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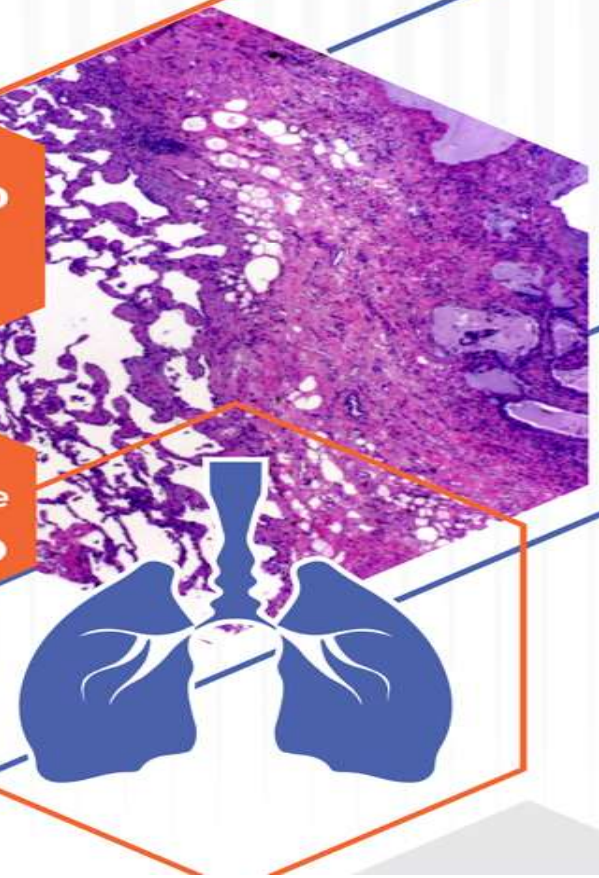
Convegno di presentazione della versione italiana delle linee guida per la diagnosi di fibrosi polmonare idiopatica

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



1 Febbraio 2020

Hotel Enterprise Milano

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Hotel Enterprise Milano

1 Febbraio 2020

LA METODOLOGIA

Sebastiano Emanuele Torrisi

Regional Centre for Interstitial and Rare Lung Diseases, Department of Clinical and Experimental Medicine, University of Catania

Methodology of

Diagnosis of Idiopathic Pulmonary Fibrosis

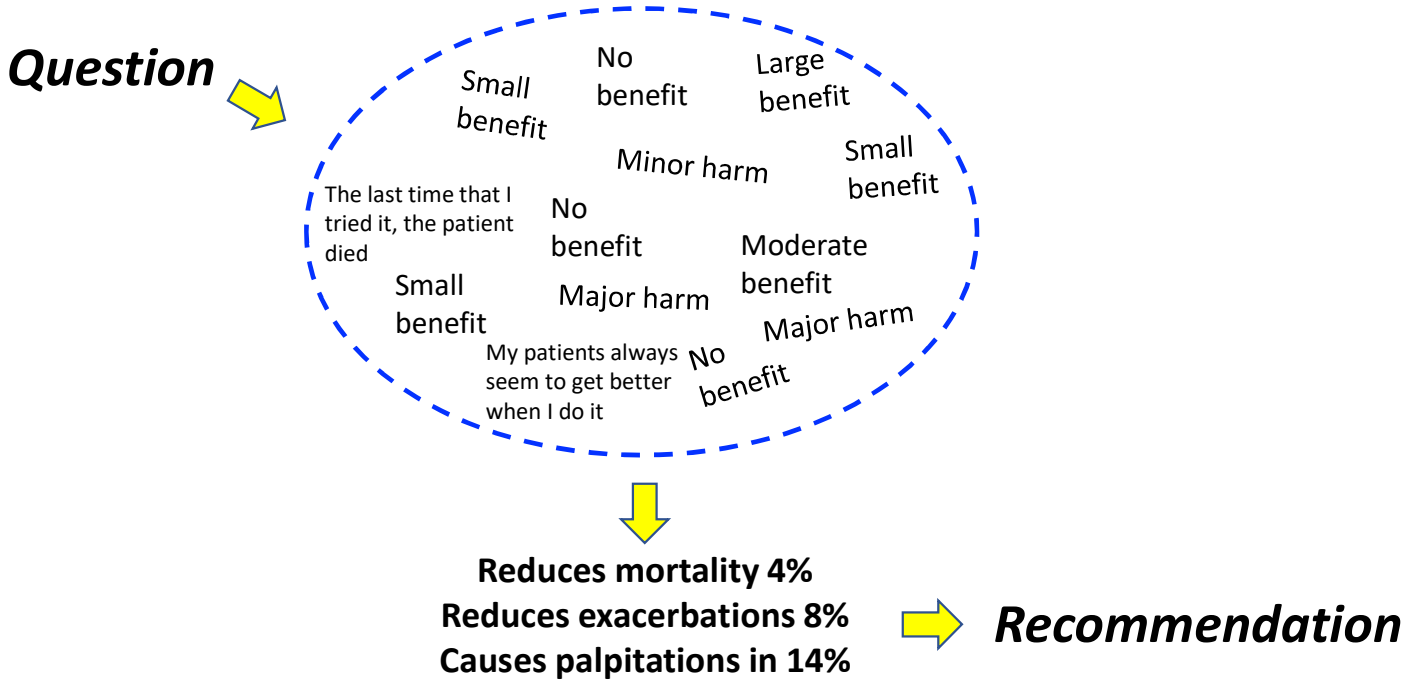
An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

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

What is a Guideline?

A guideline asks a clinical question, summarizes the body of relevant evidence, and then uses that evidence summary to inform recommendations



Richeldi L. ERS 2018

The team

2018 Diagnosis of Idiopathic Pulmonary Fibrosis
An Official ATS-ERS-JRS-ALAT Clinical Practice Guideline*

- **IPF Committee: Multidisciplinary (ATS, ERS, JRS, ALAT)**
  - **Chair**
    - Dr. Ganesh Raghu, Pulmonologist, Seattle, WA, USA
  - **Co-chairs**
    - Dr. Jeffrey L. Myers, Pathologist, Ann Arbor, MI, USA
    - Dr. Martine Remy-Jardin, Radiologist, Lille, France
    - Dr. Luca Richeldi, Pulmonologist, Rome, Italy
  - **Project manager and lead methodologist**
    - Dr. Kevin C. Wilson, Pulmonologist, Boston, MA, USA
  - **Methodology team**
    - Dr. Thomas Bice, Pulmonologist, Chapel Hill, NC, USA
    - Dr. Abjihit Duggal, Pulmonologist, Cleveland, OH, USA
    - Dr. George Mansur, Internal Medicine, St. Louis, MO, USA

Am J Respir Crit Care Med Vol 198, Iss 5, pp e44–e68, Sep 1, 2018

2018 Diagnosis of Idiopathic Pulmonary Fibrosis
An Official ATS-ERS-JRS-ALAT Clinical Practice Guideline*

- **IPF Committee: Multidisciplinary (ATS, ERS, JRS, ALAT)**
  - **Guideline Panel – North America**
    - Ganesh Raghu, Pulmonologist, Seattle, WA, USA
    - Jeff L. Myers, Pathologist, Ann Arbor, MI, USA
    - William D. Travis, Pathologist, New York, NY, USA
    - Fernando Martinez, Pulmonologist, New York, NY, USA
    - Harold Collard, Pulmonologist, San Francisco, CA, USA
    - Kevin Flaherty, Pulmonologist, Ann Arbor, MI, USA
    - David Lederer, Pulmonologist, New York, NY, USA
    - Sonye K. Danoff, Pulmonologist, Baltimore, MD, USA
    - Kevin Brown, Pulmonologist, Denver, CO, USA
    - Chris Ryerson, Pulmonologist, Vancouver, BC, Canada
    - Sudhakar Pipavath, Radiologist, Seattle, WA, USA
    - Ella Kazerooni, Radiologist, Ann Arbor, MI, USA

* Am J Respir Crit Care Med Vol 198, Iss 5, pp e44–e68, Sep 1, 2018

- **IPF Committee: Multidisciplinary (ATS, ERS, JRS, ALAT)**
  - **Guideline Panel – Europe**
    - Martine Remy-Jardin, Radiologist, Lille, France
    - Luca Richeldi, Pulmonologist, Rome, Italy
    - Athol Wells, Pulmonologist, London, UK
    - Gisli Jenkins, Pulmonologist, Nottingham, UK
    - Juergen Behr, Pulmonologist, Munich, Germany
    - Vincent Cottin, Pulmonologist, Lyon, France
    - Ferrin Morell, Pulmonologist, Barcelona, Spain
    - Demosthenes Bouros, Pulmonologist, Athens, Greece
    - Andrew Nicholson, Pathologist, London, UK
    - Simon Walsh, Radiologist, London, UK

* Am J Respir Crit Care Med Vol 198, Iss 5, pp e44–e68, Sep 1, 2018

2018 Diagnosis of Idiopathic Pulmonary Fibrosis
An Official ATS-ERS-JRS-ALAT Clinical Practice Guideline*

- **IPF Committee: Multidisciplinary (ATS, ERS, JRS, ALAT)**
  - **Guideline Panel – Mexico and Japan**
    - Moises Selman, Pulmonologist, Mexico
    - Ivette Buendia-Roldan, Pulmonologist, Mexico
    - Takeshi Johkoh, Radiologist, Japan
    - Yoshikazu Inoue, Pulmonologist, Japan
    - Arata Azuma, Pulmonologist, Japan
    - Masanori Kitaichi, Pathologist, Japan
  - **Reference Librarian**
    - Shandra L. Knight, Medical Librarian, Denver, CO, USA
  - **Patient Representative**
    - Liam Galvin, Ireland

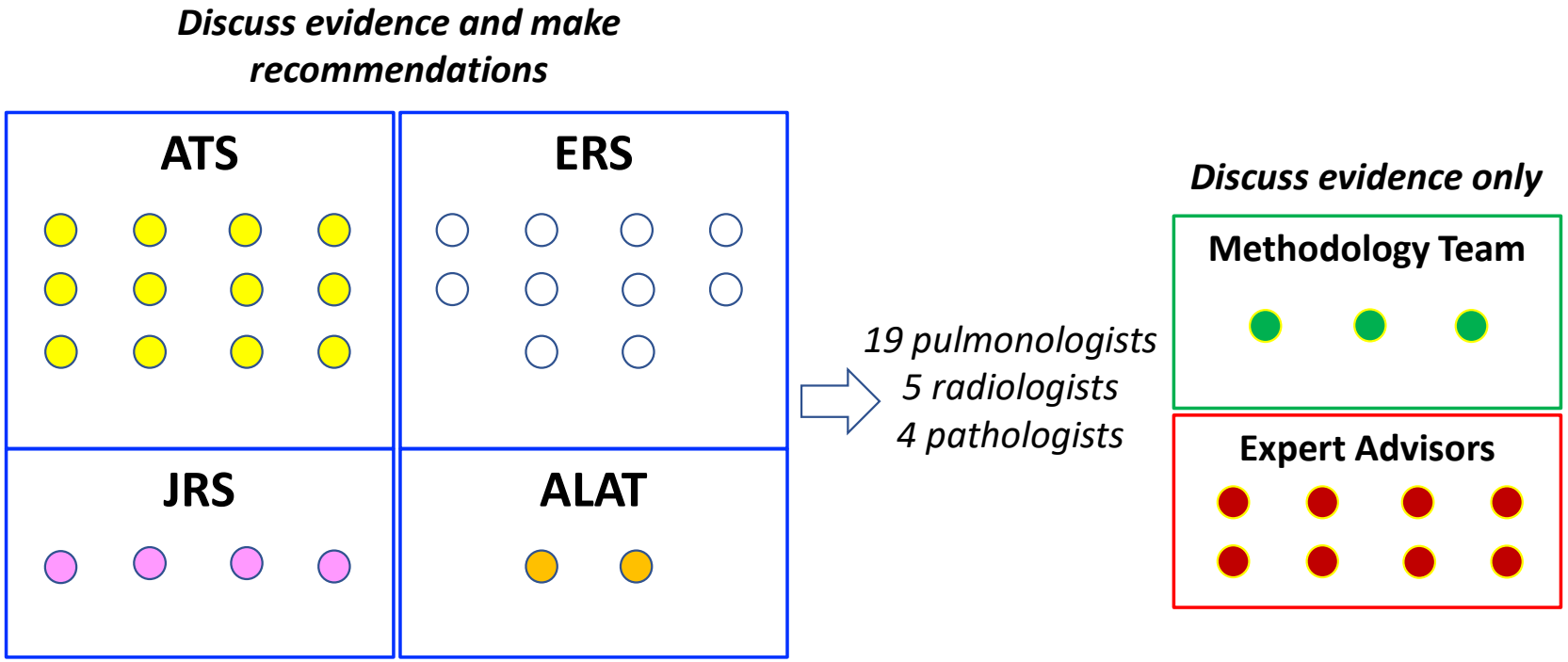
* Am J Respir Crit Care Med Vol 198, Iss 5, pp e44–e68, Sep 1, 2018

- **IPF Committee: Multidisciplinary (ATS, ERS, JRS, ALAT)**
  - **Expert Advisors**
    - Drs. Mary Armanios and David Schwartz (Genetic Factors)
    - Dr. Virginia Steen (Rheumatology)
    - Drs. Sharf Keshavjee, Walter Weden, Michael Mulligan (Thoracic Surgery)
    - Drs. Atul Mehta and Venerino Poletti (Interventional Bronchoscopy, Lung Cryobiopsy)

* Am J Respir Crit Care Med Vol 198, Iss 5, pp e44–e68, Sep 1, 2018

Panel Composition

Multi-disciplinary and multi-society



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1st step: Questions

Why are research questions so important?

"Well-crafted questions guide the systematic planning of research. Formulating your questions precisely enables you to design a study with a good chance of answering them."

Light, Singer, Willet, by Design 1990

Characteristics of a good question

- «FINER»
- F=feasible
- I=interesting
- N=novel
- E=ethical
- R=relevant

Questions

The co-chairs and methodologist drafted key clinical questions in a **PICO (Population, Intervention, Comparator, and Outcome) format**

The questions were then discussed, modified, and approved by the full guideline panel with input from the expert advisers at a face-to-face meeting held at the 2017 ATS International Conference in Washington, D.C. in May, 2017.

The evidence was assessed for all outcomes identified by the panel, but only those assigned a priority of critical (i.e., median rating of 7-9) were used to rate the quality of evidence.

Questions

«The co-chairs and methodologist drafted key clinical questions in a **PICO format»**

Am J Respir Crit Care Med Vol 198, Iss 5, pp e44–e68, Sep 1, 2018

What is PICO format?

- A useful model to help structure an answerable question
- Used to formulate clinical questions
- Breaks down the question into four key elements

Asking the clinical question: the PICO format

P Population

I Intervention or Interest area

C Comparison intervention or status

O Outcome

P	I	C	O
Patient, Population or Problem	**Intervention or exposure**	**Comparison**	**Outcome**
What are the characteristics of the patient or population? What is the condition or disease you are interested in?	What do you want to do with this patient (e.g. treat, diagnose, observe)?	What is the alternative to the intervention (e.g. placebo, different drug, surgery)?	What are the relevant outcomes (e.g. morbidity, death, complications)?

Questions Approved Face-to-face meeting at 2017 ATS Conference

- Exclusion of potential causes of ILD.
- Serological testing for CTD.
- Cellular analysis of BAL fluid.
- Surgical lung biopsy.
- Transbronchial biopsy.
- Transbronchial cryobiopsy.
- Multi-disciplinary discussion.
- Serum diagnostic biomarkers.

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2nd step *Literature search*

....

The published literature was searched by the **librarian** (SK) in the following databases:

Medline, Excerpta Medica Database (EMBASE), and Cochrane Database of Systematic Reviews

Example

Table E3. Search strategy/results for bronchoalveolar lavage

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>		
#	**Searches**	**Results**
1	bronchoalveolar lavage/ or bronchoalveolar lavage fluid/	25167
2	((lavage$ or wash$) adj2 (lung$ or bronch$ or pulmonary)).mp.	39697
3	1 or 2	39697

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3nd step Evidence synthesis

- For controlled studies, relative risk (RR) was used to report the results for dichotomous outcomes and the mean difference (MD) was used to report the results for continuous outcomes.
- For uncontrolled studies, generic inverse variance was used if possible, but studies were often pooled without weighting (i.e., generic inverse variance cannot be used if an individual study has a result of 0% or 100%, which was often the case).

The Grading, Recommendations, Assessment, Development, and Evaluation (GRADE) approach

Underlying Methodology	Quality Rating
RCT	High
Downgraded RCTs or upgraded observational studies	Moderate
Well-done observational studies with control groups	Low
Others (e.g., case reports or case series)	Very low

Definition of abbreviation: RCT = randomized controlled trial.

The Grading, Recommendations, Assessment, Development, and Evaluation (GRADE) approach

Quality of Evidence

Initial assumption based upon the study design:					
High	Randomized trial				
Moderate	--				
Low	Well-done observational study with control groups				
Very low	Other evidence, such as case reports, case series, etc.				
Downgrade the quality of evidence if:					
Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
Upgrade the quality of evidence if:					
Strong association (i.e., large magnitude of effect)		Dose-response gradient		Plausible confounders would have the opposite effect	

Confidence in the accuracy of the study results

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Guideline Development
Two processes in parallel

Methodology team

PICO questions

- Bronchoalveolar lavage (BAL) *vs* no BAL
- Surgical lung biopsy (SLB) *vs* no SLB
- Transbronchial biopsy (TBBx) *vs* no TBBx
- Cryobiopsy (CB) *vs* no CB
- Multi-disciplinary discussion (MDD) *vs* no MDD
- Peripheral blood biomarkers (BM) *vs* no BM

Remainder of panel

Other content

- Motherhood statements
- Diagnosis based upon HRCT & histopathology
- Diagnostic criteria
- Diagnostic algorithm

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Evidence to Recommendations Face-to-face meeting at 2017 ERS Congress

- **Approval of non-PICO content**
- **Then, presentation of evidence → committee discussion → recommendation formulation → voting**

Recommendations for or against an intervention are based upon:

- ✓ balance of benefits *vs* harms and burdens
- ✓ quality of evidence
- ✓ patient values and preferences
- ✓ feasibility
- ✓ costs

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Recommendations

Guideline recommendations are rated:

- **Quality of evidence**: Conveys how much *confidence* the committee has in the *accuracy of the study results*.
- **Strength of the recommendation**: Conveys how *certain* the committee is that the upsides of the recommended *course of action* outweigh the downsides.

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Strength of Recommendations

Strong	Conditional
It is the correct course of action for >95% of patients	It is the correct course of action for >50% of patients, but may not be correct for a sizeable minority
"Just do it"	"Slow down, think about it, discuss it with the patient"
Willing to tell a colleague that he/she is wrong for not following the recommendation	Not willing to tell a colleague that he/she is wrong for not following the recommendation. It is a matter of style. There is equipoise
Appropriate for a performance measure	Not appropriate for a performance measure

- **Certainty that upsides of the recommended course of action outweigh downsides**

Richeldi L. ERS 2018

Strength of Recommendations

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It is the correct course of action for >95% of patients	It is the correct course of action for >50% of patients, but may not be correct for a sizeable minority
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Appropriate for a performance measure	Not appropriate for a performance measure

- **Certainty that upsides of the recommended course of action outweigh downsides**


Sample Recommendation
We recommend treatment X rather than treatment Y for patients with condition Z
(conditional recommendation, low quality of evidence)

Review

Lancet Respir Med 2018;6:138-53

Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper

David A Lynch, Nicola Sverzellati, William D Travis, Kevin K Brown, Thomas V Colby, Jeffrey R Galvin, Jonathan G Goldin, David M Hansell, Yoshikazu Inoue, Takeshi Johkoh, Andrew G Nicholson, Shandra L Knight, Suhail Raoof, Luca Richeldi, Christopher J Ryerson, Jay H Ryu, Athol U Wells

This Review provides an updated approach to the diagnosis of idiopathic pulmonary fibrosis (IPF), based on a systematic search of the medical literature and the expert opinion of members of the Fleischner Society. A checklist is provided for the clinical evaluation of patients with suspected usual interstitial pneumonia (UIP). The role of CT is expanded to permit diagnosis of IPF without surgical lung biopsy in select cases when CT shows a probable UIP pattern. Additional investigations, including surgical lung biopsy, should be considered in patients with either clinical or CT findings that are indeterminate for IPF. A multidisciplinary approach is particularly important when deciding to perform additional diagnostic assessments, integrating biopsy results with clinical and CT features, and establishing a working diagnosis of IPF if lung tissue is not available. A working diagnosis of IPF should be reviewed at regular intervals since the diagnosis might change. Criteria are presented to establish confident and working diagnoses of IPF.

Lancet Respir Med 2017

Published Online
November 15, 2017
http://dx.doi.org/10.1016/S2213-2600(17)30433-2

See Online/Comment
http://dx.doi.org/10.1016/S2213-2600(17)30443-5

Department of Radiology (Prof D A Lynch MB), **Department of Medicine** (Prof K K Brown MD),

AMERICAN THORACIC SOCIETY DOCUMENTS

Am J Respir Crit Care Med Vol 198, Iss 5, pp e44–e68, Sep 1, 2018

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 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

Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper

Lancet Respir Med 2018;6:138-53

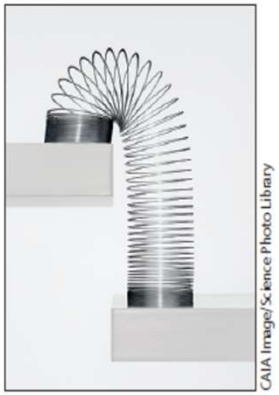
David A Lynch, Nicola Sverzellati, William D Travis, Kevin K Brown, Thomas V Colby, Jeffrey R Galvin, Jonathan G Goldin, David M Hansell, Yoshikazu Inoue, Takeshi Johkoh, Andrew G Nicholson, Shandra L Knight, Suhail Raoof, Luca Richeldi, Christopher J Ryerson, Jay H Ryu, Athol U Wells

Athol U Wells
Royal Brompton Hospital, London SW3 6HP, UK
athol.wells@rbht.nhs.uk

IPF diagnosis: flexibility is a virtue

In 2011, the joint guidelines[1] of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Thoracic Association of Latin America provided the first truly international evidence-based statement on the diagnosis of idiopathic pulmonary fibrosis (IPF). Although this statement undoubtedly underpinned international collaboration in science and interventional trials, the rigour of the 2011 diagnostic criteria effectively disenfranchised a large subgroup of patients with IPF, in whom a surgical lung biopsy (SLB) could not be done and no definite diagnosis could be made. The concept of probable IPF was not explored in the 2011 guidelines, and the

This conclusion is crucial, given the Fleischner statement that "if diagnostic tissue is not available, a working diagnosis of IPF may be made after careful multidisciplinary evaluation."[3] A working diagnosis of IPF is not a definite diagnosis, but it is a provisional diagnosis with a level of diagnostic likelihood such that IPF-specific therapy is the only logical approach. In effect, the Fleischner Society endorses the use of IPF-specific treatment in selected patients with probable UIP on HRCT and no biopsy data. To what extent is there genuine disagreement between the Fleischner Society statement and the revised joint diagnostic guidelines? Initial reaction at the American



CAIA Image/Science Photo Library

Lancet Respir Med 2018
Published Online
September 14, 2018
http://dx.doi.org/10.1016/S2213-2600(18)30374-6

In summary, the Fleischner Society statement and the 2018 joint diagnostic guidelines are broadly concordant.

EDITORIAL
IDIOPATHIC PULMONARY FIBROSIS

Diagnosing idiopathic pulmonary fibrosis in 2018: bridging recommendations made by experts serving different societies

Luca Richeldi[1], Kevin C. Wilson[2] and Ganesh Raghu[3]

https://doi.org/10.1183/13993003.01485-2018

Eur Respir J 2018; 52: 1801485

https://doi.org/10.1183/13993003.01485-2018 Eur Respir J 2018; 52: 1801485

CrossMark

Diagnosing idiopathic pulmonary fibrosis in 2018: bridging recommendations made by experts serving different societies

Luca Richeldi[1], Kevin C. Wilson[2] and Ganesh Raghu[3]

	ATS/ERS/JRS/ALAT clinical practice guideline [1]		Fleischner white paper consensus statement [2]
Number of authors	34		17
Overlapping authors		8	
Endorsing scientific societies	Multiple		Single
Multidisciplinary nature	Yes		Yes
Question-based structure	Yes		Yes
Systematic search of the literature	Yes		Yes
Evidence-based approach (Institute of Medicine standards)	Yes		No
PICO questions/format	Yes		No
Expert opinion-based approach	No		Yes
Grading of recommendations	Yes		No
Published in a peer-reviewed journal	Yes		Yes
Implementation and interest to all stakeholders (policy makers, regulating agencies, IPF community-at-large)	Yes		?

IPF: idiopathic pulmonary fibrosis; ATS: American Thoracic Society; ERS: European Respiratory Society; JRS: Japanese Respiratory Society; ALAT: Latin American Thoracic Society; PICO: population, intervention, comparison, outcome.

DIAGNOSTIC COMPONENTS FOR IPF

	ATS/ERS/JRS/ALAT clinical practice guideline [1]	Fleischner white paper consensus statement [2]
Histopathology pattern	**UIP**	**Definite UIP**
	Dense fibrosis with architecture remodelling Predominant subpleural or paraseptal distribution of fibrosis Patchy lung involvement by fibrosis Presence of fibroblastic foci	
		Probable UIP
		Honeycomb fibrosis only Fibroblastic foci may or may not be present
		Indeterminate for UIP
	Fibrosis with or without architecture distortion Some histological features from the UIP pattern	Occasional foci of centrilobular injury or scarring Rare granulomas or giant cells Minor degree of lymphoid hyperplasia or diffuse inflammation Diffuse homogenous fibrosis favouring fibrotic nonspecific interstitial pneumonia
	Alternative diagnosis	**Features most consistent with an alternative diagnosis**
	Histological findings indicative of other diseases	A UIP pattern with ancillary features strongly suggesting an alternative diagnosis A non-UIP pattern

Richeldi L ,Wislon K, Raghu G, *Eur Respir J* 6 Sept 2018

https://doi.org/10.1183/13993003.01485-2018 Eur Respir J 2018; 52: 1801485

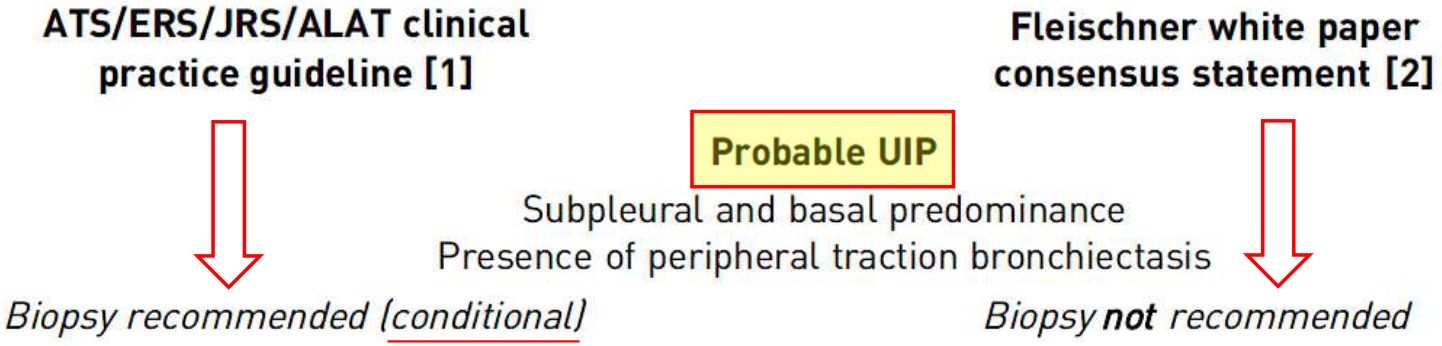
DIAGNOSTIC COMPONENTS FOR IPF

	ATS/ERS/JRS/ALAT clinical practice guideline [1]	Fleischner white paper consensus statement [2]
Age limit for increased diagnostic confidence	60 years	
HRCT pattern	**UIP**	**Typical UIP**
	Subpleural and basal predominance Presence of honeycombing with or without peripheral traction bronchiectasis	
	*Biopsy **not** recommended*	
	Probable UIP	
	Subpleural and basal predominance Presence of peripheral traction bronchiectasis	
	Biopsy recommended (conditional)	*Biopsy **not** recommended*
	Indeterminate for UIP	
	Subpleural and basal predominant May have mild GGO or distortion	Variable or diffuse Features suggestive of non-UIP pattern
	Biopsy recommended	
	Alternative diagnosis	**Most consistent with non-IPF diagnosis**
	Findings suggestive of another diagnosis	
	Biopsy recommended	

Richeldi L , Wilson K, Raghu G , *Eur Respir J* 2018 6 Sept 2018

https://doi.org/10.1183/13993003.01485-2018 Eur Respir J 2018; 52: 1801485

DIAGNOSTIC COMPONENTS FOR IPF
HIGH-RESOLUTION COMPUTED TOMOGRAPHY



The guideline panel concluded that biopsy is appropriate for a majority of patients, but may not be appropriate for a sizeable minority (up to 49%); in other words, the guidelines indicate that there is ***clinical equipoise*** *when deciding whether or not to biopsy a patient with a probable UIP pattern on HRCT.*

Richeldi L ,Wilson,K, Raghu, G *Eur Respir J* 2018 in press 6 Sept 2018

Grazie