Reply to: Cottin et al., Johannson et al., Scholand and Wells, and Crowley et al.

Ganesh Raghu, Luca Richeldi, Carey C. Thomson, Martine Remy, Kevin C. Wilson

and safety of gefapixant, a $P2X_3$ receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. *Lancet* 2022;399:909–923.
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Reply to Cottin *et al.*, to Johannson *et al.*, to Scholand and Wells, and to Crowley *et al.*

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Originally Published in Press as DOI: 10.1164/rccm.202305-0786LE on August 3, 2022

From the Authors:

We thank Cottin and colleagues, Johannson and colleagues, Scholand and Wells, and Crowley and colleagues (1–4), for their letters, published in the November 15, 2022 issue of the *Journal*, regarding our 2022 clinical practice guideline addressing both idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF), hereinafter referred to as the IPF-PPF guideline (5).

We agree with Cottin and colleagues that "[d]isease progression, at whatever rate, should lead to a reevaluation of current management, often including the institution of antifibrotic therapy" (1, p. 1294). We never intended to imply that patients who progress quickly and meet the criteria for PPF before one year need to wait the full year before being defined and managed as having PPF. In such cases, the patient has met the criteria within the past year.

We respectfully disagree with the notion that "criteria for progression should be dissociated from the timelines during which they occur" (1, p. 1294). The importance of including one year in the diagnostic criteria was to ensure that the threshold values for change in FVC and D_{LCO} are appropriate. A 5% decrease in the FVC is clinically important if it occurs over a year or less but is less likely to be clinically important if it is spread out over many years. The committee tried to be as evidence based as possible in its approach to selecting diagnostic criteria, and most studies defined changes in physiological measures over one year.

Johannson and colleagues describe two key issues related to clinical practice guideline development (2). First, how much evidence is necessary to develop a clinical practice guideline? Second, what type of content is appropriate for a clinical practice guideline?

The long-standing position of the American Thoracic Society, European Respiratory Society, and Asociación Latinoamericana de Tórax is that the need for a guideline should be based on the importance of the questions and need for guidance, not the amount or type of evidence that exists, which the Japanese Respiratory Society also accepted for this guideline as a co-sponsoring society. In theory, until the required systematic review is performed, one does not know how much evidence exists. A clinical practice guideline is defined by the approach used. Clinically important questions are asked, and then a systematic review is performed to find the best available evidence to inform the question. It is common that the systematic review fails to identify randomized trials or controlled observational evidence. In such cases, it is acceptable for guideline committees to make research recommendations or, alternatively, to use uncontrolled evidence or unsystematic clinical observations to inform clinical recommendations, as long as the poor quality of evidence is clearly acknowledged (6). Consistent with this approach, the IPF-PPF guidelines described evidence in detail, made multiple research recommendations, and provided a single clinical recommendation on the basis of very low-quality evidence (5).

Along these lines, Johannson and colleagues imply that addressing PPF in a clinical practice guideline was putting the cart before the horse; in other words, the body of evidence should have been allowed to grow before doing a guideline rather than developing a guideline during the early stages of evidence generation. We agree that more evidence would have been informative and may have yielded more clinical recommendations than research recommendations. However, the topic was deemed clinically important, with an urgent need for guidance, as the INBUILD trial had prompted an abrupt paradigm shift toward an en bloc approach

to antifibrotic therapy for fibrotic interstitial lung diseases other than IPF (7). In essence, already the horse was already out of the barn.

Johannson and colleagues are correct that clinical practice guidelines address four types of questions: who to treat, which treatment to use, on whom to perform diagnostic testing, and which diagnostic test to perform. However, hybrid documents that contain guideline content (e.g., diagnosis, treatment) and narrative content (e.g., epidemiology, definitions, radiology, pathology) have long been allowed by professional societies, because readers find the breadth of such documents desirable as long as the methods are clearly described. Consistent with this approach, the IPF-PPF guideline stated, "narrative portions … were created using consensus by discussion. Guideline portions address specific questions [and] … are compliant with the Institute of Medicine standards for trustworthy guidelines …" (5, p. e19).

Scholand and Wells argue on behalf of genomic classifier testing. Opinion among the guideline committee members was divided, and the views shared by Scholand and Wells are consistent with the portion of the committee that favored genomic classifier testing. Among their arguments, they state that the risk of bleeding from transbronchial biopsy is low (8). The guideline committee was aware that the risk of bleeding from transbronchial biopsy is lower than the bleeding risks from transbronchial lung cryobiopsy, even though the study that Scholand and Wells cite was not included in the guideline's systematic review because it did not meet the prespecified selection criteria (9). The bottom line remains: There were good arguments on both sides but insufficient agreement to yield a recommendation according to the committee's prespecified voting rules.

Crowley and colleagues question whether the quality of evidence was underestimated, because two randomized trials, one addressing antacid therapy (10) and one addressing antireflux therapy (11), were drowned out by multiple observational studies. In fact, even if only the randomized trials had been considered, the quality of evidence would still have been rated as very low quality because of the risk of bias, imprecision, or indirectness (12), as detailed in the systematic review that informed the guideline (13). Crowley and colleagues further ask whether recommendations should be made in the context of very low-quality evidence, a notion that was addressed earlier in response to Johannson and colleagues.

The comments from Crowley and colleagues are an important opportunity to emphasize a major point in the guideline. It is possible that antacid therapy may have beneficial effects in patients with confirmed gastroesophageal reflux (GER) that were negated by the inclusion of patients with IPF without GER in studies that enrolled all patients with IPF; therefore, the guidance might change if patients with IPF are stratified as either having or not having confirmed GER and the efficacy of antacid medication is determined for each subgroup; a larger study will need to be undertaken to determine the efficacy of antireflux surgical therapy. We look forward to the completion of the Treating people with Idiopathic Pulmonary fibrosis with the Addition of Lansoprazole (TIPAL) trial and its incorporation into future evidence-based decision making. ■

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

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