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Predictive value of prebronchodilator and postbronchodilator spirometry for COPD features and outcomes

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ABSTRACT

Introduction We compared the predictive value of prebronchodilator and postbronchodilator spirometry for chronic obstructive pulmonary disease (COPD) features and outcomes.

Methods We analysed COPDGene data of 10 192 subjects with smoking history. We created regressions models with the following dependent variables: clinical, functional and radiographic features, and the following independent variables: prebronchodilator airflow obstruction (PREO) and postbronchodilator airflow obstruction (POSTO), prebronchodilator and postbronchodilator FEV_1% predicted. We compared the model performance using the Akaike information criterion (AIC).

Results The COPD prevalence was higher using PREO. About 8.5% had PREO but no airflow obstruction in postbronchodilator spirometry (POSTN) (PREO-POSTN) and 3% of all subjects had no aiflow obstruction in prebronchodilator spirometry (PREN) but POSTO (PREN-POSTO). We found no difference in COPD features and outcomes between PREO-POSTN and PREN-POSTO subjects. Although, both prebronchodilator and postbronchodilator spirometries are both associated with chronic bronchitis, dyspnoea, exercise capacity and COPD radiographic findings, models that included postbronchodilator spirometric measures performed better than models with prebronchodilator measures to predict these COPD features. The predictive value of prebronchodilator and postbronchodilator spirometries for respiratory exacerbations, change in forced expiratory volume in 1 s, dyspnoea and exercise capacity during a 5-year period is relatively similar, but postbronchodilator spirometric measures are better predictors of mortality based on AIC.

Conclusions Postbronchodilator spirometry may be a more accurate predictor of COPD features and outcomes.

Key messages

► The chronic obstructive pulmonary disease (COPD) prevalence was higher using prebronchodilator spirometry.
► We found no difference in COPD features and outcomes between subjects with discordance in prebronchodilator and postbronchodilator spirometry.
► Although both prebronchodilator and postbronchodilator spirometries are associated with COPD features and outcomes, postbronchodilator spirometry may be a more accurate predictor.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) diagnosis is based on a spirometric definition according to Global Initiative for Chronic Obstructive Lung Diseases guidelines.[1] This diagnosis requires the presence of airflow obstruction (AFO) defined as forced expiratory volume in 1 s (FEV_1)/ forced vital capacity (FVC) below the lower limit of normal (LLN) or 0.7.[1] Several studies have compared FEV_1/FVC<LLN with FEV_1/FVC <0.7 as a diagnostic criterion for AFO.[2–4] GOLD recommends a postbronchodilator FEV_1/FVC <0.7. The rationale is based on its simplicity, independence of reference values and the fact that it is used in numerous clinical trials.[1] However, to our knowledge, there is little evidence to support the use of postbronchodilator spirometry for COPD diagnosis over prebronchodilator spirometry. A single study with 300 subjects showed that postbronchodilator spirometry is a better predictor of mortality than prebronchodilator spirometry in COPD.[5] Mannino *et al*[6] showed that both prebronchodilator and postbronchodilator lung function predict mortality with a similar accuracy.

COPD prevalence is lower when postbronchodilator spirometry is used compared with when prebronchodilator spirometry is used.[7] In the absence of a true 'gold standard' for COPD diagnosis, the utility of a diagnostic test depends on whether it can predict outcomes or change disease management. Previous studies showed conflicting results regarding the ability of prebronchodilator and postbronchodilator spirometry in predicting mortality.[5][6] Whether postbronchodilator spirometry is superior to prebronchodilator spirometry to predict outcomes other than

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mortality has not been studied. We hypothesised that prebronchodilator and postbronchodilator spirometries are associated with COPD features and predict outcomes with the same accuracy.

Subjects with significant hyperinflation, and therefore with more dyspnoea,[8] may have a reduced prebronchodilator FVC and a normal FEV_1/FVC ratio.[9] Because FVC increase is more common than FEV_1 increase after bronchodilator,[10] postbronchodilator FEV_1/FVC <0.7 (POSTO) may be more sensitive to diagnose symptomatic patients with clinically significant hyperinflation than prebronchodilator FEV_1/FVC <0.7 (PREO).[11] Therefore, it is critical to examine whether subjects with PREO and no AFO in postbronchodilator spirometry (POSTN) would have more clinical, functional and radiographic COPD features than subjects with POSTO and no AFO in prebronchodilator spirometry (PREN). Do clinical, functional and radiographic features differ between subjects with PREO and POSTN and subjects with PREN and POSTO?

We compared the predictive value of prebronchodilator and postbronchodilator FEV_1/FVC <0.7 and FEV_1% predicted for chronic bronchitis, dyspnoea, exercise capacity and COPD radiographic findings at phase 1 (baseline); respiratory exacerbations, change in dyspnoea, FEV_1 and exercise capacity from phase 1 to phase 2 visit (about 5 years apart); and mortality. We also examined whether subjects with discordance in prebronchodilator and postbronchodilator spirometry have different clinical, functional and radiographic features.

METHODS
Data collection
We conducted the study using data from the COPDGene database. GOPDGene is an ongoing study that enrolled subjects in several clinical centres through the USA (http://www.copdgene.org/). The institutional review boards at each participating centre approved the study protocol. Details of the study protocol have been published previously.[12] Briefly, all subjects provided informed consent before participation in the study. Subjects are self-identified non-Hispanic whites or African-Americans between the ages of 45 and 80 years. They completed a modified American Thoracic Society Respiratory Epidemiology Questionnaire, St. George's Respiratory Questionnaire (SGRQ) and 6 min walk test at phase 1 visit (baseline). Subjects performed prebronchodilator and postbronchodilator spirometry according to American Thoracic Society–European Respiratory Society (ATS-ERS) guidelines.[13] After prebronchodilator spirometric manoeuvres, two puffs of albuterol metered-dose inhaler were administered using a spacer. Postbronchodilator manoeuvres were performed between 15 and 40 min after albuterol administration and preferably between 15 and 20 min. Subjects performed inspiratory and expiratory chest CT scans using multidetector CT scanners as per protocol.[12] Volumetric CT

scans were obtained at maximal inspiration (total lung capacity (TLC)) and end-tidal expiration (functional residual capacity (FRC)). Emphysema and gas trapping were quantitated using 3D Slicer software (www.airway-inspector.org), and airway dimensions were measured using Pulmonary Workstation 2 (VIDA Diagnostics, Coralville, Iowa, USA).[12]

We included all subjects who participated in COPD-Gene study with at least 10 or more pack-years of smoking and who completed a phase 1 visit (n=10 192). Subjects were contacted every 6 months and completed a validated questionnaire regarding respiratory exacerbations. About 5 years after the phase 1 visit, a portion of subjects had a phase 2 visit that included questionnaire as in phase 1, a prebronchodilator and postbronchodilator spirometry and 6 min walk test. We also collected all-cause mortality data. We excluded those with incomplete prebronchodilator and postbronchodilator spirometric data.

Definitions and outcomes
Prebronchodilator AFO (PREO) was defined as prebronchodilator FEV_1/FVC <0.7. Postbronchodilator AFO (POSTO) was defined as postbronchodilator FEV_1/FVC <0.7. Prebronhodilator FEV1% predicted (Pre-FEV_1%) and postbronchodilator FEV1% predicted (post-FEV_1%) were calculated using predicted equations by Hankinson *et al*.[14] Bronchodilator response was defined as an increase in FEV_1 or FVC equal to or greater than 0.2 L and 12% according to ATS-ERS guidelines.[9]

Emphysema was defined by using the percentage of lung volume at TLC with attenuation less than −950 Hounsfield units (HU).[12 15] Expiratory CT scans were performed at FRC. Gas trapping was quantified as the percentage of lung volume at FRC with attenuation less than −856 HU.[12 15]

Exacerbations were defined as episodes of worsening respiratory symptoms requiring use of antibiotics and systemic steroids since the phase 1 visit. Severe exacerbations were defined as those requiring hospitalisations. Other variables definitions have been previously described.[12 15]

Statistical analysis
We performed a McNemar test for paired binary data to compare the prevalence rate of AFO using PREO and POSTO as diagnostic criteria.

We stratified the subjects by prebronchodilator and postbronchodilator FEV_1/FVC to:
► Prebronchodilator FEV_1/FVC ≥0.7 (PREN) and postbronchodilator FEV_1/FVC ≥ 0.7 (POSTN) = (PREN-POSTN).
► Prebronchodilator FEV_1/FVC <0.7 (PREO) and postbronchodilator FEV_1/FVC <0.7 (POSTO) =(PREO-POSTO).

- Prebronchodilator $FEV_1/FVC < 0.7$ (PREO) and post-bronchodilator $FEV_1/FVC \geq 0.7$ (POSTN) = (PREO-POSTN).
- Prebronchodilator $FEV_1/FVC \geq 0.7$ (PREN) and postbronchodilator $FEV_1/FVC < 0.7$ (POSTO) = (PREN-POSTO).

We compared characteristics at the phase 1 visit, number of exacerbations per year, changes in FEV_1, dyspnoea score and distance covered in 6 min walk from the phase 1 to the phase 2 visit between PREO-POSTN and PREN-POSTO using Fischer's exact or χ^2 test for categorical variables and Student's t-test or Wilcoxon rank sum test for normal and non-normal continuous variables, respectively. When we found a significant difference in the above measures between PREO-POSTN and PREN-POSTO in unadjusted analysis, we created multivariable regression models with PREO-POSTN versus PREN-POSTO as an independent variable.

We performed multivariable logistic regression models with chronic bronchitis at baseline as the dependent variable (outcome) and PREO, POSTO, pre-FEV_1% and post-FEV_1% as the independent variables. Similarly, we performed multivariable linear regression models with the following dependent variables: (1) dyspnoea scores, emphysema%, gas trapping% and distance covered in 6 min walk at phase 1; (2) number of respiratory exacerbations and severe exacerbations per year; and (3) changes in FEV_1, dyspnoea and distance covered in 6 min walk between phase 1 and phase 2 visit, and prebronchodilator and postbronchodilator measures as the independent variables.

We used a Cox proportional hazard regression analysis to examine the association of spirometric measures and patterns with mortality.

All regression models included the following covariates: age, sex, race, smoking status, pack-years, history of asthma (per questionnaire), diabetes, high blood pressure, stroke and sleep apnoea. We used the Akaike information criterion (AIC) to compare the performance of the various models.[16 17] Lower AIC by 7 indicates better model performance.[16] We used R software package (http://www.r-project.org/) for all statistical analysis.

RESULTS
Of 10 192 subjects with at least 10 or more pack-years of smoking, we excluded 192 with incomplete prebronchodilator and postbronchodilator spirometric data. Ten thousand subjects were included in in the analysis. We had available data regarding respiratory exacerbations for 8479 subjects. Of the 10 000 subjects, 4857 completed a phase 2 visit that included respiratory questionnaires, spirometry and 6 min walk test. We also had available mortality data for 8221 subjects.

Using PREO, the AFO prevalence was 50.2% (5016 of 10 000), whereas using POSTO, the prevalence was 44.5% (4451 of 10 000; P<0.001). There were 1167 subjects with discordant spirometry: 866 (8.7%) with PREO-POSTN

and 301 (3%) with PREN-POSTO (supplementary table 1).

Baseline characteristics at phase 1 (n=10 000)
Table 1 shows the characteristics of subjects with PREO-POSTO, PREN-POSTN, PREO-POSTN and PREN-POSTO. Compared with PREO-POSTN subjects, PREN-POSTO subjects had higher body mass index, higher prevalence of hypertension, higher dyspnoea scores, lower post-FEV_1% and shorter distance covered in 6 min walk. Bronchodilator response was more common in PREN-POSTO subjects than in PREN-POSTN subjects. Change in FEV_1% predicted after bronchodilator was smaller, but change FVC% predicted after bronchodilator was larger in PREN-POSTO subjects compared with subjects with PREO-POSTN.

To investigate further the higher dyspnoea scores and shorter distance covered in 6 min walk in PREO-POSTN subjects compared with PREN-POSTO subjects, we performed multilinear regression analysis and found that PREN-POSTO is associated with increased dyspnoea and reduced exercise capacity. (supplementary table 2). However, when we added post-FEV_1% in the models, this association disappeared.

In the adjusted analysis, both PREO and POSTO were associated with chronic bronchitis, dyspnoea scores, radiographic percent emphysema and gas trapping and distanced covered in 6 min walk at the phase 1 visit, but based on the AIC, models that included POSTO performed better than models that included PREO to predict those outcomes (table 2). We found similar results for pre-FEV_1% and post-FEV_1%.

Respiratory exacerbations (n=8479) and changes in clinical and functional features at phase 2 (n=4857)
We found no difference in the number of exacerbations and severe exacerbations per year between PREO-POSTO and PREN-POSTO subjects followed in average for 4.5±1.8 years (table 3). The drop in FEV_1 between the phase 1 and 2 visits was greater in PREO-POSTN compared with the change in PREN-POSTO subjects, whereas the change in distance covered in 6 min walk was smaller in the PREO-POSTN compared with PREN-POSTO group. In adjusted analysis, PREN-POSTO subjects had a smaller reduction in FEV_1 compared with PREO-POSTN subjects, but when we adjusted for postbronchodilator FEV_1% that association disappeared (supplementary table 3).

In multilinear regression analysis, both PREO and POSTO correlated significantly with number of exacerbations and severe exacerbations per year, dyspnoea scores and distance covered in 6 min walk between phase 1 and 2 visits (table 4). Based on AIC, models showed similar performance to predict those outcomes regardless whether PREO or POSTO was included, except models for number of exacerbations and change in SGRQ score, where those models that included POSTO performed better compared with those that included PREO.

Table 1	Baseline characteristics					
	All (n=10 000)	PREO-POSTO (n=4150)	PREN-POSTN (n=4683)	PREO-POSTN (n=866)	PREN-POSTO (n=301)	P value*
Age, year±SD	59.6±9	63.4±8.5	56.4±8.2	59.3±8.9	59.1±8.9	0.72
Female, % (n)	46.7 (4668)	43.9 (1823)	49.4 (2315)	44.6 (386)	47.8 (144)	0.36
Non-white race, % (n)	32.9 (3287)	21.6 (895)	42.9 (2010)	31.4 (272)	36.5 (110)	0.12
BMI, kg/m^2±SD	28.8±6.3	27.8±6.1	29.7±6.3	28.6±6.3	29.5±6.4	0.023
PPY±SD	44.3±24.9	52.2±27.2	37.8±20.8	41.9±22.8	43.2±24.3	0.57
Active smoking, % (n)	52.8 (5279)	42.1 (1746)	60.9 (2853)	57.4 (497)	60.8 (183)	0.33
Chronic bronchitis, % (n)	19.2 (1922)	26.5 (1101)	13.3 (621)	16.6 (144)	18.6 (56)	0.48
Asthma, % (n)	19.4 (1943)	25.3 (1049)	14.4 (674)	18.5 (160)	19.9 (60)	0.59
CAD, % (n)	6.5 (648)	9 (375)	4.4 (207)	5.4 (47)	6.3 (19)	0.67
CHF, % (n)	3.2 (320)	4.6 (192)	2 (96)	2.3 (20)	4 (12)	0.18
DM, % (n)	13 (1301)	11.9 (494)	13.6 (638)	14.2 (123)	15.3 (46)	0.64
HTN, % (n)	43.2 (4322)	48.4 (2008)	39 (1830)	39.7 (344)	46.5 (140)	0.046
OSA, % (n)	14.6 (1459)	16 (665)	13.3 (624)	14 (121)	16.3 (49)	0.39
Stroke, % (n)	2.6 (258)	3.4 (139)	1.9 (90)	2.1 (18)	3.7 (11)	0.19
SaO$_2$,%±SD	96.1±2.9	94.9±3.5	97±2.1	96.8±2.4	96.5±2.5	0.15
MMRC±SD	1.4±1.4	1.9±1.5	0.9±1.3	1±1.3	1.3±1.5	0.0011
SGRQ±SD	27.4±22.9	37.6±22.7	19.5±19.8	21.3±20.8	27.2±23.1	<0.001
Post-FEV$_1$, %±SD	76.3±25.6	55.9±22.4	92.6±15.4	84.7±15.9	77.3±17.4	<0.001
Post-FVC, %±SD	86.9±18.3	81.2±20.3	91.4±15.1	89±16.7	91.6±18.8	0.087
BDR, % (n)	21.5 (2146)	33.9 (1408)	9.2 (432)	19.5 (169)	45.5 (137)	<0.001
Delta FEV$_1$, %±SD	5.8±10.3	8.8±12.1	3±6.6	7.7±10.8	1.5±15.5	<0.001
Delta FVC, %±SD	3.9±12.6	7.5±13.2	0.9±7.5	−2.1±9.3	17.7±34.4	<0.001
Emphysema, %±SD†‡	7.6±10.6	14±12.9	2.2±2.8	2.9±3.1	3.4±5	0.45
Gas trapping, %±SD†‡	24.2±20.8	39.3±20.5	10.6±9	15±10	17.1±12.6	0.19
6-MWD, feet±SD	1351±399	1224±408.2	1443±365.3	1447±370.1	1352±382.3	<0.001

*Comparison between PREO-POSTN and PREN-POSTO using χ^2 and Student's t-test or Wilcoxon rank sum test.
†For emphysema and gas trapping analysis, data were available for 5553 and 4945 subjects, respectively.
‡Gas trapping was measured at functional residual capacity.
6-MWD, 6 min walk distance; BDR, bronchodilator response; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; Delta FEV$_1$%, % change in FEV$_1$ after bronnchodilator; Delta FVC%, % change in FVC after bronchodilator; DM, diabetes mellitus; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; HTN, hypertension; MMRC, modified Medical Research Council dyspnoea score; OSA, obstructive sleep apnoea; pre-FEV$_1$%, prebronchodilator FEV$_1$% predicted; post-FEV$_1$%, postbronchodilator FEV$_1$% predicted; PPY, pack per year; SaO$_2$, arterial oxygen saturation; SGRQ, St. George's Respiratory Questionnaire score;6-MWD = 6-min walk distance.
PREN-POSTN: prebronchodilator FEV$_1$/FVC >0.7 and postbronchodilator FEV$_1$/FVC >0.7.
PREN-POSTO: prebronchodilator FEV$_1$/FVC >0.7 and postbronchodilator FEV$_1$/FVC <0.7.
PREO-POSTNO: prebronchodilator FEV$_1$/FVC <0.7 and postbronchodilator FEV$_1$/FVC <0.7.
PREO-POSTN: prebronchodilator FEV$_1$/FVC <0.7 and postbronchodilator FEV$_1$/FVC >0.7.

Similarly, both prebronchodilator and postbronchodilator FEV$_1$% correlated significantly with the number of exacerbations and severe exacerbations per year, change in FEV$_1$, dyspnoea scores and distance covered in 6 min walk between phase 1 and 2 visits (table 4). Models showed similar performance except models for number of exacerbations (pre-FEV$_1$% models performed better) and for change in FEV$_1$ (pre-FEV$_1$% models performed better).

Spirometric pattern at phase 2
Of 377 subjects with PREO-POSTN at phase 1 who had both prebronchodilator and postbronchodilator spirometry at the phase 2 visit, the phase 2 spirometry showed PREO-POSTO in 167 (44.3%), PREN-POSTN in 120 (31.8%), PREO-POSTN in 72 (19.1%) and PREN-POSTO in 18 (4.8%) (supplementary table 4). Of those subjects who progressed to PREO-POSTO, 52.1% were active smokers; only 39.2% of those who progressed to PREN-POSTN were active smokers at the phase 2 visit (P=0.03).

Of 166 PREN-POSTO at phase 1 who had both prebronchodilator and postbronchodilator spirometry at the phase 2 visit, the phase 2 spirometry showed PREO-POSTO in 82 (49.4%), PREN-POSTN in 51 (30.7%), PREO-POSTN in 24 (14.5%) and PREN-POSTO in 9 (5.4%) (supplementary table 4). Of those subjects who progressed to PREO-POSTO, 50% were active smokers,

Table 2 Association of prebronchodilator and postbronchodilator spirometric measures with chronic bronchitis, dyspnoea scores, chest CT emphysema and air trapping and distance covered in 6 min walk test

	Prebronchodilator FEV$_1$/FVC <0.7 (PREO)			Postbronchodilator FEV$_1$/FVC <0.7 (POSTO)		
	OR (95% CI)	P value	AIC	OR (95% CI)	P value	AIC
Chronic bronchitis	2 (1.78 to 2.25)	<0.001	8910	2.14 (1.9 to 2.41)	<0.001	8882
	Coef (95% CI)	P value	AIC	Coef (95% CI)	P value	AIC
MMRC	0.72 (0.66 to 0.77)	<0.001	4849	0.85 (0.79 to 0.9)	<0.001	4605
SGRQ	13 (12.16 to 13.83)	<0.001	59145	15.3 (14.5 to 16.14)	<0.001	58811
Emphysema, %*	8.4 (7.9 to 8.9)	<0.001	24259	9.79 (9.29 to 10.29)	<0.001	23892
Gas trapping, %*†	20.2 (19.24 to 21.18)	<0.001	27241	23 (22 to 23.9)	<0.001	26738
6-MWD, feet	−137.4 (−152.9 to 121.9)	<0.001	115774	−172.8 (−188.3 to 157.2)	<0.001	115608
	Prebronchodilator FEV$_1$% predicted			**Postbronchodilator FEV$_1$% predicted**		
	OR (95% CI)	P value	AIC	OR (95% CI)	P value	AIC
Chronic bronchitis	0.98 (0.98 to 0.99)	<0.001	8833	0.98 (0.98 to 0.99)	<0.001	8833
	Coef (95% CI)	P value	AIC	Coef (95% CI)	P value	AIC
MMRC	−0.026 (−0.027 to 0.025)	<0.001	3150	−0.026 (−0.027 to 0.025)	<0.001	3065
SGRQ	−0.44 (−0.46 to 0.43)	<0.001	57014	−0.45 (−0.46 to 0.43)	<0.001	56967
Emphysema, %*	−0.23 (−0.24 to 0.22)	<0.001	22926	−0.24 (−0.25 to 0.23)	<0.001	22827
Gas trapping, %*†	−0.52 (−0.53 to 0.50)	<0.001	25519	−0.52 (−0.53 to 0.5)	<0.001	25471
6-MWD, feet	6.35 (6.07 to 6.64)	<0.001	114300	6.61 (6.3 to 6.9)	<0.001	114144

All regression models included the following covariates: age, sex, race, smoking status, pack per years, history (per questionnaire) of asthma, diabetes, high blood pressure, stroke and sleep apnoea.
*For emphysema and gas trapping analysis, data were available for 5553 and 4945 subjects, respectively.
†Gas trapping was measured at functional residual capacity.
6-MWD, 6 min walk distance; AIC, Akaike information criterion; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; MMRC, modified Medical Research Council dyspnoea score; SGRQ, St. George's Respiratory Questionnaire score.

while 52.3% of those who progressed to PREN-POSTN were active smokers at the phase 2 visit (P=0.74).

Mortality (n=8221)
Subjects were followed in average for 1956±407 days, and there were 830 deaths (10.1%). All PREO, POSTO, pre-FEV$_1$%, and post-FEV$_1$% were associated with mortality (table 5). Based on AIC, models that included post-FEV$_1$% performed better at predicting mortality than the rest. Furthermore, PREO-POSTO was associated with increased mortality, while PREO-POSTN and PREN-POSTO were not (supplementary table 5).

DISCUSSION
In this report, AFO prevalence is higher when the PREO criterion is applied. About 8.5% of all subjects had PREO-POSTN, whereas 3% had a PREN-POSTO spirometric pattern. In adjusted analysis, we found no difference in COPD features and outcomes between PREO-POSTN and PREN-POSTO subjects. Although both prebronchodilator and postbronchodilator spirometry are associated with chronic bronchitis, dyspnoea, exercise capacity and COPD radiographic findings, models that include postbronchodilator spirometric measures perform better than those with prebronchodilator

measures to predict those outcomes. The predictive value of prebronchodilator and postbronchodilator spirometries are relatively similar for respiratory exacerbations, change in FEV$_1$ and dyspnoea from phase 1 to phase 2 visits. Both prebronchodilator and postbronchodilator spirometry are associated with mortality, but models that include postbronchodilator spirometric measures perform better than models with prebronchodilator spirometry. About half of PREO-POSTN and PREN-POSTN become PREO-POSTO at Phase 2. PREO-POSTO is associated with higher mortality compared with the other patterns.

The prevalence of AFO and therefore COPD is higher using prebronchodilator spirometry in our cohort, although previous studies have shown mixed results.[7 18] Is this clinically significant? In the absence of a 'gold standard', a diagnostic test is good when it can predict outcomes and change management of a disease or condition. Both prebronchodilator and postbronchodilator spirometry were associated with chronic bronchitis, dyspnoea, radiographic emphysema and gas trapping and exercise capacity. Nevertheless, models that included postbronchodilator spirometric measures performed better compared with those that included postbronchodilator measures, indicating that postbronchodilator spirometry correlates better with those outcomes.

Table 3 Number of exacerbations and severe exacerbations per year, change in FEV1, dyspnoea scores and distance covered in 6 min walk test from phase 1 to phase 2 visit (5-year interval)

	All (n=8479)	PREO-POSTO (n=3619)	PREN-POSTN (n=3936)	PREO-POSTN (n=636)	PREN-POSTO (n=288)	P value*
Exacerbations per year±SD	0.42±0.99	0.68±1.22	0.21±0.70	0.27±0.74	0.26±0.79	0.3
Severe exacerbations per year±SD	0.14±0.52	0.24±0.66	0.07±0.34	0.1±0.5	0.09±0.3	0.069
	All (n=4857)	**PREO-POSTO (n=1889)**	**PREN-POSTN (n=2421)**	**PREO-POSTN (n=379)**	**PREN-POSTO (n=168)**	**P value***
Change in FEV_1, mL±SD	−198.1±294.5	−202.5±320.2	−198.8±268.5	−203.6±282.2	−125.6±365.5	<0.001
Change in MMRC ±SD	0.06±1.24	0.19±1.26	−0.04±1.22	0.03±1.08	0.05±1.36	0.42
Change in SGRQ ±SD	0.15±15.3	1.5±15.2	−0.8±15.4	−0.88±14.6	0.98±16	0.86
Change in 6-MWD, feet±SD	−130.9±360.6	−172.7±366.4	−103.7±357	−103±327.4	−123.5±377	<0.001

*Comparison between PREO-POSTN and PREN-POSTO using χ^2 and Student's t-test or Wilcoxon rank sum test.
6-6-MWD = 6-min walk distance; MMRC, modified Medical Research Council dyspnoea score; SGRQ, St. George's Respiratory Questionnaire score.
PREN-POSTN: prebronchodilator FEV_1/FVC >0.7 and postbronchodilator FEV_1/FVC >0.7.
PREO-POSTNO: prebronchodilator FEV_1/FVC <0.7 and postbronchodilator FEV_1/FVC <0.7.
PREO-POSTN: prebronchodilator FEV_1/FVC <0.7 and postbronchodilator FEV_1/FVC >0.7.
PREN-POSTO: prebronchodilator FEV_1/FVC >0.7 and postbronchodilator FEV_1/FVC <0.7.

When we examined the subjects with AFO discordance in prebronchodilator and postbronchodilator spirometry, which comprised 11.7% of our total cohort, PREN-POSTO subjects have a remarkable increase in FVC after bronchodilator spirometry compared with PREO-POSTN subjects, although they have similar postbronchodilator FVC%. PREN-POSTO subjects have likely more prebronchodilator air trapping than PREO-POSTN, which can be present in mild disease[19 20] and result in exertional dyspnoea and lower exercise capacity.[8 19 21] We did not observe higher radiographic air trapping in the PREN-POSTO than in the PREO-POSTN group, likely because CTs were performed after bronchodilator spirometry. When we adjusted for post-FEV_1%, PREN-POSTO was not associated with worse dyspnoea or exercise capacity compared with PREO-POSTN, which means that PREN-POSTO does not represent a different phenotype with increased air trapping but rather a group with more severe disease and lower post-FEV_1%.[22]

Prebronchodilator and postbronchodilator measures showed relatively similarly predictive value for long-term outcomes such as respiratory exacerbations, change of FEV_1, dyspnoea score and exercise capacity. Previous studies have shown that bronchodilator response is associated with clinical outcomes,[23 24] but this association could be confounded by lung function.[22 25] For that reason, we adjusted for post-FEV_1% at baseline, and we found that the discordance groups had no difference in change of FEV_1, dyspnoea score and exercise capacity.

Postbronchodilator spirometry models perform better than prebronchodilator spirometry models to predict mortality, although both are strongly associated with mortality. This is in disagreement with a previous study by Mannino et al[6] that showed that both prebronchodilator and postbronchodilator spirometry can predict mortality with the same accuracy in a similar population to ours. Although subjects were followed for 15 years in their study instead of about 5 years in our study, their study was performed almost 20 years earlier than COPDGene, and they did not also include comorbidities in their analysis as we did. In AFO discordance groups, we did not find any difference in mortality between the two groups. PREO-POSTO subjects had increased mortality compared with the other groups, which may again reflect more advanced disease with lower post-FEV_1%.[22] Although postbronchodilator may be superior to prebronchodilator spirometric measures to predict outcome, there are no available postbronchodilator spirometric reference values for a US population. Previous reports in Northern Europe[26] and South America[27] have provided postbronchodilator spirometric reference values, but their predictive value for obstructive lung disease outcomes has not been compared with that of prebronchodilator reference values.

In addition, we showed that about 50% of the subjects with AFO discordance between prebronchodilator and postbronchodilator spirometry progress to PREO-POSTO, which is a pattern with higher mortality than the rest of the groups. Interestingly, subjects with PREO-POSTN that progressed to PREO-POSTO had higher smoking rates than those that progressed to PREN-POSTN in the follow-up visit; this raises the question

Table 4 Association of prebronchodilator and postbronchodilator spirometric measures with number of exacerbations and severe exacerbations per year, change in FEV1, dyspnoea scores and distance covered in 6 min walk test from phase 1 to phase 2 visit (5-year interval)

	Prebronchodilator FEV_1/FVC <0.7 (PREO)			Postbronchodilator FEV_1/FVC <0.7 (POSTO)		
	Coef (95% CI)	P value	AIC	Coef (95% CI)	P value	AIC
Exacerbations per year	0.35 (0.31 to 0.4)	<0.001	−893	0.38 (0.34 to 0.43)	<0.001	−929
Severe exacerbations per year	0.14 (0.11 to 0.16)	<0.001	−11608	0.14 (0.12 to 0.16)	<0.001	−11614
Change in FEV_1, mL	−2.25 (−20.3 to 15.8)	0.81	54317	10 (−7.26 to 29.3)	0.24	54315
Change in MMRC	0.2 (0.12 to 0.27)	<0.001	1978	0.21 (0.13 to 0.29)	<0.001	1974
Change in SGRQ	1.92 (0.99 to 2.85)	<0.001	26399	2.56 (1.62 to 3.5)	<0.001	26387
Change in 6-MWD, feet	−22.2 (−44.3 to 0.05)	0.049	55763	−33.2 (−55.6 to 10.8)	0.004	55758
	Postbronchodilator FEV_1% predicted			Postbronchodilator FEV_1% predicted		
	Coef (95% CI)	P value	AIC	Coef (95% CI)	P value	AIC
Exacerbations	−0.011 (−0.012 to 0.01)	<0.001	−1233	−0.011 (−0.01 to 0.0097)	<0.001	−1222
Severe exacerbations	−0.004 (−0.0045 to 0.0036)	<0.001	−11787	−0.004 (−0.0045 to 0.0036)	<0.001	−11777
Change in FEV_1, mL	−1.91 (−2.28 to 1.53)	<0.001	54218	−2.76 (−3.13 to 2.39)	<0.001	54112
Change in MMRC	−0.002 (−0.0038 to 0.00065)	0.006	1996	−0.02 (−0.0036 to 0.00037)	0.016	1998
Change in SGRQ	−0.01 (−0.03 to 0.0095)	0.32	26415	−0.01 (−0.029 to 0.01)	0.34	26415
Change in 6-MWD, feet	0.99 (0.53 to 1.46)	<0.001	55749	0.9 (0.43 to 1.37)	<0.001	55753

All regression models included the following covariates: age, sex, race, smoking status, pack per years, history (per questionnaire) of asthma, diabetes, high blood pressure, stroke and sleep apnoea.
6-MWD, 6 min walk distance; AIC, Akaike information criterion; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; MMRC, modified Medical Research Council dyspnoea score; SGRQ, St. George's Respiratory Questionnaire score.

whether this group represents patients with early disease to whom we need to target interventions like smoking cessation. This finding suggest that using prebronchodilator spirometry may be a better diagnostic test for early (or future) disease although postbronchodilator spirometry correlates better with current symptoms, functional and radiographic measures and 5-year mortality.

Table 5 Mortality models

	HR (95% CI)	P value	AIC
PREO	2.46 (2.07 to 2.92)	<0.001	14194
POSTO	2.54 (2.15 to 3)	<0.001	14181
Pre-FEV_1%	0.97 (0.96 to 0.97)	<0.001	13837
Post-FEV_1%	0.97 (0.96 to 0.97)	<0.001	13806

All regression models included the following covariates: age, sex, race, smoking status, pack per years, history (per questionnaire) of asthma, diabetes, high blood pressure, stroke and sleep apnoea.
AIC, Akaike information criterion; POSTO, postbronchodilator FEV_1/FVC <0.7; pre-FEV_1%, prebronchodilator FEV_1% predicted; post-FEV_1%, postbronchodilator FEV_1% predicted; PREO, prebronchodilator FEV_1/FVC <0.7.

Apart from the fact that chest CTs were performed after bronchodilator and gas trapping was measured at FRC our study is limited by the large variability of bronchodilator response. Although, we used albuterol and the same protocol for all the bronchodilations, greater bronchodilator response may occur when spirometric manoeuvres were performed >20 min after bronchodilator administration instead of 15–20 min.[22 28] Subjects older than 80 years were not included. We only have phase 2 spirometries for half of the subjects. The follow-up period may not be long enough to detect some outcome differences, especially mortality, between the AFO discordance groups. We do not have data on the specific cause of death. We did not also detect any robust outcome differences, as both prebronchodilator and postbronchodilator spirometries were associated strongly with outcomes. Postbronchodilator spirometry superiority is based on better model performance using the AIC.[16 17] These limitations do not undermine the strengths of our study, which include the large sample size and the wealth of epidemiological data.

In conclusion, PREO was more sensitive to diagnose AFO compared with POSTO. About half of the subjects

with AFO discordance in their prebronchodilator and postbronchodilator spirometry, which compromise 11% of all subjects, progress to PREO-POSTO, which is a pattern with higher mortality compared with the other patterns. Although both prebronchodilator and post-bronchodilator spirometries are associated with clinical, functional and radiographic features of COPD, and mortality, our findings suggest that postbronchodilator spirometry may be a more accurate measure of COPD burden and should be used for COPD diagnosis and classification. This raises the question of whether post-bronchodilator spirometric reference values for the US population are needed.

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