Idiopathic Pulmonary Fibrosis:

What we have learned about risk, pathogenesis and treatment
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Disclosures

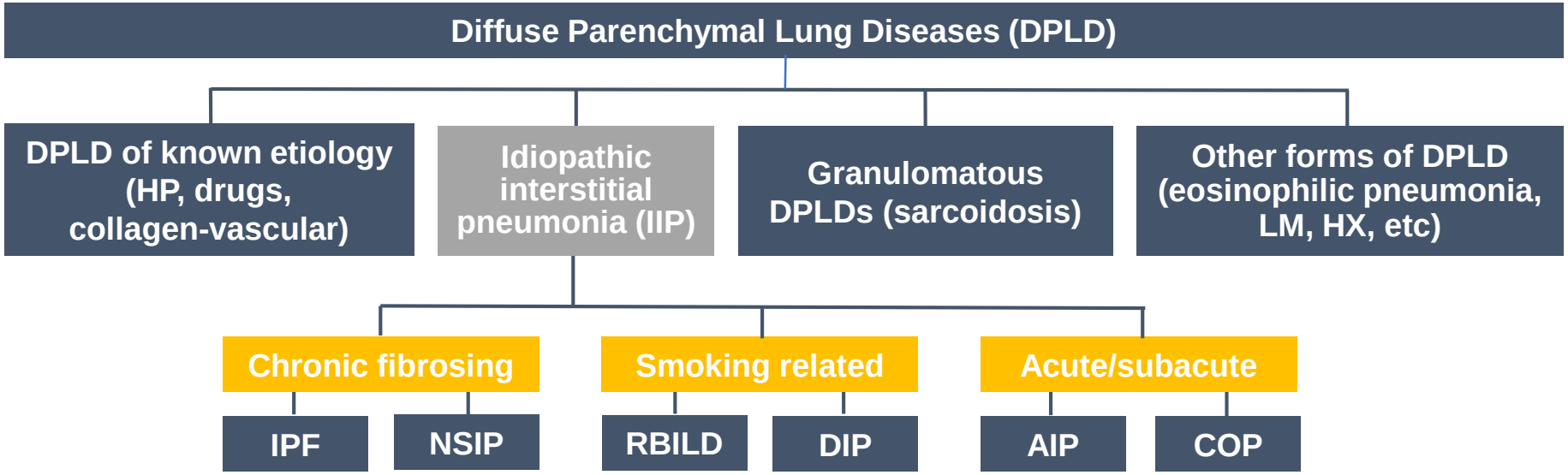
Dr. Glassberg serves on the advisory board for Actelion, Bellerophon, Boehringer-Ingelheim, Bristol-Myers-Squibb, Genentech/Roche, and Red-X.

Contracted Research for Genentech

Learning Objectives

- Upon completion of this learning activity, participants should be able to describe risk factors associated with IPF.
- Upon completion of this learning activity, participants should be able to review current ideas on pathogenesis of IPF and the development of new therapies.

Diffuse Parenchymal Lung Diseases (DPLD)

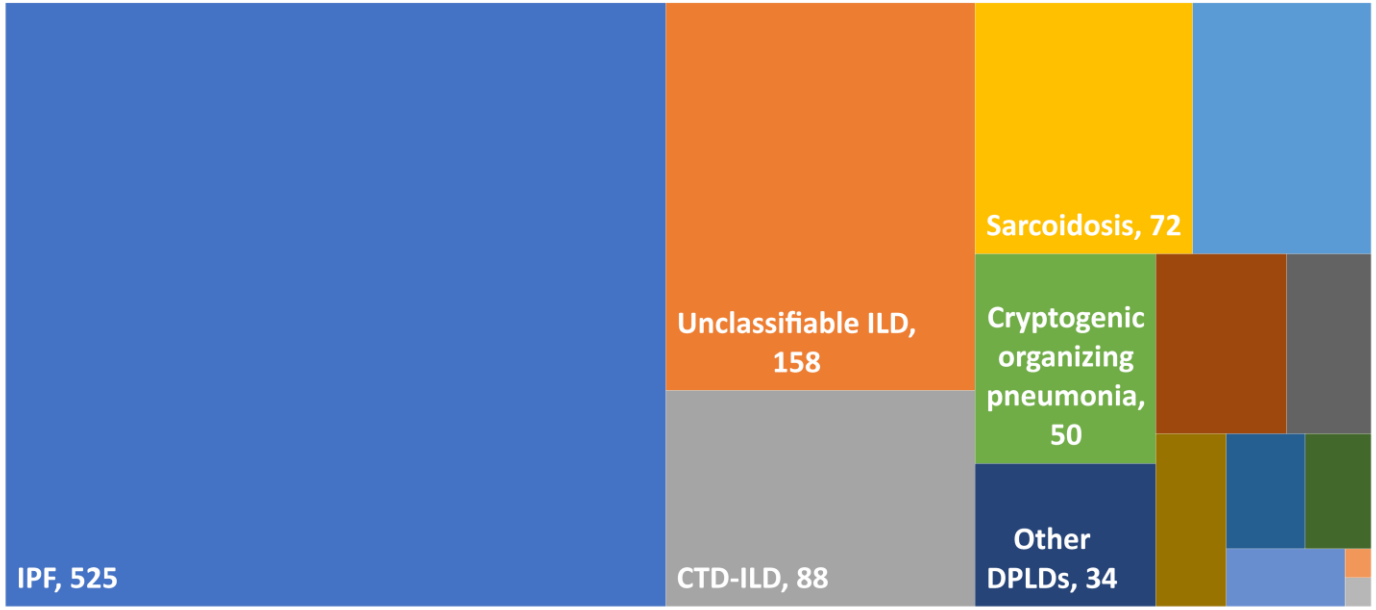


Very rare IIPs

- Idiopathic lymphocytic interstitial pneumonia (LIP)
- Idiopathic pleuroparenchymal fibroelastosis (PPFE)

1. Travis WD et al. *Am J Respir Crit Care Med*. 2013;188:733-748.

Number of Patients With ILD (European IPF Registry, 2009 to 2016)



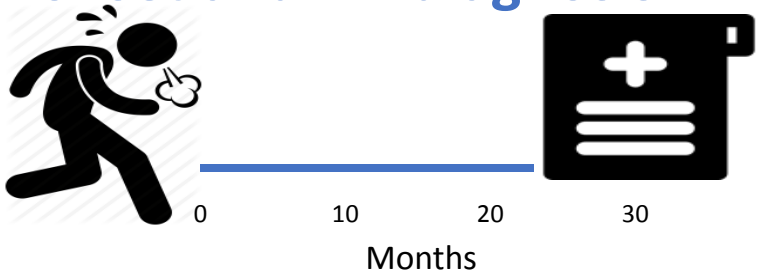
*Lymphocytic IP, 1; acute IP, 1

DIP, desquamative IP; HP, hypersensitivity pneumonitis; IP, interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung disease; NSIP, nonspecific IP; RB, respiratory bronchiolitis

Guenther A et al. *Respir Res*. 2018;19:141.

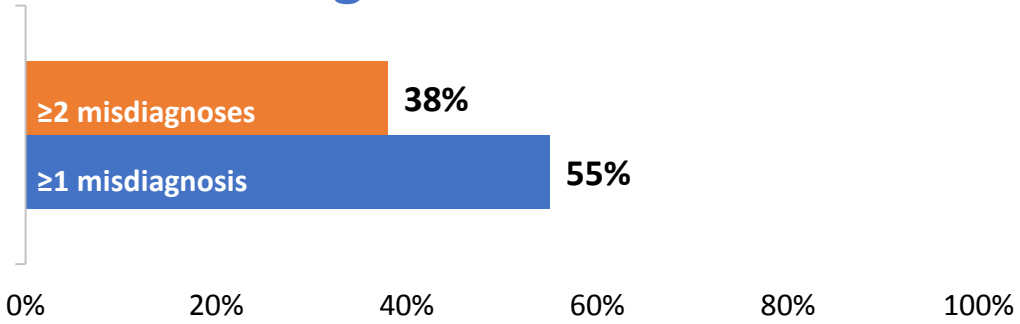
The delays in diagnosis: EXPLORE-IPF and INTENSITY

1.9 y between symptom onset and IPF diagnosis



2-3 doctors seen before receiving IPF diagnosis

More Than Half of Patients Are Misdiagnosed *at Least* Once



Common Misdiagnoses

- Asthma (14%)
- Pneumonia (13%)
- Bronchitis (12%)

Swigris JJ et al. *Chest*. 2015(suppl):1-8.; Cosgrove GP et al. *BMC Pulm Med*. 2018;8:9.

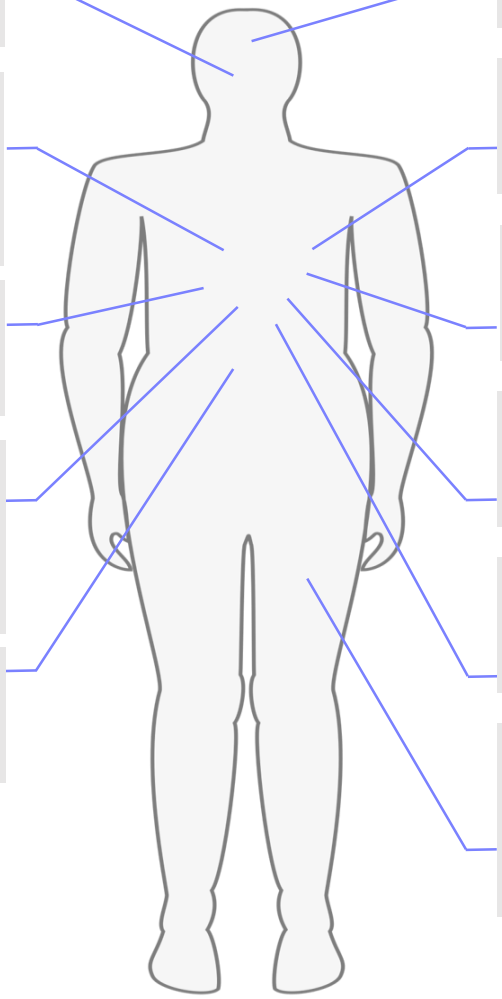
Risk Factors for IPF

- Age ≥60
- More extensive reticular densities
  - Probability of IPF: >80%
  - Specificity for IPF diagnosis: 96%
- White race
- Male sex
- American Indian descent
- Former smoker

Salisbury ML et al. *Respir Med*. 2016;118:88-95; Dove et al. Am Rev Respir Med 2019; Guenther A et al. *Respir Res*. 2018;19:141.

Comorbidities of patients with IPF

- Obstructive sleep apnea 5.9%-91%
- Gastroesophageal reflux disease 0%-94%
- Pulmonary hypertension 3%-86%
- Chronic obstructive pulmonary disease 6%-67%
- Diabetes mellitus 10%-42%



- Depression or anxiety 21%-49%
- Pulmonary embolism 3%-6%
- Congestive heart failure 4%-26%
- Coronary artery disease 3%-68%
- Lung cancer 4%-23%
- Sarcopenia prevalence poorly defined but common

King T, Nathan S. *Lancet Respir Med*. 2017;5:72-84.

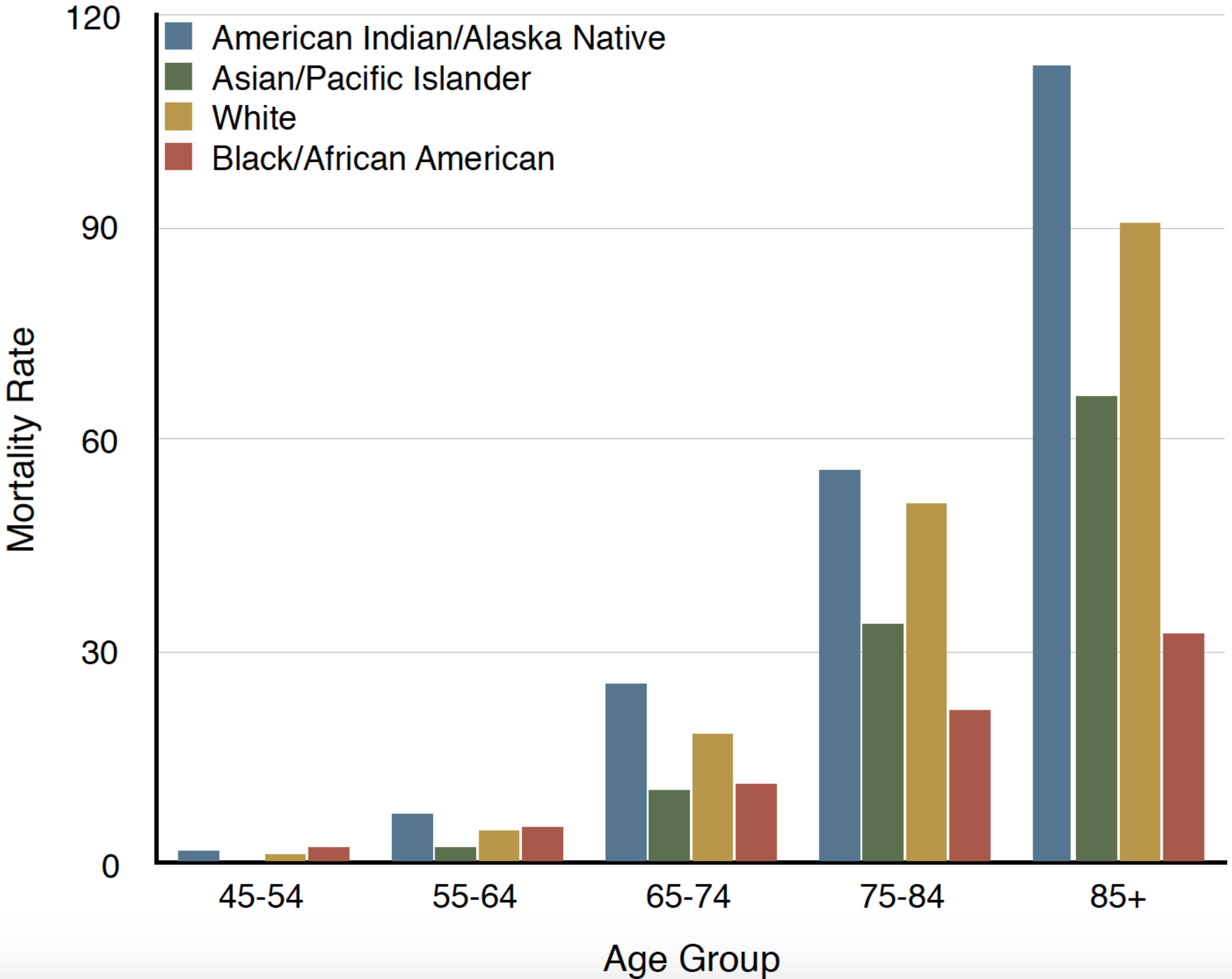
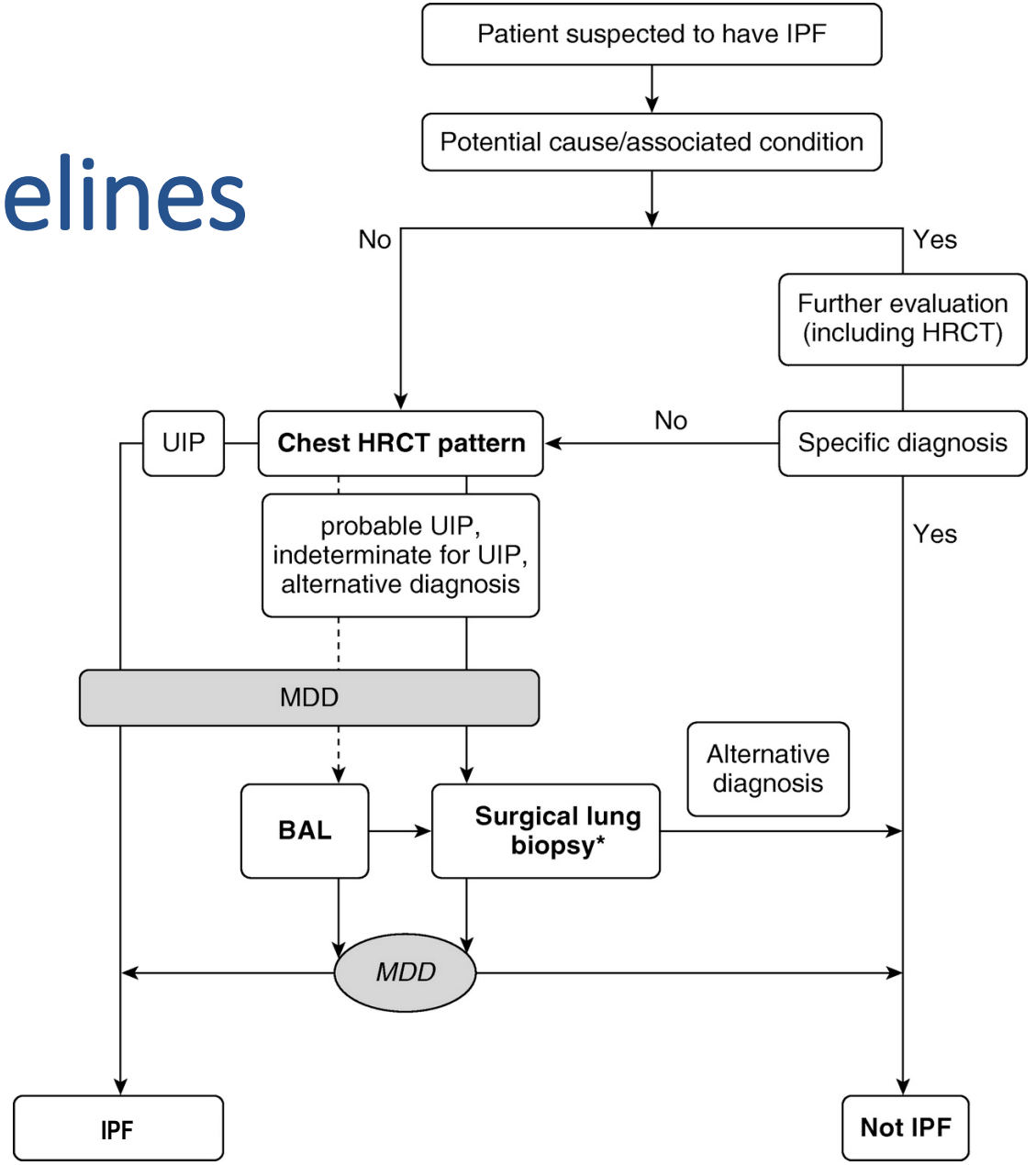


Figure 5: Differences in IPF-related mortality by age group and racial group, 2000-2017

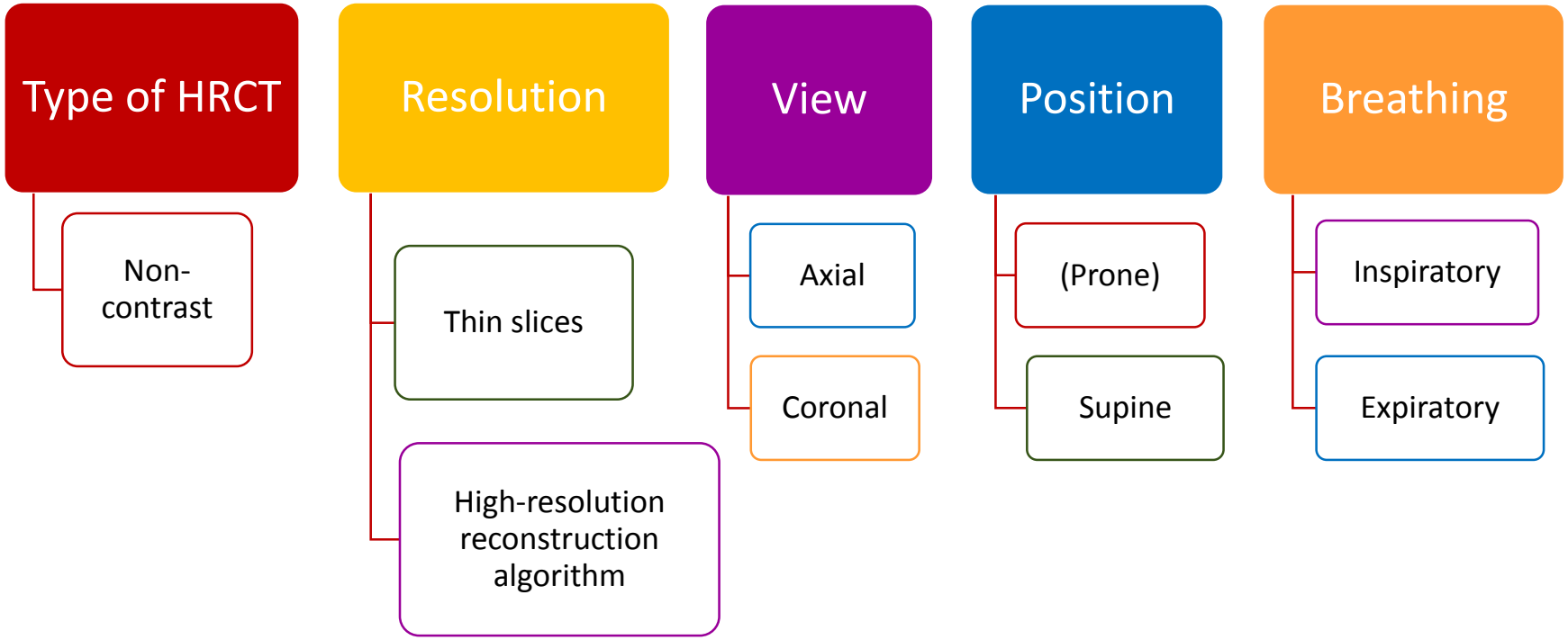
Dove et al. 2019

IPF Diagnosis: ATS/Fleischner Guidelines 2019



Raghu G et al. *Am J Respir Crit Care Med*. 2018;198(5):e44-e68.

Think ILD, Perform HRCT



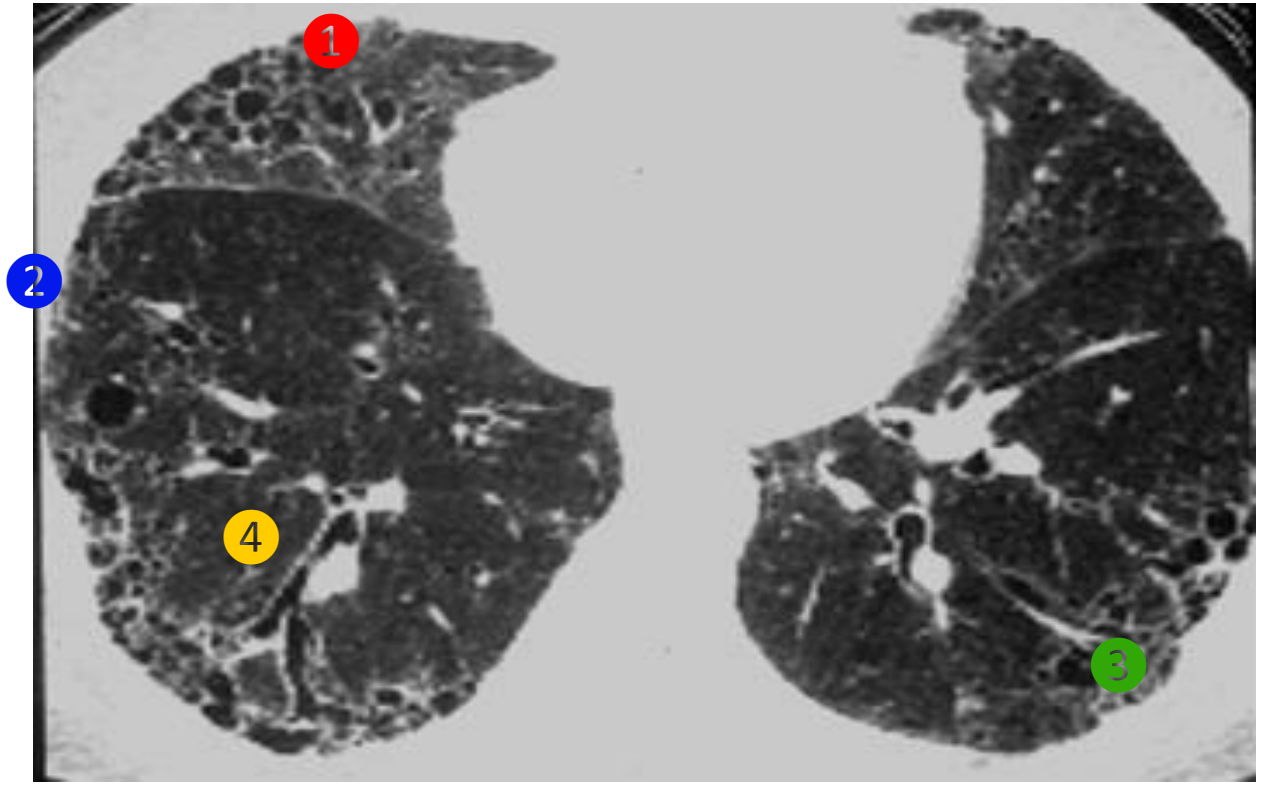
HRCT, high-resolution CT

PILOT. www.PILOTforPulmonary.org/ipf-resources/slide-library. Accessed 6/27/19.

Definite UIP Pattern: HRCT

1. Subpleural, basal predominance
2. Reticular abnormality
3. Honeycombing
4. Traction bronchiectasis

Absence of inconsistent features



The New "Probable" UIP Pattern

	Typical UIP CT pattern	Probable UIP CT pattern	CT pattern indeterminate for UIP
Distribution	Basal predominant (occasionally diffuse), and subpleural predominant; distribution is often heterogeneous	Basal and subpleural predominant; distribution is often heterogeneous	Variable or diffuse
Features	Honeycombing; reticular pattern with peripheral traction bronchiectasis or bronchiolectasis*; absence of features to suggest an alternative diagnosis	Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis*; honeycombing is absent; absence of features to suggest an alternative diagnosis	Evidence of fibrosis with some inconspicuous features suggestive of non-UIP pattern

- No change to "typical UIP" and "inconsistent" patterns
- "Probable UIP" = old possible UIP pattern + traction bronchiectasis
- "Possible UIP" no longer used
- New "indeterminate for UIP" pattern

Lynch DA, et al. *Lancet Respir Med*. 2018;6:138-53.

Exclude known causes that eliminate the “I” in IPF

Category	Information needed
Autoimmune disease	History: joints, skin, dry eyes/mouth, Raynaud’s Exam: skin and joint changes Serologies: ANA, RF, anti-CCP, others
Chronic hypersensitivity pneumonitis	History: dampness, mold, water damage, humidifiers, hot tubs, birds, down bedding
Medications/radiation therapy	History: amiodarone, nitrofurantoin, chemotherapy, etc.
Pneumoconioses	Occupational history

Role of Lung Biopsy/Genomic Classifier in IPF Diagnosis

Consider Biopsy When…

- CT pattern is indeterminate or inconsistent with UIP
- Clinical features suggest alternative diagnosis

Risk Factors for Mortality

- Male sex
- Age >65 y
- Comorbidities
- Open vs thoracoscopic surgery
- Lung-diffusing capacity <50% of predicted

Risks of Surgery

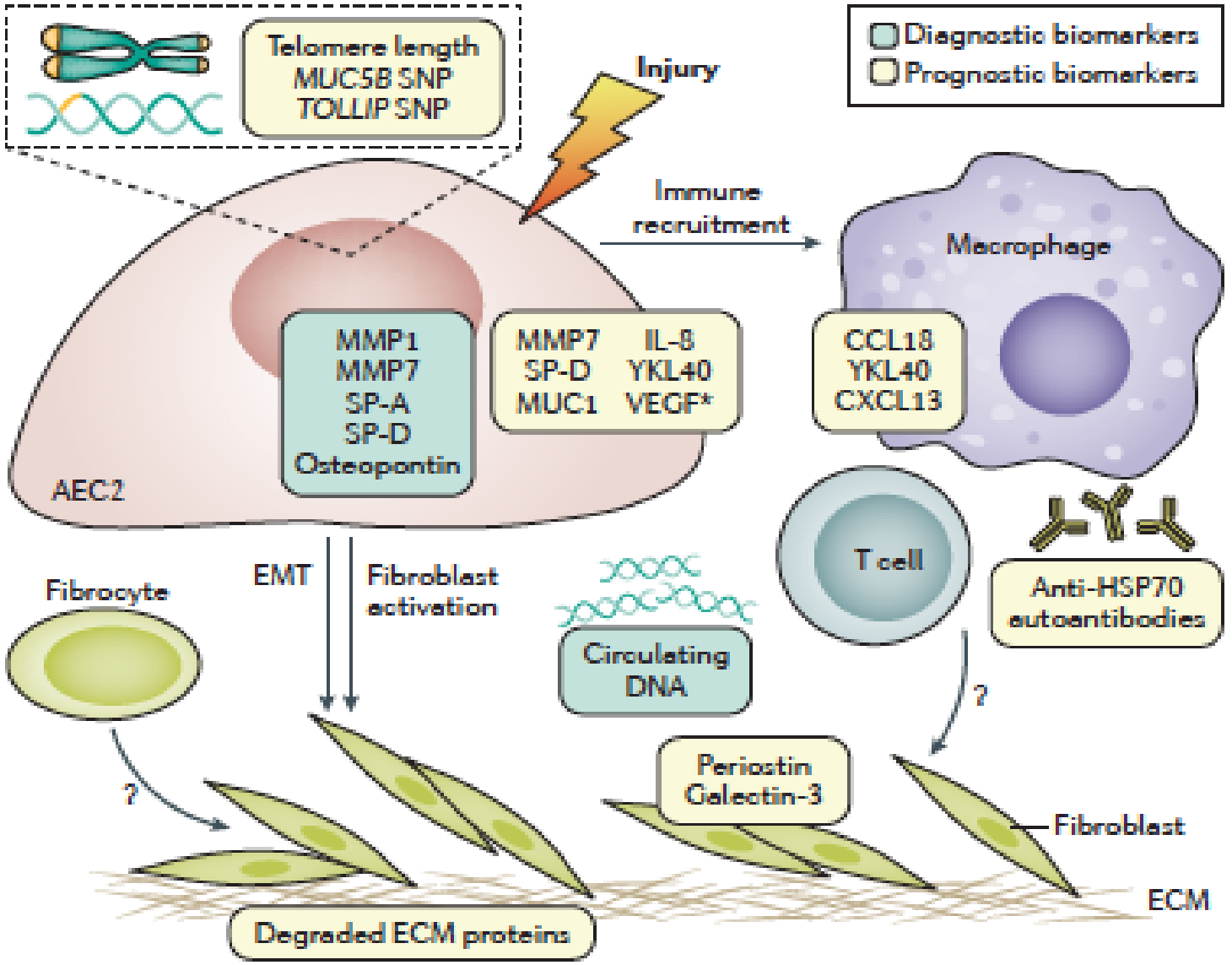
- Death
- Pneumothorax
- Pneumonia
- Protracted air leaks
- Acute exacerbations
- Infections

Lynch DA et al. *Lancet Respir Med*. 2018;6(2):138-153.

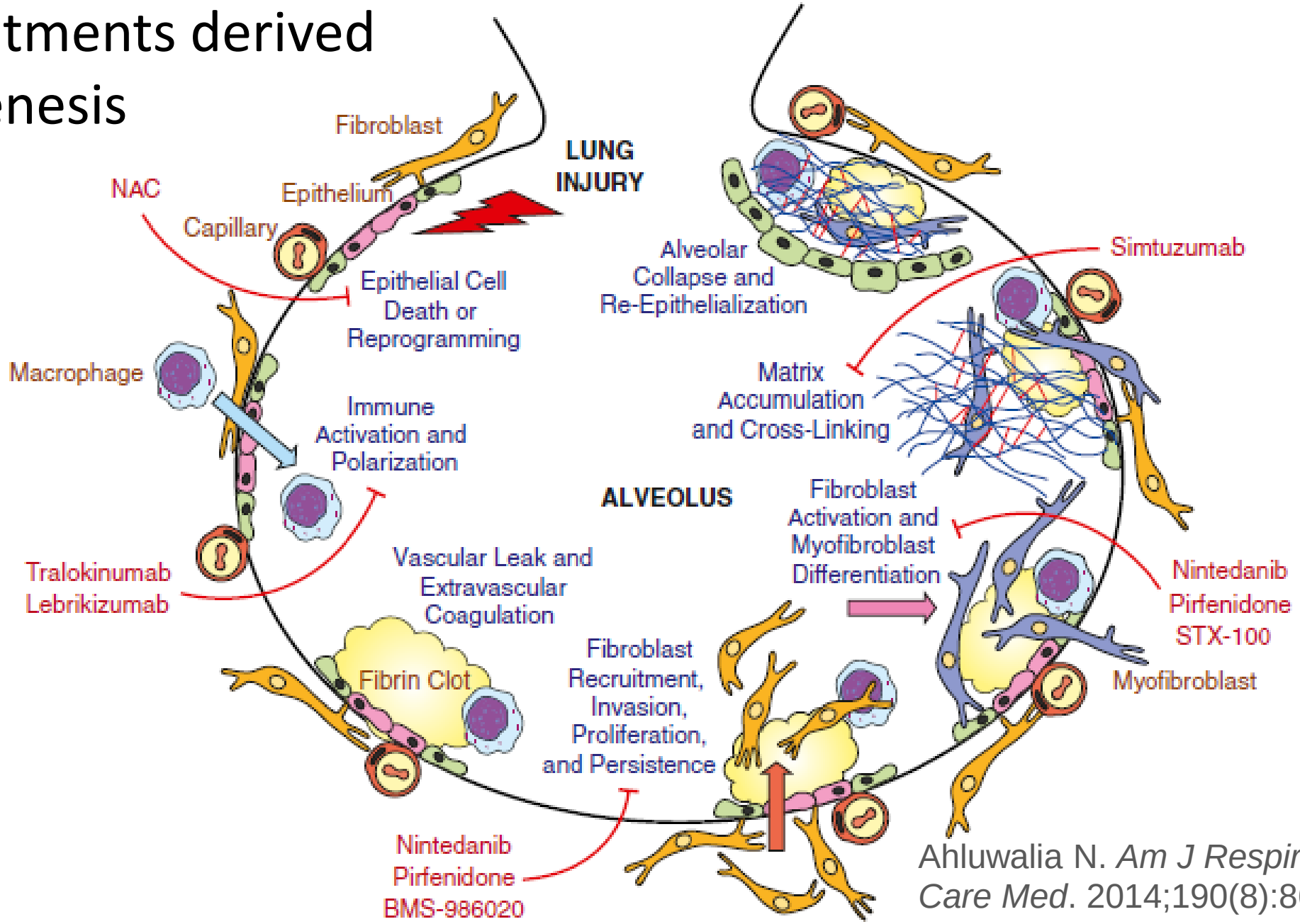
What is a Genomic Classifier?

- Samples obtained at time of bronchoscopy
- RNA whole-transcriptome sequencing and machine learning identify the usual interstitial pneumonia (UIP) pattern in the sample.
- Complements HRCT
- The Envisia classifier can detect UIP with high correlation to histopathology results – without the need for VATS
- Medicare approved
- Necessary?

Idiopathic Pulmonary Fibrosis: Pathogenesis



Potential treatments derived from pathogenesis



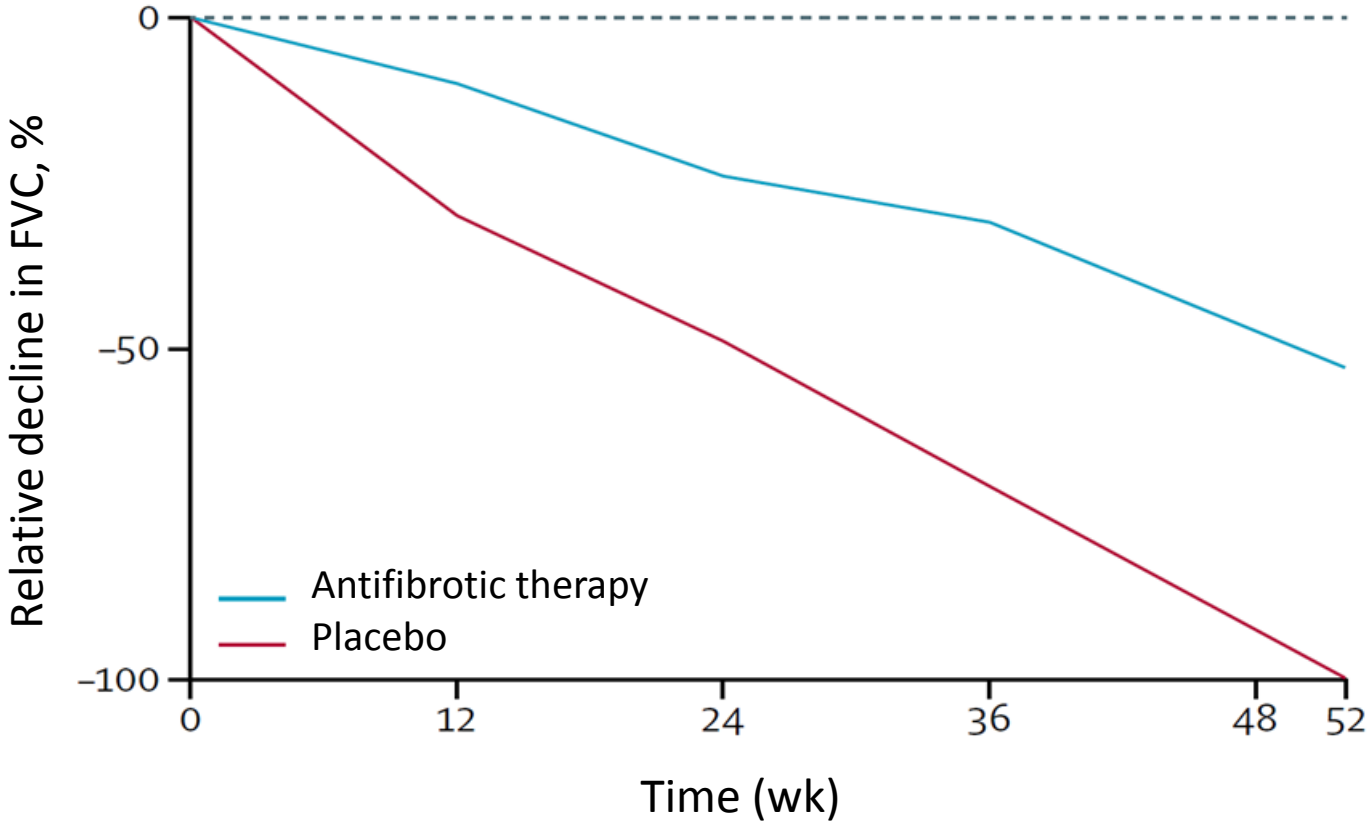
Ahluwalia N. *Am J Respir Crit Care Med*. 2014;190(8):867-878

Pharmaceutical Therapy for IPF

Potentially Harmful	Ineffective	Effective Disease-Modifying Therapies
• Ambrisenten • Everolimus • Prednisolone, azathioprine, NAC • Warfarin	• Bosentan • Imatinib • Macitentan • NAC • Sildenafil	• Pirfenidone • Nintedanib

Richeldi L et al. *Lancet*. 2017;389:1941-1952.

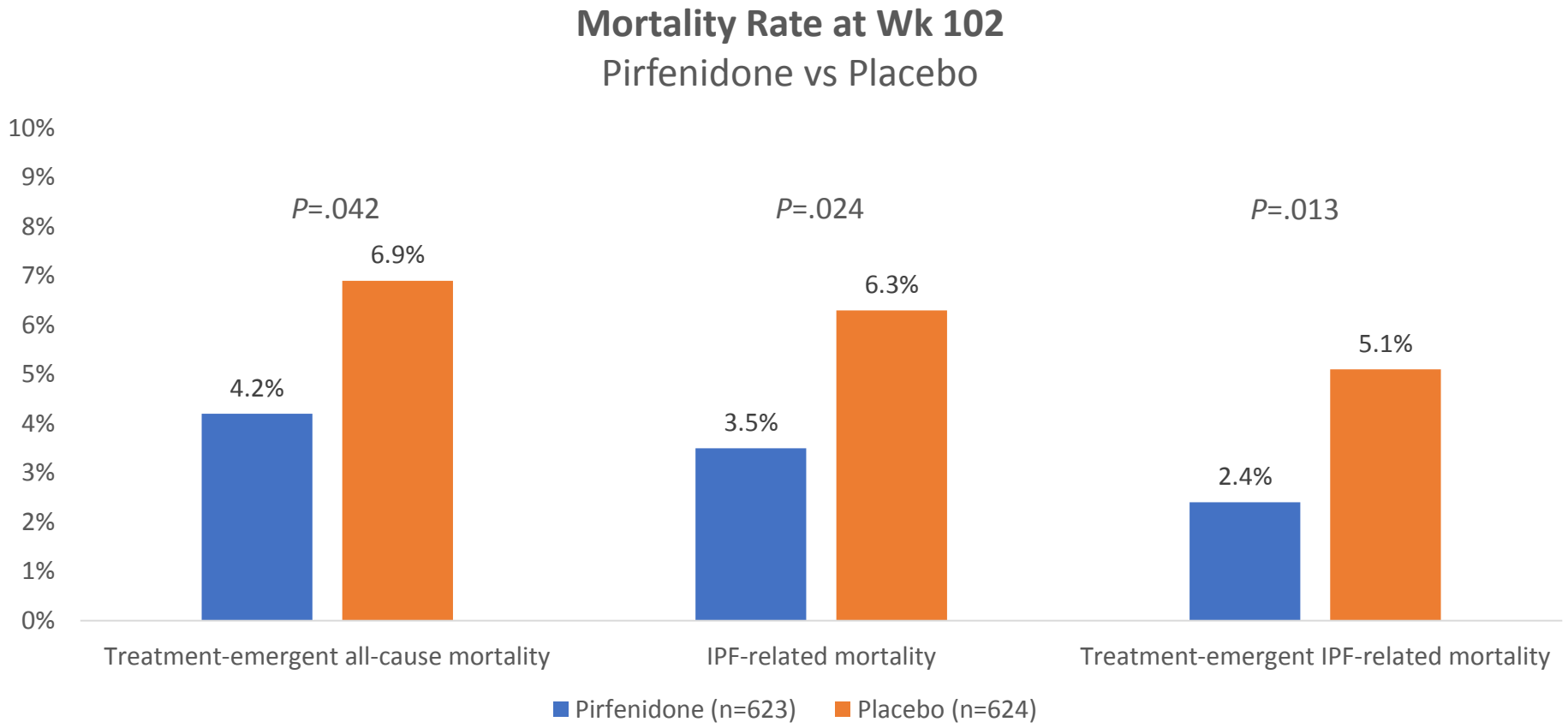
Antifibrotics Significantly Reduce Lung Function Decline in Patients With IPF



- These benefits are seen even in patients with more advanced disease at the time of antifibrotic initiation

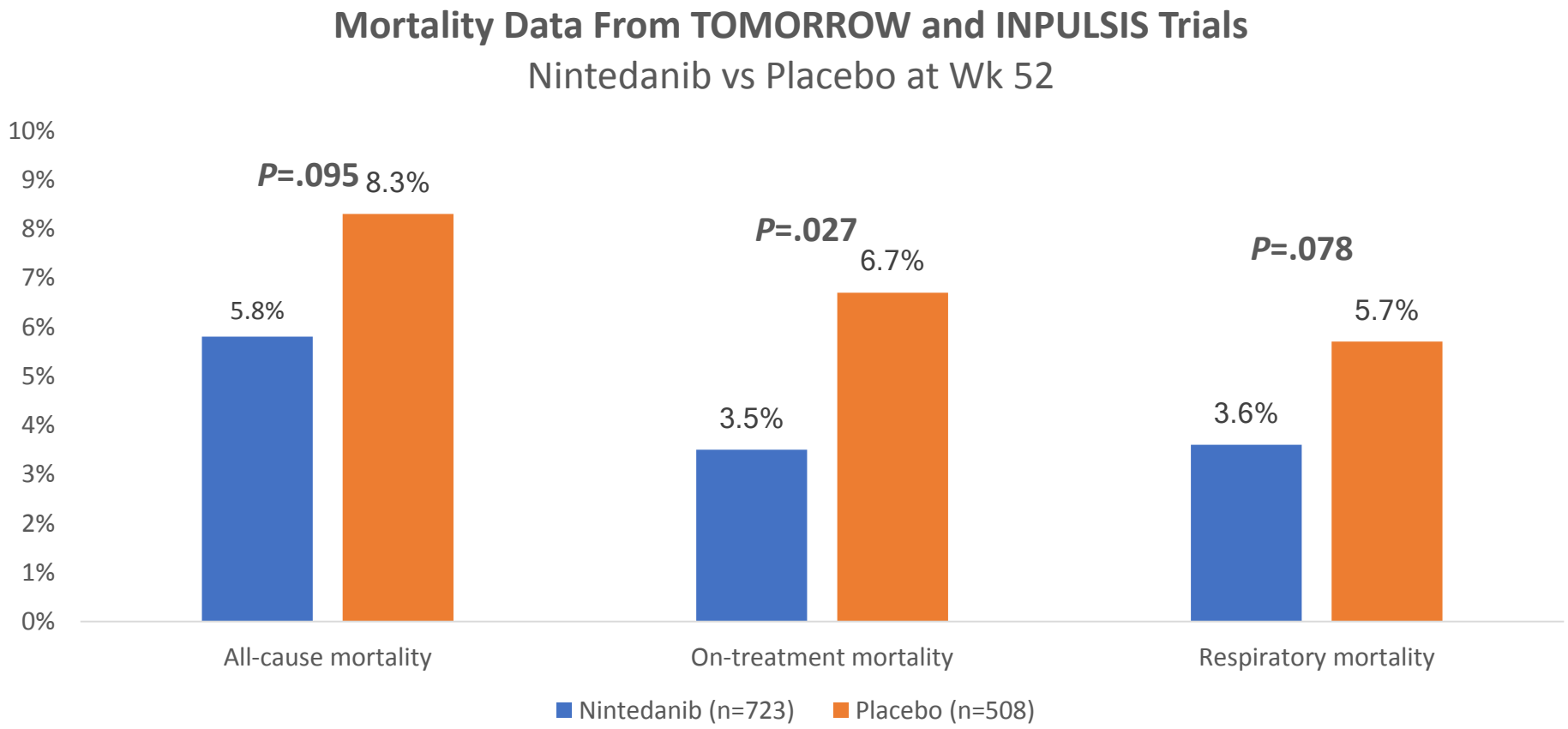
Richeldi L et al. *Lancet*. 2017;389(10082):1941-1952; Costabel U et al. *Respir Res*. 2019;20:55.

Pirfenidone Shows Trend in Favor of Mortality Reduction



Nathan SD et al. *Lancet Respir Med.* 2017;5:33-41.

Nintedanib Shows Trend in Favor of Mortality Reduction



Richeldi L et al. *Respir Med*. 2016;113:74-79.

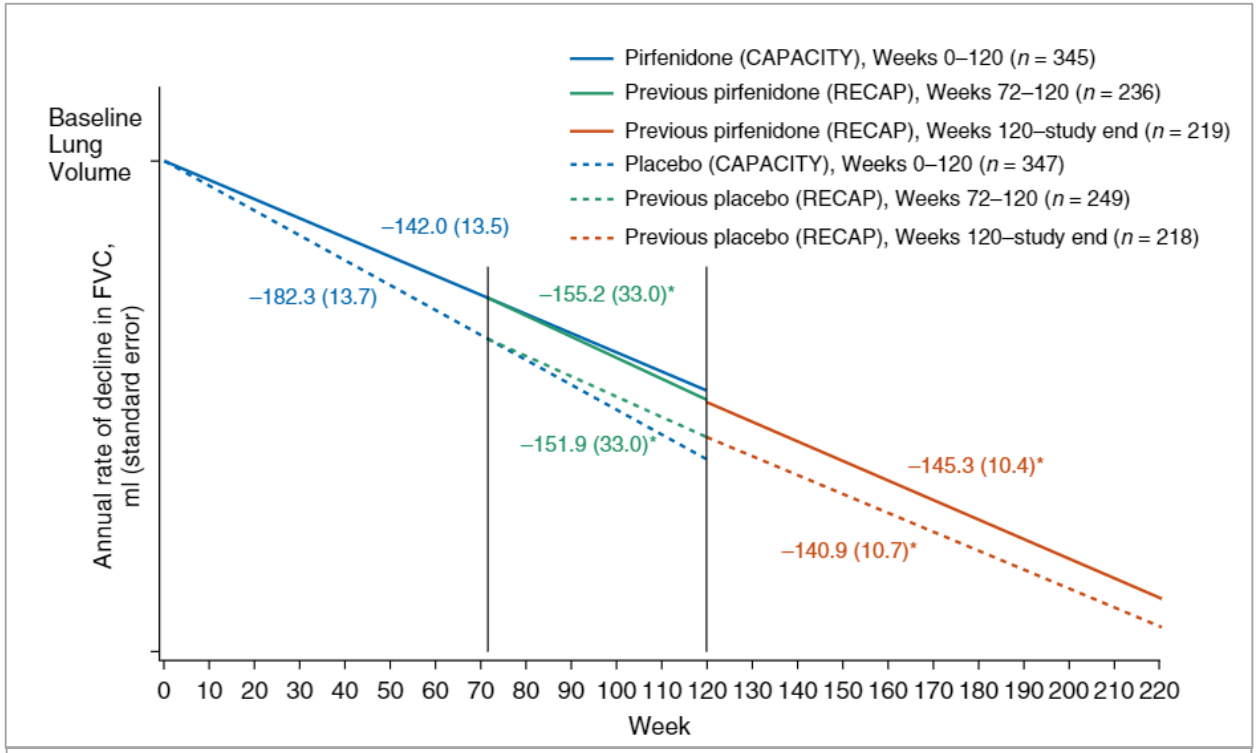
Comparison of Pirfenidone and Nintedanib: Efficacy

Efficacy vs Placebo	Pirfenidone	Nintedanib
Slows rate of FVC decline[1]	✓	✓
Lowers all-cause mortality[2]	✓	✓
Effective regardless of baseline lung function[3-5]	✓	✓
Improves progression-free survival[6]	✓	
Reduces respiratory-related hospitalizations[7]	✓	
Reduces incidence of multiple progression events[a] and death after a progression event over 1 y[8]	✓	
May reduce risk of first acute exacerbation		✓

Richeldi L et al. *Lancet*. 2017;389(10082):1941-1952.;Dempsey TM et al. *Am J Respir Crit Care Med*. 2019 Nathan SD et al. *Respir Med*. 2019;153:44-51. 4. Maher TM, Lancaster L et al. *Ann Am Thorac Soc*. 2019;16(7):927-930. 5. Kolb M et al. *Thorax*. 2017;72(4):340-346.. 7. Ley B et al. *Am J Respir Crit Care Med*. 2017;196(6):756-761. 8. Nathan SD et al. *Chest*. 2019;15594):712-719.

Initiate Antifibrotic Therapy

- 220-week open-label extension trial studying timing of pirfenidone initiation and annual FVC decline
- Pirfenidone slowed FVC decline regardless of baseline FVC
  - Efficacy maintained >4 y
  - Little change in annual rate of FVC decline after >1 y of treatment



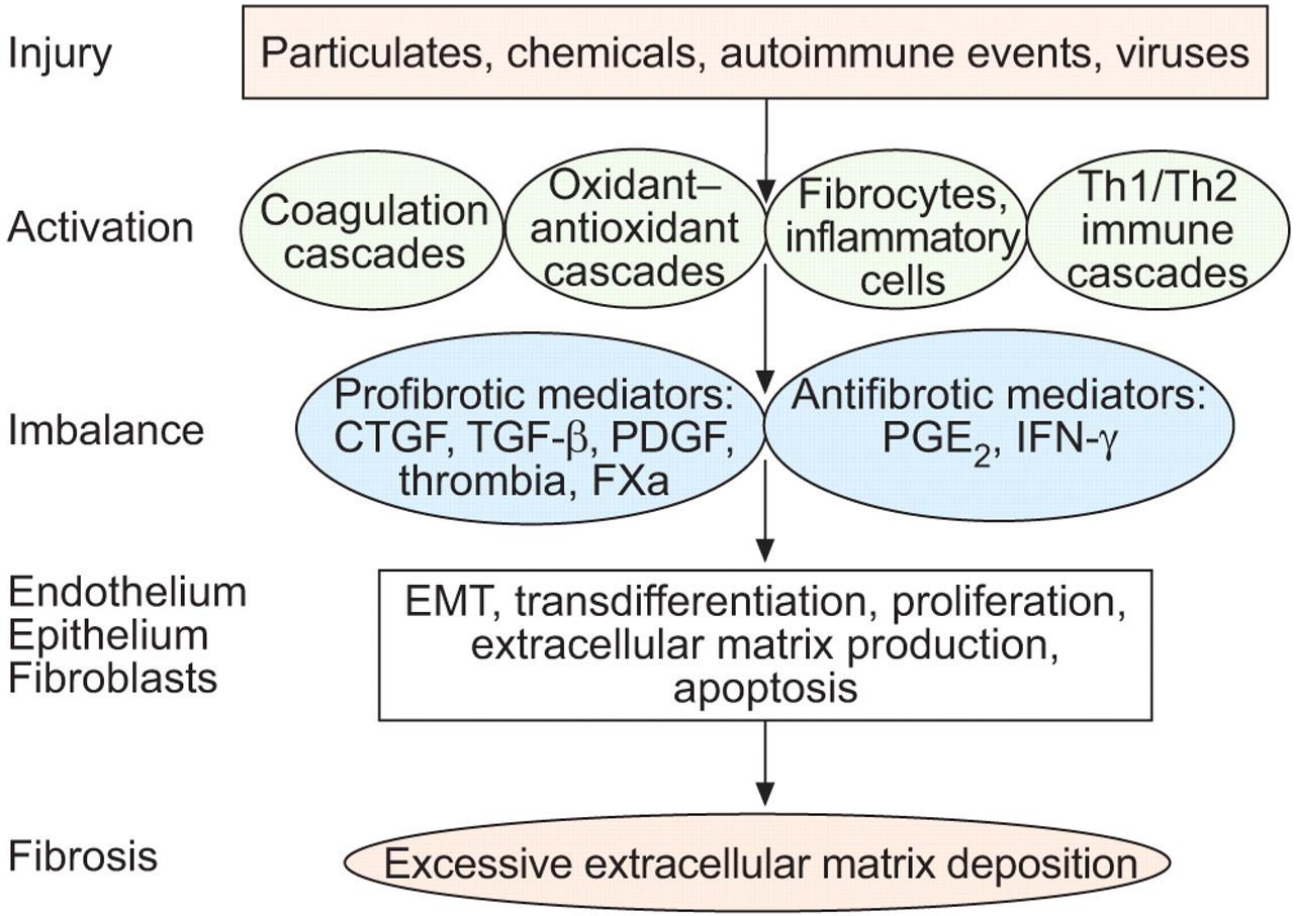
Loss of lung function incurred prior to pirfenidone initiation was not recovered after initiation

Maher TM, Lancaster L et al. *Ann Am Thorac Soc*. 2019;16(7):927-930.

Comparison of nintedanib and pirfenidone

- Dempsey TM, Sangaralingham LR, Yao X, Sanghavi D, Shah ND, Limper AH. Clinical Effectiveness of the Anti-Fibrotic Medications for Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2019 May 31. doi: 10.1164/rccm.201902-0456OC. [Epub ahead of print]PMID: 31150266;
- Hughes G, Toellner H, Morris H, Leonard C, Chaudhuri N. Real World Experiences: Pirfenidone and Nintedanib are Effective and Well Tolerated Treatments for Idiopathic Pulmonary Fibrosis. J Clin Med 2016; 5.

Future targets for treatments for patients with fibrotic lung disease-is this different from targeting IPF?



Clinical Trials in IPF