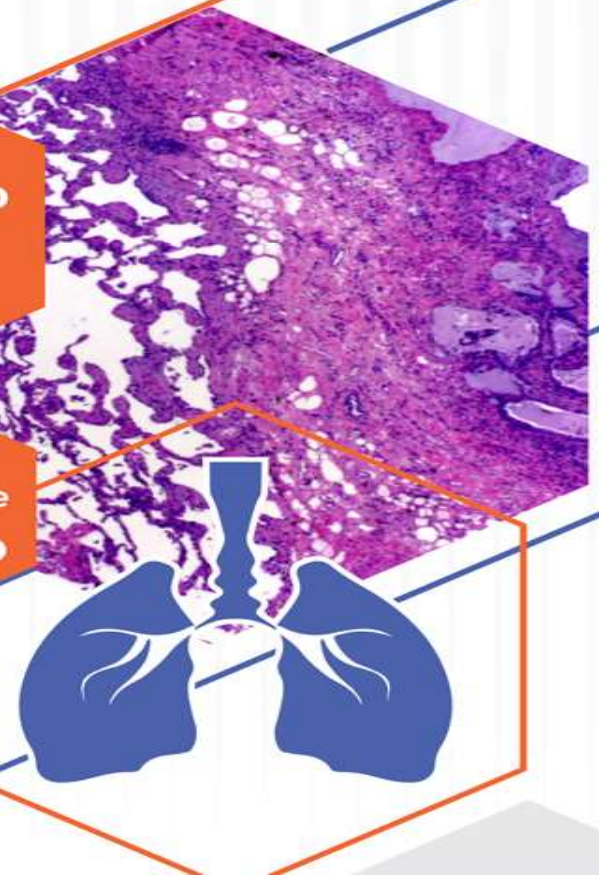
ITALIAN RESPIRATORY SOCIETY
SIP
SOCIETÀ ITALIANA DI PNEUMOLOGIA

I T S
ITALIAN THORACIC SOCIETY

AIPO
ASSOCIAZIONE ITALIANA PNEUMOLOGI OSPEDALIERI

Convegno di presentazione della versione italiana delle linee guida per la diagnosi di fibrosi polmonare idiopatica

Linee guida ufficiali ATS/ERS/JRS/ALAT per la pratica clinica



1 Febbraio 2020

Hotel Enterprise Milano

SOCIETÀ ITALIANA DI PNEUMOLOGIA

I T S ITALIAN THORACIC SOCIETY

A I P O ASSOCIAZIONE ITALIANA PNEUMOLOGI OSPEDALIERI

Convegno di presentazione della versione italiana delle linee guida per la diagnosi di fibrosi polmonare idiopatica

Linee guida ufficiali ATS/ ERS/JRS/ALAT per la pratica clinica

Hotel Enterprise Milano

1 Febbraio 2020

La diagnosi anatomo-patologica

Giulio Rossi

Anatomia Patologica, AUSL della Romagna (Ravenna/Rimini)

Classification and Natural History of the Idiopathic Interstitial Pneumonias

Dong Soon Kim, Harold R. Collard, and Talmadge E. King, Jr.

Proc Am Thorac Soc Vol 3. pp 285–292, 2006

Liebow and Carrington (1969) (1)	Katzenstein and Myers (1998) (2)	ATS/ERS (2002) (3)	
		Histologic Pattern	Clinico-Radiographic-Pathologic Diagnosis
UIP	UIP	UIP	Idiopathic pulmonary fibrosis
DIP	DIP	DIP	Desquamative interstitial pneumonia
	RB-ILD	RB	Respiratory bronchiolitis interstitial lung disease
LIP		LIP	Lymphoid interstitial pneumonia
GIP			
BIP		OP	Cryptogenic organizing pneumonia
	AIP	DAD	Acute interstitial pneumonia
	NSIP	NSIP	Nonspecific interstitial pneumonia

Diagnosis of Idiopathic Pulmonary Fibrosis

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

Ganesh Raghu, Martine Remy-Jardin, Jeffrey L. Myers, Luca Richeldi, Christopher J. Ryerson, David J. Lederer, Juergen Behr, Vincent Cottin, Sonye K. Danoff, Ferran Morell, Kevin R. Flaherty, Athol Wells, Fernando J. Martinez, Arata Azuma, Thomas J. Bice, Demosthenes Bouros, Kevin K. Brown, Harold R. Collard, Abhijit Duggal, Liam Galvin, Yoshikazu Inoue, R. Gisli Jenkins, Takeshi Johkoh, Ella A. Kazerooni, Masanori Kitaichi, Shandra L. Knight, George Mansour, Andrew G. Nicholson, Sudhakar N. J. Pipavath, Ivette Buendía-Roldán, Moisés Selman, William D. Travis, Simon L. F. Walsh, and Kevin C. Wilson; on behalf of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society

This official clinical practice guideline of the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Society (ALAT) was approved by the ATS, JRS, and ALAT May 2018, and the ERS June 2018

American Journal of Respiratory and Critical Care Medicine Volume 198 Number 5 | September 1 2018

Suspect IPF

- BAL: LOW
- TBB/CRYO: no recommendations
- SLB: LOW

IPF on clinic/HRCT

- BAL: NOT
- TBB/CRYO: NOT
- SLB: NOT

Table 1. Comparison of ATS/ERS/JRS/ALAT Recommendations for the Diagnosis of IPF in the 2011 and 2018 Guidelines

	2018 Guideline		2011 Guideline: Did Not Distinguish among Patients with Different HRCT Patterns
	HRCT Pattern of Probable UIP*, Indeterminate for UIP, and Alternative Diagnosis	HRCT Pattern of UIP*	
BAL cellular analysis	We suggest performing BAL cellular analysis (conditional)	We suggest *NOT* performing BAL cellular analysis (conditional)	"BAL cellular analysis should not be performed in the diagnostic evaluation of IPF in the majority of patients, but may be appropriate in a minority of patients."
Surgical lung biopsy	We suggest performing surgical lung biopsy (conditional)	We recommend *NOT* performing surgical lung biopsy (strong)	"Surgical lung biopsy is not required for patients with an HRCT pattern consistent with UIP."
Transbronchial lung biopsy	No recommendation was made either for or against transbronchial lung biopsy	We recommend *NOT* performing transbronchial lung biopsy (strong)	"Transbronchial biopsy should not be used in the evaluation of IPF in the majority of patients, but may be appropriate in a minority."
Lung cryobiopsy	No recommendation was made either for or against cryobiopsy	We recommend *NOT* performing cryobiopsy (strong)	Not addressed
Medical history of medication use and environmental exposures	We recommend taking a detailed history of both medication use and environmental exposures at home, work, and other places the patient frequently visits to exclude potential causes of ILD (motherhood statement)		"Diagnosis of IPF requires exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity)."
Serological testing to exclude connective tissue disease	We recommend serological testing to exclude connective tissue diseases as a potential cause of the ILD (motherhood statement)		"Diagnosis of IPF requires exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity)."
Multidisciplinary discussion	We suggest multidisciplinary discussion for decision-making (conditional)		"We recommend that a multidisciplinary discussion should be used in the evaluation of IPF."
Serum biomarkers	We recommend *NOT* measuring serum MMP-7, SPD, CCL-18, or KL-6 for the purpose of distinguishing IPF from other ILDs (strong)		Not addressed

Histopathology of UIP

UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
• 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	• Some histologic features from column 1 are present but to an extent that precludes a definite diagnosis of UIP/IPF *And* • Absence of features to suggest an alternative diagnosis *Or* • Honeycombing only	• 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†	• 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)

Definition of abbreviations: IIP = idiopathic interstitial pneumonia; IPF = idiopathic pulmonary fibrosis; LAM = lymphangioleiomyomatosis; UIP = usual interstitial pneumonia.

*Granulomas, hyaline membranes (other than when associated with acute exacerbation of IPF, which may be the presenting manifestation in some patients), prominent airway-centered changes, areas of interstitial inflammation lacking associated fibrosis, marked chronic fibrous pleuritis, organizing pneumonia. Such features may not be overt or easily seen to the untrained eye and often need to be specifically sought.

†Features that should raise concerns about the likelihood of an alternative diagnosis include a cellular inflammatory infiltrate away from areas of honeycombing, prominent lymphoid hyperplasia including secondary germinal centers, and a distinctly bronchiolocentric distribution that could include extensive peribronchiolar metaplasia.

IPF suspected*		Histopathology pattern			
		UIP	Probable UIP	Indeterminate for UIP	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Probable UIP	IPF	IPF	IPF (Likely)**	Non-IPF dx
	Indeterminate for UIP	IPF	IPF (Likely)**	Indeterminate for IPF***	Non-IPF dx
	Alternative diagnosis	IPF (Likely)** /non-IPF dx	Non-IPF dx	Non-IPF dx	Non-IPF dx

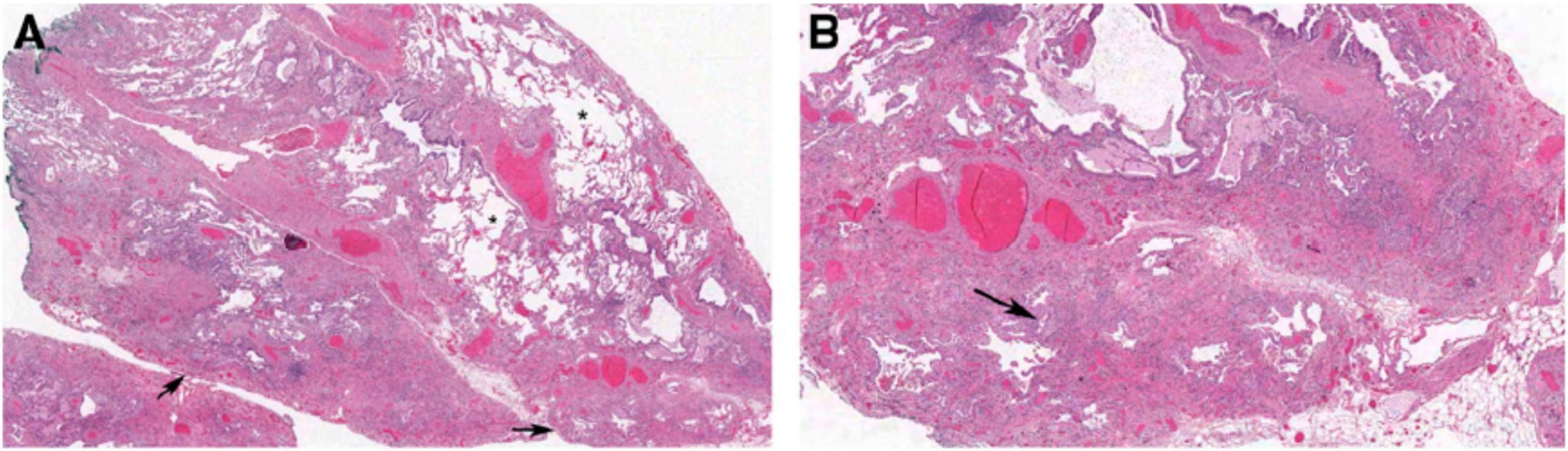
Figure 8. Idiopathic pulmonary fibrosis diagnosis based upon HRCT and biopsy patterns.
*"Clinically suspected of having IPF" = unexplained symptomatic or asymptomatic patterns of bilateral pulmonary fibrosis on a chest radiograph or chest computed tomography, bibasilar inspiratory crackles, and age greater than 60 years. (Middle-aged adults [>40 yr and <60 yr], especially patients with risks for familial pulmonary fibrosis, can rarely present with the otherwise same clinical scenario as the typical patient older than 60 years.)
**IPF is the likely diagnosis when any of the following features are present:

- Moderate-to-severe traction bronchiectasis/bronchiolectasis (defined as mild traction bronchiectasis/bronchiolectasis in four or more lobes including the lingual as a lobe, or moderate to severe traction bronchiectasis in two or more lobes) in a man over age 50 years or in a woman over age 60 years
- Extensive (>30%) reticulation on HRCT and an age >70 years
- Increased neutrophils and/or absence of lymphocytosis in BAL fluid
- Multidisciplinary discussion reaches a confident diagnosis of IPF.

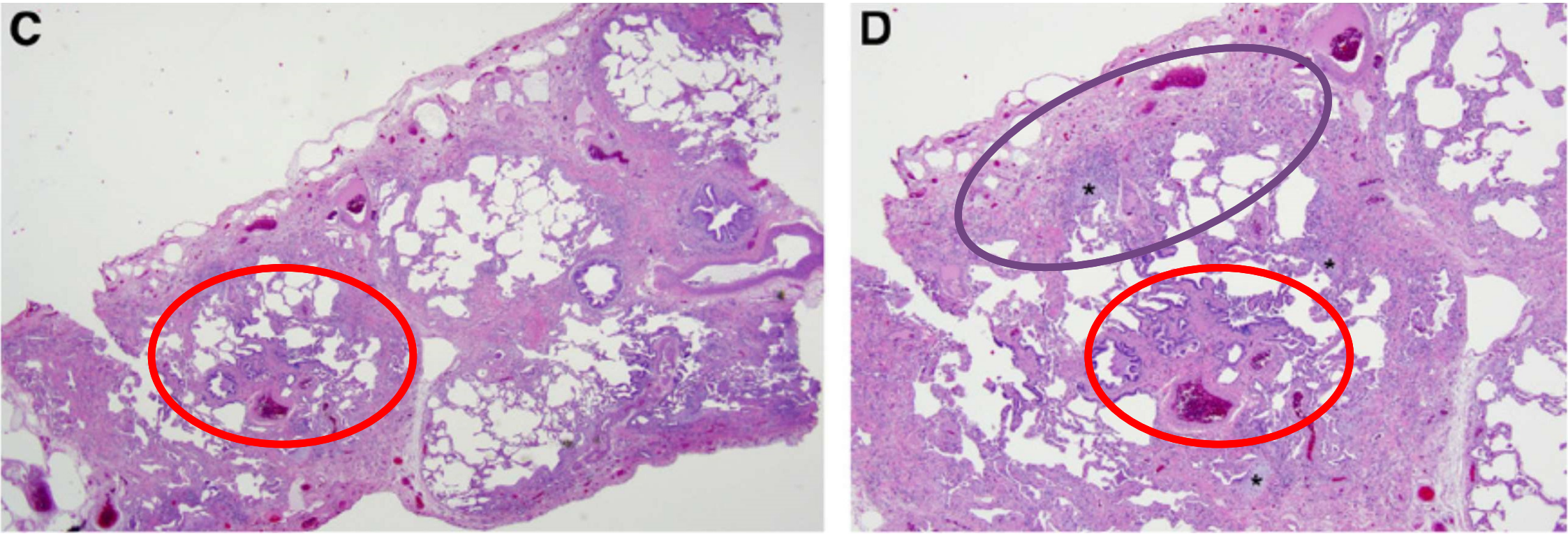
***Indeterminate for IPF

- Without an adequate biopsy is unlikely to be IPF
- With an adequate biopsy may be reclassified to a more specific diagnosis after multidisciplinary discussion and/or additional consultation.

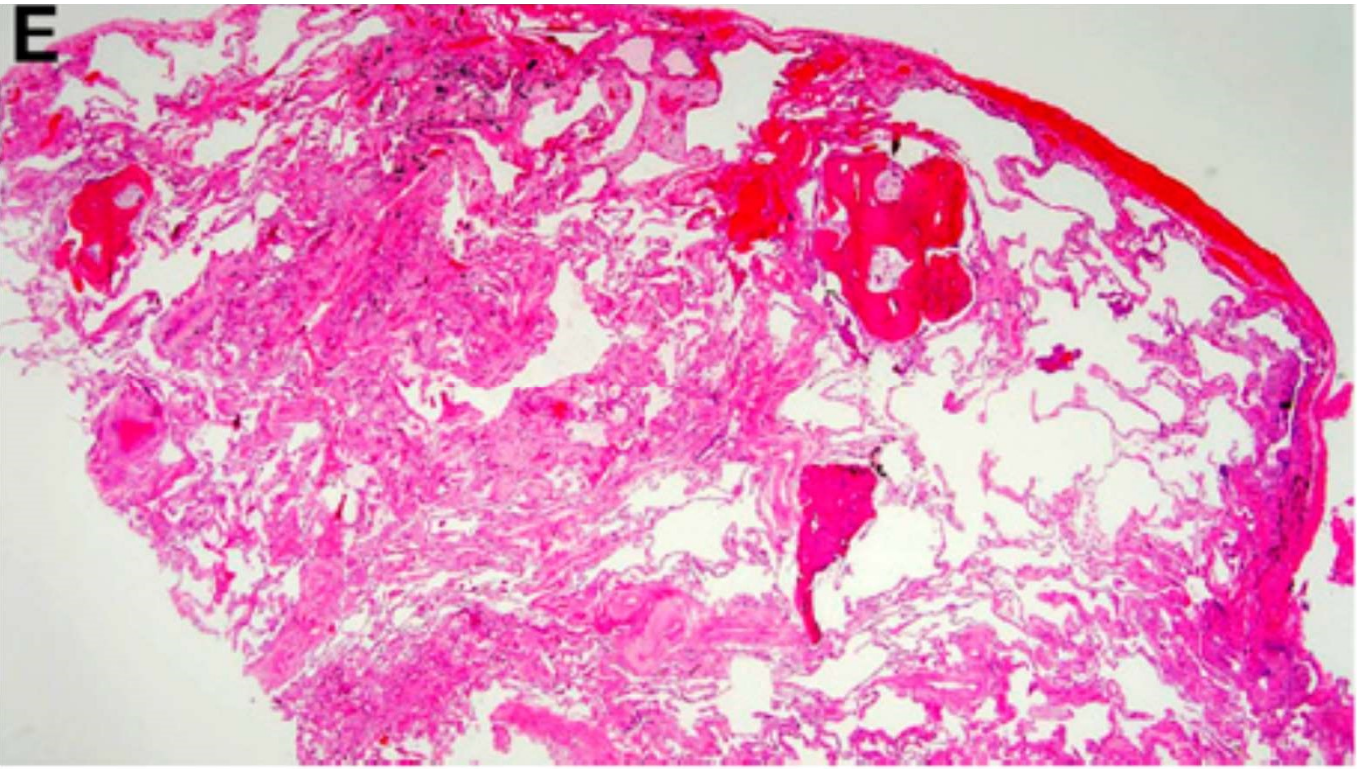
dx = diagnosis; HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis; UIP = usual interstitial pneumonia.



- **UIP pattern**: dense fibrosis with a predilection for subpleural and paraseptal parenchyma with associated architectural distortion in the form of microscopic honeycomb change (arrow) juxtaposed with relatively unaffected lung parenchyma (*). Visceral pleura is seen in the upper portion of the figure. Higher magnification photomicrograph showing subpleural scarring and honeycomb change with associated fibroblast foci (arrow).



- **Probable UIP/IPF pattern**: characterized by subpleural and paraseptal predominant patchwork fibrosis that is less well developed and lacks the degree of associated architectural distortion in the form of either destructive scarring or honeycomb change illustrated in A and B. Higher-magnification photomicrograph showing patchy fibrosis and fibroblast foci (*) but without the extent of scarring and honeycomb change illustrated in A and B.

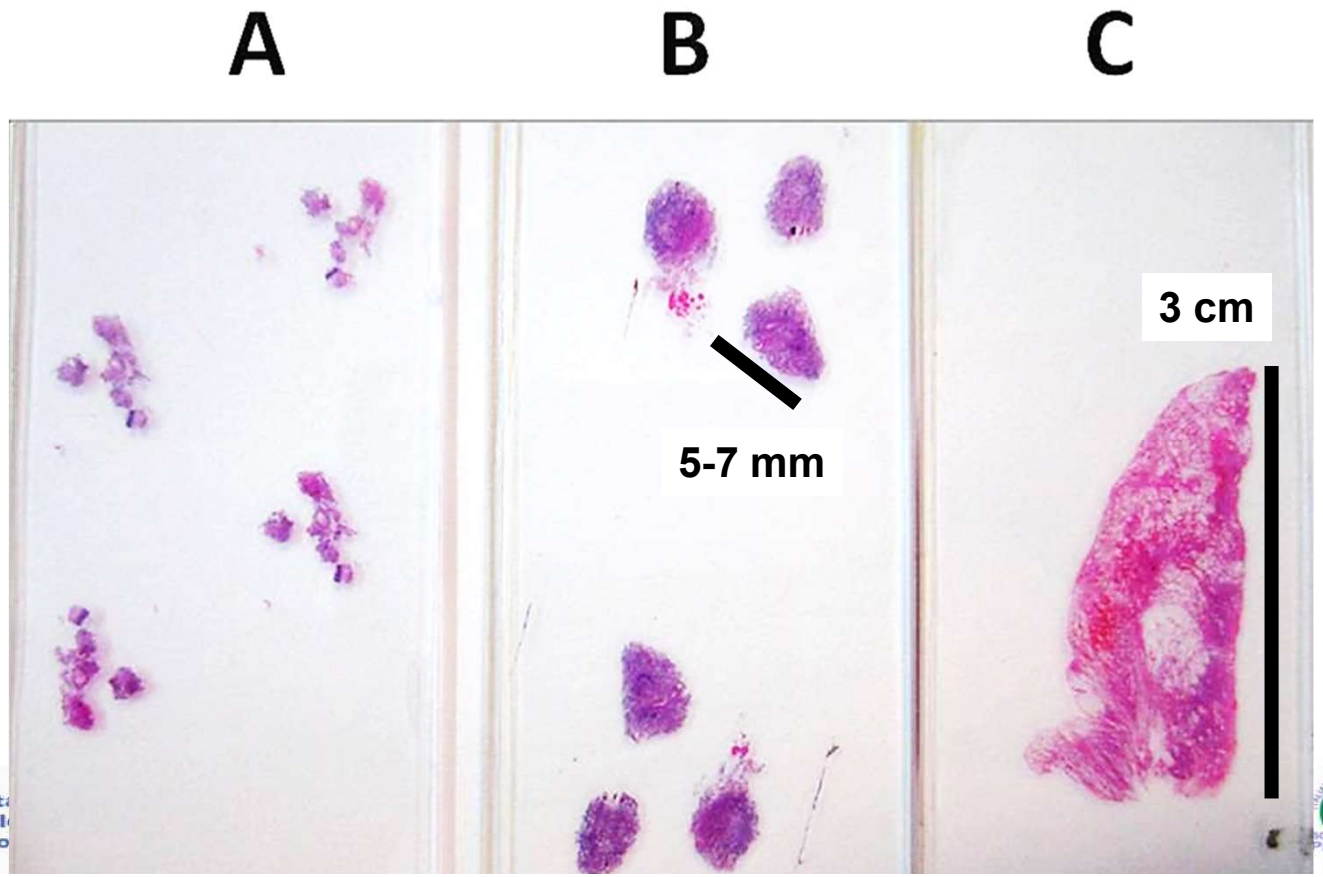


- **Indeterminate for UIP/IPF pattern**: mild nonspecific fibrosis that lacks a well developed patchy and predominantly subpleural/paraseptal distribution, architectural distortion, and fibroblast foci characteristic of classical UIP/IPF. There is associated osseous metaplasia, a common but nonspecific finding in UIP. Although these findings are not diagnostic, they do not preclude a diagnosis of UIP/IPF in a patient with supportive clinical and radiological findings

Transbronchial Cryobiopsy in the Diagnosis of Diffuse Lung Disease

Surgical Pathology 13 (2020) 197–208

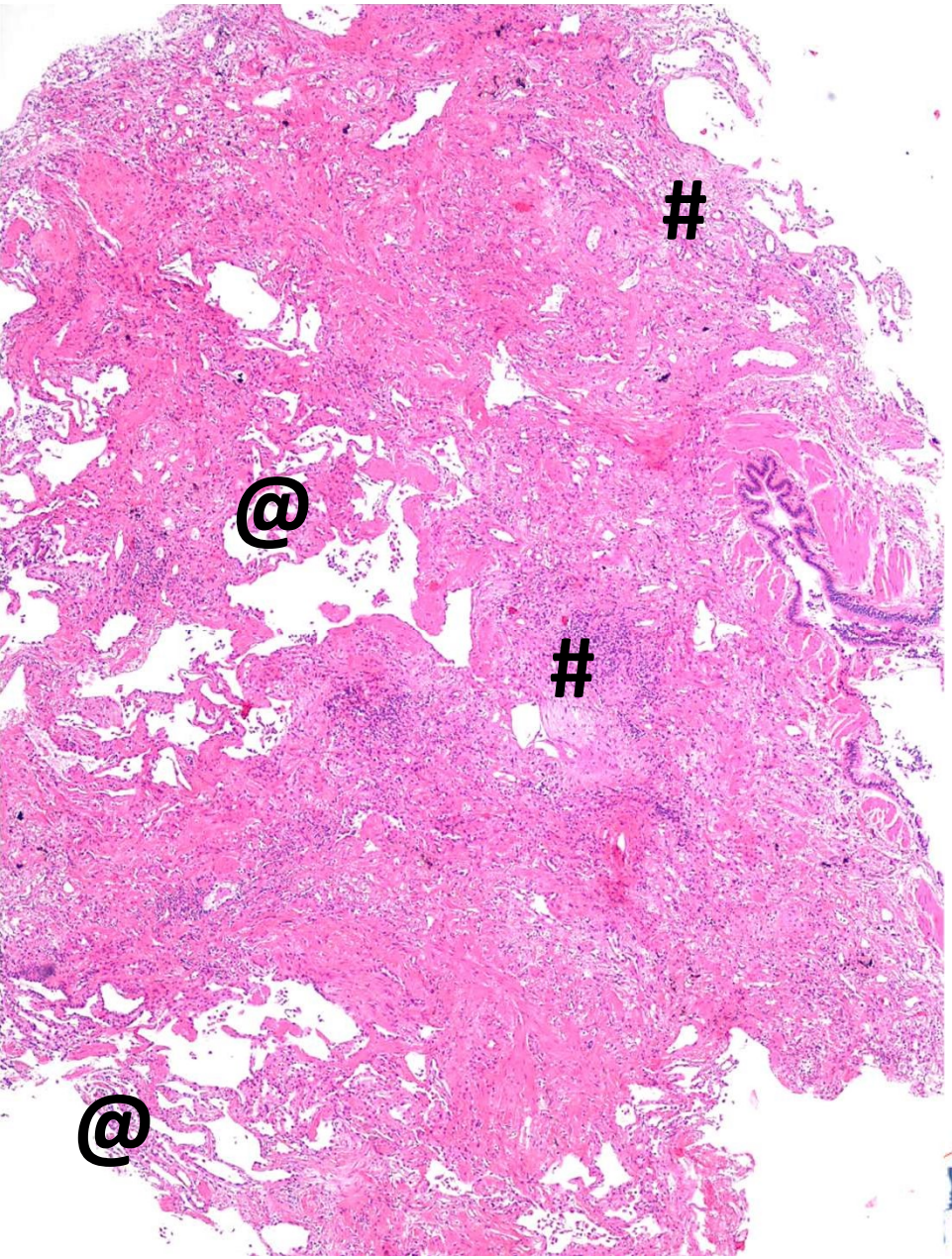
Alberto Cavazza, MD[a,*], Thomas V. Colby, MD[b], Alessandra Dubini, MD[c], Sara Tomassetti, MD[d], Claudia Ravaglia, MD[d], Venerino Poletti, MD[d], Maria Cecilia Mengoli, MD[a], Elena Tagliavini, MD[a], Giulio Rossi, MD[e]



A=TBB

B=CRYO

C=AWAKE



CRYOBIOPSY

@ = patchy

= fibroblast foci

Probable UIP

Report Standardization in Transbronchial Lung Cryobiopsy

Ravaglia C, et al. Arch Pathol Lab Med 2019

Strenght of the diagnosis

PROBABLE & INDETERMINATE = LOW CONFIDENCE

UIP = HIGH CONFIDENCE

Ancillary findings

- Chronic lymphoplasmacytic inflammation with or without lymphoid follicles
- Interstitial granulomas/giant cells,
- Bronchiolitis, pleuritis
- Bridging fibrosis
- Asbestos fibers
- Eosinophilic infiltrate

Current Opinion in Pulmonary Medicine

Critical reappraisal of underlying histological patterns in patients with suspected IPF

Rossi G & Cavazza A. 2019

Idiopathic (IPF)

Chronic hypersensitivity pneumonia

Pleuroparenchymal fibroelastosis (often co-existing with UIP)

Connective tissue diseases (particularly rheumatoid arthritis)

Anti-synthetase syndrome (anti-KS, anti-PL7, anti-EJ)

Asbestosis

Chronic sarcoidosis

Drug toxicity

Familial interstitial lung disease

IgG4 syndrome

Histologic findings	IPF	cHP	CTD
Lung involvement	Lower lobe predilection	Upper and lower lobes	Upper and lower lobes
Centrilobular fibrosis	-/+	++/+++	+/++
Interstitial inflammatory infiltrate	-/+	+/++	++/+++
Interstitial giant cells/granulomas	-	++ (often present, but not in all cases)	+ (more frequent in Sjogren)
Organizing pneumonia	-/+ (association with acute exacerbation)	++	+/++
Bridging fibrosis	-/+	++/+++	+
Fibroblastic foci	++/+++	+/++ (peribronchiolar)	+/++
Honeycombing	++	+/++	+/++
Fibrotic NSIP	-/+	+/++	++/+++
Chronic pleuritis	-	+	++

Cryobiopsy: systematic reviews and meta-analyses on diagnostic yield

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

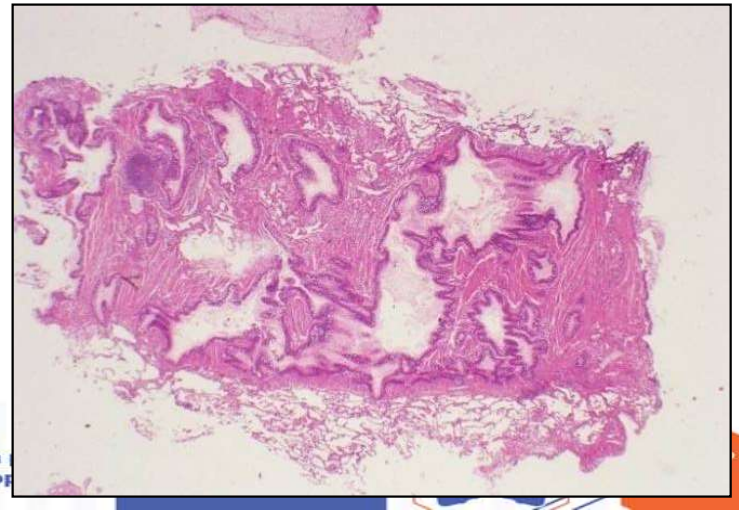
Study	Diagnostic yield
Johannson. Ann Am Thorac Soc 2016	**79%**
Ravaglia. Respiration 2016	**81%**
Iftikhar. Ann Am Thorac Soc 2017	**83.7%**
Sharp. QJM 2017	**84%**

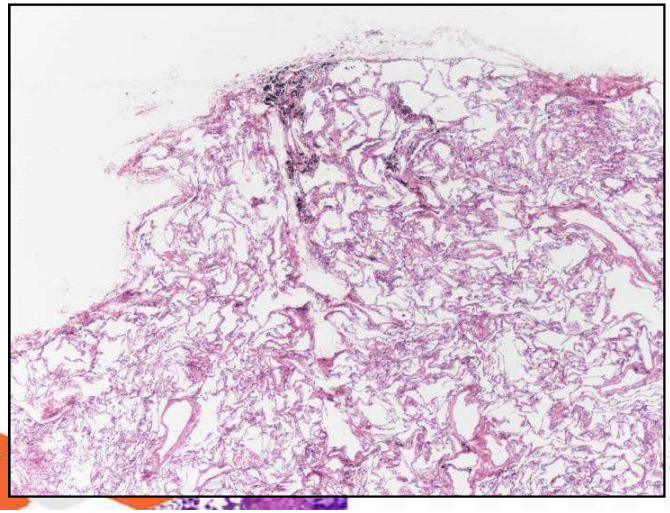
The diagnostic yield of SLB in ILD is ≅ 90-95%

RAVAGLIA ET AL. **DIAGNOSTIC YIELD AND RISK/BENEFIT ANALYSIS OF TRANS-BRONCHIAL LUNG CRYOBIOPSY IN DIFFUSE PARENCHYMAL LUNG DISEASES: A LARGE COHORT OF 699 PATIENTS.**

BMC PULMONARY MEDICINE 2019;19:16

- Diagnostic yield: 87.8% for pathological diagnoses, 90.1% for multidisciplinary diagnoses
- The diagnostic yield increased with at least 2 biopsies from at least 2 different sites
- Anectotally, cryobiopsy should be at least 5 mm (Colby et al. Arch Pathol Lab Med 2017;141:891-900)





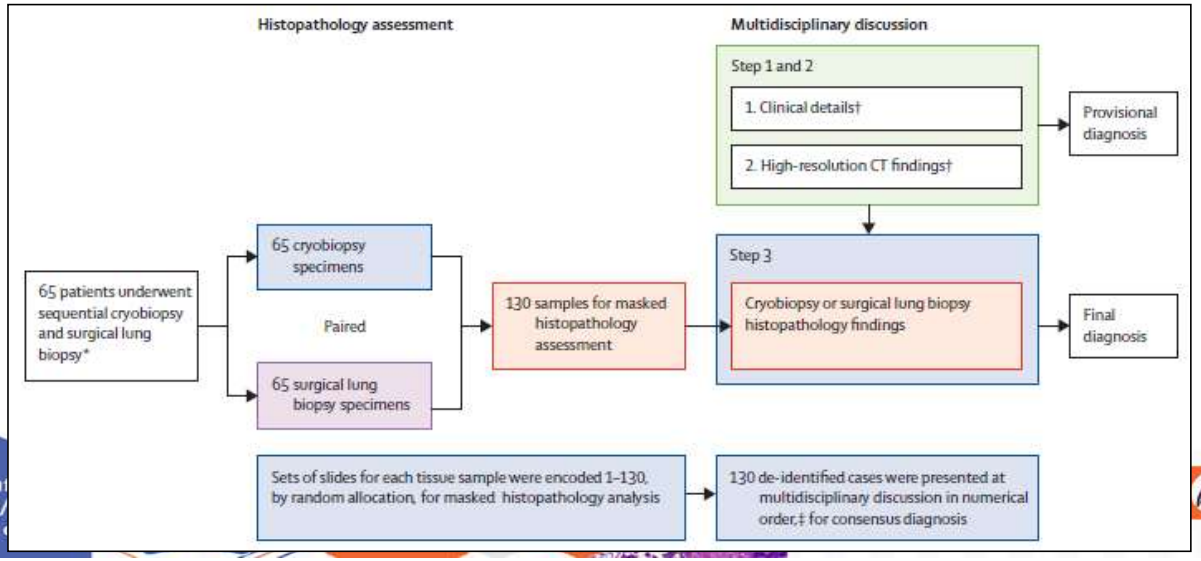
DIAGNOSTIC ACCURACY OF TRANSBRONCHIAL LUNG CRYOBIOPSY FOR INTERSTITIAL LUNG DISEASE DIAGNOSIS (COLDICE): A PROSPECTIVE, COMPARATIVE STUDY

TROY ET AL. LANCET RESPIR MED, PUBLISHED ONLINE SEPTEMBER 29

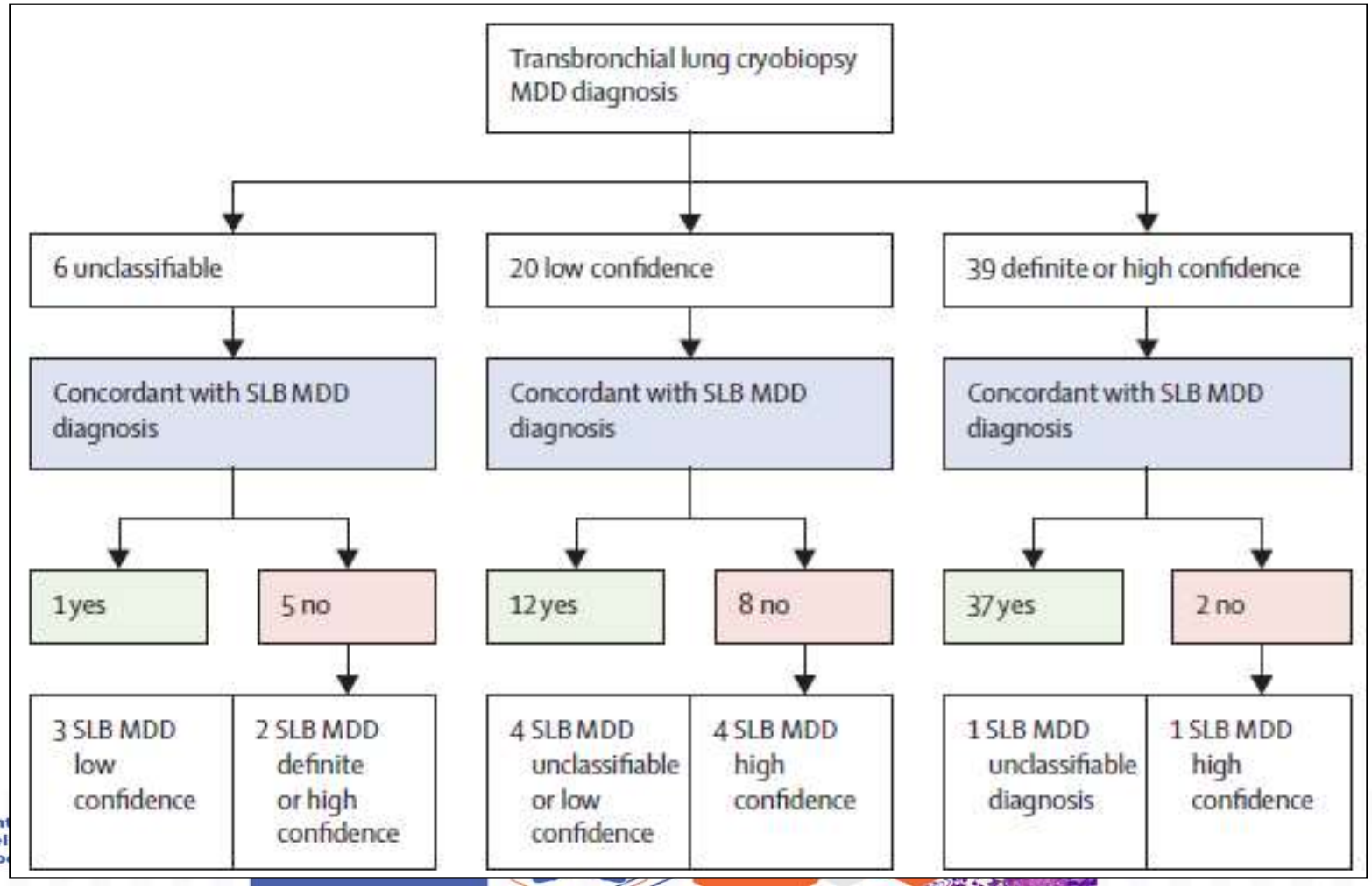
65 patients with ILD underwent cryobiopsies immediately followed by SLB in the same anatomic locations

- Review by 3 pathologists (W. Cooper, A. Mahar, J. Myers), blinded to clinical data and to pairing of cryo and surgical samples

The main goal of the study was to compare cryobiopsies and surgical lung biopsies both for histologic diagnosis and multidisciplinary diagnosis



- **Agreement between cryobiopsies and SLB at histologic diagnosis: 70.8%**
- **Agreement between cryobiopsies and SLB at multidisciplinary diagnosis: 76.9%**

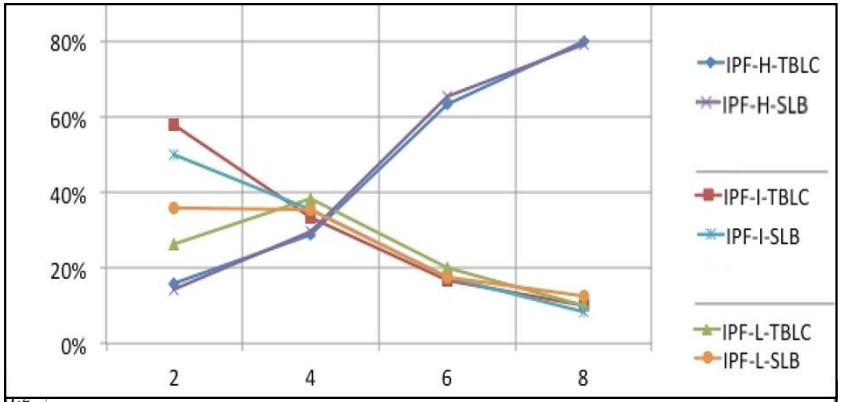


THE DIAGNOSTIC ACCURACY OF BRONCHOSCOPIC LUNG CRYOBIOPSY IN THE MULTIDISCIPLINARY DIAGNOSIS OF IDIOPATHIC PULMONARY FIBROSIS

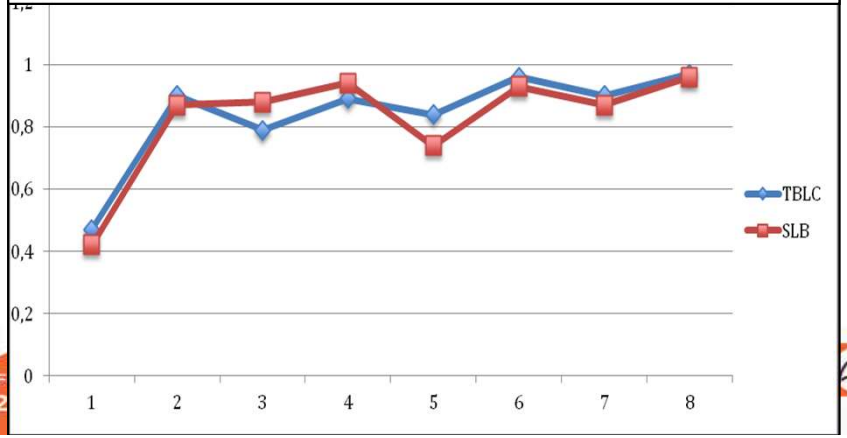
TOMASSETTI ET AL. AM J CRIT CARE MED 2016;193:745-752

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

Variation of level of confidence (for diagnosis of IPF)



Variation of interpersonal agreement



Nonintubated surgical biopsy of undetermined interstitial lung disease: a multicentre outcome analysis†

Eugenio Pompeo[a,*], Paola Rogliani[b], Cansel Atinkaya[c], Francesco Guerrera[d], Enrico Ruffini[d], Marco Antonio Iñiguez-Garcia[e], Michael Peer[f], Luca Voltolini[g], Claudio Caviezel[h], Walter Weder[h], Isabelle Opitz[h], Francesco Cavalli[b] and Roberto Sorge[i], for the ESTS awake thoracic surgery working group

Interactive CardioVascular and Thoracic Surgery 28 (2019) 744–750

Key question

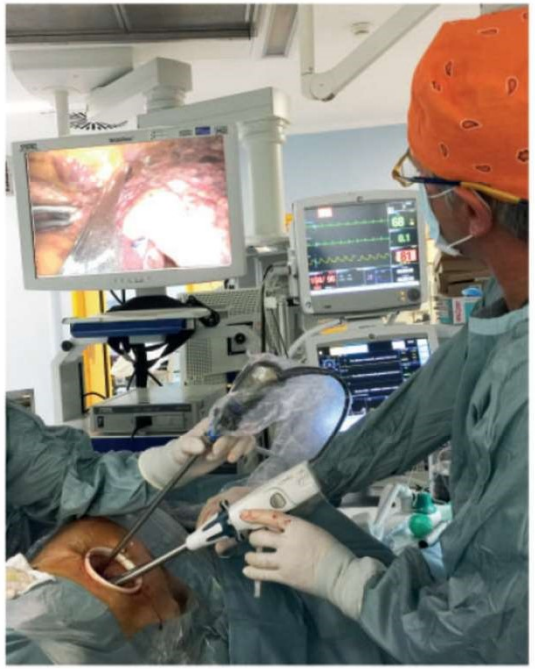
What are the outcomes of nonintubated surgical biopsy of interstitial lung disease in a multicentre investigation?

Key finding(s)

In 112 patients, feasibility, morbidity and diagnostic yield were 95%, 7.1% and 96%, respectively, with no deaths.

Take-home message

A nonintubated surgical biopsy of interstitial lung disease proved feasible, safe and highly effective in a first multicentre study.



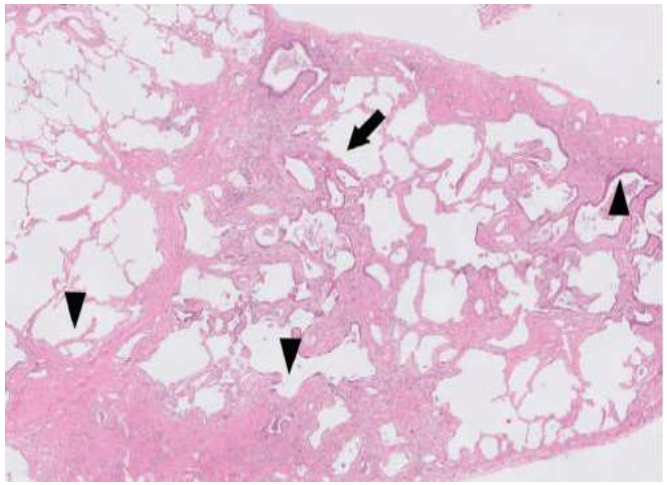
	N
Idiopathic pulmonary fibrosis	48
Non-specific interstitial pneumonia	33
Sarcoidosis	5
Hypersensitivity pneumonia	5
ILD associated with connective tissue disease	4
Desquamative interstitial pneumonia	3
Cryptogenic organizing pneumonia	3
Diffuse alveolar damage	2
Adenocarcinoma	2
Pulmonary alveolar proteinosis	2
Anthracosis	1
Mycobacteriosis	1
Drug-induced ILD	1
Unclassifiable ILD	2

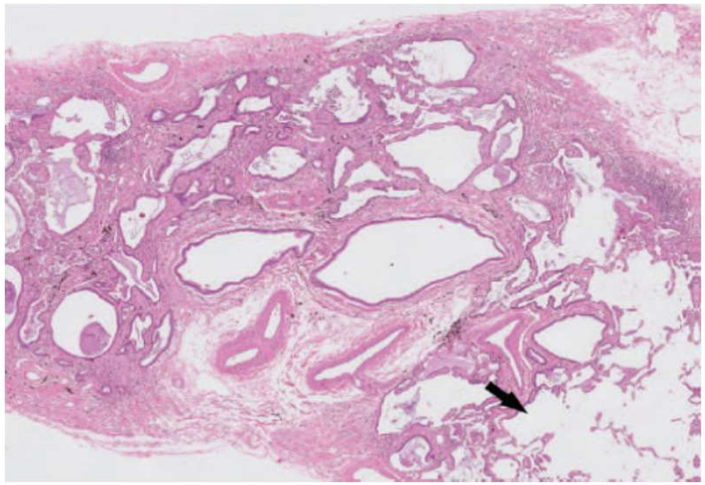
Interobserver Agreement of Usual Interstitial Pneumonia Diagnosis Correlated With Patient Outcome

Mikiko Hashisako, MD; Tomonori Tanaka, MD; Yasuhiro Terasaki, MD, PhD; Toshimasa Uekusa, MD, PhD; Rosane D. Achcar, MD; Bassam I. Aswad, MD; Hanaa S. Bamefleh, MD, chB; Vera L. Capelozzi, MD, PhD; John C. English, MD, FRCPC; Alexandre T. Fabro, MD, PhD; Kensuke Kataoka, MD, PhD; Tomayoshi Hayashi, MD, PhD; Yasuhiro Kondoh, MD, PhD; Hiroyuki Taniguchi, MD, PhD; Junya Fukuoka, MD, PhD

ARCHIVES of Pathology & Laboratory Medicine

Arch Pathol Lab Med 2016





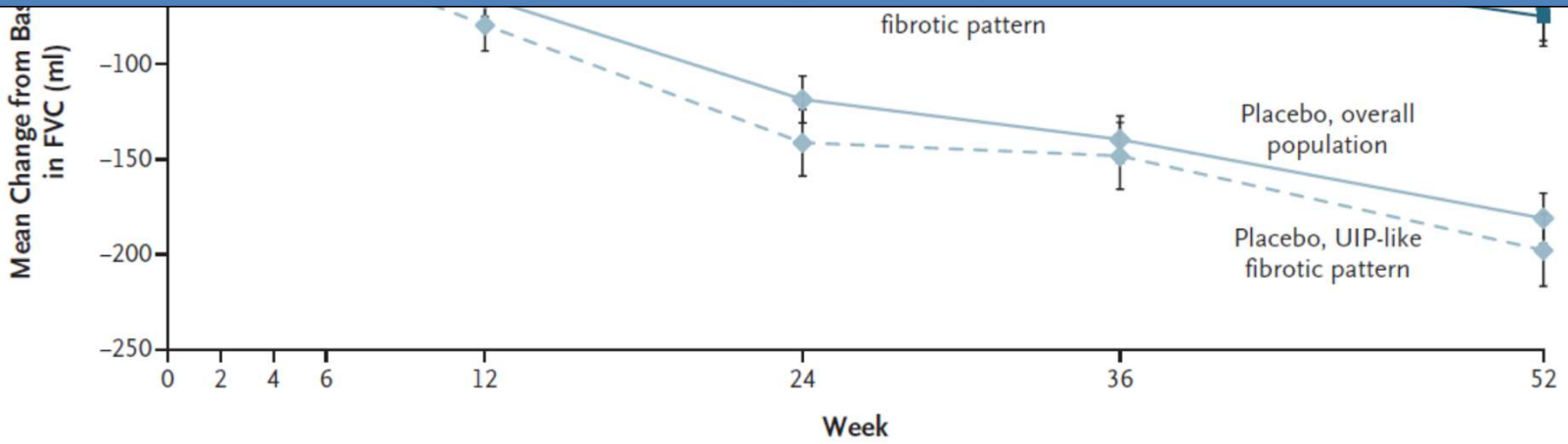
- **20 OLB / 11 pathologists /no knowledge of clinical & radiologic data**
- **The generalized K coefficient was 0.23**
- **If the diagnoses were divided into 2 groups: UIP vs non UIP K=0.37**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

UIP pattern is by far the most important pathologic feature

Do histologic ancillary findings matter ?



Clinical predictors of a diagnosis of idiopathic pulmonary fibrosis

Fell et al. Am J Respir Crit Care Med 2010;181:832-837

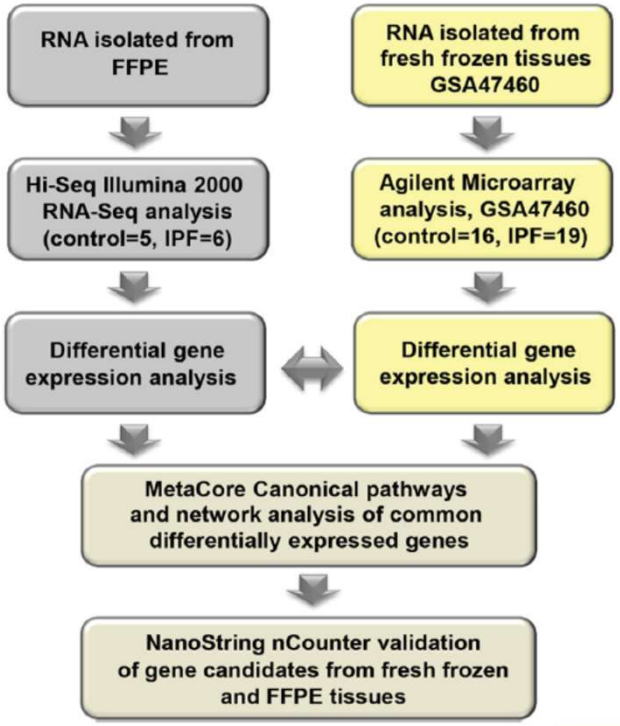
TABLE 4. POSITIVE PREDICTIVE VALUE, SPECIFICITY, SENSITIVITY, AND NEGATIVE PREDICTIVE VALUE WHEN CLASSIFYING PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS BASED ON BEING AT LEAST AS OLD AS THE AGE INDICATED

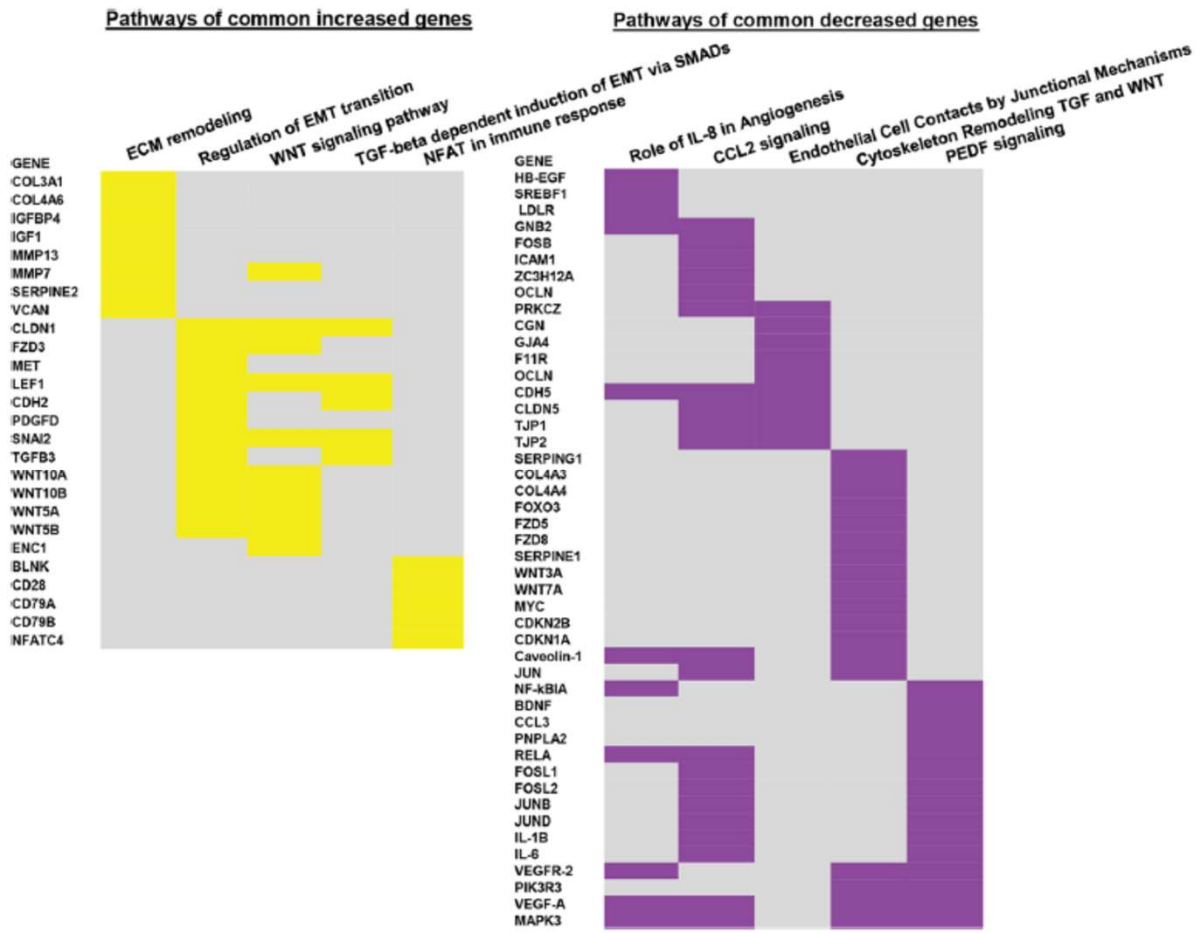
Age (*yr*)	PPV	Specificity	Sensitivity	NPV
30	72	0	100	NA
35	72	5	99	67
40	74	11	98	67
45	74	16	95	55
50	78	34	92	62
55	83	58	80	54
60	87	76	61	43
65	91	89	43	38
70	95	97	21	32
75	100	100	6	29
80	100	100	1	28

Identification and validation of differentially expressed transcripts by RNA-sequencing of formalin-fixed, paraffin-embedded (FFPE) lung tissue from patients with Idiopathic Pulmonary Fibrosis

CrossMark BMC Pulmonary Medicine (2017) 17:15

Milica Vukmirovic[7*†], Jose D. Herazo-Maya[7†], John Blackmon[1], Vesna Skodric-Trifunovic[2,3], Dragana Jovanovic[2,3], Sonja Pavlovic[4], Jelena Stojsic[5], Vesna Zeljkovic[6], Xiting Yan[7], Robert Homer[8,9], Branko Stefanovic[1†] and Naftali Kaminski[7†]

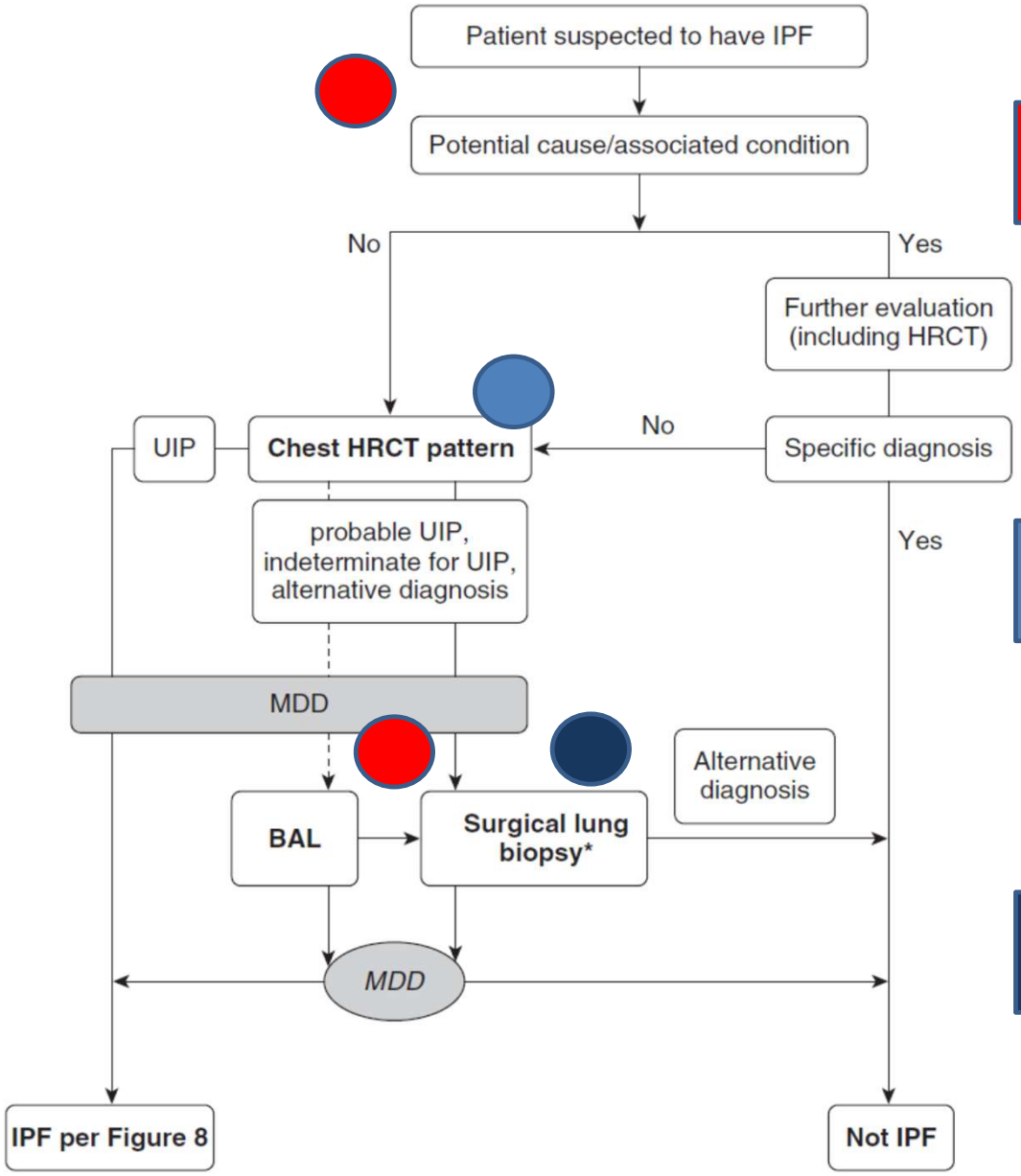




RAGHU G, ET AL. USE OF A MOLECULAR CLASSIFIER TO IDENTIFY USUAL INTERSTITIAL PNEUMONIA IN CONVENTIONAL TRANSBRONCHIAL LUNG BIO. LANCET RESPIR MED.2019 JUN;7(6):487-496. PSY SAMPLES: A PROSPECTIVE VALIDATION STUDY.

Diagnostic histopathology and RNA sequence data from 90 patients were used to train a machine learning algorithm (Envisia Genomic Classifier, Veracyte, San Francisco, CA, USA) to identify UIP pattern

- The classifier identified UIP in TBB samples from 49 patients with 88% specificity and 70% sensitivity
- Among 42 of these patients who had possible or inconsistent UIP on HRCT, the classifier showed 81% positive predictive value for underlying biopsy-proven UIP.
- Diagnostic confidence was improved by the molecular classifier results compared with histopathology results in 18 with IPF diagnoses and in all 48 patients with non-diagnostic pathology or non-classifiable fibrosis histopathology



Molecular biology

Increase imaging features

Room for CRYO & AWAKE

Takeaway messages

- **UIP/IPF: no news from histology**
- **Ancillary findings: no clear role and lack of reproducible criteria**
- **Cryobiopsy is an helpful and reproducible technique, with a diagnostic yield close to OLB**
- **Awake biopsy is another valid option to obtain tissue in ILD (quality and quantity = conventional VATS)**
- **Molecular classifiers based on RNA sequencing from conventional transbronchial biopsy could become an important method to identify idiopathic-UIP pattern in non-diagnostic HRCT or improve pathologist confidence in poorly/non diagnostic biopsy**