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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Silvia Quadrelli, Ph.D.
Sanatorio Guemes
Buenos Aires, Argentina

Juan Ignacio Enghelmayer, M.D.*
Hospital de Clínicas José de San Martín
Buenos Aires, Argentina
and
Fundación para el Estudio de Enfermedades Fibrosantes del Pulmón
Buenos Aires, Argentina

Maria Otaola, M.D.
Fundación para el Estudio de Enfermedades Fibrosantes del Pulmón
Buenos Aires, Argentina
and
Instituto de Rehabilitación Psicofísica
Buenos Aires, Argentina

Edgardo Sobrino, M.D.
Sanatorio Mater Dei
Buenos Aires, Argentina

*Corresponding author (e-mail: jiedsn@gmail.com).

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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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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.

Micaela Romagnoli, M.D., Ph.D.*
AULSS2 Marca Trevigiana
Treviso, Italy
and
University of Bologna
Bologna, Italy

Thomas V. Colby, M.D.
Mayo Clinic
Scottsdale, Arizona

Carey M. Suehs, Ph.D.
Isabelle Vachier, Ph.D.
Nicolas Molinari, Ph.D.
Arnaud Bourdin, M.D., Ph.D.
University of Montpellier
Montpellier, France

On behalf of all the authors

ORCID ID: 0000-0002-2175-3496 (C.M.S.).

*Corresponding author (e-mail: miki.romagnoli@gmail.com).

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Erratum: The Early Development of Wheeze. Environmental Determinants and Genetic Susceptibility at 17q21

There was missing disclosure information in the article by Loss and colleagues (1), published in the April 15, 2016, issue of the *Journal*. The authors omitted to mention that Erika von Mutius should have been listed as an inventor on the following patents:

- Publication number EP 1411977: Composition containing bacterial antigens used for the prophylaxis and the treatment of allergic diseases
- Publication number EP1637147: Stable dust extract for allergy protection
- Publication number EP 1964570: Pharmaceutical compound to protect against allergies and inflammatory diseases

In addition, Dr. von Mutius should have been listed as an inventor on the following patent, for which she has received royalties:

- Publication number EP2361632: Specific environmental bacteria for the protection from and/or the treatment of allergic, chronic inflammatory and/or autoimmune disorders

This information has been incorporated in the ICMJE Disclosure of Potential Conflicts of Interest form accessible from the article's online supplements tab. ■

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Erratum: Respiratory Complications of Organophosphorus Nerve Agent and Insecticide Poisoning. Implications for Respiratory and Critical Care

The authors of the article by Hulse and colleagues (1), published in the December 15, 2014, issue of the *Journal*, would like to correct several errors. In the Figure 3 legend (p. 1345), the phrase "48 hours after administration of saline into the lung" in the second sentence should be corrected to read "48 hours after sham bronchoscopy and saline BAL (at 24 and 48 h)." The words "of the same lungs" appearing in the sixth and eighth sentences should be replaced by the words "similarly affected lungs." The corrected figure legend should read:

Figure 3. Effects of hematogenous organophosphorus (OP) and aspirated OP on minipig lung. Comparison of lung architecture in anesthetized minipigs 48 hours **after sham bronchoscopy and saline BAL (at 24 and 48 h)** (control pig; *A*, *D*, and *G*), gastric contents and the agricultural OP insecticide dimethoate EC40 into the contralateral lung (indirect hematogenous injury; *B*, *E*, and *H*), and gastric contents and agricultural OP insecticide dimethoate EC40 into the right lung (direct injury; *C*, *F*, *I*). (*A–C*) Light microscopy images (original magnification: ×10–20) with hematoxylin and eosin. Compared with indirect injury, direct injury caused greater alveolar and interstitial edema, neutrophil infiltration, hemorrhage, fibrin deposition, vascular congestion, and necrosis. Images edited in PowerPoint. (*D–F*) Scanning electron microscopy images (original magnification: ×171–324) of **similarly affected** lungs. Direct injury shows extensive destruction of the alveolar capillary framework, with fibrin mesh and clot formation. (*G–I*) Transmission electron microscopy images (original magnification: ×25,000) of **similarly affected** lungs. Both indirect and direct injury cause alveolar capillary membrane swelling. The *black arrow* signifies the alveolar capillary membrane in control (*G*) and indirect (*H*) lungs. After direct injury, this has led to the alveolar epithelium peeling away into the alveolar space and fibrin deposition (*red arrow*) in and around the alveolar capillary membrane.

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