

Can CAPTURE be used to identify undiagnosed patients with mild-to-moderate COPD likely to benefit from treatment?

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Background: COPD Assessment in Primary Care To Identify Undiagnosed Respiratory Disease and Exacerbation Risk (CAPTURE™) uses five questions and peak expiratory flow (PEF) thresholds (males ≤ 350 L/min; females ≤ 250 L/min) to identify patients with a forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) < 0.70 and $FEV_1 < 60\%$ predicted or exacerbation risk requiring further evaluation for COPD. This study tested CAPTURE's ability to identify symptomatic patients with mild-to-moderate COPD (FEV_1 60%–80% predicted) who may also benefit from diagnosis and treatment.

Methods: Data from the CAPTURE development study were used to test its sensitivity (SN) and specificity (SP) differentiating mild-to-moderate COPD (n=73) from no COPD (n=87). SN and SP for differentiating all COPD cases (mild to severe; n=259) from those without COPD (n=87) were also estimated. The modified Medical Research Council (mMRC) dyspnea scale and COPD Assessment Test (CAT™) were used to evaluate symptoms and health status. Clinical Trial Registration: NCT01880177, <https://ClinicalTrials.gov/ct2/show/NCT01880177?term=NCT01880177&rank=1>.

Results: Mean age (+SD): 61 (+10.5) years; 41% male. COPD: $FEV_1/FVC=0.60$ (+0.1), $FEV_1\%$ predicted=74% (+12.4). SN and SP for differentiating mild-to-moderate and non-COPD patients (n=160): Questionnaire: 83.6%, 67.8%; PEF (≤ 450 L/min; ≤ 350 L/min): 83.6%, 66.7%; CAPTURE (Questionnaire+PEF): 71.2%, 83.9%. COPD patients whose CAPTURE results suggested that diagnostic evaluation was warranted (n=52) were more likely to be symptomatic than patients whose results did not (n=21) (mMRC > 2 : 37% vs 5%, $p < 0.01$; CAT > 10 : 86% vs 57%, $p < 0.01$). CAPTURE differentiated COPD from no COPD (n=346): SN: 88.0%, SP: 83.9%.

Conclusion: CAPTURE (450/350) may be useful for identifying symptomatic patients with mild-to-moderate airflow obstruction in need of diagnostic evaluation for COPD.

Keywords: COPD, case-finding, undiagnosed COPD, screening tool, peak expiratory flow

Introduction

COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk (CAPTURE™) was developed to identify people with severe, high-risk undiagnosed COPD, defined as a forced expiratory volume in 1 second (FEV_1) $< 60\%$ predicted or exacerbation risk, in primary care settings.^{1,2} This case-finding method uses five simple patient-completed questions and the selective use of peak expiratory flow (PEF) to uncover individuals most likely to benefit from diagnosis and treatment.^{1–8} The intent is to be as efficient as possible, using PEF selectively based on questionnaire score and reserving spirometry referrals to the subset of patients whose results warrant further diagnostic evaluation.^{1,3,4}

Although this case-finding method was developed to identify undiagnosed patients with an FEV₁% predicted <60% or at risk of exacerbation, uncovering symptomatic patients with FEV₁% predicted >60% who might also benefit from treatment could be advantageous. This study explored the extent to which CAPTURE identifies these patients.

In its initial testing, CAPTURE was able to differentiate cases of COPD (FEV₁% predicted <60% or exacerbation risk) from controls without COPD with a sensitivity (SN) of 89.7% and specificity (SP) of 93.1% (n=273). When subjects with milder COPD (FEV₁% predicted ≥60% and no/low exacerbation risk) were included in the control group, testing the ability of CAPTURE to differentiate the more severe, high-risk patients from all others, SN was 89.7% and SP was 78.1% (n=346).¹ The change in SP indicated that CAPTURE was classifying some patients with milder airflow obstruction as cases, a finding interpreted as error because the intent was to find the more severe, high-risk patients.¹ Upon further reflection, we questioned whether these “misclassified” cases may represent an additional group of patients who might also benefit from diagnosis and treatment. Although screening of asymptomatic individuals for undiagnosed COPD is not recommended,⁹ identifying symptomatic patients with mild-to-moderate airflow limitation could be advantageous, with treated individuals potentially realizing symptomatic, activity tolerance, and health-status benefits.^{10–14}

Methods

Design

This was a secondary analysis of data from the prospective, cross-sectional, multisite, case–control study used to develop CAPTURE.^{1,15} Specific methods and procedures for the larger study are presented elsewhere.¹ The study was approved by a central institutional review board (IRB) (Schulman Associates) and IRBs at each study site (Columbia University, National Jewish Health, Olmsted Medical Center, University of Kentucky, University of Michigan, and University of Nebraska Medical Center). Each patient provided written informed consent before initiating study procedures. Briefly, for questionnaire development, a pool of 44 candidate questions and criterion measures were completed by patients identified as cases (n=186; FEV₁ <60% or ≥1 exacerbation the previous 12 months) or controls (n=160; including patients with COPD and FEV₁ ≥60% predicted and no exacerbations the prior 12 months [n=73] and those without COPD [n=87]).¹ COPD was defined by physician diagnosis with prescribed pharmacologic maintenance therapy and FEV₁/FVC <0.70. COPD patients with an FEV₁%

predicted of 60%–80% were included in the control group to optimize the selection of items most sensitive to more severe, high-risk COPD during random forests analyses. The precision of the questionnaire alone, PEF alone, and CAPTURE (Questionnaire+PEF) for differentiating cases (n=186) from non-COPD controls (n=87) was also tested.¹

To address the purpose of the current study, analyses were performed on data from the original control group (n=160), with cases defined by a diagnosis of COPD, FEV₁ ≥60% predicted, and no exacerbation the prior 12 months (n=73) and those with no COPD serving as controls (n=87). The entire dataset (n=346) was used to evaluate CAPTURE across the full range of COPD (n=259), with patients without COPD (n=87) serving as controls.

Measures

The CAPTURE Questionnaire

The CAPTURE Questionnaire (Figure 1) comprises five questions assessing the presence/absence of symptoms (breathing problems and tiring easily), risk exposures, and recent history of acute respiratory illnesses. Responses are summed to yield a score ranging from 0 (no to all 5 questions) to 6 (yes to all questions and >2 respiratory events during the past year). Scores ≥2 indicate that further diagnostic assessment for COPD is warranted. In its initial testing, scores ≥2 showed an SN of 95.7% and an SP of 44.4% for differentiating COPD cases (FEV₁% predicted <60% or exacerbation risk) from controls (mild/moderate no risk COPD or no COPD) and an SN of 95.7% and an SP of 67.8% for differentiating cases from those without COPD.¹

PEF

PEF is used to increase the precision of case identification. In the development/validation study, research staff supervised PEF administration (Vitalograph® AsmaPlan® mechanical PEF meter; Vitalograph Ltd, Buckingham, UK) during the clinic visit; each subject performed three maneuvers with the highest value (L/min) used for analyses. Sex-specific thresholds were identified to facilitate rapid interpretation in clinical practice prior to referral for diagnostic spirometry: males <350 L per minute (L/min) and females <250 L/min.¹

CAPTURE (Questionnaire+PEF)

Questionnaire scores are used to select the best subset of patients for PEF testing. Those scoring 0 or 1 on the questionnaire are unlikely to have COPD and can proceed with the remainder of their clinic visit. Those scoring 5 or 6 (yes to all items and ≥1 respiratory events the past year) may have

CAPTURE*™

For each question, place an X in the box with the answer that is best for you.
There are no right or wrong answers, only answers which are right for you.

Please answer each question	No	Yes
1. Have you ever lived or worked in a place with dirty or polluted air, smoke, second-hand smoke, or dust?	<input type="checkbox"/>	<input type="checkbox"/>
2. Does your breathing change with seasons, weather, or air quality?	<input type="checkbox"/>	<input type="checkbox"/>
3. Does your breathing make it difficult to do things such as carry heavy loads, shovel dirt or snow, jog, play tennis, or swim?	<input type="checkbox"/>	<input type="checkbox"/>
4. Compared to others of your age, do you tire easily?	<input type="checkbox"/>	<input type="checkbox"/>
	0	1
		2 or more
5. In the past 12 months, how many times did you miss work, school, or other activities due to a cold, bronchitis, or pneumonia?	<input type="checkbox"/>	<input type="checkbox"/>

***COPD Assessment in Primary Care to identify Undiagnosed Respiratory Disease & Exacerbation Risk**

Figure 1 The CAPTURE™ (COPD assessment in primary care to identify undiagnosed respiratory disease and exacerbation risk) questionnaire.

Notes: Scoring: No =0; Yes =1; Item 5: 0, 1, 2. Scores are summed. © Cornell University, University of Kentucky Research Foundation, and Evidera, Inc. All rights reserved.

undiagnosed disease and can be referred directly to spirometry. Patients scoring 2–4 are clinically equivocal, with PEF values relative to thresholds used to determine next steps (spirometry and no spirometry). In the development study, this two-step process, using the 350/250 L/min thresholds, improved SN and SP over the questionnaire alone for differentiating cases and controls (89.7% and 78.1%) and cases and no-COPD controls (89.7% and 93.1%), with the added advantage of eliminating the need for PEF assessments in all patients.¹

Modified British Medical Research Council dyspnea scale (mMRC) and COPD Assessment Test (CAT™)

The mMRC^{16,17} and CAT™^{18,19} were used to assess patient-reported dyspnea and COPD-related health status, respectively. The mMRC is a 5-point (0–4) scale with higher ratings reflecting more severe breathlessness. CAT scores range from 0 to 40 with higher scores indicating poorer COPD health status. Patient-level scores <10 are interpreted as low-impact COPD, with continued health maintenance interventions advised, including smoking cessation, vaccination, and exercise. Scores 10–20 are considered moderate-impact COPD with potential for improvement with treatment, for example, maintenance therapies, reduction in aggravating factors, exacerbation prevention, and/or rehabilitation.²⁰ mMRC >2 and CAT scores >10 are used to categorize patients as “more symptomatic” under the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.²¹

Spirometry

Pre-bronchodilator spirometry (FEV₁, FEV₁% predicted, and FEV₁/forced vital capacity [FVC]) was performed if spirometry results from the past 5 years were not available. FEV₁/FVC <0.70 and FEV₁ <80% predicted were considered diagnostic of COPD. All COPD cases met COPD Foundation Guide spirometry grade 1 requirements (FEV₁ ≥60%; <80% predicted).⁷

Analyses

Group differences in sample characteristics were tested using parametric (normally distributed continuous variables) and nonparametric (categorical and non-normal continuous variables) statistics. PEF values were also compared using analysis of variance, with factors for group, sex, smoking, age, and group-by-sex interaction.

The precision of the questionnaire, PEF (350/250), and CAPTURE (Questionnaire+PEF [350/250]) for differentiating patients with and without COPD in this sample was estimated using SN, SP, overall misclassification error estimates, receiver operator characteristic curves, and area under the curve.

The SN, SP, and error for PEF alone were examined in 25 mL increments stratified by sex to determine if higher thresholds more accurately differentiated these cases of COPD from those without COPD, with consideration given to threshold values that would be easy to recall and apply in clinical settings.

The best thresholds were then tested with the questionnaire to determine if new thresholds for males and females would enhance the precision of CAPTURE in this population.

The extent to which CAPTURE was identifying COPD patients with dyspnea (mMRC levels >2) and/or poor health status (CAT scores >10) was tested using Chi-square (χ^2) or Fisher's exact (cell $n < 5$) statistics and performed using the 350/250 and the higher PEF thresholds.

Finally, SN, SP, and error for differentiating the full range of COPD ($n=259$) from no COPD ($n=87$) were assessed for the questionnaire alone, PEF alone, and CAPTURE using the 350/250 and higher PEF thresholds.

Results

Sample

Demographic and clinical characteristics of the analytical sample are shown in Tables 1 and 2. Subjects without COPD were younger and more likely to be female, employed, and have a higher educational level than the COPD group.

Of the 73 patients with milder COPD, 23 (31.5%) were GOLD airflow limitation category 1 (mild) and 50 (68.5%) were GOLD 2 (moderate).²¹ COPD patients had significantly poorer lung function, higher mMRC and CAT scores, and

Table 1 Demographic characteristics by group^a

Characteristic	n=160		p-value
	COPD ^b (n=73)	No COPD ^c (n=87)	
Age (years)			
Mean (SD)	65.2 (9.1)	58.1 (10.5)	<0.0001
Range	49–85	40–88	
Sex, n (%) male	40 (55)	26 (30)	0.0014
Ethnic background, n (%)			
Not Hispanic or Latino	68 (99)	84 (99)	1.000
Racial background, n (%) ^d			
White	66 (90)	73 (84)	0.2250 ^a
Non-white	7 (10)	14 (16)	
Employment, n (%)			
Employed (full- or part-time)	15 (21)	55 (63)	<0.0001
Not employed	58 (79)	32 (37)	
Retired	37 (51)	22 (25)	
Disabled	18 (25)	3 (3)	
Others ^e	3 (4)	7 (8)	
Education status, n (%)			0.0006
High school or less	36 (49)	18 (21)	
Some college, vocational training	14 (19)	22 (25)	
College degree or more	23 (32)	47 (54)	

Notes: ^aEnglish-speaking with informed consent and spirometry. ^bCOPD, FEV₁ 60%–80% predicted, and no history of exacerbations >12 months. ^cNo known diagnosis or treatment for COPD and FEV₁/FVC ≥ 0.70 . ^dSubject self-identified; American Indian or Alaskan Native (1,1), Asian (0,1), Black or African American (11, 5), and others (2,0). ^eOthers: homemaker, unemployed, and not specified.

Abbreviation: FEV₁, forced expiratory volume in 1 second.

Table 2 Clinical characteristics by group^a

Characteristic	n=160		p-value
	COPD ^b (n=73)	No COPD ^c (n=87)	
Smoking history, n (%)			<0.0001
Never or <100 cigarettes	2 (3)	51 (59)	
Former	48 (66)	28 (32)	
Current	23 (32)	8 (9)	
Spirometry			
FEV ₁ , median	2.0	2.6	<0.0001
Mean (SD)	2.1 (0.6)	2.6 (0.7)	
FEV ₁ % predicted	70.0	93.0	<0.0001
Mean (SD)	74.0 (12.4)	89.7 (14.6)	
FEV ₁ /FVC, mean (SD)	0.6 (0.1)	0.8 (0.1)	<0.0001
Peak flow (PEF)	316.1 (102.86)	403.5 (109.00)	<0.0001
mMRC dyspnea scale (0–4 scale)			
Median	2	1	<0.0001
Mode (n, %)	1 (34; 46)	0 (71; 82)	
mMRC >2	20 (28)	5 (6)	
CAT TM (0–40 scale)			
Median	15.0	4.0	<0.0001
Mean (SD)	15.6 (8.0)	5.5 (5.4)	
CAT >10, n (%)	57 (78)	13 (15)	<0.0001
mMRC >2 or CAT >10, n (%)	57 (78)	15 (17)	<0.0001
mMRC >2 and CAT >10, n (%)	20 (28)	3 (3)	<0.0001
Comorbid conditions (any), n (%)	73 (100)	76 (87)	0.0010
Self-report activity on most days, n (%)			0.0524
Sit, lie down, walk around home	38 (52)	32 (37)	
Very active or exercise	35 (48)	55 (63)	

Notes: ^aEnglish-speaking subjects with informed consent and spirometry. ^bCOPD, FEV₁ 60%–80% predicted, and no history of exacerbations >12 months. ^cNo known diagnosis or treatment for COPD and FEV₁/FVC ≥ 0.70 .

Abbreviations: CAT, COPD Assessment Test; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC, modified Medical Research Council dyspnea scale; PEF, peak expiratory flow.

were more likely to have a smoking history and one or more comorbid conditions than those with no COPD. PEF rates were significantly lower in the COPD group, tested alone and controlling for age ($p < 0.001$), sex ($p < 0.0001$), and smoking status ($p < 0.01$) (LS means [95% CI]: COPD [$n=73$]: 324.3 [301.6; 346.9]; no COPD [$n=87$]: 403.1 [381.2, 425.1]; $F=27.78$; $p < 0.001$).

CAPTURE performance

Performance properties of the questionnaire, PEF, and questionnaire+PEF for these milder COPD cases versus no COPD are shown in Table 3A and Figure 2A. To assist with interpretation, results for the more severe high-risk COPD cases (FEV₁ <60% or risk of exacerbation) versus no COPD controls from the original development study¹ are provided

Table 3 Performance properties for questionnaire, PEF, and CAPTURE for differentiating COPD from no COPD

A					
Milder COPD^a (n=73) versus no COPD^b (n=87)					
Property	Questionnaire	PEF ^c		CAPTURE ^d	
	Score >2	350/250 threshold	450/350 threshold	350/250 threshold	450/350 threshold
Sensitivity (%)	83.6	38.4	83.6	39.7	71.2
Specificity (%)	67.8	90.8	66.7	93.1	83.9
Error (%)	25.0	33.1	25.6	31.3	21.9
B					
Severe, high-risk COPD^a (n=186) versus no COPD^b (n=87)¹					
Property	Questionnaire	PEF ^c		CAPTURE ^d	
	Score >2	350/250 threshold		350/250 threshold	
Sensitivity (%)	95.7	88.0		89.7	
Specificity (%)	67.8	90.8		93.1	
Error (%)	13.2	11.1		9.2	
C					
Full range of COPD^a (n=259) versus no COPD^b (n=87)					
Property	Questionnaire	PEF ^c		CAPTURE ^d	
	Score >2	350/250 threshold	450/350 threshold	350/250 threshold	450/350 threshold
Sensitivity (%)	92.3	73.9	94.2	75.5	88.0
Specificity (%)	67.8	90.8	66.7	93.1	83.9
Error (%)	13.9	21.8	12.8	20.1	13.0

Notes: (A) ^aCOPD, FEV₁ 60–80% predicted and no history of exacerbations >12 months; ^bNo known diagnosis or treatment for COPD and FEV₁/FVC ≥ 0.70; ^cPeak expiratory flow (PEF) rate, liters per minute (L/min), thresholds: males/females; ^dCAPTURE = Questionnaire + PEF. (B) ^aCOPD, FEV₁ < 60% predicted or exacerbation risk; ^bNo known diagnosis or treatment for COPD and FEV₁/FVC ≥ 0.70; ^cPeak expiratory flow (PEF) rate, liters per minute (L/min), thresholds: males/females; ^dCAPTURE = Questionnaire + PEF. (C) ^aMedical diagnosis and treatment for COPD; FEV₁/FVC < 0.70; ^bNo known diagnosis or treatment for COPD and FEV₁/FVC ≥ 0.70; ^cPeak expiratory flow (PEF) rate, liters per minute (L/min), thresholds: males/females (n=344); ^dCAPTURE = Questionnaire + PEF.

Abbreviations: CAPTURE, COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow.

in Table 3B and Figure 2B. Results for all COPD versus no COPD are shown in Table 3C and Figure 2C. SN analyses for smoking status are included in Tables S1–S3, with results suggesting that this was not a confounding factor.

Questionnaire alone

Most COPD patients (61/73; 83.6%) scored ≥2 on the questionnaire, the threshold for further evaluation of COPD. The questionnaire was less sensitive differentiating milder COPD from no COPD (83.6%, Table 3A), relative to its use detecting more severe cases of COPD (95.7%, Table 3B).

PEF alone

PEF (350/250 threshold) was less sensitive differentiating milder COPD patients from those without COPD (38.4%, Table 3A) relative to its performance with more severe cases of COPD (88.0%, Table 3B). Precision estimates for PEF at 25 L/min increments are shown in Table S4A and B. Increasing the threshold by 100 L/min (to 450/350 for males/females) improved the SN of PEF from 38.4% to 83.6%, with some sacrifice in SP, from 90.8% to 66.7% (Table 3A).

CAPTURE (Questionnaire+PEF)

As one might expect given its purpose and development methods, CAPTURE (PEF 350/250) had substantially lower SN for detecting patients with milder airflow obstruction (39.7%, Table 3A) compared to the detection of patients with more severe, high-risk COPD (89.7%, Table 3B). Using CAPTURE (PEF 450/350) improved the SN from 39.7% to 71.2%, with some sacrifice in SP, from 93.1% to 83.9% (Table 3A).

Dyspnea and health status

Most of the milder COPD patients scoring ≥2 on the questionnaire reported either dyspnea (mMRC ≥2; n=50/60; 83.3%) or health status impairment (CAT ≥10/60; n=54/60; 88.5%). For patients with questionnaire scores <2, most (9/12; 75%) had an mMRC <2 (mMRC missing for one subject) or CAT <10 (9/12, 75%).

COPD patients whose CAPTURE (PEF 350/250) indicated the need for further diagnostic evaluation (n=29) were more likely to report dyspnea (mMRC scores ≥2, $p < 0.05$) than those who did not (n=44). There was no difference in health status (CAT ≥10) between the two groups (Table S5).

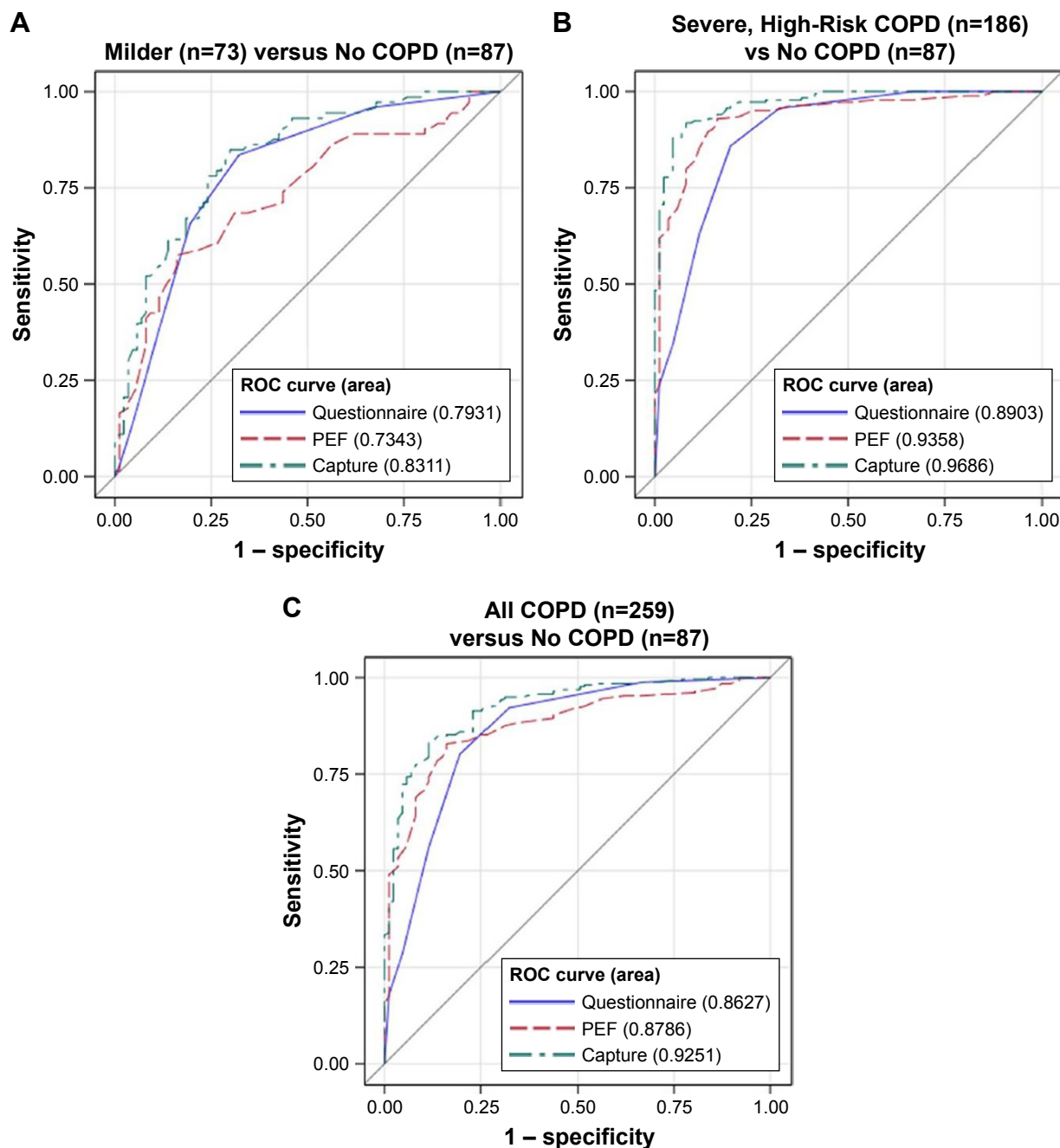


Figure 2 ROC and AUC by group.

Notes: (A) milder^a (n=73) versus No COPD^b (n=87); (B) severe, high-risk COPD^c (n=186) versus no COPD^d (n=87); (C) all COPD^e (n=259) versus no COPD^f (n=87). ^aCOPD, FEV₁ 60%–80% predicted and no history of exacerbations >12 months. ^bNo known diagnosis or treatment for COPD and FEV₁/FVC ≥0.70. ^cFEV₁ <60% or exacerbation risk. ^dNo known diagnosis or treatment for COPD and FEV₁/FVC ≥0.70. ^eMedical diagnosis and treatment for COPD; FEV₁/FVC <0.70. ^fNo known diagnosis or treatment for COPD and FEV₁/FVC ≥0.70.

Abbreviations: AUC, area under the curve; CAPTURE™, COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; ROC, receiver operating characteristics.

Using the higher PEF threshold, COPD patients whose CAPTURE (PEF 450/350) suggested further evaluation (n=52) were more likely to be symptomatic (mMRC ≥2 and CAT ≥10, $p < 0.01$) than patients whose scores suggested that no further assessment was warranted (n=21) (Table S3).

Using CAPTURE to detect a full range of COPD, mild to severe

As expected, using CAPTURE (PEF 350/250) to differentiate all patients with COPD from those without COPD alters the precision of the case-finding approach relative to its original purpose, reducing SN (89.7%–75.5%) and

increasing error (9.2%–20.1%). Increasing the PEF threshold improves SN from 75.5% to 88.0% and reduces error (20.1%–13.0%), with some sacrifice in SP (declines from 93.1% to 83.9%).

Discussion

CAPTURE was designed to help primary care health professionals efficiently identify severe, high-risk undiagnosed cases of COPD in greatest need of diagnosis and treatment. Many patients with $FEV_1 > 60\%$ are symptomatic, however, and may also benefit from treatment.^{10,11,13,14} The results of the analyses presented here suggest that CAPTURE can identify these milder patients with reasonable SN and SP when PEF thresholds of 450/350 are used. Although more patients would be referred for diagnostic spirometric testing, including those without COPD, a substantial portion of those ultimately diagnosed with COPD are likely to have dyspnea or health status impairment that may be ameliorated with treatment.

Given the performance properties of PEF in the current analyses and previous study, one might be tempted to use PEF thresholds alone to identify patients in need of spirometry. However, organizing PEF supplies and performing three coached maneuvers with all patients in primary care settings, in addition to other clinic visit assessments, could be challenging. Furthermore, results of PEF provide preliminary information on airflow obstruction only, with no insight into exposure, symptoms, or exacerbation risk prior to referral for diagnostic testing. CAPTURE was designed to balance efficiency and precision, with the carefully designed questionnaire used as an initial screen and PEF administered to a subset of patients to yield fewer false positives and reduce screening costs. The PEF thresholds enable efficient interpretation, with empirically tested quick-recall values (male/female, moderate to severe: 350/250; mild to moderate: 450/350), although clinicians can also use the observed value and clinical judgment to determine the need for further assessment and testing.

Given the relatively high CAT scores in patients with questionnaire scores ≥ 2 , one might also ask if the CAT could be used for case finding. The CAT was developed to facilitate communication between COPD patients and clinicians,¹⁸ covering eight common manifestations of COPD and scores used to guide treatment. It was neither intended for use in patients without COPD nor as a screening tool. Following diagnosis, the CAT can be used to guide treatment and monitor outcomes.²²

Several limitations of this study should be noted. First, this was an analysis of data from a subset of subjects participating in the CAPTURE development study, rather than a large prospective, population-based case-finding study. Results should be considered exploratory. Second, the COPD and no COPD groups differed on several sample characteristics. Some of these differences typify COPD and were expected; however, differences in demographics (particularly age, sex, and education) and smoking history could have affected the findings. Although there is no reason to believe that demographic differences altered patient responses to study measures, this must be recognized as a limitation with further study warranted. SN analyses in former smokers suggested that results were robust to smoking history. Third, spirometry values were measured without bronchodilator administration with the standard FEV_1/FVC diagnostic threshold of < 0.70 . Although other diagnostic indicators were also used for group assignment (medical diagnosis and treatment), the 0.70 threshold can result in an overestimation of older subjects with airflow limitation. Once again, further research is needed. Fourth, although CAPTURE has been tested and performs well identifying more severe, high-risk cases of COPD in Spanish-speaking patients,² sample size precluded testing its performance in milder symptomatic COPD. Finally, CAPTURE is a tool to identify patients requiring further evaluation for COPD; it was not intended to diagnose or evaluate treatment and may detect problems other than COPD that warrant evaluation. It was also not intended for use as an outcome measure, with the CAT best suited to that purpose following diagnosis.

Conclusion

Results of these analyses together with those from the original validation study suggest that CAPTURE can be used to identify symptomatic patients likely to have airflow limitation and in need of further clinical evaluation for possible COPD. Based on the patient's score on this questionnaire, clinicians can apply the 350/250 or 450/350 PEF thresholds as they determine the need for diagnostic spirometry. Further testing in a large prospective study of this case-finding approach and its effect on diagnosis, treatment, and patient-centered outcomes are warranted.

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Disclosure

Nancy K Leidy, PhD and Elizabeth D Bacci, PhD are employees of Evidera, a health care research firm that provides consulting and other research services to pharmaceutical, device, government, and nongovernment organizations. In this salaried position, they work with various companies and receive no direct payment or honoraria from these companies for services rendered. Karen G Malley, BA is an hourly employee of Evidera and a salaried employee of Malley Research Programming, Inc. In the latter capacity, she provides custom computer programming services to clinical research organizations. Fernando J Martinez, MD, MS has participated in Steering Committee in COPD or IPF sponsored by Bayer, Centocor, Forest, Gilead, Janssen, GSK, Nycomed/Takeda, and Promedior. He has participated in advisory boards for COPD or IPF for Actelion, Amgen, AstraZeneca, Boehringer Ingelheim, Carden Jennings, CSA Medical, Ikaria, Forest, Genentech, GSK, Janssens, Merck, Pearl, Nycomed/Takeda, Pfizer, Roche, Sudler & Hennessey, Veracyte, and Vertex. He has prepared or presented continuing medical presentations in COPD or IPF for the American College of Chest Physicians, the American Thoracic Society, CME Incite, Center for Health Care Education, Inova Health Systems, MedScape, Miller Medical, National Association for Continuing Education, Paradigm, Peer Voice, Projects in Knowledge, Spectrum Health System, St John's Hospital, St Mary's Hospital, University of Illinois Chicago, University of Texas Southwestern, University of Virginia, UpToDate, and Wayne State University. Dr Martinez has participated in data safety monitoring committees sponsored by GSK and Stromedix. He has aided with FDA presentations sponsored by Boehringer Ingelheim, GSK, and Ikaria. He has spoken on COPD for Bayer, Forest, GSK, and Nycomed/Takeda. He has participated in advisory teleconferences sponsored by the American Institute for Research, Axon, Grey Healthcare, Johnson and Johnson, and Merion. He has received book royalties from Informa. David Mannino, MD

has received honoraria/consulting fees and served on speaker bureaus for GlaxoSmithKline plc, Novartis Pharmaceuticals, Pfizer Inc., Boehringer-Ingelheim, AstraZeneca PLC, Forest Laboratories Inc., Merck, Amgen, and Sunovion. Furthermore, he has received royalties from UpToDate, is on the Board of Directors of the COPD Foundation, and has been compensated as a medical expert in legal cases. MeiLan K Han, MD, MS has consulted for GSK, Boehringer-Ingelheim, AstraZeneca, Sunovion, and Novartis. Randall W Brown, MD MPH has served on the Board of Directors for the Allergy and Asthma Network and the National Asthma Education Certification Board. Dr Brown served on medical advisory boards for the Allergy and Asthma Foundation of America, AstraZeneca, Meda, Spirosure, Teva, and Thermo Fisher. Dr Brown received honoraria/consulting fees and served on speaker bureaus for tAstraZeneca, Meda, and Teva. Dr Brown has delivered continuing medical education for the American Academy of Otolaryngic Allergy, the Allergy and Asthma Network, Medscape, National Jewish Health, NYC Health and Hospitals/One City Health, and the Pennsylvania Allergy and Asthma Association. Barry Make, MD has served on medical advisory boards for Aerocrine, AstraZeneca, Boehringer-Ingelheim, CSL Bering, GlaxoSmithKline, Forest, Novartis, Spiration, Theravance, and Sunovion. He has participated in research studies funded by AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Pfizer, Forest, Sunovion, and Pearl. Dr Make has conducted continuing medical education for American Thoracic Society, American College of Chest Physicians, Academy for Continued Healthcare Learning, Medscape, Projects in Knowledge, Catamount, Carden Jennings, Cleveland Clinic, Eastern Virginia Medical Center, Hybrid Communications, SPIRE, Foundation for Improving Patient Outcomes, Consensus, WebMD, National Jewish Health, and National Medical Association. He has received royalties from UpToDate. He has served on Data Monitoring Boards for Spiration and Baxalta. He has provided unbranded education talks for GlaxoSmithKline. Stephen Rennard, MD was employed by the University of Nebraska Medical Center during the conduct of this study and remains the Richard and Margaret Larson Professor of Pulmonary Research at UNMC and had a number of relationships with companies who provide products and/or services relevant to outpatient management of chronic obstructive pulmonary disease, including A2B Bio, Almirall, APT, AstraZeneca, Boehringer Ingelheim, Chiesi, CME Incite, CSL Behring, Dailchi Sankyo, Decision Resources, Dunn Group, Easton Associates, Forest, Gerson, GlaxoSmithKline, Johnson and Johnson, Medimmune, Novartis, Novis, Nycomed, Otsuka, Pearl,

Pfizer, PriMed, Pulmatrix, Roche, Takeda, and Theravance; these relationships include serving as a consultant, advising regarding clinical trials, speaking at continuing medical education programs, and performing funded research both at basic and clinical levels. Dr Rennard is currently employed by AstraZeneca in which he owns shares. He does not own any stock in any other pharmaceutical companies. Byron Thomashow, MD has consulted for Boehringer-Ingelheim and has been on advisory boards for GlaxoSmithKline PLC, Novartis, AstraZeneca PLC, and Forest. Barbara P Yawn, MD, MSc has received research funding from NIH, AHRQ, CDC, and from BI for research on COPD. Dr Yawn has received compensation from Merck, Novartis, AstraZeneca, and Forrest for COPD advisory boards on COPD, and Grifols for advisory board on Alpha-1 antitrypsin deficiency states. The authors report no other conflicts of interest in this work.

References

- Martinez F, Mannino D, Leidy NK, et al. A new approach for identifying patients with undiagnosed chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2017;195(6):748–756.
- Quezada W, Whippo B, Jellen P, et al. How well does CAPTURE translate? An exploratory analysis of a COPD case-finding method for Spanish-speaking patients. *Chest*. 2017;152(4):761–770.
- Han MK, Kim MG, Mardon R, et al. Spirometry utilization for COPD: how do we measure up? *Chest*. 2007;132(2):403–409.
- Han MK, Steenrod AW, Bacci ED, et al. Identifying patients with undiagnosed COPD in primary care settings: insight from screening tools and epidemiologic studies. *Chronic Obstr Pulm Dis*. 2015;2(2):103–121.
- Hooper R, Burney P, Vollmer WM, et al. Risk factors for COPD spirometrically defined from the lower limit of normal in the BOLD project. *Eur Respir J*. 2012;39(6):1343–1353.
- Qaseem A, Snow V, Shekelle P, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2007;147(9):633–638.
- Rennard S, Thomashow B, Crapo J, et al. Introducing the COPD Foundation Guide for Diagnosis and Management of COPD, recommendations of the COPD Foundation. *COPD*. 2013;10(3):378–389.
- Guirguis-Blake JM, Senger CA, Webber EM, Mularski RA, Whitlock EP. Screening for chronic obstructive pulmonary disease: evidence report and systematic review for the US preventive services task force. *JAMA*. 2016;315(13):1378–1393.
- US Preventive Services Task Force, Siu AL, Bibbins-Domingo K, et al. Screening for chronic obstructive pulmonary disease: US preventive services task force recommendation statement. *JAMA*. 2016;315(13):1372–1377.
- Jacome C, Marques A. Short- and long-term effects of pulmonary rehabilitation in patients with mild COPD: a comparison with patients with moderate to severe COPD. *J Cardiopulm Rehabil Prev*. 2016;36(6):445–453.
- O'Donnell DE, Gebke KB. Examining the role of activity, exercise, and pharmacology in mild COPD. *Postgrad Med*. 2014;126(5):135–145.
- O'Donnell DE, Neder JA, Elbehairy AF. Physiological impairment in mild COPD. *Respirology*. 2016;21(2):211–223.
- Rugbjerg M, Iepsen UW, Jorgensen KJ, Lange P. Effectiveness of pulmonary rehabilitation in COPD with mild symptoms: a systematic review with meta-analyses. *Int J Chron Obstruct Pulmon Dis*. 2015;10:791–801.
- Welte T, Vogelmeier C, Papi A. COPD: early diagnosis and treatment to slow disease progression. *Int J Clin Pract*. 2015;69(3):336–349.
- University of Michigan, United BioSource Corporation, NHBLI. Developing a COPD Case Finding Methodology for Primary Care (NCT01880177). ClinicalTrials.gov First received: June 10, 2013/Last updated; 2016.
- 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(7):581–586.
- Fletcher CM (Chairman). Standardised questionnaire on respiratory symptoms: a statement prepared and approved by the MRC Committee on the Aetiology of Chronic Bronchitis (MRC breathlessness score). *BMJ*. 1960;2:1665.
- Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Respir J*. 2009;34(3):648–654.
- Jones PW, Harding G, Wiklund I, et al. Tests of the responsiveness of the COPD assessment test following acute exacerbation and pulmonary rehabilitation. *Chest*. 2012;142(1):134–140.
- GlaxoSmithKline. COPD Assessment Test (CAT) Healthcare Professional User Guide. 2012; Available from: <http://www.catestonline.org/images/UserGuides/CATHCPUUser%20guideEn.pdf>. Accessed April 12, 2017.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of COPD. 2017. Available from: <http://goldcopd.org/>. Accessed April 2017.
- Papaioannou M, Pitsiou G, Manika K, et al. COPD assessment test: a simple tool to evaluate disease severity and response to treatment. *COPD*. 2014;11(5):489–495.

Supplementary materials

Sensitivity analyses: former smokers

Given the difference in smoking status between the two groups, SN analyses were performed, testing the performance of the questionnaire, PEF, and CAPTURE (Questionnaire+PEF [350/250 and 450/350]) for differentiating COPD and no COPD in former smokers only (n=56). Demographic and clinical characteristics of former smokers by group are shown in Tables S1 and S2. Results are presented in Table S3. SN, SP, and error were similar to values found in the entire sample (Table 3), suggesting that smoking history was not a confounding factor.

Peak expiratory flow (PEF)

Each subject performed three PEF maneuvers using a Vitalograph® AsmaPlan® mechanical PEF meter (Vitalograph Ltd, UK), with the highest value (L/min) used for analysis. Performance properties of PEF at varied thresholds in this sample stratified by sex are shown in Table S4.

Clinical characteristics of patients whose COPD Assessment in Primary Care To Identify Undiagnosed Respiratory Disease and Exacerbation Risk (CAPTURE™) suggests that further diagnostic evaluation is advised

CAPTURE was developed to identify patients in need of diagnostic evaluation for undiagnosed COPD and a forced

expiratory volume in 1 second (FEV_1) <60% or exacerbation risk. This study assessed the sensitivity (SN), specificity (SP), and error of this case-finding method for identifying patients with an $FEV_1 \geq 60\%$ predicted.

To assess whether the evaluation process was identifying symptomatic patients, dyspnea (modified Medical Research Council [mMRC] >2), or health status impairment (COPD Assessment Test [CAT™] >10) was examined. Table S5 shows the results of these analyses for the 350/250 and 450/350 PEF thresholds. In both cases, most of the patients who would be referred for further diagnostic evaluation reported impaired health status and a substantial portion reported dyspnea. Although more patients are referred for further testing when the higher PEF threshold (450/350) is used, those referred are more likely to report impaired health status or high levels of dyspnea compared to those whose scores suggested that no further testing was warranted. These results suggest that CAPTURE (PEF 450/350) may be useful for identifying cases of COPD with an $FEV_1 > 60\%$ predicted, many of whom meet GOLD guidelines for “more symptomatic” disease.

Table S1 Demographic characteristics of former smokers (N=76) by group

Characteristic	Former smokers (N=76)		p-value
	COPD ^b (n=48)	No COPD ^c (n=28)	
Age (years)			
Mean (SD)	67.4 (7.9)	62.0 (11.1)	0.0284
Range	51–85	40–88	
Sex, n (%) male	24 (50)	10 (36)	0.2270
Ethnic background, n (%)			
Not Hispanic or Latino	46 (98)	28 (100)	1.000
Racial background, n (%) ^d			
White	44 (92)	25 (89)	
Non-white	4 (8)	3 (11)	0.7039
Employment, n (%)			
Employed (full- or part-time)	10 (21)	10 (21)	0.0052
Not employed/others ^e	38 (79)	38 (79)	
Education status, n (%)			
High school or less	22 (46)	22 (46)	0.0934
Some college, vocational training	9 (19)	9 (19)	
College degree or more	17 (35)	17 (35)	

Notes: ^aEnglish-speaking with informed consent and spirometry; ^bCOPD, FEV_1 60%–80% predicted and no history of exacerbations >12 months; ^cNo known diagnosis or treatment for COPD and $FEV_1/FVC \geq 0.70$; ^dSubject self-identified; non-white: American Indian or Alaskan Native (1, 1), Asian (0, 1), Black or African American (1, 2), others (1, 0). ^eOthers: homemaker, unemployed, and not specified.

Abbreviations: FEV_1 , forced expiratory volume in 1 second; FVC, forced vital capacity.

Table S2 Clinical characteristics of former smokers (N=76) by group

Characteristic	COPD ^b (n=48)	No COPD ^c (n=28)	p-value
Spirometry, mean (SD)			
FEV ₁ , median	1.9	2.4	0.0023
Mean (SD)	2.0 (0.6)	2.5 (0.7)	
FEV ₁ % predicted, median	68.0	85.0	0.0020
Mean (SD)	73.5 (13.2)	85.0 (17.3)	
FEV ₁ /FVC	0.60 (0.06)	0.78 (0.06)	<0.0001
Peak flow (PEF)	320.9 (114.7)	396.3 (85.0)	0.0035
mMRC (0–4 scale)			
Median	1	0	<0.0001
Mode (n, %)	1 (24, 51)	0 (25, 89)	
mMRC >2, n (%)	12 (26)	1 (4)	0.0243
CAT TM			
Median	15.0	5.0	<0.0001
Mean (SD)	14.5 (6.6)	5.5 (4.7)	
CAT >10, n (%)	38 (79)	5 (18)	<0.0001
mMRC >2 and CAT >10, n (%)	12 (26)	1 (4)	0.0243
mMRC >2 or CAT >10, n (%)	38 (79)	5 (18)	<0.0001
Comorbid conditions (any), n (%), yes	48 (100)	25 (89)	0.0466
Self-report activity on most days, n (%)			
Sit, lie down, walk around home	26 (54)	10 (36)	0.1202
Very active or exercise	22 (46)	18 (64)	

Notes: ^aEnglish-speaking subjects with informed consent and spirometry; ^bCOPD, FEV₁ 60%–80% predicted and no history of exacerbations >12 months; ^cno known diagnosis or treatment for COPD and FEV₁/FVC ≥0.70.

Abbreviations: CAT, COPD Assessment Test; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council dyspnea scale.

Table S3 Performance of the questionnaire, PEF, and CAPTURE^c for differentiating COPD^a (n=48) from No COPD^b (n=28) in former smokers (N=76)

Property	Questionnaire	PEF ^c		CAPTURE ^c (Questionnaire+PEF)	
	Score >2	350/250 threshold	450/350 threshold	350/250 threshold	450/350 threshold
Sensitivity (%)	87.5	33.3	81.3	39.6	70.8
Specificity (%)	67.9	92.9	57.1	96.4	85.7
Error (%)	19.7	44.7	27.6	39.5	23.7

Notes: ^aCOPD, FEV₁ 60%–80% predicted, and no history of exacerbations >12 months; ^bno known diagnosis or treatment for COPD and FEV₁/FVC ≥0.70. ^cPEF rate (L/min), thresholds: males/females.

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow.

Table S4 Performance properties of PEF thresholds for differentiating milder cases of COPD^a from patients without COPD^b by sex

Males (n=66)							
Property	PEF threshold (L/min) ^c						
	350	375	400	425	450 ^d	475	500
Sensitivity (%)	37.5	52.5	65.0	80.0	80.0	82.5	85.0
Specificity (%)	88.5	88.5	80.8	69.2	65.4	53.8	50.0
Error (%)	42.4	33.3	28.8	24.2	25.8	28.8	28.8

Females (n=94)							
Property	PEF ^c threshold (L/min)						
	250	275	300	325	350 ^d	375	375
Sensitivity (%)	39.4	66.7	69.7	75.8	87.9	93.9	93.9
Specificity (%)	91.8	86.9	85.2	80.3	67.2	42.6	42.6
Error (%)	26.6	20.2	20.2	21.3	25.5	39.4	39.4

Notes: ^aCOPD, FEV₁ 60%–80% predicted and no history of exacerbations >12 months. ^bNo known diagnosis or treatment for COPD and FEV₁/FVC ≥0.70. ^cPEF rate, L/min. ^dSelected threshold.

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow.

Table S5 Prevalence of dyspnea and health status by CAPTURE™ Response^a in patients with COPD^b (N=73)

Characteristic	CAPTURE (PEF 350/250) ^c			CAPTURE (PEF 450/350) ^d		
	Diagnostic testing recommended			Diagnostic testing recommended		
	Yes, n=29 (40%)	No, n=44 (60%)	p-level ^e	Yes, n=52 (70%)	No, n=21 (30%)	p-level ^e
mMRC >2, n (%)	12 (43)	8 (18)	0.0227	19 (37)	1 (5)	0.0042
CAT™ >10, n (%)	26 (90)	31 (70)	0.0817	45 (86)	12 (57)	0.0060
mMRC >2 and CAT >10, n (%)	12 (43)	8 (18)	0.0227	19 (37)	1 (5)	0.0042

Notes: ^aQuestionnaire+PEF results suggest that further diagnostic evaluation is warranted (yes/no). ^bCOPD, FEV₁ 60%–80% predicted, and no history of exacerbations >12 months. ^cSensitivity=39.7%; specificity=93.1%; error=31.3% for milder patients versus no COPD. ^dSensitivity=71.2%; specificity=83.9%; error=21.9% for milder patients versus no COPD. ^eChi-square (χ^2) or Fisher's exact (cell n<5).

Abbreviations: CAT, COPD Assessment Test; FEV₁, forced expiratory volume in 1 second; mMRC, modified Medical Research Council dyspnea scale; PEF, peak expiratory flow.

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