
# Ganesh Raghu, MD, FCCP, FACP

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# Ganesh Raghu, MD

## Disclosures

**Consultant :** **Avalyn,Boehringer-Ingelheim, Biogen, BMS, Bellerophan, Fibrogen, Gilead Sciences, Nitto, Promedior, Roche-Genentech, Respivant, Sanofi-Aventis, Veracyte, Zambon**

**Research grant : National Institutes of Health(NIH), Bethesda, MD,USA**

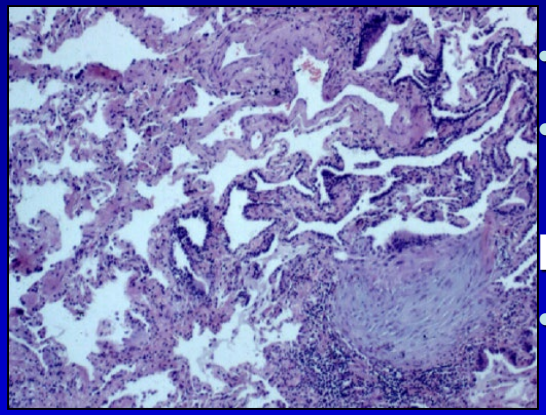
**-Idiopathic pulmonary fibrosis studies**

**Pulmonologist/Consultant :** ***longstanding interest and expertise in Interstitial lung diseases(ILD)/sarcoidosis/pulmonary fibrosis*; *dedicated to field of ILD, patient advocate***

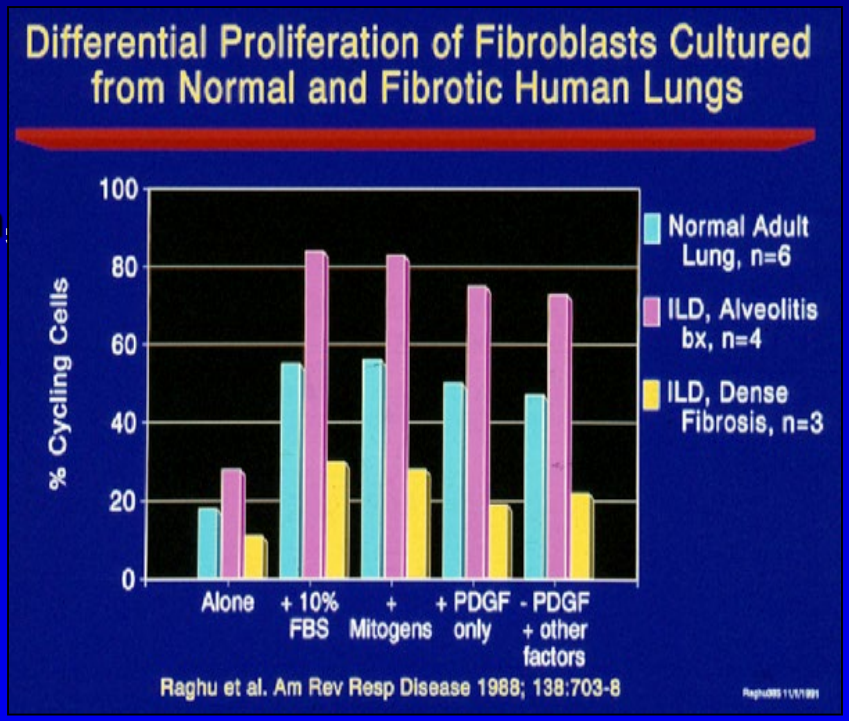
# Anti fibrotic treatment –

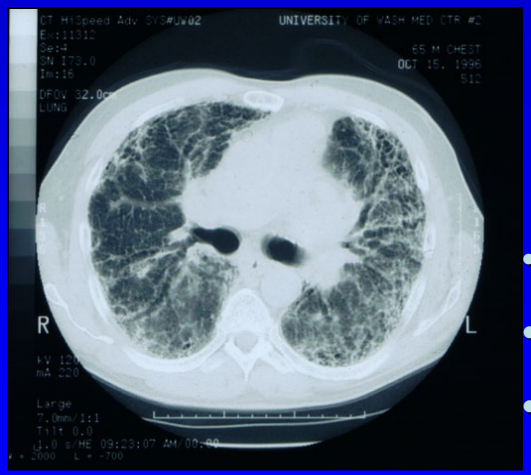
*only for IPF ?*

# Idiopathic Pulmonary Fibrosis



- Fibroblast foci
- ↑ extracellular matrix (collagens,fibronectin, proteoglycans)
- ↓ gas exchange units



## Therapy – antifibrotic

- ↓ fibroblast proliferation
- ↓ extracellular matrix
- Tissue repair (re-epithelialisation)
- ↑ gas exchange units

→ Improved outcome

# Rationale for antifibrotic treatment in NONIPF-PF:

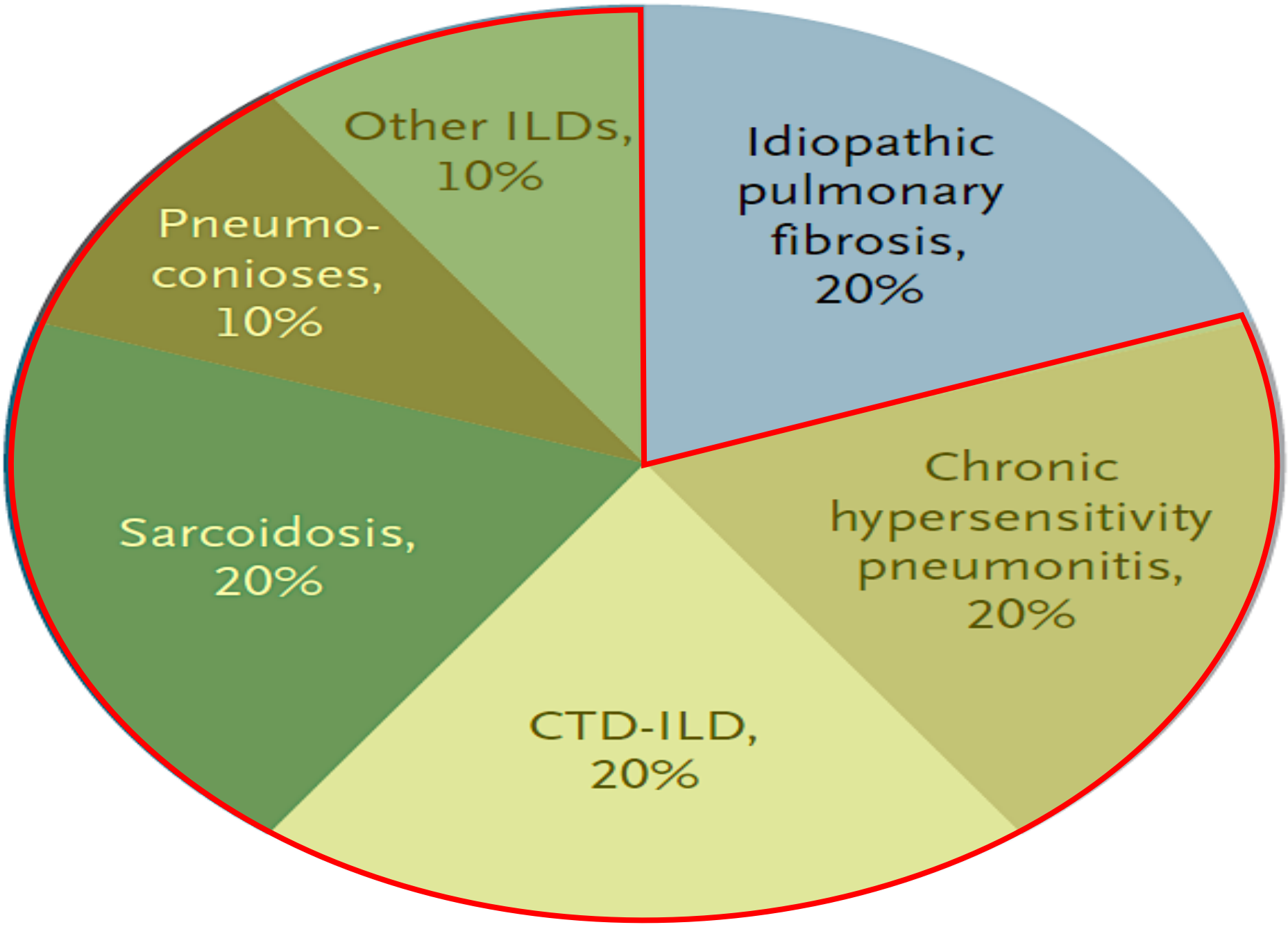
# Idiopathic Interstitial Pneumonias (IIP)
## Multidisciplinary Classification – An Update from 2002 ATS/ERS Statement*

***Differential Diagnosis***

- Collagen vascular disease/connective tissue diseases
- Occupational lung diseases- e.g., asbestosis
- Familial interstitial pneumonia
- Hypersensitivity pneumonitis
- Co-existing patterns- Combined diseases-with PPFE ? emphysema (CPFE) ? , sarcoidosis –IPF (CS-IPF)**
  Coincidental or unique phenotype ?

*** Travis et al AJCCM 2013**
****Collins et al , Respiratory Medicine , 2018**

| Type of collagen vascular disease | UIP | NSIP | COP | LIP | DAD | DAH | Airway disease |
|---|---|---|---|---|---|---|---|
| Rheumatoid arthritis | +++ | ++ | ++ | + | + | - | +++ |
| PSS | + | +++ | + | - | + | - | - |
| DM/PM | + | +++ | +++ | - | ++ | - | - |
| Sjogren | + | ++ | - | ++ | + | - | + |
| MCTD | + | ++ | + | - | - | - | - |
| SLE | + | ++ | + | + | ++ | +++ | - |




Lederer DJ and Martinez FJ, *N Engl J Med* 2018; 378: 1811

# Idiopathic Pulmonary Fibrosis

Evidence Based Guidelines for Diagnosis and Management*

## Usual interstitial Pneumonia Pattern

- Does not equate to diagnosis of IPF
- Connective tissue diseases
- Asbestosis
- Sarcoidosis ( fibrosing sarcoid; combined Sarcoid-UIP)
- Genetic syndromes
- Hypersensitivity pneumonitis due to environmental exposures – always a concern when *fibrosis is upper lobe, lymphocytic cellular pattern (BAL), co-existing multi lobular air trapping, nodules(HRCT), airway centric fibrosis(pathology)*
- *Pulmonary fibrosis of unknown cause does not equate to diagnosis of IPF*

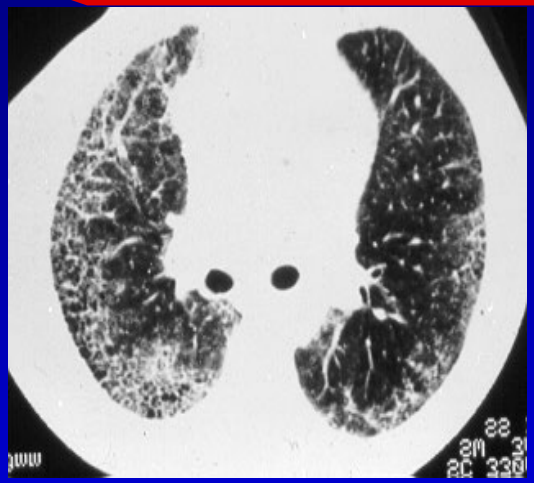
# POSSIBLE ILD DIAGNOSES

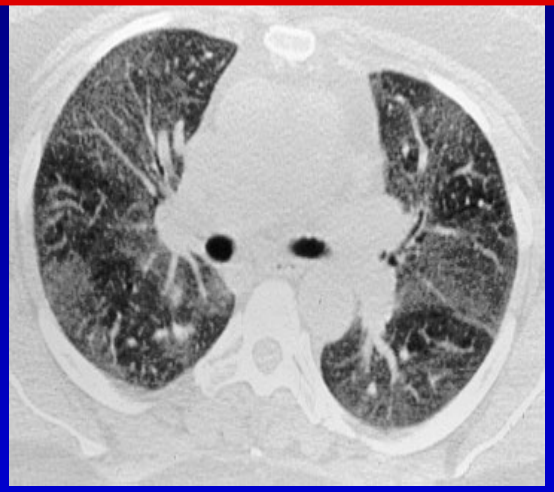
**Trial indication:**
**List of possible underlying ILD diagnoses (check only one box)**

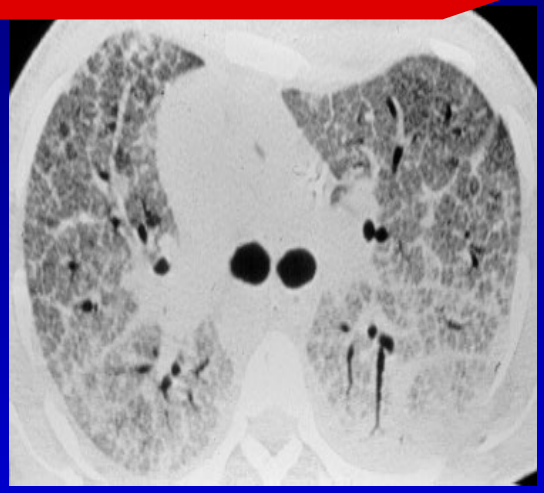
- ☐ Idiopathic nonspecific interstitial pneumonia
- ☐ Unclassifiable IIP
- ☐ Other IIP
- ☐ Hypersensitivity pneumonitis
- ☐ Rheumatoid arthritis-associated ILD
- ☐ Mixed connective tissue disease
- ☐ Systemic sclerosis-associated ILD
- ☐ Other CTD-ILD
- ☐ Exposure-related ILD
- ☐ Sarcoidosis
- ☐ Other fibrosing ILD

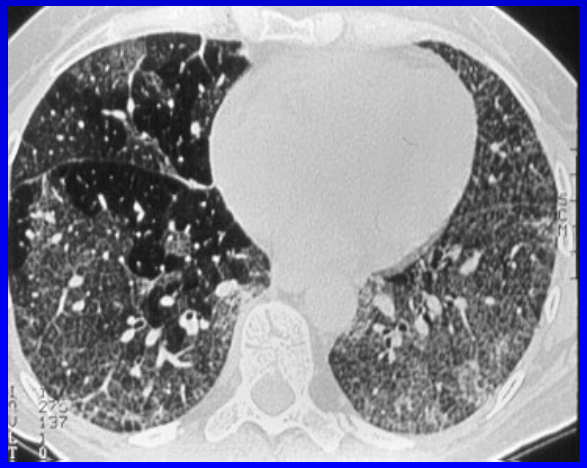
Flaherty et al, *BMJ Open Respir Res* 2017 ;4: e000212

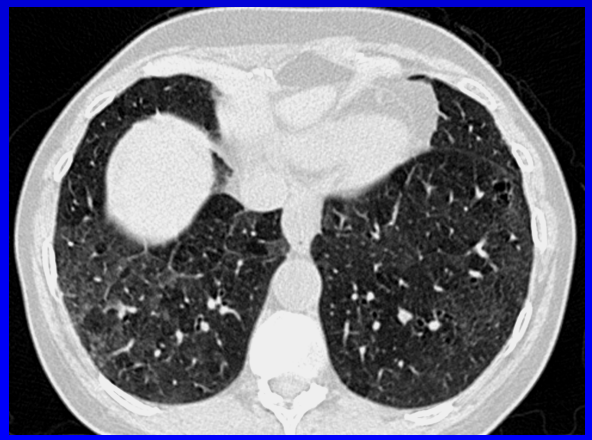
# Interstitial Lung Diseases

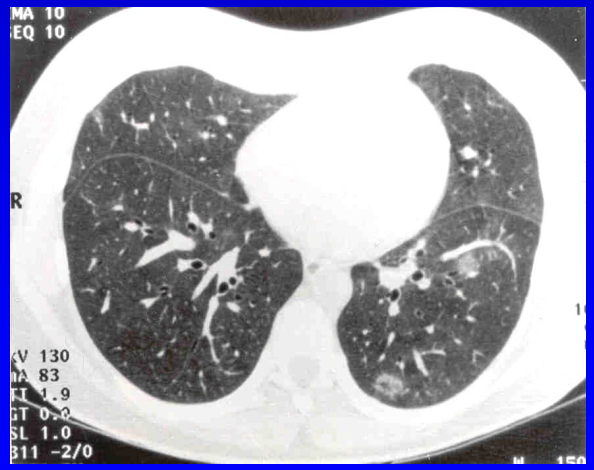


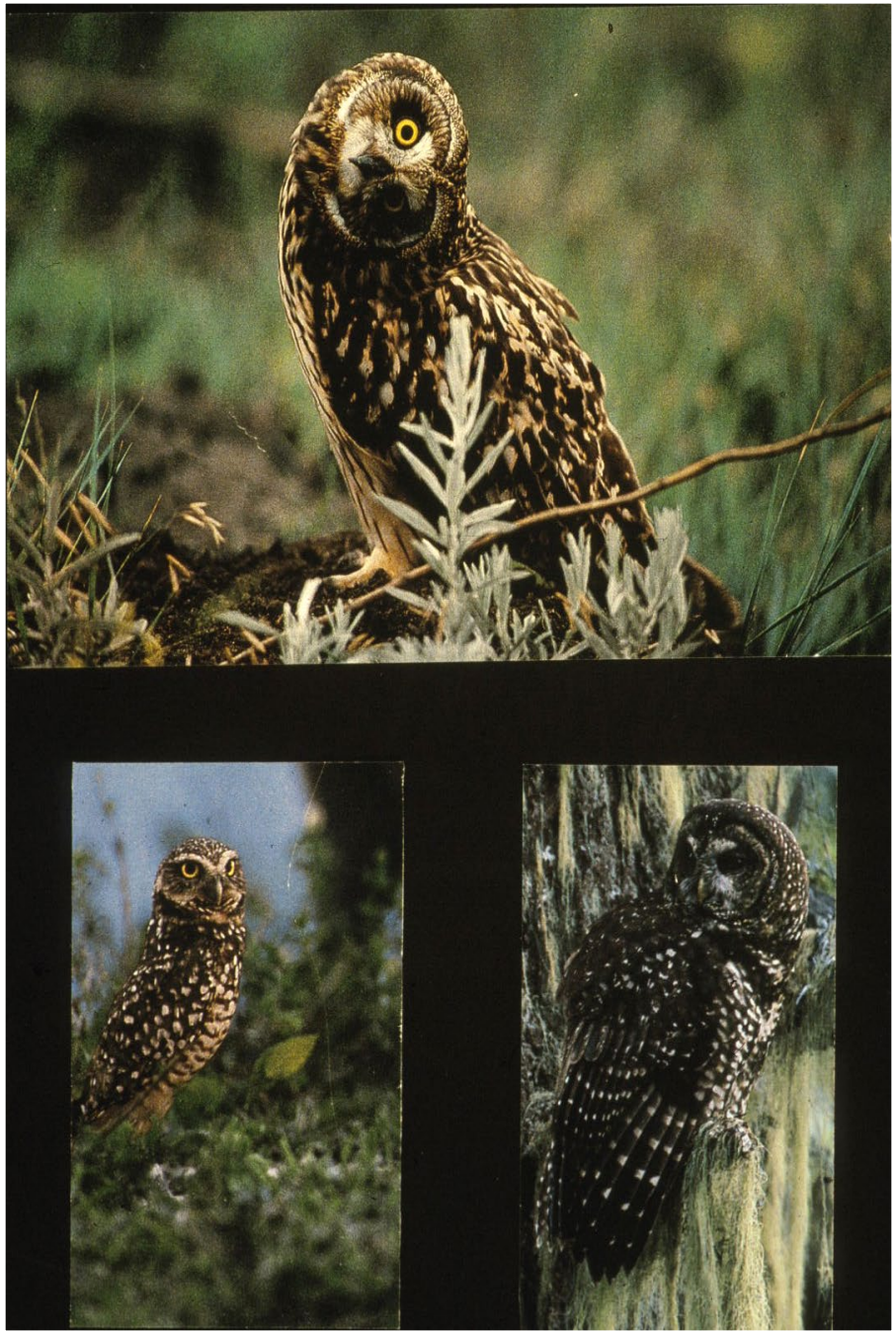












# Pulmonary fibrosis : Fibrotic lung diseases

**Current / increasing awareness:**

**pathology/pathogenesis**

***Fibrotic process***

***Increased fibroblasts (proliferating)***

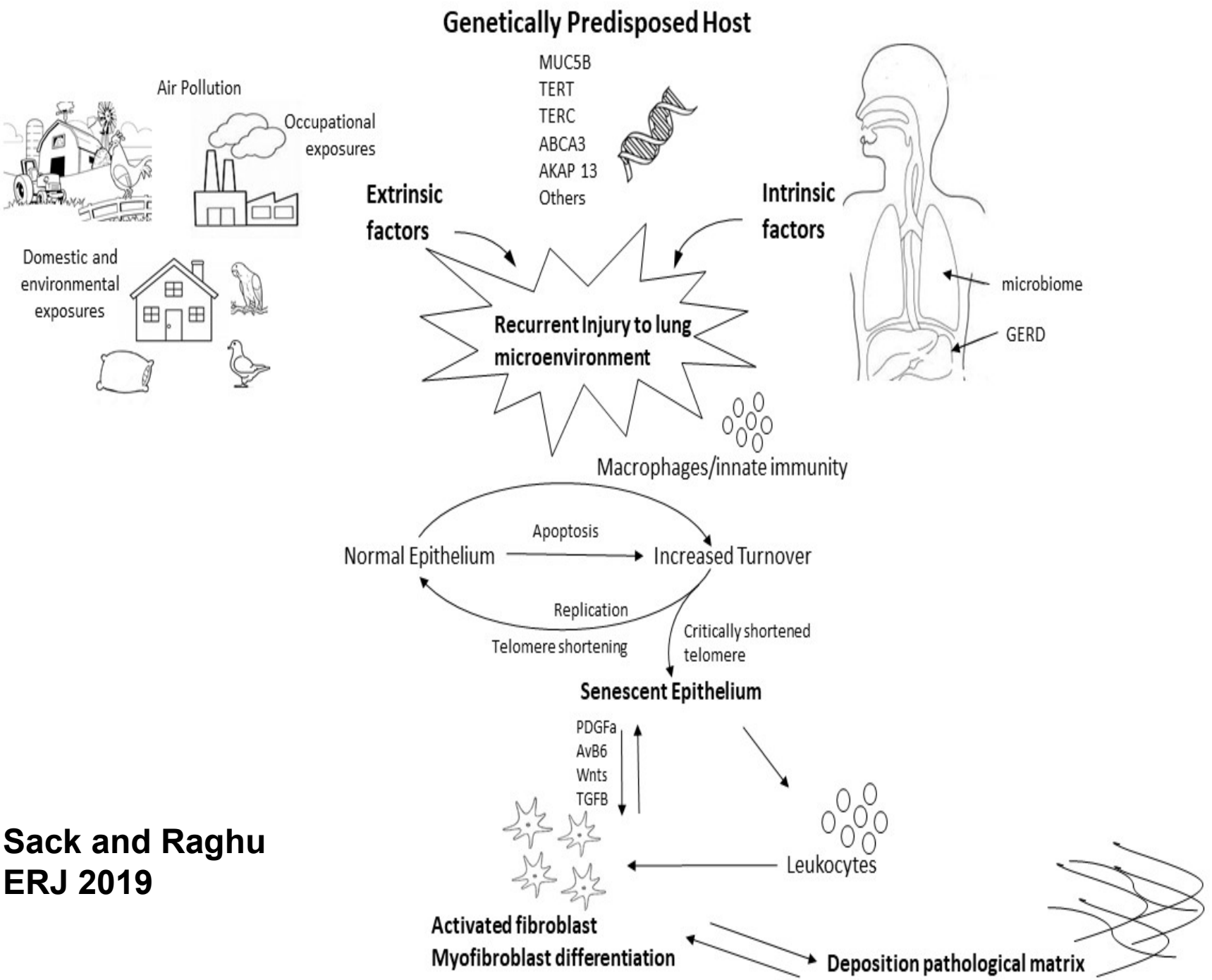
***excess collagen deposition***

# Idiopathic Pulmonary Fibrosis
## Disease Activity: Pulmonary Parenchyma

- Alveolar epithelial cells-injury;apoptosis
- Epithelial-mesenchymal transformation
- Mesenchymal cells (myofibroblasts, fibroblasts, fibrocytes)

- Genetic predisposition :

**MUC5B, TERT/TERC, TELOMERES ,ABCA3, AKAP 13 ,Others**




**Sack and Raghu**
**ERJ 2019**

The NEW ENGLAND JOURNAL of MEDICINE

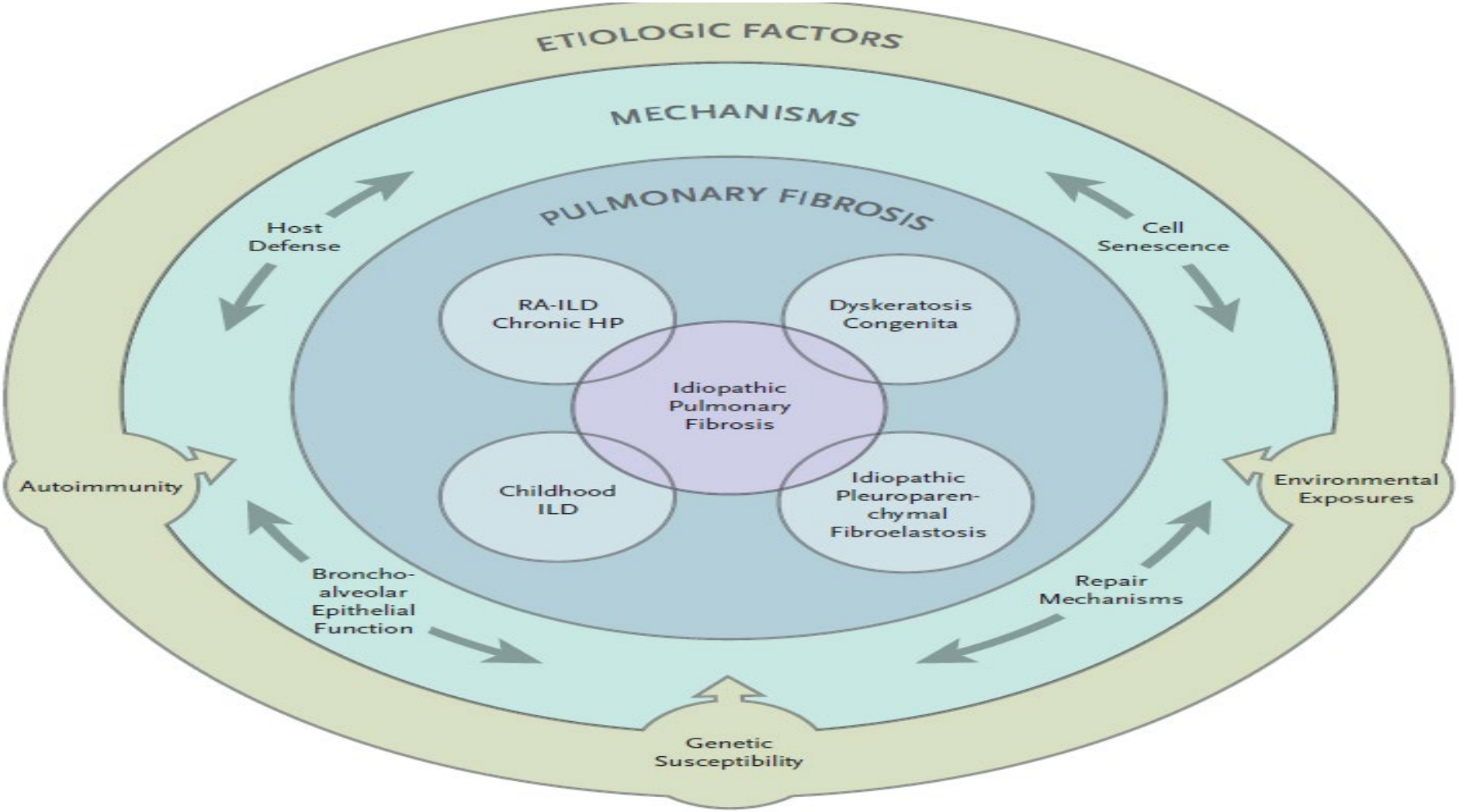
N ENGL J MED 380;1 NEJM.ORG JANUARY 3, 2019

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor*

# Revealing the Secrets of Idiopathic Pulmonary Fibrosis

Richard K. Albert, M.D., and David A. Schwartz, M.D.



ORIGINAL ARTICLE
INTERSTITIAL LUNG DISEASES
Eur Respir J 2016; 48: 1710–1720 | DOI: 10.1183/13993003.00308-2016

# Telomere-related lung fibrosis is diagnostically heterogeneous but uniformly progressive

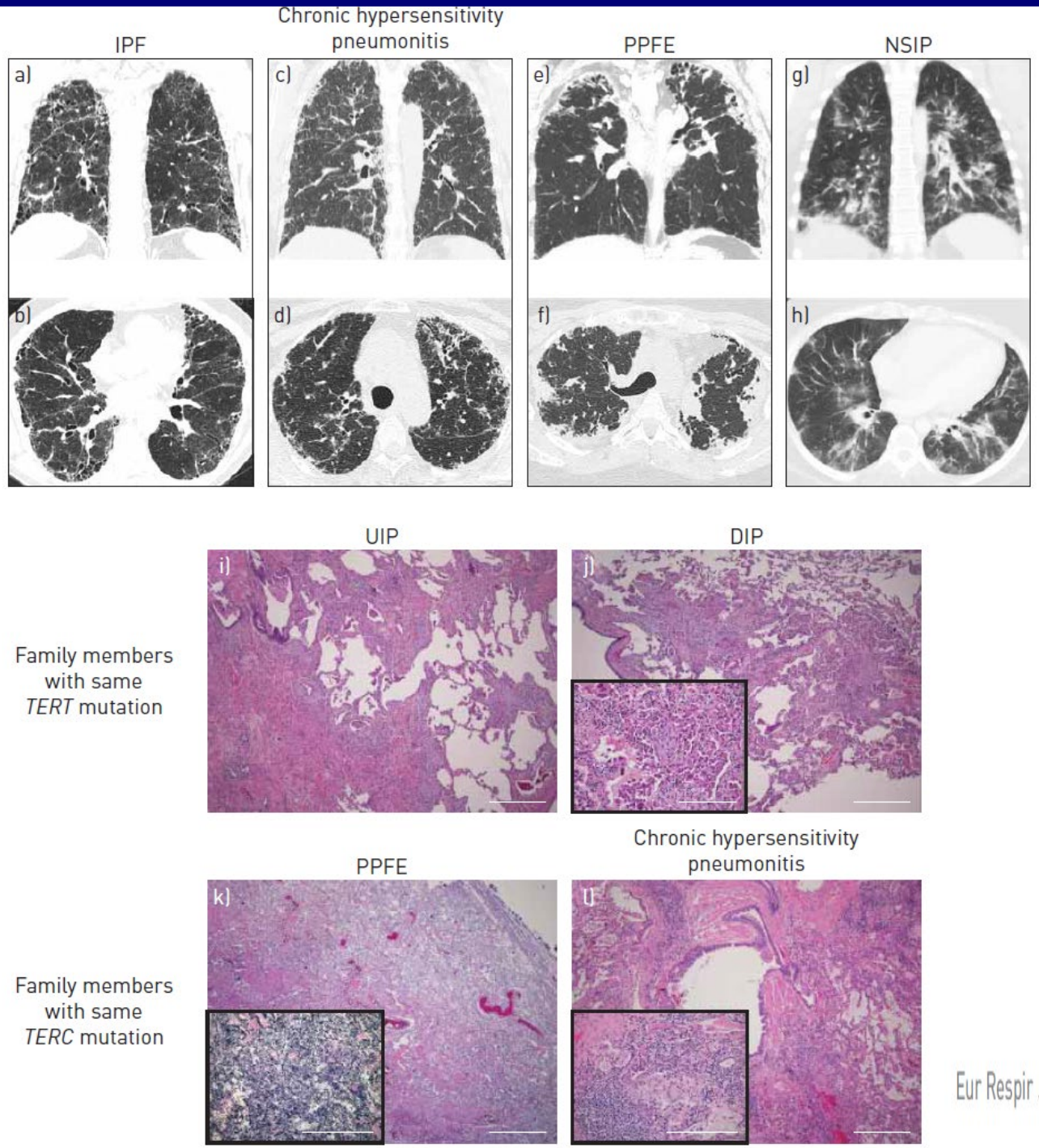
Chad A. Newton[1,2], Kiran Batra[3], Jose Torrealba[4], Julia Kozlitina[1], Craig S. Glazer[2], Carlos Aravena[5], Keith Meyer[6], Ganesh Raghu[7], Harold R. Collard[5] and Christine Kim Garcia[1,2]

ABSTRACT Heterozygous mutations in four telomere-related genes have been linked to pulmonary fibrosis, but little is known about similarities or differences of affected individuals.

115 patients with mutations in telomerase reverse transcriptase (*TERT*) (n=75), telomerase RNA component (*TERC*) (n=7), regulator of telomere elongation helicase 1 (*RTEL1*) (n=14) and poly(A)-specific ribonuclease (*PARN*) (n=19) were identified and clinical data were analysed.

Approximately one-half (46%) had a multidisciplinary diagnosis of idiopathic pulmonary fibrosis (IPF); others had unclassifiable lung fibrosis (20%), chronic hypersensitivity pneumonitis (12%), pleuroparenchymal fibroelastosis (10%), interstitial pneumonia with autoimmune features (7%), an idiopathic interstitial pneumonia (4%) and connective tissue disease-related interstitial fibrosis (3%). Discordant interstitial lung disease diagnoses were found in affected individuals from 80% of families. Patients with *TERC* mutations

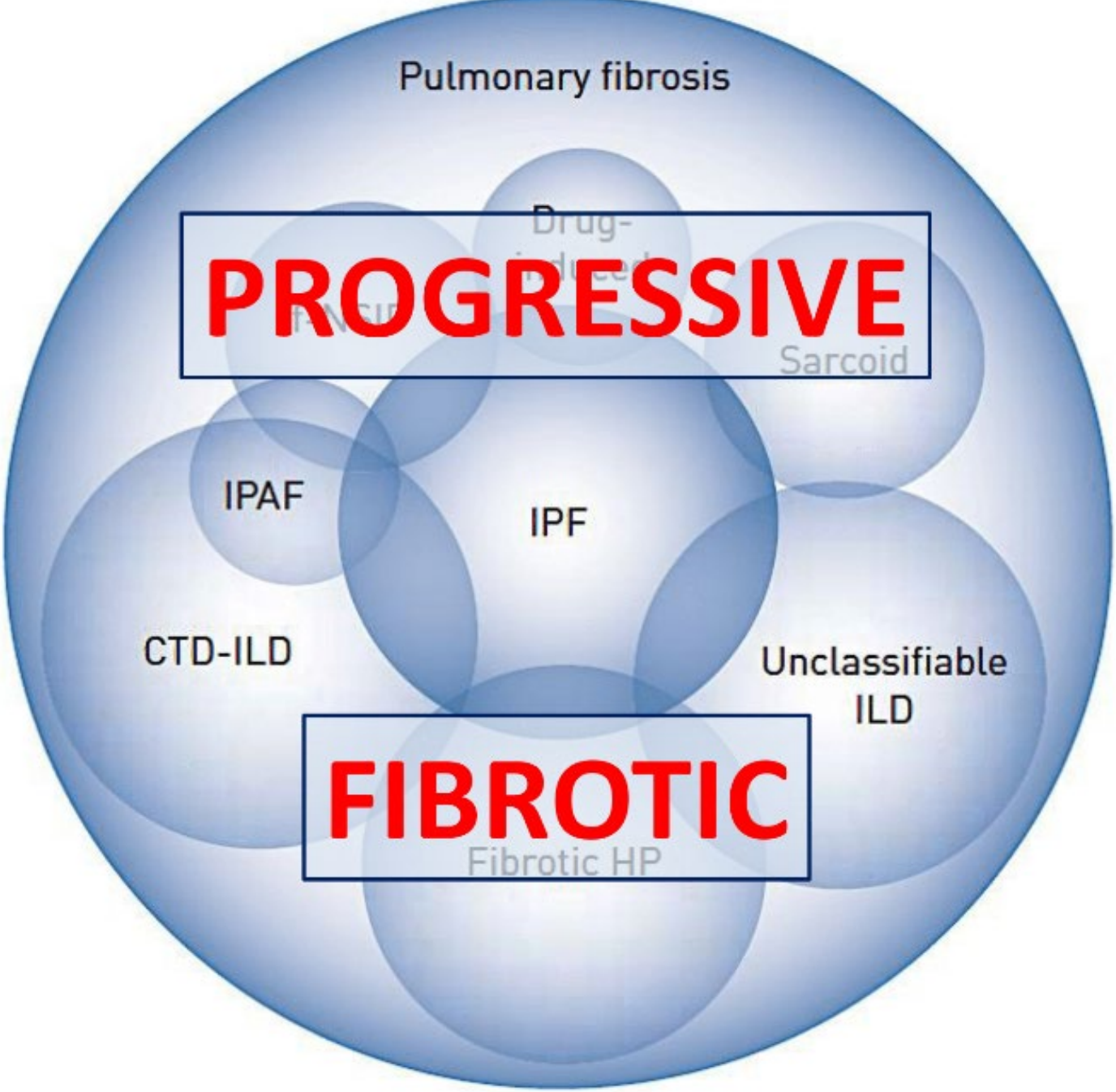
Genetic mutations in telomere related genes lead to a variety of interstitial lung disease (ILD) diagnoses that are universally progressive.




Eur Respir J 2016; 48: 1710–1720 | DOI: 10.1183/13993003.00308-2016

# Idiopathic interstitial pneumonia : Fibrotic Interstitial lung disease

**Current critical issues -**
***Challenges in diagnosis*** **and management**
**-a constellation of symptoms and signs with recognized histopathologic and clinical features and behaviour patterns but no real established criteria**
**- hopefully, biomarkers will be precise in future and therapeutic strategies developed**




Wells AU et al, *Eur Respir J* 2018; 51: 1800692

# PROGRESSIVE

Signs of progressive fibrosing lung disease:

- Symptoms
- Lung function
- Imaging (HRCT)

# FIBROTIC

Signs of fibrosing lung disease at HRCT:

- Honeycombing
- Traction bronchiectasis
- Volume loss
- Reticulation

Wells et al ERJ 2018;51: 1800692

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D., Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D., Ian Glaspole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D., Peter M. Hopkins, M.D., David Kardatzke, Ph.D., Lisa Lancaster, M.D., David J. Lederer, M.D., Steven D. Nathan, M.D., Carlos A. Pereira, M.D., Steven A. Sahn, M.D., Robert Sussman, M.D., Jeffrey J. Swigris, D.O., and Paul W. Noble, M.D., for the ASCEND Study Group*

## ABSTRACT

**BACKGROUND**

In two of three phase 3 trials, pirfenidone, an oral antifibrotic therapy, reduced disease progression, as measured by the decline in forced vital capacity (FVC) or vital capacity, in patients with idiopathic pulmonary fibrosis; in the third trial, this end point was not achieved. We sought to confirm the beneficial effect of pirfenidone on disease progression in such patients.

**METHODS**

In this phase 3 study, we randomly assigned 555 patients with idiopathic pulmonary fibrosis to receive either oral pirfenidone (2403 mg per day) or placebo for 52 weeks. The primary end point was the change in FVC or death at week 52. Secondary end points were the 6-minute walk distance, progression-free survival, dyspnea, and death from any cause or from idiopathic pulmonary fibrosis.

**RESULTS**

In the pirfenidone group, as compared with the placebo group, there was a relative reduction of 47.9% in the proportion of patients who had an absolute decline of 10 percentage points or more in the percentage of the predicted FVC or who died; there was also a relative increase of 132.5% in the proportion of patients with no decline in FVC (P<0.001). Pirfenidone reduced the decline in the 6-minute walk distance (P=0.04) and improved progression-free survival (P<0.001). There was no significant between-group difference in dyspnea scores (P=0.16) or in rates of death from any cause (P=0.10) or from idiopathic pulmonary fibrosis (P=0.23). However, in a prespecified pooled analysis incorporating results from two previous phase 3 trials, the between-group difference favoring pirfenidone was significant for death from any cause (P=0.01) and from idiopathic pulmonary fibrosis (P=0.006). Gastrointestinal and skin-related adverse events were more common in the pirfenidone group than in the placebo group but rarely led to treatment discontinuation.

**CONCLUSIONS**

Pirfenidone, as compared with placebo, reduced disease progression, as reflected by lung function, exercise tolerance, and progression-free survival, in patients with idiopathic pulmonary fibrosis. Treatment was associated with an acceptable side-effect profile and fewer deaths. (Funded by InterMune; ASCEND ClinicalTrials.gov number, NCT01366209.)

From the University of California, San Francisco (T.E.K.); Int... Brisbane (W.Z.B., E.A.F., E.G., D... Cedars–Sinai Medical Center, Lo... (P.W.N.) — all in California; N... Clínica San Borja, Lima, Per... Alfred Hospital, Melbourne, ... and Prince Charles Hospit... QLD (P.M.H.) — both in A... versity of Miami Miller Sc... cine, Miami (M.K.G.); Vand... Medical Center, Nashvill... bia University Medical C... (D.J.L.); Inova Fairfax Ho... VA (S.D.N.); Paulista S... Federal University of S... (C.A.P.); Medical Un... olina, Charleston (S... System–Overlook M... NJ (R.S.); and N... Denver (J.J.S.). A... to Dr. King at the ... University of Cal... Parnassus Ave., ... 94143-0120, or ...

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 29, 2014 VOL. 370 NO. 22

# Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D., Ph.D., Roland M. du Bois, M.D., Ganesh Raghu, M.D., Arata Azuma, M.D., Ph.D., Kevin K. Brown, M.D., Ulrich Costabel, M.D., Vincent Cottin, M.D., Ph.D., Kevin R. Flaherty, M.D., David M. Hansell, M.D., Yoshikazu Inoue, M.D., Ph.D., Dong Soon Kim, M.D., Martin Kolb, M.D., Ph.D., Andrew G. Nicholson, D.M., Paul W. Noble, M.D., Moisés Selman, M.D., Hiroyuki Taniguchi, M.D., Ph.D., Michèle Brun, M.Sc., Florence Le Maulf, M.Sc., Mannaig Girard, M.Sc., Susanne Stowasser, M.D., Rozsa Schlenker-Herceg, M.D., Bernd Disse, M.D., Ph.D., and Harold R. Collard, M.D., for the INPULSIS Trial Investigators*

## ABSTRACT

**BACKGROUND**

Nintedanib (formerly known as BIBF 1120) is an intracellular inhibitor that targets multiple tyrosine kinases. A phase 2 trial suggested that treatment with 150 mg of nintedanib twice daily reduced lung-function decline and acute exacerbations in patients with idiopathic pulmonary fibrosis.

**METHODS**

We conducted two replicate 52-week, randomized, double-blind, phase 3 trials (INPULSIS-1 and INPULSIS-2) to evaluate the efficacy and safety of 150 mg of nintedanib twice daily as compared with placebo in patients with idiopathic pulmonary fibrosis. The primary end point was the annual rate of decline in forced vital capacity (FVC). Key secondary end points were the time to the first acute exacerbation and the change from baseline in the total score on the St. George's Respiratory Questionnaire, both assessed over a 52-week period.

**RESULTS**

A total of 1066 patients were randomly assigned in a 3:2 ratio to receive nintedanib or placebo. The adjusted annual rate of change in FVC was −114.7 ml with nintedanib versus −239.9 ml with placebo (difference, 125.3 ml; 95% confidence interval [CI], 77.7 to 172.8; P<0.001) in INPULSIS-1 and −113.6 ml with nintedanib versus −207.3 ml with placebo (difference, 93.7 ml; 95% CI, 44.8 to 142.7; P<0.001) in INPULSIS-2. In INPULSIS-1, there was no significant difference between the nintedanib and placebo groups in the time to the first acute exacerbation (hazard ratio with nintedanib, 1.15; 95% CI, 0.54 to 2.42; P=0.67); in INPULSIS-2, there was a significant benefit with nintedanib versus placebo (hazard ratio, 0.38; 95% CI, 0.19 to 0.77; P=0.005). The most frequent adverse event in the nintedanib groups was diarrhea, with rates of 61.5% and 18.6% in the nintedanib and placebo groups, respectively, in INPULSIS-1 and 63.2% and 18.3% in the two groups, respectively, in INPULSIS-2.

**CONCLUSIONS**

In patients with idiopathic pulmonary fibrosis, 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. (Funded by Boehringer Ingelheim; INPULSIS-1 and INPULSIS-2 ClinicalTrials.gov numbers, NCT01335464 and NCT01335477.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Richeldi at the National Institute for Health Research, Southampton Respiratory Biomedical Research Unit, Mailpoint 813, LE75 E Level, South Academic Block, University Hospital Southampton NHS Foundation Trust, Tremona Rd., Southampton SO16 6YD, United Kingdom, or at l.richeldi@soton.ac.uk.

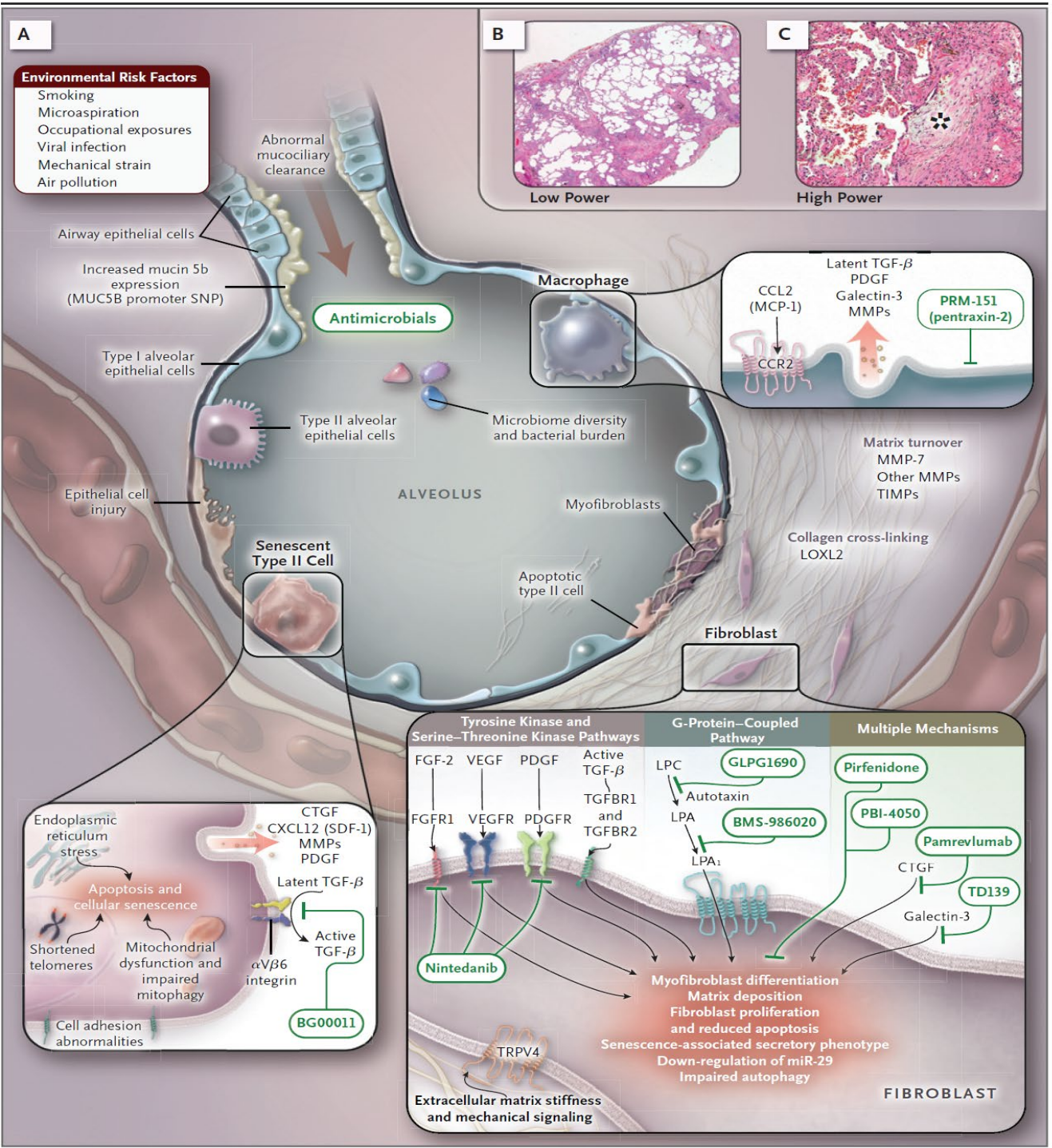
*A complete list of investigators in the INPULSIS trials is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on May 18, 2014, at NEJM.org.

N Engl J Med 2014;370:2071-82.
DOI: 10.1056/NEJMoa1402584




May 29 2014




The NEW ENGLAND JOURNAL of MEDICINE

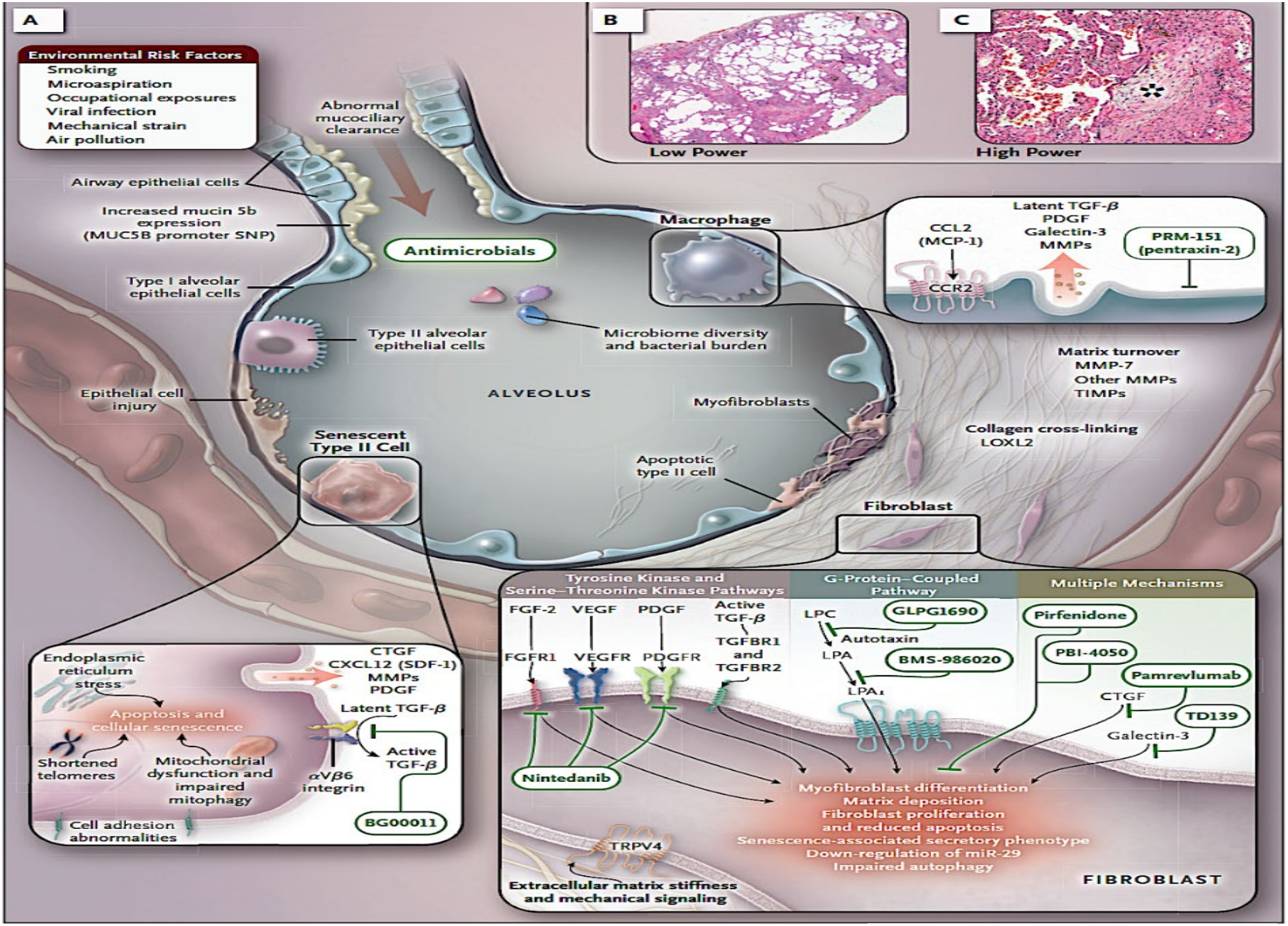
REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

# Idiopathic Pulmonary Fibrosis

David J. Lederer, M.D., and Fernando J. Martinez, M.D.

N Engl J Med 2018;378:1811-23.
DOI: 10.1056/NEJMra1705751




Lederer and Martinez,
*N Engl J Med* 2018; 378: 1811-23

# Idiopathic Pulmonary Fibrosis

## Treatment with a novel Antifibrotic Agent

**Treatment of Idiopathic Pulmonary Fibrosis with a New Antifibrotic Agent, Pirfenidone**

Results of a Prospective, Open-label Phase II Study

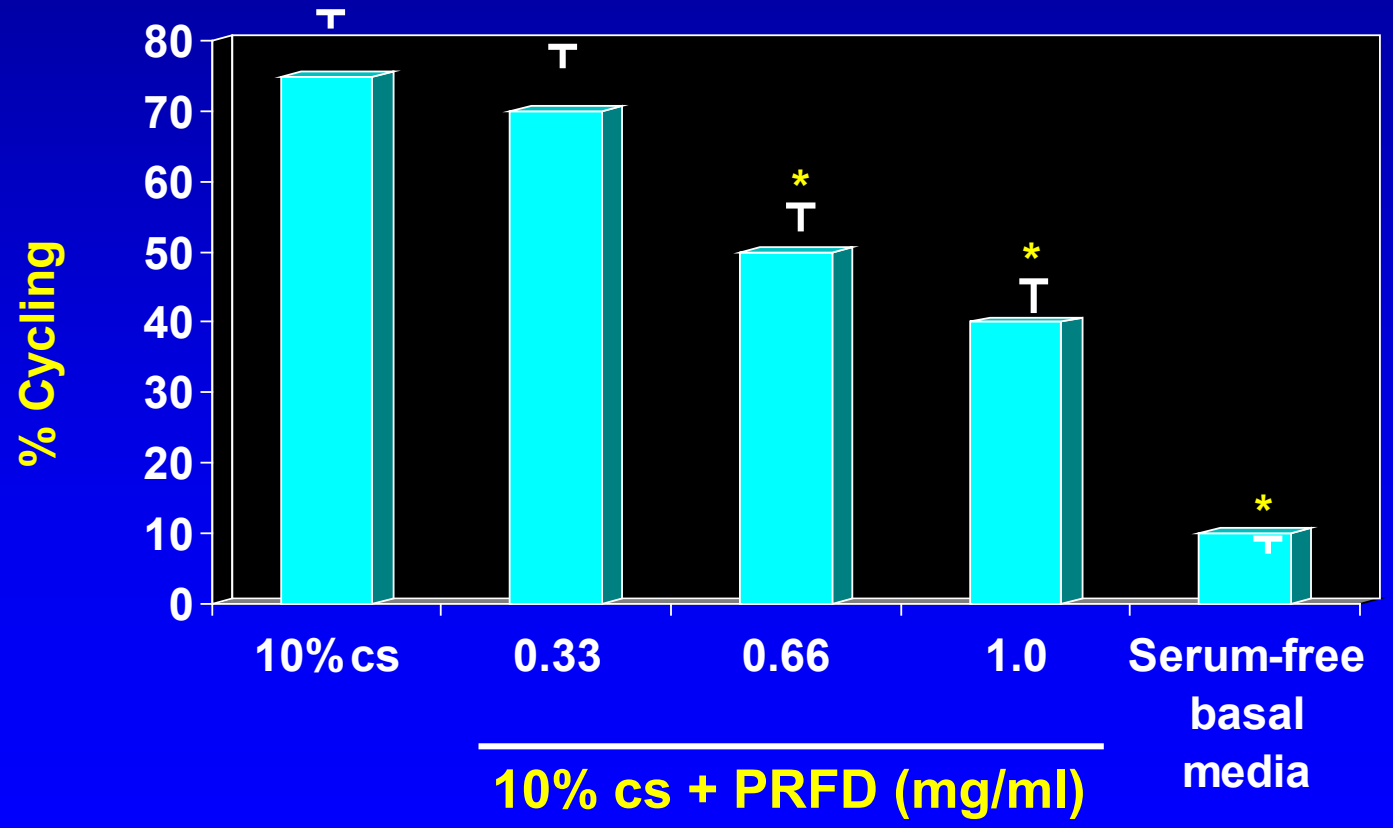
GANESH RAGHU, W. CRAIG JOHNSON, DIANE LOCKHART, and YOLANDA MAGETO

University of Washington, and Statistics and Epidemiology Research Corporation, Seattle, Washington

University of Washington Medical Center, Seattle, Washington, USA

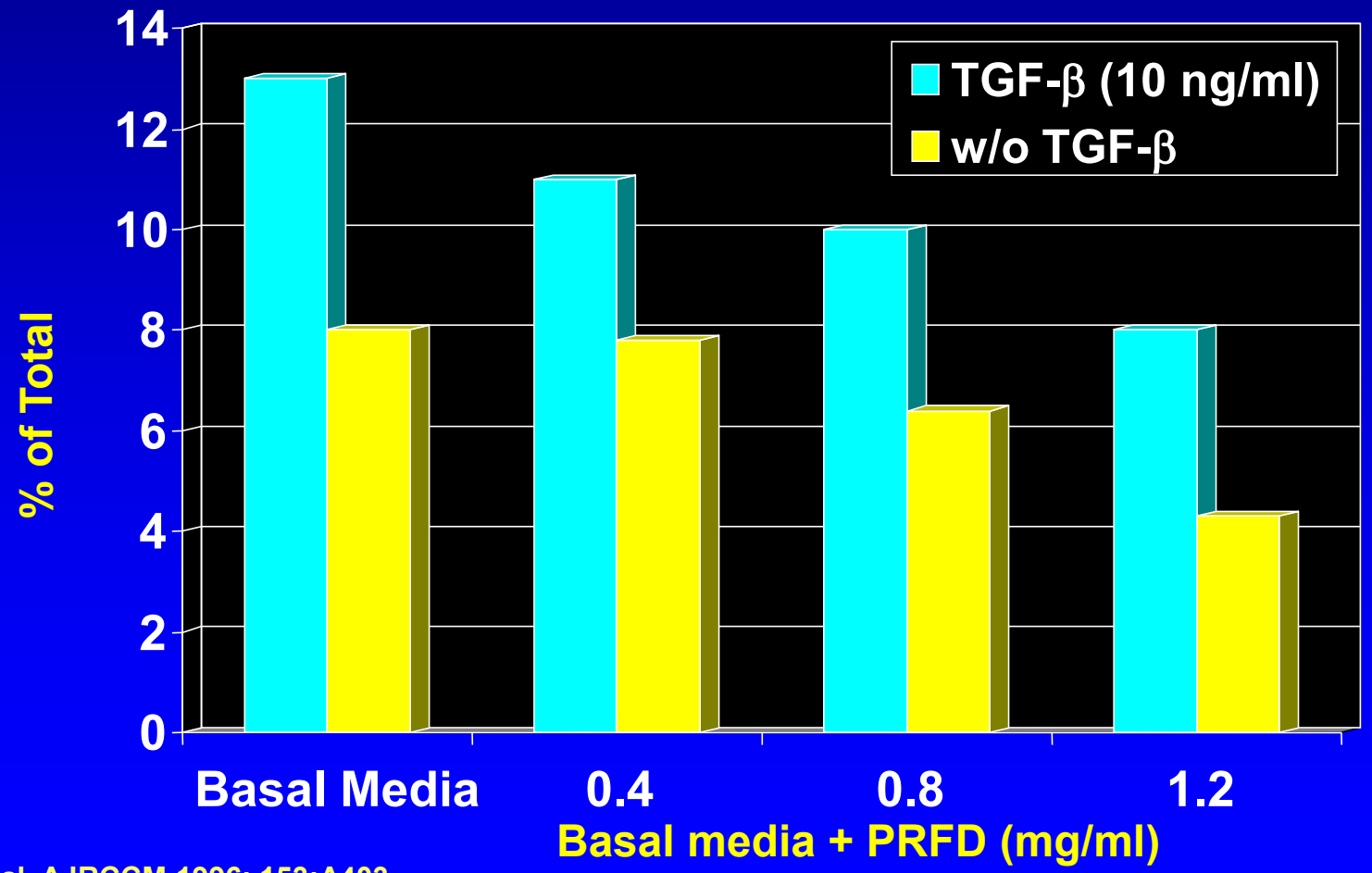
Am J Respir Crit Care Med 1999; 159:1061-9

# PRFD Inhibits Calf-Serum-Stimulated Proliferation of Human Lung Fibroblasts



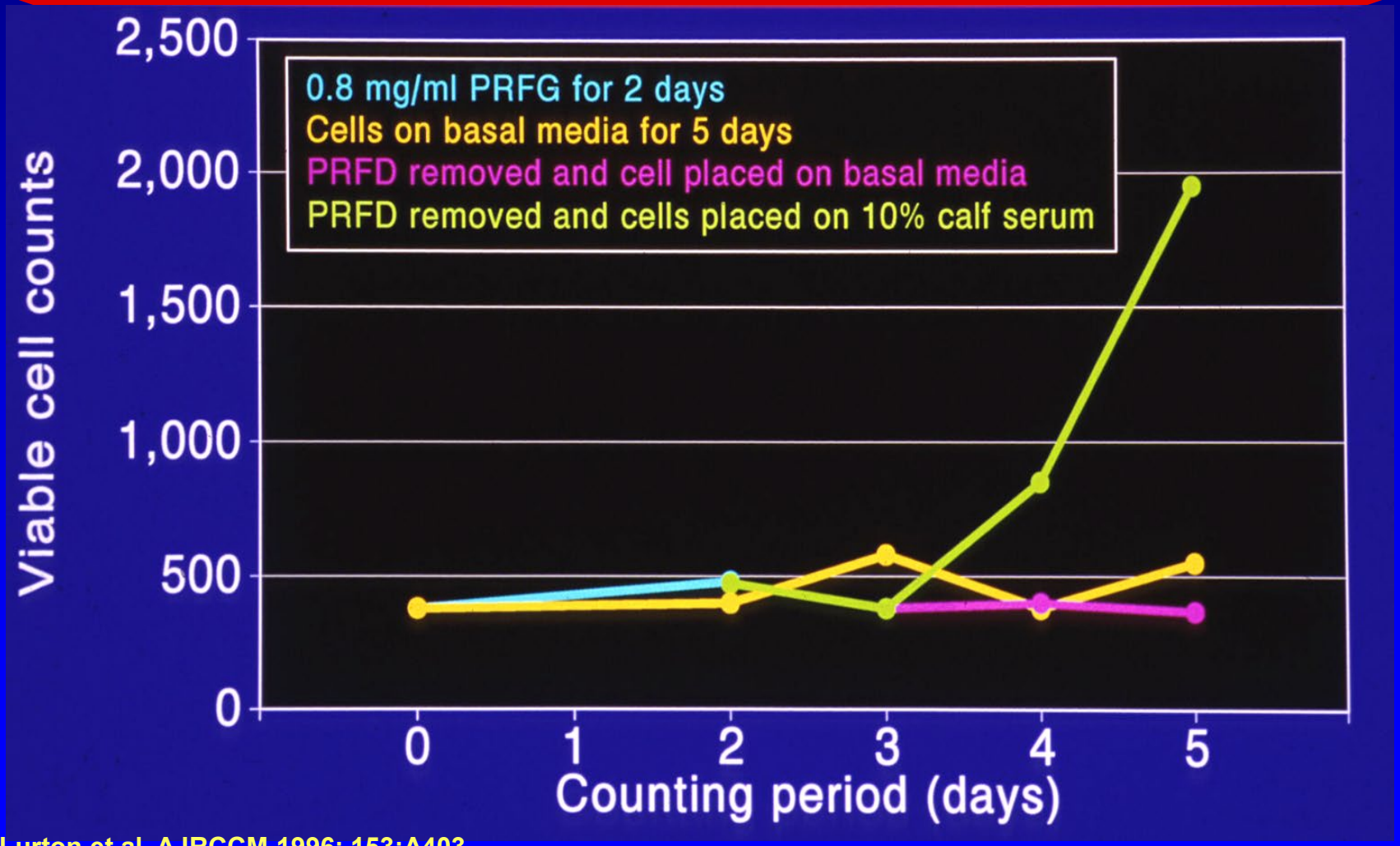

Lurton et al. AJRCCM 1996; 153:A403

# PRFD Inhibits TGF-β-Stimulated Collagen Synthesis




Lurton et al. AJRCCM 1996; 153:A403

# Cells Remain Viable and Capable of Proliferating After Removal of PRFD




Lurton et al. AJRCCM 1996; 153:A403

# Pirfenidone
## Antifibrotic Agent

- Ameliorates induced pulmonary fibrosis in animals[1,2]
- Decreases *in vivo* extracellular matrix components[1,2]
- Decreases *in vitro* human lung fibroblast growth[3]
- Decreases *in vitro* collagen synthesis[3]
- Blocks the *in vitro* mitogenic effect of PDGF, TGF-β, on human lung fibroblasts[3]


**1. Margolin SB and Lefkowitz S. FASER Journal 1994; 8 (4):A382**
**2. Iyer J et al. J Lab Clin Med 1995; 125:779-85**
**3. Lurton et al. ATS Meeting 1996;A403 (AJRCCM 1996; 153)**

# Antifibrotic treatment – beyond IPF-

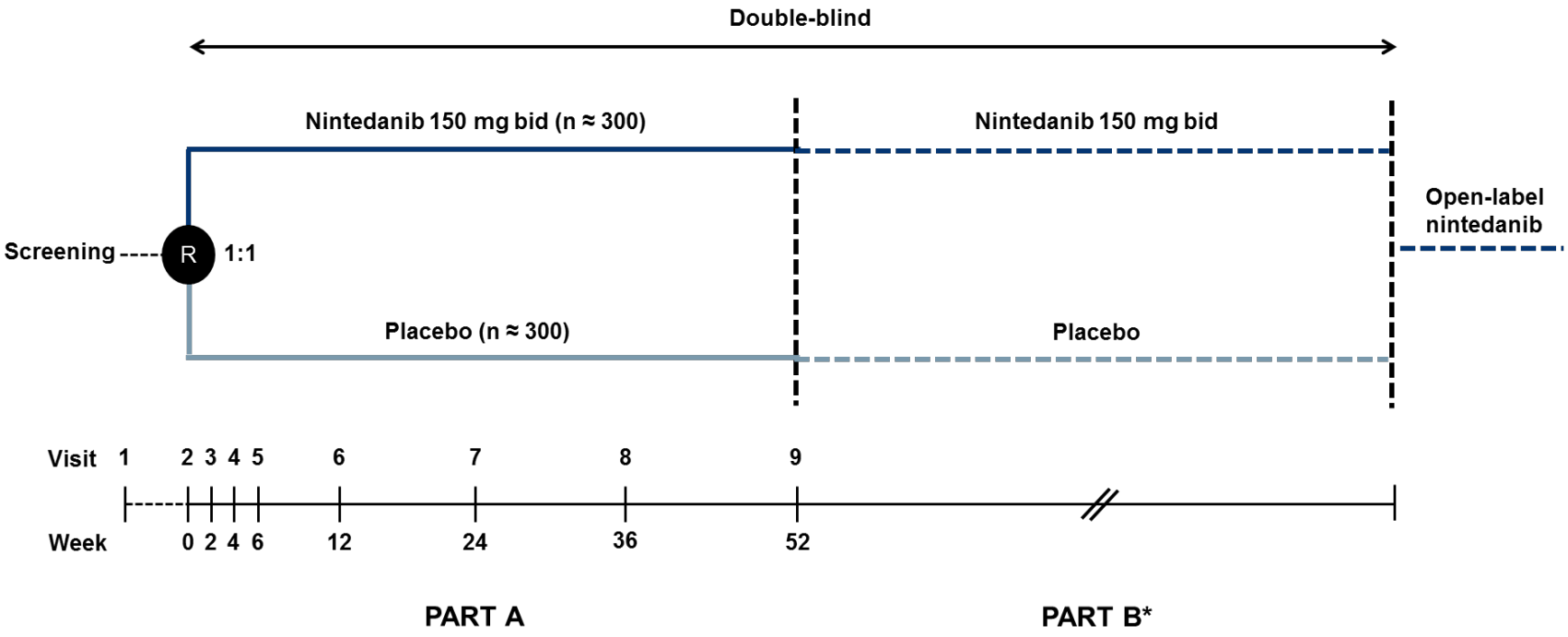
## NON IPF-PF

# Antifibrotic treatment for NON IPF-PF : ongoing clinical trials ( clinical trial.gov)

**Ongoing Clinical Trials of antifibrotic medications in nonIPF fibrotic interstitial lung disease**

| Trial ID | Name | Phase | Patients (n) | Intervention | Duration | Primary outcome | Key Secondary Outcomes |
|---|---|---|---|---|---|---|---|
| | | | **Nintedanib** | | | | |
| NCT02597933 | Safety and efficacy of 150 mg nintedanib twice daily in Systemic Sclerosis (SENSCIS) | III | 580, SSc-pulmonary fibrosis | Nintedanib 150 mg bid or placebo added to exisiting treatment (stable dose methotrexate, MMF and/or prednisone <=10 mg daily) | 52 weeks | Annual rate of decline FVC (mL) | Time to all cause mortality, absolute change dyspnea score, Modified Rodan Skin Score, SGRQ, change in FVC % predicted, change DLCO |
| NCT02999178 | Efficacy and Safety of Nintedanib in Patients With Progressive Fibrosing Interstitial Lung Disease (PF-ILD) (INBUILD®) | III | 663 patients with progressive fibrosing ILD (see text) | Nintedanib 150 mg bid or placebo | 52 weeks | Annual rate of decline FVC | Change in K-BILD score, time to first AE or death, time to progression (>=10% decrease FVC or death) |
| NCT03283007 | Nintedanib in Lung Transplant Recipients With Bronchiolitis Obliterans Syndrome Grade 1-2 (INFINITx-BOS) | III | 80 patients >=6 months post lung transplant with BOS | Nintedanib 150 mg bid or placebo (patients already on azithromycin) | 6 months | Rate of decline in FEV1 (mL) over 6 months | Change 6MWD, change SGRQ, change in BOS grade, absolute change oxygen saturation |
| NCT02496585 | Study to Evaluate the Efficacy and Safety of Nintedanib (BIBF 1120) + Prednisone Taper in Patients With Radiation Pneumonitis | II | 68 patients with radiation pneumonitis | Nintedanib 150 mg twice daily or placebo taken for 12 weeks in addition to prednisone | 52 weeks | Freedom from acute pulmonary exacerbation | None |

# INBUILD TRIAL

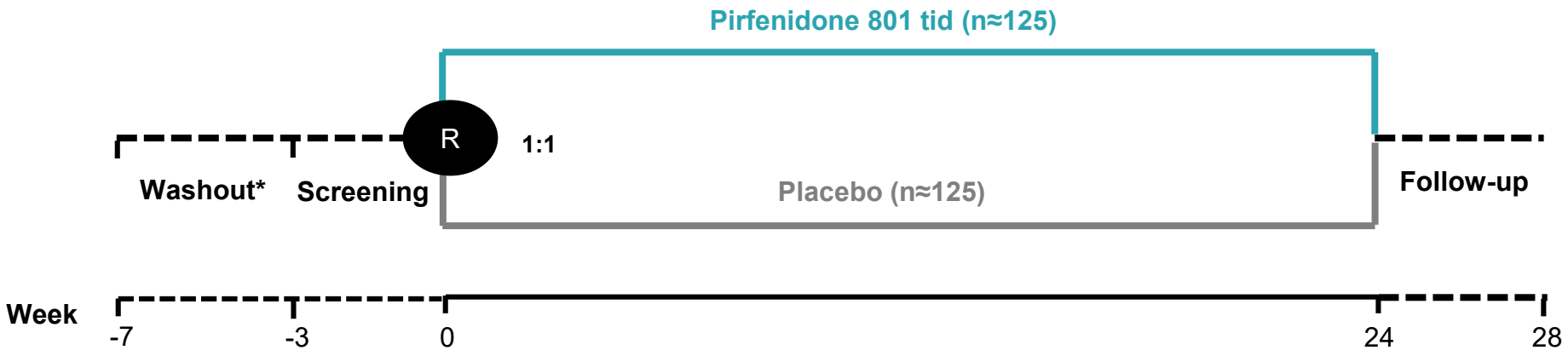



*Visits to occur every 16 weeks until end of treatment.

Eligible patients had fibrosing ILD of >10% extent on HRCT; met protocol-defined criteria for disease progression in 24 months before screening; and had FVC ≥45% predicted and Dlco >30% and <80% predicted.

Flaherty KR et al. *BMJ Open Resp Res* 2017;4:e000212

# TRIAL OF PIRFENIDONE IN PATIENTS WITH UNCLASSIFIABLE PROGRESSIVE FIBROSING ILD




*Washout period for subjects taking prohibited medications.
Eligible patients had fibrosing ILD that could not be classified with moderate to high confidence into any category of ILD following multidisciplinary team discussion; >10% extent of lung fibrosis on HRCT scan; absolute decline in FVC >5% predicted or significant symptomatic worsening in last 6 months in opinion of the investigator; FVC ≥45% predicted and Dlco ≥30% predicted.

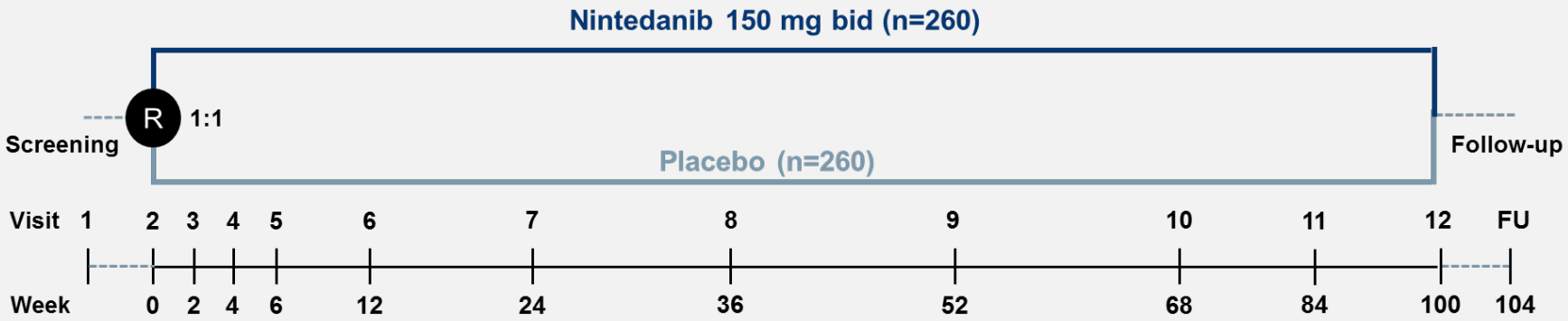
Maher TM et al. *BMJ Open Resp Res* 2018;5:e000289.

# Clinical trials of novel therapies for SSc-ILD : Recently completed and ongoing* (clinicaltrial.gov)

| Disease Entity | Agent or Intervention | Mechanism of Action | Primary Endpoint(s) | Current Status | Study Duration |
|---|---|---|---|---|---|
| SSc-ILD NCT01933334 | Pirfenidone | Antifibrotic | Tolerability | Phase 2 completed | 28 d |
| SSc-ILD (SLS III) NCT03221257 | Pirfenidone plus MMF vs. MMF | Antifibrotic plus antiinflammatory | FVC change from baseline | Phase 2 recruiting | 18 mo |
| SSc-PF NCT02597933 | Nintedanib vs. placebo | Antifibrotic | Change in FVC | Phase 3 active | 52 wk |
| SSc-PF NCT03313180 | Nintedanib vs. placebo | Antifibrotic | Safety | Open-label extension | Up to 34 mo |
| SSc-PF NCT02370693 | Bortezomib plus MMF vs. MMF | Immunosuppressive (proteasome inhibition, apoptosis induction) | Safety and tolerability | Phase 2 recruiting | 48 wk |
| SSc-ILD NCT01559129 | Pomalidomide (CC-4047) vs. placebo | • Antiangiogenesis<br>• Immunomodulation (↑interferon-γ, ↑IL-2, ↑IL-10, ↓IL-6) | Change in FVC, mRSS, and/or GI tract score<br>Adverse events | Phase 2 completed | 52 wk |
| SSc-PH NCT01086540 | Rituximab vs. placebo | Immunosuppressive | Change in pulmonary vascular resistance | Phase 2 active | 24 wk |

*Keith Meyer : Ann Am Thorac Soc Vol 15, No 11, pp 1273–1285, Nov 2018

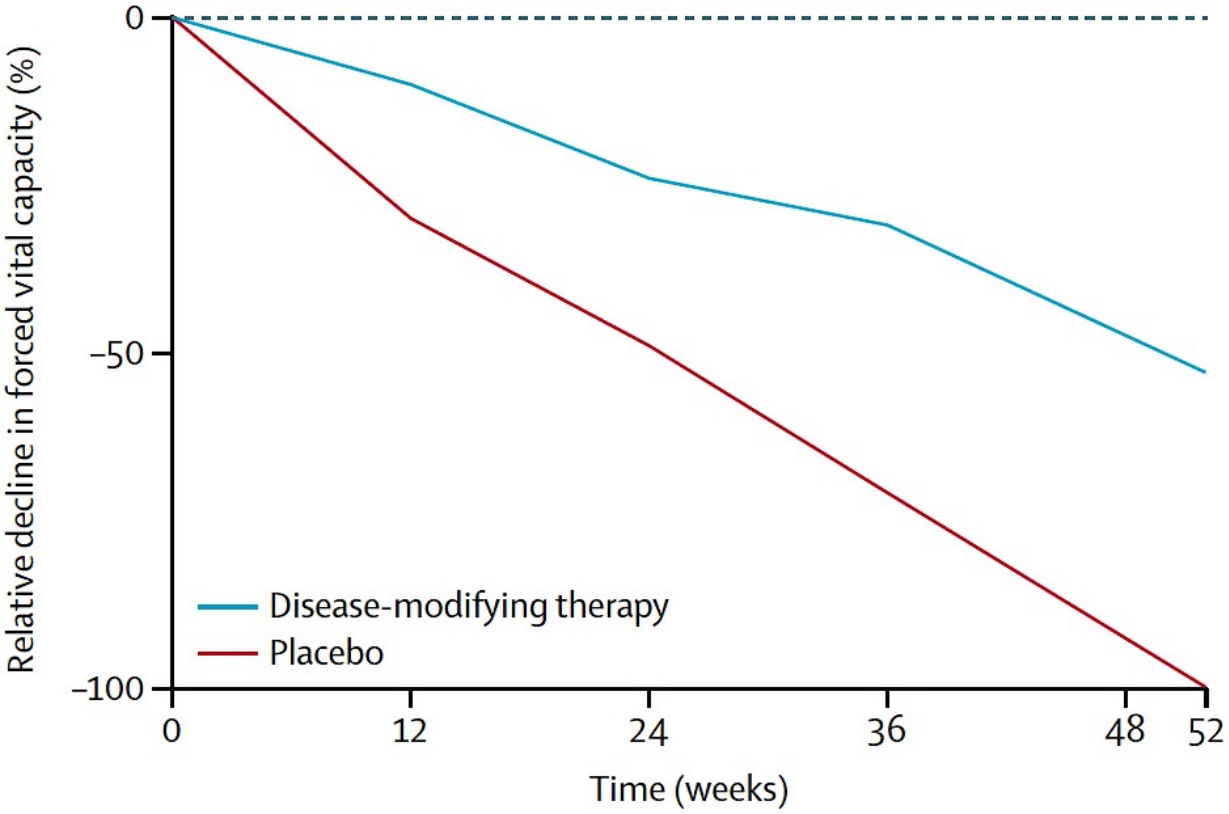
# SENSCIS TRIAL




Eligible patients had systemic sclerosis; >10% extent of lung fibrosis on HRCT scan; FVC ≥40% predicted and Dlco 30-89% predicted. Randomised patients were stratified by presence/absence of anti-topoisomerase antibody.

Distler O et al. *Clin Exp Rheumatol* 2017;35 Suppl 106:75-81.

# EFFECT OF DISEASE-MODIFYING THERAPY ON LUNG FUNCTION DECLINE




Richeldi L et al, *Lancet* 2017; 389: 1941-1952

Pulmonary Perspective

AJRCCM 2012

# Idiopathic Pulmonary Fibrosis: Clinically Meaningful Primary Endpoints in Phase 3 Clinical Trials

Ganesh Raghu[1]*, Harold R. Collard[2]*, Kevin J. Anstrom[3], Kevin R. Flaherty[4], Thomas R. Fleming[5], Talmadge E. King, Jr.[2], Fernando J. Martinez[4], and Kevin K. Brown[6]

The choice of a primary endpoint for Phase 3 clinical trials for IPF is an important and complex decision that includes scientific, practical, financial, and regulatory considerations. *We believe the most scientifically appropriate primary endpoints for Phase 3 clinical trials are clinically meaningful endpoints that directly inform how a patient feels, functions, or survives. In IPF, the endpoints that most clearly meet these criteria are all-cause mortality and all-cause nonelective hospitalization.* A composite endpoint of all cause-mortality or all-cause nonelective hospitalization is also scientifically robust. This does not mean that all Phase 3

# A single reduction in FVC>10% may not be meaningful on its own

- An isolated drop in FVC on a single occasion could occur by chance alone

- Corroborative evidence useful:
  - Downward trend in DLCO
  - Symptoms (increasing breathlessness)
  - Repeating HRCT may be helpful to confirm ILD progression/exclude other causes worsening
  - If worsening marginal, continue to observe

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DOI 10.1002/art.40769


AMERICAN COLLEGE OF RHEUMATOLOGY
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SPECIAL ARTICLE

# Proceedings of the American College of Rheumatology/ Association of Physicians of Great Britain and Ireland Connective Tissue Disease–Associated Interstitial Lung Disease Summit: A Multidisciplinary Approach to Address Challenges and Opportunities

Aryeh Fischer,[1] Mary E. Strek,[2] Vincent Cottin,[3] Paul F. Dellaripa,[4] Elana J. Bernstein,[5] Kevin K. Brown,[6] Sonye K. Danoff,[7] Oliver Distler,[8] Nik Hirani,[9] Kirk D. Jones,[10] Dinesh Khanna,[11] Joyce S. Lee,[1] David A. Lynch,[6] Toby M. Maher,[12] Ann B. Millar,[13] Ganesh Raghu,[14] Richard M. Silver,[15] Virginia D. Steen,[16] Elizabeth R. Volkmann,[17] Ronan H. Mullan,[18] David N. O'Dwyer,[11] and Seamas C. Donnelly[18]

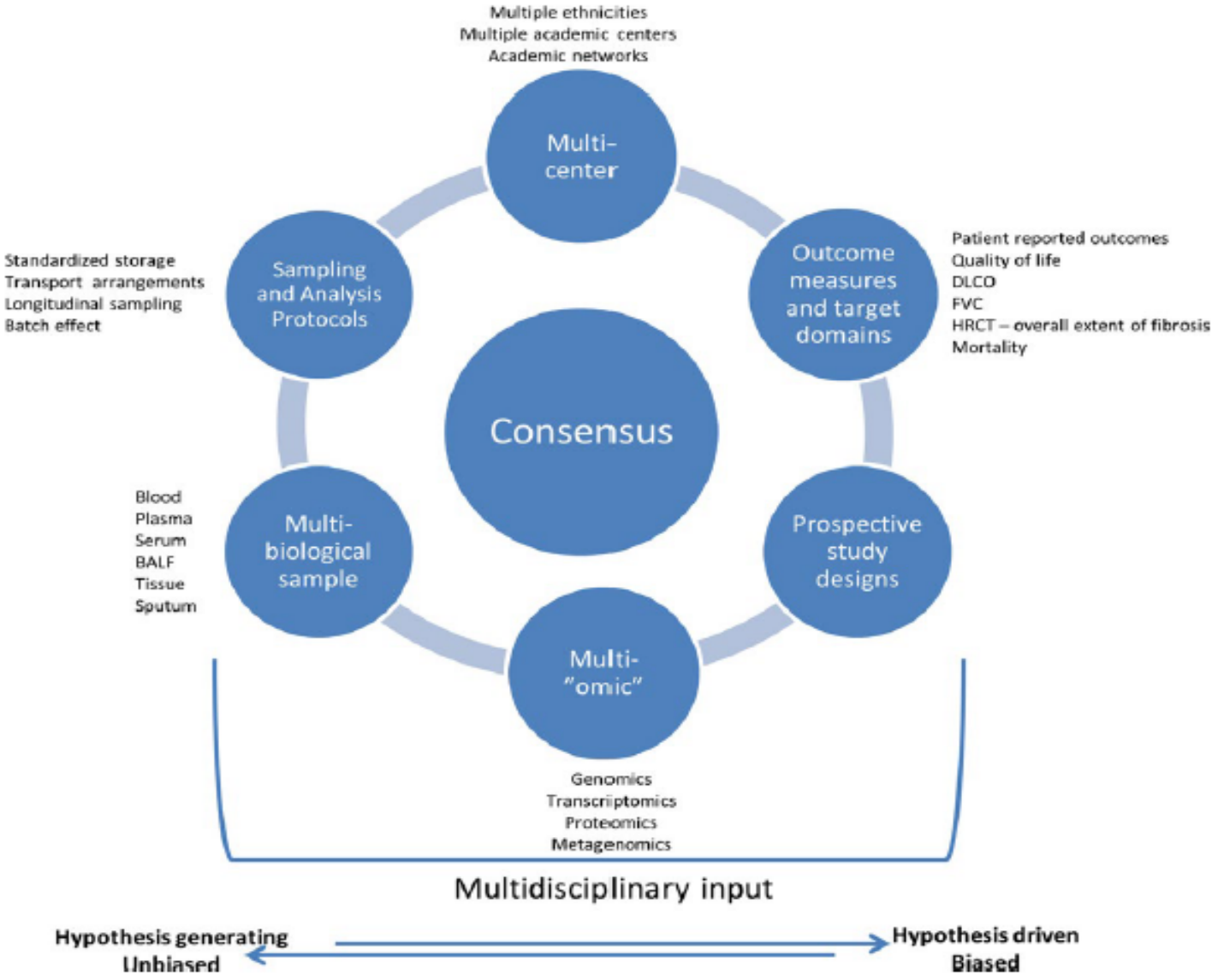


**Figure 1.** Proposed future investigative directions for the development of connective tissue disease–associated interstitial lung disease biomarkers. DLco = diffusing capacity for carbon monoxide; FVC = forced vital capacity; HRCT = high-resolution computed tomography; BALF = bronchoalveolar lavage fluid.

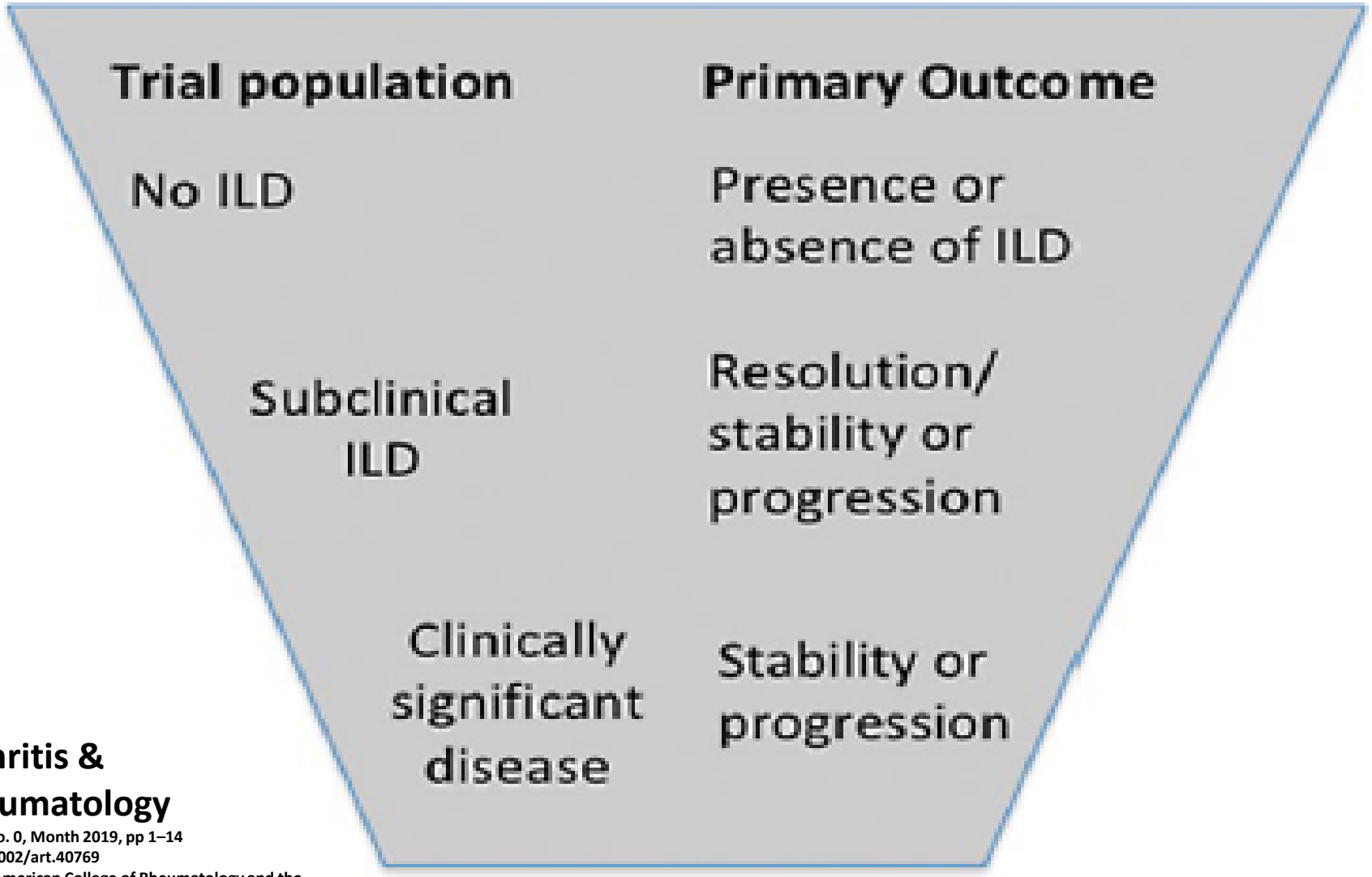


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**Figure 5.** Suggested disease population stratification, and corresponding primary trial outcome, for interstitial lung disease (ILD) clinical trials in patients with connective tissue disease.

# Trials of antifibrotic agents in non IPF ILDs

**SSc-ILD**

- Phase 2 LOTUSS Study**: pirfenidone** +/- MMF1
- NCT03221257 (SLS III): Phase 2 study combining MMF with **pirfenidone** versus placebo for 18 months
  - Recruitment to start in October 2017 – 150 patients target enrolment
- NCT02597933: Phase 3 study of **nintedanib** vs placebo (background MMF permitted stable dose)
  - 520 patients target enrolment (completion Dec 2018)
  - primary outcome: annual rate of FVC decline
  - **Results anticipated ( ATS 2019)**

**RA-ILD**

- NCT02808871: Phase 2 study of **pirfenidone** versus placebo, allows background stable immunosuppression
  - 270 patients target enrolment; estimated completion 2021

**Fibrotic HP**

- NCT02958917: Phase 2 safety and efficacy trial of **pirfenidone:** target enrolment of 40 pts

**Non IPF ILD**

- NCT02999178: Phase 3 study of **nintedanib** vs placebo in progressive, non-IPF lung fibrosis; MMF or azathioprine not allowed during first six months

- NCT03099187: Phase 3 study of **pirfenidone** in unclassifiable progressive ILD: target enrolment=250 pts; stable MMF allowed

# Treatment for CTD-ILD
## ongoing clinical trials (clinical trial.gov)

- SENSCIS ( ILD-scleroderma)- phase 3 clinical trial : Nintedanib vs placebo (allowing background therapy with mycophenolate)
- SLS III ( ILD-scleroderma )-phase 3 clinical trial : pirfenidone vs mycophenolate
- TRAIL ( ILD-Rheumatoid arthritis)-phase 3 clinical trial

  pirfenidone vs placebo ( allowing background therapy)

# Antifibrotic treatment – beyond IPF-

## NON IPF-PF

# Thank you