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A Multidimensional Diagnostic Approach for Chronic Obstructive Pulmonary Disease

COPDGene 2025 Diagnosis Working Group and CanCOLD Investigators

Editorial page 2151

Supplemental content

IMPORTANCE Individuals at risk for chronic obstructive pulmonary disease (COPD) but without spirometric airflow obstruction can have respiratory symptoms and structural lung disease on chest computed tomography. Current guidelines recommend COPD diagnostic schemas that do not incorporate imaging abnormalities.

OBJECTIVE To determine whether a multidimensional COPD diagnostic schema that includes respiratory symptoms and computed tomographic imaging abnormalities identifies additional individuals with disease.

DESIGN, SETTING, AND PARTICIPANTS This cohort study included 2 longitudinal cohorts: the Genetic Epidemiology of COPD (COPDGene), which enrolled 10 305 participants between November 9, 2007, and April 15, 2011, with longitudinal follow-up through August 31, 2022; and the Canadian Cohort Obstructive Lung Disease (CanCOLD), which enrolled 1561 participants between November 26, 2009, and July 15, 2015, with follow-up through December 31, 2023.

EXPOSURE Exposure included the new multidimensional COPD diagnostic schema, defined by (1) major diagnostic category: presence of the major criterion (airflow obstruction based on postbronchodilator forced expiratory volume in the first second of expiration [FEV_1]/forced vital capacity ratio <0.70) and at least 1 of 5 minor criteria (emphysema or bronchial wall thickening on computed tomography, dyspnea, poor respiratory quality of life, and chronic bronchitis); or (2) minor diagnostic category: presence of least 3 of 5 minor criteria (which must include emphysema and bronchial wall thickening for individuals with respiratory symptoms potentially due to other causes).

MAIN OUTCOMES AND MEASURES All-cause mortality, respiratory cause–specific mortality, exacerbations, and annualized change in FEV_1.

RESULTS Among 9416 adults in COPDGene (mean [SD] age at enrollment, 59.6 [9.0] years; 5035 [53.5%] were men; 3071 [32.6%] were Black; 6345 (67.4%) were White; 4943 [52.5%] currently smoked), 811 of 5250 individuals (15.4%) without airflow obstruction were newly classified as having COPD by minor diagnostic category, and 282 of 4166 individuals (6.8%) with airflow obstruction were classified as not having COPD. Reclassified individuals with a new COPD diagnosis had greater all-cause mortality (adjusted hazard ratio, 1.98; 95% CI, 1.67-2.35; $P < .001$) and respiratory-specific mortality (adjusted hazard ratio, 3.58; 95% CI, 1.56-8.20; $P = .003$), more exacerbations (adjusted incidence rate ratio, 2.09; 95% CI, 1.79-2.44; $P < .001$), and more rapid FEV_1 decline (adjusted $\beta = -7.7$ mL/y; 95% CI, −13.2 to −2.3; $P = .006$) compared with individuals classified as not having COPD. Among individuals with airflow obstruction on spirometry, those no longer classified as having COPD based on this new diagnostic schema had outcomes similar to those without airflow obstruction. Among 1341 adults in CanCOLD, individuals newly classified as having COPD experienced more exacerbations (adjusted incidence rate ratio, 2.09; 95% CI, 1.25-3.51; $P < .001$).

CONCLUSIONS AND RELEVANCE A new COPD diagnostic schema integrating respiratory symptoms, respiratory quality of life, spirometry, and structural lung abnormalities on computed tomographic imaging newly classified some individuals as having COPD. These individuals had an increased risk of all-cause and respiratory-related death, frequent exacerbations, and rapid lung function decline compared with individuals classified as not having COPD. Some individuals with airflow obstruction without respiratory symptoms or evidence of structural lung disease were no longer classified as having COPD.

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Group/Author Information: The COPDGene 2025 Diagnosis Working Group and CanCOLD Investigators appear at the end of the article.

Corresponding Author: Surya P. Bhatt, MD, MSPH, Center for Lung Analytics and Imaging Research (CLAIR), Division of Pulmonary, Allergy and Critical Care Medicine, University of Alabama at Birmingham, 1720 2nd Ave S, THT 422, Birmingham, AL 35294 (sbhatt@uabmc.edu).

Chronic obstructive pulmonary disease (COPD) is a leading cause of disability and death. Approximately 392 million people globally, 16 million in the United States, are estimated to have COPD.[1] The current diagnostic recommendations from global societies for COPD diagnosis require presence of airflow obstruction on postbronchodilator spirometry, with a forced expiratory volume in the first second of expiration (FEV_1)/forced vital capacity (FVC) ratio less than 0.70 or below the lower limit of normal in the appropriate clinical context for patients with respiratory symptoms.[2-4] Several studies have demonstrated that spirometry is not sensitive to the structural changes associated with COPD, which often occur before lung function decreases below the thresholds recommended for defining airflow obstruction. Up to half of individuals with a history of cigarette smoking have evidence of emphysema or airway wall thickening on chest computed tomography (CT).[5,6] Among individuals without airflow obstruction, the risk of developing it on spirometry within 5 years is 2-fold higher for those with airway wall thickening and 4-fold greater for those with emphysematous changes on chest CT compared with those who do not have structural abnormalities on chest CT.[7,8] Furthermore, 50% of individuals who currently smoke or formerly smoked and are without airflow obstruction have substantial respiratory symptoms,[6] which may be attributed to aging, weight gain, deconditioning, and smoking-induced cough, and these symptoms often are unreported.

It is increasingly recognized that spirometry does not capture all aspects of this complex heterogeneous disease and there is growing consensus in the respiratory community that a COPD diagnosis should not be based on spirometry alone. The Genetic Epidemiology of COPD (COPDGene) 2019 diagnostic criteria were the first to highlight the importance of incorporating lung imaging.[9] Those criteria were based on a 4-item scoring system and gave equal weight to the presence of 1 or more of the following: risk factors, symptoms, imaging, and impaired spirometry. The requirement that all 4 diagnostic criteria be met for a definite COPD diagnosis meant that some patients previously considered to have COPD no longer met criteria. The 2022 Lancet Commission on COPD also stated that the diagnosis should be multidimensional, although it did not specify cutoffs to operationalize the diagnostic recommendations.[10] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 document stated that the presence of emphysema or airway abnormalities should raise clinical suspicion for COPD. Chest imaging was not included in this diagnostic algorithm.[2]

This study aimed to evaluate patient reclassification using an expanded diagnostic COPD schema by testing associations with key clinical outcomes such as mortality and respiratory morbidity and to identify individuals who would not receive a diagnosis with spirometry alone. We used data from 2 large multicenter cohort studies to derive and evaluate the new COPD diagnostic schema by testing associations with clinical outcomes.

Key Points

Question Does incorporating chest computed tomographic imaging abnormalities and respiratory symptoms into the chronic obstructive pulmonary disease (COPD) diagnostic schema improve identification of individuals with poor respiratory outcomes?

Findings Among 9416 participants enrolled in a multicenter cohort study, those with newly diagnosed COPD had greater all-cause and respiratory-specific mortality, more frequent exacerbations, and faster decline of forced expiratory volume in the first second of expiration compared with individuals classified as not having COPD based on the new classification schema. Application of this new COPD diagnostic schema included additional individuals with high respiratory morbidity and excluded those with airflow obstruction who had no symptoms or evidence of structural lung disease.

Meaning This new COPD diagnostic schema, which includes chest imaging, respiratory symptoms, and spirometry, identified additional individuals at risk for poor respiratory outcomes.

Methods

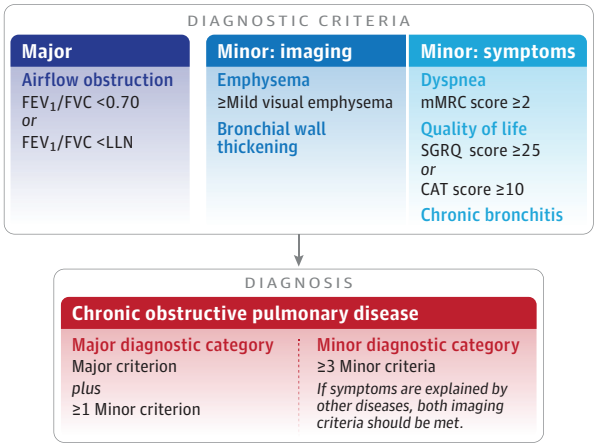
Participants

The diagnostic categories were developed and tested in the COPDGene study, a multicenter cohort of individuals who currently or formerly smoked, were aged 45 to 80 years, and were enrolled between November 9, 2007, and April 15, 2011, at 21 sites in the United States, with a median 10.5 years (25th-75th percentile, 5.3-12.3 years) of follow-up through August 31, 2022.[11] We excluded a small number (n = 107) of healthy individuals who had never smoked and were enrolled in the first phase of COPDGene. For replication, we analyzed data from the Canadian Cohort Obstructive Lung Disease (CanCOLD) study, which included individuals who had never smoked, were aged 40 years or older, and were enrolled between November 26, 2009, and July 15, 2015, at 9 sites across Canada, with a median 10.0 years (25th-75th percentile, 6.1-11.2 years) of follow-up through December 31, 2023.[12] The details of these cohorts have been previously published and major eligibility criteria are listed in eTable 1 in Supplement 1.[11,12] Age and sex were self-reported by participants at enrollment. Race and ethnicity were self-reported according to fixed categories. In both cohorts, all participants provided written informed consent before enrollment and the research activities were approved by the institutional review boards of all participating centers. The study followed STROBE reporting guidelines.

Measurements

Prebronchodilator and postbronchodilator spirometry measurements were acquired at enrollment. Airflow obstruction was defined primarily by the fixed ratio of FEV_1 to FVC of less than 0.70.[2,13] Participants with a normal ratio and FEV_1 percentage predicted of greater than or equal to 80% were categorized as GOLD stage 0, and participants with a normal FEV_1/FVC ratio and FEV_1 percentage predicted of less than 80% were categorized as having preserved ratio impaired spirometry.[14] In sensitivity analyses, we evaluated defining airflow obstruction by FEV_1/FVC below the lower limit of normal using the Global Lung Function Initiative global reference equations.[15] Volumetric thin-section chest CT scans were acquired at total lung capacity. Repeat spirometry and imaging assessments at 5 years in COPDGene and at 3 years in CanCOLD were included in the analyses. All imaging and

Figure 1. Diagnostic Schema for Chronic Obstructive Pulmonary Disease (COPD) Using Major and Minor Criteria



Diagnostic criteria indicate individual measures whose presence points toward a diagnosis. Diagnostic category indicates a broader classification or grouping of these individual criteria. Diagnosis is made when the conditions for either the major or the minor diagnostic category are met. Visual emphysema was defined by the presence of at least mild emphysema and bronchial wall thickness defined when read as definite thickening according to the Fleischner Society criteria. The modified Medical Research Council (mMRC) dyspnea scale ranges from 0 to 4, with a higher score indicating greater dyspnea. CAT indicates COPD Assessment Test, a measure of the effect of COPD on respiratory quality of life (range, 0-40, with higher scores indicating worse quality of life); FEV_1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; LLN, lower limit of normal; and SGRQ, St George's Respiratory Questionnaire, a measure of respiratory quality of life (range, 0-100, with higher scores indicating worse quality of life).

spirometry results were checked for quality according to standard procedures.

Respiratory quality of life was measured with the St George's Respiratory Questionnaire (SGRQ) in COPDGene[16] and the COPD Assessment Test score in CanCOLD.[17] Total SGRQ score greater than or equal to 25 was used as the threshold for poor quality of life in COPDGene.[18] In CanCOLD, the negative effect of COPD on quality of life was considered high if the COPD Assessment Test score was greater than or equal to 10.[2] Dyspnea was quantified with the modified Medical Research Council dyspnea scale,[19] and a score greater than or equal to 2 was deemed high.[2] Chronic bronchitis was defined by the presence of cough with sputum production on most days for at least 3 months in 2 consecutive years.

Diagnostic Criteria

The proposed diagnostic schema include major and minor criteria (**Figure 1**). The major criterion is airflow obstruction defined by a postbronchodilator FEV_1/FVC ratio less than 0.7 for the primary analyses and below the lower limit of normal in sensitivity analyses. The 5 minor criteria include 2 imaging criteria (emphysema and thickened airway walls based on visual analyses of chest CT scans and 3 symptom-based criteria [dyspnea, respiratory quality of life, and chronic bronchitis]). Sensitivity analyses include using the lower limit of normal for the FEV_1/FVC ratio instead of the fixed ratio, varying thresholds to define significant visual emphysema, and using quantitative measures of emphysema and bronchial wall thickening instead of the visual estimates on CT typically used in clinical practice. Subgroup analyses also evaluate associations by age, race, and ethnic groups. More details are provided in the eMethods in Supplement 1, including derivation of the diagnostic schema (eFigure 1 in Supplement 1).

Diagnostic Categories

Figure 1 and eFigure 2 in Supplement 1 show the diagnostic schema. Individuals are classified as having COPD if they have the major criterion and at least 1 minor criterion (major diagnostic category), which is an expansion of the current diagnostic paradigm that requires airflow obstruction and the presence of symptoms because prior statements and guidelines do not provide cutoffs for symptoms and do not include imaging.[2-4] When airflow obstruction is not present or spirometry is not available, individuals can be categorized as having COPD if at least 3 of the 5 minor criteria are met (minor diagnostic category). To increase certainty that respiratory symptoms are not due to other coexistent diseases such as coronary artery disease or congestive heart failure, 2 of the 3 minor COPD diagnostic criteria should be imaging based when the clinician attributes respiratory symptoms to other causes as much as or more than to COPD.

Reclassification and Clinical Outcomes

The classification of individuals as having COPD based on the new diagnostic schema was compared with COPD defined solely by the presence of postbronchodilator airflow obstruction. To account for a lack of symptom thresholds, we assessed reclassification of individuals by the new schema compared with airflow obstruction in the presence of a range of symptom severity to simulate the GOLD recommendations. The diagnostic categories of the new schema were tested against 4 important clinical outcomes: (1) all-cause mortality, (2) respiratory-specific mortality, (3) COPD exacerbations, and (4) disease progression as quantified by the annualized change in FEV_1 between baseline and follow-up visits.

Statistical Analysis

The clinical significance of each major and minor criterion was evaluated by testing its association with each clinical outcome, with minor criteria additionally adjusted for the presence of airflow obstruction. We also evaluated the effect of lowering symptom thresholds on COPD diagnosis. Associations between the new COPD diagnostic categories and longitudinal outcomes were tested in multivariable models. Cox proportional hazards models were created with mortality as the dependent variable and age, sex, race, body mass index (calculated as weight in kilograms divided by height in meters squared), smoking status, and pack-years of smoking as covariates. Competing risk models were created for cause-specific mortality. Exacerbation frequency was evaluated using negative binomial regression with adjustment for the covariates mentioned earlier and additionally for the number of exacerbations in the previous year, with the natural logarithm of years of follow-up as the offset variable. Generalized linear models were used to evaluate FEV_1 change, with adjustment

Table 1. Clinical and Imaging Characteristics of Participants in COPDGene by Reclassification Status

	Reclassification overall (N = 9416)			
	COPD by both old and new diagnostic schemas (n = 3884)	No airflow obstruction but COPD present according to new diagnostic schema (n = 811)	Airflow obstruction but no COPD according to new diagnostic schema (n = 282)	No COPD by both old and new diagnostic schemas (n = 4439)
Demographics				
Age, mean (SD), y	63.2 (8.6)	55.0 (7.4)	61.9 (8.9)	57.1 (8.5)
Sex, No. (%)				
Male	2184 (56.2)	365 (45.0)	161 (57.1)	2325 (52.4)
Female	1700 (43.8)	446 (55.0)	121 (42.9)	2114 (47.6)
Race and ethnicity, No. (%)[a]				
Non-Hispanic Black	865 (22.3)	429 (52.9)	46 (16.3)	1731 (39.0)
Non-Hispanic White	3019 (77.7)	382 (47.1)	236 (83.7)	2708 (61.0)
BMI, mean (SD)	27.8 (6.1)	30.5 (7.0)	28.4 (5.1)	29.4 (6.1)
Underweight (BMI <18.5), No. (%)	113 (2.9)	11 (1.4)	0	25 (0.6)
Healthy weight (BMI 18.5-24.9), No. (%)	1277 (32.9)	177 (21.8)	81 (28.7)	1057 (23.8)
Overweight (BMI 25.0-29.9), No. (%)	1295 (33.3)	234 (28.9)	106 (37.6)	1599 (36.0)
Obese (BMI ≥30), No. (%)	1199 (30.9)	389 (48.0)	95 (33.7)	1758 (39.6)
Pack-years of smoking, mean (SD)	52.7 (27.2)	46.0 (25.3)	36.6 (20.3)	37.0 (20.0)
Medications, No. (%)				
ICS/LABA	1462 (37.6)	131 (16.2)	18 (6.4)	181 (4.1)
LABA	299 (7.7)	11 (1.4)	0	15 (0.3)
LAMA	1360 (35.0)	77 (9.5)	4 (1.4)	87 (2.0)
Comorbidities, No. (%)				
Coronary artery disease[a]	358 (9.2)	8 (1.0)	17 (6.0)	241 (5.4)
Congestive heart failure[a]	173 (4.5)	10 (1.2)	4 (1.4)	100 (2.3)
Lung function, mean (SD)				
FEV_1 % predicted	56.1 (22.2)	85.2 (16.4)	81.3 (14.9)	92.8 (15.0)
Questionnaires				
Chronic bronchitis, No. (%)	1073 (27.6)	410 (50.6)	0	306 (6.9)
mMRC dyspnea score, mean (SD)[b]	2.0 (1.4)	2.5 (1.1)	0.2 (0.4)	0.6 (1.1)
mMRC dyspnea score ≥2, No. (%)[b]	2412 (62.1)	690 (85.1)	0	772 (17.4)
SGRQ total score, mean (SD)	38.4 (22.3)	46.7 (17.1)	8.6 (7.1)	14.5 (15.7)
SGRQ score ≥25, No. (%)	2705 (69.6)	765 (94.3)	0	863 (19.4)
Frequent exacerbations, No. (%)	640 (16.5)	87 (10.7)	5 (1.8)	110 (2.5)
Imaging visual estimates, No. (%)				
Emphysema (≥mild)[c]	3150 (81.1)	449 (55.4)	0	946 (21.3)
Bronchial wall thickening[c]	2757 (71.0)	416 (51.3)	0	572 (12.9)
Imaging quantitative estimates, mean (SD)				
Emphysema, % <−950 HU	12.5 (12.5)	1.6 (2.6)	3.8 (4.2)	1.9 (2.7)
Pi10, mm	2.68 (0.59)	2.48 (0.63)	2.12 (0.41)	2.06 (0.47)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; COPDGene, Genetic Epidemiology of COPD; FEV_1, forced expiratory volume in the first second of expiration; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HU, Hounsfield units; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council; Pi10, square root of the wall area of a hypothetical internal luminal perimeter of 10 mm; SGRQ, St George's Respiratory Questionnaire, a measure of respiratory quality of life (range, 0-100, with higher scores indicating worse quality of life).

[a] Self-reported.

[b] The mMRC dyspnea scale ranges from 0 to 4, with higher scores indicating greater dyspnea.

[c] Visual emphysema was defined by the presence of at least mild emphysema and bronchial wall thickness defined when read as definite thickening according to the Fleischner Society criteria.

for age, sex, race, body mass index, smoking status, pack-years of smoking, and baseline postbronchodilator FEV_1. Participants without COPD by the new criteria were treated as the reference group for all comparisons between classes. All analyses were performed with R version 4.2.2 (R Foundation for Statistical Computing). Two-sided α = .05 was deemed statistically significant.

Results

Participants

Table 1 and eTable 2 in Supplement 1 display the participant characteristics at enrollment. Of 10 305 participants enrolled in COPDGene, we excluded 107 who never smoked, 66 with

Figure 2. Reclassification of Participants by New Diagnostic Schema by Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage

GOLD stages 0 through 4 were defined using percentage predicted in accordance with the Global Lung Function Initiative global equations as greater than or equal to 80, greater than or equal to 50 to less than 80, greater than or equal to 30 to less than 50, and less than 30, respectively (vertical dashed lines). COPD indicates chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; and PRISm, preserved ratio impaired spirometry (defined by FEV_1/FVC ratio ≥0.70 [horizontal dashed line] and FEV_1 percentage predicted <80).

unacceptable spirometry result,[20] and 716 with CT scans that did not pass quality control. Of the remaining 9416 participants, 4108 (43.6%), 748 (7.9%), 1805 (19.2%), 1072 (11.4%), and 541 (5.7%) participants had GOLD disease severity grades 0 through 4, respectively; 1142 (12.1%) had preserved ratio impaired spirometry. The mean (SD) age of the cohort was 59.6 (9.0) years, 5035 (53.5%) were men, 4381 (46.5%) were women, 3071 (32.6%) were Black, and 6345 (67.4%) were White.

Associations of Criteria With Clinical Outcomes

eTable 3 in Supplement 1 shows significant associations between each of the individual major and minor diagnostic criteria and each clinical outcome in COPDGene. These associations remained significant even when the models for minor criteria were adjusted for airflow obstruction, demonstrating their added value over spirometry alone.

Reclassification

In COPDGene, 3884 of 4166 individuals (93.2%) with airflow obstruction were classified as having COPD with the new diagnostic schema. The new schema classified 811 of 5250 individuals (15.4%) without airflow obstruction as having COPD and 282 of 4166 individuals (6.8%) with airflow obstruction as no longer meeting COPD diagnostic categories (**Figure 2**; eTable 4 and eFigure 3 in Supplement 1). eFigures 4 and 5 in Supplement 1 demonstrate how participants met diagnostic criteria.

Participants newly classified as not having COPD according to the new diagnostic schema had normal lung function and minimal symptoms, and a very small proportion of participants were taking long-acting inhaled controller therapies (Table 1; eTable 5 in Supplement 1). Current spirometry-based guidelines for COPD require that patients have respiratory symptoms but do not specify how they should be quantified. When COPD was defined based on airflow obstruction and the presence of symptoms according to varying thresholds of the modified Medical Research Council and SGRQ scores, the new diagnostic schema did not miss a single individual regardless of how minimum symptoms were defined (eTable 6 in Supplement 1). Application of the new diagnostic

Table 2. Clinical and Imaging Characteristics of Participants Without Airflow Obstruction in COPDGene by Reclassification Status

	Reclassification within PRISm (n = 1142)		Reclassification within GOLD stage 0 (n = 4108)	
	No COPD according to new diagnostic schema (n = 840)	COPD by new diagnostic schema (n = 302)	No COPD according to new diagnostic schema (n = 3599)	COPD per new diagnostic schema (n = 509)
Demographics				
Age, mean (SD), y	57.6 (8.3)	56.2 (8.2)	57.0 (8.5)	54.4 (6.8)
Sex, No. (%)				
Male	398 (47.4)	124 (41.1)	1927 (53.5)	241 (47.3)
Female	442 (52.6)	178 (58.9)	1672 (46.5)	268 (52.7)
Race and ethnicity, No. (%)[a]				
Non-Hispanic Black	342 (40.7)	138 (45.7)	1389 (38.6)	291 (57.2)
Non-Hispanic White	498 (59.3)	164 (54.3)	2210 (61.4)	218 (42.8)
BMI, mean (SD)	31.7 (7.2)	32.1 (7.6)	28.9 (5.7)	29.5 (6.4)
Underweight (BMI <18.5), No. (%)	3 (0.4)	5 (1.7)	22 (0.6)	6 (1.2)
Healthy weight (BMI 18.5-24.9), No. (%)	142 (16.9)	48 (15.9)	915 (25.4)	129 (25.3)
Overweight (BMI 25.0-29.9), No. (%)	230 (27.4)	82 (27.2)	1369 (38.0)	152 (29.9)
Obese (BMI ≥30), No. (%)	465 (55.4)	167 (55.3)	1293 (35.9)	222 (43.6)
Pack-years of smoking, mean (SD)	40.6 (22.2)	47.7 (27.8)	36.1 (19.3)	45.0 (23.7)
Medications, No. (%)				
ICS/LABA	71 (8.5)	70 (23.2)	110 (3.1)	62 (12.2)
LABA	7 (0.8)	6 (2.0)	8 (0.2)	5 (1.0)
LAMA	36 (4.3)	48 (15.9)	51 (1.4)	29 (5.7)
Comorbidities, No. (%)				
Coronary artery disease[a]	79 (9.4)	3 (1.0)	162 (4.5)	5 (1.0)
Congestive heart failure[a]	44 (5.2)	9 (3.0)	56 (1.6)	1 (0.2)
Lung function, mean (SD)				
FEV_1 % predicted	71.2 (7.3)	68.7 (9.4)	97.9 (11.5)	95.0 (11.0)
Questionnaires				
Chronic bronchitis, No. (%)	58 (6.9)	145 (48.0)	248 (6.9)	265 (52.1)
mMRC dyspnea score, mean (SD)[b]	1.0 (1.3)	2.7 (1.1)	0.5 (1.0)	2.4 (1.1)
mMRC dyspnea score ≥2, No. (%)[b]	251 (29.9)	266 (88.1)	521 (14.5)	424 (83.3)
SGRQ total score, mean (SD)	21.6 (19.2)	50.5 (18.1)	12.9 (14.3)	44.4 (16.0)
SGRQ score ≥25, No. (%)	286 (34.0)	287 (95.0)	577 (16.0)	478 (93.9)
Frequent exacerbations, No. (%)	44 (5.2)	45 (14.9)	66 (1.8)	42 (8.3)
Imaging visual estimates, No. (%)				
Emphysema (≥mild)[c]	169 (20.1)	156 (51.7)	777 (21.6)	293 (57.6)
Bronchial wall thickening[c]	186 (22.1)	180 (59.6)	386 (10.7)	236 (46.4)
Imaging quantitative estimates, mean (SD)				
Emphysema, % <−950 HU	1.4 (2.5)	1.5 (2.6)	2.0 (2.7)	1.7 (2.5)
Pi10, mm	2.39 (0.52)	2.74 (0.63)	1.98 (0.42)	2.32 (0.57)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; COPDGene, Genetic Epidemiology of COPD; FEV_1, forced expiratory volume in the first second of expiration; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HU, Hounsfield units; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council; Pi10, square root of the wall area of a hypothetical internal luminal perimeter of 10 mm; PRISm, preserved ratio impaired spirometry; SGRQ, St George's Respiratory Questionnaire, a measure of respiratory quality of life (range, 0-100, with higher scores indicating worse quality of life).

[a] Self-reported.

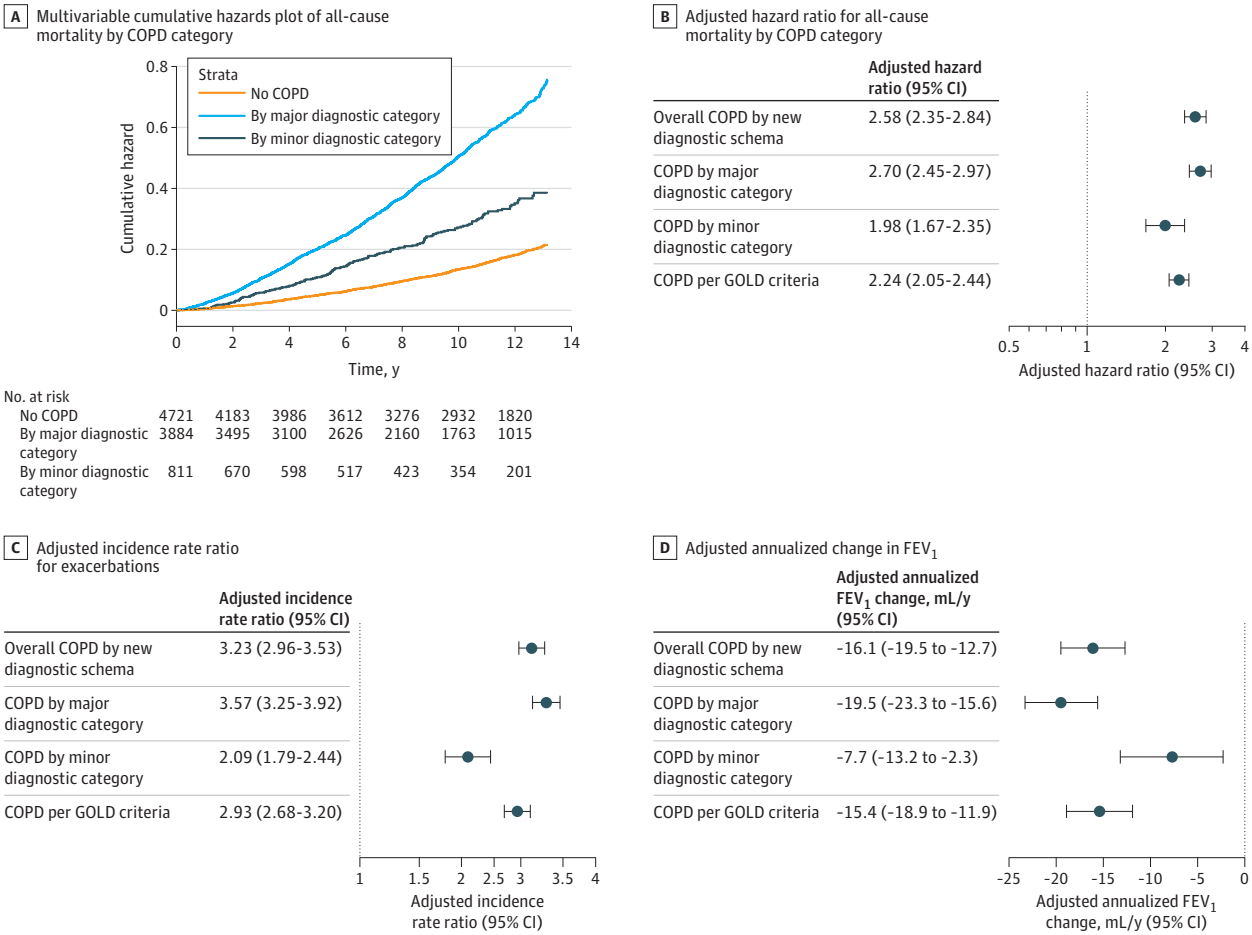
[b] The mMRC dyspnea scale ranges from 0 to 4, with higher scores indicating greater dyspnea.

[c] Visual emphysema was defined by the presence of at least mild emphysema and bronchial wall thickness defined when read as definite thickening according to the Fleischner Society criteria.

schema resulted in a diagnosis of COPD for more women (169 of 4723, 3.6%) and Black individuals (276 of 3366, 8.2%). Individuals with a diagnosis of COPD based on minor diagnostic category had a higher proportion of frequent exacerbations and were more symptomatic than those without COPD (Table 1).

Table 2 shows characteristics of participants who were reclassified from preserved ratio impaired spirometry or GOLD stage 0 as having COPD and those who were not reclassified and remained in their original diagnostic groups; 302 of 1142 participants (26.4%) were reclassified from preserved ratio impaired spirometry to COPD and 509 of 4108 (12.4%) were reclassified from GOLD stage 0 to COPD. Compared with individuals who remained in their original diagnostic group, participants who were reclassified as having COPD were more symptomatic, had a higher prevalence of chronic bronchitis,

Figure 3. Associations Between Clinical Outcomes and Chronic Obstructive Pulmonary Disease (COPD) Status by New Diagnostic Schema in Genetic Epidemiology of COPD



A, The median (25th-75th percentile) duration of observation was 11.4 (6.3-12.5) years for no COPD, 9.2 (4.9-12.1) years for the major diagnostic category, and 8.8 (3.8-12.0) years for the minor diagnostic category. B, Covariates in the Cox proportional hazards models included age, sex, race, body mass index (calculated as weight in kilograms divided by height in meters squared), smoking status, and pack-years of smoking. C, Covariates in the negative binomial regression models included age, sex, race, body mass index, smoking status, pack-years of smoking, and number of exacerbations in the previous 12 months. D, Covariates included in the generalized linear regression model included age, sex, race, body mass index, smoking status, pack-years of smoking, and baseline postbronchodilator FEV_1. Vertical dashed lines indicate reference value of 1 (B and C) or zero (D). For the new schema, no COPD by new schema was considered the reference category. For GOLD COPD, no airflow obstruction, which is defined by FEV_1/FVC ratio greater than or equal to 0.70, was considered the reference category and COPD was defined by FEV_1/FVC ratio less than 0.70. FEV_1 indicates forced expiratory volume in the first second of expiration; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

and had a higher frequency of exacerbations. Both groups with a new diagnosis were more likely to be receiving inhaled controller therapies.

Associations With Clinical Outcomes

During a median follow-up of 10.5 years (25th-75th percentile, 5.3-12.3 years) in COPDGene, 2681 of 9416 participants (28.5%) died. On multivariable analyses, with the new diagnostic schema, individuals identified as having COPD had greater all-cause mortality (46.9 vs 14.6 deaths per 1000 person-years; adjusted hazard ratio [HR], 2.58; 95% CI, 2.35-2.84), higher exacerbation frequency (53 vs 14 events per 100 person-years; adjusted incidence rate ratio, 3.23; 95% CI, 2.96-3.53), and a faster decline in FEV_1 (16.1 mL/y) compared with those without COPD (**Figure 3**). In adjusted analyses, participants who received a diagnosis of COPD solely by meeting the minor diagnostic category had greater all-cause mortality (27.4 vs 14.6 deaths per 1000 person-years; HR, 1.98; 95% CI, 1.67-2.35; $P < .001$), higher exacerbation frequency (41 vs 14 events per 100 person-years; adjusted incidence rate ratio, 2.09; 95% CI, 1.79-2.44; $P < .001$), and faster FEV_1 decline (7.7 mL/y; 95% CI, −13.2 to −2.3; $P = .006$) compared with participants without COPD (Figure 3).

Cause-specific mortality data in COPDGene were available until October 2017. During a median follow-up of 8.5 years (25th-75th percentile, 5.5-9.5 years), 1865 of 9416 individuals (19.8%) died and had mortality adjudication available. The respiratory cause-specific mortality rate was 0.5, 18.9, 1.5, and 22.3 per 1000 person-years in individuals without COPD, with COPD by new diagnostic schema, with

COPD by minor diagnostic category, and with COPD by major diagnostic category, respectively. Compared with participants without COPD, after adjusting for age, sex, race, body mass index, smoking status, and pack-years of smoking, the adjusted HR for respiratory mortality for individuals meeting the major diagnostic category was 29.4 (95% CI, 16.0-53.8; $P < .001$) and adjusted HR for individuals meeting the minor diagnostic category was 3.58 (95% CI, 1.56-8.20; $P = .003$).

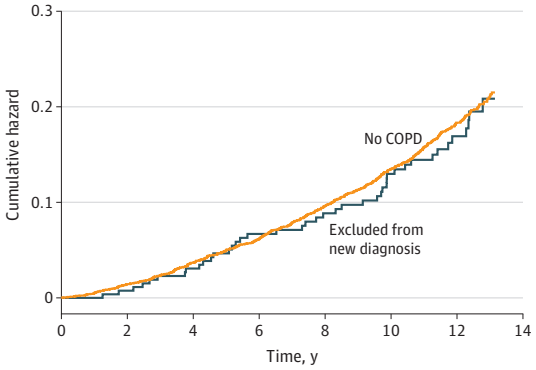
The clinical outcomes for individuals with airflow obstruction without respiratory symptoms or CT findings characteristic of COPD and who were therefore not classified as having COPD were similar for survival, exacerbation frequency, and lung function change compared with clinical outcomes for those without airflow obstruction (**Figure 4** and eTable 7 in Supplement 1).

Results of sensitivity analyses using alternative diagnostic criteria, use of the lower limit of normal for FEV_1/FVC, and changing CT and symptoms thresholds are shown in eTables 8 through 18 and eFigures 6 through 8 in Supplement 1. The use of the lower limit of normal for the FEV_1/FVC ratio instead of the fixed ratio resulted in fewer participants who met COPD diagnosis by major diagnostic category (3425 of 9416 [36.4%] with lower limit of normal vs 3884 [41.2%] with fixed ratio) and more participants who met the minor diagnostic category (945 [10.0%] vs 811 [8.6%]), but point estimates for associations with clinical outcomes were similar. Use of moderate emphysema or trace emphysema as the emphysema imaging criterion on CT instead of mild emphysema as the criterion resulted in a lower (622 [6.6%; eTable 12 in Supplement 1] with use of moderate vs 811 [8.6%] with use of mild emphysema criteria) or higher (1018 [10.8%; eTable 13 in Supplement 1] with trace vs 811 [8.6%] with mild) number of participants meeting the minor diagnostic category, respectively. Changing the symptom thresholds to lower than the GOLD-recommended treatment thresholds of SGRQ score greater than or equal to 25 or modified Medical Research Council score greater than or equal to 2 resulted in a higher number of participants who met the minor diagnostic category. eTable 19 in Supplement 1 shows that whether participants met major or minor diagnostic categories by imaging criteria, symptoms criteria, or both did not result in significant differences in associations with all-cause mortality, exacerbations, and FEV_1 change. eTable 20 in Supplement 1 shows that point estimates for clinical associations with all-cause mortality, exacerbations, and FEV_1 change were similar for each diagnostic category by subgroups of age, sex, and race. eTable 21 in Supplement 1 shows that the minor diagnostic category contained a high proportion of GOLD symptom groups B (high symptoms, 705 of 811 [86.9%] vs 1041 of 4026 [25.9%]) and E (high exacerbations, 87 of 811 [10.7%] vs 115 of 4812 [2.4%]) compared with individuals without COPD.

Evaluation in CanCOLD

Of 1561 participants enrolled in CanCOLD, we excluded 40 with no available spirometry and 180 with unavailable CT scans, resulting in 1341 participants. Application of the new diagnostic schema also resulted in substantial reclassification of participants in the CanCOLD cohort, which included a high proportion of individuals who never smoked (554 of 1341 [41.3%]) (eTables 2 and 22 in Supplement 1). In CanCOLD, 48 of 685 individuals (7.0%) without airflow obstruction were newly classified as having COPD and 105 of 656 individuals (16.0%) with airflow obstruction were reclassified as no longer having COPD (eTables 23 and 24 in Supplement 1). Associations with outcomes are shown in eTable 25 and eFigure 9 in Supplement 1. The mortality rate was low in this cohort (98 of 1341, 7.3%) and FEV_1 change was also low, and there were no statistically significant associations between the minor diagnostic category and all-cause mortality. Compared with individuals without COPD, for those with COPD there were no statistically significant associations between the major diagnostic category (10.5 vs 7.3 events per 1000 person-years; adjusted HR, 1.04; 95% CI, 0.67-1.63) and the minor diagnostic category (16.8 vs 7.3 deaths per 1000 person-years; adjusted HR, 1.36; 95% CI, 0.48-3.84) and all-cause mortality. Only the major diagnostic category was associated with FEV_1 decline (adjusted regression coefficient, −8.43 mL/y; 95% CI, −16.45 to −0.40). Compared with those without COPD, individuals classified as having COPD by the new schema and individuals classified using minor diagnostic category alone had higher exacerbation risk, 17.5 vs 6.7 events per 100 person-years (adjusted incidence rate ratio, 2.50; 95% CI, 2.02 to 3.11) and 16.1 vs 6.7 events per 100 person-years (adjusted incidence rate ratio, 2.09; 95% CI, 1.25-3.51; $P < .001$), respectively (eTable 25 in Supplement 1).

Figure 4. Associations Between the Category Excluded From Chronic Obstructive Pulmonary Disease (COPD) Diagnosis and Clinical Outcomes in the Genetic Epidemiology of COPD Study[a]



No. at risk

No COPD	4439	3920	3731	3370	3048	2721	1682
Excluded from new diagnosis	282	263	255	242	228	211	138

Multivariable cumulative hazards plot of all-cause mortality by COPD category. The median (25th-75th percentile) duration of observation was 11.4 (6.3-12.5) years for no COPD and 11.9 (9.9-12.8) years for the excluded category. Model adjusted for age, sex, race, body mass index (calculated as weight in kilograms divided by height in meters squared), smoking status, and pack-years of smoking.

[a]Reference category is individuals with no COPD according to new diagnostic schema.

Discussion

Using 2 large multicenter longitudinal cohorts of adults with varying risk of COPD, this study demonstrated that, compared with use of the GOLD diagnostic criteria for COPD, application of a new multidimensional COPD diagnostic schema resulted in inclusion of additional individuals with high mortality and respiratory morbidity and exclusion of individuals with airflow obstruction on spirometry without symptoms or evidence of structural lung disease. This new schema anchors the diagnosis of COPD to spirometry, if available, and includes additional elements (dyspnea, respiratory quality of life, and CT findings) to meet criteria for a COPD diagnosis. We used visual CT assessments as the primary criteria because these can be easily acquired in clinical practice; in contrast, quantitative imaging is not widely available and some measures, such as bronchial wall thickening, vary widely by the analytic software used. We also made allowance for symptoms to be apportioned to other diseases, such as cardiac disease, that could explain their presence as well as or better than the presence of COPD, in contrast to prior diagnostic schema that have stressed ruling out other diseases that may explain symptoms. The rule-out requirement can result in underdiagnosis because COPD often coexists with other diseases that cause similar respiratory symptoms.

The new diagnostic schema has implications for several existing diagnostic categories. Preserved ratio impaired spirometry has multiple causes, and a high proportion of individuals with preserved ratio impaired spirometry have substantial bronchial wall thickening on CT scans without meeting criteria for airflow limitation based on spirometry. Similarly, symptomatic individuals who smoke, are without airflow limitation, and meet criteria for GOLD stage 0 often have evidence of emphysema or bronchial wall thickening on chest CT. Recently, a new category, pre-COPD, was introduced for individuals without airflow obstruction and with structural abnormalities on chest CT that are not primarily attributed to other airways diseases such as asthma.[2] Some of these individuals will now be reclassified as having COPD according to the new diagnostic schema. Future studies should evaluate whether some of the imaging criteria can be substituted with other more easily available modalities such as chest radiography, which may detect severe emphysema.

Using the new diagnostic schema, this study found that a larger proportion of Black individuals were newly classified as having COPD compared with White individuals. This finding is consistent with previous findings of the higher prevalence of emphysema in Black individuals without airflow obstruction.[21] A small proportion of individuals with airflow limitation on spirometry (282 of 4166 [6.8%] in COPDGene and 105 of 656 [16.0%] in CanCOLD) were reclassified as having no COPD. In the absence of CT findings of emphysema or bronchial wall thickening and without substantial respiratory symptoms, these individuals may have other causes of airflow limitation, including age-related reductions in FEV_1/FVC or unreported asthma. The new schema did not miss a single individual who would have been classified as having COPD according to the GOLD recommendations regardless of how minimal symptoms were defined. Although spirometry continues to be a primary component in the diagnosis of COPD, the new schema allows a COPD diagnosis if spirometry is not available. For individuals who meet the diagnosis of COPD according to minor criteria alone, their current spirometry measurements may reflect a significant decline from their baseline pulmonary function although they do not meet existing diagnostic thresholds for airflow obstruction. As with any diagnostic schema, individuals who nearly meet any criterion or category threshold and those with higher grades of airflow obstruction who are no longer classified as having COPD by this new diagnostic schema should undergo close follow-up.

Our study has several strengths. In both cohorts, spirometry and imaging were acquired with stringent quality control. There was a high representation of Black individuals in COPDGene. CanCOLD included individuals who had never smoked, who are usually excluded from COPD studies.

Limitations

The study also has several limitations. First, the event rate for mortality in CanCOLD was low; nonetheless, we were able to confirm higher exacerbation risk in individuals who met the minor diagnostic category. CanCOLD also included matched subsets of participants with and without COPD, and therefore our results should be validated in a general population cohort. Second, we did not provide the usual metrics of model discrimination, such as the C-index, sensitivity, and specificity, because there is no true criterion standard for the diagnosis of COPD. Third, we were unable to evaluate the performance of the new criteria in underrepresented minority groups other than in Black individuals. Fourth, respiratory quality of life was assessed with the SGRQ score in COPDGene, which is not commonly acquired in clinical practice. However, prior studies have shown good agreement between an SGRQ score of 25 and a COPD Assessment Test score of 10,[18] which was used in CanCOLD. Fifth, the new schema requires CT imaging for assessment of emphysema and bronchial wall thickening, which may be subject to observer variation. In addition, although availability of CT scans may not be universal, more CT scans are currently being acquired worldwide than spirometry.[10] Sixth, using this new diagnostic schema, some patients with asthma may receive a diagnosis of COPD according to minor criteria, including bronchial wall thickening and the 3 symptom measures. Because there are no absolute criteria to fully distinguish asthma with chronic airflow obstruction from COPD, clinical judgment remains essential for the application of the new COPD diagnostic schema, as has been the case in existing diagnostic approaches.[2]

Conclusions

Using the new COPD diagnostic schema, compared with individuals classified as not having COPD, those with a new diagnosis of COPD had greater all-cause and respiratory-specific mortality, more frequent exacerbations, and faster FEV_1 decline. This new COPD diagnostic schema integrates multidimensional

assessments to include additional individuals with high respiratory morbidity and to exclude individuals with airflow obstruction who do not have respiratory symptoms or evidence of structural lung disease.

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COPDGene 2025 Diagnosis Working Group and CanCOLD Investigator Authors: Surya P. Bhatt, MD, MSPH; Ehsan Abadi, PhD; Antonio Anzueto, MD; Sandeep Bodduluri, PhD; Richard Casaburi, PhD, MD; Peter J. Castaldi, MD, MSc; Michael H. Cho, MD; Alejandro P. Comellas, MD; Douglas J. Conrad, MD, MS; Jeffrey L. Curtis, MD; Chandra Dass, MBBS, DMRD; Dawn L. DeMeo, MD, MPH; Mark T. Dransfield, MD; Raul San José Estépar, PhD; Eric L. Flenaugh, MD; Marilyn G. Foreman, MD, MS; Spyridon Fortis, MD, PhD, MS; Arnav Gupta, MD; MeiLan K. Han, MD, MS; Nicola A. Hanania, MD, MS; Craig P. Hersh, MD, MPH; John E. Hokanson, PhD; Stephen M. Humphries, PhD; Miranda Kirby, PhD; Ken M. Kunisaki, MD, MS; Pei Zhi Li, MSc; David A. Lynch, MB; Neil R. MacIntyre, MD; Barry J. Make, MD; David M. Mannino, MD; Fernando J. Martinez, MD, MS; Charlene E. McEvoy, MD, MPH; Bruce E. Miller, PhD; Matthew Moll, MD, MPH; Arie Nakhmani, PhD; John D. Newell Jr, MD; Katherine A. Pratte, MSPH, PhD; Elizabeth A. Regan, MD, PhD; Joseph M. Reinhardt, PhD; Stephen I. Rennard, MD; Harry B. Rossiter, PhD; Matthew J. Strand, PhD; Rajat Suri, MD, MS; Emily S. Wan, MD, MPH; Christine H. Wendt, MD; Gloria E. Westney, MD, MSc; Carla G. Wilson, MS; Robert A. Wise, MD; Kendra A. Young, PhD, MSPH; Wan C. Tan, MBBS, MD; Edwin K. Silverman, MD, PhD; James D. Crapo, MD.

Affiliations of COPDGene 2025 Diagnosis Working Group and CanCOLD Investigator Authors: Division of Pulmonary, Allergy and Critical Care Medicine, University of Alabama at Birmingham, Birmingham (Bhatt, Bodduluri, Dransfield); Center for Lung Analytics and Imaging Research, University of Alabama at Birmingham, Birmingham (Bhatt, Bodduluri, Nakhmani); Department of Radiology, Duke University Medical Center, Durham, North Carolina (Abadi); University of Texas Health, San Antonio (Anzueto); South Texas Veterans Health Care System, San Antonio (Anzueto); Respiratory Research Center, Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, California (Casaburi, Rossiter); Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, Massachusetts (Castaldi, Cho, DeMeo, Hersh, Moll, Wan, Silverman); Division of Pulmonary, Critical Care and Occupational Medicine, University of Iowa, Iowa City (Comellas, Fortis); University of California, San Diego, La Jolla (Conrad, Suri); Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor (Curtis); VA Ann Arbor Healthcare System, Ann Arbor, Michigan (Curtis); Temple University Hospital, Philadelphia, Pennsylvania (Dass); Department of Radiology, Brigham and Women's Hospital, Boston, Massachusetts (San José Estépar); Division of Pulmonary and Critical Care Medicine, Morehouse School of Medicine, Atlanta, Georgia (Flenaugh, Foreman, Westney); Division of Pulmonary, Critical Care and Sleep Medicine, National Jewish Health, Denver, Colorado (Gupta, Make, Crapo); Division of Pulmonary and Critical Care, University of Michigan, Ann Arbor (Han); Section of Pulmonary and Critical Care Medicine, Baylor College of Medicine, Houston, Texas (Hanania); Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora (Hokanson, Young); Department of Radiology, National Jewish Health, Denver, Colorado (Humphries, Lynch); Department of Physics, Toronto Metropolitan University, Toronto, Ontario, Canada (Kirby); Minneapolis Veterans Affairs Health Care System, Minneapolis, Minnesota (Kunisaki, Wendt); Montreal Chest Institute, McGill University Health Center Research Institute, McGill University, Montreal, Quebec, Canada (Li); Duke University Medical Center, Durham, North Carolina (MacIntyre); COPD Foundation, Miami, Florida (Mannino, Miller); Division of Pulmonary, Allergy, and Critical Care Medicine, University of Massachusetts Chan Medical School, Worcester (Martinez); HealthPartners Institute, St Paul, Minnesota (McEvoy); Department of Electrical and Computer Engineering, University of Alabama at Birmingham, Birmingham (Nakhmani); Department of Radiology, University of Iowa, Iowa City (Newell); Division of Biostatistics and Bioinformatics, National Jewish Health, Denver, Colorado (Pratte, Strand, Wilson); Division of Rheumatology, National Jewish Health, Denver, Colorado (Regan); Department of Biomedical Engineering, University of Iowa, Iowa City (Reinhardt); Division of Pulmonary, Critical Care and Sleep Medicine, University of Nebraska Medical Center, Omaha (Rennard); Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, University of Minnesota, Minneapolis (Wendt); Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland (Wise); Centre for Heart Lung Innovation, St Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada (Tan).

Author Contributions: Dr Bhatt had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Silverman and Crapo served as co-senior authors.
Study concept and design: Bhatt, Silverman, Crapo.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Bhatt.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Bhatt, Li.
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Participated in the recurring virtual meetings concerning the manuscript and process: Foreman.
Recruited participants: McEvoy.
Provided critical comments and suggested edits: Miller.

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AstraZeneca, Genentech, Cheisi, and Regeneron to her institution outside the submitted work; and advisory and speaker fees from Sanofi and Regeneron. Dr Hersh reported grants from NHLBI to his institution during the conduct of the study; grants from Bayer to his institution; and consulting fees from Apogee Therapeutics, Chiesi, Genentech, Ono Pharma, Sanofi, Takeda, and Verona Pharma outside the submitted work. Dr Kirby reported consulting fees from VIDA Diagnostics outside the submitted work. Dr Kunisaki reported grants from NIH during the conduct of the study and fees from Nuvaira for data and safety monitoring board activities outside the submitted work. Dr Lynch reported grants from NHLBI during the conduct of the study and consulting fees from Sanofi outside the submitted work. Dr MacIntyre reported a contract from COPDGene during the conduct of the study and consulting fees from Inogen outside the submitted work. Dr Make reported grants from NHLBI provided to and controlled by National Jewish Health for COPDGene study data collection analysis and his salary during the conduct of the study; continuing medical education activity for Mt Sinai, WebMD, Temple University, Eastern Pulmonary Conference, Pri-Med, and American College of Chest Physicians outside the submitted work; disease-state presentations for GSK and Verona Pharma; providing a medical presentation for Boston University; serving on the medical advisory board for Sanofi, Verona Pharma, Regeneron, GSK, and AstraZeneca; and serving on the data and safety monitoring board for Mt Sinai and Baystate Medical Center. Dr Mannino reported consulting fees from AstraZeneca, GSK, Chiesi, Regeneron, Amgen, Roche, UpToDate, and Schlesinger Law Firm outside the submitted work. Dr Martinez reported grants from AstraZeneca (a partner in the SPIROMICS program and NHLBI CAPTURE validation study); grants from Chiesi (a partner in the SPIROMICS program); grants and fees for consulting from GSK (a partner in the SPIROMICS program and NHLBI CAPTURE validation study); grants and consulting fees from Sanofi/Regeneron (partners in the SPIROMICS program); grants from NHLBI; grants from DevPro and Novartis for a phase 2 COPD study; conducting a COPD disease-state study without honorarium for Roche during the conduct of the study; conducting continuing medical education for UpToDate outside the submitted work; holding a patent for CAPTURE licensed to Weill Cornell Medicine; and serving on an event adjudication committee for Medtronic. Dr McEvoy reported grants from NHLBI to her institute during the conduct of the study; and grants from GSK, AstraZeneca, and the Centers for Disease Control and Prevention to her institute outside the submitted work. Dr Miller reported consulting fees from the COPD Foundation and owning stock in GSK outside the submitted work. Dr Moll reported grants from NHLBI during the conduct of the study; having a contract with Genentech; and consulting fees from Sanofi, Verona Pharma, Dialectica, Axon Advisors, Expert Witness, 2nd.MD, and Thea Health outside the submitted work. Dr Newell reported grants from NIH during the conduct of the study; consulting fees from VIDA Diagnostics; royalties from Elsevier outside the submitted work; having patents pending for the University of Iowa and VIDA Diagnostics; holding patents for VIDA Diagnostics; owning stock and stock options with VIDA Diagnostics; and serving as the medical advisor to VIDA Diagnostics. Dr Pratte reported grants from National Jewish Health (salary funded by awards R01 HL137995 and R01 HL129937) during the conduct of the study. Dr Regan reported grants from NHLBI during the conduct of the study. Dr Reinhardt reported grants from NIH to the University of Iowa, owning stock in VIDA Diagnostics, and grants from the Roy J. Carver Charitable Trust to the University of Iowa during the conduct of the study; and expert witness fees from Auris Health outside the submitted work. Dr Rennard reported serving as medical director for the Alpha-1 Foundation; consultation fees from RespirAI, RS Biotherapeutics, Roche Diagnostics, Verona Pharma, and Beyond Air outside the submitted work; serving on the advertisement board for Sanofi/Regeneron; holding a patent for diagnostics for COPD exacerbation, with royalties paid to the University of Nebraska; and serving as founder and president of Great Plains Biometric, LLC, a spinoff company developing wearable diagnostics. Dr Rossiter reported grants from NIH (R01 HL166850, R01 HL151452, and R01 HL153460), University of California Office of the President/Tobacco Related Disease Research Program (T31IP1666), and the Department of Defense/US Army Medical Research Acquisition Activity (HT9425-24-1-0249); conducting clinical research for GSK, Genentech, Mezzion, Regeneron, Respira, United Therapeutics, and Intervene Immune; consulting fees from Roche and Duke University (for NIH/1OT2HL156812) outside the submitted work; and nonfinancial support from the University of Leeds outside the submitted work. Dr Strand reported grants from NIH during the conduct of the study. Dr Suri reported serving on the advisory panel for Verona Pharma outside the submitted work. Dr Wan reported serving on the advisory panel for Verona Pharma and serving as a speaker for MJH outside the submitted work. Dr Wise reported consulting fees from Kamada; grants from Chiesi and Sanofi/Regeneron; serving on a clinical end point committee for BIPI; and serving on an advisory committee for AstraZeneca outside the submitted work. Dr Young reported grants from NIH/NHLBI during the conduct of the study. Dr Silverman reported grants from NIH during the conduct of the study and grants from Bayer and Northpond Labs outside the submitted work. No other disclosures were reported.

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