Six-Minute Walk Distance Predictors, Including CT Scan Measures, in the COPDGene Cohort

Mehdi Rambod, MD; Janos Porszasz, MD, PhD; Barry J. Make, MD, FCCP; James D. Crapo, MD, FCCP; Richard Casaburi, PhD, MD, FCCP; and the COPDGene Investigators

Background: Exercise tolerance in COPD is only moderately well predicted by airflow obstruction assessed by FEV₁. We determined whether other phenotypic characteristics, including CT scan measures, are independent predictors of 6-min walk distance (6MWD) in the COPDGene cohort.

Methods: COPDGene recruits non-Hispanic Caucasian and African American current and ex-smokers. Phenotyping measures include postbronchodilator FEV₁ % predicted and inspiratory and expiratory CT lung scans. We defined % emphysema as the percentage of lung voxels < -950 Hounsfield units on the inspiratory scan and % gas trapping as the percentage of lung voxels < -856 Hounsfield units on the expiratory scan.

Results: Data of the first 2,500 participants of the COPDGene cohort were analyzed. Participant age was 61 ± 9 years; 51% were men; 76% were non-Hispanic Caucasians, and 24% were African Americans. Fifty-six percent had spirometrically defined COPD, with 9.3%, 23.4%, 15.0%, and 8.3% in GOLD (Global Initiative for Chronic Obstructive Lung Disease) stages I to IV, respectively. Higher % emphysema and % gas trapping predicted lower 6MWD ($P < .001$). However, in a given spirometric group, after adjustment for age, sex, race, and BMI, neither % emphysema nor % gas trapping, or their interactions with FEV₁ % predicted, remained a significant 6MWD predictor. In a given spirometric group, only 16% to 27% of the variance in 6MWD could be explained by age, male sex, Caucasian race, and lower BMI as significant predictors of higher 6MWD.

Conclusions: In this large cohort of smokers in a given spirometric stage, phenotypic characteristics were only modestly predictive of 6MWD. CT scan measures of emphysema and gas trapping were not predictive of 6MWD after adjustment for other phenotypic characteristics.

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Abbreviations: 6MWD = 6-min walk distance; 6MWT = 6-min walk test; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HU = Hounsfield unit; LOWESS = locally weighted scatterplot smoothing

COPD was the fourth leading cause of death in the United States for more than a decade¹; recent data suggest that it has now risen to the third leading cause of death.² COPD is among the top five causes of disability among US adults.³ Exercise intolerance is the main disabling feature of COPD and is largely mediated by dynamic lung hyperinflation.⁴ Exercise tolerance in COPD is widely measured by the 6-min walk test (6MWT) in both clinical practice and research.⁵ Six-minute walk distance (6MWD) is correlated with functional level of patients with COPD, disease prognosis, and survival.^{5,6}

Factors previously found to predict reduced 6MWD in COPD include older age,⁷ female sex,⁸ higher

BMI,^{8,9} and more severe airflow obstruction,¹⁰ traditionally measured as decreased FEV₁ % predicted. Hyperinflation during exercise correlates with shortness of breath and exercise intolerance in COPD.^{11,12} Moreover, data from CT scan of the lungs reveals that CT scan-measured emphysema is associated with greater hyperinflation.¹³

Despite the association between exercise tolerance and lung hyperinflation in COPD, few studies have examined the association between CT scan measures of lung hyperinflation, namely emphysema and gas trapping, and exercise tolerance measured by 6MWD.¹⁴⁻¹⁶ Further, except for one study,¹⁴ sample sizes were too small ($n = 20$)^{15,16} to adequately discern

whether CT scan measures add to the predictive ability of easily measured physiologic and demographic variables. In a recent study by Diaz et al¹⁴ in 93 patients with COPD, CT scan-measured emphysema was associated with 6MWD, but this association was not adjusted for airflow obstruction measures. In 1,759 participants of the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) cohort consisting of GOLD (Global Initiative for Chronic Obstructive Lung Disease) stages II to IV,¹⁷ Spruit et al¹⁸ reported that patients with % emphysema > 5% were more likely to have a low 6MWD. This study, however, did not address whether the inverse association between the % emphysema and 6MWD is independent of lung function. Further, none of these studies addressed the association of gas trapping and 6MWD or included smokers without COPD.

Therefore, it is not known whether CT scan measures of emphysema or gas trapping provide additional predictive power of exercise tolerance among current or former smokers over measures of airflow obstruction as well as other easily assessed exercise tolerance determinants, such as age.¹⁸ In the present study, we asked whether at a given level of FEV₁ % predicted individuals with an emphysemic phenotype, a gas-trapped phenotype, or both have additional exercise intolerance. To address this question, we used data from 2,500 participants in COPDGene comprising current and former smokers with and without COPD.¹⁹

MATERIALS AND METHODS

Subject Selection

COPDGene is a multicenter investigation examining the genetic basis of COPD (www.copdgene.org). Participants are being enrolled at 21 centers throughout the United States. The COPDGene protocol is approved by the institutional review boards of all participating centers. Subjects provide written informed consent to participate (see e-Appendix 1 for site names and protocol numbers).

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Affiliations: From the Rehabilitation Clinical Trials Center (Drs Rambod, Porszasz, and Casaburi), Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA; and National Jewish Health (Drs Make and Crapo), Denver, CO.

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Correspondence to: Richard Casaburi, PhD, MD, FCCP, Rehabilitation Clinical Trials Center, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, 1124 W Carson St, Torrance, CA 90502; e-mail: casaburi@ucla.edu

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Primary inclusion criteria were self-identified racial/ethnic category of either non-Hispanic Caucasian or non-Hispanic African American aged 45 to 80 years with a ≥ 10 pack-year smoking history. Key exclusion criteria were pregnancy, a history of other lung disease except asthma, previous excision of one or more lung lobes (or lung volume reduction procedure), metal in the chest, or history of chest radiation therapy. Subjects also were excluded if a first- or second-degree relative was already enrolled. Subjects with a recent COPD exacerbation were eligible 1 month after the exacerbation.

Measurements

The study protocol included questionnaires, medical history review, physical examination, spirometric measures of lung function, high-resolution chest CT scanning, and 6MWT. Further COPDGene details are published elsewhere.¹⁹ All subjects took their usual prescribed medications.

Spirometry before and 10 min after two puffs of albuterol was done according to American Thoracic Society guidelines.²⁰ Spirometry was performed using the EasyOne Spirometer (nidd Medizintechnik AG), an ultrasound-based spirometer. Reference values of Hankinson et al²¹ were used. Only postbronchodilator values were used in the present analysis.

Subjects were scanned with 16-detector or 64-detector CT scanners. Imaging was performed during breath-hold at full inflation (total lung capacity) and end-tidal exhalation (functional residual capacity) while supine. Multislice CT scanning parameters were as follows: collimation, 0.5 mm; tube voltage, 120 kV; tube current, 200 mA; gantry rotation time, 0.5 s; and pitch, 1.1. Images for this analysis used a high-resolution reconstruction algorithm with 1-mm slice thickness and 10-mm reconstruction interval. Images were reviewed on picture archiving and communication system workstations (Centricity; GE Healthcare) using axial images, with a -700 -Hounsfield unit (HU) window level and 1,500-HU window width. Quantitative image analysis to calculate % emphysema and % gas trapping was performed using VIDA (VIDA Diagnostics, Inc) and 3D Slicer version 2.0 (Brigham and Women's Hospital).²² Lung volume with emphysema (% emphysema) was defined as percentage of total lung voxels showing attenuation of < -950 HU on the inspiratory scan.²³ The percentage of lung volume with voxels < -856 HU on the expiratory scan was defined as % gas trapping.^{24,25} The 6MWT was performed, without practice, indoors on a flat course supervised by trained study staff who provided standardized encouragement according to American Thoracic Society guidelines.¹⁰

Statistical Analysis

We included in our analysis subjects with normal spirometry (FEV₁/FVC > 70% and FEV₁ > 80% predicted) and those with GOLD stage I to IV COPD.¹⁷ We excluded 227 subjects with GOLD undetermined spirometry (FEV₁/FVC > 70% and FEV₁ < 80% predicted). Of the remaining 2,273 subjects, % emphysema and % gas trapping were unavailable in 17 and 180 subjects, respectively, leaving an analysis group of 2,256 with % emphysema and 2,093 with % gas trapping data.

Characteristics of participants are presented as mean $\pm$ SD or median and interquartile range, when appropriate. In order to compare mean 6MWD between men and women and between Caucasians and African Americans, an independent-sample *t* test was used. For illustrative data displays, scatterplots of the dependence of 6MWD on FEV₁ % predicted, % emphysema, and % gas trapping were fitted using robust, locally weighted scatterplot smoothing (LOWESS) that fits a locally best nonparametric line to data.²⁶ The resultant fitted curve allows visualization

of nonlinear associations of variables. Within each GOLD stage and the normal spirometry group, multivariate linear regression was used to examine the association of 6MWD and % emphysema or % gas trapping after controlling for other confounders, including FEV₁ % predicted, BMI, age, race, and sex. Because of potential interaction between FEV₁ % predicted and measures of emphysema and gas trapping,^{23,27} interaction terms (FEV₁ % predicted × % emphysema or FEV₁ % predicted × % gas trapping) were included. Sensitivity analyses were performed using linear mixed models to adjust for center effect. Statistical significance was declared at $P < .05$. SPSS, version 17.0 (SPSS Inc) software was used for statistical analyses.

RESULTS

General, Clinical, and Spirometric Characteristics

Table 1 presents the study population characteristics in total and within each GOLD spirometric stage. The study included current and former smokers aged 61.3 ± 9.3 years; 51.4% were men, 75.9% were non-Hispanic Caucasians, and 42.4% were current smokers. Median smoked pack-years was 40.7 (interquartile range, 28.5-56.8), and mean BMI was 28.2 ± 6.0 kg/m². Proportions of normal spirometry and GOLD stage I to IV were 44.0%, 9.3%, 23.4%, 13.6%, and 8.3%, respectively. Average 6MWD was 1,330 ft. Both mean % emphysema and % gas trapping increased from normal spirometry and across the four ascending GOLD stages (trend $P < .001$ for both). Common comorbidities in the medical history of this subject group were hypertension (41.8%), osteoporosis (11.0%), hypercholesterolemia (40.2%), diabetes (12.3%), coronary artery disease (6.2%), and peripheral vascular disease (2.3%).

Determinants of 6MWD

In the 2,273 participants, 6MWD was higher in men than in women ($1,377 \pm 460$ ft vs $1,280 \pm 440$ ft, $P < .001$) and in Caucasians than in African Americans ($1,387 \pm 442$ ft vs $1,150 \pm 439$ ft, $P < .001$). Figure 1A shows the variation of 6MWD with FEV₁ % predicted. There was great variability in 6MWD at a given FEV₁ % predicted (linear regression SE of the estimate, 397 ft). LOWESS fit to these data shows little influence of FEV₁ on 6MWD > 90% predicted; at lower values, 6MWD fell steadily as FEV₁ % predicted decreased. Figure 1B shows that most subjects had < 10% emphysema ($n = 1,605$ [71.1%]). LOWESS fit to these data shows that 6MWD did not fall for % emphysema < 5% but did fall approximately linearly for higher % emphysema. Figure 1C shows that 6MWD was approximately constant for % gas trapping values < 20% ($n = 1,032$ [49.3%]) and fell for higher % gas trapping values.

We determined whether either emphysema or gas trapping had an additional ability to predict 6MWD over that provided by FEV₁ % predicted, BMI, age, sex, and race. Given the nonlinear and nonuniform data distribution (Fig 1), we elected to perform linear regression analysis on the normal spirometry group and the 4 GOLD stages separately. The analysis in which % emphysema included in the regression (Table 2) shows that within each spirometry group, 6MWD decreased with both increasing BMI and older age; men had significantly higher 6MWD than women, and non-Hispanic Caucasians had higher 6MWD than African Americans. Importantly, neither % emphysema nor the interaction of % emphysema

Table 1—General, Clinical, Spirometric, and CT Scan Characteristics of Study Participants in Total and in Each Spirometric Stage

Characteristic	Total	Normal Spirometry	GOLD I	GOLD II	GOLD III	GOLD IV
Patients	2,273	1,000 (40)	212 (9.3)	532 (23.4)	341 (15.0)	188 (8.3)
Age, y	61.3 ± 9.3	57.8 ± 8.9	63.8 ± 9.5	63.4 ± 8.6	65.1 ± 8.3	64.6 ± 7.8
Male sex	1,169 (51.4)	493 (49.3)	128 (60.4)	266 (50.0)	174 (51)	108 (57.4)
Racial/ethnicity						
Non-Hispanic white	1,725 (75.9)	676 (67.6)	186 (87.7)	422 (79.3)	286 (83.9)	155 (82.4)
African American	548 (24.1)	325 (32.5)	26 (12.3)	110 (20.7)	55 (16.1)	33 (17.6)
Body weight, kg	81.4 ± 18.9	82.9 ± 18.2	77.6 ± 15.3	83.7 ± 19.7	80.3 ± 20.7	73.6 ± 18.3
Height, cm	169.7 ± 9.5	169.7 ± 9.4	170.1 ± 10.0	169.9 ± 9.6	169.0 ± 9.5	169.8 ± 9.6
BMI, kg/m ²	28.2 ± 6.0	28.8 ± 5.9	26.8 ± 4.9	28.9 ± 6.1	28.0 ± 6.4	25.4 ± 5.6
Smoking status						
Current smoker	964 (42.4)	519 (51.9)	99 (46.7)	215 (40.4)	105 (30.8)	26 (13.8)
Former smoker	1,309 (57.6)	481 (48.1)	113 (53.3)	317 (59.6)	236 (69.2)	162 (86.2)
Pack-y of smoking	40.7 (28.5-56.8)	34.4 (22.1-45.6)	42 (28.5-56.9)	45.7 (35.0-66.0)	50 (37.3-69.9)	48 (37.2-75.0)
FEV ₁ % predicted	74.5 ± 28.3	97.9 ± 11.9	91.6 ± 10.0	64.5 ± 8.7	39.5 ± 5.7	22.1 ± 4.6
FVC % predicted	88.3 ± 19.1	96.7 ± 12.0	108.6 ± 13.6	87.0 ± 13.4	71.4 ± 12.0	55.0 ± 13.9
% Emphysema	4.4 (1.3-12.3)	1.6 (0.6-3.8)	5.2 (2.3-8.9)	5.8 (2.4-13.6)	16.1 (7.2-26.8)	30.0 (19.3-39.9)
% Gas trapping	20.6 (9.6-42.3)	9.8 (4.9-15.7)	21.8 (14.0-30.4)	28.4 (17.8-39.5)	52.1 (36.4-61.5)	66.1 (58.3-74.0)
6-min walk distance, ft	$1,330 \pm 453$	$1,492 \pm 405$	$1,534 \pm 383$	$1,283 \pm 393$	$1,084 \pm 399$	813 ± 382

Data are presented as mean $\pm$ SD, No. (%), or median (interquartile range). GOLD = Global Initiative for Chronic Obstructive Lung Disease.

FIGURE 1. Scatterplots of 6-min walk distance as the dependent variable and FEV₁ % predicted, % emphysema, and % gas trapping as the dependent variables. A, FEV₁ % predicted. B, % Emphysema. C, % Gas trapping. Lines in each plot are locally weighed regression fits to the scatterplots.

with FEV₁ % predicted significantly predicted 6MWD in any of the five groups.

The analysis in which % gas trapping is included (Table 3) showed significant dependence of 6MWD on BMI, age, and race in all spirometry groups. Men had statistically significantly higher 6MWD than women in four of five groups. Neither % gas trapping nor interaction of % gas trapping with FEV₁ % predicted was significantly predictive of 6MWD in any group.

Notably, the measured variables explained only a small portion of 6MWD variability. In Tables 2 and 3, the coefficient of determination (r^2) ranged from 16% to 27%. In sensitivity analysis using a linear mixed model, adjustment for center effect did not alter these findings (data not shown). In this study, Caucasian participants had a higher educational level than did African American participants. However, race remained a strongly statistically significant predictor of 6MWD in each GOLD stage, even after controlling for educational status as a covariate in the regression models (data not shown).

Figure 2 provides a graphical depiction of the influence of either emphysema or gas trapping on 6MWD in a given spirometry group. For each spirometry group, mean $\pm$ SE 6MWD is plotted for each % emphysema (Fig 2A) or % gas trapping (Fig 2B) subgroup ($< 10\%$, 10% - 20% , 20% - 30% , and $< 30\%$), which comprised ≥ 20 individuals. The lack of systematic dependence of 6MWD on either % emphysema or % gas trapping can be seen.

DISCUSSION

In the largest cohort of current and ex-smokers with or without COPD ever studied, to our knowledge, we found that phenotypic characteristics, such as the degree of airflow obstruction, sex, race, age, and BMI, are independent predictors of functional exercise performance assessed by 6MWD. However, although CT scan measures of emphysema and gas trapping are correlated with 6MWD, they did not provide additional predictive ability above that of more easily measured characteristics.

Exercise intolerance is a major disabling factor in COPD.⁴ The 6MWT is a technologically uncomplicated exercise tolerance measure.¹⁰ The 6MWD has been shown to be correlated with mortality, hospitalization, and health-related quality of life in COPD.²⁸⁻³⁰ In smaller populations, it has been observed that 6MWD is lower in patients with advanced age, higher BMI, and more severe airflow obstruction and in women. However, these factors explain only a small part of 6MWD variation among subjects.³¹ This may be partly because other factors yielding exertional dyspnea, such as static and dynamic hyperinflation, may play a role in 6MWD variability.³¹

Dynamic hyperinflation is closely associated with exertional dyspnea and is a major contributor to exercise intolerance in COPD.^{32,33} Marin et al³¹ showed that dynamic hyperinflation correlated with dyspnea reported during the 6MWT. A recent study showed that dynamic hyperinflation occurs in the daily life of patients with COPD of all GOLD stages.³⁴ Furthermore, dynamic hyperinflation has been shown to predict mortality.³⁵

Table 2—Regression Coefficients in Linear Regression Analysis in Normal Spirometry and Each GOLD Stage Group

Variable	Normal Spirometry	GOLD I	GOLD II	GOLD III	GOLD IV
FEV ₁ % predicted	3.0 ^a	2.5	10.9 ^b	9.7	36.2 ^a
BMI, kg/m ²	−12.2 ^b	−24.2 ^b	−11.1 ^b	−18.8 ^b	−13.9 ^c
Age, y	−5.8 ^b	−6.7 ^a	−6.2 ^c	−7.4 ^c	−12.7 ^b
Male vs female sex	71.1 ^c	144.4 ^c	109.2 ^b	146.6 ^b	110.5 ^a
Caucasian vs African American	353.9 ^b	305.9 ^b	365.3 ^b	249.9 ^b	162.5 ^a
% Emphysema	−12.0	23.7	13.1	−4.4	6.3
Interaction (FEV ₁ % predicted × % emphysema)	0.24	−0.311	−0.20	0.7	−0.42
Coefficient of determination, r ²	0.23	0.21	0.26	0.17	0.17

Dependent variable is 6-min walk distance and independent variables are FEV₁ % predicted, BMI, age, sex, race, % emphysema, and the interaction of % emphysema with FEV₁ % predicted. See Table 1 legend for expansion of abbreviation.

^aP = .01-.05.

^bP < .001.

^cP = .001-.01.

Resting hyperinflation can be assessed from spirometry and lung volumes. Dynamic hyperinflation can be measured during cardiopulmonary exercise testing.³⁶ Lung CT scanning provides quantitative assessment of emphysema and gas trapping. Emphysema volume measurements by high-resolution CT scanning have been validated with tissue histology.^{37,38} CT scanning has been shown to provide a valid measure of % emphysema in smokers³⁹ and patients with COPD^{23,40} and is associated with respiratory symptoms⁴¹ and clinical outcomes in smokers⁴² and in patients with COPD.⁴³ Air trapping measured on expiration has been used in asthma studies to reflect failure of the lung to empty and may reflect the presence of small airways disease.^{24,25}

Several studies have shown that dynamic lung hyperinflation is associated with 6MWD and daily physical activity in COPD.^{31,34,44,45} However, only a few studies examined the association of CT scan findings with exercise tolerance.^{14-16,18} Two reports studied only 20 subjects with COPD.^{15,16} For example, Wakayama et al¹⁶ found that emphysema score correlated significantly with 6MWD ($r = -0.74$). In a recent study of

93 patients with COPD, Diaz et al¹⁴ found that subjects with higher % emphysema had lower 6MWD ($r = -0.53$, $P < .0001$). Percent emphysema remained a significant predictor when age, sex, BMI, and residual volume-to-total lung capacity ratio were entered into the regression. However, adjustment for FEV₁ % predicted was not performed. In a cohort of 1,729 patients with COPD with GOLD stages II to IV, Spruit et al¹⁸ recently reported that patients with COPD with % emphysema > 5% walked a shorter 6MWD. However, these authors did not determine whether this correlation was independent of measures of airflow obstruction. To our knowledge, the present study is the first to examine the association between CT scan measures of hyperinflation and 6MWD in smokers without COPD as well as the first to examine the association of % gas trapping and 6MWD among smokers.

In the present cohort, average 6MWD was 237 ft shorter in African Americans than in Caucasians. This correlation remained significant after adjustment for other correlates of 6MWD (Tables 2, 3). Interestingly, the difference between African Americans and

Table 3—Regression Coefficients in Linear Regression Analysis in Normal Spirometry and Each GOLD Stage Group

Variables	Normal Spirometry	GOLD I	GOLD II	GOLD III	GOLD IV
FEV ₁ % predicted	5.1 ^a	6.2	15.6 ^a	15.0	61.2
BMI, kg/m ²	−13.3 ^b	−26.5 ^b	−9.8 ^a	−16.8 ^b	−11.3 ^c
Age, y	−3.5 ^c	−3.7	−6.1 ^a	−7.0 ^a	−12.8 ^b
Male vs female sex	95.2 ^b	141.3 ^a	117.4 ^b	142.6 ^a	104.9
Caucasian vs African American	384.4 ^b	316.9 ^b	384.7 ^b	271.7 ^b	149.7 ^c
% Gas trapping	7.4	21.1	15.1	4.2	12.3
Interaction (FEV ₁ % predicted × % gas trapping)	−0.09	−0.3	−0.24	−0.10	0.55
Coefficient of determination, r ²	0.23	0.24	0.27	0.17	0.16

The dependent variable is 6-min walk distance, and the independent variables are FEV₁ % predicted, BMI, age, sex, race, % gas trapping, and the interaction of % gas trapping with FEV₁ % predicted. See Table 1 legend for expansion of abbreviation.

^aP = .001-.01.

^bP < .001.

^cP = .01-.05.

FIGURE 2. Mean $\pm$ SE of 6-min walked distance in each subgroup within the normal spirometry group and successive GOLD stages. A, % Emphysema. B, % Gas trapping (<10%, 10 to <20%, 20 to <30%, $\geq$ 30%). FEV₁ % predicted values are plotted at the mean value for the given subgroup. Subgroups with < 20 subjects were excluded. GOLD = Global Initiative for Chronic Obstructive Lung Disease.

Caucasians was more marked (averaging >300 ft) in those with normal spirometry and lower grades of obstruction. This association between race and functional exercise capacity was reported previously in a

relatively small cardiac rehabilitation cohort.⁴⁶ Studies in the general population⁴⁷ and in elderly persons^{48,49} have shown a higher prevalence of physical inactivity in African Americans than in Caucasians. In

18,885 Americans aged ≥ 20 years, Crespo et al⁴⁷ found age-adjusted prevalence of leisure time physical inactivity was nearly twice as great in African Americans (35%) as in Caucasians (18%). A recent report using data from the National Health and Nutrition Examination Survey IV showed that for men aged 20 to 49 years, the 50th percentile value for maximum oxygen consumption for non-Hispanic African Americans was 4.6% less than for non-Hispanic Caucasians.⁵⁰ In our study, average 6MWD was 17.1% shorter in African Americans than in Caucasians. This difference in the gap between racial groups possibly originates from the nature of the tests performed: 6MWT is more effort dependent than cardiopulmonary exercise testing and is maximally encouraged while the 6MWT is not. Another recent study compared 6MWD for urban vs rural individuals and found that the median 6MWD was 10.4% less in African Americans from urban areas than in Caucasians from rural areas.⁵¹ The authors suggested socioeconomic status as a possible explanation for this finding. We speculate that the observed race-related 6MWD difference might stem from differences in socioeconomic status, leisure time activity, and nutritional habits.^{51,52} In the present study, race was strongly associated with 6MWD, even after adjustment for educational status as a covariate. It should be noted that no 6MWT normal value data set has considered race as a predictor variable; this might be pursued in the future.

The present study should be considered in light of its strengths and limitations. The large COPDGene sample size allowed us to examine our hypotheses across a wide range of airway obstruction and CT scan abnormalities and provided the ability to control for other confounders in the multivariate analyses. One limitation is that we cannot rule out the possibility that subjects with airflow obstruction and extremely low % emphysema or % gas trapping have systematically different 6MWD because few of them are represented in our subject sample. Moreover, there are no nonsmoker control subjects; therefore, we were not able to examine the association of % emphysema and % gas trapping with 6MWD in nonsmokers without airflow obstruction. Another limitation is that we used 6MWT as a measure of exercise tolerance. Although 6MWD is a valid measure of functional exercise tolerance and reflects the capacity to perform day-to-day physical activities, it is only an indirect reflection of physiologic exercise capabilities. Its high variability among subjects and its strong dependence on motivation and effort may dilute its sensitivity to physiologic exercise tolerance determinants. This is confirmed in the multivariate regression analysis, which showed that only a small fraction of the variability of 6MWD among subjects could be explained by measured physiologic variables, including CT scan

characteristics. It seems plausible that a less effort-dependent exercise testing modality might have shown an independent effect of CT scan measures of emphysema and gas trapping. Moreover, we were not able to examine the correlation between the physiologic measures of hyperinflation, such as total lung capacity and CT scan measures of emphysema and gas trapping. Furthermore, COPDGene only encompasses non-Hispanic Caucasians and African Americans in the United States, which may limit the generalizability of the findings to other ethnic/racial groups or non-US patient populations.

In summary, this study demonstrated that in a large cohort of smokers and ex-smokers, lung CT scan measures of % emphysema and % gas trapping correlate with functional exercise tolerance as measured by 6MWD. However, these correlations were not independent of other predictors of exercise intolerance such as age, sex, BMI, race, and disease severity. These findings were uniformly observed in different GOLD stages and in subjects with normal spirometry. When completed, COPDGene should be able to determine whether genotypic groups⁵³ supplement phenotypic determinants as exercise tolerance predictors.

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Dr Porszasz: is coinvestigator of the COPDGene study and contributed to the study design, analysis and interpretation of data, review of drafts of the manuscript, and approval of the final version of the manuscript.

Dr Make: is clinical center project leader and investigator of the COPDGene study and contributed to the study design, analysis and interpretation of data, review of drafts of the manuscript, and approval of the final version of the manuscript.

Dr Crapo: is the principal investigator of the COPDGene study and contributed to the study design, analysis and interpretation of data, writing and review of drafts of the manuscript, and approval of the final version of the manuscript.

Dr Casaburi: is the clinical center director and investigator of the COPDGene study and contributed to the study design, analysis and interpretation of data, writing and review of drafts of the manuscript, and approval of the final version of the manuscript.

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Other contributions: A list of the COPDGene Investigators can be found in e-Appendix 2.

Additional information: The e-Appendixes can be found in the Online Supplement at <http://chestjournal.chestpubs.org/content/141/4/867/suppl/DC1>.

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