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A new bronchodilator response grading strategy identifies distinct patient populations

Short running title: A new bronchodilator response grading strategy

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This article has an online supplement.

List of Abbreviations

ACCP: American College of Chest Physicians

ACO: asthma-COPD overlap

ATS: American Thoracic Society

BDR: bronchodilator response

BMI: body mass index

COPD: chronic obstructive pulmonary disease

CT: computerized tomography

CV: coefficient of variation

ERS: European Respiratory Society

FEV_1: forced expiratory volume in 1 second

FEV_6: forced expiratory volume in 6 second

FVC: forced vital capacity

GOLD: Global Initiative for Obstructive Lung Disease

L: Liters

MCID: minimal clinically important difference

mMRC: modified Medical Research Council

OAD: obstructive airway disease

Pi15: square root wall area of a 15mm diameter airway

Pre-BD: pre-bronchodilator

Segmental WA%: segmental airway wall area percentage

SGRQ: St. George's Respiratory Questionnaire

6MWT: six-minute walking test

6MWD: six-minute walking distance

SD: standard deviation

Abstract

Background: A positive bronchodilator response (BDR) by American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines requires an increase in FEV_1 or FVC ≥200 mL and 12% after bronchodilator inhalation. This dual criterion is insensitive in those with high or low FEV_1. We aimed to establish BDR criteria with volume or percentage FEV_1 change.

Methods: The largest FEV_1 and FVC were identified from 3 pre- and 3 post-bronchodilator maneuvers in COPDGene participants. 7,741 individuals with coefficient of variation <15% for both FEV_1 and FVC formed bronchodilator categories of FEV_1 response: negative (≤0.00% or ≤0.00L), minimal (>0.00% to ≤9.00% or >0.00L to ≤0.09L), mild (>9.00% to ≤16.00% or >0.09L to ≤0.16L), moderate (>16.00% to ≤26.00% or >0.16L to ≤0.26L), and marked (>26.00% or >0.26L). These response-size categories are based on empirical limits considering average FEV_1 increase of ~160 ml and the clinically important difference for FEV_1. To compare flow and volume response characteristics, BDR-FEV_1 category assignments were applied for the BDR-FVC response.

Results: 20% met mild and 31% met moderate or marked BDR-FEV_1 criteria; whereas 12% met mild and 33% met moderate or marked BDR-FVC criteria. In contrast, only 20.6% met ATS/ERS positive criteria. Minimal, mild, moderate and marked BDR-FEV_1 categories were associated with greater six-minute walking distance, lower St. George's Respiratory Questionnaire and mMRC dyspnea scores as compared to those in negative BDR-FEV_1 category. Moderate and marked BDR-FEV_1 categories were associated with fewer exacerbations and minimal BDR was associated with lower computerized tomography airway wall thickness compared to negative BDR. Compared with negative, all BDR-FVC categories were associated

with increasing emphysema% and gas trapping%. Moderate and marked BDR-FVC categories were associated with higher SGRQ scores but fewer exacerbations and lower dyspnea scores.

Conclusions: BDR grading by FEV_1 volume or percentage response identified subjects otherwise missed by ATS/ERS criteria. BDR grades were associated with functional exercise performance, quality of life, exacerbation frequency, dyspnea and radiological airway measures. BDR grades in FEV_1 and FVC indicate different clinical and radiological characteristics.

Keywords: airflow obstruction, bronchodilator responsiveness, FEV_1

Introduction

Current criteria for identifying a positive spirometric bronchodilator response (BDR) based on American Thoracic Society (ATS) and European Respiratory Society (ERS)[1] guidelines require both 200mL and 12% increase in forced expiratory volume in 1 second (FEV_1) or forced vital capacity (FVC). If these dual criteria are not met, BDR is categorized as negative. These guidelines may not identify many individuals with potentially clinically important BDR, especially those with low baseline FEV_1 who do not meet $\Delta \geq 200$mL, or those with high baseline FEV_1 who do not meet $\Delta \geq 12\%$[2-4]. Both Pellegrino and Brusasco[5] and Calverley et al.[6] emphasized that FEV_1 BDR is a continuous variable; no threshold adequately separates responders from non-responders. Hansen et al.[4], analyzing BDR in a sample of clinical pre- and post-bronchodilator tests, showed that 224 of 313 patients (71.6%) failed ATS/ERS FEV_1 criteria, but 89 (39.7%) of those 224 who failed showed statistically significant $\Delta FEV_1 \geq 100$mL or $\geq 6.0\%$ improvement. Of those with baseline $FEV_1 < 1$L (n=44), 52.3% had $\Delta FEV_1 \geq 100$mL or $\geq 6.0\%$ while only 11.4% were ATS/ERS positive[3]. These results suggest the need to revise BDR evaluation.

The COPDGene population, with 10,311 current or ex-smokers with or without spirometrically defined COPD, is uniquely positioned to evaluate BDR[7] and forms the basis of the current evaluation.

We aimed to: a) develop a new grading system based on BDR volume or percent increase, for comparison with ATS/ERS guidelines, b) evaluate ATS/ERS recommended ΔFEV_1 versus ΔFVC values, and c) explore clinical relevance of the new BDR grades by comparing them to clinical outcomes and pulmonary structural characteristics.

Materials and Methods

We utilized the COPDGene cohort enrolled between 2007 and 2011[7]. This cohort included 10,311 non-Hispanic whites and African-Americans, 45-80 years old, with ≥10 pack-years smoking history. Key exclusion criteria were history of other lung disease (except asthma), or previous lung resection (see online supplement)[7]. Participants underwent spirometry, six-minute walking test (6MWT), quantitative computerized tomography (CT) and standard questionnaires to assess symptoms and medical history. From this population, participants who did not have FEV_1, FEV_6 and FVC values from 3 pre-bronchodilator and 3 post-bronchodilator maneuvers were excluded (n=2,084) as were those with coefficient of variance (CV, standard deviation/mean) of either pre-bronchodilator or post-bronchodilator blows >15% (n=486)[8], reducing the study population to 7,741. The COPDGene protocol was approved by Institutional Review Boards at 21 participating centers. Written informed consent was obtained from all participants.

Spirometry and proposed BDR grades

Spirometry was performed in accordance with ATS/ERS recommendations and using an ultrasound-based spirometer (NDD, EasyOne Spirometer Medizintechnik AG, Zurich, Switzerland) before and after two puffs of albuterol using a spacer[9]. Before bronchodilator reversibility testing, **s**hort-acting and long-acting inhaled bronchodilators were withheld 4 and 12 hours; short-acting and long-acting oral bronchodilators were withheld 8 and 12 hours prior to testing, respectively. The largest of 3 acceptable FEV_1 and FVC measurements were reported. Spirometric measurements were graded (range 0–4) by a centralized quality control process (range 0–4: Grade 4: fully met ATS criteria, reproducible to within 50mL, Grade 3: fully met ATS criteria, reproducible to between 50-100mL, Grade 2: fully met ATS criteria, reproducible

between 100-150mL, Grade 1: partly meeting ATS criteria and/or reproducible between 150-200mL, Grade 0: failure to meet ATS criteria and/or reproducible greater than 200mL)[10]. Pre-bronchodilator quality control grades for FEV_1 and FVC were 3.54±0.78 and 3.35±0.92, whereas post-bronchodilator quality control grades were 3.62±0.70 and 3.46±0.81, respectively, in the study group. These grades did not differ markedly among BDR categories (Table 2).

BDR was evaluated as absolute change from baseline FEV_1 (ΔFEV_1L) and percentage change from baseline FEV_1 ($\Delta FEV_1\%$). BDR is a continuous variable with an unimodal, not bimodal, response pattern[11]. Using fixed population-based criteria for both volume and percentage change in BDR is not optimal, especially considering differences in drug, dosage and administration methods in published studies[4]. We used five bronchodilator categories of FEV_1 response by using volume or percentage FEV_1 change: negative (≤0.00% or ≤0.00L), minimal (>0.00% to ≤9.00% or >0.00L to ≤0.09L), mild (>9.00% to ≤16.00% or >0.09L to ≤0.16L), moderate (>16.00% to ≤26.00% or >0.16L to ≤0.26L), and marked (>26.00% or >0.26L) BDR. The rationale for the five-point grading system including non-responders (negative), and minimal, mild, moderate and marked responders is based on several considerations: $\Delta FEV_1L \leq 0$ clearly defines the non-responder and negative responder category. We have previously asserted $\Delta FEV_1\%$ of 6 or 7% might be clinically important as it is associated with about a 90 to 100mL increase in FEV_1[3], which has been suggested as the minimum clinically important difference (MCID) for ΔFEV_1[12]; we use 90mL or 9% to separate minimal from mild response. A 9% threshold, corresponding to upper 95th percentile of BDR in FEV_1, was previously proposed to define clinical "abnormality" based on BDR in a large group of asymptomatic never-smokers[13]. After excluding non-responders, when we ordered responses by baseline FEV_1, average ΔFEV_1 in groups of 100 persons seemed to stabilize at ~160 ml (ΔFEV_1L and $\Delta FEV_1\%$ profile in Figure

1). This value (and the corresponding 16% change) was chosen to separate the mild and moderate categories. Previously, absolute increase in FEV_1 required to exclude natural variability with 95% confidence was reported as 160 mL in obstructive airway disease[14]. In distinguishing between moderate and marked response it seemed practical to utilize a further 100 ml MCID step-size, and use 260 mL or 26% increase. For ATS/ERS guidelines comparison, we placed participants into ATS/ERS groups for ΔFEV_1: 1) Positive: $\Delta FEV_1 L \geq 0.2$ L and $\Delta FEV_1\% \geq 12\%$ and 2) Negative: all others. To compare flow and volume response characteristics in bronchodilator testing, we also evaluated BDR in FVC (BDR-FVC). BDR-FVC was evaluated as absolute change from baseline FVC (ΔFVC L) and percentage change from baseline FVC (ΔFVC %). We utilized the same BDR category assignments we derived for FEV_1 for the BDR-FVC response.

Clinical and functional correlates

As clinical and functional correlates we used St. George's Respiratory Questionnaire (SGRQ) to assess health-related quality of life (scores ranging from 0-100, where a greater score indicates worse health status)[15], modified Medical Research Council (mMRC) dyspnea scale to quantify dyspnea (scores ranging from 0 to 4, a greater score indicates worse dyspnea perception)[16], and six-minute walking distance (6MWD) to assess functional exercise performance. Six-minute walking test was performed according to ATS standards[17], and at least 20 minutes after albuterol administration for post-bronchodilator spirometry. Exacerbation frequency in the prior year was recorded at enrollment, with exacerbations defined as acute worsening of respiratory symptoms requiring antibiotics and/or systemic corticosteroids [18]. CT scans were acquired at full inspiration and end-expiration (see online supplement). CT scans were obtained after bronchodilator testing. Airway wall thickness was assessed by segmental

airway wall area percentage (segmental WA% = (outer bronchus area - airway luminal area) / outer bronchus area), and square root wall area of a 15mm diameter airway (Pi_{15})[19]. Emphysema% on CT was defined as percentage of low attenuation areas below −950 Hounsfield Units (HU) on end-inspiratory CT scan[20]. Gas trapping% was defined as %lung voxels below −856 HU on expiratory scans[21].

Statistical analyses

SPSS 22.0 (IBM Corp: Armonk, NY) and Stata 15 (StataCorp LLC: Texas) procedures were used. Univariate analyses were performed between BDR grades using Chi-square test for proportions and one-way ANOVA or Kruskal-Wallis test for continuous variables (Table 2 and Table E1). P-values for pair-wise comparisons were adjusted for overall type-II error rate (5%) using Tukey's method. Relationships between BDR grades (independent variable) and quantitative CT, SGRQ and 6MWD (dependent variables) were assessed by general linear regression models using age, sex, race, smoking history, body mass index (BMI), baseline FEV_1 and CT scanner type (only for CT measures) as covariates (separately for BDR-FEV_1 and BDR-FVC response) (Tables 3 and 5). A proportional odds model was used for mMRC (Tables 3 and 5). A generalized linear regression model with negative binomial link function assessed BDR grade's independent effect on exacerbation frequency[22] (Tables 3 and 5). SGRQ, emphysema% and gas trapping% were natural-log transformed; regression coefficients for natural-log transformed variables were back-transformed and exponentiated beta values were presented to aid interpretation. Finally, to assess the relation between BDR (as separate continuous variables: ΔFEV_1L, ΔFEV_1%, ΔFVC L, ΔFVC%) and 6MWD, SGRQ and quantitative CT measures, we modeled 6MWD, SGRQ and quantitative CT measures against ΔFEV_1L, ΔFEV_1%, ΔFVC L, and ΔFVC% in the whole study population. ΔFEV_1L, ΔFEV_1%, ΔFVC L, and ΔFVC% were coded

using restricted cubic spline function with three knots, located at the 5^{th}, 50^{th}, and 95^{th} percentiles (Figure 4A, 4B). All these models were adjusted for age, sex, race, smoking history, BMI, baseline FEV_1 or FVC, and CT scanner type (for CT measures).

Analyses were performed for the whole study population. ATS/ERS criteria identified most of the participants in the marked BDR category as positive BDR. Accordingly, analyses were performed in the subgroup after excluding ATS/ERS positives (Table 5). But excluding ATS/ERS positives causes a substantial loss in sample size of marked BDR group. For that reason marked BDRs were excluded from the subgroup analysis.

Results

Characteristics of the 7,741 participants are summarized in Table 1. Within subject CV for pre-and post-bronchodilator FEV_1 was 4.12%±2.77% and 3.52%±2.54%, respectively. Distributions of absolute and percentage FEV_1 BDR are presented in Figure 2. Mean ΔFEV_1L and ΔFVCL were 0.099L and 0.092L, respectively. However, ΔFEV_1L and $\Delta FEV_1\%$ distributions were dramatically different (Figure 2). This emphasizes that volume and percentage changes need to be considered separately from each other. Table 2 shows study participants graded by BDR intensity categories. Total BDR positives were 78.9%.

ΔFEV_1L and ΔFVCL after bronchodilator inhalation are presented in Figure 3. Despite similarity of mean and SD (Table 1), ΔFVCL increased more rapidly than ΔFEV_1L above a BDR of 0.1L (Figure 3A). In contrast, $\Delta FEV_1\%$ and ΔFVC% increased similarly over the full BDR range (Figure 3B).

In Figure 1, ΔFEV_1L and $\Delta FEV_1\%$ of positive BDR participants are ordered by increasing pre-BD FEV_1 volumes to compare volume and percentage increase patterns. Conspicuously, BDR patterns expressed as ΔFEV_1L and $\Delta FEV_1\%$ differed markedly as pre-

bronchodilator FEV_1 increased. Below pre-bronchodilator FEV_1%pred of 40% (FEV_1 ~1 L), ΔFEV_1L increased rapidly up to ~0.160 L and then stabilized, whereas ΔFEV_1% averaged ~16% then gradually declined in a hyperbolic fashion to ~4% as FEV_1 increased.

BDR categories by FEV_1 response

Utilizing proposed BDR cut-offs, 27.9%, 20.0%, 18.1% and 12.9% of the population had minimal, mild, moderate and marked bronchodilator response, respectively (Table 2). 100% of the minimal responders had a minimal FEV_1-BDR by both ΔFEV_1L and ΔFEV_1%. 93.1% and 25.6% of the mild responders had mild BDR by ΔFEV_1L and ΔFEV_1%. 91.6% and 20.7% of the moderate responders had moderate BDR by ΔFEV_1L and ΔFEV_1%. 91.0% and 27.7% of the marked responders had marked BDR by ΔFEV_1L and ΔFEV_1%, respectively. On the other hand, 21.1% of the population had a negative BDR response. Mean ages of marked bronchodilator responders and non-responders were lower than that of minimal, mild and moderate responders. Female sex was more prominent in minimal and mild, whereas male sex was more prominent in marked and non-response categories. Negative responders had greater pre- and post-bronchodilator FEV_1/FVC compared to all other response categories.

In the univariate analyses, there was progressive increase in segmental WA% from negative to marked BDR ($p<0.0001$). Pi_{15} increased from minimal to marked bronchodilator responders ($p<0.0001$). Marked BDR-FEV_1 group had significantly greater segmental WA% and Pi_{15} compared to minimal, mild, moderate BDR-FEV_1 groups and non-responders (adjusted $p=0.0005$ for post-hoc comparisons, not shown). 6MWD increased from 408±123m to 431±117m as BDR-FEV_1 increased from minimal to marked ($p<0.0001$). We also observed

significant differences in SGRQ, mMRC scores and exacerbation frequency between BDR-FEV_1 groups (Table 2).

After adjusting for potential confounders, including sex, age and baseline FEV_1, patients with greater BDR-FEV_1 had greater 6MWD, better SGRQ, fewer exacerbations and lower mMRC (Table 3). There was a significant decrease in odds of being in higher mMRC category as BDR-FEV_1 category increased from minimal to marked. Mean WA and Pi_{15} of marked BDR-FEV_1 were 0.29% and 0.03mm greater compared to negative responders, respectively. 6MWD was 37 meters greater in marked BDR compared to negative responders. SGRQ was 12% less in moderate and marked BDR-FEV_1 group compared with negative responders. Relative risk of annualized exacerbation rate were 26% and 14% decreased in marked and moderate FEV_1-bronchodilator responders compared to negative category, respectively (relative risk, 0.86, $p=0.044$ and 0.74, $p<0.00001$, respectively). On the other hand, mean WA% and Pi_{15} were 0.24% and 0.01mm less in minimal FEV_1-bronchodilator responders compared to negative responders. In models assessing the relationship between ΔFEV_1L and ΔFEV_1%, as continuous variables (Figure 4A), 6MWD increased with an upward slope as ΔFEV_1 L increased, whereas 6MWD decreased with a downward slope as ΔFEV_1% increased in participants with a positive BDR. The relation between SGRQ score with ΔFEV_1% had an upward slope in positive BDRs. The relationship of ΔFEV_1% with both WA segmental% and Pi15 was more pronounced with a steeper upward slope than for ΔFEV_1L.

Comparison of BDR- FEV_1 Grading Strategy with BDR by ATS/ERS criteria

Comparison of BDR using ATS/ERS criteria to the proposed BDR grades shows striking differences (Table 4). ATS/ERS criteria identify only 20.6% of patients as positive BDR, 79.4% in the marked category, 32.3% in the moderate category, and only 8.8% in minimal and mild

BDR-FEV_1 categories. Almost 4/5 of the marked BDR group (794 of 1000) was also ATS/ERS positive. When we analyzed correlates of BDR grades after excluding ATS/ERS positives in the minimal, mild, and moderate BDR categories; we observed that minimal, mild, and moderate BDR-FEV_1 were associated with greater 6MWD and lower SGRQ compared to negative BDR category. Odds of being in a higher mMRC category decreased as BDR-FEV_1 increased from minimal to moderate when compared to non-responders (Table 5).

BDR Grading Strategy applied for BDR in FVC

By utilizing proposed BDR cut-offs, 16.4%, 12.0%, 12.1% and 22.2% of the population had minimal, mild, moderate and marked FVC-bronchodilator response, respectively (Table 3). 37.3% of the study population had a negative BDR in FVC. Pre-bronchodilator FEV_1, FVC and FEV_1/FVC decreased as volume response increased from minimal to marked FVC-bronchodilator response. In the univariate analyses (online supplement, Table E1), total SGRQ and dyspnea scores, exacerbation frequency, segmental WA%, emphysema% and gas trapping% increased as FVC-bronchodilator response increased from negative to marked ($p<0.0001$).

After adjusting for potential confounders including baseline FVC, patients with greater BDR-FVC had greater emphysema and gas trapping and fewer exacerbations and lower mMRC (Table 3). Emphysema and gas trapping were 50% and 46% greater in marked BDR compared to negative responders, respectively. Mean WA and Pi_{15} of marked BDR-FVC were 0.67% and 0.04mm greater compared to negative responders, respectively. 6MWD was ~14 meters greater in marked BDR-FVC compared to negative responders. SGRQ was 9% and 14% higher in moderate and marked BDR-FVC compared with negative responders. Participants in mild, moderate and marked BDR-FVC categories were less likely to experience exacerbations compared to negative responders. There were significantly decreased odds of being in higher

mMRC category in moderate and marked BDR-FVC categories. On the other hand, mean Pi_{15} was 0.02mm less in minimal BDR-FVC group compared to negative BDR-FVC responders.

In models assessing the relationship between ΔFVC L and ΔFVC %, as continuous variables (Figure 4B), total SGRQ score, emphysema% and gas trapping% were lowest in the region of ΔFVC L and ΔFVC % levels around -1.5 Liters and -40%, respectively. After those regions, there was a trend of increasing total SGRQ score, emphysema% and gas trapping% with an upward slope as ΔFVC L and ΔFVC % increased.

Discussion

Our approach of identifying distribution characteristics of BDR is an improvement in evaluating clinical and radiological associations of bronchodilator responsiveness. Grading systems using several categories might be more useful than those yielding only positive/negative categories. These data demonstrate the importance of separating volume and percentage BDR change rather than requiring both simultaneously, which biases against identifying meaningful BDR in subjects with small or large FEV_1.

Our categorization employs identical numerical fractions for ΔFEV_1 in L and in % units. It yields many more positive responders than does ATS/ERS positive criteria (Table 4). Logically, patients with low FEV_1 should benefit more from small FEV_1 volume increases than those with large FEV_1. Advantageously, for the 7,741 individuals studied, our grading method identified 80% with at least minimal and 50% with moderate or greater FEV_1 BDR, while the ATS/ERS method identified only 20.6% positive.

Interpretation of BDR for obstructive airways disease (OAD) patients in pulmonary laboratories has long been disputed. Nearly fifty years ago, Freedman et al. suggested that most

physicians would agree that a FEV_1 increase <10% is valueless and that a 20%-30% increase was likely useful[23]. In 1974, a CHEST advisory committee recommended positive BDR required FEV_1 change in both percent and absolute volume[24]. In 1982, Ries recommended an FEV_1 increase of both 15% and 200mL[25]. Eliasson et al.[26], reviewing 66 asthma and COPD papers, found that 14 papers used seven different BDR criteria. In 1991, an ATS committee recommended increase in FEV_1 or FVC ≥200 mL and 12% [27]. This criterion was reinforced in the 2005 ATS/ERS guidelines[1]. Considering that baseline FEV_1 of individuals assessed for BDR vary over a wide range[28], to exceed healthy population-based confidence intervals[29] for both volume and percentage values to establish positive bronchodilator response may be too restrictive.

In a 2011 review, Hanania et al.[30] examined the 5 most prevalent recommendations: including %predicted FEV_1 >10% (ERS[31]), FEV_1 increase >15% (ACCP[24]) and >12% and 200mL increase (ATS[27], ATS/ERS[1] and GOLD[18]). In response to a letter by Hansen et al.[32], Hanania et al. agreed that BDR response of <200mL in those with low baseline FEV_1 was clinically valuable[33]. In 2005, Donahue[12] recommended that >100mL FEV_1 increase in OAD patients is likely to be clinically important.

BDR may be expressed in alternate ways: as absolute change in values, as percentage change from baseline, or as change as a percentage of the subject's predicted value[34,35]. Using change in FEV_1 as % predicted was recently shown to avoid sex and size bias in the assessment of BDR[34]. Although there is no consensus on how a BDR should be expressed in the literature, most guidelines express BDR as absolute change in values and as percentage change from baseline, we employed this strategy. Additionally, in the presence of severe airway disease such as COPD, the baseline FEV_1 may be far off the predicted value which may cause an

underestimation of the BDR as compared to performance of the subject variable (change in FEV_1 as % predicted) in relatively more healthy or non-smoker populations.

BDR category assignments

Dividing BDR data into grades has often used only mean and SD values. In our study population, using a grading approach based on ΔFEV_1L or $\Delta FEV_1\%$ distribution and means (Figure 2) might cause an unbalanced strategy, since ±1 SD of Δvolume would assimilate ~68% of participants into one BDR class, with the remaining ~32% divided into several much smaller classes (e.g., ±2 SD, ±3 SD). Instead, our grading strategy is based upon profile of changes in volume and percentage change in FEV_1 (Figure 1) and other considerations to establish grading category cutoffs. This resulted in BDR response of this population being classified 21% negative, 28% minimal, 20% mild, 18% moderate and 13% marked.

Of the 7741 participants, 21.1% had negative bronchodilator response by FEV_1, compared to 37.3% by BDR-FVC. Although BDR-FVC was more frequently reported in COPD patients than that of FEV_1 response[36,37], we observed that BDR by FEV_1 was more common than BDR by FVC in our study population. FVC has the disadvantage of being dependent on expiratory time[38]. Therefore, evaluation of BDR by FVC may be noisy[39]. Figure 3 shows that, for ΔFEV_1L BDR of >100mL, the number of individuals meeting any specific volume criterion is much greater for FVC than for FEV_1, while for those meeting $\Delta FEV_1\%$ criteria >10% are similar for FVC and FEV_1. In COPD patients, the magnitude of the flow (ΔFEV_1) and volume (ΔFVC) responses after administration of albuterol differ. A particular flow response is accompanied by a higher volume response as the severity of airflow obstruction worsens in COPD. In our study, ΔFEV_1 and ΔFVC responses were similar between BDR categories (Table

2). This finding may be a result of our study population consisting of smokers, with almost 50% without airflow obstruction.

Clinical implications of BDR grades

Our results indicate that spirometric indices and CT measures of airway wall thickness increase as BDR increases. In accordance with reports suggesting inverse correlation between spirometric obstruction and bronchodilator response, baseline FEV_1/FVC decreased as BDR response increased[26]. We observed significant increase in segmental WA% and Pi_{15} as BDR increased from minimal to marked (Table 2). Similar trends persisted when we adjusted CT outcomes for baseline FEV_1 and other potential confounders. Kim et al. found that airway wall thickness independently predicted BDR in COPD and suggested that increased CT airway wall thickness in the BDR positive COPD group represented airway pathology dominated by smooth muscle hypertrophy[40]. Morphometric studies in asthmatics revealed bronchial tree zones with significant muscular hypertrophy, reflecting hyperreactivity of these segments[41]. Both the segmental WA% and Pi_{15} mainly reflect large airways. We think that our findings showing significant BDR dependence in segmental WA% and Pi_{15} may reflect an increased bronchomotor tone due to smooth muscle hypertrophy in the large airways of smokers with marked bronchodilator response.

To our knowledge, our results indicate for the first time that 6MWD – a marker of functional exercise performance – significantly and continuously increases as acute bronchodilator response grade increases. This finding is in agreement with Anthonisen and Wright's initial observations, reporting a relatively well-preserved exercise tolerance in COPD patients with large bronchodilator responses[42]. The mechanism underlying this observation is not

known but one possible explanation is that patients with a larger BD response are able to bronchodilate during the hyperpnea of exercise. Despite that the relationship between the 6MWD and ΔFEV_1L were similar to that of 6MWD and BDR-FEV_1 response grades, the relationship between the 6MWD and $\Delta FEV_1\%$ had an inverse relation (Figure 4A). One possible explanation for the difference between results of continuous modeling of 6MWD vs. $FEV_1\%$ and $\Delta FEV_1\%$ may be the fact that > 90% of the responders in each BDR category were positive by volume change in FEV_1. For that reason, associations with BDR grades may be dominated by associations with volume change in FEV_1."

Recently, Quanjer et al. suggested that an ideal BDR measure should be based on clinical outcomes, such as exacerbations, quality of life and hospitalizations[11]. Not long before, Albert and colleagues suggested that BDR did not distinguish clinical outcomes such as mortality or exacerbation rates in the ECLIPSE COPD cohort[43]. We observed significant increase in quality of life as BDR grade increased from minimal to marked. Supportingly, a greater SGRQ score was reported in poorly responsive moderate-to-very severe COPD patients in UPLIFT[44]. Moreover, to our knowledge, our analysis is the first to show exacerbation frequency reduction irrespective of baseline FEV_1 in patients with moderate and marked BDR compared to negative responders. Our analysis characterizes a group of marked BD responders with more airway disease, evidenced by greater segmental WA% and Pi_{15}, better preserved exercise performance and dyspnea, greater quality of life and fewer exacerbations compared to negative responders. Associations observed for 6MWD in the multivariable models are greater than their MCIDs[45,46]. Associations for exacerbations and CT measures can only be evaluated statistically, since validated MCIDs for those outcomes do not yet exist[47].

When we applied BDR Grading Strategy for a FVC based BDR, we observed that emphysema% and gas trapping% increased as BDR in FVC increased from minimal to marked category. Emphysema and gas trapping were prominent features of BDR-FVC responders in accordance with previous reports [48-50]. Cerveri et al. have shown that FVC responder COPD patients have more severe emphysema than both FEV_1 and FVC responders[48]. Further, Deesomchok et al. have shown that COPD patients with greatest resting lung hyperinflation shows the largest bronchodilator-induced volume response in reversibility testing[49]. The greater volume response compared to flow response in COPD patients was explained by the presence of a higher degree loss of lung elastic recoil due to emphysema and compression of small airways by the enlarged airspaces as the airflow obstruction worsened[48]. In addition to previously reported findings, BDR grading strategy defined in current study were successful in capturing an increasing trend in emphysema and gas trapping extent as BDR in FVC increased from minimal to marked response categories compared to non-responders.

BDR-FVC is associated with gas trapping. This finding is in agreement with literature findings[50,51]. Gas trapping on quantitative CT is accepted as a prominent sign of small airways disease. Supportingly, small airways diameter on spiral CT scan was previously shown to narrow in FVC responder COPD patients[48]. There was an inverse association with BDR-FVC response and exacerbation frequency in patients with mild-to-marked BDR-FVC compared to negative responders. Further, quality of life was impaired in moderate and marked BDR-FVC compared with negative responders. We theorize that impaired quality of life and increased exacerbation frequency observed in these patients may be a consequence of severe hyperinflation and emphysema present in moderate and marked BDR-FVC responders.

In this study, we demonstrate that BDR-FEV_1 and BDR-FVC are associated with different clinical, functional and radiological characteristics. While increasing bronchodilator response in FEV_1 is primarily associated with improving 6MWD, quality of life, and dyspnea, increasing bronchodilator response in FVC is primarily associated with increasing emphysema and gas trapping. Moderate or marked BDR in both measures are associated with a reduction in exacerbation frequency.

A very recent paper aimed to examine clinical, functional and radiological associations of BDR by ATS/ERS criteria[50]. In subjects with spirometrically-defined COPD, the authors have shown that ATS-BDR positive participants in the COPDGene population were associated with higher %gas trapping, Pi10, functional small airways disease, FRC and TLC% predicted, respiratory exacerbations and 6MWD compared to non-BDR group. In our study, which studied the responses of subjects with smoking history with and without spirometric evidence of COPD, ATS/ERS criteria identified most of the participants (79.4%) in the marked category as positive BDR. Despite this important clinical association of the ATS/ERS BDR criteria[50], when we excluded BDR positive participants by ATS/ERS criteria, we observed that clinical associations of BDR Grading Strategy persisted for 6MWD, SGRQ and mMRC in the adjusted multivariable analysis: patients with greater BDR had greater exercise performance, better quality of life and less dyspnea perception (Table 5).

We observed that 21.1% of our study group had a negative response (defined as ≤0.00% or ≤0.00L FEV_1 change) to albuterol. Recently, Bhatt and colleagues showed that a paradoxical response to beta-2 agonists resulting in bronchoconstriction was associated with respiratory morbidity measured by higher mMRC, frequent exacerbations and lower 6MWD[52]. Probably, some of the participants in negative response category in our study can be regarded to have a

paradoxical response to beta-2 agonists. Despite the negative category being set as the reference category in our analyses, our results are partly in accordance with Bhatt and colleagues observations, by showing a decreasing quality of life and 6MWD as BDR decreased, increasing odds for experiencing a higher dyspnea level as BDR decreased and decreasing odds for frequency of exacerbations in patients with marked and moderate BDR compared to negative response category.

In the whole study group, patients with minimal BDR-FEV_1 compared to those with mild, moderate and marked BDR-FEV_1 had lower exercise performance, lower quality of life and more dyspnea perception (Table 3). It seems logical to assume that, the minimal BDR-FEV_1 group is likely to have fixed airways obstruction, since their airways respond minimally to albuterol inhalation.

Relevance to ACO phenotype

Bronchodilator responsiveness is accepted as the key feature of asthma and COPD overlap (ACO) phenotype[53]. Although different definitions for ACO are used in various studies, a spirometric component of a widely used ACO definition requires a marked bronchodilator response (>400 mL) or at least a positive bronchodilator response (≥200 mL and 12%) in addition to persistent airflow limitation[53-55]. It might be asked whether the characteristics of the participants with marked bronchodilator response in our study resembled clinical features of patients with ACO. Cosentino et al. found that ACO subjects had less severe spirometric and radiological findings (less emphysema and gas trapping), but more segmental airway wall thickening and they were more likely to experience frequent exacerbations compared to COPD subjects[56]. Although there are several published studies aiming to characterize clinical features of

ACO phenotype in the COPDGene population[56-58], their analysis is usually limited to comparing features of ACO patients with either COPD or asthma alone, rather than comparing ACO characteristics with an overall smoker population. Having shown clinical implications of various degrees of bronchodilator response (much less than 400 mL), we suggest considering the use of bronchodilator grading, rather than an all or none evaluation system, for further ACO phenotyping studies.

Tweddale and colleagues[14] reported that, in patients with reduced FEV_1/VC ratio, absolute FEV_1 increase required to exclude natural variability with 95% confidence was 160 mL. In this context, minimal and mild categories in the proposed BDR grading system fall in the range of this natural variability. But, in our analysis we observed that minimal and mild BDR categories are associated with important patient-centered outcomes in COPD (greater 6MWD, lower SGRQ and mMRC dyspnea scores) compared to negative BDR. The fact that bronchodilator response below variability thresholds may associate with symptom and performance improvements (perhaps because BDR may be unpredictably underestimated by FEV_1 and/or FVC changes in some cases) is also acknowledged in ATS/ERS 2005 guideline[9]. Further, BDR to a short acting bronchodilator is no longer recommended to predict long term response and is not thought helpful in making therapeutic decisions[11]. Therefore, we believe this study's findings are helpful to characterize clinical associations of bronchodilator responsiveness rather than using them to make therapeutic decisions. We hope that our findings, in addition to recently reported studies that characterize BDR,[11,34] will spur guideline committees to revisit current BDR criteria.

Our study has several limitations. Although we utilized a large population, it includes only current and ex-smokers. A population-based sample of 3922 healthy non-smokers showed

that the upper 95% confidence limit for BDR was 284 ml for ΔFEV_1 and 12% for $\Delta FEV_1\%$[29]. In the ECLIPSE cohort, FEV_1 changes after an inhaled bronchodilator in smoking controls and COPD patients were significantly greater than in non-smoking controls[34,43]. Importantly, healthy never-smokers were not included in our cohort, which restricts generalisability of our results to this group. Second, whether other inhaled bronchodilators or other albuterol doses should be similarly graded is untested. Third, observations from various cohorts have shown that the presence of BDR is variable over time[59-61]. Unfortunately, our study does not include longitudinal analysis of the study cohort to allow examination of long-term implications of BDR categorization. Fourth, when defining thresholds for the BDR grading system, in distinguishing between moderate and marked response, a 100 mL MCID step-size was utilized. But, 100 mL as a MCID for FEV_1 was based on a single study that enrolled only COPD patients, which limits the generalizability of 100 mL MCID value to populations other than COPD[12]. Fifth, we acknowledge that the thresholds for the BDR grading system were derived for FEV_1 change. These thresholds may not be fully applicable to FVC change. Further study will be necessary to determine whether different thresholds may perform better for FVC response.

Lastly, blood eosinophils have strong potential as a prognostic and therapeutic biomarker in the clinical management of COPD. To evaluate association of bronchodilator responsiveness with blood eosinophil count would be a promising analysis for further research.

In conclusion, BDR in current- or ex-smokers can be graded by using either volume or percentage change in FEV_1 or FVC. Our findings, based on the largest smoker population with quantitative CT data, suggest that this BDR grading system identified patients with clinically important differences in exercise performance, quality of life, exacerbation frequency, dyspnea and pulmonary imaging. BDR-FEV_1 and BDR-FVC are associated with different clinical,

functional and radiological characteristics. Whether these BDR categories have prognostic implications remains to be tested.

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Figure legends

Figure 1. Mean FEV_1 bronchodilator response in volume (L) and in percentage (%) by clusters of 100 individuals at each point as baseline FEV_1 % predicted increases for the 6,107 participants with positive BDR. Changes in volume (y_1 axis: ΔFEV_1L) and % (y_2 axis: $\Delta FEV_1\%$) differ markedly. While ΔFEV_1L increases rapidly to ~0.16L and stabilizes at that level, $\Delta FEV_1\%$ fraction gradually declines in a hyperbolic fashion from 16% to 4%. BDR, bronchodilator response. FEV_1, forced expiratory volume in 1 second; Δ, delta; %, percentage; L, liters.

Figure 2. Distribution of change in absolute volume for largest of three pre- to post bronchodilator FEV_1 differences (ΔFEV_1L) and change in FEV_1% after bronchodilator in the whole study population (N=7,741). Dashed vertical lines represent the limits of the new BDR grading system (negative (≤0.00% or ≤ 0.00L), minimal (>0.00% to ≤9.00% or >0.00L to ≤0.09L), mild (> 9.00% to ≤16.00% or > 0.09L to ≤0.16L, moderate (>16.00% to ≤26.00% or >0.16L to ≤0.26L), and marked (>26.00% or >0.26L)). Percentage of participants in each BDR category are given in between vertical lines that represent the limits of the BDR grading system. Curves were constructed as Gaussian fits on the histogram points consisting of 24 bins with equal distance of 0.0905 L spanning from -0.63 L to 1.45 L for ΔFEV_1L and 6.46% wide bins from -31.8% to 116.8% for ΔFEV_1% change. N.B.: To demonstrate the similarities and differences in distributions, only the segments from -0.4L to 0.6L and -40% to 60% changes are shown. MIN, minimal BDR category; MOD, moderate BDR category.

Figure 3. Response trend of ΔFEV_1 and ΔFVC after bronchodilator in the total study population (N=7,741). Panel A shows response trend of mean change in absolute volume of ΔFEV_1L and $\Delta FVCL$ by 500 individuals at each point. Panel B shows response trend of mean change in $\Delta FEV_1\%$ and $\Delta FVC\%$ by 500 individuals at each point. In both panels, individuals are ordered by size of response. Δ, delta; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; L, liters; %, percentage.

Figure 4. Restricted cubic spline models of BDR (as separate continuous variables ΔFEV_1 L, ΔFEV_1 %, ΔFVC L and ΔFVC %), with 95% confidence intervals (in gray) for 6MWD, Total SGRQ score and quantitative CT measures in the total study population. Panel A shows the adjusted models of BDR - FEV_1L and BDR - FEV_1% for 6MWD, SGRQ, WA segmental% and Pi15. Panel B shows the adjusted models of BDR - FVCL and BDR - FVC % for SGRQ, emphysema% and gas trapping%. ΔFEV_1L,ΔFEV_1%, ΔFVCL, ΔFVC % were coded using a restricted cubic spline function with three knots, located at the 5^{th}, 50^{th}, and 95^{th} percentiles. Models were adjusted for age, sex, race, smoking history, BMI, baseline FEV_1 or FVC, and CT scanner type (for CT measures).

Tables

Table 1. Characteristics of the study population

Variables	**Study Population (N=7,741)**
Age, years	60.2 ± 8.9
Sex, Male %	54.5
Race: Caucasian/African American %	72.7 / 27.3
BMI, kg/m^2	28.6 ± 6.1
Smoking history, pack-years (IQ range)	40.0 (28.0 – 55.5)
Pre-Bronchodilator Spirometry	
FEV_1, L	2.14 ± 0.93
FEV_1, % predicted	72.2 ± 26.0
FVC, L	3.28 ± 1.03
FVC, % predicted	85.4 ± 19.2
FEV_1/FVC, %	63.6 ± 15.4
FEV_1/FVC<70%, n (%)	4298 (55.5)
Post-Bronchodilator Spirometry	
FEV_1, L	2.24 ± 0.93
FEV_1, % predicted	75.6 ± 25.8
FVC, L	3.37 ± 1.01
FVC, % predicted	87.8 ± 18.5
FEV_1/FVC, %	65.1± 16.0
FEV_1/FVC<70%, n (%)	3864 (49.9)
Within Subject Coefficient of Variation Among 3 Forced Exhalations	

CV for three Pre-BD FEV_1, %	4.12 ± 2.77
CV for three Pre-BD FVC, %	3.54 ± 2.46
CV for three Post-BD FEV_1, %	3.52 ± 2.54
CV for three Post-BD FVC, %	3.02 ± 2.18
Change after Bronchodilator	
ΔFEV_1, L	0.099 ± 0.015
ΔFVC, L	0.092 ± 0.030
ΔFEV_1, %	6.04 ± 9.34
ΔFVC, %	3.78 ± 10.48

Mean ± SD or median (interquartile range 25 - 75) presented as appropriate. Reported pulmonary function values are based on largest measurements. Definition of abbreviations: BMI, body mass index; CV, coefficient of variation (%); FEV_1, forced expiratory flow volume in 1 second; FVC, forced vital capacity; Δ, delta or change; L, liters; BD, bronchodilator.

Table 2. Comparison of demographic characteristics, spirometry, functional exercise capacity, and quantitative CT measures of airway abnormality among various grades of FEV_1 bronchodilator responders (N=7,741).

	NEGATIVE	**MINIMAL**	**MILD**	**MODERATE**	**MARKED**
Category range for ΔFEV_1L (L)	Δ FEV$_1$ ≤ 0	$0 < \Delta$ FEV$_1 \leq 0.09$	$0.09 < \Delta$ FEV$_1 \leq 0.16$	$0.16 < \Delta$ FEV$_1 \leq 0.26$	$0.26 > \Delta$ FEV$_1$
Category range for ΔFEV_1% (%)	Δ% FEV$_1 \leq 0$	$>0 < \Delta$% FEV$_1 \leq 9$	$9 < \Delta$% FEV$_1 \leq 16$	$16 < \Delta$% FEV$_1 \leq 26$	$26 > \Delta$% FEV$_1$
N (%)	1634 (21.1)	2159 (27.9)	1549 (20)	1399 (18.1)	1000 (12.9)
Demographics					
Age, yrs	59.1 ± 8.6	60.8 ± 8.9	60.9 ± 9.0	60.6 ± 9.1	59.0 ± 8.7
BMI, kg/m^2	28.8 ± 6.2	28.5 ± 6.3	28.5 ± 6.1	28.7 ± 6.1	28.7 ± 6.0
Smoking history, pack years	39.1 (27.7 – 54.2)	40.0 (28.0 – 55.5)	40.0 (27.0 – 55.5)	40.0 (28.5 -55.5)	40.5 (30.0 – 58.0)
Sex, Male, %	55.3	48.1	47.8	57.2	66.8
Race, Caucasian, %	64.8	72.7	76.2	76.6	74.8
ICS use, %	6.7	6.2	5.5	6.9	9.3
Spirometry					
Pre-BD FEV_1, L	2.37 ± 0.95	2.07 ± 0.92	2.05 ± 0.88	2.13 ± 0.91	2.08 ± 0.95
Post-BD FEV_1, L	2.28 ± 0.93	2.12 ± 0.93	2.17 ± 0.88	2.32 ± 0.93	2.43 ± 0.98
Pre-BD FVC, L	3.46 ± 1.03	3.17 ± 0.99	3.17 ± 0.96	3.29 ± 1.04	3.36 ± 1.14
Post-BD FVC, L	3.33 ± 1.01	3.18 ± 0.97	3.29 ± 0.93	3.50 ± 1.00	3.78 ± 1.12
ΔFEV_1, L	-0.09 ± 0.09	0.04 ± 0.02	0.12 ± 0.02	0.20 ± 0.04	0.36 ± 0.12
ΔFVC, L	-0.14 ± 0.24	0.02 ± 0.19	0.12 ± 0.21	0.21 ± 0.24	0.41 ± 0.37
ΔFEV_1, %	-3.93 ± 3.99	2.64 ± 1.96	6.95 ± 3.18	11.17 ± 5.13	21.12 ± 11.65
ΔFVC, %	-3.81 ± 7.04	1.09 ± 6.63	4.61 ± 7.78	7.95 ± 9.68	14.84 ± 13.86

Pre-BD FEV_1/FVC, %	66.87 ± 15.29	63.59 ± 16.14	63.13 ± 15.21	63.02 ± 14.73	59.87 ± 14.21
Post-BD FEV_1/FVC, %	67.09 ± 15.98	64.83 ± 16.89	64.80 ± 15.99	65.65 ± 15.19	63.21 ± 14.63
Pre-BD FEV_1, QC	3.15 ± 1.05	3.60 ± 0.67	3.71 ± 0.59	3.66 ± 0.65	3.61 ± 0.72
Post-BD FEV_1, QC	3.68 ± 0.68	3.74 ± 0.58	3.68 ± 0.60	3.55 ± 0.69	3.26 ± 0.97
Pre-BD FVC, QC	3.07 ± 1.14	3.42 ± 0.82	3.48 ± 0.77	3.43 ± 0.85	3.34 ± 0.89
Post-BD FVC, QC	3.46 ± 0.82	3.57 ± 0.68	3.51 ± 0.73	3.41 ± 0.86	3.21 ± 1.02
Functional exercise capacity, quality of life, and exacerbation frequency					
6MWD, meters	413 ± 123	408 ± 123	418 ± 118	429 ± 120	431 ± 117
SGRQ score	20.61 (5.96 – 43.27)	22.55 (6.30 – 44.79)	21.74 (7.12 – 43.50)	20.53 (6.45 – 40.82)	25.35 (8.36 – 46.27)
mMRC	1.34 ± 1.48	1.38 ± 1.44	1.31 ± 1.42	1.23 ± 1.41	1.38 ± 1.43
Exacerbations/year	0.39 ± 1.00	0.42 ± 0.93	0.43 ± 0.99	0.38 ± 0.93	0.38 ± 0.89
Quantitative CT					
$WA_{segmental}$, %	61.13 ± 3.32	61.17 ± 3.21	61.26 ± 3.19	61.40 ± 3.14	62.12 ± 3.38
Pi_{15}, SRWA	5.14 ± 0.19	5.13 ± 0.19	5.14 ± 0.20	5.15 ± 0.20	5.21 ± 0.21
Emphysema%	1.75 (0.56 – 6.17)	2.40 (0.74 – 9.49)	2.70 (0.76 – 7.93)	2.61 (0.79 – 8.01)	2.81 (0.97 – 7.12)
Gas trapping %	13.54 (6.01 – 29.90)	15.10 (6.99 – 35.47)	16.06 (7.54 – 34.46)	16.47 (7.77 – 34.14	19.35 (9.99 – 36.12)

Data are presented as mean ± SD or median (IQR 25 – 75) or as percentages. Definition of abbreviations: FEV_1, forced expiratory flow volume in 1 seconds; FVC, forced vital capacity; ICS, inhaled corticosteroid; Δ, delta; L, liters; %, percentage; BD, bronchodilator; CT, computed tomography; WA, wall area; Pi_{15} SRWA, square root wall area of a 15 mm diameter airway; QC: quality control grades for spirometry maneuver (ranging from 0 to 4); 6MWD, six-minute walking distance; SGRQ, St. George Respiratory Questionnaire total score; mMRC, modified Medical Research dyspnea score.

Table 3. Adjusted multivariable analysis for functional exercise capacity, quality of life, exacerbation frequency, dyspnea and quantitative airway CT measures with increasing FEV_1 and FVC bronchodilator response category, with negative response as reference.

		BRONCHODILATOR RESPONSE GRADES – FEV_1 response				
N (%)		**Negative 1634 (21.1)**	**Minimal 2159 (27.9)**	**Mild 1549 (20.0)**	**Moderate 1399 (18.1)**	**Marked 1000 (12.9)**
6MWD	Mean difference (95% CI)	1 (ref)	**8.46**** **(2.01 – 14.91)**	**17.60*** **(10.61 – 24.58)**	**26.94*** **(19.81 – 34.07)**	**37.00*** **(29.14 – 44.86)**
SGRQ	% difference (95% CI) e^{β}	1 (ref)	**-7.30**** **(-13.00 – -1.20)** **0.927**	**-8.30**** **(-14.40 – -1.80)** **0.917**	**-12.20*** **(-18.20 – -5.80)** **0.878**	**-12.40*** **(-18.90 – -5.30)** **0.876**
mMRC	OR (95% CI)	1 (ref)	**0.81**** **(0.71 – 0.93)**	**0.74*** **(0.64 – 0.86)**	**0.62*** **(0.53 – 0.73)**	**0.63*** **(0.53 – 0.75)**
Exacerbations/year	RR (95% CI)	1 (ref)	0.89 (0.78 – 1.01)	0.91 (0.79 – 1.05)	**0.86**** **(0.74 – 0.99)**	**0.74*** **(0.63 – 0.87)**
$WA_{segmental}$, %	Mean difference (95% CI)	1 (ref)	**-0.24**** **(-0.43 – -0.06)**	-0.18 (-0.38 – 0.01)	-0.08 (-0.28 – 0.12)	**0.29**** **(0.06 – 0.51)**
Pi_{15}	Mean difference (95% CI)	1 (ref)	**-0.01**** **(-0.03 – -0.00)**	-0.00 (-0.02 – 0.01)	-0.00 (-0.01 – 0.01)	**0.03*** **(0.01 – 0.04)**
Emphysema%	% difference (95% CI) e^{β}	1 (ref)	7.62 (-1.62 – 12.71) 1.08	5.30 (-4.41 – 15.99) 1.05	3.75 (-6.06 – 14.60) 1.04	-6.00 (-15.83 – 4.97) 0.95
Gas trapping%	% difference (95% CI) e^{β}	1 (ref)	-2.69 (-8.57 – 3.57) 0.97	1.54 (-5.06 – 8.60) 1.01	4.00 (-2.92 – 11.41) 1.04	**10.50 (2.37 – 19.28)** **1.10****
		BRONCHODILATOR RESPONSE GRADES – FVC response				
N (%)		**Negative 2885 (37.3)**	**Minimal 1273 (16.4)**	**Mild 928 (12.0)**	**Moderate 935 (12.1)**	**Marked 1720 (22.2)**
6MWD	Mean difference (95% CI)	1 (ref)	4.65 (-2.17 – 11.48)	2.38 (-5.27 – 10.03)	4.42 (-3.26 – 12.10)	**13.91*** **(7.56 – 20.27)**
SGRQ	% difference (95% CI) e^{β}	1 (ref)	4.97 (-2.28 -12.63) 1.05	4.37 (-3.50 – 12.89) 1.04	**9.39** **(1.16 – 18.29)** **1.09****	**14.33** **(7.19 – 21.95)** **1.14***

mMRC	OR (95% CI)	1 (ref)	-0.03 (-0.09 – 0.03)	0.07 (-0.01 – 0.15)	**0.12**** **(0.03 – 0.21)**	**0.20*** **(0.09 – 0.30)**
Exacerbations/year	RR (95% CI)	1 (ref)	0.06 (-0.07 – 0.19)	**0.16**** **(0.01 – 0.30)**	**0.20**** **(0.05 – 0.34)**	**0.17**** **(0.05 – 0.29)**
$WA_{segmental}$, %	Mean difference (95% CI)	1 (ref)	-0.10 (-0.29 – 0.09)	0.11 (-0.10 – 0.33)	0.27 (0.05 – 0.49)	**0.67*** **(0.49 – 0.85)**
Pi_{15}	Mean difference (95% CI)	1 (ref)	**-0.02**** **(-0.03 – -0.01)**	-0.01 (-0.02 -0.01)	0.12 (-0.00 – 0.03)	**0.04*** **(0.03 – 0.05)**
Emphysema%	% difference (95% CI) e^{β}	1 (ref)	**23.82** **(12.03 – 36.84)** **1.24***	**27.44** **(13.99 – 42.47)** **1.27***	**40.50** **(25.70 – 57.04)** **1.40***	**50.29** **(37.00 – 64.88)** **1.50***
Gas trapping%	% difference (95% CI) e^{β}	1 (ref)	**10.33** **(2.90 – 18.31)** **1.10****	**19.83** **(10.75 – 29.65)** **1.20***	**26.51** **(17.07 – 36.71)** **1.26***	**46.21** **(37.09 – 55.94)*** **1.46**

Mean value of the outcome is modeled; regression coefficient corresponds to mean difference of the outcome. The mean value of the outcome variables (6MWD, WA% and Pi15) increases/decreases by the amount of the regression coefficient in the particular BDR category compared to the reference category (negative response to bronchodilator). SGRQ, emphysema% and gas trapping% were natural log transformed. The displayed coefficients (% difference and CI 95%) for SGRQ, emphysema% and gas trapping% were back-transformed regression coefficients (e^{β}) that correspond to the relative ratio between the two groups in percent. For example for SGRQ, the mean SGRQ total score of marked bronchodilator responders are 12.4% lower than that of the reference category. OR indicates the relative odds increase for a higher score of mMRC between the two groups. For example, the estimated odds of having a one unit higher score of mMRC dyspnea score for marked bronchodilator responders is 0.63 of the odds compared with participants with a negative bronchodilator response. RR indicates the relative risk decrease in number of exacerbations/year between the risk group and the reference category. For example, relative risk of number of exacerbations/year is 26% decreased in marked bronchodilator responders compared to that of the reference category. Participants with a negative bronchodilator response are stated as reference category.

All models were controlled for sex, age, race, body mass index, smoking history, and initial pre-bronchodilator FEV_1. Additionally, models with CT outcomes were adjusted for CT scanner type. Significant associations are marked as **bold**. * $P < 0.0001$; ** $P < 0.05$.

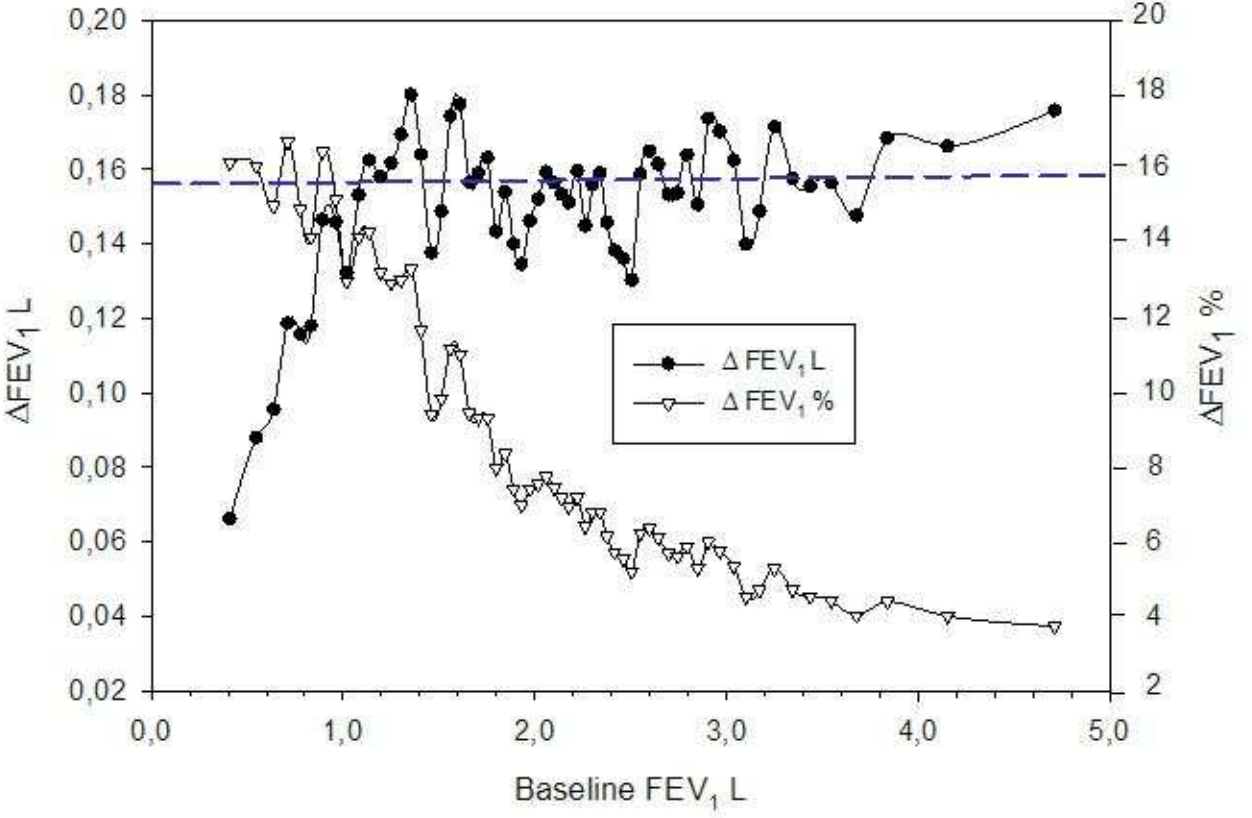
Definition of abbreviations: 6MWD, six-minute walking distance; m, meters CI, confidence interval; SGRQ, St. George Respiratory Questionnaire total score; mMRC, modified Medical Research dyspnea score; WA, wall area; Pi_{15}, square root wall area of a 15 mm diameter airway; OR, Odds ratio; RR, relative risk.

Table 4. Comparison of bronchodilator responses using ATS/ERS guidelines ($\Delta FEV_1L \geq 0.2L$ and $\Delta FEV_1\% \geq 12\%$, or $\Delta FVC \geq 0.2L$ and $\Delta FVC\% \geq 12\%$) and proposed bronchodilator response grades (based on range of ΔFEV_1L or $\Delta FEV_1\%$).

	BDR GRADES				
	Negative	**Minimal**	**Mild**	**Moderate**	**Marked**
Total number of participants	1634	2159	1549	1399	1000
Only $\Delta FEV_1\% \geq 12\%$	0	0	146	489	769
Only $\Delta FVC\% \geq 12\%$	27	121	216	345	505
Only $\Delta FEV_1L \geq 0.2$ L	0	0	0	632	955
Only $\Delta FVCL \geq 0.2$ L	88	269	448	663	761
$\Delta FEV_1L \geq 0.2L$ and $\Delta FEV_1\% \geq 12\%$	0	0	0	224	724
$\Delta FVCL \geq 0.2L$ and $\Delta FVC\% \geq 12\%$	26	111	215	338	501
BDR (+) by ATS/ERS $\Delta FEV_1L \geq 0.2L$ and $\Delta FEV_1\% \geq 12\%$ or $\Delta FVCL \geq 0.2L$ and $\Delta FVC\% \geq 12\%$	26	111	215	452	794

Numbers of participants in each particular category is presented. Definition of abbreviations: BDR, bronchodilator response; FEV_1, forced expiratory flow volume in 1 seconds; %, percentage; FVC, forced vital capacity; L, liters; ATS/ERS, American Thoracic Society/European Respiratory Society.

All models were controlled for sex, age, race, body mass index, smoking history, and initial pre-bronchodilator FEV_1. Additionally, models with CT outcomes were adjusted for CT scanner type. Significant associations are marked as **bold**. * $P < 0.0001$; † $P < 0.05$. Definition of abbreviations: 6MWD, six-minute walking distance; m, meters CI, confidence interval; SGRQ, St. George Respiratory Questionnaire total score; mMRC, modified Medical Research dyspnea score; WA, wall area; Pi_{15}, square root wall area of a 15 mm diameter airway; OR, Odds ratio; RR, relative risk.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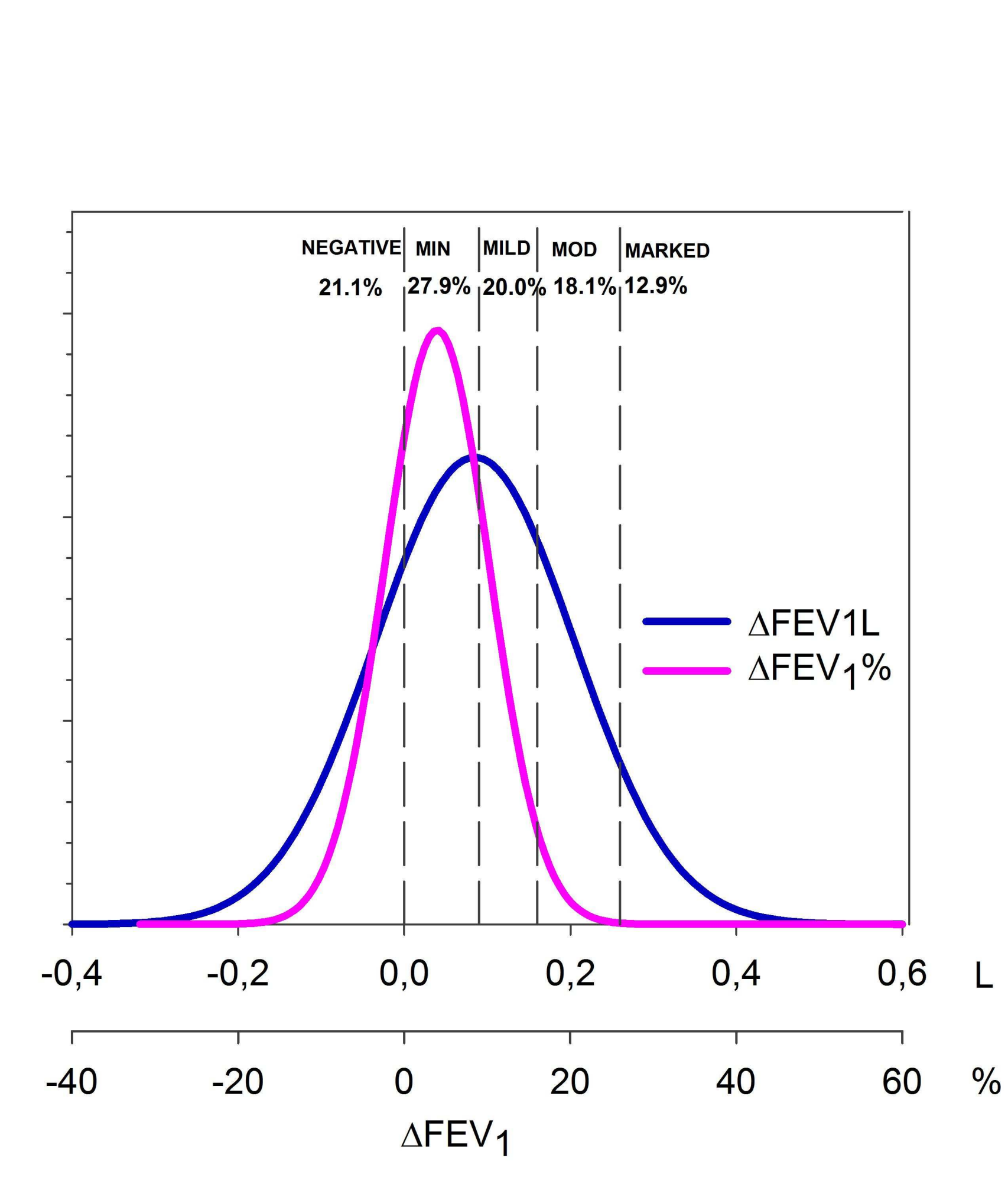
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A new bronchodilator response grading strategy identifies distinct patient populations

-- Online Data Supplement --

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Methods

Inclusion and exclusion criteria

10,311 male and female non-Hispanic White and African-American participants, 45 to 80 years old, with at least 10 pack-years of smoking history were included in the study. Exclusion criteria were history of other lung disease (except asthma), previous lung resection or lung volume reduction surgery, active cancer treatment, suspected lung cancer, metal in the chest that would interfere with CT scanning, presence of chest radiotherapy history and pregnancy[1].

Spirometry and quality control

Spirometry tests were performed by using an ultrasound-based spirometer (NDD, EasyOne Spirometer Medizintechnik AG, Zurich, Switzerland) before and after administration of short-acting β_2-agonist (albuterol) in accordance with the ERS/ATS recommendations[2]. Spirometric measurements were reviewed and graded (ranging from 0 – 4) by an automated quality assessment software package and by a centralized quality control process established for the COPDGene project[3].

Correlative measures

CT scans were acquired at full inspiration and after tidal expiration according to a standardized protocol[1]. Airway abnormality was assessed by segmental airway wall area percentage: segmental WA% = (outer bronchus area - airway luminal area)/(outer bronchus area) by using 'Pulmonary Workstation Plus' software (VIDA Diagnostics, Coralville, IA, U.S.A.)[8]. Airway wall thickness was assessed by square root of wall area of a 15mm diameter airway (Pi_{15}) by 3D SLICER[9]. Per the COPDGene protocol, CT scans were done last on the

visit day, after all pulmonary function and other functional tests and symptom assessment questionnaires.

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Table E1. Comparison of demographic characteristics, spirometry, functional exercise capacity, and quantitative CT measures of airway abnormality among various grades of FVC bronchodilator responders (N=7,741).

	BRONCHODILATOR RESPONSE GRADES – FVC response				
	NEGATIVE	**MINIMAL**	**MILD**	**MODERATE**	**MARKED**
Category range for ΔFVC (L)	Δ FVC ≤ 0	0 < Δ FVC ≤ 0.09	0.09 < Δ FVC ≤ 0.16	0.16 < Δ FVC ≤ 0.26	0.26 > Δ FVC
Category range for ΔFVC% (%)	Δ% FVC_1 ≤ 0	>0 < Δ% FVC ≤ 9	9 < Δ% FVC ≤ 16	16 < Δ% FVC ≤ 26	26 > Δ% FVC
N (%)	2885 (37.3)	1273 (16.4)	928 (12.0)	935 (12.1)	1720 (22.2)
Demographics					
Age, yrs	58.8 ± 8.8	60.3 ± 8.8	60.7 ± 9.0	60.9 ± 8.7	61.4 ± 9.1
BMI, kg/m^2	28.6 ± 6.0	28.8 ± 6.3	28.7 ± 6.3	29.1 ± 6.4	28.3 ± 5.9
Smoking history, pack years	37.3 (25.1 – 52.0)	38.9 (27.1 – 54.0)	40.5 (29.3 – 55.9)	40.7 (30.0 -57.4)	43.4 (31.7 – 60.0)
Sex, Male, %	54.8	47.3	49.5	55.7	61.2
Race, Caucasian, %	66.3	76.2	73.7	75.7	79.0
ICS use, %	4.7	6.7	6.7	7.2	9.9

Spirometry					
Pre-BD FEV_1, L	2.42 ± 0.90	2.13 ± 0.89	2.03 ± 0.90	1.97 ± 0.90	1.82 ± 0.88
Post-BD FEV_1, L	2.44 ± 0.91	2.22 ± 0.92	2.14 ± 0.93	2.11 ± 0.93	2.05 ± 0.92
Pre-BD FVC, L	3.53 ± 1.02	3.22 ± 1.00	3.12 ± 0.98	3.10 ± 1.00	3.06 ± 1.00
Post-BD FVC, L	3.37 ± 1.00	3.27 ± 1.00	3.25 ± 0.99	3.31 ± 1.00	3.54 ± 1.04
ΔFEV_1, L	-0.01 ± 0.12	0.08 ± 0.10	0.11 ± 0.10	0.14 ± 0.11	0.23 ± 0.15
ΔFVC, L	-0.17 ± 0.18	0.04 ± 0.02	0.12 ± 0.02	0.21 ± 0.03	0.48 ± 0.26
ΔFEV_1, %	0.53 ± 5.82	4.27 ± 5.18	6.44 ± 5.90	8.27 ± 7.03	15.19 ± 11.43
ΔFVC, %	-4.85 ± 4.91	1.55 ± 1.08	4.42 ± 1.81	7.46 ± 3.00	17.55 ± 10.97
Pre-BD FEV_1/FVC, %	67.44 ± 13.90	64.60 ± 15.19	63.03 ± 15.31	61.77 ± 15.90	57.75 ± 15.80
Post-BD FEV_1/FVC, %	71.05 ± 13.97	66.22 ± 15.47	64.13 ± 15.42	62.12 ± 15.90	56.57 ± 15.49
Functional exercise capacity, quality of life, and exacerbation frequency					
6MWD, meters	428 ± 122	419 ± 122	407 ± 124	404 ± 119	410 ± 115
SGRQ score	16.34 (4.21 – 38.60)	19.91 (6.26 – 41.59)	24.20 (7.26 – 44.46)	25.94 (9.19 – 47.10)	29.59 (11.78 – 49.87)
mMRC	1.14 ± 1.39	1.25 ± 1.40	1.41 ± 1.45	1.50 ± 1.47	1.60 ± 1.47
Exacerbations/year	0.30 ± 0.81	0.40 ± 0.95	0.45 ± 1.03	0.50 ± 1.06	0.51 ± 1.04
Quantitative CT					
$WA_{segmental}$, %	60.79 ± 3.21	61.03 ± 3.14	61.44 ± 3.18	61.75 ± 3.29	62.21 ± 3.22
Pi_{15}, SRWA	5.12 ± 0.19	5.11 ± 0.19	5.14 ± 0.19	5.17 ± 0.20	5.20 ± 0.21

Emphysema%	1.54 (0.54 – 4.83)	2.37 (0.79 – 6.77)	2.74 (0.77 – 9.48)	3.18 (0.91 – 10.52)	4.10 (1.89 – 13.04)
Gas trapping %	11.83 (5.45 – 24.19)	14.28 (6.56 – 30.11)	16.57 (7.61 – 34.28)	18.58 (8.63 – 39.82)	26.21 (12.34 – 45.81)

Data are presented as mean ± SD or median (IQR 25 – 75) or as percentages. Definition of abbreviations: FEV_1, forced expiratory flow volume in 1 seconds; FVC, forced vital capacity; ICS, inhaled corticosteroid; Δ, delta; L, liters; %, percentage; BD, bronchodilator; CT, computed tomography; WA, wall area; Pi_{15} SRWA, square root wall area of a 15 mm diameter airway; QC: quality control grades for spirometry maneuver (ranging from 0 to 4); 6MWD, six-minute walking distance; SGRQ, St. George Respiratory Questionnaire total score; mMRC, modified Medical Research dyspnea score**.**

Institutional Review Board Committee name and project approval number for 21 study centers.

Clinical Center	Institution Title	Protocol Number
National Jewish Health	National Jewish IRB	HS-1883a
Brigham and Women's Hospital	Partners Human Research Committee	2007-P-000554/2; BWH
Baylor College of Medicine	Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals	H-22209
Michael E. DeBakey VAMC	Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals	H-22202
Columbia University Medical Center	Columbia University Medical Center IRB	IRB-AAAC9324
Duke University Medical Center	The Duke University Health System Institutional Review Board for Clinical Investigations (DUHS IRB)	Pro00004464
Johns Hopkins University	Johns Hopkins Medicine Institutional Review Boards (JHM IRB)	NA_00011524

Los Angeles Biomedical Research Institute	The John F. Wolf, MD Human Subjects Committee of Harbor-UCLA Medical Center	12756-01
Morehouse School of Medicine	Morehouse School of Medicine Institutional Review Board	07-1029
Temple University	Temple University Office for Human Subjects Protections Institutional Review Board	11369
University of Alabama at Birmingham	The University of Alabama at Birmingham Institutional Review Board for Human Use	FO70712014
University of California, San Diego	University of California, San Diego Human Research Protections Program	070876
University of Iowa	The University of Iowa Human Subjects Office	200710717
Ann Arbor VA	VA Ann Arbor Healthcare System IRB	PCC 2008-110732
University of Minnesota	University of Minnesota Research Subjects' Protection Programs (RSPP)	0801M24949
University of Pittsburgh	University of Pittsburgh Institutional Review Board	PRO07120059
University of Texas Health Sciences Center at San Antonio	UT Health Science Center San Antonio Institutional Review Board	HSC20070644H
Health Partners Research Foundation	Health Partners Research Foundation Institutional Review Board	07-127
University of Michigan	Medical School Institutional Review Board (IRBMED)	HUM00014973
Minneapolis VA Medical Center	Minneapolis VAMC IRB	4128-A

Fallon Clinic	Institutional Review Board/Research Review Committee Saint Vincent Hospital – Fallon Clinic – Fallon Community Health Plan	1143