# The diagnosis of IPF

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# Clinical Classification

## Diffuse parenchimal lung diseases

**Exposure-related:**
- occupational
- environmental
- medication

Idiopathic interstitial pneumonias

Idiopathic pulmonary fibrosis

**Connective tissue Disease:**
- Scleroderma
- Rheum. Arthritis
- Sjogren
- UCTD

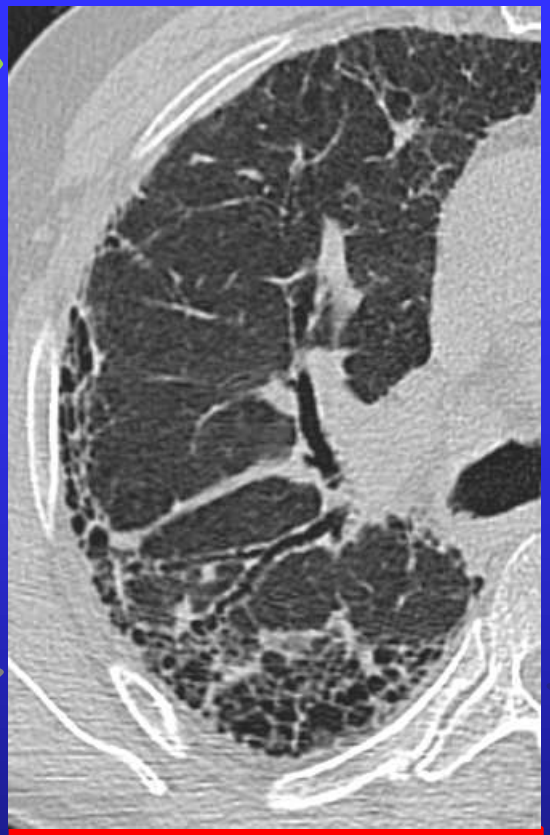
Other:
- Sarcoidosis
- Vasculitis/DAH
- LCH
- LAM
- PAP
- Eosinophilic pneumonia
- Neurofibromatosis
- Chronic aspiration
- Inflammatory bowel disease

| | |
|---|---|
| Desquamative interstitial pneumonia | Respiratory bronchiolitis interstitial lung disease |
| Acute interstitial pneumonia | Cryptogenic organising pneumonia |
| Non-specific interstitial pneumonia | Lymphocytic interstitial pneumonia |

Worldwide prevalence is estimate of at least 5 million people

Progressive deterioration is inevitable

Considerable inter- and intra patient variability



**IPF**

Lung transplantation is an option

A genetic disease?

Median survival historically is only ~3-5 years

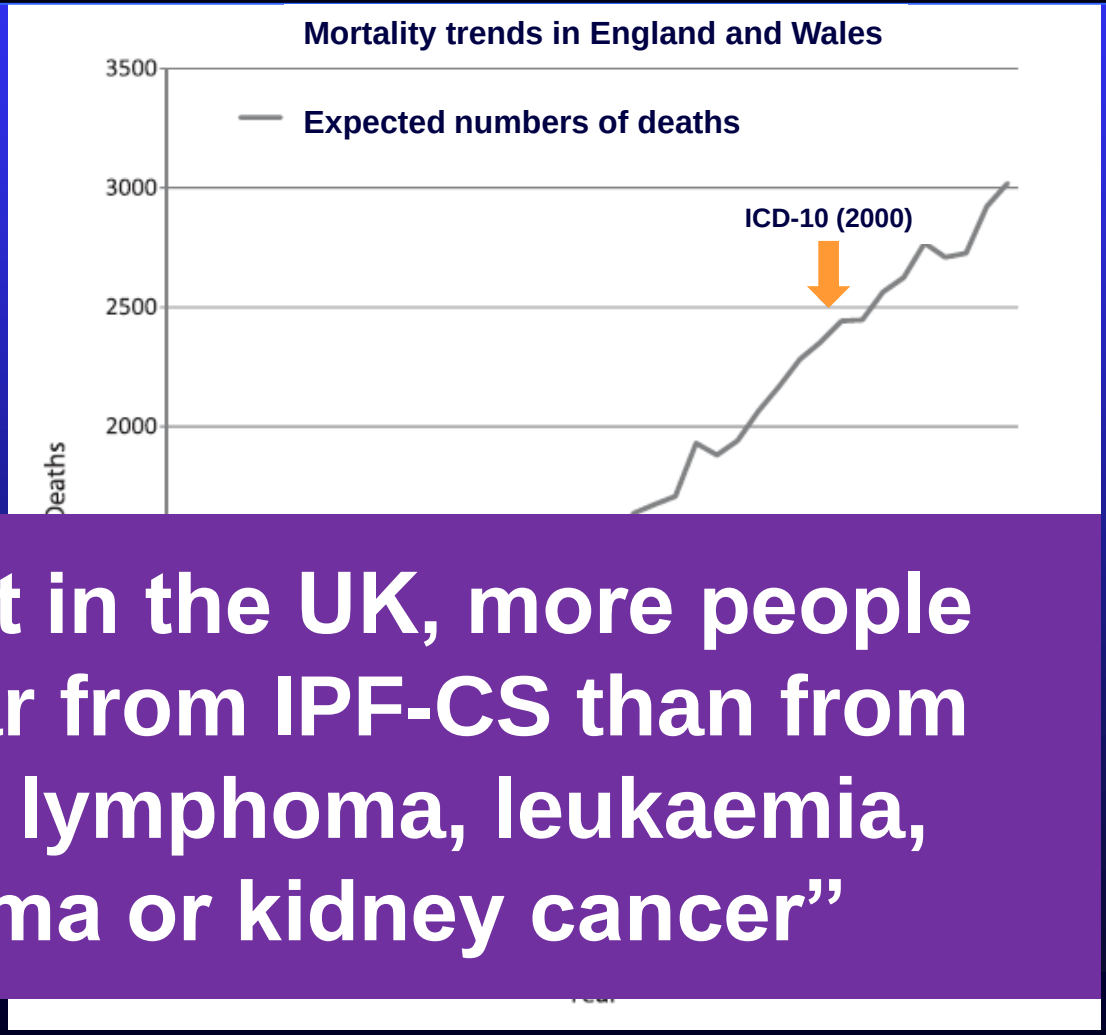
A rare disease

Limited therapeutic options

# The rising incidence of idiopathic pulmonary fibrosis in UK

Navaratnam V et al. Thorax 2011;66:462

- 15000 people in the UK have a diagnosis of IPF-CS
- each year, 5000 new cases of IPF




**"This means that in the UK, more people will die each year from IPF-CS than from ovarian cancer, lymphoma, leukaemia, mesothelioma or kidney cancer"**

# Incidence and prevalence of idiopathic pulmonary fibrosis: review of literature

Nalysnyk L et al. Eur Respir Rev 2012;21: 355 -361

- The incidence and prevalence of IPF are difficult to determine due to the lack of uniform diagnostic criteria
- Both prevalence and incidence estimates reported in the USA tended to be higher than those reported in Europe or Japan
- Prevalence and incidence estimates increased with increasing age
- In the USA, it seems that the incidence of IPF decreased in recent years, while in the UK incidence reported lately is higher than that reported previously. However, the recent incidence estimates in the USA are similar to the recent incidence estimates in the UK

The prevalence of IPF in Europe is ~ 120000 and an estimated 40000 new cases are diagnosed each year

The prevalence of IPF in Lombardy region in 2010 is 3600 patients and incidence is 450

In Lombardy, IPF prevalence increased while incidence remained stable in the last years (2005-2010)

# Familial Interstitial Pneumonia: 2-20% of case

Heterozygous mutations in SFTPC (~1%), SFTPA2 (~1%), TERT (~ 15%), and TERC (~ 1%) are responsible for about 20% of all familial interstitial pneumonias (FIPs)

Sporadic IPF, in the absence of telomerase mutations, is often associated with telomere shortening, suggesting that pathways involved in familial disease may contribute to sporadic disease

Most FIP families (80%) have evidence of vertical transmission suggesting single autosomal dominant mechanisms

A common variant in the promoter of the MUCB gene is associated with the development of both familial and sporadic IPF

# Old definition of IPF

- IPF is a distinct type of chronic fibrosing interstitial pneumonia
- Unknown cause
- Limited to the lungs
- Has typical HRCT findings
- Associated with a histologic pattern of usual interstitial pneumonia (UIP)

ATS/ERS Consensus Statement. *Am J Respir Crit Care Med*. 2002;165:277-304

ATS/ERS Consensus Statement. *Am J Respir Crit Care Med*. 2000;161:646-664

# New definition of IPF

- IPF is a specific form of ***progressive*** fibrosing interstitial pneumonia
- Unknown cause
- Occurring in older adults
- Limited to the lungs
- Associated with a histological ***and/or radiological*** pattern of usual interstitial pneumonia (UIP)

*Am J Respir Crit Care Med* 2011; 183: 788-824

# *Importance of early diagnosis of IPF*

- Begin evaluation for lung transplant earlier
- Allows for earlier referral and enrollment in clinical trials (which are generally limited to patients with mild to moderate disease)
- Emerging evidence regarding response to therapy
- Exclude other more treatable diseases

# Delayed access and survival in Idiopathic Pulmonary Fibrosis
## A Cohort study

*Lamas DJ et al. Am J Respir Crit Care Med 2011; 184: 842*

- Our results suggest that the recognition (or suspicion) of IPF should prompt early referral to a

At present, ILD screening efforts are limited to those with known risk factors for ILD or those with a history of familial IPF. Innovative studies of circulating biomarkers and quantitative imaging methods may hold the key to more accurately identifying early disease

# *Velcro crackles: the key for early diagnosis of idiopathic pulmonary fibrosis?*

*Cottin V and Cordier JF. Eur Respir J 2012; 40: 519*

We further consider that pulmonary auscultation should still be included in the initial steps of the diagnostic algorithm in patients with chronic dyspnoea, especially in those with progressive dyspnoea, as well as in patients with chronic dry cough

It cannot be ignored anymore that a longer delay in accessing a tertiary care centre is associated with a higher risk of death independent of the severity of IPF

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Edward W. Campion, M.D., *Editor*

# Fundamentals of Lung Auscultation

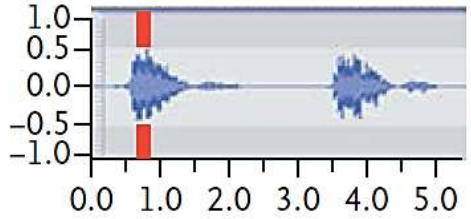
Abraham Bohadana, M.D., Gabriel Izbicki, M.D., and Steve S. Kraman, M.D.

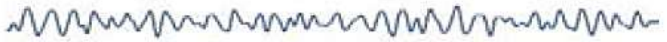
**"Chest auscultation has long been considered a useful part of the physical examination, going back to the time of Hippocrates."**

*N Engl J Med* 2014; 370: 744-51

**Normal (Vesicular) Lung Sound**

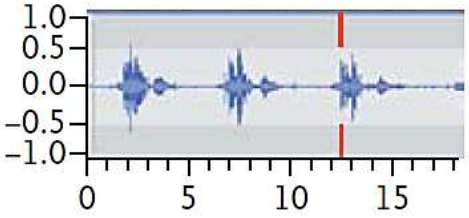
Low-pass-filtered noise
Typical frequency, 100–1000 Hz
Drop of energy at 200 Hz



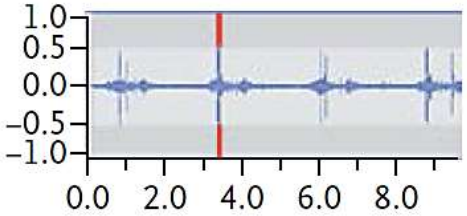
**Fine Crackle**

Rapidly dampened wave deflection
Typical frequency, about 650 Hz
Typical duration, about 5 msec




**Coarse Crackles**

Rapidly dampened wave deflection
Typical frequency, about 350 Hz
Typical duration, about 15 msec




*N Engl J Med* 2014; 370: 744-51

# Don't stop with "pulmonary fibrosis"

- Reason for a specific diagnosis:
  - many forms are treatable
  - treatments depend on diagnosis
  - prognosis varies
  - clinical trial eligibility requirements

*In idiopathic interstitial pneumonia, diagnosis is prognosis*

# Approach to the diagnosis of IPF

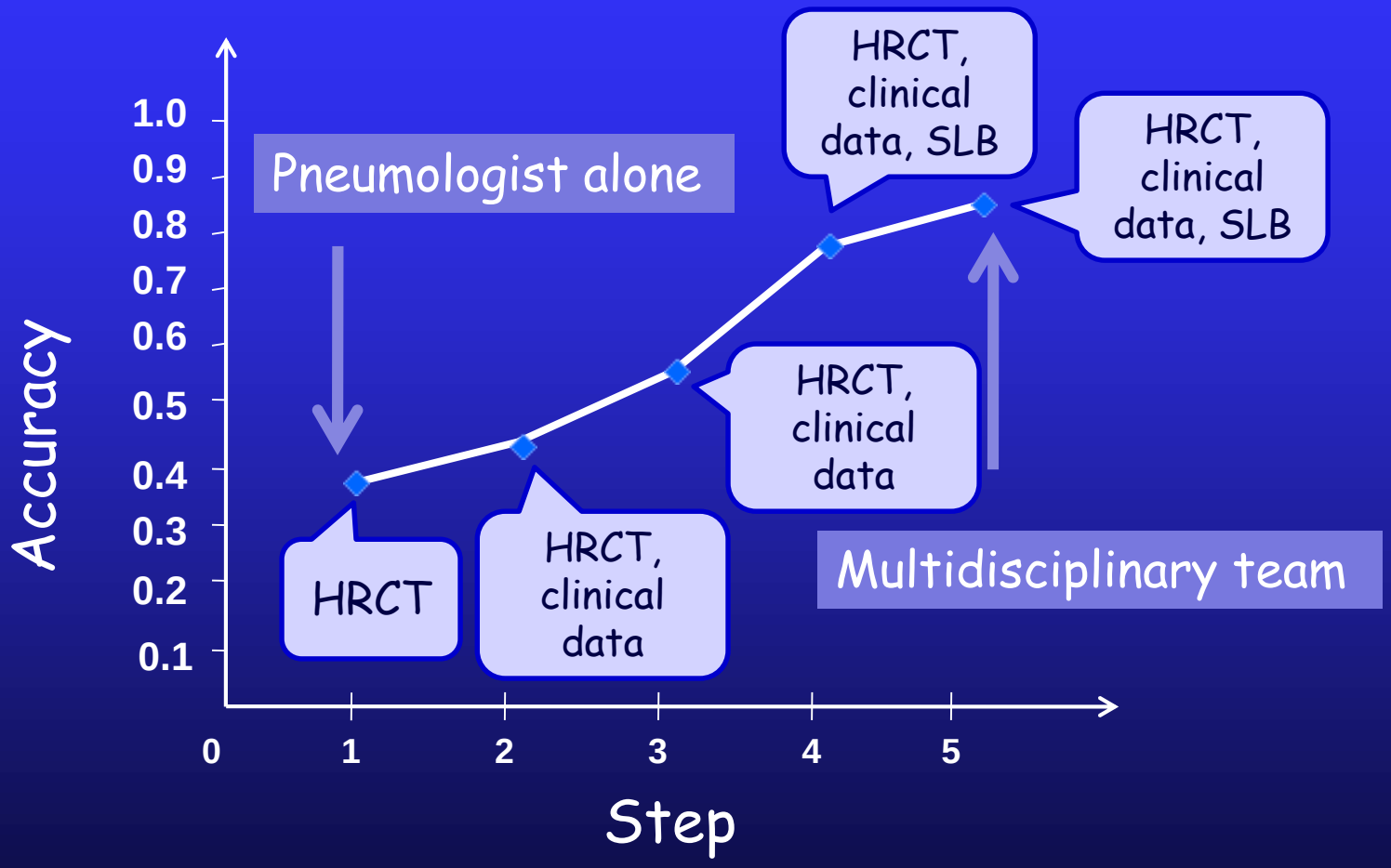
| *Clinical* | *Radiology* | *Pathology* |
|---|---|---|
| • History<br>• Physical<br>• Laboratory<br>• PFTs | • Chest X-ray<br>• HRCT | • Surgical lung biopsy |
| Primary care physicians | Pulmonologists | Radiologists | Pathologists |

Multidimensional and multidisciplinary

The gold-standard of IIP diagnosis

# Diagnosis is multidisciplinary

*Modified from: Flaherty et al. Am J Respir Crit Care Med 2004; 170:904*



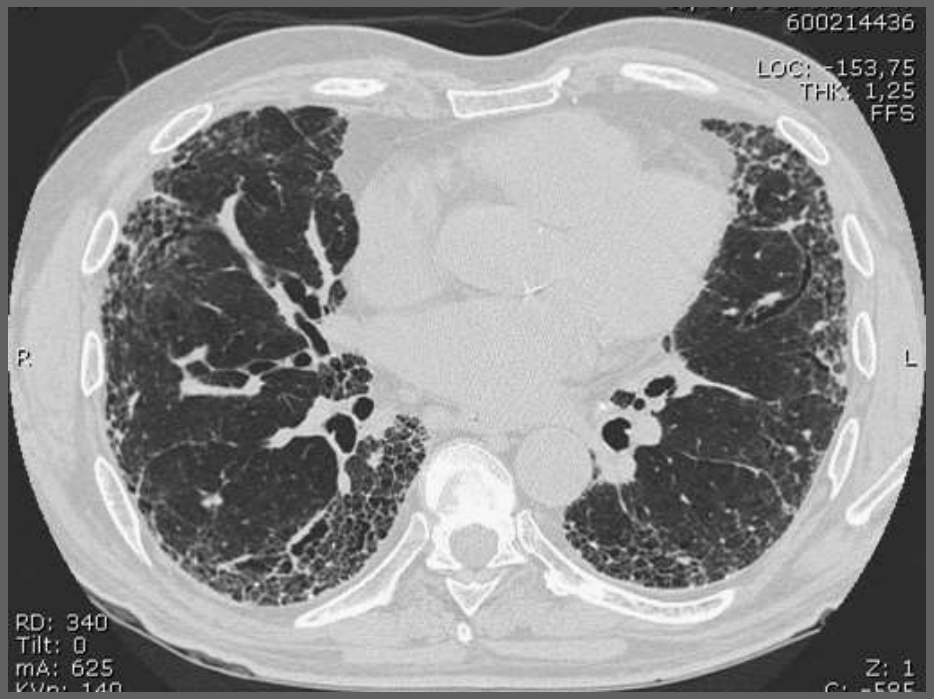

Requires pulmonologists, radiologists and pathologists working together

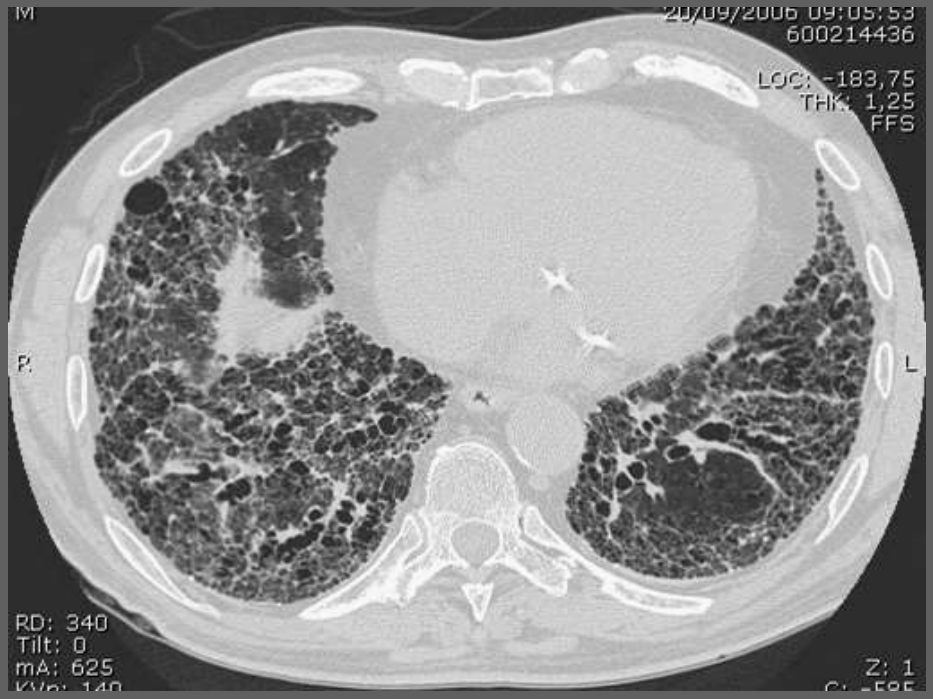
"The diagnosis of IPF *requires*:

a) exclusion of other known causes of interstitial lung disease

a) the presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy

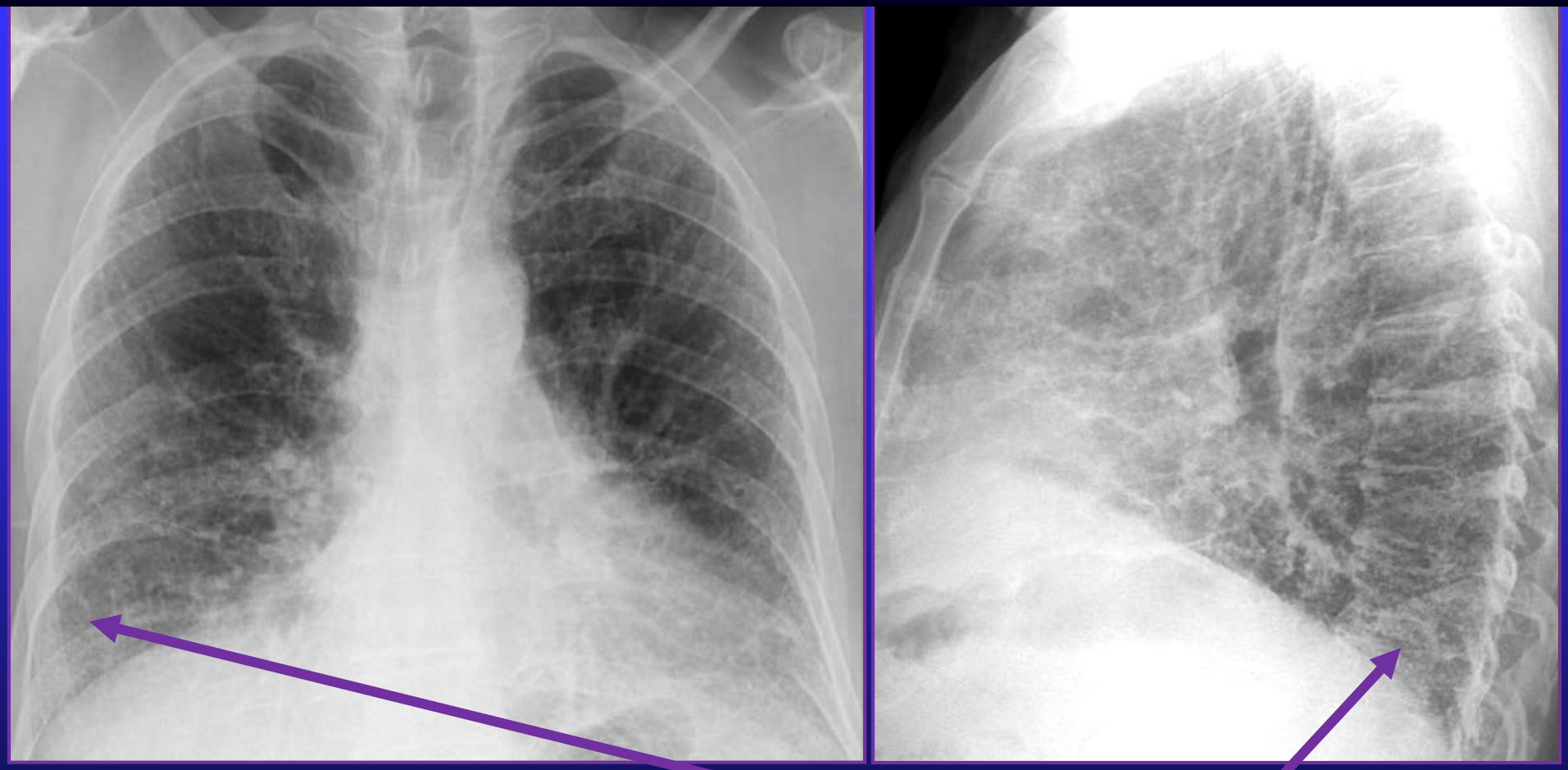
a) specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy"




***Am J Respir Crit Care Med* 2011; 183: 788-824**

# Chest radiograph in IPF




*A normal chest x-ray does not exclude IPF*

# Demystifying Idiopathic Interstitial Pneumonia

*Harold R. Collard, MD; Talmadge E. King, Jr, MD* *Arch Intern Med. 2003;163:17-29*

exercise $Pa_{O_2}$). The most useful clinical tool for distinguishing between subclasses is high-resolution computed tomography (HRCT) of the chest. The diagnostic utility of HRCT

*An **early** and **accurate** diagnosis of IPF is **critical**, particularly with the advent of novel specific treatments that may have the potential to reduce disease progression*

# *Interstitial lung abnormalities in a CT lung cancer screening population: prevalence and progression rate*

Lynch D et al. Radiology 2013; 268: 563

- In a population of current and former smokers with at least 30 p/y, 55-74 years of age fibrotic interstitial lung disease was present at systematic CT in ~ 2% of patients, 37% of whom had progressive fibrotic disease on 2-year follow-up CT
- Low dose CT scan appropriately detect subclinical fibrotic ILD likely corresponding to IPF at an early stage

# *Neglected evidence in idiopathic pulmonary fibrosis: from history to earlier diagnosis*

*Cordier JF, Cottin V Eur Respir J 2013*

The syndrome of combined pulmonary fibrosis and emphysema strikingly recapitulates the three major respiratory consequences of cigarette smoking, namely pulmonary fibrosis, emphysema, and lung cancer.

fibrosis, suggesting that the development of ILD may result from an interaction between age, smoking and genetic factors.

# *Neglected evidence in idiopathic pulmonary fibrosis: from history to earlier diagnosis*

*Cordier JF, Cottin V Eur Respir J 2013*

- IPF is a disease of ageing

In an apparent paradox, familial interstitial pneumonia predominantly occurs at a younger age as compared to non-familial IPF. Some clues as to why this may happen has arisen from the recent description of germline mutations in the genes *hTERT* and *hTR* associated to the telomerase complex

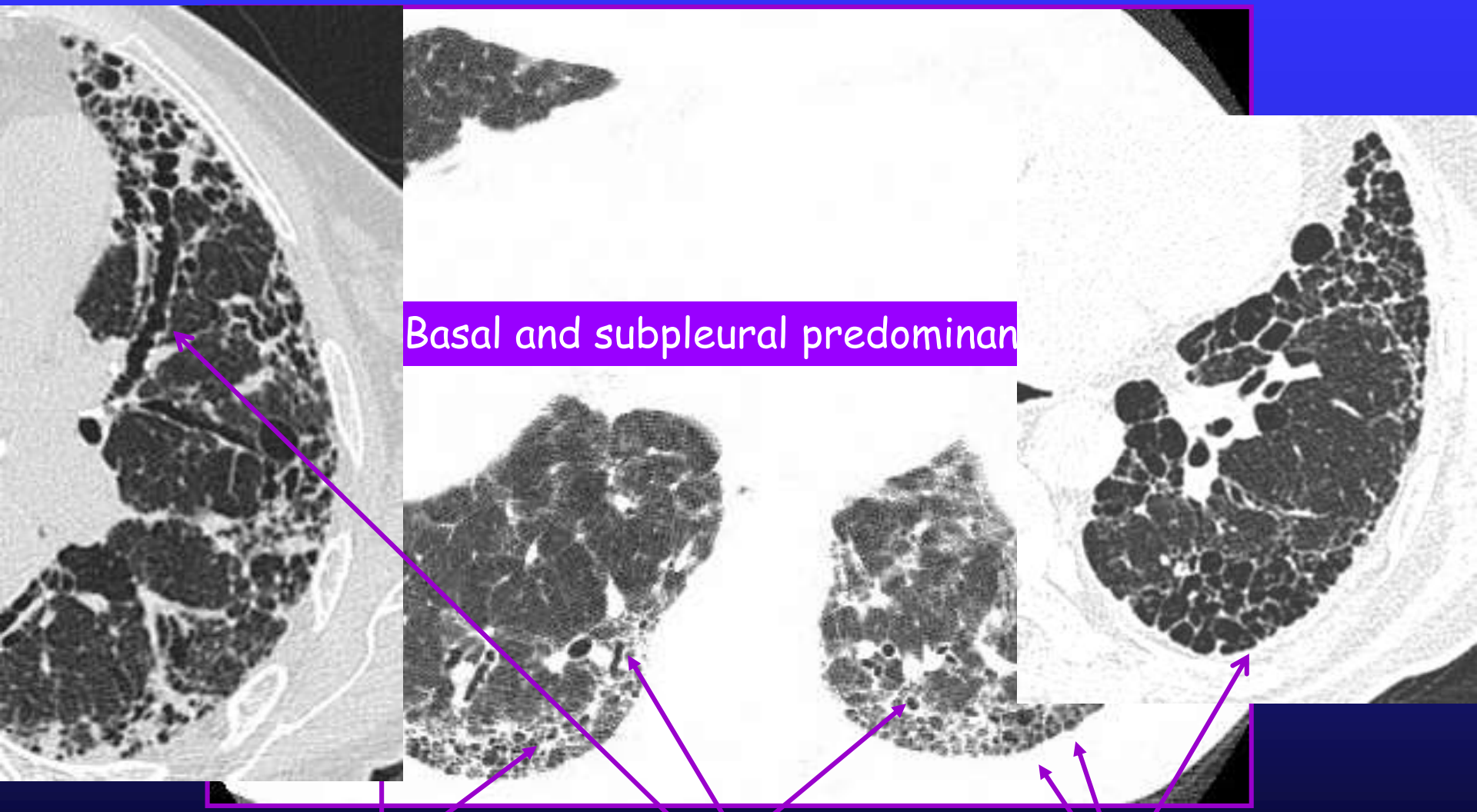
# *Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study*

*Morell et al. Lancet Respir Med 2013; 1: 684*

20 of the 46 (43%, 95% CI 29-58) patients with IPF according to 2011 guidelines had a subsequent diagnosis of chronic hypersensitivity pneumonitis

Almost half of patients diagnosed with IPF on the basis of 2011 criteria were subsequently diagnosed with chronic hypersensitivity pneumonitis, and most of these cases were attributed to exposure of occult avian antigens from commonly used feather bedding.

# Classic IPF HRCT



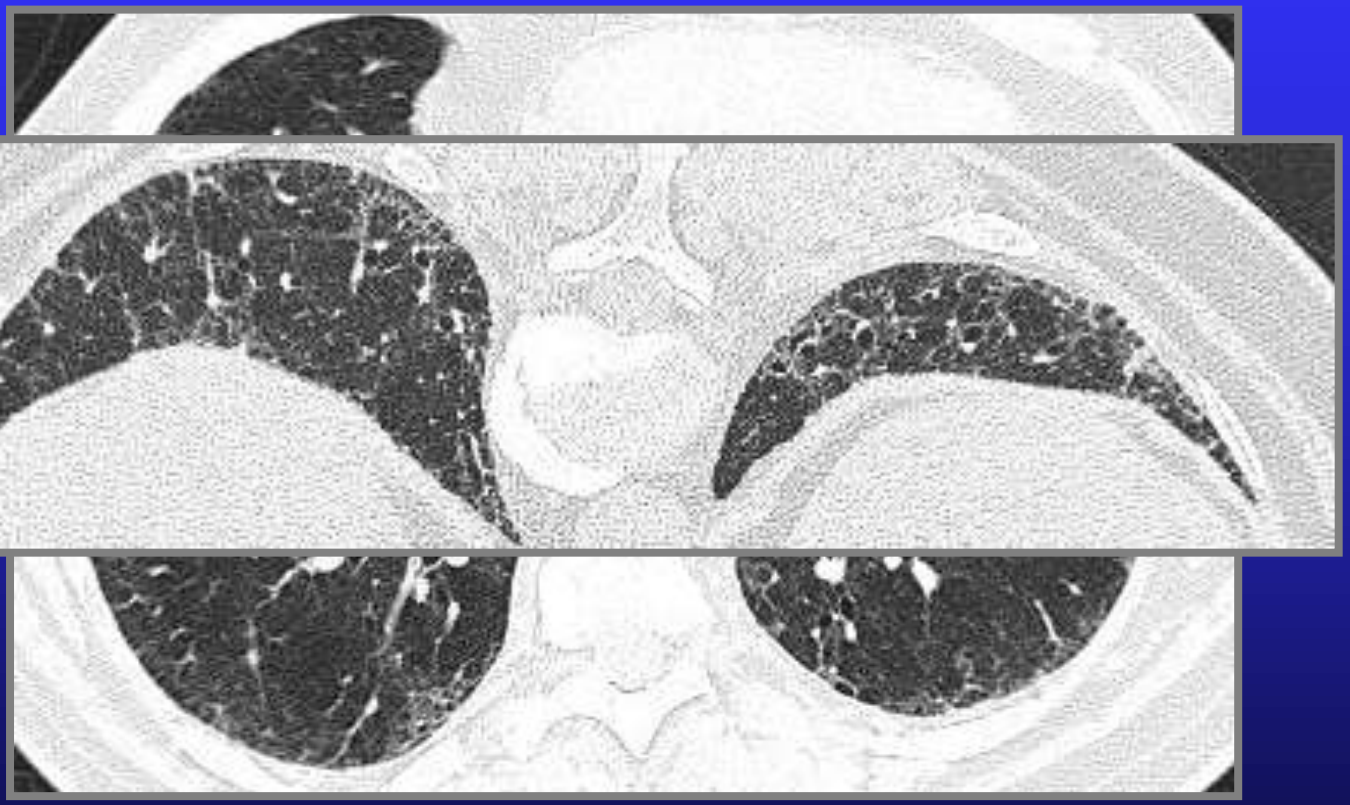
# HRCT diagnosis of IPF

| IPF Findings | Consider Alternate Diagnosis |
| --- | --- |
| *UIP pattern (all four):*<br>Sub-pleural, basal predominance<br>Reticular abnormality<br>Honeycombing with or without traction bronchiectasis<br>Absence of features listen as inconsistent with UIP | *Possible UIP pattern (all three):*<br>Subpleural, basal predominance<br>Reticular abnormality<br>Absence of features listen as inconsistent with UIP |

***Am J Respir Crit Care Med* 2011; 183: 788-824**

ATS/ERS. *Am J Respir Crit Care Med*. 2000;161:646-664.

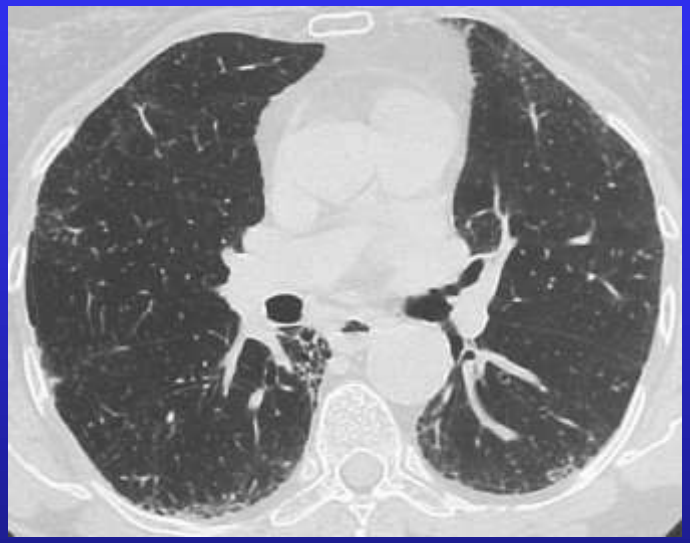
# Use of prone Imaging



# UIP: progression of fibrosis on CT

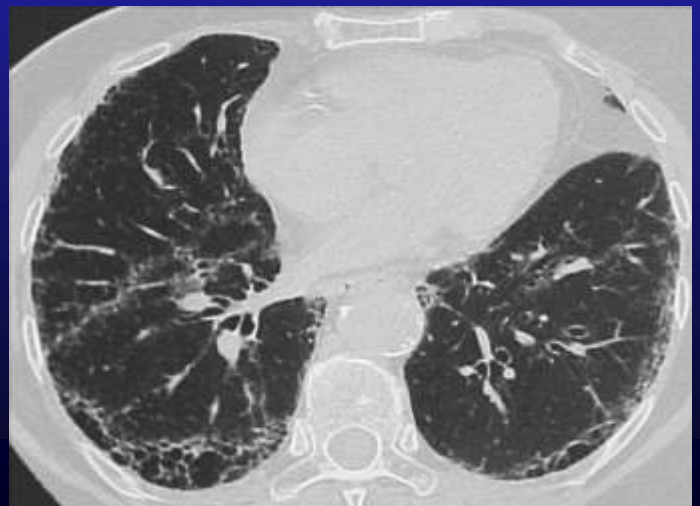
Early:

Reticular



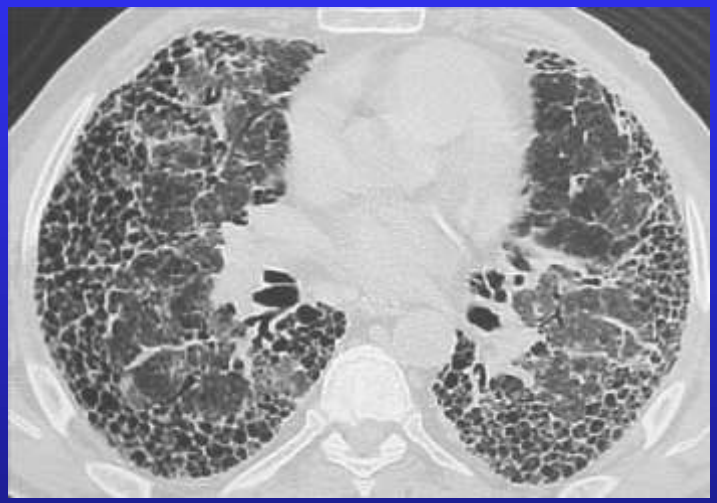
Midcourse:

Subpleural honeycombing



Late:

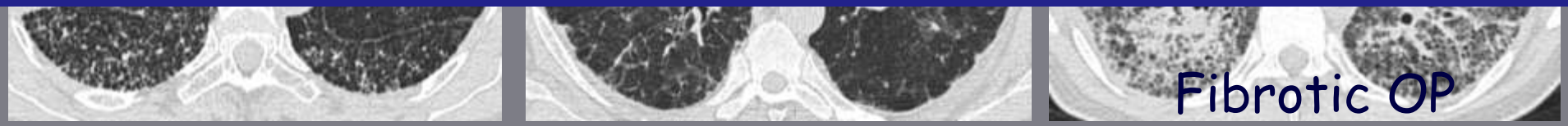
Diffuse honeycombing



## *Inconsistent with UIP pattern (any of the seven):*

- Upper or mid-lung predominance
- Peribronchovascular predominance
- Extensive groud 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)

***Am J Respir Crit Care Med* 2011; 183: 788-824**



# Key conclusion

- Typical HRCT features of IPF in association with a compatible clinical profile obviate surgical biopsy

**BUT**

*High-Resolution Computed Tomography and the Many Faces of Idiopathic Pulmonary Fibrosis*

# *The spectrum of atypical HRCT appearances in IPF*

- Exploration of biopsy-proven IPF (n=55)
- As expected, a high prevalence of atypical HRCT findings (n=34, 62%), as judged by three observers
- Alternative HRCT diagnoses analysed

**Sverzellati N et al. Radiology 2010; 254:957-64**

# *Atypical HRCT appearances in IPF*

- Alternative first choice diagnoses were NSIP (53%), chronic HP (12%), sarcoidosis (9%), “unclassifiable” (23%)

- Cases with atypical appearances had the same IPF-like outcome as those with typical HRCT appearances

**Sverzellati N et al. Radiology 2010; 254:957-64**

UIP pattern (all four):

- Evidence of marked fibrosis/architectura distortion ±honeycombing in a predominantly sub-pleural/paraseptal distribution
- Patchy involvement of lung parenchima
- Fibroblastic foci
- Absence of features against a diagnosis of UIP

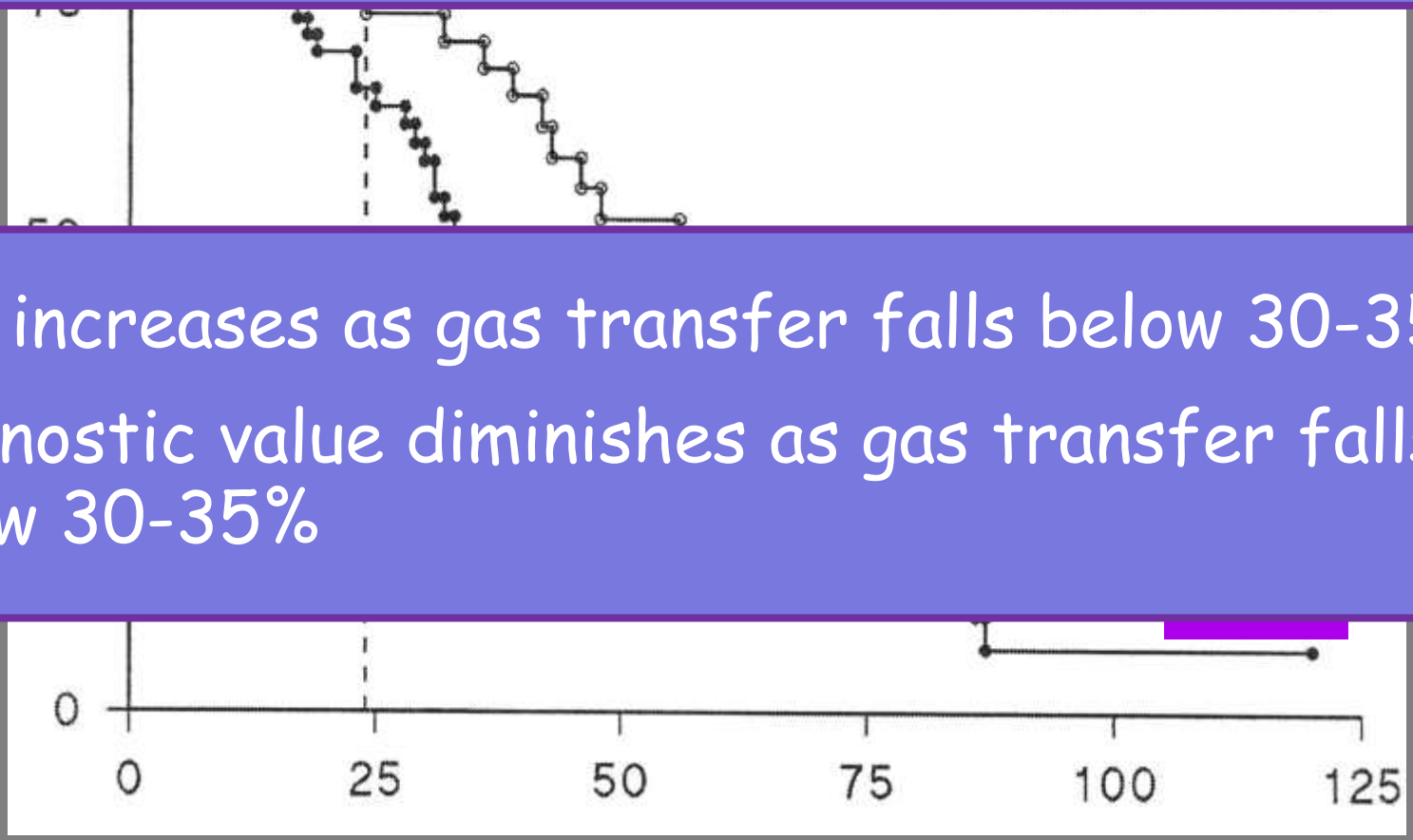
***Am J Respir Crit Care Med* 2011; 183: 788-824**

| Probable UIP pattern | Possible UIP pattern (All three criteria) | Not UIP pattern (any of the six criteria) |
|---|---|---|
| ❖Evidence of marked fibrosis/architectural distortion, ± honeycombing | ❖Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation | ❖ Hyaline membranes |
| | | ❖ Organizing pneumonia |
| ❖ Absence of either patchy involvement or fibroblastic foci, but not both | ❖Absence of other criteria for UIP | ❖ Granulomas |
| | | ❖ Marked interstitial inflammatory cell infiltrate away from honeycombing |
| ❖ Absence of features against a diagnosis of UIP suggesting an alternate diagnosis<br>OR | ❖Absence of features against a diagnosis of UIP suggesting an alternate diagnosis | ❖ Predominant airways centered changes |
| | | ❖ Other features suggestive of an alternate diagnosis |
| ❖ Honeycomb changes only | | |

# Risks of biopsy

- Morbidity increases with age
- Co-morbidity a major constraint
- In many patients, disease severity does not allow biopsy
- In severe disease, a biopsy sometimes less useful

Early mortality was associated solely with the severity of lung function impairment at presentation, but mortality after 2 years of follow-up was primarily linked to the histopathologic diagnosis




- Risk increases as gas transfer falls below 30-35%
- Prognostic value diminishes as gas transfer falls below 30-35%

Latsi PI et al. *Am J Respir Crit Care Med* 2003; 168: 531

# *Usefulness of BAL in diagnosis of IPF:*

## *Should BAL cellular analysis be performed in the diagnostic evaluation of suspected IPF?*

The most important application of BAL is in the exclusion of chonic HP; prominent lymphocitosis (>40%) should suggest the diagnosis

*Recommendation*: BAL 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)

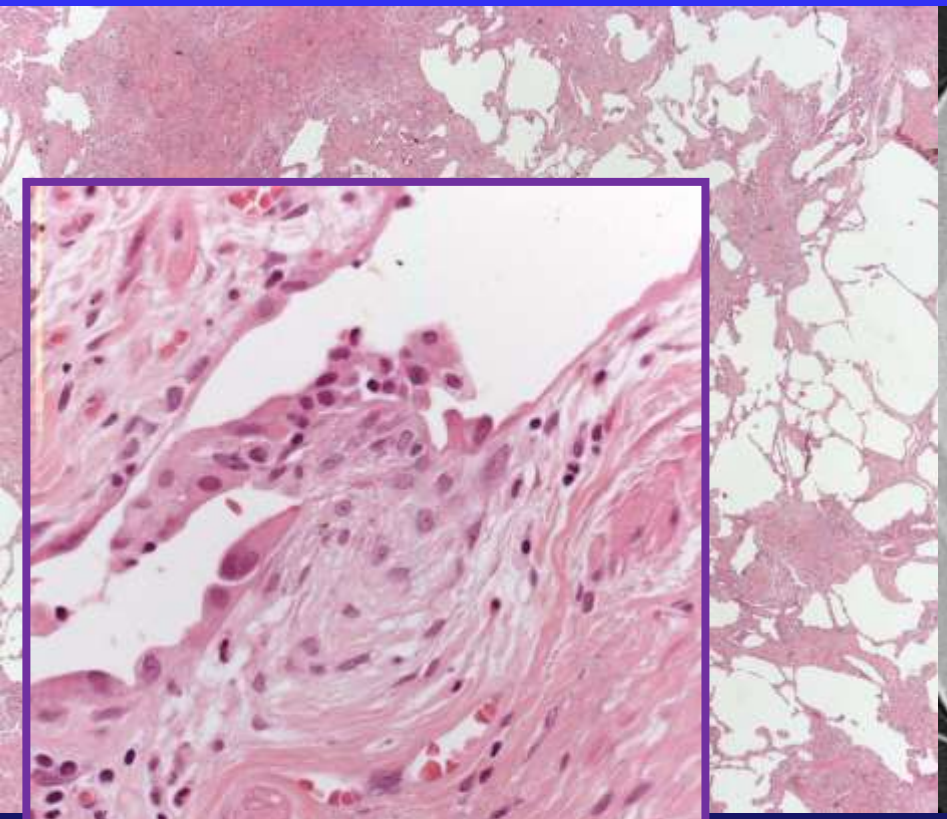
***Am J Respir Crit Care Med* 2011; 183: 788-824**

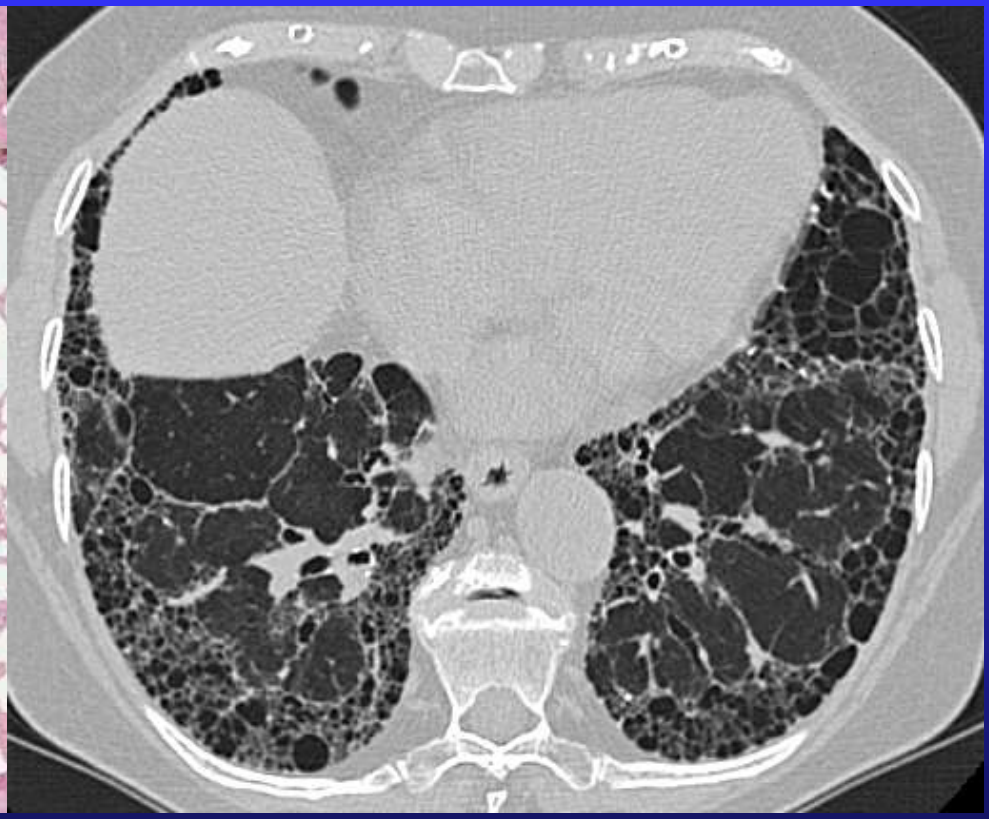
# *Should TBB be used in the evaluation of suspected IPF?*

In cases requiring histopathology, the specifity and positive predictive value of UIP pattern identified by TBB has not been rigorously studied. While TBB specimens may show all the histologic features of UIP, the sensitivity and specificity of this approach for the diagnosis for UIP pattern is unknown.

*Recommendation:* TBB should not be used in the evaluation of IPF in the majority of patients, but may be appropriate in a minority (weak recommendation, low-quality evidence)

# *Usual interstitial pneumonia*





scleroderma
RhA
DM/PM

# *Should serologic testing for connective tissues diseases be used in the evaluation of suspected IPF?*

- CTD can present with a UIP pattern
- ILD has been described as the sole clinical manifestation of these conditions
- ILD can precede the overt manifestation of a specific CTD

*Recommendation:* serologic testing for CTD should be performed in the evaluation of IPF in the majority of patients, but may be appropriate in a minority (weak recommendation, very low-quality evidence)

***Am J Respir Crit Care Med* 2011; 183: 788-824**

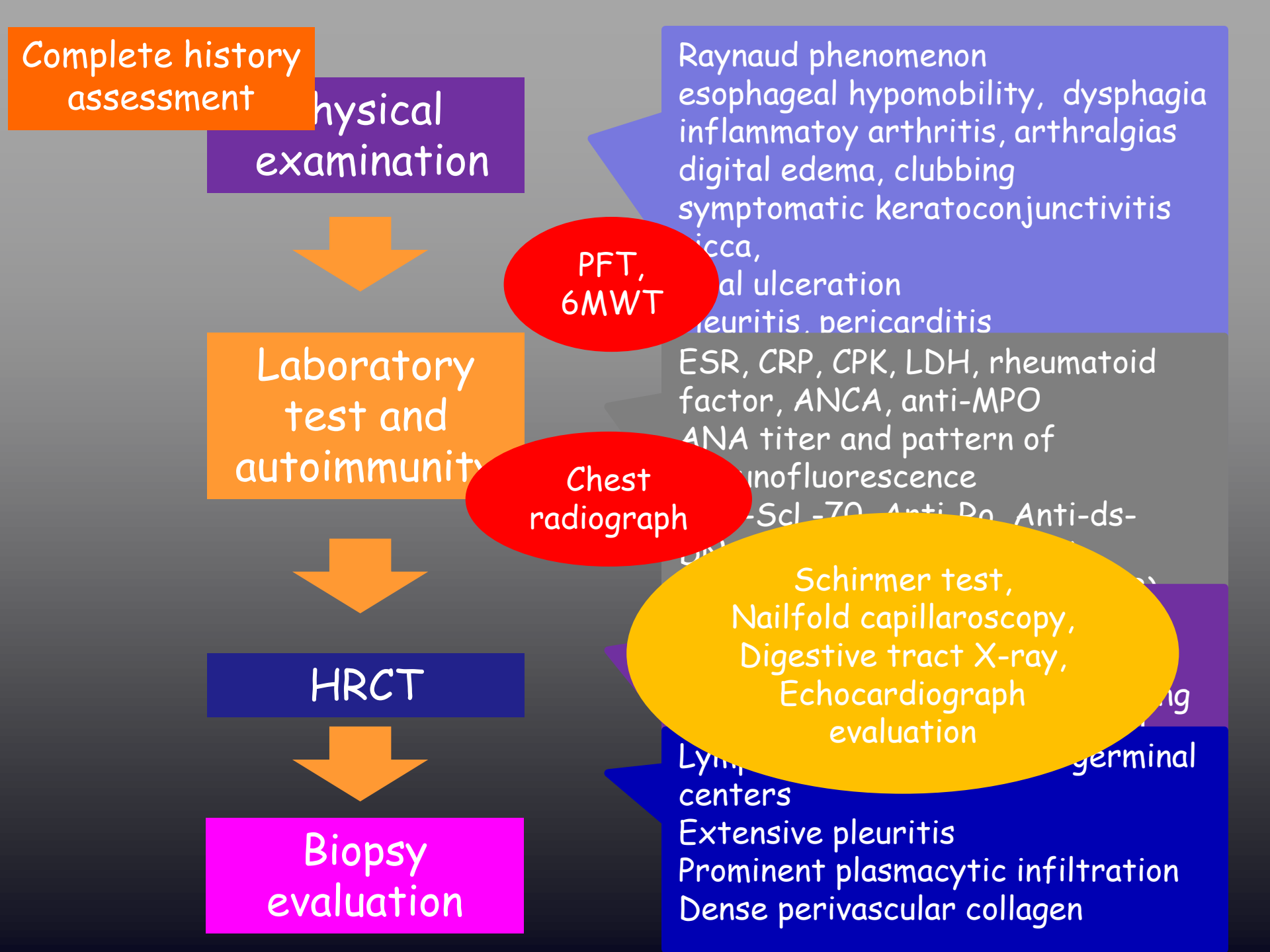
# *Serologic tests can help exclude other conditions*

**Connective tissue diseases**

- ESR
- ANA
- CCP (for RA)
- CK
- Aldolase
- Anti-myositis panel with Jo-1 antibody
- ENA panel
  - Scl-70
  - **Ro (SSA)**
  - **La (SSB)**
  - **Smith**
  - **RNP**

**Hypersensitivity pneumonitis**

- Hypersensitivity panel (if exposure history)

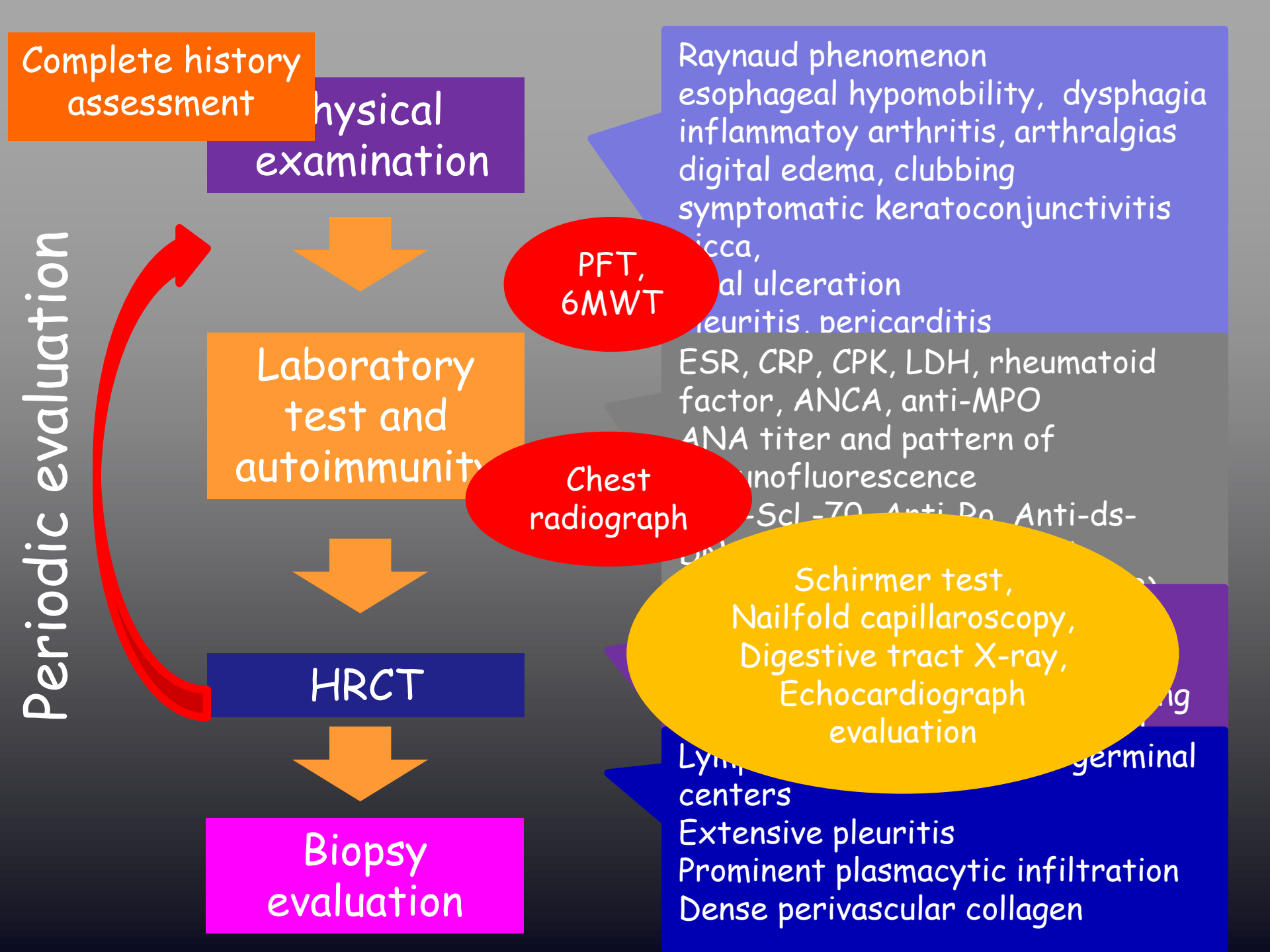

Complete history assessment
hysical examination
Laboratory test and autoimmunity
HRCT
Biopsy evaluation
PFT, 6MWT
Chest radiograph
Schirmer test, Nailfold capillaroscopy, Digestive tract X-ray, Echocardiograph evaluation
Raynaud phenomenon
esophageal hypomobility, dysphagia
inflammatoy arthritis, arthralgias
digital edema, clubbing
symptomatic keratoconjunctivitis
icca,
al ulceration
leuritis, pericarditis
ESR, CRP, CPK, LDH, rheumatoid factor, ANCA, anti-MPO
ANA titer and pattern of
nofluorescence
-Scl-70, Anti-Ro, Anti-ds-
ng
germinal centers
Extensive pleuritis
Prominent plasmacytic infiltration
Dense perivascular collagen

# *What's the problem?*

- It is not uncommon for pulmonologist to find patients with IP who are supposed to have a systemic autoimmune disease
- Within current classification schemes, many of these patients are labeled as idiopathic by default
- Despite the recognition that IP may be the *forme fruste* presentation of CTD, current classification criteria do not allow a CTD designation for ILD alone

# *Why is important to discover an occult CTD?*

- For disease prognosis
- For appropriate therapeutic approach
- For a search of additional system involvement or underlying malignancy
- For specific complications
- Is lung biopsy indicated?


Complete history assessment
hysical examination
Laboratory test and autoimmunity
HRCT
Biopsy evaluation
Periodic evaluation
PFT, 6MWT
Chest radiograph
Schirmer test, Nailfold capillaroscopy, Digestive tract X-ray, Echocardiograph evaluation
Raynaud phenomenon
esophageal hypomobility, dysphagia
inflammatoy arthritis, arthralgias
digital edema, clubbing
symptomatic keratoconjunctivitis
icca,
al ulceration
leuritis, pericarditis
ESR, CRP, CPK, LDH, rheumatoid factor, ANCA, anti-MPO
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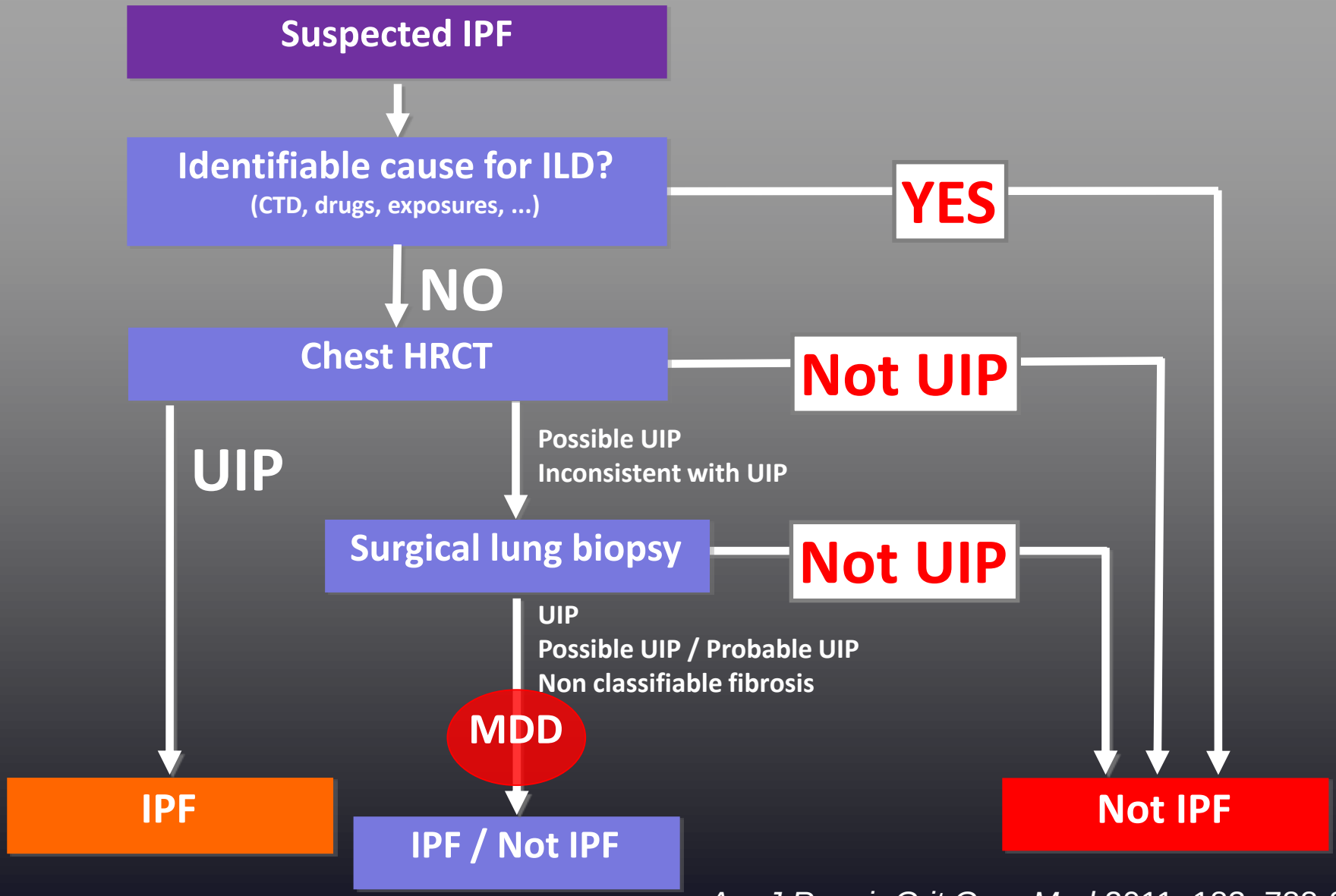
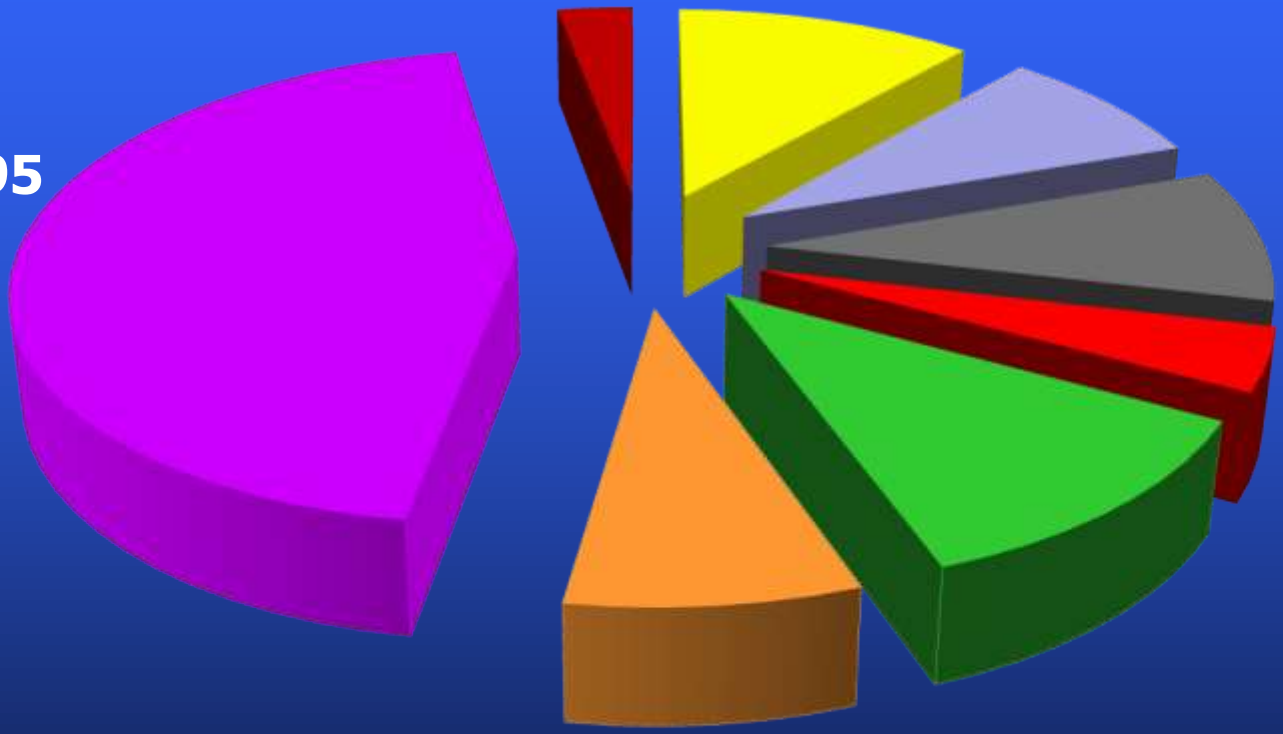
germinal centers
Extensive pleuritis
Prominent plasmacytic infiltration
Dense perivascular collagen

# Diagnostic algorithm for IPF




*Am J Respir Crit Care Med* 2011; 183: 788-824

# Ospedale San Giuseppe
# Rare lung diseases (2001-2014)
# Tot 1076 pts



# *Should a multi-disciplinary discussion be used in the evaluation of suspected IPF?*

The diagnosis of IPF is, by definition, multidisciplinary. Proper communication between the various disciplines involved in the diagnosis of IPF (pulmonary, radiology, pathology) has been shown to improve inter-observer agreement among experienced clinical experts as to the ultimate diagnosis

*Recommendation: we recommend that a multi-disciplinary discussion should be used in the evaluation of IPF (strong recommendation, low-quality evidence)*

*Timely referral to ILD experts is encouraged*

**Am J Respir Crit Care Med 2011; 183: 788-824**

# Conclusions

- The early recognition of IPF starts with a high level of clinical suspicion
- The approach to the diagnosis of IPF requires a multi-disciplinary effort (pulmonologist, radiologist, and pathologist)
- Differentiating IPF from other ILDs can direct the management and predict the prognosis of these patients

# Conclusions

- In some patients, lung involvement precedes other systemic manifestations, making the distinction between IIP and lung involvement of CTD impossible
- An association of IIP with CTD should be vigorously searched, not only at time of diagnosis but also during follow-up

# Conclusions

- It is important to look for additional minor/minimal abnormalities (clinical, radiological, histological) that may help in diagnosis of occult CTD or chronic HP
- IPF can be diagnosed on HRCT in the majority of cases but a crucial sub-group have very atypical HRCT appearances
- Perform an accurate diagnosis of ILD and IPF is very difficult and complex!