IPAF (Interstitial Pneumonia with Autoimmune Features) Should be Considered as a Distinct Phenotype
: CONs

계명의대 내과
최원일

An official European Respiratory Society/ American Thoracic Society research statement: interstitial pneumonia with autoimmune features

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Eur Respir J 2015; 46: 976–987

Classification criteria for “interstitial pneumonia with autoimmune features”

1. Presence of an interstitial pneumonia [by HRCR or surgical lung biopsy] and,
2. Exclusion of alternative aetiologies and,
3. At least one feature from at least two of these domains;
   A. Clinical domain
   B. Serologic domain
   C. Morphologic domain

Aryeh Fischer et al, Eur Respir J 2015; 46: 976–987

Clinical Domain:

A. Clinical domain

This proposed criteria did not undergo validation prior to the release of the CTD classification criteria, likely because large, high-quality patient cohorts for validation did not exist.

7. Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)

ic Domain

The inclusion of non–Jo-1 antisynthetase antibodies and other myositis-specific or myositis-associated antibodies within the classification of IPAF is perhaps the biggest issue with the current criteria. **Only anti–Jo-1 antibodies were included in the most recent criteria for myositis**

led, homogeneous patterns *or*

2. Rhe
3. Anti-CCP
4. Anti-dsDNA
5. Anti-Ro (SS-A)
6. Anti-La (SS-B)
7. Anti-ribonucleoprotein
8. Anti-Smith
9. Anti-topoisomerase (Scl-70)
10. Anti-tRNA synthetase (*e.g.* Jo-1, PL-7, PL-12; others a , tRS)
11. Anti-PM-Scl
12. Anti-MDA-5

Morphologic domain

C. Morphologic domain
1. Suggestive radiology patterns by HRCT (see text for descriptions):
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
2. Histopathology patterns or fe
   a. NSIP
   b. OP
   c. NSIP

with germinal centres
ytic infiltration (with or without lymphoid follicles)
involvement (in addition to interstitial pneumonia):
ined pleural effusion or thickening
Unexplained pericardial effusion or thickening
c. Unexplained intrinsic airways disease# (by PFT, imaging or pathology)
d. Unexplained pulmonary vasculopathy

Do they wants to select mild or early cases?
Excluding UIP pattern or probable UIP

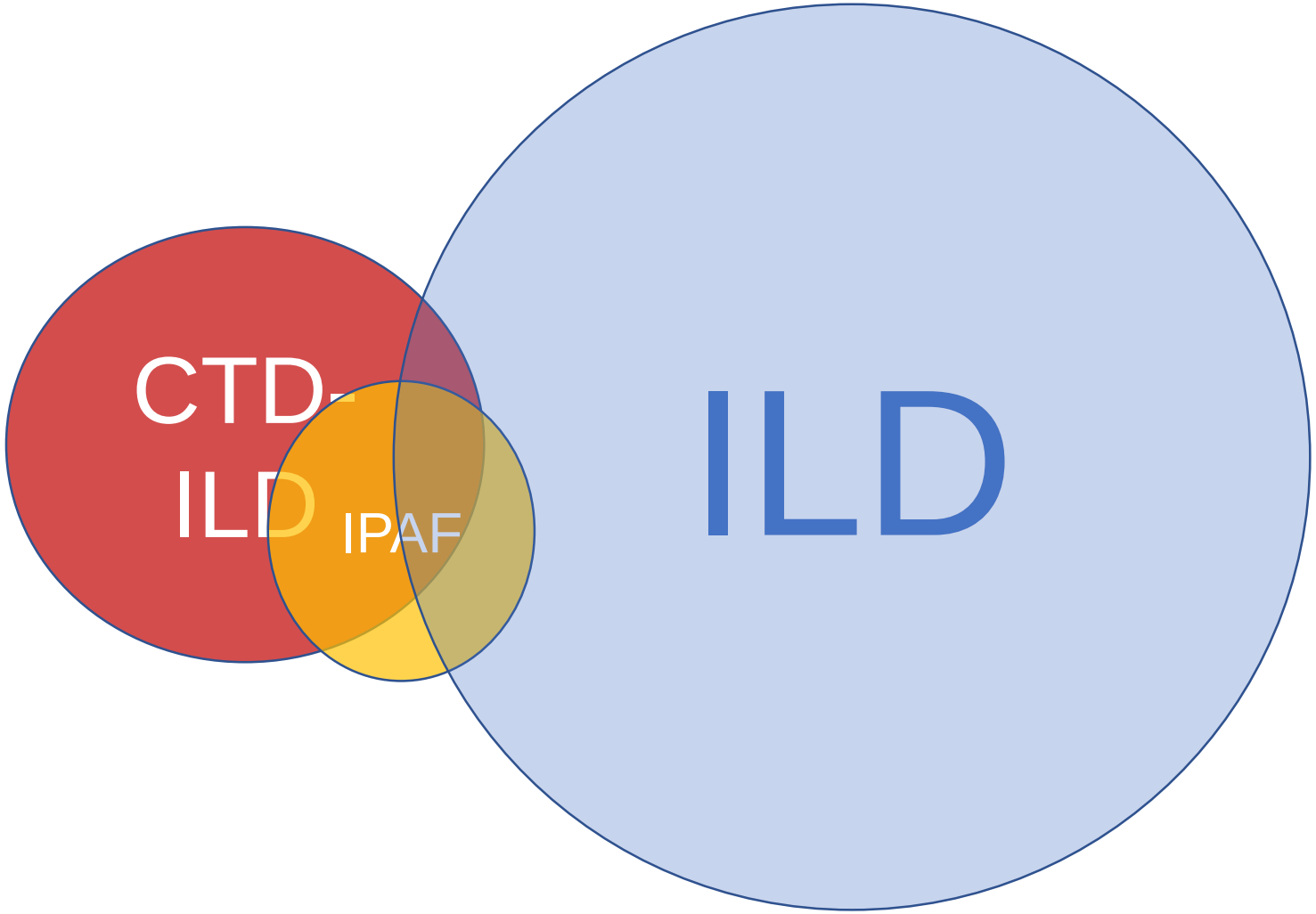
Interstitial pneumonia with autoimmune features: the new consensus-based definition for this cohort of patients should be broadened

Our primary concern with the proposed IPAF criteria is that usual interstitial pneumonia (UIP) is excluded from the morphological domain. This is problematic as UIP is a common pattern of IIP among patients with positive serology for CTD who do not meet criteria for specific CTD and do not meet clinical criteria for IPAF and, thus, are currently labelled as IPF. While this is in keeping with the 2011 criteria for the definition of IPF and may be

Raghu G, et al. ERJ 2016

Disease (DORLAND'S MEDICAL DICTIONARY, 27th Ed)

- Any deviation from or interruption of the normal structure or function of any part, organ, or system (or combination of thereof) of the body that is manifested by a characteristic set of symptoms and signs and whose etiology, pathology, and prognosis may be known or unknown



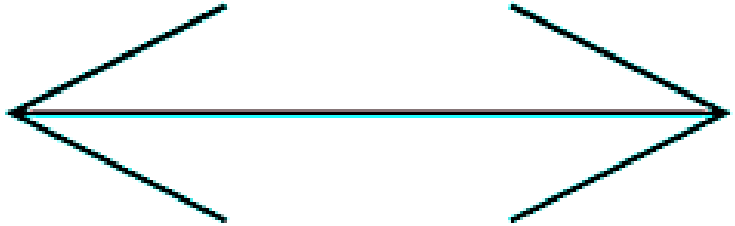
Modified from *Wells et al. ERJ 2018; 17:51*

증명:

- 귀납추론 vs 연역추론

Muller-Lyer Figure

A



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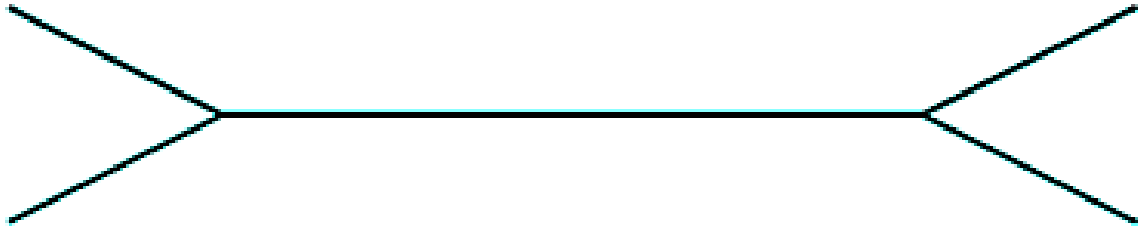


- **Sir Bradford Hill** – 9 criteria (1965년)

1. **Strength**: association의 크기(강도)
2. **Consistency**: 연구 결과가 repeatable
3. **Specificity**: A well-articulated exposure needs to be associated with a well-articulated outcome. Misspecification, misinterpretation, & measurement error 가능성을 최소화 한다
4. **Temporality**
5. **Biological gradient**: a dose-response relationship


Sir Austin Bradford Hill
1897-1991

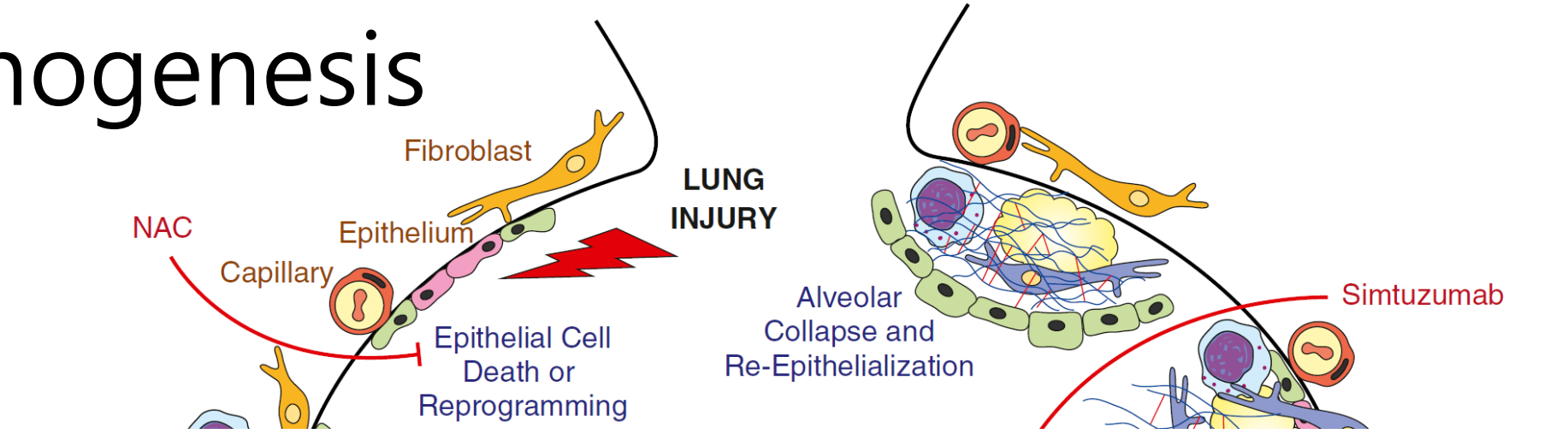
6. **Plausability**: As far as the current science allows, the relationship between the exposure & the outcome must be biologically possible

7. **Coherence**: Data generated from a given study should not seriously conflict with (what is known about) the natural history & biology of the disease process

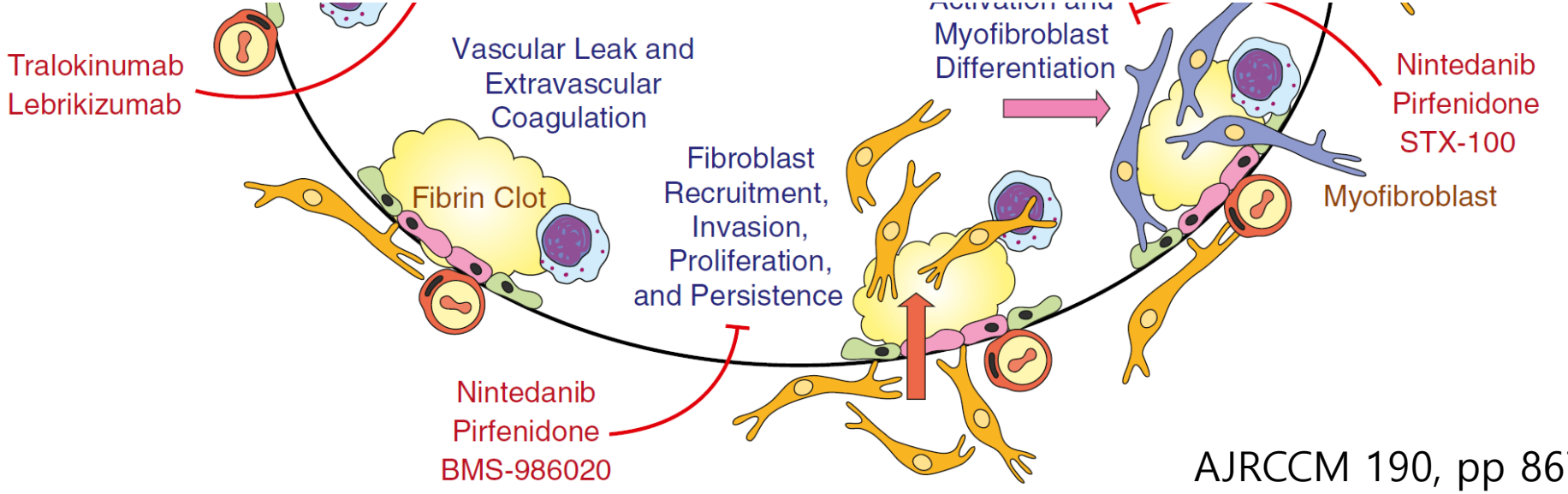
8. **Experiment**: The association should be demonstrable in a controlled manner

9. **Analogy**: Could a claim be made with similar exposure & outcome, or does this finding contradict similar relationship?

Pathogenesis

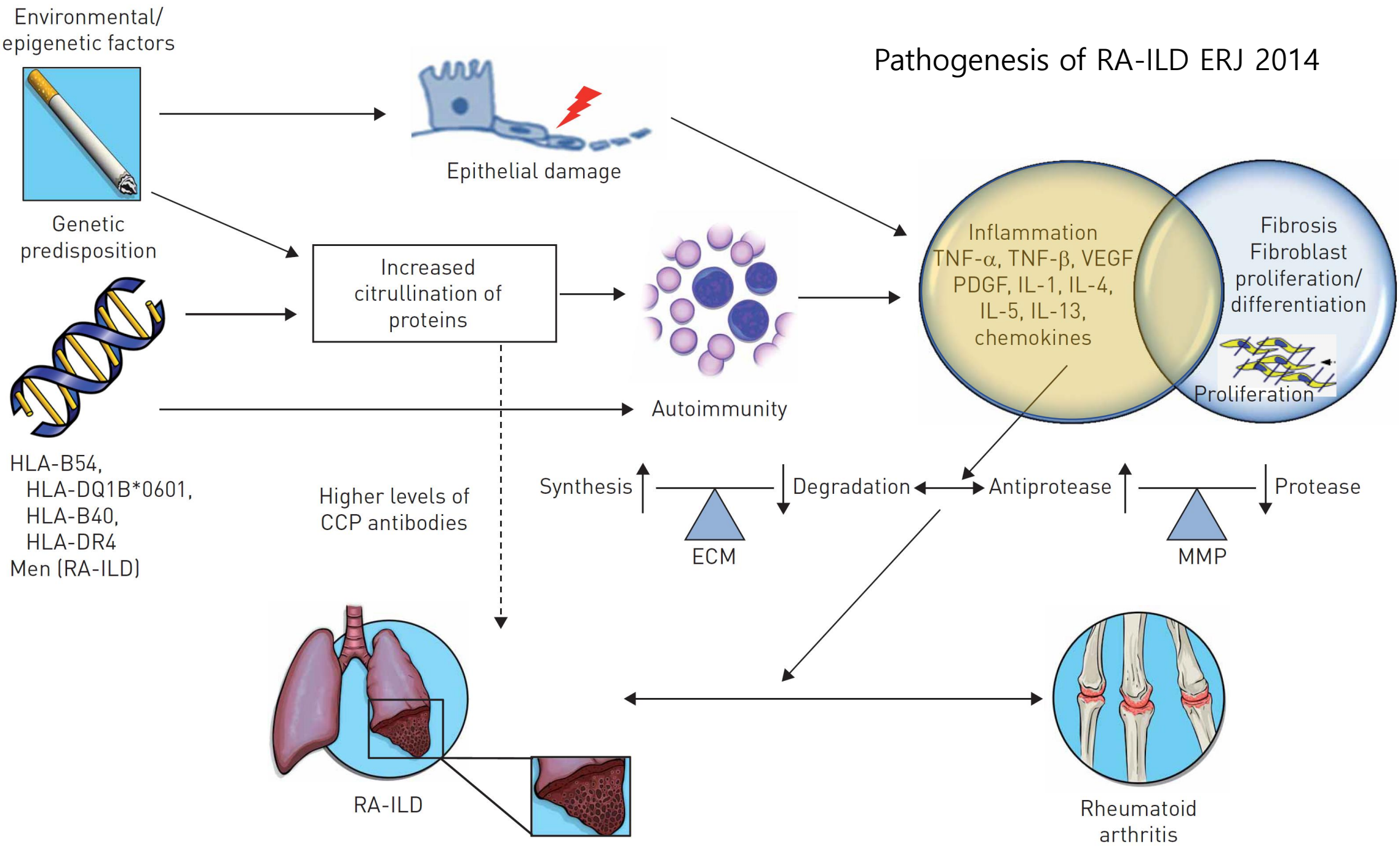


There were no specified the role of ANA or T cells in lung fibrosis



AJRCCM 190, pp 867–878, 2014

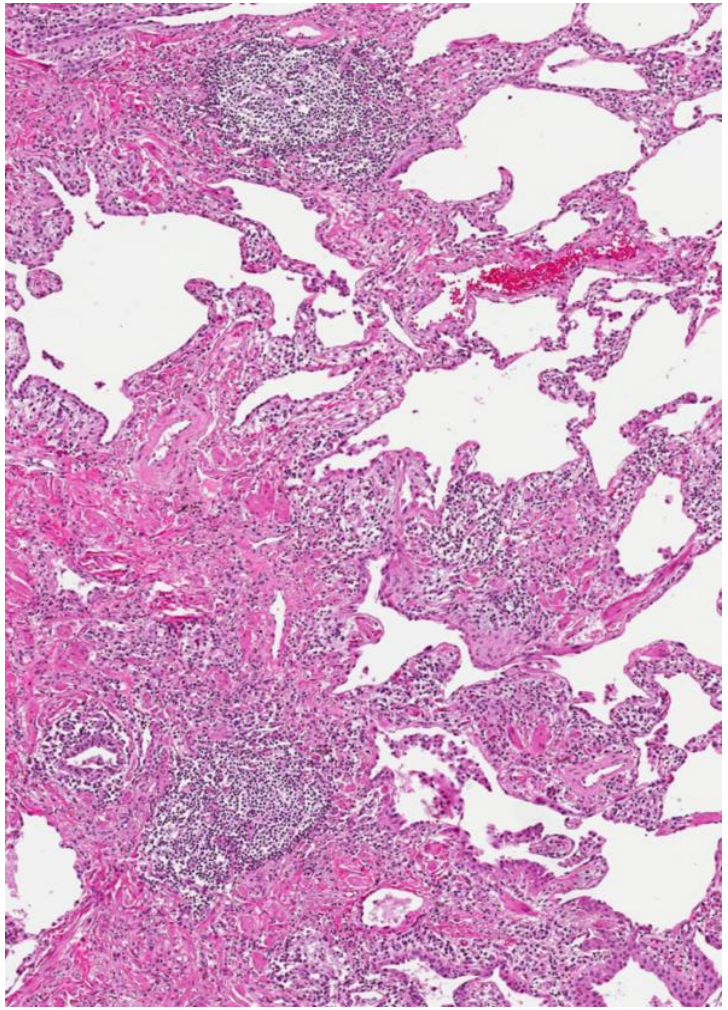
Pathogenesis of RA-ILD ERJ 2014



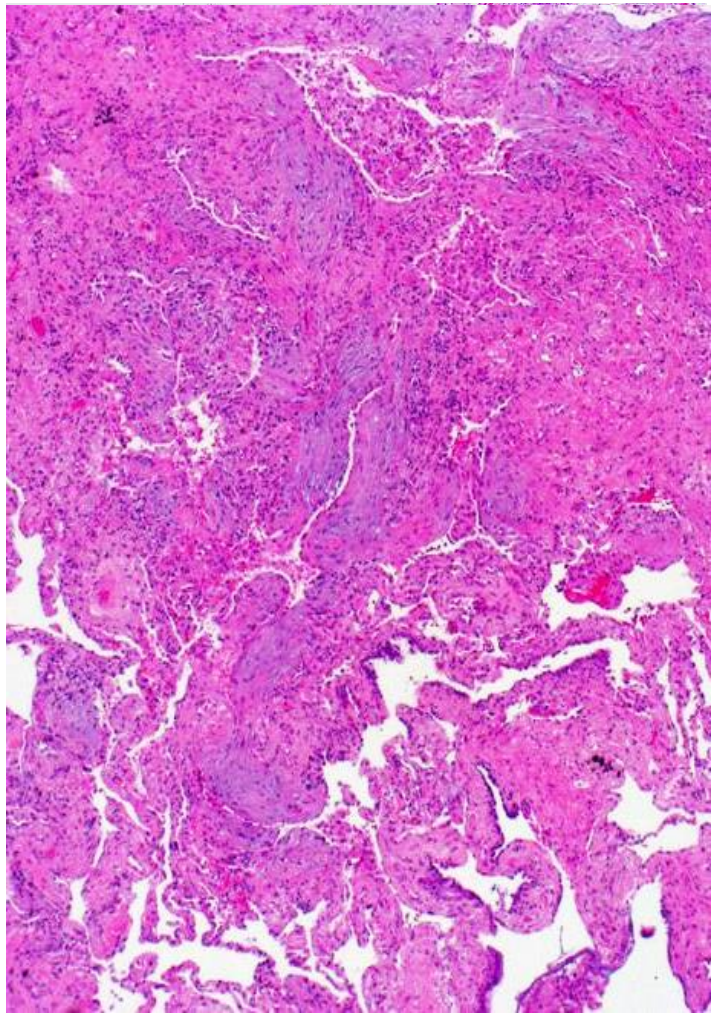
Pathology of Connective Tissue Disease-Associated Lung Diseases (CTD-LDs)

- Involvement of multiple anatomic compartments; airways, alveolar walls, alveolar spaces, pleura, and vascular structure
- Acute, subacute, and chronic lesions within the same biopsy specimen: ongoing pathophysiologic process
- Most CTD-ILDs: nonspecific histologic patterns, indistinguishable from idiopathic interstitial pneumonias of UIP, NSIP, DAD, OP or LIP

CVD-UIP patients had fewer fibroblastic foci and smaller honeycombing (HC) spaces with higher germinal centers and total inflammation scores than IPF/UIP patients. Song JW et al, CHEST 2019; 136:23-30



RA-UIP pattern



Idiopathic-UIP

Table 2. Characteristics of previously reported cohorts of patients evaluated for criteria for the classification of interstitial pneumonia with autoimmune features*

	Ahmad, 2017 (ref. 36)	Chartrand, 2016 (ref. 37)	Oldham, 2016 (ref. 35)
Location	France	Colorado	Chicago
Clinic type	Pulmonary	Rheumatology	Pulmonology
No. of patients	57	56	144
Sex, % female	49.1	71.4	52.1
Age at diagnosis, mean ± SD years	64.4 ± 14	54.6 ± 10.1	63.2 ± 11
By biopsy	29.8	NR	57.6
NSIP	8.8	23.2	13.1
OP	3.5	7.1	9.7
NSIP with OP overlap	1.8	14.3	2.1
LIP	1.8	1.8	NR
Interstitial aggregates with GCs	10.5	23.2	7.6
Diffuse lymphoplasmacytic infiltration	12.3	10.7	5.6

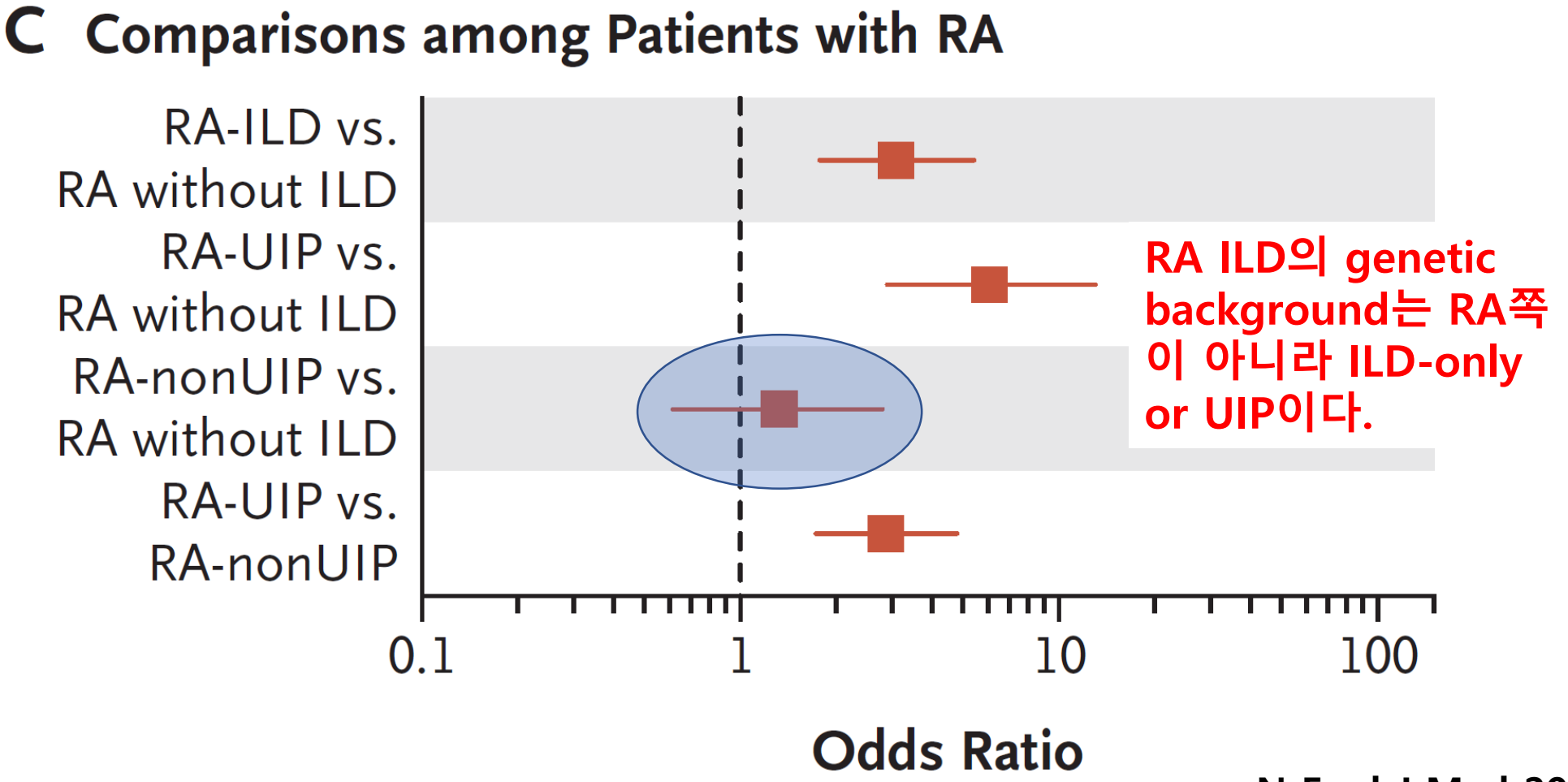
ARTHRITIS & RHEUMATOLOGY 70(12); 2018:1901–1913

The NEW ENGLAND JOURNAL of MEDICINE

MUC5B promotor variant

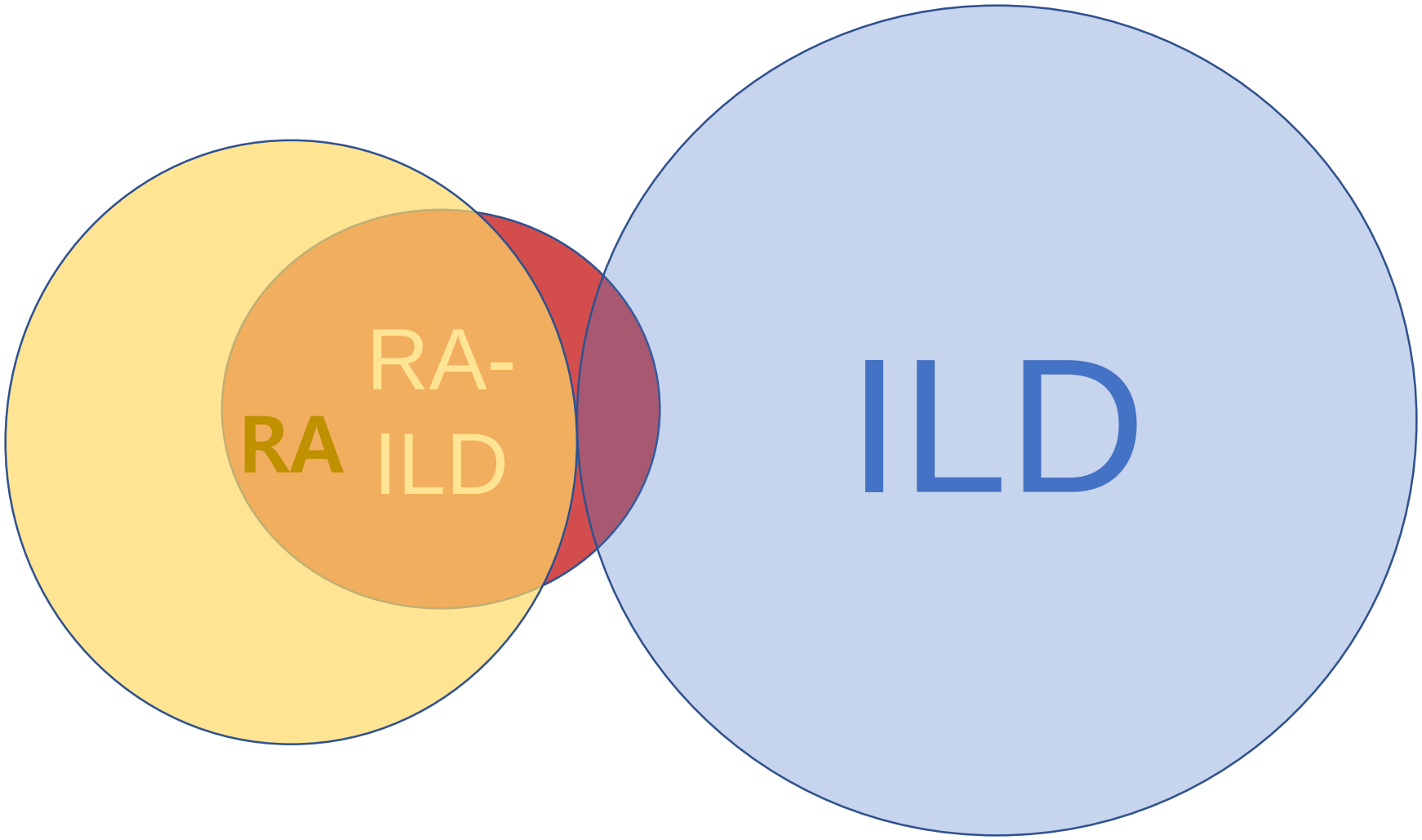
ORIGINAL ARTICLE

MUC5B Promoter Variant and Rheumatoid Arthritis with Interstitial Lung Disease



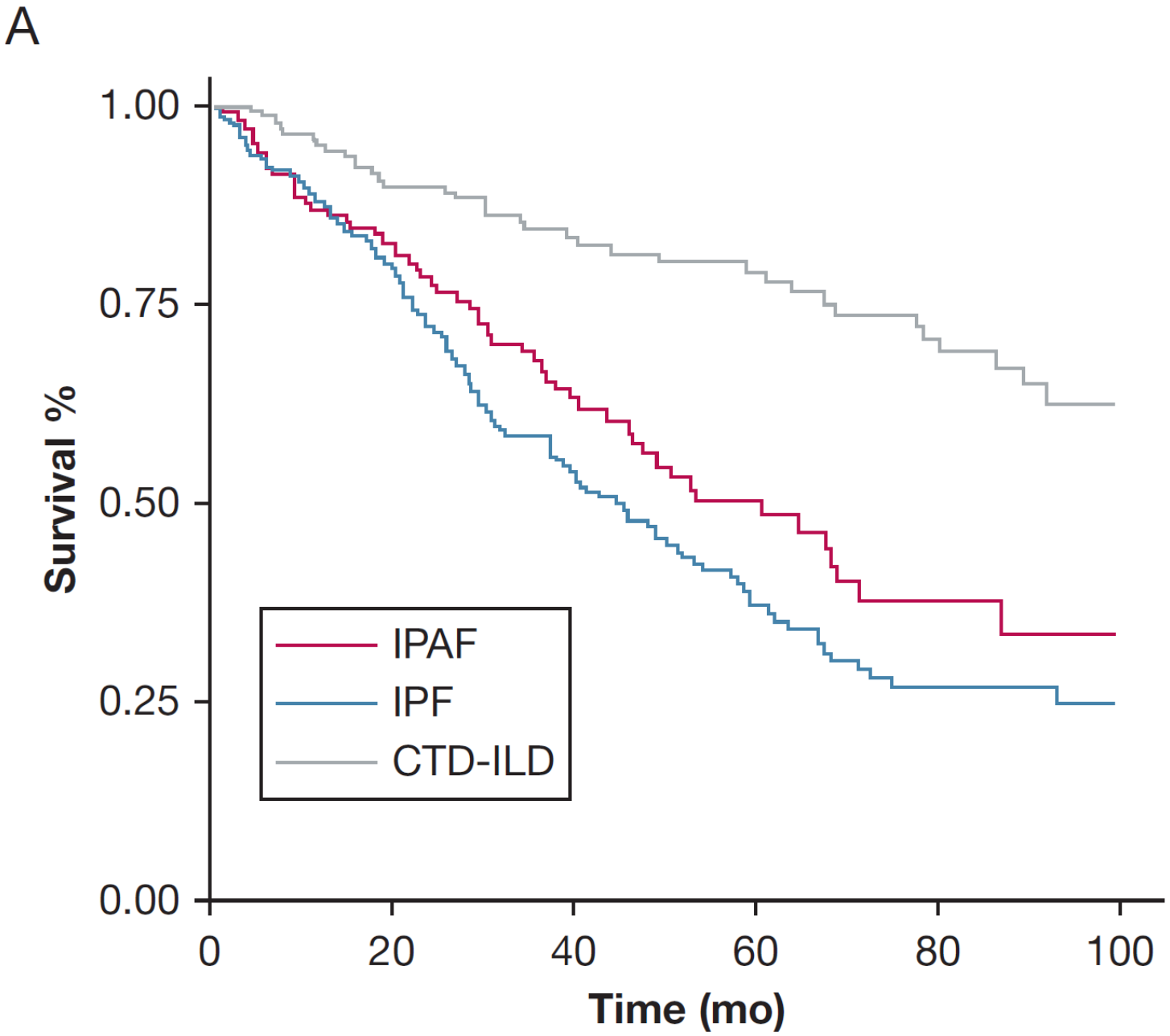
RA ILD의 genetic background는 RA쪽이 아니라 ILD-only or UIP이다.

N Engl J Med 2018;379:2209-19.



Modified by *N Engl J Med 2018;379:2209-19*

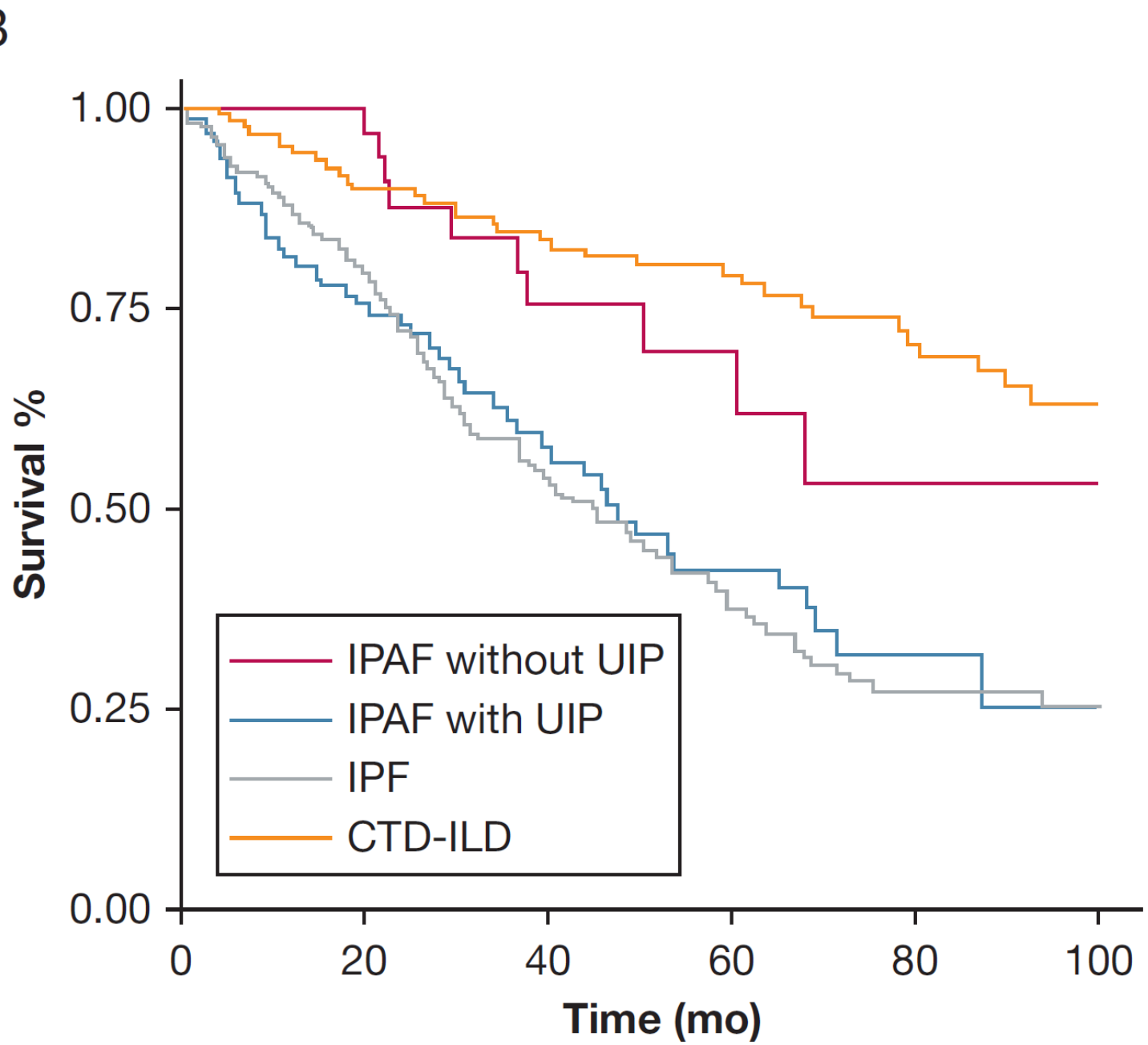
IPAF natural course?



ERJ 2016;47:1767-1775

IPAF natural course?

Prognosis of IPAF is Dependent by FIBROSIS



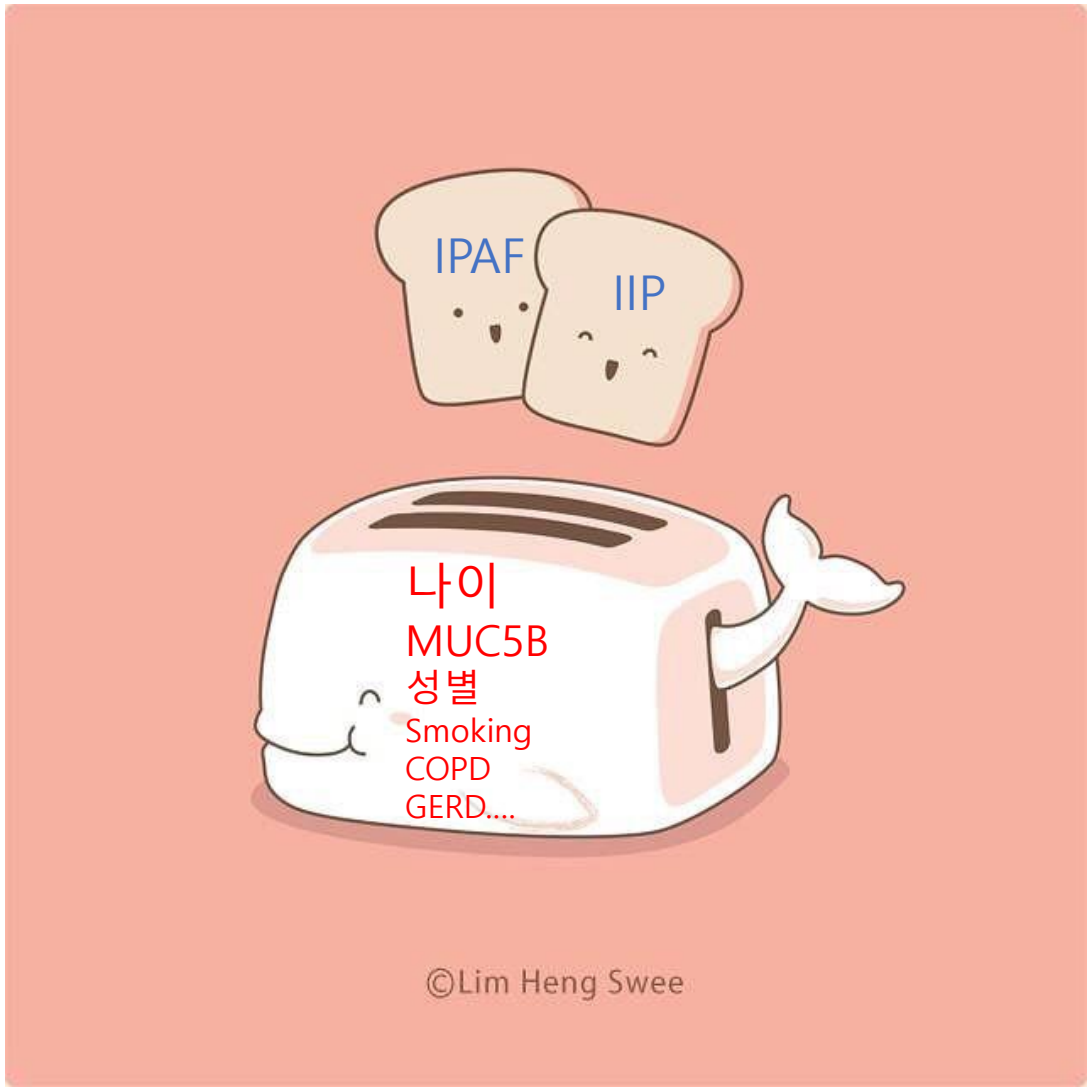
ERJ 2016;47:1767-1775

Prognosis of IPAF is Based on Pulmonary Fibrosis and Vasculopathy

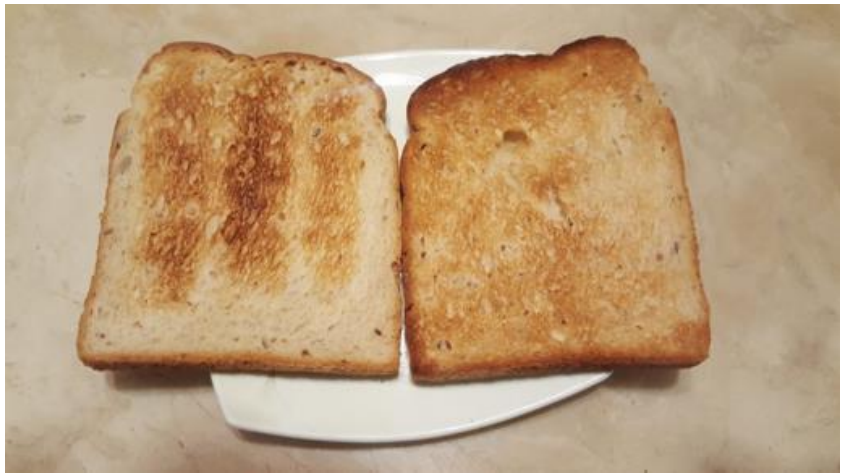
Table 4. Prognostic Value of Pathologic Features[a]

Variables	IIP						IPAF					
	Unadjusted, n = 169			Adjusted,[b] n = 166			Unadjusted, n = 84			Adjusted,[b] n = 81		
	HR	*P* value	95% CI	HR	*P* value	95% CI	HR	*P* value	95% CI	HR	*P* value	95% CI
IPAF histopathologic criteria	**0.55**	**.05**	**0.31–1.00**	0.77	.41	0.41–1.44	0.82	.63	0.37–1.81	1.07	.87	0.47–2.46
UIP Pattern	**7.31**	**.006**	**1.77–30.13**	**4.64**	**.04**	**1.08–20.00**	**6.11**	**.01**	**1.43–26.08**	**5.35**	**.03**	**1.21–23.67**
NSIP	0.48	.12	0.19–1.22				0.71	.50	0.26–1.90			
OP	0.59	.31	0.21–1.64				0.99	.98	0.34–2.90			
Interstitial lymphoid aggregates with GCs	0.9	.83	0.36–2.72				1.12	.84	0.38–3.29			
Diffuse lymphoplasmacytic infiltrates	1.13	.79	0.48–2.64				1.58	.37	0.58–4.26			
Pulmonary vasculopathy	1.65	.07	0.96–2.83				**2.50**	**.04**	**1.05–5.92**			

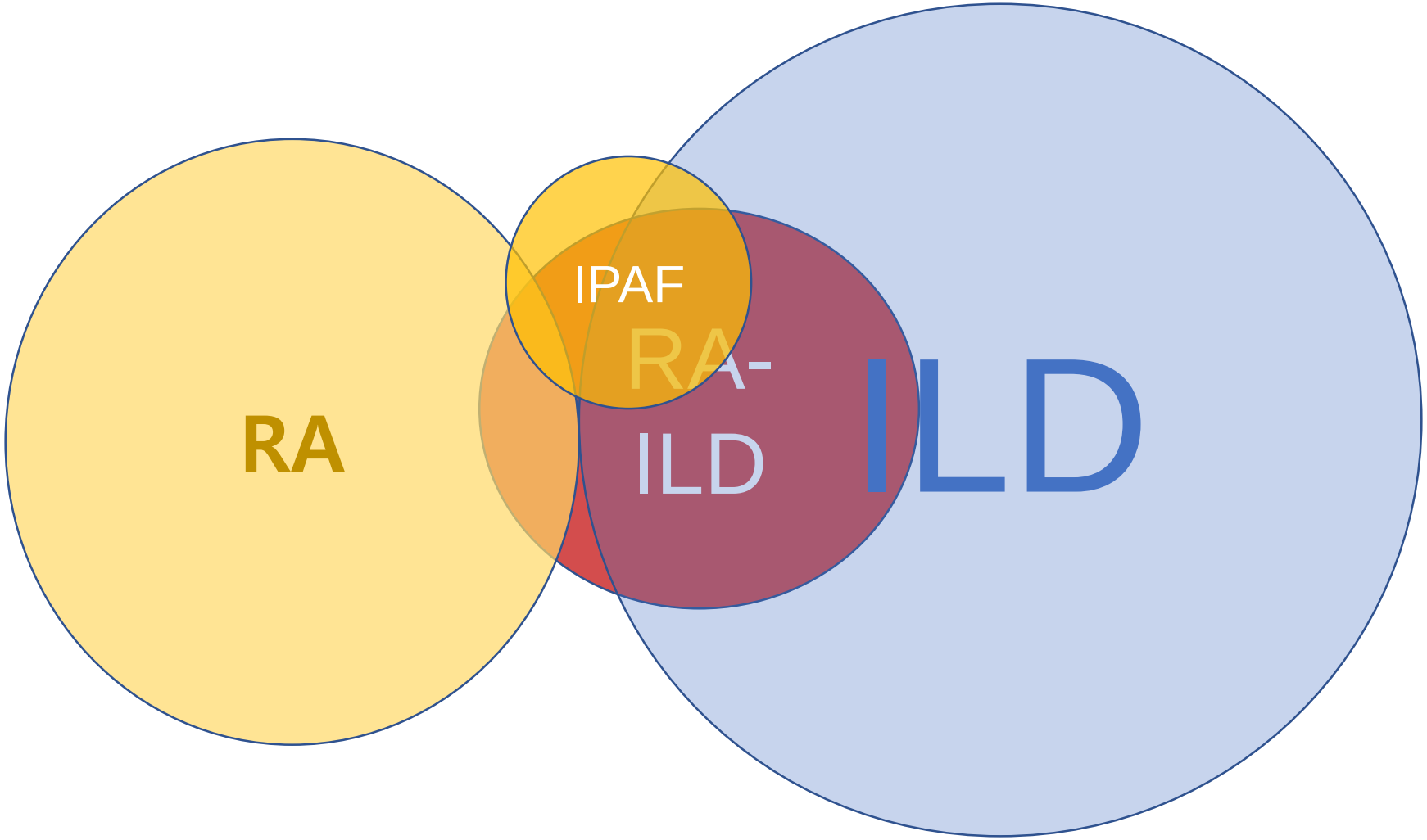
Arch Pathol Lab Med 2017; 141: 960-969



Fibrosis
Vasculopathy



If the genetic background and prognosis of **IPAF** is significantly linked with fibrosis, the classification should be based on… **in the context of fibrosis**



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4. **Temporality**
5. **Biological gradient**: a dose-response relationship


Sir Austin Bradford Hill
1897-1991

Current RCT

Curr Opin Pulm Med 2017, 23:418–425

Table 1. Ongoing RCTs in nonidiopathic pulmonary fibrosis interstitial lung disease[a]

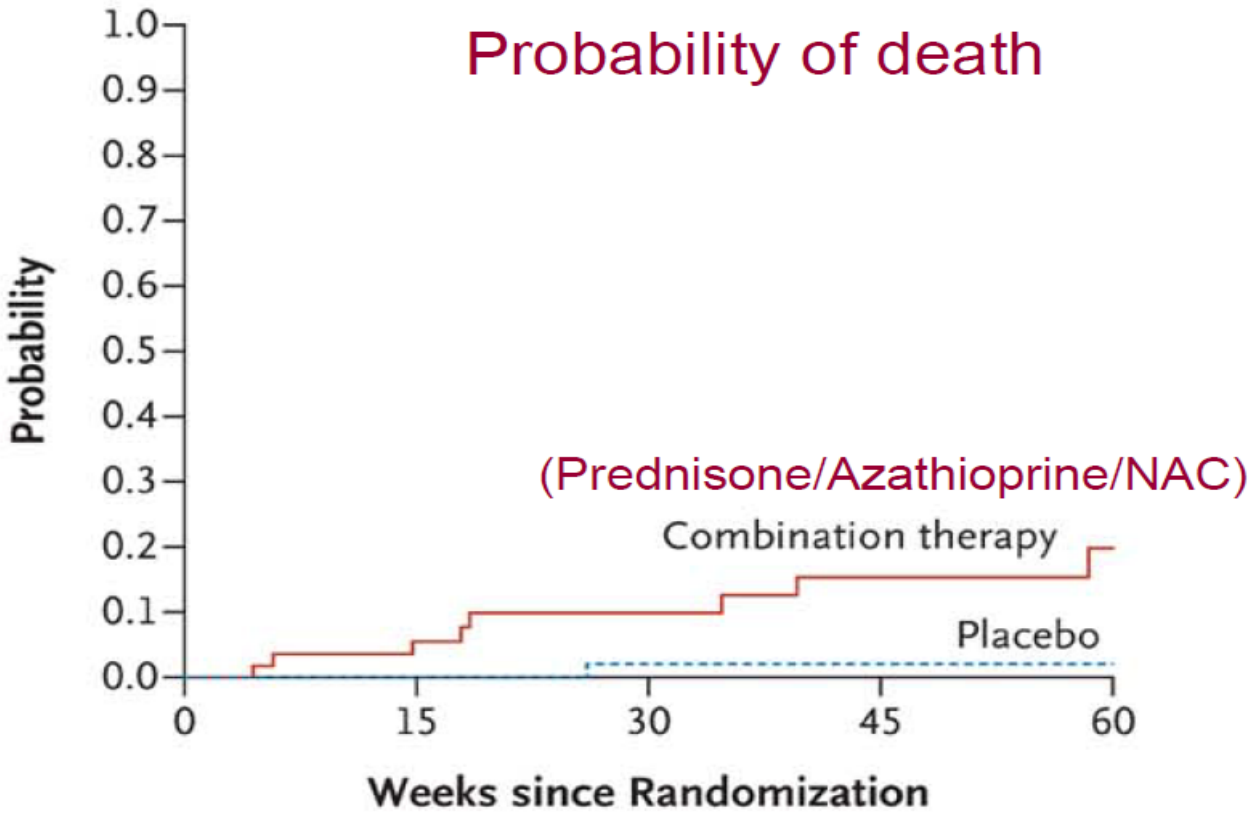
Study identifier [Ref]	Study	Target disease	Treatment (*n*)	Primary outcomes	Secondary outcomes	Duration (phase)
EudraCT 2014–000861-32 DRKS00009822 [53,54]	Exploring efficacy and safety of oral pirfenidone for progressive, non-IPF lung fibrosis (RELIEF)	CTD-ILD; fNSIP; cHP; ALF	2403 mg daily for 48 weeks; add-on to existing treatment ($n=374$)	Absolute change in % predicted FVC	Time to disease worsening; changes in DL_{CO}, 6MWT distance, and quality of life scores (SGRQ and EQ-5D); safety and tolerability	48 weeks (phase 2)
NCT02808871 [55]	Phase 2 study of pirfenidone in patients with RA-ILD	RA-ILD	2403 mg daily; add-on to existing treatment ($n=270$)	Composite endpoint; progression free survival (≥10% decline in FVC or death)	Relative decline in DL_{CO} (≥15%), % predicted FVC (≥10%), incidence of acute exacerbations, dyspnea scores; SGRQ scores; safety and tolerability	52 weeks (phase 2)
NCT02958917 [56]	Study of efficacy and safety of pirfenidone in patients with fibrotic hypersensitivity pneumonitis	fHP	2403 mg daily ($n=40$)	Mean change in % predicted FVC	PFS; ≥5% mean change in %FVC; acute exacerbations; decrease in 6MWT distance; safety and tolerability	52 weeks (phase 2)
NCT02496182 [52]	Pirfenidone in the cHP treatment (Picheon)	cHP	1800 mg or 1200 mg daily; add-on to existing treatment ($n=60$)	FVC at week 26 and week 52	Inflammation and fibrosis grade on HRCT using Kazerooni scale; 6MWT distance; SGRQ Scores; safety and tolerability	52 weeks (phase 2/3)
NCT03099187 [57]	Multicenter, international, double-blind, two-arm, randomized, placebo-controlled phase 2 trial of pirfenidone in patients with unclassifiable progressive fibrosing ILD	unclassifiable fibrosing ILD	2403 mg daily; patients may continue with MMF ($n=250$)	Rate of decline in FVC (ml)	Change in % predicted FVC; change in % predicted DL_{CO}; change in 6MWT distance; patient reported outcomes (including SGRQ); safety and tolerability	24 weeks (phase 2)
NCT02821689 [58]	Pirfenidone in progressive ILD associated with clinically amyopathic dermatomyositis	CADM	1800 mg daily; add-on to existing treatment ($n=60$)	Overall survival	Changes in HCRT features; pulmonary function; safety and tolerability	52 weeks (phase 4)
NCT02597933 [59]	SENSCIS (Safety and Efficacy of Nintedanib in Systemic SClerosIS) study	SSc-ILD	150 mg twice daily ($n=520$)	Annual rate of decline in FVC	Change in the mRSS; change in SGRQ score; change in % predicted FVC and % predicted DL_{CO}; change in digital ulcer burden.	52 weeks (phase 3)
NCT02999178 [60]	Efficacy and safety of nintedanib in patients with PF-ILD	PF-ILD	150 mg twice daily ($n=600$)	Annual rate of decline in FVC	Change in K-BILD score; time to first exacerbation; overall survival.	52 weeks (phase 3)
NCT02262299 [61]	European Trial of Pirfenidone in BOS, a European multicenter study (EPOS)	BOS	2403 mg daily ($n=80$)	Change in FEV_1	Change in FVC; change in % predicted DL_{CO}; change in 6MWT distance; change in BOS grade; hospitalization, survival and retransplantation rates; safety and tolerability	26 weeks (phase 2/3)

ERS/ATS가 IPAF라는 category를 등장시킨 이유

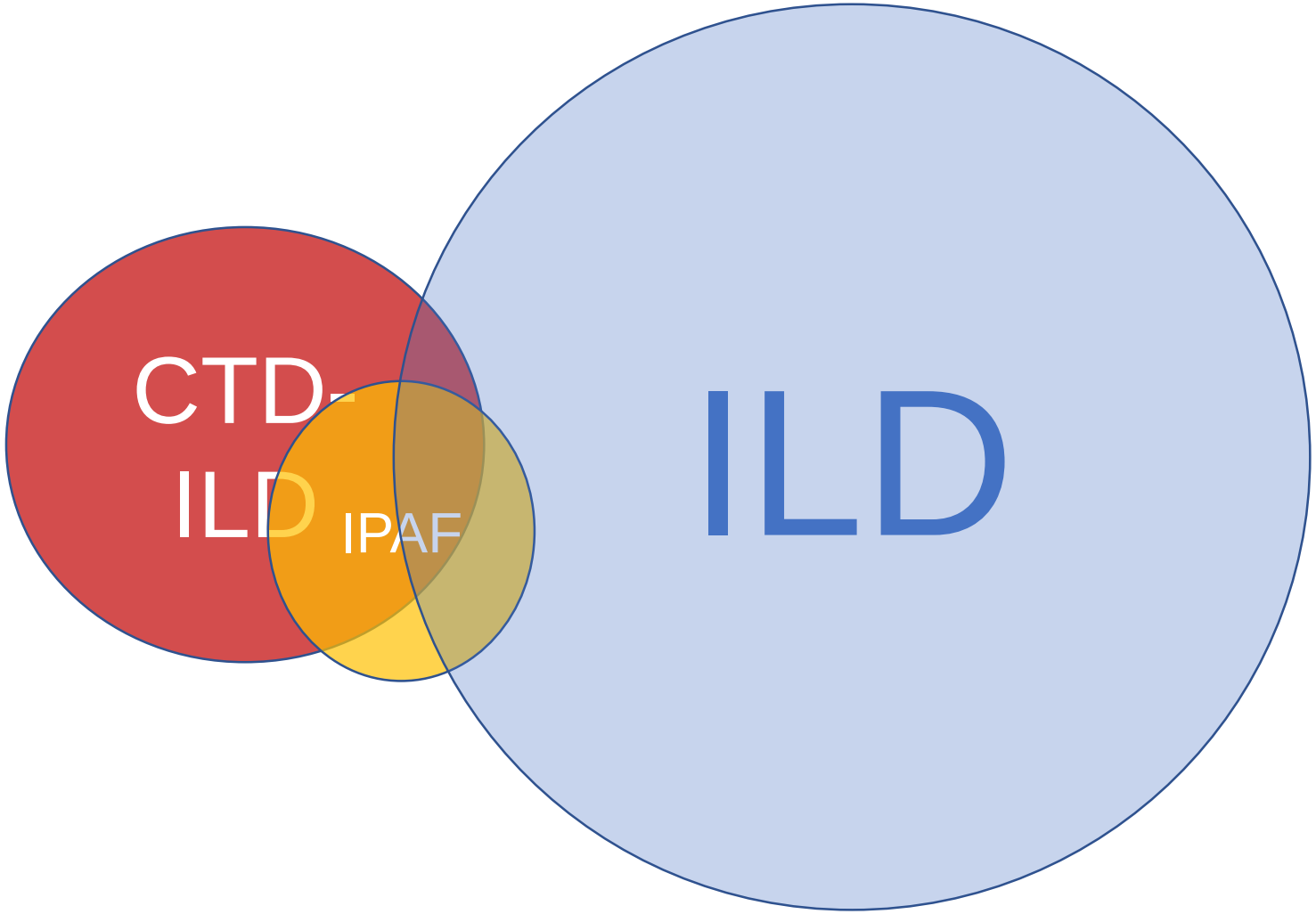
- The task force aimed to derive a uniform name and set of classification criteria for patients with IIP and an autoimmune "flavour" with the hope of developing a sound platform from which to launch future research investigations.

Increased Risk of Death with Traditional Targeting Lymphocytic Inflammation

PANTHER-IPF Trial



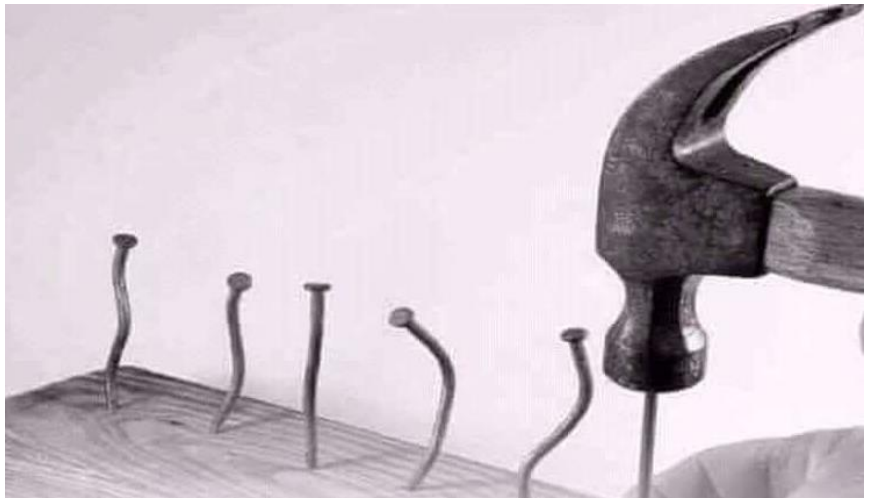
The Idiopathic Pulmonary Fibrosis Clinical Research Network, *N Engl J Med* 2012



Modified from *Wells et al. ERJ 2018; 17:51*

My conclusions

- IPAF라는 category를 만든 이유는 Early form of (autoimmune) ILD를 솎아내어 다양한 약제(immune modulator 포함)로 clinical trials을 시도하기 위한 하나의 방편으로 보인다.

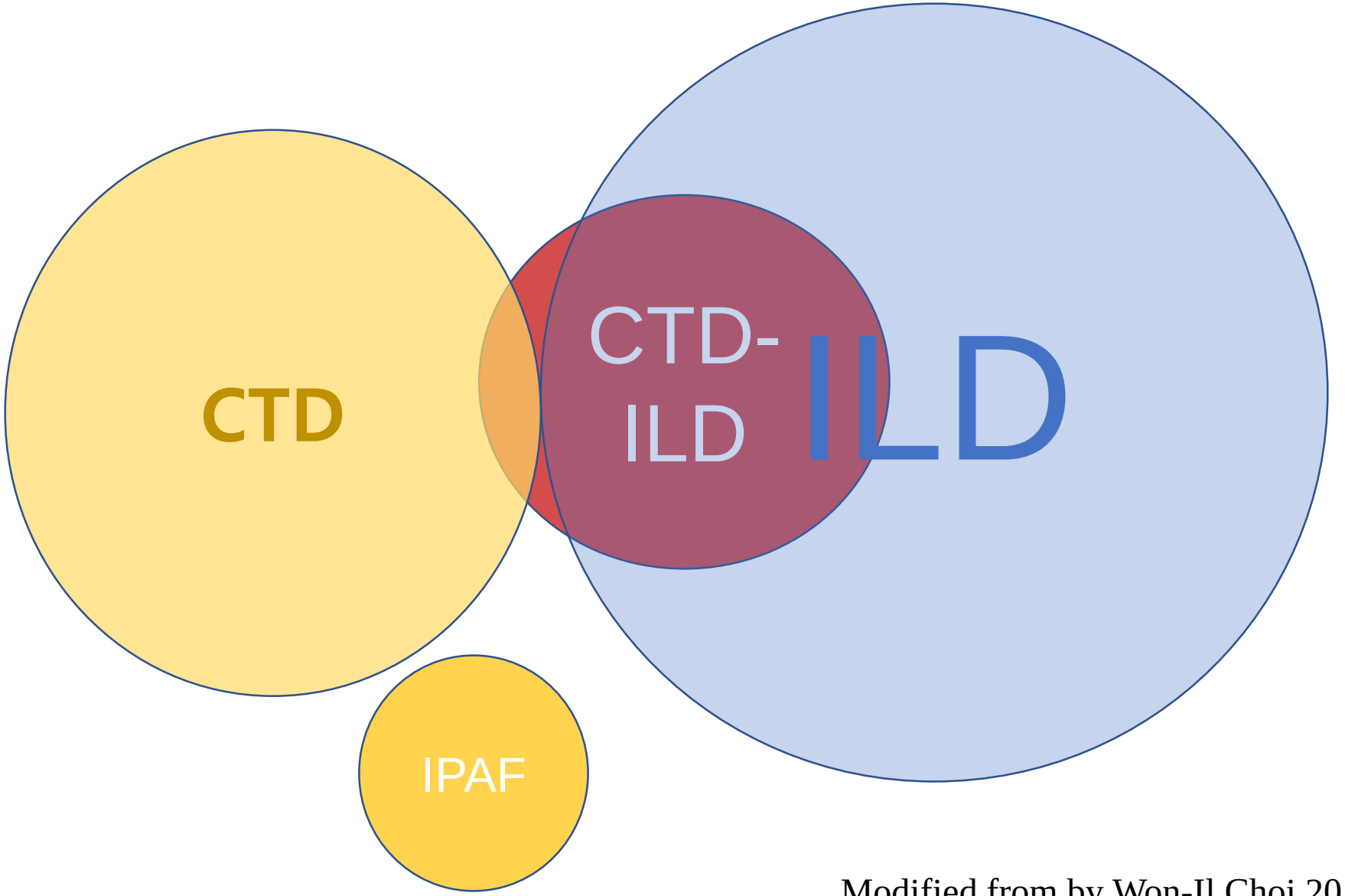


Overall structure of IPAF

- The criteria state up-front several a priori requirements for the classification of IPAF:
- Individuals must have evidence of interstitial pneumonia by high-resolution computed tomography (HRCT) imaging and/or by surgical lung biopsy, a thorough clinical evaluation during which

만약 CTD disease definition에
lung involvement를 포함해서 criteria가 revision 된다면?

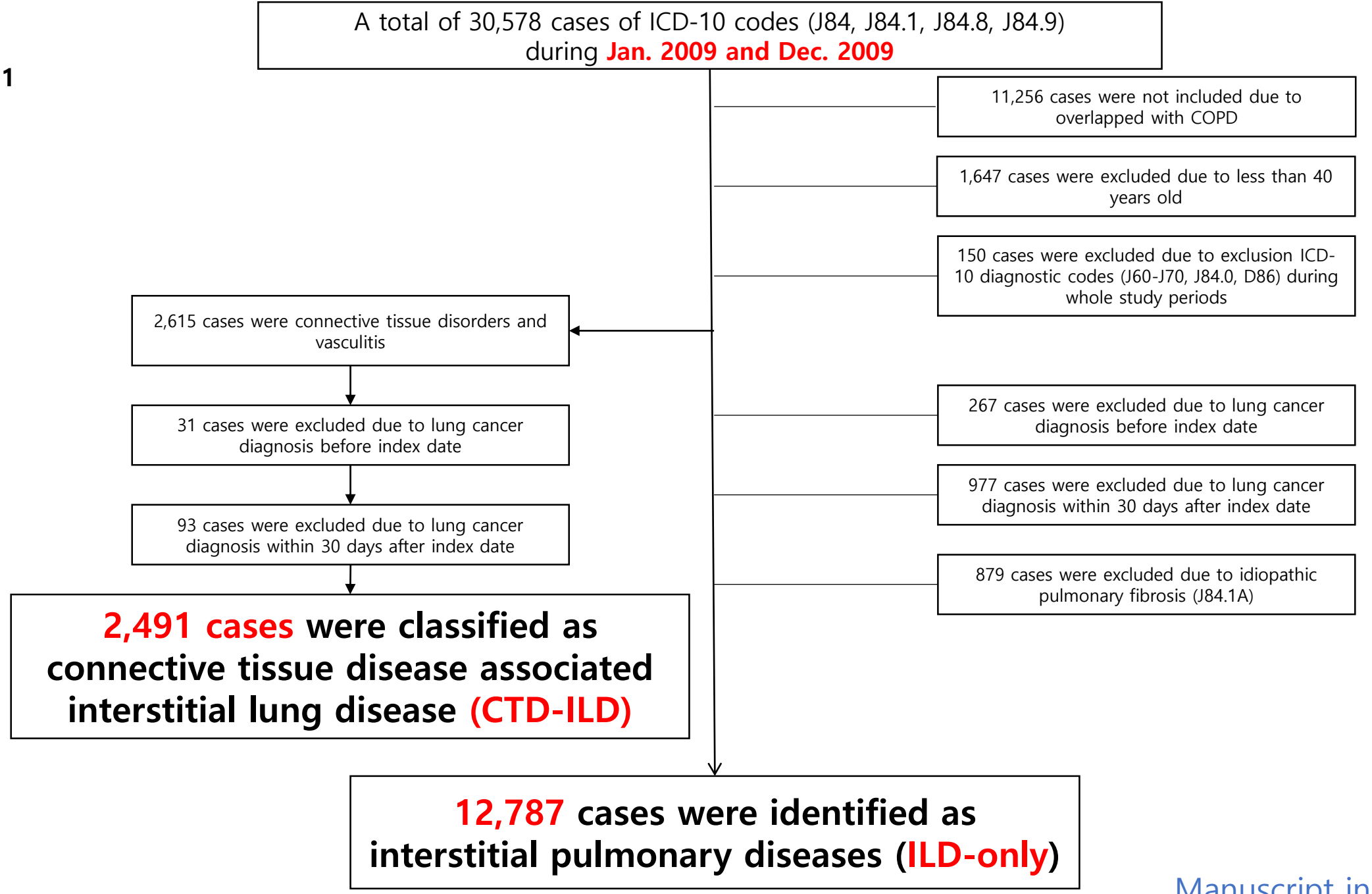
Aryeh Fischer et al, Eur Respir J 2015; 46: 976–987



Modified from by Won-Il Choi 2019

국내 심평원 자료 분석
CTD-ILD vs. ILD-only

Figure 1



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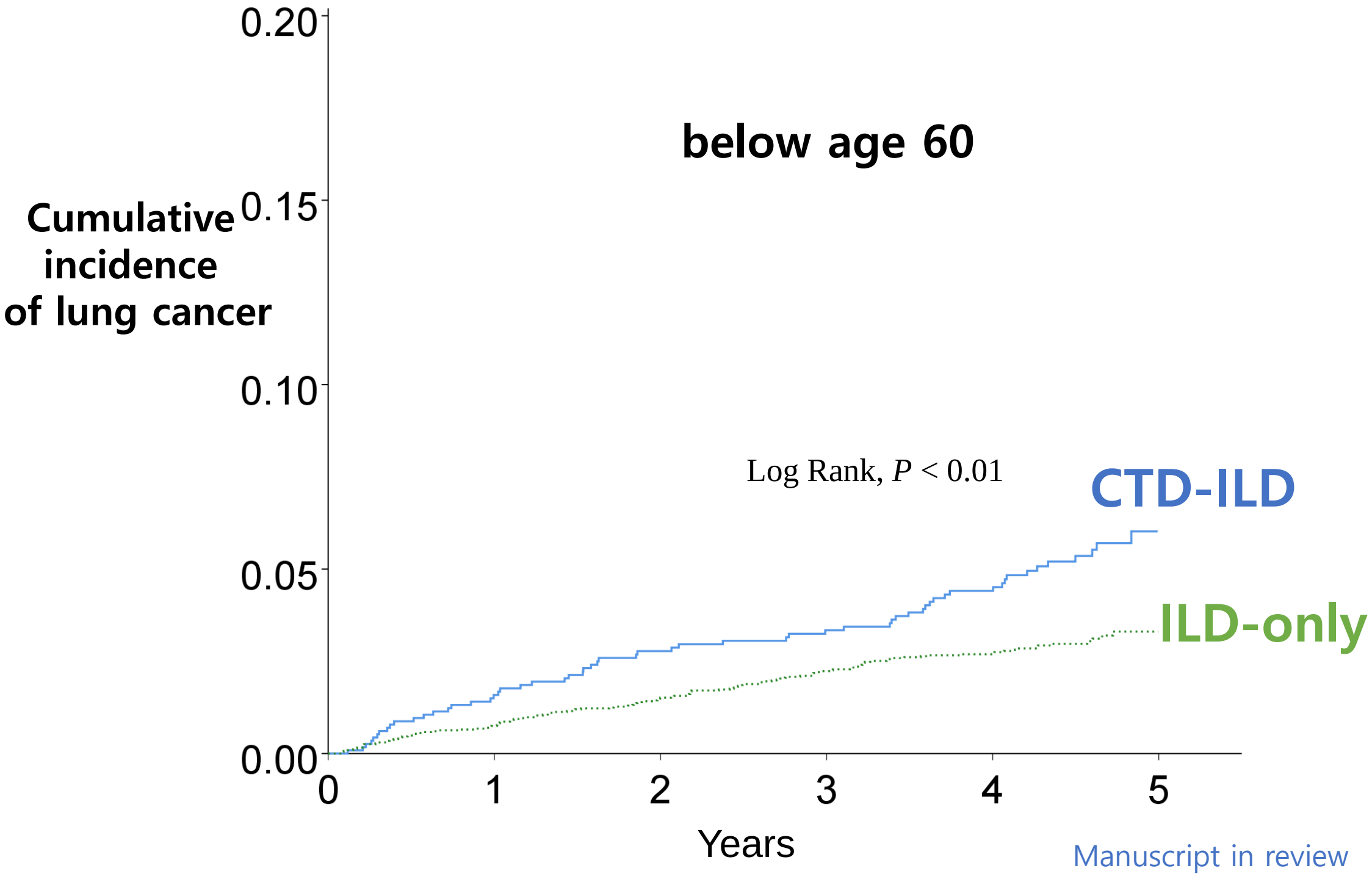

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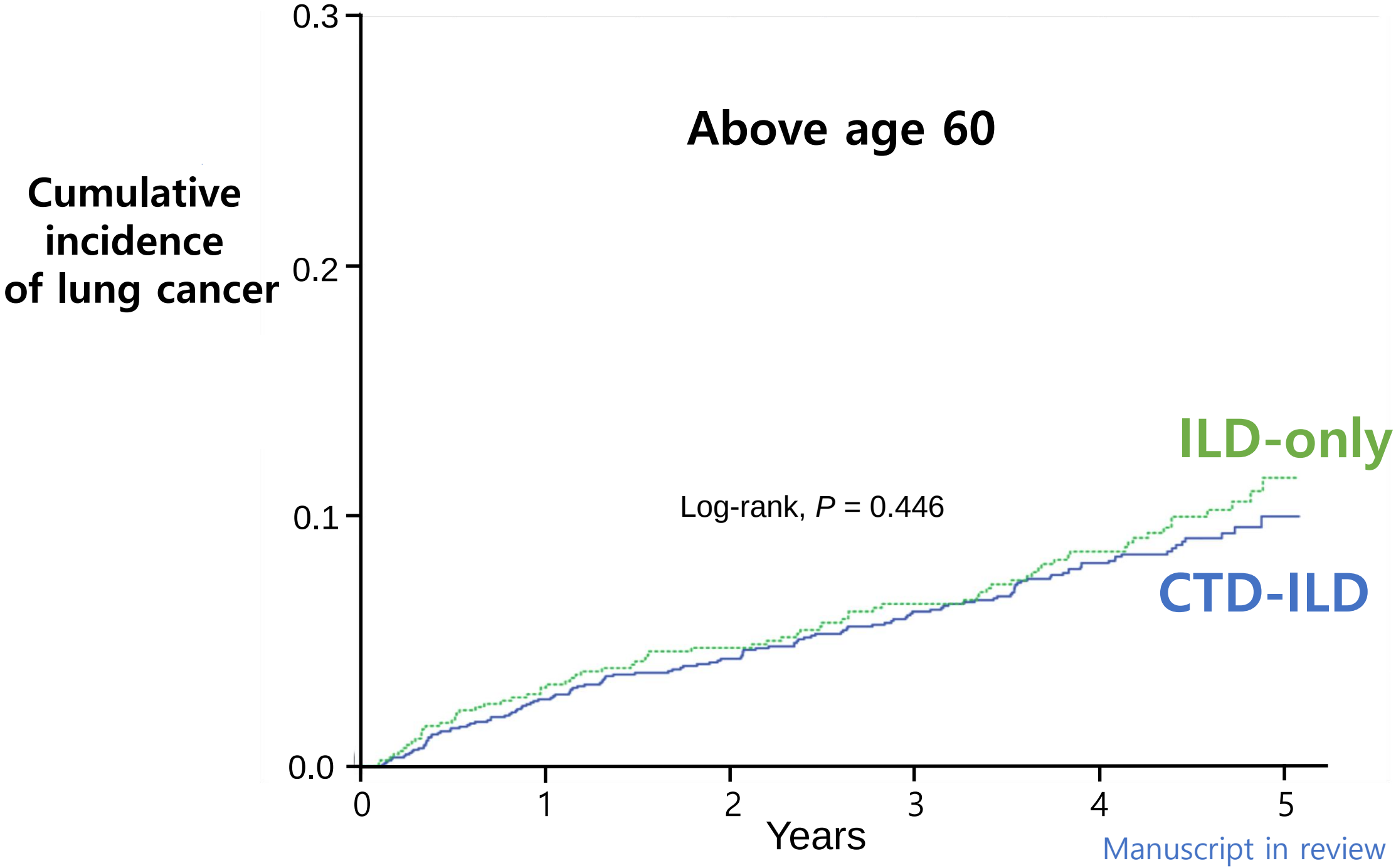

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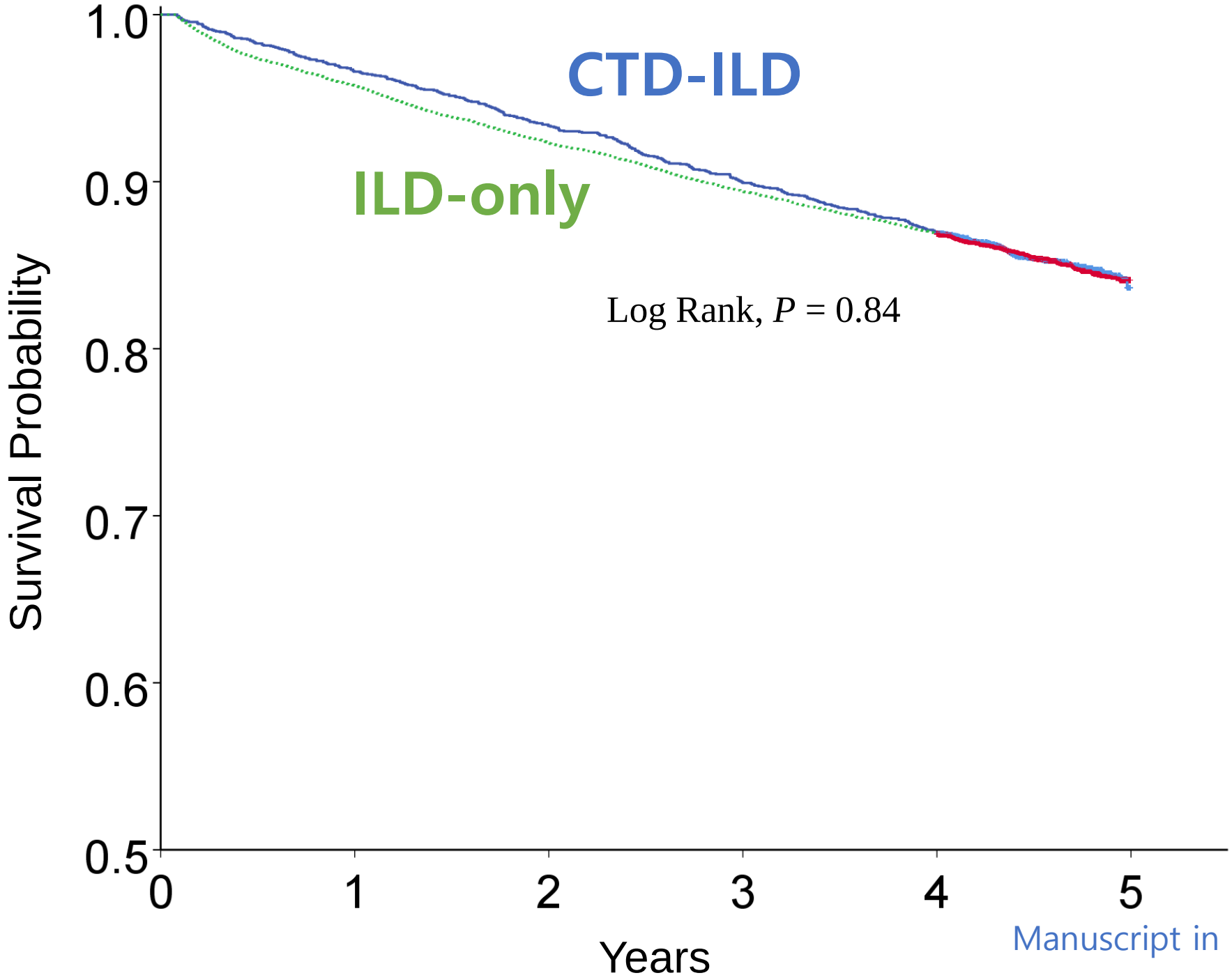

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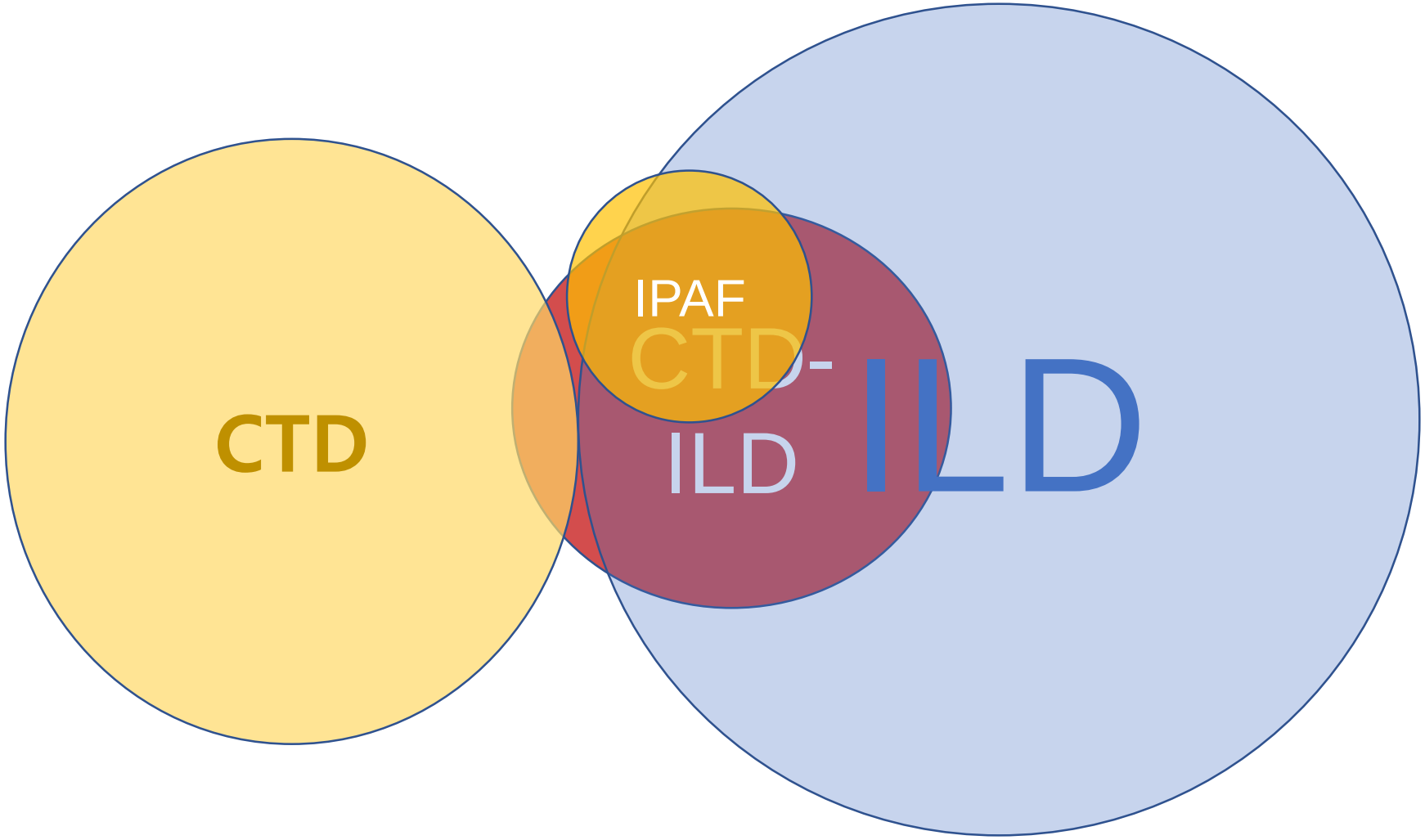
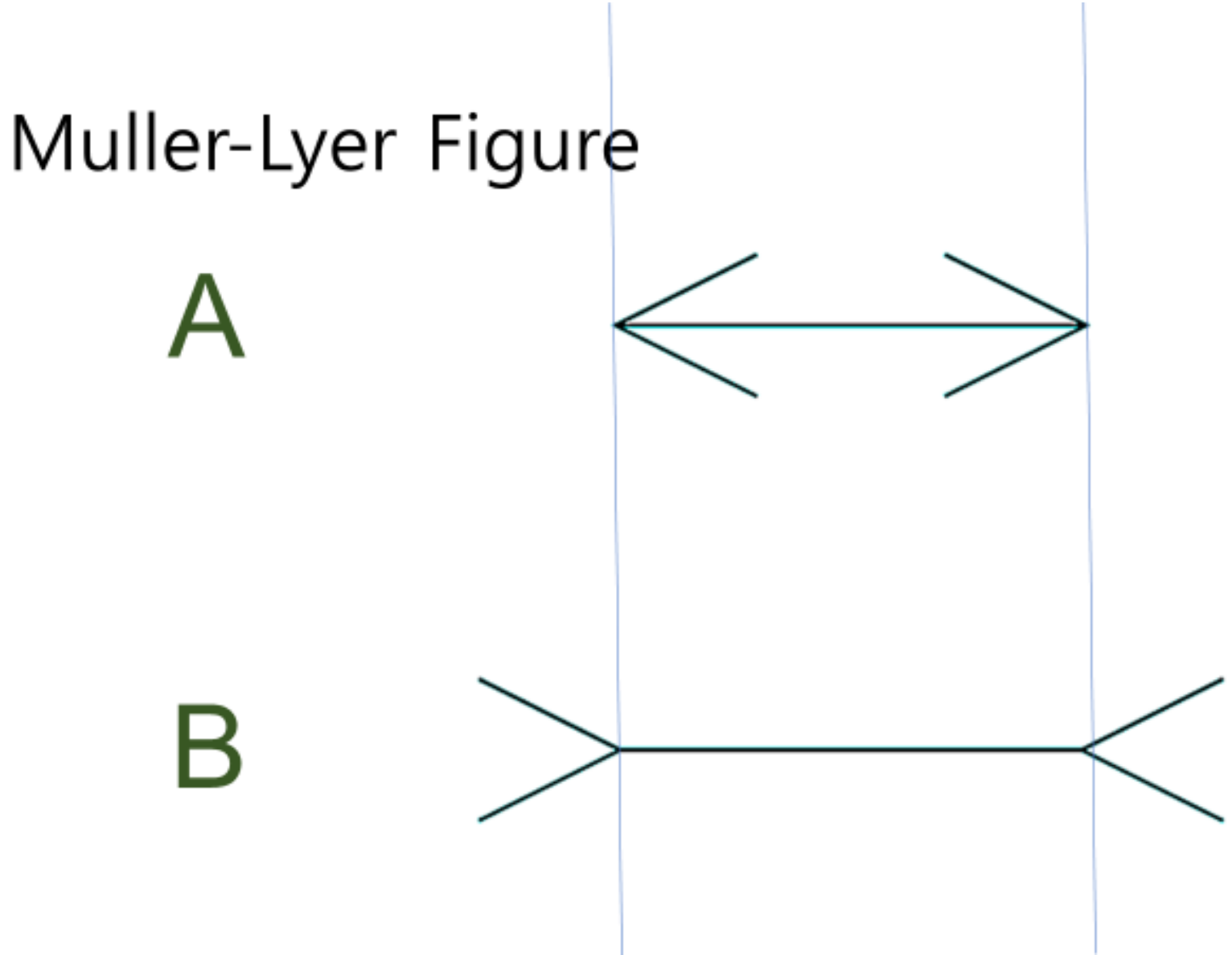


Modified from by Won-Il Choi 2019

Come to think of IPAF vs IIP



Idiopathic Pneumonia

Idiopathic Pneumonia Autoimmune Feature

The question!

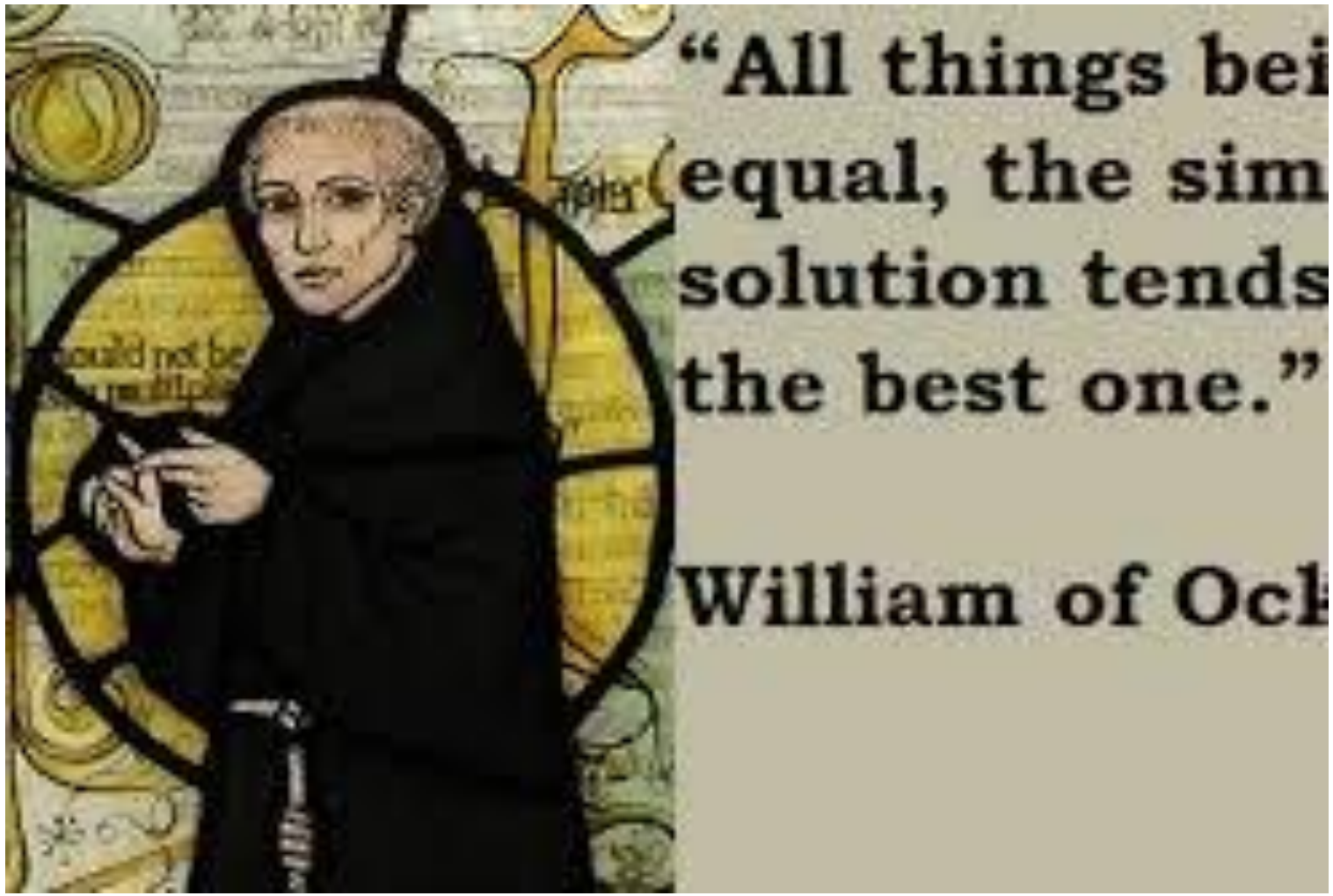
- Predictive accuracy 측면에서 nature 를 잘 흉내내는 models 은 복잡(complex) 하고 불가해(inscrutable) 한 것이라는 것이라는 믿음이 있는데,

- 이러한 딜레마는 애초에 질문을 잘못 한 것임을 깨달으면 해결 될 수 있다

-

Black box – complex & unknown interior

Leo Breiman. Statistical Science, Vol. 16, No. 3 (Aug., 2001), pp. 199-215



"무언가를
다양한 방법으로
설명할 수
있다면 우리는
그중에서 가장
적은 수의
가정을 사용하여
설명해야 한다"

결 론

1. Idiopathic pneumonia with autoimmune features를 잘 정의할 만한 뛰어난 코호트가 없이 define되었고
2. IPAF 진단 Domain 각각에 대해서 논란이 존재하며
3. RCT를 위해 잠재적으로 IPAF category를 만든 것으로 보이며
4. 만약 CTD의 criteria에 lung involvement를 포함한다면 IPAF는 독립적인 형태가 아니라 CTD에 속하게 될 수 있으며,

결 론

5. IPAF의 pathogenesis는 CTD를 따르거나 ILD를 따를 것으로 보이는데
6. CTD-ILD의 genetic background가 CTD가 아니라 ILD에 가까우므로 CTD-ILD의 early form으로 볼 수 있는 IPAF도 ILD에 속할 것으로 보인다.
7. 또한, IPAF의 예후는 autoimmune feature에 의해 결정되는 것이 아니라 섬유화 정도에 의해 결정되고
8. 이와 마찬가지로 CTD-ILD의 예후는 ILD(fibrosis)에 의해 예후가 결정되므로
9. **IPAF의 경우 New category로 분류할 것이 아니라 기존의 IIP로 분류되어야 할 것으로 보인다.**

Rebuttal

Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases

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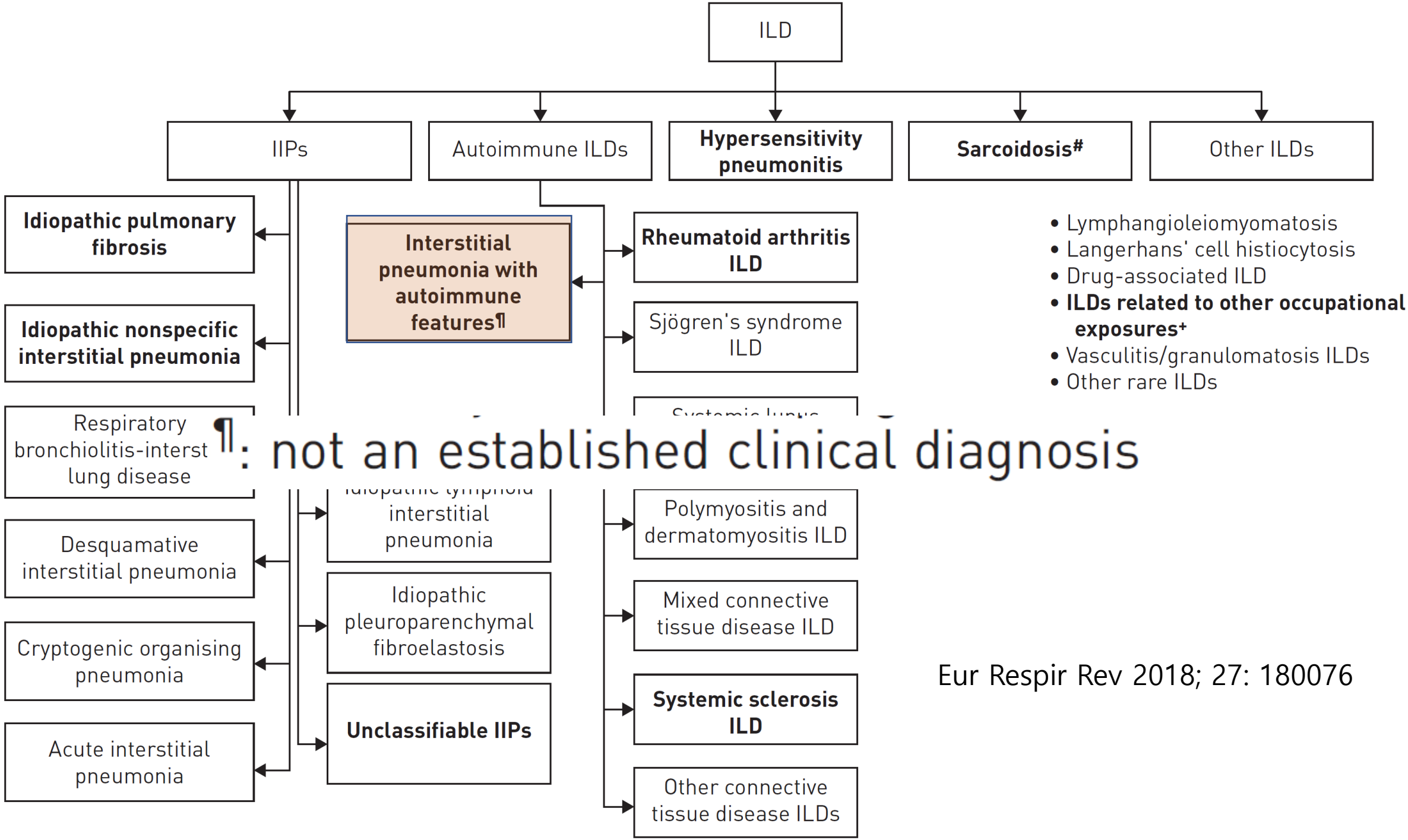

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