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## Identifying “Real” Patients in the Real World

To the Editor:

I applaud Dr. Dempsey and colleagues on their recent article, “Clinical Effectiveness of Antifibrotic Medications for Idiopathic Pulmonary Fibrosis,” investigating the effects of nintedanib and pirfenidone in idiopathic pulmonary fibrosis (IPF) (1). This study provides the first description of these medications in real-world clinical practice and compares patients with IPF who received antifibrotic therapy with matched subjects who received no antifibrotic therapy. The article’s illustration of patients and their demographics was heartening, especially given pulmonologists’ experience in caring for patients significantly older than those included in the INPULSIS (Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis) and ASCEND (Efficacy and Safety of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis)

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trials (2, 3). Their findings support the use of antifibrotic therapies perhaps in a larger cohort than is typically perceived to derive benefit from them.

Despite the retrospective nature of this study, the authors were able to apply an extremely rigorous methodology to ascertain the effects of these medications by using propensity score matching and local International Classification of Diseases (ICD)-9 and ICD-10 validation strategies. One additional step that might shed further light on antifibrotic effects would be to control the analysis for treatment origin site (i.e., whether the prescribing physician originated from an academic center or a community practice). As interstitial lung disease physicians, we perceive high levels of discordance among interstitial lung disease diagnoses between academic and community physicians (4). Numerous drivers explain these discrepancies, including variability in regular multidisciplinary conference participation and the infrequency with which providers may see these complex patients (5, 6). Regular practices such as multidisciplinary conferences are associated with higher diagnostic accuracy rates (7).

One could speculate about what the actual rate of “true” IPF diagnoses is in the insurance database used in this article, given the retrospective nature of the study and the use of ICD codes to identify patients. The authors astutely recognize these limitations in their discussion, although there appear to be opportunities to further enrich this analysis. Accounting for the origination site of antifibrotic therapy would provide a greater degree of confidence that they are identifying patients with IPF, as those patients would run the gauntlet of the multidisciplinary conference and would be more likely to be cared for by practitioners experienced with IPF. One representative example of this point is the large number of patients with rheumatoid arthritis, which would suggest an alternative diagnosis in >8% of the dataset’s population. Although it is not a certainty, one could envision that such misinterpretations would not occur in a setting that has more experience with this kind of patient. It is unclear what effect this modification would have on the study results, but the degree of benefits may even be intensified given that academic center–affiliated clinicians would likely have more experience in prescribing these medications, as well as more expertise in managing their adverse effects.

I would again like to commend the authors for this tremendous article demonstrating the practical effects of antifibrotics over a half decade after their approval by the U.S. Food and Drug Administration. I hope the article spurs further research in the field of IPF and leads clinicians to offer more patients the option of antifibrotic therapy. ■

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

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## Reply to Callahan

From the Authors:

We thank Dr. Callahan for his letter regarding our recent publication on the clinical effectiveness of pirfenidone and nintedanib for patients with idiopathic pulmonary fibrosis (IPF) (1). We appreciate his remarks on our methodology, and agree that controlling for index treatment site (academic vs. community practice) would be a valuable addition to the literature. Unfortunately, as with all retrospective studies, our analysis was limited by the confines of the dataset we used. Although our data allow for subgroup analysis by region, they do not allow for separation by the granular geographic detail necessary to divide the cohort into patients with IPF treated in academic centers and those treated in community practice. Our hope is to analyze the effectiveness of these medications again with a Medicare fee-for-service cohort, which would allow for treatment variation analyses by entities such as “hospital referral regions,” a methodology that has allowed for the study of geographic differences and academic medical center practice variation in the past (2, 3).

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We also endorse his support for treatment initiation in consultation with disease experts, as well as the importance of multidisciplinary discussions to confirm the diagnosis of “true” IPF—practices that have been corroborated by many of the recent guidelines and literature (4, 5). As acknowledged in our article, the diagnosis of IPF can be clinically challenging, which then makes the use of billing codes in this population quite complex and susceptible to some degree of misidentification. With the local cohort validation, we believe we were able to identify a population largely consisting of patients with “true” IPF, although (as described) miscoding is still possible.

The potential for misidentification is perceptively highlighted by Dr. Callahan in his identification of the proportion of patients in our cohort with rheumatoid arthritis (RA). Although we agree that the patients with concomitant RA in the cohort make alternative diagnoses possible, the number is small enough that it should not affect the overall analysis. In addition, patients with RA and a usual interstitial pneumonia pattern on imaging (as is likely for those in our cohort, given their coded diagnosis of IPF) have been shown to have mortality similar to that observed in those with “true” IPF, which makes it even more unlikely that the outcomes were modified by the less than 9% of individuals in the cohort with RA (6).

Once again, we thank Dr. Callahan for his letter and very much appreciate his discussion about the value of multidisciplinary teams when diagnosing IPF, and his advocacy for an analysis comparing academic medical centers and community practices when determining the effectiveness of pirfenidone and nintedanib. We look forward to further studies evaluating these and other important questions surrounding the antifibrotic medications for patients with IPF. ■

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