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Approach to Diagnosis and Management of Interstitial Lung Disease : Changing Landscape

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No Conflicts Of Interest

Objectives

1. Review the diagnostic approach to a patient with ILD

2. Identify the indications for surgical lung biopsy

3. Recognize the newer treatment options available for Idiopathic Pulmonary Fibrosis

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PULMONARY FIBROSIS

(literally "scarring of the lungs")

is responsible for

40,000 deaths each year–

the same number

as breast cancer.

We help the world breathe®

PULMONARY • CRITICAL CARE • SLEEP

#Breathtember #ThoracicFact

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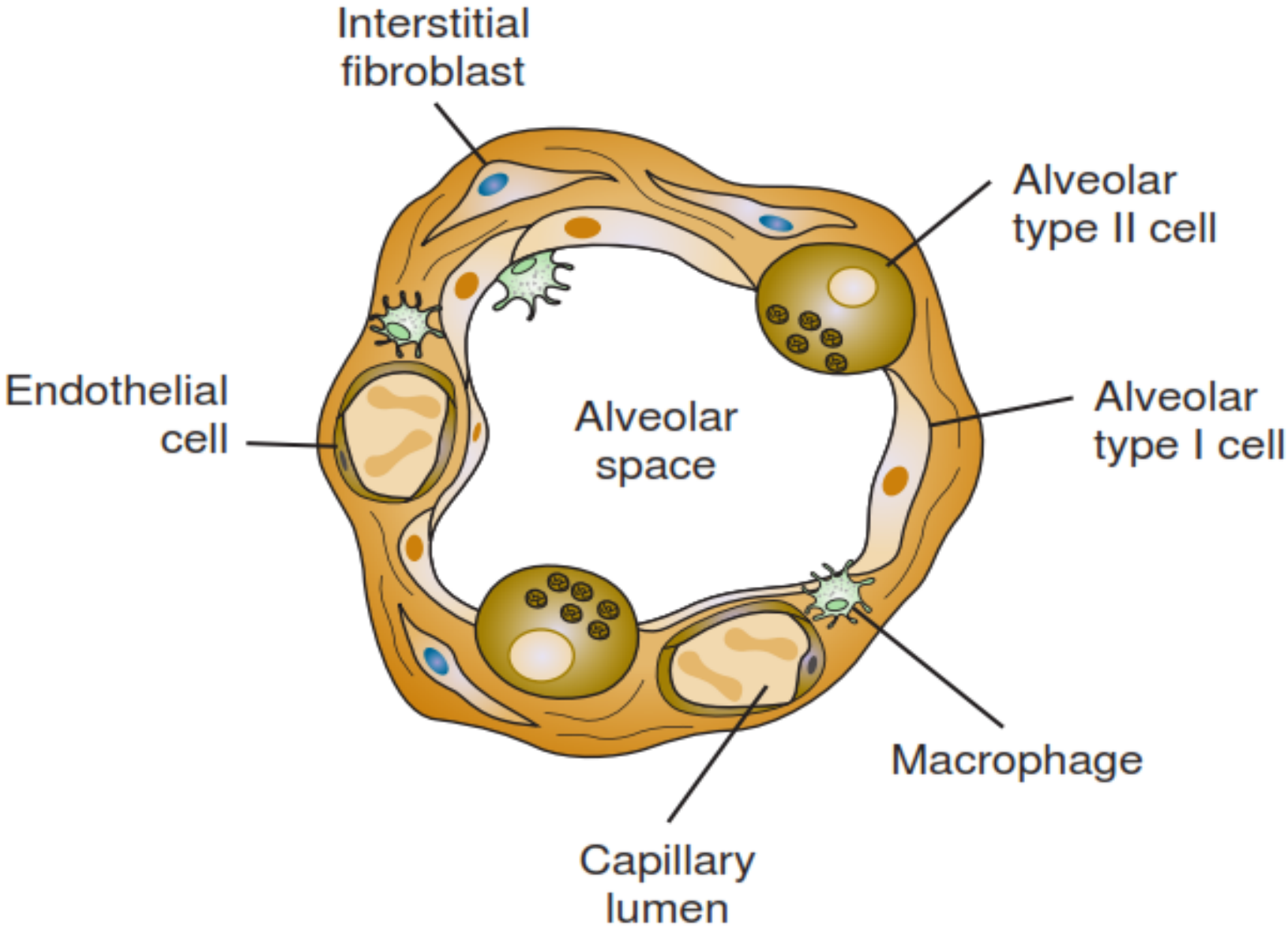
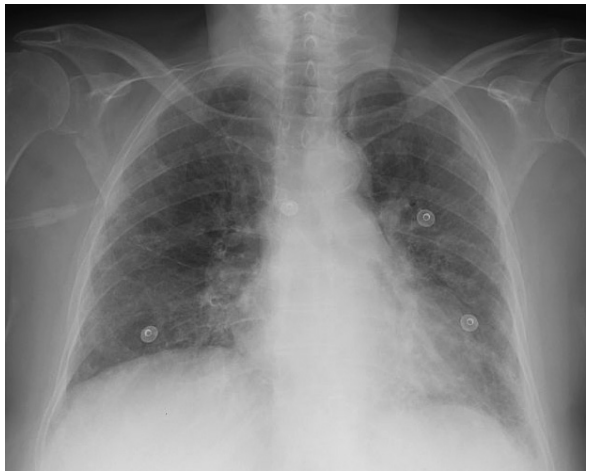
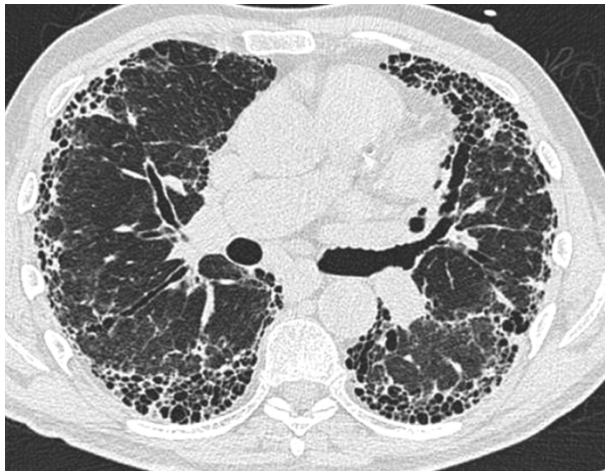

Interstitial fibroblast
Alveolar type II cell
Endothelial cell
Alveolar space
Alveolar type I cell
Macrophage
Capillary lumen



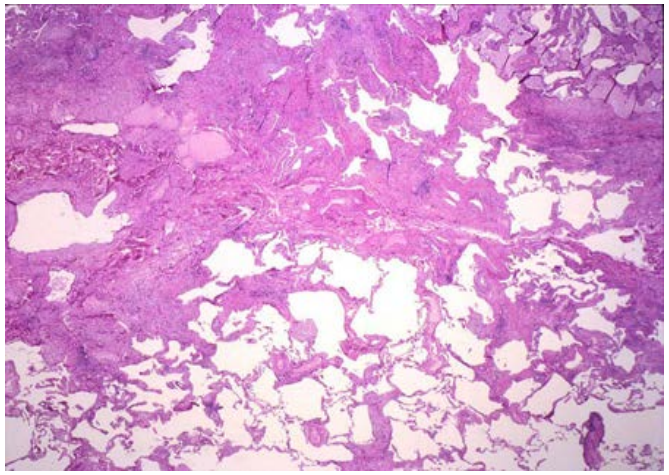
Exposures

- Drugs
- Hypersensitivity pneumonitis – bird, molds
- Radiation
- Infections



Connective tissue Diseases

- Rheumatoid arthritis
- Lupus
- Scleroderma
- Sjogren's syndrome
- Mixed connective tissue disease



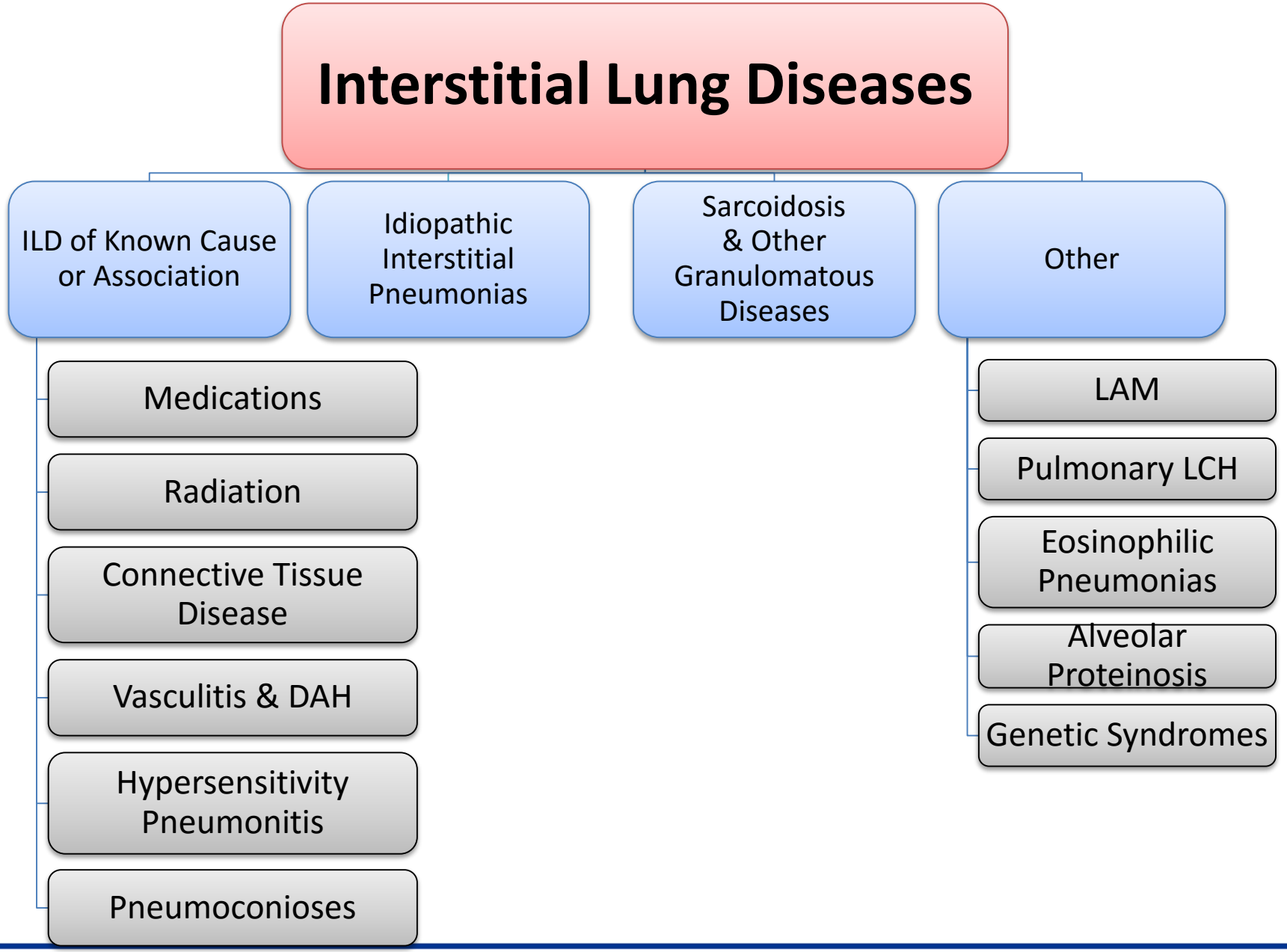
Genetic

- FPF

Idiopathic

- Sarcoidosis
- IIP

Interstitial Lung Diseases



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

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REVISED ATS/ERS CLASSIFICATION OF IDIOPATHIC INTERSTITIAL PNEUMONIAS: MULTIDISCIPLINARY DIAGNOSES

Major idiopathic interstitial pneumonias

Idiopathic pulmonary fibrosis
Idiopathic nonspecific interstitial pneumonia
Respiratory bronchiolitis–interstitial lung disease
Desquamative interstitial pneumonia
Cryptogenic organizing pneumonia
Acute interstitial pneumonia

Rare idiopathic interstitial pneumonias

Idiopathic lymphoid interstitial pneumonia
Idiopathic pleuroparenchymal fibroelastosis

Unclassifiable idiopathic interstitial pneumonias*

W Travis . AJRCCM 2013;188,733–748

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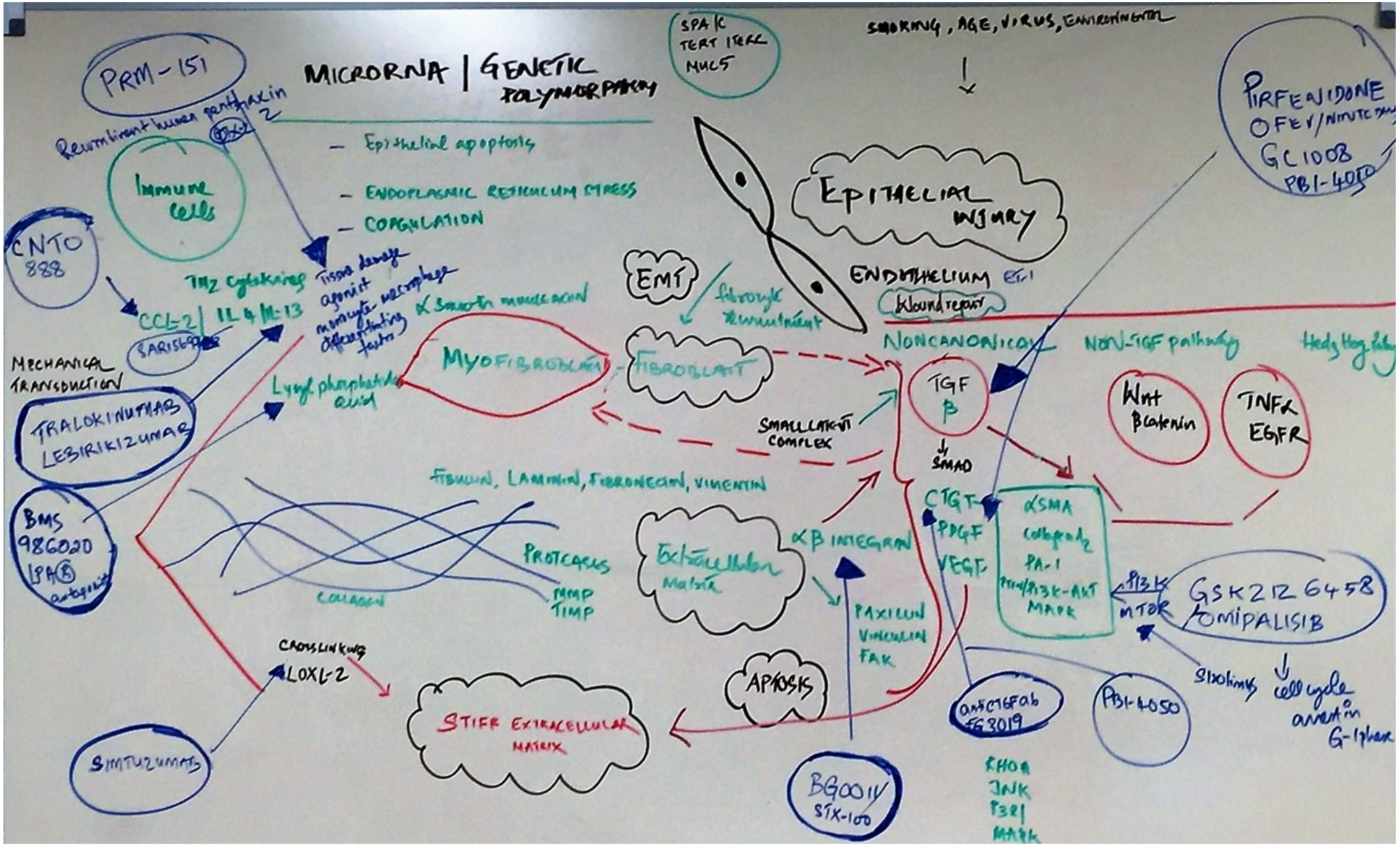
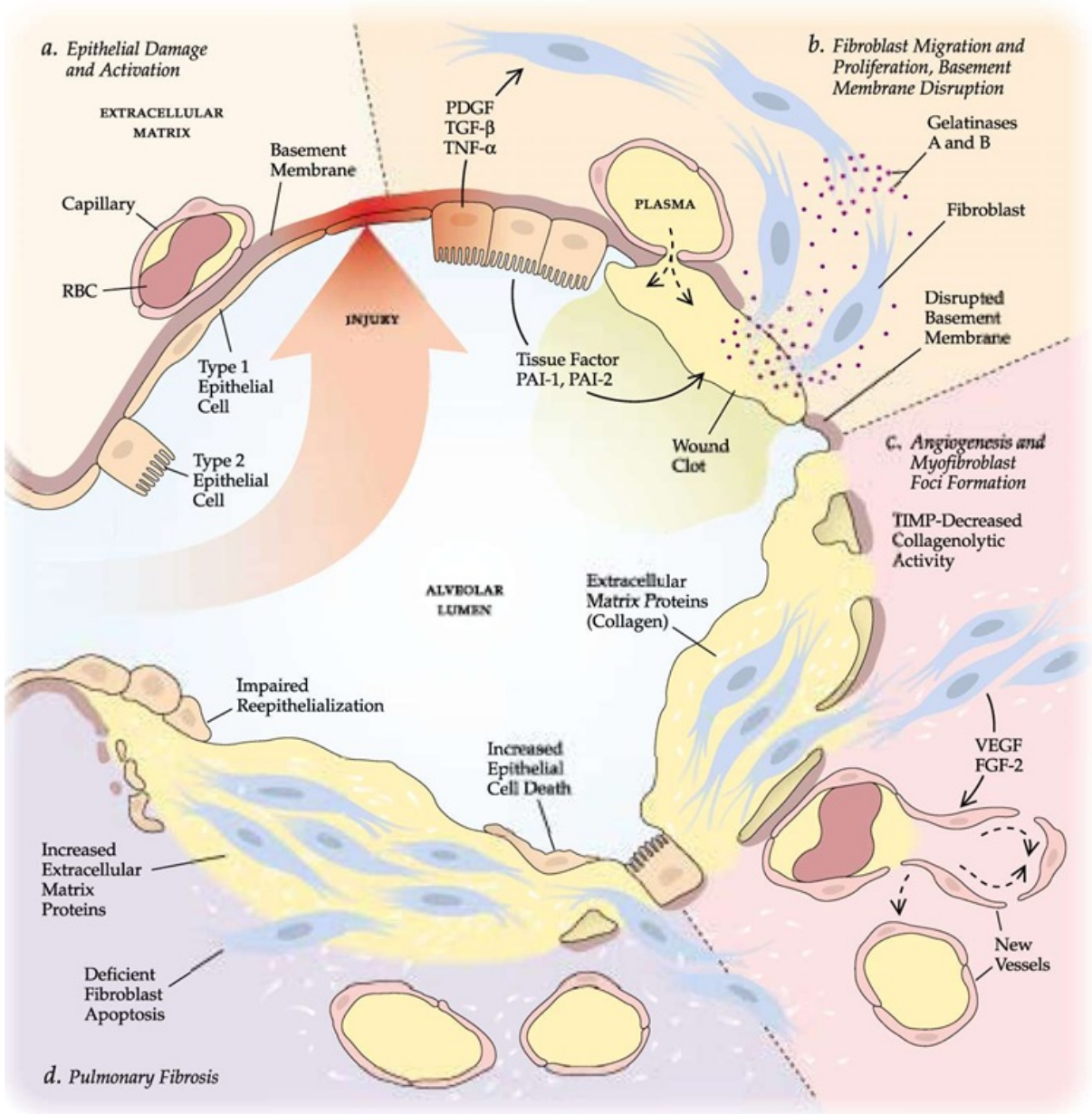
Disease Mechanisms


PRM-151
Recombinant human pentraxin 2
MICRORNA | GENETIC POLYMORPHISM
SPARC TERT TERC MUC5
SMOKING, AGE, VIRUS, ENVIRONMENTAL
PIRFENIDONE
OFEV/NINTEDANIB
GC1008
PBI-4050
Immune cells
Epithelial apoptosis
ENDOPLASMIC RETICULUM STRESS
COAGULATION
EPITHELIAL INJURY
CNTO 888
Th2 cytokines
CCL-2
IL-4 IL-13
SARILUMAB
Tissue damage agonist
monocyte macrophage differentiating factors
α Smooth muscle actin
EMT
fibrocyte recruitment
ENDOTHELIUM
Blood report
MECHANICAL TRANSDUCTION
TRALOKINUMAB
LEBRIKIZUMAB
Lysyl phosphatidic acid
MYOFIBROBLAST
FIBROBLAST
NONCANONICAL
NON-TGF pathway
Hedgehog
TGF β
Wnt β catenin
TNFα EGFR
SMALL LATENT COMPLEX
SMAD
FIBULIN, LAMININ, FIBRONECTIN, VIMENTIN
BMS 986020
LPA1 antagonist
CTGF
PDGF
VEGF
αSMA
collagen I
PA-1
PI3K-AKT MAPK
PROTEASES
MMP
TIMP
COLLAGEN
Extracellular Matrix
αβ INTEGRIN
PAXILLIN
VINCULIN
FAK
PI3K
MTOR
GSK2126458
OMIPALISIB
CROSSLINKING
LOXL-2
APOPTOSIS
STIFF EXTRACELLULAR MATRIX
SIMTUZUMAB
BG00111
STX-100
ANTI CTGF Ab FG3019
PBI-4050
sirolimus
cell cycle arrest in G-1 phase
RHOA
JNK
P38
MAPK



S. Puglisi. Semin Respir Crit Care Med 2016;37,358–367.

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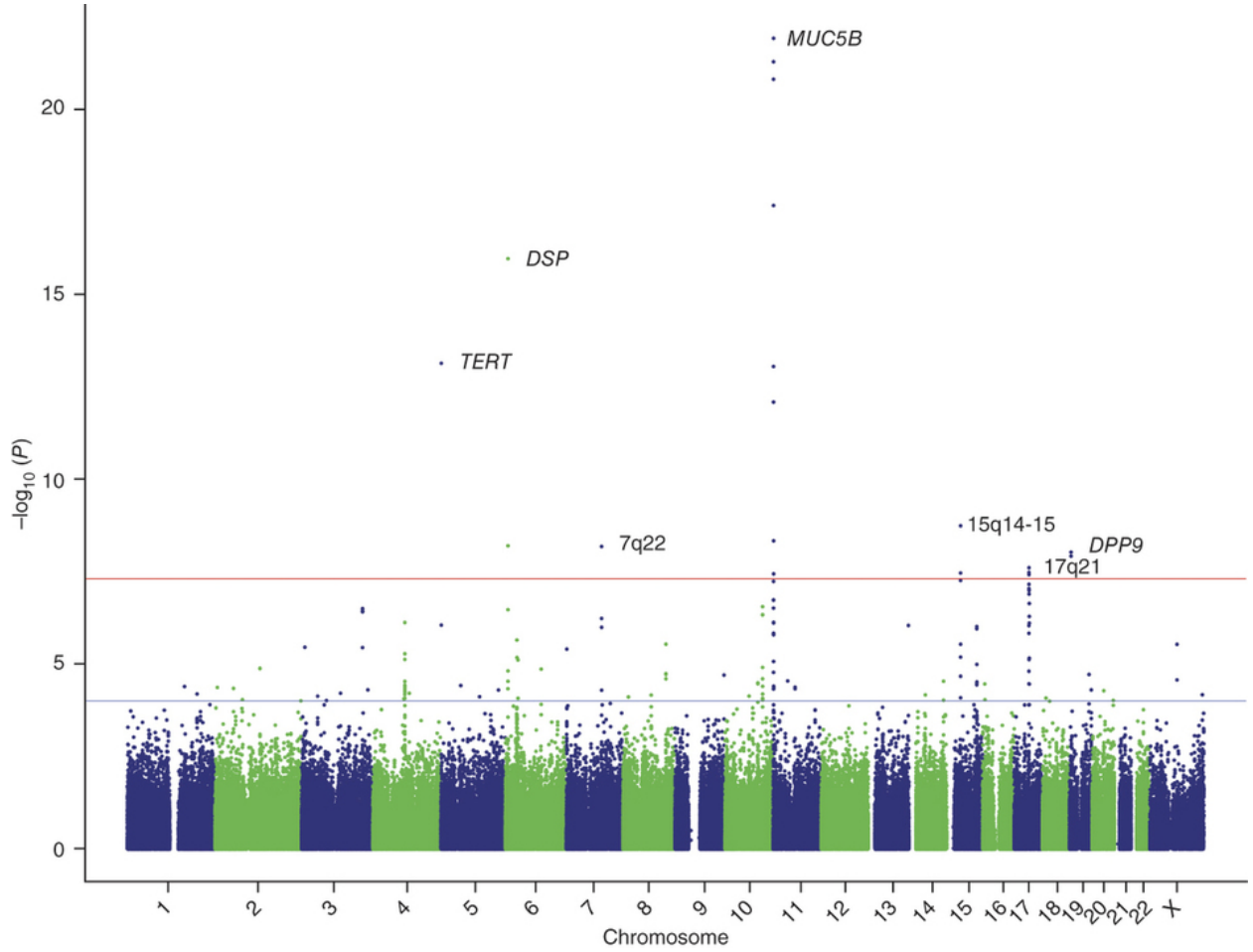
Genetics



Fingerlin et al Nat Genet. 2013; 45, 613–620

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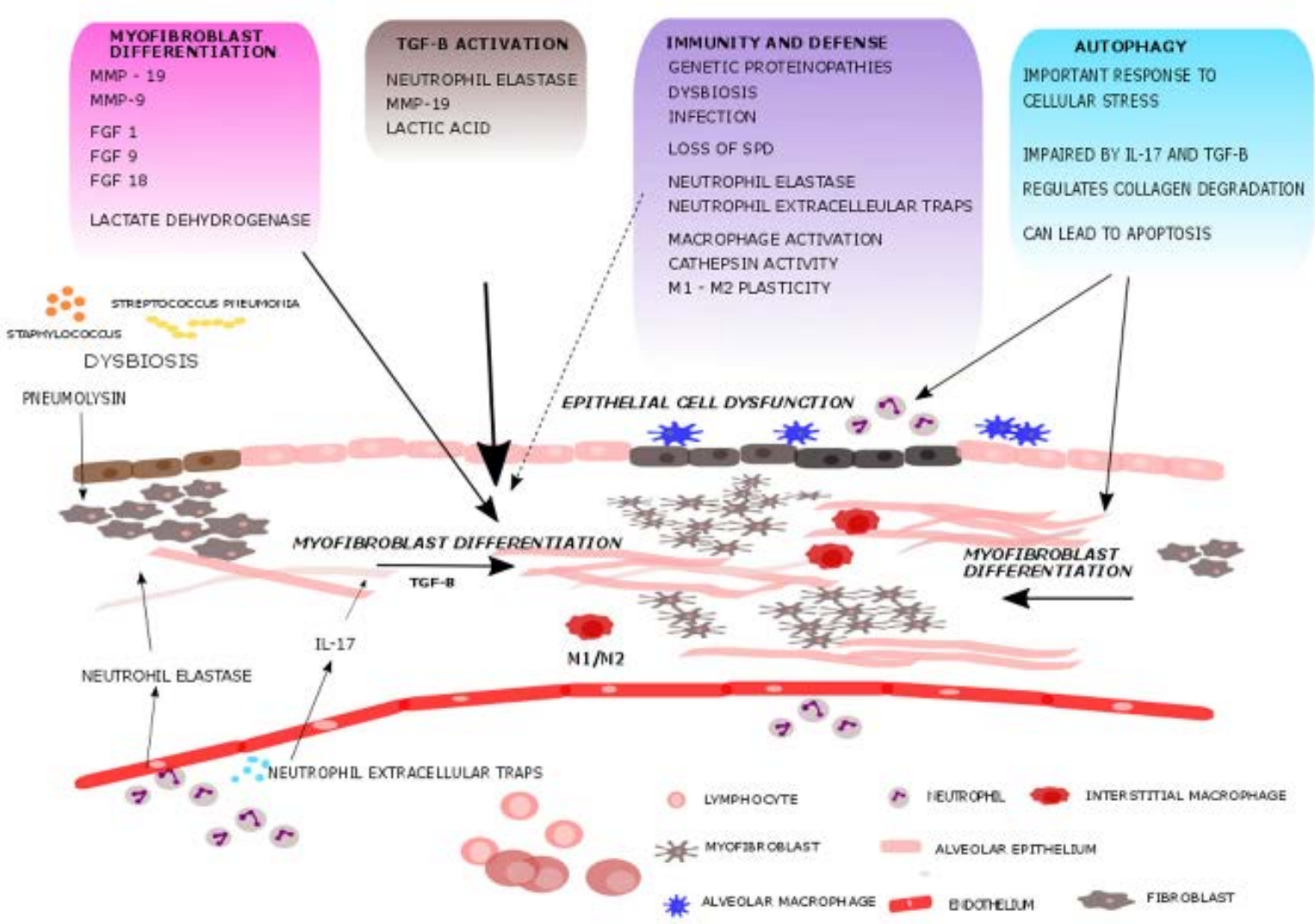
Influences of Innate Immunity



D. O'Dwyer. Am J Physiol Lung Cell Mol Physiol (July 29, 2016)

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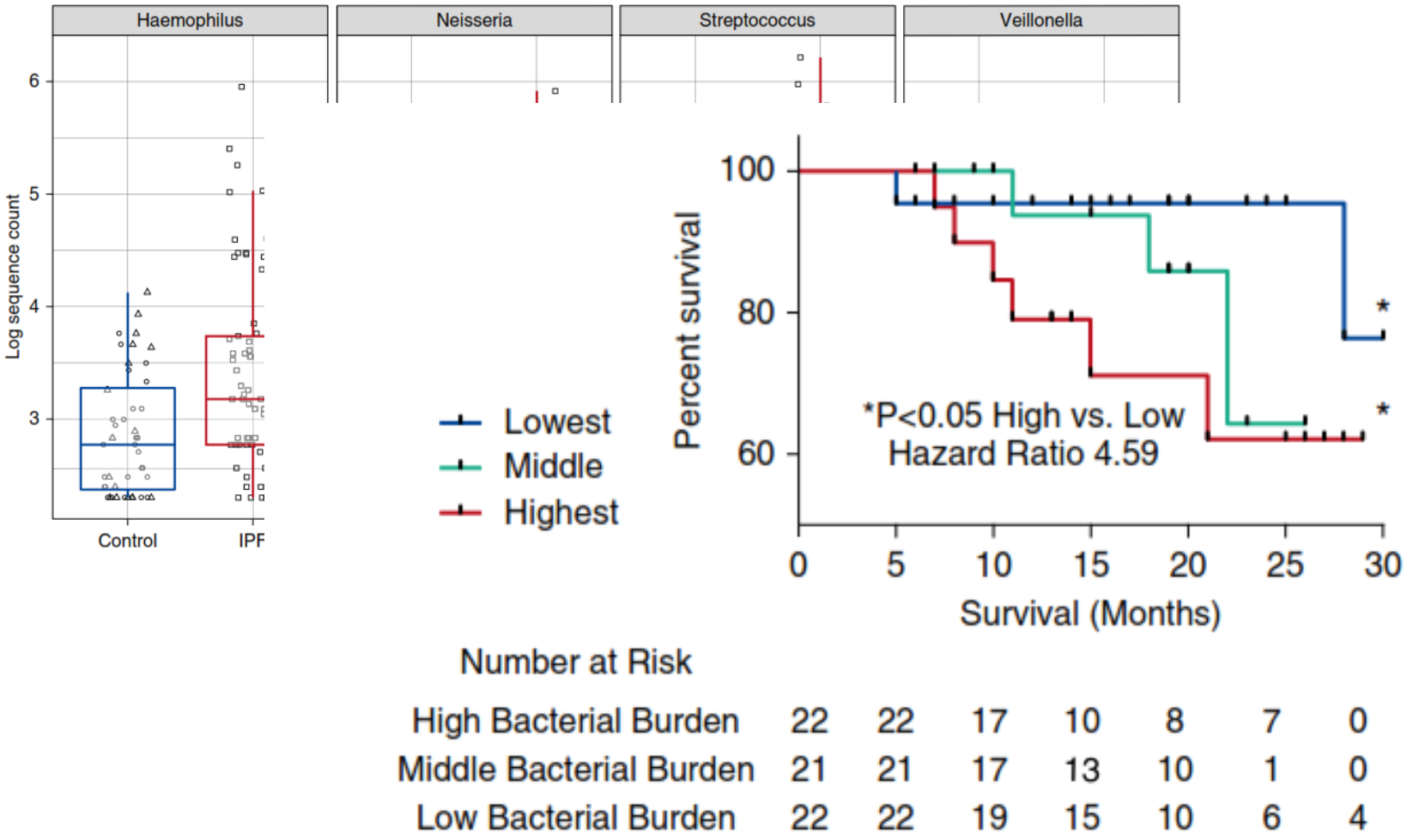
Role of Bacteria in the Pathogenesis and Progression of IPF



Molyneaux. AJRCCM 2014; 190, 906–913

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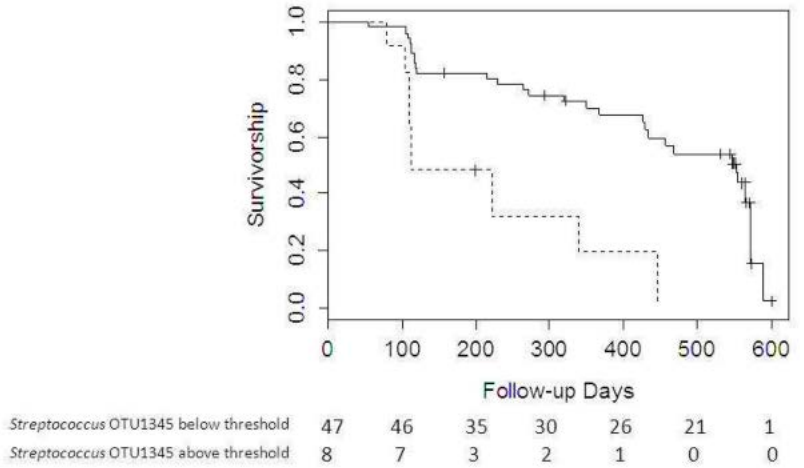
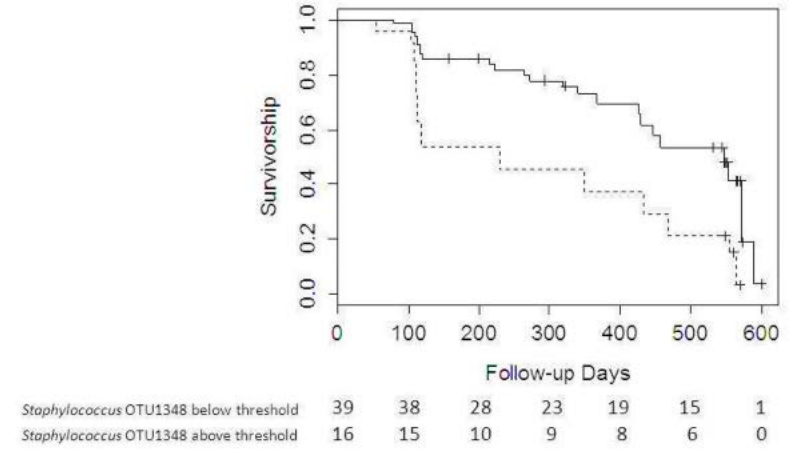
Lung Microbiome





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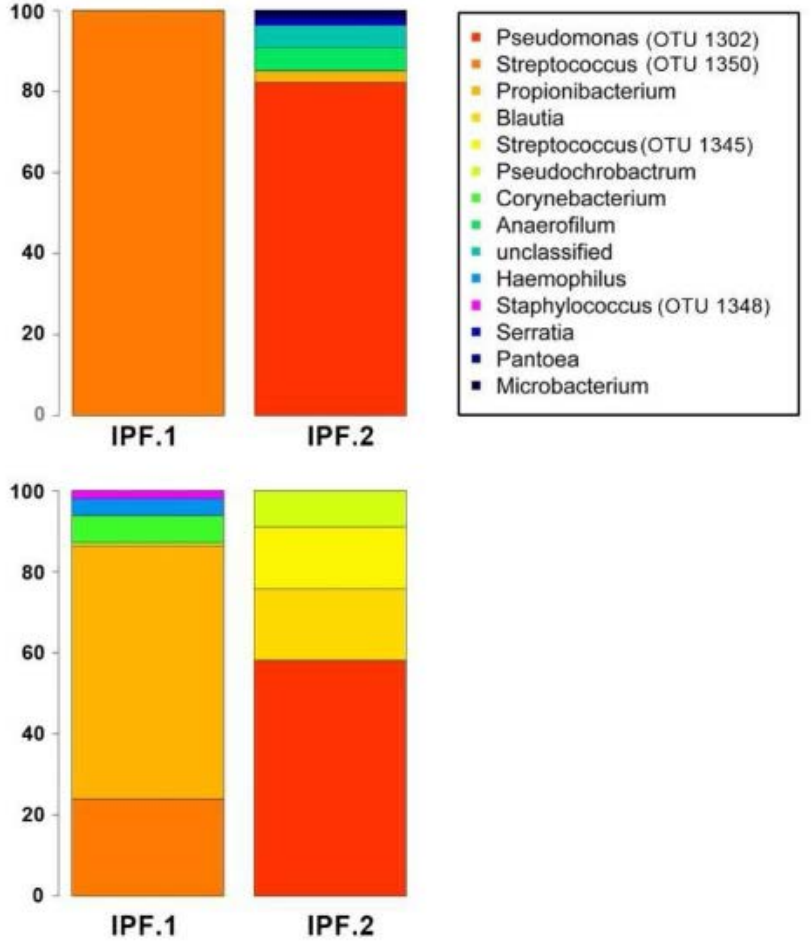

M. Han, F. Martinez. Lancet Respir Med 2014; 2, 548–556

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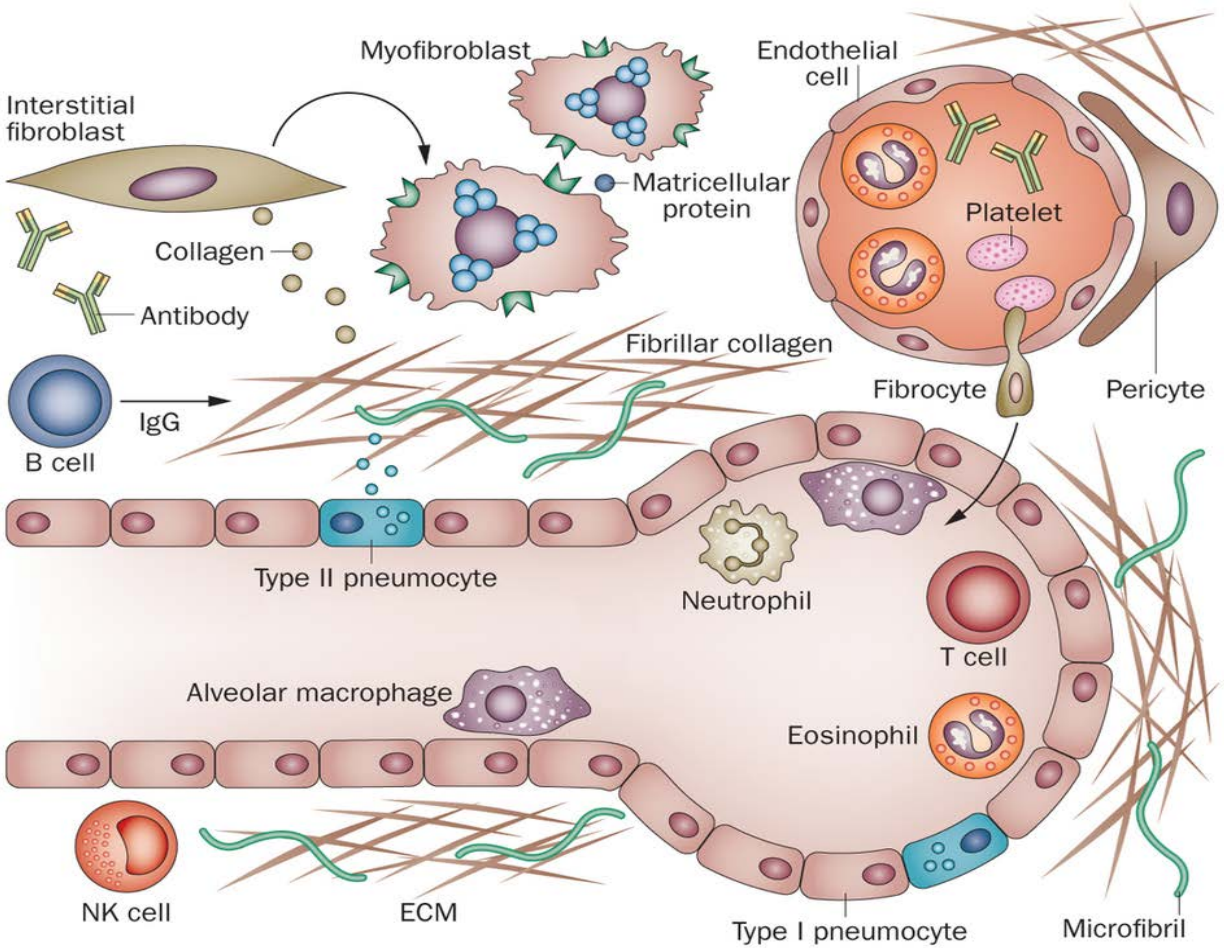
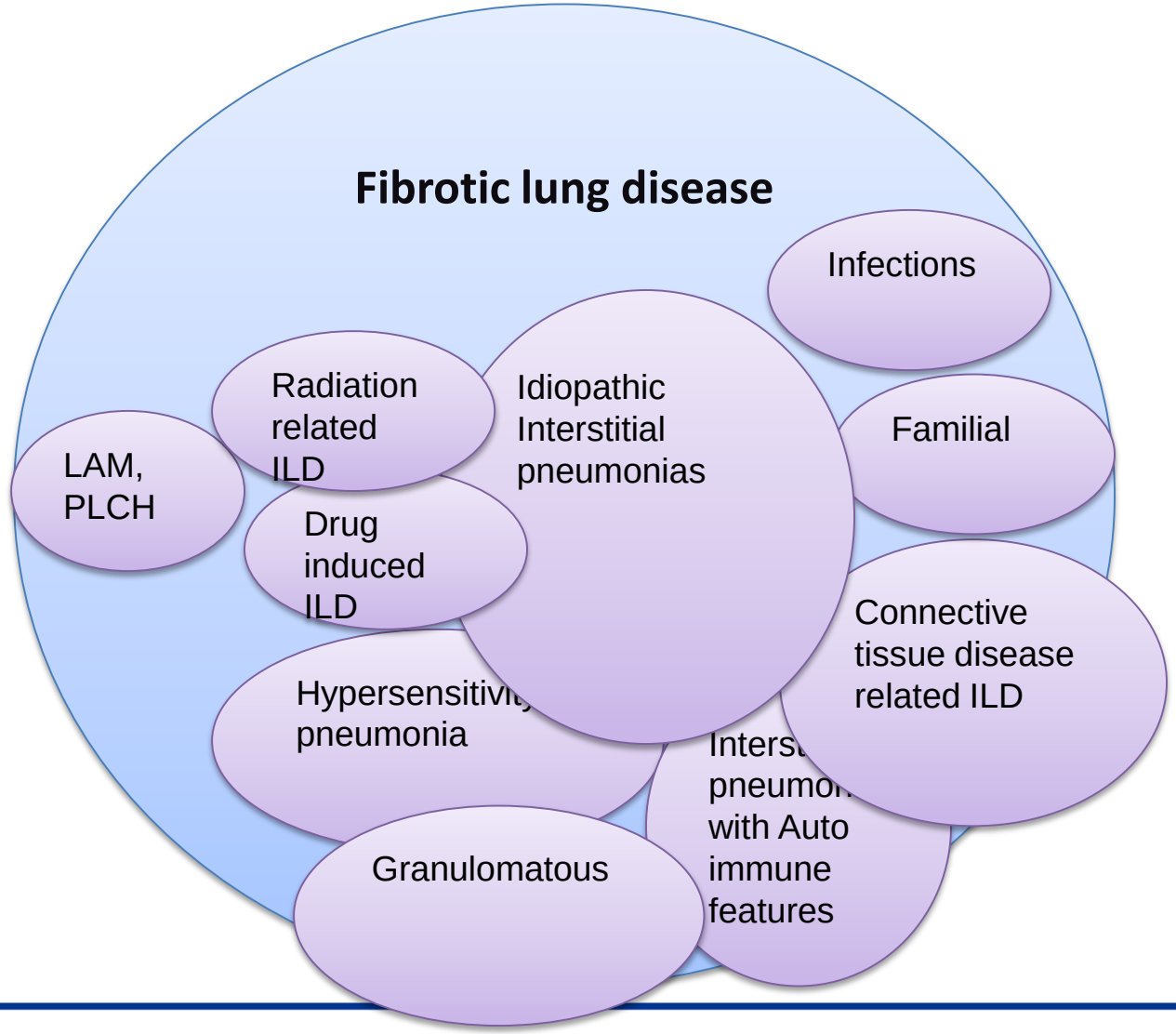
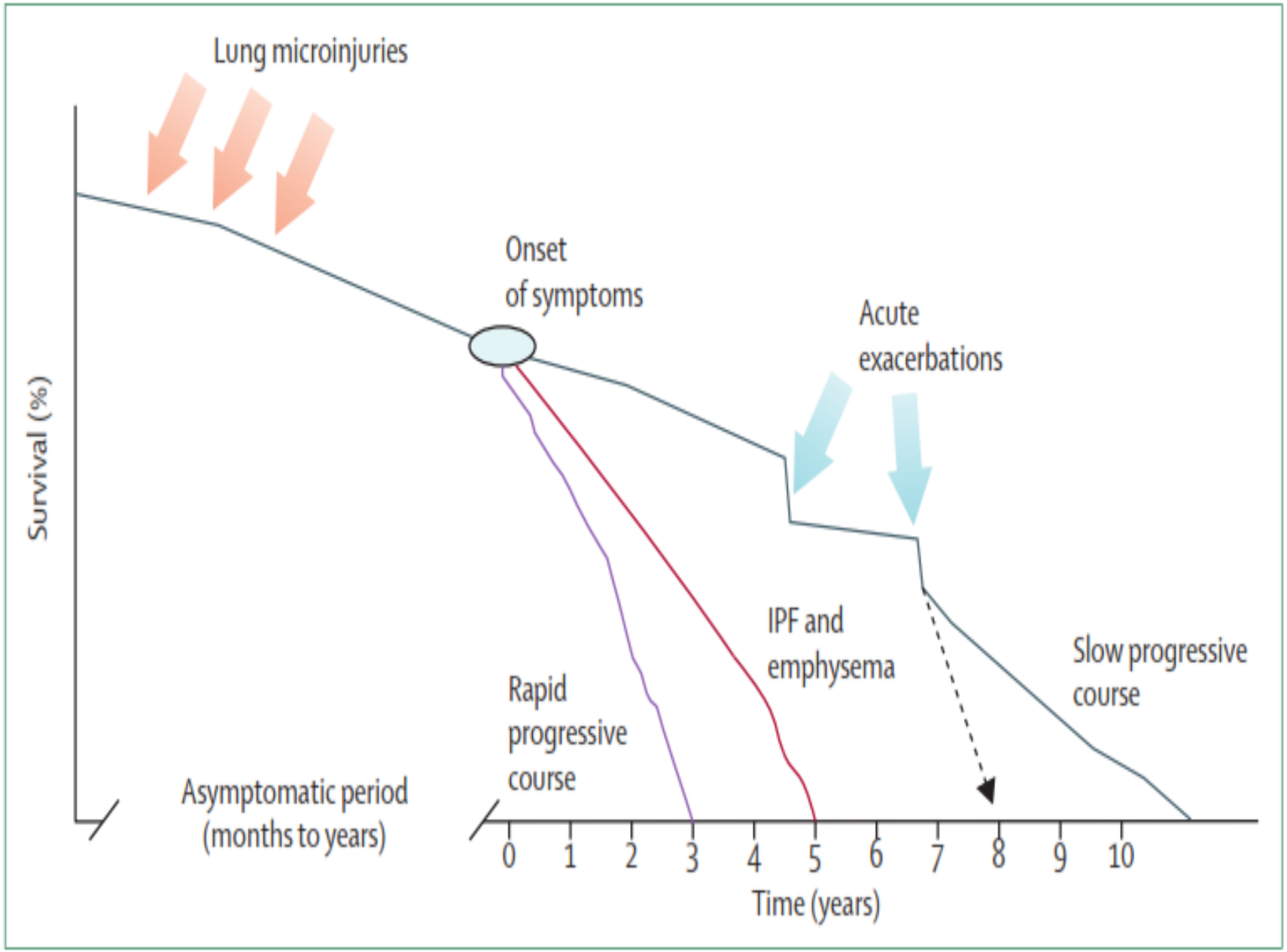

Myofibroblast
Interstitial fibroblast
Matricellular protein
Endothelial cell
Platelet
Collagen
Antibody
Fibrillar collagen
Fibrocyte
Pericyte
IgG
B cell
Type II pneumocyte
Neutrophil
T cell
Alveolar macrophage
Eosinophil
NK cell
ECM
Type I pneumocyte
Microfibril
Pathogenic stages
Initiation
Epithelial damage
Endothelial activation
Immune-cell infiltration
Inflammation
Progression
Fibroblast proliferation
Fibrocyte recruitment
Epithelial–mesenchymal transition
Ongoing epithelial damage
Failed resolution
Myofibroblast persistence
Altered matricellular interaction
Perturbed epithelial repair
Ongoing epithelial damage

Diagnosis


Fibrotic lung disease
Infections
Radiation related ILD
Idiopathic Interstitial pneumonias
Familial
LAM, PLCH
Drug induced ILD
Connective tissue disease related ILD
Hypersensitivity pneumonia
Granulomatous
with Auto immune features



King TE. Lancet 2011; 378, 1949–61

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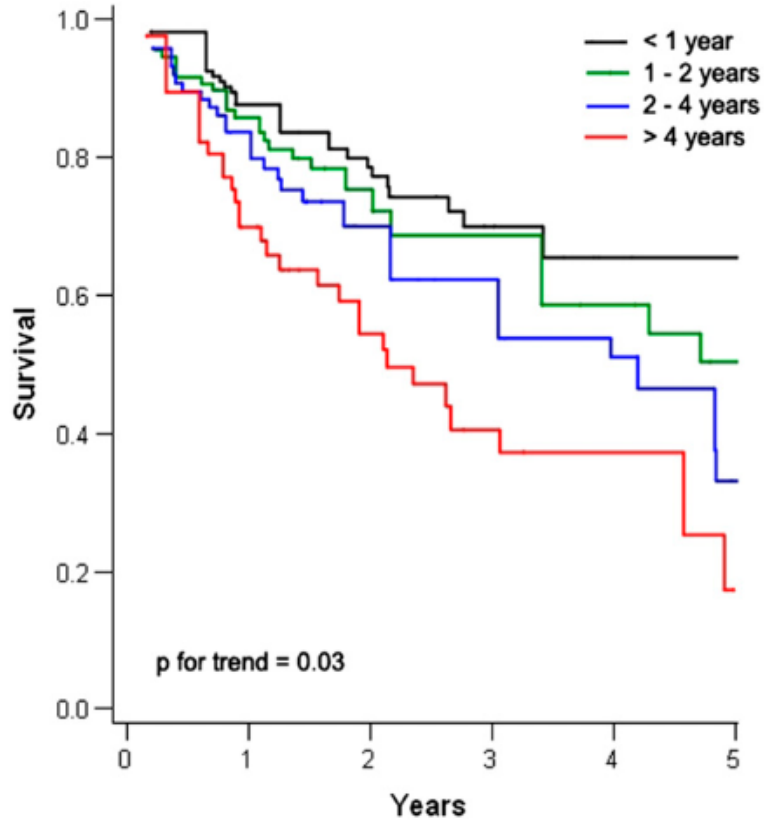
Delayed Access to subspecialty and Survival in IPF

- Prospective cohort study of 129 adults
- Onset of dyspnea to be seen at tertiary care center
- A longer delay was associated with an increased risk of death independent of age, sex, forced vital capacity, third-party payer, and educational attainment



Lamas. AJRCCM 2011; 184, 842–847

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Interstitial Lung Disease

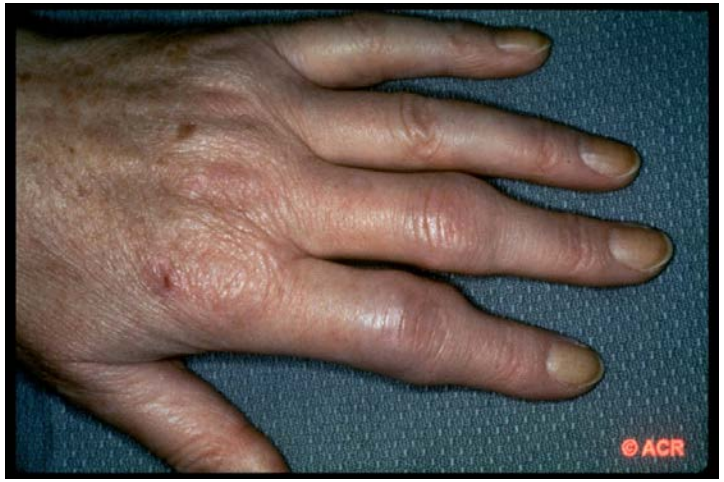
- Clinical context
- Tempo or evolution of the disease
- Radiographic pattern

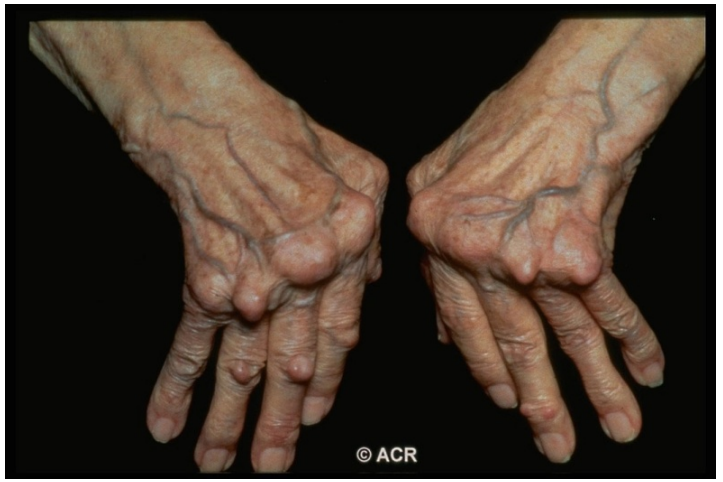
Clinical presentation

- ‘I am feeling tired than usual’
- ‘I used to walk several blocks – but can’t anymore’
- ‘Have this dry cough’
- Examination may show clubbing and inspiratory bibasilar “velcro-like” crackles on auscultation

Physical Examination

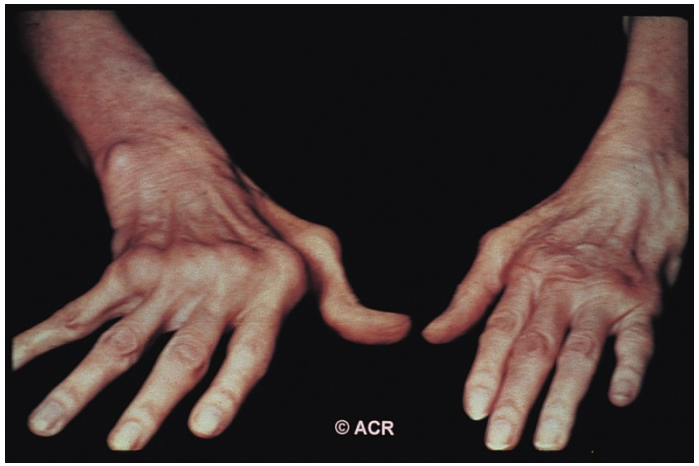
Fusiform Swelling

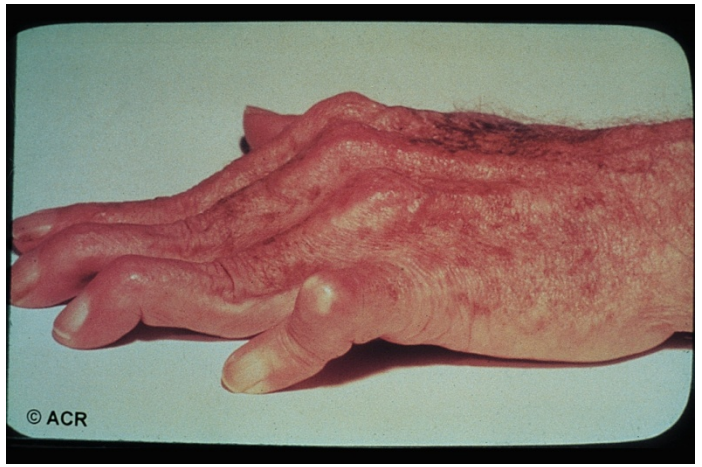




Symmetry

Ulnar Deviation





Swan Neck Deformity

Mixed Connective Tissue Disease

Puffy hands (polyarthritis)
Raynaud's phenomenon
Low blood counts
Myositis- muscle disease

Sjogren's Syndrome

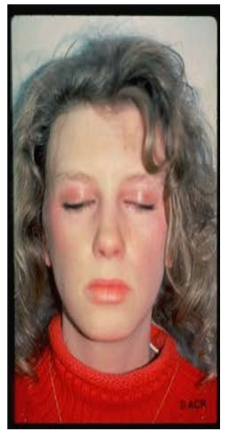
Dry Eyes
Dry Mouth
salivary/parotid swelling

Scleroderma

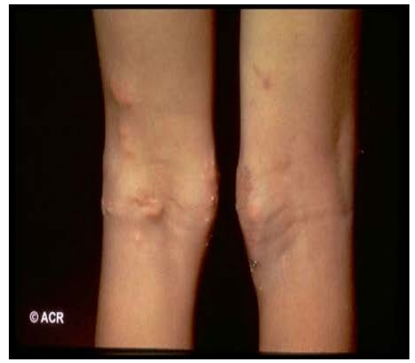
Skin thickening
Joint and tendon contractures
Raynaud's
Distal skin thickening
Calcinosis
Telangiectasia

Polymyositis/Dermatomyositis

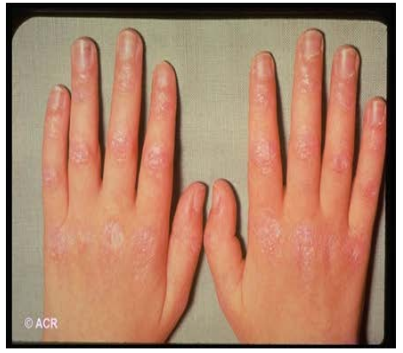
Symmetric, proximal muscle weakness
Dermatologic findings



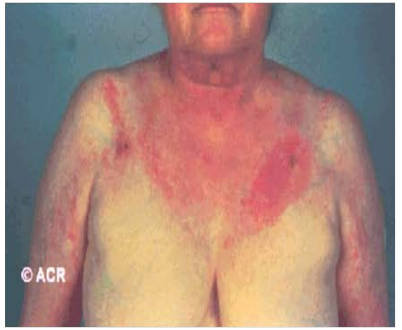
Heliotrope rash



Calcinosis cutis



Gottren's papules



Shawl sign

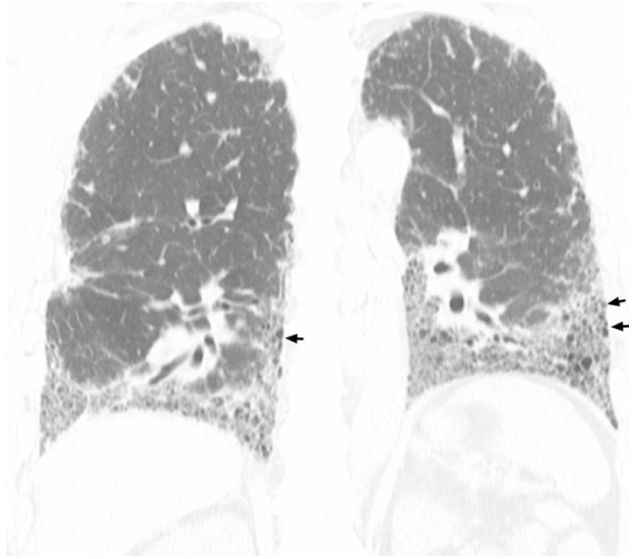
Serological Evaluation

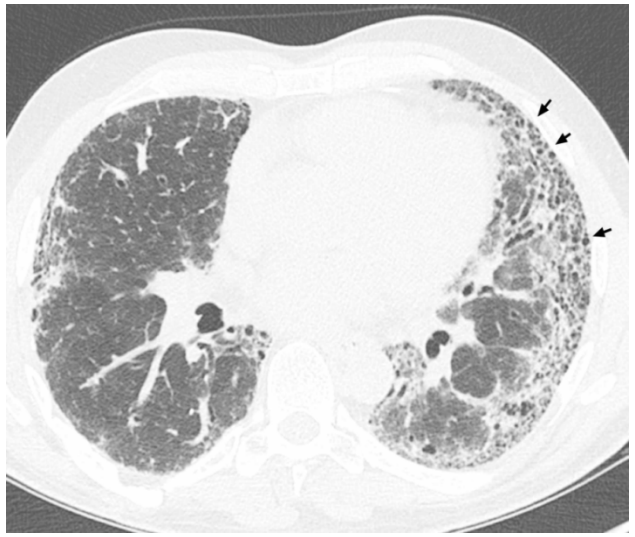
- Performed before surgical biopsy
- 1 step: ANA, RF, CCP, ESR, CRP, Hypersensitivity pneumonitis panel
- Based on history & physical exam:
  - ✓ Extractable nuclear antigen (ENA) autoantibody panel
  - ✓ Anti-centromere antibody
  - ✓ MPO/PR3 (ANCA) antibodies
  - ✓ Anti-cardiolipin antibodies, lupus anticoagulant
  - ✓ Creatine kinase, aldolase

Pulmonary Function study
Six minute walk test
Echocardiogram

UIP Pattern

Inconsistent with UIP Pattern – Any of the 7 features
Upper or mid-lung predominance
Peribronchovascular predominance
Extensive ground glass abnormality (extent > reticular abnormality)
Profuse micronodules (bilateral, predominantly upper lobes)
Discrete cysts (multiple, bilateral, away from areas of honeycombing
Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes)
Consolidation in bronchopulmonary segment(s)/lobe(s)





AJRCM. 2011; 183,788–824

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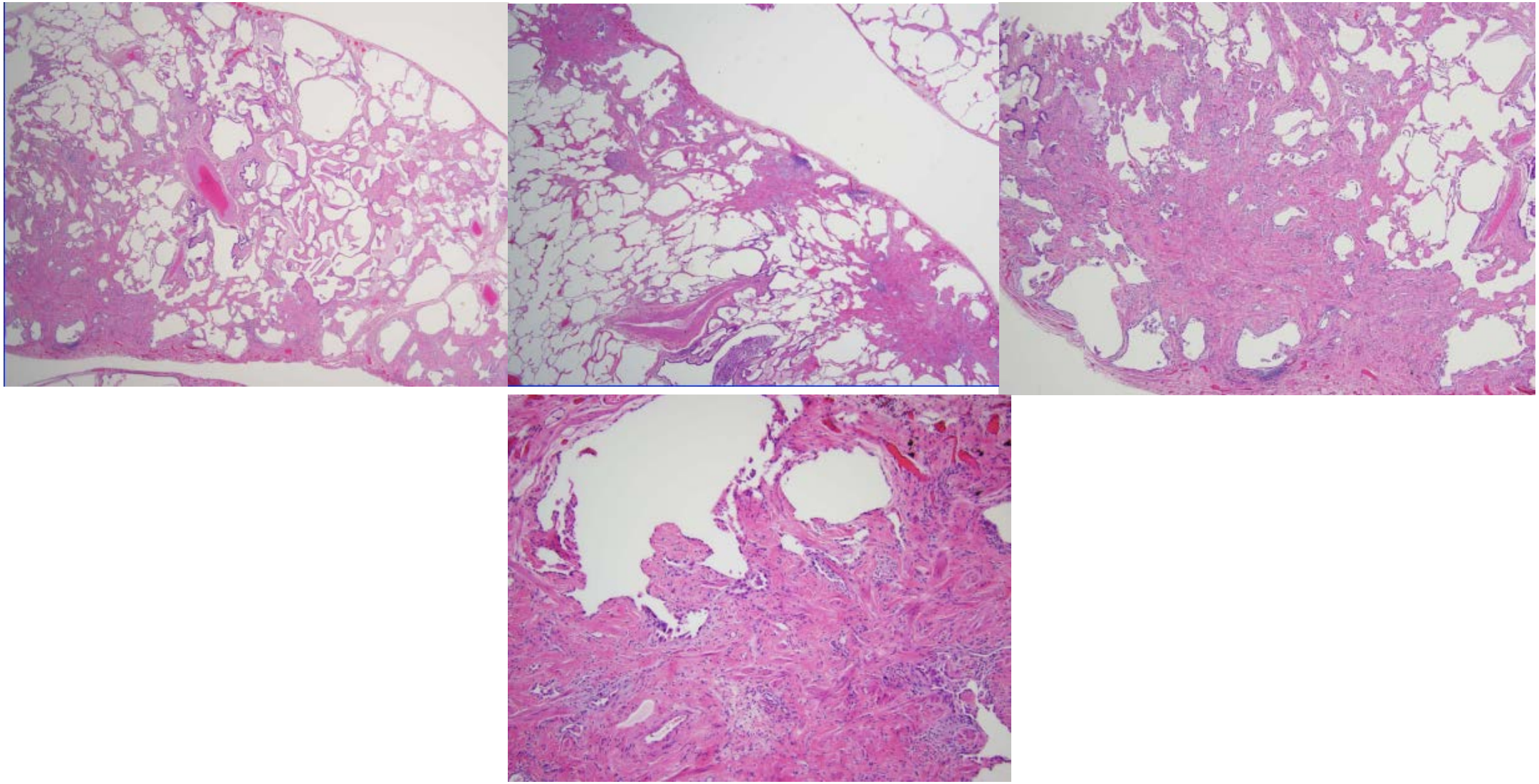
UIP Pattern



AJRCM. 2011; 183.788–824

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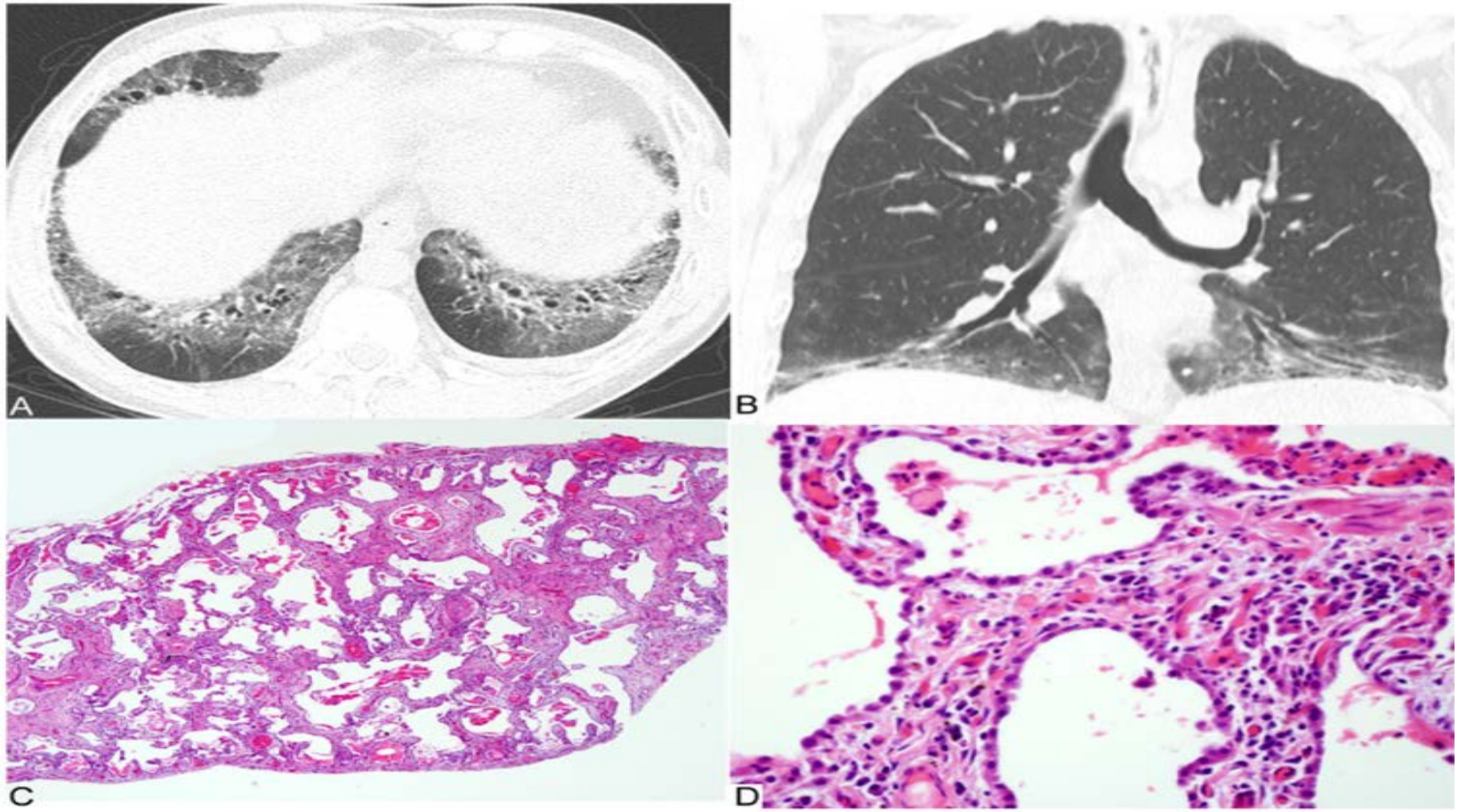
NSIP Pattern



AJRCM. 2011; 183,788–824

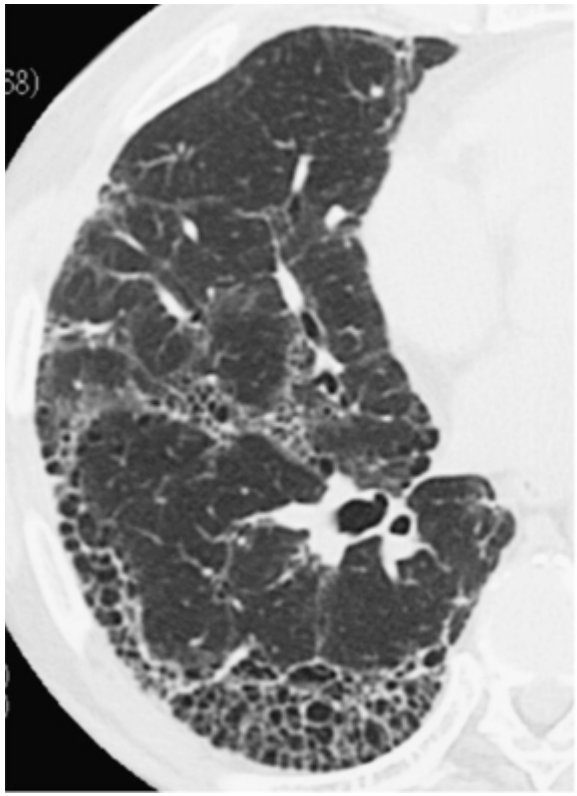
Honeycombing in UIP

- Present in 70-80% of cases of UIP

  Strongest indicator of UIP on CT

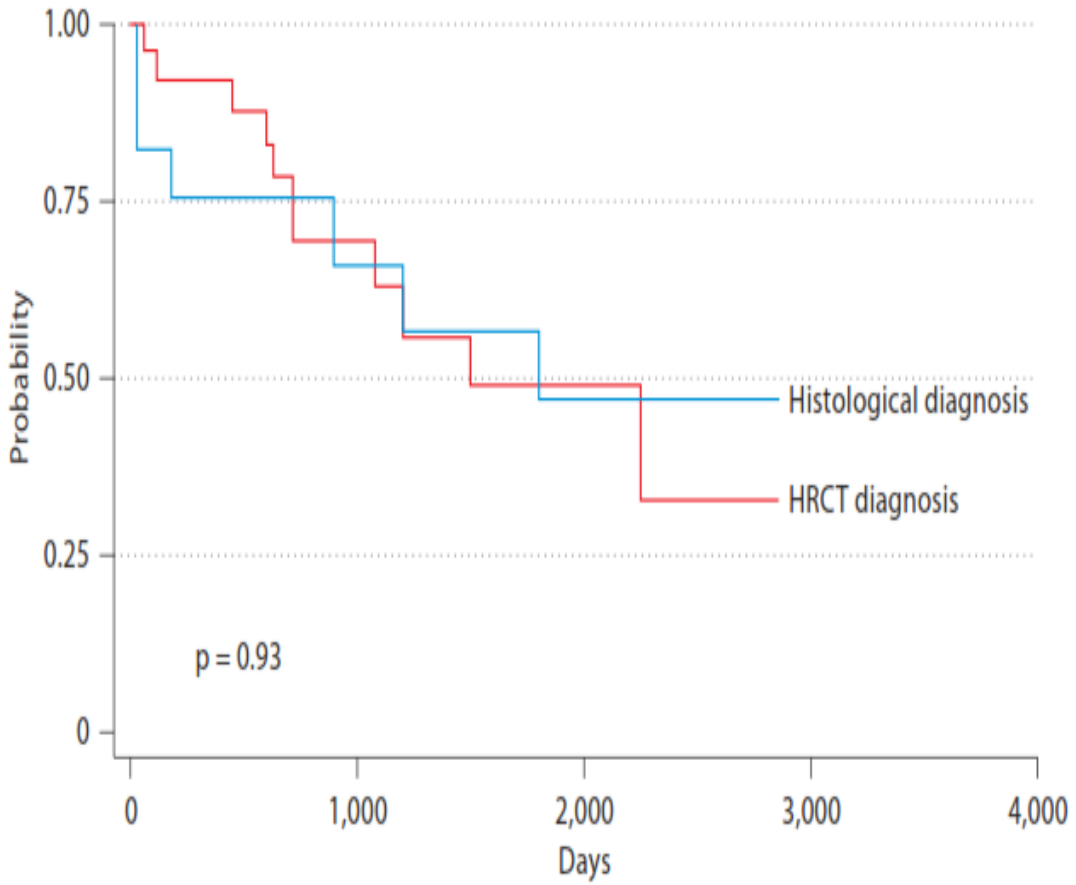
- Median survival

  UIP with honeycombing: 2.1 years
  UIP without honeycombing: 5.8 years



Hunninghake GW, et al. Chest 2003;124:1215-1223.
Elliot TL. J Comput Assist Tomogr 2005;29:339-345.
Flaherty KR, et al. Thorax 2003;58:143-148.

Mortality HRCT diagnosis compared to surgical lung biopsy diagnosis of UIP



5-year survival in months
histological vs. radiological diagnosis

45.4 vs. 34.6%; p = 0.799

Quadrelli Respiration 2010;79,32–37

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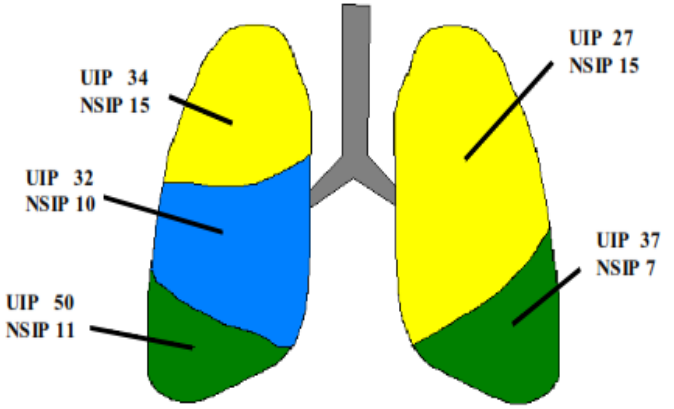
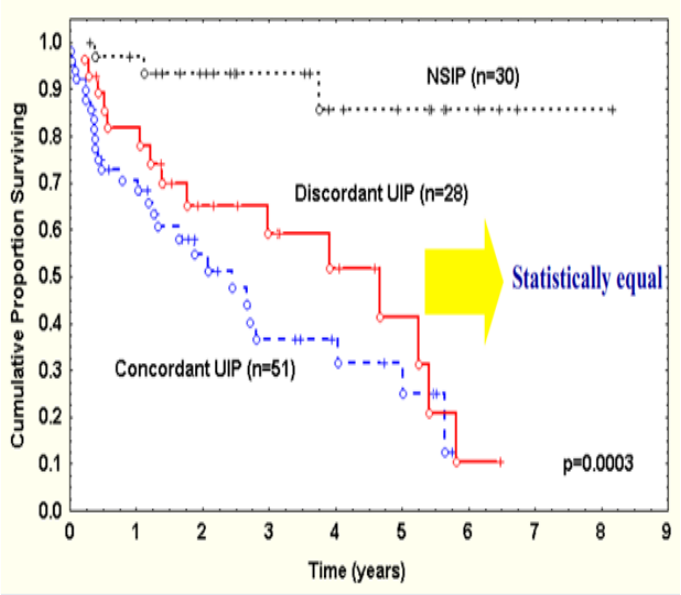
Surgical biopsy – it is important to sample multiple lobes

- SLBs from 168 patients
- 109 patients multiple lobes biopsied
- Reviewed by three pathologists
- Significant intrapatient heterogeneity
- Prognosis in patients with at least one lobe positive for UIP worse compared to non-UIP pattern





Flaherty AJRCCM 2001;164, 1722–27

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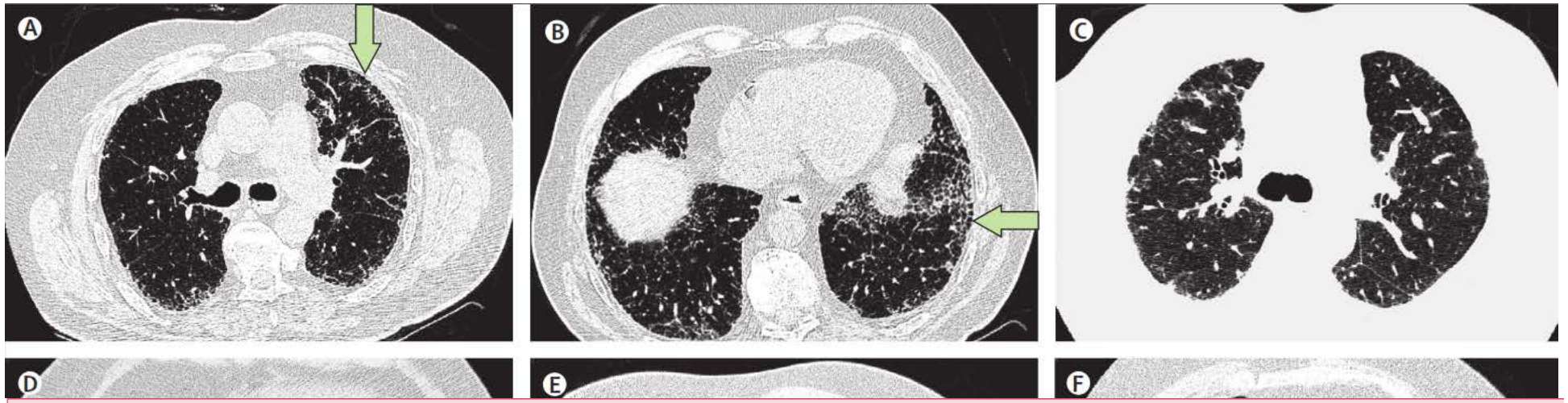
Diagnosis of idiopathic pulmonary fibrosis with high-resolution CT in patients with little or no radiological evidence of honeycombing



	Patients with a concordant histological diagnosis	Patients without a concordant histological diagnosis	Positive predictive value	Negative predictive value
UIP on high-resolution CT (n=111)	108 (84 UIP, 24 probable UIP)	3 (1 possible UIP, 2 not UIP)	108/111 (97·3%, 95% CI 92·3–99·4)*	..
Possible UIP on high-resolution CT (n=84)	79 (65 UIP, 14 probable UIP)	5 (4 possible UIP, 1 not UIP)	79/84 (94·0%, 95% CI 86·7–98·0)*	..
Inconsistent with UIP on high-resolution CT (n=120)	22 (10 possible UIP, 12 not UIP)	98 (76 UIP, 22 probable UIP)	..	22/120 (18·3%, 95% CI 11·9–26·4)*

UIP=usual interstitial pneumonia. *Clopper-Pearson 95% CI.

G Raghu. Lancet Respir Med 2014; 2, 277–84

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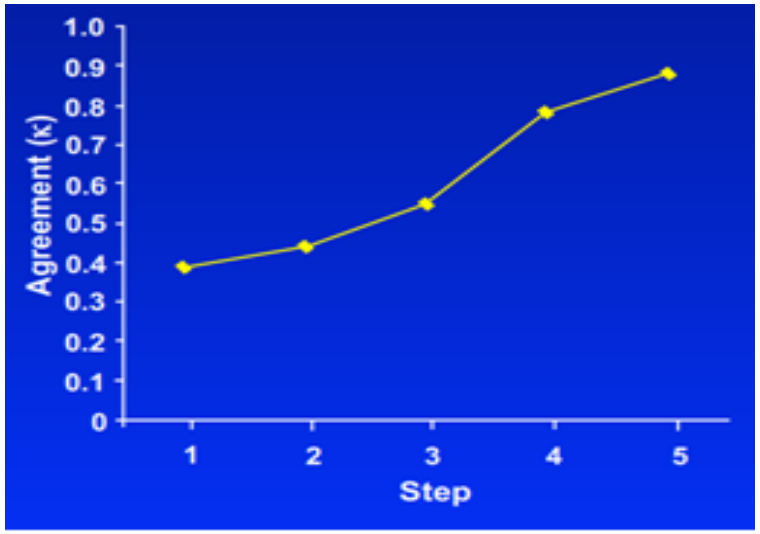
Multidisciplinary approach To IIP Diagnosis

- 58 suspected IIP
- 3 clinicians, 2 radiologists, 2 pathologists
- Information in sequential manner
- Clinicians identified 75% and radiologists 48% of IPF prior to histopathologic information was provided
- Dynamic interactions between specialists improve inter-observer agreement and diagnostic confidence

Information Provided	Participants	Output
Step 1 - Individual HRCT	Clinicians Radiologists	Diagnosis & Confidence Confidence of IPF
Step 2 - Individual HRCT + Standardized clinical data	Clinicians Radiologists	Diagnosis & Confidence Confidence of IPF
Step 3 - Group Discussion HRCT + Standardized clinical data	Clinicians Radiologists	Diagnosis & Confidence Confidence of IPF
Step 4 - Group Discussion HRCT + Standardized clinical data + SLB	Clinicians Radiologists Pathologists	Diagnosis & Confidence Confidence of IPF
Step 5 - Group Discussion HRCT + Standardized clinical data + SLB	Clinicians Radiologists Pathologists	Consensus Diagnosis & Confidence



Flaherty, King, Raghu. AJRCCM 2004;170,904–910

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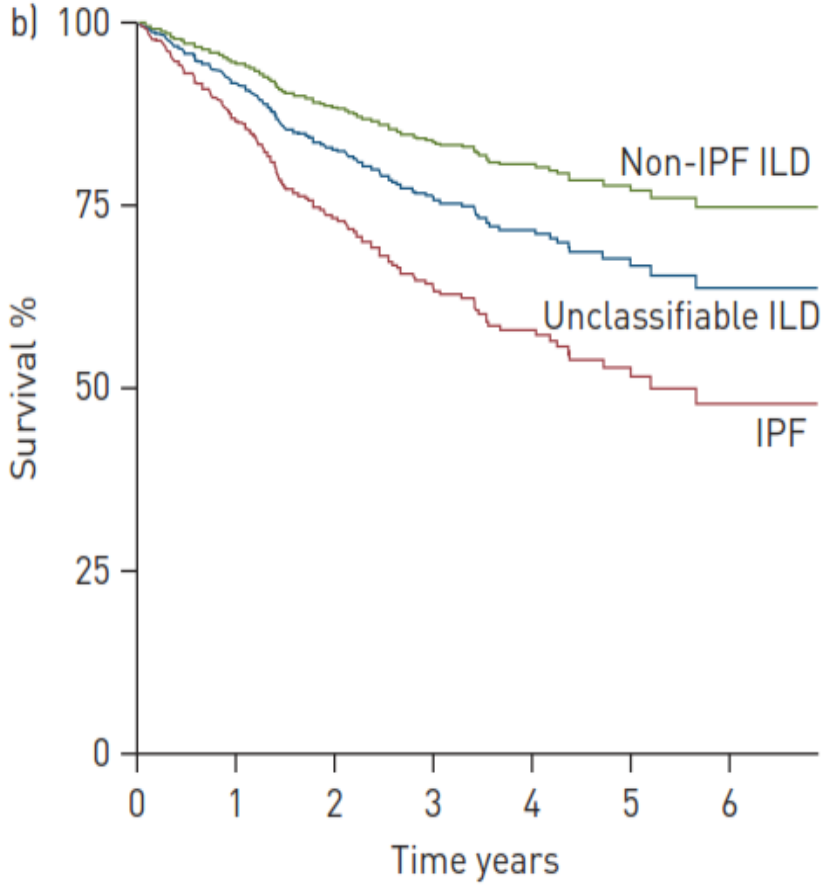
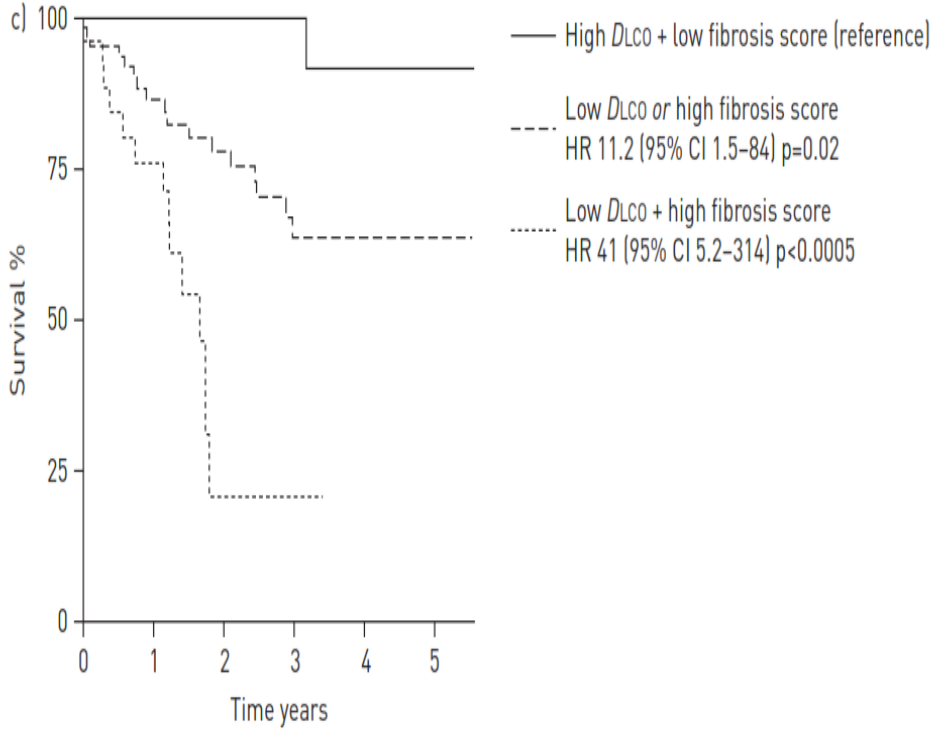
Unclassifiable Idiopathic Interstitial Pneumonia





Ryerson. Eur Respir J 2013; 42, 750–757

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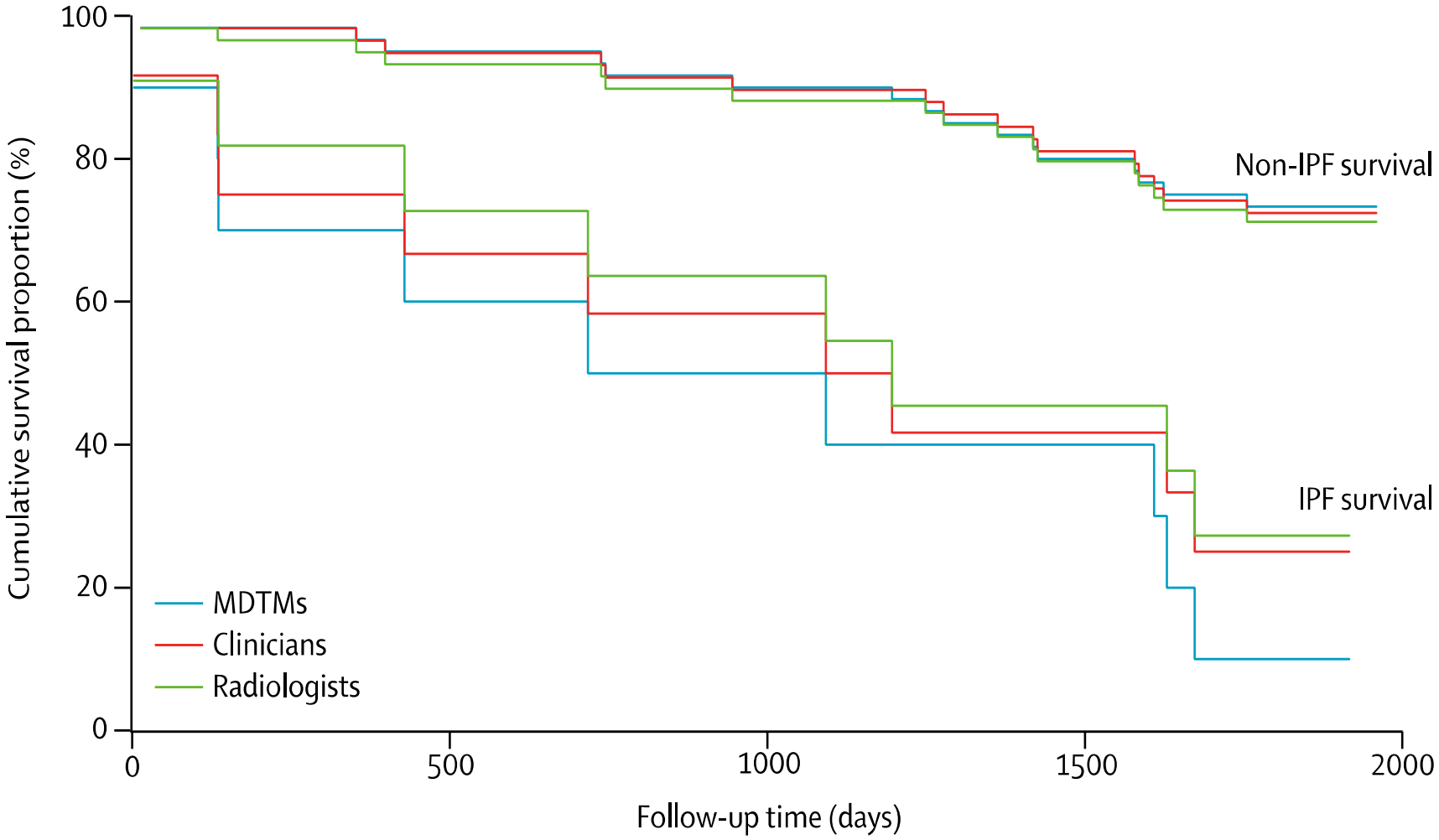
IPAF Interstitial Pneumonitis with Autoimmune Features

1) ILD by HRCT or Lung Bx
2) Other etiologies for ILD excluded
3) Does not meet criteria for AI Dz
4) 1 feature from @ least 2/3 Domains
   - Clinical
   - Serologic
   - Morphologic (HRCT or Lung Bx)

Multicenter Evaluation of Multidisciplinary Meeting

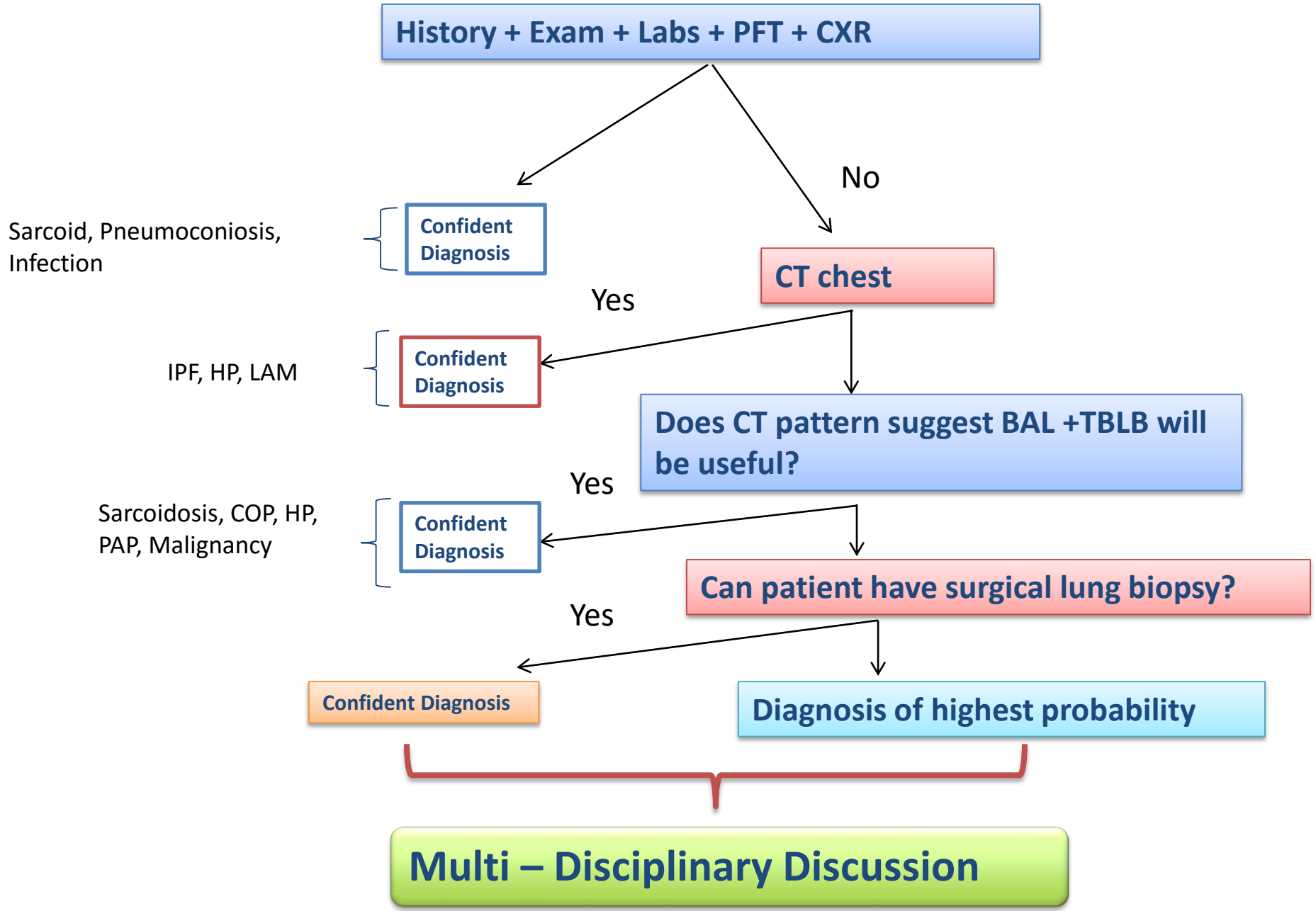
	Clinici
	Total (n=70)
Overall total	0·45
Idiopathic pulmonary fibrosis total	0·59
Non-specific interstitial pneumonia total	0·19
Connective tissue disease-related interstitial lung disease total	0·57
Hypersensitivity pneumonitis total	0·25

MDTM=multidisciplinary team meeting.



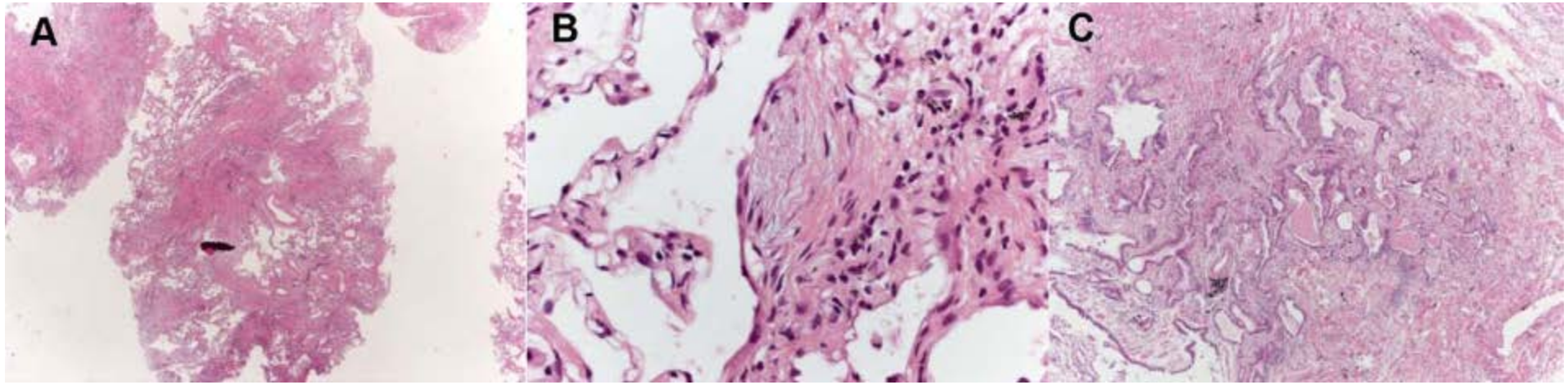
Walsh S. Lancet Respir Med 2016; 4, 557-65

Beaumont


History + Exam + Labs + PFT + CXR
No
Sarcoid, Pneumoconiosis, Infection
Confident Diagnosis
CT chest
Yes
IPF, HP, LAM
Confident Diagnosis
Does CT pattern suggest BAL +TBLB will be useful?
Yes
Sarcoidosis, COP, HP, PAP, Malignancy
Confident Diagnosis
Can patient have surgical lung biopsy?
Yes
Confident Diagnosis
Diagnosis of highest probability
Multi – Disciplinary Discussion

Newer Modalities of Diagnosis

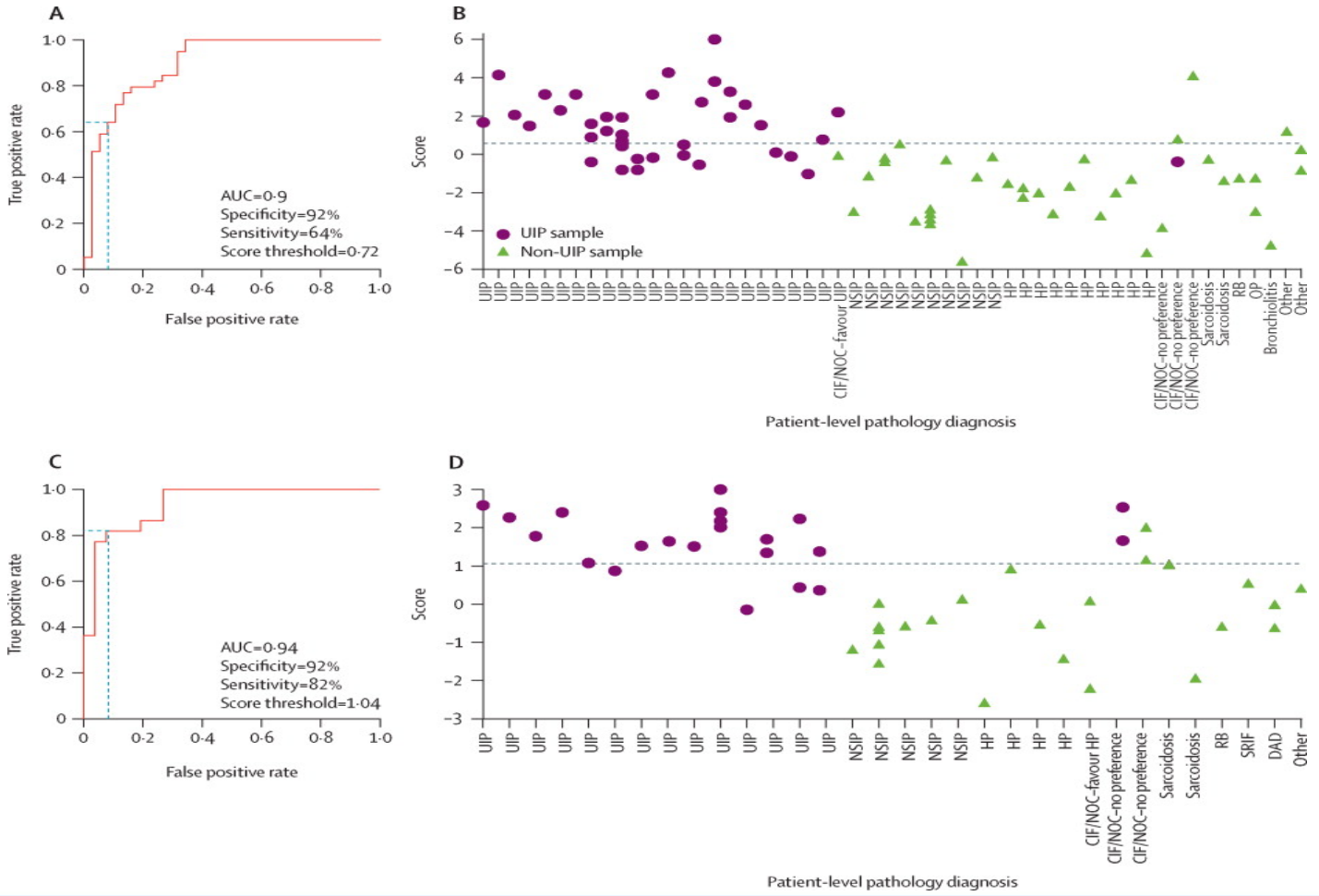
Trans-bronchial Lung Cryobiopsy



Casoni. PloS one 2014;9:e86716

Beaumont

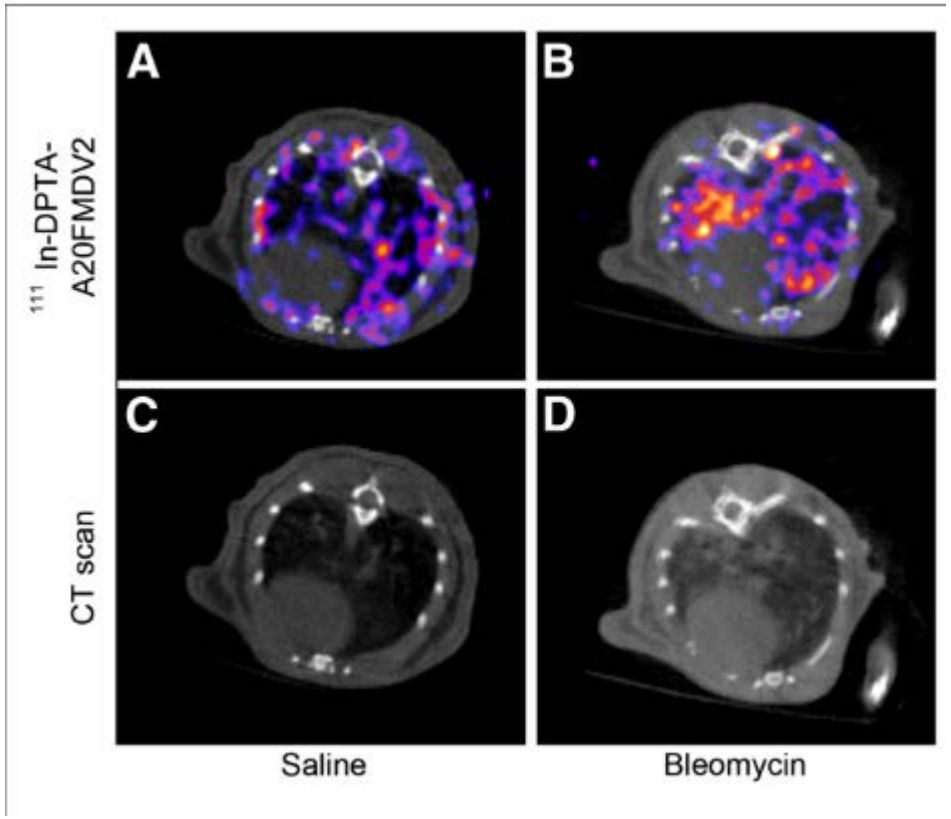
Differentiating UIP based on Transcriptional Data

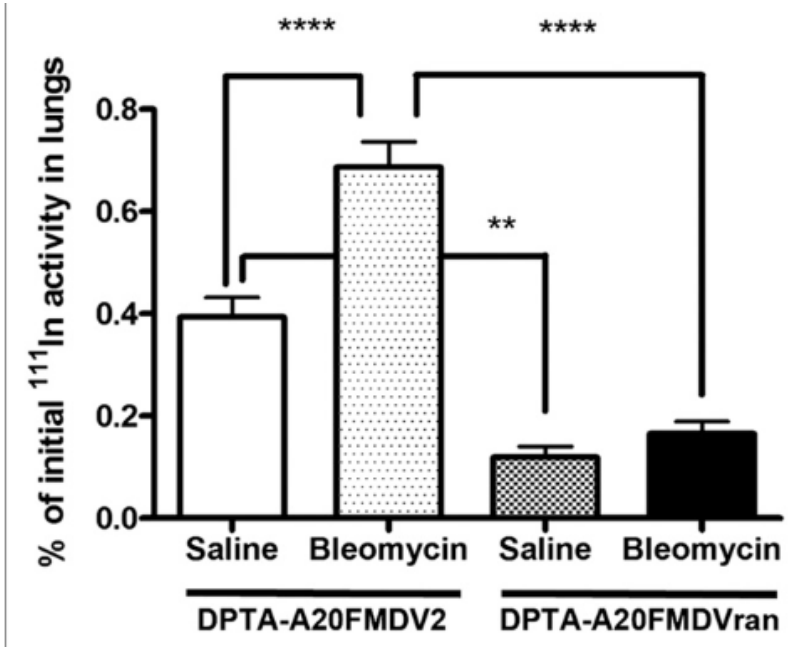


Kim. Lancet Respir Med 2015, 3(6):473-82

Beaumont

SPECT/CT Imaging using Integrins





John. AE J Nucl Med 2013; 54,2146–2152

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Noninvasive Imaging of Experimental Lung Fibrosis

- Mic
- Pro
- Hyp
- Res
- PET
- PET rface

Feature	Modality			
	Micro-CT	MRI	Nuclear Medicine Imaging (PET/SPECT)	Bimodality Imaging (PET/CT, SPECT/CT)
Spatial resolution	Excellent (up to 1 μm)	Good (up to 25–100 μm)	Poor (~1 mm)	Excellent
3D lung assessment	Yes	Yes	Yes	Yes
Assessment of lung structure, function, and/or molecular mechanisms	Structure	Structure and function	Molecular mechanisms	Molecular mechanisms and structure
Potential for distinguishing lung inflammation versus fibrosis	No	Yes	Yes (with specific molecular tracers)	Yes (with specific molecular tracers)
Acquisition time	Fast (minutes)	Slow (minutes to hours)	Fast (minutes)	Fast
Ionizing radiation	Yes	No	Yes	Yes
Cost	Less expensive ($200,000–$400,000)	Most expensive (~$2,000,000)	Expensive (<$1,000,000)	Expensive

Zhou Y. Am J Respir Cell Mol Biol 2015; 53,8–13

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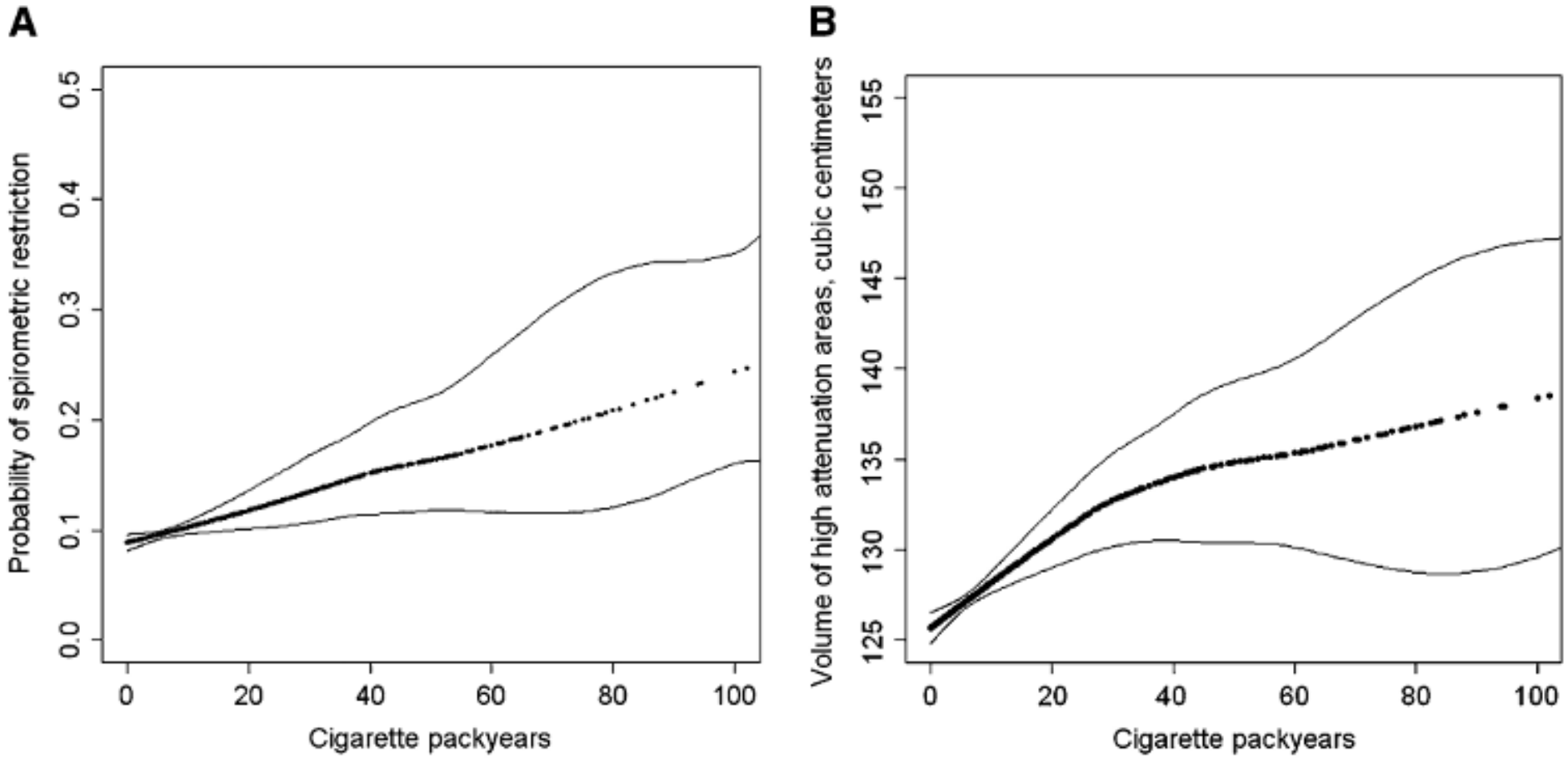
Early Diagnosis

HIGH ATTENUATION ON CT – SMOKING & RESTRICTION ON SPIROMETRY



Lederer. AJRCCM 2009 ;180, 407–414.

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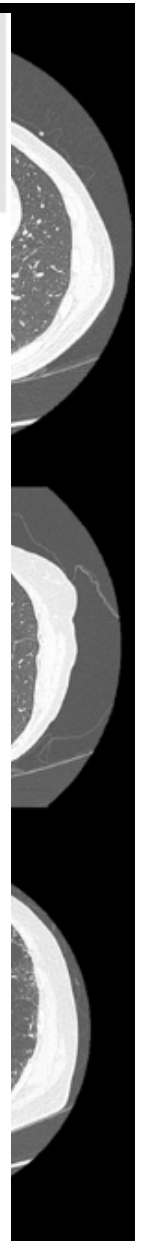
Variable	Percent or Median/Means Where Appropriate and Noted: Research Subjects with ILA: MESA*	Nagano, Japan†	COPDGene‡	MILD§	FHS‖	NLST¶	Patients with IPF**
Prevalence of ILA, %	2	3	8	4	7	10	0.01–0.04
Radiologic features, %							
Reticular markings	4–9	62	85	21	97	24	All
Ground glass	61–93	15	97	90	100	78	Occasional
Centrilobular nodules	—	—	28	28	20		Rare
Cysts	—	—	51	—	47	27	Rare
Traction bronchiectasis	—	—	30	21	50		Common
Honeycombing	2–13	9	9	7	3	10	Common
High-attenuation areas in >10% of the lung	100% (by definition)	—	—	—	—		Unknown (but likely elevated)
Demographic parameters							
Age, yr	—	62	64	60	70	62	66
Sex, female, %	—	26	50	14	52	28	41–49
History of smoking, current or former, %	—	70	100	100	62	100	60–72
Respiratory symptoms, %							
Chronic cough, yes	—	13	41	—	12	—	73–86
Chronic shortness of breath, yes	—	15	60	—	18	—	Present in most patients
Physical examination findings							
Fine crackles, %	—	26	—	—	—	—	Present in most patients
Pulmonary physiologic testing							
FVC % predicted	—	113–116	88	101	101	—	68–89
Total lung capacity % predicted	—	—	95	—	79	—	46–78
Diffusion capacity of carbon monoxide, % predicted	—		—	—	86	—	46–61
6-min walk distance, m	—	555–573	403	—	—	—	373–392
Radiologic progression, %, follow-up time							
Improvement	—	16, 4 yr	—	0, 3 yr	—	33, 2 yr	The median survival of IPF patients is 3 yr
Unchanged		40, 4 yr		75, 3 yr		47, 2 yr	
Overall progression	—	46, 4 yr	—	25, 3 yr	—	20, 2 yr	
Progression to UIP pattern	—	5, 4 yr	—	8, 3 yr	—	—	—



Putman, Rosas, Hunninghake. Am J Respir Crit Care Med 2014;189,770–78

Beaumont

Early Diagnosis

Changes in CT Findings at 2-year Follow-up in 79 Participants with ILA

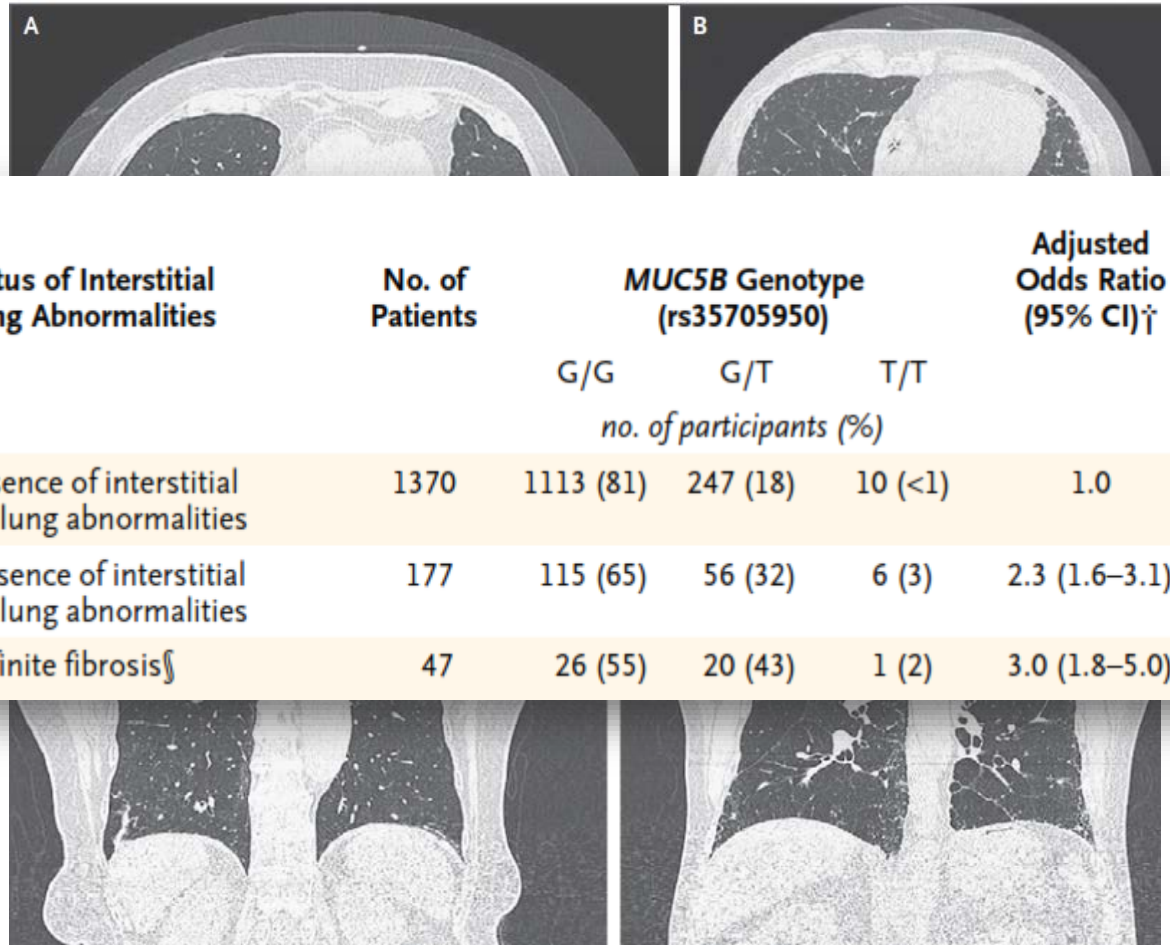
Parameter	No.	Findings at 2-year Follow-up: Improved	Same	Progression
Overall extent of abnormality*		26 (32.9)	37 (46.8)	16 (20.3)
Nonfibrotic ILA	47	23 (48.9)	19 (40.2)	5 (10.9)
Fibrotic ILA	19	0	12 (63.2)	7 (36.8)
Mixed nonfibrotic and fibrotic ILA	13	3 (23.1)	6 (46.2)	4 (30.7)
Individual CT findings				
Nonfibrotic ILA				
GGO	32	13 (40.6)	9 (28.1)	10 (31.3)
Mosaic attenuation	40	0	37 (92.5)	3 (7.5)
Consolidation	9	2 (22.3)	7 (66.7)	0
Mixed nonfibrotic and fibrotic ILA				
GGO	5	3 (60)	0	2 (40)
Mosaic attenuation	4	0	4 (100)	0
Consolidation	1	0	1 (100)	0
GGO with reticular abnormality	7	0	4 (57.1)	3 (42.9)
Pure reticular abnormality	2	0	2 (100)	0
Honeycombing	5	0	5 (100)	0
Fibrotic ILA				
GGO with reticular abnormality	12	0	5 (41.7)	7 (58.3)
Pure reticular abnormality	9	0	5 (55.6)	4 (44.4)
Honeycombing	9	0	5 (55.6)	4 (44.4)

- CT scan of 884 smokers lung cancer screening
- ILA 9.7%- 2.1% fibrotic,5.9% non fibrotic
- 2 years non-fibrotic ILA improved 48.9%, while fibrotic did not improved in anyone and progressed in 36.8%.

Gong Yong Jin. Radiology 268: August 2013

Beaumont

Interstitial Lung Abnormalities and MUC5B Genotype in the Framingham Heart Study



Status of Interstitial Lung Abnormalities	No. of Patients	*MUC5B* Genotype (rs35705950)			Adjusted Odds Ratio (95% CI)†	P Value	Adjusted Odds Ratio with Covariates (95% CI)‡	P Value
		G/G	G/T	T/T				
		no. of participants (%)						
Absence of interstitial lung abnormalities	1370	1113 (81)	247 (18)	10 (<1)	1.0		1.0	
Presence of interstitial lung abnormalities	177	115 (65)	56 (32)	6 (3)	2.3 (1.6–3.1)	<0.001	2.8 (2.0–3.9)	<0.001
Definite fibrosis§	47	26 (55)	20 (43)	1 (2)	3.0 (1.8–5.0)	<0.001	6.3 (3.1–12.7)	<0.001

Hunninghake. N Engl J Med 2013;368,2192-200

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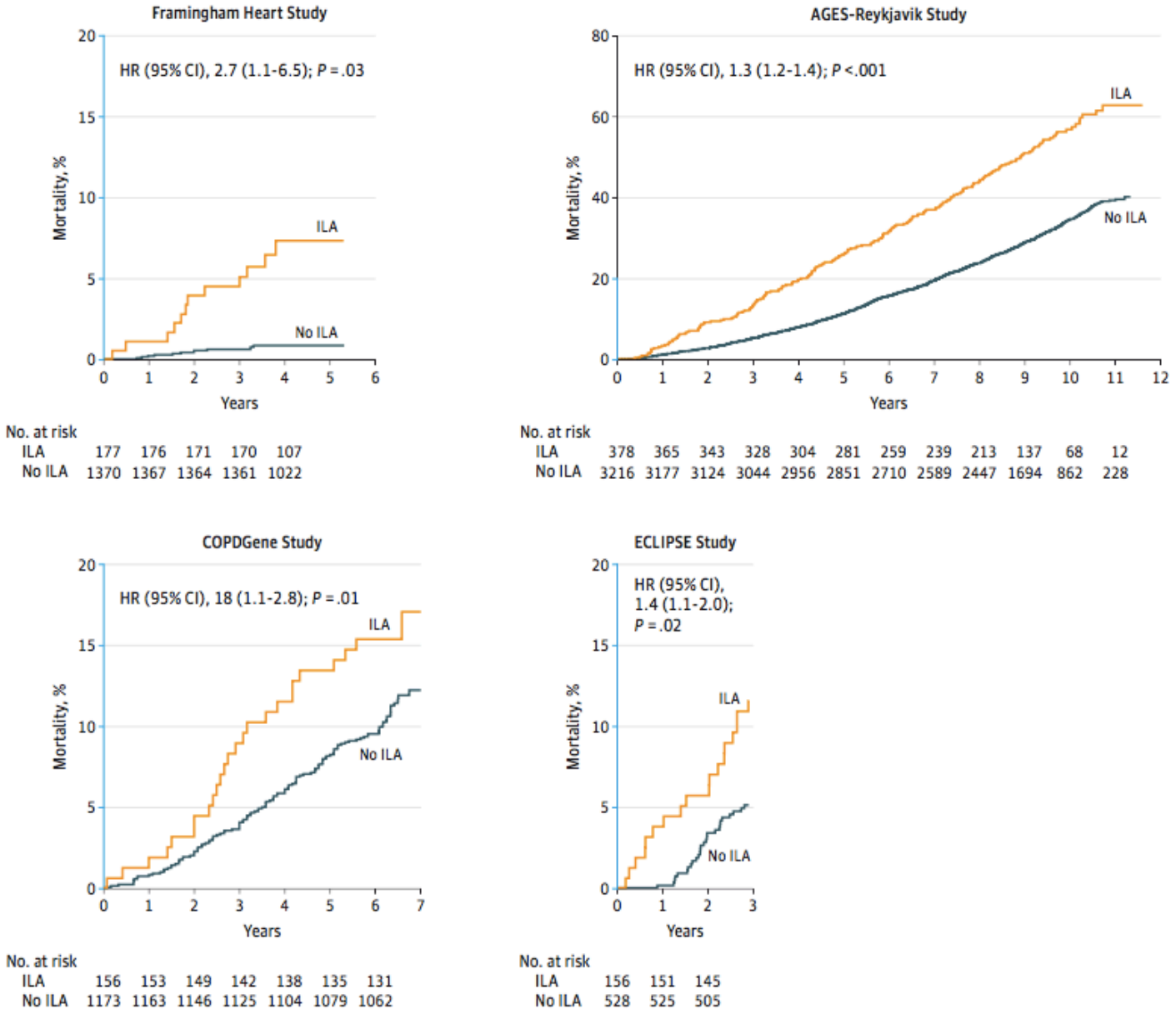
Association Between ILA and All-Cause Mortality



Putman. JAMA 2016;315,672-681

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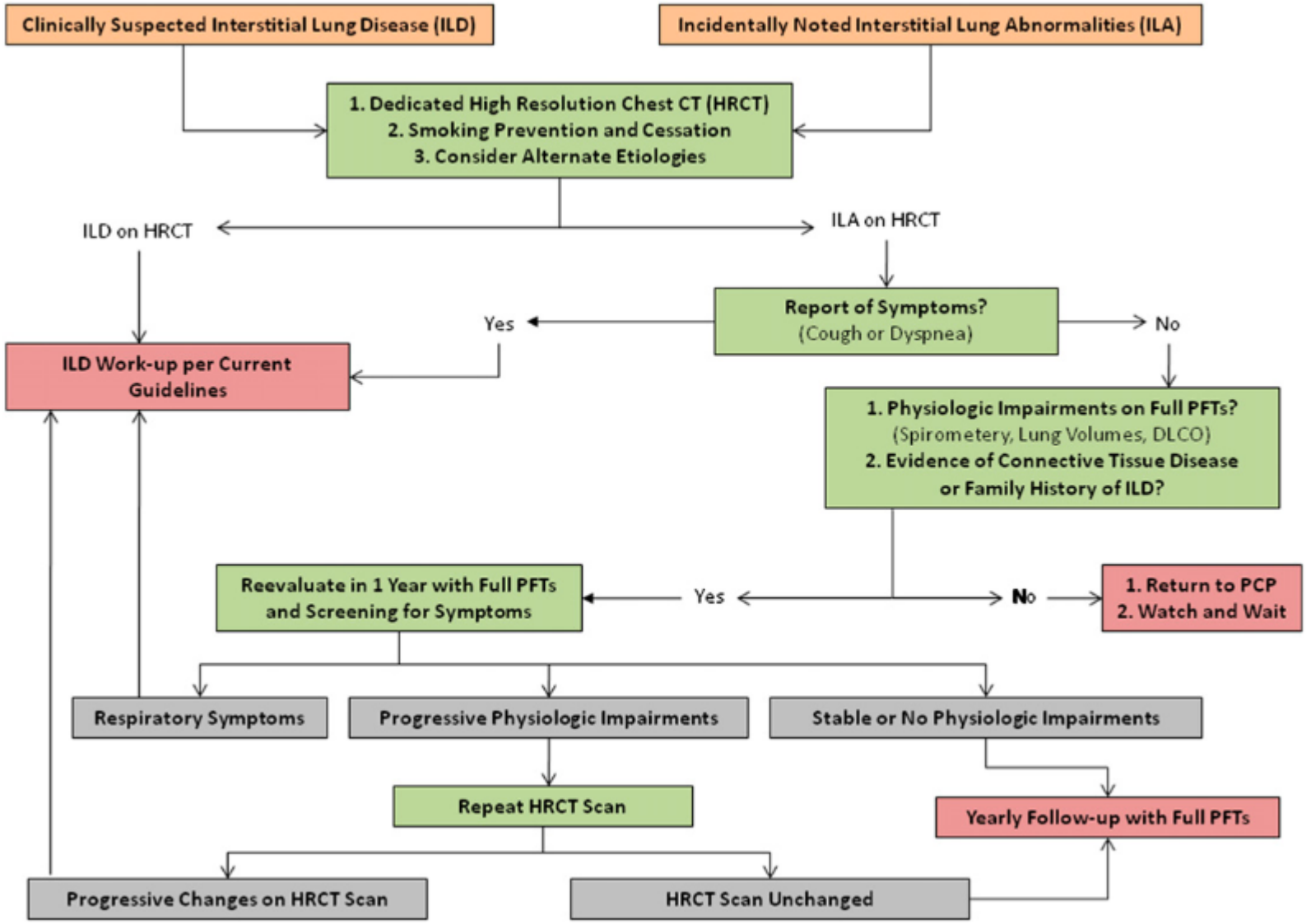

Doyle, Rosas, Hunninghake. Am J Respir Crit Care Med 2012(185)1147–1153
Putman, Rosas, Hunninghake. Am J Respir Crit Care Med 2014 (189)770–78

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Disease Predictors

IPF – Predictors of Survival

Clinical Predictors	Radiographic Predictors	Physiologic Predictors	Pathologic Predictors	Biomarker Predictors
Demographic	HRCT	Pulmonary function tests	Histopathology	Blood
Age	UIP pattern	FVC	UIP pattern	BNP
Sex	Extent of fibrosis	TLC	Fibroblastic foci	Albumin
Ethnicity		D_{LCO}		KL-6M
Smoking status		CPI		MP-7
Symptom-based		Change in FVC		CCL-18
Dyspnea scores		Change in D_{LCO}		SP-A & -D
				Circulating fibrocytes
Physical examination		Exercise tests		BAL
Clubbing		6MWT		SP-A & -D
BMI		Desaturation		MMP-3, -7, -8, -9
Comorbidities		Distance		CCL-2, -17, -22
Emphysema		Heart rate recovery		Neutrophilia
Pulmonary hypertension		Others		
		15-step test		
		4-min step test		

Definition of abbreviations: BAL = bronchoalveolar lavage; BMI = body mass index; BNP = b-type natriuretic peptide; CCL = CC-chemokine; CPI = composite physiologic index; D_{LCO} = diffusing capacity of carbon monoxide; HRCT = high-resolution computed tomography; KL = Krebs von den Lungen; MMP = matrix metalloproteinase; 6MWT = 6-minute walk test; SP = surfactant protein; UIP = usual interstitial pneumonia.

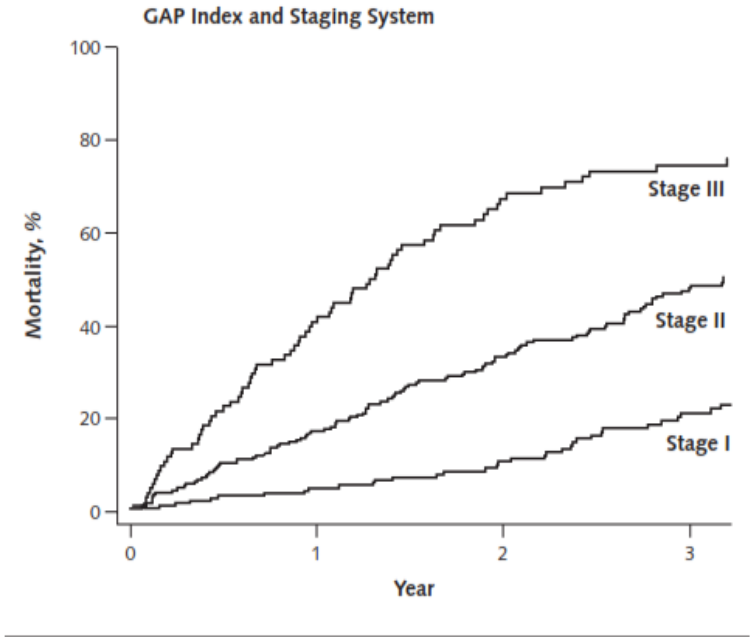
Raghu. AJRCCM 2011,183,431–440

Beaumont

GAP Index

	Predictor	Points
G	Gender	
	Female	0
	Male	1
A	Age, y	
	≤60	0
	61–65	1
	>65	2
P	Physiology	
	FVC, % *predicted*	
	>75	0
	50–75	1
	<50	2
	DLCO, % *predicted*	
	>55	0
	36–55	1
	≤35	2
	Cannot perform	3
	Total Possible Points	8

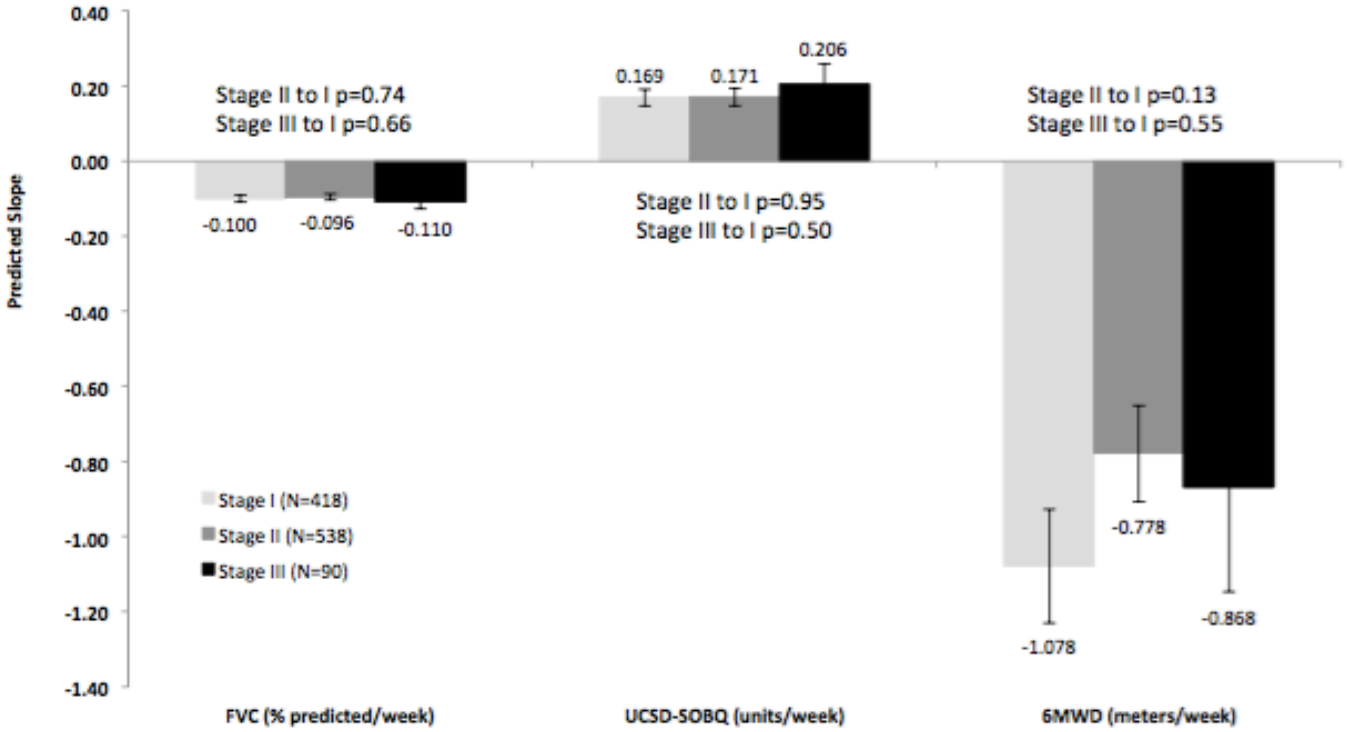
Stage	I	II	III
Points	0–3	4–5	6–8
Mortality			
1-y	5.6	16.2	39.2
2-y	10.9	29.9	62.1
3-y	16.3	42.1	76.8

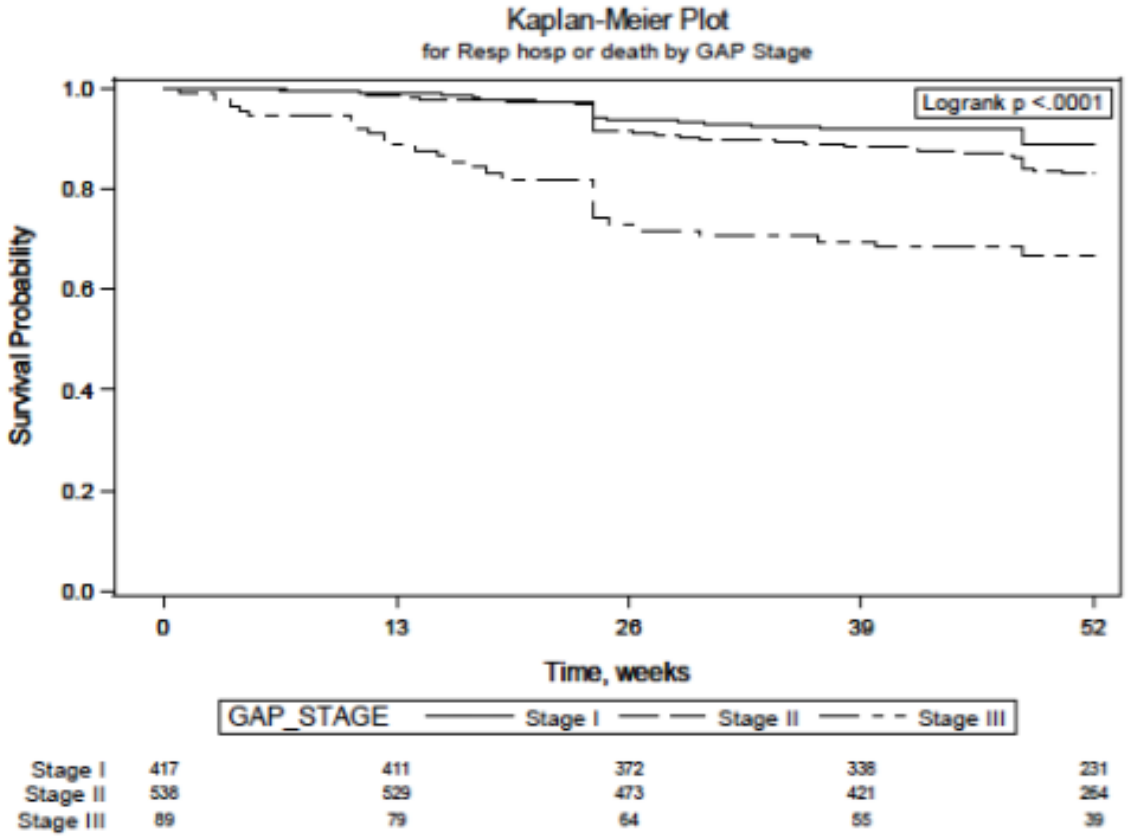


Ley. Ann Intern Med 2012;156,684–91
Ryerson CJ. Chest 2014 Apr;145,723-8

Beaumont

Predictors of Mortality are Poor Predictors of Disease Progression





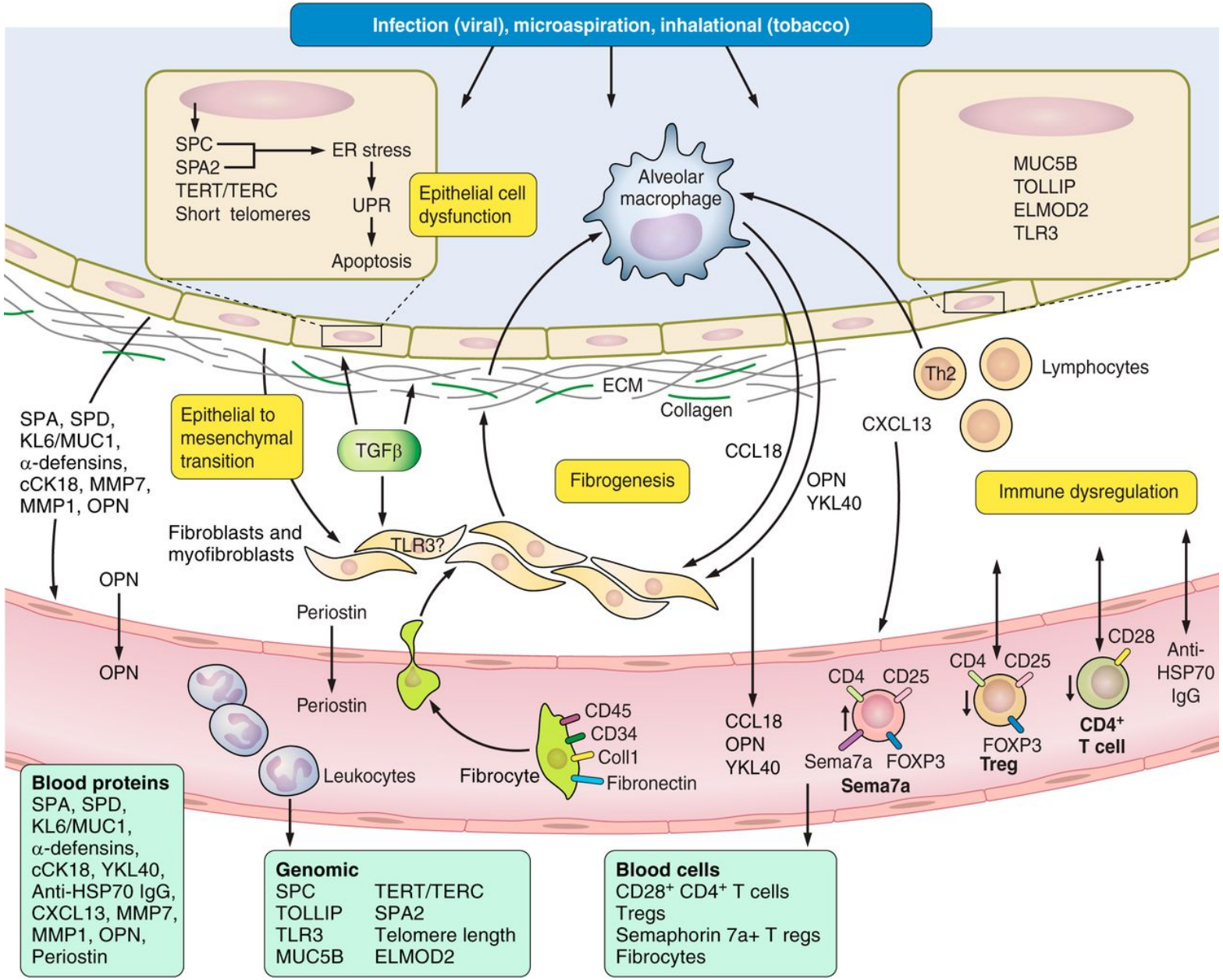
Ley B. AJRCCM Mar 2016

Beaumont

Personalized Medicine

Biomarker

- Identify patients at risk of progression
- More accurate and less invasive diagnostic tool
- Response to treatment
- Prediction of disease outcome



Am J Physiol Lung Cell Mol Physiol 2014 ;307(9)

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BIOMARKERS FOR OUTCOME IN BLOOD AND BRONCHOALVEOLAR LAVAGE -HIGHER LEVELS PREDICTING POOR SURVIVAL

Alveolar Epithelial Cell Dysfunction

- Surfactant Proteins
- Krebs Von Den Lungen-6/Mucin 1
- MUC5B
- Telomeres
- Caspase-Cleaved Cytokeratin-18

Immune Dysregulation

Innate Immunity

- Toll-like Receptor 3
- Toll-Interacting Protein

Alveolar Macrophage Activation

- CC Chemokine Ligand 18
- S100A12

Adaptive Immunity

- Anti-HSP70 Antibodies
- C-X-C Motif Chemokine 13
- Costimulatory Signal During T Cell Activation
- Semaphorin 7a

Microbiome

Extracellular Matrix Remodeling and Fibroproliferation

- Matrix Metalloproteinases
- Matrix Metalloproteinase-Degraded Extracellular Matrix Proteins
- Lysyl Oxidase-like Protein-2

Epigenetic Markers

Metabolomics

Spagnolo. Curr Opin Pulm Med 2015;21,470-478

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MMP-7, KL-6 and SP-A as Predictors of Outcome

Models	C-index	95% CI	*P* value
MMP-7	0.596	0.537-0.667	…
KL-6	0.585	0.537-0.647	…
SP-A	0.642	0.558-0.722	…
SP-D	0.582	0.508-0.662	…
MMP-7 and SP-A	0.681	0.611-0.766	…
KL-6 and MMP-7	0.635	0.579-1.714	…
KL-6, MMP-7, and SP-A	0.688	0.626-0.772	…
Clinical variables[a]	0.686	0.629-0.771	Reference
Clinical variable + KL-6	0.677	0.642-0.776	.423
Clinical variable + MMP-7	0.697	0.644-0.784	.279
Clinical variable + SP-A	0.714	0.664-0.802	.165
Clinical variable + MMP-7 and SP-A	0.731	0.683-0.818	.061
Clinical variable + KL-6 and MMP-7	0.702	0.658-0.789	.174
Clinical variable + KL-6 and SP-A	0.716	0.669-0.806	.136
Clinical variable + MMP-7, KL-6, and SP-A	0.730	0.691-0.824	.037

Song CHEST 2013; 143(5):1422–1429

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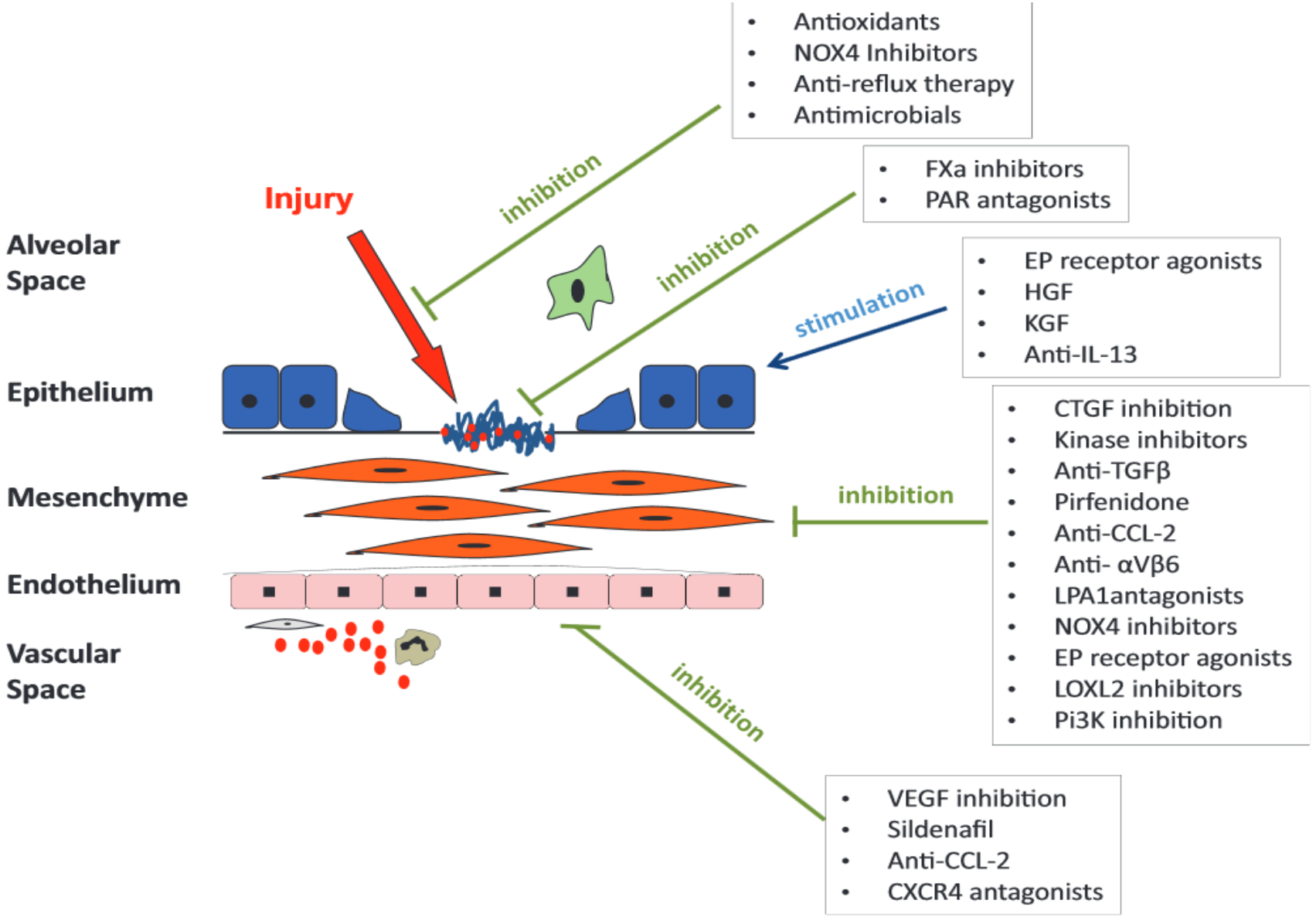
Treatment Targets



Maher TM. Clin Chest Med 2012,33,69-83.

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NEGATIVE TRIALS IN IPF

Drug	Primary Endpoint	N	Trial length (weeks)
Imatinib mesylate	FVC drop 10% or death	119	96
Etanercept	FVC and $DL_{CO,}$ % predicted, A-a gradient	88	48
Bosentan (BUILD 1)	Change 6MWT	158	52
Bosentan (BUILD 3)	Dz prog/Death/Exac	616	Events
Ambrisentan	Dz prog/Death/Resp Hosp	660	Events
Warfarin (ACE-IPF)	Death/drop FVC/non-elective hospitalization	248	48
Everolimus	2nd of FVC/TLC drop 10%, DLCO drop 15%, SaO_2 -4%	104	156

AMERICAN THORACIC SOCIETY DOCUMENTS

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis

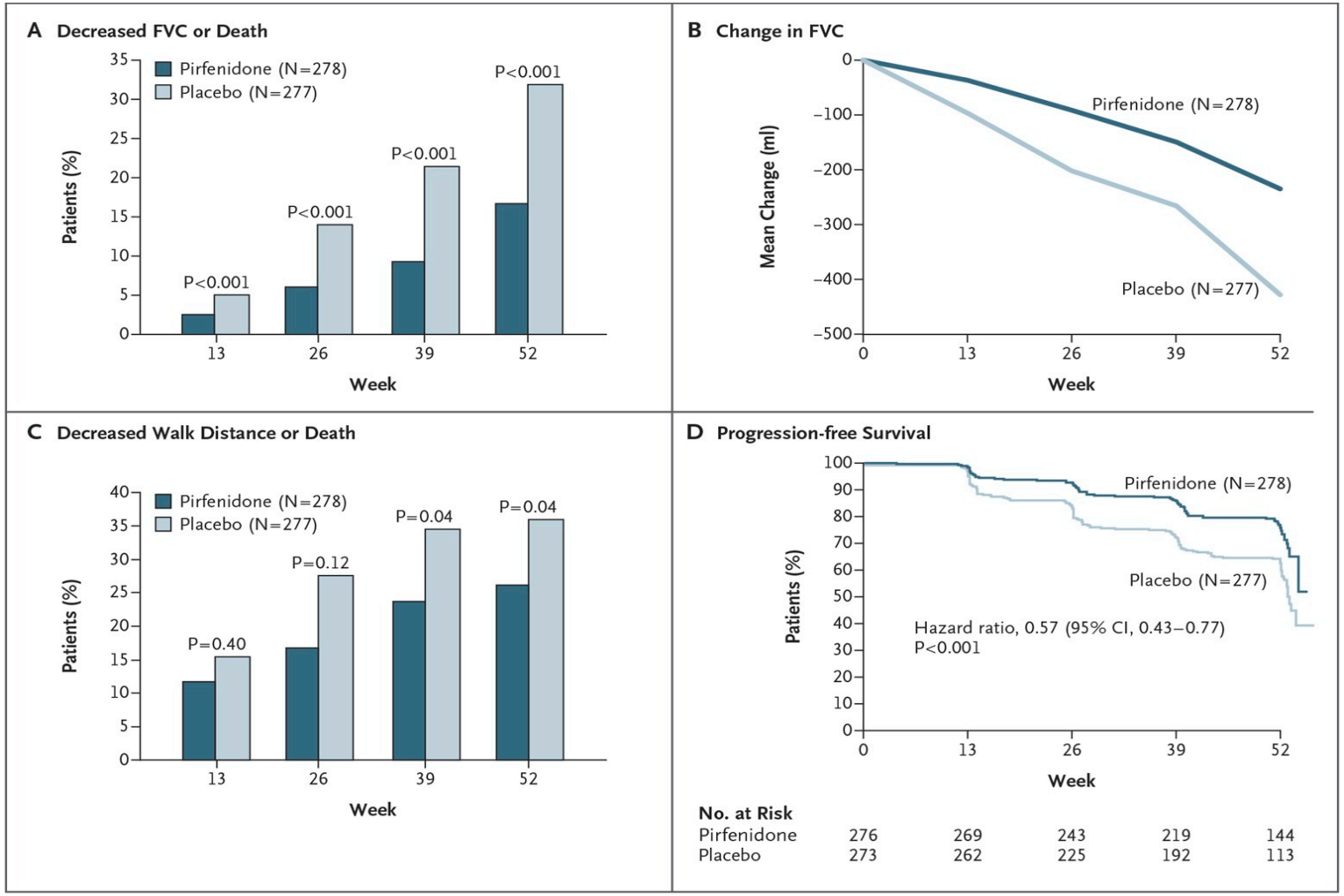
An Update of the 2011 Clinical Practice Guideline

Ganesh Raghu, Bram Rochwerg, Yuan Zhang, Carlos A. Cuello Garcia, Arata Azuma, Juergen Behr, Jan L. Brozek, Harold R. Collard, William Cunningham*, Sakae Homma, Takeshi Johkoh, Fernando J. Martinez, Jeffrey Myers, Shandra L. Protzko, Luca Richeldi, David Rind, Moisés Selman, Arthur Theodore, Athol U. Wells, Henk Hoogsteden, and Holger J. Schünemann; on behalf of the ATS, ERS, JRS, and ALAT

This guideline is dedicated to the memory of Mr. William Cunningham (June 7, 1935–October 23, 2014)

This Official Clinical Practice Guideline of the American Thoracic Society (ATS) was approved by the ATS, May 2015, the European Respiratory Society (ERS), April 2015, the Japanese Respiratory Society (JRS), April 2015, and the Latin American Thoracic Association (ALAT), April 2015

ASCEND Study



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

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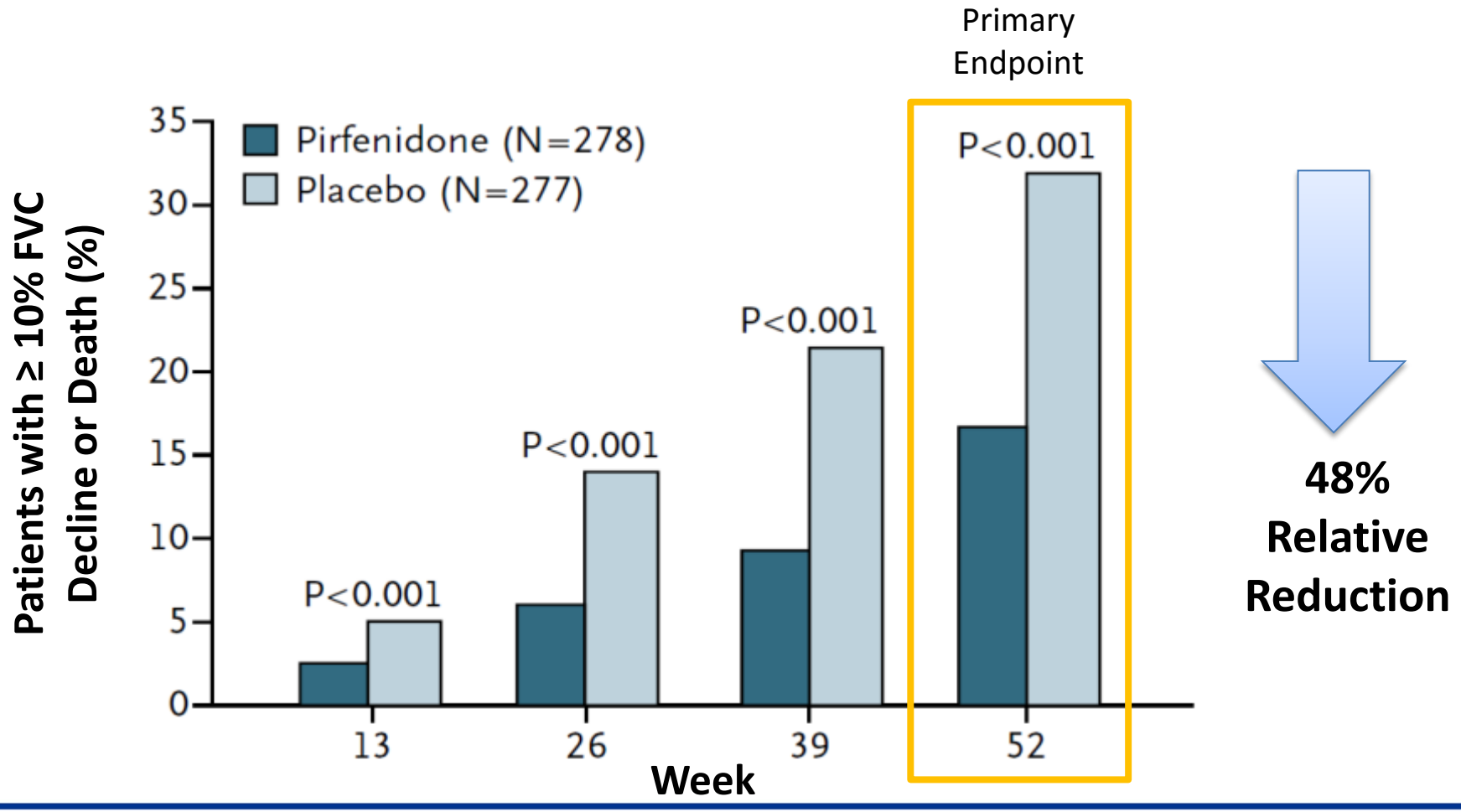
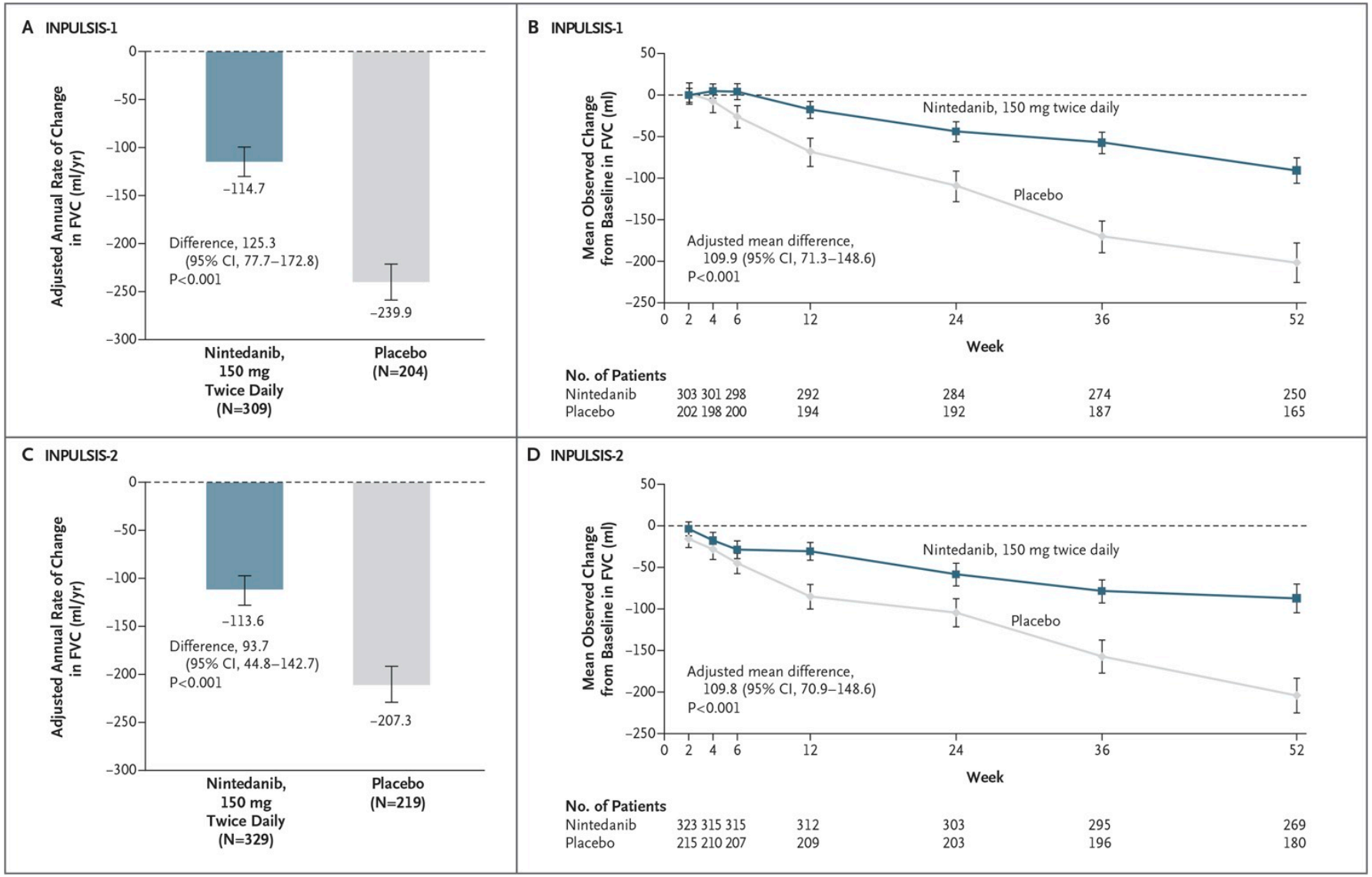


King TE, et al. N Engl J Med 2014;370, 2083-2092.

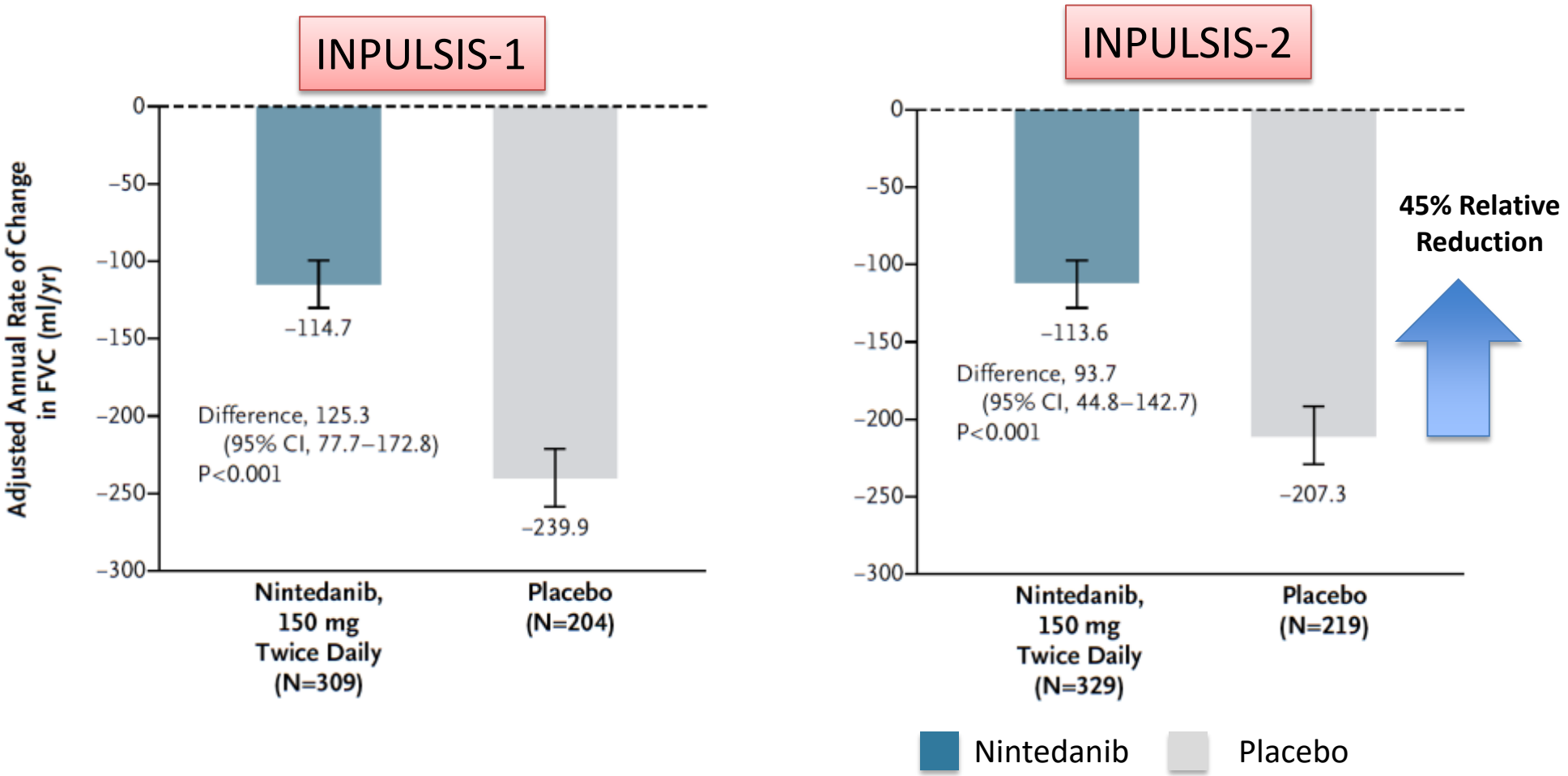
INPULSIS Trials



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

Beaumont

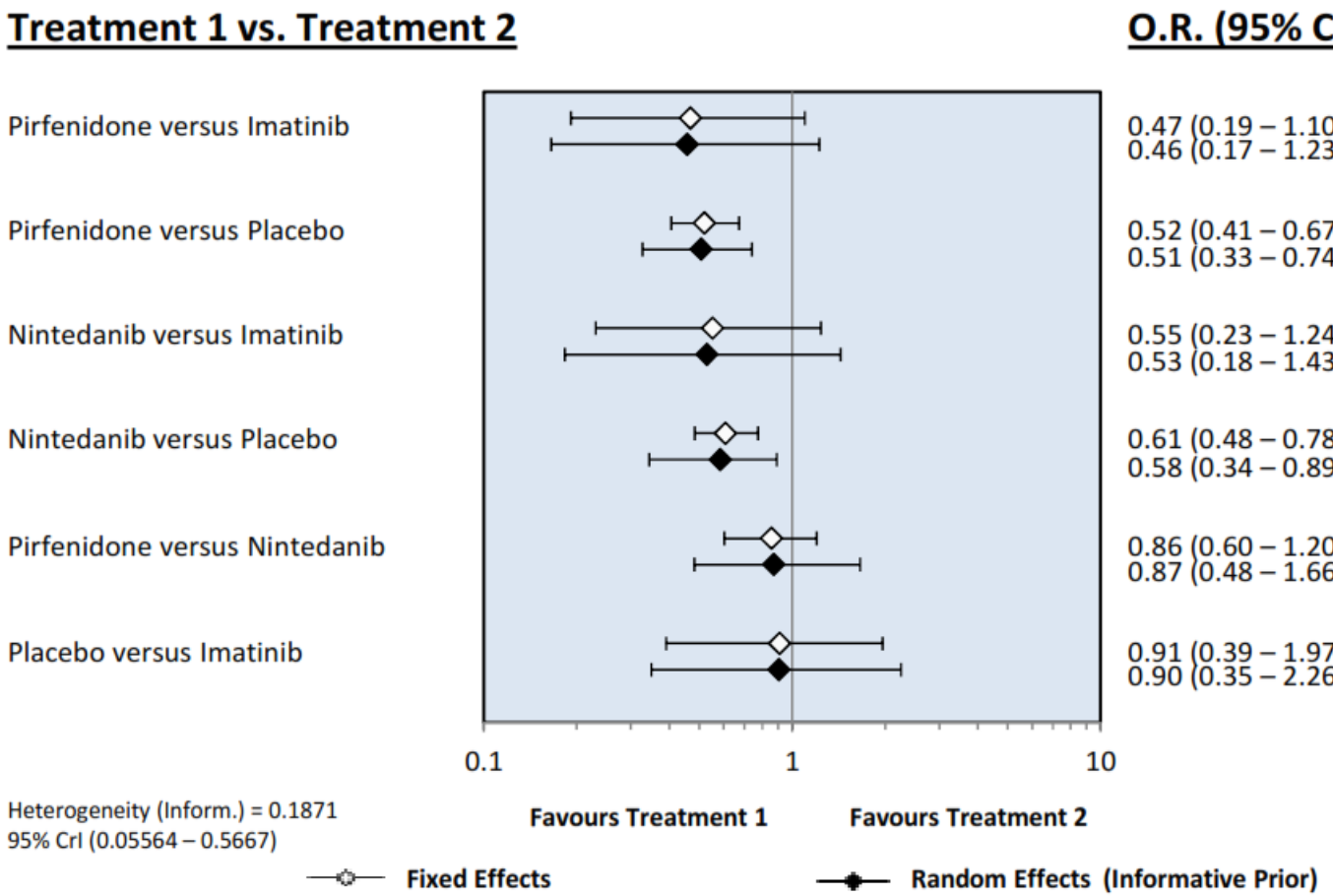
Annual Rate of Change of FVC



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

Beaumont

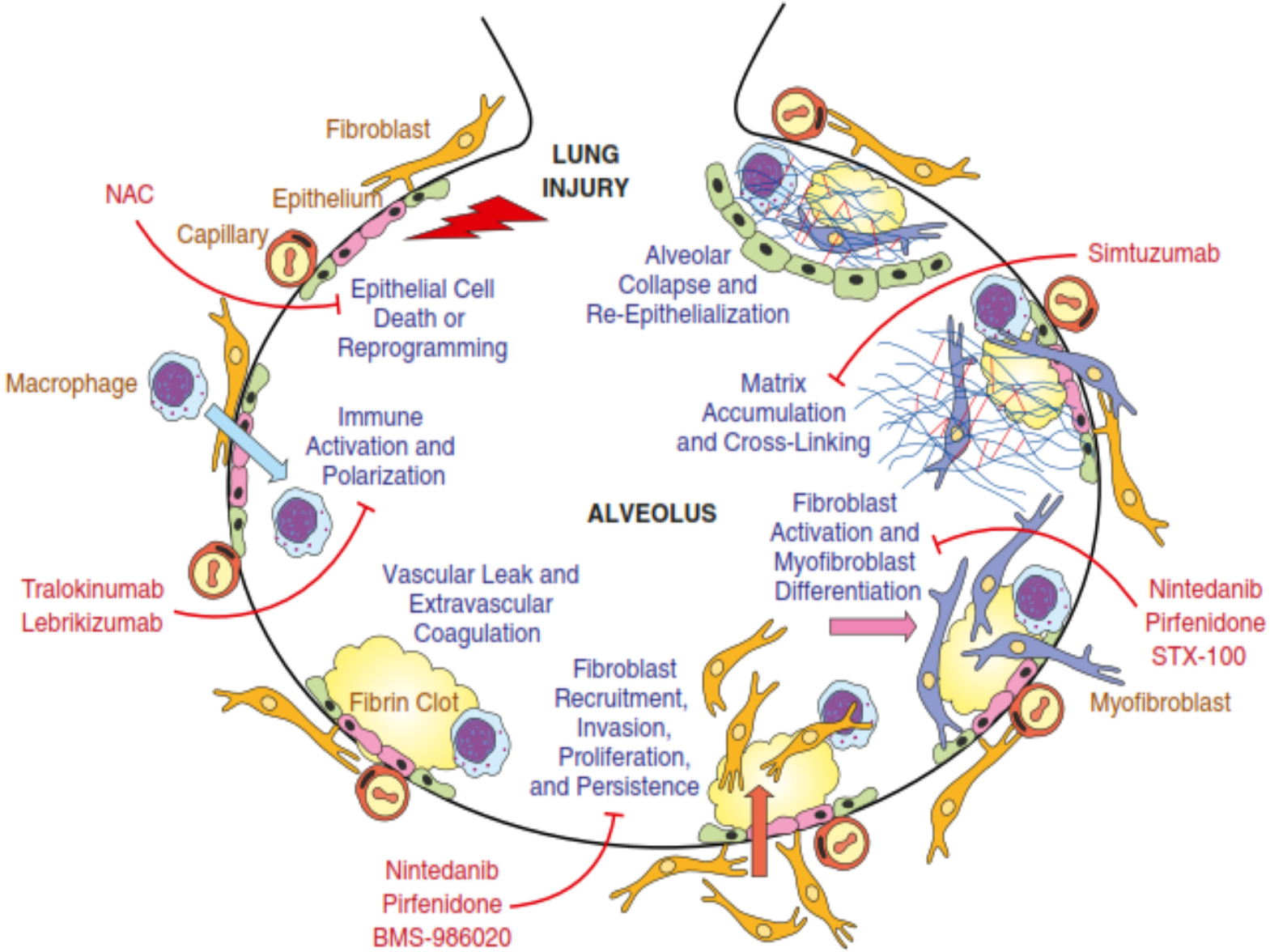
Treatment of IPF: Systematic Review and Network Meta-Analysis



Decrease in Percent Predicted FVC by =10%

W. Canestaro, G. Raghu CHEST 2016

Beaumont



N. Ahluwalia. AJRCCM, 2014, 190, 867–878

Beaumont

Agent	Potential mechanism of action	Clinical trial registry number	Study design	Endpoints	Outcomes
GC1008	Anti-TGFβ antibody	NCT00125385	Phase I study ,non-randomized , open label, single group assignment (n=25)	Primary end point : Safety and tolerability	Completed. Awaiting results.
BG00011 (formerly known as STX-100)	Anti-αvβ6 integrin	NCT01371305			
Phase II study, randomized, placebo-controlled	Primary end point: Safety and tolerability	Trial ongoing.			
FG-3019	Connective tissue growth factor inhibitor	NCT01890265	Phase II, randomized, placebo-controlled study	Primary end point: Change from baseline in FVC (percent of predicted value) at Week 48	Trial ongoing.
PBI-4050	Connective tissue growth factor and collagen I mRNA expression inhibitor	NCT02538536	Phase II, open-label, Single-arm study	Primary end point: Safety and tolerability	Trial ongoing.
CNTO 888 (Carlumab)	Anti-CCL2 antibody	NCT00786201	Phase II randomized, placebo-controlled study	Primary end points: Safety and efficacy	Trial completed. No benefit on IPF.
QAX576	Anti-IL-13 antibody	NCT00532233	Phase II ,open label study (n=50)	Primary end point: IL-13 serum levels Secondary end point: change in designated serum biomarkers	Completed. Awaiting results.
		NCT01266135	Phase II, randomized, Double-blind, Placebo-controlled study.	Primary end point: Safety, tolerability, and effect on lung function. Change in forced vital capacity (FVC)	Trial terminated.

Nair GB, Expert Rev Respir Med 2016;10, 699-711

Beaumont

Tralokinumab	**Anti-IL-13 antibody**	**NCT01629667**	**Phase II study, prospective, double-blinded, randomized placebo-controlled; (n=186)**	**Primary end point: Absolute change from baseline in percent predicted forced vital capacity (FVC)**	**Trial ongoing**
Lebrikizumab	Anti-IL-13 antibody	NCT01872689	Phase II, randomized, multicenter, double-blind, placebo-controlled, parallel-group study	Primary end point: Absolute change from baseline in percent predicted forced vital capacity (FVC)	Trial ongoing.
SAR156597	Anti-IL-13 and IL-4 antibody	NCT01529853	Phase II study, prospective, double-blinded, randomized placebo-controlled study	Primary end point: Safety and tolerability Secondary end point: change in FVC, DlCO and dyspnea score from baseline	Completed. Awaiting results.
		NCT02345070	Phase II, randomized, double-blind, placebo-controlled study	Primary end point: Efficacy and Safety Absolute change from baseline in percent predicted FVC at 52 weeks Secondary end points: -Proportion of patients with disease progression. -Number of deaths (All causes)	Trial ongoing.
BMS-986020	Lysophosphatidic Acid receptor antagonist	NCT01766817	Phase II, randomized, placebo-controlled study	Primary end point: safety and efficacy Rate of change in forced vital capacity	Trial ongoing
Simtuzumab (GS-6624)					
Anti-LOXL2 antibody	NCT01362231	Part A: Phase I, randomized, placebo-controlled. Part B: Phase I randomized, open label.	Primary end point: Safety, tolerability and pharmacokinetics.	Sponsor aborted trial after interval Data monitoring Committee report	
		NCT01769196	Phase 2 randomized, placebo-controlled, multicenter study.	Primary end point: progression free survival defined as all –cause mortality or decrease in percent predicted in FVC Secondary end point: All-cause mortality.	Trial ongoing.

Nair GB, Expert Rev Respir Med 2016;10, 699-711

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PRM-151	**An anti-fibrotic and immunomodulator**	**NCT02550873**	**Phase 2, randomized, double-blind, placebo controlled, pilot study .**	**Primary end point: Safety and efficacy. Forced vital capacity (FVC) percent predicted change from baseline.**	**Trial ongoing.**
GSK2126458 (Omipalisib)	PI3Kα and mTOR inhibitor	NCT01725139	Phase I randomized, placebo-controlled study.	Primary end point: pharmacodynamics measured by inhibition of pAKT/AKT in platelet-rich plasma and BAL cells and inhibition of glucose uptake measured by thoracic PET/CT	Trial ongoing.
Sirolimus	mTOR inhibitor	NCT01462006	Randomized, double-blind, placebo-controlled pilot study	Primary end point: - Fibrocytes change in peripheral blood concentration of CXCR4+ fibrocytes -Number of subjects with drug side-effects	

Disease Specific Treatment

Scleroderma – MMF vs. Cytoxan

Tashkin. N Engl J Med 354:2655–2666, 2006
Clements 2015 ACR/ARHP Annual Meeting
Ann Rheum Dis 2015 Jun;74(6):1188-94

Rheumatoid Arthritis

Treatment with anti-inflammatory and/or immunosuppressive agents is recommended regardless of the pattern of fibrosis

Corticosteroids
Cyclophosphamide
Azathioprine
Mycophenalate

Fischer A, J Rheumatol 2013; 40: 640–646.
Assayag D Respirology 2014; 19: 493–500

Non-Pharmacological Treatment

Non – Pharmacological Therapies

- Long term oxygen therapy

Recommendation: We recommend that patients with IPF and clinically significant resting hypoxemia should be treated with long-term oxygen therapy (strong recommendation, very low-quality evidence).

- Mechanical ventilation

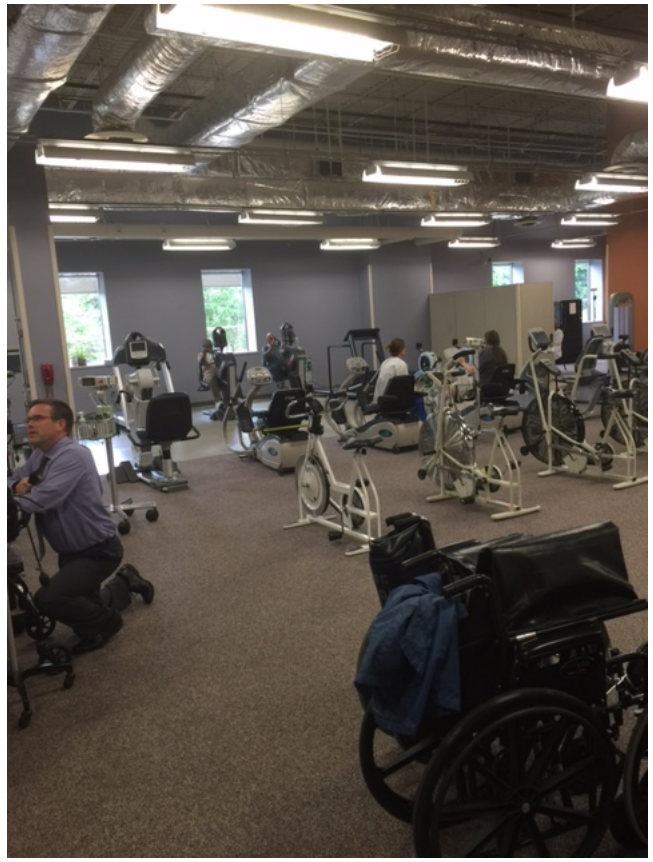
Recommendation: The majority of patients with respiratory failure due to IPF should not receive mechanical ventilation, but mechanical ventilation may be a reasonable intervention in a minority (weak recommendation, low-quality evidence).

- Palliative care

Specific goals for palliative care include relief from physical and emotional suffering and consideration for psychological and spiritual support for patients and caregivers. Such care will need to be individualized. Palliative care should be considered an adjunct to disease-focused care.

Am J Respir Crit Care Med 183. 788–824, 2011

Pulmonary rehabilitation

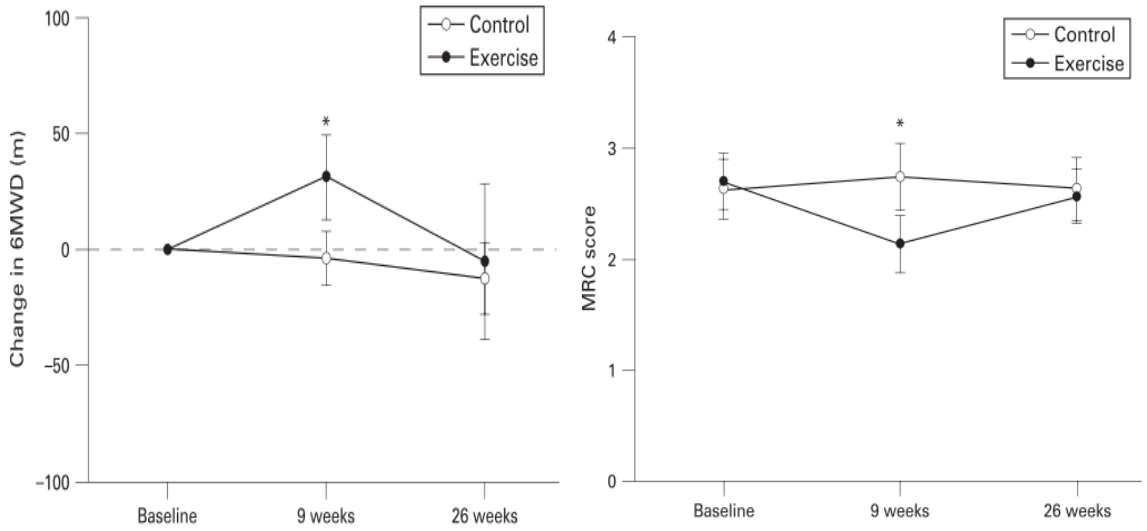


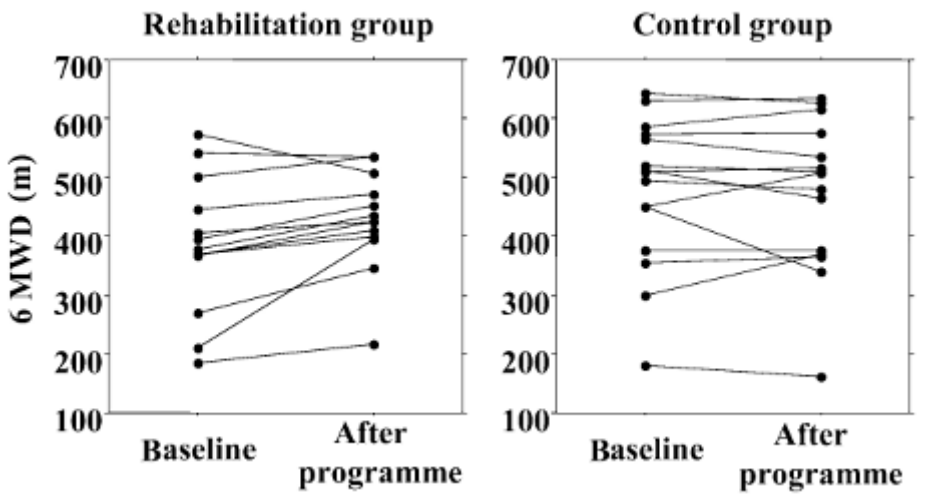
Non – Pharmacological Therapies

- Altered respiratory mechanics
- Impaired gas exchange
- Circulatory limitation
- Peripheral muscle dysfunction

Pulmonary rehabilitation

- **Improves 6 minute walk distance**
- **Decreased dyspnea score**
- **Improved health – related quality of life**





Holland Thorax 2008;63:549–554
Nishiyama Respirology 2008; 1: 394–399
Am J Respir Crit Care Med 188, e13–e64, Oct 15, 2013

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Phase	Frequency	Type	Time	Intensity	Considerations
Initial (0–6 weeks)	2–3 times a week	Aerobic Resistance Flexibility Breathing	20–40 min 10–20 min 10–15 min 5 min	50–60% of peak work rate 70–80% of average walking speed on 6MWT Borg scale 3–5	Adjust workloads to be tolerable by the patient Oxygen supplementation for desaturated patients (S_{pO_2} 85–88%) Use interval training modality emphasising that rest periods between exercise bouts allow for resaturation Consider reassessment of patients at the end of 6 weeks
Improvement (6 weeks to 6 months)	2–4 times a week	Aerobic Resistance Flexibility Breathing	20–50 min 20–30 min 10–15 min 5 min	60–85% of peak work rate 80–100% of average walking speed on 6MWT Borg scale 4–7	Gradually increase time and intensity with patient tolerance Oxygen supplementation for desaturated patients (S_{pO_2} 85–88%) Use interval training modality emphasising that rest periods between exercise bouts allow for resaturation Consider reassessment of patients at the end of 3 and 6 months
Maintenance (≥6 months)	3–4 times a week	Aerobic Resistance Flexibility Breathing	20–50 min 20–30 min 10–15 min 5 min	70–85% of peak work rate 85–100% of average walking speed on 6MWT Borg scale 5–7	Maintain the exercise intensity where possible Oxygen supplementation for desaturated patients (S_{pO_2} 85–88%) Use interval modality emphasising that rest periods between exercise bouts allow for resaturation Consider reassessment of patients at 12 months and every 6 months

Vainshelboim B. Exercise training in idiopathic pulmonary fibrosis: is it of benefit? Breathe 2016; 12: 130–138

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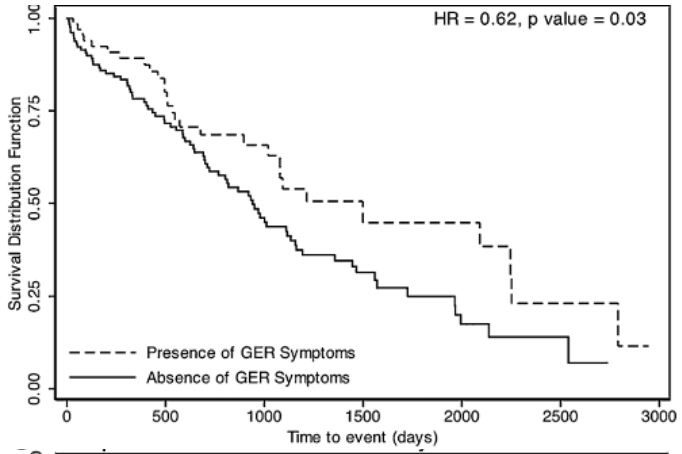
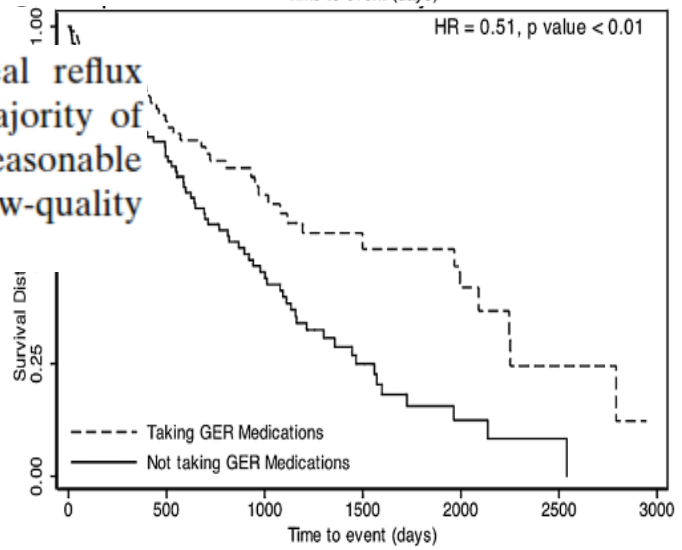
Treatment of GERD

- Role of chronic microaspiration
- 204 patients with IPF
- Symptoms of GER (34%), a history of GER di
  GER m
- Anti-re
  increased survival and decreased radiological fibrosis score

Recommendation: Asymptomatic gastroesophageal reflux disease should be medically treated in the majority of patients with IPF, but treatment may not be reasonable in a minority (weak recommendation, very low-quality evidence).





Lee. AJRCCM 2011 184. 1390–1394

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Pulmonary Fibrosis Support Group

Summary