Cryobiopsy: lesson learned and future perspectives

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I have no conflicts of interest to declare

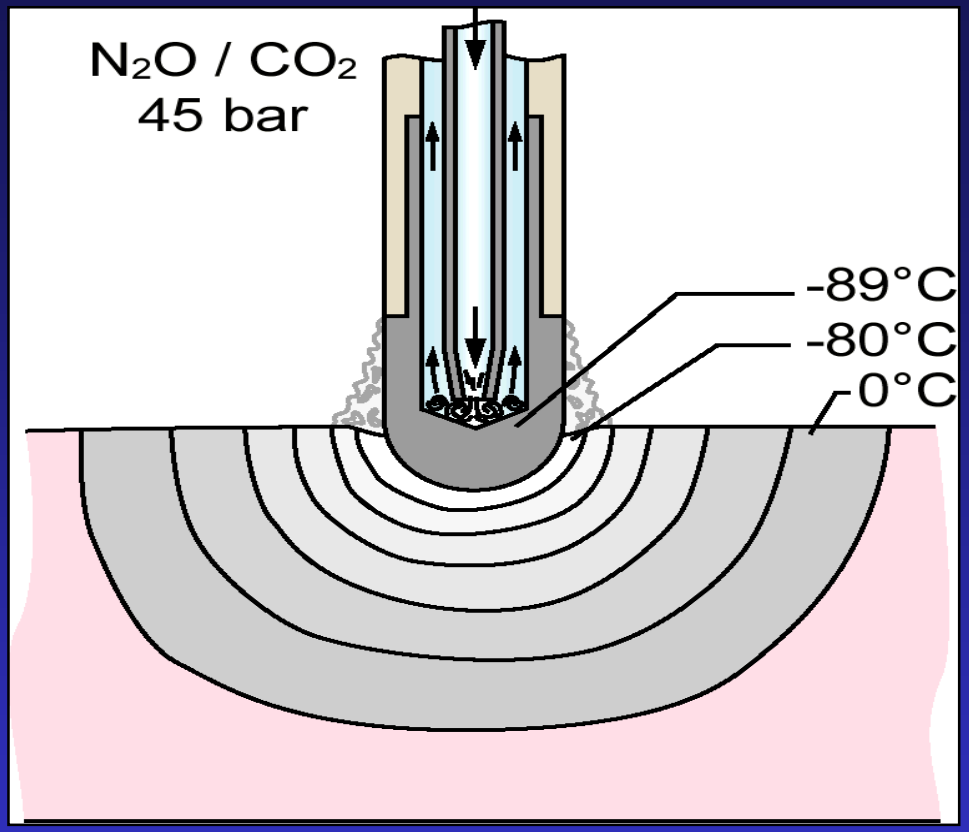
Problems of surgical lung biopsies in ILD

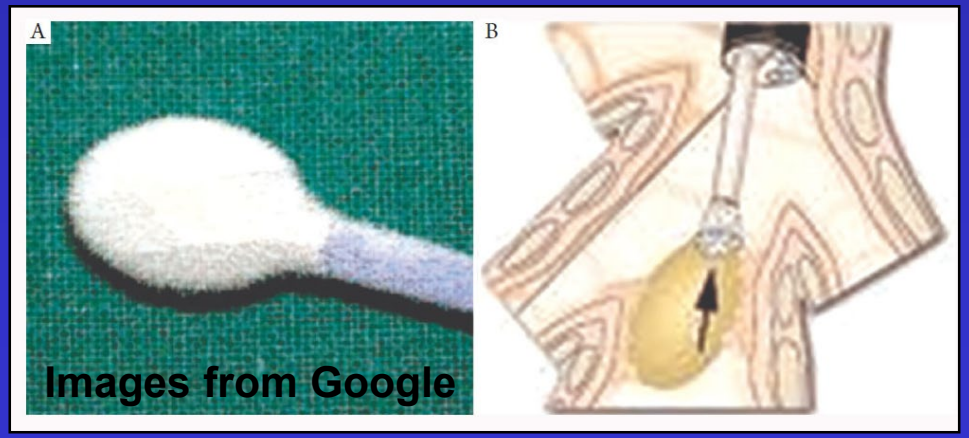
- Complications: 1.7% in-hospital mortality for elective procedures, infections, 3-12% of prolonged air leak, >50% of pain at 12 months
- Can not be performed in many patients because of advanced age, comorbidities, severity of disease or patient deny
- For risk-benefit considerations, only about 10-20% of patients with fibrotic ILD undergoes a surgical lung biopsy

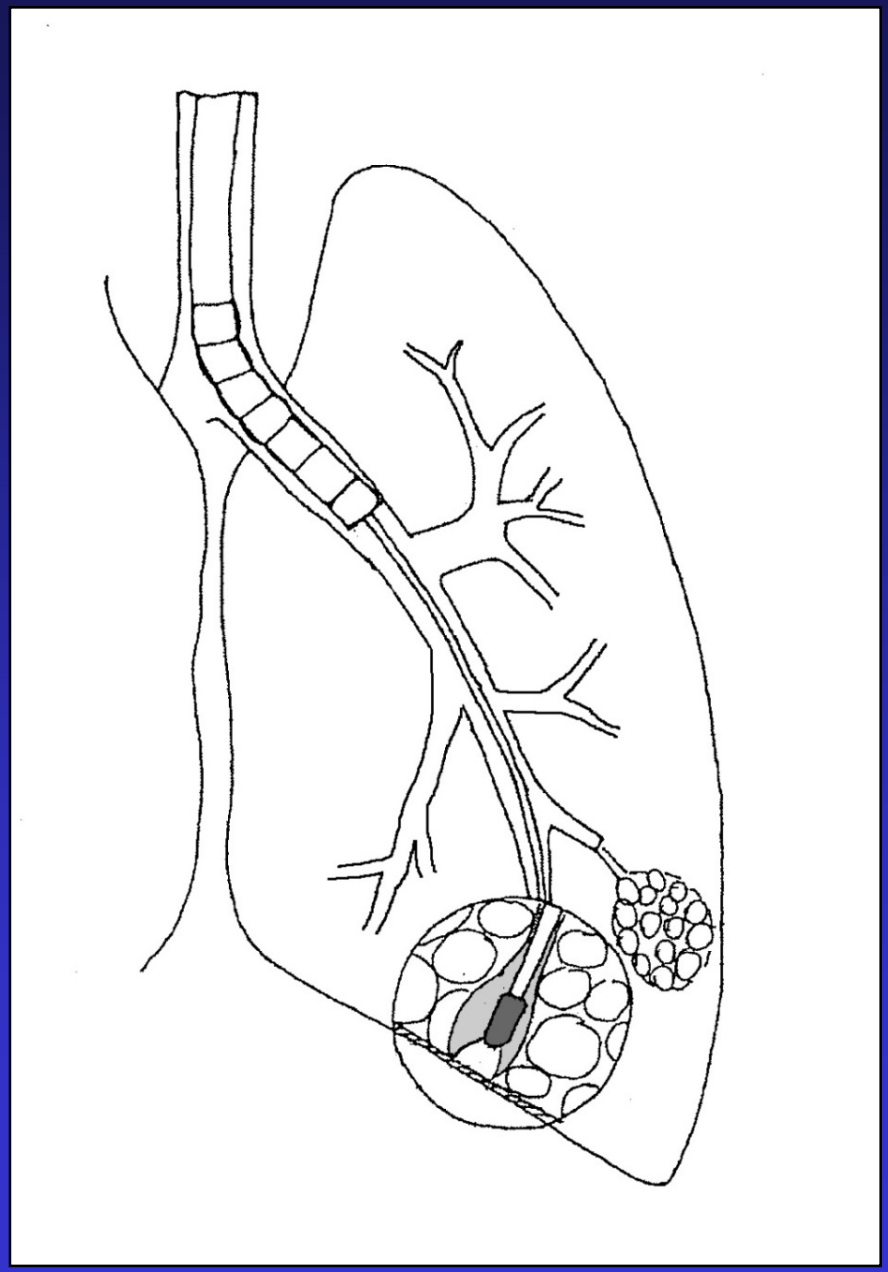
… an alternative mode of biopsy that overcomes these problems without substantial loss of diagnostic accuracy would be invaluable…..

Margaritopoulos, Wells. Rev Port Pneumol 2012;18:61-63

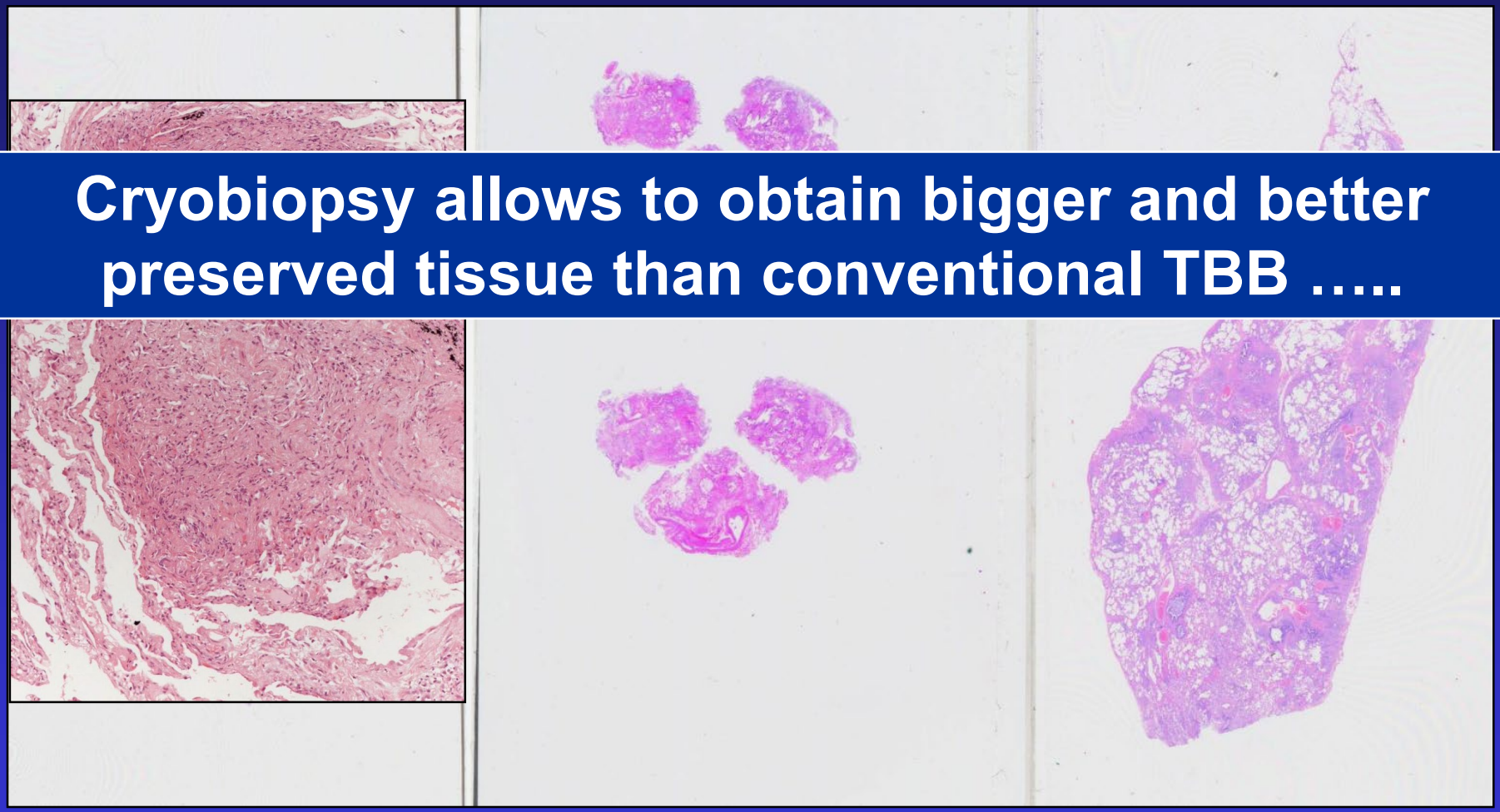
Cryobiopsy: the technique







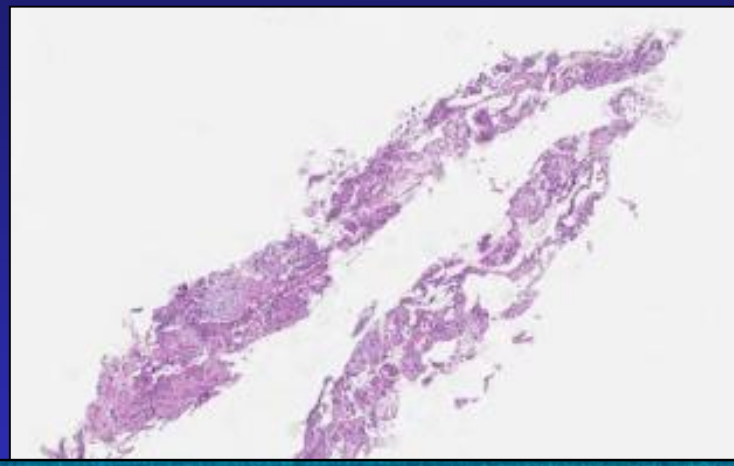
TBB Cryobiopsy VATS



Cryobiopsy allows to obtain bigger and better preserved tissue than conventional TBB …..

…. but not always!

- The mean size of cryobiopsy varies in the literature from 3 mm (9 mm^2) to 8 mm (64 mm^2)
- A cryobiopsy should be at least 4-5 mm
- A small cryobiopsy is better than a conventional TBB



Safety and diagnostic yield of transbronchial lung cryobiopsy in diffuse parenchymal lung diseases: a comparative study versus video-assisted thoracoscopic lung biopsy and a systematic review of the literature

Ravaglia et al. Respiration 2016;91:215-227

Table 2. Safety profile results for SLB (VATS) and TBLC

	SLB (VATS) (n = 150)	TBLC (n = 297)	p value
Days of hospitalization	6.1 (3–48)	2.6 (0–17)	*<0.0001*
Adverse events			
Severe bleeding	0 (0.0)	0 (0.0)	
Persistent fever	7 (4.7)	0 (0.0)	
Prolonged air leak	5 (3.3)	1 (0.3)	
Acute exacerbation	5 (3.3)	1 (0.3)	
Pneumonia/empyema	3 (2.0)	0 (0.0)	
Transient respiratory failure	0 (0.0)	2 (0.7)	
Miscellanea	0 (0.0)	2 (0.7)	
Pneumothorax (in total)	NA (NA)	60 (20.20)	
Pneumothorax with drainage	NA (NA)	46 (15.50)	
Days of drainage	3.75 (2–40)	4.65 (2–15)	0.138
Patients with 0 adverse events	131 (87.3)	220 (74.1)	
Patients with 1 adverse event	16 (10.7)	75 (25.3)	
Patients with 2 adverse events	3 (2.0)	1 (0.3)	
Patients with 3 adverse events	0 (0.0)	1 (0.3)	
Time to 1st adverse event after biopsy, days	27.5±73.9	0.6±2.0	*<0.0001*
Mortality due to adverse event	4/150 (2.7)	1/297 (0.3)	*0.045*
	4/20 (20.0)	1/66 (1.5)	*0.01*
Survival			
Alive	88 (58.7)	272 (91.6)	
Dead	43 (28.7)	13 (4.4)	
Transplantation	4 (2.7)	1 (0.3)	

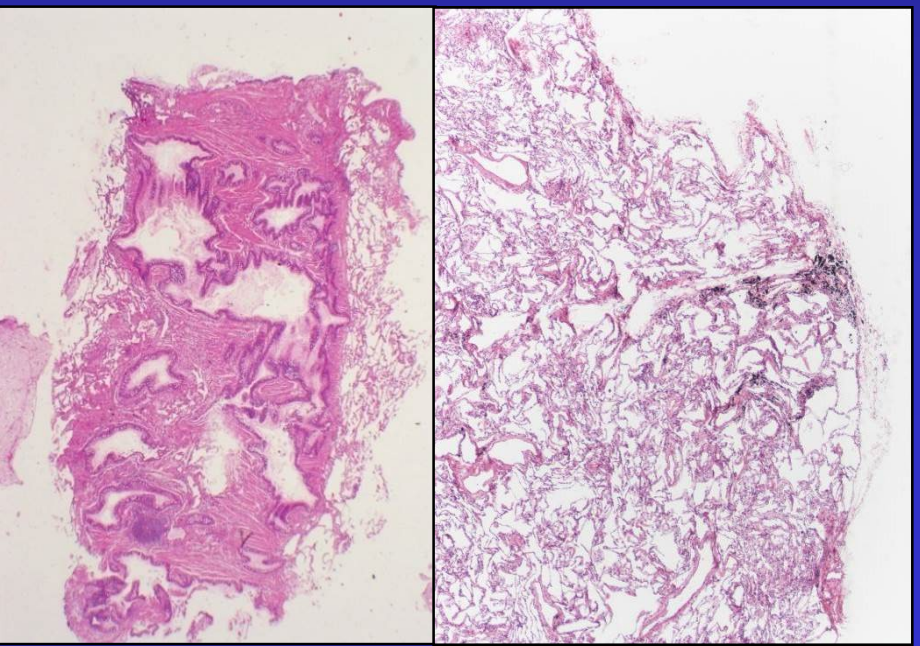
Cryobiopsy: systematic reviews and meta-analyses on diagnostic yield

Study	Diagnostic yield
Johannson. Ann Am Thorac Soc 2016	**79%**
Ravaglia. Respiration 2016	**81%**
Iftikhar. Ann Am Thorac Soc 2017	**83.7%**
Sharp. QJM 2017	**84%**

Diagnostic yield and risk/benefit analysis of trans-bronchial lung cryobiopsy in diffuse parenchymal lung diseases: a large cohort of 699 patients

Ravaglia et al. BMC Pulmonary Medicine 2019;19:16

- 87.8% of pathological diagnoses
- 90.1% of multidisciplinary diagnoses
- The diagnostic yield increases with at least 2 biopsies from at least 2 different sites



Endobronchial optical coherence tomography
Hariri, AJRCCM 2018

Confocal laser endomicroscopy
Wijmans, Respiration 2018

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The diagnostic yield of conventional TBB in fibrotic ILD is ≅ 30%

The diagnostic yield of SLB in ILD is ≅ 90-95%

The diagnostic accuracy of bronchoscopic lung cryobiopsy in the multidisciplinary diagnosis of idiopathic pulmonary fibrosis (Tomassetti et al. Am J Crit Care Med 2016;193:745-752)

117 patients with fibrotic ILDs, 59 submitted to surgical lung biopsy and 58 to cryobiopsy

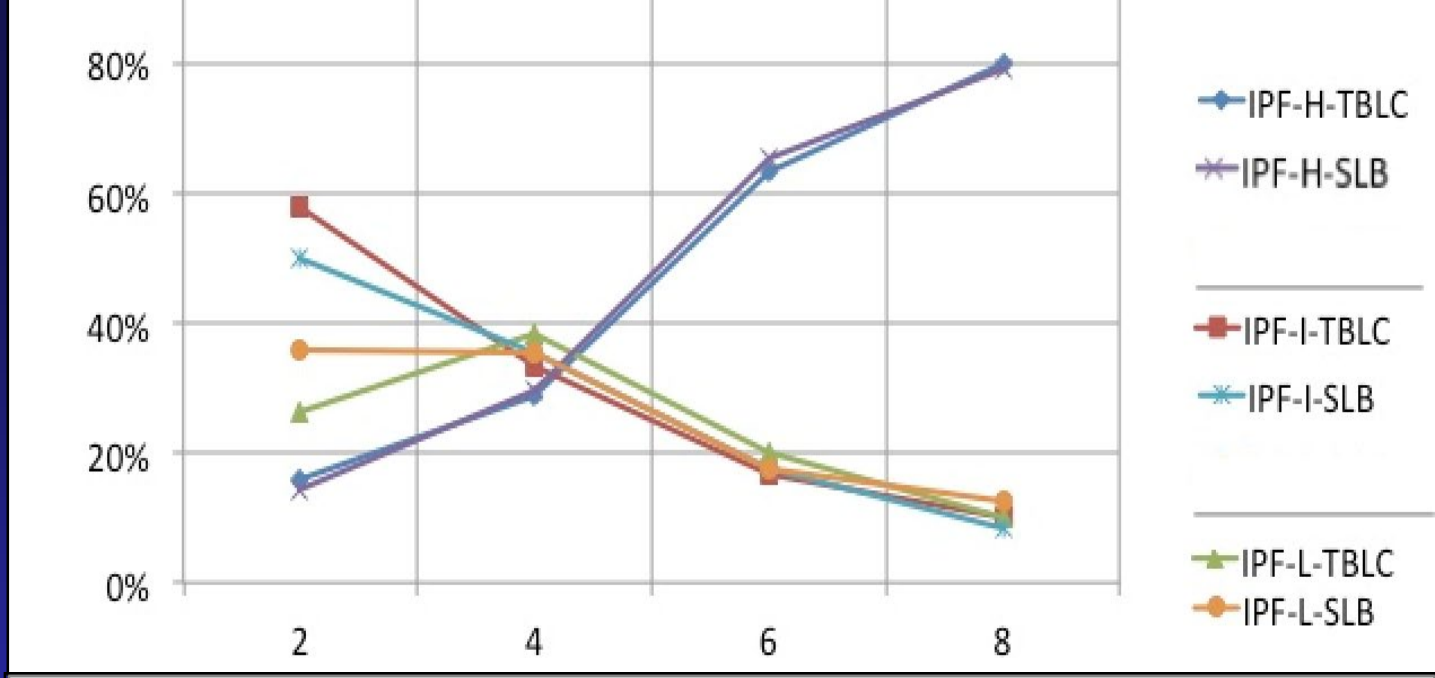
- Individual blinded review of biopsies by 3 pathologists (T. Colby, G. Rossi, A. Cavazza)
- 2 clinicians (U. Costabel, A.W. Wells), 2 radiologists (A. Carloni, N. Sverzellati) and 2 pathologists (G. Rossi, A. Cavazza) met to discuss the cases

The main goal of the study was to compare cryobiopsy and surgical lung biopsy for the variation (during the 8 steps) of 2 parameters: level of confidence and interpersonal agreement

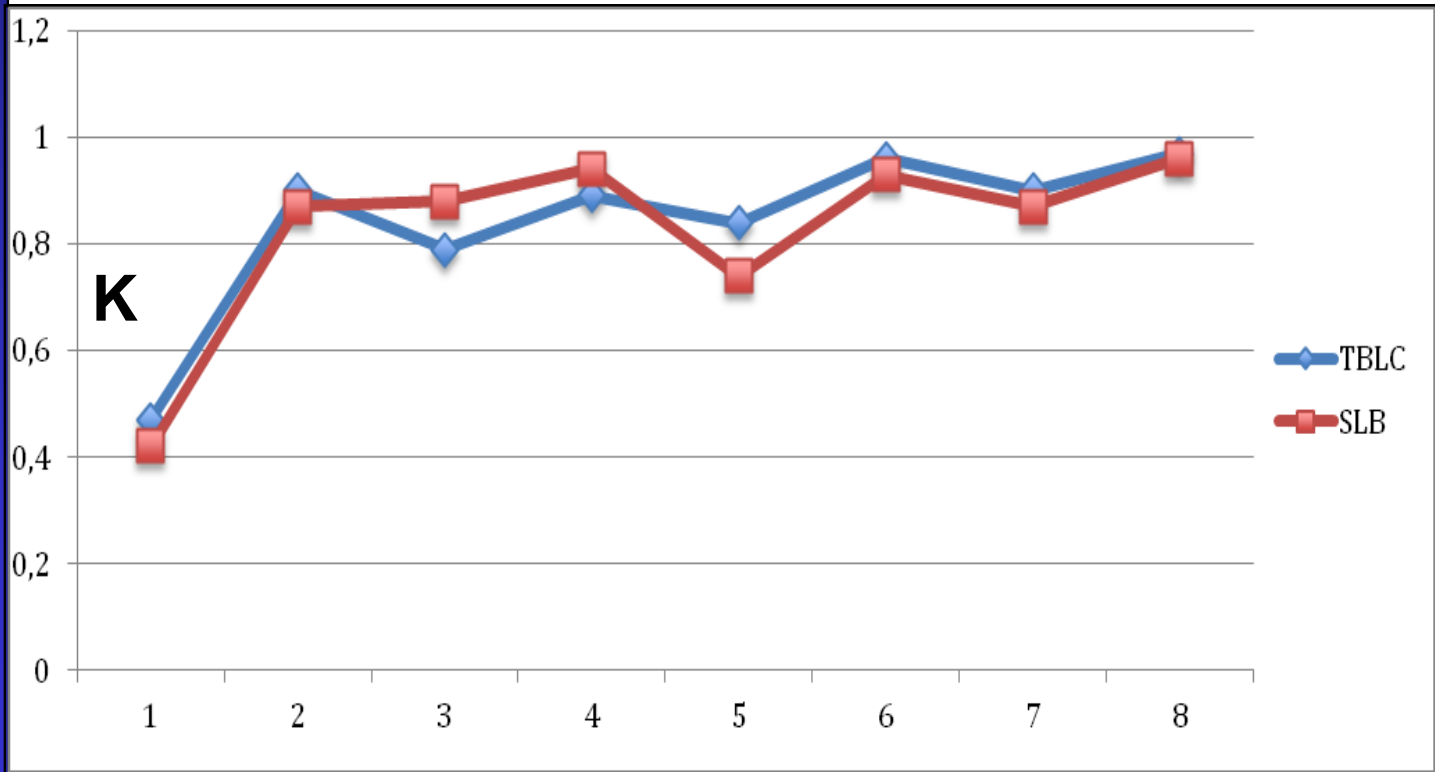
Step	Data	Participants	Discussion
1	Clinical-radiologic	Clinicians+ radiologists	Individual
2			Group
3	BAL	Clinicians+ radiologists+ pathologists	Individual
4			Group
5	Biopsy	Clinicians+ radiologists+ pathologists	Individual
6			Group
7	Follow-up	Clinicians+ radiologists+ pathologists	Individual
8			Group

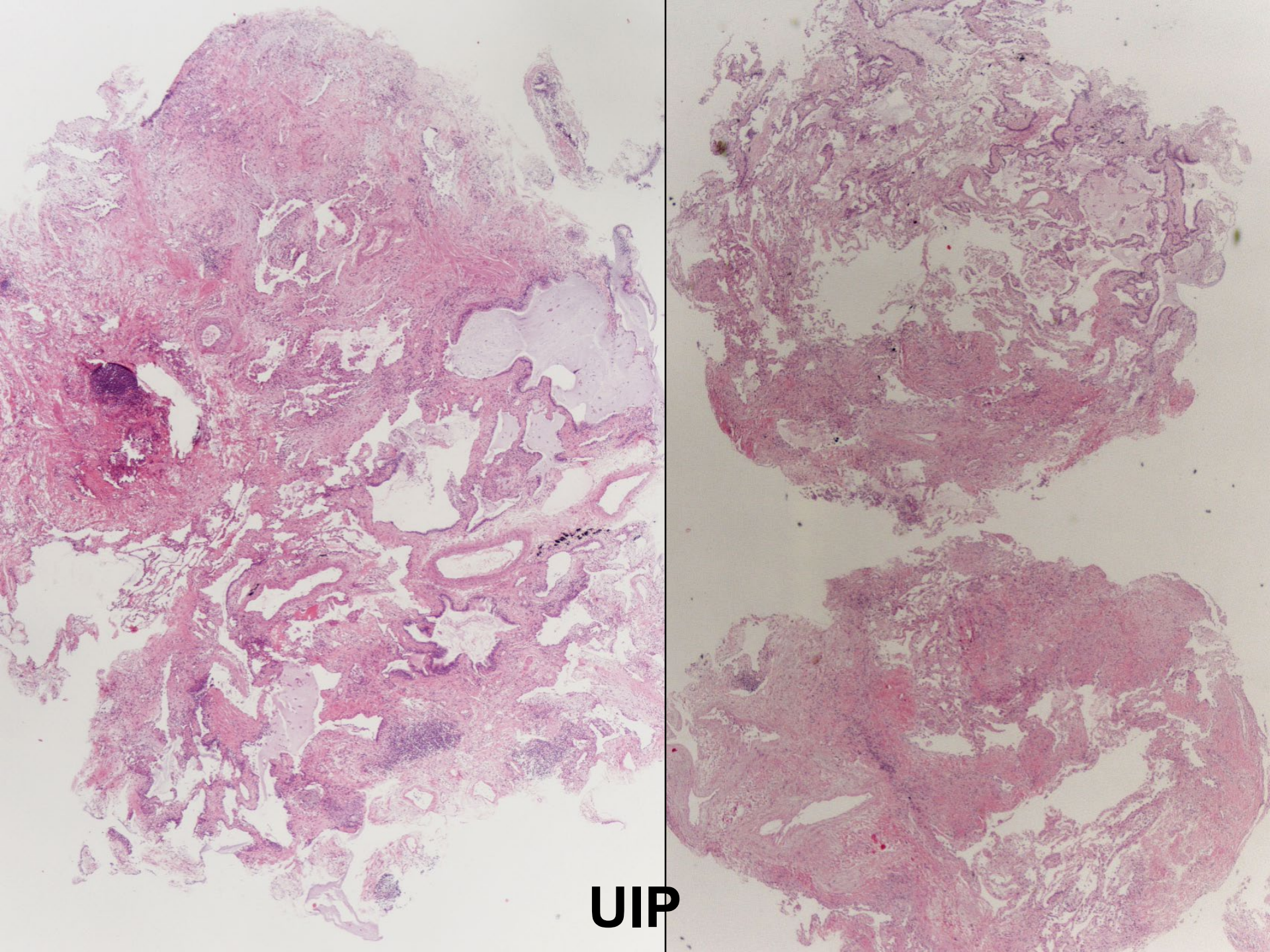
Design modified from Flaherty et al. Am J Respir Crit Care Med 2004;170:904-910

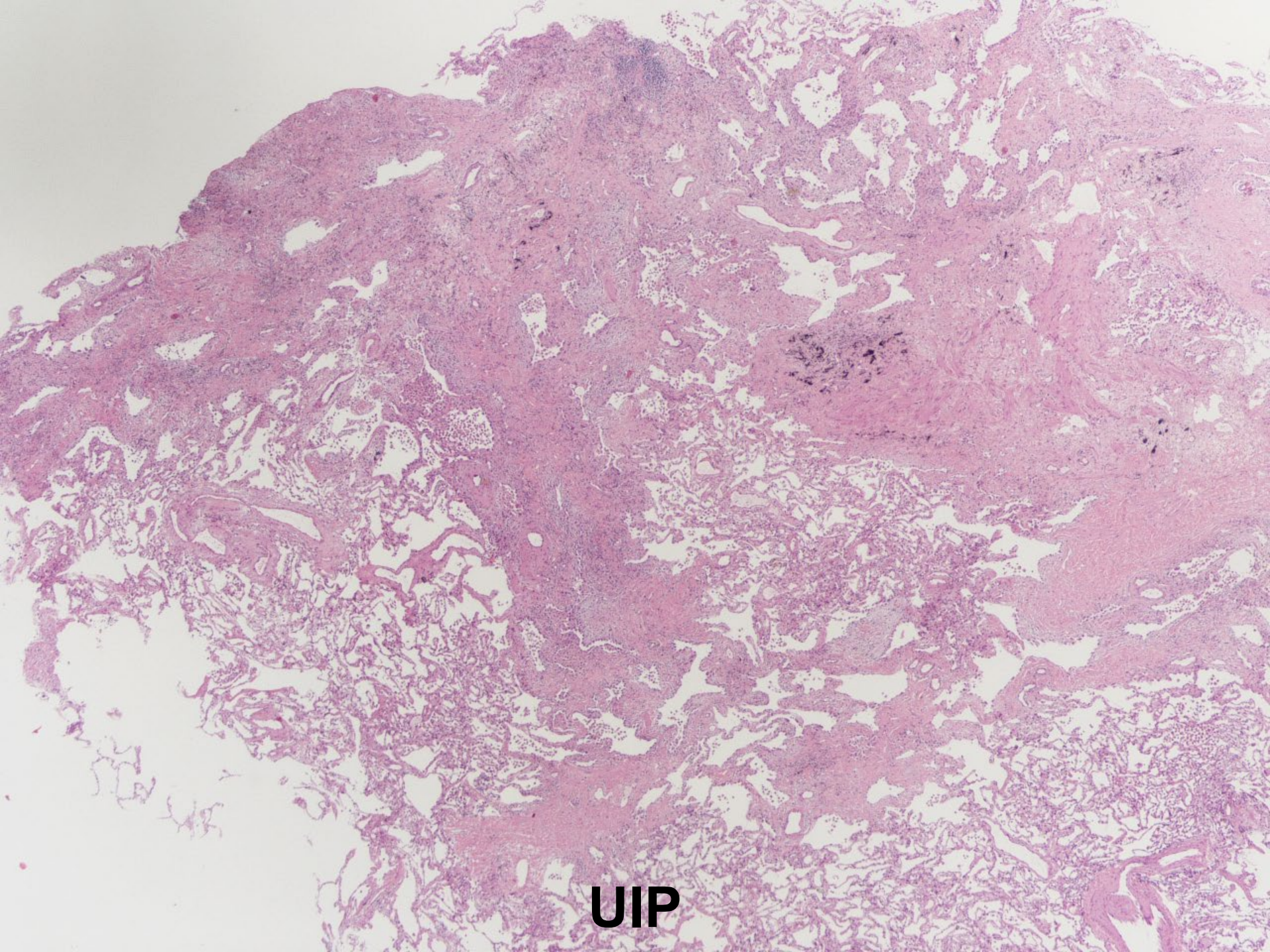
Variation of level of confidence (for diagnosis of IPF)

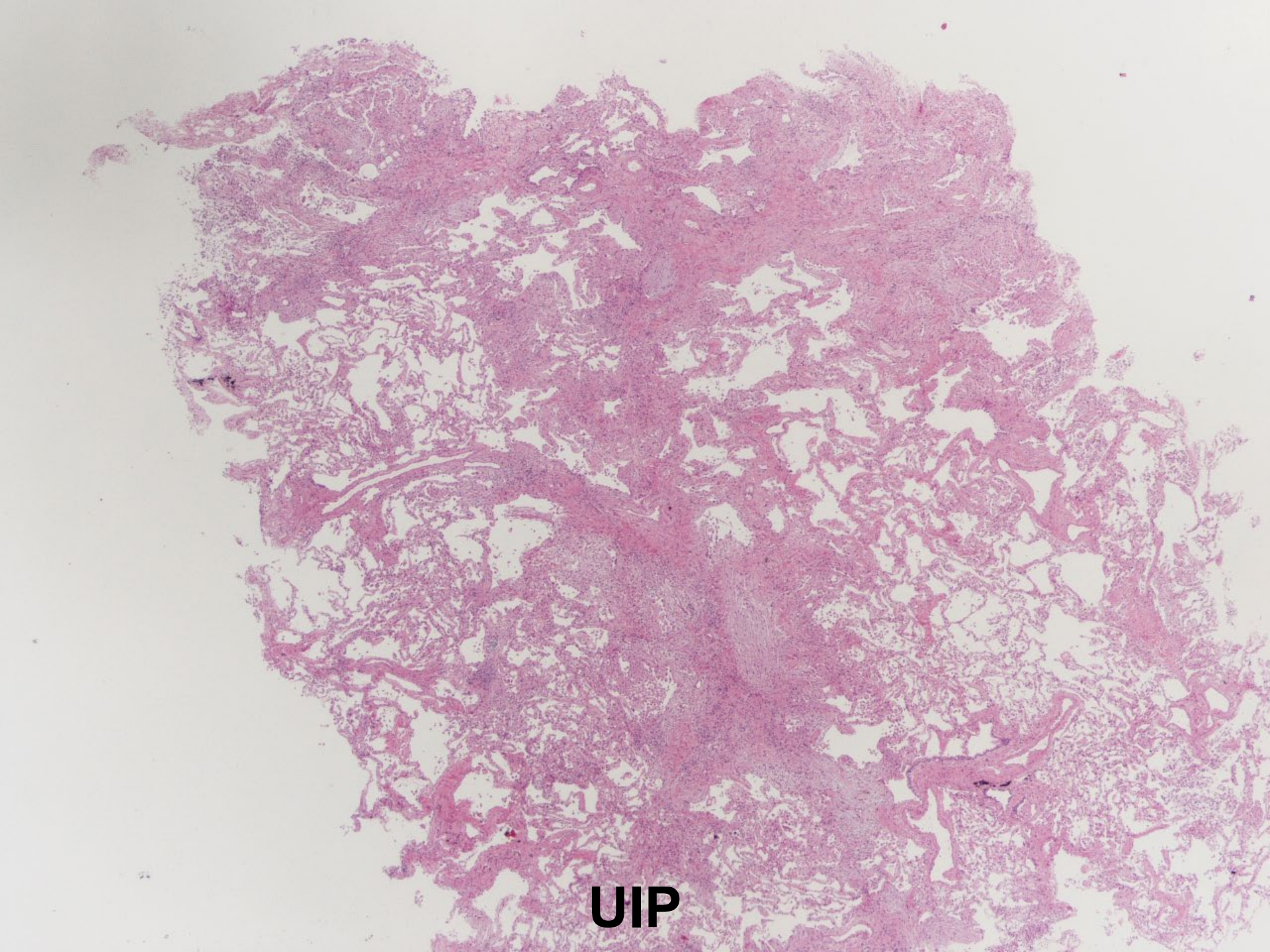


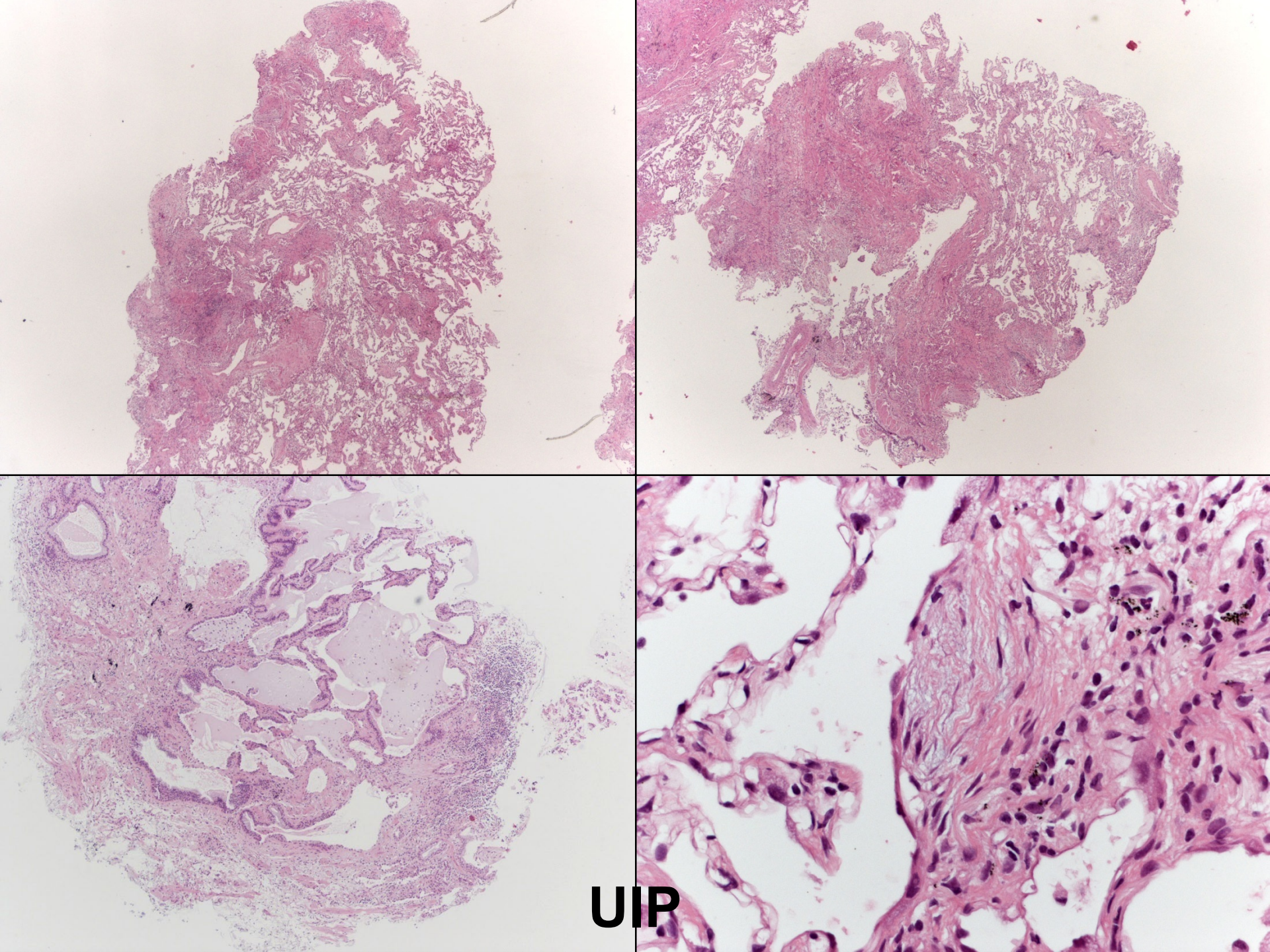
Variation of interpersonal agreement



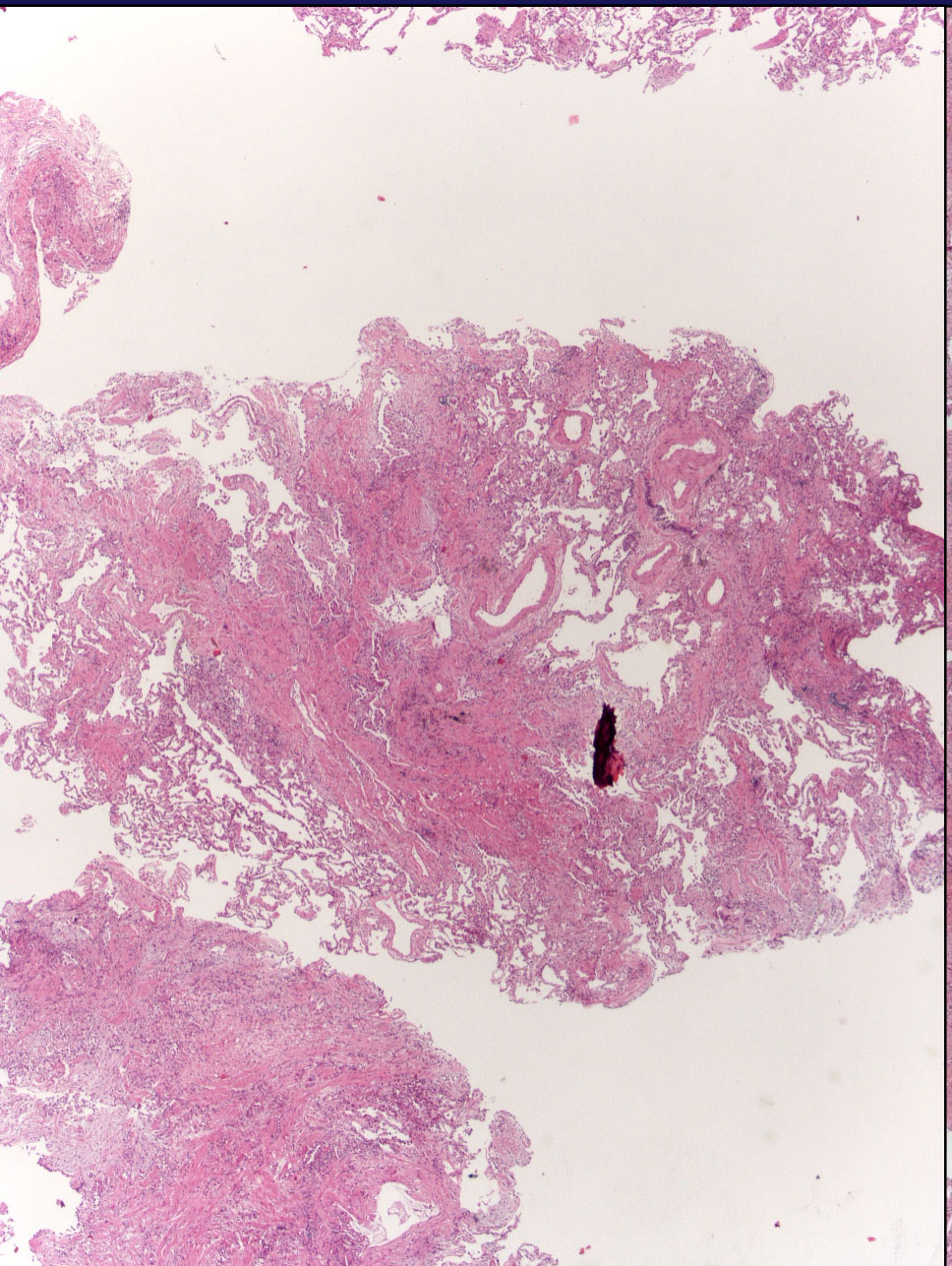

UIP


UIP

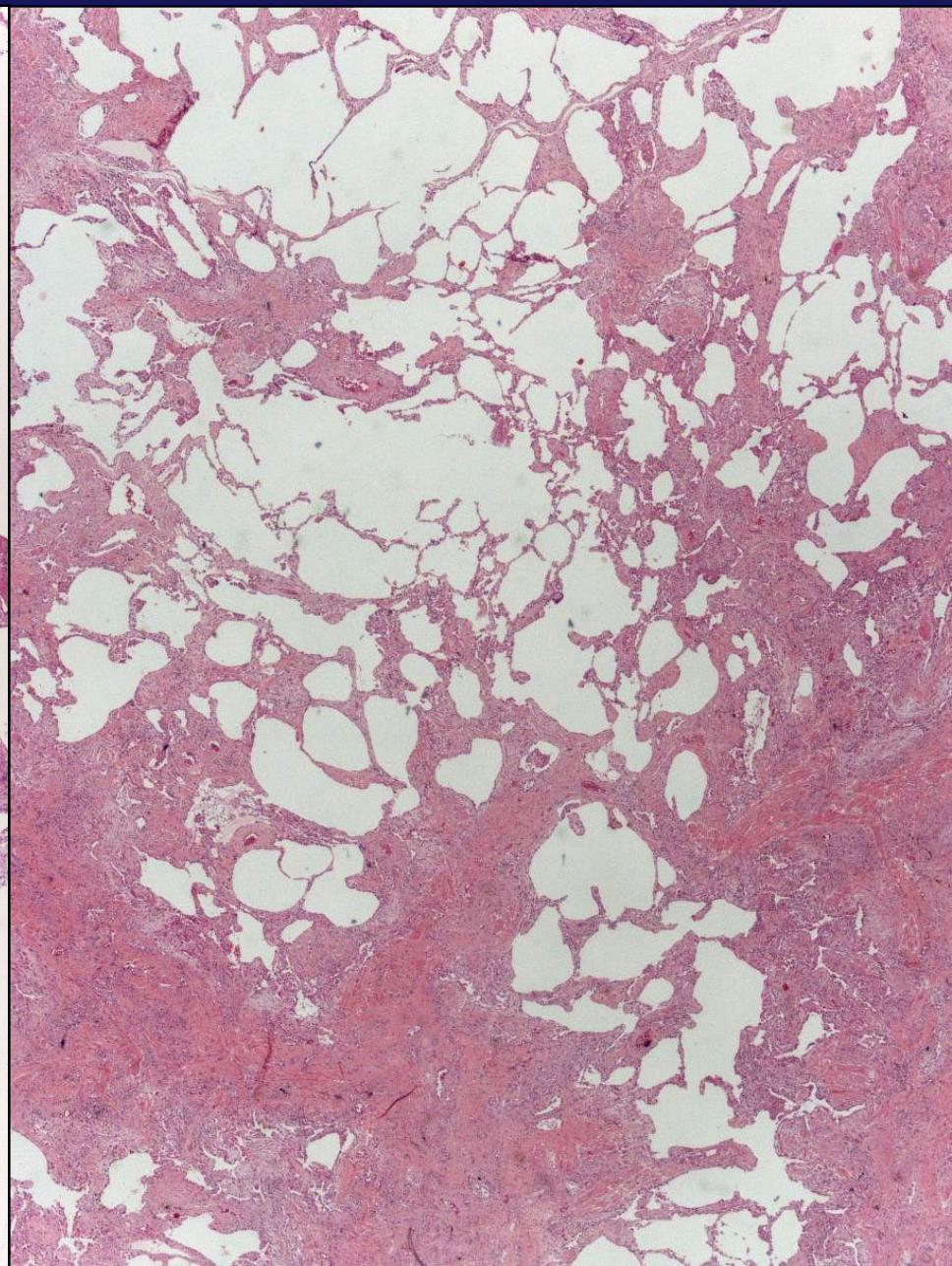

UIP

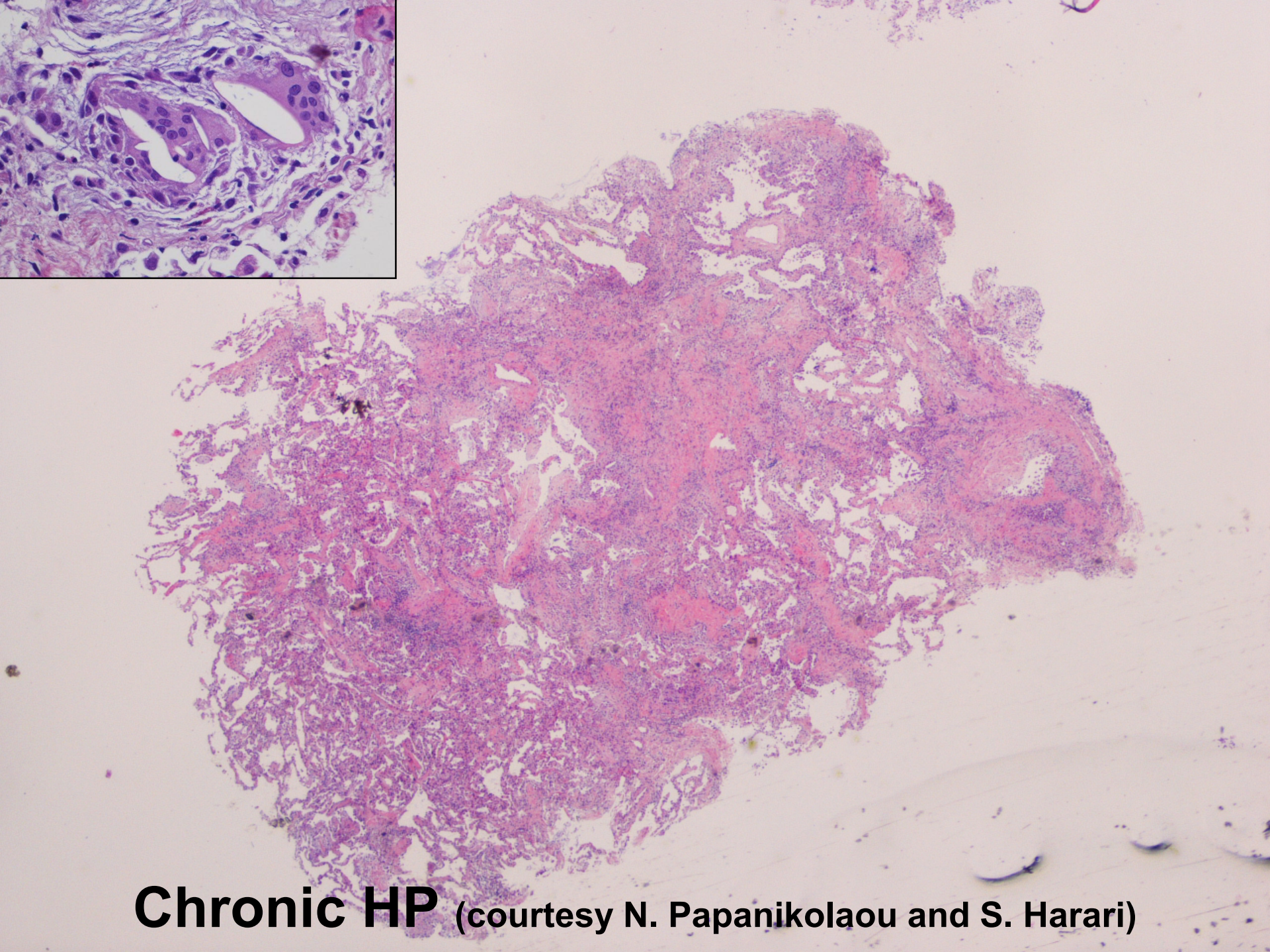

UIP

UIP on cryo

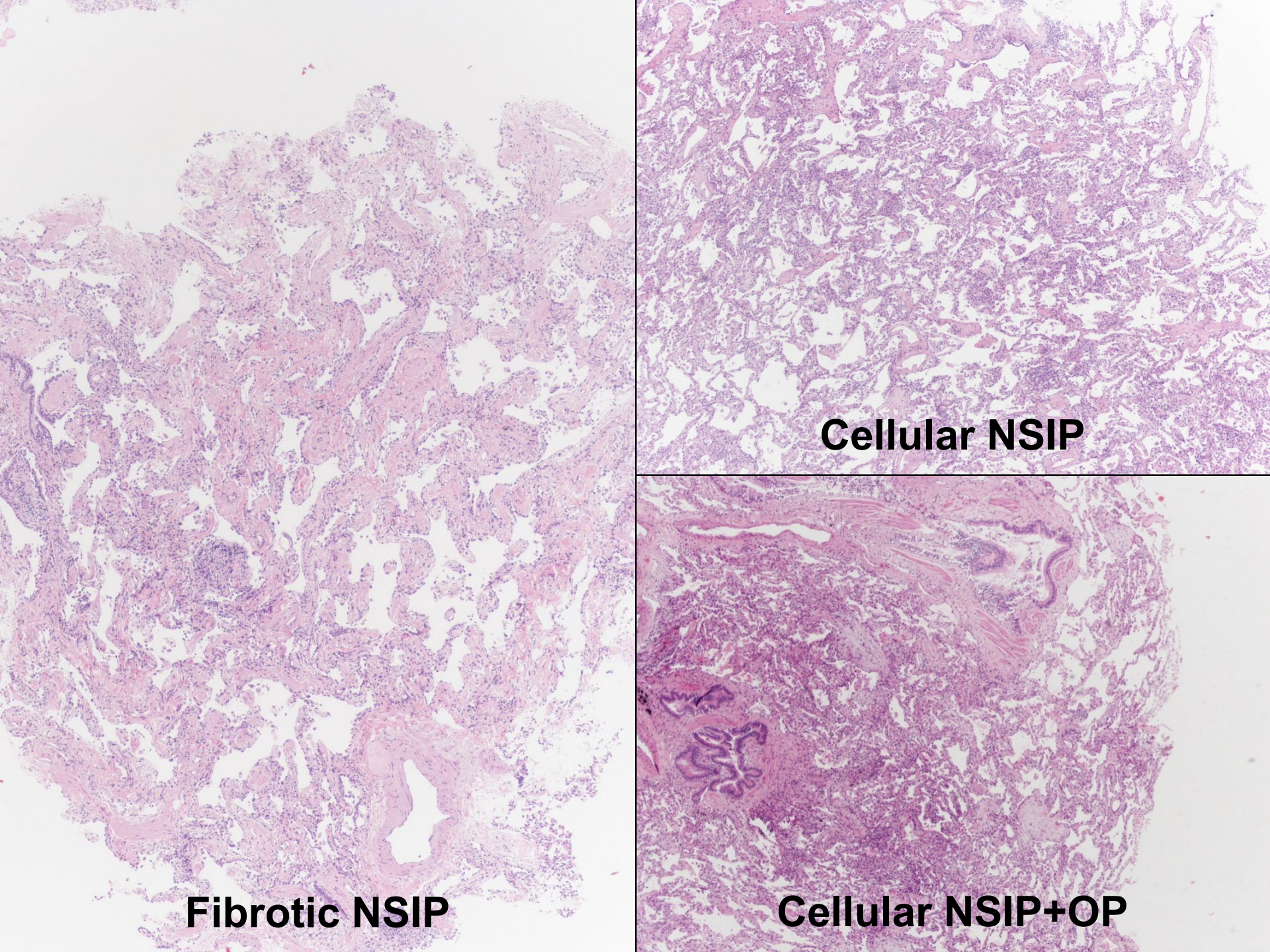


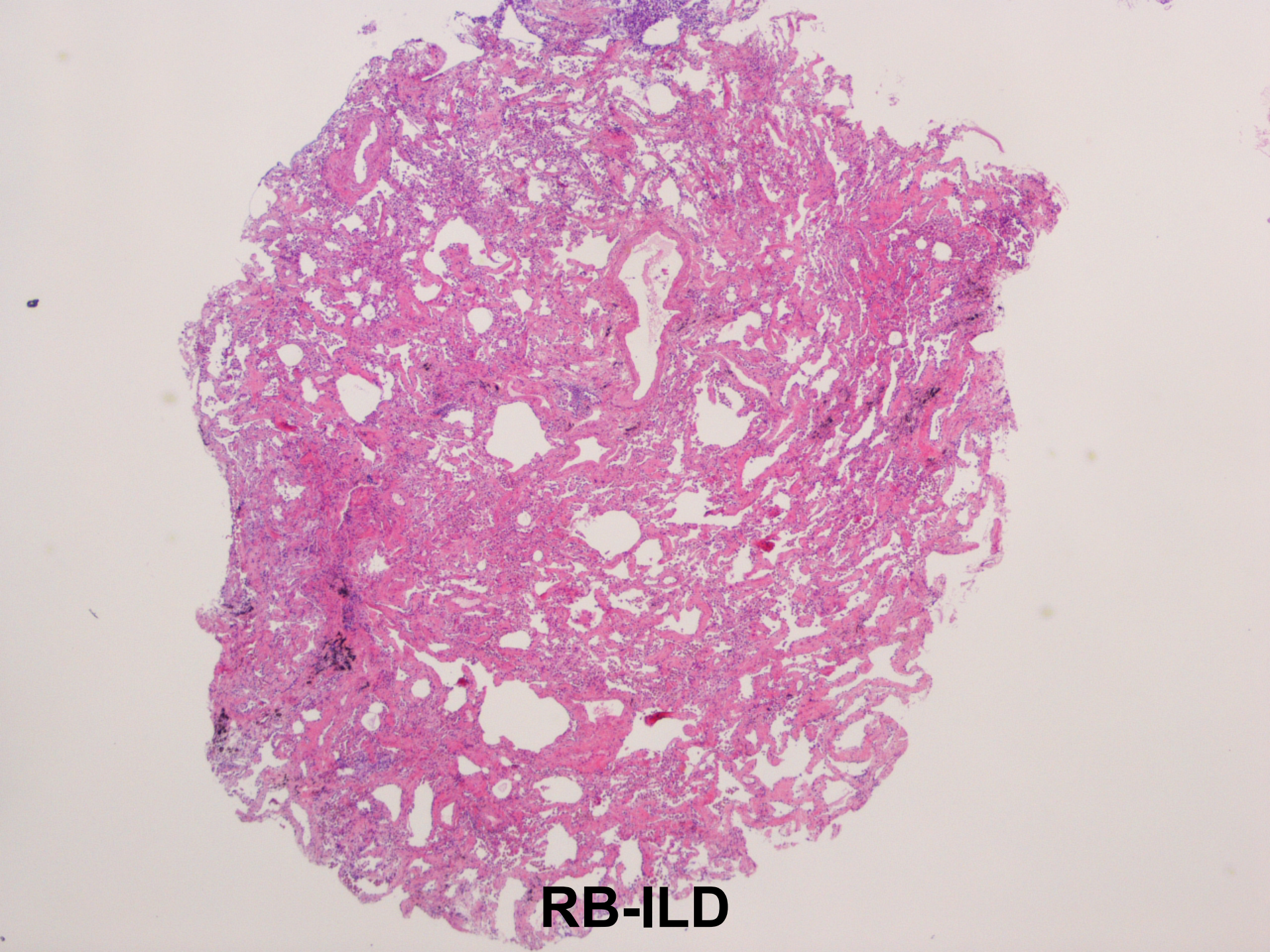
UIP on VATS

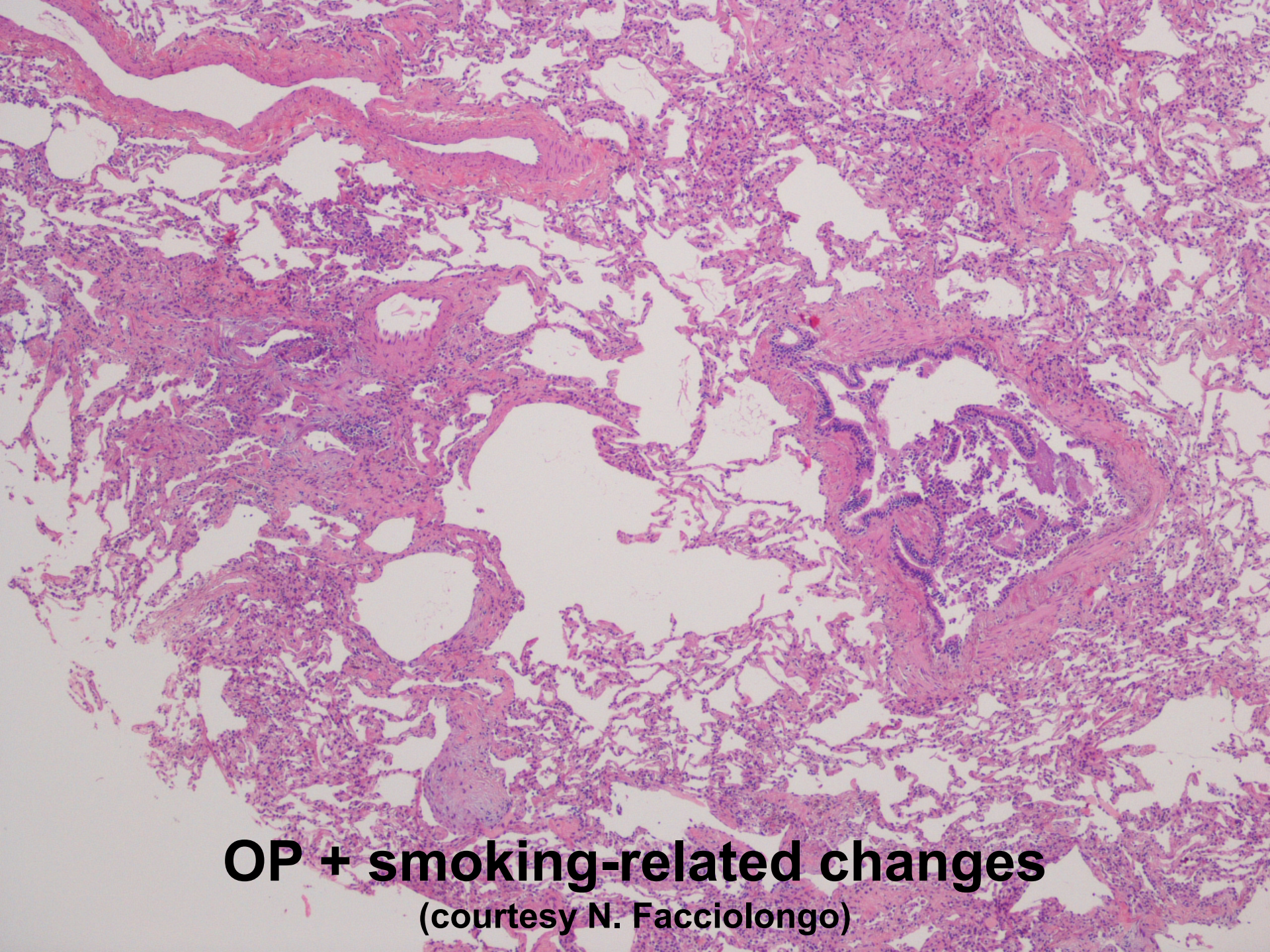




Chronic HP (courtesy N. Papanikolaou and S. Harari)

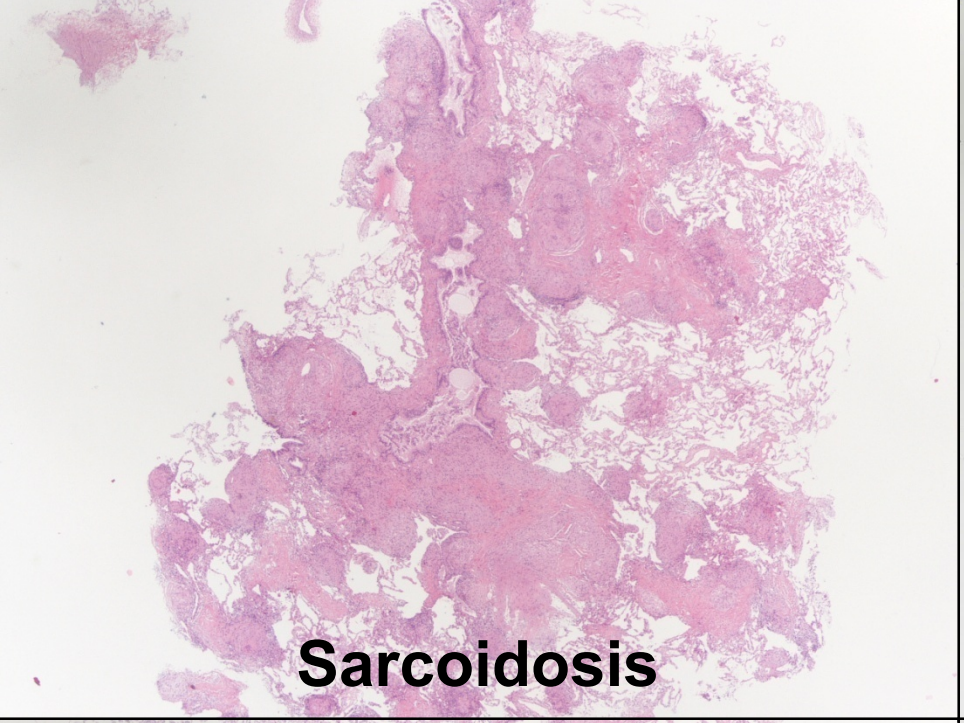

Cellular NSIP
Fibrotic NSIP
Cellular NSIP+OP

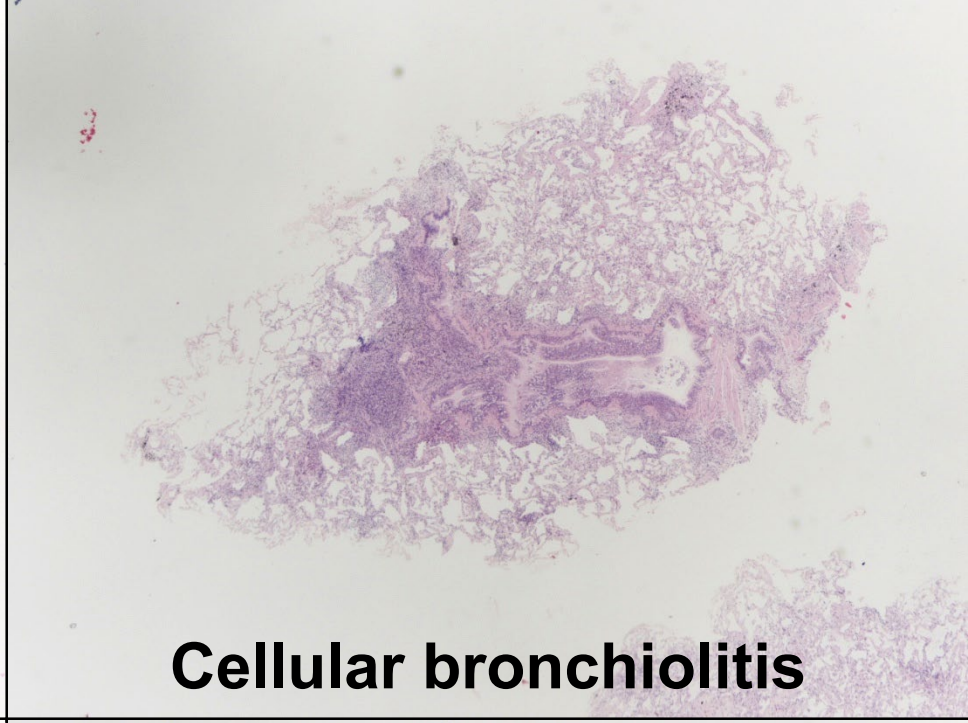

RB-ILD

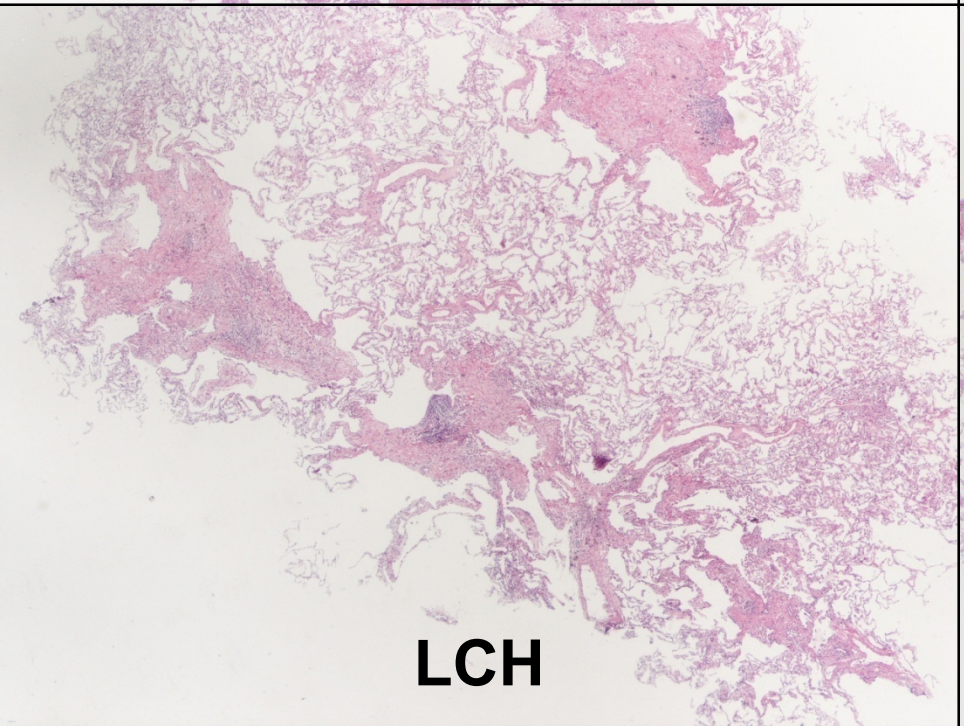


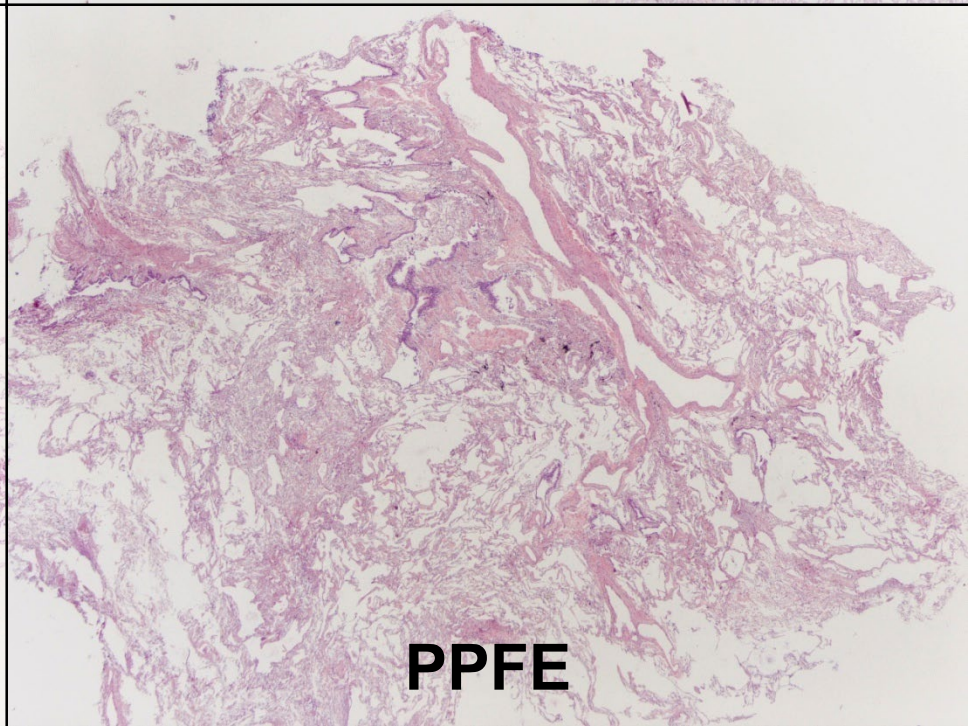
OP + smoking-related changes

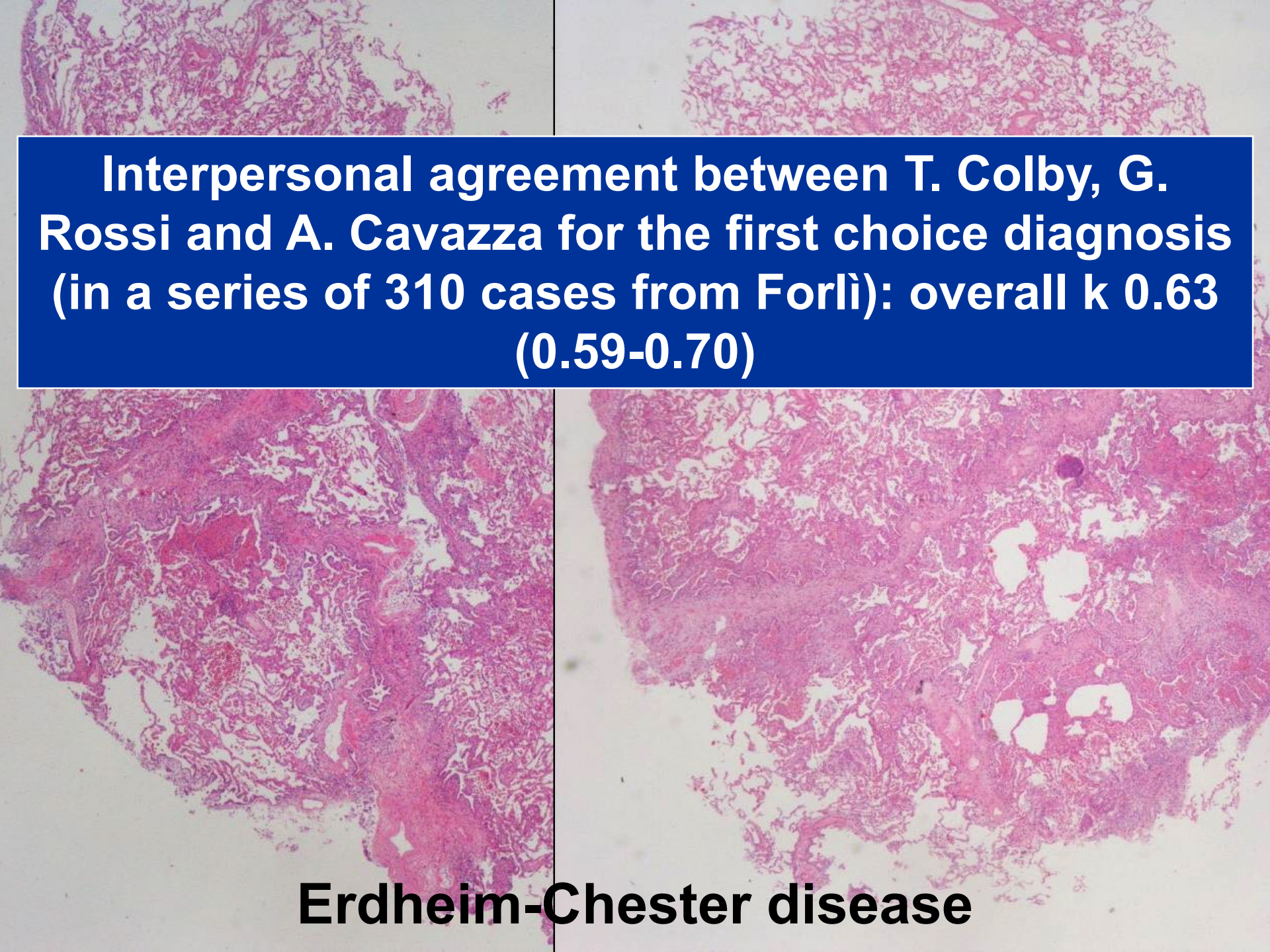
(courtesy N. Facciolongo)


Sarcoidosis


Cellular bronchiolitis


LCH


PPFE


Interpersonal agreement between T. Colby, G. Rossi and A. Cavazza for the first choice diagnosis (in a series of 310 cases from Forlì): overall k 0.63 (0.59-0.70)
Erdheim-Chester disease

Cryobiopsy in ILD
Some conclusive remarks

- Cryobiopsy provides enough informations to reach a multidisciplinary diagnosis in the majority of the patients with ILD, at a reduced risk compared with surgical lung biopsy

- Cryobiopsy may be the first invasive diagnostic step in many patients, potentially reducing the need for surgical lung biopsy and increasing the number of patients with ILD who can benefit from histology

Frequency

UIP on histology in surgical lung resections for cancer	**. 15% in mild smokers, 23% in moderate/heavy smokers (572 patients)** **(Kawabata, Histopathology 2008)** **. 5% in smokers (20 patients)** **(Katzenstein, Hum Pathol 2010)** **. 16% (526 patients, mostly smokers)** **(Watanabe, Respir Med 2017)**

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Interstitial lung abnormalities on CT scan in the screened population	**≅ 6%**

Cryobiopsy may provide the opportunity for an early diagnosis of IPF in a subset of patients with interstitial lung abnormalities