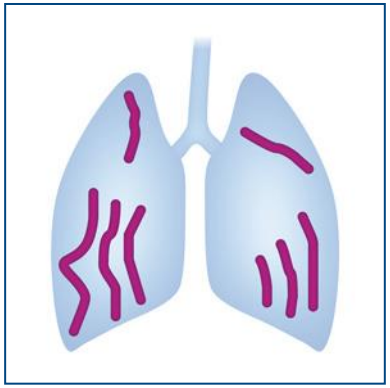
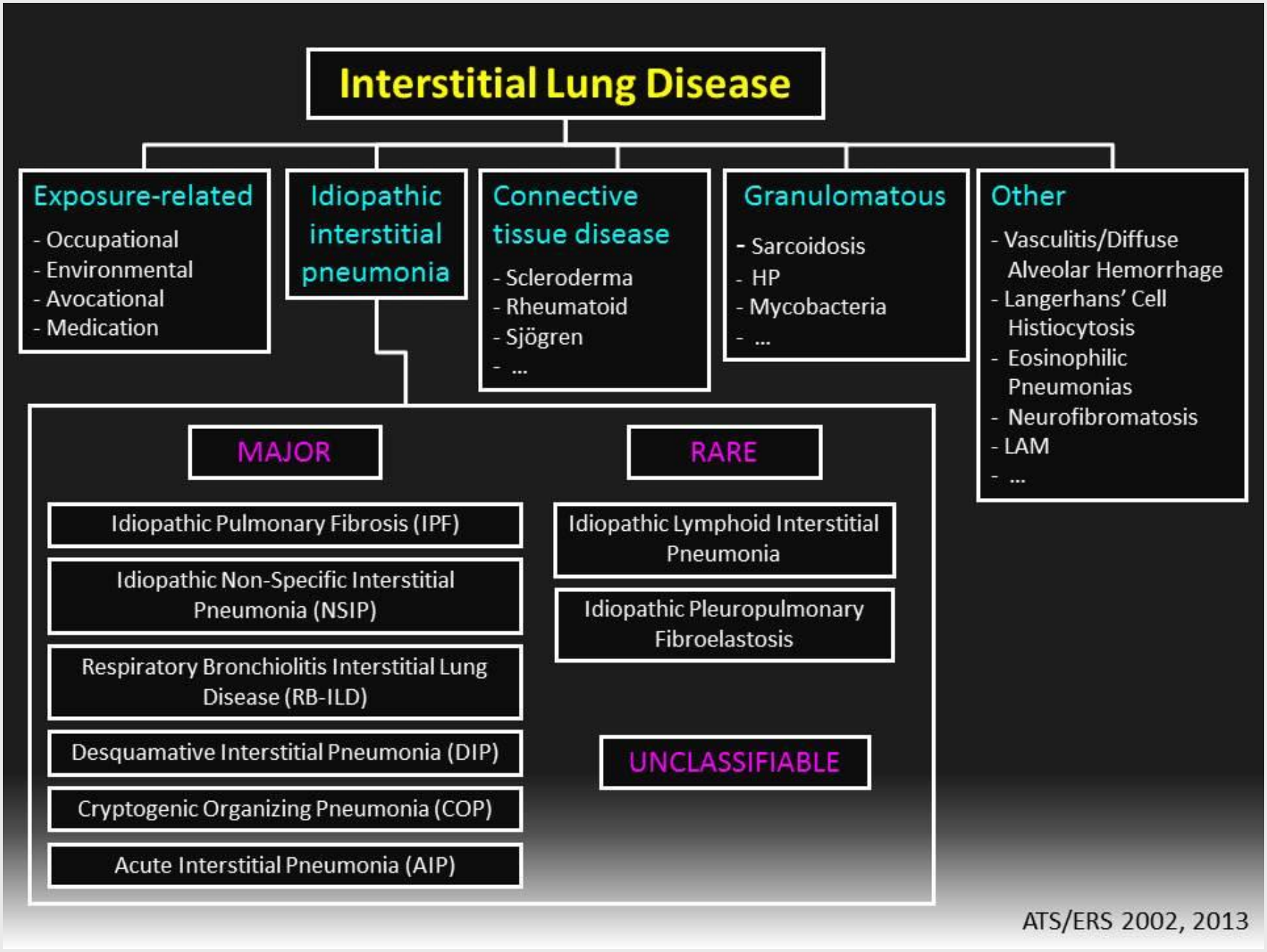
Pneumo Update Europe 2016

24-25 June, Prague

Interstitial Lung Diseases



Luca Richeldi, UK


Interstitial Lung Disease
Exposure-related
- Occupational
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- Avocational
- Medication
Idiopathic interstitial pneumonia
Connective tissue disease
- Scleroderma
- Rheumatoid
- Sjögren
- ...
Granulomatous
- Sarcoidosis
- HP
- Mycobacteria
- ...
Other
- Vasculitis/Diffuse Alveolar Hemorrhage
- Langerhans' Cell Histiocytosis
- Eosinophilic Pneumonias
- Neurofibromatosis
- LAM
- ...
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
ATS/ERS 2002, 2013

SUBTOPICS

1. The fine line of autoimmunity
2. The challenge of “idiopathic”
3. IPF: why, how and when
4. IPF: the role of genes

SUBTOPICS

1. **The fine line of autoimmunity**
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3. **IPF: why, how and when**
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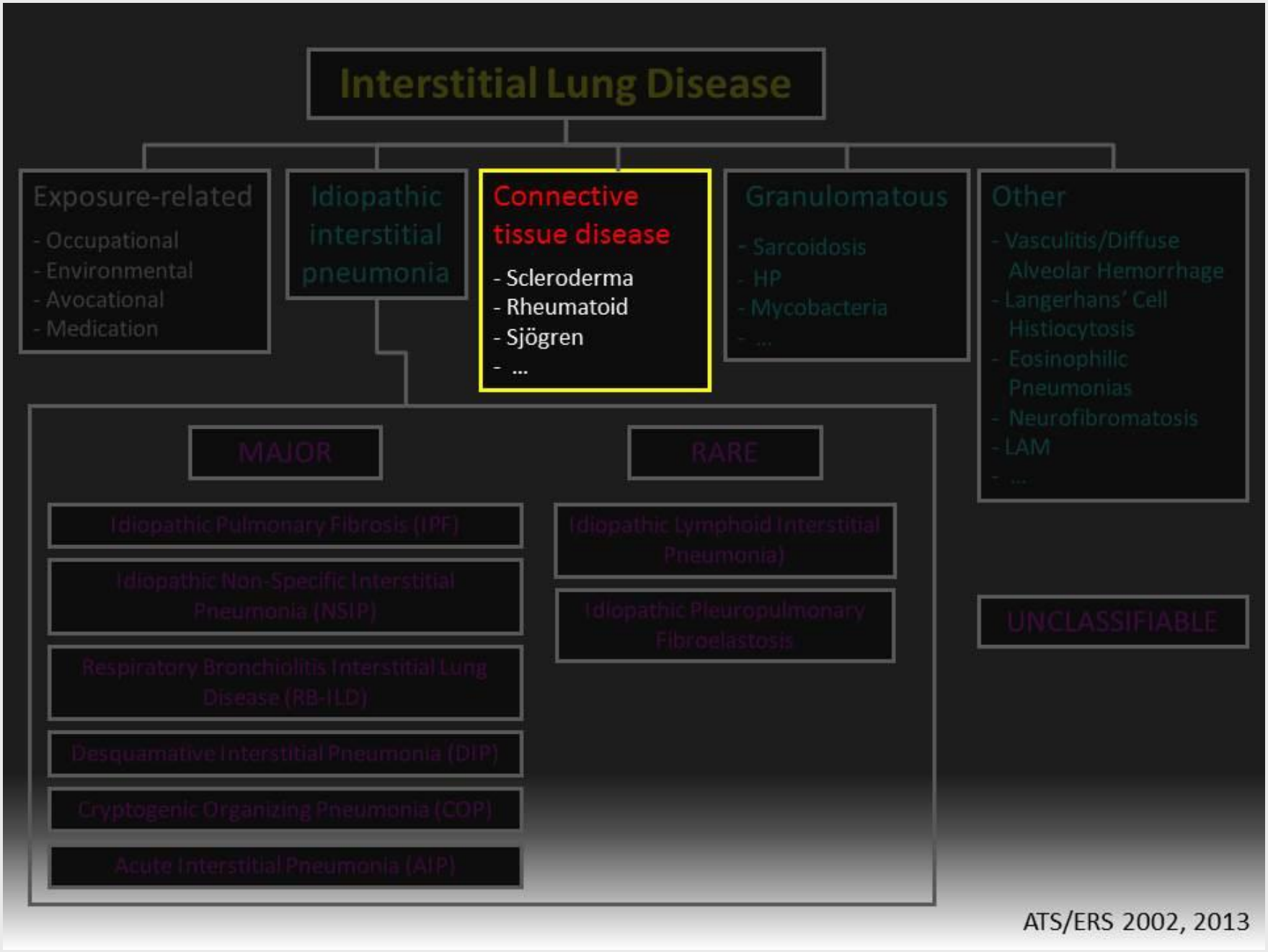
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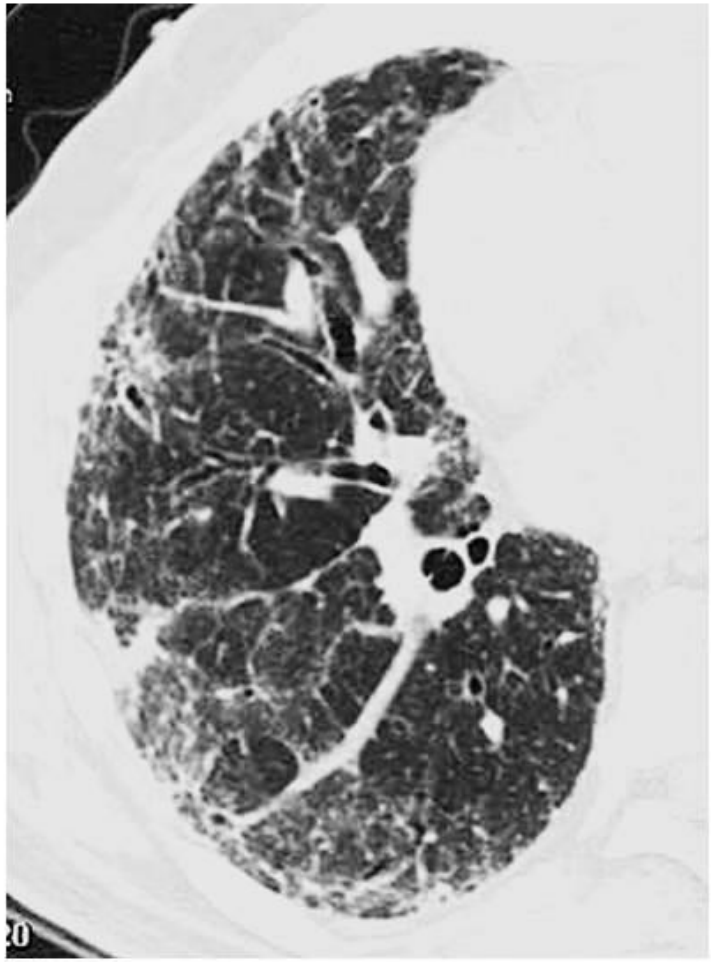
UNCLASSIFIABLE
ATS/ERS 2002, 2013

Cottin V et al, Springer 2015

55 year old man
RF and CCP both high-positive, no arthritis

RA-ILD?



IPF?

TASK FORCE REPORT
ERS/ATS RESEARCH STATEMENT

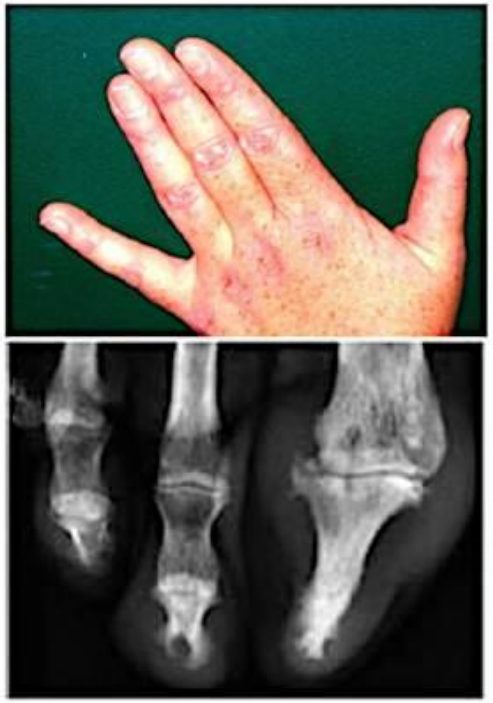
An official European Respiratory Society/ American Thoracic Society research statement: interstitial pneumonia with autoimmune features

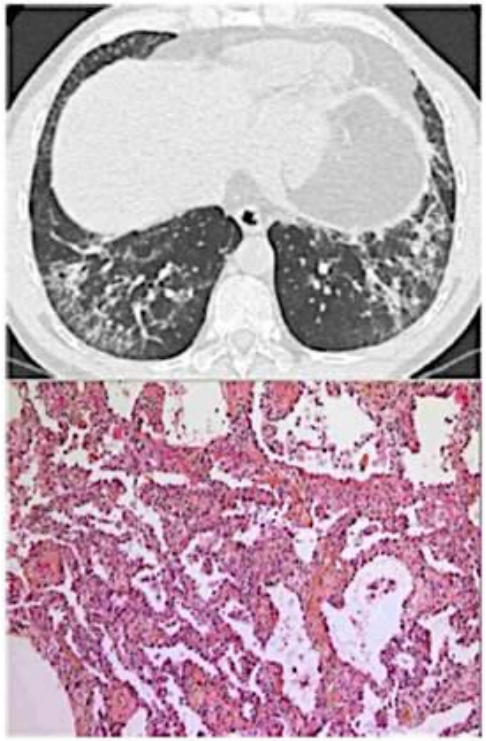
Aryeh Fischer[1,17,18], Katerina M. Antoniou[2], Kevin K. Brown[3], Jacques Cadranel[4], Tamera J. Corte[5,18], Roland M. du Bois[6], Joyce S. Lee[7,18], Kevin O. Leslie[8], David A. Lynch[9], Eric L. Matteson[10], Marta Mosca[11], Imre Noth[12], Luca Richeldi[13], Mary E. Strek[12,18], Jeffrey J. Swigris[3,18], Athol U. Wells[14], Sterling G. West[15], Harold R. Collard[7,18,19] and Vincent Cottin[16,18,19], on behalf of the "ERS/ATS Task Force on Undifferentiated Forms of CTD-ILD"

ERJ 2015; 46: 976-87

"Interstitial Pneumonia with Autoimmune Features"

IPAF





Fischer A et al, *ERJ* 2015; 46: 976-87

ORIGINAL ARTICLE
INTERSTITIAL LUNG DISEASES

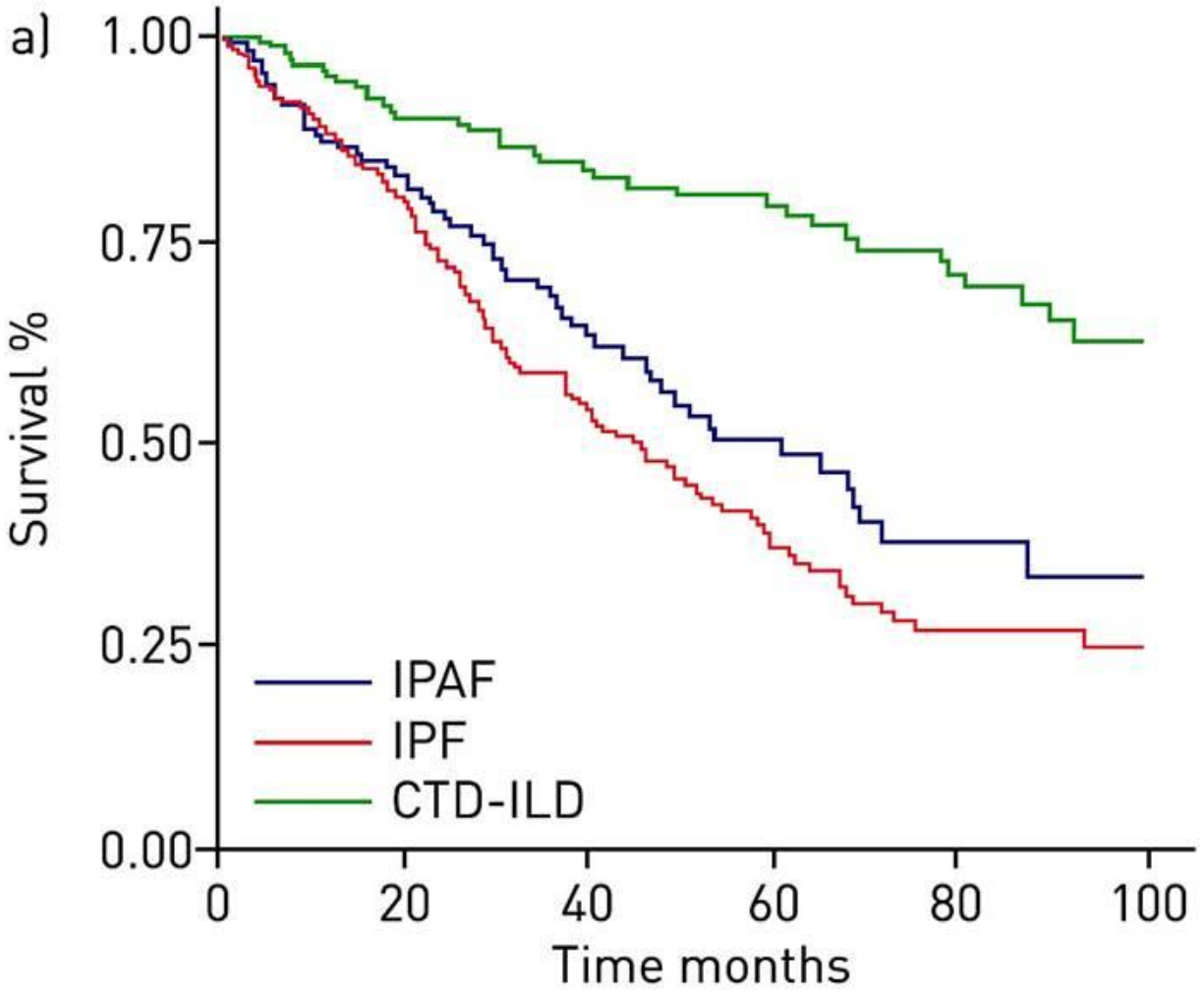
Characterisation of patients with interstitial pneumonia with autoimmune features

Justin M. Oldham[1,8], Ayodeji Adegunsoye[2,8], Eleanor Valenzi[3], Cathryn Lee[3], Leah Witt[2], Lena Chen[2], Aliya N. Husain[4], Steven Montner[5], Jonathan H. Chung[5], Vincent Cottin[6], Aryeh Fischer[7], Imre Noth[2], Rekha Vij[2,9] and Mary E. Strek[2,9]

ERJ 2016; 47: 1622-4

Domains met	IPAF cohort	Initial diagnosis			
		NSIP/COP	IPF	UCTD-ILD	Unclassifiable
Subjects	144	9	49	72	14
Clinical and serological	21 (14.6)	0 (0)	3 (6.1)	17 (23.6)	1 (7.1)
Clinical and morphological	12 (8.3)	2 (22.2)	0 (0)	6 (8.3)	4 (28.6)
Serological and morphological	73 (50.7)	7 (77.8)	43 (87.8)	16 (22.2)	7 (50)
All three domains	38 (26.4)	0 (0)	3 (6.1)	33 (45.8)	2 (14.3)

Oldham JM et al, *ERJ* 2016; 47: 1622-4



Oldham JM et al, *ERJ* 2016; 47: 1622-4

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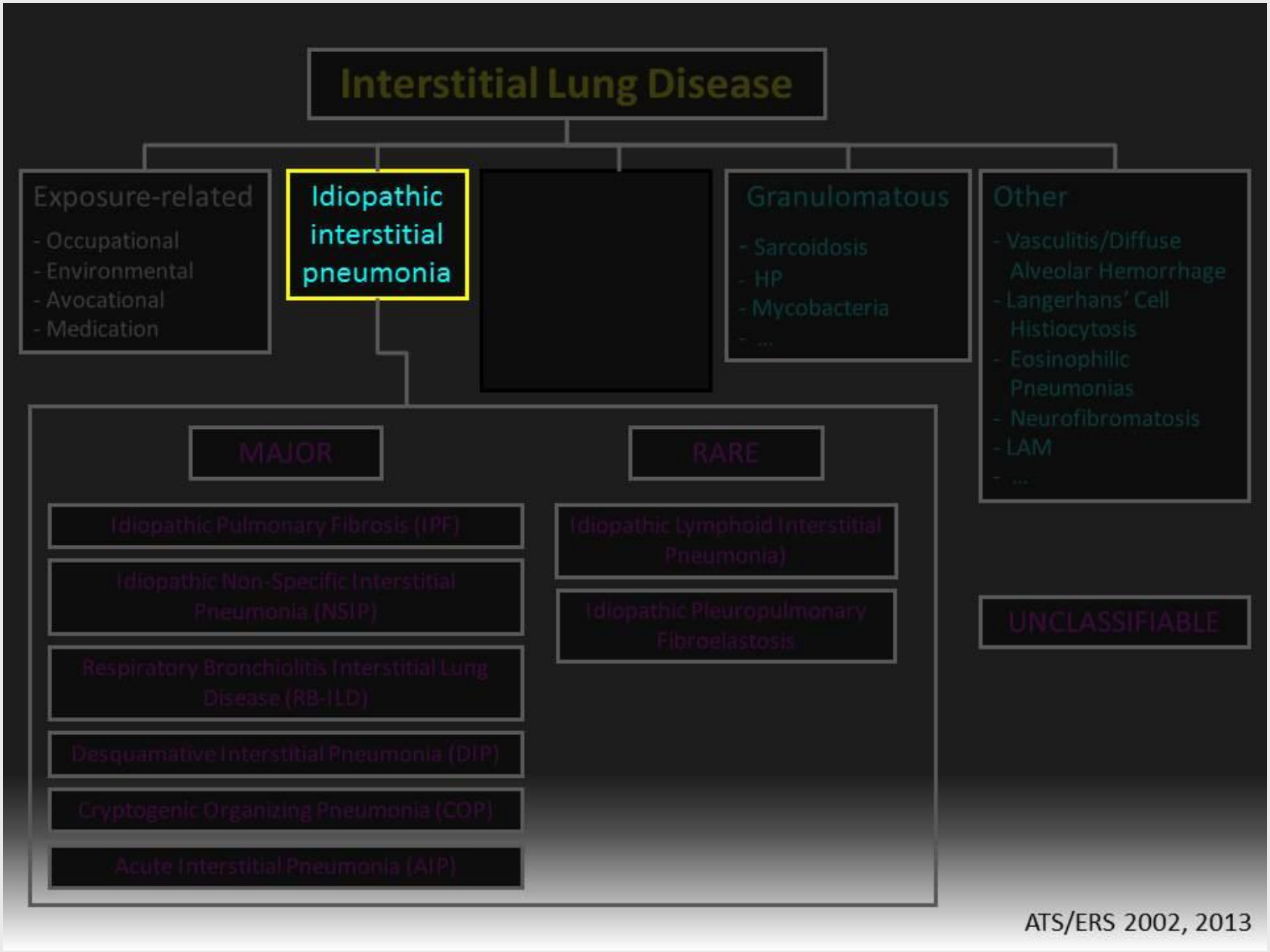
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Idiopathic Pleuropulmonary Fibroelastosis
UNCLASSIFIABLE
ATS/ERS 2002, 2013

An Official American Thoracic Society/European Respiratory Society Statement: Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias

William D. Travis, Ulrich Costabel, David M. Hansell, Talmadge E. King, Jr., David A. Lynch, Andrew G. Nicholson, Christopher J. Ryerson, Jay H. Ryu, Moisés Selman, Athol U. Wells, Jurgen Behr, Demosthenes Bouros, Kevin K. Brown, Thomas V. Colby, Harold R. Collard, Carlos Robalo Cordeiro, Vincent Cottin, Bruno Crestani, Marjolein Drent, Rosalind F. Dudden, Jim Egan, Kevin Flaherty, Cory Hogaboam, Yoshikazu Inoue, Takeshi Johkoh, Dong Soon Kim, Masanori Kitaichi, James Loyd, Fernando J. Martinez, Jeffrey Myers, Shandra Protzko, Ganesh Raghu, Luca Richeldi, Nicola Sverzellati, Jeffrey Swigris, and Dominique Valeyre; on behalf of the ATS/ERS Committee on Idiopathic Interstitial Pneumonias

AJRCCM 2013; 188: 733-748

REVISED ATS/ERS IIPs CLASSIFICATION:
CATEGORIZATION OF MAJOR IIPs

CATEGORY	CLINICAL-RADIOLOGICAL-PATHOLOGICAL DX	ASSOCIATED MORPHOLOGIC PATTERNS
Chronic fibrosing IP	**IPF** **I-NSIP**	UIP NSIP
Smoking-related IP	**RB-ILD** **DIP**	RB DIP
Acute/Subacute IP	**COP** **AIP**	OP DAD

AJRCCM 2013; 188: 733-748

REVISED ATS/ERS IIPS CLASSIFICATION:
CLASSIFICATION ACCORDING TO DISEASE BEHAVIOR - 1

CLINICAL BEHAVIOR	TREATMENT GOAL	MONITORING STRATEGY
Reversible and self-limited (e.g. RB-ILD)	**Remove possible cause**	Short-term (3-6 months) observation to confirm disease regression
Reversible with risk of progression (e.g. some NSIP, COP, DIP)	**Initially for a response and then rationalize longer term therapy**	Short-term observation to confirm response: long-term observation to ensure gains are preserved
Stable with residual disease (e.g. some NSIP)	**Maintain status**	Long-term observation to assess disease course

AJRCCM 2013; 188: 733-748

REVISED ATS/ERS IIPS CLASSIFICATION:
CLASSIFICATION ACCORDING TO DISEASE BEHAVIOR - 2

CLINICAL BEHAVIOR	TREATMENT GOAL	MONITORING STRATEGY
Progressive, irreversible with potential for stabilization (e.g. some NSIP)	**To stabilize**	Long-term (3-6 months) observation to assess disease course
Progressive, irreversible despite therapy (e.g. some NSIP, IPF)	**To slow progression**	Long-term observation to assess disease course and need for transplant or effective palliation

AJRCCM 2013; 188: 733-748

EXECUTIVE SUMMARY

- NSIP is now much better defined.
- Smoking-related ILD commonly diagnosed without surgical lung biopsy.
- A classification based on disease behavior is proposed, in particular for patients difficult to classify.
- A substantial percentage of patients with IIP are difficult to classify.

AJRCCM 2013; 188: 733-748

EXECUTIVE SUMMARY

- The rapidly evolving field of molecular markers is promoted to help diagnosis, and potentially prognosis and treatment.

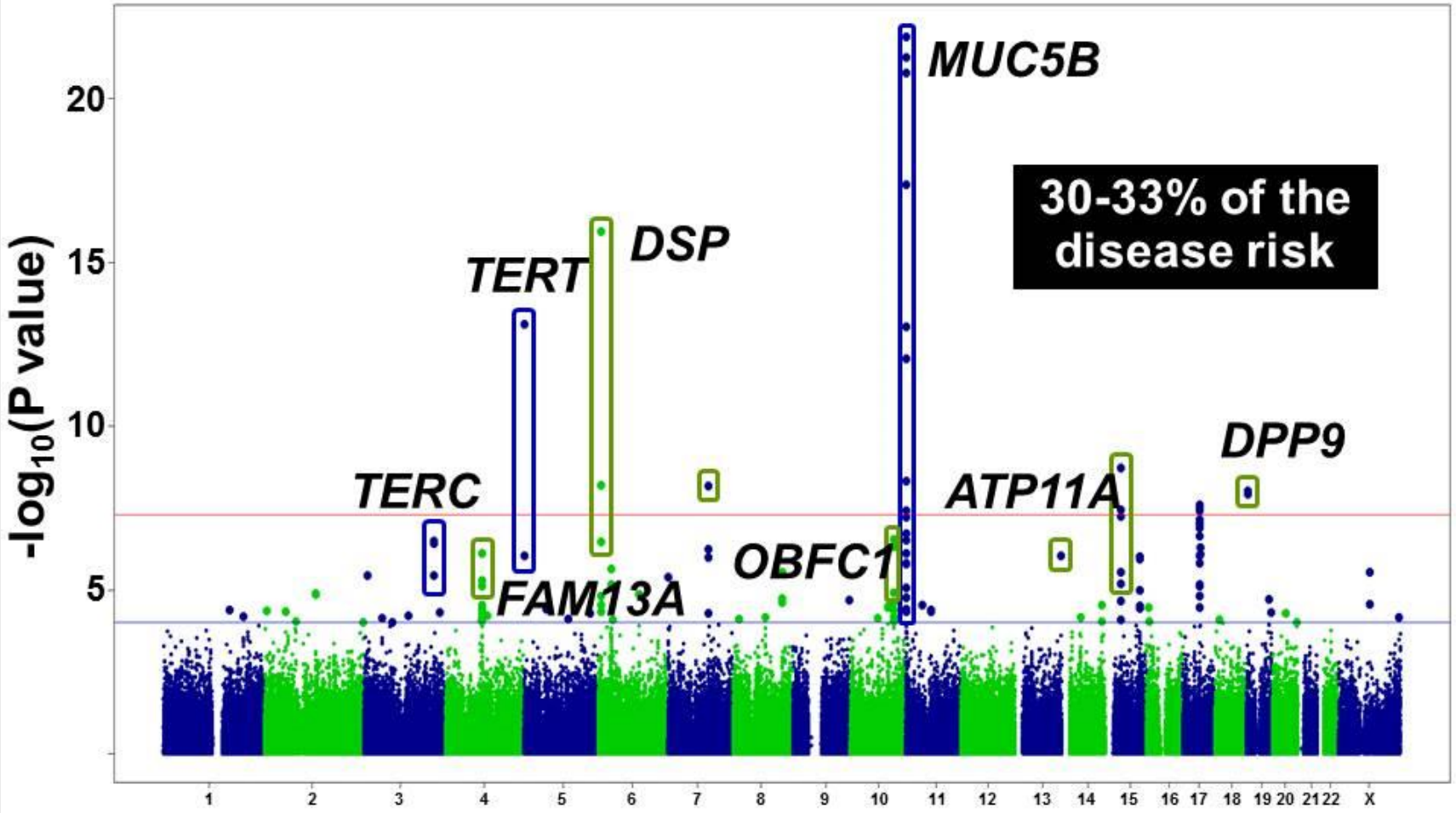
Travis WD et al, *AJRCCM* in press

A Common *MUC5B* Promoter Polymorphism and Pulmonary Fibrosis

Max A. Seibold, Ph.D., Anastasia L. Wise, Ph.D., Marcy C. Speer, Ph.D.,*
Mark P. Steele, M.D., Kevin K. Brown, M.D., James E. Loyd, M.D.,
Tasha E. Fingerlin, Ph.D., Weiming Zhang, Ph.D.,
Gunnar Gudmundsson, M.D., Ph.D., Steve D. Groshong, M.D., Ph.D.,
Christopher M. Evans, Ph.D., Stavros Garantziotis, M.D.,
Kenneth B. Adler, Ph.D., Burton F. Dickey, M.D., Roland M. du Bois, M.D.,
Ivana V. Yang, Ph.D., Aretha Herron, B.A., Dolly Kervitsky, B.A., Janet L. Talbert, M.S.,
Cheryl Markin, B.A., Joungjoa Park, B.A., Anne L. Crews, B.A., Susan H. Slifer, Ph.D.,
Scott Auerbach, Ph.D., Michelle G. Roy, B.A., Jia Lin, B.A., Corinne E. Hennessy, M.S.,
Marvin I. Schwarz, M.D., and David A. Schwartz, M.D.

N Engl J Med 2011; 364: 1503-12

Genome Wide Association Study in IIP



Courtesy David Schwartz

Fingerlin. *Nat Genet* 2013; 45:613

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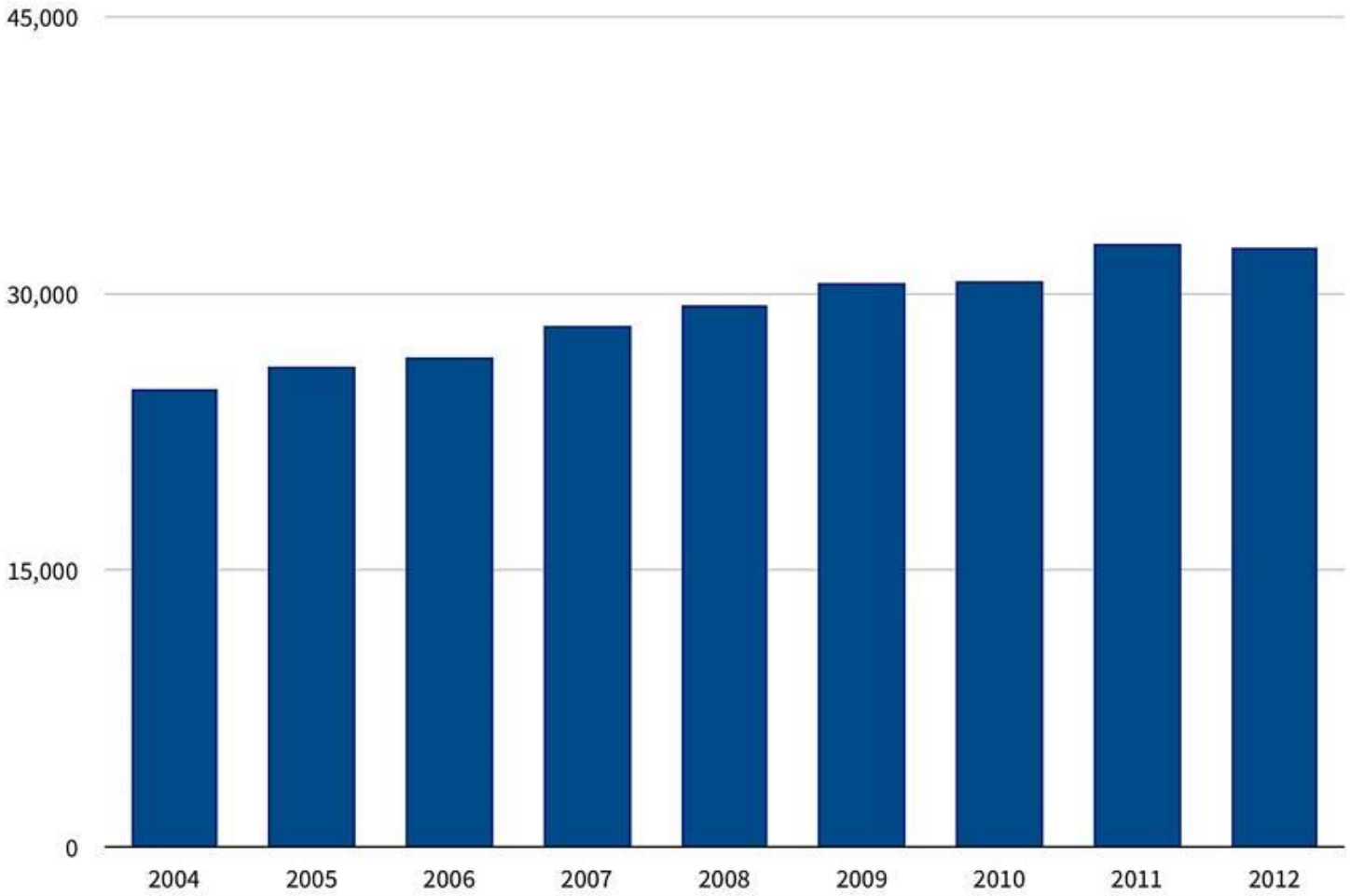
Idiopathic pulmonary fibrosis statistics

Our statistics about the prevalence, incidence and mortality of IPF in the UK, and how they affect different demographics.

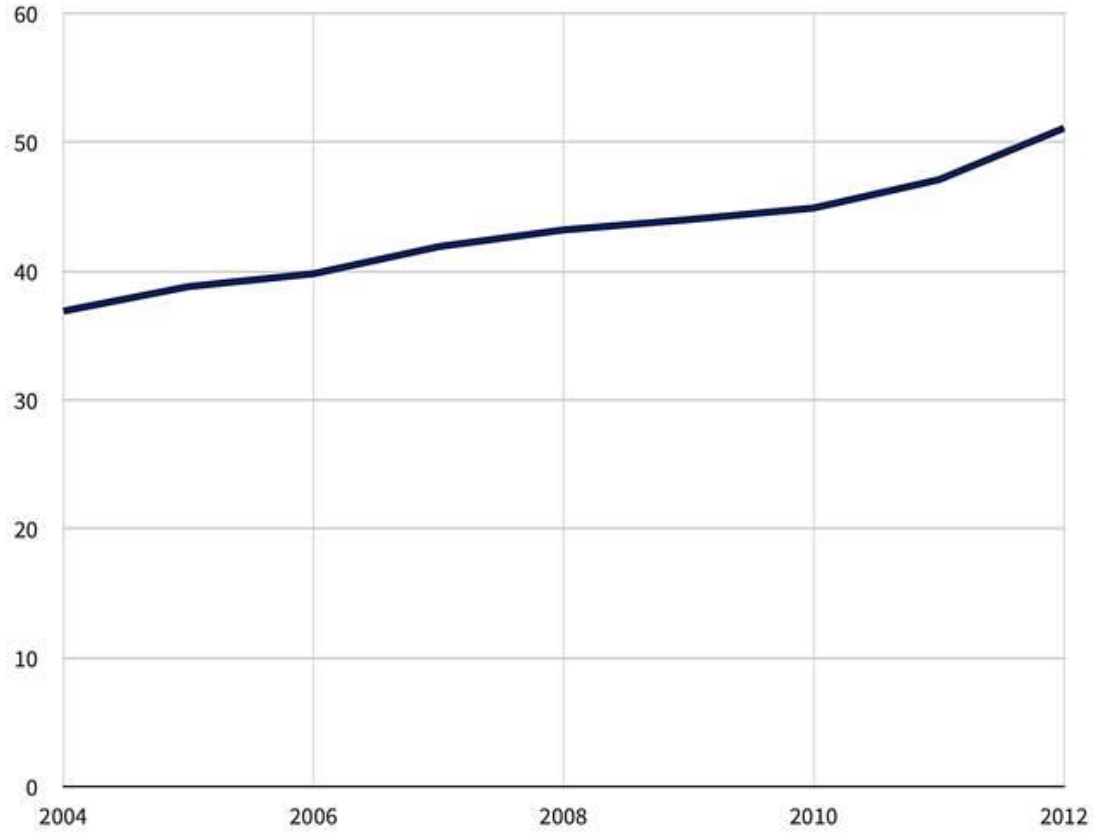
https://www.blf.org.uk/support-for-you/idiopathic-pulmonary-fibrosis-ipf/statistics

Estimated numbers of people with idiopathic pulmonary fibrosis 2004–12



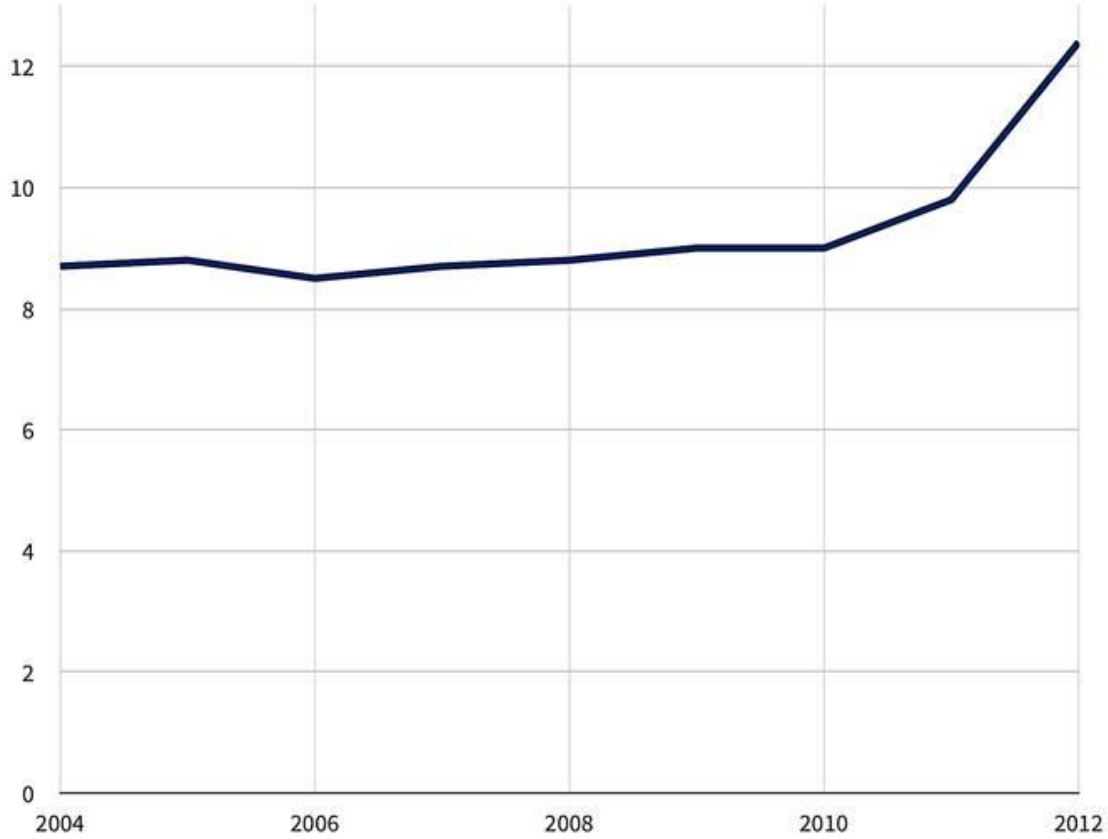
https://www.blf.org.uk/support-for-you/idiopathic-pulmonary-fibrosis-ipf/statistics

Number of living people per 100,000 ever diagnosed with idiopathic pulmonary fibrosis, 2004-2012



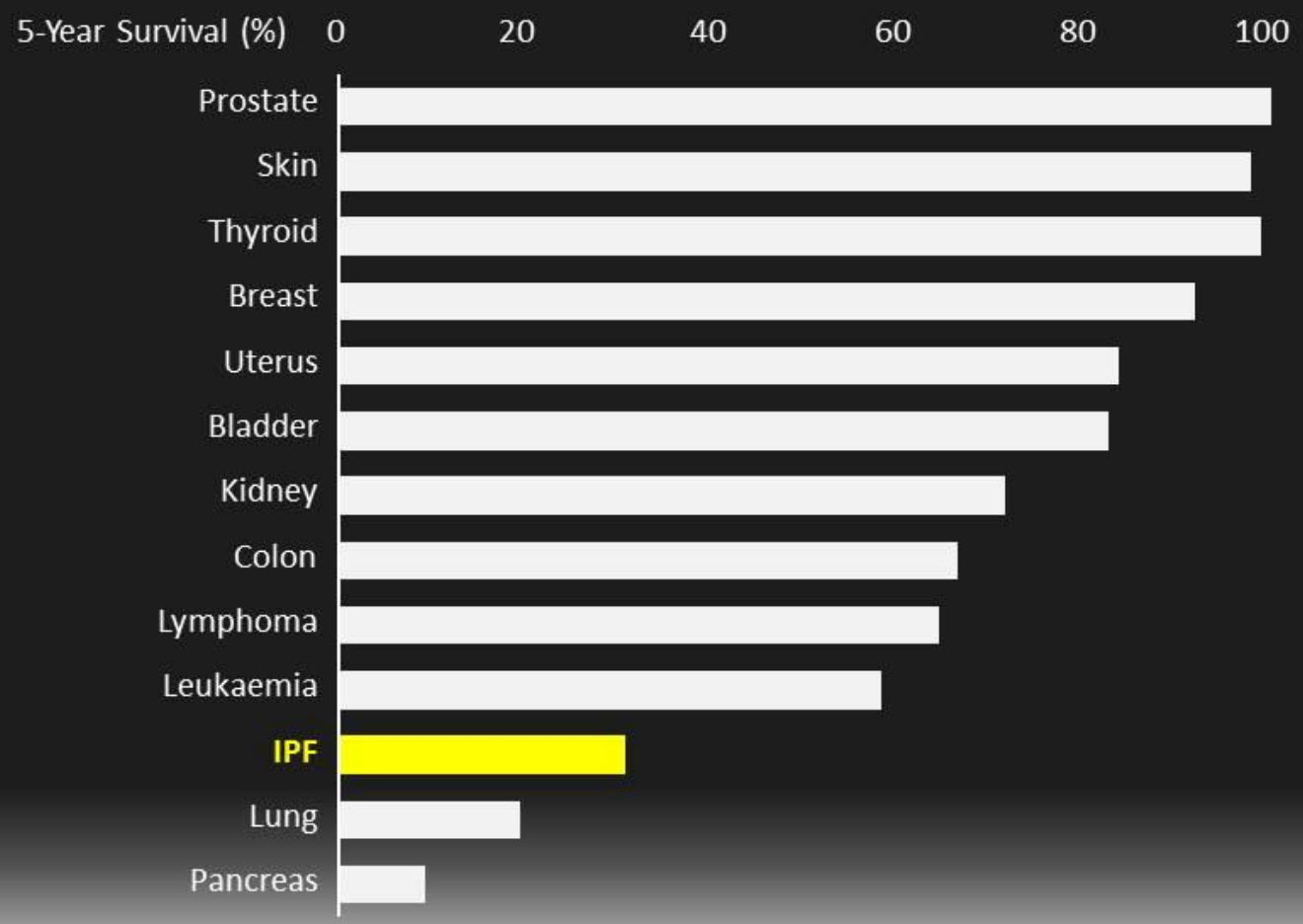
https://www.blf.org.uk/support-for-you/idiopathic-pulmonary-fibrosis-ipf/statistics

Number of people per 100,000 newly diagnosed with idiopathic pulmonary fibrosis, each year, 2004–12



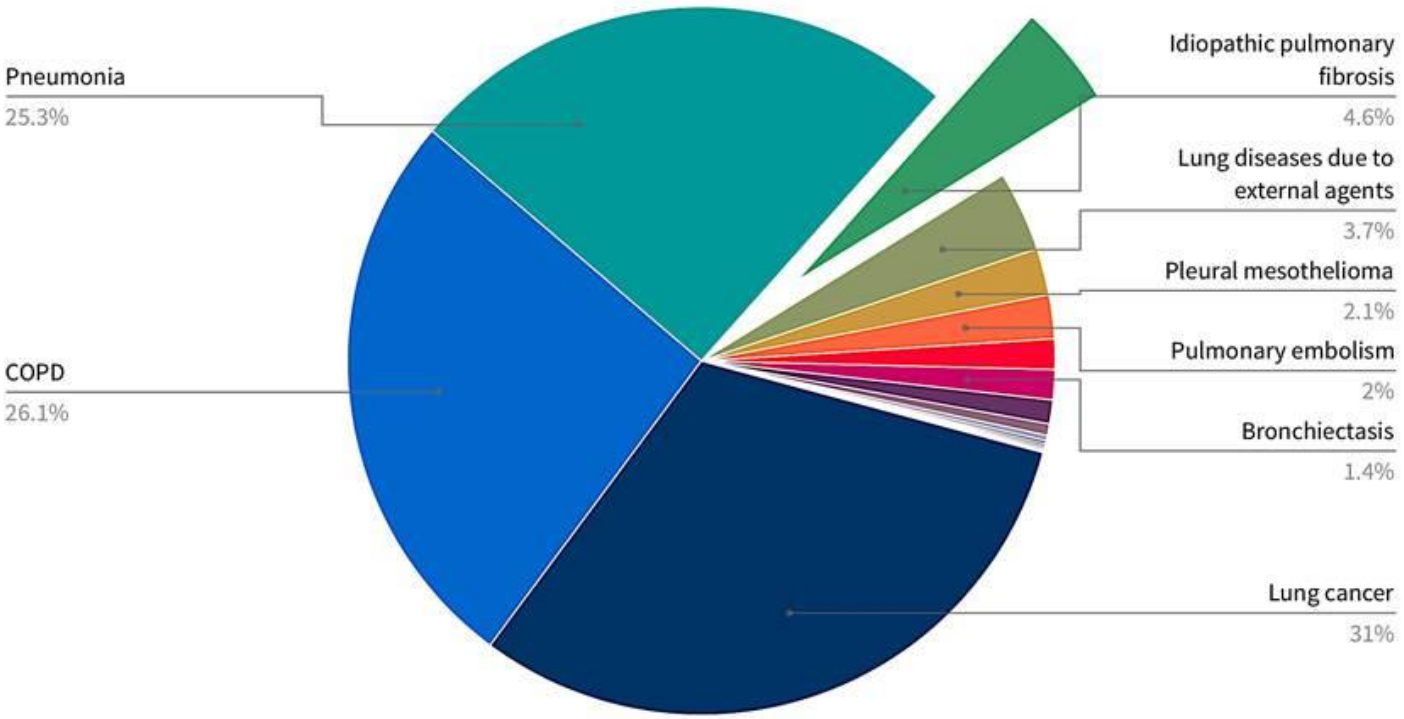
https://www.blf.org.uk/support-for-you/idiopathic-pulmonary-fibrosis-ipf/statistics

IPF: PROGNOSIS WORSE THAN MOST CANCERS



Vancheri et al, *Eur Respir J* 2010; 35: 496-504

UK deaths from idiopathic pulmonary fibrosis compared with other lung diseases, 2012



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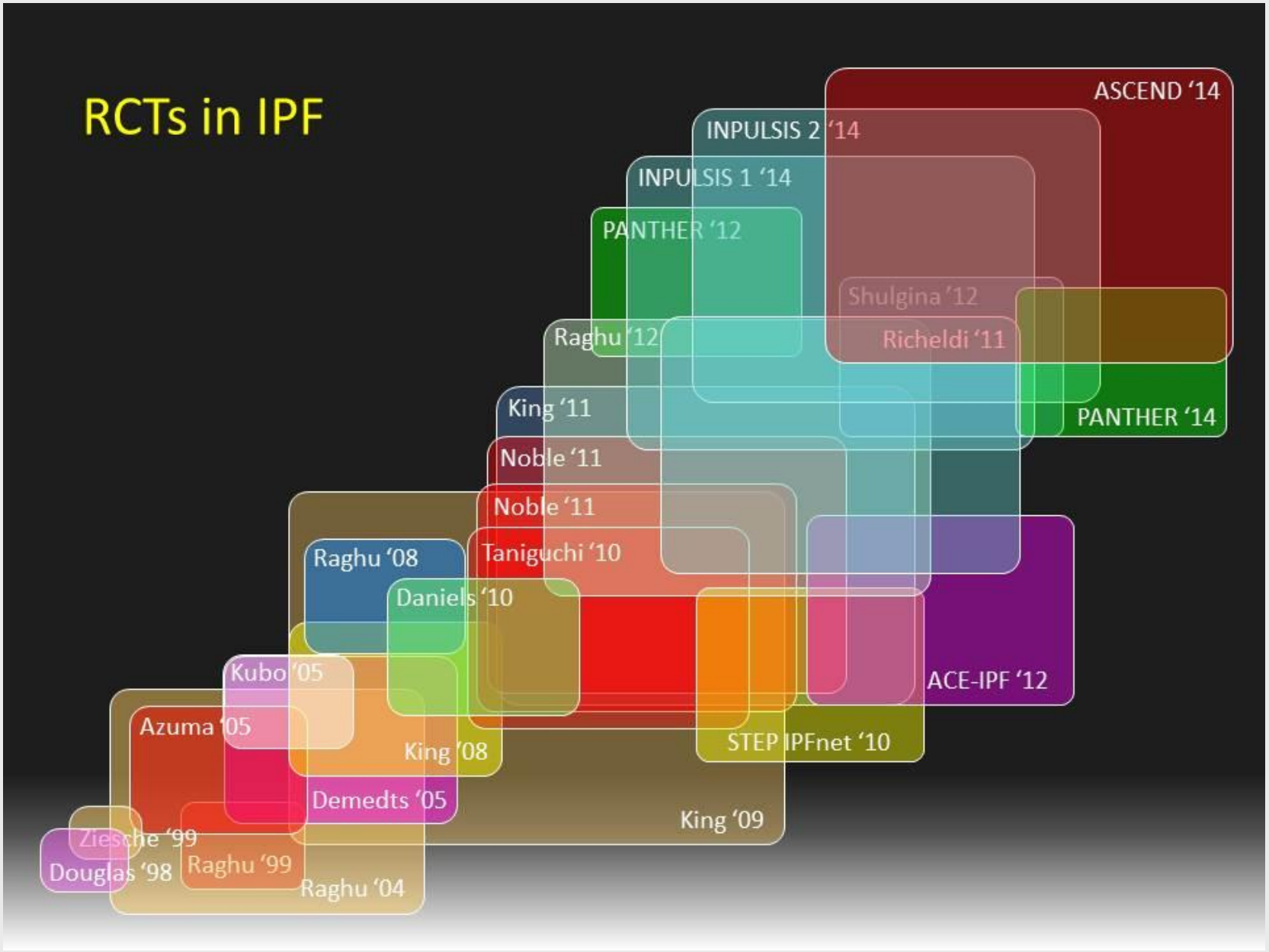

RCTs in IPF
ASCEND '14
INPULSIS 2 '14
INPULSIS 1 '14
PANTHER '12
Shulgina '12
Richeldi '11
Raghu '12
PANTHER '14
King '11
Noble '11
Noble '11
Taniguchi '10
Raghu '08
Daniels '10
ACE-IPF '12
Kubo '05
Azuma '05
King '08
STEP IPFnet '10
Demedts '05
King '09
Ziesche '99
Douglas '98
Raghu '99
Raghu '04

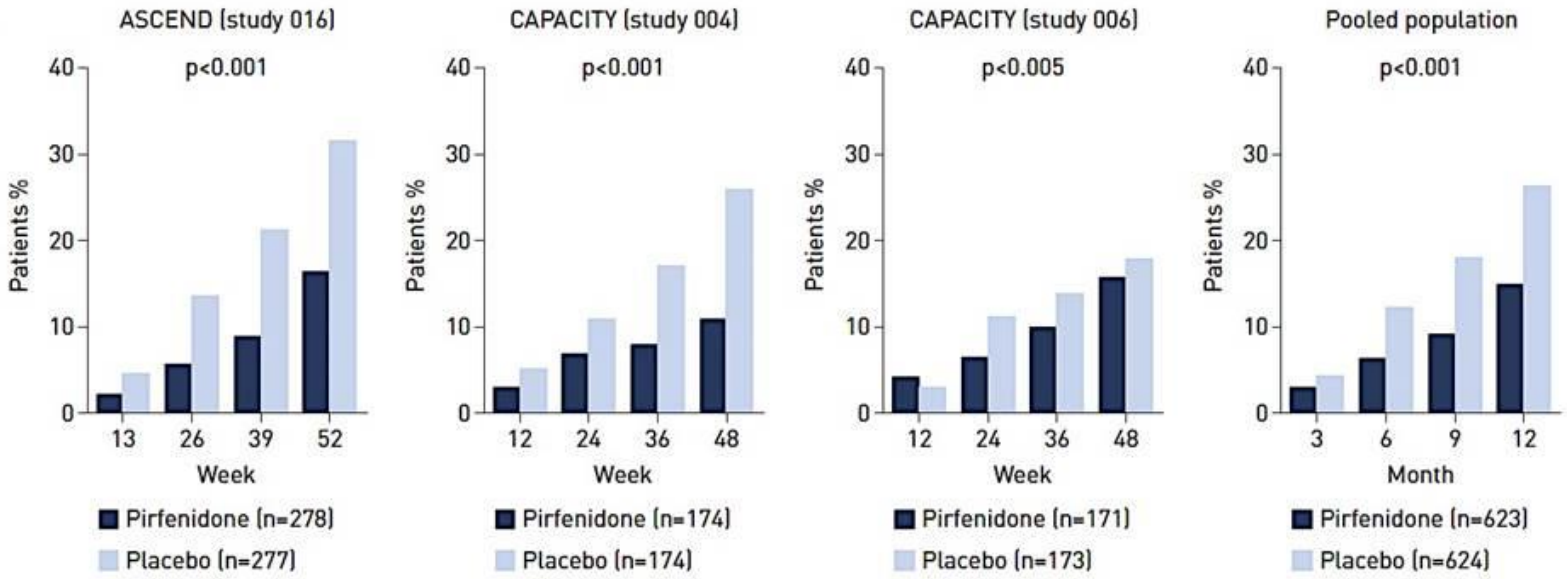
Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials

Paul W. Noble[1], Carlo Albera[2], Williamson Z. Bradford[3], Ulrich Costabel[4], Roland M. du Bois[5], Elizabeth A. Fagan[3], Robert S. Fishman[3], Ian Glaspole[6], Marilyn K. Glassberg[7], Lisa Lancaster[8], David J. Lederer[9], Jonathan A. Leff[3], Steven D. Nathan[10], Carlos A. Pereira[11], Jeffrey J. Swigris[12], Dominique Valeyre[13] and Talmadge E. King Jr[14]

ERJ 2016; 47: 27-30

PROPORTION OF PATIENTS WITH FORCED VITAL CAPACITY PERCENT PREDICTED DECLINE >10% OR DEATH

Rank ANCOVA (pirfenidone 2403 mg/day versus placebo)



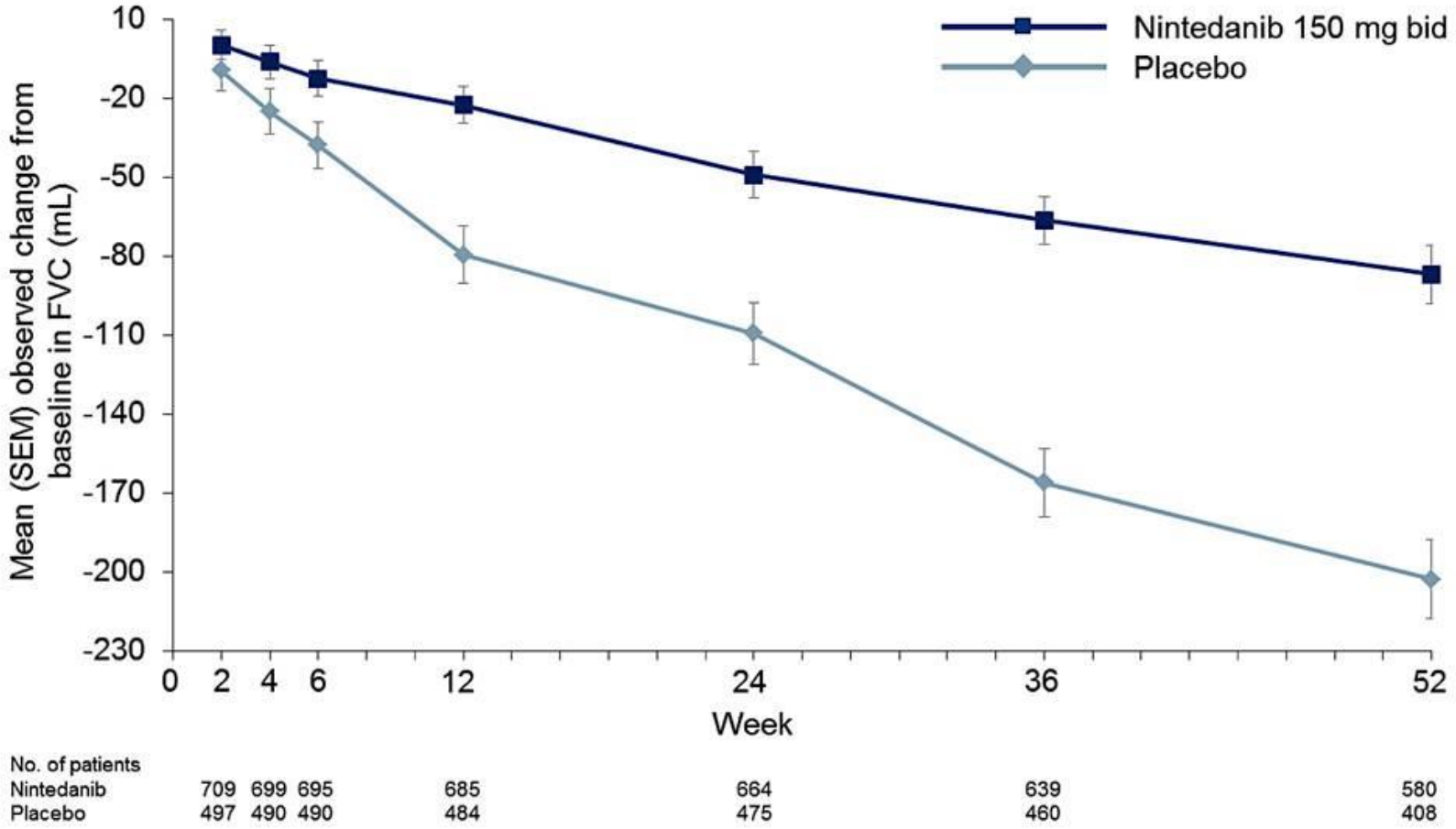
Noble PW et al, *ERJ* 2016; 47: 27-30

Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the TOMORROW and INPULSIS® trials

Luca Richeldi [a, *], Vincent Cottin [b], Roland M. du Bois [c], Moisés Selman [d], Toshio Kimura [e], Zelie Bailes [f], Rozsa Schlenker-Herceg [g], Susanne Stowasser [e], Kevin K. Brown [h]

Resp Med 2016; 113: 74-9

CHANGES IN FORCED VITAL CAPACITY OVER TIME
POOLED DATA FROM THE TOMORROW AND INPULSIS TRIALS



Richeldi L et al, *Resp Med* 2016; 113: 74-9

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

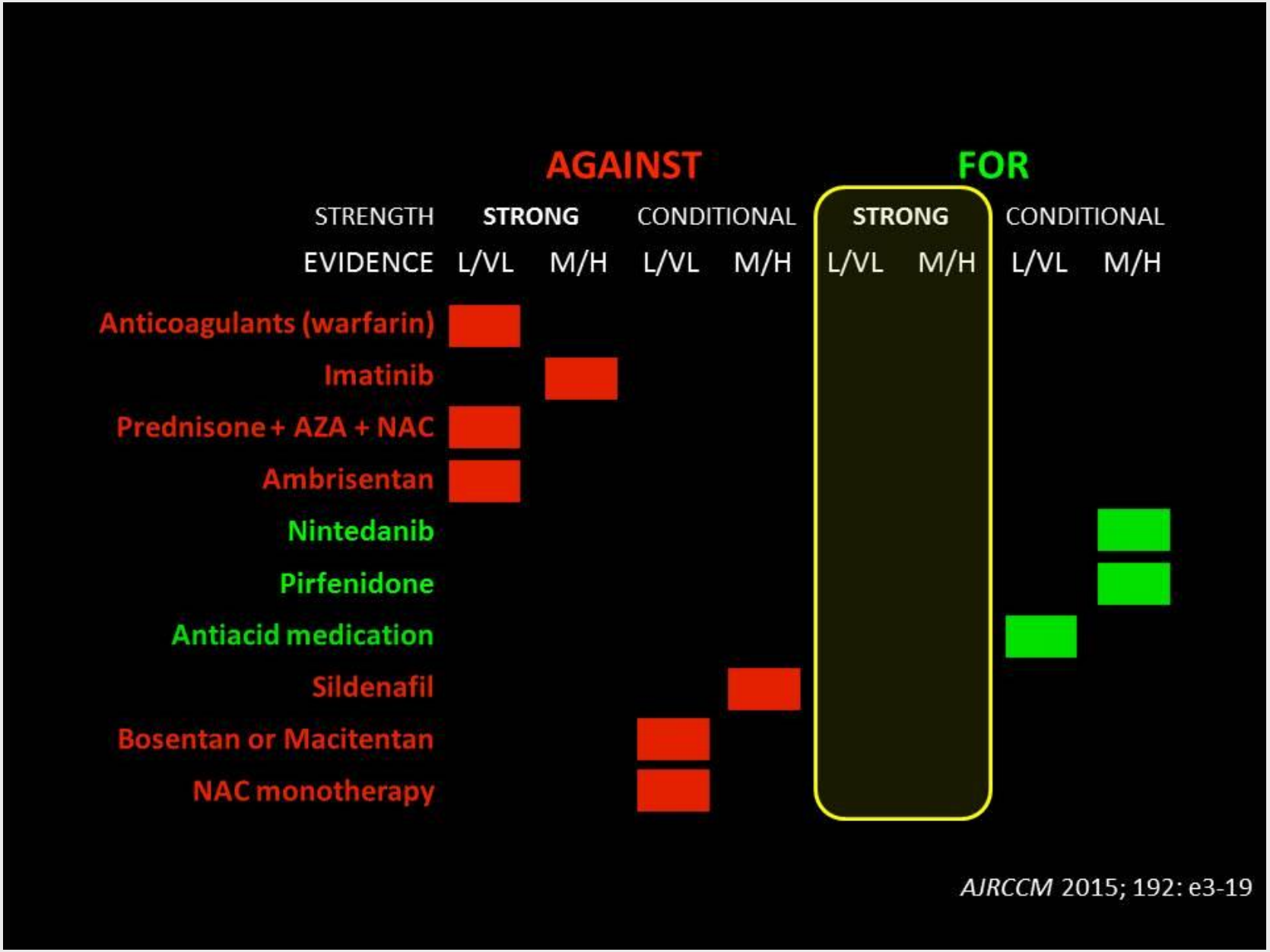
An Update of the 2011 Clinical Practice Guideline

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

AJRCCM 2015; 192: e3-19


AGAINST
FOR
STRENGTH
STRONG
CONDITIONAL
STRONG
CONDITIONAL
EVIDENCE
L/VL
M/H
L/VL
M/H
L/VL
M/H
L/VL
M/H
Anticoagulants (warfarin)
Imatinib
Prednisone + AZA + NAC
Ambrisentan
Nintedanib
Pirfenidone
Antiacid medication
Sildenafil
Bosentan or Macitentan
NAC monotherapy
AJRCCM 2015; 192: e3-19

Combination therapy: the future of management for idiopathic pulmonary fibrosis?

Wim A Wuyts, Katerina M Antoniou, Keren Borensztajn, Ulrich Costabel, Vincent Cottin, Bruno Crestani, Jan C Grutters, Toby M Maher, Venerino Poletti, Luca Richeldi, Carlo Vancheri, Athol U Wells

Lancet Resp Med 2014; 11: 933-42

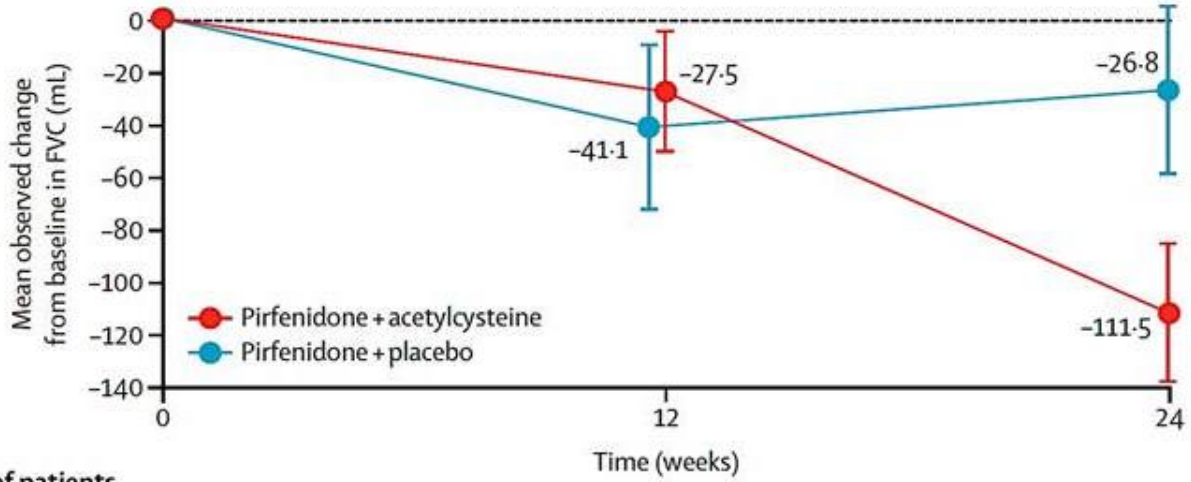
	Pathways targeted	Example of efficacious combination therapy
Lung cancer[41,42]	Crosslinking of DNA (platinum); microtubule toxin (vinorelbine); nucleoside analogue; gemcitabine; EGFR (erlotinib, gefitinib)	Platinum-based drug (cisplatin or carboplatin) with vinorelbine or gemcitabine; so-called traditional cytotoxic drugs and inhibitors of EGFR
COPD[43,44]	Longacting β agonists, longacting muscarinic antagonists, inhaled corticosteroids, phosphodiesterase 4 inhibitor	Longacting β agonists with longacting muscarinic antagonists; longacting β agonists with inhaled corticosteroids; glycopyrronium with indacaterol; umeclidinium with vilanterol; longacting β agonists with inhaled corticosteroids and vilanterol
Asthma[45,46]	Longacting β agonists, longacting muscarinic antagonists, inhaled corticosteroids	Longacting β agonists with inhaled corticosteroids, longacting muscarinic antagonists with inhaled corticosteroids
Pulmonary arterial hypertension[47-49]	Guanylate cyclase–phosphodiesterase-5 pathway; endothelin receptor pathway; prostanoid pathway	Riociguat in addition to background therapy with an endothelin receptor antagonist or a prostanoid; macitentan in addition to background sildenafil; ambrisentan with tadalafil

Table 2: **Combination regimens used in other chronic lung diseases**

Lancet Resp Med 2014; 11: 933-42

Safety and tolerability of acetylcysteine and pirfenidone combination therapy in idiopathic pulmonary fibrosis: a randomised, double-blind, placebo-controlled, phase 2 trial

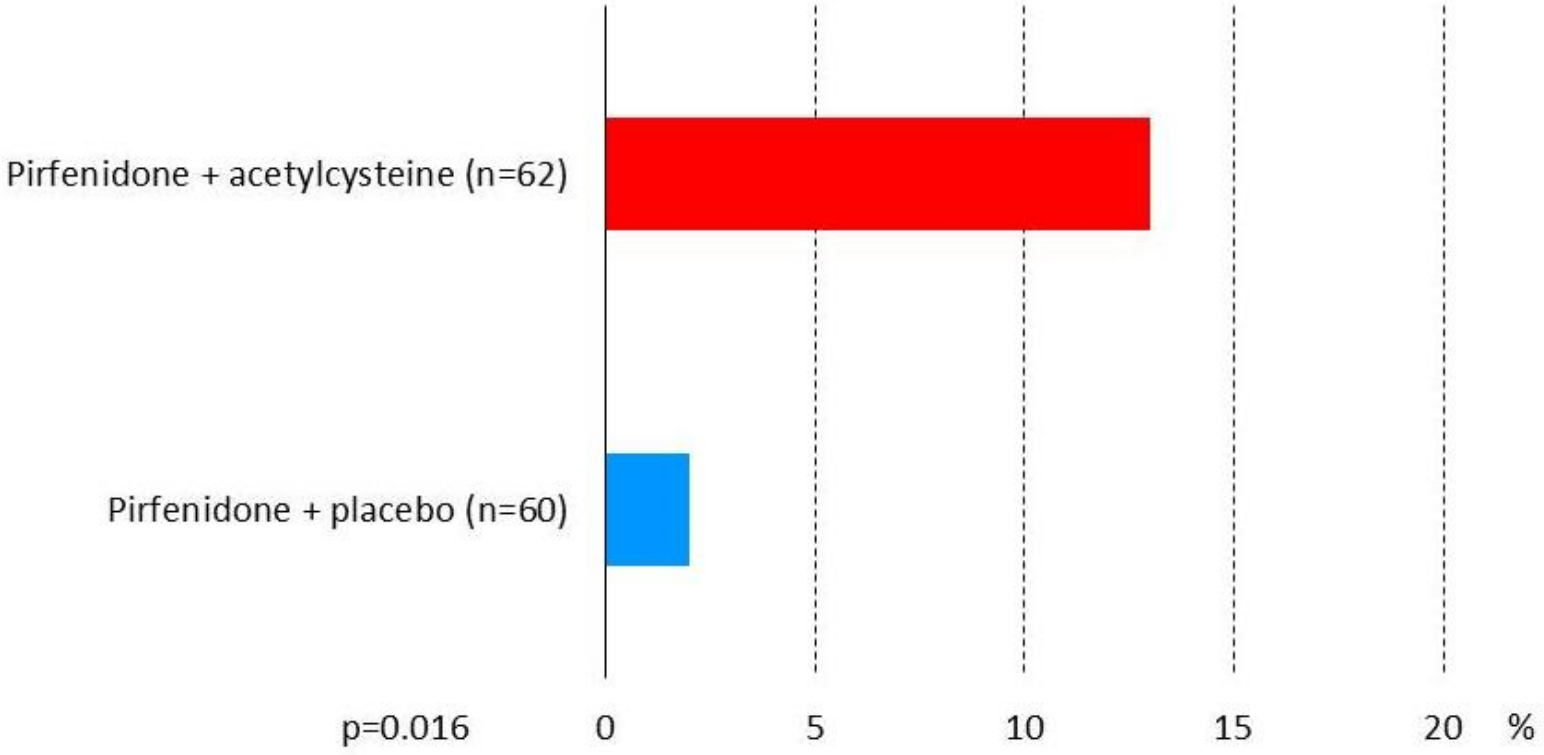
Jürgen Behr, Elisabeth Bendstrup, Bruno Crestani, Andreas Günther, Horst Olschewski, C Magnus Sköld, Athol Wells, Wim Wuyts, Dirk Koschel, Michael Kreuter, Benoît Wallaert, Chin-Yu Lin, Jürgen Beck, Carlo Albera



Number of patients			
Acetylcysteine	60	54	51
Placebo	62	57	55

Lancet Resp Med, Published online May 5, 2016

TREATMENT-EMERGENT PHOTOSENSITIVITY REACTIONS



Modified from data in Behr et al, *Lancet Resp Med*, Published online May 5, 2016

Investigation of drug-drug interaction between nintedanib and pirfenidone in patients with IPF

(an open-label, multiple dose, two group study)

EudraCT: 2015-000732-15

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Nintedanib for the treatment of Idiopathic pulmonary fibrosis – initial experience in a UK cohort

SV Fletcher[1], MG Jones[1], E Renzoni[2], H Parfrey[3], R Hoyles[4], K Spinks[5], M Kokosi[2], A Kwok[6], C Warburton[6], V Titmuss[5], M Thillai[3], N Simler[3],T Maher[2], F Chua[2], A Wells[2], L Richeldi[1], LG Spencer[6].

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BTS Winter Meeting, London 2nd December 2015

Methods

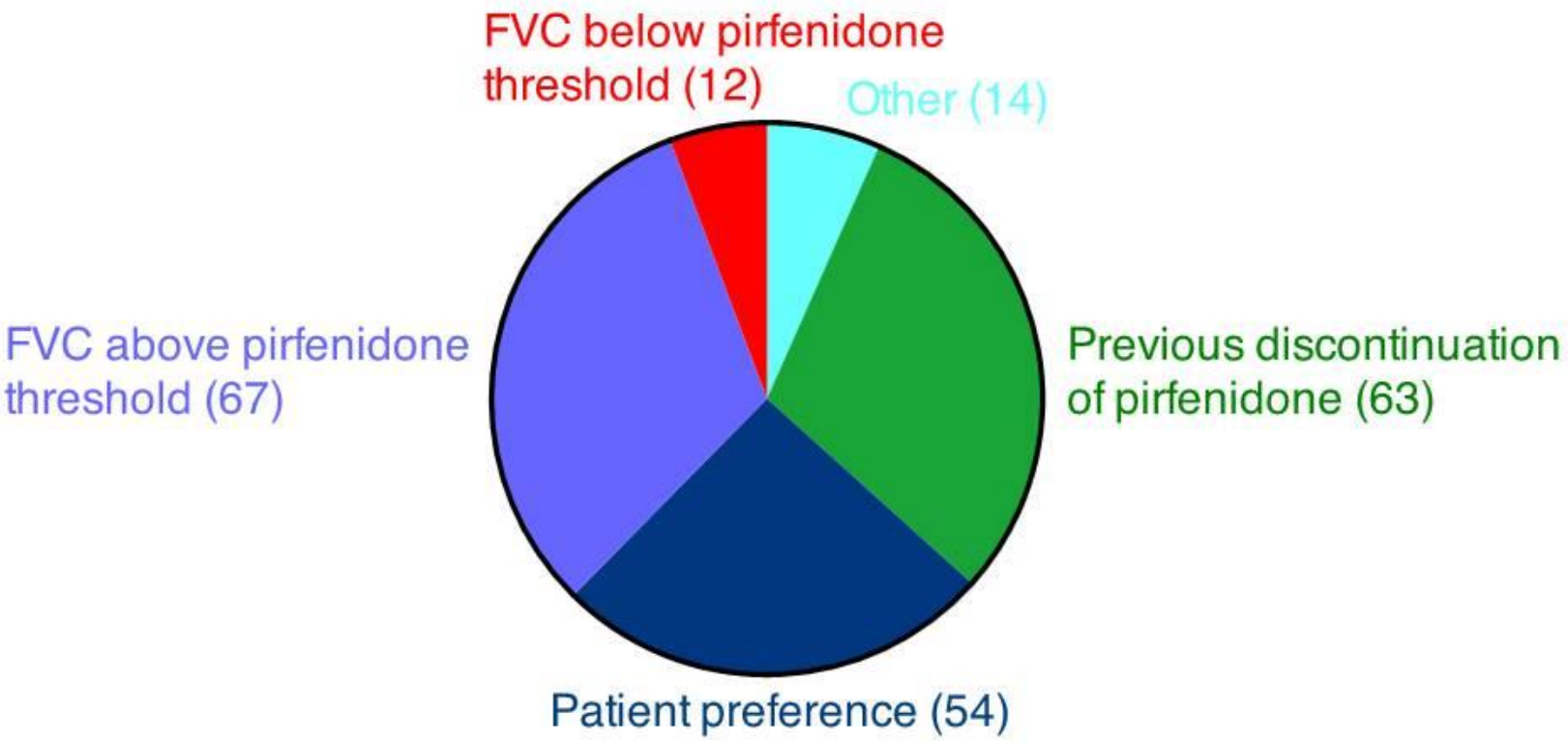
- A multi-centre, cohort review was undertaken across 6 NHS Trusts.
- Data were collected from clinical records of individuals commencing nintedanib for the treatment of IPF between October 2014 and July 2015.
- Data collection is ongoing at three-monthly follow up visits.

Results

- From October 2014 to July 2015 a total of 210 patients commenced nintedanib.
- Follow up data was available for 158 patients at 3 months and 76 at 6 months
- Mean duration of treatment was 4.4 months (range 0 – 9)

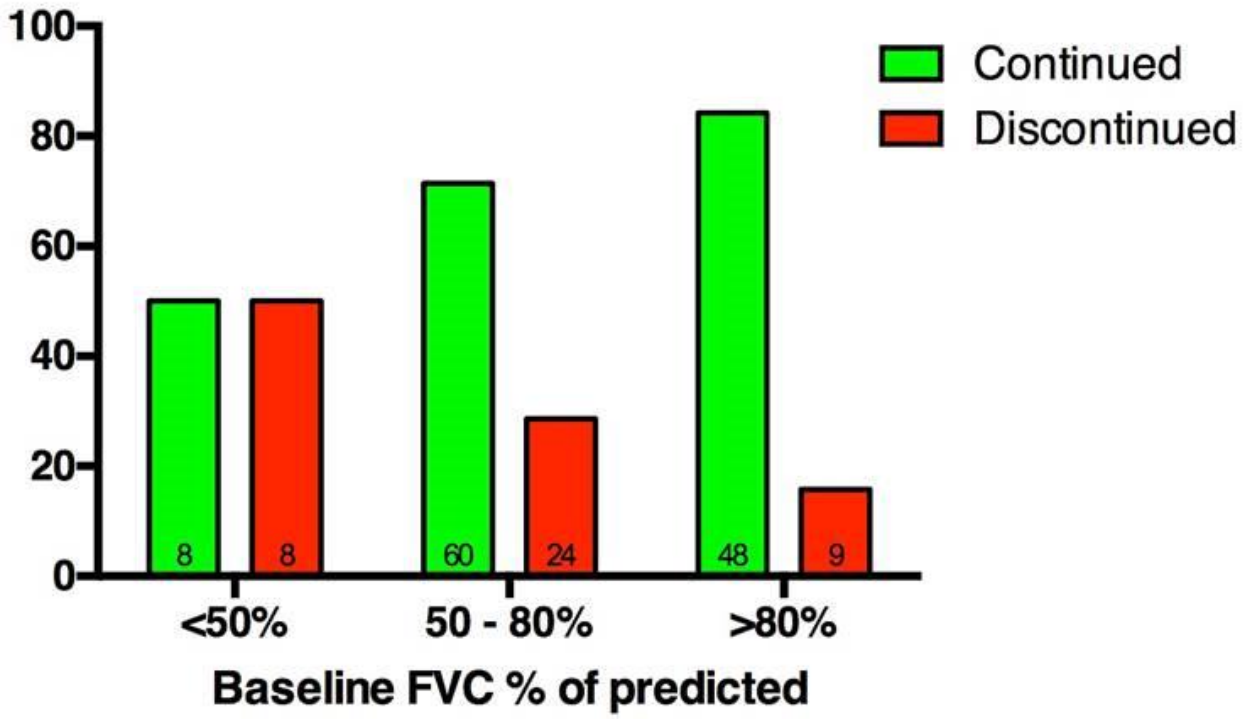
Fletcher S et al, BTS Winter Meeting, London 2nd December 2015

PRIMARY REASON FOR NINTEDANIB COMMENCEMENT



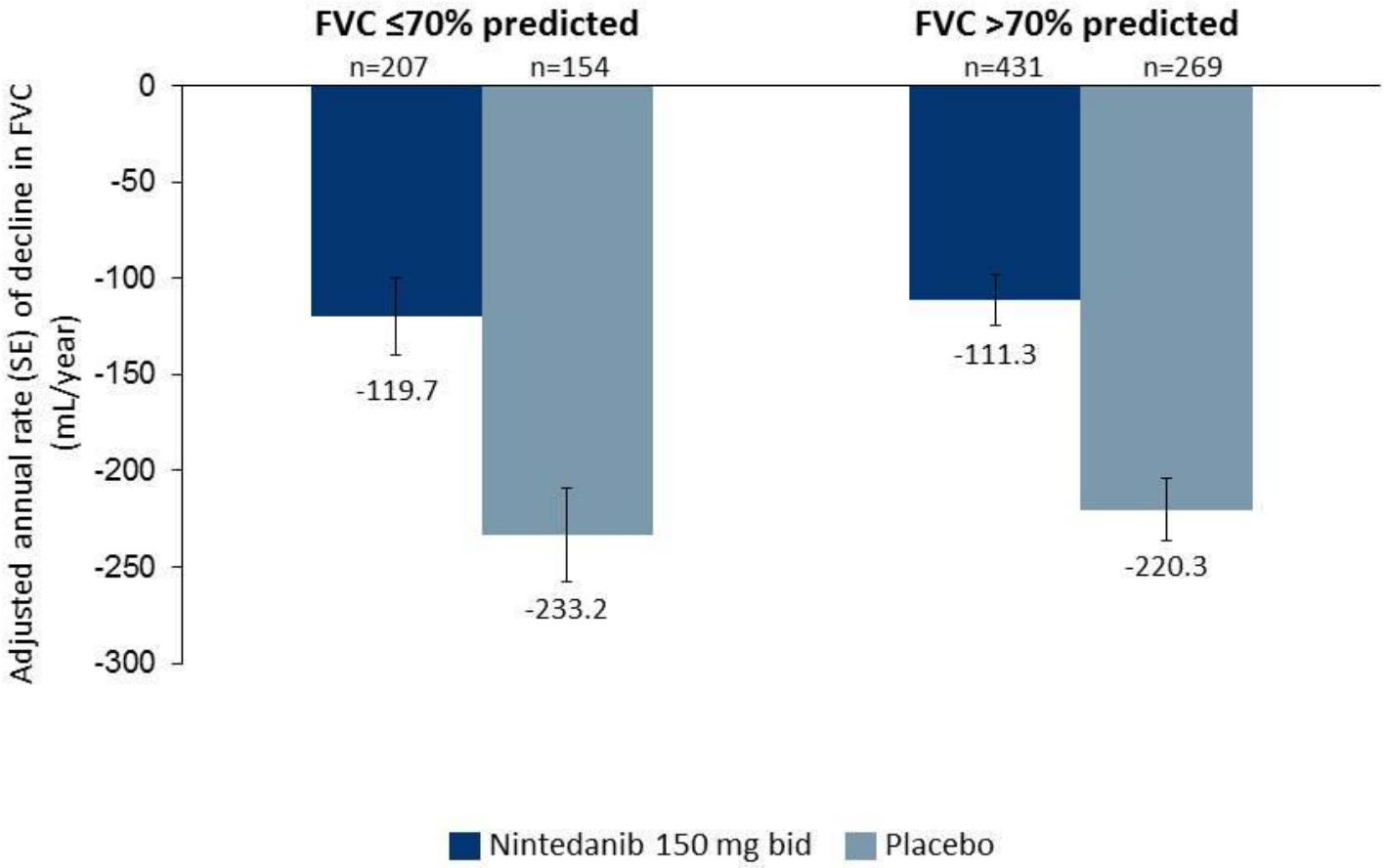
Fletcher S et al, BTS Winter Meeting, London 2nd December 2015

PERCENTAGE OF PATIENTS DISCONTINUING NINTEDANIB STRATIFIED BY BASELINE FVC % PREDICTED



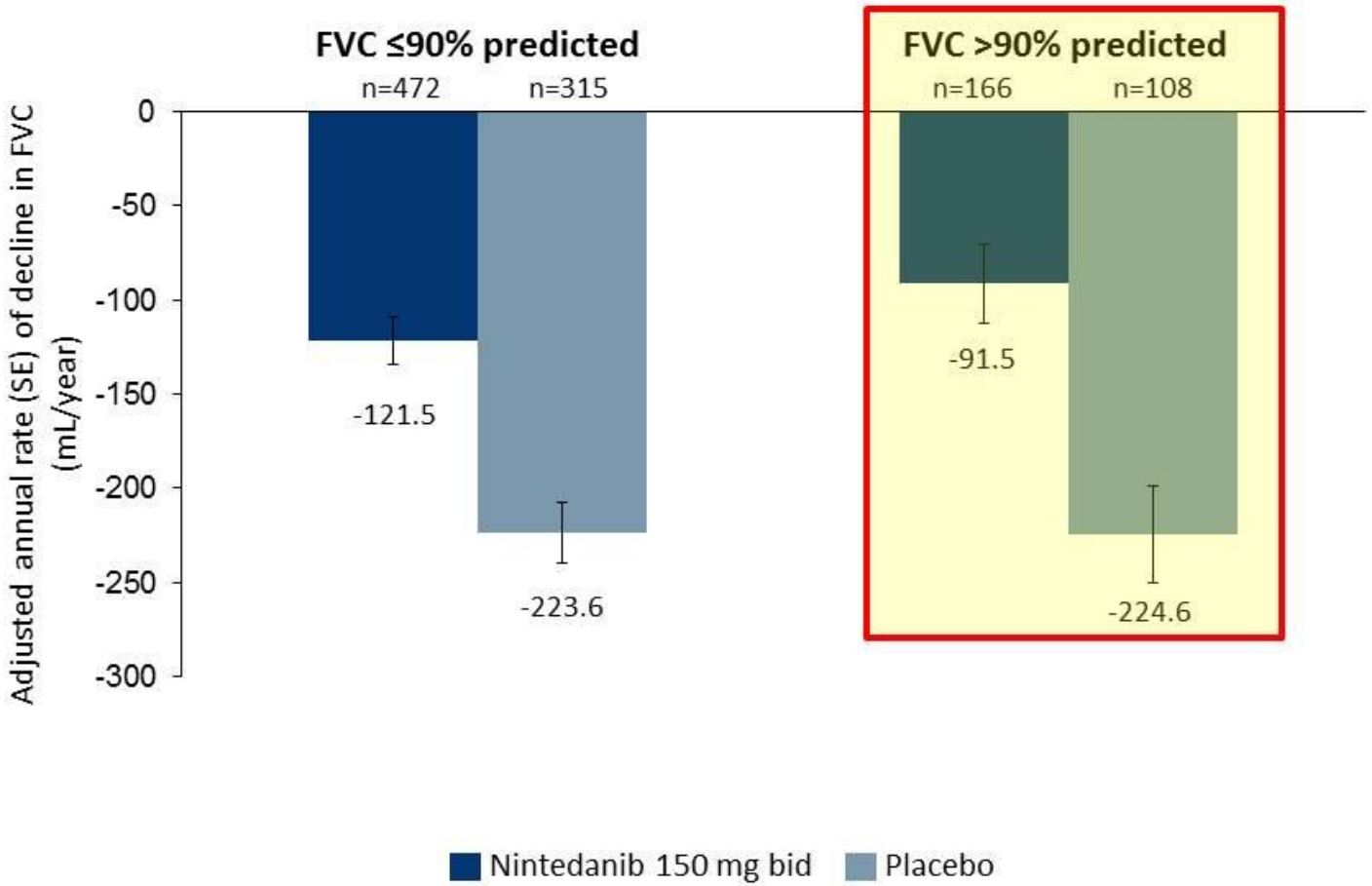
Fletcher S et al, BTS Winter Meeting, London 2nd December 2015

ANNUAL RATE OF DECLINE IN FVC BY BASELINE FVC %PREDICTED ≤70% VS >70%



Costabel U et al. *Am J Respir Crit Care Med* 2016; 193: 178-85

ANNUAL RATE OF DECLINE IN FVC BY BASELINE FVC %PREDICTED ≤90% VS >90%



Kolb M et al. American Thoracic Society International Conference, Denver (USA) 16 May 2015

SUBTOPICS

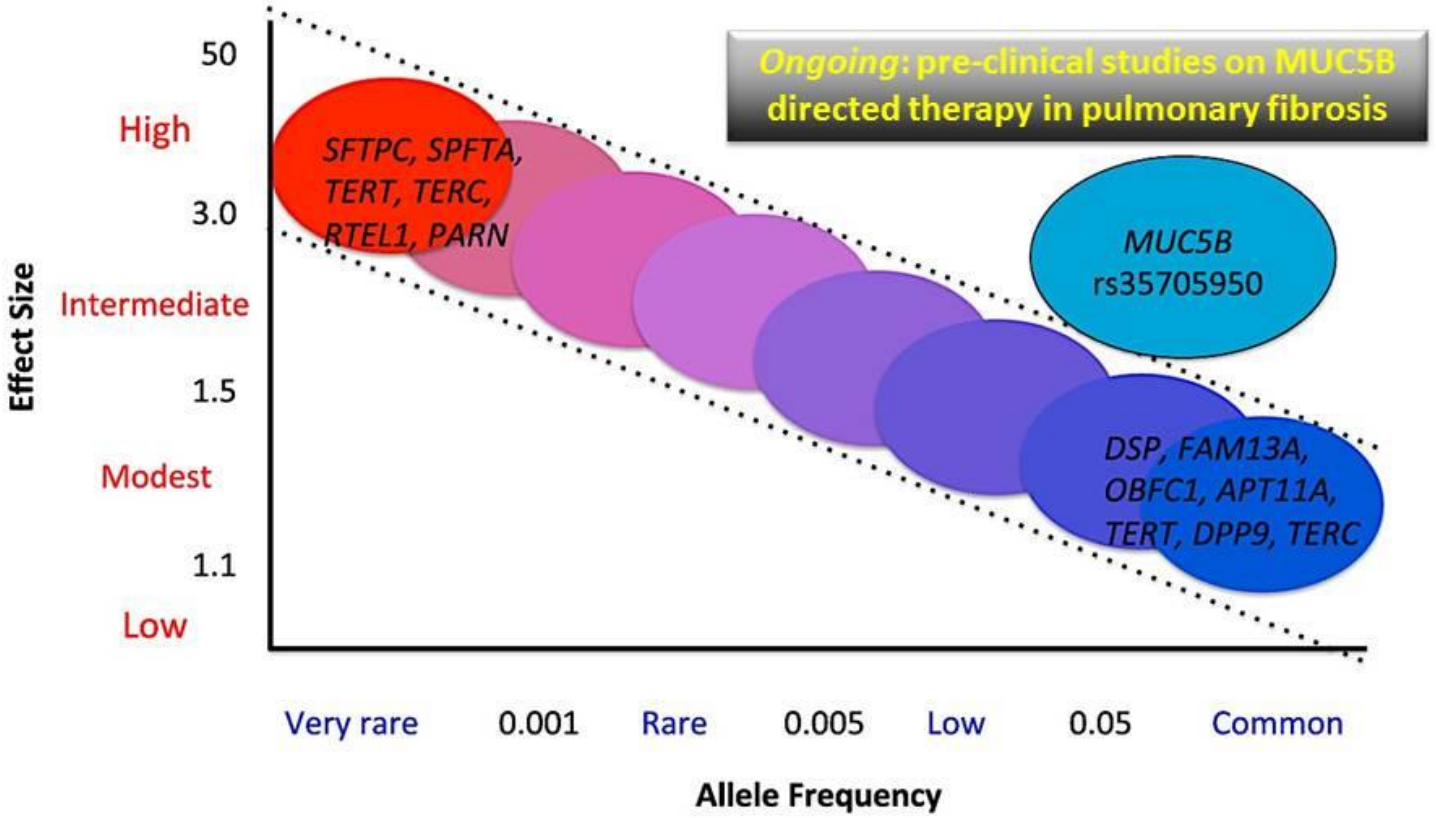
1. The fine line of autoimmunity
2. The challenge of “idiopathic”
3. IPF: why, how and when
4. **IPF: the role of genes**

Mathai et al. BMC Medicine (2015) 13:191
DOI 10.1186/s12916-015-0434-0

Idiopathic pulmonary fibrosis: diagnosis, management and new therapies

Incorporating genetics into the identification and treatment of Idiopathic Pulmonary Fibrosis

Susan K. Mathai*, Ivana V. Yang, Marvin I. Schwarz and David A. Schwartz



Mathai et al, *BMC Med* 2015; 13: 191

TOLLIP, *MUC5B*, and the Response to *N*-Acetylcysteine among Individuals with Idiopathic Pulmonary Fibrosis

Justin M. Oldham[1]*, Shwu-Fan Ma[1]*, Fernando J. Martinez[2], Kevin J. Anstrom[3], Ganesh Raghu[4], David A. Schwartz[5], Eleanor Valenzi[1], Leah Witt[1], Cathryn Lee[1], Rekha Vij[1], Yong Huang[1], Mary E. Strek[1], and Imre Noth[1]; for the IPFnet Investigators

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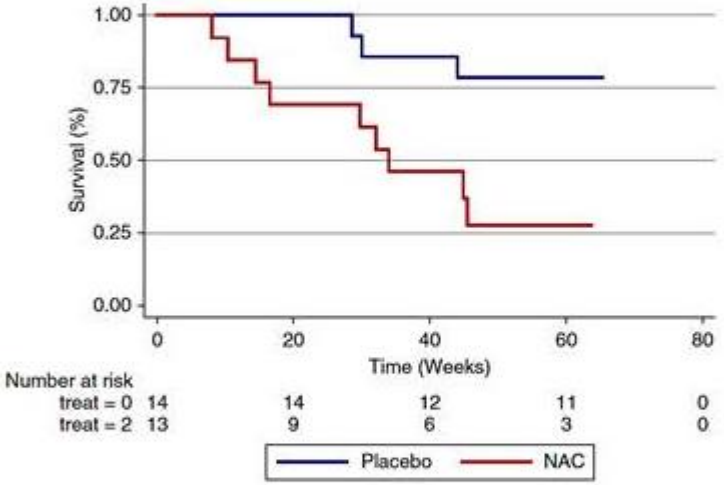
AJRCCM 2015; 192: 1475-82

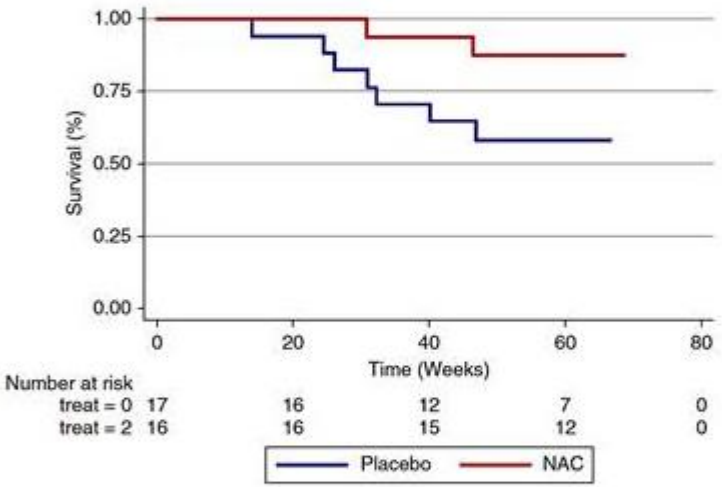
STRATIFICATION BY TOLLIP GENOTYPE

CC GENOTYPE



HR 3.23
95% CI 0.79-13.16
P=0.10

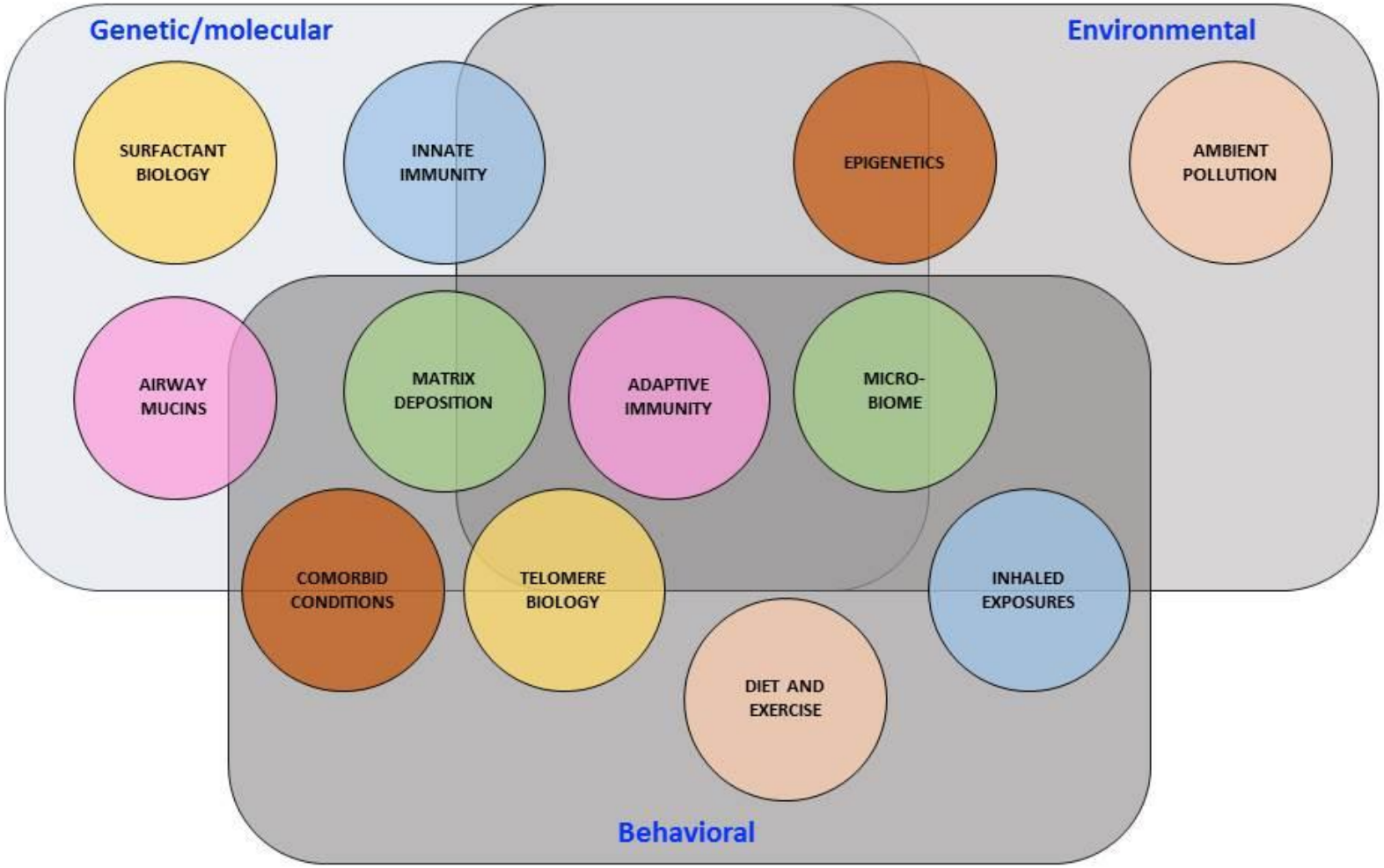
TT GENOTYPE



HR 0.14
95% CI 0.02-0.83
P=0.03

Oldham et al, *AJRCCM* 2015; 192: 1475-82

IPF IN THE ERA OF PRECISION MEDICINE



Brownell R et al, *AJRCCM* 2016 193: 1213-8

TAKE-HOME MESSAGES

1. Autoimmunity plays a role
2. Disease behaviour
3. IPF: safe drugs, treat early
4. IPF: genetic factors are emerging

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18. Costabel U et al, *AJRCCM* 2016; 193: 178-85
19. Kolb et al, Am. Thoracic Society Intl Conf., Denver (USA), 16 May 2015
20. Mathai et al, BMC Med 2015; 13: 191
21. Oldham et al, *AJRCCM* 2015; 192: 1475-82
22. Brownell R et al, *AJRCCM* 2016 193: 1213-8