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

Spyridon Fortis,1,2 Michael Eberlein,1 Dimitris Georgopoulos,2,3 Alejandro P Comellas1

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 FEV1 % 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 airflow 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 (FEV1)/forced vital capacity (FVC) below the lower limit of normal (LLN) or 0.7.1 Several studies have compared FEV1/FVC<LLN with FEV1/FVC <0.7 as a diagnostic criterion for AFO.2–4 GOLD recommends a postbronchodilator FEV1/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 in predicting 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 al6 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...
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?\(^2\)

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.\(^15\) 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 COPDGene study with at least 10 or more pack-years of smoking and who completed a phase 1 visit (n=10192). 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. Prebronchodilator FEV\(_1\)% predicted (Pre-FEV\(_1\)%), and postbronchodilator FEV\(_1\)% 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 \( \text{FEV}_1/\text{FVC} < 0.7 \) (PREO) and post- 
bronchodilator \( \text{FEV}_1/\text{FVC} \geq 0.7 \) (POSTN) = (PREO-POSTN).

► Prebronchodilator \( \text{FEV}_1/\text{FVC} \geq 0.7 \) (PREN) and 
postbronchodilator \( \text{FEV}_1/\text{FVC} < 0.7 \) (POSTO) = (PREN-POSTO).

We compared characteristics at the phase 1 visit, 
number of exacerbations per year, changes in \( \text{FEV}_1 \), 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 \( \chi^2 \) test for categor- 
ical 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 exacer- 
bations and severe exacerbations per year; and (3) 
changes in \( \text{FEV}_1 \), dyspnoea and distance covered in 6 min 
walk between phase 1 and phase 2 visit, and prebroncho- 
dilator and postbronchodilator measures as the indepen- 
dent 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 covari- 
aties: age, sex, race, smoking status, pack-years, history of 
asthma (per questionnaire), diabetes, high blood pres- 
sture, stroke and sleep apnoea. We used the Akaike infor- 
mation criterion (AIC) to compare the performance of 
the various models.\(^\text{16, 17}\) Lower AIC by 7 indicates better 
model performance.\(^\text{16}\) 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 prebroncho- 
dilator and postbronchodilator spirometric data. Ten 
thousand subjects were included in in the analysis. We 
had available data regarding respiratory exacerbations 
for 8,479 subjects. Of the 10,000 subjects, 4,857 completed 
a phase 2 visit that included respiratory questionnaires, 
spirometry and 6 min walk test. We also had available 
mortality data for 8,221 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 PREO-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-POSTO subjects. 
Change in FEV\(_1\)% predicted after bronchodilator was 
smaller, but change FVC% predicted after bronchodili- 
ator 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- 
POSTO 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 
distance 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=8,479) and changes in clinical 
and functional features at phase 2 (n=4,857)

We found no difference in the number of exacerba- 
tions 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 exacerba- 
tions 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

<table>
<thead>
<tr>
<th></th>
<th>All (n=10 000)</th>
<th>PREO-POSTO (n=4 150)</th>
<th>PREN-POSTN (n=4 683)</th>
<th>PREO-POSTN (n=866)</th>
<th>PREN-POSTO (n=301)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year±SD</td>
<td>59.6±9</td>
<td>63.4±8.5</td>
<td>56.4±8.2</td>
<td>59.3±8.9</td>
<td>59.1±8.9</td>
<td>0.72</td>
</tr>
<tr>
<td>Female, % (n)</td>
<td>46.7 (4 668)</td>
<td>43.9 (1 823)</td>
<td>49.4 (2 315)</td>
<td>44.6 (386)</td>
<td>47.8 (144)</td>
<td>0.36</td>
</tr>
<tr>
<td>Non-white race, % (n)</td>
<td>32.9 (3 287)</td>
<td>21.6 (895)</td>
<td>42.9 (2 010)</td>
<td>31.4 (272)</td>
<td>36.5 (110)</td>
<td>0.12</td>
</tr>
<tr>
<td>BMI, kg/m²±SD</td>
<td>28.8±6.3</td>
<td>27.8±6.1</td>
<td>29.7±6.3</td>
<td>28.6±6.3</td>
<td>29.5±6.4</td>
<td>0.023</td>
</tr>
<tr>
<td>PPY±SD</td>
<td>44.3±24.9</td>
<td>52.2±27.2</td>
<td>37.8±20.8</td>
<td>41.9±22.8</td>
<td>43.2±24.3</td>
<td>0.57</td>
</tr>
<tr>
<td>Active smoking, % (n)</td>
<td>52.8 (5 279)</td>
<td>42.1 (1 746)</td>
<td>60.9 (2 853)</td>
<td>57.4 (497)</td>
<td>60.8 (183)</td>
<td>0.33</td>
</tr>
<tr>
<td>Chronic bronchitis, % (n)</td>
<td>19.2 (1 922)</td>
<td>26.5 (1 101)</td>
<td>13.3 (621)</td>
<td>16.6 (144)</td>
<td>18.6 (56)</td>
<td>0.48</td>
</tr>
<tr>
<td>Asthma, % (n)</td>
<td>19.4 (1 943)</td>
<td>25.3 (1 049)</td>
<td>14.4 (674)</td>
<td>18.5 (160)</td>
<td>19.9 (60)</td>
<td>0.59</td>
</tr>
<tr>
<td>CAD, % (n)</td>
<td>6.5 (648)</td>
<td>9 (375)</td>
<td>4.4 (207)</td>
<td>5.4 (47)</td>
<td>6.3 (19)</td>
<td>0.67</td>
</tr>
<tr>
<td>CHF, % (n)</td>
<td>3.2 (320)</td>
<td>4.6 (192)</td>
<td>2 (96)</td>
<td>2.3 (20)</td>
<td>4 (12)</td>
<td>0.18</td>
</tr>
<tr>
<td>DM, % (n)</td>
<td>13 (1 301)</td>
<td>11.9 (494)</td>
<td>13.6 (638)</td>
<td>14.2 (123)</td>
<td>15.3 (46)</td>
<td>0.64</td>
</tr>
<tr>
<td>HTN, % (n)</td>
<td>43.2 (4 322)</td>
<td>48.4 (2 008)</td>
<td>39 (1 830)</td>
<td>39.7 (344)</td>
<td>46.5 (140)</td>
<td>0.046</td>
</tr>
<tr>
<td>OSA, % (n)</td>
<td>14.6 (1 459)</td>
<td>16 (665)</td>
<td>13.3 (624)</td>
<td>14 (121)</td>
<td>16.3 (49)</td>
<td>0.39</td>
</tr>
<tr>
<td>Stroke, % (n)</td>
<td>2.6 (258)</td>
<td>3.4 (139)</td>
<td>1.9 (90)</td>
<td>2.1 (18)</td>
<td>3.7 (11)</td>
<td>0.19</td>
</tr>
<tr>
<td>SaO₂,%±SD</td>
<td>96.1±2.9</td>
<td>94.9±3.5</td>
<td>97±2.1</td>
<td>96.8±2.4</td>
<td>96.5±2.5</td>
<td>0.15</td>
</tr>
<tr>
<td>MMRC±SD</td>
<td>1.4±1.4</td>
<td>1.9±1.5</td>
<td>0.9±1.3</td>
<td>1±1.3</td>
<td>1.3±1.5</td>
<td>0.0011</td>
</tr>
<tr>
<td>SGRQ±SD</td>
<td>27.4±22.9</td>
<td>37.6±22.7</td>
<td>19.5±19.8</td>
<td>21.3±20.8</td>
<td>27.2±23.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-FEV₁,%±SD</td>
<td>76.3±25.6</td>
<td>55.9±22.4</td>
<td>92.6±15.4</td>
<td>84.7±15.9</td>
<td>77.3±17.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-FVC,%±SD</td>
<td>86.9±18.3</td>
<td>81.2±20.3</td>
<td>91.4±15.1</td>
<td>89±16.7</td>
<td>91.6±18.8</td>
<td>0.087</td>
</tr>
<tr>
<td>BDR, % (n)</td>
<td>21.5 (2 146)</td>
<td>33.9 (1 408)</td>
<td>9.2 (432)</td>
<td>19.5 (169)</td>
<td>45.5 (137)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delta FEV₁,%±SD</td>
<td>5.8±10.3</td>
<td>8.8±12.1</td>
<td>3±6.6</td>
<td>7.7±10.8</td>
<td>1.5±15.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delta FVC,%±SD</td>
<td>3.9±12.6</td>
<td>7.5±13.2</td>
<td>0.9±7.5</td>
<td>−2.1±9.3</td>
<td>17.7±34.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emphysema, %±SD†‡</td>
<td>7.6±10.6</td>
<td>14±12.9</td>
<td>2.2±2.8</td>
<td>2.9±3.1</td>
<td>3.4±5</td>
<td>0.45</td>
</tr>
<tr>
<td>Gas trapping, %±SD†‡</td>
<td>24.2±20.8</td>
<td>39.3±20.5</td>
<td>10.6±9</td>
<td>15±10</td>
<td>17.1±12.6</td>
<td>0.19</td>
</tr>
<tr>
<td>6-MWD, feet±SD</td>
<td>1351±399</td>
<td>1224±408.2</td>
<td>1443±365.3</td>
<td>1447±370.1</td>
<td>1352±382.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Comparison between PREO-POSTN and PREN-POSTO using χ² and Student’s t-test or Wilcoxon rank sum test.

†For emphysema and gas trapping analysis, data were available for 5 553 and 4 945 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 FEV₁,% % change in FEV₁ after bronchodilator; Delta FVC%, % change in FVC after bronchodilator; DM, diabetes mellitus; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; HTN, hypertension; MMRC, modified Medical Research Council dyspnoea score; OSA, obstructive sleep apnoea; pre-FEV₁%, prebronchodilator FEV₁% predicted; post-FEV₁%, postbronchodilator FEV₁% predicted; PPY, pack per year; SaO₂, arterial oxygen saturation; SGRQ, St. George’s Respiratory Questionnaire score; 6-MWD = 6-min walk distance.

PREO-POSTO in 167 (44.3%), PREO-POSTN in 120 (31.8%), PREN-POSTO in 72 (19.1%) and PREN-POSTN 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%), PREO-POSTN in 51 (30.7%), PREN-POSTO in 24 (14.5%) and PREN-POSTN in 9 (5.4%) (supplementary table 4). Of those subjects who progressed to PREO-POSTO, 50% were active smokers.

Similarly, both prebronchodilator and postbronchodilator FEV₁,% correlated significantly with the number of exacerbations and severe exacerbations per year, change in FEV₁, 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-FEV₁% models performed better) and for change in FEV₁ (pre-FEV₁% 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%), PREO-POSTN in 120 (31.8%), PREN-POSTO in 72 (19.1%) and PREN-POSTN 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).

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

<table>
<thead>
<tr>
<th></th>
<th>Prebronchodilator FEV1/FVC &lt;0.7 (PREO)</th>
<th>Postbronchodilator FEV1/FVC &lt;0.7 (POSTO)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>2 (1.78 to 2.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMRC</td>
<td>0.72 (0.66 to 0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SGRQ</td>
<td>13 (12.16 to 13.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emphysema, %*</td>
<td>8.4 (7.9 to 8.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gas trapping, %†</td>
<td>20.2 (19.24 to 21.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6-MWD, feet</td>
<td>−137.4 (−152.9 to 121.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prebronchodilator FEV1% predicted</td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>0.98 (0.98 to 0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMRC</td>
<td>−0.026 (−0.027 to 0.025)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SGRQ</td>
<td>−0.44 (−0.46 to 0.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emphysema, %*</td>
<td>−0.23 (−0.24 to 0.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gas trapping, %†</td>
<td>−0.52 (−0.53 to 0.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6-MWD, feet</td>
<td>6.35 (6.07 to 6.64)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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; FEV1, 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-FEV1%, and post-FEV1% were associated with mortality (table 5). Based on AIC, models that included post-FEV1% performed better at predicting mortality than the rest. Furthermore, PREO-POSTN 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 FEV1, 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. 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)

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>PREO-POSTO</th>
<th>PREN-POSTN</th>
<th>PREO-POSTN</th>
<th>PREN-POSTO</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=8479)</td>
<td>(n=3619)</td>
<td>(n=3936)</td>
<td>(n=636)</td>
<td>(n=280)</td>
<td></td>
</tr>
<tr>
<td>Exacerbations per year±SD</td>
<td>0.42±0.99</td>
<td>0.68±1.22</td>
<td>0.21±0.70</td>
<td>0.27±0.74</td>
<td>0.26±0.79</td>
<td>0.3</td>
</tr>
<tr>
<td>Severe exacerbations per year±SD</td>
<td>0.14±0.52</td>
<td>0.24±0.66</td>
<td>0.07±0.34</td>
<td>0.1±0.5</td>
<td>0.09±0.3</td>
<td>0.069</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>PREO-POSTO</th>
<th>PREN-POSTN</th>
<th>PREO-POSTN</th>
<th>PREN-POSTO</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=4857)</td>
<td>(n=1889)</td>
<td>(n=2421)</td>
<td>(n=379)</td>
<td>(n=168)</td>
<td></td>
</tr>
<tr>
<td>Change in FEV1, mL±SD</td>
<td>−198.1±294.5</td>
<td>−202.5±320.2</td>
<td>−198.8±268.5</td>
<td>−203.6±282.2</td>
<td>−125.6±365.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in MMRC ±SD</td>
<td>0.06±1.24</td>
<td>0.19±1.26</td>
<td>−0.04±1.22</td>
<td>0.03±1.08</td>
<td>0.05±1.36</td>
<td>0.42</td>
</tr>
<tr>
<td>Change in SGRQ ±SD</td>
<td>0.15±15.3</td>
<td>1.5±15.2</td>
<td>−0.8±15.4</td>
<td>−0.88±14.6</td>
<td>0.98±16</td>
<td>0.86</td>
</tr>
<tr>
<td>Change in 6-MWD, feet±SD</td>
<td>−130.9±360.6</td>
<td>−172.7±366.4</td>
<td>−103.7±357</td>
<td>−103±327.4</td>
<td>−123.5±377</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Comparison between PREO-POSTN and PREN-POSTO using χ² 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 FEV1/FVC >0.7 and postbronchodilator FEV1/FVC >0.7.
PREO-POSTNO: prebronchodilator FEV1/FVC <0.7 and postbronchodilator FEV1/FVC <0.7.
PREO-POSTN: prebronchodilator FEV1/FVC <0.7 and postbronchodilator FEV1/FVC >0.7.
PREN-POSTO: prebronchodilator FEV1/FVC >0.7 and postbronchodilator FEV1/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 and result in exertional dyspnoea and lower exercise capacity. 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-FEV1%, 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-FEV1%.

Prebronchodilator and postbronchodilator measures showed relatively similarly predictive value for long-term outcomes such as respiratory exacerbations, change of FEV1, dyspnoea score and exercise capacity. Previous studies have shown that bronchodilator response is associated with clinical outcomes, but this association could be confounded by lung function. For that reason, we adjusted for post-FEV1% at baseline, and we found that the discordance groups had no difference in change of FEV1, 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 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-FEV1%. 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 and South America 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)

<table>
<thead>
<tr>
<th></th>
<th>Prebronchodilator FEV1/FVC &lt;0.7 (PREO)</th>
<th>Postbronchodilator FEV1/FVC &lt;0.7 (POSTO)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coef (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Exacerbations per year</td>
<td>0.35 (0.31 to 0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe exacerbations per year</td>
<td>0.14 (0.11 to 0.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in FEV1, mL</td>
<td>−2.25 (−20.3 to 15.8)</td>
<td>0.81</td>
</tr>
<tr>
<td>Change in MMRC</td>
<td>0.2 (0.12 to 0.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in SGRQ</td>
<td>1.92 (0.99 to 2.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in 6-MWD, feet</td>
<td>−22.2 (−44.3 to 0.05)</td>
<td>0.049</td>
</tr>
</tbody>
</table>

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; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MMRC, modified Medical Research Council dyspnoea score; SGRQ, St. George’s Respiratory Questionnaire score.

### Table 5
Mortality models

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREO</td>
<td>2.46 (2.07 to 2.92)</td>
<td>&lt;0.001</td>
<td>14194</td>
</tr>
<tr>
<td>POSTO</td>
<td>2.54 (2.15 to 3)</td>
<td>&lt;0.001</td>
<td>14181</td>
</tr>
<tr>
<td>Pre-FEV,%</td>
<td>0.97 (0.96 to 0.97)</td>
<td>&lt;0.001</td>
<td>13837</td>
</tr>
<tr>
<td>Post-FEV,%</td>
<td>0.97 (0.96 to 0.97)</td>
<td>&lt;0.001</td>
<td>13806</td>
</tr>
</tbody>
</table>

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 FEV1/FVC <0.7; pre-FEV, %, prebronchodilator FEV1/ FVC % predicted; post-FEV, %, postbronchodilator FEV1/ FVC % predicted; PREO, prebronchodilator FEV1/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. 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. 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 postbronchodilator 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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Collaborators COPDGene investigators

Contributors All authors made substantial contributions to the study. SF participated in study conception and design, data analysis and interpretation and drafting of the manuscript. ME participated in study design, data interpretation and drafting of the manuscript. DG participated in data interpretation. AC participated in study conception and design, data interpretation and drafting of the manuscript.

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Competing interests  None declared.

Ethics approval  The institutional review boards at each participating center outlined below approved the study protocol. Details of the study protocol have been published previously.12

Provenance and peer review  Not commissioned; externally peer reviewed.

Data sharing statement  Please contact COPD gene investigators for additional data request.

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