Diagnosis of Idiopathic Pulmonary Fibrosis:

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

Online supplement

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METHODS

Panel Composition

The project was proposed by the lead co-chair through a joint application to the American Thoracic Society (ATS) and European Respiratory Society (ERS). Upon approval, the Japanese Respiratory Society (JRS) and Latin American Thoracic Society (ALAT) were invited to collaborate. The project commenced January 1, 2017.

Co-chairs and potential panelists were proposed by the lead co-chair based on their expertise in interstitial lung disease and/or clinical practice guideline development. The co-chair also proposed a panel of expert advisers that included a rheumatologist, interventional pulmonologists, thoracic surgeons, and experienced clinical investigators of genetic predisposition and circulating biomarkers for IPF. All potential panelists and expert advisers disclosed their conflicts of interest, which were vetted and managed according to the policies and procedures of the ATS and agreed upon by the other societies. The decision of the selected and final number of panelists representing the respective societies was based on the policies of the ATS and ERS and the final panel was appointed by the leadership of the ATS, ERS, JRS and ALA .

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. Outcomes that might be affected by each of the interventions were numerically rated (from 1 to 9) according to their importance. 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.

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

(Tables E3-E6). Searching was conducted in April 2017 by the librarian and then a targeted updated was performed in September 2017 by the lead methodologist. The methodology team reviewed all publications retrieved from the literature searches in duplicate for relevance, initially screening based on title and/or abstract and then reviewing the full text of potentially relevant publications. The bibliographies of included studies and related systematic reviews were also reviewed.

Evidence synthesis

Findings from relevant publications were extracted into data tables. When data were amenable to weighted pooling, the random effects model was implemented in the Cochrane Collaboration Review Manager, version 5.3. 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). Regardless of the approach used to pool individual studies, the accompanying 95% confidence interval (CI) was determined. Statistical heterogeneity of the pooled results was measured using the I^2 and Chi^2 tests, considering an I^2 value of $\geq$50% or a Chi^2 $p<0.05$ to indicate significant heterogeneity. Results are provided in the evidence tables.

We used the Grading, Recommendations, Assessment, Development, and Evaluation (GRADE) approach to assess certainty in the estimated effects (i.e., the quality of evidence) for each intervention on each outcome of interest (1). The methodologist created evidence profiles using the Guideline Development Tool (2), which categorized the overall certainty in the evidence

into one of four levels: high, moderate, low, or very low. Each level represents the certainty in the accuracy of the estimated effects for a specific intervention. The full guideline panel reviewed the evidence profiles and provided input and feedback.

Recommendations

The guideline panel met at the 2017 ERS Congress in Milan, Italy to review and discuss the evidence syntheses, and to develop recommendations to answer each PICO question. The panelists made decisions about whether to recommend for or against an intervention based on: the balance of desirable consequences (benefits) and undesirable consequences (burdens, adverse effects, and costs), quality of evidence, feasibility, and acceptability to patients (i.e., patient values and preferences). Using the GRADE approach, each recommendation was rated as either "strong" or "conditional". All recommendations were formulated and graded by voting following discussion.

Manuscript preparation

The initial draft of the manuscript was written by the lead co-chair (GR) and the lead methodologist (KW). Individual sections, tables, and figures were written/composed by the co-chairs (MRJ, JLM, LR) and two section co-leads designated by the lead co-chair (CJR, DJL, JB, VC, SHD, FM, KF, AW, FJM). All members of the guideline panel reviewed the manuscript; all comments were addressed by the co-chairs and then incorporated into the revised manuscript by the lead methodologist. The manuscript was redistributed to the full panel including the expert advisers, patient advocate (LG), and the librarian (SLK) for further review. The final product was

the result of collective work from all the panelists, expert advisers, and the methodologists. Once the manuscript was approved by the full panel, it was submitted for external peer review.

Peer review

External peer review was simultaneously conducted by the four collaborating societies. Comments from the reviewers were collated into a single decision letter by the ATS Documents Editor and sent to the lead co-chair. The manuscript was subsequently revised by the panel according to feedback received from the peer reviewers. Following several cycles of review and revisions, the manuscript was deemed satisfactory and sent to the leadership of each society for further review and final approval.

Methods references:

1. Schunemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A, Fahy BF, Gould MK, Horan KL, Krishnan JA, et al. An Official ATS Statement: Grading the Quality of Evidence and Strength of Recommendations in ATS Guidelines and Recommendations. Am J Respir Crit Care Med 2006; 174:605-614.
2. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from gradepro.org.

TABLE E1. Checklist of Recommended Computed Tomography Scanning Parameters

	UIP/IPF pattern	**Probable UIP/IPF pattern**	**Indeterminate pattern** *("early UIP pattern")*	**Indeterminate pattern** *("truly indeterminate")*	**Features suggestive of an alternative diagnosis for lung fibrosis**
CT features					
-honeycombing -peripheral bronchiolectasis	□ □	□			
-mild GGO	□	□	□		
-reticulation	□	□	□		
-distortion			□		
-pulmonary ossification					
-cysts					□ □

-marked mosaic attenuation -predominant GGO -profuse micronodules -centrilobular nodules -nodules -consolidation					□ □ □ □ □
-non-specific features of lung infiltration				□	
Predominant distribution					
-subpleural lung *(peripheral)* -peribronchovascular lung *(central)* -perilymphatic -diffuse	□ □ *occasionally*	□	□		 □ □
-anterior lung -posterior lung	 □	 □			□
-upper lung -mid lung -lower lung	 □	 □	 □		□ □
-symetrical -asymetrical	□ □ *occasionally*				
-homogeneous -heterogeneous	 □	 □			
-absence of predominant distribution				□	

Table E2. Connective Tissue Disease Associated Interstitial Lung Disease

Connective Tissue Disease	Type of ILD	Estimated Prevalence of ILD	CTD is Occult
Dermatomyositis Polymyositis Anti-synthetase syndrome	NSIP with OP NSIP OP UIP	40%	Often

Sjogren's syndrome	NSIP UIP LIP	Up to 40%	Less often
Systemic sclerosis	NSIP UIP	> 50% (80% subclinical)	Less often
Rheumatoid arthritis	UIP NSIP OP	10% (30% subclinical)	Less often
Interstitial pneumonia with autoimmune features	NSIP OP NSIP/OP UIP	100%	Often

3.

4. CTD: Connective tissue disease; ILD: Interstitial lung disease; LIP: Lymphocytic interstitial pneumonia;
OP: Organizing pneumonia; UIP: Usual interstitial pneumonia.

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

4	(exp fibrosing alveolitis/ and cryptogenic.mp.) or (cryptogenic adj4 (fibros$ or fibrotic or fibrous) adj4 alveolitis).mp.	438
5	pulmonary fibrosis/	17238
6	exp Fibrosis/ and (exp Respiratory Tract Diseases/ or exp Respiratory System/)	4422
7	((lung$ or respir$ or pulmonary or alveol$) adj4 (fibros$ or fibrotic or fibrous)).mp.	33071
8	5 or 6 or 7 [lung AND fibrosis terms]	36705
9	(cryptog$ or idiopa$).tw.	106853
10	4 or (8 and 9) [lung AND fibrosis AND idiopath terms]	6812
11	idiopathic interstitial pneumonias/	256
12	idiopathic pulmonary fibrosis/	2165
13	((usual or idiopa$ or ordinary or cryptog$) adj4 interstitial adj4 (lung$ or respir$ or pulmonary or alveol$ or pneumo$)).tw.	2191
14	Lung Diseases, Interstitial/ or (interstitial adj3 (lung$ or pneumonia$)).tw.	16312
15	(((unknow$ or uncertain$) adj4 (origin$ or cause$ or aetiol$ or etiol$)) or (cryptog$ or idiopa$)).tw.	147426
16	14 and 15 [idiopathic AND ILD terms]	3287
17	10 or 11 or 12 or 13 or 16	8670
18	..l/ 17 lg=en [limited to English language]	7334
19	limit 18 to humans	6116
20	limit 18 to animal	1057
21	18 not 19 not 20	904
22	19 or 21 [human or not indexed]	7020
23	limit 22 to yr="2010 -Current"	3743
24	3 and 23	286

Embase <1996 to 2017 Week 10>

#	Searches	Results
1	*lung lavage/ or bronchoalveolar lavage fluid/	6127
2	((lavage$ or wash$) adj2 (lung$ or bronch$ or pulmonary)).ti,ab.	34301
3	1 or 2	35166
4	(exp fibrosing alveolitis/ and cryptogenic.mp.) or (cryptogenic adj4 (fibros$ or fibrotic or fibrous) adj4 alveolitis).mp.	323
5	pulmonary fibrosis/	8410
6	exp Fibrosis/ and (exp Respiratory Tract Diseases/ or exp Respiratory System/)	61343
7	((lung$ or respir$ or pulmonary or alveol$) adj4 (fibros$ or fibrotic or fibrous)).mp.	47490
8	5 or 6 or 7 [lung AND fibrosis terms]	69202
9	(cryptog$ or idiopa$).tw.	116414
10	4 or (8 and 9) [lung AND fibrosis AND idiopath terms]	11044
11	interstitial pneumonia/ and idiopathic.mp.	2813
12	((usual or idiopa$ or ordinary or cryptog$) adj4 interstitial adj4 (lung$ or respir$ or pulmonary or alveol$ or pneumo$)).tw.	3085
13	Lung Diseases, Interstitial/ or (interstitial adj3 (lung$ or pneumonia$)).tw.	19504
14	(((unknow$ or uncertain$) adj4 (origin$ or cause$ or aetiol$ or etiol$)) or (cryptog$ or idiopa$)).tw.	161854
15	13 and 14 [idiopathic AND ILD terms]	4951
16	Idiopathic Pulmonary Fibrosis.mp.	9196
17	10 or 11 or 12 or 15 or 16	13529
18	..l/ 17 lg=en [limited to English language]	12179
19	limit 18 to humans	10998
20	limit 18 to animal	596
21	18 not 19 not 20	585

22	19 or 21 [human or not indexed]	11583
23	limit 22 to yr="2010 -Current"	8591
24	3 and 23	676
25	limit 24 to conference abstract	392
26	24 not 25	284

Table E4. Search strategy/results for surgical lung biopsy, transbronchial biopsy, and lung cryobiopsy

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>		
#	**Searches**	**Results**
1	(exp fibrosing alveolitis/ and cryptogenic.mp.) or (cryptogenic adj4 (fibros$ or fibrotic or fibrous) adj4 alveolitis).mp.	438

2	pulmonary fibrosis/	17238
3	exp Fibrosis/ and (exp Respiratory Tract Diseases/ or exp Respiratory System/)	4422
4	((lung$ or respir$ or pulmonary or alveol$) adj4 (fibros$ or fibrotic or fibrous)).mp.	33084
5	2 or 3 or 4 [lung AND fibrosis terms]	36718
6	(cryptog$ or idiopa$).tw.	106907
7	1 or (5 and 6) [lung AND fibrosis AND idiopath terms]	6816
8	interstitial pneumonia/ and idiopathic.mp.	1346
9	((usual or idiopa$ or ordinary or cryptog$) adj4 interstitial adj4 (lung$ or respir$ or pulmonary or alveol$ or pneumo$)).tw.	2191
10	Lung Diseases, Interstitial/ or (interstitial adj3 (lung$ or pneumonia$)).tw.	16319
11	(((unknow$ or uncertain$) adj4 (origin$ or cause$ or aetiol$ or etiol$)) or (cryptog$ or idiopa$)).tw.	147499
12	10 and 11 [idiopathic AND ILD terms]	3289
13	Idiopathic Pulmonary Fibrosis.mp.	5968
14	7 or 8 or 9 or 12 or 13	8726
15	..l/ 14 lg=en [limited to English language]	7393
16	limit 15 to humans	6138
17	limit 15 to animal	1075
18	15 not 16 not 17	937
19	16 or 18 [human or not indexed]	7075
20	limit 19 to yr="2010 -Current"	3802
21	((bronch$ or transbronch$ or surg$ or lung$) adj2 (cryobiosp$ or biops$)).mp.	19918
22	20 and 21	363

Embase <1996 to 2017 Week 10>

#	Searches	Results
1	(exp fibrosing alveolitis/ and cryptogenic.mp.) or (cryptogenic adj4 (fibros$ or fibrotic or fibrous) adj4 alveolitis).mp.	438
2	pulmonary fibrosis/	17238
3	exp Fibrosis/ and (exp Respiratory Tract Diseases/ or exp Respiratory System/)	4422
4	((lung$ or respir$ or pulmonary or alveol$) adj4 (fibros$ or fibrotic or fibrous)).mp.	33084
5	2 or 3 or 4 [lung AND fibrosis terms]	36718
6	(cryptog$ or idiopa$).tw.	106907
7	1 or (5 and 6) [lung AND fibrosis AND idiopath terms]	6816
8	interstitial pneumonia/ and idiopathic.mp.	1346
9	((usual or idiopa$ or ordinary or cryptog$) adj4 interstitial adj4 (lung$ or respir$ or pulmonary or alveol$ or pneumo$)).tw.	2191
10	Lung Diseases, Interstitial/ or (interstitial adj3 (lung$ or pneumonia$)).tw.	16319
11	(((unknow$ or uncertain$) adj4 (origin$ or cause$ or aetiol$ or etiol$)) or (cryptog$ or idiopa$)).tw.	147499
12	10 and 11 [idiopathic AND ILD terms]	3289
13	Idiopathic Pulmonary Fibrosis.mp.	5968
14	7 or 8 or 9 or 12 or 13	8726
15	..l/ 14 lg=en [limited to English language]	7393
16	limit 15 to humans	6138
17	limit 15 to animal	1075
18	15 not 16 not 17	937
19	16 or 18 [human or not indexed]	7075
20	limit 19 to yr="2010 -Current"	3802
21	((bronch$ or transbronch$ or surg$ or lung$) adj2 (cryobiosp$ or biops$)).mp.	19918

22	20 and 21	363
23	limit 22 to conference abstract	659
24	22 not 23	799

Table E5. Search strategy/results for multi-disciplinary discussion

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>		
#	**Searches**	**Results**
1	(exp fibrosing alveolitis/ and cryptogenic.mp.) or (cryptogenic adj4 (fibros$ or fibrotic or fibrous) adj4 alveolitis).mp.	438
2	pulmonary fibrosis/	17238

3	exp Fibrosis/ and (exp Respiratory Tract Diseases/ or exp Respiratory System/)	4422
4	((lung$ or respir$ or pulmonary or alveol$) adj4 (fibros$ or fibrotic or fibrous)).mp.	33084
5	2 or 3 or 4 [lung AND fibrosis terms]	36718
6	(cryptog$ or idiopa$).tw.	106907
7	1 or (5 and 6) [lung AND fibrosis AND idiopath terms]	6816
8	idiopathic interstitial pneumonias/	256
9	idiopathic pulmonary fibrosis/	2165
10	((usual or idiopa$ or ordinary or cryptog$) adj4 interstitial adj4 (lung$ or respir$ or pulmonary or alveol$ or pneumo$)).tw.	2191
11	Lung Diseases, Interstitial/ or (interstitial adj3 (lung$ or pneumonia$)).tw.	16319
12	(((unknow$ or uncertain$) adj4 (origin$ or cause$ or aetiol$ or etiol$)) or (cryptog$ or idiopa$)).tw.	147499
13	11 and 12 [idiopathic AND ILD terms]	3289
14	7 or 8 or 9 or 10 or 13	8675
15	..l/ 14 lg=en [limited to English language]	7339
16	limit 15 to humans	6116
17	limit 15 to animal	1057
18	15 not 16 not 17	909
19	16 or 18 [human or not indexed]	7025
20	limit 19 to yr="2000 -Current"	5701
21	(interdisciplin$ or multidisciplin$ or inter-disciplin$ or multi-disciplin$).mp.	101272
22	patient care team/	58301
23	clinical decision-making/	1339
24	21 or 22 or 23	146203

25	20 and 24	153

Embase <1996 to 2017 Week 10>		
#	**Searches**	**Results**
1	(exp fibrosing alveolitis/ and cryptogenic.mp.) or (cryptogenic adj4 (fibros$ or fibrotic or fibrous) adj4 alveolitis).mp.	323
2	pulmonary fibrosis/	8410
3	exp Fibrosis/ and (exp Respiratory Tract Diseases/ or exp Respiratory System/)	61343
4	((lung$ or respir$ or pulmonary or alveol$) adj4 (fibros$ or fibrotic or fibrous)).mp.	47490
5	2 or 3 or 4 [lung AND fibrosis terms]	69202
6	(cryptog$ or idiopa$).tw.	116414
7	1 or (5 and 6) [lung AND fibrosis AND idiopath terms]	11044
8	interstitial pneumonia/ and idiopathic.mp.	2813
9	((usual or idiopa$ or ordinary or cryptog$) adj4 interstitial adj4 (lung$ or respir$ or pulmonary or alveol$ or pneumo$)).tw.	3085
10	Lung Diseases, Interstitial/ or (interstitial adj3 (lung$ or pneumonia$)).tw.	19504
11	(((unknow$ or uncertain$) adj4 (origin$ or cause$ or aetiol$ or etiol$)) or (cryptog$ or idiopa$)).tw.	161854
12	10 and 11 [idiopathic AND ILD terms]	4951
13	Idiopathic Pulmonary Fibrosis.mp.	9196
14	7 or 8 or 9 or 12 or 13	13529
15	..l/ 14 lg=en [limited to English language]	12179
16	limit 15 to humans	10998
17	limit 15 to animal	596
18	15 not 16 not 17	585

19	16 or 18 [human or not indexed]	11583
20	limit 19 to yr="2010 -Current"	8591
21	(interdisciplin$ or multidisciplin$ or inter-disciplin$ or multi-disciplin$).mp.	135268
22	teamwork/	15305
23	21 or 22	147114
24	20 and 23	311

Table E6. Search strategy/results for serum biomarkers

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>		
#	**Searches**	**Results**
1	(exp fibrosing alveolitis/ and cryptogenic.mp.) or (cryptogenic adj4 (fibros$ or fibrotic or fibrous) adj4 alveolitis).mp.	438

2	pulmonary fibrosis/	17238
3	exp Fibrosis/ and (exp Respiratory Tract Diseases/ or exp Respiratory System/)	4422
4	((lung$ or respir$ or pulmonary or alveol$) adj4 (fibros$ or fibrotic or fibrous)).mp.	33084
5	2 or 3 or 4 [lung AND fibrosis terms]	36718
6	(cryptog$ or idiopa$).tw.	106907
7	1 or (5 and 6) [lung AND fibrosis AND idiopath terms]	6816
8	idiopathic interstitial pneumonias/	256
9	idiopathic pulmonary fibrosis/	2165
10	((usual or idiopa$ or ordinary or cryptog$) adj4 interstitial adj4 (lung$ or respir$ or pulmonary or alveol$ or pneumo$)).tw.	2191
11	Lung Diseases, Interstitial/ or (interstitial adj3 (lung$ or pneumonia$)).tw.	16319
12	(((unknow$ or uncertain$) adj4 (origin$ or cause$ or aetiol$ or etiol$)) or (cryptog$ or idiopa$)).tw.	147499
13	11 and 12 [idiopathic AND ILD terms]	3289
14	7 or 8 or 9 or 10 or 13	8675
15	..l/ 14 lg=en [limited to English language]	7339
16	limit 15 to humans	6116
17	limit 15 to animal	1057
18	15 not 16 not 17	909
19	16 or 18 [human or not indexed]	7025
20	limit 19 to yr="2010 -Current"	3748
21	(KL-6 or Krebs von den Lungen).mp.	593
22	Mucin-1/ or (muc1 or mucin 1 or mucin1).mp.	6986
23	(MMP 7 or MMP7).mp.	1944

24	exp Matrix Metalloproteinases/ or (matrix adj metalloproteinas$).mp.	53530
25	(CCL-18 or CCL18).mp.	448
26	Chemokines, CC/ or (chemokine adj ligand$).mp.	5702
27	((surfactant adj2 (protein$ or glycoprotein$)) or (lung adj protein d)).mp.	6067
28	or/21-27	72470
29	20 and 28	243

Embase <1996 to 2017 Week 10>		
#	**Searches**	**Results**
1	(exp fibrosing alveolitis/ and cryptogenic.mp.) or (cryptogenic adj4 (fibros$ or fibrotic or fibrous) adj4 alveolitis).mp.	438
2	pulmonary fibrosis/	17238
3	exp Fibrosis/ and (exp Respiratory Tract Diseases/ or exp Respiratory System/)	4422
4	((lung$ or respir$ or pulmonary or alveol$) adj4 (fibros$ or fibrotic or fibrous)).mp.	33084
5	2 or 3 or 4 [lung AND fibrosis terms]	36718
6	(cryptog$ or idiopa$).tw.	106907
7	1 or (5 and 6) [lung AND fibrosis AND idiopath terms]	6816
8	idiopathic interstitial pneumonias/	256
9	idiopathic pulmonary fibrosis/	2165
10	((usual or idiopa$ or ordinary or cryptog$) adj4 interstitial adj4 (lung$ or respir$ or pulmonary or alveol$ or pneumo$)).tw.	2191
11	Lung Diseases, Interstitial/ or (interstitial adj3 (lung$ or pneumonia$)).tw.	16319
12	(((unknow$ or uncertain$) adj4 (origin$ or cause$ or aetiol$ or etiol$)) or (cryptog$ or idiopa$)).tw.	147499
13	11 and 12 [idiopathic AND ILD terms]	3289

14	7 or 8 or 9 or 10 or 13	8675
15	..l/ 14 lg=en [limited to English language]	7339
16	limit 15 to humans	6116
17	limit 15 to animal	1057
18	15 not 16 not 17	909
19	16 or 18 [human or not indexed]	7025
20	limit 19 to yr="2010 -Current"	3748
21	(KL-6 or Krebs von den Lungen).mp.	593
22	Mucin-1/ or (muc1 or mucin 1 or mucin1).mp.	6986
23	(MMP 7 or MMP7).mp.	1944
24	exp Matrix Metalloproteinases/ or (matrix adj metalloproteinas$).mp.	53530
25	(CCL-18 or CCL18).mp.	448
26	Chemokines, CC/ or (chemokine adj ligand$).mp.	5702
27	((surfactant adj2 (protein$ or glycoprotein$)) or (lung adj protein d)).mp.	6067
28	or/21-27	72470
29	20 and 28	243

Table E7. Evidence tables for bronchoalveolar lavage

a) Individual studies

Study	UIP/IPF	NSIP, all	NSIP, cellular	NSIP, fibrotic	BOOP	HP	Sarcoidosis	Eosinophilic pneumonia	Rb-ILD	LIP
Total cell count (x10^5/mL)										
Reported as mean +/- SD										

Lee 2015	5.21 +/- 4.69	8.69 +/- 9.82			7.52 +/- 4.61	8.47 +/- 7.62	5.48 +/- 3.31	9.04 +/- 6.04		
Schlidge 2016	15.80 +/- 1.62	16.6 +/- 11.6			23.18+/-25.87	26.8 +/- 17.8			16.1 +/- 12.7	21.5 +/- 13.9
Nagai 2010	1.87 +/- 0.87	4.41 +/- 6.86	3.17 +/- 2.65	5.89 +/- 9.84	3.52 +/- 2.54					
Ohshimo 2009	1.58 +/- 1.62									
Reported as median (IQR)										
Welker 2004	3.4 (2.0-5.8)	4.9 (1.8-7.5)			3.2 (1.7-6.4)	5.6 (2.9-9.1)	2.9 (1.6-5.0)			
Ryu 2007	7 (0-85)	3 (0-38)	3.5 (1-25)	3 (0-38)						
Veeraraghavan 2003	2.4 (0.4-11.6)	2.0 (0.4-11.4)								
Neutrophils (%)										
Reported as mean +/- SD										
Lee 2015	22.08 +/- 26.84	8.81 +/- 9.52			7.70 +/- 12.61	15.54 +/- 24.24	1.39 +/- 1.85	5.29 +/- 6.78		
Schlidge 2016	16.6 +/- 16.7	14.0 +/- 13.0			14.9 +/- 15.0	11.8 +/- 11.4			4.8 +/- 6.7	9.2 +/- 10.8
Nagai 2010	5.9 +/- 9.8	8.0 +/- 2.8	2.5 +/- 3.9	13.9 +/- 18.4	6.4 +/- 3.7					
Ohshimo 2009	12 +/- 13									
Efared 2017	14.97 +/- 23.65						14.22 +/- 18.13			
Reported as median (IQR)										
Welker 2004	6.0 (3.0-11.0)	4.0 (1.0-9.5)			2.0 (1.0-3.0)	3.0 (1.0-11.0)	1.0 (0.0-3.0)			
Veeraraghavan 2003	9 (1-58)	9 (2-57)								
Macrophages (%)										
Reported as mean +/- SD										
Lee 2015	49.18 +/- 26.44	40.67 +/- 24.77			56.1 +/- 31.4	55.31 +/- 33.95	54.40 +/- 26.25	23.13 +/- 13.55		
Schlidge 2016	73.7 +/- 18.7	55.5 +/- 18.6			43.1 +/- 25.4	35.8 +/- 21.9			89.2 +/- 11.6	37.1 +/- 20.3
Nagai 2010	83.0 +/- 14.7	47.4 +/- 5.2	51.8 +/- 20.6	42.3 +/- 27.3	45.5 +/- 7.1					
Ohshimo 2009	75 +/- 17									
Efared 2017	55.5 +/- 23.93						46.1 +/- 22.87			
Reported as median (IQR)										
Veeraraghavan 2003	73 (24-89)	71 (25-92)								
Eosinophils (%)										
Reported as mean +/- SD										
Lee 2015	7.50 +/- 15.02	6.96 +/- 15.81			2.50 +/- 4.45	8.88 +/- 20.79	0.34 +/- 0.51	56.44 +/- 12.92		
Nagai 2010	3.3 +/- 5.1	5.5 +/- 7.1	5.7 +/- 12.7	5.4 +/- 7.4	2.2+/- 3.1					

Ohshimo 2009	4 +/- 5									
Efared 2017	2.39 +/- 1.27						1.89 +/- 5.24			
Reported as median (IQR)										
Welker 2004	2.0 (1.0-6.0)	1.0 (0-4.0)			2.0 (0-3.0)	0 (0-2.0	0 (0-1.0)			
Veeraraghavan 2003	7 (0-32)	7 (1-28)								
Lymphocytes (%)										
Reported as mean +/- SD										
Lee 2015	21.21 +/- 21.65	43.54 +/- 31.64			33.68 +/- 29.07	19.92 +/- 17.72	43.77 +/- 26.08	14.92+/- 7.06		
Schlidge 2016	9.1 +/- 8.9	30.2 +/- 18.4			41.0 +/- 24.0	51.4 +/- 22.7			5.8 +/- 9.3	52.3 +/- 17.9
Nagai 2010	7.2 +/- 7.4	37.3 +/- 5.2	40 +/- 19.2	34.4 +/- 27.3	44.4 +/- 7.3					
Ohshimo 2009	8 +/- 6									
Efared 2017	26.7 +/- 19.23						38.13 +/- 26			
Reported as median (IQR)										
Welker 2004	11.0 (6.0-21.5)	13.5 (5.0-35.0)			22 (10.0-29.0)	48.0 (36.0-60.0)	27 (17.0-41.0)			
Ryu 2007	5.5 (0-68)	29 (4-76)	40.5 (29-76)	19 (4-71)						
Veeraraghavan 2003	4 (0-42)	5 (0-18)								
CD4/C8 ratio										
Reported as mean +/- SD										
Lee 2015	1.98 +/- 2.69	0.56 +/- 0.33			0.89 +/- 1.07	1.44 +/- 1.01	7.47 +/- 4.65	2.33 +/- 0.87		
Nagai 2010	1.5 +/- 1.71	0.63 +/- 1.08	0.30 +/- 0.17	1.20 +/- 1.63	0.97 +/- 1.35					
Efared 2017	7.2 +/- 7.4									
Reported as median (IQR)										
Welker 2004	1.4 (0.7-2.8)	1.3 (0.5-3.3)			0.7 (0.4-1.1)	1.7 (0.9-3.8)	3.6 (2.3-6.1)			

b) Neutrophil counts

Evidence Profile – Neutrophil count for IPF/UIP vs. other ILDs

Bibliography (only includes studies that reported mean +/- SD and not studies that reported median (IQR):

1) Lee W, Chung WS, Hong KS, Huh J. Clinical usefulness of bronchoalveolar lavage cellular analysis and lymphocyte subsets in diffuse interstitial lung diseases. Ann Lab Med. 2015; 35:220-5.
2) Efared B, Ebang-Atsame G, Rabiou S, et al. The diagnostic value of the bronchoalveolar lavage in interstitial lung diseases. J Negat Results Biomed. 2017; 16:4.
3) Nagai S, Kitaichi M, Itoh H, et al. Idiopathic nonspecific interstitial pneumonia/fibrosis: comparison with idiopathic pulmonary fibrosis and BOOP. Eur Respir J 1998; 12:1010–1.
4) Schildge J, Frank J, Klar B, et al. The Role of Bronchoalveolar Lavage in the Diagnosis of Idiopathic Pulmonary Fibrosis: An Investigation of the Relevance of the Protein Content. Pneumologie 2016; 70(7):435-41.

Quality assessment							Groups		Effect (%)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	IPF (patients)	Other ILD (patients)			
vs. all NSIP											
3[1]	case series	none	serious[2]	serious[3]	serious[4]	none	262	67	MD = -+1.43 (95% CI, -4.33 to +7.19)	⊕OOO VERY LOW	NOT IMPORTANT
vs. cellular NSIP											
1[5]	case series	none	N/A	serious[3]	serious[4]	none	64	16	MD = +3.40 (95% CI, +0.33 to +6.47)	⊕OOO VERY LOW	NOT IMPORTANT
vs. fibrotic NSIP											
1[5]	case series	none	N/A	serious[3]	serious[4]	none	64	15	MD = -8.00 (95% CI, -17.62 to +1.62)	⊕OOO VERY LOW	NOT IMPORTANT
vs. BOOP											
3[1]	case series	none	serious[2]	serious[3]	none	none	262	228	MD = +1.43 (95% CI, -2.38 to +5.24)	⊕OOO VERY LOW	NOT IMPORTANT

vs. Hypersensitivity Pneumonitis											
2[6]	case series	none	none	serious[3]	none	none	198	127	MD = +4.84 (95% CI, +1.70 to +7.98)	⊕OOO VERY LOW	NOT IMPORTANT
vs. Sarcoidosis											
2[7]	case series	none	serious[2]	serious[3]	serious[4]	none	37	42	MD = +10.42 (95% CI, -9.11 to +29.95)	⊕OOO VERY LOW	NOT IMPORTANT
vs. Eosinophilic Pneumonia											
1[8]	case series	none	N/A	serious[3]	serious[4]	none	15	5	MD = +16.79 (95% CI, +1.96 to +31.62)	⊕OOO VERY LOW	NOT IMPORTANT
vs. Rb-ILD											
1[9]	case series	none	N/A	serious[3]	serious[4]	none	183	97	MD = +11.80 (95% CI, +9.04 to +14.56)	⊕OOO VERY LOW	NOT IMPORTANT
vs. LIP											
1[9]	case series	none	N/A	serious[3]	serious[4]	none	183	41	MD = +7.40 (95% CI, +3.30 to +11.50)	⊕OOO VERY LOW	NOT IMPORTANT

[1] Lee 2015, Nagai 1998, and Schlidge 2016.
[2] I^2 statistic was elevated.
[3] The question is intended for patients with ILD of unknown cause, but the study was done in patients with confirmed diagnoses.
[4] The ends of the confidence interval may lead to different decisions (assume +/- 10% changes decision) and/or at least one group with <100 patients
[5] Nagai 2010.
[6] Lee 2015 and Schlidge 2016.
[7] Lee 2015 and Efared 2017.
[8] Lee 2015.
[9] Schlidge 2016.

c) Macrophage counts

Evidence Profile – Macrophage count for IPF/UIP vs. other ILDs

Bibliography (only includes studies that reported mean +/- SD and not studies that reported median (IQR):

1) Lee W, Chung WS, Hong KS, Huh J. Clinical usefulness of bronchoalveolar lavage cellular analysis and lymphocyte subsets in diffuse interstitial lung diseases. Ann Lab Med. 2015; 35:220-5.
2) Efared B, Ebang-Atsame G, Rabiou S, et al. The diagnostic value of the bronchoalveolar lavage in interstitial lung diseases. J Negat Results Biomed. 2017; 16:4.
3) Nagai S, Kitaichi M, Itoh H, et al. Idiopathic nonspecific interstitial pneumonia/fibrosis: comparison with idiopathic pulmonary fibrosis and BOOP. Eur Respir J 1998; 12:1010–1.
4) Schildge J, Frank J, Klar B, et al. The Role of Bronchoalveolar Lavage in the Diagnosis of Idiopathic Pulmonary Fibrosis: An Investigation of the Relevance of the Protein Content. Pneumologie 2016; 70(7):435-41.

Quality assessment							Groups		Effect (%)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	IPF (patients)	Other ILD (patients)			
vs. all NSIP											
3[1]	case series	none	serious[2]	serious[3]	serious[4]	none	262	67	MD = -+23.07 (95% CI, +7.55 to +38.59)	⊕OOO VERY LOW	NOT IMPORTANT
vs. cellular NSIP											
1[5]	case series	none	N/A	serious[3]	serious[4]	none	64	16	MD = +31.20 (95% CI, +20.48 to +41.92)	⊕OOO VERY LOW	NOT IMPORTANT
vs. fibrotic NSIP											
1[5]	case series	none	N/A	serious[3]	serious[4]	none	64	15	MD = +40.70 (95% CI, +26.42 to +54.98)	⊕OOO VERY LOW	NOT IMPORTANT
vs. BOOP											
3[1]	case series	none	serious[2]	serious[3]	none	none	262	228	Too different to be pooled: Lee found MD -6.29 (95% CI -25.88 to +12.04), while Nagai found MD +37.50 (95% CI +32.49 to +42.51) and Schlidge found MD +30.60 (95% cI +26.09 to +35.11).	⊕OOO VERY LOW	NOT IMPORTANT

vs. Hypersensitivity Pneumonitis											
2[6]	case series	none	serious[2]	serious[3]	serious[4]	none	198	127	Too different to be pooled: Lee found MD -6.13 (95% CI -32.03 to +19.77), while Schlidge found MD +37.90 (95% CI +33.11 to +42.69).	⊕OOO VERY LOW	NOT IMPORTANT
vs. Sarcoidosis											
2[7]	case series	none	none	serious[3]	serious[4]	none	37	42	MD = +4.16 (95% CI, -9.58 to +17.90)	⊕OOO VERY LOW	NOT IMPORTANT
vs. Eosinophilic Pneumonia											
1[8]	case series	none	N/A	serious[3]	serious[4]	none	15	5	MD = +26.05 (95% CI, +8.32 to +43.78)	⊕OOO VERY LOW	NOT IMPORTANT
vs. Rb-ILD											
1[9]	case series	none	N/A	serious[3]	serious[4]	none	183	97	MD = -15.50 (95% CI, -19.06 to -11.94)	⊕OOO VERY LOW	NOT IMPORTANT
vs. LIP											
1[9]	case series	none	N/A	serious[3]	serious[4]	none	183	41	MD = +36.60 (95% CI, +29.82 to +43.38)	⊕OOO VERY LOW	NOT IMPORTANT

[1] Lee 2015, Nagai 1998, and Schlidge 2016.
[2] I^2 statistic was elevated.
[3] The question is intended for patients with ILD of unknown cause, but the study was done in patients with confirmed diagnoses.
[4] The ends of the confidence interval may lead to different decisions (assume +/- 10% changes decision) and/or at least one group with <100 patients.
[5] Nagai 2010.
[6] Lee 2015 and Schlidge 2016.
[7] Lee 2015 and Efared 2017.
[8] Lee 2015.
[9] Schlidge 2016.

d) Eosinophil counts

Evidence Profile – Eosinophil count for IPF/UIP vs. other ILDs

Bibliography (only includes studies that reported mean +/- SD and not studies that reported median (IQR):

1) Lee W, Chung WS, Hong KS, Huh J. Clinical usefulness of bronchoalveolar lavage cellular analysis and lymphocyte subsets in diffuse interstitial lung diseases. Ann Lab Med. 2015; 35:220-5.
2) Efared B, Ebang-Atsame G, Rabiou S, et al. The diagnostic value of the bronchoalveolar lavage in interstitial lung diseases. J Negat Results Biomed. 2017; 16:4.
3) Nagai S, Kitaichi M, Itoh H, et al. Idiopathic nonspecific interstitial pneumonia/fibrosis: comparison with idiopathic pulmonary fibrosis and BOOP. Eur Respir J 1998; 12:1010–1.

Quality assessment							Groups		Effect (%)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	IPF (patients)	Other ILD (patients)			
vs. all NSIP											
2[1]	case series	none	none	serious[2]	serious[3]	none	79	38	MD = -2.06 (95% CI, -4.80 to +0.68)	⊕OOO VERY LOW	NOT IMPORTANT
vs. cellular NSIP											
1[4]	case series	none	N/A	serious[2]	serious[3]	none	64	16	MD = -2.40 (95% CI, -8.75 to +3.95)	⊕OOO VERY LOW	NOT IMPORTANT
vs. fibrotic NSIP											
1[4]	case series	none	N/A	serious[2]	serious[3]	none	64	15	MD = -2.10 (95% CI, -6.05 to +1.85)	⊕OOO VERY LOW	NOT IMPORTANT
vs. BOOP											
2[1]	case series	none	none	serious[2]	serious[3]	none	79	21	MD = +1.52 (95% CI, -0.39 to +3.43)	⊕OOO VERY LOW	NOT IMPORTANT
vs. Hypersensitivity Pneumonitis											

1[5]	case series	none	N/A	serious[2]	serious[3]	none	15	9	MD = -1.38 (95% CI, -16.94 to +14.18)	⊕OOO VERY LOW	NOT IMPORTANT
vs. Sarcoidosis											
2[6]	case series	none	none	serious[3]	serious[4]	none	37	42	MD = +2.77 (95% CI, -3.42 to +8.96)	⊕OOO VERY LOW	NOT IMPORTANT
vs. Eosinophilic Pneumonia											
1[5]	case series	none	N/A	serious[3]	serious[4]	none	15	5	MD = -48.94 (95% CI, -62,58 to -35.30)	⊕OOO VERY LOW	NOT IMPORTANT

[1] Lee 2015 and Nagai 1998.
[2] The question is intended for patients with ILD of unknown cause, but the study was done in patients with confirmed diagnoses.
[3]The ends of the confidence interval may lead to different decisions (assume +/- 10% changes decision) and/or at least one group with <100 patients.
[4] Nagai 2010.
[5] Lee 2015.
[6] Lee 2015 and Efared 2017.
[8] Lee 2015.
[9] Schlidge 2016.
I^2 statistic was elevated.

e) Lymphocyte counts

Evidence Profile – Lymphocyte count for IPF/UIP vs. other ILDs

Bibliography (only includes studies that reported mean +/- SD and not studies that reported median (IQR):

1) Lee W, Chung WS, Hong KS, Huh J. Clinical usefulness of bronchoalveolar lavage cellular analysis and lymphocyte subsets in diffuse interstitial lung diseases. Ann Lab Med. 2015; 35:220-5.
2) Efared B, Ebang-Atsame G, Rabiou S, et al. The diagnostic value of the bronchoalveolar lavage in interstitial lung diseases. J Negat Results Biomed. 2017; 16:4.
3) Nagai S, Kitaichi M, Itoh H, et al. Idiopathic nonspecific interstitial pneumonia/fibrosis: comparison with idiopathic pulmonary fibrosis and BOOP. Eur Respir J 1998; 12:1010–1.
4) Schildge J, Frank J, Klar B, et al. The Role of Bronchoalveolar Lavage in the Diagnosis of Idiopathic Pulmonary Fibrosis: An Investigation of the Relevance of the Protein Content. Pneumologie 2016; 70(7):435-41.

Quality assessment							Groups		Effect (%)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	IPF (patients)	Other ILD (patients)			
vs. all NSIP											
3[1]	case series	none	serious[2]	serious[3]	serious[4]	none	262	67	MD = -26.0 (95% CI, -33.62 to -18.38)	⊕OOO VERY LOW	NOT IMPORTANT
vs. cellular NSIP											
1[5]	case series	none	N/A	serious[3]	serious[4]	none	64	16	MD = -32.8 (95% CI, -42.38 to -23.22)	⊕OOO VERY LOW	NOT IMPORTANT
vs. fibrotic NSIP											
1[5]	case series	none	N/A	serious[3]	serious[4]	none	64	15	MD = -27.20 (95% CI, -41.13 to -13.27)	⊕OOO VERY LOW	NOT IMPORTANT
vs. BOOP											
3[1]	case series	none	none	serious[3]	none	none	262	228	MD = -31.43 (95% CI, -38.78 to -24.08)	⊕OOO VERY LOW	NOT IMPORTANT
vs. Hypersensitivity Pneumonitis											

2[6]	case series	none	serious[2]	serious[3]	serious[4]	none	198	127	Too different to be pooled: Lee found MD +1.29 (95% CI -14.65 to +17.23), while Schlidge found MD -42.30 (95% CI -46.59 to -38.01)	⊕OOO VERY LOW	NOT IMPORTANT
vs. Sarcoidosis											
2[7]	case series	none	none	serious[3]	serious[4]	none	37	42	MD = -14.87 (95% CI, -25.09 to -4.65)	⊕OOO VERY LOW	NOT IMPORTANT
vs. Eosinophilic Pneumonia											
1[8]	case series	none	N/A	serious[3]	serious[4]	none	15	5	MD = +6.29 (95% CI, -6.29 to +18.87)	⊕OOO VERY LOW	NOT IMPORTANT
vs. Rb-ILD											
1[9]	case series	none	N/A	serious[3]	serious[4]	none	183	97	MD = +3.30 (95% CI, +1.04 to +5.56)	⊕OOO VERY LOW	NOT IMPORTANT
Vs. LIP											
1[9]	case series	none	N/A	serious[3]	serious[4]	none	183	41	MD = -43.20 (95% CI, -48.83 to -37.57)	⊕OOO VERY LOW	NOT IMPORTANT

[1] Lee 2015, Schildge 2016, and Nagai 1998.
[2] I^2 statistic was elevated.
[3] The question is intended for patients with ILD of unknown cause, but the study was done in patients with confirmed diagnoses.
[4] The ends of the confidence interval may lead to different decisions (assume +/- 10% changes decision) and/or at least one group with <100 patients.
[5] Nagai 2010.
[6] Lee 2015 and Schildge 2016.
[7] Lee 2015 and Efared 2017.
[8] Lee 2015.
[9] Schlidge 2016.

f) CD4/CD8 ratio

Evidence Profile – CD4/CD8 ratio for IPF/UIP vs. other ILDs

Bibliography (only includes studies that reported mean +/- SD and not studies that reported median (IQR):

1) Lee W, Chung WS, Hong KS, Huh J. Clinical usefulness of bronchoalveolar lavage cellular analysis and lymphocyte subsets in diffuse interstitial lung diseases. Ann Lab Med. 2015; 35:220-5.
2) Nagai S, Kitaichi M, Itoh H, et al. Idiopathic nonspecific interstitial pneumonia/fibrosis: comparison with idiopathic pulmonary fibrosis and BOOP. Eur Respir J 1998; 12:1010–1.

Quality assessment							Groups		Effect (%)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	IPF (patients)	Other ILD (patients)			
vs. all NSIP											
2[1]	case series	none	none	serious[2]	serious[3]	none	262	67	MD = +0.95 (95% CI, +0.43 to +1.47)	⊕OOO VERY LOW	NOT IMPORTANT
vs. cellular NSIP											
1[4]	case series	none	N/A	serious[2]	serious[3]	none	64	16	MD = +1.20 (95% CI, +0.77 to +1.63)	⊕OOO VERY LOW	NOT IMPORTANT
vs. fibrotic NSIP											
1[4]	case series	none	N/A	serious[2]	serious[3]	none	64	15	MD = +0.30 (95% CI, -0.63 to +1.23)	⊕OOO VERY LOW	NOT IMPORTANT
vs. BOOP											
2[1]	case series	none	none	serious[2]	serious[3]	none	79	37	MD = +0.66 (95% CI, -0.03 to +1.35)	⊕OOO VERY LOW	NOT IMPORTANT
vs. Hypersensitivity Pneumonitis											

1[5]	case series	none	N/A	serious[2]	serious[3]	none	15	9	MD = +0.54 (95% CI, -0.97 to +2.05)	⊕OOO VERY LOW	NOT IMPORTANT
vs. Sarcoidosis											
1[5]	case series	none	N/A	serious[2]	serious[3]	none	15	12	MD = -5.49 (95% CI, -8.45 to -2.53)	⊕OOO VERY LOW	NOT IMPORTANT
vs. Eosinophilic Pneumonia											
1[5]	case series	none	N/A	serious[2]	serious[3]	none	15	5	MD = -0.35 (95% CI, -1.91 to +1.21)	⊕OOO VERY LOW	NOT IMPORTANT

[1] Lee 2015 and Nagai 1998.
[2] The question is intended for patients with ILD of unknown cause, but the study was done in patients with confirmed diagnoses.
[3] The ends of the confidence interval may lead to different decisions (assume +/- 1.0 changes decision) and/or at least one group with <100 patients.
[4] Nagai 2010.
[5] Lee 2015.

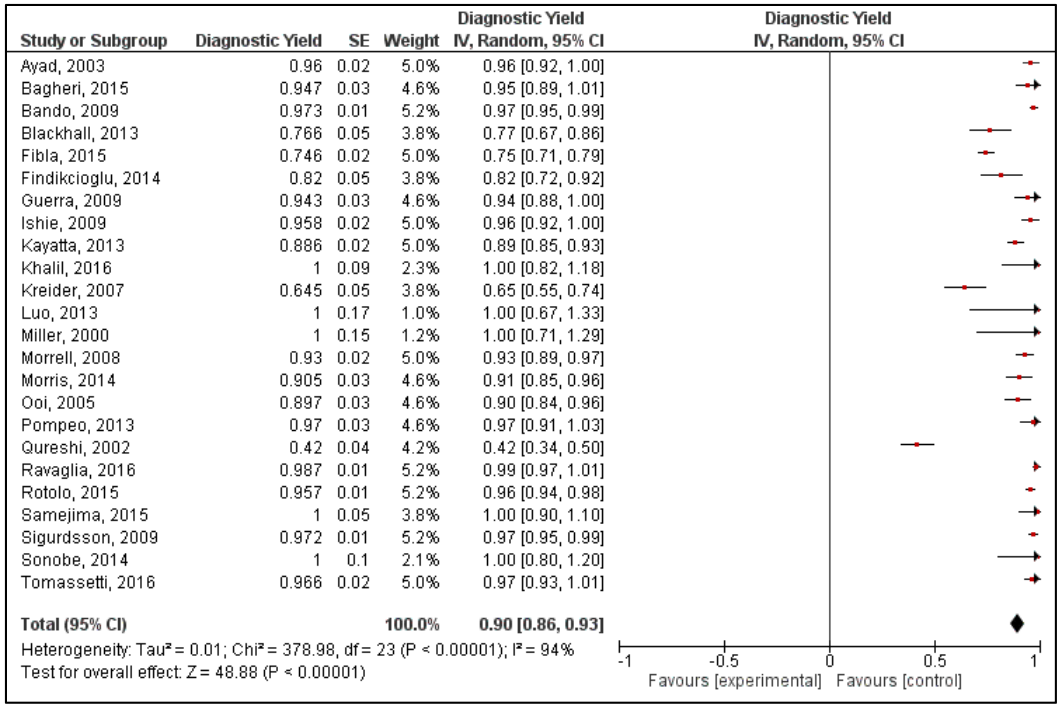
Table E8. Evidence tables for surgical lung biopsy

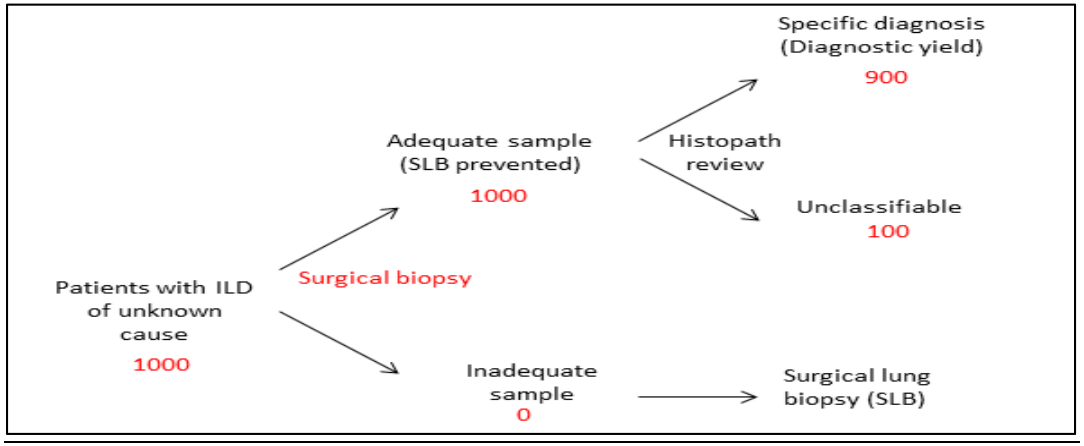
Surgical lung biopsy individual studies

Diagnostic yield					
Study	**Inadequate sample**	**Adequate sample**	**Specific diagnosis**	**Unclassifiable**	**Diagnostic yield**
Ayad 2003	0/79 (0%)	79/79 (100%)	76/79 (96%)	3/79 (4)	76/79 (96%)
Morris, 2014	0/66 (0%)	66/66 (100%)	60/66 (90.5%	6/66 (9.5%)	60/66 (90.5%)
Bagheri, 2015	0/38 (0%)	38/38 (100%)	36/38 (94.74%)	2/38 (5.26%)	36/38 (94.74%)
Bando, 2009	0/113 (0%)	113/113 (100%)	110/113 (97.3%)	3/113(2.7%)	110/113 (97.3%)
Blackhall, 2013	NR	NR	72/103 (69.9%)	31/103 (30.1%)	72/103 (69.9%)
Blanco	NR	NR	131/171 (76.6%)	40/171 (23.4%)	131/171 (76.6%)
Blewett	0/32 (0%)	32/32 (100%)	32/32 (100%)	0/32 (0%)	32/32 (100%)
Fibla, 2015	NR	NR	232/311 (74.6%)	79/311 (25.4%)	232/311 (74.6%)
Findikcioglu, 2014	0/45 (00%)	45/45 (100%)	37/45 (82%)	8/45 (18%)	37/45 (82%)
Guerra, 2009	NR	NR	50/53 (94.3%)	3/53 (5.7%)	50/53 (94.3%)
Ishie, 2009	NR	NR	46/48 (95.8%)	2/48 (4.2%)	46/48 (95.8 %)
Kayatta, 2013	0/194 (0%)	194/194 (100%)	172/194 (88.6%)	22/194 (11.4%)	172/194 (88.6%)
Khalil, 2016	NR	NR	115/115 (100%)	0/115 (0%)	115/115 (100%)
Kreider, 2007	NR	NR	44/68 (64.5%)	24/68 (35.5%)	44/68 (64.5%)
Luo, 2013	NR	NR	32/32 (100%)	0/32 (0%)	32/32 (100%)
Miller, 2000	NR	NR	42/42 (100%)	0/42 (0%)	42/42 (100%)
Ooi, 2005	0/78 (0%)	78/78 (100%)	70/78 (89.7%)	8/78 (11.3%)	70/78 (89.7%)

Pompeo, 2013	NR	NR	29/30 (97%)	1/30 (3%)	29/30 (97%)
Qureshi, 2002	NR	NR	42/100 (42%)	58/100 (58%)	42/100 (42%)
Rotolo, 2015	NR	NR	154/161 (95.7%)	7/161 (5.3%)	154/161 (95.7%)
Samejima, 2015	NR	NR	285/285 (100%)	0/285 (0%)	285/285 (100%)
Sigurdsson, 2009	NR	NR	71/73 (97.2%)	2/73 (2.8%)	71/73 (97.2%)
Sonobe, 2014	0/64 (0%)	64/64 (100%)	64/64 (100%)	0/64 (0%)	64/64 (100%)
Tomassetti, 2016	0/59 (0%)	59/59 (100%)	57/59 (96.6%)	2/59 (3.4%)	57/59 (96.6%)
Ravaglia, 2016	0/150 (0%)	150/150 (100%)	148/150 (98.7%)	2/150 (1.3%)	148/150 (98.7%)
Morrell, 2008	NR	NR	131/141 (93%)	10/141 (7%)	131/141 (93%)
Pooled result (unweighted)	***0/918 (0%)*** ***(95% CI 0-0.01%)***	***918/918 (100%)*** ***(95% CI 99-100%)***	***2338/2651 (88.2%)*** ***(95% CI 86.9-89.4%)***	***313/2651 (11.8%)*** ***(95% CI 10.6-13.1%)***	***2338/2651 (88.2%)*** ***(95% CI 86.9-89.4%)***
Pooled result (weighted using inverse variance)	***See note***	***See note***	***See note***	***See note***	***90%*** ***(95% CI 86-93%)***

Note: Pooling by inverse variance does not account for studies whose result is 0% or 100%; thus, not used when such results exist.


Study or Subgroup | Diagnostic Yield | SE | Weight | Diagnostic Yield IV, Random, 95% CI
Ayad, 2003 0.96 0.02 5.0% 0.96 [0.92, 1.00]
Bagheri, 2015 0.947 0.03 4.6% 0.95 [0.89, 1.01]
Bando, 2009 0.973 0.01 5.2% 0.97 [0.95, 0.99]
Blackhall, 2013 0.766 0.05 3.8% 0.77 [0.67, 0.86]
Fibla, 2015 0.746 0.02 5.0% 0.75 [0.71, 0.79]
Findikcioglu, 2014 0.82 0.05 3.8% 0.82 [0.72, 0.92]
Guerra, 2009 0.943 0.03 4.6% 0.94 [0.88, 1.00]
Ishie, 2009 0.958 0.02 5.0% 0.96 [0.92, 1.00]
Kayatta, 2013 0.886 0.02 5.0% 0.89 [0.85, 0.93]
Khalil, 2016 1 0.09 2.3% 1.00 [0.82, 1.18]
Kreider, 2007 0.645 0.05 3.8% 0.65 [0.55, 0.74]
Luo, 2013 1 0.17 1.0% 1.00 [0.67, 1.33]
Miller, 2000 1 0.15 1.2% 1.00 [0.71, 1.29]
Morrell, 2008 0.93 0.02 5.0% 0.93 [0.89, 0.97]
Morris, 2014 0.905 0.03 4.6% 0.91 [0.85, 0.96]
Ooi, 2005 0.897 0.03 4.6% 0.90 [0.84, 0.96]
Pompeo, 2013 0.97 0.03 4.6% 0.97 [0.91, 1.03]
Qureshi, 2002 0.42 0.04 4.2% 0.42 [0.34, 0.50]
Ravaglia, 2016 0.987 0.01 5.2% 0.99 [0.97, 1.01]
Rotolo, 2015 0.957 0.01 5.2% 0.96 [0.94, 0.98]
Samejima, 2015 1 0.05 3.8% 1.00 [0.90, 1.10]
Sigurdsson, 2009 0.972 0.01 5.2% 0.97 [0.95, 0.99]
Sonobe, 2014 1 0.1 2.1% 1.00 [0.80, 1.20]
Tomassetti, 2016 0.966 0.02 5.0% 0.97 [0.93, 1.01]
Total (95% CI) 100.0% 0.90 [0.86, 0.93]
Heterogeneity: Tau² = 0.01; Chi² = 378.98, df = 23 (P < 0.00001); I² = 94%
Test for overall effect: Z = 48.88 (P < 0.00001)
Diagnostic Yield IV, Random, 95% CI
-1 -0.5 0 0.5 1
Favours [experimental] Favours [control]


Specific diagnosis (Diagnostic yield)
900
Adequate sample (SLB prevented)
1000
Histopath review
Unclassifiable
100
Patients with ILD of unknown cause
1000
Surgical biopsy
Inadequate sample
0
Surgical lung biopsy (SLB)

Mortality							
	Overall	**Procedure related**	**30 day**	**60 day**	**90 day**	**Hospital**	**Unspecified**
Ayad, 2003	1/79 (1.5%)					1/79 (1.3%)	
Bagheri, 2015	0/38 (0%)					0/38 (0%)	
Bando, 2009	2/113 (1.7%)						2/113 (1.7%)
Backhall, 2013	5/103 (4.9%)		5/103 (4.9%)				
Blanco, 2013	10/171(5.8%)*					10/171(5.8%)*	
Blewett, 2001	0/32 (0%)[$]	0/32 (0%)[$]					
Fibla, 2105	0/311 (0%)[#]					0/311 (0%)[#]	
Findikcioglu, 2014	2/45 (4.4%)	2/45 (4.4%)					
Guerra, 2009	1/53 (1.9%)	1/53 (1.9%)					
Khalil, 2016	0/115 (0%)		0/115 (0%)			0/115 (0%)	
Kreider, 2007	3/68 (4.4%)			3/68 (4.4%)			
Luo, 2013	1/32 (5.2%)		0/32 (0%)		1/32 (3.1%)		
Miller, 2000	0/42 (0%)						0/42 (0%)
Morris, 2014	1/66 (1.5%)		1/66 (1.5%)				
Ooi, 2005	1/78 (1.8%)					1/78 (1.8%)	
Pompeo, 2013	0/30 (0%)	0/30 (0%)				0/30 (0%)	
Qureshi, 2002	0/100 (0%)	0/100 (0%)					

Rotolo, 2015	5/161 (3.1%)		5/161 (3.1%)				
Samejima, 2015	0/285 (0%)		0/285 (0%)				
Sigurdsson, 2009	2/73 (2.7%)		2/73 (2.7%)				
Sonobe, 2014	0/64 (0%)			0/64 (0%)			
Tomassetti, 2016	2/59 (3.4%)						2/59 (3.4%)
Ravaglia, 2016	43/150 (28.7%)	4/150 (2.7%)					43/150 (28.7%)
Pooled result (unweighted)	***79/2268 (3.5%) (95% CI 2.8-4.3%)***	***7/410 (1.7%) (95% CI 0.8-3.5%)***	***13/835 (1.6%) (95% CI 0.9-2.6%)***	***3/132 (2.3%) (95% CI 0.8-6.5%)***	***1/32 (3.1%) (95% CI 0.6-15.7%)***	***12/822 (1.5%) (95% CI 0.8-2.5%)***	***47/364 (12.9%) (95% CI 9.9-16.8%)***
Pooled result (weighted using inverse variance)	***See note***	***See note***	***See note***	***See note***	***One study***	***See note***	***See note***

*Reported as deaths spanned from 0-33 days; $ Procedures were done in the outpatient setting; # In the methods reported as peri-operative mortality, but in results they discuss hospital mortality; Note: Pooling by inverse variance does not account for studies whose result is 0% or 100%; thus, not used when such results exist.

Other complications

Study	Exacerbations / Respiratory Failure	Bleeding (all)	Bleeding (severe)	Pneumothorax	Prolonged air leak (>48 hours)	Respiratory infection	Neuro-pathic pain	Delayed wound healing
Ayad 2003	1/79 (1.3%)			5/79 (6.3%)				
Morris, 2014	1/66 (1.5%)			7/66 (10.6%)	1/66 (1.5%)	4/66 (6.1%)	3/66 (4.5%)	2/66 (3%)
Bagheri, 2015					5/38 (13.1%)	2/38 (5.2%)		
Bando, 2009	2/113 (1.7%)			5/ 113 (4.4%)	17 /113 15%)	1/113 (0.8%)		

Blackhall, 2013	4/103 (3.9%)			1/103 (1%)	2/103 (2%)			2/103 (2%)
Blanco, 2013	7/171 (4%)	2/171 (1%)						
Blewett, 2001				0/32 (0%)		0/32 (0%)		
Fibla, 2015	81/311 (26.1%)				31/311 (10.2%)			
Findikcioglu, 2014								
Guerra, 2009		1/53 (1.9%)	1/53 (1.9%)	1/53 (1.9%)	3/53 (5.7%)			
Ishie, 2009				1/48 (2%)				
Khalil, 2016	1/115 (0.8%)							
Kreider, 2007	4/68 (5.9%)				3/68 (4.4%)	2/68 (2.9%)		
Luo, 2013	1/32 (3%)	1 (3%)		8/32 (25%)		18/32 (56.3%)		
Miler, 2000				1/42 (2.4%)	1 (2.4%)	1 (2.4%)		
Ooi, 2005		1/78 (1.8%)		1/78 (1.8%)				
Pompeo, 2013								
Qureshi, 2002	1/100 (1%)							7/100 (7%)
Rotolo, 2015	4/161 (2.5%)				8/161 (5%)			3/161 (1.9%)
Samejima, 2015	3 (285 (1%)	0/285 (0%)	0/285 (0%)		2/285 (0.7%)			
Sigurdsson, 2009	2/73 (2.7%)	1/73 (1.3%)			9/73 (12%)	3/73 (4%)		

Sonobe, 2014	0/64 (0%)	0/64 (0%)	0/64 (0%)	4/64 (6%)	2/64 (3%)	1/64 (2%)		
Tomassetti, 2016			0/59 (0%)					
Ravaglia, 2016	4/150 (2.7%)				5/150 (3.3%)			
Pooled result (unweighted)	***116/1891 (6.1%) (95% CI 5.1 – 7.3%)***	***6/756 (0.8%) (95% CI 0.4 – 1.7%)***	***1/461 (0.2%) (95% CI 0.04 – 1.2%)***	***34/678 (5.0%) (95% CI 3.6 – 6.9%)***	***90/1527 (5.9%) (95% CI 4.8 – 7.2%)***	***32/496 (6.5%) (95% CI 4.6 – 9.0%)***	***3/66 (4.5%) (95% CI 1.6 – 12.5%)***	***14/430 (3.3%) (95% CI 2.0 – 5.4%)***
Pooled result (weighted using inverse variance)	***See note***	***See note***	***See note***	***See note***	***5% (95% CI 3-4%)***	***See note***	***One study***	***3% (95% CI 1-4%)***

Note: Pooling by inverse variance does not account for studies whose result is 0% or 100%; thus, not used when such results exist.

Surgical lung biopsy evidence profile

Evidence Profile – Surgical lung biopsy

Bibliography:
26 studies, will be listed here at a later date.

Quality assessment							# Patients	Effect[6]	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**				
Diagnostic yield										
24[1]	case series	none	serious[2]	serious[3]	none	none	2516	90% (95% CI 87- 93%)	⊕OOO VERY LOW	CRITICAL
Mortality										

23[4]	case series	none	none	serious[3]	none	none	2268	79/2268 (3.5%) (95% CI 2.8-4.3%)	⊕OOO VERY LOW	CRITICAL
Exacerbation/Respiratory failure										
15[5]	case series	none	none	serious[3]	none	none	1891	116/1891 (6.1%) (95% CI 5.1 – 7.3%)	⊕OOO VERY LOW	CRITICAL
Bleeding, all										
7[5]	case series	none	none	serious[3]	none	none	756	6/756 (0.8%) (95% CI 0.4 – 1.7%)	⊕OOO VERY LOW	CRITICAL
Bleeding, severe										
4[5]	case series	none	none	serious[3]	none	none	461	1/461 (0.2%) (95% CI 0.04 – 1.2%)	⊕OOO VERY LOW	CRITICAL
Pneumothorax										
10[5]	case series	none	none	serious[3]	none	none	678	34/678 (5.0%) (95% CI 3.6 – 6.9%)	⊕OOO VERY LOW	CRITICAL
Prolonged air leak, >48 hours										
13[5]	case series	none	none	serious[3]	none	none	1527	5% (95% CI 3-4%)	⊕OOO VERY LOW	CRITICAL
Respiratory infection										
9[5]	case series	none	none	serious[3]	none	none	496	32/496 (6.5%) (95% CI 4.6 – 9.0%)	⊕OOO VERY LOW	CRITICAL

Delayed wound healing										
4[5]	case series	none	none	serious[3]	none	none	430	3% (95% CI 1-4%)	⊕OOO VERY LOW	CRITICAL
Neuropathic pain										
1[5]	case series	none	N/A	serious[3]	serious[5]	none	66	3/66 (4.5%) (95% CI 1.6 – 12.5%)	⊕OOO VERY LOW	CRITICAL

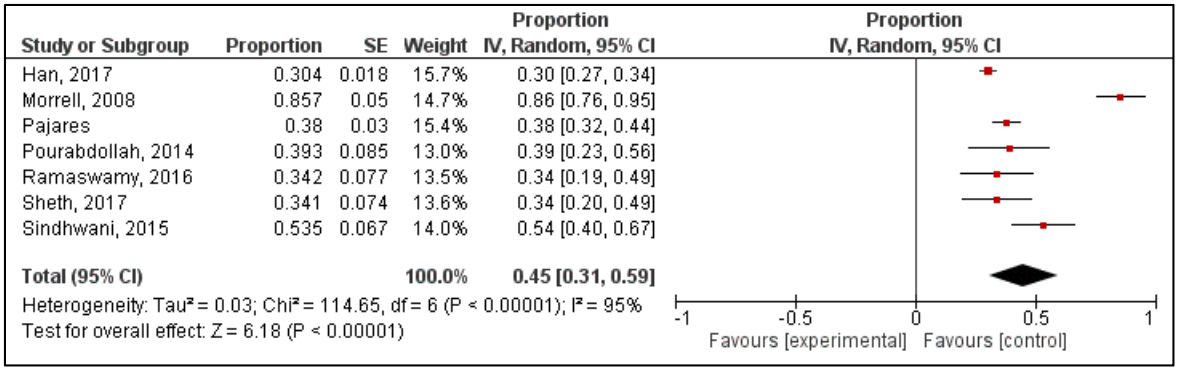
[1] See studies in first table above.
[2] I^2 statistic was elevated.
[3] The question is intended for patients with ILD of unknown cause and a HRCT pattern other than "consistent with UIP"; however, most studies did not exclude patients with such a HRCT pattern.
[4] See studies in the second table above.
[5] See studies in the third table above.
6 When possible, numbers are pooled and weighted by inverse variance; however, the method does not account for studies whose result is 0% so, in such cases, we report the unweighted results instead.

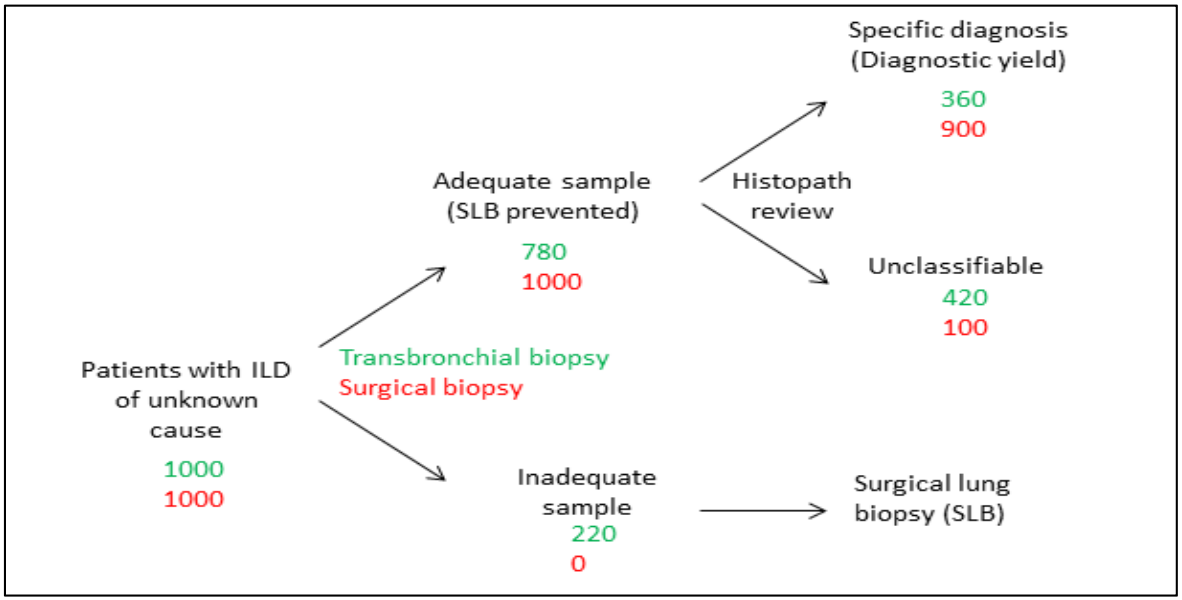
Table E9. Evidence tables for transbronchial biopsy

Transbronchial biopsy individual studies

Diagnostic yield					
Study	**Inadequate sample**	**Adequate sample**	**Specific diagnosis**	**Unclassifiable**	**Diagnostic yield**
Han 2017	155/664 (23.3%)	509/664 (76.6%)	202/509 (39.7%)	307/509 (60.3%)	202/664 (30.4%)
Sindhwani 2015	0/49 (0%)	49/49 (100%)	42/49 (85.7%)	7/49 (14.3%)	42/49 (85.7%)
Morel, 2008	NR	NR	95/252 (38%)	157/252 (62%)	95/252 (38%)
Sheth, 2017	6/33 (18.2%)	27/33 (81.2%)	13/27 (48%)	14/27 (52%)	13/33 (39.3%)
Pajares, 2014	9/38 (23.7%)	29/38 (76.3%)	13/29 (44.8%)	16/29 (55.2%)	13/38 (34.2%)
Pourabdollah, 2014	15/41 (36.2%)	26/41 (63.4%)	14/26 (53.8%)	12/26 (46.2%)	14/41 (34.1%)
Ramaswamy, 2016	NR	NR	30/56 (53.5%)	20/56 (46.5%)	30/56 (53.5%)
Pooled result (unweighted)	***185/825 (22.4%) (95% CI 19.7-25.4%)***	***640/825 (77.6%) (95% CI 74.6-80.3%)***	***409/948 (43.1%) (95% CI 40-46.3%)***	***539/948 (56.9%) (95% CI 53.7-60%)***	***409/1133 (36.1%) (95% CI 33.4-38.9%)***
Pooled result (weighted using inverse variance)	***See note***	***See note***	***52% (95% CI 39-66%)***	***48% (95% CI 35-61%)***	***45% (95% CI 31-59%)***

Note: Pooling by inverse variance does not account for studies whose result is 0% or 100%; thus, not used when such results exist.


Study or Subgroup
Proportion
SE
Weight
Proportion IV, Random, 95% CI
Proportion IV, Random, 95% CI
Han, 2017 0.304 0.018 15.7% 0.30 [0.27, 0.34]
Morrell, 2008 0.857 0.05 14.7% 0.86 [0.76, 0.95]
Pajares 0.38 0.03 15.4% 0.38 [0.32, 0.44]
Pourabdollah, 2014 0.393 0.085 13.0% 0.39 [0.23, 0.56]
Ramaswamy, 2016 0.342 0.077 13.5% 0.34 [0.19, 0.49]
Sheth, 2017 0.341 0.074 13.6% 0.34 [0.20, 0.49]
Sindhwani, 2015 0.535 0.067 14.0% 0.54 [0.40, 0.67]
Total (95% CI) 100.0% 0.45 [0.31, 0.59]
Heterogeneity: Tau² = 0.03; Chi² = 114.65, df = 6 (P < 0.00001); I² = 95%
Test for overall effect: Z = 6.18 (P < 0.00001)
-1
-0.5
0
0.5
1
Favours [experimental]
Favours [control]


Specific diagnosis (Diagnostic yield)
360
900
Adequate sample (SLB prevented)
780
1000
Histopath review
Unclassifiable
420
100
Patients with ILD of unknown cause
1000
1000
Transbronchial biopsy
Surgical biopsy
Inadequate sample
220
0
Surgical lung biopsy (SLB)

Complications							
Study	**Mortality**	**Exacerbations / Respiratory Failure**	**Bleeding (all)**	**Bleeding (severe)**	**Pneumothorax**	**Prolonged air leak (>48 hours)**	**Respiratory infection**
Sindhwani 2015	0/49 (0%)				5/49 (10.2%)	3/49 (6.1%)	
Pooled result (unweighted)	*0/49 (0%) (95% CI 0-7.3%)*	*No studies*	*No studies*	*No studies*	*5/49 (10.2%) (95% CI 4.4-21.8%)*	*3/49 (6.1%) (95% CI 2.1-16.5%)*	*No studies*
Pooled result (weighted using inverse variance)	*One study*	*No studies*	*No studies*	*No studies*	*One study*	*One study*	*No studies*

Transbronchial biopsy evidence profile

Evidence Profile – Transbronchial biopsy

Bibliography:

1) Han Q, Luo Q. The evaluation of clinical usefulness of transbronchoscopic lung biopsy in undefined interstitial lung diseases: A retrospective study. Clin Respir J 2017; 11: 168-175.
2) Morell F, Reyes L.Diagnoses and Diagnostic Procedures in 500 Consecutive Patients With Clinical Suspicion of Interstitial Lung Disease. Arch Bronconeumol. 2008;44(4):185-91.
3) Pajares V, Puzo C. Diagnostic yield of transbronchial cryobiopsy in interstitial lung disease: A randomized trial. Respirology (2014) 19, 900–906.
4) Pourabdollah M, Shamaei M. Transbronchial lung biopsy: the pathologist's point of view. The Clinical Respiratory Journal (2014).
5) Ramaswamy A, Homer R. Comparison of Transbronchial and Cryobiopsies in Evaluation of Diffuse Parenchymal Lung Disease. J Bronchol Intervent Pulmonol 2016;23:14–21.
6) Sheth JS, Belperio JA. Utility of Transbronchial vs Surgical Lung Biopsy in the Diagnosis of Suspected Fibrotic Interstitial Lung Disease. CHEST 2017; 151(2):389-399
7) Sindhwani G, Shirazi N. Transbronchial lung biopsy in patients with diffuse parenchymal lung disease without 'idiopathic pulmonary fibrosis pattern' on HRCT scan - Experience from a tertiary care center of North India. Lung India, Vol 32, Issue 5, Sep - Oct 2015.

Quality assessment							# Patients	Effect[1]	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**				
Diagnostic yield										
7[2]	case series	none	Serious[3]	Serious[4]	none	none	1133	45% (95% CI 31-59%)	⊕OOO VERY LOW	CRITICAL

Mortality, overall										
1[5]	case series	none	none	Serious[4]	Serious[6]	none	49	0/49 (0%) (95% CI 0-7.3%)	⊕OOO VERY LOW	CRITICAL
Pneumothorax										
1[5]	case series	none	none	Serious[4]	Serious[6]	none	49	5/49 (10.2%) (95% CI 4.4-21.8%)	⊕OOO VERY LOW	CRITICAL
Prolonged air leak, >48 hours										
1[5]	case series	none	none	Serious[4]	Serious[6]	none	49	3/49 (6.1%) (95% CI 2.1-16.5%)	⊕OOO VERY LOW	CRITICAL

Footnotes:

[1] When possible, numbers are pooled and weighted by inverse variance; however, the method does not account for studies whose result is 0% or 100% so, in such cases, we report the unweighted results instead.

[2] All studies in the bibliography.

[3] I^2 statistic was elevated.

[4] The question is intended for patients with ILD of unknown cause and a HRCT pattern other than “consistent with UIP”; however, most studies did not exclude patients with such a HRCT pattern.

[5] Sindhwani 2015

[6] The ends of the confidence interval would leave to different clinical decisions and/or fewer than 100 patients are included.

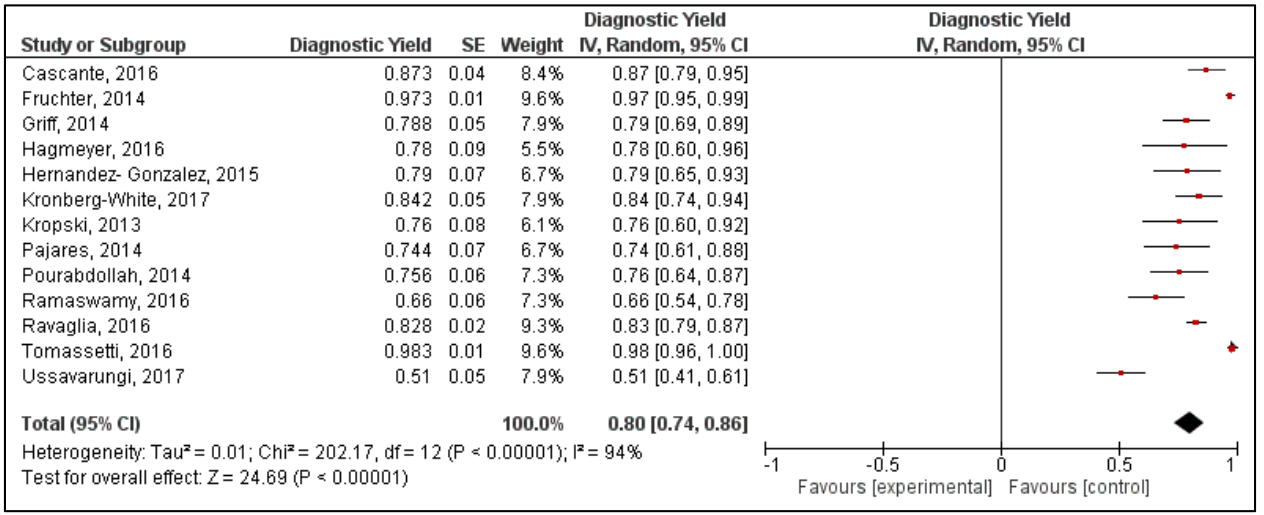
Table E10. Evidence tables for lung cryobiopsy

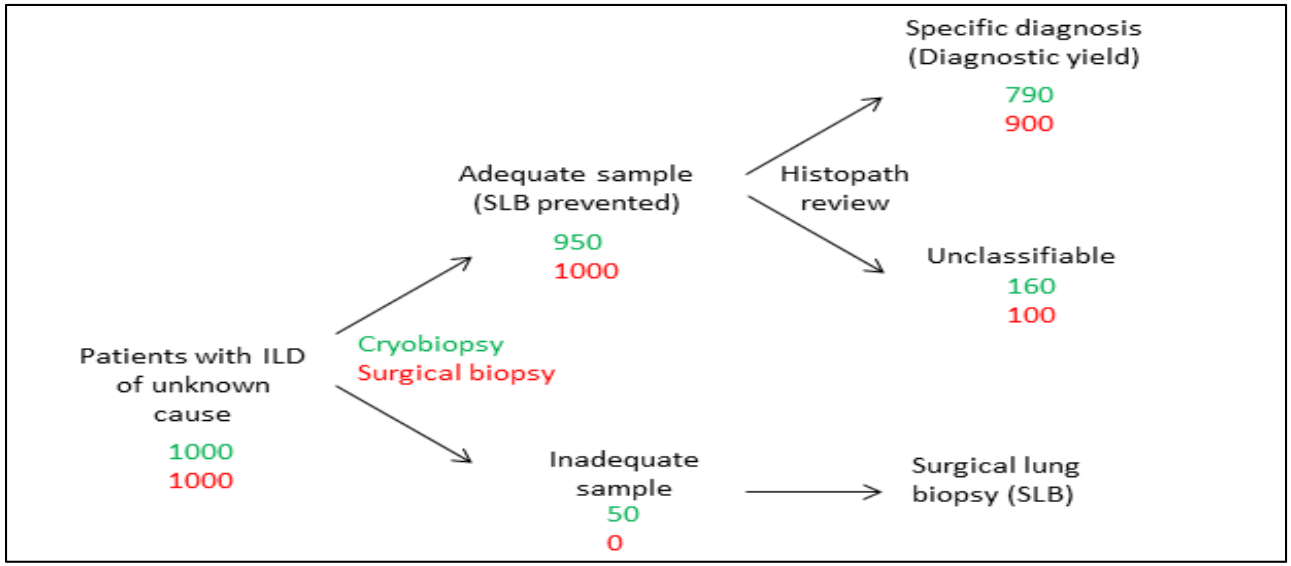
Lung cryobiopsy individual studies

Diagnostic yield					
Study	**Adequate sample**	**Inadequate sample**	**Among adequate samples**		**Diagnostic yield**
			Specific diagnosis	**Unclassifiable**	
Cascante 2016	55/55 (100%)	0/55 (0%)	48/55 (87.3%)	7/55 (12.7%)	48/55 (87.3%)
Fruchter, 2014	75/75 (100%)	0/75 (0%)	73/75 (97.3%)	2/75 (2.7%)	73/75 (97.3)
Griff, 2014	48/52 (92%)	4/52 (8%)	41/48 (85.4%)	7/48 (14.6%)	41/52 (78.8%)
Hagmeyer, 2016	NR	NR	15/19 (78%)	4/19 (22%)	15/19 (78%)
Hernandez- Gonzalez, 2015	31/33 (94%)	2/33 (6%)	26/31 (83.8%)	5/31 (16.2%)	26/33 (79%)
Kronberg- White, 2017	NR	NR	32/38 (84.2%)	6/38 (15.8%)	32/38 (84.2%)
Kropski, 2013	24/25 (96%)	1/25 (4%)	19/24 (79.1%)	5/24 (20.9%)	19/25 (76%)
Pajares, 2014	39/39 (100%)	0/39 (0%)	29/39 (74.4%)	10/39 (25.6%)	29/39 (74.4%)
Pourabdollah, 2014	40/41 (97.5%)	1/41 (2.5%)	31/40 (77.5%)	9/40 (22.5%)	31/41 (75.6%)
Ramaswamy, 2016	NR	NR	37/56 (66%)	19/56 (34%)	37/56 (66%)
Ravaglia, 2016	282/297 (94.9%)	15/297 (5.1%)	246/282 (87.2%)	36/282 (12.8%)	246/297 (82.8%)
Tomassetti, 2016	58/58 (100%)	0/58 (0%)	57/58 (98.3%)	1/58 (1.7%)	57/58 (98.3%)
Ussavarungi, 2017	68/74 (91.8%)	6/74 (8.2%)	38/68 (55.8%)	30/68 (44.2%)	38/74 (51%)
Pooled result (unweighted)	***720/749 (96%)***	***29/749 (4%)***	***692/833 (83%)***	***141/833 (17%)***	***692/862 (80 %)***

	(95% CI 94-97%)	*(95% CI 4–6%)*	*(95% CI 80-85%)*	*(95% CI 15-20%)*	*(95% CI 77 - 83%)*
Pooled result (weighted using inverse variance)	***See note***	***See note***	***82%*** ***(95% CI 76-89%)***	***18%*** ***(95% CI 11-24%)***	***80%*** ***(95% CI 74 - 86%)***

Note: Pooling by inverse variance does not account for studies whose result is 0% or 100%; thus, not used when such results exist.





Mortality						
	Overall	**Procedure Related**	**30 day**	**60 day**	**90 Day**	**Unspecified**
Cascante 2016	0/55 (0%)		0/55 (0%)		0/55 (0%)	
Hagmeyer* 2016	1/19 (5.3%)		1/19 (5.3%)			
Kronenberg- White 2017	0/38 (0%)					0/38 (0%)
Tommassetti 2016	1/58 (1.7%)					1/58 (1.7%)
Ravaglia 2016	14/297 (4.7%)	1/297 (0.3%)		13/297(4.4%)[$]		
Ramaswamy 2017	0/56 (0%)	0/56 (0%)				
Ussavarungi 2017	0/74 (0%)	0/74 (0%)				
Pooled results (unweighted)	***16/597 (2.7%) (95% CI 1.7-4.3%)***	***1/427 (0.2%)***	***1/74 (1.4%)***	***13/297 (4.4%)***	***0/55 (0%)***	***1/96 (1%)***

		(95% CI 0.04-1.3%)	*(95% CI 0.2-7.3%)*	*(95% CI 2.6-7.3%)*	*(95% CI 0-6.5%)*	*(95% CI 0.2-5.7%)*
Pooled result (weighted using inverse variance)	***See note***	***See note***	***See note***	***One study***	***One study***	***See note***

*Reporting only on the interim report from the prospective cohort from the Hagmeyer study.

$ Presumed 60-day because the surgical lung biopsy outcomes in the same study were reported at Day 60.

Note: Pooling by inverse variance does not account for studies whose result is 0% or 100%; thus, not used when such results exist.

Other complications

Study	Exacerbations / Respiratory Failure	Bleeding (all)	Bleeding (severe)	Pneumothorax	Prolonged air leak (>48 hours)	Respiratory infection
Cascante 2016		6/55 (10.9%)	1/55 (1.8%)		1/55 (1.8%)	
Fruchter 2014			3/75 (4%)	2/75 (2.6%)		
Griff, 2014		0/52 (0%)	0/52 (0%)			
Hagmeyer, 2016	1/19 (5.3%)			5/19 (26%)		
Hernandez-Gonzalez, 2015	0/38 (0%)	6/38 (15%)	1/38 (2.5%)	10/38 (26%)		2/38 95%)
Kropski, 2013	0/25 (0%)	0/25 (0%)	0/25 (0%)	0/25 (0%)		
Ravaglia, 2016		0/297 (0%)	0/297 (0%)	60/297 (20.2%)	46/297 (15.5%)	0/297 (0%)
Tomassetti, 2016			0/58 (0%)	19/58 (33%)		
Ussavarungi, 2017		16/74 (22%)	0/74 (0%)	1/74 (1.4%)		1/74 (1.4%)
Pooled results (unweighted)	**1/82 (1.2%) (95% CI 0.2-6.6%)**	**28/541 (5.2%) (95% CI 3.6-7.4%)**	**5/674 (0.7%) (95% CI 0.3-1.7%)**	**97/586 (16.5%) (95% CI 13.8-19.8%)**	**47/352 (13.4%) (95% CI 10.2-17.3%)**	**3/409 (0.7%) (95% CI 0.2-2.1%)**
Pooled result (weighted using inverse variance)	**See note**	**See note**	**See note**	**See note**	**9% (95% CI 0-22%)**	**See note**

Note: Pooling by inverse variance does not account for studies whose result is 0% or 100%; thus, not used when such results exist.

Lung cryobiopsy evidence profile

Evidence Profile – Cryobiopsy

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Quality assessment							# Patients	Effect[1]	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other				
Diagnostic yield										
13[2]	case series	none	Serious[3]	Serious[4]	none	none	862	80% (95% CI 74 - 86%)	⊕OOO VERY LOW	CRITICAL
Mortality, overall										
6[5]	case series	none	none	Serious[4]	none	none	511	16/597 (2.7%) (95% CI 1.7-4.3%)	⊕OOO VERY LOW	CRITICAL
Exacerbation/Respiratory failure										
3[6]	case series	none	none	Serious[4]	Serious[7]	none	82	1/82 (1.2%) (95% CI 0.2-6.6%)	⊕OOO VERY LOW	CRITICAL
Bleeding, all										

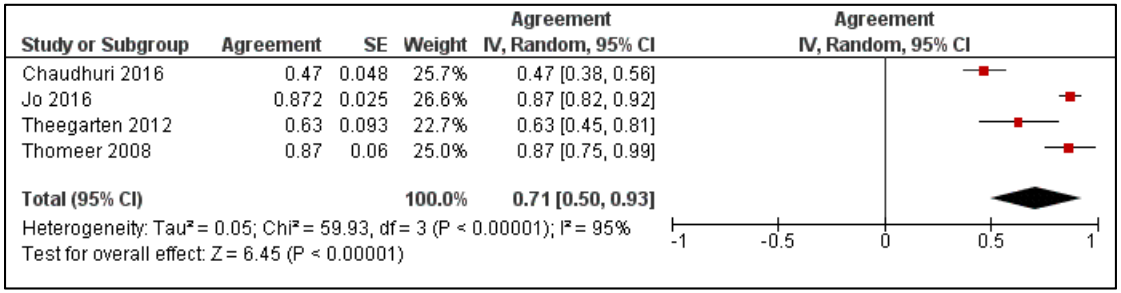
6[8]	case series	none	none	Serious[4]	none	none	541	28/541 (5.2%) (95% CI, 3.6-7.4%)	⊕OOO VERY LOW	CRITICAL
Bleeding, severe										
8[9]	case series	none	none	Serious[4]	none	none	674	5/674 (0.7%) (95% CI, 0.3-1.7%)	⊕OOO VERY LOW	CRITICAL
Pneumothorax										
7[10]	case series	none	none	Serious[4]	none	none	586	97/586 (16.5%) (95% CI 13.8-19.8%)	⊕OOO VERY LOW	CRITICAL
Prolonged air leak, >48 hours										
2[11]	case series	none	none	Serious[4]	none	none	352	47/352 (13.4%) (95% CI, 10.2-17.3%)	⊕OOO VERY LOW	CRITICAL
Respiratory infection										
3[12]	case series	none	none	Serious[4]	none	none	409	3/409 (0.7%) (95% CI, 0.2-2.1%)	⊕OOO VERY LOW	CRITICAL

[1] When possible, numbers are pooled and weighted by inverse variance; however, the method does not account for studies whose result is 0% so, in such cases, we report the unweighted results instead.
[2] All studies in the bibliography.
[3] I^2 statistic was elevated.
[4] The question is intended for patients with ILD of unknown cause and a HRCT pattern other than "consistent with UIP"; however, most studies did not exclude patients with such a HRCT pattern.
[5] Hagmeyer, Hernandez-Gonzalez, Kropski, Ravaglia, Tomassetti, and Ussavarungi.
[6] Hagmeyer, Hernandez-Gonzalez, and Kropski.
[7] The ends of the confidence interval would leave to different clinical decisions and/or fewer than 100 patients are included.
[8] Cascante, Griff, Hernadez-Gonzalez, Kropski, Ravaglia, and Ussavarangi.
[9] Cascante, Fruchter, Griff, Hernandez-Gonzalez, Kropski, Ravaglia, Tomassetti, and Ussavarangi.
[10] Fruchter, Hagmeyer, Hernandez-Gonzalez, Kropski, Ravaglia, Tomassetti, and Ussavarangi.
[11] Cascante and Ravaglia.
[12] Hernandez-GonzalezRavaglia, and Ussavarangi.

Table E11. Evidence tables for multi-disciplinary discussion

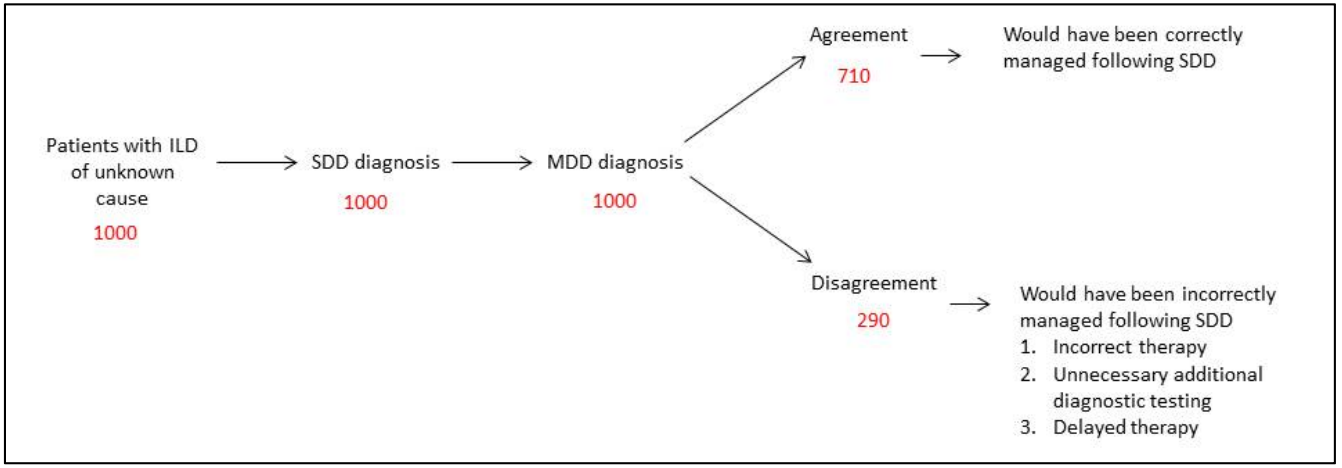
MDD Individual studies

Agreement between SDD and MDD reported as a proportion				
Study	**Population**	**SDD**	**MDD**	**Agreement**
Chaudhuri 2016	Adults with SDD dx of various types of ILD	Single respiratory clinician	Respiratory clinician + radiologist + pathologist	50/107 (47%, 95% CI 38-56%)
Thomeer 2008	Adults with SDD dx of IPF	Single respiratory clinician	Radiologist + pathologist	156/179 (87.2%, 95% CI 81-91%)
Jo 2016	Adults with SDD dx of various types of ILD	Single respiratory clinician (70%), single internist (30%)	Respiratory clinician + radiologist + pathologist	17/27 (63%, 95% CI 44-78%)
Theegarten 2012	Adults with SDD dx of various types of ILD	Group of pathologists	Respiratory clinician + pathologist	27/31 (87%, 95% CI 71-95%)
Range				***47.0% – 87.2%***
Pooled result using Generic Inverse Variance				***71% (95% CI 50-93%)***



Agreement between SDD and MDD reported as a Cohen's Kappa score*				
Study	**Population**	**SDD**	**MDD**	**Agreement**
Singh 2017	Adults with SDD dx of various types of ILD	Single respiratory clinician	United States respiratory clinician + radiologist + pathologist	K = 0.331, 95% CI 0.269-0.392
			Indian respiratory clinician + radiologist + pathologist	K = 0.366, 95% CI 0.309-0.422

* >0.8 = almost perfect; 0.6-0.8 = substantial, 0.4-0.6 = moderate, 0.2-0.4 = fair, 0.0-0.2 = slight, and <0.0 = poor.



MDD Evidence profile

Bibliography:
1) Chaudhuri N, Spencer L, Greaves M, Bishop P, Chaturvedi A, Leonard C. A Review of the Multidisciplinary Diagnosis of Interstitial Lung Diseases: A Retrospective Analysis in a Single UK Specialist Centre. J Clin Med 2016;5:66.
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Quality assessment							Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Agreement (proportion of cases achieving agreement)									
4[1]	Accuracy study	serious[2]	serious[3]	serious[4]	serious[5]	none	71.0% (95% CI 50-93%)	⊕OOO VERY LOW	CRITICAL
Agreement (Cohen's kappa score)									
1[6]	Accuracy study	serious[7]	not serious	serious[8]	serious[5]	none	For United States . . . K= 0.331 (95% CI 0.269-0.392) For India . . . K= 0.366 (95% CI 0.309-0.422)	⊕OOO VERY LOW	CRITICAL

Footnotes:
[1] Chaudhuri 2016, Thomeer 2008, Jo 2016, and Theegarten 2012.
[2] None of the studies reported that there was true diagnostic uncertainty among the cases or that patients were consecutively enrolled. In addition, two studies reported large amounts of absent data.
[3] The I^2 statistic was 95%.
[4] The question is specific for patients suspected of having IPF, but three of the four studies did not report suspicion of IPF.
[5] Either the ends of the 95% CI lead to a different clinical decision, or at least one group had an n<100.
[6] Singh 2017.
[7] The study did not report that there was true diagnostic uncertainty among the cases or that patients were consecutively enrolled.
[8] The question is specific for patients suspected of having IPF, but the study did not report suspicion of IPF.

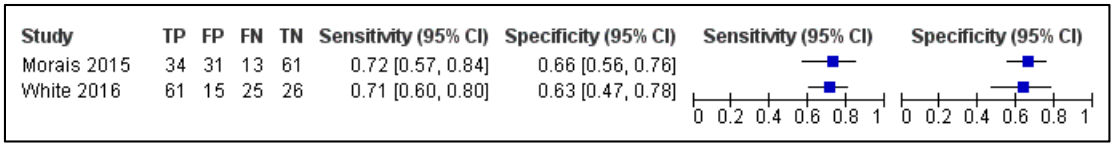
Table E12. Evidence tables for serum biomarker measurement

A) Matrix metalloproteinase-7 (MMP-7)

MMP-7 Individual studies

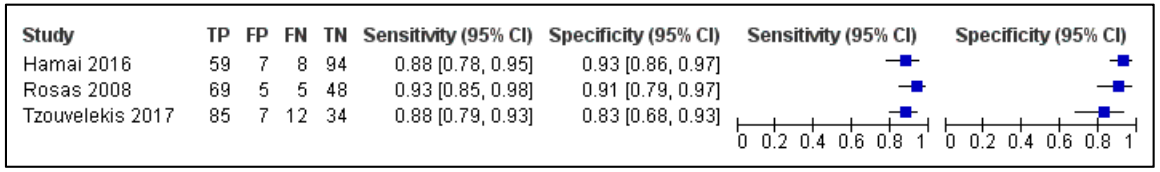
Distinguishing IPF from other ILDs											
Study	**Disease**	**No disease**	**Threshold for positive test**	**TP**	**FN**	**TN**	**FP**	**Sensitivity**	**Specificity**	**Accuracy**	**Diagnostic odds ratio**
Morais 2015	IPF	HP, CTD, drugs, NSIP, sarcoid, healthy	3.92 ng/mL	34*	13*	61*	31*	72.3%	66.3%	68.3%*	5.1
White 2016	IPF	Other ILD (not specified)	1.75 ng/mL	61*	25*	26*	15*	71.0%	63.0%	68.5%*	4.2
Median								***71.7%***	***64.4%***	***68.4%***	***4.7***
Range								***71.0-72.3%***	***63.0-66.3%***	***68.3-68.5%***	***4.2-5.1***
Pooled results (unweighted)				*95*	*38*	*87*	*46*	*71.4%*	*65.4%*	*68.4%*	*2.1*
Pooled results (weighted by inverse variance)								*72% (95% CI 66-77%)*	*65% (95% CI 59-71%)*	*68% (95% CI 63-74%)*	*Not estimable*

* Calculated from reported data.



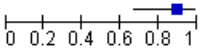
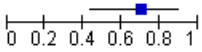
Distinguishing IPF from no ILD											
Study	**Disease**	**No disease**	**Threshold for positive test**	**TP**	**FN**	**TN**	**FP**	**Sensitivity**	**Specificity**	**Accuracy**	**Diagnostic odds ratio**
Hamai 2016	IPF	Healthy + pneumonia	5.56 ng/mL	59*	8*	94*	7*	87.7%	93.2%	91.4%	99.0
Tzouvelekis 2017	IPF	Healthy	8.18 ng/mL	85*	12*	34*	7*	87.6%	83.0%	86.2%*	34.4
Rosas 2008	IPF	Healthy	1.99 ng/mL	69	5	48	5	93.2%	90.6%*	92.1%*	132.5
Median								***87.7%***	***90.6%***	***91.4%***	***99.0***
Range								***87.6-93.2%***	***83.0-93.2%***	***86.2-92.1%***	***34.4-132.5***

* Calculated from reported data.



Distinguishing ILD from no ILD											
Study	**Disease**	**No disease**	**Threshold for positive test**	**TP**	**FN**	**TN**	**FP**	**Sensitivity**	**Specificity**	**Accuracy**	**Diagnostic odds ratio**
Kennedy 2015	IPF + SSc w/ ILD	Healthy + SSc w/o ILD	1.28 ng/mL	17*	2*	12*	5*	89.5%	73.3%	80.6%*	20.4

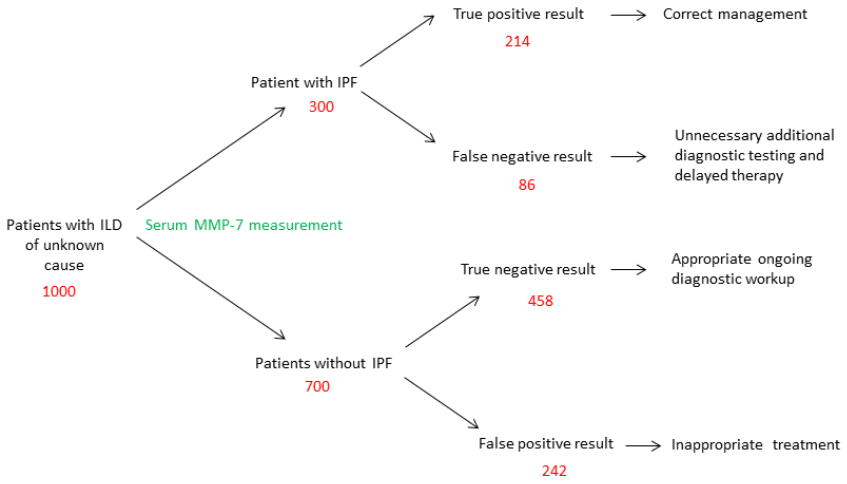
* Calculated from reported data.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Kennedy 2015	17	5	2	12	0.89 [0.67, 0.99]	0.71 [0.44, 0.90]		

Distinguishing IPF from other ILDs							
	Serum MMP-7 level (p-value c/w IPF)						
Study	Units	IPF	Non-IPF UIP	Idiopathic NSIP	CTD-related NSIP	Sarcoidosis	SSc w/ ILD
Morais 2015	Mean ng/ml +/- SD	5.79 +/- 3.07	4.02 +/- 3.85 (p=0.003)	4.32 +/- 2.90 (NS)	3.76 +/- 2.62 (p<0.001)	2.39 +/- 1.68 (p<0.001)	-
Kennedy 2015	Median ng/ml, IQR	2.85, 1.5-3.6	-	-	-	-	5.41, 2.6-7.2 (p<0.001)

Since the question indicates that the patients of interest have already been determined to have ILD, the evidence profile isbased only upon the accuracy data in the first table and the comparative data in the last table distinguishing IPF from other ILDs. In other words, accuracy data distinguishing IPF from no ILD and ILD from no ILD was not considered.

* Assumption – among patients with ILD, 30% have IPF



Therefore, for every 1000 patients with ILD of unknown cause who undergo serum MMP-7 testing, 672 (TP + TN) will receive correct management, but 328 (FP + FN) will either receive unnecessary treatment or unnecessary additional diagnostic testing with delayed treatment.

MMP-7 Evidence profile

Bibliography:
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Quality assessment							Groups		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPF	Other ILD			
Sensitivity for distinguishing IPF from other ILDs											
2[1]	Accuracy study	serious[2]	not serious	Serious[3]	Serious[4]	none	133	133	Median 71.7% Range 71-72.3%	⊕OOO VERY LOW	CRITICAL
Specificity for distinguishing IPF from other ILDs											
2[1]	Accuracy study	serious[2]	not serious	Serious[3]	Serious[4]	none	133	133	Median 64.4% Range 63-66.3%	⊕OOO VERY LOW	CRITICAL
Accuracy for distinguishing IPF from other ILDs											
2[1]	Accuracy study	serious[2]	not serious	Serious[3]	Serious[4]	none	133	133	Median 68.4% Range 68.3-68.5%	⊕OOO VERY LOW	CRITICAL
Diagnostic odds ratio for distinguishing IPF from other ILDs											

2[1]	Accuracy study	serious[2]	not serious	Serious[3]	Serious[4]	none		133	133	Mean 4.7 Range 4.2-5.1	⊕OOO VERY LOW	CRITICAL
Serum MMP-7 levels												
IPF versus non-IPF UIP (mean +/- SD)												
1[5]	Case series (uncontrolled)	not serious	not serious	Serious[3]	Serious[6]	none	5.79 ng/ml +/- 3.07 ng/ml	4.02 ng/ml +/- 3.85 ng/ml	MD +1.77 ng/ml (95% CI +0.24 - +3.30)		⊕OOO VERY LOW	NOT IMPORTANT
IPF versus idiopathic NSIP (mean +/- SD)												
1[5]	Case series (uncontrolled)	not serious	not serious	Serious[3]	Serious[6]	none	5.79 ng/ml +/- 3.07 ng/ml	4.32 ng/ml +/- 2.90ng/ml	MD +1.47 ng/ml (95% CI -0.28 - +3.22)		⊕OOO VERY LOW	NOT IMPORTANT
IPF versus CTD-related NSIP (mean +/- SD)												
1[5]	Case series (uncontrolled)	not serious	not serious	Serious[3]	Serious[6]	none	5.79 ng/ml +/- 3.07 ng/ml	3.76 ng/ml +/- 2.62 ng/ml	MD +2.03 ng/ml (95% CI +0.73 - +3.33)		⊕OOO VERY LOW	NOT IMPORTANT
IPF versus sarcoidosis (mean +/- SD)												
1[5]	Case series (uncontrolled)	not serious	not serious	Serious[3]	Serious[6]	none	5.79 ng/ml +/- 3.07 ng/ml	2.39 ng/ml +/- 1.68 ng/ml	MD +3.40 ng/ml (95% CI +2.13 - +4.67)		⊕OOO VERY LOW	NOT IMPORTANT
IPF versus scleroderma-related ILD (median [IQR])												

1[7]	Case series (uncontrolled)	not serious	not serious	Serious[3]	Serious[8]	none	2.85 ng/ml (1.5-3.6)	5.41 ng/ml (2.6-7.2)	P<0.001[9]	⊕OOO VERY LOW	NOT IMPORTANT

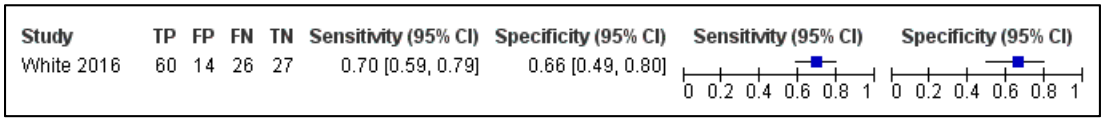
[1] Morais 2015 and White 2016
[2] Morais did not explicitly state that MDD was reference standard; neither study reported if patients consecutively enrolled. 3.76
[3] Question is about patients with ILD of unknown cause for whom there is a clinical suspicion for IPF; the studies were performed in patients with confirmed ILD diagnoses.
[4] In Morais, the disease-positive (IPF) group had <50 patients; In White, the disease-positive group had <100 patients.
[5] Morais 2015.
[6] All groups had <50 patients and most of the groups had <20 patients.
[7] Kennedy 2015.
[8] The IPF group had only 13 patients and the scleroderma-related ILD group had only 6 patients.
[9] Insufficient crude data reported to calculate a summary measure.

B) Surfactant protein D (SPD)

SPD Individual studies

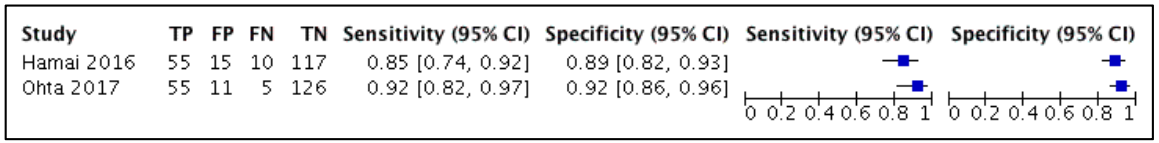
Distinguishing IPF from other ILDs											
Study	**Disease**	**No disease**	**Threshold**	**TP**	**FN**	**TN**	**FP**	**Sensitivity**	**Specificity**	**Accuracy**	**Diagnostic OR**
White 2016	IPF	Other ILD (not specified)	31 ng/ml	60*	26*	27*	14*	70%	65%	68.5%*	3.1

* Calculated from reported data.



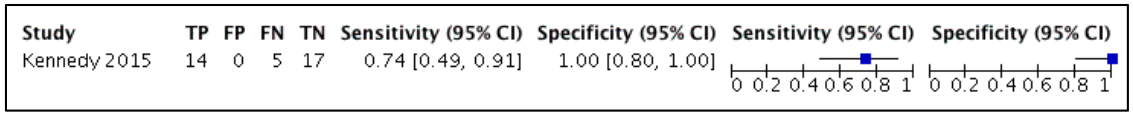
Distinguishing IPF from no ILD											
Study	**Disease**	**No disease**	**Threshold**	**TP**	**FN**	**TN**	**FP**	**Sensitivity**	**Specificity**	**Accuracy**	**Diagnostic OR**
Hamai 2016	IPF	Healthy + pneumonia	107.0 ng/ml	55*	10*	117*	15*	84.6%	88.6%	87.3%	42.9*
Ohta 2017	IPF	Healthy	96 ng/ml	55*	5*	126*	11*	91.7%	92.0%	91.0%*	126*
Median								***88.2%***	***90.3%***	***89.2%***	***84.5***
Range								***84.6-91.7%***	***88.6-92.0%***	***87.3-91.0%***	***42.9-126***

* Calculated from reported data.



Distinguishing ILD from no ILD											
Study	**Disease**	**No disease**	**Threshold**	**TP**	**FN**	**TN**	**FP**	**Sensitivity**	**Specificity**	**Accuracy**	**Diagnostic OR**
Kennedy 2015	IPF + SSc w/ ILD	Healthy + SSc w/o ILD	321.8 ng/ml	14*	5*	17*	0*	73.7%	100%	86.1%*	Incalculable

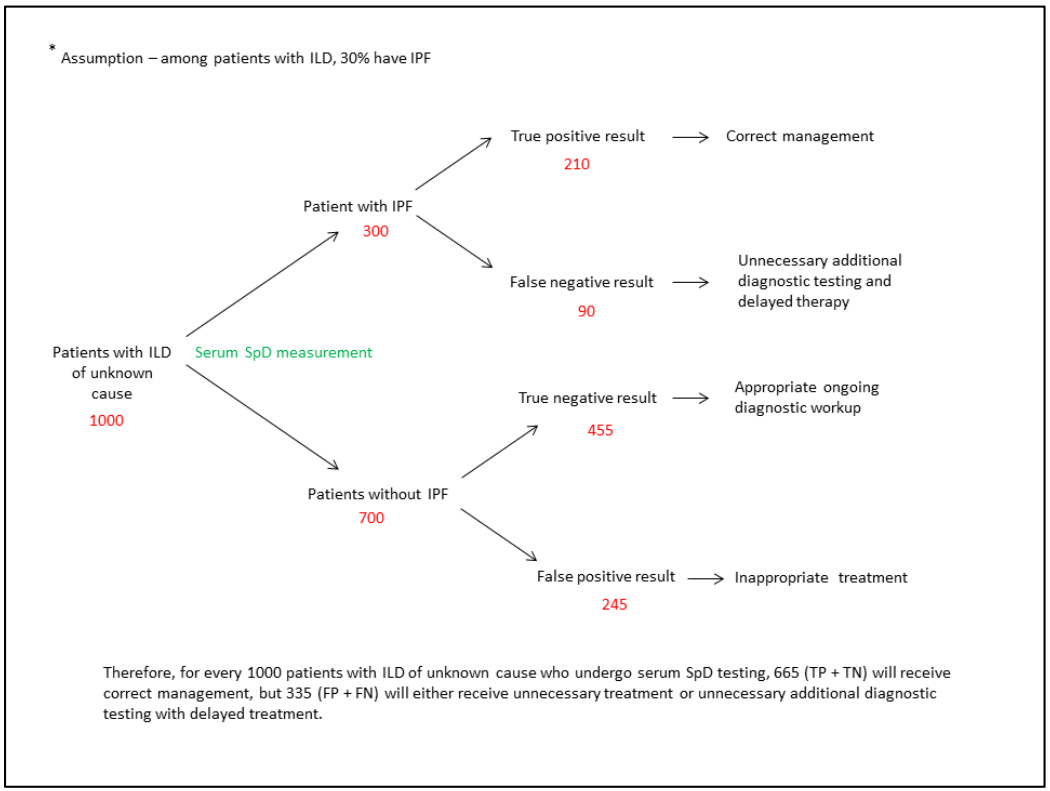
* Calculated from reported data.



Distinguishing IPF from other ILDs							
	Serum SpD level (p-value c/w IPF)						
Study	Units	IPF	Non-IPF UIP	Idiopathic NSIP	CTD-related NSIP	Sarcoidosis	SSc w/ ILD
Nishikiori 2014	Median ng/ml, IQR	272.0, 172.0-441.8	-	-	-	75.0, 48.8-97.3 (p<0.001)	-
Doubkova 2016	Median ng/ml	623.1	-	-	-	148.2 (NS)	-
Kennedy 2015	Median ng/ml, IQR	542, 305-577	-	-	-	-	398, 190-727 (NS)
White 2016	Mean ng/ml ± SD	111.07 ± 69.09	72.34 ± 82.84	-	-	-	-

Ohta 2017	Mean ng/ml ± SD	230.2 ± 167.2		170.9 ± 89.7	-	-	-

Since the question indicates that the patients of interest have already been determined to have ILD, the evidence profile isbased only upon the accuracy data in the first table and the comparative data in the last table distinguishing IPF from other ILDs. In other words, accuracy data distinguishing IPF from no ILD and ILD from no ILD was not considered.



SPD Evidence profile

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Quality assessment							# patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPF	Control			
Sensitivity for distinguishing IPF from other ILDs											
1[1]	Accuracy study	serious[2]	N/A	serious[3]	serious[4]	none	86	41	Sensitivity 70% (95% CI 59-79%)	⊕OOO VERY LOW	CRITICAL
Specificity for distinguishing IPF from other ILDs											
1[1]	Accuracy study	serious[2]	N/A	serious[3]	serious[4]	none	86	41	Specificity 65% (95% CI 49-80%)	⊕OOO VERY LOW	CRITICAL
Accuracy for distinguishing IPF from other ILDs											
1[1]	Accuracy study	serious[2]	N/A	serious[3]	serious[4]	none	86	41	Accuracy 68.5%	⊕OOO VERY LOW	CRITICAL
Diagnostic odds ratio for distinguishing IPF from other ILDs											

1[1]	Accuracy study	serious[2]	N/A	serious[3]	serious[4]	none	86	41	Odds ratio 3.1	⊕OOO VERY LOW	CRITICAL
Serum Sp-D levels											
IPF versus non-IPF UIP (mean +/- SD)											
1[1]	Case series (uncontrolled)	none	N/A	serious[3]	serious[4]	none	111.07 +/- 69.09 ng/ml	72.34 +/- 82.84 ng/ml	MD +38.73 ng/ml (95% CI +9.47 - +67.99 ng/mL)	⊕OOO VERY LOW	NOT IMPORTANT
IPF versus idiopathic NSIP (mean +/- SD)											
1[5]	Case series (uncontrolled)	none	N/A	serious[3]	serious[4]	none	230.2 +/- 167.2 ng/ml	170.9 +/- 89.7 ng/ml	MD +59.30 ng/ml (95% CI -19.47 - +138.07 ng/mL)	⊕OOO VERY LOW	NOT IMPORTANT
IPF versus CTD-related NSIP											
No studies	-	-	-	-	-	-	-	-	-	-	NOT IMPORTANT
IPF versus sarcoidosis (median, IQR)											
2[6]	Case series (uncontrolled)	none	serious[7]	serious[3]	serious[4]	none	Study #1 272, 172-441.8 ng/mL	Study #1 7.5, 48.8 – 97.3 ng/mL	Study #1 p <0.001	⊕OOO VERY LOW	NOT IMPORTANT
							Study #2 623.1 ng/mL (IQR NR)	Study #2 148.2 ng/mL (IQR NR)	Study #2 NS		
IPF versus scleroderma-related ILD (median, IQR)											

1[8]	Case series (uncontrolled)	none	N/A	serious[3]	serious[4]	none	542, 305-577 ng/mL	398, 190-727 ng/mL	NS	⊕OOO VERY LOW	NOT IMPORTANT

Footnotes:

1. White 2016.
2. Reference standard assumed, not stated. Did not comment on enrolling consecutive patients or there being true diagnostic uncertainty.
3. The question is about patients with ILD of unknown cause, but patients in the study had a known diagnosis.
4. The ends of the confidence interval would lead to different clinical decisions and/or there was fewer than 100 patients in one group.
5. Ohta 2017.
6. Nishikiori 2014 and Doubkova 2016.
7. One study found a statistically significant difference, but the other did not.
8. Kennedy 2015.

Figure E1: Combined pulmonary fibrosis and emphysema syndrome

Combined presence of upper lobe emphysema and lower lobe fibrosis more pronounced in the right lung. Note the additional presence of fibrotic changes in the right middle lobe and lingula.

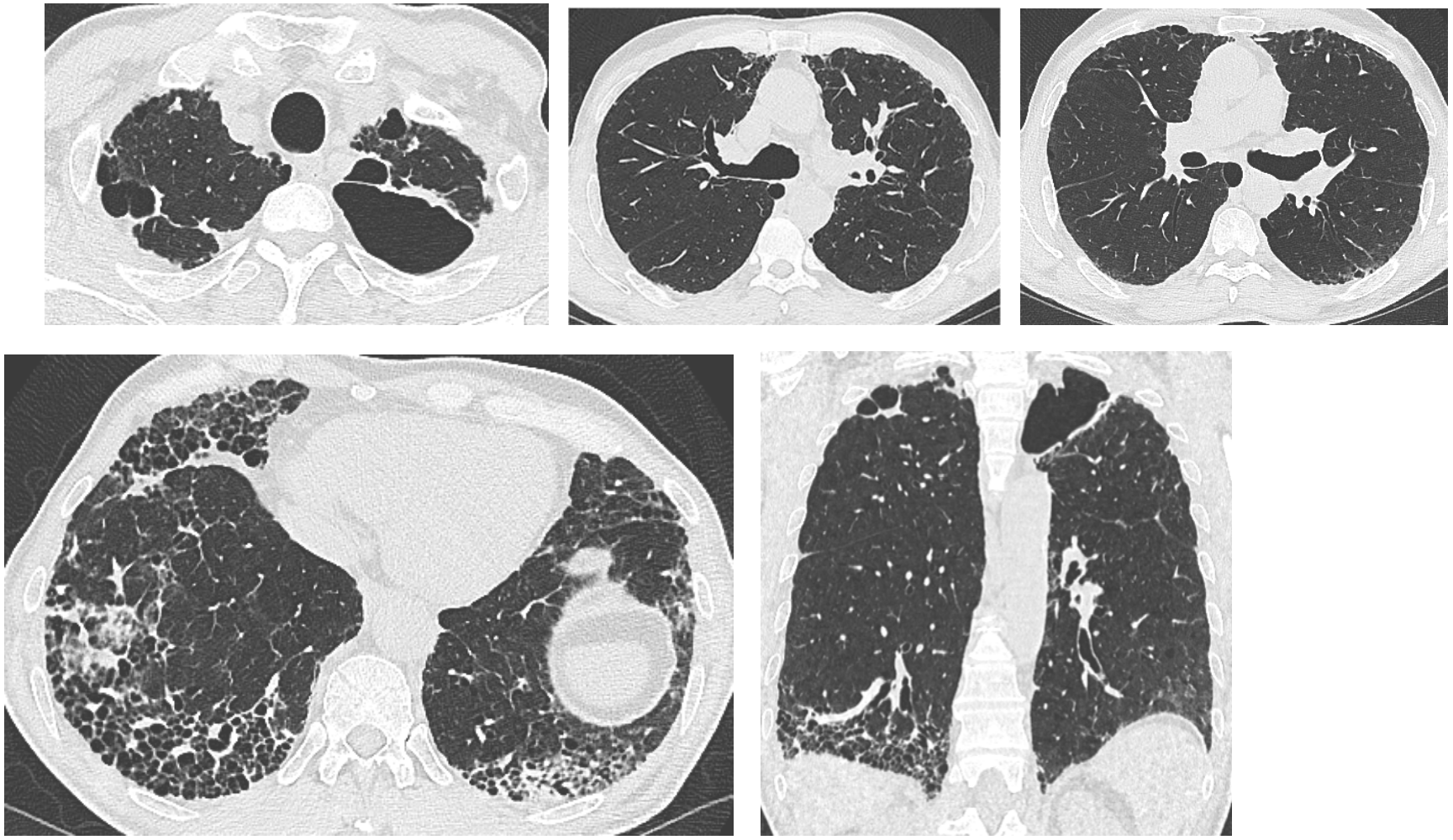
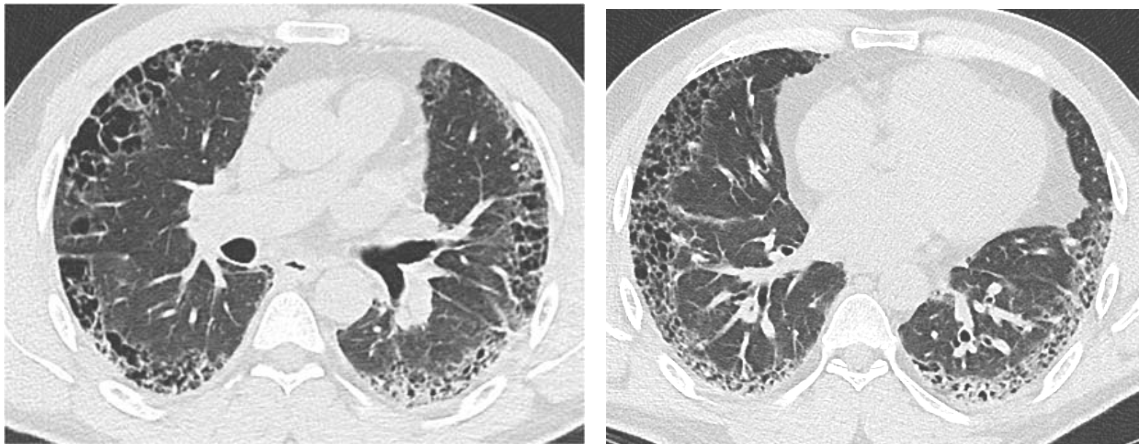


Figure E2: Influence of the level of inspiration on the interpretation of lung abnormalities

Transverse CT sections obtained at moderate inspiration, showing a reticular pattern in the subpleural regions of both lungs, suggestive of honeycombing. Note the concurrent presence of marked increased lung attenuation in peripheral lung.



Same anatomical levels acquired at deep inspiration. The microcystic pattern is now replaced by large areas of lung destruction. Diffuse ground glass opacification has been cleared.

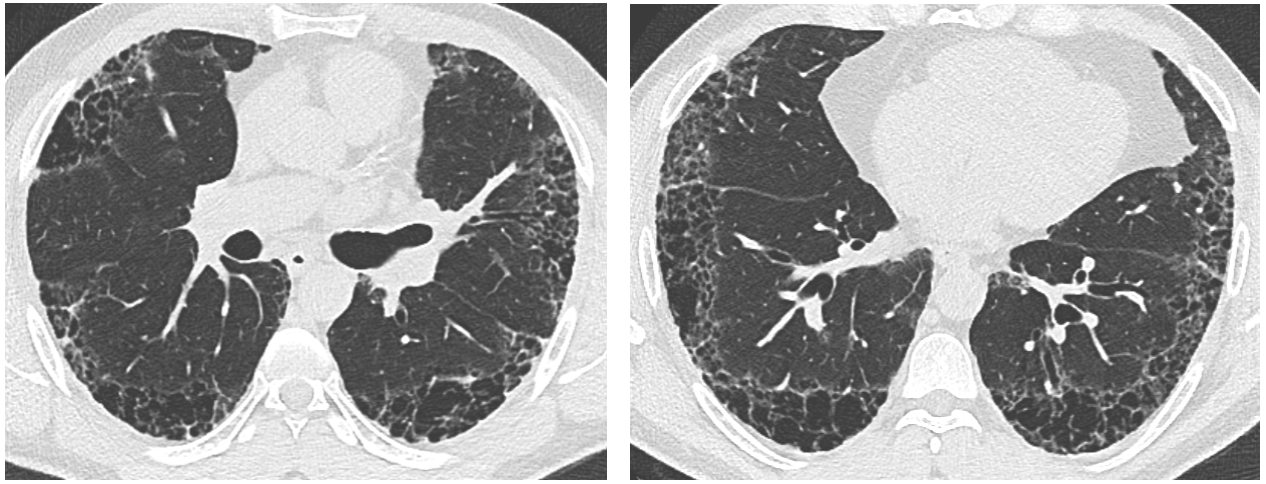


Figure E3. Bronchoalveolar lavage cell type differences among IPF vs. other types of ILD

Bronchoalveolar lavage cell counts in the fluid the patients with IPF were compared to those in the fluid of patients with other types of interstitial lung disease. Statistically significant differences of >10% are indicated with thick red lines.