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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.,
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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 unifying 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

can be tested with a sample size of 19). The methodology we used was “straight” and linear: we obtained lung tissue samples with the two different procedures at the same lobes/segments within two different lobes in the same patient during the same surgical session. The study was approved by ethical committees at two acknowledged academic hospitals (Montpellier and Bologna).

We had high hopes for this study, with no preconceived bias toward TBLC. After the blinded reading of the slides, we decided to publish the data as planned, despite the discouraging lack of high concordance, because they tell an important story. In hindsight, we are not surprised that a 0.5- to 1-cm maximal diameter sample obtained through airways (TBLC) does not sample lung tissue the same as a 3- to 4-cm diameter SLB.

We would like to emphasize that we clearly stated that our blinded histology “exercise” was artificial and outside the routine clinical workflow. We do, however, believe that our data fill an obvious gap in the literature and are thus happy to join the debate generated by our findings. Our study, which was small because of logistic and patient accrual constraints, should be viewed as an open door for discussion and not a threat toward further research.

Several discussants addressed how best to analyze our results. Providing clinical/radiological details to the blinded pathologist would have resulted in a memorization bias, which was out of the question for us. For similar future studies, we suggest assessing 1) a hierarchy of all differential diagnoses for a given sample, 2) the level of confidence assigned by the pathologist, and 3) concordance for the presence/absence of different types of histologic lesions (beyond histologic diagnosis alone). In addition, the integration of nondiagnostic cases in the final analysis deserves careful consideration. As properly noted by some correspondents, considering such cases as discordant lowers the κ coefficient. However, we considered this situation close to the clinical reality faced in MDA and thus appropriate, because a nondiagnostic result from either procedure will not provide additional information. Furthermore, withdrawing cases where the paired biopsy method “does not work” also pushes results toward cherry-picking. If such *a posteriori* case selections were applied, a sensitivity analysis would be a way to maintain proper transparency.

We agree that the role of MDA is fundamental and deserves specific attention. The results deserve further analysis by juxtaposing the influence of SLB and TBLC in different MDA situations. In the end, this will also address the question of what role they should play in ILD management. An MDA was shown to improve interobserver agreement and diagnostic confidence 15 years ago (2) and is nowadays accepted as the gold standard for ILD diagnosis (3–5). Although adopted worldwide, there are no formal recommendations for an MDA process or its composition. Thus, a “minimum MDA standard” is still hard to define (6), and the low agreement among MDAs for ILDs other than idiopathic pulmonary fibrosis remains a concern (7). As concerns our study, a 1-year follow-up diagnostic review of all 21 patients in the article (often seen as an acceptable gold standard) demonstrated perfect agreement with diagnoses as published; no later changes in diagnosis/management were observed.

For us, the take-home message is that cryobiopsies are not interchangeable with surgical biopsies and that further studies of this issue are warranted (4, 5). This does not mean that we are “freezing out” cryobiopsies or have “thrown the baby out with the bathwater.” We will be pursuing research in this domain and encourage others to do so (8).

In conclusion, if one considers TBLC as “the baby,” we suggest that the bathwater is dirty and requires a paradigm change. As long as the diagnosis of ILDs critically depends on patterns whose patchiness can exceed cryobiopsy dimensions, sampling error can occur. Further research designed to circumvent this situation (e.g., molecular classifiers for usual interstitial pneumonia patterns in small lung biopsies [9]), should be a top priority. If we can “clean up” the bathwater via robust pathological markers that render the probability of diagnosis independent of biopsy size, the baby will be much more comfortable.

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

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