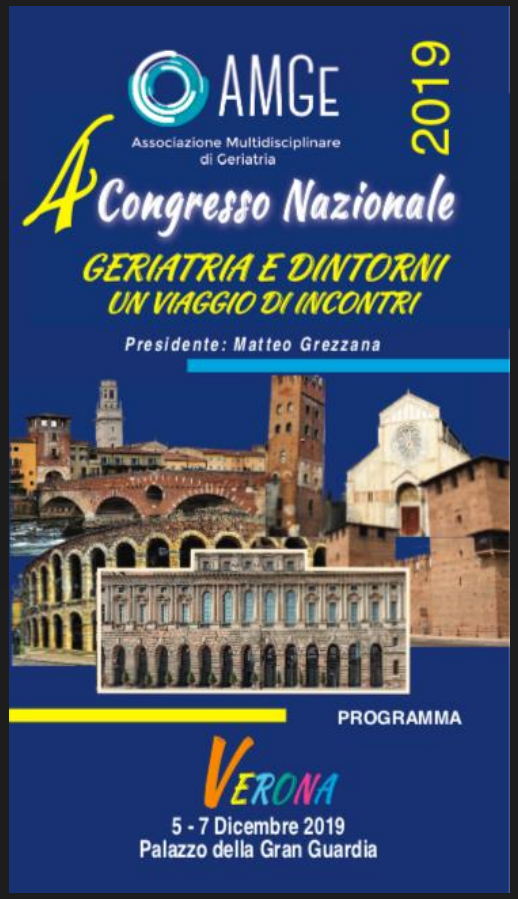


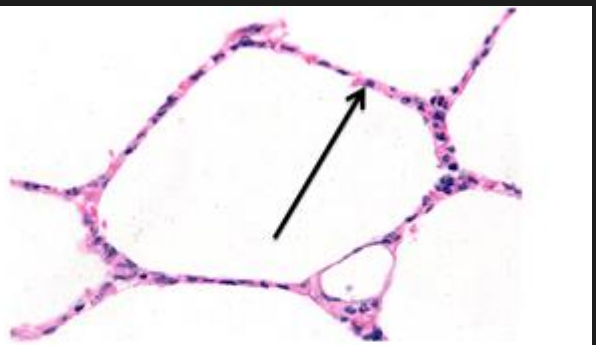
INTERSTIZIOPATIE POLMONARI

Paolo Spagnolo
Unità Operativa Complessa di Pneumologia
Dipartimento di Scienze Cardio-Toraco-Vascolari e Sanità Pubblica
Università di Padova

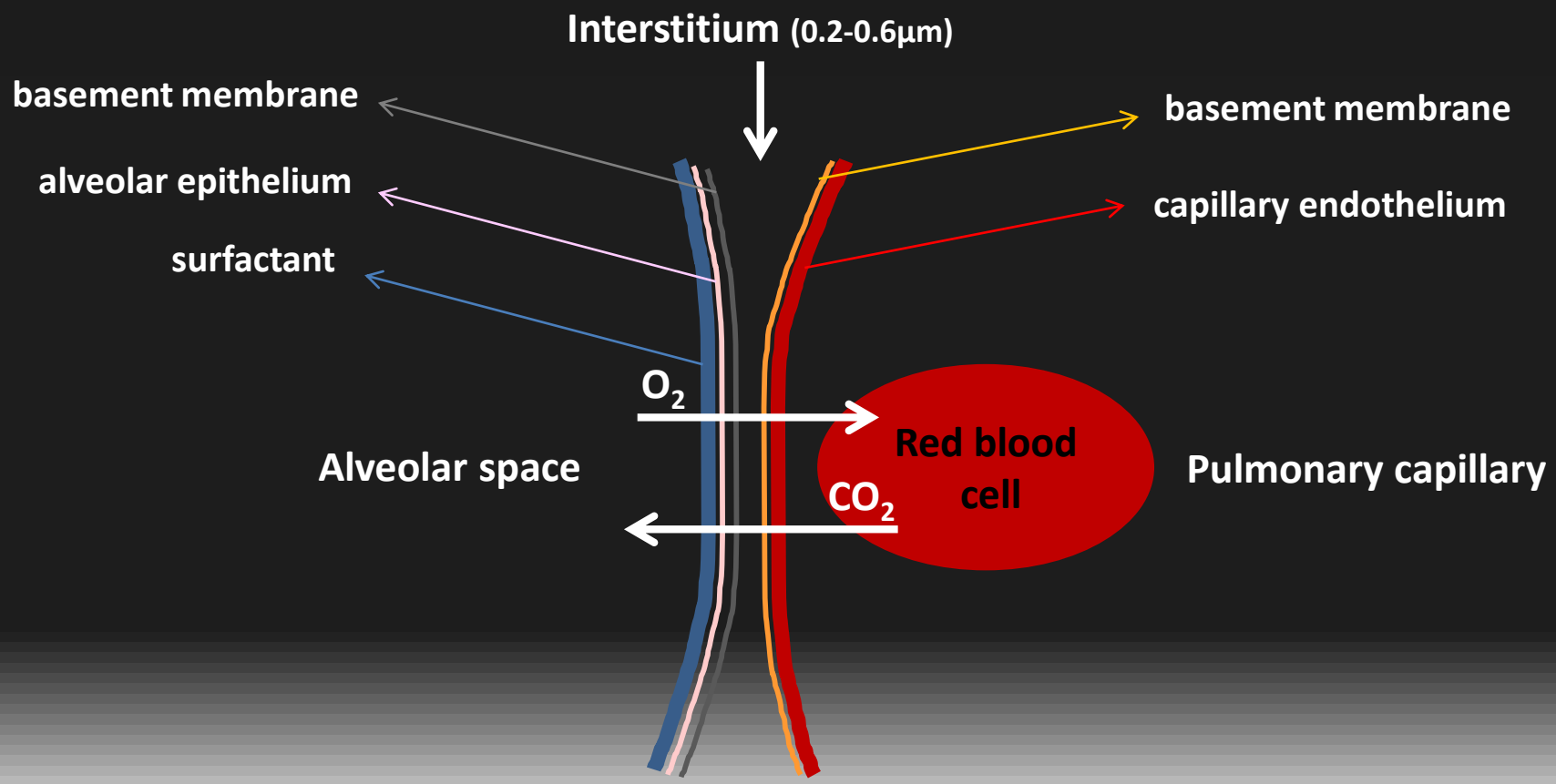
DISCLOSURE

Consulting fees	PPM Services, Boehringer-Ingelheim, Roche, Galapagos, Chiesi, Zambon, Strekin
Advisory board fees	Boehringer-Ingelheim, Roche, Galapagos, Red-X Pharma, Zambon
Speaker's fees	Roche, Boehringer-Ingelheim, Galapagos, Chiesi, Zambon
Institutional grants	PPM Services, Boehringer-Ingelheim

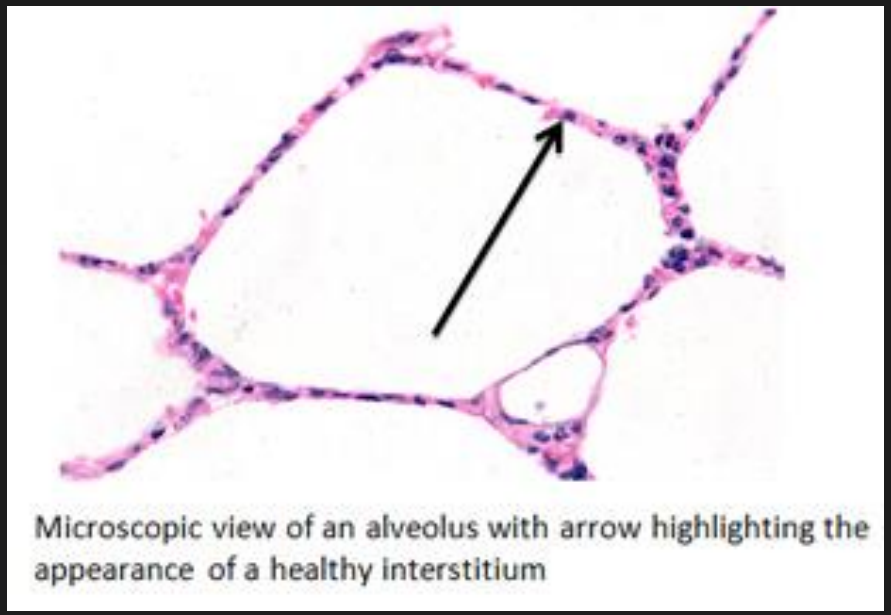
The interstitium (normal)



Microscopic view of an alveolus with arrow highlighting the appearance of a healthy interstitium



The interstitium (abnormal)



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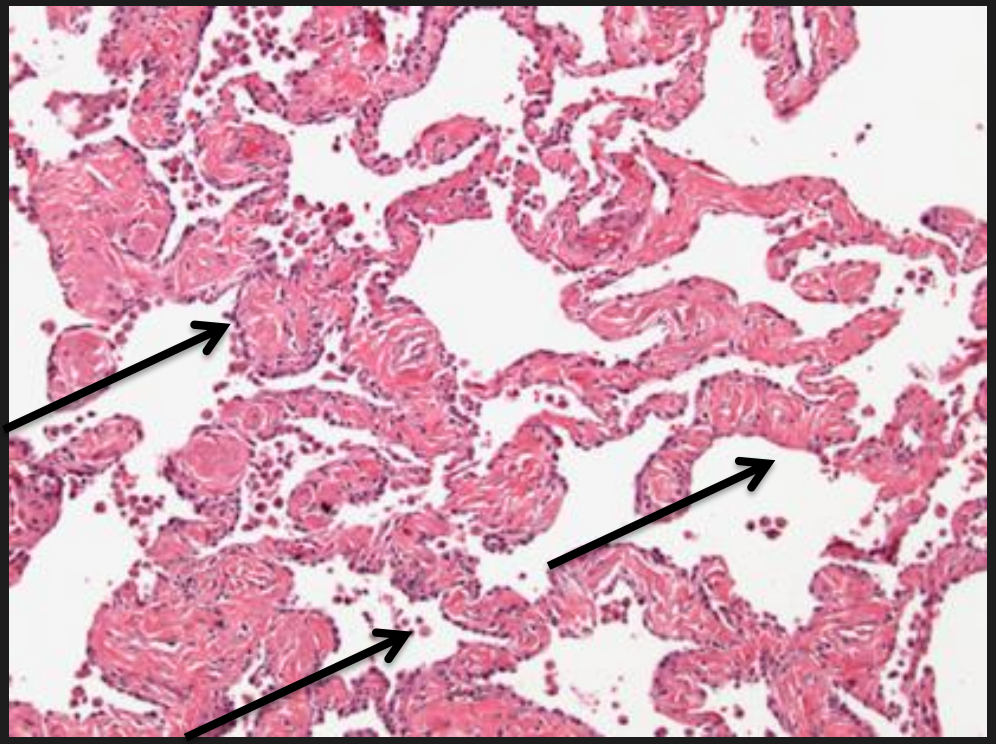

Interstitial Lung Disease

Exposure-related
- Occupational
- Environmental
- Avocational
- Medication

Idiopathic interstitial pneumonia

MAJOR
- Idiopathic Pulmonary Fibrosis (IPF)
- Idiopathic Non-Specific Interstitial Pneumonia (NSIP)
- Respiratory Bronchiolitis Interstitial Lung Disease (RB-ILD)
- Desquamative Interstitial Pneumonia (DIP)
- Cryptogenic Organizing Pneumonia (COP)
- Acute Interstitial Pneumonia (AIP)

RARE
- Idiopathic Lymphoid Interstitial Pneumonia
- Idiopathic Pleuropulmonary Fibroelastosis

UNCLASSIFIABLE

Connective tissue disease
- Scleroderma
- Rheumatoid
- Sjögren
- …

Granulomatous
- Sarcoidosis
- HP
- Mycobacteria
- …

Other
- Vasculitis/Diffuse Alveolar Hemorrhage
- Langerhans' Cell Histiocytosis
- Eosinophilic Pneumonias
- Neurofibromatosis
- LAM
- …

Interstitial Lung Disease

Exposure-related
- Occupational
- Environmental
- Avocational
- Medication

Idiopathic interstitial pneumonia

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- …

IDIOPATHIC PULMONARY FIBROSIS

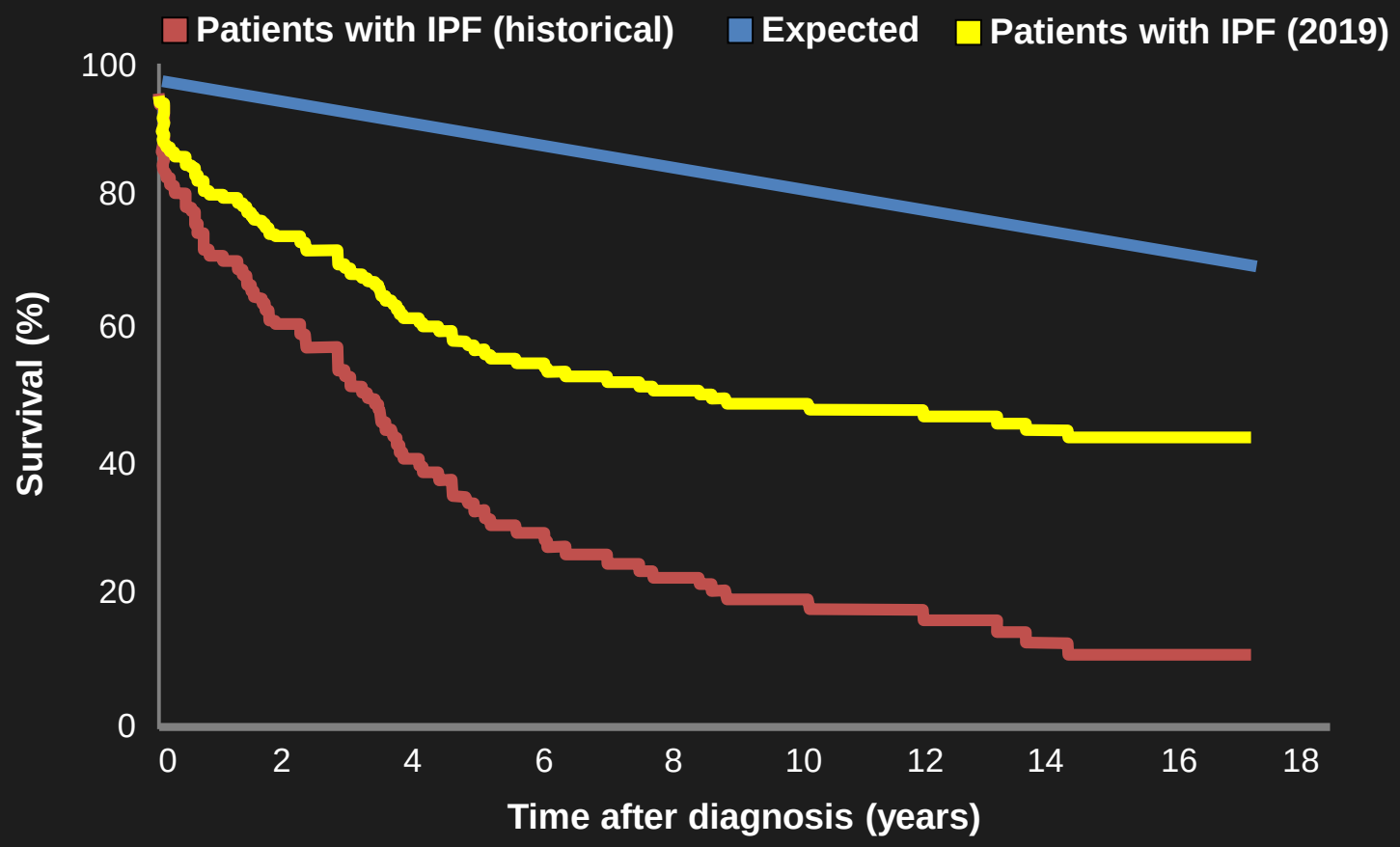
IPF is a chronic progressive and ultimately fatal fibrotic interstitial pneumonia of unknow cause/s with a 5-year survival of 20-30%

IPF occurs primarily in older adults, and is associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP)

IPF = idiopathic UIP

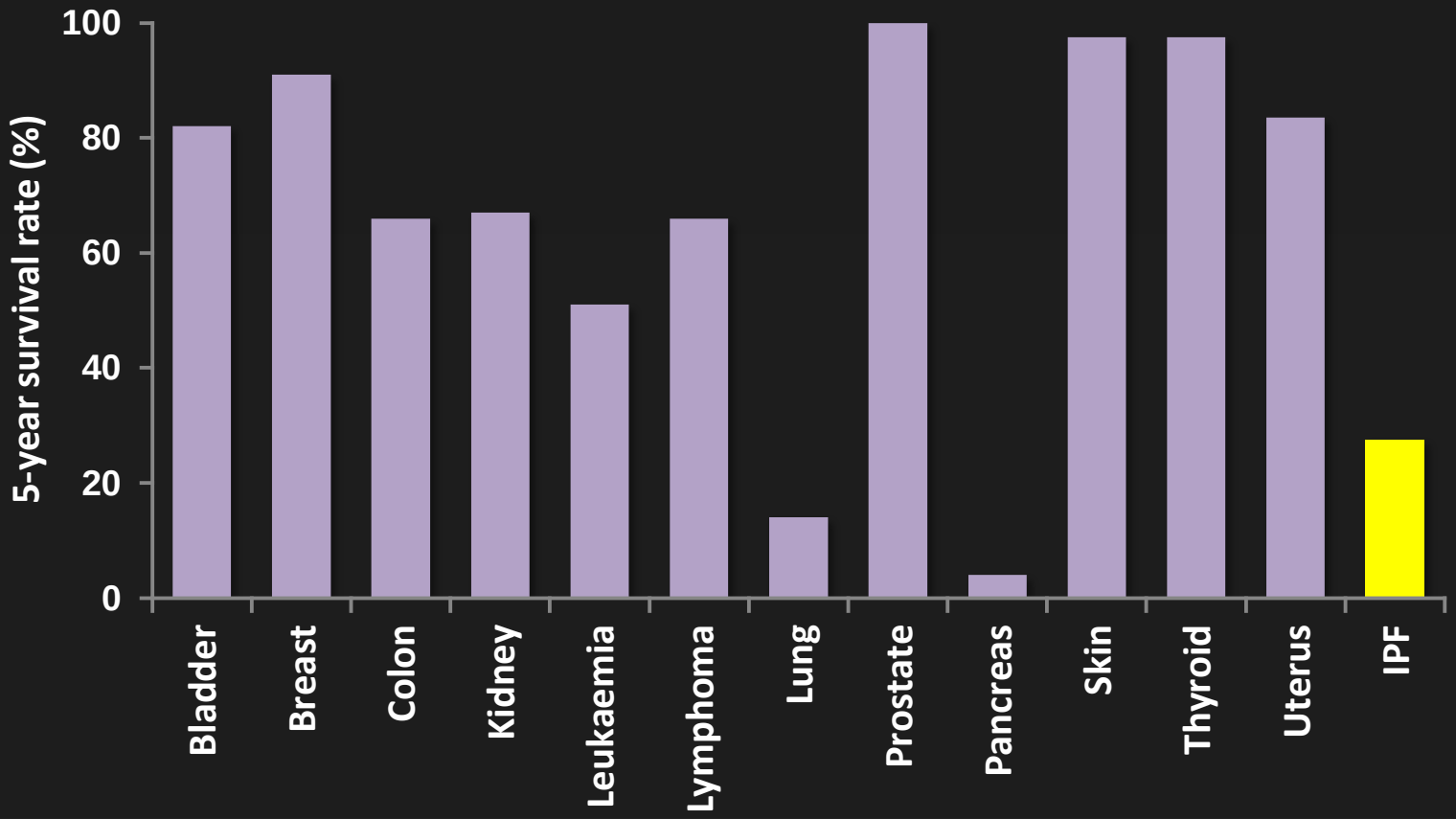
Lederer DJ et al. N Engl J Med 2018; 378: 1811-23

PATIENTS WITH IPF EXHIBIT A POOR PROGNOSIS

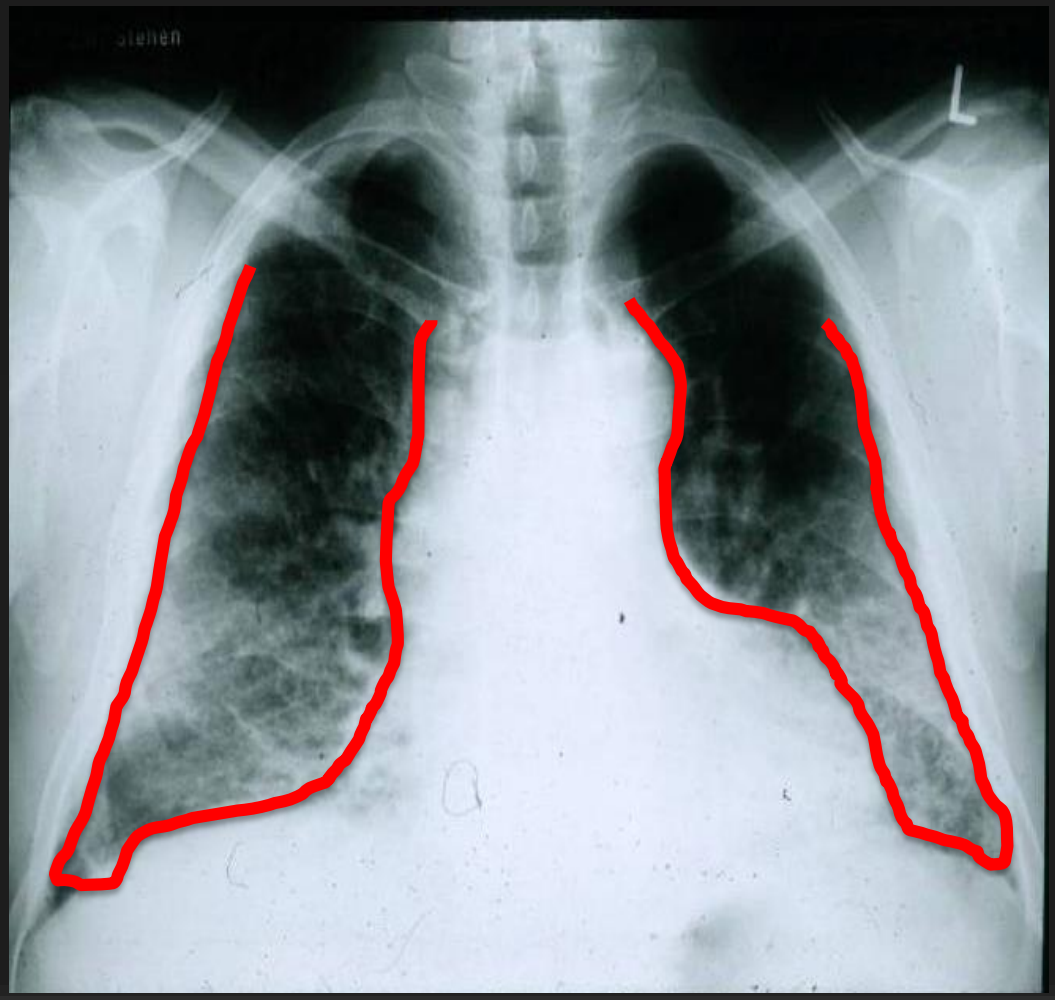


Modified from Bjoraker JA et al. *Am J Respir Crit Care Med* 1998; 157: 199-203

5-YEAR MEDIAN SURVIVAL OF IPF IS WORSE THAN THAT OF MANY CANCERS

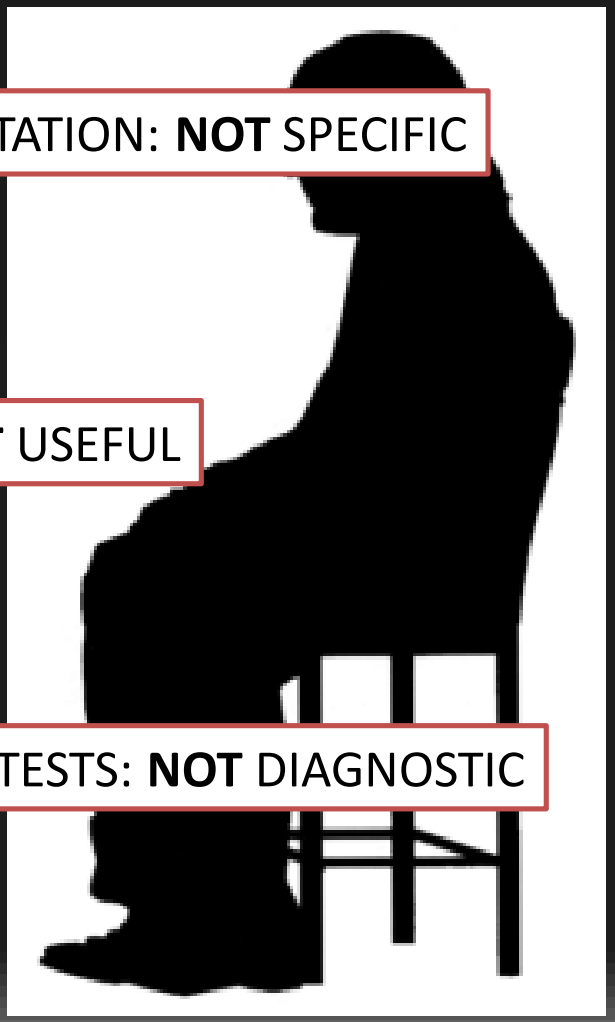


Vancheri C et al. Eur Respir J 2010; 35: 496-504

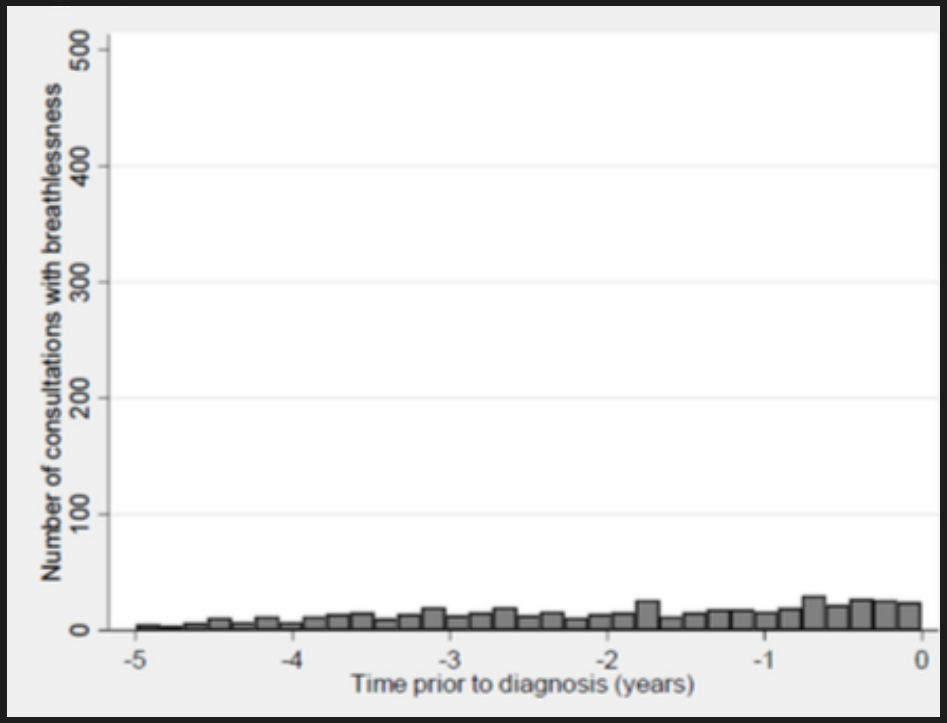

L

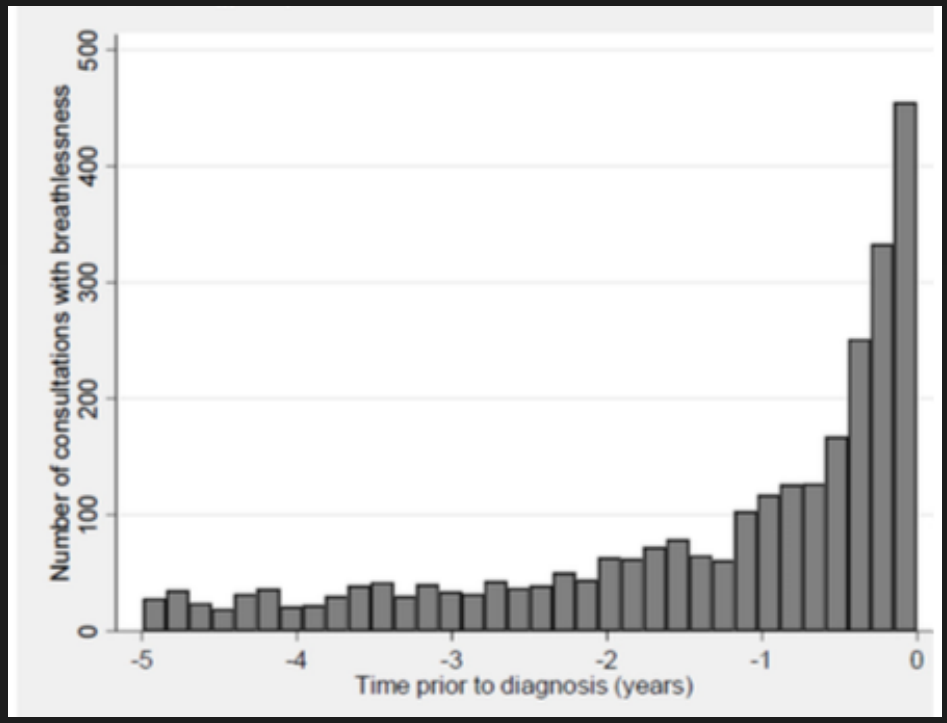
"MISTER IPF"

- 65 year old man
- Former smoker
- Dyspnea on exertion
- Chronic dry cough
- Bibasilar "velcro-type" crackles
- CXR: nonspecific/normal
- PFTs: Mixed restriction/obstruction with a low DL_{CO}
- Often previously diagnosed with a different lung disease

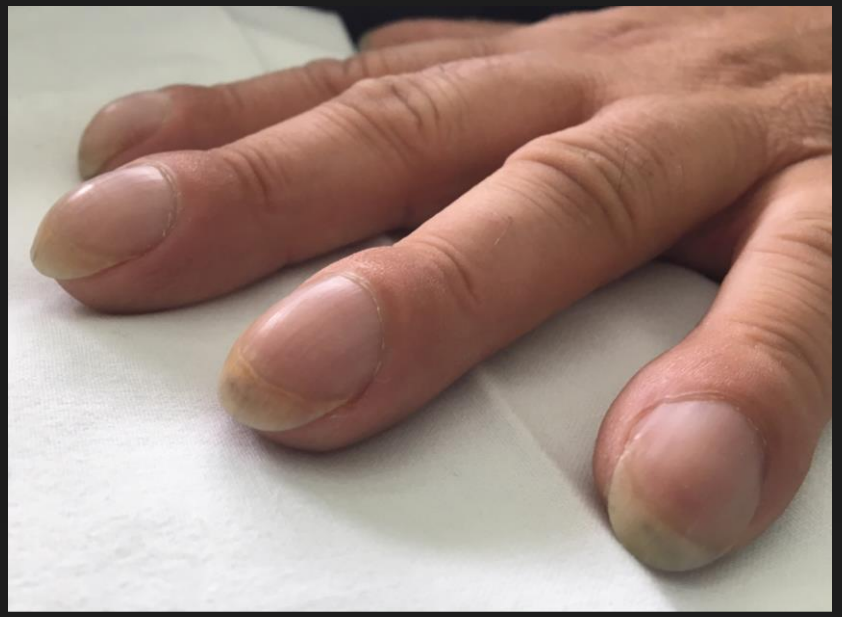


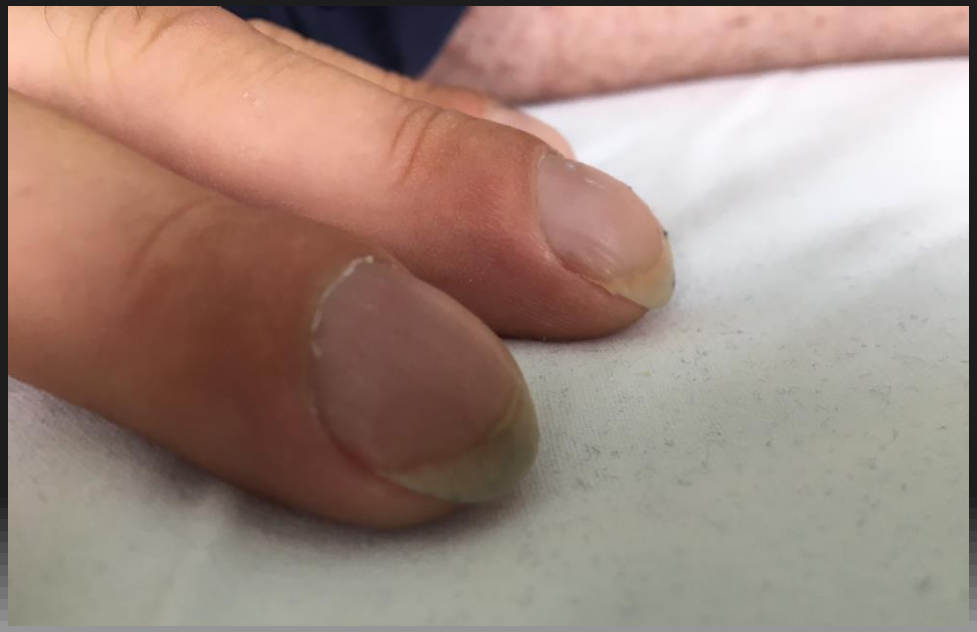
NUMBER OF CONSULTATIONS FOR DYSPNOEA IN IPF PATIENTS AND MATCHED CONTROLS OVER 5 YEARS PRIOR TO DIAGNOSIS

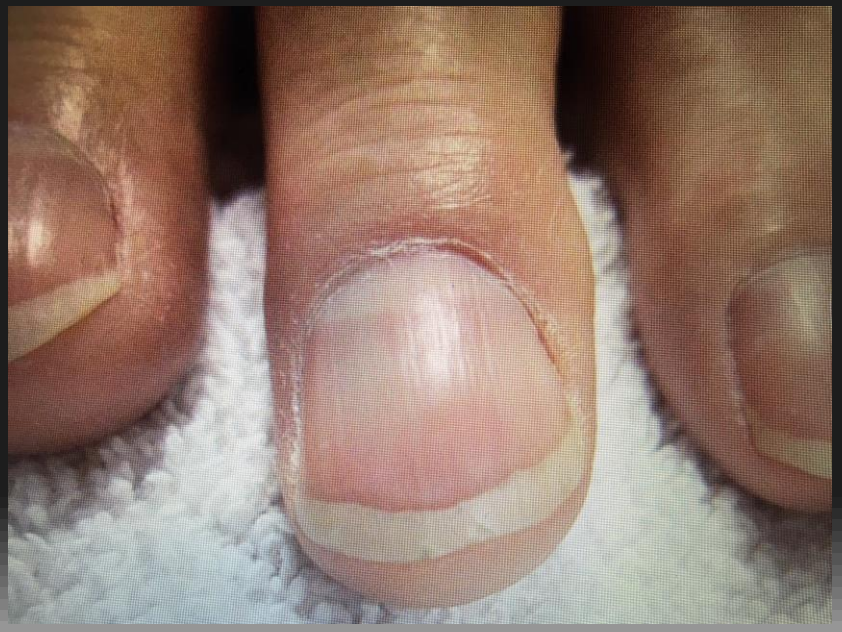




Hewson T, et al. Thorax. 2017 Oct 11. pii: thoraxjnl-2017-210177. doi: 10.1136/thoraxjnl-2017-210177. [Epub ahead of print]







RISK FACTORS AND POSSIBLE ETIOLOGIES FOR IPF

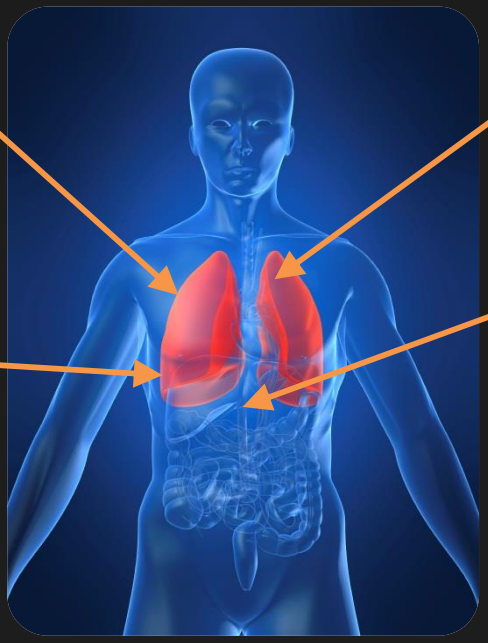
Environmental factors

Cigarette smoking

- Strongly associated with IPF

Environmental pollutants

- Associated with an increased risk of IPF
- Exposure to metal and wood dusts, farming, raising birds, hairdressing, stone cutting/polishing, and exposure to livestock, vegetables or animal dust



Other

Infection

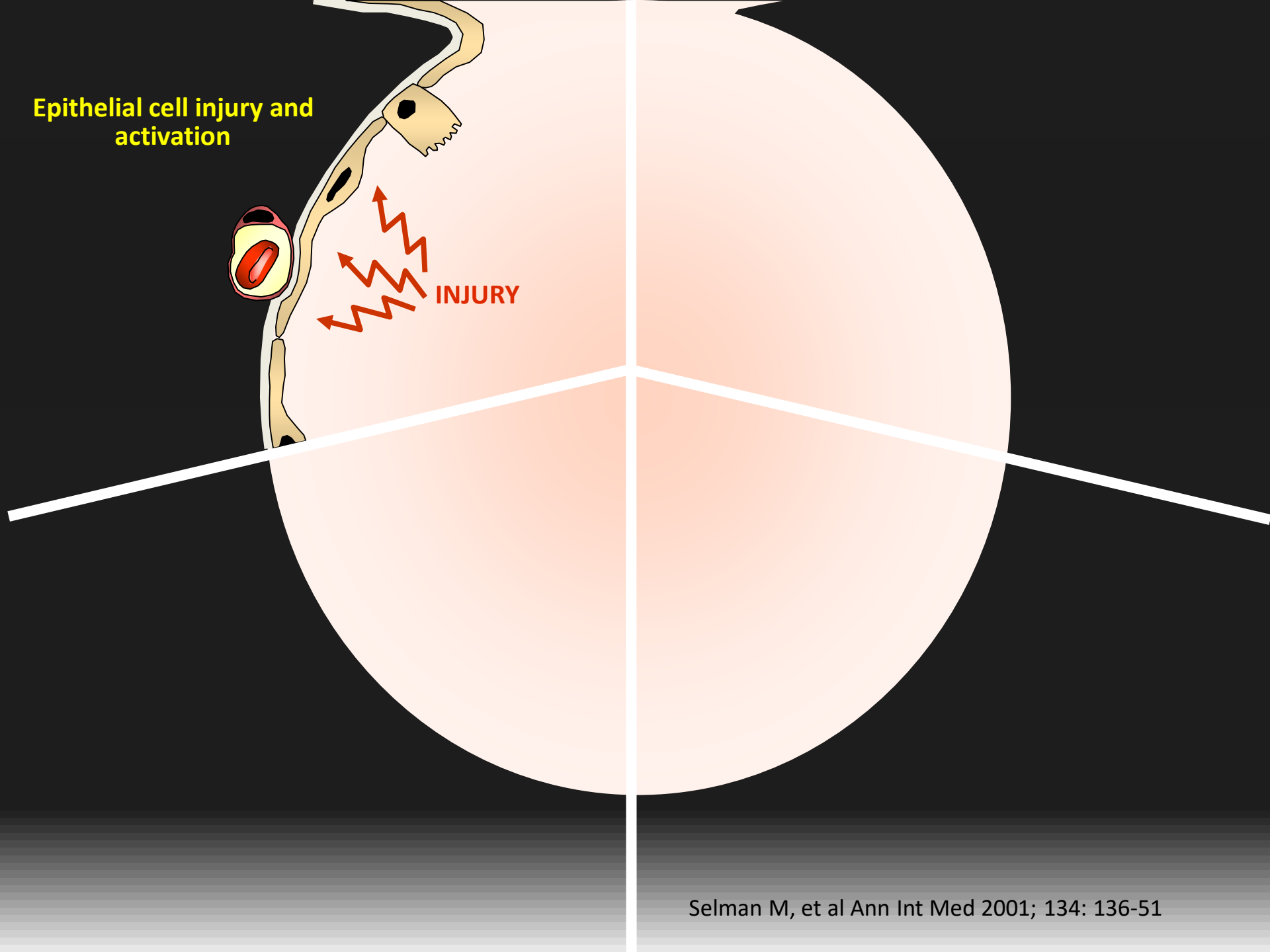
- A large number of studies have examined this, but findings are not conclusive

Gastroesophageal reflux disease

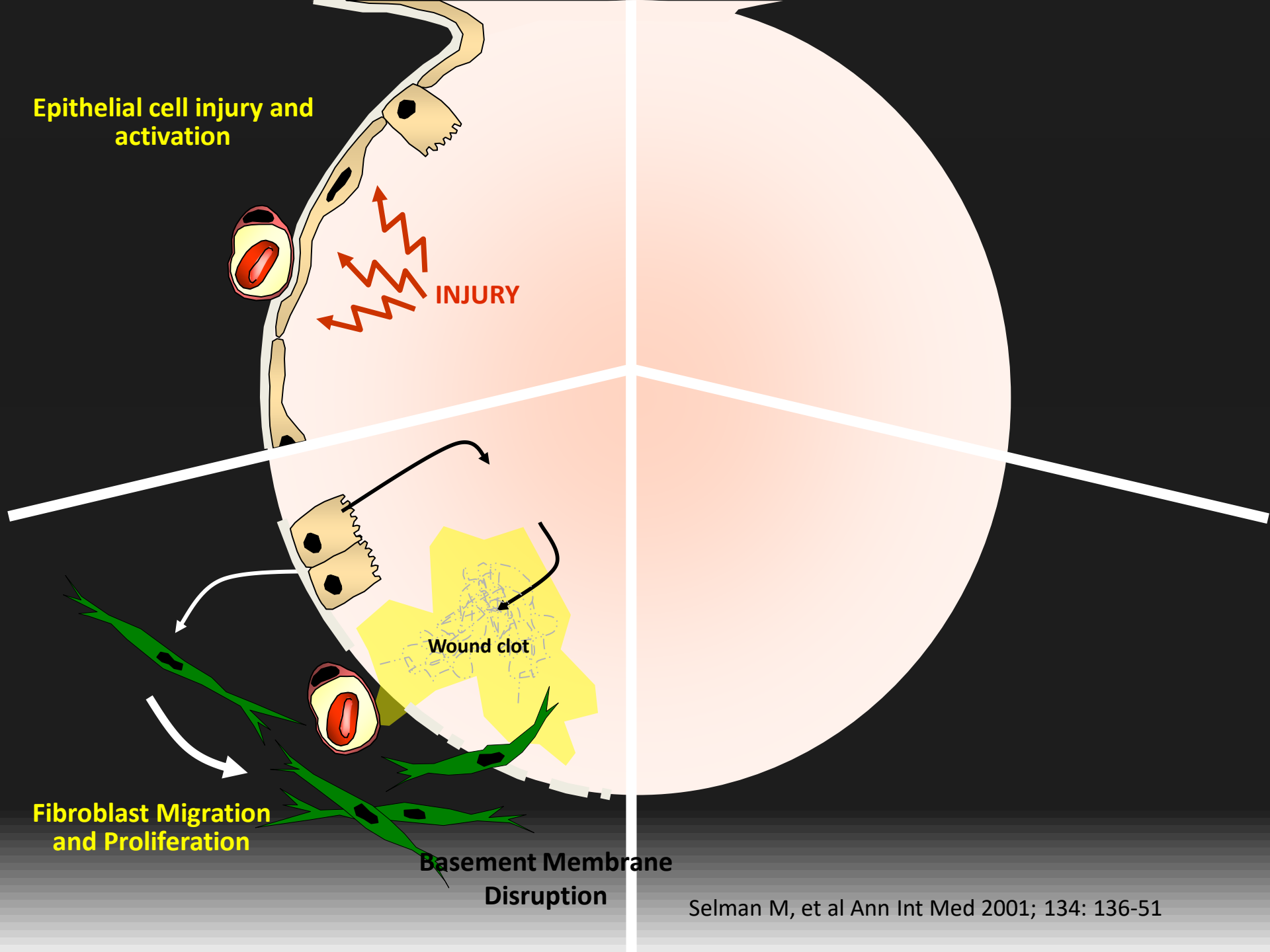
- Proposed cause of repeated micro-injury

Genetic factors

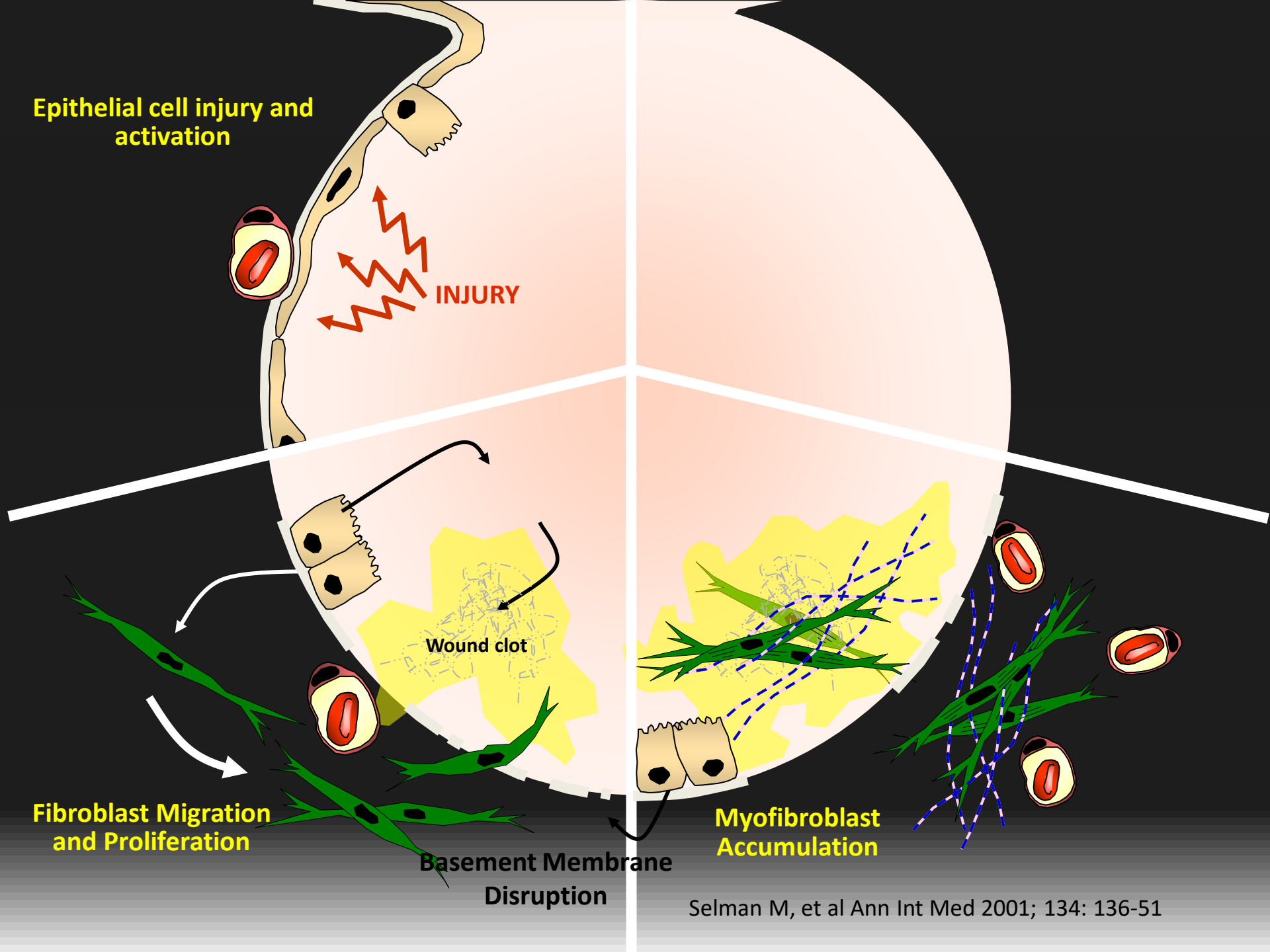
- Familial pulmonary fibrosis accounts for around 10% of total population with IPF



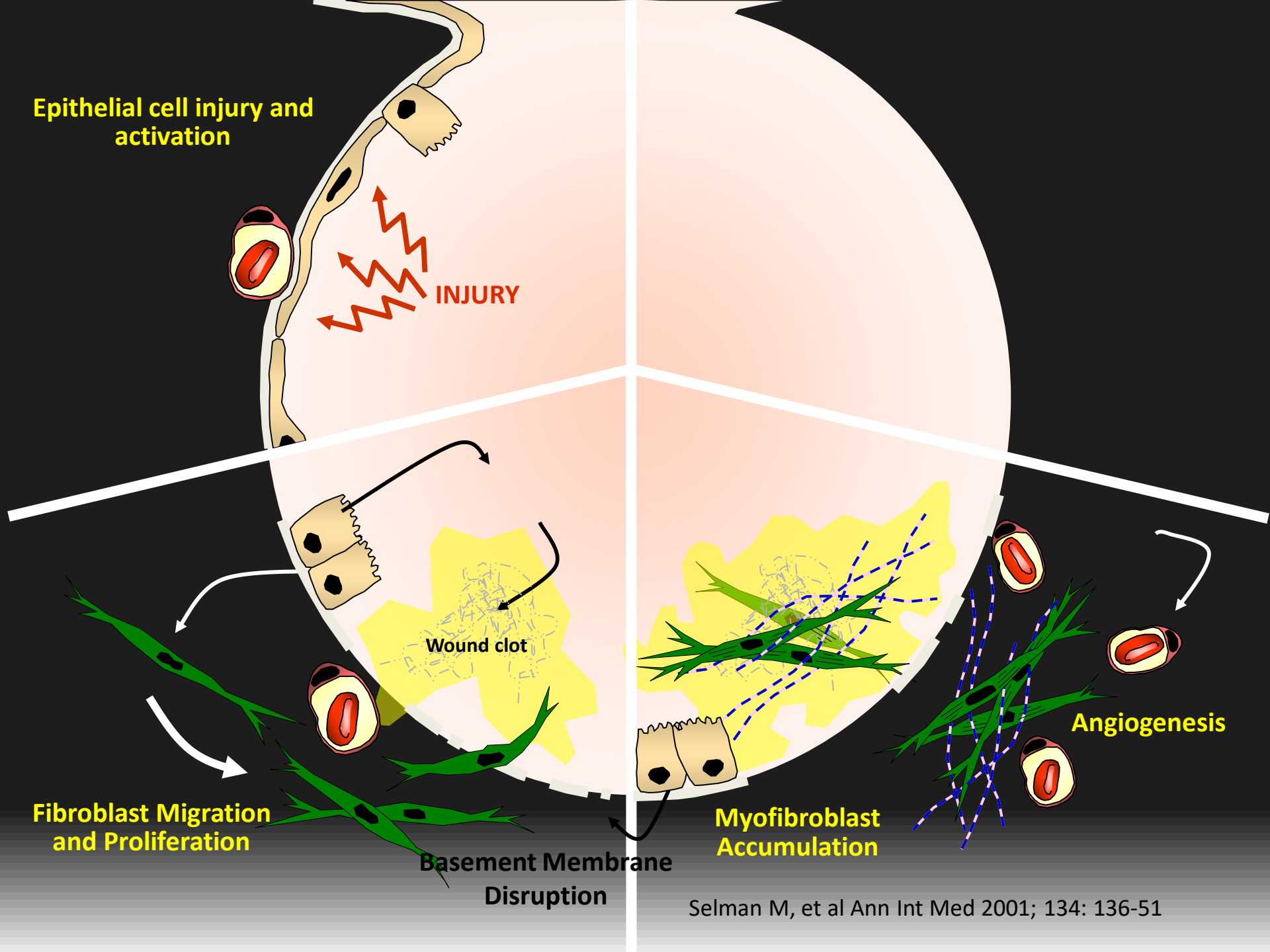
Selman M, et al Ann Int Med 2001; 134: 136-51



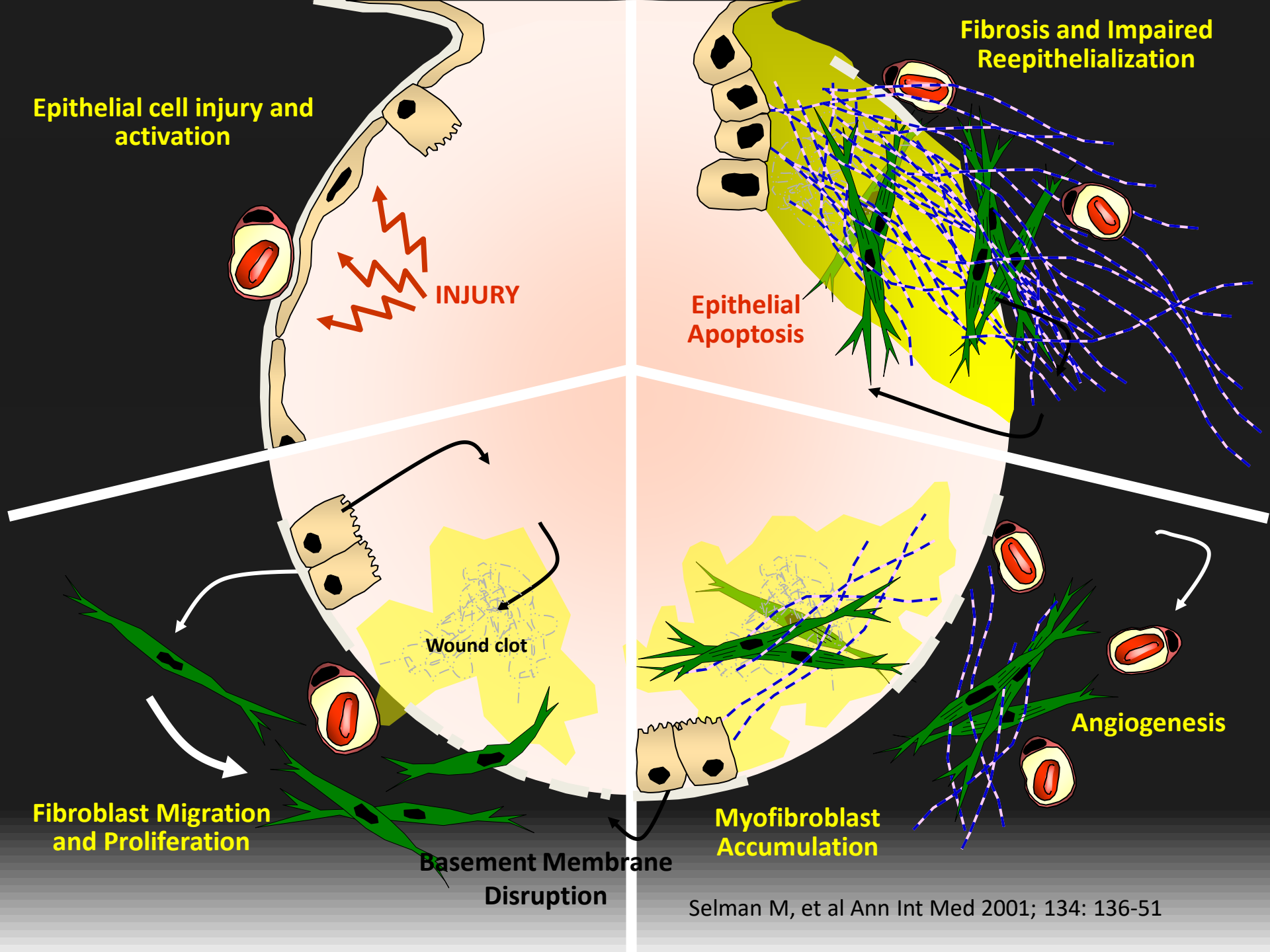
Selman M, et al Ann Int Med 2001; 134: 136-51



Selman M, et al Ann Int Med 2001; 134: 136-51



Selman M, et al Ann Int Med 2001; 134: 136-51



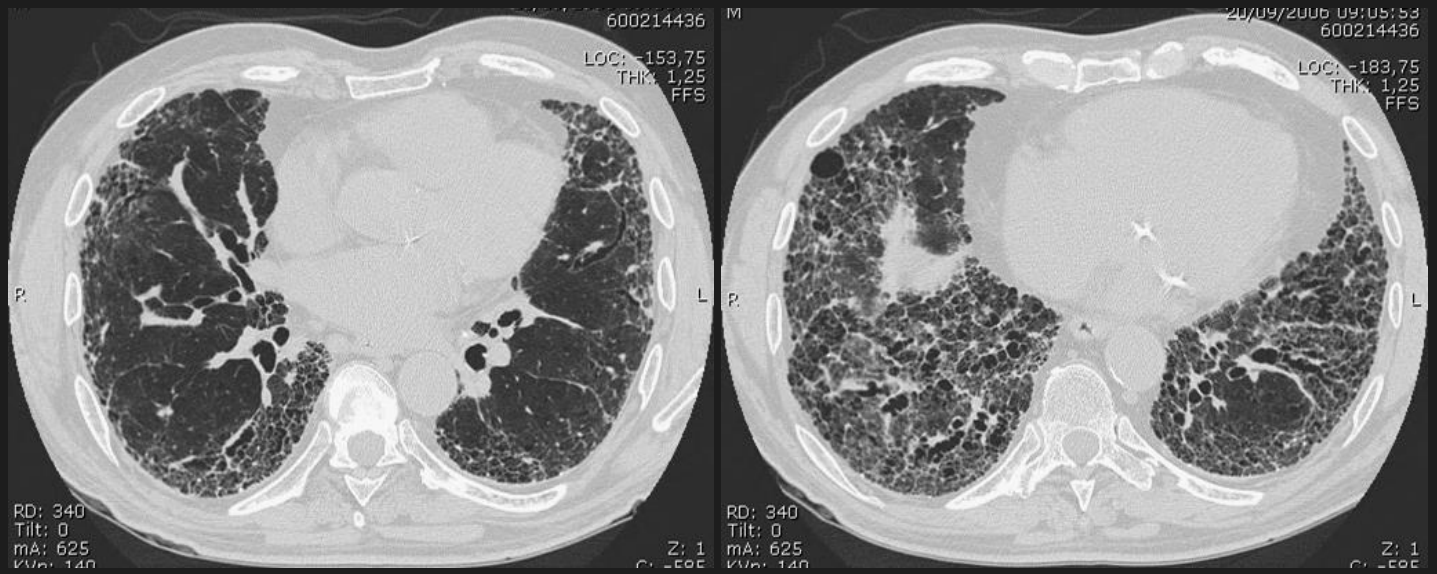
Selman M, et al Ann Int Med 2001; 134: 136-51

DIAGNOSIS OF IPF

Exclusion of known causes of interstitial lung disease

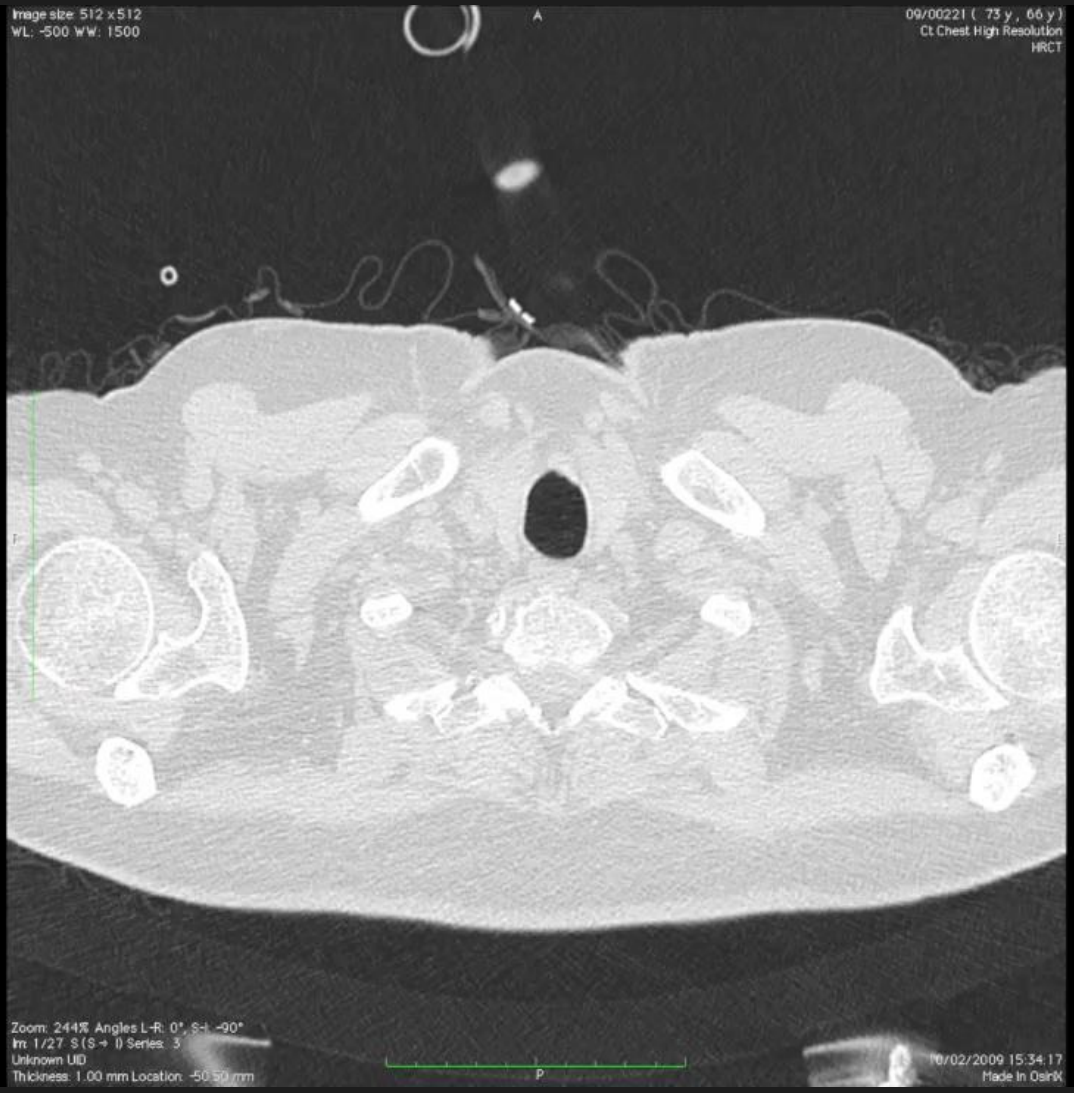
Presence of a *definite* UIP pattern on HRCT

Specific combinations of HRCT and SLB patterns



SLB: surgical lung biopsy

Raghu G et al. Am J Respir Crit Care Med 2018; 198: e44-e68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WL: -500 WW: 1500
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HRCT
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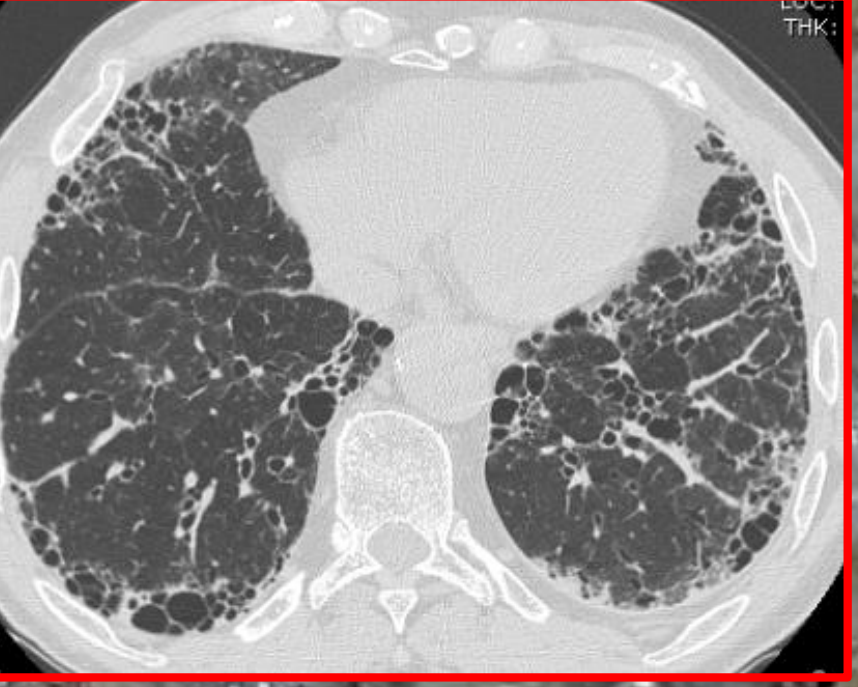
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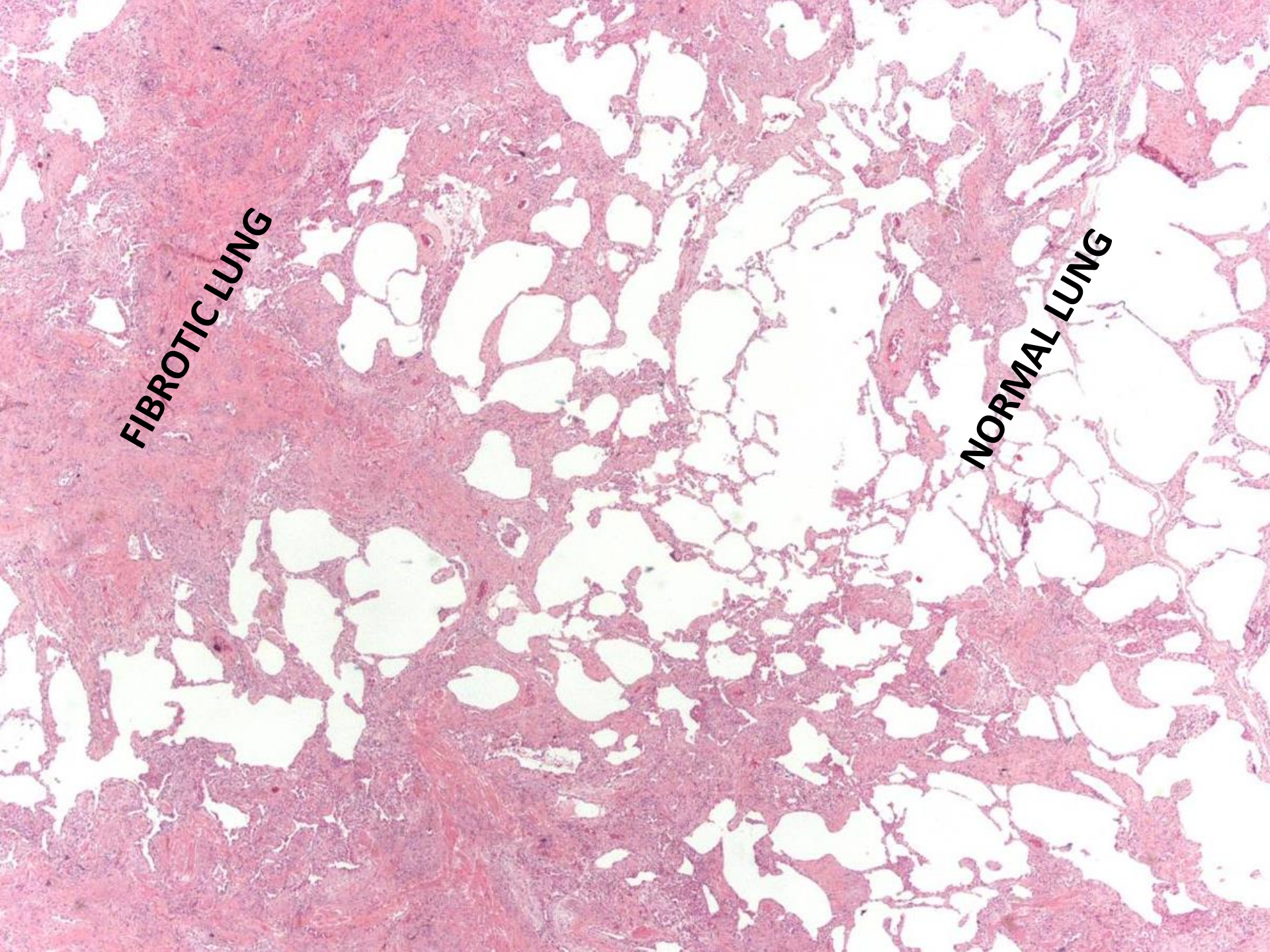
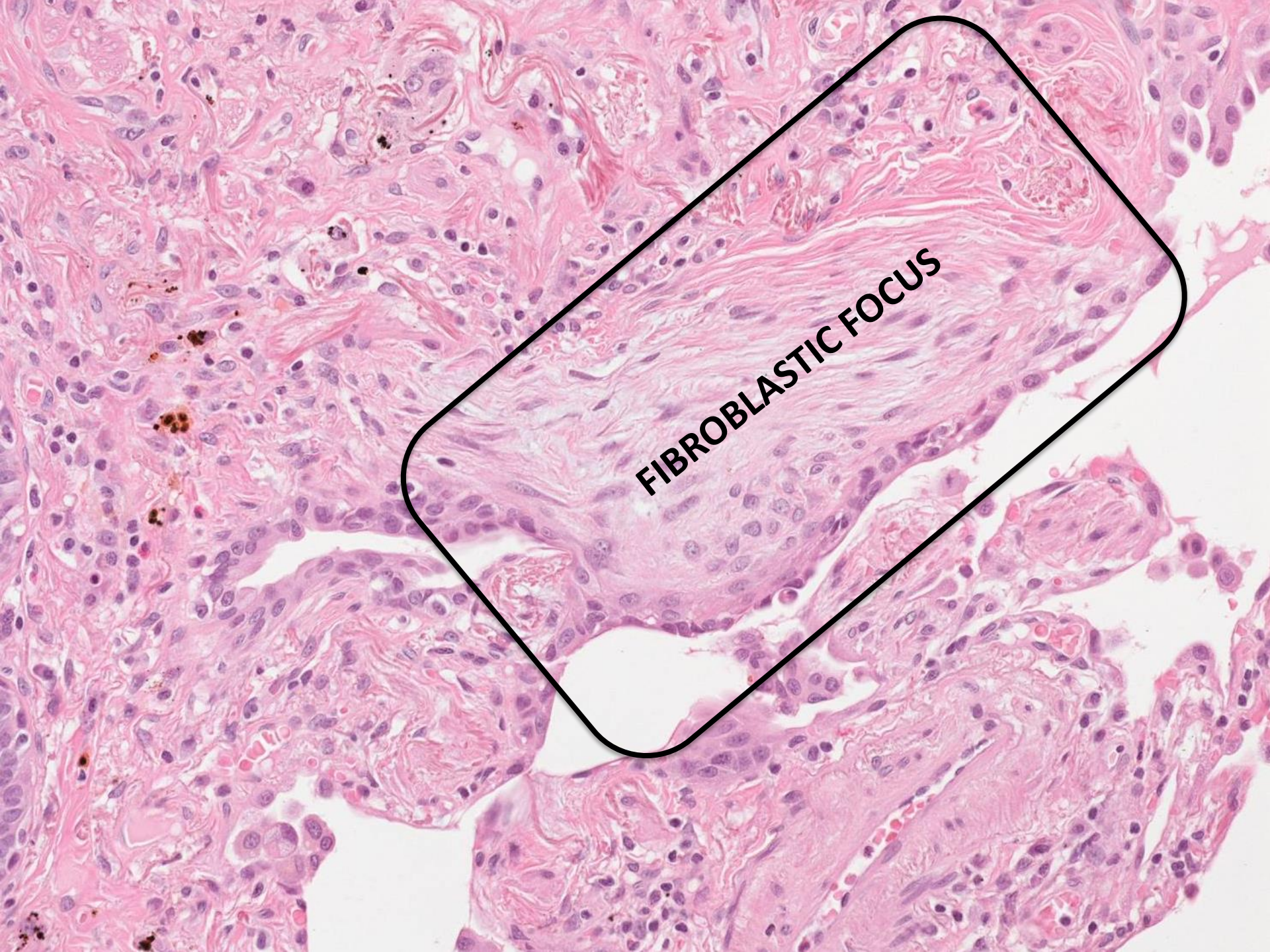
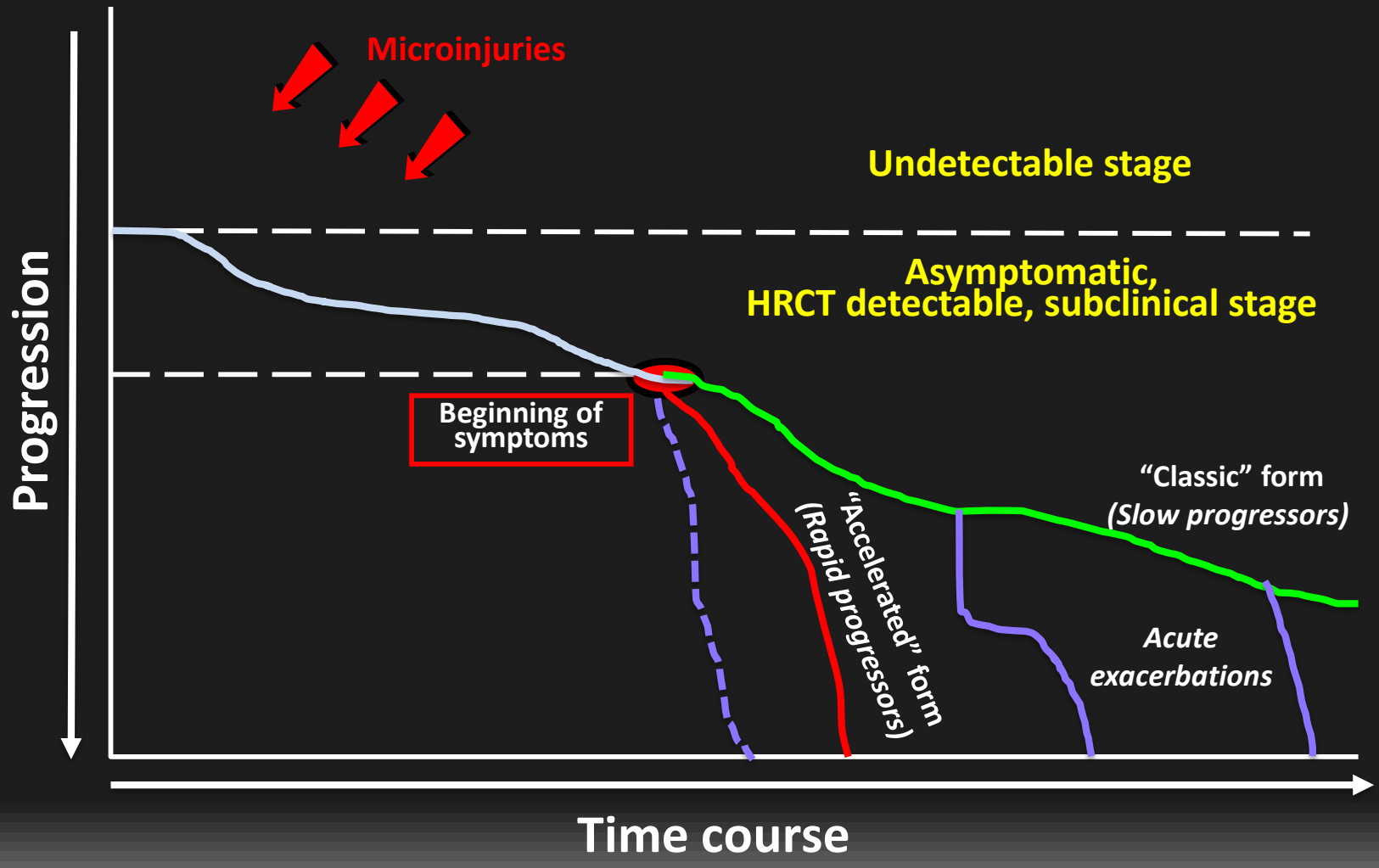
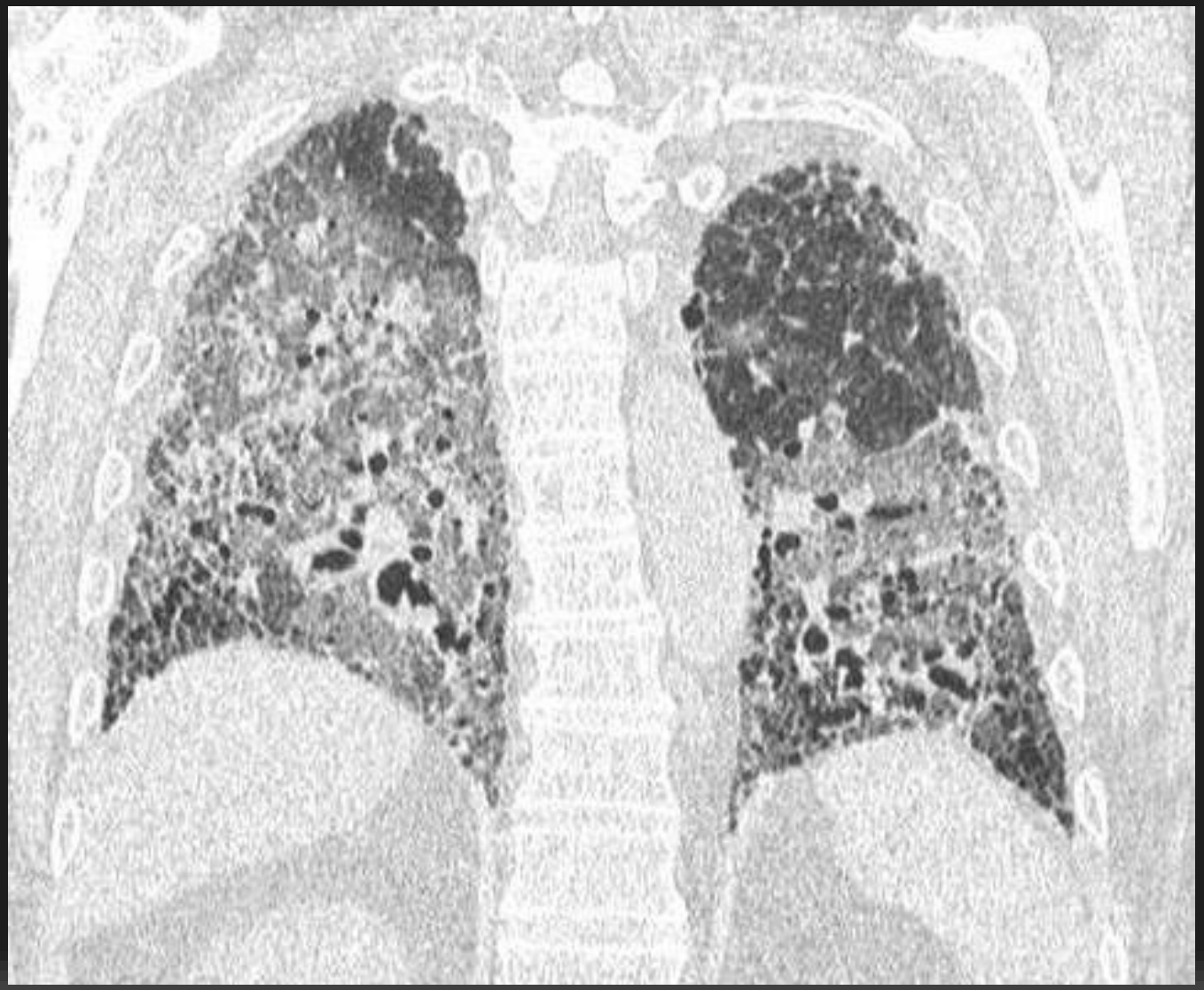

FIBROTIC LUNG
NORMAL LUNG


FIBROBLASTIC FOCUS

NATURAL HISTORY OF IPF

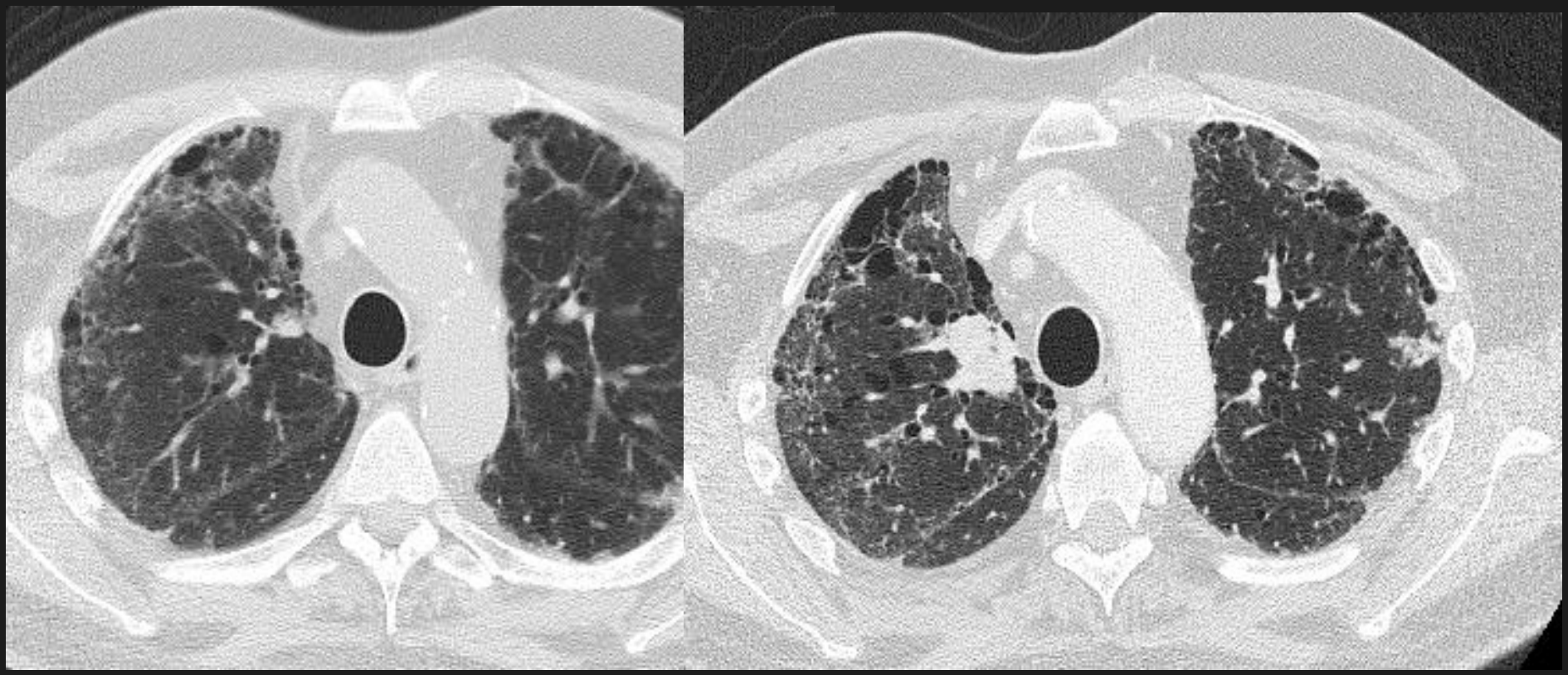


Modified from Selman et al. PLoS One 2007;2(5):e482



October 2016

December 2017



TREATMENT

American Thoracic Society

Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment

International Consensus Statement

THIS JOINT STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS), AND THE EUROPEAN RESPIRATORY SOCIETY (ERS) WAS ADOPTED BY THE ATS BOARD OF DIRECTORS, JULY 1999 AND BY THE ERS EXECUTIVE COMMITTEE, OCTOBER 1999

The authors thank Drs. Thomas Colby, David Hansell, Masanori Kitaichi, and William Travis for their critical review of the manuscript.

This statement was prepared by an ad-hoc committee of the Assembly on Clinical Problems. Members of the committee are:

TALMADGE E. KING, JR., M.D., *Chair*
ULRICH COSTABEL, M.D.
JEAN-FRANÇOIS CORDIER, M.D.
GUILLERMO A. DOPICO, M.D.
ROLAND M. DU BOIS, M.D.
DAVID LYNCH, M.B.
JOSEPH P. LYNCH, III, M.D.
JEFFREY MYERS, M.D.
RALPH PANOS, M.D.
GANESH RAGHU, M.D.
DAVID SCHWARTZ, M.D.
CECILIA M. SMITH, D.O.

Am J Respir Crit Care Med 2000; 161: 646-64

Until adequate studies are conducted that define the best treatment for patients with IPF, this committee suggests the following *combined therapy* (corticosteroid and either azathioprine or cyclophosphamide) for those patients who have been given adequate information regarding the merits and pitfalls of treatment and who possess features consistent with a more likely favorable outcome (*see above*):

- *Corticosteroid* therapy (prednisone or equivalent) at a dose of 0.5 mg/kg (lean body weight [LBW]) per day orally for 4 wk, 0.25 mg/kg (LBW) per day for 8 wk, and then tapered to 0.125 mg/kg (ideal body weight [IBW]) daily or 0.25 mg/kg (LBW) every other day as initial therapy for IPF. (Lean body weight is the ideal weight expected for a patient of this age, sex, and height)
- *Azathioprine* at 2–3 mg/kg lean body weight (LBW) per day to a maximum dose of 150 mg/d orally. Dosing should begin at 25–50 mg/d and increase gradually, by 25-mg increments, every 7 to 14 d until the maximum dose is reached

or

- *Cyclophosphamide* at 2 mg/kg LBW per day to a maximum dose of 150 mg/d orally. Dosing should begin at 25–50 mg/d and increase gradually, by 25-mg increments, every 7 to 14 d until the maximum dose is reached

Am J Respir Crit Care Med 2000; 161: 646-64

RECOMMENDATIONS IN THE 2015 IPF GUIDELINES

Agent	2015 guidelines
Anticoagulant	Strong recommendation against use
Combination prednisone/azathioprine/NAC	Strong recommendation against use
Ambrisentan	Strong recommendation against use
Imatinib	Strong recommendation against use
Pirfenidone	Conditional recommendation for use
Nintedanib	Conditional recommendation for use
Macitentan, bosentan	Conditional recommendation against use
Sildenafil	Conditional recommendation against use
Antiacid therapy	Conditional recommendation for use
NAC monotherapy	Conditional recommendation against use

Modified from Raghu G et al. Am J Respir Crit Care Med 2015; 192: e3-e19

PIRFENIDONE

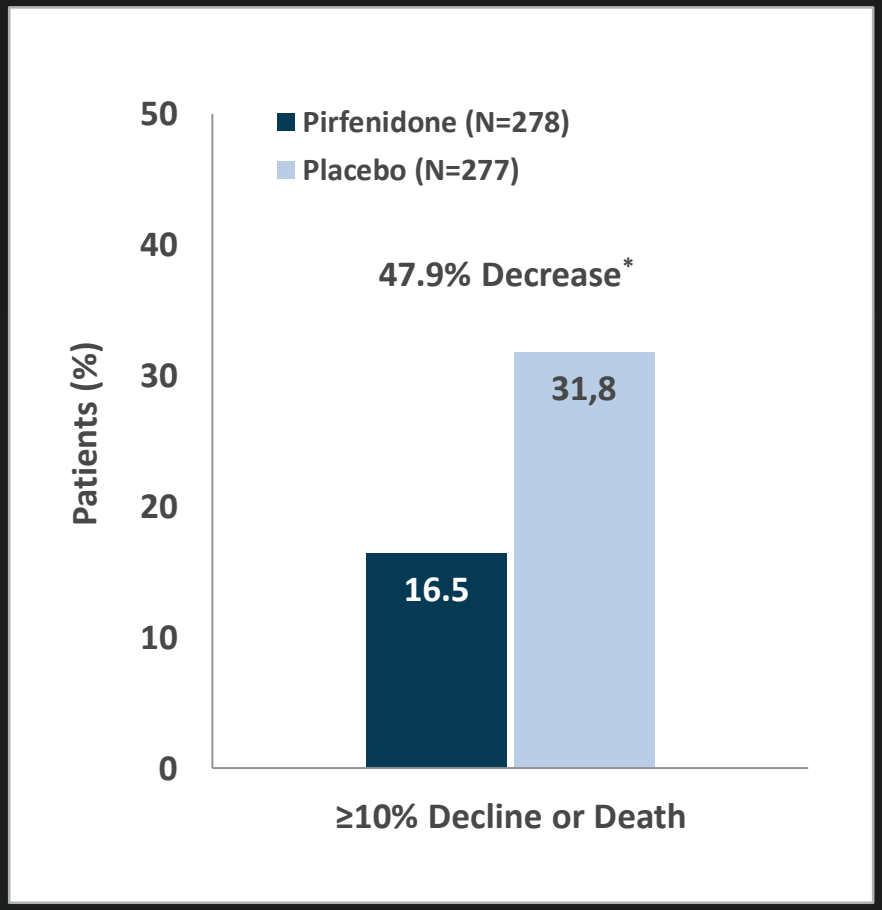
- Pirfenidone is an orally available, synthetic, pyridone compound with anti-inflammatory, anti-oxidant and anti-fibrotic properties

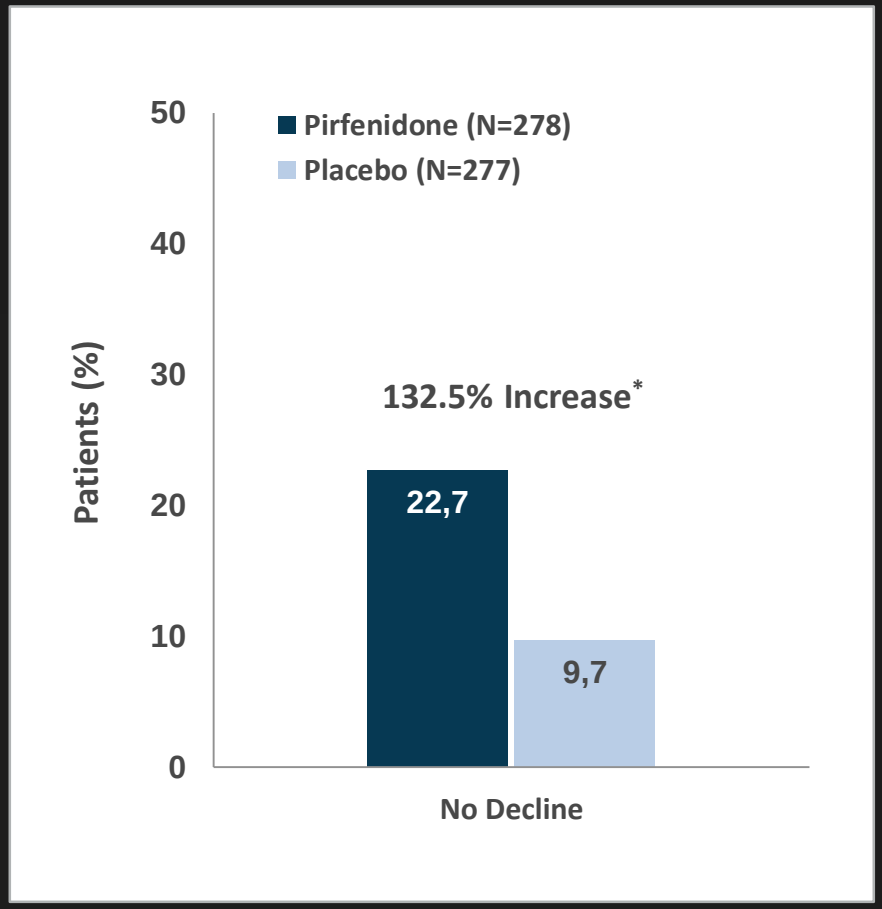
- The mechanism of action is only partially understood

- The drug is believed to act on multiple pathways, with *in vitro* cell-based studies and *in vivo* studies in animal models of pulmonary fibrosis providing insight into its anti-fibrotic activity

Oku H et al. Eur J Pharmacol 2008: 590: 400-8; Kim ES, Keating GM. Drugs 2015; 75: 219-30

PRIMARY EFFICACY ANALYSIS: %FVC CHANGE AT WEEK 52





* Rank ANCOVA P-value <0.000001

King TE Jr et al. N Engl J Med 2014; 370: 2083-92

ADVERSE EVENTS MORE COMMON IN THE PIRFENIDONE ARM AND REPORTED IN AT LEAST 10% OF PATIENTS

Adverse event	Pirfenidone (n = 278)	Placebo (n = 277)
Nausea	100 (36.0%)	37 (13.4%)
Rash	78 (28.1%)	24 (8.7%)
Dyspepsia	49 (17.6%)	17 (6.1%)
Anorexia	44 (15.8%)	18 (6.5%)
Vomiting	36 (12.9%)	24 (8.7%)
Decrease in weight	35 (12.6%)	22 (7.9%)
Gastroesophageal reflux	33 (11.9%)	18 (6.5%)
Insomnia	31 (11.2%)	18 (6.5%)

King TE Jr et al. N Engl J Med 2014; 370: 2083-92; Lancaster L et al. BMJ Open Respir Res 2016; 3: e000105

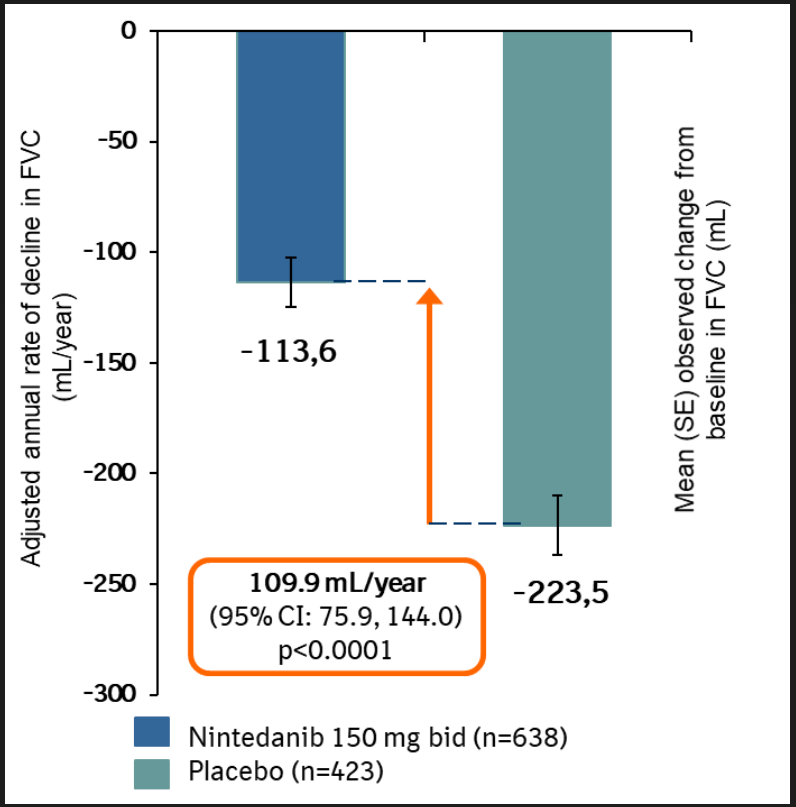
NINTEDANIB

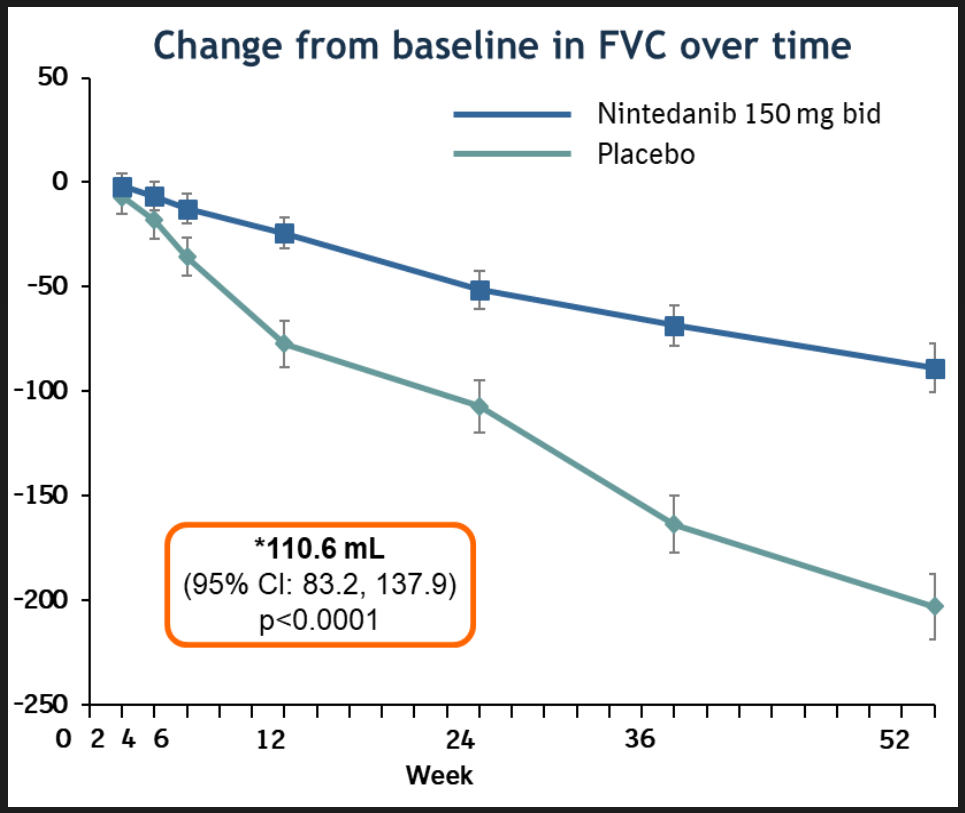
- Nintedanib is an orally available, small molecule, tyrosine kinase inhibitor originally developed for cancer
- It acts primarily downstream of FGF, PDGF and VEGF, which are all involved in the pathogenesis of IPF
- Nintedanib blocks the intracellular signaling needed for the proliferation, migration and differentiation of lung fibroblasts to myofibroblast, thus reducing extracellular matrix deposition
- The efficacy of nintedanib in IPF has been evaluated in two phase III RCTs

FGF: fibroblast growth factor; PDGF: platelet-derived growth factor; VEGF: vascular endothelial growth factor

Wollin L et al. Eur Respir J 2015; 45: 2071-1434

NINTEDANIB – ANNUAL RATE OF DECLINE IN FVC





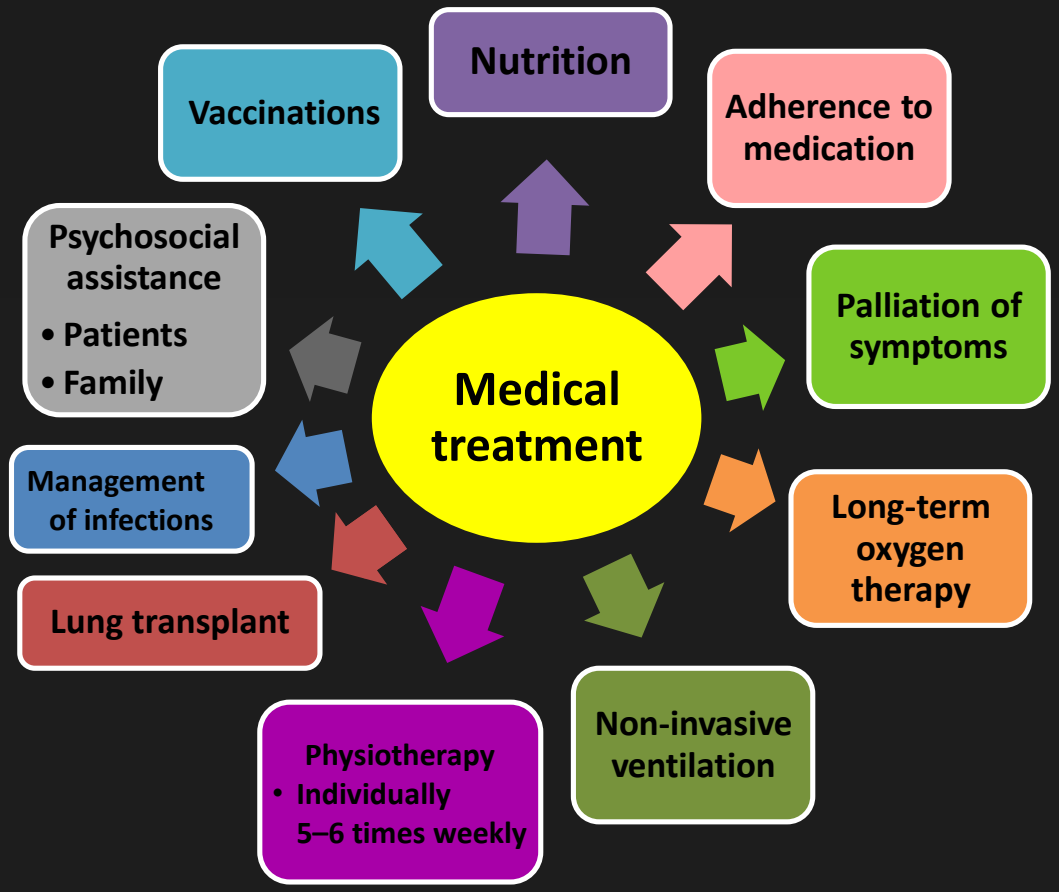
Richeldi L et al. N Engl J Med 2014; 370: 2071-82; Richeldi L et al. Respir Med 2016; 113: 74-9

ADVERSE EVENTS MORE COMMON IN THE NINTEDANIB ARM AND REPORTED IN AT LEAST 10% OF PATIENTS

Adverse event	Nintedanib (n = 638) INPULSIS-1 – INPULSIS-2	Placebo (n = 423) INPULSIS-1 – INPULSIS-2
Diarrhea	62% - 63%	19% - 18%
Nausea	23% - 26%	6% - 7%
Decreased appetite	8% - 13%	7% - 5%
Vomiting	13% - 10%	2% - 3%
Decrease in weight	8% - 11%	6% - 1%

Richeldi L et al. N Engl J Med 2014; 370: 2071-82

THE HOLISTIC APPROACH



Spagnolo P et al. Frontiers in Medicine 2018; 5: 148

CONCLUSIONS

- IPF IS A DEADLY DISEASE THAT REMAINS LARGELY UNDERDIAGNOSED
- THE APPROVAL OF PIRFENIDONE AND NINTEDANIB HAS CHANGED THE LANDSCAPE OF TREATMENT OF IPF
- THIS REMARKABLE ACHIEVEMENT SHOULD BE SEEN AS “THE END OF THE BEGINNING”