The level of agreement between SLB and MDA was 62% (95% confidence interval, 38–82%), which is somewhat low for a gold standard. Although this is slightly higher than the level of agreement between TBLC and MDA (48%), it is not significantly different (95% confidence interval, 26–70%). Besides overlapping confidence intervals, it is possible that a bias shifted the scale toward SLB, as SLB and TBLC were discussed simultaneously in one MDA meeting. This might be problematic, because clinicians and pathologists are more familiar with SLB than with TBLC. Furthermore, the SLB samples were on average 5–10 times larger than the TBLC samples, as would be expected. Taken together, these observations suggest that the SLB diagnosis probably influenced the MDA significantly more than the TBLC diagnosis. Therefore, the better concordance between the blinded pathological diagnosis of SLB and the MDA seems inherent to the process itself.

A better assessment would be to conduct two separate MDA discussions, one using TBLC and the other using SLB samples, and calculate the concordance between them or between each blinded assessment and its corresponding MDA. In addition, it would have been prudent to subject the samples to blinded assessments by at least two pathologists rather than one.

Thus, we believe that rejecting the role of TBLC in the assessment of ILD is premature. We agree that further prospective studies to assess the role of TBLC in the diagnostic evaluation of ILD are warranted. The ongoing prospective COLDICE (Cryobiopsy versus Open Lung Biopsy in the Diagnosis of Interstitial Lung Disease) study (6) is designed to address many of the aforementioned issues, and is expected to provide more conclusive evidence for the role of TBLC in ILD diagnosis. ■

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Reply to Wand *et al.*

From the Authors:

We read with interest the letter to the editor from Wand and colleagues, who highlighted some concerns about the findings in our recent article, which showed a poor concordance between lung histology from sequential transbronchial lung cryobiopsies (TBLC) and surgical lung biopsies (SLB) obtained prospectively from the same patient during the same surgical procedure.

We obviously agree with the authors regarding the critical importance of multidisciplinary assessments (MDAs) in the diagnostic evaluation of interstitial lung diseases (ILDs) (1, 2), despite the reported low agreement among MDAs for ILDs that are not idiopathic pulmonary fibrosis (3). However, the role of MDAs was not the main focus of our study. Our goal was to assess the concordance of pathological diagnoses *per se* obtained by two different procedures (TBLC and SLB) performed in the same patient, blinded to any clinical information—something that has never been done before. We do believe that our blinded histology approach was somewhat artificial, and we agree that it was outside the routine clinical workflow, as clearly stated in our article (1). However, we

Originally Published in Press as DOI: 10.1164/rccm.201909-1736LE on September 19, 2019

also believe that this was the only way to compare pathological outcomes from the two techniques while avoiding significant bias.

We had considered assessing the concordance between the blinded pathologist and the other two local pathologists but concluded that this was not an appropriate comparison because the methodologies used in these two contexts were different (e.g., blinded vs. nonblinded). In fact, the two nonblinded pathologists were not only informed about clinical and radiological information but were also "biased" by the fact that they were simultaneously assessing both TBLC and SLB for the same patient at the same time. Although the agreement level of 57.1% Wand and colleagues calculated from the provided data is correct, we considered this calculation problematic because the two approaches (blinded vs. nonblinded) cannot be directly compared, and we decided not to include it in our report. If anything, this would indicate that all pathologists involved held to a high diagnostic standard.

We also considered involving two or more blinded pathologists but, based on discussions with the statistician (N.M.), concluded that the addition of another blinded pathologist would have introduced more confusion than improvement in data readability. Indeed, the community should keep in mind that concordance among experts in this domain is traditionally fair to poor, and the cases involved are inherently difficult to diagnose.

Our study demonstrates that in several cases, TBLC alone would have led to a completely different diagnosis. One of these cases, chronic lymphocytic leukemia (at blinded TBLC) versus desquamative interstitial pneumonia (at SLB), can be discussed as an insightful example of poor concordance. Clearly, this case is related to a sampling issue and would likely have been sorted out in MDA discussions even with the TBLC alone (considering the patient's history of smoking and lymphoproliferative disease, among other factors).

The suggestion by Wand and colleagues to discuss either sampling technique in a separate MDA is interesting. We are planning to conduct such an analysis and will report our findings.

In conclusion, we definitely do not completely reject the role of TBLC in the assessment of ILDs. However, our findings suggest that for now, TBLC should not be considered interchangeable with SLB in the management of ILDs (1, 2). Although we all agree that we need further studies and data, we suggest that TBLC in patients with ILD should not be encouraged in routine clinical practice (4) and should only be performed in the setting of registered, ethically approved clinical trials involving clearly informed patients (5), or in patients who deliberately refuse or are not suitable for SLB. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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