Appendix 9: PICO question 3 evidence synthesis

Tables and figures included in this appendix:

Table 1: QUADAS-2 assessment

Author	Q1a.1 Was a consecutive or random sample of patients enrolled?	Q1a.2 Was a case-control design avoided?	Q1a.3 Did the study avoid inappropriate exclusions?	Q1a.4 Was the data collection prospective?	Could the selection of patients have introduced bias?	Q1b Are there concerns that the included patients do not match the review question?	Q2b Are there concerns that the index test, its conduct, or its interpretation differ from the review question?	Q4a.4 Were all patients included in the analysis (2x2 table)?	Could the patient flow have introduced bias?
Babiak, A	Yes	Yes	Unclear	No	Yes	Unclear	No	Yes	No
Bango-Álvarez, A	Unclear	Yes	Unclear	Yes	Unclear	Yes	No	Yes	No
Bondue, B	Unclear	Yes	Unclear	Yes	Unclear	Unclear	No	No	Yes
Cascante, J	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes
Cho, R	Unclear	Yes	Unclear	No	Yes	Unclear	No	Unclear	Unclear
Fruchter, O	Yes	Yes	Unclear	No	Yes	Unclear	No	No	Yes
Hagmeyer, L (2016)	Unclear	Yes	Unclear	No	Yes	Unclear	No	Unclear	Unclear
Hagmeyer, L (2019)	Unclear	Yes	Yes	Yes	Unclear	No	No	No	Yes
Hernandez-Gonzalez, F	Unclear	Yes	Unclear	No	Yes	Yes	No	No	Yes
Hetzel, J	Yes	Yes	Unclear	Yes	Unclear	Unclear	No	No	Yes
Koslow, M	Unclear	Yes	Unclear	No	Yes	Unclear	No	No	Yes
Kronborg-White, S	Unclear	Yes	Unclear	Yes	Unclear	Unclear	No	No	Yes
Kropski, J	Unclear	Yes	Unclear	No	Yes	Unclear	No	Unclear	Unclear
Lentz, R	Yes	Yes	Unclear	No	Yes	Unclear	No	No	Yes
Marcoa, R	Yes	Yes	Unclear	Yes	Unclear	Yes	No	No	Yes
O'Mahony	Yes	Yes	Unclear	No	Yes	Yes	No	No	Yes
Ramaswamy, A	Yes	Yes	Unclear	No	Yes	Unclear	No	Unclear	Unclear
Ravaglia, C (2019)	Unclear	Yes	Unclear	No	Yes	Unclear	No	Yes	No
Romagnoli, M	Yes	Yes	Yes	Yes	No	No	No	Yes	No
Samitas, K	Yes	Yes	Unclear	No	Yes	No	No	No	Yes
Shkeiri, R	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	No	No	Yes
Troy, L	Yes	Yes	Yes	Yes	No	No	No	Yes	No
Turan, D	Unclear	Yes	Unclear	No	Yes	Yes	No	No	Yes
Ussavaringsi, K	Unclear	Yes	Unclear	No	Yes	Unclear	Unclear	No	Yes
Walsher, J	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes
Zaizen, Y	Unclear	Yes	Yes	No	Yes	No	No	Unclear	Unclear

Table 2: Diagnostic yield, (change in) diagnostic confidence, and adverse events in studies evaluating SLB or second TBLC in patients with ILD and a non-informative initial TBLC

First author Year Country	**Test performed after an inconclusive initial TBLC:** -2nd TBLC -SLB	**Number of patients:** Undergoing initial TBLC (number with diagnostic TBLC / number with inconclusive or non-diagnostic TBLC)	**Number of patients:** No subsequent test (SLB or 2nd TBLC) performed and reason	**Number of patients:** Subsequent test (SLB or 2nd TBLC) performed after inconclusive initial TBLC	**Number of patients:** Specific histopathological diagnosis obtained by subsequent test (SLB or 2nd TBLC)	**Number of patients:** Change in confidence or histopathological diagnosis after subsequent test (SLB or 2nd TBLC)	**Diagnostic yield** Proportion of diagnostic subsequent tests (SLB or 2nd TBLC)	**Other outcomes** Complications and other outcomes (e.g. costs) of subsequent tests (SLB or 2nd TBLC)
Babiak, A 2009 Germany	SLB	41 (39/2) -n=39: definitive diagnosis based on history, noninvasive testing and TBLC/TBLB -n=2: non-diagnostic	0	2	2 -n=1: NSIP -n=1: IPF	NR/NA	SLB: 100% (2/2)	Complications SLB: -NR
Bango-Álvarez, A 2017 Spain	SLB	106 (91/15) -n=91: definitive diagnosis after consensus of the MDD (informed by TBLC results) -n=15: inconclusive	12 -n=12: SLB contra-indicated	3	3 -n=1: mild interstitial fibrosis -n=1: unclassifiable interstitial pneumonia -n=1: DIP	NR/NA	SLB: 100% (3/3)	Complications SLB: -n=1: prolonged air leak
Bondue, B 2020 Belgium	SLB	81 (68/13) -n=52: specific histological pattern other than NSIP -n=16: NSIP -n=13: no definite histological diagnosis	5 -n=4: SLB refused -n=1: diagnoses as chronic HP in MDD	8	8 -n=2: HP -n=6: UIP	NR/NA	SLB: 100% (8/8)	Complications SLB: -NR
Cascante, J 2016 Spain	SLB	55 (48/7) -n=38: certain diagnosis -n=10: highly likely diagnosis -n=7: undiagnosed	6 -n=5: SLB contra-indicated -n=1: diagnosis obtained through BAL	1	1 -n=1: UIP	NR/NA	SLB: 100% (1/1)	Complications SLB: -NR
Cho, R 2019 USA	SLB	40 (34/6) -n=34: diagnostic specimens -n=6: non-diagnostic specimens	4 -n=4: NR	2	2 -n=1: RB-ILD -n=1: NSIP	NR/NA	SLB: 100% (2/2)	Complications SLB: -NR
Fruchter, O 2014 Israel	SLB	75 (73/2) -n=52: definite clinicopathological consensus diagnosis -n=21: probable clinicopathological diagnosis -n=2: normal lung tissue	1 -n=1: SLB refused	1	1 -n=1: UIP/IPF	NR/NA	SLB: 100% (1/1)	Complications SLB: -NR
Hagmeyer, L 2016 Germany	SLB	32 (23/9) -n=23: TBLC showed strong congruence with initially suspected diagnosis -n=6: TBLC showed only approximate congruence -n=3: TBLC described an unspecific pattern	1 -n=1: NR	8	6: -n=4: definite UIP -n=1: OP -n=1: sarcoidosis *Non-diagnostic cases:* -n=1: possible UIP -n=1: possible NSIP	-n=7: MDD informed by SLB resulted in definitive diagnosis -n=1: MDD informed by SLB resulted in a probable diagnosis	SLB: 75% (6/8)	Complications SLB: -n=2: died within 30 days after SLB due to acute exacerbation of lung fibrosis
Hagmeyer, L 2019 Germany	SLB	61 (46/15) -n=46: MDD consensus -n=15: SLB recommended	2 -n=2: SLB refused	13	12 -n=12: conclusive clinical diagnosis could be achieved after SLB	-n=3: SLB led to MDD consensus with change of the recorded	SLB: 92% (12/13)	Complications SLB: -n=1: an overnight stay at ICU due to prolonged respiratory and

						histopathological pattern -n=5: SLB led to MDD consensus with an improved confidence -n=4: MDD consensus but no change of pattern or improved confidence -n=1: no MDD consensus		cardiovasculatory instability
Hernandez-Gonzalez, F 2015 Spain	SLB	33 (26/7) -n=26: specific diagnosis obtained -n=5: non-diagnostic sample -n=2: invalid sample	6 -n=3: SLB contra-indicated -n=3: diagnosed as ILD of unknown origin	1	1 -n=1: peribronchiolar metaplasia	NR/NA	SLB: 100% (1/1)	Complications SLB: -NR
Hetzel, J 2020 Germany	SLB	128 -n=69: confident diagnosis -n=35: provisional diagnosis with high confidence -n=18: provisional diagnosis with low confidence/ unclassifiable ILD -n=6: no consensus after CR+BAL+TBLC	NR	3 *An additional 6 patients also underwent SLB (based on MDD decision) despite a confident diagnosis or provisional diagnosis with high confidence; these were not included here*	1 -n=1: DIP	-n=1: no consensus changed to confident diagnosis	SLB: 33% (1/3)	Complications SLB: -NR
Koslow, M 2020 USA	SLB	120 (75/45) -n=66: diagnostic -n=9: non-diagnostic but clinically useful -n=45: non-diagnostic	35 -n=35: NR	10	8 -n=2: UIP/IPF -n=3: chronic HP -n=1: cryptogenic constrictive bronchiolitis -n=1: DIP -n=1: PVOD	NR/NA	SLB 80% (8/10)	Complications SLB: -NR
Kronborg-White, S 2021 Denmark	SLB 2nd TBLC	250 (180/70) -n=180: specific pattern -n=70: no diagnosis after MDD	46 -n=46: consensus diagnosis of unclassifiable ILD	24 -n=16: SLB -n=8: 2nd TBLC	19 SLB: -n=11: UIP -n=1: fibrotic HP -n=1: RB-ILD -n=1: asbestosis 2nd TBLC: -n=3: UIP -n=1: fibrotic HP -n=1: COPD	NR/NA	SLB: 88% (14/16) 2nd TBLC: 63% (5/8)	Complications SLB: -NR
Kropski, J 2013 USA	SLB	25 (19/6) -n=19: specific clinical-pathologic diagnosis -n=6: non-diagnostic	3 -n=1: normal tissue at TBLC considered sufficient to rule out DPLD -n=2: NR	3	2 -n=1: UIP -n=1: COP	NR/NA	SLB: 67% (2/3)	Complications SLB: -NR
Lentz, R 2018 USA	SLB	104 (71/33) -n=46: confident histopathological diagnosis based on TBLC	28 -n=28: NR ("offered but declined" in several cases)	5	3 -n=1: UIP/IPF -n=1: T-cell lymphoma -n=1: OP	-n=1: SLB confirmed the suspected histological results obtained from TBLC	SLB: 60% (3/5)	Complications SLB: -NR

		-n=25: less-than-definite histopathological diagnosis based on TBLC, but confident consensus at MDD -n=33: non-diagnostic				-n=2: SLB showed a different histological pattern than TBLC and a change in diagnosis		
Marcoa, R 2017 Portugal	SLB	90 (62/28) -n=62: definite diagnosis at MDD informed by TBLC -n=2: lost to follow-up -n=26: no definite diagnosis	20 -n=1: SLB refused -n=5: SLB contra-indicated -n=11: working diagnosis based on clinical and radiological evalution and MDD -n=3: remain under investigation	6	6 -n=1: HP -n=2: secondary UIP -n=1: IPF -n=1: NSIP -n=1: silicosis	NR/NA	SLB: 100% (6/6)	Complications SLB: -NR
O'Mahony 2021 Ireland	SLB	100 (72/28) -n=72: histological diagnosis -n=3: inadequate -n=25: non-diagnostic	25 -n=19: clinical-radiological diagnosis -n=5: unclassifiable ILD -n=1: contra-indicated	3	1 -n=1: eosinophilic pneumonia	NR/NA	SLB: 33% (1/3)	Complications SLB: -NR
Ramaswamy, A 2016 USA	SLB	56 (37/19) -n=37: definitive pathologic diagnosis -n=19: no definite diagnosis	17 -n=4: definitive pathologic diagnosis made by TBLB -n=6: infectious diagnosis by bronchoscopy -n=4: non-specific inflammation -n=2: clinical diagnosis established n=1: NR	2	2 -n=1: UIP -n=1: GVHD	NR/NA	SLB: 100% (2/2)	Complications SLB: -NR
Ravaglia, C 2019 Italy	SLB 2nd TBLC	699 (614/85) -n=614: Specific histological pattern -n=85: non-diagnostic or uncertain	43 -n=16: diagnosis reached in MDD -n=20: unclassifiable ILD -n=6: subsequent CT-guided lung biopsy performed -n=1: subsequent mediastinoscopy performed	42 -n=38: SLB -n= 4: 2nd TBLC	42 SLB: -n=1: OP -n=16: IPF -n=1: vasculitis -n=1 cocaine-lung -n=3 chronic HP -n=1: ACFE -n=1: ECD -n=4: lung cancer -n=3: iNSIP -n=2: RB-ILD -n=1: lymphoma -n=1: PLCH -n=1: alveolar proteinosis -n=1: CTD-ILD -n=1: diffuse inflammatory myofibroblastic tumour 2nd TBLC: -n=1: alveolar proteinosis -n=1: IPF	NR/NA	SLB: 100% (38/38) 2nd TBLC: 100% (4/4)	Complications SLB: -NR

					-n=1: lymphoma -n=1: ACFE			
Romagnoli, M 2019 Italy	SLB	21 (17/4) -n=17: histologic diagnosis -n=4: non-diagnostic	0	4 (all patients in the study had both TBLC and SLB)	4 -n=1: PLCH -n=2: UIP -n=1: ALI	NR/NA	SLB: 100% (4/4)	Complications SLB: -NR
Samitas, K 2019 Greece	SLB	50 (40/10) -n=40: histologic diagnosis (but TBLC contributed to MDD final diagnosis in n=38) -n=10: no histologic diagnosis	8 -n=5: SLB not suggested (reason unclear) -n=3: SLB refused	2	2 -n=1: B-cell low grade lymphoma -n=1: fNSIP	NR/NA	SLB: 100% (2/2)	Complications SLB: -NR
Shkeiri, R 2020 Israel	SLB	97 (52/45) -n=52: histopathologic diagnosis -n=45: nonspecific histologic findings	42 -n=NR	3	3 -n=1: UIP -n=1: DAD -n=1: extranodal marginal cell lymphoma	NR/NA	SLB: 100% (3/3)	Complications SLB: -NR
Troy, L 2020 Australia	SLB	65 (6/59) -n=59: diagnostic -n=3: unclassifiable -n=3: non-diagnostic *For MDD:* -n=39: high confidence or definite final MDD diagnoses -n=26: unclassifiable or low-confidence TBLC	0	6 (all patients in the study had both TBLC and SLB)	5 -n=2: UIP-IPF -n=1: HP -n=1: DIP/RB-ILD -n=1: NSIP	-n=6: in the n=26 with unclassifiable or low-confidence diagnosis at MDD+TBLC, n=6 (23%) were reclassified into alternative high confidence or definite diagnoses by SLB	SLB: 83% (5/6)	Complications SLB: -NR
Turan, D 2021 Turkey	SLB	147 (98/49) -n=98: histopathological diagnosis -n=49: non-diagnostic	23 -n=11: MDD diagnosis -n=12: SLB refused or contra-indicated	26	21 -n=11: UIP -n=5: HP -n=2: adenocarcinoma -n=1: NSIP -n=1: emphysema -n=1: anthracosis	NR/NA	SLB: 81% (21/26)	Complications SLB: -NR
Ussavarungsi, K 2017 USA	SLB	74 (38/36) -n=38: definite MDD diagnosis -n=36: non-diagnostic (n=31 with non-diagnostic biopsy results; n=5 with discrepancies between histopathologic diagnosis and MDD)	29 -n=8: SLB refused -n=21: possible diagnosis reached in MDD (despite a non-diagnostic TBLC)	7	7 -n=1: lymphomatoid granulomatosis -n=1: ANCA-associated vasculitis -n=2: UIP -n=1: HP -n=1: HP/UIP -n=1: granulomatous inflammation associated with CVID	-n=7: in all patients undergoing subsequent SLB, this resulted in a final diagnosis at MDD	SLB: 100% (7/7)	Complications SLB: -NR
Walscher, J 2018 Germany	SLB	109 (80/29) -n=80: histological diagnosis -n=29: non-specific disease pattern	21 -n=2: SLB refused -n=3: SLB contra-indicated -n=5: no SLB proposed by MDD (watch-and-wait strategy) -n=11: MDD diagnosis reached	8	8 -n=3: HP -n=2: IPF -n=1: iNSIP -n=1: IgG4 associated-ILD -n=1: sarcoidosis	NR/NA	SLB: 100% (8/8)	Complications SLB: -NR
Zaizen, Y 2019	SLB	35 (NR/7)	NR	7	7 -n=4: UIP	-n=7: in all patients undergoing	SLB: 100% (7/7)	Complications SLB: -No adverse events

Japan		-n=7: non-diagnostic			-n=1: ACIF -n=1: DPO -n=1: NSIP with OP	subsequent SLB, this resulted in a final diagnosis at MDD -Pathological diagnosis with TBLC and SLB had agreement in 5 cases, and the diagnosis was changed from indeterminate for UIP pattern with TBLC to probable UIP with SLB in the remaining 2 cases.		

Legend:

Abbreviations: ACFE = airway-centered fibroelastosis. ACIF = airway centered interstitial fibrosis. ALI = acute lung injury. ANCA = antineutrophil cytoplasmic antibodies. BAL = bronchoalveolar lavage. CI = confidence interval. COP = cryptogenic organizing pneumonia. COPD = chronic obstructive pulmonary disease. CR = clinicoradiological data. CTD = connective tissue disease. CVID = common variable immunodeficiency disorder. DAD = diffuse alveolar damage. DIP = desquamative interstitial pneumonia. DPLD: diffuse parenchymal lung disease. ECD = Erdheim Chester disease. GVHD = graft versus host disease. HP = hypersensitivity pneumonitis. ICU = intensive care unit. ILD = interstitial lung disease. iNSIP = idiopathic non-specific intersitial pneumonia. IPF = idiopathic pulmonary fibrosis. fNSIP = fibrotic non-specific intersitial pneumonia. MDD = multidisciplinary discussion. NA = not applicable. NR = not reported. NSIP = non-specific interstitial pneumonia. OP = organizing pneumonia. PLCH = pulmonary Langerhans cell histiocytosis. PVOD = pulmonary veno-occlusive disease. RB-ILD = respiratory bronchiolitis interstitial lung disease. SLB = surgical lung biopsy. TBLB = transbronchial lung biopys. TBLC = transbronchial lung cryobiopsy. UIP = usual intersitial pneumonia. VATS = video-assistend thoracic surgery.

Figure 1a: Meta-analysis of diagnostic yield of SLB in ILD patients with an non-informative initial TBLC

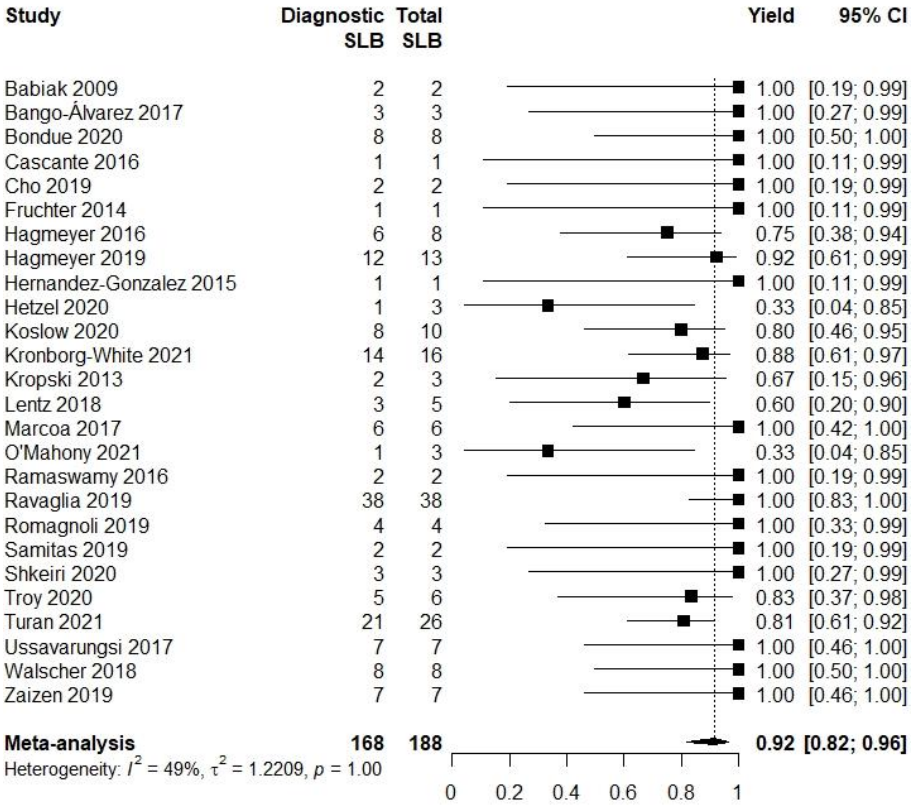

Figure 1b: Meta-analysis of diagnostic yield of SLB in ILD patients with an non-informative initial TBLC, excluding studies contributing <10 patients

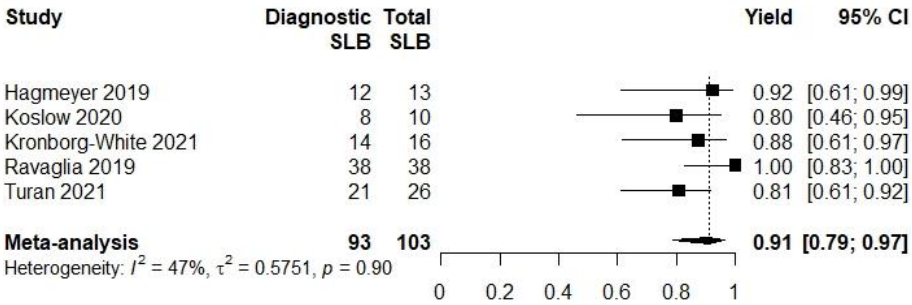

Table 3: GRADE tables for PICO question 3

PICO question:

In patients with undiagnosed ILD and a non-informative TBLC, is step-up SLB or second TBLC a valid add-on test?

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Diagnostic yield step-up SLB (after inconclusive initial TBLC)									
26[1-26]	observational studies	serious[a]	not serious	serious[b]	not serious	none	Summary diagnostic yield in meta-analysis:0.92 (0.82 to 0.96)	⨁◯◯◯ Very low	CRITICAL
Diagnostic confidence step-up SLB (after inconclusive initial TBLC)									
2[3,7]	observational studies	serious[c]	not serious	not serious	serious[d]	none	Hagmeyer et al: In 15 patients, step-up SLB was recommended because a confident MDD-diagnosis was not reached after TBLC, which was performed in 13. A conclusive clinical diagnosis was made in 92% (n=12) of them (change in histopatholoigcal diagnosis (n=3), improved MDD confidence (n=5), no additional information (n=4)). Bondue et al: In 29 patients, step-up SLB was recommended because of an uncertain histopathological diagnosis (n=13) or a NSIP pattern (n=16), which was performed in 14. This showed UIP pattern in 79% (n=11), HP pattern in 14% (n=2), and NSIP pattern in 7% (n=1). Of the six patients with an NSIP pattern at TBLC undergoing subsequent SLB, this showed a UIP pattern in five, and confirmed a NSIP pattern in only one.	⨁◯◯◯ Very low	CRITICAL
Complications step-up SLB (after inconclusive initial TBLC)									
4[2,7,8,26]	observational studies	serious[e]	not serious	not serious	serious[f]	none	Complications reported for SLB in 4/31 patients for whom this information was reported: prolonged airleak (n=1); death within 30 days after SLB due to acute exacerbation of lung fibrosis (n=2); an overnight stay at ICU due to prolonged respiratory and cardiovasculatory instability (n=1)	⨁◯◯◯ Very low	CRITICAL
Diagnostic yield second TBLC (after inconclusive initial TBLC)									
2[12,18]	observational studies	serious[g]	not serious	serious[b]	serious[h]	none	Diagnostic yield was 100% (4/4 patients) in Ravaglia 2019 and 62.5% (5/8 patients) in Kronborg-White 2021.	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval

Explanations

a. Risk of bias was high in at least one QUADAS-2 domain for 23/26 studies, mainly due related to the patient selection process, as step-up SLB was rarely systematically performed or considered in all consecutive patients with a non-informative TBLC, but only in a poorly defined subset. Applicability concerns were high in 7/20 studies.

b. Unclear if diagnostic yield sufficiently correspond to the final MDD-diagnosis and to patient-important outcomes.

c.Risk of bias was high in at leas one QUADAS-2 domain in 2/2 studies.

d. Only 2 studies (including a total of 27 patients undergoing SLB after a non-conclusive inital TBLC) reported on diagnostic confidence. No meta-analysis was performed.

e. Risk of bias was high in at least one QUADAS-2 domain for 3/4 studies. Applicability concerns were high in 1/4 studies.

f. Only 4 studies (including a total of 31 patients undergoing SLB after a non-conclusive inital TBLC) reported on complications. No meta-analysis was performed.

g. Risk of bias was high in at least one QUADAS-2 domain for 2/2 studies. Applicability concerns were high in 0/2 studies.

h. Only 12 patients (from 2 studies) who underwent a second TBLC after an initial inconclusive TBLC were included for this outcome. No meta-analysis was performed.

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Table 4: Evidence to decision framework for PICO question 3

PICO question:

In patients with undiagnosed ILD and a non-informative TBLC, is step-up SLB or second TBLC a valid add-on test?

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Diagnostic yield of TBLC in patients with ILD is, on average, 72.9% (based on the systematic review by Sethi 2019). A considerable proportion of patients with a non-diagnostic TBLC remain, and addititional diagnostic testing may be required.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	SLB: Diagnostic yield of SLB in patients with a non-diagnostic TBLC was on average 92% in meta-analysis. TBLC: Too little information is available to make statements about the diagnostic yield of a second TBLC.	-SLB: 'moderate' desirable effect. -Second TBLC: 'don't know' (there is too little information to make a judgement).
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	SLB: Only a small number of studies included in the meta-analysis on the diagnostic yield of SLB after a non-diagnostic TBLC reported on complications. Complications occured in 4 out of 31 (12.9%) patients for whom this information was explicitly reported.	-Judgement applies to both SLB and second TBLC.

	TBLC: Complication rates are not available for second TBLC in these patients. However, despite this limited evidence, it is likely that the overall complication rates of SLB and TBLC in ILD patients (PICO question 1) can be extrapolated to patients with an initial non-diagnostic initial TBLC.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Overall certainty of the evidence was 'very low'.	-Judgement applies to both SLB and second TBLC.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		-It is unlikely that there is considerable variability in how much the main outcomes are valued, both for physicians and patients. However, some may put more value to establishing a diagnosis, while others may put more value to safety (i.e. preventing adverse events from additional invasive testing). -SLB: 'probably no important uncertainty or variability'. -Second TBLC: 'possibly important uncertainty or variability' (due to limited evidence). -Summary of patient feedback (one patient who underwent TBLC, one who underwent SLB): "The evidence indicates that SLB is more likely to give an accurate answer than TBLC but is associated with higher risks. Given the data on the scale of these benefits and risks, we consider that most patients would opt for a TBLC but, if that does not work, would then prefer to have a SLB, rather than a second TBLC."

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		-Performing SLB after a non-diagnostic initial TBLC will improve diagnostic yield of the diagnostic process. Whether this is also the case for a second TBLC is unknown due to limited evidence; diagnostic yield is likely to be lower than for SLB. SLB (and second TBLC) are associated with additional adverse events and costs. In general, we believe that these disadvantages are outweighed by the need to obtain a diagnosis. These are all patients that had an indication to undergo TBLC for diagnosing ILD. Because initial TBLC was non-diagnostic, the indication to undergo invasive diagnostic testing remains. Therefore, the balance is probably in favor of performing an additional test. -SLB: 'probably favors the intervention'. -Second TBLC: 'don't know' (due to limited evidence).

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	Our PICO questions did not focus on cost-effectiveness, and such studies are not available in the subgroup of patients with a non-diagnostic initial TBLC.	A second invasive test (i.e. SLB or second TBLC) after a non-diagnostic initial TBLC will lead to additional costs. However, establishing a correct diagnosis may result in cost-reduction (e.g. by preventing incorrect treatment). Evidence to weigh these costs is not available in this subgroup of patients.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate		

○ High ● No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	Our PICO questions did not focus on cost-effectiveness, and such studies are not available in the subgroup of patients with a non-diagnostic initial TBLC.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		There is no reason to assume that performing a second invasive test after a non-diagnostic initial TBLC will have an impact on health equity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes	Performing SLB (or second TBLC) after a negative initial TBLC will increase diagnostic yield of the diagnostic process, as illustrated in the meta-analysis (Figure XX). However, it will also lead to additional costs and adverse events.	Some stakeholders may weigh these advantages and disadvantages in doing an additional test; others may not. Yet, in general, there is no reason to assume that an additional diagnostic procedure is considered unacceptable by any of the stakeholders.

○ Varies ○ Don't know		

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		Both SLB and TBLC have been implemented in many healthcare centers worldwide, as illustrated by the large number of studies evaluating diagnostic yield and/or complications of TBLC (n=59) and/or SLB (n=55) in patients with ILD identified in our searches.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**

	JUDGEMENT						
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

For patients with undiagnosed ILD and a non-informative TBLC, the task force suggests performing step-up SLB if obtaining histopathological data is indicated (conditional recommendation, very low certainty of evidence).

For patients with undiagnosed ILD and a non-informative TBLC, the task force makes no recommendation about performing second TBLC if obtaining histopathological data is indicated, as there is no evidence.

Justification

Performing SLB after a non-diagnostic initial TBLC will improve diagnostic yield of the diagnostic process. Whether this is also the case for a second TBLC is unknown due to limited evidence; diagnostic yield is likely to be lower than for SLB. SLB (and second TBLC) are associated with additional adverse events and costs. In general, we believe that these disadvantages are outweighed by the need to obtain a diagnosis. These are all patients that had an indication to undergo TBLC for diagnosing ILD. Because initial TBLC was non-diagnostic, the indication to undergo invasive diagnostic testing remains. Therefore, the balance is probably in favor of performing an additional test. Yet, this should be decided upon on a case-by-case level by the physician in discussion with a well-informed patient, taking into account factors such as (relative) contra-indications (e.g. severe lung function or cardiac impairment) to undergo additional testing.

Subgroup considerations

No subgroup analysis was performed in our meta-ananalysis, or the underlying studies.

Implementation considerations

Both SLB and TBLC have already been implemented by many specialised clinics worldwide. Currently, clinics in which TBLC is available will most likely also be able to offer SLB.

Monitoring and evaluation

Healthcare centers that offer step-up SLB or second TBLC after a non-informative initial TBLC are advised to collect data on important outcomes such as diagnostic yield and complications.

Research priorities

It is adviced that prospective studies are performed, evaluating the added value (in terms of diagnostic yield, adverse events and costs) of performing SLB or second TBLC after a non-diagnostic initial TBLC are performed. This can be singe-arm studies (i.e. SLB or second TBLC only), or two-arm studies (ideally a randomized clinical trial) in which both tests are compared.