A New Approach for Identifying Patients with Undiagnosed Chronic Obstructive Pulmonary Disease

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At a Glance Commentary:

Scientific Knowledge on the Subject

The challenges associated with efficiently identifying people with undiagnosed COPD in primary care settings are well-known. Identifying symptomatic patients with more severe airflow obstruction or at risk for exacerbation who will benefit from currently available therapeutic intervention has immediate clinical importance for these individuals. To date, questionnaires have been designed to identify people with COPD through population or clinic-based screening programs without reference to disease severity or exacerbation risk, resulting in the identification of a high proportion of patients with mild disease. The use of peak expiratory flow (PEF) has been proposed using various methods for gathering and interpreting the data.

What This Study Adds to the Field

This study used a novel multi-method approach to develop a process for identifying undiagnosed cases of COPD requiring treatment. CAPTURE™©, a simple 5-item patient-completed questionnaire, plus PEF, using an inexpensive easy to use mechanical device and interpretive thresholds, are able to differentiate cases and controls with remarkable precision, suggesting this is a viable approach for patient screening and COPD case identification in primary care settings. Further study is warranted.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

ABSTRACT

Objective: Develop a method for identifying undiagnosed COPD requiring treatment with currently available therapies (FEV_1 <60% predicted and/or exacerbation risk).

Methods: Multi-site, cross-sectional, case-control study in U.S. pulmonary and primary care clinics that recruited subjects from primary care settings. Cases: COPD and ≥ 1 exacerbation past year or FEV_1 <60% predicted without exacerbation past year. Controls: No COPD or mild COPD (FEV_1 ≥ 60% predicted, no exacerbation past year). Random forests analyses identified the smallest set of questions plus peak flow (PEF) with optimal sensitivity (SN) and specificity (SP).

Measurements and Main Results: PEF and spirometry were recorded in 186 cases and 160 controls; Mean (SD) age=62.7 (10.1) years; 55% female; 86% white; 16% never smoked. FEV_1% predicted for cases = 42.5% (14.2); controls=82.5% (15.7). A 5-item questionnaire (CAPTURE™©) assesses exposure, breathing problems, tiring easily, and acute respiratory illnesses. CAPTURE™© exhibited a SN of 95.7% and SP of 44.4% for differentiating cases from all controls, and SN of 95.7% and SP of 67.8% for differentiating cases from no-COPD controls. PEF [males < 350 liters per minute (L/min); females < 250 L/min] SN was 88.0% and SP was 77.5% for differentiating cases from all controls and 88.0%/90.8% for distinguishing cases from no-COPD controls. The CAPTURE ™© plus PEF exhibited improved SN (89.7%) and SP (78.1%) for all cases versus all controls, and 89.7%/93.1% for all cases versus no-COPD controls, respectively.

Conclusions: CAPTURE™© with PEF can identify COPD patients who would benefit from currently available therapy and require further diagnostic evaluation.

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Keywords: screening, COPD, primary care, questionnaire, random forests

Trial Registration: NCT01880177

INTRODUCTION

Evidence suggests that chronic obstructive pulmonary disease (COPD) is under-diagnosed in primary care settings, with most cases identified during an exacerbation or after significant loss of lung function (1). Undiagnosed patients have been suggested to have impaired health status (2) and outcomes (3, 4). Therapies are available to improve lung function, reduce exacerbations, and improve health status in patients with COPD, with evidence of therapeutic benefit clearly demonstrated and strongly recommended by the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society, in symptomatic people with forced expiratory volume in one second (FEV_1) <60% predicted or who are at risk for acute exacerbations (5, 6). The efficient identification of this group of unrecognized COPD patients, who we arbitrarily label as suffering from 'clinically significant COPD,' would therefore be important clinically.

To date, spirometry has served as the "gold standard" for COPD diagnosis (7) but as recently noted in the U.S. Preventive Services Task Force (USPSTF) report, it is not recommended for routine, general population or practice-based screening in asymptomatic patients (8). Questionnaires offer a practical triage or case-finding method for identifying symptomatic people in practice settings who may have unrecognized COPD and would benefit from treatment. The USPSTF noted that little data exist to support the widespread use of case-finding approaches as improved clinical outcomes and the limitations of overdiagnosis have not been established (8). Existing questionnaires were generally designed to identify people with COPD without reference to disease severity or exacerbation risk, resulting in the identification of a high proportion of patients with mild disease (9-17). To date, no methodology has been designed explicitly for the identification of people with undiagnosed COPD who are most likely to benefit from currently

available therapies (18). Several studies have tested the accuracy of handheld flow meters (FEV_1, FEV_6, peak expiratory flow [PEF]) for case identification with varying sensitivity and specificity (17). Although informative in terms of airflow obstruction, flow meters are unable to identify patients at risk of exacerbation nor to identify symptomatic patients. To overcome these weaknesses one investigative group suggested that a three-staged approach (risk-factor questionnaire, PEF, and spirometry) for identifying moderate to severe COPD (FEV_1<60% predicted) might improve sensitivity and specificity (19).

Although identification of patients with mild COPD is important for research into COPD natural history and disease prevention (6, 8, 20), identification of patients with symptomatic disease, more severe airflow obstruction (20) or at risk for exacerbation has immediate clinical importance for individual patients (5, 6, 21). An NHLBI task force reviewed the available literature and suggested the identification of these patients may prove to be an ideal, initial stage in systematically evaluating the potential impact of COPD case finding in primary care (22). We hypothesized that a combination of a questionnaire and PEF would optimally identify patients who would benefit from further diagnostic evaluation, e.g., those with an FEV_1 < 60% predicted and/or at risk of an exacerbation in primary care settings (17, 18). This paper describes the empirical methods used to develop a new COPD case-finding methodology, prior to testing its performance properties in a large prospective study in primary care setting across the United States.

METHODS

Design

This was a prospective, cross-sectional, multi-site, case-control study (Clinicaltrials.gov: NCT01880177) to select the best, smallest set of questions capable of differentiating cases and

controls, with and without PEF. COPD was defined by medical diagnosis with prescribed pharmacologic maintenance therapy and an $FEV_1/FVC < 0.70$. To address our primary goal cases included subjects with COPD and a history of ≥ 1 exacerbation in the prior 12 months (Group 1) or COPD with moderate to severe airflow obstruction ($FEV_1 < 60\%$ predicted) and exacerbation free > 12 months (Group 2). Controls included those with no known diagnosis or treatment for COPD (Group 3) and those with mild COPD ($FEV_1 > 60\%$ predicted and no exacerbation in the prior 12 months) (Group 4). The mild COPD group was included in the control group to focus the item selection process on identifying COPD patients most likely to benefit from currently available therapies. Identifying milder, symptomatic patients with undiagnosed disease would be an added benefit, but was not the intent of this study. An adjudication step was included to ensure unequivocal group assignment (see Online supplement).

Procedures

The investigators engaged primary care clinicians to identify males and females ≥ 40 years of age in 6 diverse geographical locations in the United States. The protocol was reviewed and approved by a central institutional review board (IRB) and IRBs at each investigative site. Following informed consent, each subject participated in one study visit, completing a questionnaire booklet with candidate items and sociodemographic- and health-related questions, PEF, and spirometry (see Online Supplement). To evaluate questionnaire test-retest reliability, a subset of subjects (n=111) completed the questionnaire booklet a second time, with additional questions to identify stable patients, defined as little or no self-reported change in breathing-related health during the past week. This booklet was completed at home 7 to 14 days following the clinic visit and returned by mail.

Measures

Questionnaire Candidate Item Pool

Results of earlier work, including a comprehensive literature review (18), qualitative interviews with patients from the target population (23), and analyses of existing data sets (24) were used to create 44 candidate items covering 6 content areas: exposure (6 items), family and personal health history (7 items), respiratory events during the prior 12 months (6 items), respiratory symptoms (12 items), other symptoms (5 items), and impact or effect of breathing-related issues on daily life (8 items). For ease of use, all items were dichotomous (Yes/No), with the exception of frequency of respiratory events (scored on a 3-point scale; none, 1, 2 or more).

CAT and mMRC Questionnaires

The COPD Assessment Test (CAT™) (25) and modified medical research council dyspnea scale (mMRC) (26) questionnaires were used to assess the presence and magnitude of respiratory symptoms in the sample and test the final questionnaire.

Analyses

A model-free data mining approach using random forests (27) [RF; R package randomForest (28)] analysis was used to derive the best, smallest set of questions from the pool of 44 candidate questions. Additional information on these analytical methods is provided in the Online Supplement.

The following predictive precision estimates were used to test the questionnaire and PEF: receiver operator characteristic (ROC) curves, area under the curve (AUC)(29), sensitivity, specificity, and overall misclassification error estimates. Questionnaire scores were also tested using traditional validation methods, including test-retest (intraclass correlation coefficient [ICC]) reliability and validity, including relationship with pulmonary function, CAT and mMRC

scores, and patient self-assessment of breathing-related health during the past week (Pearson product-moment). Analysis of covariance (ANCOVA) was used to examine scores by GOLD and COPD Foundation (COPDF) airflow limitation categories (6, 7), controlling for sex, smoking status, age, and group-by-sex interaction. Non-significant control variables were removed and the model was re-tested with the final variable set.

Performance properties of PEF alone were evaluated, including relationship to spirometry (Pearson product-moment), and GOLD and COPDF airflow limitation categories (6, 7). Predictive precision estimates were systematically tested using 50 ml increments stratified by sex to determine the optimal cut-off for differentiating cases and controls. Results were used to develop guidelines for using the questionnaire and PEF to refer patients for further diagnostic workup for COPD.

RESULTS

Sample

Three hundred ninety three English-speaking subjects were enrolled in the study and 380 subjects provided spirometry data for confirmation of case/control status (196 cases; 184 controls). Of these, 47 subjects exhibited spirometric values and clinical characteristics inconsistent with group assignment and were excluded from the analyses, yielding an analytical sample of 346 (186 cases, 184 with peak flow; 160 controls, all with peak flow).

Demographic and clinical characteristics for the analytical sample, cases, and controls are shown in Table 1. Sample characteristics for groups comprising cases [Groups 1 (n=97) and 2 (n=89)] and controls [Groups 3 (n=87) and 4 (n=73)] are provided in Table E1 and Table E2.

Questionnaire/Item Reduction

Using RF, the 44 candidate items were reduced to 34-item, 21-item, and finally to one 8-item and two different 5-item sets. Throughout the reduction process, the item sets maintained good performance, consistently misclassifying fewer than 27% of cases and controls, and with sensitivity greater than 80% and specificity greater than 70% (Figure E1a). Segregating cases versus controls with no COPD was more precise, misclassifying fewer than 14% of subjects, and with sensitivity greater than 85% and specificity greater than 88% (Figure E1b). All estimates improved with PEF in the model. Content coverage for the final three candidate sets is shown in Table E3.

Final Questionnaire

The final questionnaire selected for further testing is shown in Figure 1 and named CAPTURE™© (**C**OPD **A**ssessment in **P**rimary Care **T**o Identify **U**ndiagnosed **R**espiratory Disease and **E**xacerbation Risk). Various scoring algorithms were tested, including weighted and unweighted summation, with clinical use in mind (efficient and precise). The selected algorithm

is a simple summation of patient responses to each of the 5 items, yielding a questionnaire score ranging from 0 (no to all 5 questions) to 6 (yes to all questions and $\geq$ 2 respiratory events during the past year). Score distributions for cases and controls and by group are provided in Table E4. Precision estimates for two scoring thresholds when using the questionnaire alone, without PEF, are shown in Table E5, for clinicians who wish to use only the questionnaire to predict the need for spirometry.

The ROC curve and AUC for CAPTURE™© scores are shown in Figure 2. The performance of the final, recommended threshold for CAPTURE™© alone is shown in Table 2.

Test-retest reliability (ICC) was 0.85 (n=111). CAPTURE™© scores were significantly related to spirometry: FEV_1: r=0.47; FEV_1% predicted: r=0.53; FEV_1/FVC: r=0.50 (all $p < 0.0001$, N=344), CAT (r=0.74), mMRC rating (r=0.58), and self-assessment of breathing-related health (r=0.65) (all $p < 0.0001$, N=346). Differentiation of GOLD (F=28.67) and COPDF (F=29.59) categories was also significant (both p <0.0001). The Flesch-Kincaid grade level (United States), based on a combination of words, sentences, and syllables comprising the questionnaire, was determined to be 6.4 years, indicating this new questionnaire should be comprehensible to adults with a 6th grade education or above (https://en.wikipedia.org/wiki/Flesch%E2%80%93Kincaid_readability_tests).

Peak Flow (PEF)

PEF was significantly correlated with spirometric values (p<0.0001, N=344): FEV_1: r=0.82; FEV_1% predicted: r=0.70; and FEV_1/FVC: r=0.64 and differentiated GOLD (7) and COPDF categories (6) (Figure E2). PEF values distinguished cases and controls ($p < 0.0001$), and Groups 1-4 ($p < 0.0001$) (Figure E3), but were unable to differentiate COPD patients with previous exacerbation (Group 1) from COPD cases with an FEV_1 < 60% predicted (Group 2).

Using sensitivity and specificity data, the following cut-off scores were selected for identifying cases of clinically significant COPD using PEF alone: males: <350 L/min; females: <250 L/min (Figure E4). Sample sensitivity, specificity, and overall prediction error for these thresholds are shown in Table 2. Estimates by sex are provided in Table E6.

Questionnaire with Peak Expiratory Flow (PEF)

The best method for predicting case/control or group membership was a combination of questionnaire and PEF, where PEF is used only for mid-range scores as explained below. The performance of the questionnaire with selective use of PEF is shown in Table 2. The ROC AUC

for CAPTURE™© alone was inferior to that of CAPTURE™© with selective use of PEF ($p < 0.0001$). Similarly, the ROC AUC for PEF alone was inferior to that of CAPTURE™© with selective use of PEF ($p = 0.0065$). Under our scoring scenario, patients with scores of 0 or 1 are not considered at risk of exacerbation or COPD with an $FEV_1 < 60\%$ predicted; they would not require further evaluation. Those with a score of 5 or 6 (Yes to all items) are considered to have a high likelihood of symptomatic respiratory disease and/or exacerbation risk and should be referred for further evaluation, including spirometry. Thus, for low scores (0 or 1), or high scores (5 or 6), PEF testing is not required. Patients scoring in the middle range (2 to 4) undergo PEF testing, applying the 350/250 interpretation thresholds. In our sample, with four roughly equal-sized subject groups of exacerbation risk, severity risk, no COPD, and mild COPD, 52% of the subjects required PEF to determine if further diagnostic evaluation was indicated. The other 48% needed only the questionnaire.

DISCUSSION

COPD leads to substantial morbidity and mortality worldwide, appears to be greatly under-diagnosed, and is frequently first diagnosed after significant loss of lung function or at the time of an exacerbation. Earlier detection of COPD in patients most likely to benefit from current therapies could lead to improvement in short- and long-term patient outcomes (30). Although spirometry is the diagnostic gold standard (7), it is often perceived as time consuming and difficult to implement in primary care settings (31-33). Even the availability of less expensive and easily used spirometers, such as those used in the Burden of Lung Disease Study (34), have not resulted in increased utilization of testing in primary care settings (9). Using PEF to screen all patients in primary care is an unrealistic and expensive expectation, requiring supplies, staff time, and sufficiently careful execution to yield reliable results. Furthermore, neither spirometry

nor PEF assess clinical manifestations of disease, such as symptoms, impact, or exacerbation history. The USPSTF noted that little data exist to support the widespread use of COPD case-finding as improved clinical outcomes have not been established through their use (8). Existing questionnaires have generally identified a high proportion of patients with mild disease (9-17). No methodology has been designed explicitly for the identification of patients with undiagnosed COPD who are most likely to benefit from currently available therapies (18). Identifying these patients was recommended by an NHLBI task force as an ideal, initial stage in systematically confirming the positive impact of COPD case-finding in primary care (22). We used an innovative, multi-method approach to develop a case-finding methodology that uses a brief patient self-administered questionnaire as an initial screen, with PEF performed on a subset of patients with positive questionnaire results, to determine which patients should be referred for further diagnostic evaluation for COPD.

Our questionnaire development method used data mining to select the best, smallest set of items from a comprehensive list of candidate items derived from the literature (18), analyses of existing data (24), and qualitative research (23). This approach was unique for several reasons. First, it included focus groups and interviews with people from the target population, to inform the content and wording of the candidate questions. Second, we generated a comprehensive item pool based on the literature, existing data, and patient insight, with all questions treated as a viable candidate for the final instrument. Third, we used random forests for item selection, rather than bivariate or multi-variate statistical models. RF is completely model-free; it does not presume any distribution for predictor variables, linear or otherwise, and takes into account the entanglement, or hidden interactions, of predictor variables, which would otherwise have to be

poorly specified or missed completely. This method uses the full complexity of the data file, enabling patterns to emerge that traditional techniques would overlook.

CAPTURE™© is a short, 5-item questionnaire that can be easily completed by patients in primary care settings, prior to or during a clinic visit. Simple yes/no questions and a summated scoring algorithm are used to identify individuals who may have undiagnosed, clinically significant COPD, with PEF furthering the accuracy of case identification. Importantly, the patient-centered item reduction process we utilized resulted in a questionnaire with content that differs from previous screening or case-finding tools (17, 18). Specifically, it does *not* include an explicit question on smoking history. Rather, it asks about exposure, extending the risk assessment beyond smoking, to occupational and environmental history that can increase risk of COPD. This does not preclude clinicians from asking smokers to complete the questionnaire, but rather assesses risk beyond smoking, which is likely to be particularly useful for those in high-risk settings. Seasonal or daily variation in breathing, the impact of shortness of breath on activity, easy fatigability, and the number of missed activities due to a respiratory event the previous year complete the assessment. These items are understandable and meaningful to patients (23) and, taken together, yield important information for clinicians on risk factors for and health effects of lung disease that could be allayed through education and treatment.

We propose a case-finding methodology that integrates a simple self-administered questionnaire with the selective use of PEF measurement to optimize sensitivity, specificity, and efficiency. Individuals with mid-range CAPTURE™© scores (2 to 4) undergo PEF measurement using a familiar, inexpensive mechanical device for a quick clinical assessment of airflow obstruction using thresholds for easy interpretation. We chose PEF measurement based on previous research (19) and known difficulties establishing spirometry in primary care settings (35). Previous

investigators have used PEF in a broader fashion to identify airflow obstruction (36, 37). In our study, PEF was remarkably sensitive and specific for differentiating cases and controls, with precision improving when controls were limited to subjects with no COPD. Our estimates with a simple mechanical meter were as good or better than previous studies of handheld flow meters (17) and simpler than results obtained with diagnostic-quality spirometers (37). It is unrealistic to propose or expect PEF to be used as a screening tool in primary care settings for all patients. More importantly, PEF does not address exacerbation risk or symptomatic manifestations of disease, however, unless the risk or symptoms coincide with airway obstruction. The latter has not proven to fully be the case (38). Our approach begins with a simple questionnaire patients can complete independently, at home or in the office, with the results easily scored and interpreted by the clinician. PEF adds precision to the case-identification process, but is performed only as needed. The combination of our questionnaire and PEF exhibited improved operating characteristics than either alone. The sensitivity of CAPTURE$^{TM©}$ scores will permit fewer missed cases of clinically significant COPD, while the higher levels of specificity provided by PEF will result in fewer false positives and lower overall screening costs. The operating characteristics of our approach, that should minimize overdiagnosis, are improved over the majority of previous strategies (17, 18, 39); the others with similar or slightly better characteristics were developed in higher risk populations (40, 41).

We elected to develop an approach optimized for the identification of undiagnosed patients with significant airflow obstruction and/or exacerbation risk, i.e., those most likely to benefit from currently available therapies and included in recent therapeutic algorithms (6, 7, 21). This flows from the recommendations of an NHLBI task force that suggested the identification of these patients as an initial stage in confirming the positive impact of COPD case-finding in primary

care (22). We did not specifically attempt to separate these two groups of COPD patients that would benefit from current therapies nor did we attempt to generate a severity measure. Importantly, our approach should not be viewed as a diagnostic test but a case-finding approach to identify patients who should undergo additional, definitive diagnostic testing (7).

We did not attempt to develop a case-finding approach to identify all COPD patients. A group of smokers with symptoms, adverse clinical outcomes but without airflow obstruction has been identified (42). The role of therapy in these patients remains unclear. Treatments that could prevent COPD progression would be a major advance and would support identifications of individuals with early disease (20). The extent to which CAPTURE$^{TM©}$ and PEF would be useful for this purpose remains to be determined.

Several limitations of this study should be noted. First, sites included pulmonary clinics in addition to primary care settings, although primary clinicians were engaged at all specialty centers in identifying appropriate study subjects. Further study is needed to assure generalizability to patients in a broader number of primary care practices. Second, experienced clinical research personnel administered PEF and spirometry. The feasibility and precision of administering these tests as a complement to a simple, patient self-administered questionnaire should be evaluated in a variety of primary care clinical settings. Third, we enrolled a limited number of patients with mild airflow obstruction and exacerbation risk. Future studies should adequately sample this population as cohort studies have suggested that COPD patients with lesser airflow obstruction (38) or non-obstructed, but symptomatic smokers (42) are at risk of exacerbations. Fourth, the approach focused on the identification of obstructive airway disease; other cardiorespiratory diseases were not the target population. Fifth, RF is one of many learning machines, with new ones emerging regularly. It is possible that another learning machine applied

to the same data could be better, although in our experience, RF is competitive across a wide range of data sets. Finally, it is not known whether the identification of previously undiagnosed but symptomatic patients meeting our criteria will lead to earlier treatment and improved outcomes. Prospective studies testing the effects of case identification and treatment on patient outcomes are urgently needed.

CONCLUSION

We developed a case-finding methodology that uses 5 simple patient-reported questions and selective use of PEF for identifying patients in need of further diagnostic evaluation for COPD, initially focusing on those most likely to benefit from treatment. Results of the development work suggest this method is sensitive and specific, and may offer an efficient case-finding approach for primary care. Future study of the performance properties of this method in primary care settings is warranted.

REFERENCES

1. Ford ES, Mannino DM, Wheaton AG, Giles WH, Presley-Cantrell L, Croft JB. Trends in the prevalence of obstructive and restrictive lung function among adults in the United States: Findings from the national health and nutrition examination surveys from 1988-1994 to 2007-2010. *Chest* 2013;143:1395-1406.

2. Miravitlles M, Soriano JB, Garcia-Rio F, Munoz L, Duran-Tauleria E, Sanchez G, Sobradillo V, Ancochea J. Prevalence of COPD in Spain: Impact of undiagnosed COPD on quality of life and daily life activities. *Thorax* 2009;64:863-868.

3. Martinez CH, Mannino DM, Jaimes FA, Curtis JL, Han MK, Hansel NN, Diaz AA. Undiagnosed obstructive lung disease in the United States. Associated factors and long-term mortality. *Ann Am Thorac Soc* 2015;12:1788-1795.

4. Labonte LE, Tan WC, Li PZ, Mancino P, Aaron SD, Benedetti A, Chapman KR, Cowie R, FitzGerald JM, Hernandez P, Maltais F, Marciniuk DD, O'Donnell D, Sin D, Bourbeau J, Canadian Respiratory Research N, the CanCold Collaborative Research group. Undiagnosed COPD contributes to the burden of health care utilization: Data from the cancold study. *Am J Respir Crit Care Med* 2016.

5. Qaseem A, Snow V, Shekelle P, Sherif K, Wilt TJ, Weinberger S, Owens DK. Diagnosis and management of stable chronic obstructive pulmonary disease: A clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2007;147:633-638.

6. Rennard S, Thomashow B, Crapo J, Yawn B, McIvor A, Cerreta S, Walsh J, Mannino D. Introducing the COPD foundation guide for diagnosis and management of COPD, recommendations of the COPD foundation. *COPD* 2013;10:378-389.

7. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, Stockley RA, Sin DD, Rodriguez-Roisin R. 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.

8. 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;315:1378-1393.

9. Freeman D, Nordyke RJ, Isonaka S, Nonikov DV, Maroni JM, Price D, Halbert RJ. Questions for COPD diagnostic screening in a primary care setting. *Respir Med* 2005;99:1311-1318.

10. Hanania NA, Mannino DM, Yawn BP, Mapel DW, Martinez FJ, Donohue JF, Kosinski M, Rendas-Baum R, Mintz M, Samuels S, Jhingran P, Dalal AA. Predicting risk of airflow obstruction in primary care: Validation of the lung function questionnaire (LFQ). *Respir Med* 2010;104:1160-1170.

11. Martinez FJ, Raczek AE, Seifer FD, Conoscenti CS, Curtice TG, D'Eletto T, Cote C, Hawkins C, Phillips AL, COPD-Ps Clinician Working Group. Development and initial validation of a self-scored COPD population screener questionnaire (COPD-PS). *COPD* 2008;5:85-95.

12. Price DB, Tinkelman DG, Halbert RJ, Nordyke RJ, Isonaka S, Nonikov D, Juniper EF, Freeman D, Hausen T, Levy ML, Ostrem A, van der Molen T, van Schayck CP. Symptom-based questionnaire for identifying COPD in smokers. *Respiration* 2006;73:285-295.

13. Price DB, Tinkelman DG, Nordyke RJ, Isonaka S, Halbert RJ, COPD Questionnaire Study Group. Scoring system and clinical application of COPD diagnostic questionnaires. *Chest* 2006;129:1531-1539.

14. Raghavan N, Lam YM, Webb KA, Guenette JA, Amornputtisathaporn N, Raghavan R, Tan WC, Bourbeau J, O'Donnell DE. Components of the COPD assessment test (CAT) associated with a diagnosis of COPD in a random population sample. *COPD* 2012;9:175-183.

15. Yawn BP, Mapel DW, Mannino DM, Martinez FJ, Donohue JF, Hanania NA, Kosinski M, Rendas-Baum R, Mintz M, Samuels S, Dalal AA, Lung Function Questionnaire Working Group. Development of the lung function questionnaire (LFQ) to identify airflow obstruction. *Int J Chron Obstruct Pulmon Dis* 2010;5:1-10.

16. Kotz D, Nelemans P, van Schayck CP, Wesseling GJ. External validation of a COPD diagnostic questionnaire. *Eur Respir J* 2008;31:298-303.

17. Haroon S, Jordan R, Takwoingi Y, Adab P. Diagnostic accuracy of screening tests for COPD: A systematic review and meta-analysis. *BMJ Open* 2015;5:e008133.

18. Han MK, Steenrod AW, Bacci ED, Leidy NK, Mannino DM, Thomashow BM, Barr RG, Make BJ, Bowler RP, Rennard SI, Houfek JF, Yawn BP, Meldrum CA, Walsh JW, Martinez FJ. Identifying patients with undiagnosed copd in primary care settings: Insight from screening tools and epidemiologic studies. *Chronic Obstr Pulm Dis (Miami)* 2015;2:103-121.

19. Nelson SB, LaVange LM, Nie Y, Walsh JW, Enright PL, Martinez FJ, Mannino DM, Thomashow BM. Questionnaires and pocket spirometers provide an alternative approach for COPD screening in the general population. *Chest* 2012;142:358-366.

20. Rennard SI, Drummond MB. Early chronic obstructive pulmonary disease: Definition, assessment, and prevention. *Lancet* 2015;385:1778-1788.

21. Criner GJ, Bourbeau J, Diekemper RL, Ouellette DR, Goodridge D, Hernandez P, Curren K, Balter MS, Bhutani M, Camp PG, Celli BR, Dechman G, Dransfield MT, Fiel SB, Foreman MG, Hanania NA, Ireland BK, Marchetti N, Marciniuk DD, Mularski RA, Ornelas J, Road JD, Stickland MK. Executive summary: Prevention of acute exacerbation of COPD: American college of chest physicians and canadian thoracic society guideline. *Chest* 2015;147:883-893.

22. National Heart Lung and Blood Institute. A case-finding strategy for moderate-to-severe COPD in the United States. 2009 [cited 2016 July 4]. Available from: http://www.nhlbi.nih.gov/research/reports/2009-case-finding-exesum.

23. Leidy NK, Kim K, Bacci ED, Yawn BP, Mannino DM, Thomashow BM, Barr RG, Rennard SI, Houfek JF, Han MK, Meldrum CA, Make BJ, Bowler RP, Steenrod AW, Murray LT, Walsh JW, Martinez F, High-Risk Copd Screening Study Group. Identifying cases of undiagnosed, clinically significant COPD in primary care: Qualitative insight from patients in the target population. *NPJ Prim Care Respir Med* 2015;25:15024.

24. Leidy NK, Malley KG, Steenrod AW, Mannino DM, Make BJ, Bowler RP, Thomashow BM, Barr RG, Rennard SI, Houfek JF, Yawn BP, Han MK, Meldrum CA, Bacci ED, Walsh JW,

Martinez F. Insight into best variables for COPD case identification: A random forests analysis. *Chronic Obstr Pulm Dis (Miami)* 2016;3:406-418.

25. 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;34:648-654.

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

27. Malley JD, Malley KG, Pajevic S. Statistical learning for biomedical data. Cambridge: Cambridge University Press; 2011.

28. The Comprehensive R Archive Network. 2014 [cited 2016 24 March]. Available from: http://cran.us.r-project.org/.

29. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics* 1988;44:837-845.

30. Ramsey SD, Sullivan SD. Chronic obstructive pulmonary disease: Is there a case for early intervention? *Am J Med* 2004;117 Suppl 12A:3S-10S.

31. Ferguson GT, Enright PL, Buist AS, Higgins MW. Office spirometry for lung health assessment in adults: A consensus statement from the national lung health education program. *Chest* 2000;117:1146-1161.

32. Han MK, Kim MG, Mardon R, Renner P, Sullivan S, Diette GB, Martinez FJ. Spirometry utilization for COPD: How do we measure up? *Chest* 2007;132:403-409.

33. Joo MJ, Lee TA, Weiss KB. Geographic variation of spirometry use in newly diagnosed COPD. *Chest* 2008;134:38-45.

34. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, Menezes AM, Sullivan SD, Lee TA, Weiss KB, Jensen RL, Marks GB, Gulsvik A, Nizankowska-Mogilnicka E, Bold Collaborative Research Group. International variation in the prevalence of COPD (the BOLD Study): A population-based prevalence study. *Lancet* 2007;370:741-750.

35. Enright PL. Should we keep pushing for a spirometer in every doctor's office? *Respir Care* 2012;57:146-151;discussion 151-143.

36. Mahboub B, Alzaabi A, Soriano JB, Salameh L, Mutairi YA, Yusufali AA, Alsheikh-ali A, Almahmeed W, Haughney J. Case-finding of chronic obstructive pulmonary disease with questionnaire, peak flow measurements and spirometry: A cross-sectional study. *BMC Res Notes* 2014;7:241.

37. Perez-Padilla R, Vollmer WM, Vazquez-Garcia JC, Enright PL, Menezes AM, Buist AS, Bold, Platino Study Groups. Can a normal peak expiratory flow exclude severe chronic obstructive pulmonary disease? *Int J Tuberc Lung Dis* 2009;13:387-393.

38. Hurst JR, Vestbo J, Anzueto A, Locantore N, Mullerova H, Tal-Singer R, Miller B, Lomas DA, Agusti A, Macnee W, Calverley P, Rennard S, Wouters EF, Wedzicha JA, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints Investigators. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010;363:1128-1138.

39. Guirguis-Blake JM, Senger CA, Webber EM, Mularski R, Whitlock EP. Screening for chronic obstructive pulmonary disease: A systematic evidence review for the U.S. Preventive services task force. Evidence synthesis no. 130. Ahrq publication no. 14-05205-ef-1. Rockville, MD: Agency for Healthcare Research and Quality; 2015.

40. Zarowitz BJ, O'Shea T, Lefkovitz A, Peterson EL. Development and validation of a screening tool for chronic obstructive pulmonary disease in nursing home residents. *J Am Med Dir Assoc* 2011;12:668-674.

41. Mullerova H, Wedzicha J, Soriano JB, Vestbo J. Validation of a chronic obstructive pulmonary disease screening questionnaire for population surveys. *Respir Med* 2004;98:78-83.

42. Woodruff PG, Barr RG, Bleecker E, Christenson SA, Couper D, Curtis JL, Gouskova NA, Hansel NN, Hoffman EA, Kanner RE, Kleerup E, Lazarus SC, Martinez FJ, Paine R, 3rd, Rennard S, Tashkin DP, Han MK, Spiromics Research Group. Clinical significance of symptoms in smokers with preserved pulmonary function. *N Engl J Med* 2016;374:1811-1821.

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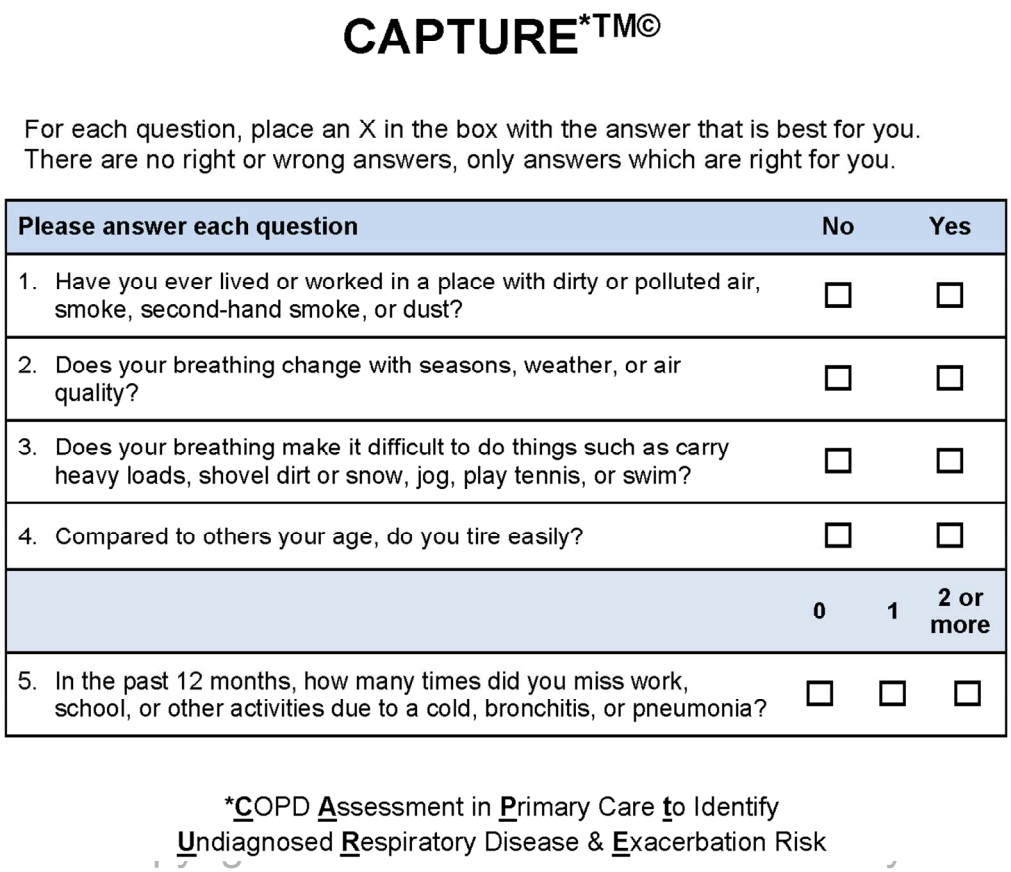
The COPD Foundation contributed PEF meters for this study, Christine Thompson assisted with statistical programming, and Kathryn Miller performed manuscript text editing and formatting.

FIGURE LEGENDS

Figure 1. CAPTURE™© (COPD Assessment in Primary Care To Identify Undiagnosed Respiratory Disease and Exacerbation Risk)



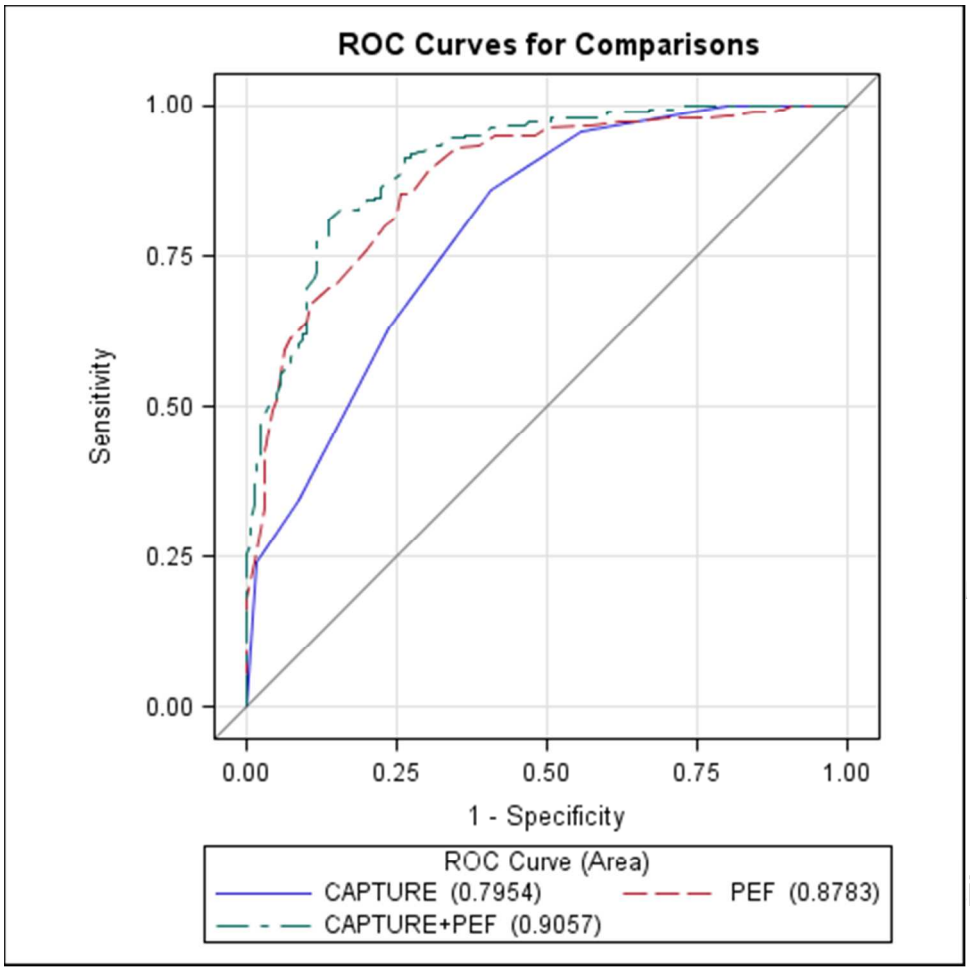
CAPTURE*™©

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?	☐		☐
2. Does your breathing change with seasons, weather, or air quality?	☐		☐
3. Does your breathing make it difficult to do things such as carry heavy loads, shovel dirt or snow, jog, play tennis, or swim?	☐		☐
4. Compared to others your age, do you tire easily?	☐		☐
	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?	☐	☐	☐

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

Figure 2. ROC Curves and AUC Statistics for Differentiating Cases and Controls Using CAPTURE™© alone, Peak Expiratory Flow (PEF) alone, and PEF+CAPTURE™©



Abbreviations: AUC=Area Under the Curve; PEF=Peak Flow

TABLES

Table 1. Demographic and Clinical Characteristics

Characteristic	Analytic Sample* (N=346)	Cases (n=186)	Controls (n=160)
Age (years)			
Mean (SD)	62.7 (10.1)	64.0 (9.7)	61 (10.5)
Range	40–88	42–88	40–88
Sex, n (%) male	154 (45)	88 (47)	66 (41)
Ethnic background, n (%)†			
Hispanic or Latino‡	7 (2)	5 (3)	2 (1)
Not Hispanic or Latino	325 (94)	173 (93)	152 (95)
Racial background, n (%)†			
White	299 (86)	160 (86)	139 (87)
Black or African American	34 (10)	18 (10)	16 (10)
American Indian; Alaska Native; Asian; Other	13 (4)	8 (4)	5 (3)
Employment, n (%)			
Employed (full- or part-time)	118 (34)	48 (26)	70 (44)
Retired	137 (40)	78 (42)	59 (37)
Disabled	69 (19)	48 (26)	21 (13)
Other§	22 (6)	12 (6)	10 (6)
Education status, n (%)			
High school or less	143 (41)	89 (48)	54 (34)
Some college, vocational training	76 (22)	40 (22)	36 (23)
College degree or more	127 (37)	57 (31)	70 (44)
Smoking history, n (%)			
Never or <100 cigarettes	60 (18)	7 (4)	53 (33)
Former	196 (57)	120 (65)	76 (48)
Current	90 (26)	59 (32)	31 (19)
Spirometry, mean (SD)			
FEV_1	1.7 (0.82)	1.2 (0.47)	2.3 (0.69)
FEV_1% predicted	61.0 (24.90)	42.5 (14.20)	82.5 (15.67)
FEV_1/FVC	0.6 (0.17)	0.5 (0.13)	0.7 (0.11)
GOLD classification, airflow limitation, n (%)			
No COPD	87 (25)	0 (0)	87 (54)
GOLD 1/2 – mild/moderate	131 (38)	58 (31)	73 (46)
GOLD 3 – severe	90 (26)	90 (48)	0 (0)
GOLD 4 – very severe	38 (11)	38 (20)	0 (0)
COPD Foundation classification, n (%)			
SG0 – Normal	68 (20)	0 (0)	68 (43)
SG1 – Mild	86 (25)	13 (7)	73 (46)
SG2 – Moderate	135 (39)	135 (73)	0 (0)
SG3 – Severe	38 (11)	38 (20)	0 (0)
SGU – Undefined	19 (6)	0 (0)	19 (12)
CAT™, mean (SD)	15.2 (9.6)	19.7 (8.4)	10.1 (8.4)
mMRC, mode	1 (34)	1 (39)	0 (56)
Co-morbid health conditions (any), n (%) yes	317 (92)	168 (90)	149 (93)
Self-report activity on most days, n %			
Sit or lie down most of the day	65 (19)	49 (26)	16 (10)
Very active or exercise	153 (44)	63 (34)	90 (56)

Abbreviations: CAT™=COPD Assessment Test; COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; GOLD= Global Initiative for Chronic Obstructive Lung Disease; mMRC= modified medical research council dyspnea scale; SG=spirometry grade

*English-speaking, Groups 1–4, with informed consent and spirometry

†Subject self-identified

‡Excludes Spanish language (n=31), analyzed separately

§Other: Homemaker, Unemployed, Not specified

Table 2. Predictive Performance of PEF Alone, Questionnaire Alone, and Questionnaire + Selective Use of PEF

Score Cut-Off Performance Indicator	Cases (Groups 1+2) vs. Controls (Groups 3+4) (N=346)	Cases (Groups 1+2) vs. No COPD (Group 3) (n=273)	COPD with Exacerbation (Group 1) vs. Controls (Groups 3+4) (n=257)	COPD with FEV_1 <60% Predicted (Group 2) vs. Controls (Groups 3+4) (n=249)
PEF alone; threshold (males < 350; females < 250)				
Sensitivity	88.0%	88.0%	91.7%	84.1%
Specificity	77.5%	90.8%	77.5%	77.5%
Overall error	16.9%	11.1%	17.2%	20.2%
Questionnaire alone; scores ≥ 2				
Sensitivity	95.7%	95.7%	96.9%	94.4%
Specificity	44.4%	67.8%	44.4%	44.4%
Overall error	28.0%	13.2%	35.8%	37.8%
Score 0–1 = control Score 5–6 = case Score 2,3,4 = PEF used for group assignment				
Sensitivity	89.7%	89.7%	93.8%	85.2%
Specificity	78.1%	93.1%	78.1%	78.1%
Overall error	15.7%	9.2%	16.0%	19.4%

Abbreviations: COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in one second; PEF=peak expiratory flow

A New Approach for Identifying Patients with Undiagnosed Chronic Obstructive Pulmonary Disease

Fernando Martinez, MD, MS; David Mannino, MD; Nancy Kline Leidy, PhD; Karen G Malley, BA; Elizabeth D Bacci, PhD; R Graham Barr, MD; Russ P Bowler, MD; MeiLan K Han, MD, MS; Julia F Houfek, PhD; Barry Make, MD; Catherine A Meldrum, PhD; Stephen Rennard, MD; Byron Thomashow, MD; John Walsh; Barbara P Yawn, MD, MSc; for the High-Risk-COPD Screening Study Group

ONLINE DATA SUPPLEMENT

Procedures

Research staff supervised PEF administration using a Vitalograph® AsmaPlan® mechanical PEF meter with SafeTway® disposable mouthpieces (Vitalograph LTD, UK). Each subject performed three maneuvers, with the highest value (liters per minute [L\min]) used for analysis. Pre-bronchodilator spirometry (FEV_1, FEV_1% predicted, FEV_1/forced vital capacity [FVC])) was performed to confirm assignment to the correct case-control group if spirometry results from the past 5 years were not available.

Case Adjudication

An adjudication step was included to ensure unequivocal group assignment. The following data profiles from subjects with contradictory spirometry and diagnostic history/group assignment were reviewed prior to database lock and data analysis: FEV_1/FVC, FEV_1% predicted, medical diagnosis of COPD or asthma, pharmacologic treatment for COPD, 12 month exacerbation history, smoking status, and age. This panel did not have information on the participant's questionnaire responses or PEF results during this stage of the study. Removal from the analytical sample was based on consensus decision of the panel of experts leading the study. Data from the excluded subjects were categorized as potential underdiagnosis (n=16) or potential overdiagnosis (n=31), and set aside for post hoc analyses.

Statistical Analyses

Item Reduction Process

A statistical analysis plan (SAP) was developed prior to database lock and used to guide the analyses. Random forests (RF; R package randomForest) (E1) were used to derive the smallest set of items that could differentiate cases and controls with a degree of accuracy comparable to or better than larger item sets. RF is a highly nonparametric machine learning, or data mining, analytical method that

builds forests of decision trees to predict a subject's group, and identify and validate variables most important in prediction (E2). In this study, the goal was to predict case/control status or membership in Groups 1, 2, 3, or 4. Decision trees are constructed with randomly selected subsets of subjects and variables, and are completely model-free, making no assumptions whatsoever about the data. The error rate for each tree is computed using the subjects who were not selected for the tree, called the out of bag set (OOB). This process is similar to setting aside a portion of data for testing, but automatically done for every tree, not just once for the analysis. There is no need, when using RF, to set aside a validation sample. This method provides an unbiased estimate of the true error. "Forests" of these trees make a prediction for each subject. With proper use of tuning parameters, RF does not overfit.

Item reduction was an iterative process; RF analyses were performed with and without PEF in the variable list, and across sub-groups (e.g., Groups 1, 2 versus 3; Group 1 versus 2, 3; Group 2 versus 2, 3) to identify robustly predictive item(s). The first RF analyses were performed with the entire set of 44 items comprising the item pool. The first RF analyses were performed with the entire set of 44 items comprising the item pool. The variable importance measure was used to remove the least important items and new RF analyses were performed, assessing error rates relative to the previous round. Variable importance is the mean decrease in prediction accuracy when the variable's values are randomly permuted, standardized to a 0–100 range with higher values indicating greater relative importance. This rating is a function of all other variables in the model; if one or more variables are removed, the importance rating changes.

The overall (out-of-bag or OOB) error rate was tracked during item reduction. This error rate is the misclassification rate resulting from each tree being tested on data not used to build the tree (the OOB sample), as described above, averaged over all trees in the forest and then over all forests in

the analysis. With the best sets identified, sensitivity and specificity of each set were computed, where sensitivity is 1 – (error rate for cases) and specificity is 1 – (error rate for controls).

Candidate Item Sets

Three best candidate items sets were selected based on the fewest number of items and best performance properties, with the case-control analyses serving as primary and group-specific analyses secondary. Performance properties with and without PEF were also examined. A description of the items comprising these sets is shown in Table E3. A question about smoking appeared in Set C, but did not appear in the other item sets.

The performance properties of the final three candidate item sets is shown in Figure E1. Item Set C had the greatest error and lowest sensitivity and specificity, with and without PEF. Balancing the number of items and the performance of Sets A and B, the study group selected set B as the final measure, which was named "CAPTURE." The questionnaire in its entirety is provided in the main paper.

Cases vs Controls by Group

The distributional properties of CAPTURE scores for cases, controls, and by group are shown in Table E4. Performance properties using two cut-off scores are shown in Table E5. The same sensitivity levels are observed for differentiating cases versus controls and cases versus no-COPD controls. The two cut-off values have greater specific and lower error differentiating cases versus no-COPD controls.

Exploratory analyses of mild COPD versus No COPD showed a specificity of 83.6%, sensitivity of 67.8%, and error of 25% using the 2-point cut-off rule, suggesting the "error" seen in the case-control analyses is attributable, in part, to the identification of mild patients. This can be seen as advantageous, allowing users to pick up not only the most severe undiagnosed cases, but milder

cases as well, with relatively few cases of non COPD. Including PEF in the screening process, using CAPTURE+PEF with the cut-off values identified in the current study, yielded sensitivity of 39.7%, specificity of 93.1% and error of 31.3%, suggesting alternative PEF values may be needed to identify milder cases. Exploratory analyses of cases versus mild COPD using CAPTURE+PEF showed a specificity of 89.7%, sensitivity of 60.3%, and error of 18.7%. Further study of the use of CAPTURE and CAPTURE plus PEF for identifying mild COPD is warranted.

References

E1. The Comprehensive R Archive Network. 2014. http://cran.us.r-project.org/. Accessed March 24, 2016.

E2. Malley JD, Malley KG, Pajevic S. Statistical learning for biomedical data. Cambridge: Cambridge University Press; 2011.

Table E1. Demographic Characteristics by Group*

Characteristic	Cases (n=186)		Controls (n=160)	
	Group 1 Exacerbation History (n=97)	Group 2 FEV_1 < 60% (n=89)	Group 3 No COPD (n=87)	Group 4 Mild COPD (n=73)
Age (years)				
Mean (SD)	63.4 (10.30)	64.6 (9.0)	58.1 (10.5)	65.2 (9.1)
Range	42–87	42–88	40–88	49–85
Sex, n (%) male	42 (43)	46 (52)	26 (30)	40 (55)
Ethnic background, n (%)†				
Hispanic or Latino‡	3 (3)	2 (2)	1 (1)	1 (1)
Not Hispanic or Latino	90 (93)	83 (93)	84 (97)	68 (93)
Racial background, n (%)†				
White	79 (81)	81 (91)	73 (84)	66 (90)
Black or African American	14 (14)	4 (5)	11 (13)	5 (7)
American Indian; Alaska Native; Asian; Other	2 (2)	2 (2)	1 (1)	1 (1)
Employment, n (%)				
Employed (full- or part-time)	24 (25)	24 (27)	55 (63)	15 (21)
Retired	38 (39)	40 (45)	22 (25)	37 (51)
Disabled	30 (31)	18 (20)	3 (3)	18 (25)
Other§	5 (5)	7 (8)	7 (8)	3 (4)
Education status, n (%)				
High school or less	46 (47)	43 (48)	18 (21)	36 (49)
Some college, vocational training	20 (21)	20 (23)	22 (25)	14 (19)
College degree or more	31 (32)	26 (29)	47 (54)	23 (32)

Abbreviations: COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in one second

*English-speaking, Groups 1–4, with informed consent and spirometry

†Subject self-identified

‡Excludes Spanish language (n=31), analyzed separately

§Other: Homemaker, Unemployed, Not specified

Table E2. Clinical Characteristics by Group*

Characteristic	Cases (n=186)		Controls (n=160)	
	Group 1 Exacerbation History (n=97)	Group 2 FEV_1 < 60% (n=89)	Group 3 No COPD (n=87)	Group 4 Mild COPD (n=73)
Smoking history, n (%)				
Never or <100 cigarettes	3 (3%)	4 (3%)	51 (59%)	2 (3%)
Former	65 (67%)	55 (62%)	28 (32%)	48 (66%)
Current	29 (30%)	30 (34%)	8 (9%)	23 (32%)
Spirometry, mean (SD)				
FEV_1	1.1 (0.5)	1.2 (0.5)	2.6 (0.7)	2.1 (0.6)
FEV_1% predicted	42.5 (16.6)	42.7 (11.1)	89.7 (14.6)	74.0 (12.4)
FEV_1/FVC	0.5 (0.1)	0.5 (0.1)	0.8 (0.1)	0.6 (0.1)
GOLD classification, airflow limitation, n (%)				
No COPD	0 (0%)	0 (0%)	87 (100%)	0 (0%)
GOLD 1/2 – Mild/Moderate	28 (29%)	30 (34%)	0 (0%)	73 (100%)
GOLD 3 – Severe	45 (46%)	45 (51%)	0 (0%)	0 (0%)
GOLD 4 – Very Severe	24 (25%)	14 (16%)	0 (0%)	0 (0%)
COPD Foundation classification, n (%)				
SG0 – Normal	0 (0%)	0 (0%)	68 (78%)	0 (0%)
SG1 – Mild	13 (13%)	0 (0%)	0 (0%)	73 (100%)
SG2 – Moderate	60 (62%)	75 (84%)	0 (0%)	0 (0%)
SG3 – Severe	24 (25%)	14 (16%)	0 (0%)	0 (0%)
SGU - Undefined	0 (0%)	0 (0%)	10 (22%)	0 (0%)
CAT™, mean (SD)	22.5 (7.7)	16.5 (8.0)	5.5 (5.4)	15.6 (8.0)
mMRC, mode	1 (42%)	1 (36%)	0 (82%)	1 (45%)
Co-morbid health conditions (any), n (%) yes	90 (93%)	78 (88%)	76 (87%)	73 (100%)
Self-report activity on most days, n %				
Sit or lie down most of the day	31 (32%)	18 (20%)	6 (7%)	10 (14%)
Very active or exercise	24 (25%	39 (44%)	55 (63%)	35 (48%)

Abbreviations: CAT™=COPD Assessment Test; COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; GOLD= Global Initiative for Chronic Obstructive Lung Disease; mMRC= modified medical research council dyspnea scale; SG=spirometry grade

*English-speaking subjects in Groups 1–4 with informed consent and spirometry

Table E3. Content Areas and Items Represented in the Final Candidate Item Sets (Questionnaires)

Content Area	Item Description	Candidate Item Sets (Questionnaires)		
		A (8 items)	B* (5 items)	C (5 items)
Exposure†	Ever lived or worked with dirty air, smoke, or dust	✓	✓	
	Change in breathing due to seasons or air quality	✓	✓	✓
	Ever smoked			✓
12-Month History of Respiratory Events‡	Missed work/activities due to an acute respiratory condition	✓	✓	✓
Symptoms – Respiratory†	Cough around perfume, grass, or smoke	✓		
	Ever short of breath	✓		
Symptoms – Other†	Tire easily	✓	✓	✓
Impact†	Breathing makes it difficult to carry heavy things, shovel snow, or play sports	✓	✓	
	Given up activities due to shortness of breath	✓		✓

*Final measure (CAPTURE™©)
†Response scales: yes/no
‡Response scale: 0, 1, ≥2

Table E4. Frequency Distribution of CAPTURE Scores for Cases and Controls and by Group

				Cases		Controls	
Score	**All Participants (N=346)**	**Cases (n=186)**	**Controls (n=160)**	**Group 1 Exacerbation History (n=97)**	**Group 2 FEV_1 < 60% Predicted (n=89)**	**Group 3 No COPD (n=87)**	**Group 4 Mild COPD (n=73)**
0	32 (9.2%)	0 (0.0%)	32 (20.0%)	0 (0.0%)	0 (0.0%)	29 (33.3%)	3 (4.1%)
1	47 (13.6%)	8 (4.3%)	39 (24.4%)	3 (3.1%)	5 (5.6%)	30 (34.5%)	9 (12.3%)
2	42 (12.1%)	18 (9.7%)	24 (15.0%)	5 (5.2%)	13 (14.6%)	11 (12.6%)	13 (17.8%)
3	69 (19.9%)	42 (22.6%)	27 (16.9%)	16 (16.5%)	26 (29.2%)	7 (8.0%)	20 (27.4%)
4	78 (22.5%)	54 (29.0%)	24 (15.0%)	23 (23.7%)	31 (34.8%)	6 (6.9%)	18 (24.7%)
5	31 (9.0%)	20 (10.8%)	11 (6.9%)	15 (15.5%)	5 (5.6%)	3 (3.4%)	8 (11.0%)
6	47 (13.6%)	44 (23.7%)	3 (1.9%)	35 (36.1%)	9 (10.1%)	1 (1.1%)	2 (2.7%)

Abbreviation: COPD=chronic obstructive pulmonary disease

Table E5. Predictive Performance of CAPTURE Alone, Using 2 Cut-Off Scores, by Group Comparison

Score Cut-Off Performance Indicator	Cases (Groups 1+2) vs. Controls (Groups 3+4) (N=346)	Cases (Groups 1+2) vs. No COPD (Group 3) (n=273)	COPD with Exacerbation (Group 1) vs. Controls (Groups 3+4) (n=257)	COPD with FEV_1 <60% Predicted (Group 2) vs. Controls (Groups 3+4) (n=249)
≥ 3				
Sensitivity	86.0%	86.0%	91.8%	79.8%
Specificity	59.4%	80.5%	59.4%	59.4%
Overall error	26.3%	15.8%	28.4%	33.3%
≥ 2				
Sensitivity	95.7%	95.7%	96.9%	94.4%
Specificity	44.4%	67.8%	44.4%	44.4%
Overall error	28.0%	13.2%	35.8%	37.8%

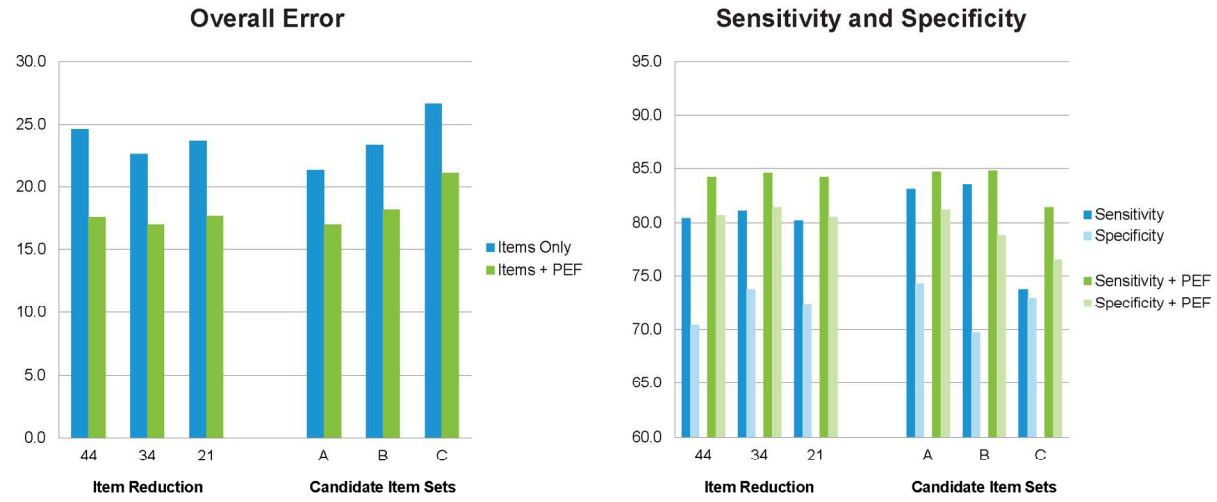
Abbreviations: COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in one second

Table E6. Predictive Performance of Peak Expiratory Flow (PEF) Alone, by Sex and Group Comparison

Sex Performance Indicator	Cases vs. Controls Groups 1–2 vs. 3–4 (N=344)	Cases vs. No COPD Groups 1–2 vs. 3 (n=271)	COPD with Exacerbation vs. Controls Group 1 vs. 3–4 (n=256)	COPD with FEV_1 <60% Predicted vs. Controls Group 2 vs. 3–4 (n=248)
Males: Threshold = 350 L\min	**(n=154)**	**(n=114)**	**(n=108)**	**(n=112)**
Sensitivity	89.8%	89.8%	90.5%	89.1%
Specificity	72.7%	88.5%	72.7%	72.7%
Overall error	17.5%	10.5%	20.4%	20.5%
Females: Threshold= 250 L\min	**(n=190)**	**(n=157)**	**(n=148)**	**(n=136)**
Sensitivity	86.5%	86.5%	92.6%	78.6%
Specificity	80.9%	91.8%	80.9%	80.9%
Overall error	16.3%	11.5%	14.9%	19.9%

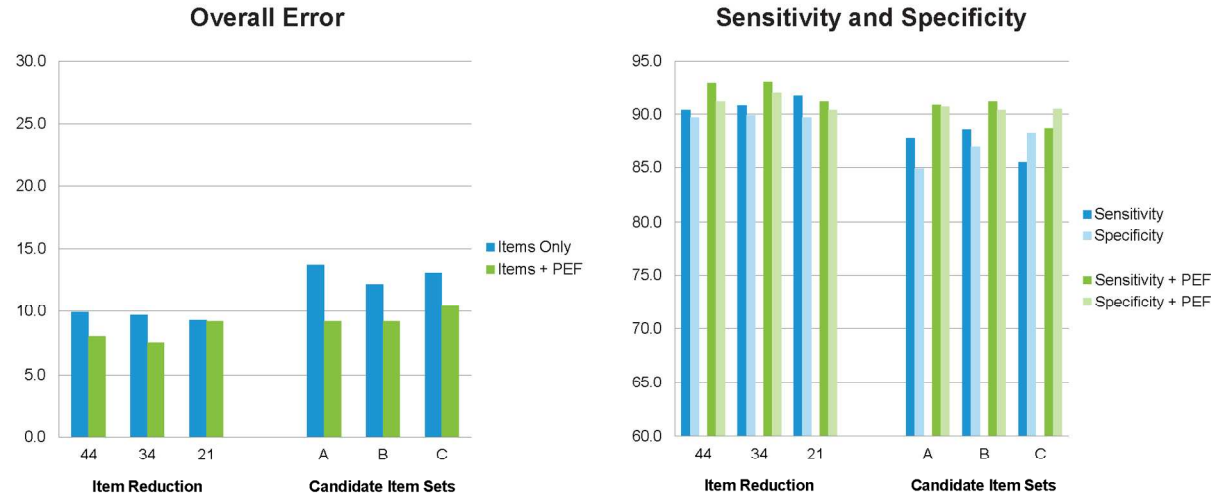
Abbreviations: COPD=chronic obstructive pulmonary disease; L\min=Liters per minute

Figure E1a. Cases versus Controls during Item Reduction and by Candidate Item Set*



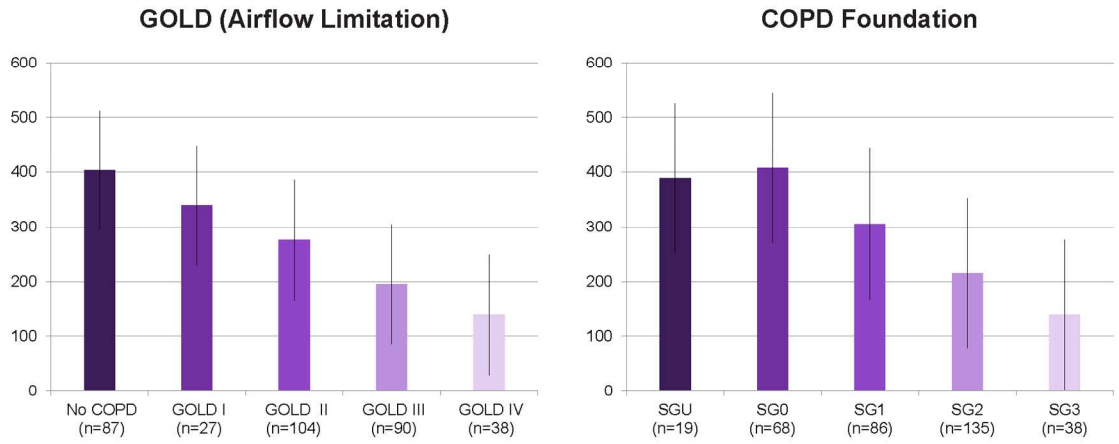
Abbreviation: PEF=peak expiratory flow
*Item Set A = 8 items; Item Set B = 5 items; Item Set C = 5 items
Overall error = out of bag (OOB) error

Figure E1b. Cases versus No COPD during Item Reduction and by Candidate Item Set*



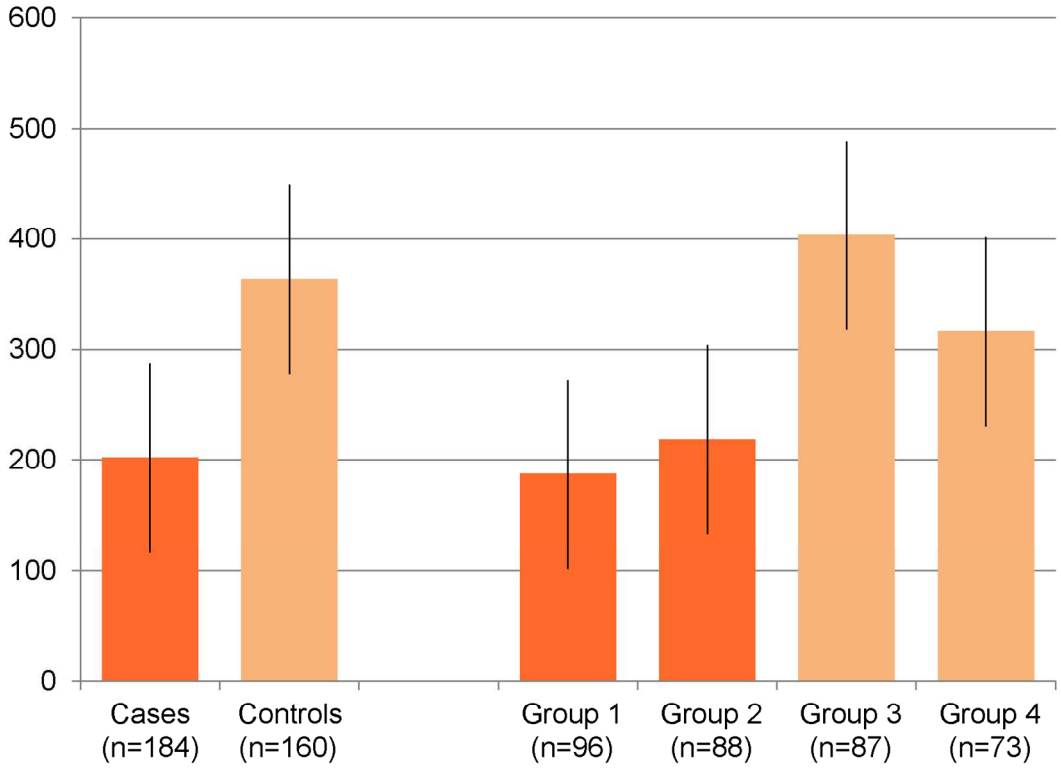
Abbreviation: PEF=peak expiratory flow
*Item Set A = 8 items; Item Set B = 5 items; Item Set C = 5 items
Overall error = out of bag (OOB) error

Figure E2. Mean (SD) PEF (L\min) by GOLD* and COPD Foundation† Categories



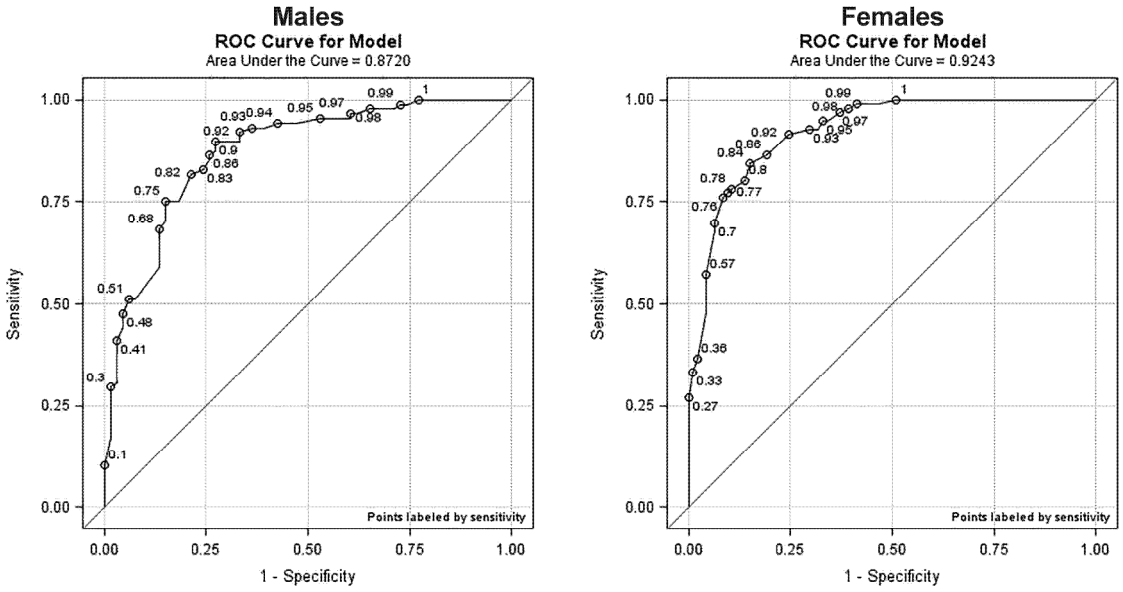
Abbreviations: COPD=chronic obstructive pulmonary disease; L\min=liters per minute; PEF=peak expiratory flow
*ANCOVA: F=61.72, p<0.0001
†ANCOVA: F=53.93, p<0.0001

Figure E3. Mean (SD) PEF (L\min) for Cases and Controls[*] and by Group[†]



Abbreviations: L\min=liters per minute; PEF=peak expiratory flow
[*]ANCOVA: F=48.79, p<0.0001
[†]ANCOVA: F=52.95, p<0.0001; Groups 1 or 2 versus 3 or 4 (p<0.0001); Groups 1 versus 2 – not significant
Group 1= Exacerbation history past 12 months; Group 2 = FEV_1 < 60% predicted; Group 3 = No COPD; Group 4 = Mild COPD (FEV_1 ≥60% predicted), exacerbation free >12 months

Figure E4. ROC Curves and AUC Statistics for Differentiating Cases and Controls using PEF, Stratified by Sex



Abbreviations: AUC=Area Under the Curve; PEF=Peak Flow; ROC=Receiver Operating Characteristic