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Idiopathic Pulmonary Fibrosis
Treatable and Not Idiopathic

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CTS 1/26/18

Disclosures

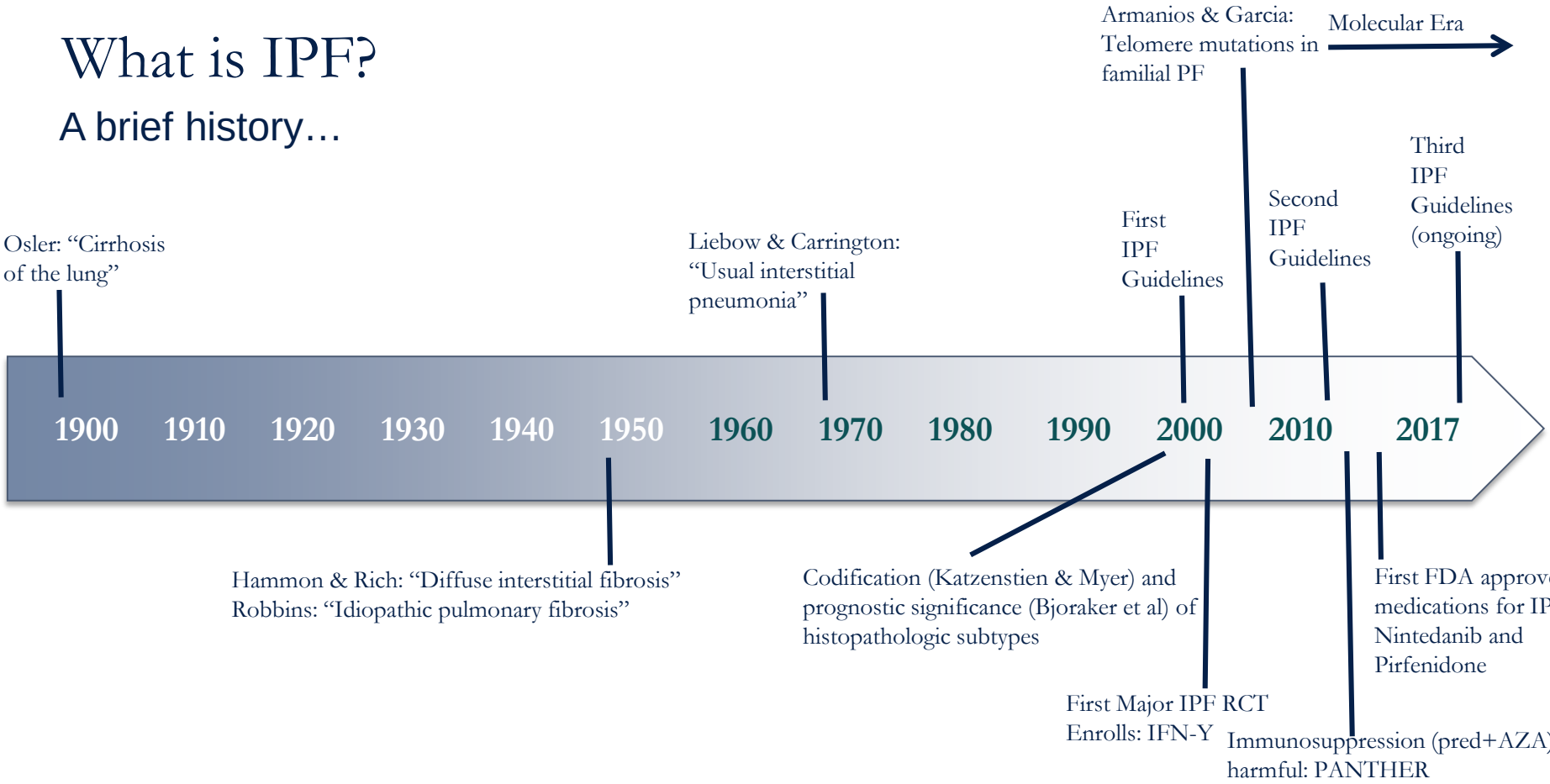
Speaker’s bureau honorarium from Genentech (makers of pirfenidone) in 2015.

Outline

- What is IPF?
- When should you suspect IPF?
- How is IPF diagnosed?
- How is IPF treated?
- What the future holds for IPF?

What is IPF?

A brief history…



Diffuse Parenchymal (Interstitial) Lung Disease

Idiopathic Interstitial Pneumonias

Major IIPs

- **Idiopathic Pulmonary Fibrosis**
- Nonspecific Interstitial Pneumonia
- Respiratory bronchiolitis ILD
- Desquamative Interstitial Pneumonia
- Cryptogenic organizing pneumonia
- Acute interstitial pneumonia

Rare IIPs:

- Lymphoid interstitial pneumonia
- Pleuroparenchymal fibroelastosis

Granulomatous Diseases

Sarcoidosis

Exposure-Related

Environmental/Occupational

- Hypersensitivity Pneumonitis
- Pneumoconioses (silicosis, asbestosis, coal)

Drug/radiation-induced

- Nitrofurantoin
- Amiodarone
- Chemotherapy
- Radiation

Smoking-related

- Desquamative interstitial pneumonia
- Respiratory bronchiolitis
- Langerhans cell histiocytosis

Connective Tissue Disease

- Systemic sclerosis
- Rheumatoid arthritis
- Myositis
- Sjogrens syndrome
- Mixed connective tissue disease
- Systemic lupus erythematosis

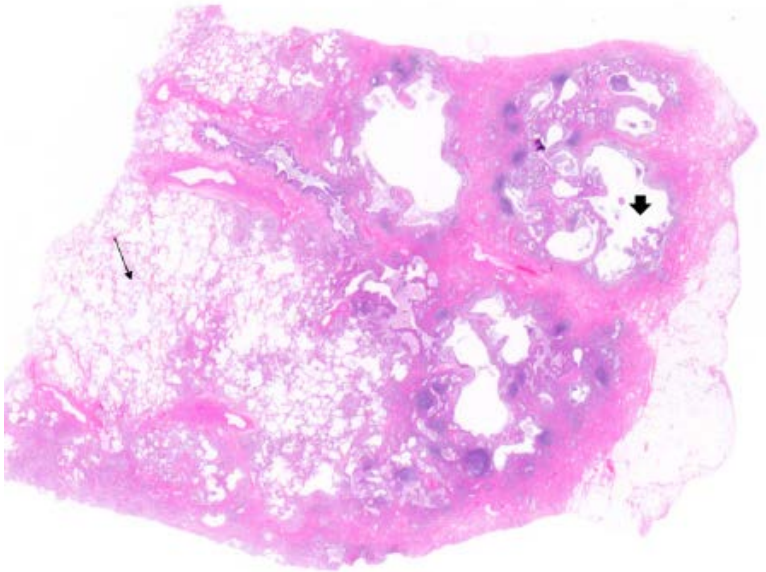
Undifferentiated connective tissue disease/Interstitial pneumonia with autoimmune features

Other/Rare

Pulmonary alveolar proteinosis
Eosinophilic pneumonia (acute and chronic)
Lymphangioleiomyomatosis
Amyloidosis
Etc.

What is IPF?

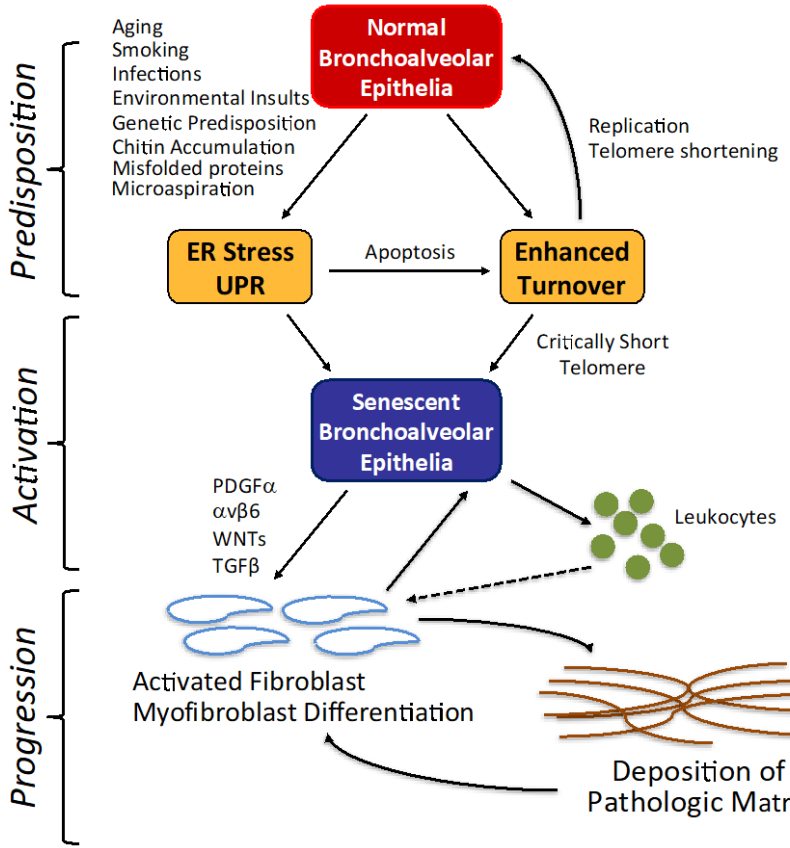
IPF is a specific from chronic **progressive fibrotic interstitial lung disease** that occurs in **older adults** and is characterized by **usual interstitial pneumonia** histopathology in the **absence of a secondary cause**.



Source: AJRCCM 2011;183:786

What is IPF?

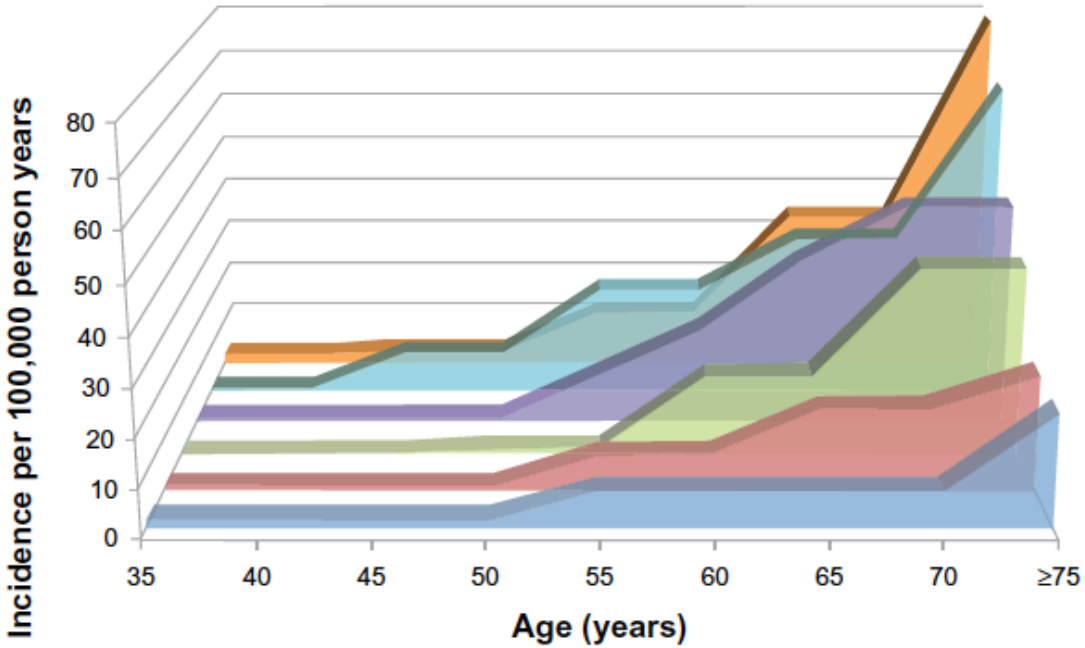
- Aging related
- Multiple insults/injuries along with genetic predisposition (short telomeres)
- Alveolar cell senescence
- Activation of profibrotic pathways and tissue remodeling
- Stiff lung results in positive (fibrotic) feedback loop



Source: Courtesy of Paul Wolters

What is IPF?

- Incidence = 3-9 per 100,000 person-years
- Incidence increases with age



Source: Clin Epidemiol 2013;5:483

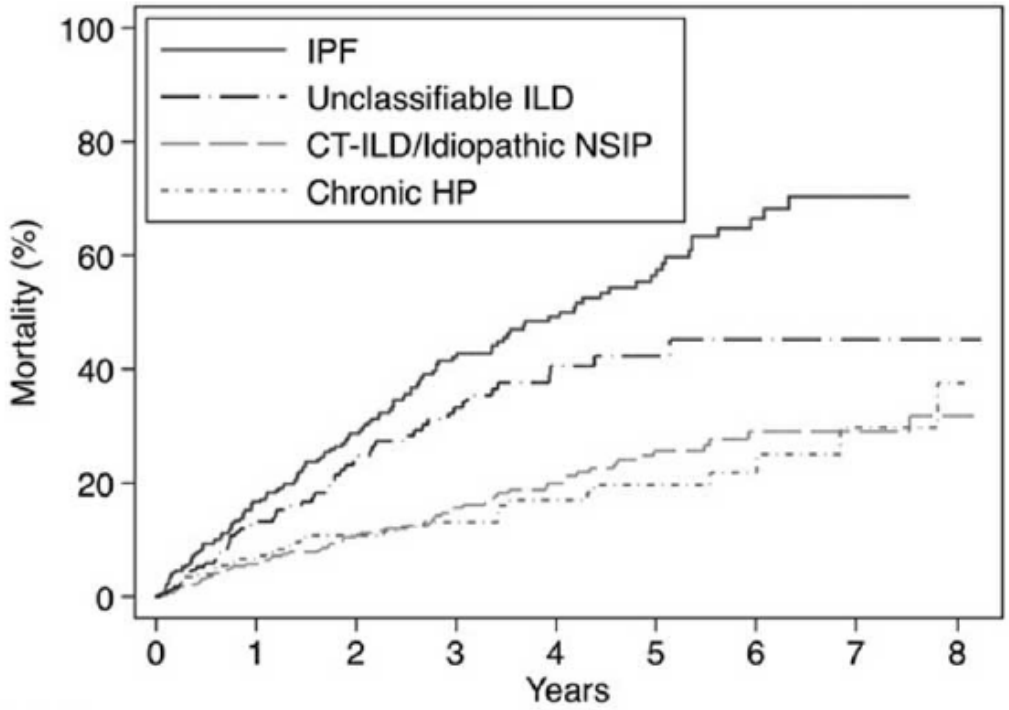
When to suspect IPF?

Clinical Scenario	• **Age > 50 with unexplained chronic cough or dyspnea** • **Family history of ILD**
Physical Exam	• **Persistent bilateral inspiratory crackles (must listen at bases)** • **Clubbing**
Pulmonary Function	• **Restriction + low diffusing capacity** • **Isolated low diffusing capacity** • **Spirometry only: parallel reduction in FVC and FEV1**
Radiology	• **CXR shows bilateral, basilar predominant interstitial opacities** • **Incidental signs of reticulation on CT**

Why is diagnosis important?

<u>Informs Prognosis</u>

- Median survival ~4 years
- Acute exacerbation rate 5-10% per year

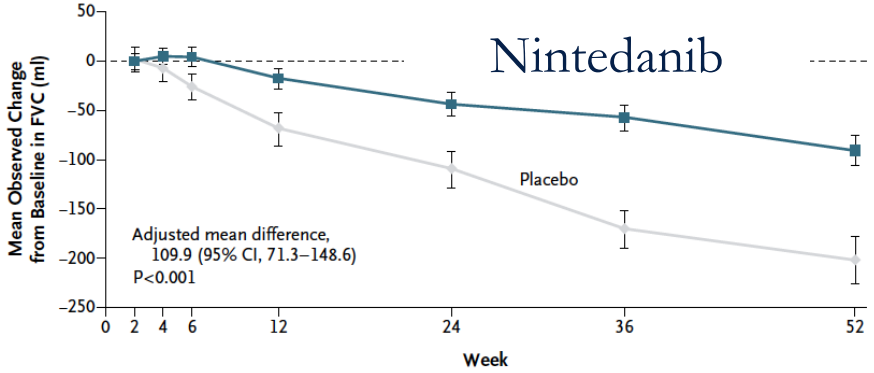


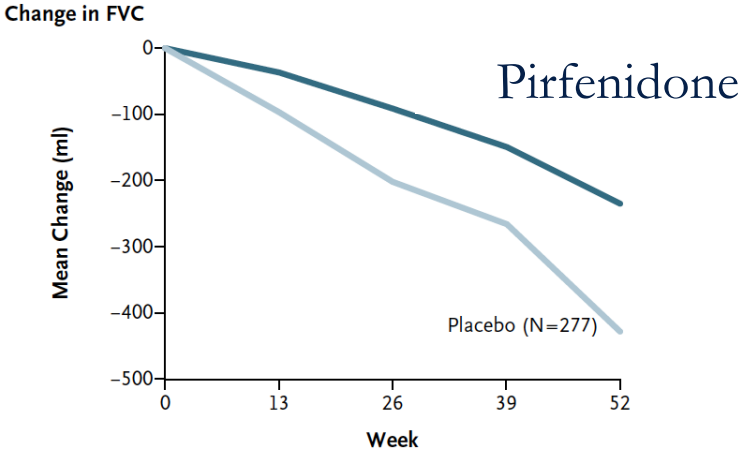
Chest 2014;145(4):723

Why is diagnosis important?

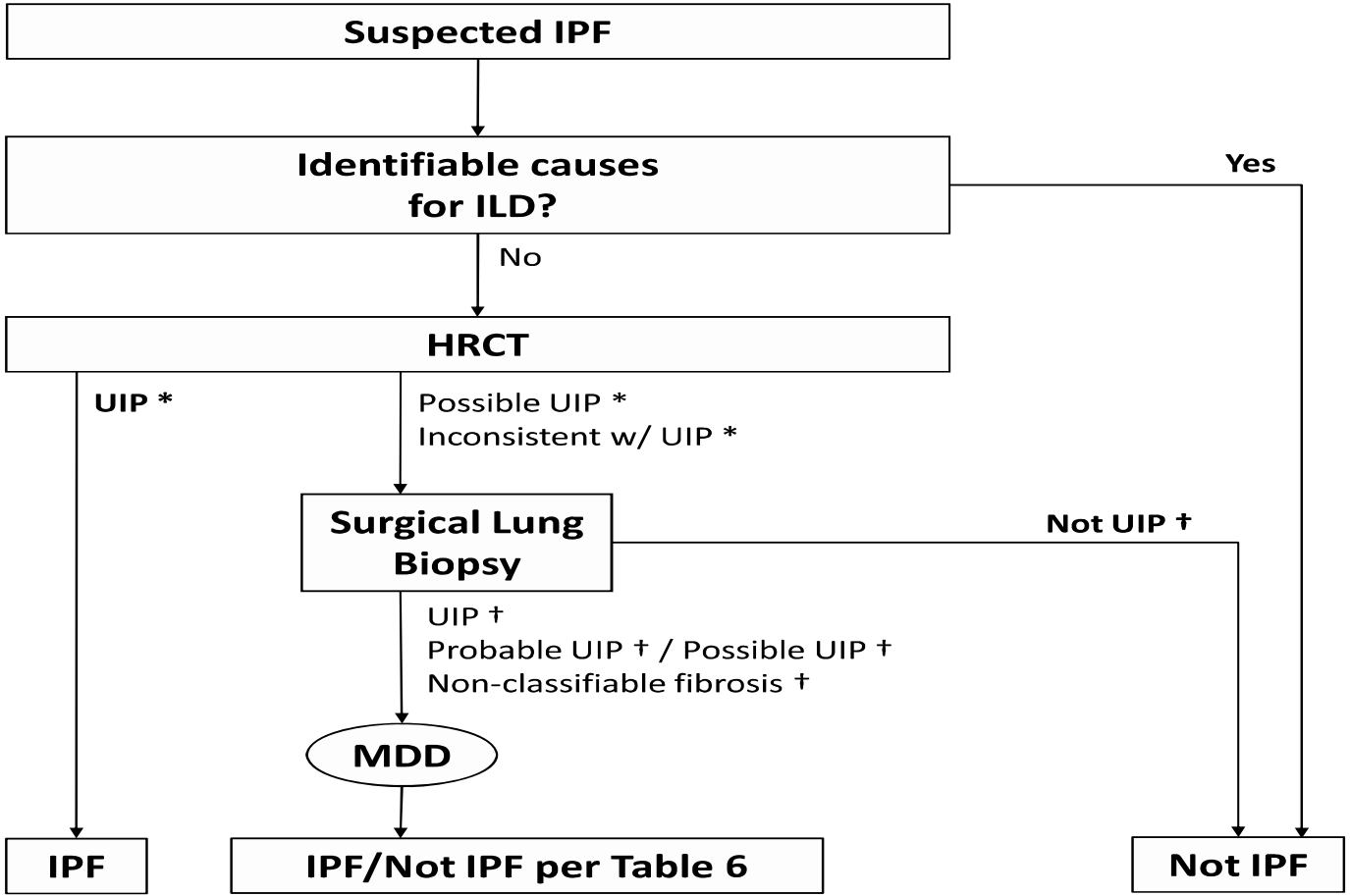
Informs Treatment

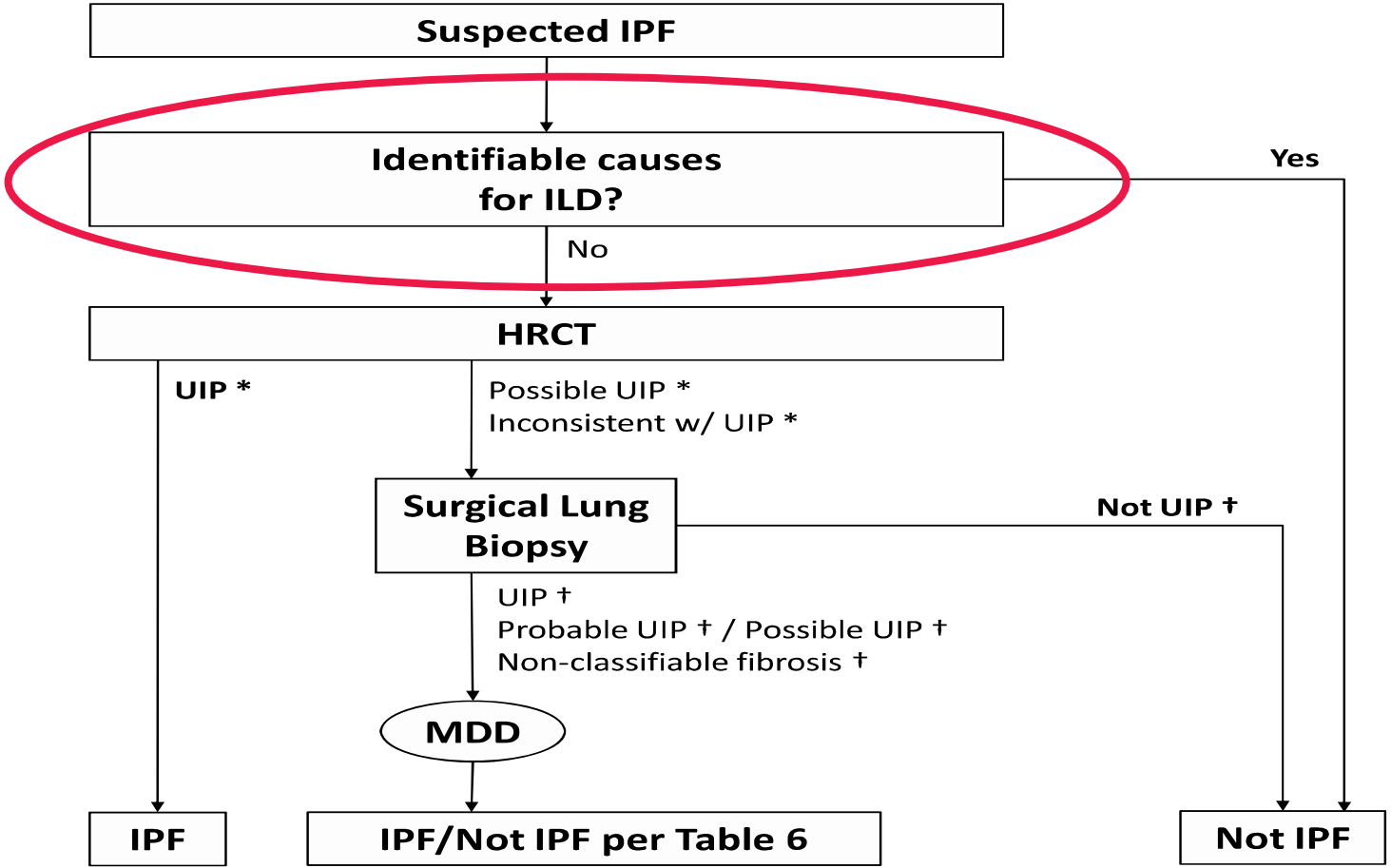
- IPF
  - Nintedanib
  - Pirfenidone
- Other fibrotic ILDs
  - immunosuppression





NEJM 2014;370:2083 & NEJM 2014;370:2071

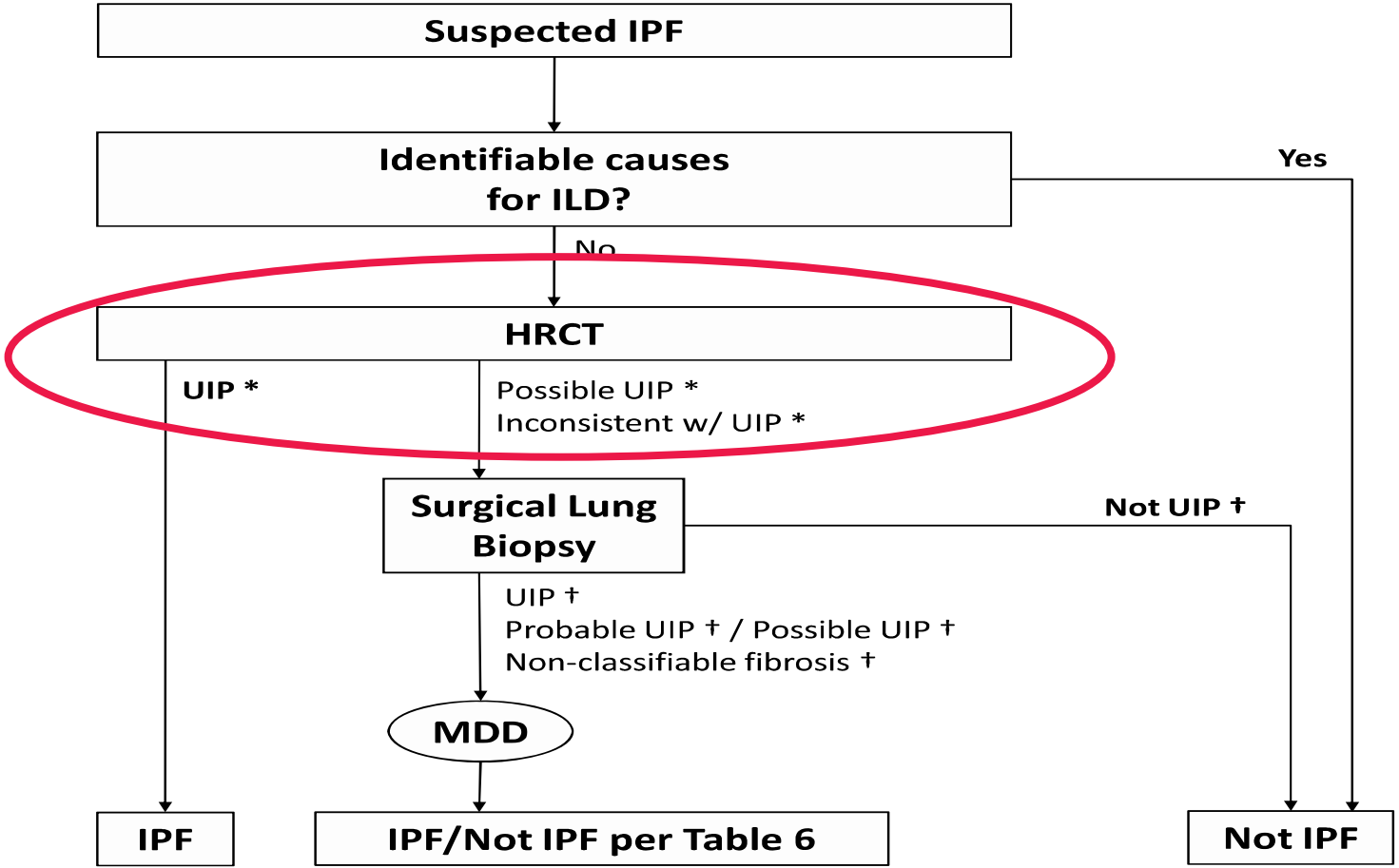

Suspected IPF
Identifiable causes for ILD?
Yes
No
HRCT
UIP *
Possible UIP *
Inconsistent w/ UIP *
Surgical Lung Biopsy
Not UIP †
UIP †
Probable UIP † / Possible UIP †
Non-classifiable fibrosis †
MDD
IPF
IPF/Not IPF per Table 6
Not IPF



IPF Guidelines: Am J Respir Crit Care Med 2011;183:788

Evaluate for Alternative Causes

- Compatible demographics?
  - Age > 50, more common in men
- Evidence of autoimmune disease?
  - Symptoms, physical exam, serologies
- Relevant environmental or occupational exposure?
  - HP exposures (avian, molds), asbestos
- Relevant medication exposure? E.g. nitrofurantoin
- Family history of ILD, personal or family history suggestive of telomere dysfunction?



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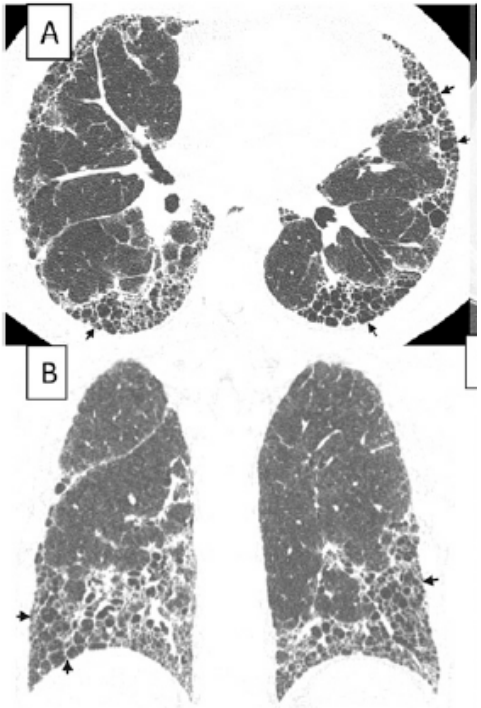
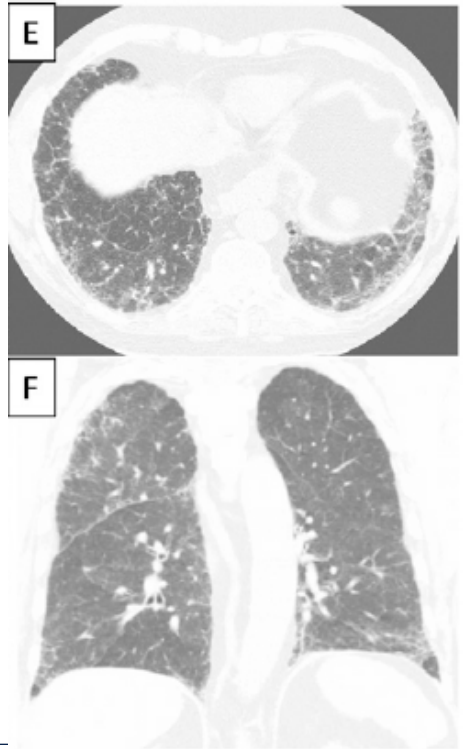
Radiologist's Role

Definite UIP



Possible UIP



Inconsistent with UIP

- No fibrotic features
- Fibrotic features plus:

1. Diffuse ground glass
2. Diffuse nodules
3. Consolidations
4. Upper-mid lung distribution
5. Peribronchovascular distribution
6. Air-trapping/mosaic perfusion
7. Discrete cysts

IPF Guidelines: Am J Respir Crit Care Med 2011;183:788

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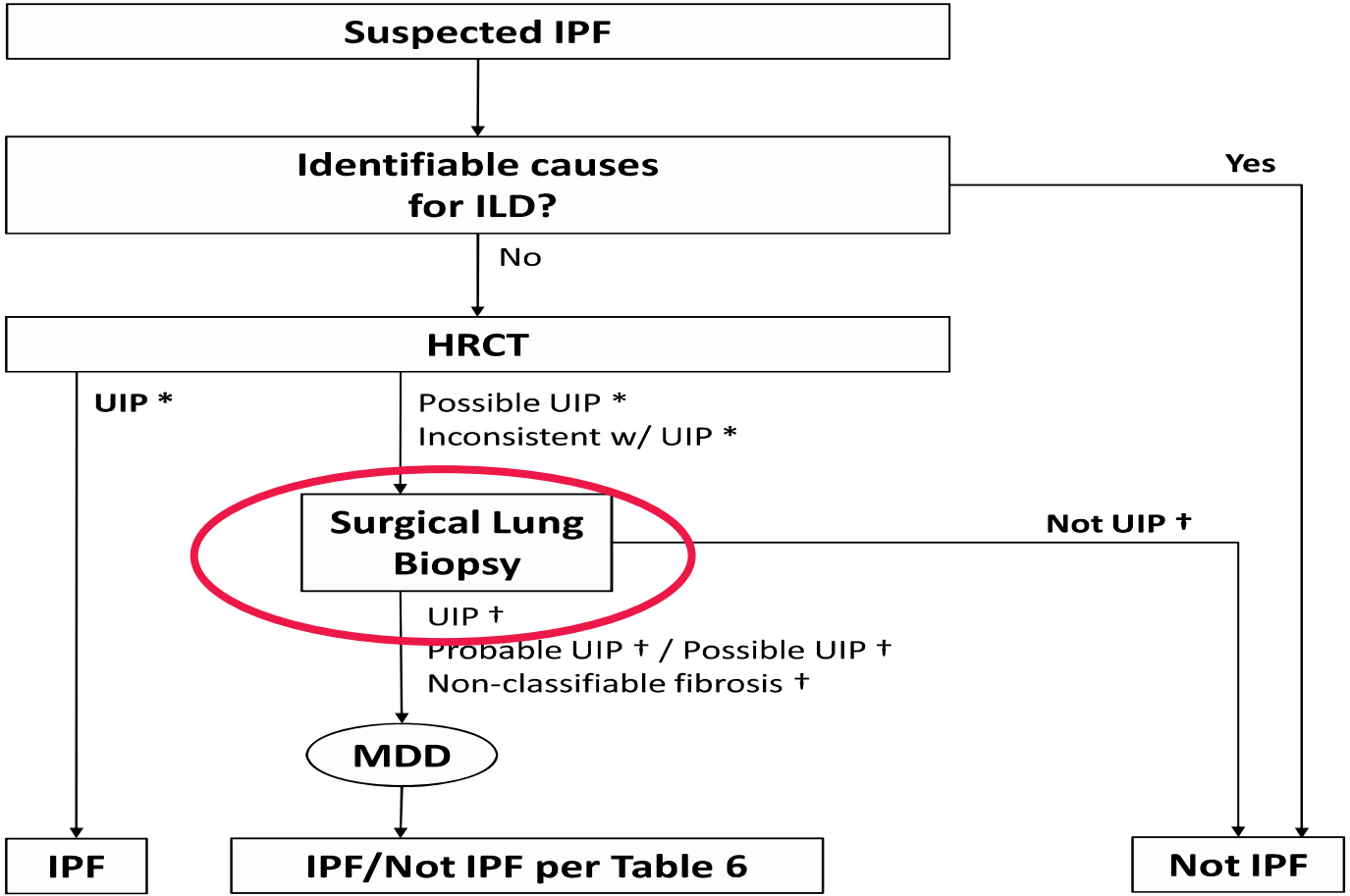
Can we expand group not needing biopsy?

	Possible UIP		Possible UIP + Age ≥60, male, & traction score ≥ 4	
	UCSF	Mayo	UCSF	Mayo
Specificity	91.2	92.7	99.6	98.2
Sensitivity	35.4	60.4	16.8	32.4
PPV	62.5	94.4	95.0	97.3
NPV	77.3	53.7	74.2	41.9
LR+	4.0	8.3	45.7	17.8

Can we expand group not needing biopsy?

	Pathologic UIP, %	
	UCSF	Mayo
Inconsistent with UIP Pattern	22.7	46.3

Thorax 2017;72:424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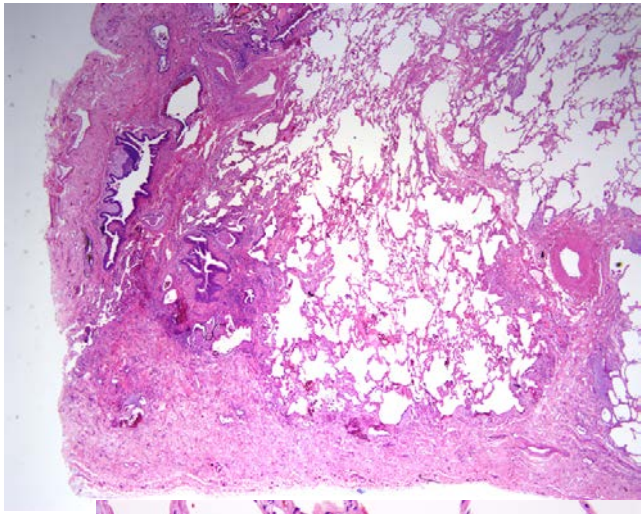
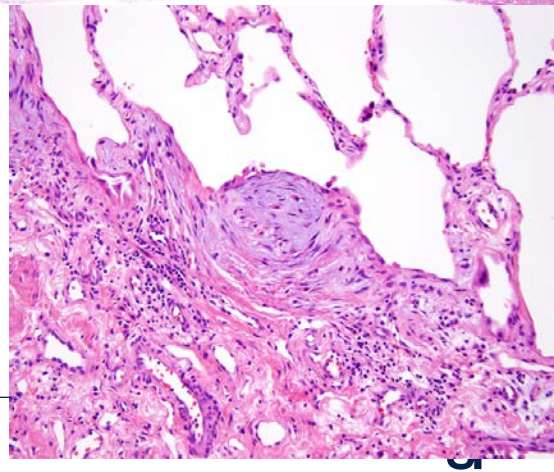
Surgical Lung Biopsy



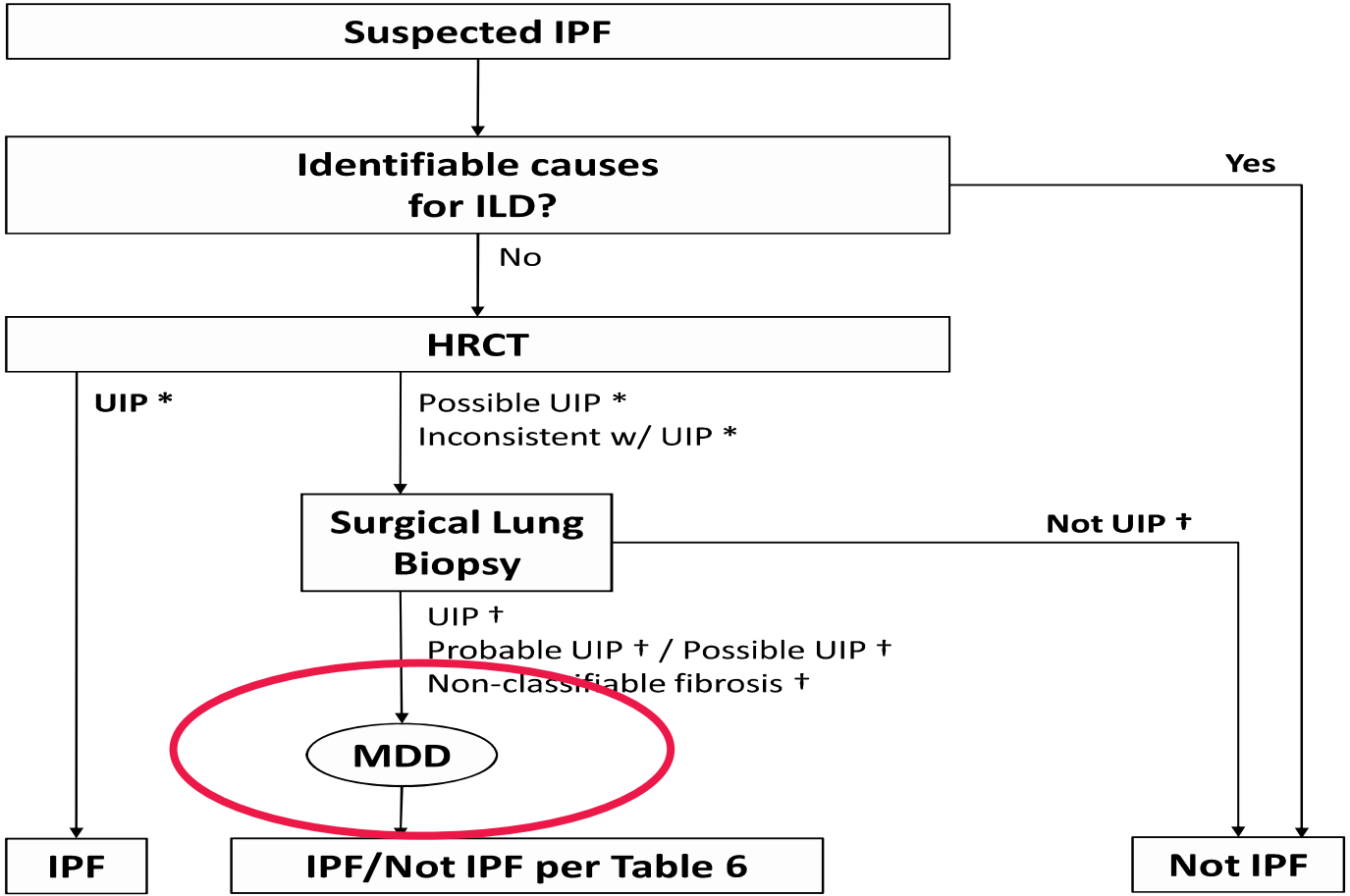


Am J Respir Crit Care Med 2016;193(10):1161

Surgical Lung Biopsy

Communicate with surgeon and anesthesiologist to optimize safety and yield!

- Surgeon
  - At least 2 lobes
  - Avoid areas of end-stage fibrosis
  - Biopsy depth at least 2 cm deep, from pleural surface
- Anesthesiologist
  - Low Tidal Volume, Lung Protective Ventilation
  - Minimize FiO2
  - Minimize peri-operative fluids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Multidisciplinary Discussion

HRCT Pattern \ Pathologic Pattern	Not performed	UIP	Probable UIP	Possible UIP	Not UIP
UIP	IPF	IPF	IPF	IPF	Not IPF
Possible UIP	Unknown	IPF	IPF	Some are IPF, some are not	Not IPF
Inconsist-ent with UIP	Unknown	Some are IPF, some are not	Not IPF	Not IPF	Not IPF

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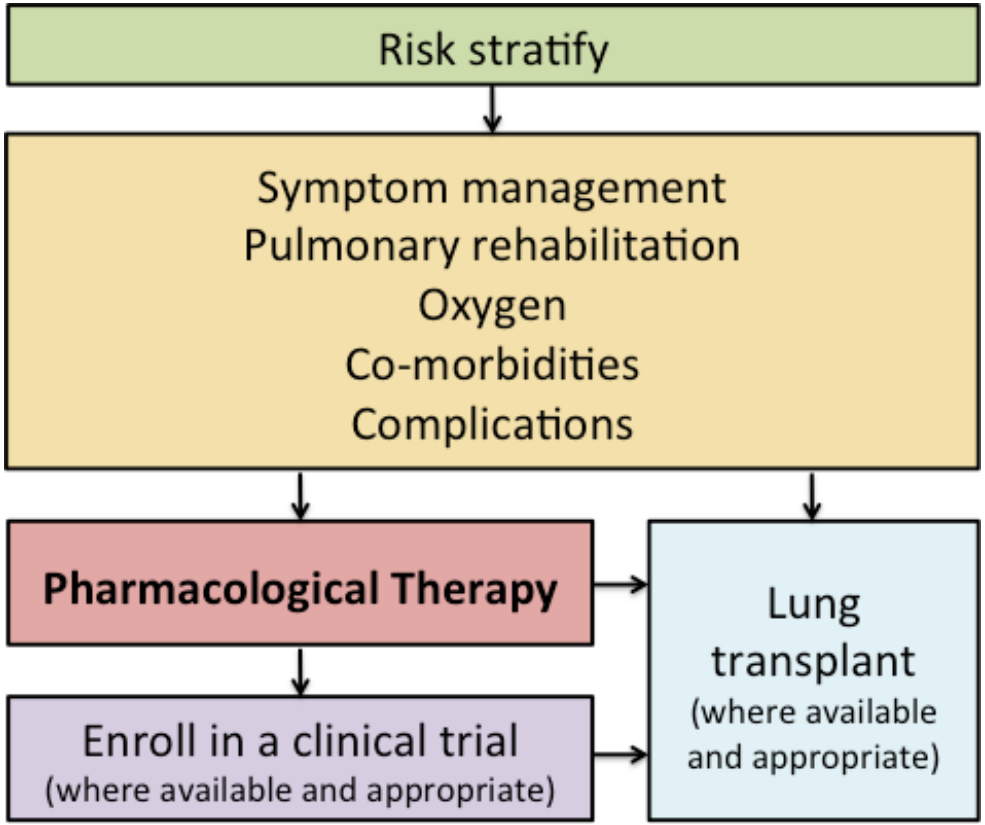
Other Diagnostic Tests

- **Bronchoscopy** – limited value in work up of fibrotic ILD
  - High BAL lymphocyte percentage (e.g. > 40%) may suggest other diagnosis such as chronic hypersensitivity pneumonitis or autoimmune disease
  - Forceps transbronchial biopsy very low yield (not worth risk in my opinion)
  - Transbronchial cryobiopsy potentially emerging role but head-to-head data with surgical lung biopsy needed (technique varies widely and essential to yield and safety)
- **Autoimmune serologies** – case dependent (minimum ANA, RF, CCP, CK)

How is IPF treated?

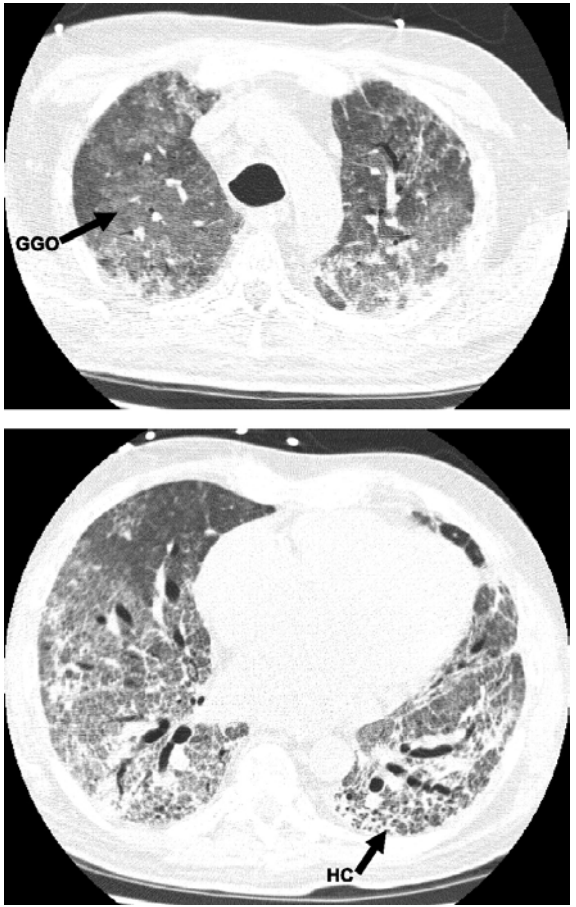


IPF Medications

	Nintedanib	Pirfenidone
Main Benefit	• About half the decline in FVC over 1 year, on average, compared to no treatment	• About half the decline in FVC over 1 year, on average, compared to no treatment
Other Possible Benefits	• Probably reduces risk of acute exacerbations	• Probably reduces 1-year mortality and risk of respiratory hospitalization
Administration	• 1 pill twice daily with food	• 3 tablets thee times daily with food
Tolerance/side effects	• Loose stools/diarrhea (~2/3) • Nausea (~1/4) • Weight loss (~1/10)	• Nausea/vomiting (~1/3) • Weight loss (~1/8) • Photosensitivity/Rash (~1/4) • Fatigue (~1/5)
Safety	• Possible increased risk of myocardial infarction (~1% increase) • Abnormal liver tests (5%)	• Abnormal liver tests (4%)
Discontinuation (1 year)	• ~20%	• ~15%
Cost per year	• $96,000	• $94,000

Acute exacerbation?

- Acute worsening of dyspnea with new bilateral ground glass opacities and/or consolidations on chest CT not fully explained by heart failure
- Very poor prognosis
  - 50% in-hospital mortality
  - 90% if requiring mechanical ventilation
- We try steroids but don't know if they work

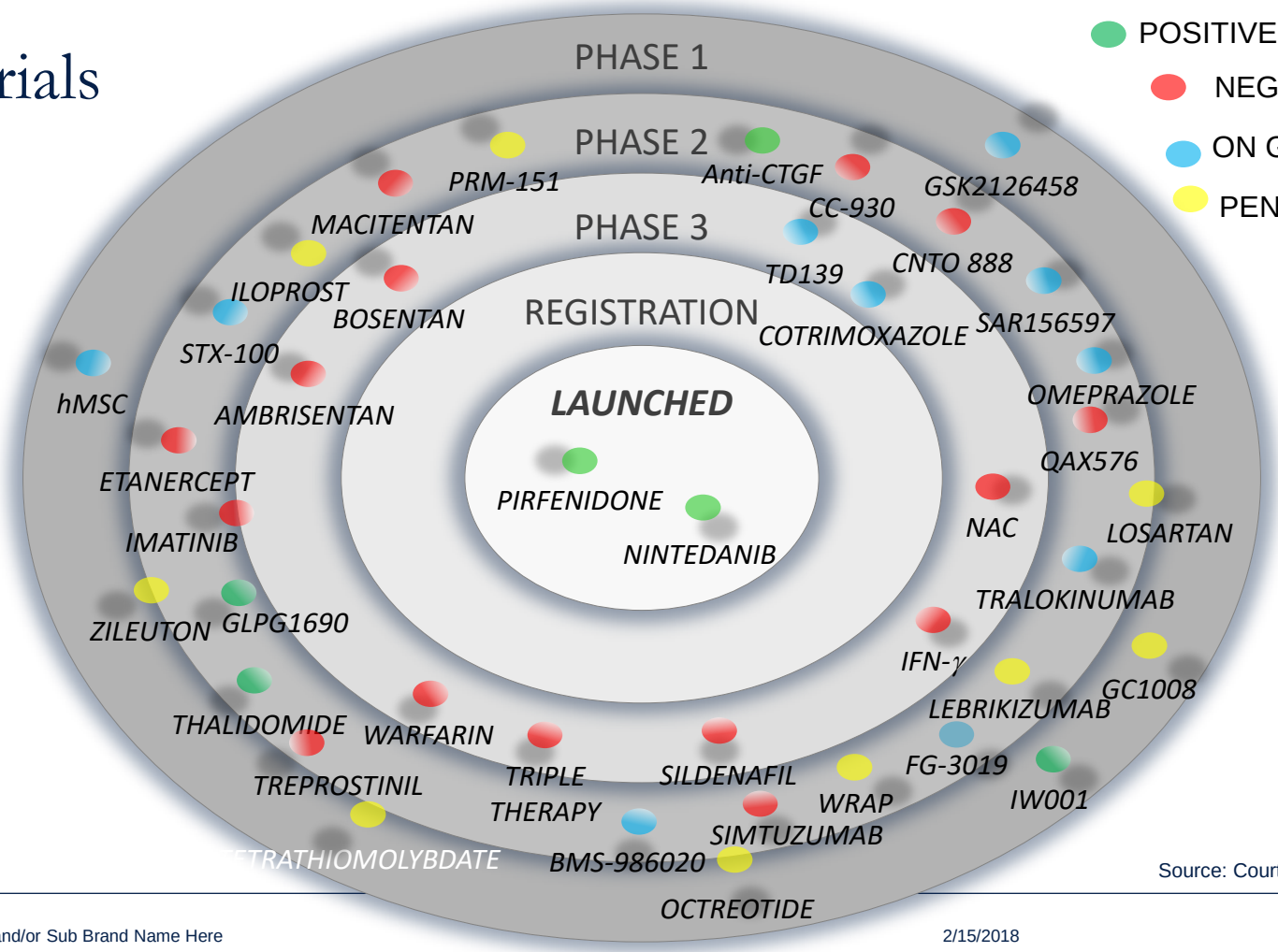


Am J Respir Crit Care Med 2016;194(3):265

Future of IPF Treatment

- Combination treatment targeting multiple pathways (similar to pulmonary arterial hypertension)
- Combination of nintedanib + pirfenidone tolerated by majority of patients and might have improved efficacy on FVC decline (Vancheri et al. AJRCCM 2017 [epub])
- Novel agents and combinations

IPF trials



Source: Courtesy of Luca Richeldi

Take home points

- IPF is a well-defined disease and we know a lot about its biology
- Accurate diagnosis is essential to patient counseling and appropriate treatment
- IPF now has effective treatments that slow, but do not stop disease progression. These should be started early in the disease course (at diagnosis with few exceptions).
- Non-pharmacologic treatments with potentially major impact include: *sufficient* oxygen supplementation, pulmonary rehabilitation, lung transplant, and palliative care
- The near future holds a lot of promise for at least stopping disease progression, likely through combination therapy with multiple agents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