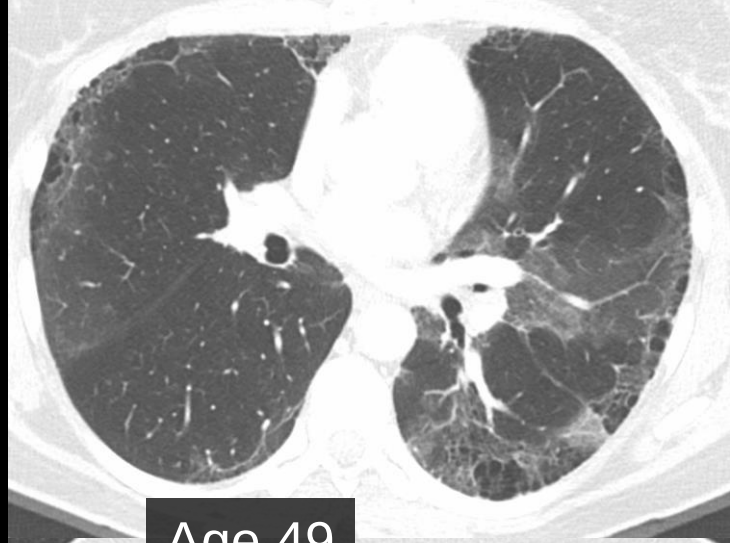
Age 42



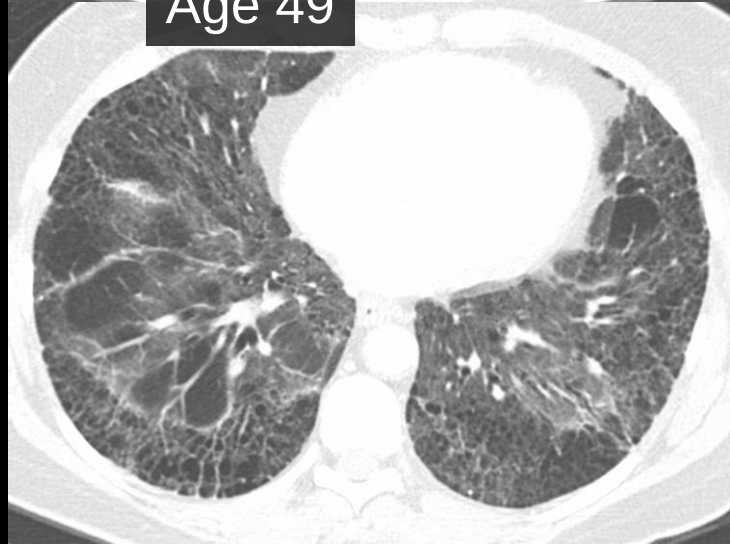
Twin B

Also went gray@18

Less progression

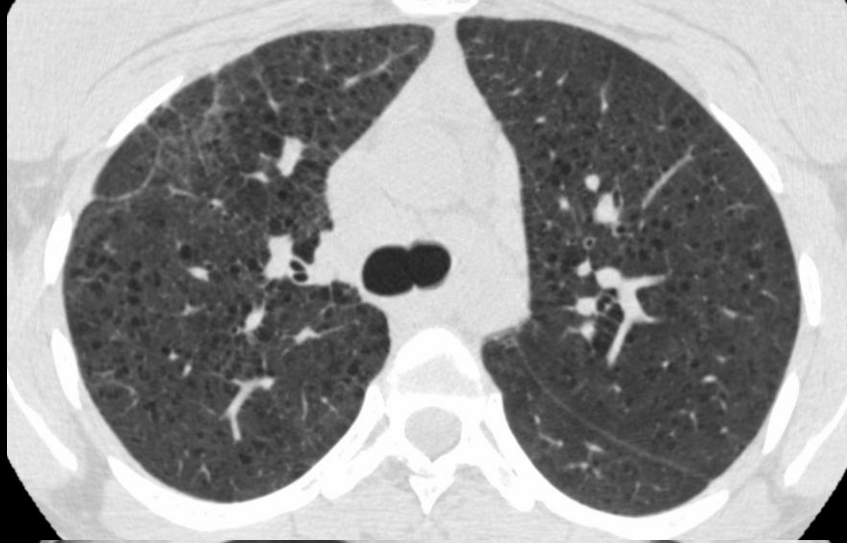


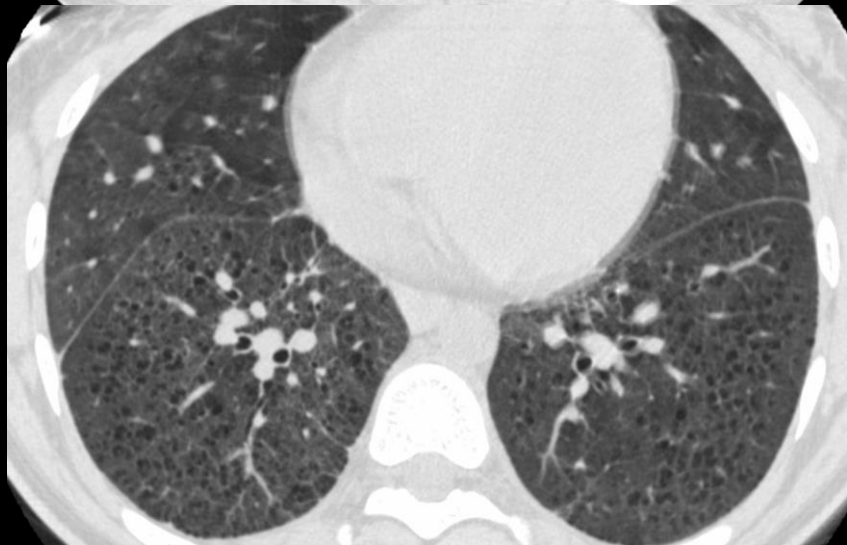
Age 49



20-year-old female

- Recurrent DAH before age 3
- MPO+ autoimmunity
- Surgical lung biopsy → follicular bronchiolitis
- Sister 8 years younger with similar symptoms





COPA Syndrome

- Identified in 2015
- Five families with autoimmune disease:
  - Arthritis
  - Lung disease
  - Autoimmunity
- Whole exome sequencing → mutation in COPA gene

nature genetics

COPA mutations impair ER-Golgi transport and cause hereditary autoimmune-mediated lung disease and arthritis

Levi B Watkin[1,2,16], Birthe Jessen[3,16], Wojciech Wiszniewski[4,16], Timothy J Vece[1], Max Jan[3], Youbao Sha[5], Maike Thamsen[3], Regie L P Santos-Cortez[6], Kwanghyuk Lee[6], Tomasz Gambin[4], Lisa R Forbes[1,2], Christopher S Law[3], Asbjørg Stray-Pedersen[2,4], Mickie H Cheng[3], Emily M Mace[1,2], Mark S Anderson[3], Dongfang Liu[1,2], Ling Fung Tang[7], Sarah K Nicholas[1,2], Karen Nahmod[1,2], George Makedonas[1,2], Debra L Canter[1,2], Pui-Yan Kwok[7,8], John Hicks[9], Kirk D Jones[10], Samantha Penney[4], Shalini N Jhangiani[11], Michael D Rosenblum[8], Sharon D Dell[12], Michael R Waterfield[13], Feroz R Papa[3], Donna M Muzny[11], Noah Zaitlen[3], Suzanne M Leal[6], Claudia Gonzaga-Jauregui[4], Baylor-Hopkins Center for Mendelian Genomics[14], Eric Boerwinkle[11,15], N Tony Eissa[5], Richard A Gibbs[4,11], James R Lupski[1,4,11,17], Jordan S Orange[1,2,17] & Anthony K Shum[3,7,17]

Unbiased genetic studies have uncovered surprising molecular mechanisms in human cellular immunity and autoimmunity[1]. We performed whole-exome sequencing and targeted sequencing in five families with an apparent mendelian syndrome of autoimmunity characterized by high-titer autoantibodies, inflammatory arthritis and interstitial lung disease. We identified four unique deleterious variants in the *COPA* gene (encoding coatomer subunit α) affecting the same functional domain. Hypothesizing that mutant COPA leads to defective intracellular transport via coat protein complex I (COPI)[2–4], we show that *COPA* variants impair binding to proteins targeted for retrograde Golgi-to-ER transport. Additionally, expression of mutant COPA results in ER stress and the upregulation of cytokines priming for a T helper type 17 (T_H17) response. Patient-derived CD4⁺ T cells also demonstrate significant skewing toward a T_H17 phenotype that is implicated in autoimmunity[5,6]. Our findings uncover an unexpected molecular link between a vesicular transport protein and a syndrome of autoimmunity manifested by lung and joint disease.

Monogenic disorders have proven powerful in elucidating biological mechanisms underlying autoimmunity[7,8] by showing that autoimmunity can arise from perturbations in several non-classical pathways[7]. Defects in the intracellular trafficking mechanisms of immune cells[9] might also be anticipated to cause autoimmunity, as disruptions in protein trafficking lead to endoplasmic reticulum (ER) stress and activation of the unfolded protein response (UPR), both of which have been implicated in autoimmune disease[10].

We identified five families with a previously undescribed mendelian syndrome of autoimmunity manifested by high-titer autoantibodies, interstitial lung disease and inflammatory arthritis (**Fig. 1a–d**, **Table 1** and **Supplementary Table 1**). The average age of presentation was 3.5 years, with a range of 6 months to 22 years. Several patients presented with pulmonary hemorrhage requiring immunosuppression, and all patients have lung disease (**Table 1** and **Supplementary Table 1**). A comparison of lung biopsies from unrelated patients identified lymphocytic interstitial infiltration with germinal center formation (**Fig. 1b,c**), findings consistent with the interstitial lung disease occurring in systemic autoimmune syndromes[11]. Immunohistochemical staining of lungs identified CD20⁺ B cells within the germinal centers and substantial numbers of lung-infiltrating CD4⁺ T cells (**Fig. 1b,c**). Autoantibodies were detected in 86% of the affected patients, including anti-nuclear antibodies (ANAs), anti-neutrophil cytoplasmic antibodies (ANCAs) and rheumatoid factor (RF) (**Table 1** and **Supplementary Table 2**). Immunoglobulin levels, absolute lymphocyte counts and CD4/CD8 cell ratios were largely normal (**Supplementary Table**
arthritis, and some initia
patients underwent renal

[1]Department of Pediatrics, Baylor College of Medicine, Houston, Texas, USA. [2]Texas Children's Hospital Center for
[3]Department of Medicine, University of California, San Francisco, San Francisco, California, USA. [4]Department of
of Medicine, Houston, Texas, USA. [5]Department of Medicine, Baylor College of Medicine, Houston, Texas, USA. [6]
of Medicine, Houston, Texas, USA. [7]Cardiovascular Research Institute, University of California, San Francisco, San
Dermatology, University of California, San Francisco, San Francisco, California, USA. [9]Department of Pathology, Te
[10]Department of Pathology, University of California, San Francisco, San Francisco, California, USA. [11]Human Gen
Houston, Texas, USA. [12]Division of Respiratory Medicine, Hospital for Sick Children, Toronto, Ontario, Canada. [13]
San Francisco, San Francisco, California, USA. [14]Houston, Texas, USA. [15]Human Genetics Center and Institute of
Health Science Center, Houston, Texas, USA. [16]These authors contributed equally to this work. [17]These authors jo
be addressed to A.K.S. (anthony.shum@ucsf.edu) or J.S.O. (orange@bcm.edu).

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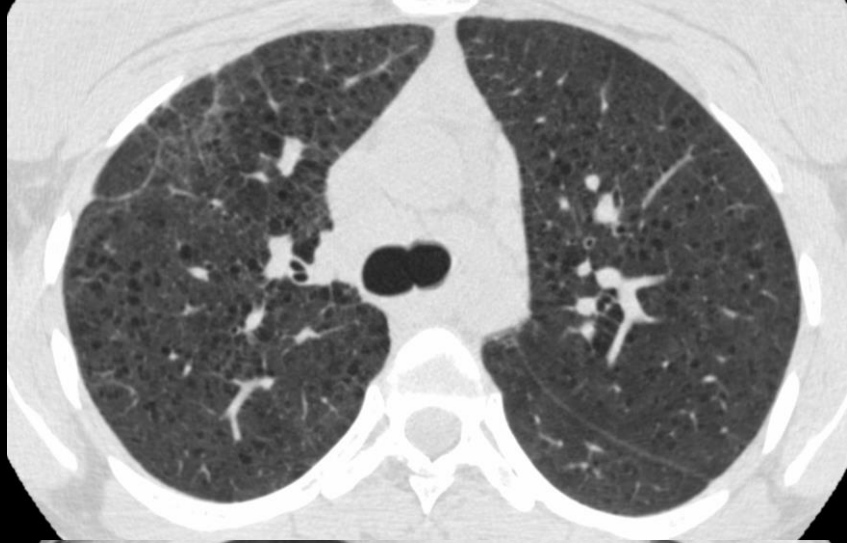
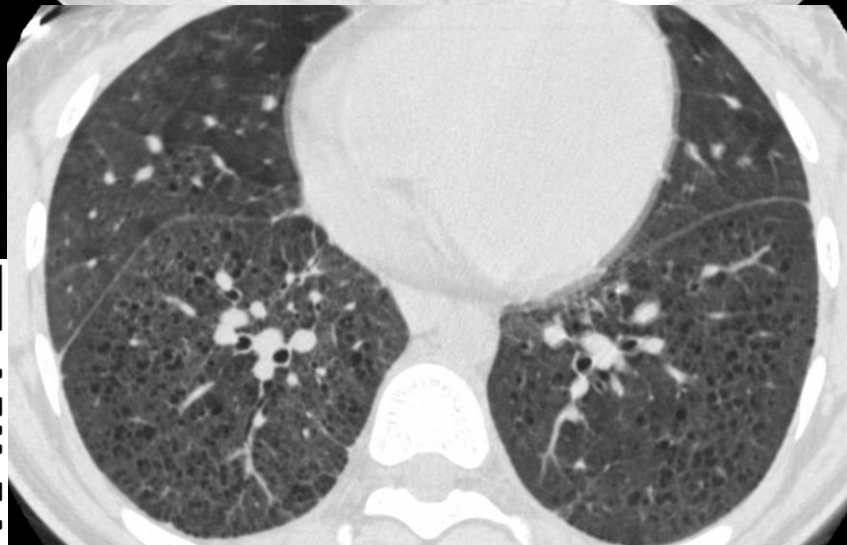
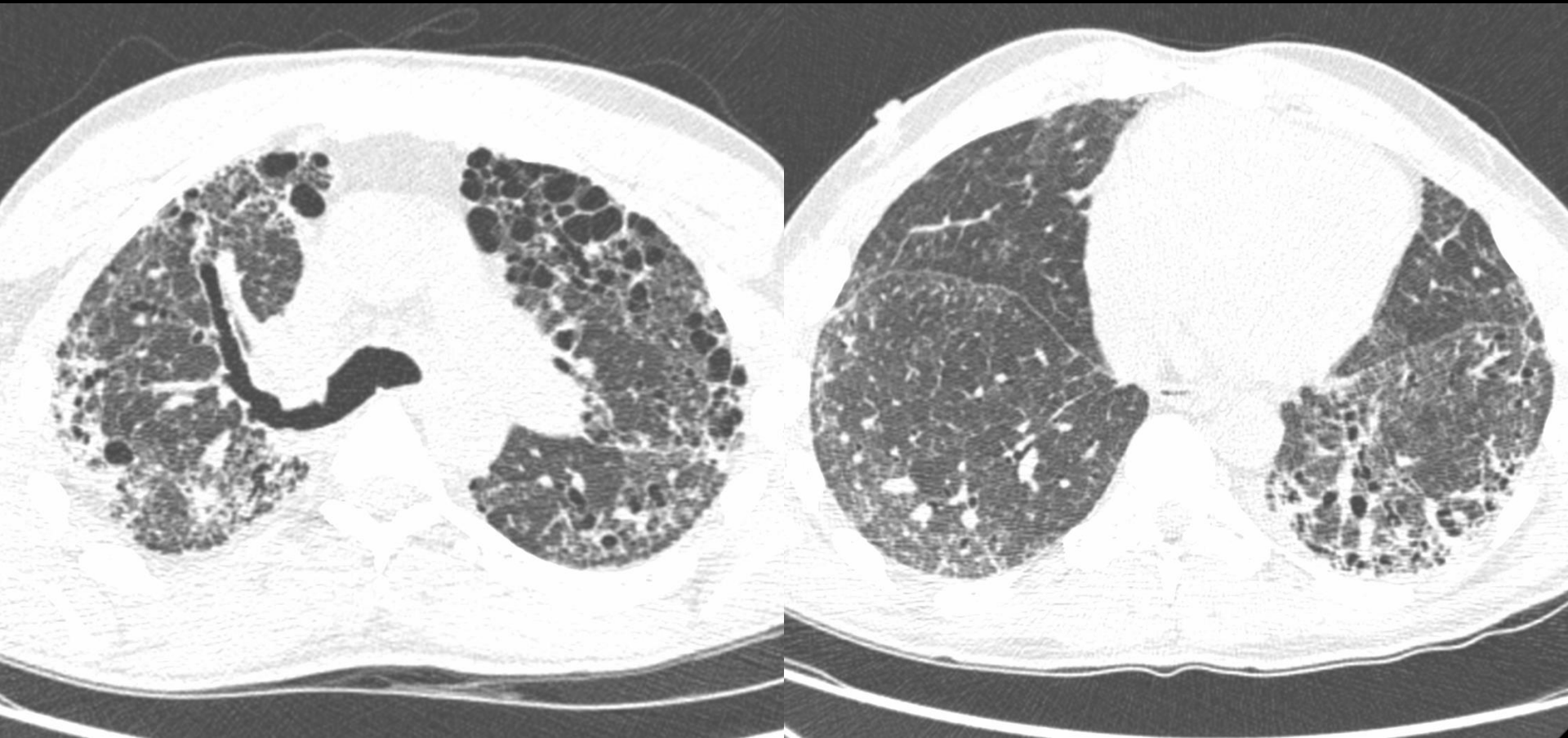
COPA Syndrome

- Mistaken for RA, JIA
  - Positive RF
  - Positive ANCA
- Present by age 12:
  - DAH (50%)
  - Lung disease (100%)
  - Arthritis (100%)
  - Renal (~25%)





50-year-old with dyskeratosis congenita



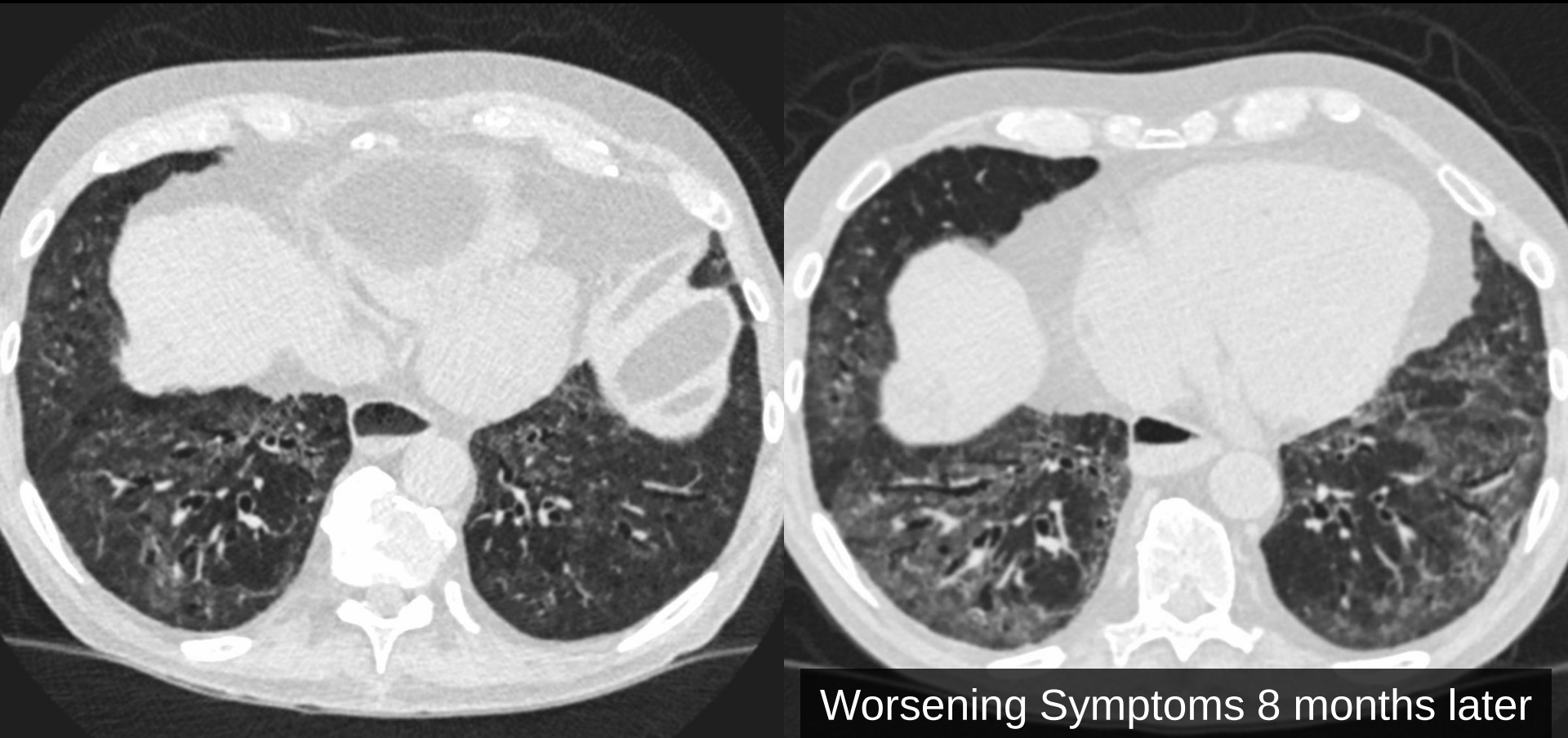
Familial Pulmonary Fibrosis

- Fibrosis in first degree relative
- Many imaging appearances, often unclassifiable

Progressive Pulmonary Fibrosis

- Defined in 2022
- Worsening fibrosis in non-IPF patient within the past year, with no alternate explanation
- Two of three criteria required:
  - Worsening symptoms
  - Worsening fibrosis on imaging
  - Worsening physiology
- Why define PPF? May treat with antifibrotics

PPF

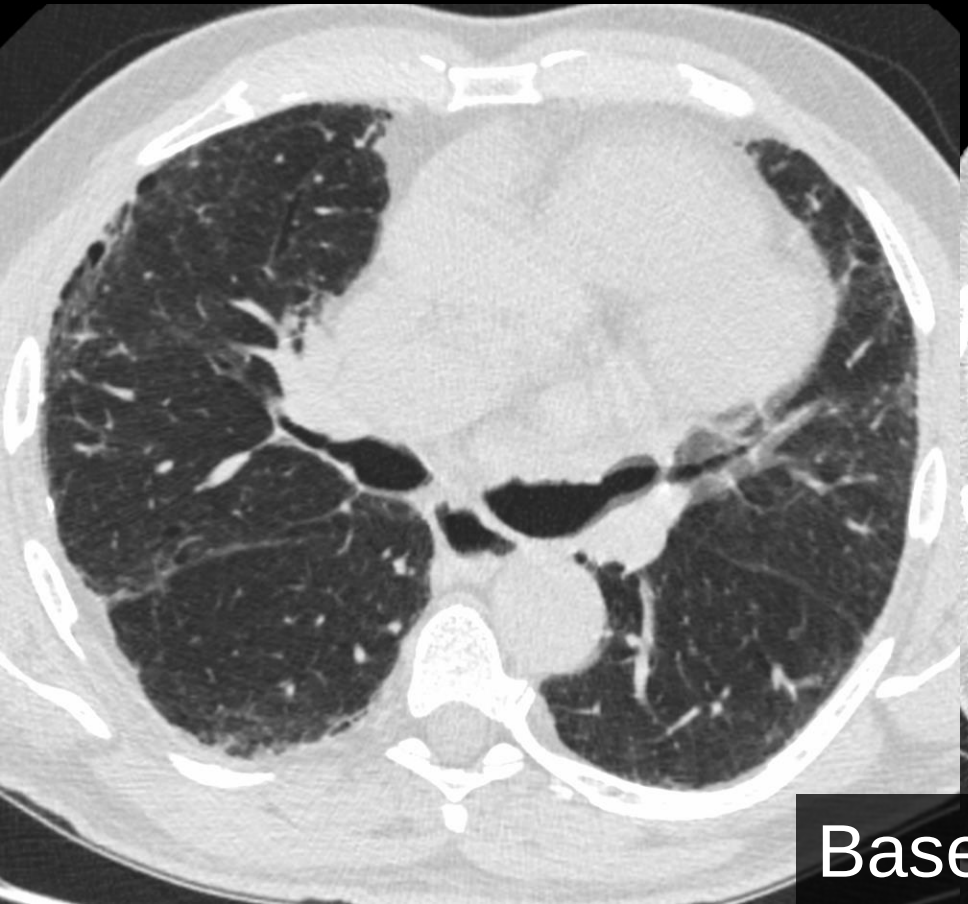


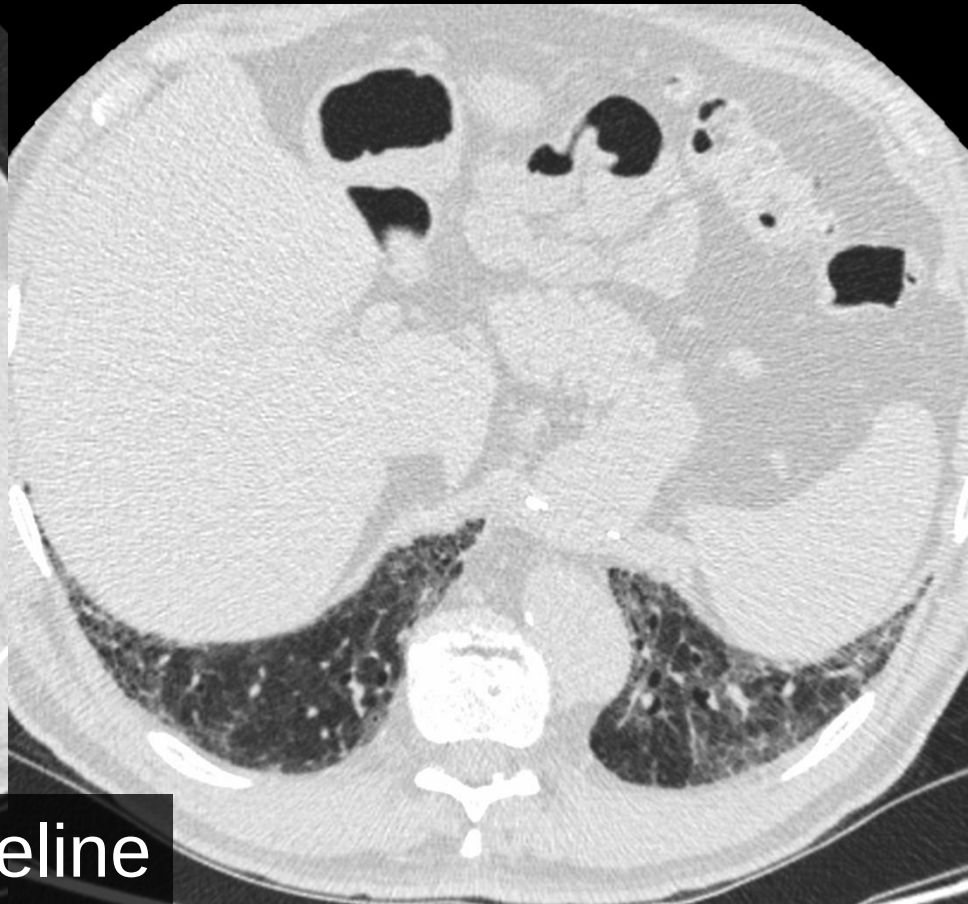
Worsening Symptoms 8 months later

Acute Exacerbation of UIP

- Acute worsening of symptoms within 1 month
- New GGO/consolidation on top of UIP pattern
- Worsening not fully explained by heart failure/volume overload
- Antifibrotics may reduce acute exacerbations?

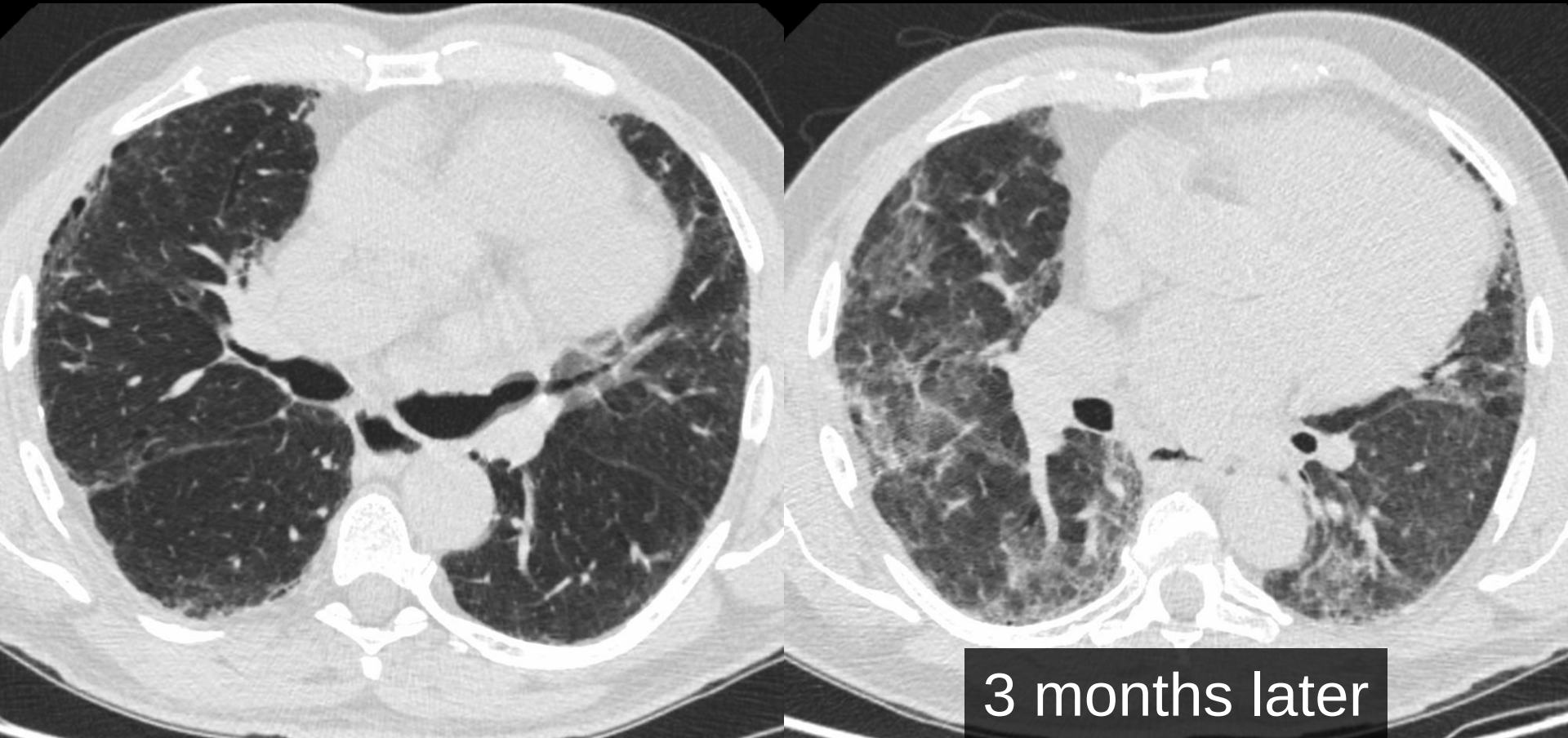
Acute Exacerbation of UIP





Baseline

Acute Exacerbation of UIP



PPF vs Acute Exacerbation

- PPF:
  - Non UIP/IPF diagnosis
  - Worsening symptoms/imaging/physiology over past year
  - Consider antifibrotics
- Acute exacerbation of UIP/IPF:
  - New worsening of symptoms
  - Infection versus other insult
  - High morbidity (>50% in hospital mortality)

Interstitial Lung Abnormality

ILA is Often an Early, Incidental ILD

Subpleural ILA may be early UIP

Subtypes of ILA

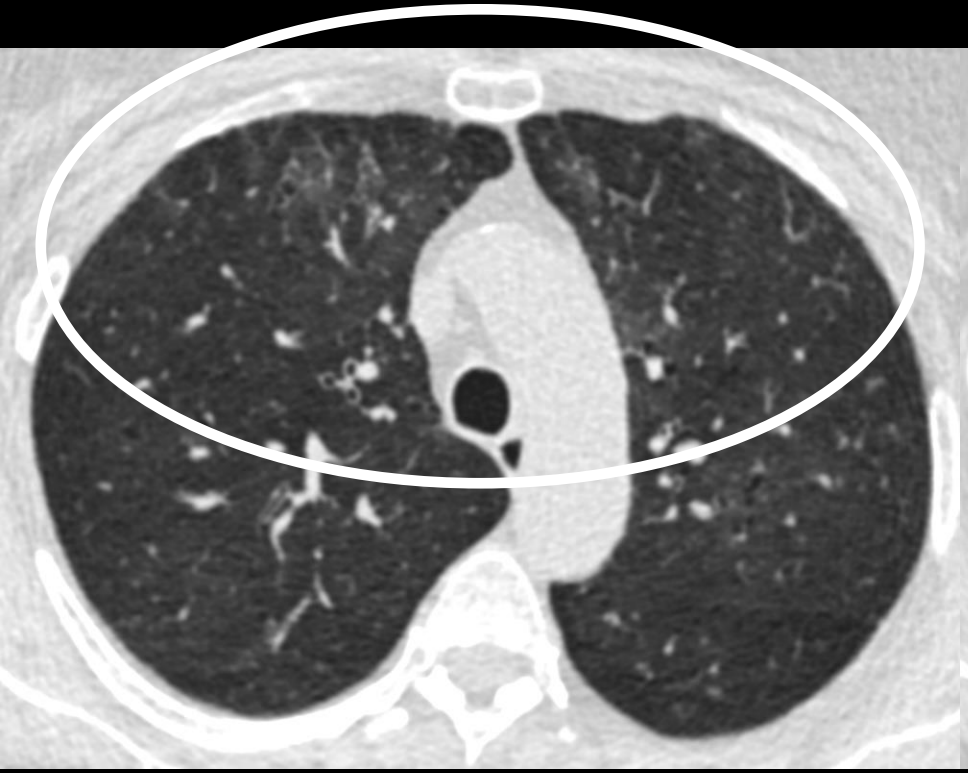
Non-subpleural → Does NOT Progress

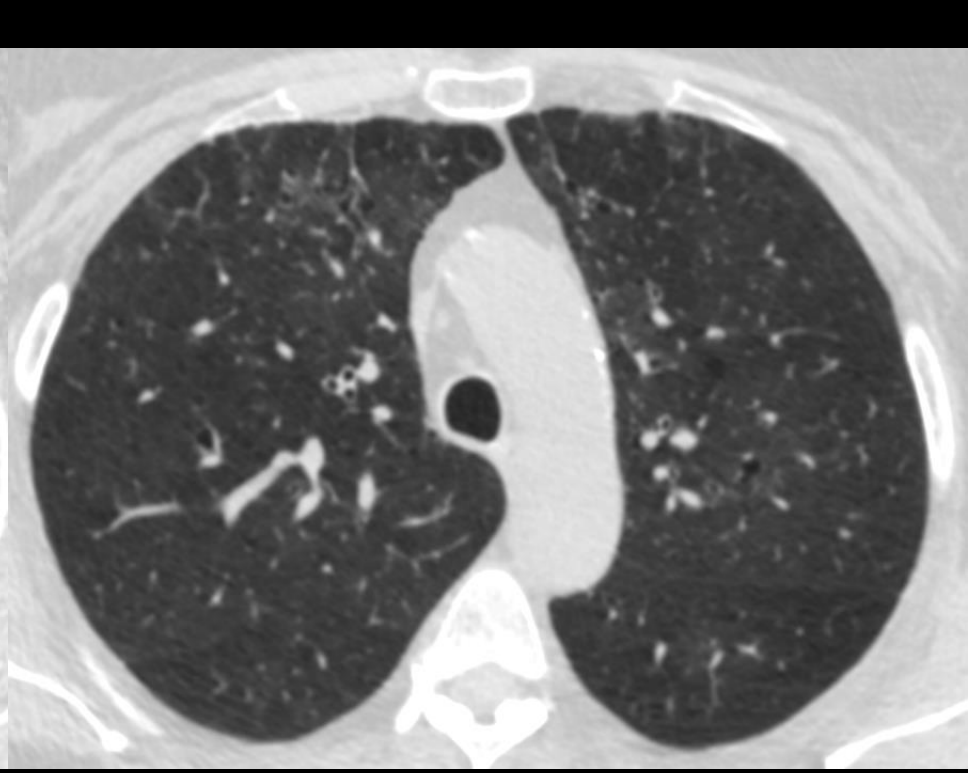
Subpleural → May Progress

Non-fibrotic

Fibrotic

Non-subpleural ILA





Lung Cancer Screening

5 years later

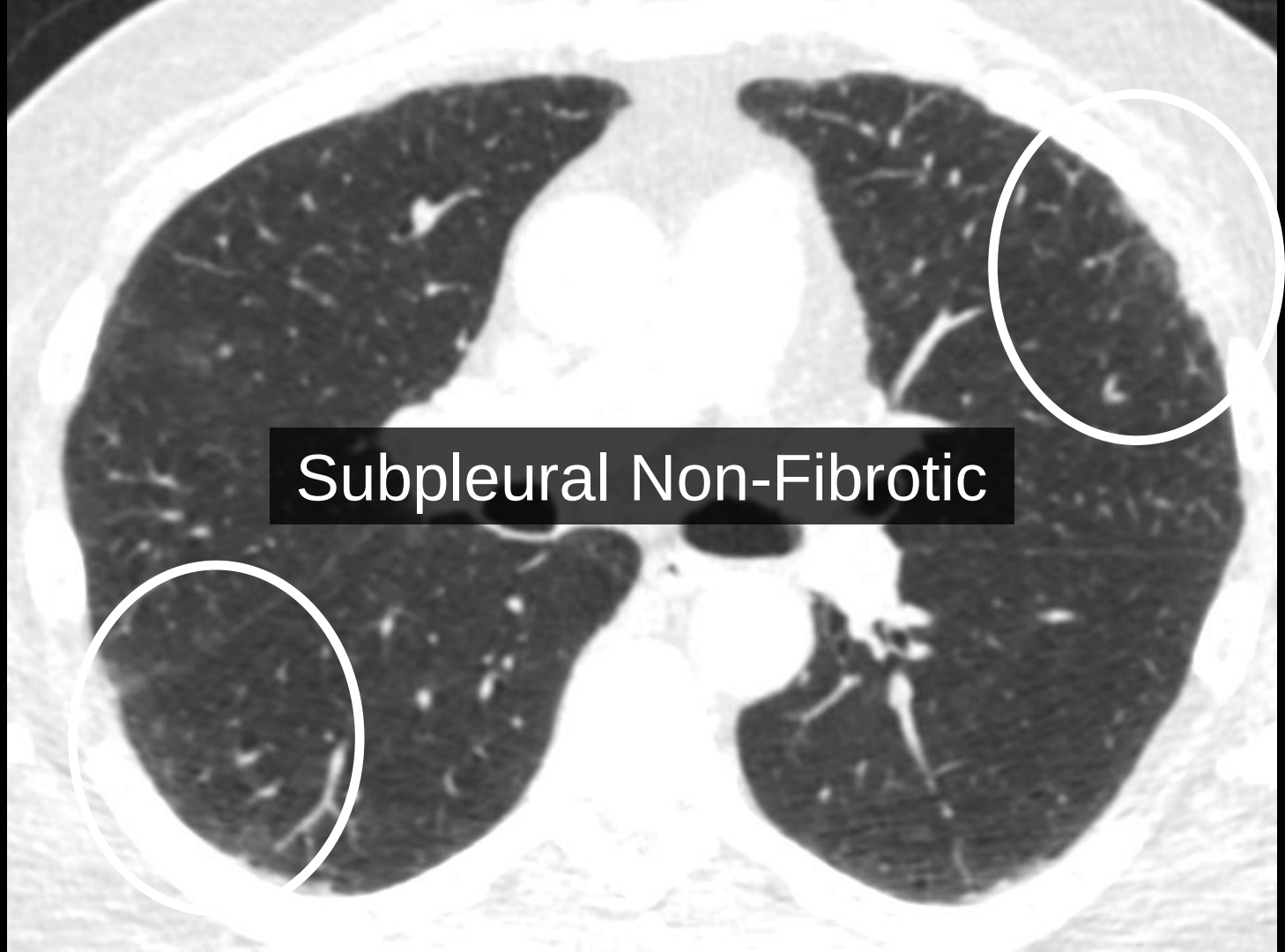
Subtypes of ILA

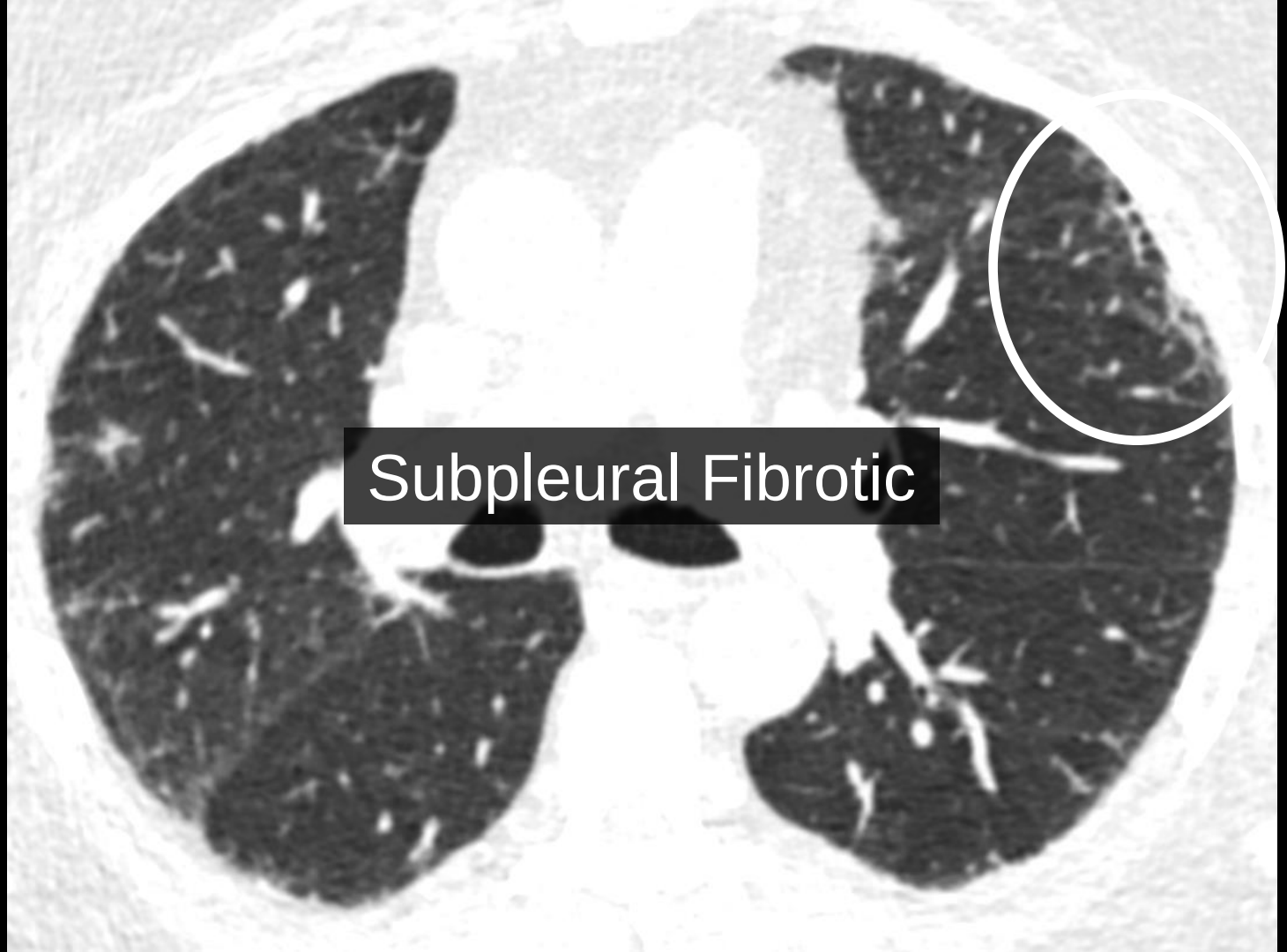
Non-subpleural → Does NOT Progress

Subpleural → May Progress

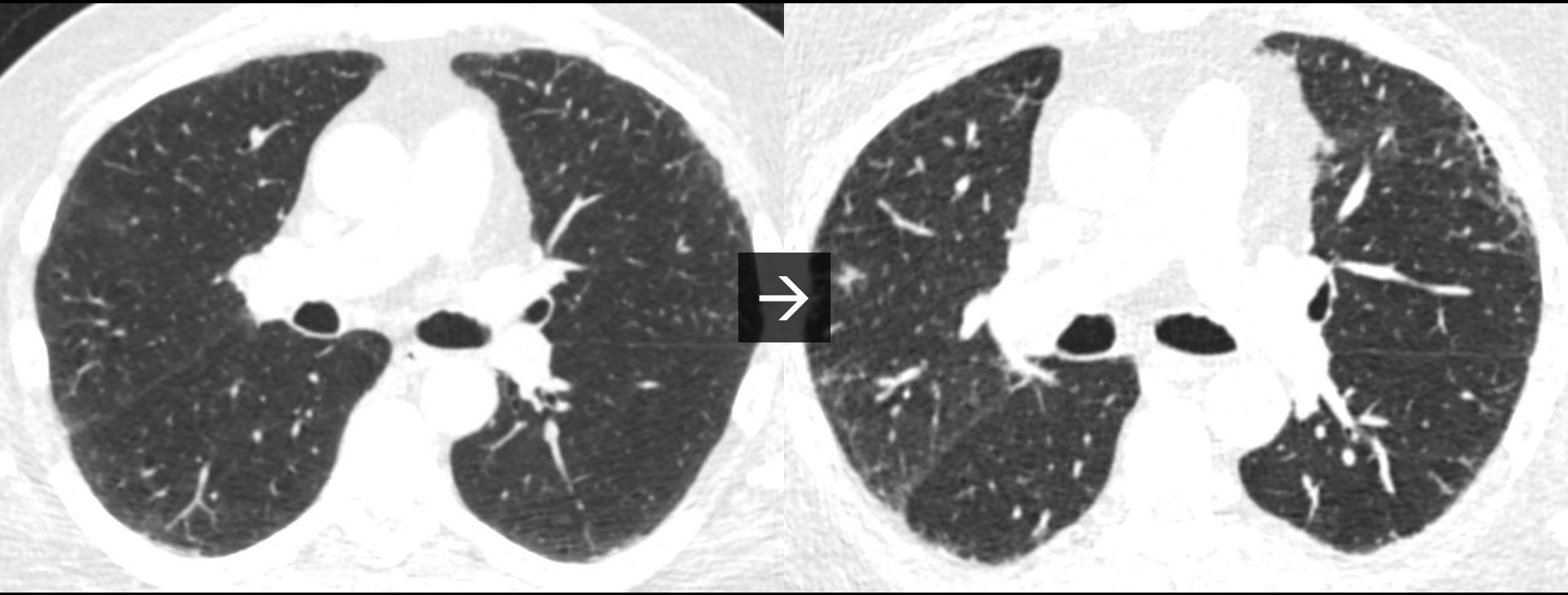
Non-fibrotic

Fibrotic


Subpleural Non-Fibrotic


Subpleural Fibrotic

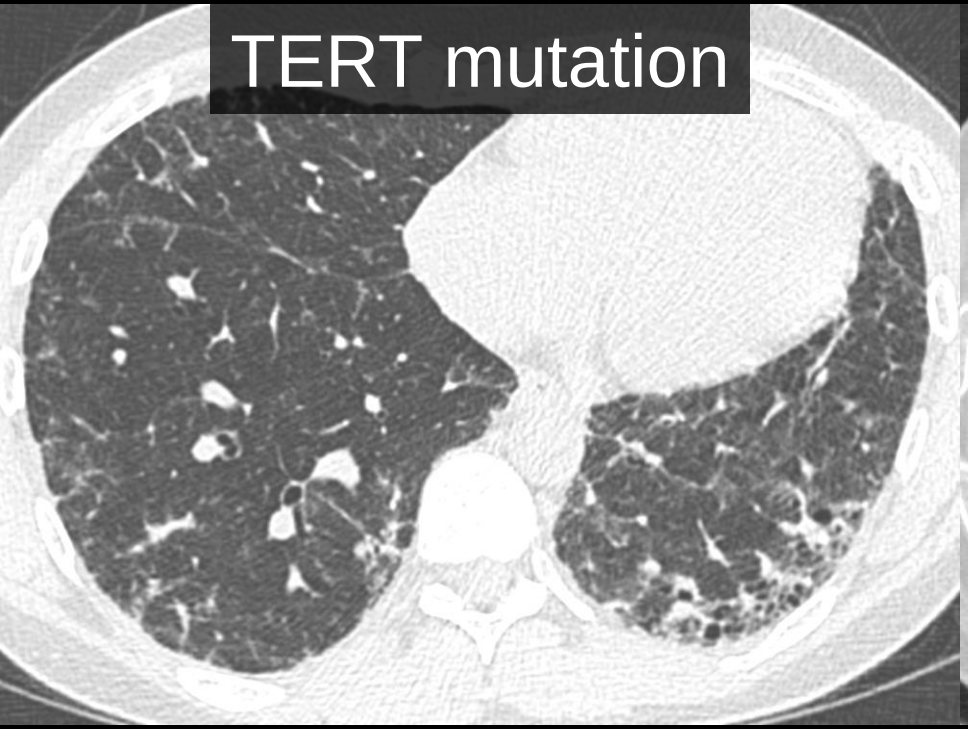
Subpleural ILA May Progress



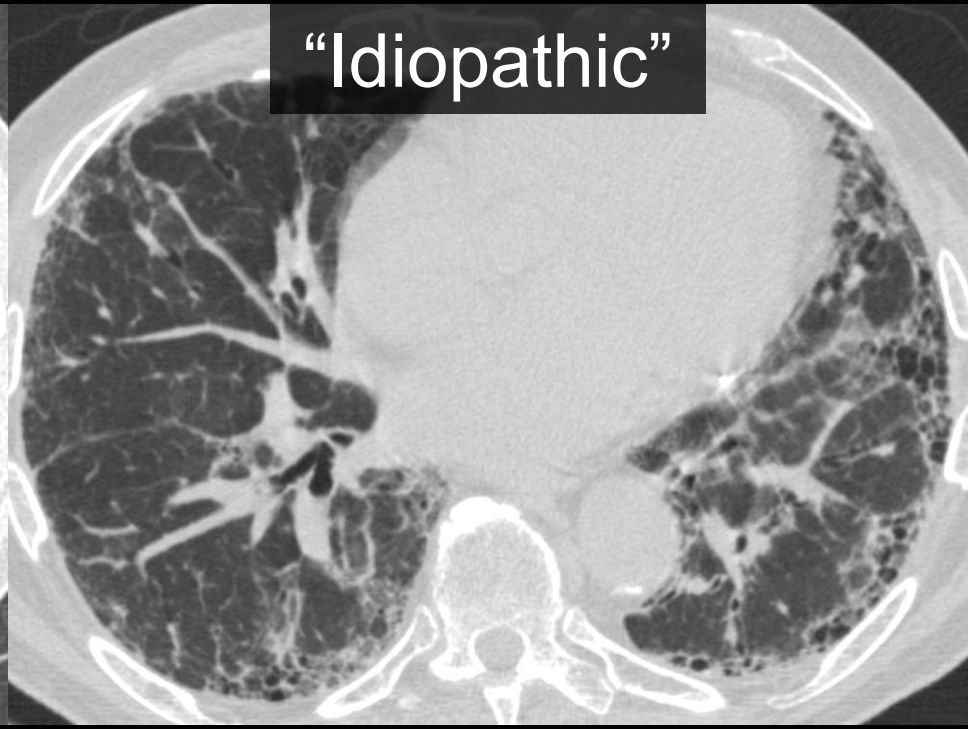
Same Patient 7 Years Later

Would we all get IPF if we lived long enough???

UIP/IPF is a Disease of Aging

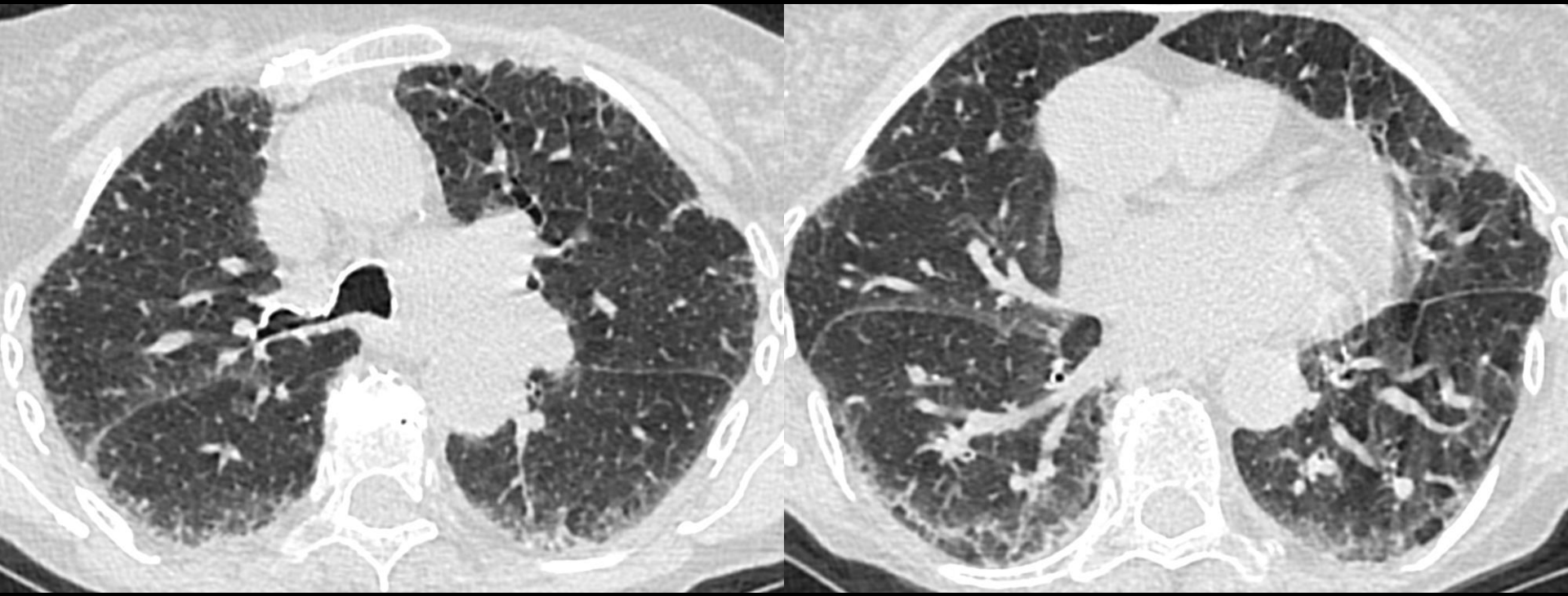


45yo



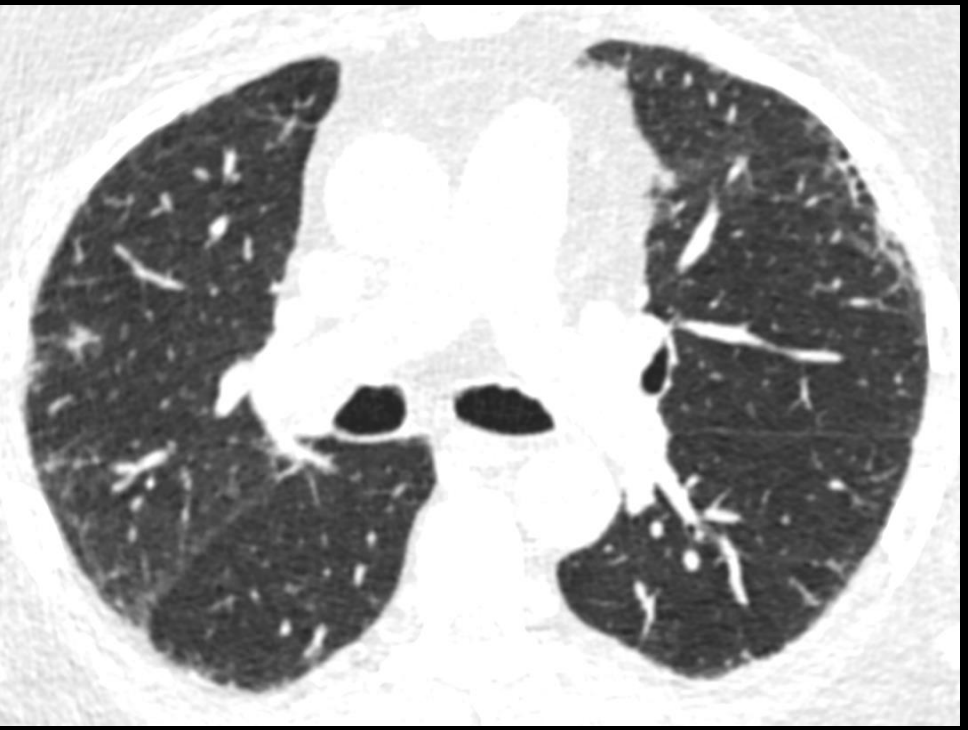
83yo

IPF is a Disease of Aging



95-year-old with dyspnea

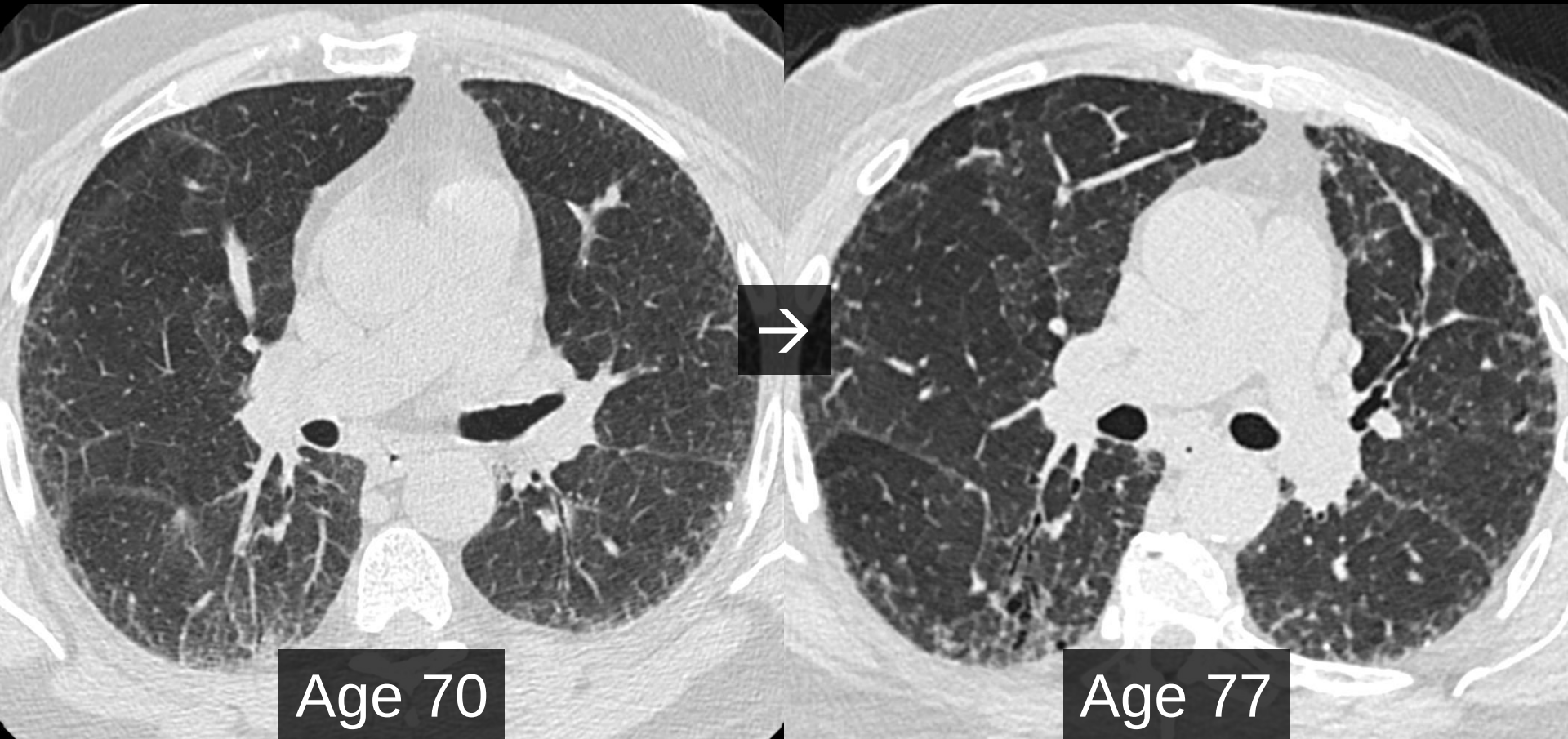
ILA vs ILD



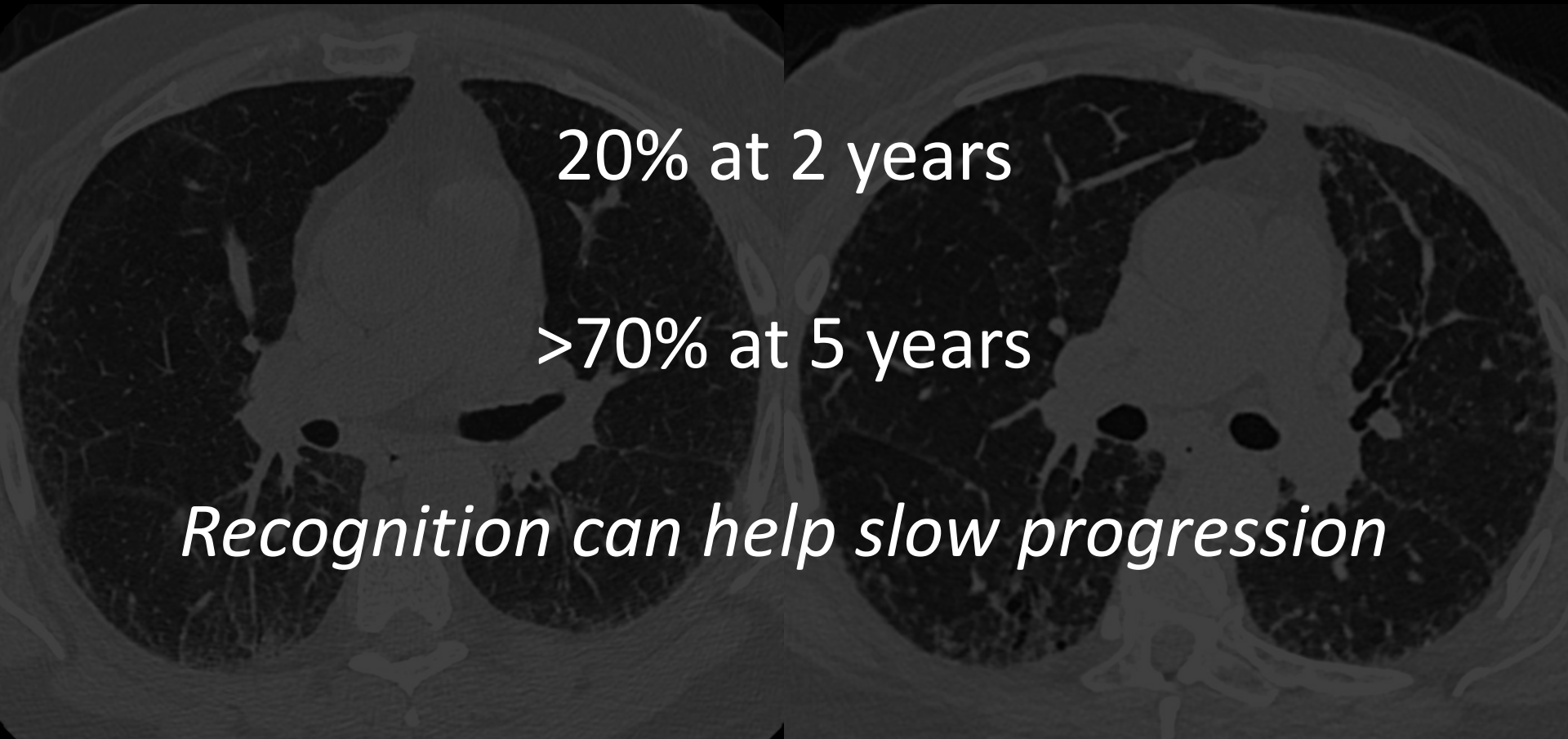
Distinction depends on symptoms

Diagnosis requires recognition of subtle findings of fibrosis

ILA Progression to UIP/IPF



ILA Progression Rate

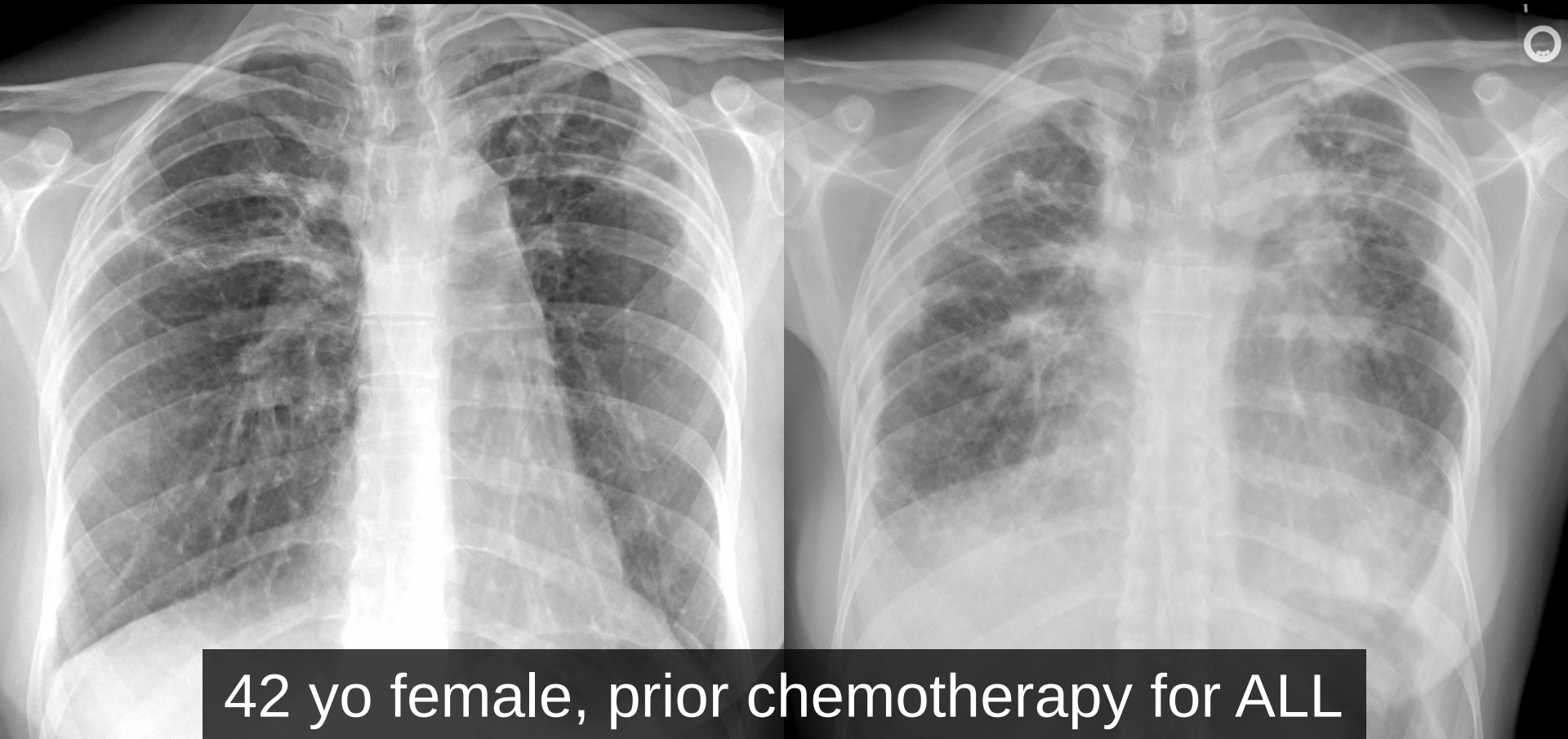


20% at 2 years

>70% at 5 years

Recognition can help slow progression

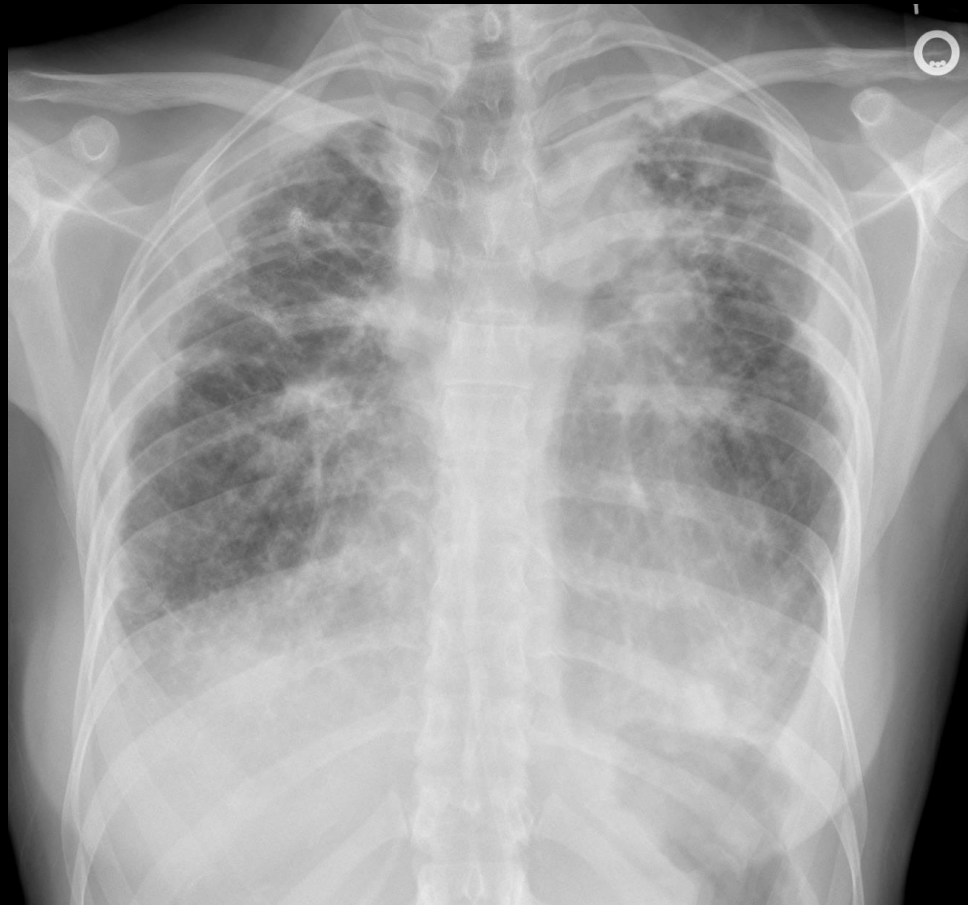
Pleuroparenchymal Fibroelastosis



42 yo female, prior chemotherapy for ALL

Pleuroparenchymal Fibroelastosis

- Dense fibrosis and consolidation which abuts the pleura
- Adjacent pleural thickening
- Upper lobe predominant
- Signs of upper lobe volume loss including hilar retraction



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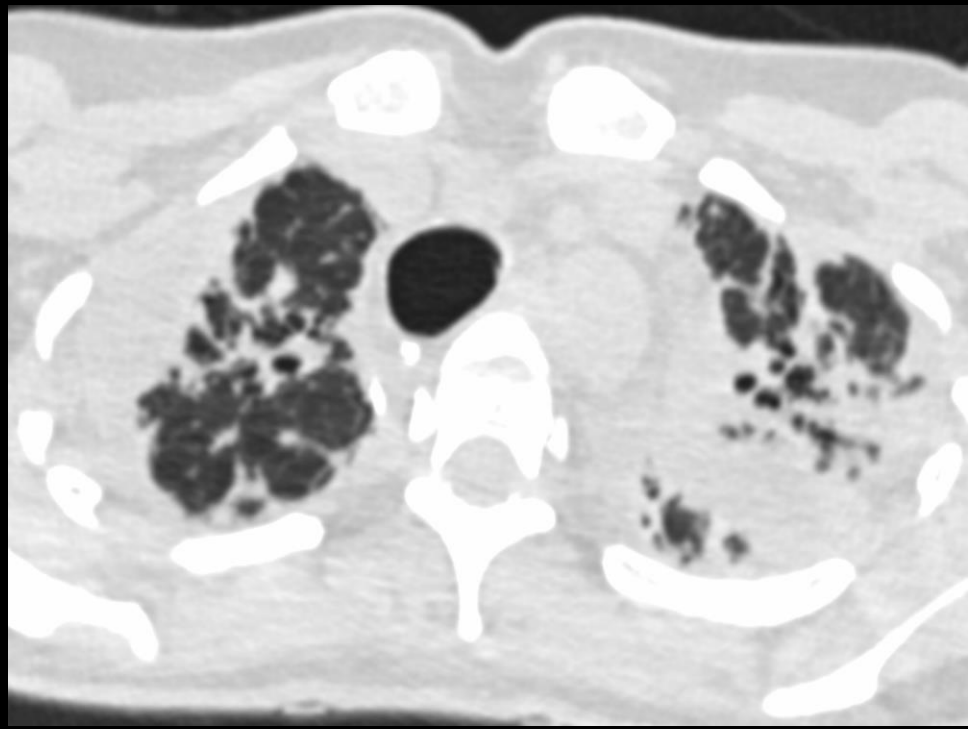
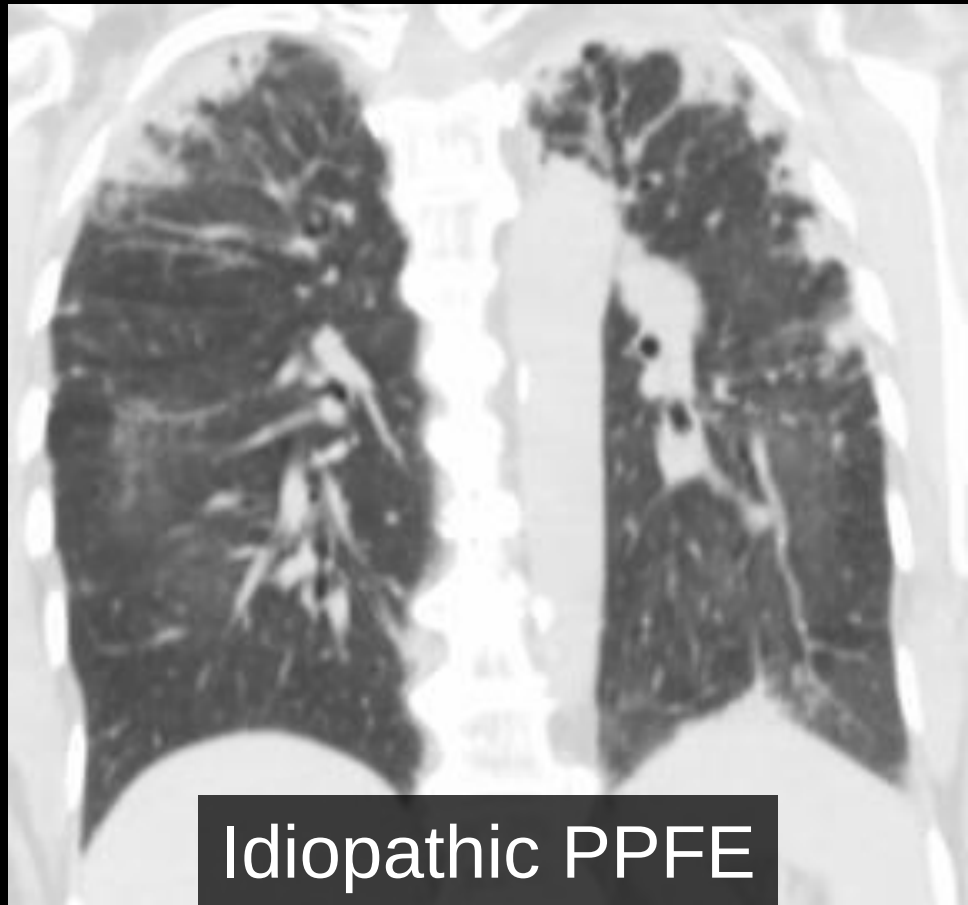


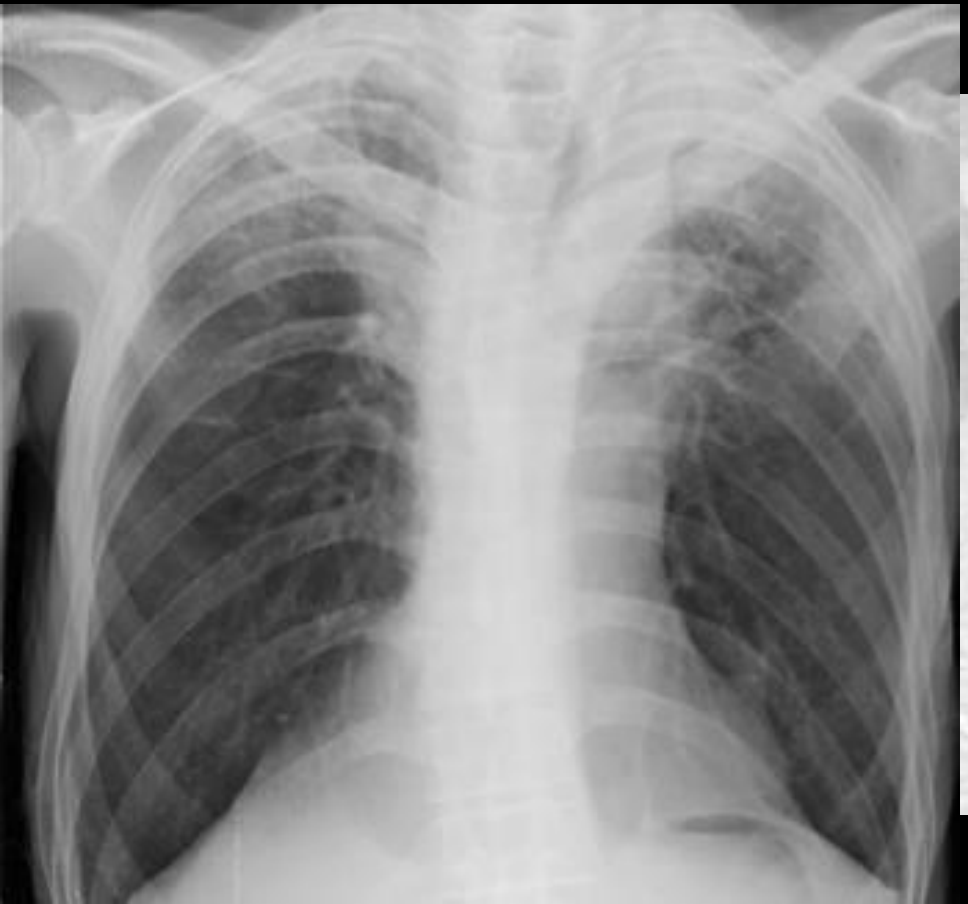
PPFE - Causes

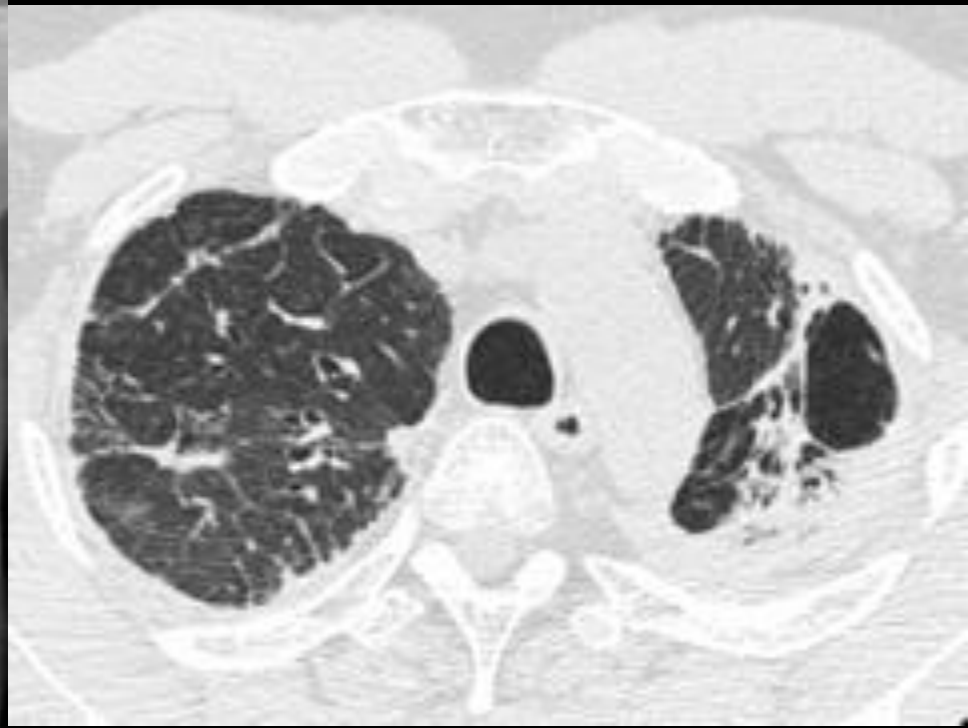
- Idiopathic
- Restrictive Allograft Syndrome
- Autoimmune/CTD
- Familial Fibrosis
- Chemotherapy/Drugs



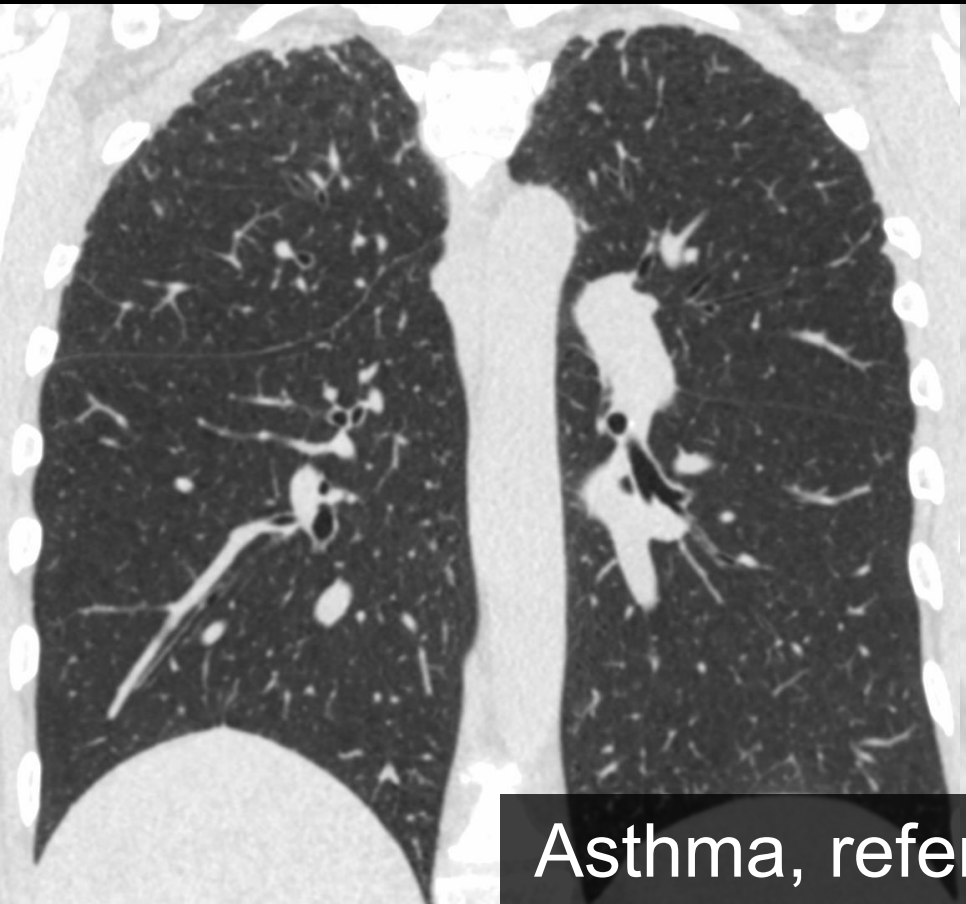
Idiopathic PPFE

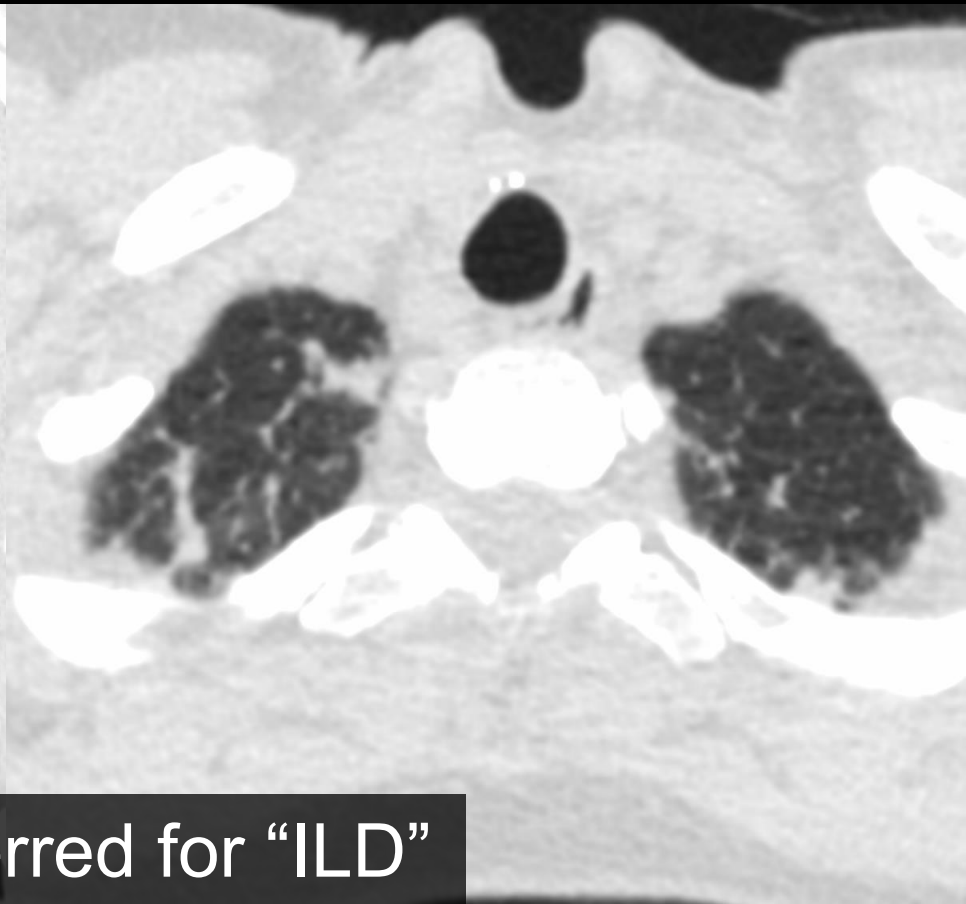
Another Idiopathic PPFE





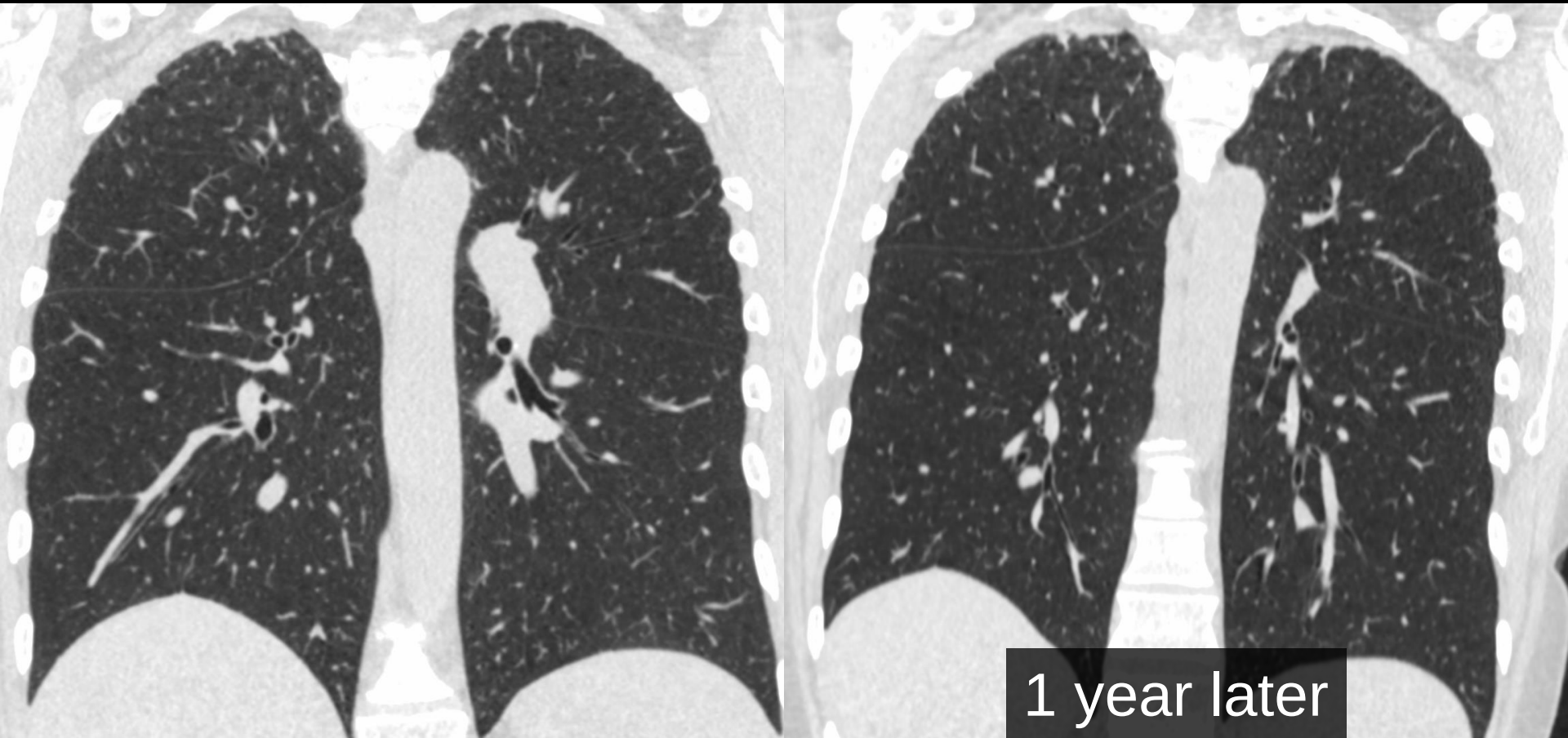
Apical Fibrous Cap





Asthma, referred for “ILD”

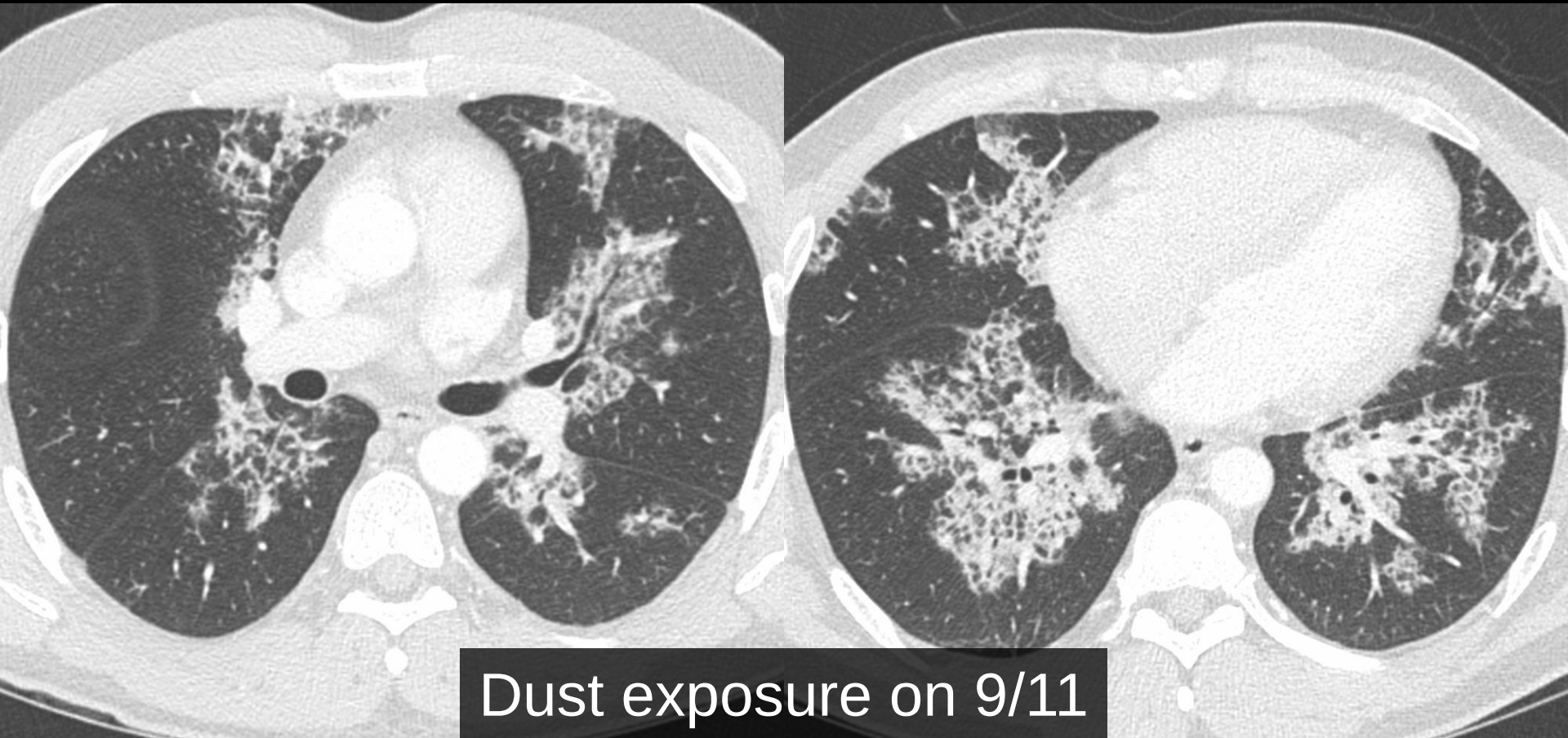
Apical Fibrous Cap



Alveolar Proteinosis

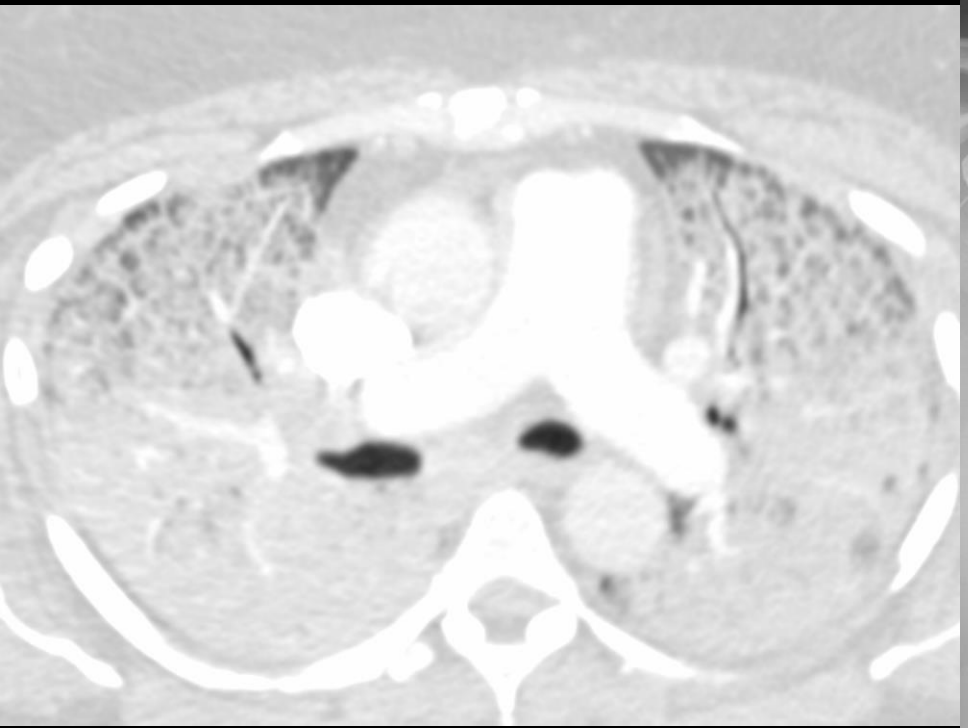
- Accumulation of lipoproteinaceous material in distal airspaces
- Autoimmune – disruption of GM-CSF signaling
  - Anti-GM-CSF antibody positive
  - Whole lung lavage usually diagnostic and therapeutic
- Secondary – dust exposure, malignancy, others

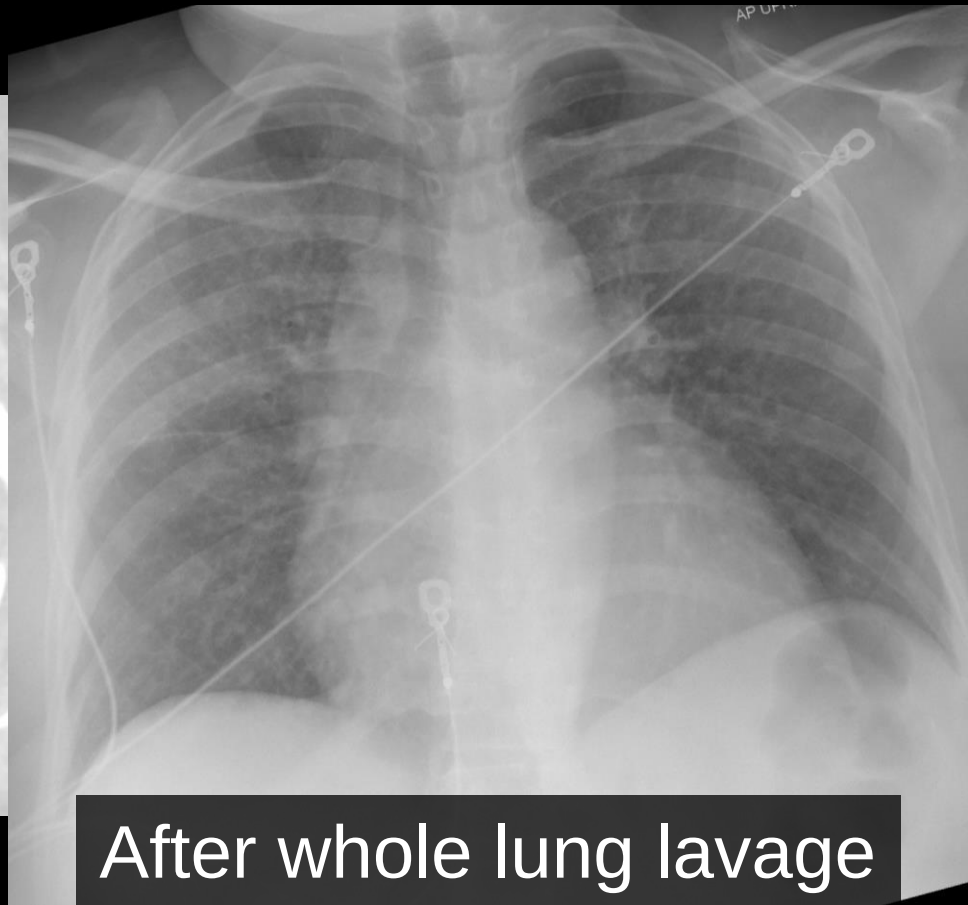
Pulmonary Alveolar Proteinosis



Dust exposure on 9/11

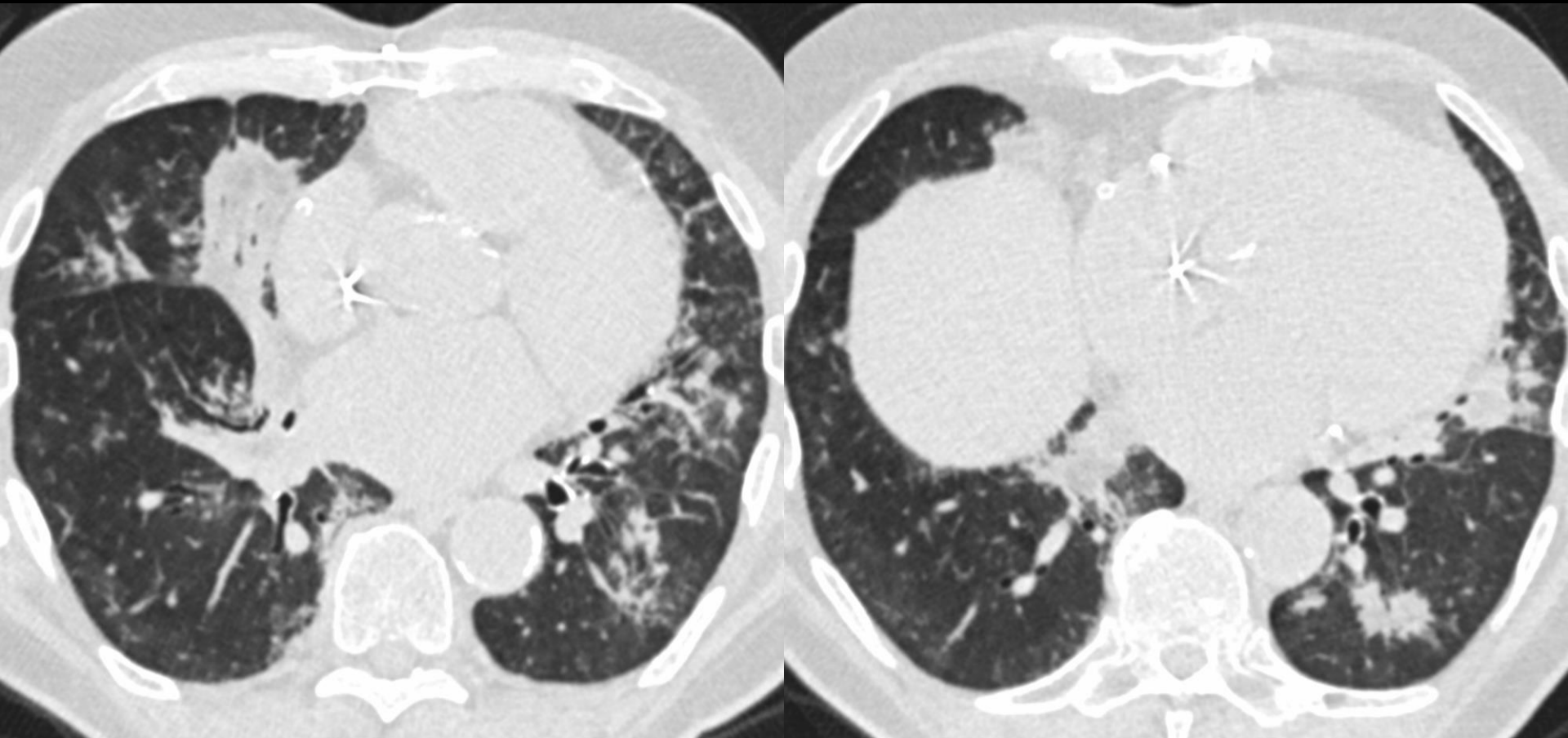
Autoimmune PAP



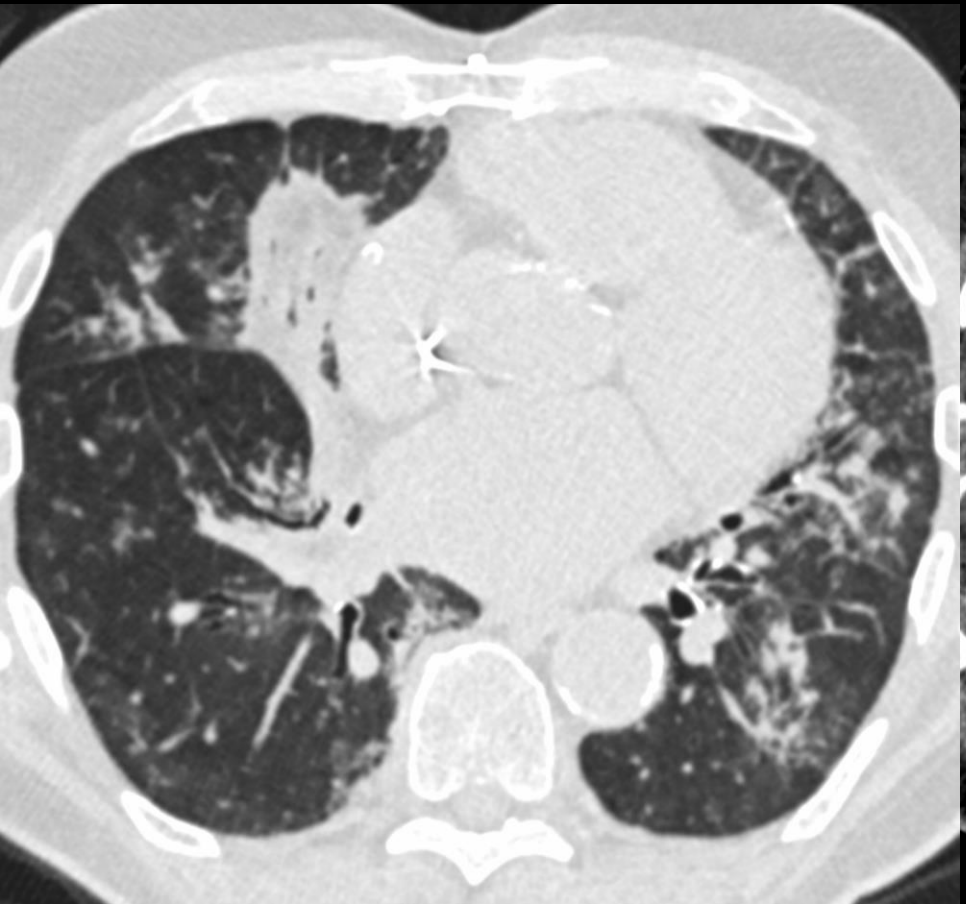


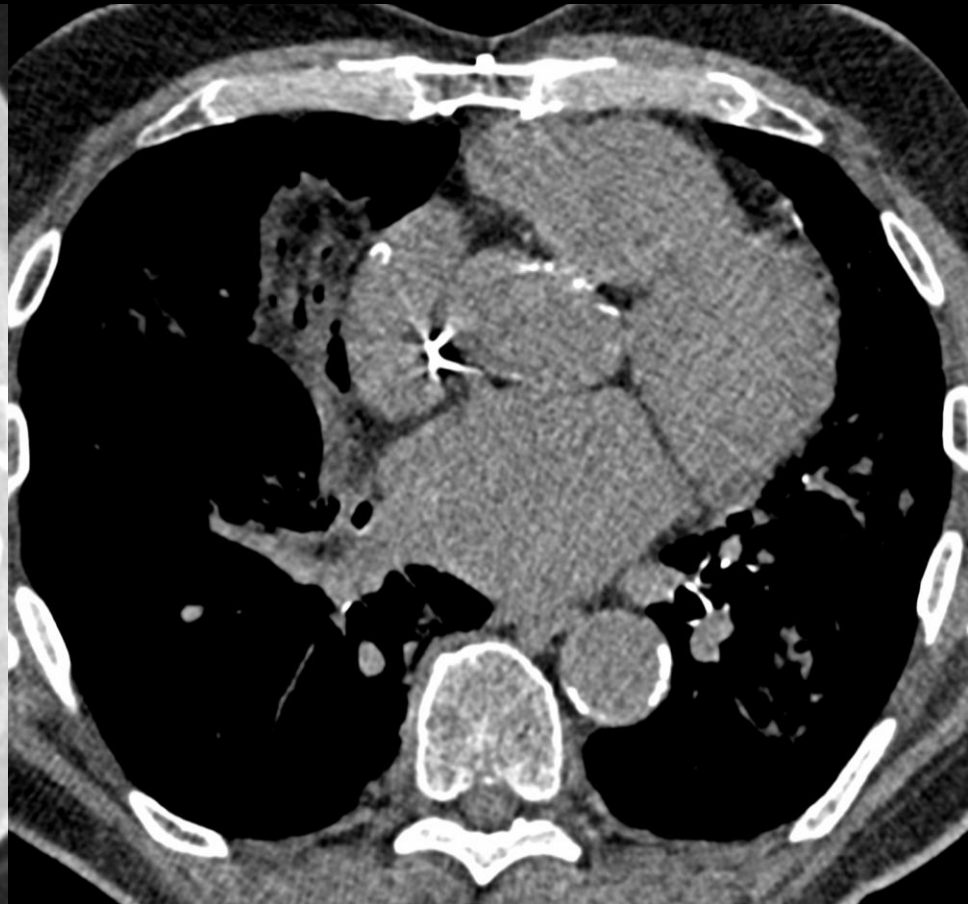
After whole lung lavage

Exogenous Lipoid Pneumonia

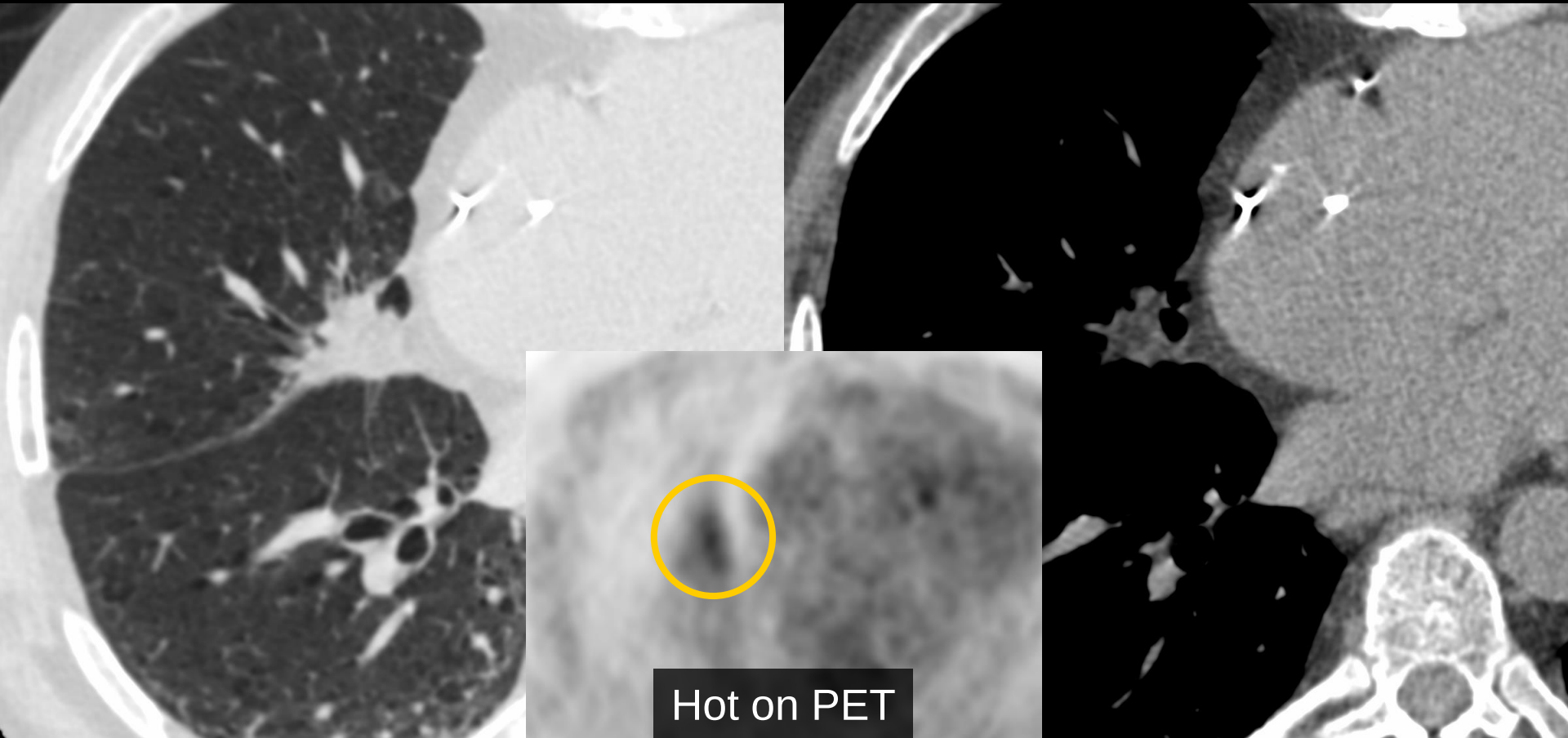


Exogenous Lipoid Pneumonia

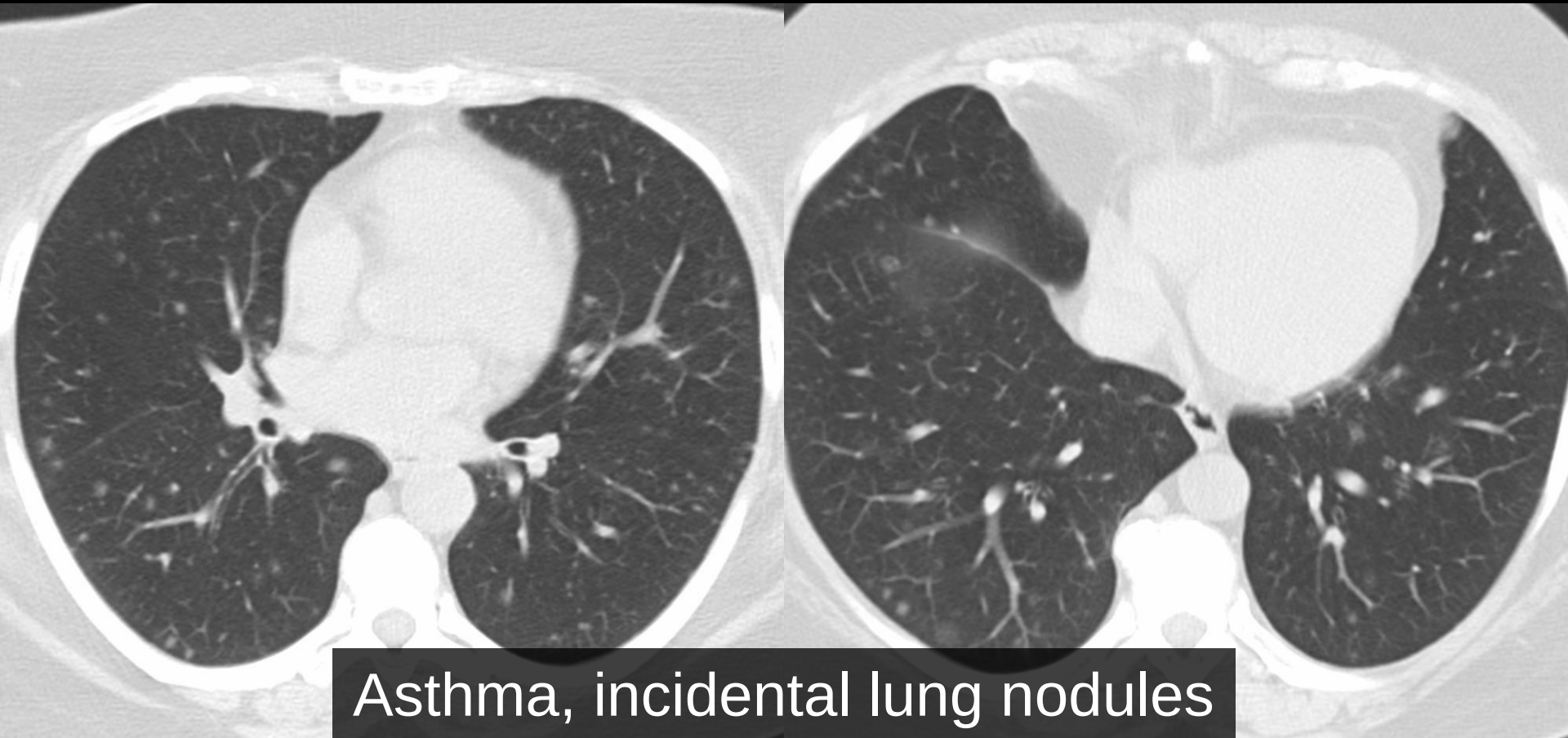




Lipoid Pneumonia (not cancer)

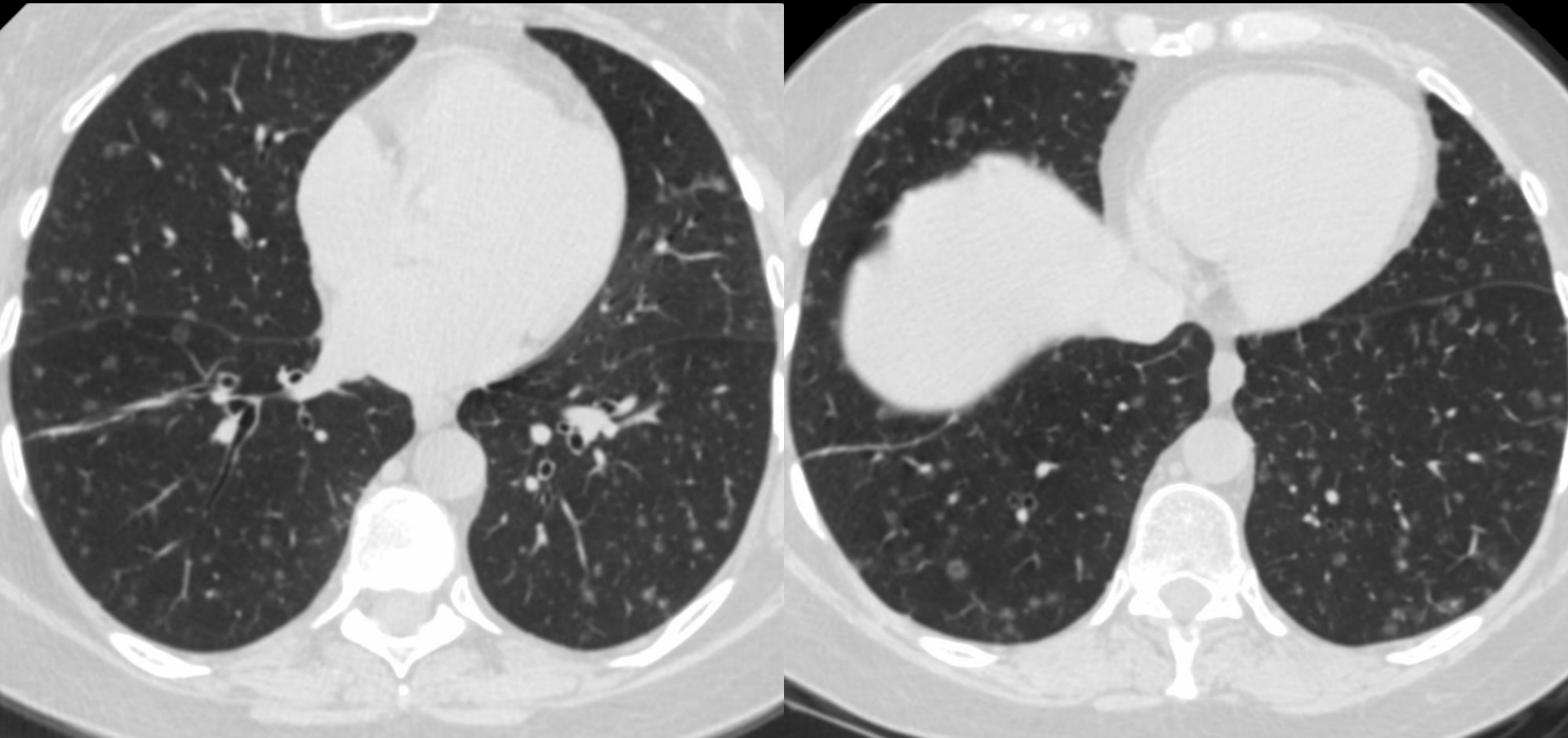


Meningothelial-Like Nodules



Asthma, incidental lung nodules

Meningothelial-Like Nodules



Questions?