

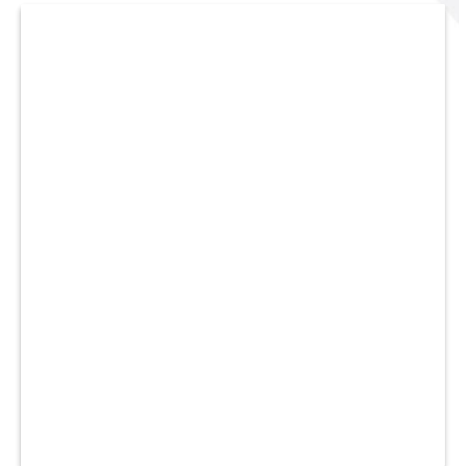
# Evolution of Pulmonary Fibrosis: From ILA's to UIP

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# Disclosures

1. Boehringer Ingelheim: Consultant
2. Genentech: speakers Bureau
3. Lecturer for CME Educational Programs ( Vindico, France Foundation )
4. PI NIH and Industry clinical trials and studies

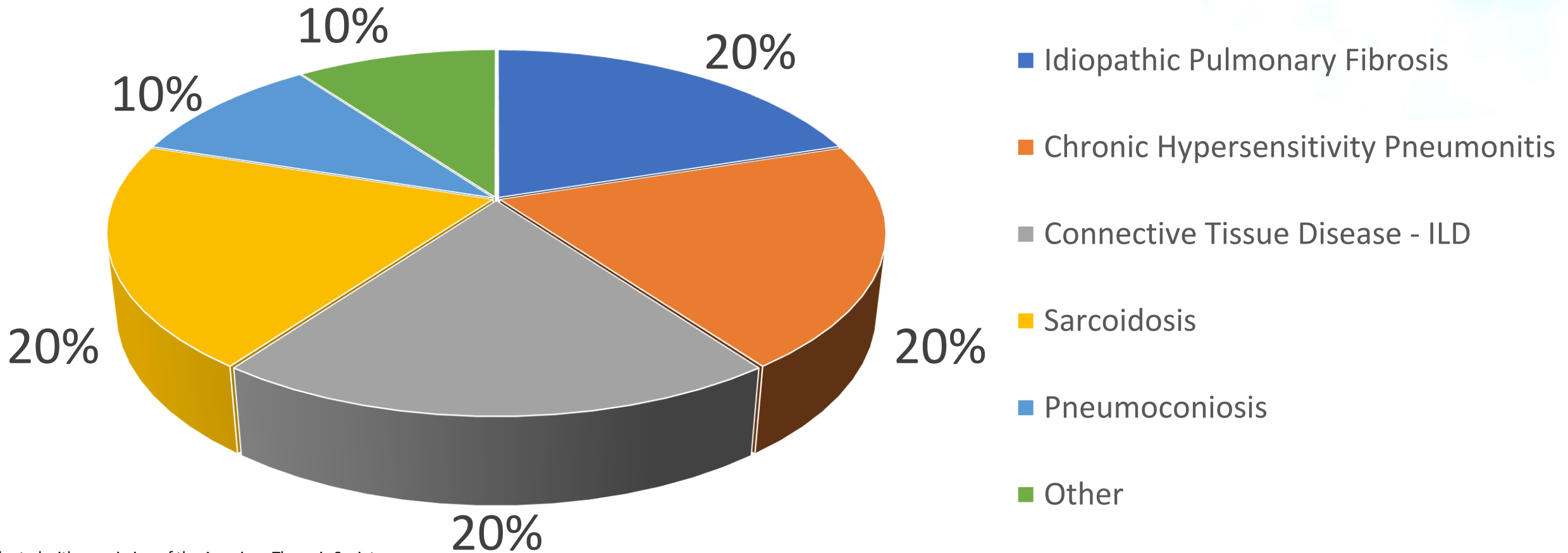
# Evolution of Pulmonary Fibrosis: From ILA's to UIP and Everything in Between

## Objectives

1. Upon completion of this learning activity, participants should be able to recognize Fibrosing ILD and ILA's and their clinical importance
2. Upon completion of this learning activity, participants should be able to develop strategies for management of ILA's and evolving fibrosing lung disease
3. Upon completion of this learning activity, participants should be able to utilize guidelines and novel diagnostic modalities to establish early diagnosis ILD and institute treatment



# What is the relative distribution of disease is ILD clinics?



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Readers are encouraged to read the entire article for the correct context at <https://www.nejm.org/doi/10.1056/NEJMra1705751>.  
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# Prevalence of progressive fibrosis interstitial lung disease.

	% with progressive phenotype	PF-ILD prevalence estimate per 10,000 persons <sup>a</sup>			
		Greece (n=967)	Belgium (n=362)	France (n=339)	USA (n=258)
IPF	100	0.34	0.13	0.88	1.70
iNSIP	32	0.02	-	0.04	-
HP	21	0.01	0.02	0.04	0.00
RA-ILD	40	0.03	-	-	0.16
SSc-ILD	21	0.02	-	-	0.05
PM/DM-ILD	16	0.00	-	-	0.01
Sjogren's ILD	24	0.00	-	-	0.00
SLE-ILD	24	0.00	-	-	0.04
MCTD-ILD	24	0.00	-	-	0.01
CTD-ILD	24	-	0.01	0.24	-
Sarcoidosis	13	0.08	0.02	0.45	0.11
Other ILDs	18	0.09	0.03	0.34	0.71
<b>PF-ILD total</b>	-	<b>0.59</b>	<b>0.22</b>	<b>2.00</b>	<b>2.80</b>
<b>Sensitivity analysis<sup>b</sup></b>	-	<b>0.84</b>	<b>0.30</b>	<b>3.12</b>	<b>3.90</b>

MEDLINE and Embase literature review & Physician surveys from 1990-2017.

Despite traditional therapies:  
**PF-ILD = 13% to 40%**

**Prevalence of ILD = 74.3 to 76.0/100,000**  
**Prevalence of PF-ILD = 20.0 to 28.0/100,000**

(IPF = 16/100,000 to ~ 500/100,000 (Medicare))

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# Health care resources utilisation and cost in patient with non-IPF progressive fibrosing interstitial lung disease.

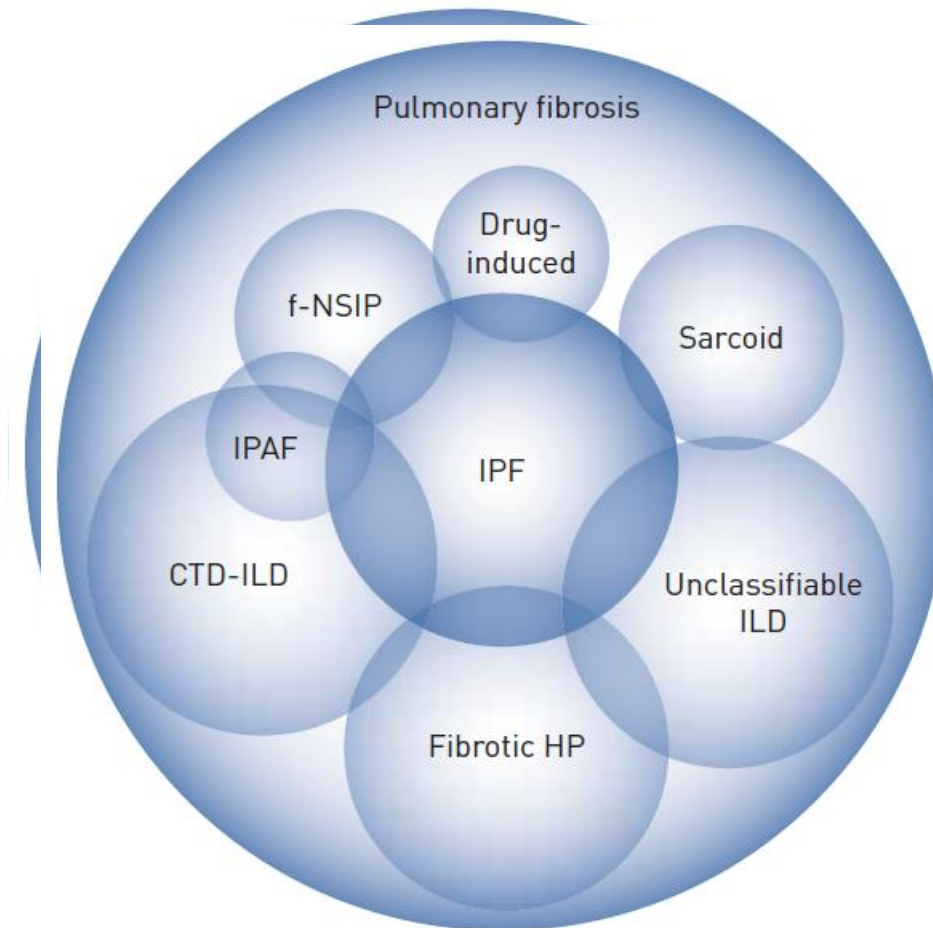
- Authors analyzed US-based medical insurance claims over 3 years (2014-2016).
- Of the 2517 patients with non-IPF ILD, 373 patients (or 15%) were considered to have PF-ILD ( $\geq 4$  pulmonologist visit in 2016 or  $\geq 3$  more pulmonologist visits in 2016 than in 2014).
  - **Physician office visits, 2016: 7.6 PF-ILD vs 4.2 ILD – as expected**
  - **Mean annual medical costs: \$35,364 PF-ILD vs. \$20,211 ILD**
  - **Hospitalizations: 10.5 PF-ILD vs. 4.7 ILD**
- Thus, patients with PF-ILD have a higher healthcare utilization and costs compared to other ILD patients.



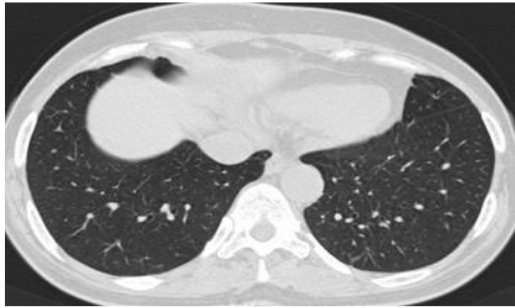


# Pulmonary Fibrosis

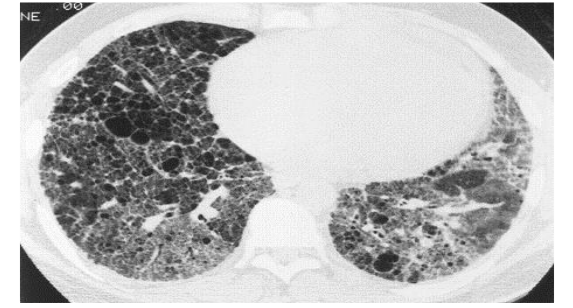
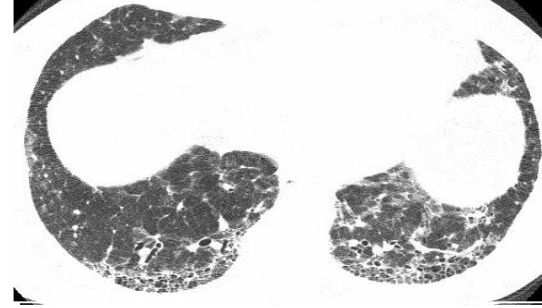
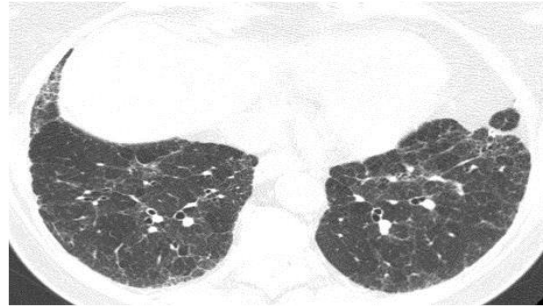
## Are ILA's the precursor??



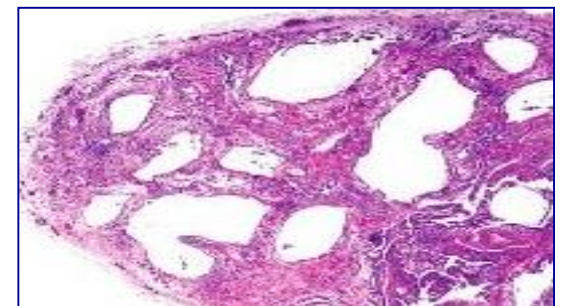
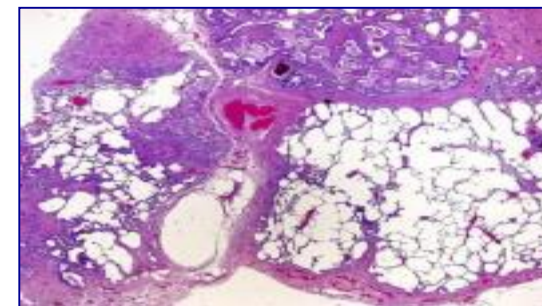
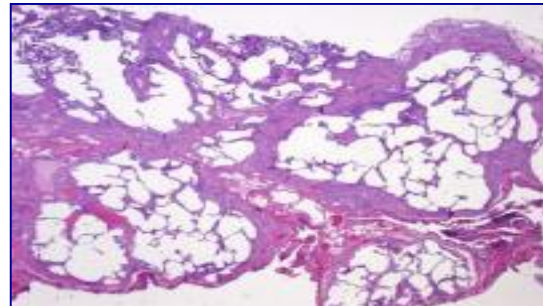
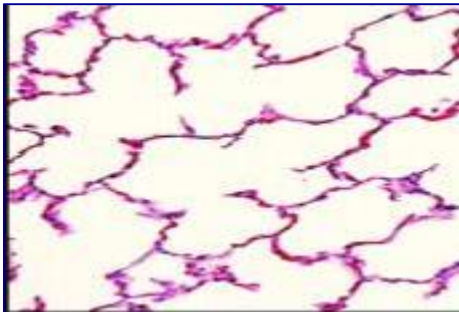
# Progression of IPF



Normal



Progressive destruction of lung architecture



5-year survival rate from diagnosis = 20 to 40%  
Age of onset : 2/3 over age 60



# What are ILA's and Why They Matter



Figure 3. Prone CT Findings



## Incidental findings on CT scans performed for various reasons.....

1. Often not recorded or reported
2. Detected on large scale research studies
3. Called :“increased interstitial markings”, “chronic interstitial markings” ‘dirty lung’  
or : “preclinical ILD”, “subclinical ILD”, or “Interstitial lung abnormalities” (ILA’s)
4. Definition used was not always consistent
5. But significant associations appreciated

# ILA's –associations

- Respiratory symptoms
- Functional impairment
- Risk of Progression
- Increase Morbidity
- Increased all-cause mortality

# ILA's

- **Araki Framingham Heart Study (2016), (Hunninghake NEJM 2013 )**
  - 1867 participants (6% with progressive ILA's, median follow up 4y)
  - MUC5 B promoter polymorphisms and increasing age, associated with decrease in FVC (-64ml/yr) and increased risk of death (HR 3.9)
  - Over age 50y +MUC5 B, ILA's (9% and fibrosis 2%), decreased DLCO
- **Washko: COPD Gene ID of early ILD in smokers**
- **Yong: Lung cancer screening (Korea)**
  - 884 participants , ILA 9.7% , fibrotic (2.1%), 0% improved and 37% progressed
- **Salvatore I-ELCAP registry** 951 participants, 6.6 %, ILD, 1.7% F

# ILA's

- Relatives (105) of IPF patients (Familial and sporadic)
  - 31 % ILA's
  - Risk similar for F-IPF vs sporadic IPF
  - Decreased TLC or DLCO had greater than 9 fold increase in odds of having ILA's



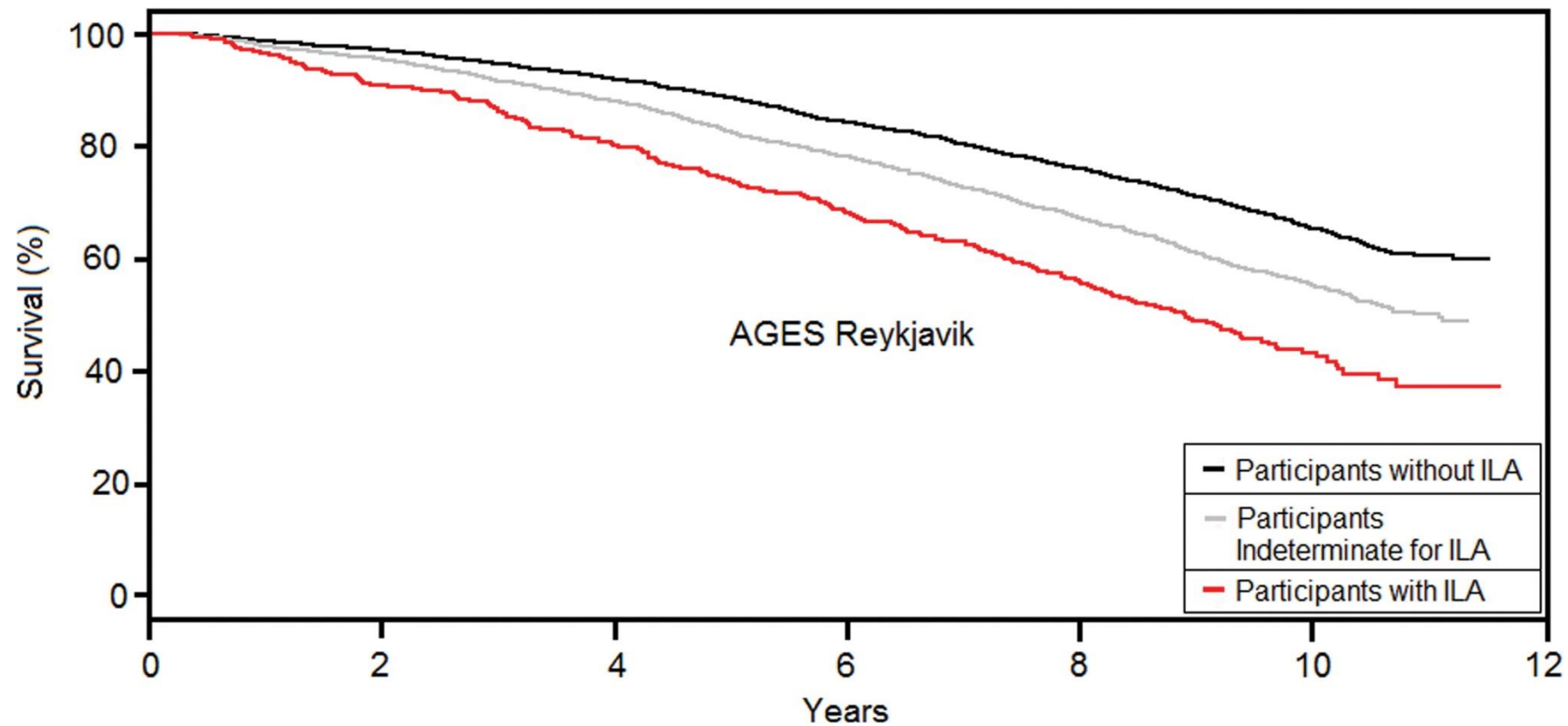


Figure 2: Graph shows survival rates according to interstitial lung abnormality (ILA) status for the Age Gene/Environment Susceptibility–Reykjavik, or AGES-Reykjavik, study. The x-axis indicates duration of follow-up in years up to 12 years, and the y-axis indicates survival range from 0% to 100%. Hazard ratio was 1.3 (95% confidence interval: 1.2, 1.4;  $P < .001$ ) between participants with and participants without ILA with use of the adjusted Cox proportional hazards model including adjustments for age, sex, body mass index, pack-years of smoking, and current or former smoking status. Created from data published in reference 8.



# 2020 :Fleischner Society Position Paper on ILA's

- Definition of ILA's
- Subcategories of ILA's
- Risk factors for ILA's
- Outcomes of ILA's
- Management of ILA's
- Future Research Directions
  
- Hatabu et al Lancet Resp Med 2020 8: 726-37

# ILA's Definition

- Radiologically based
- ILD not suspected (incidental findings)
- Excludes findings detected on at risk populations for ILD (pre-clinical ILD)
- Non-dependent abnormalities affecting more than 5% of any lung zone (excludes centrilobular nodularity)
  - Reticular abnormalities, GGO, traction bronchiectasis, architectural distortion, HC, non-emphysematous cysts
- Focal or unilateral GGO : equivocal

# ILA's

- Prevalence : 2-9.6%
- Non-fibrotic : may disappear or not progress
- Fibrotic: prevalence lower; progressive in 30-50% of cases, disappear in **0%** cases
- Progression over 2-7 y and in some cases decades (familial)
- Associated with decrease in FVC, DLCO and increased risk of death in subgroups with MUC 5B and other genetic variants

## Interstitial Lung Abnormalities

- ▶ Subtypes include:

Non-subpleural

Subpleural, non-fibrotic

Subpleural, fibrotic

- ▶ Associated with reduced lung function, lower 6MW distance and mortality.
- ▶ Progression is seen in 20-48% of higher risk smoking populations.
- ▶ Fibrotic ILA is most strongly associated with progression and mortality.



# ILA's Risk Factors

- Advanced Age
- Male gender
- Tobacco smoke exposure
- Occupational and environmental exposure (vapor, gases, fumes, dust, air pollution-MESA, Framingham)
- Genetic (MUC 5B, telomere mutations )

# Genetics and Biomarkers

- Genetic predisposition
  - **MUC 5 B**, TERT, SP -A, SP -D,
- Biomarkers
  - Diagnostic, prognostic and theragnostic
    - **Matrix metalloproteinase (MMP)-7, and Osteopontin**
    - **Tollip polymorphism : risk and treatment response**
    - **KL-6**
      - White ES, et al. *Am J Respir Crit Care Med* 2016;

# ILA's – Outcomes

- Progression (2y 20%, 5y >48% )
  - Subpleural, lower lobe reticular changes or bronchiectasis, HC
- Lung function Decline : accelerated FVC decline in progressive ILA's (~60 ml/yr)
- Increased respiratory and all cause mortality
- Increased rate of ARDS -(role in COVID infection??)
- Increased mortality in lung cancer and TAVR
- Increased risk pneumonitis from chemo, check point I and radiation (6x risk increase in drug induced pneumonitis )

# Dx/Evolution/Progression of Disease

- Imaging
  - HRCT with 1-2 mm cuts
  - Visual assessment
  - Quantitative Imaging
    - Assessment of High-Attenuation Areas (Histogram)
    - Deep learning textural evaluation (Data driven texture analysis)

Fig1a

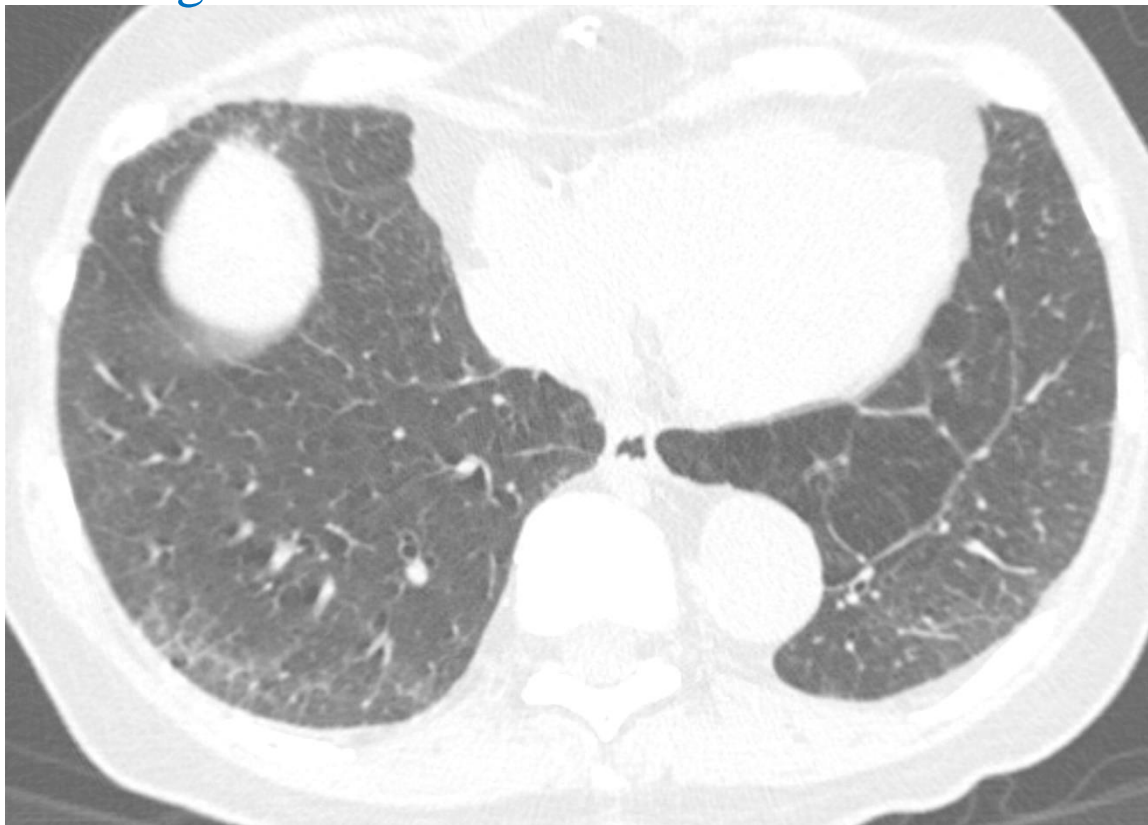


Fig1b

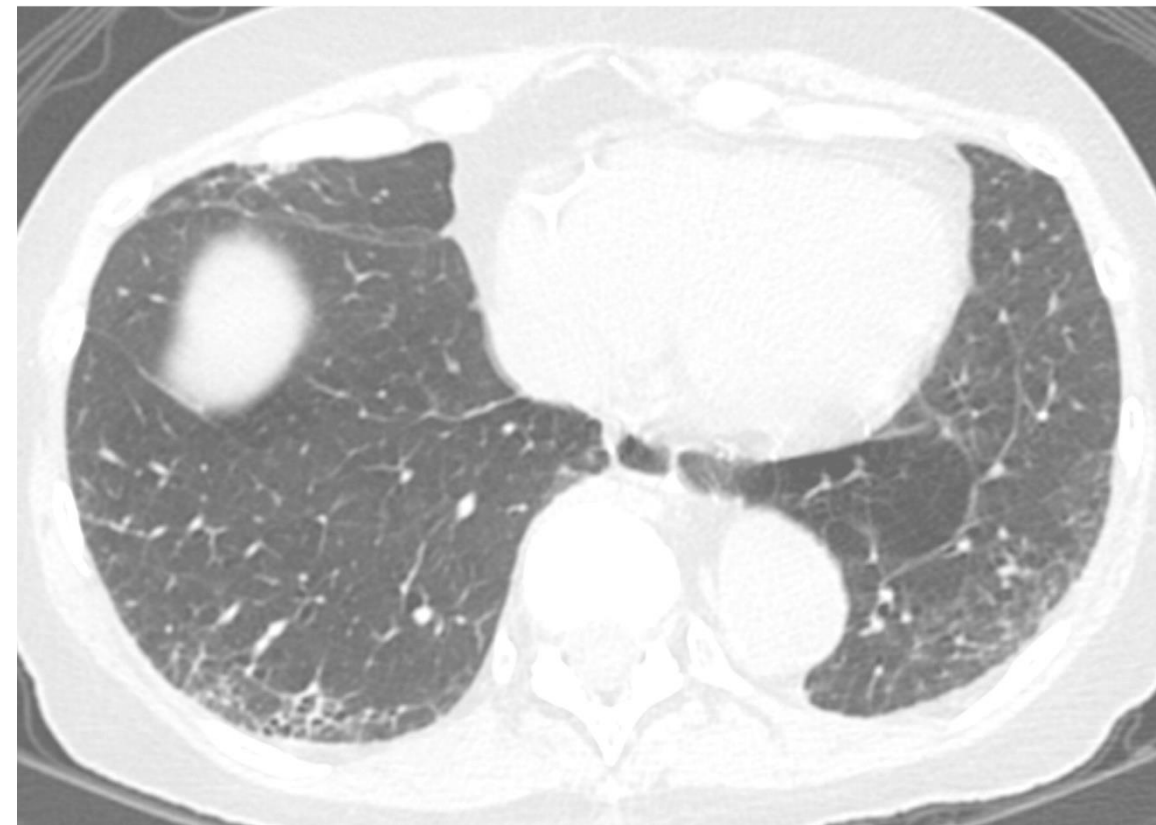


Figure 1a: Images in 73-year-old female participant in the COPDGene Study. **(a)** Baseline noncontrast CT scan of chest shows mild ground-glass abnormalities with interlobular septal thickening with subpleural distribution. **(b)** CT scan obtained 5½ years later demonstrates reticular and ground-glass opacities with mild traction bronchiectasis and architectural distortion indicating progression. During this time period, the participant experienced an increase in respiratory symptoms and a decrease in total lung capacity.



# Progression of ILA's with DATA

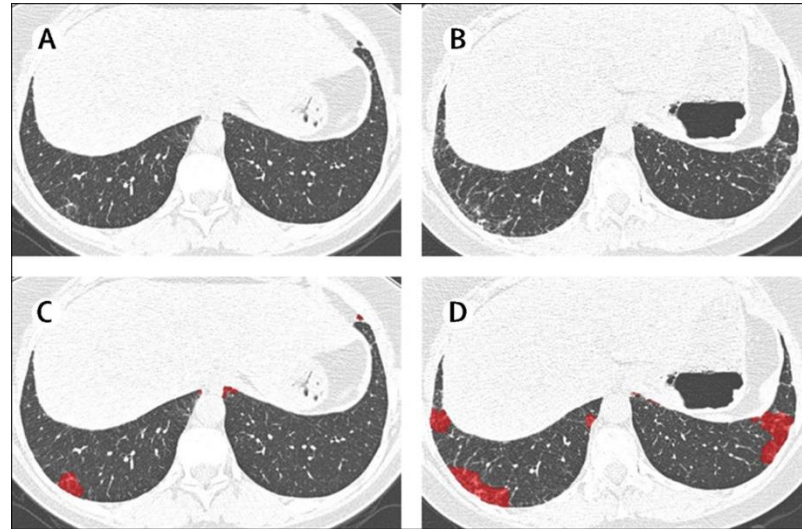


Figure 7. Quantification of progression for interstitial lung abnormalities with data-driven texture analysis

(A) A baseline CT scan shows subpleural non-fibrotic interstitial lung abnormalities with fibrotic changes. (B) CT 5 years later shows clear progression. (C) Baseline data-driven textural analysis shows overall extent of fibrosis as 1.5% (red). (D) Data-driven textural analysis of follow-up scan at 5 years shows that the extent of fibrosis increased to 4.6% (red).

# Proposed Management of ILA's

Hatabu et al Lancet Resp Med 2020 v8 726-37

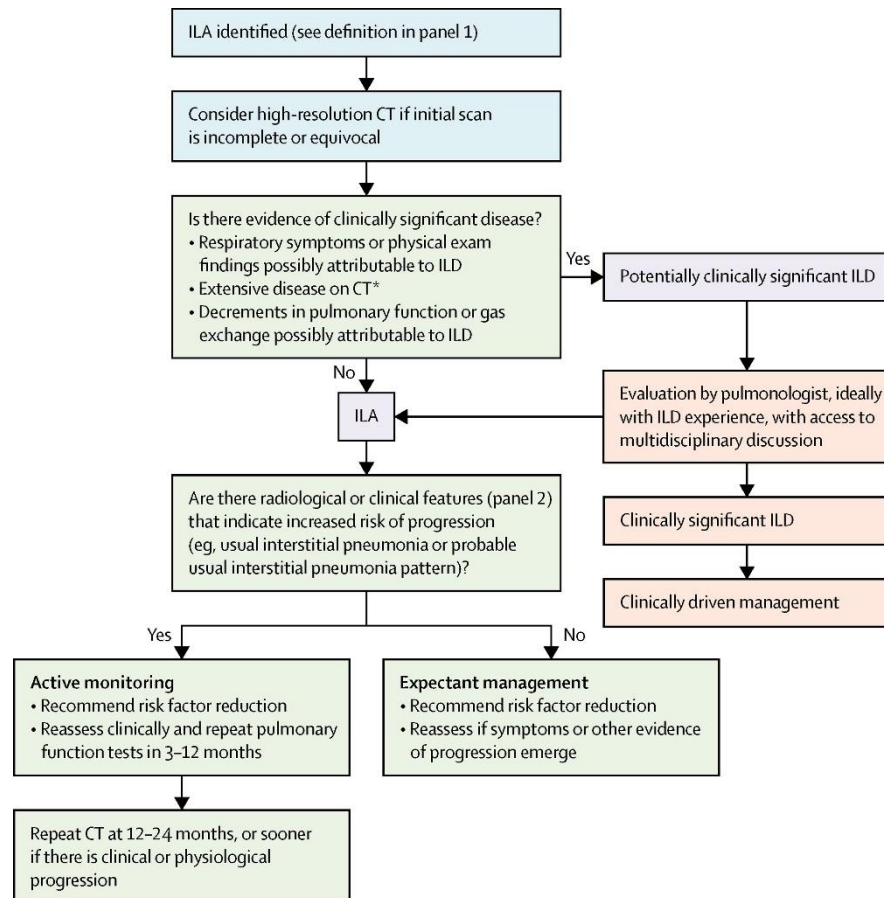


Figure 5. Proposed schema for management of interstitial lung abnormalities detected on chest CT

Action items for the radiologist are in blue, action items for the treating physician or pulmonologist are in green, and action items for a pulmonologist, ideally with ILD experience, are in orange. ILA=interstitial lung abnormality. ILD=interstitial lung disease. \*Non-trivial abnormalities present in three or more lung zones (above the bottom of the aortic arch, between the aortic arch and top of the inferior pulmonary vein, and below the inferior pulmonary vein).

# ILA's Evaluation and Monitoring

- ILA's identified
  - Is there ILD disease that requires specific therapy? ILD referral /MDD
- Is there increased risk of progression?
  - Yes: Active monitoring, risk factor reduction, PFT's 3-12mo
    - Repeat CT scan 12-24 or sooner for clinical or functional
  - No: Risk factor reduction and reassess for symptoms or signs of progression

# **Lung Cancer and Fibrosing Lung Disease**



# Comorbidities of IPF...

Comorbidity	Prevalence (n = 126 observational studies)
Gastroesophageal Reflux Disease	0%-94%
Obstructive Sleep Apnea	6%-91%
Pulmonary Hypertension	3%-86%
Coronary Artery Disease	3%-68%
Emphysema/COPD	6%-67%
Lung Cancer	3%-48%
Anxiety and Depression (Patients & Caregivers)	30%-50% ±
(Thromboembolic Disease)	~ 50% Higher than lung cancer/COPD ± *

Raghu G, et al. *Eur Respir J.* 2015;46:1113-1130.

Fulton BG, et al. *Int J Gen Med.* 2015;8:309-318. ±

Sprunger DB, Olson AL, et al. *Eur Respir J.* 2012;39:125-132. \*

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

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

*CHEST*

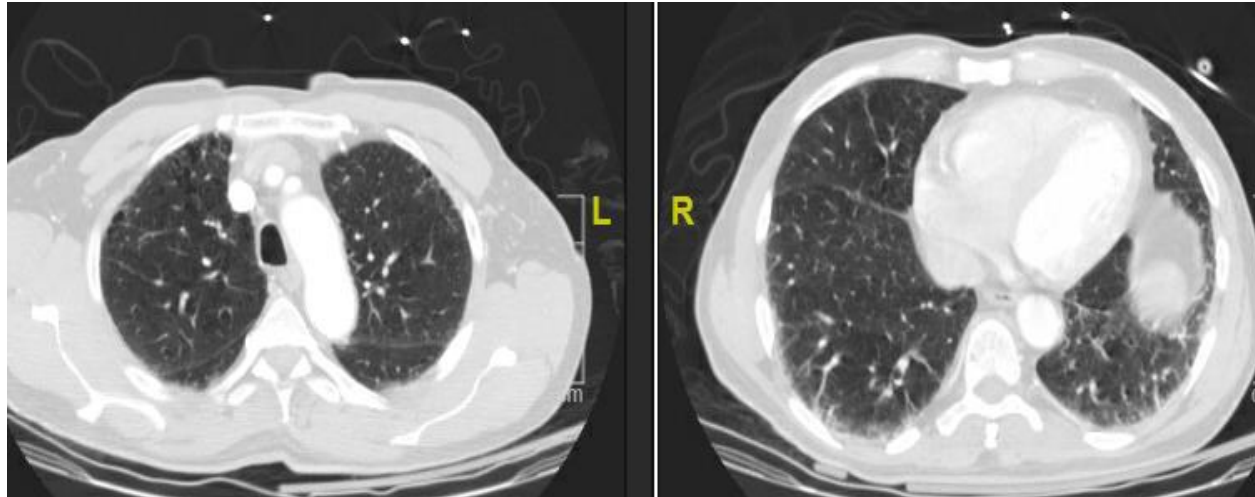
Volume 156 Issue 6 Pages 1195-1203 (December 2019)



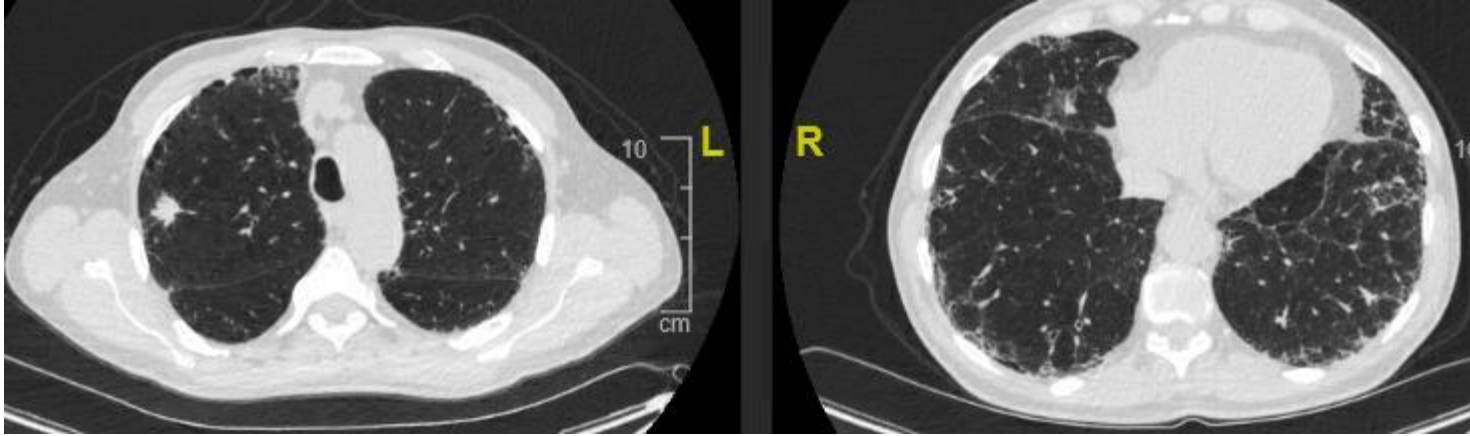
# What would you do with this report ?

- ▶ CT Chest 2013 at time of MVA

**IMPRESSION: Minimal right pneumothorax. Emphysema. Small pulmonary nodules.**



## 5 Y later: mild cough



### CT scan report :

#### IMPRESSION:

17 x 16 mm solid spiculated right upper lobe nodule, corresponding to findings from recent chest x-ray, new since 2013, concerning for primary lung neoplasm.

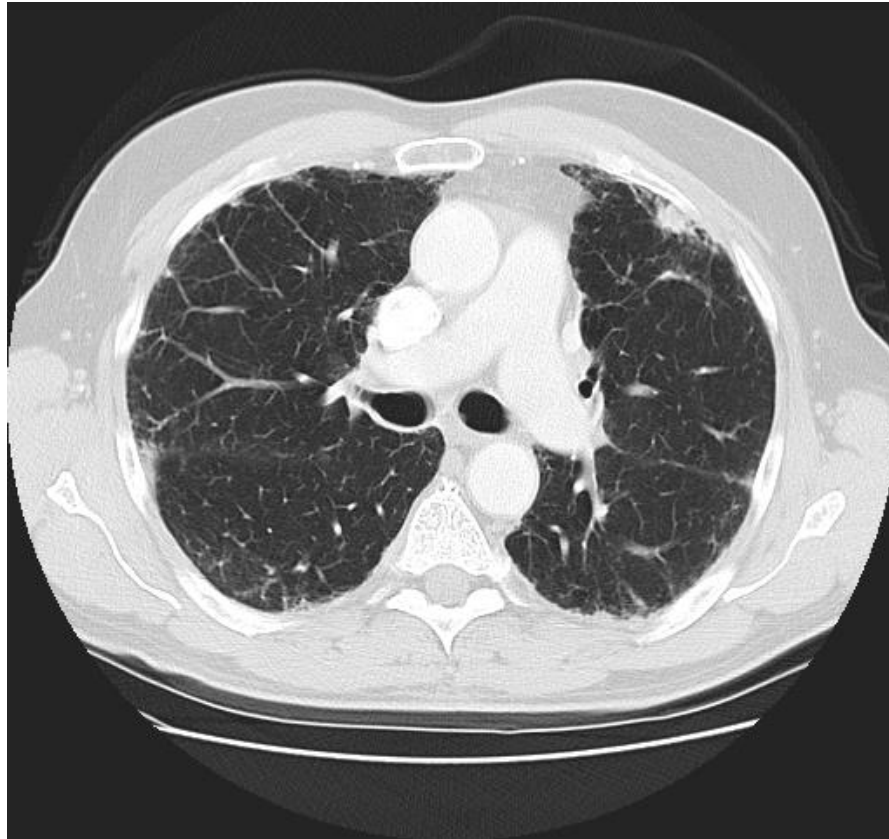
A 9 x 6 mm left upper lobe nodule demonstrates interval increase in density without significant change in size when compared with 2013 and is also suspicious for malignancy.

A 5 mm right lower lobe nodule is stable.

Interval mild progression of background of pulmonary fibrosis since 2013 examination.



# ILA's and Lung Cancer



Don't Ignore the Interstitial Lung Abnormalities

## ILA and Lung Cancer Risk

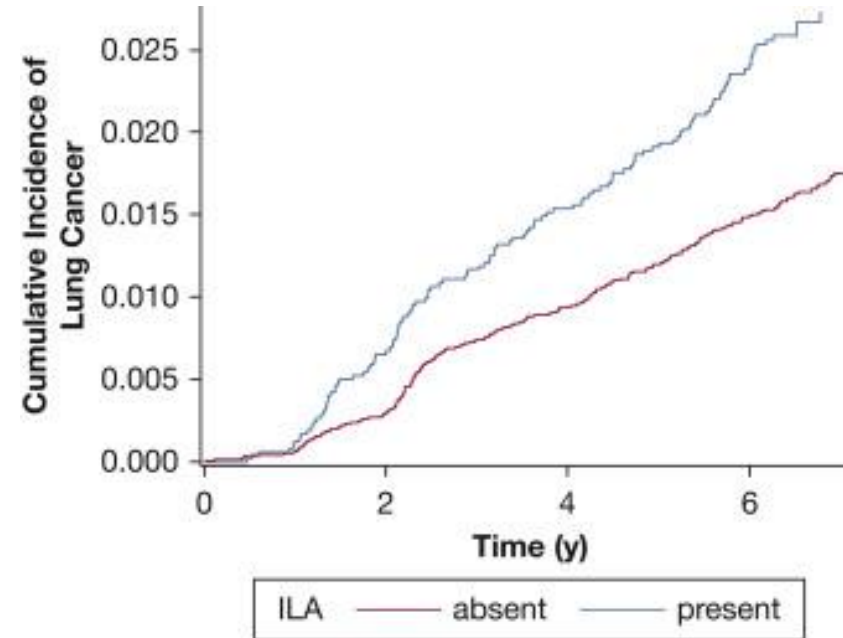
<b>Model</b>	<b>HR</b>	<b>95% CI</b>
<b>Definite fibrosis</b>		
<b>Lung cancer diagnoses</b>		
Unadjusted	5.49	2.91-10.4
Adjusted	3.95	2.07-7.57
<b>Mortality from lung cancer</b>		
Unadjusted	8.86	4.94-15.9
Adjusted	5.98	3.29-10.9
<b>Without fibrosis</b>		
<b>Lung cancer diagnoses</b>		
Unadjusted	3.10	1.81-5.32
Adjusted	2.26	1.29-3.96
<b>Mortality from lung cancer</b>		
Unadjusted	2.53	1.33-4.79
Adjusted	1.68	0.86-3.29

## ILA's associated with Lung Cancer

- ▶ Using the National Lung Cancer Screening Trial

Adjusted LC incidence: IRR 1.39

Adjusted LC mortality: HR 1.58

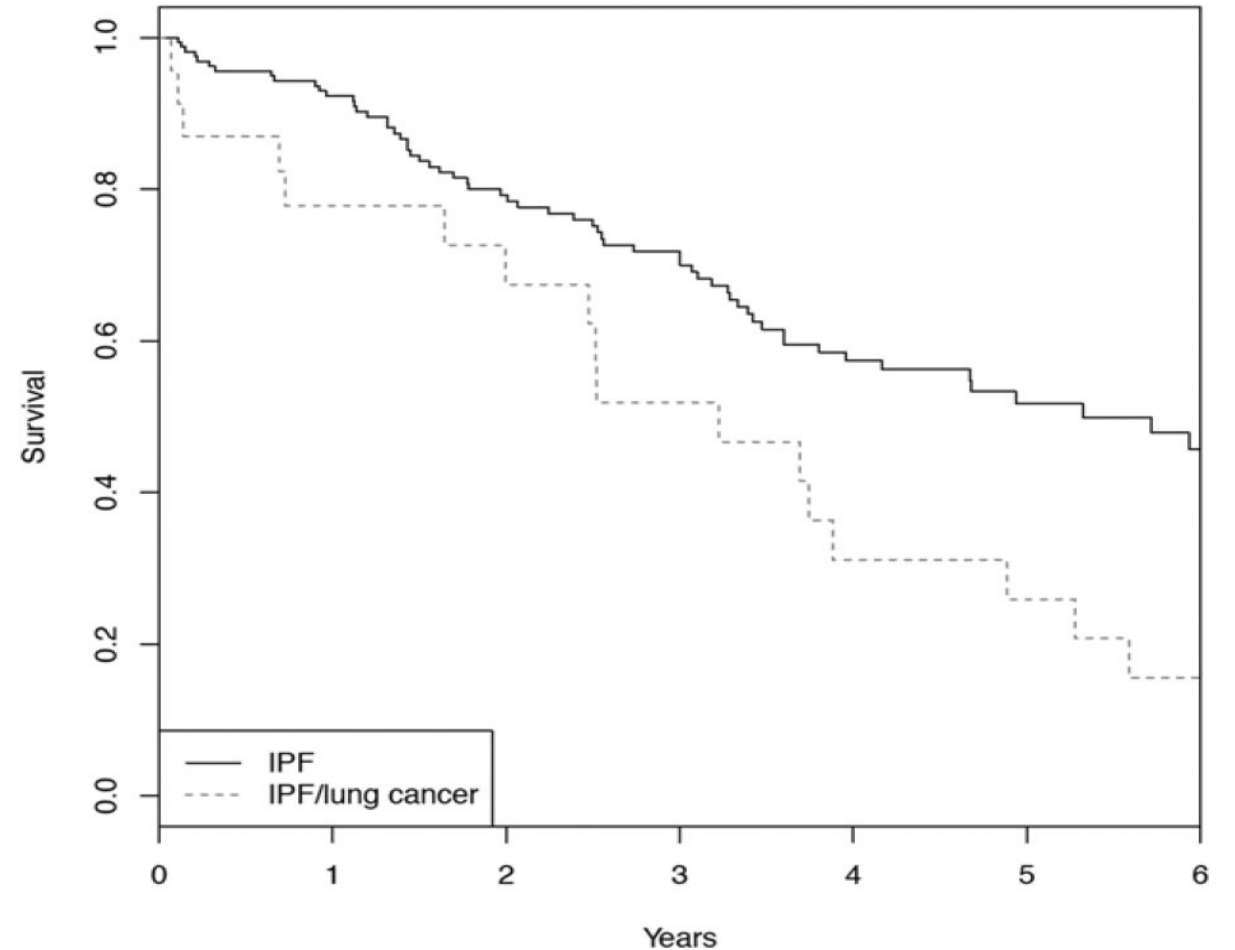


# Implications

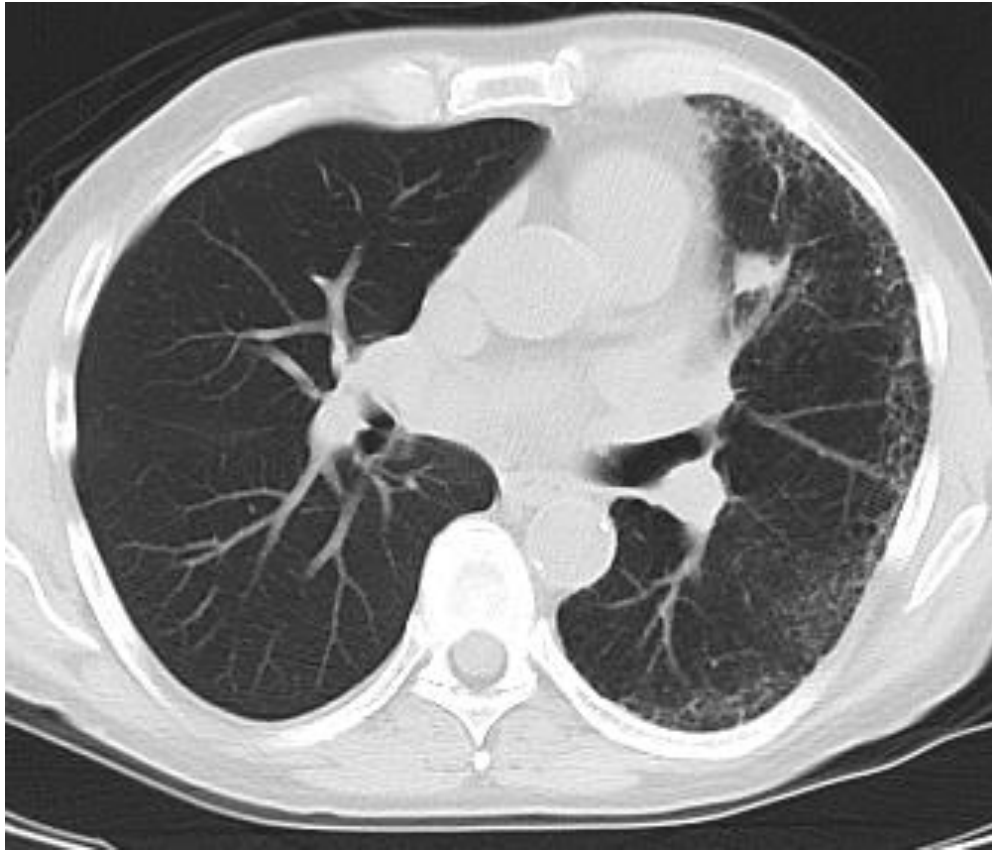
- ▶ Both ILAs and ILD are associated with increased lung cancer incidence AND mortality.
- ▶ ILA's and pulmonary fibrosis have increased risk of Acute exacerbation when undergoing procedures or treatment (Pulm resection, radiation, TAVR or other non pulmonary surgery)
- ▶ ILA's share certain genetic mutations that may lead to common pathways for neoplasia
- ▶ Interstitial lung abnormalities are frequently seen on lung cancer screening CTs, and may need to be incorporated into risk models as a negative prognostic factor.

## Cause of Death in Patients with Lung Cancer and IPF

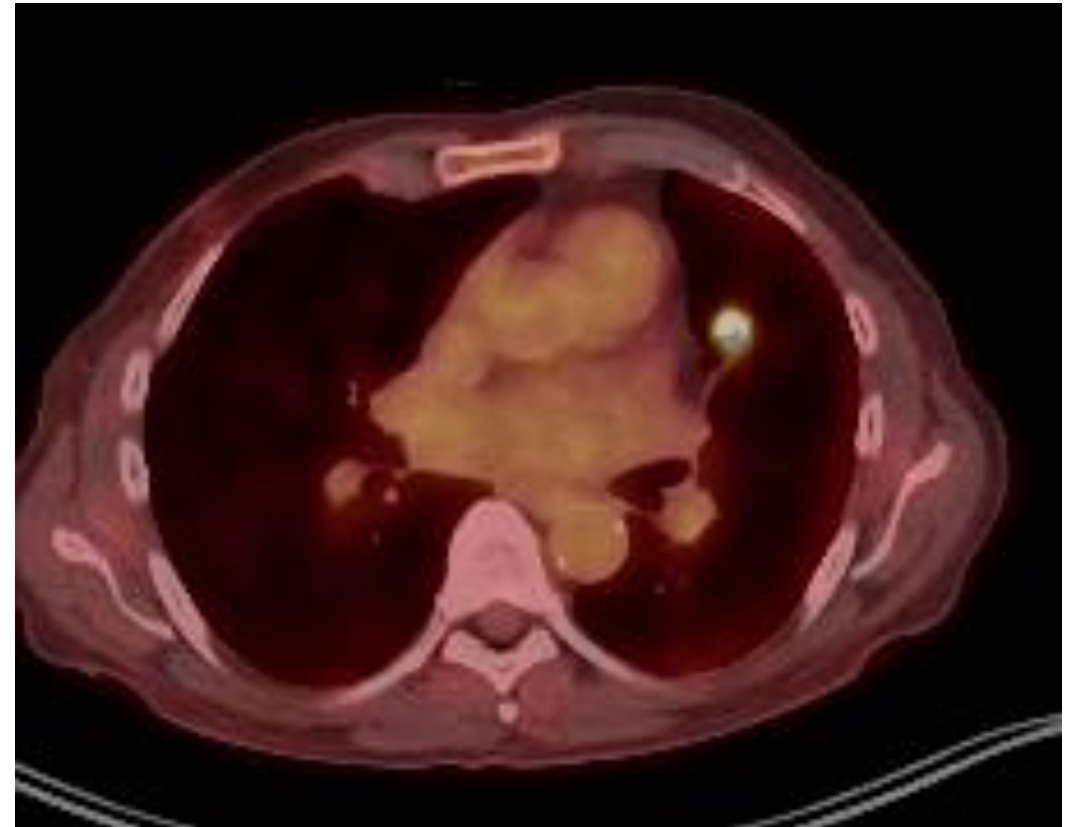
- ▶ A cohort of 181 cases of IPF, 23 (13%) with lung cancer.
  - ❖ 43% AE-IPF
  - ❖ **17% lethal complications and treatment**
  - ❖ 13% LC progression



**UIP/Squamous Cell Carcinoma**  
**Left Upper lobectomy/Chemotherapy**

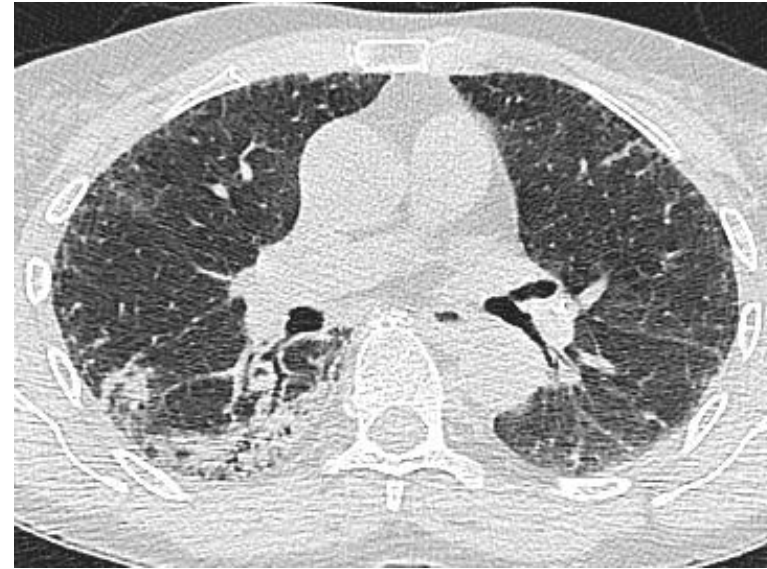
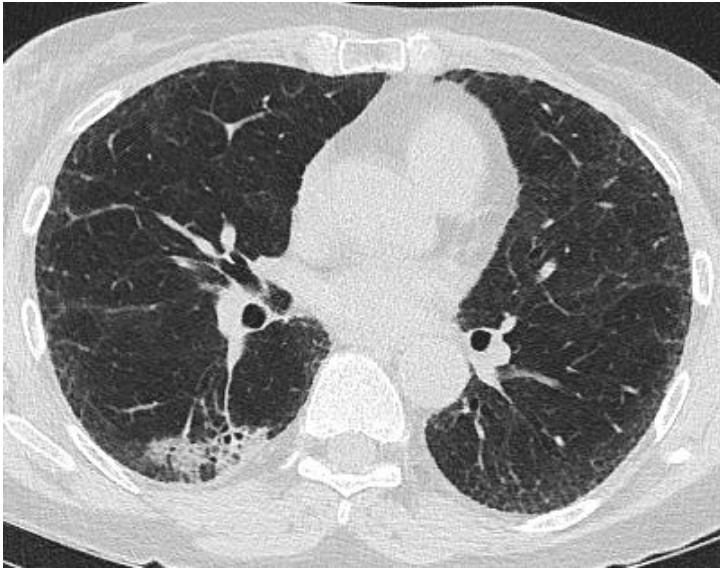


Doubling time 22 Days

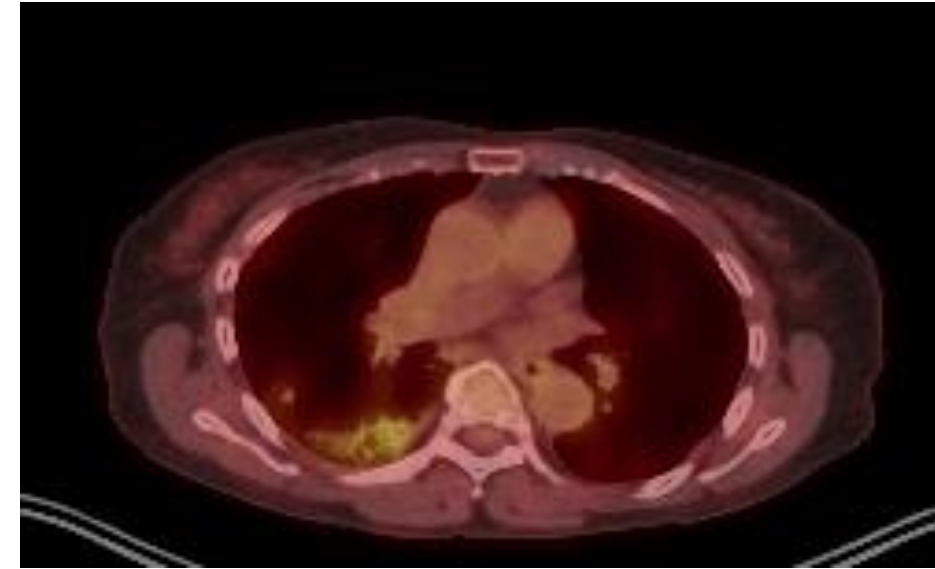


SUV 13.7

## UIP/Mucinous Adenocarcinoma



Doubling time 397 days

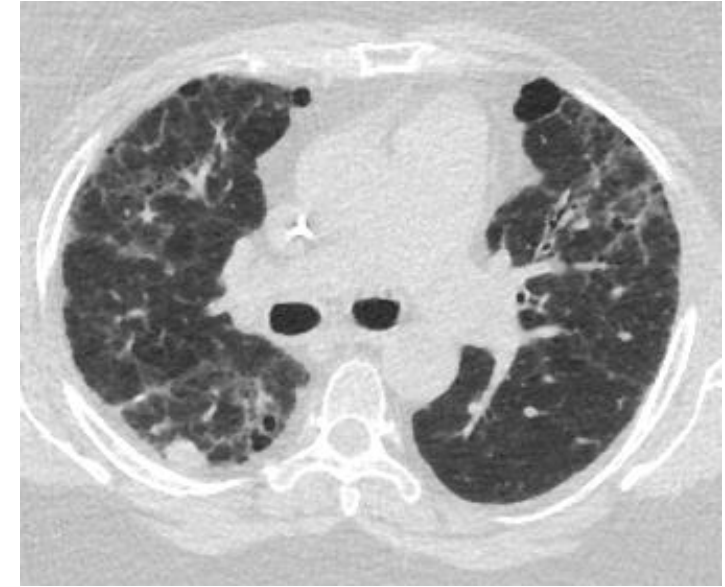


SUV 3.9 and 1.6

Courtesy Mary Salvatore MD



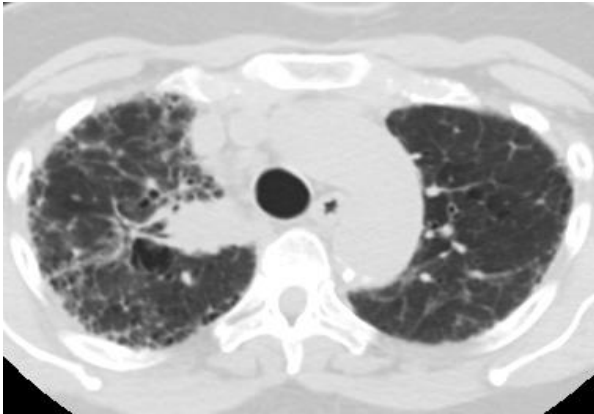
# CHP/Adenocarcinoma Chemotherapy



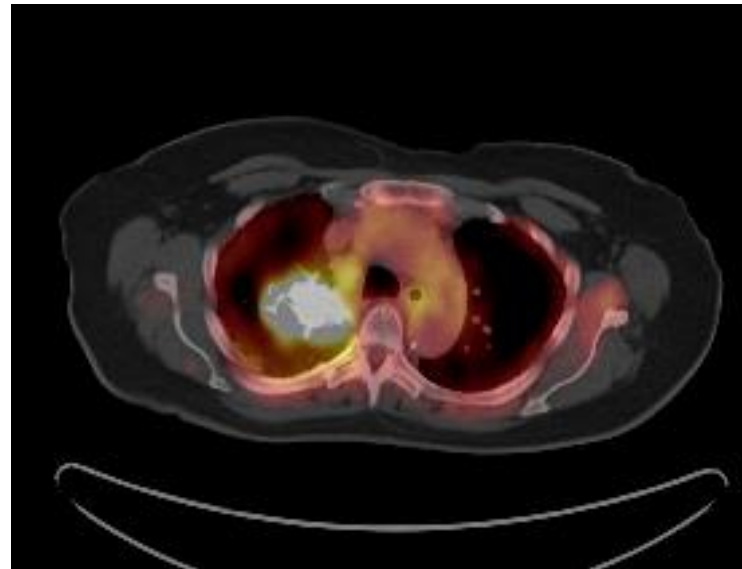
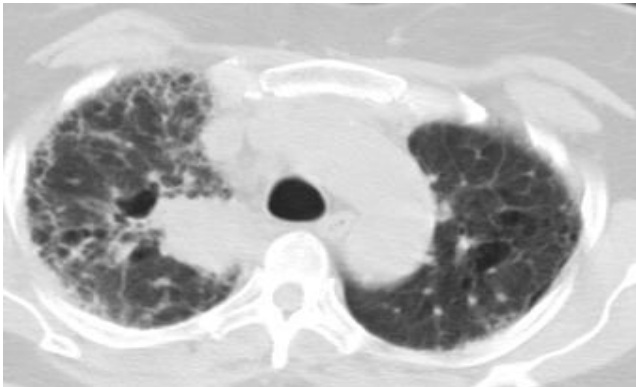


# Lung Cancer

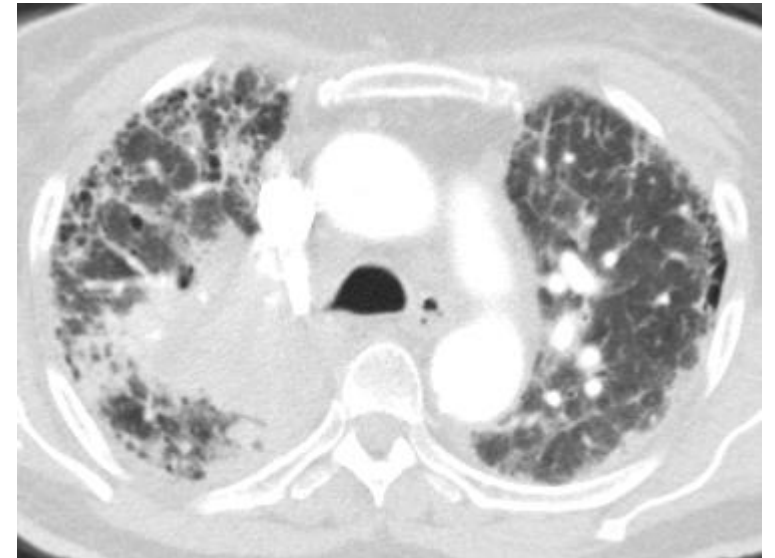
## Chronic Hypersensitivity Pneumonitis



Doubling time 57 Days



SUV 29.7



12 months from dx patient passed away

## Screening for lung cancer in patients with fibrosis

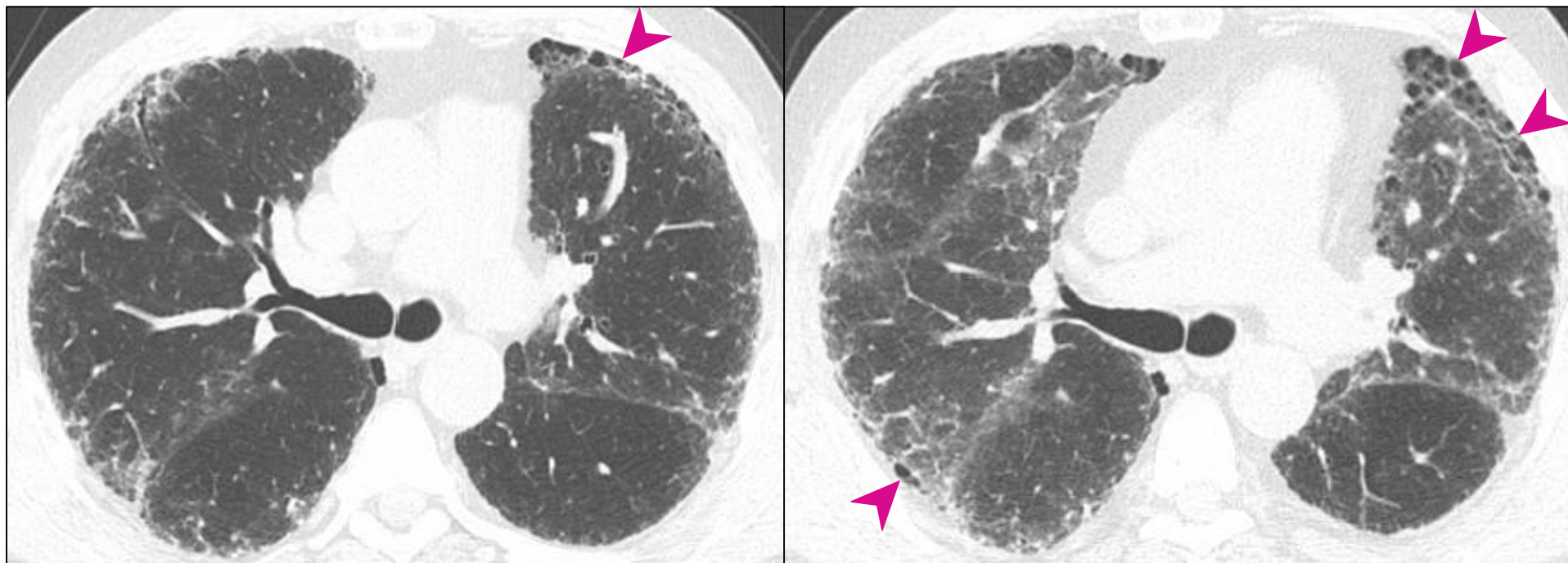
- ▶ HRCT once a year in all patients with IPF.
- ▶ For nodules < 8 mm : close monitoring with HRCT every 3–6 months.
- ▶ For nodules > 8 mm, PET-CT scan is recommended.
- ▶ If PET uptake indicates tumor lesion, recommend biopsy
- ▶ For advanced tumor lesions, consider no further diagnostic procedures and mild therapeutic regimens including palliative care.

Tzouvelekis A, Spagnolo P, Bonella F, et al. Patients with IPF and lung cancer: diagnosis and management. *The Lancet Respiratory Medicine*. 2018; 6(2): 86–88

## Lung Cancer in ILD

- ▶ Can be mistaken for foci of fibrosing lung disease
- ▶ All histologic patterns
- ▶ Atypical locations (peripheral, lower lobes)
- ▶ Rapid doubling time
- ▶ High morbidity and mortality associated with interventions
  
- ▶ ILA's also associated with increased incidence of lung CA

# The Progression of Honeycombing Over Time Can Be Evaluated With HRCT<sup>a</sup>



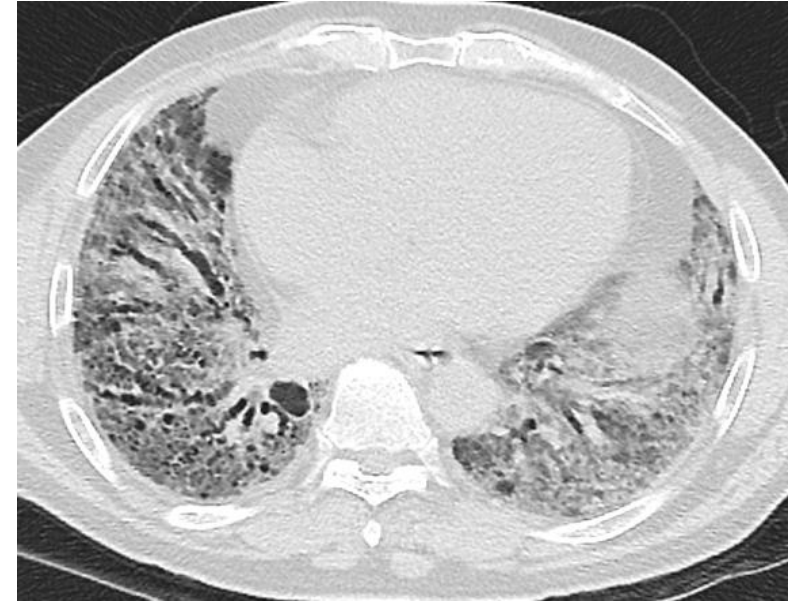
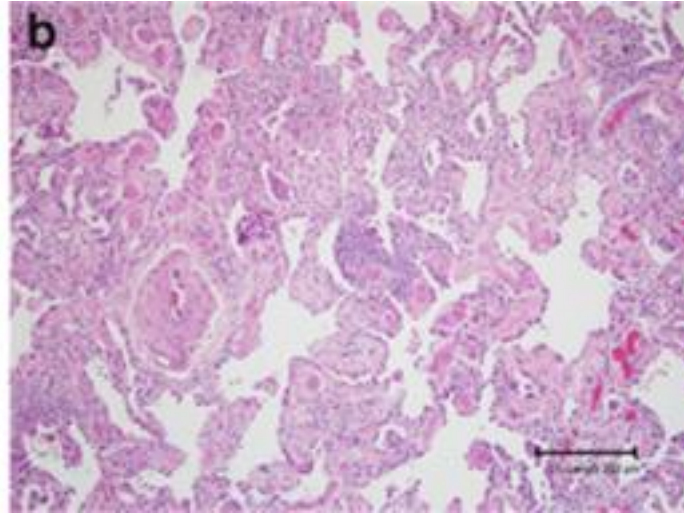
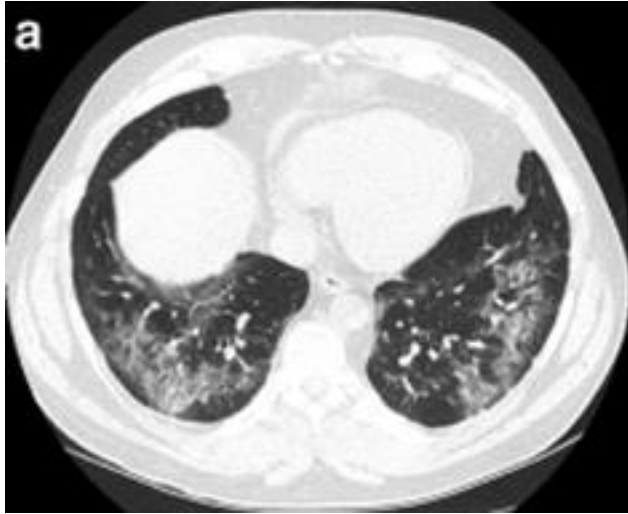
Baseline HRCT of 64-year-old man  
with biopsy-confirmed UIP

Follow-up HRCT 3 years after

Honeycombing ➤

<sup>a</sup>Images, descriptions, and labeling courtesy of David Lynch, MD.  
Raghu et al. *Am J Respir Crit Care Med.* 2011;183:788-824.

# Idiopathic non-specific interstitial pneumonia





# Treatment of ILD/IPF

# Goals of Treatment of IPF

- Slow decline in progression
- Improve Functional Status
- Improve survival
- (4 R's : Reverse, Repair, Retard , Replace)
  
- Does early intervention(before definite UIP/IPF CT Dx) prevent progression of clinical and radiographic IPF and improve survival?
- Does intervention in “early” UIP reverse findings?

# How Early Can We Treat? What is Early ILD Early UIP/IPF?

- Interstitial Lung abnormalities (ILA's)?
- UIP without honeycombing? “Probable” UIP ?
- Absence of or minimal Symptoms
- Subnormal PFT's ?
- Genetic/ Biomarkers profile?



# When Does Imaging Trigger Rx?

- Definite UIP/IPF
  - No argument
  - Clinical trial Support
  - FDA approval
- Probable UIP/IPF
  - Evidence suggests need to treat and documents benefit derived from treatment
  - Radiology/pathology suggests probable UIP is IPF

# When Does Imaging Trigger Rx?

- ILA's: fibrotic and non-fibrotic
  - NO
- Progressive ILA's
  - NO/perhaps, more research needed
- Progressive Fibrotic ILA's - ??????
  - With associated genetics/biomarkers; physiologic impairment, symptoms (increased mortality risk)
  - Longitudinal studies may help define the natural history of subclinical IPF

# When Does Imaging Trigger Rx?

## Non-fibrotic ILA's



**NO**

Most will disappear on repeat imaging or be inflammatory

## Fibrotic ILA's

Figure 3. Prone CT Findings



**NO**...But in at risk patient may elucidate IPF pathogenesis

# When Does Imaging Trigger Rx?

**UIP/IPF**



**YES**

**Probable UIP**



**Yes**

In appropriate setting

# Early Diagnosis

- Radiology-HRCT
  - Possible UIP, reticulations, traction bronchiectasis and NO honeycombing
  - Interstitial lung abnormalities (incidentally detected) in combination with genetic and biomarkers shedding light in the preclinical stages of pulmonary fibrosis
  - Application of Novel technology to measure tissue density and fibrosis (computerized algorithms)

# Evolving Pulmonary Fibrosis : Conclusions

- PF associated with major co-morbidities and increased mortality
- Knowledge and understanding of disease is evolving
- Early and precise diagnosis is critical to intervention and improved survival
- Therapeutic modalities are available for established disease
- ILA's may represent earliest manifestation of ILD /and are associated with increased morbidity and mortality
- HRCT imaging is essential to Dx ILD. ILA's need to be reported
- Use of new modalities for Dx of fibrosis on imaging and biomarker profile will identify earlier Dx of ILD/PF which may benefit from treatment/intervention

# Evolution of Pulmonary Fibrosis: ILA's to UIP and Everything in Between

- Thank You

# Interstitial Abnormalities

- ▶ Incidental Non-dependent abnormalities affecting more than 5% of any lung zone
- ▶ Seen on CT Scans of 4-9% of smokers
- ▶ Features may include: groundglass or reticulation, traction bronchiectasis, honeycombing, non-emphysematous cysts
- ▶ Most recent Fleischner statement excludes centrilobular nodules (typically RB-ILD)



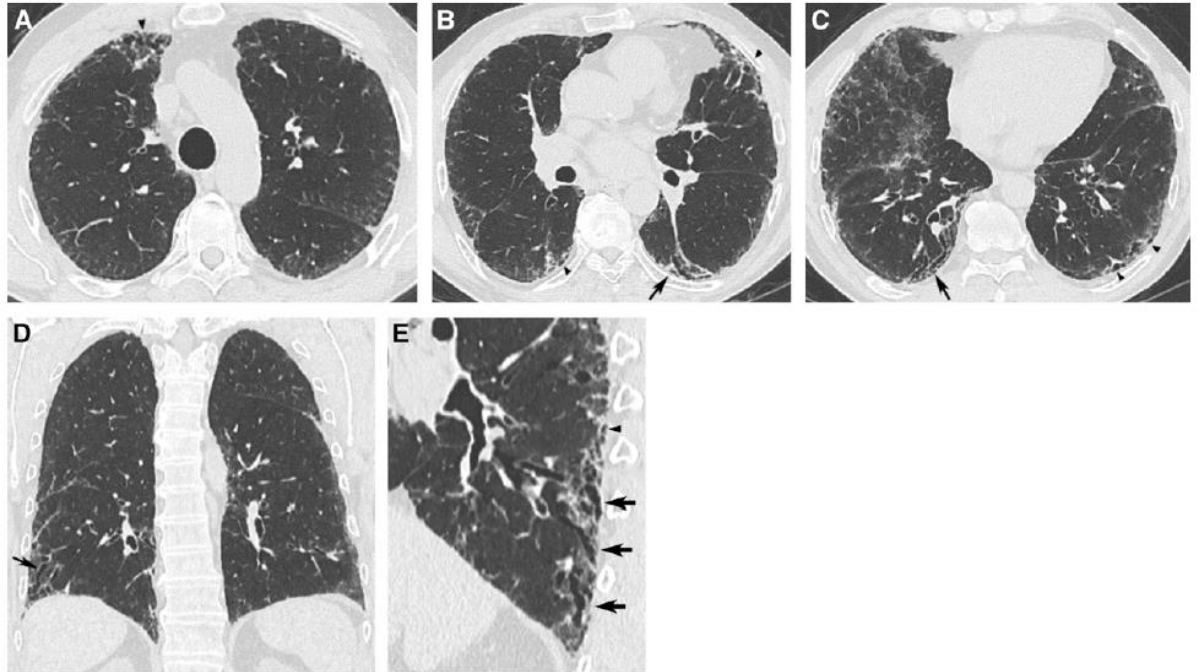
# Interstitial Lung Abnormalities (ILA's)

- Incidental detection of non-dependent findings on CT scans obtained for screening of other conditions (lung cancer, CAD, COPD, F-ILD)
- Definition of abnormalities(GGO, reticulations, traction bronchiectasis, honeycombing, nonemphysematous cysts) involving at least 5% of lung
- Sequential studies at varying intervals
- Correlation with genetics/biomarkers, physiology and survival



# Probable UIP Pattern

- Subpleural and basal predominant
- Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis
- May have mild GGO
- (No Honeycombing)



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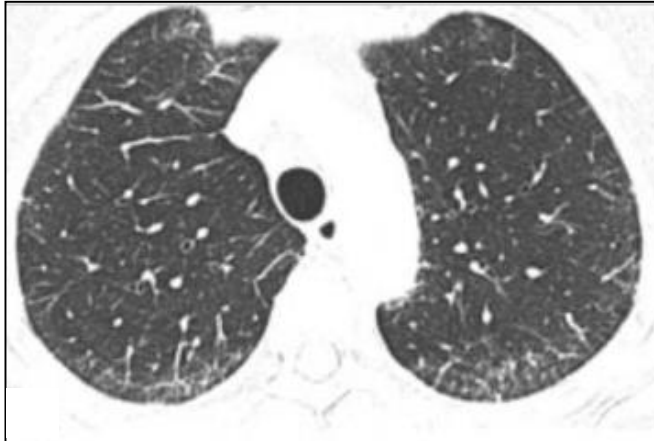
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## *Nonspecific Interstitial Pneumonia (NSIP)*

Upper



Mid



Lower



- ▶ HRCT images show a typical pattern of fibrotic NSIP:
  - Subpleural and basilar predominance of abnormalities
  - Irregular reticulation
  - Traction bronchiectasis