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# Longitudinal Phenotypes and Mortality in Preserved Ratio Impaired Spirometry in the COPDGene Study

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## Abstract

**Rationale:** Increasing awareness of the prevalence and significance of Preserved Ratio Impaired Spirometry (PRISm), alternatively known as restrictive or Global Initiative for Chronic Obstructive Lung Disease (GOLD)-unclassified spirometry, has expanded the body of knowledge on cross-sectional risk factors. However, longitudinal studies of PRISm remain limited.

**Objectives:** To examine longitudinal patterns of change in lung function, radiographic characteristics, and mortality of current and former smokers with PRISm.

**Methods:** Current and former smokers, aged 45 to 80 years, were enrolled in COPDGene (phase 1, 2008–2011) and returned for a 5-year follow-up (phase 2, 2012–2016). Subjects completed questionnaires, spirometry, chest computed tomography scans, and 6-minute-walk tests at both study visits. Baseline characteristics, longitudinal change in lung function, and mortality were assessed by post-bronchodilator lung function categories: PRISm ( $FEV_1/FVC < 0.7$  and  $FEV_1 < 80\%$ ), GOLD0 ( $FEV_1/FVC > 0.7$  and  $FEV_1 > 80\%$ ), and GOLD1–4 ( $FEV_1/FVC < 0.7$ ).

**Measurements and Main Results:** Although the prevalence of PRISm was consistent (12.4–12.5%) at phases 1 and 2, subjects with PRISm exhibited substantial rates of transition to and from other lung function categories. Among subjects with PRISm at phase 1, 22.2% transitioned to GOLD0 and 25.1% progressed to GOLD1–4 at phase 2. Subjects with PRISm at both phase 1 and phase 2 had reduced rates of  $FEV_1$  decline ( $-27.3 \pm 42.1$  vs.  $-33.0 \pm 41.7$  ml/yr) and comparable proportions of normal computed tomography scans (51% vs. 52.7%) relative to subjects with stable GOLD0 spirometry. In contrast, incident PRISm exhibited accelerated rates of lung function decline. Subjects with PRISm at phase 1 had higher mortality rates relative to GOLD0 and lower rates relative to the GOLD1–4 group.

**Conclusions:** PRISm is highly prevalent, is associated with increased mortality, and represents a transitional state for significant subgroups of subjects. Additional studies to characterize longitudinal progression in PRISm are warranted.

**Keywords:** spirometry classification; spirometry statistics and numerical data; spirometry mortality; lung disease epidemiology

Proportionate reductions in the  $FEV_1$  and FVC on spirometry, variably referred to in the medical literature as restrictive, Global Initiative for Chronic Obstructive Lung

Disease (GOLD)-unclassified (1), nonspecific (2), or Preserved Ratio Impaired Spirometry (PRISm) (3) patterns, are estimated to have a cross-sectional

prevalence between 5% and 19% (3–6) and are associated with increased respiratory symptoms (7–9) and mortality (5, 6, 10–14). Risk factors for this spirometric

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A complete list of COPDGene Investigators may be found before the REFERENCES.

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This article has an online supplement, which is accessible from this issue's table of contents at [www.atsjournals.org](http://www.atsjournals.org).

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## At A Glance Commentary

### Scientific Knowledge on the

**Subject:** Preserved Ratio Impaired Spirometry (PRISm), more commonly known as “restrictive spirometry,” is a heterogeneous group associated with increased mortality. Longitudinal phenotypes within PRISm, which may be associated with differential risk, remain poorly characterized.

### What This Study Adds to the

**Field:** We examine longitudinal demographic, spirometric, chest computed tomography, and mortality data in the largest cohort of subjects with PRISm reported to date. We confirm the association between PRISm and increased mortality, present evidence to support the concept that PRISm represents a transitional state in a significant proportion of individuals, and describe potentially higher (“incident PRISm”)- and lower (“stable PRISm”)-risk subtypes, which should be examined in future studies.

pattern include female sex, ever smoking cigarettes, diabetes mellitus, advanced age, extremes of body mass (both high and low), and increased central adiposity (7, 15–17). Globally, a history of tuberculosis (18–20) and exposure to biomass combustion products (21) have been identified as additional risk factors for PRISm.

Knowledge gaps in our understanding of PRISm persist, in part because of the historical exclusion of individuals with this spirometric abnormality from pulmonary research studies and to uncertainty regarding the significance of this lung function pattern. Emerging data from a modest number of longitudinal cohorts suggest that PRISm represents a transitional stage for a subset of individuals, with significant subgroups either progressing to classic airflow obstruction (defined by a reduced FEV<sub>1</sub>/FVC ratio) or normalizing their lung function over time (2, 10, 22). In this article, we examine 1) cross-sectional prevalence of PRISm at baseline and 5 years later, 2) mortality, and 3) longitudinal patterns of progression in lung function and radiographic features in a large, deeply phenotyped cohort of current and former

smokers enrolled in the COPDGene study (23). We hypothesized that a substantial fraction of COPDGene patients would transition into and out of the PRISm group and that subjects transitioning into this group would have different characteristics relative to those who persisted in the PRISm group. A portion of the work contained in this manuscript has been previously published in abstract form (24).

## Methods

### Study Population and Data

Subjects were participants in COPDGene (ClinicalTrials.gov identifier: NCT000608764), an observational study of self-identified non-Hispanic white and African American current and former smokers from 21 clinical centers throughout the United States (23). Institutional review board approval was obtained at each participating site, and all subjects provided written informed consent. At baseline, subjects (phase 1, 2008–2011) were between the ages of 45 and 80 years, with 10 or more pack-years of cigarette smoking; exclusion criteria included a history of significant lung disease other than chronic obstructive pulmonary disease (COPD) or asthma and history of lung volume reduction surgery or lung transplantation (23). Subjects enrolled in phase 1 were invited to participate in a 5-year follow-up study visit (phase 2, 2012–2016). The study protocol and related documents are available at [www.copdgene.org](http://www.copdgene.org).

Subjects completed 1) questionnaires including the modified American Thoracic Society Respiratory Epidemiology Questionnaire, modified Medical Research Council dyspnea scale, St. George’s Respiratory Questionnaire (SGRQ); 2) spirometry before and after the administration of inhaled albuterol; 3) 6-minute-walk (6MW) test; and 4) inspiratory and expiratory chest computed tomography (CT) scanning at both study visits. Quantitative imaging analysis was performed using VIDA and Thirona software to determine percentage emphysema (percentage of voxels on inspiratory CT scan with an attenuation < −950 Hounsfield units), percentage gas trapping (percentage of lung with an attenuation < −856 Hounsfield units on expiratory CT scan), and TLC. Airway wall thickness

was calculated as the square root of the wall area of a hypothetical airway with a 10-mm internal perimeter (Pi10). Visual scoring of phase 1 chest CT data was performed by at least two trained observers to denote the presence or absence of radiographic abnormalities (25). Vital status was assessed both centrally and at individual clinical centers using the Social Security Death Index (December 18, 2016 dataset; *see* online supplement). Acute respiratory events, defined as worsening respiratory symptoms requiring the use of systemic steroids and/or antibiotics, were assessed through the COPD Longitudinal Follow-up Program (26).

### Variable Definitions

Percent predicted and lower limit of normal (LLN) values were calculated using National Health and Nutrition Examination Survey III reference equations for spirometry (27). PRISm was defined as a post-bronchodilator FEV<sub>1</sub>/FVC greater than or equal to 0.7 and an FEV<sub>1</sub> less than 80% predicted (3). The GOLD0 group was defined as an FEV<sub>1</sub>/FVC greater than or equal to 0.7 and FEV<sub>1</sub> greater than or equal to 80% predicted, and classically obstructed lung disease was defined as FEV<sub>1</sub>/FVC less than 0.7 (GOLD1–4). Subjects who had a lung transplant or lung volume reduction surgery between phase 1 and phase 2 visits were excluded from lung function analysis at phase 2.

### Statistical Analyses

Univariate comparisons between subjects with PRISm and subjects with GOLD0 and GOLD1–4 spirometry were made using chi-square or Fisher exact test for categorical variables and Student’s *t* test or Wilcoxon rank sum test for continuous or ordinal variables. Univariate and Cox proportional hazards models adjusting for baseline age, race, sex, current smoking status, cumulative smoke exposure, and body mass index (BMI) were constructed to examine survival by lung function group. All analyses were conducted using the R statistical software (version 3.4.3) using the base, *rmngb* (28), *survival* (29), and *survminer* (30) packages.

## Results

Among 10,199 current and former smokers from phase 1 and 6,284 subjects from phase

2, 10,133 (phase 1) and 5,621 (phase 2) had valid spirometry data available. The prevalence of PRISm among individuals with spirometry data available remained relatively unchanged at 12.4% (phase 1) and 12.5% (phase 2). Characteristics of the subjects with PRISm relative to subjects with GOLD0 and GOLD1–4 spirometry at phases 1 and 2 are shown in Table 1. At both phases 1 and 2, subjects with PRISm have the highest average BMI, are enriched for African Americans and current smokers, and have the lowest TLC and quantitative emphysema measurements.

### Mortality by Lung Function Category

Subjects with lung function data at phase 1 and subsequent assessment of vital status available ( $n_{\text{total}} = 8,800$ ) were included in an analysis of mortality rates by lung function category. Subjects with PRISm at phase 1 (PRISm-P1) had unadjusted mortality rates intermediate between subjects with GOLD0 and GOLD1–4 spirometry (Figure 1). Hazard ratios by lung function category from Cox proportional hazards models adjusted for age, sex, race, current smoking status, BMI, and pack-years are shown in Figure 2. PRISm remained a significant predictor for increased mortality in models that adjusted for center of enrollment (data

not shown) and when BMI was examined as a three-level categorical variable (see Figure E1 in the online supplement). When we examined mortality rates in PRISm relative to individual GOLD1–4 spirometry categories, unadjusted mortality rates for PRISm were intermediate between GOLD1 and GOLD2 strata (Figure E2). In Cox proportional hazards models adjusted for age, sex, race, current smoking, and BMI, PRISm mortality rates were not significantly different from the GOLD2 strata (Figure E3). In a subgroup analysis of individuals with PRISm-P1, African American race was no longer a risk factor for increased mortality, and increasing BMI was associated with a trend toward increased risk instead of decreased risk, as noted in the full cohort model (Figure E4).

### Longitudinal Change in Lung Function

Of the 6,284 COPDGene subjects who returned for the 5-year follow-up visit, 5,593 subjects had valid lung function data available at both phases 1 and 2. The rate of FEV<sub>1</sub> and FVC decline per year by lung function category is shown in Table 2; as a group, subjects with PRISm-P1 had lower average rates of lung function decline relative to subjects with either GOLD0 or GOLD1–4 spirometry.

The modest decline in average lung function among individuals with PRISm-P1 is due, in part, to a substantial minority (22.2%) who improved their lung function at phase 2 (i.e., transitioned from PRISm to GOLD0 spirometry); Figures 3 and E5 illustrate the transitions between lung function categories of subjects with PRISm-P1 and PRISm-P2 (PRISm-P2). A higher proportion of subjects with PRISm-P1 transitioned to a different lung function category at phase 2 (47.4%) relative to individuals with GOLD0 spirometry or GOLD1–4 spirometry (20.4% and 11.8%, respectively).

### Longitudinal Lung Function Change in Subjects with PRISm-P1

A significant number of subjects with PRISm-P1 transitioned to a different lung function category at phase 2. Baseline characteristics of individuals with PRISm-P1 by lung function category at phase 2 are shown in Table 3. There were no differences in sex, race, baseline symptoms (modified Medical Research Council dyspnea scale, SGRQ), or exercise capacity (6MWD distance) associated with future lung function category at phase 2. Reduction in BMI was associated with transitioning from PRISm-P1 to GOLD0 spirometry at phase 2 (Table 3). In a

**Table 1.** Cohort Characteristics at Phase 1 and Phase 2 by Spirometric Lung Function Class

	Phase 1			Phase 2		
	PRISm	GOLD0	GOLD1–4	PRISm	GOLD0	GOLD1–4
Subjects, <i>n</i> (%)	1,260 (12.4)	4,389 (43.3)	4,484 (44.3)	703 (12.5)	2,424 (43.1)	2,494 (44.4)
Female sex, <i>n</i> (%)	678 (53.8)	2,068 (47.1)*	1,977 (44.1)*	390 (55.5)	1,283 (52.9)	1,113 (44.6)*
African American, <i>n</i> (%)	541 (42.9)	1,807 (41.2)	1,018 (22.7)*	291 (41.4)	836 (34.5)*	589 (23.6)*
Age at study visit, yr	57.2 (8.2)	56.6 (8.4)*	63.1 (8.6)*	62.4 (8.1)	63.3 (8.3)*	68.0 (8.3)*
BMI, kg/m <sup>2</sup>	31.9 (7.3)	28.9 (5.8)*	27.9 (6.1)*	32 (7.5)	29.2 (6.0)*	28 (6.2)*
Current smoker, <i>n</i> (%)	802 (63.7)	2,619 (59.7)*	1,944 (43.4)*	346 (49.3)	967 (39.9)*	881 (35.3)*
Pack-years	42.6 (24.2)	37.2 (20.2)*	51.6 (27.2)*	41.9 (23.1)	37.5 (20.7)*	50.8 (25.2)*
FEV <sub>1</sub> % predicted	70.2 (8.4)	97.4 (11.5)*	57.4 (22.8)*	70.1 (8)	97.7 (11.8)*	60.6 (22.7)*
FVC % predicted	71.5 (9.2)	96.6 (11.9)*	81.8 (20.3)*	70.8 (8.9)	95.8 (11.7)*	82.5 (20.0)*
TLC % predicted <sup>†</sup>	80.3 (13.4)	92.7 (14.8)*	102.2 (16.8)*	81.5 (13.4)	94.2 (14.2)*	101.5 (16)*
Percent emphysema <sup>†</sup>	1.6 (2.6)	2.1 (2.7)*	12.0 (12.4)*	1.4 (3.3)	1.7 (2.5)*	10.8 (11.9)*
BDR, <i>n</i> (%) <sup>‡</sup>	171 (13.8)	431 (10.0)*	1495 (33.6)*	95 (13.6)	247 (10.3)*	767 (30.8)*
SGRQ	29.8 (23.1)	17 (18)*	36.9 (22.9)*	24.5 (21.3)	14.6 (16.7)*	32.0 (21.8)*
6MWD, m	385.9 (112.0)	454.8 (106.8)*	375.7 (124.3)*	369.0 (123.7)	432.5 (121.9)*	360.2 (135.5)
Chronic bronchitis, <i>n</i> (%)	225 (17.9)	552 (12.6)*	1,164 (26.0)*	80 (11.4)	210 (8.7)*	561 (22.5)*

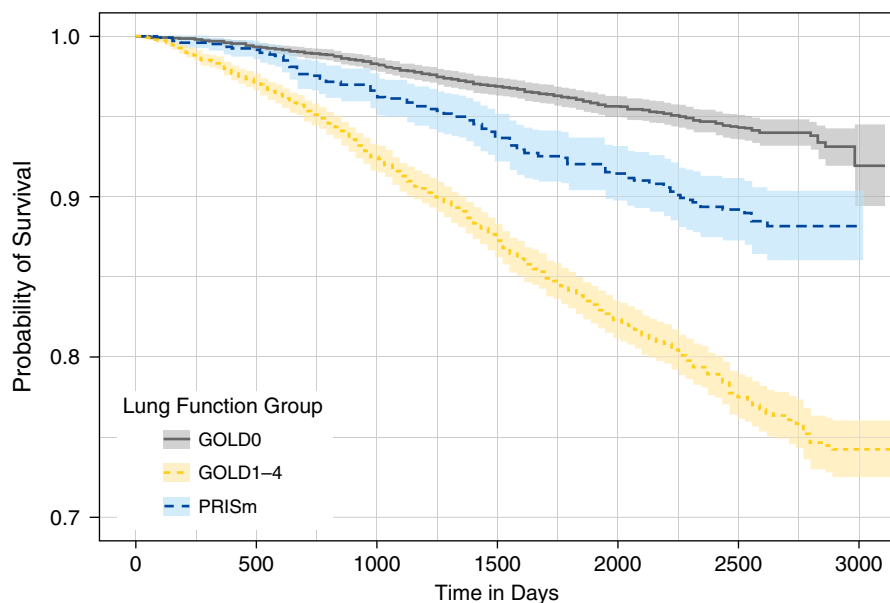
*Definition of abbreviations:* 6MWD = 6-minute-walk distance; BDR = bronchodilator responsive; BMI = body mass index; GOLD = Global Initiative for Chronic Obstructive Lung Disease; PRISm = Preserved Ratio Impaired Spirometry; SGRQ = St. George's Respiratory Questionnaire.

Data are expressed as mean (SD) unless otherwise noted.

\**P* value < 0.05 relative to PRISm.

<sup>†</sup>Numbers of subjects with quantitative computed tomography imaging available: PRISm = 1,139, GOLD0 = 4,104, GOLD1–4 = 4,178 (phase 1); PRISm = 465, GOLD0 = 1,819, GOLD1–4 = 1,831 (phase 2).

<sup>‡</sup>BDR defined as  $\geq 200$  ml and  $\geq 12\%$  increase in either FEV<sub>1</sub> or FVC after administration of inhaled albuterol. Numbers of subjects with BDR data: PRISm = 1,243, GOLD0 = 4,309, GOLD1–4 = 4,451 (phase 1); PRISm = 700, GOLD0 = 2,390, GOLD1–4 = 2,491 (phase 2).



**Figure 1.** Kaplan-Meier plot of mortality by lung function category in the COPDGene cohort ( $n_{\text{GOLD0}} = 3,783$ ,  $n_{\text{PRISM}} = 1,058$ ,  $n_{\text{GOLD1-4}} = 3,959$ ). PRISM:  $\text{FEV}_1/\text{FVC} \geq 0.7$  and  $\text{FEV}_1 < 80\%$  predicted; GOLD0:  $\text{FEV}_1/\text{FVC} \geq 0.7$  and  $\text{FEV}_1 \geq 80\%$  predicted; GOLD1-4:  $\text{FEV}_1/\text{FVC} < 0.7$ . GOLD = Global Initiative for Chronic Obstructive Lung Disease; PRISM = Preserved Ratio Impaired Spirometry.

multivariate model adjusting for age, sex, race, current smoking status, and pack-years, decreasing BMI remained a significant predictor of the PRISM-P1 to GOLD0 in phase 2 transition (Table E1). In a secondary analysis of subjects with PRISM-P1, which also adjusted for change in TLC ( $n_{\Delta\text{TLCavailable}} = 474$ ), decreasing BMI remained a significant predictor of transitioning from PRISM to GOLD0 spirometry (data not shown).

#### Subgroup Analysis: Stable PRISM

Approximately half of the subjects who had PRISM-P1 continued to demonstrate PRISM at P2 (i.e., stable PRISM). The average rate of decline in  $\text{FEV}_1$  among subjects with stable PRISM was significantly less than that observed in subjects with stable GOLD0 spirometry at phases 1 and 2 ( $-27.2 \pm 42.2$  ml/yr vs.  $-33 \pm 41.6$  ml/yr, respectively). This difference remained significant in multivariate regression models adjusting for age, sex, race, cumulative cigarette smoking, and current smoking status at enrollment (Table E2). Subjects with stable PRISM had comparable rates of decline in FVC relative to subjects with stable GOLD0 spirometry (data not shown). Among subjects with visual scoring of baseline CT scan data available ( $n_{\text{stablePRISM}} = 297$ ,  $n_{\text{stableNormal}} = 1,857$ ), subjects with

stable PRISM had a comparable proportion of scans judged by expert reviewers to be normal relative to subjects with stable GOLD0 spirometry (51.2% vs. 52.8%,  $P = 0.6$ ).

#### Subgroup Analysis: PRISM to GOLD1-4 Transition

Subjects who transitioned from PRISM-P1 to GOLD1-4 at phase 2 exhibited higher mean rates of decline in  $\text{FEV}_1$  and lower mean rates of decline in FVC relative to other subjects with PRISM at phase 1 (Table 3); higher variances in the rates of lung function decline were also observed. These subjects also had the highest average cumulative cigarette smoke exposure, TLC% predicted, percent emphysema, and percent gas trapping at baseline relative to subjects who remained PRISM or normalized their lung function. In analyses of subjects with available quantitative CT data using multivariate logistic regression models, baseline TLC% predicted and percentage gas trapping remained significant predictors of transitioning to GOLD1-4 at phase 2 (Table E3).

#### Incident PRISM Exhibits Accelerated Lung Function Decline

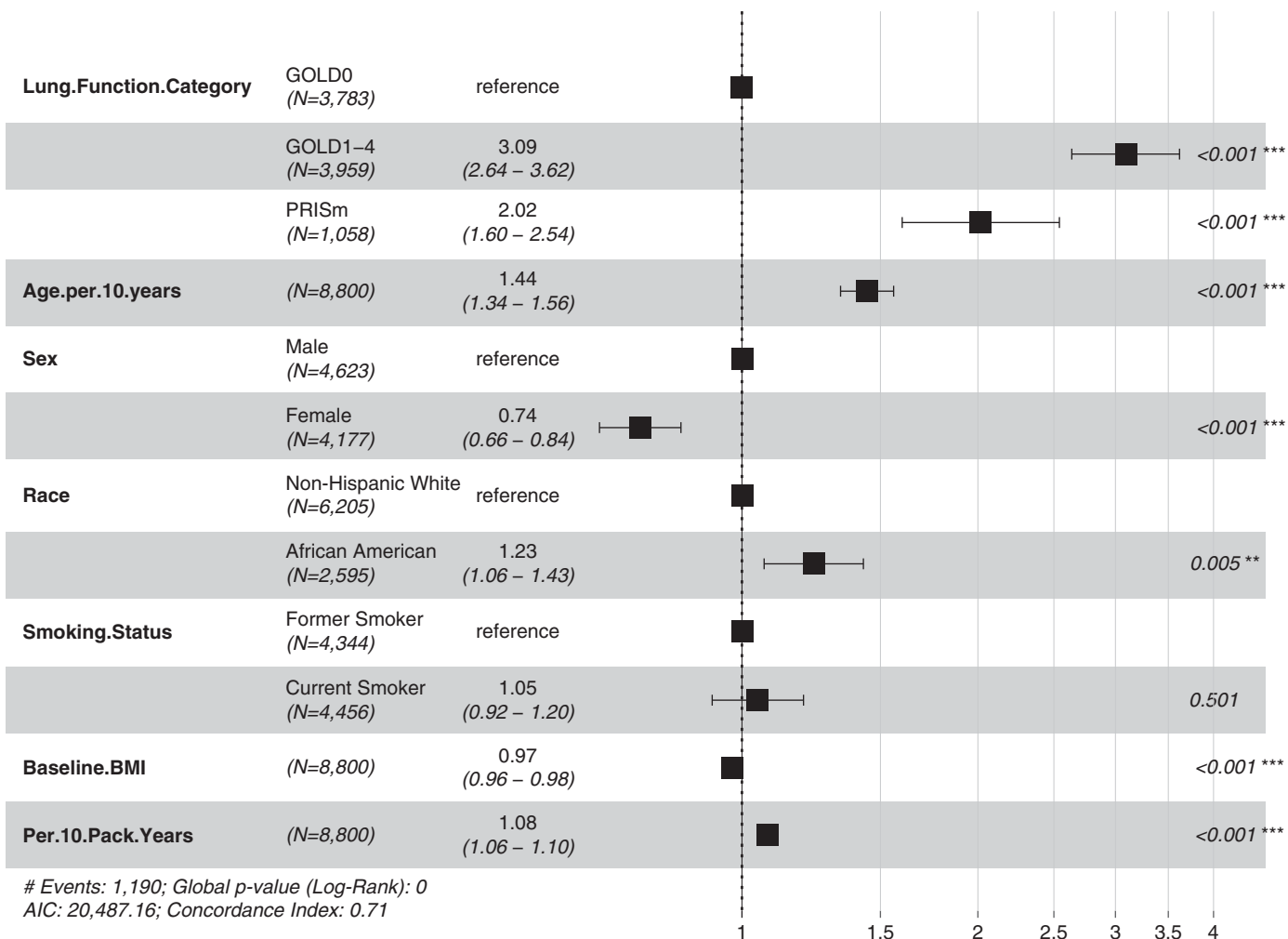
Approximately one-third of the subjects with PRISM-P2 had GOLD0 spirometry at

phase 1 (i.e., incident PRISM). The subjects who developed incident PRISM had a higher average rate of decline in both  $\text{FEV}_1$  ( $-88 \pm 42.5$  ml/yr) and FVC ( $-105.4 \pm 60.7$  ml/yr) relative to all other COPDGene subjects with lung function data available at phase 1 and phase 2 ( $-35.8 \pm 50.7$  ml/yr of  $\text{FEV}_1$  and  $-44.3 \pm 77.6$  ml/yr of FVC). In multivariate models adjusting for age, sex, race, current smoking status at enrollment, and cumulative cigarette smoke exposure, incident PRISM status remained independently associated with an accelerated rate of decline in  $\text{FEV}_1$  (Table E4). The rate of decline in  $\text{FEV}_1$  in incident PRISM also exceeded the rate of decline in subjects who developed incident classical obstruction (GOLD0-P1 to GOLD1-4; data not shown).

Baseline characteristics of subjects who developed incident PRISM-P2 relative to subjects with GOLD0 spirometry at baseline who did not develop PRISM are shown in Table E5. Subjects who developed incident PRISM were younger and had higher average BMI as well as increased proportions of current smokers and African Americans. Subjects who developed incident PRISM had less radiographic emphysema and gas trapping but greater airway wall thickness (Pi10) relative to subjects who did not develop incident PRISM. Subjects who developed incident PRISM also had more dyspnea and worse functional status (as indicated by higher SGRQ scores and lower 6MW distance) at baseline and the largest increase in average BMI between phase 1 and phase 2. Such subjects were also more likely to have bronchodilator responsiveness at baseline. In both univariate and multivariate models, decreased baseline TLC% predicted and percentage emphysema and greater change in BMI were robust independent predictors of incident PRISM status at phase 2 among individuals with GOLD0 spirometry at phase 1 (Table E6).

#### LLN Analyses

Because the use of fixed threshold cutoffs can lead to overestimation of obstructive lung disease in older individuals, we repeated selected key analyses using LLN thresholds (29) to define PRISM-LLN ( $\text{FEV}_1/\text{FVC} \geq \text{LLN}$  and  $\text{FEV}_1 < 80\%$  predicted), COPD-LLN ( $\text{FEV}_1/\text{FVC} < \text{LLN}$ ), and normal-LLN ( $\text{FEV}_1/\text{FVC} \geq \text{LLN}$ ,  $\text{FEV}_1 \geq 80\%$  predicted). Among subjects with lung function measurements



**Figure 2.** Forest plot of hazard ratios for mortality from Cox proportional hazards model. PRISm: FEV<sub>1</sub>/FVC ≥ 0.7 and FEV<sub>1</sub> < 80% predicted; GOLD0: FEV<sub>1</sub>/FVC ≥ 0.7 and FEV<sub>1</sub> ≥ 80% predicted; GOLD1-4: FEV<sub>1</sub>/FVC < 0.7. \*\*P < 0.01; \*\*\*P < 0.001. AIC = Akaike information criterion; BMI = body mass index; GOLD = Global Initiative for Chronic Obstructive Lung Disease; PRISm = Preserved Ratio Impaired Spirometry.

available, the prevalence of PRISm-LLN was 14.9% at phase 1 and 16.5% at phase 2. Subjects with PRISm-LLN at phase 1 continued to demonstrate increased rates of transitioning to a different lung function category at phase 2 (42.0%) relative to

normal-LLN (17.0%) and COPD-LLN (15.6%). Among PRISm-LLN phase 1 subjects with lung function measurements available at phase 2, 20.2% transitioned to COPD-LLN (Figure E6). In Cox proportional hazards models adjusted for age, sex, race,

current smoking status, pack-years, and BMI, PRISm-LLN was associated with increased mortality relative to the normal-LLN group (Figure E7).

## Discussion

Increasing awareness of the prevalence and significance of proportional impairments in FEV<sub>1</sub> and FVC on spirometry has led to an increase in the average number of publications on the topic from 15 per year (1996–2000) to 47 per year (2010–2015) (31) (Table E7). The vast majority of studies are cross-sectional, with a small number examining change in cross-sectional prevalence over time (32). Longitudinal studies of PRISm remain limited but are beginning to demonstrate

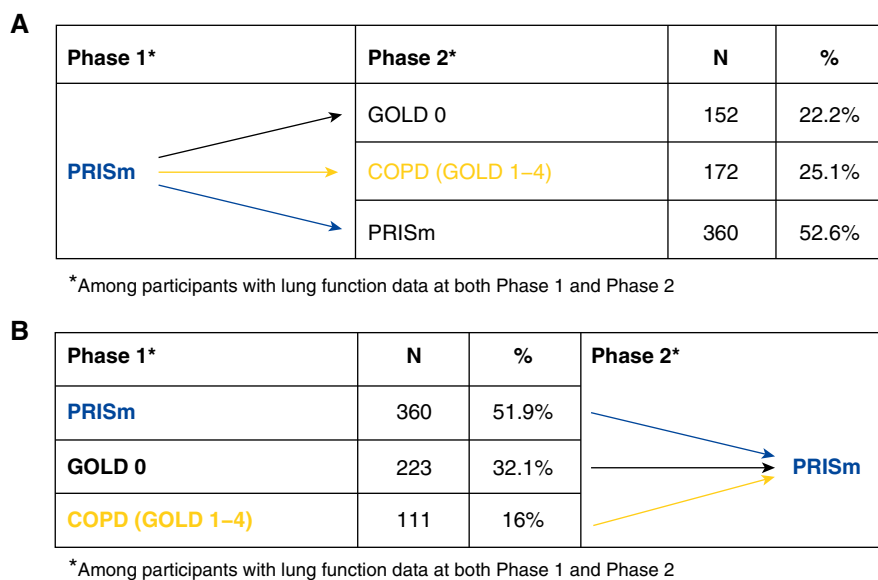
**Table 2.** Rate of Lung Function Decline by Lung Function Category at Enrollment

	Lung Function Category at Phase 1		
	PRISm (n = 684)	GOLD0 (n = 2,641)	GOLD1-4 (n = 2,268)
ΔFEV <sub>1</sub> , ml/yr	-18.9 (52.6)	-41.8 (47.1)*	-38.9 (54.5)*
ΔFVC, ml/yr	-9.8 (68.1)	-41.9 (63.5)*	-63.4 (90.4)*

Definition of abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease; PRISm = Preserved Ratio Impaired Spirometry.

Data are expressed as mean (SD).

\*P < 0.05 relative to PRISm.



**Figure 3.** Change in lung function categories among subjects with Preserved Ratio Impaired Spirometry (PRISm) at (A) phase 1 and (B) phase 2. COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

trends that may help to inform patterns of progression and prognosis.

Although the cross-sectional prevalence of PRISm within COPDGene remained unchanged, individual membership in PRISm was fluid, with nearly half of individuals either transitioning to or from another lung function category. The increased rate of transitions was observed regardless of whether fixed threshold or LLN criteria were used. Frequent transitions between lung function groups among patients with PRISm have been reported in other cohorts; similar proportions of transitions over 5 years were observed in heavy smokers enrolled in the Lovelace Smokers Cohort (22). During more than 24 years of follow-up in the TESAOD (Tuscon Epidemiological Study of Airway Obstructive Disease) cohort (10), more than half of the cohort with PRISm demonstrated either an “inconsistent” or “mixed” pattern of lung function impairment. Artfactual transitions in lung function resulting from “noise” in spirometry testing among individuals who straddle cutoff thresholds between categories are possible; however, the consistently increased proportion of individuals with PRISm who transition between lung function categories in independent cohorts supports the concept that these changes in lung function may reflect time-varying biological or pathological

processes or potentially greater spirometric variability in the PRISm group.

We have confirmed the association between PRISm and increased mortality relative to individuals with GOLD0 spirometry (5, 10) and have expanded our analyses to consider the effects of race, sex, current smoking, and cumulative cigarette smoke exposure. Among the entire COPDGene cohort, female sex and increased BMI were both protective from mortality, whereas increasing age, cumulative cigarette smoke exposure, and African American race were associated with increased risk of death. These results were consistent regardless of whether PRISm was defined using fixed threshold or LLN criteria. Within the subgroup of individuals with PRISm at phase 1, African American race was not significantly associated with differential mortality, whereas increasing BMI was associated with increased, rather than decreased, mortality risk. This apparent “reversal” in the effect of BMI is likely due to the higher mean BMI among subjects with PRISm and the well-established J-shaped relationship between BMI and mortality; many subjects in the PRISm group reside firmly on the “ascending” arm of BMI mortality (33). The lack of significance of African American race as a predictor for increased mortality among PRISm may be due to a loss of statistical power in the PRISm subgroup

analysis. Alternatively, less-accurate lung function prediction equations for African Americans may have led to an artifactual enrichment in PRISm rather than being indicative of lung pathology.

A second important finding was that the aggregate rate of lung function decline in PRISm was lower than the rate for other subjects enrolled in COPDGene, despite increased rates of current smoking at enrollment. This finding is both counterintuitive and distinct from a study of Peruvian adults, in whom PRISm was associated with accelerated decline in FEV<sub>1</sub> (34). Differences in the populations examined in each of the studies (ethnicity, exposures, etc.) as well as considerable heterogeneity within PRISm populations likely contributed to these discrepancies. As noted above, although the aggregate rate of lung function decline in PRISm was modest, certain subgroups (e.g., incident PRISm) demonstrated accelerated rates of lung function decline, and other groups (resolving PRISm) demonstrated improvements in lung function.

Characterizing longitudinal patterns among patients with PRISm will be critical in informing the development of clinical management strategies. We hypothesize that, given the heterogeneity evident within PRISm, higher- and lower-risk subgroups likely exist. Between 15% and 40% of individuals with PRISm progress to develop classic airflow obstruction (i.e., COPD) (2, 10, 22). Because many of these prior studies examined older populations with the use of fixed ratio-defined obstruction, it is possible that a proportion of these PRISm-to-obstruction transitions resulted from age-related decline in the FEV<sub>1</sub>/FVC ratio. Within COPDGene, the rate of transition from PRISm to classic obstruction decreased modestly when using LLN relative to fixed-ratio thresholds but continued to account for a significant proportion of subjects. Given the increased mortality observed in COPD (5), as well as longitudinal data suggesting that individuals who transition between PRISm and classically obstructed states have increased mortality (10), we assert that this represents a higher-risk subgroup within PRISm. Although radiographic features such as higher TLC% predicted and increased gas trapping were independent predictors of developing classically obstructed spirometry in the future within the PRISm population in COPDGene,

**Table 3.** Characteristics of Subjects with Preserved Ratio Impaired Spirometry at Phase 1 by Lung Function Category at Phase 2

	Lung Function Category at Phase 2		
	PRISm (n = 360)	GOLD0 (n = 152)	GOLD1–4 (n = 172)
Months between phase 1 and phase 2 visits	67.6 (9.6)	67.5 (9.4)	67.3 (9.0)
Age, yr	56.7 (8.1) <sup>*†</sup>	58.6 (8.1)	59.3 (8.8)
Female sex, n (%)	200 (55.6)	94 (61.8)	89 (51.7)
African American race, n (%)	141 (39.2)	61 (40.1)	69 (40.1)
BMI, kg/m <sup>2</sup>	32.7 (7.7) <sup>†</sup>	32.4 (6.7)	31.2 (7.2)
Current smoker, n (%)	219 (60.8) <sup>*</sup>	77 (50.7)	97 (56.4)
Pack-years	40.4 (22.3) <sup>†</sup>	38.8 (20.6) <sup>‡</sup>	45.9 (25.0)
FEV <sub>1</sub> % predicted, baseline	69.5 (8.1) <sup>*</sup>	74.8 (5.5) <sup>‡</sup>	68.2 (8.8)
FVC% predicted, baseline	70.2 (8.9) <sup>*†</sup>	75.0 (6.8) <sup>‡</sup>	71.9 (9.7)
TLC <sub>CT</sub> % predicted <sup>§</sup>	79.3 (13.2) <sup>†</sup>	80.5 (13.9) <sup>‡</sup>	84.2 (15.0)
Chronic bronchitis, n (%)	63 (17.5) <sup>*</sup>	15 (9.9)	28 (16.3)
mMRC	1.4 (1.4)	1.4 (1.4)	1.4 (1.4)
SGRQ	28.1 (23.2)	25.2 (19.5)	29.1 (23.5)
6MWD, m	402.1 (111.4)	401.7 (102.6)	384.4 (106.6)
Percent emphysema <sup>§</sup>	1.5 (3.2) <sup>†</sup>	1.6 (2.1) <sup>‡</sup>	2.2 (2.9)
Percent gas trapping <sup>  </sup>	8.2 (6.6) <sup>†</sup>	9.7 (7.6) <sup>‡</sup>	12.6 (8.2)
Pi10, mm <sup>**</sup>	3.72 (0.12)	3.72 (0.12)	3.71 (0.14)
Acute respiratory events/yr <sup>††</sup>	0.3 (0.6) <sup>†</sup>	0.3 (0.8)	0.4 (0.8)
ΔFEV <sub>1</sub> , ml/yr	−27.2 (42.2) <sup>*†</sup>	28.0 (44.5) <sup>‡</sup>	−42.9 (53.8)
ΔFVC, ml/yr	−32.6 (56.8) <sup>*†</sup>	35.7 (59.4) <sup>‡</sup>	−2.6 (75.2)
ΔBMI, kg/m <sup>2</sup>	0.0 (3.8) <sup>*</sup>	−1.3 (3.8) <sup>‡</sup>	−0.4 (3.5)
ΔAdjusted lung density, g/L <sup>‡‡</sup>	−0.2 (12.5)	−2.4 (11.2)	−2.7 (12.1)

*Definition of abbreviations:* 6MWD = 6-minute-walk distance; BMI = body mass index; CT = computed tomography; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified Medical Research Council; P1 = phase 1; P2 = phase 2; Pi10 = square root of the wall area (in mm) of a hypothetical airway with an internal perimeter of 10 mm; PRISm = Preserved Ratio Impaired Spirometry; SGRQ = St. George's Respiratory Questionnaire; TLC<sub>CT</sub> = total lung capacity by computed tomography.

Data are expressed as mean (SD) unless otherwise noted. Data are shown for subjects with lung function data at P1 and P2.

\* $P < 0.05$  between PRISm-P2 and GOLD0 spirometry at P2.

<sup>†</sup> $P < 0.05$  between PRISm-P2 and GOLD1–4 spirometry at P2.

<sup>‡</sup> $P < 0.05$  between GOLD0 and GOLD1–4 at P2.

<sup>§</sup>Subjects with quantitative CT imaging available for analysis: PRISm = 331, GOLD0 = 138, GOLD1–4 = 154.

<sup>||</sup>Subjects with quantitative CT imaging available for analysis: PRISm = 272, GOLD0 = 112, GOLD1–4 = 122.

\*\*Subjects with quantitative CT imaging available for analysis: PRISm = 329, GOLD0 = 138, GOLD1–4 = 152.

<sup>††</sup>Subjects with longitudinal follow-up data on acute respiratory events as assessed by interview every 6 months: PRISm = 341, GOLD0 = 142, GOLD1–4 = 166.

<sup>‡‡</sup>Subjects with change in CT lung density data: PRISm = 250, GOLD0 = 108, GOLD1–4 = 116.

significant heterogeneity within this group exists, and additional features and methods to identify the subset at risk are needed.

Individuals who transition from GOLD0 spirometry to PRISm (incident PRISm) may also warrant consideration as a higher-risk subgroup. Accelerated lung function decline and increased respiratory morbidity in the incident PRISm subgroup were observed in our cohort and have also been reported in an independent study of young adults over nearly 30 years of follow-up (35). In the TESAOD cohort, the subset of subjects with incident PRISm demonstrated a trend toward increased all-cause mortality, which did not reach statistical significance (10). Within the Lovelace Smokers Cohort, recent-onset PRISm was associated with increased rates of “beneficial transitions,” especially in individuals with excess weight (22); a

similar trend is implied from the association of change in BMI with both incident PRISm and resolving PRISm.

Of the longitudinal phenotypes observed in our study, a subset of subjects with stable PRISm may qualify for consideration as a lower-risk subtype. Subjects with stable PRISm appear to have normal, or even subnormal, rates of lung function decline and a comparable proportion of chest CT scans judged by expert reviewers to be entirely normal relative to individuals with stable normal spirometry. We hypothesize that some members of the stable PRISm subgroup may represent individuals who did not attain maximal lung function in early adulthood and, without additional pathological processes, have typical age-related decline in lung function (36, 37). Given reduced reserve, these individuals would be expected

to become symptomatic earlier and may have increased mortality relative to their counterparts with normal pulmonary reserve, an observation that appears to be supported indirectly by data from the TESAOD cohort (10, 38). Although low maximal lung function has been shown to be a risk factor for the development of classic obstructive lung disease, the same has not been explicitly investigated for PRISm. Additional longitudinal studies of this stable PRISm subgroup are warranted to determine their rate of lung function decline and their risk of mortality.

In summary, we have demonstrated that PRISm 1) is associated with increased mortality relative to individuals with GOLD0 spirometry, 2) has a high rate of transitioning to other lung function categories, and 3) is likely composed of distinct subgroups. The major strengths



of our study include the large number of deeply phenotyped individuals with longitudinal lung function, radiographic, and clinical acute respiratory event data; the use of post-bronchodilator spirometry (4); and the inclusion of African Americans. Limitations include the lack of races/ethnicities other than non-Hispanic whites and African Americans (39), longitudinal assessments at only two time points, and the exclusion of nonsmokers and lighter smokers (<10 pack-years cumulative exposure) as well as individuals younger than 45 years of age. Given the increasing prevalence of light smoking (which includes nondaily and social smoking) among young adults (40, 41) and increased prevalence of respiratory symptoms in this population (42), studies that include these individuals are needed. Last, differential rates of subject participation in phase 2 could lead to either under- or overestimation of effects. Within our cohort, individuals with worse lung function at baseline had lower rates of enrollment in phase 2 (Table E8), suggesting that our cohort may have a “healthy subject” bias (analogous to the “healthy worker” bias), whereby individuals who are more ill are less likely to participate. We acknowledge these relative weaknesses limit the generalizability of our findings, but we contend that the size and detail within our cohort allowed for hypothesis generation regarding the existence of clinically relevant subgroups within PRISm. Future studies, both within COPDGene and in additional independent cohorts with longitudinal data, are warranted to refine and quantify the consequences and trajectories of progression of distinct PRISm subtypes. ■

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