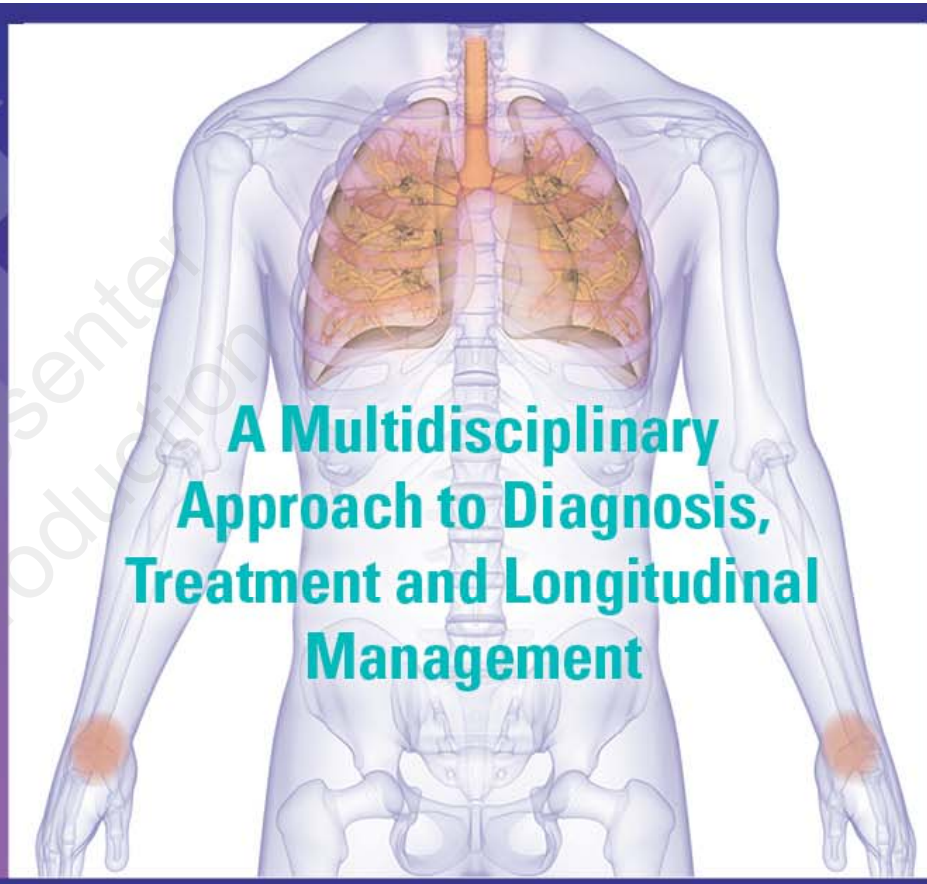
Systemic Sclerosis Interstitial Lung Disease (SSc-ILD)



A Multidisciplinary Approach to Diagnosis, Treatment and Longitudinal Management

Respiratory Institute®

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Learning Objectives

1. Identify clinical features and risk factors of SSc-ILD based upon best practices for diagnosis.
2. Apply practice guidelines and clinical evidence related to current and emerging therapies to select treatments for patients with SSc-ILD.
3. Evaluate strategies for longitudinal management of SSc-ILD using a multidisciplinary approach.

Case 1

- 36 year-old Hispanic male
- 3 mos exertional dyspnea
- 12 mos of hand and foot edema ("Mickey Mouse hands and feet")
- 9 mos white and blue fingers when cold
- 7 months of thick, dark skin patches on the trunk and skin tightening of the tip of fingers
- Skin biopsy: Morphea
- PMHx: none
- FHx: Maternal grandmother bone cancer

  Maternal grandfather: CVA, colon cancer with mets to the lungs
- Soc/En/Occ: Engineer, construction project manager

  Smoked 1 pack/wk, ages 16-34

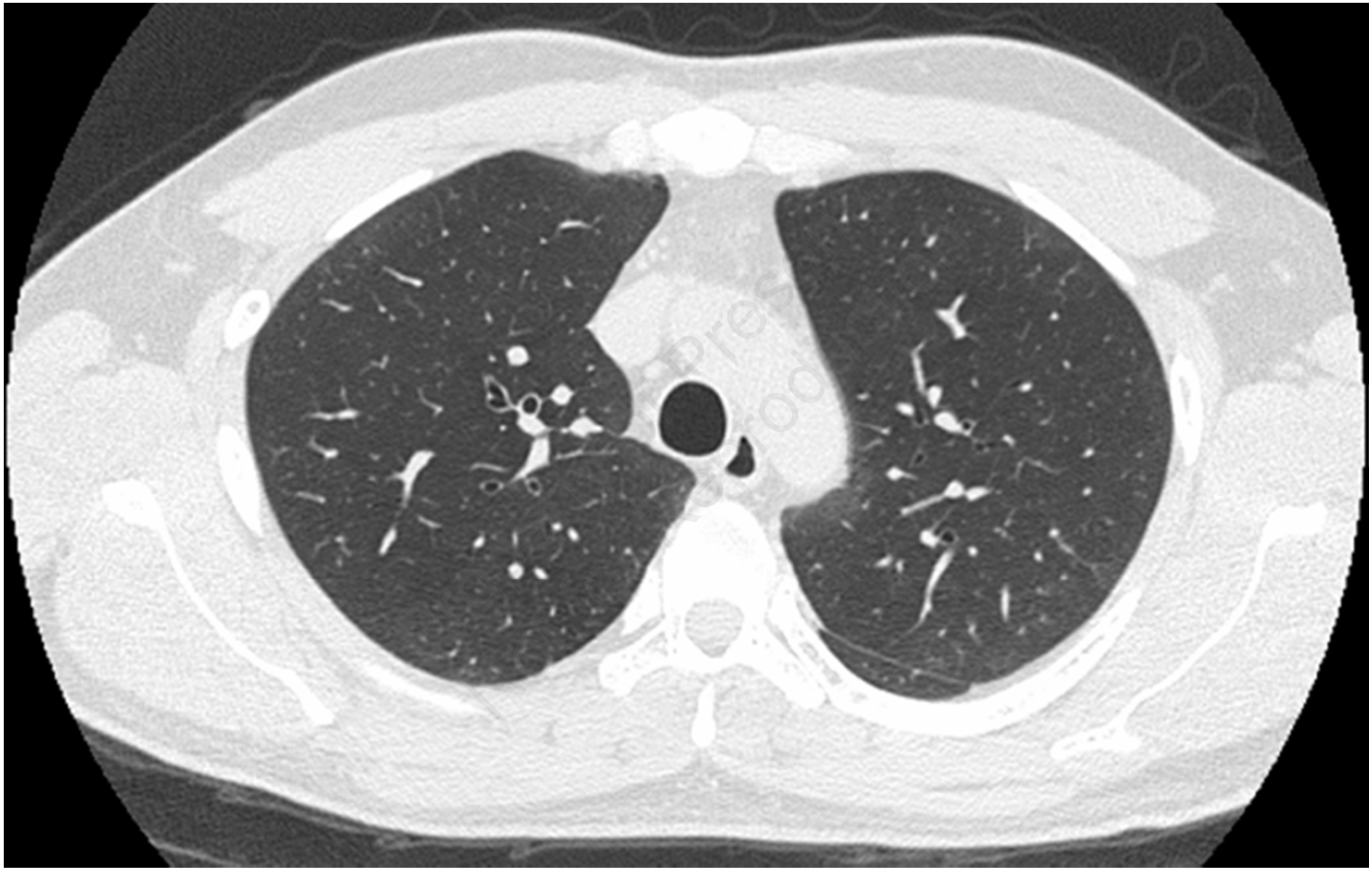
Case 1

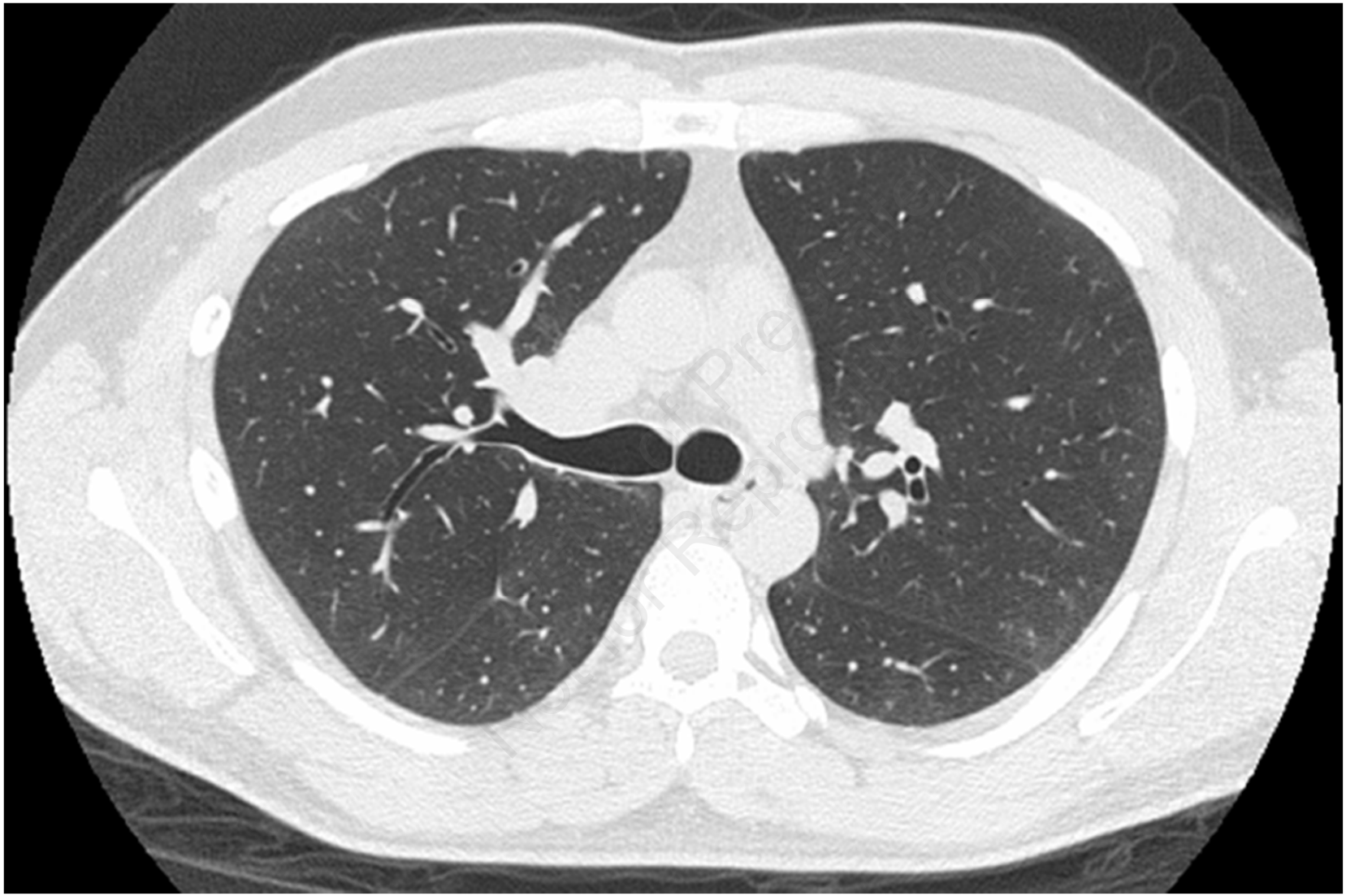
Physical examination

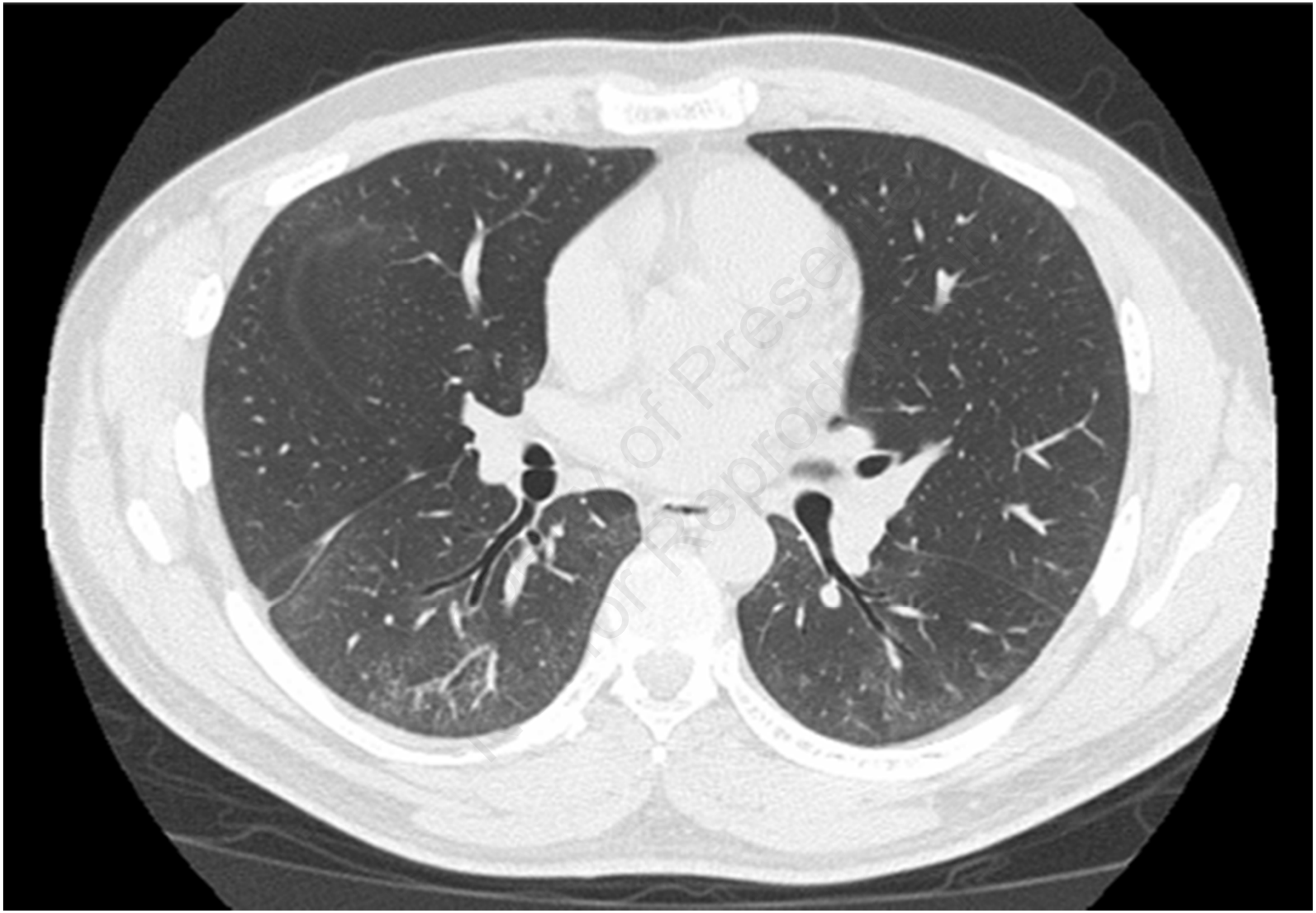
- Puffy hands and feet, few palmar telangiectasia, periungual erythema, abnormal nailfold capillaroscopy, sclerotic patches on his trunk & mild sclerodactyly
- P2 normal
- Crackles at the bases
- PFTs: FVC=3.5L (70%), DLCO=19.83 (52%)
- Gas exchange: 6MWD=1430 feet, SpO2=85%

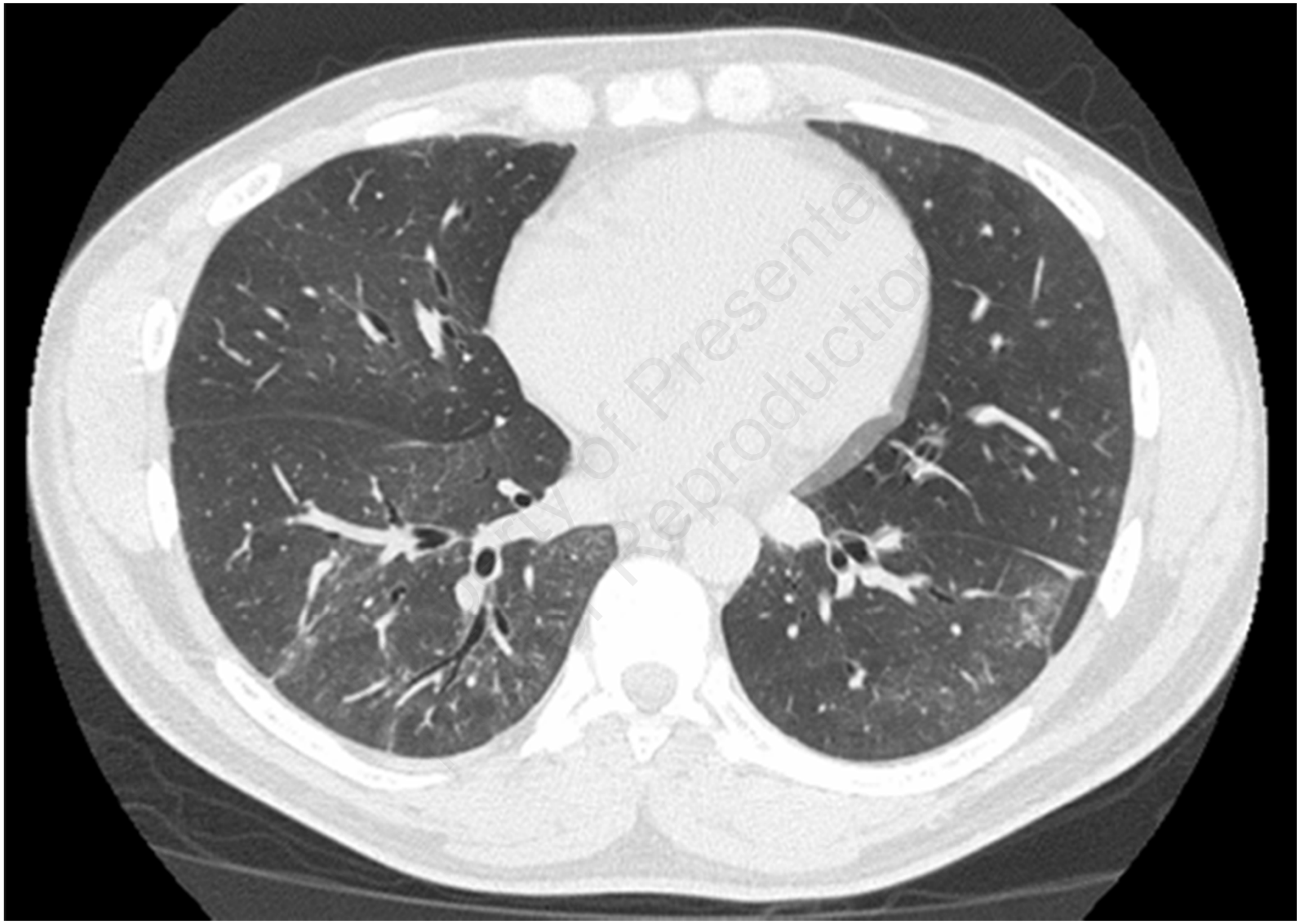
Serology

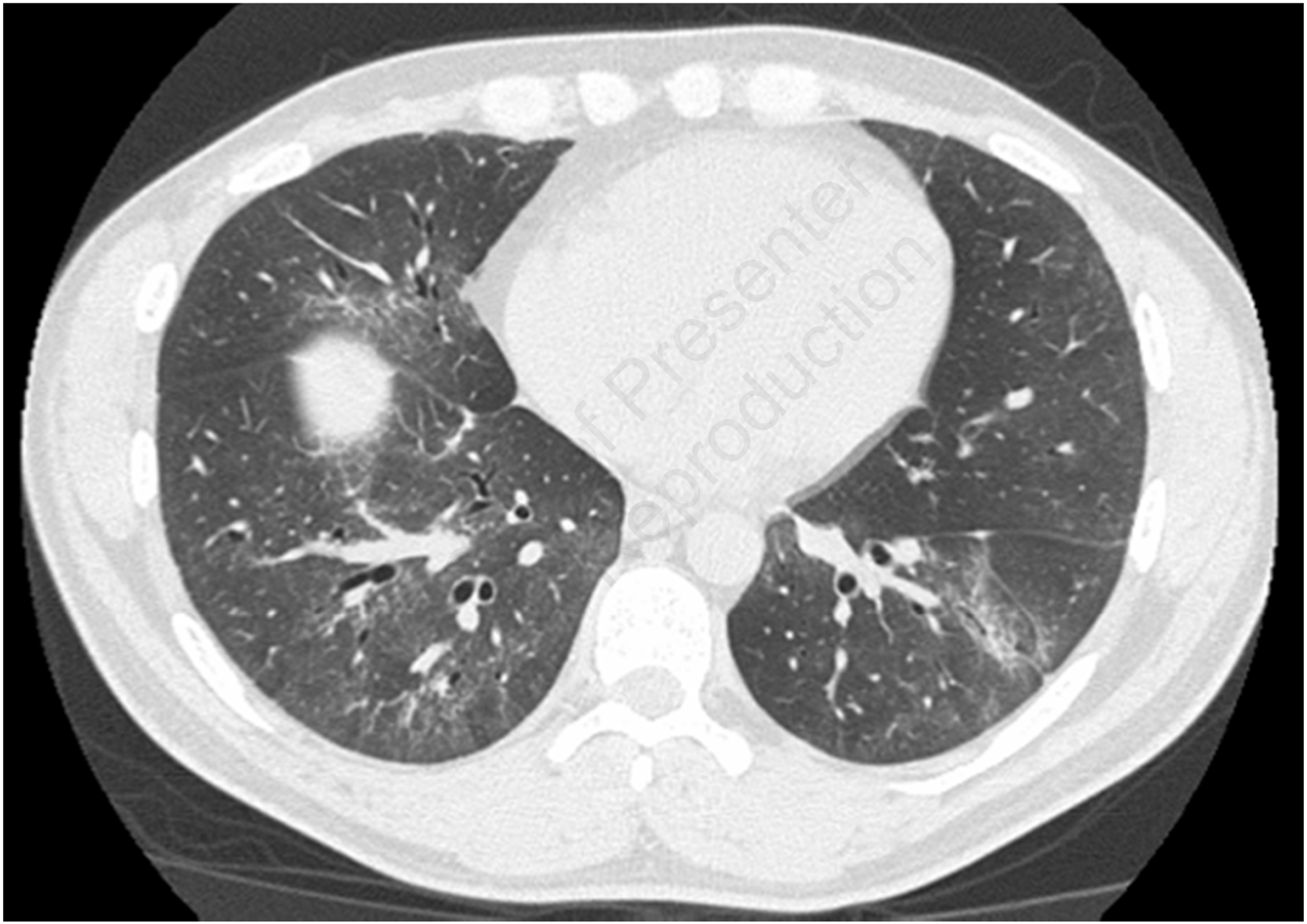
- ANA >1:5120 homogenous pattern
- High-titer Scl-70 at 136 units

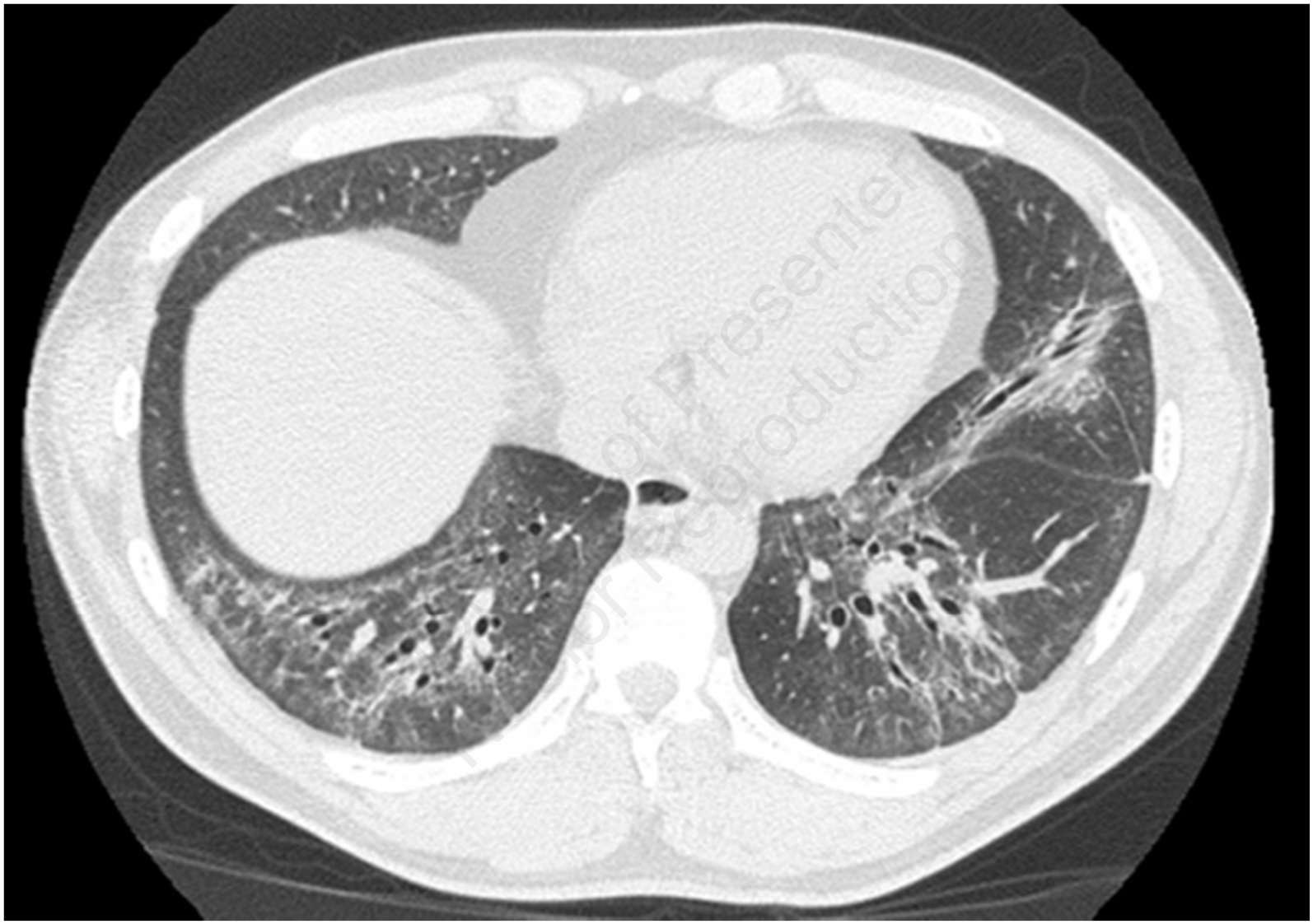


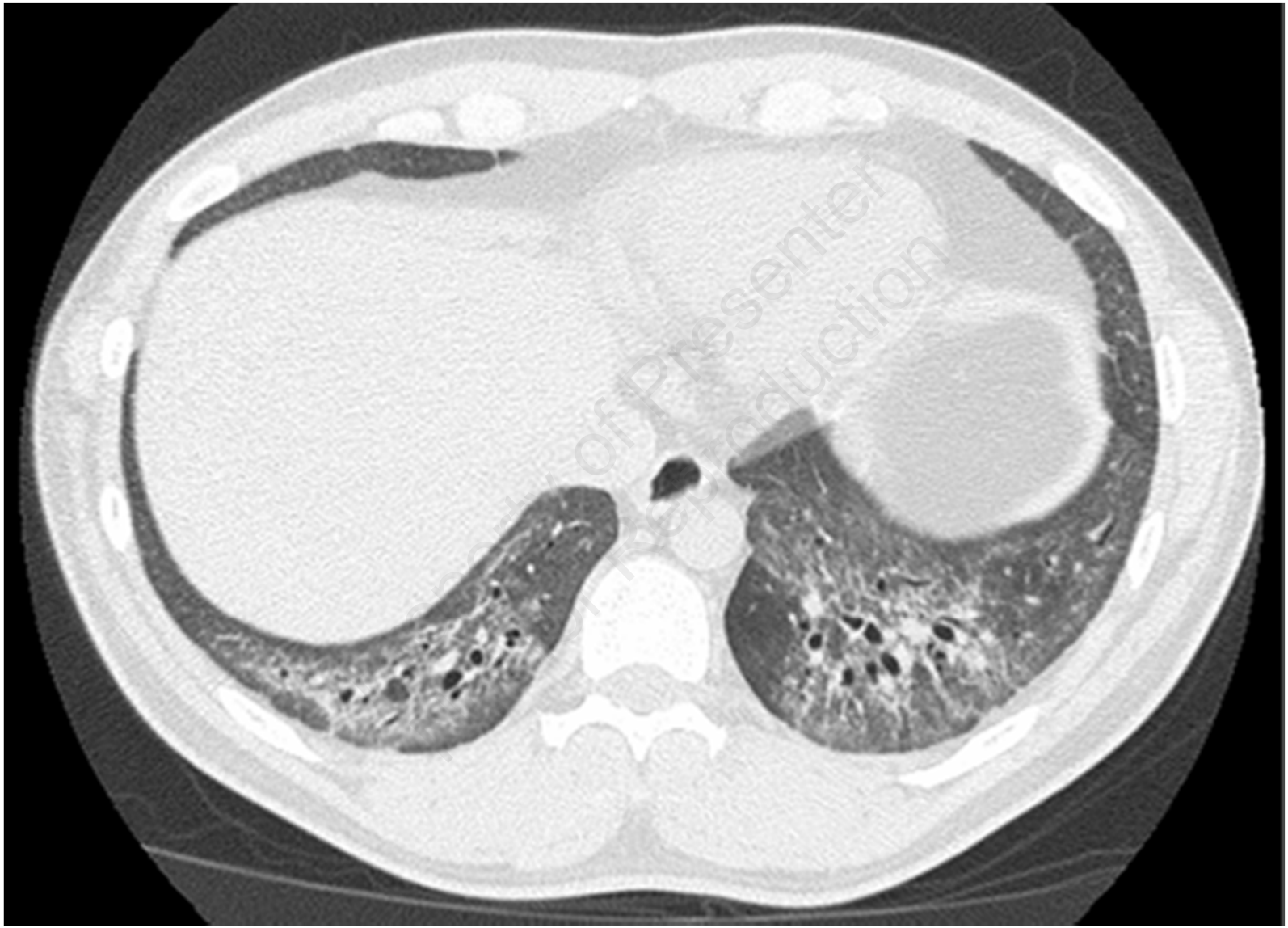


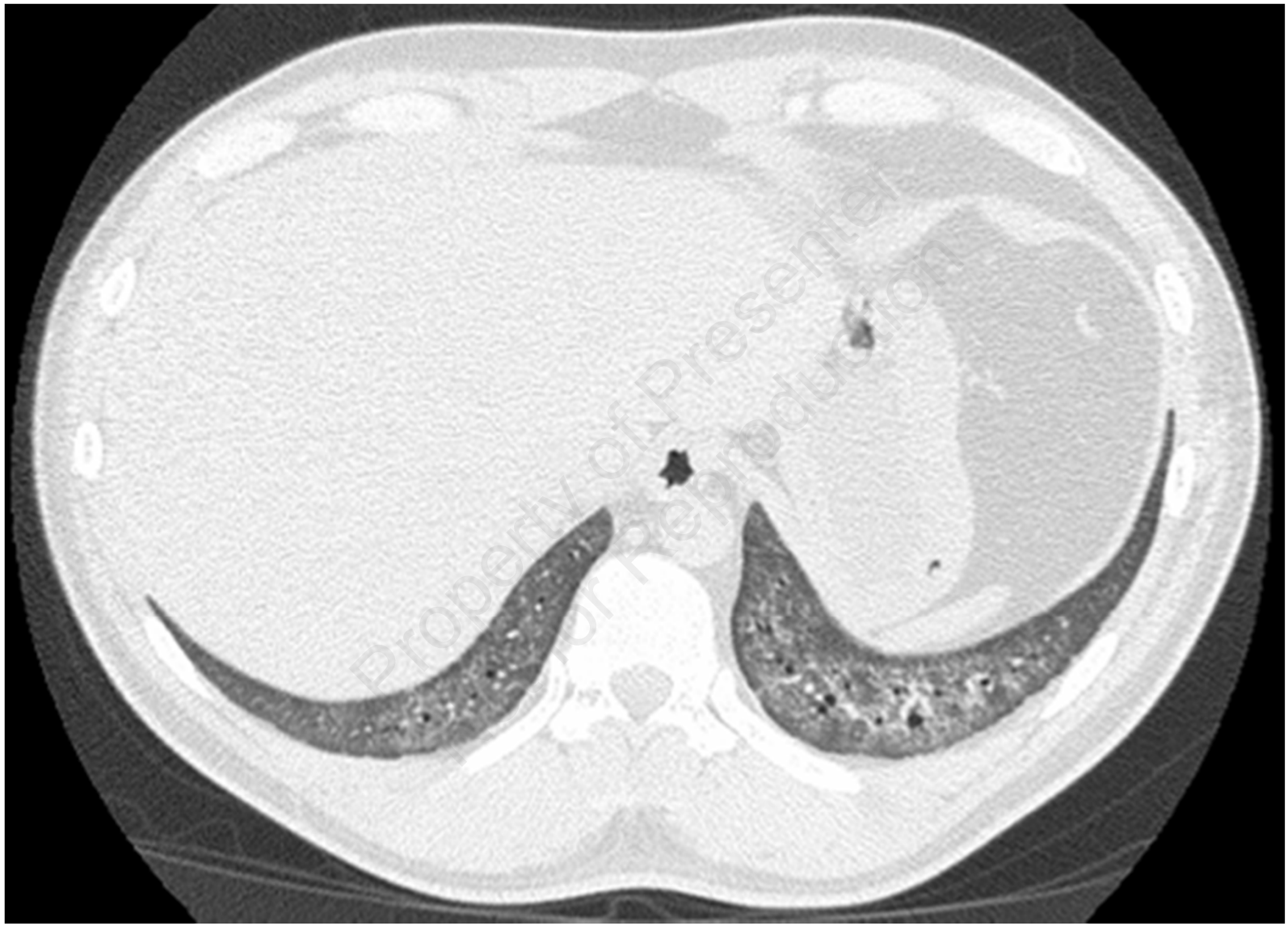




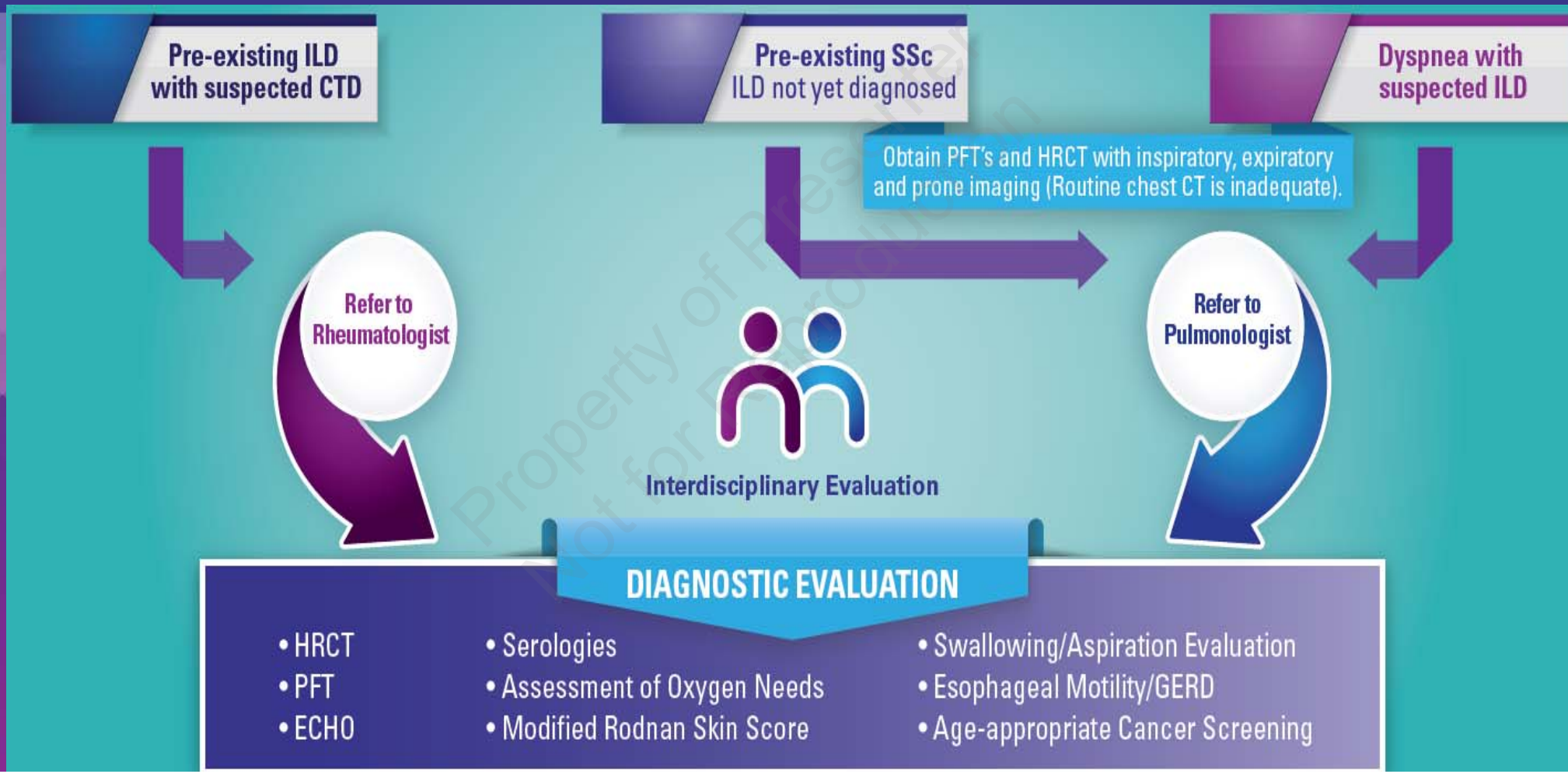








Introduction to Infographic



Overview of the epidemiology, diagnostic criteria and clinical manifestations of systemic sclerosis in adults

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National Jewish Health

Systemic Sclerosis Epidemiology

- The prevalence rates of scleroderma-like conditions range from 4 to 489 cases per million individuals [1].

- Incidence figures for SSc are 0.6 to 122 per million persons per year; the actual prevalence is probably at the high end of the range noted above [1].

- Higher rates in:
  - United States and Australia than in Japan or Europe
  - African Americans than Caucasians
  - Females than males

1 Chifflot H, et al. Semin Arthritis Rheum. 2008 Feb;37(4):223-35. Epub 2007 Aug 9.

Types of Systemic Sclerosis and Serology

- Scleroderma sine scleroderma
- Limited cutaneous SSc (CREST)
- Diffuse cutaneous SSc (modified Rodnan score system)
- Scleroderma overlap syndrome

Serology

ANA [(nucleolar (AnoA & centromere (ACA)], anti-Th/To: ***Limited skin disease, more PAH***

Anti-topoisomerase I (Scl-70), anti-topoisomerase III, anti-RNP I,II, III: ***Diffuse skin disease, more ILD***

Anti polymyositis/scleroderma(PM/Scl), Anti-Ku, anti-Ro (SSA), antiphospholipid Abs (aPL),

anti-Smith-(anti-Sm) : ***Scleroderma overlap***

2013 ACR/EULAR Criteria for Classification of SSc

- Three hallmarks of SSc:
- Fibrosis of the skin and/or internal organs
- Specific autoantibodies
- Vasculopathy
- Sensitivity : 0.91
- Specificity : 0.92
- Total score of ≥ 9 classified as definite SSC

Item	Sub-item(s)	Weight/score ¶
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	–	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	–	3
SSc-related autoantibodies (anticentromere, anti-topoisomerase I [anti-Scl-70], anti-RNA polymerase III) *(maximum score is 3)*	Anticentromere Anti-topoisomerase I Anti-RNA polymerase III	3

ACR/EULAR criteria for the classification of systemic sclerosis.

ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; SSc: systemic sclerosis.
" These criteria are applicable to any patient considered for inclusion in an SSc study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (eg, nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).
¶ The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥9 are classified as having definite SSc.

From: van den Hoogen F, Khanna D, Fransen J, et al. 2013 Classification Criteria for Systemic Sclerosis: An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. Arthritis Rheum 2013; 65:2737. Copyright © 2013 by the American College of Rheumatology. Reproduced with permission from John Wiley & Sons, Inc. All rights reserved.

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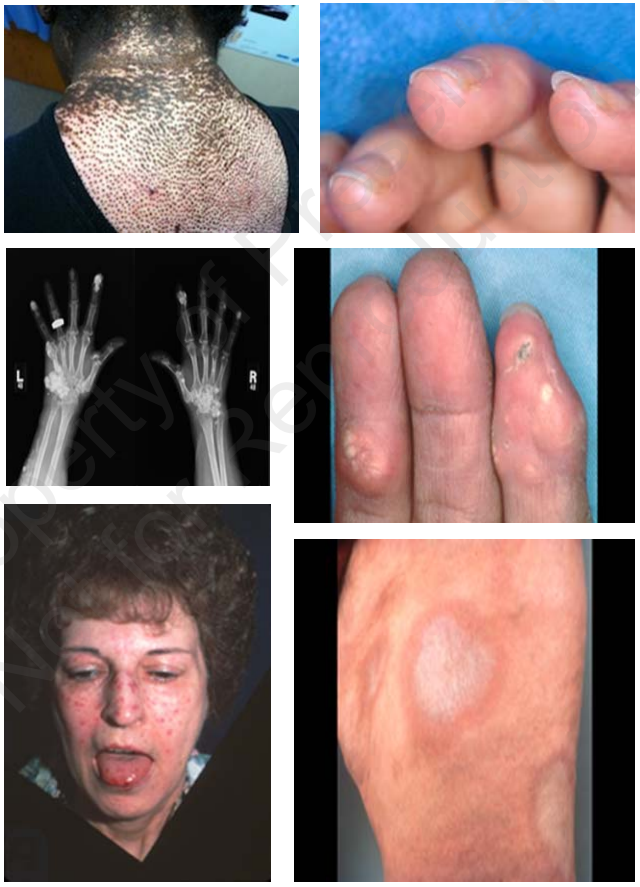
van den Hoogen F, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheumatology*. 2013;65(11):2737-2747.

Systemic Sclerosis manifestations

- Fatigue (76%)
- Stiff joints (74%)
- Loss of strength (68%)
- Pain (67%)
- Sleep difficulties (66%)
- Skin discoloration (47 %)

Skin Involvement

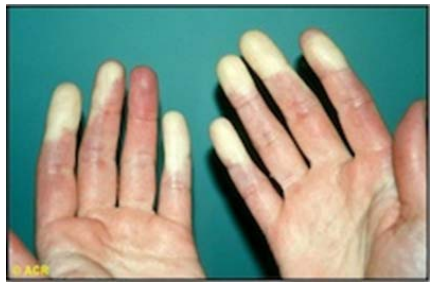
- Pruritus and edema, early
- Hypopigmentation & depigmentation ("salt-and-pepper")
- Loss of hair
- Dry skin
- Telangiectasia
- Lipoatrophy

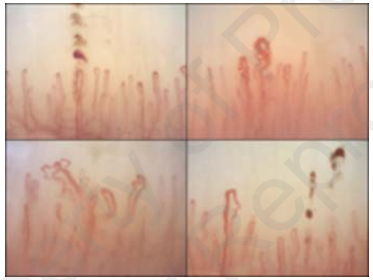


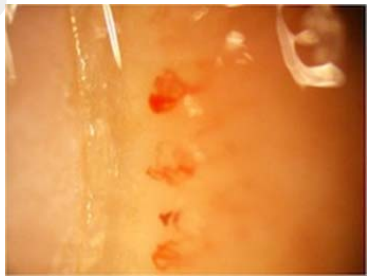
- Sclerodactyly
- Diffuse sclerosis (Modified Rodnan score system)
- Digital tip ulcers
- Pitting at the fingertips
- Calcinosis cutis

Vascular involvement

- Raynaud phenomenon and capillaroscopy





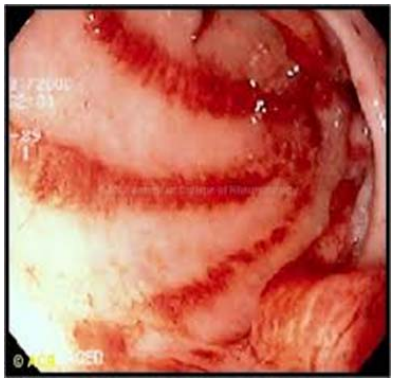


- Increased risk of venous thromboembolism (VTE)

Gastrointestinal involvement

- GI dysmotility
- GERD
- Chronic esophagitis and stricture formation
- Barrett's esophagus
- Pulmonary microaspiration
- Gastric antral vascular ectasia

("watermelon stomach")



Cardiac involvement

- Pulmonary hypertension
  - WHO I (PAH or PVOD* or PCH**) and/or III (in the setting of ILD) and/or VI (CTPH***)
- Pericardial dz (7-20%)
- Myocardial dz: Patchy myocardial fibrosis, pathological hallmark
- Myocardial ischemia
- Coronary vasospasm
- Arrhythmias/conduction defects
- Systolic and diastolic dysfunction

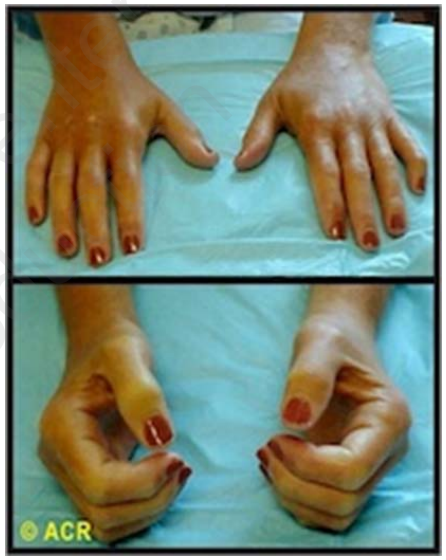
* Pulmonary veno-occlusive disease

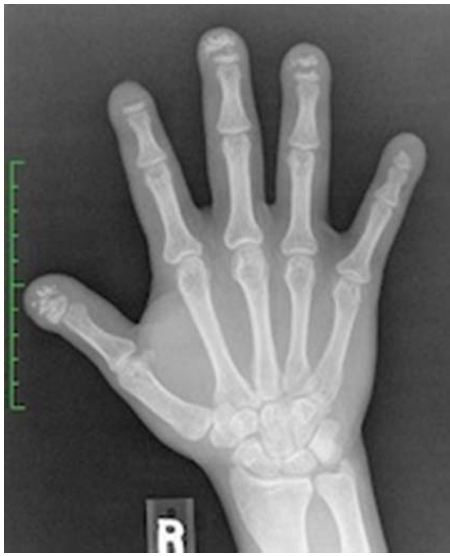
** Pulmonary capillary hemagiomatosis

*** Chronic thromboembolic pulmonary hypertension

Musculoskeletal involvement

- Tendon friction rubs
- Joint pain, immobility and contractures
- Acro-osteolysis
- Frank inflammatory arthritis is uncommon





Renal involvement

- Scleroderma renal crisis with schistocyte and MAHA
- Glomerulonephritis is uncommon /rarely (ANCA)-associated vasculitis
- Microalbuminuria
- Mild elevation in the plasma creatinine concentration
- Hypertension

Neuromuscular involvement

- Neuropathy

  Cranial, peripheral, cutaneous, entrapment and autonomic

- Myopathy and inflammatory myositis

- Headache, seizures, stroke

- Radiculopathy & myopathy

Genitourinary involvement

- Men
- Erectile dysfunction

- Women
- Decreased vaginal lubrication

- Constriction of the vaginal introitus

- Dyspareunia

Cancer Risk

- Lung cancer

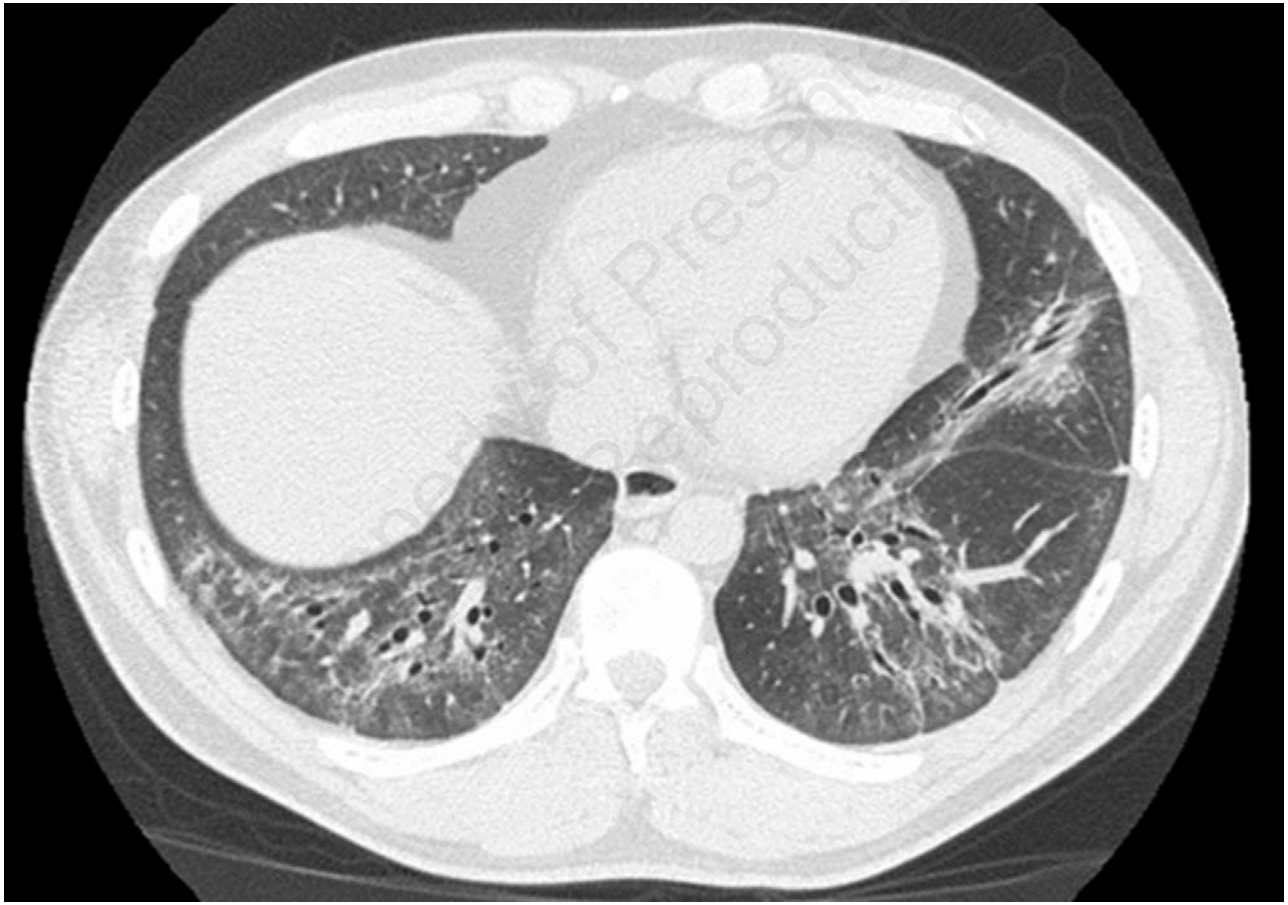
  A close temporal relationship between the onset of cancer and of SSc has been observed among patients with autoantibodies to RNA polymerase I/III.

- Hematologic cancers

- Esophageal carcinoma

- Oro-pharyngeal carcinoma

Interstitial lung disease (ILD)



Effective Treatment Options for SSc-ILD

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CEO, Jane & Leonard Korman Respiratory Institute –

Jefferson Health and National Jewish Health

Enterprise Division Chief, Pulmonary, Allergy and Critical Care Medicine

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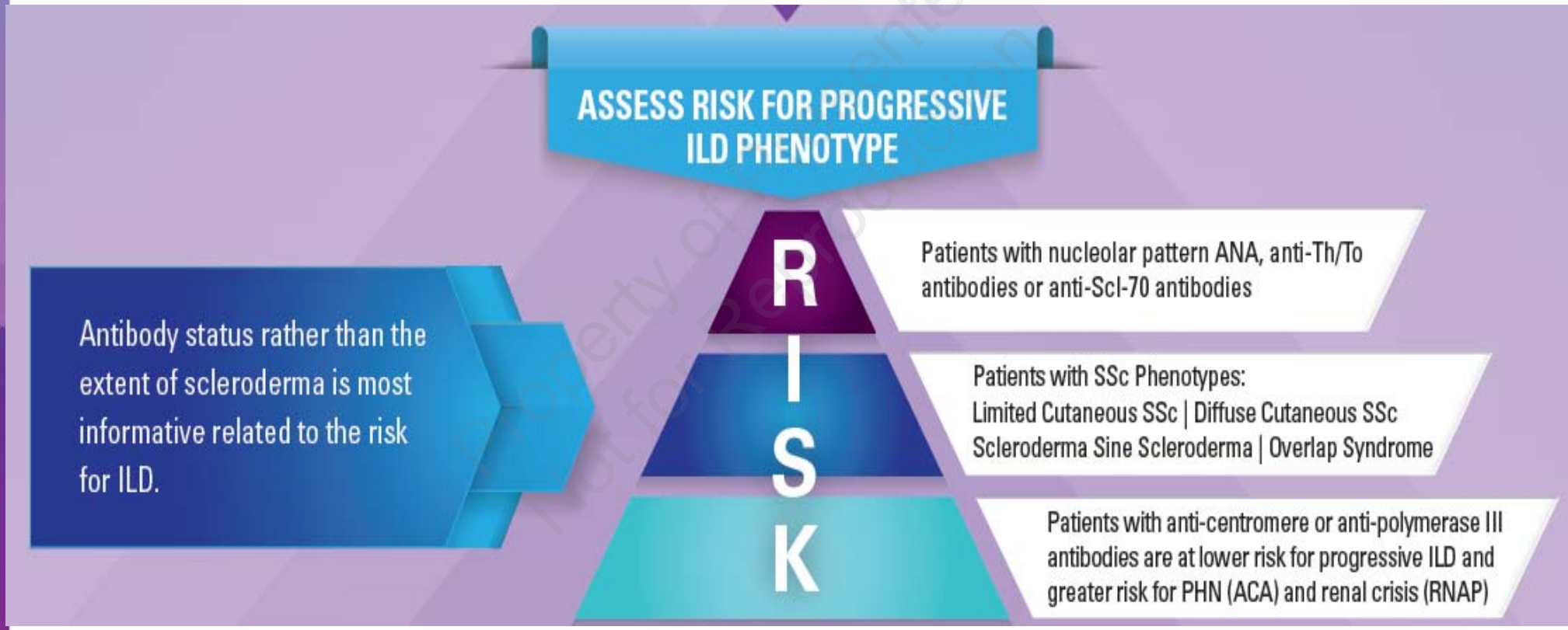
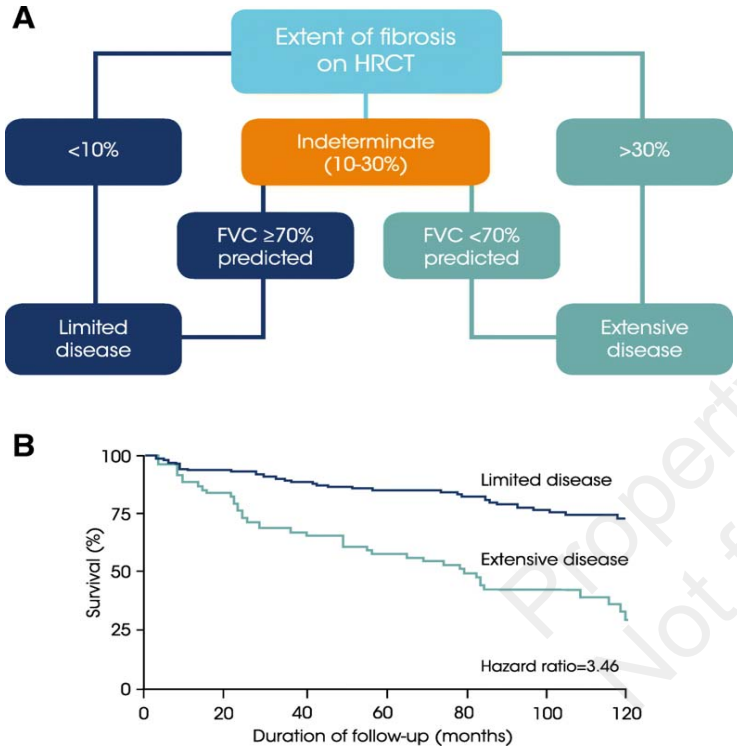
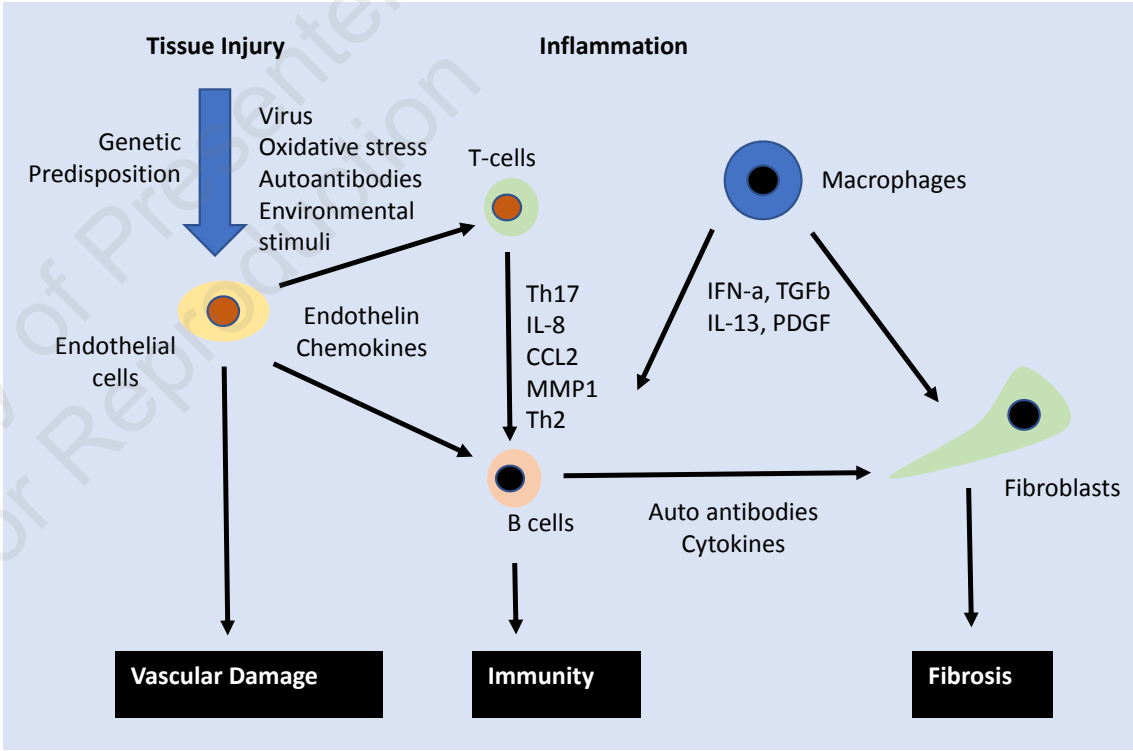
Risk for Progressive ILD Phenotype



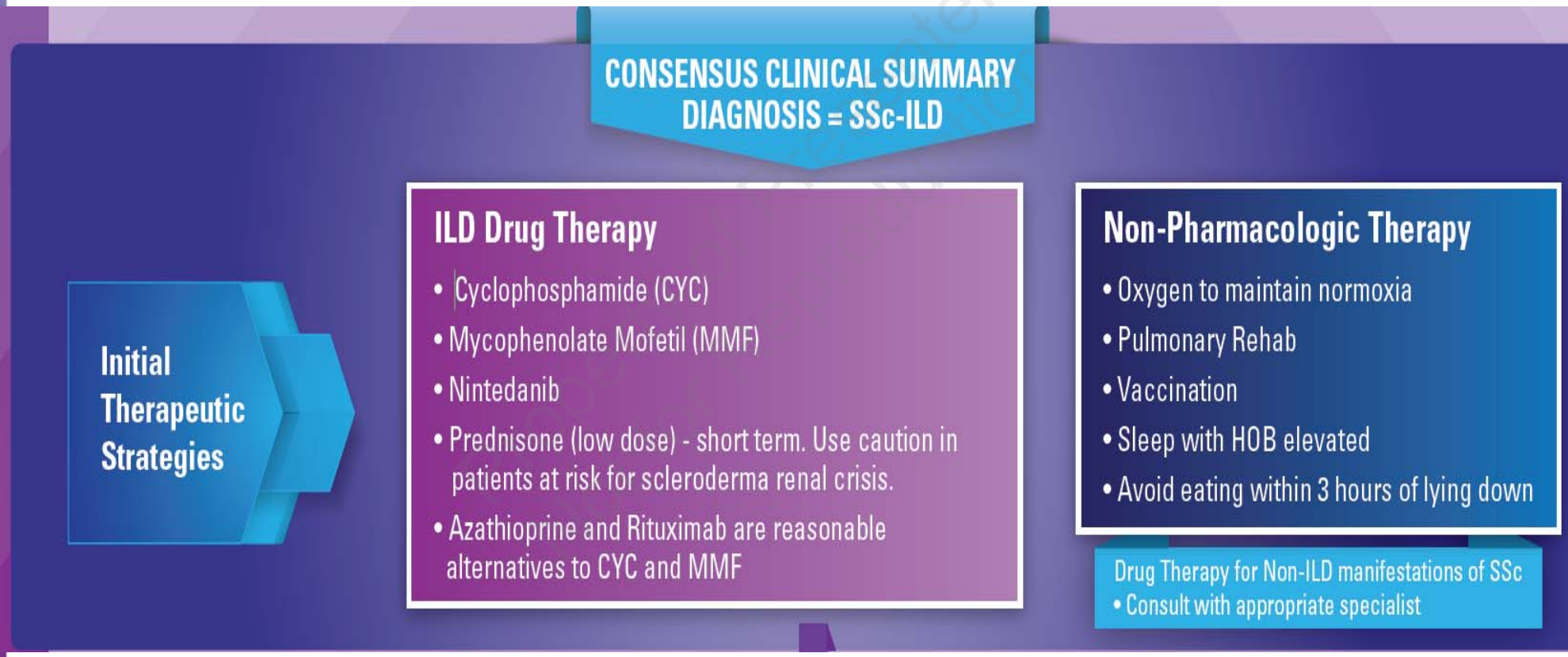
Pulmonary fibrosis worsens prognosis in SSc





Cottin and Brown Respiratory Research (2019) 20:13 https://doi.org/10.1186/s12931-019-0980-7

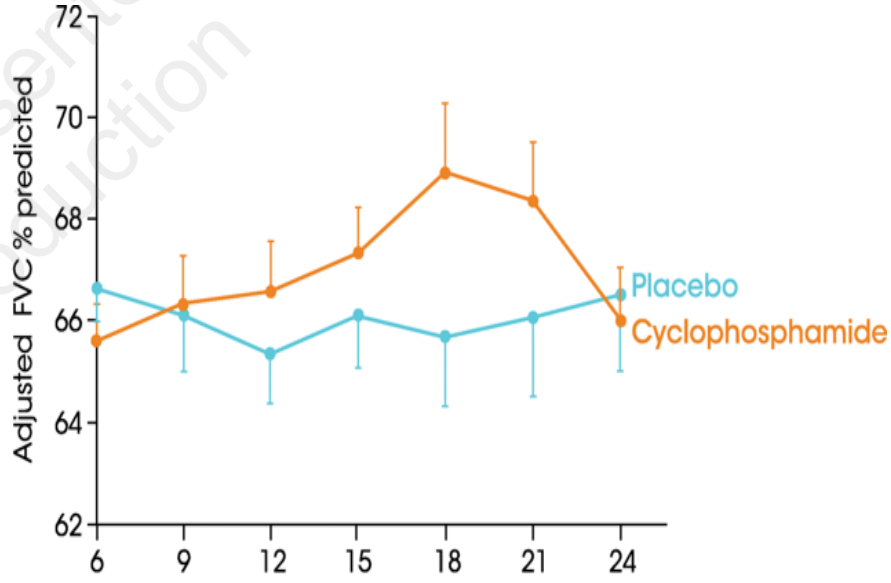
Summary of treatment approach



Oral cyclophosphamide had a significant, but modest beneficial effect

Scleroderma Lung Study

- Double-blind, randomized, placebo controlled
- Effect of oral cyclophosphamide vs. placebo
- Study design:
  - -SSc and dyspnea
  - -Restriction on PFTs (FVC 45-85%, DLCO >30%)
  - -Inflammation ILD on BAL or GGO on HRCT
  - -CYC 2 mg/kg/day (avg. 100 mg) or placebo x 1 yr
  - -2nd year follow-up OFF therapy
  - -Primary end-point FVC at 12 months
- Conducted by NIH at 13 centers



Number of patients							
Cyclophosphamide	67	64	66	57	52	51	54
Placebo	70	65	65	55	56	51	55

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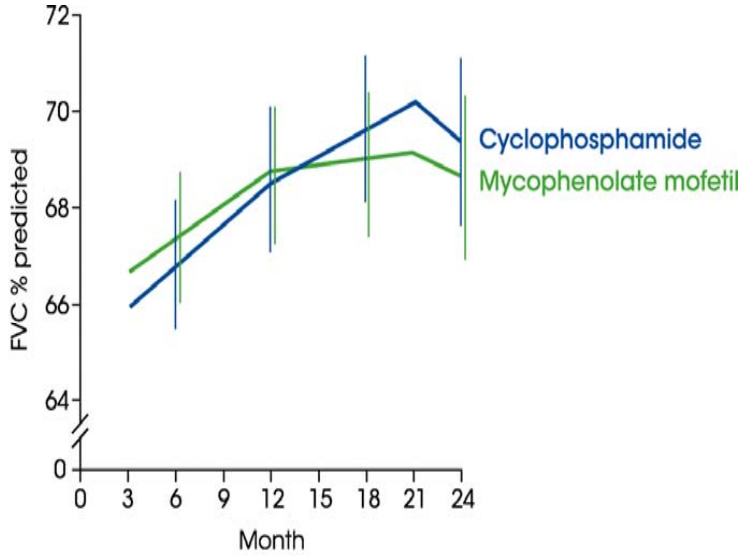
Mycophenolate mofetil and cyclosphosphamide appear equally effective

Study:

- Double-blind, randomized
- Effect of oral cyclophosphamide vs. MMP
- 142 randomized
- 69 MMP (53 with 24 mo data)
  - -20 D/C drug (19 withdrew, 0 failed, 1 died on drug)
  - - 4 death after withdrawal
- 73 CYC (53 with 24 mo data)
  - -36 D/C (32 withdrew, 2 failed, 2 died on drug)
  - - 9 deaths after withdrawal



Number of patients									
Cyclophosphamide	72	62	56	51	51	44	46	40	51
Mycophenolate mofetil	69	64	60	54	59	51	49	47	53

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Autologous hematopoietic stem cell transplantation and lung transplantation are options

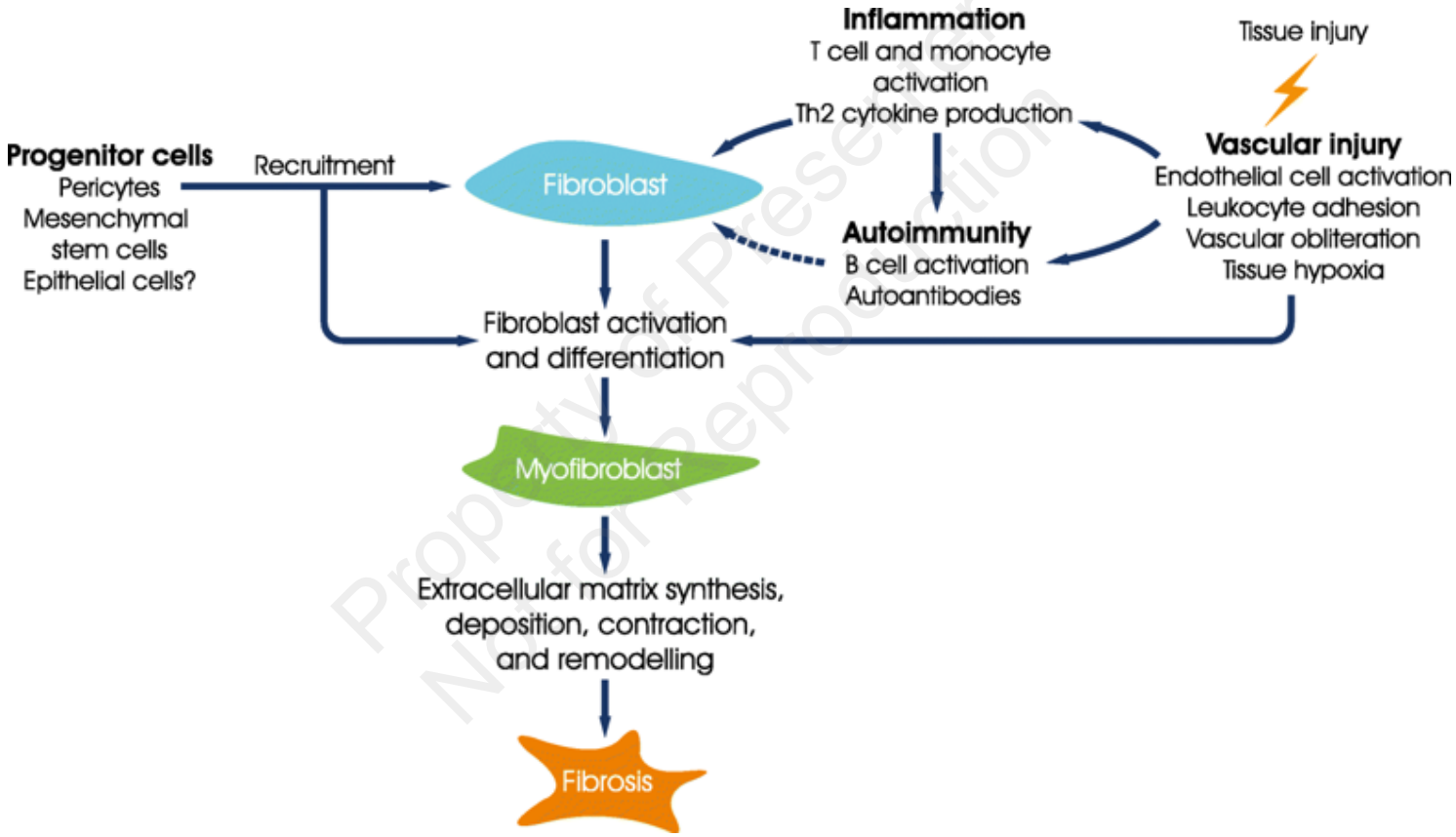
Autologous hematopoietic stem cell transplantation increased mortality in first year, but conferred long-term benefit

Van Laar et al. JAMA 311:2490-2498, 2014.

Post-transplant survival rates and freedom from chronic lung allograft dysfunction in SSc-ILD are similar to those with other reasons for transplantation

Prederex et al. J Heart Lung Transplantation 37: 903-911, 2018

Considering anti-fibrotic therapies



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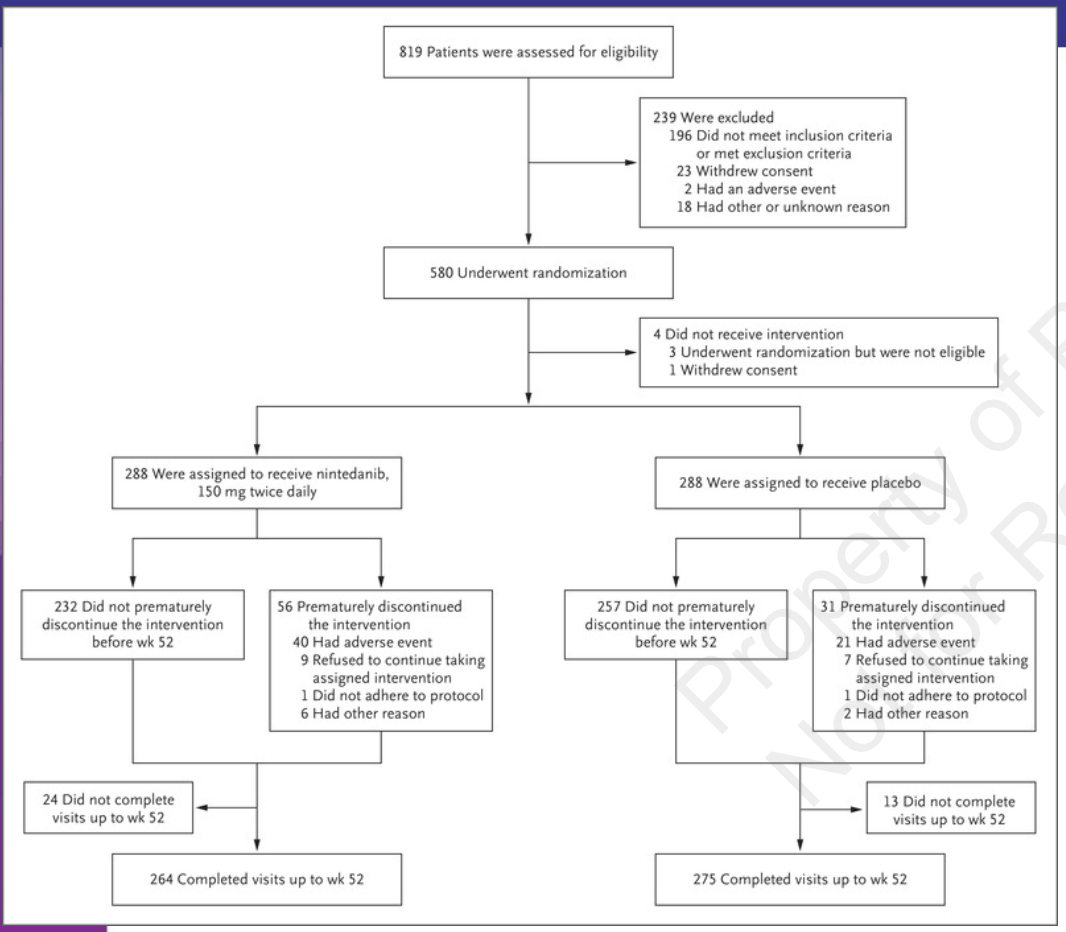
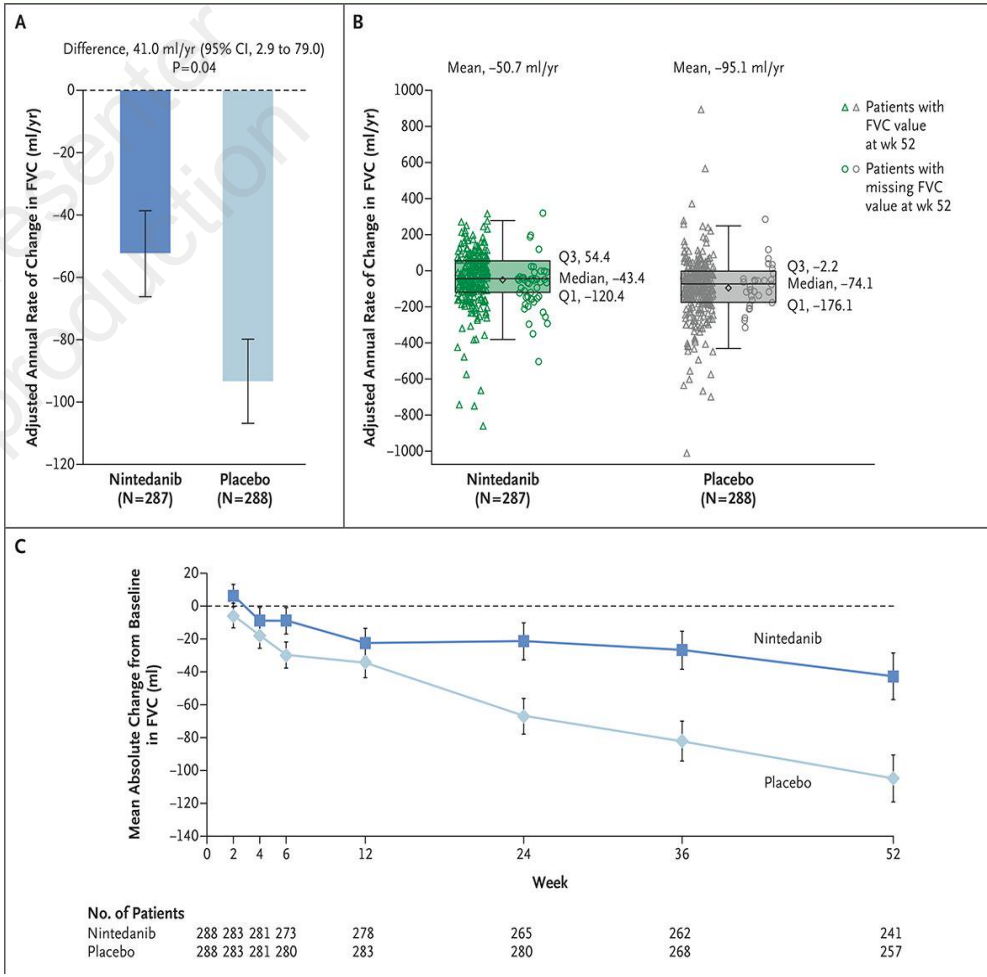
Nintedanib for systemic sclerosis-associated ILD





Distler et al. Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease. NEJM 380: 2518-28, 28, 2019.

Patients on nintedanib did not experience worse side effects

Table 3. Adverse Events.*

Event	Nintedanib (N=288)	Placebo (N=288)
	no. of patients (%)	
Any adverse event	283 (98.3)	276 (95.8)
Most common adverse events†		
Diarrhea	218 (75.7)	91 (31.6)
Nausea	91 (31.6)	39 (13.5)
Skin ulcer	53 (18.4)	50 (17.4)
Vomiting	71 (24.7)	30 (10.4)
Cough	34 (11.8)	52 (18.1)
Nasopharyngitis	36 (12.5)	49 (17.0)
Upper respiratory tract infection	33 (11.5)	35 (12.2)
Abdominal pain	33 (11.5)	21 (7.3)
Fatigue	31 (10.8)	20 (6.9)
Weight decrease	34 (11.8)	12 (4.2)
Severe adverse event‡	52 (18.1)	36 (12.5)
Serious adverse event§	69 (24.0)	62 (21.5)
Fatal adverse event	5 (1.7)	4 (1.4)
Adverse event leading to discontinuation of the intervention	46 (16.0)	25 (8.7)

* Adverse events, as reported over 52 weeks plus a 28-day post-treatment period, were coded according to the preferred terms in the *Medical Dictionary of Regulatory Activities*. Data are shown for the patients who had at least one such adverse event.

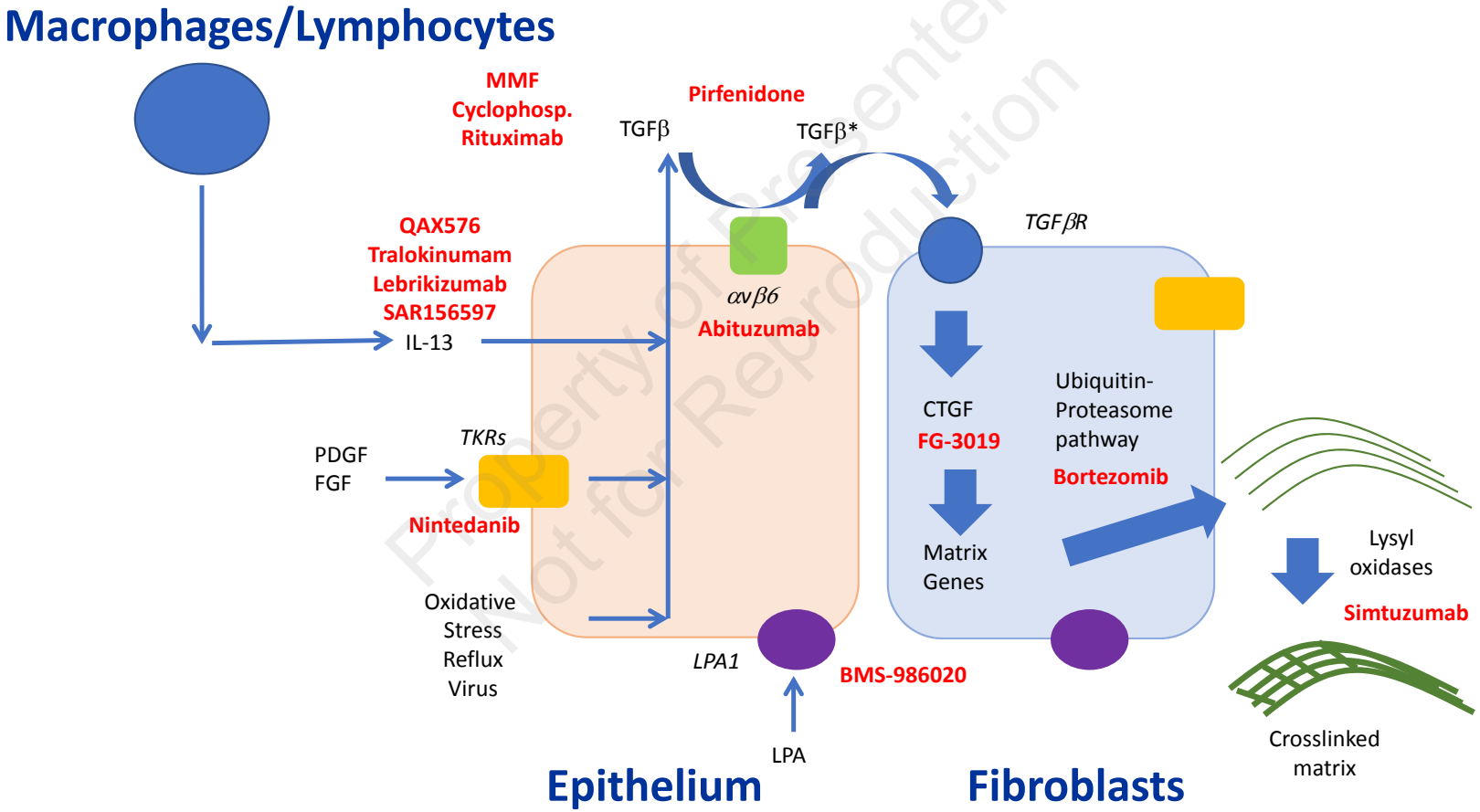
† The most common adverse events were those that were reported in more than 10% of the patients in either trial group.

‡ A severe adverse event was defined as an event that was incapacitating or that caused an inability to work or to perform usual activities.

§ A serious adverse event was defined as an event that resulted in death, was life-threatening, resulted in hospitalization or prolongation of hospitalization, resulted in persistent or clinically significant disability or incapacity, was a congenital anomaly or birth defect, or was deemed to be serious for any other reason.

Distler et al. Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease. NEJM 380: 2518-28, 28, 2019.

Future Therapies in SSc-ILD



Adapted from Khanna et al. Rheumatology, 58:567-579, 2019

Systemic Sclerosis ILD: Strategies for Longitudinal Management

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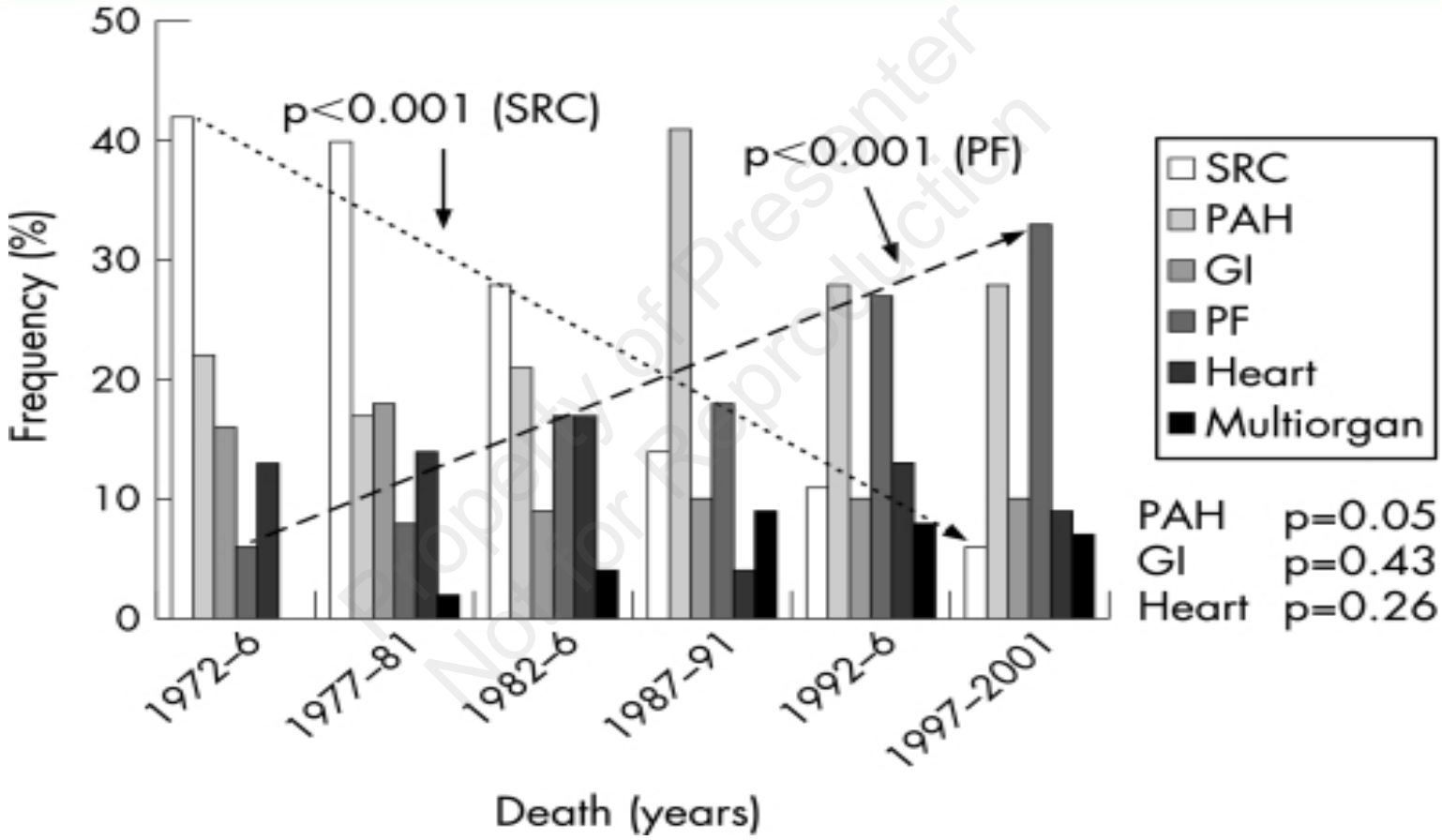
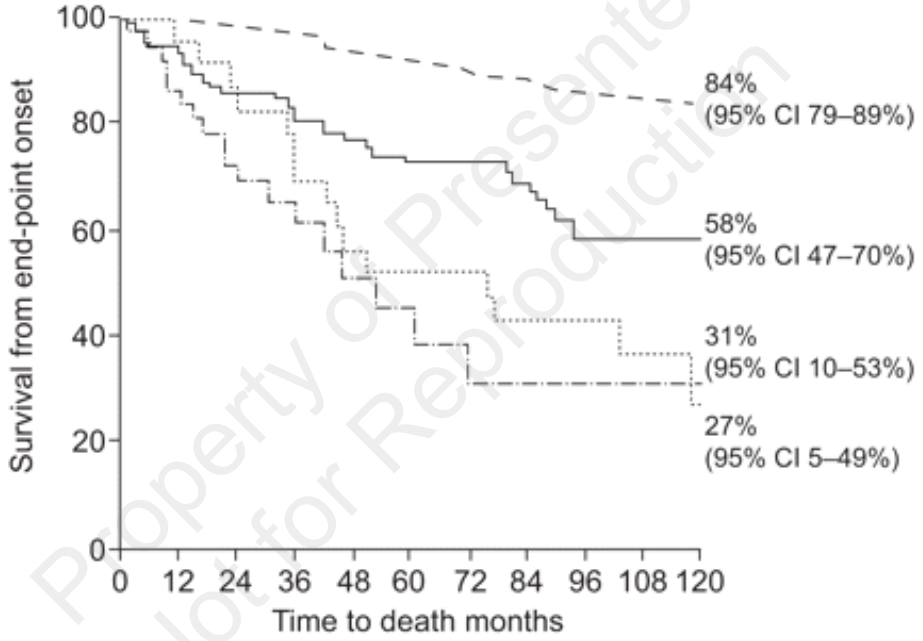
Causes of Death in Systemic Sclerosis



Virginia D Steen, Thomas A Medsger Changes in causes of death in systemic sclerosis, 1972–2002 Ann Rheum Dis 2007; 66:940–944

Impact of Complications on Survival in SSc



Subjects at risk n

No	247	222	175
PF	90	49	19
PAH	38	7	0
PF+PH	23	12	3

C.P. Denton, E. Hachulla, European Respiratory Review 2011 20: 270-276
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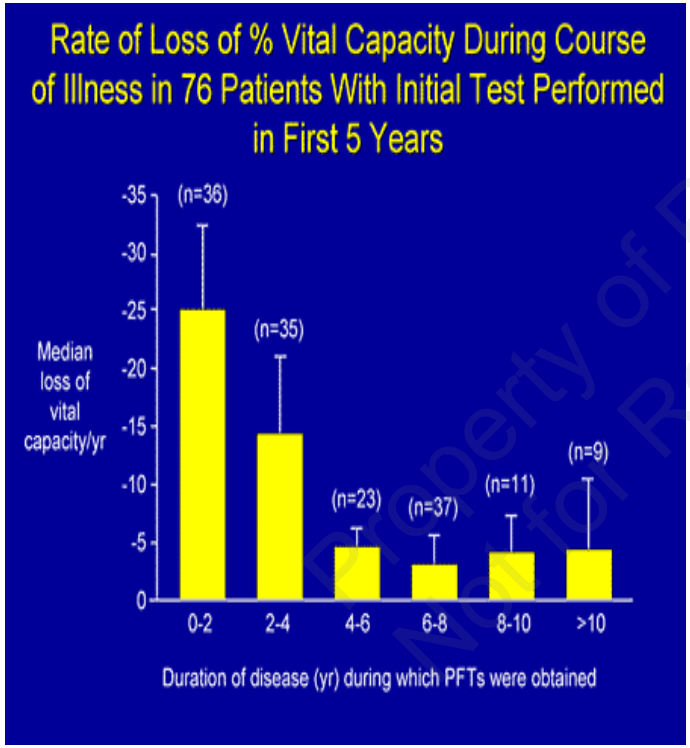
Risk Factors for ILD in SSc

- Dx of diffuse cutaneous Systemic Sclerosis (dcSSc)
- African American ethnicity
- Older age at disease onset
- Shorter disease duration
- Presence of Scl-70 Ab
- Absence of Anticentromere Ab

Cottin and Brown Respiratory Research 2019 20:13

Pulmonary Function Tests and SSc

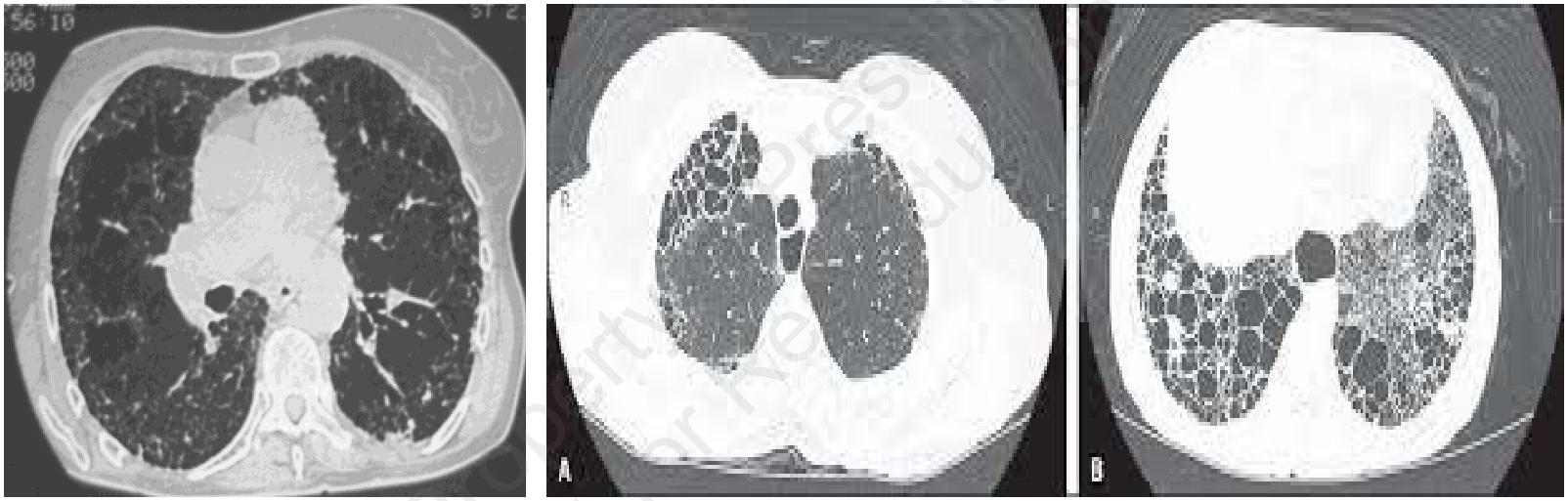


DLCO decline >15% at 24 months associated with decreased survival

FVC%/DLCO % > 1.6 associated with presence of PAH

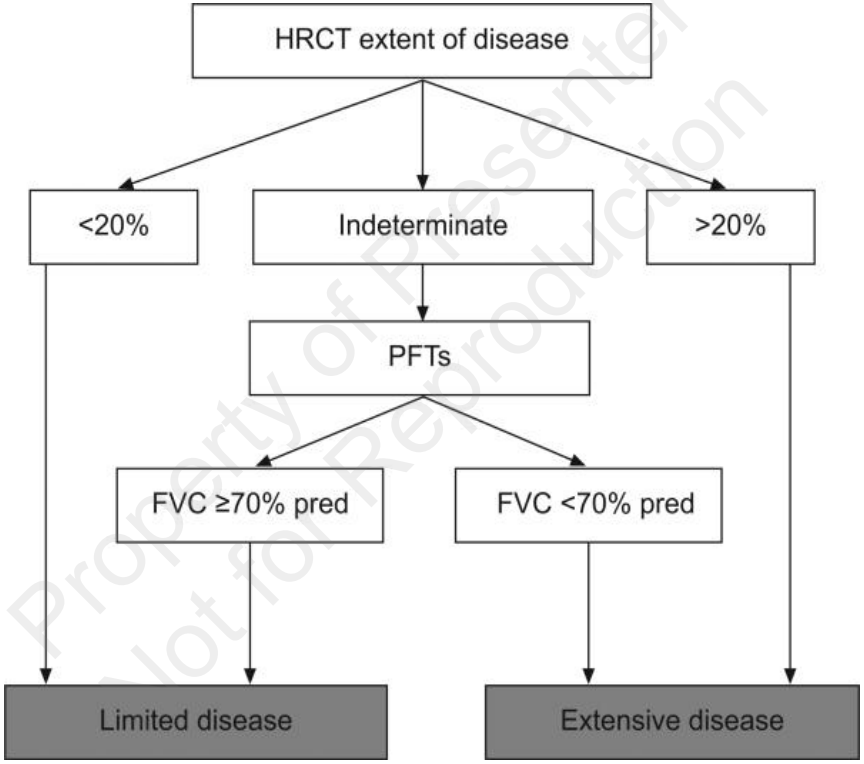
Steen, V, Medsger T. The Lung in Systemic Sclerosis. *Journal of clinical rheumatology* 2005; 11(1):40-46.

HRCT in SSc



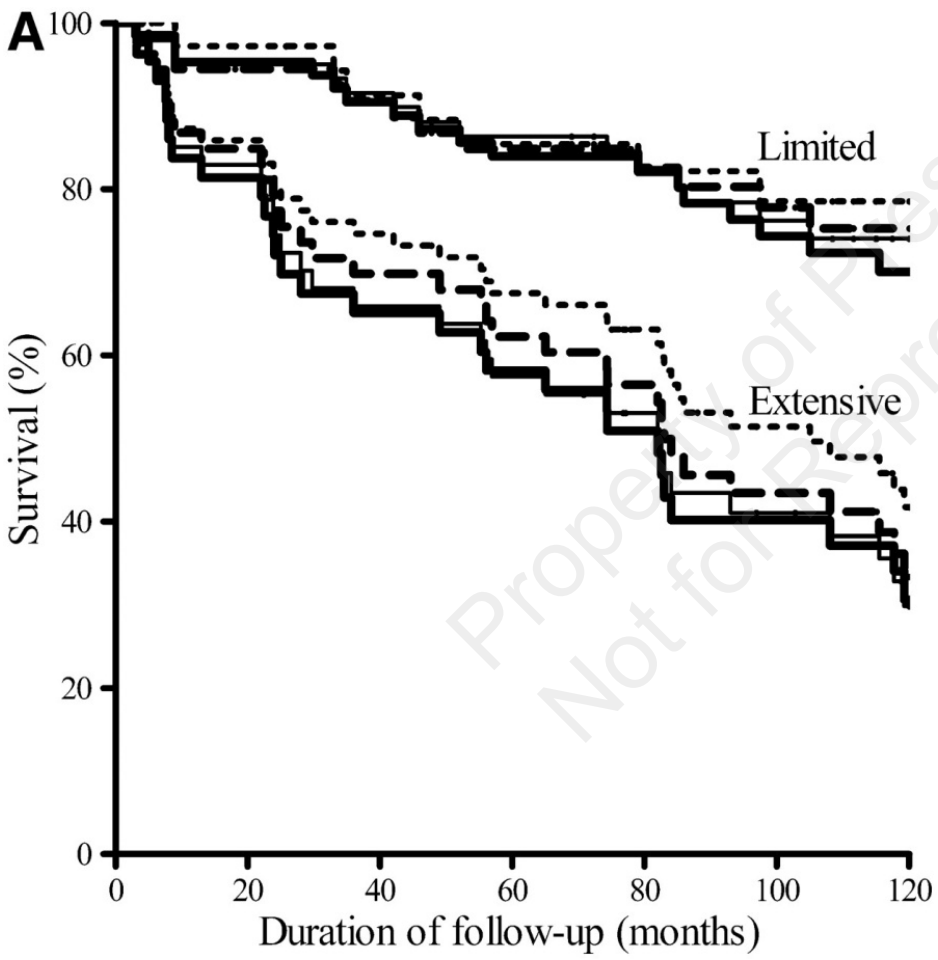
Extent of Involvement : Minimal (Limited to Extensive)
Extent reflected on PFT’s

Combining FVC and HRCT

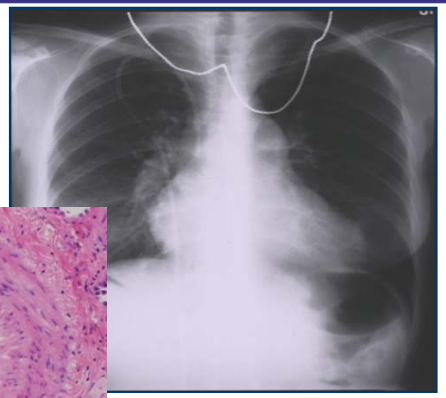


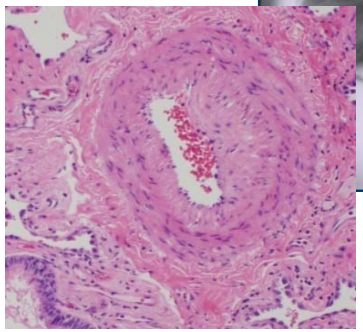
Goh NS, Desai SR, Veeraraghavan S, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med 2008; 177: 1248–1254.
Joshua J. Solomon, Amy L. Olson, Aryeh Fischer, Todd Bull, Kevin K. Brown, Ganesh Raghu
European Respiratory Review 22 (127) 6-19

Classification Based on CT and FVC

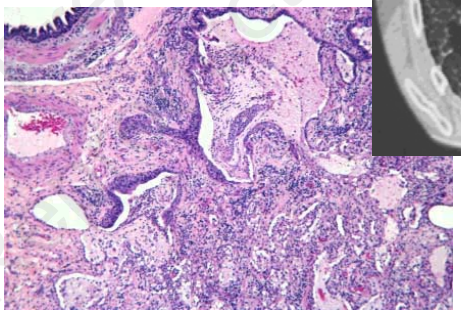


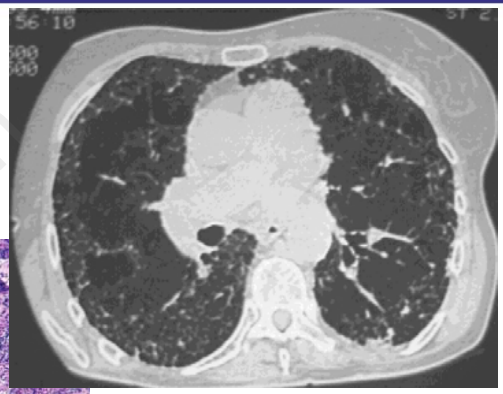
PH in Systemic Sclerosis



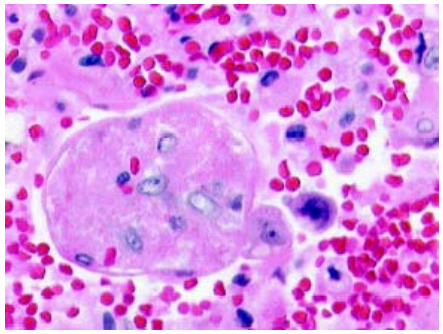


PAH

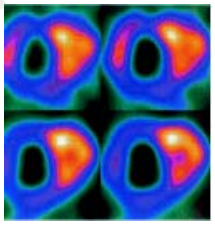




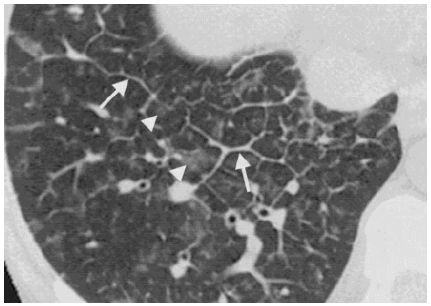
fibrosis



in-situ thrombosis



myocardial disease



PVOD

PHN in Systemic Sclerosis – Suspect in ALL and Screen Appropriately

Screen with ECHOCARDIAGRAM

1. ANTICENTROMERE > SCL-70
2. lcSSC>dsSSC
3. DLCO < 50%
4. FVC%/DLCO >1.6
5. PA SIZE >30 mm
6. EKG
7. ELEVATED Pro-BNP
8. ELEVATED URIC ACID
9. Use of algorithms
10. Nail Capillaroscopy

Confirm with RIGHT HEART CATH

1. RVSP >40 mm HG
2. TR jet Velocity>3 m/sec
3. PERICARDIAL EFFUSION
4. SIGNS AND SYMPTOMS OF PH
5. ABNORMAL RVS/FUNCTION
6. EXCLUDE ALT. CAUSES: PE, OSA
7. Hemodynamic testing
8. Evaluate LVD

Clinical Assessment of Scleroderma ILD/PHN

- **Baseline**
  - PE, mRSS
  - PFT's (FVC, TLC, DLCO)
  - 6 MWT
  - HRCT
  - Echocardiogram
  - Electrocardiogram
  - cMRI as indicated

- **Longitudinal**
  - PFT's Q 3-4 mo for the first 3 y then Q 6 mo
  - 6 MWT Q 6-12 mo
  - HRCT ~ Q 12 mo or as indicated by symptoms
  - Echocardiogram (Q12 mo +/- Stress)
  - RHC as indicated
  - cMRI

SSc-ILD Pearls

- AA ethnicity and anti-topoisomerase (Scl70) and anti-U3-RNP positive patients have worse disease (Gelber Ann Rheum Dis 2013)
- Baseline FVC may predict lung function decline and survival (Plastiras A&R 2006;GohAm J Respir Crit Care Med 2008)
- Fibrosis on HRCT predicts worse outcome (SLS study; Goh Am J Respir Crit Care Med 2008)
- ILD and PAH: 60% of Scleroderma related deaths
- Screen and detect early as interventions may improve outcomes

SSc-ILD: A Multidisciplinary Discussion

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Denver, CO

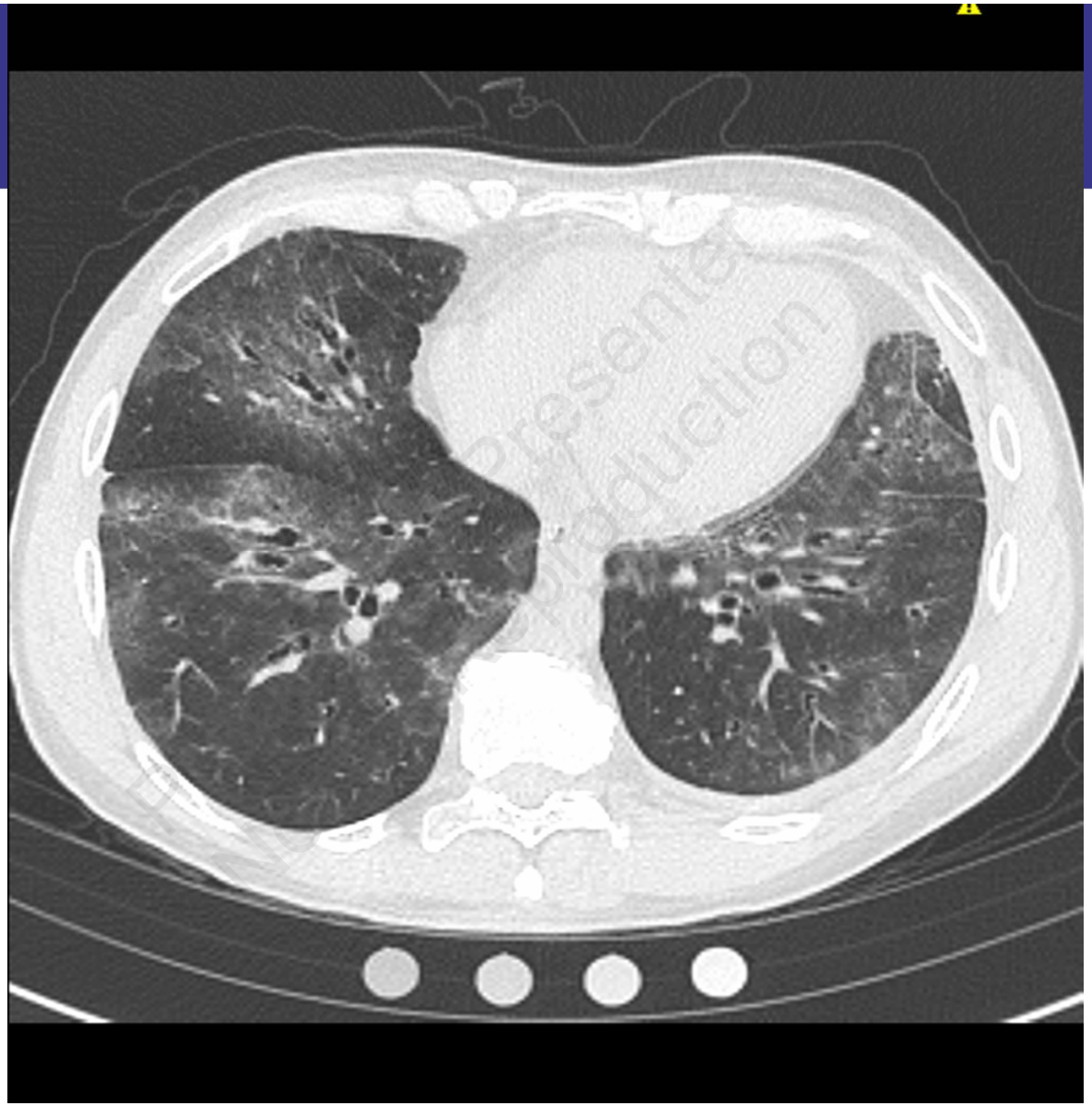
Case 2 Referred for IPF Trial Enrollment

- 70 yo M, former smoker
- DOE x 3yrs, dry cough
- Noted “blueing” of fingers 2yrs ago
- PMHx: CAD, GERD, hyperlipidemia
- SocHx: 20 pk-yr smoker (quit 10 yrs ago) exposure to agent orange
- FamHx: no ILD, psoriasis, celiac disease
- PCP ordered CXR → abnormal; referred to pulmonologist

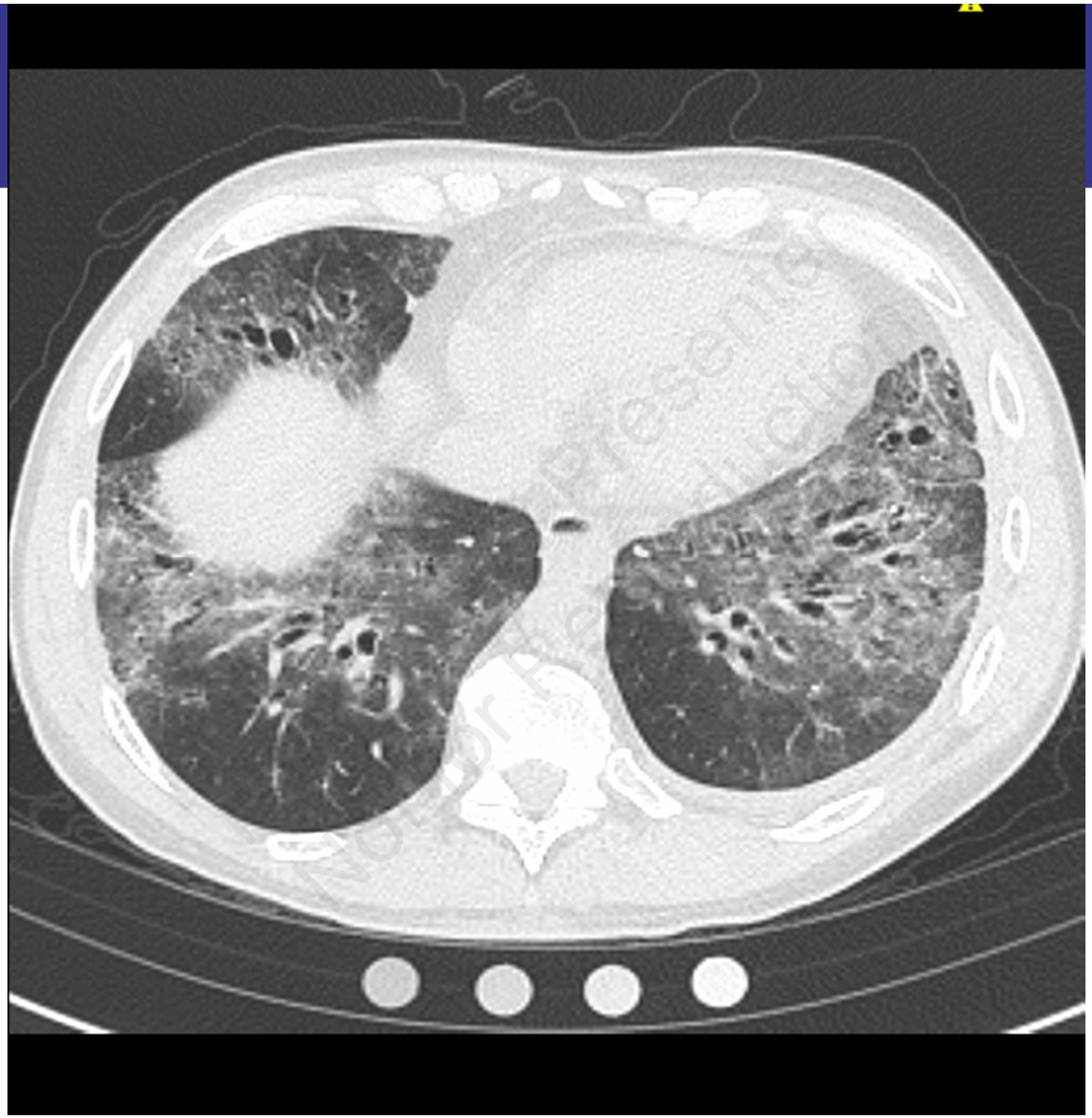
Case 2 Evaluation by Outside Pulmonologist

- Outside pulmonologist work-up
  - PFTs: FVC=3.25 (68%), DLCO=15.5 (68%)
  - HRCT scan: fibrosing interstitial pneumonia
  - Cardiac evaluation was negative
  - Referred for VATS Bx

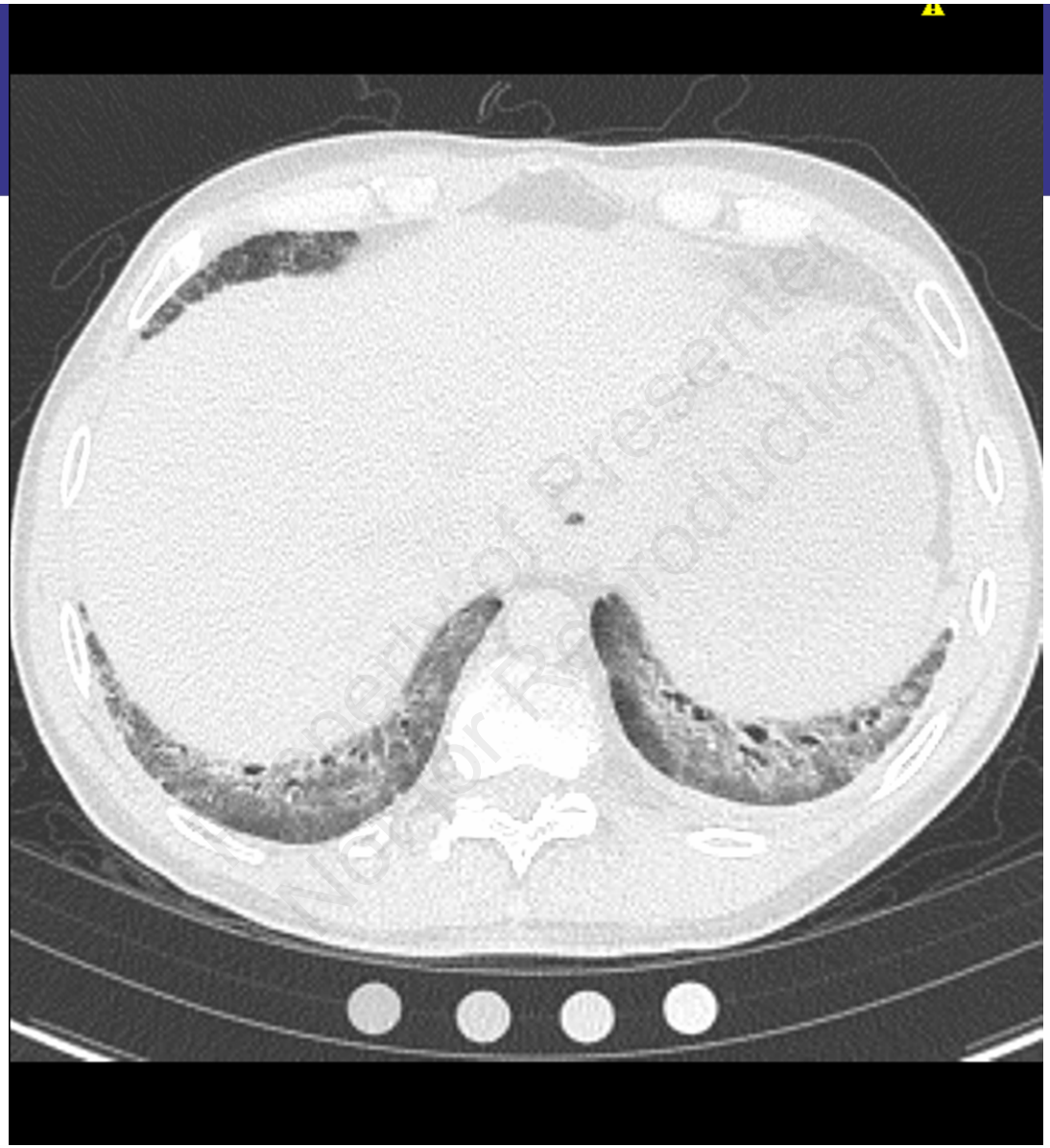
Case 2



Case 2



Case 2



Case 2 Evaluation by Pulmonologist

- VATS Bx showed fibrosing interstitial pneumonia with fibroblastic foci in a pattern of UIP with NSIP-like areas

- Diagnosed with IPF and started on pirfenidone

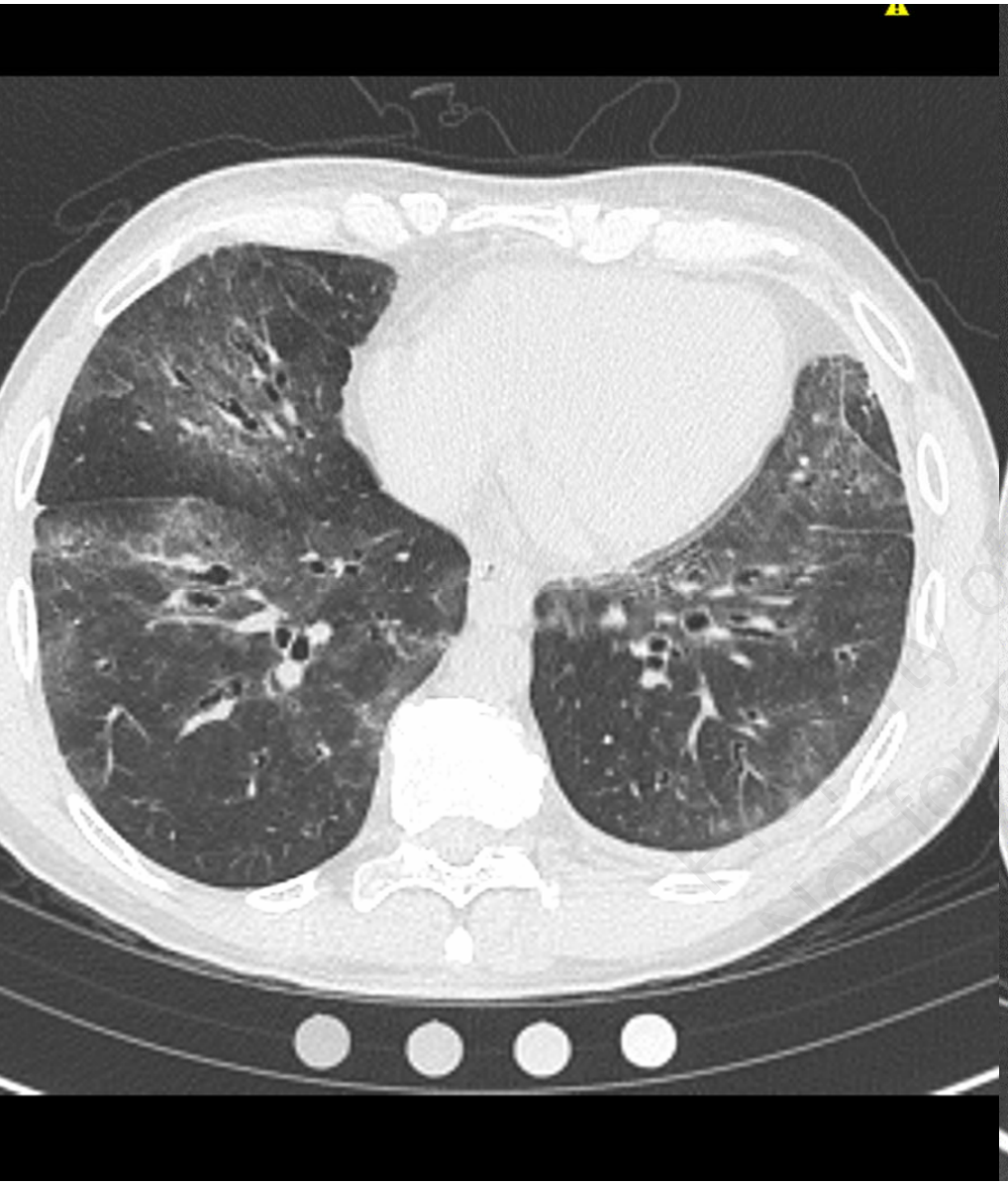
Case 2

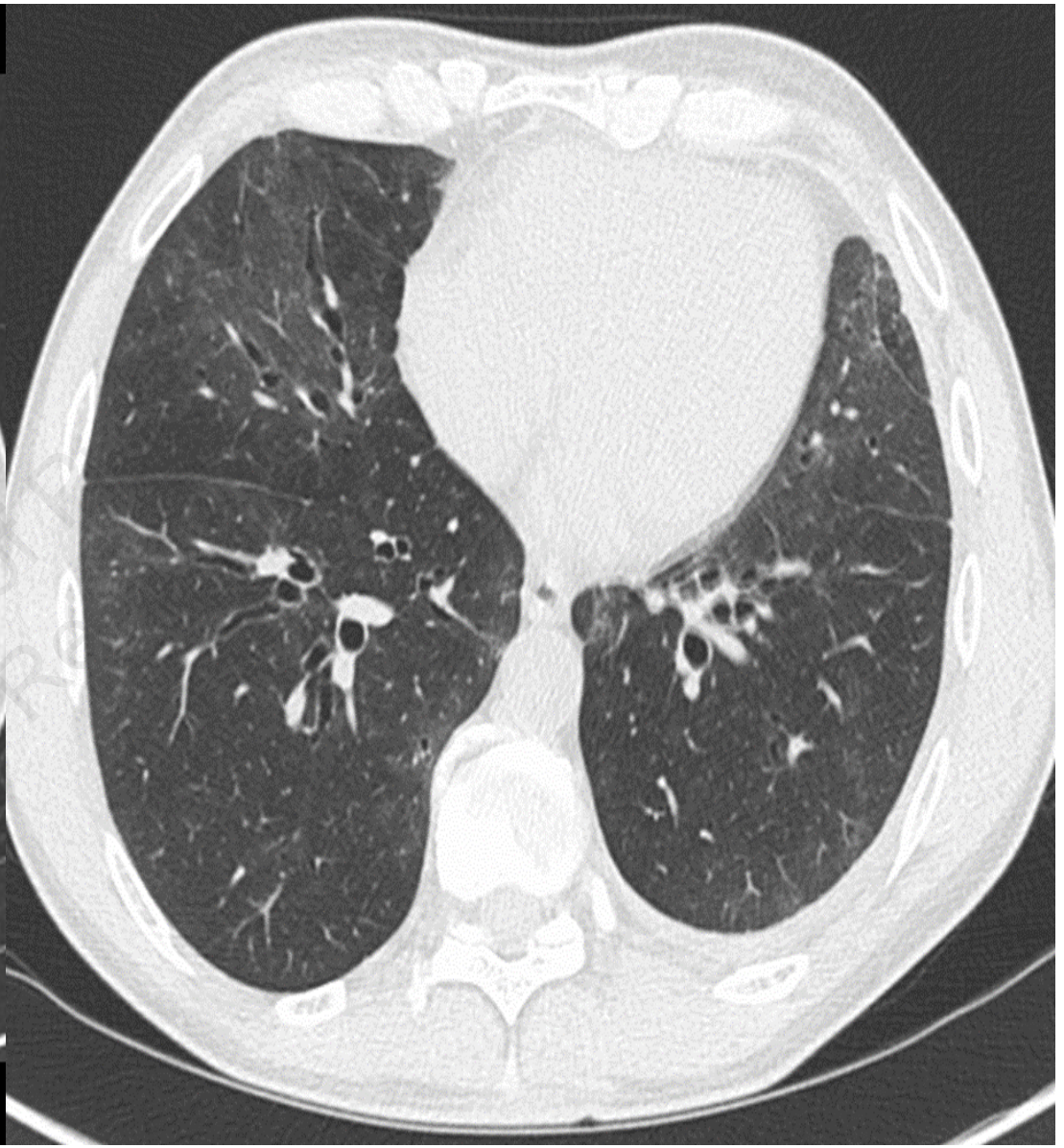
- Referred to ILD Center: evaluated by ILD and Rheumatology
  - History elicited:
    - Blueing of fingers = Raynauds (3 points)
  - Subtle exam findings:
    - Abnormal nailfolds (3 points)
    - Puffy fingers (2 points)
  - ILD (2 points)
  - Labs (3 points)
    - Anti-RNA polymerase I/III => Elevated
    - ANA => 1:1280 (nucleolar)
    - Anti-centromere antibody => Negative

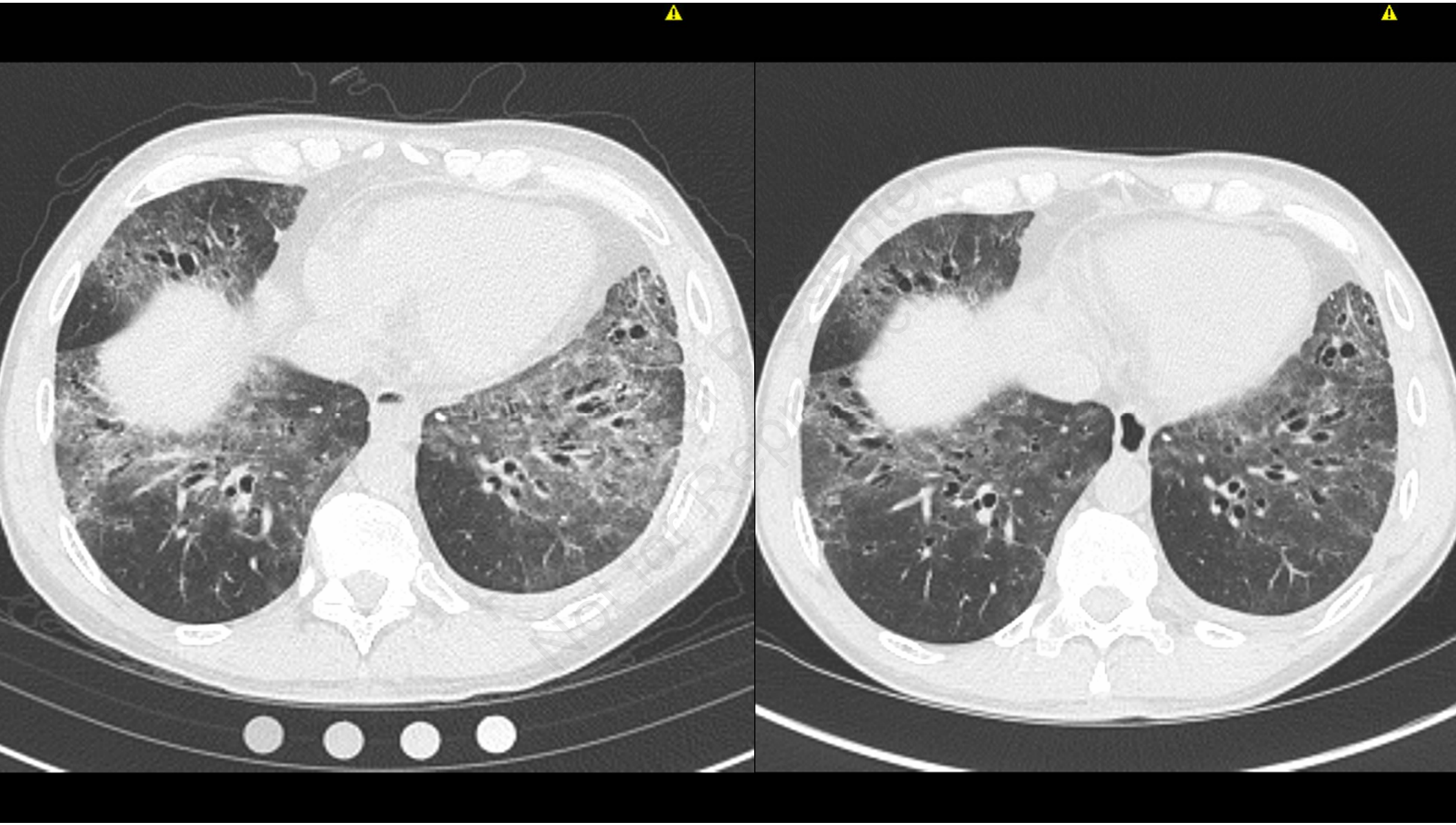
- **Correct diagnosis = systemic sclerosis**

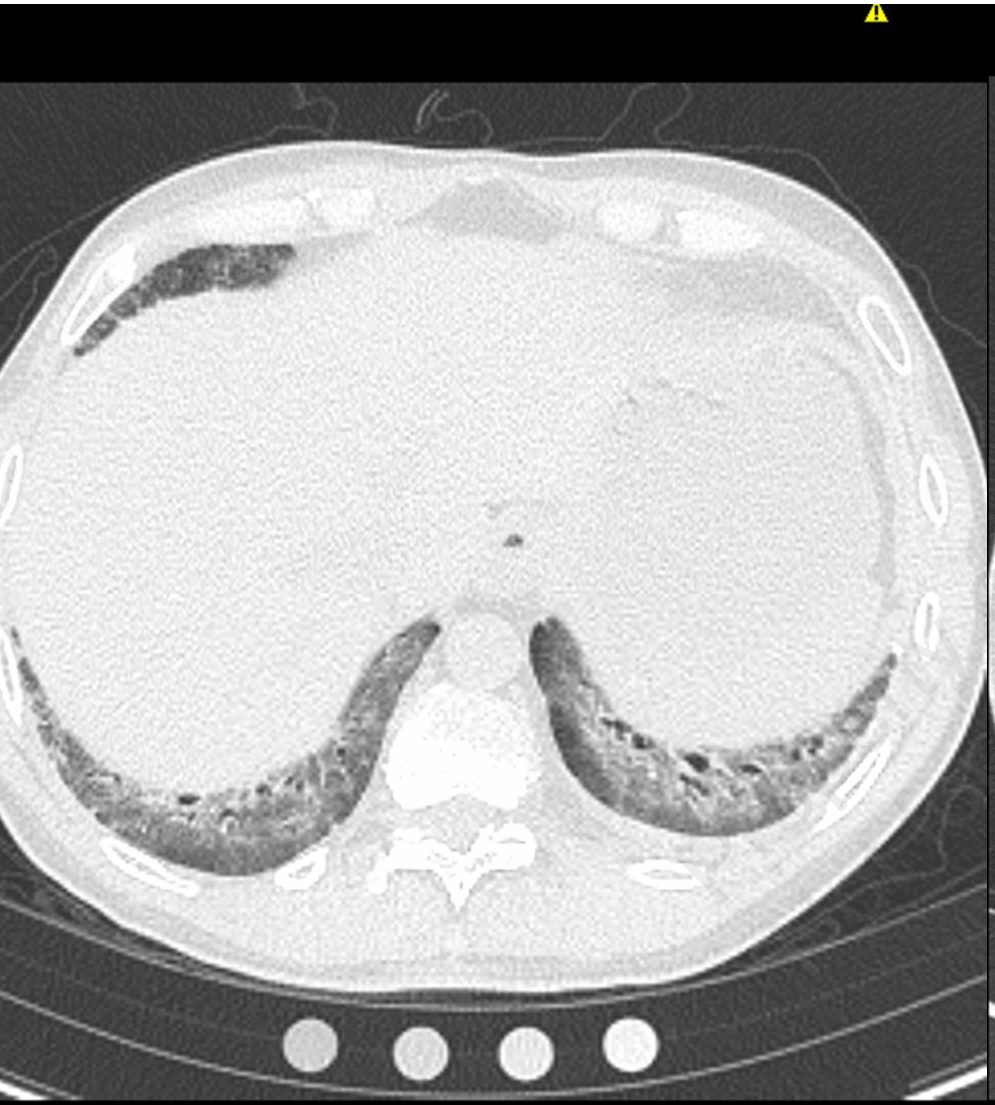
Case 2 PFT's

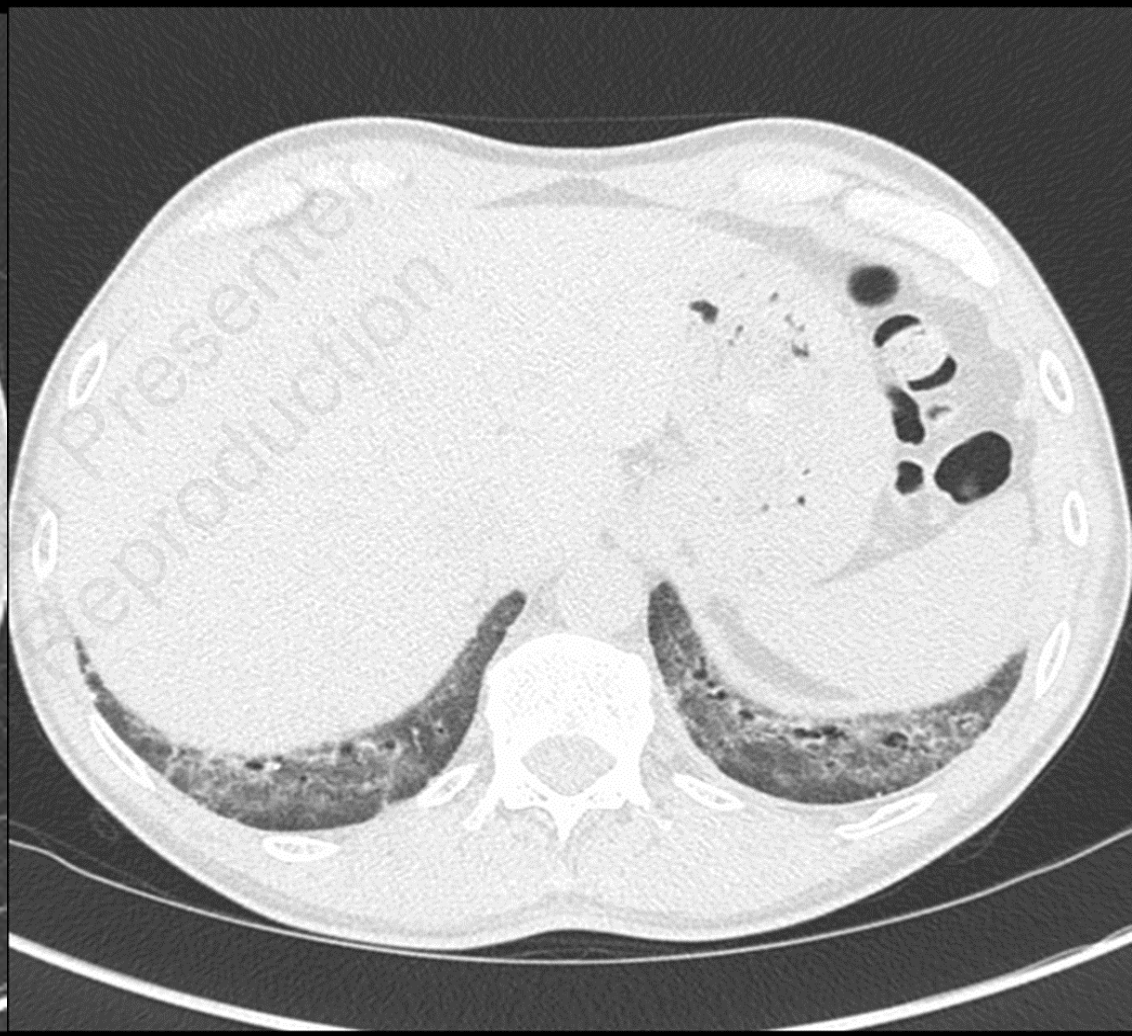
DATE	FVC	DLCO
12/08/18 (Pre VATS Bx)	3.25 (68 %)	15.5 (68)
3/8/19 (Pirfenidone x 3mos)	3.15 (66%)	14.3 (63%)
4/8/19: Started on daily PO cyclophosphamide		
7/8/19 (On Cyc x 3 mos)	3.34 (70%)	16.5 (72%)
10/15/19 (On Cyc x 6 mos)	3.48 (73%)	17.1 (75%)










Non présentée
reproduction

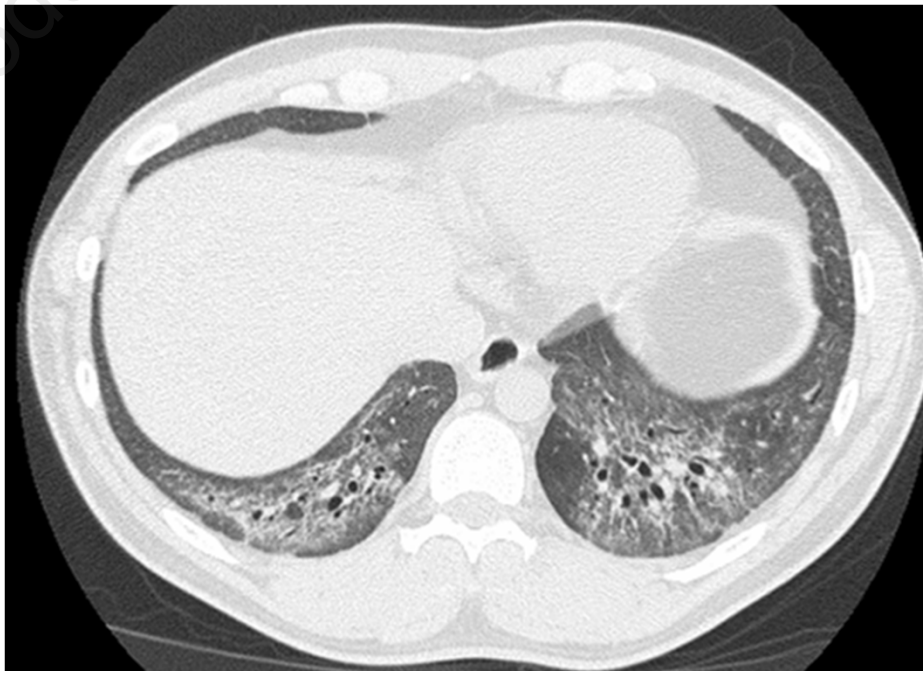
Multidisciplinary Discussion Questions

- How would you approach therapy moving forward?
- How should we think about the nintedanib data vs. the cyclophosphamide or mycophenolate mofetil data?
- What is your level of concern that he has PH?

Case 1

DcSSc with ILD

- PFTs: FVC=3.5L (70%), DLCO=19.83 (52%)
- Gas exchange: 6MWD=1430 feet, SpO2=85%



- How should we treat his ILD?
- What about his skin?
- When should he be seen in clinic?

Summary

- Patients presents in various ways
  - SSc found to have ILD
  - ILD found to SSc
  - Dyspnea found to have SSc-ILD
- Interdisciplinary evaluation is key to making correct diagnosis
- Drug therapy: choices, nuances…know the data, manage expectations
- Other therapy: vaccines, O2, pulmonary rehabilitation
- Longitudinal evaluation
  - Interdisciplinary: based on manifestations and risks
  - Spiro, DLCO, walk, O2 needs, HRCT, echo