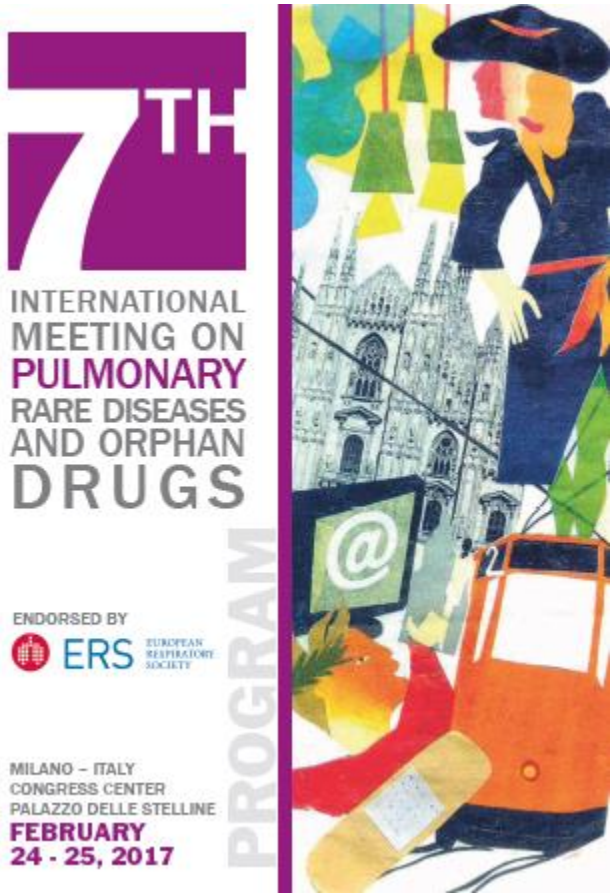


IDIOPATHIC PULMONARY FIBROSIS: WHERE WE ARE GOING TO

Chairpersons: *Harold Collard (San Francisco, CA - USA), Paola Rottoli (Siena, Italy), Athol Wells (London, UK)*

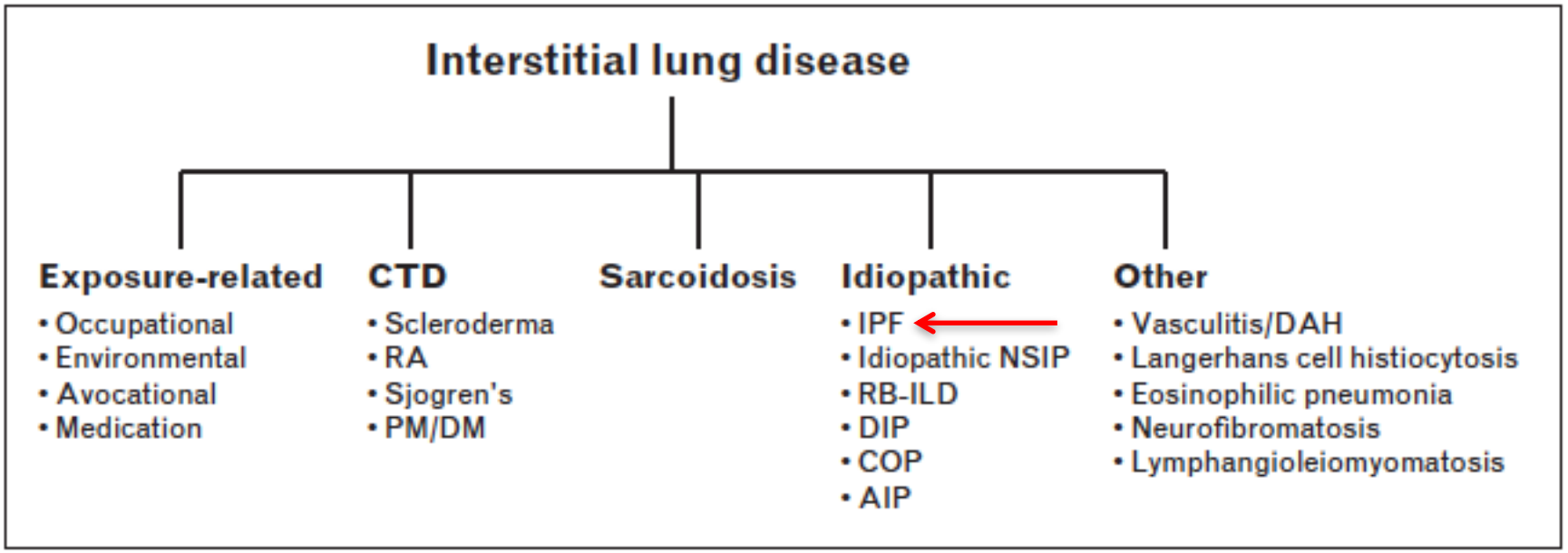
IPF with autoimmune features (IPAF): do we need new approaches?
Katerina Antoniou (Heraklion, Greece)

Katerina M. Antoniou

Faculty of Medicine, University of Crete

ERS ILD Chair

Overview of ILD classification



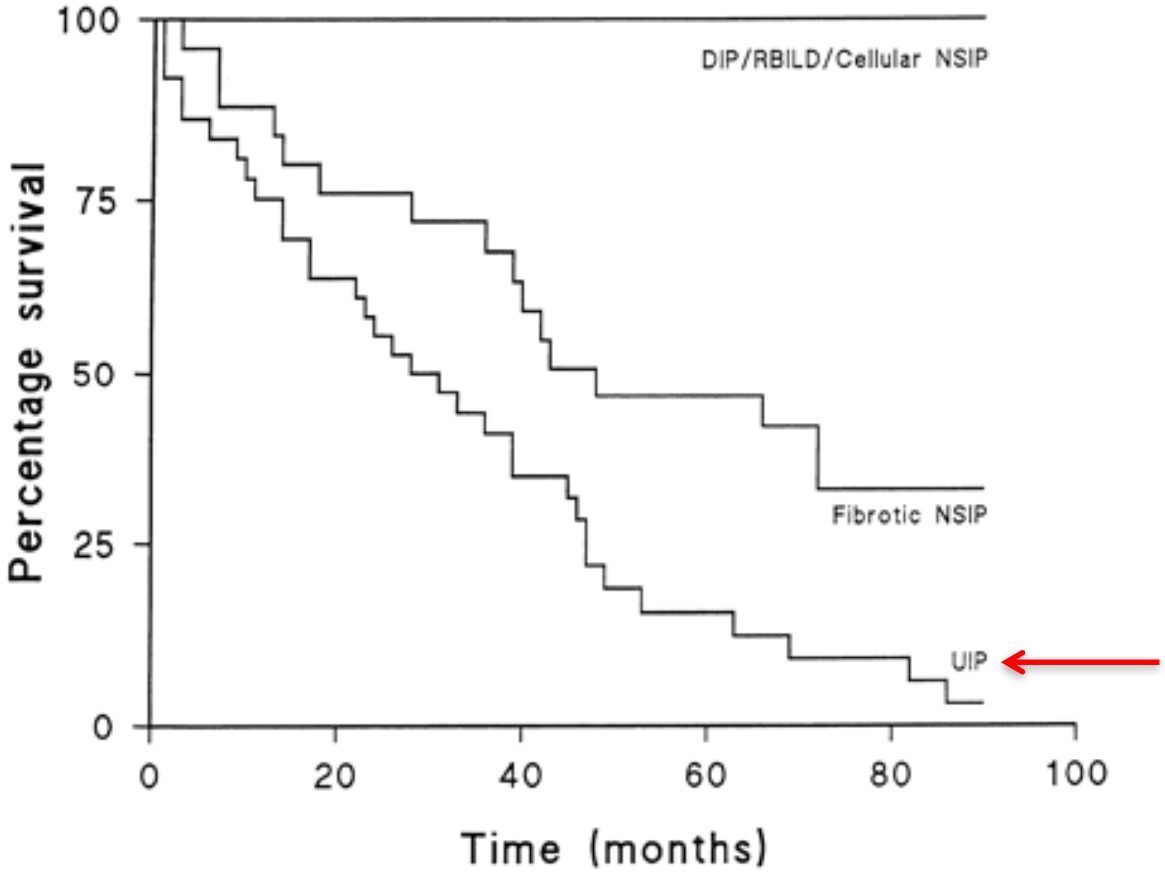
Interstitial lung disease (ILD) comprises a large group of diseases characterised by inflammation or fibrosis of the lung parenchyma

ILDs can be caused by environmental exposures or may be secondary to another condition, such as connective tissue disease (CTD)

Alternatively, the ILD may not have a clear predisposing factor (idiopathic interstitial pneumonias)

Ryerson and Collard. Curr Op Pulm Med 2013

Prognostic implications of idiopathic UIP (idiopathic pulmonary fibrosis)



Nicholson et al. *Am J Respir Crit Care Med* 2000;162:2213-2217

Relevance of a CTD-ILD diagnosis

A CTD-ILD diagnosis may impact:

- **Treatment**
  - **Use of immunosuppression as opposed to anti-fibrotics**
- **Prognosis**

Park, Kim, Park, *et al.*: Prognosis of Fibrotic Interstitial Pneumonia

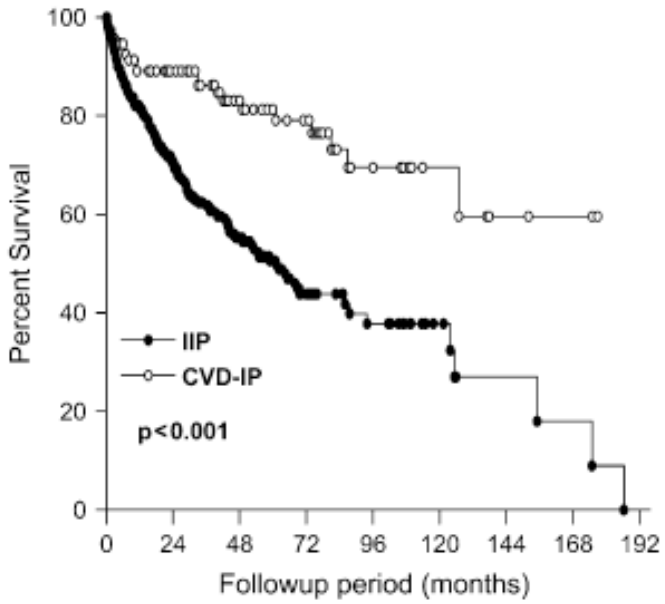
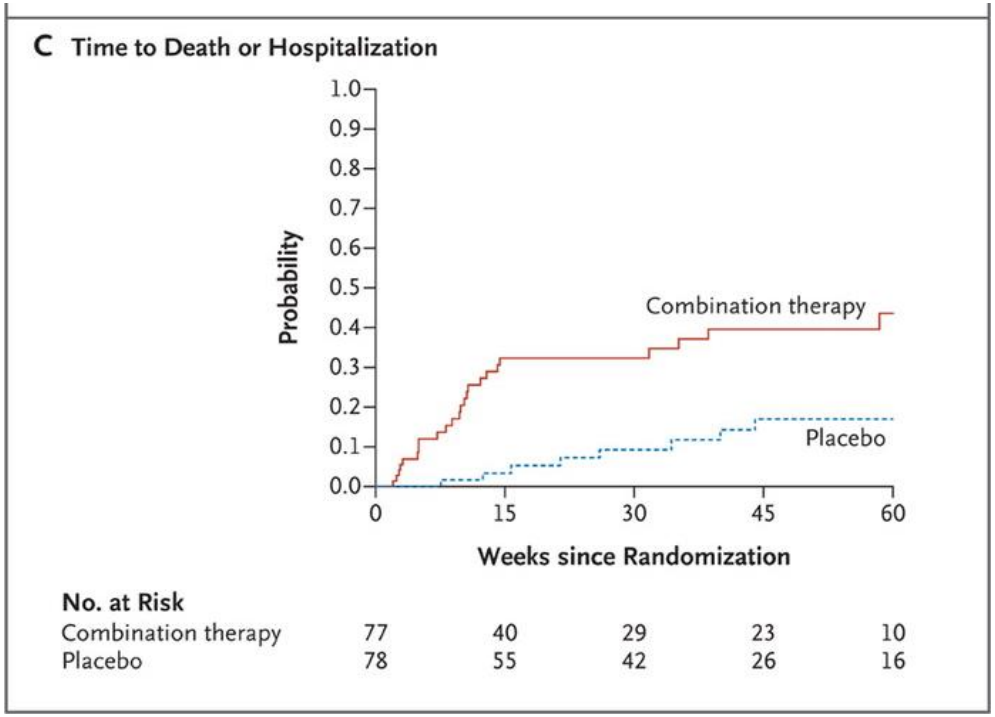


Figure 1. Survival of total subjects with idiopathic interstitial pneumonia (IIP) and interstitial pneumonia associated with collagen vascular disease (CVD-IP).

Park et al. AJRCCM 2007

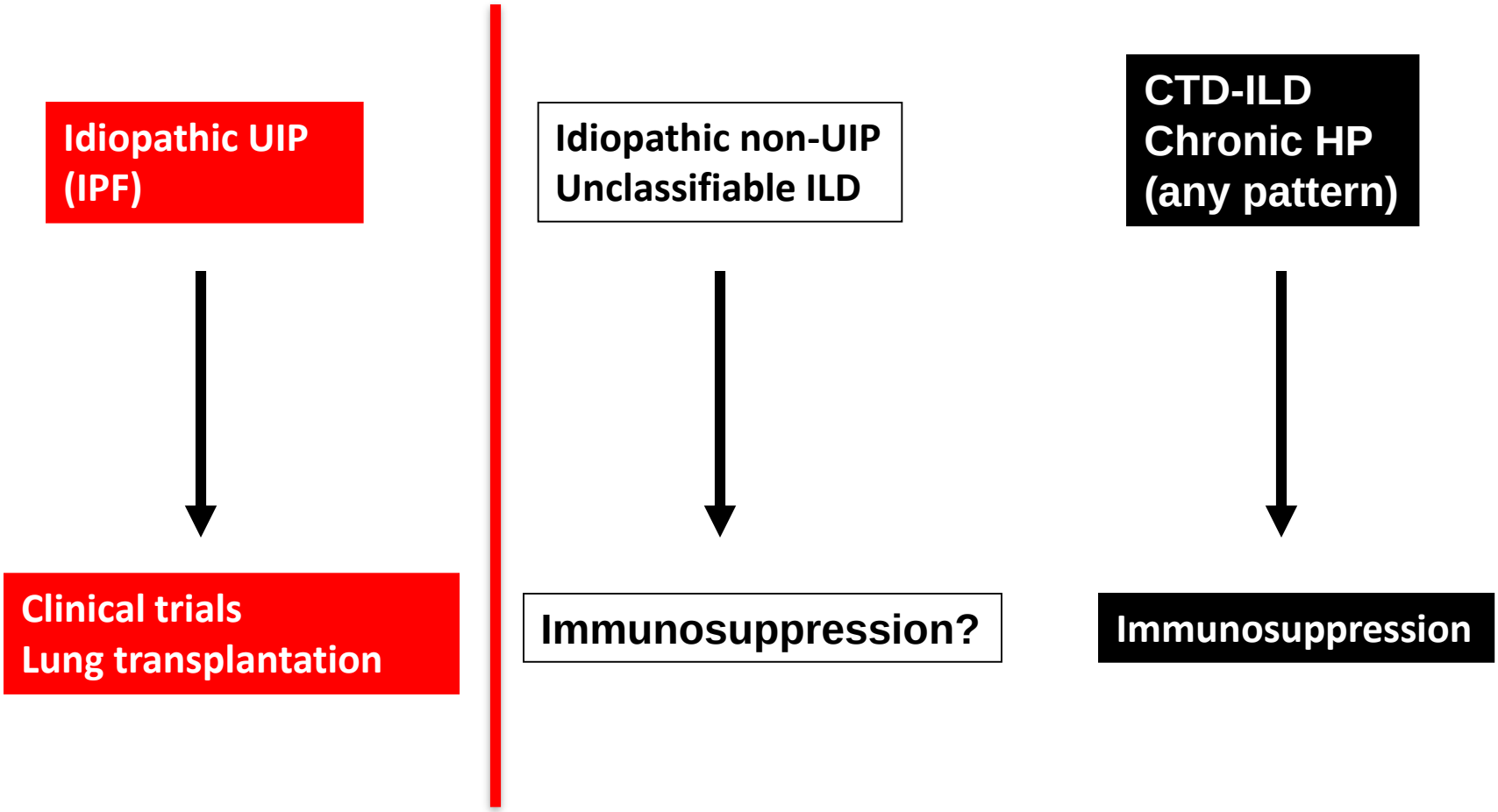
PANTHER trial

Increased risks of death and hospitalization were observed in patients with IPF treated with a combination of prednisone, azathioprine, and n-acetylcysteine



The Idiopathic Pulmonary Fibrosis Clinical Research Network. N Engl J Med 2012

The treatment paradigm until very recently…



ASCEND Trial

- Pirfenidone, as compared with placebo, reduced disease progression, as reflected by lung function, exercise tolerance, and progression-free survival, in IPF

- GI symptoms (nausea, dyspepsia, GERD) and rash were most common side effects

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

INPULSIS Trial

- In patients with IPF, nintedanib reduced the decline in FVC

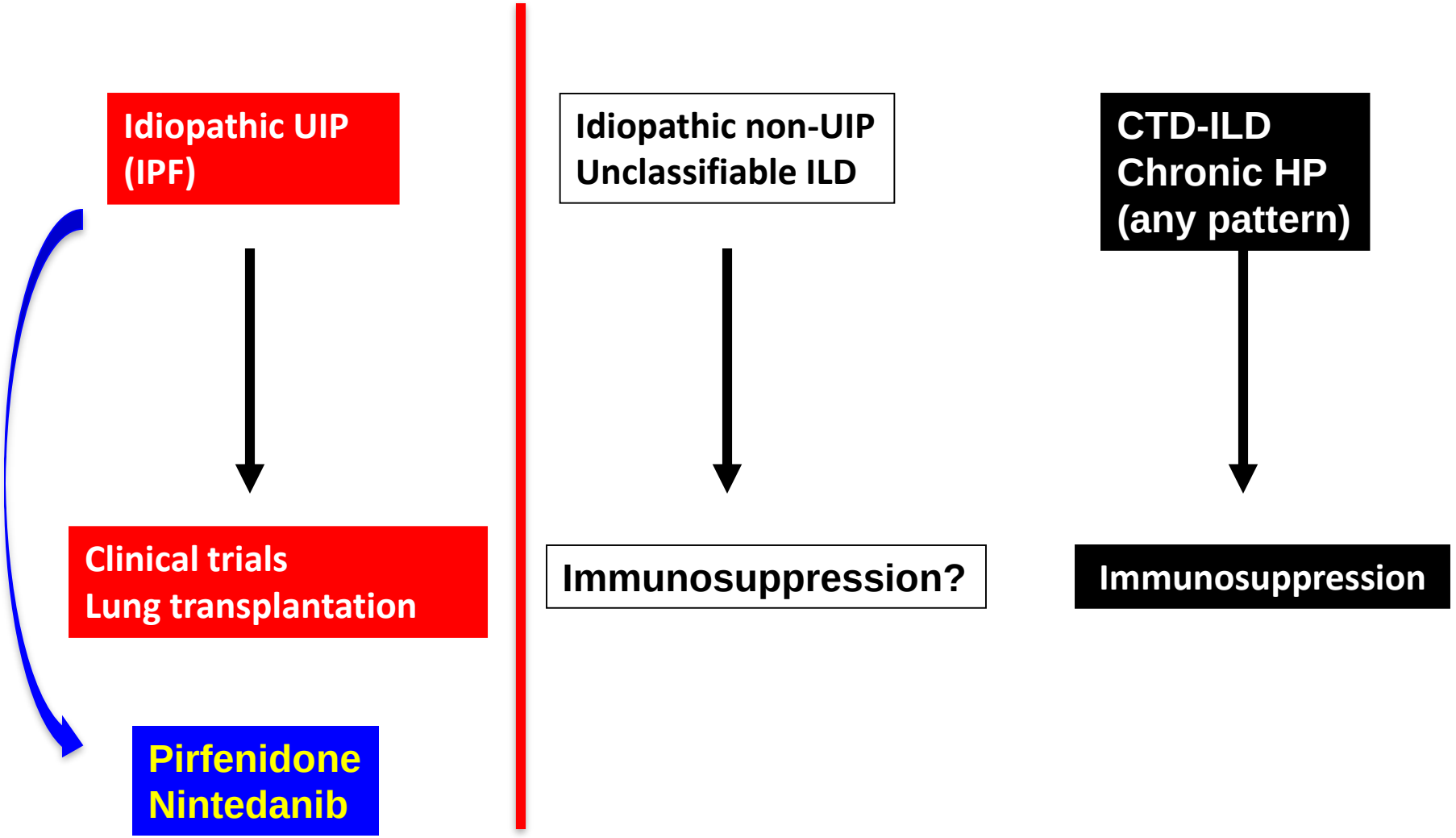
- Nintedanib was frequently associated with diarrhea (62%)

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

- There are important differences with regards to natural history and approaches to treatment of the various ILDs

- Novel anti-fibrotic therapies proven effective in IPF, are not available for other forms of fibrotic ILD

Current approach to treatment



The problem

- Many patients with IIP have subtle features suggestive of an autoimmune etiology – BUT are not considered as definite CTD-ILD

- Previous terminology with disparate criteria:
  - "UCTD", "lung-dominant CTD", and "auto-immune featured ILD"
    - Each have their own set of proposed criteria

- A uniform platform and multicenter, multidisciplinary prospective studies are needed to study this amorphous cohort

Survival in interstitial pneumonia with features of autoimmune disease: A comparison of proposed criteria

Deborah Assayag [a], Eunice J. Kim [b], Brett M. Elicker [c], Kirk D. Jones [d], Jeffrey A. Golden [e], Talmadge E. King Jr. [e], Laura L. Koth [e], Anthony K. Shum [e], Paul J. Wolters [e], Harold R. Collard [e], Joyce S. Lee [e,*]

Background: Some patients with chronic fibrosing interstitial pneumonia (IP) have clinical, serological, and morphological features suggestive of, but not diagnostic for, a connective tissue disease. Several names and diagnostic criteria for this entity have been proposed. The objective of this study was to compare the clinical characteristics and behavior of each of the proposed diagnostic criteria.

Methods: Patients with chronic fibrosing IP were identified from an ongoing, longitudinal cohort. Four published diagnostic criteria for what we generically label as "IP with features of autoimmunity" were applied to all patients to identify four unique cohorts (Kinder, Vij, Corte, and Fischer). Kaplan–Meier survival functions compared differences in survival in each cohort between patients meeting and not meeting criteria. Unadjusted and adjusted Cox proportional hazard regression models identified predictors of survival.

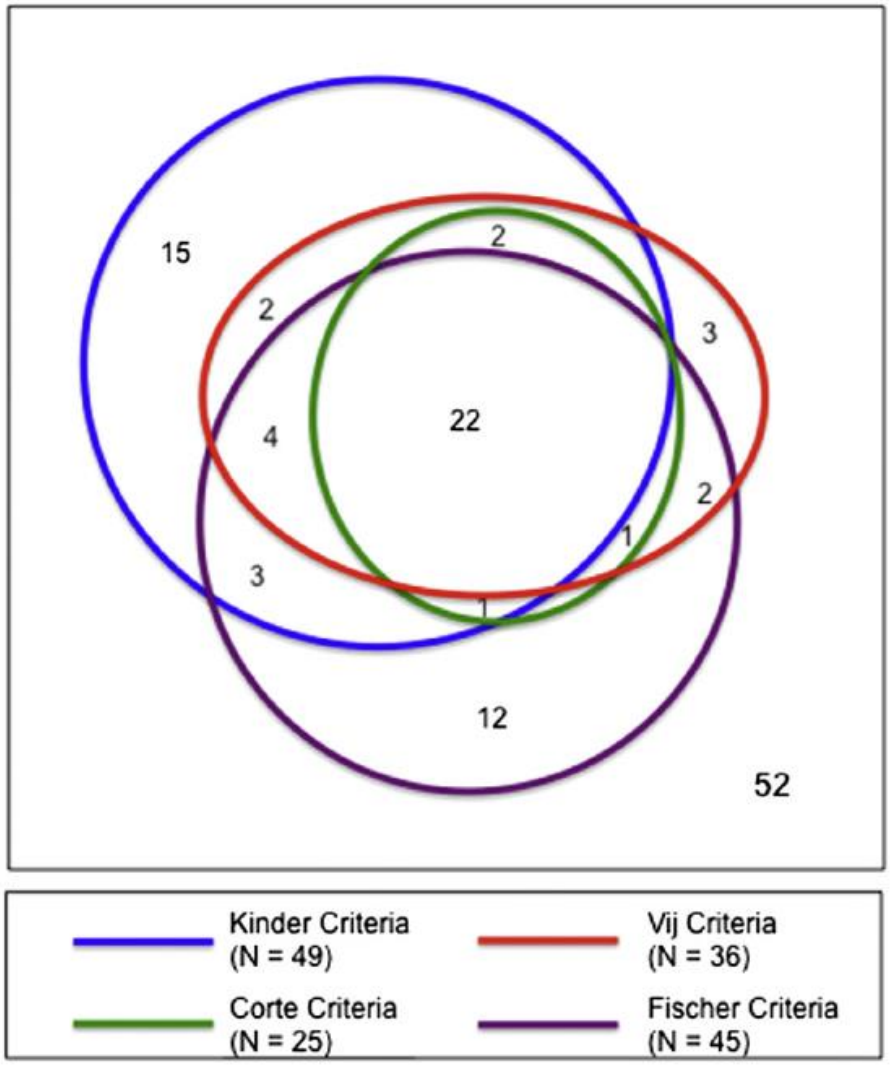
Results: The study cohort included 119 patients, 40% of whom were female. The mean age was 65.5 years. There was overlap between the four different criteria, identifying patients with similar clinical characteristics. Interstitial pneumonia patients with features of autoimmunity tended to have improved survival compared to those without these features (p-value range 0.03–0.10) on univariate analysis. After adjusting for disease severity using the gender-age-physiology score, only the Corte criteria was an independent predictor of survival (p-value 0.04).

Conclusion: Interstitial pneumonia with features of autoimmunity may be associated with improved survival compared to those patients without these features depending on which criteria is used to define the population. These data support the efforts being made to standardize the definition.

Will these identify the same group of patients?

	Extra-thoracic symptoms	Serology / Histopathology
Broader UCTD-ILD	Non-specific symptoms	Non-specific serologies
Stricter UCTD-ILD	More specific symptoms	More specific serologies
Autoimmune-featured ILD	Non-specific symptoms	Non-specific serologies
Lung-dominant CTD	N/A	Specific serologies or specific histopathology

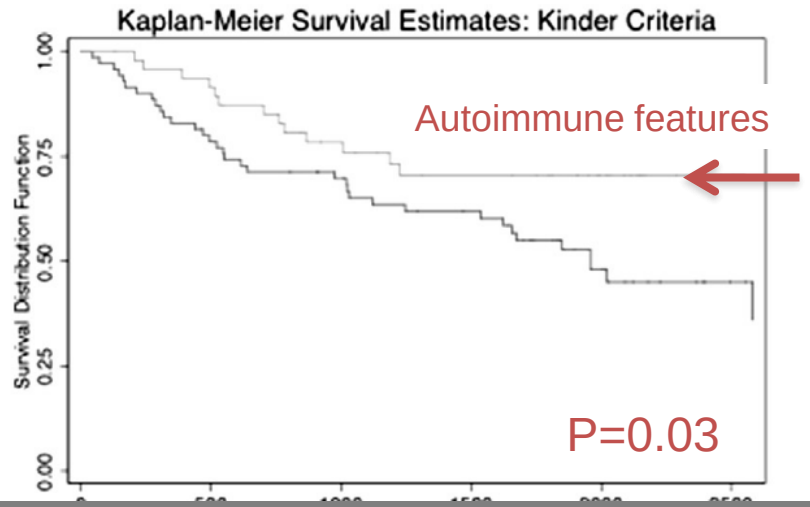
Existing criteria only partly overlap

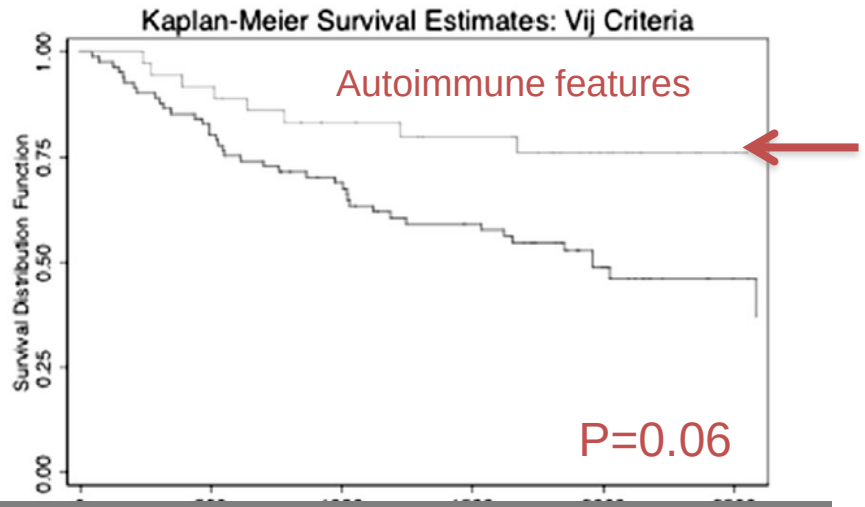


- 119 patients with chronic fibrosing interstitial pneumonia
- 4 different set of criteria for interstitial pneumonia with features of autoimmunity

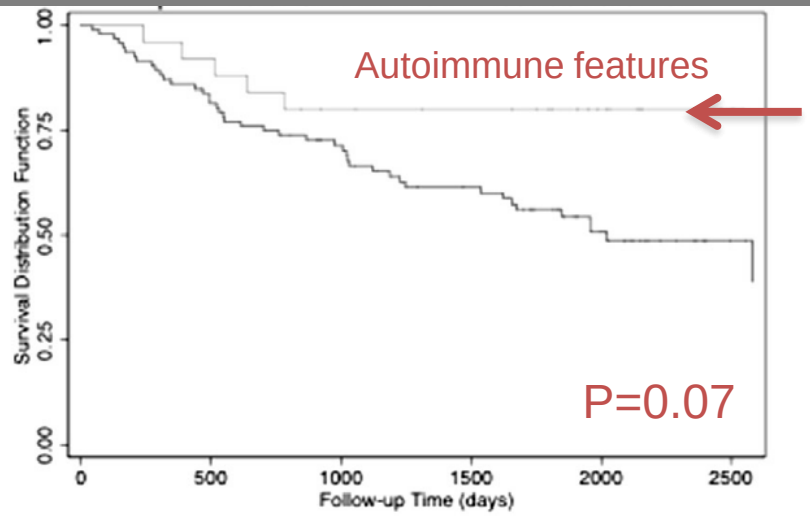
Assayag D et al, *Respir Med* 2015

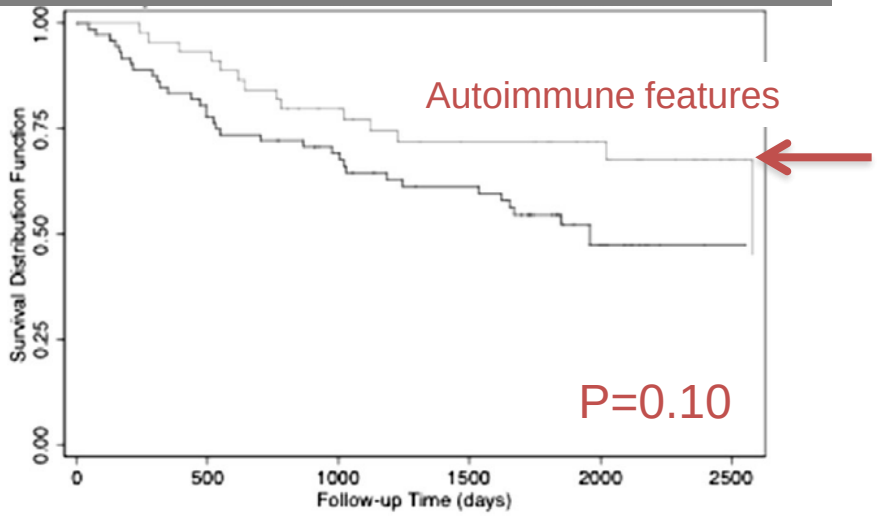
Patients with interstitial pneumonia with features of autoimmune disease have improved survival compared to patients that do not





These data support the efforts to standardize the definition





Assayag D et al, *Respir Med* 2015

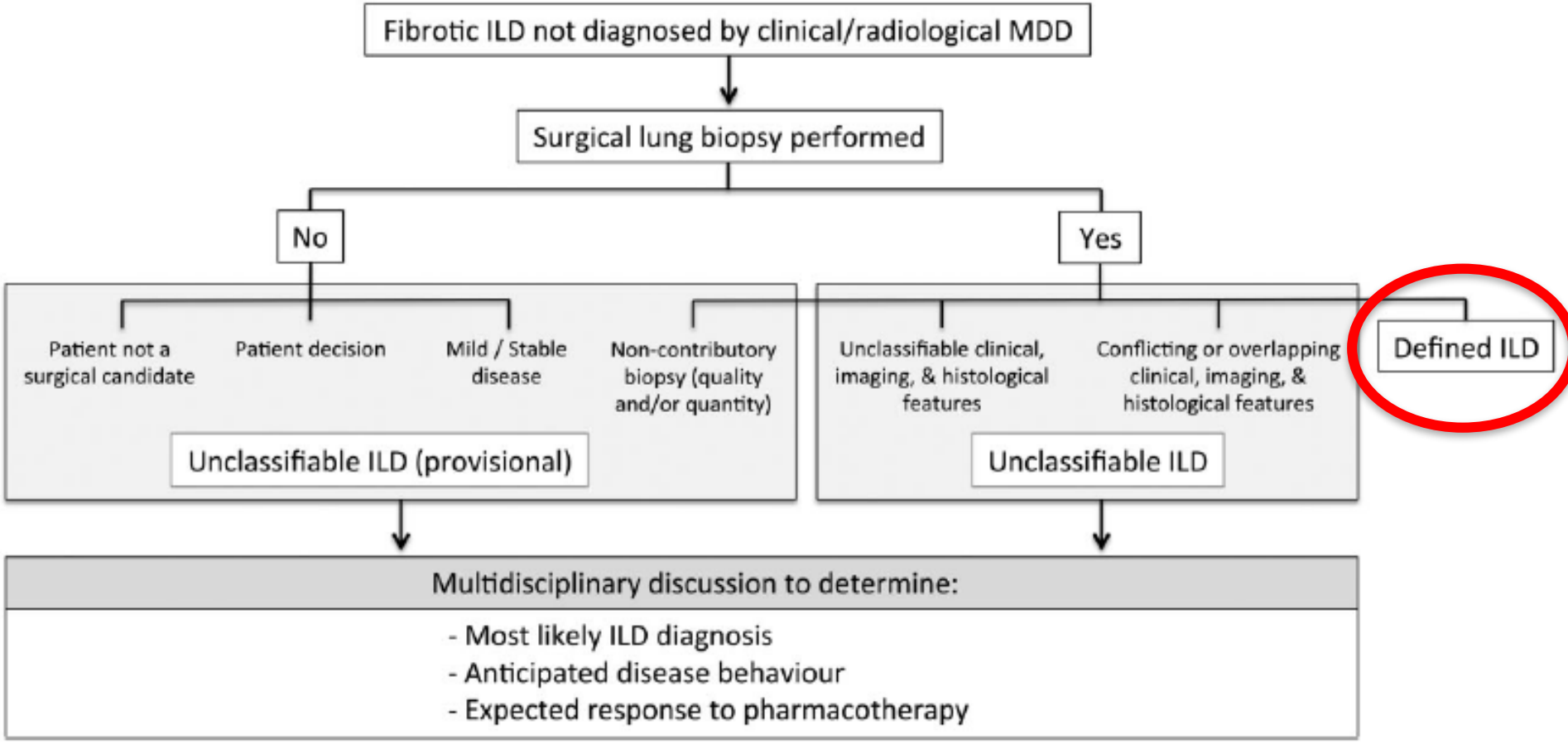
“Unclassifiable ILD” (uILD)

- 4–15% of patients with ILD cannot be given a specific diagnosis even after thorough investigation by a multidisciplinary team (Ryerson et al. 2013; Hyldgaard et al. 2014; Karakatsani et al. 2009; Troy et al. 2014; Zhang and Liu 2010; Musellim et al. 2014)

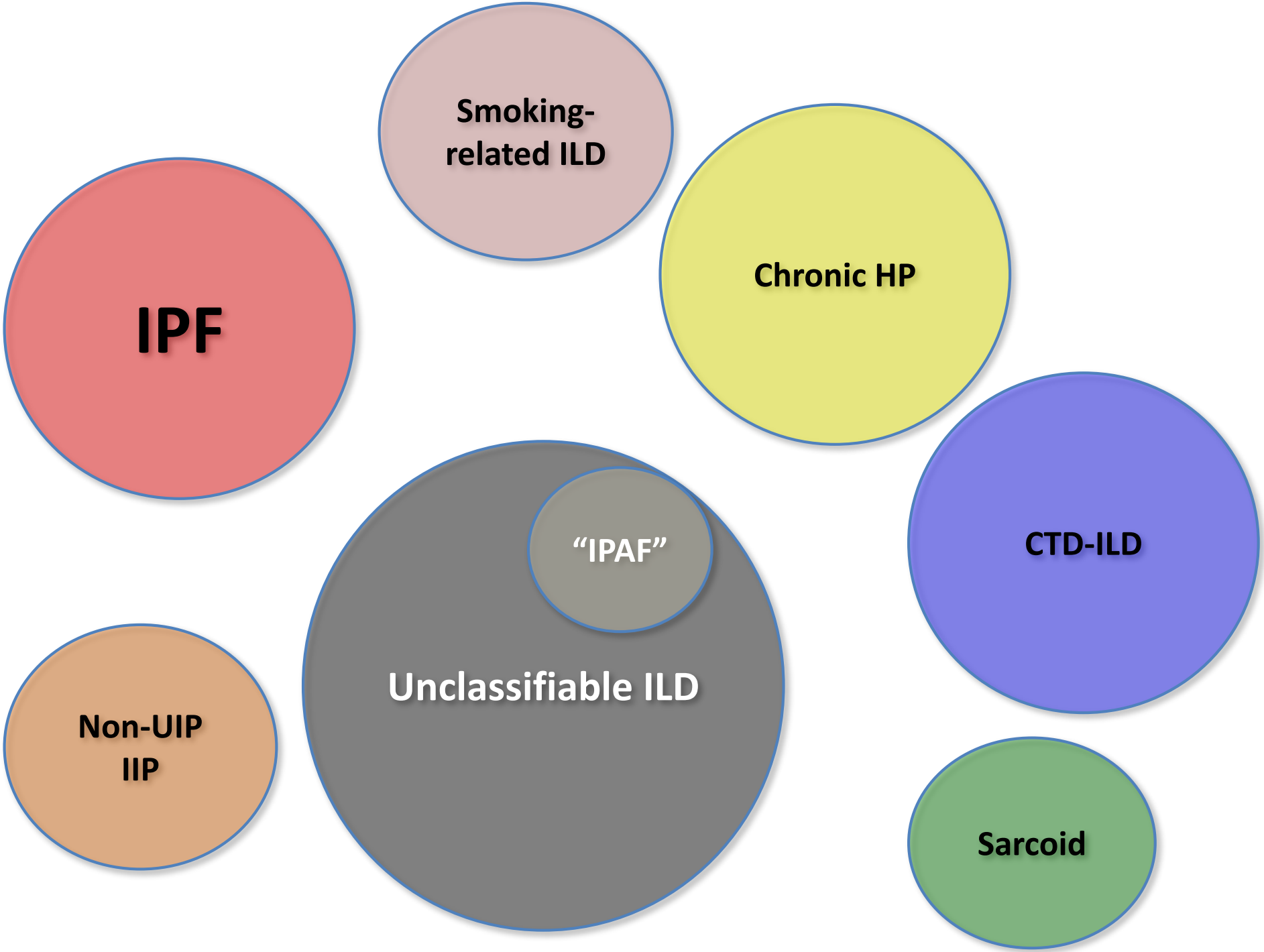
- In these cases, the disease is referred to as 'unclassifiable ILD’ (Ryerson and Collard 2013; Travis et al. 2013; American Thoracic Society and European Respiratory Society 2002)

- uILD represents a heterogeneous collection of undiagnosed ILDs with patients displaying clinical features of IPF and other non-IPF ILDs (Travis et al. 2013; American Thoracic Society and European Respiratory Society 2002)

Proposed approach to the categorization of uILD



Skolnik & Ryerson Respirology 2016


Smoking-related ILD
IPF
Chronic HP
"IPAF"
CTD-ILD
Unclassifiable ILD
Non-UIP IIP
Sarcoid

ERS/ATS Task Force on Undifferentiated forms of CTD-ILD

1. Develop consensus criteria – and nomenclature – for the classification of suggestive forms of CTD-ILD

2. Identify key areas of uncertainty that warrant further multi-center study

ERS/ATS TASK FORCE
INTERSTITIAL LUNG DISEASE

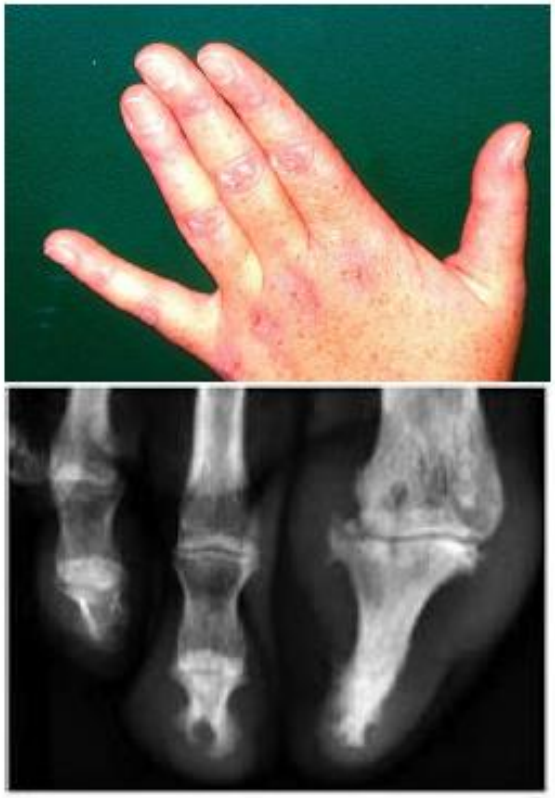
An official European Respiratory Society/ American Thoracic Society research statement: interstitial pneumonia with autoimmune features

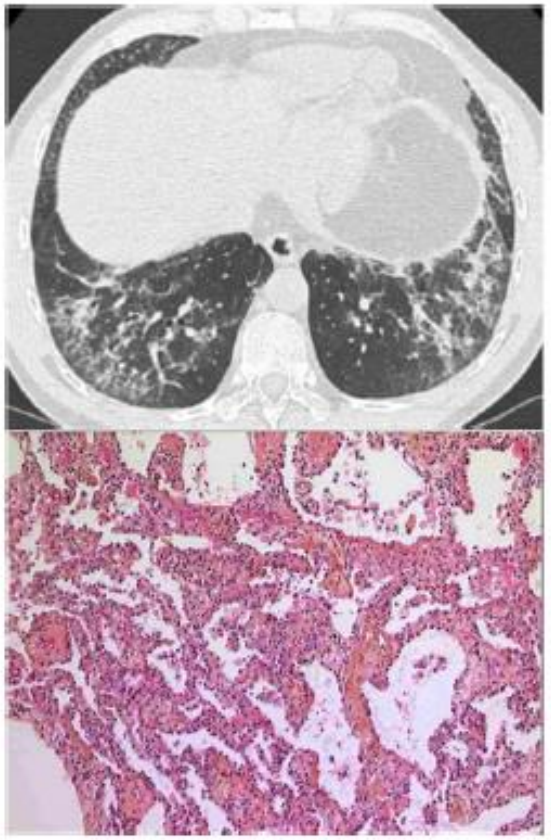
Aryeh Fischer[1,17,18], Katerina M. Antoniou[2], Kevin K. Brown[3], Jacques Cadranel[4], Tamera J. Corte[5,18], Roland M. du Bois[6], Joyce S. Lee[7,18], Kevin O. Leslie[8], David A. Lynch[9], Eric L. Matteson[10], Marta Mosca[11], Imre Noth[12], Luca Richeldi[13], Mary E. Strek[12,18], Jeffrey J. Swigris[3,18], 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"

Eur Respir J 2015;

ERS/ATS task force provides nomenclature and classification criteria for patients with IIP and autoimmune features

“Interstitial Pneumonia with Autoimmune Features” (IPAF)





1. Nomenclature (Sept 9, 2013): **Interstitial Pneumonia with Autoimmune Features** (IPAF)
2. Combination of clinical manifestations, serology, and morphological characteristics of the interstitial pneumonia → *research statement*

Courtesy of Prof V Cottin

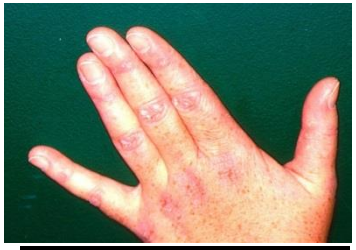
Fischer et al ERJ July 2015

Interstitial Pneumonia with Autoimmune Features (IPAF)

1. **Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) and,**
2. **Exclusion of alternative etiologies and,**
3. **Does not meet criteria of a defined CTD and,**
4. **At least one feature from at least two of these domains:**

A

Clinical domain

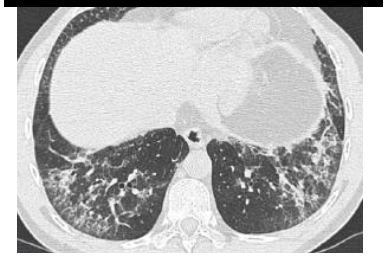


B

Serologic domain

C

Morphologic domain



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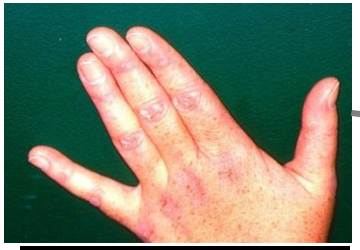
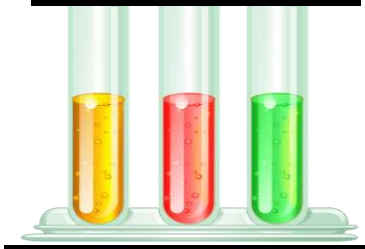


- Distal digital fissuring (i.e. 'mechanic hands')
- Distal digital tip ulceration
- Inflammatory arthritis *or* polyarticular morning joint stiffness ≥ 60 minutes
- Palmar telangiectasia
- Raynaud's phenomenon
- Unexplained digital edema
- Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)

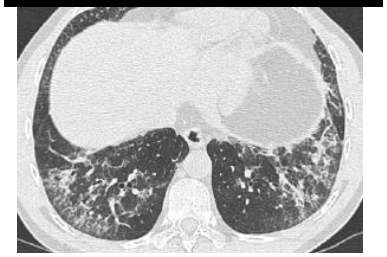
B

Serologic domain



C

Morphologic domain



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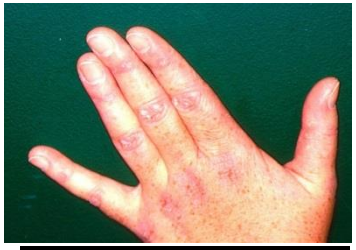

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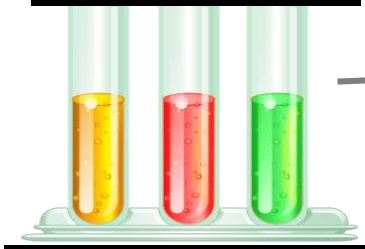
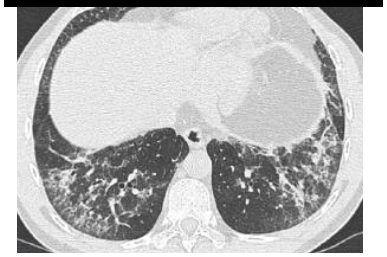
Serologic domain



C

Morphologic domain



- ANA>1:320 titer, diffuse, speckled, homogeneous patterns or
  - ANA nucleolar pattern (any titer) or
  - ANA centromere pattern (any titer)
- Rheumatoid Factor > 2 X ULN
- Anti-CCP
- Anti-dsDNA
- Anti-Ro (SS-A)
- Anti-La (SS-B)
- Anti-ribonucleoprotein
- Anti-Smith
- Anti-topoisomerase (Scl-70)
- Anti-tRNA synthetase (eg, Jo-1, PL-7, PL-12, (others are: EJ, OJ, KS, Zo, tRS)
- Anti-PM-Scl
- Anti-MDA-5

Interstitial Pneumonia with Autoimmune Features (IPAF)

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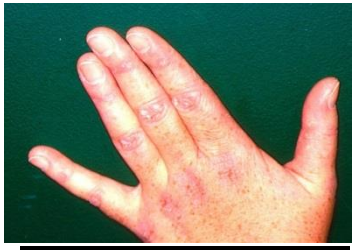
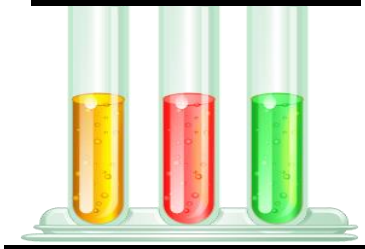


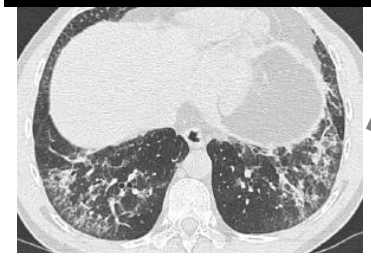
B

Serologic domain



C

Morphologic domain



- Suggestive radiology patterns by HRCT:
  - NSIP
  - OP
  - NSIP with OP overlap
  - LIP

- Histopathology patterns or features on biopsy:
  - NSIP
  - OP
  - NSIP with OP overlap
  - LIP
  - Interstitial lymphoid aggregates with germinal centers
  - Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)

- Multi-compartment involvement (in addition to IP)
  - Unexplained pleural effusion or thickening
  - Unexplained pericardial effusion or thickening
  - Unexplained intrinsic airways disease
  - Unexplained pulmonary vasculopathy

Morphologic domain: What about UIP?

- Not given the same "credit" as NSIP, OP, LIP ***but patients with UIP can have IPAF***

  – need to have at least one feature from the other two domains (clinical and serologic) or another pulmonary morphologic feature
    - unexplained multi-compartment involvement
    - secondary CTD features on lung biopsy

Fischer et al ERJ April 2016

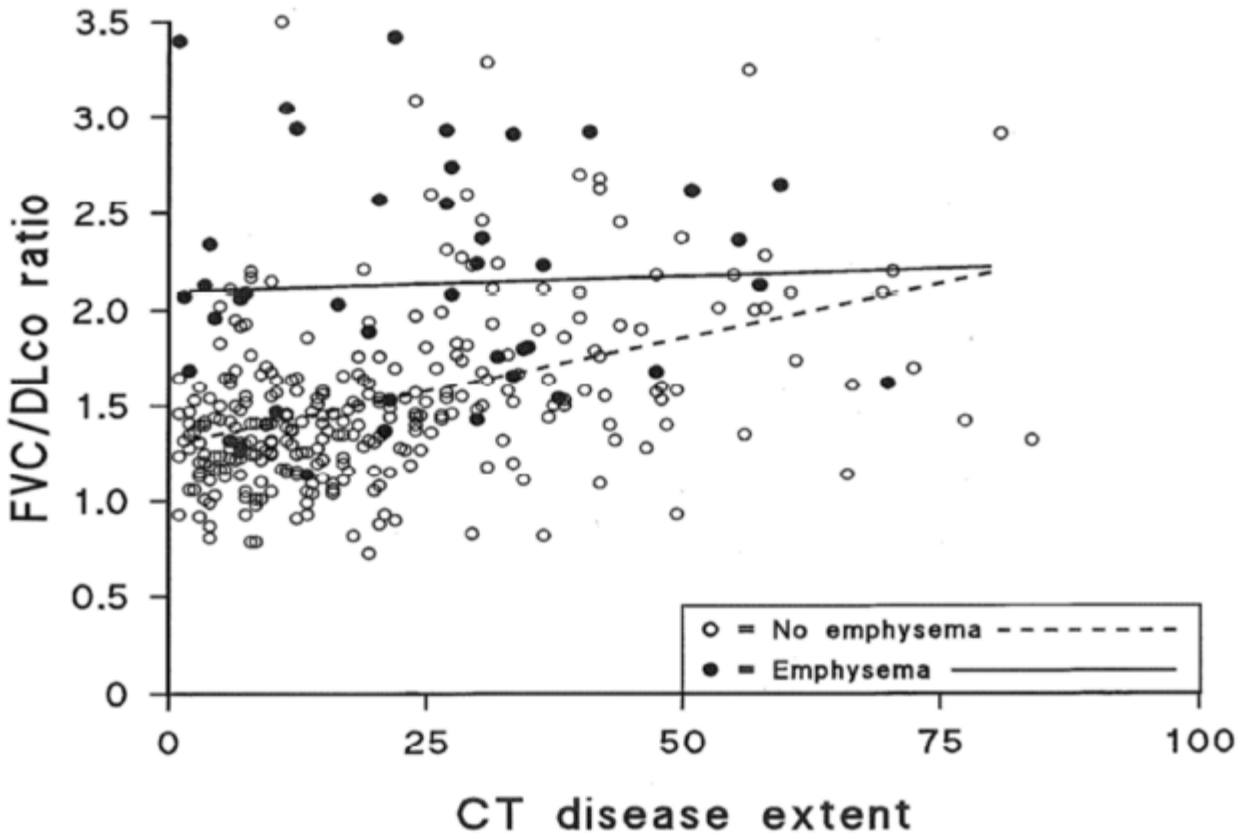
Multicompartment disease

- Morphologic domain satisfied in a patient with UIP if:

present. When assessing multicompartment criteria within the morphologic domain, intrinsic airways disease was noted when forced expiratory volume in 1 s (FEV_1)/FVC was <70, histopathologic bronchiolitis was present on SLB or when mosaic attenuation was seen on HRCT. Pulmonary vasculopathy was noted when FVC/D_{LCO} ratio was >1.6 based on previously published data showing correlation between this metric and pulmonary vasculopathy [11, 12]. Because multicompartment criteria apply only when findings cannot otherwise be explained, intrinsic airways disease and pulmonary vasculopathy were only considered in nonsmokers, as these findings can be seen in concurrent chronic obstructive pulmonary disease.

- Thus, in UIP patients, selective evaluation of vasculopathy and airways disease only in non-smokers

- In IPF, at what point is an elevated FVC/DLco ratio indicative of undue vasculopathy?



Antoniou KM et al. Arthritis Rheum 2016.

How is airway involvement defined?

- Histologically?
- HRCT?
- Pulmonary function tests?

The formal IPAF definition allows for any of these three variables to be used

Limitations

- NOT evidence based
- Expert panel opinion
- Could have been more multi-disciplinary
  - 13 pulmonologists
  - 4 rheum, 1 thoracic radiologist, 1 pulmonary pathologist

- Notable omissions of features, serologies
- Morphologic aspects
- Does it really matter?

Strengths

- Multi-disciplinary, international
- Included the groups that had put forth criteria
- Collective buy-in that a “reset” was needed
- Recognition that revisions will likely be needed – when informed by data
- A new platform for further investigation of a uniform cohort is in place

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]

Eur Respir J 2016; 47: 1767–1775

Interstitial pneumonitis with autoimmune features (IPAF): a work in progress

Fabrizio Luppi[1] and Athol U. Wells[2]

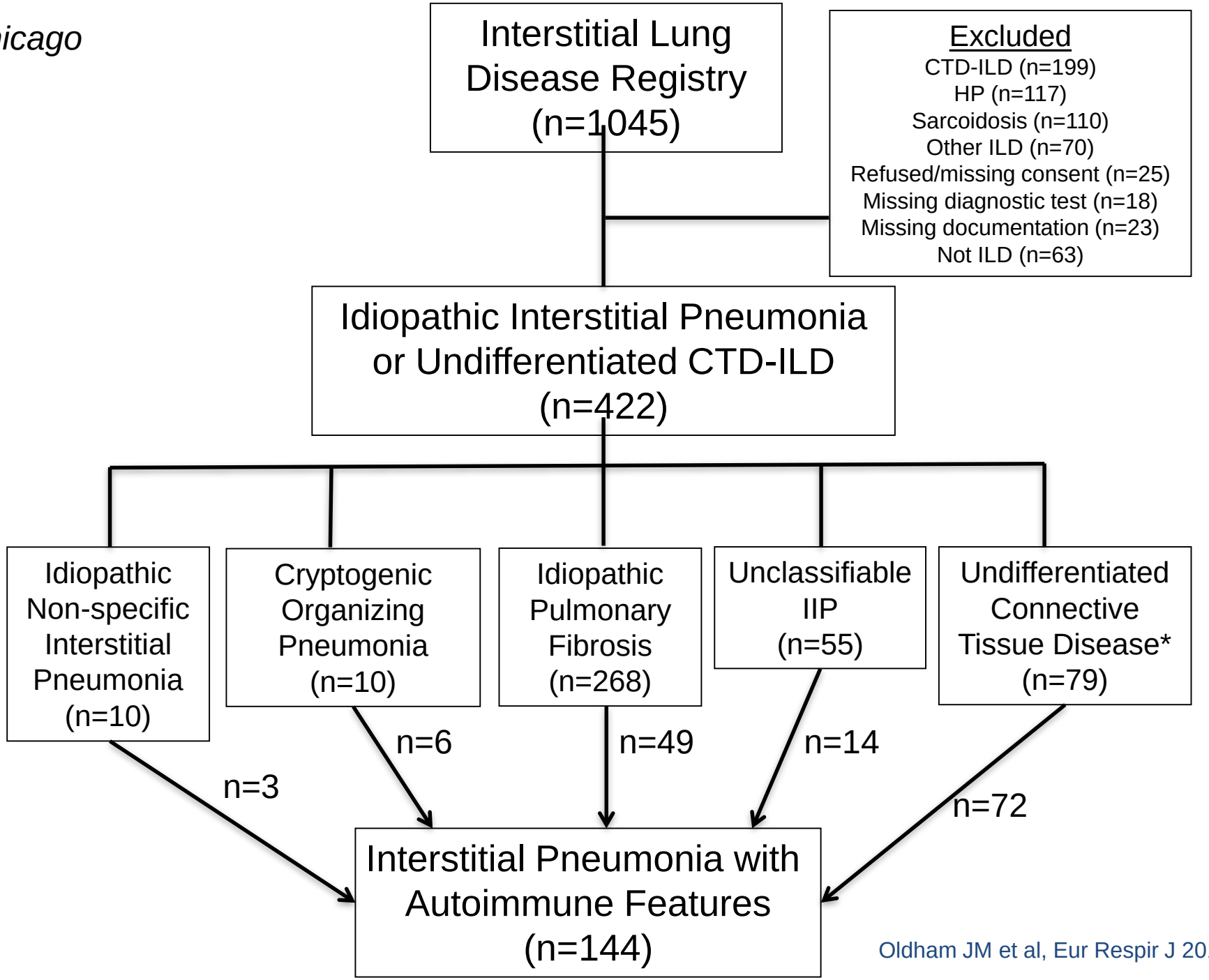
Eur Respir J 2016; 47: 1622–1624

The Chicago cohort explores the application of IPAF in clinical practice

Did an IPAF designation add prognostic value?

Specifically, was a change from an IPF diagnosis validated by outcome differences?

Chicago



Oldham JM et al, Eur Respir J 2016

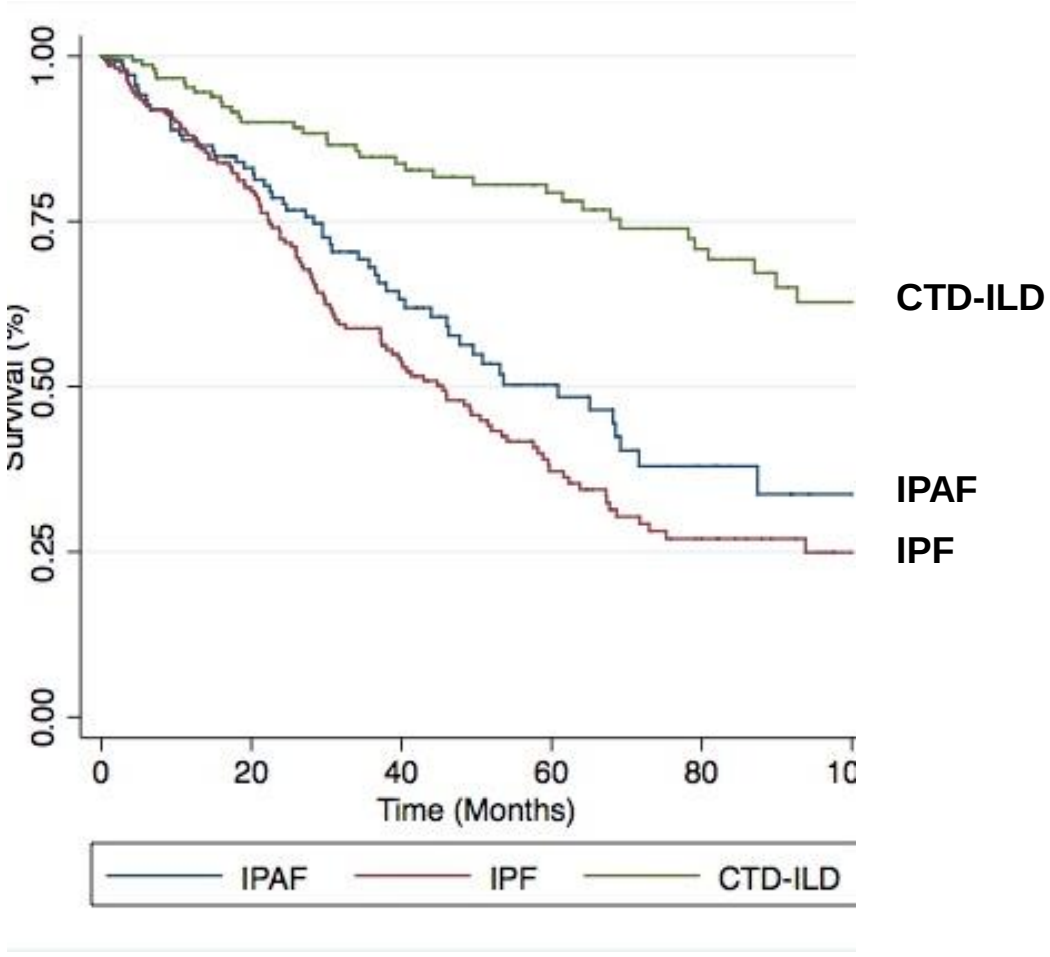
Table 1. IPAF Cohort Baseline Demographic and Clinical Characteristics (n=144)	
Age, mean (±SD)	63.2 (11)
Female Gender, n (%)	75 (52.1)
Gastroesophageal reflux, n (%)	76 (52.8)
Ever Smoker, n (%)	79 (54.9)
Crackles, n (%)	125 (89.3)
Clubbing, n (%)	21 (18.9)
UIP by HRCT, n (%)	77 (54.6)
UIP by SLB, n (%)	61 (73.5)
FVC (% predicted)	61.9 (18.3)
DLCO (% predicted)	45.3 (20.6)

Oldham JM et al, Eur Respir J 2016

Survival by diagnosis

U of Chicago: 144 patients

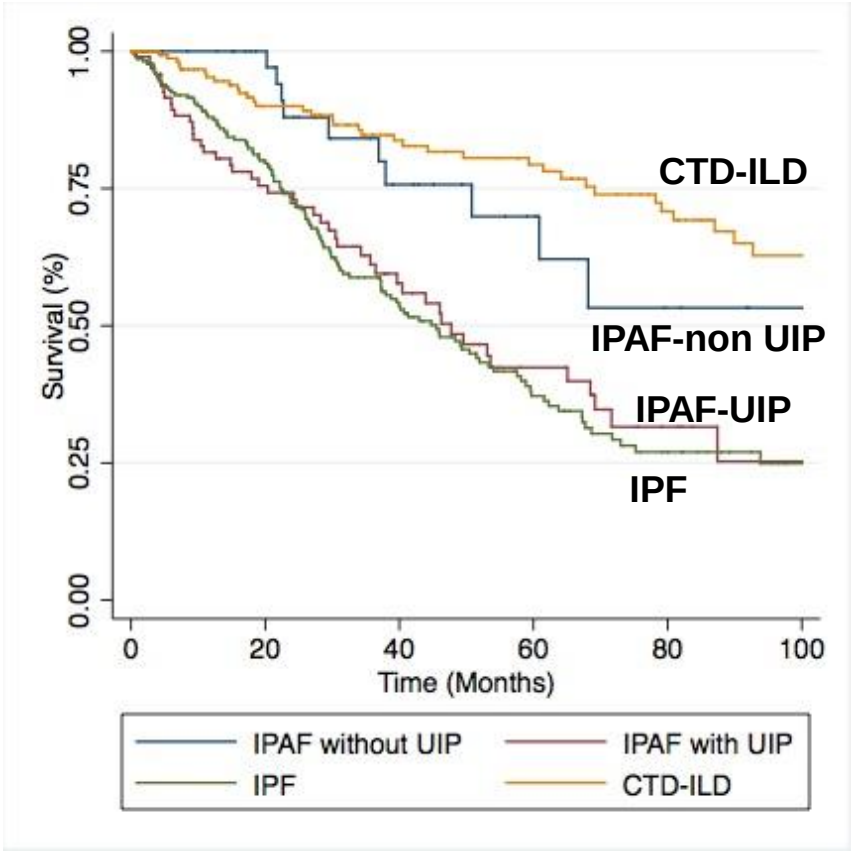
~50% men, ~ 70% UIP



CTD-ILD

IPAF

IPF



CTD-ILD

IPAF-non UIP

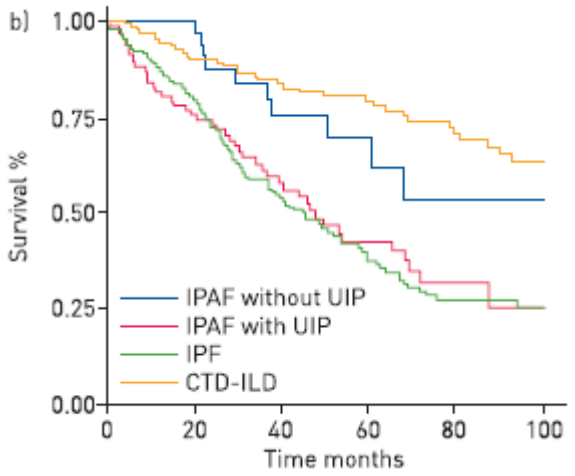
IPAF-UIP

IPF

Oldham JM et al, Eur Respir J 2016

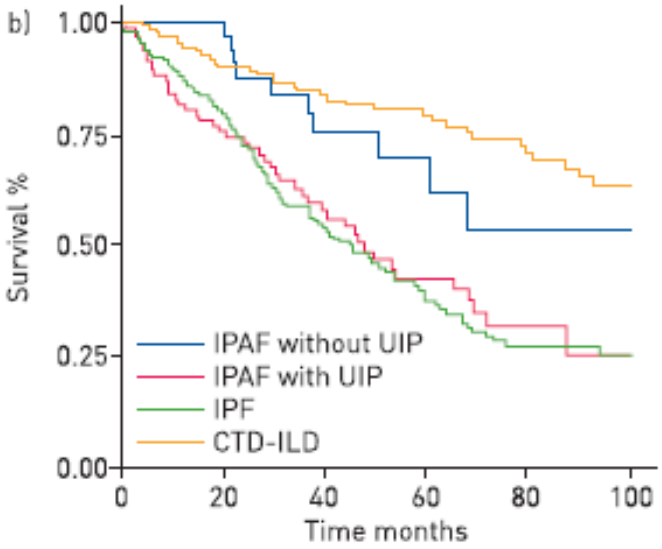
Mortality…..

- IPAF with UIP has the same mortality as IPF
- IPAF without UIP has the same mortality as CTD-ILD
- Once distinction made between UIP and non-UIP, how exactly does the IPAF designation help?



IPAF is, at this point, no more than a hypothesis in progress

- Search for a validated IPAF syndrome amply justified
- IPAF syndrome designation is not currently justified by clinical utility
- Need to focus on accuracy of rheumatologic evaluation and exact definition of multi-compartment disease



Do the Chicago data invalidate IPAF?

- Absolutely not
- Problem areas identified
- Fitting the sub-groups right sub-groups does create a better outcome
- Very high biopsy rate – without biopsy definition, how would other IPAF criteria help in “possible UIP”?

Scope of the problem

	N=235
SSc	88 (37%)
IPAF	**56 (24%)**
RA	42 (18%)
PM/DM	26 (11%)
SjS	14 (6%)
SLE	7 (3%)
MCTD	2 (<1%)

Clinical phenotypes of "autoimmune" ILD in an ILD Program:

After SSc-ILD, the next most common form of autoimmune ILD was IPAF

Chartrand et al ATS 2017 submitted

Clinical features and natural history of interstitial pneumonia with autoimmune features: A single center experience

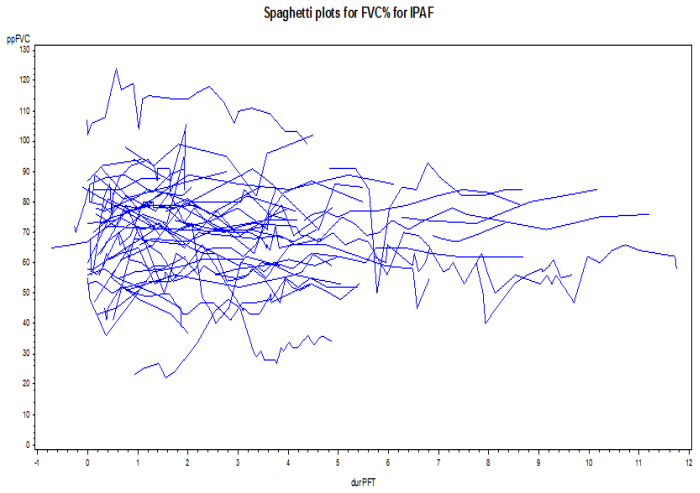
Sandra Chartrand [a], Jeffrey J. Swigris [b, c], Lina Stanchev [c], Joyce S. Lee [c], Kevin K. Brown [b, c]
Aryeh Fischer [c, *]

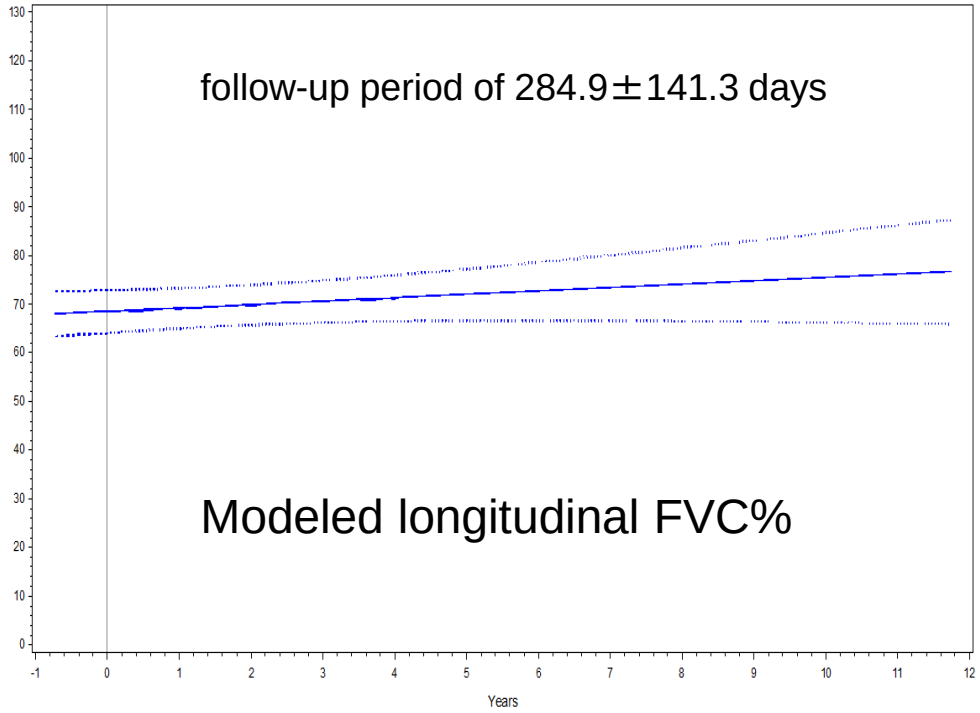
Methods: A retrospective, single center study of 56 patients with IPAF evaluated between February 2008 and August 2014. All clinical data were extracted from the electronic medical record and longitudinal changes in forced vital capacity (FVC) were analyzed with mixed-effects, piecewise linear regression models that considered time as a continuous factor.

Results: All patients fulfilled classification criteria for IPAF. The majority were women (71%) and never smokers (68%). The most frequently identified clinical features were Raynaud's phenomenon (39%), distal digital fissuring (29%), Gottron's sign (18%) and inflammatory arthropathy (16%). The most frequently identified serologies were antinuclear antibody (ANA) (48%), anti-Ro (SSA) (43%) and anti-tRNA-synthetase antibodies (36%). Nonspecific interstitial pneumonia (NSIP) (57.1%) followed by NSIP with organizing pneumonia (18%) were the most common radiologic patterns, while usual interstitial pneumonia was identified in only 9%. All but one patient was treated with immunosuppression: prednisone (82%) and mycophenolate mofetil (76%) were the most frequently used agents. During a follow-up period of 284.9 ± 141.3 days, modeled longitudinal FVC% was stable (slope = 0.69/year) and no deaths were observed in the cohort.

Conclusions: In this single center study, patients with IPAF were predominately non-smoking women with high-resolution computed tomography scans that suggested NSIP. Their pulmonary physiology was stable, and during limited follow-up, no deaths were observed. Prospective and multi-center studies are needed to better inform our understanding of IPAF.

NJH: 56 patients
~70% women, ~75% NSIP





Chartrand et al Resp Med 2016

Interstitial pneumonia with autoimmune features: Clinical, radiologic, and histological characteristics and outcome in a series of 57 patients

Kais Ahmad, Thomas Barba, Delphine Gamondes, Marylise Ginoux, Chahera Khouatra, Paolo Spagnolo, Mary Strek, Françoise Thivolet-Béjui, Julie Traclet, Vincent Cottin

Objective: to report on a series of patients with IPAF, and to compare their outcome to that of a cohort of patients with idiopathic pulmonary fibrosis (IPF).

Methods: Retrospective analysis of consecutive patients in a single institution over a 3-year period.

Results: Out of 778 consecutive patients with interstitial lung disease, 55% had idiopathic interstitial pneumonia (including 20.1% with IPF), 21.5% had connective tissue disease, and 7.3% had IPAF. Patients (49% of females) had a mean FVC of 64% and a mean DLco of 49%. Serologic criteria for IPAF were the most frequent (93%), followed by "morphologic" criteria (79%), and clinical criteria (47%). Fifty three percent of patients had a NSIP pattern on CT. Nailfold capillaroscopy found giant capillaries in 13/30 patients tested (23%). No significant was found in overall survival between patients with IPAF and those with IPF.

Conclusion: The recently defined criteria for IPAF are fulfilled by a significant proportion of patients referred for interstitial lung disease. As compared to those with IPF, patients with IPAF are more frequently females, have distinctive characteristics, have relatively frequent abnormalities at nailfold capillaroscopy, with no difference in age or in overall survival. Prospective studies are needed to guide the management of IPAF.

IPAF is NOT a clinical diagnosis

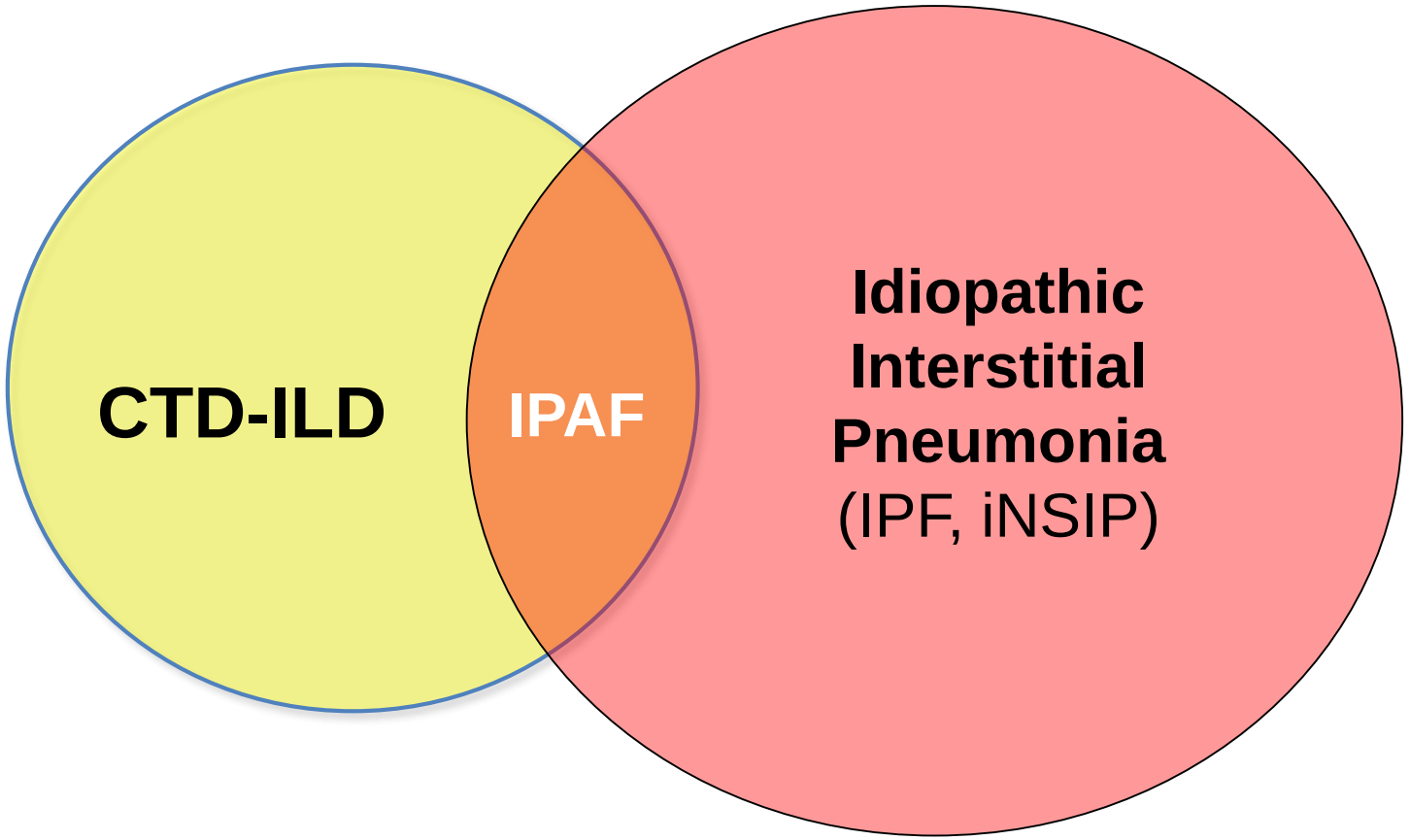
The published statement is a research statement; NOT a clinical guideline

Patients that fulfill classification as IPAF are managed clinically as CTD-ILD or idiopathic interstitial pneumonia – as per the discretion of their treating provider

Current clinical management???

- If a patient with IPF on other grounds has convincing evidence of systemic immune dysregulation, but not a classic CTD….
- Doing nothing is not an option unless disease is sub-clinical or definitely non-progressive
- Reasonable to start with immunomodulation but not azathioprine and NOT high dose corticosteroid
- If disease progresses despite therapy, switch to anti-fibrotic therapy
- Do not withdraw immunomodulation at this point?????

The IPAF “intersect”



WASOG 2018

International Conference on Sarcoidosis & Interstitial Lung Diseases

07-09 June
Heraklion Crete
Greece

Save the Date