Respiratory Symptoms Items from the COPD Assessment Test Identify Ever-Smokers with Preserved Lung Function at Higher Risk for Poor Respiratory Outcomes

An Analysis of the Subpopulations and Intermediate Outcome Measures in COPD Study Cohort

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Abstract

Rationale: Ever-smokers without airflow obstruction scores greater than or equal to 10 on the COPD Assessment Test (CAT) still have frequent acute respiratory disease events (exacerbation-like), impaired exercise capacity, and imaging abnormalities. Identification of these subjects could provide new opportunities for targeted interventions.

Objectives: We hypothesized that the four respiratory-related items of the CAT might be useful for identifying such individuals, with discriminative ability similar to CAT, which is an eight-item questionnaire used to assess chronic obstructive pulmonary disease impact, including nonrespiratory questions, with scores ranging from 0 to 40.

Methods: We evaluated ever-smoker participants in the Subpopulations and Intermediate Outcomes in COPD Study without airflow obstruction ($FEV_1/FVC \geq 0.70$; FVC above the lower limit of normal). Using the area under the receiver operating characteristic curve, we compared responses to both CAT and the respiratory symptom–related CAT items (cough, phlegm, chest tightness, and breathlessness) and their associations with longitudinal exacerbations. We tested agreement between the two strategies

(κ statistic), and we compared demographics, lung function, and symptoms among subjects identified as having high symptoms by each strategy.

Results: Among 880 ever-smokers with normal lung function (mean age, 61 yr; 52% women) and using a CAT cutpoint greater than or equal to 10, we classified 51.8% of individuals as having high symptoms, 15.3% of whom experienced at least one exacerbation during 1-year follow-up. After testing sensitivity and specificity of different scores for the first four questions to predict any 1-year follow-up exacerbation, we selected cutpoints of 0–6 as representing a low burden of symptoms versus scores of 7 or higher as representing a high burden of symptoms for all subsequent comparisons. The four respiratory-related items with cutpoint greater than or equal to 7 selected 45.8% participants, 15.6% of whom experienced at least one exacerbation during follow-up. The two strategies largely identified the same individuals (agreement, 88.5%; $\kappa = 0.77$; $P < 0.001$), and the proportions of high-symptoms subjects who had severe dyspnea were similar between CAT and the first four CAT questions (25.9% and 26.8%, respectively), as were the proportions reporting impaired quality of life (66.9% and 70.5%, respectively) and short walking distance (22.4% and 23.1%, respectively). There was no difference in area under the receiver operating characteristic curve to predict 1-year follow-up exacerbations (CAT score ≥ 10, 0.66; vs. four respiratory items from

CAT ≥ 7 score, 0.65; $P = 0.69$). Subjects identified by either method also had more depression/anxiety symptoms, poor sleep quality, and greater fatigue.

Conclusions: Four CAT items on respiratory symptoms identified high-risk symptomatic ever-smokers with preserved spirometry as

well as the CAT did. These data suggest that simpler strategies can be developed to identify these high-risk individuals in primary care.

Keywords: obstructive lung disease; health status; questionnaires; symptoms; quality of life

The presence of airflow obstruction (defined by FEV_1/FVC ratio >0.7) is one of the requirements for the diagnosis of chronic obstructive pulmonary disease (COPD) (1). However, there is growing recognition of the presence of chronic bronchitis symptoms (2), physical activity limitation, and acute respiratory events (exacerbation-like episodes) (3, 4) among ever-smokers without airflow obstruction so defined (2, 3, 5).

The COPD Assessment Test (CAT) is an eight-item questionnaire that includes not only items focused on respiratory symptoms (first four questions) but also questions regarding activity limitation, energy, and sleep (last four questions) (6). Woodruff and colleagues recently demonstrated that the well-validated CAT, using the cutpoint of greater than or equal to 10 points as recommended by Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, can reasonably discriminate those individuals at risk of exacerbations (3). The CAT is indicated for use in patients meeting a spirometry-based diagnosis of COPD, however, and is not widely used in primary care, making it necessary to develop and test novel strategies for identification of these high-risk subjects.

In the present study, using data from the same cohort, we tested if these subjects with normal airflow but at high risk for respiratory events could be more easily identified using selected questions from the CAT, a strategy with potential for wider use in primary care. Specifically, we hypothesized that among ever-smokers without spirometrically defined airflow obstruction, rating of respiratory symptoms using the first four items (respiratory symptom–related questions) from the CAT would identify similar individuals and would perform similarly to the CAT in the ability to identify subjects with increased risk for acute respiratory events.

Methods

Study Design and Participants
This is a cross-sectional and longitudinal analysis of data from selected participants in the National Institutes of Health–sponsored Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) (7), a prospective cohort study in which researchers enrolled 2,981 participants with the goals of identifying new COPD subgroups and intermediate markers of

disease progression. SPIROMICS included subjects aged 40–80 years in different strata, including healthy never-smokers (≤ 1 pack-year of tobacco smoking history) and current or former smokers with a smoking history of greater than 20 pack-years, with or without obstructive lung disease.

For the present analyses, we included ever-smoker (current or former) SPIROMICS participants without airflow obstruction (defined as post-bronchodilator $FEV_1/FVC \geq 0.70$ and FVC greater than the lower limit of normal). SPIROMICS was approved by the institutional review boards at all participating centers, including the University of Michigan, where the present analyses were performed. All participants provided written informed consent.

Measurements
Participants provided information on demographics, smoking status (former or current) and history, and physician-diagnosed diseases via standardized questionnaires. All participants had baseline spirometry measures, for which SPIROMICS uses post-bronchodilator spirometry values, with spirometry performed following American Thoracic Society recommendations on a

pneumotachograph spirometer, with predicted values based on Hankinson reference equations (8).

At enrollment, we obtained information on the following markers of respiratory impairment: presence of chronic bronchitis symptoms (defined as cough and phlegm production for ≥3 consecutive mo per yr for 2 or more yr, based on the response to the questions on cough and phlegm production from the American Thoracic Society Respiratory Epidemiology Questionnaire) (9), dyspnea severity using the modified Medical Research Council dyspnea scale (mMRC) score (10) (further categorized as 0–1 and 2–4 as per GOLD recommendations [1]), distance walked in a 6-minute walk test (used in analyses as a continuous variable or further categorized as <250 m and ≥250 m) (5), respiratory events or exacerbations in the 1 year prior to enrollment, and health-related quality-of-life metrics using the St. George's Respiratory Questionnaire (continuous variable and with scores categorized as ≤25 and >25) (11).

We also collected information on the presence of anxiety and depression symptoms using the Hospital Anxiety and Depression Scale (further categorized as score ≥8 representing high symptoms) (12), sleep quality measured by the Pittsburgh Sleep Quality Index (with score >5 indicating poor sleep quality) (13), fatigue using the Functional Assessment of Chronic Illness Therapy–Fatigue scale (with values ≤33 considered as significant fatigue) (14), and exercise tolerance using the Veterans Specific Activity Questionnaire (with predicted ability less than 5 metabolic equivalents being considered as low exercise tolerance) (15). Participants in the present analysis were followed every 3 months for 1 year to identify acute respiratory disease events (hereafter described as exacerbations), defined as use of antibiotic agents, systemic glucocorticoids, or both or as need for unplanned office, emergency department, or admissions because of respiratory symptoms (exacerbations requiring health care use) (7).

To identify subjects with a high burden of symptoms, we used the CAT, a validated health status questionnaire with recall time of 6 weeks, which includes eight questions, each rated on a 5-point scale (6). CAT is a copyrighted instrument used in SPIROMICS under license agreement with

its proprietor. We selected CAT as the definition of symptom burden because it is part of the GOLD recommendations (1).

For the present analyses, we compared two different strategies to identify high-symptoms subjects. In the first, we used the CAT (scale 0–40, with 0–9 classified as low symptom burden and ≥10 as high symptom burden, as recommended by GOLD strategy document) (1). In the alternate method, we used only the first four items (respiratory symptom–related questions) of the CAT, which resulted in a score of 0–20. We identified a cutpoint for the four questions testing associations between all possible scores and based on its associations with any 1-year follow-up exacerbation. We took this approach because there are no normative values derived from four items, but for the complete instrument (16), CAT questionnaires were applied at enrollment by trained research coordinators who were unaware of the planned analyses.

Statistical Analysis

Descriptive statistics were based on proportions and means (with SD), according to the variable of interest. The agreement between CAT and the respiratory question subset of CAT to identify similar groups of participants as having a high burden of symptoms was calculated using the κ statistic. To compare both CAT and the first four questions with the predefined cutpoints, we tested their association with other measures of health impact and impairment, which were selected as the reference standard.

For a cross-sectional comparison, we tested associations with health-related quality of life, which we measured by St. George's Respiratory Questionnaire total score, walking distance, and baseline exacerbations. During longitudinal follow-up, we used as a reference the associations with exacerbations/acute respiratory events during 1-year follow-up. The association was measured by the area under the receiver operating characteristic curve (AUC), and the AUCs were compared. The analysis assumed an AUC of 0.68 for the association between CAT and any exacerbation during the 1-year follow-up, and, using a probability of type I error of 5% and a power of 80% to detect a 5% difference between CAT and the respiratory item subset, inclusion of at least 707 participants would allow detection of a difference of 0.05 between AUCs.

We also calculated the sensitivity and specificity of CAT and the first four items to predict any exacerbation during follow-up. Finally, in prespecified analyses, we tested if the strategies had similar performance across different demographic groups defined by age, sex, and race. All analyses were conducted using STATA version 12 software (StataCorp, College Station, TX), and a P value less than 0.05 was considered significant.

Results

We included 880 ever-smokers with preserved lung function among the 2002 SPIROMICS participants. Figure E1 in the online supplement shows the flow of participants through the present study. Overall, half of the ever-smokers with preserved lung function were women, one-fourth were of African American race, and half were current smokers. Participants described the presence of chronic bronchitis symptoms (18.6%), dyspnea with mMRC score greater than or equal to 2 (15.5%), and short walking distance (15.9%). Among different comorbid conditions reported were obesity (defined as body mass index [BMI] ≥30 kg/m^2) in 40% and asthma in 18% (Table E1).

After testing sensitivity and specificity of different scores of the first four questions to predict any 1-year follow-up exacerbation, we selected scores of 0–6 as a low burden of symptoms and 7 or higher as a high burden of symptoms, and these were used as cutpoints for all subsequent comparisons. The sensitivity and specificity for all possible cutpoints are presented in Table E2. Using the CAT with a cutpoint of greater than or equal to 10 points, we identified 456 participants with high symptom burden. Using the four respiratory items of CAT only, score greater than or equal to 7 points identified 403 subjects with high symptom burden. The agreement was 88.5% (κ = 0.77; P < 0.001). Both groups had similar demographic and clinical characteristics (Table 1). At enrollment, the proportion of high-symptoms subjects who had severe dyspnea was similar between the CAT and the first four CAT questions (25.9% and 26.8%, respectively), as were the frequencies with which subjects reported impaired quality of life (66.9% and 70.5%, respectively) and had short walking distance (22.4% and 23.1%, respectively) (Table 2).

Table 1. Description of participants with preserved spirometry identified as high symptom burden by two different methods (n = 880)

	Identified by CAT ≥10 points (*n = 456*)	Identified by Respiratory Questions of CAT ≥7 points (*n = 403*)	*P* Value
Demographics			
Age, yr, mean (SD)	59.4 (9.9)	59.1 (9.7)	0.74
Female sex, %	55.7	56.6	0.78
African American race, %	33.8	33.5	0.92
BMI, kg/m^2, mean (SD)	29.8 (5.4)	29.8 (5.4)	1
Smoking history			
Pack-years, mean (SD)	46.1 (26.4)	45.8 (26.6)	0.59
Currently smoking, %	57.2	58.3	0.74
Lung function			
FEV$_1$, L, mean (SD)	2.61 (0.70)	2.61 (0.70)	1
FEV$_1$, % predicted, mean (SD)	92.0 (14.7)	92.2 (14.0)	0.38
Comorbid conditions, %			
Obesity (BMI ≥30 kg/m^2)	48.7	48.1	0.85
Asthma	27.6	29.3	0.58
Diabetes	19.3	19.1	0.94
Coronary artery disease	5.9	5.7	0.99
Markers of respiratory impact, %			
Any respiratory event prior to enrollment	22.8	24.6	0.53
Chronic bronchitis symptoms*	30.9	35.0	0.20
mMRC dyspnea score ≥2[†]	25.9	26.8	0.76
Short distance during 6-min walk test[‡]	22.4	23.1	0.81
Impaired quality of life measured by SGRQ total score[§]	66.9	70.5	0.25
Any of the above	80.7	83.6	0.26
CAT score, mean (SD)	17.9 (6.4)	18.3 (6.7)	0.20

Definition of abbreviations: BMI = body mass index; CAT = COPD Assessment Test; mMRC = modified Medical Research Council dyspnea scale; SGRQ = St. George's Respiratory Questionnaire.
P value represents comparison of means or proportions among those identified by each strategy.
*Chronic bronchitis was defined as cough and phlegm production for at least 3 consecutive months per year for at least 2 years.
[†]Dyspnea was defined as mMRC score greater than or equal to 2.
[‡]Short walking distance was defined as distance walked in 6 minutes less than 250 m.
[§]Impaired quality of life was defined as an SGRQ total score greater than 25.

Among participants identified with high symptom burden by CAT, 15.1% had at least one exacerbation during the first year of follow-up. For those identified by the respiratory symptoms questions of CAT, the frequency was 14.1%. The association between high symptom burden by CAT (score ≥10 points) and any exacerbation during follow-up had an AUC of 0.66, whereas for the first four CAT questions (score ≥7 points), the AUC was 0.65 (*P* = 0.69 for comparison of the two curves).

When exacerbations were classified by use of antibiotics/steroids, the AUCs were 0.65 and 0.65, respectively (*P* = 0.76 for comparison of both curves). For exacerbations requiring health care use, the AUCs were 0.65 and 0.64, respectively (*P* = 0.58 for comparison of the two curves) (Table 2). A cutpoint of 10 using CAT was associated with a sensitivity of 0.80 and a specificity of 0.52 for any exacerbation, whereas the cutpoint of 7 for the selected respiratory items of CAT resulted in a sensitivity of 0.73 and a specificity of 0.58.

Similar associations were found for the presence of different markers of respiratory-related impairment at enrollment. The association between high symptom burden by CAT (score ≥10 points) and impaired quality of life at enrollment showed an AUC of 0.81, whereas for the first four CAT questions (score ≥7 points), the AUC was 0.81 (*P* = 0.87 for comparison of both curves). The association of CAT score greater than or equal to 10 points and short walking distance showed an AUC of 0.62, whereas for the selected CAT items (score ≥7 points), the AUC was 0.62 (*P* = 0.86 for comparison of both curves) (Table 2).

Because CAT includes questions on health status that are not necessarily respiratory related, we also tested whether subjects identified with high symptoms (using any strategy) could also have other markers of health impairment not related exclusively to respiratory function. We found that, compared with those in the low-symptom category, subjects reported with higher frequency a high burden of anxiety and depression symptoms, more frequently had low ability to exercise, and reported fatigue and had poor-quality sleep with higher frequency. These additional health concerns had a similar frequency in the high-symptom group, regardless of the strategy used to identify them (CAT or respiratory questions of CAT) (Table 3).

The two scoring strategies had an agreement of 88.5% in subject classification (400 subjects classified as low risk and 379 as high risk by both strategies), leaving 101 discordant subjects. The majority of discordant cases (n = 77) were subjects classified as having low symptoms on the basis of the first four questions of CAT but as having high symptoms using the CAT questionnaire. When we compared these 77 discordant subjects with the 400 judged as having low symptoms on the basis of both

Table 2. Use of two strategies used to identify subjects with high symptom burden to predict quality of life, physical activity, and exacerbations (n = 880)

	CAT ≥10 points AUC (95% CI)	Respiratory Questions of CAT ≥7 points AUC (95% CI)	P Value
Cross-sectional associations			
Any respiratory event prior to enrollment	0.66 (0.62–0.70)	0.67 (0.63–0.71)	0.77
Dyspnea*	0.70 (0.67–0.74)	0.69 (0.66–0.73)	0.59
Short distance in 6-min walk test†	0.62 (0.58–0.66)	0.62 (0.57–0.66)	0.86
Impaired quality of life measured by SGRQ total score‡	0.81 (0.79–0.83)	0.81 (0.78–0.83)	0.87
Longitudinal exacerbations (during 1-yr follow-up)			
Any	0.66 (0.61–0.70)	0.65 (0.60–0.70)	0.69
Any requiring steroids or antibiotics	0.65 (0.60–0.70)	0.65 (0.60–0.71)	0.76
Any requiring health-care use	0.65 (0.60–0.69)	0.64 (0.58–0.69)	0.58

Definition of abbreviations: AUC = area under the receiver operating characteristic curve; CAT = COPD Assessment Test; CI = confidence interval; SGRQ = St. George's Respiratory Questionnaire.
P value is for the comparison of AUCs.
*Dyspnea was defined as modified Medical Research Council dyspnea scale score greater than or equal to 2.
†Short walking distance was defined as distance walked in 6 minutes less than 250 m.
‡Impaired quality of life was defined as SGRQ total score higher than 25.

strategies, they were more frequently current smokers, had higher BMI, and more frequently were of African American race (Table E3). We found that compared with results for male participants, when applied to females, both strategies had higher sensitivity but lower specificity. Similarly, higher sensitivity and lower specificity were found for both strategies in African American participants (compared with whites) and current smokers (versus former smokers). CAT also had slightly higher sensitivity than CAT respiratory

questions when applied to women and African Americans (Table E4).

Finally, we tested if just asking participants about the presence of dyspnea (mMRC greater than or equal to 2), the alternate way to identify subjects with high-symptoms COPD according to the GOLD recommendations (1), could identify subjects similarly to the four respiratory-related items of CAT. We found that the AUC of 0.59 (95% confidence interval, 0.60–0.70) to predict 1-year exacerbations was significantly lower when using mMRC

greater than or equal to 2 (P = 0.04 for comparison of the two curves).

Discussion

We found that the four respiratory symptom items of the CAT, using a threshold of 7 points or higher, identified a group of former or current smokers with preserved spirometry similar to those selected using the CAT with a threshold 10 points or higher. Both groups had similar symptom burden, and both strategies were comparable in their prediction of respiratory events (exacerbations) during longitudinal follow-up. These findings confirm previous reports about the high frequency of symptoms of respiratory impairment among ever-smokers who do not satisfy the current spirometric definition of COPD (2, 3, 5), and they also provide a proof of the concept that simpler strategies can be developed and tested to identify these subjects in primary care. For example, in the present study, the decision about the cutpoint selection when using the selected items of CAT was based on a trade-off between sensitivity and specificity of all possible scores in the participant population, but it is unclear if this can be extrapolated to other studies without further validation.

The current definition of COPD relies on the presence of spirometric measures of airflow obstruction (1). However, it is clear that not all current and former smokers

Table 3. Additional markers of health impairment among participants with preserved lung function identified as high symptom burden by two different methods (n = 880)

	Identified by CAT ≥10 points (n = 456)	Identified by Respiratory Questions of CAT ≥7 points (n = 403)	P Value
High burden of anxiety symptoms*	42.8	44.9	0.53
High burden of depression symptoms†	24.3	25.8	0.61
Poor sleep quality‡	63.2	67.5	0.18
Fatigue§	41.9	41.9	1.0
Low exercise tolerance‖	59.9	60.8	0.78

Definition of abbreviation: CAT = COPD Assessment Test.
Data shown as percentage. *P* value represents comparison of means or proportions among those identified by each strategy.
*High burden of anxiety symptoms was defined as Hospital Anxiety and Depression Scale anxiety score greater than or equal to 8.
†High burden of depression symptoms was defined as Hospital Anxiety and Depression Scale depression score greater than or equal to 8.
‡Poor sleep quality was defined as Pittsburgh Sleep Quality Inventory score greater than 5.
§Fatigue defined was defined as Functional Assessment of Chronic Illness Therapy–Fatigue scale score greater than or equal to 33.
‖Low exercise was defined as Veterans Specific Activity Questionnaire score less than 5 metabolic units.

without airflow obstruction are free of a disease. Growing evidence from several cohorts suggests that individuals with smoking history without airflow obstruction may still have significant respiratory symptoms and are at risk for poor outcomes, in some cases similar to those of individuals with established airflow obstruction. Efforts to prevent further clinical deterioration and poor outcomes among smokers with preserved spirometry should start by testing different tools to identify this at-risk population.

SPIROMICS investigators have previously demonstrated that the well-validated CAT, using the cutpoint of 10 points or o higher as recommended by GOLD guidelines, can reasonably discriminate those individuals at risk of exacerbations (3), findings that are aligned with what is known about subjects with established COPD. We extend these findings by showing that using the respiratory questions of CAT with a cutpoint score of 7 points or higher has similar associations with clinical descriptors of respiratory impairment (short walking distance, more severe dyspnea, impaired quality of life) and longitudinal exacerbations, as shown by similar AUCs using any of those strategies.

The differences between subjects scoring less than 7 points versus those scoring 7 points or higher on the four respiratory questions of CAT are similar in magnitude and direction to those previously reported by Woodruff and coworkers (3), as shown in Table E5. Our findings provide evidence that using only respiratory symptom–related questions could facilitate identification of these subjects by busy primary care providers, expanding the available tools for identification of ever-smokers without airflow obstruction but at risk of poor outcomes. In the present study, CAT and selected CAT respiratory questions not only had a similar overall classification of high-symptoms subjects, as measured by the AUC, but also had very similar sensitivity and specificity. CAT was associated with a sensitivity of 0.80 and a specificity of 0.52 for any 1-year follow-up exacerbation, whereas the respiratory questions of the CAT had a sensitivity of 0.73 and a specificity of 0.58.

CAT and the selected CAT respiratory questions exhibited significant agreement in determining subjects with high burden of symptoms, but they also were discordant in some subjects. Some of the discordant individuals belong to groups for whom there is previous evidence of disparities in respiratory care; hence, we examined them in more detail. Women have been recognized as being diagnosed with obstructive lung disease with lower frequency than men (17), even in the presence of similar symptoms. We found that both strategies to identify high symptoms in smokers with normal lung function have similar AUC, whereas the specificity of the respiratory items of CAT is slightly better than that of CAT. The strategies to identify subjects with high symptom burden also perform well among former smokers, and actually using the first four questions of CAT had high sensitivity and specificity in this group.

An interesting finding which deserves further exploration is that both CAT and the respiratory questions of CAT were associated with a low specificity among participants of African American race, although the specificity was slightly higher with the respiratory questions. This finding is relevant because African Americans are a population group for whom there is a need to develop better models to understand the impact of tobacco-related lung disease (18, 19). Still, among African Americans, the sensitivity of both strategies was as high as or higher than in other groups. Overall, it is worth recognizing that the classification statistics (sensitivity and specificity) and discriminative ability (AUCs around 0.65) of both strategies need to be improved in the future. Still, they represent an advance because they are calling attention to a group of subjects previously considered "healthy smokers" owing to the absence of airflow obstruction, at least as defined by FEV_1/FVC less than 70%. The values are also similar to what was previously reported using the CAT with similar subjects (3).

Limitations
Our study is subject to several limitations. The most important is that it is not based on a representative sample of the population; it is based on research volunteers recruited at tertiary care medical centers. However, the sample was inclusive and had a large proportion of women and minority participants, which makes the results easier to translate into clinical practice. Our analyses could be interpreted as a comparison of diagnostic and prognostic tools, and we agree with that idea and present a complete description using the Standards for Reporting Diagnostic Accuracy Studies recommendations in Table E6 (20).

Unfortunately, the two diagnostic strategies lack a clearly defined gold standard with which to be compared. To minimize this potential limitation, we used for comparison an outcome standard (exacerbation during follow-up) and additional cross-sectional reference standards using patient characteristics not included in the CAT (walking distance, quality-of-life metrics).

In the present study, we used the responses to selected CAT items to understand which areas of the participants' health were more affected and if they were strongly associated with exacerbations. Nonetheless, we should note that the CAT was validated as an eight-item questionnaire and that using questions independently of each other could change the integrity and measurement properties of the questionnaire; an assessment of the measurement properties that result from reducing the number of items in this questionnaire is beyond the scope of this paper. Equally important, CAT was designed to be applied to subjects with a diagnosis of COPD, whereas our study population consisted of participants without airflow obstruction. Strengths of the study include the detailed characterization of participants, careful follow-up to identify the outcome standard selected to compare the two strategies of using the CAT, and the robustness of results in different disease spectra and subgroups of subjects.

Conclusions
Using the four respiratory questions of the CAT with a cutpoint score of 7 or higher identifies a group of smokers with preserved spirometry similar to that identified with the CAT cutpoint score of 10 or higher, who have a greater burden of dyspnea, chronic bronchitis, activity limitation, and impaired quality of life, as well as increased risk for future exacerbations. These findings provide further evidence of a relationship between respiratory symptoms and risk for respiratory events, and they provide support for future development of simpler strategies to identify these high-risk subjects in primary care. ■

References

1 Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2013;187:347–365.

2 Martinez CH, Kim V, Chen Y, Kazerooni EA, Murray S, Criner GJ, Curtis JL, Regan EA, Wan E, Hersh CP, et al.; COPDGene Investigators. The clinical impact of non-obstructive chronic bronchitis in current and former smokers. *Respir Med* 2014;108:491–499.

3 Woodruff PG, Barr RG, Bleecker E, Christenson SA, Couper D, Curtis JL, Gouskova NA, Hansel NN, Hoffman EA, Kanner RE, et al.; SPIROMICS Research Group. Clinical significance of symptoms in smokers with preserved pulmonary function. *N Engl J Med* 2016;374:1811–1821.

4 Tan WC, Bourbeau J, Hernandez P, Chapman KR, Cowie R, FitzGerald JM, Marciniuk DD, Maltais F, Buist AS, O'Donnell DE, et al.; CanCOLD Collaborative Research Group. Exacerbation-like respiratory symptoms in individuals without chronic obstructive pulmonary disease: results from a population-based study. *Thorax* 2014;69: 709–717.

5 Regan EA, Lynch DA, Curran-Everett D, Curtis JL, Austin JH, Grenier PA, Kauczor HU, Bailey WC, DeMeo DL, Casaburi RH, et al.; Genetic Epidemiology of COPD (COPDGene) Investigators. Clinical and radiologic disease in smokers with normal spirometry. *JAMA Intern Med* 2015;175:1539–1549.

6 Jones P, Harding G, Wiklund I, Berry P, Leidy N. Improving the process and outcome of care in COPD: development of a standardised assessment tool. *Prim Care Respir J* 2009;18:208–215.

7 Couper D, LaVange LM, Han M, Barr RG, Bleecker E, Hoffman EA, Kanner R, Kleerup E, Martinez FJ, Woodruff PG, et al.; SPIROMICS Research Group. Design of the Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS). *Thorax* 2014;69:491–494.

8 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179–187.

9 Ferris BG. Epidemiology standardization project (American Thoracic Society). *Am Rev Respir Dis* 1978;118:1–120.

10 Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;54:581–586.

11 Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respir Med* 1991;85(Suppl B):25–31; discussion 33–37.

12 Breeman S, Cotton S, Fielding S, Jones GT. Normative data for the Hospital Anxiety and Depression Scale. *Qual Life Res* 2015;24: 391–398.

13 Buysse DJ, Hall ML, Strollo PJ, Kamarck TW, Owens J, Lee L, Reis SE, Matthews KA. Relationships between the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and clinical/ polysomnographic measures in a community sample. *J Clin Sleep Med* 2008;4:563–571.

14 Andersson M, Stridsman C, Rönmark E, Lindberg A, Emtner M. Physical activity and fatigue in chronic obstructive pulmonary disease – a population based study. *Respir Med* 2015;109: 1048–1057.

15 Myers J, Bader D, Madhavan R, Froelicher V. Validation of a specific activity questionnaire to estimate exercise tolerance in patients referred for exercise testing. *Am Heart J* 2001;142:1041–1046.

16 Pinto LM, Gupta N, Tan W, Li PZ, Benedetti A, Jones PW, Bourbeau J; CanCOLD study group. Derivation of normative data for the COPD Assessment Test (CAT). *Respir Res* 2014;15:68.

17 Pinkerton KE, Harbaugh M, Han MK, Jourdan Le Saux C, Van Winkle LS, Martin WJ II, Kosgei RJ, Carter EJ, Sitkin N, Smiley-Jewell SM, et al. Women and lung disease: sex differences and global health disparities. *Am J Respir Crit Care Med* 2015;192:11–16.

18 Han MK, Curran-Everett D, Dransfield MT, Criner GJ, Zhang L, Murphy JR, Hansel NN, DeMeo DL, Hanania NA, Regan EA, et al.; COPDGene Investigators. Racial differences in quality of life in patients with COPD. *Chest* 2011;140:1169–1176.

19 Putcha N, Han MK, Martinez CH, Foreman MG, Anzueto AR, Casaburi R, Cho MH, Hanania NA, Hersh CP, Kinney GL, et al.; the COPDGene® Investigators. Comorbidities of COPD have a major impact on clinical outcomes, particularly in African Americans. *Chronic Obstr Pulm Dis* 2014;1:105–114.

20 Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, Lijmer JG, Moher D, Rennie D, de Vet HC, et al.; STARD Group. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ* 2015;351:h5527.