An Approach To The Patient With Interstitial lung Disease

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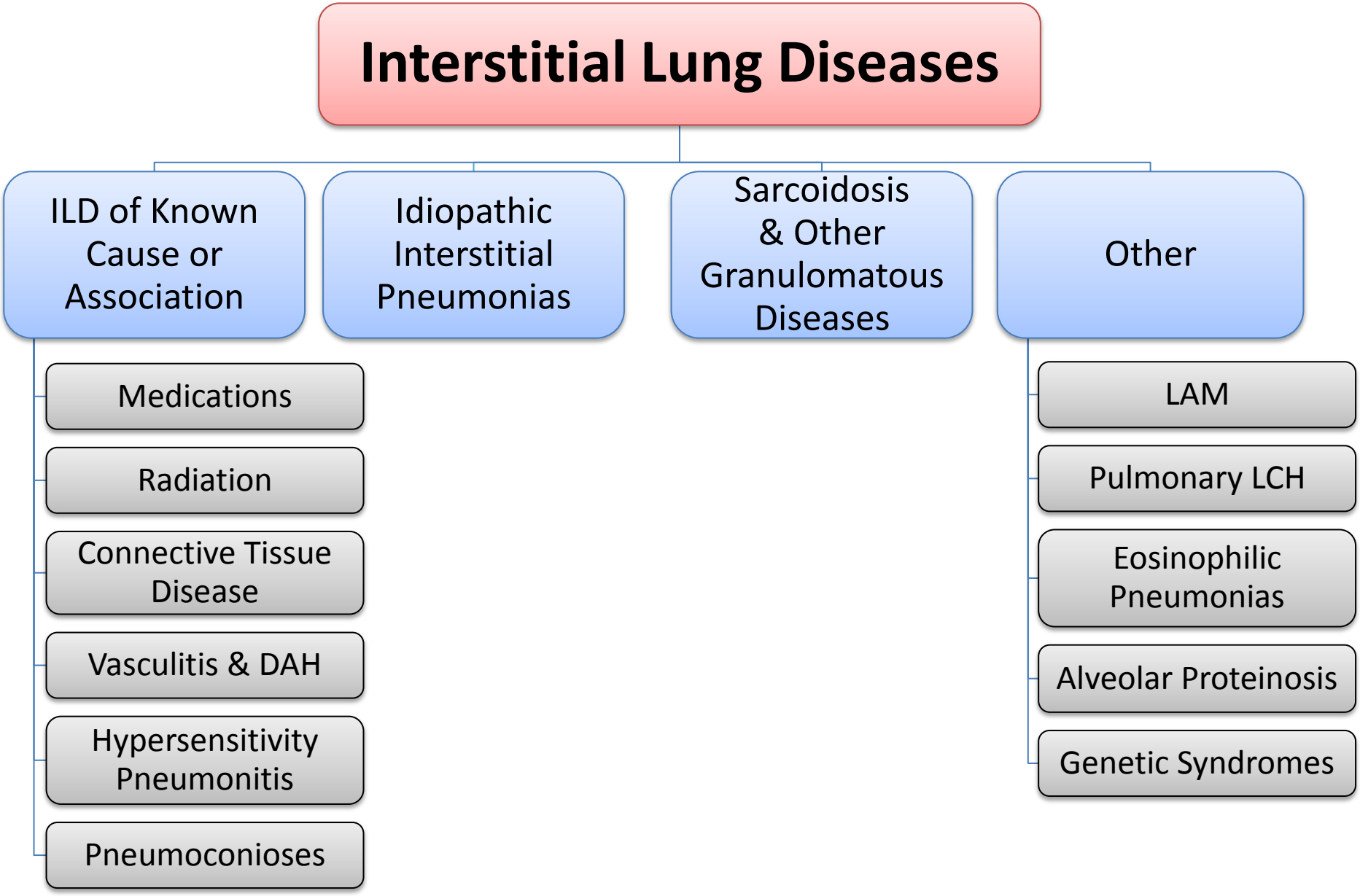
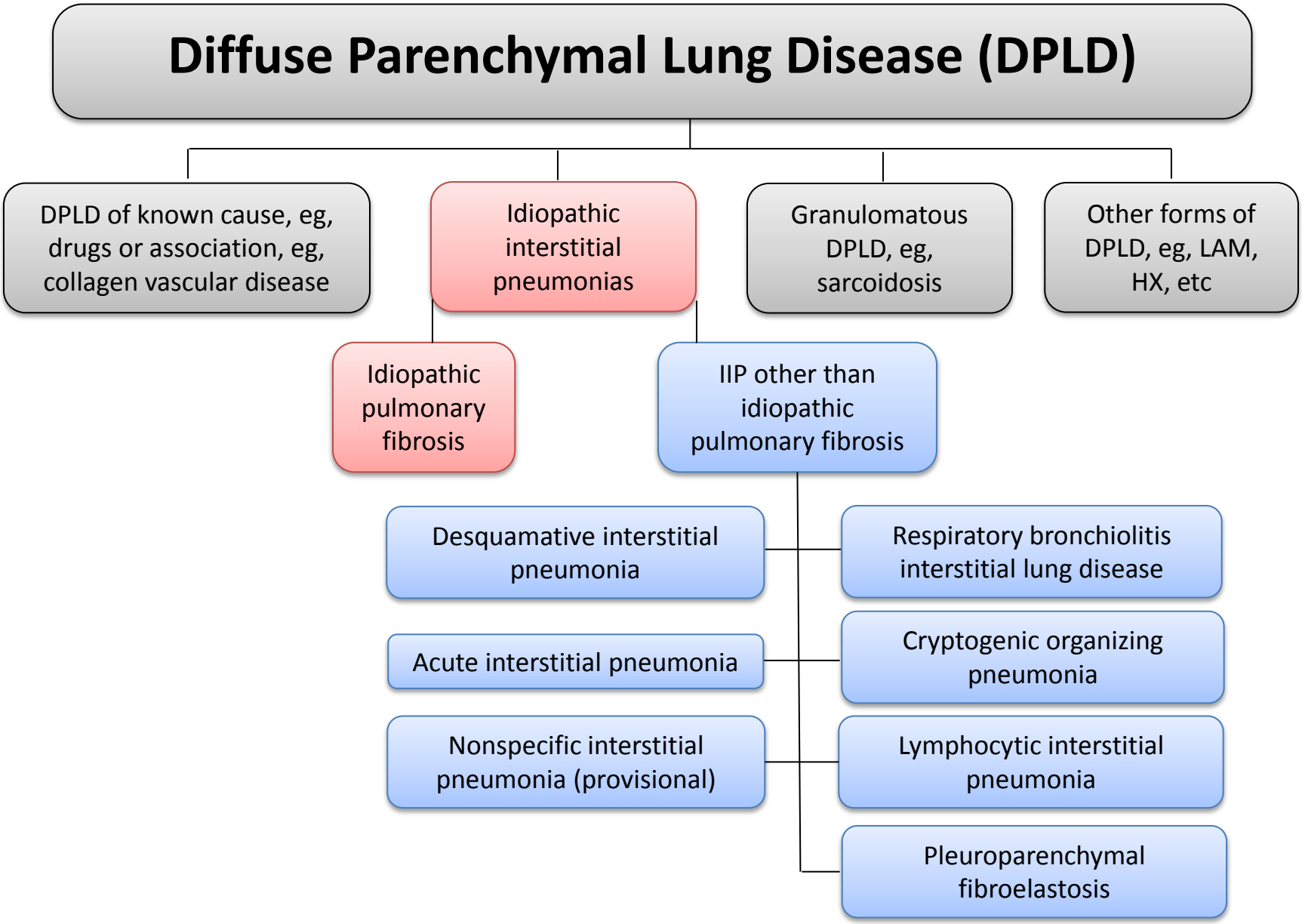
BHR NHS Trust



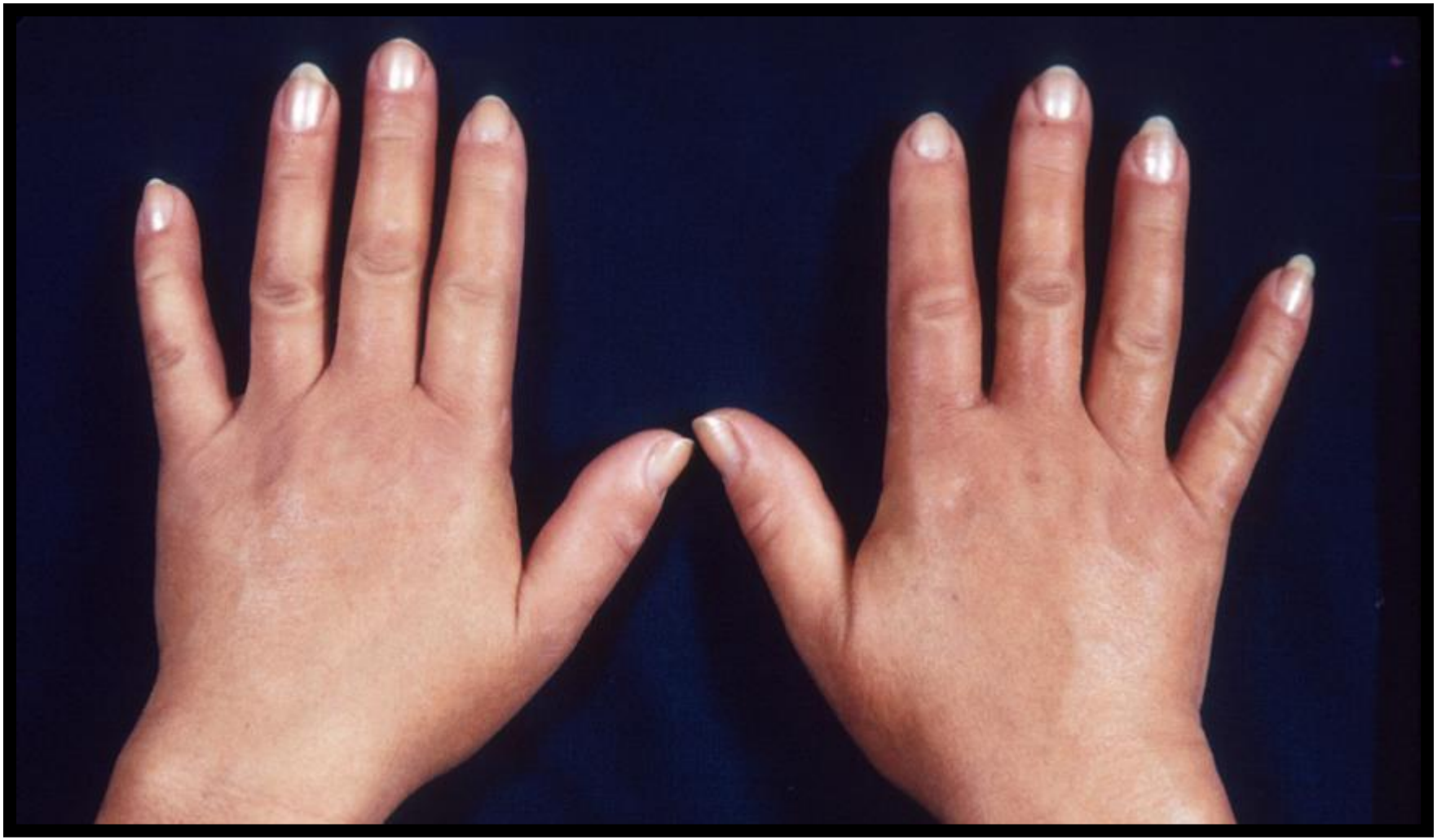
Adapted from: ATS/ERS Guidelines for IIP. *AJRCCM*. 2002;165:277-304.



Travis WD, et al; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. *Am J Respir Crit Care Med*. 2013;188(6):733-748.

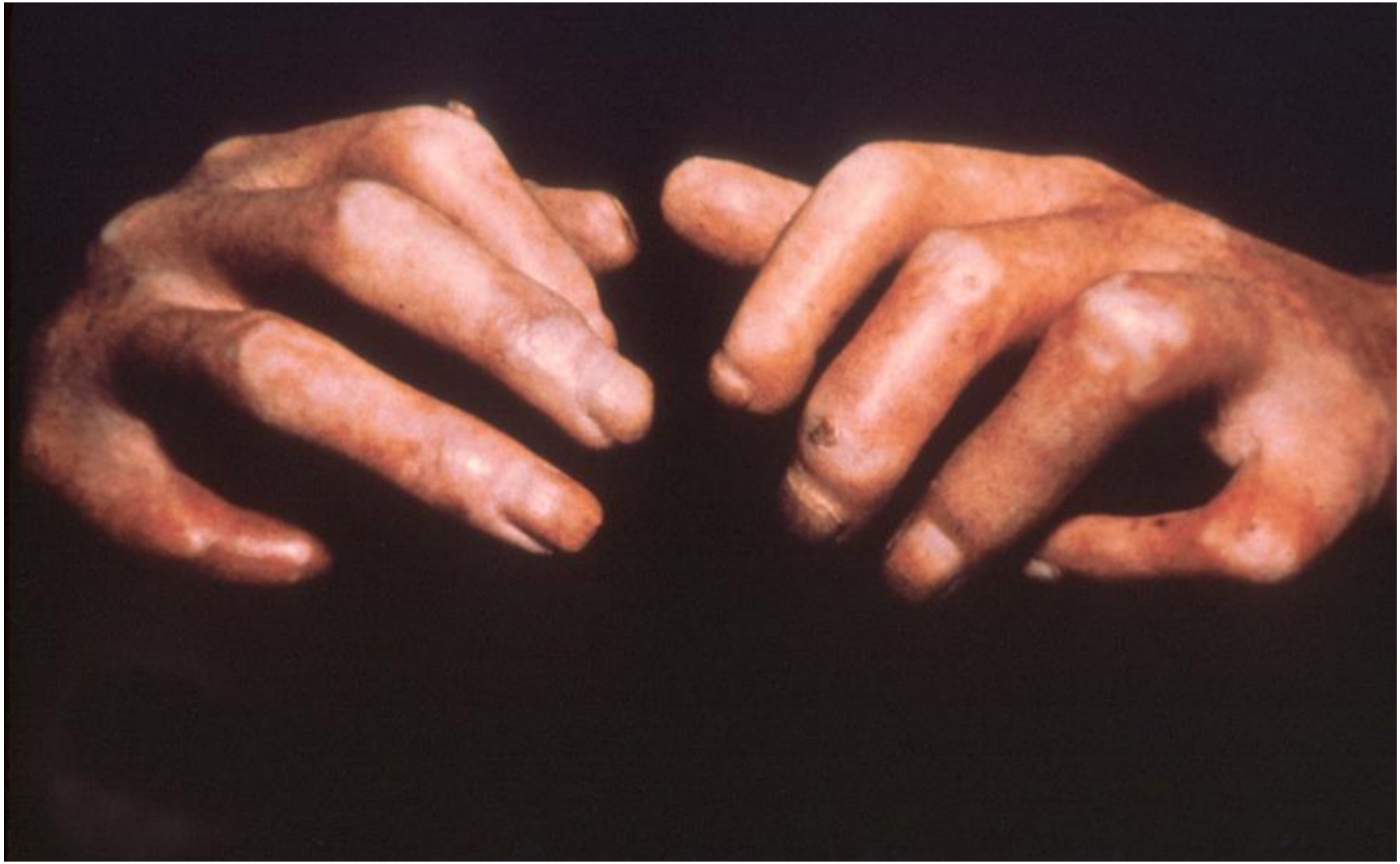
- Age and sex
- Drug history (e.g Amiodarone, Nitrofurantoin)
- Occupational exposures
- Pets
- Joint pain / inflammation or morning stiffness
- Raynaud's phenomenon
- Stiffness in fingers or toes or skin ulceration
- Dry eyes/dry mouth
- Family history of chest disease

Puffy Fingers in Early Scleroderma or Mixed CTD



http://images.rheumatology.org. Accessed July 2014.

Advanced Sclerodactyly



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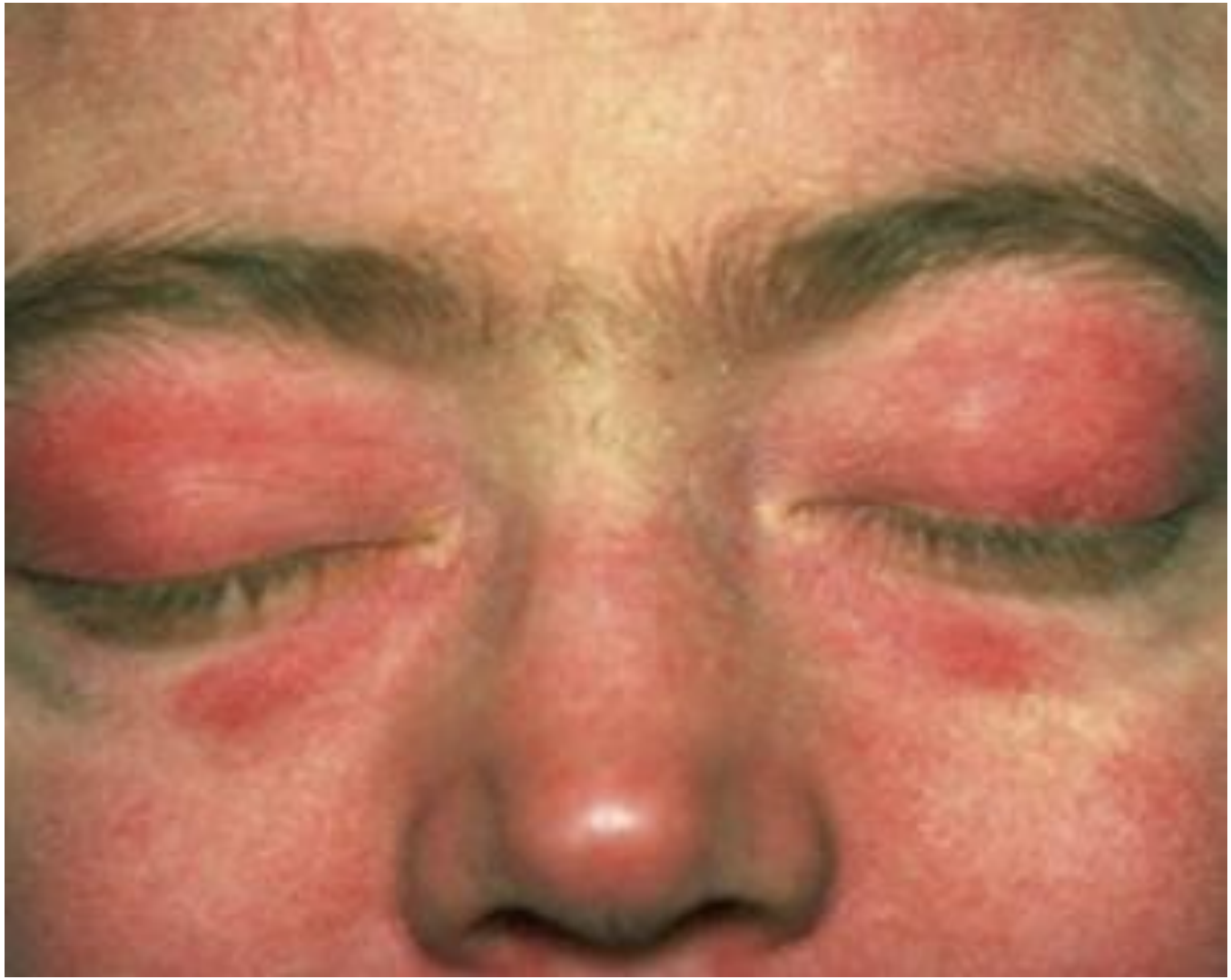

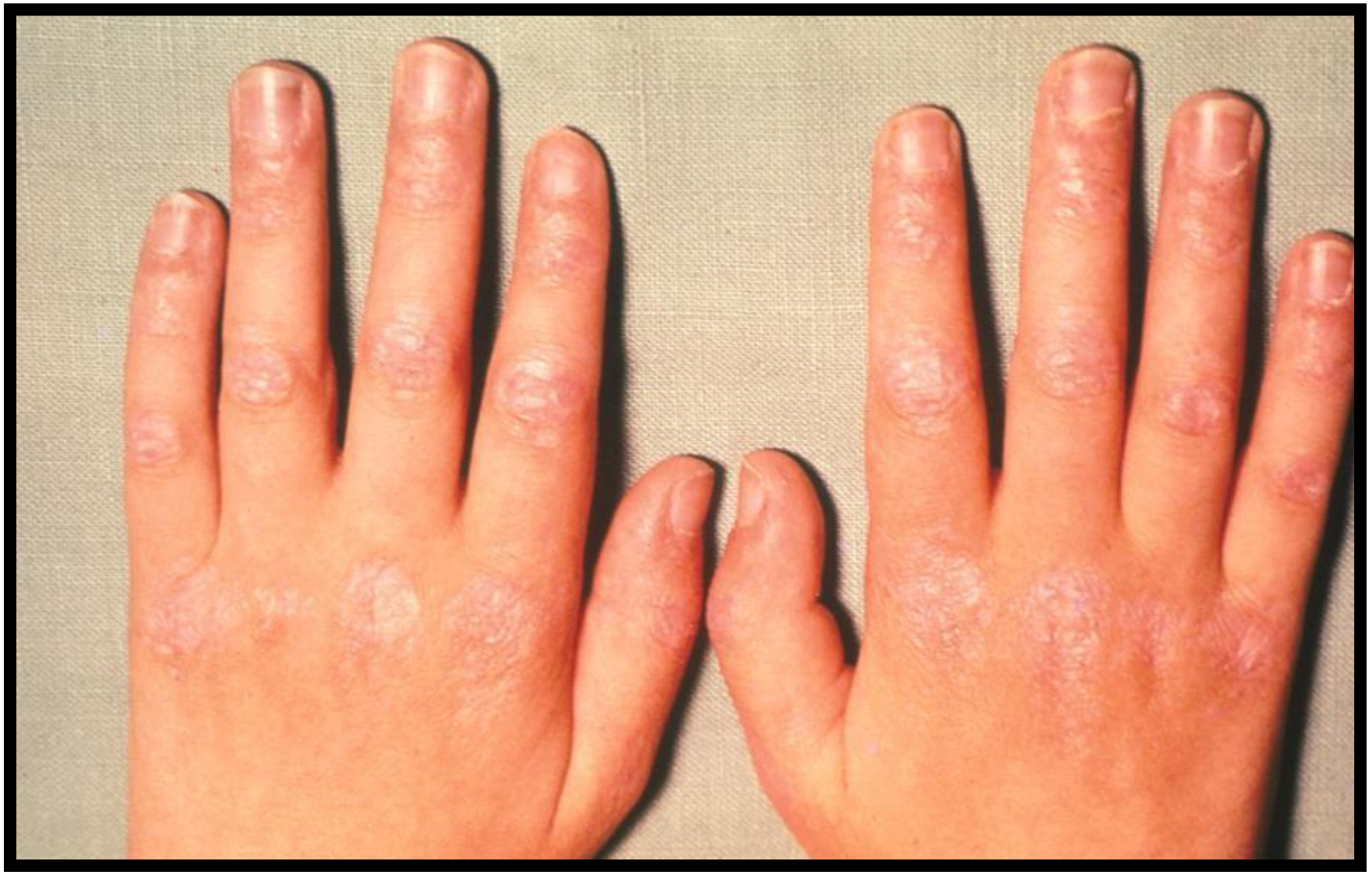

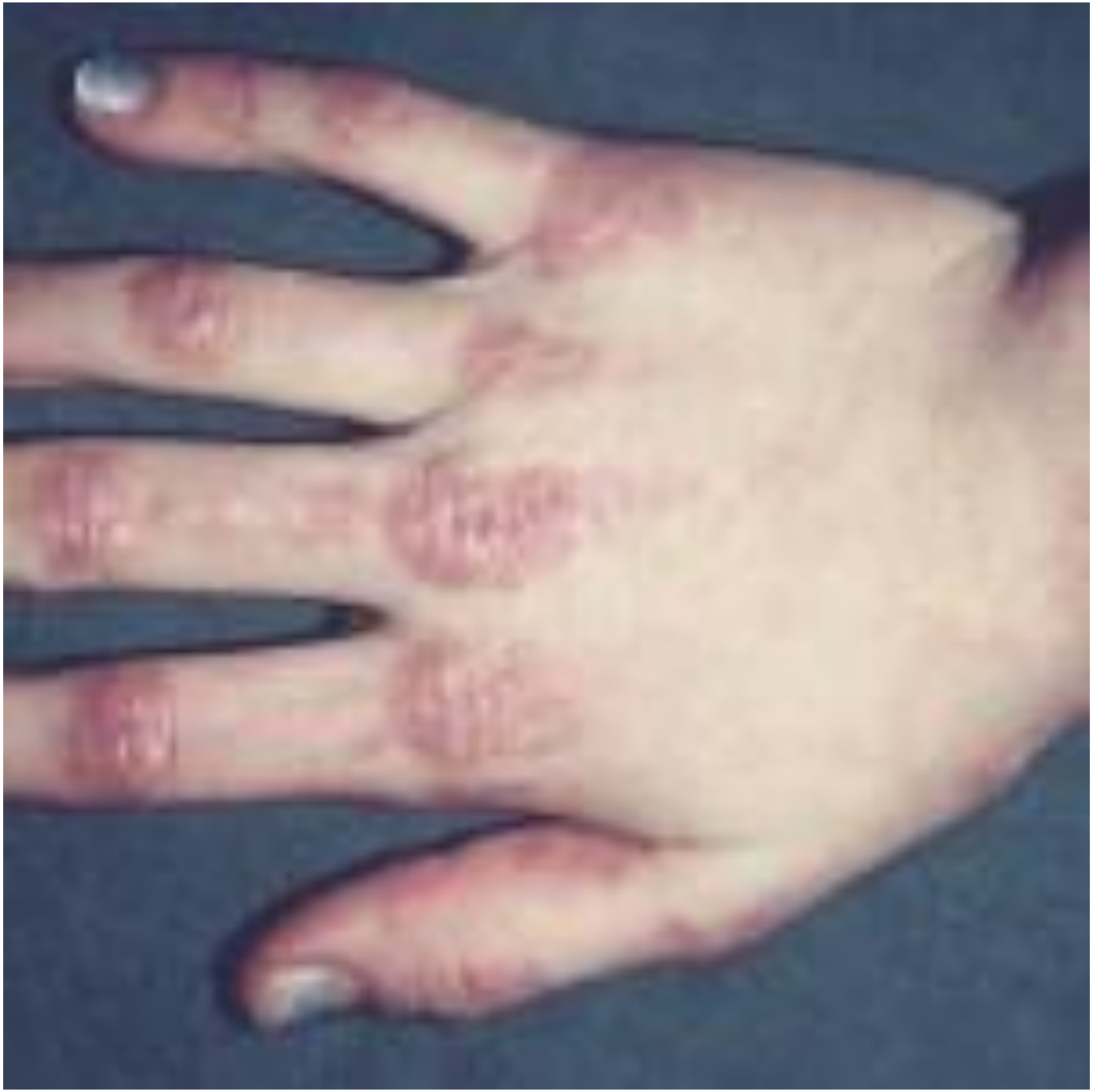

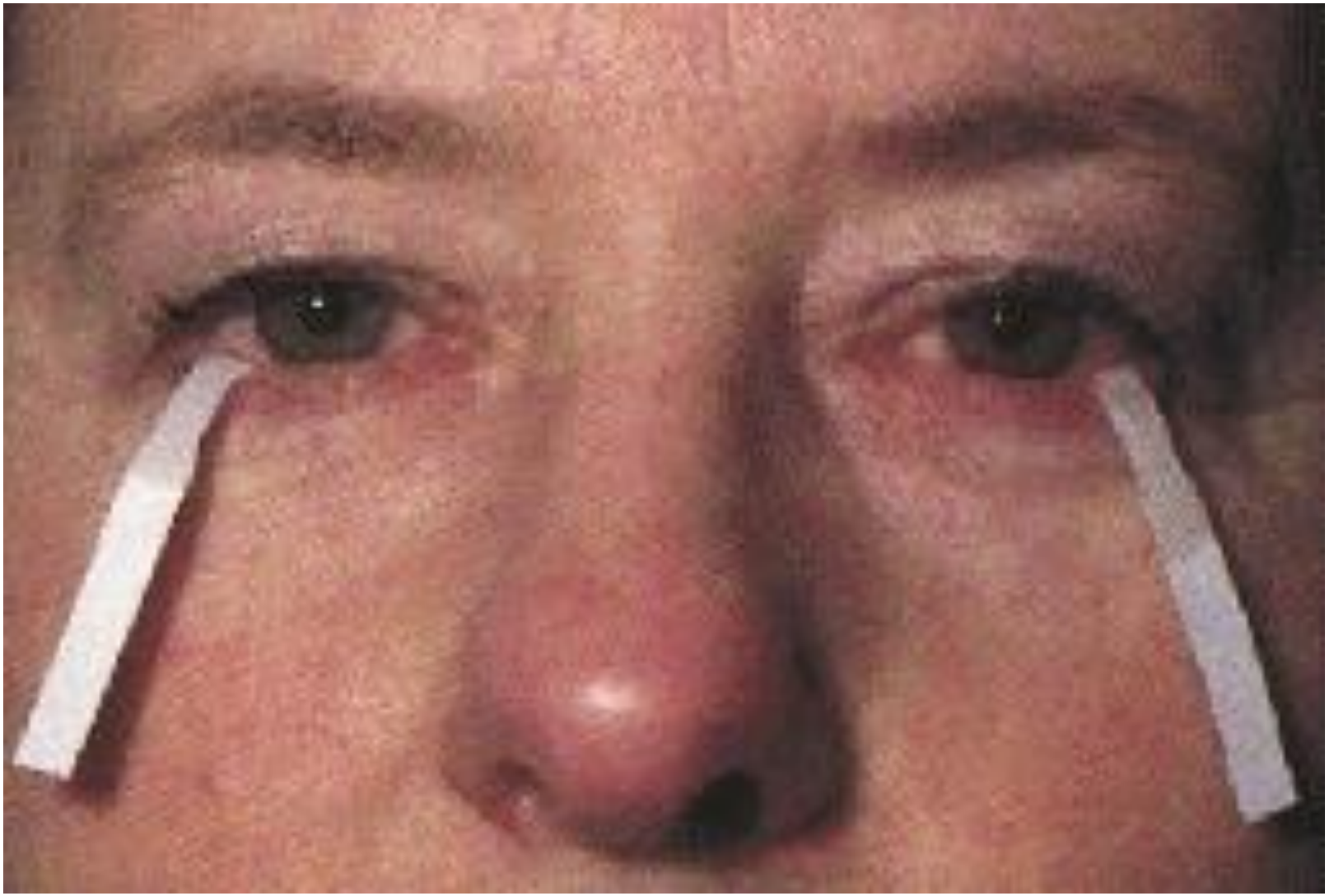

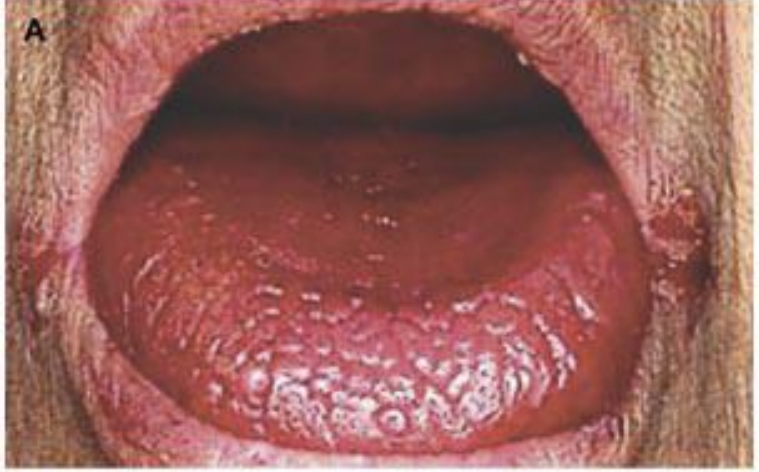
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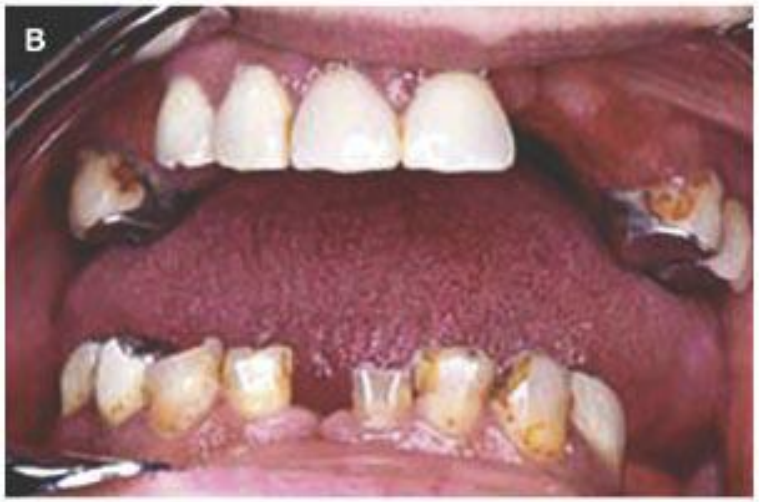
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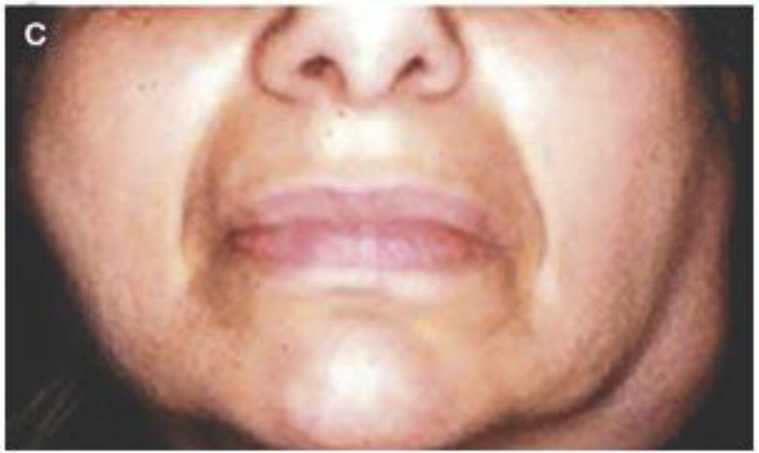
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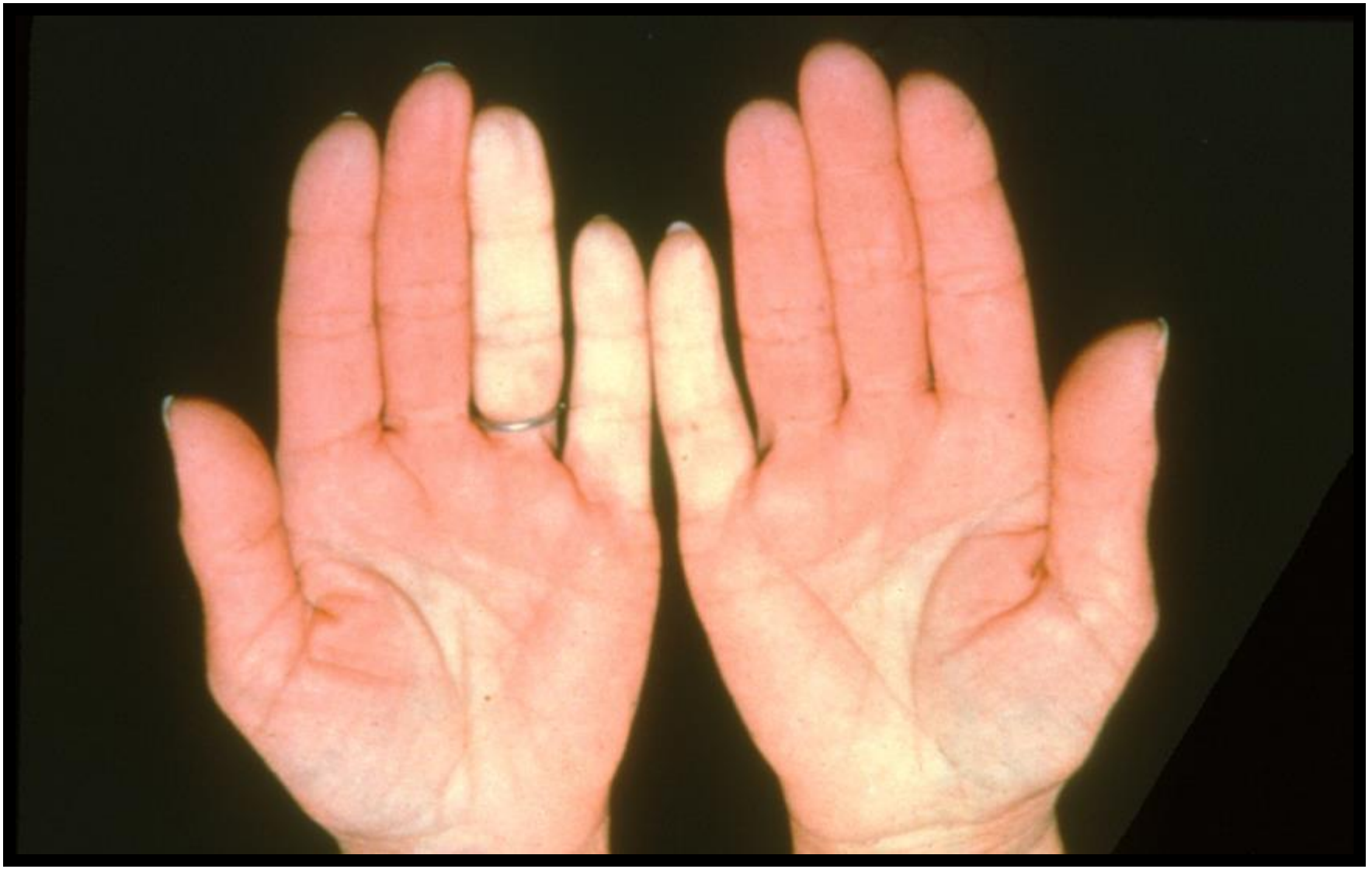
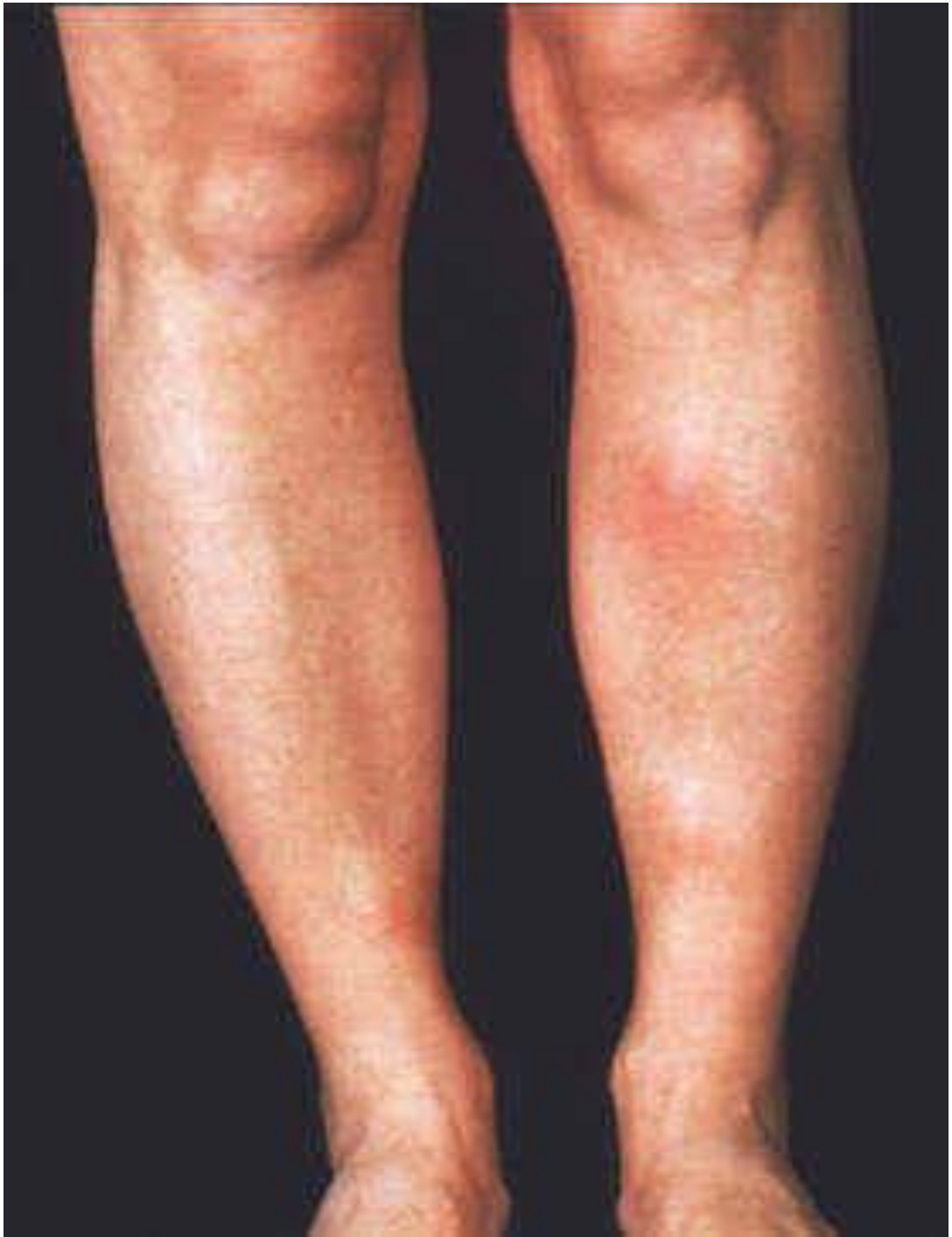
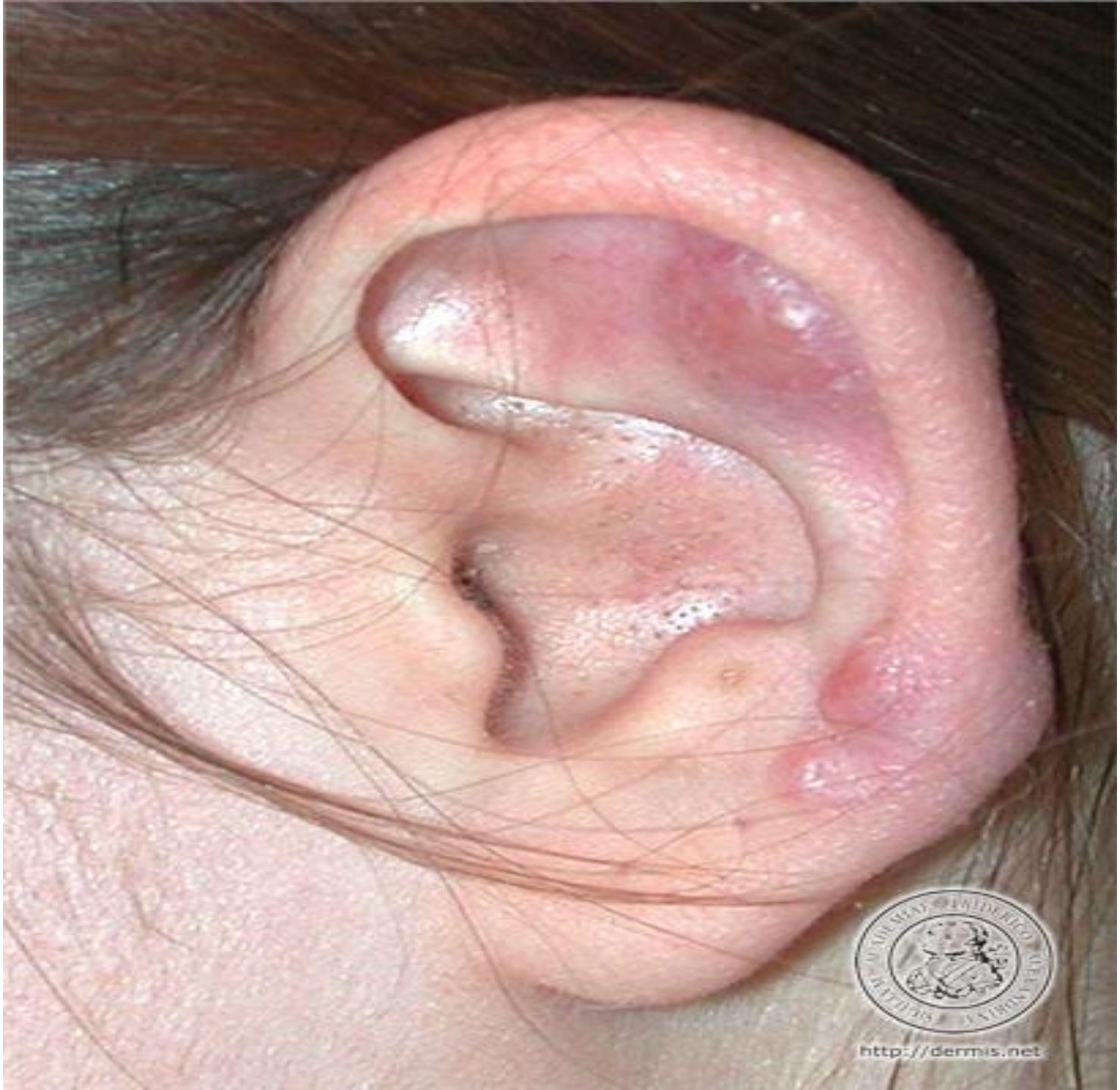
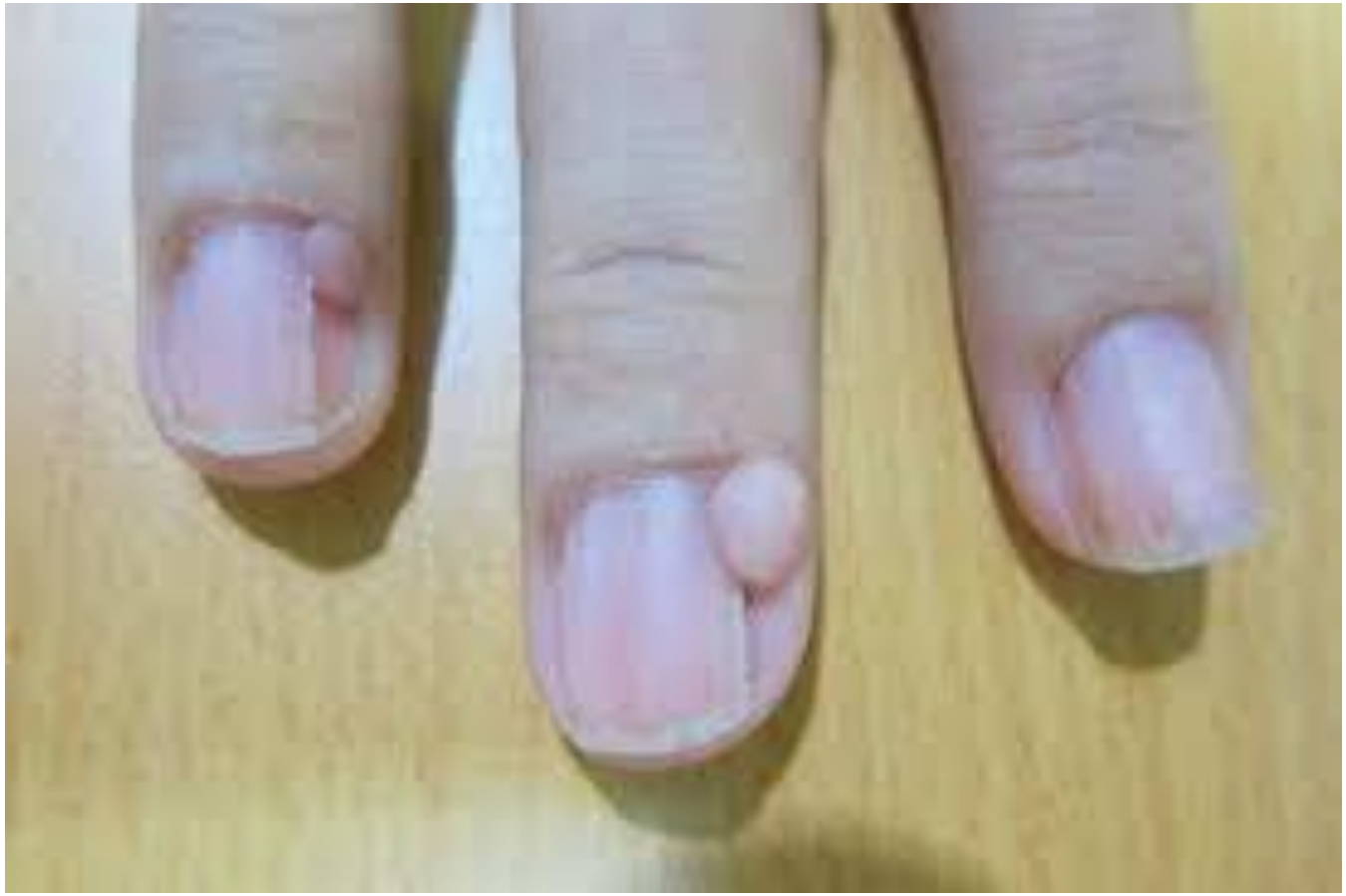
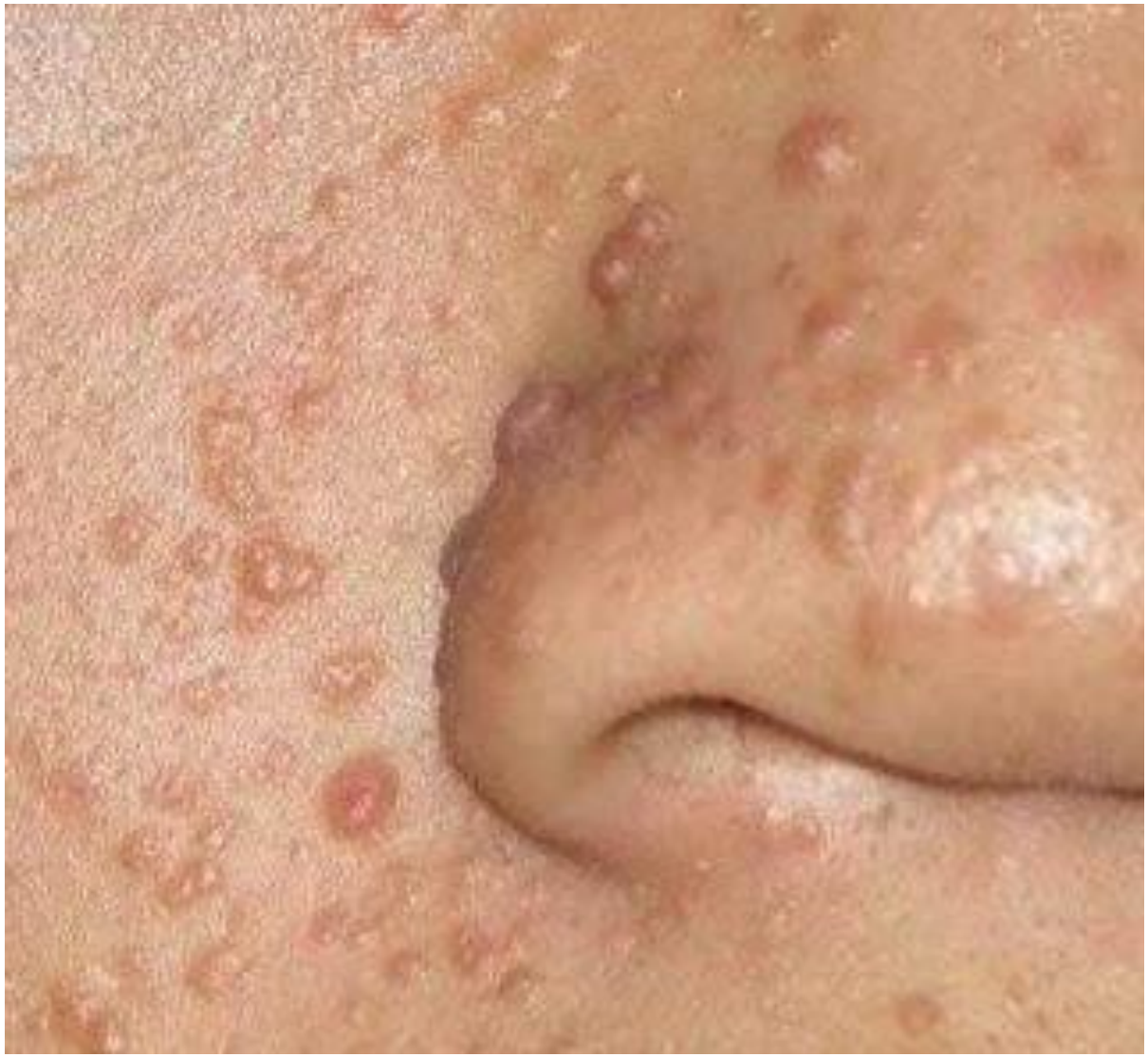
Raynaud's Phenomenon



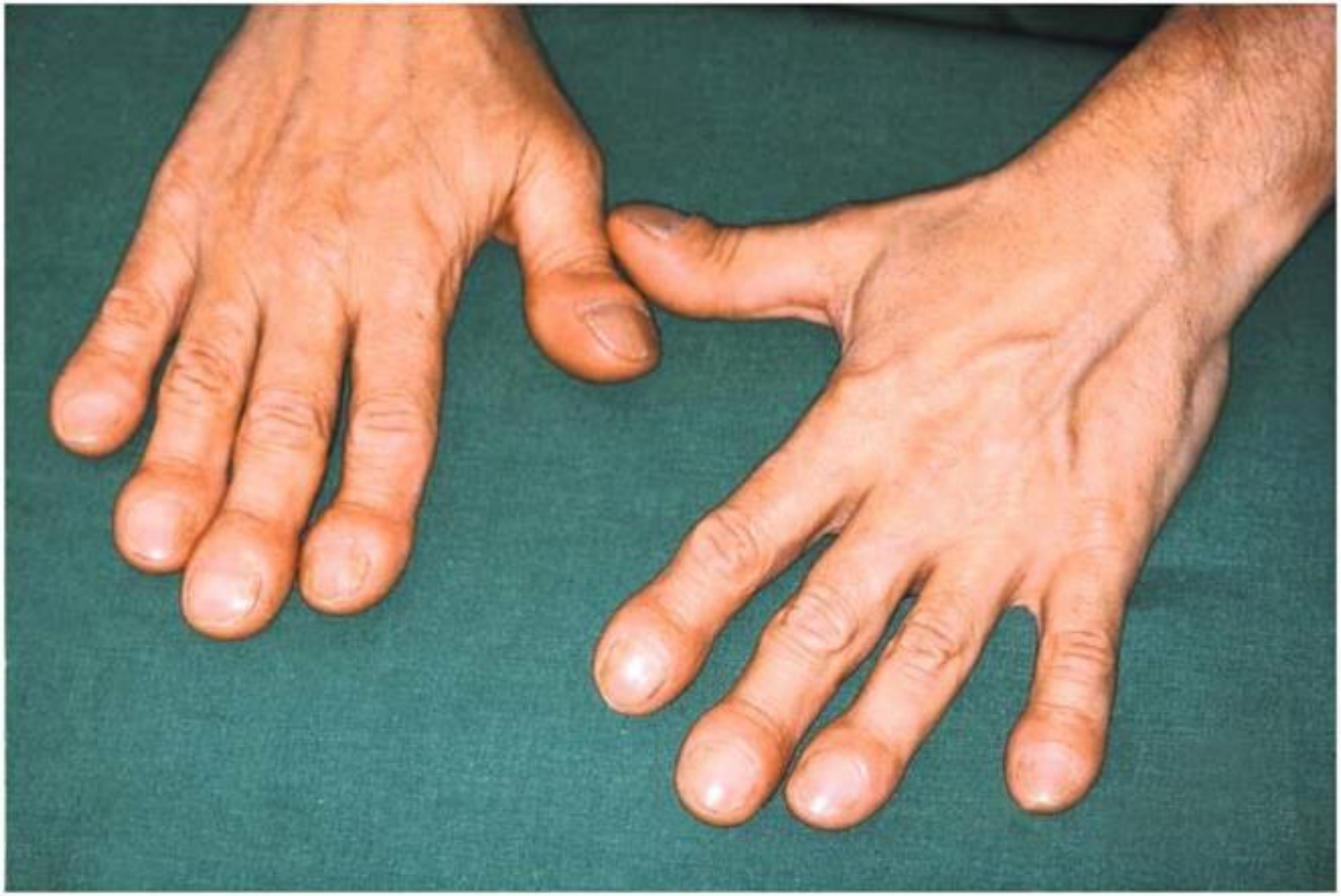



http://dermis.net

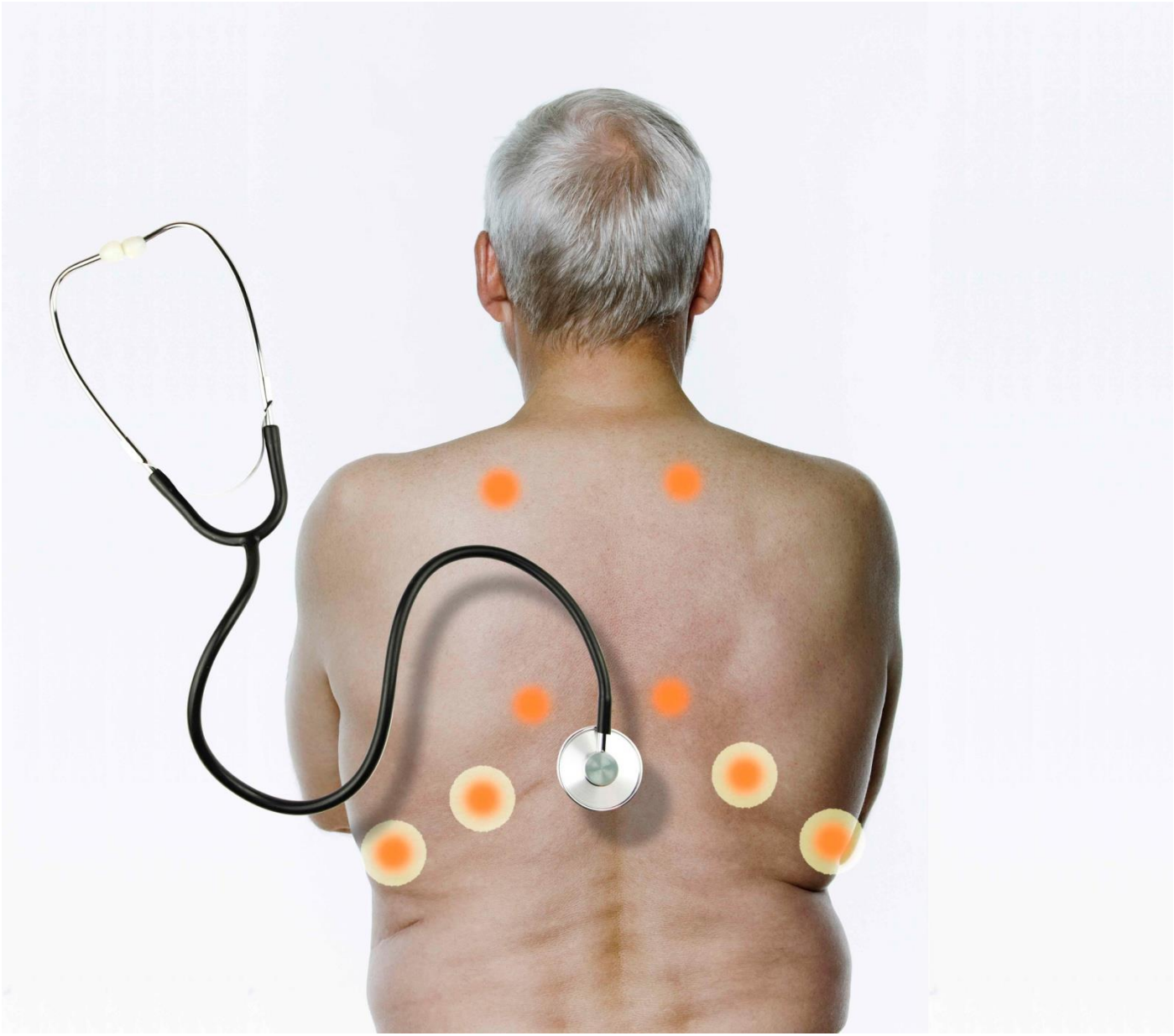




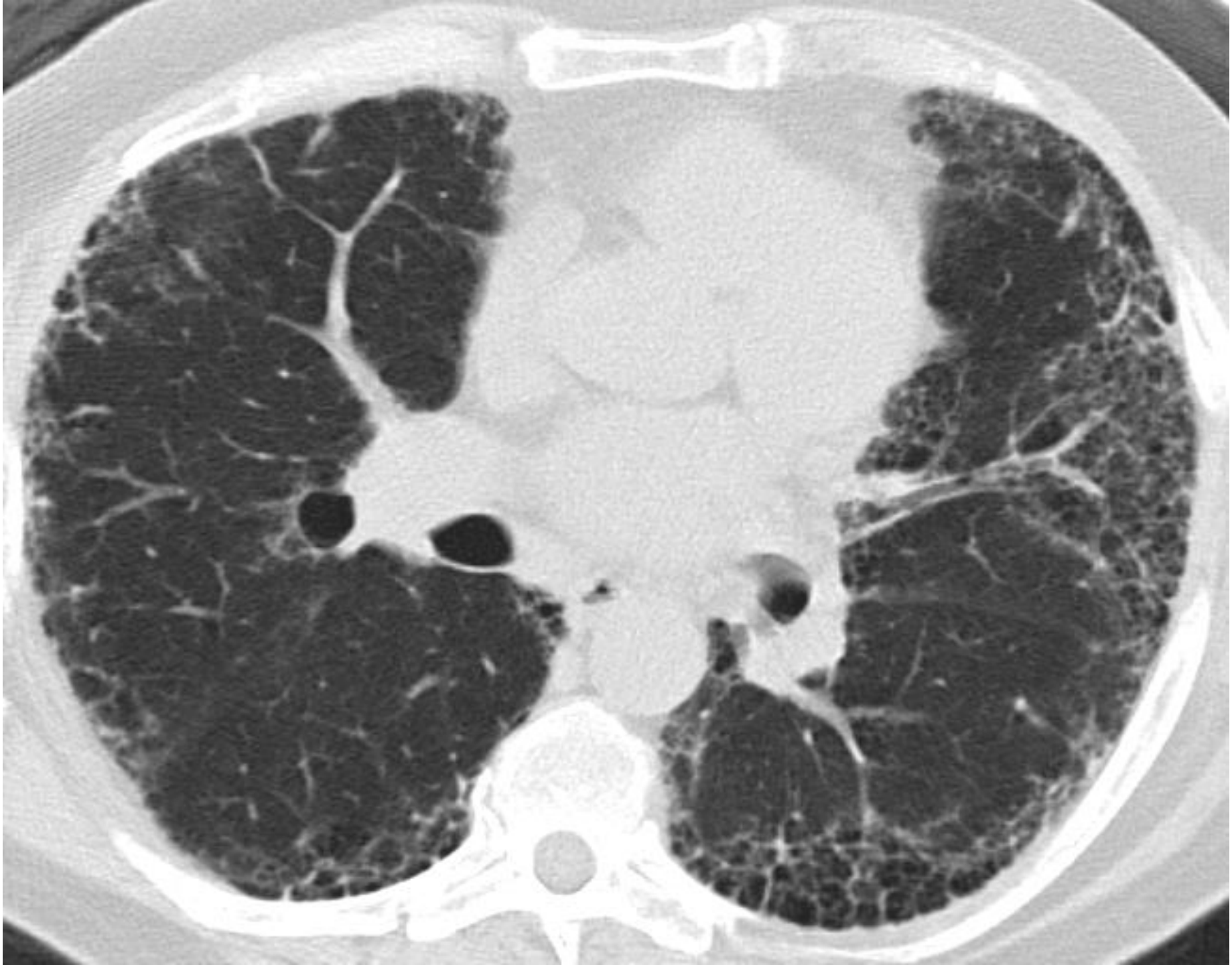
Digital Clubbing

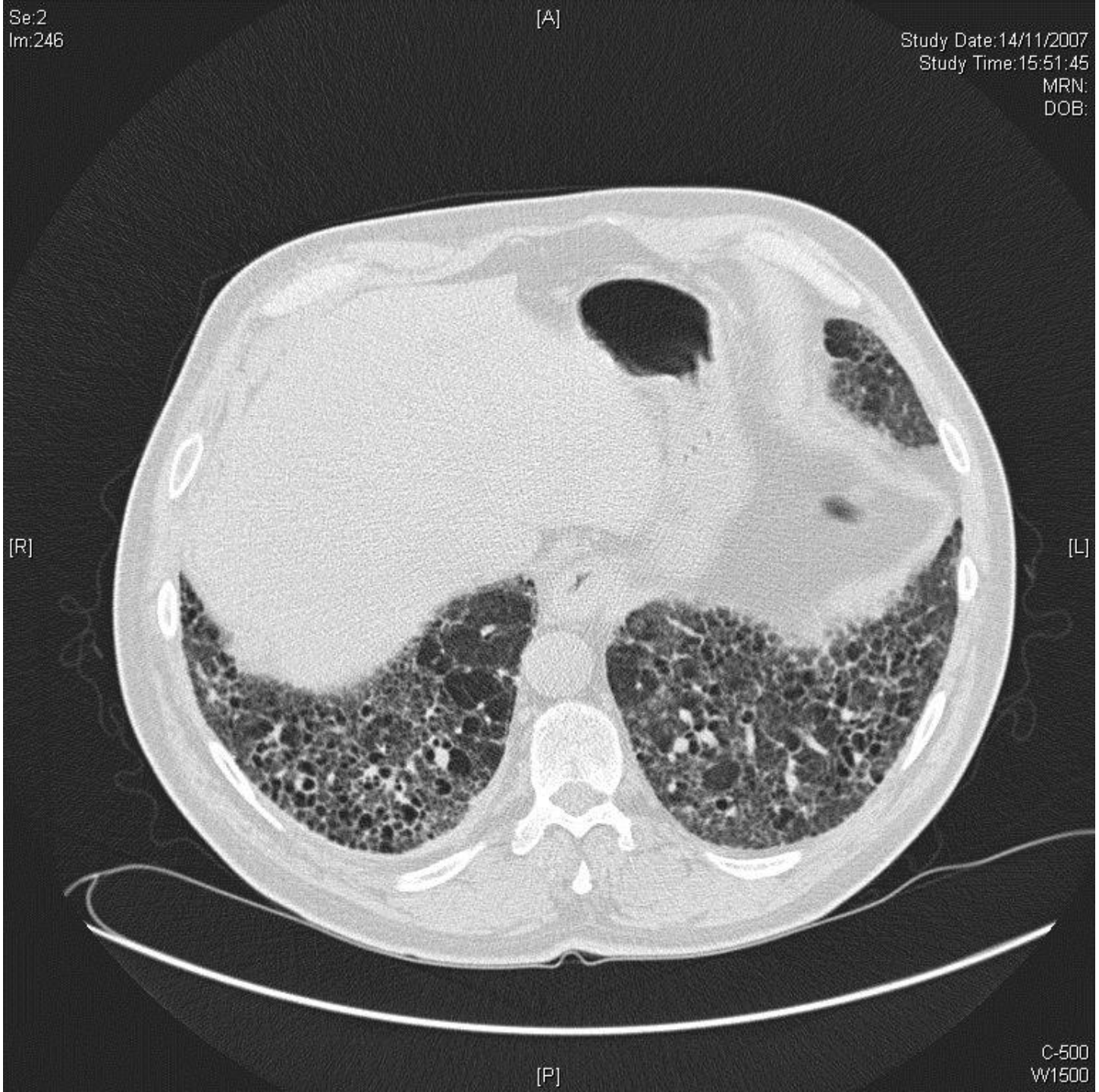


Reynen K, et al. *N Engl J Med.* 2000; 343:1235



diagnoseIPF.com

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[A]
Study Date:14/11/2007
Study Time:15:51:45
MRN:
DOB:
[R]
[L]
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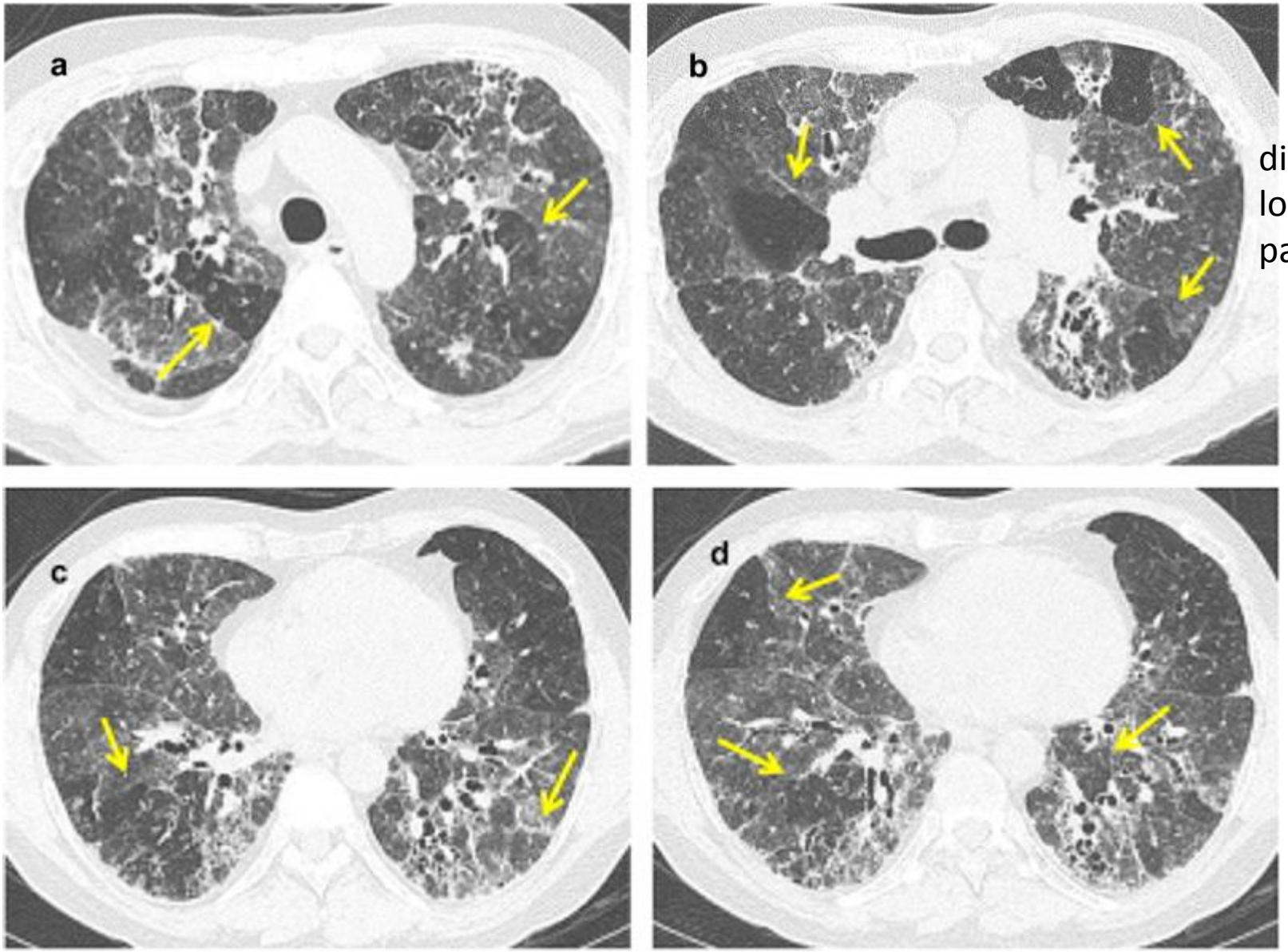
C-500
W1500

HRCT features *inconsistent* with IPF

Inconsistent Features
Upper lobe predominant
Peribronchovascular predominance
Ground-glass > extent of reticular abnormality
Profuse micronodules
Discrete cysts
Diffuse mosaic attenuation/gas-trapping
Consolidation

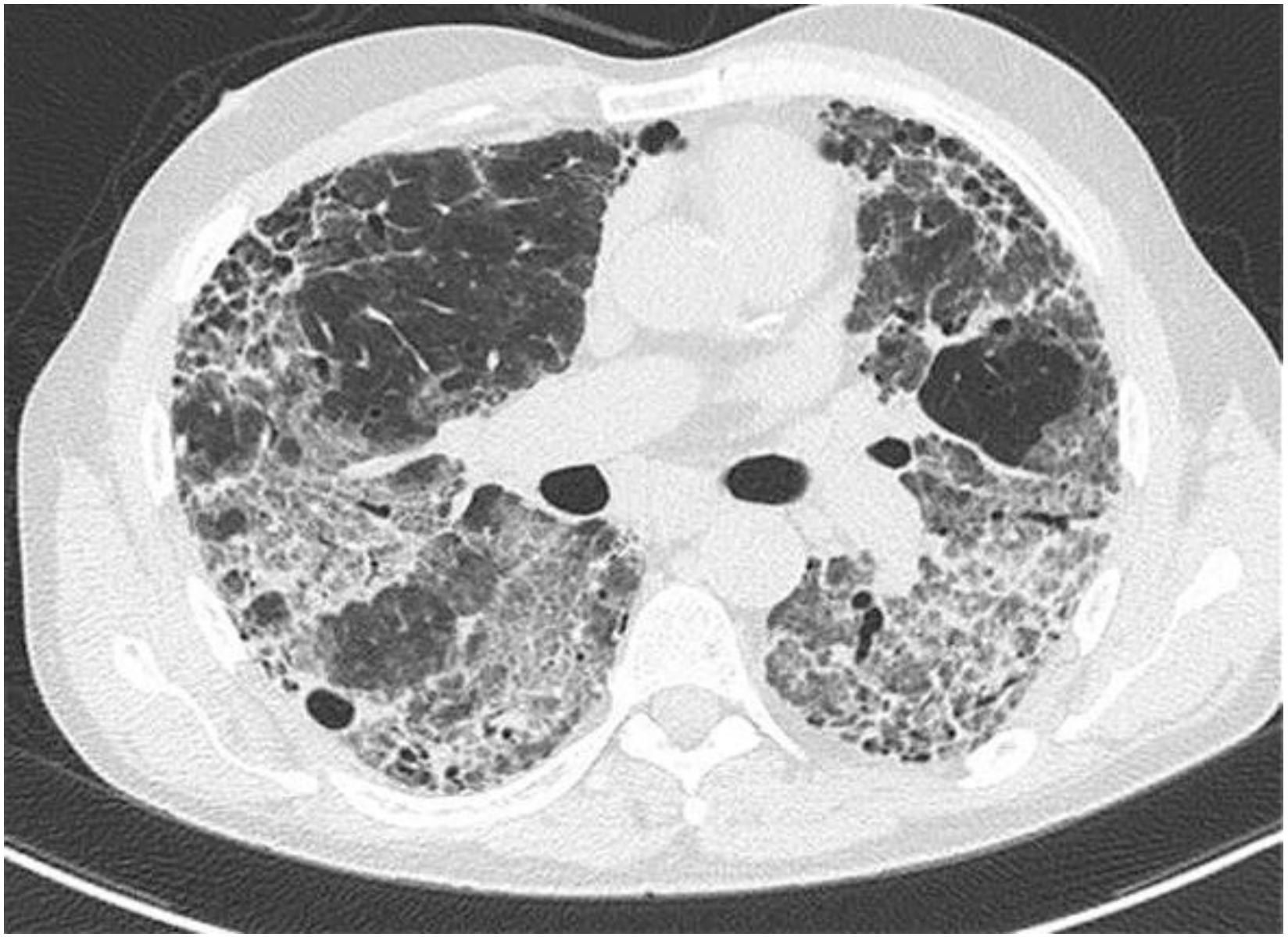
Raghu G, et al. *Am J Respir Crit Care Med*. 2011;183:788-824.

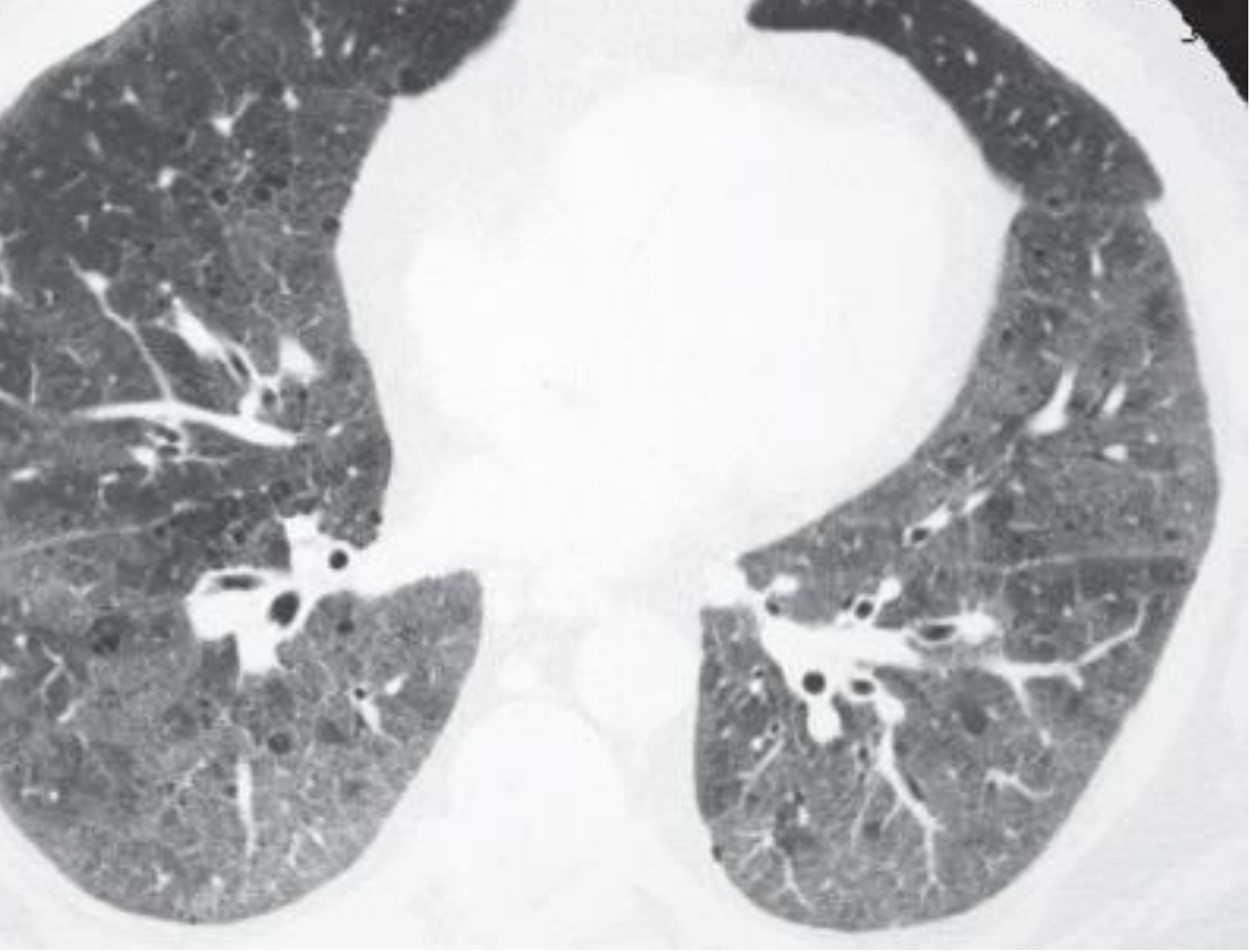
Inconsistent With UIP

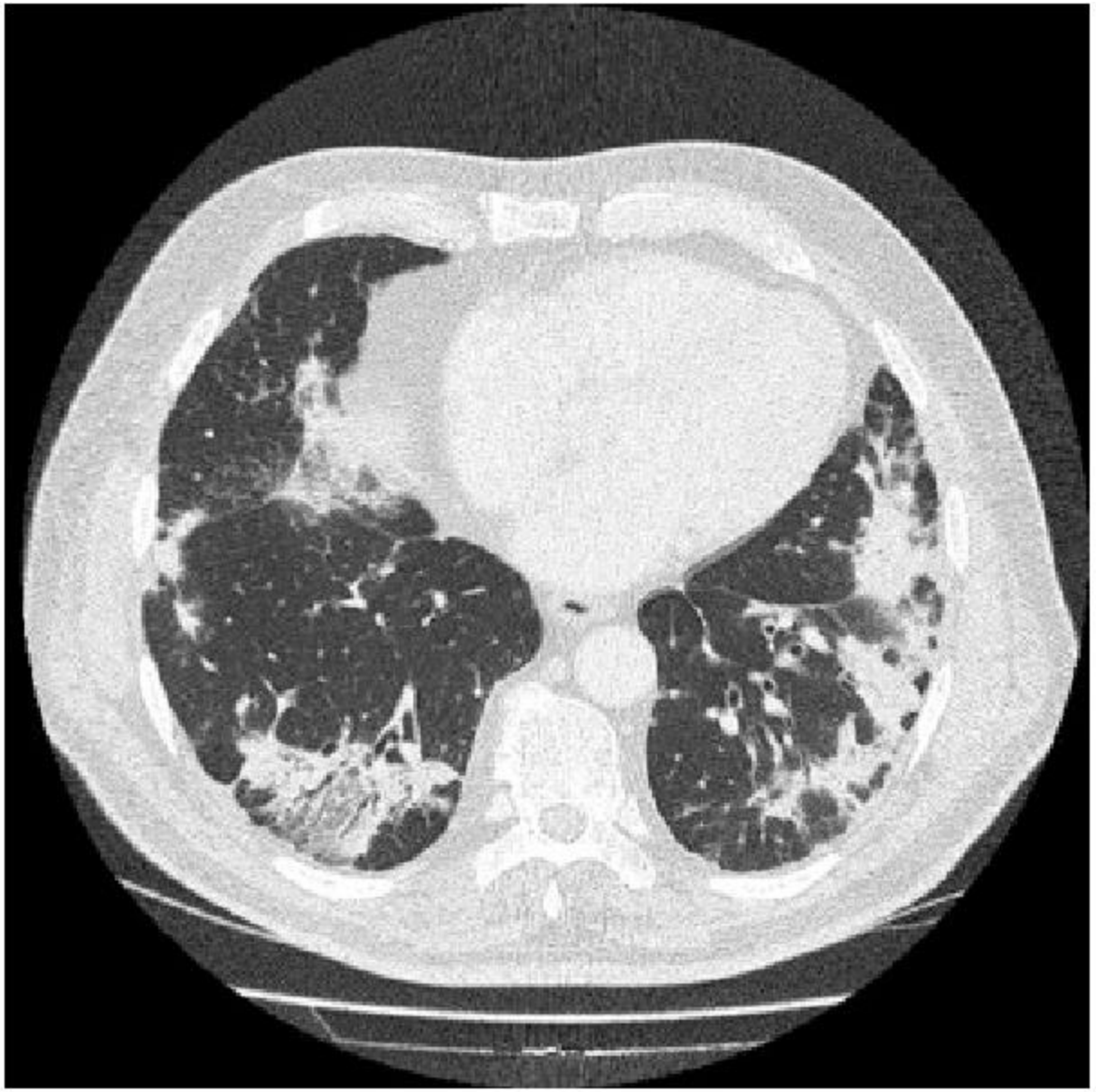


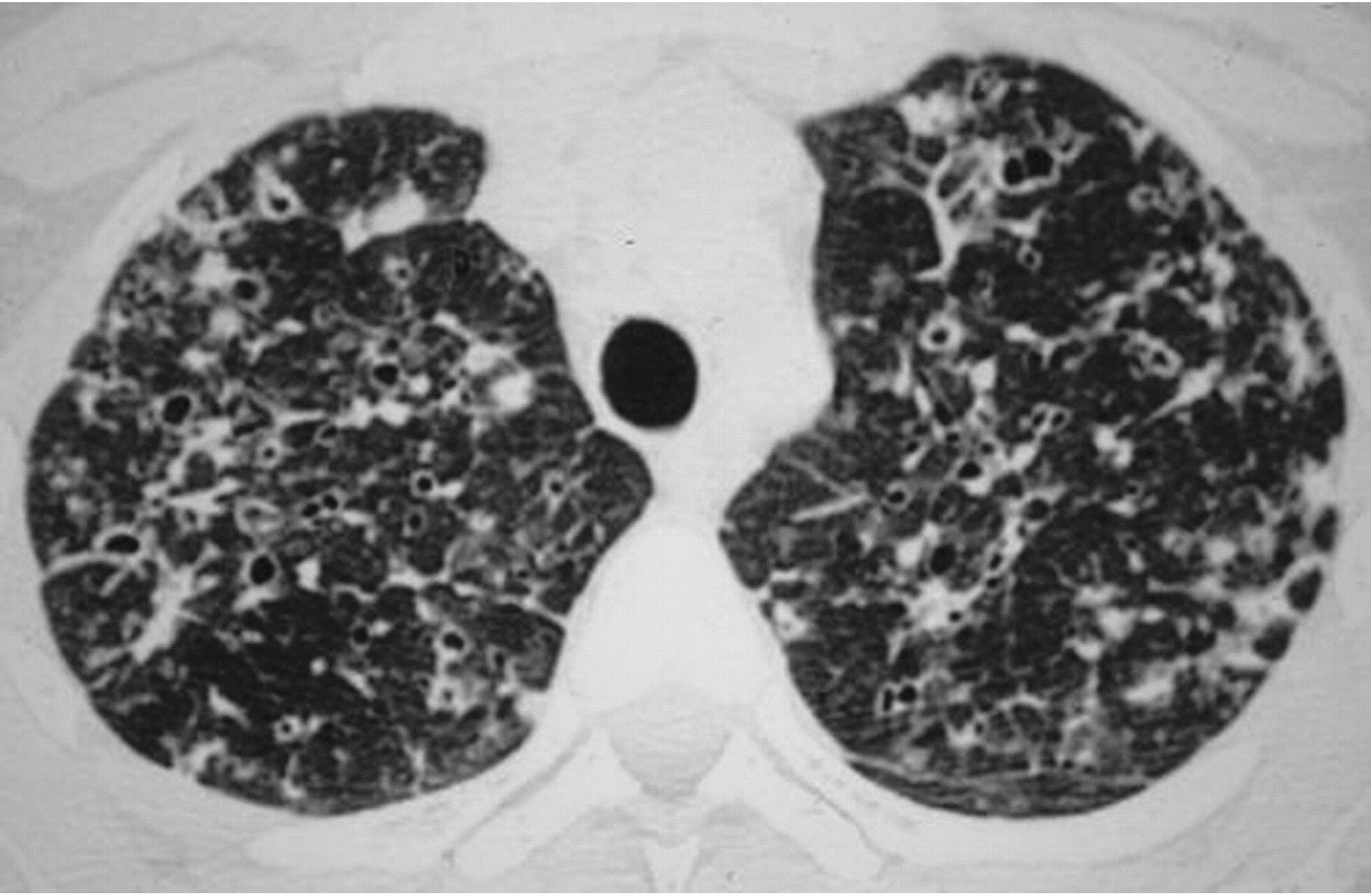
distinct lobular pattern

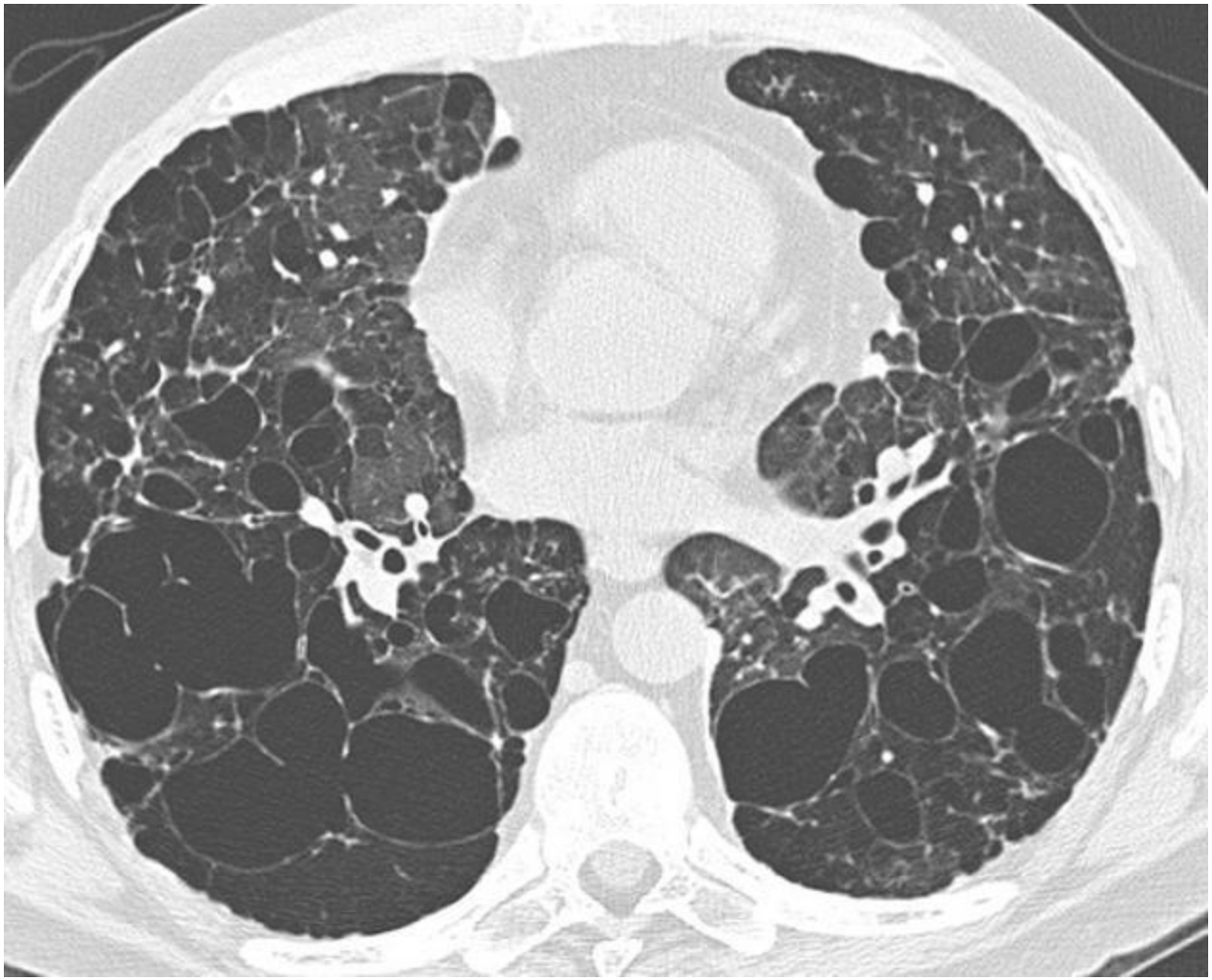
Hodnett PA, et al. *Am J Respir Crit Care Med.* 2013;188:141-149.

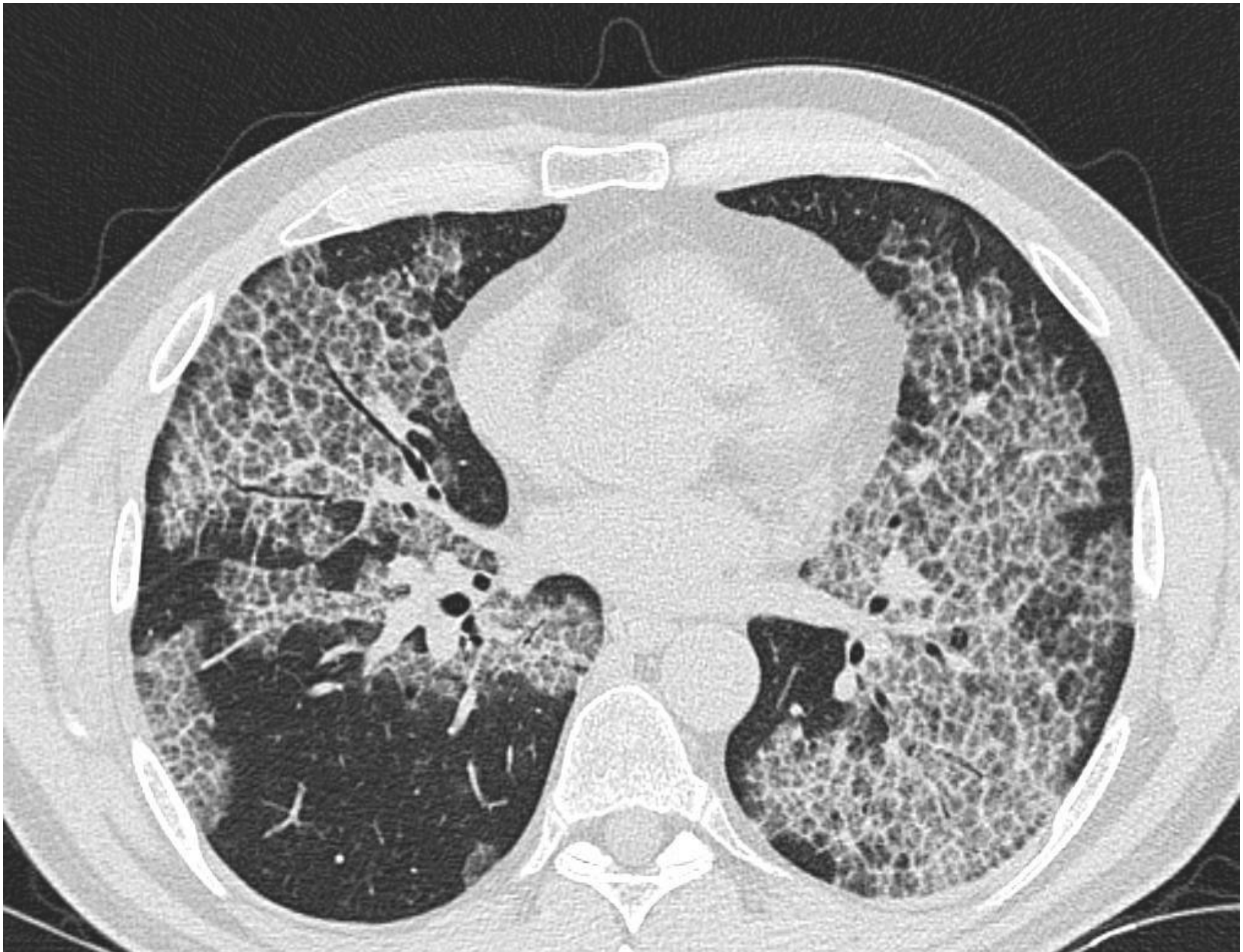


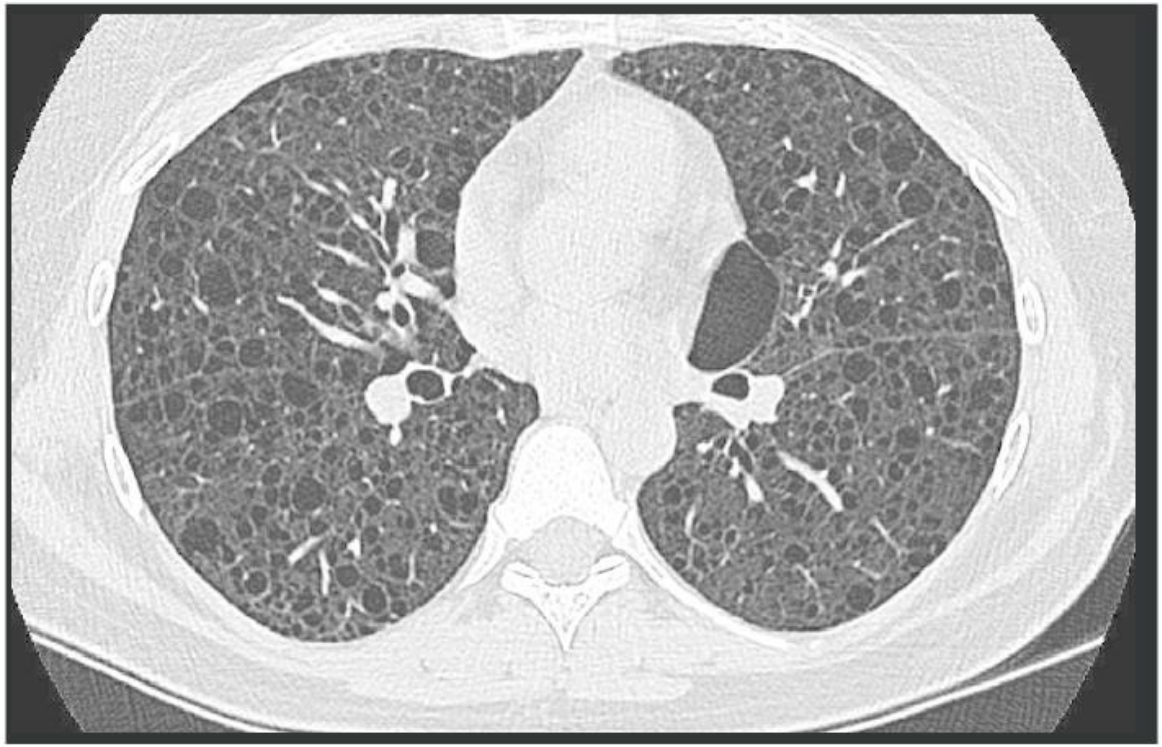


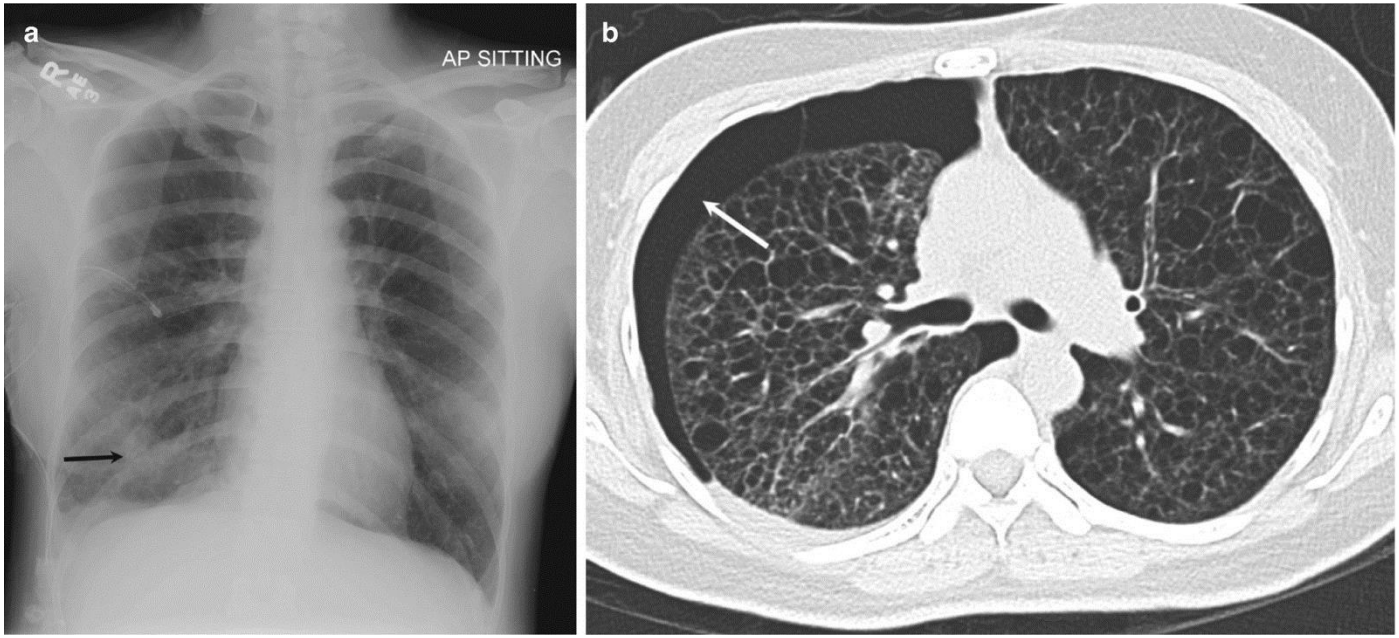










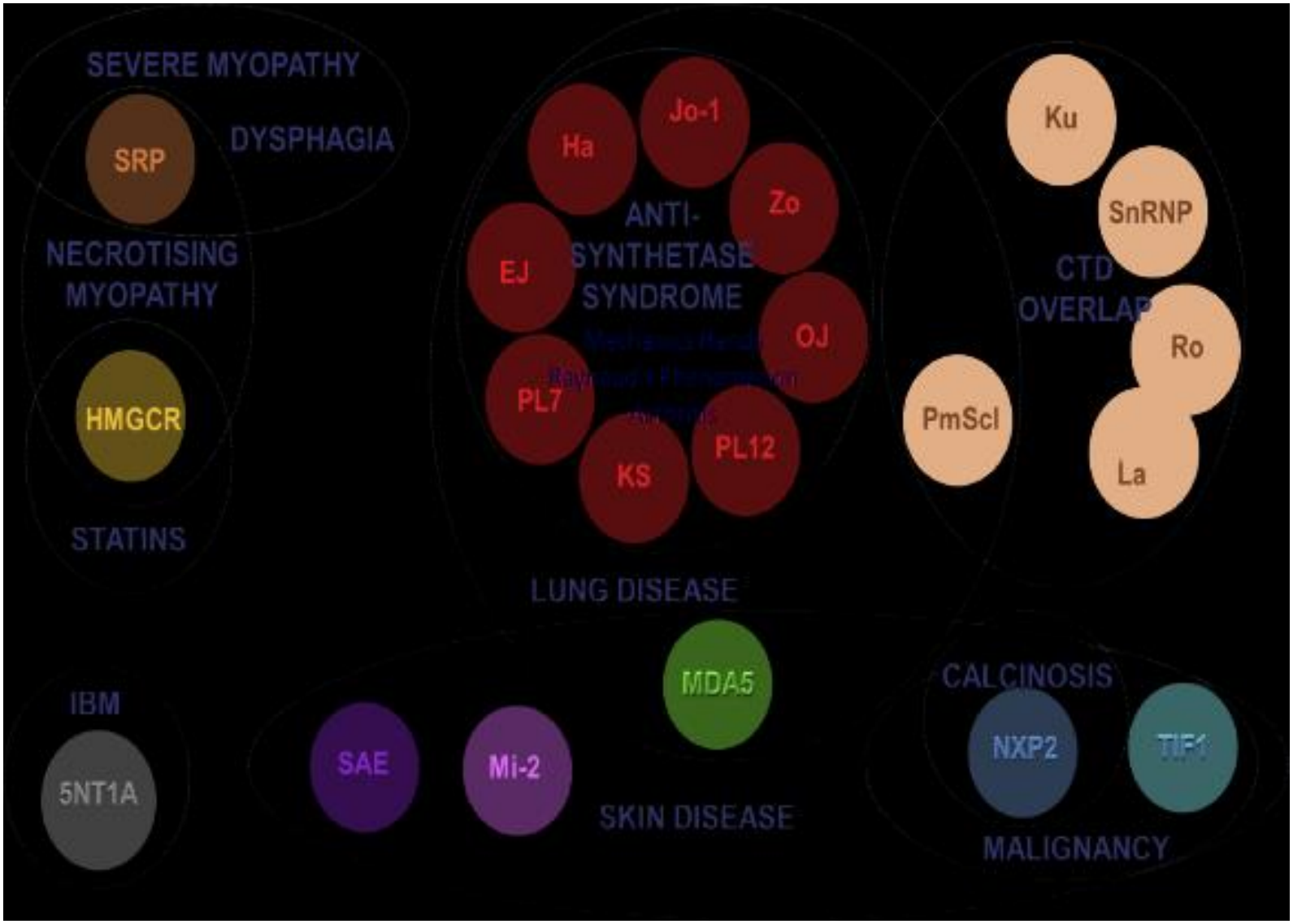

a
AP SITTING
b

Pulmonary Function Tests

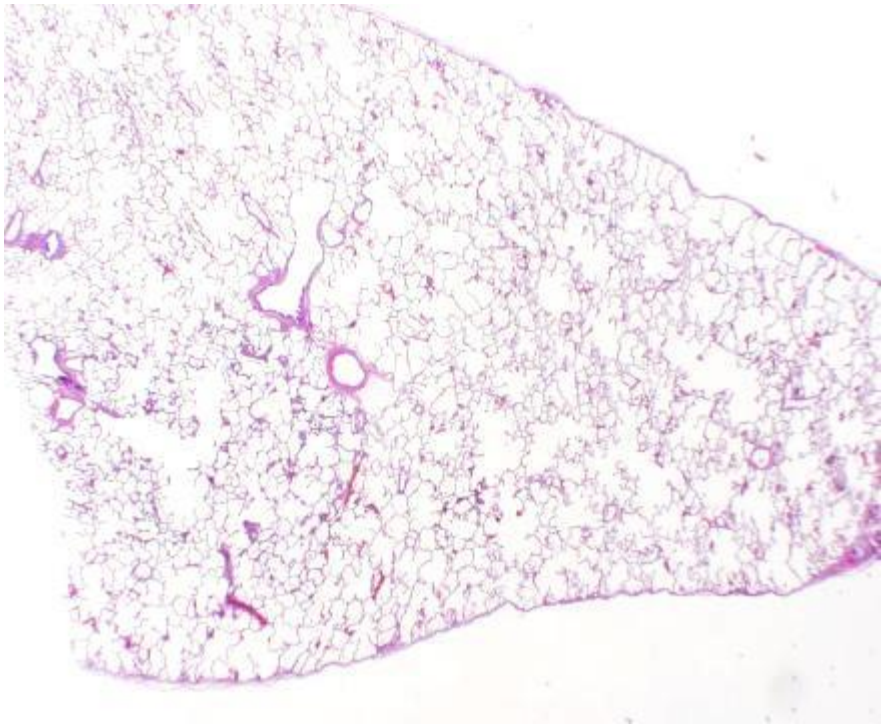
- Spirometry
  - Reduced FVC and TLC
  - Normal or increased FEV_1/FVC ratio
- Restriction often accompanied by some obstruction
- Impaired gas exchange
  - Decreased DL_{CO}, PaO_2
  - Desaturation on exercise oximetry
  - Increased A-aPO_2 gradient
- Normal PFTs do not exclude ILD
  - Emphysema + Interstitial Lung Disease

Blood Tests

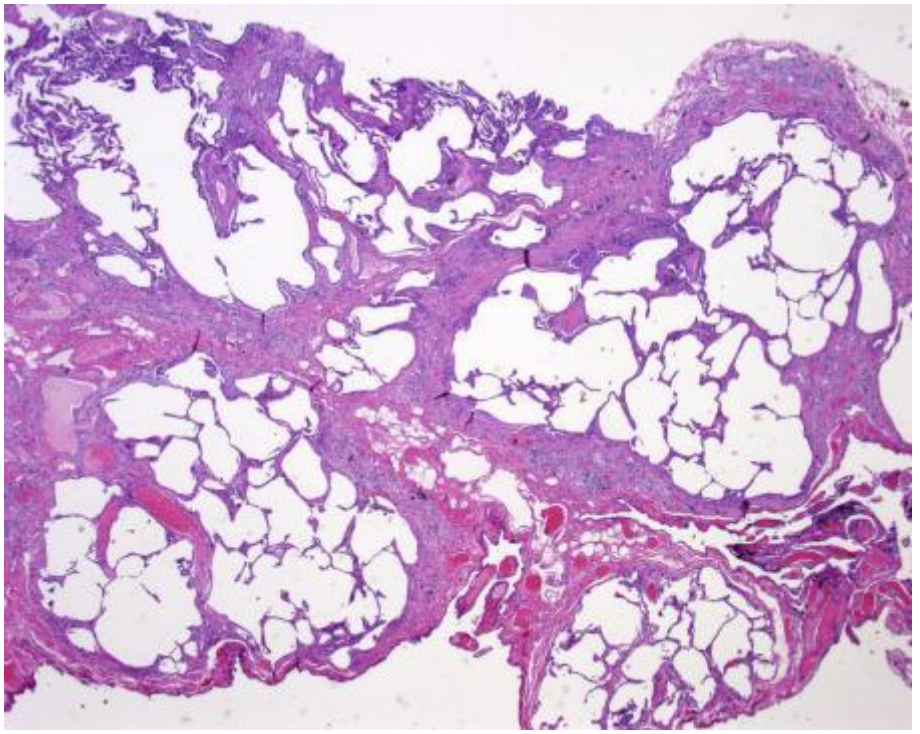
- Serum ACE
- CTD screen
- Vasculitis screen


SEVERE MYOPATHY
DYSPHAGIA
SRP
NECROTISING MYOPATHY
HMGCR
STATINS
Ha
Jo-1
Zo
EJ
ANTI-SYNTHETASE SYNDROME
OJ
PL7
KS
PL12
LUNG DISEASE
Ku
SnRNP
CTD OVERLAP
Ro
PmScl
La
MDA5
IBM
5NT1A
SAE
Mi-2
SKIN DISEASE
CALCINOSIS
NXP2
TIF1
MALIGNANCY

Idiopathic Pulmonary Fibrosis

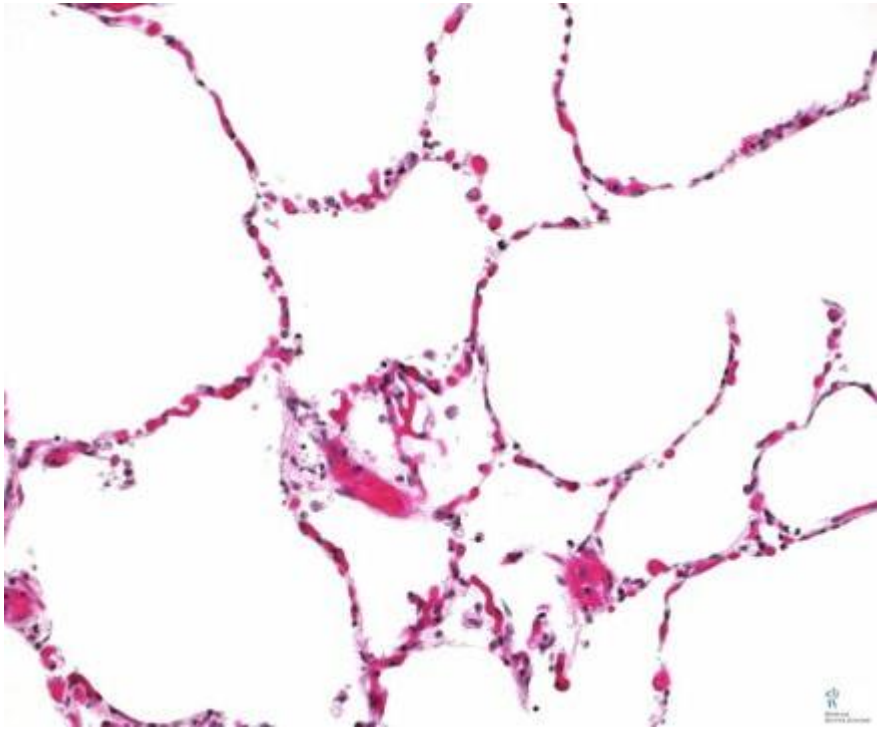


Normal Lung

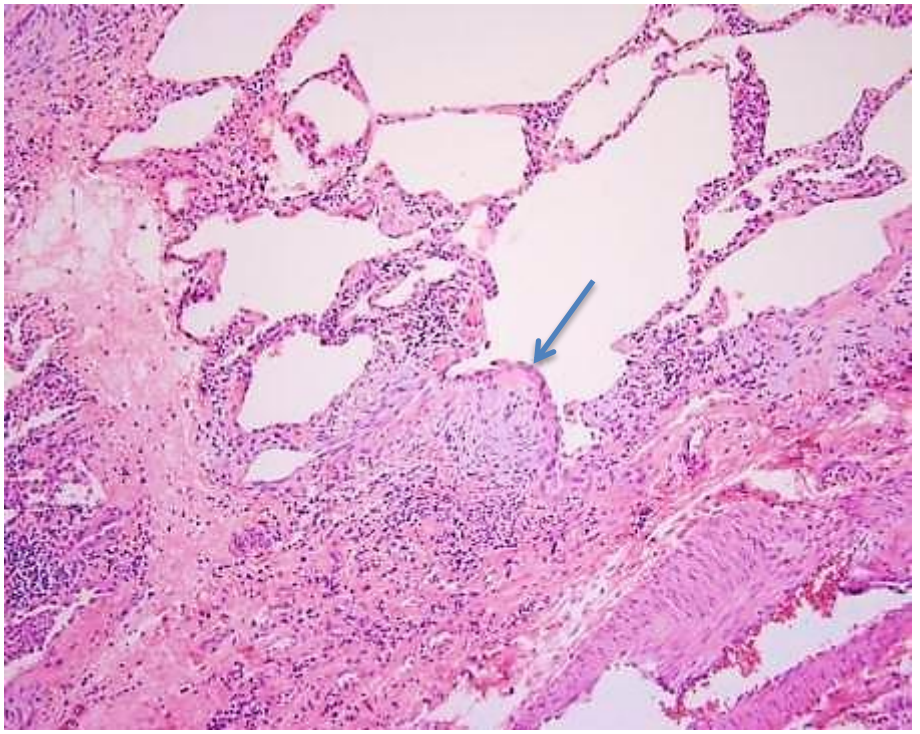


Usual Interstitial Pneumonia

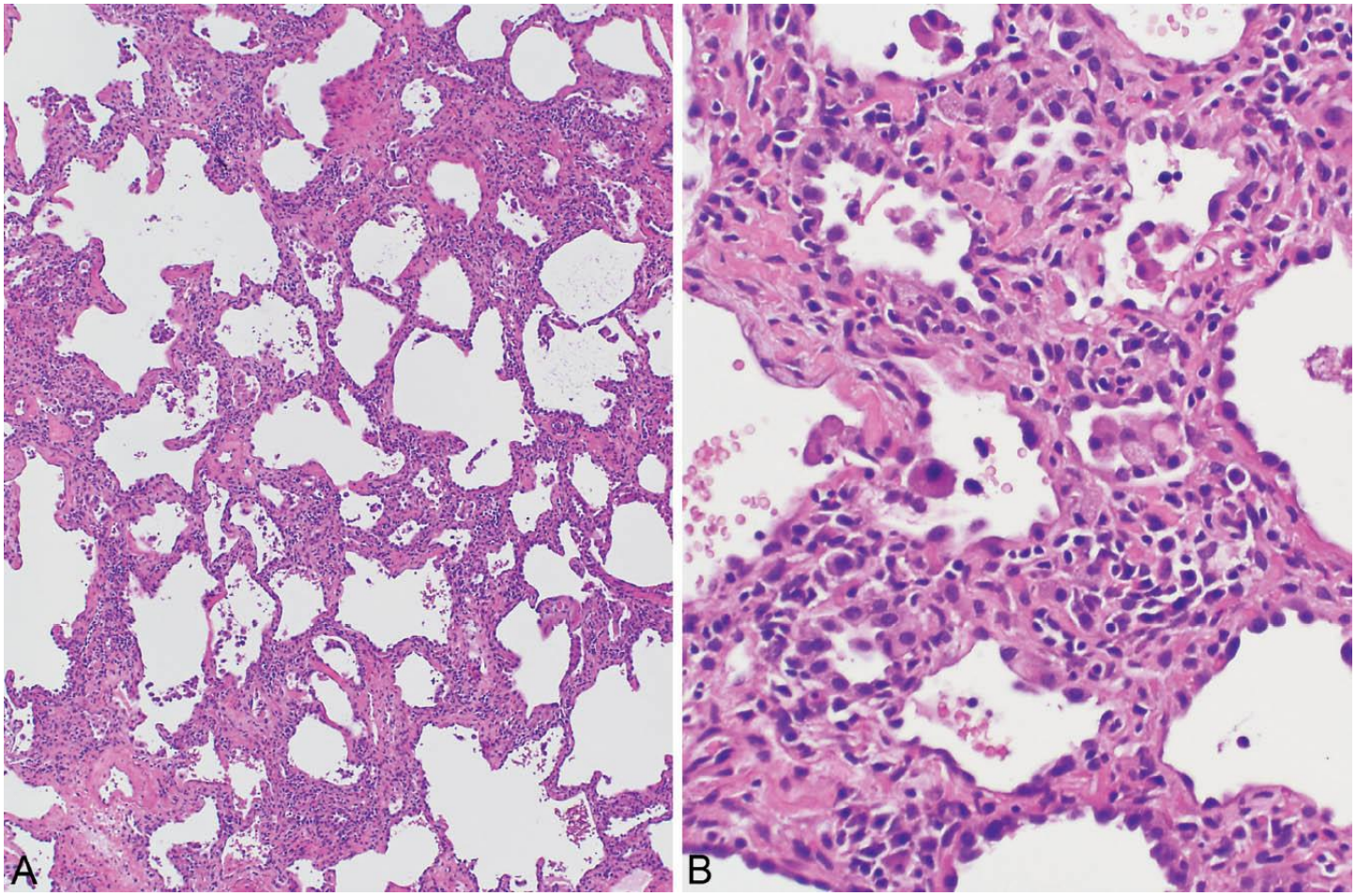
Idiopathic Pulmonary Fibrosis

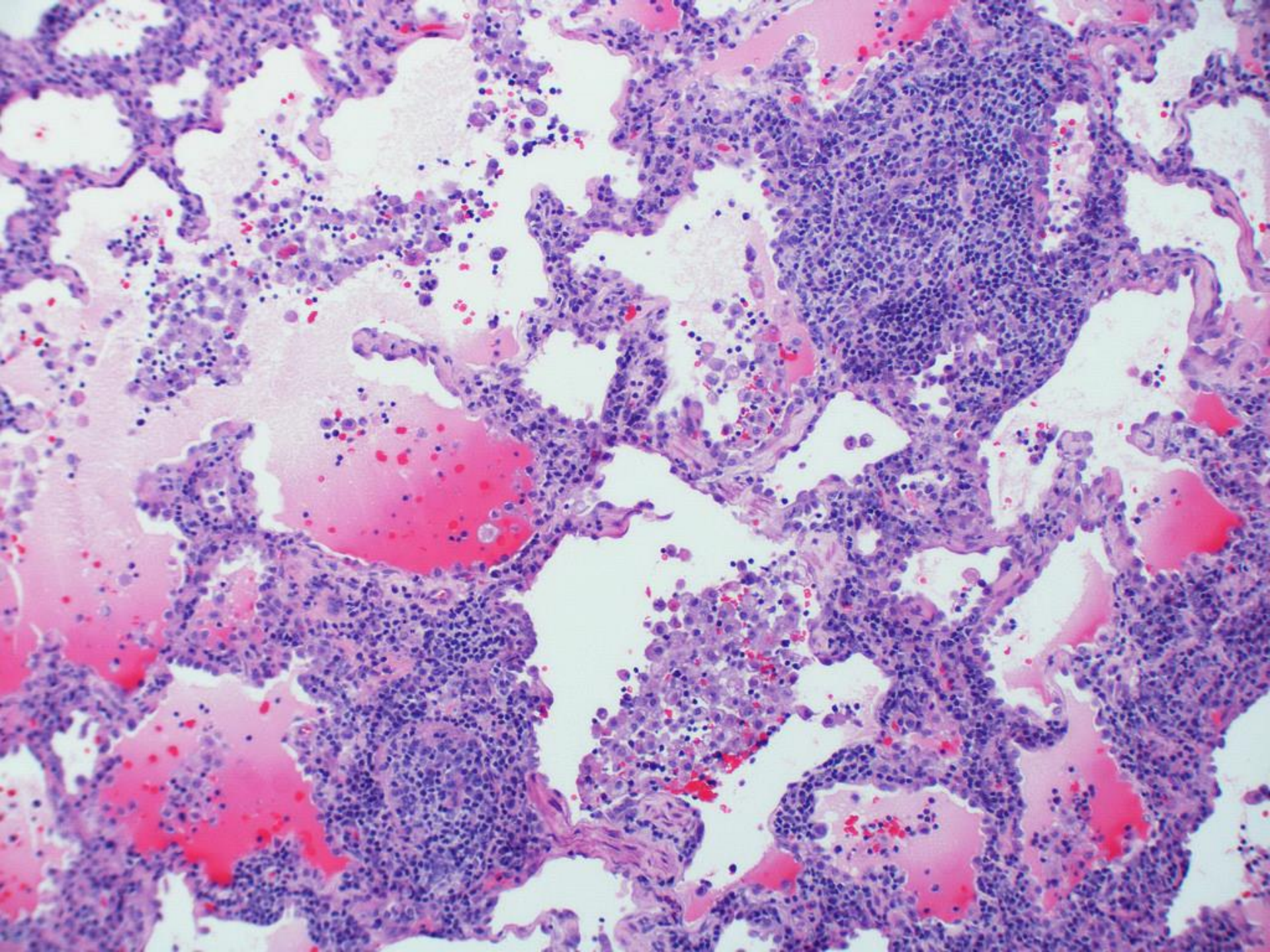


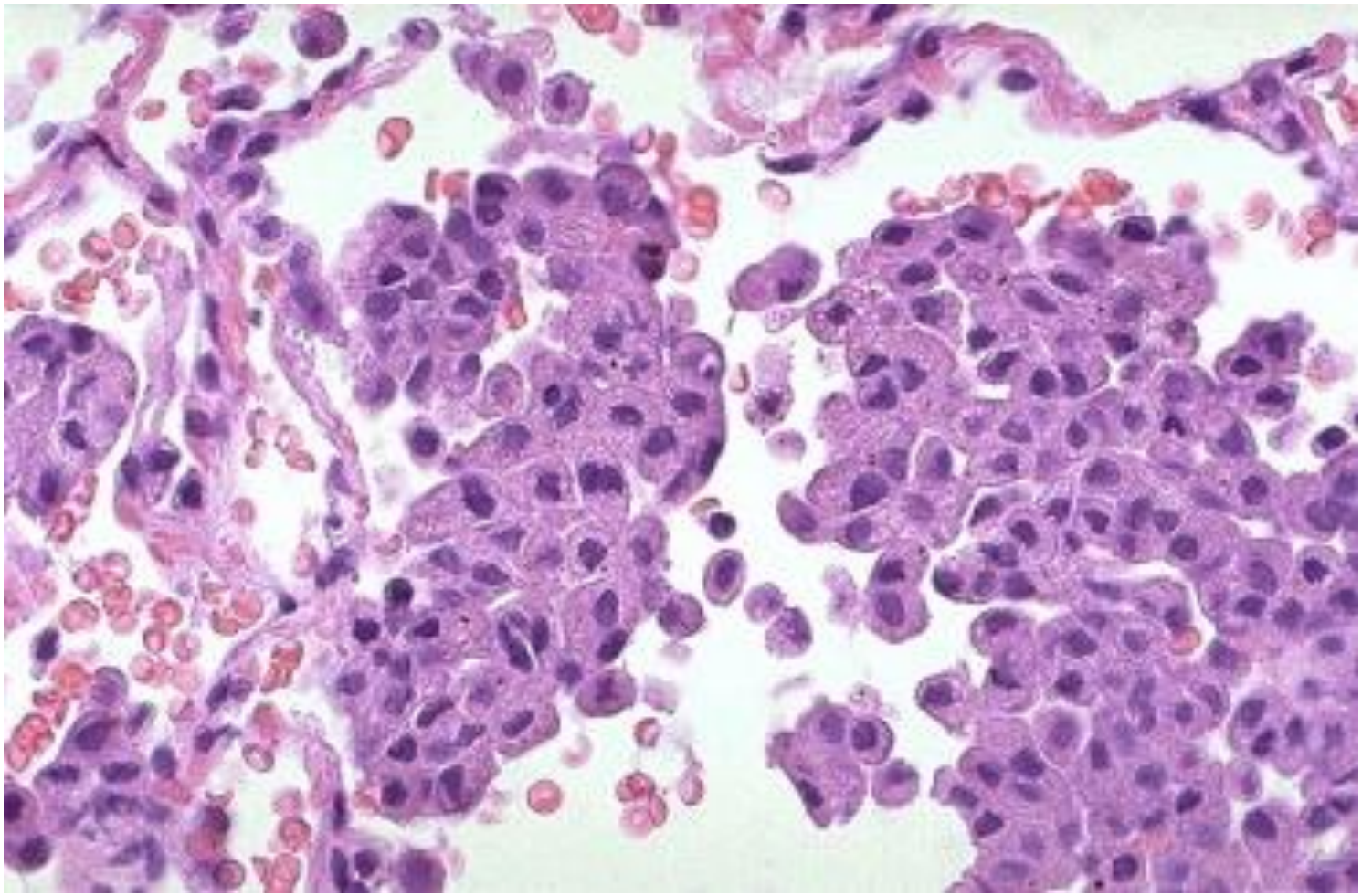
Normal Lung



Fibroblastic Focus in
Usual Interstitial Pneumonia


A
B





Idiopathic Pulmonary Fibrosis

- 5000 new cases per year in UK
- Median age at presentation 68 yr, rare under 40 yrs
- M:F 2:1
- 60% smokers
- 5000 deaths per year

Gribben et al Thorax 2006

- **Progressive fibrotic lung disease**
- **Median survival is around 3 years**

NICE

Be aware of idiopathic pulmonary fibrosis
when assessing a patient with

- age over 45 years
- persistent breathlessness on exertion
- persistent cough
- bilateral inspiratory crackles when listening to the chest
- clubbing of the fingers
- normal or impaired spirometry usually with a
restrictive pattern but sometimes with an obstructive pattern

.

2011 ATS/ERS Diagnostic Criteria for IPF

Exclusion of known causes of ILD*

AND

UIP pattern on HRCT without surgical biopsy

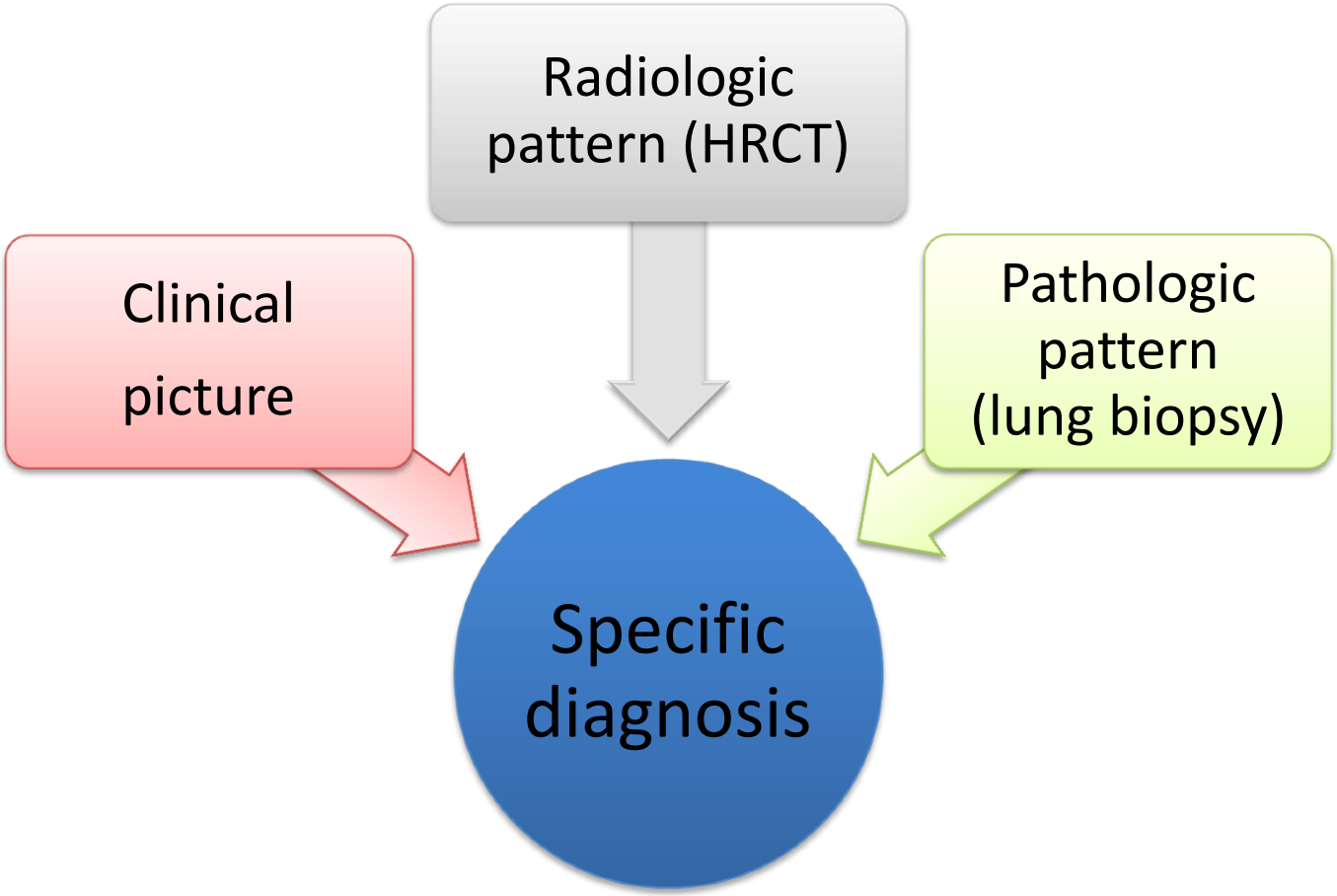
OR

Definite/possible UIP pattern on HRCT with a surgical lung biopsy showing definite/probable UIP

*also known as diffuse parenchymal lung disease, DPLD

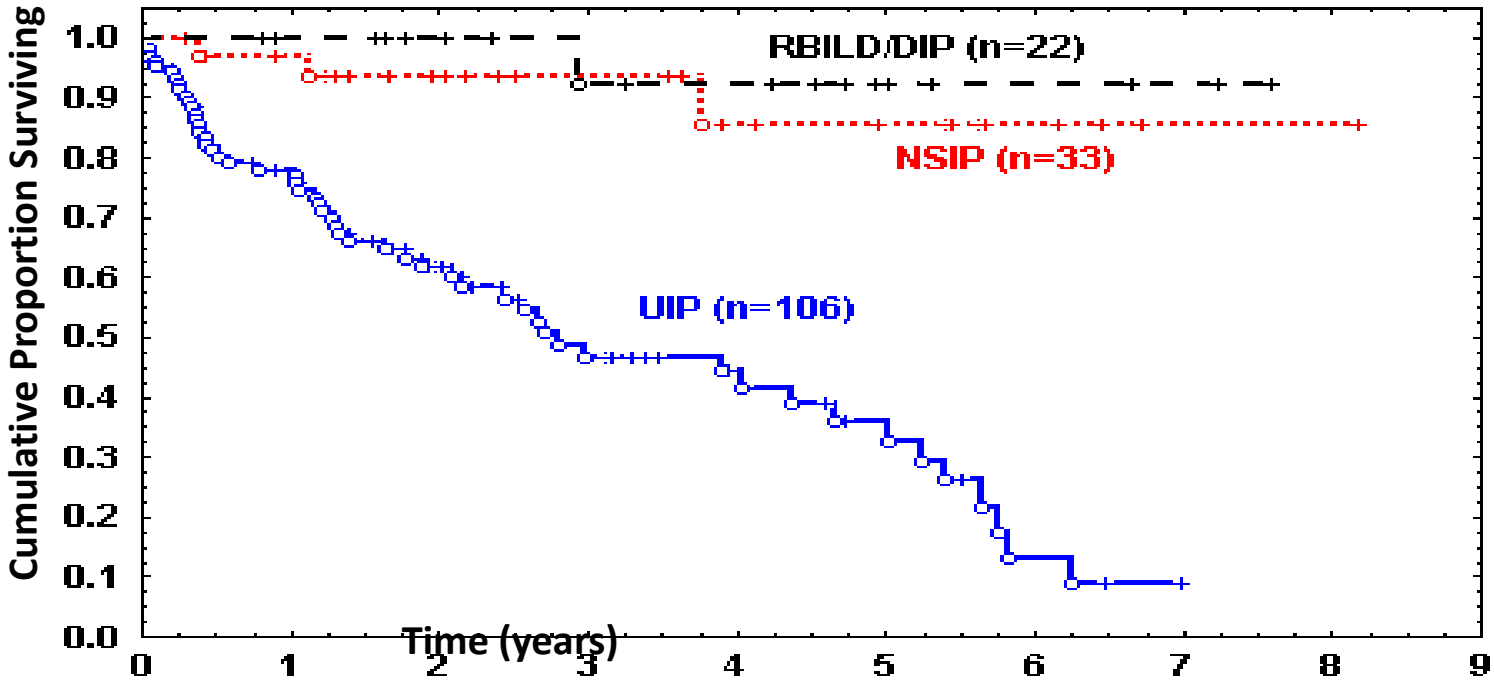
Raghu G, et al. *Am J Respir Crit Care Med*. 2011;183:788-824.

Clinical-Radiologic-Pathologic Approach to ILD



Diagnosis Matters!

IPF/UIP Confers a Poor Prognosis



Correct diagnosis → appropriate management

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

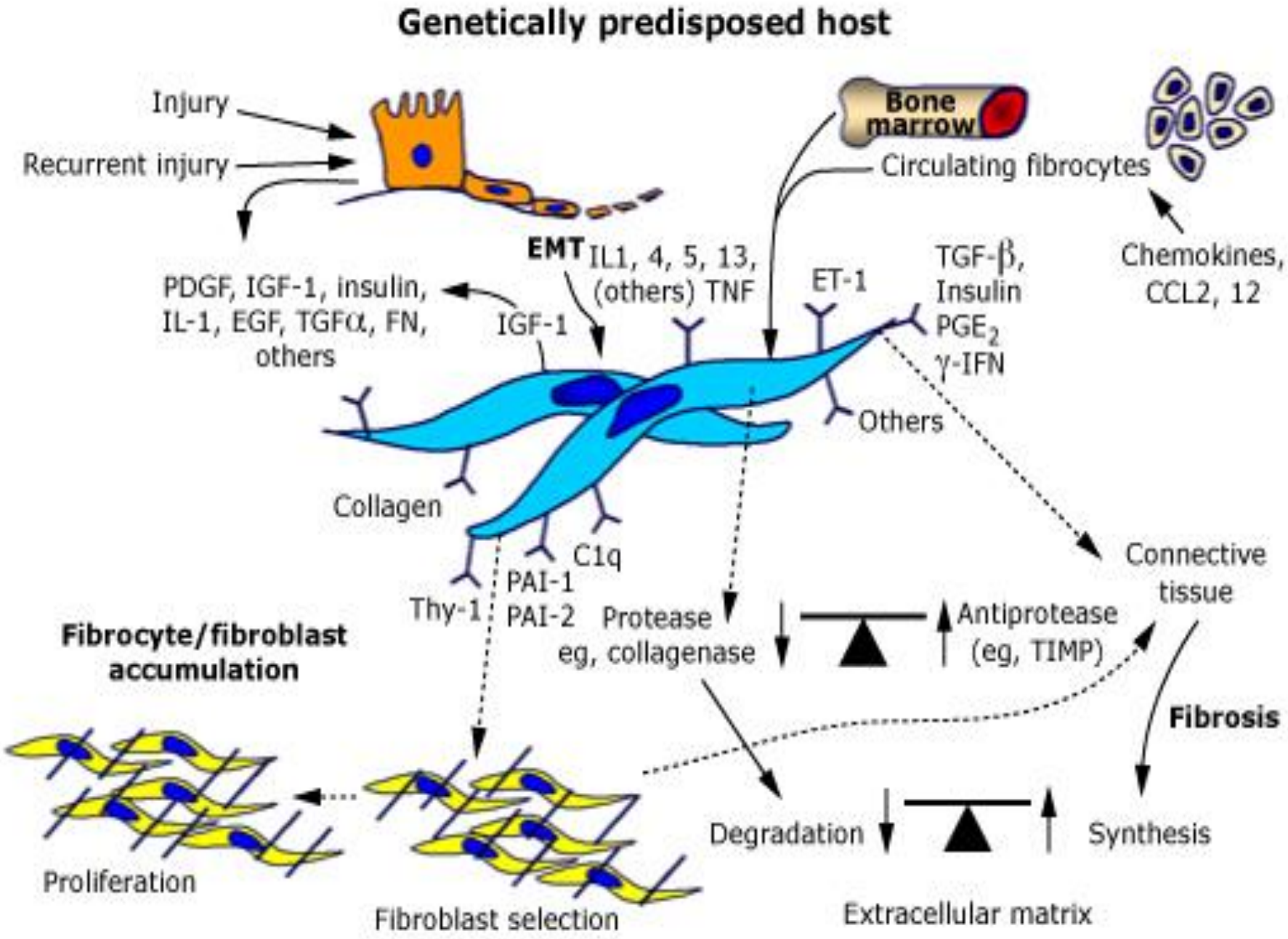
Genetic Factors

-Familial (autosomal dominant, up to 20%-25% of cases)

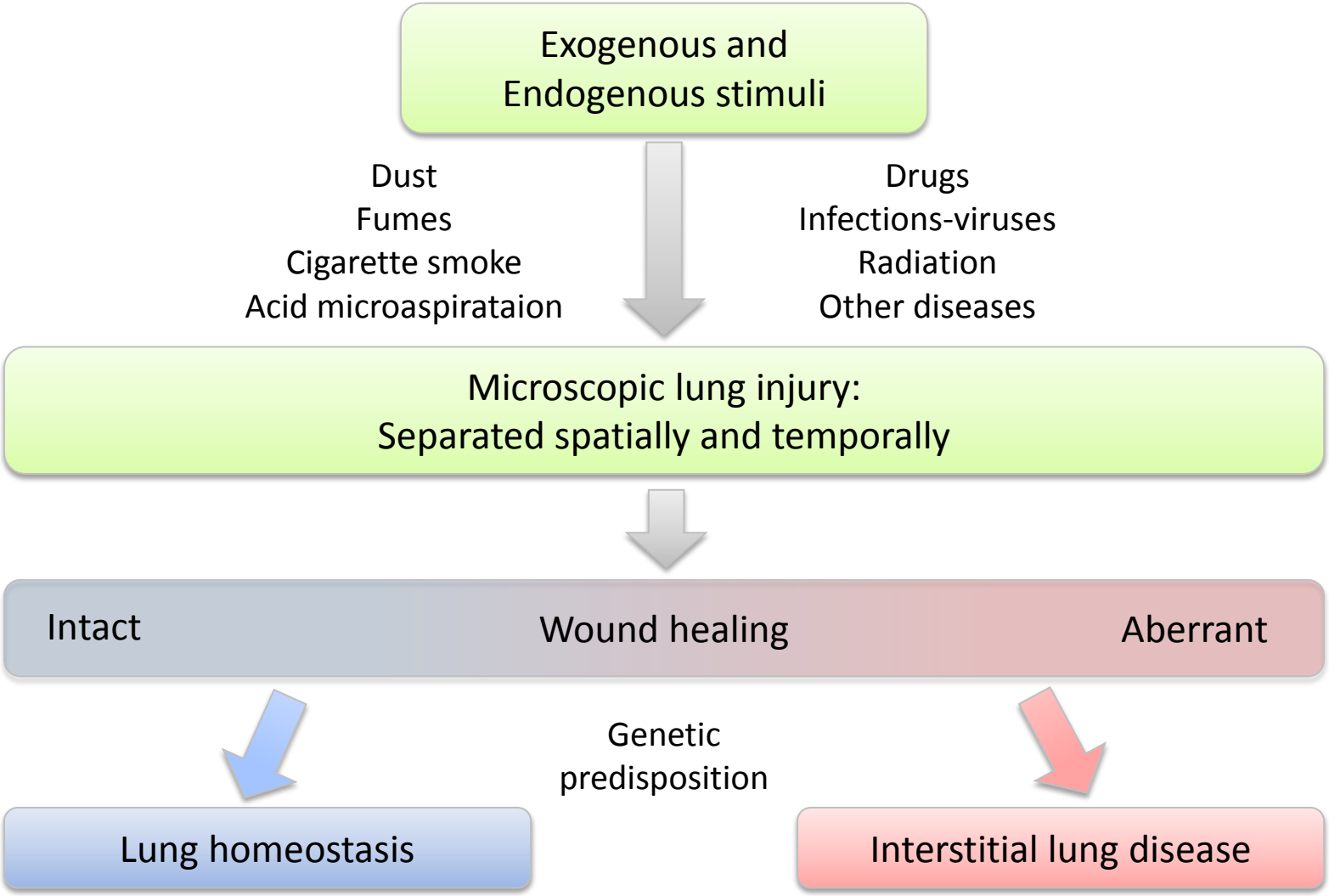
– Telomerase mutations in ~10% (TERT, TERC)

– Surfactant C mutations

– Muc 5B variants


Genetically predisposed host
Injury
Recurrent injury
Bone marrow
Circulating fibrocytes
Chemokines, CCL2, 12
EMT
IL1, 4, 5, 13, (others) TNF
PDGF, IGF-1, insulin, IL-1, EGF, TGFα, FN, others
IGF-1
ET-1
TGF-β, Insulin PGE2 γ-IFN
Others
Collagen
C1q
PAI-1
PAI-2
Thy-1
Protease eg, collagenase
Antiprotease (eg, TIMP)
Connective tissue
Fibrocyte/fibroblast accumulation
Fibrosis
Proliferation
Fibroblast selection
Degradation
Synthesis
Extracellular matrix

ILD Disease Progression



Steele MP, Schwartz DA. *Annu Rev Med.* 2013;64:265-276.

Definition Of Exacerbation Of IPF

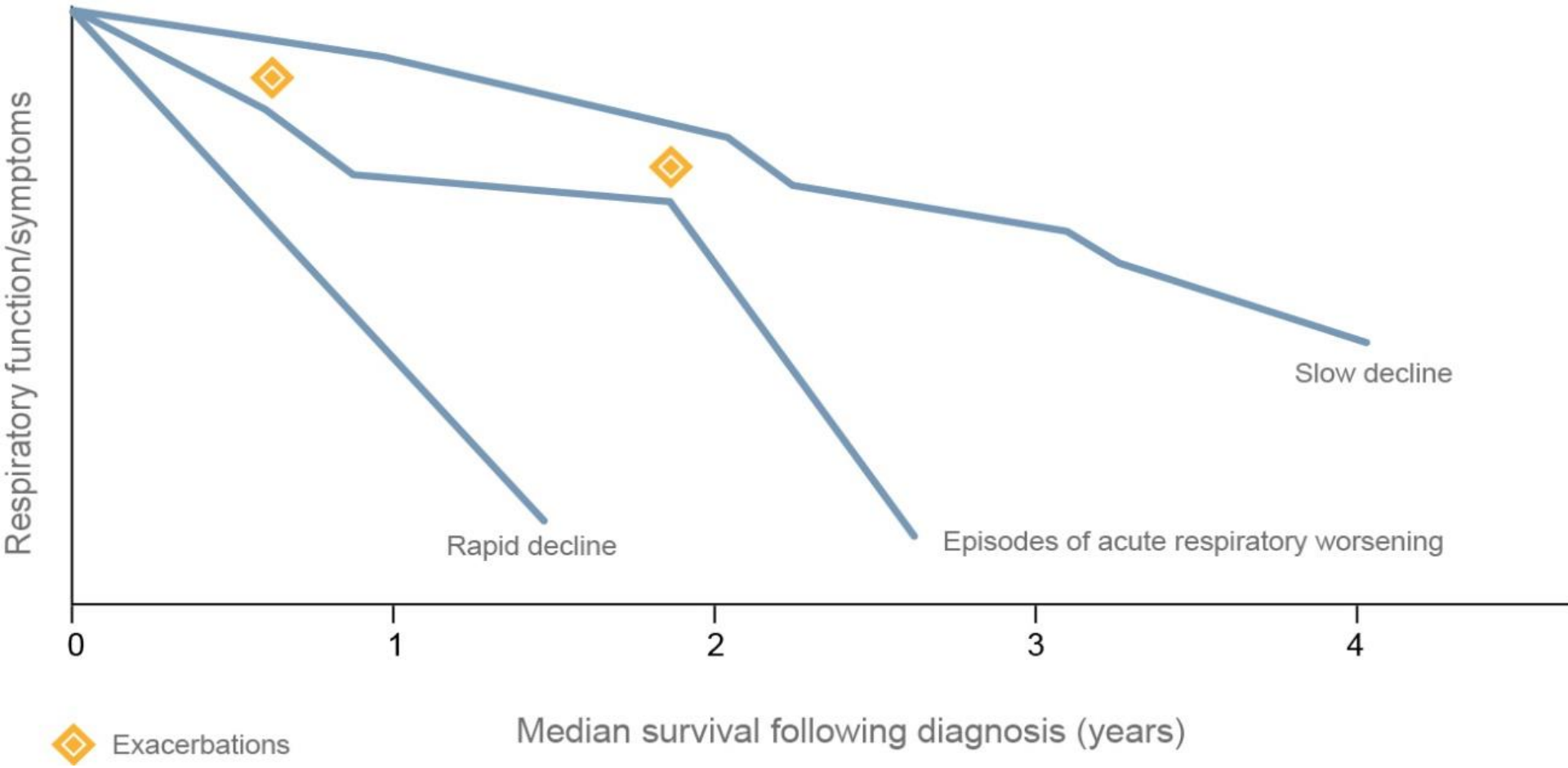
- Unexplained development or worsening of dyspnea within 30 days

- HRCT with new bilateral ground-glass abnormality and/or consolidation superimposed on a background of UIP

- No evidence of pulmonary infection by bronchoalveolar lavage

- Exclusion of alternative causes, including left heart failure, pulmonary embolism, and other identifiable causes of acute lung injury

Disease progression of untreated patients after diagnosis



Predictors of Disease Severity and Progression in IPF

TESTS/ CLINICAL FACTORS	PREDICTIVE VALUE
FVC	• Initial value and change over time correlate with mortality
DL_{CO}	• < 35% predicted → lower survival
6MWT	• O_2 sat ≤ 88% → increased mortality risk for IPF & NSIP • Walk distance correlates with mortality • Heart rate recovery correlates with mortality
Pulmonary hypertension	• Associated with higher mortality
Dyspnea score	• Correlates with survival
Hospitalization	• Predicts worse survival

Ley B, et al. *Am J Respir Crit Care Med*. 2011;183(4):431-440.

NICE QUALITY STANDARDS

- Quality statement 1: MDT diagnosis of idiopathic pulmonary fibrosis
- Quality statement 2: Access to a specialist nurse
- Quality statement 3: Assessment for oxygen therapy
-
- Quality statement 4: Pulmonary rehabilitation
-
- Quality statement 5: Palliative care

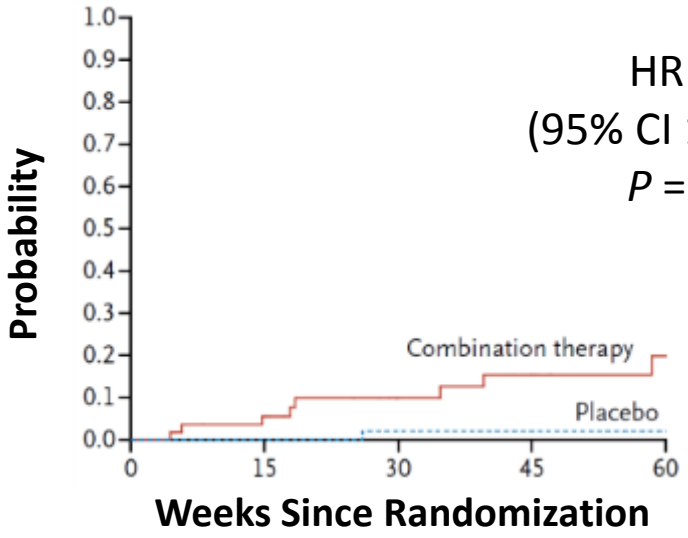
PANTHER 2012 Interim Results

Primary	Triple Therapy	Placebo	P-value
FVC (liters)	-0.24	-0.23	0.85

- Triple therapy has no benefit for FVC
- Increased risk of death

Time to Death

Kaplan–Meier Analysis



HR 9.26
(95% CI 1.16-74.1)
P = 0.01

Raghu G, et al. *N Engl J Med.* 2012;366:1968-1977.

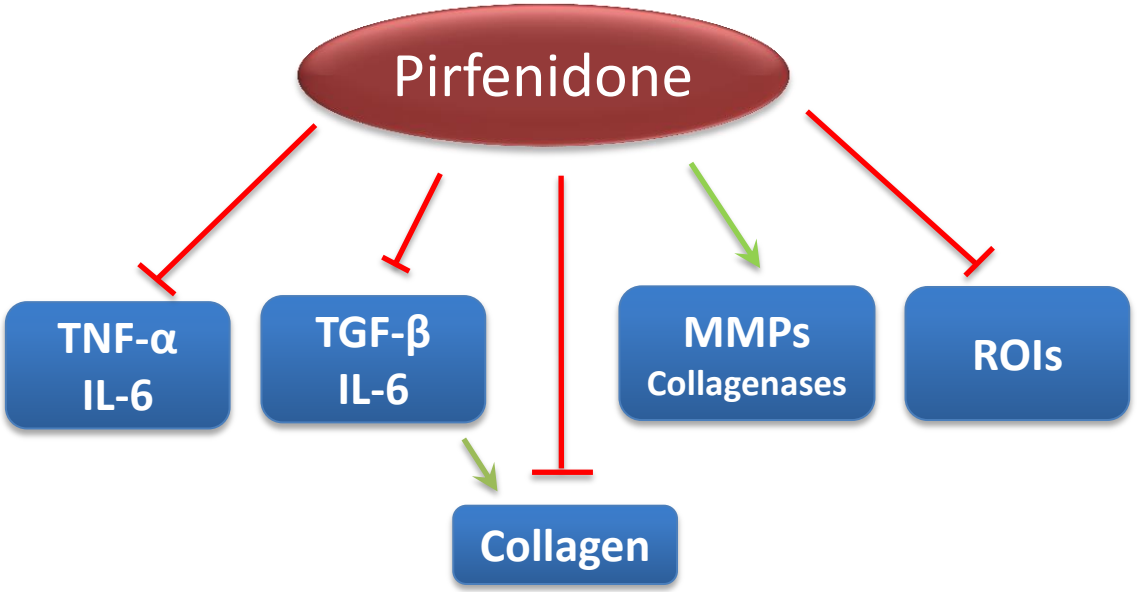
Three **IPF Clinical Trials**

American Thoracic Society 2014

- PANTHER — N-acetylcysteine (NAC)
- ASCEND — pirfenidone
- INPULSIS — nintedanib (BIBF1120)

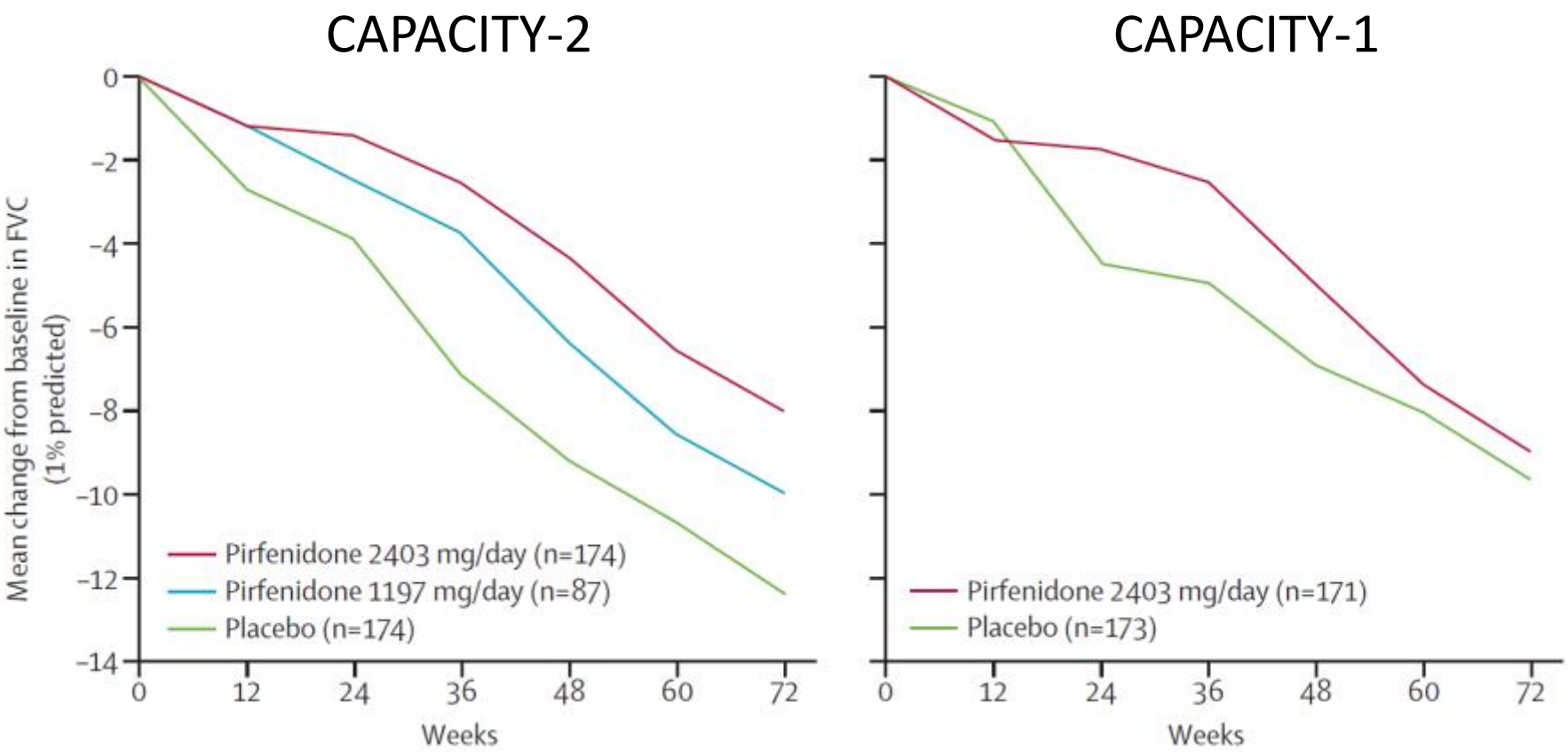
Possible Mechanisms of Pirfenidone Action

- Antifibrotic
- Molecular target unclear
- Active in several animal models of fibrosis (lung, liver, kidney)



Hilberg O, et al. *Clin Respir J.* 2012;6:131-143.

CAPACITY 2011



- One pirfenidone trial was positive, one was negative
- CAPACITY-1 placebo group FVC declined more slowly than expected

Noble P, et al. *Lancet.* 2011;377:1760-1769.

CAPACITY Endpoints

Endpoint	CAPACITY-2	CAPACITY-1
FVC	✓	X
Overall survival	X	X
Progression-free survival	✓	X
Six-minute walk distance	X	✓
DL_{CO}	X	X
Dyspnea	X	X
Exertional desaturation	X	X

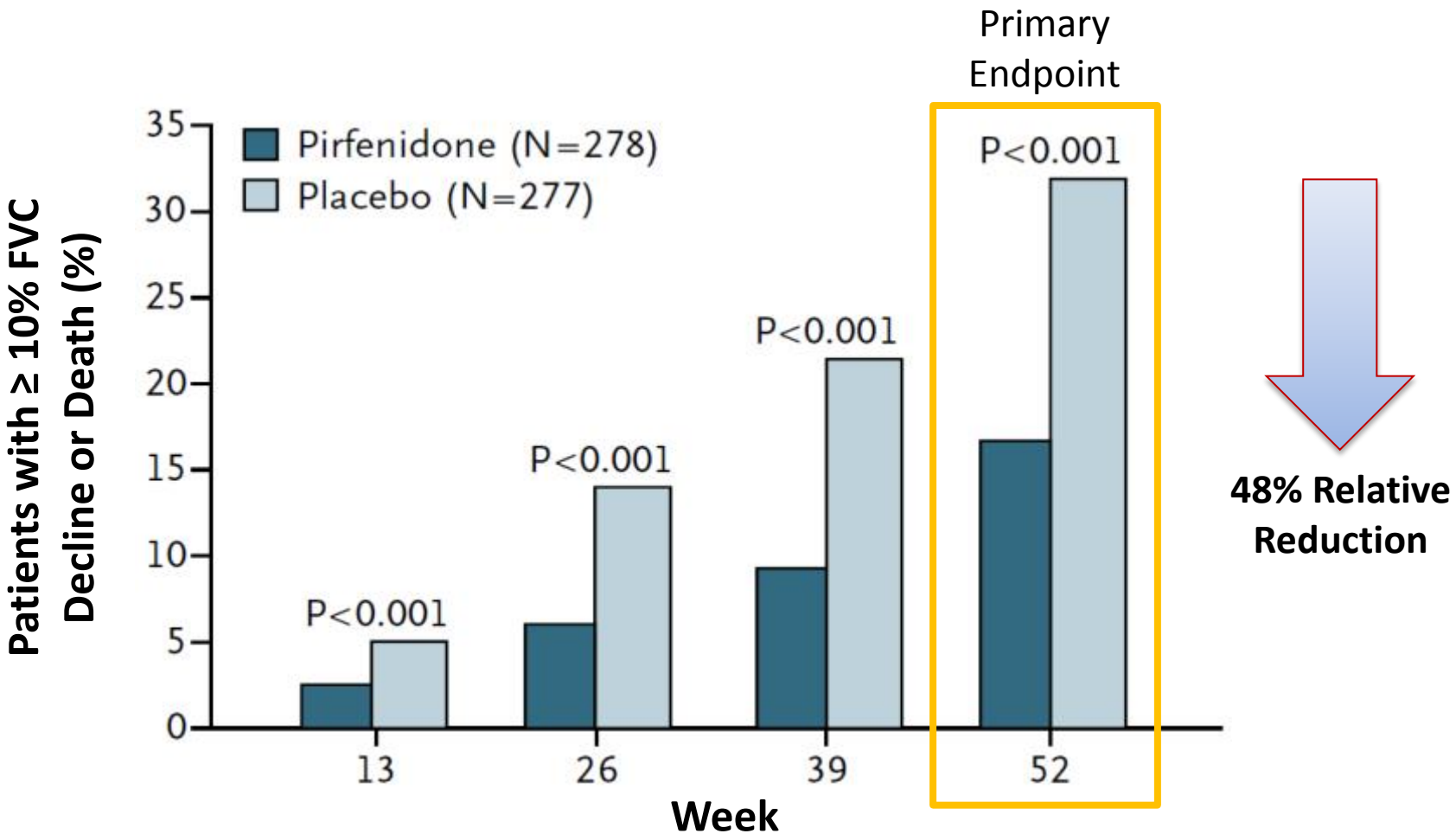
Noble P, et al. *Lancet.* 2011;377:1760-1769.

- **FVC: between 50% and 80% predicted**

- **The manufacturer provides pirfenidone with the discount agreed in the patient access scheme**

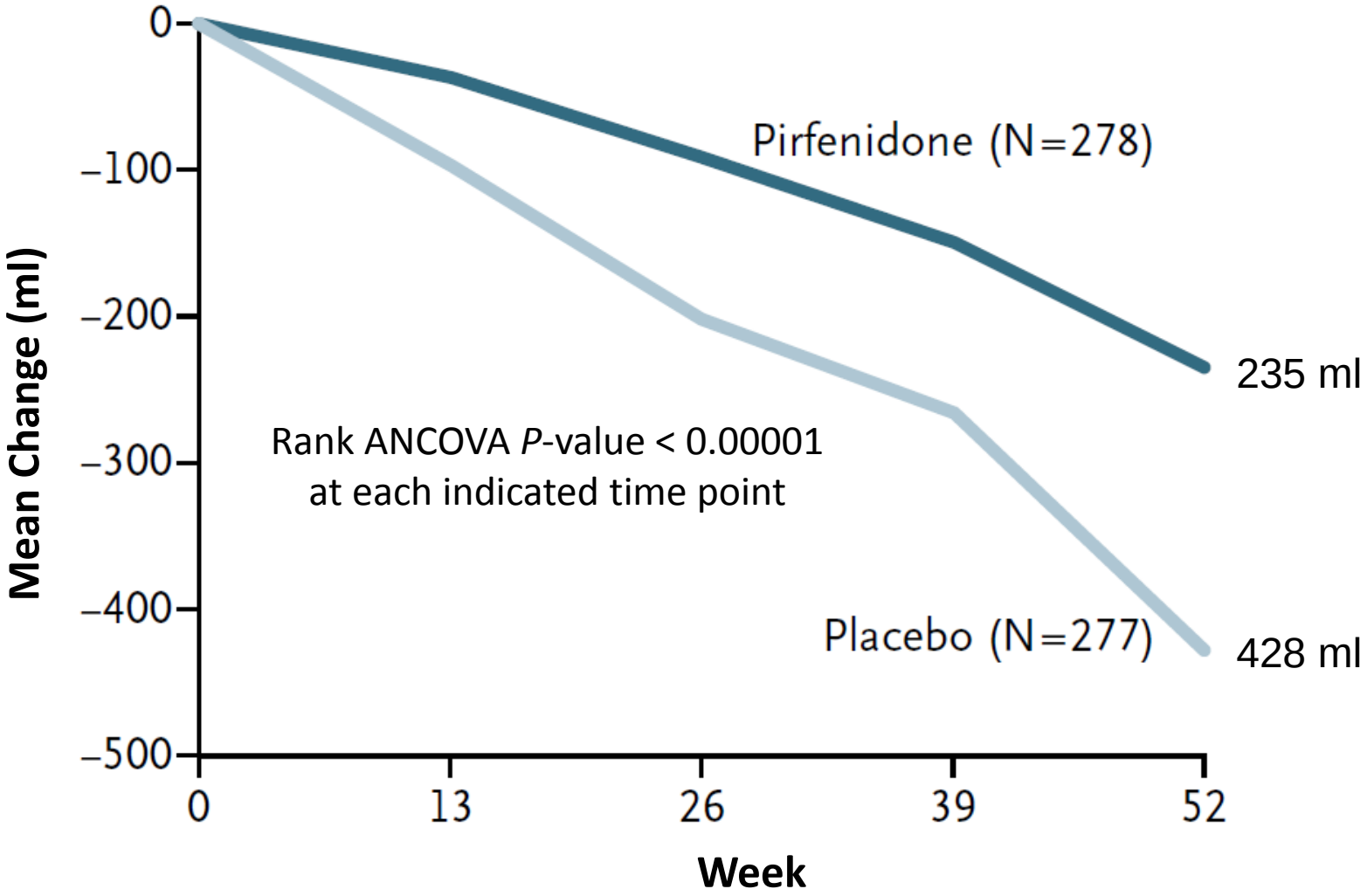
. Treatment with pirfenidone should be discontinued if there is evidence of disease progression (a decline in FVC of 10% or more within any 12-month period).

Primary ASCEND Endpoint Achieved



King TE, et al. *N Engl J Med.* 2014;370(22):2083-2092.

Pirfenidone Reduces Loss of FVC



King TE, et al. *N Engl J Med.* 2014;370(22):2083-2092.

ASCEND Summary

- Treatment with pirfenidone for 52 weeks significantly reduced disease progression, as measured by
  - Changes in % predicted FVC *(P* < 0.001)
  - Changes in 6-minute walk distance (*P* = 0.04)
  - Progression-free survival (*P* < 0.001)
- Treatment with pirfenidone reduced all-cause mortality and treatment emergent IPF-related mortality in pooled analyses at week 52
- Pirfenidone was generally safe and well tolerated

King TE, et al. *N Engl J Med.* 2014;370(22):2083-2092.

Pirfenidone Warnings and Precautions

Temporary dosage reductions or discontinuations may be required

- Elevated liver enzymes: ALT, AST, and bilirubin elevations have occurred with pirfenidone. Monitor ALT, AST, and bilirubin before and during treatment.
- Photosensitivity and rash: Photosensitivity and rash have been noted with pirfenidone. Avoid exposure to sunlight and sunlamps. Wear sunscreen and protective clothing daily.
- Gastrointestinal disorders: Nausea, vomiting, diarrhea, dyspepsia, gastro-esophageal reflux disease, and abdominal pain have occurred with pirfenidone.

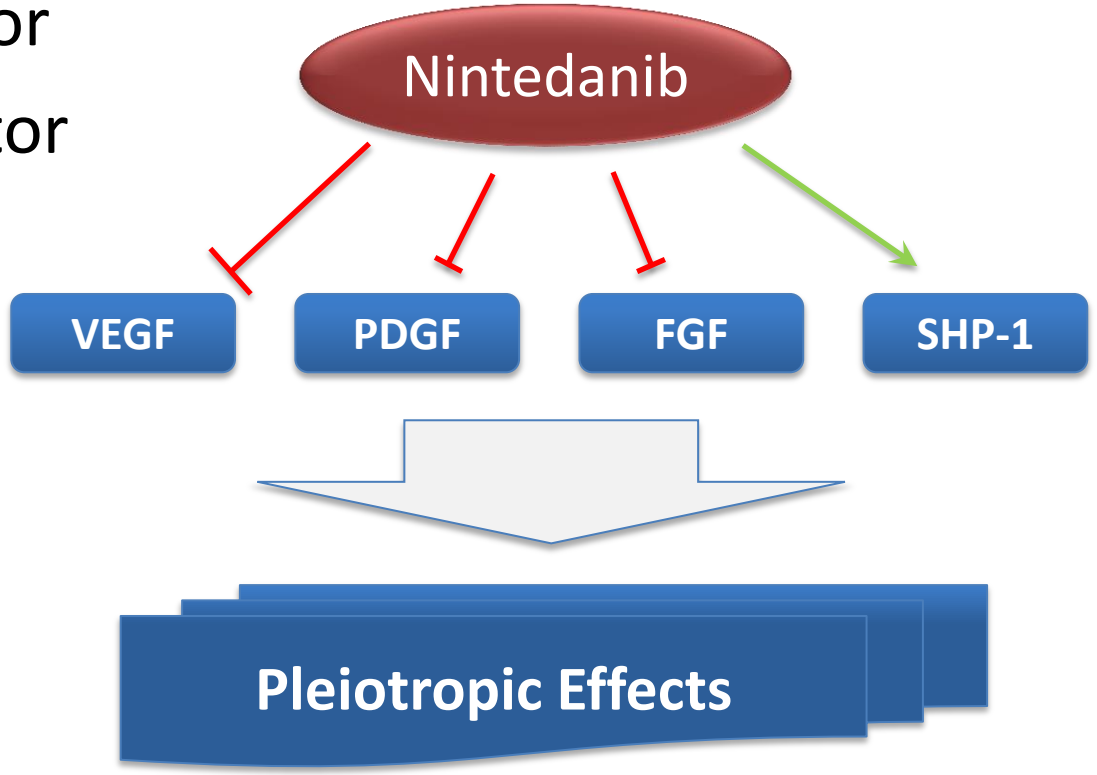
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails/. Accessed October 2014.

INPULSIS

Nintedanib

Possible Mechanisms of Nintedanib Action

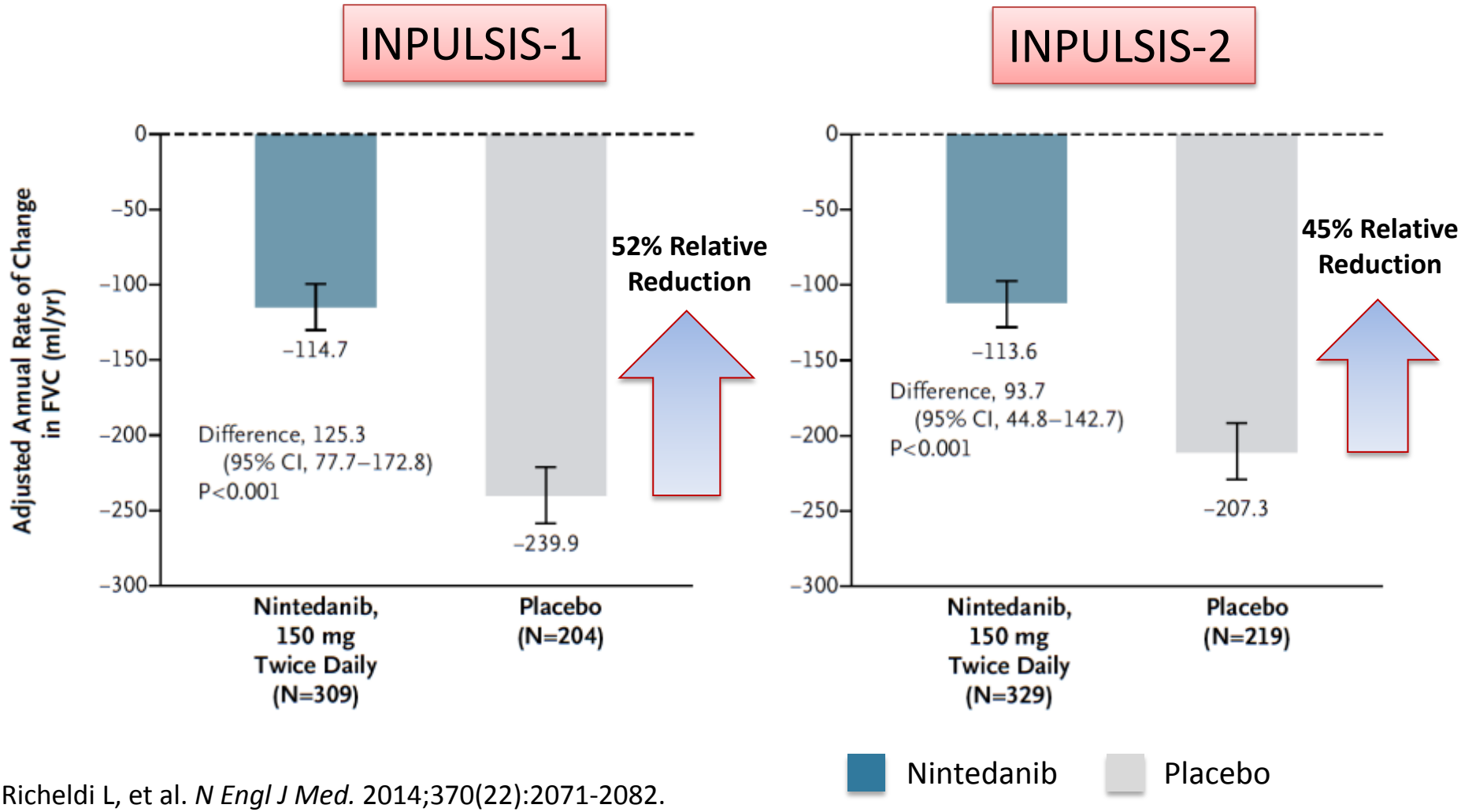
- Triple kinase inhibitor
- Phosphatase activator
- Antiangiogenic, antitumor activity



Hilberg F, et al. *Cancer Res*. 2008;68(12):4774-4782.
Tai WT, et al. *J Hepatol*. 2014;61(1):89-97.

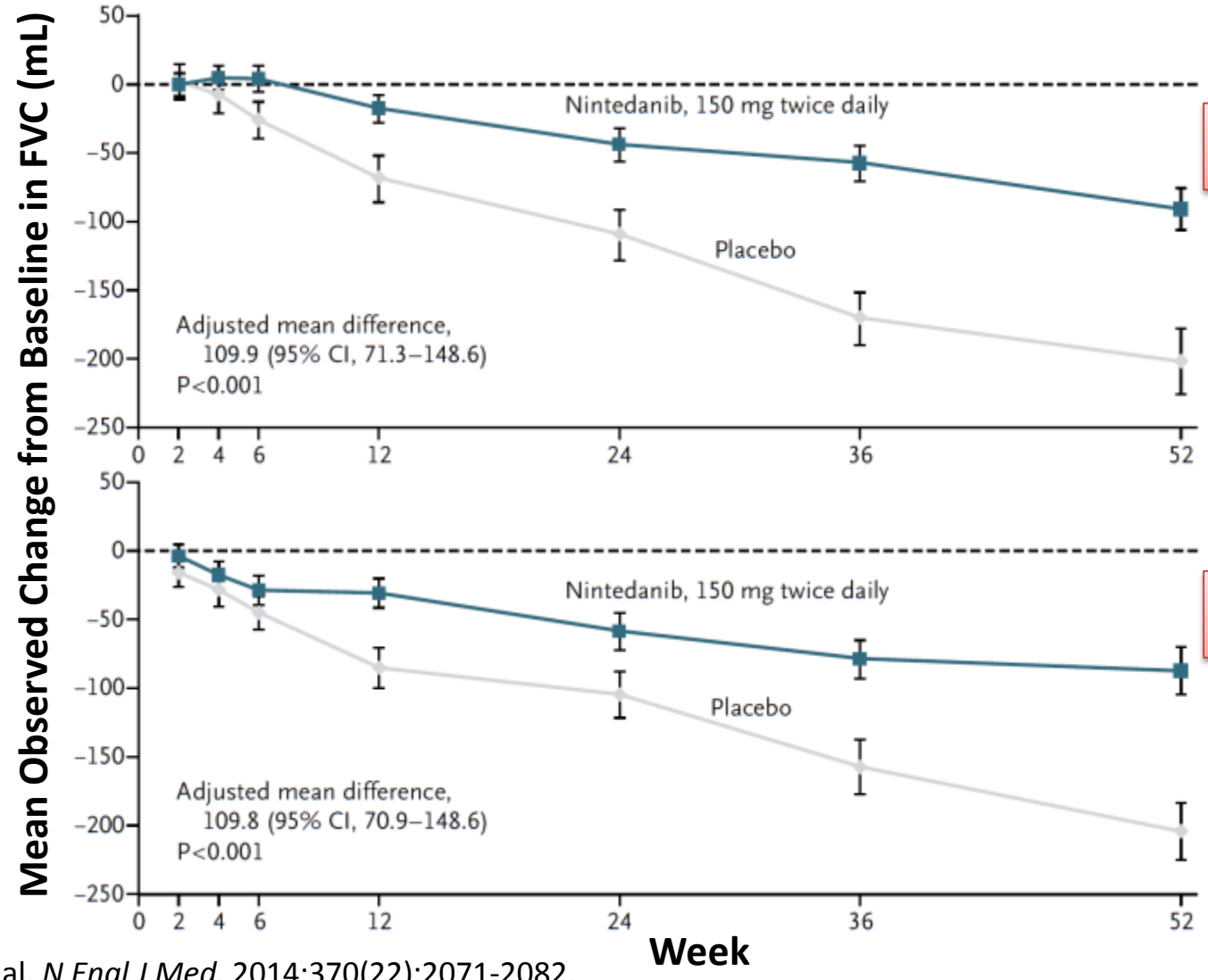
Primary INPULSIS Endpoint Achieved

Annual Rate of Change of FVC



Richeldi L, et al. *N Engl J Med.* 2014;370(22):2071-2082.

Nintedanib Reduces Loss of FVC

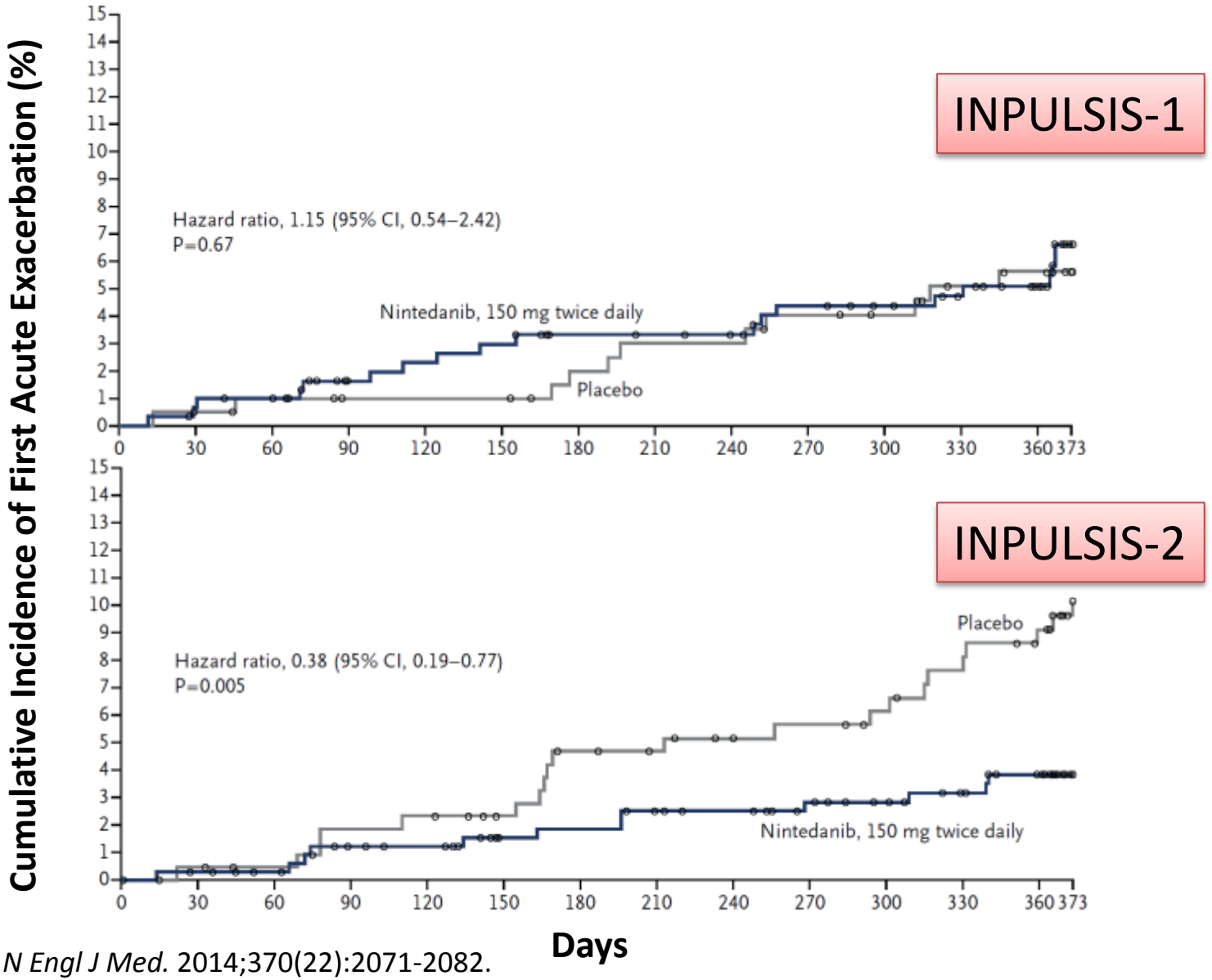


INPULSIS-1

INPULSIS-2

Richeldi L, et al. *N Engl J Med.* 2014;370(22):2071-2082.

Mixed Findings for Time to First Acute Exacerbation



Richeldi L, et al. *N Engl J Med.* 2014;370(22):2071-2082.

Common Nintedanib Adverse Events

Event	INPULSIS-1		INPULSIS-2	
	Nintedanib (n = 309)	Placebo (n = 204)	Nintedanib (n = 329)	Placebo (n = 219)
Any (%)	96	89	94	90
Diarrhea (%)	62	19	63	18
Nausea(%)	23	6	26	7

Richeldi L, et al. *N Engl J Med.* 2014;370(22):2071-2082.

INPULSIS Conclusions

- Nintedanib reduced the decline in FVC, which is consistent with a slowing of disease progression
- Nintedanib was frequently associated with diarrhea, which led to discontinuation of the study medication in less than 5% of patients

Richeldi L, et al. *N Engl J Med.* 2014;370(22):2071-2082.

Consider follow-up of people with idiopathic pulmonary fibrosis:

- **every 3 months or sooner if they are showing rapid disease progression or rapid deterioration of symptoms or**

- **every 6 months or sooner if they have steadily progressing disease or**

- **initially every 6 months if they have stable disease and then annually if they have stable disease after 1 year.**

NICE

In follow-up appointments for people with idiopathic pulmonary fibrosis:

- assess lung function
- assess for oxygen therapy
- assess for pulmonary rehabilitation
- offer smoking cessation advice, in line with Smoking cessation services
- identify exacerbations and previous respiratory hospital admissions
- consider referral for assessment for lung transplantation in people who do not have absolute contraindications
- consider psychosocial needs and referral to relevant services as appropriate
- consider referral to palliative care services
- assess for comorbidities (which may include: anxiety, bronchiectasis, depression, diabetes, dyspepsia, ischaemic heart disease, lung cancer and pulmonary hypertension).

QUESTIONS?