IPF: diagnosis, differential diagnosis and treatment

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AUW has received consultancy fees from Actelion, Bayer, Boehringer Ingelheim, Centocor, Encysive, Genentech, Gilead, GSK, Intermune, MedImmune, Novartis, Takeda

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Plan

- **Diagnosis: what we can all agree about**
- **Diagnosis: why the 2011 ATS/ERS/JRS/ALAT IPF guidelines are broken**
- **Treatment: a brave new world …..**

American Thoracic Society Documents

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

Ganesh Raghu, Harold R. Collard, Jim J. Egan, Fernando J. Martinez, Juergen Behr, Kevin K. Brown, Thomas V. Colby, Jean-François Cordier, Kevin R. Flaherty, Joseph A. Lasky, David A. Lynch, Jay H. Ryu, Jeffrey J. Swigris, Athol U. Wells, Julio Ancochea, Demosthenes Bouros, Carlos Carvalho, Ulrich Costabel, Masahito Ebina, David M. Hansell, Takeshi Johkoh, Dong Soon Kim, Talmadge E. King, Jr., Yasuhiro Kondoh, Jeffrey Myers, Nestor L. Müller, Andrew G. Nicholson, Luca Richeldi, Moisés Selman, Rosalind F. Dudden, Barbara S. Griss, Shandra L. Protzko, and Holger J. Schünemann, on behalf of the ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis

This Official Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and the Latin American Thoracic Association (ALAT) Was Approved by the ATS Board of Directors, November 2010, the ERS Executive Committee, September 2010, the JRS Board of Directors, December 2010, and the ALAT Executive Committee, November 2010

This Statement has been formally endorsed by the Society of Thoracic Radiology and by the Pulmonary Pathology Society

Am J Respir Crit Care Med 2011; 183: 788

The 2011 IPF guidelines: two *major* advantages

Patients with classical IPF well served

A structured approach to pharmaceutical trials

Diagnosis of IPF

The diagnosis requires:

Exclusion of known causes of interstitial lung diseases: domestic/occupational environmental exposures, connective tissue disorders or drug toxicity

The presence of a UIP pattern on HRCT.

When all these features are confirmed by HRCT, a surgical lung biopsy is not essential for confirmation of IPF diagnosis

In the absence of a UIP pattern on HRCT, a surgical lung biopsy is required for confident diagnosis

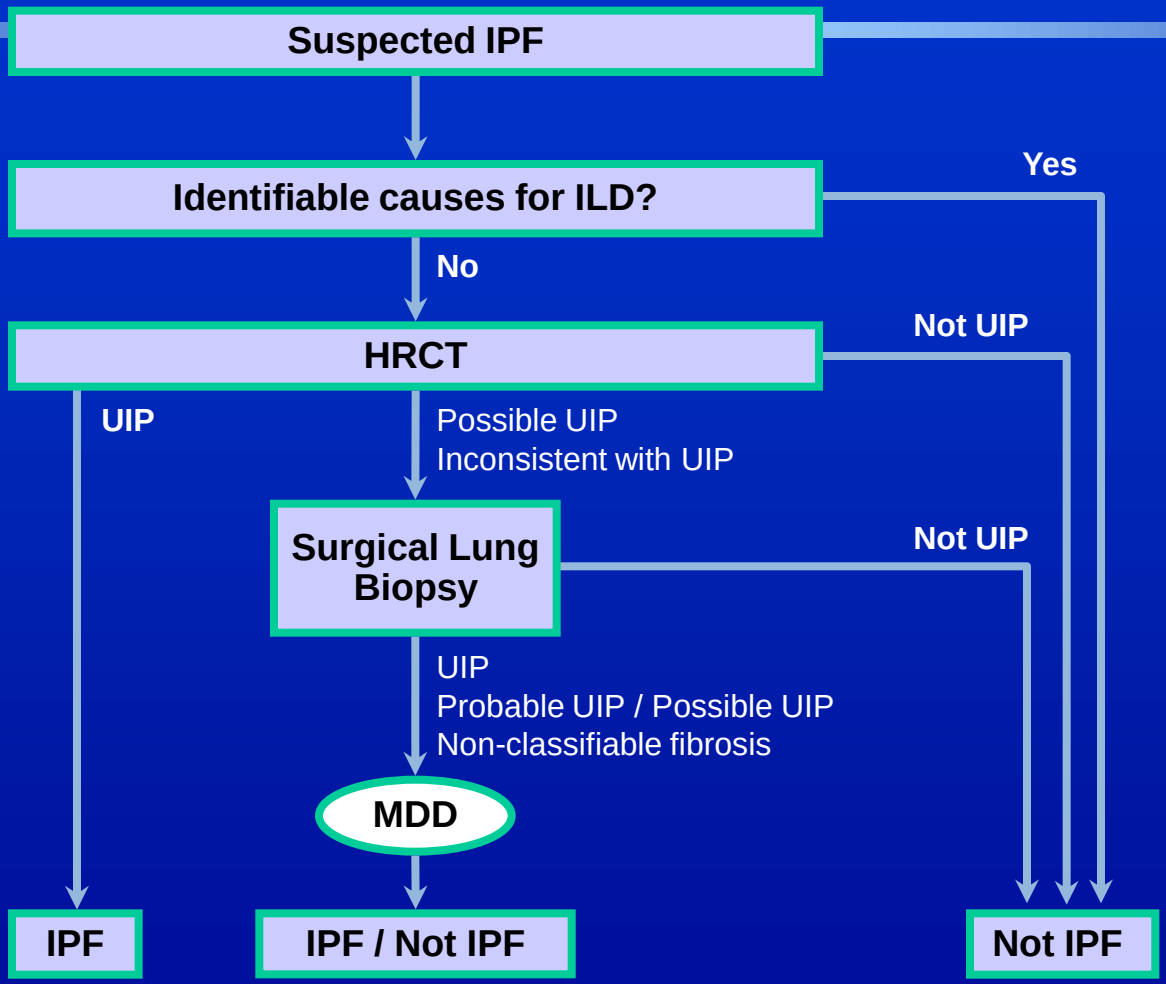
Raghu G, Collard HR, Egan JJ, et al. Am J Respir Crit Care Med 2011;183:788-824.

Radiological Features of IPF

UIP pattern (all four features)	Possible UIP pattern (all three features)	Inconsistent with UIP pattern (any one of seven features)
• Subpleural basal predominance	• Subpleural basal predominance	• Upper or mid lung predominance • Peribronchovascular predominance
• Reticular abnormality	• Reticular abnormality	• Extensive ground glass abnormality (extent > reticular abnormality) • Profuse micronodules (bilateral, predominantly upper lobes)
• **Honeycombing with or without traction bronchiectasis**		• Discrete cysts (multiple bilateral, away from areas of honeycombing) • Diffuse mosaic attenuation/air trapping (bilateral in three or more lobes)
• Absence of features listed as inconsistent with UIP pattern	• Absence of features listed as inconsistent with UIP pattern	• Consolidation in broncho-pulmonary segment(s)/lobe(s)

Raghu G, Collard HR, Egan JJ, et al. Am J Respir Crit Care Med 2011;183:788-824.

IPF Diagnostic Algorithm



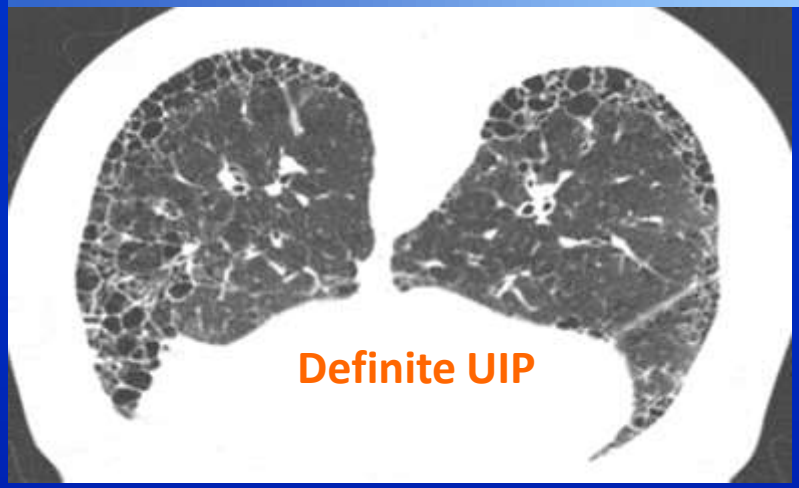
Adapted from: Raghu G, Collard HR, Egan JJ, et al. Am J Respir Crit Care Med 2011;183:788-824.

The goal of IPF guidelines is to allow less expert doctors to achieve optimal outcomes based on a secure diagnosis

In IPF, guidelines work if the answer to one of these questions is “yes”

- **Can IPF be diagnosed using HRCT in almost all cases?**
- **If not, is a biopsy diagnosis in virtually all cases realistic when HRCT fails?**
- **If not, is the same broad management appropriate for all realistic differential diagnoses?**

The CT spectrum of IPF



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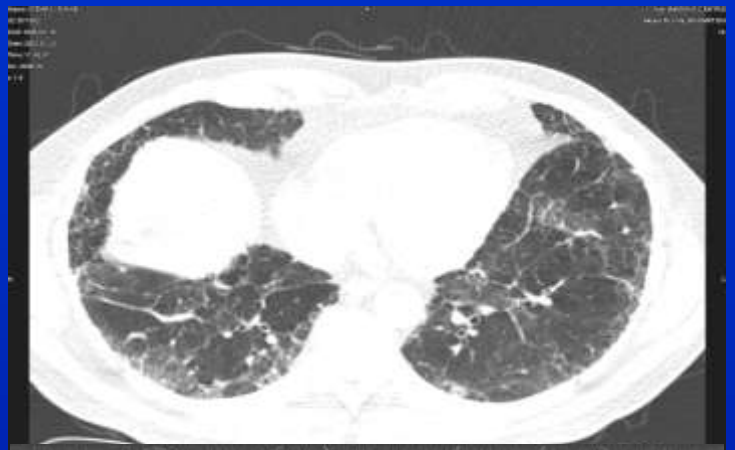

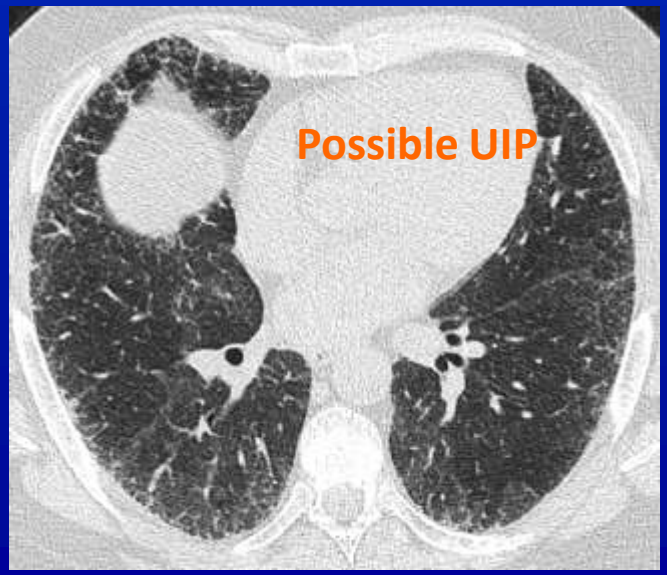

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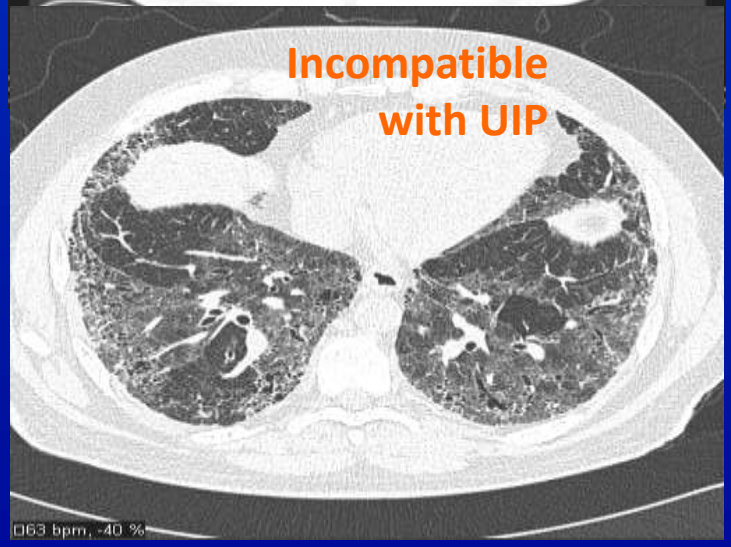
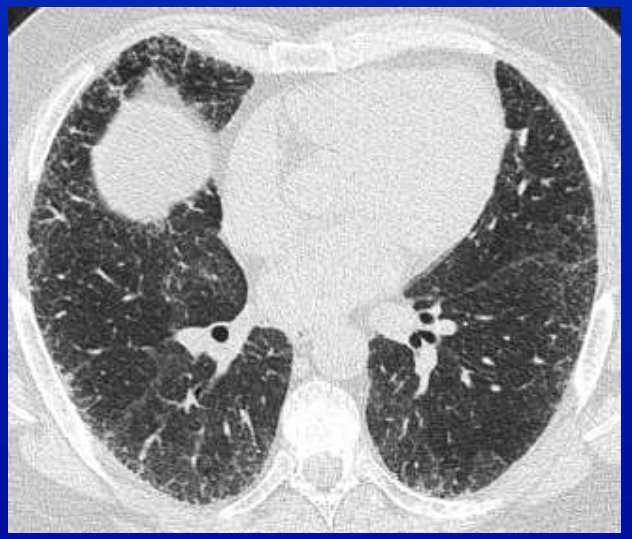


5-10%

Fibrotic IIP without honeycombing on HRCT

- 135 biopsied patients (IPF, n=97)
- Over age 65, patients with changes of moderately extensive “possible UIP”, had a >95% likelihood of UIP at biopsy
- Is “possible” UIP a useful term?
- Findings needs to be reproduced
- Issues: HP underepresented?
- Age 65-70 – patient numbers?

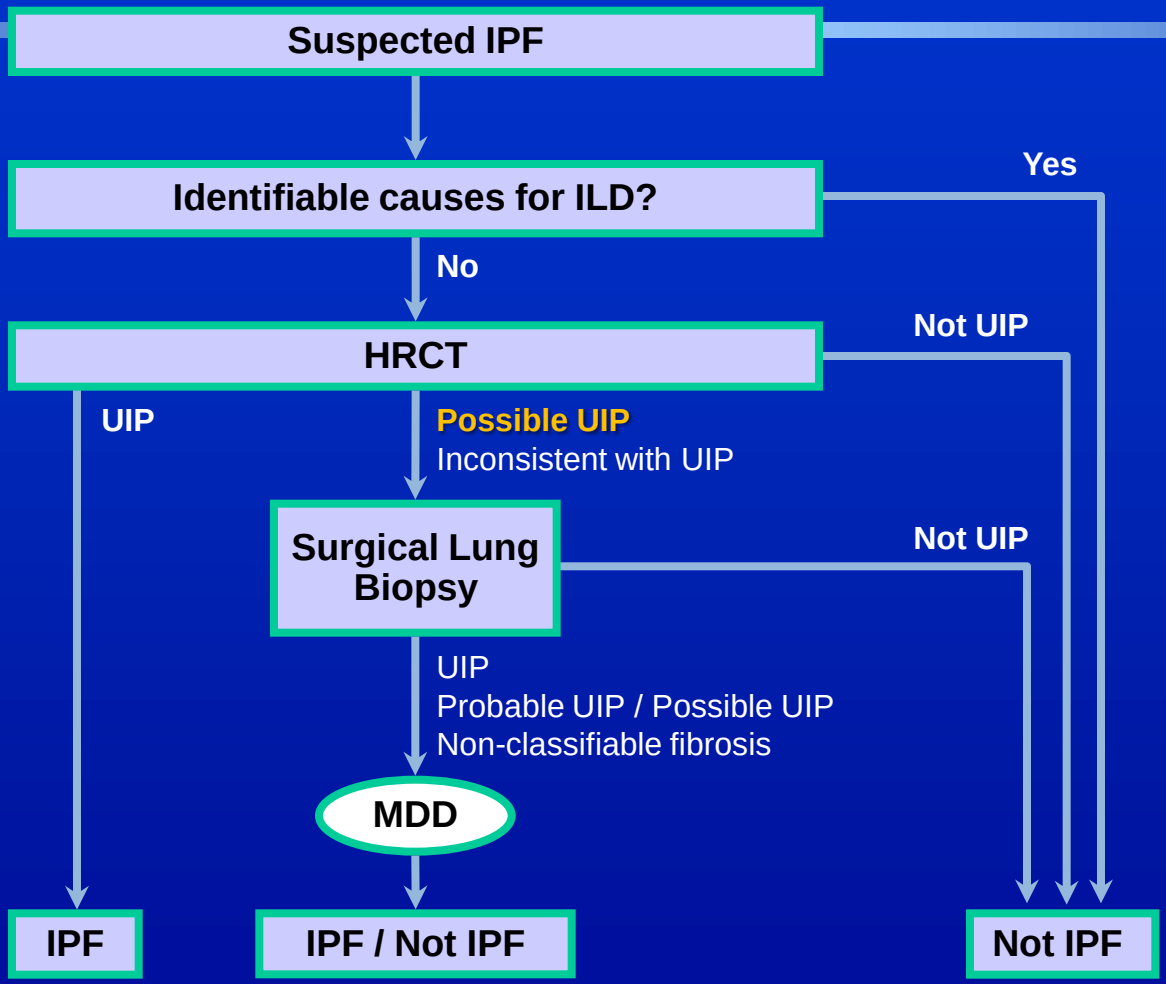


Fell CD et al. Am J Respir Crit Care Med 2010;181:832-7.

In IPF, guidelines work if the answer to one of these questions is “yes”

- Can IPF be diagnosed using HRCT in almost all cases? NO
- If not, is a biopsy diagnosis in virtually all cases realistic when HRCT fails?
- If not, is the same broad management appropriate for all realistic differential diagnoses?

IPF Diagnostic Algorithm



Adapted from: Raghu G, Collard HR, Egan JJ, et al. Am J Respir Crit Care Med 2011;183:788-824.

Contraindications to biopsy

- Severity
- Age
- Comorbidity
- Lack of timely access
- Patient disinclination

The ATS/ERS/JRS/ALAT recommendation to biopsy “possible UIP” can be carried out in perhaps 15% of cases

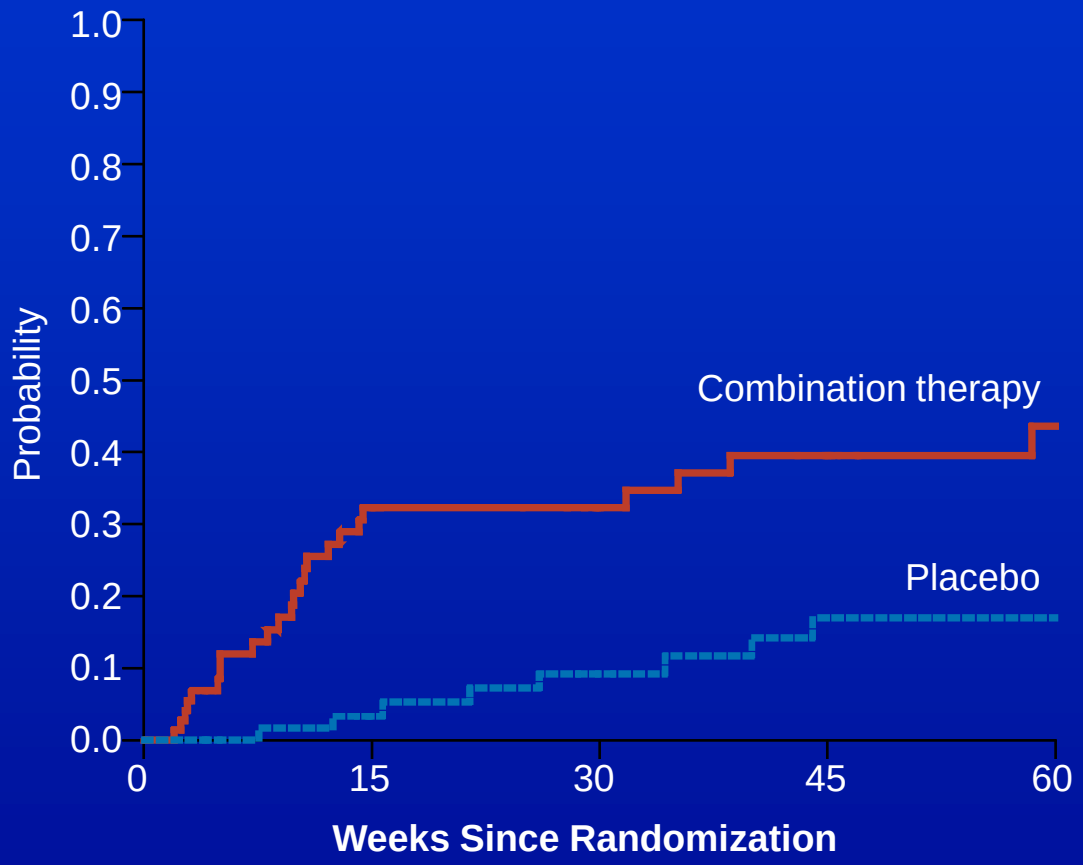
In IPF, guidelines work if the answer to one of these questions is “yes”

- Can IPF be diagnosed using HRCT in almost all cases? **No**
- If not, is a biopsy diagnosis in virtually all cases realistic when HRCT fails? **No**
- If not, is the same broad management appropriate for all realistic differential diagnoses?

Does the same treatment approach work for IPF, NSIP and chronic HP?

- Before the PANTHER study, the answer was “yes”
- Triple therapy seemed to be broadly reasonable for all three diagnoses
- The guideline worked OK in clinical practice
- Commendable rigour in IPF diagnosis for trial purposes

Time to Death or Hospitalization



No. at Risk					
Combination therapy	77	40	29	23	10
Placebo	78	55	42	26	16

Raghu G et al. N Engl J Med 2012; 366:1968-77.

In IPF, guidelines work if the answer to one of these questions is “yes”

- **Can IPF be diagnosed using HRCT in almost all cases?** **No!**
- **If not, is a biopsy diagnosis in virtually all cases realistic when HRCT fails?** **No!**
- **If not, is the same broad management appropriate for all realistic differential diagnoses?** **No!**

As all three answers are NO, guidelines are unequal to diagnosis in a large sub-group

The ATS/ERS guideline post PANTHER

40% of IPF patients have unclassifiable disease based on recommendations

In these patients, clinicians now have to guess whether to manage as for IPF or for the alternative diagnoses

The ATS/ERS guidelines fail the Potchen test in this patient sub-group

IPF: Multidisciplinary CT with Histopathological Input

HRCT Pattern	Surgical Lung Biopsy Pattern (when performed)	Diagnosis of IPF?
UIP	UIP Probable UIP Possible UIP Non-classifiable fibrosis	YES
	Not UIP	No
Consistent with UIP	UIP Probable UIP	YES
	Possible UIP Non-classifiable fibrosis	Probable
	Not UIP	No
Inconsistent with UIP	UIP	Possible
	Probable UIP Possible UIP Non-classifiable fibrosis Not UIP	No

Raghu G, Collard HR, Egan JJ, et al. Am J Respir Crit Care Med 2011;183:788-824.

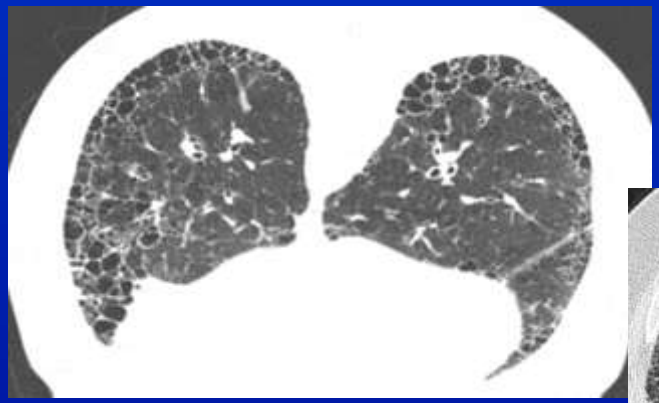
The heart of the problem is that HRCT has been given too large a role

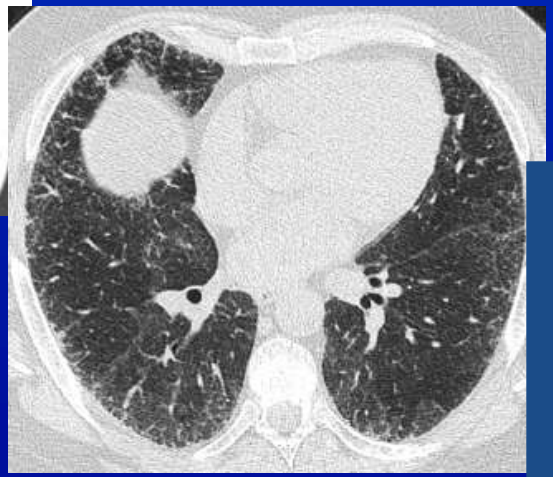
The conceptual flaw for clinical practice is that diagnosis must be based on standardised data.

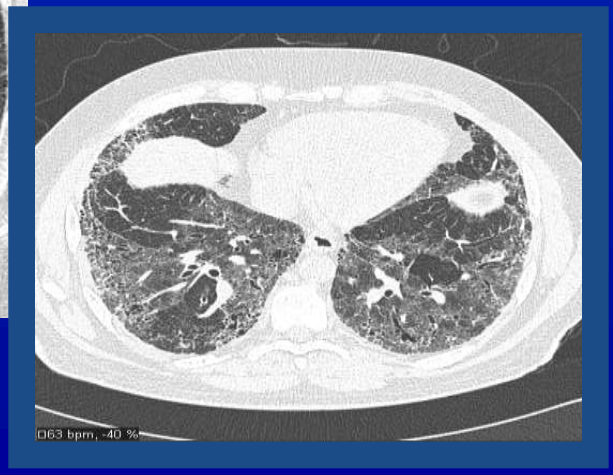
“One size fits all” does not work

The solution (1)

The HRCT spectrum (UIP/ possible UIP/ incompatible with UIP) should be viewed as providing pre-multidisciplinary likelihoods only.







The solution (2)

The goal of the multi-disciplinary process should be to establish whether or not a *working diagnosis* of IPF can be made, whether definite or probable

A "working diagnosis" means that the likelihood is sufficiently high to warrant IPF therapy i.e. definite or highly probably IPF

The solution (3)

True multidisciplinary evaluation, NOT .....

HRCT Pattern	Surgical Lung Biopsy Pattern (when performed)	Diagnosis of IPF?
UIP	UIP Probable UIP Possible UIP Non-classifiable fibrosis	YES
	Not UIP	No
Consistent with UIP	UIP Probable UIP	YES
	Possible UIP Non-classifiable fibrosis	Probable
	Not UIP	No
Inconsistent with UIP	UIP	Possible
	Probable UIP Possible UIP Non-classifiable fibrosis Not UIP	No

Multidisciplinary data should include….

BAL data (in a large patient sub-group)

Rheumatological and detailed serological evaluation in selected patients

Serial PFT and other “disease behaviour” data

Responsiveness to previous therapy

The identification of occult CTD

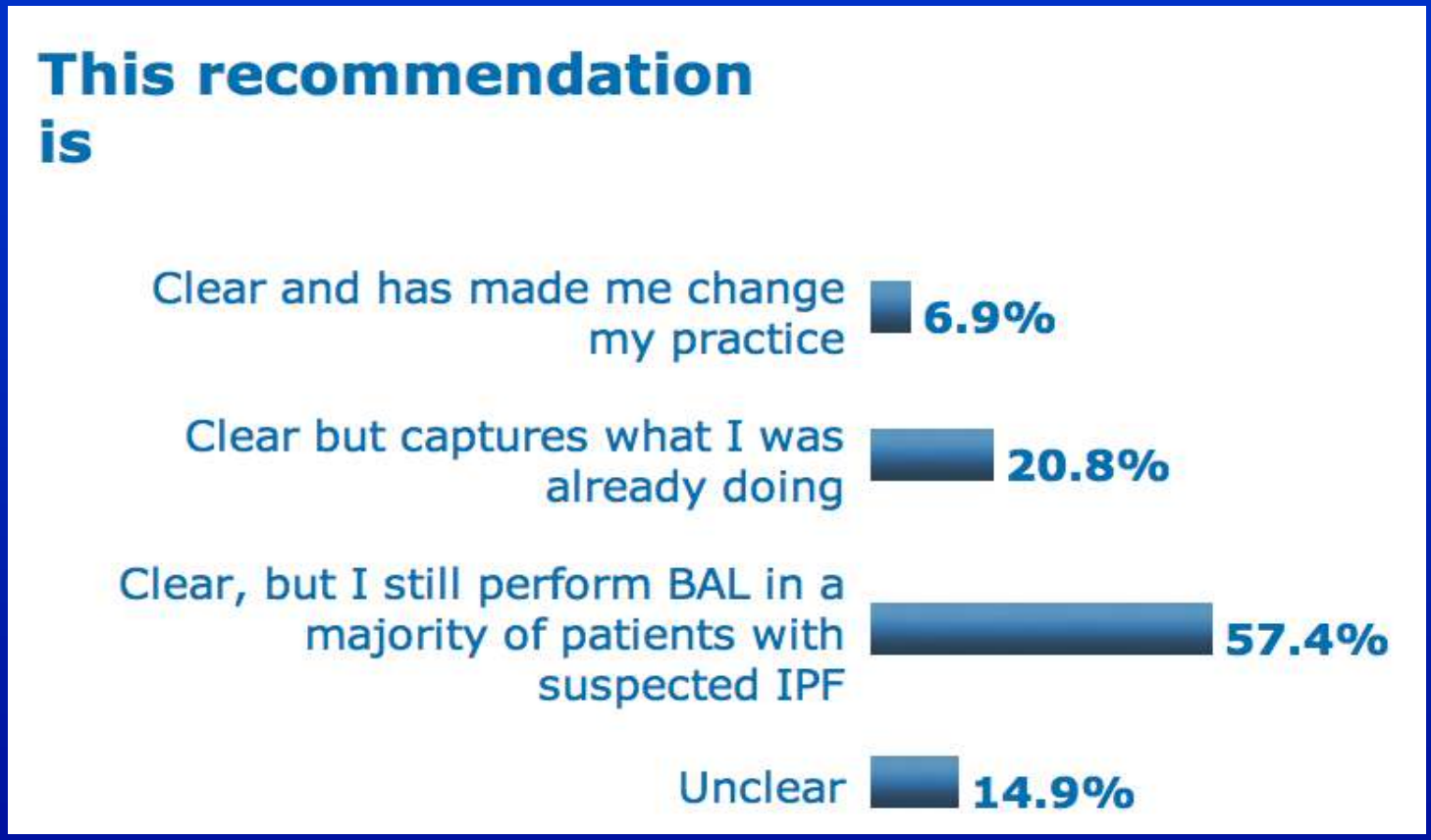
- **Discipline is essential. We want to make diagnoses other than IPF.**
- **“Sicca symptoms” and reflux symptoms particularly problematic in this regard**
- **Ideally, if in doubt, a rheumatologist should assess the patient**

2011 IPF guiideline

Should bronchoalveolar lavage cellular analysis be performed in the diagnostic evaluation of suspected IPF?

Bronchoalveolar lavage cellular analysis should not be performed in the diagnostic evaluation of IPF in the majority of patients, but may be appropriate in a minority (weak recommendation; low quality evidence).

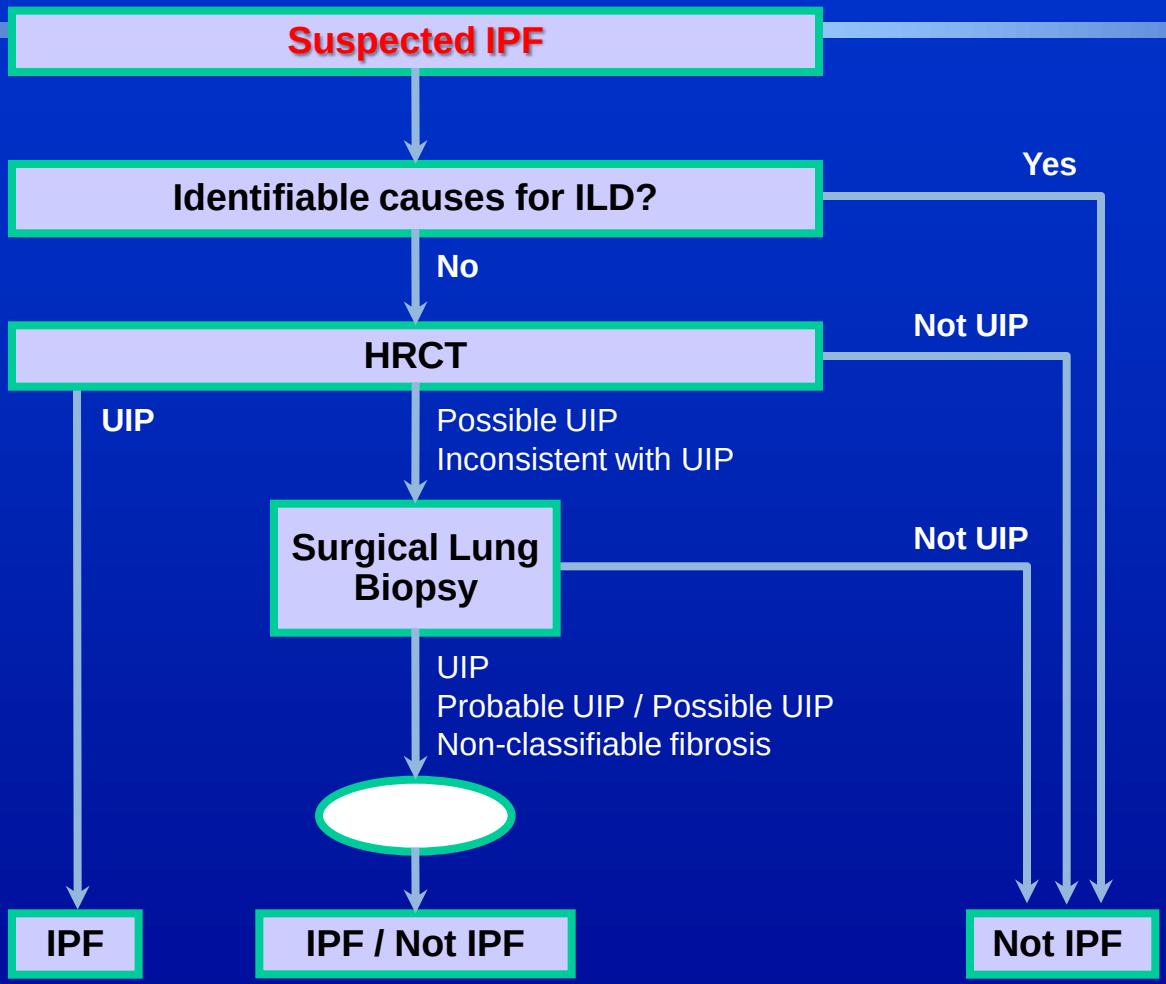
Raghu G, Collard HR, Egan JJ, et al. Am J Respir Crit Care Med 2011;183:788-824.



Berlin IPF AIR meeting, November 2011

What is “suspected IPF”?

IPF Diagnostic Algorithm



Adapted from: Raghu G, Collard HR, Egan JJ, et al. Am J Respir Crit Care Med 2011;183:788-824.

This recommendation averages two very separate scenarios

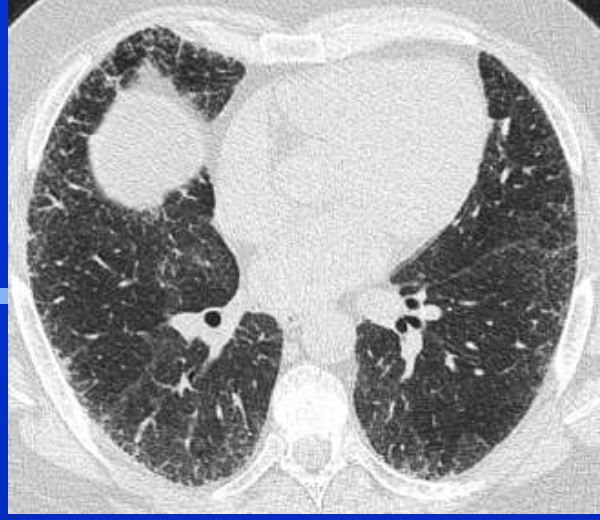
- **Classical UIP HRCT features, correct clinical context** = definite IPF, NOT "suspected IPF"

- **If the HRCT features are not classical for UIP**, the patient has "suspected IPF or NSIP"; "suspected IPF or HP" or some other "suspected" permutation. **BAL should be performed**

- ***Is it useful to combine these two scenarios in a "meaningless mean statement"?***

Integrating all of this.....

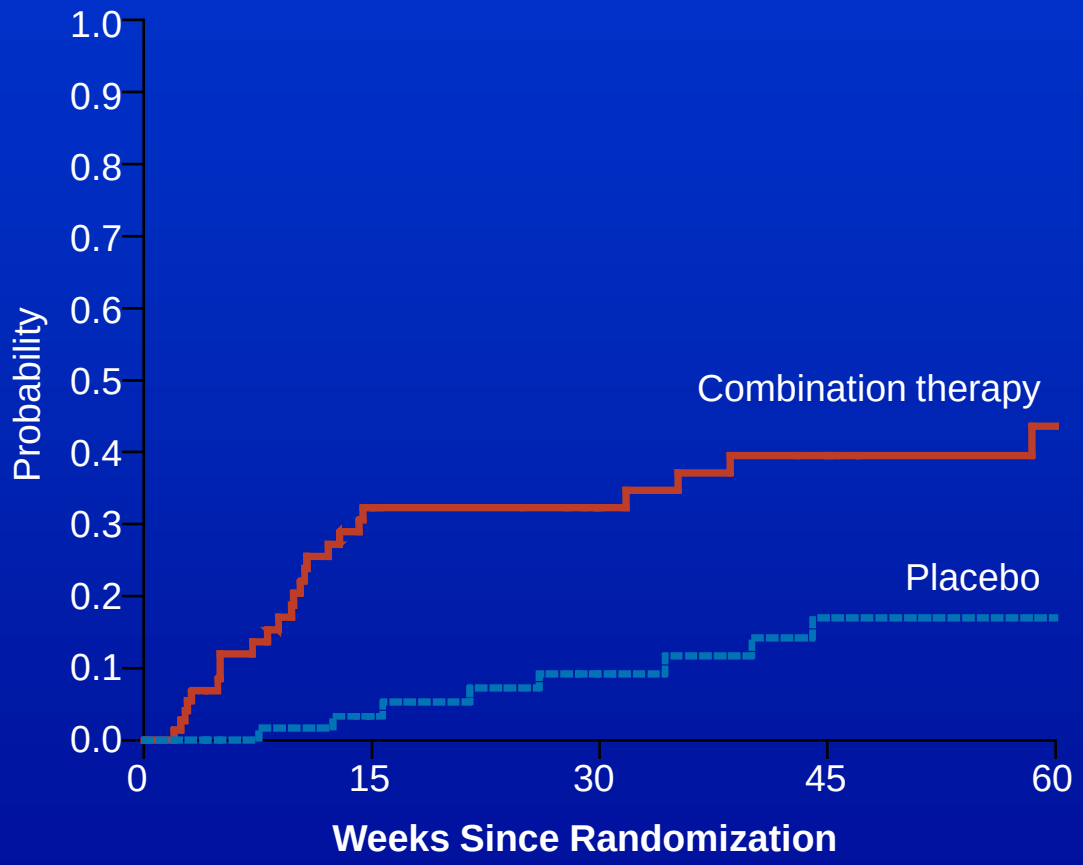
In the specific scenario of..



- Aged over 65, “is there any reason I cannot make a working diagnosis of IPF”?
- Aged under 65, investigate intensively including, if necessary, a diagnostic surgical biopsy
- A period of treatment as for CHP/NSIP is also a diagnostic test, with outcome information fed into multidisciplinary evaluation

Treatment should not include high dose corticosteroid therapy!

Death or hospitalization



No. at Risk					
Combination therapy	77	40	29	23	10
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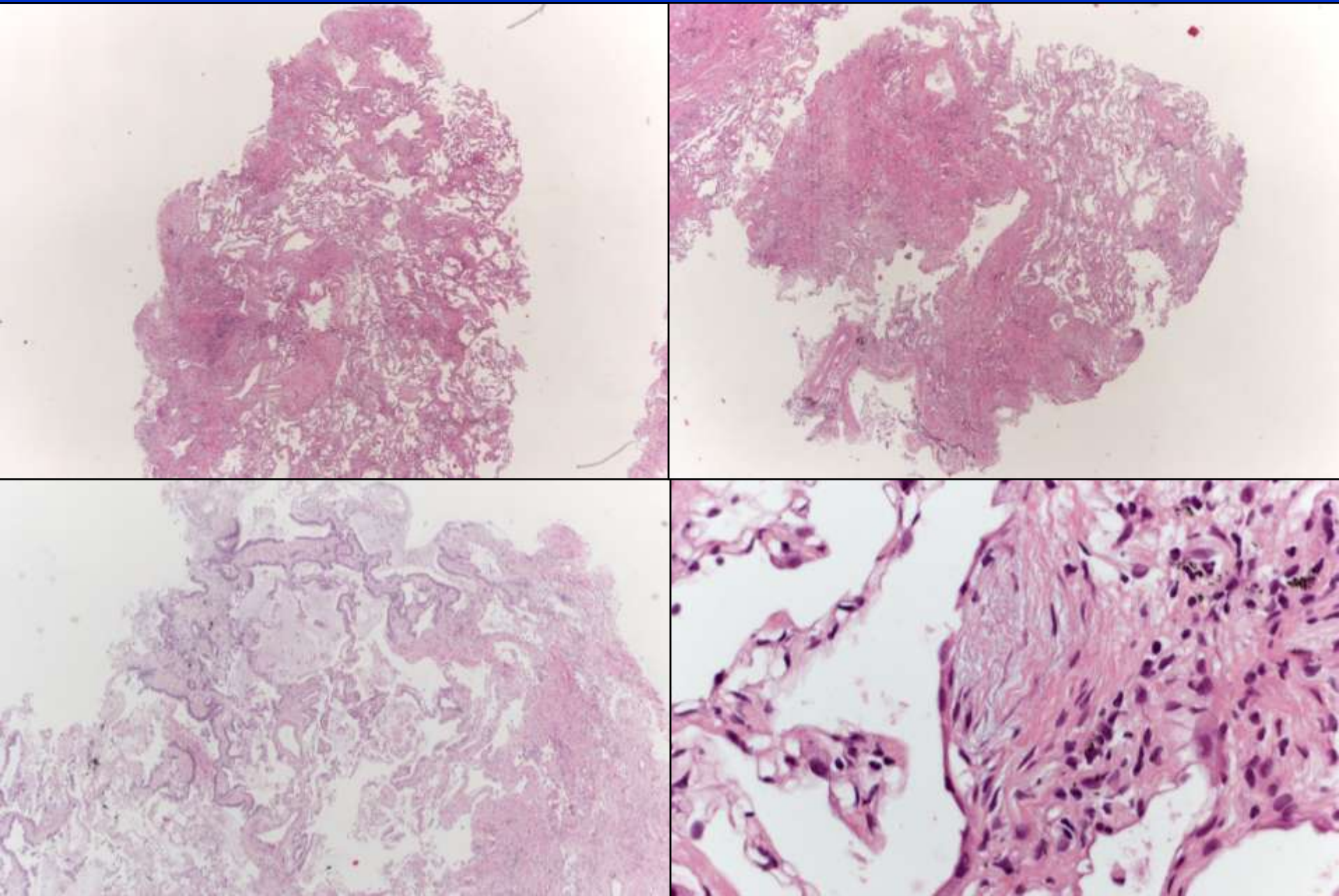
Cryobiopsy: background

- Transbronchial biopsy: inadequate in IIPs - strong -ve recommendation in 2011 IPF guideline
- With a freezing technique, able to achieve much larger biopsies (technique of Juergen Hertzel）
- Four to six biopsies routinely taken

My thanks to Venerino Poletti

Cryobiopsy: UIP with high confidence



Prospective study of transbronchial lung cryobiopsy

- 69 cases
- Three pathologists (Cavazza A, Colby TV, Rossi G)
- Pathologists highly confident that material sufficient to define pattern in 52 of 68 cases (76%), including 36 patients with a pattern of UIP
- Excellent agreement between pathologists on the presence of a UIP pattern (kappa = 0.83)
- TBLC in the diagnosis of fibrotic ILD appears safe and feasible and may offer an alternative to SLB – this requires further studies

Casoni GL et al. PLoS One 2014; e86716.

Issues

- **Mortality - in three series and >400 patients, <1%**
- **Pneumothoraces in over 20% - but beleeding rare with central biopsies**
- **Prognostic value yet to be quantified**

Treatment - key points

Until recently, no proven *radical* therapy other than lung transplantation

USA IPF net studies negative for anti-oxidant monotherapy and for triple therapy

Major design issues with both studies. But unlikely that striking benefits a la pirfenidone or nintedanib have been missed.

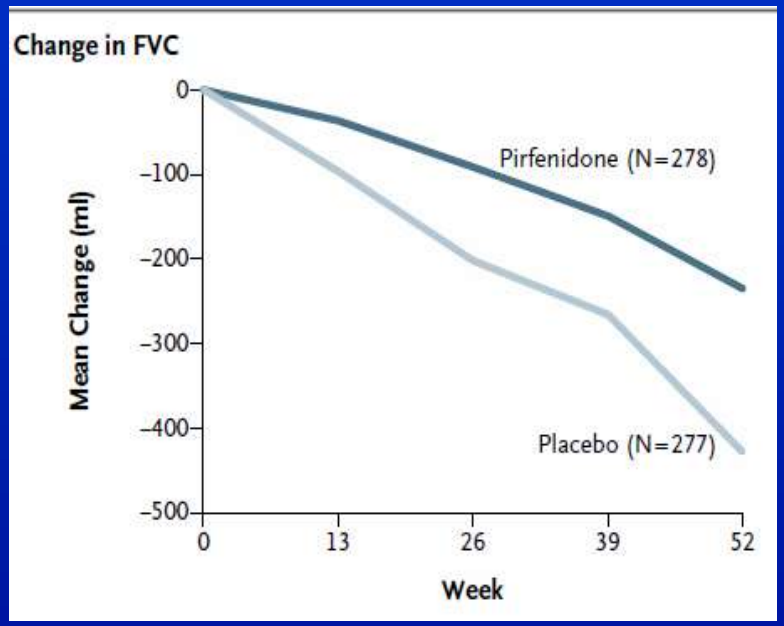
Other issues

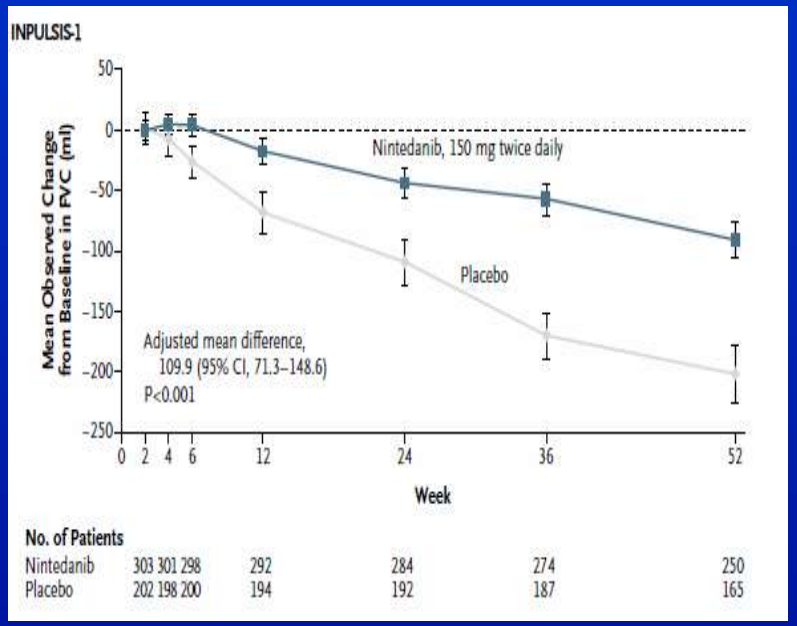
Transplantation…… advanced care planning …..optimal palliative care ….. Best use of oxygen ….. Rehabilitation ….. Early antibiotic therapy ….. Access to psychological support

Treatment of pulmonary hypertension

Anti-reflux therapy

Ground-breaking recent results

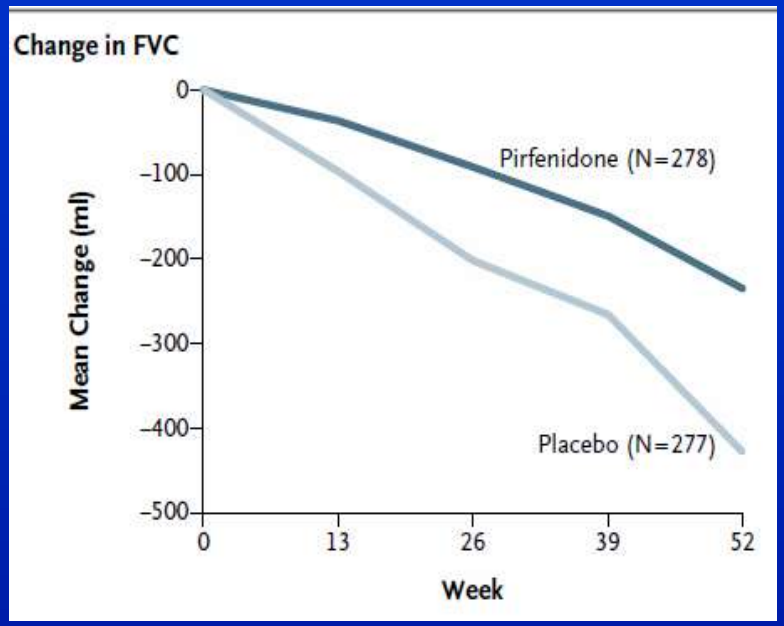


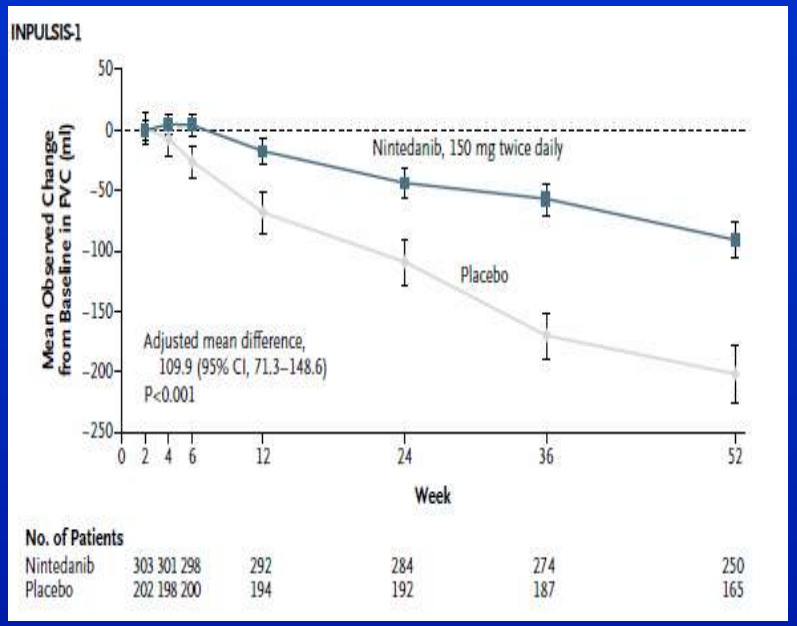


King TE Jr et al. N Engl J Med 2014; 370:2083-92.

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

We have major issues!





Future study design?

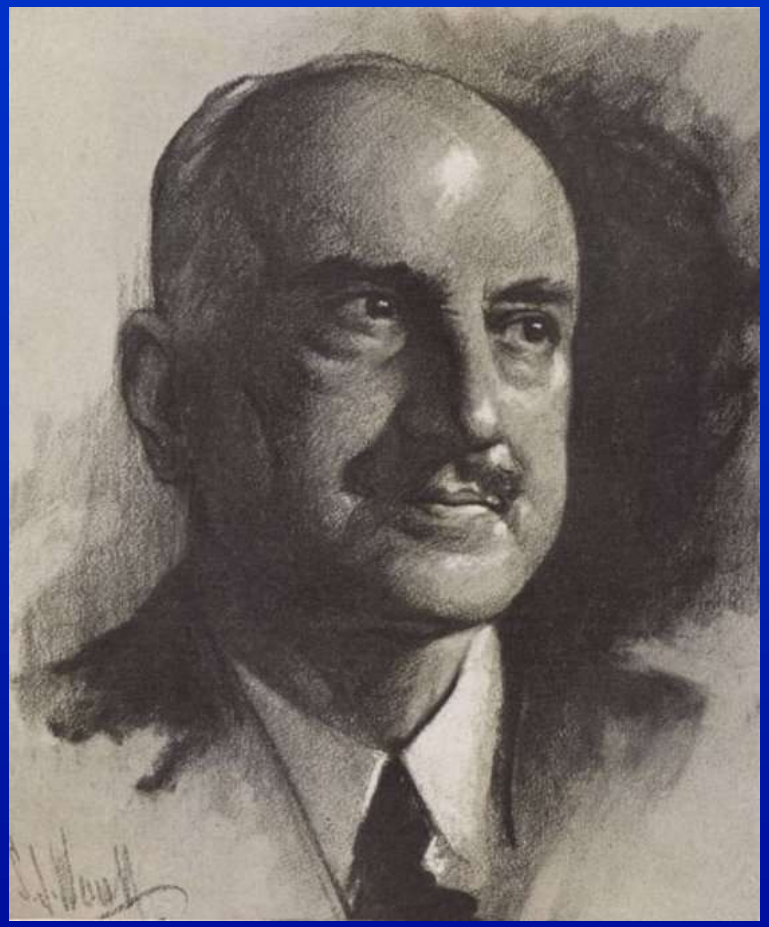
Do we have a *best current treatment*?

How long will these treatment effects endure?

George Santayana (1863-1952)

“Those who cannot remember the past are condemned to repeat it”

“Those who forget the errors of history are doomed to repeat them”



How this might play out in IPF

- In 1999, IPF was viewed as a single disease
- In 2014, IPF is viewed as a single disease
- But it is not the same disease
- In 2029, IPF will be viewed as a different disease for treatment purposes

Summary – diagnostic issues

The problem of “possible UIP” is the major current diagnostic problem in chronic fibrotic ILD

The diagnostic goal should be a **working IPF diagnosis** for practical treatment purposes, using full MD evaluation, including BAL and exclusion of occult CTDILD

If the distinction between IPF and alternative diagnoses remains in doubt after full evaluation, a period of treatment as for HP or NSIP is also a diagnostic test

Watch further cryobiopsy developments