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Screening for Chronic Obstructive Pulmonary Disease: A Systematic Evidence Review for the U.S. Preventive Services Task Force

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Structured Abstract

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

Purpose: We conducted this systematic review to support the U.S. Preventive Services Task Force in updating its recommendation on screening for COPD. Our review addresses eight questions: 1) Does screening asymptomatic adults age 40 years and older for COPD with pre-bronchodilator screening spirometry improve health-related quality of life or reduce morbidity or mortality? 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 in predicting diagnosis of COPD based on confirmation using post-bronchodilator 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? 6) What are the adverse effects of COPD screening, including the impact of targeted preventive services in this population? 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?

Data Sources: We searched MEDLINE, PubMed Publisher-Supplied Records, and the Cochrane Collaboration Registry of Controlled Trials to identify literature that was published from January 2000 or 2005 through January 2015, depending on Key Question (KQ). We supplemented our searches with reference lists from the previous review, relevant existing systematic reviews, suggestions from experts, and Clinicaltrials.gov to identify ongoing trials.

Study Selection: Two investigators independently reviewed identified abstracts and full-text articles against a set of a priori inclusion and quality criteria.

Data Analysis: One investigator abstracted data into an evidence table and a second investigator checked these data. We qualitatively synthesized the data for each key question; quantitative synthesis was not appropriate due to heterogeneity and few trials for any given intervention and outcome.

Results: We identified three externally validated COPD questionnaires, the COPD Diagnostic Questionnaire (CDQ), the Lung Function Questionnaire (LFQ), and the COPD Population Screener (COPD-PS). The CDQ, an eight-item self-administered, symptom- and risk-factor based questionnaire, was externally validated in two good- and three fair-quality diagnostic accuracy studies (n=3,048). Validation populations recruited exclusively or at least partly from primary care practices excluding participants with known lung disease, and most studies recruited at least half of their participants with a smoking history. Most external validation studies reported that a CDQ score of greater than 16.5 had a sensitivity in the low 90 percent range and specificity in the high-30 to mid-40 percent range for diagnosing spirometrically-

confirmed COPD. The LFQ, a five-item self-administered risk factor- and symptom-based questionnaire, was externally validated in one fair-quality, multicenter primary care study (n=1,288) in the United States of ever smokers with a greater than or equal to 10 pack-year exposure. The study reported a high rate of unacceptable spirometry (31%), as well as an estimated sensitivity of 88 percent and specificity of 25 percent. The COPD-PS, a five-item, self-administered, risk factor- and symptom-based questionnaire, was externally validated in a single, fair-quality population-based study (n=2,357) in a rural Japanese town and reported a sensitivity of 67 percent and specificity of 73 percent.

We identified two fair-quality Burden of Obstructive Lung Disease (BOLD) population-based studies of pre-bronchodilator peak flow. These studies used different index test thresholds and different gold standard thresholds for defining COPD in both low and high index countries without exclusion of known COPD; these studies do not provide sufficient information to make conclusions regarding peak flow screening accuracy. We identified one good- and one fair-quality study of pre-bronchodilator microspirometry measuring forced expiratory flow in one second/forced expiratory flow in six seconds (FEV_1/FEV_6) reporting consistent sensitivities in the low 50 percent range and specificities in the 90 percent range. We identified one fair-quality study of post-bronchodilator microspirometry measuring FEV_1/FEV_6 in a population of approximately half ever smokers, which reported a higher sensitivity (80%) and specificity (95%).

One fair-quality study examined a staged approach whereby the screening test was considered positive only if both the CDQ and FEV_1/FEV_6 tests were positive. Sensitivity and specificity were 72 and 97 percent, respectively, in the entire population and similar in a subset of smokers only.

Evidence of screening harms from diagnostic accuracy studies was limited; only false positives and false negatives associated with screening were reported and few studies reported data for the calculation of number of missed cases.

We identified five randomized, controlled trials (RCTs) (n=1,620) addressing the effectiveness of COPD screening in influencing smoking cessation rates. Of the three RCTs reporting biochemically confirmed abstinence, only one fair-quality U.K. primary care-based RCT (n=561) reported a statistically significant difference in smoking cessation at 1 year with a number needed to treat of 14; this trial measured the incremental value of adding lung age to standardized counseling. The other two underpowered RCTs of biochemically validated abstinence reported no difference or a nonstatistically significant trend favoring reduction in the spirometry group. No studies examined the effectiveness of screening to increase vaccination rates.

There were no treatment trials identified in screen-detected patients; thus, we included trials with either subanalyses of participants with mild-to-moderate COPD or trials where the mean FEV_1 percent predicted was 60 percent or greater. We identified a total of one good-quality and 13 fair-quality RCTs meeting these criteria providing analysis of mild-to-moderate COPD participants; there were two long-acting beta agonist (LABA) studies (n=3,174), one inhaled corticosteroid (ICS)-LABA combination study (n=1,097), five tiotropium studies (n=4,592), and

six ICS studies (n=3,983). Overall, subanalyses were limited due to post hoc timing, underpowering for subgroups, lack of data to confirm baseline comparability for the subgroup, lack of interaction testing, and lack of control for confounders. However, available subanalyses suggest no benefit in all-cause mortality, but a decrease in annual rates of exacerbations with LABA, LABA-ICS, tiotropium, and ICS. Because absolute rates of exacerbations were less than 1 in patients with mild-to-moderate COPD, the clinical magnitude of this benefit is uncertain. Data was too limited to make conclusions regarding other patient focused outcomes (e.g., exercise capacity, dyspnea, and quality of life).

We identified eight effectiveness RCTs reporting harms data, but few trials report harms for any individual drug class, making conclusions about treatment-related adverse events challenging. Concerns about pneumonia and bone demineralization with ICS medications could not be confirmed because few trials reported these outcomes. U.S. Food and Drug Administration drug labels for the considered drug classes report side effects as generally mild, ranging from dry mouth and coughing to vomiting and pneumonia.

Conclusions: There is no direct evidence to quantify the benefits and harms of COPD screening with questionnaires or handheld spirometry, nor is there evidence to estimate the treatment benefits in screen-detected populations. The evidence gaps identified in this systematic review suggest that there is a need for future research examining the treatment benefit in asymptomatic screen-detected populations or populations with mild disease.

Table of Contents

Figure

Tables

Appendixes

Chapter 1. Introduction

Condition Definition

Chronic obstructive pulmonary disease (COPD) is defined by a reduction in airflow that is not entirely reversible.[1-6] This reduction in airflow is typically progressive and is related to an inflammatory response of the lungs to harmful particles or vapors, principally caused by cigarette smoking. While COPD mainly impacts the lungs, it can also result in substantial systemic consequences, such as progressive dyspnea, chronic cough, and chronic production of sputum.[1-6] Asthma has distinct pathogenic causes and responds differently to treatment than COPD, and, while some overlap occurs, should be considered a different condition.[6]

Both current guidelines and the community standard for diagnostic spirometry in the United States require that fixed obstructive physiology be identified by a post-bronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) less than 0.70.[6] The severity of obstruction is further characterized by the post-bronchodilator FEV_1 percent predicted. This is calculated as a ratio of volume exhaled in the first second over the volume predicted by any of a number of reference equations based on age, gender, race, and height.[6,7] The classification of severity in patients is described in **Table 1**.

Although the fixed ratio of FEV_1/FVC less than 0.70 is the current standard for diagnostic confirmation of obstructive physiology, it has been demonstrated that this fixed ratio results in underestimation of airflow obstruction among young adults and an overdiagnosis of obstruction in the elderly due to normal aging processes.[8-10] An alternative approach has been proposed using a statistically derived lower limit of normal (LLN) FEV_1/FVC criteria for a threshold determination of obstruction, which is usually defined by the lower fifth percentile or defined by more complex statistical variations against some healthy reference population.[8,10,11] While the LLN is anticipated to be more physiologically accurate, and some epidemiological studies support clinical utility in individuals younger than ages 45 to 50 years or older than age 70 years, experts disagree on the utility of the LLN and the preferred methodology of this measure. Misidentification of obstruction using LLN is generally limited to approximately 5 to 15 percent if these individuals are at the age extremes.[8,10,12-14] Generally, the LLN has little advantage over the fixed ratio for diagnostic accuracy in a typical adult screening population with a medium age in the 5th to 6th decades.[11,15-17]

Prevalence and Burden of Disease

It is estimated that approximately 13.7 million individuals in the United States are impacted annually by COPD, and in 2010 the disease was responsible for approximately 10.3 million visits to physicians, 1.5 million visits to the emergency room, and 699,000 hospital discharges.[18] In 2013, the Centers for Disease Control and Prevention (CDC) reported that chronic lower respiratory disease, composed chiefly of COPD, was the third leading cause of death in the United States.[19] COPD also has significant economic consequences. The national health care costs related to COPD in the United States, for example, are estimated to be approximately $32.1

billion per year. After adding the total absenteeism related to the disease ($3.9 billion annually), the total annual burden of COPD-attributable costs are estimated at $36 billion per year.[20]

The prevalence of COPD in U.S. adults varies from approximately 5 to 20 percent, depending on the geographic location and the disease definition used. The highest prevalence of COPD is seen in states grouped along the Ohio and lower Mississippi rivers.[3,6,21-25] Measurements of the prevalence and burden of COPD are variable because prevalence estimates rely on a mix of self-report, lung function testing, and administrative sources. Data from the U.S. National Health and Nutrition Examination Survey (NHANES) from 2007 to 2010 estimated a COPD prevalence of 14 percent among adults ages 40 to 79 years based on post-bronchodilator spirometry. The prevalence was highest for mild disease (7.2%) followed by moderate (5.0%) and severe/very severe disease (0.8%).[25]

Recent data from the 2011 Behavioral Risk Factor Surveillance System (BRFSS) shows that 6.3 percent of U.S. adults reported their physician or other health professional told them they had COPD.[26] A subset of this survey data from 21 states, the District of Columbia, and Puerto Rico found that 76.0 percent of individuals with COPD reported completing a diagnostic breathing test, 64.2 percent felt that shortness of breath negatively impacted their quality of life, and 55.6 percent took at least one daily COPD medication. Approximately 43.2 percent of respondents with COPD reported visiting a physician for COPD-related symptoms in the preceding 12 months, and 17.7 percent had either visited an emergency department or been admitted to a hospital for their COPD during that time. An American Lung Association survey discovered that half of all COPD patients reported restrictions to their ability to work, participated in normal physical activities (70%), completed chores around the house (56%), participated in social events (53%), slept (50%), and participated in activities with their families (46%).[27]

Deterioration of lung function over time is associated with a decline in health-related quality of life (HrQOL) among COPD patients. Studies examining this relationship have focused on patients with advanced disease and unsurprisingly have shown a substantial decline in HrQOL related to COPD.[6,28-30] Studies assessing the impact on HrQOL among COPD patients with mild disease have found similar results, although this impact is not as significant as in those with advanced disease.[31,32]

The St. George's Respiratory Questionnaire (SGRQ) is the primary HrQOL measurement tool used in studies of COPD. The SGRQ is a standardized self-administered 50-item questionnaire designed to measure impaired health and perceived well-being in patients with obstructive airway disease.[33] The SGRQ is a two-part questionnaire with three components that assess the frequency and severity of symptoms, activities that cause or are limited by breathlessness, and "impacts" such as social functioning and psychological disturbances.[34] A score is calculated for each section and the total score ranges from 0 to 100, with higher scores indicating higher levels of limitations.[34] Clinically significant thresholds were established based on empirical data and interviews with patients, with a mean change score of 4 considered the minimum threshold for clinically meaningful change.[35]

We can estimate COPD screening yield and disease severity distribution using studies of screen-detected patients examining COPD case finding. A 2011 primary care screening study of adults

older than age 40 years with no medically confirmed obstructive lung disease (n=1,250) found that the majority of cases were found to be mild-to-moderate COPD, as defined by GOLD (36% mild, 48% moderate), and 14 percent were found to have severe COPD.[36]Additionally, a Belgian screening study of adults seen in primary care, ages 35 to 70 years, included only adults who did not use bronchodilators or inhaled steroids during the previous 12 weeks (n=3,158). This study found similar results, with the majority of patients having mild (39.0%) or moderate COPD (51.0%). The study found that 9 percent had severe COPD.[37] Severity results among high-risk patients (based on age and smoking status) appear to have a similar distribution. A recently published U.S.- and U.K.-based COPD screening study (n=818) focused on asymptomatic patients with a history of smoking and no prior diagnosis of any chronic respiratory disease who were seen in primary care reported case-finding results by disease severity.[38] Among the 155 patients diagnosed with COPD, 57.4 percent had mild disease as defined by GOLD, 36.8 percent had moderate disease, and 5.8 percent had severe disease. None of the participants had very severe disease. Further, a 2011 Australian screening study focused on primary care patients with a history of smoking and no prior diagnosis of COPD (n=237) found a COPD prevalence of 27.9 percent. Fewer patients showed mild COPD (33.3%), 61.4 percent were found to have moderate COPD, 5.2 percent had severe COPD, and no participants had very severe COPD.[39] Thus, screening yield in the general primary and asymptomatic population would be very unlikely to identify more than 5 to 14 percent of the population as having severe COPD, even among high-risk patients.

Etiology and Natural History

COPD is a progressive, chronic condition without a known cure. COPD is characterized by continual respiratory decline associated with acute exacerbations that often result in hospitalization and ultimately death.[6,28,40] Although lung function that declines over time is a characteristic of the disease, the trajectory of decline can vary significantly among patients. Some patients experience a higher rate of exacerbations than is typical, while others have lung function that remains relatively stable for extended periods of time. Others experience a decrease in lung function at a more rapid rate than the rest of the COPD population.[2,40] While the reasons behind these differences are not precisely known, researchers suspect that environmental and genetic factors likely play a role.[6,28,41]

As a result of the slow progression of disease and the risk associated with long-time smoking, COPD is more common in patients over the age of 40.[42-44] Recent data from NHANES examining pre- and post-bronchodilator results found COPD present in 9.2 percent of 40- to 59-year-olds compared with 22.6 percent of 60- to 79-year-olds.[25] If a patient under the age of 45 years is identified as having COPD, national guidelines recommend that they undergo testing for alpha-1 antitrypsin deficiency.[6,45]

Although the pathobiology of COPD involves systemic abnormal inflammation, inflammation is principally centered in the lungs.[1-6] Changes can be characterized in the peripheral airways, central airways, pulmonary vasculature, and lung parenchyma. These changes vary across individuals with the disease and suggest different clinical phenotypes.[2,6,28] The pathogenesis includes chronic inflammation that involves an imbalance of proteinases and antiproteinase, as

well as oxidative stress resulting in physiological irregularities that include: hypersecretion of mucous and ciliary dysfunction; restricted airflow and hyperinflation; abnormalities in gas exchange; pulmonary hypertension; and other systemic effects.[2,6]

Risk Factors

Given that the primary risk factors for COPD are modifiable (i.e., exposure to smoke or fumes), the disease could be preventable by eliminating such exposures.[2,6] A history of exposure to cigarette smoke, either directly or indirectly, has been highly correlated with developing COPD and with COPD mortality.[6,21,23,27,46] Data from the Burden of Obstructive Lung Disease (BOLD) project found that more than 70 percent of COPD occurred among current or former smokers and that this result had a dose-response relationship (odds ratio [OR], 1.24 [95% confidence interval (CI), 1.05 to 1.47] for each 10 pack-year increase).[46,47] Screening data from the third NHANES identified obstructive lung disease (including COPD and asthma) in 12.5 percent of current smokers and 9.4 percent of former smokers.[21] Historically, researchers have estimated that 15 to 20 percent of smokers develop COPD. A more recent study, however, found that this number may be closer to 50 percent.[48]An epidemiological study evaluating 50-year trends in smoking-related mortality using data from longitudinal cohort studies found that current smokers were 4 to 22 times more likely to die from COPD-related causes than those who had never smoked.[49]

COPD prevalence and mortality have been increasing more rapidly among women than men over the past 20 years. This is thought to be due to a variety of factors, including increasing smoking rates among women, differences in environmental exposures, and potential biological or hormonal mechanisms affecting the susceptibility to COPD. Additionally, epidemiological studies have demonstrated that women may be more vulnerable to the negative health effects of smoking than men.[6] A recent report summarizing data from the National Health Interview Survey of adults over the age of 18, for example, found that from 1998 to 2009 women had a consistently higher prevalence of self-reported COPD than men (~6% vs. ~4%).[50] This trend was true across the lifespan, except for those aged 75 to 84 years, where more men than women reported having the disease (11.2% vs. 9.7%). Similarly, data from the 2011 BRFSS reported more women aged 18 years or older self-reported receiving a diagnosis of COPD compared with men (6.7% vs. 5.2%).[26] Some of these numbers may reflect a gender bias in the self-reporting of a COPD diagnosis. Recent data based on post-bronchodilator spirometry (not self-reported diagnoses) in the nationally representative NHANES sample of adults aged 40 to 79 found a higher prevalence in men than women (~17% vs. ~10%).[25]

COPD prevalence also appears to vary by racial/ethnic group. Data based on post-bronchodilator spirometry in the 2007-2010 NHANES found the highest prevalence of COPD among non-Hispanic whites (14.9%) followed by non-Hispanic blacks (12.8). Mexican Americans were least likely to have COPD with a prevalence of 5.8 percent.[25] After adjustment for demographic factors, socioeconomic status, and COPD risk factors, Mexican Americans have been found to have decreased odds of obstructive lung disease (including COPD and asthma) compared to non-Hispanic whites (OR, 0.72 [95% CI, 0.54-0.95]). This decreased risk, however, has not been shown to provide any COPD mortality advantage.[51] Other groups including Asian, Native Hawaiian/Pacific Islanders, American Indians, Alaska Natives, and multiracial individuals have

been found to have a rate between that of Hispanics and non-Hispanic whites.[26]

While smoking is associated with the majority of COPD cases, research has shown that several occupational and environmental exposures increase the risk of developing COPD. Certain occupations, such as farming and industrial work, which expose individuals to irritants (e.g., toxins, dust, industrial chemicals), have been associated with the development of COPD. These occupational sources are estimated to contribute to 15 percent of COPD cases. The most common environmental exposures linked to COPD include traffic pollutants and wood smoke.[52] Additionally, exposure to secondhand smoke, heredity, a history of childhood respiratory infections, asthma, and low socioeconomic status have been shown to increase the risk of developing the disease.[3,6,52-55]

Rationale for Screening/Screening Strategies

Primary care providers can identify COPD by screening asymptomatic individuals or targeting a high-risk asymptomatic population, such as patients with a history of smoking, by using screening spirometry administered without medication (i.e., pre-bronchodilator testing).[6] The diagnosis of COPD requires persistent airway obstruction after an additional step of spirometry testing following the administration of an inhaled medication like albuterol (i.e., post-bronchodilator spirometry).[4,6] Screening strategies using spirometry can be conducted sequentially in medical settings, which will allow both tests (pre- and post-bronchodilator) to be combined into a single screening episode. They can also be conducted as separate screening steps, allowing the pre-bronchodilator screening to be done by personnel not authorized to administer medications (e.g., medical assistants). After identifying obstruction with screening, patients can then be administered diagnostic spirometry in primary care or be referred to pulmonary specialty clinics for diagnostic spirometry, including post-bronchodilator testing. Spirometry testing in primary care settings must be administered by trained individuals using equipment that may require maintenance and/or calibration to achieve acceptable testing quality.[7,38,56,57]Additionally, spirometry requires technical expertise to maximize the FVC maneuver, including proficiency in coaching the participant; reproducibility standards set for repeated measurements can be difficult to achieve in primary care settings.[7,38,58-60] Concerns have been raised over the yield, complexity, and quality of spirometric measures in primary care settings.[38,56,57,59,61] The reliability and quality of measures in nonspecialty settings, however, can be improved by sufficient training and quality control measures.[58,62-64] Recent population- and primary care-based screenings using FEV_1/FVC spirometry, for example, have achieved greater than 90 percent reliability and acceptability.[58,63]An alternative approach to FEV_1/FVC using the exhaled volume after 6 seconds of maximal effort expiration (FEV_6) for a ratio (FEV_1/FEV_6) is being considered for screening. This is because this ratio is more explicitly defined and the breathing measure is easier to achieve by patients and nonspecialized practitioners administering the test. Additionally, some devices are handheld and require minimal maintenance and calibration (e.g., COPD-6, PiKo-6). While research has shown that the FEV_1/FEV_6 may be a reliable screening index in less sophisticated settings, it is not sufficient for diagnostic criteria.[9,11,15,65-67]

Full-reference spirometry, including post-bronchodilator testing, requires 40 minutes to

administer and has the above mentioned requirements. Pre-bronchodilator handheld screening devices, however, require less than 10 minutes to administer in an exam room and can be administered by medical assistant personnel with 10 hours or less of training and minimal (≤5 minutes) daily calibration time. Using these devices, providers can obtain valid results in more than 85 to 95 percent of pre-bronchodilator tests.[7,38,56,57] Additionally, questionnaires to rule out those who would not need screening spirometry require less than 5 to 10 minutes to self-administer and score, which can easily be accomplished in an exam room.

Less than half of the estimated 24 million U.S. adults who have airflow obstruction after spirometry testing were previously diagnosed with COPD.[21,22,68] This is the result of the often indeterminate symptoms experienced in the earlier stages of COPD. Consequently, patients are typically diagnosed with the disease in the advanced stages, which leads to poorer treatment outcomes and higher economic costs.[2,6,69,70] Earlier COPD diagnosis using spirometry testing might, therefore, potentially have a substantial impact on patient outcomes if better disease management and treatment in earlier stages of COPD was shown to result in fewer exacerbations, less dyspnea, and an overall improvement in HrQOL. Additionally, the benefits of screening could include an increase in smoking cessation for current smokers, an increase in targeted preventive services (e.g., influenza and pneumococcal vaccines), and possibly the initiation or optimization of therapies that could reduce disease progression. Recently, some authors have developed and internally validated 10-year COPD prediction models in primary care.[71]

This systematic review targeted asymptomatic individuals, defined as those who are free of the disease; those in whom the disease is present, but who have physical symptoms that are undetected by the patient or the clinician (e.g., have mild dyspnea that goes unnoticed); or those who have nonspecific symptoms (e.g., sporadic sputum production or cough) that have gone unrecognized as being related to COPD. The distinction between patients who are symptomatic and those who are undetected or who present with nonspecific symptoms is difficult to determine from available clinical research. This is particularly true for smokers, many of whom have a chronic cough and some limited activity without presenting these complaints to their physicians. Additionally, identifying asymptomatic individuals may also be challenging for clinical practice until screening/case-finding tools can be developed to identify individuals based on sociodemographic characteristics, such as age or a particular smoking history.

Interventions/Treatment

Smoking cessation interventions should play an integral part in the medical management of COPD in all stages of the disease because exposure to cigarette smoke is the primary risk factor for developing COPD and accelerates the deterioration of lung function in patients with the disease.[6,72,73] Patients with COPD also have greater resistance to smoking cessation interventions than other smoking adults, which is likely due to their advanced age and increased pack-year history.[74] Additionally, patients with COPD have reported increased rates of depression compared to general smokers, which can lead to more failed quit attempts and higher relapse rates.[75] A 2012 systematic review assessed the effectiveness of smoking cessation interventions in this population and found that cessation interventions can be successful if they are high

intensity and combined with nicotine replacement therapies.[76]

Pharmacotherapy can be used to alleviate symptoms, reduce the incidence and severity of exacerbations in patients with symptomatic COPD, while improving overall HrQOL.[6] Currently, the American College of Physicians (ACP), American College of Chest Physicians (ACCP), American Thoracic Society (ATS), and the European Respiratory Society (ERS) joint guideline recommends against treating asymptomatic individuals, with or without spirometric evidence of airflow obstruction, regardless of the presence or absence of risk factors for airflow obstruction.[4] The guideline recommends using inhaled bronchodilators for stable COPD patients with respiratory symptoms and moderate to very severe disease (FEV_1 <60% of predicted).[4] For symptomatic moderate disease (FEV_1 60 to 80% predicted), inhaled bronchodilator therapy may also be used to aid in the reduction of symptoms.[4] For symptomatic patients with moderate to very severe disease (FEV_1 <60%), monotherapy with long-acting beta agonists (LABAs) or long-acting inhaled anticholinergics are recommended.[4] Combining bronchodilators of varying pharmacological classes may increase efficacy, while reducing the risk of side effects, compared with increasing the dose of a single bronchodilator.[6,70] Other primary pharmacologic therapies for COPD include inhaled corticosteroids (ICS) and phosphodiesterase-4 inhibitors (specifically in severe to very severe COPD with chronic bronchitis and a history of exacerbations).

The effectiveness of treatments for COPD patients with severe or very severe disease (FEV_1 <50% predicted) has been well-studied, while the effectiveness of COPD treatments in patients with mild-to-moderate COPD (FEV_1 ≥50% predicted) have been less robustly studied. Treatments specific to patients with more advanced COPD include pulmonary rehabilitation, oxygen therapy, surgery, and lung transplantation. Pulmonary rehabilitation is recommended for symptomatic patients with FEV_1 less than 50 percent predicted and can be comprised of a multitude of services, including exercise training, nutritional counseling, training on breathing strategies, and energy conservation methods.[4,77] Evidence has demonstrated that COPD patients who receive these services can experience reduced hospitalizations and improved HrQOL.[77] Oxygen therapy is recommended for COPD patients with severe resting hypoxemia and typically involves the continuous administration of oxygen for more than 15 hours a day. Although this type of therapy has been found to be mildly disruptive to the patient, evidence suggests that it can lead to improved survival.[6,78] For patients with very severe COPD, surgical treatment aimed at reducing lung volume and lung transplantation can offer a survival benefit and improvements in HrQOL.[6,79] Observational studies, for example, have shown that COPD patients with severe or very severe disease constitute a very small minority of those identified by asymptomatic spirometry screening (<5%).[22,38,61] Therefore, we will not consider treatment modalities recommended specifically for these patients (i.e., pulmonary rehabilitation, oxygen therapy, surgical treatment, and lung transplantation) in this review.

Current Clinical Practice

In 2011, the ACP, ACCP, ATS, and the ERS issued a joint clinical practice guideline on the diagnosis and management of COPD.[4] After reviewing the evidence related to the value of screening asymptomatic patients for COPD using spirometry, the panel recommended against this practice, citing there was no evidence of benefit based on moderate-quality evidence. They

did recommend case finding with spirometry, however, in patients reporting COPD-related symptoms. Similarly, in 2010 the National Institute for Health and Clinical Excellence (NICE) recommended against screening asymptomatic patients for COPD using spirometry.[3] The NICE guidance went on to recommend that only patients who are aged 35 years and older with an established risk factor (e.g., a history of smoking, family history of lung disease, exposure to occupational pollutants) and who present with respiratory symptoms associated with the disease should be evaluated with spirometry. The GOLD guidelines updated in 2015 include similar recommendations related to the appropriate case finding population.[6]

Generally, screening for COPD using pre-bronchodilator testing is not widely used in primary care practice in the United States. Additionally, data suggests that using spirometry for case finding in a manner consistent with guideline recommendations is vastly underutilized.[3,6,21,22] In the NHANES III, for example, 63.3 percent of adults who were found to have airflow obstruction reported never having received a previous diagnosis of COPD.[21] This lack of use stems from a number of causes, including its low diagnostic yield and complexity of the testing.[38,61,68,80-82] In work conducted by the U.K. National Screening Committee to update COPD screening policy, for example, both patients and providers noted low acceptability of spirometry.[83] Additionally, concerns over test characteristics and alternate spirometric measures have been raised.[84,85] The reliability, reduced quality of measures in nonspecialty settings, and the risk of overdiagnosis further decrease the use of spirometry in primary care.[57,58,62]

As current guidelines support the use of spirometry for case finding in those with symptoms, researchers and practitioners are employing strategies to increase the identification of patients with unreported respiratory symptoms using a variety of screening questionnaires and sending those who prescreen positive to screening spirometry or diagnostic spirometry.[86-89] Two possible strategies for targeted screening spirometry include basic risk factor questionnaires that are easily and quickly administered to patients or the identification of high-risk subpopulations through patient history inquirees,[83,90-92] and several prescreening or risk identification tools have been developed to increase the efficacy of case-finding. These include the Lung Function Questionnaire (LFQ),[86,93] the COPD Diagnostic Questionnaire (CDQ),[94,95] and the COPD population screener (COPD-PS).[88]

Previous USPSTF Recommendation

In 2008, the U.S. Preventive Services Task Force (USPSTF) recommended against screening asymptomatic adults for COPD using spirometry (D recommendation).[96] The USPSTF concluded that there was at least moderate certainty that this method had no net benefit and had large associated opportunity costs. They also found good-quality evidence demonstrating that patient history and clinical examination are not often accurate predictors of airflow limitation. Additionally, they reported fair-quality evidence that demonstrated that giving smokers the results of spirometry screening does not independently improve smoking cessation rates. Further, the USPSTF found fair-quality evidence that annual influenza vaccination may reduce COPD exacerbations, but did not identify any studies which examined whether screening with spirometry results in an increased rate of influenza vaccination. Additionally, the USPSTF found good-quality evidence indicating that pharmacologic therapy prevents the worsening of

symptoms and need for medical interventions related to COPD. It also found, however, that pharmacologic therapy does not impact hospitalization rates or all-cause mortality in symptomatic patients who have ever smoked, are 40 years of age or older, and who have severe or very severe COPD (FEV_1 <50% of predicted). Further, fair-quality evidence demonstrated that both pharmacotherapy and pulmonary rehabilitation improve health status measures related to respiration and that supplemental oxygen reduces mortality among patients with resting hypoxia. Overall, the incremental benefits of screening asymptomatic patients for COPD using spirometry were judged to be minimal.

Chapter 2. Methods

Scope and Purpose

This systematic review addresses the benefits and harms of screening for COPD using spirometry, the diagnostic accuracy of associated screening instruments, the effect of spirometric screening on uptake of targeted preventive services, and the effectiveness and associated harms of treating mild-to-moderate COPD. The USPSTF will use this review to update its 2008 recommendation on this topic.[96] This review included all trials from the previous review that met current inclusion and exclusion criteria as well as newly identified studies.

Key Questions and Analytic Framework

Using the USPSTF's methods,[97] we developed an analytic framework (**Figure 1**) and eight Key Questions (KQs) in consultation with the Agency for Healthcare Research and Quality (AHRQ) Medical Officer and three members of the USPSTF. These KQs were adapted from questions addressed in the previous review.[98] The KQs related to the diagnostic accuracy of prescreening questionnaires and pulmonary function tests are unique to this review.

Key Questions

1. Does screening asymptomatic adults age 40 years and older for COPD with pre-bronchodilator 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 (i.e., 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 (e.g., pre-bronchodilator screening spirometry, peak flow meter) in predicting diagnosis of COPD based on confirmation using post-bronchodilator 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 to usual care?
   b. Does screening for COPD increase relevant immunization rates among asymptomatic adults compared to usual care?
6. What are the adverse effects of COPD screening, including the impact of targeted preventive services in this population (e.g., 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?

Data Sources and Searches

In addition to considering all studies from the previous review for inclusion in the current review, we performed a comprehensive search of MEDLINE, PubMed Publisher-Supplied Records, the Cumulative Index to Nursing and Allied Health Literature, and the Cochrane Collaboration Registry of Controlled Trials.

For evidence related to the effect of screening on health outcomes literature, we searched for studies published between January 2005 and January 31, 2015, building on the literature published in the previous review. For evidence related to the use of prescreening questionnaires and pulmonary function tests, we searched for studies published between January 2000 and January 31, 2015. The literature related to the use of screening questionnaires and pulmonary function tests are new to this review. Our search on this literature, however, is limited to literature published beginning in the year 2000. This is based on the introduction of the requirement for obstruction to be not fully reversible in the 2001 GOLD guidelines, which introduced the need for post-bronchodilator spirometry (our gold standard in the review).[99] For evidence related to the effect of spirometry on smoking cessation rates, we searched between January 2012 and January 31, 2015 and built this search on a previously published evidence review on the topic.[100] We searched for evidence related to the effect of spirometry on vaccination rates between database inception and January 31, 2015. For evidence related to the treatment of mild-to-moderate COPD, we searched for evidence published from January 2010 to January 31, 2015. This search was built upon two previous published reviews on COPD treatment.[101,102] In the cases where we based our KQs off previously published reviews, we evaluated all of the included studies in the review for inclusion in the current review and bridged forward for new primary literature.

We worked with a medical librarian to develop our search strategies (**Appendix A**). All searches were limited to articles published in the English language. We managed literature search results using version 12.0 of Reference Manager® (Thomson Reuters, New York, NY), a bibliographic management software database. For a complete summary of our searches by KQ and the associated rationale, please see **Table 2**.

To ensure comprehensiveness of our retrieval strategy, we reviewed the reference lists of included studies and relevant systematic reviews and meta-analyses to identify relevant articles that were published before our search dates or were not identified in our literature searches. We also obtained references from outside experts. We also searched federal agency trial registries for ongoing trials (**Appendix B**).

Study Selection

Two reviewers independently reviewed the title and abstracts of all identified articles using Abstrackr[103] to determine if the study met our inclusion and exclusion criteria for design, population, intervention, and outcomes (**Appendix A Table 1**). Two reviewers then independently evaluated the full-text article(s) of all potentially relevant studies against the complete inclusion and exclusion criteria. Disagreements in the abstract and/or full-text review were resolved by discussion and consultation with a third reviewer, if necessary. Excluded studies and reasons for exclusion are listed in **Appendix C**.

We developed an a priori set of criteria for inclusion and exclusion of studies based on criteria from the previous review and our understanding of the literature (**Appendix A Table 1**). For KQs 1-6, we considered studies including asymptomatic adults aged 40 years and older (limited to current smokers for KQ 5a). For KQs 7 and 8, we restricted the population further to only include asymptomatic adults aged 40 years and older who were also diagnosed (preferably based on screening) with mild (FEV_1 ≥80% normal) to moderate (FEV_1 50%-79% normal) COPD or a mean population FEV_1 greater than or equal to 60 percent predicted to approximate a population of mild-to-moderate COPD. We defined asymptomatic patients as those in one of the following states: those who are free of the disease; those in whom the disease is present, but who have physical symptoms that are undetected by the patient or the clinician (e.g., have mild dyspnea that goes unnoticed); or those who have nonspecific symptoms (e.g., sporadic sputum production or cough) that have gone unrecognized as being related to COPD. For KQs 1-6, we excluded studies of patients with previously diagnosed COPD or other respiratory conditions (KQ 1 only), patients with identified alpha-1 antitrypsin deficiency, and pregnant women. For KQs 7 and 8, we excluded patients diagnosed with severe (FEV_1 ≥30%-49% normal) or very severe (FEV_1 <30% normal) COPD, pregnant women, and patients with identified alpha-1 antitrypsin deficiency. While the ideal literature related to treatment would focus on screen-detected patients, we recognized that many studies would be population-based. As such, we included some proportion of patients with previously diagnosed disease, making the criteria of excluding patients with COPD-related symptoms not pragmatic (e.g., persistent dyspnea, chronic sputum production and/or cough). Additionally, we looked for risk factor-based prescreening questionnaires for KQ 2, but were not able to locate any such questionnaires. As a result, we included screening questionnaires that used a combination of risk factors and symptom-based questions.

For KQs 1-4, we examined studies that used pre-bronchodilator screening spirometry, screening questionnaires, or risk assessment tools, peak flow meters, and confirmatory post-bronchodilator spirometry. For KQs 5 and 6, we focused on studies providing pulmonary function testing with the addition of smoking cessation or immunization intervention/counseling. For KQs 7 and 8, we focused on pharmacotherapy interventions appropriate for mild-to-moderate COPD (including short- and long-acting beta agonists, anticholinergics, ICS, or combinations of these treatments).[6] For KQ 7, we required studies to have at least 6 months of followup.

We considered a broad range of outcomes for each KQ, including all-cause mortality and COPD-related morbidity (KQs 1 and 7); test performance including sensitivity, specificity, and positive/negative predictive values compared to the gold standard of pre- or post-bronchodilator

screening (KQ 2) or post-bronchodilator screening only (KQ 3); and self-reported or biologically validated smoking abstinence or immunization rates (KQ 5). For KQ 7, we did not consider evidence related to disease progression as measured by pulmonary function (i.e., stable FEV_1). Instead, we focused on more patient-centered outcomes. For the KQs that examined harms of screening (KQs 4 and 6), we considered the false-positive rate, the proportion of diagnoses missed by screening, and adverse events associated with the uptake of targeted preventive services (e.g., false reassurance for screen-negative smokers). For the harms associated with treatment (KQ 8), we included serious adverse events as defined by study authors, as well as individual incidence rates of any adverse events. Additionally, we considered adverse events reported by greater than or equal to 3 percent of the study population reported on the U.S. Food and Drug Administration (FDA) drug labels of included COPD treatments.

For KQs 1, 5, and 7, we limited the study design to randomized, controlled trials (RCTs). For KQs 2 and 3, we limited our studies to diagnostic accuracy studies (including observational/cohort studies). For KQs 4 and 6, we considered RCTs, large screening registry or database observational studies, and cohort studies. When evaluating harms associated with the treatment of COPD (KQ 8), we limited the data to that which was reported in the included efficacy trials included in KQ 7, large screening registries, systematic reviews, and supplemented the data with information reported by the FDA. For all KQs, we considered all systematic reviews of included study designs. We limited our included studies to those published in English that we rated as good- or fair-quality using USPSTF quality rating standards.[104] We excluded studies that we rated as poor quality and those that did not publish results in English. The outcomes that were reviewed are fully listed in **Appendix A Table 1**.

Quality Assessment and Data Abstraction

Two reviewers independently assessed the methodological quality of each study using predefined criteria developed by the USPSTF[104] and supplemented with the NICE methodology checklists for observational studies and the Quality Assessment of Diagnostic Accuracy Studies (QUADAS I and II) tool for diagnostic accuracy (**Appendix A Table 2**).[105-107] Disagreements in quality were resolved by discussion. Each study was given a final quality rating of good, fair, or poor.

Good-quality RCTs had adequate randomization procedures and allocation concealment, blinded outcome assessment, reliable outcome measures, similar groups at baseline (i.e., little to no statistically significant differences between groups in baseline characteristics), low attrition (≥90% of participants had followup data with <10 percentage point difference in loss to followup between groups), used intent-to-treat (ITT) analysis, and reported diagnostic criteria for outcome ascertainment. We rated trials as fair quality if they were unable to meet the majority of the good-quality criteria. We rated trials as poor quality if attrition was greater than 40 percent or differed between groups by 20 percentage points, or if there were any other "fatal" flaws that seriously affected internal validity, as agreed upon by two independent investigators.

We abstracted data from all included studies into standard evidence tables using Microsoft Word® (Microsoft Corporation, Redmond, WA). A second reviewer checked the data for

accuracy. We abstracted information on study design, baseline data, intervention details, diagnostic accuracy outcomes, behavioral outcomes (smoking cessation, vaccination rates), health outcomes, and adverse events.

Data Synthesis and Analysis

We created separate tables for the results for each KQ and additional summary tables that included key study characteristics. We qualitatively examined these tables to identify a range of results. Given the heterogeneity of studies, meta-analyses were not conducted for any of the KQs in this report.

For studies of diagnostic accuracy we used 2x2 tables constructed from data reported in the primary studies. In cases where 95 percent CIs were not reported for diagnostic accuracy estimates, we calculated these intervals in Stata using Jeffrey's CIs. For diagnostic accuracy studies, in addition to the standard test performance characteristics (i.e., sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV]), we calculated the following outcomes: COPD prevalence in the population (true positives plus false negatives, divided by the number of patients screened, multiplied by 100), percent of patients screening positive (true positives plus false positives, divided by the number of patients screened, multiplied by 100), false-positive rate (false positives divided by the false positives plus the true negatives, multiplied by 100), and the percent of diagnosed missed by screening (false negatives divided by the true positives, plus false negatives, multiplied by 100).

Expert Review and Public Comment

A draft of the analytic framework, KQs, and inclusion/exclusion criteria was posted on the USPSTF website for public comment from February 20, 2014 to March 19, 2014. We received comments from nine individuals or organizations. All comments were reviewed and addressed as appropriate. The final research plan was posted on the USPSTF website on May 29, 2014. The full draft report was reviewed by invited experts from January 30, 2015 through February 13, 2015. We compiled and addressed (where appropriate) the comments received from the reviewers.

USPSTF Involvement

AHRQ funded this research under a contract to support the work of the USPSTF. The authors worked with three USPSTF liaisons at key points throughout the review process to develop and refine the scope, analytic framework, and KQs; to resolve issues around the review process; and to finalize the evidence synthesis. AHRQ had no role in study selection, quality assessment, or evidence synthesis. AHRQ staff provided project oversight, reviewed the draft evidence synthesis, and distributed the initial evidence report for external review of content by outside experts, including representatives of professional societies and federal agencies.

Chapter 3. Results

Literature Search

Our literature search yielded 13,141 unique citations. From these, we provisionally accepted 465 articles for review based on titles and abstracts (**Appendix A Figure 1**). After screening the full-text articles, we judged that 33 studies (48 articles) met the inclusion criteria (**Appendix A Table 1**). We excluded the remaining 428 articles (**Appendix C**).

Key Question 1. Does Screening Asymptomatic Adults Age 40 Years and Older for COPD With Pre-Bronchodilator Screening Spirometry Improve Health-Related Quality of Life or Reduce Morbidity or Mortality?

We found no trials that directly assessed if screening asymptomatic adults for COPD, presumably followed by appropriate health management strategies, improves health-related quality of life or reduces morbidity or mortality.

Key Question 2. Can High-Risk Asymptomatic Adults Who Are More Likely to Test Positive on Screening for COPD Be Reliably Identified Using Prescreening Questionnaires?

Summary of Findings

We identified three externally validated prescreening questionnaires to select high-risk patients for screening spirometry—the CDQ, LFQ, and COPD-PS. The predictive accuracy of these questionnaires was measured against the post-bronchodilator FEV_1/FVC reference standard, considered the gold standard in the field when conducted according to quality standards based on the criteria defined by the 2005 ATS/ERS Task Force on Standardization of Lung Function Testing (**Appendix D**).[108,109] The CDQ has been externally validated in European and Australian populations (**Table 3**). Despite a lack of direct U.S. validation, the quality of the CDQ's development methodology and external validation studies make this questionnaire the most promising to date. Five fair- to good-quality external validation studies were identified for the CDQ, focusing mainly on a primary care population in which the majority of patients found to have COPD were identified as having mild or moderate disease (83.8% to 94.7%) (**Tables 3**, **4**). The populations varied from the derivation population (ever smokers) in three studies, enrolled about half ever smokers,[36] all current smokers with at least a 10-year pack-year history,[89] or a general population with an unknown smoking history (**Table 3**).[110] Most external validation studies reported that a CDQ score of greater than 16.5 had a sensitivity in the low 90 percent range and specificity in the high-30 to mid-40 percent range for identifying those who test positive using spirometric confirmation for COPD. Choosing a higher cutpoint (19.5) reduced

sensitivity and NPV, but increased specificity and PPV (**Table 4**). While targeting ever smokers ages 50 years and older, which corresponds to the derivation population, maximizes efficiency, this tactic will not include some cases of screen-detected COPD in never smokers. As such, the best approach for screening would depend on availability and costs of valid spirometry and potential downsides of missing mild cases, which could be minimized in the context of repeated screening and/or patient education encouraging early symptom-based care.

The LFQ, developed and internally validated in the U.S. population, was derived from the NHANES III (**Table 5**).[86,93] The LFQ development approach, however, was limited by its use of a population solely with self-reported physician-diagnosed chronic bronchitis (not reflective of a population targeted for screening) and the use of pre-bronchodilator spirometry to diagnose any airway obstruction rather than COPD specifically.[86] When externally validated using data from 36 U.S.-based primary care centers in a population of smokers (n=849), the LFQ showed a sensitivity of 88 percent and specificity of 25 percent.[111]

The COPD-PS development sample (n=295) was derived from an enriched sample of largely U.S.-based pulmonary specialty and primary care practices (**Table 3**).[88] External validation in a single population-based Japanese study (n=2,357) showed a sensitivity of 67 percent and specificity of 73 percent using a cutpoint of 4; however, it is unclear if these accuracies are generalizable to a U.S. primary care screening population.[112]

Three other questionnaires, the COPD Assessment Test (CAT),[113] the Case Finding Questionnaire (CFQ),[114] and an independent questionnaire developed by Buffels and colleagues,[37] have each published development studies (**Table 6**). While only one of these, the CAT, has been internally validated, none of the questionnaires have been externally validated.

Across studies, the proportion of field-based spirometry screening that was incomplete or of insufficient quality ranged from 12.4 to 30.7 percent. Therefore, quality control issues would be important for any noncentralized, office-based screening program.

Detailed Results

We identified 11 fair- to good-quality studies (12 publications) that described three externally validated risk factor- and symptom-based self-administered prescreening questionnaires—the CDQ, LFQ, and COPD-PS. We also identified three studies describing the three nonexternally validated COPD prescreening questionnaires—the CAT,[113] CFQ,[114] and the questionnaire by Buffels (**Tables 3**, **5**, and **6**).[37] The following results focus on the three questionnaires with external validation (CDQ, LFQ, and COPD-PS), since more research is needed on the questionnaires that lack external validation to determine their usefulness in clinical practice.

CDQ

The CDQ is an externally validated, eight-item, self-administered, symptom- and risk factor-based COPD prescreening questionnaire used to select high-risk patients for screening spirometry (**Appendix D**).[94,95] The CDQ assigns scores for the following variables: age, pack-years of smoking, body mass index (BMI); presence or absence of weather-dependent cough,

sputum-productive cough, wheezing, and history of allergies. Possible scores range from 0 to 38, 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 <25.4 kg/m^2), while the symptoms are scored as present or absent (score 0 for no symptom; score 3 or 4 for presence of specific symptom). Two cutpoints (16.5 and 19.5) have been proposed to select patients for screening spirometry based on receiver operating characteristic (ROC) curves from the original development study.[95] The internal validation and four out of five external validation studies included in this review variably reported on scores of less than 16.5, greater than 16.5, and greater than 19.5, which correspond to low-, intermediate- to high-, and high-risk of COPD, respectively (**Table 4**).[36,39,89,95,115] The CDQ is also referred to as the International Primary Care Airways Guideline (IPAG) questionnaire and the Respiratory Health Screening Questionnaire (RHSQ).

Originally developed by the COPD Questionnaire Study Group in order to design a questionnaire that could screen for COPD in a primary care clinical setting, the original development and internal validation study was a cross-sectional study of 818 prior and current smokers aged 40 years and older (**Table 5**).[94,95] These patients were required to have no prior respiratory diagnoses or respiratory medication use in the previous year and were recruited from primary care practices in the United States and the United Kingdom (Denver, Colorado and Aberdeen, UK). Participants were mostly white (87.0% non-Hispanic white), with a mean age of 58.2 years. Almost half (44.5%) of the participants were current smokers and the remaining participants (55.5%) were former smokers with 25.6 mean pack-years of smoking. The original list of 54 candidate questions, created from literature review and Delphi panel, were administered to a total of 572 patients as part of the development sample. Univariate and bivariate analysis followed by sequential logistic regression yielded eight questions determined to be statistically significantly associated with COPD diagnosis. These final eight questions were administered to a performance sample of 246 patients (70:30 split sampling for development and internal validation) to generate an ROC curve. Spirometry was performed according to ATS/ERS standards[108,109] and 8.9 percent of participants had spirometric results unsuitable for analysis (these were removed from analysis).

In the entire development sample (n=818), 19.0 percent of participants were diagnosed with COPD based on spirometry, although the prevalence was not reported separately for the development and validation subsets (**Table 5**).[94,95] An article published later identified two cutpoints that optimized the negative and positive predictive values of the questionnaire: 16.5 and 19.5, respectively.[95]

External validation: characteristics of included studies. We identified two good- and three fair-quality cross-sectional external validation studies for the CDQ with a total of 4,237 participants (**Table 3**).[36,39,89,110,115] Two fair- to good-quality studies were performed in Australia,[39,115] two fair- to good-quality studies in the Netherlands,[89,110] and one fair-quality study in Greece.[36] The largest two studies were an Australian study[115] (n=1,631) and the Greek study[36] (n=1,250). Mean ages of the four studies reporting this baseline characteristic ranged from 52.3 to 65.3 years; 31.0 to 48.2 percent of participants were women. Three of these studies exclusively recruited current and/or former smokers.[39,89,115] In one study, for example, nearly half of the participants were current and or former smokers,[36] and the other study did not report smoking history.[110] Mean

pack-years of smoking exposure ranged from 19.5 to 40.4 pack-years.[36,39,89,111,115] Three studies did not have any respiratory symptom-based inclusion/exclusions,[39,110,115] whereas one study excluded patients with acute respiratory infections[36] and one study required participants to have at least one respiratory symptom (cough, sputum, shortness of breath).[89] All five studies excluded participants with preexisting respiratory diagnoses. Three studies recruited participants exclusively from primary care practices,[36,110,115] while the other two studies recruited from the general population through advertising and primary care practice centers.[39,89]

Patients self-administered the CDQ questionnaire in three studies,[36,89,110] a nurse administered the questionnaire in one study,[115] and one study did not report who administered the questionnaire.[39] The percentage of incomplete questionnaires was reported in three trials and ranged from a low of 1.3 percent,[39] to a mid-range of 4.8 percent,[89] to a high of 10.9 percent.[115] Three of the studies were administered in languages other than English.[36,89,110] Questionnaires were scored by different personnel in the studies: physicians,[36] a practice assistant,[110] a study programmer,[39] and nurses.[115] Spirometry was performed by pulmonary specialists,[36] nurses,[110,115] trained operators,[39] or research assistants.[89] Likewise, spirometry was centralized in only one study.[89] Spirometry evaluation was performed by pulmonary specialists in two of the five studies.[36,89] No study reported if the personnel administering the spirometry were blinded to the questionnaire results. Only one study performed blinded adjudication of spirometry.[89]

The diagnosis of COPD was defined as post-bronchodilator FEV_1/FVC less than 0.7 in all studies. Additionally, one study required physician evaluation[110] and another required lack of reversibility (≤200 mL and ≤12% improvement from baseline pre-bronchodilator FEV_1).[39] Due to the spirometric criteria, only this latter study was able to discriminate between COPD and asthma, while the other trials actually diagnosed obstructive lung disease. Four[36,39,89,115] out of the five studies specified that "acceptable" spirometry must meet the ATS/ERS standards.[108,109] Four[36,39,89,115] of the five studies administered both the questionnaire and spirometry to all analyzed participants and one study only administered spirometry to those whose CDQ questionnaire stratified them into the high-risk category (score >19.5).[110]

Four out of five studies reported the percent of recruited participants excluded from analyses because spirometry either did not meet quality criteria or was not completed. This ranged from 12.4[39] to 24.4 percent; one study[115] reported that over a third of tests were excluded from the analysis due to unacceptable spirometry or incomplete questionnaires (35%). One other study reported no difference in the baseline characteristics of those analyzed and those excluded from the final analysis due to invalid spirometry, but did report that those with incomplete questionnaires had a lower post-bronchodilator FVC than those with complete questionnaires (mean ± standard deviation [SD], 3.51 ± 0.76 vs. 3.98 ± 0.95 L; p=0.002).[89] The remaining three studies did not report baseline characteristics of those in the excluded group.[36,39,110]

COPD was diagnosed by spirometry in 10.3 to 41.1 percent in each of the four studies that reported this outcome (**Table 4**).[36,39,89,115] The highest prevalence of COPD (41.1%) was seen in the study conducted by Kotz,[89] which was the only study that required that participants be current smokers with at least a 10 pack-year history and have at least one respiratory symptom; these participants were essentially prescreened, thereby selecting for those most likely to have COPD. Prevalence of COPD in studies recruiting ever smokers ranged from 13.1 to 27.9

percent,[39,115] and one general population study with more than half nonsmoking participants had an overall COPD prevalence of 10.3 percent that was higher (17.2%) among ever smokers.[36] Four studies reported the COPD severity in those diagnosed with COPD, showing that 83.8 to 94.7 percent had mild-to-moderate COPD according to GOLD criteria.[36,39,89,115,116]

External validation: outcomes. Three studies reported that 55.1, 56.6, and 81.2 percent of those taking the questionnaire had a score greater than 16.5.[36,89,115] The highest percentage was in the study by Kotz that essentially prescreened its participants. Therefore, it can be expected that in a selected screening population (based on age, with or without ever-smoking history) about 50 percent of individuals would prescreen as having at least intermediate risk of COPD on the CDQ and would move forward to spirometry (**Table 4**).[36,89,115] Four studies reported that 17.1, 28.0, 34.3, and 54.1 percent of those taking the questionnaire scored greater than 19.5, placing them at high risk for COPD.[36,89,110,115] The test positive rate for screening as high risk for COPD based on the CDQ was lowest in general populations that recruited regardless of smoking status (17.1% to 28%), intermediate in those recruiting ever smokers (34.3%), and highest in current smokers with symptoms (54.1%). For all of these findings, the highest outlier prevalence, yields, and screen positive results were seen in the Kotz study, where patients were already preselected based on the presence of current smoking and symptoms.[89] Therefore, about one third of persons in a screening population based on age and a history of ever smoking would be expected to screen at high risk for COPD.

Three studies (all in ever smokers or in current smokers) reported AUCs ranging from 0.65 to 0.72.[39,89,115] Sensitivity for the greater than 16.5 cutpoint ranged from 80 to 91 percent, with a clustering of sensitivities around 89 to 91 percent;[36,39,89,115] the highest sensitivity of 93 percent was seen in the smokers-only subgroup analysis of the Greek study (**Table 7**).[36] Specificity for this cutpoint ranged from 24 to 49 percent. PPVs ranged from 17 to 45 and NPVs ranged from 76 to 98 percent, with a clustering around 91 to 97 percent. Not surprisingly, the highest PPV and lowest NPV were seen in the study that preselected participants with symptoms.[89] For the best-quality study examining an age- and smoking-based selection strategy,[39] sensitivity of CDQ at 16.5 among ever smokers aged 50 years and older for spirometry-confirmed, nonreversible COPD was 91 percent and specificity was 37 percent, with a PPV of 36 percent and an NPV of 91 percent.

Sensitivity for the greater than 19.5 cutpoint ranged from 63 to 72 percent and the specificity ranged from 54 to 77 percent (**Table 7**).[36,39,89,115] PPVs ranged from 23 to 50 percent and the NPV ranged from 69 to 96 percent.[36,39,89,110,115] For the best-quality study examining an age- and smoking history-based prescreening strategy,[39] sensitivity of CDQ at 19.5 among ever smokers aged 50 years and older for spirometry-confirmed, nonreversible COPD was 71 percent and specificity was 62 percent, with a PPV of 42 percent and an NPV of 85 percent.

Given the higher prevalence of COPD among current and former smokers, it can be expected that the yield of screening would improve when applied to ever smokers only. In a subanalysis of Sichletidis limiting the population to ever smokers, the percent of individuals who screened positive (CDQ score >16.5) increased from 55.1 to 66.5, corresponding with an increasing prevalence of COPD in the screened population from 10.3 to 17.2 percent (**Table 4**).[36] Limiting to the ever-smoking population, however, missed detection of 21 cases of obstructive lung

disease among never smokers (out of 111 screen-detected cases in the entire population). If the CDQ were applied to the full population, 10 of 111 cases of COPD would be missed, but half of all screened individuals would require spirometry. If the CDQ were applied only to ever smokers, 27 of 111 cases of COPD would be missed, at the savings of about 250 diagnostic spirometries. Thus, while there appears to be higher utility in screening a general practice population limited to current and former smokers using the CDQ, this approach will result in a number of undetected cases in never smokers.

Critical appraisal. The recruitment strategies used in these studies largely represent primary care populations at risk for COPD; all studies recruited exclusively or at least partly from primary care practices, all excluded participants with known lung disease, and most recruited at least half of their participants with a smoking history.[36,39,89,115] Additionally, two of the five studies were large (recruited >1,000 participants).[36,115] While all studies used post-bronchodilator FEV_1/FVC less than 0.7 as a diagnosis for COPD, only one study included criteria for reversibility.[39] In this study, the reported COPD specificity may be lower than other studies given that the patients in other studies with reversibility would have been counted as true positives.[39] Overall, approximately 65 to 86 percent of the screened population was analyzed, with up to one quarter of spirometries judged to be unacceptable by ATS/ERS standards. This variability in acceptable spirometries, though not ideal, may reflect the reality of screening using spirometry in primary care practice, and would reflect an important consideration on handling indeterminate findings for a broad-based screening effort.

Diagnostic accuracy results were fairly consistent across the studies despite some clinical heterogeneity (e.g., different countries, different smoking exposures, different baseline COPD prevalence). One major limitation of this body of literature is that none of the external validation studies were performed in the United States.

LFQ

The LFQ is a five-item self-administered risk factor- and symptom-based questionnaire which assigns scores to the following variables: age, smoking history (pack-years, never/current/former smoker); and presence of wheezing, dyspnea, and mucous productive cough (**Appendix D**).[86] The questionnaire was originally developed using data from 387 NHANES III participants aged 40 years and older with a self-reported doctor diagnosis of chronic bronchitis, in order to design a screening tool for primary care to identify airflow obstruction (**Table 5**). Airflow obstruction was defined as pre-bronchodilator FEV_1/FVC less than 0.70 (no post-bronchodilator spirometry was performed in NHANES III). Fifty-one percent of these 387 participants had confirmed obstruction on pre-bronchodilator spirometry. The development study began with eight candidate questions based on risk factors for airflow obstruction, and compared risk factors in those with and without airflow obstruction among those with self-reported chronic bronchitis (case-control fashion). Step-wise logistic regression for item reduction followed by qualitative assessment of validity using physician focus groups and patient interviews resulted in the final five-item questionnaire. One of the final five items (the presence of phlegm) was added to the questionnaire because of its clinical importance, despite the lack of statistical association in logistics regression. Preliminary scoring assigned one point in a dichotomous fashion for each of the items: age (50 years or older), wheezing (presence), dyspnea (presence), phlegm (presence),

and smoking (20 years duration or longer), with an AUC of 0.72 regardless of decision threshold.

Limitations of the LFQ development study include its derivation in a population solely with self-reported physician-diagnosed chronic bronchitis (not reflective of a population targeted for screening) and the use of pre-bronchodilator spirometry to indicate any airway obstruction rather than COPD specifically.

Scoring was further tested (five-point ordinal scale vs. binary yes/no scoring) in an internal validation study by Hanania where 837 patients aged 40 years or older from two family physician group practices in Kentucky completed the LFQ and spirometry (937 initially participated, 837 analyzed) (**Table 5**).[93] No other exclusions were made in the population other than patient age. Obstructive lung disease was defined as pre-bronchodilator FEV_1/FVC less than 0.70. Personnel administering spirometry and blinding were not reported; 61.6 percent of participants were female and the majority were white (86.9%). Additionally, 18.6 percent of the participants had spirometrically confirmed obstructive airway disease. Using a five-point ordinal scale for each of the five questions (maximum score of 25; lower scores associated with higher risk) at a cutpoint of less than or equal to 18, the AUC was 0.652. Sensitivity and specificity were reported as 82.6 and 47.8 percent, respectively.

External validation: characteristics of included studies. We identified one fair-quality external validation study meeting our selection criteria for the LFQ (**Table 3**).[111] This study recruited 1,288 current or former smokers aged 30 years or more, with greater than or equal to 10 pack-year history from 36 U.S.-based primary care centers to receive both the questionnaire and spirometry. Patients were excluded if they had a known diagnosis of "substantial lung conditions"; however, a previous diagnosis of obstructive lung disease was allowed if the patient did not use daily respiratory medications in the 4 weeks prior to the study. Half of the patients were female and the mean age of participants was 54.0 years. Additionally, 59.0 percent were current smokers, 41.0 percent were former smokers, and participants had a mean of 33.4 pack-years of smoking exposure.

The reference standard used in this study was post-bronchodilator spirometry ($FEV_1/FVC < 0.7$) and spirometry was required to meet the criteria of the ATS/ERS standards on lung function testing.[108,109] All of those with LFQ scores of 18 or less (n=1,215) were invited for spirometry while a selected subset of those who screened negative on the LFQ (n=73) were invited to spirometry. Of those attempting spirometry, 30.7 percent did not complete the spirometry per protocol or did not meet the ATS/ERS standards. A total of 849 participants remained in the analysis (**Table 4**).

External validation: outcomes. Spirometrically confirmed COPD prevalence was not reported, as only a subset of those with LFQ scores greater than 18 underwent further screening with spirometry. Of those screened, 77.2 percent were identified as at risk with LFQ scores of less than or equal to 18. Obstructive lung disease was detected among 21.2 percent of those who screened positive on LFQ (score of ≤18) and in 10.2 percent among the subset of patients tested who screened negative (>18) (**Table 4**).[111] The estimated sensitivity was 88 percent and specificity was 25 percent, with PPV and NPV of 21 and 90 percent, respectively (**Table 8**).

Critical appraisal. Overall, the LFQ has been externally validated in only a single study in primary care U.S.-based practices. This study may have overestimated the accuracy because some patients were included with known COPD/obstructive lung disease, but not taking daily medications, which may have enriched the sample. Overall, however, the participants reflect those who might be targeted for screening in primary care (current or former smokers with ≥10 pack-year exposure), although the mean age in this LFQ validation study was younger than those studied in most CDQ studies. The high rate of unacceptable spirometry (30.7%) might also lead to overestimating the accuracy of the questionnaire, but it may also reflect the reality of spirometry performed in primary care practices.

COPD-PS

The COPD-PS is an externally validated, five-item, self-administered and self-scored symptom- and risk factor-based COPD prescreening questionnaire used to select high-risk patients from the general population for screening spirometry (**Appendix D**).[88] The COPD-PS assigns scores for the following variables: 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. Internal and external validation studies have explored various cutpoints ranging from 1 to 7, and have identified 4 to 6 as the ideal cutpoints.[88,112]

The original development and internal validation was performed in a U.S. multisite, cross-sectional study of patients from four pulmonary clinics and eight general practices who had scheduled office visits during the study period (**Table 5**). The final analysis sample (n=295) came largely from pulmonary specialty settings (190 patients from pulmonology practices and 105 from primary care practices). Patients aged 35 years and older, regardless of smoking history, were included without exclusion for preexisting COPD or other pulmonary diagnoses, although those seeking care for acute respiratory problems were excluded (**Table 5**). Participants were mostly white (82.5%), with a mean age of 62.1 years. More than half were ever-smokers (16.4% current smokers, 48.1% former smokers). The original working group developed a list of 23 candidate questions, which was narrowed to the five final questions using step-wise logistic regression models. Spirometry was performed according to ATS/ERS standards, and 48 percent of the initial 697 recruited patients were removed from the analysis because spirometry did not meet ATS standards.[108,109]

In the development sample (n=295), 38.4 percent of the participants were diagnosed with COPD based on spirometry (post-bronchodilator $FEV_1/FVC < 0.7$) (**Table 5**). Using the original sample for internal validation (n=697), a 1,000 bootstrapping sample logistic regression model yielded an AUC of 0.81. Authors concluded that a cutpoint of 5 to 6 provided an acceptable sensitivity and specificity tradeoff.

The major limitation of the COPD-PS development sample was its applicability to primary care asymptomatic populations. The development/internal validation sample may not be reflective of a primary care screened population for several reasons: more than half of the patients analyzed came from pulmonary clinics; patients with previously diagnosed COPD were not excluded; and almost half of the initial sample was censored because of unacceptable spirometry per ATS standards. Additionally, this population was an enriched sample, as evidenced by a high

prevalence (38.4%) of any spirometrically confirmed airway obstruction (post-bronchodilator $FEV_1/FVC < 0.7$), and participants found to have mostly moderate-to-severe disease (85%).

External validation: characteristics of included studies. We identified one fair-quality cross-sectional external validation study for the COPD-PS (**Table 3**).[112] This study (n=2,357 analyzed) recruited a random sample of registered residents in a rural Japanese town aged 40 to 79 years, excluding those with physician-diagnosed asthma or lung resection. The prevalence of previously diagnosed COPD was not reported. Approximately half of patients were female (56.6%) and the mean age was 61 years. Slightly less than half of participants were ever-smokers, with 16.8 percent being current smokers and 26.0 percent former smokers. Participants had a mean of 13.0 pack-years smoking exposure.

The reference standard used in the study was post-bronchodilator spirometry, defining airway obstruction as FEV_1/FVC less than 0.7. Spirometry was reviewed by two study pulmonologists for acceptability. A small number (6%) of those initially recruited were excluded for "poor study data."

External validation: outcomes. Overall prevalence of COPD in the sample was low, with 6.5 percent (153/2,357) of the study sample found to have spirometrically confirmed COPD (**Table 4**).[112] Of those identified with the disease, the majority (94.1%) were found to have mild or moderate COPD. COPD-PS scores greater than or equal to 4 showed a sensitivity of 67 percent and specificity of 73 percent (**Table 9**). COPD-PS scores greater than or equal to 5 demonstrated a sensitivity of 35 percent and specificity of 79 percent. The overall AUC was 0.748.

Critical appraisal. The COPD-PS has been externally validated in a single population-based study, in a small Japanese rural town. The population studied had a relatively low mean pack-year smoking exposure without exclusion of known obstructive lung disease. Data was largely complete, with few poor-quality spirometry results, and more than half of the town's population (65.3%) in the eligible age range participated in the study during health checkups. It is unclear, however, whether the diagnostic accuracy reported could be generalizable to a U.S.-based primary care screened population.

Other Prescreening Questionnaires With Model Development Studies (Not Externally Validated)

In addition to the CDQ and the LFQ, we identified three COPD prescreening questionnaires that have been reported in five articles describing their development and/or internal validation; none of these four questionnaires have been externally validated (**Table 6**). These questionnaires include the CAT,[113] CFQ,[114] and an independent questionnaire created by Buffels.[37] Two of the questionnaires have publications reporting their development tested in 2,923[37] and 996 patients,[114] but we identified no internal validation studies for the Buffels questionnaire or CFQ. The other questionnaire was internally validated in 532[113] patients using a bootstrapping technique.

These questionnaires are three- to five-item risk factor- and symptom-based, self-administered questionnaires including some of the following variables: age, smoking history, dyspnea,

phlegm, functional limitations due to dyspnea, allergy history, wheezing, cough, and frequent colds. Two questionnaires were studied in Ontario, Canada[113,114] and one in Belgium.[37] Two recruited from general practices[37,114] and one recruited from the general population.[113] One of the studies included participants with self-reported COPD diagnoses, resulting in a prevalence of previously diagnosed COPD of 10.9 percent.[88,114] One study recruited smokers only, with a 20 or more pack-year exposure.[114] Reference standards varied, with three studies using pre-bronchodilator or post-bronchodilator FEV_1/FVC less than 0.7,[88,113,117] one using post-bronchodilator FEV_1/FVC less than 0.7 plus FEV_1 less than 0.8,[114] and one using pre-bronchodilator FEV_1/FVC less than 0.885 in men and 0.893 in women.[37]

The prevalence of COPD varied widely in these studies, from 7.4 to 20.7 percent with spirometry-confirmed COPD (**Table 6**). In the Buffels study reporting COPD severity identified by the questionnaire, 90 percent[37] were classified as mild-to-moderate COPD based on the GOLD criteria. Reported AUCs ranged from 0.623 to 0.77.

While these three questionnaires show promise as prescreening tools in primary care, until they are externally validated in other U.S. primary care populations, limited conclusions can be made about their validity.

Key Question 3. What Is the Test Performance of Screening Pulmonary Function Tests in Predicting Diagnosis of COPD Based on Confirmation Using Post-Bronchodilator Spirometry to Identify Fixed Airflow Obstruction in Asymptomatic Adults?

Summary of Findings

We identified one good- and four fair-quality studies evaluating two different pulmonary function screening tests against a post-bronchodilator FEV_1/FVC reference standard: peak flow (PEF) and FEV_1/FEV_6 (**Table 10**). In all but one study,[36] screening tests were administered in the pre-bronchodilator state. The included populations varied in their selectivity in terms of age, smoking status, and symptomatology/exclusion of pre-existing COPD. Two studies of PEF by Jithoo et al and Perez-Padilla et al evaluated the largest number of patients (n=23,098);[67,91] however, these two studies are from the population-based international BOLD initiative, whose primary aim was to describe the prevalence of COPD internationally. Thus, BOLD results are less applicable to the screening accuracy questions in this review, since BOLD did not exclude those with pre-existing COPD and included several low index countries not generalizable to the United States. Also, the PEF evaluation by Jithoo et al defined those with mild COPD as disease negative, while the other reported results mainly for a more selected group of those screened, greatly limiting the applicability of these PEF test results to a primary care screening population. Three studies reported the screening test performance of FEV_1/FEV_6 and were conducted in Australia, Greece, and Sweden (n=1,587).[36,39,118] In the two studies utilizing pre-bronchodilator FEV_1/FEV_6 among ever smokers (Frith et al and Thorn et al), the sensitivities were similar (51% and 53%), as were specificities (90% and 93%) (**Table 11**). The reported sensitivity in the

Sichletidis study that recruited about half ever smokers but utilized post-bronchodilator FEV_1/FEV_6 for screening was much higher (80%), and specificity was also good (95%). In a subsample limited to ever smokers, post-bronchodilator screening appeared relatively similar to screening test performance in the entire population, but we could not confirm, as reported data were incomplete.

Detailed Results

We identified five publications describing two index tests used for COPD screening: pre-bronchodilator PEF and pre- and post-bronchodilator FEV_1/FEV_6 (**Table 10**). Two studies describe the screening accuracy of PEF[67,91] and three studies report the screening accuracy of FEV_1/FEV_6.[36,39,118]

PEF

Description of included studies. Two studies (n=23,098) explored the screening accuracy of PEF in COPD diagnosis (**Table 10**). PEF cutoffs differed in the two studies; Jithoo used absolute thresholds of 1.3, 1.8, and 2.2 L/s/m^2, while Perez-Padilla used percent predicted cutpoints of 70 and 80 percent. Both studies administered post-bronchodilator spirometry as the reference test;[108,109] however, only one study required tests to meet ATS/ERS quality standards.[67] The threshold for COPD diagnosis was defined differently across studies; Jithoo required FEV_1/FVC less than the LLN and FEV_1 less than 80 percent predicted,[67] while Perez-Padilla used FEV_1/FVC ratio less than 0.7.[91] Jithoo also defined those with mild COPD by GOLD criteria as disease free, limiting the applicability of its results to screen detection of mild COPD, whereas Perez-Padilla considered those with mild COPD by GOLD criteria to be disease positive. Both studies were performed internationally as part of the BOLD initiative in countries recruiting general population patients aged 40 years and older; Perez-Padilla additionally included patients from the Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar (PLATINO) study, which aimed to describe the epidemiology of COPD in five major Latin American cities.[91] Jithoo included 19.7 percent with pre-existing self-reported COPD, emphysema, chronic bronchitis, or asthma, while Perez-Padilla did not report pre-existing respiratory disease; however, since participants came from the BOLD and PLATINO studies, we would expect some proportion of individuals to already have respiratory disease. Approximately half (57.2% and 45.2%) had a smoking history, with a mean smoking exposure of 26.6 (male) and 19.3 (female) pack-years in one study[67] and 22.7 pack-years (both sexes combined) in the other study.[91] The mean age was approximately 56 years in both studies. Perez-Padilla report results stratified into "a priori" increased risk of having COPD versus low risk. The increased risk group represented about three fourths of the entire population and was defined by any of the following criteria: "usually" coughing or bringing up phlegm, wheezing in the last year, and dyspnea on exertion (Medical Research Council [MRC] Dyspnea Scale score >1), more than 10 pack-years of smoking, more than 200 hour-years of exposure to biomass smoke or coal smoke, more than 5 years of workplace exposure to dust or smoke, or a previous medical diagnosis of asthma, COPD, chronic bronchitis or emphysema.

Outcomes. COPD prevalence for moderate to severe COPD was 8.1 percent in the general population study by Jithoo and colleagues, with 56.2 percent of these patients having moderate

COPD (**Table 12**).[67] In this study, 3.0 to 21.7 percent screened positive for moderate-to-severe COPD depending on the PEF threshold (1.3, 1.8, or 2.2 L/s/m^2). In the more applicable general population study by Perez-Padilla, the prevalence of COPD was 16.9 percent, with 90.1 percent of these patients having mild or moderate COPD. The prevalence was higher among those a priori classified as having increased risk of disease (19.5% compared to 7.9% in the low risk group) and had fewer patients with mild-to-moderate disease (89.2% compared to 97.5% in the low risk group).

The sensitivity reported in Jithoo ranged from 31 (for PEF <1.3 L/s/m^2) to 84 percent (for PEF <2.2 L/s/m^2) and specificity ranged from 84 (for PEF <2.2 L/s/m^2) to 99 percent (for PEF <1.3 L/s/m^2) for detection of moderate-to-severe COPD (**Table 11**).[67] The PPV ranged from 31 (for PEF <2.2 L/s/m^2) to 83 percent (for PEF <1.3 L/s/m^2); the NPV ranged from 94.3 (for PEF <1.3 L/s/m^2) to 98.3 percent (for PEF <2.2 L/s/m^2) for detection of moderate-to-severe COPD. However, it is unclear how these estimates could be used to anticipate the performance of PEF screening in primary care given that mild COPD patients were counted as disease negative.

In the study by Perez-Padilla and colleagues, the AUC for any severity of COPD was 0.66 for a threshold of less than 80 percent predicted for the detection of COPD among patients at low risk for COPD; however, other test performance characteristics were not reported for patients at low risk of COPD (**Table 11**).[91] Test performance characteristics for the a priori increased risk group represented those with already diagnosed asthma, COPD, chronic bronchitis, or emphysema symptoms, and/or 10-year smoking history or other environmental exposure. Thus, the performance characteristics in this population would not be applicable to a full screening population. Sensitivity and specificity for using a threshold of less than 70 percent were reported by GOLD stage and only for stages corresponding to moderate or more severe disease, but not for mild COPD. Sensitivity was 96 percent for detecting severe-to-very severe COPD and 54 percent for detecting moderate COPD. Using a less than 80 percent predicted PEF threshold in the high risk patients, sensitivity was 97 percent for severe to very severe COPD (NPV, 99.9%) and 70 percent for moderate COPD (NPV, 98%). Given that these analyses are limited to a preselected, high-risk population enriched with patients with pre-existing disease, it is unclear how these estimates could be used to anticipate the performance of PEF screening in primary care.

Critical appraisal. Overall, neither of these two large PEF studies (>20,000 patients) is directly applicable to U.S. primary care populations, because despite large population-based sampling, the sample is enriched with those with known pre-existing obstructive lung disease and includes participants from low index countries with high environmental exposures. Heterogeneity in index test thresholds and reference standard cutoffs for COPD diagnosis (especially defining mild COPD as disease free) make robust, generalizable conclusions regarding screening accuracy impossible.

FEV_1/FEV_6

Description of included studies. One good- and two fair-quality cross-sectional diagnostic accuracy studies (n=1,587) explored the predictive accuracy of FEV_1/FEV_6 in COPD diagnosis (**Table 10**).[36,39,118] Two studies examined the use of pre-bronchodilator FEV_1/FEV_6 generated

using a handheld mini-spirometer (COPD-6) or flow meter (PiKo-6)[39,118] and one study used post-bronchodilator FEV_1/FEV_6 based on the handheld flow meter (PiKo-6).[36] Studies were in Australia,[39] Greece,[36] and Sweden.[118] Two of these studies recruited patients from primary care practices[36,118] and one study recruited from primary care practices and local newspapers.[39] The lower age limit for recruitment was 40 years; mean or median age ranged from 61.0 to 65.3 years. Women represented 31.0 to 56.7 percent of the recruited population. Two studies excluded those with prior lung disease,[36,39] while one did not exclude prior lung disease and did not report proportion of recruited population with known lung disease.[118] Two studies[39,118] only recruited participants with a smoking history and one required participants to have a smoking history of greater than or equal to 15 pack-years;[118] one study recruited both smokers and nonsmokers with approximately half being ever smokers (48.8%).[36] Mean smoking exposures in the three studies ranged from 19.5 to 39.0 pack-years.[36,39,118]

All three studies used post-bronchodilator FEV_1/FVC as the reference standard and required that spirometry meet ATS/ERS quality reference standards.[108,109] All three studies used an absolute post-bronchodilator FEV_1/FVC cutpoint of less than 0.7;[36,39,118] one of these additionally specified irreversibility.[39] Two studies reported the number of recruited participants excluded for incomplete or unacceptable spirometry, which ranged from 12.4 to 13.8 percent (**Table 12**).[36,39] Two of the studies used a pre-bronchodilator FEV_1/FEV_6 cutpoint of less than 0.70 for a positive screening test and also examined the impact of higher cutpoints.[39,118] One study used post-bronchodilator FEV_1/FEV_6 cutpoint of less than 0.70 for a positive screening test.[36]

Outcomes. Spirometrically-confirmed prevalence of any stage COPD ranged from 10.3 in a general population to 27.9 percent, with the highest prevalence reported in the Australian study of ever smokers with a mean of 39 pack-years of smoking exposure (**Table 12**).[39] This study also required evidence of irreversibility as part of its diagnostic criteria for COPD. The majority (84% to 99%) of these COPD patients had mild-to-moderate COPD. Using screening FEV_1/FEV_6 cutpoints of less than 0.7, 12.9 to 21.3 percent of those screened tested positive on the index test. The lowest rate of screen positives occurred in the general population group, whose screening was based on post-bronchodilator flow meter results. The two studies using pre-bronchodilator results for screening reported AUCs of 0.84 and 0.85 for the FEV_1/FEV_6 threshold of less than 0.7 (**Table 11**).[39,118] The corresponding sensitivity for pre-bronchodilator screening ranged from 51 to 53 percent, while specificity ranged from 89.5 to 93.0 percent (PPV, 63% to 73%; NPV, 83% to 85%). For the study using post-bronchodilator screening, sensitivity was 80.2 percent and specificity was 95 percent (PPV, 64%; NPV, 98%).

The study from Greece by Sichletidis, which used post-bronchodilator FEV_1/FEV_6, clearly excluded those with pre-existing disease but was based in a primary care population. Authors reported test performance in a subanalysis limited to current smokers. Although within-study results potentially offer the best comparative test performance information, comparative results should be viewed as unsubstantiated since data were insufficiently reported to allow the independent computation of 2x2 tables for screening pulmonary function tests in the subpopulation of smokers, as was also the case for the use of the CDQ questionnaire in the same study. The data we did derive (**Table 12**) are consistent with an increase in test positives when screening in ever smokers, as is logical. However, limiting to ever smokers results in missing 21 cases of COPD in never smokers, in addition to the six cases missed in smokers due to imperfect

sensitivity.

Critical appraisal. In terms of applicability, none of the three FEV_1/FEV_6 studies was performed in a U.S. population. The results from Sichletidis may most closely resemble a population that would be considered for screening in the United States because it was performed in more than 1,000 patients from primary care clinics, includes a subanalysis of smokers only, and excludes participants with known COPD; however, there may be different environmental exposures in this nonU.S.-based setting.[36] In addition, this study was performed using screening with post-bronchodilator FEV_1/FEV_6, which may limit its applicability in general practice due to the need for providing bronchodilator agents. The Australian study by Frith utilizes pre-bronchodilator FEV_1/FEV_6 screening and may also be considered close to a U.S. primary care population of smokers with a heavy smoking exposure burden without known preexisting disease.[39] Both Sichletidis and Frith have a similar percentage of patients that screened positive. Frith has a much lower sensitivity for the 0.7 cutpoint (51.0% vs. 80.2%). It appears that the use of bronchodilator agents during screening may greatly improve the performance of FEV_1/FEV_6 screening. However, the lower performance reported in Frith may be due to the fact that this study requires a reversibility component of the reference standard (post-bronchodilator spirometry $FEV_1/FVC < 0.7$, reversibility ≤200 mL, and ≤12% from baseline pre-bronchodilator FEV_1), which could result in moving screen-positive patients from those who are disease positive to those who are disease negative. Therefore, there are fewer people in the numerator for the sensitivity analysis, making the sensitivity look worse than other studies without the same reference standard components.

Combined Accuracy of Questionnaire and FEV_1/FEV_6

One cross-sectional diagnostic accuracy study by Sichletidis (n=1,078), already reviewed for the CDQ and FEV_1/FEV_6 index tests above, also reported the combined accuracy of screening using the CDQ screening questionnaire and the FEV_1/FEV_6 index test.[36] Authors performed analyses considering combination results from both tests, as might be seen in a sequential screening approach, although complete test performance data were not reported for a strategy of either test positive.

In this study set in Greece, adults aged 40 years and older without prior diagnoses of pulmonary disease were recruited from primary care clinics.[36] All patients received both the CDQ questionnaire and the FEV_1/FEV_6 post-bronchodilator screening test, followed by confirmatory post-bronchodilator FEV_1/FVC spirometry. In the analysis whereby the screening test was considered positive only if both CDQ and FEV_1/FEV_6 tests were positive, the reported sensitivity and specificity were 72 and 97 percent, respectively, in the entire population; reported sensitivity and specificity in a subset of smokers only were similar, although data were insufficient to confirm any of these test performance data through replication of 2x2 tables. The PPV was reported as 71 percent and the NPV was 97 percent in the entire population. In the subset of smokers only the reported PPV was 82 percent and the NPV was 95 percent. Overall, as would be expected with a more stringent standard, the sensitivity for the combined tests was lower than that of either the pulmonary testing or CDQ alone (72% vs. 80% and 91%, respectively). However, the specificity of testing was marginally improved over FEV_1/FEV_6 testing alone (97% vs. 95%) and significantly better than that of the CDQ alone (49%). NPVs

remained similar; however, the PPV was increased over pulmonary tests or the CDQ alone, particularly in the analysis limited to smokers only.

Key Question 4. What Are the Adverse Effects of Screening for COPD Using Prescreening Questionnaires or Screening Pulmonary Function Tests?

Summary of Findings

Evidence of screening harms from diagnostic accuracy studies was limited; only false positives and false negatives associated with screening were reported, and few studies reported data so the number of missed cases could be calculated. Additionally, for each screening strategy, relatively few studies were available. The proportion of cases missed by the CDQ (false-negative rate) varied widely, from 9.0 to 37.0 percent, and was lowest when using the most sensitive screening threshold. For the CDQ threshold of less than 16.5 for screen negatives, and limiting to studies in which fewer than 20 percent of spirometries were invalid or incomplete, the proportion of missed spirometry-diagnosed COPD was around 10 percent. In these same studies, increasing the screening threshold to less than 19.5 increased the number of missed COPD cases to 27.9 to 34.2 percent. Missed diagnosis and the false-positive rate could not be reliably estimated for the LFQ, because only a subset of screen-negative patients received diagnostic spirometry in the single external validation study of this questionnaire; however, the majority of those who screened positive on the questionnaire were determined to be false positives (74.2%). The COPD-PS had a much lower false-positive rate compared to the CDQ or LFQ; at a cutpoint of greater than or equal to 4, the COPD-PS resulted in a false-positive rate of 27 percent, with 33 percent missed cases (**Table 13**).

Similarly, the false-negative rate associated with the two screening pulmonary function tests (pre-bronchodilator PEF, pre- and post-bronchodilator FEV_1/FEV_6) ranged broadly from 14.3 to 68.9 percent of cases missed based on test and cutoff applied; however, data is scant for these tests (**Table 14**). False-positive rates varied widely based on the screening test and threshold for positivity, with rates of around 28 percent for the most sensitive screening thresholds. Given the clinical application of prescreening questionnaires to enrich a population for more intensive, but still relatively harmless, spirometric screening, minimizing false negatives may take precedence over minimizing false positives.

We identified no qualitative studies on psychological, quality of life, or other harms associated with screening questionnaires or pulmonary function tests.

Detailed Results

False Negatives and False Positives for Prescreening Questionnaires

False positives were common in the external validation studies of the CDQ prescreening questionnaire, and, for a CDQ score of greater than 16.5, the number of false positives exceeded

true positives in all populations. False-positive rates (percent of COPD-free patients who will screen positive) were highest (76%) in a population of current smokers and the lowest (51%) in the general population. Increasing the CDQ cutpoint to above 19.5 considerably improved false-positive rates, but at the cost of more missed COPD cases (**Table 13**).[36,39,89,115] False-negative rates (missed diagnoses) at a CDQ cutpoint of greater than 16.5 ranged from 9 to 20 percent;[36,39,89,115] when limited to studies with higher quality spirometry (≤20% invalid/incomplete results), around 10 percent of diagnoses would be missed using the 16.5 cutpoint.[36,89] Raising the CDQ cutpoint to 19.5 or higher greatly increased false-negative rates (28% to 34% in best estimates).[36,89] When considering reported results in subgroups (i.e., results reported among ever smokers only), false-negative rates understate the actual missed diagnoses. In the one study that did so, fewer diagnoses appear to be missed among smokers than among the general population (6.7% vs. 9.0%); however, screening limited to smokers would have missed additional COPD diagnoses occurring in 3.8 percent of the nonsmokers in the population.[36] Thus, the true missed diagnoses in an ever smoker strategy compared to a general population strategy would represent false negatives in smokers and all cases in never smokers (27 individuals, about one quarter of all those with spirometry-detected COPD).

False-negative and false-positive rates could not be reliably estimated for the LFQ, because only a subset of screen-negative patients received diagnostic spirometry in the single external validation study of this questionnaire; however, the majority of those who screened positive on the questionnaire were determined to be false positive (74.2%) (**Table 13**).[111]

The COPD-PS demonstrated a lower false-positive rate compared to the CDQ. At a cutpoint of greater than or equal to 4, the COPD-PS resulted in a false-positive rate of 27 percent, with 33 percent missed cases. At a cutpoint of greater than or equal to 5, the false-positive rate was 21 percent, with more than half of cases missed (65% false negatives).

False Negatives and False Positives for Pre-Bronchodilator Screening Pulmonary Function Tests

The false-negative and false-positive rate for PEF was only reported in one[67] of the two included PEF studies (**Table 12**). False-negative rates would be underestimated since mild disease was considered to be screen negative. Reported false-negative rates (missed diagnoses) ranged from 16 to 69 percent of moderate-to-severe cases being missed, depending on the cutpoints used for prescreening PEF. False-positive rates ranged from less than 1 to 16 percent, again depending on the PEF threshold used. These results are of limited utility for primary care screening due to the population targeted and the design of the study to classify mild disease as screen negatives.[67]

The two studies[39,118] examining the pre-bronchodilator FEV_1/FEV_6 in ever smokers only and one study[36] examining the post-bronchodilator FEV_1/FEV_6 pulmonary function test in the general population reported false-negative rates (proportion of total diagnoses missed) ranging from 14 to 49 percent, depending on the threshold used. For the FEV_1/FEV_6 index test threshold of less than 0.70, the lowest false-negative rate (19.8%) was seen after post-bronchodilator index testing[36] (**Table 12**). Using a pre-bronchodilator FEV_1/FEV_6 cutoff of less than 0.7, the missed cases in two of the trials approached 50 percent.[39,118] False-positive rates also varied with index test cutpoint. For the threshold of less than 0.7, false-positive rates ranged from 5 to 10.5

percent,[36,39,118] with the lowest rate seen in those screened using post-bronchodilator testing.[36] While relatively similar rates of false positives, false negatives, and missed diagnoses were reported for post-bronchodilator screening among a subgroup limited to smokers only, these results are misleading from a population perspective. As was the case for data about screening with the CDQ, a screening strategy limited to ever smokers would miss a greater number and proportion of COPD diagnoses than are accounted for in the subsample test performance calculations. Considering all of the 21 missed diagnoses in nonsmokers as well as the 18 false negative results in smokers, an even larger number and proportion of spirometrically-detected COPD cases (39 total cases [35%]) would be missed through prescreening only ever smokers using office spirometry.[36] When analyzed to consider a combination screening approach requiring a positive screen of 16.5 on the CDQ plus post-bronchodilator FEV_1/FEV_6, even more cases would be missed (estimated at 28% in the general population), but the false-positive rate would be improved (estimated at 3%). Data were not available to evaluate combined screening using a threshold for either test positive.[36]

Key Question 5. Does Identifying Asymptomatic Adults With Fixed Airflow Obstruction Through Screening Improve the Delivery and Uptake of Targeted Preventive Services? Does Screening for COPD Increase Smoking Cessation Rates Among Asymptomatic Adults Compared to Usual Care? Does Screening for COPD Increase Relevant Immunization Rates Among Asymptomatic Adults Compared to Usual Care?

Summary of Findings

We identified five fair-quality studies addressing the effectiveness of COPD screening or lung function testing in influencing smoking cessation rates (**Table 15**). We identified no studies examining the effectiveness of screening in increasing vaccination rates.

We did not find robust data to support the premise that supplying smokers with spirometry results improves smoking cessation rates (**Table 16**). However, 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 or not and in whether smoking cessation support was tailored based on spirometry or other medical exam findings. Thus, available studies test the incremental value of adding spirometry to existing smoking cessation programs. Of the three RCTs reporting biochemically confirmed abstinence, only one fair-quality trial[119] telling patients their lung age reported a statistically significant difference in the intervention compared to the control group; one underpowered U.S. Department of Veterans Affairs (VA) trial[120] showed a trend toward reduction, and the one 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 months in the intervention and active treatment control groups.[121] This trial was likely underpowered, however, particularly for incremental comparative

effectiveness.

Two U.S.-based studies powered to detect differences of at least 10 percent in self-reported abstinence rates showed no difference in abstinence at 6-, 9-, and 12-month followup in the intervention compared to the control group (**Table 16**).[122,123]

Characteristics of Included Studies

We identified five fair-quality studies addressing the effectiveness of COPD screening or lung function testing in influencing smoking cessation rates (1,694 participants) (**Table 15**).[119-123] While this KQ would ideally be based on trials screening individuals for COPD, some of the included trials simply focused on the measurement of participants' lung function, without also reporting to patients their COPD status. Only one study informed patients they had COPD,[121] while four studies only reported on decreased lung function or a patients "lung age."[119,120,122,123] Three studies were conducted in the United States,[120,122,123] one in the Netherlands,[121] and the largest study (n=561) was conducted in the United Kingdom.[119] Inclusion criteria for one study required a smoking exposure of at least 10 pack-years,[121] but otherwise participants with any history of smoking were included. Two trials recruited participants from primary care clinics,[119, 122] two recruited participants from the general population,[121,123] and one trial recruited U.S. veterans participating in a general preventive intervention VA demonstration project.[120] The third largest study, which was from the Netherlands, specifically recruited 296 patients interested in quitting smoking, and this study was also the only study that analyzed screen-detected COPD patients.[121] Two studies had a lower age limit of 35 years,[119,121] two trials had a lower age limit of 18 years,[122,123] and one did not specify a lower age limit.[120] The mean age ranged from 38.6 to 54.0 years, with 4.4 to 62.5 percent of participants being women (**Table 17**). The mean pack-years of smoking exposure ranged from 28.9 to 60.4 pack-years. Only one study specifically excluded those with a prior respiratory diagnosis,[121] while the others presumably would have included those who already had known diagnoses of COPD. Three trials reported the percent of participants with previous quit attempts, which ranged from 10.1 to 82.0 percent.[120,122,123] A measure of previous quit attempts was reported in three studies; one study reported that participants had a mean of 3.8 prior quit attempts,[121] another reported a mean of 1.56 prior attempts,[123] while a third study reported that more than half of participants had one to two prior quit attempts.[120] The mean baseline post-bronchodilator FEV_1 percent predicted was fairly high (mean, 81.5% to 89.5% in the three studies reporting it), indicating that most participants likely had no or mild COPD, which makes these studies potentially quite applicable to a screened population.[119,121,122] One study only included patients who screened positive for mild-to-moderate COPD (FEV_1 ≥50% but ≤70%), had at least one respiratory symptom, and who were motivated to quit.[121] Three studies reported motivational stage of change; one reported that 36 percent were prepared to quit,[122] one reported that 17 percent were prepared to quit and 22 percent were actively trying to change or had a quit attempt in the past year,[119] and a third trial reported that 75.2 percent were in the contemplation or preparation stage at baseline.[123] Additionally, one study reported that 20 percent of participants had comorbidity[119] and one VA study reported that 21 percent consumed more than four drinks per day.[120]

Interventions and controls varied in the five trials. None of the trials involved completely untouched controls, which complicates the interpretation of primarily null findings. In two of the

five trials,[119,121] spirometry was administered to all participants (intervention and all control groups); in one of these studies,[119] the control group received the raw FEV_1 results without explanation, while the intervention group received the results communicated in terms of their "lung age." In the other of the two RCTs,[121] the intervention group received confrontational counseling using spirometry results, and the control group did not receive any spirometry results. In two studies, spirometry was only administered in the intervention group (**Table 15**).[120,122] Counseling likewise varied in the trials. In the Netherlands trial, the intervention group received four 40-minute, medium-intensity counseling sessions plus nortriptyline.[121] Additionally, the intervention group participated in a discussion of results from spirometry, prognosis of COPD, and challenging irrational beliefs about smoking, while one control group received the four 40-minute, medium-intensity counseling sessions plus nortriptyline, and the second control group received a referral to a primary care physician for smoking cessation treatment without information about spirometry results or airflow limitation.[121] Thus, this trial addresses the impact of confrontational counseling about screen-detected COPD on smoking cessation in a select group of individuals, but was not strictly an efficacy trial of spirometry screening since there was no untreated control group. In one U.S.-based trial, the intervention group received an individual cessation plan, cessation counseling, solicitation of a quit date, and clinic or telephone followup at 1 and 4 weeks after the quit date (for patients in preparation stage), plus educational interpretation of spirometry and carbon monoxide (CO) measurement results.[122] The control group received identical counseling, excluding spirometry and CO measure interpretation. In the VA trial, the intervention group received a 50-minute educational intervention with a self-help program, invitation to nine one-on-one skills training sessions and counseling program, plus a 10-minute motivational intervention based on spirometry, CO level, and discussion of pulmonary symptoms.[120] The control group received the same education as the intervention group without any spirometry or symptom discussion. In the third U.S.-based trial, the intervention group received baseline counseling given to the control group, plus a personally-tailored report with self-reported smoking-related symptoms, smoking-related medical conditions, CO level and the normal CO values of nonsmokers, spirometry test results (FEV_1, FVC, forced expiratory flow $[FEF]_{25-75}$), lung age for individuals with FEV_1 less than 80 percent predicted, a graph demonstrating the effect of smoking cessation on lung function, and information on the association between smoking and various health conditions, while the control group received a personalized health risk report and brief (~20 minute) counseling; advice to quit smoking, smoking cessation materials, and access to a free phone counseling program.[123] In the U.K.-based study, all patients had an assessment interview and spirometry, along with smoking cessation counseling, but only the intervention group received their "lung age" verbally using a graphic display and were counseled that smoking cessation would help to slow down the rate of deterioration of the lung function, while the control group received their lung function scores (i.e., FEV_1) in the mail with no further explanation.[119]

The mean followup ranged from 9 to 12 months in the included studies. All five studies used ITT analysis and imputed results conservatively, assuming that all of those lost to followup continued to smoke. One study had a high loss to followup rate at 12 months, with 33.3 to 40.0 percent missing biochemically validated smoking status results.[120] Otherwise, the other three trials had loss to followup in the control and intervention groups ranging from 11.0 to 18.6 percent in either group.[119,121,122]

Detailed Results

Biochemically Validated Smoking Abstinence

Three studies measured abstinence with biochemical confirmation at 12 months (**Table 16**).[119-121] The largest study (n=561), which was conducted among U.K. primary care patients in various stages of change, showed a statistically significant difference in biochemically validated abstinence rates (13.6% vs. 6.4%; validated quit rate difference, 7.2% [95% CI, 2.2 to 12.1]; p=0.005), comparing those that received spirometry-based lung age versus those that did not. This study was not powered to detect that a smoker in the "active" phase of quitting would find feedback on lung age more useful than someone in earlier stages of change.[119] One underpowered RCT (n=90) from the VA conducted in patients without any required motivation to quit showed a trend toward, but no statistically significant difference between, higher validated abstinence rates in the intervention compared to the control group (20.0% vs. 6.7%; p=0.06).[120] The third RCT (n=296) of general population screen-detected mild-to-moderate COPD patients motivated to quit showed nearly identical biochemically validated smoking abstinence in the intervention and control groups in adjusted and unadjusted analyses (adjusted [adj] OR, 0.88 [95% CI, 0.38 to 2.03]).[121]

Self-Reported Smoking Abstinence

Two RCTs reported abstinence rates which were ascertained only by self-report (**Table 16**).[122,123] One adequately powered U.S.-based primary care RCT (n=205) with a mean of 9 months of followup reported no statistically significant difference in self-reported abstinence after adjusting for age and sex (9.0% vs. 14.0%; adjOR, 0.6 [95% CI, 0.2 to 1.4]); likewise, there was no difference in quit rates when only those with abnormal spirometry were analyzed (adjOR, 0.6 [95% CI, 0.1 to 2.7]).[122] The second larger and adequately powered U.S.-based study (n=536) showed no difference in the primary outcome of 7-day self-reported abstinence rates measured at 6 or 12 months of followup after adjusting for baseline differences (6 months: 12.0% vs. 14.1%; adjOR, 0.77; p=0.33; 12 months: 13.1% vs. 14.9%; adjOR, 0.86; p=0.38).[123] Interestingly, there were fewer abstainers in the experimental group reporting 30-day abstinence at the 6-month followup (6.4% vs. 10.8%; adjOR, 0.51; p=0.04).

Quit Attempts

Three trials reported the percentage of participants in each group reporting at least one quit attempt during the trial period (**Table 16**).[120,122,123] The VA trial showed more participants self-reporting at least one quit attempt in the intervention group (40.0% vs. 16.3%; p=0.015).[120] The other two trials showed no statistically significant differences in the percent of patients having at least one quit attempt between treatment groups (48.0% vs. 36.0%; OR, 1.6 [95% CI, 0.9 to 2.8];[122] 62.4% vs. 61.5%; OR, 0.96 [95% CI not reported]; p=0.84).[123]

Cigarette Consumption

Only one trial reported the outcome of mean change in self-reported cigarette consumption, showing a statistically significantly reduction in the mean number of cigarettes consumed in the

intervention group compared to the control group (11.7 vs. 13.7; p=0.03) (**Table 16**).[119] This was the same primary care-based U.K. study reporting a statistically significant reduction in biochemically confirmed abstinence.

Critical Appraisal

Generally, the evidence evaluating the effectiveness of tailored feedback or counseling using spirometry showed mixed results. Unfortunately, the largest RCT[119] and only trial reporting a statistically significant difference in biochemically confirmed smoking cessation rates had some design issues, namely that patients with a prior diagnosis of obstructive lung disease were included (7.0% and 9.4% with medical history of COPD and asthma, respectively), potentially limiting its applicability to a screen-detected COPD population. The only study that specifically recruited screen-detected patients with mild-to-moderate COPD further restricted participants to those that had at least a 10 pack-year smoking history, mild-to-moderate COPD with at least one symptom, and an interest in quitting smoking, found no difference (11.2% vs 11.6%) in smoking cessation rates in the confrontational counseling group compared to the control group, although this study was underpowered to fully evaluate this outcome. Overall, data are scant to make firm conclusions regarding the effectiveness of utilizing spirometry results to motivate smokers in order to improve cessation rates.

Key Question 6. What Are the Adverse Effects of COPD Screening, Including the Impact of Targeted Preventive Services in This Population?

Summary of Findings

There is scant evidence examining the potential negative impact of COPD screening on targeted preventive services, including the impact on smoking cessation and immunization rates.

Characteristics of Included Studies

One of the fair-quality RCTs included in KQ 5,[121] which recruited participants with mild-to-moderate screen-detected COPD from the general population and primary care practices in the Netherlands, reported on the harms of COPD screening for smoking cessation using a qualitative study design in a separate publication.[124] Authors administered semistructured interviews to 205 smokers aged 35 to 70 years with greater than or equal to 10 years of smoking history and experiencing at least one respiratory symptom. These participants were interested in quitting smoking and all underwent spirometry testing; however, only the intervention group received a tailored counseling intervention that included a discussion of spirometry results. Participants rated four statements regarding their perception of the effectiveness of spirometry on smoking cessation attempts and the ethics of screening on a 5-point Likert scale.

Detailed Results

Nearly half (46%) of all participants felt that measuring lung function positively influenced their attempt to quit smoking and most (86%) felt that it was justifiable to measure lung function in heavy smokers. However,7.8 percent of participants stated that routinely measuring lung function in smokers would interfere with one's freedom of choice, and 1.2 percent said it was not justified to confront them with a COPD diagnosis.

Key Question 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?

We searched for treatment efficacy literature for all of the following COPD drug classes or combinations of any of the following: LABAs, long-acting anticholinergics, and ICS. No trials recruited screen-detected patients. In order to most closely reflect the COPD severity (GOLD definition of mild-to-moderate disease) which would be expected to most closely reflect a screen-detected population, we included trials with either subanalyses of participants with mild-to-moderate COPD or trials where the mean FEV_1 percent predicted was 60 percent or greater. We identified a total of 20 studies of 14 distinct trials meeting these inclusion criteria (**Table 18**). Among these 14 relevant trials, we found two trials of LABAs,[125,126] one RCT of ICS-LABA,[126] five RCTs of the long-acting antimuscarinic (LAMA) tiotropium, which is in the class of long-acting anticholinergic drugs,[125,127-129] and six RCTs of ICS.[126,130-134] For ease of interpretation, the associated efficacy results are presented by drug class.

LABAs

Summary of Findings

Although no RCTs examined the clinical effectiveness of LABAs in screen-detected populations, we identified two industry-sponsored post hoc subanalyses of almost exclusively moderate COPD (94% moderate; 6% mild) treatment with LABAs with 6 months to 3 years of followup. Most of the patient-important outcomes we sought were not reported at all (i.e., exercise capacity) or were reported in just one of the two analyses (i.e., exacerbations, all-cause mortality, dyspnea scores); subgroup analyses were further limited by power and not controlling for confounders. Based on reporting from the subanalysis of the Towards a Revolution in COPD Health (TORCH) trial only, LABAs did not appear to provide an all-cause mortality benefit at 3 years for any stage of COPD.[126] It was not clear whether exacerbations were reduced since the only trial reporting this outcome (TORCH) did not provide statistical analysis by treatment arm for the subgroup; however, there was no evidence that stage of COPD modified the impact of LABAs on reduced exacerbations in the larger population. In pooled analysis of different LABAs, there was a statistically significant short-term impact on dyspnea scores after 6 months, although more robust evidence would be needed to make firm conclusions. Further, although both analyses reported HrQOL outcomes, they found mixed results. One analysis by Decramer

showed short-term improvement in the proportion achieving clinical meaningful improvements in HrQOL with LABAs compared to placebo treatment at 6 months; in contrast, the TORCH-based analysis showed no difference in mean HrQOL between treatment groups after several years of followup in those with predominantly moderate disease or in all patients regardless of disease severity. The overall strength of evidence for the effect of LABAs on health outcomes in moderate COPD patients is insufficient for exercise capacity and low for other health outcomes.

Overview of Available Studies

No RCTs examined the clinical effectiveness of LABAs in screen-detected populations. We identified two industry-sponsored post hoc subanalyses of mild-to-moderate COPD treatment with LABAs: one subanalysis of mild-to-moderate COPD (>90% moderate) by Decramer[125] pooling three unique, double-blind placebo-controlled RCTs[135-137] of different LABAs (formoterol, salmeterol, and indacaterol) and one subanalysis of the double-blind placebo-controlled TORCH trial analyzing LABA-treated (salmeterol) participants with a FEV_1 of 50 percent predicted or greater, where 99 percent had moderate COPD (**Table 18**).[126]

The Decramer subanalysis pooled the fair-quality international INdacaterol: Value in COPD: Longer Term Validation of Efficacy and Safety (INVOLVE), INdacaterol to Help Achieve New COPD treatment Excellence (INHANCE), and INdacaterol efficacy evaLuation using 150 µg doses witH COPD paTients (INLIGHT)-2 trials (n=4,417; n=2,353 with moderate COPD) examining formoterol (12 µg/twice a day), indacaterol (150 or 300 µg/day), or salmeterol (50 µg/twice a day) compared to placebo with 6-month followup.[125] These three primary trials recruited patients aged 40 years or older with moderate-to-severe COPD (FEV_1 ≥30% and <80% predicted, FEV_1/FVC <70%), and a smoking history of 20 pack-years or more. Although inclusion criteria would exclude patients with mild disease, authors note that approximately 7 percent of the included population was found to have mild COPD because one trial began administering post- rather than pre-bronchodilator spirometry, thereby relabeling some participants previously defined as moderate to the mild category. Patients with a recent respiratory tract infection or COPD exacerbation were excluded; however, concomitant short-acting beta agonists and stable ICS use were allowed. The primary outcomes in these trials were trough FEV_1 (the change from baseline in FEV_1 after a 24-hour dosing interval) and secondary outcomes included dyspnea and quality of life at 6-months followup. In the subanalysis of only patients with moderate COPD (FEV_1 50% to 79% predicted), the mean age was 64 years, with 32.7 percent of participants being women (**Table 19**).[125] The majority of participants were former smokers (56%), with 44 percent indicating that they were current smokers without any reported mean pack-year exposure. Almost 5 percent (4.6%) of participants had at least one nonrecent exacerbation in the preceding year. The mean FEV_1 percent predicted for this moderate COPD subpopulation was 64.0 percent, and the baseline HrQOL as measured by the SGRQ was 41.2, indicating that the population had moderate limitations. Withdrawal rate was approximately 25 percent in two of the three trials overall and approximately 14 percent among those with moderate disease.[135,136] Each of the included trials used ITT analysis.

The TORCH subanalysis examined those with FEV_1 of 50 to 60 percent predicted from the fair-quality international TORCH trial (n=6,184; 28 mild; 2,155 moderate), examining salmeterol (50 µg/twice a day), fluticasone propionate (500 µg/twice a day), salmeterol/fluticasone propionate

combination (50 µg/500 µg/twice a day) or placebo in COPD patients with a 36-month followup (**Table 18**).[126,138] Results for the salmeterol and placebo arms only are reported here. This trial included current or former smokers with a history of greater than or equal to 10 pack-years, aged 40 to 80 years, with a confirmed diagnosis of COPD and an FEV_1 of less than 60 percent predicted. Although the main trial was limited to patients with moderate-to-severe COPD, authors state that the subanalysis included 28 patients who were diagnosed with mild COPD (FEV_1 ≥80% predicted). Additionally, enrolled patients were required to show less than 10 percent reversibility and a pre-bronchodilator of FEV_1/FVC of less than 0.70. Patients with nonCOPD respiratory disorders were excluded, along with those diagnosed with any condition likely to cause death within 3 years, those with previous lung volume reduction surgery and/or lung transplantation, those requiring the use of oxygen therapy for at least 12 hours per day, patients using oral corticosteroid therapy, and patients who were hospitalized during the run-in period. Concomitant COPD medications (except oral or inhaled corticosteroids and LABAs) were allowed. The primary outcome of the TORCH trial was all-cause mortality and secondary outcomes included exacerbation rate, health status, lung function, and adverse events. The mean age of those with mild-to-moderate COPD was 64.9 years, with 28.0 percent of participants being women (**Table 19**). Approximately half of participants in the subanalysis were former smokers (53.0%), with 47 percent reporting that they were current smokers. The mean number of exacerbations among the participants with moderate COPD requiring hospitalizations in the preceding year was 0.2, and the mean post-bronchodilator FEV_1 was 58.8 percent predicted. The baseline HrQOL as measured by the SGRQ was 45.4, indicating that the population had moderate limitations. The withdrawal rate and loss to followup were high in the main trial (36.9% in the LABA arm and 44.2% in the placebo arm), although withdrawal rates and loss to followup were not reported in the subanalysis. Analysis was done by ITT; however, the withdrawals were included in the exacerbation and HrQOL analysis.

Both of these studies were post hoc analyses; neither performed interaction testing and only one[125] controlled for confounders (**Table 20**). Groups were matched at baseline in both analyses.

Detailed Results

Exacerbations. Only one trial, TORCH (n=1,057 from salmeterol and placebo arms only, analyzed for this outcome), reported exacerbations (**Table 21**).[126] The TORCH subanalysis among participants with mild-to-moderate COPD (99% moderate) showed that the annual rate of moderate-to-severe exacerbations (defined as symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalization, or a combination of these) were 0.71 in the salmeterol group and 0.82 in the placebo group (no statistical testing done by treatment arm) at 36 months. In the main analysis including those with all stages of COPD, there was a reduction in moderate- to-severe exacerbations in the salmeterol compared to placebo group (relative risk [RR], 0.82 [95% CI,0.76 to 0.89]), and no evidence of a difference in treatment effect on exacerbations by COPD disease stage (p=0.254).

All-cause mortality. Only one trial, TORCH (n=1,057),[126] reported all-cause mortality in patients with mild-to-moderate COPD, finding similar rates across treatment groups (9.2% in the salmeterol group vs. 11.4% in the placebo group) at 36 months (no statistical testing done by treatment arm) (**Table 21**). The main analysis including all participants (n=6,112) showed no

statistically significant difference in the primary outcome of all-cause mortality across all treatments.

Dyspnea scores. Only the Decramer subanalysis reported dyspnea scores as an outcome (**Table 22**).[125] The Decramer subanalysis (n=2,117) showed that the ORs for the percent of patients achieving a meaningful difference (≥1 point) in dyspnea scores (measured by the Transition Dyspnea Index) was higher in each of the LABA groups compared to placebo at 6 months (salmeterol 50 µg/twice a day, 1.72 [95% CI, 1.12 to 2.66]; indacaterol 150 µg/day, 1.99 [95% CI, 1.45 to 2.74]; indacaterol 300 µg/day, 2.44 [95% CI, 1.79 to 3.31]; formoterol 12 µg/twice a day, 1.91 [95% CI, 1.29 to 2.85]).

HrQOL. Both studies reported HrQOL outcomes among participants with mild-to-moderate COPD, showing mixed results (**Table 22**). The Decramer subanalysis showed that the ORs for the percent achieving a meaningful clinical difference (≥4 units) in HrQOL (measured by the SGRQ) was higher in the LABA groups compared to placebo at 6 months (salmeterol, 1.98 [95% CI,1.31 to 2.99]; indacaterol 150 µg, 2.14 [95% CI, 1.59 to 2.88]; indacaterol 300 µg, 1.78 [95% CI, 1.34 to 2.37]; formoterol 12 µg/twice a day, 1.63 [95% CI, 1.15 to 2.30]).[125] Conversely, the TORCH subanalysis showed that there was no clinically meaningful difference in HrQOL (measured by the SGRQ) from baseline in either the salmeterol or the placebo group at 26 months (mean change from baseline, -1.5 vs. -1.3 in the intervention and control group, respectively; no statistical testing done by treatment arm).[126] Further, the main trial (all severities of COPD) showed no statistically significant difference in HrQOL in the salmeterol group compared to placebo (difference, -1.0 [95% CI, -2.0 to 0]).

Exercise capacity. We found no trials that reported changes in exercise capacity among patients with mild-to-moderate COPD treated with LABAs.

Critical Appraisal

The lack of efficacy RCTs of LABAs in screen-detected COPD populations limits the strength of evidence for this question. One post hoc subanalysis of a large four-arm RCT and one post hoc pooled subanalysis from three other RCTs provide data on patients with mild-to-moderate COPD.[125,126] Both of these studies were large, totaling over 2,000 patients with mild-to-moderate COPD; however, almost all participants had moderate COPD, with the TORCH trial recruiting participants on the more severe end of moderate (FEV_1 % predicted ~60%), and only one of these trials provides longer-term followup (TORCH, 3 years; Decramer, 6 months). There was a number of limitations in these subgroup analyses, including: 1) the primary trials were powered for the entire population, not subgroups; 2) both analyses were post hoc; 3) neither analyses performed interaction testing; and 4) only Decramer controlled for confounders. The inconsistency in reported outcomes across the studies further limited the strength of available evidence.

ICS-LABA Combination

Summary of Findings

Although no RCTs examined the clinical effectiveness of ICS-LABA combinations among screen-detected COPD populations, we found a single post hoc subgroup analysis from the TORCH trial on the impact of ICS-LABA combined treatment on selected patient-important outcomes in those with almost exclusively moderate COPD (98.5% moderate; 1.5% mild). An additional RCT by Lapperre included an ICS-LABA arm; however, there were no patient-oriented outcomes reported for this treatment. Low strength of evidence supports an improvement in exacerbations, while very low strength of evidence supports improved mortality but no change in HrQOL. Strength of evidence is insufficient for exercise capacity and dyspnea symptomatology.

Overview of Available Studies

We found no RCTs examining the clinical effectiveness of ICS-LABA among screen-detected COPD populations. One subanalysis from the TORCH trial[126] provided data on the effectiveness of a ICS-LABA treatment combination among patients with mild-to-moderate COPD, and a four-arm trial by Lapperre included a ICS-LABA arm and placebo arm (in addition to two fluticasone arms); however, there were no patient-oriented outcomes reported for the combination arm (**Table 18**).[132]

The subanalysis of the four-arm TORCH trial, discussed previously, examined the efficacy of ICS-LABA (salmetrol/fluticasone) combination compared to placebo.[126,138] Results from the salmeterol/fluticasone propionate combination (50 µg/500 µg/twice a day) arm and the placebo arm were analyzed in a post hoc subanalysis (n=1,097) at 3 years followup for patients with moderate COPD.[126]

Only the post hoc subanalysis from the TORCH trial provides data on the patient-oriented outcomes of all-cause mortality, exacerbations, and HrQOL (**Tables 23** and **24**).[126] The all-cause mortality benefit seen in the analysis was not consistent with interaction testing, which showed no heterogeneity of effect by COPD stage. Statistically significant improvements in HrQOL did not meet the threshold of clinically meaningful changes. There were fewer annual rates of exacerbations in the ICS-LABA arm of this analysis, but it is unclear if this is clinically meaningful.

Detailed Results

Exacerbations. Only one study, the subanalysis of the TORCH trial, reported exacerbations by stage of COPD, finding that the annual rate of moderate-to-severe exacerbations (defined as symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalization, or a combination of these) was lower in the ICS-LABA treatment combination group compared with the placebo group (0.57 in intervention vs. 0.82 in control group; annual reduction rate in intervention group, 31% [95% CI, 19 to 40]) (**Table 23**).[126]

All-cause mortality. One subanalysis of the TORCH trial reported all-cause mortality among patients with moderate COPD, finding a statistically significant reduction between those receiving the ICS-LABA combination versus those on placebo at 3 years of followup (3.6% absolute reduction; 7.8% vs. 11.4%; hazard ratio [HR], 0.67 [95% CI, 0.45 to 0.98]) (**Table 23**).[126] Interaction testing, however, showed no difference in treatment effect across the GOLD stages on all-cause mortality (p=0.402), and the main TORCH results showed no difference for probability of death at 3 years (adjHR, 0.82 [95% CI, 0.68 to 1.00]).[138]

Dyspnea scores. We found no trials that reported changes in dyspnea scores among mild-to-moderate COPD patients treated with ICS-LABA combination.

HrQOL. Only one study, the TORCH subanalysis, reported HrQOL (measured by the SGRQ) in patients with moderate COPD (**Table 24**).[126] Results showed that there was a greater reduction in the change in HrQOL among patients in the ICS-LABA treatment group from baseline compared to the placebo group; however, neither arm achieved a clinically meaningful change (defined as ≥4 units) from baseline (-3.7 vs. -1.3 in intervention vs. control group, respectively; difference, -2.3 [95% CI, -4.0 to -0.7]).

Exercise capacity. We found no trials that reported changes in exercise capacity among patients with mild-to-moderate COPD treated with ICS-LABA combination.

Critical Appraisal

Data assessing the effectiveness of combination ICS-LABA treatment is limited to one post hoc subanalysis among patients with mild-to-moderate COPD (98.5% of participants had moderate COPD and were on the more severe end of moderate; FEV_1 % predicted, ~60%).[126] The evidence available suggests a possible all-cause mortality benefit among this subpopulation that was not seen in the main trial across all stages of COPD, as well as possible improvement in HrQOL and a reduction in exacerbations; however, more evidence is required to make firm conclusions. Interpretation of this evidence should be made with caution given that this analysis was done post hoc and interaction testing indicated no difference among outcomes across all stages of disease. It is unclear whether the difference reported in exacerbation rates would be clinically meaningful in practice; the changes found in HrQOL were determined to not be clinically meaningful by study authors.

Long-Acting Anticholinergics/LAMAs (Tiotropium)

Summary of Findings

Although we found no RCTs of tiotropium to treat screen-detected COPD, we found a single trial from Troosters et al that included only untreated patients with moderate (stage II) COPD and five subgroup analyses examining those with moderate or milder COPD derived from three individual trials (Understanding Potential Long-term Impacts on Function with Tiotropium [UPLIFT], French trial from Tonnel et al, and VA trial from Nieoehner et al) and from one pooled analysis of subgroup data from the tiotropium arm of the INHANCE trial reported by Decramer. All trials used tiotropium at doses of 18 µg daily in the intervention group and

placebo in the control group. There were at least three different studies reporting outcomes for exacerbations or HrQOL, but just one study for the other three outcomes (exercise capacity, dyspnea, and all-cause mortality). Results were somewhat mixed for tiotropium's effect on exacerbations and HrQOL, although the bulk of the evidence suggested a beneficial effect on both. The trial from Troosters et al, with the population most approximating a screen-detected population, showed a statistically significant reduction in exacerbations and a statistically significant, but probably not clinically meaningful, difference in work productivity scores. The overall strength of evidence for the effect of tiotropium on health outcomes in screen-detected COPD patients is low to moderate for exacerbations, low for HrQOL, and insufficient for other health outcomes.

Overview of Available Studies

We found no RCTs examining the clinical effectiveness of the LAMA tiotropium among screen-detected COPD populations. One fair-quality, international trial specifically recruited patients with moderate COPD who were naïve to previous maintenance therapy (**Table 18**).[139] Four subanalyses examined patients with moderate COPD,[125,127-129] with one additional post hoc subanalysis further analyzing participants with milder stage 2 COPD (defined as FEV_1 60% to 70% predicted).[140] Two subanalyses (one prespecified and one post hoc)[127,140] are from one fair-quality, international trial (UPLIFT),[141] one subanalysis is from a fair-quality French trial,[129] one is from a good-quality U.S.-based trial in the VA system,[128] and one is a post hoc subanalysis of the tiotropium arm from the INHANCE trial.[125] The pooled data from Decramer contained a small number (~7%) of patients with mild COPD (FEV_1 ≥80% predicted). Two analyses recruited participants on the more severe end of moderate COPD.[128,129] The number of patients analyzed with moderate COPD ranged from 198 to 2,739, comprising a total of 4,592 patients. All primary trials required a minimum smoking history of 10 pack-years, with one subanalysis requiring a minimum smoking history of 20 pack-years.[125] All primary trials excluded patients with a recent COPD exacerbation or respiratory tract infection (within 4 to 6 weeks of recruitment). Two trials excluded persons with asthma[128,129] and three trials had some comorbidity exclusions.[128,129,141] The minimum age was 40 years in all trials, with a mean age of 61.7 to 67.8 years (**Table 19**). The proportion of women ranged from 1.5 percent in the VA trial[128] to 33.0 percent,[125] and the mean pack-years of smoking exposure ranged from 44.0 to 68.4 years. None of the trials reported the mean number of exacerbations in the year preceding study recruitment; however, one subanalysis reported that 3.2 percent of the participants had at least one exacerbation in the preceding year, with more exacerbations in the placebo arm compared to the tiotropium arm at baseline (1.3% vs. 5.0%).[125] The mean FEV_1 percent predicted at baseline was reported for four analyses for patients with moderate COPD and ranged from 59 to 65.7 percent predicted.[125,127,139,140] Three analyses reported the mean baseline HrQOL, which was 41.5 for patients with moderate disease,[127] 40.0 for the subset of patients with baseline FEV_1 60 to 70 percent of predicted,[140] and 41.2 in one pooled analysis of three RCTs.[125] Only one trial reported baseline physical activity, reporting a mean of 6,402.7 steps per day across all participants.[139]

The primary outcome varied across studies and was change in FEV_1 in two trials,[127,139] trough FEV_1 in one subanalysis,[125] percent of patients with greater than or equal to 4 units of improvement in HrQOL in another trial,[129] and the percentage of patients with an exacerbation or

hospitalization due to an exacerbation in one trial (**Table 18**).[128] Secondary outcomes included change in physical activity levels (measured via activity monitor), exacerbations, time to first exacerbation, dyspnea, mortality, quality of life, hospitalization utilization, pulmonary function test changes, and adverse events. Followup was 6 months in three trials,[125,128,139] 9 months in one trial,[129] and 48 months in UPLIFT, the largest trial.[127]

All trials used tiotropium at doses of 18 µg daily in the intervention group and placebo in the control group (**Table 18**). One four-arm RCT was open label for the tiotropium arm,[125] whereas the rest of the RCTs were double blinded. One subanalysis provided outcomes data for the tiotropium and placebo arms among patients with mild-to-moderate COPD,[125] while the other analysis was from clinical effectiveness trials of tiotropium compared to placebo. All trials allowed concomitant COPD inhaler medications.

Baseline characteristics were similar in the tiotropium and placebo groups, with three notable exceptions (**Table 19**). In the Tonnel trial, the placebo group had more current smokers and higher baseline HrQOL scores compared to the tiotropium group;[129] the INHANCE subanalysis placebo arm had more participants with a recent COPD exacerbation compared to the tiotropium arm;[125] and the UPLIFT trial subanalysis had statistically significantly fewer current smokers in the tiotropium group compared to the control group (29% vs. 36%; p=0.011).[140]

Discontinuation was reported in three of the trials among patients with moderate COPD.[125,127,139] Discontinuation rates in the UPLIFT trial at 4 years were high for patients in this subpopulation, in both the intervention and control groups (30.6% and 34.7%, respectively),[127] and in the INHANCE subanalysis, discontinuation rates were also notable, with 22 percent of the open label tiotropium group and 26 percent of the placebo group discontinuing therapy at 6 months.[125] The discontinuation rate at 6 months in the Troosters trial was lower at 11.3 and 9.6 percent in tiotropium and placebo groups, respectively.[139] All trials analyzed results using ITT methods described as the inclusion of all participants receiving medications or taking at least one inhaled capsule and providing any followup after baseline data. All trials were sponsored by the pharmaceutical industry.

Detailed Results

Exacerbations. Three trials (n=3,483) report outcomes related to exacerbations among patients with moderate disease showing mixed results (**Table 25**).[127,128,139] Two subanalyses showed a difference in exacerbation rates among those treated with tiotropium, while one underpowered subanalysis showed no difference in exacerbation rates in the tiotropium group compared to the placebo group. Two of these three trials defined what they considered to be an exacerbation.[127, 128] Exacerbations in the UPLIFT trial were defined as an increase/new onset of one or more respiratory symptoms for greater than or equal to 3 days requiring antibiotic and/or systemic steroid treatment.[127] Exacerbations in the VA trial were defined as a complex of respiratory symptoms, including an increase or new onset of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness with a duration of at least 3 days requiring treatment with antibiotics or systemic steroids, hospitalization, or both.[128]

The UPLIFT trial's subanalysis of patients with moderate COPD (n=2,739) reported that the

time to first exacerbation and mean number of exacerbations were statistically significantly lower in the tiotropium group compared to placebo at 4 years (time to first exacerbation, 23.1 vs. 17.5 months; HR, 0.82 [95% CI, 0.75 to 0.90]; p<0.0001; mean number of exacerbations, 0.56 vs. 0.70; RR, 0.80 [95% CI, 0.72 to 0.88]; p<0.0001) (**Table 25**).[127] There was no interaction of treatment effect on exacerbations and GOLD stage (p=0.237), and the main trial (including patients with all COPD severities) showed a decrease in exacerbations in the tiotropium group compared to the placebo group (0.73 vs. 0.85 exacerbations per patient-year; RR, 0.86 [95% CI, 0.81 to 0.91]). The Troosters trial (n=457) also showed a reduction in exacerbations among patients in the tiotropium group compared to the placebo group at 6 months (4.6% vs. 11.0%; OR, 0.42 [95% CI, 0.21 to 0.84]).[139] Similar results were seen in the UPLIFT subanalysis (**Table 25**). Conversely, the VA trial (n=287) reported no difference in exacerbations among moderate COPD patients in the tiotropium group compared to the placebo group at 6 months, but this trial was not powered to adequately asses this outcome for the subanalysis.[128]

Only the two UPLIFT subanalyses reported exacerbations requiring hospitalization among patients with moderate COPD at 4 years (**Table 25**).[127,140] Both analyses showed no difference among those treated with tiotropium compared to placebo. Specifically, the UPLIFT subanalysis including patients with moderate disease reported no difference in the mean number of patients hospitalized with exacerbations per patient-year compared to placebo (0.08 vs. 0.10; RR, 0.80 [95% CI, 0.63 to 1.03]), but found a reduction in time to first hospitalization due to an exacerbation (HR, 0.74 [95% CI, 0.62 to 0.88]).[127] The UPLIFT subanalysis for patients with a subset of moderate COPD (FEV_1 60% to 70% of predicted) showed no difference in patients with one or more hospitalizations due to exacerbations (13% vs.15%; HR, 0.86 [95% CI, 0.64 to 1.16]).

All-cause mortality. The two subanalyses from the UPLIFT trial provide the only information on all-cause mortality among patients with moderate COPD (**Table 25**).[127,140] The first analysis (n=2,739) found that all-cause mortality and mortality due to lower respiratory tract infections were similar in the tiotropium and placebo groups at 48 months (9.2% vs. 10.8%; HR, 0.84 [95% CI, 0.66 to 1.07]; 1.4% vs. 1.8%; HR, 0.81 [95% CI, 0.45 to 1.46]).[127] Conversely, in the post hoc subanalysis of participants with FEV_1 60 to 70 percent predicted (n=1,210), all-cause mortality was statistically significantly lower in the tiotropium group compared to the placebo group (7.4% vs. 11.1%; HR, 0.66 [95% CI, 0.45 to 0.96]).[140] Further, there were more cardiac deaths and deaths due to COPD exacerbation in the placebo group and more absolute deaths due to cancer in the tiotropium group (data not reported).

Dyspnea scores. Only one study (the post hoc subanalysis of the INHANCE trial; n=658) reported dyspnea scores among patients with mild to moderate COPD (**Table 26**).[125] Results showed that more patients achieved a meaningful clinical difference (≥1 point) in dyspnea scores in the tiotropium group compared with the placebo group at 6 months (64.6% vs. 49.3%; OR, 1.59 [95% CI, 1.07 to 2.37]).

HrQOL. Four trials provide HrQOL outcomes for patients with moderate COPD (**Table 26**).[125, 127,129,139] The only trial exclusively recruiting patients with moderate disease reported statistically significant, although modest, differences in work productivity and activity impairment scores, but it is unlikely that these represent a clinically meaningful difference.[139] One subanalysis

reported no difference in HrQOL (measured by SGRQ) changes from baseline in the tiotropium group compared to the placebo group.[129]

Conversely, two subanalyses (one post hoc and one a priori) reported more patients with a clinically meaningful change in HrQOL scores (measured by SGRQ) among participants in the tiotropium group compared to the placebo group (**Tables 20** and **26**).[125,127] Specifically, the Troosters trial (n=426) reported changes in Work Productivity and Activity Impairment (WPAI) scores, a six-item questionnaire measuring health problem related impairments, absenteeism, and presenteeism in paid and unpaid work during the past 7 days; however, no minimum clinically meaningful change has been validated for COPD. Authors reported an improvement in WPAI scores in the tiotropium group and deterioration of WPAI scores in the placebo group, but the CIs are wide (difference, -3.76 [95% CI, -7.39 to -0.13]) at 24 weeks.[139] The percentage of work time missed due to ill health was similar between the tiotropium and placebo groups (mean difference, -2.33% [95% CI, -7.39 to 2.73]). Additionally, more patients were rated by their physicians as having excellent global health assessments of overall health status in the tiotropium group compared to the placebo group at week 24 (18.1% vs. 10.9%). The Tonnel subanalysis (n=198) reported similar changes in mean HrQOL scores among patients in the tiotropium and placebo groups (-8.85 vs. -7.38; absolute difference, 1.47 [95% CI, -5.37 to 2.44]).[129] The main Tonnel trial, whose primary outcome was HrQOL change (as measured by SGRQ) (which included patients with all stages of COPD), showed a statistically significant difference in the percentage of patients achieving a minimal clinically meaningful change in HrQOL, with interaction testing showing no heterogeneity of effect by COPD severity (p=0.078). The INHANCE subanalysis for patients with mild-to-moderate COPD reported a -5.2 raw mean change from baseline in HrQOL (measured by SGRQ) in the tiotropium group and -3.1 in the placebo group at 6 months (minimally clinical difference defined as -4.0), with more achieving a clinically meaningful change in HrQOL scores in the tiotropium group compared to the placebo group (51.8% vs. 42.0%; OR, 1.46 [95% CI, 1.01 to 2.10]).[125] The UPLIFT trial subanalysis reported an improvement in HrQOL scores among both groups in the first 6 months of treatment, with a subsequent worsening in scores at similar rates over time (0.89 vs. 0.99 units per year; p=0.58).[127] At any given time point, the difference in HrQOL scores between the tiotropium and placebo groups ranged from 2.7 to 4.0 units. For the UPLIFT subgroup analysis of COPD patients with FEV_1 60 to 70 percent predicted, the tiotropium group was more likely to experience a clinically meaningful change in HrQOL compared to the placebo group (52% vs. 44%; p<0.05).[140]

Exercise capacity. Only the Troosters trial, which recruited only patients with moderate COPD, reported the outcome of exercise capacity at 6 months (**Table 26**).[139] The mean activity rate measured with activity monitors was not statistically significantly different in the tiotropium group compared to those receiving placebo at 6 months (proportion of inactive patients [<6,000 steps/day], 39.8% vs. 43.4%; OR, 0.86 [95% CI, 0.57 to 1.30]). There was a statistically significantly lower proportion of inactive patients in the tiotropium group compared to the placebo group at 12 weeks (p=0.047).

Critical Appraisal

No trials examining the effectiveness of tiotropium among patients with mild-to-moderate COPD

were found; however, the Troosters trial population is the closest identified to a screen-detected population due to the fact that the trial only recruited patients with moderate COPD who were naïve to maintenance therapy. It was also the only trial specifically recruiting this population, so was not subject to the limitations of subanalyses; however, it was powered to detect disease-oriented outcome of FEV_1 change, not the outcomes considered in this review. Despite being underpowered to fully evaluate exacerbations, however, it did find a statistically significant difference in this outcome when comparing those treated with tiotropium to those on placebo. The HrQOL outcomes from Troosters, while improved in the tiotropium group, are unlikely to be clinically meaningful.

The trial durations of the included subanalyses were short (≤9 months) in all but one trial, which provided 4-year followup, limiting the ability to assess patient-centered outcomes over time. All but two[125,127] subanalyses were prespecified. Two of the five subanalyses performed interaction testing for the reported outcomes, showing no heterogeneity of treatment effect by COPD severity.[127,129] Additionally, three subanalyses controlled for confounders for at least one outcome.[125,129,140] Overall, reporting for tiotropium outcomes was scant, and for three outcomes (exercise capacity, dyspnea, and all-cause mortality), only one trial reported results, making conclusions difficult. The only outcome with data from more than one trial was quality of life, which showed that there may be a modest, statistically significant improvement in the percentage of patients who experience a clinically meaningful change, but further research is needed to confirm this finding.

ICS

Summary of Findings

While there were more trials of ICS among patients with mild-to-moderate COPD than for the other medications we examined, there were still relatively few trials evaluating the effectiveness of ICS for each of the patient-important outcomes. Unlike the other medication classes in our review (LABAs, ICS-LABA, long acting anticholinergics/LAMAs), ICS is the only medication class in which mild COPD participants are represented in greater number. Data were further limited by representing primarily subgroup analyses, since the European Respiratory Society study on Chronic Obstructive Pulmonary Disease (EUROSCOP) was the only RCT that specifically aimed to recruit patients with mild disease (patients with moderate disease were also included).[130] EUROSCOP reported exacerbations and all-cause mortality, as did three other trials. Most reported data, including the EUROSCOP results, supported a reduction in exacerbations with ICS, although differences in the definition of this outcome limited robust conclusions. All-cause mortality appeared similar between ICS and placebo groups, although relatively low mortality rates and lack of long-term followup limit the robustness of these findings. For HrQOL or dyspnea symptoms, data are very sparse and limited, since only subanalyses from two trials were available and no outcome data were reported for exercise capacity. The overall strength of evidence for the effect of ICS on exacerbations in screen-detected COPD patients is insufficient for exercise capacity and low for other health outcomes.

Overview of Available Studies

Six fair-quality RCTs (n=3,983) examined the effectiveness of ICS compared to placebo in populations with either mild-to-moderate COPD or in populations with a mean FEV_1 percent predicted of greater than or equal to 60 percent (**Table 18**).[126,130-134] No RCTs examined the clinical effectiveness of ICS in a screen-detected COPD population. The EUROSCOP trial (n=1,277) was the only RCT that exclusively recruited patients with mild-to-moderate COPD.[130] Two post hoc subanalyses[126,133] of larger RCTs by Calverley[133] and the TORCH trial[138] provided outcome data on patients with mild-to-moderate COPD; neither trial controlled for confounders or performed interaction testing. Three RCTs[131,132,134] are included in this review because their mean FEV_1 percent predicted was greater than or equal to 60 percent (63.0%, 67.8%, and 86.6%), with the Vestbo trial having the highest mean FEV_1 of 86.6 percent.[131] None of these three RCTs provided subanalyses of strictly mild-to-moderate COPD patients.

Two trials recruited patients from centers internationally;[126,133] one trial each was performed in the United States,[134] the Netherlands,[132] western Europe,[130] and Denmark (**Table 18**).[131] Three of the analyses, Lung Health Study (LHS) II, a subanalysis of the TORCH trial, and EUROSCOP, were large, with greater than 1,000 patients each;[126,134,142] two analyses recruited more than 200 patients,[131,133] and one study was small with less than 100 patients.[132] The lower age limit was as low as 30 years in two trials,[130,131] with EUROSCOP having an upper age cutoff of 60 years;[130] the mean age in the six trials ranged from 52.4 to 65.1 years (**Table 19**). The majority of participants were men, with percentage of women ranging from 13.9 to 39.6 percent. All studies, except the population-based Vestbo trial,[131] only recruited former or current smokers. Three RCTs had minimum smoking exposure requirement of 5[130] to 10 pack-years,[126,132] although only two RCTs reported mean smoking exposures, which were 39.3 and 43.5 pack-years. Five trials had exclusions for serious medical comorbidities.[130,131,133,134,138] Only the TORCH trial reported the mean number of exacerbations requiring hospitalization in the preceding year across treatment groups, which was 0.2.[126] Five RCTs reported the mean baseline post-bronchodilator FEV_1 percent predicted, which ranged from 58.8 to 86.6 percent.[126,130-132,134] Two analyses were composed entirely of moderate COPD patients,[132,133] one analysis recruited almost entirely moderate COPD patients (98.7%),[126] and three studies[130,131,134] did not report the proportion of patients with mild COPD, but two of these likely included a fair number of mild patients since the baseline FEV_1 percent predicted was greater than 80 percent.[130,131] Baseline HrQOL (measured by SGRQ) was reported in two trials,[126,132] with mean scores of 45.4 and 30.0 across the population; the TORCH trial[126] included symptomatic patients, as reflected by the baseline HrQOL, and the majority of patients with moderate COPD had FEV_1 percent predicted on the more severe end of the range (50% to <60%). The LHS II[134] excluded those who used bronchodilators or corticosteroids (inhaled or systemic) in the past year, the Vestbo trial excluded those using oral or inhaled steroids in the past 6 months,[131] and the Lapperre trial excluded those with ICS in the past 6 months.[132]

Two RCTs were four-armed trials with additional combination ICS-LABA arms,[126,132] and one RCT had three arms examining two doses of ICS compared to placebo (**Table 18**).[133] One trial examined mometasone furoate (800 µg/day),[133] two RCTs examined budesonide (800 to 1200 µg/day),[130,131] two RCTs examined fluticasone (1000 µg/day),[126,132] and one examined the effectiveness of triamcinalone (1200 µg/day);[134] all inhalers were dosed daily or twice a day.

Concomitant COPD medications were allowed in all the trials except the EUROSCOP trial, which did not allow LABAs or cromolyn.[130]

Primary outcomes in the included trials varied from all-cause mortality,[126] mean post-bronchodilator FEV_1[133] or change in FEV_1,[130,131,134] and inflammatory cell counts in bronchial biopsies and induced sputum (**Table 18**).[132] Secondary outcomes included exacerbations, respiratory symptoms, cause-specific morbidity and mortality, airway reactivity in response to methacholine, HrQOL, and adverse events. Followup ranged from 9 to 54 months.

Three RCTs measured compliance with canister weights or hidden canister counters,[130,132,134] one RCT used patient self-report for compliance,[133] and two RCTs did not report compliance ascertainment methods.[131,138] Four of the six trials reported high compliance rates in the primary trials.[130-133] The EUROSCOP and Calverly trials excluded those with less than 75 and 80 percent adherence, respectively, during the run-in periods,[130,133] and the Lapperre trial (the only trial not using ITT) excluded patients with less than 70 percent adherence.[132] In the Lapperre trial, no patients in the ICS group and five out of 29 patients in the placebo group were excluded for nonadherence. The Vestbo trial reported that few patients had less than 75 percent compliance, although it was one of the trials that did not report compliance ascertainment methods.[131] The LHS II reported 54 percent compliance in the ICS group and 59 percent in the placebo group as measured by canister weight.[134]

Withdrawal, discontinuation, and loss to followup rates were reported inconsistently in the six trials. Discontinuation rates varied widely in the four RCTs reporting this data and ranged from 5 percent in the LHS II[134] to as high as 42.4 percent in the Calverly trial.[133] Similarly, ITT was handled variably in the five trials using ITT.[130,131,133,134,138] One trial included only those participants with at least one dose of treatment, one baseline, and one post-baseline visit (806 analyzed/911 randomized).[133] The TORCH trial included all patients in the efficacy analysis, except 72 of the 6,184 randomized due to site standardization issues. The EUROSCOP and Vestbo trials analyzed all randomized participants meeting inclusion criteria and run-in compliance thresholds.[130] The LHS II reported ITT without providing additional details and the Lapperre trial did not use ITT. All trials except the LHS II were sponsored by the pharmaceutical industry.

Detailed Results

Exacerbations. Four RCTs reported exacerbation rates among patients with mild-to-moderate COPD (n=2,803),[126,130,131,133] but only two performed statistical testing to detect differences among treatment groups (**Table 27**). Trials defined exacerbations variably, leading to wide variations in exacerbation rates. The EUROSCOP trial (n=1,277), which recruited patients with mild-to-moderate COPD, reported a statistically significantly lower yearly rate of severe exacerbations (defined as exacerbation requiring oral corticosteroids), but overall the absolute difference was very small in both groups at 3 years (0.05 vs. 0.07; RR, 0.63 [95% CI, 0.47 to 0.85]).[130] A subanalysis of the TORCH trial of patients with mild-to-moderate COPD (n=1,072) reported a lower annual rate of moderate to severe exacerbations (defined as symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalization, or a combination of these) for the fluticasone group compared to the placebo group (0.68 vs.

0.82) without providing statistical testing by treatment arm.[126] The main trial showed a reduction in moderate or severe exacerbations in the fluticasone group compared to placebo (RR, 0.82 [95% CI, 0.76 to 0.89]).[138] Similarly, the post hoc subanalysis of the Calverley trial (n=266) including patients with moderate COPD reported more patients with exacerbations (defined as clinically significant worsening of COPD symptoms requiring treatment with antibiotics and/or systemic steroids) in the placebo group compared to either of the mometasone furoate groups (18% [800 µg/daily] vs. 27% [400 µg/twice a day] vs. 35% [placebo]; no statistical testing provided) at 1 year.[133] These subanalysis results should be interpreted with caution, however, as the subanalysis did not report baseline characteristics for the patients with moderate COPD, making it impossible to assess differences among treatment groups. The LHS II (n=1,116) reported comparable rates of hospitalizations (0.99 vs. 2.1; p=0.07) and emergency department visits (1.3 vs. 1.0; p=0.36) for respiratory conditions per 100 patient-years for the triamcinolone and placebo groups at 40 months.[134] The Vestbo trial (n=290) reported no statistically significant difference in annual exacerbations or in exacerbations requiring hospital admission at 3 years, but the definition of exacerbations was inconsistent with that of the field, so these results are not comparable to the other studies (exacerbations defined as affirmative answer to the question "Have you since your last visit experienced more cough and phlegm than usual?").[131]

All-cause mortality. Four fair-quality RCTs reported all-cause mortality among patients with mild-to-moderate COPD (n=3,653),[126,131,134,142] but only the EUROSCOP trial and the LHS II performed statistical testing, showing no statistical difference between treatment groups (**Table 27**).[130,134] Mortality was rare (<5%) in all trials, except the 36-month TORCH trial, where all-cause mortality was 9.9 percent (53/537) in the fluticasone group and 11.4 percent (61/535) in the placebo group; the main trial showed no all-cause mortality benefit from fluticasone over placebo.[126,138] This higher number of deaths in the TORCH trial subanalysis may be because most participants with moderate COPD were on the more severe end (63% of those with moderate disease had FEV_1 % predicted of 50% to <60%). In the EUROSCOP trial (n=1,277), deaths were similarly rare in the ICS and placebo groups at 3 years (8/593 [1.3%] vs. 10/582 [1.7%]; p=0.64).[130] The only death related to COPD was in the placebo group; other causes of death were bronchial carcinoma (3 vs. 3 subjects), sudden cardiac arrest (2 vs. 2), trauma (2 in the control group), myocardial infarction (2 vs. 1), pulmonary embolism (1 in the control group), sudden cardiac arrest (1 in the intervention group), ruptured aortic aneurysm (1 in the intervention group), and gastric carcinoma (1 in the intervention group). In the LHS II (n=1,116), which was the longest trial (up to 54 months; mean, 40 months, with a mean FEV_1 % predicted of 67.8%), all-cause mortality rates were relatively rare (<5%) and similar in both groups (15/559 vs. 19/557; p=0.49), as were the causes of death from cardiovascular disease (6 intervention vs. 2 control subjects; p=0.16), lung cancer (5 vs. 4; p=0.74), and other or unknown cause (2 vs. 3; p=0.65), except for other cancer (2 vs. 10; p=0.02). The Vestbo trial reported a low death rate, with none of the deaths attributable to COPD or treatment at 3 years (2.8% vs. 3.4%).[131]

Dyspnea score. Two fair-quality RCTs with a mean baseline FEV_1 greater than or equal to 60 percent predicted, Lapperre and LHS II, reported self-reported dyspnea scores (as measured by the MRC) (**Table 28**).[132,134] The LHS II reported that statistically significantly fewer participants in the triamcinolone group experienced dyspnea compared to the placebo group at 36 months (p=0.02); MRC score changes from baseline were not reported, however, so it is not clear if this

finding is clinically important.[134] The Lapperre trial reported a statistically significant lower MRC dyspnea score in the fluticasone group compared to the control group over months 7 to 24 of the trial (mean difference of -0.2 points/year [95% CI, -0.3 to -0.06]; p=0.003); however, neither the treatment or placebo groups had a minimum clinically important difference in MRC scores from baseline (minimum >1 point).[132]

HrQOL. Two fair-quality RCTs (post hoc subanalysis of the TORCH trial and RCT by Lapperre with baseline mean FEV_1 ≥60%) reported mean HrQOL (measured by SGRQ) changes from baseline among patients with mild-to-moderate COPD (**Table 28**).[126,132] Both trials showed that neither the fluticasone nor the placebo group had changes reaching the threshold for a minimum clinically important difference (≥4 units) over the 30- to 36-month trial periods. The TORCH trial reported changes in HrQOL from baseline that did not meet minimum clinical important difference in the fluticasone or placebo groups (mean SGRQ change, -2.1 vs. -1.3); neither the treatment or placebo groups had a HrQOL mean difference over 3 years meeting the threshold for a minimum clinically important change.[126] Conversely, the Lapperre trial reported a statistically significantly greater change in mean SGRQ activity scores in the fluticasone group, but changes in each group again did not meet the threshold for a minimum clinically important change (change during months 7 to 24, -3.1 points/year [95% CI, -5.5 to -0.7]; p=0.012).[132]

Exercise capacity. We found no trials that reported changes in exercise capacity among patients with mild-to-moderate COPD treated with ICS.

Critical Appraisal

Overall, there were few trials evaluating the effectiveness of ICS among patients with mild-to-moderate COPD. The EUROSCOP trial was the only RCT identified that specifically aimed to recruit patients with mild disease.[130] Additionally, one large and one smaller post hoc subanalysis of an RCT (both with limitations) and two RCTs with mean baseline FEV_1 greater than or equal to 60 percent provided data for patient-oriented outcomes for patients of interest to this review. Most trials had limitations due to variably defined ITT analyses, high withdrawal rates, and the exclusion of noncompliant patients during run-in periods, which may not reflect clinical practice. The two subanalyses had serious limitations, including the lack of baseline comparability reporting, [133] lack of interaction testing,[133] lack of control for confounders,[126,133] and post hoc timing (**Table 20**).[126,133]

Despite the scant evidence and limitations, overall results seem to indicate a reduction in exacerbations with ICS; however, exacerbations were variably defined, and therefore annual rates of exacerbations varied widely. Results from the one trial in patients with mild-to-moderate COPD (EUROSCOP; n=1,175) does show a statistical difference in exacerbation rates, but as expected, the annual rates of exacerbations are very low (<0.1 exacerbations/year) in patients with milder COPD severities, so the absolute difference is very small (0.02 exacerbations per year).[130]

Results for the other patient-centered outcomes were similarly scant. The four trials reporting all-cause mortality suggest that it is rare among patients with moderate COPD (<5%) and that there is no all-cause mortality benefit up to 54 months of followup. Dyspnea scores come from two

RCTs of all stages—one not clinically meaningful and one RCT where it is uncertain if clinically meaningful—with overall evidence too limited to make any firm conclusions about the impact of ICS treatment on dyspnea. HrQOL was only reported in one trial with baseline FEV_1 greater than or equal to 60 percent and one subanalysis, with both showing that neither ICS nor placebo group met the thresholds for a minimum clinically important change over 30 to 36 months. More evidence is needed, however, to fully evaluate the impact of ICS on HrQOL.

Key Question 8. What Are the Adverse Effects of COPD Treatments in Patients With Mild-to-Moderate COPD?

We searched for treatment harms literature for all of the following COPD drug classes or combinations of any of the following: LABAs, long-acting anticholinergics, and ICS. There were no RCTs evaluating the harms of treatment among a screen-detected COPD population. The evidence on treatment harms in patients with mild-to-moderate disease is limited to the available trials including patients with milder stages of COPD and to subanalyses of larger treatment trials that report results by disease stage. Overall, there were fewer than five trials reporting harms for any individual medication class, limiting the ability to make firm conclusions regarding the risk of treating patients with early disease.[130-134] In addition to evaluating the treatment harms reported in the RCTs included for KQ 7, we evaluated the harms reported by 3 percent or more of the study population on FDA drug labels for the considered drug classes, which ranged from dry mouth and coughing to vomiting and pneumonia (**Appendix E**).

LABAs

Summary of Findings

One treatment effectiveness RCT[126] and one post hoc analysis of pooled trial data by Decramer[125] provided data on harms associated with treating mild-to-moderate COPD patients with LABAs (**Table 29**). Details regarding the study characteristics of these RCTs have been discussed previously (see KQ 7). Results were scantily reported, with only the subanalysis of mild-to-moderate COPD patients in the TORCH trial reporting reduced rates of withdrawal and pneumonia in those on salmeterol; both analyses reported somewhat mixed results, but overall there were few differences between treated and untreated groups for a variety of individual adverse events.

Detailed Results

Withdrawal rates. The subanalysis of the TORCH trial is the only study identified reporting withdrawal rates for mild-to-moderate COPD patients treated with the LABA salmeterol; however, reasons for withdrawal were not indicated (**Table 29**).[126] Withdrawal rates were found to be greater among participants in the control group (35.0%) compared to those in the treatment group (27.0%), although statistical testing was not provided.

Composite and individual adverse events. The Decramer post hoc analysis of data pooled from three unique treatment RCTs reports adverse event rates from four separate LABA arms:

formoterol (12 µg/twice a day), salmeterol (50 µg/twice a day), and indacaterol (150 µg/day and 300 µg/day).[125] Overall, adverse events were mostly similar across each of the LABA intervention groups and the placebo group (**Table 29**). The incidence of any adverse event between participants in the formoterol and placebo groups was found to be similar (57.9% vs. 55.9%; no statistical testing provided). Additionally, the incidence of nasopharyngitis, upper respiratory tract infections, and cough were comparable in the formoterol and placebo groups (8.7% vs. 8.2%, 2.6% vs. 3.3%, and 4.2 vs. 4.3%, respectively). Decramer reported similar findings in adverse events between patients treated with both doses of indacaterol (150 and 300 µg/day) and those treated with placebo (58.9% vs. 61.3% vs. 55.9%, no statistical testing provided). Additionally, the incidence of nasopharyngitis was similar between the indacaterol groups and placebo group; however, upper respiratory tract infections and cough were slightly more common in the treatment groups, but no statistical testing was done (6.5% vs. 5.0% vs. 3.3% and 5.6% vs. 7.3% vs. 4.3%, respectively). Rates of any adverse event were higher in those on placebo (55.9%) compared to those treated with salmeterol (45.0%); however, rates of nasopharyngitis, upper respiratory tract infections, and cough were mixed (**Table 29**).

The subanalysis of the TORCH trial reported the incidence of any adverse events, serious adverse events, and fatal adverse events, showing mixed results between those treated with salmeterol and those treated with placebo (any adverse event, 89.0% vs 87.0%; serious adverse event, 33.0% vs 36.0%; fatal adverse event, 5.0 % vs. 7.0%; no statistical testing provided) (**Table 29**).[126] The treatment association of adverse events was not reported or commented on by study authors. Common adverse events (incidence ≥3% of study population) reported on FDA labels were generally mild and ranged from cough and headaches to chest pain and vomiting (**Appendix E**).

Pneumonia. Only the subanalysis of mild-to-moderate COPD of the TORCH trial reported the incidence of pneumonia and the Kaplan-Meier probability of pneumonia between those treated with salmeterol and those on placebo (**Table 29**).[126] Results showed a numerically higher probability of developing pneumonia among participants in the control group compared to the treatment group (10.6% vs. 9.4%; no statistical testing provided). Additionally, there was a higher incidence rate of pneumonia in the control group (43 per 1,000 treatment-years) than the treatment group (36 per 1,000 treatment-years). Overall, there was no evidence of treatment differences by severity of COPD (p=0.402).[126]

ICS-LABA Combination

Summary of Findings

Two treatment effectiveness RCTs provide data on harms associated with treating mild-to-moderate COPD patients with the combination of LABAs and ICS (**Table 30**).[126,132] Details regarding the study characteristics of these RCTs have been discussed previously (see KQ 7). Withdrawal rates appeared to be mixed, with the subanalysis of the TORCH trial reporting lower rates of withdrawal among patients treated with salmeterol/fluticasone than those treated with placebo, and the Lapperre trial reporting similar rates of withdrawal between treatment groups. Only the subanalysis of the TORCH trial reported on the incidence of composite or individual adverse events, finding relatively 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.[126] Paucity of data makes robust conclusions challenging.

Detailed Results

Withdrawal rates. Both the Lapperre trial and the subanalysis of the TORCH trial reported rates of withdrawals; however, neither analysis provides reasons for withdrawals (**Table 30**).[126,132] The subanalysis of the TORCH trial reported lower rates of withdrawal in the fluticasone/salmeterol combination group compared to the placebo group (27.0% vs. 35.0%; no statistical testing provided).[126] Conversely, the Lapperre trial, an RCT with a mean baseline FEV_1 percent predicted of 63.0 percent, reported similar numbers of withdrawals between patients treated with fluticasone/salmeterol combination and those on placebo (19.0% vs. 20.0%; no statistical testing provided).[132]

Composite and individual adverse events. Only the subanalysis of mild-to-moderate COPD of the TORCH trial reported the incidence of composite adverse events (**Table 30**).[126] Results of the incidence of any adverse event, serious adverse events, and fatal adverse events were found to be similar between those treated with fluticasone/salmeterol and those treated with placebo (86.2% vs 86.6%, 35.0% vs 36.0%, and 4.8% vs. 6.8%, respectively; no statistical testing provided). The treatment association of adverse events was not reported or commented on by study authors. Common adverse events (incidence ≥3% of study population) reported on FDA labels were generally mild and ranged from throat irritation and headaches to pneumonia and dizziness (**Appendix E**).

Pneumonia. Only the subanalysis of mild-to-moderate COPD of the TORCH trial reported the incidence of pneumonia and the Kaplan-Meier probability of pneumonia between those treated with salmeterol/fluticasone and those on placebo (**Table 30**).[126] Results showed a higher Kaplan-Meier probability of developing pneumonia among participants in the treatment group compared to the control group (15.3% vs. 10.6%; no statistical testing provided). Additionally, there was a higher incidence rate of pneumonia in the treatment group (56 cases per 1,000 treatment-years) than the control group (43 cases per 1,000 treatment-years). Overall, there was no evidence of treatment differences by severity of COPD (p=0.402).[126]

Long-Acting Anticholinergics/LAMAs (Tiotropium)

Summary of Findings

Two treatment effectiveness RCTs[127,139] and one post hoc analysis of pooled study data[125] provided data on harms associated with treating mild-to-moderate COPD patients with the LAMA tiotropium (**Table 31**). Details regarding the study characteristics of these RCTs have been discussed previously (see KQ 7). Overall reporting of adverse events was scant, with a single trial[127] reporting very similar withdrawal rates with and without tiotropium, and two studies reporting incidence of a mix of adverse events, with both suggesting up to a 10 percent increase in any adverse events in those on tiotropium, but no difference in serious events.

Detailed Results

Withdrawal rates. Only the two subanalyses of the UPLIFT trial reported withdrawals due to adverse events among patients with moderate COPD randomized to tiotropium versus placebo (**Table 31**).[127,140] Reported results showed a similar risk of adverse events leading to discontinuation in both the subanalysis of participants with moderate COPD[127] and the narrower subanalysis of participants with a baseline FEV_1 greater than or equal to 60 percent predicted[140] (17.0% vs. 17.8% and 15.5% vs 15.2%, respectively; no statistical testing provided).

Composite and individual adverse events. One RCT by Troosters and the post hoc analysis of pooled study data done by Decramer reported on the incidence of composite adverse events or individual adverse events among patients with mild-to-moderate COPD, showing slightly higher rates among those treated with tiotropium compared to those on placebo (**Table 31**).[125,139] The post hoc pooled analysis reported higher rates of any adverse event among patients treated with tiotropium compared to those on placebo; however, no statistical testing was performed (67% vs. 55.9%).[125] Both studies report individual adverse events experienced by study participants. Trooster's trial reports serious adverse events occurring in 1 percent or greater of the population, which included hip fractures, abdominal abscesses, tendon disorders, cerebral artery occlusions, cerebral infarctions, joint abscesses, bladder cancer, pancreatic cysts, and strep infection.[139] Overall, individual rates of serious events were rare and were similar between treatment groups (4.1% vs. 4.4%; statistical testing not provided). Additionally, the post hoc analysis of pooled trial data by Decramer reports slightly higher rates of adverse events among patients treated with tiotropium; however, no statistical testing was provided.[125] Specifically, the incidence of nasopharyngitis was found to be higher in the tiotropium group compared to the placebo group (10.2% vs. 8.2%), as were the incidence of upper respiratory tract infections (5.5% vs. 3.3%) and cough (5.0% vs. 4.3%). Common adverse events (incidence ≥3% of study population) reported on FDA labels were generally mild and ranged from dry mouth and cough to urinary tract and respiratory infections (**Appendix E**).

Pneumonia. We found no studies of long-acting anticholinergics that reported the incidence of pneumonia among patients with mild-to-moderate COPD.

ICS

Summary of Findings

Six RCTs reported treatment harms associated with ICS among patients with mild-to-moderate COPD (**Table 32**).[126,130-134] Details regarding the study characteristics of these RCTs have been discussed previously (see KQ 7). Overall, withdrawal rates between treatment groups were similar in the four trials that reported this data. 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 density, and fractures were sparse and mixed. One post hoc subanalysis reported more ischemic cardiac events among those in the placebo group, although these results should be interpreted with caution due to study methods.

Detailed Results

Withdrawals. Four of the six ICS effectiveness trials reported withdrawals,[126,130-132] with two of these trials specifically reporting withdrawals due to adverse events (**Table 32**).[130,131] The EUROSCOP trial, which recruited only patients with mild-to-moderate COPD who were naïve to maintenance therapy reported that withdrawals due to adverse events were similar in the budesonide and placebo groups (11.8% vs. 10.6%; p=0.51).[130] Likewise, the Vestbo trial reports similar withdrawals due to adverse events among patients in the budesonide group compared to the placebo group (11.0% vs. 11.7%; statistical testing not reported).[131] The subanalysis of mild-to-moderate COPD patients from the TORCH trial reported high withdrawal rates for any reason in both the fluticasone and placebo groups, without specifying reason for withdrawal (32.0% vs. 35.0%).[126] Additionally, the Lapperre trial reports similar withdrawal rates without reason in both the fluticasone and placebo groups (13.0% vs. 18.1% vs. 20.0%).[132]

Composite and individual adverse events. Three treatment effectiveness RCTs reported composite outcomes of any adverse events or serious adverse events in the ICS group compared to the placebo group (**Table 32**).[126,130,131] The EUROSCOP trial reported no differences in serious adverse events among patients in the budesonide group compared to those taking placebo (29.8% vs. 27.7%; p=0.37).[130] Conversely, the Vestbo trial reported a significantly higher rate of serious adverse events in the placebo group compared to the budesonide group (9.7% vs. 28.3%; p=0.001); however, none of the serious adverse events were thought to be related to treatment or treatment failure.[131] The TORCH trial subanalysis reported similar rates of any adverse event, serious adverse events, and fatal adverse events in both the fluticasone and placebo groups, without statistical testing reported (88.4% vs. 86.6%, 31.1% vs. 36.2%, and 6.9% vs. 6.8%, respectively).[126] Similarly, the LHS II reported no statistically significant difference in thrush, easy bruising, cataracts, diabetes, or myopathy in the triamcinalone group compared to the placebo group, but did report more moderate or severe mouth irritation in the triamcinalone group compared to placebo (2.3% vs. 1.1%; p=0.02).[134] Common adverse events (incidence ≥3% of study population) reported on FDA labels were generally mild and ranged from headache and rash to vomiting and respiratory infection (**Appendix E**).

Pneumonia. Two treatment effectiveness RCTs report the rates of pneumonia among patients with mild-to-moderate COPD as an adverse event, but do not provide any statistical significance testing (**Table 32**).[126,131] The subanalysis of the TORCH trial reported a Kaplan-Meier probability of developing pneumonia of 12.8 percent in the fluticasone group and 10.6 percent in the placebo group; however, when the authors re-examined Kaplan Meier probability and time to first pneumonia, there was no evidence of treatment differences by COPD severity (p=0.402).[126] Additionally, there was a higher incidence rate of pneumonia in the treatment group (58 case per 1,000 treatment-years) than the control group (43 cases per 1,000 treatment-years). Conversely, the Vestbo trial reported the incidence of pneumonia more frequently among patients in the placebo group than in the budesonide group (11.0% vs. 16.6%).[131]

Additional adverse events. One treatment effectiveness RCT in patients with mild-to-moderate COPD reported fractures[130] and one RCT with a mean post-bronchodilator baseline FEV_1 of 67.8 percent reported bone mineral change as an intermediate measure of harm (**Table 32**).[134] The EUROSCOP trial reported no difference in new lumbar fractures based on radiographs

available for a subset of the population in the budesonide group compared to the placebo group (5 vs. 3 new lumbar fractures for a subset of 653 patients with x-rays; p=0.50). The LHS II reported similar bone mineral densities at the femoral neck for the triamcinalone and placebo groups at all timepoints; however, the percent bone mineral change from baseline to 36 months was statistically significantly different between treated and control groups, although it is unclear if this change is clinically meaningful (-2.00% vs. -0.22%; p<0.001).[134]

One post hoc subanalysis by Lofdahl of the EUROSCOP trial reported cardiac events experienced by participants during followup (**Table 32**).[142] Results found that there were fewer ischemic cardiac events in the budesonide group compared to the placebo group; however, caution should be taken in interpreting this post hoc analysis, as the ascertainment of cardiac events was collected only if spontaneously reported by a primary care physician (3.0% vs. 5.3%; p=0.048).

Chapter 4. Discussion

We found no population-based screening trials that provided direct evidence on whether systematic screening for COPD in primary care improves health outcomes. The evidence for this screening is derived from an indirect pathway considering discrete bodies of evidence. We evaluated test performance of various screening approaches in populations that are representative of primary care and the benefits and harms of treating mild-to-moderate COPD, which are the stages of COPD that represent most screen-detected disease. We also considered whether identifying undiagnosed COPD might improve the effectiveness of other preventive services by enhancing service delivery or motivation to participate, including smoking cessation or immunizations. **Table 33** provides a summary of evidence by KQ.

Studies of Screening for COPD

We identified relatively scant data for any specific prescreening or screening approach using primary care feasible questionnaires with or without pulmonary function measures. Additionally, because we identified no risk factor only screening questionnaires, we used screening questionnaires that relied on a combination of risk factor- and symptom-based questions. The evidence was further complicated by the heterogeneity of screening approaches, involving various questionnaires and office pulmonary function measures, which were used alone or in combination. The populations selected for screening also varied across studies, and were generally selected based on age alone (at least 40 or 50 years) or age in addition to smoking history (usually ever smoking, sometimes with a minimal pack-years of exposure). Similarly, recruitment strategies, and in some cases diagnostic criteria, variously excluded those with prior COPD or pre-existing asthma, affecting applicability. Further, studies varied in their primary goal. Some studies, for example, assessed the utility of questionnaires to prescreen patients for more selected in office pulmonary function screening measures, while others used questionnaires or pulmonary function measures (before or after bronchodilation) to identify candidates for diagnostic spirometry. Additionally, others studies primarily or secondarily evaluated various screening test cutpoints to optimize screening performance. Thus, the perspective and reporting of data varied substantially across studies. Nonetheless, we summarized available data as consistently as possible to examine the test performance of various primary care screening strategies using feasible questionnaires and/or handheld devices for identifying undiagnosed early-stage COPD.

The prevalence of COPD in studies applicable to a screening (undiagnosed) population ranged from approximately 10 percent in primary care patients aged 40 years and older to 13 to 28 percent in ever smokers aged 40 to 50 years or older. Newly identified cases of COPD were predominantly (84% to 95%) in the mild-to-moderate stage.

Among several published questionnaires, only the CDQ, LFQ, and COPD-PS have been externally validated, which is a minimum requirement before they can be used in clinical practice.[112,143,144] The eight-item risk factor- and symptom-based CDQ was the most extensively studied screening questionnaire, with external validation in five populations, all outside of the

United States. This tool, however, has reasonably consistent test performance characteristics for detecting spirometrically-confirmed COPD in different languages and populations, which could strengthen its applicability. In general, the CDQ (also called IPAG questionnaire and RHSQ) had a sensitivity in the low 90 percent range and specificity in the high-30 to mid-40 percent range for scores greater than 16.5. Although this is a relatively low specificity for a screening test, the PPV was highest when applied to ever smokers (also the derivation population for this tool). These false positives, however, would primarily be exposed to inconvenience and cost for diagnostic spirometry, a noninvasive test. NPV was greater than 90 percent in all populations (except for current smokers with a 10-year pack history and at least one respiratory symptom), as would be desirable in case-finding. Although the LFQ was specifically developed in the NHANES population and studied in U.S. primary care practices, data for this questionnaire was limited to a single validation study. This study, however, had quality concerns (31% of spirometry was invalid or incomplete) and relatively poorer test performance than the CDQ. The LFQ had a very high test positive rate (77%) among ever smokers with a 10-year pack history, but tended toward lower sensitivity, specificity, PPV, and NPV than the CDQ when used in similar populations. We could not assess the harms of screening (i.e., rate of false positives or proportion of missed cases) using the LFQ because only a subset of those with scores less than 18 were selected for spirometry. Investigators examining the LFQ concluded that the questionnaire could be used as part of a staged approach to identify patients for pre-bronchodilator screening in primary care as an alternative to mass screening. Insufficient information on the missed cases and false positives, however, make it impossible to assess the tradeoffs of screening. While the COPD-PS was derived in an enriched sample of U.S. pulmonary and primary care clinics, its external validation in a single Japanese population-based study makes conclusions regarding generalizability of accuracy results limited. The COPD-PS has recently been applied in a multisite U.S.-based primary care, pragmatic COPD screening trial (n=8,770); however, this trial did not include gold standard reference spirometry for accuracy estimation.[117]

For primary care screening using handheld tools measuring various pulmonary functions, we identified studies examining PEF or FEV_1/FEV_6. Peak flow studies were conducted in large international populations that included individuals with pre-existing COPD who had more prevalent environmental exposures. As such, test performance results are difficult to extrapolate to a U.S.-based primary care population. While we found three studies of FEV_1/FEV_6 screening in over 1,500 individuals, robust data for a specific screening approach were limited by variability in measures and populations. Two smaller studies, however, used pre-bronchodilator measurement in ever smokers, while one study of about 1,000 individuals—about half of whom were ever smokers—used post-bronchodilator FEV_1/FEV_6 for screening. One small study used pre-bronchodilator measurements, and this study also required minimal evidence of airway obstruction reversibility for spirometry-diagnosed COPD to eliminate persons with asthma. Nonetheless, only post-bronchodilator FEV_1/FEV_6 had reasonable sensitivity (at least 80%) at a FEV_1/FEV_6 cutpoint of less than 0.70. For pre-bronchodilator FEV_1/FEV_6 screening, a higher cutpoint (<0.75) was necessary to achieve this sensitivity. While these pulmonary function measures tended to have better specificity and PPV than questionnaires, they had similarly high NPV (>90%).

Three primary care screening strategies, or a combination of these strategies, have been proposed

and tested: 1) targeted screening with spirometry in those with risk factors (e.g., all ever smokers with smoking history of ≥10 pack-years); 2) prescreening questionnaires and/or handheld pre-bronchodilator measures of pulmonary function to identify those who should undergo diagnostic spirometry; or 3) some sequential combination of these approaches. Rather than simply screening all smokers using full spirometry, the prescreening questionnaire approach provides a simple way to screen out those who do not need spirometry. This convenience, however, comes at the expense of some missed cases. Both prescreening questionnaires and handheld devices are relatively simple, inexpensive approaches, and the primary harms would stem from false positives or missed cases. We did not identify any other studies that reported on any other direct harms of this screening. While there is some uncertainty about the natural history of early COPD, we can assume that these missed early cases would eventually be identified at clinical presentation during later medical contacts. Any treatment benefits that could have occurred in the interim would theoretically be lost. As a result, we sought to quantify any potential benefits realized through increased preventive services uptake or early treatment initiation prior to clinical presentation in order to bound the incremental benefit from early COPD identification through screening.

We constructed simple tables to compare screening test performance using the CDQ or FEV_1/FEV_6 across a range of populations using the mean sensitivity and specificity of associated studies (excluding Kotz for the CDQ) (**Tables 34** and **35**). In a population of 1,000 people screened with the CDQ (using a cutpoint of 16.5), assuming a COPD prevalence of 10 percent (as might be expected in screening those aged 40 and older, sensitivity in the high 80s [87%] and specificity in the mid-40s [44%]), approximately 591 patients would go on to spirometry. Only 87 of these 591 patients (15%) would actually have spirometrically-confirmed COPD. Using a prescreening questionnaire would save 409 patients from spirometric testing at the expense of 13 missed cases, compared with screening the entire population. If the CDQ were applied to a higher prevalence population with 20 percent COPD (as might be expected in ever smokers aged 40 to 50 or older), with the same sensitivity and specificity (87% and 44%, respectively), 622 would go onto spirometry, and 174 of these 622 patients (28%) would have spirometrically- confirmed COPD. Using the CDQ to target the patients who are more likely to screen positive on spirometry would reduce the number sent to spirometry by 378 patients at the expense of 26 missed cases (**Table 34**).

In a population of 1,000 patients screened with pre-bronchodilator FEV_1/FEV_6 using a cutpoint of less than 0.7, we estimate that 124 patients would be sent on to spirometry, and 52 of these 124 patients (42%) would have spirometrically-confirmed COPD, assuming a COPD prevalence of 10 percent, sensitivity of 52 percent, and specificity of 92 percent. Therefore, using the pre-bronchodilator FEV_1/FEV_6 to target patients compared with screening the entire population with spirometry would save 876 patients from spirometry at the expense of 48 missed cases. Therefore, pre-bronchodilator FEV_1/FEV_6 screening alone with a cutpoint of 0.7 would result in diagnosing nearly the same number of patients as the missed cases (only half of COPD cases would be identified with this strategy), thereby limiting its use as a stand-alone screening test. Changing the threshold to less than 0.75 (sensitivity 84%, specificity 72%) would result in 336 patients being sent to spirometry and 84 (25%) of these would have spirometrically-confirmed COPD at the expense of 16 missed cases. Further, post-bronchodilator FEV_1/FEV_6 with a sensitivity of 80 percent and specificity of 95 percent would send 125 patients to spirometry, 80

(24%) of whom would have spirometrically-confirmed COPD at the expense of 20 missed cases. In a population with 20 percent prevalence, assuming the same sensitivity and specificity as the post-bronchodilator FEV_1/FEV_6, 200 patients would be sent to spirometry and 160 (80%) of these would have spirometrically-confirmed COPD at the expense of 40 missed cases (**Table 35**).

The value assigned to results from various screening approaches, or to screening for COPD in general, is somewhat subjective, and depends on several judgments. First, there are judgments as to the sufficiency of the evidence. While available evidence was relatively sparse in an applicable population, we identified several ongoing studies aimed to estimate the diagnostic yield and accuracy of various primary care-based screening approaches, including using microspirometry FEV_1/FEV_6 for screening, and a validation study of the COPD-PS prescreening questionnaire, as well as several novel screening tool development studies (**Appendix B**). The expectation of better evidence in the near future might influence judgments about how to use current evidence. Second, judgments about the value of earlier identification for some cases, paired with the "harms" of missing some cases or false-positive diagnostic evaluations, are required. In the following sections, we summarize the evidence on the value of earlier identification through considering efficacy of treatment in early-stage disease cases and any impact on warranted preventive services.

Treating Patients With Mild-to-Moderate COPD

We identified no treatment trials in asymptomatic, screen-detected populations. We identified no trials that addressed the effectiveness of any treatment to improve health outcomes in patients with mild COPD. Almost all treatment trials almost exclusively included individuals with moderate COPD, primarily the severe end of moderate (e.g., FEV_1 % predicted of ~60% in many studies). Absolute treatment benefit estimates would be expected to be lower in a screen-detected, largely mild disease population than in these selected trials in our systematic review. We found only one treatment trial that clearly recruited a population with moderate COPD who were naïve to maintenance medications, which would be considered closer to a screen-detected population. In this trial, treatment with tiotropium reduced exacerbations and inactivity at 6 months with no treatment-attributable adverse events reported.[139] Beyond this trial, there were limited data for any treatment class from trials that recruited solely mild-to-moderate COPD participants, as prior systematic reviewers have also found.[5,101] Even when we supplemented with subgroup analyses from trials with the full range of disease severity, data remained very sparse. Additionally, subgroup analyses all had serious limitations, including being conducted post hoc, lacking control for confounders, not reporting baseline characteristics of the subgroup, and not providing interaction testing for differences in subgroup effects (**Table 20**). Nonetheless, these relatively weak data consistently support some reduction in exacerbations for each of the treatment classes in our review (LABAs, LABA-ICS, tiotropium, and ICS). Furthermore, LABA and tiotropium may decrease dyspnea scores as well, but this evidence came from a single post hoc subgroup analysis, and thus is only suggestive. Overall, strength of evidence for a reduction in exacerbations and dyspnea scores with early treatment in patients with moderate COPD is low, and the clinical significance of the observed reduction may be limited. Epidemiologic studies report that patients with mild-to-moderate COPD have an average of less than one

exacerbation per year;[6] one systematic review of RCTs and cohort studies reported an annual event-based exacerbation frequency (defined as doctor's visits, antibiotics, steroids, or hospitalizations) of 0.82 (95% CI, 0.46 to1.49) for mild disease and 1.17 (95% CI, 0.93 to 1.50) for moderate disease.[145] Those with screen-detected COPD might be expected to have even fewer exacerbations, which would render the absolute benefit as modest, at best.

A challenging issue when considering screening for COPD is the requirement for an asymptomatic population. Questionnaires such as the CDQ incorporate symptoms and their severity as part of their scoring, and the rationale for "screening" has largely been a case-finding one (i.e., there is a large proportion of undiagnosed disease seen in primary care). This systematic review only included asymptomatic individuals, defined as those who are free of the disease; those in whom the disease is present, but who have physical symptoms that are undetected by the patient or the clinician (e.g., have mild dyspnea that goes unnoticed); or those who have nonspecific symptoms (e.g., sporadic sputum production or cough) that have gone unrecognized as being related to COPD. The distinction between patients who are symptomatic and those who are undetected or who present with nonspecific symptoms is difficult to determine from available clinical research. This is particularly true for smokers, many of whom have a chronic cough and some limited activity without presenting such complaints to their physicians. Additionally, this task will be challenging for use in clinical practice unless screening/case-finding efforts are based on sociodemographics, such as age or a particular smoking history. Consistent evidence shows that COPD is underdiagnosed[21,117,146] and limited data on harms reported in the treatment effectiveness trials suggests that there are no substantial serious adverse effects for most medications (i.e., upper respiratory symptoms, cough). Some concerns do remain, however, about ICS-containing medications increasing incidence of pneumonia in patients with more severe COPD[147,148] and effects on bone mineral density and fracture risk. Data were too limited to make firm conclusions regarding this potential harm in our included trials of mild-to-moderate COPD.

The greatest potential benefit that could be achieved through screening would be increasing smoking cessation rates, since smoking cessation is the only proven beneficial treatment for reducing progression in mild-to-moderate COPD.[149] Systematic reviews have confirmed that counseling and pharmacotherapy smoking cessation interventions are effective in those with COPD,[72,150,151] even though there is some evidence that smokers with COPD differ in their motivation to quit compared to smokers without COPD.[74,152-154] Our systematic review identified four trials[120-123] that examined the incremental value of adding screening spirometry to smoking cessation counseling interventions and one trial that examined the incremental value of adding "lung age" as introduced by Morris in the mid 1980s[155] to spirometry and counseling.[119] The Parkes trial was the only study that reported a statistically significant absolute increase in biochemically confirmed cessation rates (7%) when screening results reported lung age to participants (number needed to treat=14).[119] Since both groups received spirometry and counseling, however, this trial tested only the incremental value of adding "lung age" and suggested that the communication of lung damage might be the key. These early positive results have not been replicated in other trials that incorporate the feedback of lung age based on spirometry, including another community-based U.S. trial by McClure, which measured a less reliable self-reported cessation outcome.[123] Our finding a lack of robust literature to support a smoking cessation benefit are consistent with those of the prior systematic review used by the

USPSTF.[156] Further, we did not identify literature to support the premise that false reassurance in those with normal spirometry may dampen motivation to quit. We identified four ongoing Spanish RCTs of screening spirometry in addition to counseling compared to counseling alone that will measure 12-month smoking abstinence rates (**Appendix B**). Results from these trials could add to this relatively underdeveloped literature base. We identified no completed or pending trials reporting the effect of awareness of COPD diagnosis influencing recommended immunization uptake rates.

In summary, given the paucity of data on screening accuracy and treatment benefit in screen-detected COPD, controversy about whether population screening or primary care case-finding should be implemented with any strategy remains. Advocates argue that the high prevalence of undiagnosed COPD (10% to 20%),[38] as well as clinical COPD misdiagnoses in smokers who in fact have alternate treatable diagnoses (e.g., congestive heart failure) could be considered as potential benefits with few screening-related harms, since spirometry is a simple, noninvasive test.[157] The underutilization of spirometric confirmation of clinically suspected COPD may result in misdiagnosis and inappropriate use of medications with potential harms, or a delay in the correct diagnosis resulting in a deferral of appropriate therapeutic interventions.[158] The critics remain skeptical of the patient-focused benefits of population screening efforts in largely asymptomatic patients, particularly in light of the inadequate evidence on the prognostic markers for mild disease progression, little evidence on treatment benefit in mild disease, and high monthly costs of these inhaled medications.[159-161]

Limitations

Due to the fact that we found so few trials and there was so much variability between those studies that do exist, our systematic review was limited to a descriptive analysis, as meta-analysis would be inappropriate and imply false precision. The literature on screening instruments was limited by few questionnaires with external validation and heterogeneous populations with differing baseline COPD prevalence. Literature on treatment for COPD was limited by mostly short trial durations, differential withdrawal rates, and high premature drug termination with missing data for some outcomes in those discontinuing the medications. Additionally, the majority of patients studied in the treatment RCTs had moderate COPD, with very scant evidence for patients with mild disease, which reduces our ability to assess treatment effectiveness in these patients. Our *a priori* methods only specified patient-focused outcomes and did not include changes in FEV_1 as an outcome. Not including this outcome, however, is consistent with USPSTF methods, particularly since it is unclear how changes in FEV_1 correlate with change in exacerbation rates. Further, we relied on harms data as reported in the effectiveness RCTs and thus may not have captured the full range of potential side effects or their population-based incidence. It is unlikely, however, that observational studies in screen-detected populations applicable to U.S.-based primary care are readily available given current practice.

Future Research Needs

Ideally, primary care-based staged screening RCTs of ever smokers using the externally validated CDQ or LFQ prescreening questionnaire followed by microspirometry and reporting patient-focused outcomes data are needed. In the absence of such direct evidence, there are several areas for future research. These areas, however, might not fit into the USPSTF definition of screening. In 2009, the National Heart, Lung, and Blood Institute made specific recommendations for future research, including the identification and validation of case-finding tools focused on identifying moderate-to-severe disease, specifically those with less than 60 percent FEV_1 predicted, as well as the development and validation of a three-stage approach to case-finding (risk factor-based questionnaire followed by a simple measure of expiratory flow and then confirmed with diagnostic spirometry).[90] This approach, focused on moderate-to-severe disease, would be similar to the staged approach examined in a few studies in this review. Further investigation of the promising findings from Parkes' lung age screening trial would require an RCT with the intervention group receiving screening spirometry with lung age reporting plus counseling compared to a control group receiving counseling alone. Results of such a trial would be incredibly informative. Additionally, long-term epidemiologic studies could provide a better understanding beyond what is currently known about the natural history and heterogeneity of early stage COPD,[162-164] and epidemiologic studies evaluating prognostic markers for progression would help to identify those at greatest risk for clinical deterioration. Furthermore, long-term treatment RCTs of asymptomatic and minimally symptomatic screen-detected patients with minimal loss to followup would help to inform the discussion around the net benefits of screening.

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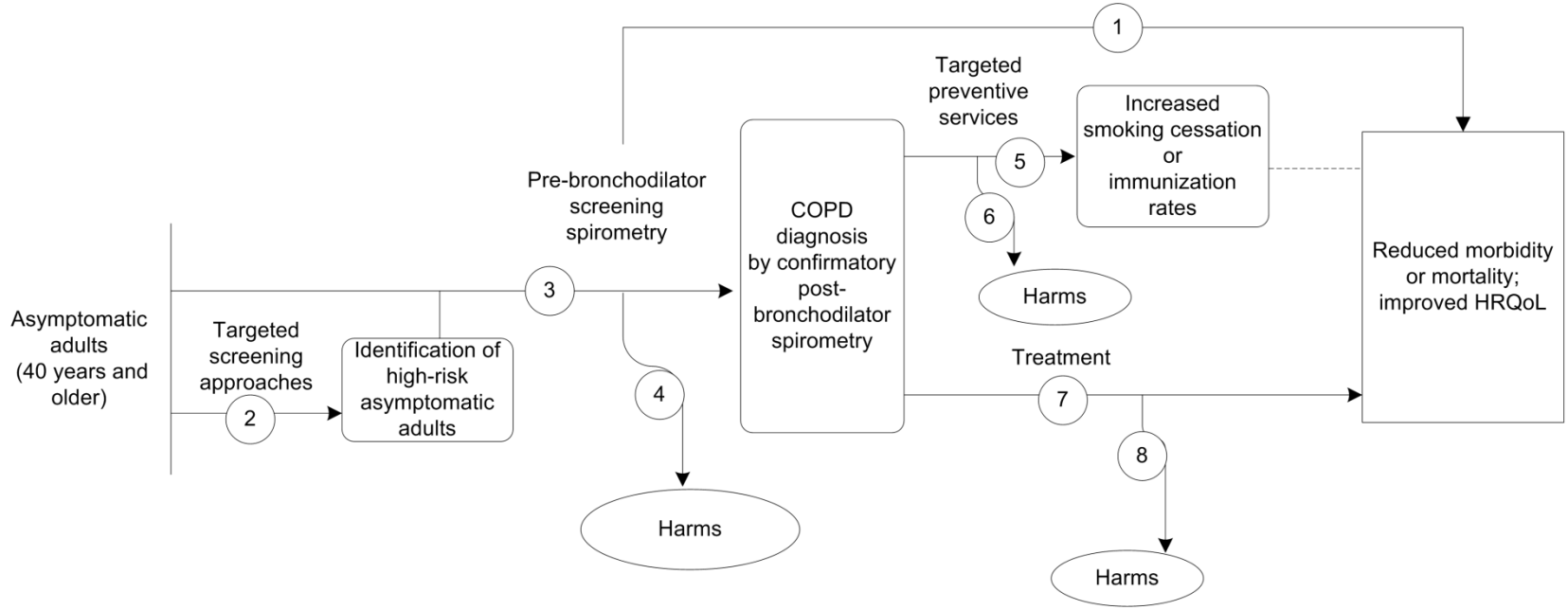
Figure 1. Analytic Framework



Abbreviations: COPD = chronic obstructive pulmonary disease; HRQoL = health-related quality of life.

Table 1. Classification of Severity as Defined by Global Initiative for Chronic Obstructive Lung Disease (GOLD)[6]

COPD Severity	FEV_1 Percent Predicted
Mild	FEV_1 ≥80% predicted
Moderate	FEV_1 ≥50% predicted but <80% predicted
Severe	FEV_1 ≥30% predicted but <50% predicted
Very severe	FEV_1 <30% predicted

Table 2. Search Summary and Rationale for Search Dates

Key Question	Search Dates	Rationale
1	January 2005 – January 31, 2015	Bridging from previous USPSTF review
2 to 4	January 2000 – January 31, 2015	Based on introduction of the requirement for post-bronchodilator diagnostic testing in the GOLD 2001 guidelines
5 and 6 (smoking)	January 2012 – January 31, 2015	Building off a recently published evidence review[100]
5 and 6 (immunization)	Database inception – January 31, 2015	New key question with no previous reviews to build from
7 and 8	January 2010 – January 31, 2015	Building on two recently published reviews on COPD treatment[101,102]

Table 3. Study and Baseline Characteristics for Externally Validated COPD Prescreening Questionnaires

Screening Instrument	Study, Year Quality	Country	N Screened N Analyzed (%)	Selection Criteria	Age, mean	% Female	% Smokers	% Preexisting Respiratory Diagnosis	Reference Standard
CDQ	Stanley, 2014[115] Fair	Australia	1,631 1,054 (64.6)	Aged 40-85 yrs; former or current smokers with no previous diagnosis of COPD or other obstructive lung disease. Recruitment setting/strategy: patients from a case-finding recruitment group for an RCT, 36 primary care centers.	61.0	48.2 [c]	Current: 22.3 Former: 77.7 [c] Mean pack years: 24.1	0	Post-BD spirometry‡ (FEV_1/FVC <0.7)
CDQ (RHSQ)	Dirven, 2013[110] Fair	Netherlands	293 39 (78.0)†	Aged 40-70 yrs; no previous diagnosis of respiratory disease, no use of oxygen supplementation, no COPD screening in last five years. Recruitment setting/strategy: 10 general practices, strategy NR	NR	NR	NR Mean pack Years: NR	0	Post-BD spirometry (FEV_1/FVC <0.7) plus physician's clinical evaluation
CDQ	Frith, 2011[39] Good	Australia	237 201 (84.8)	Aged ≥ 50 yrs; current or former smokers with no previous diagnosis of obstructive or non-obstructive lung disease and no treatment of for obstructive lung disease in the past year; without symptoms of unstable heart disease or contraindications to spirometry. Recruitment setting/strategy: patients recruited from primary care visits, or local newspaper advertising, strategy NR.	61.0§	31.0 [c]§	Current: 45.0§ Former: 55.0§ Mean pack years: 39§	0§	Post-BD spirometry‡ (FEV_1/FVC <0.7) and reversibility ≤200 mL and ≤12% from baseline pre-BD FEV_1

Table 3. Study and Baseline Characteristics for Externally Validated COPD Prescreening Questionnaires

Screening Instrument	Study, Year Quality	Country	N Screened N Analyzed (%)	Selection Criteria	Age, mean	% Female	% Smokers	% Preexisting Respiratory Diagnosis	Reference Standard
CDQ (IPAG)	Sichletidis, 2011[36] Fair	Greece	1,250 1,078 (86.2)	Aged >40 yrs; no medically confirmed diagnosis of obstructive lung disease, medical history of any other pulmonary disease, thoracic surgery in past 6 months, acute respiratory infection, or uncontrolled cardiac disease. Recruitment setting/ strategy: Primary care clinics of 50 general practitioners, the first 50 patients aged 40 years and over seen in the primary care clinic.	65.3	42.9 [c]	Current/former: 48.8 Mean pack years: 19.5 [c]	0	Post-BD spirometry‡ (FEV_1/FVC <0.7)
CDQ	Kotz, 2008[89] Good	Netherlands	826 676 (81.8)	Aged 40-70 yrs; current smokers with ≥ 10 pack-year history who were motivated to quit smoking with at least one respiratory symptom (cough, sputum, shortness of breath); without spirometry in past 12 months or previous respiratory diagnosis. Recruitment setting/ strategy: general population recruited through advertising in newspapers, flyers, posters, and mailings. Patients also recruited during primary care visits.	52.3	41.3 [c]	100 Mean pack years: 40.4	0	Post-BD spirometry‡ (FEV_1/FVC <0.7)

Table 3. Study and Baseline Characteristics for Externally Validated COPD Prescreening Questionnaires

Screening Instrument	Study, Year Quality	Country	N Screened N Analyzed (%)	Selection Criteria	Age, mean	% Female	% Smokers	% Preexisting Respiratory Diagnosis	Reference Standard
LFQ	Mintz, 2011[111] Fair	US	1,288 849 (65.9)*	Age ≥ 30 yrs; current for former smokers with ≥ 10 pack-year history with no previous diagnosis of substantial lung conditions or regular use of respiratory medications in previous 4 weeks. Recruitment setting/strategy: 36 primary care centers, strategy NR	54.0 [c]	50.6 [c]	Current: 59.0 [c] Former: 41.0 [c] Mean pack years: 33.4	NR	Post-BD spirometry‡ (FEV_1/FVC <0.7)
COPD-PS	Tsukuya, 2015 Fair	Japan	2,643 2,357 (89.2)	Age 40-70 yrs; no previous diagnosis of asthma or lung resection. Recruitment setting/ strategy: town-wide health screening	61.0 [c]	56.6 [c]	Current: 16.8 [c] Former: 26.0 [c] Mean pack years: 13.0 [c]	NR	Post-BD spirometry (FEV_1/FVC <0.7)

* Only a subset of those who screened negative on the LFQ was invited to spirometry.
† Only those who scored in the high risk category of the CDQ were invited to undergo spirometry. 39 of 50 (78%) screen positive patients underwent diagnostic testing.
‡ Spirometry required to meet the criteria of the American Thoracic Society/European Respiratory Society task force on standardization of lung function testing[108,109]
§ Baseline information based on 204 patients with spirometry, not 201 patients with CDQ results

Abbreviations: BD = bronchodilator; c = calculated; CDQ = COPD Diagnostic Questionnaire; COPD = Chronic Obstructive Pulmonary Disease; FEV_1= forced expiratory volume in 1 second; FVC = forced vital capacity; IPAG = International Primary Care Airways Guidelines; LFQ = Lung Function Questionnaire; mL = milliliter; N = number; NR = not reported; RCT = randomized controlled trial; RHSQ = Respiratory Health Screening Questionnaire; US = United States; yrs = years.

Table 4. Screening Yield for Externally Validated COPD Prescreening Questionnaires

Tool	Study, Year Quality	Population	Incomplete questionnaire, (%) Invalid or incomplete spirometry, (%)	COPD Prevalence in Population ([TP+FN]/N analyzed), (%) Mild to Moderate diagnoses, (%)	Cutoff	Screen positives ([TP+FP]/N analyzed), (%)
CDQ	Stanley, 2014[115,116] Fair	Current or former smokers	178/1631 (10.9) 399/1631 (24.4)‖	138/1054 (13.1) 128/138 (92.7) §	Intermediate/high likelihood (>16.5)	597/1054 (56.6)§
					High likelihood (>19.5)	361/1054 (34.3)§
	Dirven, 2013[110] Fair	General population	NR	NR	High likelihood (>19.5)	50/293 (17.1)* §
	Frith, 2011[39] Good	Current or former smokers	3/233 (1.3) 29/233 (12.4)¶	57/204 (27.9)§ 54/57 (94.7)§	Intermediate/high likelihood (>16.5)	NR
					High likelihood (>19.5)	NR
	Sichletidis, 2011[36] Fair	Smokers & nonsmokers from primary care	NR 172/1250 (13.8)#	111/1078 (10.3) 93/111 (83.8)§	Intermediate/high likelihood (>16.5)‡	594/1078 (55.1)§
					High likelihood (>19.5)‡	302/1078 (28.0)§
				90/522 (17.2)§ NR	Intermediate/high likelihood (>16.5)‡ **in smokers only**	347/522 (66.5)§
	Kotz, 2008[89] Good	Current smokers	40/826 (4.8) 110/826 (13.3)¶	278/676 (41.1)§ 261/278 (93.9)§	Intermediate likelihood (>16.5)	549/676 (81.2)§
					High likelihood (>19.5)	366/676 (54.1)§
LFQ	Mintz, 2011[111] Fair	Current or former smokers	NR 376/1225 (30.7)† ‖	NR† NR	≤ 18	1216/1575 (77.2)§
COPD-PS	Tsukuya, 2015 Fair	General Population	NR**	153/2357 (6.5) NR (94.1)	≥ 4	700/2357 (29.7)§
					≥ 5	509/2357 (21.6)§

* Only screen positive patients underwent diagnostic spirometry. 39 of 50 screen positive patients underwent diagnostic testing.
† Patients recruited for diagnostic spirometry included all screen positive patients (LFQ≤18) and a subset of screen negative patients (49 of 359).
‡ Study used the cutpoints of ≥ 17 points for intermediate likelihood and ≥ 20 points for high likelihood.
§ Calculated
‖ Not meeting quality criteria
¶ Spirometry invalid, incomplete, not undertaken
# Refused or unacceptable spirometry
** 159/2643 (6.0%) were excluded for poor study data (details not given)

Abbreviations: CDQ = COPD Diagnostic Questionnaire; COPD = Chronic Obstructive Pulmonary Disease; FN = false negative; FP = false positive; KQ = key question; N = number; NR = not reported; TP = true positive.

Table 5. Screening Yield for Derivation and Internal Validation Studies for COPD Prescreening Questionnaires With External Validation

Questionnaire	# of questions Risk factors/ symptoms addressed	Original Development Population	% in sample with pre-existing COPD dx	Reference Standard	Internal Validation	N analyzed % with spirometry dx COPD	Initial Sensitivity Specificity	AUC	% screened positive	COPD severity identified by questionnaire
CDQ Price, 2006[94] Price, 2006[95]	8 Age, smoking history, BMI, weather-affected cough, phlegm without a cold, morning phlegm, wheeze, history of allergies	US/UK patients age 40+ current and former smokers from primary care without respiratory disease	0%	PostBD FEV_1/FVC <0.7	Price 2006a[94] Split sample (7:3)	818 19%	Price 2006a[94] 80.4% 72.0% Price 2006n[95] Cutpoint* 16.5 Sensitivity: 80.4% Specificity: 57.5% Cutpoint* 19.5 Sensitivity: 58.7% Specificity: 77.0%	0.8158	Price 2006b[95] Proportion of population in each zone: High likelihood: 29.7% Intermediated likelihood: 19.9% Low likelihood: 50.4%	NR
LFQ Yawn, 2010[86] Hanania, 2010[93]	5 Age; smoking history; presence of wheeze, dyspnea, and phlegm	Yawn 2010[86] NHANES III data, patients with self-reported chronic bronchitis Hanania 2010[93] US family practice patients age 40+	Yawn 2010[86] 51%† Hanania 2010[93] NR	PreBD FEV_1/FVC <0.7	None	Yawn 2010[86] 387 51% Hanania 2010[93] 837 18.6%	Yawn 2010[86] 73.2%‡ 58.2%‡ Hanania 2010[93] 82.6% 47.8%	Yawn 2010[86] 0.720 Hanania 2010[93] 0.652	NR	NR
COPD-PS Martinez, 2008[88]	5 Shortness of breath, presence of phlegm and/or mucus, functional limitations due to breathing problems, smoking history, age	US, general practice patients age 35+	38.2%	PostBD FEV_1/FVC <0.7	1000 bootstrap samples generated from original data set (N=697)	295 38.4%	Continuous score† 59.6% 83.2%	Continuous score: 0.81	NR	NR

* Numbers are switched from the data in Price 2006 because the direction of the sensitivity and specificity indicate that the cutpoints are mislabeled in table 3[95]
† 100 percent of patients had self-reported chronic bronchitis, 51% had airflow obstruction confirmed by pre-bronchodilator spirometry
‡ Sensitivity and specificity for detecting airflow obstruction

Abbreviations: BD = bronchodilator; BMI = body mass index; CDQ = COPD Diagnostic Questionnaire; COPD = Chronic Obstructive Pulmonary Disease; dx= diagnosed; FEV_1= forced expiratory volume in 1 second; FVC = forced vital capacity; LFQ = Lung Function Questionnaire; N = number; NHANES III = The third National Health and Nutrition Examination Survey; NR = not reported; UK = United Kingdom; US = United States

Table 6. Screening Yield for Derivation and Internal Validation Studies for COPD Prescreening Questionnaires Without External Validation

Questionnaire	# of questions Risk factors/symptoms addressed	Original Development Population	% in sample with pre-existing COPD dx (self-report)	Reference Standard	Internal Validation	N analyzed % with spirometry dx COPD	Initial Sensitivity Specificity	AUC	% screened positive	COPD severity identified by questionnaire
Raghavan et al (based on CAT) Raghavan, 2012[113]	3 Age, smoking status (current and previous), symptoms of breathlessness, phlegm	Ontario, Canada general population age 40+	NR	PreBD FEV_1/FVC <0.7	1000 bootstrap samples generated from original data set	532 13.9%	77.6% 64.9%	0.772	NR	NR
Buffels Buffels, 2004[37]	5 Cough, difficulty breathing, wheezing, allergies/hay fever	Belgian patients 35-70 from general practice without use of BDs or steroids	0%‡	PreBD FEV_1/FVC <0.885 (men), <0.893 (women)	None	2,923 7.4%	58%§ 78%§	NR	23%	Mild: 39% Moderate: 51% Severe/Very severe: 9%/<1%
CFQ Hill 2011[114]	5 Cough, phlegm and/or sputum, shortness of breath, wheezing, frequent colds	Ontario, Canada general practice smokers age 40+; 20 pack-years or more smoking history	10.9%	PostBD FEV_1/FVC <0.7, FEV_1 <0.8	None	996 20.7%	NR	0.6233	27.6%ǁ	NR

* Only individuals who screened positive on the COPD-PS were given diagnostic spirometry
† Examined multiple score cutoffs
‡ Based on no reported use of pulmonary medications
§ Sensitivity and specificity of detecting COPD or asthma
ǁ Score ≥3

Abbreviations: BD = bronchodilator; CAT = COPD Assessment Test; CFQ = Case Finding Questionnaire; COPD = Chronic Obstructive Pulmonary Disease; COPD-PS = COPD population screener; dx= diagnosed/diagnosis; FEV_1= forced expiratory volume in 1 second; FVC = forced vital capacity; N = number; NR = not reported; UK = United Kingdom; US = United States.

Table 7. Diagnostic Accuracy of the COPD Diagnostic Questionnaire (CDQ)

Study	Population	Cut-off A (16.5)				Cut-off B (19.5)				AUC
		Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	
Stanley, 2014[115]	Current or former smokers	80 (72 to 86)‡	47 (44 to 50)‡	18 (15 to 22)‡	94 (91 to 96)‡	63 (55 to 71)‡	70 (67 to 73)‡	24 (20 to 29)‡	93 (91 to 94)‡	0.71
Dirven, 2013*[110]	General population	NR	NR	NR	NR	NR	NR	23 (12 to 38)	NR	NR
Frith, 2011[39]	Current or former smokers	91 (80 to 97)	37 (29 to 45)	36 (28 to 44)	91 (81 to 97)	71 (58 to 83)	62 (54 to 70)	42 (32 to 53)	85 (77 to 91)	0.72
Sichletidis, 2011[36] †	Smokers & nonsmokers from primary care	91 (85 to 95)‡	49 (46 to 52)‡	17 (14 to 20)‡	98 (96 to 99)‡	72 (63 to 80)‡	77 (74 to 80)‡	26 (22 to 32)‡	96 (94 to 97)‡	NR
Sichletidis, 2011[36]	Smokers only	93	39	24	97	NR	NR	NR	NR	NR
Kotz, 2008[89]	Current smokers	89 (85 to 92)‡	24 (20 to 29)‡	45 (41 to 49)‡	76 (68 to 83)‡	66 (60 to 71)‡	54 (49 to 59)‡	50 (45 to 55)‡	69 (64 to 74)‡	0.65

* Only screen positive patients underwent diagnostic spirometry. 39 of 50 screen positive patients underwent diagnostic testing.
† Study used the cutpoints of ≥ 17 points for intermediate likelihood and ≥ 20 points for high likelihood.
‡ Calculated

Abbreviations: AUC = area under the curve; CI = confidence interval; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.

Table 8. Diagnostic Accuracy of the Lung Function Questionnaire (LFQ)

Study	Population	Cut-off ≤ 18				AUC
		Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	
Mintz, 2011[111]	Current or former smokers	88 (75 to 94)*†	25 (22 to 28)*†	21 (18 to 24)*†	90 (78 to 97)*†	NR

* Used the Beggs and Greenes method to adjust for lack of spirometric verification in all subjects[165]
† Calculated

Abbreviations: AUC = area under the curve; CI = confidence interval; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.

Table 9. Diagnostic Accuracy of the COPD-Population Screener (COPD-PS)

Study	Population	Cut-off A (4)				Cut-off B (5)				AUC
		Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	
Tsukuya, 2015	General Population	67 (60 to 74)*	73 (71 to 75)*	15 (12 to 17)*	97 (96 to 98)*	35 (27 to 42)*	79 (78 to 81)*	10 (8 to 13)*	95 (93 to 96)*	0.75

* Calculated

Abbreviations: AUC = area under the curve; CI = confidence interval; COPD-PS= COPD Population Screener; NPV = negative predictive value; PPV = positive predictive value.

Table 10. Study and Baseline Characteristics for Pulmonary Function Screening Tests

Screening Measure	Study, Year Quality	Country	N Screened N Analyzed (%)	Selection Criteria	Age, mean	% Female	% Smokers	% Preexisting Respiratory Diagnosis	Reference Standard
PEF	Jithoo, 2013[67] Fair	International (14 BOLD countries*)	10,712 9,390 (87.6)	Age ≥40 years; non-institutionalized. Recruitment setting/strategy: general population patients participating in the BOLD study.	56.1	52.3	57.2 [c] Mean pack years: 26.6 (males), 19.3 (females)	Asthma: 12.3 COPD: 7.4‖	Post-BD spirometry‡ (FEV_1/FVC <LLN *and* FEV_1 <80% predicted)#
PEF	Perez-Padilla 2009[91] Fair	International (17 BOLD/ PLATINO countries§)	NR 13,708 (NR)	Aged ≥40 years; non-institutionalized. Recruitment setting/ strategy: general population patients participating in the BOLD/ PLATINO studies.	56.0	55.5	Ever smokers: 45.2 Mean pack years: 22.7	Unknown, but some patients with preexisting disease	Post-BD spirometry (FEV_1/FVC <0.7)
PreBD FEV_1/FEV_6 <0.7 (using PiKo-6 hand-held flow meter)	Frith, 2011[39] Good	Australia	237 204 (86.1)	Aged ≥50 years; current or former smokers with no previous diagnosis of obstructive or nonobstructive lung disease and no treatment for obstructive lung disease in the past year; without symptoms of unstable heart disease or contraindications to spirometry. Recruitment setting/ strategy: 4 primary care centers, recruited on prescheduled study days or from local newspaper ads.	61.0	31.0 [c]	Current: 45.0 Former: 55.0 Mean pack years: 39	0	Post-BD spirometry‡ (FEV_1/FVC <0.7) and reversibility ≤200 mL and ≤12% from baseline pre-BD FEV_1
PreBD FEV_1/FEV_6 <0.7 (using COPD-6 hand-held mini-spirometer	Thorn, 2012[118] Fair	Sweden	NR 305 (NR)	Aged 45-85; smoking history of ≥15 pack-years. Recruitment setting/ strategy: 21 primary care clinics, consecutive patient recruitment.	61.2	56.7	100 Mean pack years: 30.3	NR	Post-BD spirometry‡ (FEV_1/FVC <0.7)
PostBD FEV_1/FEV_6 <0.7 (using PiKo-6 hand-held flow meter)	Sichletidis, 2011[36] Fair	Greece	1,250 1,078 (86.2)	Aged >40 years; no medically confirmed diagnosis of obstructive lung disease or medical history of any other pulmonary disease, thoracic surgery in past 6 months, acute respiratory infection, or uncontrolled cardiac disease. Recruitment setting/strategy: primary care clinics of 50 general practitioners, the first 50 patients aged >40 years seen in the clinic.	65.3	42.9 [c]	Current/former: 48.8 Mean pack years: 19.5 [c]	0	Post-BD spirometry‡ (FEV_1/FVC <0.7)

* China, Turkey, Austria, Iceland, South Africa, Poland, Germany, Norway, Canada, Philippines, USA, Australia, United Kingdom, Sweden

‡ Spirometry required to meet the criteria of the American Thoracic Society/European Respiratory Society task force on standardization of lung function testing[108,109]

Table 10. Study and Baseline Characteristics for Pulmonary Function Screening Tests

[§]PLATINO: Conducted in 5 Latin American cities: Sao Paulo, Brazil, Mexico City, Mexico, Montevideo, Uruguay, Santiago de Chile, and Caracas; Additionally, 12 sites from BOLD were used: Guangzhou, China; Adana, Turkey; Salzburg, Austria; Hannover, Germany; Kracow, Poland; Sydney, Australia; Reykjavik, Iceland; Vancouver, BC, Canada; Lexington, Kentucky, USA; Manila, the Philippines; Cape Town, South Africa; and Bergen, Norway.
‖ Ever told by a health care provider they had chronic bronchitis, emphysema, or COPD
Mild disease is classified as disease negative based on this definition

Abbreviations: BD = bronchodilator; BOLD = Burden of Obstructive Lung Disease; COPD = Chronic Obstructive Pulmonary Disease; FEV_1= forced expiratory volume in 1 second; FEV_6= forced expiratory volume in 6 seconds; FVC = forced vital capacity; LLN = lower limit of normal; mL = milliliter; N = number; NR = not reported; PLATINO = Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar; yrs = years.

Table 11. Diagnostic Accuracy of Pulmonary Function Screening Tests, Sorted by Index Test

Study, Year Quality	Population	Index Test	Index Test Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC
Jithoo, 2013[67] Fair	General population	PEF (L/s/m^2)	<2.2 L/s/m^2	84* (81 to 86)¶	84* (83 to 85)¶	31* (29 to 33)¶	98* (98 to 99)¶	NR
			<1.8 L/s/m^2	64* (60 to 67)¶	95* (95 to 96)¶	55* (51 to 58)¶	97* (96 to 97)¶	NR
			<1.3 L/s/m^2	31* (28 to 34)¶	99* (99 to 100)¶	83* (79, 87)¶	94* (94, 95)¶	NR
Perez-Padilla 2009[91] Fair	General population	PEF (L/s/m^2) in low risk patients	<80% predicted	NR	NR	NR	NR	0.66
		PEF (L/s/m^2) in increased risk patients‡	<70% predicted	GOLD Stages III-IV: 96 (95 to 96) GOLD Stage II: 54 (53 to 54)	NR	NR	GOLD Stages III-IV: 99.9 (99.9 to 99.9) GOLD Stage II: 97 (96 to 97)	GOLD Stages I-IV (high risk): 0.76
			<80% predicted	GOLD Stages III-IV: 97 (96 to 96) GOLD Stage II: 70 (70 to 71)	NR	NR	GOLD Stages III-IV: 99.9 (99.9 to 99.9) GOLD Stage II: 98 (97 to 98)	
Frith, 2011[39] Good	Current or former smokers	PreBD FEV_1/FEV_6	FEV_1/FEV_6 <0.70	51 (37 to 64)	93 (87 to 96)	73 (56 to 85)	83 (76 to 88)	0.85
			FEV_1/FEV_6 <0.75	81 (68 to 90)	71 (63 to 79)	52 (41 to 63)	91 (84 to 95)	
Thorn, 2012[118 #] Fair	Current or former smokers	PreBD FEV_1/FEV_6	FEV_1/FEV_6 <0.70	53 (42 to 64)¶	90 (85 to 93)¶	63 (51 to 74)¶	85 (80 to 89)¶	0.84
			FEV_1/FEV_6 <0.73	79 (69 to 87)¶	80 (75 to 85)¶	58 (48 to 67)¶	92 (88 to 95)¶	
			FEV_1/FEV_6 <0.75	86 (77 to 92)¶	72 (66 to 78)¶	51 (43 to 60)¶	94 (89 to 97)¶	
Sichletidis, 2011[36] Fair	Smokers & nonsmokers from primary care	PostBD FEV_1/FEV_6	FEV_1/FEV_6 <0.70	80 (72 to 87)¶	95 (93 to 96)¶	64 (56 to 72)¶	98 (97 to 99)¶	NR
		PostBD FEV_1/FEV_6 in **smokers only**	FEV_1/FEV_6 <0.70	80	94	75	96	NR

*Moderate or severe disease only
‡Considered increased risk of they met any of the following criteria: 'usually' coughing or bringing up phlegm, wheezing in the last year, and dyspnea on exertion (Medical Research Council [MRC] Dyspnea Scale score >1), more than 10 pack-years of smoking, more than 200 hour-years of exposure to biomass smoke or coal smoke, more than 5 years of workplace exposure to dust or smoke, or a previous medical diagnosis of asthma, COPD, chronic bronchitis or emphysema.
¶Calculated
#Reports post-testing dizziness (n=1), chest pain (n=1), shortness of breath (n=1)

Abbreviations: AUC = area under the curve; BD = bronchodilator; CI = confidence interval; FEV_1= forced expiratory volume in 1 second; FEV_6= forced expiratory volume in 6 seconds; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; L/s/m^2 = liters per second per meters squared; NPV = negative predictive value; NR = not reported; PEF = peak expiratory flow; PPV = positive predictive value.

Table 12. Screening Yield of Pulmonary Function Screening Tests, Sorted by Index Test

Study, Year Quality	Population	Index Test	Incomplete index test, (%) Incomplete reference spirometry, (%)	COPD Prevalence in Population ([TP+FN]/N analyzed), (%) Mild to Moderate diagnoses, (%)	Index Test Cutoff	Screen positives ([TP+FP]/N analyzed), (%)
Jithoo, 2013[67]	General population	PEF (L/s/m^2)	711/10,712 (6.6)* †	756/9,390 (8.1)†	<2.2 L/s/m^2	2033/9390 (21.7)§
					<1.8 L/s/m^2	881/9390 (9.4)§
Fair			711/10,712 (6.6)* †	425/756 (56.2)‡	<1.3 L/s/m^2	282/9390 (3.0)§
Perez-Padilla 2009[91]	General population	PEF (L/s/m^2) in low risk patients	NR	244/3092 (7.9)	<80% predicted	275/3092 (8.9)§
			NR	238/244 (97.5)§		
Fair		PEF (L/s/m^2) in increased risk patients‖		2070/10616 (19.5)§	<70% predicted	NR
					<80% predicted	2293/10616 (21.6)§
				1847/2070 (89.2)§		
Frith, 2011[39]	Current or former smokers	PreBD FEV_1/FEV_6	NR	57/204 (27.9)§	FEV_1/FEV_6 <0.70	39/204 (19.1)§
Good			29/233 (12.4)¶	54/57 (94.7)§	FEV_1/FEV_6 <0.75	88/204 (43.1)§
Thorn, 2012[118]	Current or former smokers	PreBD FEV_1/FEV_6	NR	77/305 (25.2)	FEV_1/FEV_6 <0.70	65/305 (21.3)§
			NR	76/77 (98.7)§	FEV_1/FEV_6 <0.73	106/305 (34.8)§
Fair					FEV_1/FEV_6 <0.75	129/305 (42.3)§
Sichletidis, 2011[36]	Smokers & nonsmokers from primary care	PostBD FEV_1/FEV_6	NR 172/1250 (13.8)#	111/1078 (10.3)	FEV_1/FEV_6 <0.70	139/1078 (12.9)§
				93/111 (83.8)§		
Fair		PostBD FEV_1/FEV_6 in **smokers only**		90/522 (17.2)§	FEV_1/FEV_6 <0.70	98/522 (18.8)§
				NR		

*Poor quality spirometry
†Moderate or severe disease only
‡Moderate disease only
§Calculated
‖Considered increased risk of they met any of the following criteria: 'usually' coughing or bringing up phlegm, wheezing in the last year, and dyspnea on exertion (Medical Research Council [MRC] Dyspnoea Scale score >1), more than 10 pack-years of smoking, more than 200 hour-years of exposure to biomass smoke or coal smoke, more than 5 years of workplace exposure to dust or smoke, or a previous medical diagnosis of asthma, COPD, chronic bronchitis or emphysema.
¶ Spirometry invalid, incomplete, not undertaken
# Refused or unacceptable spirometry

Abbreviations: BD = bronchodilator; c = calculated; COPD = Chronic Obstructive Pulmonary Disease; 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; KQ = key question; L/s/m^2 = liters per second per meters squared; ml = milliliter; N = number; NR = not reported; PEF = peak expiratory flow; TP = true positive.

Table 13. Screening Harms for Externally Validated COPD Prescreening Questionnaires

Tool	Study, Year Quality	Population	Cutoff	False Positive Rate (FP/FP+TN)	Proportion of COPD diagnoses missed (FN/TP+FN), (%)
CDQ	Stanley, 2014[115] Fair	Current or former smokers	Intermediate/high likelihood (>16.5)	487/916 (53.2)*	28/138 (20.3)*
			High likelihood (>19.5)	274/916 (29.9)*	51/138 (37.0)*
	Dirven, 2013[110] Fair	General population	High likelihood (>19.5)	NR	NR
	Frith, 2011[39] Good	Current or former smokers	Intermediate/high likelihood (>16.5)	NR (73)*	NR (9)*
			High likelihood (>19.5)	NR (38)	NR (29)
	Sichletidis, 2011[36] Fair	Smokers & nonsmokers from primary care	Intermediate/high likelihood (>16.5)‡	493/967 (51.0)*	10/111 (9.0)*
			High likelihood (>19.5)‡	222/967 (23.0)*	31/111 (27.9)*
			Intermediate/high likelihood (>16.5)‡ **in smokers only**	263/432 (60.9)*	6/90 (6.7)*
	Kotz, 2008[89] Good	Current smokers	Intermediate likelihood (>16.5)	301/398 (75.6)*	30/278 (10.8)*
			High likelihood (>19.5)	183/398 (46.0)*	95/278 (34.2)*
LFQ	Mintz, 2011[111] Fair	Current or former smokers	≤18	NR†	NR†
COPD-PS	Tsukuya, 2015	General population	≥4	597/2,204 (27.1)*	50/153 (32.7)*
			≥5	456/2,204 (20.7)*	100/153 (65.4)*

* Calculated

† Patients recruited for diagnostic spirometry included all screen positive patients (LFQ≤18) and a subset of screen negative patients (49 of 359). 5/49 patients who were false negatives (10.2%)

‡ Study used the cutpoints of ≥ 17 points for intermediate likelihood and ≥ 20 points for high likelihood.

Abbreviations: CDQ = COPD Diagnostic Questionnaire; COPD = Chronic Obstructive Pulmonary Disease; FN = false negative; FP = false positive; KQ = key question; LFQ = Lung Function Questionnaire; NR = not reported; TP = true positive.

Table 14. Screening Harms for Pulmonary Function Screening Tests, Sorted by Index Test

Study, Year Quality	Population	Index Test	Index Test Cutoff	False Positive Rate (FP/FP+TN)	Proportion of COPD diagnoses missed (FN/TP+FN), (%)
Jithoo, 2013[67]	General Population	PEF (L/s/m^2)	<2.2 L/s/m^2	1399/8634 (16.2)[§ ¶]	122/756 (16.1)[¶]
			<1.8 L/s/m^2	399/8634 (4.4)[§ ¶]	274/756 (36.2)[¶]
Fair			<1.3 L/s/m^2	47/8634 (0.5)[§ ¶]	521/756 (68.9)[¶]
Perez-Padilla 2009[91]	General Population	PEF (L/s/m^2) in low risk patients	<80% predicted	NR	NR
		PEF (L/s/m^2) in increased risk patients[‖]	<70% predicted	NR	NR
Fair			<80% predicted	NR	NR
Frith, 2011[39¶]	Current or former smokers	PreBD FEV_1/FEV_6	FEV_1/FEV_6 < 0.70	11/147 (7.5)[¶]	28/57 (49.1)[¶]
			FEV_1/FEV_6 < 0.75	42/147 (28.6)[¶]	11/57 (19.3)[¶]
Good					
Thorn, 2012[118]	Current or former smokers	PreBD FEV_1/FEV_6	FEV_1/FEV_6 < 0.70	24/228 (10.5)[¶]	36/77 (46.8)[¶]
			FEV_1/FEV_6 <0.73	45/228 (19.7)[¶]	16/77 (20.8)[¶]
Fair			FEV_1/FEV_6 <0.75	63/228 (27.6)[¶]	11/77 (14.3)[¶]
Sichletidis, 2011[36]	Smokers & nonsmokers from primary care	PostBD FEV_1/FEV_6	FEV_1/FEV_6 < 0.70	50/967 (5.2)[¶]	22/111 (19.8)[¶]
		PostBD FEV_1/FEV_6 in **smokers only**	FEV_1/FEV_6 < 0.70	26/432 (6.0)[¶]	18/90 (20.0)[¶]
Fair					

§ Mild disease counted as a false positive
‖Considered increased risk of they met any of the following criteria: 'usually' coughing or bringing up phlegm, wheezing in the last year, and dyspnea on exertion (Medical Research Council [MRC] Dyspnoea Scale score >1), more than 10 pack-years of smoking, more than 200 hour-years of exposure to biomass smoke or coal smoke, more than 5 years of workplace exposure to dust or smoke, or a previous medical diagnosis of asthma, COPD, chronic bronchitis or emphysema.
¶Calculated

Abbreviations: BD = bronchodilator; COPD = Chronic Obstructive Pulmonary Disease; FEV_1= forced expiratory volume in 1 second; FEV_6= forced expiratory volume in 6 secons; FN = false negative FP = false positive; FVC = forced vital capacity; KQ = key question; L/s/m^2 = liters per second per meters squared; ml = milliliter; NR = not reported; PEF = peak expiratory flow; TP = true positive.

Table 15. Study Characteristics of Smoking Cessation Trials

Study, Year Quality	Country Recruitment	N Randomized	Followup	Inclusion	Exclusion	Treatment Comparison	Primary Outcome(s)	Secondary Outcome(s)
Kotz, 2009[121] Kotz, 2007[166] Kotz, 2009[124] Kotz, 2009[167] Fair	Netherlands General population (ads, flyers, posters, and mailings) and primary care practices	296	12 months	35-70 years; ≥10 pack-year history; read/speak Dutch; ≥1 respiratory symptom (cough, sputum, shortness of breath); mild or moderate COPD*; interested in quitting smoking	Prior respiratory diagnosis; spirometry in past 12 months; contraindication to nortriptyline; FEV_1 <50% predicted; FEV_1/FVC >70%	IG1: CG1 intervention plus discussion of results from spirometry, prognosis of COPD, and challenging irrational beliefs about smoking CG1: Four 40 minute medium-intensity counseling plus nortriptyline CG2: Referral to GP for smoking cessation treatment without information about spirometry results or airflow limitation	Prolonged abstinence from smoking (biochemically validated)	Nicotine dependence (FTND), respiratory health (CCQ), HRQoL (CRQ)
Sippel, 1999[122] Fair	US Primary care clinics, invitation of all smokers among routinely scheduled outpatients	205	9 months	Smokers aged 18+	Non-English-speaking patients, walk-in cases considered emergent	IG: CG intervention plus educational interpretation of spirometry and CO measurement results CG: Individual cessation plan; cessation counseling; solicitation of quit date and clinic or telephone followup at 1 and 4 weeks after quit date (for patients in preparation stage)	Smoking cessation rate (self-reported)	Quit attempts, change in motivational stage
Risser, 1990[120] Fair	US Randomly selected VA outpatients	90	12 months	Smokers participating in a general preventive intervention VA Demonstration Project	NR	CG: 50-minute educational intervention with self-help program, invitation to a 4-month (9 sessions) one-on-one skills training and counseling program IG: CG intervention plus 10-minute motivational intervention based on spirometry, CO level, and discussion of pulmonary symptoms	Smoking status (self-reported and biochemically validated)	Quit attempts

Table 15. Study Characteristics of Smoking Cessation Trials

Study, Year Quality	Country Recruitment	N Randomized	Followup	Inclusion	Exclusion	Treatment Comparison	Primary Outcome(s)	Secondary Outcome(s)
Parkes 2008[119] Fair	UK Five general practices	561	12 months	Aged ≥35 yrs; patient record indicates was a smoker within the last 12 months	Patients receiving oxygen; those with a history of lung cancer, TB, asbestosis, silicosis, bronchiectasis, or pneumonectomy	IG: Assessment interview including spirometry. Strongly encouraged to give up smoking and access local smoking cessation clinics. Patients received their "lung age"† verbally using a graphic display and were counselled that smoking cessation would help to slow down the rate of deterioration of the lung function. CG: Patients underwent an assessment interview, which included spirometry. Strongly encouraged to give up smoking and advised out to access local smoking cessation clinics. Patients received their lung function scores (FEV_1) in the mail with no further explanation. In both groups, if testing indicated asthma participants were advised to attend GP for management and GP was informed separately. When spirometry suggested restrictive lung disease, participant and GP were sent letter to advise them on further investigation and guidelines on referral to secondary care.	Smoking cessation (biochemically validated)	Change in daily consumption of cigarettes; identification of new diagnoses

Table 15. Study Characteristics of Smoking Cessation Trials

Study, Year Quality	Country Recruitment	N Randomized	Followup	Inclusion	Exclusion	Treatment Comparison	Primary Outcome(s)	Secondary Outcome(s)
McClure, 2009[123] McClure, 2009[168] McClure, 2010[169] Fair	US Community (health plan records, Quitline data, mailing list of smokers, ads)	542	12 months	Smokers; age 18+; read and write English; CO level consistent with current smoking (≥10 ppm) and an average of 15 cigarettes per day for the past year or 10 cigarettes per day for 10 years or more	Currently receiving cessation treatment; significant physical or mental impairments that prevent the use of a computer or phone or impaired comprehension ability; medical contraindication for spirometry	IG: CG intervention plus personally-tailored report with self-reported smoking-related symptoms, smoking related medical conditions, CO level and values of normal CO of non-smokers, spirometry test and results (FEV_1, FVC, FEF_{25-75}), lung age‡ for individuals with FEV_1 less than 80% predicted, graph of demonstrating the effect of smoking cessation on lung function, information on the association between smoking and various health conditions. CG: Personalized health risk report and brief (~20 minute) counseling; advice to quit smoking, smoking cessation materials, access to free phone-counseling program	Use of counseling program, 7 day point prevalent abstinence (self-reported)	Motivation to quit, quit attempts, use of other smoking cessation treatments, 30 day point prevalent abstinence (self-reported)

* Postbronchodilator $FEV_1/FVC<70\%$ and $FEV_1 \geq 50\%$ predicated

† Men: Lung age= 2.87 x height (in inches) – (31.25 x observed FEV_1 (liters) - 39.375; Women: Lung age= 3.56 x height (in inches) – (40 x observed FEV_1 (liters) - 77.28

‡ Calculated using method Morris and Temple method[155]

Abbreviations: CCQ = Clinical COPD Questionnaire; CG = control group; CO = carbon monoxide; COPD = Chronic Obstructive Pulmonary Disease; CRQ = Chronic Respiratory Questionnaire; FEF_{25-75} = average forced expiratory flow during the mid (25 - 75%) portion of the FVC; FEV_1= forced expiratory volume in 1 second; FTND = Fagerstrom Test for Nicotine Dependency; FVC = forced vital capacity; GP = general practitioner; HRQoL = healh-related quality of life; IG = intervention group; N = number; NR = not reported; ppm= parts per million; TB = tuberculosis; UK = United Kingdom; US = United States; yrs = years.

Table 16. Smoking Cessation Outcomes for Included Trials

Study, Year Quality	Study Group	N Analyzed[†]	Followup	At least 1 quit attempt, %	Self-reported Smoking Abstinence, %	Biochemically-Validated Smoking Abstinence, %	IG vs. CG	Additional Cessation Outcomes	IG vs. CG
Kotz, 2009[121] Kotz, 2007[166] Kotz, 2009[124] Kotz, 2009[167] Fair	IG	116	12 months	NR	NR	11.2	OR (95% CI): 0.88 (0.38 to 2.03)[§]	5 week abstinence (validated): 50.9% Abstinence at 5 to 26 weeks (validated): 30.2%, CG1- 23.2	5 week abstinence: OR (95% CI): 1.6 (0.95 to 2.7) p=0.08[§] Abstinence at 5 to 26 weeks: OR (95% CI): 1.43 (0.79 to 2.58); p=0.236[§]
	CG1	112	12 months	NR	NR	11.6		5 week abstinence (validated): 39.3% Abstinence at 5 to 26 weeks (validated): 23.2%	
Sippel, 1999[122] Fair	IG	103	9 months	48.0	9.0	NR	Self-reported OR (95% CI)[‡]: Any spirometry performed: 0.6 (0.2 to 1.4) Abnormal spirometry results: 0.6 (0.1 to 2.7)	At least one quit attempt during study: 48.0%	OR (95% CI): 1.6 (0.9 to 2.8)
	CG	102	9 months	36	14.0	NR		At least one quit attempt during study: 36.0%	
Risser, 1990[120] Fair	IG	45[‖]	12 months	40.0	24.4[‖]	20.0[‖]	Self-reported conservative estimate p=0.08[‖] Validated conservative estimate p=0.06[‖] Quit attempts: p=0.015	NR	NA
	CG	45[‖]	12 months	16.3	11.1[‖]	6.7[‖]		NR	
Parkes 2008[119] Fair	IG	280	12 months	NR	NR	13.6	Validated quit rate difference: 7.2% (95% CI: 2.2% to 12.1%); p=0.005	Used smoking cessation help (clinic, NRT, bupropion, acupuncture): 10.7% Cigarette consumption, Self-reported mean (SD): 11.7 (9.7)	Used smoking cessation help: p=0.2 Cigarette consumption: p=0.03
	CG	281	12 months	NR	NR	6.4		Used smoking cessation help (clinic, NRT, bupropion, acupuncture): 7.8% Cigarette consumption, Self-reported mean (SD): 13.7 (10.5)	

Table 16. Smoking Cessation Outcomes for Included Trials

Study, Year Quality	Study Group	N Analyzed†	Followup	At least 1 quit attempt, %	Self-reported Smoking Abstinence, %	Biochemically-Validated Smoking Abstinence, %	IG vs. CG	Additional Cessation Outcomes	IG vs. CG
McClure, 2009[123] McClure, 2009[168] McClure, 2010[169] Fair	IG	267	12 months#	61.5††	30 day abstinence: 0.9¶†† 7 day abstinence: 13.1¶††	NR	30 day abstinence: OR (95% CI): 0.77 (NR); p=0.34¶, 7 day abstinence: OR (95% CI): 0.86 (NR); p=0.38¶,	Motivation to quit, mean: 3.20**†† Motivation to quit (6 months), mean: 3.26**	Motivation to quit (12 months): p= 0.03
	CG	269	12 months#	62.4	30 day abstinence: 13.0¶ 7 day abstinence: 14.9¶	NR		Motivation to quit, mean: 3.42**	

*7.8% of participants stated that routinely measuring lung function in smokers would interfere with one's freedom of choice; 1.2% said it was not justified for a nurse to confront them with COPD diagnosis
†All studies assume that anyone lost to followup was a smoker
‡Adjusted for age and sex
§Adjusted for age, sex, level of education, number of previous cessation attempts, anxiety, nicotine addiction
‖This analysis includes all patients in the final analysis and assumed missing patients to be smokers. Analysis also available using data only from subjects with known followup smoking status: N analyzed IG: 32, CG: 39 (self-report); IG: 27, CG: 30 (validated); cessation: IG: 34.4%, CG: 12.8%, p= 0.03 (self-reported); IG: 33.3%, CG: 10%, p=0.03 (validated)
¶ Similar values seen in analysis using data only from subjects with known followup smoking status.
#Self-reported smoking abstinence at 6 months: 30 day abstinence: IG 6.4%, CG: 10.8%; OR (95% CI): 0.51 (NR). p= 0.04; 7 day abstinence: IG: 12.0%; CG: 14.1%; OR (95% CI): 0.77 (NR). p= 0.3; motivation to quit, mean**: IG: 3.3, CG: 3.4, p=0.12
** Measured on a five point Likert scale ranging from 1 to 5 (from 'not at all' to 'extremely'). Motivation to quit measured among smokers only.
†† No significant difference reported between smokers with impaired lung function and those with non-impaired lung function in the intervention group.

Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; N = number; NA = not applicable; NR = not reported; NRT = nicotine replacement therapy; OR = odds ratio; SD = standard deviation.

Table 17. Baseline Characteristics of Smoking Cessation Trials

Study, Year Quality	N Randomized	Age, years (mean)	Female, %	Smoking history, pack-years (mean)	Any previous quit attempt, %	Number of previous quit attempts	Lung function postBD, FEV_1 % predicted of normal (mean)	Patients with previously diagnosed COPD, %
Kotz, 2009[121] Kotz, 2007[166] Kotz, 2009[124] Kotz, 2009[167] Fair	296	54.0 [c]	37.5 [c]	43.5 [c]	NR	3.8 (mean) [c]	81.5†	0‡
Sippel, 1999[122] Fair	205	38.6 [c]	62.5 [c]	28.9 [c]	82.0 [c]	NR‡	87.0* (range: 31-141)	NR
Risser, 1990[120] Fair	90	NR	4.4 [c]	60.4	75.6 [c]	0: 24.0% 1-2: 56.0% 3+: 20.0%	NR	NR
Parkes 2008[119] Fair	561	53.0 [c]	53.8 [c]	30.7 [c]	NR§	NR	89.5	7.0 [c]
McClure, 2009[123] McClure, 2009[168] McClure, 2010[169] Fair	542	50.8	53.2	NR	10.1	1.6 (mean)	NR	NR

* Reported for intervention group only, does not report if measurements are pre or post-bronchodilator
†All had mild/moderate COPD (54% mild, 46% moderate)
‡ Patients with pre-existing respiratory disease excluded

Abbreviations: BD = bronchodilator; c = calculated; COPD = Chronic Obstructive Pulmonary Disease; FEV_1= forced expiratory volume in 1 second; N = number; NR = not reported.

Table 18. Trial Characteristics for Treatment Efficacy RCTs, All Drug Classes

Study, Year Quality	Country	N Randomized	Recruitment	Followup	Inclusion	Exclusion	Treatment Comparison	Concomitant Therapies Allowed	Primary Outcome(s) Secondary Outcome(s)
Troosters, 2014[139] Troosters, 2011[170] Fair	International	457	70 centers in 10 countries	6 months	GOLD stage II (postBD FEV_1/FVC ratio <0.7; FEV_1 ≥50 and <80% predicted; MRC dyspnea score ≥2) patients previously naïve to maintenance therapy; aged 40-80 years; smoking history of ≥10 pack-years; ability to demonstrate compliance with HandiHaler, a salbutamol exercise stress test; follow study procedures	Prior maintenance medication (LABAs, inhaled or systemic corticosteroids, theophylline, leukotriene receptor antagonists) within 6 months prior to screening; current treatment with systemic steroids; diagnosis of asthma; history of CF; upper/lower respiratory tract infection or COPD exacerbation in 6 weeks prior to or during screening	IG: tiotropium bromide (18 µg per day) CG: Placebo	Salbutamol; corticosteroids for up to 2 weeks for acute exacerbations	Change in FEV_1 Change in physical activity levels; global health assessment; adverse events; exacerbations
Decramer, 2013[125] Fair	International	4417 (Full population of original trials) NR (Stage II)	INVOLVE: NR INHANCE: NR INLIGHT-2: NR	6 months	≥40 years; moderate-to-severe COPD (FEV_1 ≥30% and <80% predicted, FEV_1/FVC <70%); smoking history of ≥20 pack-years	Recent respiratory tract infection or COPD exacerbation	CG: Placebo IG1: indacaterol (150 µg/day) IG2: indacaterol (300 µg/day) IG3: tiotropium bromide (18 µg/day) IG4: formoterol (12 µg/twice a day) IG5: salmeterol (50 µg/twice a day)	Stable ICS; SABA	Trough FEV_1 Dyspnea (TDI), Quality of Life (SGRQ)
UPLIFT Decramer 2009[127] Tashkin 2012[140] Tashkin 2008[141] Fair	International	5993 (full pop) 2739 (stage II) 1210 (FEV_1 ≥60% pred. [range 60-78%])*	490 investigational centers in 37 countries	48 months	≥40 years; smoking history of ≥10 pack-years; PostBD FEV_1 <70% predicted; FEV_1/FVC ≤70%	History of asthma, COPD exacerbation or respiratory infection within 4 weeks before screening, a history of pulmonary resection, use of supplemental oxygen for >12 hours/day, presence of a coexisting illness that could preclude participation in the study or interfere with the study results.	IG: tiotropium bromide (18 µg/day) CG: Placebo	All respiratory medications except other inhaled anticholinergic drugs	Decline in mean FEV_1 Decline in mean FVC and SVC; HRQoL; exacerbations; hospitalization; rate of death

Table 18. Trial Characteristics for Treatment Efficacy RCTs, All Drug Classes

Study, Year Quality	Country	N Randomized	Recruitment	Followup	Inclusion	Exclusion	Treatment Comparison	Concomitant Therapies Allowed	Primary Outcome(s) Secondary Outcome(s)
TORCH Jenkins, 2009[126] Calverley, 2007[138] Fair	International	Full study population: 6,184 Stage I/II: NR	42 countries, 444 centers	9 months	Current or former smokers with a history of ≥10 pack-years; aged 40 antod 80 years; confirmed diagnosis of COPD and preBD of FEV_1 <60% of predicted; required to show <10% reversibility and a preBD of FEV_1/FVC ≤0.70	Patients with a diagnosis of asthma or other nonCOPD respiratory disorder; any condition likely to cause death within 3 years; previous lung volume reduction surgery and/or lung transplantation; requirement of oxygen therapy for ≥12 hours/day; current use of oral corticosteroid therapy; hospitalization during the run-in period	IG1: salmeterol (50 µg/twice a day) IG2: fluticasone propionate (500 µg/twice a day) IG3: salmeterol/ fluticasone propionate combination (50 µg/500 µg) twice a day CG: Placebo	All medications for COPD except corticosteroids and inhaled long-acting bronchodilators	All-cause mortality Exacerbation rate; health status; lung function; adverse events
Lapperre 2009[132] Fair	The Netherlands	114	Family practices using electronic medical records and ads in local newspapers	30 months	Aged 45-75 years; current or former smokers; smoked for ≥10 pack-years; lung function levels compatible with GOLD stages II and III	Asthma; receipt of ICS within 6 months prior to randomization	IG1: fluticasone propionate (500 µg/twice a day) for the 1st 6 months and then placebo IG2: fluticasone propionate (500 µg/twice a day) for 30 months IG3: fluticasone propionate (500 µg/twice a day) plus salmeterol (50 µg/ twice a day) for 30 months CG: Placebo	Short-acting bronchodilators	Inflammatory cell counts in bronchial biopsies and induced sputum postBD spirometry; hyper-responsiveness to methachoine PC20; dyspnea score by MRC; SGRQ, CCQ

Table 18. Trial Characteristics for Treatment Efficacy RCTs, All Drug Classes

Study, Year Quality	Country	N Randomized	Recruitment	Followup	Inclusion	Exclusion	Treatment Comparison	Concomitant Therapies Allowed	Primary Outcome(s) Secondary Outcome(s)
Calverley, 2008[133] Fair	International	911 (full study) 266 (Stage II)	95 sites in 11 countries	12 months	≥40 years; current smokers who failed a smoking cessation program or former smokers who had stopped smoking ≤12 months before the study; spirometry diagnosed COPD: FEV_1/FVC ≤70%, FEV_1 30-70%, low FEV_1 reversibility (<10%).	Asthma or other significant medical illness other than COPD; exacerbation within 3 months, ventilator support in past year; lobectomy, pnuemonectomy, or lung volume reduction surgery; lung cancer in past 5 years; CPAP or oxygen use; initiation of pulmonary rehabilitation in past 3 months; treatment with chronic or prophylactic antibiotics; inability to use inhalers; <80% adherence in diary data between screening and baseline	IG1: mometasone furoate (800 µg/day) IG2: mometasone furoate (400 µg/twice a day) CG: Placebo once or twice daily	Ipratropium Bromide, theophylline, SABA, LABA	Post BD FEV_1 Exacerbations, COPD symptom scores, SGRQ, SF-36, PreBD FEV_1, FEF_{25-75}

Table 18. Trial Characteristics for Treatment Efficacy RCTs, All Drug Classes

Study, Year Quality	Country	N Randomized	Recruitment	Followup	Inclusion	Exclusion	Treatment Comparison	Concomitant Therapies Allowed	Primary Outcome(s) Secondary Outcome(s)
Tonnel, 2008[129] Fair	France	555 (full study) Stage I/II: 198	123 outpatient centers	9 months	Outpatients aged ≥40 years; clinical diagnosis of COPD (FEV_1 20-70%) and SVC ≤70%; smoking history of >10 pack years	History of asthma, allergic rhinitis, or atopy; regular use of daytime oxygen therapy; a recent respiratory tract infection (within the previous 6 weeks); a recent history of MI (within the previous 6 months); cardiac arrhythmia requiring drug therapy (within the previous year); hospitalization for heart failure or pulmonary edema (within the previous 3 years)	IG: tiotropium bromide (18 µg per day) CG: Placebo	Salbutamol delivered via metered-dose inhaler allowed as needed; theophylline preparations (excluding 24 hour preparations), mucolytics, ICS, oral steroids (<10 mg prednisone daily or equivalent) allowed if dosage was stabilized for ≥6 weeks before study entry. One 10-day course of oral steroids for treatment of exacerbations was allowed. Antibiotics as deemed necessary for treatment of exacerbations.	Percentage of patients with ≥4 units of improvement in SGRQ total score Total SGRQ and VSRQ scores; exacerbations; lung function; exacerbations; adverse events

Table 18. Trial Characteristics for Treatment Efficacy RCTs, All Drug Classes

Study, Year Quality	Country	N Randomized	Recruitment	Followup	Inclusion	Exclusion	Treatment Comparison	Concomitant Therapies Allowed	Primary Outcome(s) Secondary Outcome(s)
EUROSCOP Lofdahl 2007[142] Pauwels 1999[130] Fair	9 western European countries	1,277	39 study centers	36 months	Age 30-60; current smokers (≥5 cigarettes per day); smokes for ≥ 10 years or had a history of at least 5 pack years; postBD FEV_1 of 50-100% of the predicted normal value; ratio of preBD FEV_1 to slow vital capacity of <70%; reversibility of FEV_1 with 1 mg inhaled terbutaline of <10%; participated in 3 month smoking-cessation program but continued to smoke; demonstrated at least 75% compliance with treatment during 3 month run in period; change in FEV_1 during run-in period <15%	History of asthma; allergic rhinitis or allergic eczema; patients with a concomitant disease that could interfere with the interpretation of the study; patients used B-receptor antagonists; patients who had used oral glucocorticoids for >4 weeks during the preceding 6 months	IG: Budesonide (800 ug a day) CG: placebo	postBD FEV_1 change from BL	Severe exacerbations; adverse events

Table 18. Trial Characteristics for Treatment Efficacy RCTs, All Drug Classes

Study, Year Quality	Country	N Randomized	Recruitment	Followup	Inclusion	Exclusion	Treatment Comparison	Concomitant Therapies Allowed	Primary Outcome(s) Secondary Outcome(s)
Niewoehner, 2005[128] Good	US	1829 (full population) Stage I/II: 287	Patients at participating VA medical centers	6 months	Patients in the VA system; aged ≥40 years; a cigarette smoking history of ≥10 pack-years; clinical diagnosis of COPD; FEV_1 of ≤60% predicted and ≤70% of the FVC	Clinical diagnosis of asthma; MI within previous 6 months; a serious cardiac arrhythmia or hospitalization for heart failure within previous year; known moderate to severe renal impairment; moderate to severe symptomatic prostatic hypertrophy or bladder-neck obstruction; narrow-angle glaucoma; current radiation or chemotherapy for a malignant condition; inability to give informed consent; taking systemic corticosteroids at unstable or regular daily doses of ≥20 mg of prednisone; not fully recovered from an exacerbation for ≥30 days before first study visit	IG: tiotropium bromide (18 ug per day) CG: Placebo	Patients continued taking all other respiratory medications (including corticosteroids and LABAs), except no open-label anticholinergic broncho-dilators; primary providers were allowed to prescribe additional meds as needed (e.g., systemic steroids, antibiotics)	Percentage of patients with an exacerbation; hospitalization due to an exacerbation Time to first exacerbation; time to first hospitalization due to an exacerbation; frequencies of exacerbations; exacerbation-related health care utilization; frequencies of all-cause hospitalization; hospitalization days; results of spirometry
Lung Health Study II, 2000[134] Fair	US	1116	Patients who had participated in or been screened for the Lung Health I Study	Up to 54 months (mean: 40 months)	40 to 69 years of age; had airflow obstruction with a ratio of FEV_1/FVC of <0.70 and a value of FEV_1 that was 30 to 90% of the predicted value; current smokers or had quit within the previous 2 years	Patients with medical conditions such as cancer, recent MI, alcoholism, heart failure, insulin-dependent DM, and neuropsychiatric disorders; used bronchodilators or oral or inhaled corticosteroids in the previous year	IG: Inhaled corticosteroid (triameinolone acetoneide) given in a metered dose of 6 inhalations (100 ug per inhalation) twice a day, resulting in a total dose of 1200 ug per day CG: Placebo inhaler	NR	Rate of decline in FEV_1 after the administration of bronchodilator Respiratory symptoms; cause-specific morbidity and mortality; airway reactivity in response to methacholine; HrQOL (SF-36)

Table 18. Trial Characteristics for Treatment Efficacy RCTs, All Drug Classes

Study, Year Quality	Country	N Randomized	Recruitment	Followup	Inclusion	Exclusion	Treatment Comparison	Concomitant Therapies Allowed	Primary Outcome(s) Secondary Outcome(s)
Vestbo, 1999[131] Fair	Demark	290	Random age stratified sample from around Righospitalet in Copenhagen.	36 months	Age 30-70; Participant in the Copenhagen City Heart Study; $FEV_1/FVC<0.7$; reversibility <15% following post BD spirometry and 10 days oral prednisolone.	Long-term treatment with oral or inhaled steroids in last 6 months; pregnancy or lactation; serious systemic disease; chronic alcohol or drug use; participation in other clinical studies of COPD within 1 month of inclusion.	IG: budesonide 1200 µg/day (800 µg morning 400 µg evening) for 6 months µg; 400 µg/twice a day for 30 months CG: Placebo	Stable β_2-agnoists, theophylline, disodium chromoglycate, and mucolytics. Up to 4 weeks of oral, inhaled, or parenteral steroids for up to 3 4-week periods a year	FEV_1 decline Exacerbations

* Inclusion criteria was $FEV_1<70\%$ but 23 patients were $FEV_1>70$ (protocol violation) but included in the analysis.

Abbreviations: BL = baseline; CCQ = clinical COPD questionnaire; CF = cystic fibrosis; CG = control group; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; DM = diabetes mellitus; EUROSCOP = European Respiratory Society study on Chronic Obstructive Pulmonary Disease; FEV1/FVC = forced expiratory volume in 1 second/forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HrQOL = health-related quality of life; ICS = inhaled corticosteroids; IG = intervention group; INHANCE = INdacaterol to Help Achieve New COPD treatment Excellence; INLIGHT = INdacaterol efficacy evaLuation using 150 ug doses witH COPD paTients; INVOLVE = INdacaterol: Value in COPD: Longer Term Validation of Efficacy and Safety; LABA = long-acting beta-agonist; MI = myocardial infarction; µg = microgram; mg = milligram; MRC = Medical Research Council; N = number; NR = not reported; pop = population; postBD = post-bronchodilator; preBD = pre-bronchodilator; SABA = short-acting beta-agonist; SF-36 = short form-36; SGRQ = St. George's Respiratory Questionnaire; SVC = slow vital capacity; TDI = transition dyspnea index; TORCH = Towards a Revolution in COPD Health; UPLIFT = Understanding Potential Long-term Impacts on Function with Tiotropium; US = United States; VA = US Department of Veterans Affairs; VSRQ = visual simplified respiratory questionnaire

Table 19. Baseline Characteristics for Treatment Efficacy RCTs, All Drug Classes

Study, Year Quality	N Randomized	Age, years (mean)	Female, %	Smoking status, %	Smoking history, pack-years (mean)	Number of exacerbations in the preceding year (mean)	Lung function postbronchodilation, FEV_1 % predicted of normal (mean)	HrQOL	Exercise capacity
Troosters, 2014[139] Troosters, 2011[170] Fair	457	61.7‖	31.5‖	Current: 59.4‖	44.0‖	NR	65.7‖	WPAI: Activity impairment due to health, %: 26.8‖	Steps, number/day: 6,402.7‖ Time in age-appropriate moderate or higher activity, min/day: 20.0‖
Decramer, 2013[125] Fair	Stage II: 2353	64	32.7‖	Former: 56‖ Current: 44‖	NR	At least 1: 4.6%‖	64.0‖	SGRQ total score mean: 41.2‖	NR
UPLIFT Decramer 2009[127] Tashkin 2012[140] Tashkin 2008[141] Fair	Stage II: 2739 FEV_1 ≥60%: 1210	Stage II: 64.5‖ FEV_1 ≥60%: 64	Stage II: NR FEV_1 ≥60%: 29.9%‖	Stage II: Current: 33.0%‖ Former: 67.0%‖ FEV_1≥60%: Current: 32.3%‖ Former: 67.7%‖	Stage II: 47.5‖ FEV_1 ≥60%: 47.6‖	Stage II: NR FEV_1 ≥60%: NR	Stage II: 59‖ FEV_1 ≥60%: 64	SGQR total score mean: Stage II: 41.5‖ FEV_1 ≥60%: 40	Stage II: NR FEV_1 ≥60%: NR
TORCH Jenkins, 2009[126] Calverley, 2007[138] Fair	Stage I/II: 2183	64.9*	28.0*‖	Current: 47.0* Former: 53.0*‖	NR	Requiring hospitalization, mean (SD): 0.2 (0.5)*	58.8*	SGRQ score, mean (SD)*: Total: 45.4 (17.7) Symptom score: 60.3 (21.0) Activity score: 57.1 (20.6) Impact score: 33.6 (19.6)	NR
Lapperre 2009[132] Fair	114	61.8†‖	13.9†‖	Current: 63.4†‖	43.5†‖	NR	63.0†	SGRQ total score mean: 30.0†‖	NR
Calverley, 2008[133] Fair	Full pop: 911 Stage II: 266	Full pop: 65.1 Stage II: NR	Full pop: 31.7 Stage II: NR	Full pop: Current- 27.4; former- 72.6 Stage II: NR	Full pop: NR Stage II: NR	Full pop: NR Stage II: NR	Full pop: 46.7 Stage II: NR	Full pop: NR Stage II: NR	Full pop: NR Stage II: NR

Table 19. Baseline Characteristics for Treatment Efficacy RCTs, All Drug Classes

Study, Year Quality	N Randomized	Age, years (mean)	Female, %	Smoking status, %	Smoking history, pack-years (mean)	Number of exacerbations in the preceding year (mean)	Lung function postbronchodilation, FEV_1 % predicted of normal (mean)	HrQOL	Exercise capacity
Tonnel, 2008[129] Fair	Full pop: 555 Stage II: 198	Full pop: 64.2‡‖ Stage II: NR	Full pop: 13.9‡‖ Stage II: NR	Full pop: Current: 27.0‡‖ Stage II: NR	Full pop: 43.7‡‖ Stage II: NR	Full pop: NR Stage II: NR	Full pop: 46.8‡‖ Stage II: NR	SGRQ total score mean: Full pop: 47.4‡‖ Stage II: NR	Full pop: NR Stage II: NR
EUROSCOP Lofdahl 2007[142] Pauwels 1999[130] Fair	1,277	52.4‖	27.2‖	Current: 100.0	39.3‖	NR	76.8§‖	NR	NR
Niewoehner, 2005[128] Good	Full pop: 1829 Stage I/II: 287	Full pop: 67.8‖ Stage I/II: NR	Full pop: 1.5‖ Stage I/II: NR	Full pop: Current: 29.3‖ Stage I/II: NR	Full pop: 68.4‖ Stage I/II: NR	Full pop: NR Stage I & II: NR	Full pop: 35.6‖ Stage I & II: NR	Full pop: NR Stage I & II: NR	Full pop: NR Stage I & II: NR
Lung Health Study, 2000[134] Fair	1116	56.3‖	36.9‖	Current: 90.2‖	NR	NR	67.8‖	NR	NR
Vestbo, 1999[131] Fair	290	59.0‖	39.6‖	Current: 76.6‖ Never: 4.1‖	NR	NR	86.6	NR	NR

* Baseline characteristics only include the 2156 patients included in the efficacy analysis
† Baseline characteristics include only the 101 adherent patients included in the analysis
‡ Baseline characteristics include only the 554 patients who received treatment
§Prebronchodilator spirometry measure
‖Calculated

Abbreviations: EUROSCOP = European Respiratory Society study on Chronic Obstructive Pulmonary Disease; FEV_1= forced expiratory volume in 1 second; HrQOL = health-related quality of life; N = number; NR = not reported; pop = population; SD = standard deviation; SGRQ = St. George's Respiratory Questionnaire; TORCH = Towards a Revolution in COPD Health; UPLIFT = Understanding Potential Long-term Impacts on Function with Tiotropium; WPAI = work productivity and activity impairment questionnaire

Table 20. Subgroup Credibility Table

Study, year Quality	Subgroup	Timing of analysis	Interaction testing performed?	Groups matched at baseline?	Controlled for confounders?
Decramer, 2013[125] Fair	COPD Stage II	Post-hoc	No	Yes	Yes
Decramer, 2009[127] Fair	COPD Stage II	Pre-specified (published later)	Yes (for exacerbations only)	Yes	No
TORCH Jenkins, 2009[126] Fair	FEV_1 ≥ 50% predicted	Post-hoc	Yes: only for ICS-LABA arm There was no evidence of a difference in treatment effect across GOLD stages on all-cause mortality (p=0.402), exacerbations (p=0.254), or SGRQ (p=0.321)	Groups not evenly distributed by FEV_1, but characteristics were similar across groups	NR
Calverley, 2008[133] Fair	COPD Stage II	Post-hoc	No	NR	No
Tashkin, 2012[140] Fair	FEV_1≥60% predicted	Post-hoc	No	Only difference is statistically significantly more smokers in CG than IG (36% vs. 29%; p=0.011)	For HrQOL analysis only
Tonnel, 2008[129] Fair	Stage II (FEV_1 50-70%)	NR	Yes (p= 0.0787)	NR by stage	Adjusted for baseline SGRQ
Niewoehner, 2005[128] Good	FEV_1 >49% predicted	Unspecified	NR	NR	No

Abbreviations: CG = control group; COPD = chronic obstructive pulmonary disease; FEV1= forced expiratory volume in 1 second; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HrQOL = health-related quality of life; IG = intervention group; NR = not reported; SGRQ = St. George's Respiratory Questionnaire; TORCH = Towards a Revolution in COPD Health

Table 21. Event-Based Outcomes for LABAs

Drug Class	Study, Year Quality	Treatment Comparison	Study Group	N Analyzed	Followup	Exacerbations	IG vs. CG	Hospital Utilization	IG vs. CG	All-Cause Mortality	IG vs. CG
LABA-Formoterol	Decramer, 2013[125] Fair	IG: formoterol (12 µg/twice a day) CG: Placebo	IG	NA	6 months	NR	NR	NR	NR	NR	NR
			CG	NA							
LABA-Indacaterol	Decramer, 2013[125] Fair	IG1: indacaterol (150 µg/day) IG2: indacaterol (300 µg/day) CG: Placebo	IG1	NA	6 months	NR	NR	NR	NR	NR	NR
			IG2	NA							
			CG	NA							
LABA-Salmeterol	Decramer, 2013[125] Fair	IG: salmeterol (50 µg/twice a day) CG: Placebo	IG	NA	6 months	NR	NR	NR	NR	NR	NR
			CG	NA							
	TORCH Jenkins, 2009[126] Calverley, 2007[138] Fair	IG: salmeterol (50 ug twice a day) CG: Placebo	IG	522	36 months	Annual rate of moderate or severe exacerbations: 0.71*	NR	NR	NA	48 (9.2%)	NR
			CG	535		Annual rate of moderate or severe exacerbations: 0.82*				61 (11.4%)	

* Symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalization, or a combination of these.

Abbreviations: CG = control group; IG = intervention group; LABA = long-acting beta-agonist; µg = microgram; N = number; NA = not applicable; NR = not reported; TORCH = Towards a Revolution in COPD Health; Vs = versus

Table 22. Questionnaire- or Event-Based Outcomes for LABAs

Drug Class	Study, Year Quality	Treatment Comparison	Study Group	N Analyzed	Followup	Dyspnea Score	IG vs CG	HrQOL	IG vs CG	Exercise Capacity	IG vs CG
LABA-Formoterol	Decramer, 2013[125] Fair	IG: formoterol (12 µg/twice a day) CG: Placebo	IG	309	6 months	% achieving a minimally clinical difference on the TDI: 57.3%*	OR: 1.91 (1.29, 2.85)	% achieving a minimally clinical difference on the SGRQ total score: 52.2%†	OR: 1.63 (1.15, 2.30)	NR	NR
			CG	675		% achieving a minimally clinical difference on the TDI: 49.3%*		% achieving a minimally clinical difference on the SGRQ total score: 42.0%†			
LABA-Indacaterol	Decramer, 2013[125] Fair	IG1: indacaterol (150 µg/day) IG2: indacaterol (300 µg/day) CG: Placebo	IG1	448	6 months	% achieving a minimally clinical difference on the TDI: 63.8%*	IG1: OR (vs CG): 1.99 (1.45, 2.74) IG2: OR (vs CG): 2.44 (1.79, 3.31)	% achieving a minimally clinical difference on the SGRQ total score: 57.0%†	IG1: OR (vs CG): 2.14 (1.59, 2.88) IG2: OR (vs CG): 1.78 (1.34, 2.37)	NR	NR
			IG2	496		% achieving a minimally clinical difference on the TDI: 66.8%*		% achieving a minimally clinical difference on the SGRQ total score: 55.5%†			
			CG	675		% achieving a minimally clinical difference on the TDI: 49.3%*		% achieving a minimally clinical difference on the SGRQ total score: 42.0%†			
LABA-Salmeterol	Decramer, 2013[125] Fair	IG: salmeterol (50 µg/twice a day) CG: Placebo	IG	189	6 months	% achieving a minimally clinical difference on the TDI: 56.9%*	OR: 1.72 (1.12, 2.66)	% achieving a minimally clinical difference on the SGRQ total score: 50.3%†	OR: 1.98 (1.31, 2.99)	NR	NR
			CG	675		% achieving a minimally clinical difference on the TDI: 49.3%*		% achieving a minimally clinical difference on the SGRQ total score: 42.0%†			
	TORCH Jenkins, 2009[126] Calverley, 2007[138] Fair	IG: salmeterol (50 ug twice a day) CG: Placebo	IG	522	36 months	NR	NR	Adjusted change in SGRQ total score from BL, mean‡: -1.5	NR	NR	NR
			CG	535				Adjusted change in SGRQ total score from BL, mean‡: -1.3			

Table 22. Questionnaire- or Event-Based Outcomes for LABAs

* % achieving a meaningful clinical difference (≥ 1 point)
† % achieving a meaningful clinical difference (≥- 4 units)
‡ Adjusted for age, gender, BMI, baseline FEV_1, baseline SGRQ, region, and smoking status

Abbreviations: BL = baseline; BMI = body mass index; CG = control group; HrQOL = health-related quality of life; IG = intervention group; LABA = long-acting beta-agonist; µg = microgram; N = number; NR = not reported; OR = odds ratio; SGRQ = St. George's Respiratory Questionnaire; TDI = transition dyspnea index; TORCH = Towards a Revolution in COPD Health; Vs = versus

Table 23. Event-Based Outcomes for ICS and LABA Combination Therapy

Drug Class	Study, Year Quality	Treatment Comparison	Study Group	N Analyzed	Followup	Exacerbations	IG vs. CG	Hospital Utilization	IG vs. CG	All-Cause Mortality	IG vs. CG
ICS/LABA-Salmeterol/ fluticasone propionate	TORCH Jenkins, 2009[126] Calverley, 2007[138] Fair	IG: salmeterol/ fluticasone propionate combination (50 ug/500 ug) twice a day CG: Placebo	IG	562	36 months	Annual rate of moderate or severe exacerbations: 0.57*	Reduction in annual rate of moderate or severe exacerbations (vs CG): 31% (95% CI: 19 to 40%)	NR	NA	44 (7.8%)	HR: 0.67 (95% CI: 0.45 to 0.98)
			CG	535		Annual rate of moderate or severe exacerbations: 0.82*				61 (11.4%)	
	Lapperre 2009[132] Fair	IG: fluticasone propionate (500 ug twice a day) plus salmeterol (50 ug twice a day) for 30 months CG: Placebo	IG	NA	30 months	NR	NA	NR	NA	NR	NR
			CG	NA							

* Symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalization, or a combination of these.

Abbreviations: CI = confidence interval; CG = control group; HR = hazard ratio; ICS = inhaled corticosteroids; IG = intervention group; LABA = long-acting beta-agonist; µg = microgram; N = number; NA = not applicable; NR = not reported; TORCH = Towards a Revolution in COPD Health; Vs = versus

Table 24. Questionnaire- or Event-Based Outcomes for ICS and LABA Combination Therapy

Drug Class	Study, Year Quality	Treatment Comparison	Study Group	N Analyzed	Followup	Dyspnea Score	IG vs. CG	HrQOL	IG vs. CG	Exercise Capacity	IG vs. CG
ICS/LABA-Salmeterol/ fluticasone propionate	TORCH Jenkins, 2009[126] Calverley, 2007[138] Fair	IG: salmeterol/ fluticasone propionate combination (50 ug/500 ug) twice a day CG: Placebo	IG	562	36 months	NR	NR	Adjusted change in SGRQ total score from BL, mean*: -3.7	Difference in adjusted mean change vs. CG*: -2.3 (95% CI, -4.0 to -0.7)	NR	NR
			CG	535				Adjusted change in SGRQ total score from BL, mean*: -1.3			
	Lapperre 2009[132] Fair	IG: fluticasone propionate (500 ug twice a day) plus salmeterol (50 ug twice a day) for 30 months CG: placebo	IG	21	30 months	NR	NR	NR	NR	NR	NR
			CG	20							

*Adjusted for age, gender, BMI, baseline FEV_1, baseline SGRQ, region, and smoking status

Abbreviations: BL = baseline; BMI = body mass index; CI = confidence interval; CG = control group; HrQOL = health-related quality of life; IG = intervention group; µg = microgram; N = number; NR = not reported; SGRQ = St. George's Respiratory Questionnaire; TORCH = Towards a Revolution in COPD Health; Vs = versus

Table 25. Event-Based Outcomes for Tiotropium

Drug Class	Study, Year Quality	Treatment Comparison	Study Group	N Analyzed	Followup	Exacerbations	IG vs. CG	Hospital Utilization	IG vs. CG	All-Cause Mortality	IG vs. CG
Long-acting anti-cholinergic (tiotropium)	UPLIFT Decramer 2009[127] Tashkin 2012[140] Tashkin 2008[141]	IG: tiotropium bromide (18 µg/day) CG: Placebo	IG	Stage II: 1384 FEV_1 ≥60%: 632	48 months	Stage II: ≥1: 59.5% (824/1384)*§ Median months to first: 23.1 (95% CI, 21.0 to 26.3) * Mean number: 0.56 (95% CI, 0.52 to 0.60)* FEV_1 ≥60%: ≥1: 56%*	Stage II: Time to first exacerbation: HR: 0.82 (95% CI, 0.75 to 0.90), p<0.0001 Mean number: RR: 0.80 (95% CI, 0.72 to 0.88), p<0.0001 FEV_1≥60%: ≥1: HR: 0.83 (95% CI, 0.71 to 0.96), p= 0.011	Stage II: ≥1 hospitalized exacerbations: 15.2% (211/1384)§ Median months to first hospitalized exacerbation: NR Mean number of hospitalized exacerbation: 0.08 (0.07 to 0.09) FEV_1≥60%: ≥1 hospitalized exacerbations: 13%	Stage II: Time to first hospitalized exacerbation: HR: 0.74 (95% CI, 0.62 to 0.88), p=0.001 Mean number of hospitalized exacerbation: RR: 0.80 (95% CI, 0.63 to 1.03), p=0.082 FEV_1 ≥60%: ≥1 hospitalized exacerbations: HR: 0.86 (95% CI, 0.64 to 1.16), p= 0.334	Stage II: All-cause mortality: 9.2% (128/1384)§ Mortality from lower respiratory disease: 1.4% (20/1384)§ FEV_1≥60%: All-cause mortality: 7.4% (47/632)§	Stage II: All-cause mortality HR: 0.84 (95% CI, 0.66 to 1.07) Mortality for lower respiratory tract infection HR: 0.81 (95% CI, 0.45 to 1.46) FEV_1≥60%: All-cause mortality HR: 0.66 (95% CI, 0.45 to 0.96), p=0.031 More cardiac deaths and deaths due to COPD exacerbation occurred in the CG and numerically more deaths due to cancer occurred in the IG (data not reported)
			CG	Stage II: 1355 FEV_1 ≥60%: 578		Stage II: ≥1: 65.1% (882/1355)*§ Median months to first: 17.5 (95% CI, 15.9 to 19.7)* Mean number: 0.70 (95% CI, 0.65 to 0.75)* FEV_1 ≥60%: ≥1: 62%*		Stage II: ≥1 hospitalized exacerbations: 19.5% (264/1355)§ Median months to first hospitalized exacerbation: NR Mean number of hospitalized exacerbations: 0.10 (95% CI, 0.08 to 0.12) FEV_1 ≥60%: exacerbation requiring hospitalization: 15%		Stage II: All-cause mortality: 10.8% (147/1355)§ Mortality from lower respiratory disease: 1.8% (24/1355)§ FEV_1≥60%: All-cause mortality: 11.1% (64/578)§	

Table 25. Event-Based Outcomes for Tiotropium

Drug Class	Study, Year Quality	Treatment Comparison	Study Group	N Analyzed	Followup	Exacerbations	IG vs. CG	Hospital Utilization	IG vs. CG	All-Cause Mortality	IG vs. CG
	Decramer, 2013[125] Fair	IG: tiotropium bromide (18 µg/day) CG: Placebo	IG	NA	6 months	NR	NR	NR	NR	NR	NR
			CG	NA							
	Niewoehner, 2005[128] Good	IG: tiotropium bromide (18 ug per day) CG: Placebo	IG	NR‖	6 months	NR	OR for ≥1 exacerbation: NS (numbers NR)†	NR	NA	NR	NR
			CG	NR‖							
	Tonnel, 2008[129] Fair	IG: tiotropium bromide (18 ug per day) CG: Placebo	IG	NA	9 months	NR	NA	NR	NA	NR	NR
			CG	NA							
	Troosters, 2014[139] Troosters, 2011[170] Fair	IG: tiotropium bromide (18 ug per day) CG: Placebo	IG	238	6 months	4.6% (11/238)‡	OR: 0.42 (95% CI: 0.21 to 0.84)	NR	NA	0	NR
			CG	219		11.0% (24/219)‡				0	

* Increase/new onset >1 respiratory symptom for ≥ 3 days requiring antibiotic and/or systemic steroid
† A complex of respiratory symptoms (increase or new-onset) of more than 1 of the following: cough, sputum, wheezing, dyspnea, or chest tightness with a duration of at least 3 days requiring treatment with antibiotics or systemic steroids, hospitalization, or both
‡ Definition of exacerbation not reported
§Calculated
‖ Ns not reported individually for intervention and control groups. Total analyzed for stages I and II is 287.

Abbreviations: CI = confidence interval; CG = control group; COPD = chronic obstructive pulmonary disease; FEV_1= forced expiratory volume in 1 second; HR = hazard ratio; IG = intervention group; µg = microgram; N = number; NA = not applicable; NR = not reported; NS = not significant; OR = odds ratio; RR = risk ratio; UPLIFT = Understanding Potential Long-term Impacts on Function with Tiotropium; Vs = versus

Table 26. Questionnaire- or Test-Based Outcomes for Tiotropium

Drug Class	Study, year Quality	Treatment Comparison	Study Group	N Analyzed	Followup	Dyspnea Score	IG vs. CG	HrQOL	IG vs. CG	Exercise capacity	IG vs. CG
Long-acting anti-cholinergic (tiotropium)	UPLIFT Decramer 2009[127] Tashkin 2012[140] Tashkin 2008[141]	IG: tiotropium bromide (18 µg/day) CG: Placebo	IG	Stage II: 908 FEV_1 ≥60%: NR (632 randomized)	48 months	NR	NR	Stage II: deterioration of mean SGRQ total score: 0.89 units/ year (SE 0.13) FEV_1 ≥60%: % achieving a minimally clinical difference on the SGRQ total score: 52%†	p<0.05	NR	NR
			CG	Stage II: 839 FEV_1≥60%: NR (578 randomized)				Stage II: deterioration of mean SGRQ total score: 0.99 units/ year (SE 0.13) FEV_1 ≥60%:% achieving a minimally clinical difference on the SGRQ total score: 44%†	p=0.58		
	Decramer, 2013[125] Fair	IG: tiotropium bromide (18 µg/day) CG: Placebo	IG	236	6 months	% of patients achieving a minimally clinical difference on TDI: 64.6%*	OR: 1.59 (1.07-2.37)	% of patients achieving a minimally clinical difference on SGRQ total score: 51.8%†	OR: 1.46 (1.01-2.10)	NR	NR
			CG	675		% of patients achieving a minimally clinical difference on TDI: 49.3%*		% of patients achieving a minimally clinical difference on SGRQ total score: 42.0%†			
	Niewoehner, 2005[128] Good	IG: tiotropium bromide (18 ug per day) CG: Placebo	IG	NR	6 months	NR	NR	NR	NR	NR	NR
			CG	NR							

Table 26. Questionnaire- or Test-Based Outcomes for Tiotropium

Drug Class	Study, year Quality	Treatment Comparison	Study Group	N Analyzed	Followup	Dyspnea Score	IG vs. CG	HrQOL	IG vs. CG	Exercise capacity	IG vs. CG
	Tonnel, 2008[129] Fair	IG: tiotropium bromide (18 ug per day) CG: Placebo	IG	105	9 months	NR	NR	Adjusted change in SGRQ total score from BL, mean (SE)‡: -8.85 (1.37)	Difference in change in score from BL, mean (SE)‡: -1.47 (1.99); 95% CI (-5.37 to 2.44); p=0.46	NR	NR
			CG	93				Adjusted change in SGRQ total score from BL, mean (SE)‡: -7.38 (1.44)			
	Troosters, 2014[139] Troosters, 2011[170] Fair	IG: tiotropium bromide (18 ug per day) CG: Placebo	IG	221	6 months	NR	NR	Change in WPAI score from BL: 2.1 (± 22%)	Least-squares mean difference in change in WPAI score from BL: -3.76 (-7.39 to -0.13); p=0.043	Min/day of light activity, mean (SD): 111.4 (±81.7) Proportion of inactive patients (<6000 steps/day), n (%): 78 (39.8)	Proportion of inactive patients: OR: 0.86 (95% CI: 0.57 to 1.30); p=0.48§
			CG	205				Change in WPAI score from BL: -5.6 (± 20%)		Min/day of light activity, mean (SD): 101.4 (±79.9) Proportion of inactive patients (<6000 steps/day), n (%): 79 (43.4)	

* % achieving a meaningful clinical difference (≥ 1 point)
† % achieving a meaningful clinical difference (≥- 4 units)
‡Adjusted for baseline SGRQ total scores
§Between group difference only significant at 12 weeks: p=0.047

Abbreviations: BL = baseline; CG = control group; FEV_1= forced expiratory volume in 1 second; IG = intervention group; Min = minutes; µg = microgram; N = number; NR = not reported; OR = odds ratio; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; TDI = transition dyspnea index; UPLIFT = Understanding Potential Long-term Impacts on Function with Tiotropium; Vs = versus; WPAI = work productivity and activity impairment questionnaire

Table 27. Event-Based Outcomes for ICS

Drug Class	Study, Year Quality	Treatment Comparison	Study Group	N Analyzed	Followup	Exacerbations	IG vs. CG	Hospital Utilization	IG vs. CG	All-Cause Mortality	IG vs. CG
ICS-Budesonide	EUROSCOP Lofdahl 2007[142] Pauwels 1999[130] Fair	IG: Budesonide (800 ug a day) CG: Placebo	IG	593	36 months	Yearly rate of severe exacerbations: 0.05*	RR (95% CI): 0.63 (0.47 to 0.85); p=0.002	NR	NR	Deaths, n (%): 8 (1.3)†	Deaths: p=0.64
			CG	582		Yearly rate of severe exacerbations: 0.07*				Deaths, n (% 10 (1.7) †	
	Vestbo, 1999[131] Fair	IG: Budesonide 1200 µg/day (800 µg morning 400 µg evening) for 6 months µg; 400 µg/twice a day for 30 months CG: Placebo	IG	145	36 months	155 exacerbations (unclear % of patients)‡	"Difference was not significant"	0.7% admitted to hospital for exacerbation (1 patient admitted twice)	NR	Death: 4 (2.8%)§	NR
			CG	145		161 exacerbations (unclear % of patients)‡		0.7% admitted to hospital for exacerbation (1 patient admitted once)		Death: 5 (3.4%)§	
ICS-Fluticasone propionate	TORCH Jenkins, 2009[126] Calverley, 2007[138] Fair	IG: Fluticasone propionate (500 ug twice a day) CG: Placebo	IG	537	36 months	Annual rate of moderate/ severe exacerbations: 0.68‖	NR	NR	NA	53 (9.9%)	NR
			CG	535		Annual rate of moderate/ severe exacerbations: 0.82‖				61 (11.4%)	
	Lapperre 2009[132] Fair	IG1: Fluticasone propionate (500 ug twice a day) for the 1st 6 months and then placebo for 24 months IG2: Fluticasone propionate (500 ug twice a day) for 30 months. CG: Placebo	IG1	NA	30 months	NR	NA	NR	NA	NR	NR
			IG2	NA							
			CG	NA							

Table 27. Event-Based Outcomes for ICS

Drug Class	Study, Year Quality	Treatment Comparison	Study Group	N Analyzed	Followup	Exacerbations	IG vs. CG	Hospital Utilization	IG vs. CG	All-Cause Mortality	IG vs. CG
ICS-mometasone furoate	Calverley, 2008[133] Fair	IG1: Mometasone furoate (800 µg/day) IG2: Mometasone furoate (400 µg/twice a day) CG: Placebo	IG1	NR (97 random-ized)	12 months	18% (Numbers NR)¶	NR	NR	NR	NR	NR
			IG2	NR (88 random-ized)		27% (Numbers NR)¶					
			CG	NR (81 random-ized)		35% (Numbers NR)¶					
ICS-Triamcinolone acetonide	Lung Health Study II, 2000[134] Fair	IG: Triameinolone acetoneide 6 inhalations (100 ug per inhalation) twice a day, total dose of 1200 ug per day CG: Placebo	IG	NR (559 random-ized)	40 months	NR	NA	Hospitalizations per 100-py for respiratory conditions: 0.99 ED visits not resulting in hospitalization per 100-py for respiratory conditions: 1.3	Hospitalizations per 100-py for respiratory conditions: p=0.07 ED visits not resulting in hospitalization per 100-py for respiratory conditions: p=0.36	All-cause mortality, n: 15# CVD related mortality, n: 6	All-cause mortality: p=0.49 CVD-related mortality: p=0.16
			CG	NR (557 random-ized)				Hospitalizations per 100-py for respiratory conditions: 2.1 ED visits not resulting in hospitalization per 100-py for respiratory conditions: 1.0		All-cause mortality, n (%): 19 (3.4)# CVD related mortality, n (%): 2 (0.4)	

* Event requiring a course of oral corticosteroids

† The causes of death in the placebo group were bronchial carcinoma (3 subjects), sudden cardiac arrest (2), trauma (2), myocardial infarction (1), pulmonary embolism (1), and exacerbation of COPD (1). The causes of death in the budesonide group were bronchial carcinoma (3), myocardial infarction (2), sudden cardiac arrest (1), ruptured aortic aneurysm (1), and gastric carcinoma (1).

‡ Affirmative answer to the question "Have you since your last visit experienced more cough and phlegm than usual?"

§ Deaths unrelated to COPD or treatment

‖ Symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalization, or a combination of these.

¶ Clinically significant worsening of COPD symptoms requiring treatment with antibiotics and/or systemic steroids

The causes of death in the placebo group were cardiovascular disease (2 subjects), lung cancer (4 subjects), other cancer (10 subjects), other or unknown cause (3 subjects). The causes of death in the Triamcinolone group were cardiovascular disease (6 subjects), lung cancer (5 subjects), other cancer (2 subjects), other or unknown cause (2 subjects).

Table 27. Event-Based Outcomes for ICS

Abbreviations: CG = control group; COPD = chronic obstrctive pulmonary disease; CVD = cardiovascular disease; ED = emergency department; EUROSCOP = European Respiratory Society study on Chronic Obstructive Pulmonary Disease; ICS = inhaled corticosteroids; IG = intervention group; µg = microgram; N = number; NA = not applicable; NR = not reported; Py = person-years RR = risk ratio; TORCH = Towards a Revolution in COPD Health; Vs = versus

Table 28. Questionnaire- or Test-Based Outcomes for ICS

Drug Class	Study, year Quality	Treatment Comparison	Study Group	N Analyzed	Followup	Dyspnea Score	IG vs. CG	HrQOL	IG vs. CG	Exercise capacity	IG vs. CG
ICS-Budesonide	EUROSCOP Lofdahl 2007[142] Pauwels 1999[130] Fair	IG: Budesonide (800 ug a day) CG: placebo	IG	593	36 months	NR	NR	NR	NR	NR	NR
			CG	582							
	Vestbo, 1999[131] Fair	IG: budesonide 1200 µg/day (800 µg morning, 400 µg evening) for 6 months; 400 µg/ twice a day for 30 months CG: Placebo	IG	NA	36 months	NR	NR	NR	NR	NR	NR
			CG	NA		NR					
ICS-Fluticasone propionate	TORCH Jenkins, 2009[126] Calverley, 2007[138] Fair	IG: fluticasone propionate (500 ug/twice a day) CG: Placebo	IG	537	36 months	NR	NR	Change in SGRQ from BL, mean:-2.1	NR	NR	NR
			CG	535				Change in SGRQ from BL, mean:-1.3			
	Lapperre 2009[132] Fair	IG1: fluticasone propionate (500 ug/twice a day) for 1st 6 months and then placebo for 24 months IG2: fluticasone propionate (500 ug twice a day) for 30 months. CG: Placebo	IG1	23	30 months	NR	IG1 vs CG: NR IG2 vs CG: Change in MRC dyspnea score compared to CG during months 7-24: -0.2 point/ yr (95% CI, -0.3 to -0.06); p=0.003	NR	IG1 vs CG: NR IG2 vs CG: Change in SGRQ activity score compared to CG during months 7-24: -3.1 point/yr (95% CI, -5.5 to -0.7); p=0.012	NR	NR
			IG2	22							
			CG	20							

Table 28. Questionnaire- or Test-Based Outcomes for ICS

Drug Class	Study, year Quality	Treatment Comparison	Study Group	N Analyzed	Followup	Dyspnea Score	IG vs. CG	HrQOL	IG vs. CG	Exercise capacity	IG vs. CG
ICS-Mometasone furoate	Calverley, 2008[133] Fair	IG1: mometasone furoate (800 µg/day) IG2: mometasone furoate (400 µg/twice day) CG1: Placebo	IG1	NA	12 months	NR	NR	NR	NR	NR	NR
			IG2	NA							
			CG	NA							
ICS-Triamcinolone acetonide	Lung Health Study II, 2000[134] Fair	IG: Triamcinolone acetoneide) 6 inhalations (100 ug per inhalation) twice a day, total dose of 1200 ug per day CG: Placebo	IG	NR (559 random-ized)	36 months	Highest dyspnea level, %: No dyspnea, %: 68.2 Dyspnea walking up a slight hill or hurrying, %: 20.8 Walks more slowly than similarly aged people, %: 4.4 More severe dyspnea, %: 6.6	Highest dyspnea level: p=0.02	NR	NR	NR	NR
			CG	NR (557 random-ized)		Highest dyspnea level, %: No dyspnea, %: 61.5 Dyspnea walking up a slight hill or hurrying, %: 22.7 Walks more slowly than similarly aged people, %: 6.7 More severe dyspnea, %: 9.1					

Abbreviations: BL = baseline; CI = confidence interval; CG = control group; EUROSCOP = European Respiratory Society study on Chronic Obstructive Pulmonary Disease; HrQOL = health-related quality of life; ICS = inhaled corticosteroids; IG = intervention group; µg = microgram; MRC = Medical Research Council; N = number; NA = not applicable; NR = not reported; SGRQ = St. George's Respiratory Questionnaire; TORCH = Towards a Revolution in COPD Health; Vs = versus; Yr = year

Table 29. Withdrawals and Adverse Events Reported in Treatment Efficacy RCTs: LABAs

Drug Class	Study, year Quality	Treatment Comparison	Study Group	N Analyzed	Followup	Withdrawals	IG vs CG	Adverse Events	IG vs CG
LABA-Formoterol	Decramer, 2013[125] Fair	IG: formoterol (12 µg/twice a day) CG: Placebo	IG	309	6 months	NR	NR	Any adverse event: 57.9% COPD worsening: 15.2% Nasopharyngitis: 8.7% Upper RTI: 2.6% Cough: 4.2%	NR
			CG	675	6 months			Any adverse event: 55.9% COPD worsening: 17.8% Nasopharyngitis: 8.2% Upper RTI: 3.3% Cough: 4.3%	
LABA-Indacaterol	Decramer, 2013[125] Fair	IG1: indacaterol (150 µg/day) IG2: indacaterol (300 µg/day) CG: Placebo	IG1	448	6 months	NR	NR	Any adverse event: 58.9% COPD worsening: 14.5% Nasopharyngitis: 7.8% Upper RTI: 6.5% Cough: 5.6%	NR
			IG2	496				Any adverse event: 61.3% COPD worsening: 13.9% Nasopharyngitis: 10.1% Upper RTI: 5.0% Cough: 7.3%	
			CG	675				Any adverse event: 55.9% COPD worsening: 17.8% Nasopharyngitis: 8.2% Upper RTI: 3.3% Cough: 4.3%	
LABA-Salmeterol	Decramer, 2013[125] Fair	IG: salmeterol (50 µg/twice a day) CG: Placebo	IG	189	6 months	NR	NR	Any adverse event: 45.0% COPD worsening: 14.8% Nasopharyngitis: 10.1% Upper RTI: 0.0% Cough: 2.7%	NR
			CG	675				Any adverse event: 55.9% COPD worsening: 17.8% Nasopharyngitis: 8.2% Upper RTI: 3.3% Cough: 4.3%	
	TORCH Jenkins, 2009[126] Calverley, 2007[138]	IG1: salmeterol (50 ug twice a day) CG: Placebo	IG1	531	36 months	Withdrawal rate (reasons NR), %: 27.0	NR	Any adverse event, n (%): 471 (89.0) Serious adverse event, n (%): 174 (33.0) Fatal adverse event, n (%): 29 (5.0) Probability of pneumonia*, %: 9.4 Incidence of pneumonia, rate per 1000 treatment years: 36	NR

Table 29. Withdrawals and Adverse Events Reported in Treatment Efficacy RCTs: LABAs

Drug Class	Study, year Quality	Treatment Comparison	Study Group	N Analyzed	Followup	Withdrawals	IG vs CG	Adverse Events	IG vs CG
	Fair		CG	543		Withdrawal rate (reasons NR), %: 35.0		Any adverse event, n (%): 470 (87.0) Serious adverse event, n (%): 197 (36.0) Fatal adverse event, n (%): 37 (7.0) Probability of pneumonia*, %: 10.6 Incidence of pneumonia, rate per 1000 treatment years: 43	

*Kaplan-Meier probability. When investigating time to first pneumonia, there was no evidence of treatment differences by severity (p=0.402).

Abbreviations: CG = control group; COPD = chronic obstructive pulmonary disease; IG = intervention group; LABA = long-acting beta-agonist; µg = microgram; N = number; NR = not reported; RCT = randomized controlled trial; RTI = respiratory tract infection; TORCH = Towards a Revolution in COPD Health; Vs = versus

Table 30. Withdrawals and Adverse Events Reported in Treatment Efficacy RCTs: ICS and LABA Combination Therapy

Drug Class	Study, year Quality	Treatment Comparison	Study Group	N Analyzed	Followup	Withdrawals	IG vs CG	Adverse Events	IG vs CG
ICS/LABA-Salmeterol/ Fluticasone Priopionate	TORCH Jenkins, 2009[126] Calverley, 2007[138] Fair	IG: salmeterol/ fluticasone propionate combination (50 ug/500 ug) twice a day CG: Placebo	IG	565	36 Months	Withdrawal rate (reasons NR), %: 27.0	NR	Any adverse event, n (%): 487 (86.2) Serious adverse event, n (%): 198 (35.0) Fatal adverse event, n (%): 27 (4.8) Probability of pneumonia*, %: 15.3 Incidence of pneumonia, rate per 1000 treatment years: 56	NR
			CG	543		Withdrawal rate (reasons NR), %: 35.0		Any adverse event, n (%): 470 (86.6) Serious adverse event, n (%): 197 (36.0) Fatal adverse event , n (%): 37 (6.8) Probability of pneumonia*, %: 10.6 Incidence of pneumonia, rate per 1000 treatment years: 43	
	Lapperre 2009[132] Fair	IG: fluticasone propionate (500 ug twice a day) plus salmeterol (50 ug twice a day) for 30 months CG: Placebo	IG	21	30 Months	4 (1 in months 0 to 6, 3 in months 7 to 30), reason NR	NA	NR	NA
			CG	20		4 (3 in months 0 to 6, 1 in months 7 to 30), reason NR			

*Kaplan-Meier probability. When investigating time to first pneumonia, there was no evidence of treatment differences by severity (p=0.402).
Abbreviations: CG = control group; ICS = inhaled corticosteroids; IG = intervention group; LABA = long-acting beta-agonist; µg = microgram; N = number; NR = not reported; RCT = randomized controlled trial; TORCH = Towards a Revolution in COPD Health; Vs = versus

Table 31. Withdrawals and Adverse Events Reported in Treatment Efficacy RCTs: Tiotropium

Drug Class	Study, year Quality	Treatment Comparison	Study Group	N analyzed	Followup	Withdrawals	IG vs CG	Adverse Events	IG vs CG
Long acting anticholinergic-Tiotropium	UPLIFT Decramer 2009[127] Tashkin 2012[140] Tashkin 2008[141]	IG: tiotropium bromide (18 µg/day) CG: Placebo	IG	Stage II: 1384 FEV_1 ≥60%: 632	48 months	Stage II: 30.6% (424/1384) (17% adverse event, 8.4% consent withdrawn, 1.4% protocol noncompliance, 2.7% lost to followup; 1.1% other)† FEV_1 ≥60%: 30.4% (192/632) (15.5% adverse event, 9.5% consent withdrawn, 2.2% protocol noncompliance, 2.0% lost to followup; 1.1% other)†	Stage II: Rate of discontin-uation: p=0.024	Stage II: Adverse events leading to discontinuation: 17.0% (235/1384)† FEV_1 ≥60%: Adverse events leading to discontinuation: 15.5% (98/632)†	NR
			CG	Stage II: 1355 FEV_1 ≥60%: 578		Stage II: 34.7% (470/1355) (17.8% adverse event, 11.7% consent withdrawn, 2.3% protocol noncompliance, 2.0% lost to followup; 1.0% other)† FEV_1 ≥60%: 31.5% (182/578) (15.2% adverse event, 11.1% consent withdrawn, 1.7% protocol noncompliance, 2.2% lost to followup; 1.2% other)†		Stage II: Adverse events leading to discontinuation: 17.8% (241/1355)† FEV_1 ≥60%: Adverse events leading to discontinuation: 15.2% (88/578)†	
	Decramer, 2013[125] Fair	IG: tiotropium bromide (18 µg/day) CG: Placebo	IG	236	6 months	NR	NR	Any adverse event: 67.0% COPD worsening: 13.1% Nasopharyngitis: 10.2% Upper RTI: 5.5% Cough: 5.0%	NR
			CG	675				Any adverse event: 55.9% COPD worsening: 17.8% Nasopharyngitis: 8.2% Upper RTI: 3.3% Cough: 4.3%	
	Niewoehner, 2005[128] Good	IG: tiotropium bromide (18 µg/day) CG: Placebo	IG	NR	6 months	NR	NA	NR	NA
			CG	NR					
	Tonnel, 2008[129] Fair	IG: tiotropium bromide (18 µg/day) CG: Placebo	IG	105	9 months	NR	NA	NR	NA
			CG	93					

Table 31. Withdrawals and Adverse Events Reported in Treatment Efficacy RCTs: Tiotropium

Drug Class	Study, year Quality	Treatment Comparison	Study Group	N analyzed	Followup	Withdrawals	IG vs CG	Adverse Events	IG vs CG
	Troosters, 2014[139] Troosters, 2011[170] Fair	IG: tiotropium bromide (18 ug per day) CG: Placebo	IG	221	6 months	NR	NA	Serious adverse events, n (%)*: Hip fracture: 1 (0.5) Abdominal abscess: 1 (0.5) Tendon disorder: 1 (0.5) Cerebral artery occlusion: 1 (0.5) Cerebral infarction: 1 (0.5) Joint abscess: 1 (0.5) Bladder transitional cell carcinoma: 1 (0.5) Pancreatic cyst: 1 (0.5) Streptococcal infection: 1 (0.5)	NR
			CG	205				Serious adverse events, n (%)*: Renal failure: 2 (1.0) Cardiac failure: 1 (0.5) MI: 1 (0.5) Acute respiratory failure: 1 (0.5) Angina pectoris: 1 (0.5) Rectal polyp: 1 (0.5) Acute pancreatitis: 1 (0.5) Coronary disease: 1 (0.5)	

*All serious adverse events were considered unrelated to the study drug and all patients recovered.
†Calculated

Abbreviations: CG = control group; COPD = chronic obstructive pulmonary disease; FEV_1= forced expiratory volume in 1 second; IG = intervention group; µg = microgram; N = number; NA = not applicable; NR = not reported; RCT = randomized controlled trial; RTI = respiratory tract infection; UPLIFT = Understanding Potential Long-term Impacts on Function with Tiotropium; Vs = versus

Table 32. Withdrawals and Adverse Events Reported in Treatment Efficacy RCTs: ICS

Drug Class	Study, year Quality	Treatment Comparison	Study Group	N analyzed	Followup	Withdrawals	IG vs CG	Adverse Events	IG vs CG
ICS-Budesonide	EUROSCOP Lofdahl 2007[142] Pauwels 1999[130] Fair	IG: budesonide (800 ug a day) CG: placebo	IG	593	36 months	Withdrawal due to adverse events, n: 70 (11.0%)	p=0.51	Serious adverse events, n (%): Total: 177 (29.8) Neoplasm: 21 (3.5) CV disorder: 28 (4.7) GI disorder: 17 (2.9) Respiratory disorder: 17(2.9) Musculoskeletal disorder: 14 (2.4) Ischemic cardiac event[§]: 3.0% New lumbar fractures, n (%): 5 (NR)*	Serious adverse event: p=0.37 New lumbar fractures: p=0.50 Ischemic cardiac event: p=0.048[§]
			CG	582		Withdrawal due to adverse events, n: 62 (10.6%)		Serious adverse events, n (%): Total: 161 (27.7) Neoplasm: 25 (4.3) CV disorder: 32 (5.5) GI disorder: 15 (2.6) Respiratory disorder: 14 (2.4) Musculoskeletal disorder: 16 (2.7) Ischemic cardiac event[§]: 5.3% New lumbar fractures, n (%): 3 (NR)*	
	Vestbo, 1999[131] Fair	IG: budesonide 1200 µg/day (800 µg morning, 400 µg evening) for 6 months; 400 µg/twice a day for 30 months CG: Placebo	IG	145	36 months	36 (16 adverse events, 3 disease deterioration, 17 other)	NR	Serious adverse events: 14 events in 10 patients (9.6%)[†] Worsening of COPD: 36 (24.8%) Pneumonia: 16 (11.0%) Viral infection: 34 (23.4%)	Adverse events: p= 0.001[†]
			CG	145		51 (17 adverse events, 7 disease deterioration, 27 other)		Serious adverse events: 41 events in 34 patients (28.3%)[†] Worsening of COPD: 34 (23.4%) Pneumonia: 24 (16.6%) Viral infection: 34 (23.4%)	
ICS-Fluticasone Propionate	TORCH Jenkins, 2009[126] Calverley, 2007[138] Fair	IG: fluticasone propionate (500 ug twice a day) CG: Placebo	IG	544	36 months	Withdrawal rate (reasons NR), %: 32.0	NR	Any adverse event, n (%): 481 (88.4) Serious adverse event, n (%): 169 (31.1) Fatal adverse event, n (%): 38 (6.9) Probability of pneumonia[‡], %: 12.8 Incidence of pneumonia, rate per 1000 treatment years: 58	NR
			CG	543		Withdrawal rate (reasons NR), %: 35.0		Any adverse event, n (%): 470 (86.6) Serious adverse event, n (%): 197 (36.2) Fatal adverse event, n (%): 37 (6.8) Probability of pneumonia[‡], %: 10.6 Incidence of pneumonia, rate per 1000 treatment years: 43	

Table 32. Withdrawals and Adverse Events Reported in Treatment Efficacy RCTs: ICS

Drug Class	Study, year Quality	Treatment Comparison	Study Group	N analyzed	Followup	Withdrawals	IG vs CG	Adverse Events	IG vs CG
	Lapperre 2009[132] Fair	IG1: fluticasone propionate (500 ug twice a day) for the 1st 6 months and then placebo for 24 months IG2: fluticasone propionate (500 ug twice a day) for 30 months CG: placebo	IG1	23	30 months	3 (13.0%) (2 in months 0 to 6, 1 in months 7 to 30), reason NR	NR	NR	NR
			IG2	22		4 (18.1%) (0 in months 0 to 6, 4 in months 7 to 30), reason NR			
			CG	20		4 (20.0%) (3 in months 0 to 6, 1 in months 7 to 30), reason NR			
ICS-Mometasone	Calverley, 2008[133] Fair	IG1: mometasone furoate (800 µg/day) IG2: mometasone furoate (400 µg/twice a day) CG: Placebo	IG1	NA	12 months	NR	NR	NR	NR
			IG2	NA					
			CG	NA					
ICS-Triamcinolone acetonide	Lung Health Study II, 2000[134] Fair	IG: Triameinolone acetoneide) 6 inhalations (100 ug per inhalation) twice a day, total dose of 1200 ug per day	IG	158 (lumbar spine); 176 (Femoral neck) NR (other events) (559 random-ized)	36 months	NR	NA	Bone Mineral Density (g/cm^2), mean (SE): Lumbar spine: 0.985 (0.013) Lumbar spine % Change from BL: -0.35 (0.33) Femoral neck: 0.747 (0.010) Femoral neck % Change from BL: -2.00 (0.35)	Bone Mineral Density (g/cm^2): Lumbar spine: p=0.89 Lumbar spine % Change from BL: p=0.007 Femoral neck: p=0.73 Femoral neck % Change from BL:

Table 32. Withdrawals and Adverse Events Reported in Treatment Efficacy RCTs: ICS

Drug Class	Study, year Quality	Treatment Comparison	Study Group	N analyzed	Followup	Withdrawals	IG vs CG	Adverse Events	IG vs CG
		CG: Placebo inhaler	CG	170 (lumbar spine); 183 (Femoral neck) NR (other events) (557 random-ized)		NR		Bone Mineral Density (g/cm^2), mean (SE): Lumbar spine: 0.988 (0.014) Lumbar spine- % Change from BL: 0.98 (0.36) Femoral neck: 0.752 (0.010) Femoral neck- % Change from BL: -0.22 (0.32)	p<0.001

*Radiographs only on a subset of patients (653) N not given for each group
† None of the serious adverse events were believed to be related to treatment or treatment failure.
‡Kaplan-Meier probability. When investigating time to first pneumonia, there was no evidence of treatment differences by severity (p=0.402).
§Event only collected if spontaneously reported by a primary care physician.

Abbreviations: BL = baseline; CG = control group; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; EUROSCOP = European Respiratory Society study on Chronic Obstructive Pulmonary Disease; g/cm2 = grams per centimeters squared; GI = gastrointestinal; IG = intervention group; µg = microgram; N = number; NR = not reported; RCT = randomized controlled trial; SE = standard error; TORCH = Towards a Revolution in COPD Health; Vs = versus

Table 33. Summary of Evidence

Key Question	Population	No. of Studies, Observations (n), Design	Summary of Findings	Consistency/ Precision	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
Key question 1 (health outcomes)	Asymptomatic adults		We identified no trials examining the efficacy of COPD screening on health outcomes.				INSUFFICIENT	
Key question 2: questionnaires	Adults in the general population and primary care with and without smoking history	**CDQ diagnostic accuracy observational studies** Development: K=1; N=572 Internal validation: K=1; N=246 External validation: K=5; N=3,048	CDQ: 3 out of 5 external validation studies were in ever-smoking adults. Most external validation studies reported that a CDQ score of >16.5 had a sensitivity in the low 90% range and specificity in the high 30% to mid 40% range for diagnosing spirometrically-confirmed COPD. Choosing a higher cutpoint (19.5) reduced sensitivity and NPV but increased specificity and PPV.	Reasonably consistent; imprecise	Fair	Heterogeneous populations in external validation studies as reflected by wide variation in COPD prevalence in ever smokers (13%-28%).	MODERATE	Derivation population included U.S. site. None of the external validation studies performed in U.S.
	Ever-smoking adults in primary care	**LFQ diagnostic accuracy observational studies** Development/ validation of scoring: K=1; N=387 Internal validation: None External validation: K=1; n=849	Based on 1 external validation study, the LFQ showed a sensitivity of 88% and specificity of 25%.	Unknown: 1 external validation study	Fair	Derived from NHANES III survey of self-reported physician-diagnosed chronic bronchitis; spirometry used pre-BD FEV_1/FVC. Single external validation study.	LOW	Single external validation study conducted in 36 U.S. primary care sites.

Table 33. Summary of Evidence

Key Question	Population	No. of Studies, Observations (n), Design	Summary of Findings	Consistency/ Precision	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
	Adults in the general population and primary care with and without smoking history	**COPD-PS diagnostic accuracy observational studies** Development: K=1; N=295 Internal validation: K=1; N=697 External validation: K=1; N=2,357	COPD-PS: Single external validation population-based study in Japanese rural town shows that for cutpoint of 4, sensitivity is 67% and specificity is 73%. Choosing a higher cutpoint of 5 lowers the sensitivity to 35% with a slightly higher specificity of 79%.	Unknown; 1 external validation study	Fair	External validation study in single Japanese rural community without exclusion of preexisting COPD.	VERY LOW	Development sample recruited participants from U.S. pulmonary and primary care clinics, but external validation study setting may not be generalizable to U.S. primary care screening population.
	Adults in the general population and primary care with and without smoking history	**Other (3)** questionnaires not externally validated in diagnostic accuracy observational studies: k=4; n=4,451 **Buffels**: k=1; n=2923 (development only) **CAT:** k=1; n=532 (same n for development and internal validation) **CFQ**: k=1; n=996 (development only)	Of the 3 questionnaires not externally validated, only 1 had internal validation (CAT). 1 study in ever smokers in primary care and the remainder in general population or primary care regardless of smoking history. Insufficient evidence to make conclusions regarding accuracy.	Unknown: 1 study		Not externally validated	INSUFFICIENT	2 studies from Canada. 1 study in ever smokers in primary care and the remainder in general population or primary care regardless of smoking history.

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Key Question	Population	No. of Studies, Observations (n), Design	Summary of Findings	Consistency/ Precision	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
Key Question 3: simple PFTs	Adults in the general population	**PEF diagnostic accuracy observational studies**: k=2; n=23,098	2 population based studies with different index test thresholds; gold standard tests and definitions of COPD in low and high index countries without exclusion of known COPD do not provide sufficient information to make conclusions regarding accuracy.	Unknown: 2 existing studies use different PEF index test cutpoint units (L/s/m^2 vs % predicted) and different gold standard cutpoints (FEV_1/FVC <0.7 vs <LLN). 1 study defined mild COPD as disease negative.	Fair	BOLD and PLATINO population based samples do not exclude or report baseline known COPD, so enriched sample.	LOW	Serious concerns regarding applicability to U.S. population given that many countries in BOLD and PLATINO were low development index countries with different environmental and occupational exposures
	preBD FEV_1/FEV_6: Ever smokers in primary care postBD FEV_1/FEV_6: Primary care with and without smoking history	**preBD FEV_1/FEV_6 diagnostic accuracy observational studies:** k=2; n=509 **postBD FEV_1/FEV_6 diagnostic accuracy observational studies:** k=1; n=1,078	In 2 studies of pre-BD FEV_1/FEV_6 among ever smokers, sensitivities were similar (51.0% and 53.2%) at <0.70 cutpoint, as were specificities (89.5% and 93.0%). Cutpoint of 0.75 increased sensitivity to >80% and specificity remained relatively high (low 70%). Reported sensitivity in Sichletidis study that recruited about half ever smokers but utilized post-BD FEV_1/FEV_6 <0.70 for screening was 80%, and specificity was 95%.	Consistent	Fair	Only 2 studies (N=509) for pre-BD FEV_1/FEV_6	LOW	Conducted in Australia, Sweden for preBD studies; Greece for post-BD. Most likely reasonably applicable to U.S. primary care population, although environmental /occupational exposures might vary.

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Key Question	Population	No. of Studies, Observations (n), Design	Summary of Findings	Consistency/ Precision	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
	Ever smokers in primary care	**Staged approach ($CDQ+FEV_1/FEV_6$) diagnostic accuracy observational studies: K=1; n=1,078)**	In the analysis whereby the screening test was considered positive only if both CDQ and FEV_1/FEV_6 tests were positive, sensitivity and specificity were 72 and 97 percent respectively in the entire population and similar in a subset of smokers only. The PPV was reported as 71 percent and the NPV was 97 percent in the entire population.	Unknown: one study	Fair to poo based on inadequate reporting of data for staged approach (and in ever smokers)	Single study, did not report raw data to create 2x2 tables for ever smoker subpopulation or for staged approach in general	INSUFFICIENT	Single Greek study; environmental and occupational exposures differ from U.S.
Key question 4: screening harms	Adults in the general population and primary care with and without smoking history	**CDQ diagnostic accuracy observational studies**: K=4; N=3,009	>16.5 threshold: Missed cases (false-negative rate) ranged from 9%-20%; in studies in which <20% of spirometries were invalid or incomplete (best estimate), the proportion of missed spirometry-diagnosed COPD was around 10%. False-positive rate varied, from 51% to 76% for >16.5; in studies with <20% spirometries invalid or incomplete, false-positive rate was similar. >19.5 threshold: Missed cases ranged from 11% to 37%; in studies in which <20% of spirometries were invalid or incomplete, missed cases ranged from 28%-34%. False-positive rate varied, from 23% to 46%, with similar range for best estimate (<20% missed, incomplete spirometry).	Inconsistent	Fair	Heterogeneous populations with smokers vs general population	LOW	Derivation population included U.S. site. None of external validation studies performed in U.S.

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Key Question	Population	No. of Studies, Observations (n), Design	Summary of Findings	Consistency/ Precision	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
	Ever-smoking adults in primary care	**LFQ diagnostic accuracy observational studies**: K=1; n=849	Missed diagnosis and false-positive rate could not be reliably estimated for the LFQ because only a subset of screen-negative patients received diagnostic spirometry in the single external validation study of this questionnaire; however, the majority of those who screened positive on the questionnaire were determined to be false positive (74.2%).	Unknown: 1 study	Poor	Single external validation study	INSUFFICIENT	Validated in 36 U.S. primary care sites.
	General population including smokers and nonsmokers	**COPD-PS:** K=1; N=2,357	At a cutpoint of ≥4, false positives were 27% and false negatives were 33%. At a cutpoint of ≥5, false positives were 21% and false negatives were 65%.	Unknown; 1 external validation study	Fair	Single study set in Japanese rural town	VERY LOW	May not be generalizable to U.S. primary care screening population.
		PEF diagnostic accuracy observational studies: k=1; n=9,390	False-negative rate reported in the 1 BOLD study reporting this outcome ranged from 16%-69% depending on the threshold used. False-positive rate ranged from 0.5% to 16% depending on the threshold used.	Unknown: 1 study reporting false negative and false positive rate	Insufficient	BOLD population based samples do not exclude or report baseline known COPD, so enriched sample.	LOW	Serious concerns regarding applicability to U.S. population given that many countries in BOLD were low development index countries with different environmental and occupational exposures

Table 33. Summary of Evidence

Key Question	Population	No. of Studies, Observations (n), Design	Summary of Findings	Consistency/ Precision	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
	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 diagnostic accuracy observational studies:** k=2; n=509 **post-BD FEV_1/FEV_6 diagnostic accuracy observational studies:** k=1; n=1,078	2 pre-BD FEV_1/FEV_6 studies reported false-negative rates for threshold <0.7 of 47% and 49% and false-positive rate of 8 and 10%. The 1 study using post-BD FEV_1/FEV_6 reported more favorable rates of 20% and 5%, respectively.	FP and FN rates reported in the 2 pre-BD FEV_1/FEV_6 were consistent.	Fair	Only 2 studies for pre-BD FEV_1/FEV_6	LOW	All 3 studies are outside U.S., with the 2 pre-BD FEV_1/FEV_6 studies in current or former smokers and the pos-tBD FEV_1/FEV_6 study in general population
Key question 5a: smoking cessation	Adult smokers in the general population and primary care	RCTs: K=5; n=1,620	Of the 3 RCTs reporting biochemically confirmed abstinence, only 1 fair-quality RCT communicating lung age reported a statistically significant difference in the intervention vs control group; 1 underpowered VA trial[120] showed a trend toward reduction 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 months in the intervention and active treatment control groups.	Inconsistent	Fair	Studies tested the incremental value of adding spirometry to counseling alone.	LOW	Only 1 RCT recruited screen-detected patients who were motivated to quit. All other trials included patients with prior diagnoses of COPD (prevalence not reported in 3 of the 5 RCTs).
Key Question 5b: immunization rates	Asymptomatic adults		We identified no trials examining the effectiveness of screening in increasing vaccination rates.				INSUFFICIENT	

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Key Question	Population	No. of Studies, Observations (n), Design	Summary of Findings	Consistency/ Precision	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
Key question 6: Harms screening on preventive services	Adult smokers in the general population and primary care	K=1 observational qualitative study; n=205	No conclusions based on scant available data. 1 qualitative study of semistructured interviews reporte that 8% of patients stated that routine PFTs in smokers would interfere with freedom of choice	Unknown: 1 study	Insufficient	Scant data	INSUFFICIENT	Unknown
Key question 7: treatment efficacy	Screen-detected COPD		We identified no trials examining treatment effectiveness on health outcomes in patients with screen detected COPD.				INSUFFICIENT	
	Moderate COPD	LABAs: k=2 (1 pooled subanalysis of RCTs plus 1 RCT); n=3,174	**ACM** (k=1; n=1057): TORCH trial subanalysis reports ACM of 9.2% vs 11.4% without statistical testing. **Exacerbations** (k=1; n=1057): TORCH trial subanalysis reports annual exacerbation rate of 0.71 vs 0.82 without statistical testing. **Dyspnea scores** (k=1; n=2,117): Post hoc pooled subanalysis of 3 RCTs showed there was a statistically significant short-term impact on dyspnea scores after 6 months. **QOL** (k=2; n=3,174): RCTs reported mixed results regarding LABAs' effects on SGRQ scores. **Exercise capacity:** no trials.	Unknown: single subanalysis for ACM and exacerbation single pooled analysis for dyspnea; mixed results for QOL	Fair-to-Poor	Subanalyses with several limitations: the primary trials were powered for entire population not subgroup; both analyses were post hoc; neither performed interaction testing; and only 1 analysis controlled for confounders.	INSUFFICIENT for exercise capacity. LOW for exacerbations, ACM, dyspnea, QOL scores	Subgroup had moderate COPD disease and more severe range of moderate COPD (FEV_1 % predicted 50%-60%). No treatment naïve patients who could be considered similar to screen detected, asymptomatic population.

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Key Question	Population	No. of Studies, Observations (n), Design	Summary of Findings	Consistency/ Precision	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
	Moderate COPD	LABA-ICS: K=1; n=1,097	**ACM** (k=1 subanalysis RCT; n=1,097): TORCH post hoc subanalysis of mild to moderate COPD reported a reduction in ACM (HR: 0.67 [95% CI: 0.45 to 0.98]) but interaction testing revealed no heterogeneity of effect by COPD severity and the main trial showed no ACM difference at 3 years. **Exacerbations** (k=1 post hoc subanalysis RCT; n=1,097): The annual rate of moderate-to-severe exacerbations was lower in the ICS-LABA treatment combination group compared with those on placebo (0.57 in IG vs. 0.82 in CG; annual reduction rate in IG 31% [95% CI: 19 to 40%]) **Dyspnea scores:** no trials. **QOL** (k=1; n=1,097): TORCH subanalysis showed that neither the LABA-ICS or control groups achieved clinically meaningful changes in SGRQ. **Exercise capacity:** no trials	Unknown consistency: single subanalysis	Poor	Single post hoc subanalysis not powered to detect outcomes in subgroup.	INSUFFICIENT for exercise capacity and dyspnea scores. (VERY) LOW for ACM, QOL. LOW for exacerbations.	Subgroup had moderate COPD disease (FEV_1 % predicted 50-60%). No treatment naïve patients who could be considered similar to screen detected, asymptomatic population.
	Moderate COPD	Tiotropium K=5; n=4,592	**ACM** (k=2; n=3196): UPLIFT subanalysis reports no difference in ACM: 9.2% vs. 10.8%; HR: 0.84 [95% CI: 0.66 to 1.07]. **Exacerbations** (k=3; n=3,483): 2 of 3 RCT subanalyses show reduction in mean number of exacerbations (RR: 0.80 [95% CI: 0.72 to 0.88]), and	ACM, dyspnea, exercise: unknown single study Exacerbation reasonably consistent	Fair	Most trials short ≤9 months. Single trial in moderate treatment naïve COPD patients. Subanalyses all post hoc or unspecified timing except 1. 2 of 5 subanalyses	LOW to MODERATE for exacerbations. LOW for QOL. INSUFFICIENT for dyspnea scores, exercise capacity, ACM.	Single RCT in moderate stage COPD naïve to maintenance medications but otherwise patients were not treatment naïve and almost

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Key Question	Population	No. of Studies, Observations (n), Design	Summary of Findings	Consistency/ Precision	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
			4.6% vs. 11.0%; OR: 0.42 [95% CI: 0.21 to 0.84]). VA subanalysis showed no difference in exacerbations without reporting statistics. **Dyspnea scores** (k=1; n=911): 1 post hoc subanalysis of the INHANCE trial reported more patients achieved a meaningful clinical difference (≥1 point) in dyspnea scores in the tiotropium vs. placebo group (64.6% vs. 49.3%; OR: 1.59 [95% CI: 1.07, 2.37]). **QOL** (k=4; n=3,282): 1 RCT in treatment-naïve moderate disease reports improvement in WPAI scores but uncertain if clinically meaningful, and 3 subanalyses (1 prespecified; 1 post hoc report; 1 NR timing) reported mixed results on SGRQ scores: 2 showed no difference and 1 INHANCE subanalysis reported a statistically significant difference in patients achieving clinically meaningful change in tiotropium group (51.8% vs. 42.0%; OR: 1.46 [95% CI: 1.01 to 2.10]). For the additional UPLIFT subgroup analysis of COPD patients with FEV_1 60% to 70% predicted, the tiotropium group was more likely to experience a clinically meaningful change in QOL compared to the placebo			performed interaction testing for the reported outcomes, showing no treatment effect heterogeneity by COPD severity. 3 of 5 subanalyses controlled for any confounders for at least 1 outcome.		exclusively moderate COPD. Unclear if these results can be extrapolated to screen-detected patients.

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Key Question	Population	No. of Studies, Observations (n), Design	Summary of Findings	Consistency/ Precision	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
			group (52% vs. 44%; p<0.05). **Exercise capacity** (K=1; n=426): The 1 trial in treatment naïve moderate COPD patients showed no difference in mean activity rate measured with activity monitors at 6 months but did report fewer inactive patients in the tiotropium group at 12 weeks (p=0.047).					
	Mild to moderate COPD	ICS K=6; n=3,983	**ACM** (k=4; n=3,653): 4 trials report similar rates of ACM in the ICS and placebo groups (only 2 reported statistical significance testing, neither reports interaction testing; 1 reported no statistical testing). **Exacerbations** (k=4; n=2,803): 3 trials with somewhat comparable definitions of exacerbations report similar trends of lower exacerbations in 2 trials but no statistical testing and 1 trial (EUROSCOP0, which specifically recruited mild to moderate COPD patients, reported a statistically significantly lower yearly rate of exacerbations requiring corticosteroids (0.05 vs. 0.07; RR: 0.63 [95% CI: 0.47 to 0.85]). **Dyspnea scores** (k=2; n=1,158): LHS showed that fewer patients experiencing dyspnea in the ICS group compared to placebo but	Dyspnea: unknown QOL: reasonably consistent ACM: reasonably consistent Exacerbation reasonably consistent	fair	Only 1 trial exclusively recruited patients with mild to moderate COPD (EUROSCOP). Other evidence was derived from large and 1 smaller post hoc subanalysis of RCTS (both with limitations), and 2 RCTs with mean baseline FEV_1 ≥60% predicted. Most trials had limitations due to variably defined ITT analyses, high withdrawal rates, and the exclusion of noncompliant patients during run-in periods, which may not reflect clinical practice. The 2 subanalyses had	INSUFFICIENT for exercise capacity. LOW for QOL, ACM, exacerbations, and dyspnea scores.	Populations largely moderate in severity although some mild COPD included in analyses. Unclear if these results can be extrapolated to screen-detected patients.

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Key Question	Population	No. of Studies, Observations (n), Design	Summary of Findings	Consistency/ Precision	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
			unclear if clinically meaningful (p=0.02). 1 trial showed lower MRC dyspnea scores in ICS group but neither the ICS nor placebo group had minimally important changes in MRC dyspnea scores. **QOL** (k=2 n=1114): Both trials showed that neither the fluticasone nor the placebo group had changes reaching the threshold for a minimum clinically important difference (≥4 units) over the 30 to 36 month trial periods. **Exercise capacity:** no trials			serious limitations, including the lack of baseline comparability reporting, lack of interaction testing, lack of control for confounders, and post hoc timing		
Key question 8: treatment harms	Asymptomatic screen detected patients		We identified no trials examining treatment harms in screen detected patients.					
	Mild to moderate COPD	LABAs: k=2 (1 pooled subanalysis of RCTs plus 1 RCT); n=3191	**Withdrawal rates** (k=1; n=1074): TORCH subanalysis reported lower withdrawals in LABA compared to placebo (27% vs 35%; no stat testing). **Adverse events** (k=2; n=3191): 1 pooled subgroup analysis of 3 RCTs reported mostly similar across each of the LABA and placebo groups. TORCH subanalysis reported mixed results with some adverse events slightly more common in the LABA and some slightly more common in the placebo group, but no statistical testing was provided so it is unclear if there is a	Withdrawal rates: unknown single study Adverse events: unknown Pneumonia: unknown single study	Poor	Subgroup analyses with serious limitations. No statistical testing. Reasons for withdrawals not consistently reported.	INSUFFICIENT	Uncertain if harms can be extrapolated to asymptomatic screen detected patients.

Table 33. Summary of Evidence

Key Question	Population	No. of Studies, Observations (n), Design	Summary of Findings	Consistency/ Precision	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
			meaningful difference. **Pneumonia** (K=1; n=1074): TORCH subanalysis reported higher probability of developing pneumonia among participants in the control vs treatment group (10.6% vs. 9.4%; no statistical testing provided)					
	Mild to moderate COPD	LABA-ICS: K=2; n=1,149	**Withdrawals** (k=2; n=1,149): 1 subanalysis reported fewer withdrawals in the LABA-ICS group compared to placebo (27% vs 35%; no statistical testing). Laperre reported similar withdrawal rates in LABA-ICS and placebo group but only analyzed those with ≥70% adherence. **Composite adverse events** (k=1; n=1,108): TORCH subanalysis reported similar adverse events in LABA-ICS and placebo group. **Pneumonia** (k=1; n=1,108): TORCH subanalysis reported higher pneumonia in LABA-ICS group compared to placebo but no statistical testing (15.3% vs 10.6%)	Withdrawals: unknown different method-ologies Adverse events: unknown single study Pneumonia: unknown single study	Poor	Single trial subanalysis reporting each outcome. Reasons for withdrawals not consistently reported.	INSUFFICIENT	Uncertain if harms can be extrapolated to asymptomatic screen detected patients.

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Key Question	Population	No. of Studies, Observations (n), Design	Summary of Findings	Consistency/ Precision	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
	Mild to moderate COPD	Tiotropium K=3; n=4,076	**Withdrawal** (k=1; n=2,739): UPLIFT subanalysis of moderate COPD reported similar withdrawals in the tiotropium and placebo groups. **Composite adverse events (**k=2; n=1,337): Troosters trial of treatment naïve moderate COPD patients reported similar rates of serious events in the tiotropium and placebo groups (4.1% vs 4.4%; statistical testing not provided). The post hoc pooled analysis reported higher rates of any adverse event among patients treated with tiotropium compared to those on placebo; however, no statistical testing was performed (67% vs. 55.9%). **Pneumonia**: no trials	Withdrawal: unknown single study Composite adverse events: inconsistent	Poor	Most trials short (≤9 months). Single trial in moderate treatment naïve COPD patients. Harms reported variably in trials. Reasons for withdrawals not consistently reported.	LOW	Uncertain if harms can be extrapolated to asymptomatic screen detected patients.
	Mild to moderate COPD	ICS K=5; n=3,732	**Withdrawal** (k=4; n=2,617): All trials report similar withdrawal rates ranging from 11%-35% in ICS and placebo groups. **Composite adverse events** (k=3; n=2552): 2 of 3 trials show similar rates of composite adverse events; 1 trial reported more adverse events in the placebo group. **Pneumonia** (k=2; n=1,377): 2 trials report mixed results: 1 reported higher pneumonia rates in the ICS group and 1 repored higher pneumonia rates in the placebo group.	Withdrawal: consistent Composite adverse events: inconsistent Pneumonia: inconsistent Bone density/ fractures unknown single study	Poor	Harms reported variably in trials. Reasons for withdrawals not consistently reported.	LOW	Uncertain if harms can be extrapolated to asymptomatic screen detected patients.

Table 33. Summary of Evidence

Key Question	Population	No. of Studies, Observations (n), Design	Summary of Findings	Consistency/ Precision	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
			Bone density femoral neck (k=1; n= 359): LHS II subanalysis reported similar BMD at femoral neck in the ICS vs placebo groups but greater percent change from baseline in the ICS group, unlikely to be clinically meaningful. **Lumbar fracture (**k=1; n=1175): EUROSCOP trial of moderate COPD patients reported similar rates of new lumbar fractures in the ICS and placebo groups.					

Abbreviations: ACM = all-cause mortality; BD = bronchodilator; BMD = bone mineral density; BOLD = Burden of Obstructive Lung Disease; CAT = COPD Assessment Test; CDQ = COPD Diagnostic Questionnaire; CFQ = Case Finding Questionnaire; CG = control group; CI = confidence interval; COPD = Chronic Obstructive Pulmonary Disease; COPD-PS = COPD population screener; EUROSCOP = European Respiratory Society study on Chronic Obstructive Pulmonary Disease; 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; IG = intervention group; INHANCE = INdacaterol to Help Achieve New COPD treatment Excellence; ITT= Intention-to-treat analysis; LFQ = Lung Function Questionnaire; K = number of studies; LABA = long-acting beta-agonist; LHS = Lung Health Study II; LLN = lower limit of normal; L/s/m2 = liters per second per meters squared; MRC = Medical Research Council; N = number; NHANES III = The third National Health and Nutrition Examination Survey; NPV = negative predictive value; NR = not reported; OR = odds ratio; PEF = peak expiratory flow; PFT = pulmonary function test; PLATINO = Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar; PPV = positive predictive value; QOL = quality of life; RCT = randomized controlled trial; RR = risk ratio; SGRQ = St. George's Respiratory Questionnaire; TORCH = Towards a Revolution in COPD Health; UPLIFT = Understanding Potential Long-term Impacts on Function with Tiotropium; US = United States; VA = US Department of Veterans Affairs; WPAI = work productivity and activity impairment questionnaire

Table 34. Results of CDQ Screening in a Hypothetical Population*

COPD prevalence	Screen Positive, N	False Positives, N	Missed Cases, N
10%	591	504	13
20%	622	448	26

*n=1,000; cutpoint=16.5; sensitivity=87%; specificity=44%.

Abbreviations: CDQ = COPD Diagnostic Questionnaire; COPD = chronic obstructive pulmonary disease; N= number.

Table 35. Results of FEV_1/FEV_6 Screening in a Hypothetical Population*

Cutpoint	Test Performance	COPD prevalence	Screen Positive, N	False Positives, N	Missed Cases, N
<0.7 (preBD)	Sensitivity: 52% Specificity: 92%	10%	124	72	48
		20%	168	64	96
<0.75 (preBD)	Sensitivity: 84% Specificity: 72%	10%	336	252	16
		20%	392	224	32
<0.7 (postBD)	Sensitivity: 80% Specificity: 95%	10%	125	45	20
		20%	200	40	40

*n=1,000.

Abbreviations: BD = bronchodilator; COPD = Chronic Obstructive Pulmonary Disease; FEV_1= forced expiratory volume in 1 second; FEV_6= forced expiratory volume in 6 seconds; N = number.

Systematic Review Literature Search Strategies

AHRQ
Screening for Chronic Obstructive Pulmonary Disease Using Spirometry – 2008
http://www.uspreventiveservicestaskforce.org/uspstf/uspscopd.htm

BMJ Clinical Evidence
COPD – June 2011
http://clinicalevidence.bmj.com/x/systematic-review/1502/overview.html

Cochrane Database of Systematic Reviews
#1 "chronic obstructive pulmonary disease":ti,ab,kw
#2 "chronic obstructive airway disease":ti,ab,kw
#3 "chronic airflow limitation":ti,ab,kw
#4 "chronic obstructive respiratory disease":ti,ab,kw
#5 "obstructive lung" next disease*:ti,ab,kw
#6 "chronic bronchitis":ti,ab,kw
#7 COPD:ti,ab,kw or COAD:ti,ab,kw
#8 spirometry:ti,ab,kw
#9 bronchospirometry:ti,ab,kw
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 from 2008 to 2013, in Cochrane Reviews (Reviews only)

Database of Abstracts of Reviews of Effects (via CRD)
1 (((COPD) OR (COAD) OR (chronic obstructive pulmonary disease) OR (obstructive lung disease) OR (chronic obstructive airway disease) OR (chronic airflow limitation) OR (chronic obstructive respiratory disease) OR (chronic bronchitis))) IN DARE FROM 2008 TO 2013
2 (spiromet*) OR (bronchospiromet*) IN DARE FROM 2008 TO 2013
3 #1 OR #2

Health Technology Assessment (via CRD)
1 (((COPD) OR (COAD) OR (chronic obstructive pulmonary disease) OR (obstructive lung disease) OR (chronic obstructive airway disease) OR (chronic airflow limitation) OR (chronic obstructive respiratory disease) OR (chronic bronchitis))) IN HTA FROM 2008 TO 2013
2 (spiromet*) OR (bronchospiromet*) IN HTA FROM 2008 TO 2013
3 #1 OR #2

Institute of Medicine

A Nationwide Framework for Surveillance of Cardiovascular and Chronic Lung Diseases - July 2001
http://www.iom.edu/Reports/2011/A-Nationwide-Framework-for-Surveillance-of-Cardiovascular-and-Chronic-Lung-Diseases.aspx

National Institute for Health and Clinical Excellence

Chronic obstructive pulmonary disease: Management of chronic obstructive pulmonary disease in adults in primary and secondary care - June 2010

Appendix A. Detailed Methods

http://guidance.nice.org.uk/CG101/NICEGuidance/pdf/English

Chronic obstructive pulmonary disease quality standard – July 2011
http://publications.nice.org.uk/chronic-obstructive-pulmonary-disease-quality-standard-qs10

Roflumilast for the management of severe chronic obstructive pulmonary disease – January 2012
http://guidance.nice.org.uk/TA244/Guidance/pdf/English

PubMed

#14	Search **#9 OR #13** Filters: **Publication date from 2008/01/01 to 2013/12/31; English**	624
#13	Search **#12 AND systematic[sb]**	159
#12	Search **#10 OR #11 AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])**	4004
#11	Search **spirometry[tiab] OR bronchospirometry[tiab]**	10586
#10	Search **COPD[tiab] OR COAD[tiab] OR chronic obstructive pulmonary disease[tiab] OR chronic obstructive airway disease[tiab] OR chronic airflow limitation[tiab] OR chronic obstructive respiratory disease[tiab] OR obstructive lung disease*[tiab] OR chronic bronchitis[tiab]**	38182
#9	Search **#8 AND systematic[sb]** Filters: **English**	952
#8	Search **#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7**	36698
#7	Search **spirometry[title] OR bronchospirometry[title]**	1656
#6	Search **COPD[title] OR COAD[title] OR chronic obstructive pulmonary disease[title] OR chronic obstructive airway disease[title] OR chronic airflow limitation[title] OR chronic obstructive respiratory disease[title] OR obstructive lung disease*[title] OR chronic bronchitis[title]**	22030
#5	Search **"Bronchospirometry"[Majr:NoExp]**	192
#4	Search **"Spirometry"[Majr:NoExp]**	3773
#3	Search **"Lung Diseases, Obstructive"[Majr:NoExp]**	13093
#2	Search **"Bronchitis, Chronic"[Majr:NoExp]**	529
#1	Search **"Pulmonary Disease, Chronic Obstructive"[Majr:NoExp]**	16952

Search Strategies to Identify Relevant Literature for Key Questions

Key:
/ = MeSH subject heading
MH = CINAHL subject heading
$ = truncation
* = truncation
ti = word in title
ab = word in abstract
fs = floating subheading
adj# = adjacent within x number of words
N# = adjacent within x number of words
pt = publication type
kw = keyword
tx = all text

CINAHL – all KQ

S32 (S16 OR S31)
S31 (S26 OR S30)
S30 (S10 AND S22 AND S29) Limiters - English Language
S29 (S27 OR S28)
S28 TI ((influenza or flu or pneumococcal) N5 (vaccinat* or immuniz* or shot*)) OR AB ((influenza or flu or pneumococcal) N5 (vaccinat* or immuniz* or shot*))
S27 (MH "Immunization") OR (MH "Immunization Programs") OR (MH "Influenza Vaccine") OR (MH "Pneumococcal Vaccine")
S26 (S10 AND S22 AND S25) Limiters - Published Date: 20120101-20151231; English Language 21
S25 (S23 OR S24)
S24 TI (smok* N10 (cessation or quit* or stop* or abstain* or abstinence)) OR AB (smok* N10 (cessation or quit* or stop* or abstain* or abstinence)) OR TI (cigarette* N10 (cessation or quit* or stop* or abstain* or abstinence)) OR AB (cigarette* N10 (cessation or quit* or stop* or abstain* or abstinence))
S23 (MH "Smoking Cessation") OR (MH "Smoking Cessation Programs")
S22 S17 OR S18 OR S19 OR S20 OR
S21 TI ((biofeedback or feedback)) OR AB ((biofeedback or feedback))
S20 TI "health assessment" OR AB "health assessment" OR TI "risk assessment" OR AB "risk assessment"
S19 TI "respiratory function*" OR AB "respiratory function*" OR TI "lung function*" OR AB "lung function*"
S18 TI spiromet* OR AB spiromet* OR TI bronchospiromet* OR AB bronchospiromet*
S17 (MH "Respiratory Function Tests+")
S16 S9 AND S15 Limiters - Published Date: 20000101-20151231; English Language; Exclude MEDLINE records
S15 (S10 OR S11 OR S12 OR S13 OR S14)
S14 (TI longitudinal OR AB longitudinal OR TI "follow up" OR AB "follow up" OR TI followup OR AB followup)
S13 (TI database* OR AB database*) OR (TI registry OR AB registry) OR (TI registries OR AB registries)
S12 TX cohort OR TX observational OR TX nonrandom* OR TX non-random*

S11 (MH "Prospective Studies") OR (MH "Concurrent Prospective Studies") OR (MH "Nonconcurrent Prospective Studies") OR (MH "Correlational Studies") 179,301
S10 (MH "Meta Analysis") OR (MH "Control Group") OR (MH "Single-Blind Studies") OR (MH "Double-Blind Studies") OR (MH "Triple-Blind Studies") OR (MH "Randomized Controlled Trials") OR (MH "Clinical Trials") OR (MH "Random Assignment") OR (TX clinical n1 trial*) OR (TX controlled n1 trial*) OR (PT Clinical trial) OR (PT randomized controlled trial) 237,468
S9 (S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8)
S8 (TI "copd" OR AB "copd") OR (TI "coad" OR AB "coad")
S7 TI "chronic bronchitis" OR AB "chronic bronchitis"
S6 TI "obstructive lung disease*" OR AB "obstructive lung disease*"
S5 TI "chronic obstructive respiratory disease*" OR AB "chronic obstructive respiratory disease*"
S4 TI "chronic airflow limitation*" OR AB "chronic airflow limitation*"
S3 TI "chronic obstructive airway disease*" OR AB "chronic obstructive airway disease*"
S2 TI "chronic obstructive pulmonary disease*" OR AB "chronic obstructive pulmonary disease*"
S1 (MH "Pulmonary Disease, Chronic Obstructive") OR (MH "Bronchitis, Chronic") OR (MH "Lung Diseases, Obstructive")

CENTRAL – All KQ
Issue 11 of 12, November 2014

Search Name: COPD_all KQ_FINALrev
Date Run: 18/12/14 20:27:21.122
Description: sal 12.18.2014 _ USE FOR BRIDGE (added separate KQ5 search)

ID	Search	Hits
#1	"chronic obstructive pulmonary" next disease*:ti,ab,kw	4543
#2	"chronic obstructive airway" next disease*:ti,ab,kw	59
#3	"chronic airflow" next limitation*:ti,ab,kw	93
#4	"chronic obstructive respiratory" next disease*:ti,ab,kw	13
#5	"obstructive lung" next disease*:ti,ab,kw	1349
#6	"chronic bronchitis":ti,ab,kw	1311
#7	COPD:ti,ab,kw or COAD:ti,ab,kw	7061
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7	10374
#9	(prescreen* or pre-screen* or screen*):ti,ab,kw	20930
#10	(early or earlier):ti,ab,kw near/3 (identif* or test* or detect*):ti,ab,kw	2799
#11	(spiromet* or bronchospiromet*):ti,ab,kw	3516
#12	(respiratory or lung):ti,ab,kw near/3 test*:ti,ab,kw	4588
#13	("peak flow" or "peak expiratory flow"):ti,ab,kw	3923
#14	questionnaire*:ti,ab,kw	40364
#15	(famil* near/3 histor*):ti,ab,kw	1514
#16	#9 or #10 or #11 or #12 or #13 or #14 or #15	70804
#17	#8 and #16 Publication Year from 2000 to 2014, in Trials	1547
#18	(treat* or therap*):ti	206863
#19	bronchodilator*:ti,ab,kw	5818
#20	anticholinergic*:ti,ab,kw	2006
#21	beta*:ti,ab,kw near/3 (agonist* or adrenegenic or adrenoceptor):ti,ab,kw	4869
#22	(SABA or LABA):ti,ab,kw	268
#23	Albuterol:ti,ab,kw	3243

#24	Salbutamol:ti,ab,kw	3071	
#25	Fenoterol:ti,ab,kw	815	
#26	Levalbuterol:ti,ab,kw	75	
#27	Xopenex HFA:ti,ab,kw	0	
#28	Pirbuterol:ti,ab,kw	60	
#29	Maxair Autohaler:ti,ab,kw	8	
#30	Terbutaline:ti,ab,kw	1269	
#31	Spiriva:ti,ab,kw	34	
#32	Arformoterol:ti,ab,kw	37	
#33	Brovana:ti,ab,kw	0	
#34	Formoterol:ti,ab,kw	1671	
#35	Foradil:ti,ab,kw	77	
#36	Indacaterol:ti,ab,kw	172	
#37	Onbrez breezhaler:ti,ab,kw	1	
#38	Arcapta:ti,ab,kw	0	
#39	Salmeterol:ti,ab,kw	2038	
#40	Serevent diskus:ti,ab,kw	6	
#41	Olodaterol:ti,ab,kw	20	
#42	Vilanterol:ti,ab,kw	83	
#43	(muscarin* next antagonist*):ti,ab,kw	716	
#44	antimuscarin*:ti,ab,kw	359	
#45	(anti next muscarin*):ti,ab,kw	33	
#46	(SAMA or LAMA):ti,ab,kw	61	
#47	Ipratropium:ti,ab,kw	1350	
#48	Aclidinium:ti,ab,kw	97	
#49	Tudorza Pressair:ti,ab,kw	1	
#50	Glycopyrronium bromide:ti,ab,kw	197	
#51	Seebri breezhaler:ti,ab,kw	2	
#52	Tiotropium:ti,ab,kw	697	
#53	Respimat:ti,ab,kw	90	
#54	HandiHaler:ti,ab,kw	53	
#55	glucocorticoid*:ti,ab,kw	5045	
#56	corticosteroid:ti,ab,kw	5487	
#57	Beclomethasone:ti,ab,kw	1843	
#58	Qvar:ti,ab,kw	30	
#59	Betamethasone:ti,ab,kw	1513	
#60	Budesonide:ti,ab,kw	2928	
#61	Pulmicort flexhaler:ti,ab,kw	0	
#62	Ciclesonide:ti,ab,kw	374	
#63	Alvesco:ti,ab,kw	1	
#64	Formoterol:ti,ab,kw	1671	
#65	Symbicort:ti,ab,kw	148	
#66	Flunisolide:ti,ab,kw	199	
#67	Aerobid:ti,ab,kw	5	
#68	Fluticasone:ti,ab,kw	3064	
#69	Flovent:ti,ab,kw	14	
#70	Mometasone:ti,ab,kw	658	
#71	Asmanex:ti,ab,kw	4	

#72 Triamcinolone:ti,ab,kw 1502
#73 (dry next powder* next inhaler*):ti,ab,kw 742
#74 (metered next dose* next inhaler*):ti,ab,kw 1849
#75 (breath next actuated* next inhaler*):ti,ab,kw 23
#76 Accuhaler:ti,ab,kw 86
#77 Turbohaler:ti,ab,kw 97
#78 Diskhaler:ti,ab,kw 159
#79 (nebulizer* or nebuliser*):ti,ab,kw 2333
#80 {or #18-#79} 230089
#81 #8 and #80 Publication Year from 2010 to 2014, in Trials 1082
#82 (smok* or cigarette*):ti,ab,kw near/5 (stop* or cessat* or cease or abstin* or abstain* or control* or quit*):ti,ab,kw 7366
#83 (influenza or flu or pneumococcal):ti,ab,kw near/5 (vaccinat* or immuniz* or shot*):ti,ab,kw 1671
#84 (spiromet* or bronchospiromet*):ti,ab,kw 3516
#85 (respiratory or lung):ti,ab,kw next (function* or test*):ti,ab,kw 8102
#86 (health or risk):ti,ab,kw next assessment:ti,ab,kw 10655
#87 (biofeedback or feedback):ti,ab,kw 6849
#88 {or #84-#87} 27662
#89 #82 and #88 Publication Year from 2012 to 2014, in Trials 93
#90 #83 and #88 in Trials 47
#91 #17 or #81 or #89 or #90 2439

Medline

KQ1 - Screening

Database: Ovid MEDLINE(R) without Revisions <1996 to April Week 5 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 07, 2014>, Ovid MEDLINE(R) Daily Update <May 07, 2014>
Search Strategy:
---
1 Pulmonary Disease, Chronic Obstructive/ (21575)
2 Bronchitis, Chronic/ (758)
3 Lung Diseases, Obstructive/ (5633)
4 chronic obstructive pulmonary disease$.ti,ab. (23299)
5 chronic obstructive airway disease$.ti,ab. (143)
6 chronic airflow limitation$.ti,ab. (126)
7 chronic obstructive respiratory disease$.ti,ab. (37)
8 obstructive lung disease$.ti,ab. (2547)
9 chronic bronchitis.ti,ab. (3055)
10 copd.ti,ab. (22187)
11 coad.ti,ab. (82)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (40054)
13 Mass screening/ (54347)
14 Spirometry/ (6858)
15 Bronchospirometry/ (50)
16 Respiratory Function Tests/ (17034)
17 screen$.ti,ab. (359518)

18 spiromet$.ti,ab. (10662)
19 bronchospiromet$.ti,ab. (2)
20 ((respiratory or lung) adj2 function test$).ti,ab. (2313)
21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (401003)
22 12 and 21 (7258)
23 Pulmonary Disease, Chronic Obstructive/di [Diagnosis] (3577)
24 Bronchitis, Chronic/di (123)
25 Lung Diseases, Obstructive/di (833)
26 22 or 23 or 24 or 25 (9749)
27 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ (168286)
28 control groups/ or double-blind method/ or single-blind method/ (95648)
29 meta-analysis as topic/ (11332)
30 Random$.ti,ab. (566948)
31 clinical trial$.ti,ab. (174767)
32 controlled trial$.ti,ab. (102034)
33 meta analy$.ti,ab. (57428)
34 27 or 28 or 29 or 30 or 31 or 32 or 33 (832073)
35 26 and 34 (1647)
36 limit 35 to (english language and yr="2005 -Current") (1047)
37 remove duplicates from 36 (1047)

KQ2 – Targeted screening/risk stratification

Database: Ovid MEDLINE(R) without Revisions <1996 to August Week 1 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <August 19, 2014>, Ovid MEDLINE(R) Daily Update <August 19, 2014>
Search Strategy:
---
1 Pulmonary Disease, Chronic Obstructive/ (22311)
2 Bronchitis, Chronic/ (775)
3 Lung Diseases, Obstructive/ (5646)
4 chronic obstructive pulmonary disease$.ti,ab. (24173)
5 chronic obstructive airway disease$.ti,ab. (149)
6 chronic airflow limitation$.ti,ab. (129)
7 chronic obstructive respiratory disease$.ti,ab. (40)
8 obstructive lung disease$.ti,ab. (2620)
9 chronic bronchitis.ti,ab. (3104)
10 copd.ti,ab. (23050)
11 coad.ti,ab. (90)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (41375)
13 Risk Assessment/ (164921)
14 Risk factors/ (465571)
15 risk factor$.ti,ab. (303338)
16 (risk adj3 assess$).ti,ab. (55062)
17 (risk adj3 identif$).ti,ab. (42244)
18 ((high or increase$ or elevated) adj3 risk).ti,ab. (325626)
19 at risk.ti,ab. (85844)

20 13 or 14 or 15 or 16 or 17 or 18 or 19 (981501)
21 Mass screening/ (55328)
22 Questionnaires/ (256126)
23 Genetic predisposition to disease/ (86380)
24 screen$.ti,ab. (371043)
25 prescreen$.ti,ab. (1071)
26 pre screen$.ti,ab. (687)
27 questionnaire$.ti,ab. (263412)
28 (famil$ adj3 histor$).ti,ab. (36947)
29 ((early or earlier) adj3 (identif$ or test$ or detect$)).ti,ab. (63026)
30 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 (897008)
31 12 and 20 and 30 (1620)
32 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/ (178003)
33 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt. (502715)
34 Random$.ti,ab. (585176)
35 control groups/ or double-blind method/ or single-blind method/ (97386)
36 clinical trial$.ti,ab. (181062)
37 controlled trial$.ti,ab. (106461)
38 meta analy$.ti,ab. (61215)
39 cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ (1019077)
40 cohort.ti,ab. (231970)
41 longitudinal.ti,ab. (111196)
42 (follow up or followup).ti,ab. (494927)
43 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 (2206572)
44 31 and 43 (771)
45 limit 44 to (english language and yr="2000 -Current")

KQ3 – Test performance/Dx accuracy

Database: Ovid MEDLINE(R) without Revisions <1996 to August Week 1 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <August 19, 2014>, Ovid MEDLINE(R) Daily Update <August 19, 2014>
Search Strategy:
---
1 Pulmonary Disease, Chronic Obstructive/ (22311)
2 Bronchitis, Chronic/ (775)
3 Lung Diseases, Obstructive/ (5646)
4 chronic obstructive pulmonary disease$.ti,ab. (24173)
5 chronic obstructive airway disease$.ti,ab. (149)
6 chronic airflow limitation$.ti,ab. (129)
7 chronic obstructive respiratory disease$.ti,ab. (40)
8 obstructive lung disease$.ti,ab. (2620)
9 chronic bronchitis.ti,ab. (3104)
10 copd.ti,ab. (23050)
11 coad.ti,ab. (90)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (41375)

13 Mass screening/ (55328)
14 Spirometry/ (7020)
15 Bronchospirometry/ (50)
16 Respiratory Function Tests/ (17283)
17 Peak Expiratory Flow Rate/ (2808)
18 screen$.ti,ab. (371043)
19 spiromet$.ti,ab. (10972)
20 bronchospiromet$.ti,ab. (2)
21 ((respiratory or lung) adj2 function test$).ti,ab. (2363)
22 peak flow.ti,ab. (2686)
23 peak expiratory flow.ti,ab. (3646)
24 (test$ or detect$).ti. (318894)
25 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (701053)
26 12 and 25 (8273)
27 Pulmonary Disease, Chronic Obstructive/di [Diagnosis] (3715)
28 Bronchitis, Chronic/di (125)
29 Lung Diseases, Obstructive/di (836)
30 26 or 27 or 28 or 29 (10699)
31 "Sensitivity and Specificity"/ (250038)
32 "Predictive Value of Tests"/ (123921)
33 ROC Curve/ (27949)
34 False Negative Reactions/ (7749)
35 False Positive Reactions/ (12818)
36 Diagnostic Errors/ (15459)
37 "Reproducibility of Results"/ (249704)
38 Reference Values/ (90327)
39 Reference Standards/ (24352)
40 Observer Variation/ (27474)
41 Receiver operat$.ti,ab. (33075)
42 ROC curve$.ti,ab. (13779)
43 sensitivit$.ti,ab. (398115)
44 specificit$.ti,ab. (239264)
45 predictive value.ti,ab. (46839)
46 accuracy.ti,ab. (188213)
47 false positive$.ti,ab. (28994)
48 false negative$.ti,ab. (16366)
49 miss rate$.ti,ab. (229)
50 error rate$.ti,ab. (7478)
51 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 (1169692)
52 30 and 51 (1923)
53 limit 52 to (english language and yr="2000 -Current") (1543)
54 remove duplicates from 53 (1543)
55 limit 52 to (english language and yr="2000 -Current")

KQ 4, 6 – Screening harms

Appendix A. Detailed Methods

Database: Ovid MEDLINE(R) without Revisions <1996 to April Week 5 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 07, 2014>, Ovid MEDLINE(R) Daily Update <May 07, 2014>
Search Strategy:

---

1 Pulmonary Disease, Chronic Obstructive/ (21603)
2 Bronchitis, Chronic/ (760)
3 Lung Diseases, Obstructive/ (5634)
4 chronic obstructive pulmonary disease$.ti,ab. (23351)
5 chronic obstructive airway disease$.ti,ab. (143)
6 chronic airflow limitation$.ti,ab. (126)
7 chronic obstructive respiratory disease$.ti,ab. (37)
8 obstructive lung disease$.ti,ab. (2555)
9 chronic bronchitis.ti,ab. (3056)
10 copd.ti,ab. (22246)
11 coad.ti,ab. (82)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (40131)
13 Mass screening/ (54403)
14 Spirometry/ (6866)
15 Bronchospirometry/ (50)
16 Respiratory Function Tests/ (17041)
17 screen$.ti,ab. (359803)
18 spiromet$.ti,ab. (10674)
19 bronchospiromet$.ti,ab. (2)
20 ((respiratory or lung) adj2 function test$).ti,ab. (2313)
21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (401318)
22 12 and 21 (7266)
23 Pulmonary Disease, Chronic Obstructive/di [Diagnosis] (3580)
24 Bronchitis, Chronic/di (123)
25 Lung Diseases, Obstructive/di (834)
26 22 or 23 or 24 or 25 (9760)
27 Mortality/ (15506)
28 Morbidity/ (12726)
29 Death/ (4360)
30 safety.ti,ab. (233647)
31 harm$.ti,ab. (82227)
32 mortality.ti,ab. (347296)
33 complication$.ti,ab. (421796)
34 (death or deaths).ti,ab. (398868)
35 (adverse adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab. (202261)
36 side effect$.ti,ab. (113733)
37 adverse effects.fs. (807421)
38 mortality.fs. (267483)
39 false reassurance.ti,ab. (84)
40 false assurance.ti,ab. (6)
41 (unnecessar$ adj3 (treat$ or therap$)).ti,ab. (2358)
42 overtreat$.ti,ab. (1889)
43 Arrhythmias, Cardiac/ (17745)

44 cardiac ectop$.ti,ab. (20)
45 ectopic heartbeat$.ti,ab. (9)
46 arrhythmia$.ti,ab. (35782)
47 premature atrial contraction$.ti,ab. (122)
48 premature ventricular contraction$.ti,ab. (718)
49 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 (2104318)
50 26 and 49 (3083)
51 limit 50 to (english language and yr="2005 -Current") (1810)

KQ 5 – Spirometry/respiratory tests and smoking cessation/vaccination

Database: Ovid MEDLINE(R) <1946 to November Week 3 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 11, 2014>, Ovid MEDLINE(R) Daily Update <November 19, 2014>
Search Strategy:
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1 Smoking cessation/ (22129)
2 "Tobacco Use Cessation"/ (817)
3 Smoking/pc [Prevention & Control] (16116)
4 ((smok$ or cigarette$) adj10 (cessation or quit$ or stop$ or abstain$ or abstinence)).ti,ab. (28363)
5 1 or 2 or 3 or 4 (45364)
6 Immunization/ (43536)
7 Vaccination/ (57981)
8 Immunization Programs/ (7906)
9 Influenza vaccines/ (17540)
10 Pneumococcal Vaccines/ (5169)
11 ((influenza or flu or pneumococcal) adj5 (vaccinat* or immuniz* or shot*)).ti,ab. (13136)
12 6 or 7 or 8 or 9 or 10 or 11 (123196)
13 Spirometry/ (18008)
14 Bronchospirometry/ (715)
15 Respiratory Function Tests/ (39767)
16 spiromet$.ti,ab. (16391)
17 bronchospiromet$.ti,ab. (217)
18 ((respiratory or lung) adj3 (function$ or test$)).ti,ab. (46458)
19 health assessment.ti,ab. (5497)
20 risk assessment.ti,ab. (34715)
21 (biofeedback or feedback).ti,ab. (96905)
22 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (231679)
23 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/ (286881)
24 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt. (757319)
25 Random$.ti,ab. (772026)
26 control groups/ or double-blind method/ or single-blind method/ (154325)
27 clinical trial$.ti,ab. (238000)
28 controlled trial$.ti,ab. (133172)
29 meta analy$.ti,ab. (73510)
30 23 or 24 or 25 or 26 or 27 or 28 or 29 (1477927)
31 5 and 22 and 30 (490)

32 limit 31 to (english language and yr="2012 -Current") (97)
33 12 and 22 and 30 (114)
34 limit 33 to english language (109)
35 32 or 34 (205)
36 Animal/ not (Human/ and Animal/) (4006515)
37 35 not 36 (199)
38 remove duplicates from 37 (174)

KQ 7 – Tx

Database: Ovid MEDLINE(R) without Revisions <1996 to August Week 1 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <August 19, 2014>, Ovid MEDLINE(R) Daily Update <August 19, 2014>
Search Strategy:
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1 Pulmonary Disease, Chronic Obstructive/ (22311)
2 Bronchitis, Chronic/ (775)
3 Lung Diseases, Obstructive/ (5646)
4 chronic obstructive pulmonary disease$.ti,ab. (24173)
5 chronic obstructive airway disease$.ti,ab. (149)
6 chronic airflow limitation$.ti,ab. (129)
7 chronic obstructive respiratory disease$.ti,ab. (40)
8 obstructive lung disease$.ti,ab. (2620)
9 chronic bronchitis.ti,ab. (3104)
10 copd.ti,ab. (23050)
11 coad.ti,ab. (90)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (41375)
13 Bronchodilator Agents/ (10069)
14 Cholinergic Antagonists/ (3214)
15 Adrenergic beta-Agonists/ (10398)
16 Adrenergic beta-2 Receptor Agonists/ (1548)
17 "Nebulizers and Vaporizers"/ (5367)
18 Expectorants/ (1015)
19 Muscarinic Antagonists/ (6055)
20 Adrenal Cortex Hormones/ (20492)
21 Albuterol/ (4944)
22 Fenoterol/ (356)
23 Ipratropium/ (729)
24 Terbutaline/ (921)
25 Bronchodilator$.ti,ab. (5995)
26 anticholinergic$.ti,ab. (4956)
27 (beta$ adj3 (agonist$ or adrenegenic or adrenoceptor)).ti,ab. (16200)
28 (SABA or LABA).ti,ab. (957)
29 Albuterol.ti,ab. (1527)
30 Salbutamol.ti,ab. (3184)
31 Fenoterol.ti,ab. (414)
32 Levalbuterol.ti,ab. (126)
33 Xopenex HFA.ti,ab. (1)

34 Pirbuterol.ti,ab. (18)
35 Maxair Autohaler.ti,ab. (2)
36 Terbutaline.ti,ab. (1132)
37 Spiriva.ti,ab. (48)
38 Arformoterol.ti,ab. (31)
39 Brovana.ti,ab. (1)
40 Formoterol.ti,ab. (1412)
41 Foradil.ti,ab. (51)
42 Indacaterol.ti,ab. (207)
43 Onbrez breezhaler.ti,ab. (5)
44 Arcapta.ti,ab. (2)
45 Salmeterol.ti,ab. (1803)
46 Serevent diskus.ti,ab. (7)
47 Olodaterol.ti,ab. (27)
48 Vilanterol.ti,ab. (79)
49 muscarin$ antagonist$.ti,ab. (1229)
50 antimuscarin$.ti,ab. (1338)
51 anti muscarin$.ti,ab. (141)
52 (SAMA or LAMA).ti,ab. (592)
53 Ipratropium.ti,ab. (976)
54 Aclidinium.ti,ab. (83)
55 Tudorza Pressair.ti,ab. (2)
56 Glycopyrronium bromide.ti,ab. (40)
57 Seebri breezhaler.ti,ab. (2)
58 Tiotropium.ti,ab. (903)
59 Respimat.ti,ab. (95)
60 HandiHaler.ti,ab. (86)
61 glucocorticoid$.ti,ab. (33132)
62 (inhal$ and corticosteroid$).ti,ab. (7605)
63 Beclomethasone.ti,ab. (1435)
64 Qvar.ti,ab. (61)
65 Betamethasone.ti,ab. (2084)
66 Budesonide.ti,ab. (3304)
67 Pulmicort flexhaler.ti,ab. (1)
68 Ciclesonide.ti,ab. (271)
69 Alvesco.ti,ab. (8)
70 Formoterol.ti,ab. (1412)
71 Symbicort.ti,ab. (119)
72 Flunisolide.ti,ab. (172)
73 Aerobid.ti,ab. (4)
74 Fluticasone.ti,ab. (2681)
75 Flovent.ti,ab. (20)
76 Mometasone.ti,ab. (592)
77 Asmanex.ti,ab. (3)
78 Triamcinolone.ti,ab. (3650)
79 Dry powder$ inhaler$.ti,ab. (1219)
80 Metered dose inhaler$.ti,ab. (1986)
81 Breath actuated inhaler$.ti,ab. (34)

82 Accuhaler.ti,ab. (65)
83 Turbohaler.ti,ab. (71)
84 Diskhaler.ti,ab. (118)
85 Nebuli?er$.ti,ab. (2511)
86 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 (111811)
87 12 and 86 (6603)
88 Pulmonary Disease, Chronic Obstructive/dt (4605)
89 Bronchitis, Chronic/dt (251)
90 Lung Diseases, Obstructive/dt (994)
91 87 or 88 or 89 or 90 (8607)
92 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/ (178003)
93 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt. (502715)
94 Random$.ti,ab. (585176)
95 control groups/ or double-blind method/ or single-blind method/ (97386)
96 clinical trial$.ti,ab. (181062)
97 controlled trial$.ti,ab. (106461)
98 meta analy$.ti,ab. (61215)
99 92 or 93 or 94 or 95 or 96 or 97 or 98 (1072456)
100 91 and 99 (3045)
101 limit 100 to (english language and yr="2010 -Current")

KQ8 – Tx harms

1. Pulmonary Disease, Chronic Obstructive/
2. Bronchitis, Chronic/
3. Lung Diseases, Obstructive/
4. chronic obstructive pulmonary disease$.ti,ab.
5. chronic obstructive airway disease$.ti,ab.
6. chronic airflow limitation$.ti,ab.
7. chronic obstructive respiratory disease$.ti,ab.
8. obstructive lung disease$.ti,ab.
9. chronic bronchitis.ti,ab.
10. copd.ti,ab.
11. coad.ti,ab.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. Bronchodilator Agents/
14. Cholinergic Antagonists/
15. Adrenergic beta-Agonists/
16. Adrenergic beta-2 Receptor Agonists/
17. "Nebulizers and Vaporizers"/
18. Expectorants/
19. Muscarinic Antagonists/
20. Adrenal Cortex Hormones/

21. Albuterol/
22. Fenoterol/
23. Ipratropium/
24. Terbutaline/
25. Bronchodilator$.ti,ab.
26. anticholinergic$.ti,ab.
27. (beta$ adj3 (agonist$ or adrenegenic or adrenoceptor)).ti,ab.
28. (SABA or LABA).ti,ab.
29. Albuterol.ti,ab.
30. Salbutamol.ti,ab.
31. Fenoterol.ti,ab.
32. Levalbuterol.ti,ab.
33. Xopenex HFA.ti,ab.
34. Pirbuterol.ti,ab.
35. Maxair Autohaler.ti,ab.
36. Terbutaline.ti,ab.
37. Spiriva.ti,ab.
38. Arformoterol.ti,ab.
39. Brovana.ti,ab.
40. Formoterol.ti,ab.
41. Foradil.ti,ab.
42. Indacaterol.ti,ab.
43. Onbrez breezhaler.ti,ab.
44. Arcapta.ti,ab.
45. Salmeterol.ti,ab.
46. Serevent diskus.ti,ab.
47. Olodaterol.ti,ab.
48. Vilanterol.ti,ab.
49. muscarin$ antagonist$.ti,ab.
50. antimuscarin$.ti,ab.
51. anti muscarin$.ti,ab.
52. (SAMA or LAMA).ti,ab.
53. Ipratropium.ti,ab.
54. Aclidinium.ti,ab.
55. Tudorza Pressair.ti,ab.
56. Glycopyrronium bromide.ti,ab.
57. Seebri breezhaler.ti,ab.
58. Tiotropium.ti,ab.
59. Respimat.ti,ab.
60. HandiHaler.ti,ab.
61. glucocorticoid$.ti,ab.
62. (inhal$ and corticosteroid$).ti,ab.
63. Beclomethasone.ti,ab.
64. Qvar.ti,ab.
65. Betamethasone.ti,ab.
66. Budesonide.ti,ab.
67. Pulmicort flexhaler.ti,ab.
68. Ciclesonide.ti,ab.

69. Alvesco.ti,ab.
70. Formoterol.ti,ab.
71. Symbicort.ti,ab.
72. Flunisolide.ti,ab.
73. Aerobid.ti,ab.
74. Fluticasone.ti,ab.
75. Flovent.ti,ab.
76. Mometasone.ti,ab.
77. Asmanex.ti,ab.
78. Triamcinolone.ti,ab.
79. Dry powder$ inhaler$.ti,ab.
80. Metered dose inhaler$.ti,ab.
81. Breath actuated inhaler$.ti,ab.
82. Accuhaler.ti,ab.
83. Turbohaler.ti,ab.
84. Diskhaler.ti,ab.
85. Nebuli?er$.ti,ab.
86. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85
87. 12 and 86
88. Pulmonary Disease, Chronic Obstructive/dt
89. Bronchitis, Chronic/dt
90. Lung Diseases, Obstructive/dt
91. 87 or 88 or 89 or 90
92. Mortality/
93. Morbidity/
94. Death/
95. "Drug-Related Side Effects and Adverse Reactions"/
96. safety.ti,ab.
97. harm$.ti,ab.
98. mortality.ti,ab.
99. toxicity.ti,ab.
100. complication$.ti,ab.
101. (death or deaths).ti,ab.
102. (adverse adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
103. side effect$.ti,ab.
104. adverse effects.fs.
105. toxicity.fs.
106. mortality.fs.
107. Dizziness/
108. Headache/
109. Xerostomia/
110. Constipation/
111. Urinary Retention/
112. Urinary Tract Infections/

113. Muscle Cramp/
114. Hematoma/
115. Candidiasis, Oral/
116. Bone Density/de [Drug Effects]
117. Fractures, Bone/
118. Cataract/
119. Glaucoma/
120. Glaucoma, open-angle/
121. Cough/
122. Bronchial Spasm/
123. Arrhythmias, Cardiac/
124. Tachycardia/
125. Heart Failure/
126. Heart Arrest/
127. Heart Rate/de [Drug Effects]
128. Myocardial Infarction/
129. Cardiomyopathies/
130. xerostomia$.ti,ab.
131. dry mouth.ti,ab.
132. headache$.ti,ab.
133. tremor$.ti,ab.
134. constipat$.ti,ab.
135. urinary retention.ti,ab.
136. urinary tract infection$.ti,ab.
137. muscle cramp$.ti,ab.
138. (bruise$ or bruising).ti,ab.
139. h?ematoma$.ti,ab.
140. ((oral or oropharyngeal) adj candidiasis).ti,ab.
141. ((low or decrease$) adj3 (body mass density or BMD)).ti,ab.
142. fracture$.ti,ab.
143. cataract$.ti,ab.
144. glaucoma.ti,ab.
145. paradoxical bronchospasm$.ti,ab.
146. bronchial spasm$.ti,ab.
147. respiratory death$.ti,ab.
148. cardiovascular event$.ti,ab.
149. arrhythmi$.ti,ab.
150. tachycardi$.ti,ab.
151. palpitation$.ti,ab.
152. ((rapid or increase$ or elevat$) adj3 (heart rate or heartbeat)).ti,ab.
153. myocardial infarction$.ti,ab.
154. cardiomyopath$.ti,ab.
155. (heart adj (failure$ or attack$)).ti,ab.
156. cardiac death$.ti,ab.
157. 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137

or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156
158. 91 and 157
159. limit 158 to (english language and yr="2010 -Current")

Targeted immunization uptake search

Database: Ovid MEDLINE(R) without Revisions <1996 to April Week 5 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 07, 2014>, Ovid MEDLINE(R) Daily Update <May 07, 2014>
Search Strategy:
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1 Pulmonary Disease, Chronic Obstructive/ (21601)
2 Bronchitis, Chronic/ (760)
3 Lung Diseases, Obstructive/ (5634)
4 chronic obstructive pulmonary disease$.ti,ab. (23386)
5 chronic obstructive airway disease$.ti,ab. (144)
6 chronic airflow limitation$.ti,ab. (126)
7 chronic obstructive respiratory disease$.ti,ab. (37)
8 obstructive lung disease$.ti,ab. (2556)
9 chronic bronchitis.ti,ab. (3061)
10 copd.ti,ab. (22271)
11 coad.ti,ab. (82)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (40171)
13 Immunization/ (16139)
14 Vaccination/ (29248)
15 Immunization Programs/ (6769)
16 Influenza vaccines/ (11809)
17 Pneumococcal Vaccines/ (4213)
18 13 or 14 or 15 or 16 or 17 (59646)
19 ((influenza or flu or pneumococcal) adj5 (vaccinat* or immuniz* or shot*)).ti,ab. (9511)
20 13 or 14 or 15 or 16 or 17 or 18 or 19 (61940)
21 12 and 20 (346)
22 limit 21 to (english language and yr="2005 -Current") (195)
23 remove duplicates from 22 (193)

Appendix A. Detailed Methods

Pubmed, publisher-supplied All KQ

Search	Query	Items found
#16	Search **(((#13 OR #14 OR #15)) AND publisher[sb]) AND English[Language]**	756
#15	Search **(#5 AND #11 AND #12)**	336
#14	Search **(#5 AND #11 AND #12) AND ("2012"[Date - Publication] : "3000"[Date - Publication])**	74
#13	Search **(#4) AND ("2000"[Date - Publication] : "3000"[Date - Publication])**	31664
#12	Search **random*[tiab] OR trial*[tiab]**	1138451
#11	Search **#7 or #8 or #9 or #10**	176023
#10	Search **biofeedback[tiab] OR feedback[tiab]**	92412
#9	Search **health assessment[tiab] OR risk assessment[tiab]**	39593
#8	Search **respiratory function*[tiab] OR lung function*[tiab]**	33105
#7	Search **spirometr*[tiab] OR bronchospiromet*[tiab]**	15424
#6	Search **vaccinat*[tiab] OR immuniz*[tiab]**	194038
#5	Search **(smok*[tiab] OR cigarette*[tiab]) AND (cessation[tiab] OR quit*[tiab] OR stop*[tiab] OR abstain*[tiab] OR abstinence[tiab])**	29021
#4	Search **#1 OR #2 OR #3**	47520
#3	Search **COPD[title] OR COAD[title]**	10813
#2	Search **obstructive lung disease*[tiab] OR chronic bronchitis[tiab]**	13886
#1	Search **chronic obstructive pulmonary disease*[tiab] OR chronic obstructive respiratory disease*[tiab] OR chronic obstructive airway[tiab] OR chronic airflow limitation*[tiab]**	30163

Appendix A Figure 1. Literature Flow Diagram

Appendix A Table 1. Inclusion and Exclusion Criteria

	KQs	Inclusion	Exclusion
Populations	1-4	Asymptomatic adults* aged 40 and over†	Patients with diagnosed COPD or other respiratory conditions (KQ1 only); patients with identified alpha-1 antitrypsin deficiency; pregnant women
	5-6	5a/6a: Asymptomatic adults* aged 40 and over†; current smokers 5b/6b: Asymptomatic adults* aged 40 and over†;	Patients with identified alpha-1 antitrypsin deficiency; pregnant women
	7-8	Asymptomatic adults* aged 40 and over with screen detected fixed airway obstruction; patients with mild (FEV_1 ≥ 80% normal) to moderate (FEV_1 50-79% normal) COPD‡; or a population representative of mild or moderate disease (mean population FEV_1 ≥ 60% normal)	Patients with severe (FEV_1 30-49% normal) or very severe (FEV_1 <30% normal) COPD‡; pregnant women; patients with COPD-related symptoms (e.g. persistent dyspnea, chronic sputum production and/or cough); patients with identified alpha-1 antitrypsin deficiency
Setting	1-8	Primary or specialty care or community-based settings; developed countries, as defined by Human Development Index (HDI) in "very high human development" category (>0.8)§	Inpatient settings; countries not categorized as "very high human development (>0.8)"
Interventions	1-4	Pre-bronchodilator screening spirometry, questionnaires or risk assessment tools; peak flow meter; confirmatory post-bronchodilator spirometry	Spirometry or other modalities used for disease monitoring or management
	5-6	5a/6a: Screening pulmonary function testing with or without smoking cessation interventions and counseling 5b/6b: Screening pulmonary function testing with or without vaccination promotion interventions and counseling	Spirometry or other modalities used for disease monitoring or management
	7-8	Pharmacotherapy (including short and long acting beta-agonists, anticholinergics, inhaled corticosteroids, or combinations of these treatments)	Oxygen therapy, surgical therapies, lung transplant, systemic corticosteroids, phosphodiesterase-4 inhibitors, mucolytic agents, pulmonary rehabilitation‖
Comparisons	1	Usual care; no screening	
	2-4	KQ2/4: pre- or post-bronchodilator spirometry as the reference standard KQ3/4: post-bronchodilator spirometry as the reference standard	
	5-6	5a/6a: Smoking cessation counseling or interventions not including screening pulmonary function tests; usual care 5b/6b: Immunization promotion counseling or interventions not including screening pulmonary function tests; usual care	
	7-8	Usual care; placebo; no treatment	
Outcomes	1	All-cause mortality, disease specific mortality, COPD-related morbidity; HRQoL	
	2	fixed airflow obstruction requisite for COPD diagnosis as determined by established diagnostic standards (i.e. $FEV_1/FVC < 0.70$); test performance including: sensitivity and specificity (per person); positive (PPV) and negative (NPV) predictive value (per person); diagnostic yield by disease severity	

Appendix A Table 1. Inclusion and Exclusion Criteria

	KQs	Inclusion	Exclusion
	3	fixed airflow obstruction requisite for COPD diagnosis as determined by established diagnostic standards (i.e. $FEV_1/FVC < 0.70$) ; test performance including: sensitivity and specificity (per person); positive (PPV) and negative (NPV) predictive value (per person); diagnostic yield by disease severity	
	4, 6, 8	Serious adverse events requiring unexpected or unwanted medical attention and/or resulting in death (e.g., requiring hospitalization), adverse events reported by ≥ 5% of the study population, false reassurance for screen-negative smokers, false positive rate and missed diagnoses from screening	
	5	Self-reported or biologically validated smoking abstinence rates, sustained abstinence over the course of the study, number of quit attempts; immunization rates	
	7	All-cause mortality, disease specific mortality, COPD-related morbidity; HRQoL	
Study Designs	1, 5, 7	RCTs, systematic reviews (of included study designs)	Cohort studies, case-control studies, case series
	2-3	Diagnostic accuracy studies (including observational/cohort studies), systematic reviews (of included study designs)	
	4, 6	RCTs, large screening registry or database observational studies, cohort studies, systematic reviews (of included study designs)	
	8	RCTs included for KQ7, large screening registries, systematic reviews (of included study designs), FDA labels	
Study Quality	1-8	Good- & fair-quality	Poor-quality
Language	1-8	English	Non-English studies
Language	1-8	English	Non-English studies

* We will consider asymptomatic patients to be made up of individuals in one of the following states: those who are free of the disease; those in whom the disease is present, but who have physical symptoms that are undetected by the patient or the clinician (e.g., have mild dyspnea that goes unnoticed); or those who have nonspecific symptoms (e.g., sporadic sputum production or cough) that have gone unrecognized as being related to COPD.
†Recent survey data shows that the prevalence of COPD is highest in adults aged 65-84 years (8.3% in men 65-74 years; 11.2% in women 75-84 years of age). Epidemiological surveys suggest an incidence of 3 to 5% amongst adults aged 45 and under. Based on these data, this evidence review will focus on adults aged 40 and older.
‡Based on the GOLD criteria COPD classifications
§Settings: Included Countries: All countries listed as "very high" human development on Human Development Index (http://hdr.undp.org/en/statistics/): Andorra, Argentina, Australia, Austria, Barbados, Belgium, Brunei Darussalam, Canada, Chile, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, New Zealand, Norway, Poland, Portugal, Qatar, Seychelles, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Arab Emirates, United Kingdom, United States
‖Patients with severe disease would constitute a very small minority of those identified by asymptomatic screening spirometry and thus the treatment modalities recommended for these patients will not be considered in this evidence review (i.e. pulmonary rehabilitation, oxygen therapy, surgical treatment to reduce lung volume, and lung transplantation).

Appendix A Table 2. Quality Assessment Criteria

Design	USPSTF quality rating criteria[104]	National Institute for Health and Clinical Excellence methodology checklists[105]	QUADAS I and IITools[106,107]
Systematic reviews and meta-analyses	• Comprehensiveness of sources considered/search strategy used • Standard appraisal of included studies • Validity of conclusions • Recency and relevance are especially important for systematic reviews	• The study addresses an appropriate and clearly focused question • A description of the methodology used is included • The literature search is sufficiently rigorous to identify all the relevant studies • Study quality is assessed and taken into account • There are enough similarities between the studies selected to make combining them reasonable	Not applicable
Randomized controlled trials (RCTs)	• Initial assembly of comparable groups employs adequate randomization, including first concealment and whether potential confounders were distributed equally among groups • Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination) • Important differential loss to followup or overall high loss to followup • Measurements: equal, reliable, and valid (includes masking of outcome assessment) • Clear definition of the interventions • All important outcomes considered	• The study addresses an appropriate and clearly focused question • The assignment of subjects to treatment groups is randomized • An adequate concealment method is used • Subjects and investigators are kept 'blind' about treatment allocation • The treatment and control groups are similar at the start of the trial • The only difference between groups is the treatment under investigation • All relevant outcomes are measured in a standard, valid and reliable way • What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed? • All the subjects are analyzed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis) • Where the study is carried out at more than one site, results are comparable for all sites	Not applicable
Cohort studies	• Initial assembly of comparable groups employs consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts • Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination) • Important differential loss to followup or overall high loss to followup • Measurements: equal, reliable, and valid (includes masking of outcome assessment) • Clear definition of the interventions • All important outcomes considered	• The study addresses an appropriate and clearly focused question • The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation • The study indicates how many of the people asked to take part did so, in each of the groups being studied • The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis • What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed? • Comparison is made between full participants and those lost to followup, by exposure status • The outcomes are clearly defined • The assessment of outcome is made blind to exposure status	Not applicable

Appendix A Table 2. Quality Assessment Criteria

Design	USPSTF quality rating criteria[104]	National Institute for Health and Clinical Excellence methodology checklists[105]	QUADAS I and IITools[106,107]
		• Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome • The measure of assessment of exposure is reliable • Evidence from other sources is used to demonstrate that the method of outcome assessment is valid & reliable • Exposure level or prognostic factor is assessed more than once • The main potential confounders are identified and taken into account in the design and analysis • Have confidence intervals been provided?	
Diagnostic Accuracy Studies	• Screening test relevant, available for primary care, adequately described • Study uses a credible reference standard, performed regardless of test results • Reference standard interpreted independently of screening test • Handles indeterminate result in a reasonable manner • Spectrum of patients included in study • Sample size • Administration of reliable screening test	• The nature of the test being studied is clearly specified • The test is compared with an appropriate gold standard • Where no gold standard exists, a validated reference standard is used as a comparator • Patients for testing are selected either as a consecutive series or randomly, from a clearly defined study population • The test and gold standard are measured independently (blind) of each other • The test and gold standard are applied as close together in time as possible • Results are reported for all patients that are entered into the study • A pre-diagnosis is made and reported	• Test clearly described (or referenced) • Was the spectrum of patients representative of the patients who will receive the test in primary care? • Was the selection process clearly defined? • Were the index test results interpreted without knowledge of the reference standard results? • If a threshold was used, was it prespecified? • Are there concerns that the index test, its conduct, or its interpretation differ from the review question? • Is the reference standard acceptable for correctly classifying the target? • Were the reference standard results interpreted without knowledge of the index test? • Did the whole or partial selection of sample receive reference test • Was there an appropriate interval between the index test and reference standard? • Did all patients receive the same reference standard? • Were all patients included in the analysis?

Appendix B. Ongoing Studies

Study Country	Aim	Population Country	Intervention	Control	Relevant Outcomes	Status
TargetCOPD: a randomized controlled trial of targeted case finding for COPD versus routine practice in primary care ISRCTN14930255	Compare the benefits and cost effectiveness of two alternative case finding approaches for identifying undiagnosed COPD in GP (targeted case finding vs usual care)	Current and former smokers, age 40-79; UK	Mailed lung health questionnaire; those with respiratory symptoms invited to spirometry. Also, flagged in the GP's computer and if they come into practice for any reason, they are given a questionnaire.	Flagged in the GP computer and given the questionnaire if they show up in the GP practice for any reason.	Economic evaluation of case finding for COPD (cost per case identified)	Recruiting Estimated completion: January 2015
DOC Study: Determining the Optimal approach to identifying individuals with Chronis Obstructive Pulmonary Disease	Determining the optimal approach to identifying individuals with chronic obstructive pulmonary disease	Current smokers age 35+ in GP practices	Lung function tests and a case-finding questionnaire with immediate feedback	Lung function tests and a case-finding questionnaire with no results given for 6 months	Efficacy and cost-effectiveness of case-finding; impact on smoking behavior	Completed (not published) Completion date: July 2012
Early Detection of COPD Patients in GOLD 0 (Smokers) Population (MARKO) NCT01550679	Development of the MARKO questionnaire for detection of COPD	Current and former smokers, age 45-60 Croatia	MARKO questionnaire +/- COPD6 lung function measurement	Gold Standard: Pulmonologist diagnosis	Discriminative power, prevalence of COPD, sensitivity	Recruiting Estimated completion: December, 2016
Microspirometry as a 'point of care' test in diagnosing COPD by the general practitioner; a cluster-randomised trial (EMPERIC). NTR4041	Compare proportion of diagnostic spirometric assessment to determine presence or absence of COPD within 3 months after visit to GP.	Current or former smokers, age 50+, with respiratory symptoms that could indicate COPD Netherlands	Microspirometry measurement of FEV_1/FEV_6 in patients with symptoms of COPD	Usual care	Proportion of diagnostic assessments resulting in diagnosis of COPD, efficiency of testing	Status NR Estimated completion: September 2014
Developing a COPD Case Finding Methodology for Primary Care NCT01880177	Develop a new screening measure for identifying at-risk COPD cases in primary care	Current and former smokers, age 40+ US	Focus groups	NA	Development of COPD case finding tool	Recruiting Estimated completion: May 2015

Appendix B. Ongoing Studies

Study Country	Aim	Population Country	Intervention	Control	Relevant Outcomes	Status
Evaluation of a symptom-based COPD population screener (COPD-PS) questionnaire for screening of COPD in primary care UMIN000011433	Examine the usefulness of the COPD population screener (COPD-PS) questionnaire with a handheld spirometric device to identify undiagnosed COPD in primary care	Age 20+, patients with chronic disease who treated at primary care physicians Japan	COPD-PS, handheld device (not specified)	Gold Standard: Not specified	New COPD diagnosis	Enrolling Estimated completion: March 2016
Effectiveness of Spirometry as a Motivational Tool to Quit Smoking (ESPIMOAT) NCT01821885	Asses the efficacy of the spirometry and a minimal smoking cessation counselling intervention to quit smoking in smokers without an existing COPD diagnosis	Current smokers, age 40+ Spain	Spirometry and a brief advice to quit smoking	Brief advice to quit smoking	Smoking cessation rate (12 months), number of cigarettes, smoking abstinence difference between patients with COPD and without	Ongoing Estimated completion: February 2015
Effectiveness of Regular Reporting of Spirometric Results on Smoking Quit Rate. (ESPIROTAB) NCT01296295	Evaluate the effectiveness of regular reporting of spirometric results combined with smoking cessation advice on smoking quit rate in adult smokers in primary care	Current smokers, age 18+ Spain	Brief structured smoking cessation advice combined with a detailed and structured discussion of spirometric results	Brief structured smoking cessation advice	Smoking abstinence (12 months)	Unknown (Protocol published 2011)
Effectiveness of Smoking Cessation Advice Combined With Spirometric Results in Adult Smokers (ESPITAP) NCT01194596	Evaluate the effectiveness of the spirometric results information with smoking cessation advice compared to smoking cessation advice alone	Current smokers, age 35-70 Spain	Brief structured smoking cessation advice together with a detailed and structured discussion of spirometric results	Brief structured smoking cessation advice	Smoking abstinence (12 months), smoking reduction	Unknown (Protocol published 2011)

Appendix B. Ongoing Studies

Study Country	Aim	Population Country	Intervention	Control	Relevant Outcomes	Status
Multicentric Randomized Clinical Trial to Evaluate the Long-term Effectiveness of a Motivational Intervention Against Smoking, Based on the Information Obtained From Spirometry in Primary Care. (RESET-ESPITAP2) NCT02153047	Evaluate the effectiveness of smoking cessation advice with spirometry data compared to smoking cessation advice alone	Current smokers, age 35-70 Spain	Brief structured smoking cessation advice together with a detailed and structured 20-minutes visit with details of the spirometry data	Brief structured smoking cessation advice	Smoking cessation (12 months), smoking reduction	Ongoing Estimated completion: November 2014
The Get Quit - Stay Quit Study (GQSQ) NCT01980485	Evaluate the effectiveness of Lung Age feedback compared to scores from spirometry alone	Current smokers, age 18+	Feedback on lung age and exhaled carbon monoxide	Informed of scores on the spirometry.	Use of tobacco in last seven days, time to relapse (time frame 6 months)	Ongoing Estimated completion: December 2013
Study to Evaluate the Effect of Fluticasone Furoate/Vilanterol on Survival in Subjects With Chronic Obstructive Pulmonary Disease NCT01313676	Determine if fluticasone furoate/vilanterol improves survival in patients with chronic obstructive pulmonary disease with a history of or increased risk of heart disease	COPD patients age 40-80; current or former smokers; $FEV_1/FVC \leq 0.70$; FEV_1 50-70% predicted; increased heart disease risk (established CAD. PVD, stroke, MI, diabetes, organ disease, or hypercholesterolemia)	IG1: Fluticasone fuorate/vilaterol (100/25 mcg) once daily IG2: Fluticasone furoate (100mcg) once daily IG3: Vilanterol (25 mcg) once daily	Placebo	All-cause mortality; time to cardiovascular composite endpoint (death, MI, stroke, unstable angina, TIA)	Ongoing Estimated Completion: January 2015

Abbreviations: CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; FEV_1/FEV_6 = forced expiratory volume in 1 second/ forced expiratory volume in 6 seconds; FEV_1/FVC = forced expiratory volume in 1 second/forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; GP = general practice; mcg = microgram; MI = myocardial infarction; NA = not applicable; PVD = peripheral vascular disease; TIA = transient ischemic attack; UK = United Kingdom

Appendix C. Excluded Studies

Exclusion Code	Definition
E1	Study relevance
E2	Setting a. Not HDI > 0.9 b. Not generalizable to primary care
E3	Population a. Majority not mild –to-moderate disease b. Doesn't meet asymptomatic criteria c. Not Adults 40+ d. Not COPD
E4	Study quality
E5	Study design a. Not an approved study design for the KQ b. Comparative effectiveness c. Not appropriate reference standard d. Effectiveness, not uptake (KQ5) e. Not a screening tool (e.g., prognostic assessment) f. KQ5-8- Preventive service uptake not prompted by spirometry g. Uses preBD as the reference standard h. No subanalysis by disease severity (KQ7) i. N too small (≤ 10 per arm)
E6	No relevant outcomes
E7	Intervention a. Not a questionnaire (KQ2) b. Not a device (KQ3) c. Treatment not considered in our review (e.g. P4-inhibitors) d. Follow-up less than 6 months (KQ7)
E8	Article not in English
I1	Study included for designated Key Question

1. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. COMBIVENT Inhalation Aerosol Study Group. Chest 1994 May;105(5):1411-9. PMID: 8181328. **KQ7E7d.**
2. Routine nebulized ipratropium and albuterol together are better than either alone in COPD. The COMBIVENT Inhalation Solution Study Group. Chest 1997 Dec;112(6):1514-21. PMID: 9404747. **KQ7E7d.**
3. Aalbers R, Ayres J, Backer V, et al. Formoterol in patients with chronic obstructive pulmonary disease: a randomized, controlled, 3-month trial. Eur Respir J 2002 May;19(5):936-43. PMID: 12030736. **KQ7E7d.**
4. Aaron SD, Vandemheen KL, Fergusson D, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med 2007 Apr 17;146(8):545-55. PMID: 17310045. **KQ7E5b.**
5. Abrahams R, Ramsdell J, Moroni ZP, et al. Comparison of BEA2180 to tiotropium and placebo via respimat in patients with chronic obstructive pulmonary disease (COPD). Respirology 2012;17:46. PMID: None. **KQ7E5h.**
6. Abrahams R, Moroni-Zentgraf P, Ramsdell J, et al. Safety and efficacy of the once-daily anticholinergic BEA2180 compared with tiotropium in patients with COPD. Respiratory Medicine 2013 Jun;107(6):854-62. PMID: 23490224. **KQ7E5h.**
7. Abramson M, Schattner R, Lucas K, et al. Spirometry and regular follow-up are not associated with improved quality of life in General Practice patients [Abstract]. Respirology 2009;14:A30. PMID: None. **KQ1E3b.**
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13. Alfageme I, Vazquez R, Reyes N, et al. Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. Thorax 2006 Mar;61(3):189-95. PMID: 16227328. **KQ5bE5d.**
14. Anar C, Bicmen C, Yapicioglu S, et al. Evaluation of clinical data and antibody response following influenza vaccination in patients with chronic obstructive pulmonary disease. New Microbiologica 2010 Apr;33(2):117-27. PMID: 20518273. **KQ5bE5d.**
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20. Balamurugan S, Mehta R, Bhargava S, et al. Efficacy and safety of two HFA formulations of ipratropium bromide MDI in patients with mild to moderate chronic obstructive pulmonary disease. 7th International Primary Care Respiratory Group World Conference Athens 21 24 May, 2014 2014:O012-OTHU. PMID: None. **KQ7E5b.**
21. Balkan A, Bulut Y, Fuhrman CR, et al. COPD phenotypes in a lung cancer screening population. Clin Respir J 2014 Jul 3 **KQ2E7a, KQ3E7a.**
22. Balkissoon R. Concurrent use of indacaterol plus tiotropium in patients with COPD provides superior bronchodilation compared with tiotropium alone: A randomised, double-blind comparison. Copd: Journal of Chronic Obstructive Pulmonary Disease 2012;9:441. PMID: None. **KQ7E7d.**
23. Barnes TA, Fromer L. Spirometry use: detection of chronic obstructive pulmonary disease in the primary care setting. Clinical Interventions In Aging 2011;6:47-52. PMID: 21472091. **KQ2E5a.**
24. Bateman ED, Tashkin D, Siafakas N, et al. A one-year trial of tiotropium Respimat plus usual therapy in COPD patients. Respiratory Medicine 2010 Oct;104(10):1460-72. PMID: 20620037. **KQ7E5a.**
25. Bateman ED, Welte T, Hashimoto S, et al. Dual bronchodilation with once-daily QVA149 provides superior bronchodilation compared to its mono-components and tiotropium in all subgroups of patients with COPD: the SHINE study. American journal of respiratory and critical care medicine 2013;187:A4263. PMID: None. **KQ7E6.**
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35. Beier J, Kirsten AM, Mróz R, et al. Efficacy and safety of aclidinium bromide vs placebo and tiotropium in COPD: A phase IIIb study. European Respiratory Society Annual Congress, 2013 Sept 7 11, Barcelona, Spain 2013;42:4s. PMID: None. **KQ7E7d.**
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Appendix D. Scoring Details for Externally Validated Prescreening Questionnaires

Screening Questionnaire	Questionnaire Items	Answers (points assigned)	Scoring & Interpretation
Lung Function Questionnaire (LFQ)	How often do you cough up mucus?	Never (5) Rarely (4) Sometimes (3) Often (2) Very often (1)	If score is 18 or less, person may be at risk for COPD[93]
	How often does your chest sound noisy (wheezy, whistling, rattling) when you breathe?	Never (5) Rarely (4) Sometimes (3) Often (2) Very often (1)	
	How often do you experience shortness of breath during physical activity (walking up a flight of stairs or walking up an incline without stopping to rest)?	Never (5) Rarely (4) Sometimes (3) Often (2) Very often (1)	
	How many years have you smoked?	Never smoked (5) 10 years or less (4) 11-20 years (3) 21-30 years (2) More than 30 years (1)	
	What is your age?	Less than 40 years (5) 40-49 years (4) 50-59 years (3) 60-69 years (2) 70 years or older (1)	
COPD Diagnostic Questionnaire (CDQ) *Also known as: International Primary Care Airways Guidelines (IPAG)*	How old are you?	40-49 (0) 50-59 (4) 60-69 (8) 70+ (10)	Total score ≥17 suggests increased risk of COPD being present[36]
	What is your weight? What is your height? BMI = weight/height	<25.4 (5) 25.4-29.7 (1) >29.7 (0)	
	How many cigarettes do you smoke daily (if you are an ex-smoker how many cigarettes did you used to smoke daily)? How many years did/do you smoke? Packs per day = cigarettes per day/20 cigarettes per pack Pack-years = packs per day x years smoked	0-14 pack-years (0) 15-24 pack-years (2) 25-49 pack-years (3) 50+ pack-years (7)	
	Does the weather affect your cough?	Yes (3) No (0)	
	Do you ever cough up phlegm (sputum) from your chest when you don't have a cold?	Yes (3) No (0)	
	Do you usually cough up phlegm (sputum) from your chest first thing in the morning?	Yes (0) No (3)	
	How frequently do you wheeze?	Sometimes or often (4) Never (0)	
	Do you have or have you had any allergies?	Yes (0) No (3)	
COPD Population Screener (COPD-PS)	During the past 4 weeks, how much of the time did you feel short of breath?	None of the time (0) A little of the time (0) Some of the time (1) Most of the time (2) All of the time (2)	Total score scale ranges from 0 (unlikely to have fixed airflow obstruction) to 10 (likely to have fixed airflow obstruction).
	Do you ever cough up any "stuff", such as mucus or phlegm?	No, never (0) Only with occasional colds or chest infections (0) Yes, a few days a month (1) Yes, most days a week (1) Yes, every day (2)	

Appendix D. Scoring Details for Externally Validated Prescreening Questionnaires

Screening Questionnaire	Questionnaire Items	Answers (points assigned)	Scoring & Interpretation
	Please select the answer that best describes you in the past 12 months. I do less than I used to because of my breathing problems.	Strongly disagree (0) Disagree (0) Unsure (0) Agree (1) Strongly agree (2)	Development study suggests a cut point in the range of 5 to 6 provides a good trade-off between sensitivity and specificity. [88]
	Have you smoked at least 100 cigarettes in your entire life?	No (0) Yes (2) Don't know (0)	
	How old are you?	Age 35 to 49 (0) Age 50 to 59 (1) Age 60 to 69 (2) Age 70+ (2)	

Appendix E. Adverse Events Reported on FDA Labels of Drugs Included in KQ7

Drug Class	Drug	Black Box Warning	Brand	Approved indication(s)	FDA common adverse events: incidence ≥3% (and higher than placebo group)
Long-Lasting Anticholinergics	Tiotropium	None	Spiriva Respimat	COPD	Pharyngitis, cough, dry mouth, and sinusitis.
			Spiriva	COPD	Chest pain, edema (dependent), dry mouth, dyspepsia, abdominal pain, constipation, vomiting, myalgia, infection, moniliasis, upper respiratory tract infection, sinusitis, pharyngitis, rhinitis, epistaxis, rash, urinary tract infection
Inhaled Corticosteroids	Budesonide	None	Pulmicort Flexhaler	Asthma	Respiratory infection, sinusitis, headache, pain, back pain, fever
			Pulmicort Respules	Asthma	Respiratory infection, rhinitis, coughing, otitis media, viral infection, moniliasis, gastroenteritis, vomiting, diarrhea, abdominal pain, ear infection, epistaxis, conjunctivitis, rash
			Pulmicort Turbuhaler (discontinued)	Asthma	Respiratory infection, pharyngitis, sinusitis, voice alteration, headache, flu syndrome, pain, back pain, fever, oral candidiasis, dyspepsia, gastroenteritis, nausea
	Fluticasone propionate	None	Flovent (discontinued)	Asthma	Pharyngitis, nasal congestion, sinusitis, nasal discharge, dysphonia, allergic rhinitis, oral candidiasis, upper respiratory infection, influenza, headache
			Flovent Rotadisk (discontinued)	Asthma	Pharyngitis, nasal congestion, sinusitis, rhinitis, dysphonia, oral candidiasis, upper respiratory infection, influenza, bronchitis, headache, diarrhea, back problems, fever
			Flovent diskus	Asthma	Upper respiratory tract infection or inflammation, throat irritation, sinusitis, rhinitis, oral candidiasis, nausea and vomiting, gastrointestinal discomfort, fever, cough, bronchitis, and headache.
			Flovent HFA	Asthma	Upper respiratory tract infection or inflammation, throat irritation, sinusitis, dysphonia, candidiasis, cough, bronchitis, and headache.
	Mometasone furoate	None	Asmanex twisthaler	Asthma	Headache, allergic rhinitis, pharyngitis, upper respiratory infection, sinusitis, candidiasis (oral), dysmenorrhea, musculoskeletal pain, back pain, dyspepsia, myalgia, abdominal pain, nausea
			Asmanex HFA	Asthma	Nasopharyngitis, headache, sinusitis, bronchitis, and influenza.
	Triamcinolone acetonide	None	Azmacort (discontinued)	Asthma	Sinusitis, pharyngitis, headache, flu syndrome, back pain
Inhaled corticosteroid/ Long-acting Beta-agonist	Salmeterol/ Fluticasone propionate	Yes: Asthma Only*	Advair Diskus	Asthma, COPD	Pneumonia, oral candidiasis, throat irritation, dysphonia, viral respiratory infections, headaches, musculoskeletal pain.
			Advair HFA	Asthma	Upper respiratory tract infection or inflammation, throat irritation, dysphonia, headache, dizziness, nausea and vomiting.

Appendix E. Adverse Events Reported on FDA Labels of Drugs Included in KQ7

Drug Class	Drug	Black Box Warning	Brand	Approved indication(s)	FDA common adverse events: incidence ≥3% (and higher than placebo group)
Long-acting Beta-agonist	Formoterol Fumarate	Yes: Asthma only*	Foradil	Asthma, COPD	Upper respiratory tract infection, back pain, pharyngitis, chest pain
			Foradil certihaler (discontinued)	Asthma	Nasopharyngitis, headache, upper respiratory tract infection, cough, pyrexia, vomiting
			Perforomist	COPD	Diarrhea, nausea, nasopharyngitis, dry mouth
	Indacaterol maleate	Yes: Asthma Only*	Arcapta neohaler	COPD	Cough, nasopharyngitis, headache
	Salmeterol	None†	Serevent	Asthma, COPD	Upper respiratory tract infection, nasopharyngitis, disease of nasal cavity/sinus, sinus headache, stomach ache, headache, tremor, cough lower respiratory infection

* Black box warning on long-acting beta2-adrenergic agonists (LABA) warns of an increased risk of asthma-related death.
† Ongoing FDA investigation does not appear to be related to COPD