Idiopathic Pulmonary Fibrosis Diagnosis & Treatment

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Disclosure Information

- I have the following financial relationships to disclose:
  Consultant for: Boehringer Ingelheim, Roche/
  Genentech, Veracyte, Biogen, Gilead,
  Pharmakea, Aeolus
  Speaker's Bureau for: None
  Grant/Research Support from: Afferent, Boehringer
  Ingelheim, Roche/Genentech
  Stockholder in: None
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  Employee of: None
- I will not discuss off label use or investigational use in my presentation.

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Speaker Name/Email Address

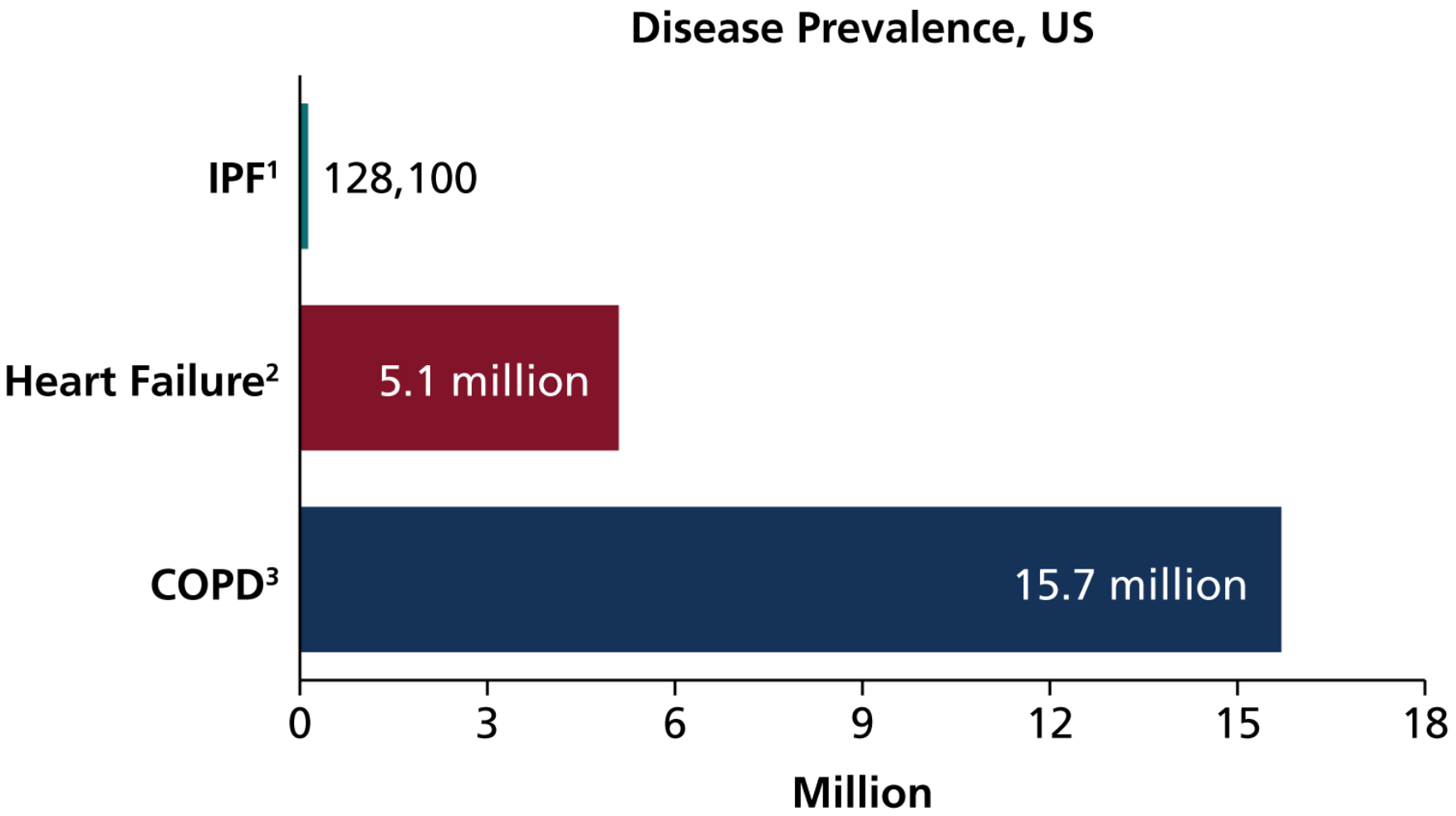
Outline & Objectives

- Understand the classification and diagnosis of Interstitial Lung Diseases and IPF
- Recognize typical patterns of disease on HRCT
- Discuss the potential benefits and adverse reactions of approved therapies for IPF

Interstitial Lung Diseases - Difficulties

- Diverse group of disorders (130+)
- Similar symptoms, physiology, radiology
- Difficult nomenclature
- Limited, often toxic, treatments

Distinguishing Dyspnea: IPF Prevalence



COPD: chronic obstructive pulmonary disease; IPF: idiopathic pulmonary fibrosis.

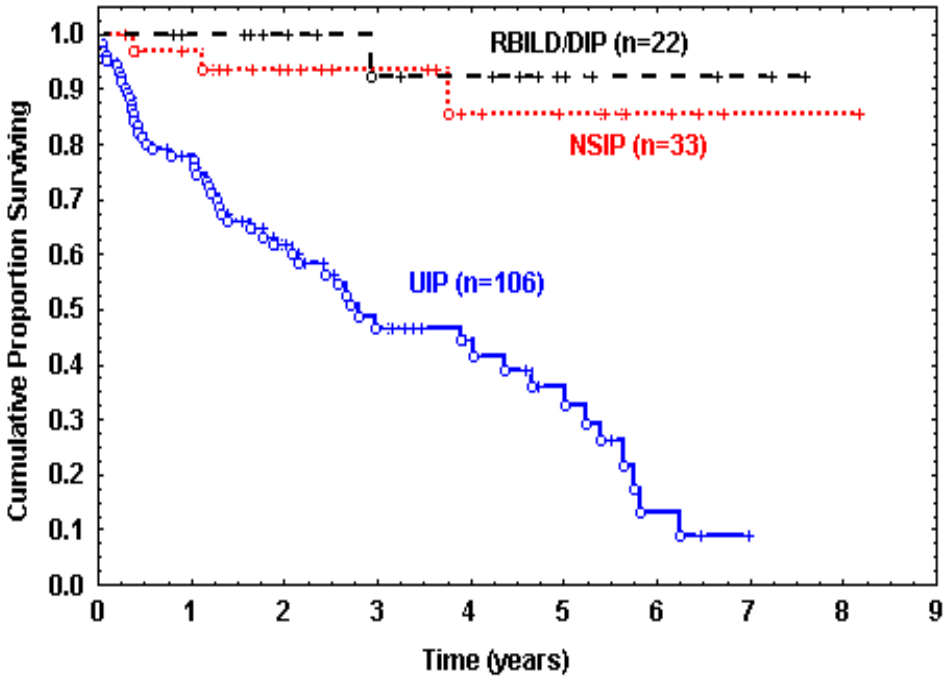
1. Raghu G et al. *Resp Crit Care Med.* 2006;174:810-816. 2. Go AS et al. *Circulation*. 2013;127:e6-e245.
3. Wheaton AG et al. *MMWR Morb Mortal Wkly Rep*. 2015;64:289-295.

Diffuse Parenchymal Lung Disease (DPLD)

- DPLD of known cause, eg, drugs or association, eg, collagen vascular disease
- Idiopathic Interstitial Pneumonias
  - Major
    - **Idiopathic Pulmonary Fibrosis**
    - Nonspecific interstitial pneumonia (idiopathic)
    - Acute Interstitial Pneumonia
    - Respiratory bronchiolitis interstitial lung disease
    - Desquamative Interstitial Pneumonia
    - Cryptogenic Organizing Pneumonia
  - Rare
    - Lymphoid Interstitial Pneumonia
    - Pleuroparenchymal Fibroelastosis
  - Unclassifiable
- Granulomatous DPLD, eg, sarcoidosis
- Other forms of DPLD, eg, LAM, HX, etc

ATS/ERS Consensus Statement. *Am J Respir Crit Care Med.* 2002;165:277-304
Travis et al., *Am J Resp Crit Care Med* 2013; 188(6):733-48

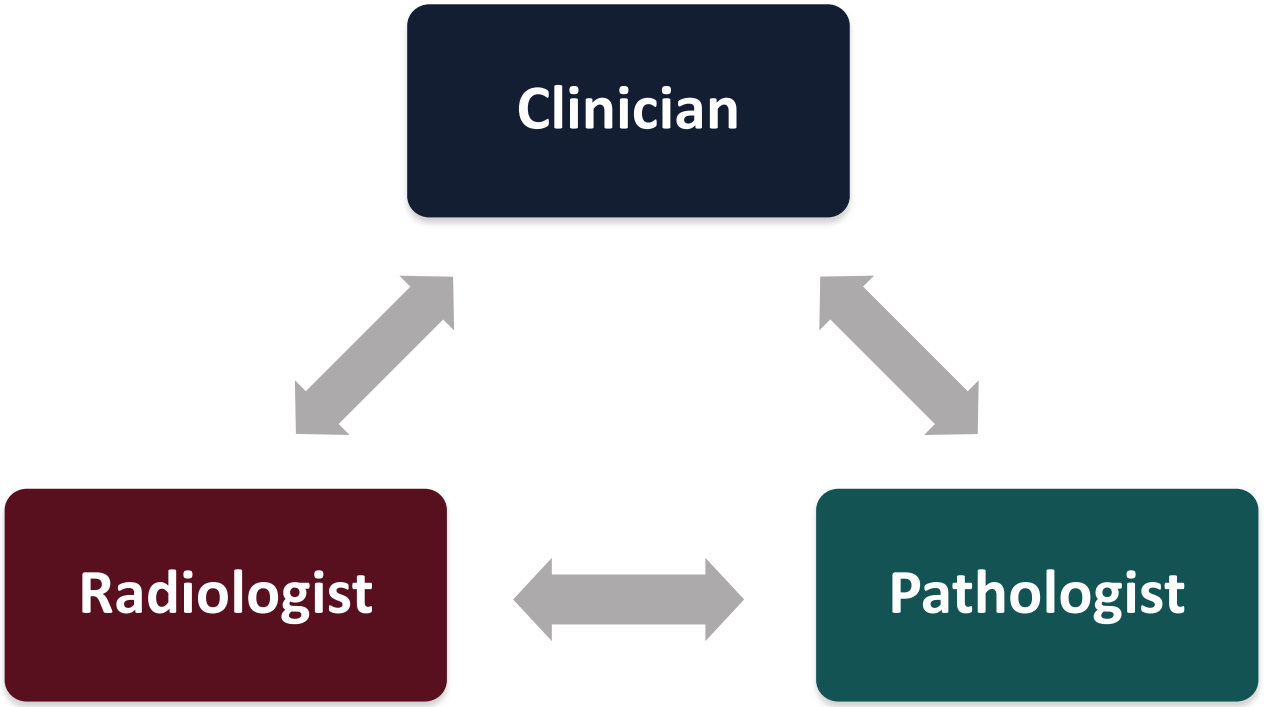
Diagnosis Matters!
IPF/UIP confers a poor prognosis



Parameter	HR (95% CI)
IPF diagnosis	28.46 (5.5, 147)
Age	0.99 (0.95, 1.03)
Female sex	0.31 (0.13, 0.72)
Smoker	0.30 (0.13, 0.72)
Physio CRP	1.06 (1.01, 1.11)
Onset Sx (yrs)	1.02 (0.93, 1.12)
CTfib score $\geq$2	0.77 (0.29, 2.04)

Flaherty et al. *Eur Respir J*. 2002;19:275-283.

Interstitial Lung Disease Diagnostic Team



Communication among multidisciplinary team members is essential for an accurate diagnosis

Clinical Tools for Diagnosis

Clinical

- History and physical
- PFT
- Lab

- Raise suspicion that ILD is present
- Identify the cause of the disease
  - Infection
  - Systemic disorders
  - Exposures (eg, occupational, environment, hobby)
  - Idiopathic

Radiographic Tools for Diagnosis

Radiographic

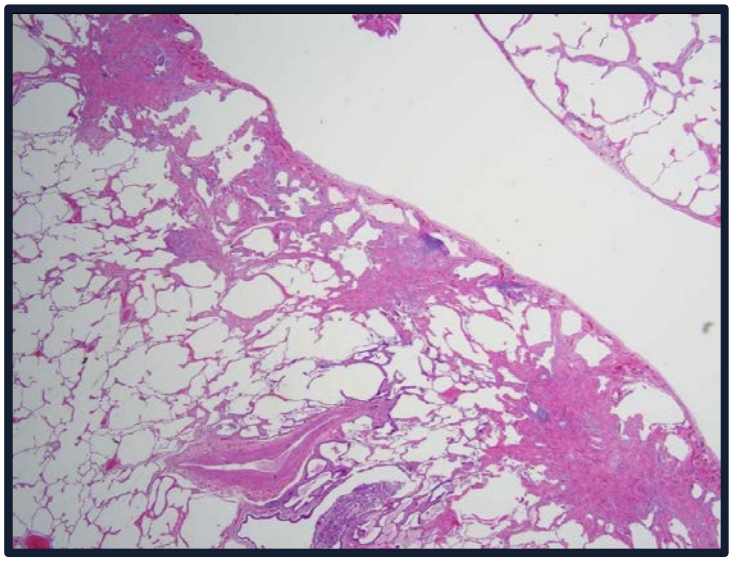
HRCT: allows detailed evaluation of the lung parenchyma

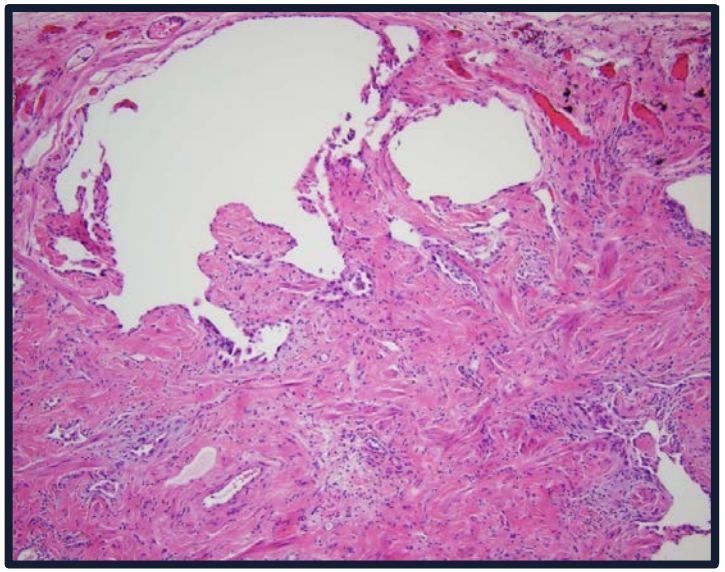
HRCT Features	HRCT Distribution
• Ground glass attenuation • Honeycombing/cysts • Lines/reticular thickening • Consolidation • Nodules • Decreased lung attenuation	• Upper • Lower • Central • Peripheral • Diffuse/bilateral

Histologic Tools for Diagnosis

Histology

- Bronchoscopy
- Surgical lung biopsy





UIP Pattern

- Marked fibrosis/architectural distortion ± honeycombing, predominantly subpleural/paraseptal
- Patchy fibrosis
- Fibroblastic foci
- Absence of features to suggest alternative diagnosis

1. Images courtesy of Steven Nathan, MD.
2. Raghu G et al. *Am J Respir Crit Care Med*. 2011;183:788-824.

Putting the Pattern in Context

Usual Interstitial Pneumonia (UIP)

Idiopathic Pulmonary Fibrosis (IPF)

Rheumatoid Lung

Chronic Exposures
-Hypersensitivity pneumonia
-Occupational

Nonspecific Interstitial Pneumonia (NSIP)

Idiopathic

-Connective Tissue Disease
- Hypersensitivity Pneumonia

Organizing Pneumonia

Idiopathic
COP/BOOP

OP due to:
- a very long list….

Causes of OP

Table 1. Causes of SOP

- Associated with connective tissue disorders
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Sjogren syndrome
  - Polymyositis-dermatomyositis
  - Polymyalgia rheumatica
  - Systemic sclerosis
  - Behcet's disease
  - Ankylosing spondylitis
  - Mixed connective tissue disease
- Associated with immunological disorders
  - Common variable immunodeficiency syndrome
  - Essential mixed cryoglobulinemia
- Associated with infectious disease
  - Bacterial
    - Streptococcus pneumoniae
    - Legionella pneumophila
    - Mycoplasma pneumoniae
    - Coxiella burnetti
    - Nocardia asteroides
    - Chlamydia pneumoniae
    - Staphylococcus aureus
  - Viral
    - Adenovirus
    - Cytomegalovirus
    - Influenza and parainfluenza
    - Human immunodeficiency virus
    - Herpes virus
  - Fungal
    - Cryptococcus neoformans
    - Pneumocystis jiroveci
  - Parasites
    - Plasmodium vivax
- Associated with aspiration pneumonia
- Associated with radiation therapy for breast cancer
- Associated with organ transplantation
  - Bone marrow
  - Lung
  - Renal
  - Liver
- Drug-related (see Table 2)
- Miscellaneous
  - Inflammatory bowel disease
  - Primary biliary cirrhosis
  - Polyarteritis nodosa
  - Chronic thyroiditis
  - Hematological malignancies (myelodysplastic syndrome, T-cell leukemia, lymphoma)
  - Coronary artery bypass graft surgery
  - Environmental exposure (textile printing dye, house fire, cocaine abuse)
  - Sweet's syndrome

Table 2. Drug-Associated OP

Most common:
Amiodarone, bleomycin, carbamazepine, interferon-a, -b, gold salts

Less common:
Acebutolol, doxorubicin, mesalamine, sulphasalazine, nitrofurantoin, sirolimus

Rare:
Amphotericin B, bucillamine, busulfan, chlorambucil, cefradin, erlotinib, fluvastatin, L-tryptophan, minocycline, nilutamide, phenytoin, risedronate, rituximab, tacrolimus, temozolomide, thalidomide, ticlopidine, trastuzumab, vinbarbital

Adapted from Pneumotox (www.pneumotox.com).

Drakopanagiotakis et al, *Am J Med Sci* 2008;335:34-9

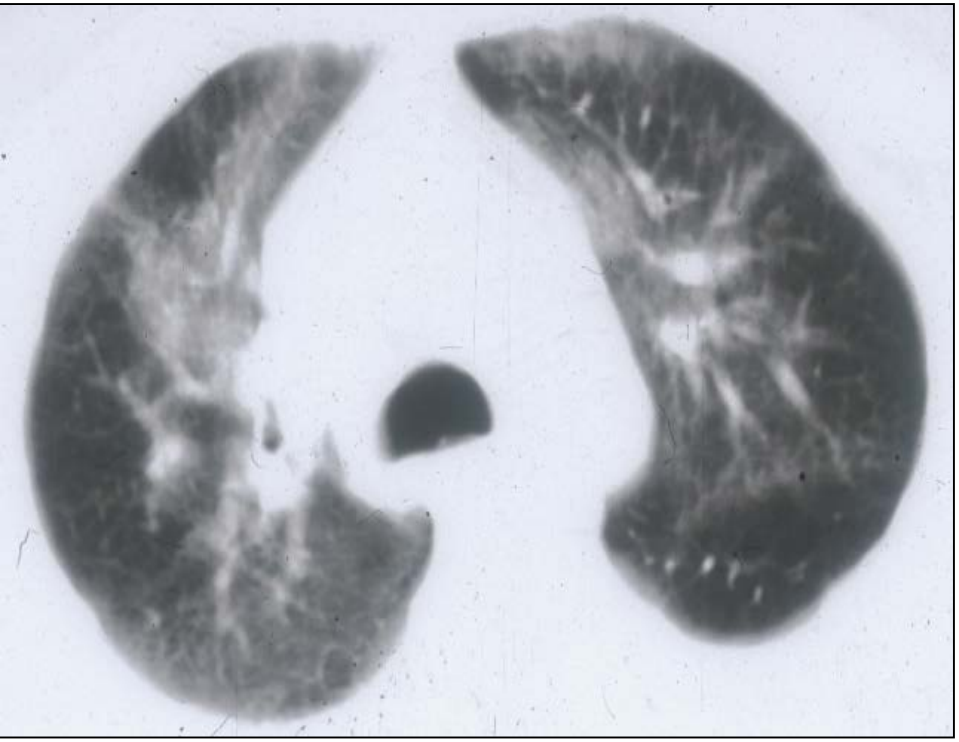
High Resolution Computed Tomography

- Does NOT use contrast
- Thin collimation
  - HRCT, approximately 1mm slice thickness
  - MDCT (contiguous slices) preferred
    - Close tracking of subtle parenchymal and airway abnormalities
    - Avoids missing small/subtle abnormalities
- Should use Low Dose (~80 mA)
- Reconstruction with specific Windows
- Inspiration, Expiration, and prone images

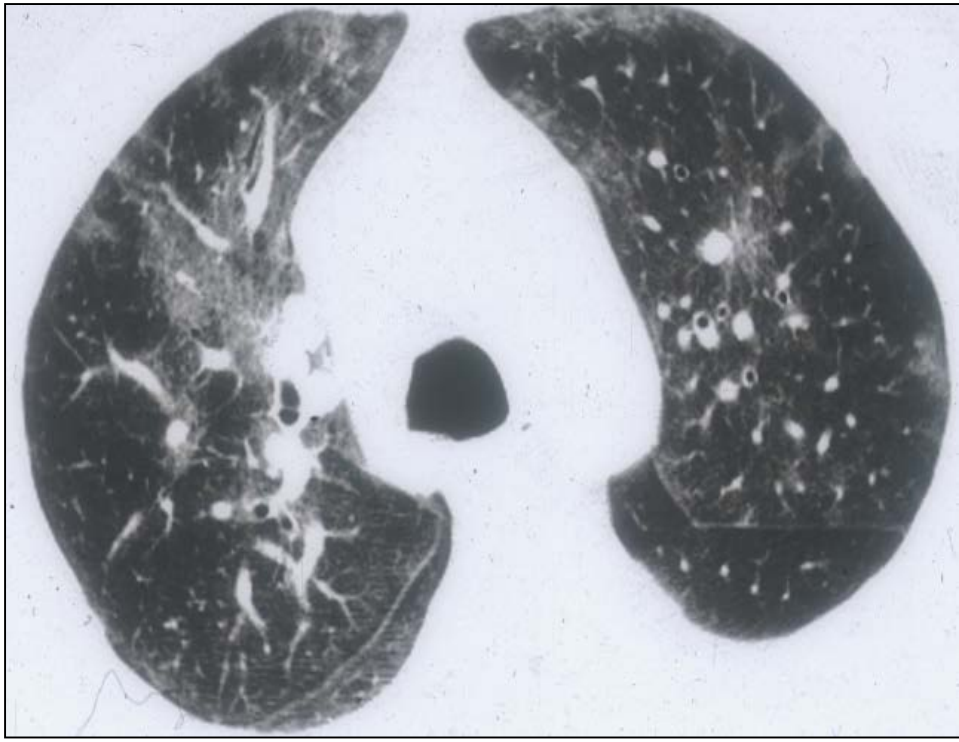
High Resolution Computed Tomography

- Examines the entire lungs
  - Avoids sampling error (like surgical biopsy)
  - Can visualize mixed disease patterns
- Expiratory images add physiologic element
- Key Limitation is resolution
  - Ground Glass may be inflammation, fibrosis, infection, water, blood, etc.
  - Microscopic honeycomb change
  - Histopathologic features

Impact of Thickness & Algorithm



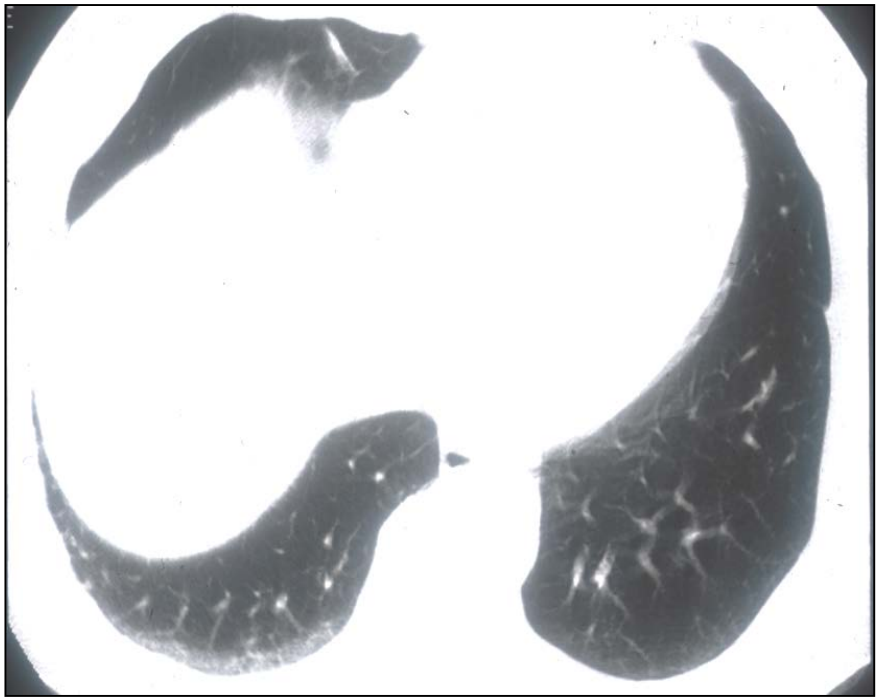
CT
10-mm
standard algorithm

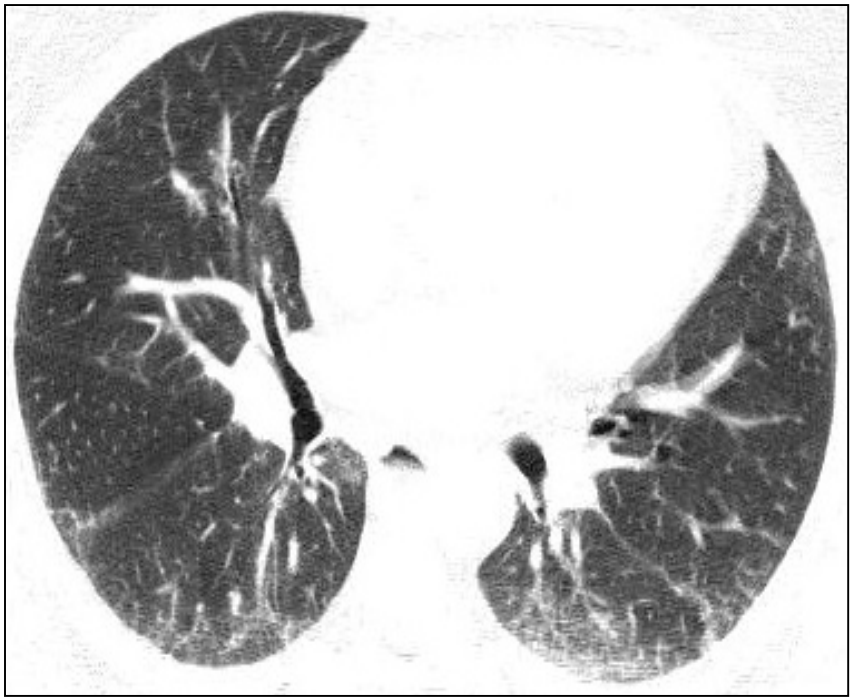


HRCT
1.5-mm
high resolution algorithm

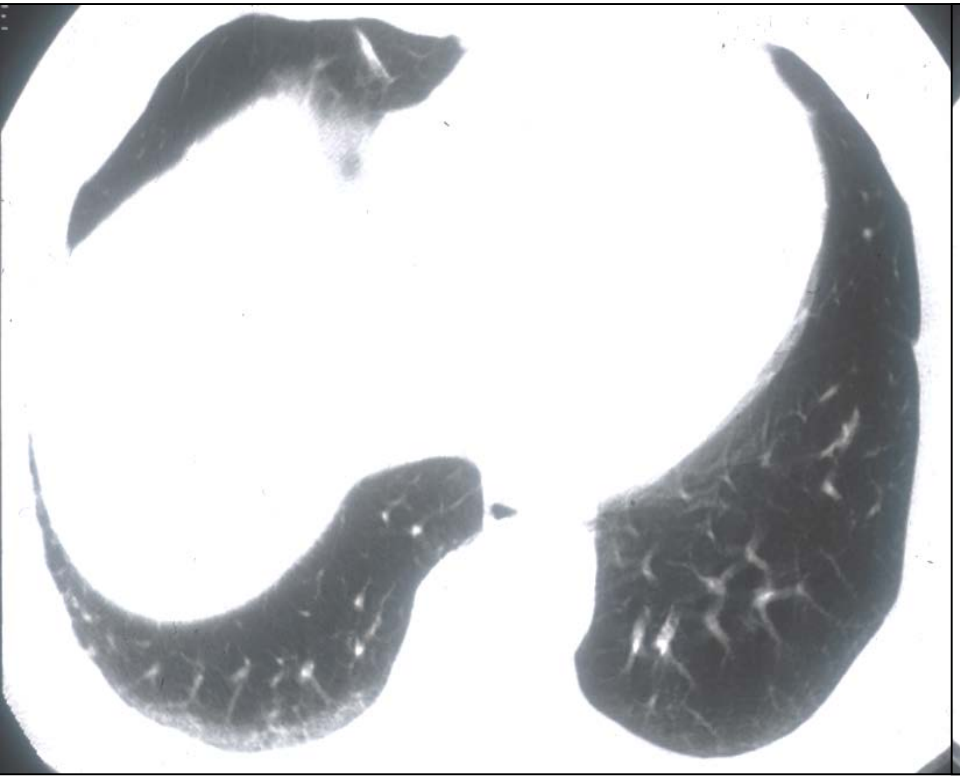
HRCT Pitfalls

- Dependent atelectasis mimics ground glass opacity
  - More common in smokers and with increased age
  - Always do prone images

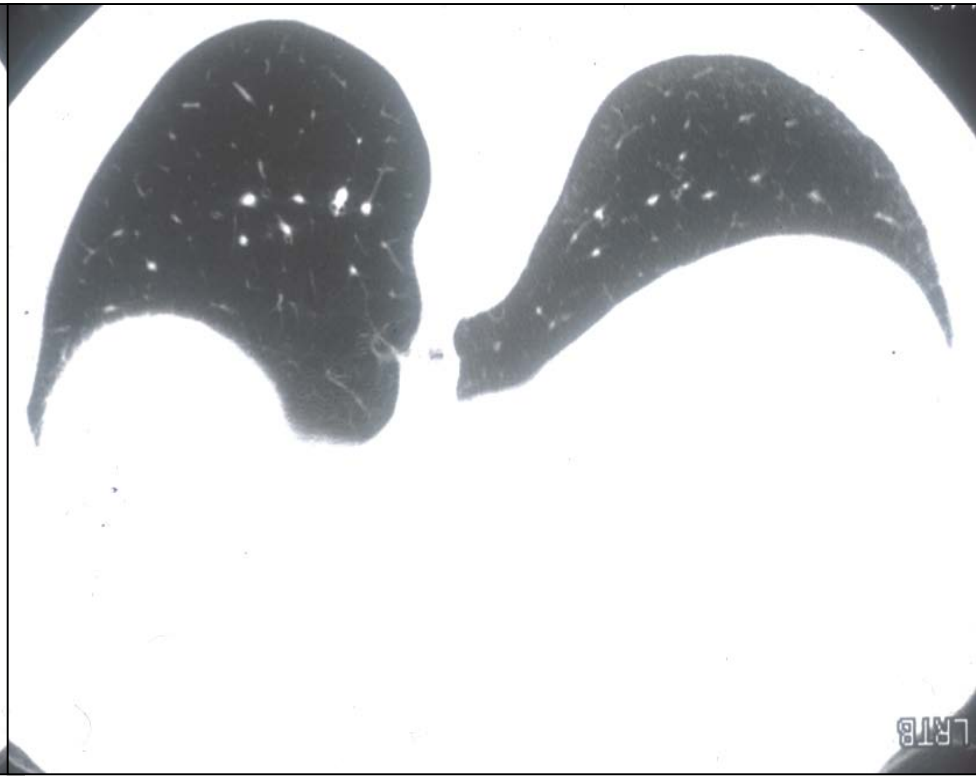




Dependent Opacity: Normal

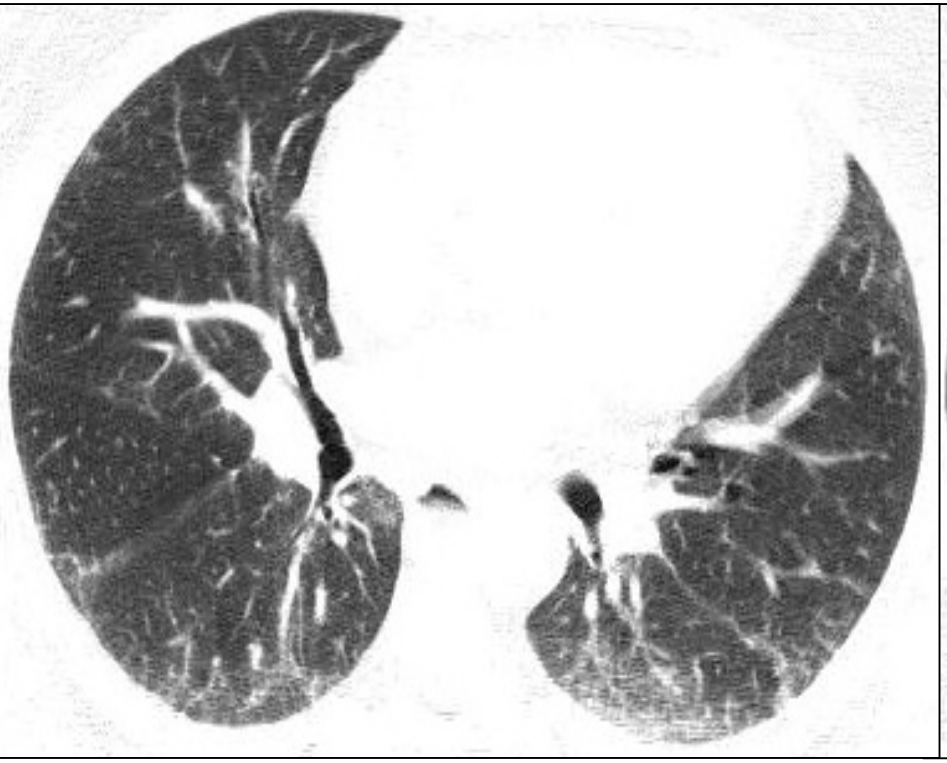


supine



prone

Dependent Opacity: Disease



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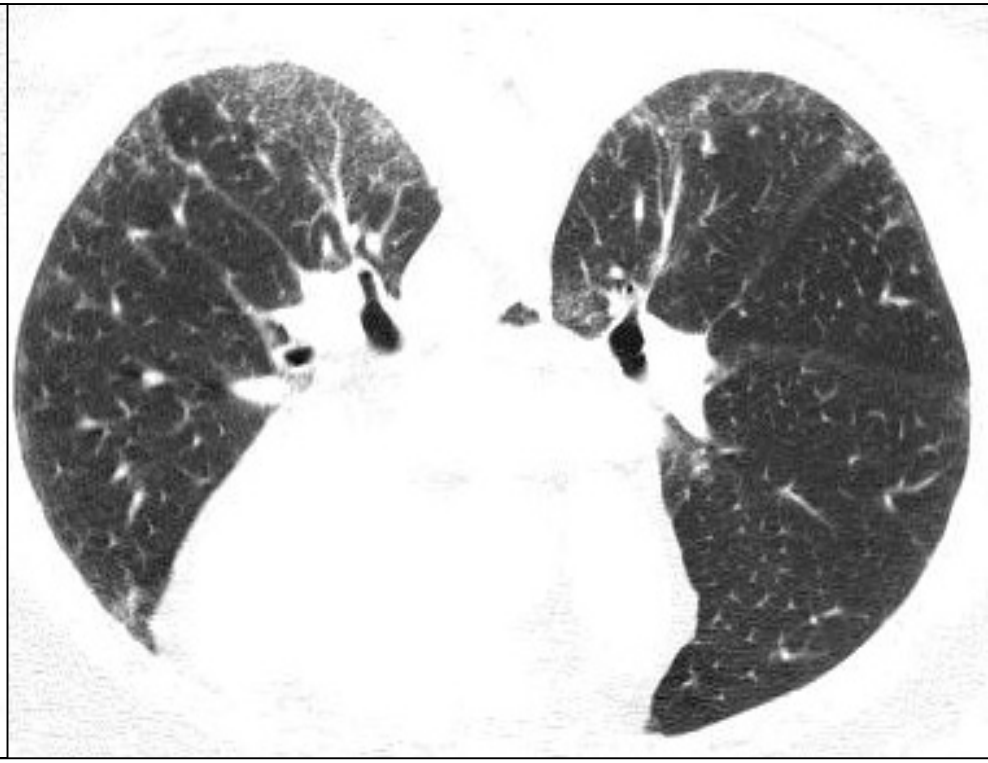

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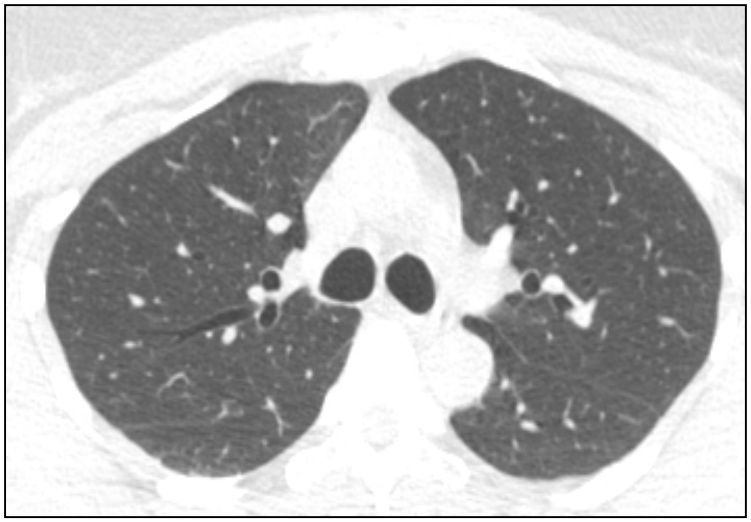
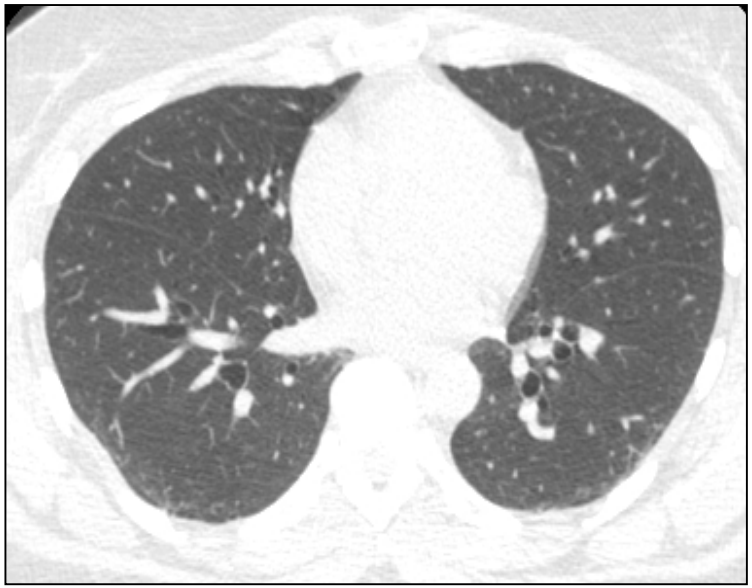
Normal HRCT

- Clear 1 cm periphery
- Few interlobular septa
- Should see no airways in the peripheral 1/3 of the lungs; bronchioles not visible
- Dependent opacity

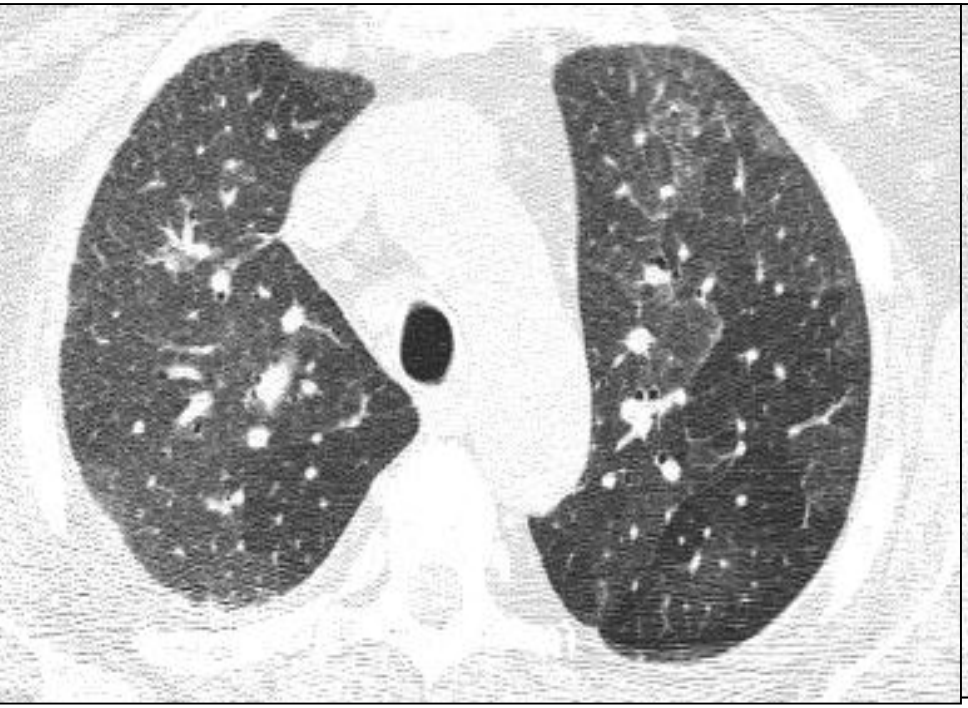




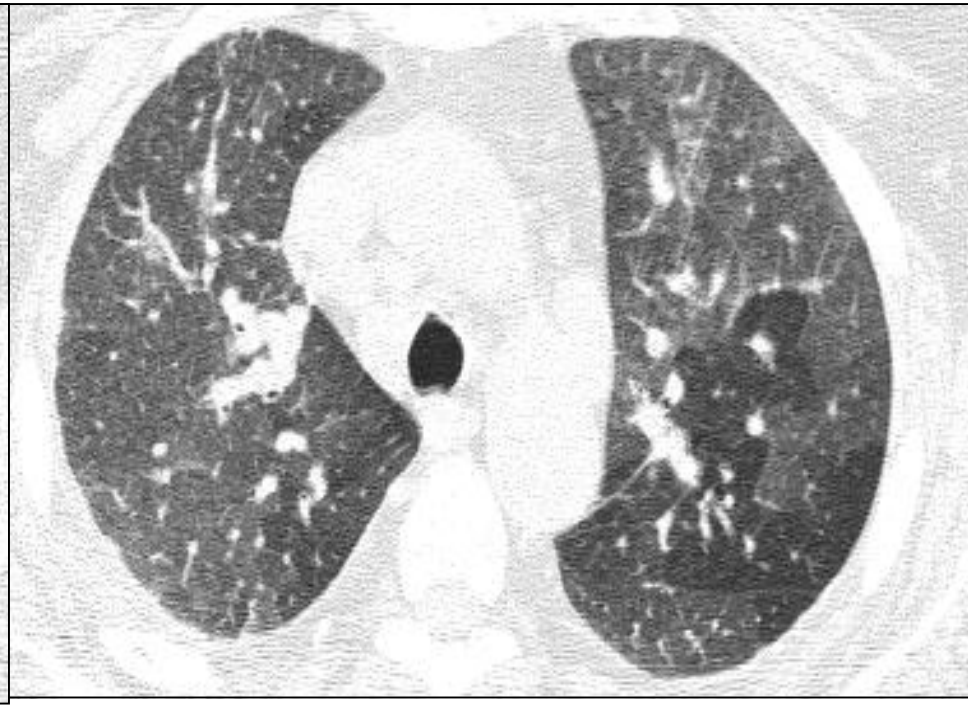
Mosaic Attenuation
(aka mosaic perfusion)

- wedge-shaped areas of alternating attenuation
- altered perfusion
  - » pulmonary emboli
- altered ventilation
  - » air-trapping
  - » small airway disease
- patchy ground glass (ILD)

Inspiratory/ Expiratory HRCT

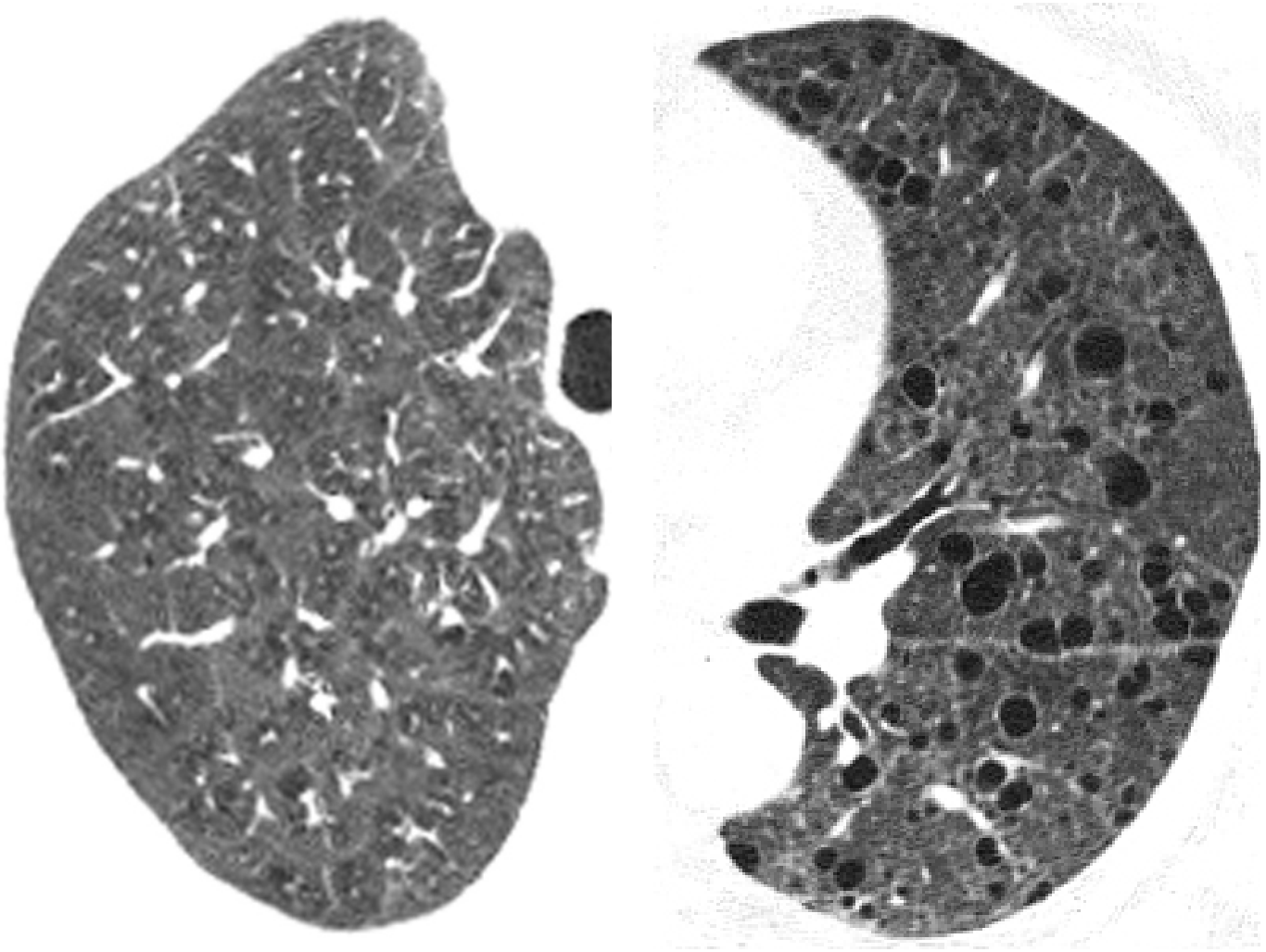


inspiration



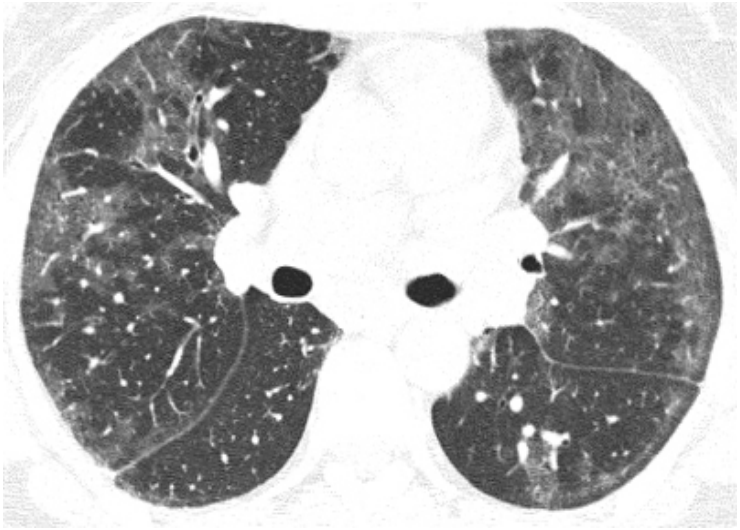
expiration

Emphysema vs. Cyst



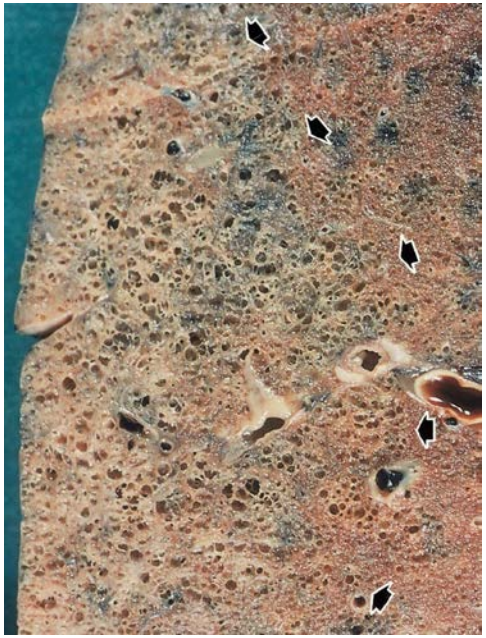
Ground Glass

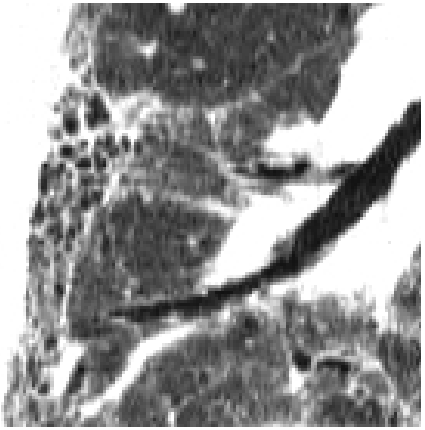
- Hazy opacity you can see through
  - Less opaque than consolidtion
  - Able to see bronchial & vascular markings
- Partial filling of airspaces
  - Fluid (water, blood)
  - Infection
  - Fibrosis



Honeycombing

- Clustered cystic air spaces
- Well – defined walls
- Usually comparable diameter (3-10mm)
- Usually subpleural
- Can be confused with traction bronciectasis





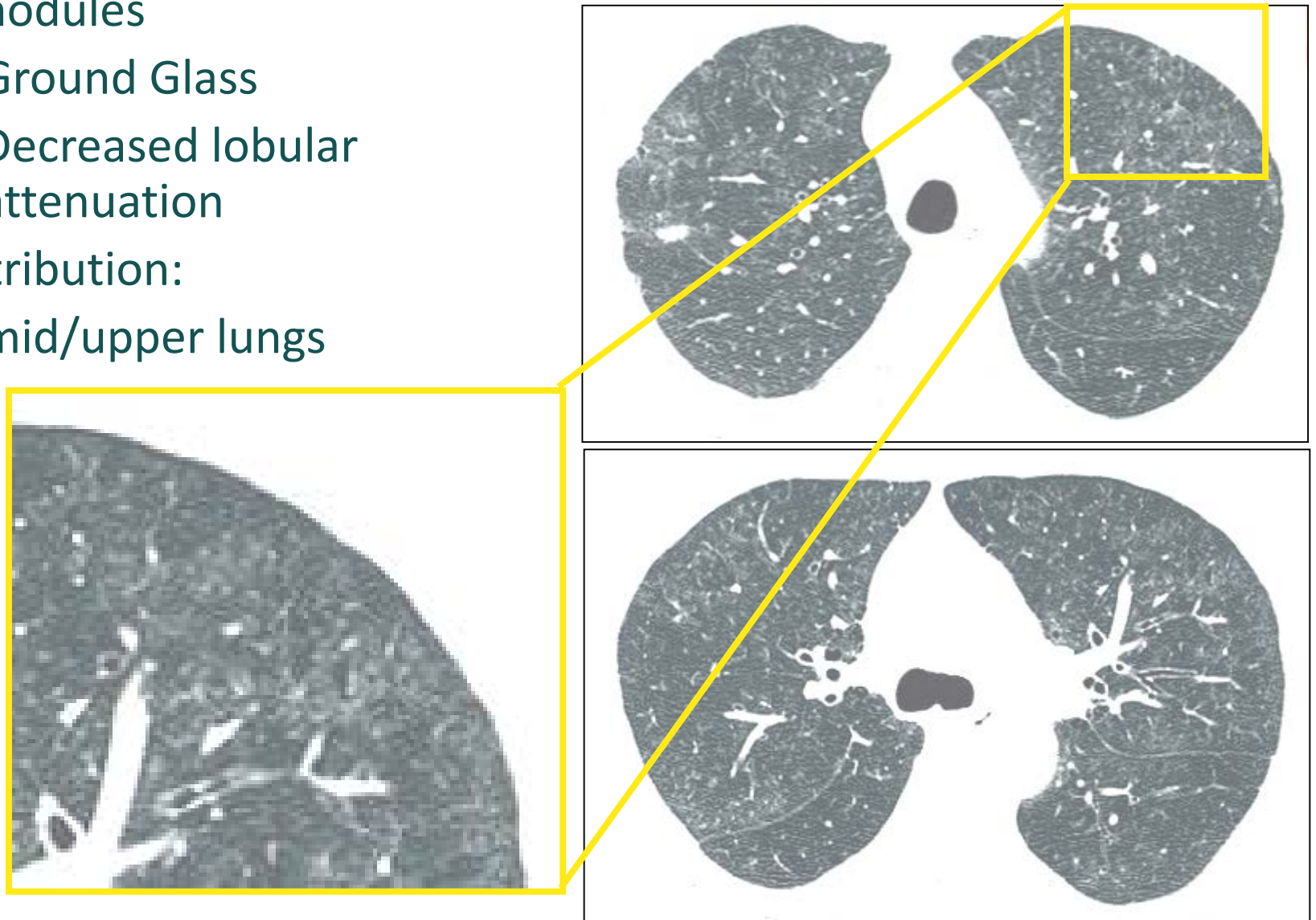
Respiratory Bronchiolitis / ILD

Pattern:

- Ill defined centrilobular nodules
- Ground Glass
- Decreased lobular attenuation

Distribution:

- mid/upper lungs



Langerhans Histiocytosis (aka EG)

Pattern:

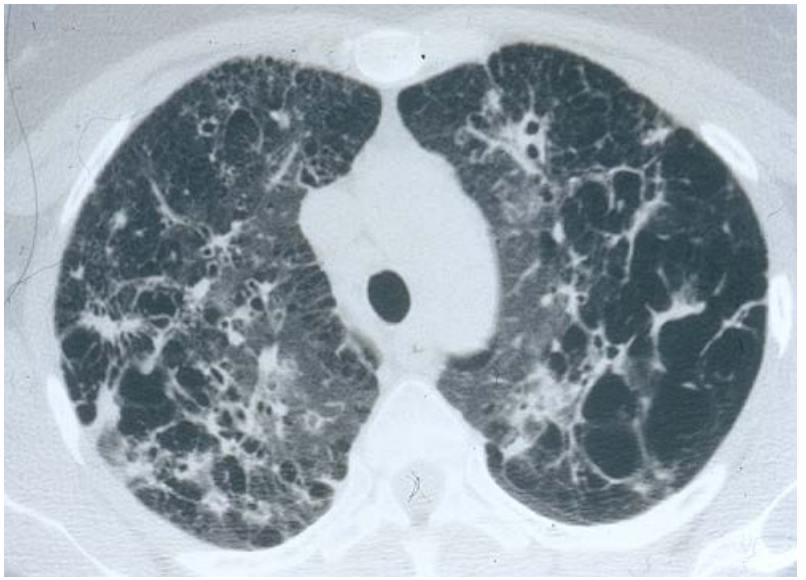
- Numerous cysts (often bizarre shapes
- Peribronchiolar nodules
- Interstitial changes/scar

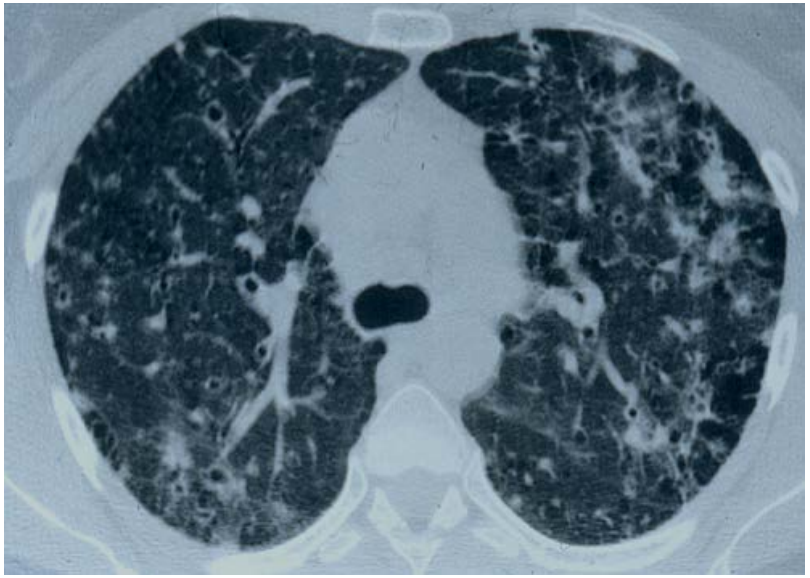
Distribution:

- Upper lobe

Progression:

- Nodules → cavitary nodules → cysts → confluent cysts





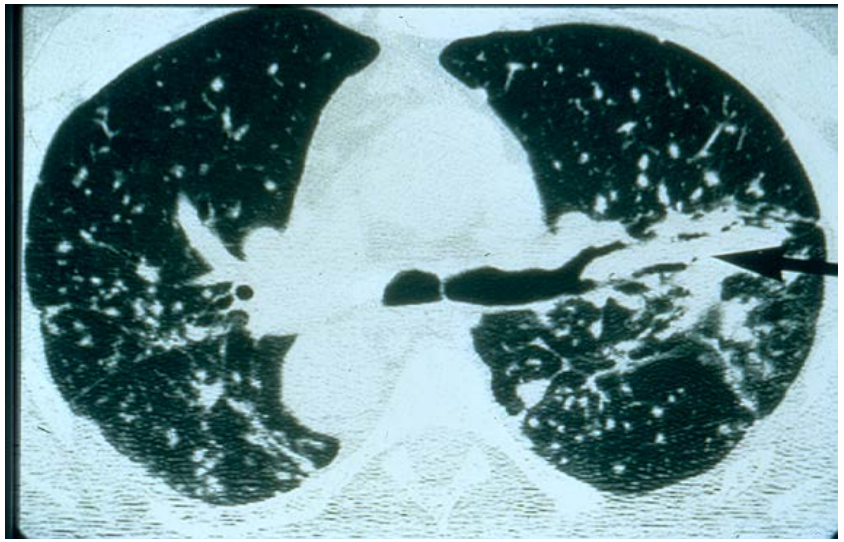
Sarcoidosis

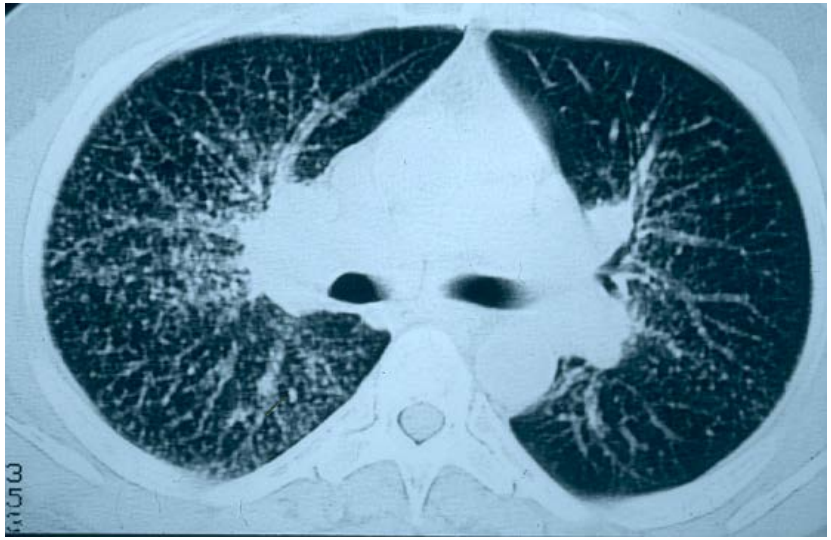
Pattern:

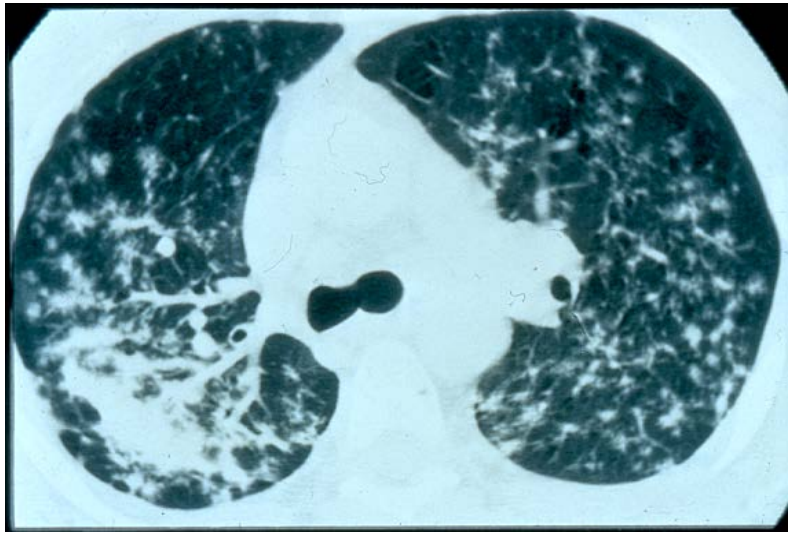
- Nodules
- Confluent alveolar spaces
- Distortion, fibrosis, cysts

Distribution:

- Upper lobe
- Central/bronchovascular







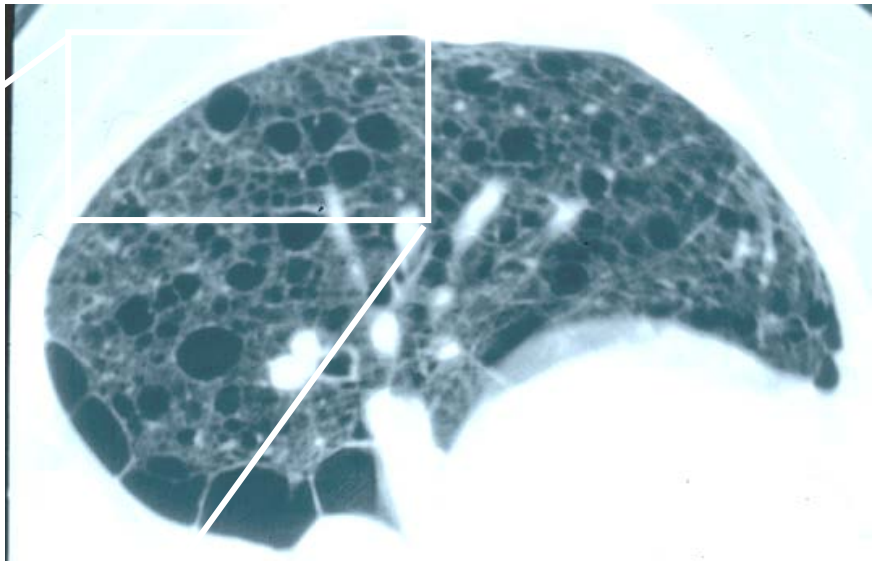
Lymphangioleiomyomatosis

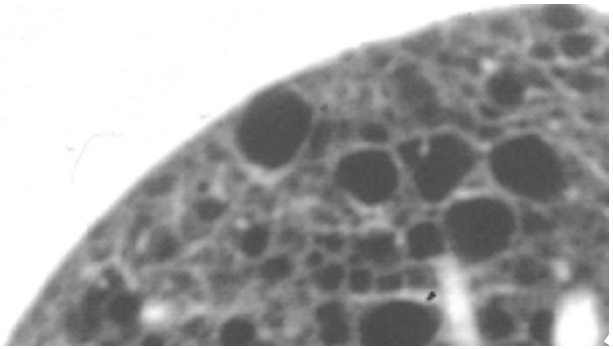
Pattern:

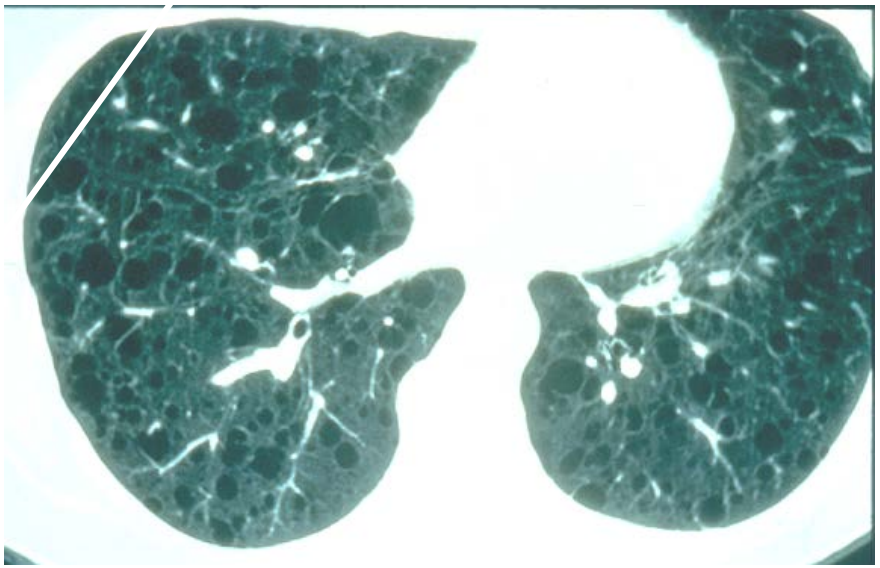
- Numerous thin-walled cysts
- No nodules or fibrosis

Distribution:

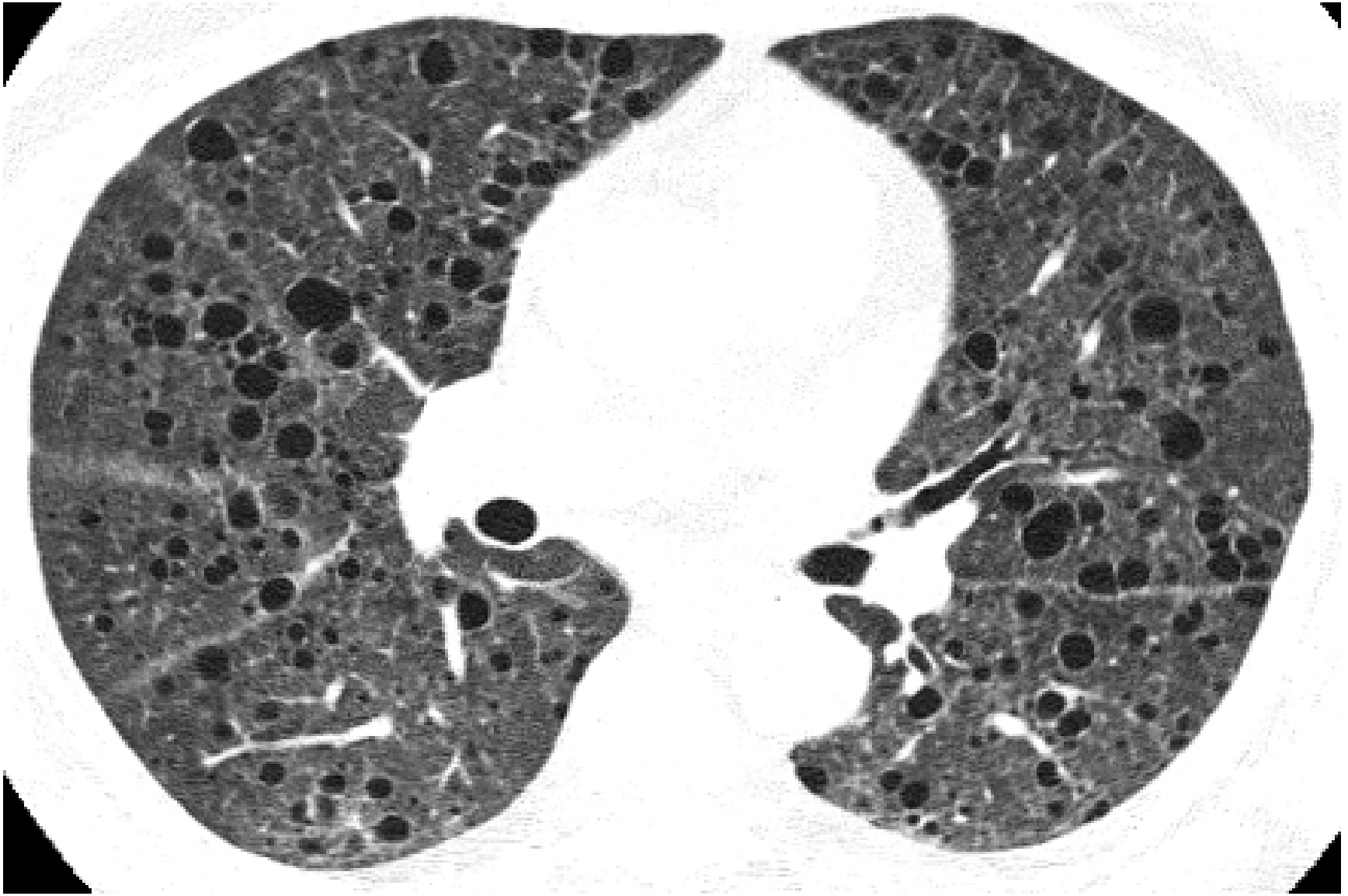
- Diffuse, no predominance







Lymphangioleiomyomatosis



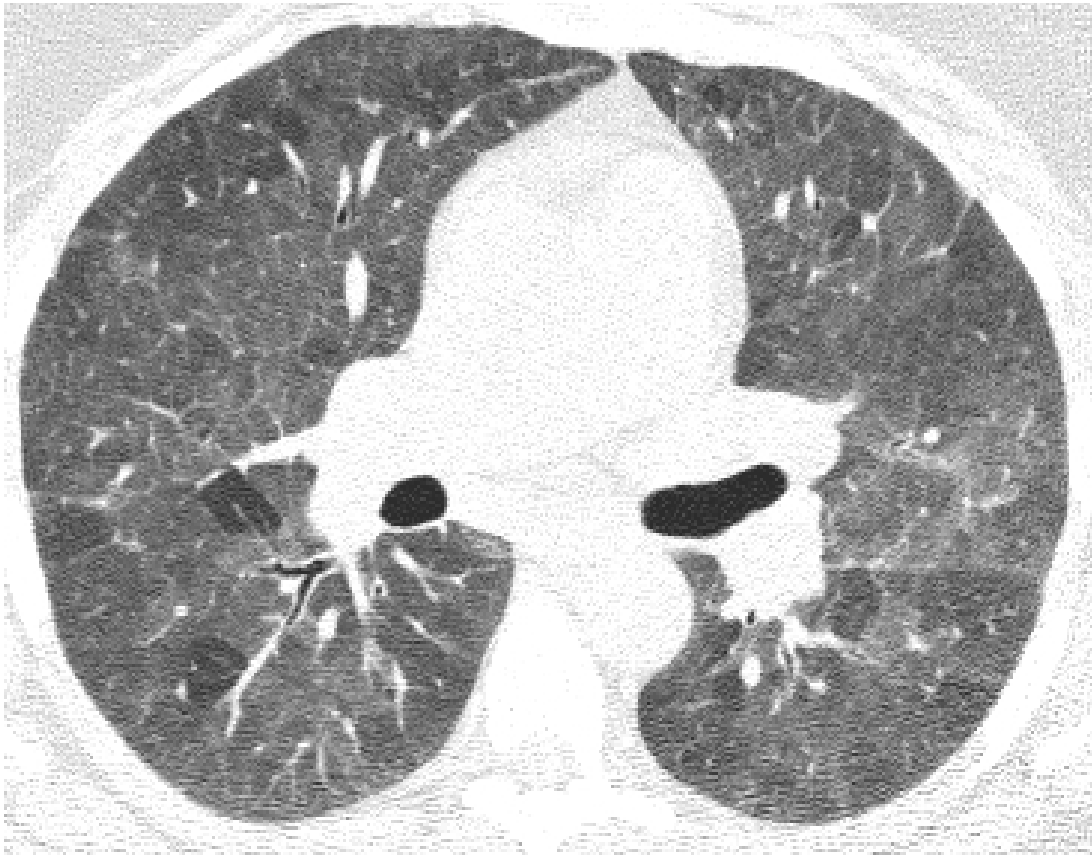
Hypersensitivity Pneumonitis

Pattern:

- Ground Glass
- Mosaic attenuation
- Peribronchiolar thickening

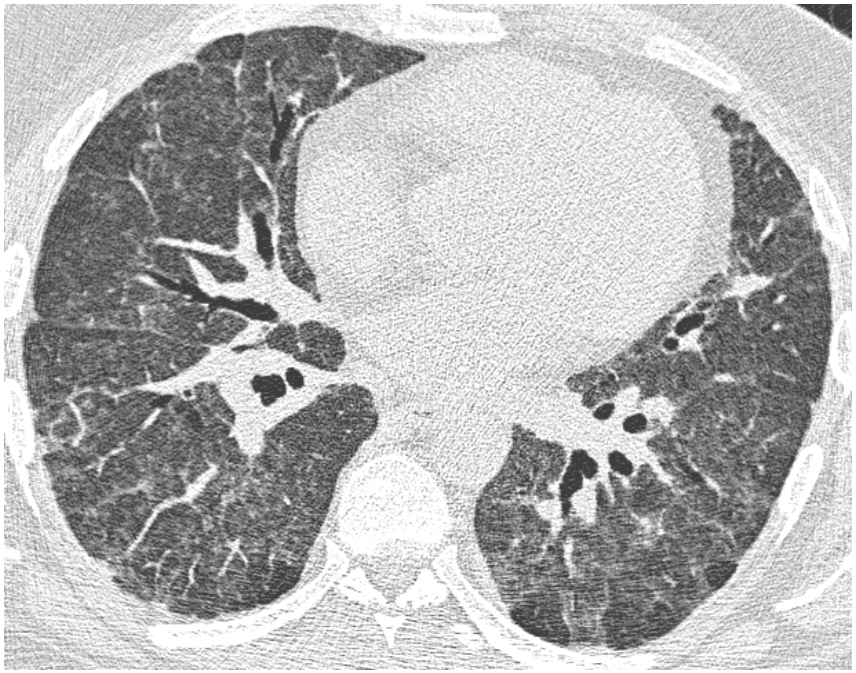
Distribution:

- Upper / Diffuse

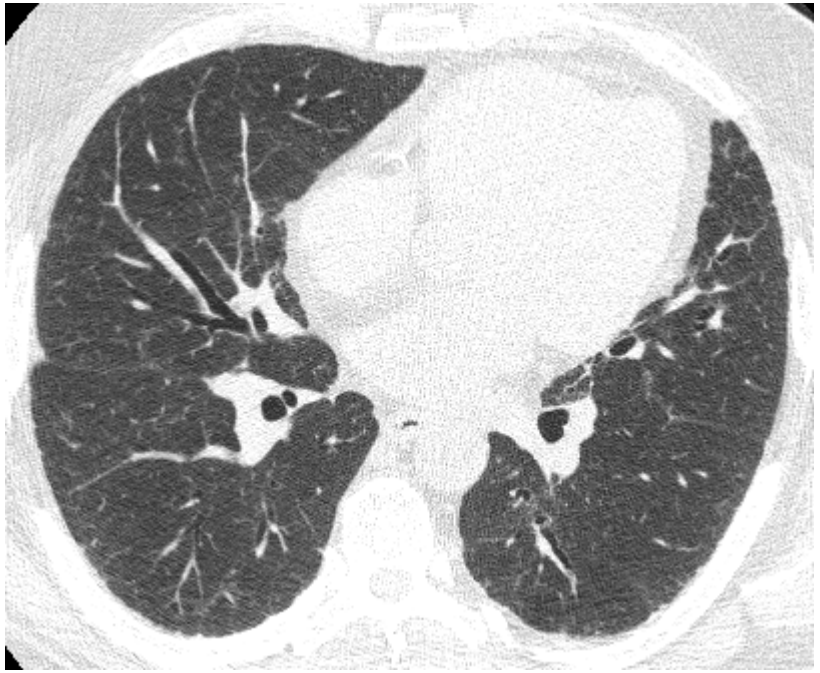


50 year old male with Hypersensitivity Pneumonia – Treated with removal of doves and immunosuppression

	06/18/13	06/20/16
FEV1 (% pred)	1.95 (50%)	2.93 (78%)
FVC (% pred)	2.04 (38%)	3.22 (61%)
DLCO (% pred)	12.25 (38%)	25.22 (81%)

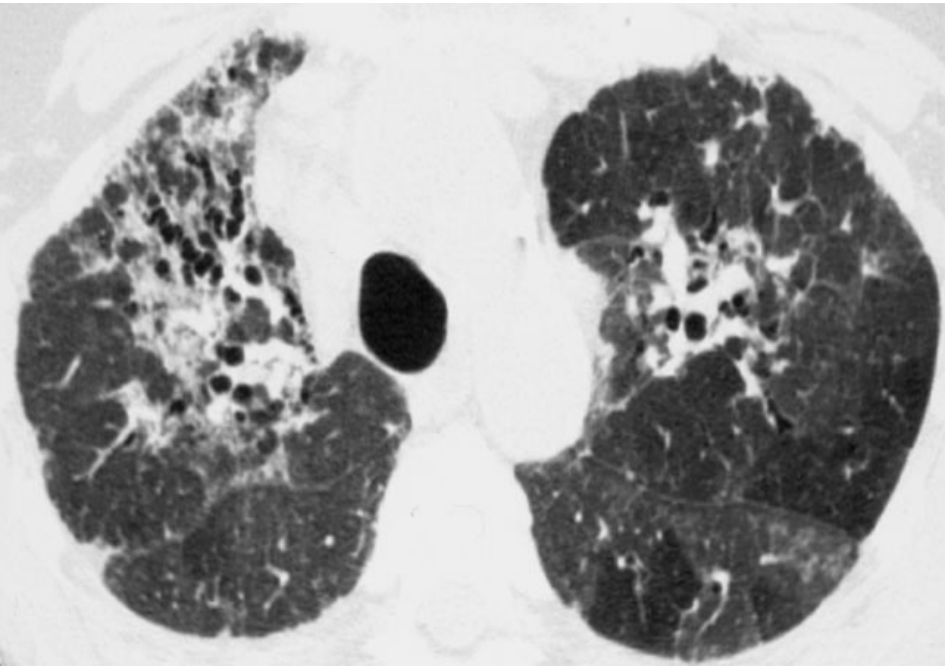


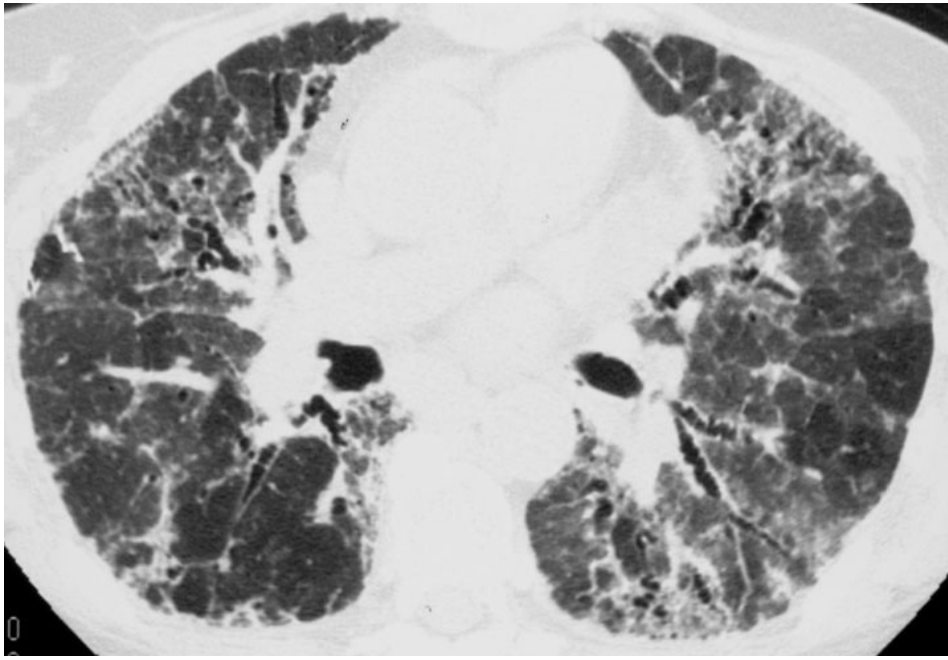
04/05/13



06/20/16

Hypersensitivity Pneumonitis - Chronic





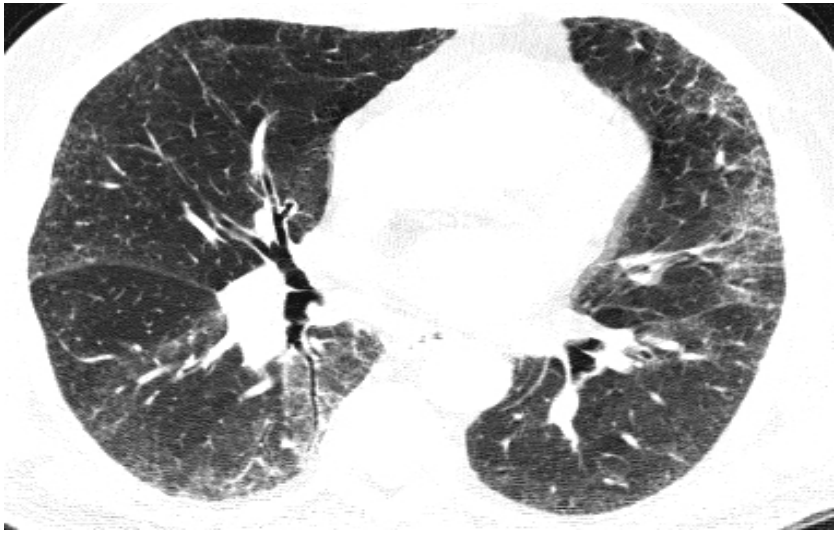
Nonspecific interstitial pneumonia

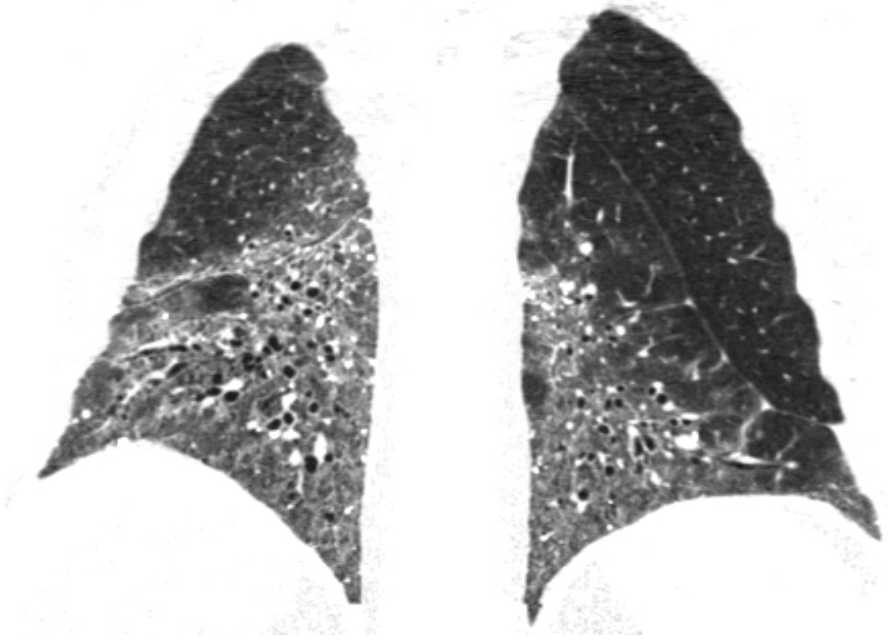
Pattern:

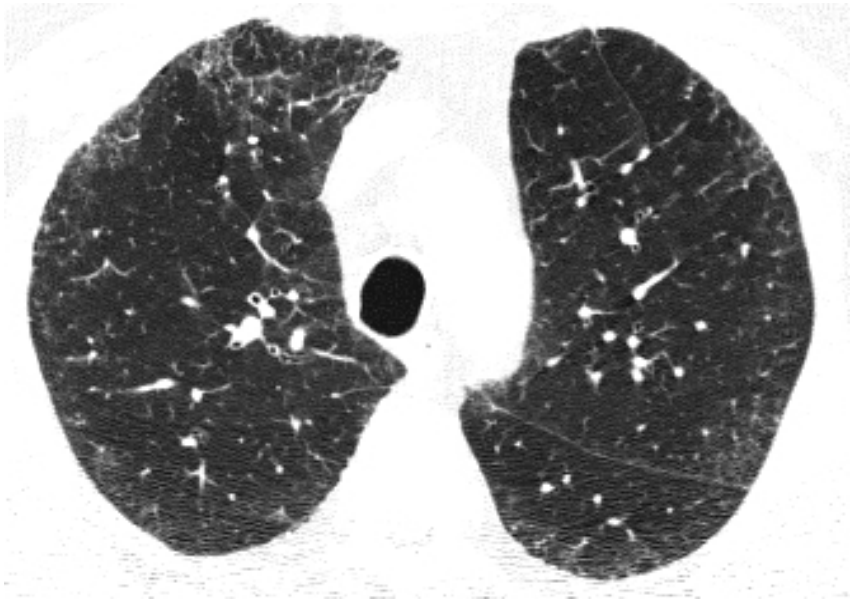
- Reticulation
- Traction Bronchiectasis
- Ground Glass
- Honeycomb rare (5%)

Distribution:

- Lower
- Peripheral / Diffuse







Updated Consensus Statement for Diagnosis of IPF

The diagnosis of IPF requires:

1. Exclusion of other known causes of interstitial lung disease
2. Presence of UIP pattern on HRCT (in patients without surgical biopsy)
3. A HRCT pattern of definite/possible UIP with a Surgical lung biopsy showing Definite/Probable UIP

The Major and Minor Criteria proposed in the 2000 ATS/ERS Consensus Statement were Eliminated

Raghu et al., *Am J Respir Crit Care Med* 2011; 183:788-24

Role of HRCT in Diagnosing UIP

UIP Pattern (All 4 Features)	Possible UIP (All 3 Features)	Inconsistent With UIP (Any)
• Subpleural, basal predominance • Reticular abnormality • Honeycombing with/without traction bronchiectasis • Absence of features listed as inconsistent with UIP (column 3)	• Subpleural, basal predominance • Reticular abnormality • Absence of features listed as inconsistent with UIP (column 3)	• Upper or mid-lung predominance • Peribronchovascular predominance • Extensive ground glass abnormality (extent > reticular abnormality) • Profuse micronodules (bilateral, predominantly upper lobe) • Discrete cysts (multiple, bilateral, away from areas of honeycombing) • Diffuse mosaic attenuation/ air-trapping (bilateral, in ≥3 lobes) • Consolidation in bronchopulmonary segment(s)/lobe(s)

Raghu G et al. *Am J Respir Crit Care Med*. 2011;183:788-824.

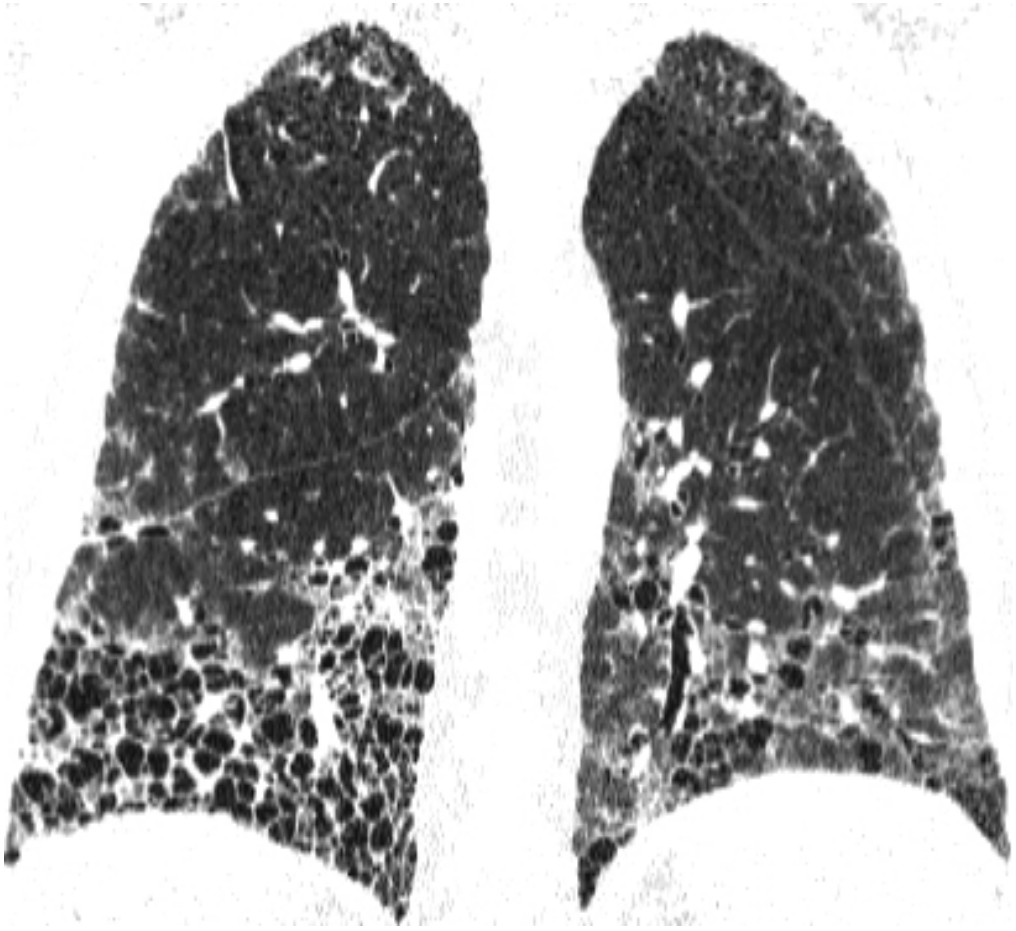
Usual Interstitial Pneumonia

Pattern:

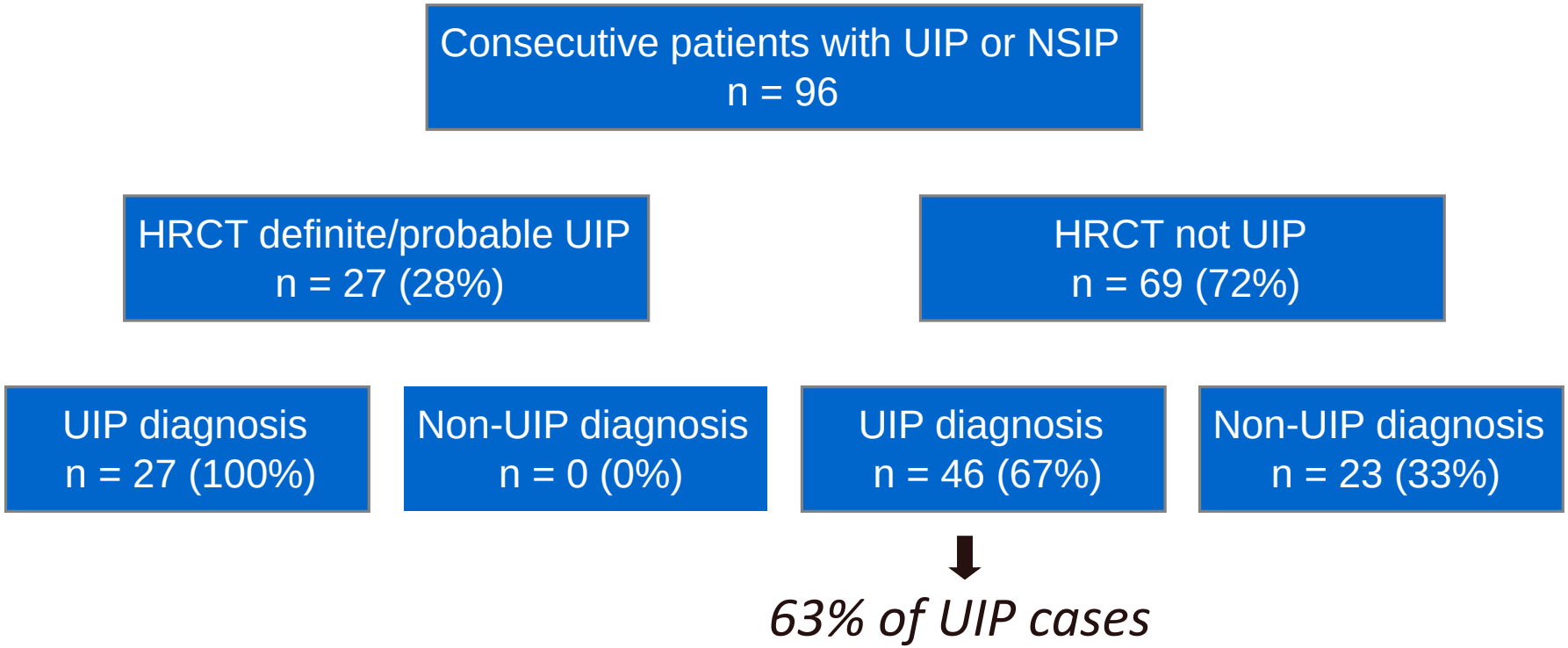
- irregular septal lines & honeycombing
- ground glass opacity (not predominant)
- traction bronchiectasis

Distribution:

- lower > upper lung
- subpleural distribution



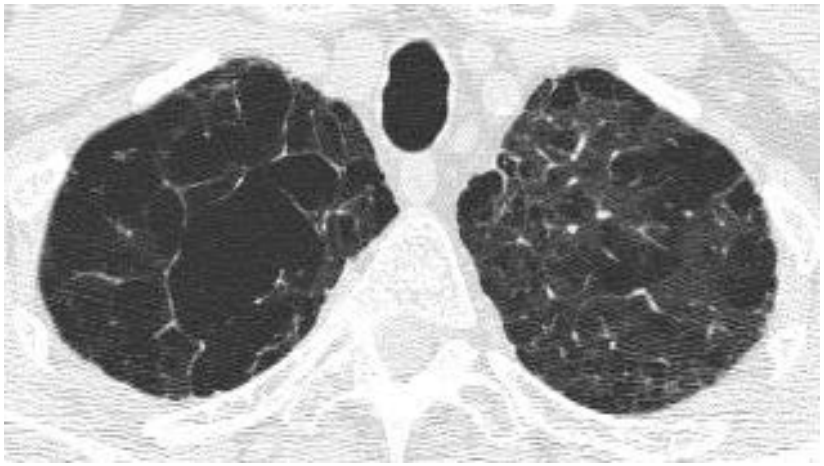
Radiology (HRCT) Diagnosis of IPF/UIP Versus NSIP

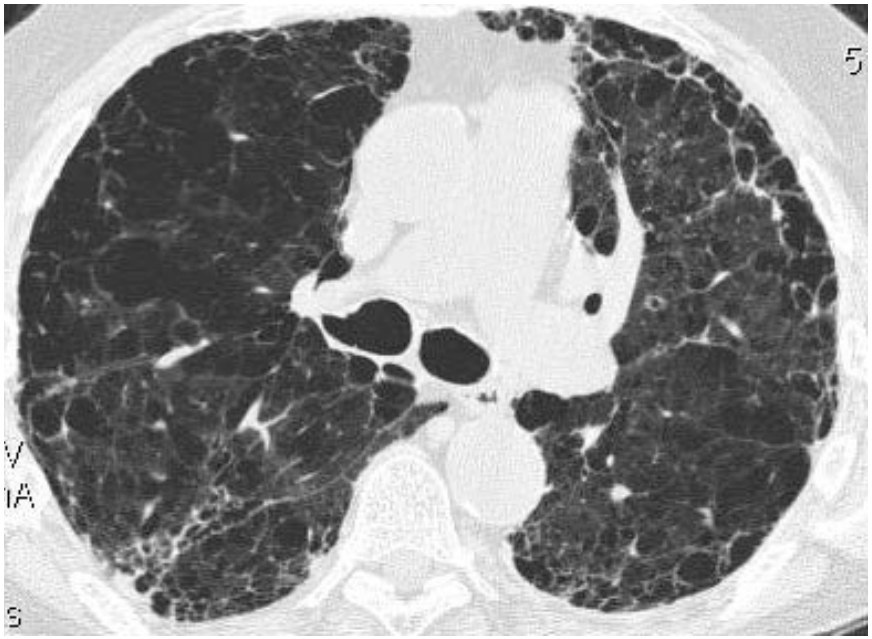


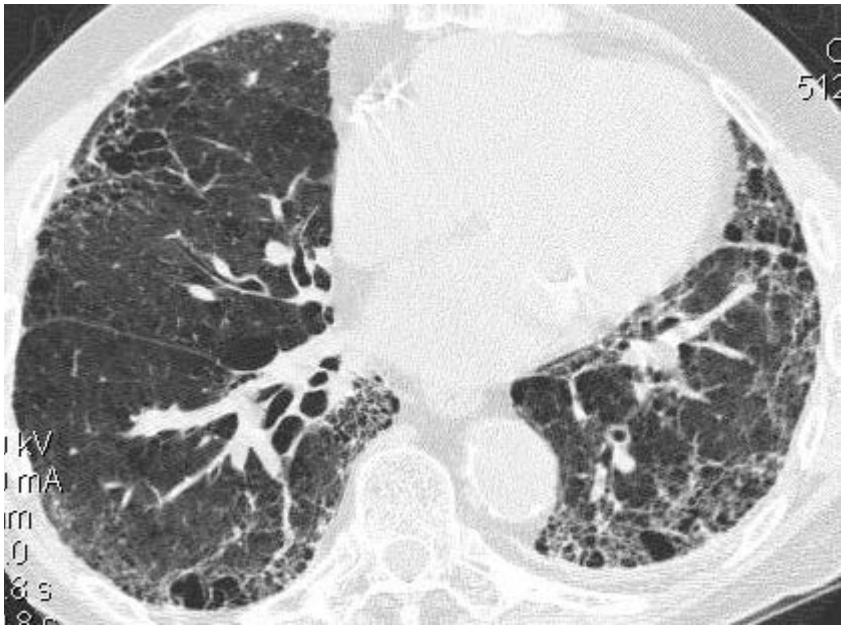
Flaherty K, et al. *Thorax.* 2003;58:143-148.

Emphysema + IPF/UIP

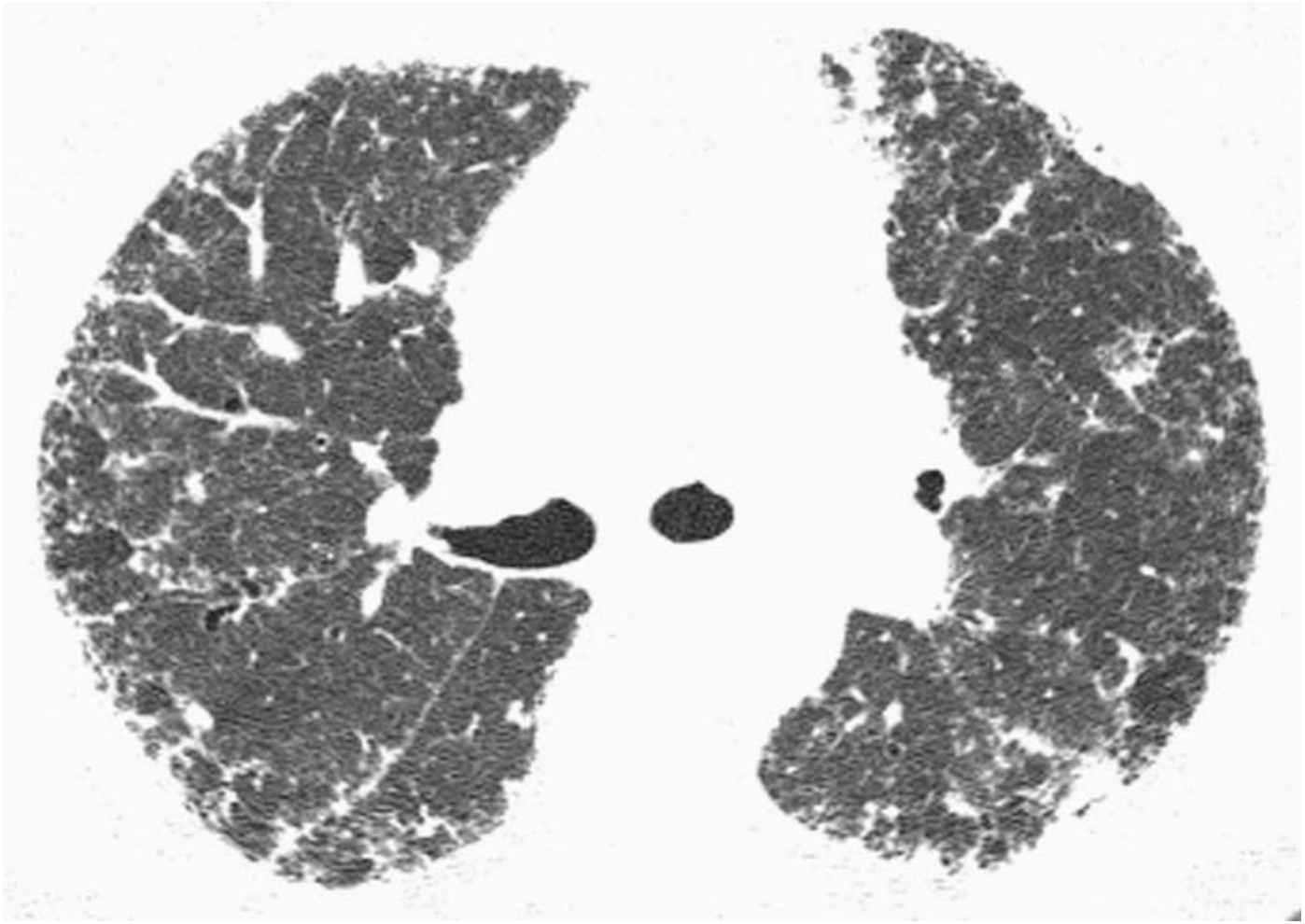
FVC	3.63 (89%)
FEV_1	2.74 (102%)
FEV_1/FVC	115%
RV	2.67 (113%)
TLC	6.30 (98%)
DL_{CO}	11.90 (48%)





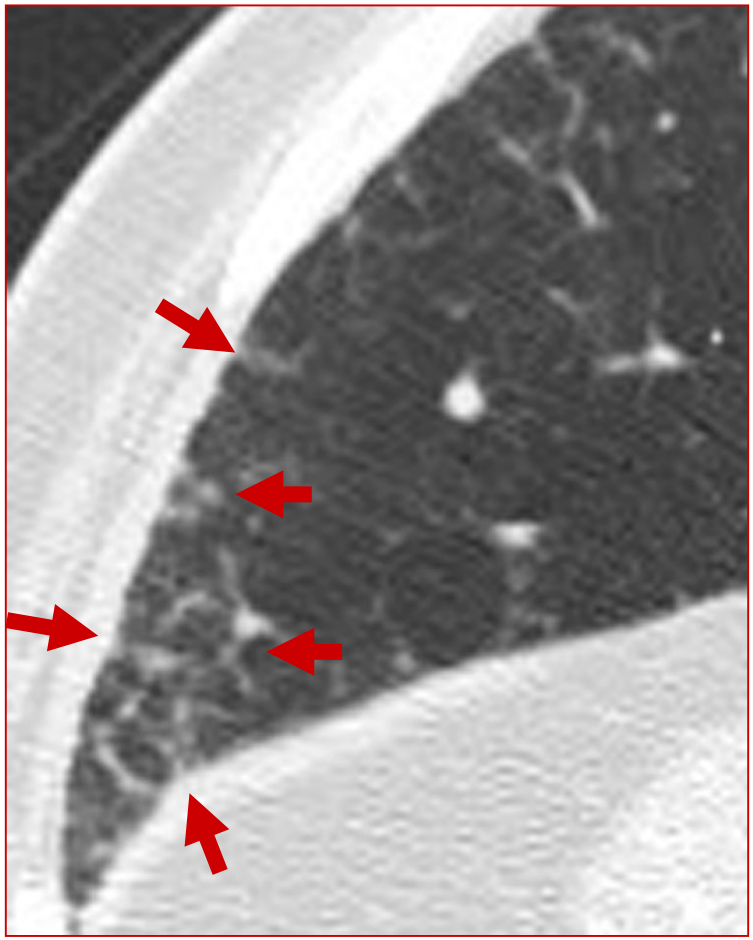


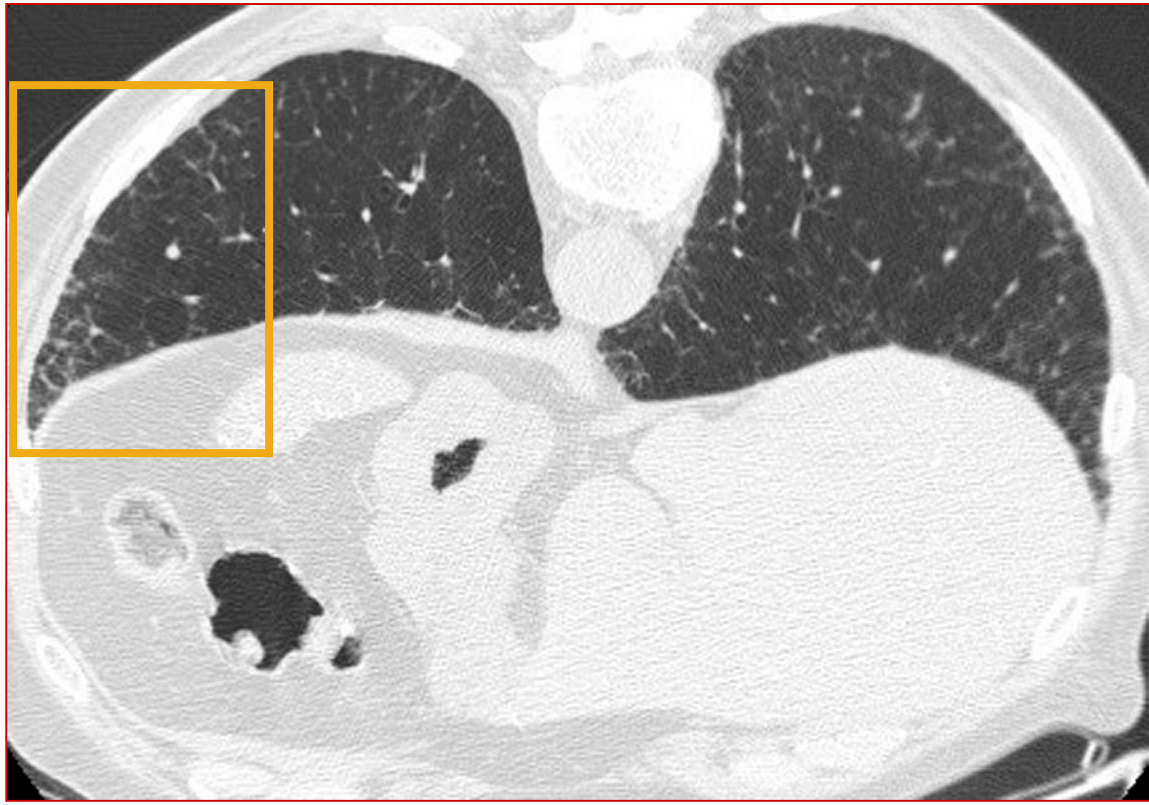
UIP: Irregular Reticular Opacities



Courtesy of W. Richard Webb, MD.

Early HRCT Findings in IPF

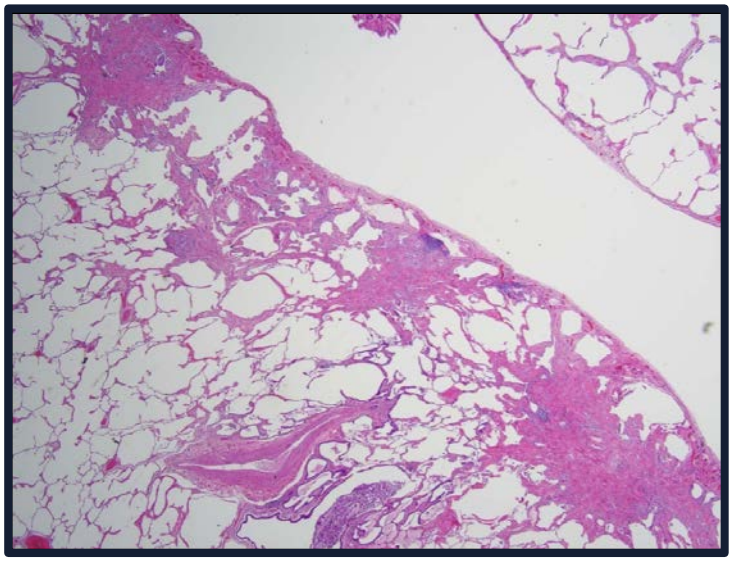


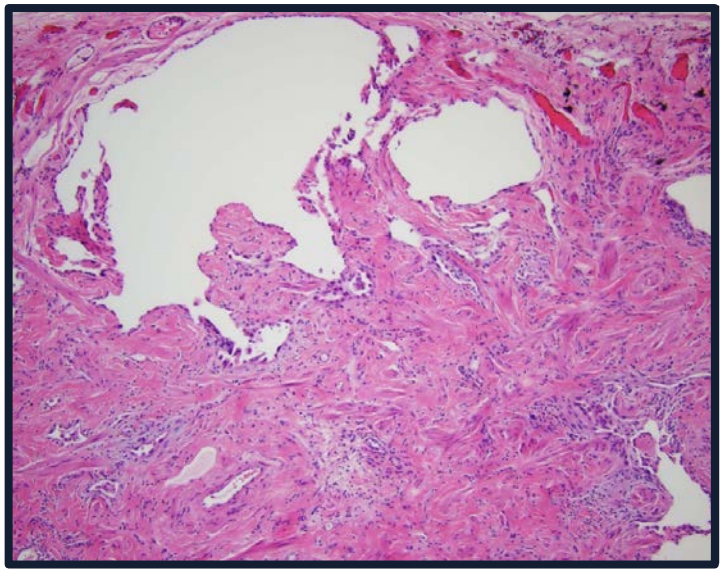


Histologic Tools for Diagnosis

Histology

- Bronchoscopy
- Surgical lung biopsy





UIP Pattern

- Marked fibrosis/architectural distortion ± honeycombing, predominantly subpleural/paraseptal
- Patchy fibrosis
- Fibroblastic foci
- Absence of features to suggest alternative diagnosis

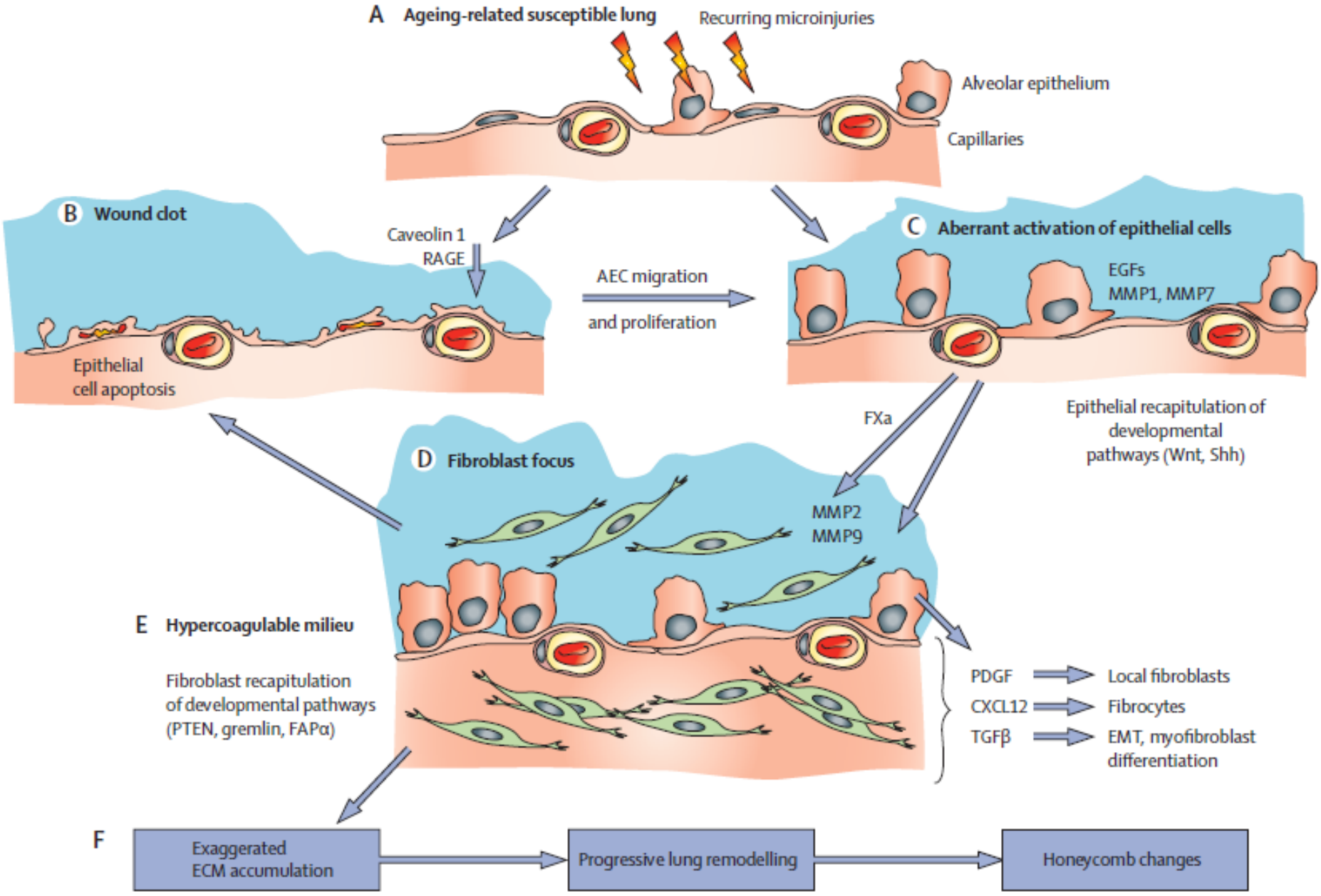
1. Images courtesy of Steven Nathan, MD.
2. Raghu G et al. *Am J Respir Crit Care Med*. 2011;183:788-824.

Idiopathic Pulmonary Fibrosis

A specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, and limited to the lungs.

It is characterized by progressive worsening of dyspnea and lung function and is associated with a poor prognosis.

Raghu et al., *Am J Respir Crit Care Med* 2011; 183:788-24


A Ageing-related susceptible lung
Recurring microinjuries
Alveolar epithelium
Capillaries
B Wound clot
Caveolin 1
RAGE
Epithelial cell apoptosis
AEC migration and proliferation
C Aberrant activation of epithelial cells
EGFs
MMP1, MMP7
Epithelial recapitulation of developmental pathways (Wnt, Shh)
FXa
D Fibroblast focus
MMP2
MMP9
E Hypercoagulable milieu
Fibroblast recapitulation of developmental pathways (PTEN, gremlin, FAPα)
PDGF → Local fibroblasts
CXCL12 → Fibrocytes
TGFβ → EMT, myofibroblast differentiation
F
Exaggerated ECM accumulation
Progressive lung remodelling
Honeycomb changes

Having a Conversation With the Patient Newly Diagnosed With IPF

- Spend adequate time to explain the prognosis and assess patient's preferences and values
- Burden and morbidity of IPF can be emotionally overwhelming and will likely impact family members as well
- Each individual patient with IPF is different; consider physiology, exercise tolerance, radiology, and pathology when choosing a course of treatment
- Patients who are at increased risk of mortality should be referred for lung transplantation early in the course

2015 Treatment Recommendations for IPF

Strong Recommendation Against Use:
Anticoagulation (warfarin), Pred/Aza/NAC, ambrisentan, Imatinib
Conditional Recommendation for Use:
Nintedanib, pirfenidone, GERD
Conditional Recommendation Against Use:
NAC, macitentan, bosentan, sildenafil

Raghu, et al. *Am J Respir Crit Care Med* 2015;192:e3-19

High Dose Acetylcysteine in Idiopathic Pulmonary Fibrosis

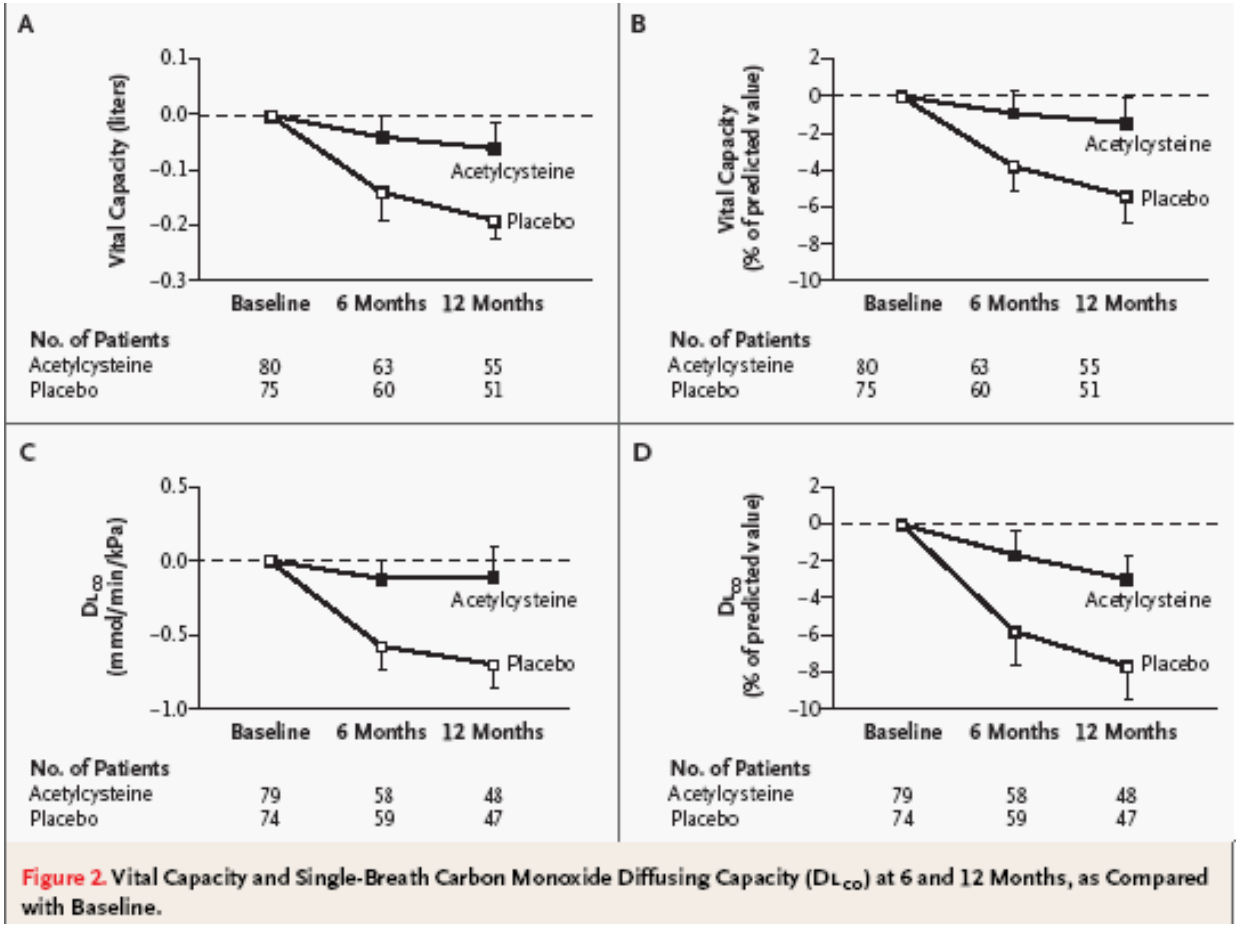


Figure 2. Vital Capacity and Single-Breath Carbon Monoxide Diffusing Capacity ($D_{L_{CO}}$) at 6 and 12 Months, as Compared with Baseline.

Mortality
NAC = 9%
Placebo = 11%
p=0.69

Demedts et al; *NEJM* 2005;353:2229-42

PANTHER

Prednisone-Azathioprine-N-acetyl cysteine: A Trial THat Evaluates Responses in IPF

Diagnosis of IPF with FVC $\geq$ 50%, DLCO $\geq$ 30% predicted

Three arms

- Placebo
- N-acetyl cysteine
- Pred/aza/NAC

Primary Endpoint – Change in FVC over 60wks

IPFnet

ORIGINAL ARTICLE

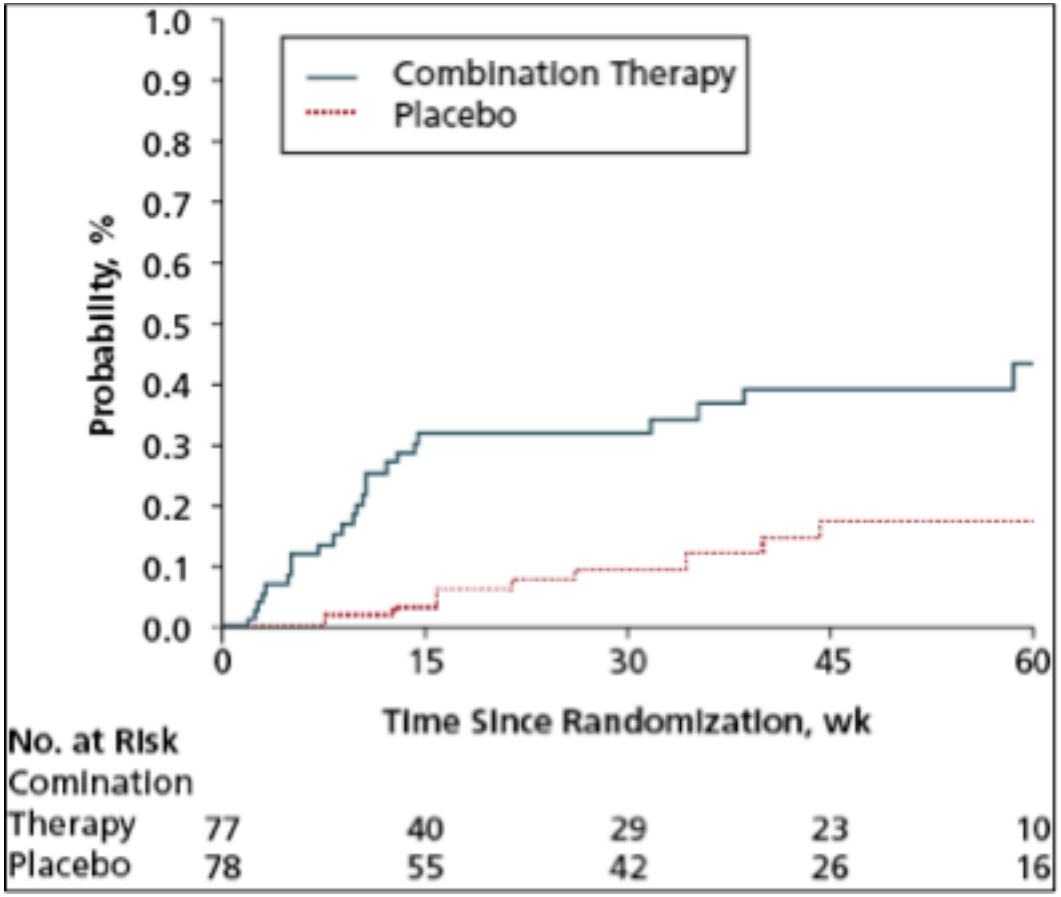
Prednisone, Azathioprine, and *N*-Acetylcysteine for Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

IPFnet

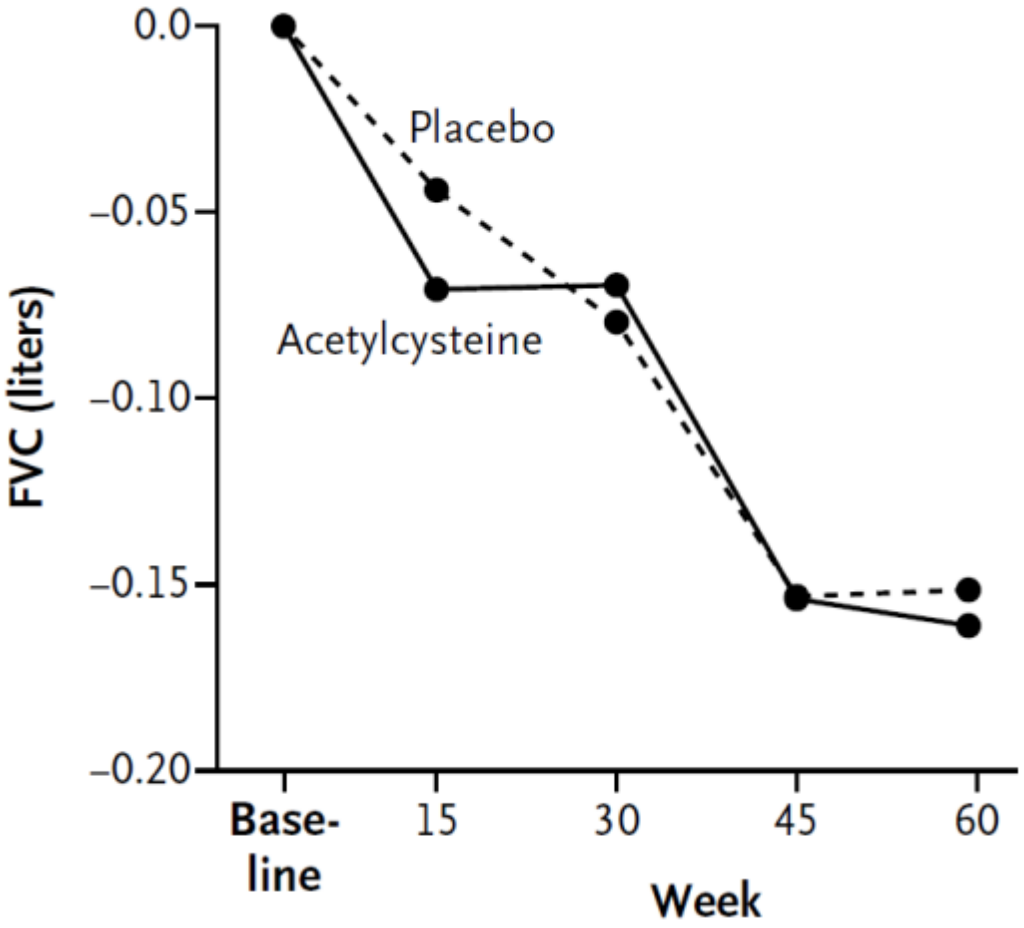
- Interim Analysis with 50% data
  - Combination n = 77, Placebo n= 78
  - Increased Death 8 vs 1, p=0.01
  - Increased Hosp 23 v 7, p<0.001
  - No physio/clinical benefit

- Termination of combination therapy at mean of 32 weeks
- Recommendation against use of pred/azthioprine/N-acetyl cysteine



Raghu et al. *N Engl J Med* 2012; 366:1968-71

NAC Does Not Reduce FVC Decline



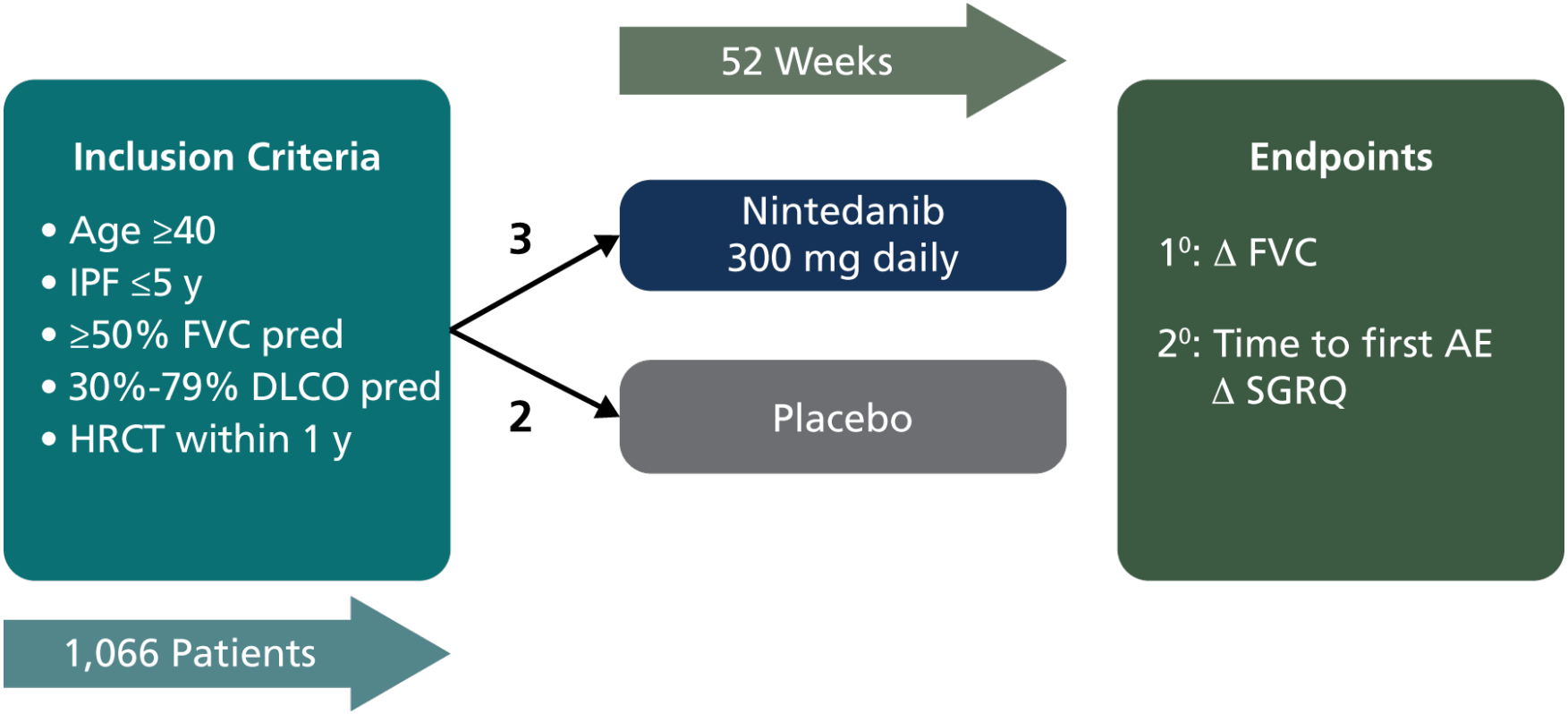
Martinez FJ, et al. *N Engl J Med.* 2014;370(22):2093-2101.

2015 Treatment Recommendations for IPF

Strong Recommendation Against Use:
Anticoagulation (warfarin), Pred/Aza/NAC, ambrisentan, Imatinib
Conditional Recommendation for Use:
Nintedanib, pirfenidone, GERD
Conditional Recommendation Against Use:
NAC, macitentan, bosentan, sildenafil

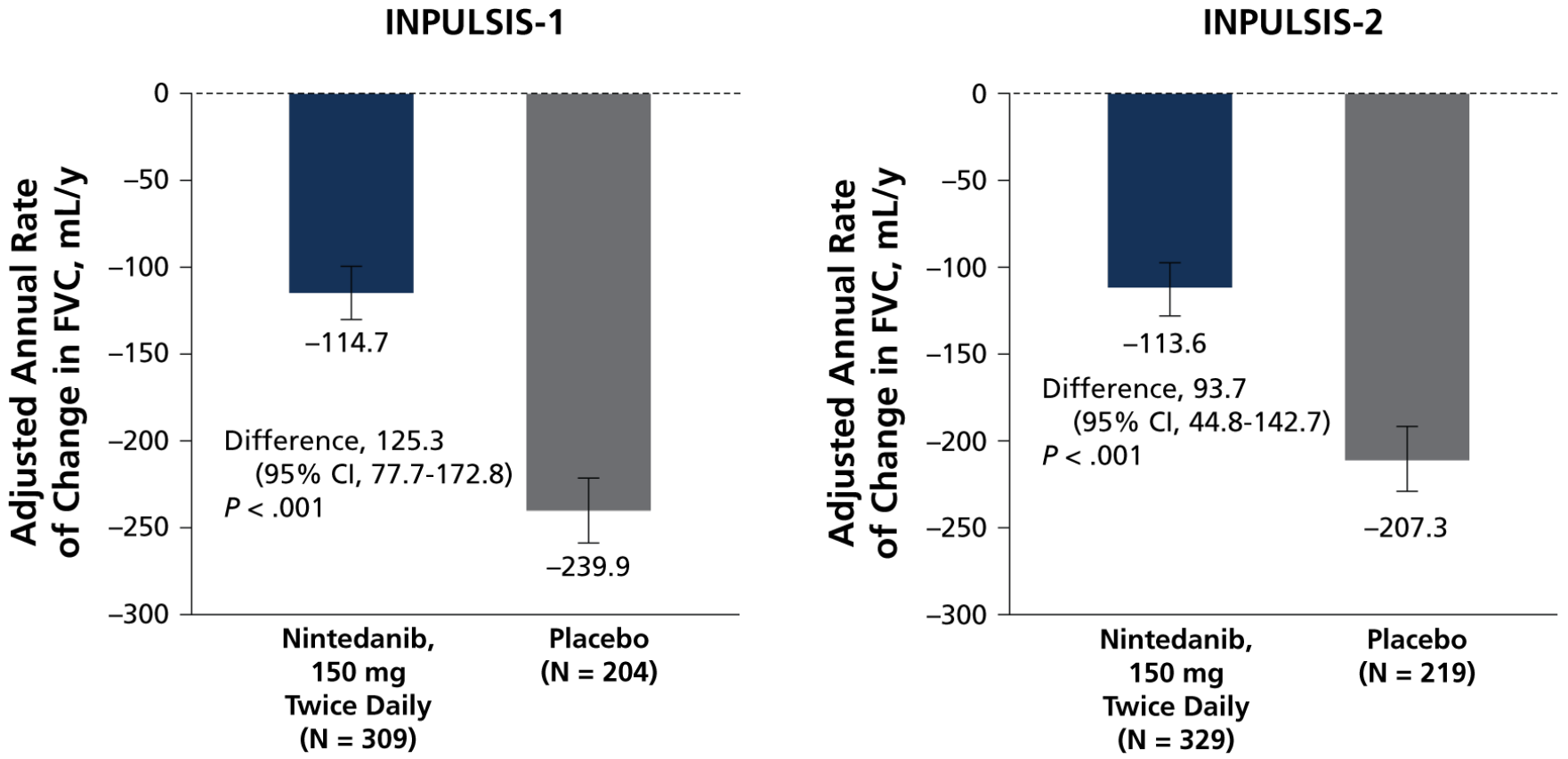
Raghu, et al. *Am J Respir Crit Care Med* 2015;192:e3-19

Nintedanib: INPULSIS-1 and INPULSIS-2 Trial Design



Richeldi L et al. *N Engl J Med*. 2014;370:2071-2082.

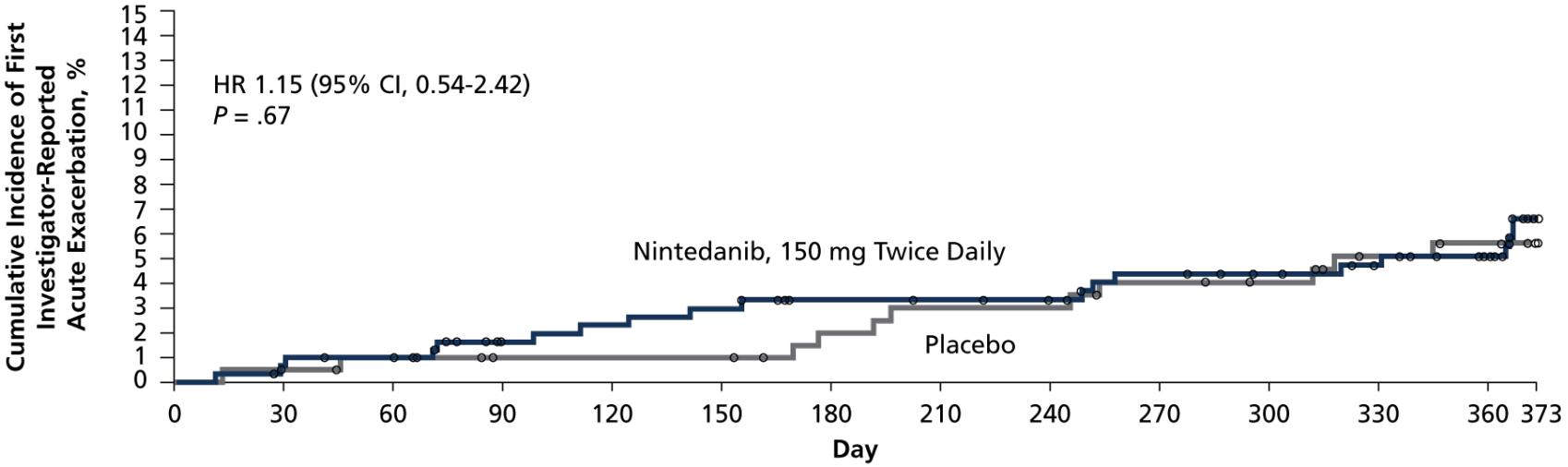
INPULSIS Primary Endpoint: Adjusted Annual Rate of Decline in FVC



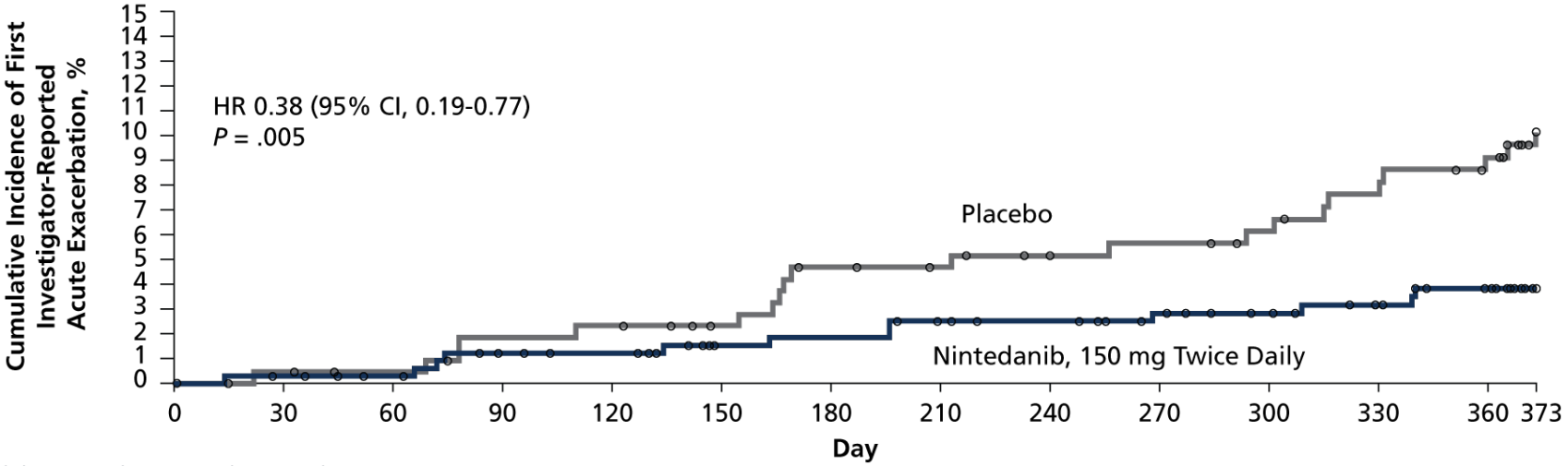
Richeldi L et al. *N Engl J Med*. 2014;370:2071-2082.

INPULSIS: Time to First Investigator-Reported Acute Exacerbation

INPULSIS-1

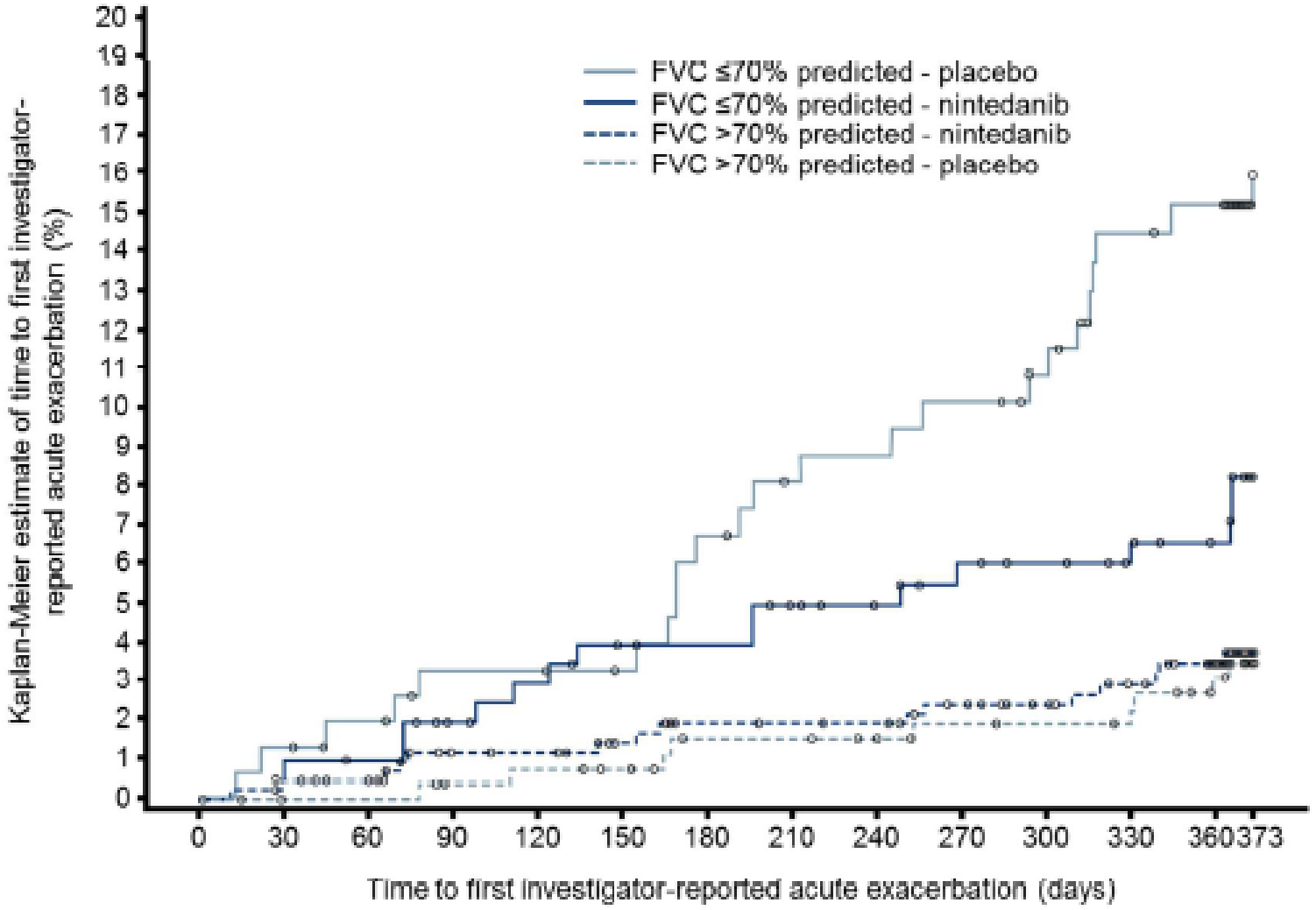


INPULSIS-2



Richeldi L et al. *N Engl J Med*. 2014;370:2071-2082.

Nintedanib – Time to First Exacerbation Statified by FVC +/- 70% predicted



Costabel, et al. *Am J Respir Crit Care Med* 2015; epub

Nintedanib – Safety & Tolerability

	Nintedanib (n=638)	Placebo (n=423)
Dose Reduction*	178 (28%)	16 (4%)
Treatment Interruptions*	151 (24%)	42 (10%)
	Incidence/Discontinue	**Incidence/Discontinue**
Diarrhea	63% / 4.4%	18% / 0.2%
Nausea	25% / 2.0%	7% / 0%
	Mild/Mod/Severe (%)	**Mild/Mod/Severe (%)**
Diarrhea	57 / 38 / 5	77 / 20 / 3
Nausea	74 / 24 / 2	93 / 7 / 0

* No particular time

Corte, et al. *Respir Research.* 2015;16:116

FDA Approval of Nintedanib

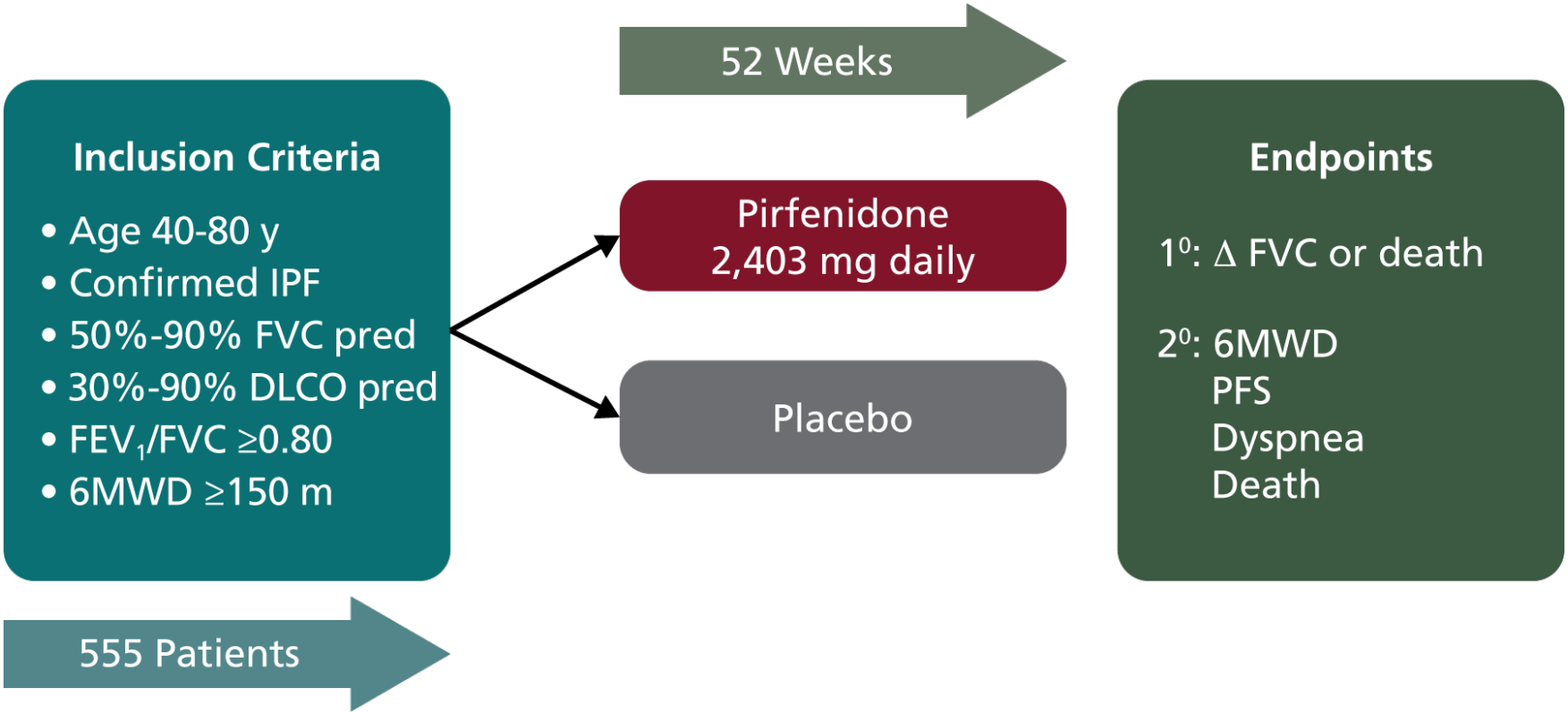
Approved October 15, 2014, for the treatment of IPF

Liver function tests required prior to treatment and should be evaluated every 3 months in first year

Dosage and administration

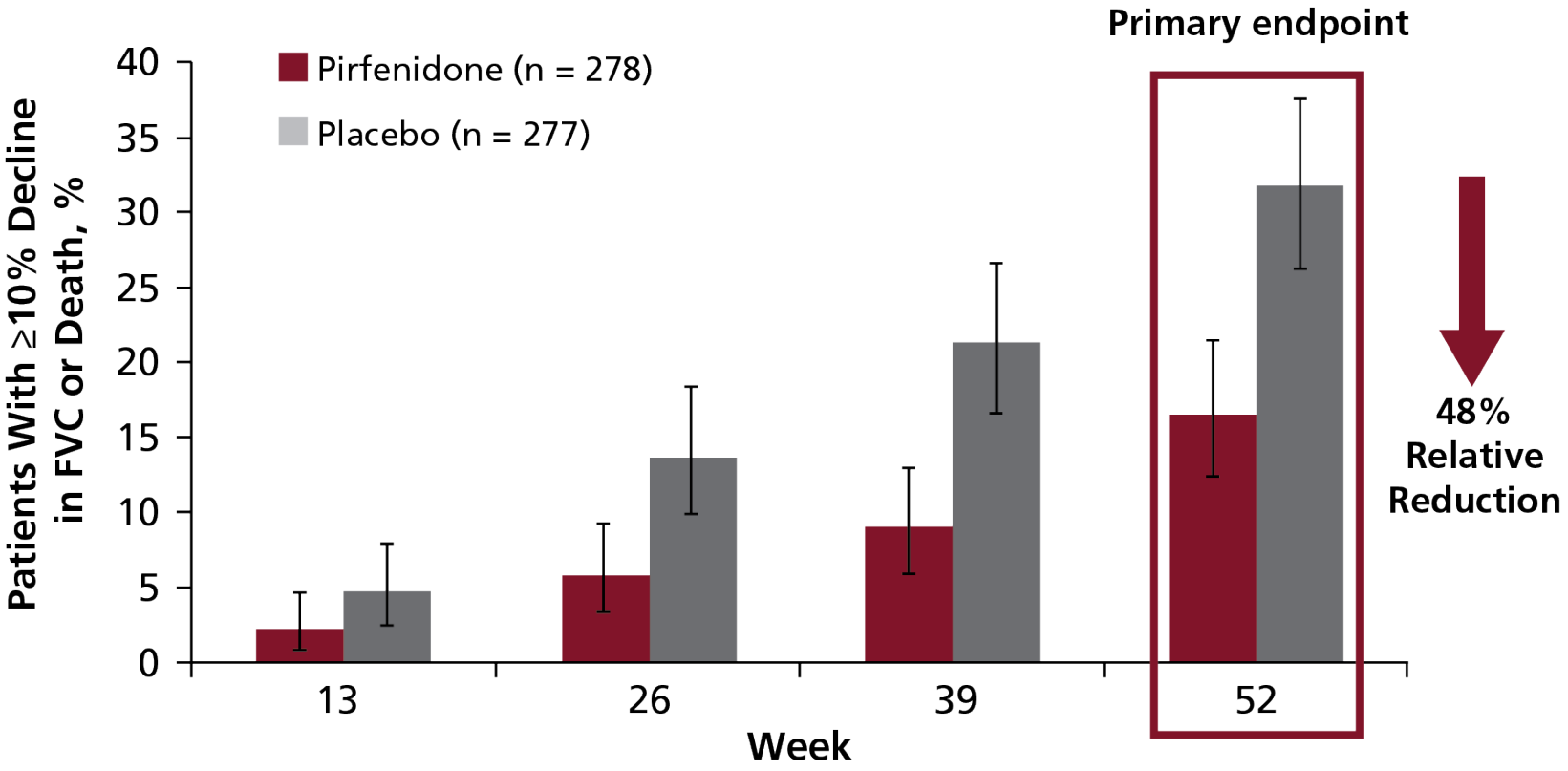
- 150 mg twice daily with food
- Take each dose approximately 12 h apart
- Adverse reactions? Consider temporary dose reduction to 100 mg, temporary interruption, or discontinuation

Pirfenidone: ASCEND Trial Design



King TE Jr et al. *N Engl J Med*. 2014;370:2083-2092.

ASCEND: Primary Efficacy Analysis



Absolute difference	2.5%	7.9%	12.3%	15.3%
Relative difference	54.0%	58.0%	57.8%	47.9%
Rank ANCOVA *P*	< .001	< .001	< .001	< .001

ANCOVA: analysis of covariance.

King TE Jr et al. *N Engl J Med*. 2014;370:2083-2092.

Pirfenidone: Meta Analysis

Table 2. Summary of finding form Pirfenidone for idiopathic pulmonary fibrosis.

Outcomes	Anticipate absolute effects (Study population) (95% CI)		Relative Effect	NO of participants	Quality of the evidence (GRADE)
	Risk with placebo	Risk with Pirfenidone			
All cause-mortality	67 per 1000	36 per 1000 (22 to 59)	RR 0.53 (0.32 to 0.88)	1247 (3 RCTs)	⊕⊕⊕◯ MODERATE1
Progression free-survival	442 per 1000	372 per 1000 (332 to 416)	RR 0.83 (0.75 to 0.94)	728 (3 RCTs)	⊕⊕⊕◯ MODERATE1
Acute exacerbation	26 per 1000	15 per 1000 (5 to 47)	RR 0.59 (0.19 to 1.84)	235 (2 RCTs)	⊕⊕◯◯ LOW1,2
Worsening of IPF	168 per 1000	107 per 1000 (84 to 139)	RR 0.64 (0.50 to 0.83)	1615 (5 RCTs)	⊕⊕⊕◯ MODERATE1
Change on 6MWT	417 per 1000	308 per 1000 (267 to 358)	RR 0.74 (0.64 to 0.86)	1236 (3 RCTs)	⊕⊕⊕⊕ HIGH
Change on aminotransferases	30 per 1000	68 per 1000 (40 to 115)	RR 2.26 (1.33 to 3.83)	764 (5 RCTs)	⊕⊕⊕◯ MODERATE1

1: Non primary outcome from RCTs, 2: High heterogeneity; 6MWT: Six minutes walk test; RCT: Randomized controlled trial; RR: Risk ratio; CI: confidence interval.

Aravena et al. *PLoS One* 2015;10:e0126160

ASCEND: Treatment-Emergent Adverse Events more common in pirfenidone group

- Nausea (36% vs 13%)
- Rash (28% vs 9%)

- Adverse events (AEs) generally mild to moderate severity, reversible, and without clinically significant sequelae

King TE Jr et al. *N Engl J Med*. 2014;370:2083-2092.

FDA Approval of Pirfenidone

Approved October 15, 2014, for the treatment of IPF

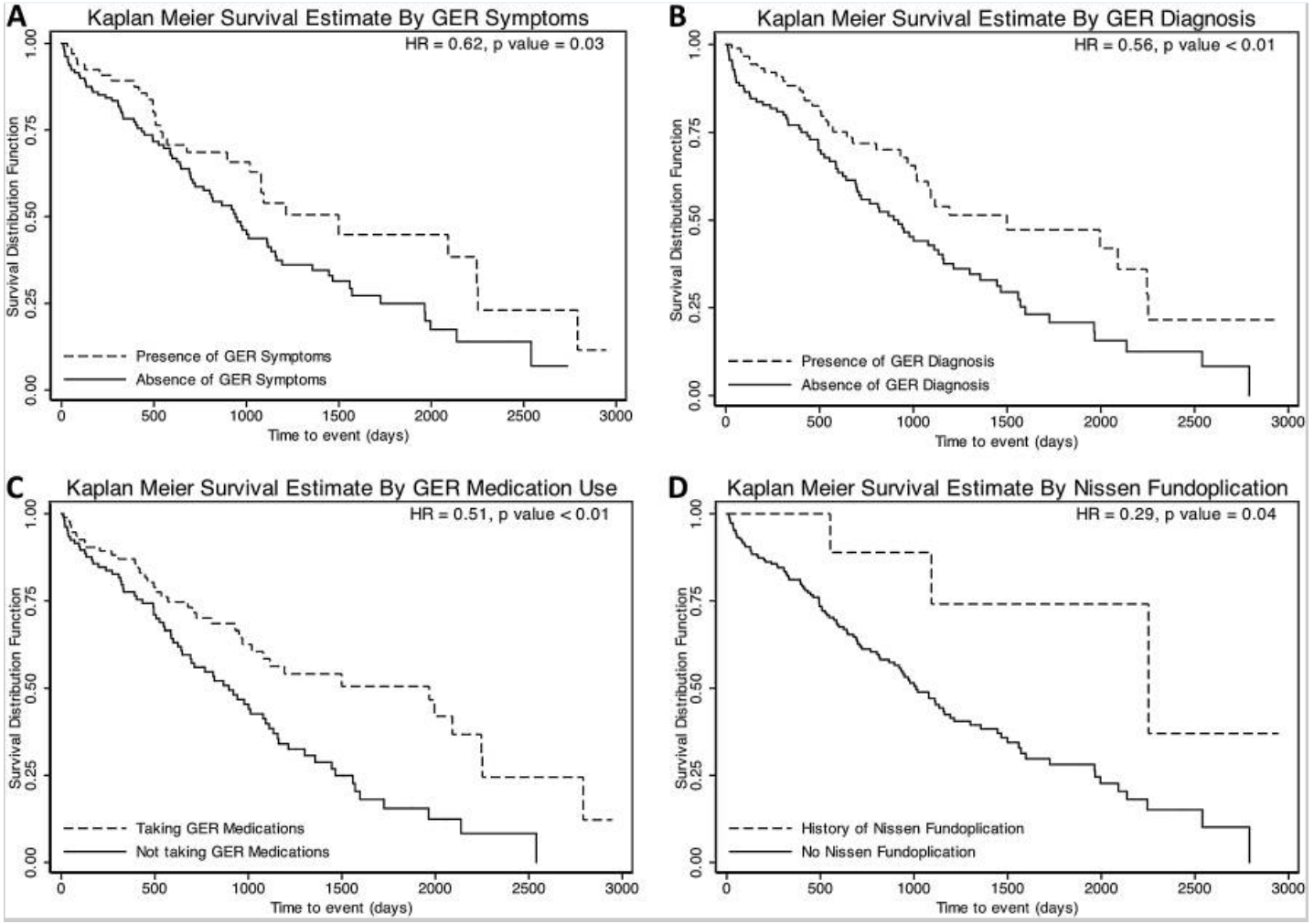
Liver function tests required prior to treatment and should be evaluated every 3 months in first year

Dosage and administration

- 801 mg 3x daily with food (three 267-mg capsules per dose)
- Take each dose at the same time each day
- Initiate with titration
  - Days 1-7: one capsule 3x daily
  - Days 8-14: two capsules 3x daily
  - Days 15 onward: three capsules 3x daily
- Adverse reactions? Consider temporary dosage reduction, treatment interruption, or discontinuation

Gastroesophageal reflux (GERD) in IPF

- GER is highly prevalent in patients with IPF
- Observational study (n = 204); 47% received GER medical therapy, and 5% surgical



Lee JS, et al. Am J Respir Crit Care Med. 2011;184:1390-1394.

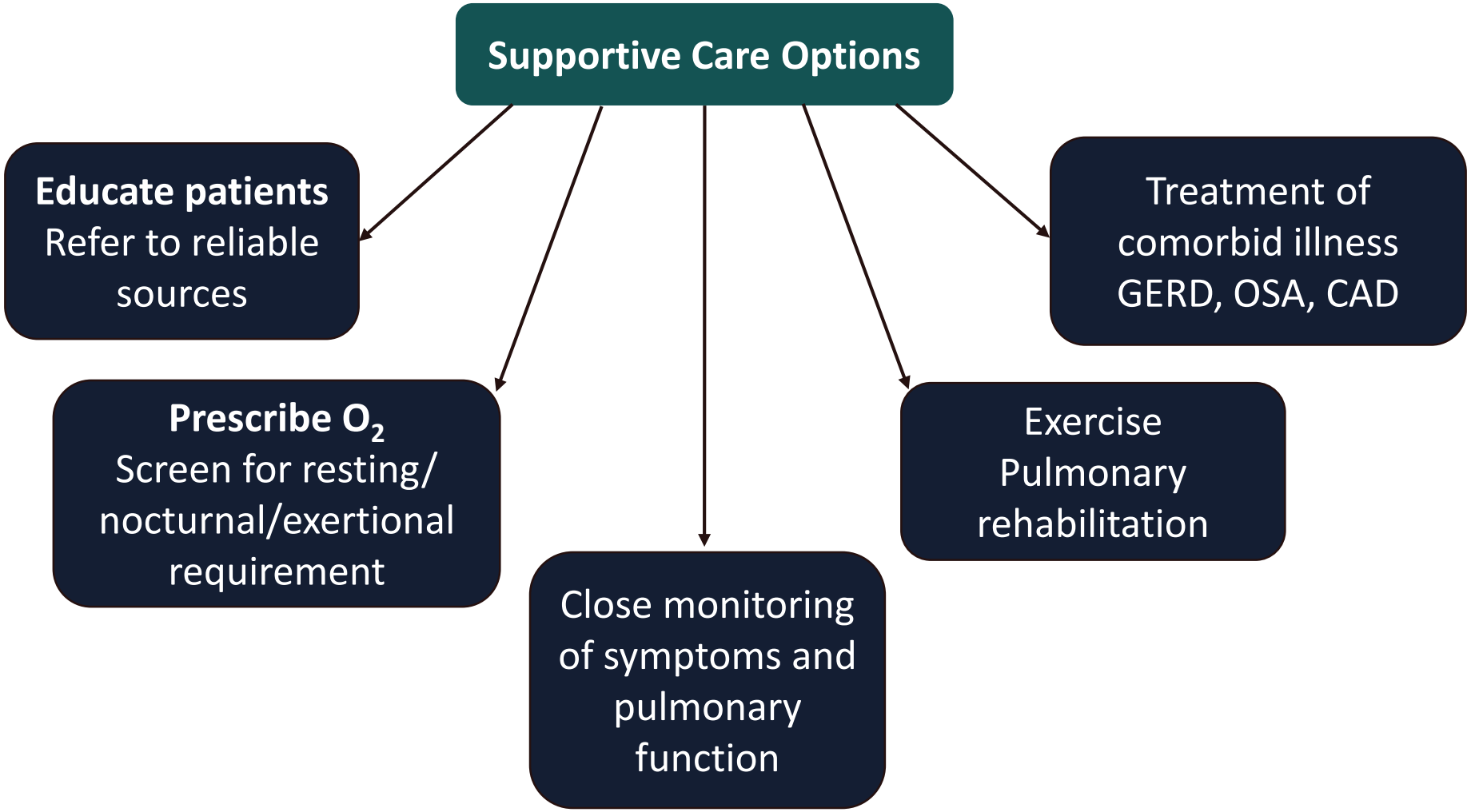
Engaging in a Shared Decision-Making Process

- Discuss the efficacy and safety of FDA-approved therapies
- Listen to patient's preferences and concerns
- Focus on symptom control and management of comorbidities
- Set treatment expectations
- Look at the option of lung transplantation

Members of the IPF Care Team

- Multidisciplinary Team of Physicians
  - Pulmonary, Radiology, Pathology, Rheumatology, Cardiology, Thoracic Surgery, Lung Transplant
- Social Work
- Clinical Nurse Specialist
- Palliative Care
- Students/Residents/Fellows
- Research Coordinator
- Support Group

Supportive Care for Patients With IPF



OSA: obstructive sleep apnea.

Lung Transplantation for Pulmonary Fibrosis: Referral and Listing Guidelines

Referral

- Diagnosis of IPF (histologic or radiographic)
- Diagnosis of fibrotic NSIP (histologic)

Transplantation

- DL_{CO} < 39% predicted
- Decline in FVC by ≥ 10% over 6 months
- Oxyhemoglobin saturation < 88% with 6MWT
- Honeycombing on HRCT
- Histologic evidence of NSIP and
  - DL_{CO} < 35% predicted
  - Decline in FVC of ≥ 10% over 6 months
  - Decline in DL_{CO} of ≥ 15% over 6 months

Orens JB, et al. *J Heart Lung Transplant.* 2006;25:745-755.

Pulmonary Fibrosis
FOUNDATION

www.pulmonaryfibrosis.org

We Imagine a World Without
Pulmonary Fibrosis