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## Reply to Moodley and to Ravaglia et al

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## Reply to Moodley and to Ravaglia *et al.*

From the Authors:

We thank Moodley for surfacing potential concerns about the radiological and histopathological features of idiopathic pulmonary fibrosis (IPF) that we refined in the new clinical practice guideline focused on the diagnosis of IPF (1).

The probable UIP pattern is based on the depiction of the second major radiological feature that enables the radiologist to assess lung fibrosis, namely traction bronchiolectasis. In this category, the high-resolution computed tomography (HRCT) features of reticulation, ground glass opacification (GGO), and distortion are minor changes, variably associated with peripheral traction bronchiolectasis.

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We introduced the subcategory of early usual interstitial pneumonia (UIP) to alert the individual clinical scenario of IPF relatively early in the disease course. This interest is triggered by the possibility of detection of subclinical interstitial lung disease in smokers that can evolve toward obvious fibrosis on CT follow-up (2–6). Although uncertainty still remains regarding the long-term prognostic implications of subclinical interstitial lung disease (3), it may be relevant to investigate these situations in select populations, with the ultimate goal of recognizing and treating IPF earlier.

The degree of lung attenuation is influenced by numerous variables on HRCT examinations, varying from the degree of inspiration to the kernels of reconstruction. Therefore, there is no recommendation for defining GGO with quantitative variables. Although they can be proposed in clinical research programs, they are not applicable to routine clinical practice.

Contrary to Moodley’s statement, the presence of traction bronchiectasis was not clearly stated in the previous “possible UIP” category. The only difference was the absence of honeycombing.

Removing GGO from the probable category would not make great differences in the categorization of patients. The indeterminate pattern (“truly indeterminate”) corresponds to HRCT features that do not correspond to an HRCT pattern of UIP, nor do they suggest any specific etiology for lung fibrosis. Among the HRCT features reported as indeterminate for UIP on CT sections, one can describe GGO of high attenuation; this HRCT feature has no further diagnostic value.

Moodley also raises an important issue, acknowledging that in circumstance of uncertainty regarding the histopathologic features conveyed by terms like “probable” or “indeterminate,” the uncertainty often centers on the difficulty of consistently separating the fibrotic variant of nonspecific interstitial pneumonia (NSIP) from UIP/IPF. The histologic features that define fibrotic NSIP are nonspecific, as the term implies, precisely because this same histology can occur focally (“NSIP-like changes”) in other conditions, including UIP/IPF. For that reason, deciding that a biopsy diagnosis of a fibrotic NSIP pattern is representative of a patient’s underlying condition is necessarily a matter of exclusion. In that sense, patients with biopsy diagnoses of fibrotic NSIP may indeed have UIP/IPF, depending on other information.

Because HRCT is imperfect in separating patients with fibrotic NSIP from patients with UIP/IPF who lack diagnostic radiological findings, it remains true that some patients considered to have fibrotic NSIP at diagnosis will ultimately prove to have UIP/IPF over time. This reflects the imperfect state of the art and the vulnerabilities that persist even in the context of multidisciplinary discussion. We agree that different groups of pulmonologists, radiologists, and pathologists may resolve these levels of uncertainty differently, meaning that patients assigned to a category of fibrotic NSIP in one institution may legitimately be assigned to other categories, including UIP/IPF, by others. This remains a key area for further investigation, with the hope of greater diagnostic reproducibility and precision.

Finally, Moodley raises the consideration of using combinations of antiinflammatory agents besides antifibrotic treatment strategy for patients with a new diagnosis of IPF, because subjects with subtle inflammation (suggested by allowance of some GGO in the appropriate clinical setting and meeting other criteria of the UIP pattern in the new guideline for the diagnosis of IPF) will be diagnosed with IPF from now on. Because the guideline focused on the diagnosis of IPF, the discussion regarding the therapeutic role of antifibrotics

and/or other antiinflammatory agents is indeed beyond the scope of the 2018 guideline and is a subject of much-needed future studies.

We also thank Ravaglia and colleagues for their interest in the new clinical practice guidelines (CPG) that we developed on diagnosis of IPF (1). In the guidelines, we pointed out that transbronchial lung cryobiopsy (TLCB) and surgical lung biopsy (SLB) have procedural mortalities of 0.2% and 1.7%, respectively.

As summarized in the new CPG, there were (and are to date, to our knowledge) no randomized controlled trials that offer a comparison of patient outcomes for TLCB compared with SLB. Conclusions and recommendations were made based on pooling studies of selected cohorts. The authors express concern that the approach for which they advocate—TLCB followed by SLB when the former is inadequate or nondiagnostic—will be construed as having a procedural mortality of 1.9%. The authors argue that the diagnostic yield of TLCB indicates that only 20% of patients require both procedures, with an anticipated average procedural mortality of 1.9%; most patients require only TLCB, with an average procedural mortality of only 0.2%. We agree; however, we advocate that this information be conveyed by presenting both ends of the spectrum, because it cannot be known in advance whether one or two procedures will be needed.

The reported SLB procedural mortality of 1.7% may not reflect the mortality risks in patients who are more severely ill; it is probably higher among more severely ill patients. We were unable to stratify the procedural mortality for SLB according to severity of illness; however, procedural mortality ranged from 0% to 4.4%, and the variation may have reflected differences in severity of illness, operator experience, etc. The potential for higher risk of mortality and complications associated with SLB in patients who are more sick with more severe impairment in lung function tests, oxygenation, and/or associated pulmonary hypertension is indeed a concern and is described in the guideline (“Surgical lung biopsy is not indicated in patients at high risk for intra-, peri-, or postoperative complications [e.g., severe hypoxemia at rest and/or severe pulmonary hypertension with a diffusion capacity less than 25% after correction for hematocrit]”). The risk of the complications/mortality associated with TLCB in similar patients is unknown. The data reported to date with TLCB are for patients who are ambulatory, and TLCB is performed as an elective outpatient procedure in most, if not all, patients. Further studies comparing TLCB to SLB in comparable cohorts controlled for disease severity are needed to support the argument made by Ravaglia and colleagues. In addition, the standard of care for SLB that has evolved over the last several years is to obtain wedge biopsies from two to three different lobes to increase the diagnostic yield, and this is based on the documented histopathologic variability in SLB from different lobes (7). The majority of reports to date for TLCB indicate that tissue is obtained from one lobe; complication rates and diagnostic yield for TLCB from different lobes are not yet known.

We trust that readers will understand that our reported procedural mortality reflects the average patient and will recognize that procedural mortality associated with TLCB and/or SLB may be higher in more severely ill patients and lower in less severely ill patients. As proposed in the new CPG for the diagnosis of IPF, the procedure and technique for TLCB suffers from lack of standardization—thus, the importance of restricting TLCB in its

current state to experienced experts (1). Well-designed studies with sequential lung biopsies (TLCB and SLB) from the same lobe are needed to settle the question of TLCB versus SLB as most appropriate diagnostic procedures to obtain the lung biopsy for histopathology diagnosis. It is hoped that ongoing and future studies worldwide will provide the much-needed results and settle the issue. ■

**Author disclosures** are available with the text of this letter at [www.atsjournals.org](http://www.atsjournals.org).

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Diagnosis of IPF

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**Erratum: Implications of Procalcitonin Testing in Critically Ill Patients with Sepsis**

There was an error in the order of the authors for the January 15, 2019, Recommended Reading feature: Dr. Jessica L. Nelson

should have been listed as the first author. The corrected author line should read:

Jessica L. Nelson, Christopher K. Hansen, Thomas M. Scupp, and Jason C. Brainard. ■

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**Reference**

1. Hansen C, Scupp T, Nelson J, Brainard J. Implications of procalcitonin testing in critically ill patients with sepsis. *Am J Respir Crit Care Med* 2019;199:232–234.

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