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In Reply.—We appreciate the interest in our study investigating diagnostic agreement between surgical lung biopsies (SLBs) and transbronchial lung cryobiopsy in patients who underwent both procedures for the diagnosis of interstitial lung disease (ILD) as part of the COLDICE (Cryobiopsy versus Open Lung Biopsy in the Diagnosis of Interstitial Lung Disease Alliance) study.1 In our cohort, histologic guideline features for the diagnosis of usual interstitial pneumonia (UIP)2 were assessed, and “patchy fibrosis” together with “fibroblast foci” and “absence of alternate diagnostic features” in cryobiopsies strongly predicted UIP-pattern in paired SLBs. We would like to stress that this was a histologic pattern of UIP and not the final multidisciplinary discussion (MDD) diagnosis of idiopathic pulmonary fibrosis (IPF) that is characterized by a UIP-pattern histologically but also requires correlation with clinical, serologic, and radiologic findings at MDD to exclude other known causes of ILD and reach a definite diagnosis.2 As guidelines for the diagnosis of hypersensitivity pneumonitis (HP) were not published at the time, we did not test any specific diagnostic criteria for HP.

Churg et al have provided data indicating that mock (in silico) “cryobiopsies” derived from outlining circles (of similar size and quantity to cryobiopsies) on SLBs from cases with 60% or greater probability of fibrotic HP at MDD often have 2 histologic features of UIP (combination of fibroblastic foci and patchy fibrosis). However, when a third crucial feature for a histologic diagnosis of UIP-pattern—“absence of alternative diagnostic features”—is also included, only 14% or less of their cases would be “misclassified” as UIP-pattern from 4 “cryobiopsies.” As data were not provided on the number of their cases with giant cells/granulomas or peribronchiolar metaplasia in greater than 50% of bronchioles, the proportion of “misclassified” cases could be even lower than 14%. In our study, the median number of cryobiopsies was 5 (range, 2–7) meaning “misclassification” would differ slightly, but Churg et al have not provided data on 5 mock “cryobiopsies.” We do not think the comparison with 8 mock “cryobiopsies” is meaningful, as this was beyond the number of cryobiopsies obtained from any of our patients.

There are several other limitations with the data presented by Churg et al. Cryobiopsies selectively sample centrilobular parenchyma owing to their transbronchial approach; however, the mock “cryobiopsies” in the study of Churg and colleagues were selected by dividing whole, peripheral, video-assisted thoracoscopic surgery SLB into nonoverlapping rings, increasing the chance of undersampling histologic features with a centrilobular distribution. In addition, there was an inherent selection bias in their retrospective cohort that favored a final MDD diagnosis of HP. In selected patients who require SLB for diagnosis of their ILD, 10% to 30% are likely to have a final MDD diagnosis of HP,3 suggesting that the proportion of “misclassified” cases using cryobiopsies in real-world ILD clinic settings would likely be lower than what Churg et al have suggested.

The histologic pattern of UIP is characteristic of IPF but is not unique to this diagnosis and can also be seen in other conditions including fibrotic HP amongst others,4 underscoring the importance of clinicopathologic correlation and MDD in reaching the final diagnosis of any ILD. It is important to distinguish fibrotic HP from UIP/IPF owing to differences in treatment, although the impact on natural history and prognosis is less certain given that a UIP-pattern that includes fibroblast foci in patients with fibrotic HP predicts for shorter transplant-free survival.5 Nonetheless we agree that all attempts should be made to identify clues to fibrotic HP in biopsy specimens as clinical evidence of antigen exposure may be difficult to elicit, especially in chronic cases, and radiologic features may also overlap with UIP/IPF.3 Churg and associates previously observed that 2 (of 18) SLBs from patients with previously established diagnoses of “chronic” HP “could not be morphologically distinguished from idiopathic UIP,” attesting to the importance of MDD in establishing the diagnosis of fibrotic HP with greater confidence. Similarly, in the COLDICE study, 12% of surgical lung biopsies showing definite or probable UIP-pattern on histology, using guideline criteria, were subsequently diagnosed as fibrotic HP at MDD.7 Others have made similar observations.3,5,6,15 In many cases of fibrotic HP with UIP-like fibrosis there are additional features that may enable a histologic diagnosis of HP, including poorly formed granulomas/giant cells, centrilobular cellular interstitial pneumonia, cellular bronchiolitis and/or airway-centered fibrosis, peribronchiolar metaplasia, or bridging fibrosis, demonstrating the importance of sampling in influencing biopsy interpretation.3,14

In the COLDICE study, of 35 cases with an SLB-based MDD diagnosis of IPF (considered the gold standard), 32 matched cryobiopsy cases (91.4%) reached a MDD diagnosis of IPF, while the remaining 3 (8.6%) were
diagnosed as HP at cryobiopsy-based MDD. However, of 18 cases with an SLB-based MDD diagnosis of HP (considered the gold standard), 11 of 18 paired cryobiopsy-based MDD (61.1%) had a concordant diagnosis of HP, 5 (27.8%) had a cryobiopsy-based MDD diagnosis of IPF, and 2 (11.1%) were unclassifiable, suggesting HP may be more difficult to diagnose from cryobiopsy specimens in some cases. Discordant histologic diagnoses between paired cryobiopsies and SLBs were mostly fibrotic HP and UIP, highlighting the common challenge faced by pathologists. Fibrotic HP was the favored differential diagnosis made by pathologists after a diagnosis of UIP/IPF in both cryobiopsies and SLBs. A higher number of cryobiopsy samples was associated with a greater likelihood of concordant histologic diagnosis between cryobiopsy and SLB.

We agree that there are overlapping histologic features between UIP/IPF and some cases of fibrotic HP, leading to possible misclassification of some cases. While fibroblast foci and patchy fibrosis alone do not separate UIP/IPF and fibrotic HP, addition of “absence of features to suggest an alternate diagnosis,” as we have suggested, is useful in the distinction. We found that despite the challenges of overlapping histologic features in biopsy specimens, the correct diagnosis could be reached following MDD in most SLB and cryobiopsy cases. Further studies prospectively assessing the diagnostic value of real transbronchial cryobiopsies are required to evaluate and refine guideline criteria for histologic diagnosis of ILDs including IPF and fibrotic HP.

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