Review | EVIDENCE REPORT FOR THE USPSTF

Screening for Chronic Obstructive Pulmonary Disease
Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the United States.

OBJECTIVE To systematically review literature on the accuracy of screening questionnaires and office-based screening pulmonary function testing and the efficacy and harms of treatment of screen-detected COPD.

DATA SOURCES MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials for relevant English-language studies published through January 2015.

STUDY SELECTION Two reviewers independently screened abstracts and studies. The search yielded 13 141 unique citations; 465 full-text articles were reviewed, and 33 studies met the inclusion criteria.

DATA EXTRACTION AND SYNTHESIS Two reviewers rated the quality of each study using USPSTF criteria.

MAIN OUTCOMES AND MEASURES Diagnostic accuracy (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]; treatment efficacy (COPD exacerbations, all-cause mortality, quality of life, and dyspnea); and treatment harms.

RESULTS All screening questionnaires were based on symptoms as well as risk factors such as age and smoking history. The COPD Diagnostic Questionnaire was the most extensively studied (5 studies, n = 3048), with moderate overall performance for COPD detection: area under the receiver operating characteristic curve (AUC), 0.65 to 0.72; sensitivity, 80% to 93%; and specificity, 24% to 49%, at a threshold of greater than 16.5. Positive predictive value and NPV ranged from 17% to 45% and 76% to 98%, respectively. For pulmonary function–based screening tools, FEV_1/FEV_6 was the best studied (3 studies, n = 1587), with AUC ranging from 0.84 to 0.85. Sensitivity ranged from 51% to 80%. Specificity (range, 90%-95%) and PPV (range, 63%-75%) appeared better than questionnaires. There was not strong evidence to support that screening and supplying smokers with spirometry results improves smoking cessation rates. Treatment trials were unavailable for screen-detected patients. Trials that reported outcomes in patients with mild to moderate COPD included 2 trials of long-acting β-agonists (LABAs) (n = 3174), 1 RCT of LABAs and inhaled corticosteroids (ICS) (n = 1097), 5 RCTs of the long-acting muscarinic antagonist tiotropium (n = 4592), and 6 RCTs of ICS (n = 3983). They suggested no benefit in all-cause mortality, but a decrease in annual rates of exacerbations with pharmacologic treatments. Few trials reported harms for any individual drug class. Adverse effects were generally mild (eg, dry mouth and cough).

CONCLUSIONS AND RELEVANCE There was no direct evidence available to determine the benefits and harms of screening asymptomatic adults for COPD using questionnaires or office-based screening pulmonary function testing or to determine the benefits of treatment in screen-detected populations. Indirect evidence suggests that the COPD Diagnostic Questionnaire has moderate overall performance for COPD detection. Among patients with mild to moderate COPD, the benefit of pharmacotherapy for reducing exacerbations was modest.

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Chronic lower respiratory disease, composed chiefly of chronic obstructive pulmonary disease (COPD), was the third leading cause of death in the United States in 2013.[1,2] Cigarette smoke exposure, either directly or indirectly, has been highly correlated with the development of COPD and COPD mortality.[3-7] In theory, primary care physicians can identify undetected COPD by screening relatively unselected, asymptomatic individuals or by targeting a high-risk asymptomatic population using screening spirometry, followed by confirmatory diagnostic spirometry in primary care or pulmonary specialty clinics.[7,8] Current clinical practice guidelines recommend against screening for COPD in asymptomatic patients; however, many professional organizations recommend case-finding among patients presenting with respiratory symptoms associated with the disease, such as dyspnea, chronic cough, or sputum production.[7-9]

In 2008, the US Preventive Services Task Force (USPSTF) recommended against screening asymptomatic adults for COPD using spirometry (grade D).[10] The USPSTF concluded that this method had no net benefit and had large associated opportunity costs. The aim of this systematic review is to update the evidence on the benefits and harms of screening for COPD using questionnaires and spirometry, including the diagnostic accuracy of primary care–feasible screening instruments; the effect of spirometric screening on uptake of targeted preventive services; and the effectiveness, benefits, and harms of treating screen-detected patients (generally those with mild to moderate COPD) since the last recommendation.

Methods

Scope of the Review

To conduct this review, an analytic framework was developed with 8 key questions (KQs) (**Figure 1**) that examined the effect of screening asymptomatic adults 40 years and older for COPD on health outcomes (KQ1); the accuracy and harms of screening questionnaires and pulmonary function tests (KQs 2-4); the effectiveness and harms of COPD screening on the uptake of targeted preventive services (KQs 5 and 6); and the effectiveness and harms of treatment of asymptomatic mild to moderate COPD (KQs 7 and 8). Detailed methods and results are available in the full evidence report (http://www.uspreventiveservicestaskforce.org/Page/Document/final-evidence-review143/chronic-obstructive-pulmonary-disease-screening).[11] The analytic framework, review questions, and methods for locating and qualifying evidence reflect public input after posting on the USPSTF website.

Data Sources and Searches

Searches included MEDLINE, PubMed, the Cumulative Index to Nursing and Allied Health Literature, and the Cochrane Central Register of Controlled Trials from January 2000 to January 2015, supplemented by checking reference lists from relevant systematic reviews. Evaluating the effect of a COPD diagnosis on pneumococcal and influenza immunization rates was a new question to this review; therefore, databases were searched from inception through January 2015. Since January 2015, we have continued to conduct ongoing surveillance through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and therefore the related USPSTF recommendation. The last surveillance was conducted on January 22, 2016, and identified no new studies.

Study Selection

Two reviewers independently reviewed 13 141 unique citations and 465 full-text articles against a priori inclusion criteria (**Figure 2** and eMethods in the Supplement). For KQs 1 through 6, we initially considered studies including asymptomatic adults 40 years and older (limited to current smokers for KQ5a). For questions 7 and 8, we restricted the population further to include only asymptomatic adults 40 years and older who were also diagnosed with mild COPD (forced expiratory volume in 1 second [FEV_1] ≥80% normal) to moderate COPD (FEV_1 50%-79% normal) or a mean population FEV_1 greater than or equal to 60% predicted to approximate a population of mild to moderate COPD. Asymptomatic patients were defined as those in 1 of the following states: free of the disease; the disease is present, but the patient has physical symptoms that are undetected by the patient or the clinician; or the patient has nonspecific symptoms that have gone unrecognized as being related to COPD. For KQs 2 and 4, we analyzed COPD prescreening questionnaires feasible in primary care with published studies describing their original development, internal validation, and external validation; results are reported only for COPD screening questionnaires with external validation, which is the minimal requirement for consideration in clinical practice.[12,13] For KQ2, the initial search was for risk factor–only based screening questionnaires, which would capture an asymptomatic population. However, because none were identified, risk factor– and symptom-based prescreening questionnaires were included. For KQ3, we examined primary care–feasible screening pulmonary function tests (eg, handheld devices or prebronchodilator testing requiring minimal personnel training).

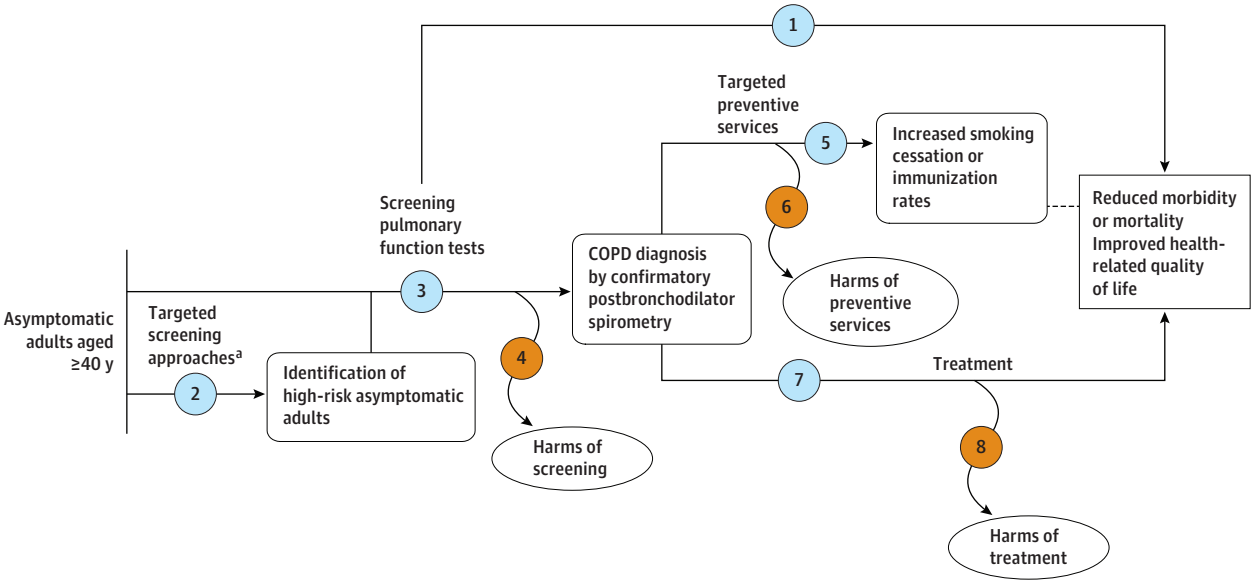
For the treatment questions, the search included treatment efficacy literature for the following COPD drug classes or combinations of any of the following: long-acting β-agonists (LABAs), long-acting anticholinergics, and inhaled corticosteroids (ICS). Because there were no trials in screen-detected or asymptomatic populations, the included population was expanded to those diagnosed with mild to moderate disease because observational studies show that 84% to 95% of screen-detected patients are expected to have mild to moderate COPD.[14-17]

For KQs 1, 5, and 7, the study design was limited to randomized clinical trials (RCTs). For KQs 2 and 3, designs were limited to diagnostic accuracy studies (including cross-sectional and cohort studies) with a reference standard COPD definition of a postbronchodilator ratio of FEV_1 to forced vital capacity (FVC) of less than 0.70.[7] For KQs 4 and 6, RCTs, large screening registry or database observational studies, and cohort studies were considered. When evaluating harms associated with the treatment of COPD (KQ8), the data were limited to what was reported in the efficacy trials included in KQ7, large screening registries, and systematic reviews, supplemented with information reported by the US Food and Drug Administration.

Data Extraction and Quality Assessment

One reviewer extracted study-level data into standardized evidence tables; a second checked for accuracy. Articles meeting inclusion criteria were critically appraised by 2 independent reviewers

Figure 1. Analytic Framework



Key questions

1 Does screening asymptomatic adults 40 years and older for COPD with prebronchodilator screening spirometry improve health-related quality of life or reduce morbidity or mortality?

a. Does the effect of screening among asymptomatic adults vary across strategy (ie, selective subgroups [age, presence of certain comorbidities, sex, race/ethnicity, smoking history, or others] vs general population)?

2 Can high-risk asymptomatic adults who are more likely to test positive on screening for COPD be reliably identified using prescreening questionnaires?

3 What is the test performance of screening pulmonary function tests (eg, prebronchodilator screening spirometry, peak flow meter) in predicting diagnosis of COPD based on confirmation using postbronchodilator spirometry to identify fixed airflow obstruction in asymptomatic adults?

4 What are the adverse effects of screening for COPD using prescreening questionnaires or screening pulmonary function tests?

5 Does identifying asymptomatic adults with fixed airflow obstruction through screening improve the delivery and uptake of targeted preventive services?

a. Does screening for COPD increase smoking cessation rates among asymptomatic adults compared with usual care?

b. Does screening for COPD increase relevant immunization rates among asymptomatic adults compared with usual care?

6 What are the adverse effects of COPD screening, including the effect of targeted preventive services in this population (eg, false reassurance for screen-negative smokers)?

7 Does treatment for asymptomatic adults identified with mild to moderate COPD through screening improve health-related quality of life or reduce morbidity or mortality?

8 What are the adverse effects of COPD treatments in this population?

The process of screening asymptomatic adults for chronic obstructive pulmonary disease (COPD) can either involve a targeted screening approach (with questionnaires [key question 2]) or no risk stratification whereby asymptomatic unselected adults go directly to pulmonary function screening tests (key question 3). The dashed line indicates an established association between an intermediate outcome and a health outcome.

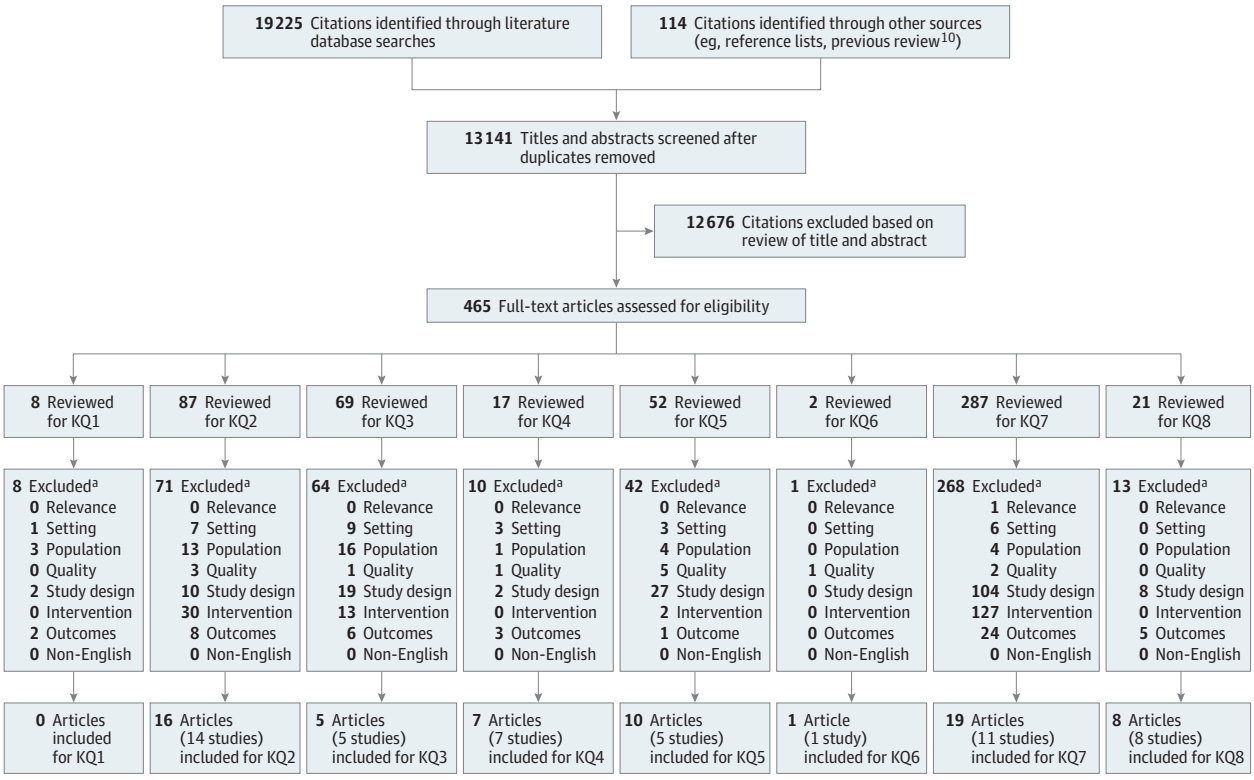
[a] Using prescreening questionnaires.

using predefined criteria[18-21] with disagreements resolved by a third investigator. Included studies were limited to those published in English that were rated as good or fair quality using USPSTF quality rating standards.[18] (Details are available in eTables 1 and 2 in the Supplement.)

Data Synthesis and Analysis

Data from the included studies were qualitatively examined to identify a range of results. Given the clinical heterogeneity of studies, meta-analyses were not conducted for any of the questions in this review.

Figure 2. Literature Flow Diagram



Diagnostic criterion for chronic obstructive pulmonary disease is a postbronchodilator ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) of less than 0.70. KQ indicates key question.

[a] Details about reasons for exclusion are as follows. Relevance: study aim not relevant. Setting: study was not conducted in a country relevant to US practice. Population: study was not conducted in asymptomatic adults 40 years and older. Quality: study did not meet criteria for fair or good quality (ie, it was poor quality). Study design: study did not use an included design. Intervention: study used an excluded intervention or screening approach. Outcomes: study did not have relevant outcomes or had incomplete outcomes. Non-English: study was published in a non-English language.

For studies of diagnostic accuracy, 2 × 2 tables were constructed from data reported in the primary studies. When 95% CIs were not reported for diagnostic accuracy estimates, these intervals were calculated using Jeffrey confidence intervals (Stata version 13.1). For diagnostic accuracy studies, in addition to the standard test performance characteristics (area under the receiver operating characteristic [ROC] curve, sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV]), we calculated the following outcomes: COPD prevalence in the population, percentage of patients screening positive, false-positive rate, and the percentage of missed cases.

Results

Thirty-three studies (48 articles) met the inclusion criteria for this systematic review (Figure 2). This article provides a summary of results that supported the USPSTF recommendation process.

Effect of Screening on Health Outcome

KQ1: Does screening asymptomatic adults 40 years and older for COPD with prebronchodilator screening spirometry improve health-related quality of life or reduce morbidity or mortality?

There was no direct evidence comparing the effectiveness of COPD screening and no screening on patient health outcomes.

Screening Questionnaires

KQ2: Can high-risk asymptomatic adults who are more likely to test positive on screening for COPD be reliably identified using prescreening questionnaires?

KQ4: What are the adverse effects of screening for COPD using prescreening questionnaires?

No relevant studies of COPD screening questionnaires in asymptomatic populations were identified that were based solely on risk factors. Three externally validated prescreening questionnaires were identified that assessed risk factors and respiratory symptoms to select high-risk patients for screening spirometry: the COPD Diagnostic Questionnaire (CDQ), the Lung Function Questionnaire (LFQ), and the COPD Population Screener (COPD-PS). The predictive accuracy of these questionnaires in all included studies was measured against the postbronchodilator FEV_1/FVC reference standard according to the Global Initiative for Chronic Obstructive Lung Disease COPD definition and American Thoracic Society and European Respiratory Society quality standards.[7,22,23]

The CDQ is an externally validated, 8-item, self-administered, symptom- and risk factor–based COPD prescreening questionnaire

used to select high-risk patients for screening spirometry, which assigns scores for established risk factors including age, pack-years of smoking, and body mass index (BMI) as well as symptoms and allergy history (**Table 1**).[14,17,24-28] Possible scores range from 0 to 38 (higher scores associated with higher COPD risk), with highest scores attributed to older age (score 10 for ≥70 years), greater pack-years (score 7 for ≥50 pack-years), and lower BMI (score 5 for BMI). Two cut points (16.5 and 19.5) have been proposed to select patients for screening spirometry based on ROC curves from the original development study.[30] The original development and internal validation was performed in a primary care–based US and UK cross-sectional study of 818 past and current smokers 40 years and older.[31]

The CDQ has been externally validated in 5 fair- to good-quality diagnostic accuracy studies mainly focusing on primary care European and Australian populations.[14,17,24-26] The study populations varied; 3 studies recruited solely current or ever-smokers from primary care, the general population, or both,[17,24,26] and 2 studies recruited patients from primary care clinics without regard to smoking history.[14,25] Chronic obstructive pulmonary disease was diagnosed by spirometry in 10.3% to 41.1% of participants in each of the 4 studies that reported this outcome, with the highest prevalence (41.1%) being reported in a study that required participants to be current smokers with at least a 10 pack-year history and have at least 1 respiratory symptom; these participants were essentially prescreened, thereby selecting for those most likely to have COPD.[26] Prevalence of COPD in the studies recruiting ever-smokers ranged from 13.1% to 27.9%,[17,24] and 1 general population study with more than half nonsmoking participants had an overall COPD prevalence of 10.3%, which was higher (17.2%) among ever-smokers.[14] The majority of patients found to have COPD were identified as having mild or moderate disease (83.8%-94.7%).

Most external validation studies reported that a CDQ score greater than 16.5 had a sensitivity ranging from 80% to 91% and specificity ranging from 24% to 49% for identifying those who test positive using spirometric confirmation for COPD (Table 1). Choosing a higher cut point (19.5) reduced sensitivity and NPV but increased specificity and PPV. The proportion of cases missed by the CDQ (false-negative rate) varied widely, from 9.0% to 37.0%, and was lowest when using the most sensitive screening threshold (see full evidence report[11]). For the threshold of less than 16.5 for screen negatives, and limiting to studies in which fewer than 20% of spirometry tests were invalid or incomplete, the proportion of missed spirometry-diagnosed COPD was around 10%. In these studies, increasing the screening threshold to less than 19.5 increased the missed COPD cases to 27.9% to 34.2% in best estimates.

Simple tables were constructed to compare screening test performance using the CDQ across a range of populations, using the mean sensitivity and specificity of applicable studies. **Table 2** shows the trade-offs with missed cases and false-positive tests in populations with varying COPD prevalence at the 2 cut points (16.5 and 19.5).

The LFQ and COPD-PS are both 5-item self-administered risk factor– and symptom-based questionnaires (Table 1). The LFQ assigns scores to age; smoking history (pack-years, never/current/former smoker); and presence of wheezing, dyspnea, and mucous productive cough. Possible scores range from 5 to 25, with lower scores associated with higher COPD risk. A threshold of 18 or less has been proposed as a cut point for COPD risk warranting pulmonary function diagnostic workup. Although the LFQ was specifically developed in the National Health and Nutrition Examination Survey population with chronic bronchitis and studied in US primary care practices,[32,33] data for this questionnaire were limited to a single validation study.[27] This external validation study, however, had quality concerns (31% of spirometry was invalid or incomplete) and relatively poorer test performance than the CDQ (lower sensitivity, specificity, PPV, and NPV) when used in similar populations. In addition, we could not assess the harms of screening (ie, rate of false positives or proportion of missed cases) using the LFQ because only a subset of screen-negative patients were selected for spirometry.

The COPD-PS assigns scores for age, smoking history, dyspnea, sputum production, and dyspnea-related functional limitations. Possible scores range from 0 to 10, with higher scores being associated with a higher risk of COPD. A threshold of 5 to 6 or more has been proposed as a cut point for COPD risk warranting pulmonary function test workup. Although the COPD-PS was derived in an enriched sample of US pulmonary and primary care clinics,[34] its external validation in a single Japanese population-based study makes conclusions regarding generalizability of accuracy results limited.[28] The COPD-PS has recently been applied in a multisite, US-based primary care, pragmatic COPD screening trial (n = 8770); however, this trial did not include the reference standard of spirometry for accuracy estimation.[35]

Screening Pulmonary Function Tests

KQ3: What is the test performance of screening pulmonary function tests in predicting diagnosis of COPD based on confirmation using postbronchodilator spirometry to identify fixed airflow obstruction in asymptomatic adults?

KQ4: What are the adverse effects of screening for COPD using screening pulmonary function tests?

One good-quality and 4 fair-quality diagnostic accuracy studies were identified that evaluated 2 different handheld pulmonary function screening tests against a postbronchodilator FEV_1/FVC reference standard: FEV_1/FEV_6[14,17,36] (delivered either before or after the bronchodilator) (**Table 3**) and peak expiratory flow (PEF).[37,38] The included populations varied in their selectivity in terms of age, smoking status, symptomatology, and exclusion of preexisting COPD.

Three studies (1 good-quality and 2 fair-quality) reported the screening test performance of FEV_1/FEV_6 (n = 1587).[14,17,36] Two studies assessing prebronchodilator FEV_1/FEV_6 among ever-smokers found similar sensitivities (51% and 53%) and specificities (90% and 93%) (Table 3).[17,36] The third study[14] used postbronchodilator FEV_1/FEV_6 for screening; sensitivity was much higher (80%) than the 2 prebronchodilator studies,[17,36] and specificity was as good or better (95%).[14] However, the sample was enriched with current smokers, which would increase the predictive value. In a subsample limited to ever-smokers, postbronchodilator screening appeared similar to screening test performance in the entire population, suggesting that postbronchodilator FEV_1/FEV_6 performs better than prebronchodilator testing.

Harms of screening pulmonary function testing included false positives and false negatives (missed cases). False-negative rates (proportion of total diagnoses missed) ranged from 14% to 49%, depending on the threshold used (see full evidence report[11]). The FEV_1/FEV_6 index test threshold of less than 0.70 showed the lowest rate of false negatives (19.8%) seen after postbronchodilator index testing.[14] Using a prebronchodilator cutoff of FEV_1/FEV_6 less than

Table 1. Range of Diagnostic Accuracy Values for COPD Screening Questionnaires in Included External Validation Studies (Key Question 2)

Risk Factors and Symptoms Included	Source	No. Screened	Country	Reference Standard	Population	Positive Screening Cutoff	% (95% CI)				AUC	Quality
							Sensitivity	Specificity	PPV	NPV		
8-Item CDQ (Score Range, 0-38)												
Age, smoking history, BMI, weather-affected cough, phlegm without a cold, morning phlegm, wheeze, history of allergies	Stanley et al,[24] 2014	1631	Australia	Post-BD spirometry (FEV_1/FVC <0.70)	Current or former smokers	>16.5	80 (72-86)[a]	47 (44-50)[a]	18 (15-22)[a]	94 (91-96)[a]	0.71	Fair
						>19.5	63 (55-71)[a]	70 (67-73)[a]	24 (20-29)[a]	93 (91-94)[a]		
	Dirven et al,[25] 2013[b]	293	Netherlands	Post-BD spirometry (FEV_1/FVC <0.70) plus physician's clinical evaluation	General population	>19.5	NR	NR	23 (12-38)	NR	NR	Fair
	Frith et al,[17] 2011	237	Australia	Post-BD spirometry (FEV_1/FVC <0.70) and reversibility ≤200 mL and ≤12% from baseline pre-BD FEV_1	Current or former smokers	>16.5	91 (80-97)	37 (29-45)	36 (28-44)	91 (81-97)	0.72	Good
						>19.5	71 (58-83)	62 (54-70)	42 (32-53)	85 (77-91)		
	Sichletidis et al,[14] 2011[c]	1250	Greece	Post-BD spirometry (FEV_1/FVC <0.70)	Smokers and nonsmokers from primary care	>16.5	91 (85-95)[a]	49 (46-52)[a]	17 (14-20)[a]	98 (96-99)[a]	NR	Fair
						>19.5	72 (63-80)[a]	77 (74-80)[a]	26 (22-32)[a]	96 (94-97)[a]		
					Smokers only	>16.5	93	39	24	97	NR	
	Kotz et al,[26] 2008	826	Netherlands	Post-BD spirometry (FEV_1/FVC <0.70)	Current smokers	>16.5	89 (85-92)	24 (20-29)	45 (41-49)	76 (68-83)	0.65	Good
						>19.5	66 (60-71)	54 (49-59)	50 (45-55)	69 (64-74)		
5-Item LFQ (Score Range, 5-25)												
Age; smoking history; presence of wheeze, dyspnea, and phlegm	Mintz et al,[27] 2011	1288	United States	Post-BD spirometry (FEV_1/FVC <0.70)	Ever-smokers	≤18	88 (75-94)[a,d]	25 (22-28)[a,d]	21 (18-24)[a,d]	90 (78-97)[a,d]	NR	Fair
5-Item COPD-PS (Score Range, 0-10)												
Shortness of breath, presence of phlegm or mucus, functional limitations due to breathing problems, smoking history, age	Tsukuya et al,[28] 2015		Japan		Smokers and nonsmokers	≥4	67 (60-74)[a]	73 (71-75)[a]	15 (12-17)[a]	97 (96-98)[a]	0.70	Fair
						≥5	35 (27-42)[a]	79 (78-81)[a]	10 (8-13)[a]	95 (93-96)[a]	0.57	

Abbreviations: AUC, area under the receiver operating characteristic curve; BD, bronchodilator; BMI, body mass index; CDQ, COPD Diagnostic Questionnaire; COPD, chronic obstructive pulmonary disease; COPD-PS, COPD Population Screener; FEV_1, forced expiratory volume in 1 second; FEV_6, forced expiratory volume in 6 seconds; LFQ, Lung Function Questionnaire; NPV, negative predictive value; NR, not reported; PPV, positive predictive value.

[a] Calculated.

[b] Only screen-positive patients underwent diagnostic spirometry; 39 of 50 screen-positive patients underwent diagnostic testing.

[c] Study used the cut points of ≥17 points for intermediate likelihood and ≥20 points for high likelihood.

[d] Estimates calculated using the Begg and Greenes[29] method to adjust for lack of spirometric verification in all participants.

Table 2. Results of Screening in a Hypothetical Population (n = 1000) Using CDQ or FEV_1/FEV_6 (Key Questions 2 and 3)

COPD Prevalence	No. Screen Positive	No. False Positive	No. Missed Cases
CDQ >16.5: sensitivity 87%, specificity 44%			
10%	591	504	13
20%	622	448	26
CDQ >19.5: sensitivity 69%, specificity 70%			
10%	339	270	31
20%	378	240	62
FEV_1/FEV_6 <0.70 (pre-BD): sensitivity 52%, specificity 92%			
10%	124	72	48
20%	168	64	96
FEV_1/FEV_6 <0.70 (post-BD): sensitivity 80%, specificity 95%			
10%	125	45	20
20%	200	40	40

Abbreviations: BD, bronchodilator; CDQ, COPD Diagnostic Questionnaire; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FEV_6, forced expiratory volume in 6 seconds.

Table 3. Range of Diagnostic Accuracy Values for FEV_1/FEV_6 in Included Studies (Key Question 3)

Source	No. Screened	Country	Reference Standard	Population	Positive Screening Cutoff	% (95% CI) Sensitivity	Specificity	PPV	NPV	AUC	Quality
Prebronchodilator FEV_1/FEV_6											
Frith et al,[17] 2011	237	Australia	Post-BD spirometry (FEV_1/FVC <0.70) and reversibility ≤200 mL and ≤12% from baseline pre-BD FEV_1	Current or former smokers	<0.70	51 (37-64)	93 (87-96)	73 (56-85)	83 (76-88)	0.85	Good
Thorn et al,[36] 2012	305[a]	Sweden	Post-BD spirometry (FEV_1/FVC <0.70)	Current or former smokers	<0.70	53 (42-64)[b]	90 (85-93)[b]	63 (51-74)[b]	85 (80-89)[b]	0.84	Fair
Postbronchodilator FEV_1/FEV_6											
Sichletidis et al,[14] 2011	1250	Greece	Post-BD spirometry (FEV_1/FVC <0.70)	Smokers and nonsmokers	<0.70	80 (72-87)[b]	95 (93-96)[b]	64 (56-72)[b]	98 (97-99)[b]	NR	Fair
				Smokers only	<0.70	80	94	75	96	NR	

Abbreviations: AUC, area under the receiver operating characteristic curve; BD, bronchodilator; FEV_1, forced expiratory volume in 1 second; FEV_6, forced expiratory volume in 6 seconds; NPV, negative predictive value; NR, not reported; PPV, positive predictive value.

[a] No. analyzed; No. screened was not reported.

[b] Calculated.

0.70, the missed cases in 2 of the trials approached 50% (see full evidence report[11]).[17,36] False-positive rates for the less than 0.70 threshold ranged from 5.2% to 10.5%,[14,17,36] with the lowest rate seen in the single study using postbronchodilator testing.[14]

Mean sensitivity and specificity were used to construct simple tables to compare screening test performance using the prebronchodilator and postbronchodilator FEV_1/FEV_6 across a range of populations. Table 2 shows the trade-offs with missed cases and false-positive tests in populations with varying COPD prevalence.

Two fair-quality studies of PEF evaluated the largest number of patients (n = 23 098).[37,38] However, these were based on large population-based studies whose primary aims were to describe the prevalence of COPD internationally. Because the studies did not exclude persons with preexisting COPD and also included several developing countries with environmental exposures that would be not be considered generalizable to the United States, their results are less applicable to screening.

Targeted Preventive Services

KQ5: Does identifying asymptomatic adults with fixed airflow obstruction through screening improve the delivery and uptake of targeted preventive services?

KQ5a: Does screening for COPD increase smoking cessation rates among asymptomatic adults compared with usual care?

KQ5b: Does screening for COPD increase relevant immunization rates among asymptomatic adults compared with usual care?

KQ6: What are the adverse effects of COPD screening, including the effect of targeted preventive services in this population?

Five fair-quality studies (n = 1694) were identified that addressed the incremental value of adding spirometry to existing smoking cessation counseling interventions to improve smoking cessation rates (**Table 4**).[39-43] There was not strong evidence to support the premise that supplying smokers with spirometry results improves smoking cessation rates. No trials randomized patients without known COPD diagnoses to screening spirometry vs no spirometry in order to estimate the independent value of screening spirometry. Instead, in all studies control groups received almost the same smoking cessation support as the spirometry group; studies varied in whether the control group received spirometry testing[39,41] or not[40,42,43] and in whether smoking cessation support was tailored based on spirometry or other medical examination findings. Of the 5 included RCTs, a single fair-quality trial giving patients their "lung age" reported a statistically significant difference in biochemically validated abstinence in the intervention group compared with

Table 4. Study Characteristics and Abstinence Outcomes of Smoking Cessation Trials (Key Question 5a)

Source	No. Randomized	Population Summary	Follow-up, mo	Treatment Comparison	Smoking Abstinence, No. (%)	Quality
Kotz et al,[39] 2009	296	Aged 35-70 y; ≥10 pack-year history; ≥1 respiratory symptom (cough, sputum, shortness of breath); mild or moderate COPD[a]	12	IG: Counseling plus discussion of spirometry results	13 (11.2)[b,c]	Fair
				CG: Counseling alone or referral to smoking cessation treatment	13 (11.6)[b,c]	
McClure et al,[40] 2009	542	Smokers aged ≥18 y; smoked average of 15 cigarettes/d for the past year or 10 cigarettes/d for ≥10 y	12	IG: Counseling plus discussion of spirometry, "lung age," and CO results[d]	29 (10.9)[c,e]	Fair
				CG: Health risk report and general advice to quit smoking	35 (13.0)[c,e]	
Parkes et al,[41] 2008	561	Aged ≥35 y; patient record indicates was a smoker within the last 12 mo	12	IG: Counseling and confrontation with "lung age"	38 (13.6)[b,f]	Fair
				CG: General advice to quit smoking and lung function scores via mail with no further explanation	18 (6.4)[b,f]	
Sippel et al,[42] 1999	205	Smokers aged ≥18 y	9	IG: Counseling plus discussion of spirometry and CO results	9 (9.0)[c,e]	Fair
				CG: Counseling alone	14 (14.0)[c,e]	
Risser and Belcher,[43] 1990	90	Smokers participating in a general preventive intervention Veterans Administration demonstration project	12	IG: Counseling plus discussion of spirometry and CO results	9 (20.0)[c,e]	Fair
				CG: Counseling alone	3 (6.7)[c,e]	

Abbreviations: CG, control group; CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IG, intervention group; RCT, randomized clinical trial.

[a] Postbronchodilator FEV_1/FVC <70% and FEV_1 ≥50% predicted.

[b] Biochemically validated smoking abstinence.

[c] Not statistically significant.

[d] "Lung age" given to those with FEV_1 <80%.

[e] Self-reported smoking abstinence.

[f] Statistically significant difference; validated quit rate difference, 7.2% (95% CI, 2.2%-12.1%); P = .005.

the control group rates after 12 months of follow-up (n = 561; 13.6% vs 6.4%; validated quit rate difference, 7.2% [95% CI, 2.2%-12.1%]; number needed to treat [NNT], 14); however, both the control and treatment groups underwent spirometry, so the trial actually tested the method of communicating spirometry results rather than the value of the screening spirometry itself.[41] Most of the other trials either reported higher abstinence rates that were not statistically significant or no difference in the intervention group compared with control (Table 4).

There was little evidence examining the potential negative effect of COPD screening on targeted preventive services; little can be concluded from the included qualitative study reporting that some smokers felt that confrontation with spirometry would interfere with personal choice.[39]

No trials were identified reporting the effect of COPD screening on recommended immunization uptake rates.

Treatment Efficacy and Harms

KQ7: Does treatment for asymptomatic adults identified with mild to moderate COPD through screening improve health-related quality of life or reduce morbidity or mortality?

KQ8: What are the adverse effects of COPD treatments in this population?

Twenty studies of 14 distinct trials were identified for the 3 included drug classes and 1 combination treatment: 2 trials of LABAs,[44,45] 1 RCT of LABAs plus ICS,[45] 5 RCTs of the long-acting muscarinic antagonist (LAMA) tiotropium,[44,46-48] and 6 RCTs of ICS[45,49-53] (**Table 5**).[54,55]

No studies were found in patients with screen-detected COPD and relatively few in patients with mild COPD (FEV_1 ≥80% predicted). Most of the subanalyses of patients with mild to moderate COPD in treatment trials included populations at the more severe end of moderate COPD.

LABAs

One post hoc subanalysis of a large 4-group RCT and 1 post hoc pooled subanalysis from 3 other RCTs (n = 3174) were identified (Table 5).[44,45] Based on 1 subanalysis reporting each outcome (all-cause mortality, exacerbations, health-related quality of life [HrQOL], and dyspnea scores), LABAs appeared to reduce exacerbations and dyspnea scores; results were mixed for HrQOL, and no trials reported exercise capacity. Results for harms were rarely reported, with few differences between treated and untreated groups for a variety of individual adverse events; however, lower rates of study withdrawal and pneumonia were reported in 1 trial in patients treated with salmeterol (**Table 6**).[44-46,50,51,53-55]

ICS

One trial of patients with mild to moderate COPD, 2 post hoc subanalyses of RCTs, and 2 RCTs of patients with a mean FEV_1 greater than or equal to 60% (n = 3983) were identified (Table 5). Despite the rarely reported outcomes and limitations, overall results seemed to indicate a reduction in COPD exacerbations with ICS; however, exacerbations were variably defined, and therefore annual rates of exacerbations varied widely. Results from the 1 trial in patients with mild to moderate COPD (EUROSCOP; n = 1175) showed a statistically significant difference in exacerbation rates, but because the annual rates of exacerbations were very low (<0.1 exacerbations/y) in patients with milder COPD severities, the absolute difference was very small (absolute difference of 0.02 exacerbations/y).[49] Data were

Table 5. Summary of Findings: Treatment Efficacy (Key Question 7)

	LABA	ICS	LABA-ICS	LAMA Tiotropium
Population	Moderate COPD	Mild to moderate COPD	Moderate COPD	Moderate COPD
Overall No. of studies	2[44,45]	6[45,50-54]	1[45]	5[44,46-48,55]
Overall No. of participants	3174	3983	1097	4592
All-Cause Mortality				
No. of studies	1[45]	4[45,50,53,54]	1[45]	2[46,55]
No. of participants	1057	3653	1097	3196
Data summary	IG: 9.2% CG: 11.4% Statistical testing not provided	Similar rates reported in IG vs CG	Reduction in IG vs CG (HR, 0.67 [95% CI, 0.45-0.98]); interaction testing revealed no heterogeneity of effect by COPD severity; main trial showed no difference at 3 y	IG: 9.2% CG: 10.8% HR, 0.84 (95% CI, 0.66-1.07)
Exacerbations				
No. of studies	1[45]	4[45,50,52,54]	1[45]	3[46,47,55]
No. of participants	1057	2803	1097	3483
Data summary	Annual rate of moderate to severe exacerbation: IG: 0.71 CG: 0.82 Statistical testing not provided	3 RCTs report similar trends of lower exacerbations but no statistical testing; 1 RCT reported a significantly lower yearly rate of exacerbations in IG vs CG (RR, 0.63 [95% CI, 0.47-0.85])	Annual rate of moderate to severe exacerbations: IG: 0.57 CG: 0.82 Annual reduction rate in IG, 31% (95% CI, 19%-40%)	2 of 3 subanalyses showed reduction in mean number of exacerbations; other study showed no difference in exacerbations without reporting statistics
Health-Related Quality of Life				
No. of studies	2[44,45]	2[45,51]	1[45]	4[44,46,48,55]
No. of participants	3174	1114	1097	3282
Data summary	Mixed results	Neither IG nor CG had changes reaching the threshold for a minimum clinically important difference	Neither group achieved clinically meaningful changes	1 RCT in treatment-naive moderate disease reported improvement in scores, but uncertain if clinically meaningful and 3 subanalyses reported mixed results on scores
Dyspnea Scores				
No. of studies	1[44]	2[51,53]	0	1[44]
No. of participants	2117	1158	NA	911
Data summary	Pooled subanalysis of 3 RCTs showed there was a statistically significant short-term effect after 6 mo	Fewer patients experienced dyspnea in IG vs CG, but unclear if clinically meaningful	No trials	Patients achieving a meaningful clinical difference in scores: IG: 64.6% CG: 49.3% OR, 1.59 (95% CI, 1.07-2.37)

Abbreviations: CG, control group; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; ICS, inhaled corticosteroids; IG, intervention group; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; OR, odds ratio; NA, not applicable; RCT, randomized clinical trial; RR, relative risk.

not sufficiently reported to make firm conclusions about the effect of ICS treatment on dyspnea or HrQOL.

Six RCTs reported treatment harms associated with ICS among patients with mild to moderate COPD (Table 6).[45,49-53] Overall, withdrawal rates between treatment groups were similar in the 4 trials that reported these data.[45,49-51] Results of the composite outcome of any adverse event or serious adverse events were mixed but generally showed few differences between treated and untreated groups. Data on pneumonia, bone mineral density, and fractures were sparse and mixed. One post hoc subanalysis reported more ischemic cardiac events among those in the placebo group (3.0% vs 5.3%; *P* = .048), although these results should be interpreted with caution due to study methods (see full evidence report[11]).[54]

LABAs and ICS

The 1 included post hoc subanalysis among patients with moderate COPD (n = 1097) suggested a possible all-cause mortality benefit that was not seen in the main trial across all stages of COPD (Table 5).[45] In addition, data showed a statistically significant, but probably not clinically meaningful, improvement in HrQOL and a reduction in exacerbations; however, more evidence is required to make firm conclusions.

Two treatment effectiveness RCTs provided data on harms associated with treating patients with mild to moderate COPD with the combination of LABAs and ICS (Table 6).[45,51] Withdrawal rates appeared to be mixed, with the subanalysis of the TORCH trial reporting lower rates of withdrawal among patients treated with salmeterol and fluticasone than those treated with placebo,[45] and another trial reporting similar rates of withdrawal between treatment groups.[51] Only the subanalysis of the TORCH trial reported on the incidence of composite or individual adverse events. It showed similar rates between treated and control groups, except perhaps a higher risk for pneumonia with treatment, in contrast to findings for LABAs in the same study.[45] Paucity of data made robust conclusions challenging.

Table 6. Summary of Findings: Treatment Harms (Key Question 8)

	LABA	ICS	LABA-ICS	LAMA Tiotropium
Population	Moderate COPD	Mild to moderate COPD	Moderate COPD	Moderate COPD
Overall No. of studies	2[44,45]	5[45,50,51,53,54]	2[45,51]	3[44,46,55]
Overall No. of participants	3191	3732	1149	4076
Withdrawals				
No. of studies	1[45]	4[45,50,51,54]	2[45,51]	1[46]
No. of participants	1074	2617	1149	2739
Data summary	IG: 27% CG: 35% Statistical testing not provided	Similar rates reported between groups	1 subanalysis reported fewer withdrawals in IG vs CG (27% vs 35%; statistical testing not provided); other RCT reported similar withdrawal between groups	IG: 30.6% CG: 34.7% Statistical testing not provided
Composite Adverse Events				
No. of studies	2[44,45]	3[45,50,54]	1[45]	2[44,55]
No. of participants	3191	2552	1108	1337
Data summary	1 pooled subgroup analysis of 3 RCTs reported mostly similar rates across groups; 1 subanalysis reported mixed results with some adverse events slightly more common in the IG and some slightly more common in the CG, but unclear if there was a meaningful difference	2 of 3 RCTs showed similar rates between groups; 1 trial reported more events in CG vs IG	IG: 86.2% CG: 86.6% Statistical testing not provided	1 RCT of treatment-naive patients reported similar rates between groups (4.1% vs 4.4%; statistical testing not provided); 1 pooled analysis reported higher rates in IG vs CG (67% vs 55.9%; statistical testing not provided)
Fractures				
No. of studies	0	1[53]	0	0
No. of participants	NA	653	NA	NA
Data summary	No trials	New lumbar fractures: IG: 5% CG: 3% Statistical testing not provided	No trials	No trials
Pneumonia				
No. of studies	1[45]	2[45,50]	1[45]	0
No. of participants	1074	1377	1108	NA
Data summary	IG: 9.4% CG: 10.6% Statistical testing not provided	Mixed results: 1 RCT reported higher rates in the IG (12.8% vs 10.6%); 1 reported higher rates in the CG (11.0% vs 16.6%)	IG: 15.3% CG: 10.6% Statistical testing not provided	No trials

Abbreviations: CG, control group; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; IG, intervention group; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; NA, not applicable; RCT, randomized clinical trial.

LAMA

A single trial of the LAMA tiotropium in patients naive to maintenance treatment with moderate COPD (n = 457)[55] and 4 subgroup analyses examining those with mild to moderate COPD were identified (Table 5).[44,46-48] Results were mixed for the effect of tiotropium on exacerbations and HrQOL, although the majority of the evidence suggested a beneficial effect on both outcomes. The trial of treatment-naive patients with moderate COPD most approximated a screen-detected population and showed a statistically significant reduction in exacerbations and statistically significant, but probably not clinically meaningful, difference in work productivity scores.[55]

Two treatment effectiveness RCTs[46,55] and 1 post hoc analysis of pooled study data[44] provided few data on harms associated with tiotropium (Table 6). One trial[46] reported very similar withdrawal rates with and without tiotropium, with approximately half of these withdrawals attributed to adverse events in both groups; 1 study reported higher rates of any adverse event in the tiotropium group compared with control (67% v 55.9%, no statistical testing), but 1 study reported no difference in serious events.[44,55]

Overall, the treatment literature was largely based on patients with COPD on the more severe range of moderate, so applicability to a screen-detected asymptomatic population may not be appropriate. Furthermore, there were a number of limitations in the included subgroup analyses for all classes of medications, such as (1) the primary trials were powered for the entire population, not the subgroup; (2) analyses were mostly post hoc; and (3) interaction testing and adjustment for confounders were rarely performed. The inconsistency in reported outcomes across the studies further limited the strength of available evidence. The most inconsistency was seen in the definitions of exacerbations used in the studies. Most studies defined an exacerbation as requiring treatment with an antibiotic or systemic corticosteroid; however, other studies included patient-reported increase in symptoms. Fewer than 5 trials

Table 7. Summary of Evidence Table

Key Question	Population	No. of Studies	No. of Participants	Study Design	Summary of Findings	Consistency	Body of Evidence Limitations	Applicability	Overall Study Quality
Key question 1: Health outcomes	Asymptomatic adults				No trials examined the efficacy of COPD screening on health outcomes				
Key question 2: Questionnaires	Adults in the general population and primary care with and without smoking history	5	3048	CDQ diagnostic accuracy	CDQ score >16.5: Sensitivity low 90% range; Specificity high-30% to mid-40% range	Reasonably consistent	Heterogeneous populations with wide variation in COPD prevalence in ever-smokers (13%-28%)	All external validation studies performed outside United States	Fair
	Ever-smoking adults in primary care	1	849	LFQ diagnostic accuracy	LFQ score ≤18: Sensitivity 88% Specificity 25%	Unknown: 1 external validation study	Derived from NHANES III survey of self-reported physician-diagnosed chronic bronchitis; COPD defined using pre-BD FEV_1/FVC. Single external validation study	External validation study conducted in 36 US primary care sites	Fair
	Adults in the general population and primary care with and without smoking history	1	2357	COPD-PS diagnostic accuracy	COPD-PS score ≥4: Sensitivity 67% Specificity 73% COPD-PS score ≥5: Sensitivity 35% Specificity 79%	Unknown: 1 external validation study	External validation study in single Japanese rural community without exclusion of preexisting COPD	Development sample recruited participants from US pulmonary and primary care clinics, but external validation study setting may not be generalizable to US primary care screening population	Fair
Key question 3: Simple pulmonary function test	Adults in the general population	2	23 098	PEF diagnostic accuracy	Two population-based studies with different index test thresholds; gold-standard tests and COPD definitions do not provide sufficient information to estimate accuracy	Unknown due to studies' heterogeneity	BOLD and PLATINO population-based samples do not exclude nor report baseline COPD diagnoses	Serious concerns regarding applicability to US population given that many countries in BOLD and PLATINO are developing countries with different environmental and occupational exposures	Fair
	Pre-BD FEV_1/FEV_6: ever-smokers in primary care Post-BD FEV_1/FEV_6: primary care with and without smoking history	Pre-BD FEV_1/FEV_6: 2 Post-BD FEV_1/FEV_6: 1	Pre-BD FEV_1/FEV_6: 509 Post-BD FEV_1/FEV_6: 1078	FEV_1/FEV_6 diagnostic accuracy	Pre-BD FEV_1/FEV_6 <0.70: Sensitivity low 50% range Specificity low 90% range Post-BD FEV_1/FEV_6 <0.70: Sensitivity 80% Specificity 95%	Consistent	Few studies	Conducted in Australia, Sweden for pre-BD studies; Greece for post-BD. Most likely reasonably applicable to US primary care population, although environmental/ occupational exposures might vary.	Fair

(continued)

Table 7. Summary of Evidence Table (continued)

Key Question	Population	No. of Studies	No. of Participants	Study Design	Summary of Findings	Consistency	Body of Evidence Limitations	Applicability	Overall Study Quality
Key question 4: Screening harms	Adults in the general population and primary care with and without smoking history	4	3009	CDQ diagnostic accuracy	CDQ >16.5 threshold: Missed cases, 9%-20% FP rate, 51%-76%	Inconsistent	Heterogeneous populations with smokers vs general population	All external validation studies performed outside of United States	Fair
	Ever-smoking adults in primary care	1	849	LFQ diagnostic accuracy	LFQ: Missed diagnosis and FP rate could not be reliably estimated	Unknown: 1 study	Single external validation study	Validated in 36 US primary care sites	Poor
	General population including smokers and nonsmokers	1	2357	COPD-PS diagnostic accuracy	COPD-PS ≥4 Missed cases 33% FP rate, 27% COPD-PS ≥5 Missed cases 65% FP rate, 21%	Unknown: 1 external validation study	Single study set in Japanese rural town	May not be generalizable to US primary care screening population	Fair
	General population including smokers and nonsmokers	1	9390	PEF diagnostic accuracy	Missed cases 16%-69% depending on the threshold used; FP rate 0.5%-16% depending on the threshold used	Unknown: 1 study reporting FN and FP rates	BOLD population-based samples did not exclude or report baseline known COPD so enriched sample	Serious concerns regarding applicability to US population given that many countries in BOLD were low-development-index countries with different environmental and occupational exposures	Insufficient
	Pre-BD FEV_1/FEV_6: Ever-smokers in primary care Post-BD FEV_1/FEV_6: Primary care with and without smoking history	Pre-BD FEV_1/FEV_6: 2 Post-BD FEV_1/FEV_6: 1	Pre-BD FEV_1/FEV_6: 509 Post-BD FEV_1/FEV_6: 1078	FEV_1/FEV_6 diagnostic accuracy	Pre-BD FEV_1/FEV_6 <0.70: Missed cases, high-40% range FP rate, 8%-10% Post-BD FEV_1/FEV_6 <0.70 Missed cases, 20% FP rate, 5%	The FP and FN rates reported in the 2 pre-BD FEV_1/FEV_6 were consistent	Only 2 studies for pre-BD FEV_1/FEV_6	All 3 studies were outside United States	Fair
Key question 5a: Smoking cessation	Adult smokers in the general population and primary care	5	1620	RCT	Of 3 RCTs reporting biochemically confirmed abstinence, only 1 fair-quality RCT communicating lung age reported a statistically significantly higher abstinence rate in intervention group; 1 underpowered VA trial showed a trend toward higher abstinence rates in the intervention group, and 1 trial of screen-detected patients with mild to moderate COPD who were motivated to quit showed almost identical rates of biochemically confirmed abstinence rates at 12 mo in intervention and active treatment control groups	Inconsistent	Studies tested incremental value of adding spirometry to counseling alone rather than the value of COPD screening	Only 1 RCT recruited screen-detected patients who were motivated to quit. All other trials included patients with prior COPD diagnoses.	Fair

(continued)

Table 7. Summary of Evidence Table (continued)

Key Question	Population	No. of Studies	No. of Participants	Study Design	Summary of Findings	Consistency	Body of Evidence Limitations	Applicability	Overall Study Quality
Key question 5b: Immunization rates	Asymptomatic adults				No trials examined effectiveness of screening to increase vaccination rates				
Key question 6: Harms screening on preventive services	Adult smokers in the general population and primary care	1	205	Observational qualitative study	No conclusions possible because of scant data	Unknown: 1 study	Scant data	Unknown	Insufficient
Key question 7: Treatment efficacy	Screen-detected COPD				No trials examined treatment effectiveness on health outcomes in screen-detected patients				
	Mild to moderate COPD	LABA: 2 LABA-ICS: 1 Tiotropium: 5 ICS: 6	LABA: 3174 LABA-ICS: 1097 Tiotropium: 4592 ICS: 3983	LABA: 1 pooled subanalysis of RCTs, 1 RCT; LABA-ICS: RCT; Tiotropium: RCT; ICS: RCT	Subanalyses from 1-4 RCTs for each drug class for individual outcomes support reduction in exacerbation rates, no difference in ACM, mixed findings for QOL in patients with moderate COPD; however, baseline annual exacerbation rates in control group <1/y. Evidence examining dyspnea scores and exercise capacity scant.	Unknown: single subanalysis identified for most drug classes and outcomes	Most subanalyses limited by small sample sizes, short trial durations, post hoc or unspecified analysis timing, and lack of statistical testing for interaction	Nearly all subanalyses in populations of patients with symptomatic, moderate COPD, thereby limiting applicability to asymptomatic screen-detected populations	Poor to fair
Key question 8: Treatment harms	Asymptomatic screen-detected patients				No trials examining treatment harms in screen-detected patients				
	Mild to moderate COPD	LABA: 2 LABA-ICS: 1 Tiotropium: 3 ICS: 5	LABA: 3191 LABA-ICS: 1149 Tiotropium: 4076 ICS: 3732	LABA: 1 pooled subanalysis of RCTs, 1 RCT; LABA-ICS: RCT; Tiotropium: RCT; ICS: RCT	Subanalyses from 1-4 RCTs for each drug class for withdrawals and adverse events too limited to make conclusions	Unknown: single subanalysis identified for most drug classes and outcomes	Most subanalyses limited by few studies, short trial durations, post hoc or unspecified analysis timing, lack of statistical testing for interaction, and variable adverse event reporting	Nearly all subanalyses in populations of patients with symptomatic, moderate COPD, thereby limiting applicability to asymptomatic screen-detected populations	Poor

Abbreviations: ACM, all-cause mortality; BD, bronchodilator; BOLD, Burden of Obstructive Lung Disease study; CDQ, COPD Diagnostic Questionnaire; COPD, chronic obstructive pulmonary disease; COPD-PS, COPD Population Screener; FEV_1, forced expiratory volume in 1 second; FEV_6, forced expiratory volume in 6 seconds; FN, false negative; FP, false positive; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting β-agonist; LFQ, Lung Function Questionnaire; NHANES III, Third National Health and Nutrition Examination Survey; PEF, peak expiratory flow; PLATINO, Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar; QOL, quality of life; RCT, randomized clinical trial; VA, US Department of Veterans Affairs.

reported harms for any individual medication class in patients with mild to moderate COPD, limiting the ability to make firm conclusions regarding the risk of treating patients with early disease.

Discussion

An overall summary of the evidence is presented in **Table 7**. No population-based trials were identified that compared screening with no screening to determine whether primary care screening for COPD improves health outcomes. Through the indirect evidence pathway, we found that the CDQ appears to be the strongest risk factor– and symptom-based questionnaire, demonstrating reasonable sensitivity and specificity for scores greater than 16.5, based on 5 external validation studies. However, no treatment trials in screen-detected populations were identified; treatment trials and subanalyses in populations with symptomatic mild to moderate COPD supported a modest reduction in exacerbation frequency. Strong evidence was not found to support screening as a means to improve smoking cessation rates or other preventive services.

The value assigned to screening for COPD depends not only on the accuracy of screening tools; it requires judgments about the evidence for the benefit of earlier identification balanced against the harms of missed cases, false-positive diagnostic workups, and treatment harms. Earlier identification could lead to net screening benefits if there was evidence of beneficial outcomes derived from downstream treatment in early-stage asymptomatic disease or improvements in the uptake of preventive interventions. However, the treatment literature was largely limited to subgroup analyses, almost exclusively among individuals with moderate COPD and primarily the severe end of moderate (eg, FEV_1% predicted of approximately 60% in many studies). Even among these groups, the benefits on exacerbations and dyspnea scores with early treatment in patients with moderate COPD are not strongly established, and the clinical significance of the observed reduction may be limited. Absolute treatment benefit estimates would be expected to be lower in screen-detected populations with mostly mild disease compared with the populations in the trials available for this systematic review. Epidemiologic studies report that patients with mild to moderate COPD have an average of less than 1 exacerbation per year.[7] A systematic review of RCTs and cohort studies reported an annual event-based exacerbation frequency (defined as physician office visits, antibiotic use, steroid use, or hospitalizations) of 0.82 (95% CI, 0.46-1.49) for mild disease and 1.17 (95% CI, 0.93-1.50) for moderate disease.[56] Patients with screen-detected COPD might be expected to have even fewer exacerbations, which would render the absolute benefit as at best modest. Limited data on harms reported in the treatment effectiveness trials suggest that there are no substantial serious adverse effects for most medications. However, some concerns remain about ICS-containing medications increasing the incidence of pneumonia in patients with more severe COPD and effects on bone mineral density and fracture risk.[57,58] Data were too limited to make firm conclusions regarding this potential harm in the included trials for screen-detected individuals with mild to moderate COPD.

Arguments have been made that the high prevalence of undiagnosed COPD (10%-20%),[16] as well as clinical COPD misdiagnoses in smokers who are found to have alternate treatable diagnoses (eg, congestive heart failure) could be considered as potential benefits with few screening-related harms, because spirometry is a simple, noninvasive test.[59,60] In contrast, however, are concerns about the patient-focused benefits of population screening efforts in largely asymptomatic patients, particularly in light of little evidence on treatment benefit in mild disease, opportunity costs associated with screening, and high monthly costs of these inhaled medications.[61-63]

A large potential benefit from COPD screening would be increasing smoking cessation rates, because smoking cessation is the only proven beneficial treatment for reducing progression in mild to moderate COPD.[64] Smoking cessation counseling and pharmacotherapy are effective in patients with COPD,[65-67] even though there is some evidence that smokers with COPD differ in their motivation to quit compared with smokers without COPD.[68-71] The lung age trial by Parkes et al[41] was the only trial reporting a statistically significant absolute increase in biochemically confirmed cessation rates (7%) when screening results reported lung age to participants (NNT = 14). Because both groups received spirometry and counseling, the communication of lung damage might be the critical component in counseling. However, these positive results have not been replicated in other trials.[40] On the other hand, we did not identify literature to support the premise that false reassurance in those with normal spirometry may dampen motivation to quit. No completed or pending trials reporting the effect of COPD screening on recommended immunization uptake rates were identified.

A challenging issue when considering screening for COPD is the requirement for an asymptomatic population. All questionnaires included symptoms as part of their scoring, and the rationale for screening has largely been a case-finding one (ie, there is substantial undiagnosed disease seen in primary care). As per USPSTF scope, the systematic review was focused on asymptomatic individuals. However, the distinction between patients who are symptomatic and those who are undetected or who present with nonspecific symptoms was difficult to determine from available clinical research. Because there were few RCTs or screening studies, and the ones identified were clinically and methodologically diverse, we were limited to qualitative analysis. Our a priori methods specified patient-focused outcomes and did not include changes in FEV_1 because it is unclear how changes in FEV_1 correlate with changes in patient-oriented health outcomes such as exacerbation rates. In addition, we relied on harms data as reported in the effectiveness RCTs and thus may not have captured the full range of potential adverse effects or their population-based incidence. It is unlikely, however, that observational studies in screen-detected populations applicable to US-based primary care are readily available given current practice.

Conclusions

There was no direct evidence available to determine the benefits and harms of screening asymptomatic adults for COPD using questionnaires or office-based screening pulmonary function testing or to determine the benefits of treatment in screen-detected populations. Indirect evidence suggests that the CDQ has moderate overall performance for COPD detection. Among patients with mild to moderate COPD, the benefit of pharmacotherapy for reducing exacerbations was modest.

ARTICLE INFORMATION

Author Contributions: Dr Guirguis-Blake had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: Guirguis-Blake, Senger, Webber, Whitlock.
Drafting of the manuscript: Guirguis-Blake, Senger, Webber, Whitlock.
Critical revision of the manuscript for important intellectual content: Guirguis-Blake, Senger, Webber, Mularski.
Statistical analysis: Senger, Webber.
Obtained funding: Whitlock.
Administrative, technical, or material support: Senger, Webber, Mularski.
Study supervision: Guirguis-Blake, Senger.

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