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## Ⓐ Preserved Ratio Impaired Spirometry and Interstitial Lung Abnormalities in Smokers

To the Editor:

I read with great interest the paper by Wan and coworkers evaluating the preserved ratio impaired spirometry (PRISm) functional pattern ( $FEV_1/FVC \geq 0.7$  and  $FEV_1 > 80\%$ ) in their longitudinal study of a large cohort of current or ex-smokers (1). The prevalence of this heterogeneous condition is remarkable (12.4% and 12.5% at baseline and follow-up, respectively) and its association with increased mortality, comparable to that observed in Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2 subjects, deserves special consideration. Individuals with PRISm are characterized by a significantly lower TLC% predicted and percent emphysema, as measured on quantitative computed tomography scans, in comparison with GOLD 0 and GOLD 1–4 groups.

In the study cohort, the PRISm status was not stable at 5-year follow-up; in particular, the authors report a transition to GOLD 0 in 22% of the subjects with PRISm and a transition to PRISm in about one-third of baseline GOLD 0 individuals. The latter group was characterized by a lesser amount of emphysema and air trapping on computed tomography scans, an increase in body mass index, and decreased TLC% predicted and percent emphysema at baseline. Moreover, this group exhibited the largest functional decline (either  $FEV_1$  or FVC) in comparison with all other groups, suggesting a restrictive physiologic impairment.

Interstitial lung abnormalities have been found in a substantial minority of a cohort of smokers enrolled in the COPDGene (Genetic Epidemiology of Chronic Obstructive Pulmonary Disease) study (1 out of 12) and were associated with a reduced TLC and a lesser amount of emphysema. Smokers with interstitial lung abnormalities were more likely to have an “unclassified” spirometric pattern, analogous to PRISm (2). Under this definition are grouped various morphological pictures that may represent static imaging findings or the early stage of a progressive fibrosing disease (3).

The evidence of many similarities between smokers identified as carriers of interstitial lung abnormalities and those functionally classified as having PRISm makes me think that at least a small subset of baseline GOLD 0 subjects who transitioned to the

PRISm group could have developed a smoke-related interstitial disorder. ■

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

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## Reply to Marruchella



From the Authors:

On behalf of our coauthors, we thank Dr. Marruchella for his interest in the longitudinal analysis of Preserved Ratio Impaired Spirometry (PRISm) ( $FEV_1/FVC \geq 0.7$  and  $FEV_1 < 80\%$  predicted) in the COPDGene (Genetic Epidemiology of Chronic Obstructive Pulmonary Disease) study (1) and for bringing attention to the possible role of interstitial lung abnormalities in PRISm. Among the first 2,500 subjects enrolled in phase 1 of the COPDGene study, a significantly higher prevalence of interstitial lung abnormalities on chest computed tomography imaging was noted among the PRISm subgroup, then referred to by the moniker “GOLD-Unclassified,” relative to the remainder of the COPDGene cohort (22% vs. 10–13% among GOLD 0–4) (2). This same research group subsequently extended their visual assessment

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of interstitial lung abnormalities to a subset of individuals with serial chest computed tomography data from the Framingham Heart Study and reported accelerated loss of FVC among individuals with radiographic progression of interstitial changes (relative to individuals without interstitial lung abnormalities or with stable interstitial lung abnormalities) (3). Within COPDGene, individuals who developed “incident PRISm” (i.e., transitioned from normal spirometry [“GOLD 0”] at phase 1 to PRISm at phase 2) also exhibited higher rates of lung function decline, albeit in both FEV<sub>1</sub> and FVC rather than isolated declines in FVC (1). The degree to which interstitial lung abnormalities contribute to this transition has not yet been fully characterized.

Assessment of the *de novo* development of interstitial lung abnormalities as well as progression of existing interstitial lung abnormalities are active areas of investigation within COPDGene. Notably, a significant number of subjects with PRISm in COPDGene had anatomical abnormalities that were not limited to interstitial parenchymal changes, including chest wall and diaphragmatic deformities as well as a smaller internal transverse thoracic diameter in phase 1 (4). In addition to anatomical and parenchymal changes, functional differences, such as small airway disease (5) and gas transfer abnormalities, represent additional domains that should be explored in PRISm.

We continue to assert that the PRISm cohort is heterogeneous and is likely composed of subgroups with distinct pathobiological processes (6); interstitial lung abnormalities likely contribute to the development and progression of lung disease in a subset of subjects with PRISm. Future studies, both within and beyond COPDGene, to characterize the predictors and risks associated with distinct subgroups within PRISm are needed. ■

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## Robust Methods Are Needed to Evaluate the Pharmacologic Treatment of Obstructive Sleep Apnea



To the Editor:

We read with interest the recent article by Taranto-Montemurro and colleagues on the impact of atomoxetine plus oxybutynin on obstructive sleep apnea (OSA) severity (1). Although we hope there is a potential role for this new pharmacologic approach, we are concerned about methodological choices that may introduce bias into estimates of the efficacy of this treatment.

First, there is the problem of missing data. In this crossover trial, two out of 12 subjects (17%) randomized to atomoxetine–oxybutynin as the first treatment dropped out, versus zero of 10 subjects (0%) randomized to placebo first. Such dropouts are typically differential in nature, and ignoring them by using a complete-case analysis tends to overestimate the benefits of atomoxetine–oxybutynin. Methods such as mixed-effects models that use all collected data would provide a more robust estimate of the true effect of atomoxetine–oxybutynin while also allowing for the evaluation of any crossover effects (2).

Second, and of more concern, the authors focus on a *post hoc* analysis in which they stratified patients on the apnea–hypopnea index (AHI) while the patients were receiving a placebo (those with AHI > 10 events/h on placebo treatment). Stratification on an observed value of the study outcome is well understood to provide biased results. Performing a comparison of atomoxetine–oxybutynin versus placebo while restricting the analysis to patients with poor results on placebo would result in a positively biased estimate of the treatment effect. If the treatment were to have no effect whatsoever, one could still create the appearance of a “positive” effect by selecting only the patients with poor results on placebo—this is a variation of the commonly

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