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ORIGINAL ARTICLE

Phenotype of Normal Spirometry in an Aging Population

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Abstract

Rationale: In aging populations, the commonly used Global Initiative for Chronic Obstructive Lung Disease (GOLD) may misclassify normal spirometry as respiratory impairment (airflow obstruction and restrictive pattern), including the presumption of respiratory disease (chronic obstructive pulmonary disease [COPD]).

Objectives: To evaluate the phenotype of normal spirometry as defined by a new approach from the Global Lung Initiative (GLI), overall and across GOLD spirometric categories.

Methods: Using data from COPDGene (n = 10,131; ages 45–81; smoking history, ⩾10 pack-years), we evaluated spirometry and multiple phenotypes, including dyspnea severity (Modified Medical Research Council grade 0–4), health-related quality of life (St. George's Respiratory Questionnaire total score), 6-minute-walk distance, bronchodilator reversibility (FEV_1 % change), computed tomography–measured percentage of lung with emphysema (% emphysema) and gas trapping (% gas trapping), and small airway dimensions (square root of the wall area for a standardized airway with an internal perimeter of 10 mm).

Measurements and Main Results: Among 5,100 participants with GLI-defined normal spirometry, GOLD identified respiratory impairment in 1,146 (22.5%), including a restrictive pattern in 464 (9.1%), mild COPD in 380 (7.5%), moderate COPD in 302 (5.9%), and severe COPD in none. Overall, the phenotype of GLI-defined normal spirometry included normal adjusted mean values for dyspnea grade (0.8), St. George's Respiratory Questionnaire (15.9), 6-minute-walk distance (1,424 ft [434 m]), bronchodilator reversibility (2.7%), % emphysema (0.9%), % gas trapping (10.7%), and square root of the wall area for a standardized airway with an internal perimeter of 10 mm (3.65 mm); corresponding 95% confidence intervals were similarly normal. These phenotypes remained normal for GLI-defined normal spirometry across GOLD spirometric categories.

Conclusions: GLI-defined normal spirometry, even when classified as respiratory impairment by GOLD, included adjusted mean values in the normal range for multiple phenotypes. These results suggest that among adults with GLI-defined normal spirometry, GOLD may misclassify normal phenotypes as having respiratory impairment.

Keywords: COPDGene; phenotype; normal spirometry; COPD; emphysema

Aging populations have a high prevalence of dyspnea, often prompting an evaluation of respiratory disease (1–5). Given that pathologic confirmation is invasive and not routinely available, respiratory disease is frequently established spirometrically as airflow obstruction (e.g., chronic obstructive pulmonary disease [COPD] and asthma) or restrictive pattern (e.g., interstitial lung disease, among other causes), collectively referred to as respiratory impairment (1–5).

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At a Glance Commentary

Scientific Knowledge on the Subject: Normal spirometry as commonly defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has limitations in aging populations. The Global Lung Initiative (GLI) provides an alternative approach, accounting for age-related changes in lung function, but whether it offers advantages over GOLD in establishing normal spirometry has not yet been evaluated.

What This Study Adds to the Field: In the absence of pathologic confirmation, the diagnostic accuracy of normal spirometry can be based on phenotype. Using data from COPDGene, we evaluated the phenotype of normal spirometry as defined by GLI, overall and across GOLD spirometric categories. Our results showed that GLI-defined normal spirometry, even when classified as respiratory impairment by GOLD, yielded adjusted mean values and 95% confidence intervals in the normal range for multiple phenotypes, including computed tomography–measured emphysema, gas trapping, and small airway dimensions. These results suggest that among adults with GLI-defined normal spirometry, GOLD may misclassify normal phenotypes as having respiratory impairment.

Aging populations also experience increased multimorbidity and adverse events related to polypharmacy (6, 7), highlighting the importance of diagnostic accuracy when establishing disease. For example, in the evaluation of dyspnea, if normal lung function as measured by spirometry is misclassified as respiratory impairment, then an overdiagnosis of respiratory disease may occur, leading to inappropriate use of respiratory medications and delays in considering alternative diagnoses. In particular, the misclassification of normal spirometry can arise when diagnostic thresholds fail to account for age-related changes in lung function (2, 8–15).

The diagnostic thresholds that establish normal spirometry and respiratory impairment are commonly based on criteria from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (3, 16, 17). The GOLD approach is structured and has provided many benefits and insights, but it also has limitations, especially in aging populations (2, 8–15). Specifically, because aging impacts respiratory mechanics, the fixed GOLD threshold of less than 0.70 for the ratio FEV_1 to FVC frequently misclassifies normal-for-age spirometry as airflow obstruction. Such misclassification can occur in otherwise asymptomatic never-smokers, starting at about age 45–50 (2, 8–15). Moreover, although aging increases variability in spirometric performance, starting at age 40 (9), the GOLD-based FVC and FEV_1 % predicted thresholds for establishing restrictive pattern and COPD severity, respectively, assume incorrectly the equivalence of spirometric variability across the lifespan (18).

A rigorous approach to establishing spirometric thresholds should recognize these age-related effects. One new approach, the lambda–mu–sigma method, accounts for age-related changes in lung function by using spirometric z scores that incorporate the median (mu), representing how spirometric measures change based on predictor variables (age and height); the coefficient of variation (sigma), representing the spread of reference values; and the skewness (lambda), representing departure from normality (9). A z score of -1.64 defines the lower limit of normal (LLN) as the fifth percentile of distribution (9). Of note, using data from large reference populations of asymptomatic lifelong nonsmokers, the Global Lung Initiative (GLI) has published equations that expand the availability of lambda–mu–sigma–calculated spirometric z scores, now including an age range of up to 95 years and applicable to multiple ethnicities (10).

In the absence of pathologic confirmation, the diagnostic accuracy of normal spirometry can be based on phenotype. In this context, and using data from the Genetic Epidemiology of COPD study (COPDGene) (19), we evaluated the phenotype of GLI-defined normal spirometry relative to GOLD-defined spirometric categories. The phenotypic features included dyspnea severity; health-related quality of life; exercise capacity; bronchodilator (BD) reversibility; and volumetric computed chest tomography (CT)-measured emphysema, gas trapping, and small airway dimensions. In a secondary analysis, because prior work suggests that emphysema may occur in the absence of airflow obstruction (20), we also evaluated the phenotype of GLI-defined normal spirometry stratified by the presence or absence of CT-diagnosed emphysema (19).

Methods

Study Population

COPDGene is a multicenter study designed to identify genetic factors in COPD and related phenotypes (19). Twenty-one clinical study centers throughout the United States enrolled participants for a genome-wide association study analysis, with a sample size large enough to provide statistical power to detect genetic variants exerting modest effects on risk (19). The planned study population therefore included 10,000 participants with two-thirds non-Hispanic white persons and one-third African American persons, ages 45–81, and a smoking history greater than or equal to 10 pack-years, distributed across the full spectrum of COPD severity and both sexes. Enrollment was completed between 2007 and 2011 (19). Participants were excluded if they had diagnosed lung diseases other than COPD or asthma (n = 63, including 30 with bronchiectasis and 33 with interstitial lung disease), or had not completed spirometry (n = 170). Hence, of 10,364 participants, the analytical sample included 10,131 (97.8%): 6,818 white subjects and 3,313 African American subjects.

The study protocol was approved by the institutional review boards of the 21 participating centers, and informed consent was obtained from all participants (19).

Baseline Characteristics and Phenotypes

Demographic and clinical characteristics included age, height, sex, ethnicity, education, body mass index (BMI), smoking history, and self-reported medical conditions and comorbidity count (21) (obstructive pulmonary diseases were not included because these were evaluated separately by spirometry). The phenotypes included dyspnea severity; health-related quality of life; exercise capacity; BD reversibility; and CT-measured

emphysema, gas trapping, and small airway dimensions.

Dyspnea was graded on a scale of 0–4, using the Modified Medical Research Council questionnaire (higher grades denote greater severity) (22). Clinically meaningful dyspnea was defined by a grade 2 or higher, given that it included a comparison with a peer group of the same age, occurred at a low exercise workload, and is associated with health outcomes (22–24). Health-related quality of life was evaluated by the St. George's Respiratory Questionnaire (SGRQ), with a total score ranging from 0 to 100 (higher scores denote worse health-related quality of life) (25). A SGRQ 25 and higher corresponded to a COPD Assessment Test 10 and higher (25).

Exercise capacity was evaluated by the 6-minute-walk test (26), with participants instructed to achieve maximal distance (6-minute-walk distance [6MWD]). An abnormal exercise capacity was defined by a 6MWD less than 1,282 ft (391 m), representing 2 SD below the mean 6MWD of a healthy population aged 40–80 (mean ± SD, 1,873 ± 295 ft [571 ± 90 m]) (27). A 6MWD threshold less than 1,282 ft (391 m) is greater than (i.e., more permissive than) the value of less than 984 ft (300 m) associated with mortality in heart failure (28), and also greater than the value of less than 1,148 ft (350 m) associated with mortality in COPD (29).

BD reversibility was evaluated during spirometric testing (described later), calculated as percentage change in FEV_1, post-BD versus baseline (pre-BD) (5). BD reversibility was considered present if the post-BD FEV_1 showed an increase of greater than 12% (5).

Volumetric chest CT evaluated emphysema (% emphysema), gas trapping (% gas trapping), and small airway dimensions (19, 30, 31). Percentage emphysema was calculated as the percentage of the lung having a low-attenuation area less than −950 HU on inspiratory scan ($LAA950_{insp}$); values greater than 5% are considered abnormal as per expert consensus (19, 31). Percentage gas trapping was calculated as the percentage of the lung having a low-attenuation area less than −856 HU on the expiratory scan ($LAA856_{exp}$); values greater than 15% are considered abnormal as per expert consensus (19, 31). Small airway dimensions were evaluated by the square root of the wall area (SRWA) for a standardized airway with an internal perimeter of 10 mm (Pi10-SRWA) (19, 31). Prior work has identified a mean value for Pi10-SRWA of 4.94 (SD = 0.33 mm) in GOLD-defined COPD (31). As a basis for establishing small airway disease, we set an abnormal threshold for Pi10-SRWA as greater than 4.28 mm, corresponding to 2 SDs below the mean of 4.94 mm.

Spirometry

Spirometric data were collected by certified staff using the ndd EasyOne Spirometer (ndd Medical Technologies, Andover, MA), as per protocols from the American Thoracic Society and European Respiratory Society (5, 32). Spirometric performance was evaluated by an independent overreader who evaluated each set of spirometry tracings. Grades were assigned to each FEV_1 and FVC, where "C" or better ratings were used in the analysis. Further oversight was provided by a COPDGene quality control committee, with the goal of achieving American Thoracic Society/European Respiratory Society acceptability and reproducibility criteria (5, 32).

The spirometric measures included pre-BD values for FEV_1 and FVC, with FEV_1/FVC calculated from the largest FEV_1 and FVC values that were recorded in any of the accepted spirometric maneuvers (5, 32). The use of pre-BD values may be questioned but offers at least three advantages over the current standard of using post-BD values. First, older persons have limited capacity to perform multiple FVC maneuvers (pre- and post-BD), and may have an adverse response to a BD (33, 34). Second, post-BD values have limited clinical relevance in distinguishing COPD from asthma, and have low reproducibility over time (35–37). Third, the diagnostic thresholds for spirometric interpretation are based on reference populations that only recorded pre-BD values (BDs were not administered) (10, 38).

Using GOLD criteria (3) and pre-BD values, the % predicted values for FEV_1 and FVC were calculated as (measured ÷ predicted) × 100, with predicted values derived from regression equations (38). Participants were classified as having normal spirometry by FEV_1/FVC greater than or equal to 0.70 and FVC greater than or equal to 80% predicted, as restrictive pattern by FEV_1/FVC greater than or equal to 0.70 and FVC less than 80% predicted, and as COPD (airflow obstruction) by FEV_1/FVC less than 0.70. COPD severity was evaluated as mild, moderate, and severe, based on FEV_1 greater than or equal to 80%, 50–79%, and less than 50% predicted, respectively (3).

Using GLI equations (10), *z* scores were also calculated for FEV_1, FVC, and FEV_1/FVC (10). The diagnostic algorithm was initially based on a single threshold, namely a *z* score of −1.64 (defining the LLN at the fifth percentile of distribution), used as follows: normal spirometry was defined by FEV_1/FVC greater than or equal to LLN and FVC greater than or equal to LLN, restrictive pattern by FEV_1/FVC greater than or equal to LLN and FVC less than LLN, and COPD (airflow obstruction) by FEV_1/FVC less than LLN (5, 9, 10). COPD severity was evaluated as mild, moderate, and severe using two diagnostic thresholds: FEV_1 *z* scores greater than or equal to −1.64, less than −1.64 but greater than or equal to −2.55, and less than −2.55, respectively, with a z score of −2.55 corresponding to the 0.5 percentile distribution (15, 39). These *z* score cutpoints are associated with health outcomes (15, 39). Methodology regarding the GLI calculation of spirometric *z* scores and the spirometers that include GLI software can be found at http://www.lungfunction.org/

Statistical Analysis

Demographic, clinical, and phenotypic features were first summarized as means and SDs, or counts and percentages. Next, the frequency distributions of spirometric classifications by GLI were cross-tabulated with GOLD.

The primary analysis was GLI-defined normal spirometry, cross-tabulated with GOLD, and included calculation of adjusted mean values with 95% confidence intervals (95% CIs) for the phenotypic features of interest. Several covariates, identified *a priori* as clinically plausible confounders, were entered into adjusted models, including age, height, sex, BMI, ethnicity, education (<high school), and current smoking. In addition, backward elimination was used to retain medical conditions using a *P* less than or equal to 0.05 significance level. Higher-order terms were tested for age, height, and BMI, and included in the model if significant at the *P* less than or equal to 0.01 level. Generalized estimating equations were used to obtain robust variance estimates to account for the clustering of individuals within different centers. For each model, adjusted least squares means and 95% CIs

were estimated by spirometric group and in the overall sample.

In a secondary analysis, given that a CT-based diagnosis of emphysema may occur in the absence of airflow obstruction (20), but may also represent normal aging (senile emphysema) (2, 40), the adjusted mean values (95% CIs) of the noted phenotypes were similarly calculated for those with GLI-defined normal spirometry in strata based on % emphysema less than or equal to 5% and greater than 5%.

The statistical models used to calculate the adjusted means were selected based on the distribution of the phenotypic measure and examination of model residuals: a negative binomial model for the Modified Medical Research Council dyspnea grade, a gamma distribution for SGRQ, and % gas trapping; a normal distribution for 6MWD, BD reversibility, and Pi10-SRWA; and a log-normal distribution estimated by a mixed model with random center effect for % emphysema. Model goodness of fit was assessed by analysis of residuals, and influence diagnostics were calculated. In sensitivity analyses, observations with larger values were removed from the dataset, with their removal having little impact on the reported results (data not shown).

Baseline clinical data in COPDGene were nearly complete, with less than 2% missing for most factors, but the $LAA950_{insp}$ was reported in 93.4% (9,459 of 10,131), $LAA856_{exp}$ in 84.5% (8,558 of 10,131), and Pi10-SRWA in 91.6% (9,285 of 10,131) of participants. The pattern, nature, and mechanism of missing data were assessed. For instance, indicator variables for missing values for each phenotypic variable were created and explanatory variables regressed on binary outcomes. Variables associated with these missingness indicators were then used in a multiple imputation analysis. Ten datasets were imputed, using fully conditional specification methods. Multiple imputation was performed using PROC MI (SAS 9.3; SAS Institute Inc. Cary, NC), and PROC MIANALYZE (SAS 9.3) combined the imputations to obtain the relevant adjusted mean values and standard errors.

SAS version 9.3 software (SAS Institute Inc.) was used in the analyses.

Results

Table 1 summarizes baseline characteristics (n = 10,131). The mean age was 59.6; 46.9%

Table 1. Baseline Characteristics (N = 10,131)

Characteristic	N	Mean ± SD or No. (%)
Age, yr	10,131	59.6 ± 9.0
Aged ⩾60 yr		4,711 (46.5)
Height, m		1.7 ± 0.1
Female		4,751 (46.9)
Ethnicity/race (non-Hispanic)		
White	10,131	6,818 (67.3)
African American		3,313 (32.7)
Education: <high school	10,130	1,368 (13.5)
BMI, kg/m^2	10,131	28.8 ± 6.3
Smoking history		
Smoking pack-years	10,023	44.3 ± 24.9
Current smokers	10,131	5,299 (52.3)
Former smokers		4,832 (47.7)
Medical conditions*		
Hypertension	10,130	4,365 (43.1)
Gastroesophageal reflux		2,525 (24.9)
Osteoarthritis		1,923 (19.0)
Diabetes mellitus	10,131	1,316 (13.0)
Osteoporosis	10,130	901 (8.9)
Rheumatoid arthritis		732 (7.2)
Coronary artery disease	10,131	651 (6.4)
Cancer†		497 (4.9)
Compression fractures‡		479 (4.7)
Blood clots (legs or lungs)	10,130	434 (4.3)
Congestive heart failure	10,131	321 (3.2)
Pneumothorax		325 (3.2)
Stroke	10,129	260 (2.6)
Peripheral vascular disease	10,130	230 (2.3)
Comorbidity count§	10,126	1.48 ± 1.44
Phenotypes‖		
Dyspnea: MMRC grade¶	10,117	1.4 ± 1.4
MMRC grade ⩾ 2		4,193 (41.5)
HRQL: SGRQ total score**	10,128	27.1 ± 23.0
SGRQ total score ⩾ 25		4,686 (46.3)
Exercise capacity: 6MWD, feet††	9,992	1,354 ± 400
6MWD < 1,282 ft		3,963 (39.7)
BD reversibility: FEV_1 % change‡‡	10,131	5.7 ± 10.3
FEV_1 % change > 12%		1,804 (17.8)
% Emphysema: $LAA950_{insp}$§§	9,459	6.2 ± 9.6
% Emphysema > 5%		2,865 (30.3)
% Gas trapping: $LAA856_{exp}$‖‖	8,558	21.9 ± 19.9
% Gas trapping > 15%		4219 (49.3)
Small airway: Pi10-SRWA, mm¶¶	9,285	3.68 ± 0.13
Pi10-SRWA > 4.28 mm		13 (0.1)

Definition of abbreviations: % emphysema = percentage of lung with emphysema; % gas trapping = percentage of lung with gas trapping; BD = bronchodilator; BMI = body mass index; HRQL = health-related quality of life; HU = Hounsfield units; LAA = low-attenuation area (computed tomography imaging); $LAA856_{exp}$ = LAA less than −856 HU on expiratory scan (evaluates air trapping); $LAA950_{insp}$ = LAA less than −950 HU on inspiratory scan (evaluates emphysema); MMRC = Modified Medical Research Council; Pi10-SRWA = square root of wall area for a standardized airway with internal perimeter of 10 mm; SGRQ = St. George's Respiratory Questionnaire; 6MWD = distance in the 6-minute-walk test.

*Self-reported, physician-diagnosed.

†Minor skin cancers are not included.

‡Limited to those in the back.

§Based on number of medical conditions.

‖See METHODS section for supporting citations regarding abnormal phenotypes.

¶Grade ranges from 0 to 4. A grade of at least 2 indicated clinically meaningful dyspnea at a moderate-to-severe level: "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level." In contrast, a grade of 1 indicates mild dyspnea: "I get short of breath when hurrying on the level or walking up a slight hill."

**Total score ranges from 0 to 100, with values greater than or equal to 25 defined as abnormal.

††Values less than 1,282 ft were defined as abnormal.

‡‡[(Post-BD–pre-BD)/pre-BD FEV_1] × 100%, with values greater than 12% defining reversibility.

§§Values greater than 5% emphysema were defined as abnormal.

‖‖Values greater than 15% gas trapping were defined as abnormal.

¶¶Values greater than 4.28 defined as abnormal.

were female, 32.7% were African American, 13.5% had less than a high school education, and mean BMI was 28.8 kg/m^2. Smoking history averaged 44.3 pack-years. The five most prevalent medical conditions were hypertension (43.1%), gastroesophageal reflux (24.9%), osteoarthritis (19.0%), diabetes mellitus (13.0%), and osteoporosis (8.9%); participants averaged 1.48 medical conditions (comorbidity count). Phenotypes as unadjusted mean values included dyspnea grade of 1.4, SGRQ of 27.1, 6MWD of 1,354 ft (413 m), BD reversibility of 5.7%, % emphysema of 6.2%, % gas trapping of 21.9%, and Pi10-SRWA of 3.68 mm. Abnormal phenotypes were highly prevalent (range, 17.8–49.3%), except for small airways disease (<1%).

Table 2 shows the distributions of GLI- and GOLD-defined spirometric categories. Normal spirometry was identified by GLI in 50.3% (5,100 of 10,131) and by GOLD in 39.0% (3,954 of 10,131). Among 5,100 participants who had GLI-defined normal spirometry, GOLD identified 1,146 (22.5%) as having respiratory impairment, including restrictive pattern in 464 (9.1%), mild COPD in 380 (7.5%), moderate COPD in 302 (5.9%), and severe COPD in none. In contrast, only five participants (<0.1%) with normal spirometry by GOLD had respiratory impairment by GLI (all mild COPD).

Although not the focus of this study, Table 2 shows two other discordant classifications. First, 33.2% (222 of 669) of participants with mild COPD by GLI had moderate COPD by GOLD, whereas 19.7% (496 of 2,522) with severe COPD by GLI had moderate COPD by GOLD, suggesting discordance in COPD severity. Second, 14.5% (141 of 975) of those with restrictive pattern by GLI had moderate or severe COPD by GOLD, suggesting discordance in restrictive pattern as COPD.

Table 3 shows adjusted mean values, including abnormal thresholds, for the phenotype of GLI-defined normal spirometry, initially without stratification by GOLD categories (*All* column). Participants with GLI-defined normal spirometry had a mean age of 58.1; a mean comorbidity count of 1.26; and adjusted mean values in the normal range for dyspnea grade (0.8), SGRQ (15.9), 6MWD (1,424 ft [434 m]), BD reversibility (2.7%), % emphysema (0.9), % gas trapping (10.7), and Pi10-SRWA (3.65 mm). Corresponding 95% CIs were similarly in the normal range.

Table 3 also shows adjusted mean values for the phenotype of GLI-defined normal spirometry, cross-tabulated with GOLD categories. The phenotype across these spirometric classifications included increased age and comorbidity count for the discordant classifications. For example, participants with normal spirometry by GLI and GOLD had a mean age of 56.3 and a mean comorbidity count of 1.26, whereas those with normal spirometry by GLI, but moderate COPD by GOLD had a mean age of 66.1 and a mean comorbidity count of 1.90. Importantly, GLI-defined normal spirometry retained a normal phenotype across GOLD categories, including adjusted mean values in the normal range for dyspnea grade (0.7–1.2), SGRQ (15.3–19.1), 6MWD (1,358–1,455 ft [414–443 m]), BD reversibility (2.4–4.9%), % emphysema (0.8–1.4), % gas trapping (10.0–12.2), and Pi10-SRWA (3.64–3.68 mm); corresponding 95% CIs were similarly in the normal range. In addition, although a gradient was observed within the GLI-defined normal spirometry group (as expected for clinical phenomena occurring along a continuum), all adjusted mean values and 95% CIs still did not cross abnormal thresholds.

Table 4 shows adjusted mean values, including abnormal thresholds, for the phenotype of GLI-defined normal spirometry, stratified by the 5% emphysema threshold. Among those with GLI-defined normal spirometry, participants were on average older if they had % emphysema greater than 5% versus less than or equal to 5% (mean age, 62.4 and 57.5, respectively). Otherwise, GLI-defined normal spirometry had a similar

Table 2. Baseline Frequency Distributions of Spirometric Classifications by GLI Cross-tabulated with GOLD Classifications (N = 10,131)

GOLD Spirometric Classification*	GLI Spirometric Classification‡					
		COPD				
	Normal†	Mild	Moderate	Severe	Restrictive Pattern	Total
Normal	3,954 (39.0)	5 (<0.1)	0 (0)	0 (0)	0 (0)	3,959 (39.1)
COPD						
Mild	380 (3.8)	442 (4.4)	0 (0)	0 (0)	0 (0)	822 (8.1)
Moderate	302 (3.0)	222 (2.2)	860 (8.5)	496 (4.9)	112 (1.1)	1,992 (19.7)
Severe	0 (0)	0 (0)	4 (<1)	2,023 (20.0)	29 (<1)	2,056 (20.3)
Restrictive pattern	464 (4.6)	0 (0)	1 (<1)	3 (<1)	834 (8.2)	1,302 (12.9)
Total No. (%)	5,100 (50.3)	669 (6.6)	865 (8.5)	2,522 (24.9)	975 (9.6)	10,131 (100)

Definition of abbreviations: BD = bronchodilator; COPD = chronic obstructive pulmonary disease; GLI = Global Lung Initiative; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LLN_5 = lower limit of normal at the fifth percentile of distribution.

Data are given as no. (%); all percentages are based on N = 10,131.

*Using Third National Health and Nutrition Examination Survey equations and pre-BD values, normal spirometry was defined by FEV_1/FVC greater than or equal to 0.70 and FVC greater than or equal to 80% predicted; COPD by FEV_1/FVC less than 0.70; and restrictive pattern by FEV_1/FVC greater than or equal to 0.70 and FVC less than 80% predicted. COPD severity is then defined as mild, moderate, or severe based on FEV_1 % predicted of greater than or equal to 80, 50–79, and less than 50, respectively.

†Shaded cells represent GLI-defined normal spirometry stratified by GOLD-defined COPD or restrictive pattern.

‡Using GLI equations and pre-BD values, normal spirometry was defined by FEV_1/FVC and FVC both greater than or equal to LLN_5; COPD by FEV_1/FVC less than LLN_5; and restrictive pattern by FEV_1/FVC greater than or equal to LLN_5 and FVC less than LLN_5. COPD severity is then defined as mild, moderate, or severe based on FEV_1 *z* scores of greater than or equal to −1.64, less than −1.64 but greater than or equal to −2.55, and less than −2.55, respectively.

Table 3. Adjusted Mean Values for Phenotypic Measures of GLI-defined Normal Spirometry (N = 5,100) Cross-tabulated with GOLD Classifications, and with Missing Phenotypic Values Provided by Multiple Imputation

		GLI-defined Normal Spirometry† [*Adjusted Mean (95% Confidence Interval)*]‡				
			GOLD Spirometric Classification†			
				COPD§		Restrictive
Phenotype	Abnormal Threshold*	All (*N = 5,100*)	Normal (*n = 3,954*)	Mild (*n = 380*)	Moderate (*n = 302*)	Pattern (*n = 464*)
Age, yr	—	58.1 (57.8–58.3)	56.3 (56.1–56.6)	65.8 (65.1–66.6)	66.1 (65.3–66.9)	61.2 (60.4–61.9)
Comorbidity count‖	—	1.26 (1.23–1.30)	1.14 (1.10–1.18)	1.43 (1.29–1.56)	1.90 (1.73–2.06)	1.73 (1.60–1.87)
Dyspnea: MMRC grade¶	⩾2.0	0.8 (0.7–0.9)	0.7 (0.6–0.8)	0.8 (0.6–1.0)	1.2 (1.0–1.4)	1.0 (0.8–1.1)
HRQL: SGRQ total score**	⩾25	15.9 (13.8–18.8)	15.3 (12.9–17.7)	16.4 (13.8–19.0)	19.1 (15.6–22.5)	17.5 (14.7–20.3)
Exercise capacity: 6MWD, ft	<1,282	1,424 (1,347–1,501)	1,434 (1,355–1,513)	1,455 (1,378–1,531)	1,358 (1,282–1,435)	1,384 (1,316–1,453)
BD reversibility: FEV_1 % change††	>12	2.7 (2.4–3.1)	2.4 (2.1–2.7)	3.9 (3.1–4.7)	4.9 (4.2–5.5)	3.4 (2.7–4.1)
% Emphysema: $LAA950_{insp}$	>5	0.9 (0.6–1.2)	0.8 (0.6–1.2)	1.4 (1.0–2.0)	1.2 (0.8–1.7)	0.6 (0.4–0.9)
% Gas trapping: $LAA856_{exp}$	>15	10.7 (9.2–12.7)	10.5 (8.8–12.1)	12.1 (10.1–14.1)	12.2 (10.3–14.1)	10.0 (8.3–11.7)
Small airway: Pi10-SRWA, mm	>4.28	3.65 (3.64–3.66)	3.65 (3.64–3.66)	3.64 (3.62–3.65)	3.68 (3.66–3.70)	3.68 (3.67–3.70)

Definition of abbreviations: % emphysema = percentage of lung with emphysema; % gas trapping = percentage of lung with gas trapping; BD = bronchodilator; COPD = chronic obstructive pulmonary disease; GLI = Global Lung Initiative; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HRQL = health-related quality of life; HU = Hounsfield units; LAA = low-attenuation area (computed tomography imaging); $LAA856_{exp}$ = LAA less than −856 HU on expiratory scan (evaluates air trapping); $LAA950_{insp}$ = LAA less than −950 HU on inspiratory scan (evaluates emphysema); MMRC = Modified Medical Research Council; Pi10-SRWA = square root of wall area for a standardized airway with internal perimeter of 10 mm; SGRQ = St. George's Respiratory Questionnaire; 6MWD = distance in the 6-minute-walk-test.

For multiple imputation method, *see text*.

*See METHODS section for supporting citations.

†See footnotes to Table 2 for diagnostic thresholds.

‡Adjusted for age, height, sex, BMI, ethnicity, education, current smoking, and type of medical condition. However, when age and comorbidity count were the phenotypic features, the mean values were not adjusted.

§There was no discordant classification of GLI-defined normal spirometry but GOLD-defined severe COPD.

‖Based on number of medical conditions.

¶Grade ranges from 0 to 4. A grade greater than or equal to 2 denotes clinically meaningful dyspnea (indicating that the dyspnea is more severe than a reference group of the same age and occurs at a low exercise workload).

**Total score ranges from 0 to 100.

††[(Post-BD − pre-BD)/pre-BD FEV_1] × 100%.

comorbidity count and retained a normal phenotype across the 5% emphysema threshold, including adjusted mean values in the normal range for dyspnea grade (0.8–0.9), SGRQ (15.8–16.9), 6MWD (1,423–1,437 ft [433–438 m]), BD reversibility (2.7–3.1%), % gas trapping (10.3–14.1), and Pi10-SRWA (3.62–3.66 mm). In addition, except for the 95% CI upper limit for % gas trapping (16.5), the corresponding 95% CIs among participants who had greater than 5% emphysema were similarly in the normal range.

The online supplement provides results supplemental to Table 2, including mean values for FEV_1/FVC, FEV_1 % predicted, and FVC % predicted, cross-tabulated by GLI-defined normal spirometry and GOLD categories (*see* Appendix Table in the online supplement). Briefly summarized, a substantial age-effect was noted in these additional analyses, similar to that observed in Tables 3 and 4.

Discussion

Analyzing data on 10,131 participants from COPDGene, aged 45–81 and with a smoking history greater than or equal to 10 pack-years, we found that the phenotype of the 5,100 participants with GLI-defined normal spirometry included adjusted mean values and 95% CIs within the normal range for dyspnea grade; SGRQ; 6MWD; BD reversibility; and CT-measured % emphysema, % gas trapping, and Pi10-SRWA (Table 3). In addition, the phenotype of the 1,146 participants who had the discordant classification of GLI-defined normal spirometry, but GOLD-defined respiratory impairment (COPD or restrictive pattern), included adjusted mean values and 95% CIs within the normal range for corresponding measures (Table 3).

Based on these results, we posit that the phenotype of GLI-defined normal spirometry suggests the absence of clinically meaningful respiratory disease, even when classified as respiratory impairment by GOLD. The current study is consistent with, and provides a mechanistic explanation for, prior work showing that the GOLD misclassification of normal spirometry as respiratory impairment was not associated longitudinally with adverse outcomes, such as impaired mobility, COPD hospitalization, or mortality (14, 15, 41).

The current study also shows the expected impact of age on spirometric classification. For example, we found that COPDGene participants who had the discordant classification of GLI-defined normal spirometry, but GOLD-defined moderate COPD, were substantially older than those who had normal spirometry by both GLI and GOLD, with mean ages of 66.1 and 56.3, respectively. Importantly, despite having moderate COPD by GOLD, participants who otherwise had normal spirometry by GLI had adjusted mean values and 95% CIs in the normal range for dyspnea grade, SGRQ, 6MWD, BD reversibility, % emphysema, % gas trapping, and Pi10-SRWA (Table 3). These results suggest that GOLD misclassifies a normal phenotype as respiratory impairment in older persons, a consequence of the previously described age-related limitations regarding use of a fixed ratio for FEV_1/FVC, and of % predicted for FEV_1 and FVC (2, 8–15).

The current study also shows that a CT-based diagnosis of emphysema may

Table 4. Adjusted Mean Values for Phenotypic Measures of GLI-defined Normal Spirometry According to the 5% Emphysema Threshold, and with Missing Values Provided by Multiple Imputation

Phenotype	Abnormal Threshold*	GLI-defined Normal Spirometry† (*N = 5,100*) [*Adjusted Mean (95% Confidence Interval)*‡]	
		⩽5% Emphysema ($LAA950_{insp}$)‡ (*n = 4,509*)	>5% Emphysema ($LAA950_{insp}$)§ (*n = 591*)
Age, yr	—	57.5 (57.2–57.7)	62.4 (61.6–63.1)
Comorbidity count‖	—	1.25 (1.21–1.29)	1.36 (1.26–1.46)
Dyspnea: MMRC grade¶	⩾2.0	0.8 (0.6–0.9)	0.9 (0.7–1.0)
HRQL: SGRQ total score**	⩾25	15.8 (13.4–18.2)	16.9 (13.9–19.9)
Exercise capacity: 6MWD, ft	<1282	1,423 (1,345–1,501)	1,437 (1,360–1,515)
BD reversibility: FEV_1 % change††	>12	2.7 (2.4–3.0)	3.1 (2.6–3.7)
% Gas trapping: $LAA856_{exp}$	>15	10.3 (8.7–11.8)	14.1 (11.8–16.5)
Small airway: Pi10-SRWA, mm	>4.28	3.66 (3.64–3.67)	3.62 (3.58–3.66)

Definition of abbreviations: % emphysema = percentage of lung with emphysema; % gas trapping = percentage of lung with gas trapping; BD = bronchodilator; BMI = body mass index; GLI = Global Lung Initiative; HRQL = health-related quality of life; HU = Hounsfield units; LAA = low-attenuation area (computed tomography imaging); $LAA856_{exp}$ = LAA less than −856 HU on expiratory scan (evaluates air trapping); $LAA950_{insp}$ = LAA less than −950 HU on inspiratory scan (evaluates emphysema); MMRC = Modified Medical Research Council; Pi10-SRWA = square root of wall area for a standardized airway with internal perimeter of 10 mm; SGRQ = St. George's Respiratory Questionnaire; 6MWD = distance in the 6-minute-walk test.
For multiple imputation method, *see text*.
*See METHODS section for supporting citations.
†See footnote to Table 2.
‡Adjusted for age, height, sex, BMI, ethnicity, education, current smoking, and type of medical condition. However, when age and comorbidity count were the phenotypic features, the mean values were not adjusted.
§An abnormal value is defined by % emphysema ($LAA950_{inspiration}$) greater than 5%.
‖Based on number of medical conditions.
¶Grade ranges from 0 to 4. A grade greater than or equal to 2 denotes clinically meaningful dyspnea (indicating that the dyspnea is more severe than a reference group of the same age and occurs at a low exercise workload).
**Total score ranges from 0 to 100.
††[(Post-BD − pre-BD)/pre-BD FEV_1] × 100%.

occur in the absence of airflow obstruction. We found, for example, that 11.6% (591 of 5,100) of COPDGene participants who had GLI-defined normal spirometry crossed the expert consensus diagnostic threshold of 5% emphysema and, among those who had greater than 5% emphysema, the range of % gas trapping values exceeded the expert consensus diagnostic threshold of 15% (Table 4). Although these results indicate that CT-diagnosed COPD can be present in a small proportion of participants who had GLI-defined normal spirometry, an alternative explanation is that the threshold values for % emphysema and % gas trapping are limited in differentiating normal aging from respiratory disease.

In particular, prior work has shown that CT-measured % emphysema may be as high as 30% in otherwise healthy persons with normal lung function (42), and another study has shown that persons with normal lung function and a negative methacholine-bronchoprovocation test had a wide range of values for CT-measured % gas trapping, with mean ± SD of 12.3% ± 16.7% (43). The wide range of values for CT-measured % emphysema and % gas trapping in otherwise healthy populations may represent an age-effect, because normal aging can lead to structural changes of the lung parenchyma and airways, yielding senile emphysema and increased gas trapping, respectively (2, 40). Unfortunately, age-specific reference equations for % emphysema and % gas trapping as determined in healthy populations of asymptomatic lifelong nonsmokers are unavailable (44).

The results of our study reinforce the importance of considering the effects of normal aging on CT-measured emphysema and gas trapping. Among COPDGene participants who had GLI-defined normal spirometry, we found that those with % emphysema greater than 5% were on average older than those with % emphysema less than or equal to 5% (mean age, 62.4 and 57.5, respectively). Nonetheless, participants with GLI-defined normal spirometry retained a normal phenotype across the 5% emphysema threshold, including dyspnea grade, SGRQ, 6MWD, BD reversibility, and Pi10-SRWA (Table 4). These results suggest that crossing the threshold of 5% emphysema among participants who otherwise have normal spirometry by GLI may not establish clinically meaningful respiratory diseases but, instead, simply reflect normal aging.

In addressing a different research question, a prior study concluded that a LLN threshold for FEV_1/FVC, when compared with the GOLD approach, fails to identify pulmonary pathology as defined by expert consensus thresholds for CT-measured emphysema and gas trapping (30). Several explanations can reconcile the results across studies. First, spirometric classification in the prior study only evaluated FEV_1/FVC (30), potentially misidentifying normal spirometry and restrictive pattern, because these classifications require the additional consideration of FVC alone. Second, the LLN in the prior study was calculated as the fifth percentile distribution of reference values (30), using equations from the Third National Health and Nutrition Examination Survey (38). The Third National Health and Nutrition Examination Survey calculated LLN has been shown to misidentify COPD, when compared with LLN calculated as the fifth percentile distribution of *z* scores (as done

in GLI) (11–13). Third, in the prior study, the discordant classification of COPD by GOLD, but normal by LLN, occurred most often in those aged 61–80 (30), reflecting (as shown in the current work) the age-related limitations of the GOLD fixed-ratio of 0.70 for FEV_1/FVC (2, 8–15), and the potential misidentification of senile emphysema as COPD (2, 40).

Other work has additionally suggested that, in the absence of airflow obstruction, CT-measured emphysema is clinically meaningful given its association with all-cause mortality (20). Potential limitations in interpreting this prior work include the lack of a threshold association and, more importantly, the use of spirometric criteria for defining "without airflow obstruction" that only included FEV_1/FVC (i.e., FVC was not evaluated separately). Hence, participants who were characterized as "without airflow obstruction" may have included those with a reduced FVC, a consequence of normal aging or restrictive pattern. A reduced FVC has been shown to be a strong predictor of cardiovascular events and mortality (45, 46), and may have confounded the association between CT-measured emphysema and mortality.

Finally, in a discussion of the spirometric criteria for respiratory disease, it is important to note that the reality of clinical decisions often require a three-zone interpretation of present, absent, or uncertain, rather than yes versus no (47). The current study builds on prior work (14, 15, 41), suggesting that GLI-defined normal spirometry is likely to establish the absence of clinically meaningful respiratory disease but uncertainty may persist in a small proportion of (older) adults, thus requiring clinical judgment (1, 47). In addition, the interpretation of diagnostic thresholds for % emphysema and % gas trapping requires caution, pending the development of age-specific reference equations from healthy populations of asymptomatic lifelong never-smokers (44). Based on these age-specific norms, the diagnostic accuracy of GLI-defined normal spirometry can thereafter be more definitively assessed.

In conclusion, COPDGene participants with GLI-defined normal spirometry had a normal phenotype, including adjusted mean values and 95% CIs in the normal range for dyspnea grade; SGRQ; 6MWD; BD reversibility; and CT-measured % emphysema, % gas trapping, and small airway dimensions. Similarly, the phenotype of the discordant classification of normal spirometry by GLI, but respiratory impairment by GOLD, included adjusted mean values and 95% CIs in the normal range for corresponding measures. These results suggest that among adults who have GLI-defined normal spirometry, GOLD may misclassify a normal phenotype as respiratory impairment and, in turn, may lead to a presumption of respiratory disease. ■

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