Appendix 10: PICO question 4 evidence synthesis

Tables included in this appendix:

Table 1: QUADAS-2 assessment for the finally included studies in PICO question 4

Table 2: GRADE table for PICO question 4

Table 3: Evidence to decision framework for PICO question 4

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?
Almeida 2017	Unclear	Yes	No	No	Yes	No	No	Yes	No
Kronborg-White 2017	Unclear	Yes	Unclear	Yes	Unclear	No	No	Yes	No

Table 2: GRADE tables for PICO question 4.

PICO question:

Is formal training in TBLC recommended to optimize diagnostic yield and minimize adverse events in patients with undiagnosed ILD?

Certainty assessment						Anticipated effects				Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Early procedures[e]	Late procedures[f]	Relative (95% CI)	Absolute (95% CI)		
Diagnostic yield (assessed with: Number of procedures for which TBLC provided a definitive diagnosis)											
1[1]	observational studies	serious[a]	not serious	very serious[b]	not serious	37/50 (74.0%)	45/50 (90.0%)	**OR 3.16** (1.03 to 9.69)	**66 more per 1.000** (from 3 more to 89 more)	⨁◯◯◯ Very low	CRITICAL
Median sample length (assessed with: Sample length in mm)											
1[1]	observational studies	serious[a]	not serious	very serious[b]	not serious	5.0 mm (range 2.5-16.0)	6.0 mm (range 4.0-12.0)	p<0.001 (reported by authors based on Mann-Whitney U test for median differences)		⨁◯◯◯ Very low	NOT IMPORTANT
Median sample area (assessed with: Sample area in mm^3)[c,1]											
1[1]	observational studies	serious[a]	not serious	very serious[b]	not serious	17.5 mm^3 (range 6.0-42.0)	21.5 mm^3 (range 10.0-49.0)	p<0.001 (reported by authors based on Mann-Whitney U test for median differences)		⨁◯◯◯ Very low	NOT IMPORTANT
AE: pneumothoraxes (assessed with: Occurrence of pneumothorax after TBLC)											
2[1,2]	observational studies	serious[a]	not serious	very serious[b]	serious[c]	18/70 (25.7%)	10/68 (14.7%)	**OR 0.50** (0.21 to 1.18)	**68 fewer per 1.000** (from 112 fewer to 22 more)	⨁◯◯◯ Very low	CRITICAL
AE: bleedings (assessed with: Occurrence of moderate pulmonary bleedings after TBLC according to BTS definitions)											
1[1]	observational studies	serious[2,a]	not serious	very serious[b]	very serious[d]	1/50 (2.0%)	2/50 (4.0%)	**OR 1.96** (0.17 to 22.32)	**4 more per 100** (from 3 fewer to 44 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations

a. Assessed independently by two authors using QUADAS-2. Bias could have been introduced through study design and patient selection.

b. The study did not compare training vs. no training when using TBLC. Furthermore, it is not clear what degree of training the bronchoscopist received along the way and how baseline experience regarding invasive procedures may have impacted the outcome.

c. The 95% CI crosses 1 and includes appreciable benefit and appreciable harm.

d. The 95% CI crosses 1, includes appreciable benefit and appreciable harm, and there are very few events.

e. Early procedures in Almeida 2017: procedures 1-50, in Kronborg-White 2017: procedures 1-20.

f. Late procedures in Almeida 2017: procedures 51-100, in Kronborg-White 2017: procedures 21-38.

References

1. Almeida LM, Lima B, Mota PC, et al. Learning curve for transbronchial lung cryobiopsy in diffuse lung disease. Rev Port Pneumol (Barc). 2017;22:22.

2. Kronborg-White S, Folkersen B, Rasmussen TR, et al. Introduction of cryobiopsies in the diagnostics of interstitial lung diseases - experiences in a referral center. Eur Clin Respir J. 2017;4(1):1274099.

Table 3: Evidence-to-Decision framework for PICO question 4.

PICO question:

Is formal training in TBLC recommended to optimize diagnostic yield and minimize adverse events in patients with undiagnosed ILD?

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The prevalence of interstitial lung disease (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 represents a considerable fraction of chronic respiratory disorders (*Olson et al. Advances in Therapy 2021: 38:854-867*). Currently, surgical lung biopsy (SLB) is often performed in these patients, with high costs and high complication rates. Transbronchial Lung Cryobiopsy (TBLC) might be a reasonable diagnostic alternative to SLB. The impact of formal TBLC training on outcomes is uncertain.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	-Desirable effects of formal training in TBLC could not be evaluated Two studies were included that reported some of the prioritized outcomes in early and late procedures, reflecting the impact of increasing experience on procedure outcomes -No information about bronchoscopists' baseline TBLC experience or the amount of training they received	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ○ Small ○ Trivial	-Undesirable effects of formal training in TBLC could not be evaluated -Two studies were included that reported some of the prioritized outcomes in early and late procedures, reflecting the impact of increasing experience on procedure outcomes	

○ Varies ● Don't know	-No information about bronchoscopists' baseline TBLC experience or the amount of training they received	

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	The overall certainty of 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		Most probably, the values of the various outcomes vary in-between stakeholders. Some believe in a high value of training programs, e.g., using simulators and educational programs, some prefer clinical training.

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	We could not evaluate whether formal TBLC training had more desirable or undesirable effects on the prioritized outcomes because none of the studies evaluated the effect of training.	Probably high variability depending on the design of the training program.

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	No cost-benefit analyses for formal TBLC training are, to our knowledge, available.	The costs will depend on the design of the formal training. From a logical point of view, formal TBLC training will most certainly cost more than no training. However, one must take possible beneficial effects on TBLC outcomes into account.

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	No cost-benefit analyses for formal TBLC training are, to our knowledge, available.	

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 cost-benefit analyses for formal TBLC training are, to our knowledge, available.	

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	None.	Certain patient groups, especially those with more co-morbidities and/or lower lung function, may benefit from formal training, e.g. in simulators or patients with less frailty.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	None.	Depending on the design and implementation of formal TBLC training, we consider that it would probably be acceptable to key stakeholders.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	None.	The feasibility of formal TBLC training will probably depend on design, implementation, and local conditions.

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**
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

The task force suggests that TBLC-operators should undergo training (conditional recommendation, 'very low' certainty of evidence), but a recommendation on the optimal type of training cannot be made due to lack of evidence.

Justification

The task force considers training crucial, as diagnostic yield increases and adverse events decrease with operator experience. For other invasive procedures, it has been shown that formal training programs can increase operator experience. No studies have, so far, evaluated the impact of formal TBLC training on outcomes in TBLC. However, the task force believes that a certain level of experience is indeed needed to perform TBLC in a safe and effective way and formal training can be the way to gain this experience. Further research is needed to establish the impact of formal training on outcomes in TBLC and we, hereby, strongly recommend to design and conduct studies evaluating formal training programs in TBLC.

Subgroup considerations

Patients with different frailty levels or co-morbidities (high- vs. low-risk groups) may benefit in various degrees of TBLC training.

Implementation considerations

If implemented, formal TBLC training programs must be developed and defined properly. We recommend an implementation under protocolled conditions.

Monitoring and evaluation

If implemented, the impact of formal TBLC training programs must be monitored closely by evaluating – as a minimum – all outcomes prioritized as critical (diagnostic yield, diagnostic accuracy, adverse events, mortality, survival, learning curves) or important (diagnostic confidence, quality of life, lung function, exercise tolerance, costs).

Research priorities

Studies on the impact of formal training on TBLC outcomes are urgently needed. Firstly, formal training programs must be defined and developed. Secondly, we recommend direct comparisons of formal training programs and no formal TBLC training on the outcomes. This can either be done by performing a randomized trial, or by performing observational studies which include bronchoscopists undergoing different types of training. We recommend that future studies evaluate – as a minimum – all outcomes prioritized as critical (diagnostic yield, diagnostic accuracy, adverse events, mortality, survival, learning curves) or important (diagnostic confidence, quality of life, lung function, exercise tolerance, costs).