Approach to Interstitial Lung Disease

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Objectives

- Understand the definition of ILD and its importance for internists
- Develop an approach to the diagnostic evaluation of ILD using an algorithm and a case
- Know the benefits and side effect profile of nintedanib and pirfenidone

Objective 1: Definition of ILD

- Progressive scarring or inflammation of the lung
- An umbrella term that encompasses > 100 conditions

ILD is important for the internist

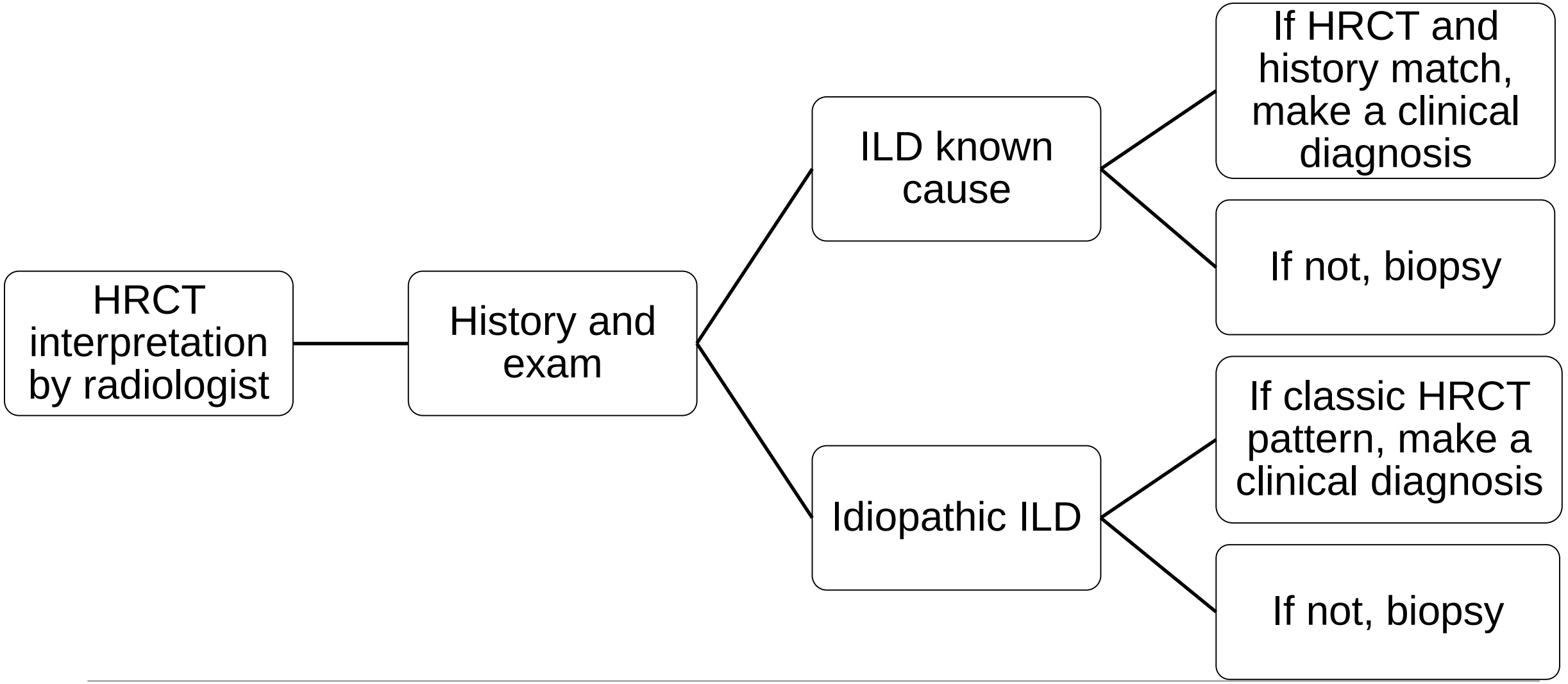
- ILD is common
  - Early ILD can be seen in 2-7% of patients over age 60 undergoing CT Chest
- ILD can have a progressive course with high mortality
- Therapies for ILD can slow progression but cannot reverse fibrosis, so we want to start treatment early

Jeganathan N, et al. ERJ Open Res 2022;8:00630
Hatabu H, et al. Lancet Resp Med 2020;8:726-37

When to suspect ILD

- Prolonged cough
- Dyspnea on exertion
- Fine crackles on lung auscultation
- Reticulations on CXR
- Restriction or reduced diffusing capacity on PFTs
- Refer all patients with ILD to pulmonary clinic

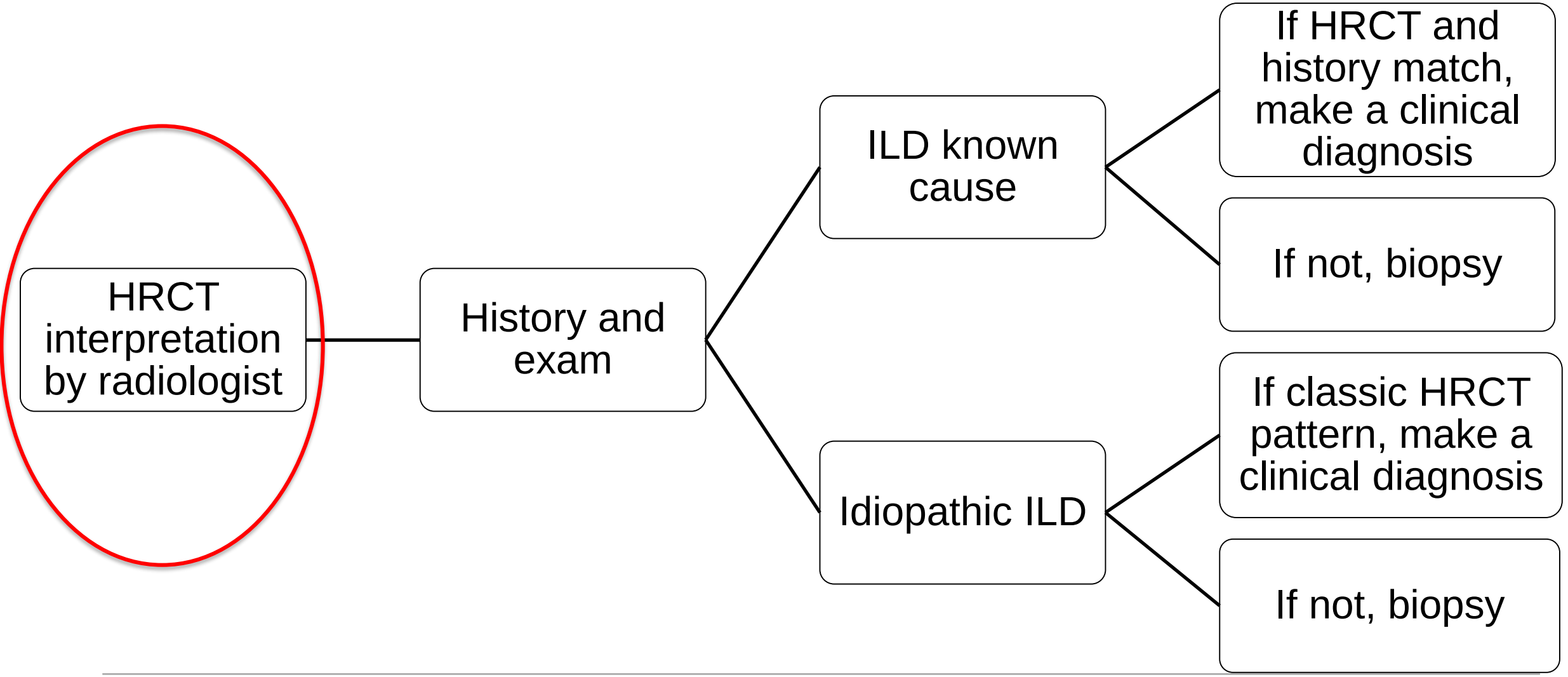
Objective 2: Algorithm for evaluation of ILD



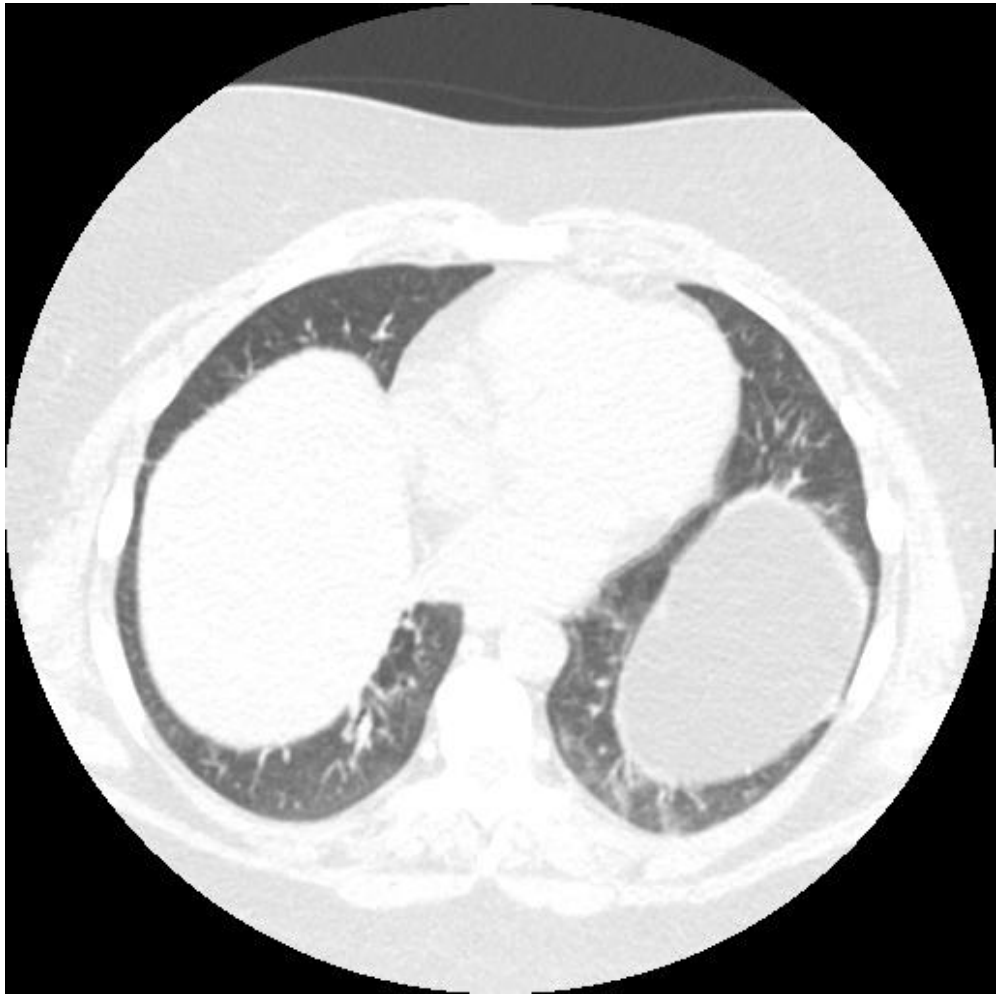
Case 1

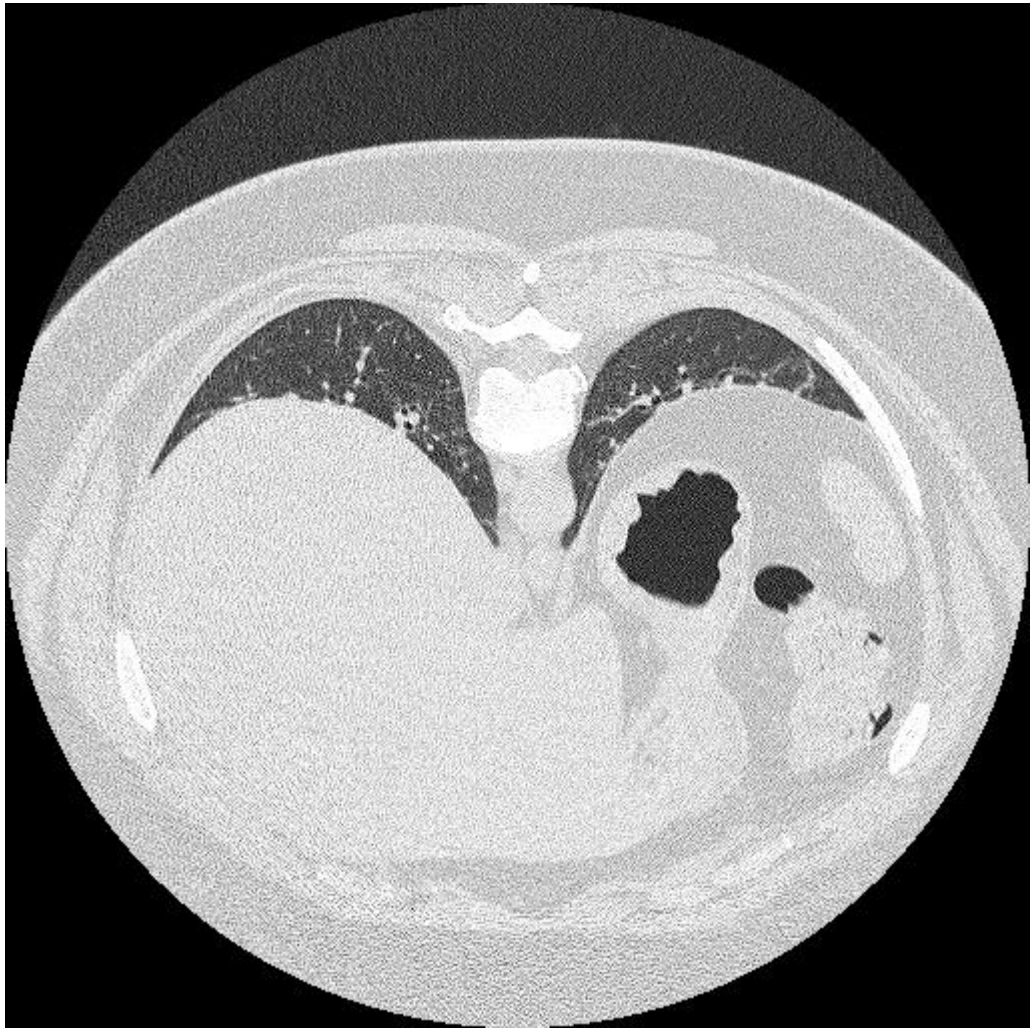
- You are seeing a patient in clinic who complains of progressive shortness of breath.
- You order a chest x-ray, which is read as reticulations in the lower lobes suggestive of interstitial lung disease.
- What is your next step?

HRCT is an important first step but HRCT pattern is not the same as clinical diagnosis

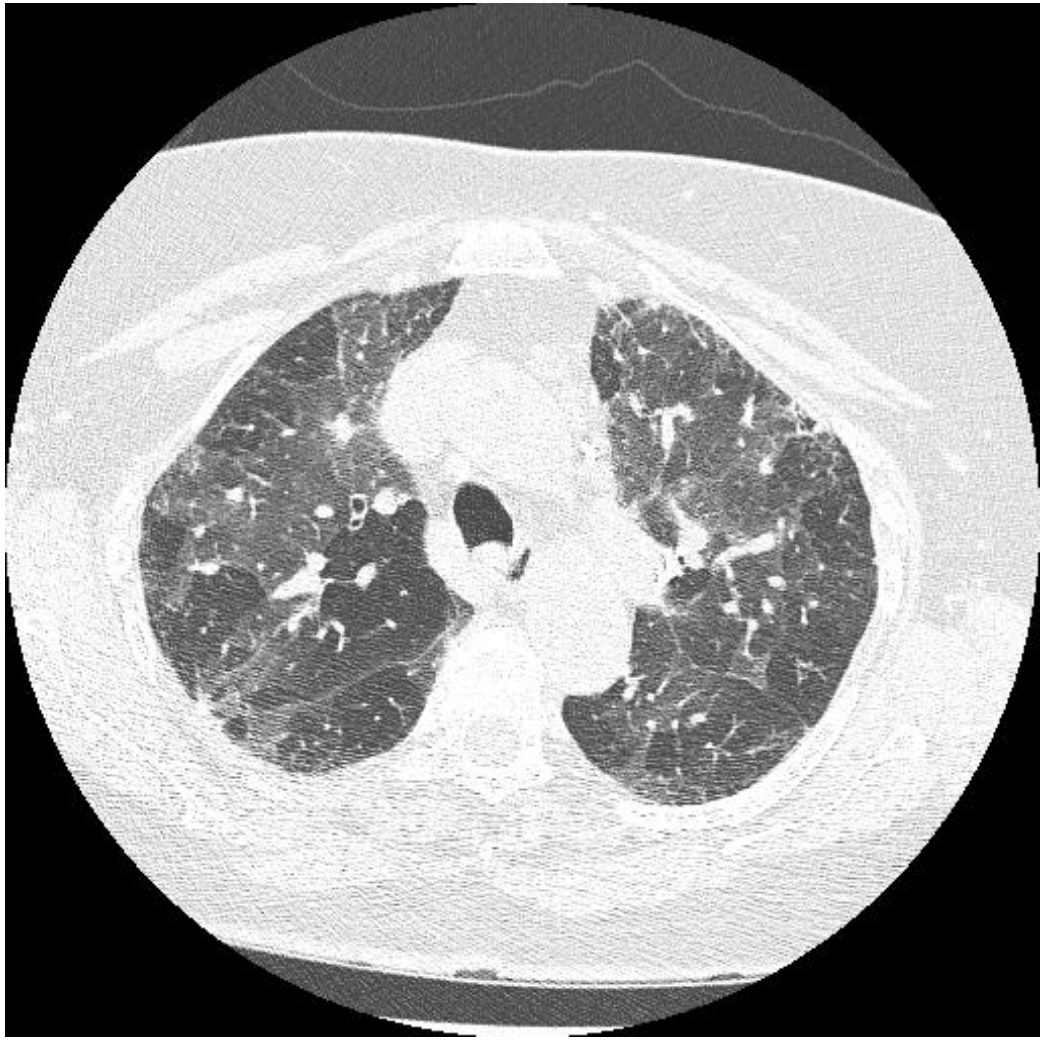


HRCT includes prone and supine images

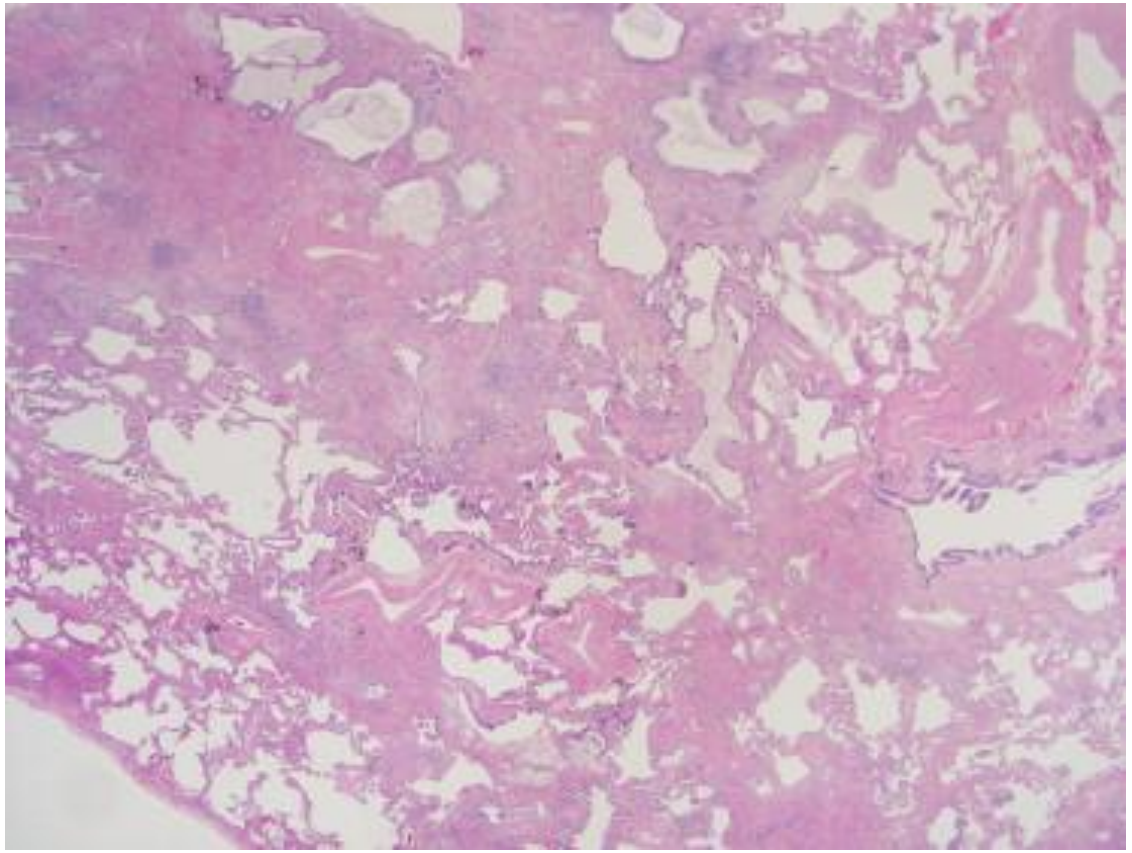




HRCT includes inspiratory and expiratory images

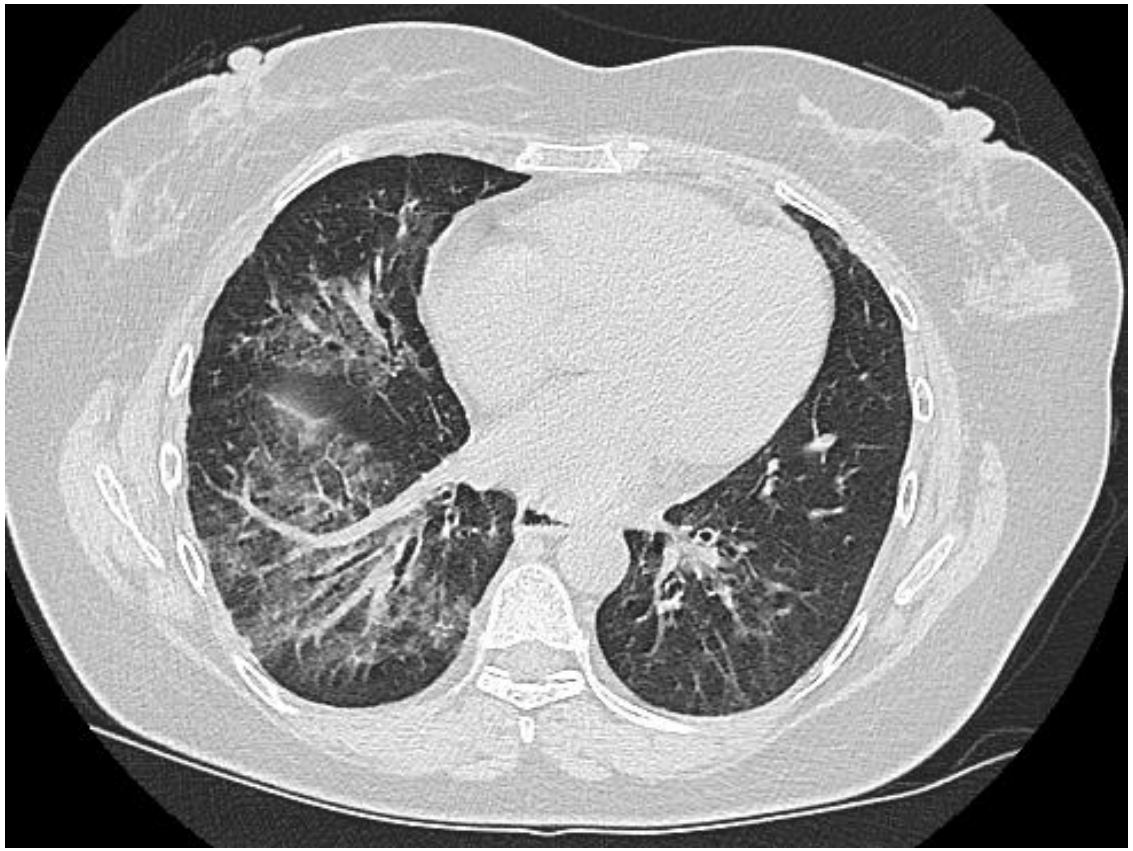


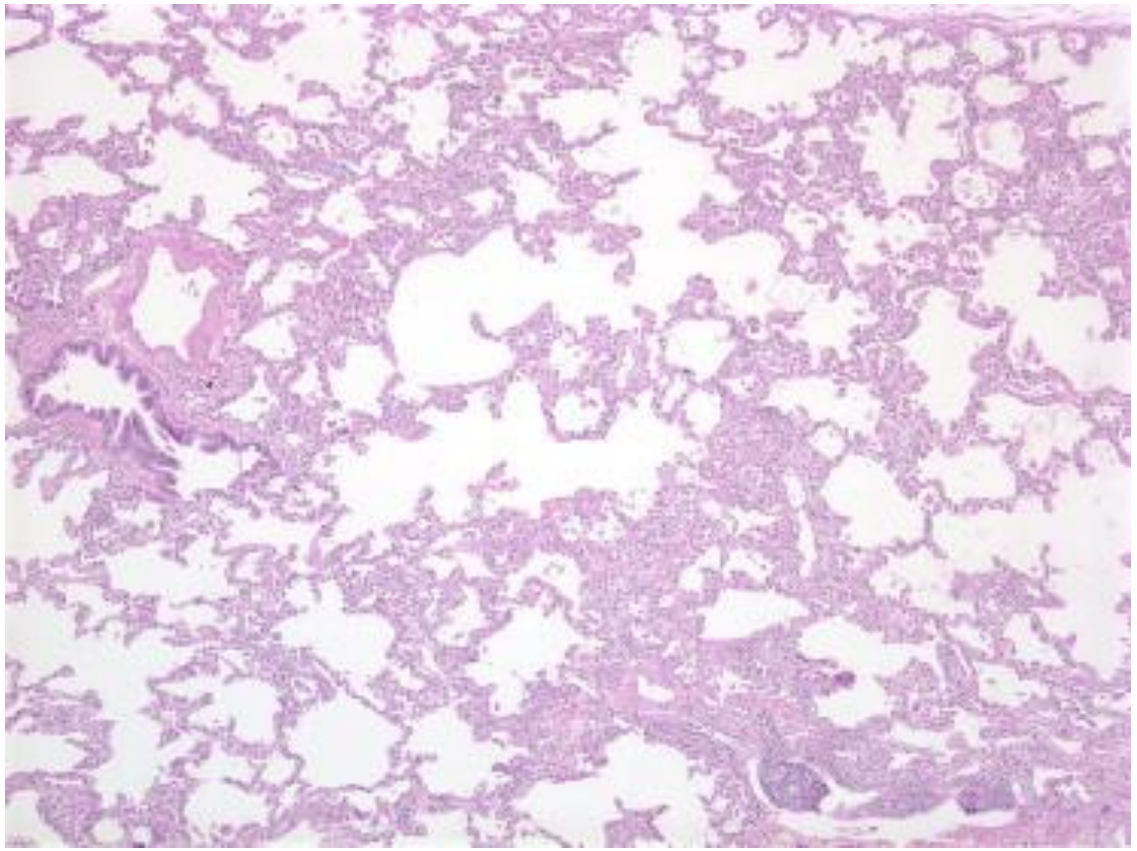
UIP is a common HRCT pattern and correlates with UIP histology but is not a diagnosis



Myers, JL. *Semin Diagn Pathol* 2007;24:183-7

NSIP is a common HRCT pattern and correlates with NSIP pathology pattern but is not a diagnosis

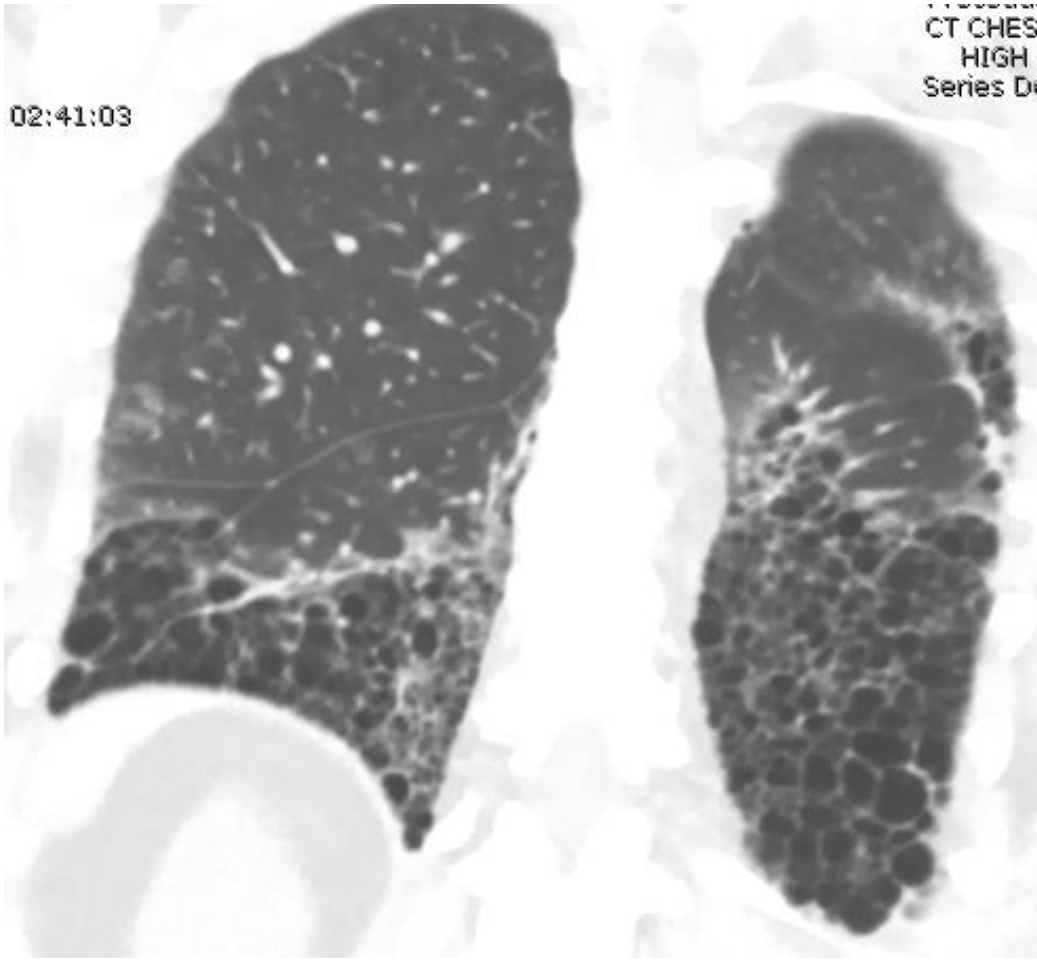




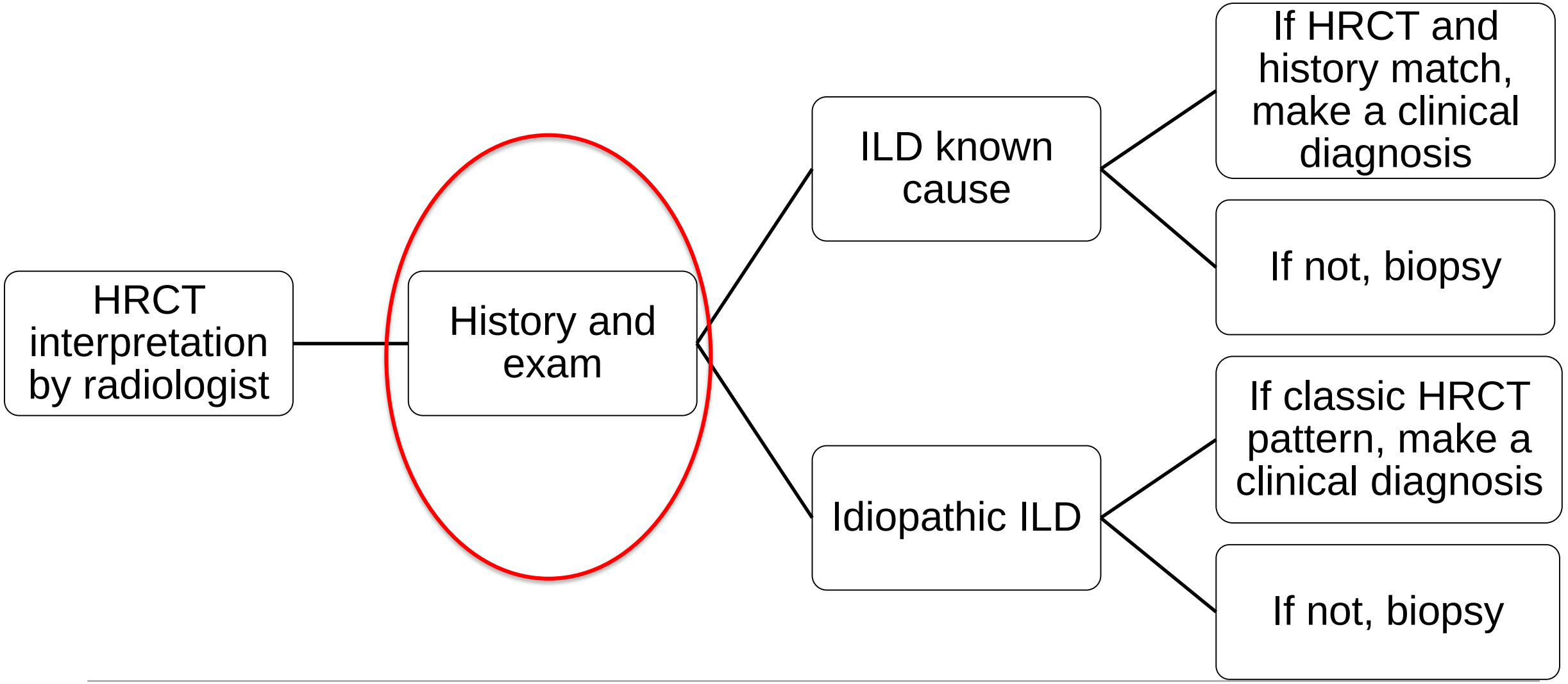
Myers, JL. *Semin Diagn Pathol* 2007;24:183-7

Case 1, continued

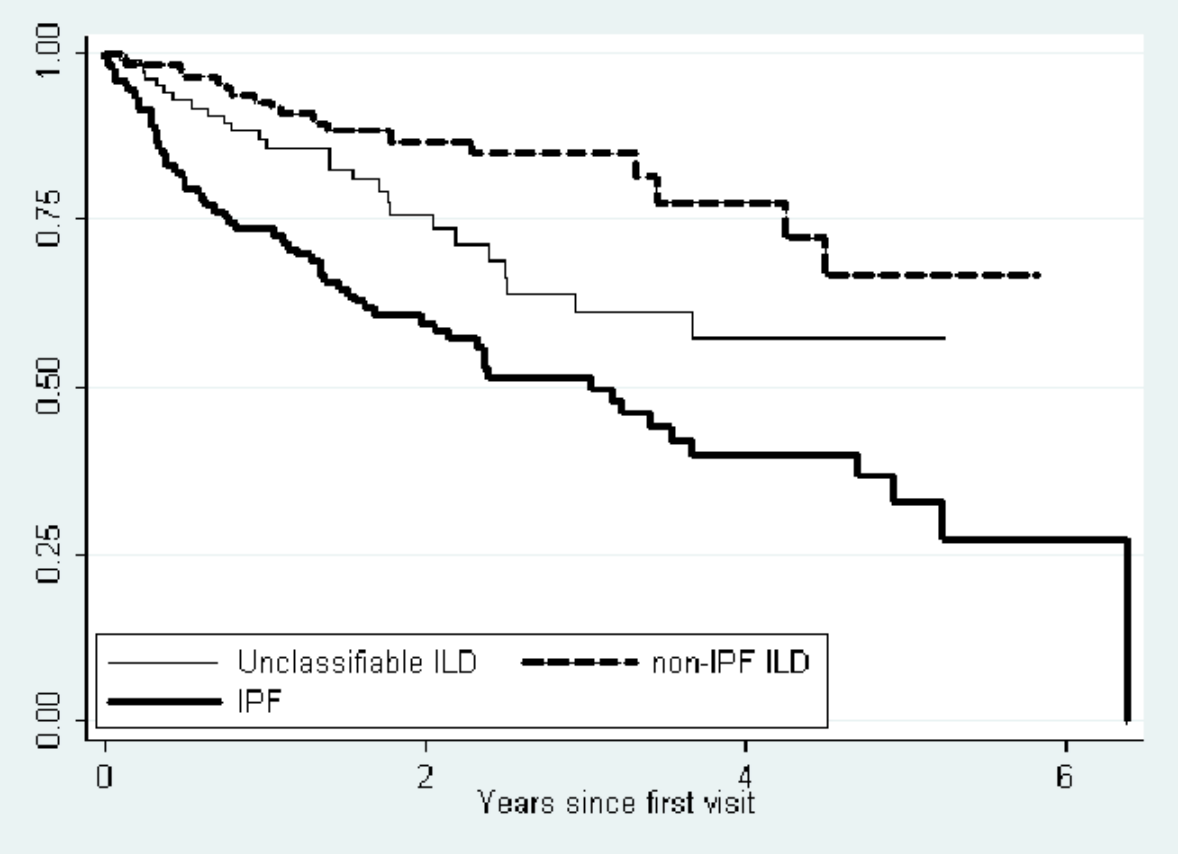
- You order HRCT.
- Radiology report from HRCT states: “Basilar predominant peripheral reticulation, traction bronchiectasis, and honeycombing consistent with a UIP pattern.”
- Is UIP the clinical diagnosis?
- What are the next steps in evaluation of this patient?



Use the H&P to classify as idiopathic ILD or ILD of known cause



Prognosis and treatment varies by etiology



Hyldgaard C, et al; *Respirology* 2017;22:494-500

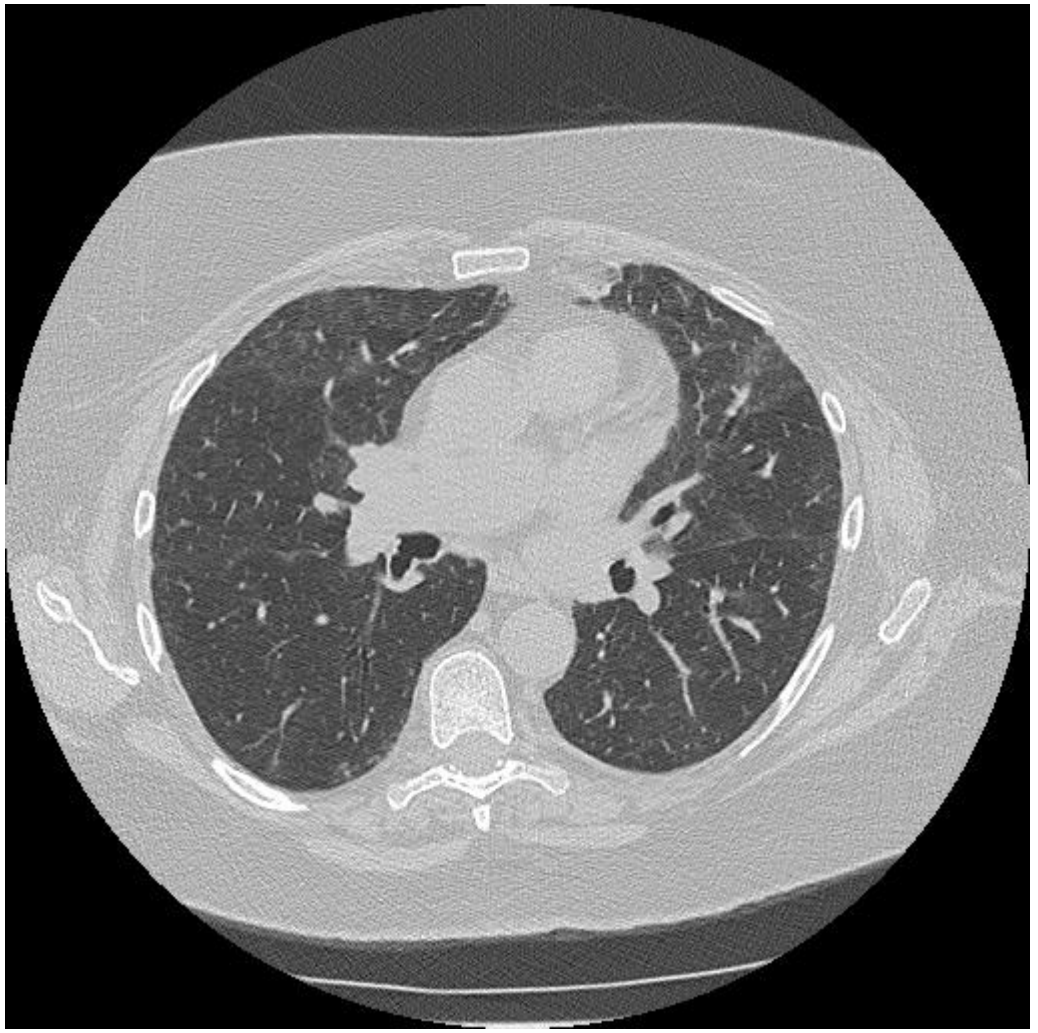
Use the H&P to distinguish between ILDs of known cause and idiopathic ILD

- HPI: Time course, age
- PMH
- Medications
- ROS: Connective tissue disease
- Social history:
  - Exposures
  - Occupational history
  - Smoking
- Family history

Medications are a common cause of ILD

Hematology/Oncology	Chemotherapy Radiation Checkpoint inhibitors
Cardiology	Amiodarone
Infectious diseases	Nitrofurantoin Trimethoprim/sulfamethoxazole

Medication-related ILD may resolve with discontinuation of the offending medication



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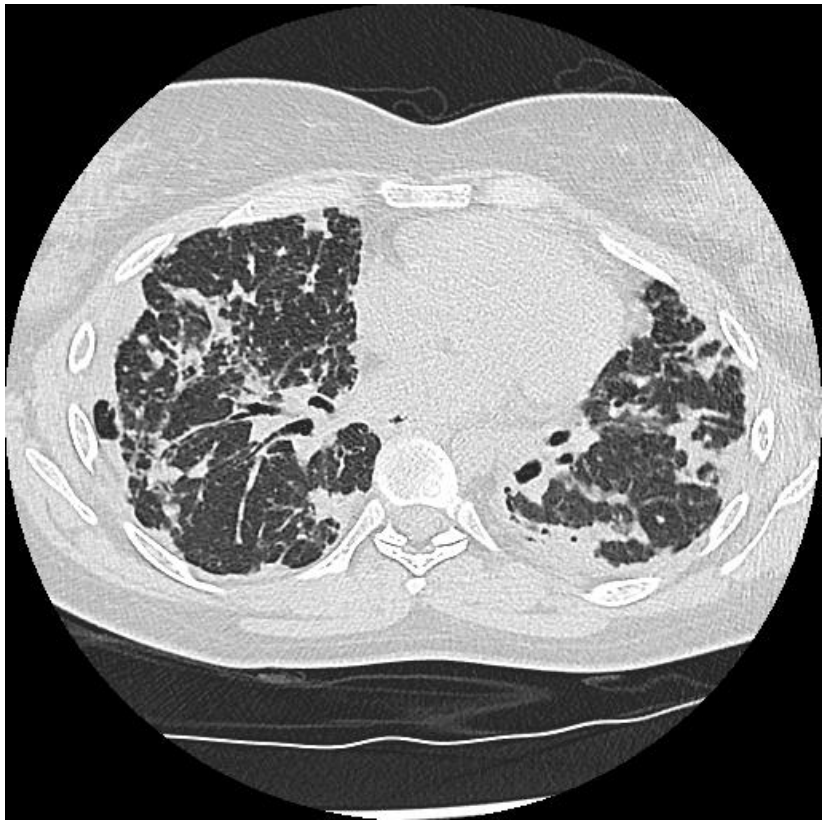
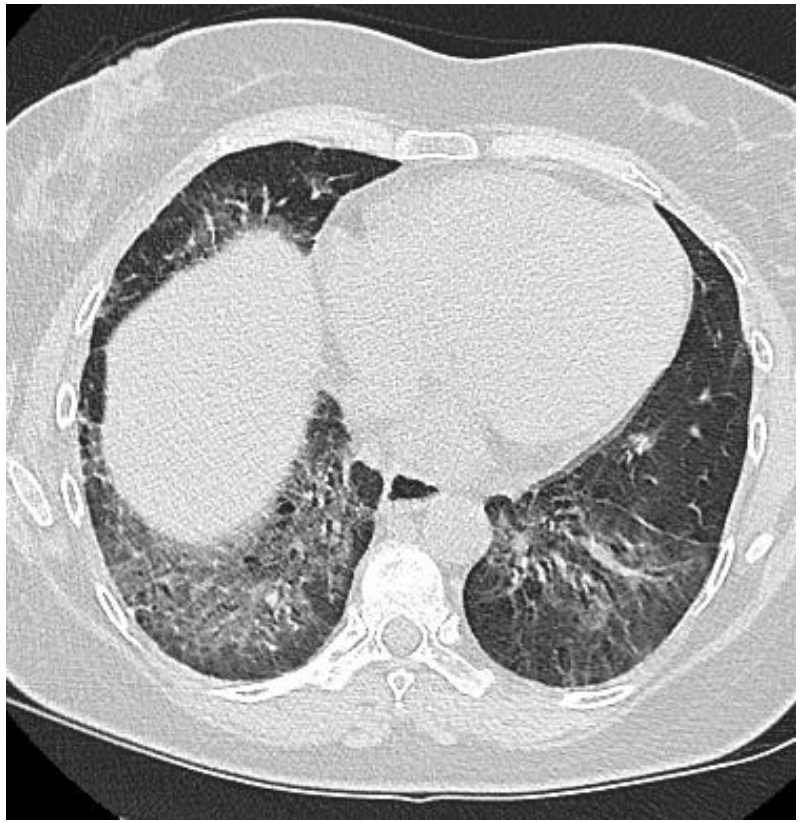
- Medications
- **ROS: Connective tissue disease**
- Social history:
  - Exposures
  - Occupational history
  - Smoking
- Family history

Connective tissue disease is a common cause of ILD

- Start with screening questions and physical exam for:
  - Scleroderma
  - Rheumatoid arthritis
  - Sjogrens
  - Polymyositis or dermatomyositis
  - Systemic lupus erythematosus
- Send serologies: ANA, ENA, RF, CCP, ESR, CRP, CK, aldolase, myositis panel

CTD-ILD can have any HRCT pattern



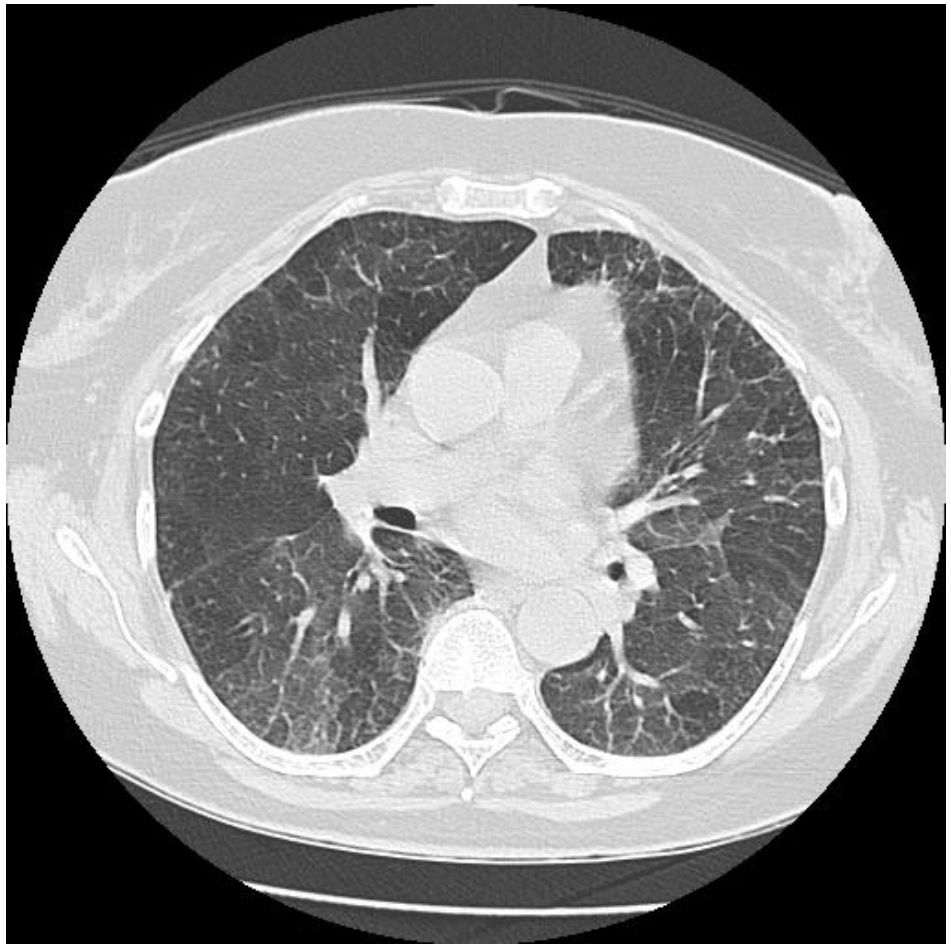


How to make the diagnosis

- HPI: Time course, age
- PMH
- Medications
- ROS: Connective tissue disease
- **Social history:**
  - **Exposures**
  - **Occupational history**
  - **Smoking**
- Family history

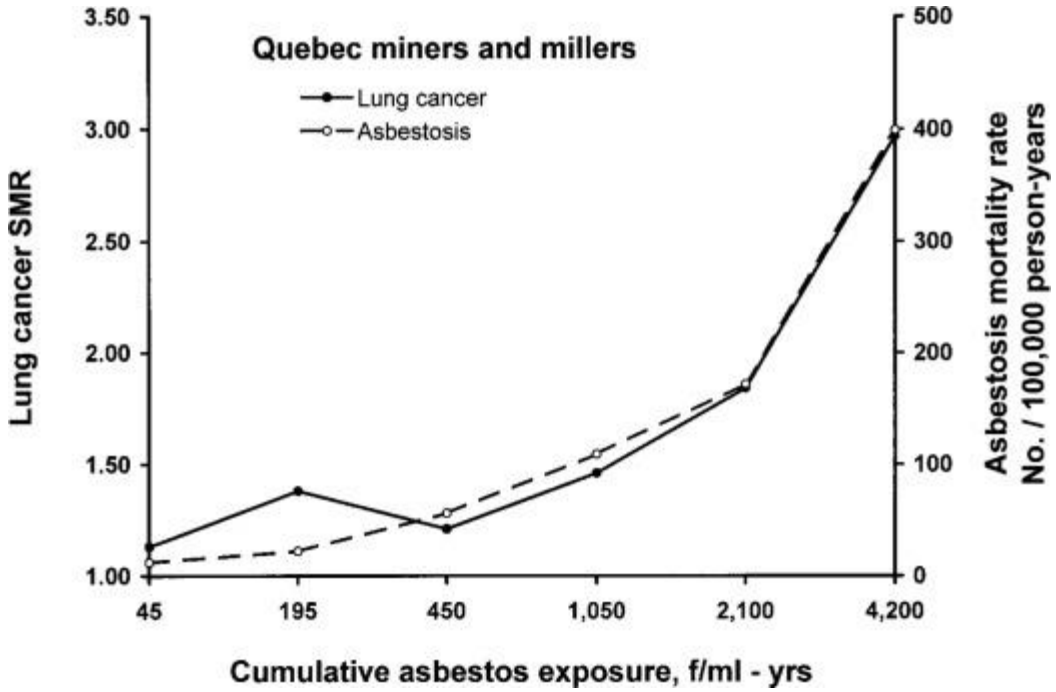
Hypersensitivity pneumonitis

- Exposure to bird or mold
  - May improve with exposure removal
- HRCT suggests airway involvement and inflammation +/- fibrosis
- Often need bronchoscopy or surgical lung biopsy for confirmation



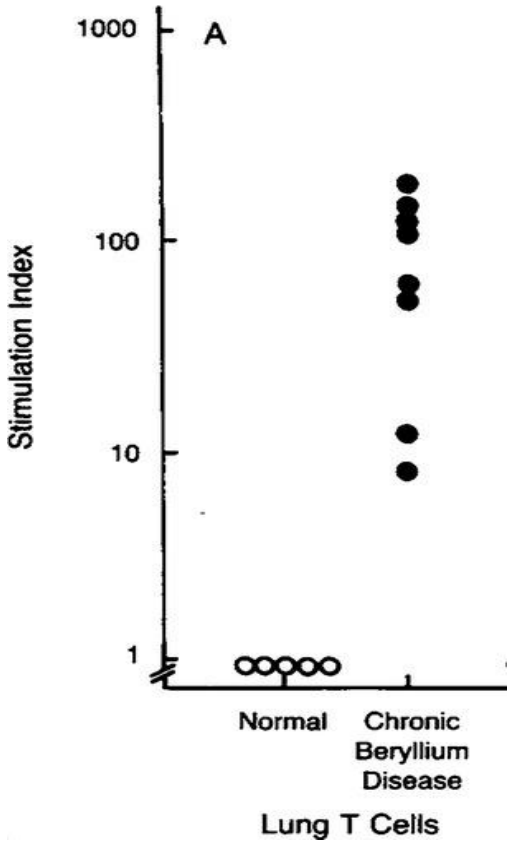
Barnes H, et al. *Chest* 2020;157:1506-12
Raghu G, et al. *AJRCCM* 2020;202:e36-69

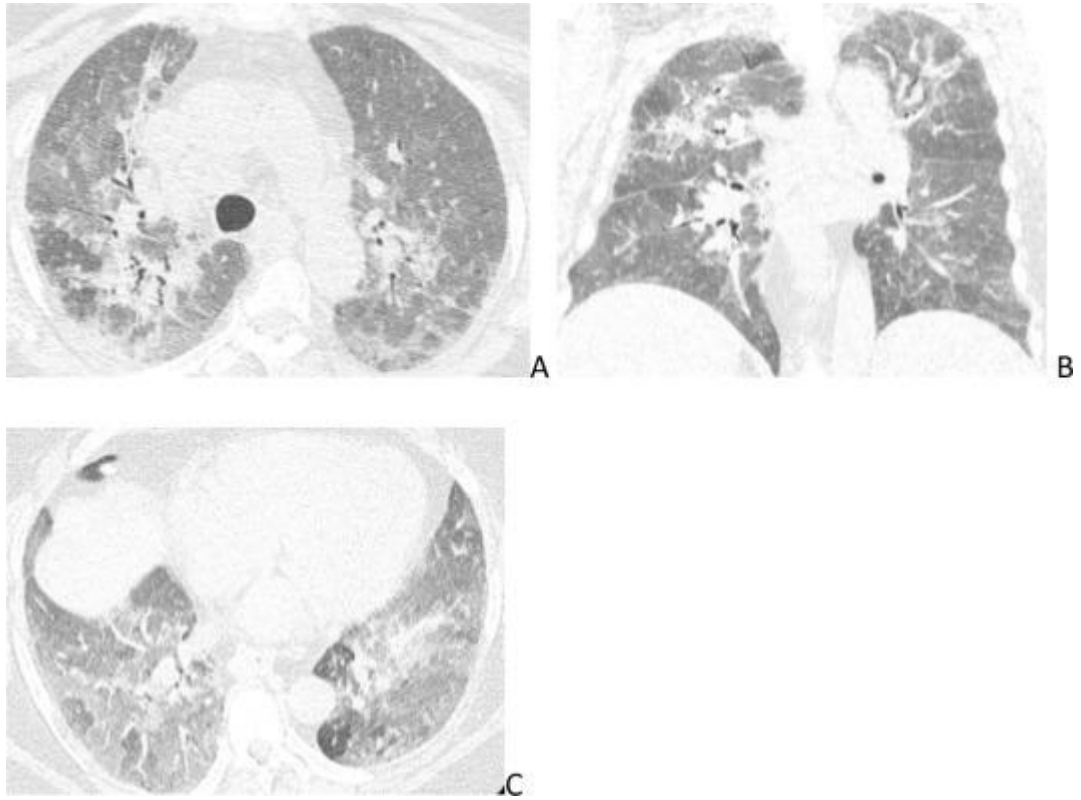
Occupational lung diseases of long latency



Weiss W. Chest. 1999;115:536-49

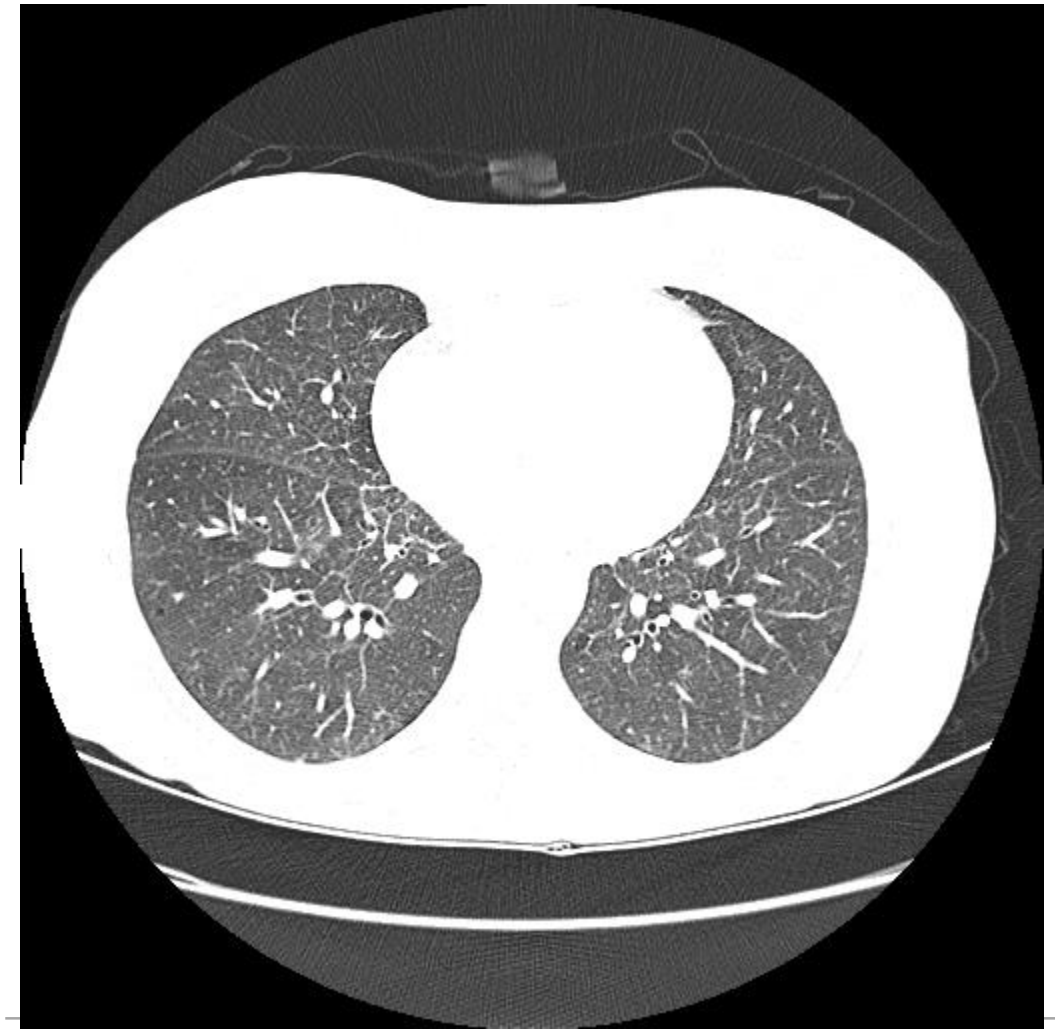
Occupational lung diseases of variable latency

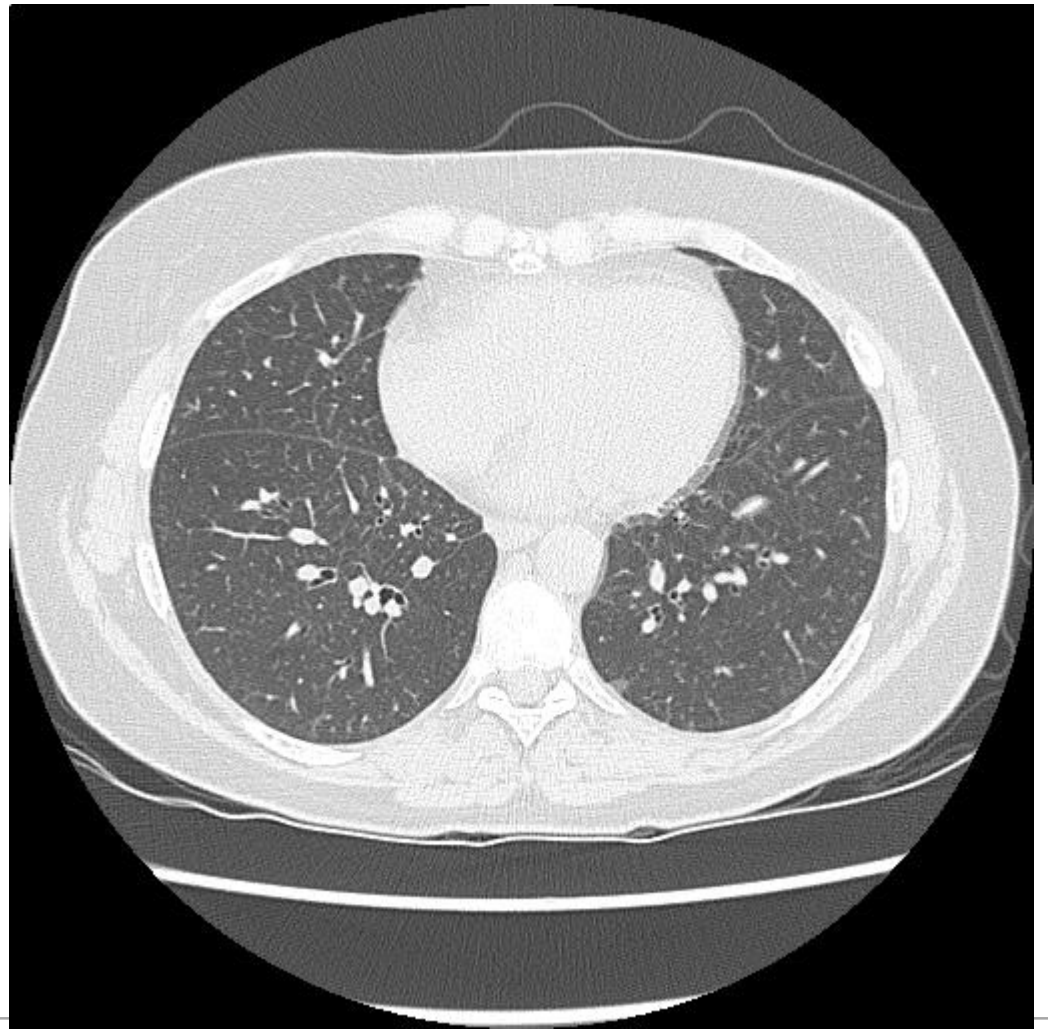




Saltini C. NEJM. 1989:320:1103-09
Adams TN. Resp Med. 2017;129:91-97

Smoking-related ILD

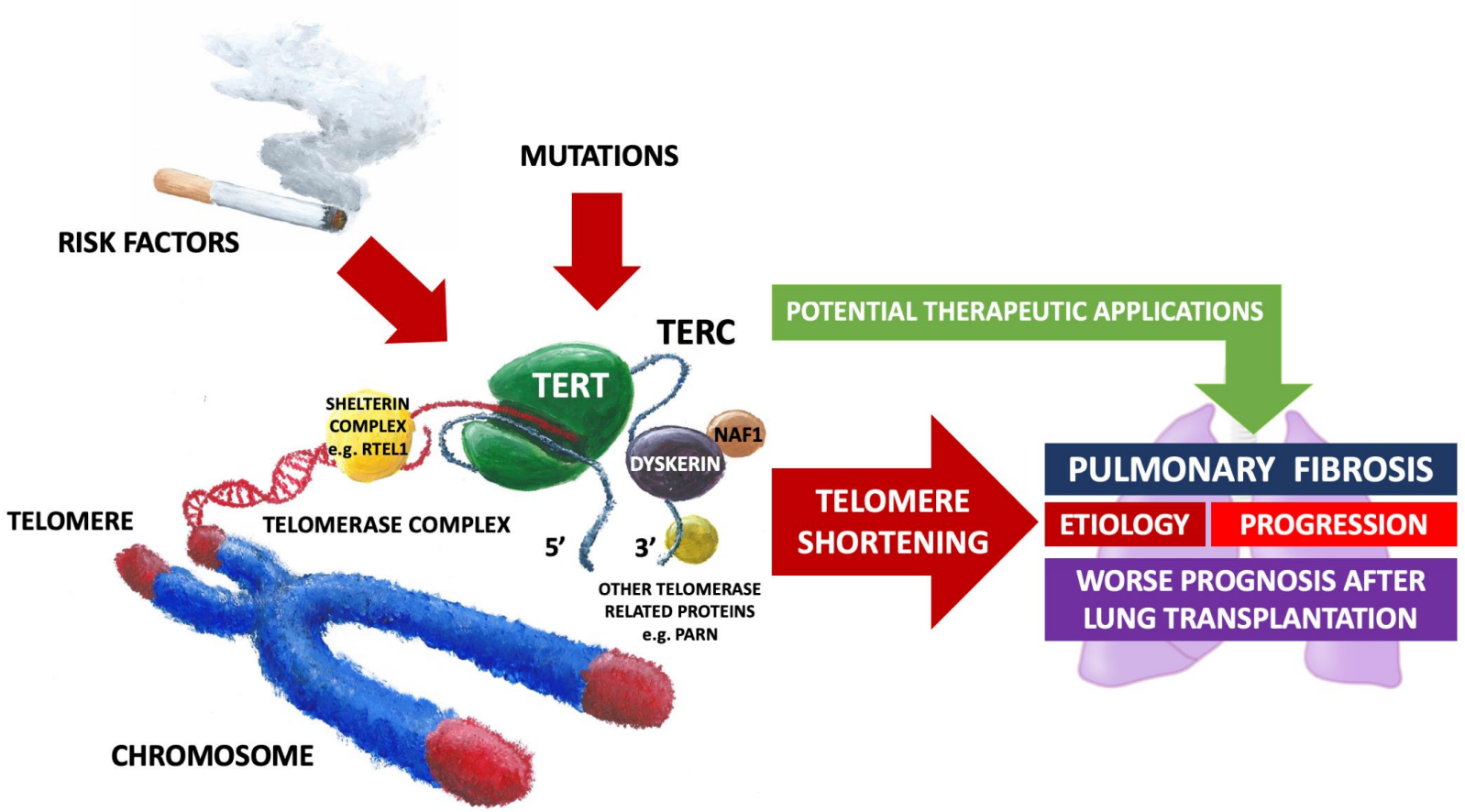




Family history

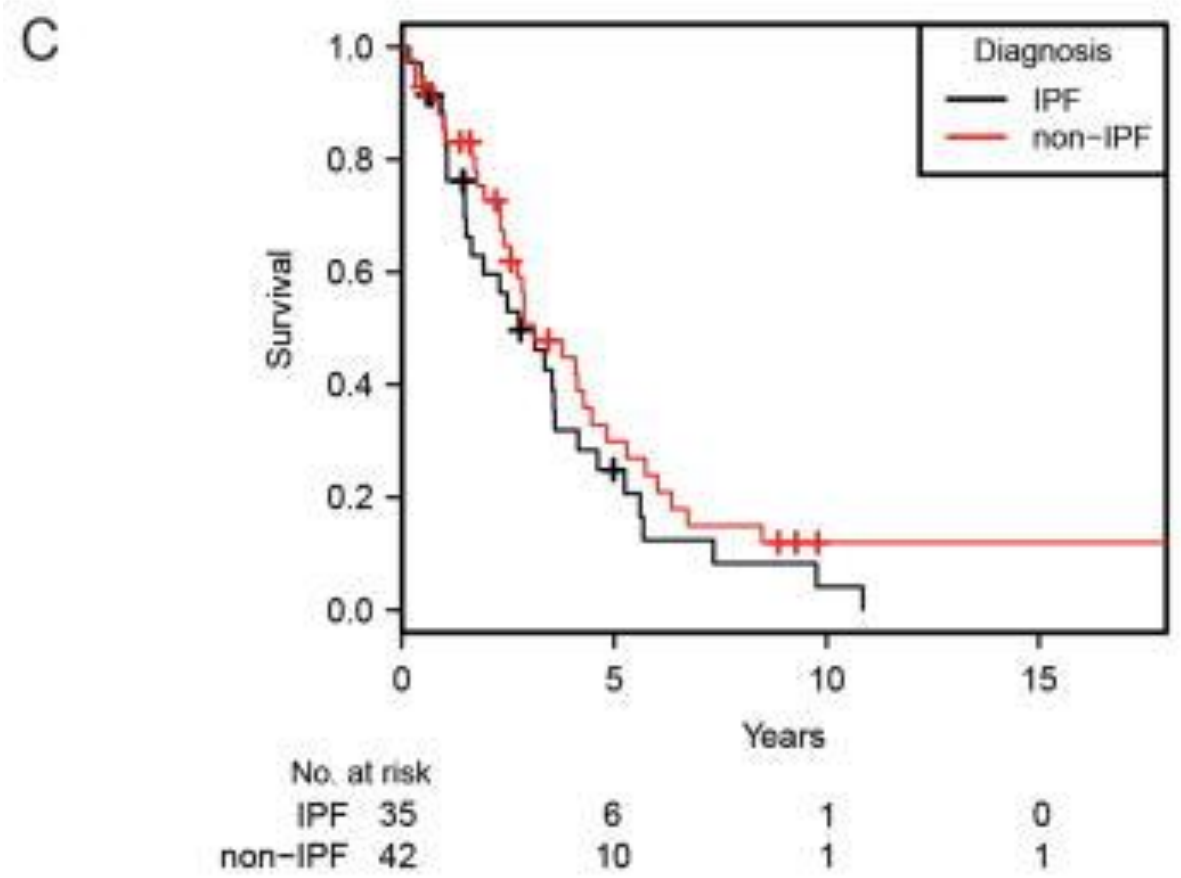
- HPI: Time course, age
- PMH
- Medications
- ROS: Connective tissue disease
- Social history:
  - Exposures
  - Occupational history
  - Smoking
- **Family history**

Telomerase mutations are the most common genetic cause of ILD



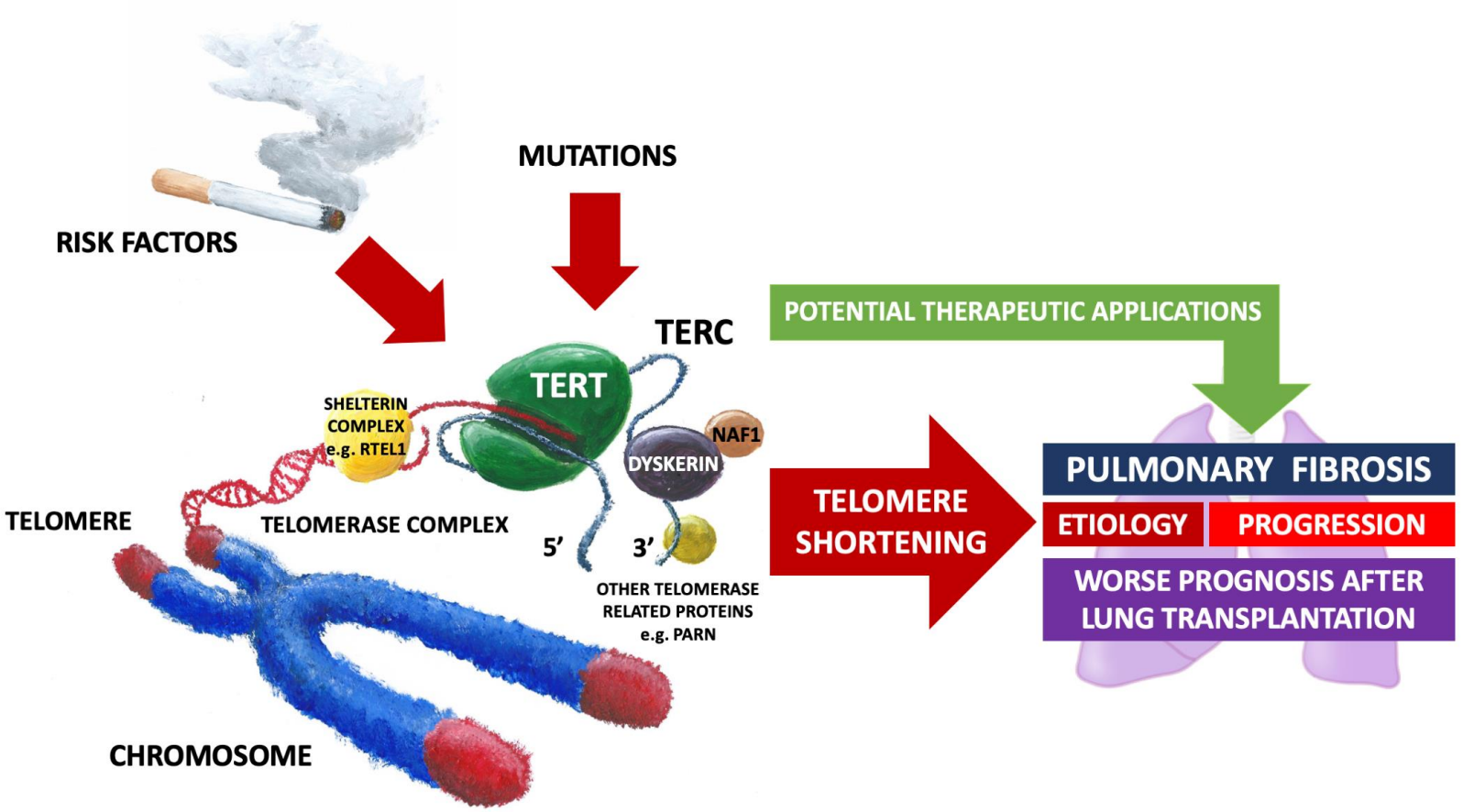
Bilgili H, Bialas AJ. Telomere abnormalities in the pathobiology of IPF. *J Clin Med* 2019;8:1232

Telomerase mutations predict poor prognosis regardless of ILD subtype



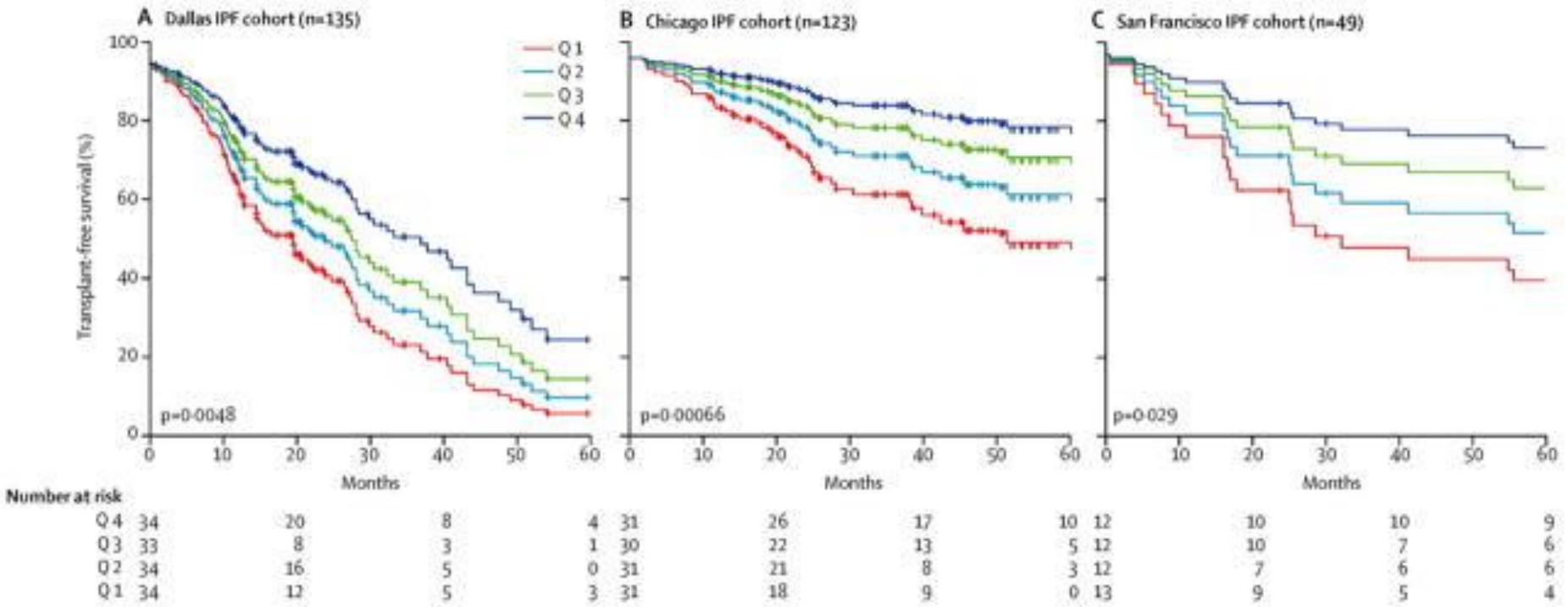
Newton CA, et al. *ERJ* 2016;48:1710-20

Multiple causes of short telomeres



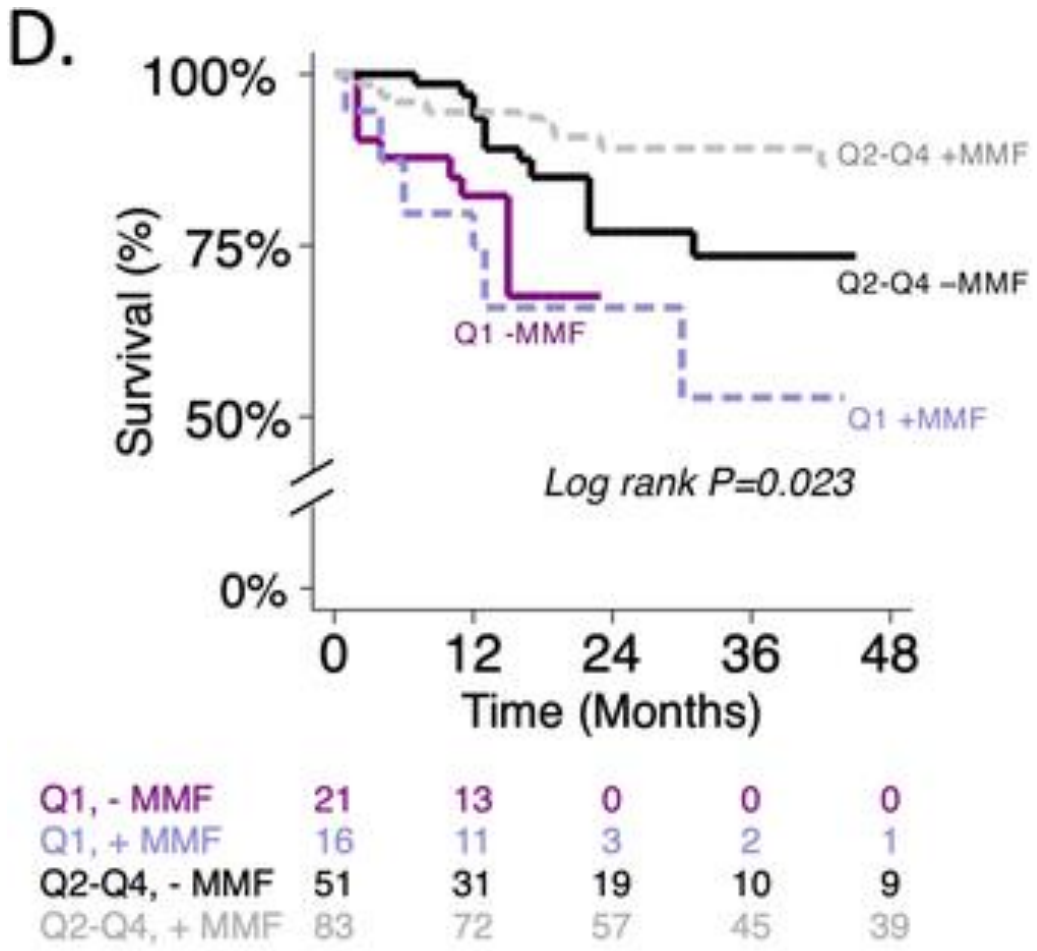
Bilgili H, Bialas AJ. Telomere abnormalities in the pathobiology of IPF. *J Clin Med* 2019;8:1232

Short telomeres with or without telomerase mutation predict poor prognosis



Stuart B, et al. *Lancet Resp Med* 2014;2:557-65

Short telomere length may predict poor response to immunosuppression

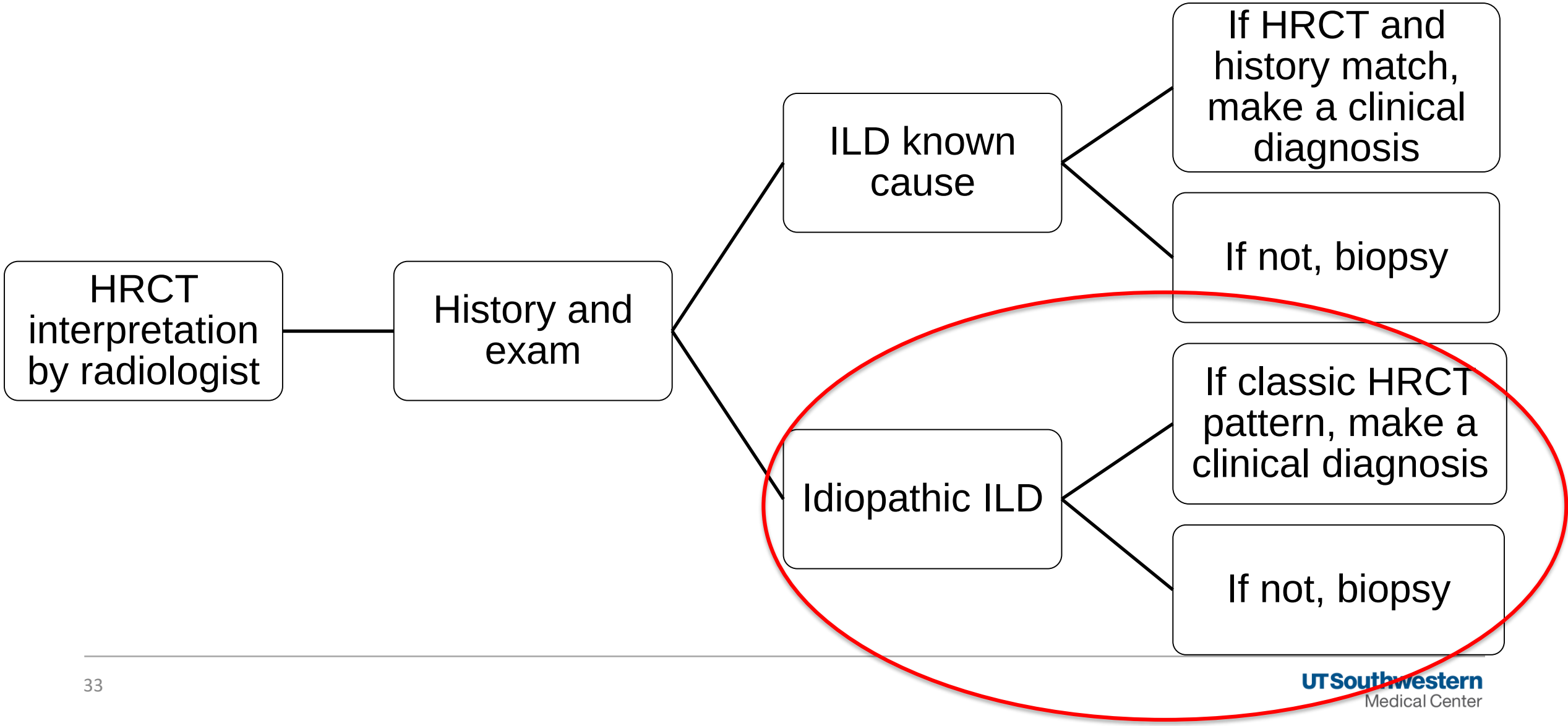


Adegunsoye A, et al. *ERJ* 2021;57:2002872

Case, continued

- You take a very thorough history.
- No offending medications
- No CTD signs or symptoms, negative CTD serologies
- No bird or mold exposure
- No family history of ILD
- No occupational exposures
- What is the next step in diagnostic evaluation?

Evaluation of Idiopathic ILD

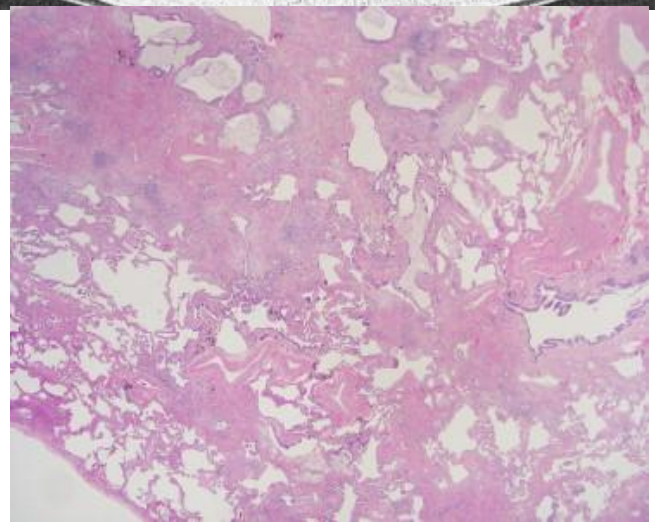


HRCT patterns and idiopathic clinical diagnosis

HRCT and/or pathologic pattern	**Clinical diagnosis if idiopathic**
Usual interstitial pneumonia (UIP)	Idiopathic pulmonary fibrosis (IPF)
Nonspecific interstitial pneumonia (NSIP)	Idiopathic NSIP

Idiopathic pulmonary fibrosis (IPF)

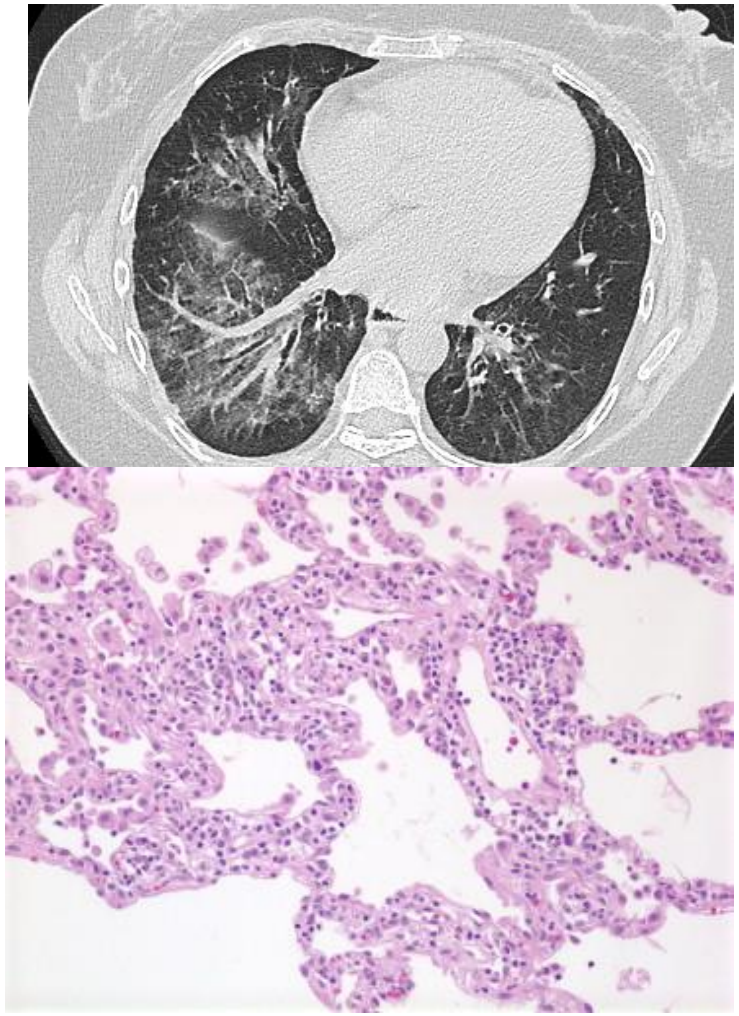
- IPF is UIP pattern without another cause
- Can make this diagnosis with a classic HRCT scan for UIP without a biopsy
- Most prevalent ILD in most centers
- Most common in older white men
- Median survival 3-5 years



Myers, JL. *Semin Diagn Pathol* 2007;24:183-7
Smith, ML. *Mod Pathol* 2022;35:8-14

Idiopathic NSIP

- Idiopathic NSIP is NSIP pattern without another cause
- Can make this diagnosis with an NSIP pattern on HRCT without a biopsy
- Rare
- Better survival than IPF
- Treated with immunosuppression



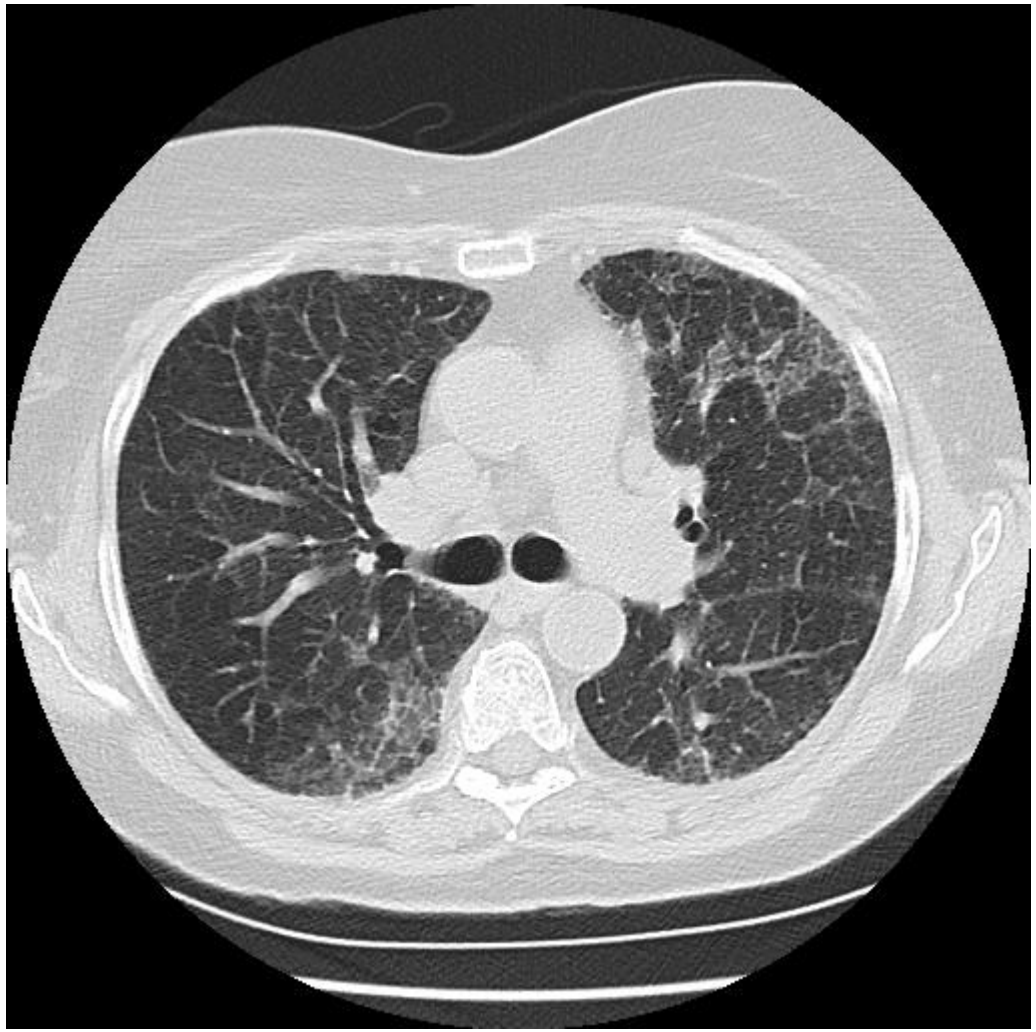
Teoh AKY, Corte TJ. *Semin Respir Crit Care Med.* 2020;41:184-201.
Myers, JL. *Semin Diagn Pathol* 2007;24:183-7

The reason this is confusing…

- Radiologist will identify an HRCT pattern such as UIP or NSIP
- This is not the same as a clinical diagnosis
- In every case we are looking for a known cause to differentiate idiopathic ILD from ILD of known cause.
- If imaging and history are consistent, we make a clinical diagnosis.
- We reserve surgical lung biopsy for cases where we cannot make a clear diagnosis based on history and HRCT

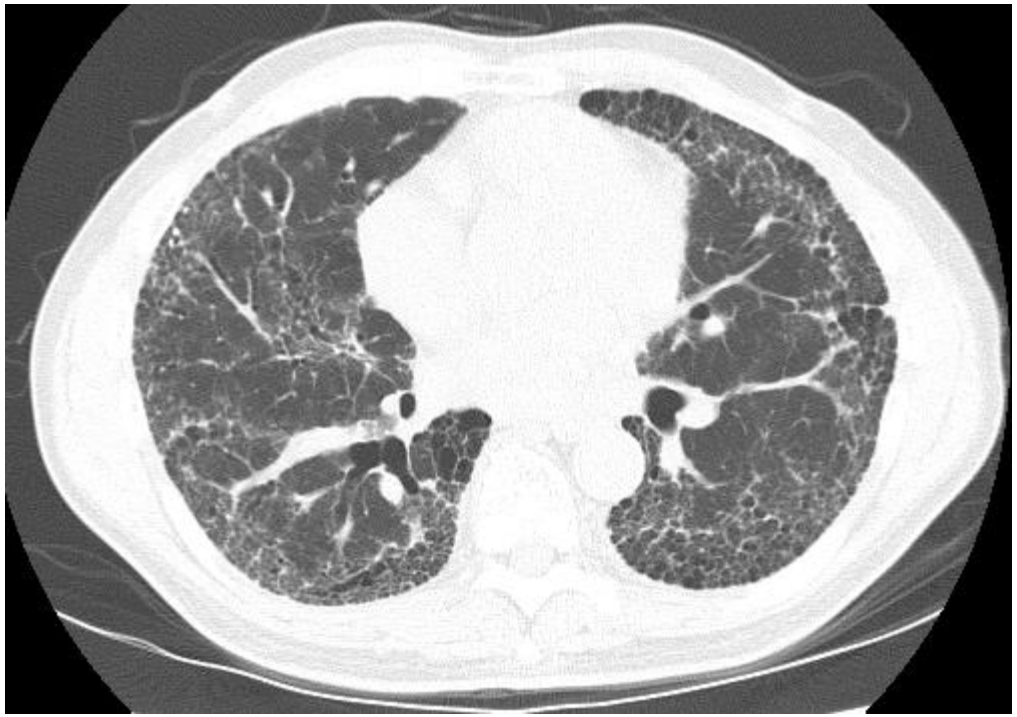
Surgical lung biopsy

- 1-2% mortality from the procedure
- Can often accurately predict histologic pattern based on HRCT pattern
- Used in cases where history and imaging are not fully diagnostic



Case, continued

- History does not reveal any known causes of ILD
- Imaging reveals typical UIP scan
- What is the diagnosis?
- What treatment would you start?



Objective 3: differentiate risks and benefits of pirfenidone and nintedanib

Pirfenidone

- TID medication which reduces compliance
- Upper GI side effects
- Photosensitivity
- Hepatotoxicity
- Slows progression in IPF

Nintedanib

- BID medication
- Diarrhea
- Bleeding
- Hepatotoxicity
- Rare bowel perforation
- Slows progression in IPF or progressive fibrotic ILD

Conclusion

- When evaluating a patient with ILD, start with the HRCT, then take a history and look for a known cause.
- If there is no known cause, we try to assign the idiopathic designation based on the imaging +/- pathology.
- IPF treatment options include pirfenidone and nintedanib

Acknowledgments

- Interstitial lung disease group
  - Kiran Batra, MD
  - Luis De Las Casas, MD
  - Craig Glazer, MD
  - John Fitzgerald, MD
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  - Corey Kershaw, MD
  - Megan Kypreos, MD
  - Chad Newton, MD
  - Elishba Sinha
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