Top 5 ILD Stories of 2015

What I Thought You Might Be Interested in Hearing About

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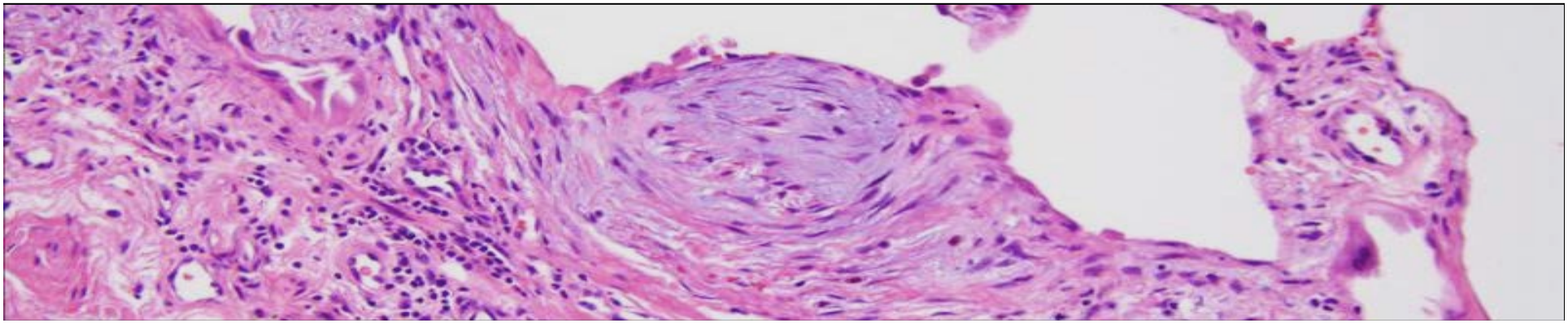
Disclosures

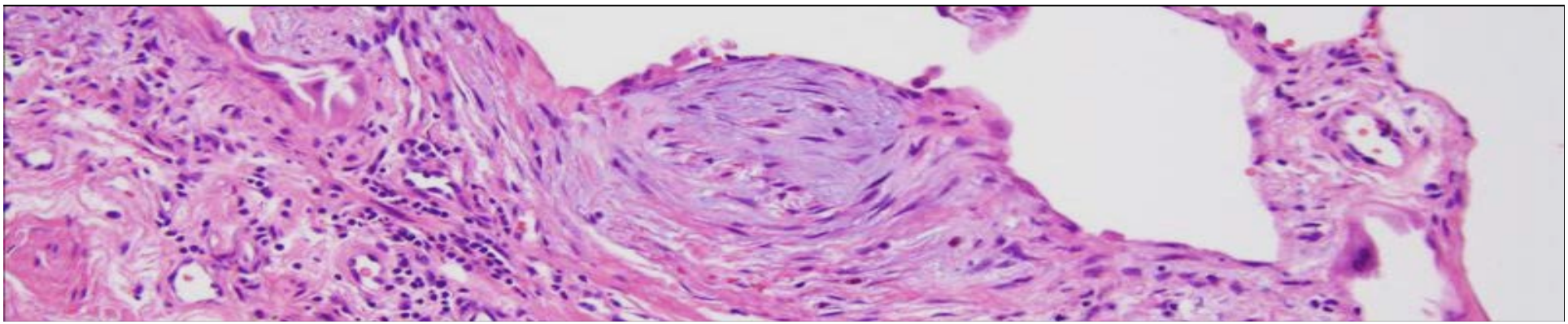
- I have financial relationships with the following organizations:
  - Research Grants and Contracts:
    Boehringer-Ingelheim, NIH/NHLBI
  - Consulting Contracts:
    AstraZeneca/MedImmune, Bayer, Biogen, FibroGen, Five Prime, Genoa, Gilead, GlaxoSmithKline, Mesoblast, Moerae Matrix, Patients Like Me, Pfizer, Promedior, Prometic, Pulmonary Fibrosis Foundation, Roche/ Genentech/InterMune

Top 5 ILD Stories of 2015

- IPAF
- MUC5B
- GERD
- Transbronchial cryobiopsy (I couldn't leave it completely out!)
- New therapies for IPF



Interstitial Fibrosis with Autoimmune Features (IPAF)



The clinical problem

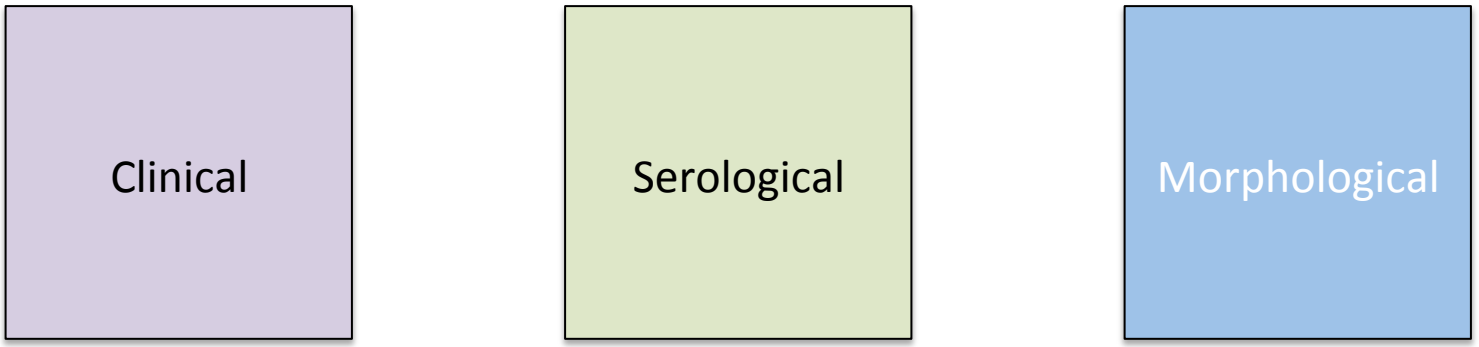
- Many patients with idiopathic ILD have an "autoimmune flavor".
- There is no unified terminology or criteria by which to identify these patients:
  - "Undifferentiated CTD"
  - "Lung-dominant CTD"
  - "Autoimmune-featured ILD"
- A consensus terminology and definition was needed for research to proceed efficiently.

Fischer Arthritis Care & Research 2014

"IPAF" criteria

- Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) *and* exclusion of alternative etiologies *and* does not meet criteria of a defined CTD *and*:

- At least <u>one</u> feature from at least <u>two</u> of these domains:



Fischer. ERJ 2015, In Press

Morphologic domain

Suggestive radiology patterns by HRCT

- NSIP
- OP
- NSIP with OP overlap
- LIP

Multicompartment involvement

- Unexplained pleural or pericardial effusion/thickening
- Unexplained airways disease
- Unexplained pulmonary vasculopathy

Histopathology patterns or features by surgical lung biopsy

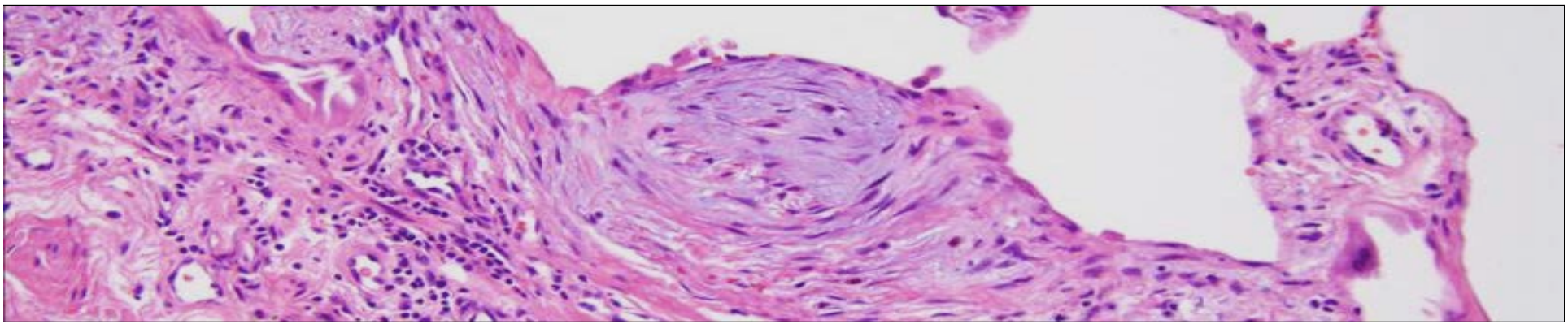
- NSIP
- OP
- NSIP with OP overlap
- LIP
- Interstitial lymphoid aggregates with germinal centers
- Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)

Fischer. ERJ 2015, In Press

Summary

- IPAF encompasses individuals with ILD and features suggestive of a CTD.
- Not intended to be a guide for clinical care.
- Prospective studies needed to understand clinical significance of this entity.

MUC5B

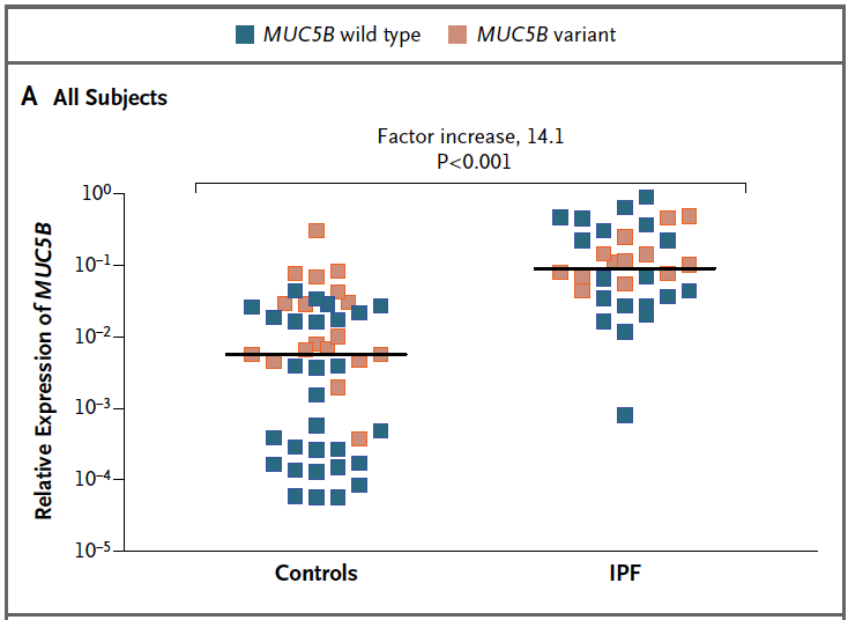


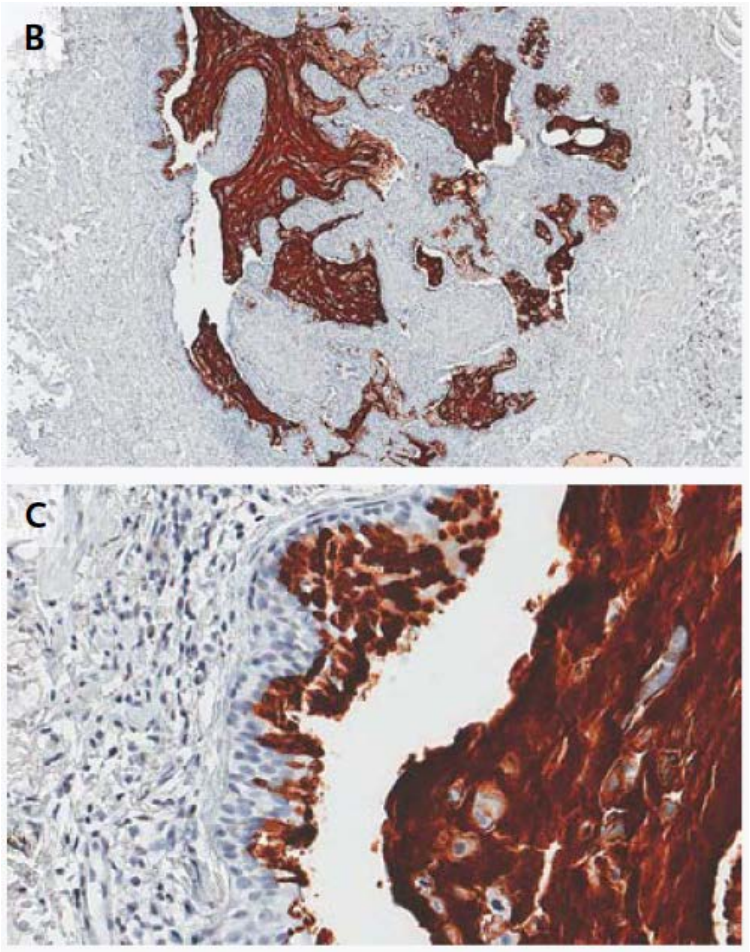
MUC5B Polymorphism

- MUC5B encodes a secreted airway mucin.
- A SNP in the MUC5B promoter is associated with risk of IPF ($p = 0.00004$).
  - This SNP is common in the general population (~9%) and present in 34-38% of IPF patients.
  - Associated with increased MUC5B expression in controls but not in IPF patients (see figure A next slide).
  - MUC5B accumulates in "honeycomb cysts" (see figure B/C next slide).

Seibold. NEJM 2011;364:1503

MUC5B expression and location

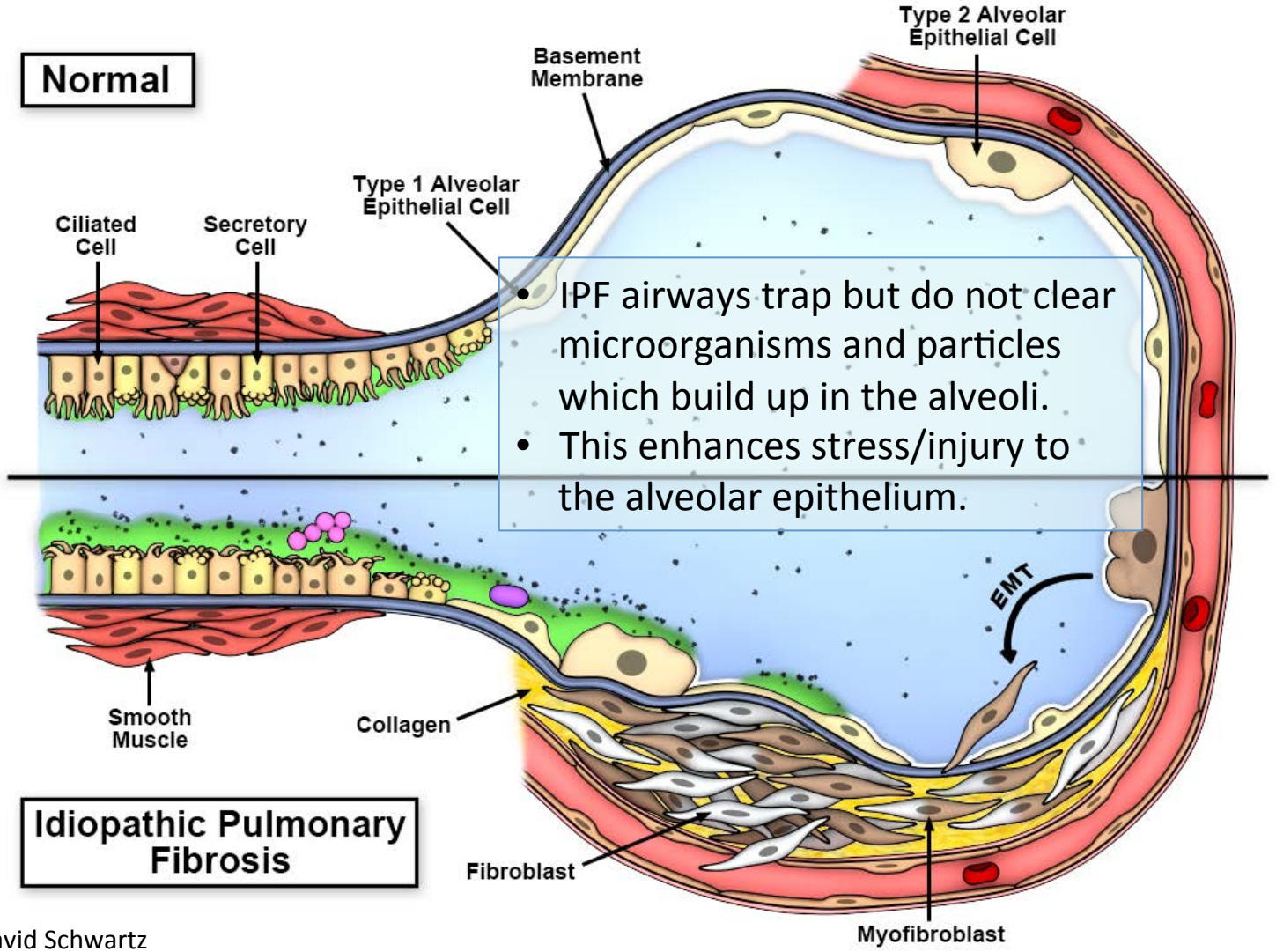




Seibold. NEJM 2011;364:1503

Conceptual Model

- Increased MUC5B secretion leads to increased mucus in distal airways and impaired muco-ciliary clearance



- IPF airways trap but do not clear microorganisms and particles which build up in the alveoli.
- This enhances stress/injury to the alveolar epithelium.

Modified from slide courtesy of David Schwartz

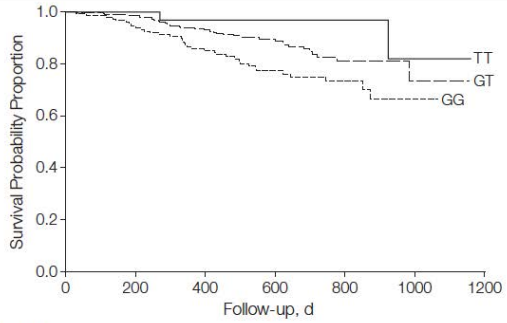
MUC5B Status and Outcomes

- Retrospective study of two cohorts of IPF patients (n = 438 and n = 148).
- Risk allele (T) frequency was ~60% for heterozygous genotype (GT) and ~6% for homozygous genotype (TT).
- Patients with GT or TT genotype had an improved survival in both cohorts.
  (see figures next slide)

Peljto. JAMA 2013;309:2232

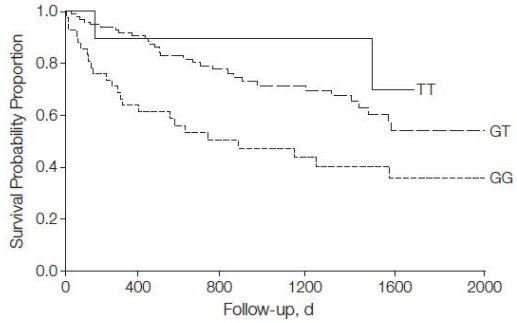
MUC5B Status and Outcomes

Figure 1. Kaplan-Meier Survival Curves by *MUC5B* Genotypes, INSPIRE Cohort



No. at risk						
TT	31	26	21	11	3	0
GT	255	224	122	55	8	0
GG	140	115	67	36	5	0

Figure 2. Kaplan-Meier Survival Curves by *MUC5B* Genotypes, Chicago Cohort



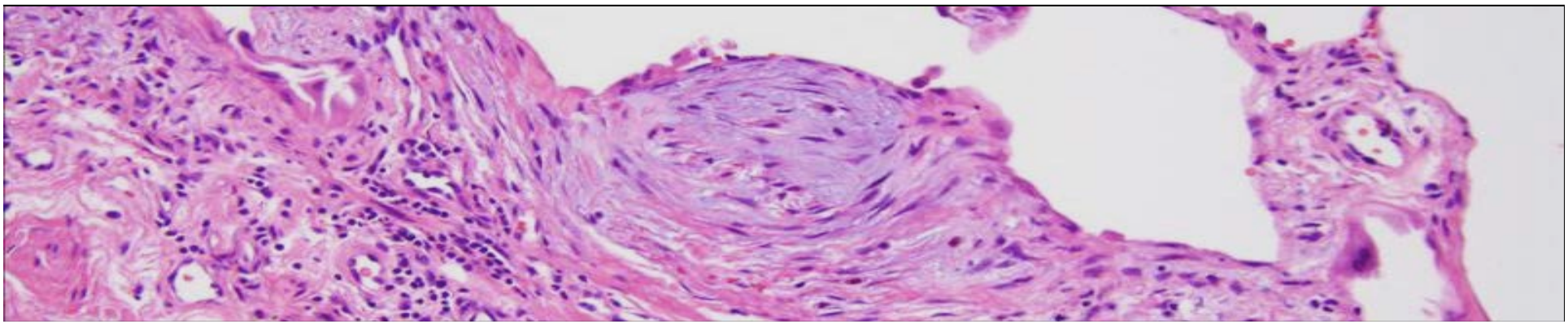
No. at risk					
TT	7	4	4	1	0
GT	78	47	35	15	1
GG	24	16	10	7	1

Peljto. JAMA 2013;309:2232

Summary

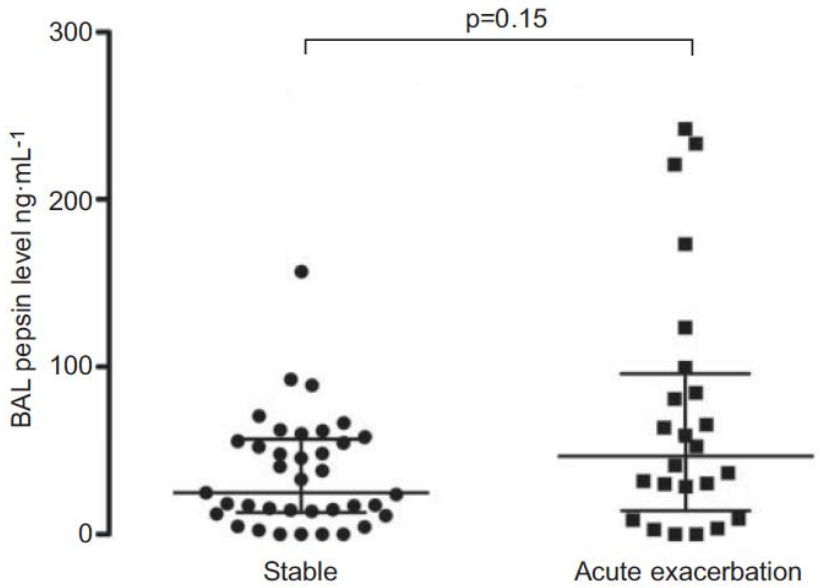
- A polymorphism in MUC5B is associated with IPF.
- The mechanism is unclear but may involve impaired clearance and increased epithelial cell stress.
- Subjects with one or more MUC5B risk alleles have improved survival.
- MUC5B status may prove to have clinically important predictive and prognostic application.

Gastroesophageal reflux disease (GERD)



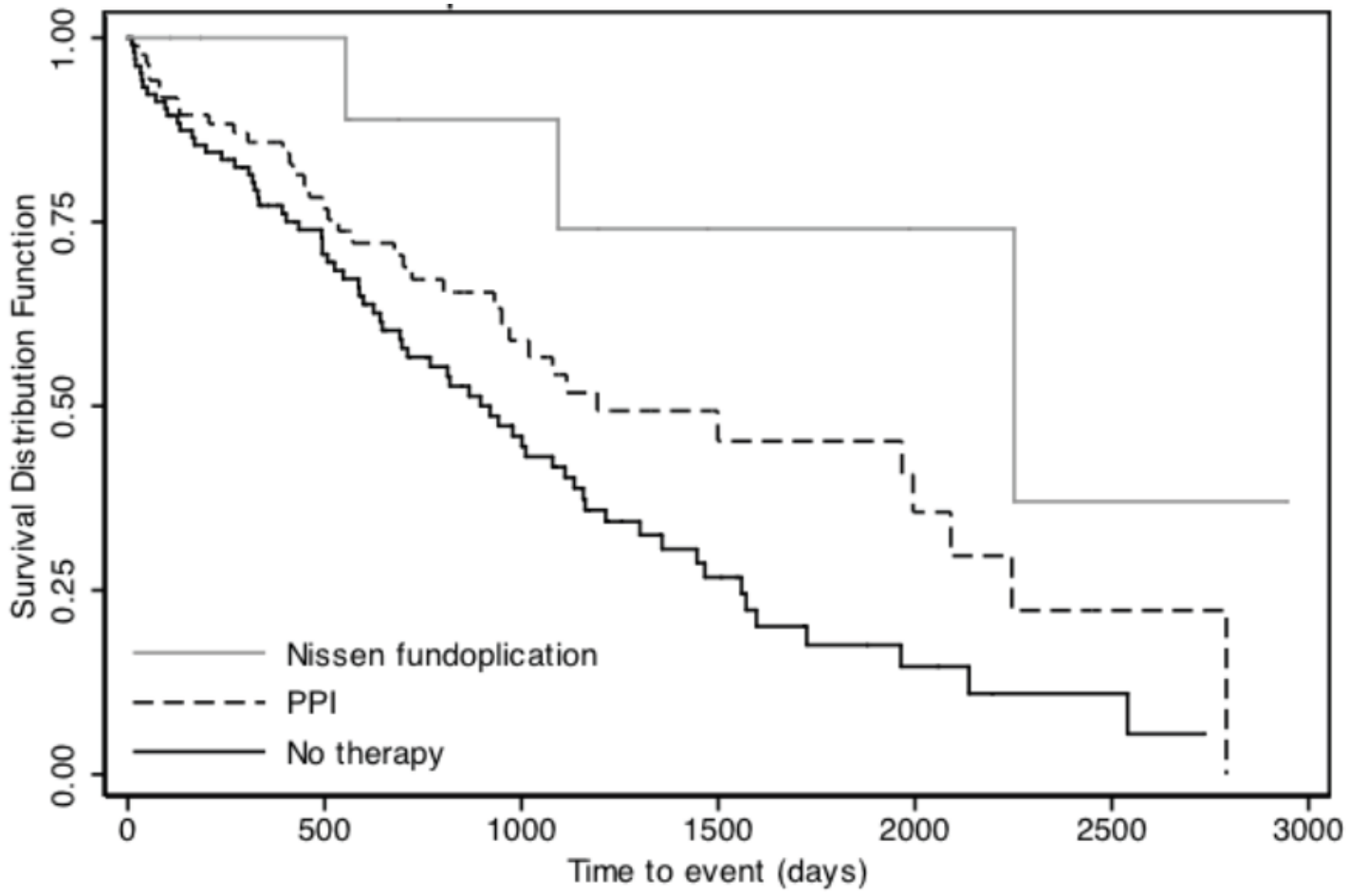
Evidence of Pepsin in IPF BAL

- Study of 30 stable IPF and 24 acute exacerbation of IPF cases who underwent bronchoscopy
  - Bronchoalveolar lavage pepsin present in most cases
  - Pepsin level was associated with acute exacerbation status ($p = 0.04$)



Lee et al. ERJ 2012;39:352

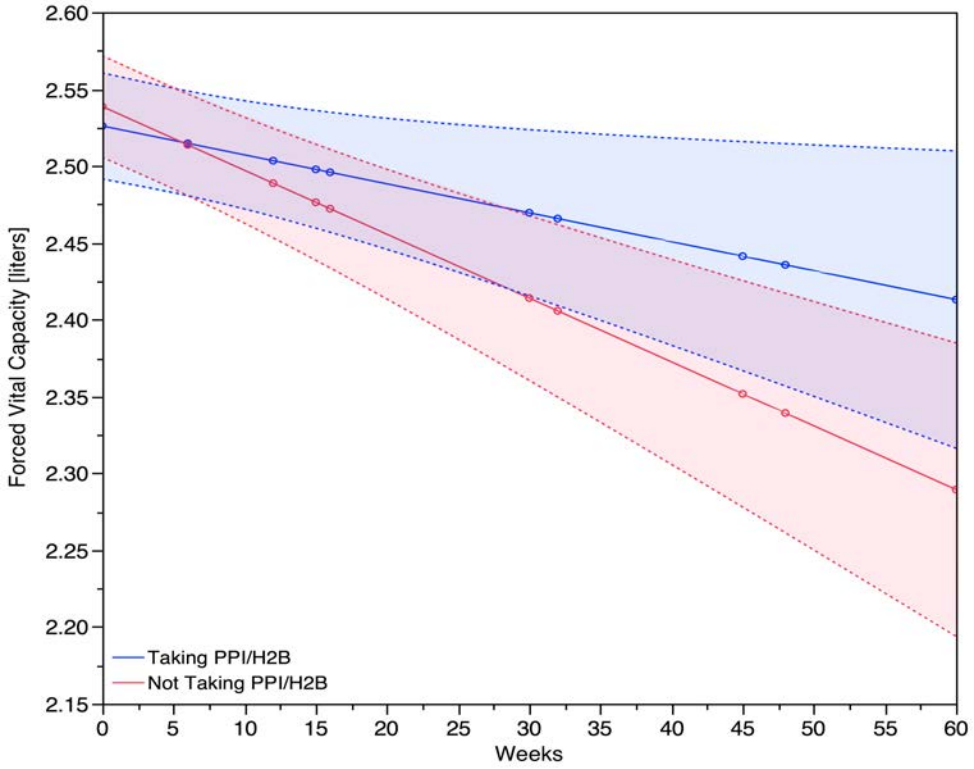
Effect of GERD Treatment on Survival



Modified from Lee et al. AJRCCM 2011;184:1390

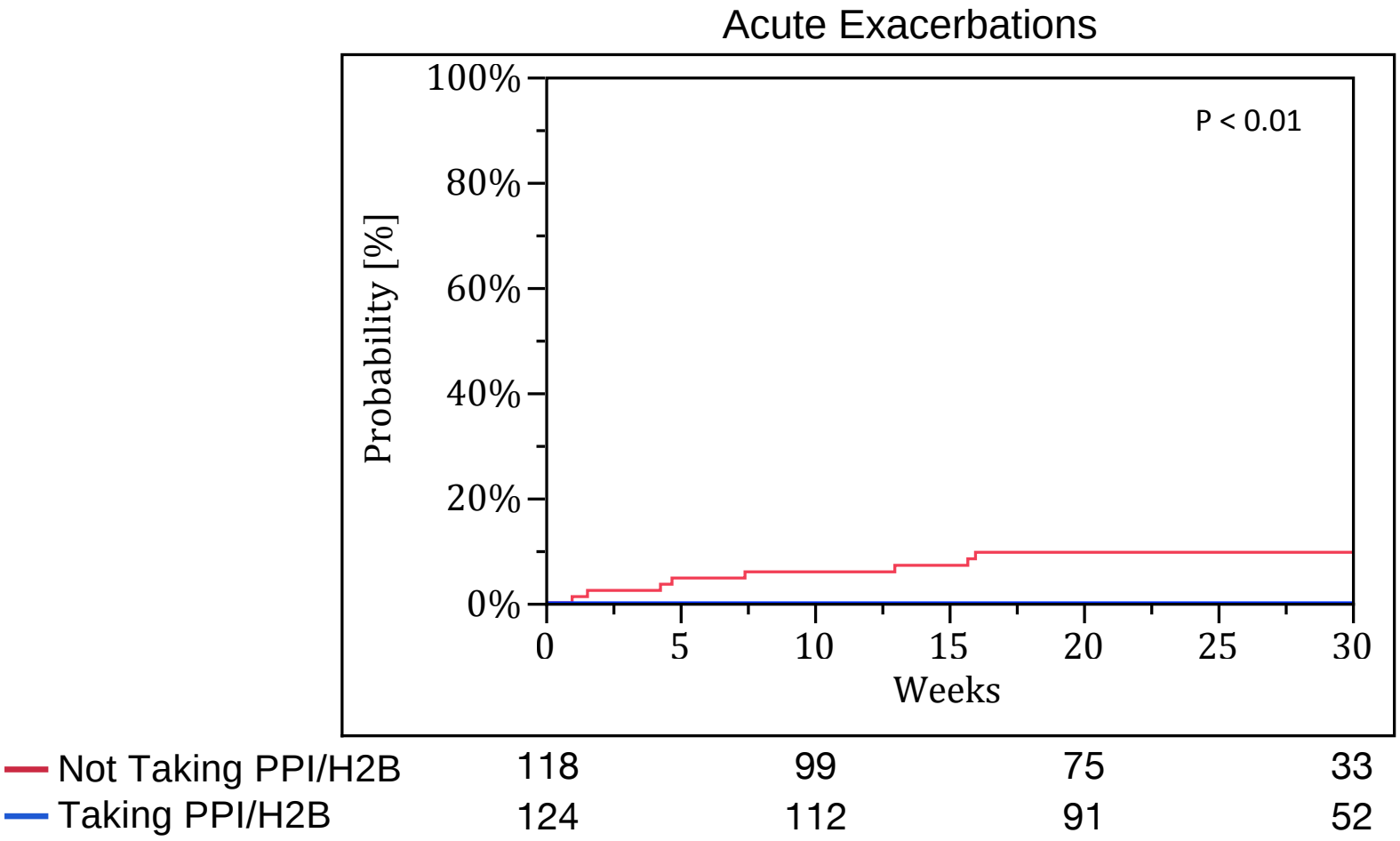
Effect of GERD Treatment on FVC Change

- Secondary data analysis of 242 placebo patients from IPFnet
- FVC decline by treatment group (PPI/H2B or not)



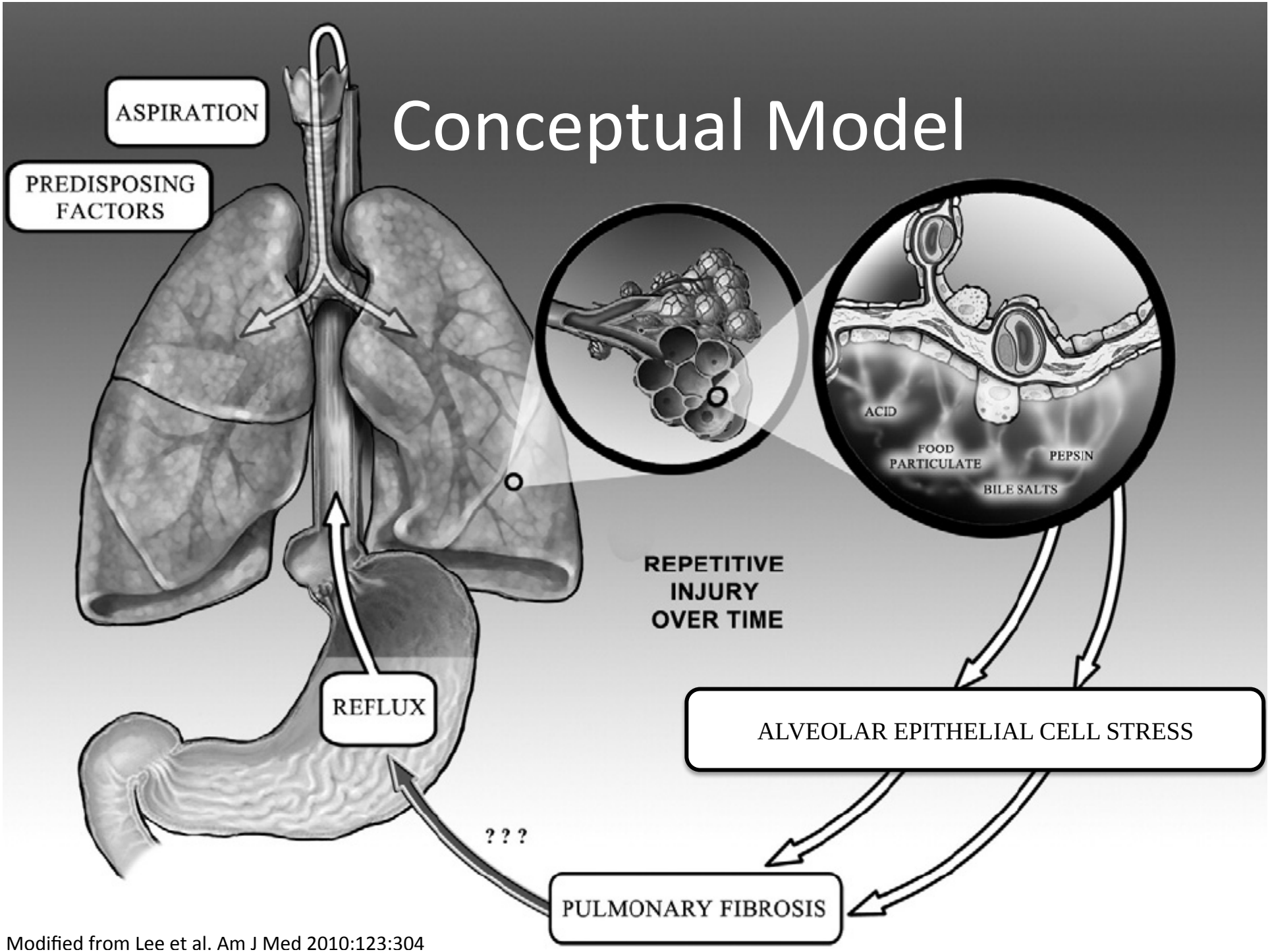
Lee et al. Lancet Resp Med 2014

Effect of GERD Treatment on AEX



Lee et al. Lancet Resp Med 2014

Conceptual Model

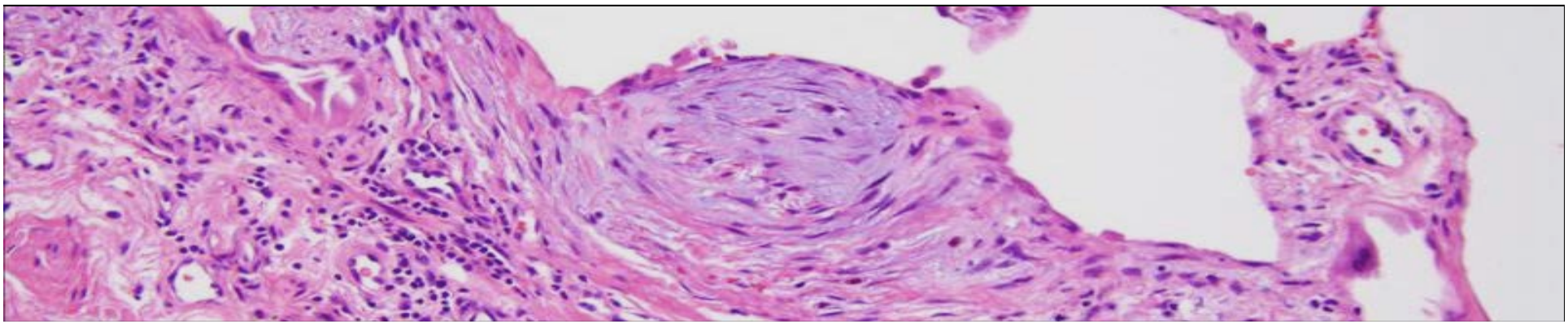


Modified from Lee et al. Am J Med 2010:123:304

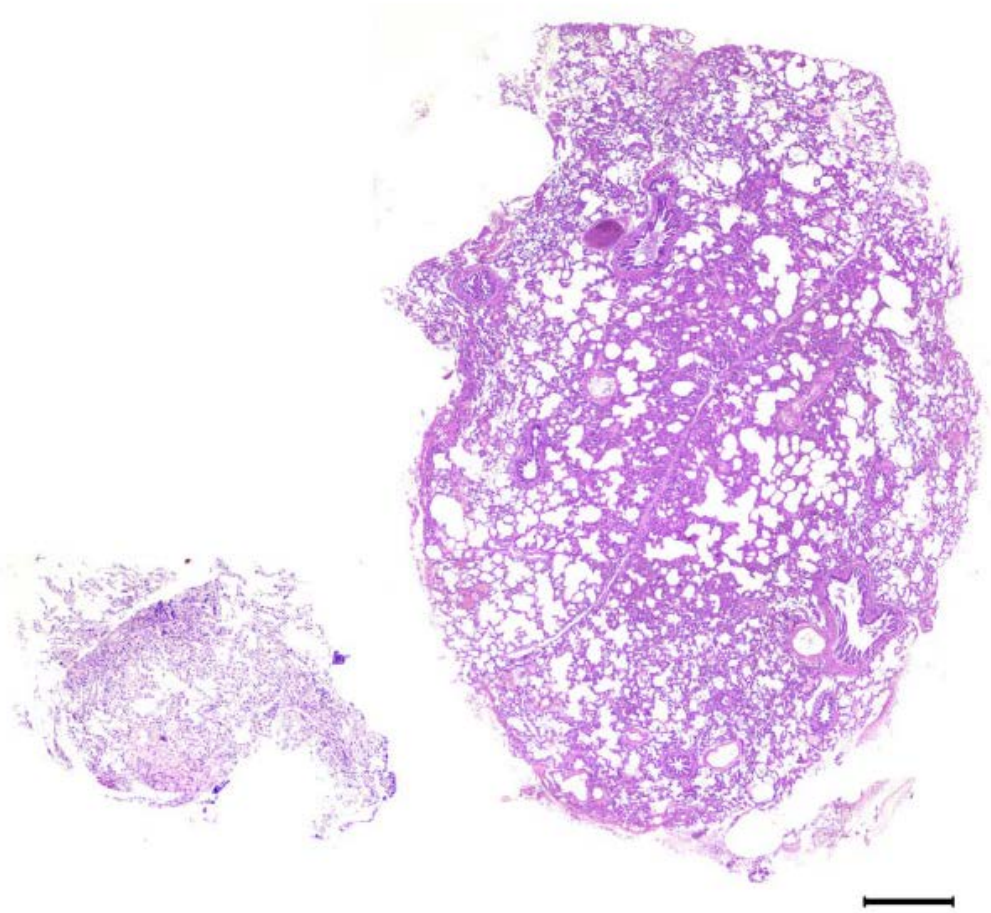
Summary

- GERD is common in IPF and appears to result in microaspiration of pepsin and other elements.
- Treatment of GERD may slow disease progression, prevent exacerbation, and prolong survival.
- Prospective randomized clinical trial now underway to test this hypothesis.

Transbronchial Cryobiopsy



Transbronchial cryobiopsy



Pajares. Respirology 2014;19:900

Transbronchial Cryobiopsy

Courtesy of Drs. Casoni, Tomassetti and Poletti. GB Morgagni Hospital, Forli, Italy

Diagnostic Yield

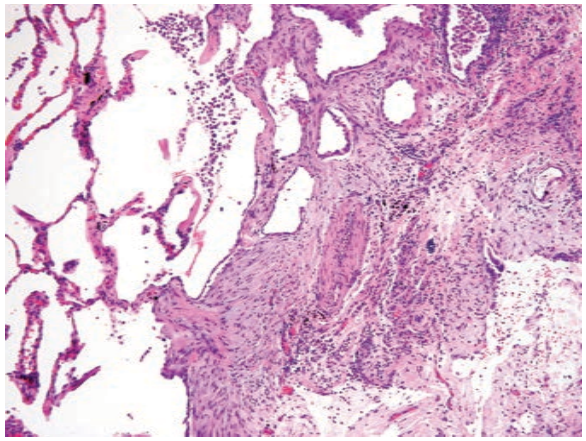
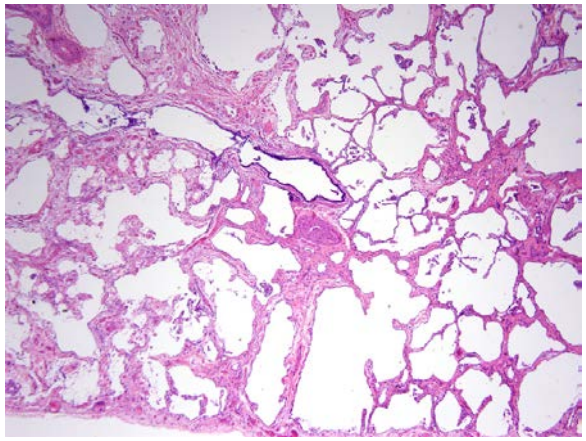
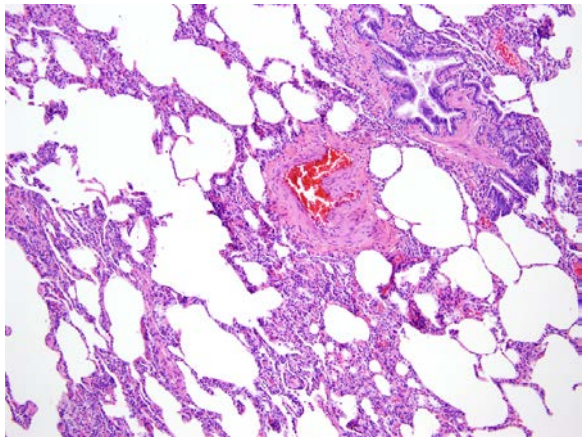
Study	"Diagnostic yield"
Kropski et al. PLoS ONE 2013;8:e78674	20/25 (80%)
Pajares et al. Respirology 2014;19:900	20/39 (52%)
Casoni et al. PLoS ONE 2014;9:e86716	33/69 (48%)
Hagmeyer et al. Clin Respir J 2015;epublished	23/32 (72%)
OVERALL EXPERIENCE	**96/165 (58%)**

Safety

Study	Bleeding	Pneumothorax
Kropski et al. PLoS ONE 2013;8:e78674	0/25 (0%)	0/25 (0%)
Pajares et al. Respirology 2014;19:900	22/39 (56%) Managed endoscopically	3/39 (8%)
Casoni et al. PLoS ONE 2014;9:e86716	1/69 (1%) Prophylactic Fogarty use	19/69 (28%) 14 required chest tube
Hagmeyer et al. Clin Respir J 2015;epublished	17/25 (53%) 2 required rigid bronch	6/25 (19%) All required chest tube
OVERALL EXPERIENCE	**40/165 (24%)**	**28/165 (17%)**

The Problem

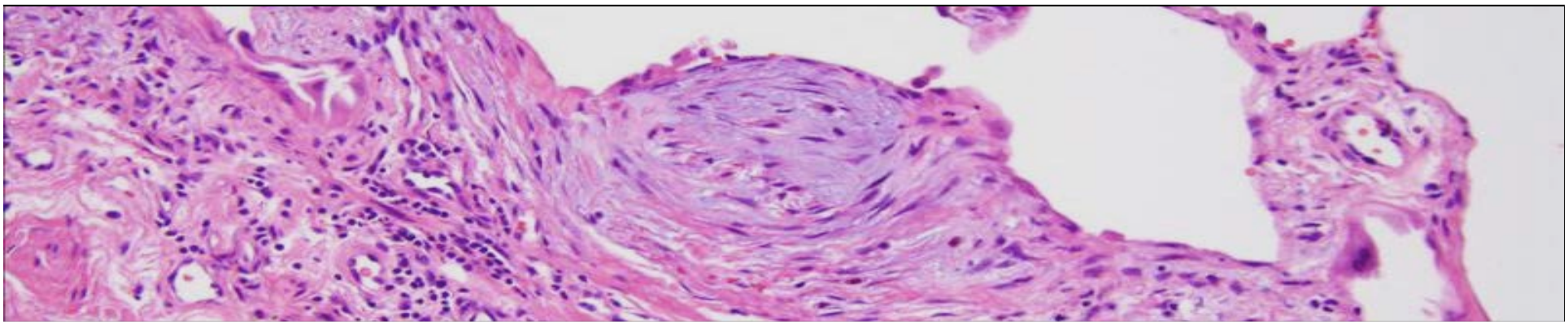
- No gold standard
  - We don't know what a surgical lung biopsy in patients undergoing cryobiopsy would show.
  - We don't know how the surgical lung biopsy in these patients might change the final multidisciplinary diagnosis.

Summary

- Transbronchial cryobiopsy is a promising new approach to lung biopsy.
- The diagnostic accuracy and safety appear good, but it is unclear how they compare to VATS surgical lung biopsy.
- Two small trials are underway to compare transbronchial cryobiopsy and VATS approaches.

New Therapies for IPF

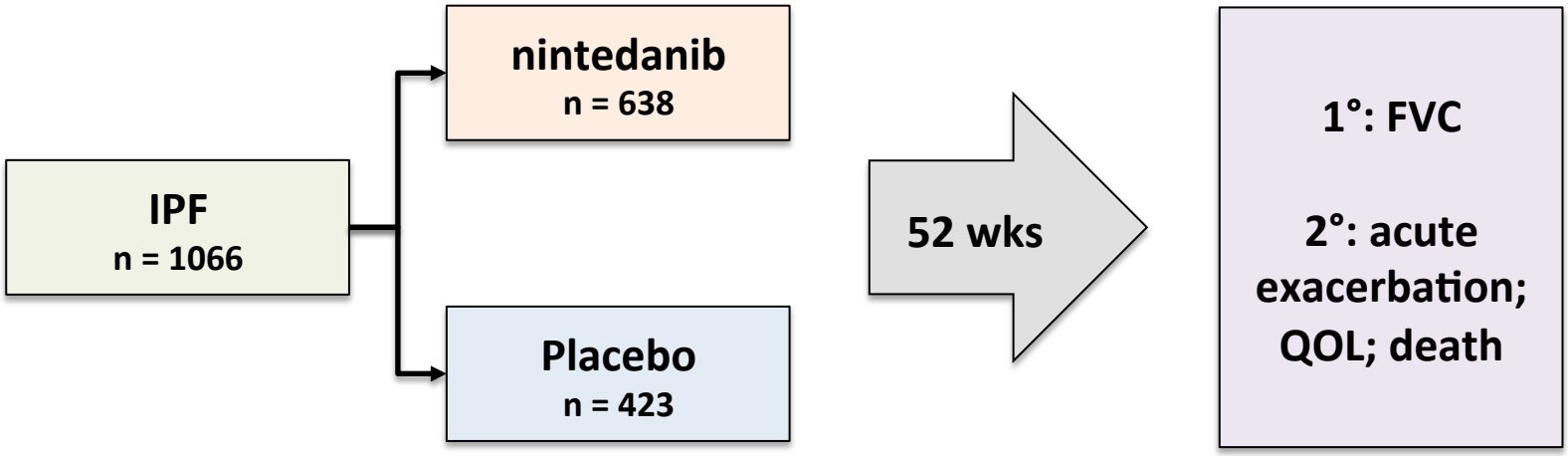


NINTEDANIB

Richeldi et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. NEJM 2014;370:2071

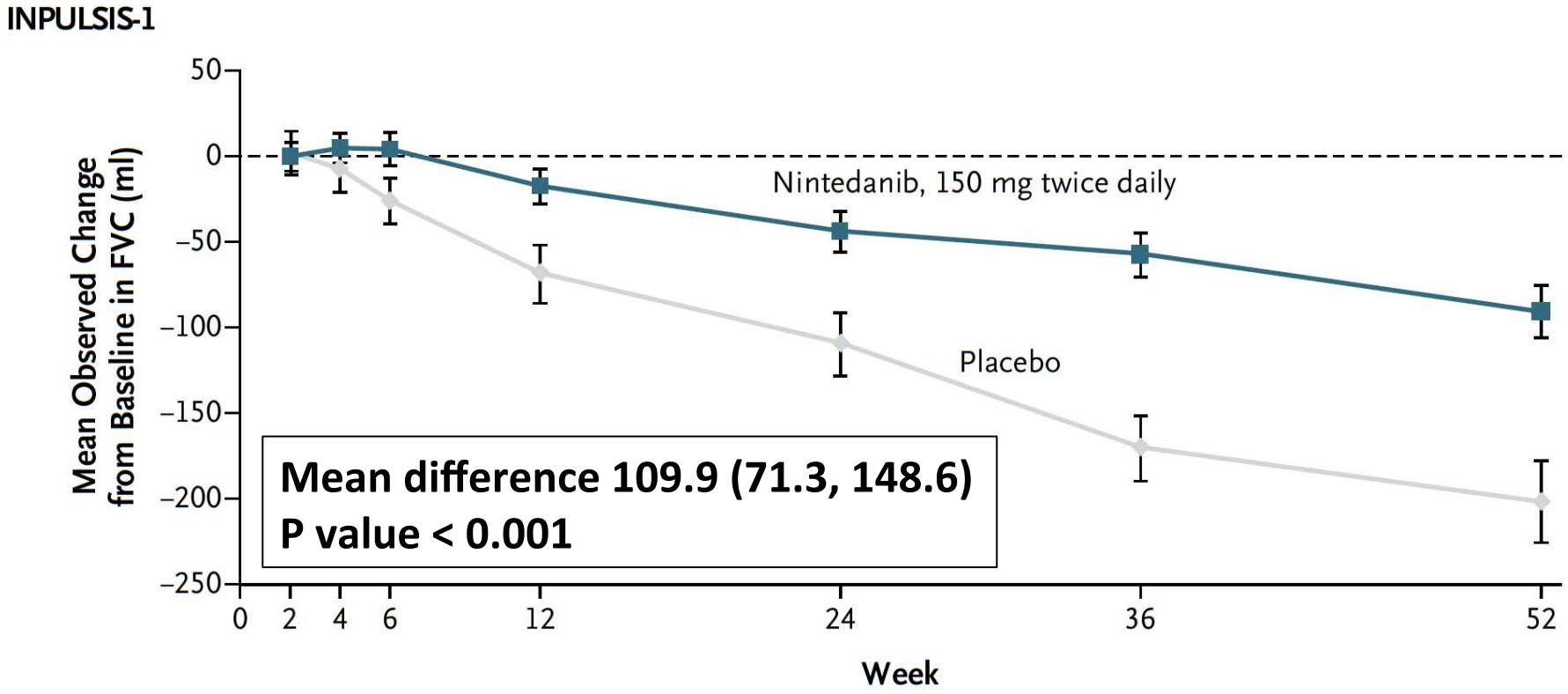
INPULSIS: Study design

- Enrolled 1066 patients with IPF/likely IPF
- Randomized (3:2) to nintedanib/placebo for 52 wks
  - Primary endpoint: Change in FVC
  - Secondary endpoints: time to acute exacerbation; quality of life (SGRQ); categorical change in FVC; death (any cause, respiratory)



Richeldi NEJM 2014;370:2071

INPULSIS: 1° Endpoint



Richeldi NEJM 2014;370:2071

INPULSIS: Safety and tolerability

- No difference in SAEs (3x LFT increase 5.1% vs 0.7%)
- Myocardial infarction in 1.5% (0.4% in placebo)
- Treatment discontinuation 23.7-25.2% vs 17.6-20.1%

Adverse event (combined TOMORROW and INPULSIS I/II)	Nintedanib (n = 723)	Placebo (n = 508)
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain	15%	6%
Vomiting	12%	3%
Decreased appetite	11%	5%

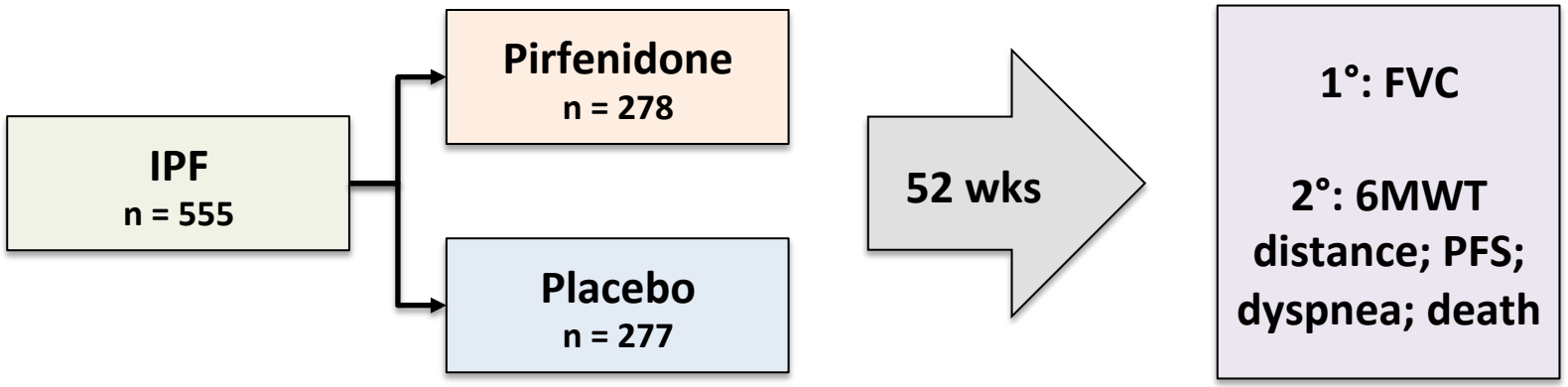
Richeldi NEJM 2014;370:2071
www.ofev.com/hcp/prescribing-information

PIRFENIDONE

King et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. NEJM 2014;370:2083

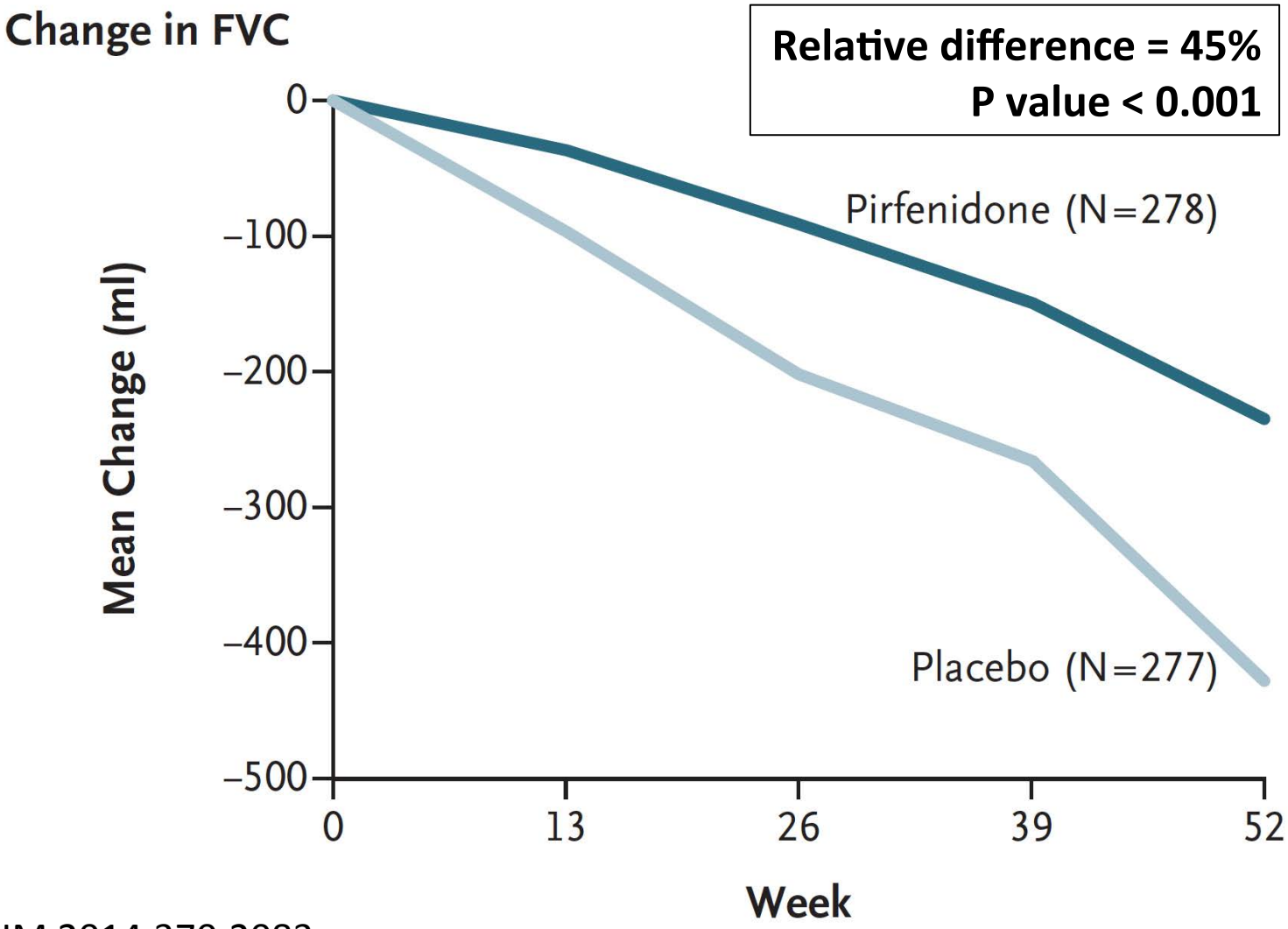
ASCEND: Study design

- Enrolled 555 highly-selected patients with IPF
- Randomized to pirfenidone or placebo for 52 weeks
  - Primary endpoint: Change in FVC
  - Secondary endpoints: 50 meter decline in 6MWT; 20 point increase in UCSD dyspnea score; PFS (10% FVC decline, 50 meter 6MWT decline, or death); death (any cause and related to IPF)



King. NEJM 2014;370:2083

ASCEND: 1° Endpoint



King. NEJM 2014;370:2083

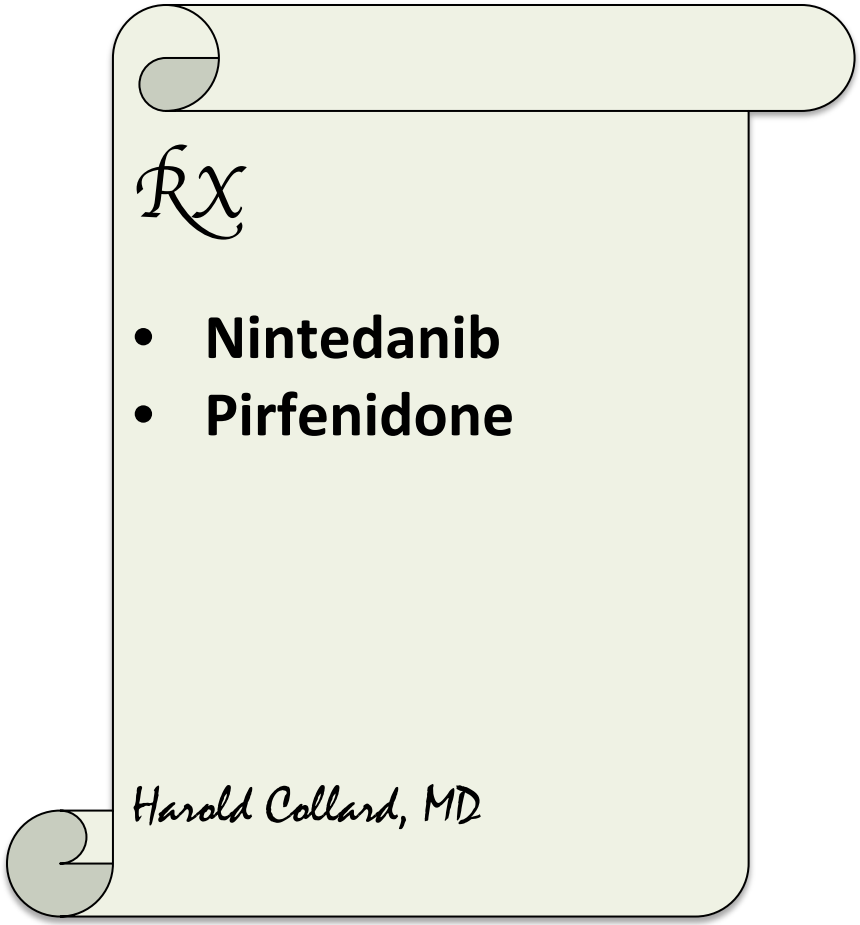
ASCEND: Safety and tolerability

- No difference in SAEs (3x LFT increase 2.9% vs 0.7%)
- Treatment discontinuation in 14.4% vs 10.8%

Adverse event (combined ASCEND and CAPACITY I/II)	**Pirfenidone** (n = 623)	**Placebo** (n = 624)
Nausea	36%	16%
Rash	30%	10%
Diarrhea	26%	20%
Fatigue	26%	20%
Headache	22%	19%

King. NEJM 2014;370:2083
www.esbriethcp.com/content/adverse-reactions

Summary



- Both nintedanib and pirfenidone slow disease progression as measured by change in FVC over time.
  - Appear to have equal efficacy
  - Appear to have equal safety
  - Differing tolerability profiles

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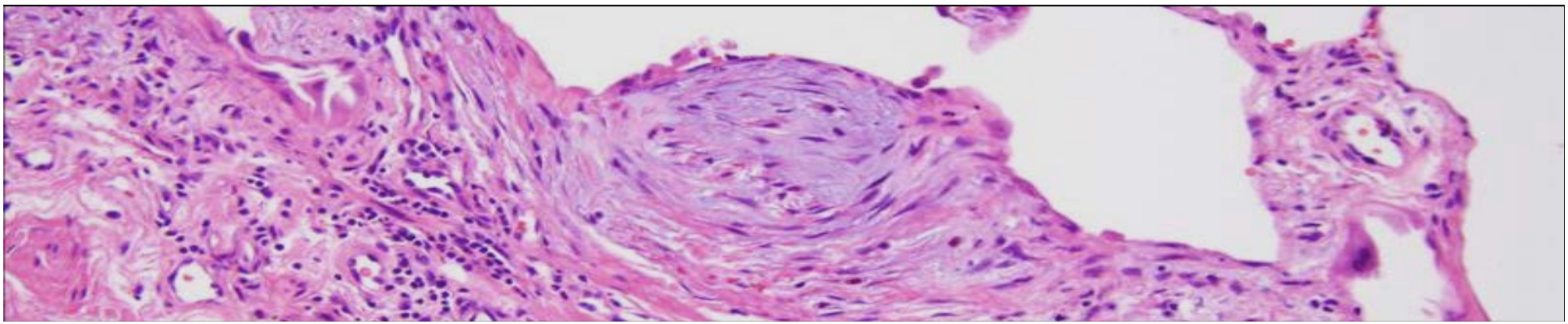

Thank You

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