

Lung Biopsy in the Diagnosis of ILD

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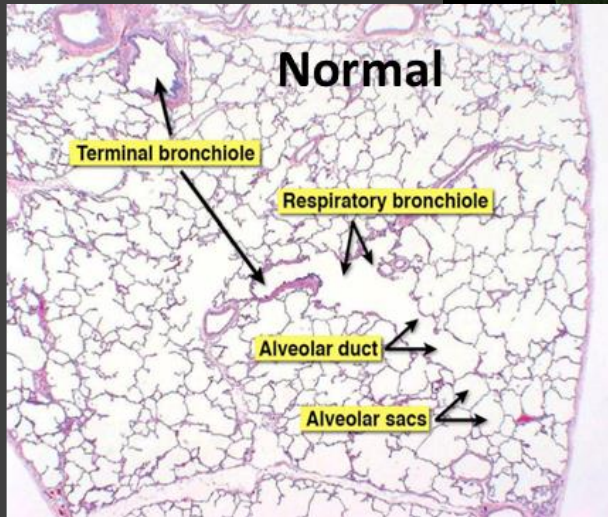


Importance of establishing a diagnosis in ILD

Important to distinguish various ILDs for the following reasons:

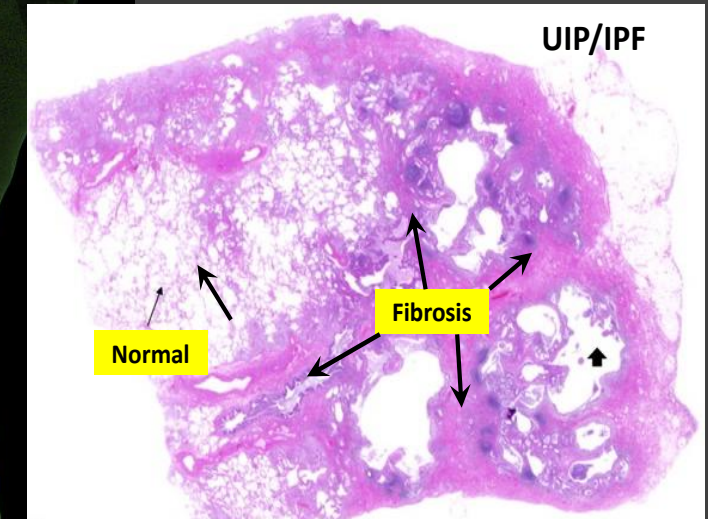
- Establish a high-confidence diagnosis
- Make informed decisions about therapeutic strategy
- Provide information about prognostic implications

Normal lung: Intact alveolar architecture with thin delicate walls



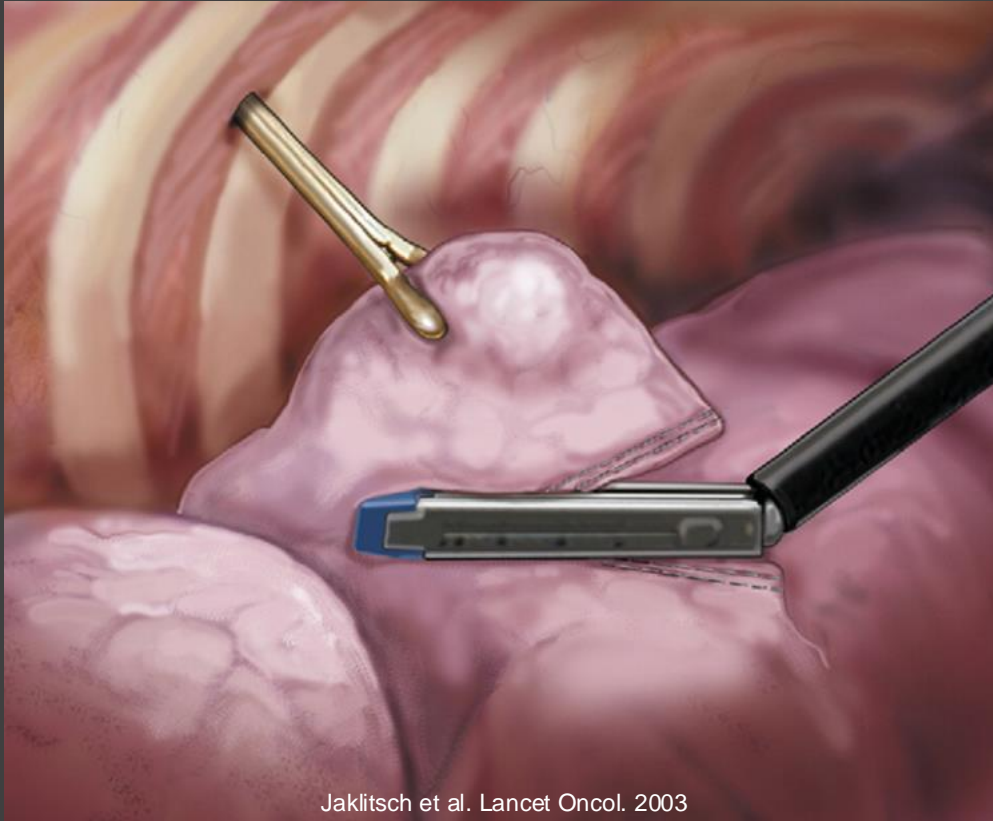
Slide courtesy of Dr. H. Tazelaar, Mayo Clinic, Scottsdale, AZ

UIP/IPF: Fibrosis destroys and replaces normal alveolar lung



Raghu et al. AJRCCM. 2018

Surgical Lung Wedge Biopsy



Jaklitsch et al. Lancet Oncol. 2003

Surgical procedure where a walnut-sized piece of lung removed for microscopic pathology assessment

Typically, biopsies taken from 3 sites (Upper, Middle, and Lower Lobe) to assess disease distribution and heterogeneity

Risk of perioperative morbidity

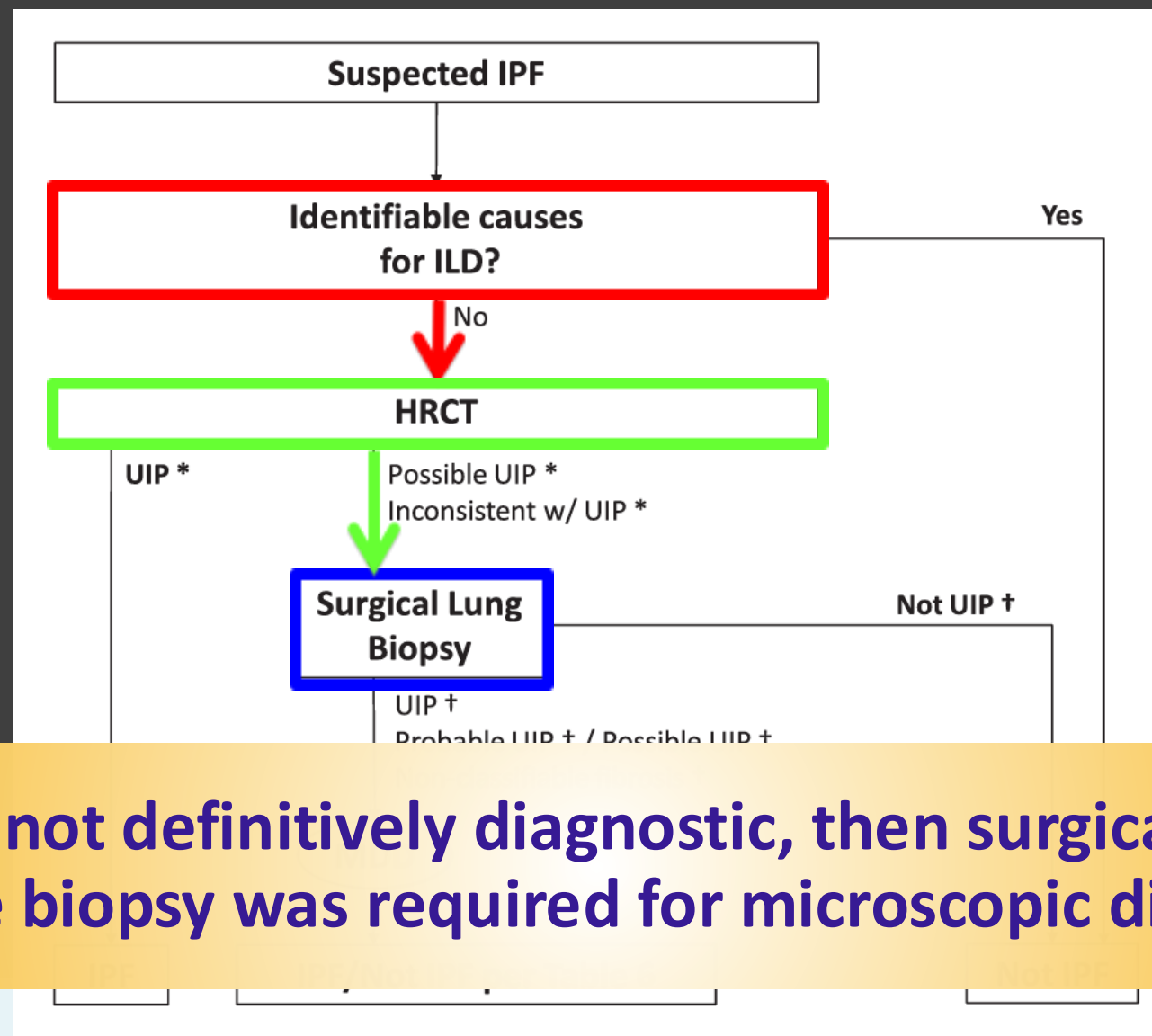
Prolonged hospitalization,
pneumonia, acceleration of disease

Risk of Mortality

Elective: 1-2% mortality

Non-elective: 4-20% mortality

2011 ATS Diagnostic Work Flow

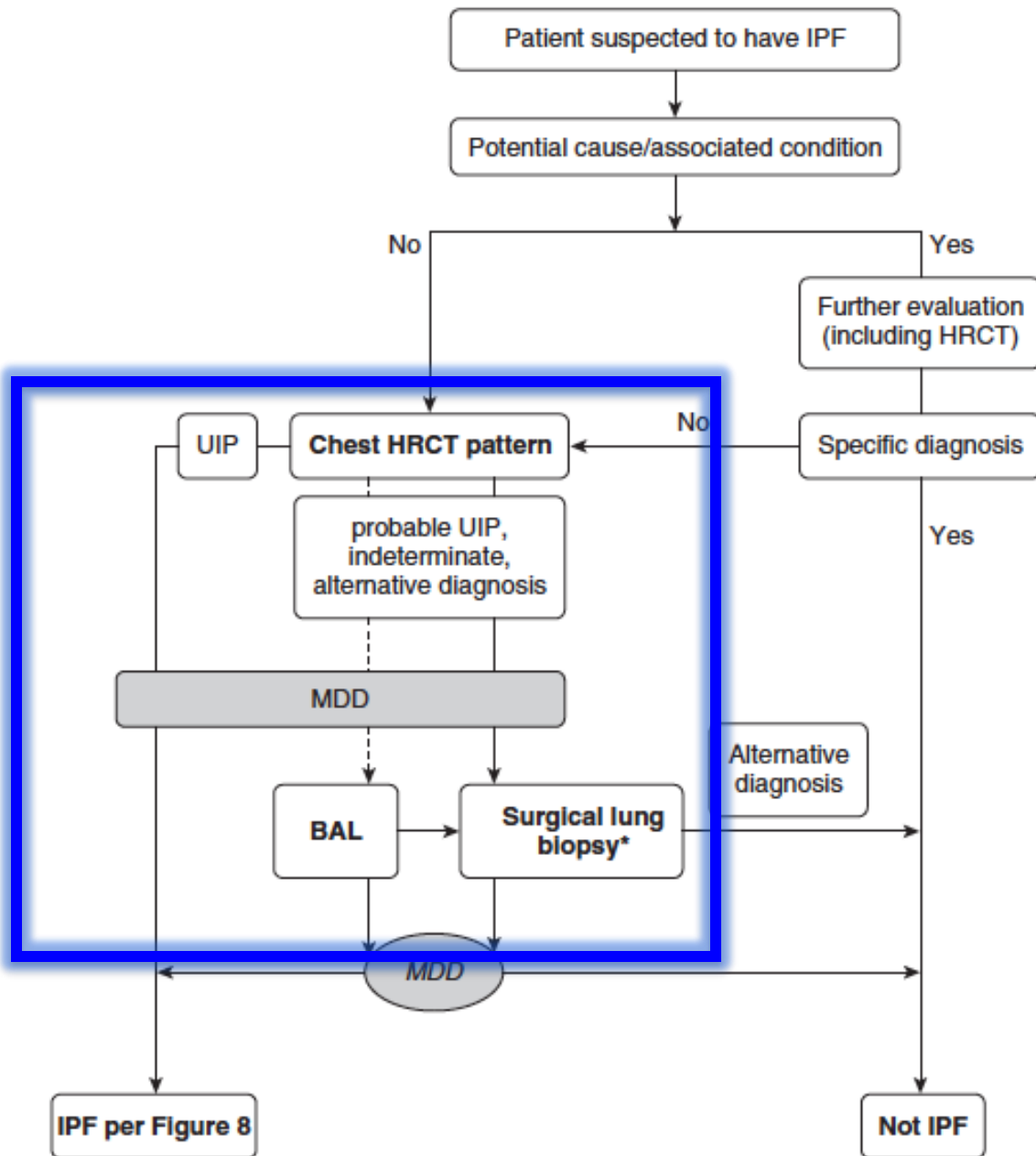


If CT not definitively diagnostic, then surgical lung wedge biopsy was required for microscopic diagnosis

HRCT: Diagnostic Requirements in 2011

UIP Pattern (all 4 features)	Possible UIP (all 3 features)	Inconsistent with UIP (Any of 7 features)
Subpleural, basal predominance	Subpleural, basal predominance	Upper or mid-lung predominance
Reticular abnormality	Reticular abnormality	Peribronchovascular predominance
Honeycombing With Or without Traction bronchiectasis	Absence of Inconsistent features	Extensive ground-glass abnormality
Absence of Inconsistent features		Profuse micronodules
		Discrete cysts
		Mosaic attenuation or air-trapping
		Consolidation in bronchopulmonary segments(s) or lobe(s)

ATS 2018 Guidelines



Fleischner Guidelines

Panel 3: Pathways to a confident working multidisciplinary diagnosis of IPF

When can one make a confident diagnosis of IPF without biopsy?

- Clinical context of IPF*, with CT pattern of typical or probable UIP

When is a diagnostic biopsy necessary to make a confident diagnosis of IPF?

- Clinical context of IPF* with CT pattern either indeterminate or suggestive of an alternative diagnosis
- Clinical context indeterminate for IPF† with any CT pattern

When is multidisciplinary diagnosis necessary in the context of suspected IPF?

- When the clinical context or the CT pattern, or both, are indeterminate; the outcome of multidisciplinary discussion will be a decision whether to perform an additional clinical evaluation, bronchoalveolar lavage, or diagnostic biopsy, or some combination of these procedures
- After biopsy, to integrate the clinical, imaging, and histological features
- To re-review patients in whom the longitudinal course of disease is discordant with the previously established multidisciplinary diagnosis
- When diagnostic tissue is not available, to consider a working diagnosis of IPF

What should be done when diagnostic tissue is not available?

- Multidisciplinary diagnosis with consideration of the patient's age, sex, smoking status, findings on bronchoalveolar lavage, and longitudinal disease behaviour
- In this context, a working diagnosis of IPF can be made in the presence of a progressive fibrosing interstitial pneumonia, and in the absence of an alternative explanation; the level of diagnostic confidence of such a working diagnosis should be recorded, and the diagnosis should be reviewed at regular intervals, since it might change over time

IPF=idiopathic pulmonary fibrosis. UIP=usual interstitial pneumonia. *Clinical context of IPF includes all of the following: older than 60 years, absence of clinically significant environmental or medication exposure, no evidence of connective tissue disease. †Clinical context indeterminate for IPF includes any of the following: aged 60 years or younger, potentially significant environmental or medication exposure, or evidence of connective tissue disease.

HRCT: Diagnostic Requirements in 2018



UIP Pattern	Probable UIP (all 4 features)	Indeterminate	Alternate Diagnosis
Subpleural, basal predominance	Subpleural, basal predominance	Subpleural, basal predominance	Upper or mid-lung predominance
Reticular abnormality	Reticular abnormality	Reticular abnormality	Peribronchovascular predominance
Honeycombing With Or without Traction bronchiectasis	Peripheral traction bronchiectasis	Absence of Inconsistent features	Extensive ground-glass abnormality
Absence of Inconsistent features	Absence of Inconsistent features		Profuse micronodules
			Discrete cysts
			Mosaic attenuation or air-trapping
			Consolidation in bronchopulmonary segments(s) or lobe(s)

>95 % PPV

~80% PPV

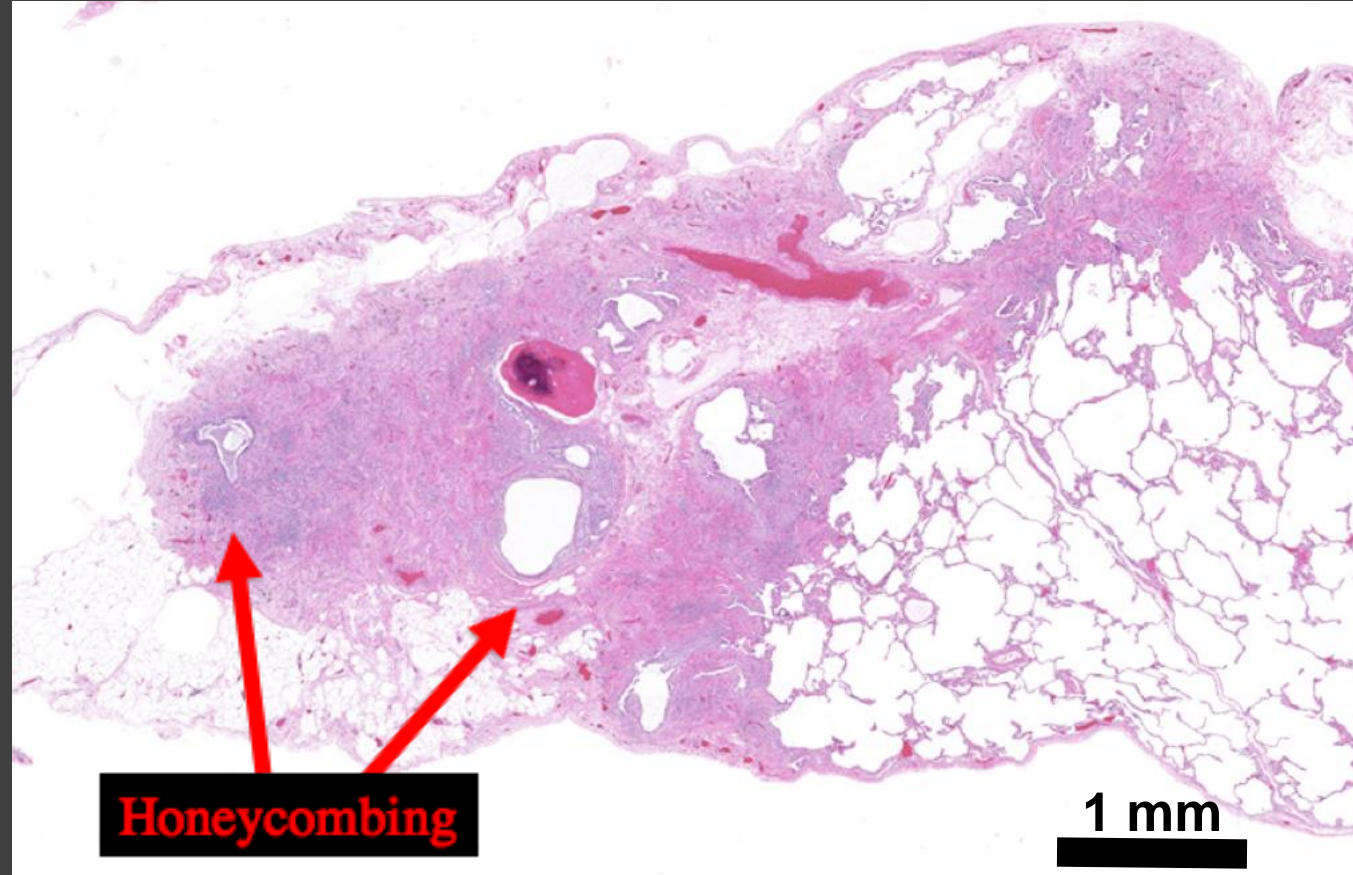
~50% PPV

Lynch et al. Fleischner IPF Diagnostic Guidelines. Lancet Respir Med 2017.

Raghu et al. ATS/ERS/JRS/ALAT IPF Diagnostic Guidelines. AJRCCM 2018.



HRCT resolution is $\sim 2\text{mm}$



- Challenging to visualize “microscopic” honeycombing $< 2\text{-}3\text{ mm}$ diameter
 - Difficult to distinguish true honeycombing from traction bronchiectasis (TB)
- UIP can have TB, but not all ILD with TB is UIP

Histology Criteria for UIP Pattern: ATS / ERS / JRS / ALAT 2018 Statement



UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
<ul style="list-style-type: none"> • Dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing) • Predominant subpleural and/or paraseptal distribution of fibrosis • Patchy involvement of lung parenchyma by fibrosis • Fibroblast foci • Absence of features to suggest an alternate diagnosis 	<ul style="list-style-type: none"> • Some histologic features from column 1 are present but to an extent that precludes a definite diagnosis of UIP/IPF <p style="text-align: center;"><i>And</i></p> <ul style="list-style-type: none"> • Absence of features to suggest an alternative diagnosis <p style="text-align: center;"><i>Or</i></p> <ul style="list-style-type: none"> • Honeycombing only 	<ul style="list-style-type: none"> • Fibrosis with or without architectural distortion, with features favoring either a pattern other than UIP or features favoring UIP • secondary to another cause* • Some histologic features from column 1, but with other features suggesting an alternative diagnosis[†] 	<ul style="list-style-type: none"> • Features of other histologic patterns of IIPs (e.g., absence of fibroblast foci or loose fibrosis) in all biopsies • Histologic findings indicative of other diseases (e.g., hypersensitivity pneumonitis, Langerhans cell histiocytosis, sarcoidosis, LAM)

Lynch et al. Fleischner IPF Diagnostic Guidelines. Lancet Respir Med 2017.

Raghu et al. ATS/ERS/JRS/ALAT IPF Diagnostic Guidelines. AJRCCM 2018.

Usual Interstitial Pneumonitis (UIP)

Spatial heterogeneity

Alternating areas of:

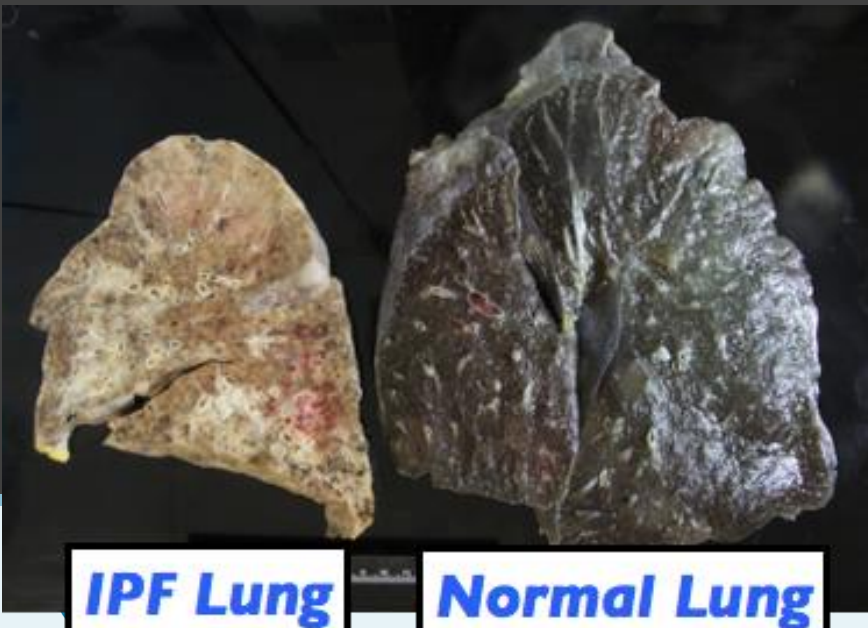
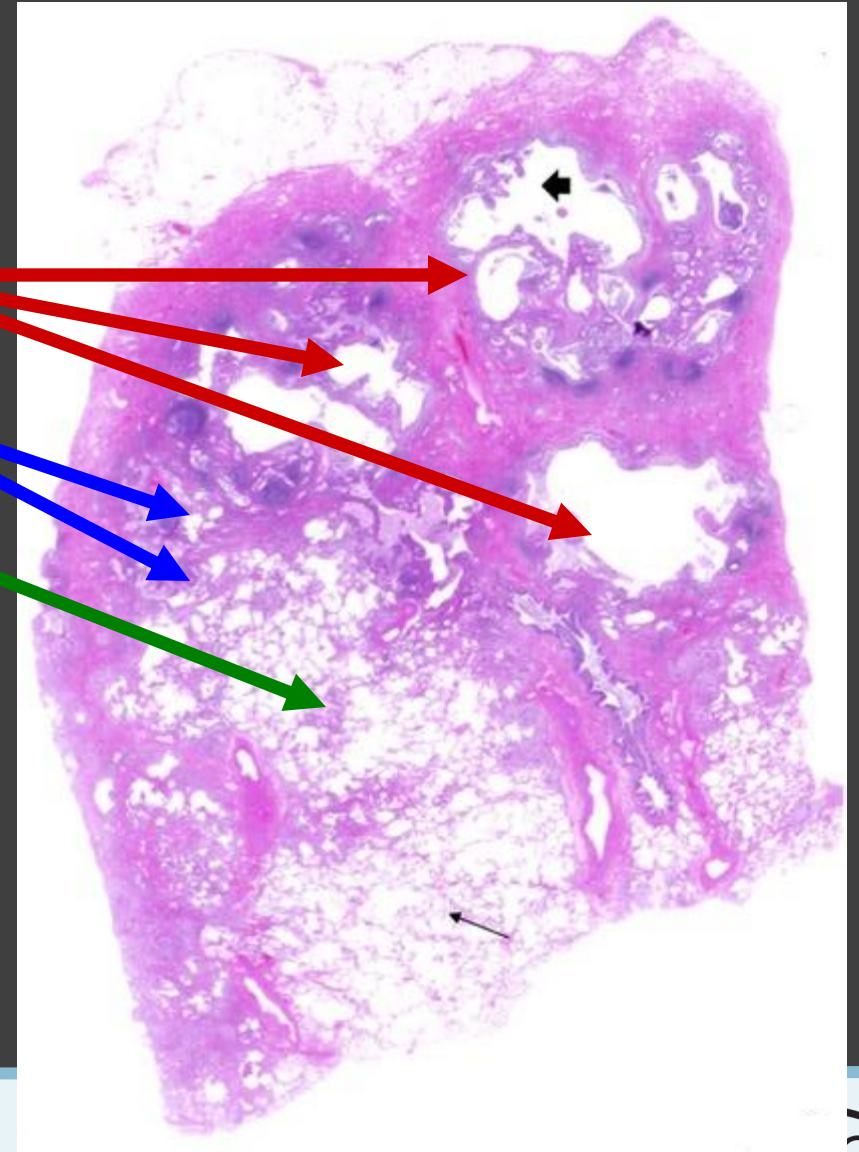
- Honeycomb change
- Fibrosis / distorted architecture
- Normal lung

Subpleural / paraseptal Predominance

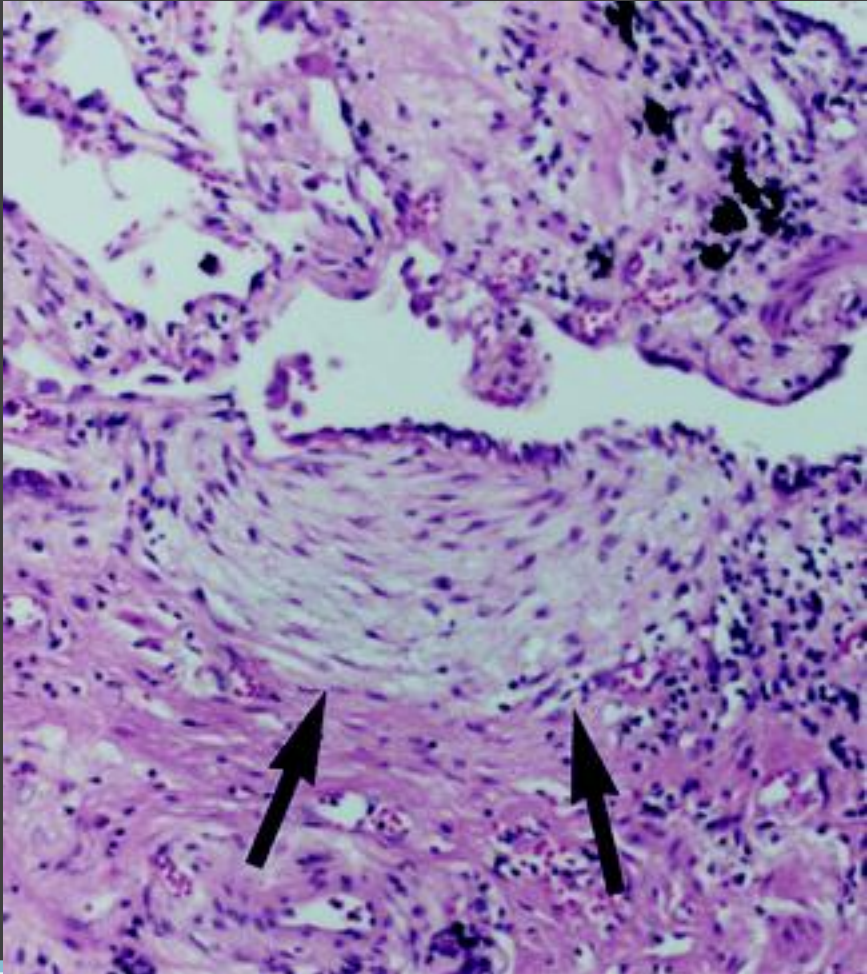
Lower Lobe Predominant

Temporal heterogeneity

Fibroblastic foci



Pathology Criteria for UIP Pattern: Fibroblastic Foci



- Small aggregates of actively proliferating fibroblasts/myofibroblasts
- Sites of active collagen synthesis
- Not pathognomonic for UIP, but necessary for the diagnosis
- Number of fibroblastic foci inversely correlates with survival

Histology Criteria for UIP Pattern: ATS / ERS / JRS / ALAT 2018 Statement

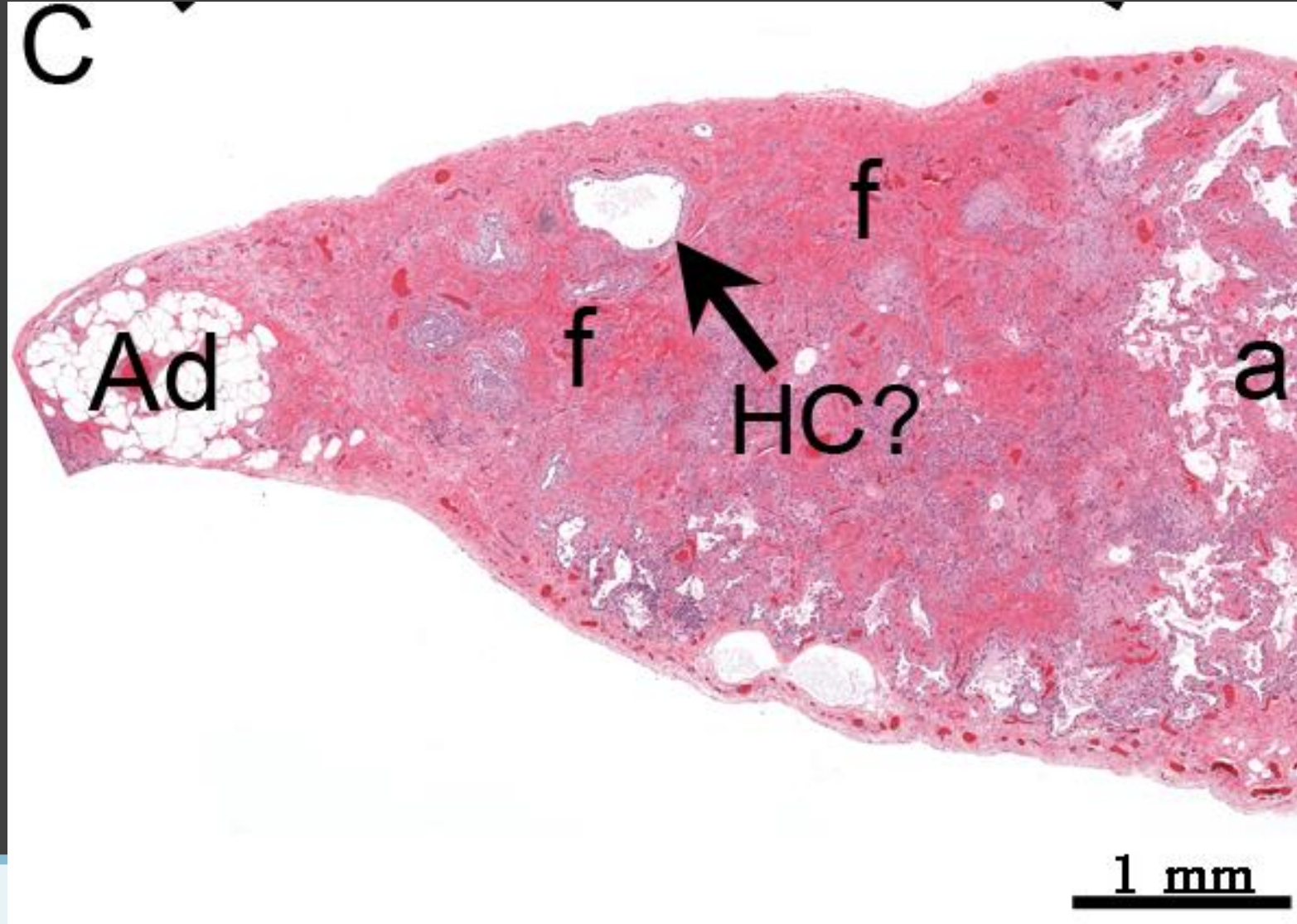


UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
<ul style="list-style-type: none"> • Dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing) • Predominant subpleural and/or paraseptal distribution of fibrosis • Patchy involvement of lung parenchyma by fibrosis • Fibroblast foci • Absence of features to suggest an alternate diagnosis 	<ul style="list-style-type: none"> • Some histologic features from column 1 are present but to an extent that precludes a definite diagnosis of UIP/IPF <p style="text-align: center;"><i>And</i></p> <ul style="list-style-type: none"> • Absence of features to suggest an alternative diagnosis <p style="text-align: center;"><i>Or</i></p> <ul style="list-style-type: none"> • Honeycombing only 	<ul style="list-style-type: none"> • Fibrosis with or without architectural distortion, with features favoring either a pattern other than UIP or features favoring UIP • Secondary to another cause* • Some histologic features from column 1, but with other features suggesting an alternative diagnosis[†] 	<ul style="list-style-type: none"> • Features of other histologic patterns of IIPs (e.g., absence of fibroblast foci or loose fibrosis) in all biopsies • Histologic findings indicative of other diseases (e.g., hypersensitivity pneumonitis, Langerhans cell histiocytosis, sarcoidosis, LAM)

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Probable UIP



Histology Criteria for UIP Pattern: ATS / ERS / JRS / ALAT 2018 Statement

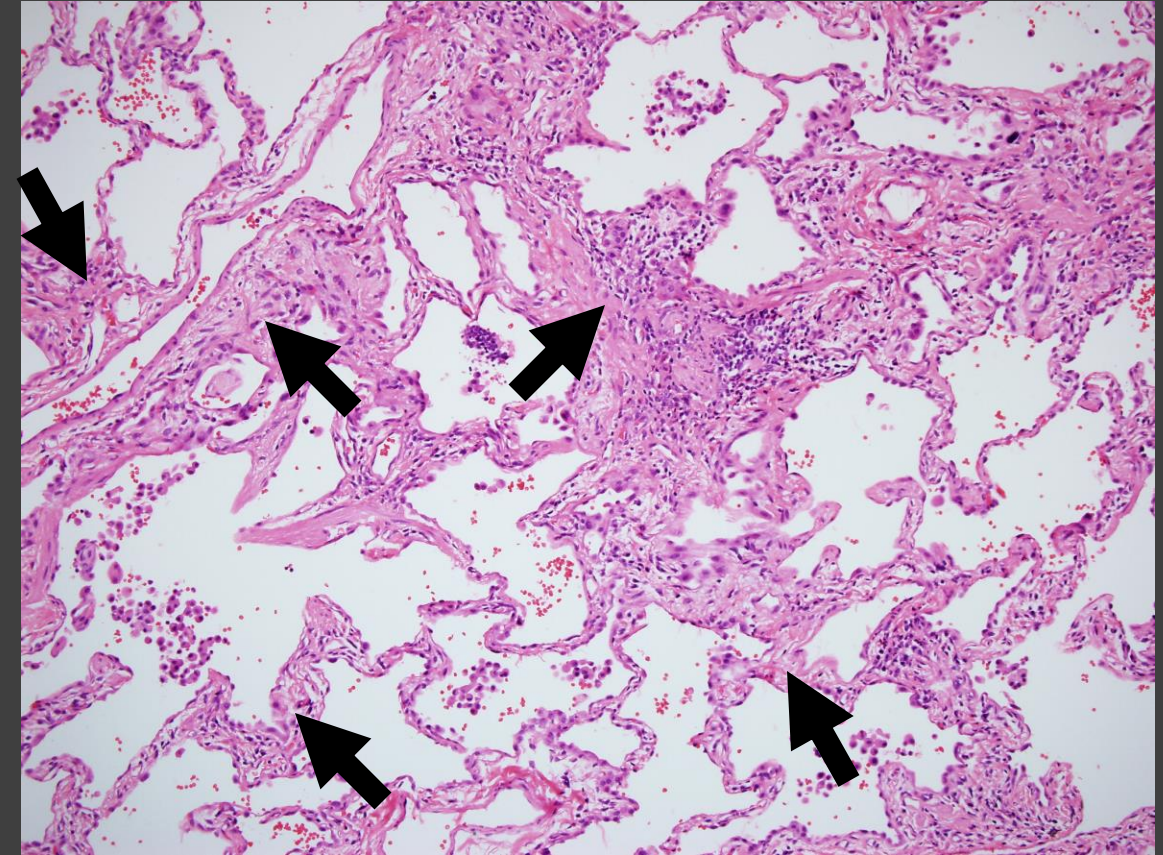
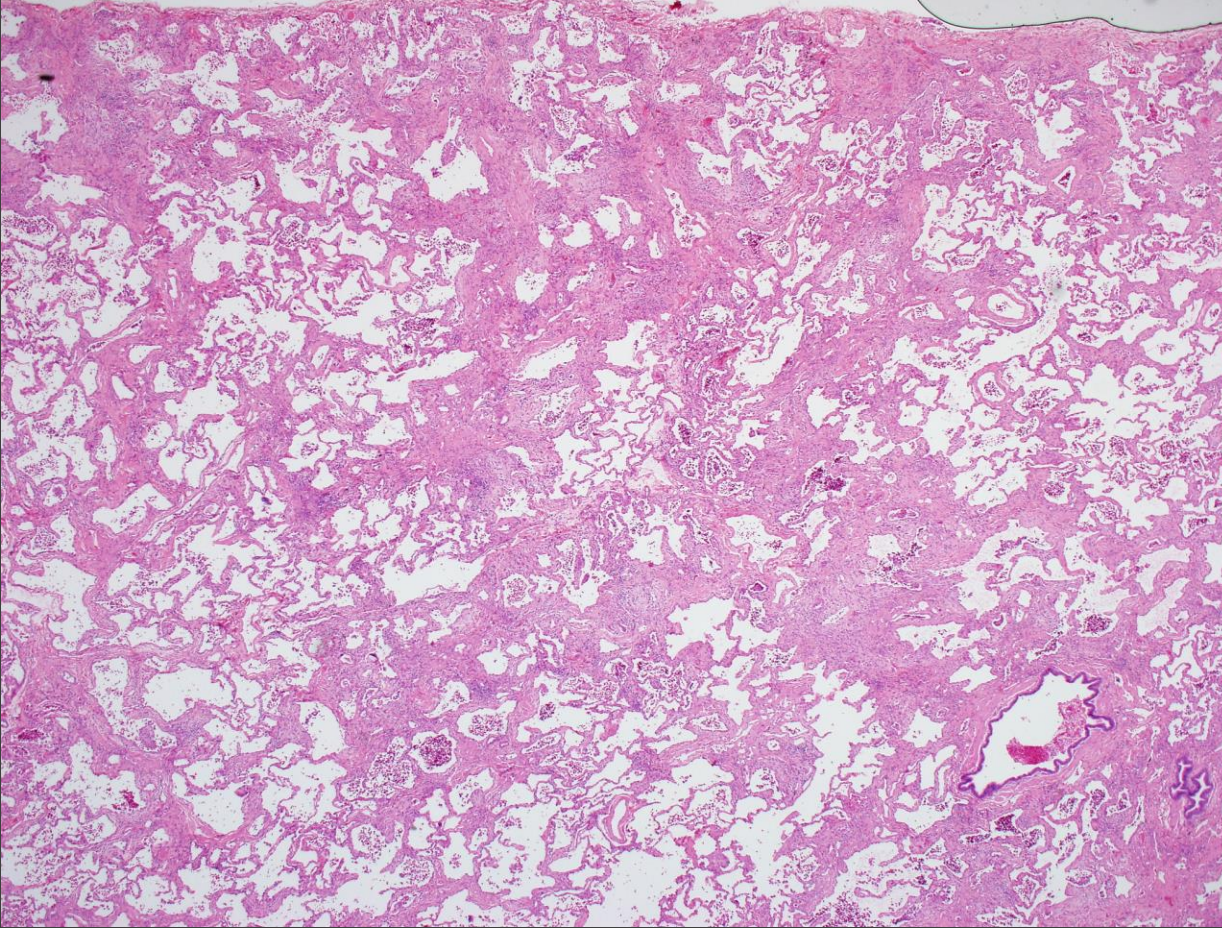


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Raghu et al. ATS/ERS/JRS/ALAT IPF Diagnostic Guidelines. AJRCCM 2018.

Pattern: Non-Specific Interstitial Pneumonitis (NSIP)

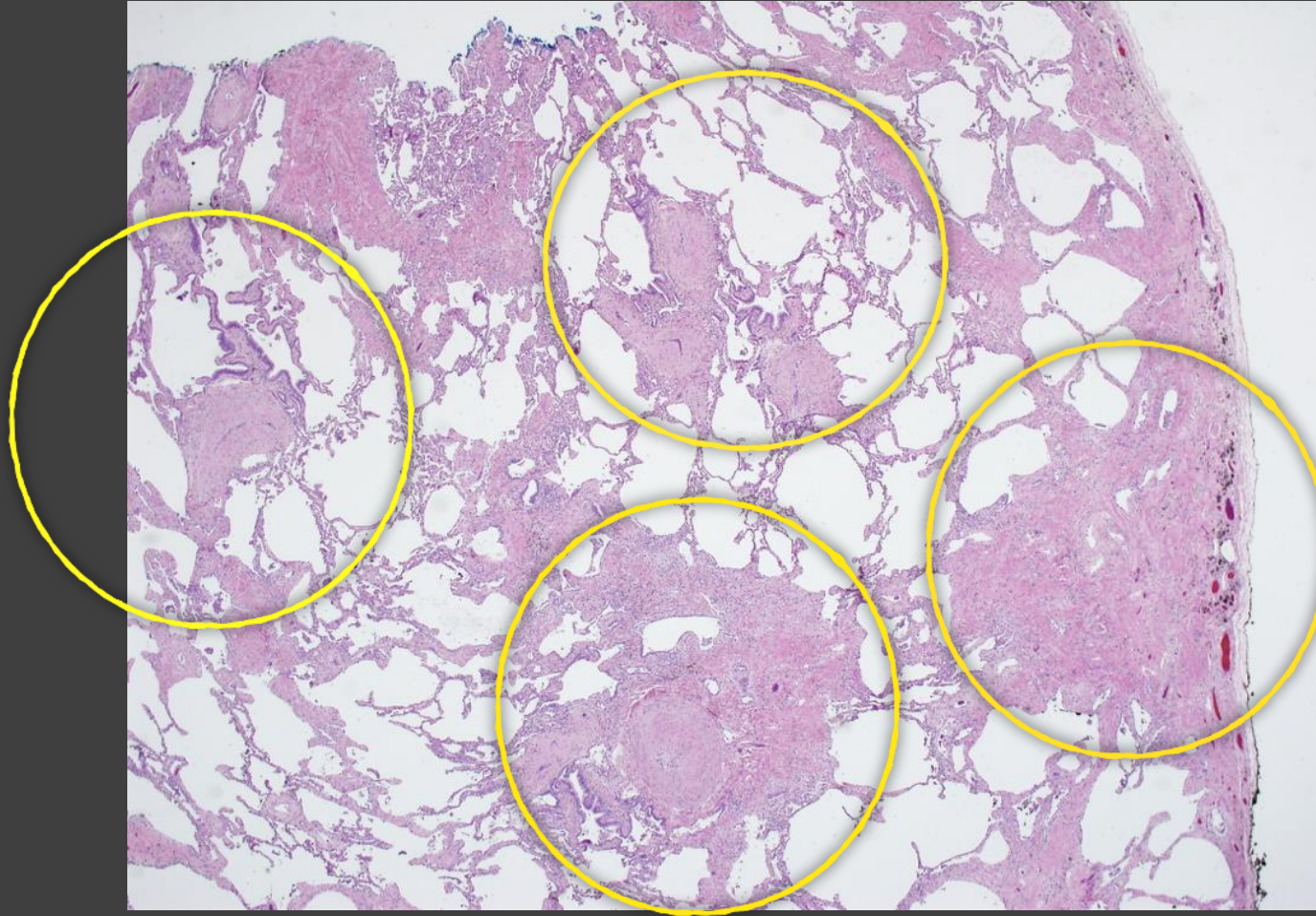


Homogenous diffuse fibrotic thickening of alveolar walls

No destructive fibrosis, spatial heterogeneity, or honeycomb change

Etiology: Can be idiopathic or secondary to chronic HP or autoimmune related ILD

Pattern: Airway-Centered Fibrosis



Etiology: Chronic exposure to inhaled allergen (Chronic Hypersensitivity Pneumonitis)
Autoimmune related interstitial lung disease
May see this pattern in familial ILD

Idiopathic (No identifiable underlying cause)

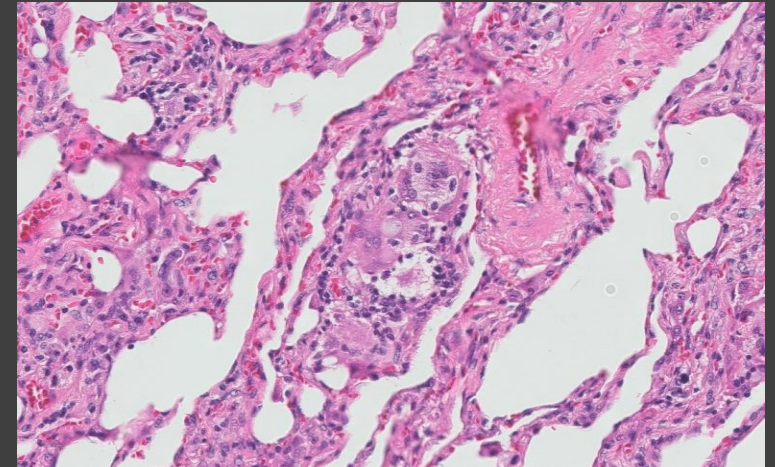
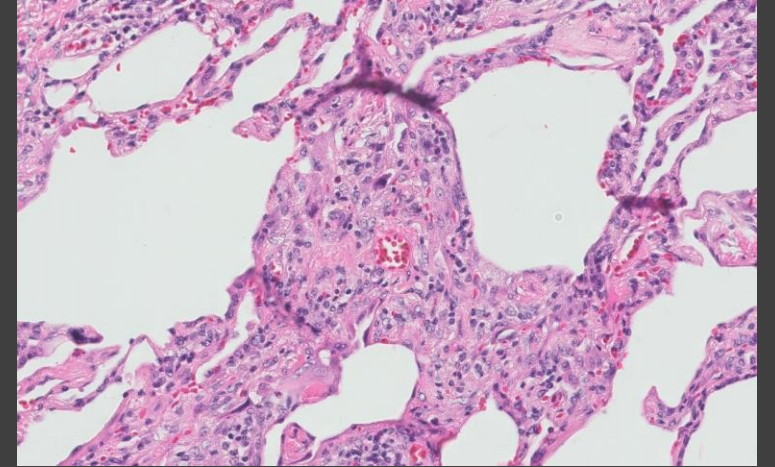
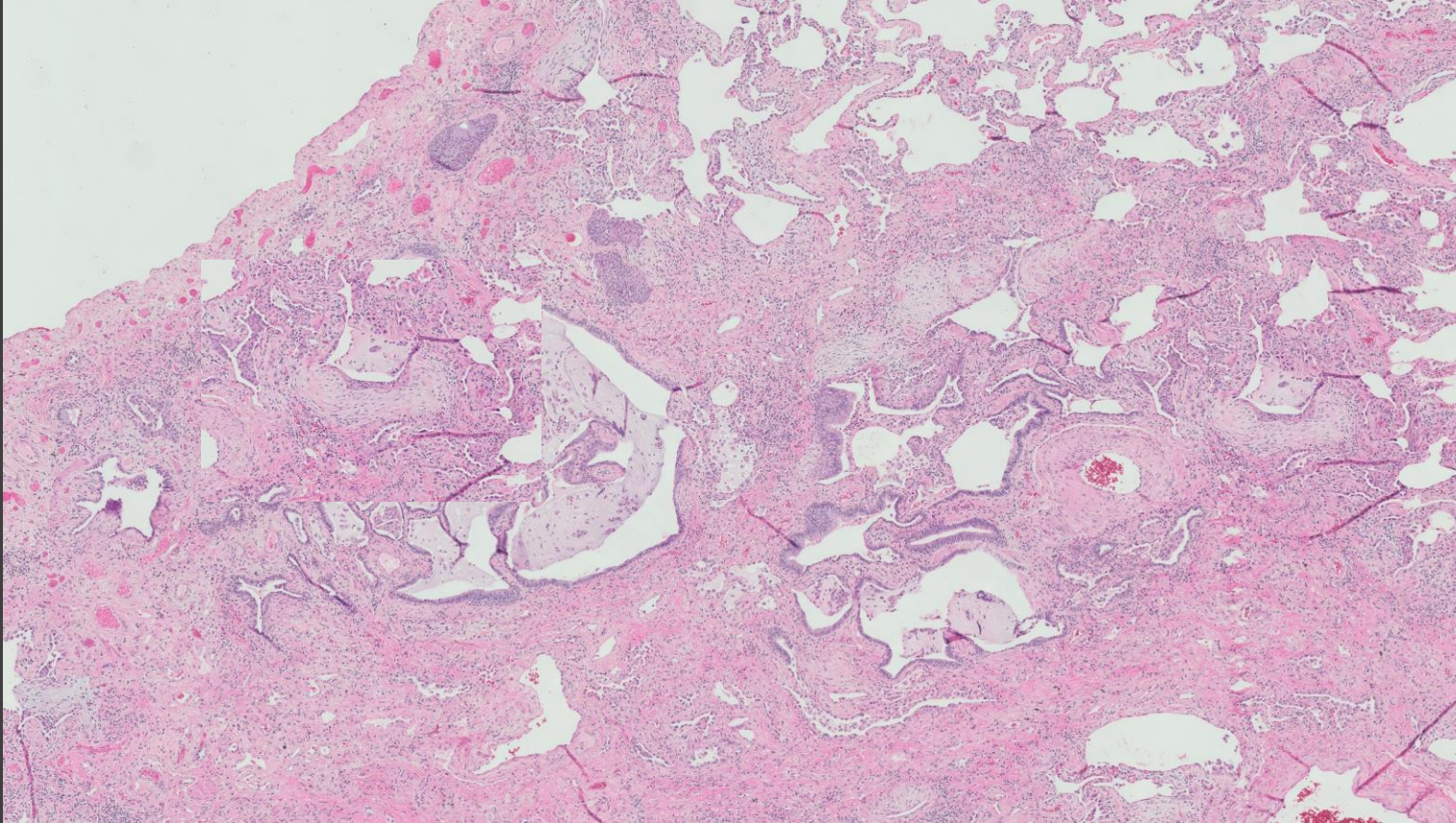
- Idiopathic pulmonary fibrosis: UIP with no known underlying cause
- Idiopathic fibrotic NSIP: NSIP with no known underlying cause

Secondary (Identifiable underlying cause)

- Chronic Hypersensitivity Pneumonitis
- Connective tissue disease (CTD) ILD



Diagnosis: Chronic Hypersensitivity Pneumonitis

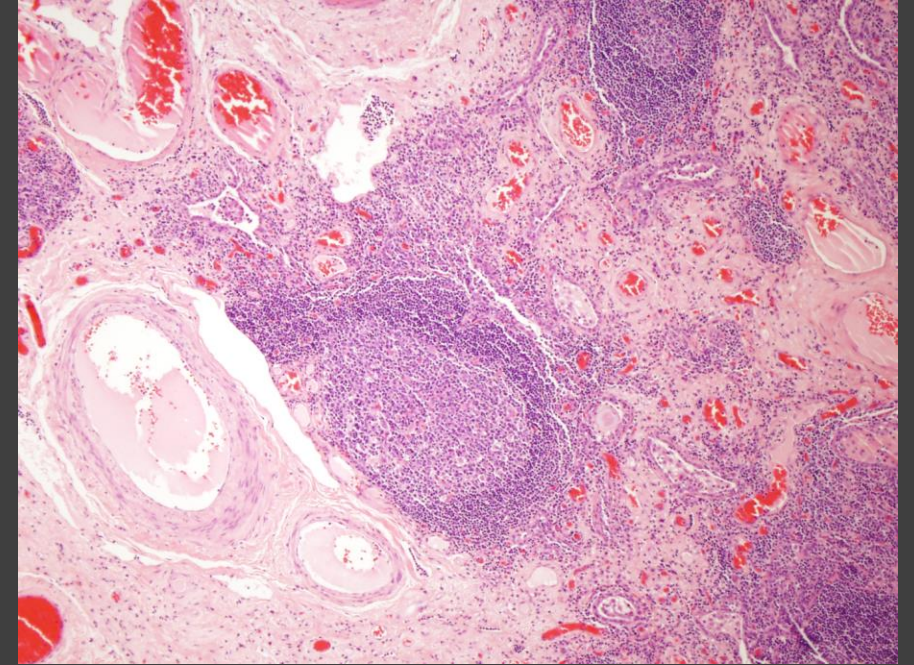
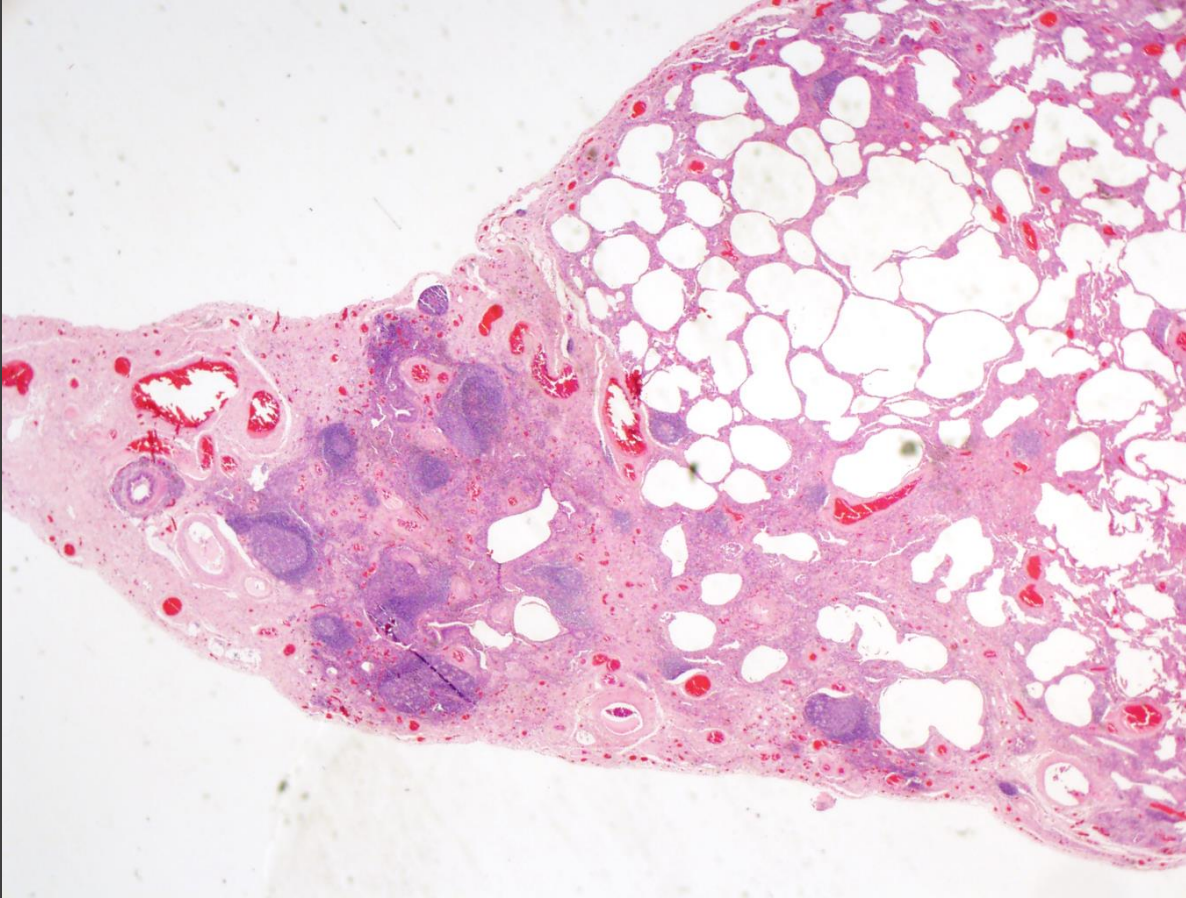


Chronic exposure to inhaled allergen: Mold, bird dander, some thermophilic bacteria

Classically has patchy peribronchiolar granulomatous inflammation

Chronic form can have UIP pattern, NSIP pattern, Airway centered fibrosis, or a mix

Diagnosis: Connective Tissue Disease Related ILD



**Can have UIP pattern, NSIP pattern, Airway centered fibrosis, or a mix
Presence of a mixed fibrosis pattern, or lymphoid aggregates can be histological clues
Sometimes lung manifestations are the initial presenting symptom, and can even precede serology**

Other types of biopsy in ILD

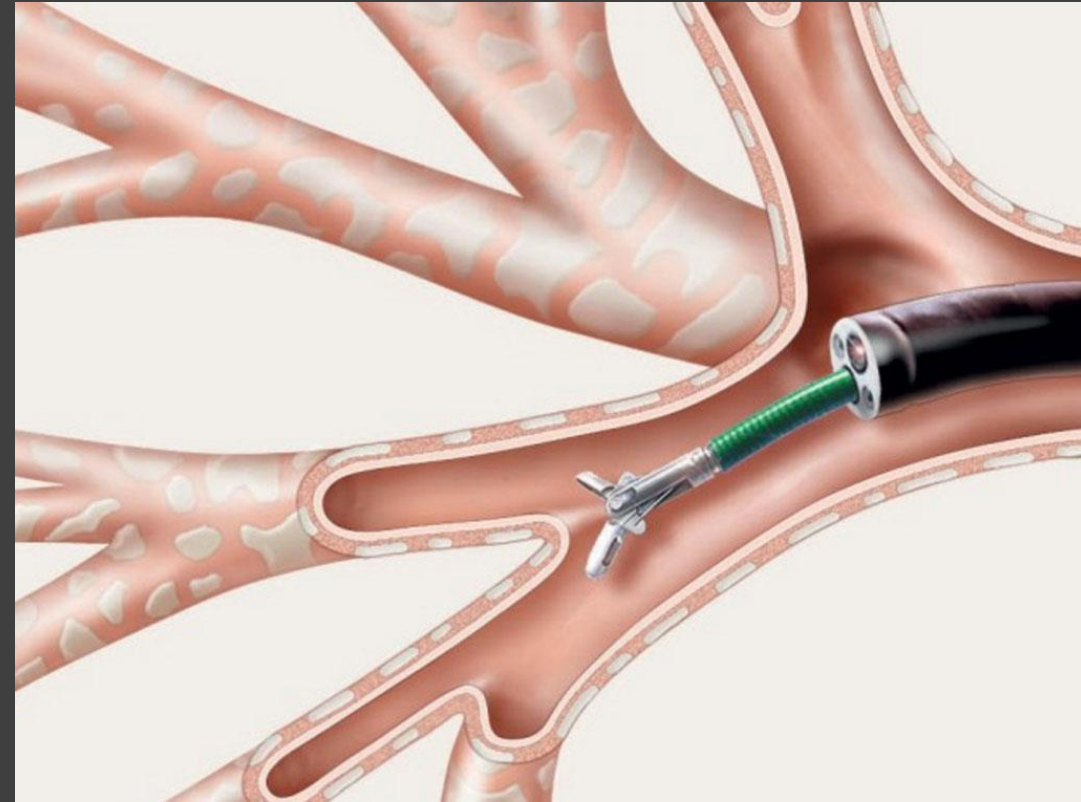
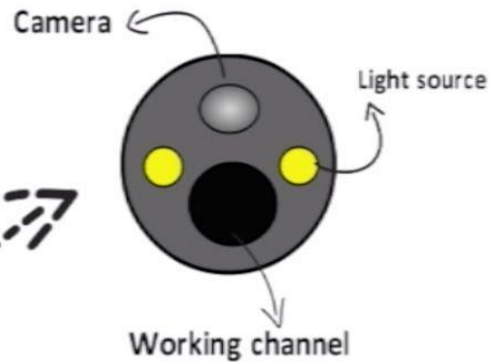
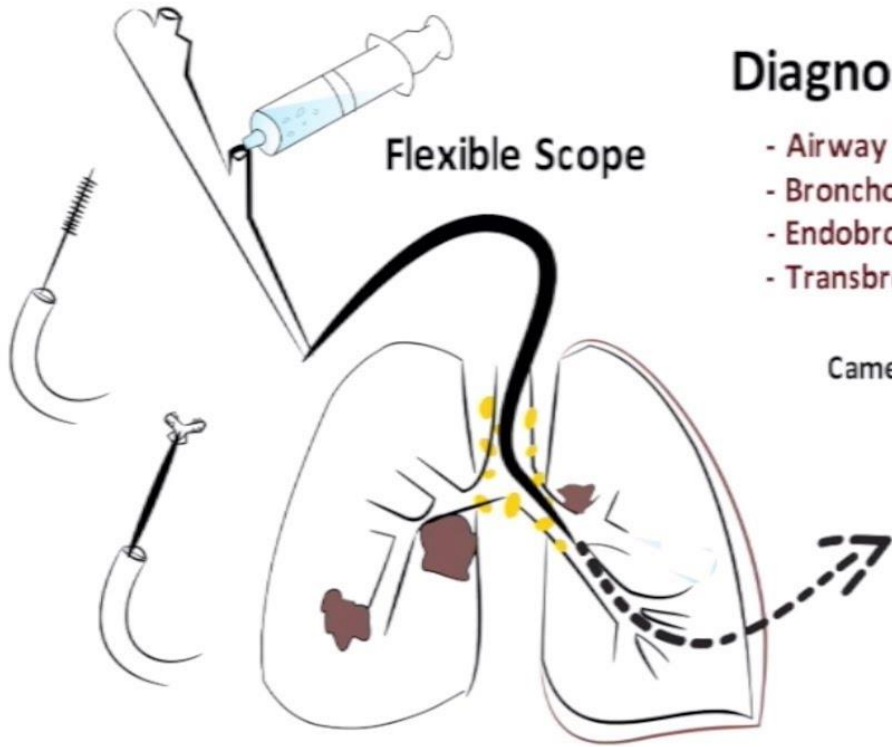


Transbronchial Biopsy

Insufficient for diagnosis in most ILDs

Diagnostic Bronchoscopy

- Airway inspection
- Bronchoalveolar lavage (BAL)
- Endobronchial brushing
- Transbronchial biopsy



Best of ATS Video Lecture

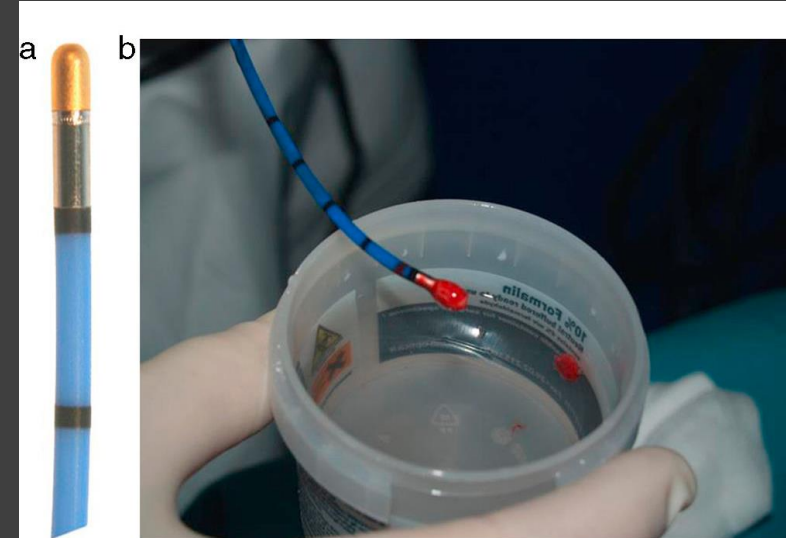
<https://www.pedilung.com>

Bronchoscopic Cryobiopsy

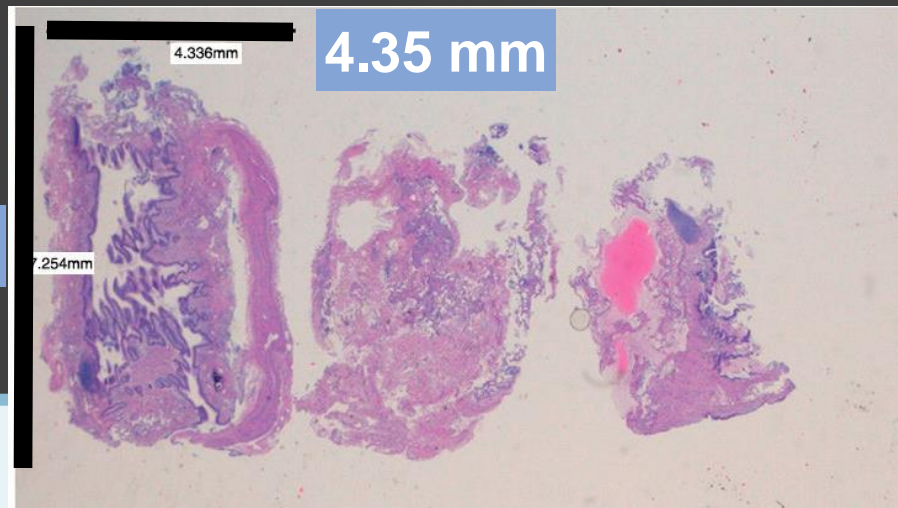
Uses a freezing probe to adhere and remove lung tissue



<http://www.erbe-med.com>



7.25 mm



Casoni GL et al. Rev Port
Pneumol. 2012.

Cryobiopsy vs Surgical Lung Biopsy

Romagnoli et al. 2019 (N=21)

Comparison	% Agreement (95% CI)	K (95% CI)
TBLC versus SLB	38% (18%-62%)	0.22 (0.01-0.44)
TBLC versus MDA2	48% (26%-70%)	0.31 (0.06-0.56)
SLB versus MDA2	62% (38%-82%)	0.51 (0.27-0.75)

COLDICE Trial (N=65)

- Histopathological agreement between TBCB and SLB was 70.8%, with diagnostic agreement at MDD at 76.9% (κ 0.62, 0.47–0.78).
- 60% of cases TBCB with MDD was felt to provide high confidence in the diagnosis, and in those cases concordance between TBCB and SLB diagnosis was high (95%).
- 40% of cases where TBCB with MDD did not provide a high confidence diagnosis, concordance with SLB was low.

What biopsy type to use in ILD and when?

- **Surgical Lung Biopsy (SLB)**

- Patients with low confidence ILD diagnosis
- SLB is likely to alter treatment decisions (immunosuppression vs anti-fibrotics vs dual therapy)
- Patient not at excessively increased risk for post-operative complication

- **Transbronchial Cryobiopsy (TBCB)**

- ATS 2022: Conditional recommendation was made to regard transbronchial lung cryobiopsy as an acceptable alternative to surgical lung biopsy in centers with appropriate expertise. (conditional recommendation, very low quality evidence).
- Lack of standardization in procedure performance, number/size of specimens, and locations of sampling
- May be considered as an alternative to SLB in some circumstances

- **Transbronchial Biopsy (TBB)**

- NOT recommended in ILDs that do not have a peribronchial component due to insufficient tissue size and sampling error
- i.e. sarcoidosis, HP, eosinophilic pneumonia, organizing pneumonia

