(presumably with access to clinical information as well as both TBLC and SLB specimens) and the final diagnosis made at the second multidisciplinary assessment (MDA2) occurred in 17 of 21 cases. This is better than the concordance observed between both blinded SLB and MDA2 (13/21 cases) and TBLC and MDA2 (10/21 cases). Although the additional tissue that local pathologists would have had may be responsible for this difference, we wondered if access to clinical information may have been the major driver.

Finally, if an MDA meeting is taken as the gold standard for ILD diagnosis, both blinded SLB and TBLC performed poorly, and the difference in concordance between pathology specimens and MDA2 (13/21 cases for SLB vs. 10/21 cases for TBLC) did not appear dramatic. Given the potential morbidity associated with either biopsy approach, many questioned whether lung biopsy of any kind truly leads to meaningful improvements in clinical outcomes in ILD (6, 7).

In conclusion, we commend the authors for their well-done study, and acknowledge our ongoing confusion about the utility of lung histology for ILD diagnosis. Despite the poor concordance between TBLC and SLB, we hope cryobiopsy remains an area of study, as this paper has not completely "cooled off" our interest in this new and less invasive diagnostic technique. ■

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Comparing Transbronchial Cryobiopsy and Surgical Biopsy in Idiopathic Pulmonary Fibrosis

To the Editor:

In 2018, the Fleischner Society (1) and American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (2) guidelines for idiopathic pulmonary fibrosis were published. The American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association biopsy recommendations were made only for surgical lung biopsy (SLB), indicating that there was a lack of evidence to make a recommendation for or against performing transbronchial lung biopsy or transbronchial lung cryobiopsy (TBLC) (2).

Large studies evaluating TBLC have shown it to be an accurate and safer alternative to SLB (3). The concerns about the TBLC are related mostly to the substantial procedural variability among centers and the consequent variable diagnostic yields and complication rates (4).

Comparing two methods with a nonnegligible rate of complications in the same patient raises considerable ethical concerns about the possibility of duplicating the harms of each method without offering more benefit (5).

Romagnoli and colleagues (6) report the results of a prospective study designed to compare histopathological features in paired lung biopsy specimens from TBLC and SLB obtained sequentially from the same patient. The authors conclude that the tissue samples obtained for evaluation of interstitial lung disease demonstrated poor concordance, and that consequently, TBLC has not only lower sensitivity but also lower accuracy than SLB. However, some factors impose important limitations on the study.

The first factor is the high proportion of patients who were excluded by nonconsent. Among the initial 62 patients, 29 had autoimmune features; therefore, only 33 patients were actually eligible, and 12 of these patients (36%) were excluded by nonconsent. It is plausible that the excluded patients were different from those who were finally included in the study, confounding the accuracy of the analysis ("spectrum bias"). Additionally, TBLC was nondiagnostic in four cases, which therefore had to be excluded from the analysis, leaving only 17 cases.

Also, taking into account the spatial heterogeneity of idiopathic pulmonary fibrosis and the frequent overlap of different patterns of

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interstitial pneumonias, SLB and cryobiopsy samples should be taken from the same area. Unfortunately, the authors do not report whether the samples were obtained from the same area, and if so, how the procedure was done.

The κ concordance coefficient between TBLC and the final diagnosis at the second multidisciplinary assessment (MDA2, or after biopsy) was 0.31 (95% confidence interval, 0.06–0.56), and that between SLB and the final diagnosis was 0.51 (95% confidence interval, 0.27–0.75). Sample-size calculation is required for studies that apply inferential statistics, and should be included in all protocols according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, as failing to do so can lead to erroneous conclusions. Although the κ coefficient does not have a defined sample-size calculation (as there is no standard null hypothesis value) and is highly dependent on the prespecified minimum acceptable level of agreement (not provided in this paper), as a general rule, sample sizes should not consist of fewer than 30 comparisons. One would expect conclusions drawn from only 17 cases to have little statistical value.

Additionally, the results reported in this study are very difficult to interpret because the data were not blinded for the members of the MDA2. This means that three of the most influential biases that can affect the internal validity of any diagnostic accuracy study are present: clinical review bias (experimental tests are interpreted with knowledge of the participants' clinical characteristics), test review bias (experimental tests are interpreted with knowledge of the reference standard test results), and diagnostic review bias (the reference standard test results are interpreted with knowledge of the experimental test results).

Romagnoli and colleagues' study makes an interesting contribution to the discussion about TBLC versus SLB. It will be difficult to conduct larger, statistically reliable series due to safety and ethical concerns. In view of the enormous potential of TBLC, however, it is important to address issues regarding diagnostic yield and safety in multicenter, randomized controlled trials. ■

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Cryobiopsy Compared with Surgical Lung Biopsy in ILD: Reply to Maldonado *et al.*, Froidure *et al.*, Bendstrup *et al.*, Agarwal *et al.*, Richeldi *et al.*, Rajchgot *et al.*, and Quadrelli *et al*.

To the Editor:

We are pleased with the lively discussion our study (1) has generated regarding cryobiopsy and how multidisciplinary assessment (MDA) of interstitial lung disease (ILD) should function. Obviously, the uniting argument of all contributions—including ours—is improved patient care.

We do believe that proper methodology is essential when dealing with complex diseases such as ILD. Every time a "new" procedure is put forth to replace a "gold standard," it is methodologically correct to start by comparing the two methods. Our prospective study (1) started from a general enthusiasm for cryobiopsy and a perceived need for such a comparison of transbronchial lung cryobiopsy (TBLC) with surgical lung biopsy (SLB). The initial hypothesis optimistically assumed high concordance between TBLC and SLB samples (an anticipated $\kappa = 0.9$, with a 95% confidence interval of 0.4, which

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