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Before Freezing Out Cryobiopsy, We Need to Thaw Out Flaws in the Diagnosis of Interstitial Lung Disease

To the Editor:

We read with great interest the study by Romagnoli and colleagues (1) and commend the authors for exploring this important area, but we wish to express a number of concerns regarding their analysis.

First, we believe that there are a number of notable methodological issues with the current analysis. Our major concern is that the study should have compared the contributions of cryobiopsy and surgical lung biopsy (SLB) using the final multidisciplinary discussion (MDD) as the gold standard. In the seminal study by Flaherty and colleagues, pathologists modified their consensus SLB diagnosis in 19% of cases after they reviewed the clinical and radiological data (2). We suggest that the inclusion of four cases in which cryobiopsy was nondiagnostic in the outcome analysis may be misleading, as cryobiopsy would not influence management in this situation. Considering the remaining 17 cases, we note that there were two cases in which the cryobiopsy histologic diagnosis was endorsed by the MDD over the SLB and five cases in which SLB was endorsed over cryobiopsy.

Therefore, we suggest that the correct analysis would be a comparison between each modality against the final multidisciplinary diagnosis using the McNemar chi-squared test. There were seven cases in which cryobiopsy and SLB were concordant, and three cases in which neither was concordant with the final diagnosis. These 10 cases should be excluded because the McNemar chi-squared test confines analysis to cases in which tests give divergent results against a reference standard. Analysis based on the five cases in which SLB was concordant with MDD over cryobiopsy and the two cases in which cryobiopsy was concordant with MDD over SLB is nonsignificant ($P = 0.26$, rising to $P = 0.34$ with Yates correction).

Given the small sample size and some potential limitations of the analysis, we believe that the authors have overstated their conclusions about cryobiopsy, and that interpretation of this study should be far more limited.

A primary concern regarding cryobiopsy noted by the authors of this study involves two cases that were diagnosed as usual interstitial pneumonia (UIP) by cryobiopsy but were subsequently found to represent nonspecific interstitial pneumonia on SLB (the case of UIP on cryobiopsy that was found to represent chronic hypersensitivity pneumonia on SLB is arguably less problematic). However, it is difficult to interpret these data. The assumption that the diagnosis obtained via SLB is correct begs the question. The prior study by Flaherty and colleagues showed that SLB from multiple lobes can show different pathologies and the patient's course is determined by a finding of UIP (i.e., the worst pathology determines the clinical course) (3). It is entirely possible that cryobiopsy in these cases captured areas of true UIP outside the areas sampled by SLB. The only way to evaluate this is to follow the patients prospectively for their clinical course.

The use of blinded histologic slide review limits the generalizability of this study. The assessment of histologic samples in isolation from clinical and radiographic data for the diagnosis of interstitial lung disease (ILD) makes little sense given that the last decade of research in ILD diagnosis has taught us that ILD diagnosis is wholly a multidisciplinary process (2). Thus, assessing the contribution of a histologic diagnosis in a vacuum is misleading.

Lastly, this study does not reflect best clinical practice in the use of histology to reach a multidisciplinary diagnosis. The histologic diagnoses in this study were restricted to the single favored (blinded) diagnosis of the pathologist, and did not take into account any potential differential diagnostic considerations or the pathologist's confidence in the diagnosis, both of which could have come into play in the setting of an MDD. Like a clinical diagnosis, a histologic diagnosis ideally should be presented as a differential diagnosis (as the histologic features of many clinical entities overlap) rather than an arbitrarily restricted one. The use of differential and likelihood in a pathologic diagnosis of ILD is well demonstrated in the studies of Nicholson and colleagues, in which diagnostic considerations were given a percentage of likelihood summing to 100% (4).

There have been justified questions regarding the limitations and risks of cryobiopsy in the ILD community (5–7). The present study, however, is limited by substantial methodological limitations. We agree that robust data should be available before cryobiopsy is embraced as an accepted alternative to SLB for the diagnosis of ILD. However, given the lack of a historical alternative, SLB has benefited from a level of immunity in light of the morbidity and mortality risks recently reported in the literature, especially in patients over the age of 65 with suspected IPF (8). Clearly, transbronchial cryobiopsy requires considerable expertise for optimal results (3), a point that is not broached in this study. We call on the ILD community to move forward on a path to clarify the optimal biopsy modality options to ensure patient safety and improve clinical care. ■

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Bad Performance of Lung Cryobiopsy in the Diagnosis of Interstitial Lung Diseases: Don't Throw the Baby Out with the Bathwater

To the Editor:

Multidisciplinary management is the gold standard for interstitial lung disease (ILD) diagnosis and treatment (1). In the recent American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association guidelines, experts did not make any recommendation for or against transbronchial lung cryobiopsy (TBLC), mostly due to a lack of strong data and the absence of standardization for the procedure. To date, most experts agree that TBLC provides a proper diagnosis in 80% of cases (2, 3), and data suggest that cryobiopsy can have a significant impact when performed in the setting of multidisciplinary management of ILD (4). In a recent issue of the *Journal*, Romagnoli and colleagues reported the first study to directly compare surgical lung biopsy (SLB) with TBLC for the diagnosis of ILD (5). After samples were read and a diagnosis was made by local pathologists, the samples were blinded and read by an external expert pathologist. The results revealed poor concordance between the two techniques as compared with the final diagnosis retained by local teams, which clearly casts a shadow on the spreading use of TBLC.

The authors must be acknowledged for conducting the first study on sequential SLB and TBLC. However, some points should be noted to preclude any hasty conclusions. First, the fact that only 21 patients were included does not allow for a strong statistical analysis. In addition, when we look at each case, some of the apparent discrepancies were expected, as we know that some patients have two different pathology patterns in their lungs (6). On the other hand, some differences between SLB and TBLC in a single patient are quite surprising (e.g., in patient #15 in the study, TBLC showed Langerhans histiocytosis and SLB showed usual interstitial pneumonia).

The authors report that TBLC would have led to a different treatment if SLB had not been performed in 11 of 21 cases (52%).

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