Appendix 8: PICO question 2 evidence synthesis

Tables included in this appendix:

Table 1: GRADE tables for PICO question 2

Table 2: Evidence to decision framework for PICO question 2

Table 1: GRADE tables for PICO question 2

PICO question:

In patients with undiagnosed ILD not considered eligible to undergo SLB, does TBLC increase the diagnostic confidence of the multidisciplinary team discussion?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLB	[comparison]	Relative (95% CI)	Absolute (95% CI)		
Diagnostic yield												
1[1]	observational studies	serious[a]	not serious	serious[b]	serious[c]	none	**Matta et al**: diagnostic yield of TBLC was 88% in 17 critically ill ILD patients with acute hypoxemic respiratory failure, who were considered poor candidates for SLB, or refused this (n=12 interventions were performed at bedside in ICU).				⨁◯◯◯ Very low	CRITICAL
Adverse events												
2[1,2]	observational studies	not serious	serious[d]	not serious	serious[e]	none	**Matta et al**: pneumothorax in 35%, moderate bleeding in 6%, 30-day ICU mortality in 47% (although non directly attributable to TBLC) in 17 critically ill ILD patients with acute hypoxemic respiratory failure. **Bondue et al**: numbers of bleeding, pneumothorax, mortality and hospital stay were equal between 58 patients at low risk of SLB versus 38 patients at high risk of SLB (defined as age ≥75-years, BMI ≥35, sPAP by echocardiography ≥45 mmHg, FVC <50%, DLCO <30%, and/or significant cardiac comorbidities). See narrative question 2 for adverse event rates of TBLC in high-risk patients.				⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval

Explanations

a. High risk of selection bias: retrospective chart review of non-consecutive patients.

b. Patients with severe hypoxemic respiratory failure only, with a considerable proportion of procedures performed in ICU.

c. Only one study, limited number of patients.

d. Adverse event rates vary considerable across the two studies, probably due to very high risk patients with severe hypoxemic respiratory failure (Matta et al) versus lower risk patients (Bondue et al).

e. Only two studies, limited number of patients.

References

1. Matta A, Gupta E, Swank Z, Aragaki-Nakahodo A, Cooley J, Caudell-Stamper DN, Benzaquen S. The use of transbronchial cryobiopsy for diffuse parenchymal lung disease in critically ill patients with acute hypoxemic respiratory failure-A case series. The clinical respiratory journal 2021: 18: 18.

2.Mathieu S, Boutron I, Moher D, Altman DG, Ravaud P. Comparison of registered and published primary outcomes in randomized controlled trials. JAMA 2009: 302(9): 977-984.

3.Bondue B, Schlossmacher P, Allou N, Gazaille V, Taton O, Gevenois PA, Vandergheynst F, Remmelink M, Leduc D. Trans-bronchial lung cryobiopsy in patients at high-risk of complications. BMC Pulmonary Medicine 2021: 21(1): 135.

Table 2: Evidence to decision framework for PICO question 2

PICO question:

In patients with undiagnosed ILD not considered eligible to undergo SLB, does TBLC increase the diagnostic confidence of the multidisciplinary team discussion?

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The prevalence of ILD is estimated to be 6.3-76.0 per 100,000 people in Europe, and 74.3 per 100,000 in the USA. Of these 13-40% are estimated to develop progressive fibrosing ILD, with an overall prevalence estimate of 2.2-20.0 per 100,000 in Europe, and 28.0 per 100,000 in the USA. This reresents a considerable fraction of chronic respiratory disorders (*Olson et al. Advances in Therapy 2021: 38:854-867*). For the majority of patients with ILD, a MDD of clinical and radiological data results in a diagnosis. However, for around one third of these, MDD indicates that histopathological interpretation of a lung biopsy is needed. Currently, SLB is often performed in these patients, with high costs and high complication rates: Summary incidence of surgical morbidity (n=18 studies): 12.9% (95%CI 9.3-16.9%). Summary incidence of mortality within 30 days (n=21 studies): 2.3% (95%CI 1.3-3.6%). Some ILD patients have severe respiratory or comorbid disease, and they may not be able to tolerate SLB. In these patients, TBLC could be an alternative.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		No evidence was obtained on diagnostic accuracy or related outcomes of TBLC in ILD patients not considered eligible to undergo SLB. However, it is anticipated that these outcomes can be extrapolated from patients that are eligible to undergo SLB (see 'desirable effects' in PICO question 1), although there is no data to confirm this.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	-TBLC appaers to be safe in ILD patients in whom lung biopsy is at high-risk of complications (based on high age, BMI, lung impairment and/or cardiac comorbidities), with equal numbers of bleeding, pneumothorax, mortality and hospital stay compared to low-risk patients (based on one study with a limited number of patients (Bondue et al)). -Mortality rates appear to be high (47%) in critically ill patients with acute hypoxemic respiratory failure, yet it is unclear if TBLC contributed to this (based on one study with a limited number of patients (Matta et al)).	-Evidence on adverse events from TBLC in ILD patients not considered eligible to undergo SLB is very limited. -Narrative question 2 reports on adverse events in high-risk populations, indicating that hospitalized patients appear to be at higher complication risk than non-hospitalized patients (Cooley 2018, Pannu 2019), but that there appear to be no major differences based on anticoagulation use or age, although data are limited. -Overall, the Task Force considers the risk of severe adverse events to vary considerably, depending on, for example, the rapidness of disease progression and the extent of respiratory failure.

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’.	

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		-Some may favor having more diagnostic certainty by undergoing TBLC, others may not based on risk of adverse events. -No evidende is available on patient values.

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		-Some may favor having more diagnostic certainty by undergoing TBLC, others may not based on risk of adverse events. -The Task Force acknowledges that the variety of potential patients (and corresponding risk of performing TBLC) in this context is wide, and balancing of effects will vary accordingly.

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		Unclear to which extent obtaining more diagnostic certainty (with - for example -the potential consequence of avoiding the initation of an innapropriate treatment) will lead to cost reductions, as compared to not performing the test in ILD patients not considered eligible to undergo SLB.

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		Unclear to which extent obtaining more diagnostic certainty (with - for example -the potential consequence of avoiding the initation of an innapropriate treatment) will lead to cost reductions, as compared to not performing the test in ILD patients not considered eligible to undergo SLB.

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		No data available on cost-effectiveness in patients ineligible to undergo SLB.

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		TBLC provides an alternative diagnostic test to obtain a histopathological diagnosis in patients not considered eligible to undergo SLB.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		Some may favor having more diagnostic certainty by undergoing TBLC, others may not based on risk of adverse events.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		TBLC has been implemented in many healthcare centers worldwide, as illustrated by the large number of studies evaluating diagnostic yield and/or complications of TBLC in patients with ILD (n=59) identified in our searches. It does require well-trained endoscopists (see PICO question 4) and TBLC-equipment.

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**
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**

	JUDGEMENT						
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 not considered eligible to undergo SLB, the task force suggests TBLC if obtaining histopathological data is indicated (conditional recommendation, very low certainty of evidence).

Remark: this recommendation applies to centers experienced in performing TBLC; the advantages of potentially increasing diagnostic certainty by performing TBLC against the disadvantages of potential serious adverse events should be weighed in each individual patient.

Justification

TBLC could provide a histopathological diagnosis in patients not considered eligible to undergo SLB. Although evidence is limited, we anticipate that diagnostic accuracy (and related) outcomes is likely to be similar as for patients considered eligible to undergo SLB (PICO question 1). Data on safety is limited, and the Task Force acknowledges that the variety of potential patients (and corresponding risk of performing TBLC) in this context is wide, and weighing the advantages and disadvantages of performing TBLC will vary accordingly.

Subgroup considerations

Narrative question 2 reports on adverse events in high-risk populations, indicating that hospitalized patients appear to be at higher complication risk than non-hospitalized patients (Cooley 2018, Pannu 2019), but that there appear to be no major differences based on anticoagulation use or age, although data are limited.

Implementation considerations

TBLC has already been implemented by many specialised clinics worldwide. TBLC does not need to be offered in any healthcare center monitoring or treating patients with ILD; patients can be referred for TBLC to a specialised clinic.

Monitoring and evaluation

Healthcare centers that offer TBLC in patients not considered eligible to undergo SLB are advised to collect data on important outcomes such as diagnostic yield and complications.

Research priorities

Prospective studies evaluating diagnostic yield, adverse events and patient-important outcomes of TBLC in high-risk patients not considered eligible to undergo SLB could be initiated in experienced centers, clarifying which patients are at particularly high risk of undergoing TBLC.