Disease Monitoring of Pulmonary Fibrosis

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Overview

- Current methods of monitoring disease
  - Pulmonary function testing
  - Computed tomography

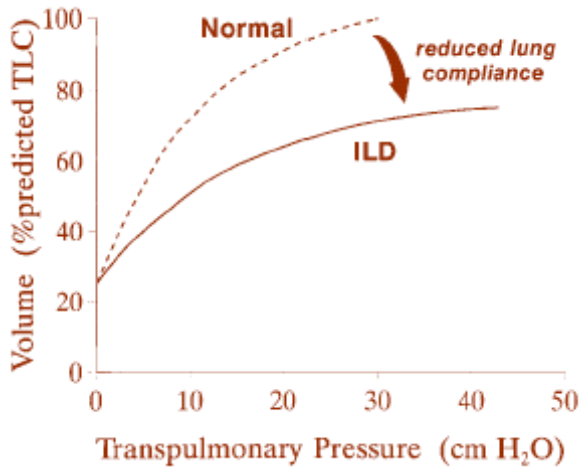
- Investigational methods of monitoring disease

Pulmonary Function Tests

- A mainstay of ILD evaluation
- Used in diagnosis (restriction)
- Used in monitoring
  - Changes in forced vital capacity (FVC) and DLCO as markers of disease progression
- Used in clinical trials
  - Change in forced vital capacity over 52 weeks

PFTs and ILD Physiology

- Pulmonary Mechanics
  - Lungs have ↓ compliance



→ PFTs show restrictive defect

- Lung volumes
  - ↓ TLC
  - ↓ RV
- Spirometry
  - ↓ VC
  - FEV_1/FVC normal or even increased

PFTs and ILD Natural History

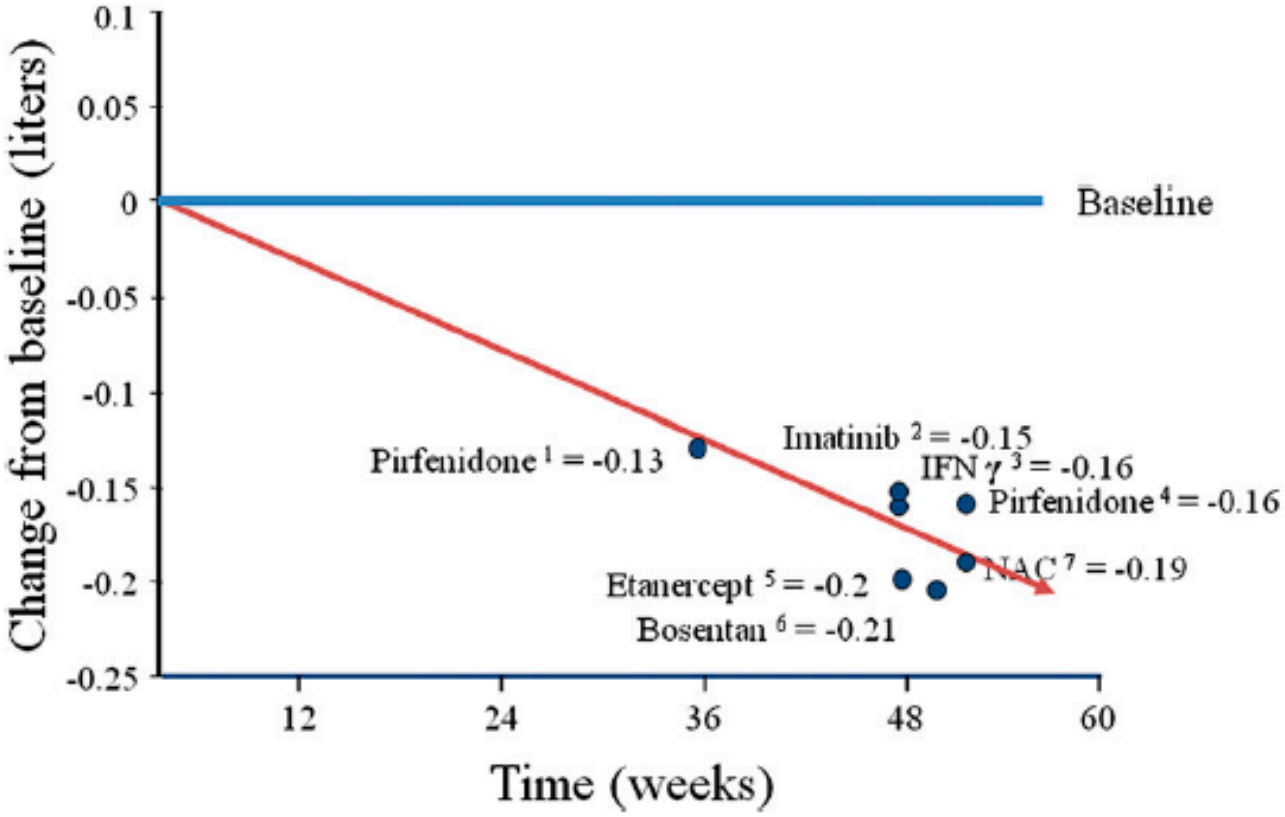
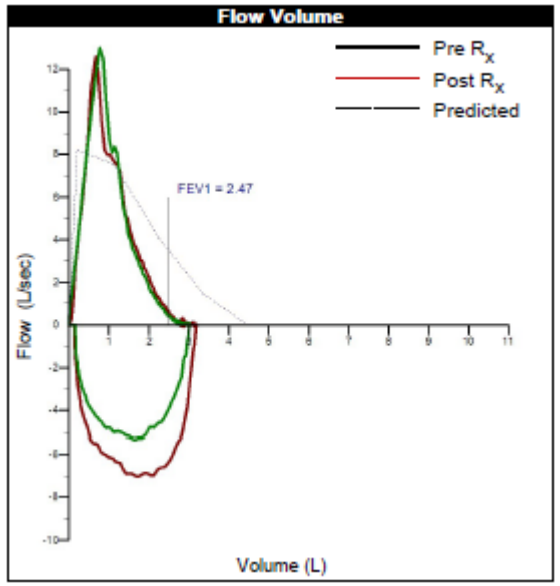


Figure 2. Decline in FVC in idiopathic pulmonary fibrosis (IPF). Shown are the mean rates of FVC found in the placebo arms of clinical trials in patient with IPF. The FVC declines approximately 150 to 200 ml/yr in patients with IPF. Data from the placebo arms of the following clinical trials: [1]Pirfenidone (27), [2]Imatinib (29), [3]Interferon γ-1b (IFNγ) (25), [4]Pirfenidone (30), [5]Etanercept (26), [6]Bosentan (24), [7]N-Acetylcysteine (NAC) (28).

Ley et al, Am J Respir Crit Care Med, 2011; 183: 431-440



Oximetry		O2 Delivery	O2 Sat	Pulse
Normal room air values		L/Min	95 to 98	
			%	
Rest	(Room Air)	None	95.0	97
Rest				
Exercise			88.0	107

Spirometry at BTPS — ATS ✔ — Pre Bronchodilator

		Actual	Predicted	% Pred	CI Range			
FEV_1	L	2.47	3.49	71	2.65	4.33	A	m
FVC	L	3.01	4.48	67	3.36	5.60	A	m
FEV_1 / FVC	%	82	78	105	70	----	N	
FEF_{25-75}	L/s	2.76	3.27	84	1.60	4.94		
PEFR	L/s	12.98	8.22	158	4.33	12.11		
FIVC	L	2.85	4.48	64	3.36	5.60		

Plethysmography — ATS ✔ — Pre Bronchodilator

		Actual	Predicted	% Pred	CI Range			
TLC	L	4.74	6.74	70	5.13	8.35	A	m
FRC	L	2.12	3.55	60	2.09	5.01	N	
ERV	L	0.47	1.29	36	----	----		
RV	L	1.65	2.26	73	1.50	3.02	N	
RV/TLC	%	35	34	103	23	45	N	
VC	L	3.09	4.48	69	3.36	5.60		

Resistance

Raw	cmH2O/L/s	2.59	< = 2.80		----	----	N	
sGaw	L/s/cmH2O	0.21	> = 0.12		----	----	N	

Diffusion — ATS ⊘ — Pre Bronchodilator

		Actual	Predicted	% Pred	CI Range			
DLCO	mL/min/mmHg	14.48	27.06	54	19.07	35.05		
DLCO [Hb]	mL/min/mmHg	14.10	27.06	52	19.07	35.05	A	m
Hb	g/dl	15.6	14.6	----	12.0	16.0		
VA [BTPS]	L	3.91	6.78	58	5.17	8.39		
DLCO/VA	mL/min/mmHg/L	3.61	4.17	87	2.97	5.37	N	

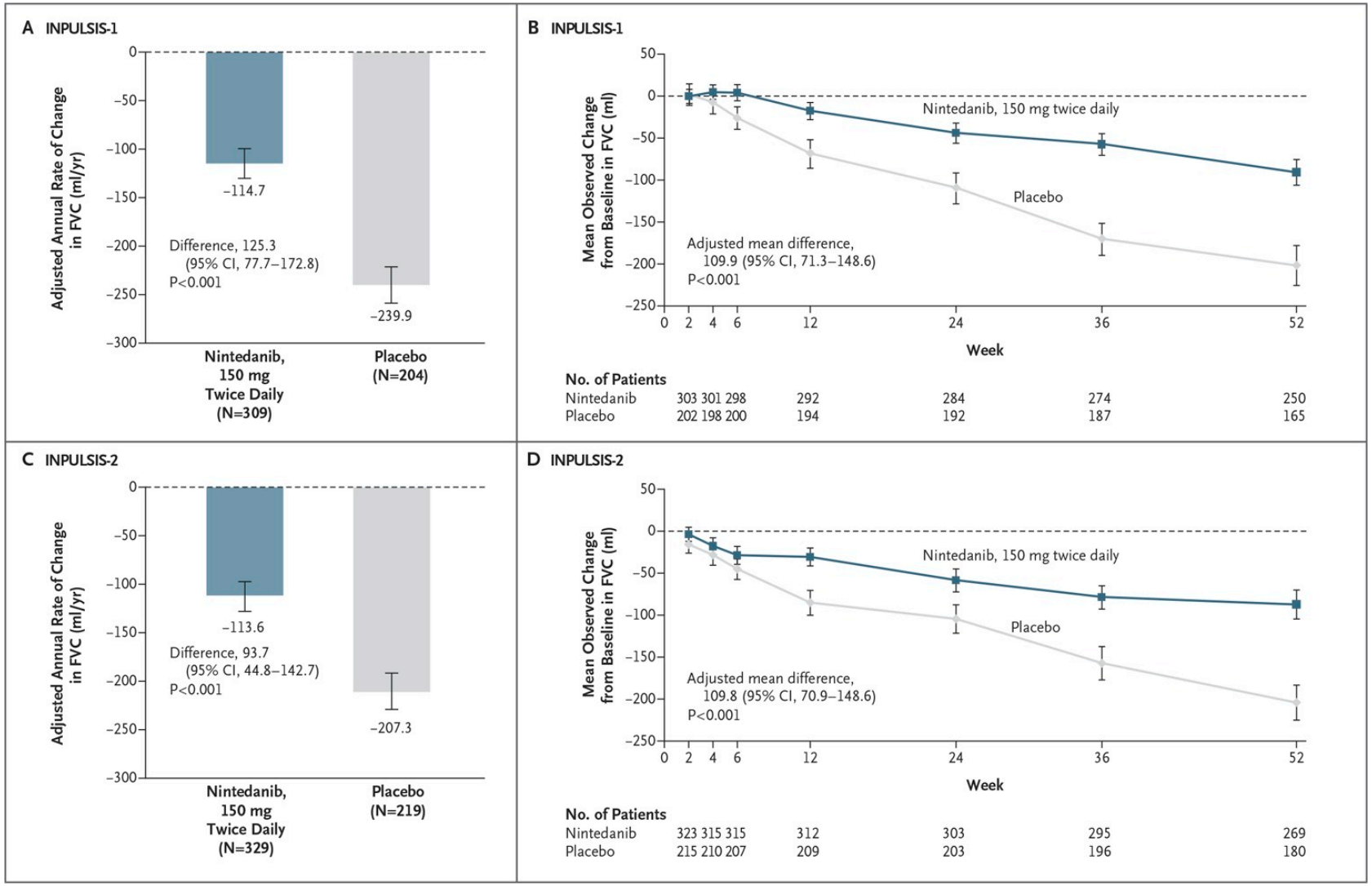
It’s change over time that important

Parameter	Units	**Today**	**History of Previous**	
		18-Sep-20	05-Mar-20	30-Dec-99
FVC	L	**2.39**	3.77	----
FEV_1	L	**1.63**	3.20	----
FEV_1 / FVC	%	**68**	85	----
FET	sec	**5.93**	8.10	----
TLC	L	**----**	5.50	----
FRC	L	**----**	3.77	----
RV	L	**----**	1.62	----
VC	L	**----**	3.88	----
DLCO [Hb]	mL/min/mmHg	**8.28**	17.69	----

PFTs and Advantages

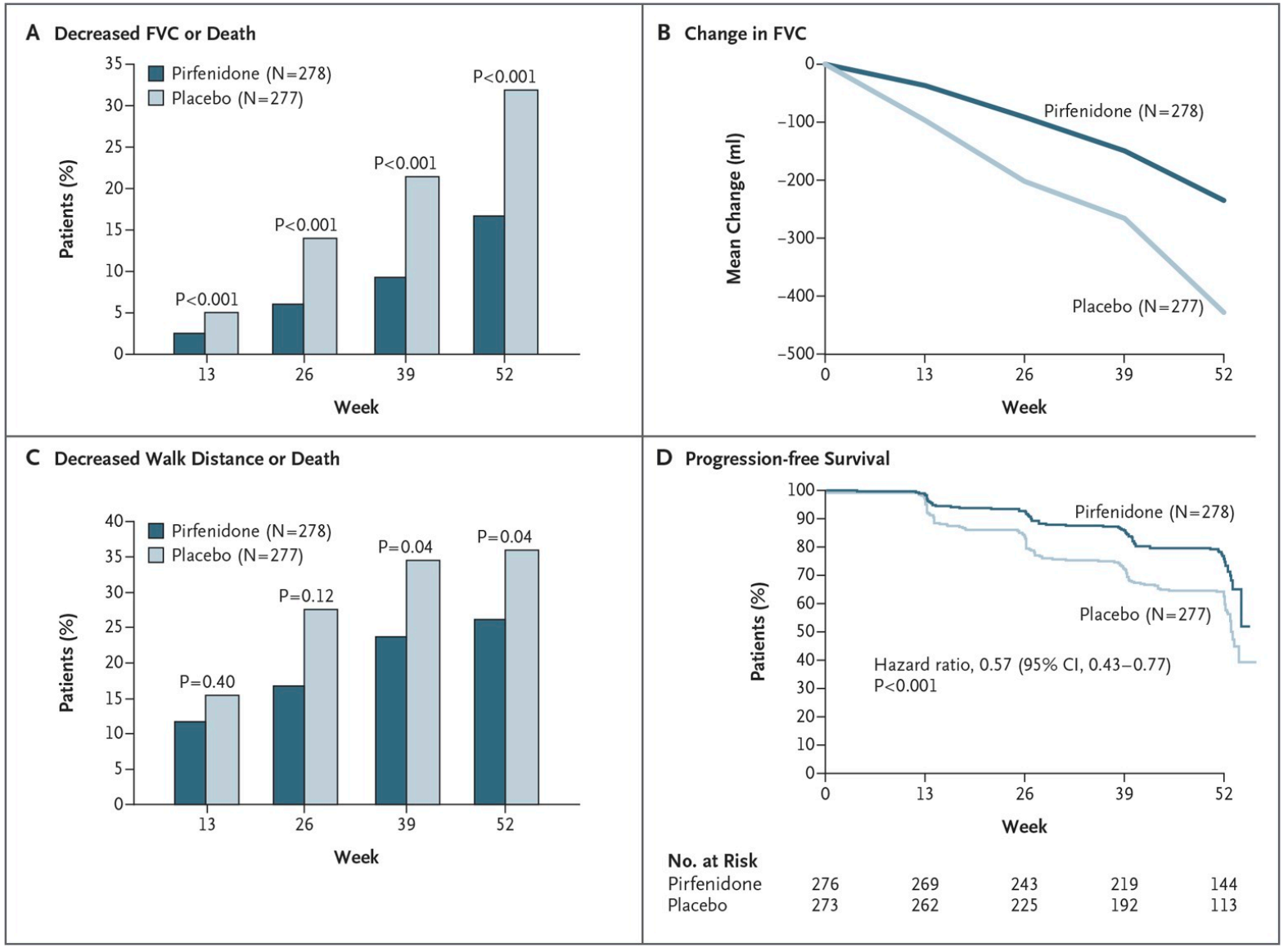
- Easy to perform
- Reproducible and standardized (can have performed at different locations and still be comparable)
- Low cost
- Changes have clinical significance
- Primary outcome of clinical trials

Nintedanib and FVC



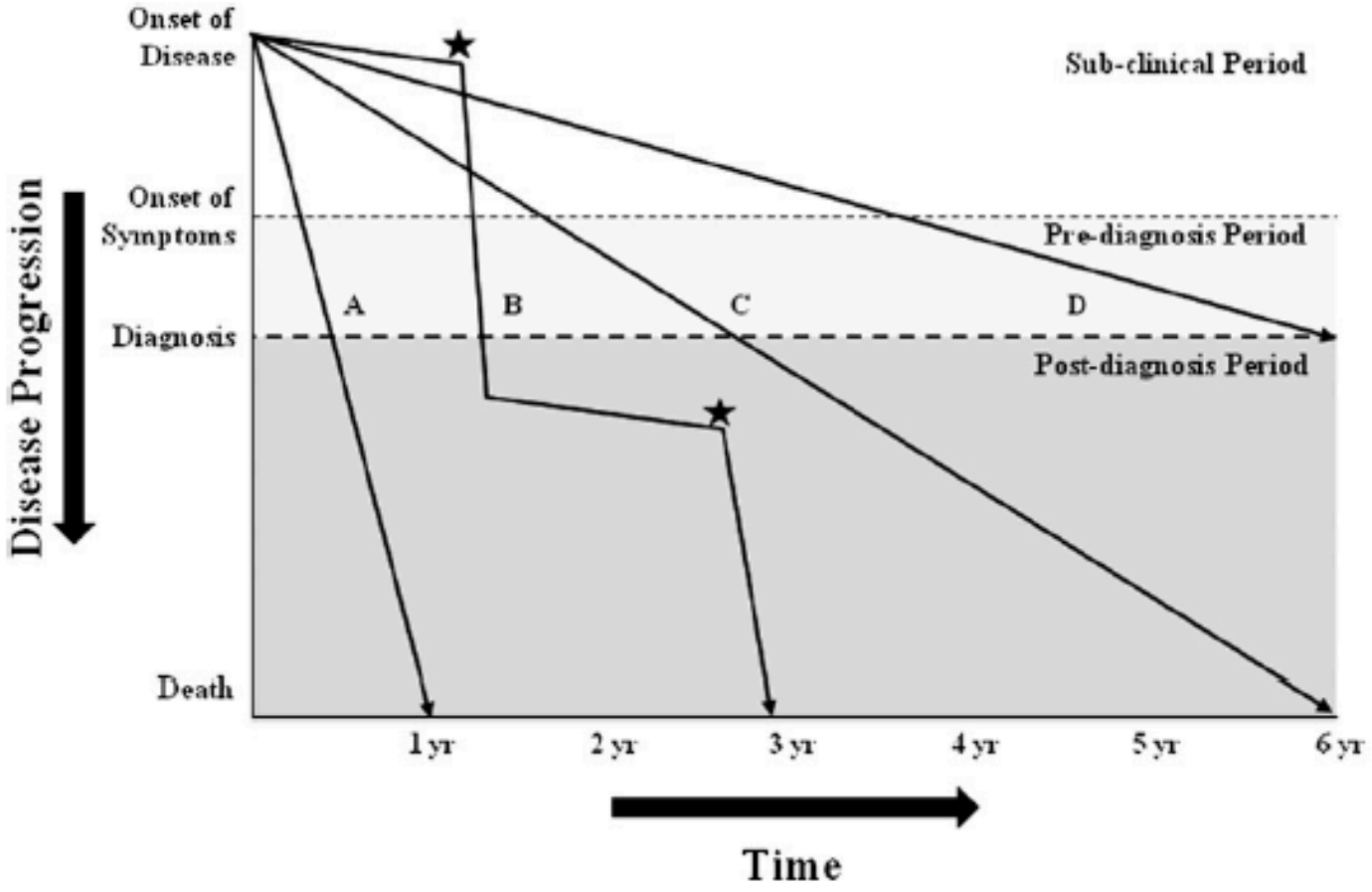
Richeldi L et al, *N Engl J Med* 2014; 370:2071-2082

Pirfenidone and FVC



King TE et al, *N Engl J Med* 2014; 370:2083-2092

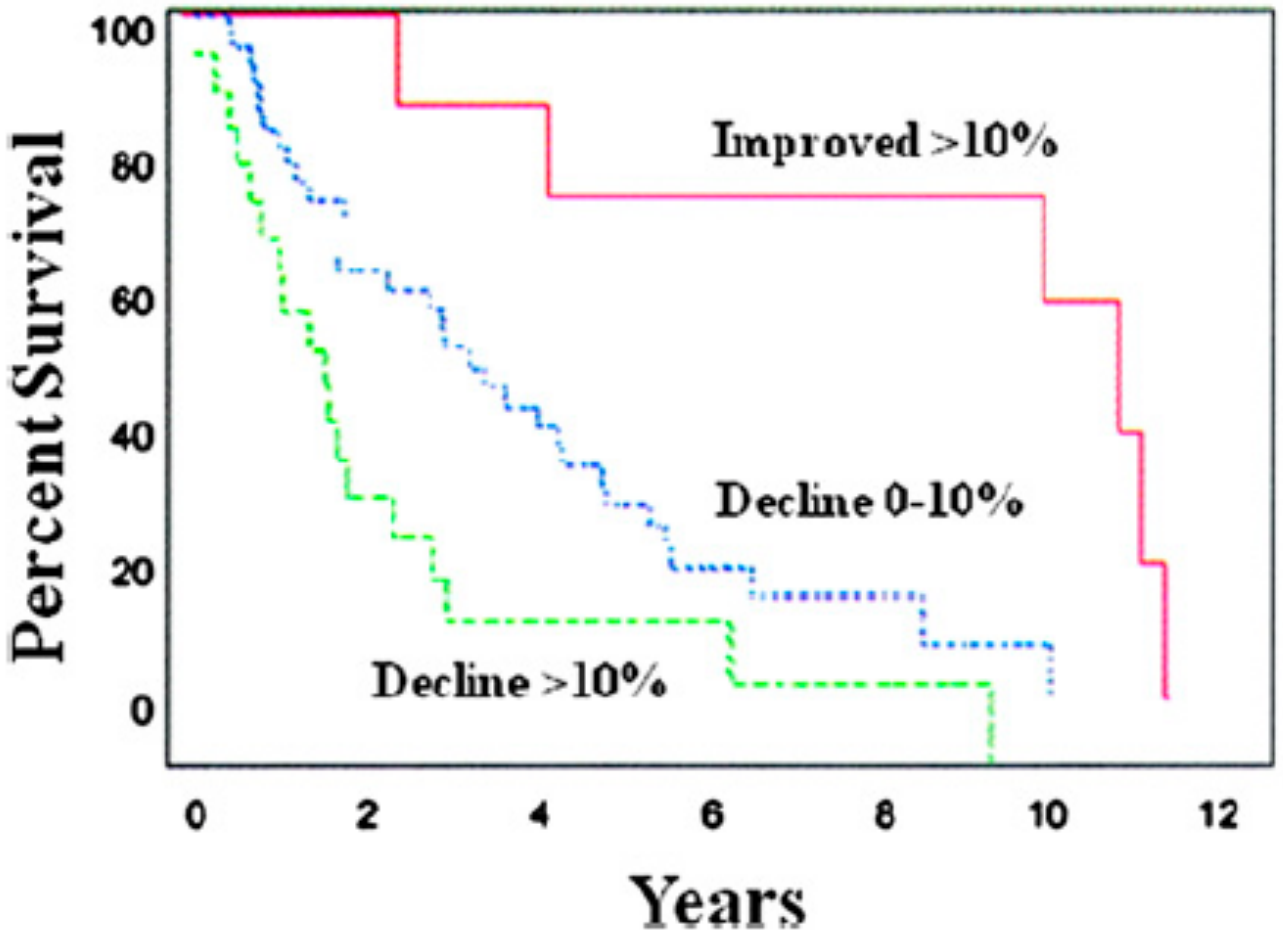
PFTs and Limitations



- Difficult to predict subsequent progression based on one measurement

Ley et al, Am J Respir Crit Care Med, 2011; 183: 431-440

PFTs and Change over Time

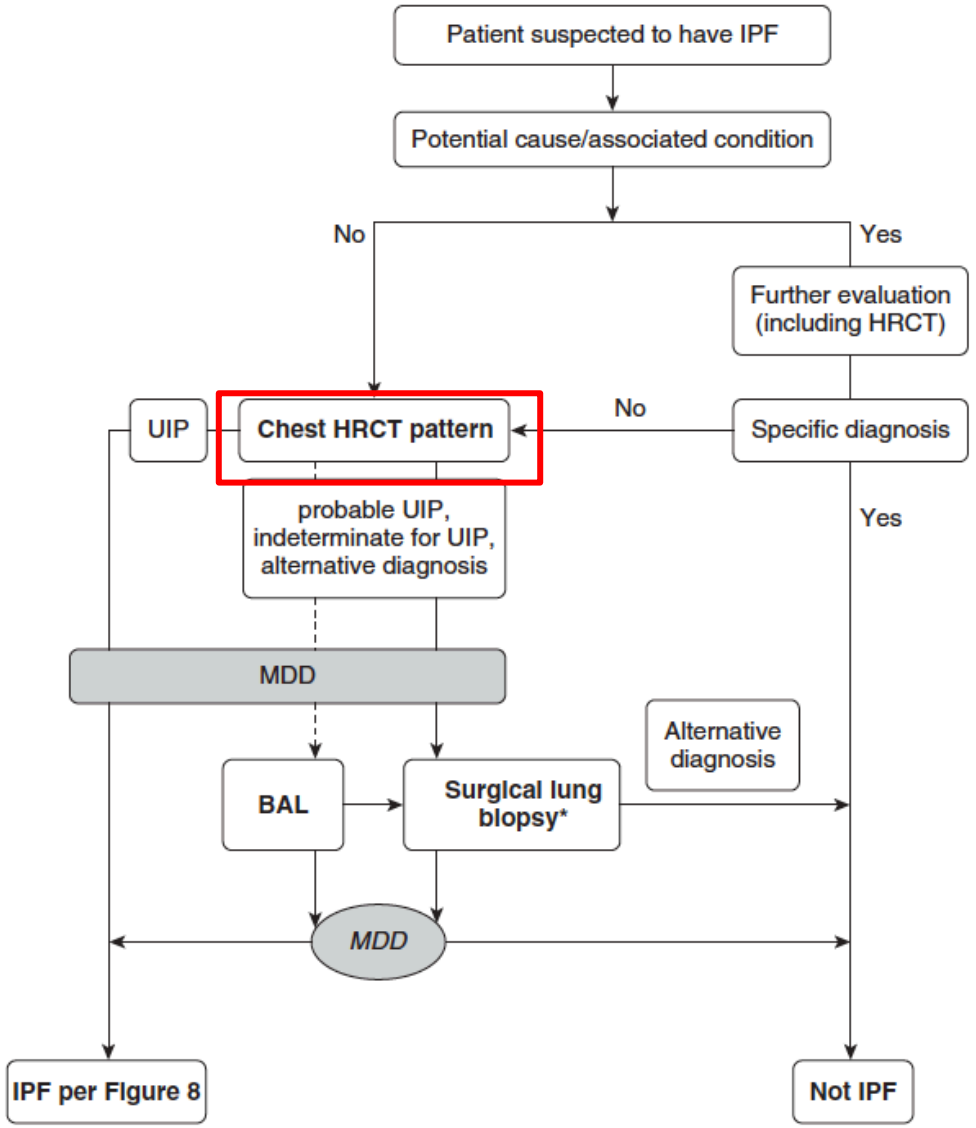


Ley et al, Am J Respir Crit Care Med, 2011; 183: 431-440

Computed Tomography (CT)

- Mainstay of ILD diagnosis
- Used to inform as to ILD pattern type
- Presence of certain findings (UIP pattern) has prognostic significance
- Not used as an outcome measure in clinical trials

IPF Diagnostic Approach

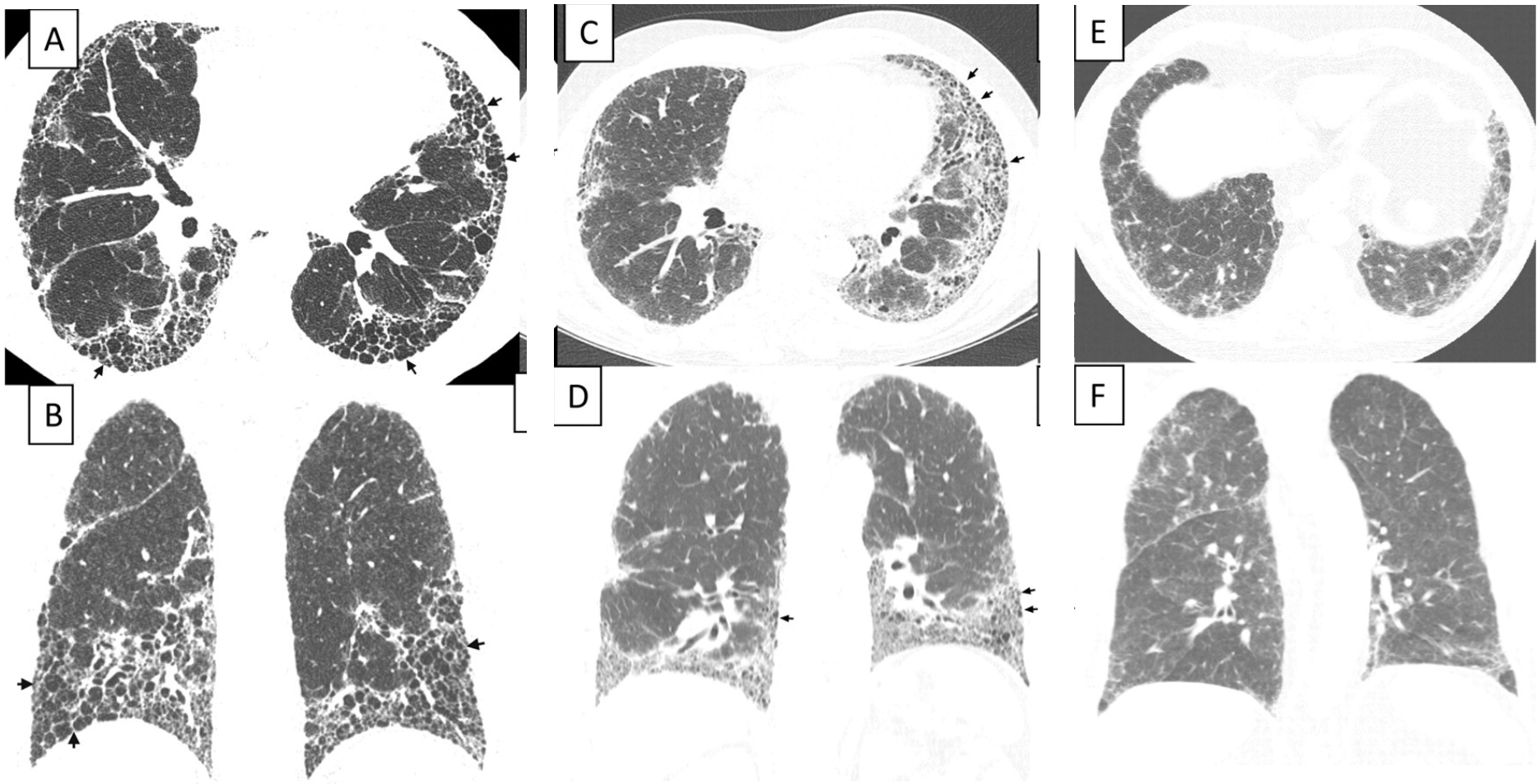


CT Pattern Examples

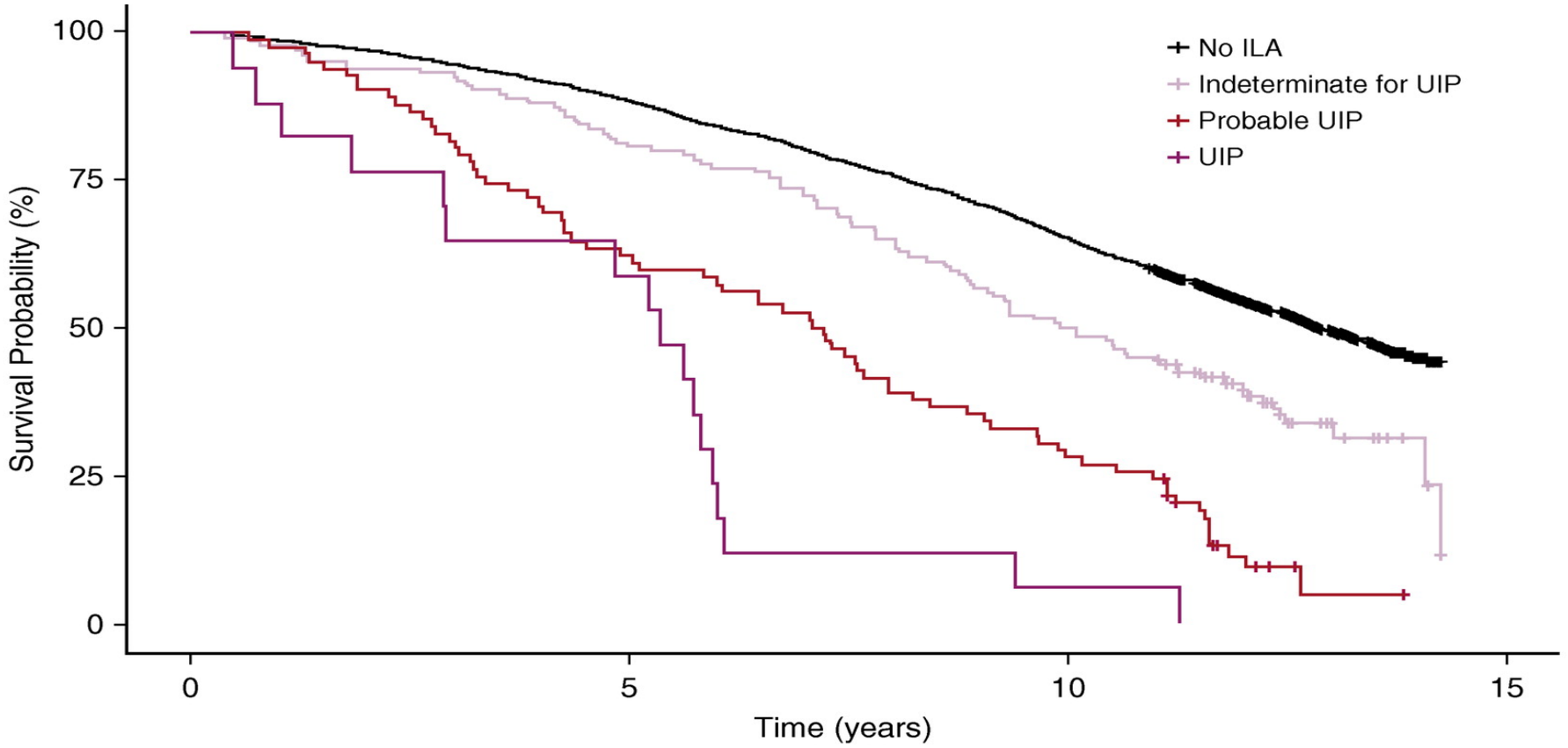
UIP Pattern

UIP Pattern

Indeterminate for UIP Pattern



CT Patterns and Outcomes



Putman, Am J Respir Crit Care Med, 2019; 200:175-183

Need for a disease activity measure

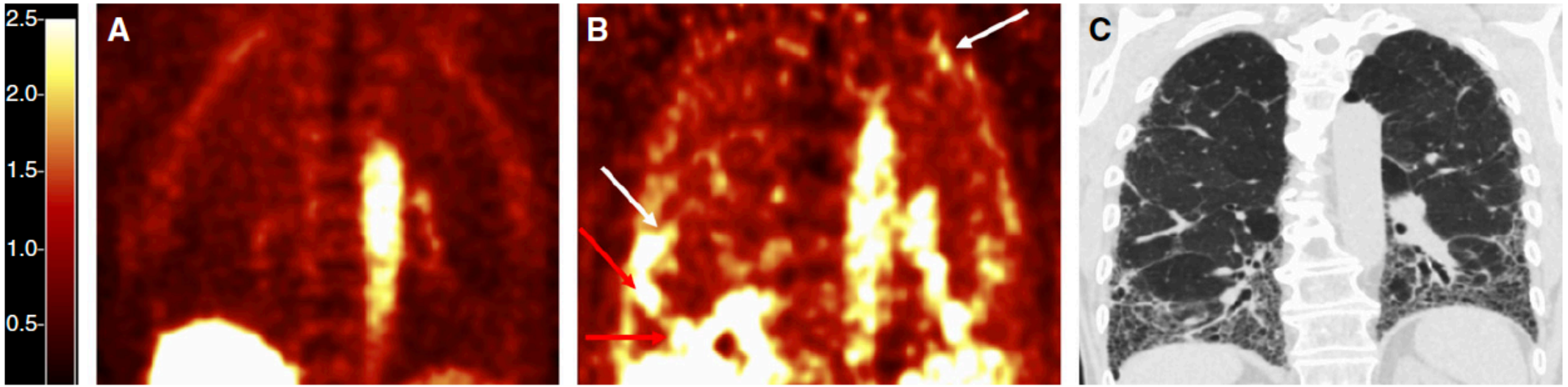
- Current methods of monitoring (CT and PFTs) measure the end result of scarring and inform as to disease progression over time
  - Do not inform as to disease activity at any one measure
- **A measure of disease activity in IPF would:**
  - **Improve clinical care by enabling treatment plans to be tailored for an individual and enhancing prognostication**
  - **Advance clinical trials by enabling cohort enrichment strategies and enrolling of patients most likely to have a benefit from treatment**

Type I Collagen Imaging

- Accumulation of type I collagen is the hallmark of fibrosis
- Current imaging approaches (e.g. CT) only can visualize the end result of collagen deposition
- **^{68}Ga-CBP8** is a PET probe that **binds type I collagen** with high specificity (Désogere et al, *Sci Trans Med*. 2017)
- **^{68}Ga-CBP8** can **detect treatment response** to anti-fibrotic therapy in a mouse model of pulmonary fibrosis (Désogere et al, *Sci Trans Med*. 2017)
- Pre-clinical data suggest that **^{68}Ga-CBP8** preferentially binds freshly synthesized as opposed to mature collagen and thus may be ideal imaging marker of **disease activity**

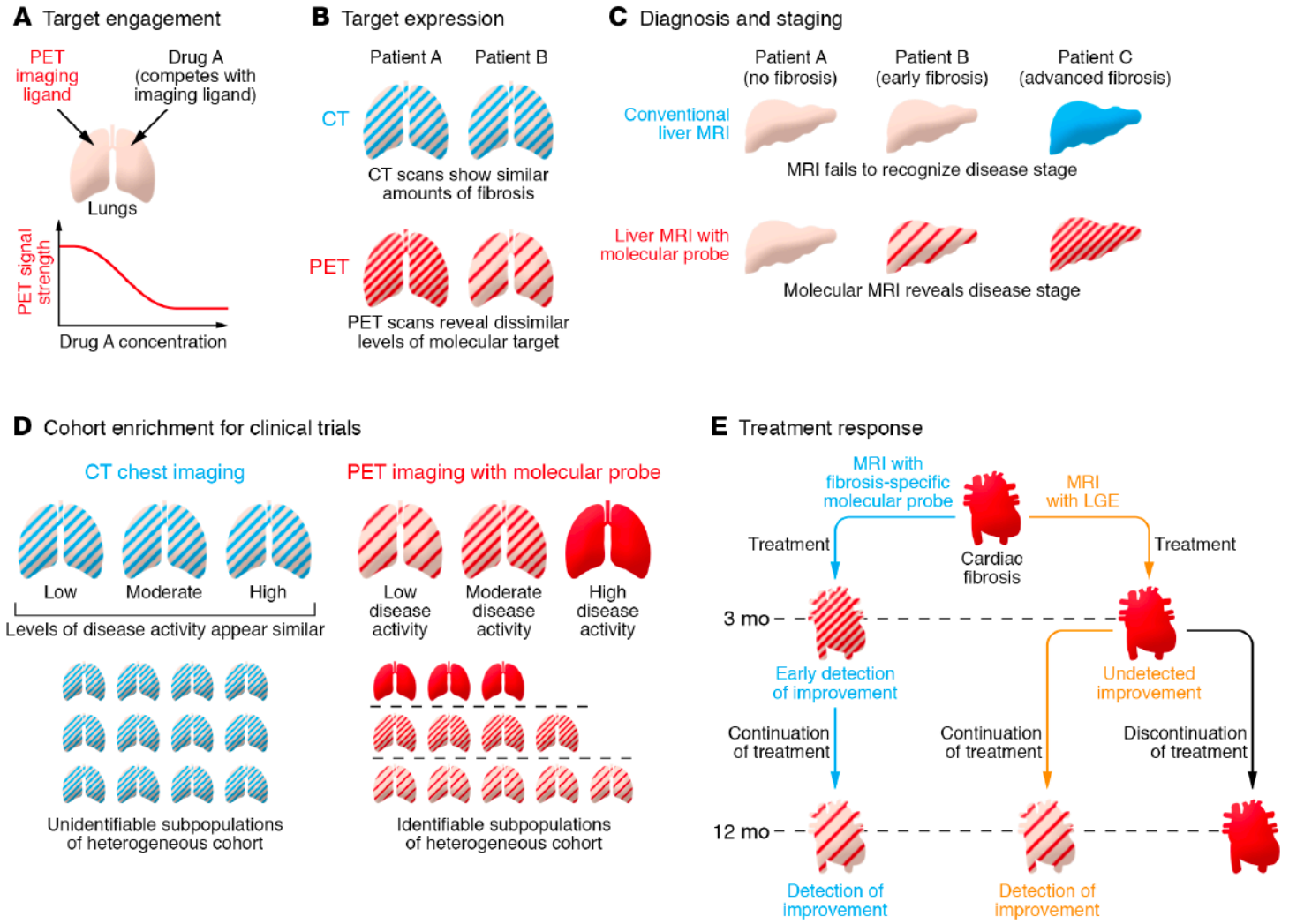
^{68}Ga-CBP8 Detects Increased Collagen in IPF patients and *Active Disease*

Healthy Volunteer | **IPF Patient** | **CT of IPF Patient**



Montesi et al, *Am J Respir Crit Care Med*. 2019

Future Directions



Montesi et al, *J Clin Invest.* 2019

Questions