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Early View

Task force report

European Respiratory Society guidelines on transbronchial lung cryobiopsy in the diagnosis of interstitial lung diseases

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ABSTRACT

Background: In patients with interstitial lung diseases (ILD), histopathological input is often required to obtain a diagnosis. Surgical lung biopsy (SLB) is considered the reference standard, but many patients are clinically unfit to undergo this invasive procedure, and adverse events, length of hospitalization and costs are considerable. This guideline provides evidence-based clinical practice recommendations for the role of transbronchial lung cryobiopsy (TBLC) in obtaining tissue-based diagnosis in patients with undiagnosed ILD.

Materials and methods: The European Respiratory Society task force consisted of clinical experts in the field of ILD and/or TBLC, and methodological experts. Four PICO questions and two narrative questions were formulated. Systematic literature searches were performed in Medline and Embase (up to June 2021). GRADE (Grading, Recommendation, Assessment, Development and Evaluation) methodology was applied.

Results: In patients with undiagnosed ILD and an indication to obtain histopathological data: (1) TBLC is suggested as replacement test in patients considered eligible to undergo SLB, (2) TBLC is suggested in patients not considered eligible to undergo SLB, (3) SLB is suggested as add-on test in patients with a non-informative TBLC, (4) no recommendation is made for or against second TBLC in patients with a non-informative TBLC, and (5) TBLC-operators should undergo training, but no recommendation is made for the type of training required.

Conclusion: TBLC provides important diagnostic information in patients with undiagnosed ILD. Diagnostic yield is lower compared to SLB, at reduced serious adverse events and length of hospitalization. Certainty of the evidence is mostly ‘very low’.

INTRODUCTION

Accurate diagnosis of interstitial lung diseases (ILD) is important for guiding treatment decisions and prognosis. In the majority of patients with ILD, integration of clinical, laboratory and radiological data within a multi-disciplinary discussion (MDD) results in a diagnosis.[1, 2] For a subset of patients, however, a diagnosis cannot be made with sufficient confidence based on these data, and histopathological evaluation of lung tissue may be indicated.[3]

Multiple tests can be used to obtain cyto- or histopathological information in the diagnostic work up of ILD. Bronchoalveolar lavage (BAL) is associated with a very low rate of adverse events, but its diagnostic value is mostly limited to disorders that are typically intra-alveolar (e.g. infection, alveolar proteinosis, eosinophilic pneumonia, organizing pneumonia, alveolar hemorrhage and diffuse alveolar damage).[4] Transbronchial lung biopsy (TBLB) with regular forceps is mainly indicated in disorders that involve the centrilobular zones and are characterized by 'easy-to-identify' morphological alterations (e.g. carcinomatous lymphangitis, sarcoidosis, organizing pneumonia and diffuse alveolar damage).[5] Complications are rare, but diagnostic yield is limited by small specimens, sampling errors and crush artifacts. In particular, TBLB is poorly sensitive for the diagnosis of complex histopathologic patterns such as usual interstitial pneumonia (UIP).[6]

Surgical lung biopsy (SLB) is generally obtained thoracoscopically and is currently considered the reference standard when less invasive approaches fail or are not feasible. Samples are large and contain peripheral structures of the secondary pulmonary lobule, with a diagnostic yield of approximately 90%.[6, 7] However, SLB is associated with significant morbidity and mortality. In-hospital mortality in elective procedures is estimated to be around 2%, and significantly higher in nonelective procedures.[8] Many patients are not clinically fit to undergo this invasive procedure. Risk is particularly increased in those who may have UIP, are at older age, have significant lung function impairment, or are experiencing an acute exacerbation of ILD. In addition, length of hospital admission and associated costs can be considerable.[8, 9]

In recent years, transbronchial lung cryobiopsy (TBLC) has been explored as a less invasive alternative to SLB.[10] With this approach, larger samples without crush artifacts can be obtained compared to standard TBLB. Although consensus statements and guidelines dealing with the standardization of TBLC are available,[11-14] to date there have been no guidelines for its clinical application. The European Respiratory Society (ERS) established a task force to develop guidelines aimed at providing evidence-based clinical practice recommendations on the role of TBLC in patients with undiagnosed ILD.

MATERIALS and METHODS

Scope and purpose

The purpose of this project was to evaluate the role of TBLC in obtaining tissue-based diagnosis in patients with undiagnosed ILD, aiming to provide evidence-based clinical practice recommendations for its application. Advantages and disadvantages of TBLC, with respect to diagnostic confidence, diagnostic yield, diagnostic accuracy, adverse events and patient-important outcomes, were assessed and compared with those of SLB. This was done across various subgroups, including patients eligible to undergo SLB, patients not considered eligible to undergo SLB (e.g. due to lung function impairment, rapidly progressive disease or comorbid disease), patients at high risk of undergoing TBLC, patients with an initial non-informative TBLC, and patients with specific high-resolution computed tomography (HRCT) findings.

Task force composition and conflict of interest declaration

The task force consisted of 16 members: 11 clinical experts in the field of TBLC and/or ILD (JC, LH, JH, FM, AM, CR, ST, LT, AW, JA, VP), one pathologist (TC), one thoracic radiologist (JV), and three junior pulmonologists (in training) with experience in literature syntheses (DK, SC, MF). An ERS methodologist had the overview of all the methodological steps (TT). Task force members disclosed all potential financial conflicts of interest, which are reported at the end of this manuscript.

Formulation of questions

A list of potential guideline questions (both PICO and narrative questions) was developed by two task force members (SC, VP). These were then discussed in detail, prioritized and refined in a live task force meeting (November 2019, Florence, Italy), in a subsequent task force phone meeting (November 2019), and through task force e-mail discussions. Guideline questions were finalized in a task force phone meeting in January 2020. Six questions were selected for the guideline. Of these, four were PICO questions that formed the basis of this guideline. In addition, two were narrative questions to be addressed in a descriptive manner, with no intention of making clinical practice recommendations. An overview of guideline questions is provided in **Table 1**, with detailed questions in **Appendix 1**.

Literature searches and study selection

A single search strategy was developed by a medical information specialist (RS, with help of DAK), that covered all guideline questions. Medline and Embase were searched from inception in May 2020, and searches were updated in June 2021. Search terms focused on a combination of the tests of interest (TBLC or SLB) and the condition of interest (ILD). The full search strategy is provided in **Appendix 2**.

Study selection was done in a two-step approach. First, two task force members (DAK, SC) independently assessed titles and abstracts of all search results, and those that were considered potentially relevant for at least one of the guideline questions by at least one of them were selected. After this, two task force members

(DAK, SC, MF, JC, CR, ST) per guideline question independently assessed all full-texts of selected studies, to determine final inclusion. Disagreements were resolved through discussion.

Detailed selection criteria per guideline question are reported in **Appendix 3**. The study selection process was summarized in PRISMA-DTA flowcharts.[15, 16] Not all studies fulfilling the inclusion criteria were (directly) considered in the evidence syntheses. Instead, for each outcome, we primarily focused on included studies that directly compared TBLC and SLB in patients with undiagnosed ILD, either by performing both tests in each patient (paired direct comparison), or by randomizing patients to undergo either procedure (unpaired direct comparison). If direct comparisons were not available for a specific outcome, we focused on studies that indirectly compared TBLC and SLB (i.e. a group of patients undergoing TBLC was compared with a group of patients undergoing SLB, without randomization). Finally, in the absence of direct or indirect comparisons for a specific outcome, we focused on non-comparative studies that only evaluated TBLC or only evaluated SLB in patients with undiagnosed ILD. If available for a specific outcome, we selected a previously published systematic review summarizing non-comparative studies, rather than focusing on individual studies, to avoid duplication of review efforts. In such cases, we used the most recently published systematic review that was not part of a clinical guideline or position statement, and in which an adequate study quality assessment had been performed.

Assessment of evidence quality and recommendation strength

In line with the GRADE (Grading, Recommendation, Assessment, Development and Evaluation) approach, task force members participated in an online survey to rate the importance of each outcome per PICO question on a scale from 1 to 9 for its perceived importance for clinical decision-making. Mean scores of 7-9 were considered a 'critical' outcome, of 4-6 an 'important but not critical' outcome, and of 1-3 a 'not important' outcome. Survey results are provided in **Appendix 4**. For each PICO question, one task force member (DK, SC, MF) developed an evidence profile, with input from the ERS methodologist (TT) and the two chairs (VP, JA). Data were summarized in evidence tables. The QUADAS-2 (quality assessment of diagnostic accuracy studies) tool was used to assess risk of bias and applicability concerns of studies.[18] The evidence was graded according to GRADE.[19] Certainty of the evidence of each outcome was initially rated as 'high' if it originated from randomized trials or from well-developed diagnostic accuracy studies, and as 'low' if it originated from observational data.[20] Certainty was subsequently downgraded if there was high risk of bias, serious inconsistency in results across studies, indirectness of the evidence, imprecision in effect sizes or point estimates, or evidence of publication bias. Data extraction, study quality assessment and performing GRADE was done by one of the three task force members (DAK, SC, MF), and checked by another, with disagreements being resolved through discussion.

One task force member (DK, MF) then drafted GRADE evidence-to-decision tables for each PICO question, taking into account the quality of evidence, balance of desirable and undesirable effects, patient values and preferences, resources required, health equity (i.e. potential differences in effectiveness in disadvantaged

subgroups), acceptability of the tests by key stakeholders, and feasibility of implementation of the tests.[21] This resulted in a recommendation that could either be 'strong' (phrased as "the task force recommends") or 'conditional' (phrased as "the task force suggests"). The evidence-to-decision process was discussed in detail in a task force video meeting in December 2021, in which 15 of 17 members participated, where recommendations were finalized and agreed upon. Members who did not participate in this meeting confirmed their agreement via e-mail. A draft manuscript was prepared by one task force member (DK, with input from SC, MF, TT, JA, VP), and shared with the complete task force for input and approval.

Patient input

Three patient representatives (one with experience in TBLC, one in SLB, and one in TBLC and SLB) from the European Lung Foundation's Pulmonary Fibrosis Patient Advisory Group provided input on the evidence-to-decision tables, recommendations and manuscript.

RESULTS

An overview of recommendations per PICO question is provided in **Table 1**, with a proposed diagnostic algorithm in **Figure 1**.

Search results

Overall, 4325 records were retrieved in our literature searches (n=3969 in the initial search, and n=356 in the update), of which 250 remained after screening of titles and abstracts. Of these, 119 were included: all of them fulfilled the inclusion criteria for PICO question 1, whereas a subset also fulfilled the inclusion criteria for any of the other guideline questions (PICO question 2: n=2; PICO question 3: n=26; PICO question 4: n=3; narrative question 1: n=0; narrative question 2: n=10). Flowcharts and list of included studies per guideline question are provided in **Appendix 5**.

PICO question 1: In patients with undiagnosed ILD considered eligible to undergo SLB, is TBLC a valid replacement test?

Recommendation

For patients with undiagnosed ILD considered eligible to undergo SLB, the task force suggests performing TBLC if obtaining histopathological data is indicated (conditional recommendation for the intervention, 'very low' certainty of evidence). Remark: this recommendation applies to centers experienced in performing TBLC.

Background

In the majority of patients with ILD, amalgamation of clinical, laboratory and radiological data will result in a diagnosis at MDD. However, in a considerable proportion, lung biopsy is recommended by MDD to establish a confident diagnosis.[22] Historically, SLB has been considered the reference standard for lung tissue acquisition in these patients, but costs, adverse events and length of hospital admission can be considerable.[7] TBLC could serve as replacement test in these patients, especially if sufficiently accurate (i.e. high diagnostic agreement between TBLC and SLB) and resulting in fewer serious adverse events.[23]

Evidence summary

An overview of studies included in PICO question 1, ordered by type of study, is provided in **Appendix 6.** Evidence summary tables, results from study quality assessment, GRADE tables, and evidence-to-decision tables for PICO question 1 are provided in **Appendix 7**. Overall, 119 studies were included for this PICO question, but the majority of these were not (directly) considered in the evidence syntheses.

Regarding direct comparisons between TBLC and SLB, no randomized trials were found (although the task force is aware of one in progress; Netherlands Trial Registry number NL7634), but two studies were identified that performed both tests in a group of patients with undiagnosed ILD (paired direct comparison; **Table 1, 2 and 3 in Appendix 7**).[24, 25] Romagnoli et al performed both tests in 21 patients with a nondefinitie UIP pattern on HRCT, with blinded pathologists, and one final MDD per patient that was informed by results from both

tests.[24] Troy et al performed both tests in 65 patients with undiagnosed ILD, with blinded pathologists, and two separate MDD's per patient: one informed by TBLC results and one informed by SLB results.[25] Both studies were considered at high risk of bias.

In addition, three studies were found that indirectly compared TBLC and SLB, by comparing a group of patients that underwent TBLC with a group of patients that underwent SLB (**Table 4 in Appendix 7**).[26-28] Risk of selection bias was considered high in these studies, because no randomization was performed. Ravaglia et al included 297 patients undergoing TBLC and 150 patients undergoing SLB, all with ILD in whom a diagnosis could not be achieved noninvasively.[26] Tomassetti et al included patients with fibrotic ILD without a typical UIP pattern on HRCT, of whom 58 had TBLC and 59 had SLB.[27] A second study by Tomassetti et al included patients with suspected ILD without a definite UIP pattern on HRCT, of whom 266 had TBLC and 160 had SLB.[28]

Finally, a large number of non-comparative studies was found that evaluated TBLC only or SLB only (n=54 and n=50, respectively), or systematic reviews thereof (n=11). The task force focused on two recent systematic reviews (**Table 5 in Appendix 7**).[7, 23] Sethi et al included 31 studies (18 full-texts and 13 abstracts) on patients with suspected ILD undergoing TBLC, of which 27 could be included in meta-analysis (n=1443 patients).[23] Risk of bias according to QUADAS-2 was considered high or unclear in 80.6% (n=25) of studies. Sharp et al included 24 studies (n=2665 patients) on patients undergoing video assisted thoracoscopic (VATS) biopsy in patients with ILD.[7] Risk of selection bias according to the Cochrane Collaboration risk of bias tool was high in all studies.

Overall, outcomes that could be taken into account in PICO question 1 were diagnostic agreement, diagnostic confidence, diagnostic yield, diagnostic accuracy, survival after idiopathic pulmonary fibrosis (IPF) diagnosis, and adverse events. Limited evidence was available on costs, and this was only discussed narratively. No comparative evidence of TBLC versus SLB was identified on (long-term) patient-important outcomes (i.e. quality of life, lung function, mortality, exercise tolerance, or survival).

Diagnostic agreement (**Table 2 and 7 in Appendix 7**): This is moderate, based on two direct comparisons. Romagnoli et al reported a diagnostic agreement between the TBLC result and final MDD (which was informed by both TBLC and SLB results) of 47.6% (95%CI 26-70), and a fair kappa agreement of 0.31 (95%CI 0.06-0.56).[24] Troy et al reported a diagnostic agreement between MDD informed by TBLC results and MDD informed by SLB results of 76.9%, and a substantial kappa agreement of 0.62 (95%CI 0.47-0.78).[25] The evidence was judged as 'very low' (downgraded for risk of bias, indirectness and imprecision).

High or definite confidence final diagnosis (**Table 2 and 7 in Appendix 7**): This can be obtained in the majority of patients, with both TBLC and SLB, based on one direct comparison. Troy et al reported that a high or definite confidence diagnosis could be obtained in MDD informed by TBLC results in 60.0% (n=39), and in MDD

informed by SLB results in 73.8% (n=48; p=0.090).[25] In 94.8% (n=37) of patients with a high or definite confidence diagnosis in MDD informed by TBLC results, the same diagnosis was reached in MDD informed by SLB results. In 23.1% (n=6) of patients with a low confidence or unclassifiable diagnosis in MDD informed by TBLC results, a high or definite confidence diagnosis was reached in MDD informed by SLB results. The evidence was judged as 'very low' (downgraded for risk of bias, indirectness and imprecision).

Increase in diagnostic confidence (**Table 6 and 7 in Appendix 7**): This is significant for TBLC, based on an indirect comparison and a non-comparative study. Tomassetti et al reported that the percentage increase in IPF diagnosis made with high level of confidence in MDD changed from 29% to 63% before and after adding TBLC results (p=0.0003), and from 30% to 65% before and after adding SLB results (p=0.0016).[27] Hetzel et al reported among 128 patients a percentage increase in confidence (i.e. confident diagnosis or provisional diagnosis with high confidence) from 60.2% (n=77) after clinicoradiological discussion and BAL, to 81.2% (n=104) when adding TBLC results (p<0.0001); this implies that in 51 patients with no consensus diagnosis or with a provisional diagnosis with low confidence after BAL, TBLC led to a definite or confident provisional diagnosis in 62.7% (n=32).[29] The evidence was judged as 'very low' (downgraded for risk of bias and imprecision).

Diagnostic yield for a histopathological diagnosis (**Table 2, 4, 5 and 7 in Appendix 7**): This is high for TBLC, yet somewhat higher for SLB, based on both comparative and non-comparative studies. In the direct comparison by Romagnoli et al, a diagnostic pattern was obtained in 81.0% for TBLC and 100% for SLB, with histopathological agreement between the two in 38.1% (95%CI 18-62), and a kappa agreement of 0.22 (95%CI 0.01-0.44).[24] In the direct comparison by Troy et al, a diagnostic pattern was obtained in 90.8% and 96.9%, respectively, with a histopathological agreement (for guideline-refined pattern) of 70.8%, and a weighted kappa agreement of 0.70 (95%CI 0.55-0.86).[25] The indirect comparison by Ravaglia et al reported a diagnostic yield of 82.8% for TBLC and 98.7% for SLB (p=0.013).[26] The evidence of the comparative studies was judged as 'very low' (downgraded for risk of bias and imprecision). Similar results were found in the non-comparative studies. In the meta-analyses of studies only reporting on TBLC or only reporting on SLB, summary diagnostic yield was 72.9% (95%CI 67.9-77.7) and 91.1% (95%CI 86.9-93.2), respectively.[7, 23] The evidence of the non-comparative studies was judged as 'very low' (downgraded for risk of bias and indirectness).

Diagnostic accuracy for diagnosing IPF (**Table 3 and 7 in Appendix 7**): This is moderate for (MDD informed by) TBLC, based on two direct comparisons. In Romagnoli et al, sensitivity and specificity for diagnosing IPF against a reference standard of final MDD (informed by TBLC and SLB results) were 66.7% (95%CI 31-91) and 75.0% (95%CI 43-93), respectively (recalculated based on reported data).[24] In Troy et al, sensitivity and specificity for diagnosing IPF against a reference standard of MDD (informed by SLB results) were 91.4% (95%CI 76-98) and 80.0% (95%CI 61-92), respectively (recalculated based on reported data).[25] The evidence was judged as 'very low' (downgraded for risk of bias, indirectness and imprecision).

Survival after IPF diagnosis (**Table 4 and 7 in Appendix 7**): In the indirect comparison by Tomassetti et al, an MDD diagnosis of IPF (versus another ILD) based on TBLC or SLB were both significantly associated with 5-year transplant-free survival (TBLC: adjusted HR 2.98 (95%CI 1.19-1.47; p=0.02), and SLB: adjusted HR 4.07 (95%CI 2.01-8.24; p<0·0001)). [28] The evidence was judged as 'very low' (downgraded for risk of bias and indirectness).

Adverse events - mortality (**Table 4, 5 and 7 in Appendix 7**): This is lower in TBLC compared to SLB, based on two indirect comparisons and on non-comparative studies. Ravaglia et al reported that mortality due to an adverse event occurred in 0.3% (n=1) in the TBLC group and in 2.7% (n=4) in the SLB group (p=0.045).[26] In Tomassetti et al, mortality was 1.7% (n=1) in the TBLC group and 3.4% (n=2) in the SLB group.[27] The evidence for the indirect comparison was judged as 'very low' (downgraded for risk of bias and indirectness). Similar results were found in the non-comparative studies. In the systematic review on studies evaluating TBLC only, summary incidence of mortality within 30 days was 0.3% (95%CI not reported; based on 33 studies).[23] In the systematic review on studies evaluating SLB only, summary incidence of mortality within 30 days of 2.3% (95%CI 1.3-3.6; based on 21 studies).[7] The evidence of the non-comparative studies was judged as 'very low' (downgraded for risk of bias).

Adverse events - time of hospitalization (**Table 4 and 7 in Appendix 7**): This is shorter for TBLC compared to SLB, based on two indirect comparisons. Ravaglia et al reported a mean time of hospitalization of 2.6 days (range 0-17) for TBLC, and 6.1 days (range 3-48) for SLB (p<0.0001).[26] Tomassetti et al reported a mean time of hospitalization of 3 days (range 0-9) for TBLC, and 6 days (range 3-17) for SLB (p-value not reported).[27] The evidence was judged as 'very low' (downgraded for risk of bias and indirectness).

Adverse events - other (**Table 2, 4, 5 and 7 in Appendix 7**): These are more frequent for TBLC, based on comparative and non-comparative studies. However, this is mainly because pneumothorax as a complication is only relevant for TBLC, as it occurs by definition in 100% of cases for SLB. In the direct comparison by Romagnoli et al, serious adverse events occurred in 9.5% (n=2: pneumothorax) for TBLC, and in 0% for SLB.[24] In the direct comparison by Troy et al, no serious adverse events occurred for TBLC (one pneumothorax was not considered as such by the study authors), and in 3.1% for SLB (n=1: rehospitalization due to chest pain; n=1: bleeding requiring intervention).[25] In the indirect comparison by Ravaglia et al, pneumothorax occurred in 20.2% (n=60) of patients undergoing TBLC; no severe bleeding was reported for either TBLC or SLB.[26] In the indirect comparison by Tomassetti et al, pneumothorax occurred in 32.8% (n=19) of patients undergoing TBLC; no severe bleeding was reported for either TBLC or SLB.[27] The evidence for the comparative studies was judged as 'very low' (downgraded for risk of bias, indirectness and imprecision). In the systematic review on TBLC, overall complication rate was 23.1% (95%CI not reported; based on 31 studies), with summary incidence of pneumothorax of 9.4% (95%CI 6.7-12.5) and summary incidence of moderate-severe bleeding of 14.2% (95%CI 7.9-21.9). In the systematic review on SLB, summary incidence of surgical morbidity was 12.9% (95%CI

9.3-16.9; based on 18 studies).[7, 23] The evidence for the studies on TBLC or SLB only was judged as 'very low' (downgraded for risk of bias).

Costs: These appear to be lower for TBLC compared to SLB, based on two studies reporting on a cost-analysis. Hernández-González et al estimated that the systematic use of TBLC in their clinic (involving 33 patients over a 3-year period) had reduced overall costs up to 59.846 euro, compared to systematically performing SLB.[30] Sharp et al (theoretical cost-analysis) estimated that the systematic use of TBLC (followed by SLB if inconclusive) reduced costs up to 647 pound per patient per year.[7] No evidence grading was performed for this outcome due to limited data.

Justification of the recommendation

Overall certainty of the evidence was considered 'very low' (**Table 7 and 8 in Appendix 7**). Taking the abovementioned results into account, the task force concludes that TBLC adds important information to MDD, which results in increase in diagnostic confidence. Diagnostic yield is likely to be somewhat lower than for SLB, although the extent to which this is the case is unclear, with varying results across studies. Overall adverse event rates are difficult to compare between TBLC and SLB, because populations and definitions of complications varied across studies, and because pneumothorax is not considered a complication for SLB because all patients require chest tube drainage. Taking these considerations into account, the task force put most emphasis on a reduction in serious adverse events (especially mortality) and a shorter period of post-procedural hospitalization for TBLC. Costs are expected to be reduced in TBLC. Data on patient preferences is unavailable, but the three patient representatives who provided input indicated that they assumed that most patients would opt for TBLC as initial diagnostic procedure. The task force is not aware of major issues in health equity, acceptability or feasibility of implementation of TBLC. The use and availability of TBLC have increased rapidly over the past years, and are likely to further do so in the coming years. Among patients recruited in the European IPF registry (eurIPFreg; an internet-based registry, consisting of IPF patients from a range of European centers), SLB was performed in 32% in 2009, versus 8% in 2016, likely due to increased use of TBLC.[31] However, availability varies across countries, and not all patients may have easy access to it. A systematic evaluation of ILD diagnostic practice across 457 centers in 64 countries in 2017 showed that around one third of centers applied TBLC.[32]

Overall, the task force considers the reduction in serious adverse events to outweigh the reduced diagnostic yield, in centers experienced in performing TBLC. Minimum requirements for safe implementation of TBLC should include elements such as the availability of competent TBLC-operators (see PICO question 4), and the ability to safely apply sedation, promptly manage complications and ensure airway protection. Best practice documents, consensus statements and guidelines on standardization of the TBLC-procedure have been published previously.[11-14, 33] In addition, adequate patient selection in an MDD-setting should be ensured. Essential features of an ILD MDD have recently been suggested through an international Delphi survey.[34]

Recommendations for monitoring and future research

For quality assurance, healthcare centers that offer TBLC or SLB are advised to keep track of outcomes such as diagnostic yield and complications. Regarding future research, additional direct comparisons between TBLC and SLB are recommended. Ideally, a large randomized trial is performed. In addition to outcomes related to diagnostic accuracy, adverse events and costs, such studies should focus on long-term patient-important outcomes such as disease control and mortality (based on the diagnosis made by either test and the subsequent treatment initiated).

PICO question 2: In patients with undiagnosed ILD not considered eligible to undergo SLB, does TBLC increase the diagnostic confidence of the multidisciplinary team discussion?

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.

Background

Some patients with ILD have severe respiratory or comorbid disease, and they may not be able to tolerate SLB. Others may have rapidly progressive ILD, and risk of further acceleration may be increased after performing SLB.[35] In these patients, TBLC could provide a less invasive alternative to obtain a histopathological diagnosis.

Evidence summary

GRADE tables and evidence-to-decision tables for PICO question 2 are provided in **Appendix 8**. Although it is likely that several of the studies evaluating TBLC included in PICO question 1 may have also selected patients that were not considered eligible to undergo SLB, this information was rarely explicitly reported. Overall, only two studies were identified that explicitly reported on outcomes in such patients. The only outcomes that could be evaluated were diagnostic yield and adverse events.

Diagnostic yield for a histopathological diagnosis (**Table 1 in Appendix 8**): This is high, based on one non-comparative study. Matta et al reported on 17 critically ill patients with ILD and acute hypoxemic respiratory failure, who were considered poor candidates for SLB, or refused this.[36] Twelve interventions were performed at bedside in the intensive care unit (ICU). Overall, diagnostic yield was 88.2% (95%CI 64-99) and histopathological data led to management changes in 88.2% (95%CI 64-99). However, diagnostic yield may be considered inflated by a subset of patients with nonspecific patterns inconsistent with their profound respiratory failure, and it is unclear whether the reported management changes actually influenced clinical outcomes. The evidence was judged as 'very low' (downgraded for risk of bias, indirectness and imprecision).

Adverse events (**Table 1 in Appendix 8**): These vary, based on two non-comparative studies. This was probably due to considerable differences in disease severity across included patients. In the same study by Matta et al, pneumothorax occurred in 35.3% (n=6) and moderate bleeding in 5.9% (n=1), with 30-day ICU mortality of 47.1% (n=8; although, according to the authors, none directly attributable to TBLC). Bondue et al compared adverse events of TBLC in 38 patients with undiagnosed ILD at high risk of SLB (defined as age ≥75-years, body mass index (BMI) ≥35, systolic pulmonary artery pressure (sPAP) by echocardiography ≥45 mmHg, forced vital capacity (FVC) <50%, diffusing capacity for carbon monoxide (DLCO) <30%, and/or significant cardiac comorbidities with reduced heart ejection fraction) with 58 patients at low risk.[37] Numbers of bleeding, pneumothorax, mortality and hospital stay were equal between both groups (see narrative question 2). The evidence was judged as 'very low' (downgraded for inconsistency and imprecision).

Justification of the recommendation

Evidence is mostly lacking for answering this PICO question, and overall certainty of the evidence is 'very low' (**Table 1 and 2 in Appendix 8**). The task force assumes that diagnostic yield is likely to be similar as for patients considered eligible to undergo SLB (PICO question 1), but there are no data to confirm this. Regarding adverse events, 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. Limited evidence suggests safety in high-risk patients described in the study by Bondue et al.[37] However, the risk of accelerating disease in patients who are critically ill or have rapidly progressive ILD, such as in the study by Matta et al,[36] may be unacceptably high. If obtaining histopathological data is indicated, TBLC is suggested, but the advantages of potentially increasing diagnostic certainty against the disadvantages of potential adverse events should be carefully weighed in each patient.

Recommendations for monitoring and future research

Healthcare centers that offer TBLC in patients not considered eligible to undergo SLB are advised to collect data on outcomes such as diagnostic yield, complications and patient-important outcomes. Regarding future research, prospective studies evaluating these outcomes of TBLC in high-risk patients not considered eligible to undergo SLB could be initiated in experienced centers, clarifying which patients are at relatively low risk.

PICO question 3: In patients with undiagnosed ILD and a non-informative TBLC, is step-up SLB or second TBLC a valid add-on test?

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.

Background

As illustrated in PICO question 1, performing TBLC does not always result in a high confidence diagnosis at MDD, and it may be decided that additional efforts to obtain a histopathological diagnosis are warranted. Step-up SLB or a second TBLC could serve as add-on test in these patients, if diagnostic yield or confidence is sufficiently improved, and if the number of adverse events is not unacceptably high.

Evidence summary

Evidence summary tables, results from study quality assessment, GRADE tables and evidence-to-decision tables for PICO question 3 are provided in **Appendix 9**. No studies were identified that directly compared outcomes of step-up SLB versus second TBLC (either by randomizing patients, or by performing both tests in each patient) in patients with undiagnosed ILD and a non-informative initial TBLC. Also no systematic reviews were found in this specific patient population. Overall, we identified 26 studies that reported on at least one patient with a non-informative initial TBLC and subsequent step-up SLB, and two studies in which at least one patient had second TBLC. Risk of bias was high in the majority of studies, mainly due to retrospective, non-consecutive inclusion of patients (**Table 1 in Appendix 9**). The outcomes that could be evaluated were diagnostic yield, diagnostic confidence and adverse events.

Diagnostic yield for a histopathological diagnosis (**Table 2 and 3 in Appendix 9**): For step-up SLB, this is high, based on random-effects meta-analysis of 26 studies (188 patients), with a summary estimate of diagnostic yield of 92% (95%CI 82-96; **Figure 1a in Appendix 9**). However, besides the high risk of bias, it should be noted that only five studies included more than ten patients; when only including these five studies in the meta-analysis, results are similar with a summary diagnostic yield of 91% (95%CI 79-97; **Figure 1b in Appendix 9**). The evidence for step-up SLB was judged as 'very low' (downgraded for risk of bias and indirectness). For second TBLC, evidence on diagnostic yield is limited: this was 100% (95%CI 39.8-100) in one study (based on only four patients),[38] and 62.5% (95%CI 24.5-91.5) in another (based on eight patients).[39] The evidence for second TBLC was judged as 'very low' (downgraded for risk of bias, indirectness and imprecision).

Diagnostic confidence (**Table 2 and 3 in Appendix 9**): For step-up SLB, this seems to increase, based on two studies that explicitly aimed to prospectively evaluate the added value of performing step-up SLB after a non-informative TBLC. [40, 41] Hagmeyer et al evaluated a diagnostic algorithm, proposing TBLC as initial diagnostic, with SLB as optional step-up procedure when findings remained inconclusive.[40] Among 61 patients, a confident diagnosis was reached in MDD after TBLC in 75.4% (n=46). In the remaining 15 cases, step-up SLB was recommended, which was performed in 13, and a conclusive clinical diagnosis could be achieved in 92.3% (n=12) of them (change in histopathological diagnosis: n=3; histopathological diagnosis confirmed with increased confidence leading to increased MDD confidence: n=5; histopathological diagnosis confirmed with same confidence leading to revision of initial MDD working diagnosis: n=4). Bondue et al evaluated a diagnostic algorithm in which patients with ILD initially underwent TBLC, followed by SLB in case of an uncertain histopathological diagnosis or a non-specific interstitial pneumonia (NSIP) pattern after initial TBLC, hypothesizing that co-existent UIP pattern could have been missed.[41] Of 81 patients undergoing TBLC, 16.0%

(n= 13) had no histopathological diagnosis, and 19.8% (n=16) had a pattern suggestive of NSIP. Of these, 14 patients had subsequent SLB, showing UIP pattern in 78.6% (n=11), hypersensitivity pneumonitis (HP) pattern in 14.3% (n=2), and NSIP pattern in 7.1% (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. The evidence for step-up SLB was judged as 'very low' (downgraded for risk of bias and imprecision). For second TBLC, no evidence on this was identified.

Adverse events (**Table 2 and 3 in Appendix 9**): For step-up SLB, only four studies (n=13 patients) reported on this, which occurred in 11.8% (prolonged air leak: 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 cardiovascular instability: n=1). The evidence for step-up SLB was judged as 'very low' (downgraded for risk of bias and imprecision). For second TBLC, no evidence on adverse events was identified.

Justification of the recommendation

Overall certainty of the evidence was considered 'very low' (**Table 3 and 4 in Appendix 9**). Based on our meta-analysis of diagnostic yield, it seems that step-up SLB after an initial non-informative TBLC often results in a histopathological diagnosis. Insufficient evidence was obtained to be able to make similar statements for second TBLC. Evidence on adverse events in this subgroup of patients is low, but it is likely that overall complication rates of SLB and TBLC in patients with ILD (PICO question 1) can be extrapolated to patients with a non-informative initial TBLC. No evidence is available on costs. The task force is not aware of major issues in health equity, acceptability of either test, or feasibility of performing a second procedure. The patient representatives who provided input indicated that it is their opinion that, if initial TBLC is non-informative, most patients would opt for step-up SLB rather than second TBLC as subsequent diagnostic. In general, the task force believes that the potential disadvantages (adverse events and costs) are outweighed by the need to obtain a histopathological diagnosis, if MDD judges that this is indicated. Therefore, the balance is probably in favor of performing an additional test. Yet, this should be decided upon on a case-by-case level, taking into account factors such as (relative) contra-indications (e.g. severe lung function or cardiac impairment) to undergo additional testing.

Recommendations for monitoring and future research

Healthcare centers that offer step-up SLB or second TBLC after a non-informative initial TBLC are advised to collect data on outcomes such as diagnostic yield and complications. Regarding future research, prospective studies should be performed, evaluating the added value (in terms of diagnostic yield, adverse events and costs) of performing step-up SLB or second TBLC. This can be single-arm studies (i.e. step-up SLB or second TBLC only), or two-arm studies (ideally a randomized trial) in which both tests are compared.

PICO question 4: Is formal training in TBLC recommended to optimize diagnostic yield and minimize adverse events in patients with undiagnosed ILD?

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.

Background

DiBardino et al reported that the introduction of TBLC at a large academic medical center in the United States was linked to a high rate of complications.[42] It has previously been demonstrated in bronchoscopy and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) that formal training, often using simulators, can shorten learning curves and assure safe and efficient procedures.[43-45] Similar formal training may increase diagnostic yield and reduce adverse events in TBLC.

Evidence summary

Results from study quality assessment, GRADE tables, and evidence-to-decision tables for PICO question 4 are provided in **Appendix 10**. Studies directly addressing the PICO question were not identified, but three studies were found that evaluated outcomes in early versus late procedures, which was considered as a surrogate for operator experience. Of these, one study reported cumulated sum (CUSUM) scores for some of the prioritized outcomes.[46] However, as these scores were not comprehensible and raw data regarding the outcomes were not published, the task force decided to exclude the study from the analyses. The remaining two studies were included.[47, 48] Risk of bias was high or unclear in both of them (**Table 1 in Appendix 10**). The outcomes that could be evaluated were diagnostic yield (including surrogate outcomes sample length and sample area) and adverse events.

Diagnostic yield for a histopathological diagnosis, sample length and sample area (**Table 2 in Appendix 10**): This seems to be positively associated with operator experience, based on one study. Almeida et al reported a diagnostic yield of 74.0% in the first 50 TBLC-procedures performed, versus 90.0% in the subsequent 50 procedures (p=0.04).[47] Furthermore, sample area and sample length significantly increased with increasing operator experience. The evidence for these outcomes was judged as 'very low' (downgraded for risk of bias and indirectness).

Adverse events (**Table 2 in Appendix 10**): This seems to reduce in late versus early procedures, based on two studies. Almeida et al reported pneumothoraxes in 24.0% (n=12) in the first 50 TBLC-procedures performed, and 12.0% (n=6) in the subsequent 50 procedures (p=0.12).[47] Kronborg-White et al reported pneumothoraxes in 30.0% (n=6) in the first 20 TBLC-procedures, and in 22.2% (n=4) in the subsequent 18 procedures (p=0.59).[48] Data on bleeding was limited to one study: Almeida et al reported bleeding events in 2.0% (n=1) versus 4.0% (n=2) in early versus late procedures (p=0.56). The evidence for these outcomes was judged as 'very low' (downgraded for risk of bias, indirectness and imprecision).

Justification of the recommendation

Overall certainty of the evidence was considered 'very low' (**Table 2 and 3 in Appendix 10**). The task force considers training important to achieve operator competency, as diagnostic yield increases and adverse events decrease with experience. Introducing TBLC in less experienced centers may result in higher rates of complications.[42] For other invasive procedures, it has been shown that formal training programs can increase operator competency.[43-45] However, formal training in TBLC to shorten the learning curve and improve procedure outcomes in suspected ILD has not yet been evaluated. None of the identified studies assessed learning curves between bronchoscopists that received formal training versus those that did not. The included studies could not deliver definite answers about desirable and undesirable effects, the required resources or equity. Comparisons could only be made between earlier and later procedures, but none of them described (1) the bronchoscopists' baseline experience regarding TBLC or other invasive procedures, or (2) the kind of training the bronchoscopists had received before and during the study.

Recommendations for monitoring and future research

The task force believes that a certain level of training is needed to perform TBLC in a standardized, safe, and effective way. If implemented, the impact of formal TBLC training programs must be monitored closely. It is strongly recommended that studies evaluating the impact of formal training programs in TBLC are designed and conducted. Firstly, formal training programs must be defined and developed. Secondly, it is recommended that direct comparisons of formal training and apprentice-based training on the prioritized outcomes are performed. This can be done either by performing a randomized trial, or by performing observational studies which include bronchoscopists undergoing different types of training.

Narrative question 1: Are there specific HRCT findings which would lead to TBLC as the first choice for biopsy?

Evidence summary

The task force aimed to identify studies that evaluated the performance and safety of TBLC in (subgroups of) patients with specific HRCT findings (e.g. areas with increased lung attenuation, areas with decreased lung attenuation, nodular and micronodular patterns, centrilobular distribution, random distribution, or reticular pattern). However, no such studies were identified. It is recommended that prospective studies are performed, evaluating diagnostic yield and adverse events of TBLC in patients with specific HRCT findings, compared to other methods to obtain histopathological data (e.g. TBLB with forceps and SLB).

Narrative question 2: What are the procedural risks of TBLC in patients with undiagnosed ILD??

Background

Procedural adverse events are frequent in TBLC, although most are minor (see PICO question 1). The most frequent adverse events are pneumothorax and mild bleeding. Serious adverse events, such as major bleeding, respiratory failure, exacerbation of ILD or mortality, are uncommon in the reported literature. Several previous studies evaluated predictors of adverse events. Aburto et al analyzed 257 TBLC procedures, with complications

in 15.2%, and 5.4% requiring hospital admission on the day of the procedure.[49] Variables significantly associated with hospital admission were modified Medical Research Council (MRC) dyspnea score ≥2, FVC <50%, and Charlson Comorbidity index score ≥2. To minimize adverse events, it is useful to evaluate which groups of patients are at particularly high procedural risk, so that this risk can be weighed against the added value of increasing diagnostic confidence.

Evidence summary

Evidence summary tables for narrative question 2 are provided in **Appendix 11**. The task force aimed to identify which subgroups of patients are at higher procedural risk, specifically focusing on those with lung function impairment (FVC <50%, DLCO <35%), pulmonary hypertension (sPAPs >40 mmHg), advancing age (>65 years), acute exacerbation of ILD (respiratory failure or rapid worsening), major comorbidities, or increased bleeding risk. Two types of studies were selected: (1) those evaluating adverse events of TBLC in patients with ILD at high procedural risk only (n=3 studies identified; **Table 1 in Appendix 11**),[36, 38, 50] and (2) those comparing adverse events in patients at high versus low procedural risk (n=7 studies identified; **Table 2 in Appendix 11**).[37, 39, 51-55] Pooling of data was not performed due to heterogeneity in study populations and reported outcomes.

Overall high procedural risk: Bondue et al compared adverse events of TBLC in 38 patients with ILD 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 with reduced heart ejection fraction) with 58 patients at low risk with equal numbers of moderate bleeding (28.9% (n=11) versus 29.3% (n=17); p=0.969), severe bleeding (2.6% (n=1) versus 5.2% (n=3); p=0.542), pneumothorax (13.2% (n=5) versus 20.7% (n=12); p=0.419), mortality (2.6% (n=1) versus 0% (n=0)), and median hospital stay (1 day versus 1 day; p=0.675).[37]

Lung function impairment: Three studies reported on adverse events in patients with lung function impairment, and one study compared adverse events in patients with more and less lung function impairment. Matta et al included 17 critically ill patients with acute hypoxemic respiratory failure, in whom pneumothorax occurred in 35.3% (n=6), moderate hemorrhage in 5.9% (n=1), and 8-day mortality (although not directly related to TBLC) in 47.1% (n=8).[36] Ravaglia et al reported on adverse events in a subgroup of 31 patients with FVC <50% and/or DLCO <35%; pneumothorax occurred in 19.4% (n=6), mild-moderate bleeding in 19.4% (n=6), and empyema in 3.2% (n=1).[38] She et al reported on TBLC in a subgroup of 15 patients with DLCO <40%, and identified that no increased rate of complications occurred in these patients, although no further details were provided.[50] Finally, Bondue et al compared a subgroup of 15 patients with severe pulmonary impairment (FVC <50% or DLCO <30%) versus 58 low risk patients, reporting 6.7% (n=1) versus 20.7% (n=12) pneumothoraxes (p=0.316), respectively, and no differences in bleeding.[37]

Hospitalized patients: Three studies reported on adverse events in patients that were already hospitalized versus non-hospitalized patients, although reasons for hospitalization – and if these were related to ILD – were

unclear in two of these. Cooley et al compared adverse events in 17 hospitalized patients (n=15 due to respiratory failure, n=1 due to fatigue, and n=1 due to kidney injury) versus 142 outpatients.[51] Pneumothorax occurred in 23.5% (n=4) versus 9.9% (n=14; p=0.11), respectively, with persistent air leak in 5.9% (n=1) and 0.7% (n=1; p=0.20). ICU transfer within 48 hours after the procedure occurred in 11.8% (n=2) versus 2.1% (n=3; p=0.09), and 30-day mortality in 5.9% (n=1) and 1.4% (n=2; p=0.29). Kropski et al compared adverse events in four hospitalized patients (reason for hospitalization not reported) versus 33 outpatients, but no pneumothoraxes or bleeding occurred. One (25.0%) of the hospitalized patients required ICU admission due to post-procedural hypoxemia, and one (3.0%) of the outpatients required hospitalization due to hemoptysis.[54] Finally, Pannu et al compared 30-day mortality in eight hospitalized patients (reason for hospitalization not reported) versus 189 outpatients, identifying that this was 25.0% (n=2) and 1.1% (n=2), respectively.[55]

Age: Hetzel et al compared moderate-severe bleeding rates in 189 patients aged ≥65 years versus 160 patients <65 years, identifying that this occurred in 20.1% (n=38) and 10.6% (n=17; p=0.018), respectively.[53]

BMI: Bondue et al compared a subgroup of 15 patients with BMI ≥35 versus 58 low risk patients, reporting pneumothoraxes in 6.7% (n=1) versus 20.7% (n=12; p=0.206), respectively, and no differences in bleeding.[37]

Anticoagulants: Hetzel et al compared moderate-severe bleeding rates in 51 patients with aspirin use versus 303 patients without aspirin use, identifying that this occurred in 25.5% (n=13) and 14.9% (n=45; p=0.067), respectively.[53] Kronborg-White et al did the same in 86 patients with any anticoagulant (n=64 acetyl salicylic acid; n=13 platelet inhibitors; n=15 direct oral anticoagulants; n=18 vitamin K antagonists; all patients ceased individual anticoagulants before the procedure according to national guidelines) versus 164 patients without anticoagulants.[39] Moderate-severe bleeding occurred in 22.1% (n=19) versus 22.0% (n=36; p=0.98).

Summary and recommendations for future research

Evidence regarding adverse events from TBLC in patients at high procedural risk is limited, and most of the abovementioned studies only included a small number of patients, resulting in limited power and wide confidence intervals. Data from high-volume centers suggests that TBLC may be performed relatively safely in patients with advancing age, elevated BMI, cardiac impairment or (non-acute) pulmonary impairment (even at FVC <50% or DLCO <30%). The risk of serious adverse events seems to be particularly high in hospitalized patients with acute hypoxemic respiratory failure or rapidly progressing ILD. Despite some reassurances from the literature, a conservative approach for patient selection is recommended for centers with less experience in real world practice. Future prospective studies performed in expert centers are needed to assess in which high-risk patients TBLC can be performed relatively safely.

DISCUSSION

This ERS guideline aimed to establish evidence-based recommendations for the use of TBLC in patients with undiagnosed ILD in clinical practice. The guideline was developed in line with GRADE principles, and every guideline question was informed by a thorough systematic review of the published literature.

Several potential limitations should be taken into account. Although a considerable number of clinical experts were involved in the development of the guideline, these mostly included pulmonologists with expertise in TBLC, and only one pathologist and one radiologist. In future updates, we will consider expanding the task force, to further ensure that all clinical stakeholders involved in the diagnostic process of ILD are sufficiently represented. For several PICO questions, TBLC and SLB were compared. In this comparison, we focused on the a priori defined and prioritized outcomes (**Appendix 4**), and these were carefully weighed in the evidence-to-decision process to arrive at a final recommendation. However, whether or not a test is considered a 'valid replacement test' (PICO question 1) or a 'valid add-on test' (PICO question 4) may depend on many factors, including diagnostic yield, adverse events, downstream consequences of test results, prevalence and costs,[56] and others may weigh the relative importance of each outcome differently. Although many studies on TBLC and SLB in patients with ILD have been published, the number of included studies was low for most of the guideline questions. In addition, certainty of the evidence was 'very low' for most outcomes. The task force formulated recommendations for future research for each guideline question, which may form the basis for studies in upcoming years.

Taking into account the evidence obtained in PICO questions 1 and 3, the task force believes that a step-up strategy is in most situations preferred (**Figure 1**): patients would initially undergo TBLC (at reduced risk of severe adverse events, days of hospitalization and costs), and if insufficiently informative, this would be followed by SLB. This diagnostic approach was also preferred by the three patient representatives who provided input. The task force acknowledges that the recommendations apply to centers that are experienced in performing TBLC. Furthermore, the spectrum of potential patients with ILD (with regard to severity of underlying illness, extent of comorbid disease, level of diagnostic certainty from clinical, laboratory and radiological data, and importance of obtaining a histopathological diagnosis) is broad in the clinical setting. As it is impossible to formulate recommendations that equally apply to every different situation, the advantages and disadvantages of performing invasive testing should be carefully weighed on a case-by-case level in each individual patient.

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CONFLICTS OF INTEREST (alphabetical)

-Jouke T. Annema has nothing to declare.

-Juliette Camuset has nothing to declare.

-Thomas V. Colby has nothing to declare.

-Sara Colella has nothing to declare.

-Markus Fally has nothing to declare.

-Lars Hagmeyer has received honoraria for lectures and presentations from Boehringer Ingelheim and Roche, and participated in advisory boards for Boehringer Ingelheim and Roche.

-Juergen Hetzel has received honoraria for lectures and presentations from Erbe and GlaxoSmithKline, and research support from Boehringer Ingelheim and AstraZeneca.

-Daniël A. Korevaar has nothing to declare.

-Fabien Maldonado has nothing to declare.

-Antonio Morais has received honaria for presentations from Boehringer Ingelheim, Roche, Pfizer, AstraZeneca and Sanofi, and research grants from Roche, Boehringer Ingelheim and GlaxoSmithKline.

-Venerino Poletti has received honoraria for lectures and presentations from Boehringer Ingelheim, Roche and Erbe, and participated in advisory boards for Boehringer Ingelheim, Roche and Ambu.

-Claudia Ravaglia has nothing to declare.

-René Spijker has nothing to declare.

-Sara Tomassetti has received honoraria for presentations from Roche and Boehringer Ingelheim.

-Thomy Tonia acts as ERS Methodologist

-Lauren K. Troy has received honoraria for presentations from Boehringer Ingelheim, has been a member of an advisory board for Roche, and has received research support from Erbe.

-Johny A. Verschakelen has nothing to declare.

-Athol U. Wells has received personal fees from Roche and Boehringer Ingelheim.

-The patient representatives have nothing to declare.

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APPENDICES

TABLES

Table 1: Guideline questions and recommendations.

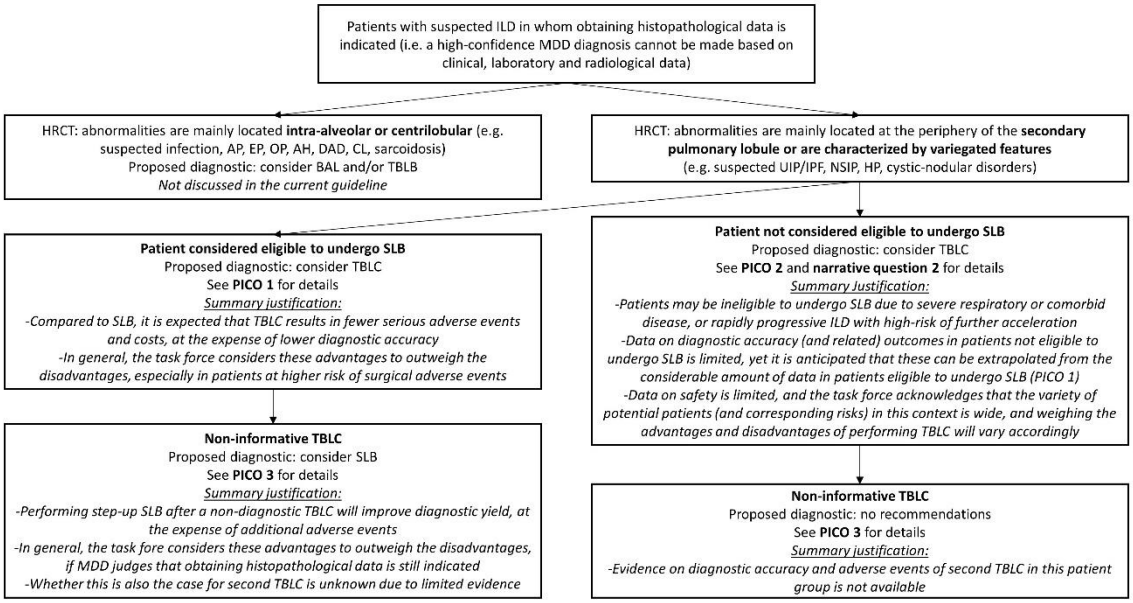
PICO question 1	***Question***: In patients with undiagnosed ILD considered eligible to undergo SLB, is TBLC a valid replacement test? ***Recommendation***: For patients with undiagnosed ILD considered eligible to undergo SLB, the task force suggests performing TBLC if obtaining histopathological data is indicated (conditional recommendation for the intervention, 'very low' certainty of evidence). Remark: this recommendation applies to centers experienced in performing TBLC.
PICO question 2	***Question***: In patients with undiagnosed ILD not considered eligible to undergo SLB, does TBLC increase the diagnostic confidence of the multidisciplinary team discussion? ***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.
PICO question 3	***Question***: In patients with undiagnosed ILD and a non-informative TBLC, is step-up SLB or second TBLC a valid add-on test? ***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.
PICO question 4	***Question***: Is formal training in TBLC recommended to optimize yield and minimize adverse events in patients with undiagnosed ILD? ***Recomendation***: 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.
Narrative question 1	***Question***: Are there specific HRCT findings which would lead to TBLC as the first choice for biopsy?
Narrative question 2	***Question***: What are the procedural risks of TBLC in patients with undiagnosed ILD?

Legend: Detailed questions are provided in Appendix 1.

Abbreviations: HRCT = high-resolution computed tomography. ILD = interstitial lung disease. SLB = surgical lung biopsy. TBLC = trans-bronchial lung biopsy.

FIGURES

Figure 1: Proposed diagnostic algorithm in patients with undiagnosed interstitial lung diseases.



Abbreviations: AH = alveolar hemorrhage. AP = alveolar proteinosis. BAL = bronchoalveolar lavage. CL = carcinomatous lymphangitis. DAD = diffuse alveolar damage. EP = eosinophilic pneumonia. HP = hypersensitivity pneumonitis. HRCT = high-resolution computed tomography. ILD = interstitial lung disease. MDD = multi-disciplinary discussion. OP = organizing pneumonia. SLB = surgical lung biopsy. TBLB = transbronchial lung biopsy. TBLC = trans-bronchial lung biopsy. UIP/IPF = usual interstitial pneumonia/idiopathic pulmonary fibrosis.

Appendix 1: Guideline questions

PICO question 1:

In patients with undiagnosed ILD considered eligible to undergo SLB, is TBLC a valid replacement test?

P: patients with undiagnosed ILD considered eligible to undergo SLB

I: index test: adding TLBC (to the MDD)

C: comparator/reference standard: adding SLB (to the MDD), or MDD (without an intervention)

O: outcomes: diagnostic yield, diagnostic accuracy, diagnostic confidence, complication rate, costs, or patient important outcomes (i.e. quality of life, lung function, mortality, exercise tolerance, survival)

PICO question 2:

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

P: patients with undiagnosed ILD considered not eligible to undergo SLB

I: index test: adding TLBC (to the MDD)

C: comparator/reference standard: MDD (without an intervention)

O: outcomes: diagnostic yield, diagnostic accuracy, diagnostic confidence, complication rate, costs, or patient important outcomes (i.e. quality of life, lung function, mortality, exercise tolerance, survival)

PICO question 3:

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

P: patients with undiagnosed ILD who already received TBLC which resulted in inconclusive results

I: index tests: adding a second TBLC (to the MDD), or adding SLB (to the MDD)

C: comparator/reference standard: MDD (without an additional intervention)

O: outcomes: diagnostic yield, diagnostic accuracy, diagnostic confidence, complication rate, costs, or patient important outcomes (i.e. quality of life, lung function, mortality, exercise tolerance, survival)

PICO question 4:

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

P: health-care professionals performing TBLC in patients with suspected ILD

I: specific training in TBLC procedure

C: no specific training in TBLC procedure

O: outcomes: diagnostic yield, diagnostic accuracy, diagnostic confidence, complication rate, costs, or patient important outcomes (i.e. quality of life, lung function, mortality, exercise tolerance, survival)

Narrative question 1:

Are there specific HRCT findings which would lead to TBLC as the first choice for biopsy?

HRCT findings of specific interest:

-Areas with increased lung attenuation (lung consolidation, ground glass opacity other opacities)

-Areas with decreased lung attenuation (oligemia, mosaic oligemia, cysts)

-Nodular and micronodular pattern in a (peri)lymphatic distribution

-Centrilobular distribution including tree in bud pattern

-Random distribution including miliary pattern

-Reticular pattern in a (peri)lymphatic distribution

Narrative question 2:

What are the procedural risks of TBLC in patients with undiagnosed ILD?

Subgroups of specific interest:

-Forced vital capacity <50%

-Diffusing capacity for carbon monoxide <35%

-Systolic pulmonary artery pressure >40 mmHg

-Age >65 years old

-Suspected acute exacerbation (respiratory failure or rapid worsening)

-Major comorbidities

-Major bleeding risk (e.g. use of anticoagulants)

Appendix 2: Search strategy

Background:

Final searches were performed on June 21st 2021, without date restrictions.

Medline (Ovid MEDLINE(R) ALL):

	Search terms	**Results**
1	exp Lung Diseases, Interstitial/ or exp Pulmonary Fibrosis/	77550
2	((interstitial adj3 (disease* or abnormalit* or pneumonia)) or ((pulmonary or lung) adj3 fibrosis) or ILD or IPF or UIP or (Diffuse adj2 lung-disease*)).ti,ab,kf.	46080
3	1 or 2	99446
4	(VATS or (Video adj3 thoracoscop*)).ti,ab,kf.	9501
5	cryo*.ti,ab,kf.	97382
6	((surgic* or open or forceps or transbronch*or thoracoscop*) adj3 biop*).ti,ab,kf.	16327
7	4 or 5 or 6	122723
18	3 and 7	2540

Embase (embase.com):

	Search terms	**Results**
1	'interstitial lung disease'/exp OR 'interstitial lung disease' OR 'lung fibrosis'/exp OR 'lung fibrosis'	138170
2	((interstitial NEAR/3 (disease* OR abnormalit* OR pneumonia)):ti,ab,kw) OR (((pulmonary OR lung) NEAR/3 fibrosis):ti,ab,kw) OR ild:ti,ab,kw OR ipf:ti,ab,kw OR uip:ti,ab,kw OR ((diffuse NEAR/2 'lung disease*'):ti,ab,kw)	75817
3	#1 OR #2	154243
4	vats:ti,ab,kw OR ((video NEAR/3 thoracoscop*):ti,ab,kw)	14171
5	cryo*:ti,ab,kw	130953
6	((surgic* OR open OR forceps OR transbronch* OR thoracoscop*) NEAR/3 biop*):ti,ab,kw	33484
7	#4 OR #5 OR #6	176821
8	#3 AND #7	6283
9	#8 NOT 'conference abstract'/it	4004
10	#9 AND [embase]/lim	3341

Total number of records identified:

Total number of search results in Medline and Embase: 5881

Total number of search results after removal of duplicates: 4325

Appendix 3: Selection criteria for study inclusion

General selection criteria (applying to each guideline question):

Studies were only considered for inclusion if they were performed in human subjects with (suspected) ILD. In case a study corresponded to multiple study reports with overlapping study periods, we included the most recent report. However, if a study corresponded to multiple study reports but each addressed another guideline question or different outcomes within a PICO, all relevant reports were included. Both prospective and retrospective studies were eligible for inclusion. We included both comparative studies (e.g. randomized trials comparing two types of tests, or comparative cross-sectional type studies in which multiple tests were applied and compared in the same group of patients), as well as non-comparative studies (e.g. diagnostic accuracy studies that evaluated the accuracy or yield of only one test). However, in case comparative studies were available for a specific PICO outcome, the non-comparative studies were only used as additional/supportive evidence.

We excluded:

- Case reports and studies including 10 patiënts or less
- Studies reported in languages other than English
- Studies only reported as conference abstract
- Commentaries, editorials and letters not reporting original research data
- Studies in children only
- Studies published before 2000

Specific selection criteria for PICO question 1:

In patients with undiagnosed ILD considered eligible to undergo SLB, is TBLC a valid replacement test?

Studies were included if they compared the diagnostic yield, diagnostic accuracy, diagnostic confidence, complication rate, costs and/or other patient important outcomes of TBLC and SLB in patients with undiagnosed ILD. We included studies in which TBLC and SLB were directly compared, either by applying both tests in the same group of patients (comparative cross-sectional type study), or by randomly assigning a group of patients to undergo TBLC versus SLB (randomized trial). However, we also included studies that evaluated the abovementioned outcomes by performing only TBLC or only SLB, or studies in whom a group of patients undergoing TBLC was compared with a group of patients undergoing SLB, but in whom the tests were not randomly assigned.

Specific selection criteria for PICO question 2:

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

Studies were included if they evaluate the diagnostic yield, diagnostic accuracy, diagnostic confidence, complication rate, costs and/or other patient important outcomes of TBLC in patients with undiagnosed ILD.

We included studies in patients explicitly not eligible to undergo SLB, but excluded studies in which patients were explicitly eligible to undergo SLB, or in whom this information was not explicitly reported. We included comparative studies in which a group of patients was randomly assigned to undergo TBLC versus MDD (without any intervention). However, we also included studies that evaluated the abovementioned outcomes by only performing TBLC in patients ineligible to undergo SLB.

Specific selection criteria for PICO question 3:

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

Studies were included if they evaluated the diagnostic yield, diagnostic accuracy, diagnostic confidence, complication rate, costs and/or other patient important outcomes of TBLC and/or SLB in patients with undiagnosed ILD who have already had a TBLC with inconclusive results. We only included studies in which patients already had a TBLC with inconclusive results, and excluded studies for which this was not the case or unclear. We included studies that evaluated these outcomes by performing only TBLC or only SLB in a group of patients (non-comparative cross-sectional type study), studies that evaluated these outcomes by performing both TBLC and SLB in a group of patients (comparative cross-sectional type study), and studies that randomly assigned a group of patients to undergo TBLC versus SLB or MDD (without intervention) (randomized trial).

Specific selection criteria for PICO question 4:

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

Studies were included if they compared diagnostic yield, diagnostic accuracy, diagnostic confidence, complications rate and/or other patient important outcomes in operators undergoing specific training in the TBLC procedure with those undergoing no specific training. Both randomized and non-randomized comparative studies were eligible for inclusion. We will also include non-comparative studies on learning curves for these outcomes.

Specific selection criteria for narrative question 1:

Are there specific HRCT findings which would lead to TBLC as the first choice for biopsy?

Studies were included if they compared the diagnostic yield, diagnostic accuracy, diagnostic confidence, complication rate, costs and/or other patient important outcomes of TBLC and SLB or conventional forceps TBB in patients with undiagnosed ILD with the specific HRCT findings described in the PICO question. We included studies both in patients considered eligible and not considered eligible to undergo SLB. We included studies in which TBLC is directly compared with SLB, conventional forceps or MDD (without any intervention), either by applying two of these tests in the same group of patients (comparative cross-sectional type study), or by randomly assigning a group of patients to undergo TBLC versus SLB, conventional forceps or MDD (without any intervention) (randomized trial). However, we included studies that evaluated the abovementioned outcomes by performing only TBLC in patients with the reported specific HRCT findings.

Specific selection criteria for narrative question 2:

What are the procedural risks of TBLC in patients with undiagnosed ILD?

Studies were included if they evaluated complication or mortality rates of TBLC in patients at high procedural risk (as described in the narrative question; e.g. only patients included with an FVC <50% or age >65 years), or if they compared complication or mortality rates of TBLC in specific subgroups of patients with suspected ILD at higher versus lower procedural risk (e.g. a subgroup of patients with FVC <50% or age >65 years, is compared with a subgroup of patients with FVC ≥50% or age ≤65 years) within a single study. In the narrative question, clear cutoffs for subgroups of specific interest were defined (i.e., FVC <50%, DLCO <35%, PAPs >40 mmHg, or age >65 years-old), but studies using slightly different thresholds were also eligible; roughly a 20% deviation was considered acceptable. We included studies both in patients who were considered eligible and were not considered eligible to undergo SLB. Both studies directly comparing TBLC with SLB, as well as non-comparative studies in which only TBLC was applied (with or without a separate group of patients undergoing SLB) were included, as long as they compared complication rates or mortality rates in these specific subgroups. We excluded studies only reporting on SLB but not TBLC.

Appendix 4: Rating of outcomes

Background:

Twelve task force members participated in the survey. For each PICO, they were asked to rate its importance (from a patient-perspective) a scale from 1 to 9, where 1 corresponds to 'extremely irrelevant' and 9 to 'extremely relevant'. The outcomes per PICO were as follows:

PICO question 1:

In patients with undiagnosed ILD considered eligible to undergo SLB, is TBLC a valid replacement test?

	Average	Final
Diagnostic yield	7.8	Critical
Diagnostic accuracy	7.8	Critical
Diagnostic confidence	7.3	Critical
Complication rate	7.7	Critical
Costs	5.6	Important
Quality of life	6.7	Important
Lung function	6.2	Important
Mortality	8.7	Critical
Exercise tolerance	5.8	Important
Survival	7.0	Critical

PICO question 2:

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

	Average	Final
Diagnostic yield	7.3	Critical
Diagnostic accuracy	7.4	Critical
Diagnostic confidence	7.3	Critical
Complication rate	6.7	Important
Costs	5.5	Important
Quality of life	5.7	Important
Lung function	5.5	Important
Mortality	7.6	Critical
Exercise tolerance	5.7	Important
Survival	7.0	Critical

PICO question 3:

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

	Average	Final
Diagnostic yield	7.8	Critical
Diagnostic accuracy	7.9	Critical
Diagnostic confidence	8.0	Critical
Complication rate	7.2	Critical
Costs	5.8	Important
Quality of life	6.6	Important
Lung function	5.7	Important
Mortality	8.4	Critical
Exercise tolerance	6.0	Important
Survival	8.1	Critical

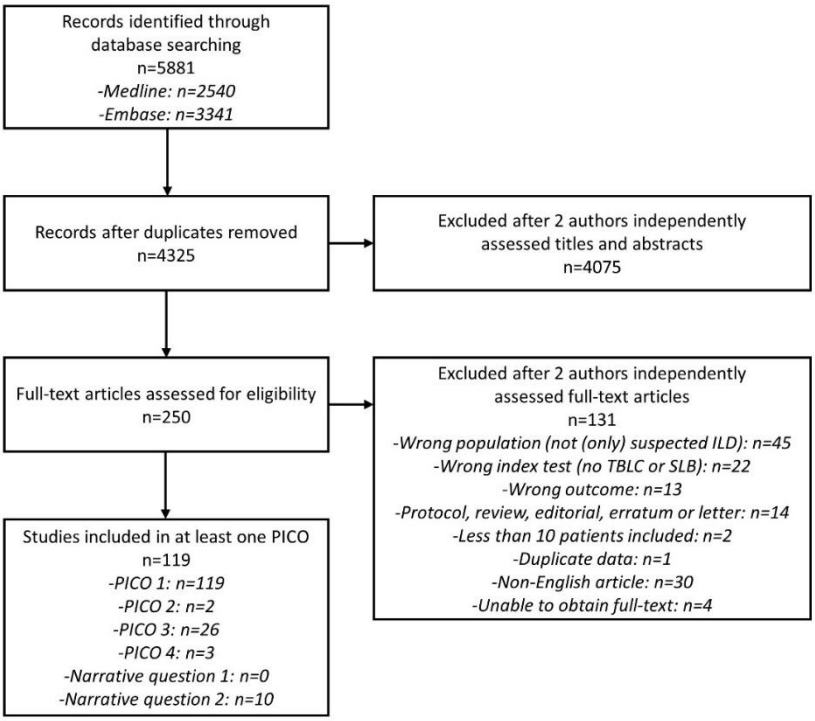
PICO question 4:

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

	Average	Final
Diagnostic yield	7.0	Critical
Diagnostic accuracy	6.7	Important
Diagnostic confidence	6.4	Important
Complication rate	7.9	Critical
Costs	5.2	Important
Quality of life	5.3	Important
Lung function	4.8	Important
Mortality	8.1	Critical
Exercise tolerance	5.0	Important
Survival	6.8	Critical

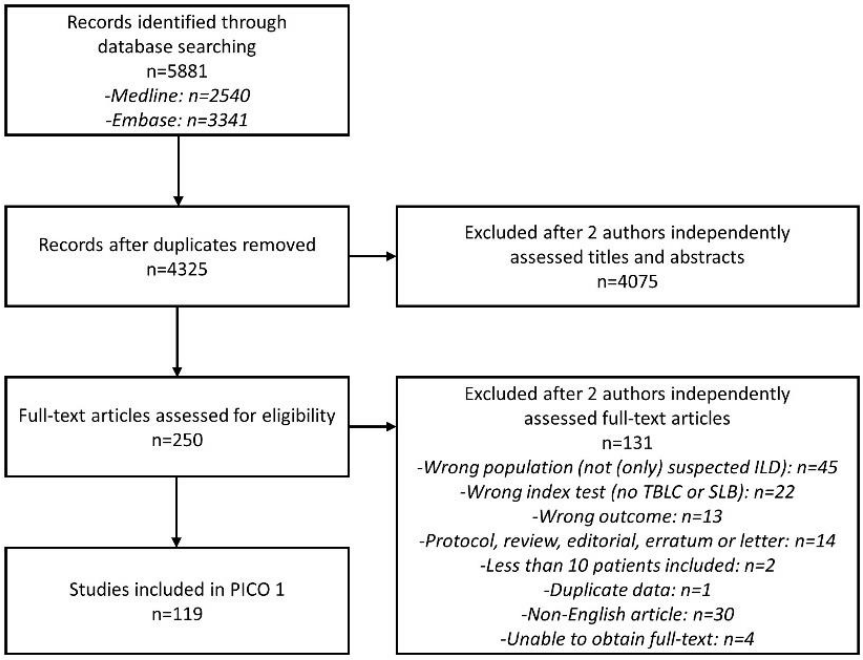
Appendix 5: Included studies per guideline question

Overall flowchart:



Flowchart PICO question 1:

In patients with undiagnosed ILD considered eligible to undergo SLB, is TBLC a valid replacement test?



Final included PICO question 1 (n=119):

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PJC, Ng BJ, Oldmeadow C, Raghu G, Lau EMT, Cryobiopsy versus Open Lung biopsy in the Diagnosis of Interstitial lung disease alliance I. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. Lancet Respir Med 2020: 8(2): 171-181.

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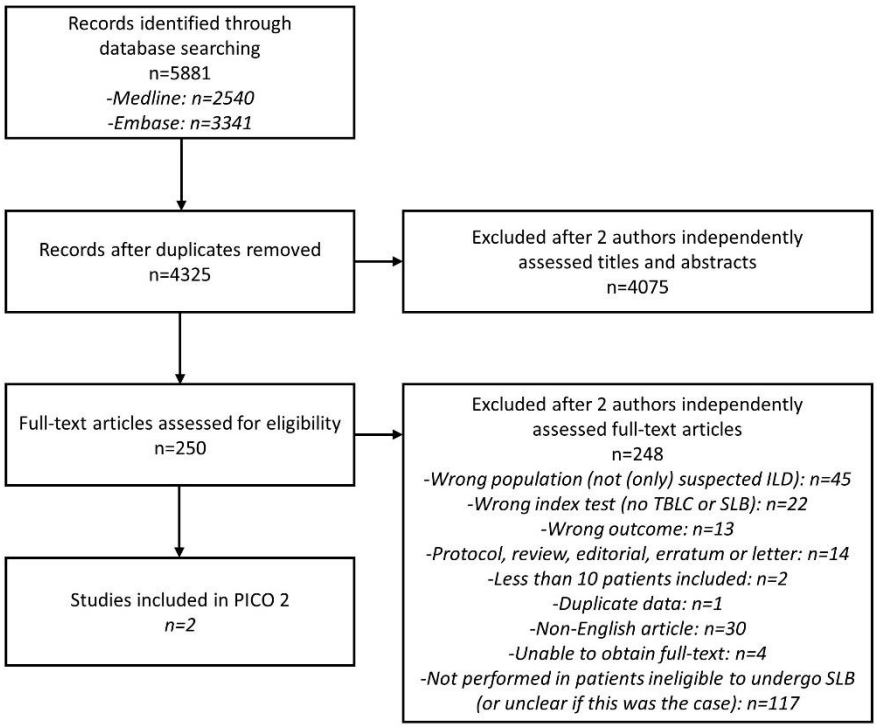
Flowchart PICO question 2:

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



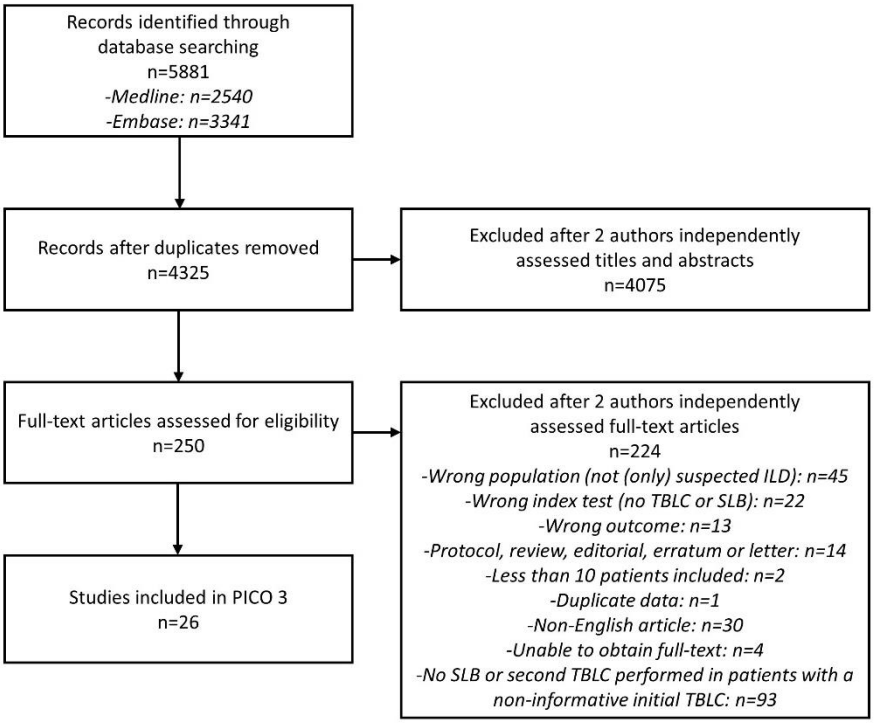
Final included PICO question 2 (n=2):

1. 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 polm 2021: 21(1): 135.

2. 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. Clin Respir J 2021: 18: 18.

Flowchart PICO question 3:

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



Final included PICO question 3 (n=26):

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2. Bango-Alvarez A, Ariza-Prota M, Torres-Rivas H, Fernandez-Fernandez L, Prieto A, Sanchez I, Gil M, Pando-Sandoval A. Transbronchial cryobiopsy in interstitial lung disease: experience in 106 cases - how to do it. ERJ open res 2017: 3(1).
3. Bondue B, Leduc D, Froidure A, Pieters T, Taton O, Heinen V, Alexander P, Hoton D, Dome F, Remmelink M. Usefulness of surgical lung biopsies after cryobiopsies when pathological results are inconclusive or show a pattern suggestive of a nonspecific interstitial pneumonia. Respiratory Research 2020: 21(1): 231.
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5. Cho R, Zamora F, Gibson H, Dincer HE. Transbronchial Lung Cryobiopsy in the Diagnosis of Interstitial Lung Disease: A Retrospective Single-center Experience. J Bronchology Interv Pulmonol 2019: 26(1): 15-21.
6. Fruchter O, Fridel L, El Raouf BA, Abdel-Rahman N, Rosengarten D, Kramer MR. Histological diagnosis of interstitial lung diseases by cryo-transbronchial biopsy. Respirology 2014: 19(5): 683-688.
7. Hagmeyer L, Theegarten D, Wohlschlager J, Hager T, Treml M, Herkenrath SD, Hekmat K, Heldwein M, Randerath WJ. Transbronchial cryobiopsy in fibrosing interstitial lung disease: modifications of the procedure lead to risk reduction. Thorax 2019: 74(7): 711-714.

8. Hagmeyer L, Theegarten D, Wohlschlager J, Treml M, Matthes S, Priegnitz C, Randerath WJ. The role of transbronchial cryobiopsy and surgical lung biopsy in the diagnostic algorithm of interstitial lung disease. Clin Respir J 2016: 10(5): 589-595.

9. Hernandez-Gonzalez F, Lucena CM, Ramirez J, Sanchez M, Jimenez MJ, Xaubet A, Sellares J, Agusti C. Cryobiopsy in the diagnosis of diffuse interstitial lung disease: yield and cost-effectiveness analysis. Archivos de Bronconeumologia 2015: 51(6): 261-267.

10. Hetzel J, Wells AU, Costabel U, Colby TV, Walsh SLF, Verschakelen J, Cavazza A, Tomassetti S, Ravaglia C, Bockeler M, Spengler W, Kreuter M, Eberhardt R, Darwiche K, Torrego A, Pajares V, Muche R, Musterle R, Horger M, Fend F, Warth A, Heusel CP, Piciucchi S, Dubini A, Theegarten D, Franquet T, Lerma E, Poletti V, Hantschel M. Transbronchial cryobiopsy increases diagnostic confidence in interstitial lung disease: a prospective multicentre trial. European Respiratory Journal 2020: 56(6): 12.

11. Koslow M, Edell ES, Midthun DE, Mullon JJ, Kern RM, Nelson DR, Sakata KK, Moua T, Roden AC, Yi ES, Reisenauer JS, Decker PA, Ryu JH. Bronchoscopic Cryobiopsy and Forceps Biopsy for the Diagnostic Evaluation of Diffuse Parenchymal Lung Disease in Clinical Practice. Mayo Clinic Proceedings Innovations, Quality & Outcomes 2020: 4(5): 565-574.

12. Kronborg-White S, Sritharan SS, Madsen LB, Folkersen B, Voldby N, Poletti V, Rasmussen TR, Bendstrup E. Integration of cryobiopsies for interstitial lung disease diagnosis is a valid and safe diagnostic strategy-experiences based on 250 biopsy procedures. Journal of Thoracic Disease 2021: 13(3): 1455-1465.

13. Kropski JA, Pritchett JM, Mason WR, Sivarajan L, Gleaves LA, Johnson JE, Lancaster LH, Lawson WE, Blackwell TS, Steele MP, Loyd JE, Rickman OB. Bronchoscopic cryobiopsy for the diagnosis of diffuse parenchymal lung disease. PLoS ONE 2013: 8(11): e78674.

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15. Marcoa R, Linhas R, Apolinario D, Campainha S, Oliveira A, Nogueira C, Loureiro A, Almeida J, Costa F, Wen X, Neves S. Diagnostic yield of transbronchial lung cryobiopsy in interstitial lung diseases. Rev Port Pneumol 2017: 23(5): 296-298.

16. O'Mahony AM, Burke L, Cavazza A, Maher MM, Kennedy MP, Henry MT. Transbronchial lung cryobiopsy (TBLC) in the diagnosis of interstitial lung disease: experience of first 100 cases performed under conscious sedation with flexible bronchoscope. Irish Journal of Medical Science 2021: 20: 20.

17. Ramaswamy A, Homer R, Killam J, Pisani MA, Murphy TE, Araujo K, Puchalski J. Comparison of Transbronchial and Cryobiopsies in Evaluation of Diffuse Parenchymal Lung Disease. J Bronchology Interv Pulmonol 2016: 23(1): 14-21.

18. Ravaglia C, Wells AU, Tomassetti S, Gurioli C, Gurioli C, Dubini A, Cavazza A, Colby TV, Piciucchi S, Puglisi S, Bosi M, Poletti V. Diagnostic yield and risk/benefit analysis of trans-bronchial lung cryobiopsy in diffuse parenchymal lung diseases: a large cohort of 699 patients. BMC polm 2019: 19(1): 16.

19. Romagnoli M, Colby TV, Berthet JP, Gamez AS, Mallet JP, Serre I, Cancellieri A, Cavazza A, Solovei L, Dell'Amore A, Dolci G, Guerrieri A, Reynaud P, Bommart S, Zompatori M, Dalpiaz G, Nava S, Trisolini R, Suehs

CM, Vachier I, Molinari N, Bourdin A. Poor Concordance between Sequential Transbronchial Lung Cryobiopsy and Surgical Lung Biopsy in the Diagnosis of Diffuse Interstitial Lung Diseases. Am J Respir Crit Care Med 2019: 199(10): 1249-1256.

20. Samitas K, Kolilekas L, Vamvakaris I, Gkogkou C, Filippousis P, Gaga M, Zervas E. Introducing transbronchial cryobiopsies in diagnosing diffuse parenchymal lung diseases in Greece: Implementing training into clinical practice. PLoS ONE 2019: 14(6): e0217554.

21. Shkeiri R, Schneer S, Avarmovich A, Adir Y. Transbronchial Cryobiopsy in Diffuse Parenchymal Lung Diseases in a Community Medical Center. Israel Medical Association Journal: Imaj 2020: 22(12): 781-783.

22. Troy LK, Grainge C, Corte TJ, Williamson JP, Vallely MP, Cooper WA, Mahar A, Myers JL, Lai S, Mulyadi E, Torzillo PJ, Phillips MJ, Jo HE, Webster SE, Lin QT, Rhodes JE, Salamonsen M, Wrobel JP, Harris B, Don G, Wu PJC, Ng BJ, Oldmeadow C, Raghu G, Lau EMT, Cryobiopsy versus Open Lung biopsy in the Diagnosis of Interstitial lung disease alliance I. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. Lancet Respir Med 2020: 8(2): 171-181.

23. Turan D, Ugur Chousein EG, Koc AS, Cortuk M, Yildirim Z, Demirkol B, Ozgul MA, Cinarka H, Akalin N, Yardimci AH, Cetinkaya E. Transbronchial cryobiopsy for diagnosing parenchymal lung diseases: real-life experience from a tertiary referral center. Sarcoidosis Vasc Diffuse Lung Dis 2021: 38(1): e2021004.

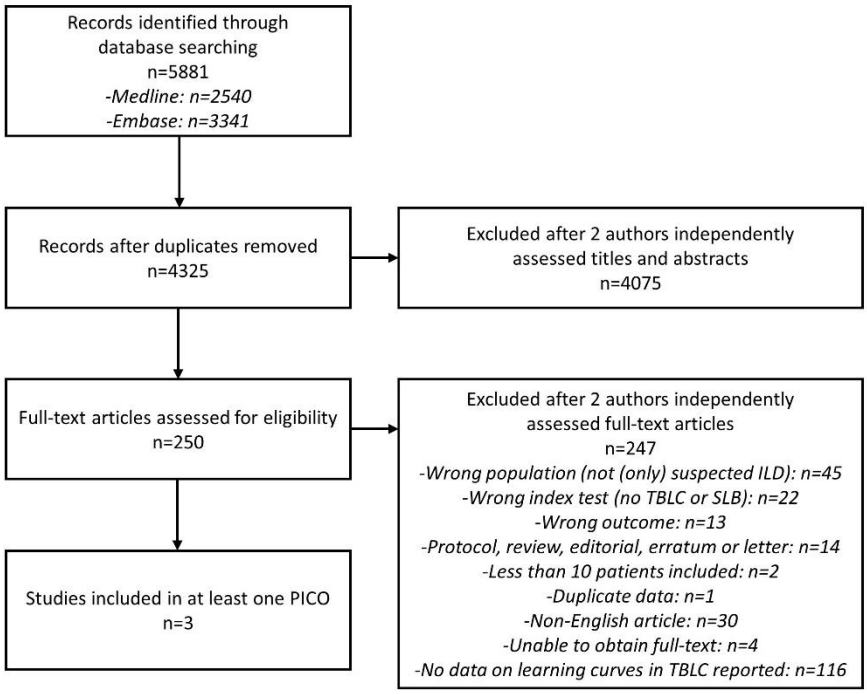
24. Ussavarungsi K, Kern RM, Roden AC, Ryu JH, Edell ES. Transbronchial Cryobiopsy in Diffuse Parenchymal Lung Disease: Retrospective Analysis of 74 Cases. Chest 2017: 151(2): 400-408.

25. Wälscher J, Gro B, Eberhardt R, Heussel CP, Eichinger M, Warth A, Lasitschka F, Herth FJF, Kreuter M. Transbronchial Cryobiopsies for Diagnosing Interstitial Lung Disease: Real-Life Experience from a Tertiary Referral Center for Interstitial Lung Disease. Respiration 2019: 97(4): 348-354.

26. Zaizen Y, Kohashi Y, Kuroda K, Tabata K, Kitamura Y, Hebisawa A, Saito Y, Fukuoka J. Concordance between sequential transbronchial lung cryobiopsy and surgical lung biopsy in patients with diffuse interstitial lung disease. Diagn Pathol 2019: 14(1): 131.

Flowchart PICO question 4:

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



Final included PICO question 4 (n=3):

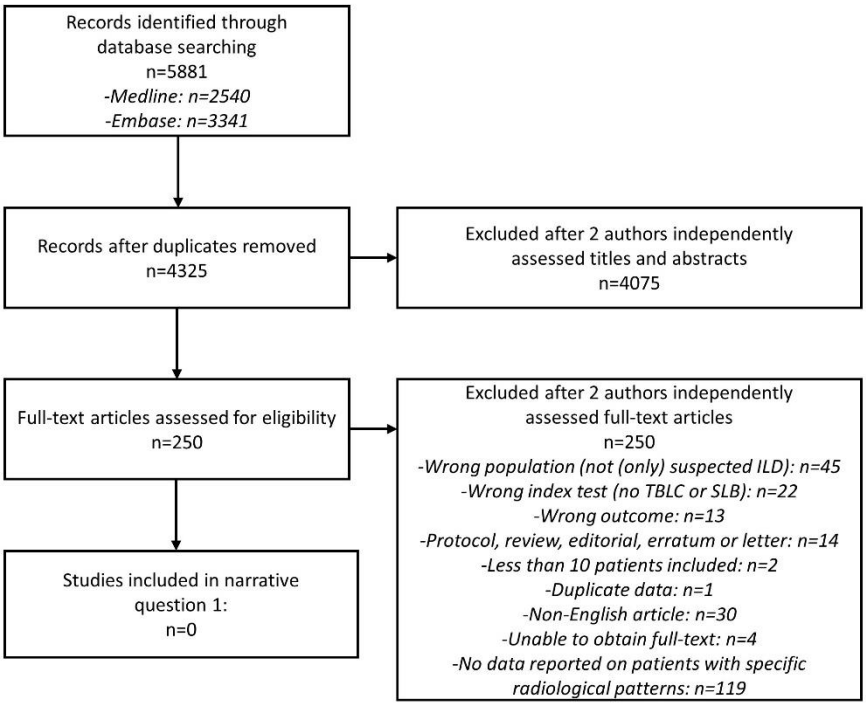
1. Almeida LM, Lima B, Mota PC, Melo N, Magalhaes A, Pereira JM, Moura CS, Guimaraes S, Morais A. Learning curve for transbronchial lung cryobiopsy in diffuse lung disease. Rev Port Pneumol 2017: 22: 22.

2. Davidsen JR, Skov IR, Louw IG, Laursen CB. Implementation of transbronchial lung cryobiopsy in a tertiary referral center for interstitial lung diseases: a cohort study on diagnostic yield, complications, and learning curves. BMC polm 2021: 21(1): 67.

3. Kronborg-White S, Folkersen B, Rasmussen TR, Voldby N, Madsen LB, Rasmussen F, Poletti V, Bendstrup E. Introduction of cryobiopsies in the diagnostics of interstitial lung diseases - experiences in a referral center. Eur Clin Respir J 2017: 4(1): 1274099.

Flowchart narrative question 1:

Are there specific HRCT findings which would lead to TBLC as the first choice for biopsy?

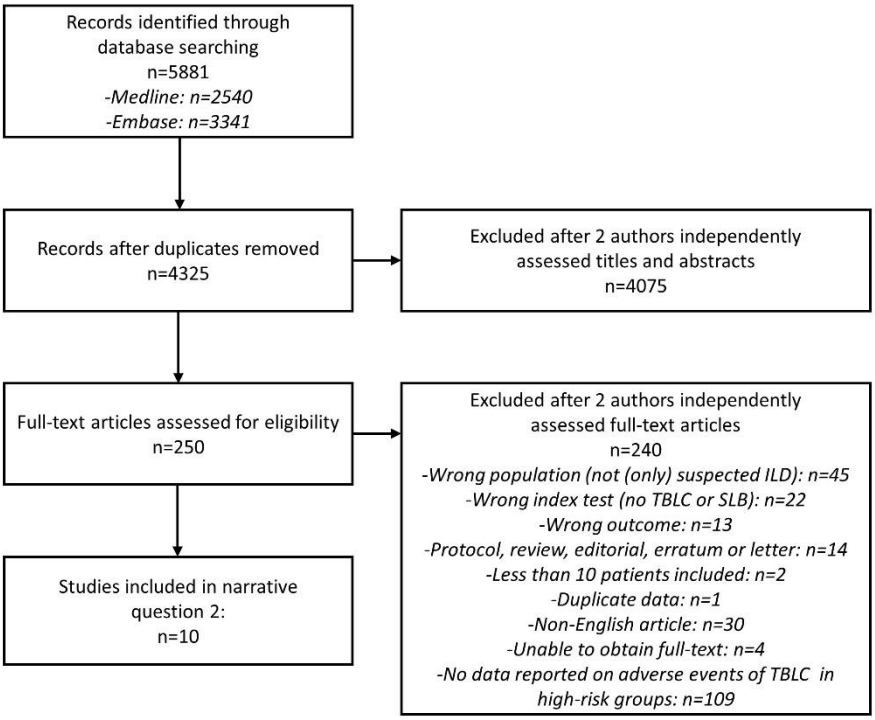


Final included narrative question 1 (n=0):

No studies included.

Flowchart narrative question 2:

What are the procedural risks of TBLC in patients with undiagnosed ILD?



Final included narrative question 2 (n=10):

1. 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 polm 2021: 21(1): 135.

2. Cooley J, Balestra R, Aragaki-Nakahodo AA, Caudell Stamper DN, Sriprasart T, Swank Z, Baughman RP, Benzaquen S. Safety of performing transbronchial lung cryobiopsy on hospitalized patients with interstitial lung disease. Respir Med 2018: 140: 71-76.

3. Gershman E, Fruchter O, Benjamin F, Nader AR, Rosengarten D, Rusanov V, Fridel L, Kramer MR. Safety of Cryo-Transbronchial Biopsy in Diffuse Lung Diseases: Analysis of Three Hundred Cases. Respiration 2015: 90(1): 40-46.

4. Hetzel J, Eberhardt R, Petermann C, Gesierich W, Darwiche K, Hagmeyer L, Muche R, Kreuter M, Lewis R, Ehab A, Boeckeler M, Haentschel M. Bleeding risk of transbronchial cryobiopsy compared to transbronchial forceps biopsy in interstitial lung disease - a prospective, randomized, multicentre cross-over trial. Respiratory Research 2019: 20(1): 140.

5. Kronborg-White S, Sritharan SS, Madsen LB, Folkersen B, Voldby N, Poletti V, Rasmussen TR, Bendstrup E. Integration of cryobiopsies for interstitial lung disease diagnosis is a valid and safe diagnostic strategy-experiences based on 250 biopsy procedures. Journal of Thoracic Disease 2021: 13(3): 1455-1465.

6. Kropski JA, Pritchett JM, Mason WR, Sivarajan L, Gleaves LA, Johnson JE, Lancaster LH, Lawson WE, Blackwell TS, Steele MP, Loyd JE, Rickman OB. Bronchoscopic cryobiopsy for the diagnosis of diffuse parenchymal lung disease. PLoS ONE 2013: 8(11): e78674.
7. 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. Clin Respir J 2021: 18: 18.
8. Pannu J, Roller LJ, Maldonado F, Lentz RJ, Chen H, Rickman OB. Transbronchial cryobiopsy for diffuse parenchymal lung disease: 30- and 90-day mortality. European Respiratory Journal 2019: 54(4).
9. Ravaglia C, Wells AU, Tomassetti S, Gurioli C, Gurioli C, Dubini A, Cavazza A, Colby TV, Piciucchi S, Puglisi S, Bosi M, Poletti V. Diagnostic yield and risk/benefit analysis of trans-bronchial lung cryobiopsy in diffuse parenchymal lung diseases: a large cohort of 699 patients. BMC polm 2019: 19(1): 16.
10. She S, Steinfort DP, Ing AJ, Williamson JP, Leong P, Irving LB, Jennings BR, Saghaie T. Transbronchial Cryobiopsy in Interstitial Lung Disease: Safety of a Standardized Procedure. J Bronchology Interv Pulmonol 2020: 27(1): 36-41.

Appendix 6: Included studies in PICO question 1, ordered by type of study

Background:

Not all studies fulfilling the inclusion criteria were (directly) considered in the evidence syntheses. Instead, for each outcome, we primarily focused on included studies that directly compared TBLC and SLB in patients with undiagnosed ILD (n=2 studies identified), either by performing both tests in each patient (paired direct comparison), or by randomizing patients to undergo either procedure (unpaired direct comparison). If direct comparisons were not available for a specific outcome, we focused on studies that indirectly compared TBLC and SLB (i.e. a group of patients undergoing TBLC was compared with a group of patients undergoing SLB, without randomization; n=3 studies identified). Finally, in the absence of direct or indirect comparisons for a specific outcome, we focused on non-comparative studies that only evaluated TBLC (n=54 identified) or only evaluated SLB (n=50 identified) in patients with undiagnosed ILD. If available for a specific outcome, we selected a previously published systematic review summarizing non-comparative studies, rather than focusing on individual studies, to avoid duplication of review efforts (n=11 systematic reviews identified). Included studies are reported below. Numbers below add up to 120 instead of 119, because Ravaglia 2016 is both a systematic review and a primary (indirect comparison) study.

Direct comparison of TBLC and SLB (either by applying both tests in the same group of patients (comparative cross-sectional type study), or by randomly assigning a group of patients to undergo TBLC versus SLB (randomized trial)):

(n=2)

- Troy LK, Grainge C, Corte TJ, Williamson JP, Vallely MP, Cooper WA, Mahar A, Myers JL, Lai S, Mulyadi E, Torzillo PJ, Phillips MJ, Jo HE, Webster SE, Lin QT, Rhodes JE, Salamonsen M, Wrobel JP, Harris B, Don G, Wu PJC, Ng BJ, Oldmeadow C, Raghu G, Lau EMT, Cryobiopsy versus Open Lung biopsy in the Diagnosis of Interstitial lung disease alliance I. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. Lancet Respir Med 2020: 8(2): 171-181.
- Romagnoli M, Colby TV, Berthet JP, Gamez AS, Mallet JP, Serre I, Cancellieri A, Cavazza A, Solovei L, Dell'Amore A, Dolci G, Guerrieri A, Reynaud P, Bommart S, Zompatori M, Dalpiaz G, Nava S, Trisolini R, Suehs CM, Vachier I, Molinari N, Bourdin A. Poor Concordance between Sequential Transbronchial Lung Cryobiopsy and Surgical Lung Biopsy in the Diagnosis of Diffuse Interstitial Lung Diseases. Am J Respir Crit Care Med 2019: 199(10): 1249-1256.

Indirect comparisons (studies in whom a group of patients undergoing TBLC was compared with a group of patients undergoing SLB, but in whom the tests were not randomly assigned):

(n=3)

- Ravaglia C, Bonifazi M, Wells AU, Tomassetti S, Gurioli C, Piciucchi S, Dubini A, Tantalocco P, Sanna S, Negri E, Tramacere I, Ventura VA, Cavazza A, Rossi A, Chilosi M, La Vecchia C, Gasparini S, Poletti V. Safety and Diagnostic Yield of Transbronchial Lung Cryobiopsy in Diffuse Parenchymal Lung Diseases: A Comparative Study

versus Video-Assisted Thoracoscopic Lung Biopsy and a Systematic Review of the Literature. Respiration 2016: 91(3): 215-227.

- Tomassetti S, Ravaglia C, Wells AU, Cavazza A, Colby TV, Rossi G, Ley B, Ryu JH, Puglisi S, Arcadu A, Marchi M, Sultani F, Martinello S, Donati L, Gurioli C, Gurioli C, Tantalocco P, Hetzel J, Dubini A, Piciucchi S, Klersy C, Lavorini F, Poletti V. Prognostic value of transbronchial lung cryobiopsy for the multidisciplinary diagnosis of idiopathic pulmonary fibrosis: a retrospective validation study. Lancet Respir Med 2020: 8(8): 786-794.
- Tomassetti S, Wells AU, Costabel U, Cavazza A, Colby TV, Rossi G, Sverzellati N, Carloni A, Carretta E, Buccioli M, Tantalocco P, Ravaglia C, Gurioli C, Dubini A, Piciucchi S, Ryu JH, Poletti V. Bronchoscopic Lung Cryobiopsy Increases Diagnostic Confidence in the Multidisciplinary Diagnosis of Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2016: 193(7): 745-752.

Indirect comparisons (systematic reviews of studies that performed only TBLC or only SLB):

Systematic review or guideline of TBLC:

(n=7)

- Dhooria S, Agarwal R, Sehgal IS, Aggarwal AN, Goyal R, Guleria R, Singhal P, Shah SP, Gupta KB, Koolwal S, Akkaraju J, Annapoorni S, Bal A, Bansal A, Behera D, Chhajed PN, Dhamija A, Dhar R, Garg M, Gopal B, Hibare KR, James P, Jindal A, Jindal SK, Khan A, Kishore N, Koul PA, Kumar A, Kumar R, Lall A, Madan K, Mandal A, Mehta RM, Mohan A, Nangia V, Nath A, Nayar S, Patel D, Pattabhiraman V, Raghupati N, Sarkar PK, Singh V, Sivaramakrishnan M, Srinivasan A, Swarnakar R, Talwar D, Thangakunam B. Bronchoscopic lung cryobiopsy: An Indian association for bronchology position statement. Lung India 2019: 36(1): 48-59.
- Dhooria S, Sehgal IS, Aggarwal AN, Behera D, Agarwal R. Diagnostic Yield and Safety of Cryoprobe Transbronchial Lung Biopsy in Diffuse Parenchymal Lung Diseases: Systematic Review and Meta-Analysis. Respir Care 2016: 61(5): 700-712.
- Ganganah O, Guo SL, Chiniah M, Li YS. Efficacy and safety of cryobiopsy versus forceps biopsy for interstitial lung diseases and lung tumours: A systematic review and meta-analysis. Respirology 2016: 21(5): 834-841.
- Johannson KA, Marcoux VS, Ronksley PE, Ryerson CJ. Diagnostic Yield and Complications of Transbronchial Lung Cryobiopsy for Interstitial Lung Disease. A Systematic Review and Metaanalysis. Ann Am Thorac Soc 2016: 13(10): 1828-1838.
- Maldonado F, Danoff SK, Wells AU, Colby TV, Ryu JH, Liberman M, Wahidi MM, Frazer L, Hetzel J, Rickman OB, Herth FJF, Poletti V, Yarmus LB. Transbronchial Cryobiopsy for the Diagnosis of Interstitial Lung Diseases: CHEST Guideline and Expert Panel Report. Chest 2019: 27: 27.
- Ravaglia C, Bonifazi M, Wells AU, Tomassetti S, Gurioli C, Piciucchi S, Dubini A, Tantalocco P, Sanna S, Negri E, Tramacere I, Ventura VA, Cavazza A, Rossi A, Chilosi M, La Vecchia C, Gasparini S, Poletti V. Safety and Diagnostic Yield of Transbronchial Lung Cryobiopsy in Diffuse Parenchymal Lung Diseases: A Comparative Study versus Video-Assisted Thoracoscopic Lung Biopsy and a Systematic Review of the Literature. Respiration 2016: 91(3): 215-227.

- Sethi J, Ali MS, Mohananey D, Nanchal R, Maldonado F, Musani A. Are Transbronchial Cryobiopsies Ready for Prime Time?: A Systematic Review and Meta-Analysis. J Bronchology Interv Pulmonol 2019: 26(1): 22-32.

Systematic review or guideline of SLB:

(n=1)

- Han Q, Luo Q, Xie JX, Wu LL, Liao LY, Zhang XX, Chen RC. Diagnostic yield and postoperative mortality associated with surgical lung biopsy for evaluation of interstitial lung diseases: A systematic review and meta-analysis. J Thorac Cardiovasc Surg 2015: 149(5): 1394-1401.e1391.

Systematic review or guideline of TBLC and SLB:

(n=3)

- Iftikhar IH, Alghothani L, Sardi A, Berkowitz D, Musani AI. Transbronchial Lung Cryobiopsy and Video-assisted Thoracoscopic Lung Biopsy in the Diagnosis of Diffuse Parenchymal Lung Disease. A Meta-analysis of Diagnostic Test Accuracy. Ann Am Thorac Soc 2017: 14(7): 1197-1211.
- Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, Behr J, Cottin V, Danoff SK, Morell F, Flaherty KR, Wells A, Martinez FJ, Azuma A, Bice TJ, Bouros D, Brown KK, Collard HR, Duggal A, Galvin L, Inoue Y, Gisli Jenkins R, Johkoh T, Kazerooni EA, Kitaichi M, Knight SL, Mansour G, Nicholson AG, Pipavath SNJ, Buendía-Roldán I, Selman M, Travis WD, Walsh S, Wilson KC. Diagnosis of idiopathic pulmonary fibrosis An Official ATS/ERS/JRS/ALAT Clinical practice guideline. American Journal of Respiratory and Critical Care Medicine 2018: 198(5): e44-e68.
- Sharp C, McCabe M, Adamali H, Medford AR. Use of transbronchial cryobiopsy in the diagnosis of interstitial lung disease-a systematic review and cost analysis. Qjm 2017: 110(4): 207-214.

Indirect comparisons (studies that performed only TBLC or only SLB):

Studies performing only TBLC and included in a systematic review:

(n=23)

- Almeida LM, Lima B, Mota PC, Melo N, Magalhaes A, Pereira JM, Moura CS, Guimaraes S, Morais A. Learning curve for transbronchial lung cryobiopsy in diffuse lung disease. Rev Port Pneumol 2017: 22: 22.
- Babiak A, Hetzel J, Krishna G, Fritz P, Moeller P, Balli T, Hetzel M. Transbronchial cryobiopsy: A new tool for lung biopsies. Respiration 2009: 78(2): 203-208.
- Bango-Alvarez A, Ariza-Prota M, Torres-Rivas H, Fernandez-Fernandez L, Prieto A, Sanchez I, Gil M, Pando-Sandoval A. Transbronchial cryobiopsy in interstitial lung disease: experience in 106 cases - how to do it. ERJ open res 2017: 3(1).
- Bondue B, Pieters T, Alexander P, De Vuyst P, Ruiz Patino M, Hoton D, Remmelink M, Leduc D. Role of Transbronchial Lung Cryobiopsies in Diffuse Parenchymal Lung Diseases: Interest of a Sequential Approach. Pulm Med 2017: 2017: 6794343.

- Cascante JA, Cebollero P, Herrero S, Yague A, Echegoyen A, Elizalde J, Hueto J. Transbronchial Cryobiopsy in Interstitial Lung Disease: Are We on the Right Path? J Bronchology Interv Pulmonol 2016: 23(3): 204-209.
- Casoni GL, Tomassetti S, Cavazza A, Colby TV, Dubini A, Ryu JH, Carretta E, Tantalocco P, Piciucchi S, Ravaglia C, Gurioli C, Romagnoli M, Gurioli C, Chilosi M, Poletti V. Transbronchial lung cryobiopsy in the diagnosis of fibrotic interstitial lung diseases. PLoS ONE 2014: 9(2): e86716.
- Cooley J, Balestra R, Aragaki-Nakahodo AA, Caudell Stamper DN, Sriprasart T, Swank Z, Baughman RP, Benzaquen S. Safety of performing transbronchial lung cryobiopsy on hospitalized patients with interstitial lung disease. Respir Med 2018: 140: 71-76.
- Dhooria S, Mehta RM, Srinivasan A, Madan K, Sehgal IS, Pattabhiraman V, Yadav P, Sivaramakrishnan M, Mohan A, Bal A, Garg M, Agarwal R. The safety and efficacy of different methods for obtaining transbronchial lung cryobiopsy in diffuse lung diseases. Clin Respir J 2018: 12(4): 1711-1720.
- Echevarria-Uraga JJ, Perez-Izquierdo J, Garcia-Garai N, Gomez-Jimenez E, Aramburu-Ojembarrena A, Tena-Tudanca L, Miguelez-Vidales JL, Capelastegui-Saiz A. Usefulness of an angioplasty balloon as selective bronchial blockade device after transbronchial cryobiopsy. Respirology 2016: 21(6): 1094-1099.
- Fruchter O, Fridel L, El Raouf BA, Abdel-Rahman N, Rosengarten D, Kramer MR. Histological diagnosis of interstitial lung diseases by cryo-transbronchial biopsy. Respirology 2014: 19(5): 683-688.
- Gershman E, Fruchter O, Benjamin F, Nader AR, Rosengarten D, Rusanov V, Fridel L, Kramer MR. Safety of Cryo-Transbronchial Biopsy in Diffuse Lung Diseases: Analysis of Three Hundred Cases. Respiration 2015: 90(1): 40-46.
- Griff S, Schonfeld N, Ammenwerth W, Blum TG, Grah C, Bauer TT, Gruning W, Mairinger T, Wurps H. Diagnostic yield of transbronchial cryobiopsy in non-neoplastic lung disease: a retrospective case series. BMC polm 2014: 14: 171.
- Hagmeyer L, Theegarten D, Wohlschlager J, Treml M, Matthes S, Priegnitz C, Randerath WJ. The role of transbronchial cryobiopsy and surgical lung biopsy in the diagnostic algorithm of interstitial lung disease. Clin Respir J 2016: 10(5): 589-595.
- Hernandez-Gonzalez F, Lucena CM, Ramirez J, Sanchez M, Jimenez MJ, Xaubet A, Sellares J, Agusti C. Cryobiopsy in the diagnosis of diffuse interstitial lung disease: yield and cost-effectiveness analysis. Archivos de Bronconeumologia 2015: 51(6): 261-267.
- Kronborg-White S, Folkersen B, Rasmussen TR, Voldby N, Madsen LB, Rasmussen F, Poletti V, Bendstrup E. Introduction of cryobiopsies in the diagnostics of interstitial lung diseases - experiences in a referral center. Eur Clin Respir J 2017: 4(1): 1274099.
- Kropski JA, Pritchett JM, Mason WR, Sivarajan L, Gleaves LA, Johnson JE, Lancaster LH, Lawson WE, Blackwell TS, Steele MP, Loyd JE, Rickman OB. Bronchoscopic cryobiopsy for the diagnosis of diffuse parenchymal lung disease. PLoS ONE 2013: 8(11): e78674.
- Lentz RJ, Taylor TM, Kropski JA, Sandler KL, Johnson JE, Blackwell TS, fdonado F, Rickman OB. Utility of Flexible Bronchoscopic Cryobiopsy for Diagnosis of Diffuse Parenchymal Lung Diseases. J Bronchology Interv Pulmonol 2018: 25(2): 88-96.

- Marcoa R, Linhas R, Apolinario D, Campainha S, Oliveira A, Nogueira C, Loureiro A, Almeida J, Costa F, Wen X, Neves S. Diagnostic yield of transbronchial lung cryobiopsy in interstitial lung diseases. Rev Port Pneumol 2017: 23(5): 296-298.
- Pajares V, Puzo C, Castillo D, Lerma E, Angeles Montero M, Ramos-Barbõn D, Amor-Carro O, De Bernabé AG, Franquet T, Plaza V, Hetzel J, Sanchis J, Torrego A. Diagnostic yield of transbronchial cryobiopsy in interstitial lung disease: A randomized trial. Respirology 2014: 19(6): 900-906.
- Ramaswamy A, Homer R, Killam J, Pisani MA, Murphy TE, Araujo K, Puchalski J. Comparison of Transbronchial and Cryobiopsies in Evaluation of Diffuse Parenchymal Lung Disease. J Bronchology Interv Pulmonol 2016: 23(1): 14-21.
- Ravaglia C, Wells AU, Tomassetti S, Dubini A, Cavazza A, Piciucchi S, Sverzellati N, Gurioli C, Gurioli C, Costabel U, Tantalocco P, Ryu JH, Chilosi M, Poletti V. Transbronchial Lung Cryobiopsy in Diffuse Parenchymal Lung Disease: Comparison between Biopsy from 1 Segment and Biopsy from 2 Segments - Diagnostic Yield and Complications. Respiration 2017: 93(4): 285-292.
- Sriprasart T, Aragaki A, Baughman R, Wikenheiser-Brokamp K, Khanna G, Tanase D, Kirschner M, Benzaquen S. A Single US Center Experience of Transbronchial Lung Cryobiopsy for Diagnosing Interstitial Lung Disease With a 2-Scope Technique. J Bronchology Interv Pulmonol 2017: 24(2): 131-135.
- Ussavarungsi K, Kern RM, Roden AC, Ryu JH, Edell ES. Transbronchial Cryobiopsy in Diffuse Parenchymal Lung Disease: Retrospective Analysis of 74 Cases. Chest 2017: 151(2): 400-408.

Studies performing only TBLC and <u>NOT</u> included in a systematic review:
(n=31)

- Abdelghani R, Thakore S, Kaphle U, Lasky JA, Kheir F. Radial Endobronchial Ultrasound-guided Transbronchial Cryobiopsy. J Bronchology Interv Pulmonol 2019: 26(4): 245-249.
- Aburto M, Pérez- Izquierdo J, Agirre U, Barredo I, Echevarria-Uraga JJ, Armendariz K, García S, Bronte O, Gorordo I, Egurrola M, Aramburu A, España PP, Esteban C. Complications and hospital admission in the following 90 days after lung cryobiopsy performed in interstitial lung disease, M. Aburto, Servicio de Neumología, Hospital Universitario de Galdakao-Usansolo, Barrio Labeaga 46A, Galdakao, Bizkaia, Spain, 2020.
- Bondue B, Leduc D, Froidure A, Pieters T, Taton O, Heinen V, Alexander P, Hoton D, Dome F, Remmelink M. Usefulness of surgical lung biopsies after cryobiopsies when pathological results are inconclusive or show a pattern suggestive of a nonspecific interstitial pneumonia. Respiratory Research 2020: 21(1): 231.
- 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 polm 2021: 21(1): 135.
- Cho R, Zamora F, Gibson H, Dincer HE. Transbronchial Lung Cryobiopsy in the Diagnosis of Interstitial Lung Disease: A Retrospective Single-center Experience. J Bronchology Interv Pulmonol 2019: 26(1): 15-21.
- Cirak AK, Katgi N, Erer OF, Cimen P, Tuksavul FF, Hakoglu B. Diagnostic approach in parenchymal lung diseases: transbronchial lung biopsy or cryobiopsy? Turkish Journal of Medical Sciences 2020: 50(6): 1535-1539.

- Davidsen JR, Skov IR, Louw IG, Laursen CB. Implementation of transbronchial lung cryobiopsy in a tertiary referral center for interstitial lung diseases: a cohort study on diagnostic yield, complications, and learning curves. BMC polm 2021: 21(1): 67.
- Gnass M, Filarecka A, Pankowski J, Soja J, Bugalho A, Szlubowski A. Transbronchial lung cryobiopsy guided by endobronchial ultrasound radial miniprobe in interstitial lung diseases: preliminary results of a prospective study. Pol Arch Intern Med 2018: 128(4): 259-262.
- Hagmeyer L, Theegarten D, Wohlschlager J, Hager T, Treml M, Herkenrath SD, Hekmat K, Heldwein M, Randerath WJ. Transbronchial cryobiopsy in fibrosing interstitial lung disease: modifications of the procedure lead to risk reduction. Thorax 2019: 74(7): 711-714.
- Harari S, Cereda F, Pane F, Cavazza A, Papanikolaou N, Pelosi G, Scarioni M, Uslenghi E, Zompatori M, Caminati A. Lung Cryobiopsy for the Diagnosis of Interstitial Lung Diseases: A Series Contribution to a Debated Procedure. Medicina (B Aires) 2019: 55(9): 19.
- Hetzel J, Eberhardt R, Petermann C, Gesierich W, Darwiche K, Hagmeyer L, Muche R, Kreuter M, Lewis R, Ehab A, Boeckeler M, Haentschel M. Bleeding risk of transbronchial cryobiopsy compared to transbronchial forceps biopsy in interstitial lung disease - a prospective, randomized, multicentre cross-over trial. Respiratory Research 2019: 20(1): 140.
- Hetzel J, Wells AU, Costabel U, Colby TV, Walsh SLF, Verschakelen J, Cavazza A, Tomassetti S, Ravaglia C, Bockeler M, Spengler W, Kreuter M, Eberhardt R, Darwiche K, Torrego A, Pajares V, Muche R, Musterle R, Horger M, Fend F, Warth A, Heusel CP, Piciucchi S, Dubini A, Theegarten D, Franquet T, Lerma E, Poletti V, Hantschel M. Transbronchial cryobiopsy increases diagnostic confidence in interstitial lung disease: a prospective multicentre trial. European Respiratory Journal 2020: 56(6): 12.
- Hussein S, Elhadidy A, Amin H, Tantawy A, Negm M. Transbronchial cryobiopsy as a new tool for lung biopsies in diagnosis of diffuse parenchymal lung diseases, S. Hussein, Department of Pulmonology, Faculty of Medicine, Cairo University, Cairo, Egypt, 2020.
- Ikeda T, Nakao A, Igata F, Kinoshita Y, Kushima H, Matsumoto T, Ishii H, Nabeshima K, Fujita M. Feasibility, utility, and safety of transbronchial cryobiopsy for interstitial lung diseases in Japan. Multidiscip 2021: 16(1): 731.
- Koslow M, Edell ES, Midthun DE, Mullon JJ, Kern RM, Nelson DR, Sakata KK, Moua T, Roden AC, Yi ES, Reisenauer JS, Decker PA, Ryu JH. Bronchoscopic Cryobiopsy and Forceps Biopsy for the Diagnostic Evaluation of Diffuse Parenchymal Lung Disease in Clinical Practice. Mayo Clinic Proceedings Innovations, Quality & Outcomes 2020: 4(5): 565-574.
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- Linhas R, Marcoa R, Oliveira A, Almeida J, Neves S, Campainha S. Transbronchial lung cryobiopsy: Associated complications. Rev Port Pneumol 2017: 23(6): 331-337.

- 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. Clin Respir J 2021: 18: 18.
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Studies performing only SLB and included in a systematic review:

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- Blanco M, Obeso GA, Duran JC, Rivo JE, Garcia-Fontan E, Pena E, Rodriguez M, Albort J, Canizares MA. Surgical lung biopsy for diffuse lung disease. Our experience in the last 15 years. Rev Port Pneumol 2013: 19(2): 59-64.
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Appendix 7: PICO question 1 evidence synthesis

Tables included in this appendix:

Table 1: QUADAS-2 assessment of prospective studies directly comparing TBLC and SLB in patients with ILD

First author	Q1a.1	Q1a.2	Q1a.3	**Could the selection of patients have introduced bias?**	**Are there concerns that the included patients do not match the review question?**	Q2a.1	**Could the conduct or interpretation of the index test have introduced bias?**	**Are there concerns that the index test, its conduct, or its interpretation differ from the review question?**	Q3a.1	Q3a.2	**Could the reference standard, its conduct or its interpretation have introduced bias?**	**Are there concerns that the target condition as defined by the reference standard does not match the review question?**	Q4a.1	Q4a.2	Q4a.3	Q4a.4	**Could the patient flow have introduced bias?**
Romagnoli, M	Yes	Yes	Yes	**No**	**No**	No	**Yes**	**No**	Yes	No	**Yes**	**No**	Yes	Yes	Yes	Yes	**No**
Troy, L	Yes	Yes	Yes	**No**	**No**	No	**Yes**	**No**	Yes	No	**Yes**	**No**	Yes	Yes	Yes	Yes	**No**

Legend:

- **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?
- **Q2a.1:** Was the index test (assumed to be (MDD of) TBLC) performed without knowledge of the results of the reference standard (assumed to be (MDD of) SLB)?
- **Q3a.1:** Is the reference standard likely to correctly classify the target condition?
- **Q3a.2:** Were the reference standard results (assumed to be (MDD of) SLB) interpreted without knowledge of the results of the index test (assumed to be (MDD of) TBLC)***?***
- **Q4a.1:** Was there an appropriate interval between index tests and reference standard?
- **Q4a.2:** Did all patients included in the 2x2 table receive a reference standard (partial verification bias)?
- **Q4a.3:** Did all patients in the 2x2 table receive the same reference standard (differential verification bias)?
- **Q4a.4:** Were all patients included in the analysis (2x2 table)?

Abbreviations: ILD = interstitial lung disease. MDD = multidisciplinary discussion. SLB = surgical lung biopsy. TBLC = transbronchial lung cryobiopsy.

Table 2: Histopathological and diagnostic agreement in prospective studies directly comparing TBLC and SLB in patients with ILD

First author Year Country	**Tests performed**	**Numer of patients undergoing both tests**		**Diagnostic pattern**	**Histopathological agreement between TBLC and SLB for specific pattern**	**Diagnostic agreement between TBLC and final MDD***	**Diagnostic agreement between MDD TBLC and MDD SLB****	**Deemed helpful at MDD*****	**High or definite confidence diagnosis at MDD**	**Complications**
Romagnoli, M 2019 Italy	TBLC and SLB	21		*TBLC:* 17 (81%) *SLB:* 21 (100%)	*Percentage agreement (for specific pattern):* 38% (95%CI 18-62) *Kappa agreement (for specific pattern):* 0.22 (95%CI 0.01-0.44)	*Percentage agreement:* 48% (95%CI 26-70) *Kappa agreement:* 0.31 (95%CI 0.06-0.56)	-	-	-	*Serious adverse events TBLC:* -n=2: pneumothorax *Serious adverse events SLB:* -n=0
Troy, L 2020 Australia	TBLC and SLB	65		*TBLC:* 59 (91%) *SLB:* 63 (97%)	*Percentage agreement (for specific pattern):* 69.2% *Kappa agreement (for specific pattern):* 0.47 (95%CI 0.30-0.64) *Percentage agreement (for guideline-refined pattern):* 70.8% *Weighted Kappa agreement (for guideline-refined pattern):* 0.70 (95%CI 0.55-0.86)	-	*Percentage agreement:* 76.9% *Kappa agreement:* 0.62 (95%CI 0.47-0.78)	*TBLC:* 48 (74%) *SLB:* 50 (77%) p=0.55	*MDD+TBLC:* 39 (60%) *MDD+SLB:* 48 (74%) p=0.090 *Additional:* 37/39 (95%) of MDD+TBLC high or definite confidence diagnoses were concordant with MDD+SLB diagnoses 6/26 (23%) of MDD+TBLC low confidence or unclassifiable diagnoses were reclassified to alternative high or definite confidence diagnosis in MDD+SLB	*Adverse events TBLC:* -n=14: mild airway bleeding -n=1: pneumothorax *Serious adverse events TBLC:* -n=0 *Adverse events SLB:* -n=1: chest wall wound infection *Serious adverse events SLB:* -n=1: rehospitalization due to chest pain -n=1: bleed requiring intervention *Adverse events either TBLC or SLB:* -n=1: hypotension from anaesthetic -n=1: desaturation during procedure -n=1: bronchospasm *Serious adverse events either TBLC or SLB:* -n=2: acute exacerbation of IPF -n=1: death within 90 days -n=1: rehospitalization due to mild hypoxia

Legend:

*In the Romagnoli study, MDD was informed by both the TBLC and SLB results.

**In the Troy study, two separate MDDs were undertaken: one informed by TBLC results, and one informed by SLB results.

***The addition of biopsy information was deemed helpful if it changed the diagnosis from low to high confidence or definite, or provided an unanticipated diagnosis (as compared to MDD that only included clinical details and imaging findings).

Abbreviations: CI = confidence interval. ILD = interstitial lung disease. MDD = multidisciplinary discussion. SLB = surgical lung biopsy. TBLC = transbronchial lung cryobiopsy.

Table 3: Diagnostic accuracy of TBLC for UIP/IPF in prospective studies directly comparing TBLC and SLB in ILD patients

First author Year Country	**Index test**	**Reference standard for UIP/IPF**	**Total number of patients**	**Number of patients with UIP/IPF according to the reference standard**	**Agreement between TBLC and SLB for definite or probable UIP versus indeterminate for UIP or other diagnosis**	**Sensitivity of index test for diagnosing UIP/IPF**	**Specificity of index test for diagnosing UIP/IPF***	**PPV of index test for diagnosing UIP/IPF**	**NPV of index test for diagnosing UIP/IPF**
Romagnoli, M 2019 Italy	TBLC histology	SLB histology (specific pattern)	21	8	NR	UIP: 63% (5/8) (95%CI 26-90)	UIP: 69% (9/13) (95%CI 39-9%)	UIP: 56% (5/9) (95%CI 23-85)	UIP: 75% (9/12) (95%CI 43-93)
	TBLC histology	MDD after TBLC and SLB**	9	9	NR	IPF: 67% (6/9) (95%CI 31-91)	IPF: 75% (9/12) (95%CI 43-93)	IPF: 67% (6/9) (95%CI 31-91)	IPF: 75% (9/12) (95%CI 43-93)
Troy, L 2020 Australia	TBLC histology	SLB histology (specific pattern)	65	39	*Percentage agreement:* 70.8% *Kappa agreement:* 0.70 (0.55-0.86)	UIP: 87% (34/39) (95%CI 72-95)	UIP: 73% (19/26) (95%CI 52-88)	UIP: 83% (34/41) (95%CI 67-92)	UIP: 79% (19/24) (95%CI 57-92)
	MDD after TBLC	MDD after SLB***	65	35	NR	IPF: 91% (32/35) (95%CI 76-98)	IPF: 80% (24/30) (95%CI 61-92)	IPF: 84% (32/38) (95%CI 68-93)	IPF: 89% (24/27) (95%CI 70-97)

Legend:

*Specificity was calculated as the number of patients with a 'non-UIP/IPF' diagnosis according to the index test, divided by the total number of patients with a 'non-UIP/IPF' diagnosis according to the reference standard. This implies that patients that were considered as 'true negatives' may still have had an index test result that was discrepant from the reference standard result (i.e. different 'non-UIP/IPF' diagnoses).

**Both the TBLC and SLB result were take into account in the MDD.

***Two separate MDDs were undertaken in this study: one including the TBLC results, and one including the SLB results. In this study, IPF diagnosis in MDD was categorized as 'definite', 'high probability' and 'low probability'; in the calculation of sensitivity, these subcategories were al considered as 'IPF positive'.

Abbreviations: CI = confidence interval. ILD = interstitial lung disease. IPF = idiopathic lung fibrosis. MDD = multidisciplinary discussion. NPV = negative preditive value. NR = not reported. PPV = positive predictive value. SLB = surgical lung biopsy. TBLC = transbronchial lung cryobiopsy. UIP = usual interstitial pneumonia.

Table 4: Studies performing indirect comparisons between TLBC and SLB in patients with ILD

First author Year Country	**Inclusion**	**Number of patients undergoing tests**	**Number of patients in whom a specific diangosis was obtained by the test**	**Diagnostic yield** Proportion of diagnostic tests	**Increase in IPF diagnostic confidence in MDD after addition of the test**	**Complications** Proportion of patients with a complication	**Other outcomes** Other outcomes related to testing
Ravaglia, C 2016 Italy	Patients with ILD in whom a diagnosis could not be achieved noninvasively	TBLC: -n=297 SLB: -n=150	TBLC: -n=246 SLB: -n=148	TBLC: -82.8% (246/297) SLB: -98.7% (148/150) -p=0.013	NR/NA	*Pneumothorax:* -TBLC: n=60 (20.2%) -SLB: NA *Pneumothorax requiring drainage:* -TBLC: n=46 (15.5%) -SLB: NA *Severe bleeding:* -TBLC: n=0 -SLB: n=0 *Mortality due to adverse event:* -TBLC: n=1 (0.3%) -SLB: n=4 (2.7%) -p=0.045	*Mean time of hospitalization:* -TBLC: 2.6 days (range 0-17) -SLB: 6.1 days (range 3-48) -p<0.0001
Tomassetti, S 2016 Italy	Patients with fibrotic ILD, without a typical UIP pattern on HRCT *All patients in this study were also included in Tomassetti 2020, which reports on other outcomes in a wider group of patients*	TBLC: -n=58 SLB: -n=59	NR/NA	NR/NA	TBLC: -From 29% to 63% p=0.0003 SLB: -From 30% to 65% -p=0.0016	*Pneumothorax:* -TBLC: n=19 (32.8%) -SLB: NA *Pneumothorax requiring drainage:* -TBLC: n=15 (25.9%) -SLB: NA *Severe bleeding:* -TBLC: n=0 -SLB: n=0 *Mortality:* -TBLC: n=1 (1.7%) -SLB: n=2 (3.4%)	*Mean time of hospitalization:* -TBLC: 3 days (range 0-9) -SLB: 6 days (range 3-17) -p-value NR
Tomassetti, S 2020 Italy	Patients with suspected ILD, without a definite UIP pattern on HRCT	TBLC: -n=266 SLB: -n=160	NR/NA	NR/NA	NR/NA	NR	*Mortality in MDD diagnosis of IPF versus other ILD:* -TBLC: adjusted HR 2.98 (95%CI 1.19-7.47; p=0.02) -SLB: adjusted HR 4.07 (95%CI 2.01-8.24; p<0·0001) *Mortality in UIP pattern versus other patterns:* -TBLC: adjusted HR 2.64 (95%CI 1.11-6.36; p=0.03) -SLB: adjusted HR 4.87 (95%CI 2.27-10.42; p=0.002)

Legend:

Abbreviations: CI = confidence interval. HR = hazard ratio. HRCT = high resolution comuted tomography. ILD = interstitial lung disease. IPF = idiopathic lung fibrosis. MDD = multidisciplinary discussion. NPV = negative preditive value. NA = not applicable. NR = not reported. PPV = positive predictive value. SLB = surgical lung biopsy. TBLC = transbronchial lung cryobiopsy. UIP = usual interstitial pneumonia.

Table 5: Recent systematic reviews on the diagnostic yield and complication rate of TBLC and SLB in patients with ILD

First author Year Country	**Test**	**Selection criteria**	**Searching details**	**Number of studies and patients included**	**Meta-analysis results: Diagnostic yield** Proportion of patients with a diagnostic test	**Meta-analysis results: Diagnostic yield in subgroups** Proportion of patients with a diagnostic test in subgroups	**Meta-analysis results: Complications** Proportion of patients with a complication	**Study designs and study quality assessment**
Sethi, J 2019 USA	TBLC	*Inclusion criteria:* -TBLC in patients with suspected DPLD -Diagnosis confirmed based on characteristic histopathologic findings or after MDD -Data provided on diagnostic yield or complications *Exclusion criteria:* -<10 patients included -TBLC performed for pulmonary nodules -Review articles -No language restrictions	*Sources searched:* -Medline -Embase -Google scholar -Reference lists -Conference abstract proceedings *Date of searching:* -12-2016 *Unique search results:* -n=252	*Studies included in systematic review:* -n=31 (n=18 full-texts; n=13 abstracts) -Published between 2009 and 2017 *Studies included in meta-analysis of diagnostic yield:* -n=27 *Patients included in meta-analysis of diagnostic yield:* -n=1443 -Range of patients across studies: 10-300	*Summary diagnostic yield (n=27 studies):* -72.9% (95%CI 67.9-77.7) *Range of diagnostic yield across studies:* -40.0% to 95.1%	*Summary diagnostic yield based on study design:* *-Retrospective (n=16 studies):* 71.8% (95%CI 65.8-77.5) *-Prospective (n=11 studies):* 74.3% (95%CI 64.9-82.8) *Summary diagnostic yield based on publication type:* *-Abstract (n=12 studies):* 71.4% (95%CI 63.9-78.3) *-Full-text (n=15 studies):* 74.0% (95%CI 67.2-80.3) *Summary diagnostic yield based on probe size:* *-1.9mm only (n=7 studies):* 70.4% (95%CI 58.8-80.8) *Summary diagnostic yield based on QUADAS-2*: *-Low risk of bias only (n=6 studies):* 73.1% (95%CI 63.0-82.1)	*Overall complication rate (n=31 studies):* -23.1% *Summary incidence of pneumothorax (n=30 studies):* -9.4% (95%CI 6.7-12.5%) *Summary incidence of moderate-severe bleed (n=27 studies):* -14.2% (95%CI 7.9-21.9%) *Summary incidence of mortality within 30 days (n=33 studies):* -0.3% (6 events in total)	*Study design:* -Prospective: n=11 (35.5%) -Retrospective: n=20 (64.5%) *QUADAS-2 assessment:* -High or unclear risk of bias: n=25 (80.6%)
Sharp, C 2017 UK	VATS	*Inclusion criteria:* -VATS-biopsy in patients with ILD *Exclusion criteria:* -No language restrictions	*Sources searched:* -Medline -Embase *Date of searching:* -02-2016 *Unique search results:* -n=166	*Studies included in systematic review and meta-analysis:* -n=24 -Published between 1992 and 2015 *Patients included in meta-analysis of diagnostic yield:* -n=2665 -Range of patients across studies: 30-432	*Summary diagnostic yield (n=24 studies):* -91.1% (95%CI 86.9-93.2) *Range of diagnostic yield across studies:* -NR	NR	*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)	*Study design:* -Prospective: n=3 (12.5%) -Retrospective: n=21 (87.5%) *Cochrane Collaboration risk of bias tool assessment:* -High risk of selection bias: n=24 (100%)

Legend:

Abbreviations: CI = confidence interval. DPLD: diffuse parenchymal lung disease. ILD = interstitial lung disease. MDD = multidisciplinary discussion. NR = not reported. SLB = surgical lung biopsy. TBLC = transbronchial lung cryobiopsy. VATS = video-assistend thoracic surgery.

Table 6: Studies reporting on MDD diagnostic confidence before and after TBLC in patients with ILD

First author Year Country	**Test**	**Patients**	**Patient included**	**Increase in diagnostic confdience at MDD**
Hetzel, J 2020 Germany	TBLC	Suspected IIP	128	*Percentage increase in confident diagnosis (likelihood ⩾90%) or provisional diagnosis with high confidence (likelihood ⩾70%):* -50.0% after clinicoradiological discussion -60.2% after BAL -81.2% after TBLC -p<0.0001 (TBLC vs BAL) *Percentage increase in confident diagnosis (likelihood ⩾90%):* -11.7% after clinicoradiological discussion -22.7% after BAL -53.9% after TBLC -p=0.001 (TBLC vs BAL)
Tomassetti, S 2015 Italy	TBLC SLB	Fibrotic ILD	117 *58 TBLC* *59 SLB*	*Percentage increase in IPF diagnosis made with high level of confidence in MDD:* *TBLC:* -29% after clinicoradiological discussion -63% after TBLC -p=0.0003 *SLB:* -30% after clinicoradiological discussion -65% after SLB -p=0.0016

Legend:

Abbreviations: BAL = bronchoalveolar lavage. IIP = idiopathic interstitial pneumonia. ILD = interstitial lung disease. MDD = multidisciplinary discussion. SLB = surgical lung biopsy.

TBLC = transbronchial lung cryobiopsy.

Table 7: GRADE tables for PICO question 1

PICO question:

In patients with undiagnosed ILD considered eligible to undergo SLB, is TBLC a valid replacement test?

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Diagnostic agreement between TBLC and final MDD									
2[a,1,2]	non-randomised trials	serious[b]	not serious	serious[c]	serious[d]	none	**Romagnoli et al** (n=21; diagnostic agreement between TBLC and TBLC+SLB+MDD): *Percentage agreement:* 48% (95%CI 26-70). *Kappa agreement:* 0.31 (95%CI 0.06-0.56).[e.] **Troy et al** (n=65; diagnostic agreement between TBLC+MDD and SLB+MDD): *Percentage agreement:* 76.9% (95%CI NR). *Kappa agreement:* 0.62 (95%CI 0.47-0.78).[f]	⨁◯◯◯ Very low	CRITICAL[s]
High confidence final diagnosis at TBLC+MDD versus SLB+MDD									
1[a,2]	non-randomised trials	serious[b]	not serious	serious[c]	serious[d]	none	**Troy et al** (n=65): TBLC+MDD: 60% (39/65); TBLC+MDD: 74% (48/65); p=0.090. Also, 95% (37/39) of TBLC+MDD high or definite confidence diagnoses were concordant with SLB+MDD diagnoses. And 23% (6/26) of MDD+TBLC low confidence or unclassifiable diagnoses were reclassified to alternative high or definite confidence diagnosis in MDD+SLB.[f]	⨁◯◯◯ Very low	CRITICAL
Increase in MDD diagnostic confidence									
2[3]	observational studies	serious[g]	not serious	not serious	serious[h]	none	**Hetzel et al** (n=128): increase in confident diagnosis or provisional diagnosis with high confidence in MDD from 50.0% to 81.2% (p<0.0001) after TBLC. **Tomassetti et al** (n=117, 58 TBLC, 59 SLB): increase in IPF diagnosis with high level of confidence in MDD from 29% to 63% (p=0.0003) for TBLC, and from 30% to 65% (p=0.0016) for SLB.	⨁◯◯◯ Very low	CRUCIAAL
Diagnostic yield of TBLC versus SLB									
2[a,1,2,4]	non-randomised trials	serious[b]	not serious	serious[c]	serious[i]	none	**Romagnoli et al** (direct comparison of TBLC versus SLB; n=21): *Percentage agreement:* 38% (95%CI 18–62). *Kappa agreement:* 0.22 (95%CI 0.01-0.44). *Diagnostic pattern:* 81% for TBLC, and in 100% for SLB. **Troy et al** (direct comparison of TBLC versus SLB; n=65): *Percentage agreement:* 70.8% (95%CI NR). Weighted Kappa agreement (for guideline-refined pattern):0.70 (95%CI 0.55.-0.86). *Diagnostic pattern:* 91% for TBLC, and 97% for SLB. **Ravaglia et al** (n=447, indirect comparison of TBLC and SLB): *Diagnostic yield:* 82.8% for TBLC and 98.7% for SLB (p=0.013).	⨁◯◯◯ Very low	CRITICAL
Diagnostic yield of TBLC									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
27[5]	observational studies	serious[k]	not serious	serious[c]	not serious	none	*Summary diagnostic yield* after meta-analysis: 72.9% (95%CI 67.9-77.7).[l]	⨁◯◯◯ Very low	CRITICAL
Diagnostic yield of SLB									
24[a,6]	observational studies	serious[m]	not serious	serious[c]	not serious	none	*Summary diagnostic yield* after meta-analysis: 91.1 (95%CI 86.9–93.2).[n]	⨁◯◯◯ Very low	CRITICAL
Diagnostic accuracy of TBLC for diagnosing IPF									
2[a,1,2]	non-randomised trials	serious[b]	not serious[i]	serious[c]	serious[j]	none	**Romagnoli et al** (n=21, accuracy of TBLC histology, against MDD informed by TBLC and SLB as reference standard): *Sensitivity:* 67% (95%CI 31-91). *Specificity*: 75% (95%CI 43-93).[o] **Troy et al** (n=65, accuracy of MDD informed by TBLC, against MDD informed by SLB as reference standard): *Sensitivity:* 91% (95%CI 76-98). *Specificity*: 80% (95%CI 61-92).[f,p]	⨁◯◯◯ Very low	CRITICAL
Survival after IPF diagnosis									
1[7]	observational studies	serious[q]	not serious	serious[r]	not serious	none	**Tomassetti et al** (indirect comparison of TBLC (n=266) versus SLB (n=160): an MDD diagnosis of IPF (versus another ILD) based on TBLC or SLB were both significantly associated with 5-year transplant-free survival (TBLC: adjusted HR 2.98 (95%CI 1.19-1.47; p=0.02), and SLB: adjusted HR 4.07 (95%CI 2.01-8.24; p<0·0001)).	⨁◯◯◯ Very low	CRITICAL
Adverse events of TBLC versus SLB: mortality									
1[4]	observational studies	serious[q]	not serious	serious[r]	not serious	none	**Ravaglia et al** (indirect comparison of TBLC (n=297) versus SLB (n=150)): *Mortality:* 0.3% (n=1) in TBLC versus 2.7% (n=4) in SLB (p=0.045). **Tomassetti et al** (indirect comparison of TBLC (n=58) and SLB (n=59)): *Mortality:* 1.7% (n=1) in TBLC versus 3.4% (n=2) in SLB.	⨁◯◯◯ Very low	CRITICAL
Adverse events of TBLC: mortality									
33[5]	observational studies	serious[b]	not serious	not serious	not serious	none	*Summary incidence of 30-day mortality*: 0.3%.[l]	⨁◯◯◯ Very low	CRITICAL
Adverse events of SLB: mortality									
21[6]	observational studies	serious[b]	not serious	not serious	not serious	none	*Summary incidence of 30-day mortality*: 2.3% (95%CI 1.3-3.6).[n]	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Adverse events of TBLC versus SLB: time of hospitalization									
2[4,8]	observational studies	serious[q]	not serious	serious[r]	not serious	none	**Ravaglia et al** (indirect comparison of TBLC (n=297) versus SLB (n=150)): *Mean time of hospitalization:* 2.6 days (range 0-17) for TBLC and 6.1 days (range 3-48) for SLB (p<0.0001). **Tomassetti et al** (indicrect comparison of TBLC (n=58) and SLB (n=59): *Mean time of hospitalization:* 3 days (range 0-9) for TBLC and 6 days (range 3-17) for SLB.	⨁◯◯◯ Very low	CRITICAL
Adverse events of TBLC versus SLB: other									
2[a,1,2]	non-randomised trials	serious[b]	not serious	serious[r]	serious[l]	none	**Romagnoli et al** (direct comparison of TBLC versus SLB (n=21)): *Serious adverse events:* 9.5% for TLBC (n=2 with pneumothorax), and 0% for SLB. **Troy et al** (direct comparison of TBLC versus SLB (n=65)): *Serious adverse events:* 0% for TBLC (additionally n=1 with pneumothorax was not considered as serious adverse event), and 3.1% for SLB (n=1 with rehospitalisation due to chest pain, and n=1 with bleeding requiring intervention). **Ravaglia et al** (indirect comparison of TBLC (n=297) versus SLB (n=150)): *Pneumothorax:* 15.5% for TBLC. *Severe bleeding:* 0% for TBLC, and 0% for SLB. **Tomassetti et al** (indicrect comparison of TBLC (n=58) and SLB (n=59): *Pneumothorax:* 25.9% for TBLC. *Severe bleeding:* 0% for TBLC, and 0% for SLB.	⨁◯◯◯ Very low	CRITICAL
Adverse events of TBLC: other									
31[5]	non-randomised trials	serious[k]	not serious	not serious	not serious	none	*Overall complication rate:* 23.1%, with summary incidence of pneumothorax of 9.4% (95%CI 6.7-12.5) and summary incidence of moderate-severe bleeding of 14.2% (95%CI 7.9-21.9).[l]	⨁◯◯◯ Very low	CRITICAL
Adverse events of TBLC: other									
18[6]	observational studies	serious[m]	not serious	not serious	not serious	none	*Summary incidence of surgical morbidity:* 12.9% (95%CI 9.3-16.9, based on 18 studies).[n]	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval

Explanations

a. In the GRADE approach, appropriately designed test accuracy studies start as high certainty evidence.

b. Risk of bias was unclear in the index test domain for both studies, because it is unclear if TBLC may have been performed differently (e.g. taking less time for the procedure) with the knowledge that SLB would also be performed in the same patient. Risk of bias was high in the reference standard domain, because MDD was not blinded to TBLC results (for Romagnoli et al), or likely to be not completely blinded to TBLC results (Troy et al).

c. Unclear if a histopathological diagnosis, agreement, diagnostic accuracy or diagnostic yield sufficiently correspond to the final MDD-diagnosis and to patient-important outcomes .

d. Only one study; small number of included patients.

e. For Romagnoli et al, both the TBLC and SLB result were taken into account in the MDD.

f. Two separate MDDs were undertaken: one including the TBLC results, and one including the SLB results.

g. High risk of incorporation bias in both studies.

h. No confidence intervals reported around increase in diagnostic confidence.

i. Although the results substantially differ between the two included studies, no downgrading for inconsistency was done as we already downgraded for risk of bias and imprecision, which could explain the inconsistency.

j. Studies not pooled; small number of included patients.

k. In the systematic review by Sethi et al on TBLC, risk of bias according to QUADAS-2 was high or unclear in 25 studies (80.6%).

l. Results from the systematic review by Sethi et al.

m. In the systematic review by Sharp et al on SLB, risk of selection bias according to the Cochrane Collaboration risk of bias tool assessment was high in 24 studies (100%).

n. Results from the systematic review by Sharp et al.

o. These accuracy estimates were not reported by Troy et al and Romagnoli et al, but could be recalculated.

p. These accuracy estimates were not reported by Troy et al, but could be recalculated.

q. High risk of selection bias, as no randomization was performed.

r. Indirect comparison of TBLC and SLB.

s. The outcome 'agreement' was not prespecified and addressed in the survey of assessment of outcome importance within the TF members , but was considered a surrogate of 'diagnostic accuracy', which was considered 'critical'

References

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8. Tomassetti S, Wells AU, Costabel U, Cavazza A, Colby TV, Rossi G, Sverzellati N, Carloni A, Carretta E, Buccioli M, Tantalocco P, Ravaglia C, Gurioli C, Dubini A, Piciucchi S, Ryu JH, Poletti V. Bronchoscopic Lung Cryobiopsy Increases Diagnostic Confidence in the Multidisciplinary Diagnosis of Idiopathic Pulmonary Fibrosis. American Journal of Respiratory & Critical Care Medicine 2016: 193(7): 745-752.

Table 8: Evidence to decision framework for PICO question 1

PICO question:

In patients with undiagnosed ILD considered eligible to undergo SLB, is TBLC a valid replacement test?

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%).	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Severe complications are anticipated to be lower in TBLC than SLB: -Overall mortatlity rate is lower: 0.3% versus 2.3% (based on the included meta-analyses of studies only focusing on TBLC or only focussing on SLB), and 0.3% versus 2.7% (based on one study indirectly comparing both tests). -Mean time of hospitalization is shorter: 2.6 days for TBLC and 6.1 days for SLB (based on one study indirectly comparing both tests), and 3 days for TBLC and 6 days for SLB (based on a second study indirectly comparing both tests). -Overall complication rate is higher: 23.1% versus 12.9% (based on the included meta-analyses of studies only focusing on TBLC or only focussing on SLB).	-Complication rates are difficult to compare considering the fact that (a) definitions of complications varied and (b) populations varied (e.g. the TBLC population may have also included patients not considered eligible to undergo SLB). -The Task Force put most emphasis on a potential reduction in serious adverse events (especially mortality). -Reported overall complication rate between TBLC and SLB cannot be compared: inTBLC-studies, pneumothorax is considered an adverse event, while in SLB-studies, it is not because all patients require chest tube drainage. -Complications are likely to be influenced by operator experience (see PICO question 4). -TBLC complications are generally lower in 'later' studies, where

		endobronchial balloons were used.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	Diagnostic accuracy is anticipated to be lower for TBLC than SLB: -Diagnostic agreement between TBLC+MDD and SLB+MDD is 76.9% (based on one study directly comparing both tests). -95% of TBLC+MDD high or definite confidence diagnoses are concordant with SLB+MDD diagnoses; 23% of MDD+TBLC low confidence or unclassifiable diagnoses were reclassified to alternative high or definite confidence diagnosis in MDD+SLB (based on one study directly comparing both tests). -Increase in diagnostic confidence of MDD after adding TBLC is: from 60% to 81% (based on one study only performing TBLC). -Increase in IPF diagnosis made with high level of confidence in MDD is similar for TBLC and SLB: from 29% to 63% for TBLC, and from 30% to 65% for SLB (based on one study indirectly comparing both tests). -Histopathological agreement between TBLC and SLB is between 38% and 69.2% (based on two studies directly comparing both tests). -Diagnostic yield of TBLC is lower: 72.9% versus 91.1% (based on the included meta-analyses of studies only focusing on TBLC or only focussing on SLB). -Diagnostic accuracy of TBLC+MDD for diagnosing IPF is: sensitivity 91% and specificity 80% (based on one study).	Troy and colleagues and Romagnoli and collagues are both indirect comparisons of TBLC versus SLB, yet the first is considered to be at lower risk of bias, and has a much larger sample size, and therefore more relative weight was put to its results in the Task Force discussion.

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 a more accurate test. Others may favor a test with less adverse events and lower costs. -Most patients are unlikely to choose SLB, if TBLC (i.e. a less invasive test) is an alternative, especially taking into account that a step-up strategy may be proposed where patients could still undergo SLB after a non-diagnostic initial TBLC. -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.” -Summary of patient feedback (one patient undergoing both TBLC and SLB): “I truly believe that TLBC should be the first technique to be proposed in case the diagnosis requires it.”

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 a more accurate test. Others may favor a test with less adverse events and lower costs. -In centers with sufficient experience in TBLC, the balance of effects probably leans towards performing TBLC instead of SLB.

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	Data on costs are limited. Two studies were identified that report some information.-Hernández-González et al (n=33): estimated that the systematic use of TBLC (followed by SLB if inconclusive) overall reduced costs up to 59846 euro (33 patients over a 3-year period), compared to systematically performing SLB. -Sharp et al (theoratical cost-analysis): estimated that the systematic use of TBLC (followed by SLB if inconclusive) reduced costs up to 647 pound per patient per year.	-It is generally accepted that TBLC results in lower costs than SLB. -A major cost driver is considered to be the number of days in the hospital, which is considered to be higher in 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		-It is generally accepted that TBLC results in lower costs than SLB. -A major cost driver is considered to be the number of days in the hospital, which is considered to be higher in 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		-Studies on cost-effectiveness are not available. -It is generally accepted that TBLC results in lower costs than SLB. -It is unknown to which extent reduced diagnostic accuracy for TBLC results in higher costs down the line, compared to 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		Due to the anticipated lower proportion of serious adverse events of TBLC compared to SLB, also patients who are no candidates for SLB (e.g. due to poor respiratory status) can now be offered a diagnostic approach.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		Overall, diagnostic accuracy of the intervention test (TBLC) is considered lower than for the comparator test (SLB) which it aims to replace, at expected reduced costs and serious adverse events. These are likely to be the most important arguments for or against replacing SLB by TBLC. Some physicians or patients may weigh these advantages and disadvantages in favor of TBLC, others in favor of SLB.

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 pathologists, 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**
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 considered eligible to undergo SLB, the task force suggests performing TBLC if obtaining histopathological data is indicated (conditional recommendation for the intervention, very low certainty of evidence).

Remark: this recommendation applies to centers experienced in performing TBLC.

Justification

Compared to SLB, it is expected that TBLC results in lower serious adverse events and costs, at the expense of lower diagnostic accuracy. These advantages and disadvanteges should be weighed in each individual patient. Overall, the Task Force considers the reduction in serious adverse events to outweigh the reduced diagnostic accuracy. This especially applies to patients considered at higher risk of surgical adverse events.

Subgroup considerations

Although evidence of safety of TBLC in high-risk groups was limited (PICO question 4), no considerable differences seem to exist in terms of adverse events in high- versus low-risk groups.

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

For quality assurance, healthcare centers that offer TBLC or SLB are advised to keep track of important outcomes such as diagnostic yield and complications.

Research priorities

Additional direct comparisons between TBLC and SLB are recommended. Ideally, a large randomized trial is performed. In addition to outcomes related to diagnostic accuracy, complications and costs, such studies should focus on long-term patient-important outcomes such as disease control and mortality (based on the diagnosis made by either test and the subsequent treatment initiated).

Appendix 7: PICO question 2 evidence synthesis

Tables included in this appendix:

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

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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.

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 histopathological	SLB: 92% (12/13)	Complications SLB: -n=1: an overnight stay at ICU due to prolonged respiratory and cardiovasculatory

						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		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 -n=25: less-than-definite	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 -n=2: SLB showed a	SLB: 60% (3/5)	Complications SLB: -NR

		histopathological diagnosis based on TBLC, but confident consensus at MDD -n=33: non-diagnostic				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 -n=1: lymphoma	NR/NA	SLB: 100% (38/38) 2nd TBLC: 100% (4/4)	Complications SLB: -NR

					-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

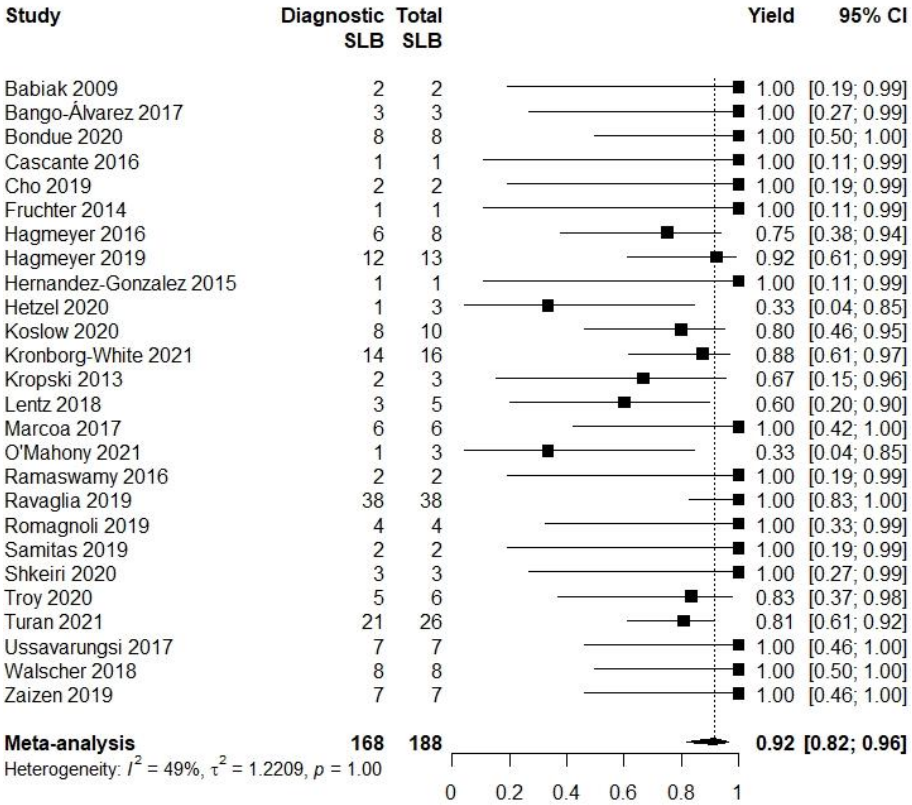

Figure 1b: Meta-analysis of diagnostic yield of SLB in ILD patients with an non-informative initial TBLC, excluding studies contributing <10 patients

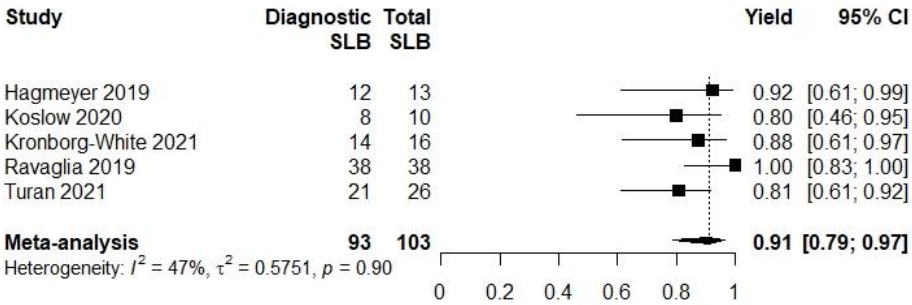

Table 3: GRADE tables for PICO question 3

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. 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	-Judgement applies to both SLB and second TBLC.

	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 ○ Varies	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.

○ 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**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the	Probably favors the intervention	Favors the intervention	Varies	**No included studies**

	JUDGEMENT						
			comparison				
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.

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)											

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)		
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.

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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 ○ Varies	-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 -No information about bronchoscopists' baseline TBLC experience or the amount of training they	

● Don't know	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

	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).

Appendix 11: Narrative question 2 evidence synthesis

Tables and figures included in this appendix:

Table 1: Studies reporting on complication or mortality rates in patients at high procedural risk only

Table 2: Studies comparing complication or mortality rates in subgroups of patients at high versus low procedural risk

Table 1: Studies reporting on complication or mortality rates of TBLC in patients with ILD at high procedural risk only

First author Year Country	**Specification of high risk group**	**Total number of patients at high procedural risk undergoing TBLC**	**Complications: Pneumothorax**	**Complications: Bleeding**	**Complications: Other**	**Mortality**
Matta A, 2021 USA	-Critically ill patients with acute hypoxemic respiratory failure	n=17	*Pneumothorax:* -n=6 (35.3%) *Pneumothorax requiring drainage:* -n=5 (29.4%) *Pneumothorax with persistent air leak (> 5 days):* -n=4 (23.5%)	*Moderate bleeding:* -n=1 (5.9%) *Severe bleeding:* -n=0 (0%)	*Moderate hemorrhage:* -n= 1 (5.9%) *Severe hemorrhage:* -n=0 (0%)	*Mortality at 8 days:* -n=8 (47.1%)
Ravaglia C 2019 Italy	-Patients with FVC <50% and/or DLCO <35%	n=31	*Pneumothorax:* -n=6 (19.4%) *Pneumothorax requiring drainage:* -n=5 (16.1%)	*Mild bleeding:* -n=2 (6.4%) *Moderate bleeding:* -n=4 (12.9%) *Severe bleeding:* -n=0 (0%)	Other (empyema) -n=1 (3.2%)	NR
She S 2020 Australia	-Patients with DLCO <40%	n=15	"In our cohort, 15 (12.4%) patients had a diffusing capacity of the lungs for carbon monoxide <40%, but we did not note differences in the rate of complications in this subgroup." No further details were reported.			NR

Legend:

Abbreviations: DLCO = diffusing capacity for carbon monoxide. FVC = forced vital capacity. ILD = interstitial lung disease. NR = not reported. TBLC = transbronchial lung cryobiopsy.

Table 2: Studies comparing complication or mortality rates of TBLC in subgroups of patients with ILD at high versus low procedural risk

First author Year Country	**Specification of high risk group and low risk group**	**Total number of patients undergoing TBLC per subgroup**	**Complications: Pneumothorax**	**Complications: Bleeding**	**Complications: Other**	**Mortality**
Bondue B 2021 Belgium	*Risk:* -High-risk patients (defined as presence of any of the following: age ≥75-years, BMI ≥35, sPAP by echocardiography ≥45 mmHg, FVC <50%, DLCO <30%, and/or significant cardiac comorbidities with reduced heart ejection fraction) -Low-risk patients (not fulfilling the definition of high-risk) *Additional subgroups:* -Subgroup of BMI ≥35 versus low risk patients -Subgroup of severe pulmonary impairment (FVC <50% or DLCO <30%) versus low risk patients	*High-risk patients:* -n=38 (40%) *-n=15 BMI ≥35* *-n=15 severe pulmonary impairment* *-n=4 sPAP ≥45 mmHg* *-n=4 ≥75-year-old* *-n=3 cardiac comorbidities*) *Low-risk patients:* -n=58 (60%) *Subgroup of BMI ≥35:* -n=15 *Subgroup of severe pulmonary impairment:* -n=15	*Pneumothorax:* -n=5 (13.2%) in high-risk patients -n=12 (20.7%) in low-risk patients -p=0.419 -n=1 (6.7%) in the subgroup of patients with BMI ≥35 (p=0.206 compared to low-risk patients) -n=1 (6.7%) in the subgroup of patients with severe pulmonary impairment (p=0.316 compared to low-risk patients) *Pneumothorax requiring drainage:* -n=3 (7.9%) in high-risk patients -n=6 (10.3%) in low-risk patients -p=0.687	*Mild bleeding*: -n=24 (63.2%) in high-risk patients -n=36 (62.1%) in low-risk patients -p=0.914 *Moderate bleeding:* -n=11 (28.9%) in high-risk patients -n=17 (29.3%) in low-risk patients -p=0.969 *Severe bleeding*: -n=1 (2.6%) in high-risk patients -n=3 (5.2%) in low-risk patients -p=0.542 -no difference for sub-groups BMI ≥35 and severe pulmonary impairment (no numbers reported)	*Median hospital stay:* -1 day (range 1-12) in high-risk patients -1 day (range 1-107) in low-risk patients -p=0.675 *Other complications:* -n=0 in high-risk patients -n=3 in low-risk patients (n=1: acute exacerbation, n=1: empyema, n=1: seizure 24 hours after procedure)	*Mortality:* -n=1 (2.6%) in high-risk patients (possible acute embolic and/or coronary event) -n=0 (0%) in low-risk patients
Cooley J 2018 USA	*Hospitalization:* -Hospitalized patients -Outpatients *(Patients were hospitalized for respiratory failure, fatigue or acute kidney injury)*	*Hospitalized patients:* -n=17 (11%) *-n=15 due to respiratory failure* *-n=1 due to fatigue* *-n=1 due to kidney injury* *Outpatients:* -n=142 (89%)	*Pneumothorax:* -n=4 (23.5%) in hospitalized patients -n=14 (9.9%) in outpatients -p=0.11 *Persistent air leak:* -n=1 (5.9%) in hospitalized patients -n=1 (0.7%) in outpatients -p=0.20	NR	*ICU transfer within 48 h:* -n=2 (11.8%) in hospitalized patients -n=3 (2.1%) in outpatients -p=0.09	*Mortality at 30 days:* -n=1 (5.9%) in hospitalized patients -n=2 (1.4%) in outpatients -p=0.29
Gershman E, 2015 Germany	*Risk:* -Post-lung-transplantation patients -Immunocompromised patients -Other (non-high-risk) patients with DLD	*Post-lung-transplantation:* -n= 146 (49%) *Immunocompromised:* -n= 18 (6%) *Other patients with DLD:* -n=139 (46%)	*Pneumothorax:* -n=5 (3.4%) in post-lung-transplantation -n=2 (11.1%) in immunocompromised -n=8 (5.8%) in other DLD patients -p-value NR *Pneumothorax requiring drainage:* -n=1 (0.7%) in post-lung-transplantation -n=2 (11.1%) in immunocompromised -n=3 (2.2%) in other DLD patients -p-value NR	*Bleeding:* -n=6 (4.1%) in post-lung-transplantation -n=3 (16.6%) in immunocompromised -n=7 (5.0%) in other DLD patients -p-value NR	*Hospitalization:* -n=3 (2.1%) in post-lung-transplantation -n=1 (5.6%) in immunocompromised -n=6 (4.3%) in other DLD patients -p-value NR	NR
Hetzel J 2019 Germany	*Age:* -Age <65 years -Age ≥65 years *Aspirin use:* -Aspirin use -No aspirin use	*Age <65 years:* -n=160 (46%) *Age* ≥65 years*:* -n=189 (54%) *Aspirin use:* -n=51 (14%)	-NR	*Moderate/severe bleeding:* -n=17 (10.6%) in patients <65 years -n=38 (20.1%) in patients ≥65 years -p=0.018 -n=13 (25.5%) in patients with aspirin use -n=45 (14.9%) in patients with no aspirin use	NR	NR

		No aspirin use: -n=303 (86%)		-p=0.067		
Kronborg-White S, 2021 Denmark	*Anticoagulant therapy:* -Anticoagulant therapy -No anticoagulant therapy (*All patients ceased individual anticoagulant treatment before the procedure according to national guidelines)*	*Anticoagulant therapy:* -n= 86 *-n=64: Acetyl salicylic acid* *-n=13: Thrombocyte inhibitors* *-n=15: New oral anticoagulants* *-n=18: Vitamin K antagonists* *No anticoagulant therapy:* -n=164	NR	*Moderate or severe bleeding:* -n=19 (22.1%) in anticoagulant therapy -n=36 (22.0%) in no anticoagulant therapy -p=0.98	NR	NR
Kropski JA, 2013 USA	*Hospitalization:* -Hospitalized patients -Outpatients (*Reasons for hospitalization NR; unclear if this is related to respiratory state)*	*Hospitalized patients:* -n=4 (11%) *Outpatients:* -n= 33 (89%)	*Pneumothorax:* -n=0 (0%) in hospitalized patients -n=0 (0%) in outpatients	*Bleeding:* -n=0 (0%) in hospitalized patients -n=0 (0%) in outpatients	*Other complications:* -n=1 (25.0%) for hospitalized patients (n=1: ICU admission for post-procedural hypoxemia for 1 day) -n=1 (3.0%) for outpatients (n=1: hospitalization for hemoptysis)	NR
Pannu J 2019 USA	*Hospitalization:* -Hospitalized patients -Outpatients (*Reasons for hospitalization NR; unclear if this is related to respiratory state)*	*Hospitalized patients:* -n=8 (4.1%) *Outpatients:* -n=189 (95.9%)	NR	NR	NR	*Mortality at 30 days:* -n=2 (25%) in hospitalized patients -n=2 (1.1%) in outpatients -p-value NR

Legend:

Abbreviations: BMI = body mass index. DLCO = diffusing capacity for carbon monoxide. DLD = diffuse lung disease. FVC = forced vital capacity. ICU = intensive care unit. ILD = interstitial lung disease. NR = not reported. sPAP = systolic pulmonary artery pressure. TBLC = transbronchial lung cryobiopsy.