Evidence Report/Technology Assessment
Number 121

Use of Spirometry for Case Finding, Diagnosis, and Management of Chronic Obstructive Pulmonary Disease (COPD)

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions, and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Outcomes and Evidence, Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to **epc@ahrq.gov**.

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Structured Abstract

Context: Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality. COPD is diagnosed in symptomatic individuals through spirometric testing demonstrating irreversible airflow obstruction. Spirometry in primary care settings for case-finding, diagnosis, and management in all adults with persistent respiratory symptoms or having a history of exposure to pulmonary risk factors is controversial.

Objectives: Conduct a systematic review to determine: 1) the prevalence of COPD and airflow obstruction; 2) if spirometry improves smoking cessation; 3) if effectiveness of COPD therapies varies based on baseline or change in spirometric severity; and 4) whether spirometry provides independent prognostic value related to pulmonary outcomes.

Data Sources: Articles published in English from 1966 to May 2005 were identified by searching MEDLINE® and the Cochrane Database. Children and individuals with asthma or alpha-1 antitrypsin disease were excluded.

Study Selection: Ten cohort studies were included for prevalence; seven randomized clinical trials (RCTs) for smoking cessation; 53 RCTs and six meta-analyses for therapies; and five cohort studies for prognosis.

Data Extraction: Study and patient characteristics and outcomes were abstracted. Main outcomes according to age, race, gender, and spirometric, smoking, or symptom status by question were: 1) prevalence of airflow obstruction and clinical diagnosis of COPD; 2) smoking abstinence rates; 3) exacerbation rates, hospitalizations, mortality and respiratory health status; and 4) spirometry as an independent predictor of future COPD stage and symptoms.

Data Synthesis: Prevalence and severity of airflow obstruction, respiratory symptoms, and clinical diagnosis of COPD vary according to definition, country, and populations. Applying recent diagnostic criteria to a nationally representative U.S. survey, 7.2 percent were categorized as "at risk," 7.2 percent had mild airflow obstruction, 5.4 percent had moderate obstruction, and 1.5 percent had severe to very severe airflow obstruction. Airflow obstruction prevalence was higher in current or past smokers and older individuals. Symptoms were associated with severity of airflow obstruction, but one-third of individuals with normal airflow reported respiratory symptoms and 21 percent with severe to very severe airflow obstruction did not report respiratory symptoms. In this survey, more than 80 percent of adults reporting a clinical diagnosis of chronic bronchitis or emphysema did not have current airflow obstruction or spirometry. Evidence regarding the effect of spirometry on smoking cessation was limited and flawed. Data indicate that spirometry is of limited use in predicting a patient's future likelihood of quitting. Seven randomized studies assessed the effect of spirometry alone or with other interventions on smoking cessation. The only study designed to evaluate the independent effect of spirometry in conjunction with clinical counseling found a 1 percent greater quit rate at 12 months in the group assigned to receive spirometry plus repeat smoking cessation counseling. Spirometry is useful in adults with bothersome respiratory symptoms for determining at what threshold of airflow obstruction initiation of therapy is likely to be beneficial. COPD treatment trials evaluated inhaled medications, pulmonary rehabilitation, disease management, supplemental oxygen, or surgery. Most were less than 1 year in duration and involved subjects with severe to very-severe

airflow obstruction and frequent COPD exacerbations. Treatments reduced the percentage of subjects having one or more exacerbations by an absolute reduction of 5-6 percent but did not reduce mortality (except for oxygen in a small subset of individuals). The average magnitude of improvement for respiratory and dyspnea functional status measures was less than considered clinically significant though some subjects may notice considerable improvement.

Five large studies of greater than 1 year duration found little to no improvement in symptoms with inhaled medications among subjects with mild to moderate airflow obstruction, many of whom had respiratory symptoms and were detected based on spirometry. Analysis of one of these studies that included individuals who reported no respiratory symptoms showed that ipratropium did not prevent development of symptoms at 3 years of followup. Studies have not examined the value of spirometry to monitor need for additional therapy or to identify candidates for treatment among patients who do not report symptoms. However, it is unlikely to be effective because effectiveness of inhaled interventions are comparable, spirometry is not a useful guide for selecting among inhaled therapies, higher doses of inhaled interventions or combination therapies were not more effective than lower doses or monotherapy, clinical improvement was not associated with an individual's spirometric response to therapy, treatments other than smoking cessation did not alter spirometric decline, and interventions did not prevent symptom development in asymptomatic individuals. We estimated that the costs of routine spirometry of all adult smokers, ex-smokers, and non-smokers with any respiratory symptom would exceed $1 billion. Based on the prevalence of respiratory symptoms, levels of airflow obstruction identified in the U.S., and the effectiveness of drug therapy, we estimated that such a strategy applied to a clinic population of 10,000 adults would identify 6,588 for spirometric testing, detect 129 (1.3 percent) who would be candidates for COPD therapy, and result in 8 who would benefit from reduction in exacerbations. On average, respiratory status measures and survival would not be improved. Hospitalizations were rarely reported but the absolute reduction was 4-7 percent. If subjects with moderate airflow obstruction (FEV_1 between 50-80 percent predicted) are assumed to benefit, then 529 (5.3 percent) adults would be treatment candidates and 32 (0.3 percent) would benefit. These benefits would be retained at reduced costs and testing if spirometry was targeted to adults reporting bothersome symptoms. Spirometry provides independent prognostic value regarding morbidity and mortality. Subjects with chronic sputum production and normal spirometry are not at increased risk for developing airflow obstruction, and more than half of these subjects do not have chronic sputum production after 10 years of followup.

Conclusions: Spirometry, in addition to clinical examination, improves COPD diagnostic accuracy compared to clinical examination alone and it is a useful diagnostic tool in individuals with symptoms suggestive of possible COPD. The primary benefit of spirometry is to identify individuals who might benefit from pharmacologic treatment in order to improve exacerbations. These include adults with symptomatic, severe to very severe airflow obstruction. Spirometry for case finding among all adults with persistent respiratory symptoms or those with a history of exposure to pulmonary risk factors as well as for monitoring individuals or adjusting treatment is unlikely to be beneficial unless future studies establish that spirometry improves smoking cessation rates, treatments other than smoking cessation benefit individuals with airflow obstruction who do not report respiratory symptoms, or that relative effectiveness between therapies varies according to an individual's baseline or followup spirometry. Widespread spirometric testing is likely to label a large number of individuals (many who do not report respiratory symptoms) with disease and result in considerable testing and treatment costs and health-care resource utilization.

Contents

Evidence Report

Tables

Summary Tables

Figures

Appendixes

Appendixes and Evidence Tables are provided electronically at http://www.ahrq.gov/clinic/tp/spirotp.htm

Agency for Healthcare Research and Quality

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Number 121

Use of Spirometry for Case Finding, Diagnosis, and Management of Chronic Obstructive Pulmonary Disease (COPD)

Summary

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is manifested by chronic cough, sputum production, wheezing and, in later stages, dyspnea, poor exercise tolerance, and signs/symptoms of right-sided heart failure. Symptomatic COPD affects more than 5 percent of the adult population, is the fourth leading cause of death, and the twelfth leading cause of morbidity in the United States.[1,2] In more than 80 percent of cases, cigarette smoking is causally linked to the development of COPD. Smoking status should be assessed in all adults, and smokers should be advised to abstain from tobacco.

COPD is diagnosed in symptomatic individuals through spirometric testing that demonstrates irreversible airflow obstruction.[3] Spirometry for case-finding diagnosis and management of all adults with persistent respiratory symptoms or having a history of exposure to pulmonary risk factors has been recommended in primary care settings for all current and former smokers as well as never smokers who have persistent respiratory symptomsor have history of exposure to other COPD risk factors. This report was prepared to provide objective evidence and recommendations to inform the work of the American Thoracic Society (ATS), in collaboration with the American Academy of Family Physicians, the American College of Physicians, and the American Academy of Pediatrics Spirometry Task Force in clarifying usage of spirometry as part of the management of COPD. A systematic literature review was undertaken to address four questions:

1. What is the prevalence of COPD and airflow obstructions in various adult populations as defined by: (1) spirometry and (2) clinical examination?
2. Can use of spirometry lead to increased smoking cessation rates?
3. Does the effectiveness of COPD-specific therapies to improve clinically relevant outcomes vary based on baseline severity or change in spirometry?
4. Is prediction of future COPD status based on spirometry, with or without clinical indicators, more accurate than prediction based on clinical indicators alone?

Methods

Articles published in the English language from 1966 to May 2005 were identified by searching MEDLINE® and the Cochrane Database. Because the individual questions addressed different areas, the search strategies, types of eligible studies, populations, interventions, and outcomes varied. Emphasis was placed on studies that assessed outcomes from adults in primary care or population-based settings who had or were at risk for COPD according to race, gender, age, smoking, symptom, and spirometric status.

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Evidence-Based Practice

Children or individuals with asthma, or alpha-1 antitrypsin disease were excluded. Ten cohort studies [4-13] were included to estimate COPD/airflow obstruction prevalence and diagnostic accuracy. Seven randomized controlled trials (RCT)[14-20] met inclusion criteria for smoking cessation studies, 52 RCT[21-72] and six meta-analyses of RCT[73-78] were included for assessment of COPD-specific therapies, and five cohort studies were included for prognosis.[10, 79-82] The main outcomes according to question were:

1. Prevalence of airflow obstruction as determined by spirometry and clinical examination according to race, gender, age, smoking, and symptom status and previous diagnosis of COPD.
2. Long-term sustained smoking abstinence rates among smokers randomized to receive results of spirometry alone or in combination with other interventions compared to controls.
3. Exacerbations, hospitalizations, mortality, and respiratory health status according to type of treatment; baseline symptom status and FEV1; acute change in FEV1 or slope in FEV1 over time.
4. Independent prognostic value of airflow obstruction as determined by spirometric stage to predict future COPD status (stage and symptoms).

Data were used to estimate the number of adults according to smoking status that would require symptom and spirometric assessment and subsequent treatment to prevent COPD exacerbations, reduce mortality or hospitalizations, and improve smoking cessation or respiratory health status.

Results

More than one-third of the adult U.S. population reported respiratory symptoms compatible with symptomatic COPD. Compared to clinical examination, spirometry plus clinical examination improves diagnostic accuracy of clinically significant disease in adults who report respiratory symptoms (especially dyspnea). Based on the National Health and Nutrition Examination Survey (NHANES) III results, 12.8 percent of adults report a current or past diagnosis of obstructive lung disease (emphysema, chronic bronchitis, or asthma). However, only 17.4 percent of adults reporting a diagnosis of chronic bronchitis or emphysema (COPD) had 1987-ATS defined low lung function suggesting that many of these individuals have normal lung function. Fewer than half of individuals reporting a diagnosis of chronic bronchitis or emphysema stated that they were bothered by shortness of breath. Based on gender, age, and smoking status, between 40 and 80 percent of NHANES III participants with low lung function as determined by spirometry in the absence of bronchodilator testing reported no prior clinical diagnosis of COPD. However, there were no data regarding prevalence or type of respiratory symptoms in this group.

Spirometry, when used in primary care settings for case finding of all adults with persistent respiratory symptoms or having a history of exposure to pulmonary risk factors, is likely to label a relatively large proportion of individuals as diseased with airflow obstruction but who do not have respiratory symptoms or whose symptoms are unlikely to affect their health status. Conversely, spirometry is normal in a relatively large percentage of adults who report respiratory symptoms including dyspnea, the respiratory symptom having the greatest impact on quality of life. Prevalence and severity of airflow obstruction and symptomatic COPD vary widely according to definitions utilized and country and populations studied. The percentage of adults having normal spirometry and no respiratory symptoms (normal/asymptomatic) ranged from 56 to 91 percent. Compared with previous definitions of airflow obstruction, use of recent criteria tripled the number of adults being labeled as "at-risk" or having "low lung function" (from 6.8 to 20 percent). Normal spirometry with chronic sputum production ("at-risk") was present in 7.2 percent of subjects. An additional 13.9 percent of adults had prebronchodilator spirometrically detected airflow obstruction (mild, moderate, or severe to very severe airflow obstruction = 7.2 percent, 5.4 percent, and 1.5 percent respectively). Prevalence was higher in current smokers and older individuals. The percentage of individuals reporting respiratory symptoms increased with airflow obstruction severity. However, one-third of individuals with normal spirometry reported respiratory symptoms (21 percent reported shortness of breath). Some of these individuals may have had asthma and thus might have normal spirometry at the time of testing. Approximately, 21 percent of individuals with severe to very-severe airflow obstruction (similar to Global Initiative for Obstructive Lung Disease Stage 3,4) were asymptomatic and 35 percent did not report shortness of breath.

Smoking cessation is the most important factor in reducing the development and/or progression of airflow obstruction and symptomatic COPD. All adults should be asked about smoking and current smokers encourge to quit. However, evidence indicates that baseline symptom and spirometric status are of limited clinical use in reliably predicting a patient's future likelihood of quitting smoking. Spirometric testing as a motivational tool to improve smoking cessation rates is unlikely to provide more than a small benefit. Results from observational studies of spirometry are mixed. RCT of other biomarkers used as motivational tools for smoking cessation are generally negative. The only randomized controlled trial that

assessed the independent contribution of spirometry and counseling on smoking cessation rates reported a nonsignificant 1 percent greater quit rate at 12 months in the group assigned to receive spirometry plus repeat counseling compared to repeat counseling alone (6.5 percent vs. 5.5 percent). Quit rates were lower in the spirometry group than in participants who received repeat counseling plus nicotine replacement therapy (7.5 percent). Two other studies approximated an independent effect and their results were mixed. The self-reported 6-month point prevalent abstinence rates for the intervention group assigned to receive spirometry in combination with advice plus carbon monoxide values were lower than the group that received advice alone (9 percent vs. 14 percent). The one study that showed an improvement in smoking cessation rates compared a 50-minute educational intervention with a group that received the educational intervention plus a questionnaire and discussion of symptom status, spirometric results, and carbon monoxide levels. At 12 months, the biologically verified point prevalent quit rates were 20 percent in the intervention group and 6.7 percent in the control group. Four other trials that evaluated spirometry demonstrated an improvement in smoking cessation but all included concomitant interventions proven to increase abstinence.

Spirometry is useful for determining at what threshold of airflow obstruction initiation of therapy is likely to improve clinical outcomes in adults with bothersome respiratory symptoms. However, monitoring with spirometry to guide additional therapy or to initiate interventions in individuals who do not report bothersome respiratory symptoms does not appear to be beneficial. COPD trials typically were of short duration, they involved subjects with an established clinical diagnosis of COPD who had moderate to severe respiratory symptoms, frequent COPD exacerbations, and severe to very severe baseline airflow obstruction, and they used varying outcome definitions for exacerbations. On average, interventions reduced the relative risk of exacerbations by 20 to 25 percent and the absolute risk by 5 to 6 percent. Treatments improved measures of dyspnea and respiratory functional status, although the average improvement from inhaled bronchodilators and corticosteroids on validated health status measures failed to achieve a predetermined level of clinical significance. However, some individuals will notice greater and clinically significant improvement in respiratory symptoms. Few studies reported information on hospitalizations, but in those that did reduction was 4 to 7 percent. Mortality was similar between treatment and control groups, though there were relatively few events and the available information cannot rule out an improvement with long term inhaled treatment. Information related to the effectiveness of short-acting inhaled medications used for acute symptomatic rescue therapy was not available.

Benefits from interventions are mostly limited to reduction in exacerbations in patients having activity limiting respiratory symptoms and severe to very severe airflow obstruction (FEV1 <50 percent predicted). Five large studies of greater than 1-year duration (one assessing a short-acting anticholinergic and four evaluating inhaled corticosteroids) found little to no improvement in respiratory outcomes among subjects with mild to moderate airflow obstruction or those with normal airflow but having chronic sputum production ("at risk" individuals). Analysis of one of these studies that enrolled a subgroup of individuals that had mild to moderate airflow obstruction but denied respiratory symptoms demonstrated that ipratropium did not prevent development of symptoms at 3 years of followup. Subgroup analysis of other studies indicated that treatment benefit was almost exclusively confined to adults with bothersome respiratory symptoms and severe to very-severe airflow obstruction. Five additional comparative studies of long-acting inhaled b-agonists and corticosteroids indicated that combination therapy was similar to monotherapy regarding exacerbations (ARR 1-2 percent) and mortality (ARR 0-1 percent). Combination therapy with short- or long-acting beta-agonists plus anticholinergics was not superior to anticholinergics alone but did reduce exacerbations versus short-acting beta-agonists (ARR = 6 percent). Adverse effects of inhaled interventions during the study followup periods were generally mild but included bone loss, thrush, dry mouth, and serious cardiovascular events. About 50 percent of subjects remained compliant with therapy. Withdrawals from therapy were greater in subjects assigned to placebo than to active treatments.

Studies have not examined the value of spirometry to monitor need for additional therapy or to identify candidates for treatment among patients who do not report symptoms. It is unlikely to be beneficial because data indicated that: (1) clinical improvement was not associated with an individual's spirometric response to therapy; (2) treatments other than smoking cessation did not alter the rate of spirometric decline over time; (3) there was wide intra-individual variation in spirometric decline; (4) higher doses of inhaled interventions or combination therapy were not superior to lower doses or to monotherapy; and, (5) interventions were not effective in asymptomatic individuals or those with mild to moderate airflow obstruction.

Based on NHANES III results if all "at risk" adults (i.e., smokers and ex-smokers regardless of symptom status as well as never smokers with persistent respiratory symptom) undergo an office-based spirometric test then nearly two-thirds of the adult

population, approximately 110 million adults, would receive spirometric testing.

- If a primary care clinic was comprised of 10,000 adults with similar demographic, smoking, symptom, and spirometric status as NHANES III respondents then 6,588 would undergo spirometric testing, 129 (1.3 percent) would be potential candidates for COPD therapy and 7 (0.08 percent) would have reductions in exacerbations (i.e., an estimated 1,010 current smokers, 960 former smokers, and 2,043 never smokers would undergo spirometric and respiratory assessment to identify candidates for treatment consisting of an inhaled bronchodilator or corticosteroid to prevent an individual from having one or more exacerbations).
- If subjects with moderate airflow obstruction (FEV1 50-80 percent predicted; approximately Global Initiative for Obstructive Lung Disease Stage 2) benefit to a similar magnitude as severe to very severe airflow obstruction, then 529 adults (5.3 percent) would be candidates for treatment and 32 adults (0.3 percent) would benefit from having at least one exacerbation prevented compared with placebo. Approximately 76 (0.8%) would report a clinically noticeable improvement in respiratory health status. Reserving testing and treatment for individuals with respiratory symptoms (especially dyspnea, exercise intolerance, or exacerbations) would maintain benefits.
- If spirometry was targeted to individuals with dyspnea, regardless of smoking status, the number needed to screen and treat for severe to very severe airflow obstruction would be 475.

These estimates assume individuals with airflow obstruction and respiratory symptoms have COPD as the cause of their symptoms and that effective detection by clinical examination and treatment would not have occurred without spirometry. Based on 2004 Red Book prices the annual long-acting inhaled drug costs would be over $4.5 billion to treat the estimated 4 percent of adults with dyspnea and severe to very-severe airflow obstruction (n = 4,630,000). If combination therapy was routinely used instead of monotherapy, effectiveness would be similar but drug costs would be considerably higher. Compared to diagnosis and treatment based on clinical examination alone, spirometry may reduce the number of symptomatic individuals who are diagnosed with, and treated for, COPD but do not have airflow obstruction of severity that is likely to benefit from treatment.

Spirometry provides independent prognostic value regarding respiratory symptoms, morbidity, and mortality, though level of dyspnea is a better predictor of symptom progression and mortality. Baseline spirometry predicts rate of spirometric decline over time in male smokers. Spirometric levels may be useful as a guide for initiation of inhaled medications and pulmonary rehabilitation among individuals having disabling respiratory symptoms, especially frequent exacerbations. Subjects with chronic sputum production and normal spirometry (Stage GOLD 0 condition) are not at increased risk for developing airflow obstruction compared to individuals without chronic sputum production, and more than half of these subjects do not have chronic sputum production after 10 years of followup.

Discussion

Spirometry in addition to clinical examination improves COPD diagnostic accuracy compared to clinical examination alone and it is a useful diagnostic tool in individuals with symptoms suggestive of possible COPD. The primary benefit of spirometry is to identify individuals who might benefit from pharmacologic treatment in order to improve exacerbations. These include adults with symptomatic, severe to very severe airflow obstruction. In individuals where a diagnosis of asthma is suspected bronchodilator responsiveness, testing may be indicated. The evidence does not support widespread use of spirometry in primary care settings for all adults with persistent respiratory symptoms or having a history of exposure to pulmonary risk factors for case-finding, improving smoking cessation rates, monitoring the clinical course of COPD, or adjusting COPD interventions.

Routine spirometric testing in primary care settings is likely to result in considerable testing and treatment costs, resource utilization, and health care personnel time. It might reduce the number of individuals being labeled as having COPD or receiving disease-specific treatment in the absence of severe to very-severe airflow obstruction. However, it is likely to label a large number of individuals (many not reporting bothersome respiratory symptoms or having nondisabling symptoms) as diseased who would not benefit from testing or treatment. Treatment effectiveness (beyond short acting medications used for “acute rescue therapy”) is largely limited to reducing exacerbations among subjects who have bothersome dyspnea, frequent exacerbations, and severe to very-severe airflow obstruction. Nearly all the benefit from treatment could be obtained by reserving spirometry for those having activity limiting respiratory symptoms and targeting therapy to those who have reached a spirometric threshold of airflow obstruction of approximately a FEV1 less than 50 percent predicted. Spirometric response to therapy or change over time has not been shown to be associated with clinical outcomes, nor does it appear to be beneficial in modifying therapy. Future studies should be conducted to determine if spirometry improves

smoking cessation rates; if treatment effectiveness in established COPD varies according to an individual's baseline or followup spirometric value; if treatment benefits individuals with airflow obstruction and moderate to no reported respiratory symptoms; or if therapy improves the rate of decline of FEV1. Spirometry provides independent prognostic value for predicting respiratory and overall morbidity and mortality.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and quality (AHRQ) by the Minnesota Evidence-based Practice Center, under Contract No. 290-02-0009. It is expected to be available in September 2005. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 121, *Use of Spirometry for Case Finding, Diagnosis, and Management of Chronic Obstructive Pulmonary Disease (COPD)*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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Evidence Report

Chapter 1. Introduction

Overview

Chronic Obstructive Pulmonary Disease (COPD) is manifested by chronic cough, sputum production, and, in later stages, dyspnea, poor exercise tolerance, and signs/symptoms of right-sided heart failure. In more than 80 percent of cases, cigarette smoking is causally linked to the development of COPD. Other potentially modifiable risk factors include exposure to noxious gases, pollution, passive smoke, and chronic respiratory infections. Symptomatic COPD affects more than 5 percent of the adult population, is the fourth leading cause of death, and is the twelfth leading cause of morbidity in the United States.[1] The total economic costs of COPD were estimated to be $24 billion in 1993[2] and the total direct cost of medical care is approximately $15 billion per year. These figures likely vastly underestimate the burden of COPD because airflow obstruction is a contributor to other health conditions.[3-5]

In symptomatic individuals, COPD is diagnosed through the use of spirometric testing that demonstrates airflow obstruction that is not fully reversible which is due largely to airway narrowing and emphysema. The spirometric definition of airflow obstruction has evolved over time and varies according to criteria used. Normal values of spirometry are derived largely based on population distributions according to race, gender, and age. Most recently airflow obstruction has been defined as a postbronchodilator Forced Expiratory Volume in 1 second (FEV_1) value of less than 80 percent of predicted, in association with an FEV_1 to Forced Vital Capacity ratio (FEV_1/FVC) of less than 70 percent. Both the FEV_1 and FVC values are usually reduced in patients defined as having airflow limitation. Because the FEV_1 is affected more than the FVC, the ratio of the FEV_1 to FVC (FEV_1/FVC) also decreases.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) is comprised of an international committee of clinicians and scientists with the goal of increasing awareness of COPD and decreasing disease specific morbidity and mortality. The GOLD committee recently published a consensus report that defined COPD as "a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases."[6] Most guidelines also state that patients with COPD have an incomplete response to the inhaled bronchodilator albuterol (change in FEV_1 <200mL and 12 percent of baseline) and typically do not have evidence of airway hyper responsiveness. Although these features may be helpful in differentiating COPD from chronic asthma, they are not clear-cut, are potentially misleading, and do not predict spirometric progression.[7]

The 2003 GOLD guidelines have proposed five different stages of COPD based largely on postbronchodilator FEV_1 measures. These range from Stage 0 ("At Risk" FEV_1 normal [i.e., ≥80 percent in the presence of chronic cough and sputum production] to Stage 4 ["very severe" FEV_1 <30 percent predicted in association with FEV_1/FVC <70 percent or <50 percent plus chronic respiratory failure]). This classification, as well as recommendations for treatment does not require the presence of respiratory symptoms that include wheezing, chronic cough, sputum production, and dyspnea. GOLD guidelines recommend that a diagnosis of COPD should be considered and spirometry performed for any patient who has cough, sputum production, or

dyspnea, and/or a history of exposure to risk factors for the disease.[6,8] This includes all current and former smokers, and any adult with a history of exposure to tobacco smoke, occupational dusts and chemicals, or smoke from home cooking and heating fuels. Undiagnosed airflow obstruction, and the severity of FEV_1 impairment, is independently associated with poorer health and functional status.[3] Office-based case finding of at-risk individuals with spirometry by primary care providers is being encouraged. Symptomatic disease is often not present until advanced airflow obstruction occurs and many patients with symptomatic airflow obstruction remain undiagnosed.

Spirometric testing in primary care settings for COPD case-finding, diagnosis, and management may improve diagnostic accuracy, provide effective interventions for at risk individuals to slow progression of spirometric decline, prevent and relieve respiratory symptoms, improve exercise tolerance and health status, prevent and treat complications from end-stage lung disease, and reduce mortality. Spirometry may be resource intensive; it may identify and label as "diseased" a large group of individuals who may not have, nor develop, symptoms and in whom therapy is neither effective nor necessary. Spirometry may not improve health outcomes or smoking cessation rates. As a guide to management, it is not clear if therapy based on an individual's baseline or followup spirometry, spirometric response to treatment, or change in spirometry over time produces superior outcomes compared to therapy determined by clinical history and physical examination.

Concern has been raised about the costs associated with primary-care office based spirometry. Although a single spirometric test done without bronchodilators is relatively inexpensive, the aggregate economic and health effects of testing all adults with a history of exposure to risk factors (regardless of whether they report respiratory symptoms) and non-smoking adults with chronic respiratory symptoms are large. Followup visits, repeat office spirometry, full pulmonary function tests with bronchodilator testing, lung imaging, drug prescriptions, and smoking cessation interventions would follow initial primary-care office spirometry in many patients.[4]

The purpose of this report is to provide objective evidence and recommendations to inform the work of the American Thoracic Society (ATS), in collaboration with the American Academy of Family Physicians (AAFP), the American College of Physicians (ACP) and the American Academy of Pediatrics (AAP) Spirometry Task Force in clarifying usage of spirometry as part of the management of COPD. The Minnesota EPC (contract awardee) was requested to address the following preliminary questions using GOLD 2003 criteria as definitions of airflow obstruction:

What is the evidence that case-finding using spirometry, compared to clinical assessment, increases detection of patients with clinically significant disease?

What is the evidence that therapy based on spirometry (for initial therapy and/or followup) produces better outcomes than therapy based on clinical assessment?

What is the evidence that benefits of specific therapies to improve symptoms in COPD varies based on severity of COPD as assessed by spirometry?

What is the evidence that predictions or prognosis based on spirometry, with or without clinical indicators, are more accurate than prediction based on clinical indicators alone?

Initial discussion with representatives from ATS, AAFP, ACP, AAP, and technical expert panel members resulted in question refinement and the final Key Questions. These changes were based on development of an analytic framework that was developed to assess the key questions along the causal pathway of case finding, diagnosis, treatment, and outcomes. The framework describes the logical chain that should be supported by evidence to link spirometry to improved health outcomes. It takes the perspective of adults presenting to primary health care settings based on smoking and symptom status. It evaluates pathways related to spirometric and symptom status and potential benefits or harms of therapeutic interventions.

Key Question 1 What is the prevalence of chronic obstructive pulmonary disease (COPD) and airflow obstructions in various adult populations as defined by: 1) spirometry and 2) clinical examination?

Key Question 2 Can use of spirometry lead to increased smoking cessation rates?

Key Question 3 Does the effectiveness of specific therapies to improve clinically relevant outcomes in COPD vary based on baseline or followup spirometry, short-term spirometric response due to initial therapy, or spirometric progression over time?

Key Question 4 Is prediction of prognosis based on spirometry, with or without clinical indicators, more accurate than prediction based on clinical indicators alone?

Background

Less than half of the estimated 24 million Americans with impaired lung function have physician-diagnosed COPD.[5] A clinical diagnosis of COPD is often not made until patients have fairly advanced diseases that result in considerable functional impairment. Additionally, in the absence of spirometric testing, some individuals with dyspnea, wheezing, cough, or poor exercise tolerance due to COPD may not receive effective treatment because their symptoms are attributed to other etiologies (e.g., congestive heart failure) or conversely are misdiagnosed and treated erroneously for COPD when symptoms are due to other conditions. Because cigarette smoking is the greatest risk factor for development and progression of COPD, spirometric assessment of lung function may serve as a motivational tool to enhance smoking cessation rates. Spirometry may also be useful as a guide to 1) initiating treatment, 2) monitoring treatment effectiveness, 3) adjusting COPD specific therapies, and 4) establishing patient prognosis.

Case finding using office-based spirometry to detect impaired lung function has been proposed in selected "at-risk" individuals in primary care settings. In particular, the 2003 Executive Summary of GOLD recommends that "a diagnosis of COPD should be considered in any patient who has cough, sputum production, or dyspnea, and/or a history of exposure to risk factors for the disease. The diagnosis is confirmed by an objective measure of airflow limitation, preferably spirometry." These individuals include anyone with a current or past history of smoking as well as nonsmoking adults with persistent respiratory symptoms.[8] Therapy is outlined at each stage of COPD. This includes inhaled therapies and rehabilitation for individuals

with postbronchodilator spirometry demonstrating at least moderate airflow obstruction (FEV_1 <80 percent predicted) with or without respiratory symptoms.

Case finding with spirometry has the potential to provide early identification of airflow obstruction in asymptomatic individuals or those with nonspecific symptoms of cough and sputum production prior to the development of dyspnea that limits daily activities. If interventions are effective in these individuals, identification and treatment could prevent development of considerable morbidity and mortality. Routine spirometric testing may prompt health care providers to more aggressively and successfully implement appropriate early interventions, including smoking cessation, avoidance of environmental hazards exercise, enhanced compliance with influenza and pneumococcal vaccination programs, development of positive coping skills, and/or more appropriate utilization of pharmacologic therapies. Providing patients with knowledge of their lung function may improve healthy lifestyle and medication compliance. Assessing lung function among symptomatic individuals to determine if airflow obstruction is present (and quantifying its severity) could lead to improved diagnostic accuracy of COPD compared to clinical examination and more appropriate utilization of disease-specific interventions.

A recent systematic review and quantitative meta-analysis evaluated randomized clinical trials and assessed the impact of long-acting bronchodilators, inhaled corticosteroids, noninvasive mechanical ventilation, pulmonary rehabilitation, domiciliary oxygen therapy, lung volume reduction surgery, and disease management programs.[9] The authors concluded that "a significant body of evidence supports the use of long-acting bronchodilators and inhaled corticosteroids in reducing exacerbations in patients with moderate to severe COPD. Domiciliary oxygen therapy is the only intervention that has been demonstrated to prolong survival, but only in patients with resting hypoxia." Inhaled long-acting anticholingergics, and corticosteroids alone or in combination with a long-acting β2 agonist resulted in an improvement in health related quality of life and functional status as assessed by two standardized and validated COPD instruments. However, the weighted mean units of change compared to placebo were less than previously demonstrated to be clinically significant.[10]

The National Lung Health Education Program (NLHEP) has as its theme: "Test Your Lungs—Know Your Numbers." Their mission is to create awareness about COPD as a major health problem. NLHEP promotes the use of spirometry for diagnosis and monitoring of disease, including responses to therapy. NLHEP advises spirometric testing in all current and former smokers 45 years of age or older and in anyone of any age with chronic cough or wheeze, dyspnea on exertion, or mucus hypersection (i.e., production cough and phlegm).[11] To enhance implementation of these recommendations, NLHEP has developed educational materials and seminars and enlisted a cadre of "physician champions for COPD and respiratory health."

Chapter 2. Methods

Topic Assessment and Refinement and Literature Review

We began the review process conferencing with the AHRQ and the nominee partners (ATS, AAFP, ACP, and the AAP) to clarify the scope of the project and other background information. Seven clinical experts also agreed to serve as members of a technical expert panel group (TEP, See Appendix A[*]). The comments and suggestions provided by the TEP clarified the conceptual framework and refined study questions used for the project. Based on our initial conference calls we developed a comprehensive work plan that covered an assessment and refinement of study questions and proposed literature search and review, inclusion/exclusion criteria, methods for evaluating the quality of studies, and rating the strength of evidence.

Analytic Framework

An analytic framework was developed that assesses the key questions along the causal pathway of case finding, diagnosis, treatment, and outcomes (Figure 1 on page 14). The framework describes the logical chain that should be supported by evidence to link spirometry to improved health outcomes. It takes the perspective of adults presenting to primary health care settings based on smoking and symptom status. It evaluates pathways related to the spirometric and symptom status and potential benefits or harms of therapeutic interventions.

Question 1 What is the prevalence of chronic obstructive pulmonary disease (COPD) and airflow obstructions in various adult populations as defined by: 1) spirometry and 2) clinical examination?

Diagnosis and case-finding recommendations for spirometric testing include all adults with a history of exposure to risk factors including current and former smokers and any adult with persistent respiratory symptoms of cough, phlegm, wheeze, or dyspnea. Because smoking is the main risk factor in causing COPD, the analytic framework begins with adults presenting to a primary care clinic where an assessment of COPD risk factors (smoking and symptom status) is performed. Decision nodes are based on smoking and respiratory status. Spirometry characterizes an individual as having airflow obstruction (and the stage of severity) while history and physical examination assess the presence or absence of signs or symptoms. Among former and current smokers, spirometry would be utilized regardless of symptom status (case-finding in asymptomatic individuals or those with nonspecific symptoms). Thus, the prevalence of abnormal spirometry in these two groups regardless of symptom status is assessed and subsequently the prevalence of individuals within each spirometric category that have respiratory

[*] Note: Appendixes and evidence tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/spirotp.htm

symptoms. In adults that have never smoked, proposed spirometric recommendations are limited to those with respiratory symptoms. An unknown percentage of individuals might not be diagnosed or would be misdiagnosed in the absence of spirometry. Spirometry may detect a large reservoir of asymptomatic individuals, those with mild airflow limitation, or individuals with minimal symptoms that might not benefit from detection and treatment. Adverse effects would include increased health care costs, distraction from other interventions of proven effectiveness, or labeling individuals with disease unnecessarily or incorrectly. Spirometry could create unnecessary patient worry, increase health care expense and use of ineffective therapies with adverse effects, provide false reassurance, or lead to lower utilization of treatments of known effectiveness for other conditions.[12]

The analytic framework takes the perspective that abnormal airflow (as detected by spirometry) is a likely surrogate or risk factor for COPD but is not the sole criterion for defining clinically important disease or adults requiring treatment. Compared to clinical evaluation, spirometry would be useful if it improved diagnostic accuracy of individuals with airflow obstruction who would benefit from disease-specific interventions and ruled out individuals who are otherwise being misdiagnosed and/or receiving ineffective/unnecessary treatment. Improvement in process measures include increased smoking cessation rates and more appropriate utilization of effective interventions. Clinical outcomes include improved respiratory symptoms, health status, morbidity, and mortality in the spirometrically tested group. Determining the prevalence and severity of airflow obstruction in primary care adults according to symptom and smoking status and prior clinical diagnosis is necessary to assess the number of individuals that may benefit (or be harmed) by spirometric case-finding and diagnosis compared to clinical examination.

Definitions of "airflow obstruction" and "lower limits of normal" vary and typically have become more expansive over time. Normal lung function (and thus criteria for airflow obstruction) has been statistically derived from population-based surveys rather than directly based on pathological/clinical criteria of disease.[13] Spirometrically-detected airflow impairment has been defined using equations according to subjects having an FEV_1/FVC ratio below the lowest 5 percent of the reference population (controlled for gender, height, age, and race) rather than documenting a disease state or symptom status. Most population based surveys have not conducted bronchodilator reversibility testing and thus estimates of a patient's best lung function or the presence of asthma or partial reversibility in airflow obstruction may not be accurately known. Additionally, airflow obstruction as measured by spirometry does not fully describe the disability in COPD that is manifested by dyspnea, exercise intolerance, and exacerbations. Some individuals with airflow obstruction are asymptomatic. Others with respiratory symptoms compatible with COPD may have normal spirometry. This may be due to the fact that other physiologic abnormalities (dynamic hyperinflation of the lungs and peripheral muscle abnormalities) as well as psychologic variables (coexisting anxiety) affect these clinical outcomes. Even among symptomatic individuals with airflow obstruction other conditions may be the cause of the respiratory symptoms (e.g., heart failure).

GOLD has developed recommendations for the diagnosis, management, and prevention of COPD. Their recommendations rely on results of spirometry in addition to clinical evaluation (e.g., physical examination, chest x-ray, eliciting symptoms based on clinical history).[8] Diagnosis and treatment include individuals without respiratory symptoms but who have airflow obstruction. Changing definitions of disease can profoundly alter disease prevalence.[14] In the case of COPD, this could occur by classifying individuals with disease based solely on

spirometric findings rather than a combination of symptoms and physiologic measures or changing the level of spirometry that constitutes the presence or severity of disease. Table 1 on page 7 reflects the effects of using varying spirometric definitions of airflow obstruction. The effect of new definitions on disease prevalence/incidence, symptom severity, treatment, and outcomes is not known.

Table 1. A comparison of four sets of staging criteria for COPD*

Stage	American Thoracic Society (1995)		European Respiratory Society (1995)		British Thoracic Society (1997)		GOLD (2003)	
	FEV_1 %	Symptoms	FEV_1 %	Symptoms	FEV_1 %	Symptoms	FEV_1† %	Symptoms
0 (at risk)							≥80	+
1 (mild)	≥50	NA	70	NA	60-80	±	≥80	±
2 (moderate)	35-49	NA	50-69	NA	40-59	+	50-79	+
3 (severe)	<35	NA	<50	NA	<40	++	30-49	++
4 (very severe)							<30	+++

* GOLD denotes Global Initiative for Chronic Obstructive Lung Disease, and FEV_1 forced expiratory volume one second (shown as a percentage of the predicted normal value).

† GOLD 0 has a FEV_1/FVC Ratio >0.70 while GOLD 1-4 have an FEV_1/FVC <0.70. GOLD stages are based on postbronchodilator FEV_1. In the Symptoms columns, NA denotes not applicable (staging is based on physiology only),--no symptoms, ± variable symptoms, + mild to moderate symptoms, ++ symptoms that limit exertion, and +++ symptoms that limit daily activities.

Clinically significant COPD includes individuals with dyspnea or other respiratory symptoms that reduce quality of life. Spirometry may be useful to assess the presence and severity of airflow obstruction, determine if symptoms are likely due to COPD (both in confirming a diagnosis and establishing spirometric severity or in excluding airflow obstruction as a cause), and institute appropriate disease-specific intervention. In the absence of airflow obstruction, a clinical diagnosis of and treatment for COPD is inappropriate (though individuals with asthma or a large bronchodilator response may have normal spirometry during symptom free periods). Assessing airflow in the absence of disabling symptoms or effective preventive interventions is limited to prognostic information or improving smoking cessation rates.

Question 2 Can use of spirometry lead to increased smoking cessation rates?

Smoking cessation is the most effective way to reduce the risk of developing COPD and prevent or improve respiratory symptoms. While smokers with symptoms have the greatest improvement, reduction in future respiratory symptoms is seen even among asymptomatic individuals with airflow obstruction.[15] It is the only intervention demonstrated to prevent or delay the development of airflow limitation and reduce its progression. In patients with mild to moderate airflow obstruction, abstinence from smoking results in a sustained 50 percent reduction in the rate of lung-function decline over time.[16]

Clinical Practice Guidelines issued by the U.S. Department of Health and Human Services[17] recommend that health care providers identify all smokers and advise them to quit regardless of spirometric or symptom status. Individuals attempting to quit smoking should be offered pharmacological interventions, unless there are medical reasons to withhold this form of treatment. Interventions that improve smoking cessation rates and maintain abstinence would be very valuable. However, reducing the prevalence of smoking has proven to be a formidable task.[18]

Approximately 35 percent of smokers with mild to moderate airflow obstruction enrolled in the Lung Health Study achieved abstinence at 1 year, but only 22 percent reported continued abstinence at 5 years. The 16 percent absolute reduction compared to enrollees assigned to receive "usual care" occurred with an intensive intervention that consisted of nicotine replacement (chewing gum, inhaler, spray, and a transcutaneous patch that was provided free of charge), cessation behavioral counseling, which consisted of 12 group sessions in the first 10 weeks, and a maintenance program for people who quit smoking.[19] Cost effectiveness analyses have shown that smoking cessation interventions with incremental quit rates of 3 percent to 6 percent are economically acceptable because of the large health benefits (many beyond airflow obstruction) due to smoking cessation.[4]

A key question in case-finding is to determine if obtaining spirometry and providing individuals with measures of their lung function improves smoking cessation rates among current smokers and maintains abstinence among former smokers or never smokers. Benefits could occur regardless of symptom status or spirometric value. The potential roles of spirometry in improving smoking cessation rates include its use as a: 1) "biomarker assessment of lung health" to provide feedback and encouragement for smoking cessation and continued abstinence (regardless of symptom status); 2) risk stratification or prognostic tool for identification of an individual's (or group's) likelihood of smoking cessation, and 3) guide for targeting types of smoking cessation programs. Smoking cessation counseling could be enhanced by incorporating results from spirometric testing into routine clinic visits. Health care providers may be more likely to counsel patients or recommend additional smoking cessation therapies based on spirometric findings. Smokers may be more likely to quit if presented with information about their "lung health." Adverse effects include added costs and resource use associated with initial and confirmatory spirometric testing and decreased smoking cessation rates due to false reassurance or nihilism. The potential role for, and outcome from, spirometry used as a motivational tool for smoking cessation are shown in Figure 2 on page 15.

Question 3 Does the effectiveness of specific therapies to improve clinically relevant outcomes in COPD vary based on baseline or followup spirometry, short-term spirometric response due to initial therapy, or spirometric progression over time?

Treatment goals are to reduce spirometric decline in lung function, relieve disabling respiratory symptoms (particularly dyspnea), improve exercise tolerance and health status, prevent and treat complications and exacerbations, and reduce mortality. Recommendations encourage use of spirometry to assess baseline severity of airflow obstruction and acute treatment response. Clinicians are encouraged to periodically assess symptoms and monitor objective measures of airflow limitation for development of complications and to determine when to adjust therapy. The effectiveness of this strategy is not known.

If treatments are effective in adults with mild to moderate airflow obstruction or those with absent or relatively mild respiratory symptoms, then one potential benefit of case-finding with spirometry could be identification and treatment of a large number of individuals not readily detected by clinical examination. However, if effectiveness is limited to the much smaller cohort of subjects with severe airflow obstruction and activity limiting respiratory symptoms, then

population-based spirometric case-finding is less likely to be beneficial compared to spirometric identification and treatment targeted at individuals with bothersome respiratory symptoms.

Spirometry may be useful as a guide for initial and followup management among individuals with established airflow obstruction/COPD. Among asymptomatic individuals, spirometry could be effective if it resulted in initiation of interventions for airflow obstruction that prevented the development of symptoms or reduced the decline in lung function. In symptomatic individuals, spirometry could improve diagnostic accuracy and determination of whether or not spirometric thresholds of airflow obstruction exist prior to appropriate initiation of COPD specific therapy. Monitoring patients with periodic spirometry would be useful if modification of therapeutic interventions according to spirometric response to therapy, spirometric change over time, or achieving a certain spirometric threshold reduced respiratory symptoms including exacerbations and hospitalizations and improved quality of life. Adverse effects would include the costs of using spirometry to monitor treatment or disease progression, harms related to medication use, and unnecessary or improper initiation/modification of treatments based on spirometry compared to clinical evaluation. To assess the effectiveness of interventions for COPD beyond smoking cessation we will focus on whether effectiveness varies according to symptom status (presence or absence, type, severity, or frequency of symptoms), previous clinical diagnosis of COPD, baseline or followup spirometry, acute spirometric response to treatment, spirometric slope over time, and intervention type or dose.

Question 4 Is prediction of prognosis based on spirometry, with or without clinical indicators, more accurate than prognosis based on clinical indicators alone?

Spirometry could provide independent prognosis related to quality of life, progression to more severe and symptomatic COPD, and mortality (both overall and COPD specific). Spirometry may help identify individuals at increased risk for future health problems who are in need of effective COPD-specific interventions. Spirometry may provide more accurate risk stratification and appropriate utilization of interventions for other chronic medical conditions.

The analytic pathway includes the ability of clinical examination and history to determine respiratory symptom status and etiology, spirometry to assess presence and severity of airflow obstruction, spirometry to alter smoking cessation and abstinence rates in current and former smokers, spirometry to guide initiation and modification of pharmacologic or rehabilitation therapy for individuals with established COPD, and finally spirometry as a prognostic tool for future COPD-related outcomes (especially worsening symptom status).

Final synthesis of this information will result in a pathway that evaluates the number of adults needed, according to smoking and symptom status, to receive office-based spirometry in order to identify candidates for treatment. We will estimate the number of individuals likely to have improvement in specific outcomes, the type and relative effectiveness of interventions, whether monitoring of spirometry improves clinical management and outcomes, and prognosis based on spirometric findings.

Literature Search and Data Abstraction

We conducted literature searches for the four key questions simultaneously. Because the individual questions addressed different areas, the search strategies, types of eligible studies, populations, interventions, and outcomes varied for each. The focus of this project was the identification and management of adults with, or at risk for, COPD. Emphasis was placed on studies that assessed outcomes from individuals in primary care or population-based settings of the U.S. according to race, gender, age, smoking, symptom, and spirometric status. Children, individuals with asthma, or alpha-1 antitrypsin disease were excluded.

Question 1

Data sources. Articles published in the English language from 1966 to January 2005 were identified by searching MEDLINE accessed through PubMed and Cochrane Database using the following terms: diagnosis, epidemiology, bronchospirometry, COPD, emphysema, bronchitis, respiratory function tests, airway obstruction (or airflow limitation), cohort studies, case reports, case-control studies. Because our goal was to estimate the prevalence of COPD and airflow obstruction likely to be encountered by casefinding in primary care settings, we examined population based or primary care cohort or case-control studies.

Study selection. Studies were eligible if they reported the results of spirometry testing of community-based adult populations or primary care settings and were published in English. Studies limited to patients with known COPD or symptoms such as cough, sputum production, dyspnea, or wheeze were excluded unless results were reported separately for asymptomatic individuals. Emphasis was placed on community-based studies conducted in the U.S.

Outcomes. The primary outcome was the prevalence of airflow obstruction according to GOLD stage (or other consensus criteria such as ATS) according to: spirometry, race, gender, age, symptom, and smoking status (current, past, or never), and presence of a clinical diagnosis of COPD.

Quality assessment. Quality and strength of evidence was determined by whether the included studies adequately addressed our key outcome by providing information related to spirometrically-detected COPD in general adult populations or primary care settings according to GOLD stage or other consensus criteria, race, gender, age, smoking, and symptom status. Because this report was intended to guide clinical decisions in the United States, we placed greatest emphasis on studies conducted in the U.S.

Question 2

Objective. Our primary goal was to determine if providing smokers with results from spirometric testing improves smoking cessation rates.

Data sources and study selection. A detailed search strategy was used to identify potentially relevant articles and is provided in Appendix B*. Studies were eligible if they were randomized controlled trials (RCTs), published in English, had a minimum of 25 subjects per treatment arm, involved subjects that smoked (regardless of respiratory symptoms or spirometry status), had a followup time of 6 months or longer, and provided outcomes smoking cessation rates (as measured by self-report or biochemical validation such as carbon monoxide level). The intervention had to include spirometry alone or in conjunction with other treatments as a motivational tool for smoking cessation. Studies were excluded if the control group also received notification of spirometric results. Non-controlled reports that merely reported smoking cessation rates according to spirometric value or respiratory status were excluded. However, these studies were reviewed and findings described in order to estimate whether spirometric values or respiratory status could predict smoking cessation rates. Of the 212 references identified, seven met eligibility criteria (Figure 3 on page 16). Additionally, in order to provide a context for potential magnitude and biologic plausibility of various smoking cessation strategies, we included information related to the effectiveness of established strategies for smoking cessation and rationale for use of biomarkers as a tool for enhancing smoking cessation counseling.

Literature search strategy. The literature search used Ovid MEDLINE until May 2005. To supplement this search, we examined the Cochrane Database of Systematic Reviews of Effectiveness as well as bibliographies of published articles and contacted experts in the field. Listserv members of the World Health Organization's Society for Research on Nicotine and Tobacco were contacted and invited to identify additional published, unpublished, or ongoing relevant studies. Search terms included: spirometry; smoking therapy; smoking psychology; COPD; airflow limitation; randomized controlled trials; controlled clinical trials; and case-control studies. Identified articles were reviewed along with their references to identify other key articles and to refine our search strategy. Our search strategy included articles identified to evaluate the effectiveness of interventions for patients with COPD (Question 3). Titles and abstracts of identified references were reviewed using standardized data abstraction sheets (Appendix C*). All references received an identification number.

Interventions. We considered the process of obtaining and providing the results of spirometry to smokers in combination with focused smoking cessation counseling as a single intervention consistent with a pragmatic approach likely to be employed in health care settings. Other differences in interventions between treatment and control groups such as the incorporation of results from biomarker testing (carbon monoxide or cotinine levels, chest x-rays, etc.), varying frequency, intensity, methods of counseling, or pharmacologic treatments were considered concomitant interventions that might differentially effect cessation rates.

Outcomes. Smoking cessation outcomes in clinical trials are measured in a variety of ways including short- and long-term abstinence and point-prevalent or sustained abstinence. In general, short-term abstinence refers to outcomes at less than 3 months following initiation of treatment and may include in-treatment results, depending on the duration of interventions. Long-term abstinence refers to outcomes measured at 6 to 12 months after initiation of treatment

* Note: Appendixes and evidence tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/spirotp.htm

(or later). In addition, at the measurement point, abstinence can be described as point-prevalent (usually 7-30 days prior to the measure) or sustained (ranges from 6 months to continuous from point of intervention). Finally, abstinence can be self-reported, or validated by biomarkers of exposure such as carbon monoxide (CO) or cotinine. Quit attempts are generally regarded as a less robust, secondary process outcome. Our primary outcome was long-term sustained abstinence that was validated by biomarkers. Subgroups of interest included spirometric categories, (e.g., GOLD or ATS), symptom status, race, and gender.

Quality assessment and quantitative synthesis. Quality and strength of evidence was based on the method of Schulz et al.[20] We also assessed loss to followup and whether studies provided information that would allow for determination of the independent effect of conducting spirometry and providing their results on smoking cessation rates. Because of the clinical heterogeneity of study interventions, pooled analyses were not conducted.

Question 3

Literature search strategy. Search terms were identical to those published by Sin[9] (adults >19 years of age, COPD, RCTs) to identify RCT/controlled clinical trials (CCT), meta-analyses, or reviews published since the completion of their search (i.e., between 2002 and January 2005; for inhaled therapy between 2002 and January 2005). For each of these therapies we conducted a literature search using Ovid MEDLINE. To supplement this search, we examined the Cochrane Database of Systematic Reviews of Effectiveness as well as bibliographies of published articles and contacted experts in the field. We limited our search to English-language articles. These were categorized according to type of intervention: 1) inhaled medications including: β2 agonists, long-acting anticholingerics (tiotropium), combination β agonists and anticholinergics, inhaled corticosteroids, combination inhaled corticosteroids and long-acting β 2 agonists, pulmonary rehabilitation, 2) disease management programs (which include any combination of patient education, enhanced followup, and/or self-management session); 3) long-term administration of non-invasive mechanical ventilation (NIMV); and 4) oxygen therapy.[21] We obtained additional information from the data coordinating center for one large trial (LH-1) that evaluated pharmacologic interventions in subjects with mild to moderate airflow obstruction.

Titles and abstracts of identified references in addition to those included in the report by Sin were reviewed using standardized and piloted data abstraction sheets. All references received an identification number. The number of excluded studies and reasons for exclusion are described in Figure 4 on page 16. Studies meeting preliminary eligibility criteria were retrieved in full for further assessment and data extraction.

Eligibility criteria. For intervention studies we restricted our analysis to trials that were randomized, defined by clinical diagnosis or spirometry, and provided clinically relevant outcomes. Trials of inhaled therapies were required to enroll at least 50 subjects per treatment arm. A followup time of 3 months was used as the threshold for inclusion (with the exception of pulmonary rehabilitation programs, for which 6 weeks was used as the threshold).

Studies were excluded if they only reported physiologic variables such as changes in FEV_1, because the correlation between spirometric changes and long-term clinical outcomes in COPD has been shown to be weak.[22] We examined bibliographies of these reviews and meta-

analyses.[23-37] The studies that contained the different domain of comparison between the baseline and the ending point[38] or no baseline data of spirometry as FEV_1[39] or no comparison groups at same design,[40] or cost-effectiveness analysis[41,42] were excluded. Information from the original publication was used unless additional relevant data were available in subsequent reports.

Quality of studies and strength of evidence. Two researchers independently extracted study and patient characteristics onto data sheets.[43] Disagreements were resolved by discussion or cross checking of other co-workers through project meetings.[44] The methods of Schulz et al.[20] were used to assess the quality of RCT. We evaluated whether studies were blinded, used intention-to-treat analysis, and reported attrition. The magnitude of effect across different outcomes and pharmacologic interventions (e.g., exacerbations, mortality, dyspnea, etc.) was assessed based on absolute and relative reductions as well as in comparison to previously determined minimally important clinical differences in respiratory health status measures. Subgroup analysis was attempted to determine if results varied according to disease severity based on baseline symptom and/or spirometric status, acute change in spirometry, or spirometric change in time. We attempted to focus on individuals most likely to be identified through spirometric casefinding (i.e., individuals with mild to moderate airflow obstruction and respiratory symptoms who were not diagnosed by clinical examination). We evaluated whether any trial utilized spirometry as a guide for monitoring subjects' clinical status or to modify therapy. Of the 53 studies that were eligible, 20 were new references not included in the report by Sin.

Quantitative synthesis of study outcomes. All analyses were conducted using Review Manager Version 4.2 (Revman; The Cochrane Collaboration, Oxford, England). For each end point we combined the results from individual studies to produce pooled effect estimates (relative risk ratios and absolute risk ratios). Heterogeneity of results across individual studies was checked using the Cochrane Q test. If heterogeneity was observed ($p<.10$), we used the Dersimonian and Laird random-effects model to synthesize the results; otherwise, a fixed-effects model was used.[45] As part of a sensitivity analysis for the latter situation, we used a random-effects model to determine the robustness of the data. In all cases, the results obtained from the random-effects and fixed-effects models were similar. Continuous variables were pooled using weighted mean difference technique.

Outcomes. Our primary outcome was the number of individuals with at least one exacerbation as defined by authors. Secondary outcomes included changes in St. George's Respiratory Questionnaire (SGRQ) scale scores; number of subjects with respiratory symptoms including dyspnea, cough, or sputum production; mortality; and overall and respiratory-specific hospitalizations and changes in health status between intervention and control. We attempted to evaluate results according to the following subgroups: spirometrically-determined severity of disease (GOLD or ATS stages and mean baseline FEV_1), symptom status, smoking status, gender, age (≥65 vs. <65), and race. We restricted analysis of health status and dyspnea to two well-standardized and validated instruments in COPD, SGRQ Chronic Respiratory Disease Questionnaire (CRQ).[46] These instruments quantify the extent of physical and psychological impairments related to COPD and allow investigators to determine the (beneficial) effects of specific interventions on the functional status of patients with COPD.[47] Dyspnea and exacerbations are the two most bothersome symptoms and the aspects of COPD that most influence health status. The CRQ is a 20-item COPD specific questionnaire that measures:

dyspnea (five items), fatigue (four items), emotion (seven items), and mastery (four items). A 0.5 unit change per question (on a seven-point scale) is considered the minimally important clinical change. Composite scores range from 20-140 with higher scores indicating improved health status. The SGRQ is a respiratory-specific 50 item questionnaire with domains of symptoms, activity, and impacts plus a summary total score. Lower scores indicate improved health status, and a change of four units (out of 100) is considered clinically significant. While validated these questionnaires have been found to have weak correlations with physiologic variables including FEV_1 and mild to moderate correlation with exercise capacity and assessment of dyspnea, anxiety, and depression.

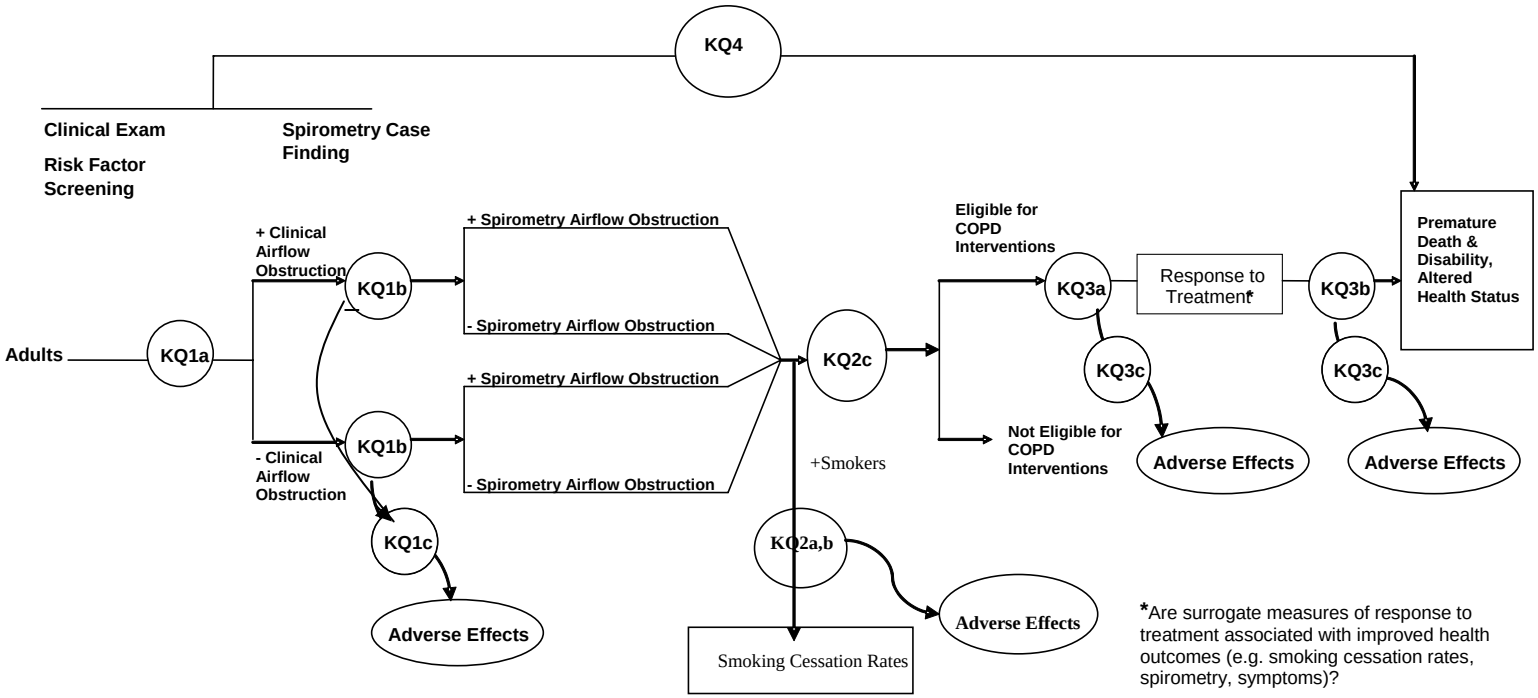
Question 4

Data sources and study selection. Articles published in English from 1966-January 2005 were identified using a search strategy similar to Question 1, which also included the key word "prognosis." Eligible studies included cohort or case-control studies that assessed the prognostic effect of spirometry on COPD progression and outcomes. Additional studies were evaluated to determine the independent effect on overall mortality, though this was not the primary focus as directed by our TEP. We obtained additional results from one of the identified studies through personal communication with the author.

Outcomes. The primary outcome was progression to more severe airflow obstruction (GOLD or other stage criteria) and development of respiratory symptoms.

Data synthesis. Data were described for each study and not pooled.

Figure 1. Spirometry for case finding of COPD—analytic framework



KQ1a&b) What is the prevalence of airflow obstruction as defined by 1) clinical examination or b) spirometry in various adult populations?

KQ1c) What are the harms of providing a diagnosis of airway obstruction by spirometry?

KQ2a Can use of spirometry lead to increased smoking cessation rates and (KQ2b) how does patient knowledge of the spirometry outcome affect smoking cessation rates?

KQ2c) Can use of initial or followup spirometry increase the probability of initiation of successful treatment compared to clinical examination?

KQ3a&b) Does effectiveness of treatment vary based on a) baseline severity or b) change in spirometry (short term due to initial therapy or progression over time)?

KQ3c) What are the harms associated with treatment based on severity or change in spirometry?

KQ4) Is prognosis based on spirometry more accurate than prognosis based on clinical examination alone?

Figure 2. Potential role for, and outcomes from, spirometry used as a motivational tool for smoking cessation

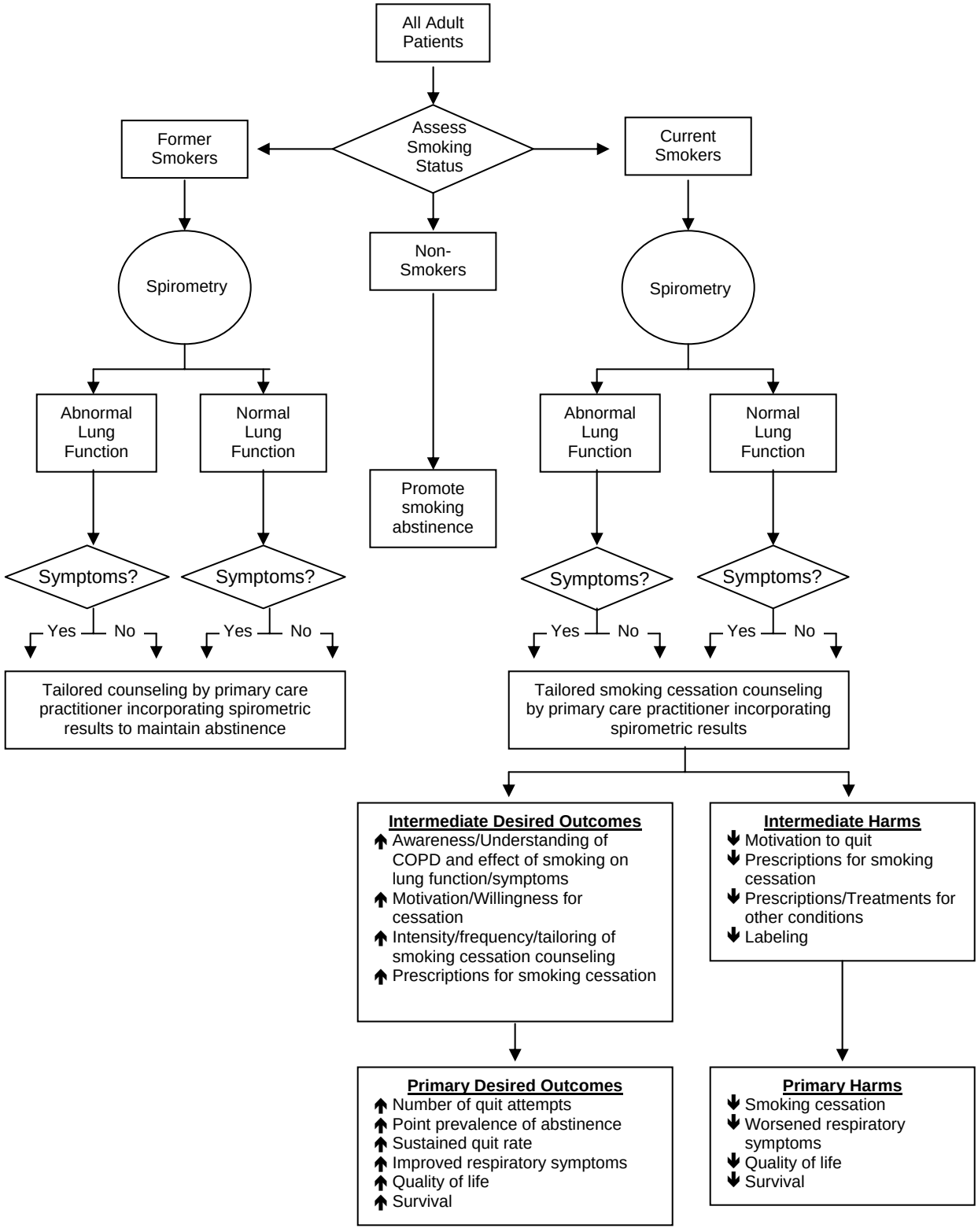


Figure 3. Flow chart—Question 2 (smoking cessation)—reference search results

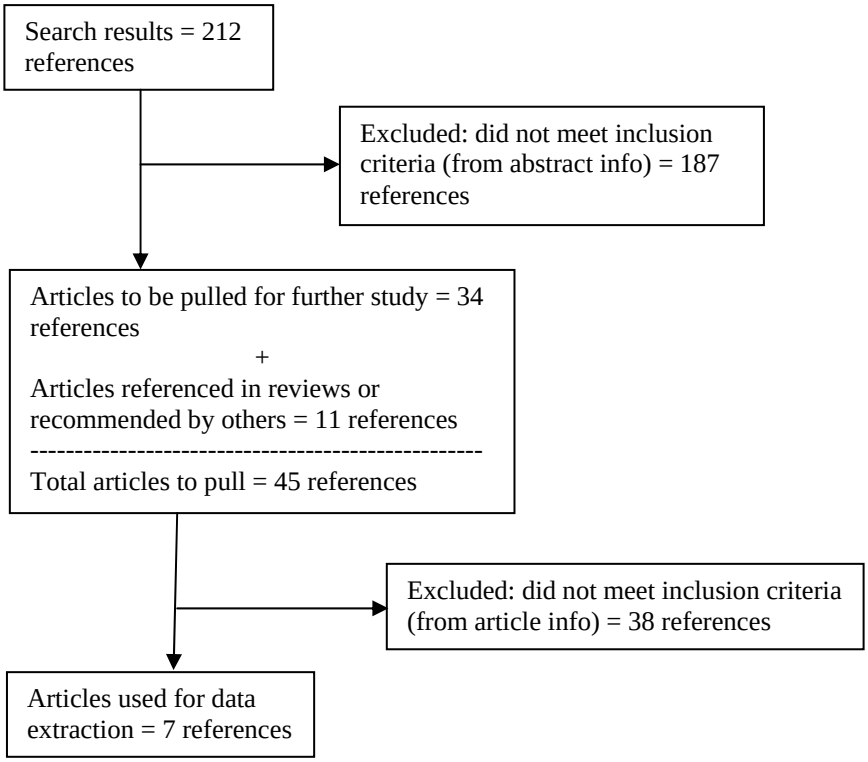
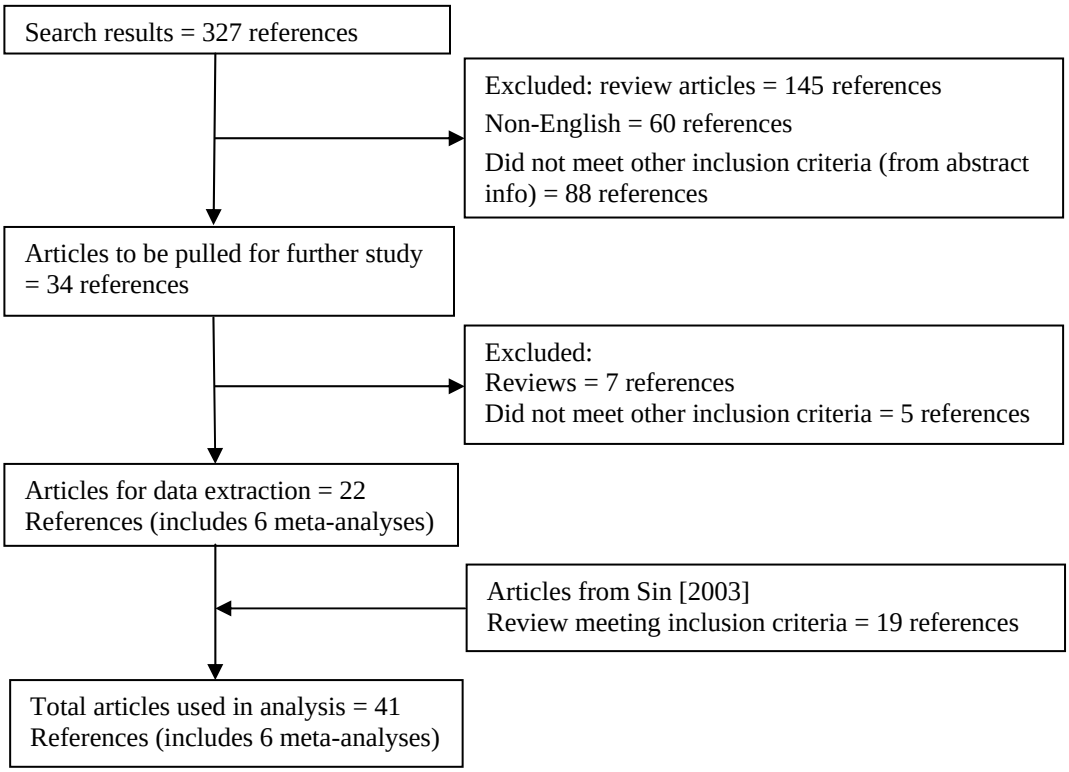


Figure 4. Flow chart—Treatments for COPD (2002-Jan 2005); inhaled therapies (2002-May 2005)—reference search results



Chapter 3. Results

Question 1
What is the prevalence of chronic obstructive pulmonary disease (COPD) and airflow obstructions in various adult populations as defined by: 1) spirometry and 2) clinical examination?

Does Clinical Examination Predict Airflow Limitation?

There are no data that directly describe the sensitivity and specificity of spirometry (i.e., the probability of developing clinical obstructive airways disease given a particular FEV_1 or FEV_1/FVC). Instead, patients with an abnormally low FEV_1 and FEV_1/FVC are said to have "airflow limitation." An FEV_1/FVC lower than the fifth percentile for age, height, and gender has been described as abnormal.[48]

Despite the lack of a "gold standard" for defining the clinical presence of COPD, a systematic review by Holleman and Simel evaluated 19 articles that assessed the clinical examination for detecting airflow limitation according to spirometry.[48] Spirometric reference standards used in studies yielding operating characteristics for individual clinical examination items varied across the studies. None used the GOLD 2003 classification. Only two studies incorporated both FEV_1 and the FEV_1/FVC as the reference standard. Factors considered in the clinical examination included history (background information such as cigarette smoking and occupational or environmental pollutants and symptoms of wheezing, dyspnea, coughing, and sputum production) and physical examination (inspection, vital signs, palpation, percussion, auscultation, and clinical measures of airflow [match test, forced expiratory time test]).

Smoking status (ever vs. never) is only a moderately good predictor of airflow limitation. Compared to "never smokers" patients who have "ever smoked" are only slightly more likely to have airflow limitation (+LR [likelihood ratio] = 1.8). Never having smoked is moderately associated with decreased likelihood of disease. The most powerful predictor was at least a 70 pack-year history of smoking (+LR = 8.0) though the sensitivity was only 40 percent. Symptoms of sputum production or wheezing are associated with a moderate increase in the likelihood of airflow limitation. However, symptoms of cough or exertional dyspnea are associated with only a slight increase in the likelihood. Additionally, the absence of dyspnea or exertional dyspnea is only moderately useful in ruling out disease (any dyspnea: +LR = 1.2; -LR = 0.55; sensitivity = 82 percent; specificity = 0.33 percent).

Physical examination findings to predict airflow limitation all had a specificity of >90 percent but were limited by poor sensitivity. Patients who have wheezing on unforced expiration almost certainly have airflow obstruction, and this increases with the severity of airflow limitation and the prior probability of disease (Positive Likelihood Ratio = 36). The presence or absence of wheezing on forced expiration is of no value in diagnosis or ruling out airflow limitation.[49,50] Absent wheezing, normal breath sound intensity, or absent rhonchi are associated

with only a moderate decrease in the likelihood of disease. (Negative Likelihood Ratio 0.85, 0.70 and 0.95 respectively). Neither the presence nor absence of rales was useful in diagnosing airflow limitation.[51-53]

Can the clinical examination predict severity of airflow limitation? Two studies reported on whether the presence of positive clinical findings could predict the severity of airflow limitation. The number of positive findings predicted the severity of airflow limitation in patients with known disease. The findings were present only if the FEV_1 was less than 50 percent predicted. Similarly, the number of positive findings predicted the severity of airflow limitation ($r = 0.6$).

Accuracy of the overall clinical impression for predicting airflow limitation. Three studies evaluated the accuracy of the overall clinical impression, or a clinician's ability to integrate all aspects of the clinical examination in forming an impression about the likelihood of airflow limitation. Clinicians' overall impressions predicted any airflow limitation only moderately well. The ability to diagnose airflow limitation clinically is variable but seems to improve as the severity of the disorder increases.

Combinations of individual findings. Six studies assessed the utility of combining clinical examination items to predict airflow limitation. Combinations of findings do not effectively rule out airflow limitation. The best combination is never having smoked, no reported wheezing, and no wheezing on examination (LR = 0.18). A patient with any combination of two findings (≥70 pack-year history of smoking, history of COPD, or decreased breath sounds) can be considered to have airflow limitation.

Prevalence and Severity of Airflow Obstruction

Population-based studies from seven different countries were identified that assessed the prevalence and severity of airflow obstruction and respiratory symptoms (Table 2 on page 19, Figures 5 and 6 on page 19, Summary Tables 1-4 on pages 55-60, and Evidence Tables 1-4 in Appendix D*). The prevalence and severity of airflow obstruction and COPD in general populations varied widely according to definitions utilized and country studied. Postbronchodilator testing or response to bronchodilators was rarely performed in these large population surveys. Respiratory symptoms were usually assessed according to responses to single item questions rather than detailed clinical probing. Additionally, subjects were generally categorized as having COPD based on a patient reported diagnosis of emphysema or chronic bronchitis. Some reports provided outcomes according to age, race, gender, smoking, respiratory symptom, and spirometric status (Summary Tables 1 and 2 on pages 55-58 and Evidence Table 1 in Appendix D*). However, none provided additional subgroup data required for assessment of a specific respiratory symptom (presence or absence or type) according to postbronchodilator spirometric value (e.g., GOLD stage) in a particular demographic category (e.g., age, race, gender, smoking). Thus, estimates of these are extrapolated from prebronchodilator results provided for larger aggregate groups. Data from one study of Spanish adults ages 40-65 indicated that the 26 percent of adults with airflow obstruction had a positive bronchodilator

* Note: Appendixes and evidence tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/spirotp.htm

response of at least 200 mL and a relative increase of at least 12 percent. However, only 5 percent had normal airflow after bronchodilator inhalation (i.e., asthma). The methodology reported in these surveys is likely to introduce only a small misclassification. Findings may more accurately reflect the results obtained using primary-care spirometry and brief respiratory symptom assessment than those obtained in pulmonary specialty practice. Determining normal airflow "at-risk" populations (approximately GOLD 0) across studies was difficult because some provided the prevalence of "any respiratory symptom" (wheeze, cough, sputum, or dyspnea) but not specifically chronic cough and sputum in subjects with GOLD stage normal airflow.

Table 2. Prebronchodilator spirometric stage according to patient's presenting symptom status*

	Patient's Presenting Symptom (%)			
GOLD Stage**	**Cough*****	**Phlegm*****	**Wheeze*****	**Dyspnea*****
Normal or 0	72.0	74.0	71.3	78.9
1 (mild)	13.3	10.5	11.3	7.9
2 (moderate)	8.3	9.9	12.4	9.1
≥3 (severe-very severe)	6.3	5.7	5.0	4.1

* From Mannino et al. *Arch Intern Med*. 2000; 160:1683-1689.. NHANES results are provided as spirometric values done without bronchodilator testing.
** GOLD stages are categorized according to post bronchodilator spirometric value: The percent overall distribution by GOLD spirometric stage for "all adults" was: normal or stage 0=86%, stage 1=7.2%, stage 2=5.3%, and ≥stage 3=1.4%.
*** The percent overall distribution of symptoms for "all adults" regardless of GOLD stage was: cough=9.4%, phlegm=8.4%, wheeze=18.3%, and dyspnea=23.4%.

Figure 5. Prebronchodilator spirometric categories according to smoking status (NHANES I)

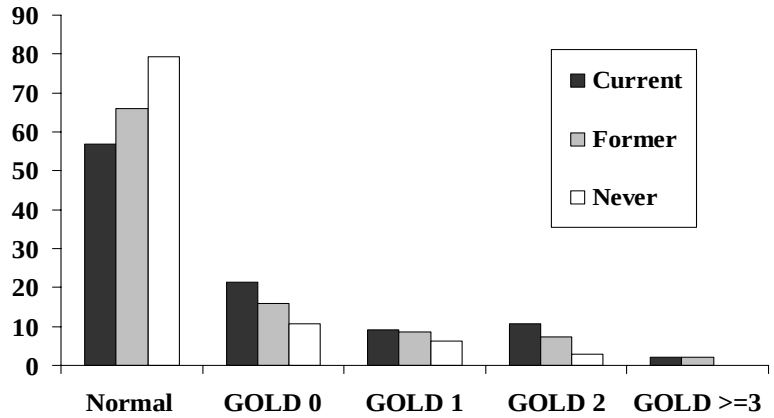
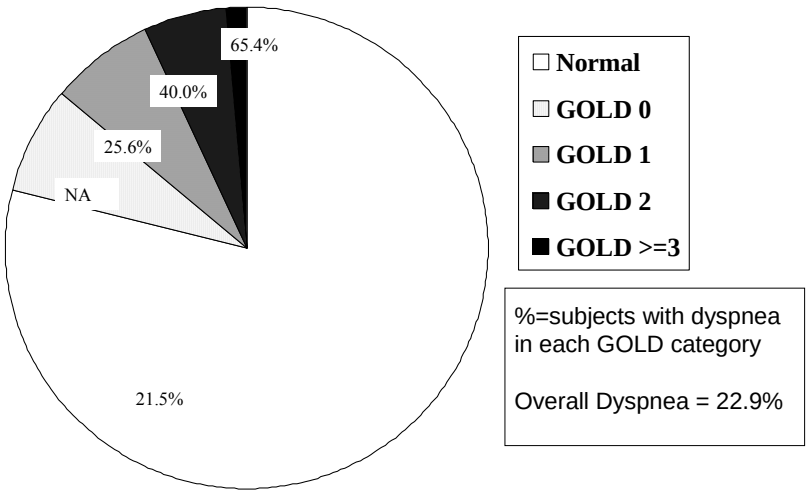


Figure 6. Proportion of spirometry categories and % with dyspnea in adults based on GOLD criteria in the United States (NHANES III)



Data derived from Mannino et al. *Arch Intern Med*. 2000; 160:1683-1689.

Data from the NHANES I and III (Summary Tables 1-3 on pages 55-59 and Evidence Tables 1-3 in Appendix D*) survey provide the most comprehensive and relevant assessment of obstructive lung disease, low lung function, and respiratory symptoms in adults in the United States. NHANES III assessed adults ages 17 years and older from 1988-1994 who classified themselves as whites or blacks and had pulmonary function testing performed without bronchodilators based on 1987 American Thoracic Society recommendations and had complete information on race, smoking status, height, and presence of respiratory symptoms. Subjects were asked if they had ever been told by a doctor that they had Obstructive Lung Disease (OLD) of asthma, chronic bronchitis, or emphysema (and if yes whether they still had that condition). Individuals who reported ever being told they had a diagnosis of emphysema or currently reported a diagnosis of chronic bronchitis were categorized by the authors as having current COPD. There was no information regarding whether any of these individuals had previously undergone spirometry or whether spirometry led to the clinical diagnosis of these conditions. However, we considered that individuals with a "current" or "previous" diagnosis of emphysema or chronic bronchitis were not detected by "primary care case finding" and that they had "clinically detected COPD."

Subjects in NHANES were classified as reporting respiratory symptoms if they gave a positive response to respiratory specific questions related to cough, phlegm, wheeze, and dyspnea. The question for dyspnea read: "Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?" For cough and sputum a positive response was considered if subjects affirmatively answered the question: "Do you usually cough (bring up phlegm) on most days for 3 consecutive months or more during the year?" Data were stratified according to national population estimates by race, sex, and smoking

* Note: Appendixes and evidence tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/spirotp.htm

status. Overall estimates were then age-adjusted to all study participants. Subjects were defined as having "low lung function" based on the 1987 ATS recommendations (i.e., subjects with an FEV_1/FVC <0.70 and an FEV_1 <80 percent predicted. This group was further divided according to ATS-1995 criteria (Stage 1 vs. Stage 2 or 3) into subjects with an FEV_1 of ≥50 percent predicted and those with <50 percent predicted). Because activity-limiting or "troubling" shortness of breath (as reported in the NHANES questionnaire) is the most clinically bothersome and relevant outcome, we judged this to be the most "clinically significant" symptom of COPD if accompanied by spirometric evidence of airflow obstruction performed in the absence of bronchodilators.

Spirometry performed in the absence of inhaled bronchodilators identified a relatively large proportion of individuals with airflow obstruction who did not report respiratory symptoms and conversely was also normal in a large percentage of adults who report respiratory symptoms. An estimated 8.5 percent of the population reported current OLD (asthma, emphysema, or chronic bronchitis) and another 4.3 percent reported OLD in the past but not currently. Approximately 28 percent of adults reporting a current diagnosis of OLD had asthma as their only type of OLD. The proportion of the population with past or current OLD and COPD varied by sex, race, and smoking status, with women reporting more disease than men, whites reporting more disease than blacks, and current or former smokers reporting more disease than never smokers. OLD was reported among 12.5 percent of current smokers, 9.4 percent of former smokers, and 5.8 percent of never smokers. Former smokers were on average older than current smokers and never smokers. Mean level of lung function was lower among smokers than never smokers and increased with age. Results from the NHANES III survey indicated that the prevalence of 1987-ATS defined "low-lung function" increased from 6.0 percent in adults ages 25-44 to 40.7 percent in those ages ≥75 years (Summary Table 3 on page 59). NHANES I results indicate that ATS 2 or 3 (approximately GOLD postbronchodilator Stage 3,4) airflow obstruction was present in 2.6 percent of adults 50-59 years old and 4.2 percent of adults ages 70-74. The prevalence of mild versus moderate to severe airflow obstruction in the Po Delta Survey in adults ages >45 years increased from 8 percent versus <3 percent to 35 percent versus 5 percent respectively when using ATS rather than European Respiratory Society (ERS) criteria (Summary Table 3 on page 59). The prevalence of low lung function was similar in whites and blacks (13.8 percent vs. 11.6 percent in NHANES III) (Evidence Table 2 in Appendix D*). Results from the NHANES I survey indicated that the percentage of whites and non-whites having normal spirometry and no respiratory symptoms was 67.6 percent and 65.3 percent respectively.

The prevalence of adults having normal spirometry and not reporting respiratory symptoms (normal/individuals not reporting respiratory symptoms) varied by country. However, the criteria used to define symptoms and airflow obstruction was the greatest factor contributing to varying prevalence estimates. It ranged from 52 percent (U.S.: NHANES III) to 89 percent (Italy: ERS Criteria) (Summary Table 2 on pages 56-58). The prevalence of normal spirometry and no respiratory symptoms in the Italian Po Delta Survey decreased from 89 percent to 60 percent when subjects were classified by ATS criteria instead of ERS criteria.

An estimated 6.8 percent of the U.S. population had ATS-1987 criteria for low lung function and 7.2 percent had an FEV_1/FVC <0.7 but an FEV_1 >80 percent predicted. When recategorizing NHANES subjects according to a 2003 GOLD staging system that uses postbronchodilator spirometric values to define airflow obstruction, the percentage of individuals labeled as having "airflow obstruction" or "at-risk" increased by more than three-fold. Only 56.4 percent of the

population had both normal spirometry and reported no chronic respiratory symptoms. Greater than 20 percent had airflow obstruction or were considered "at risk." Specifically, 7.2 percent of subjects had GOLD Stage 0 (chronic sputum and phlegm but normal spirometry), and an additional 13.9 percent of adults had airflow obstruction (approximate GOLD Stage 1, 2, 3,4 = 7.2 percent, 5.4 percent, and 1.5 percent respectively). Prevalence was higher in current smokers and with increasing age (Evidence Table 4 in Appendix D* and Figure 5 on page 19). The percentage of individuals reporting respiratory symptoms increased with worsening airflow obstruction (Summary Table 4 on page 60). However, 23 percent of individuals with normal spirometry reported respiratory symptoms and 21 percent of individuals with severe to very severe airflow obstruction (ATS 2-3; FEV_1 less than 50 percent predicted, approximate GOLD Stage 3,4) had no symptoms. Furthermore, 35 percent of individuals with an FEV_1 less than 50 percent predicted did not report being troubled by shortness of breath, the symptom felt to be most clinically bothersome and warranting intervention. (Figure 6 on page 19) Therefore, the overall prevalence of adults having both low lung function and "any respiratory symptom" is GOLD 1 = 3.6 percent, GOLD 2 = 3.2 percent, GOLD 3,4 = 1.2 percent. Findings from other population-based studies are consistent with these when attempting to account for differences in definitions of airflow obstruction and symptom status as well as use of prebronchodilator spirometric values. Between 40 and 80 percent of individuals with spirometrically determined "low lung function" had no prior diagnosis of OLD.

To assess diagnostic accuracy of spirometry the additional number of adults with clinically significant disease that would be detected by case-finding is required. These would be defined as an adult with spirometrically determined airflow obstruction who reports bothersome respiratory symptoms but not a diagnosis of COPD. However, there were no data according to previous reported diagnosis of COPD, stage severity of airflow obstruction, and symptom status (particularly dyspnea). In adults who reported a clinical diagnosis of COPD (emphysema or chronic bronchitis), (approximately 3 percent of the total NHANES respondents) only 17.4 percent had 1987-ATS defined low lung function suggesting that the vast majority of these individuals do not have COPD. Among individuals reporting a clinical diagnosis of COPD 25.6 percent reported chronic phlegm, and 48 percent reported shortness of breath.

Question 2

* Note: Appendixes and evidence tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/spirotp.htm

Can use of spirometry lead to increased smoking cessation rates?

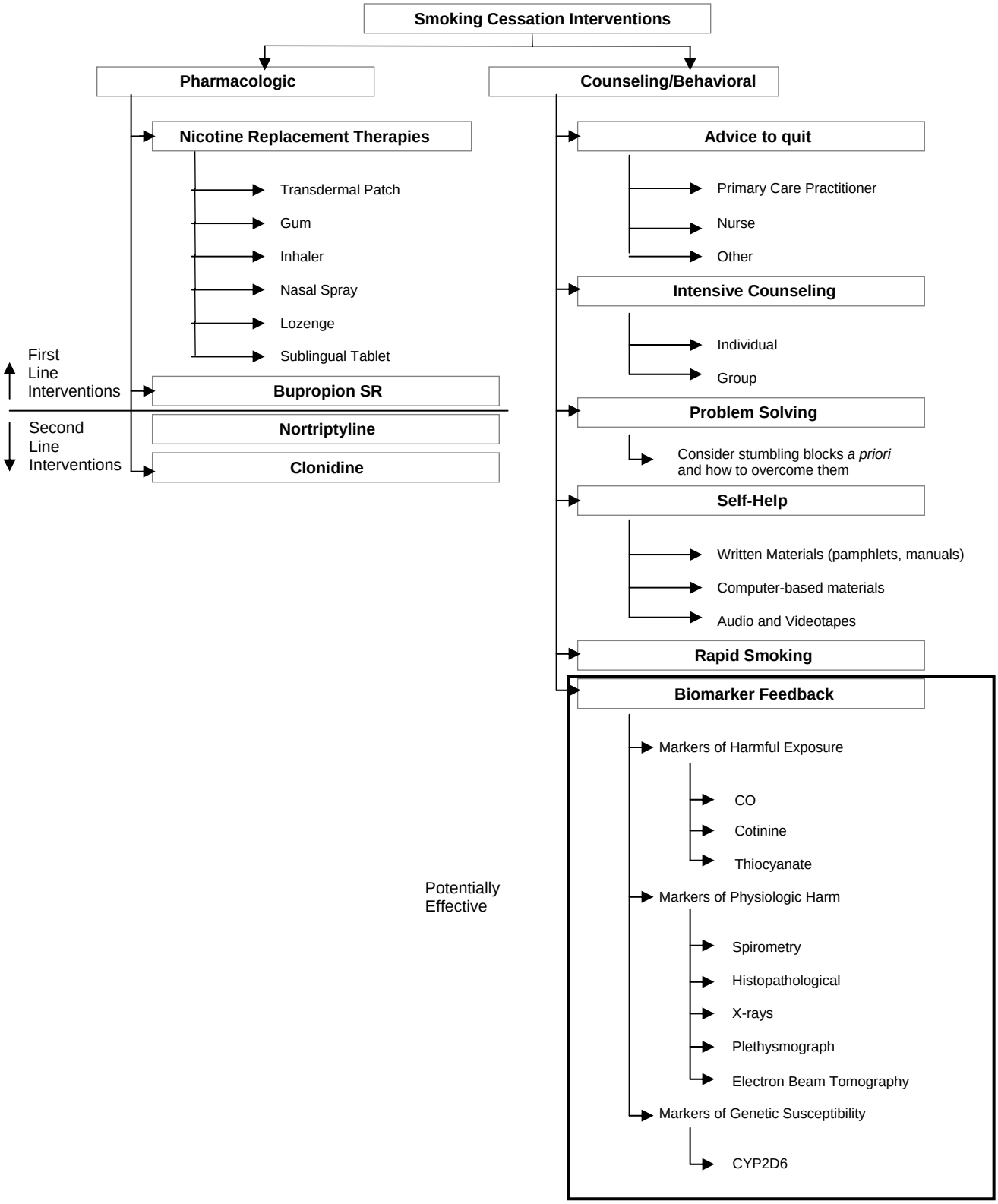
Summary of Interventions Used to Enhance Smoking Cessation

Two major categories of effective and potentially effective strategies, pharmacologic therapy and counseling/behavioral treatments, are shown in Figure 7 on page 23. Interventions can be used either alone or in combination. A summary of effectiveness is provided below.

Pharmacologic therapy. Nicotine replacement therapies (NRTs) and Buproprion SR are considered "first line" medications. The overall odds of smoking cessation in those who used NRTs (except lozenges) were 1.7 fold greater than those who did not use NRT (95 percent CI: 1.6, 1.8).[54] Separate meta-analyses of each of the first four NRTs shown in Figure 7 on page 23 were conducted and the results were statistically significant ranging from an odds ratio of 1.5 for gum to 2.7 for nasal spray. The absolute differences ranged from 6.6 percent for gum to 16.6 percent for nasal spray.[17] The results of a meta-analysis of two studies indicate that Buproprion SR improved smoking cessation rates twofold with an absolute rate difference of 13.2 percent.[17]

Counseling/behavioral therapy. Several counseling and behavioral therapy strategies have been shown to be effective with absolute differences in smoking cessation rates between control and intervention ranging from 2.3 percent to 8.0 percent. These include advice to quit by a physician,[17] nurse, or other health professional; intensive counseling, either at the group or individual level;[17] general problem-solving,[17] such as providing general information about smoking cessation and relapse, identifying potential stumbling blocks, and creating solutions to overcome them; self-help materials, including written and computer-based materials and audio- and videotapes;[54] and the technique of rapid smoking.[17] A systematic review found inconclusive evidence of effectiveness from motivational counseling,[55] including a discussion of the benefits of quitting, the risks of continued smoking, or a discussion of personal risk based on biological markers (including spirometry). The results of a meta-analysis of smoking cessation trials by Kottke et al., suggest that a smoking cessation message reinforced consistently and repeatedly over time is the best predictor of success.[56]

Figure 7. Components of smoking cessation interventions



Use of Biological Markers in Smoking Cessation

Biological markers may have a unique role as motivational aids in smoking cessation programs.[57,58] Three categories of biomarkers include markers of: 1) tobacco exposure (e.g., carbon monoxide, cotinine, thiocyanate); 2) physiologic effects (e.g., pulmonary function tests—including spirometry, histopathological changes, x-rays, plethysmography, electron beam tomography, and other diagnostic tests); and 3) genetic susceptibility (e.g., CYP2D6).[59] Several observational studies have assessed biomarkers as motivational tools for smoking cessation. However, the lack of controls makes assessment problematic. (Studies without controls: CO,[60-62] CT scans,[63] airflow limitation/spirometry,[64-66] plus others.[67-69]

Rationale for the Use of Spirometry in Smoking Cessation

Determination of smoking and respiratory symptom status as well as advice and interventions to aid cessation or maintenance of abstinence should be provided to all smokers, regardless of pulmonary function or the presence or absence of symptoms. Results from the Lung Health Study (LH-1), a 5-year multicenter randomized control trial in the United States and Canada, indicated that smoking cessation is beneficial in slowing both the clinical and spirometric progression of patients with mild/moderate airflow obstruction. If smokers quit prior to the development of symptoms, the rate of lung function decline approaches that of nonsmokers.[70,71] In LH-1, smokers who quit experienced an initial increase in lung function in the first year after quitting (mean increase of 47mL/year), followed by an annual decline comparable to declines observed in nonsmokers attributed to age (mean annual decline of 31mL/year). Subjects who continued to smoke had an annual decrease in lung function that was twice the rate seen in those who quit (mean annual decline of 62mL/year). Similar findings have been observed in other studies.[72] The standard deviation of the annual rates of decline in FEV_1 in the LH-1 (48mL/year in quitters and 55mL/year in continuing smokers) indicates that, even over 5 years of followup, confidence in a value for the annual decline in an individual is low.

Despite the evidence that smoking cessation improves clinical outcomes and measures of airflow obstruction, the concept of performing spirometry and using these test results to provide personalized encouragement for smoking cessation is controversial.[73-75] Spirometry might be useful in motivating individuals to quit smoking or maintain abstinence. It may identify individuals likely to benefit from more intensive smoking cessation counseling as well as those unlikely to quit smoking. It may motivate physicians to more carefully assess symptom and clinical status and/or provide smoking cessation counseling. Spirometric results can be provided to those at-risk in several formats, including percent FEV_1, FEV_1/FVC, FEV_1/FEV_6, or "lung age" estimations, wherein a patient's chronological age is contrasted with the physiologic age of his/her lung tissue.[76,77] However, spirometry entails time and costs, and may result in false labeling or reassurance and it is not yet known whether it improves smoking cessation rates. The available evidence suggests that cessation rates are relatively low and require fairly intensive counseling and pharmacologic intervention. Therefore, spirometry may not offer additional motivational benefit nor serve as a reliable predictor for an individual's likelihood of quitting. A conceptual model for the role of spirometry in smoking cessation is provided in Figure 2 on page 15.

Smoking Cessation Strategies in People with COPD

Most smoking cessation studies did not specifically recruit subjects with airflow obstruction or clinically diagnosed COPD, nor do they report outcomes according to spirometry or symptom status. A systematic review published in 2004 evaluated the effects of interventions for smoking cessation in people with established COPD.[78] The authors identified five randomized trials comprising 6,491 patients with COPD conducted in the U.S., Canada, and Denmark between 1991 and 2001. None of these studies used spirometry as a motivational tool for smoking cessation. However, three studies, including the largest study, used spirometry as the method to identify subjects eligible for participation. Lung Health Study One (LH-1) enrolled 5,887 current smokers who had spirometric evidence of mild to moderate airflow obstruction. Nearly 30 percent had a previous clinical diagnosis of bronchitis but only 3.2 percent had a diagnosis of emphysema. Because studies were clinically heterogeneous regarding study population (severity of obstruction and symptoms) and types of interventions, abstinence rates were not pooled.

Three trials involved 179 subjects and evaluated four different behavioral intervention strategies. Two studies involved smokers who were admitted to the hospital and may not be representative of large population-based strategies. Behavioral interventions included: 1) use of the term "smokers' lung" rather than "chronic bronchitis" when talking to patients plus an informational brochure; 2) individual counseling responsive to patients needs and questions combined with a self-help manual; and 3) behavioral reinforcement schedules that provided lottery tickets for reduced breath carbon monoxide, self-reported smoking cessation, or attendance at clinic visits. Absolute differences in self-reported and biochemically validated point prevalence or continuous abstinence at 6-12 months ranged from 10-16 percent. However, the confidence intervals were wide and there were no statistically significant differences in any of the studies.

The Lung Health Study evaluated the effect of an intensive smoking cessation intervention (combined with either the inhaled bronchodilator ipratropium bromide or placebo) on the rate of decline in FEV_1. The comparison (usual care) group received no study prescribed smoking intervention. The smoking intervention group received intensive cessation counseling (advice to quit by physician at one session plus group counseling—12 sessions in 10 weeks), nicotine gum provided at no cost, and a maintenance program for those who quit smoking. After 12 months, the smoking intervention program was significantly more effective in helping smokers to quit (RD at 5 years = 0.26, 95 percent CI: 0.23, 0.28). The differences declined but persisted throughout the 5 years of study followup (RD = 0.16, 96 percent CI: 0.14, 0.18).

Can symptom status and/or baseline spirometric values be used as risk stratification tools to assess the likelihood of smoking cessation? Observational studies reported in the 1970s provide conflicting information regarding the motivational effects of spirometric test results on smoking rates or the ability of spirometric values or symptom status to predict smoking cessation rates. Loss et al. examined the prevalence of pulmonary abnormalities at baseline and the subsequent 6-month abstinence rates in a group of 73 smokers.[67] Subjects completed pulmonary function testing and received these results along with brief counseling 1 week later via telephone. Twenty-nine percent of subjects had abnormal spirometric results and 89 percent had cough, excess sputum production, shortness of breath, or wheezing. At 6 months followup, 7 percent of those with abnormal Pulmonary Function Test (PFT) results were abstinent as compared with 11 percent of those with normal results. The authors concluded that

pulmonary testing did not provide sufficient motivation to induce smoking cessation and that the costs of the testing outweighed the benefits.

Petty et al. examined smoking cessation rates among 101 smokers that were followed for up to 7 years.[68] All subjects were notified of their spirometric results via mail. The abstinence rate at the end of followup was 18 percent in those with abnormal lung function at baseline (FEV_1/FVC <60 percent) versus 11 percent in those with values above this threshold. Cessation rates were similar in subjects with chronic bronchitis (18 percent) and those without bronchitis (19 percent).

Hepper et al. conducted a series of community screening programs for COPD.[69] Participants with abnormal lung function received their test results within 2 weeks after screening. They were encouraged to follow up with their primary care physician, who was also provided with the results of the tests, and could give them further information. Subjects from randomly selected communities (n = 553) were contacted 2 to 3 years after baseline testing to assess smoking status. The quit rate among smokers with abnormal results and no prior COPD diagnosis was 21.4 percent, compared with 11.7 percent among those with normal results and 11.9 percent among those with abnormal results and prior COPD diagnosis. These authors concluded that providing the spirometric results was enough motivation to compel smokers to quit if they had no prior clinical diagnosis of COPD and were not already aware that they had reduced pulmonary function.

Gorecka et al. reported results of a case-series of adult smokers who received smoking cessation advice along with baseline spirometric screening and 1 year followup.[64] The authors attempted to assess factors associated with smoking cessation in adult smokers (n = 558) categorized as either having "airflow limitation" (defined as FEV_1/FVC ratio <85 percent or normal lung function. Subjects with airflow limitation were further categorized as having mild (FEV_1 <70 percent of normal), moderate (FEV_1, 50-69 percent of normal) and severe (FEV_1 <50 percent of normal) airflow limitation. There was no difference in 1 year sustained smoking cessation among individuals with normal lung function compared to those with spirometrically determined airflow limitation. However, in post hoc multivariate analyses (and in contrast to findings from the LH-1 study) FEV_1 was independently inversely associated with likelihood of abstinence at 1 year. Individuals with poorer lung function as defined as an FEV_1 <88 percent had greater odds of having sustained smoking cessation than individuals with an FEV_1 >88 percent. However, the confidence intervals were wide and included one (OR = 1.61; 95 percent CI: 0.91, 2.87). The authors provide no explanation for the selection of the FEV_1 comparison values used in post hoc analyses.

Results from the LH-1 study suggest that the use of symptom status and baseline spirometric values including percent FEV_1, percent FEV_1/FVC and bronchodilator response reported as a percent of baseline are of limited clinical value in determining the likelihood of future smoking cessation. Spirometric values are strongly inversely associated with intensity of smoking, degree of addictiveness, and thus smoking cessation rates. In LH-1, differences in spirometric values between symptomatic individuals and individuals not reporting respiratory symptoms and across the type of symptoms were typically small (5-10 percent). At 5 years of followup, smoking cessation rates among enrollees with baseline respiratory symptoms (i.e., cough for ≥3 months/year, phlegm for ≥3 months/year, wheezing, dyspnea), were less than those without symptoms (14.7-15.8 percent vs.16.9-17.4 percent).[15] However, the absolute differences in quit rates according to presence or absence of baseline symptoms or type of symptoms were small (1.2-2.8 percent). Thus the presence or type of symptoms is not a reliable clinical indicator for assessing future quit rates. Conversely, regardless of the presence or type of symptoms at

baseline, there were significant differences in the point prevalence of symptoms according to the three smoking categories. All four respiratory symptoms were most common in those who continued to smoke, least common in sustained quitters, and intermediate in subjects who abstained intermittently. Symptoms were more prevalent at followup in all smoking groups among those who reported the symptom at baseline.

Additional analyses assessed the association between symptoms and changes in FEV_1 (percent predicted) during the 5-year study period. Regardless of treatment assignment or symptom status individuals with a greater loss in FEV_1 had a greater occurrence of symptoms at 5 years. The quintiles of change in spirometry ranged from a loss of ≥11 percent to a gain of ≥2 percent. The 5-year occurrence of symptoms in the intervention group from highest to lowest quintile of change ranged from 33 percent to 10 percent among individuals without baseline symptoms and 68 percent to 29 percent if a baseline symptom was present. Similar findings were observed in the usual care group. Thus there appears to be an association between change in spirometry and occurrence of symptoms. Because of the known intra-individual variability in spirometric values, it is not clear how useful these findings would be for individual patient counseling and therapeutic decisions. Both smoking cessation and the reduction in the number of cigarettes smoked per day were associated with less severe airflow obstruction at baseline. However, the magnitude of these differences was small and unlikely to be useful in clinical decisionmaking.

One study compared bupropion sustained release to placebo in 404 patients with a FEV_1/FVC ≤70 percent and clinically defined COPD.[78] At 12 months there was no statistically significant difference between subjects randomized to buproprion or placebo (10 percent vs. 7 percent abstinence; RD = 0.02; 95 percent CI = -0.04, 0.07). Prolonged abstinence rates after 26 weeks were lower in patients with more severe COPD (FEV_1 between 35 percent and 50 percent predicted) than those with more mild airflow obstruction. However, the difference was not statistically significant.

Summary of Included Study Interventions

A summary of the study characteristics, including duration, sample sizes, descriptions of control and intervention, and a brief description of participants and inclusion criteria, is provided in Summary Table 5 on pages 61-62. Only one study[79] evaluated the independent effect of obtaining and providing results of spirometry combined with targeted counseling on smoking cessation rates. In six studies[80-85] individual smoking cessation counseling was provided to intervention and control participants, although the duration, format, and intensity of this counseling varied widely across the studies. In the remaining study[83] no intervention was provided to the control group. Six study designs[80-85] involved more than one intervention being evaluated in the experimental group as compared to the control group. CO levels were incorporated into the intervention arms of two studies;[80,81] written smoking cessation materials were provided to participants assigned to the experimental group in three studies;[82-84] and to both treatment arms in three studies.[80,81,85] Blood tests,[82] chest x-rays,[85] and symptom questionnaires with feedback[80] were each included in one study.[80] Spirometric results were provided in-person to participants in six studies[79-82,84,85] and via mail in one study.[83]

Methodological Quality and Characteristics of Included Studies

Study strengths and limitations are shown in Summary Table 6 on pages 63-64. Randomization to a treatment arm was clearly adequate in one study,[79] unclear in four,[80,83-85] and inadequate in two of the studies.[81,82] Six studies[79-84] provided data such that intention to treat results could be calculated. In the study by Li et al. the analysis completed was not intended-to-treat, as the randomization was not maintained in the analysis due to poor physician compliance in delivering the appropriate intervention.[85]

Length of followup, sample size, and loss to followup. Each of the seven studies provides followup data at 9 months or longer, and two studies provide followup data at 36 months.[82,84] Approximately one-fifth of the 6,052 participants randomized to a treatment group (six trials reporting) were lost to followup (n = 1,137, 19 percent). The number lost to followup in each study is shown in Evidence Table 5 in Appendix D*. The range of attrition rates in the seven studies was between 7 percent and 36 percent of participants per treatment arm. The rates were greater in the intervention than in the control group in three of the five studies that reported attrition rates by treatment arm. The study by Risser et al. is small with large, uneven attrition; at 12 months followup 13 of 45 participants were lost to followup in the intervention group versus 6 of 45 in the control group, although their reasons for not participating were similar across the two groups. Additionally, the results of this study may not be generalizable to other populations since the participants in this study had an average of five active medical conditions, one-quarter were enrolled in psychiatric programs, and 21 percent consumed four or more alcoholic beverages daily, all characteristics that make smoking cessation more difficult.[80]

Compliance. In the Segnan study, physician compliance to the randomized treatment groups was low and study subject compliance to complete the followup visits and spirometry, if applicable, was also low.[79] Among participants, there was less than 40 percent attendance at the return visits and among those randomized to receive spirometric testing, only 50.2 percent of subjects attended this appointment. One factor contributing to the low compliance to spirometry was that subjects were asked to make a separate appointment for spirometry at another facility. In the study by Li et al., two of the four participating physicians carried out the study protocol as expected and the remaining two did not.[85] In the study by Risser et al., 7 percent of controls and 5 percent of those in the treatment group did not complete the initial 1-hour intervention.[80] Only 37 percent completed all six visits in the Richmond study.[82]

Baseline Characteristics

Summary baseline characteristics are shown in Table 3 on page 29. Six of the seven studies provided subject age at baseline; the mean age of subjects was 42.1 years (range 16-75, n = 5,962). Gender was reported in all seven studies and the vast majority of subjects were male (90.1 percent, n = 5,453). A large proportion of the participants in the two studies that supplied

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* Note: Appendixes and evidence tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/spirotp.htm

race data were white (84.5 percent, n = 662); no further information regarding race or ethnicity was provided.

Table 3. Compiled baseline characteristics from randomized control trials

Variable	# Studies Reporting	N	Mean
Personal Characteristics			
Age (years)	6	5,962	42.1
Gender (% Male)	7	6,052	90.1%
Race (% White)	2	784	84.5%
Smoking History			
Intensity (cigarettes/day)	7*	5,129	18.3
Pack-years	2	295	38.5
At least one previous quit attempt (%)	4	1,797	71.0%
Motivational state (% prepared)	1	205	36%
Symptoms			
Any (%)	1	923	51.6%
Phlegm (%)	3	4,515	35.6%
Cough (%)	2	3,112	29.2%
Dyspnea (%)	1	579	2.8%
Spirometry Results			
Mean FEV_1	1	1,445	2.64
FEV_1 (% predicted)	1	103	87.0%
FEV/FVC (%)	1	103	76.0%

* One study provided smoking intensity as categorical data and was therefore not included in the calculation of the mean.

The average intensity of smoking among participants in six of the seven studies was 18.3 cigarettes per day (n = 5,129). The average amount of smoking was 38.5 pack-years (two studies, n = 295). Just over 70 percent of subjects had previously made at least one quit attempt (71 percent; four studies n = 1,275) and one study indicated that 36 percent of participants were in the "prepared" motivational state at baseline (n = 74).

Few studies reported respiratory symptom status or spirometry at baseline (51.6 percent of participants had any symptoms, n = 476). Of those evaluated, most subjects had relatively minimal symptoms and/or mild airflow obstruction. Three studies provided specific respiratory symptom data. In three studies, 35.6 percent of participants indicated that they had excess phlegm (n = 1,608), while 29.2 percent of subjects in two studies had cough (n = 908) and 2.8 percent of those in one study reported dyspnea (n = 16). Baseline spirometry results were presented in two of the studies. The mean FEV_1 of the 1,445 participants in one study was 2.64. The other study presented FEV_1 as a percentage (87 percent) as well as the ratio of FEV_1/FVC (76 percent) among those assigned to the intervention group (n = 103). None of the studies provided outcome data according to symptom status.

None of the participants were selected based on their motivation to quit smoking. Subjects were selected as part of a cohort of outpatients in three studies,[79,81,82] as part of a cohort of workers in two studies,[84,85] and as volunteers in two studies, including volunteers of a health promotion clinic[80] and a community health survey.[83] Participants were selected for the study by Rose et al.[84] because they were at high cardiorespiratory risk. Likewise, smokers included in the study by Humerfelt et al.[83] were at high risk due to previous occupational asbestos exposure and/or adjusted FEV_1 in the lowest quartile and subjects of the study by Li et al. may have additional motivation to quit due to long-term occupational exposure to asbestos.[85]

Results

Smoking cessation outcomes data for each of the seven included trials are summarized in Summary Table 7 on pages 65-66. Smoking cessation outcomes in clinical trials are measured in a variety of ways including short- and long-term point-prevalence or sustained abstinence. In general, short-term abstinence refers to outcomes less than 3 months following treatment, and may include in-treatment results depending on the duration of treatment. Long-term abstinence refers to outcomes generally measured at 6 to 12 months. In addition, at the measurement point, abstinence can be described as point prevalent (usually 7-30 days) or sustained (ranges generally from 6 months to continually from point of intervention). Finally, abstinence can be self-reported or validated by biomarkers of exposure such as carbon monoxide or cotinine. Quit attempts are regarded as a less robust, secondary process outcome.

Due to the heterogeneity of the interventions and the diverse manner in which results were reported, the calculation of a pooled estimate of cessation rates was considered inappropriate. A summary of the individual study results is provided and displayed in Figure 8 on page 30, Figure 9 on page 31, and Summary Table 7 on pages 65-66. The study by Rose et al.[84] also provided data on change in participant pulmonary function over the course of followup.

Figure 8. Abstinence rate at 6-12 months

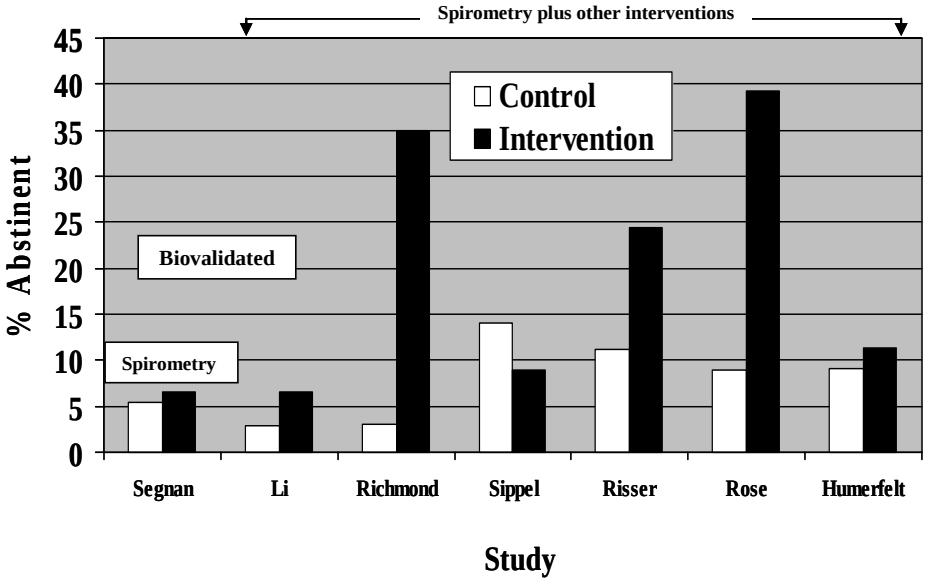
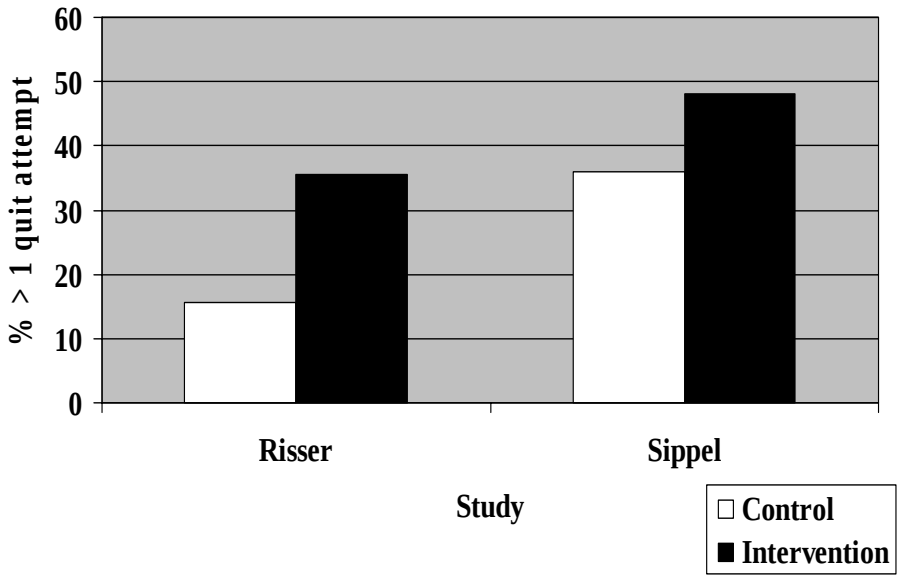


Figure 9. One or more quit attempts



Abstinence rates. Six studies reported greater smoking cessation rates among those in the experimental groups compared to those in the control groups after 6 to 12 months of followup. The results were statistically significant in two studies.[82,84] The largest study involving 2,610 subjects compared multiple interventions using a letter + informational pamphlet + questionnaire + spirometry to a group that received no intervention. The absolute difference in sustained abstinence at 12 months between groups was 1.5 percent and of borderline statistical significance.[83] One study showed a lower rate of abstinence among the intervention group as compared to the control group; this difference was not statistically significant.[81] The range of abstinence rates for the control groups was 2.8 percent to 14 percent and among intervention groups was 6.5 percent to 39.3 percent. The range of absolute rate differences (abstinence rate $_{intervention}$ − abstinence rate $_{control}$) was 1.0 percent to 33.0 percent (Figure 8 on page 30). Results for two studies are biologically verified.[79,85] Results for the remaining five studies are based on participant self-report.[80-84]

Caution must be taken in attributing differences in cessation rates to the independent contribution of spirometry (Summary Tables 6 and 7 on pages 63-66) because most studies used interventions in addition to spirometric testing that have been proven to independently improve smoking cessation. Only one study[79] assessed the independent contribution from the process of obtaining and providing the results of spirometry to smokers in combination with focused smoking cessation counseling. Two others approximated this process.[80,81] The results of these three studies[79-81] are mixed and none were statistically significant. The study most closely adhering to this principal demonstrated a nonsignificant 1 percent greater point prevalent quit rate at 12 months in the group assigned to receive spirometry plus repeat counseling compared to repeat counseling alone (6.5 percent vs. 5.5 percent).[79] Quit rates were lower in this group than in the group that received repeat counseling plus nicotine replacement therapy (7.5 percent). The self-reported 6 month point prevalent abstinence rates for the intervention group assigned to receive spirometry in combination with advice plus carbon monoxide values was lower than the

group that received advice alone (9 percent vs. 14 percent).[81] The one study that showed a beneficial effect compared a 50-minute educational intervention in the control group with a similar intervention plus spirometry, carbon monoxide values, and a questionnaire and discussion of symptom status. At 12 months the biologically verified point prevalent quit rates were 20 percent in the intervention group and 6.7 percent in the control group.[80] The effect on cessation rates that occurred in the intervention group due to carbon monoxide testing and symptom assessment/discussion is not known. A summary of the study strengths and limitations are included in Summary Table 6 on pages 63-64.

Self-reported abstinence rates. Results were similar across studies when various measures of abstinence, including self-reported point prevalence abstinence at 6 to 12 months followup and sustained abstinence over the course of the study, were examined. In the study by Richmond et al., the 6-month point prevalent self-reported abstinence rate among controls was 3.0 percent compared with 35.0 percent among those in the intervention group ($p < 0.0001$).[82] Sippel et al. reported a higher self-reported abstinence rate among controls than among those in the intervention group at 9 months followup (14 percent vs. 9 percent); however, this result was not statistically significant ($p = 0.10$).[81] The 12-month self-reported abstinence rates were 11.1 percent among controls versus 24.4 percent among the intervention group in the study by Risser et al. ($p = 0.08$),[80] 9.1 percent in controls and 11.4 percent in the intervention group in the study by Humerfelt et al. ($p = 0.05$),[83] and 8.9 percent and 39.3 percent, respectively, in the study by Rose et al. ($p < 0.0001$).[84] Rose et al. also provided self-reported abstinence rates at 36 months of followup of 14.5 percent among controls and 35.5 percent among those in the experimental group ($p < 0.0001$).[84]

Biologically verified abstinence rates. Biological validation of cessation, using varying definitions of abstinence, was performed in four studies.[79,80,82,85] Studies with self-reported abstinence rates showed higher rates of abstinence than studies with biologic confirmation of abstinence. In each of the biologically validated studies, the abstinence rate among those in the intervention group was greater than the rate among the controls; these results were statistically significant in two of the four studies.[82,85]

Li et al. reported biologically verified abstinence rates at 11 months of followup of 2.8 percent among controls and 6.5 percent among those in the intervention group ($p < 0.0001$).[85] In the study by Richmond et al.,[82] the biologically validated abstinence rates at 36 months of followup were 8.0 percent among controls and 35.7 percent among those in the experimental group ($p < 0.001$).

Sustained abstinence over the course of the study. Among the three studies that reported sustained abstinence,[82,83,85] higher abstinence rates were reported in the intervention groups compared to the control groups in all three studies. The results were statistically significant in two of the three.[82,85] In the study by Li et al.,[85] the self-reported sustained abstinence rates over the course of the study at 11 months of followup were 3.6 percent among controls and 8.4 percent among those in the experimental group ($p = 0.01$) and the self-reported 12-month rates were 3.2 percent among controls receiving no intervention versus 4.7 percent among the intervention group that receives a letter providing spirometry test results, advice to quit, and a pamphlet emphasizing behavior modification ($p = 0.05$).[83] Richmond et al. reported biologically validated sustained abstinence rates at 36 months of 2.0 percent among controls and 23.5 percent

among those in the intervention group ($p < 0.001$).[82] As previously noted the intervention group had six visits to a primary care provider for counseling and smoking cessation support versus only two visits in the control group.

Quit attempts. Risser et al. reported that 15.6 percent of participants in the control group versus 35.6 percent of participants in the intervention group had made one or more quit attempts over the 12 months of followup ($p = 0.03$)[80] and Sippel et al. reported that 36 percent and 48 percent, respectively, had attempted to quit over 9 months of followup ($p = 0.09$).[81]

Change in pulmonary function. Participant changes in pulmonary function were reported at 1 and 3 years post-intervention by Rose et al. At 1 year, those in the intervention group had a mean decline in FEV_1 of -0.075 compared with -0.115 in the control group. Likewise, the intervention group experienced a mean reduction in FVC of -0.132 versus -0.153 in the control group. At 3 years, the mean change in FEV_1 was –0.056 in the intervention group and –0.037 in the control group, while the mean change in FVC was –0.001 versus –0.002, respectively. This corresponded to an overall rate of change in lung function (FEV_1 and FVC) that was 14 percent less in the intervention group compared with the control group over 3 years, a difference that was highly significant statistically.[84]

Question 3
Does the effectiveness of specific therapies to improve clinically relevant outcomes in COPD vary based on baseline or followup spirometry, short term spirometric response due to initial therapy, or spirometric progression over time?

Demographic and Baseline Characteristic of Studies

1) Pharmacological therapies. Among the 53 studies, there is some overlap across each intervention. Most intervention trials 1) were of short duration (i.e., 6 months or less), 2) enrolled subjects with a previous clinical diagnosis of COPD, 3) had subjects with severe to very severe airflow obstruction, and 4) enrolled subjects who had symptomatic, stable COPD but relatively frequent episodes of exacerbations. Almost all studies used spirometric criteria for inclusion criteria. However few studies used spirometry for casefinding or population-based recruiting and many did not assess postbronchodilator spirometric values or categorize enrollees according to spirometric response to bronchodilators.

All studies compared a fixed dose of medications though some studies evaluated different doses of a given pharmacologic agent. Five studies were multiarm trials that compared combination therapy with inhaled long-acting beta agonists (LABA) plus corticosteroids to placebo or monotherapy with either LABA or inhaled corticosteroids. Three studies compared ipratropium monotherapy with combination therapy consisting of ipratropium with either a short or long-acting beta agonist. None titrated interventions according to short-term spirometric response to therapy, change in spirometry over time, or based on an enrollee crossing a threshold

value of spirometry. None of the studies used spirometry to begin, discontinue, adjust, or monitor treatment effectiveness.

The range of mean study baseline spirometry of enrolled subjects was typically quite narrow. Only four studies evaluating inhaled corticosteroids and one study of short-acting inhaled anticholingerics had mean baseline FEV_1 percent predicted values that were greater than GOLD stage 3,4 airflow obstruction (i.e., mild-moderate severe airflow obstruction). None of the studies published subgroup outcomes according to smoking status, previous clinical diagnosis of COPD, age, race, or gender. Only two studies reported outcomes according to spirometric stage of disease[86,87]and these involved inhaled corticosteroids. Additional outcome data according to baseline symptom and spirometric status were obtained from one study of short acting anticholinergics through personal communication with the Data Coordinating Center for LH-1 (John Connett, personal communication, 2004). The few studies that followed groups of patients for longer than 1 year did not report outcomes separately according to baseline symptom status (i.e., wheezing, dyspnea, sputum production, cough, or respiratory symptoms).

The definition of our primary outcome (COPD exacerbation) varied across studies. Most studies defined exacerbations as a subjective worsening of cough, sputum, or dyspnea that required treatment with antibiotics and/or oral/intravenous corticosteroids. Other studies defined exacerbations based only on acute changes in respiratory symptoms and did not specifically require the use of additional medications. For our analyses, an exacerbation event was defined as a subject having at least one exacerbation during the treatment period. If this outcome was not available, an exacerbation was denoted by the alternative events: 1) subject having a COPD adverse event; 2) subject requiring additional treatment for COPD; 3) exacerbation/deterioration of COPD leading to study withdrawal.

Long-acting β agonists. The baseline demographic and pulmonary characteristics of the 18 studies[46,87-103] evaluating long-acting β2 agonists are summarized in Evidence Table 6 in Appendix D[*]. One published report was a pooled analyses of a published RCT[95] and an unpublished RCT.[89] The quality of the randomization allocation concealment method was adequate in only three trials [87,93,94] and unclear in the remaining studies. Intention-to-treat analysis was reportedly used in 14 trials.[46,88,90-94,96-101,103] All studies were double-blinded. Enrolled subjects had symptomatic COPD and severe to very severe airflow obstruction. A total of 12,390 patients, with a mean FEV_1 of 1.24L (range 0.96-1.51L) and pretreatment FEV_1 range of 33 -55 percent predicted at baseline spirometry, were evaluated during 3 months to 1 year in studies assessing long-acting β agonist alone or in combination with other therapies. Long-acting β2 agonists (salmeterol or formeterol) alone were compared to placebo in 14 trials that provided exacerbation outcomes (n=6,544). Subjects randomized to active controls received tiotropium (2 trials), ipratropium (4 trials) sibenadet (1 trial), inhaled long acting corticorticosteroids fluticasone or budesonide (5 trials), or combination therapies (five with inhaled corticosteroids and one with ipratropium). Three studies compared different doses of formoterol[93,97,99] and two studies assessed different doses of salmeterol.[46,103] The mean age was 63.5 years (n=8,029) and males were 74 percent of the subjects. Five trials provided ethnicity information.[90,91,96,100,102] Nearly 95 percent of subjects were white. Smoking history was recorded in ten trials[87-92,95,96,99,102] (mean of 46 pack-years) and the duration of COPD diagnosis was about 8 years (nine trials reporting).[89,91,93,95-99,102]

[*] Note: Appendixes and evidence tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/spirotp.htm

Long-acting anticholinergics. In Evidence Table 7 in Appendix D* the general characteristics of the five clinical trials,[89,95,104-106] with tiotropium (18 ug/day) are summarized. Two of the published reports[89,105] were pooled analyses of two published RCTs[95,106] and two unpublished RCTs. The quality of the randomization allocation concealment method was unclear in all studies. Intention-to-treat analysis was reportedly used in three trials.[104-106] All studies were double-blinded. A total of 2,663 patients were enrolled. All had severe to very-severe airflow obstruction, (a mean FEV_1 of 1.11L with range 1.04L to 1.25L, and pretreatment FEV_1 of 38-42 percent predicted), respiratory symptoms and a previous diagnosis of COPD. Treatment duration ranged from 3.3 months to 1 year. Of the 2,663 patients, 1,308 (49.1 percent) received monotherapy with tiotropium. Twenty-nine percent received placebo (two reports, n=771 subjects) or ipratropium bromide (one report, n=179 subjects). The others (15 percent) were only treated by long-acting β2 agonists (salmeterol; one study). The mean age was 64.5 years and 70 percent of subjects were male. No further information regarding race or ethnicity was provided. Subjects had a mean of 48 pack-years smoking and had COPD for approximately 9 years.

Short-acting anticholinergics. There were eight published reports, five multi-armed, involving the short-acting anticholinergic ipratroprium (typically 40 ug three to four times/day).[19,98,99,100-102,105,106] Seven involved ipratropium monotherapy, (including five versus placebo, four versus long-acting β agonists and one versus tiotropium) and one combined ipratropium with salmeterol in comparison to salmeterol alone and placebo. One published report was a pooled analyses of a published RCT and an unpublished RCT[105,106]. The quality of the randomization allocation concealment method was unclear in all studies, except the LH1.[107] Intention-to-treat analysis was reportedly used in five trials.[98-100,105,106] All studies were double-blinded. Two studies compared outcomes to the long-acting anticholinergic tiotroprium. Studies providing data on exacerbations were 3 months in duration. General characteristics are summarized in Evidence Table 8 in Appendix D*. A total of 8,489 patients with moderate to severe COPD (a mean FEV_1 of 2.21L with range 1.18L to 2.64L and pretreatment FEV_1 of 33- 46 percent predicted) were evaluated during 3 months to 1 year. Of the 8,345 patients, 2,667 (31 percent) were randomized to ipratropium monotherapy and 5,466 patients (66.7 percent) to placebo, tiotropium, or usual care. Combination therapy with salmeterol was evaluated in 47 subjects. In comparison to other interventions, studies evaluating ipratroprium enrolled a higher percentage of relatively young individuals, women, subjects with mild to moderate airflow obstruction, and those without symptoms or previous clinical diagnosis of COPD. Therefore, subjects enrolled in these studies more closely represent a spectrum of the population likely to be detected by case finding in primary care settings. The mean age was 52.9 years (n=5,523). Sixty-five percent were men. Nearly 95 percent were white (n=two studies).[100,102] The mean smoking history was 41 pack-years (n=five studies)[19,99,102,105,106] and the mean duration of COPD was 9.8 years.[98,99,102,105,106]

Combination therapy with inhaled short-acting anticholinergics and β2 agonists. Combination therapy (inhaled short acting anticholinergics bronchodilators [ipratropium bromide] + short (or long)-acting β2 agonists (albuterol or salmeterol) studies are summarized in Evidence Table 8 in Appendix D*.[108-110] A total of 1,186 patients with severe to very severe airflow obstruction and symptomatic COPD (a mean FEV_1 of 0.95L with range 0.91L to 1.00L

* Note: Appendixes and evidence tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/spirotp.htm

and pretreatment FEV_1 of 34 percent to 37 percent predicted) were evaluated during 85 days. Of all patients, 404 (34.1 percent) had been treated by combination therapy. Ipratropium and albuterol, were given to 393 (33.1 percent) and 389 (32.8 percent), respectively. The mean age was 64.4 years (n=1,186) and approximately 65 percent were men. Over 93 percent of enrollees were white and the mean duration of COPD was 8.9 years.

Inhaled corticosteroids. Thirteen studies evaluated inhaled corticosteroids and are summarized in Evidence Table 9 in Appendix D*. The quality of the randomization allocation concealment method was adequate in five studies,[86,87,111-113] and unclear in the other studies. Intention-to-treat analysis was reportedly used in 11 trials.[86,88,91,92,96,111-116] All studies were double-blinded. A total of 8,849 patients were enrolled. Studies evaluating inhaled corticosteroids enrolled subjects with a relatively wide spectrum of clinical and airflow severity. Studies also assessed treatment over several years. Enrolled subjects (a mean FEV_1 of 2.0L with range 0.91L to 2.53L and pretreatment FEV_1 of 36-77 percent predicted) were evaluated from 6 months to 4.5 years. Of all patients, 3,247 (36.7 percent) had been treated by inhaled corticosteroids (fluticasone or triamcinolone; or budesonide or beclomethasone) and 3,257 patients had only taken a placebo (36.8 percent). The mean age overall was 60 years (n=6,504). The percent of males overall was about 71 percent. According to three trials[91,96,114] with ethnicity information, the proportion of white subjects was 94 percent. All subjects in ten trials[86-88,91,92,96,111,115-117] had a smoking history with a mean of 44 pack-years.

Combination corticosteroids and long-acting β agonists. Five studies evaluated inhaled corticosteroid and long-acting β agonist combination therapy (Evidence Table 9 in Appendix D*).[87,88,91,92,96] All studies were parallel-grouped, placebo-controlled, and double-blinded. The quality of the randomization allocation concealment method was adequate in one trial[87] and intention-to-treat analysis was reportedly used in four studies.[88,91,92,96] Study duration ranged from 6 to 12 months. A total of 4,713 subjects were enrolled, approximately 25 percent randomized to combination, placebo, and monotherapy arms each. The subjects were, on average, 64 years old, had a baseline FEV_1 of 1.2L (range 0.96 to 1.3, FEV_1 of 36-45 percent predicted), had a smoking history with a mean of 46 pack-years, and a median duration of COPD of 6 years (two studies reporting.[91,96] Two trials reported ethnicity and nearly all subjects were white (94 percent).[91,96]

D2 antagonist. Sibenadet was evaluated in three studies involving four study protocols[90,118,119] and summarized in Evidence Table 10 in Appendix D*. One study included two trials according to study duration (3 or 6.5 months).[119] A total of 4,077 patients with a mean FEV_1 of 1.29L (range 1.2-1.4L) and pretreatment FEV_1 of 39-42 percent predicted at baseline were evaluated during 3 to 13 months. Of all patients, 1,977 (48.5 percent) had only been treated by sibenadet. A placebo was given as treatment to 1,547 (37.9 percent). The others (13.6 percent) were treated with salmeterol. The mean age was 63.9 years (n=3,523). The percent of males was 71 percent. According to one trial[90] with ethnicity information, the proportion of whites was 97.2 percent. In four trials subjects had a mean of 47 pack-years.

* Note: Appendixes and evidence tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/spirotp.htm

Oral Purified Bacterial Extracts. A systematic review and meta-analysis identified 13 trials (1,971 patients) of oral purified bacterial (active) extracts in patients with chronic bronchitis and COPD.[120] Ten studies tested OM-85BV, two trials tested LW-50020, and one study tested SL-04.[120] Study duration ranged from 3-12 months. In trials that reported demographic information, 60 percent were male. Inclusion criteria were COPD in six trials, chronic bronchitis in ten trials, and more than three episodes of exacerbation within the previous year in eight trials. In the seven studies that reported smoking habits, almost half of analyzed patients were smokers or ex-smokers. Lung function was reported in five trials (mild to moderate COPD, four trials; severe COPD, one trial).[120]

2) Nonpharmacological therapies. The general characteristics of the seven studies[121-127] of pulmonary rehabilitation intervention are summarized in Evidence Table 11 in Appendix D*. One study included two trials according to disease severity (moderate or severe).[127] Subjects enrolled in nonpharmacological therapy trials typically had severe to very severe airflow obstruction and respiratory symptoms, already received a clinical diagnosis of COPD, and were already receiving a wide assortment of pharmacologic agents. Thus they are unlikely to be representative of the vast majority of subjects detected by casefinding with spirometry in primary care settings, whom this report is targeted to address. We provide this information for the sake of completeness.

A total of 693 patients with a FEV_1 range (0.71-1.07L) and pretreatment FEV_1 of 31-50 percent predicted at baseline were evaluated from 8 weeks to 2 years. The general characteristics of the nine studies using interventions of disease management, education, and followup are summarized in Evidence Table 12 in Appendix D*. A total of 1,997 patients with a FEV_1 range (0.78-post 1.71L) and pretreatment FEV_1 of 37-59 percent predicted at baseline were evaluated from 3 months to 1 year. Also, the general characteristics of the two studies intervened by NIMV are summarized in Evidence Table 13 in Appendix D*. A total of 220 patients with a FEV_1 range of 0.73L and pretreatment FEV_1 of 30 percent predicted at baseline were evaluated from 6 months to 2 years.

Outcomes by Intervention

1) Pharmacological therapies.

Long-acting β2 agonists as monotherapy (LABA). (Figure 10 on page 67, Evidence Figures 1 and 2 in Appendix D*, and Evidence Tables 14 and 15 in Appendix D*.) Thirteen placebo-controlled trials (6,544 patients, baseline) followed patients from 3 to 12 months. Compared to placebo, both formoterol and salmeterol reduced exacerbations as well as improved St George's Respiratory Questionnaire scores. There was a pooled 18 percent relative risk reduction (95 percent CI, 10-24 percent) and 4 percent pooled absolute risk reduction [95 percent CI, -6 to -2] in the percentage of individuals having one or more COPD exacerbation events during study followup. Reductions were consistently seen across studies with each agent and were similar in studies utilizing formeterol and those using salmeterol. Only three studies reported rates of hospitalization. They were reduced by about 5 percent compared to placebo in one study and not different in two others. The few dose comparison studies of the long acting β2 antagonists

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salmeterol or fometerol found similar improvements in all clinical outcomes at differing doses of medication. This suggests that increasing the dose of β2 antagonist beyond salmeterol 50 ug/bid or fometerol 12 ug/bid is not beneficial.

There was no significant difference in all-cause mortality between placebo and LABA (12 studies, 5,700 patients) (RR=1.07; 95 percent CI: 0.65-1.78). Absolute risk reduction was 0 percent [95 percent CI, -1 to 1]. Improvement was demonstrated in health-related quality of life scores as measured by the SGRQ in seven studies of subjects with GOLD Stage 3,4 disease (1.98-unit improvement; 95 percent CI: 0.81-3.15 vs. placebo). However, the pooled weighted mean difference in SGRQ compared to placebo failed to achieve a previously specified level of clinical significance (i.e., ≥4). Additionally, the only two studies that individually reported a clinically important difference in SGRQ enrolled subjects with severe to very severe airflow obstruction (mean FEV_1 predicted <50 percent).

The narrow range of mean baseline spirometric values (FEV_1 range=1.1-1.5; percent predicted=33-54 percent; GOLD 3,4) precludes assessment of whether treatment effectiveness varied according to baseline spirometry. The high percentage of subjects in the placebo arm that had at least one COPD exacerbation suggests that in all but one study[93] subjects had severe symptoms and frequent exacerbations. In two trials lasting 6 months (n=1,212) salmeterol provided similar reductions in exacerbations compared to tiotropium (RR=1.07; 95 percent CI 0.92 to 1.25).[89,95]

Long-acting anticholinergics: tiotropium. (Figure 11 on page 68, Evidence Figure 3 in Appendix D*, and Summary Tables 8 and 9 on pages 69-71.) Five clinical trials of the long-acting, anti-cholinergic tiotropium (n=2,956) in patients with severe to very severe airflow obstruction (mean FEV_1 percent predicted = 39-41 percent) and respiratory symptoms demonstrated a reduction in exacerbations compared with either placebo (RR = 0.84; 95 percent CI, 0.74-0.95) or with the short-acting anti-cholingeric ipratropium bromide (RR = 0.77; 95 percent CI, 0.62-0.95). Pooled absolute risk reductions were 6 percent (95 percent CI, -11 to -2) compared to placebo and 11 percent (95 percent CI, -20 to -2) versus ipratropium. Subjects enrolled in these studies had frequent episodes of exacerbations. The weighted mean percentage of subjects with at least one exacerbation during the 3-12 month study period in the control group was approximately 40 percent. Hospitalization rates were reported in three studies and found to be lower by about 7 percent compared to placebo and 4 percent versus ipratropium. All-cause mortality was decreased versus placebo (RR = 0.50; 95 percent CI 0.17 to 1.24) in two trials (n=1,723),[89,104] and the absolute risk reduction was one percent (95 percent CI, -2 to 0). The risk of all-cause mortality was increased compared with ipratropium in one trial, although not significantly (RR = 1.51; 95 percent CI 0.41 to 5.50).[105] Tiotropium also improved scores on the SGRQ health-related quality of life scale relative to placebo (2.7-3.7 unit improvement) and ipratropium (3.3 unit improvement) though the reduction failed to achieve a previously determined level of clinical significance. Exacerbations were similar compared to long-acting β2 agonists (RR for exacerbations vs. long-acting β2 agonists, 0.92; 95 percent CI, 0.75-1.11) in pooled results from two studies.[89]

Short-acting anticholinergics alone or in combination with β2 agonists. (Figure 12 on page 72, Evidence Figure 4 in Appendix D*, and Summary Tables 10 and 11 on pages 73-75.)

* Note: Appendixes and evidence tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/spirotp.htm

Ipratropium was no more effective than placebo and less effective than tiotroprium in reducing exacerbations and hospitalizations. In four trials of patients with GOLD Stage 3,4 COPD, (range of FEV_1 percent predicted = 33-45 percent) with followup of 3 months, ipratropium monotherapy did not significantly reduce the percentage of subjects having one or more COPD exacerbations compared with a placebo (ARR = 1.3 percent; RR = 0.95 [0.78 to 1.16]. Between 18 percent and 38 percent of subjects experienced a study-defined exacerbation suggesting that, on average, individuals had symptomatically severe COPD with frequent exacerbations. Three studies reported results from validated respiratory functional status questionnaires.[98,99,105] The change from baseline between control and ipratroprium was small and less than considered clinically significant (four point difference) in two studies[98,99] and favored tiotropium by three points in the other trial.[105] Exacerbation rates for LH-1 (n=3,923; mean FEV_1 = 2.6; FEV_1 percent predicted = 75 percent) have not been published. Additional outcomes from LH-1, which is the only trial that enrolled subjects with mild to moderate airflow obstruction regardless of symptoms, are described below. Combination therapy with either short or long acting β agonist (four trials) in addition to ipratropium did not reduce exacerbations compared to ipratropium alone (RR=1.03 95 percent CI=0.64 to 1.67) but did versus β agonists (RR=0.68 95 percent CI=0-.51 to 0.91).[106,108-110]

In the one study comparing ipratropium to tiotropium (n=535)[105] the percentage of subjects having at least one exacerbation was higher in the ipratroprium group (46 percent) than subjects randomized to receive tiotropium (35 percent). There was no significant difference in mortality rates between ipratropium and control groups. However, only one study (LH-1) followed patients for more than 1 year. The overall mortality rate in the placebo arm of 2.2 percent was less than the ipratropium group (2.8 percent).

Inhaled corticosteroids. (Figure 13 on page 76, Evidence Figure 5 in Appendix D*, and Summary Tables 12 and 13 on pages 77-80.) In ten placebo-controlled trials (3,734 patients)[86-88,92,96,111-113,116,117] with at least a 6-month followup period, inhaled corticosteroids led to a 22 percent relative reduction in the percentage of subjects having a COPD exacerbation event (RR 0.78; 95 percent CI, 0.70-0.88). The pooled absolute risk reduction was 5 percent (95 percent CI, -8 to -3). Six of the studies were 1 year in duration or longer and the percentage of subjects in the placebo arm that experienced at least one exacerbation was 22.4 percent.[87,88,92,111,112,117] An additional study[113] enrolled 1,116 smokers with moderate airflow obstruction (FEV_1 percent predicted = 64 percent) and is the only trial of inhaled corticosteroids to report on rates of hospitalizations. Members of the triamcinolone group had fewer overall respiratory symptoms during the course of the study (21.1 per 100 person-years vs. 28.2 per 100 person years, p = 0.005), had fewer visits to a physician because of a respiratory illness (1.2 per 100 person-years vs. 2.1 per 100 person-years), and fewer hospitalizations for respiratory conditions (0.99 per 100 person years vs. 2.1 per 100 person years). There was no significant association between triamcinolone use and specific respiratory symptoms including chronic cough, production of phlegm, or wheezing.

As shown in the meta-analysis by Sin et al.[9] and subgroup data from the study by van der Valk[86] the beneficial effect of inhaled corticosteroids was associated with the severity of airflow obstruction as measured by FEV_1. Whereas the study that had the highest mean FEV_1 value failed to demonstrate a beneficial effect of inhaled corticosteroids, trials that had a mean FEV_1 of less than 1.7L or lower (mean baseline FEV_1 percent predicted 36-57 percent) demonstrated a

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positive effect of inhaled corticosteroids on exacerbations, regardless of the duration of the study or the specific formulation used. Analysis of the subgroup of patients with a FEV_1 value less than 50 percent predicted (low FEV_1 group) suggests that the improvement time to first exacerbation due to fluticasone observed in the COPE trial is driven by this group. The hazard ratio was 2.1 (95 percent CI 1.1-36) and 1.2 (95 percent 0.8-2.0) in the low and high-FEV_1 groups respectively. Inhaled corticosteroids resulted in a 19 percent reduction in all-cause mortality though the confidence intervals were wide and not statistically significant (RR 0.81 95 percent CI = 0.60 to 1.10) and the absolute reduction was only 0.6 percent. Changes in the SGRQ reported in two trials involving 995 subjects followed from 6 months to 3 years were less than considered clinically significant.[86,111]

Combination corticosteroids and long-acting inhaled β agonists. (Figure 14 on page 81, Evidence Figures 6-12 in Appendix D*, and Summary Tables 14 and 15 on pages 82-84.) Five multi-arm trials (n=1,982 patients)[87,88,91,92,96] evaluated monotherapy with either LABA or inhaled corticosteroids compared to combination therapy with these agents and to placebo. Thus they provide direct comparative evidence regarding the relative effectiveness of either agent or combination therapy to placebo as well as to their respective monotherapies. The ARR in exacerbations compared to placebo seen with both monotherapies and combination therapy were all statistically significant and of similar magnitude (ARR compared to placebo for LABA = 3.7 percent; corticosteroids = 5.2 percent and combination therapy = 5.9 percent). The addition of inhaled corticosteroids to LABA resulted in a borderline significant reduction in exacerbations compared to LABA alone (RR = 0.82 [0.65, 1.04]; ARR = 1.3 percent). When compared to monotherapy with corticosteroids, there was approximately one-half the reduction reported for comparison to LABA monotherapy (RR = 0.92) and the absolute risk reduction was less than 1 percent. The mean baseline FEV_1 ranged from 36-45 percent predicted indicating subjects had very severe airflow obstruction (GOLD Stage ≥3). A subgroup analysis reported by Calverley indicated that therapeutic effectiveness varied by severity of baseline spirometry. While the relative risk reduction for combination therapy compared to placebo was 39 percent for all enrollees, individuals with FEV_1 >50 percent predicted had only a 10 percent relative risk reduction. Improvements in respiratory symptoms compared to placebo as measured at 1 year by the SGRQ were less than considered clinically significant in one trial) (WMD = -2.2; 95 percent CI = –3.3 to –1.1)[87] and one study demonstrated a large and clinically relevant improvement of 7.5 units.[88] Compared to placebo, combination therapy reduced all-cause mortality by 44 percent, but the confidence intervals were wide and not statistically significant and the absolute reduction was 0.7 percent (RR vs. placebo, 0.66; 95 percent CI, 0.32-1.38). (Summary Table 14 on pages 82-83 and Evidence Figure 6 in Appendix D*.) The addition of LABA to inhaled corticosteroids did not reduce mortality compared to corticosteroids alone (RR = 0.98). However, when compared to LABA, combination therapy with corticosteroids resulted in nearly a 54 percent reduction in mortality though there were relatively few deaths. Thus, monotherapy with corticosteroids may be slightly more effective in reducing exacerbations than LABA. The addition of LABA to corticosteroids does not reduce exacerbations or improve mortality or respiratory status compared to monotherapy.

* Note: Appendixes and evidence tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/spirotp.htm

Sibanet (D2 receptor/β agonist). (Evidence Figures 13 and 14 and Evidence Tables 16 and 17 in Appendix D*.) Four trials evaluated the D2 receptor/β agonist, sibanet (n=3,524 patients)[118,119,128] in patients with GOLD Stage 3,4 airflow obstruction. Compared to placebo there was no significant difference in exacerbations (RR, 0.91; 95 percent CI, 0.81 to 1.03; ARR = -0.7). Changes in the SGRQ were small and less than considered clinically important. Only one study was at least 1 year in duration and all-cause mortality was not different between sibanet and placebo (RR vs. placebo, 1.14; 95 percent CI, 0.60-12.15).

Oral purified bacterial extracts. There was a large variety in the reported end points. No more than five trials reported on the same efficacy end point. Three trials reported on the prevalence of exacerbation with OM-85BV or SL-04 over a 6-month period. Two trials (731 patients) were judged to be of high methodologic quality. The combined RR for prevention of exacerbations was 0.83 (95 percent CI, 0.55 to 1.25). Itching or cutaneous eruptions were reported in 3.3 percent of subjects who received active extracts compared with 1.0 percent of control subjects. Data on hospital admission for respiratory problems was reported in 31 of 191 patients (16.2 percent) receiving OM-85BV and in 44 of 190 patients (23.2 percent). Urologic problems (primarily urinary tract infections) were reported in 8 percent of patients who received active extracts compared with 3.0 percent of control subjects.[120]

Overall withdrawals from treatment, noncompliance, and adverse events were examined for trials 1 year or longer in duration. Subjects treated with a β agonist, tiotropium, or a corticosteroid were less likely to withdraw from treatment for any reason compared to placebo or control. The percent of β agonist subjects withdrawing was 30.8 percent compared with 37.9 percent of the placebo subjects in four trials >1 year (ARR = 7.1; RR = 0.86: 95 percent CI 0.77 to 0.96).[87,88,92,97] The overall withdrawal rate for subjects treated with tiotropium was 17.3 percent compared with 27.8 percent and 21.2 percent of placebo and ipratropium subjects, respectively (ARR = 8.3; RR = 0.69: 95 percent CI 0.56 to 0.84).[104,105] Subjects on corticosteroids had a withdrawal rate of 26.5 percent versus 31.9 percent of placebo subjects in seven trials reported withdrawal data (ARR = 5.45; RR = 0.83: 95 percent CI = 0.76 to 0.90).[87,88,92,111,112,114] The one trial of ipratropium reporting withdrawal data favored the control, tiotropium, 15.2 percent to 21.2 percent (RR = 1.40: 95 percent CI 0.96 to 2.03).[105] In trials of combination corticosteroids and long-acting β agonist, withdrawals were lower for combination therapy compared with placebo but were similar compared with either monotherapy.

Four trials reported withdrawal from treatment due to noncompliance.[87,97,105,111] The rates of withdrawal ranged from <1 to 16 percent for treatment and <1 to 16 percent for placebo or control. The LHS2 trial reported adherence to treatment based both on patient report and canister weight. Approximately 70 percent of triamcinolone and placebo subjects had satisfactory adherence to the treatment protocol based on self-report. However, these rates decreased to 53.7 percent and 58.5 percent respectively based on canister weights for triamcinolone and placebo.[114]

Treatments were generally well tolerated. Adverse events during the study followup period were usually minor and seldom more than placebo. Compared to placebo, an increased frequency of oropharyngeal candidiasis (5.1 percent vs. 2.1 percent), throat irritation (7.6 percent vs. 4.5 percent), and bruising (8.4 percent vs. 3.7 percent) was seen with corticosteroid use. Dry mouth was reported in 12 percent of subjects using anticholinergics.[104,105] A separate meta-analysis of

* Note: Appendixes and evidence tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/spirotp.htm

20 RCTs involving 6,623 subjects by Salpeter and colleagues assessed the cardiovascular effects of β agonists (primarily the long-acting β agonists salmeterol and fometerol) in patients with asthma or COPD. Treatment with β agonists was associated with a significantly increased risk for adverse cardiovascular events (RR 2.54; 95 percent CI 1.59 to 4.05; 2.7 percent vs. 0.7 percent). The vast majority of the adverse events in the β agonist group were due to sinus tachycardia (87 percent) and thus of uncertain clinical significance. However, major cardiovascular events were also higher in this group compared to placebo though not statistically different (RR = 1.66; 95 percent CI 0.76 to 3.60).[129]

2) Nonpharmacological therapies

a) *Pulmonary rehabilitation program.* (Evidence Table 18 in Appendix D*.) Patients with advanced COPD experience marked dyspnea and exercise intolerance related in part to generalized muscle weakness, cardiac impairments, and nutritional deficiencies. Pulmonary rehabilitation programs were developed to address some of these adverse physiological changes. The contents of pulmonary rehabilitation vary from center to center. However, most contain four major components: exercise training, education, behavioral modification, and outcome assessment. The intensity of the exercise training is heterogeneous. Most aerobic training is targeted at 60-90 percent of the predicted maximal heart rate for about 30 minutes. Most programs emphasize endurance training. The eight clinical trials (693 patients) indicate that pulmonary rehabilitation may improve the health status of patients with severe to very severe COPD (mean FEV_1, 0.71 to 1.07L; FEV_1 percent predicted = 31-50 percent) as assessed by SGRQ and increases exercise tolerance beyond that achieved by standard care alone (including inhaled bronchodilators), at least during the time patients are in the rehabilitation program. Three of the eight trials reported an improvement in the SGRQ between control and intervention greater than the four point minimally important difference.[123,124,127] As noted by Sin, pulmonary rehabilitation did not have any significant effect on mortality.[9]

b) Disease management, education, and followup studies. (Evidence Table 19 in Appendix D*.) Disease management is an approach to coordinate resources across the health care system with the aim of fostering continuity of care and increasing patients' knowledge and control over their chronic diseases.[130] Because the care of patients with COPD frequently requires multiple caregivers, including physicians, nurses, physiotherapists, pharmacists, and nutritionists, a process to promote integration and seamless care may improve clinical outcomes in COPD. Sin et al. noted that because of marked heterogeneity in the content of the programs and their effects, these data need to be interpreted cautiously and further study is required.[9] Patients enrolled in these programs had moderate to very severe airflow obstruction (FEV_1 percent predicted = 37-59 percent), had been previously diagnosed clinically with COPD, and were taking inhaled bronchodilators. It is likely that individuals involved in these programs represent an extremely small fraction of adults likely to be detected by case finding with spirometry. Only one trial reported exacerbation rates and rates of hospitalization were not consistently different between intervention and controls.[116] On average, these programs did not achieve a clinically meaningful improvement in health status of patients or a statistically significant impact in hospitalization rates.

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c) Non-invasive mechanical ventilation (NIMV). Respiratory muscle fatigue and dynamic hyperinflation commonly are observed in patients with severe COPD.[131-133] Patients with severe COPD work harder than patients without COPD because they have to overcome dynamic lung hyperinflation and airflow obstruction.[132,133] Long-term NIMV therapy theoretically unloads the inspiratory muscles of respiration and helps restore depleted energy stores, as well as partially reversing respiratory muscle fatigue.[128] Sin and colleagues concluded that the long-term use of NIMV cannot be recommended at this time because there is insufficient clinical trial evidence for its efficacy.[21,134-136]

d) Influenza and pneumococcal vaccinations. Elderly persons and persons with certain underlying medical conditions experience more than 80 percent of the serious complications of influenza, such as hospitalization and death.[137,138] Among elderly persons, those with a clinical diagnosis of chronic lung disease are an especially high-risk group. Their hospitalization rates for pneumonia are two to seven times those of individuals without underlying pulmonary conditions. Influenza vaccination is recommended for all adults, especially those with chronic medical conditions. High-risk elderly persons, such as those with chronic lung disease, have inadequate vaccination rates.[139] Methods to improve influenza vaccinations in these individuals would be beneficial.

A retrospective, multiseason cohort study in a large managed care organization assessed the effects of influenza and the benefits of influenza vaccination in elderly persons with a diagnosis of chronic lung disease during the previous 12 months. Influenza vaccination was associated with fewer hospitalizations for pneumonia and influenza (adjusted risk ratio, 0.48 [95 percent CI, 0.28 to 0.82]) and with lower risk for death (adjusted odds ratio, 0.30 [CI, 0.21 to 0.43]) during the influenza seasons. It was also associated with fewer outpatient visits for pneumonia and for all respiratory conditions.[140] However, there is no information assessing whether vaccination rates are improved by case finding with spirometry. Additionally, there is no information to determine whether spirometry should be used to identify asymptomatic individuals with airflow obstruction who should be considered at increased priority for influenza vaccination, especially if vaccination supplies are limited.

Streptococcus pneumoniae is a major cause of morbidity and mortality. Pneumococcal vaccination is often recommended for preventing invasive disease for the elderly and others who are at increased risk for serious pneumococcal infections and their complications. This includes individuals with chronic lung disease. A recent meta-analysis of randomized or quasi-randomized controlled trials assessed the effectiveness of pneumococcal vaccination[141] in preventing pneumonia, bronchitis, and mortality. Patient populations and type of vaccine varied in these trials. Two trials limited enrollment to subjects with COPD (n=292). The authors of the meta-analysis concluded that despite encouraging data from some very early trials, pooling trial results published from 1977 on suggest there is no significant effect on pneumonia (14 trials, n=75,008 subjects; OR = 0.77, 95 percent CI = 0.58, 1.02) or death (OR = 0.90, 95 percent CI = 0.90, 1.07). In the two small trials involving subjects with COPD, the odds of definitive pneumococcal pneumonia were actually higher in the groups receiving vaccine than control, though "all-cause pneumonia" was less common in vaccine recipients in one of these studies. The pooled results from case-control studies did demonstrate a significant efficacy in preventing invasive pneumoccocal disease (OR = 0.47 [CI = 0.37, 0.59]) as have other cohort studies among elderly persons with chronic lung disease. However, these pooled data from RCTs suggest that

pneumococcal vaccination may not reduce morbidity and/or mortality, especially in individuals with COPD. Furthermore, even if a decision is made, despite the findings from this meta-analysis of RCT, to routinely vaccinate elderly individuals or those with chronic lung disease, there is no evidence that spirometry leads to improved vaccination rates or that outcomes are improved in individuals not reporting respiratory symptoms who have airflow obstruction.

Does Treatment Effectiveness Vary According to Baseline Spirometry, Spirometric Response to Treatment, and/or Change in Spirometry Over Time?

Periodic monitoring with spirometry has been recommended as a guide to treatment response and/or patient health status.[142] However, correlation between spirometric changes and long-term clinical outcomes in COPD has been shown to be weak.[22] As noted above, most treatment trials enrolled subjects who had both moderate to severe respiratory symptoms and severe to very severe airflow obstruction. All studies used spirometry to confirm and quantify the presence and severity of airflow obstruction and used spirometric values as entry criteria and most ruled out a clinically significant bronchodilator response. None of the trial protocols involved modification of treatment according to spirometry. Results from large long-term RCTs of inhaled corticosteroids and anti-cholinergics demonstrate that these interventions do not alter the course of spirometric decline. Two studies assessed clinical response according to short-term change in spirometry.

A conceptual model and flow diagram Figure 15 on page 85 illustrates how periodic monitoring with spirometry (e.g., annually or every 3-5 years) may be used to identify symptomatic individuals with normal airflow to mild to moderate airflow obstruction who may subsequently develop severe to very severe airflow obstruction and thus be candidates for treatment. The starting point is based on the pooled summary of treatment effectiveness indicating that interventions with the exception of smoking cessation and influenza vaccinations were only effective in symptomatic individuals (regardless of smoking status) who had severe to very severe (approximately GOLD Stage 3,4) airflow obstruction. Periodic monitoring with spirometry in patients reporting respiratory symptoms would assist the health care provider in initiating or modifying therapy if data demonstrated that outcomes are improved if treatment initiation or modification is based on 1) acute spirometric response to therapy, 2) change in spirometry over time (slope of FEV_1 decline), or 3) crossing a given followup spirometric threshold (e.g., transition from mild-moderate to severe or very severe; approximately GOLD 1 or 2 to GOLD 3 or 4).

Effectiveness of Treatment According to Baseline Spirometry

All studies of long- and short-acting inhaled anti-cholinergics and long-acting β agonist, except for LH-1 evaluating ipratropium, assessed individuals with severe to very severe airflow obstruction and respiratory symptoms (mean FEV_1 ranged from 0.96-1.51 and FEV_1 percent predicted from 33-55 percent; approximately equivalent to GOLD Stage 3). Therefore it is not possible to determine the effectiveness of long-acting anti-cholinergics or β agonist in subjects with spirometry demonstrating mild to moderate airflow obstruction. However, information is available from other inhaled agents suggesting that a spirometric threshold for treatment

effectiveness exists and that treatments do not prevent the development of symptoms among individuals not reporting respiratory symptoms.

As shown by Sin and colleagues and confirmed in our results, the effectiveness of inhaled corticosteroids is associated with baseline spirometry as measured by FEV_1. Three trials enrolling approximately 2,500 subjects with a mean FEV_1 >2L (GOLD Stage 0-2) and followed for 3 or more years failed to demonstrate a benefit in clinical outcomes, although there was a trend towards a reduction of mortality. Analysis of the subgroup of patients with a FEV_1 value less than 50 percent predicted (low FEV_1 group) suggests that the improvement in time to first exacerbation due to fluticasone observed in the COPE trial is driven by this group. The hazard ratio was 2.1 (95 percent CI 1.1-36) and 1.2 (95 percent 0.8-2.0) in the low- and high-FEV_1 groups respectively. The study by Calverley and colleagues evaluated inhaled corticosteroids alone or in combination with long acting β agonists in subjects with a mean baseline FEV_1 percent predicted of 45 percent (GOLD Stage 3).[87] They observed that treatment effectiveness was associated with disease severity as measured by baseline spirometry. Compared to placebo, combination therapy resulted in a relative risk reduction in exacerbations of 39 percent. However, in the subgroup with baseline FEV_1 >50 percent (moderate airflow obstruction; GOLD Stage 2) the relative risk reduction was only 10 percent (P value and confidence intervals not provided).

The largest and longest study assessing inhaled bronchodilators (LH-1) compared outcomes of 3,923 adult smokers who were at risk for or had mild to moderate airflow obstruction and treated them with ipratropium vs. placebo over an average of 5 years. Prevalence of baseline symptoms (LH-1) according to spirometric category are shown in Table 4 on page 45. Only a small percentage of subjects had a previous diagnosis of COPD, less than one-half reported dyspnea, about 5 percent had normal spirometry and sputum production (GOLD 0), and almost 20 percent reported no respiratory symptoms. Therefore subjects enrolled in LH-1 are representative of adults likely to be detected by spirometric case finding. In unpublished data obtained from the Data Coordinating Center Director (John Connett, personal communication, 2004) there was no reduction at 3 years in respiratory hospitalizations for subjects with baseline post-bronchodilator assessed GOLD spirometric stages "Normal," 0, 1, or 2 (Evidence Table 20 in Appendix D[*]) in subjects randomized to ipratropium compared with placebo. Ipratroprium did not improve outcomes of dyspnea (31.0 percent vs. 31.2 percent), cough and sputum (14.9 vs. 15.0 percent), or respiratory hospitalizations in the overall cohort. Results were not different when assessed according to baseline spirometric stage or symptom status (Table 5 on page 46). The presence of symptoms at baseline, rather than spirometry or treatment, was the best predictor of symptoms at the 3-year followup. Additional analysis demonstrated that ipratropium did not improve the percentage of subjects having dyspnea and cough and sputum at 3 years regardless of presence or absence of these symptoms at baseline (Evidence Figures 15-18 in Appendix D*). These results along with the primary study findings from LH-1 indicate that in smokers with normal airflow to moderate airflow obstruction ipratropium was not effective in altering spirometric decline or the development of respiratory symptoms or respiratory hospitalization.

[*] Note: Appendixes and evidence tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/spirotp.htm

Table 4. Prevalence of baseline symptoms in LH-1 subjects enrolled in smoking intervention arms according to spirometric category

Spirometric Category	Sputum n (%)	Dyspnea n (%)	Any Symptom n (%)	No Symptoms n (%)
Normal FEV_1/FVC >70%	220 (25.5)*	357 (41.4)	674 (78.3)	187 (21.7)
Stage 1 FEV_1/FVC <70% FEV1 >80%	345 (27.9)	462 (37.3)	967 (78.2)	269 (21.8)
Stage 2 FEV_1/FVC <70% FEV1 50-79%	631 (34.5)	866 (47.4)	1536 (84.2)	288 (15.7)
Totals 3921 (100)	1196 (30.5)	1685 (42.9)	3177 (81)	744 (18.9)

Sputum is defined as any sputum occurring at least three months per year for at least two years.
Dyspnea is defined as shortness of breath ≥Grade 1.
Any Symptom is defined as cough, sputum, wheeze, or dyspnea. Category overlaps with sputum or dyspnea.

*Subjects with normal spirometry (FEV_1/FVC >70%) and sputum are GOLD 0 (n=220).
Percent of subjects within each spirometric category in a given symptom category is in parentheses.

The Lung Health Study-2 recruited 1,116 participants who had previously participated in or had been screened for the LH-1 study and randomized them to the inhaled corticosteroid triamcinolone or placebo. Almost 90 percent of subjects were current smokers, but fewer than 20 percent of subjects had a previous physician diagnosis of emphysema or chronic bronchitis. Approximately one-third had daily cough and phlegm and 40 percent had some level of dyspnea. The mean FEV_1 after bronchodilator was 2.3L (68 percent predicted: GOLD Stage 2). Thus, these individuals are representative of subjects who might be detected by case finding with spirometry. After a mean duration of followup of 40 months the rate of decline in the FEV_1 after corticosteroid use was similar in the 559 participants in the triamcinolone group and the 557 participants in the placebo group (mean approximately = 44mL/year). Members of the triamcinolone group had fewer overall respiratory symptoms during the course of the study (21.1 per 100 person-years vs. 28.2 per 100 person-years, $p = 0.005$) and had fewer visits to a physician because of a respiratory illness (1.2 per 100 person-years vs. 2.1 per 100 person-years). There was no significant association between triamcinolone use and the development of specific respiratory symptoms of chronic cough, production of phlegm, or wheezing.

Table 5. Outcomes at 3 years in LH-1 subjects according to baseline symptom status (no symptoms vs. any symptom) and treatment assignment

Symptoms by Spirometry Value at Baseline	Outcomes		
	Smoking Intervention/ Ipratropium n / N (%)	Smoking Intervention/ Placebo n / N (%)	Totals n / N (%)
No Symptoms	**Cough and Sputum**	**Cough and Sputum**	**Cough and Sputum**
FEV_1/FVC >70%	2/96 (2.0)	3/78 (3.8)	5/174 (2.8)
Stage 1			
FEV_1/FVC <70%, FEV_1 >80%	8/119 (6.7)	6/126 (4.7)	14/245 (5.7)
Stage 2			
FEV_1/FVC <70%, FEV_1 50-79%	12/144 (8.3)	11/129 (8.5)	23/273 (8.4)
Totals	22/359 (6.1)	20/333 (6.0)	42/692 (6.1)
Any Symptom	**Cough and Sputum**	**Cough and Sputum**	**Cough and Sputum**
FEV_1/FVC >70%	42/302 (13.9)	47/321 (14.6)	89/623 (14.2)
Stage 1			
FEV_1/FVC <70%, FEV_1 >80%	89/454 (19.6)	64/466 (13.7)	153/920 (16.6)
Stage 2			
FEV_1/FVC <70%, FEV_1 50-79%	120/715 (16.7)	142/697 (20.3)	262/1412 (18.5)
Totals	251/1471 (17.0)	253/1484 (17.0)	504/1955 (25.7)
No Symptoms	**Dyspnea**	**Dyspnea**	**Dyspnea**
FEV_1/FVC >70%	12/95 (12.6)	6/77 (7.7)	18/172 (10.4)
Stage 1			
FEV_1/FVC <70%, FEV_1 >80%	17/118 (14.4)	15/124 (12.1)	32/242 (13.2)
Stage 2			
FEV_1/FVC <70%, FEV_1 50-79%	27/142 (19.0)	17/128 (13.2)	44/270 (16.2)
Totals	56/355 (15.7)	38/329 (11.5)	94/684 (13.7)
Any Symptom	**Dyspnea**	**Dyspnea**	**Dyspnea**
FEV_1/FVC >70%	110/297 (37.0)	100/321 (31.1)	210/618 (33.9)
Stage 1			
FEV_1/FVC <70%, FEV_1 >80%	130/451 (28.8)	147/462 (31.8)	277/913 (30.3)
Stage 2			
FEV_1/FVC <70%, FEV_1 50-79%	266/706 (37.6)	279/691 (40.4)	545/1397 (39.0)
Totals	506/1454 (34.8)	526/1474 (35.6)	1032/2928 (35.2)

Sputum is defined as any sputum occurring at least 3 months per year for at least 2 years
Dyspnea is defined as shortness of breath ≥Grade 1
Any Symptom is defined as cough, sputum, wheeze, and dyspnea. Category overlaps with sputum and dyspnea.

Acute Response to Inhaled Bronchodilators to Assess and/or Modify Therapeutic Effectiveness

Several studies have assessed the short-term variability in FEV_1 and bronchodilator responsiveness in patients with obstructive ventilatory defects. GOLD spirometric classification of COPD severity is based on postbronchodilator FEV_1 and a finding that patients do not show a significant FEV_1 response (<12 percent or 200mL) to a short-acting bronchodilator. Thus, spirometry has been suggested as being useful for determining whether patients with respiratory symptoms have reversible airflow obstruction (rather than COPD) based on postbronchodilator response. Two studies have assessed the ability of bronchodilator reversibility or acute response to bronchodilator therapy to predict response to treatment in patients with COPD.

One study tested the ability of acute change in FEV_1 following inhaled short-acting β agonist to predict long-term symptomatic response to albuterol and theophylline.[143] The reproducibility of acute change over three repetitions was poor (intraclass correlation 0.17). Furthermore, the mean improvement in FEV_1 following inhaled albuterol across the three repetitions did not relate

closely to symptomatic response to either albuterol or theophylline. For example, if a bronchodilator response >15 percent was used, then the sensitivity and specificity for predicting symptomatic improvement as measured by a four-point improvement in physical function on the CRQ to albuterol was 0.86 and 0.30 respectively. If the percent response was 25 percent, then sensitivity and specificity were 0.43 and 0.80 respectively.

Calverley and colleagues assessed the bronchodilatory reversibility to determine "responders" and "non-responders" in Inhaled Steroids in Obstructive Lung Disease (ISOLDE) study. They found that mean post-bronchodilator response to salbutamol, ipratropium, and the combination was reproducible. The absolute change in FEV_1 was independent of the pre-bronchodilator value, but the percentage change correlated with pre-bronchodilator FEV_1. The rate of decline in FEV_1, decline in health status, and exacerbation rate were unrelated to bronchodilator response. They concluded that bronchodilator response was a continuous variable, the criteria used for determining asthmatic status largely arbitrary and classifying adults as responders and non-responders can be misleading and does not predict disease progression.[7] None of the trials modified therapy based on acute response to inhaled bronchodilator.

Based on these results, acute spirometric response to inhaled bronchodilators does not appear to be useful for initiating or modifying treatment in subjects with COPD or predicting spirometric decline. The effectiveness on clinical outcomes due to modification or selection of treatment based on spirometric response has not been studied in randomized trials. However, it may help identify some subjects with asthma or a large asthmatic component to COPD.

Change in Spirometric Slope Over Time as a Guide to Therapy

Long-term studies of inhaled long-acting anticholinergics and inhaled corticosteroids have demonstrated that these agents reduce exacerbations in selected individuals. However, this improvement is not related to acute response to therapy nor do pharmacologic interventions alter the course of airflow obstruction as measured by spirometric decline. In contrast to pharmacologic interventions used for treatment or prevention of symptomatic COPD which do not alter spirometry, medications used to prevent or treat heart disease, stroke, or diabetes have been shown to alter the disease specific surrogate measures (i.e., lower blood pressure, cholesterol, or glucose). Furthermore, clinically important outcomes of morbidity and mortality are directly related to both therapeutic response in these levels as well as achieving a given surrogate threshold. Trials evaluating long- and short-acting β agonists, short-acting anticholinergics, and sibanet all followed subjects for 1 year or less. None of the randomized trials adjusted interventions based on change in spirometric slope over time or whether patients' spirometry reached a certain threshold. Many studies used baseline spirometric values as entry criteria. However, inhaled bronchodilators and inhaled corticosteroids provide clinical benefits in symptomatic individuals with severe to very-severe airflow obstruction. Thus, spirometry at baseline or at an unknown interval in subjects with activity limiting respiratory symptoms is likely to be useful in identifying a threshold of airflow obstruction severity, whereby pharmacologic interventions may be effective. The available evidence suggests that this threshold appears to be approximately at an FEV_1 of 50 percent predicted or lower.

Based on the average rate of decline in FEV_1 of approximately 50mL/year, it may be reasonable to consider monitoring spirometry every 5 to 10 years in symptomatic patients with moderate airflow obstruction who are not yet receiving treatment in order to determine if they cross a threshold of spirometry where interventions may be effective. However, as shown in LH1

and cohort studies, there is considerable variability with these measurements. Thus making treatment decisions based on an individual's change in spirometry over time is problematic. Because pharmacologic interventions are not effective in individuals not reporting respiratory symptoms and likely of little benefit in those whose symptoms are mild or not bothersome, baseline or monitoring spirometry does not appear to be beneficial in these individuals. Additionally, once pharmacologic agents are initiated, evidence suggests that periodic spirometric monitoring does not provide a beneficial measure of response to treatment or guide for treatment modification. Furthermore, limited evidence indicates that response to therapy varies little by class of long-acting inhaled medications, within class effectiveness does not vary according to dose, and combination therapy compared to monotherapy does not improve respiratory functional status measures, exacerbation rates, or mortality.

Estimating Treatment Benefit, Number Needed to Screen and Treat

In an attempt to estimate the possible benefits and harms associated with case finding and treatment based on spirometry and symptom status, we used data related to the prevalence and severity of airflow obstruction and symptom status from NHANES III in combination with efficacy results from treatment intervention trials using inhaled bronchodilators and inhaled corticosteroids. Such an approach, conceptually outlined in Figure 16 on page 86, provides estimates of the number of adults required to receive testing with spirometry and treatment with interventions other than smoking cessation or vaccinations in order to reduce the percentage of adults having at least one exacerbation.

Our approach takes the following assumptions based on the available data: 1) one time spirometry without bronchodilator or bronchoconstrictor assessment would be conducted in all previous or current smokers regardless of symptoms and in "never smokers" if they had any persistent respiratory symptom (wheeze, cough, sputum, or dyspnea); 2) symptom status was the same for each spirometric stage regardless of smoking status (data were not available according to smoking status); 3) primary care based spirometry detects airflow obstruction similar to that found in large population based studies using diagnostic spirometers without bronchodilator testing; 4) all patients detected by spirometric case-finding would not have been detected in the absence of spirometric testing; 5) symptomatic subjects with a given spirometric value found in population-based studies not using bronchodilator testing have similar symptoms and outcomes as stage matched controls enrolled in intervention studies many that enrolled subjects based on postbronchodilator spirometry; 6) subjects not reporting respiratory symptoms do not benefit from any intervention other than smoking cessation regardless of severity of airflow obstruction; 7) spirometric testing does not improve smoking cessation rates beyond counseling and pharmacologic interventions; 8) effectiveness of interventions other than smoking cessation and influenza vaccination are limited to subjects with bothersome respiratory symptoms who have severe to very severe airflow obstruction (GOLD Stage 3,4) (though we provide sensitivity analyses for subjects with GOLD Stage 2 airflow obstruction); 9) prior to establishing a diagnosis COPD or beginning COPD specific therapy, spirometry is conducted to demonstrate severe to very severe airflow obstruction; 10) long-acting inhaled therapies have similar effectiveness with different adverse effects); and 11) combination therapy does not provide clinically important benefits compared to monotherapy.

Figure 17 on page 87 demonstrates the results of spirometric and symptom assessment and subsequent treatment according to smoking status as might be seen in a primary care clinic of

10,000 adults that resembled the adult population from NHANES. It represents the potential number of adults presenting that would need to be evaluated to identify candidates for treatment and then the number that are likely to benefit from assessment and treatment. Because data were not available to detect symptom status according to GOLD stage for the various smoking categories, we assumed that symptom status was the same for each spirometric stage regardless of smoking status. Smoking status is ascertained in all adults in a primary care setting regardless of symptoms. From NHANES III results we determined that the prevalence of current, former, and never smoking adults equals 29 percent, 24 percent, and 47 percent and the prevalence of any respiratory symptoms for never smokers equals 27 percent (activity limiting dyspnea = 17 percent). NHANES results indicate that GOLD Stage 3,4 is present in 3 percent of "never smokers" reporting respiratory symptoms (an additional 8.6 percent have GOLD Stage 2 airflow obstruction).

Thus, 1,288 never smokers would report respiratory symptoms and undergo spirometric testing. This would yield approximately 39 never-smoking adults who had assessment of symptoms and subsequently underwent spirometry for evaluation of symptoms who would be candidates for COPD therapy. From data indicating that treatment benefit was limited to subjects reporting respiratory symptoms and GOLD Stage 3,4 airflow obstruction the number of "never smokers" needed to receive symptom status assessment and subsequent spirometric testing in order to identify one candidate for effective COPD treatment is 120 (number needed to evaluate = 120). Based on pooled results from RCT of tiotropium demonstrating a 6 percent absolute risk reduction in subjects having COPD exacerbations (number needed to treat = 16.7) we conclude that two out of 4,700 primary care patients would be never smokers who would benefit from evaluation and treatment (0.04 percent of never smokers). Alternatively, using this approach one subject among 2,043 never smokers presenting to a primary care provider would have ≥1 COPD exacerbations prevented after 6 to 36 months of treatment.

For "increased risk individuals" based on a history of smoking, spirometry is considered regardless of symptom status. In the hypothetical population spirometry would be conducted in all 2,900 adults who were current smokers and 2,400 who were previous smokers. The prevalence of severe to very severe airflow obstruction (approximately GOLD Stage 3,4) is 2.2 percent in previous smokers and 2.1 percent for current smokers (7.3 percent and 10.6 percent have GOLD Stage 2, respectively). From population data of subjects with GOLD Stage 3,4 disease regardless of smoking status we estimate that 79 percent will have any respiratory symptom (approximately 60 percent have dyspnea). There would be 42 previous smoker and 48 current smoker candidates for treatment. Therefore, the number of previous smokers and current smokers regardless of symptom status needed to screen to identify a candidate for potentially effective treatment is 57 and 60 respectively. Assuming similar treatment efficacy regardless of baseline smoking status, we estimate that three current smokers (0.11 percent) and two former smokers (0.1 percent) would benefit. Alternatively, 960 former smokers and 1,010 current smokers would need to be initially tested with spirometry and subsequent treatment provided for the GOLD Stage 3,4 patients to prevent one adult from having ≥1 COPD exacerbation over a 6 to 36 month time period. Therefore, in a primary care population of 10,000 adults similar to NHANES III respondents, 6,588 would undergo spirometric testing, 129 (1.3 percent) would be candidates for COPD therapy, and 8 (0.07 percent) would benefit. Benefits could be maintained by reserving testing and treatment for individuals reporting bothersome respiratory symptoms (especially dyspnea, exercise intolerance, and COPD exacerbations). If spirometry was targeted

to individuals with dyspnea regardless of smoking status the number needed to screen and treat for severe to very severe airflow obstruction would be 475.

The average change in validated respiratory status scores compared to placebo did not achieve clinical significance. However, additional analyses in two studies indicated that the percentage of individuals who reported a clinically significant change in SGRQ scores (at least 4 point improvement) was greater with tiotropium than placebo (49 percent versus 35 percent; ARD = 14.4 percent). Using this information the number needed to treat for adults who are candidates for therapy to achieve a clinically significant change in SGRQ is 7. Therefore, among the 129 candidates for treatment, 18 (0.2 percent) would have a clinically noticeable improvement in their respiratory health status.

The evidence indicates that treatment other than smoking cessation and vaccinations in symptomatic subjects with airflow obstruction that is less severe than GOLD Stage 3,4 disease provides little to no benefit. Additionally, differences in health status are not evident until the development of GOLD Stage 3 and 4 disease.[144] Nonetheless, if GOLD Stage 2 subjects are considered to benefit from treatment to a similar degree as GOLD Stage 3 to 4, then the number initially needed to evaluate and subsequently treat would be 520, 273, and 208 respectively for "never smokers with respiratory symptoms," "previous smokers regardless of symptom status," and "current smokers regardless of symptom status." In a population of 10,000 adults, approximately 529 adults (5.3 percent) would be candidates for treatment and 32 (0.3 percent) would be prevented from having at least one exacerbation compared to placebo (approximately 76, or 0.8 percent, would have a clinically noticeable improvement in respiratory health status).

Our assumptions are optimistic for the following reasons. Most subjects enrolled in treatment trials demonstrating benefit had severe respiratory symptoms (especially frequent exacerbations) that would likely require and benefit from pharmacologic intervention. We chose "any respiratory symptom" as a "clinically significant"/activity limiting or bothersome symptom that would benefit from therapy. However, treatment trials indicated that the average improvements in health status and dyspnea were not clinically significant. Other clinically relevant outcomes such as rates of hospitalization were rarely reported. However, differences in the studies that selectively published hospitalizations were between 4 and 7 percent. Additionally, except for oxyen therapy in the small percentage of patients with resting hypoxemia, interventions did not reduce mortality. Therefore the benefit of interventions appears to be primarily limited to reduction in exacerbations. Treatment of individuals whose only symptoms are wheeze and cough is unlikely to be beneficial because these symptoms have little if any impact on quality of life.

We did not conduct a formal cost effectiveness analysis. However, it is important to consider the potential costs of spirometric testing and treatment. This needs to be weighed against the costs associated with symptomatic COPD including lost productivity, hospitalizations, and other medications that might occur due to potentially preventable disease progression. Additionally, based on NHANES results only 17.4 percent of adults who reported a clinical diagnosis of COPD, had 1987-ATS defined low lung function, suggesting that many individuals have an inaccurate clinical diagnosis of COPD. Furthermore, less than half of these individuals reported shortness of breath and only 25 percent had chronic sputum production (GOLD 0). Many adults may be treated unnecessarily with COPD specific medications in the absence of spirometric testing and assessment of respiratory symptoms.

The cost of a single primary care based spirometric evaluation (excluding confirmatory evaluations via diagnostic spirometry, bronchodilator testing, and/or followup office-based tests)

is estimated between $10 and $40.[2] At a cost per day ranging from $2.66 to $4.00 the annual inhaled drug cots using long-acting monotherapy would be between $971 and $1,460 per treated patient or $4.5 to $6.8 billion to treat the estimated 4 percent of adults with dyspnea and severe to very severe airflow obstruction (n = 4,630,000) (average wholesale price for a 100 unit container, or closest size in the 2004 Red Book). Effectiveness would be similar but drug costs and adverse events would be higher if combination therapy was routinely used instead of monotherapy. Compared to diagnosis and treatment based on clinical examination alone spirometry is likely to reduce the number of individuals reporting symptoms who are inaccurately diagnosed with, and treated for, COPD because they do not have airflow obstruction of severity where treatment is beneficial. Among subjects with bothersome respiratory symptoms spirometry may enhance identification of untreated patients with severe airflow obstruction. Additionally, prevalence estimates from NHANES included individuals as young as 17 years old. Because most patients attending adult primary care clinics are over age 40 the number of individuals needed to receive spirometry in order to successfully identify candidates for treatment would be lower than results we estimated. However, many current recommendations do not provide an age criteria for initiating spirometric testing and they also recommend that spirometric testing be conducted in adults without respiratory symptoms and who have no history of smoking but do have exposure to additional risk factors including passive smoke and environmental toxins. Adherence to these recommendations would increase the number needed to receive wide spread spirometric testing without adding to benefit.

Question 4
Is prediction of prognosis based on spirometry, with or without clinical indicators, more accurate than prediction based on clinical indicators alone?

Spirometry has been shown to have prognostic effect in determining mortality and disease specific morbidity. The risk of death in patients with COPD is often graded with the use of a single physiological variable (FEV_1). However, other risk factors such as hypoxemia, hypercapnia, exercise intolerance, or body mass index are also associated with mortality. Additionally, observational studies have found that the degree of dyspnea and health-status scores are more accurate predictors of the risk of death than is the FEV_1.[145] Based on discussion with our TEP we focused on studies that would provide prognostic information related to future COPD outcomes, especially respiratory symptoms and spirometric stage.

Celli and colleagues developed and tested a multidimensional grading system that assessed the respiratory and systemic expressions of COPD in predicting outcomes. They evaluated 207 patients with known COPD and found that four factors predicted the risk of death: the body-mass index (B), the degree of airflow obstruction as measured by spirometry (O), and dyspnea (D) and exercise capacity (E) as measured by the 6-minute walk test. The factors were subsequently validated in a multinational cohort of 625 patients with an assessment of death from any cause and from respiratory causes. Points were added for each variable so that the BODE index ranged from 0-10 points, with higher scores indicating a greater risk of death. FEV_1 categories used in developing the BODE index were based on American Thoracic Society 1995 categorization.

Point values contributing to the BODE index for FEV_1 percent predicted were $FEV_1 \geq 65 = 0$ points; 50-64 = 1 point; 36-49 = 2 points; ≤ 35 = 3points. At a median followup of 28 months, the probability of survival was approximately 90 percent, 90 percent, and 75 percent for subjects with Stage I, Stage II, and Stage III COPD respectively as defined by the American Thoracic Society in 1995. Patients with higher BODE scores were at higher risk for death. The probability of survival for subjects with a BODE index in the lowest Quartile was 92 percent vs. 60 percent in the highest quartile. For each one point increment in the BODE score, the hazard ratio for death from any cause was 1.34 (95 percent CI 1.26 - 1.42) and the hazard ratio for death from a respiratory cause was 1.62 (95 percent CI 1.48 - 1.77). The BODE index was better able to predict death than the FEV_1 alone.[145] It is not known how the BODE index might perform on subjects detected by case finding with spirometry, especially individuals not reporting respiratory symptoms.

Fletcher and coworkers showed a relationship between the level of FEV_1 at baseline and its slope (i.e., rate of decline over time).[146] This relationship was considered a model of the preclinical course of COPD and advocated as a method for early detection and assessment of subsequent prognosis. As such, it could be useful for early identification of subjects (especially smokers) in the preclinical state who might be at increased risk for rapid decline in lung function so that they could be especially targeted for smoking cessation programs.

As shown in the assessment of Question 1, the prevalence of respiratory symptoms is associated with severity of airflow obstruction as measured by spirometry. For example, in community-dwelling subjects ages 18 or older, the prevalence of respiratory symptoms was 23.3 percent in subjects with normal spirometry (excluding chronic sputum production, i.e., GOLD 0), 50.8 percent in GOLD 1, 60.1 percent in GOLD 2, and 79 percent in subjects with GOLD Stage 3,4. However, as we described earlier, data from LH-1 and other longitudinal cohort studies demonstrate that the presence of symptoms at baseline is a better measure of future symptoms than spirometric stage.

Several studies assessed the prognosis of baseline spirometry and/or GOLD classification on COPD and spirometric progression. Results from the LH-1 evaluated whether baseline FEV_1/FEV_6 predicted subsequent lung function decline in adult smokers. After controlling for age, gender, cigarettes per day, years of education, and bronchial hyper responsiveness, FEV_1/FEV_6 was an independent predictor of subsequent decline in lung function in both men and women. Those with the lowest decile of FEV_1/FEV_6 at baseline lost more than twice as much lung function over the next 5 years when compared to those with the least baseline airways obstruction (FEV_1 fell 93.2mL/year vs. 44.5mL/year for men). A multivariate model that included FEV_1/FEV_6 predicted 11 percent of the variance in subsequent change in lung function indicating that unmeasured factors account for nearly 90 percent of the variation in lung function decline.[147] These findings are similar to those of Fletcher and Burrows.[146,148] They suggest that baseline degree of airways obstruction as measured by spirometry is a predictor of the subsequent worsening in airway obstruction in smokers. Positive associations in the study by Burrows and colleagues were observed only in male smokers. Change in FEV_1 could not be predicted in women or exsmokers.

Table 6 on page 53 shows 5 and 15 year followup in subjects without COPD and with GOLD 0 at baseline in the Copenhagen Heart Study.[149] Subgroup results were also presented for subjects who were smoking at baseline. At 5 and 15 years GOLD 0 subjects are not more likely to progress to COPD Stages 1-3 when compared to subjects without COPD at baseline. This suggests that chronic cough and sputum production is not an independent predictor for

progression to COPD in subjects with normal baseline spirometry. Thus, based on these results, GOLD 0 subjects should not be considered "at risk."

Table 6. Prevalence of different stages of COPD after 5 and 15 years in subjects without COPD and with GOLD 0 at baseline

	No COPD at Baseline / All Subjects	No COPD at Baseline / Subjects Smoking at Baseline	Gold 0 at Baseline / All subjects	Gold 0 at Baseline / Subjects Smoking at Baseline
Copenhagen City Heart Study[149]				
5-year followup				
COPD Stage 1	4.30%	4.90%	5.70%	5.80%
COPD Stage 2	5.30%	6.70%	6.70%	7.40%
COPD Stage 3	0.10%	0.10%	0%	0%
15-year followup				
COPD Stage 1	7.20%	9.90%	13.50%	14.80%
COPD Stage 2	5.80%	8.40%	5.00%	5.70%
COPD Stage 3	0.20%	0.20%	0%	0%

Additional data provided by Dr. Vestbo (personal communication, November 2004) from the Copenhagen Heart Study evaluated the point prevalence of specific respiratory symptoms (dyspnea, cough, sputum) and the prognostic significance of GOLD classification over a 10-year period (year 5 to year 15 followup). Complete respiratory symptom data (especially dyspnea) were not available at year 0 (n=13,091) and thus we considered year 5 as baseline (n=11,734) for purposes of this reporting. It should be noted that the spirometric stages and prevalence of sputum production were similar at year 0 and year 5 thus providing some confidence in using the 5-year results as baseline data. The prevalence (and percent within each category reporting no respiratory symptoms) of GOLD stage at year 5 was: normal spirometry = 79.1 percent (58.1 percent); GOLD 0 = 6.5 percent (by definition all had sputum production); GOLD 1 = 5.4 percent (53.9 percent) and GOLD 2 = 8.6 percent (32.5 percent).

Among subjects who were GOLD 0 at year 5 and provided followup information (n=417) 10 years later, only 47.5 percent still had chronic mucous production. This suggests that over many years chronic mucous production is not a stable condition. However, these results do not include subjects who were lost to followup or died, and there is no information regarding smoking status. Over time, symptoms of breathlessness also tended to become less frequent in all spirometric stages. This may be due to selection (loss to followup of those most severely ill), variable response to the question, institution of therapy, alteration in activity due to other factors, or variability in the natural history of dyspnea. According to GOLD stage the presence of dyspnea when "hurrying on the street or while walking up hill" at year 15 among those individuals who reported similar levels of dyspnea at year 5 was GOLD Normal = 67.4 percent; GOLD 0 = 74.3 percent; GOLD 1 = 74.2 percent, and GOLD 2 = 76.7 percent. Thus, even among the small percentage of subjects who were GOLD 0 at baseline and progressed to Stage 1 or 2 after 15 years (13 percent and 5 percent respectively), many had no activity limiting respiratory symptoms. Therefore, the prognosis regarding activity limiting respiratory symptoms after 10 years among GOLD 0 subjects and those with mild to moderate airflow obstruction appears to be

quite good. Additionally, compared to subjects without COPD, individuals with Stage 0 were not at higher risk for mortality over a 15-year followup period after controlling for age, sex, smoking, and inhalation. In contrast to the above findings in patients with normal lung function, the presence of chronic mucous hypersecretion does appear be an important risk factor for spirometric decline and risk of hospitalization in subjects with baseline abnormal lung function.

Similar findings were reported by Fletcher and Peto.[146] A cohort of 792 men ages 30-59 at baseline were followed every 6 months with assessment of airflow obstruction by measuring FEV_1 and questionnaires to assess smoking status, mucus hypersecretion, and bronchial infections. Their results demonstrated that FEV_1 falls gradually over a lifetime, but in most nonsmokers and many smokers clinically significant airflow obstruction never develops. In susceptible people, smoking causes irreversible obstructive changes. If a susceptible smoker stops smoking he will not recover his lung function, but the average further rates of loss of FEV_1 will revert to normal. However, infective processes and chronic mucus hypersecretion did not cause airflow obstruction to progress more rapidly. After adjusting for FEV_1 level, smoking, age, and height there was no independent correlation between FEV_1 slope and indices of either mucus hypersecretion or bronchial infections. There also were no changes in FEV_1 level to changes in sputum production or episodes of infection. These findings indicate that chronic mucus hypersecretion in subjects with normal lung function (GOLD 0) is not independently prognostic for development of COPD.

Summary Table 1: Spirometry-based national estimates of chronic obstructive pulmonary disease prevalence and low lung function

Study (Reference)	Country	Diagnostic Criteria	Age, Year	Prevalence (%), Overall	Prevalence (%), Men	Prevalence (%), Women	Total Sample Size
NHANES III* Mannino 2000[150]	United States	Low lung function: FEV1/FVC <70%; FEV_1 <80% predicted	≥17	6.8	7.4	6.3	16,084
		FEV_1/FVC <70%; FEV_1 >80% predicted		7.2	Not reported	Not reported	
		With the addition of GOLD 0, defined as symptom of phlegm		7.2	10.2	7.1	
		Total prevalence of subjects with low lung function and at risk		21.2	Not reported	Not reported	
CCHS** Vestbo 2002[149]	Denmark	GOLD stages 1-3	≥20	14.5	18.2	11.4	13,108
		With the addition of GOLD 0		5.8	7.1	4.8	
		Total prevalence of subjects with GOLD 0-3		20.3	25.3	16.2	
Mini-Finland Health Survey von Hertzen 2000[151]	Finland	1) Clinical examination plus spirometry	≥30	Not reported	22	7	7217
		2) FEV_1/FVC <69%	≥30	Not reported	11	5	
Isoaho 1994[153]	Finland	Clinical examination plus spirometry	≥65	Not reported	12.5	3	1196
Po Delta Survey Viegi 2000[152]	Italy	European Respiratory Society (ERS) spirometric criteria, defined as FEV_1/slow vital capacity (VC) <0.88 predicted in men, <0.89 in women	≥25	11	Not reported	Not reported	1727
		American Thoracic Society (ATS) criteria, defined as FEV_1/FVC <75%		40.4			
Bakke 1991[154]	Norway	Symptoms plus spirometry	18-70	5.4	5.6	5.2	1259
		FEV_1/FVC <70%; FEV_1 <80% predicted	18-70	4.5	4.8	4.2	
IBERPOC*** Pena 2000[155]	Spain	ERS spirometric criteria plus reversibility test	40-69	9.1	14.3	3.9	4035

* National Health and Nutrition Examination Survey-NHANES III
** Copenhagen City Heart Study
*** IBERPOC Multicentre Epidemiological Study

Summary Table 2: Prevalence of COPD based upon American Thoracic Society (ATS) or Global Initiative for Chronic Obstructive Lung Disease (GOLD) category spirometric categories for general populations

Variable / Country; Study	% Normal Spirometry and No Respiratory Symptoms (n / N)	% GOLD 0 or "At Risk" / Normal Spirometry + Symptoms of Cough, Sputum (n / N)	% GOLD 1 or Mild - FEV_1/FVC <70 and FEV_1 >80% Predicted) (n / N)	% ATS 1 or GOLD 2 or "Moderate" / FEV_1/FVC <70 and FEV_1 >50 to 80-85% Predicted) (n / N)	% ATS 2 or 3 or GOLD >3 or "Severe" / FEV_1/FVC <70 and FEV_1 <50% Predicted) (n / N)	Study, Population, and Notes
National Health And Nutrition Examination Survey-NHANES III[150]						
United States	51.6	34.4 7.2 phlegm (approx. GOLD 0)	7.2 50.8% had "any symptom," (cough, phlegm, wheeze, or dyspnea)	5.4 60.1% had "any symptom," (cough, phlegm, wheeze, or dyspnea)	1.5 79% had "any symptom," (cough, phlegm, wheeze, or dyspnea)	NHANES III, Estimated prevalences based on 16,084 U.S. white or black adults selected to be a representative sample of the U.S., >17 years of age, who had pulmonary function testing performed.
National Health And Nutrition Examination Survey-NHANES I[156]						
United States	67.2 (3,725 / 5,542)	16.1 (had "any respiratory symptom," defined as cough, sputum, or wheeze)	7.9 (438 / 5542)	7.1 (393 / 5,542)	1.7 (94 / 5,542)	NHANES I, 5,542 U.S. white or black adults in the final cohort of analysis (of the original 14,407 subjects.
European Community Respiratory Health Survey[157]						
Europe	84.6 (12,567 / 14,855)	11.8 (1,751 / 14,855)	2.5 (369 / 14,855)	1.1 (168 / 14,855) (GOLD 2-3 were combined)		Multinational study of randomly selected young adults (aged 20-44) who had 2 FEV_1 and FVC measurements.

Summary Table 2: Prevalence of COPD based upon American Thoracic Society (ATS) or Global Initiative for Chronic Obstructive Lung Disease (GOLD) category spirometric categories for general populations (continued)

Variable / Country; Study	% Normal Spirometry and No Respiratory Symptoms (n / N)	% GOLD 0 or "At Risk" / Normal Spirometry + Symptoms of Cough, Sputum (n / N)	% GOLD 1 or Mild - FEV_1/FVC <70 and FEV_1 >80% Predicted) (n / N)	% ATS 1 or GOLD 2 or "Moderate" / FEV_1/FVC <70 and FEV_1 >50 to 80-85% Predicted) (n / N)	% ATS 2 or 3 or GOLD >3 or "Severe" / FEV_1/FVC <70 and FEV_1 <50% Predicted) (n / N)	Study, Population, and Notes
Differential Diagnosis Between Asthma and COPD-DIDASCO[158]						
Belgium	85.4 (Some normals reported symptoms, exact percentage unknown)	Not reported	5.7	7.4	1.4	A prospective survey of Belgian subjects aged 35 to 70, visiting general practitioner clinics. Subjects were screened for COPD. Subjects on bronchodilators were removed. 3,158 subjects were questioned regarding COPD symptoms. Spirometry was used on all symptomatic subjects (n=728) and 10% of a random sample with no symptoms (n=243 out of 2,430 total).
Copenhagen City Heart Study[149]						
Denmark	79.7 (10,441 / 13,108) Mean FEV_1 (L) = 2.7; % pred. = 97	5.9 (766 / 13,108) Mean FEV_1 (L) = 2.9; % pred. = 100	5.1 (663 / 13,108) Mean FEV_1 (L) = 2.6; % pred. = 92	9.2 (1,205 / 13,108) Mean FEV_1 (L) = 1.7; % pred. = 63	<1 (33 / 13,108) Mean FEV_1 (L) = 0.6; % pred. = 23	A prospective epidemiologic survey of randomly selected Danish subjects, age >20 who had a least one spirometric measurement. Rates are at baseline.
Mini-Finland Health Survey[151]						
Finland	58.1 (3,956 / 6,810)* (asthma and other chronic respiratory. diseases excluded)	Not reported	34.7 (2,360 / 6,810) (asthma and other chronic respiratory. diseases excluded)	6.6 (451 / 6,810) (asthma and other chronic respiratory. diseases excluded)	<1 (43 / 6,810) (asthma and other chronic respiratory diseases excluded)	Randomly selected Finnish subjects, age >30 years. Subjects with normal spirometry may or may not have symptoms.

Summary Table 2: Prevalence of COPD based upon American Thoracic Society (ATS) or Global Initiative for Chronic Obstructive Lung Disease (GOLD) category spirometric categories for general populations (continued)

Variable / Country; Study	% Normal Spirometry and No Respiratory Symptoms (n / N)	% GOLD 0 or "At Risk" / Normal Spirometry + Symptoms of Cough, Sputum (n / N)	% GOLD 1 or Mild - FEV_1/FVC <70 and FEV_1 >80% Predicted) (n / N)	% ATS 1 or GOLD 2 or "Moderate" / FEV_1/FVC <70 and FEV_1 >50 to 80-85% Predicted) (n / N)	% ATS 2 or 3 or GOLD >3 or "Severe" / FEV_1/FVC <70 and FEV_1 <50% Predicted) (n / N)	Study, Population, and Notes
Prevalence of COPD in Elderly Finns[152]						
Finland	90.1 (687 / 760)*	Not reported	1.8 (14 / 760) (FEV_1 % predicted >80)	6.4 (49 / 760) (FEV_1 % predicted 40-79)	1.3 (10 / 760) (FEV_1 % predicted <40)	Epidemiologic survey of respiratory diseases in elderly Finnish men and women (age 64-97). Severity based on FEV_1 % predicted value.
Po Delta Survey[153]						
Italy - ERS Criteria	89 (1,537 / 1,727)	1 (17 / 1727) (see notes)	8.1 (140 / 1,727)	1.4 (24 / 1,727)	0.5 (9 / 1,727)	Cross-sectional epidemiologic survey of Italian subjects, ages 25 to 73. Subjects at risk had a "possible physiological variant" NOT YET DEFINED
Italy - ATS Criteria	59.6 (1,030 / 1,727)	12 (207 / 1,727) (see notes)	25.8 (446 / 1,727)	1.3 (22 / 1,727)	1.3 (22 / 1,727)	
IBERPOC Multicentre Epidemiological Study[155]						
Spain	90.9 (3,618 / 3,981)*	Not reported	3.5 (139 / 3,981)	3.6 (144 / 3,981)	2 (80 / 3,981)	Epidemiologic survey of randomly selected Spanish men and women, ages 40-69.

* Subjects may or may not be symptomatic and include "at risk"

Summary Table 3: Prevalence of COPD based upon American Thoracic Society (ATS) or Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric categories for age

Variable / Country; Study	% Normal Spirometry and No Respiratory Symptoms (n / N)	% GOLD 0 or "At Risk" / Normal Spirometry + Symptoms of Cough, Sputum (n / N)	% GOLD 1 or Mild - FEV_1/FVC <70 and FEV_1 >80% Predicted) (n / N)	% ATS 1 or GOLD 2 or "Moderate" / FEV_1/FVC <70 and FEV_1 >50 to 80-85% Predicted) (n / N)	% ATS 2 or 3 or GOLD > 3 or "Severe" / FEV_1/FVC <70 and FEV_1 <50% Predicted) (n / N)	Study, Population, and Notes
National Health And Nutrition Examination Survey-NHANES III[150]						
Age 25-44	Not reported	Not reported	3.7	2.3	Not reported	Estimated prevalence
Age 45-54	Not reported	Not reported	8.7	7.2	Not reported	
Age 55-64	Not reported	Not reported	12.6	14.1	Not reported	
Age 64-74	Not reported	Not reported	16.5	20.7	Not reported	
Age >75	Not reported	Not reported	17.8	22.9	Not reported	
National Health and Nutrition Examination Survey-NHANES I[156]						
Age 25-39	72 (1371 / 1903)	19.2 (365 / 1903) (see notes)	4 (76 / 1903)	2.8 (53 / 1903)	0.2 (4 / 1903)	Subjects had "any respiratory symptom," defined as cough, sputum, or wheeze
Age 40-49	67.6 (792 / 1,171)	18.7 (219 / 1,171) (see notes)	7 (82 / 1,171)	5.9 (69 / 1,171)	0.8 (9 / 1,171)	
Age 50-59	64.7 (412 / 1,168)	12.8 (150 / 1,168) (see notes)	9.5 (111 / 1,168)	10.4 (121 / 1,168)	2.6 (30 / 1,168)	
Age 60-69	60.4 (584 / 967)	12.5 (121 / 967) (see notes)	12.7 (123 / 967)	10.7 (103 / 967)	3.7 (36 / 967)	
Age 70-74	56.8 (189 / 333)	11.4 (38 / 333) (see notes)	14.1 (47 / 333)	13.5 (45 / 333)	4.2 (14 / 333)	
Po Delta Survey[153]						
Age 25-45, ERS Criteria	90.3 (862 / 955)	1.4 (13 / 955) (see notes)	8 (76 / 955)	0.4 (4 / 955)	0	Described as "possible physiological variant"
ATS Criteria	73 (697 / 955)	8.2 (see notes)	18.3 (175 / 955)	0.4 (4 / 955)	<1 (1 / 955)	
Age ≥45, ERS Criteria	88.6 (684 / 772)	0.5 (4 / 772) (see notes)	8.1 (63 / 772)	2.6 (20 / 772)	<1 (1 / 772)	
ATS Criteria	43 (332 / 772)	16.7 (129 / 772) (see notes)	35.1 (271 / 772)	2.3 (18 / 772)	2.8 (22 / 772)	
Prevalence of COPD in Norwegians[154]						
Men: age 18-44	96.4*	Not reported	1.3	2.3	0	
Men: age 45-73	88.3*	Not reported	2.4	8.6	0.6	
Women: age 18-44	97.9*	Not reported	1.2	0.7	0.1	
Women: age 45-73	90.8*	Not reported	0.9	8.1	0.2	

* Subjects may or may not be symptomatic and include "at risk"

Summary Table 4: Prevalence of spirometric categories: American Thoracic Society (ATS) or Global Initiative for Chronic Obstructive Lung Disease (GOLD) category criteria for symptoms

Variable / Country; Study	% Normal Spirometry (n / N)	% GOLD 0 or "At Risk" / Normal Spirometry + Symptoms of Cough, Sputum (n / N)	% GOLD 1 or Mild - FEV_1/FVC <70 and FEV_1 >80% Predicted) (n / N)	% ATS 1 or GOLD 2 or "Moderate" / FEV_1/FVC <70 and FEV_1 >50 to 80-85% Predicted) (n / N)	% ATS 2 or 3 or GOLD > 3 or "Severe" / FEV_1/FVC <70 and FEV_1 <50% Predicted) (n / N)	Study, Population, and Notes
National Health and Nutrition Examination Survey-NHANES III[150]						
Productive cough	7.9	100	17.5	14.6	41.2	
Sputum or phlegm	7.2	100	12.2	15.4	32.7	
Wheeze	15.2	Not reported	28.8	42.6	63.6	
Dyspnea	21.5	Not reported	25.6		65.4	
Any symptom	34.4	100	50.8	60.1		Percents age-adjusted to all study participants
No symptom	65.6		49.2	39.9	21	

Summary Table 5. Characteristics of studies using spirometry as an aid in smoking cessation

Study	Study Duration (Months)	Intervention(s)	N	Control(s)	N	Description of Subjects; Inclusion Criteria
Independent effects of spirometry assessed						
Segnan et al., 1991[79] (Italy)	12	Repeated counseling (RC): minimal intervention (see control group) plus followup counseling at 1, 3, 6, and 9 months.	275	Minimal intervention: one session of counseling. An explanatory brochure was provided.	62	Male and female patients (age range = 20-60 years) who were smokers and free of any life-threatening disease.
		RC plus nicotine gum: subjects advised on use of gum; gum provided at initial and first followup visits.	294			
		RC plus spirometry: subjects given written prescription and asked to set up appointment for spirometry at another location. Results discussed at next followup visit.	292			
Effects of spirometry plus other interventions assessed						
Risser et al., 1990[80] (U.S.)	12	50-minute education and skills training intervention (see controls) plus spirometry, exhaled CO and symptom questionnaire, and discussion of results.	45	50-minute education and skills training intervention: discussion of risks/benefits, self-help manual reviewed, subjects encouraged to attend a 9-session counseling program and to select a quit date.	45	Male and female veterans who were outpatients, smokers, and who participated in a health promotion clinic, but were not selected for their initial motivation to quit.
Sippel et al., 1999[81] (U.S.)	9	Smoking cessation advice plus spirometry, exhaled CO, and uniform discussion of test results.	102	Smoking cessation advice: completion of baseline questionnaire/assessment of motivational stage. Subjects encouraged to quit smoking and received cessation plan based on motivational stage (3 or 10 min.). All participants given self-help pamphlet and list of community programs. Some received telephone followup calls at 1 and 4 weeks after their quit date and/or assistance in obtaining NRT.	103	Male and female outpatients who were smokers, English-speaking, over the age of 18 (age range = 19-75), and were not being seen for an emergency.

Summary Table 5. Characteristics of studies using spirometry as an aid in smoking cessation (continued)

Study	Study Duration (Months)	Intervention(s)	N	Control(s)	N	Description of Subjects; Inclusion Criteria
Richmond et al., 1985[82] (Australia)	6	Six visits to primary care provider, including blood tests and spirometry at baseline and 6 months, discussion of baseline test results and counseling and smoking cessation support. Manual provided.	100	Two visits (baseline and 6 month followup) to primary care provider for counseling and smoking cessation support (blood tests and spirometry performed, but patients not provided with results).	100	Male and female patients (age range = 16-65 years) who were smokers, proficient in English, and who did not intend to leave Sydney within 6 months.
Rose et al., 1978[84] (England)	36	Baseline screening including spirometry. Smoking cessation counseling and three followup visits. Two booklets provided. Smoking report cards completed by subjects.	714	Baseline screening including spirometry. Usual care (test results provided to primary care provider).	731	Men (age range = 40-59) who were smokers, participated in a cardiorespiratory screening of civil servants in London, and who were considered to have high cardiorespiratory risk.
Humerfelt et al., 1998[83] (Norway)	12	Baseline data collected at a community survey (included height, weight, spirometric values, and a questionnaire). Participants received a letter providing baseline test results, advice to quit, and a pamphlet emphasizing behavior modification.	1300	Baseline data collected at a community survey (included height, weight, spirometric values, and a questionnaire). No information/advice provided.	1310	Men (age range = 30-45) who were smokers, lived in 34 rural municipalities in western Norway, and participated in a cross-sectional community survey.
Li et al., 1984[85] (US)	11	Behavioral counseling: all components of minimal advice (see control group) plus 3-5 minutes of counseling to explain test results and to secure commitment to quit plan. Participants asked to set a quit date.	215	Minimal advice: testing (pulmonary function testing, chest x-ray, and a smoking assessment questionnaire). Participants received test results, warning to quit smoking, and pamphlet outlining quit plan.	361	Male smokers who were exposed to asbestos and were identified during an initial screening of naval shipyard workers.

Summary Table 6. Strengths and limitations of studies using spirometry as an aid in smoking cessation

Study (Reference)	Independent Assessment of Effects of Spirometry	Quality of Randomization	Length of Followup (Months)	Biochemical Validation of Smoking Cessation	Selection of Participants	Study Notes/Limitations
Independent effects of spirometry assessed						
Segnan et al., 1991[79]	Yes	Adequate	12	Yes	All smoking patients of volunteering physicians	Poor compliance by physicians administering interventions and poor compliance by participants in completing the followup visits and spirometry (<40% attendance for return visits, 50.2% subject compliance for spirometry in RC+spirometry group).
Effects of spirometry plus other interventions assessed						
Risser et al., 1990[80]	No	Unclear	12	Yes (63%)	Volunteers of a health promotion clinic	Small study size with large, uneven attrition (at t=12 mos., 13/45 lost in intervention group vs. 6/45 in control group). Results may not be very generalizable because subjects had an average of five active medical conditions, 1/4 were enrolled in psychiatric programs and 21% consumed 4+ drinks daily.
Sippel et al., 1999[81]	No	Inadequate	9	No	All outpatient smokers of two family practice clinics	Some subjects used NRT; no NRT use data by intervention group provided.
Richmond et al., 1985[82]	No	Inadequate	36	Yes	All outpatient smokers of a family practice clinic	
Rose et al., 1978[84]	No	Unclear	36	No	Participants in another screening study (employees)	Unclear whether the intervention group was told their spirometric results; patients may have been given spirometric results only if they asked for more details. The control group was not told their baseline spirometric results by researchers, but these data were given to the primary care practitioners. Participants selected for study based on high cardiorespiratory risk.
Humerfelt et al., 1998[83]	No	Unclear	12	Yes (subset)	All smokers attending community health survey (73% of population in attendance) had equal chance of being selected	Smokers included in study were at high risk for obstructive lung disease (previous occupational asbestos exposure, and/or adjusted FEV_1 in the lowest quartile). Control group did not receive any advice to stop smoking.

Summary Table 6. Strengths and limitations of studies using spirometry as an aid in smoking cessation (continued)

Study (Reference)	Independent Assessment of Effects of Spirometry	Quality of Randomization	Length of Followup (Months)	Biochemical Validation of Smoking Cessation	Selection of Participants	Study Notes/Limitations
Li et al., 1984[85]	No	Unclear	11	Yes	All naval shipyard employees who were smokers	Both control and intervention subjects received the results of their PFTs and CO tests (it is unclear how much information was given to the control group). Therefore, the effect of spirometry cannot be assessed. Researchers disregarded the randomization performed initially such that study groups were reconstructed in the analysis phase due to poor compliance by the physicians administering the interventions. Three subjects were omitted from the reconstructed groups because it was unclear what treatment was received. Subjects may have additional motivation to quit because they were exposed to asbestos.

Summary Table 7. Outcomes data for studies using spirometry as an aid in smoking cessation

Study	Group	Self-Reported Abstinence Rate		Biologically Verified Quit Rate		Continuously Abstinent Over Course of Study		One or More Quit Attempts	Notes
		6-Month	12-Month	Quit Rate	Time	Quit Rate	Time		
Independent effects of spirometry assessed									
Segnan et al., 1991[79]	Control (Minimal Intervention)			4.8%	12 months				Subjects with cotinine/creatinine ratios >100 ng/mg classified as smokers. Unverified self-reported quitters counted as smokers. Three months of abstinence required to be considered an abstainer. Prevalence of self-reported abstinence (no data provided) was twice that of biologically verified abstinence. If followup data not available, subjects assumed to be smokers.
	Repeated Counseling (RC)			5.5%	12 months				
	RC plus NRT			7.5%	12 months				
	RC plus spirometry			6.5%	12 months				
Effects of spirometry plus other interventions assessed									
Risser et al., 1990[80]	Control (50-min. educational intervention)		11.1%	6.7%	12 months			15.6%	Biochemical validation of smoking status occurred in 63% of subjects. Subjects with CO levels >10 ppm were classified as smokers. If followup data not available, subjects assumed to be smokers.
	50-min intervention + spirometry + CO + symptom discussion		24.4%	20.0%	12 months			35.6%	
Sippel et al., 1999[81]	Control (Advice)	14%*						36%	*Self-reported abstinence at 9 months followup. Subjects with CO levels >5 ppm were classified as smokers. If followup data not available, subjects assumed to be smokers. Mean length of followup was 260 ± 45 days.
	Advice + spirometry + CO	9%*						48%	
Richmond et al., 1985[82]	Control (2 visits)	3.0%		8.0%	36 months	2.0%	36 months		Subjects with cotinine levels ≥50 nmol/L or carboxyhemoglobin concentration ≥2.0% classified as smokers. Smoking status verified by friends/relatives in three cases. If followup data not available, subjects assumed to be smokers.
	6 visits + spirometry + blood tests	35.0%		35.7%	36 months	23.5%	36 months		

Summary Table 7. Outcomes data for studies using spirometry as an aid in smoking cessation (continued)

Study	Group	Self-Reported Abstinence Rate		Biologically Verified Quit Rate		Continuously Abstinent Over Course of Study		One or More Quit Attempts	Notes
		6-Month	12-Month	Quit Rate	Time	Quit Rate	Time		
Rose et al., 1978[84]	Control (Usual care)		8.9% ‡						‡ Self-reported abstinence rates at 36 months of followup were 14.5% in the control group and 35.5% in the intervention group. Denominators are number responding to questionnaire.
	4 visits + spirometry + booklets + report cards		39.3% ‡						
Humerfelt et al., 1998[83]	Control (No intervention)		9.1%			3.2%	12 months		Validation study performed in 114 subjects (non-representative sample) via CO measurement. Subjects with CO levels >10 ppm were classified as smokers. Intention-to-treat data presented.
	Letter + pamphlet + spirometry + questionnaire		11.4%			4.7%	12 months		
Li et al., 1984[85]	Control (Minimal advice + PFT + chest x-ray + questionnaire)			2.8%	11 months	3.6%	11 months		Subjects with CO levels ≥9 ppm were classified as smokers. Outcomes data from reconstructed groups based on compliance of physicians providing interventions, not groups created in original randomization.
	Behavioral counseling + PFT + chest x-ray + questionnaire			6.5%	11 months	8.4%	11 months		

Figure 10.

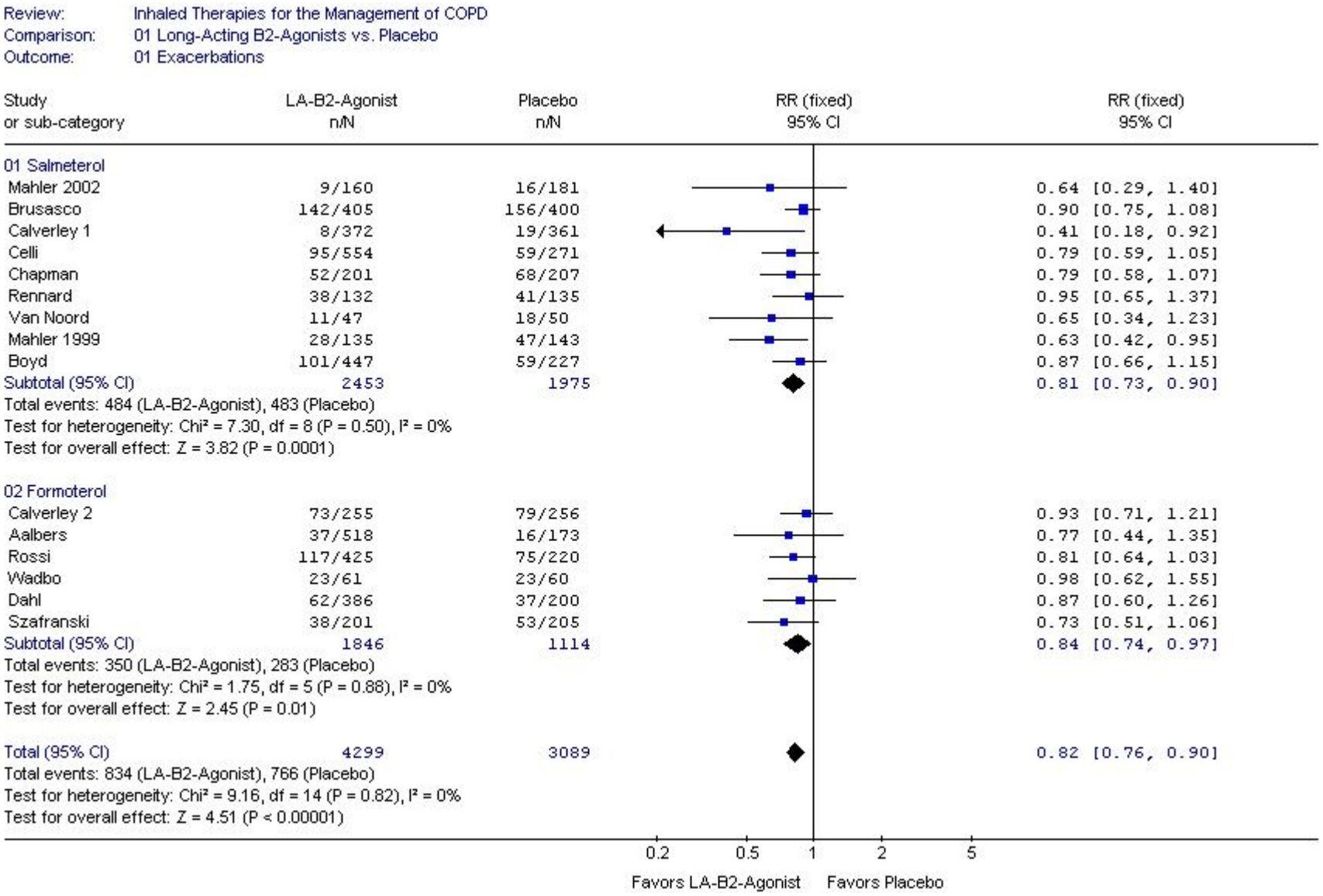
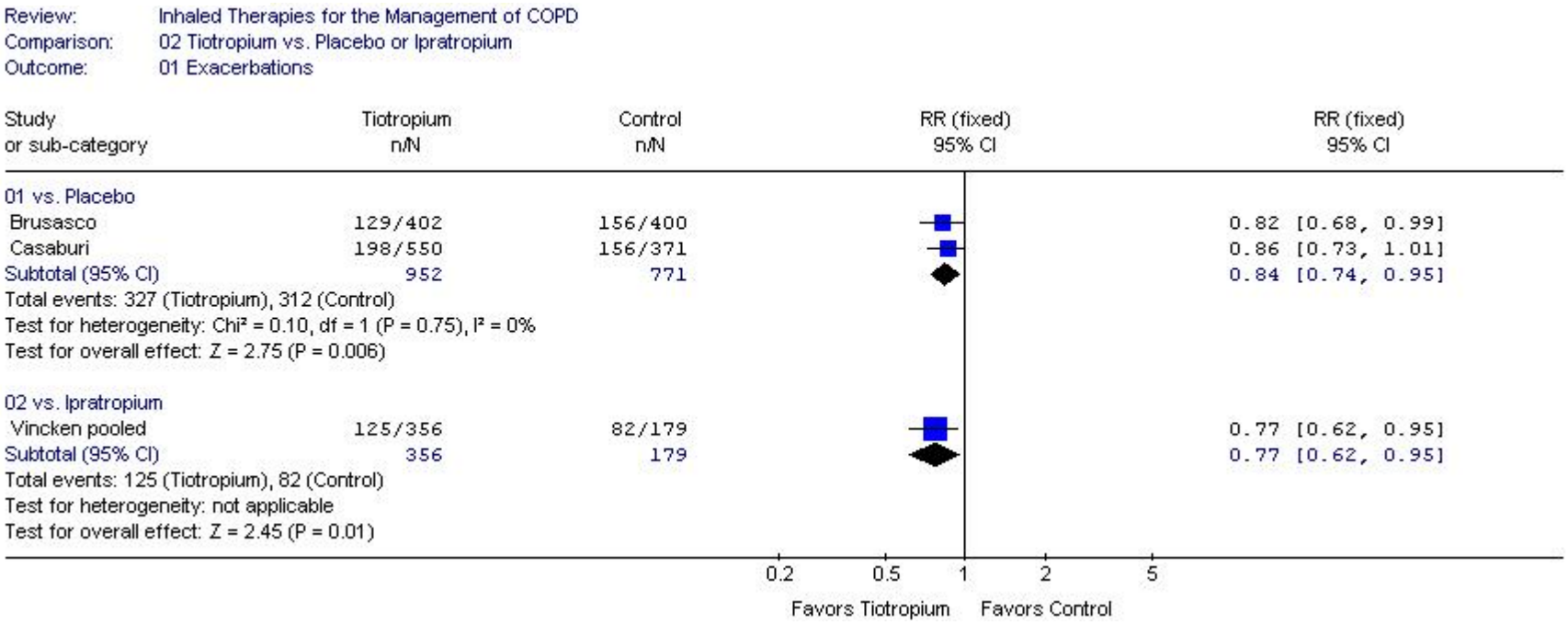

Review: Inhaled Therapies for the Management of COPD
Comparison: 01 Long-Acting B2-Agonists vs. Placebo
Outcome: 01 Exacerbations
Study or sub-category
LA-B2-Agonist n/N
Placebo n/N
RR (fixed) 95% CI
RR (fixed) 95% CI
01 Salmeterol
Mahler 2002 9/160 16/181 0.64 [0.29, 1.40]
Brusasco 142/405 156/400 0.90 [0.75, 1.08]
Calverley 1 8/372 19/361 0.41 [0.18, 0.92]
Celli 95/554 59/271 0.79 [0.59, 1.05]
Chapman 52/201 68/207 0.79 [0.58, 1.07]
Rennard 38/132 41/135 0.95 [0.65, 1.37]
Van Noord 11/47 18/50 0.65 [0.34, 1.23]
Mahler 1999 28/135 47/143 0.63 [0.42, 0.95]
Boyd 101/447 59/227 0.87 [0.66, 1.15]
Subtotal (95% CI) 2453 1975 0.81 [0.73, 0.90]
Total events: 484 (LA-B2-Agonist), 483 (Placebo)
Test for heterogeneity: Chi² = 7.30, df = 8 (P = 0.50), I² = 0%
Test for overall effect: Z = 3.82 (P = 0.0001)
02 Formoterol
Calverley 2 73/255 79/256 0.93 [0.71, 1.21]
Aalbers 37/518 16/173 0.77 [0.44, 1.35]
Rossi 117/425 75/220 0.81 [0.64, 1.03]
Wadbo 23/61 23/60 0.98 [0.62, 1.55]
Dahl 62/386 37/200 0.87 [0.60, 1.26]
Szafranski 38/201 53/205 0.73 [0.51, 1.06]
Subtotal (95% CI) 1846 1114 0.84 [0.74, 0.97]
Total events: 350 (LA-B2-Agonist), 283 (Placebo)
Test for heterogeneity: Chi² = 1.75, df = 5 (P = 0.88), I² = 0%
Test for overall effect: Z = 2.45 (P = 0.01)
Total (95% CI) 4299 3089 0.82 [0.76, 0.90]
Total events: 834 (LA-B2-Agonist), 766 (Placebo)
Test for heterogeneity: Chi² = 9.16, df = 14 (P = 0.82), I² = 0%
Test for overall effect: Z = 4.51 (P < 0.00001)
0.2
0.5
1
2
5
Favors LA-B2-Agonist
Favors Placebo

Figure 11.


Review: Inhaled Therapies for the Management of COPD
Comparison: 02 Tiotropium vs. Placebo or Ipratropium
Outcome: 01 Exacerbations
Study or sub-category
Tiotropium n/N
Control n/N
RR (fixed) 95% CI
RR (fixed) 95% CI
01 vs. Placebo
Brusasco 129/402 156/400 0.82 [0.68, 0.99]
Casaburi 198/550 156/371 0.86 [0.73, 1.01]
Subtotal (95% CI) 952 771 0.84 [0.74, 0.95]
Total events: 327 (Tiotropium), 312 (Control)
Test for heterogeneity: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%
Test for overall effect: Z = 2.75 (P = 0.006)
02 vs. Ipratropium
Vincken pooled 125/356 82/179 0.77 [0.62, 0.95]
Subtotal (95% CI) 356 179 0.77 [0.62, 0.95]
Total events: 125 (Tiotropium), 82 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 2.45 (P = 0.01)
0.2
0.5
1
2
5
Favors Tiotropium
Favors Control

Summary Table 8. Outcomes of studies of tiotropium for COPD using spirometry

Study	Intervention	Exacerbations: Total Subjects With >1 Episode n / N (%)	Exacerbations - Other/ Hospitalizations Due to COPD / or Other	Mortality: n / N (%)	St George's Respiratory Questionnaire
Brusasco et al., 2003[89]			Use of oral steroid bursts in management of COPD		Change per group
	1) Tiotropium 18 ug q.d. (n=402)	129 / 402 (32)	45 / 402 (11.2)	1 / 402 (<1)	4.2 (0.7)
	2) placebo (n=400)	156 / 400 (39)	58 / 400 (14.5)	5 / 400 (1.3)	1.5 (0.7)
Casaburi et al., 2002[104]			Patients hospitalized for exacerbation		Change per group
	1) Tiotropium 18 ug q.d. (n=550)	198 / 550 (36)	30 / 550 (5.5)	7 / 550 (1.3)	-3.2 (p<0.05)
	2) placebo (n=371)	156 / 371 (42)	35 / 371 (9.4)	7 / 371 (1.9)	0.58
Donohue et al., 2002[95]	1) Tiotropium 18 ug q.d. (n=209)	77 / 209 (36.8)	Not reported	0 / 209	Change per group -5.14 (p<0.05 vs. pbo)
	2) placebo (n=201)	92 / 201 (45.8)	Not reported	4 / 201 (2)	-2.43
Vincken et al., 2002[105]			Patients hospitalized for exacerbation		Treatment difference vs. Ipratropium
	1) Tiotropium 18 ug q.d. (n=356);	125 / 356 (35.1)	26 / 356 (7.3)	9 / 356 (2.5)	-3.3 (1.13) (p=0.004)
	2) Ipratropium bromide 40 ug q.i.d. (n=179)	82 / 179 (45.8)	21 / 179 (11.7)	3 / 179 (1.7)	
van Noord et al., 2000[106]	1) Tiotropium 18 ug *q.d.* (n=191);	21 / 191 (11)	Not reported	Not reported	Not reported
	2) Ipratropium 40 ug q.i.d. (n=97)	12 / 97 (12.4)	Not reported	Not reported	Not reported

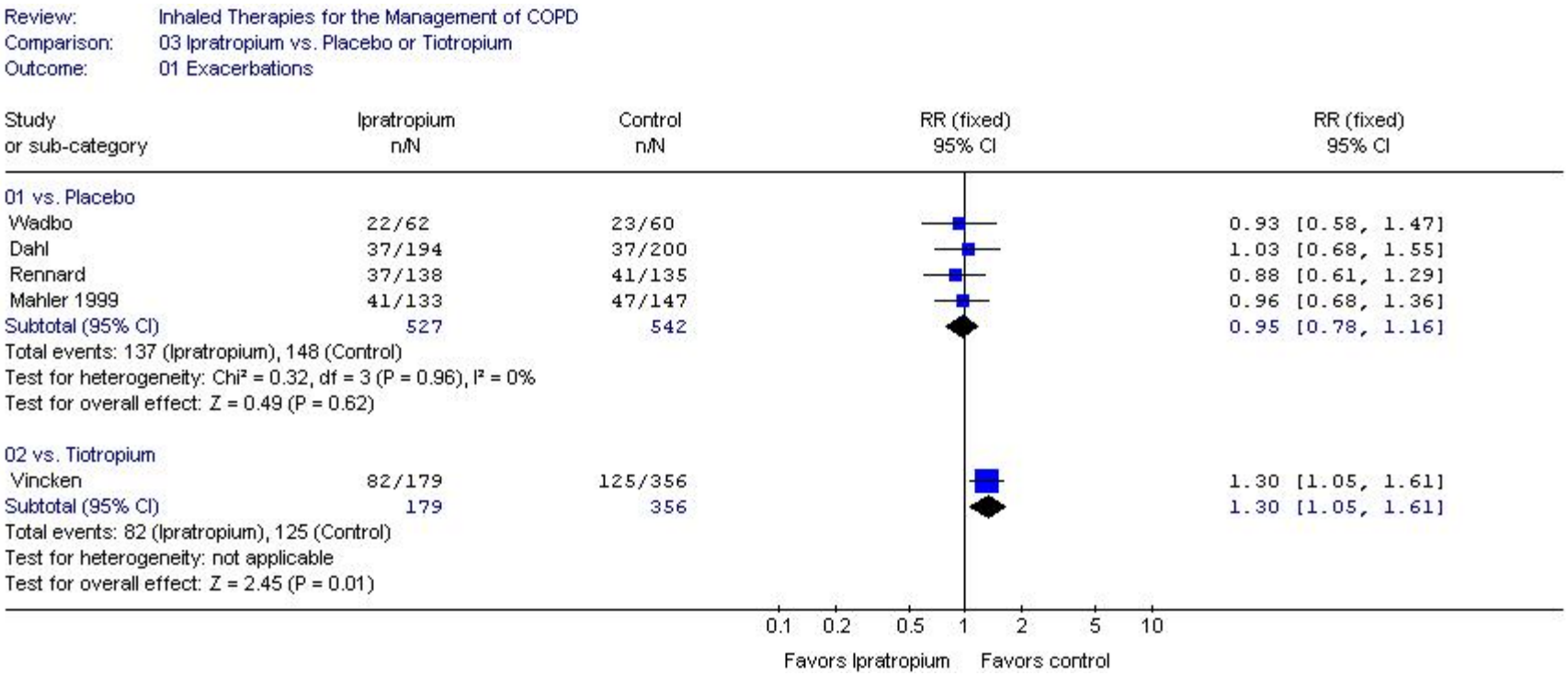
Summary Table 9. Summary of outcomes for interventions for COPD using spirometry – tiotropium

Studies	N	Duration	Tiotropium Events, %	Control Events, %	ARR % [95%CI]	Relative Risk [95%CI]	Baseline Spirometry Range (FEV_1; %) Predicted
Exacerbation vs. Placebo							
Brusasco, 2003[89]	802	6 month	32.1	39	-7 [-14 to 0]	0.82 [0.68 to 0.99]	1.1; 39%
Casaburi, 2002[104]	921	1 year	36	42	-6 [-12 to 0]	0.86 [0.73 to 1.01]	1.0; 39%
OVERALL	**1723**	**6 months - 1 year**	**34.3**	**40.6**	**-6 [-11 to -2]**	**0.83 [0.75 to 0.93]**	**1.0 to 1.1; 39%**
Exacerbation vs. Ipratropium							
Vincken, 2002[105]	**535**	**1 year**	**35.1**	**45.8**	**-11 [-20 to -2]**	**0.77 [0.62 to 0.95]**	**1.2; 41%**
Exacerbation vs. Long-Acting β2 Agonists (Salmeterol)							
Brusasco, 2003[89]	**807**	**6 months**	**32.1**	**35.1**	**-3 [-9 to 4]**	**0.92 (0.75 to 1.11)**	**1.1; 39%**
Mortality vs. Placebo;							
Brusasco, 2003[89]	802	6 month	0.25	1.3	-1 [-2 to 0]	0.20 [0.02 to 1.70]	1.1; 39%
Casaburi, 2002[104]	921	1 year	1.3	1.9	-1 [-2 to 1]	0.67 [0.24 to 1.91]	1.0; 39%
OVERALL	**1723**	**6 months - 1 year**	**0.69**	**1.6**	**-1 [-2 to 0]**	**0.40 [0.17 to 0.93]**	**1.0 to 1.1; 39%**
Mortality vs. Ipratropium							
Vincken, 2002[105]	**535**	**1 year**	**2.5**	**1.7**	**1 [-2 to 3]**	**1.51 [0.41 to 5.50]**	**1.2; 41%**
Mortality vs. Long-Acting β2 Agonists (Salmeterol)							
Brusasco, 2003[89]	**807**	**6 months**	**0.0025**	**1.5**	**-1 [-3 to 0]**	**0.17 [0.02 to 1.39]**	**1.1; 39%**

Summary Table 9. Summary of outcomes for interventions for COPD using spirometry – tiotropium (continued)

Studies	N	Duration	Tiotropium: Mean Change	Control: Change		Weighted Mean Difference (95%CI)	Baseline Spirometry Range (FEV_1; %) Predicted
St George's Respiratory Questionnaire - Mean units of change: vs. Placebo							
Brusasco, 2003[89]	802	6 months	-4.2	-1.5	Not Applicable	-2.70 [-4.64 to -0.76]	1.1; 39%
Casaburi, 2002[104]	921	1 year	-3.2	0.58	Not Applicable	-3.7 [-7.2 to -0.2]	1.0; 39%
OVERALL	***Studies not pooled, WMDs from Casaburi and Brusasco reported in study without additional data to allow pooling***						
St George's Respiratory Questionnaire - Mean units of change: vs. Ipratropium							
Vincken, 2002[105]	535	1 year	No Response	No Response	Not Applicable	-3.3 [-6.5 to -0.2]	1.2; 41%
OVERALL	***Studies not pooled, Casaburi, Brusasco and Vincken reported in study without additional data to allow pooling***						

Figure 12.


Review: Inhaled Therapies for the Management of COPD
Comparison: 03 Ipratropium vs. Placebo or Tiotropium
Outcome: 01 Exacerbations
Study or sub-category
Ipratropium n/N
Control n/N
RR (fixed) 95% CI
RR (fixed) 95% CI
01 vs. Placebo
Wadbo 22/62 23/60 0.93 [0.58, 1.47]
Dahl 37/194 37/200 1.03 [0.68, 1.55]
Rennard 37/138 41/135 0.88 [0.61, 1.29]
Mahler 1999 41/133 47/147 0.96 [0.68, 1.36]
Subtotal (95% CI) 527 542 0.95 [0.78, 1.16]
Total events: 137 (Ipratropium), 148 (Control)
Test for heterogeneity: Chi² = 0.32, df = 3 (P = 0.96), I² = 0%
Test for overall effect: Z = 0.49 (P = 0.62)
02 vs. Tiotropium
Vincken 82/179 125/356 1.30 [1.05, 1.61]
Subtotal (95% CI) 179 356 1.30 [1.05, 1.61]
Total events: 82 (Ipratropium), 125 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 2.45 (P = 0.01)
0.1 0.2 0.5 1 2 5 10
Favors Ipratropium
Favors control

Summary Table 10. Outcomes of studies of ipratropium for COPD using spirometry

Study	Intervention	Exacerbations: Total Subjects with >1 episode n / N (%)	Exacerbations -Other/ Hospitalizations Due to COPD / or Other	Mortality: n / N (%)	St George's Respiratory Questionnaire
Vincken et al., 2002[105]			Patients hospitalized for exacerbation; n/N %		Treatment difference vs. Ipratropium
	1) Ipratropium bromide 40 ug q.i.d. (n=179)	82 / 179 (45.8)	21 / 179 (11.7)	3 / 179 (1.7)	
	2) Tiotropium 18 ug q.d. (n=356)	125 / 356 (35.1)	26 / 356 (7.3)	9 / 356 (2.5)	-3.3 (1.13) (p=0.004)
Wadbo et al., 2002[98]	1) Ipratropium bromide 80 ug, t.i.d. (n=62)	"Adverse Events related to COPD" 22 / 62 (35.5)	"Deterioration of COPD leading to withdrawal"; n/N % 3 / 62 (4.8)	Not reported	Change per group -0.5% (95%CI -2.8 to 1.7)
	2) placebo (n=60)	23 / 60 (38.3)	6 / 60 (10.0)	Not reported	1.5% (95%CI -0.8 to 3.7)
Dahl et al., 2001[99]	1) Ipratropium bromide 40 ug, t.i.d. (n=194)	"COPD Adverse Events" - includes exacerbations 37 / 194 (19.1)	COPD hospitalizations; n/N % 6 / 194 (3.1)	0 / 194	Treatment difference vs. pbo 1.33 (est.) (p=0.314)
	2) placebo (n=200)	37 / 200 (18.5)	4 / 200 (2)	0 / 200	
Rennard et al., 2001[100]	1) Ipratropium 36 ug, t.i.d. (n=138)	37 / 138 (26.8)	First exacerbation during week 1; n/N % 6 / 138 (4.3)	0 / 138	*Chronic Respiratory Disease Questionnaire*; Change per group 9.2
	2) placebo (n=135)	41 / 135 (30.4)	20 / 135 (14.8)	1 / 135	6.8
van Noord et al., 2000[106]	1) Ipratropium 40 ug q.i.d. (n=97)	12 / 97 (12.4)	Not reported	Not reported	Not reported
	2) Tiotropium 18 ug q.d. (n=191)	21 / 191 (11)	Not reported	Not reported	Not reported
Mahler et al, 1999[102]	1) Ipratropium 36 ug, q.i.d. (n=133)	41 / 133 (30.8)	First exacerbation during week 1; n/N % 7 / 133 (5.3)	0 / 133	*Chronic Respiratory Disease Questionnaire*; Change per group 6.8 (1.2) (p=0.007 vs. pbo)
	2) placebo (n=143)	47 / 143 (32.9)	21 / 143 (14.7)	0 / 143	2.1 (1.3)
COMBIVENT Inhalation Study Group, 1997[109]	1) Ipratropium 50 ug, t.i.d. (n=214)	≥1 adverse event - "worsening of the lower respiratory tract symptoms was the most frequently reported event" 112 / 214 (52.3)	Discontinuations due to deterioration of COPD; n/N % 8 / 214 (3.7	1 / 214 (<1)	Not reported
	2) Ipratropium 50 ug plus Albuterol 3mg t.i.d. (n=222)	126 / 222 (56.8)	9 / 222 (4.1)	3 / 222 (1.4)	Not reported
	3) Albuterol 3 mg t.i.d. (n=216)	124 / 216 (57.4)	8 / 216 (3.7)	4 / 216 (1.9)	Not reported

Summary Table 10. Outcomes of studies of ipratropium for COPD using spirometry (continued)

Study	Intervention	Exacerbations: Total Subjects with >1 episode n / N (%)	Exacerbations -Other/ Hospitalizations Due to COPD / or Other	Mortality: n / N (%)	St George's Respiratory Questionnaire
COMBIVENT Inhalation Study Group, 1994[108]	1) Ipratropium 21 ug, q.i.d. (n=179)	"Subjects reporting adverse events or worsening of a pre-existing condition" (excluding AEs that were possibly drug-related 77 / 179 (43.0)	Not reported	0 / 179	Not reported
	2) Ipratropium 21 ug plus Albuterol 100ug q.i.d. (n=182)	76/182 (41.8)	Not reported	2 / 182 (1.1)	Not reported
	3) Albuterol 120 ug q.i.d. (n=173)	82 1 73 (47.4)	Not reported	0 / 173	Not reported

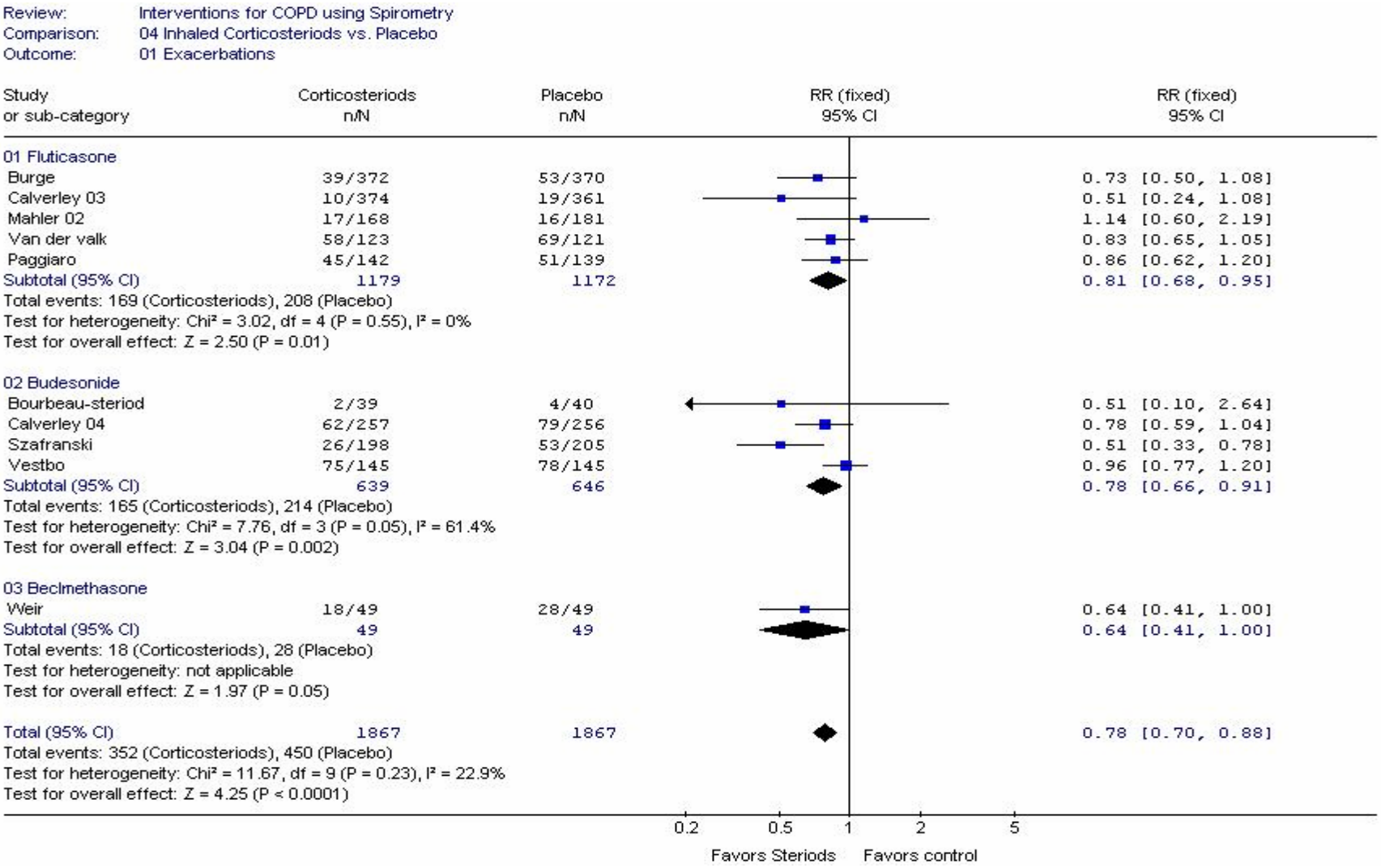
Summary Table 11. Summary of outcomes for interventions for COPD using spirometry – ipratropium

Studies	N	Duration	Ipratropium Events, %	Placebo Events, %	ARR % [95% CI]	Relative Risk [95% CI]	Mean Baseline Spirometry (FEV_1; %) Predicted
Exacerbations: vs. Placebo							
Wadbo, 2002[98]	122	3 months	35.5	38.3	-3 [-20 to 14]	0.93 [0.58 to 1.47]	33%
Dahl, 2001[99]	394	3 months	19.1	18.5	1 [-7 to 8]	1.03 [0.68 to 1.55]	1.3; 45%
Rennard, 2001[100]	273	3 months	26.8	30.4	-4 [-14 to 7]	0.88 [0.61 to 1.29]	1.3
Mahler, 1999[102]	280	3 months	30.8	32	-1 [-12 to 10]	0.96 [0.68 to 1.36]	39%
OVERALL	**1069**	**3 months**	**26**	**27.3**	**-1 [-7 to 4]**	**0.95 [0.78 to 1.16]**	**1.3; 33-45%**
Exacerbations: vs. Tiotropium							
Vincken, 2002[105]	**535**	**1 year**	**45.8**	**35.1**	**-11 [-20 to -2]**	**1.30 [1.05 to 1.61]**	**1.2; 41%**
Mortality: vs. Placebo							
Dahl, 2001[99]	394	3 months	0	0	0 [-1 to 1]	Not estimable	1.3; 45%
Rennard, 2001[100]	273	3 months	0	0.74	-1 [-3 to 1]	0.33 [0.01 to 7.94]	1.3
Mahler, 1999[102]	280	3 months	0	0	0 [-1 to 1]	Not estimable	39%
LH-1[114]	3923	5 year	2.8	2.2	1 [0 to 1]	1.23 [0.83 to 1.82]	2.6; 75%
OVERALL	**4870**	**3 months - 5 year**	**2.2**	**1.8**	**0 [0 to 1]**	**1.20 [0.81 to 1.77]**	**1.3 to 2.6; 39-75%**
Mortality: vs. Tiotropium							
Vincken, 2002[105]	**535**	**1 year**	**1.7**	**2.5**	**-1 [-3 to 2]**	**0.66 [0.18 to 2.42]**	**1.2; 41%**

Studies	N	Duration	Ipratropium: Mean Change	Control: Change	ARR	Weighted Mean Difference (95%CI)	Baseline Spirometry Range (FEV_1; %) Predicted
St George's Respiratory Questionnaire - Mean units of change: vs. Placebo							
Dahl, 2001[99]	394	3 months	Not reported	Not reported	Not Applicable	-1.2 [-3.8 to 1.4]	1.3; 45%
Wadbo et al., 2002[98]	122	3 months	-0.5	1.5	Not Applicable	-1	33 to 34%
St George's Respiratory Questionnaire - Mean units of change: vs. Tiotropium							
Vincken, 2002[105]	535	1 year	Not reported	Not reported	Not Applicable	3.3 [1.09 to 5.51]	1.2; 41%

Studies not pooled, studies did not report data to allow pooling

Figure 13.


Review: Interventions for COPD using Spirometry
Comparison: 04 Inhaled Corticosteriods vs. Placebo
Outcome: 01 Exacerbations
Study or sub-category
Corticosteriods n/N
Placebo n/N
RR (fixed) 95% CI
RR (fixed) 95% CI
01 Fluticasone
Burge 39/372 53/370 0.73 [0.50, 1.08]
Calverley 03 10/374 19/361 0.51 [0.24, 1.08]
Mahler 02 17/168 16/181 1.14 [0.60, 2.19]
Van der valk 58/123 69/121 0.83 [0.65, 1.05]
Paggiaro 45/142 51/139 0.86 [0.62, 1.20]
Subtotal (95% CI) 1179 1172 0.81 [0.68, 0.95]
Total events: 169 (Corticosteriods), 208 (Placebo)
Test for heterogeneity: Chi² = 3.02, df = 4 (P = 0.55), I² = 0%
Test for overall effect: Z = 2.50 (P = 0.01)
02 Budesonide
Bourbeau-steriod 2/39 4/40 0.51 [0.10, 2.64]
Calverley 04 62/257 79/256 0.78 [0.59, 1.04]
Szafranski 26/198 53/205 0.51 [0.33, 0.78]
Vestbo 75/145 78/145 0.96 [0.77, 1.20]
Subtotal (95% CI) 639 646 0.78 [0.66, 0.91]
Total events: 165 (Corticosteriods), 214 (Placebo)
Test for heterogeneity: Chi² = 7.76, df = 3 (P = 0.05), I² = 61.4%
Test for overall effect: Z = 3.04 (P = 0.002)
03 Beclmethasone
Weir 18/49 28/49 0.64 [0.41, 1.00]
Subtotal (95% CI) 49 49 0.64 [0.41, 1.00]
Total events: 18 (Corticosteriods), 28 (Placebo)
Test for heterogeneity: not applicable
Test for overall effect: Z = 1.97 (P = 0.05)
Total (95% CI) 1867 1867 0.78 [0.70, 0.88]
Total events: 352 (Corticosteriods), 450 (Placebo)
Test for heterogeneity: Chi² = 11.67, df = 9 (P = 0.23), I² = 22.9%
Test for overall effect: Z = 4.25 (P < 0.0001)
0.2
0.5
1
2
5
Favors Steriods
Favors control

Summary Table 12. Outcomes of studies of inhaled corticosteroids for COPD using spirometry

Study	Intervention	Exacerbations: Total Subjects with >1 Episode n / N (%)	Exacerbations - Other/ Hospitalizations Due to COPD / or Other	Mortality: n / N (%)	St George's Respiratory Questionnaire
van der Valk et al., 2002[86]			Rapid recurrent; n/N %		Treatment difference vs. pbo
	1) Fluticasone 500 ug, b.i.d. (n=123)	58 / 123 (47.2)	6 / 123 (4.9)	1 / 123	2.48 (95% CI 0.37 to 4.58)
	2) placebo (n=121)	69 / 121 (57.0)	26 / 121 (21.5)	1 / 121	
Burge et al., 2000[111]			Median annual rates		Change per group
	1) Fluticasone 500 ug, b.i.d. (n=376)	Not reported	0.99 (range 0 to 26)	32 / 376 (8.5)	2.00 (0.29)
	2) placebo (n=375)	Not reported	1.32 (0 to 30) Treatment difference -0.3 (-0.4 to 0.0)	36 / 375 (9.6)	3.17 (0.31) Treatment difference vs. pbo -1.17 (-1.95 to -0.39); p=0.004
LHS Research Group, 2000[114]			Respiratory Symptoms during course of study		
	1) Triamcinolone 600 ug, b.i.d. (n=559)	Not reported	21.1 per 100 person yrs	15 / 559 (2.9)	Not reported
	2) placebo (n=557)	Not reported	28.2 per 100 person yrs	19 / 557 (3.4)	Not reported
Pauwels et al., 1999[115]	1) Budesonide 400 ug, b.i.d. (n=634)	Not reported	Not reported	8 / 634 (1.3)	Not reported
	2) placebo (n=643)	Not reported	Not reported	10 / 643 (1.6)	Not reported
Vestbo et al., 1999[112]			Discontinuations due to deterioration of COPD; n / N %		
	1) Budesonide (800 ug, 400 ug; b.i.d.) for 6 months and (400 ug, b.i.d.) for 30 months, (n=145)	155 total	3 / 145 (2.1)	4 / 145 (2.8)	Not reported
	2) placebo (n=145)	161 total	7 / 145 (4.8)	5 / 145 (3.4)	Not reported
Weir et al., 1999[117]	1) Beclomethasone dipropionate (750 ug for less than 50 kg) and (1000 ug for greater than 50 kg), b.i.d., (n=49)	Not reported	Mean exacerbation rate/year 0.36 (0.09 SE)	Not reported	Not reported
	2) placebo (n=49)	Not Reported	0.57 (0.13 SE)	Not reported	Not reported

Summary Table 12. Outcomes of studies of inhaled corticosteroids for COPD using spirometry (continued)

Study	Intervention	Exacerbations: Total Subjects with >1 Episode n / N (%)	Exacerbations - Other/ Hospitalizations Due to COPD / or Other	Mortality: n / N (%)	St George's Respiratory Questionnaire
Bourbeau et al., 1998[116]		"Adverse events, respiratory in origin"	Discontinuations due to deterioration of COPD; n/N %		
	1) Budesonide 800 ug, b.i.d, (n=39)	10 / 39 (25.6)	0 / 39	Not reported	Not reported
	2) placebo (n=40)	15 / 40 (37.5)	1 / 40 (2.5)	Not reported	Not reported
Paggiaro et al., 1998[113]			Number of exacerbations		
	1) Fluticasone 500 ug, b.i.d. (n=142)	45 / 142 (31.7) mild 17 / 45 (38) moderate/severe 27 / 45 (60)	76	Not reported	Not reported
	2) placebo (n=139)	51 / 139 (36.7) mild 7 / 51 (14) moderate/severe 44 / 51 (86)	111	Not reported	Not reported

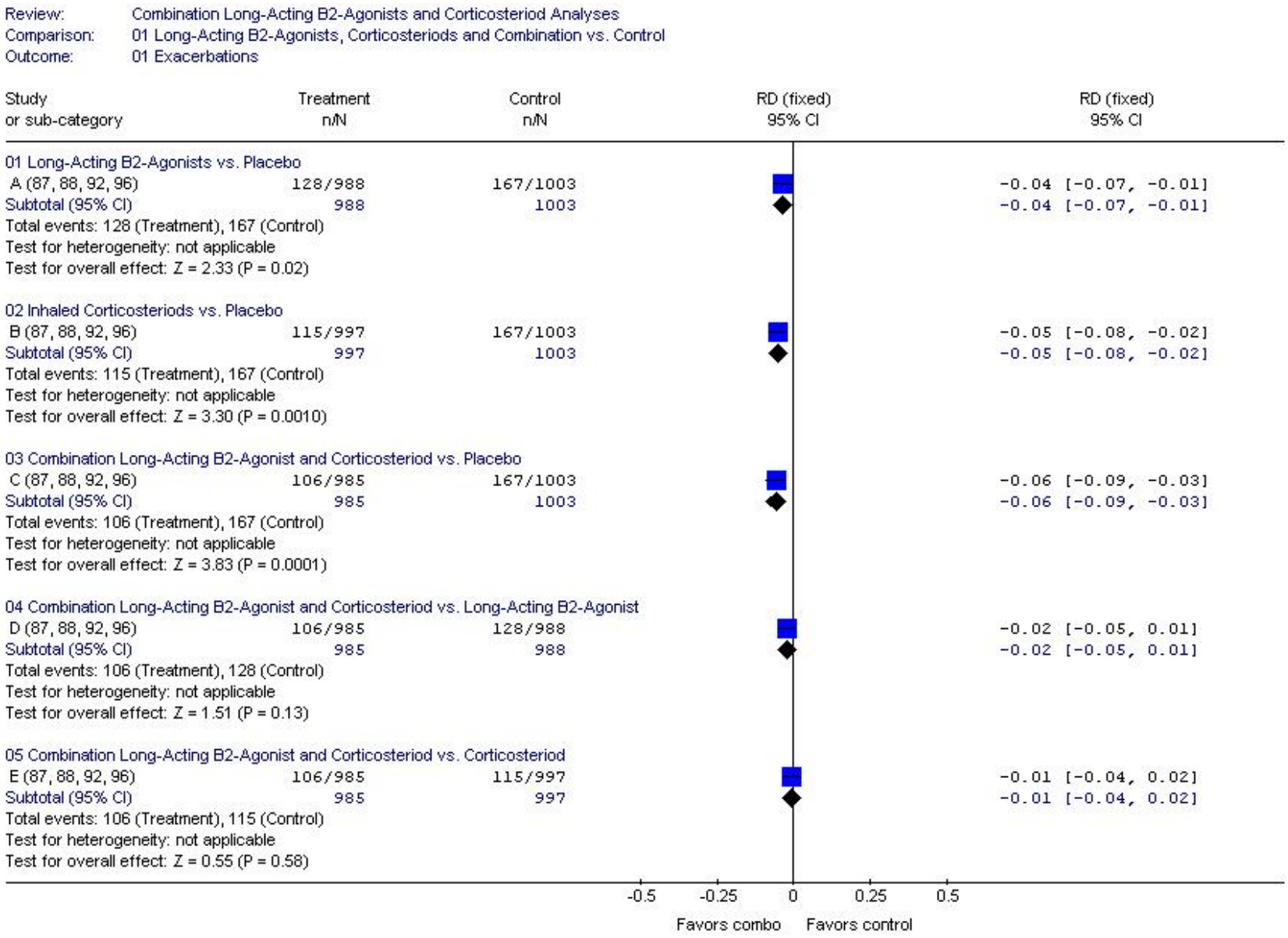
Summary Table 13. Summary of outcomes for interventions for COPD using spirometry – corticosteroids

Studies	N	Duration	Steroid Events, %	Placebo Events, %	ARR % [95% CI]	Relative Risk [95% CI]	Baseline Spirometry Range (FEV_1; %) Predicted
Exacerbations: Fluticasone							
Burge, 2000[111]	751	3 years	10.5	14.3	-4 [-9 to 1]	0.73 [0.50 to 1.08]	**Post** 1.4; 50%
Calverley, 2003[87]	735	1 year	2.5	5.3	-3 [-5 to 0]	0.51 [0.24 to 1.08]	1.3; 45%
Mahler, 2002[96]	349	6 months	10.1	8.8	1 [-5 to 7]	1.14 [0.60 to 2.19]	1.3; 41%
van der Valk, 2002[86]	244	6 months	47.2	57	-10 [-22 to 3]	0.83 [0.65 to 1.05]	**Post** 1.7; 57%
Paggiaro, 1998[113]	281	6 months	*31.7*	*36.7*	-5 [-16 to 6]	0.86 [0.62 to 1.20]	1.6; 57%
Overall	**2360**	**6 months to 3 years**	**14.3**	**17.7**	**-3 [-6 to -1]**	**0.81 [0.68 to 0.95]**	**1.3 to 1.7; 45 to 57%**
Exacerbations: Budesonide							
Calverley, 2003[88]	513	1 year	24.1	30.9	-7 [-14 to 1]	0.78 [0.59 to 1.04]	1.0; 36%
Bourbeau, 1998[116]	79	6 months	5.1	10	-5 [-16 to 7]	0.51 [0.10 to 2.64]	0.9; 37%
Vestbo, 1999[112]	290	3 years	*51.7*	*53.8*	-2 [-14 to 9]	0.96 [0.77 to 1.20]	**Post** 2.4; 87%
Szafranski, 2003[92]	406	1 year	13.1	25.9	-13 [-20 to -5]	0.51 [0.33 to 0.78]	1.0; 36%
Overall	**1288**	**6 months to 3 years**	**25.6**	**33.1**	**-7 [-12 to -3]**	**0.78 [0.66 to 0.91]**	**0.9; 37%**
Exacerbations: Beclomethasone							
Weir et al., 1999[117]	98	2 year	*36.7*	*57.1*	-20 [-40 to -1]	0.64 [0.41 to 1.00]	1.1; 41%
OVERALL	**3746**	**6 months to 3 years**	**18.9**	**24.1**	**-5 [-8 to -3]**	**0.78 [0.70 to 0.88]**	**0.9 to 2.4; 37 to 87%**
Mortality: Fluticasone							
Burge, 2000[111]	751	3 years	8.5	9.6	-1 [-5 to 3]	0.89 [0.56 to 1.40]	**Post** 1.4; 50%
van der Valk, 2002[86]	244	6 months	0.81	0.83	0 [-2 to 2]	0.98 [0.06 to 15.55]	**Post** 1.7; 57%
Hanania, 2003[91]	368	6 months	0	0	0 [-1 to 1]	Not estimable	1.3; 42%
Mahler, 2002[96]	349	6 months	0	1.7	-2 [-4 to 0]	0.15 [0.01 to 2.96]	1.3; 41%
Overall	**1712**	**6 months to 3 years**	**3.9**	**4.6**	**-0.7**	**0.83 [0.53 to 1.28]**	**1.3 to 1.7; 41 to 57%**
Mortality: Budesonide							
Calverley, 2003[88]	513	1 year	2.3	2.0	0 [-2 to 3]	1.20 [0.37 to 3.87]	1.0; 36%
Pauwels, 1999[115]	1277	3 years	1.3	1.6	-0 [-2 to 1]	0.81 [0.32 to 2.04]	2.5; 77%
Vestbo, 1999[112]	290	3 years	2.8	3.4	-1 [-5 to 3]	0.80 [0.22 to 2.92]	**Post** 2.4; 87%
Szafranski, 2003[92]	406	1 year	2.5	4.4	-2 [-5 to 2]	0.58 [0.20 to 1.69]	1.0; 36%
Overall	**2486**	**1 to 3 years**	**1.5**	**1.9**	**0 [-2 to 1]**	**0.72 [0.39 to 1.33]**	**2.4 to 2.5; 77 to 87%**
Mortality: Triamcinolone							
LHS-2[114]	1116	4.5 years	2.7	3.4	-1 [-3 to 1]	0.79 [0.40 to 1.53]	2.1; 64%
OVERALL	**5314**	**6 months to 4.5 years**	**2.7**	**3.3**	**-1 [-2 to 0]**	**0.81 [0.60 to 1.10]**	**1.3 to 2.5; 41 to 87%**

Summary Table 13. Summary of outcomes for interventions for COPD using spirometry – corticosteroids (continued)

Studies	N	Duration	Long-Acting β2 Agonists: Mean Change	Placebo: Change	ARR	Weighted Mean Difference [95%CI]	Baseline Spirometry Range (FEV_1; %) Predicted
St George's Respiratory Questionnaire - Mean units of change:							
Calverley, 2003[88]	513	1 year	Not reported	Not reported	Not applicable	-3	1.0; 36%
Burge, 2000[111]	751	3 years	Not reported	Not reported	Not applicable	-1.17 [-1.95 to -0.39]	**Post** 1.4; 50%
van der Valk, 2002[86]	244	6 months	Not reported	Not reported	Not applicable	-2.48 [-4.58 to -0.37]	**Post** 1.7; 57%
Studies not pooled, studies did not report data to allow pooling							

Figure 14.


Review: Combination Long-Acting B2-Agonists and Corticosteriod Analyses
Comparison: 01 Long-Acting B2-Agonists, Corticosteriods and Combination vs. Control
Outcome: 01 Exacerbations
Study or sub-category
Treatment n/N
Control n/N
RD (fixed) 95% CI
RD (fixed) 95% CI
01 Long-Acting B2-Agonists vs. Placebo
A (87, 88, 92, 96) 128/988 167/1003 -0.04 [-0.07, -0.01]
Subtotal (95% CI) 988 1003 -0.04 [-0.07, -0.01]
Total events: 128 (Treatment), 167 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 2.33 (P = 0.02)
02 Inhaled Corticosteriods vs. Placebo
B (87, 88, 92, 96) 115/997 167/1003 -0.05 [-0.08, -0.02]
Subtotal (95% CI) 997 1003 -0.05 [-0.08, -0.02]
Total events: 115 (Treatment), 167 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 3.30 (P = 0.0010)
03 Combination Long-Acting B2-Agonist and Corticosteriod vs. Placebo
C (87, 88, 92, 96) 106/985 167/1003 -0.06 [-0.09, -0.03]
Subtotal (95% CI) 985 1003 -0.06 [-0.09, -0.03]
Total events: 106 (Treatment), 167 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 3.83 (P = 0.0001)
04 Combination Long-Acting B2-Agonist and Corticosteriod vs. Long-Acting B2-Agonist
D (87, 88, 92, 96) 106/985 128/988 -0.02 [-0.05, 0.01]
Subtotal (95% CI) 985 988 -0.02 [-0.05, 0.01]
Total events: 106 (Treatment), 128 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 1.51 (P = 0.13)
05 Combination Long-Acting B2-Agonist and Corticosteriod vs. Corticosteriod
E (87, 88, 92, 96) 106/985 115/997 -0.01 [-0.04, 0.02]
Subtotal (95% CI) 985 997 -0.01 [-0.04, 0.02]
Total events: 106 (Treatment), 115 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.55 (P = 0.58)
-0.5
-0.25
0
0.25
0.5
Favors combo
Favors control

Summary Table 14. Summary of outcomes for interventions for COPD using spirometry - Combination of long-acting β2 agonists plus corticosteroids

Studies	N	Duration	Combo events, %	Control events, %	ARR % [95% CI]	Relative Risk [95%CI]	Baseline Spirometry range (FEV_1; %) predicted
Exacerbations: Salmeterol+Fluticasone vs. Placebo							
Calverley, 2003[87]	719	1 year	2.5	5.3	-3 [-6 to 0]	0.48 [0.22 to 1.04]	1.3; 45%
Mahler, 2002[96]	349	6 months	8.5	8.8	0 [-6 to 6]	0.96 [0.48 to 1.91]	1.3; 41%
Overall	1065	6 months to 1 year	4.4	6.5	-2 [-5 to 1]	0.69 [0.42 to 1.15]	1.3; 41-45%
Exacerbations: Formeterol+Budesonide vs. Placebo							
Szafranski, 2003[92]	413	1 year	16.8	25.9	-9 [-17 to -1]	0.65 [0.44 to 0.95]	1.0; 36%
Calverley 2003[88]	510	1 year	18.9	30.9	-12 [-19 to -5]	0.61 [0.45 to 0.84]	1.0; 36%
Overall	923	1 year	18	28.6	-11 [-16 to -5]	0.63 [0.49 to 0.80]	1.0; 36%
OVERALL	**1988**	**6 months to 1 year**	**10.8**	**16.7**	**-6 [-9 to -3]**	**0.64 [0.52 to 0.80]**	**1.0-1.3; 36-45%**
Exacerbations: Salmeterol+Fluticasone vs.Salmeterol							
Calverley, 2003[87]	730	1 year	2.5	2.2	0 [-2 to 3]	1.17 [0.46 to 3.00]	1.3; 45%
Mahler, 2002[96]	325	6 months	8.5	5.6	3 [-3 to 8]	1.51 [0.67 to 3.39]	1.3; 41%
Overall	1055	6 months to 1 year	4.4	3.2	1 [-1 to 3]	1.35 [0.73 to 2.49]	1.3; 41-45%
Exacerbations: Formeterol+Budesonide vs. Formeterol							
Szafranski, 2003[92]	409	1 year	16.8	18.9	-2 [-10 to 5]	0.89 [0.59 to 1.35]	1.0; 36%
Calverley 2003,[88]	509	1 year	18.9	28.6	-10 [-17 to -2]	0.66 [0.48 to 0.91]	1.0; 36%
Overall	918	1 year	18	24.3	-6 [-12 to -1]	0.74 [0.57 to 0.95]	1.0; 36%
OVERALL	**1973**	**6 months to 1 year**	**10.8**	**13**	**-2 [-5 to 0]**	**0.82 [0.65 to 1.04]**	**1.0-1.3; 36-45%**
Exacerbations: Salmeterol+Fluticasone vs.Fluticasone							
Calverley, 2003[87]	732	1 year	2.5	2.7	0 [-2 to 2]	0.94 [0.39 to 2.29]	1.3; 45%
Mahler, 2002[96]	333	6 months	8.5	10.1	-2 [-8 to 5]	0.84 [0.43 to 1.65]	1.3; 41%
Overall	1065	6 months to 1 year	4.4	5	-1 [-3 to 2]	0.88 [0.51 to 1.50]	1.3; 41-45%
Exacerbations: Formeterol+Budesonide vs. Budesonide							
Szafranski, 2003[92]	406	1 year	16.8	13.1	4 [-3 to 11]	1.28 [0.80 to 2.05]	1.0; 36%
Calverley 2003,[88]	511	1 year	18.9	24.1	-5 [-12 to 2]	0.78 [0.56 to 1.09]	1.0; 36%
Overall	917						
OVERALL	**1982**	**6 months to 1 year**	**10.8**	**11.5**	**-1 [-4 to 2]**	**0.92 [0.72 to 1.17]**	**1.0-1.3; 36-45%**
Mortality: Salmeterol+Fluticasone vs. Placebo							
Hanania, 2003[91]	363	6 months	0	0	0 [-1 to 1]	Not estimable	1.3; 42%
Mahler, 2002[96]	346	6 months	0	1.7	-2 [-4 to 1]	0.16 [0.01 to 3.01]	1.3; 41%
Overall	709	6 months	0	<1	-1 [-2 to 0]	0.16 [0.01 to 3.01]	1.3; 42%

Summary Table 14. Summary of outcomes for interventions for COPD using spirometry - Combination of long-acting β2 agonists plus corticosteroids (continued)

Studies	N	Duration	Combo events, %	Control events, %	ARR % [95% CI]	Relative Risk [95%CI]	Baseline Spirometry range (FEV_1; %) predicted
Mortality: Formeterol+Budesonide vs. Placebo							
Szafranski, 2003[92]	413	1 year	2.9	4.4	-2 [-5 to 2]	0.66 [0.24 to 1.81]	1.0; 36%
Calverley 2003,[88]	510	1 year	2	2	0 [-2 to 2]	1.01 [0.30 to 3.44]	1.0; 36%
Overall	923	1 year	2.4	3.0	-1 [-3 to 1]	0.78 [0.36 to 1.70]	1.0; 36%
OVERALL	**1632**	**6 months to 1 year**	**1.4**	**2.1**	**-1 [-2 to 1]**	**0.66 [0.32 to 1.38]**	**1.0-1.3; 36-42%**
Mortality: Salmeterol+Fluticasone vs.Salmeterol							
Hanania, 2003[91]	355	6 months	0	0	0 [-1 to 1]	Not estimable	1.3; 42%
Mahler, 2002[96]	325	6 months	0	0	0 [-1 to 1]	Not estimable	1.3; 41%
Overall	680	6 months	Not applicable	Not applicable	0 [-1 to 1]	Not estimable	1.3; 41-42%
Mortality: Formeterol+Budesonide vs. Formeterol							
Szafranski, 2003[92]	409	1 year	2.9	3	0 [-3 to 3]	0.97 [0.32 to 2.95]	1.0; 36%
Calverley 2003,[88]	509	1 year	2	5.1	-3 [-6 to 0]	0.39 [0.14 to 1.07]	1.0; 36%
Overall	918	1 year	2.4	4.2	2 [-4 to 1]	0.57 [0.27 to 1.19]	1.0; 36%
OVERALL	**1598**	**6 months to 1 year**	**1.4**	**2.4**	**-1 [-2 to 0]**	**0.56 [0.26 to 1.19]**	**1.0-1.3; 36-42%**
Mortality: Salmeterol+Fluticasone vs.Fluticasone							
Hanania, 2003[91]	361	6 months	0	0	0 [-1 to 1]	Not estimable	1.3; 42%
Mahler, 2002[96]	333	6 months	0	0	0 [-1 to 1]	Not estimable	1.3; 41%
Overall	694	6 months	Not applicable	Not applicable	0 [-1 to 1]	Not estimable	1.3; 41-42%
Mortality: Formeterol+Budesonide vs. Budesonide							
Szafranski, 2003[92]	406	1 year	2.9	2.5	0 [-3 to 4]	1.14 [0.35 to 3.68]	1.0; 36%
Calverley 2003[88]	511	1 year	2	2.3	0 [-3 to 2]	0.84 [0.26 to 2.73]	1.0; 36%
Overall	917	1 year	2.4	2.4	0 [-2 to 2]	0.98 [0.43 to 2.24]	1.0; 36%
OVERALL	**1611**	**6 months to 1 year**	**1.4**	**1.4**	**0 [-1 to 1]**	**0.98 [0.43 to 2.24]**	**1.0-1.3; 36-42%**

Studies	N	Duration	Combination: mean change	Control: change		Weighted Mean Difference (95%CI)	Baseline Spirometry range (FEV1; %) predicted
St George's Respiratory Questionnaire - Mean units of change: Salmeterol+Fluticasone vs. Placebo							
Calverley, 2003[87]	719	1 year	Not applicable	Not applicable	Not applicable	-2.2 [-3.3 to -1.1]	1.3; 45%
Exacerbations: Formeterol+Budesonide vs. Placebo							
Szafranski, 2003[92]	413	1 year	Not applicable	Not applicable	Not applicable	-3.9 [-6.8 to -1.0]	1.0; 36%
Calverley 2003[88]	510	1 year	Not applicable	Not applicable	Not applicable	-7.5	1.0; 36%
OVERALL	***from SIN***					**-2.4 [-3.4 to -1.4]**	**1.0-1.3; 36-45%**

Summary Table 15. Summary of outcomes for trials using combination of long-acting β2 agonists plus corticosteroids: Monotherapies and combination therapy in comparison to placebo

Outcome / study	Treatment n / N (%)	Placebo n / N (%)	Absolute Risk Reduction (%) [95% CI]	Relative Risk [95% CI]	Baseline FEV_1; % predicted*	Exacerbation definition
Exacerbations						
Calverley 2003[87]						
Salmeterol	8 / 372 (2.2)	19 / 361 (5.3)	-3 [-6 to 0]	0.41 [0.18, 0.92]	1.3; 45	Treatment-related COPD exacerbation
Fluticasone	10 / 374 (2.7)		-3 [-5 to 0]	0.51 [0.24, 1.08]		
Combination	9 / 358 (2.5)		-3 [-6 to 0]	0.48 [0.22, 1.04]		
Mahler 2002[96]						
Salmeterol	9 / 160 (5.6)	16 / 181 (8.8)	-3 [-9 to 2]	0.64 [0.29, 1.40]	1.3; 41	Exacerbation of COPD leading to study withdrawal
Fluticasone	17 / 168 (10.1)		1 [-5 to 7]	1.14 [0.60, 2.19]		
Combination	14 / 165 (8.5)		0 [-6 to 6]	0.96 [0.48, 1.91]		
Calverley 2003[88]						
Formoterol	73 / 255 (28.6)	79 / 256 (30.9)	-2 [-10 to 6]	0.93 [0.71, 1.21]	1.0; 36	Serious COPD adverse event leading to death, hospitalization, disability or withdrawal from study
Budesonide	62 / 257 (24.1)		-7 [-14 to 1]	0.78 [0.59, 1.04]		
Combination	48 / 254 (18.9)		-11 [-16 to -5]	0.61 [0.45, 0.84]		
Szafranski, 2003[92]						
Formoterol	38 / 201 (18.9)	53 / 205 (25.9)	-7[-15 to 1]	0.73 [0.51, 1.06]	1.0; 36	COPD event
Budesonide	26 / 198 (13.1)		-13 [-20 to -5]	0.51 [0.33, 0.78]		
Combination	35 / 208 (16.8)		-9 [-17 to -1]	0.65 [0.44, 0.95]		
Mortality						
Hanania, 2003[91]						
Salmeterol	0 / 177	0 / 185	0 [-1 to 1]		1.3; 42	
Fluticasone	0 / 183		0 [-1 to 1]			
Combination	0 / 178		0 [-1 to 1]			
Mahler 2002[96]						
Salmeterol	0 / 160	3 / 181	-2 [-4 to 1]	0.16 [0.01, 3.10]	1.3; 41	
Fluticasone	0 / 168		-2 [-4 to 0]	0.15 [0.01, 2.96]		
Combination	0 / 165		-2 [-4 to 1]	0.16 [0.01, 3.01]		
Calverley 2003[88]						
Salmeterol	13 / 255 (5.1)	5 / 256 (2.0)	3 [0 to 6]	2.61 [0.94, 7.21]	1.0; 36	
Budesonide	6 / 257 (2.3)		0 [-2 to 3]	1.20 [0.37, 3.87]		
Combination	5 / 254 (2.0)		0 [-2 to 2]	1.01 [0.30, 3.44]		
Szafranski, 2003[92]						
Salmeterol	6 / 201 (3.0)	9 / 205 (4.4)	-1 [-5 to 2]	0.68 [0.25, 1.88]	1.0; 36	
Budesonide	5 / 198 (2.5)		-2 [-5 to 2]	0.58 [0.20, 1.69]		
Combination	6 / 208 (2.9)		-2 [-5 to 2]	0.66 [0.24, 1.81]		

*Pooled for all treatment arms

Figure 15. Potential role of spirometry for monitoring patients with symptomatic COPD

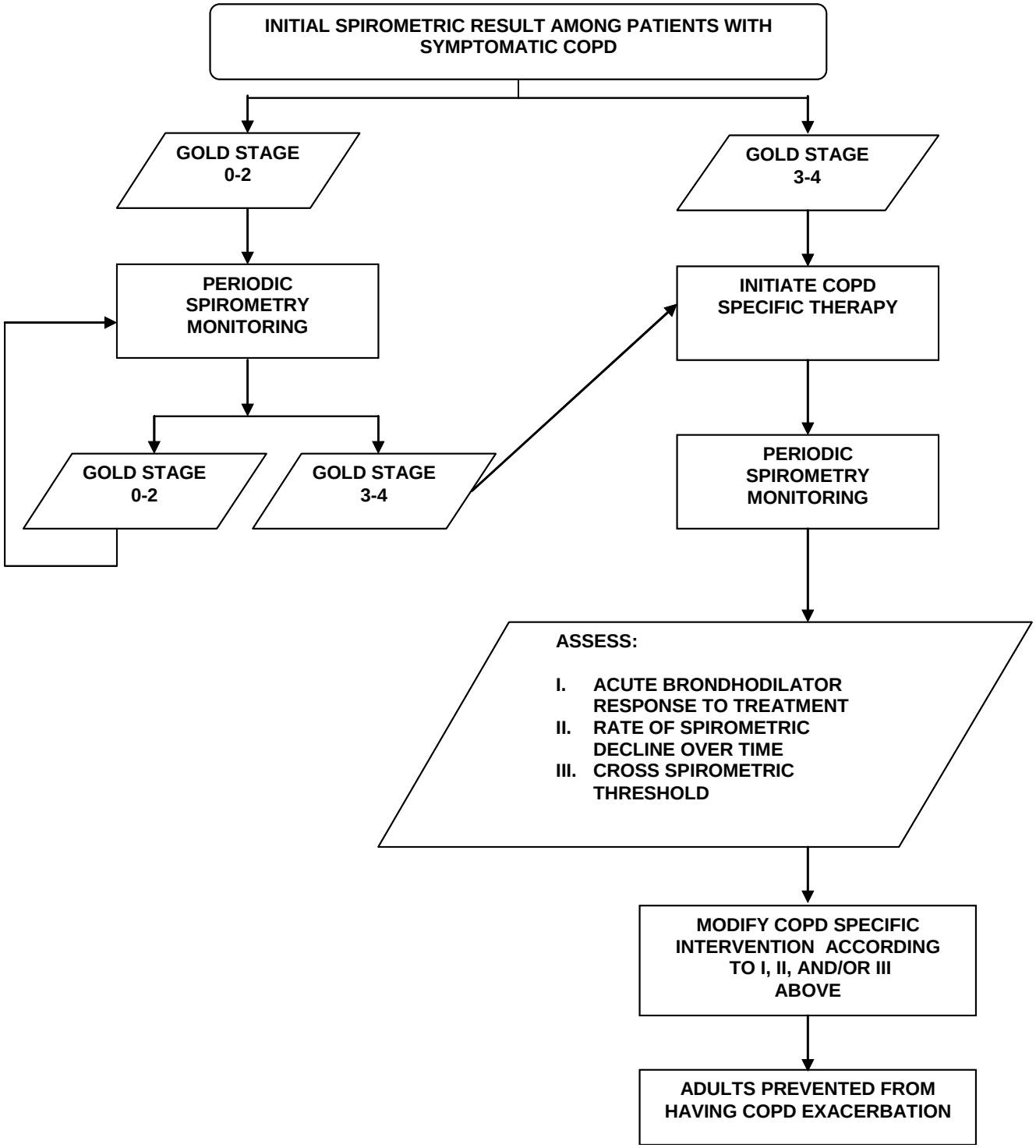


Figure 16. Spirometric and symptom evaluation and subsequent treatment according to smoking, symptom, and spirometric status among adults in primary care clinic

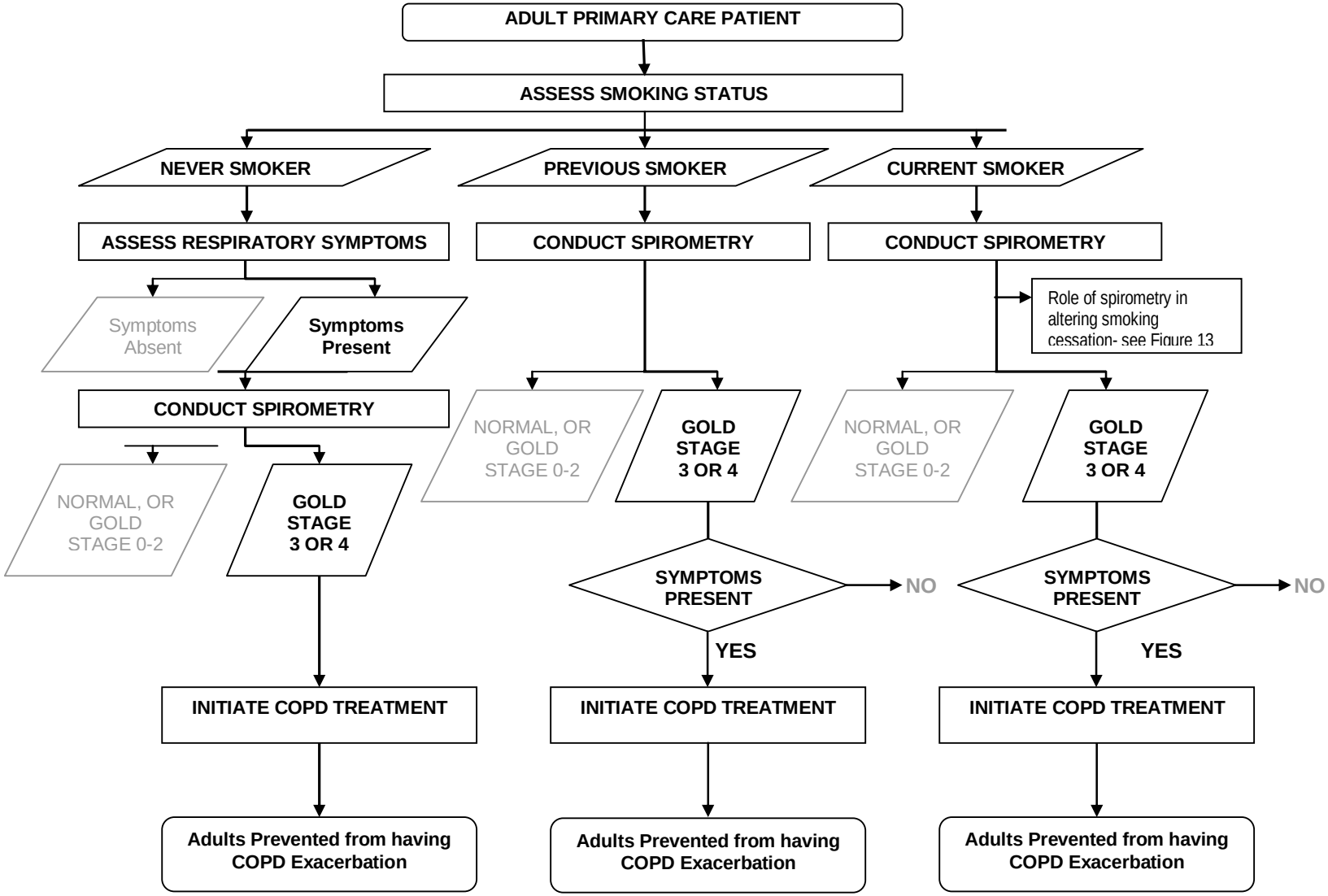
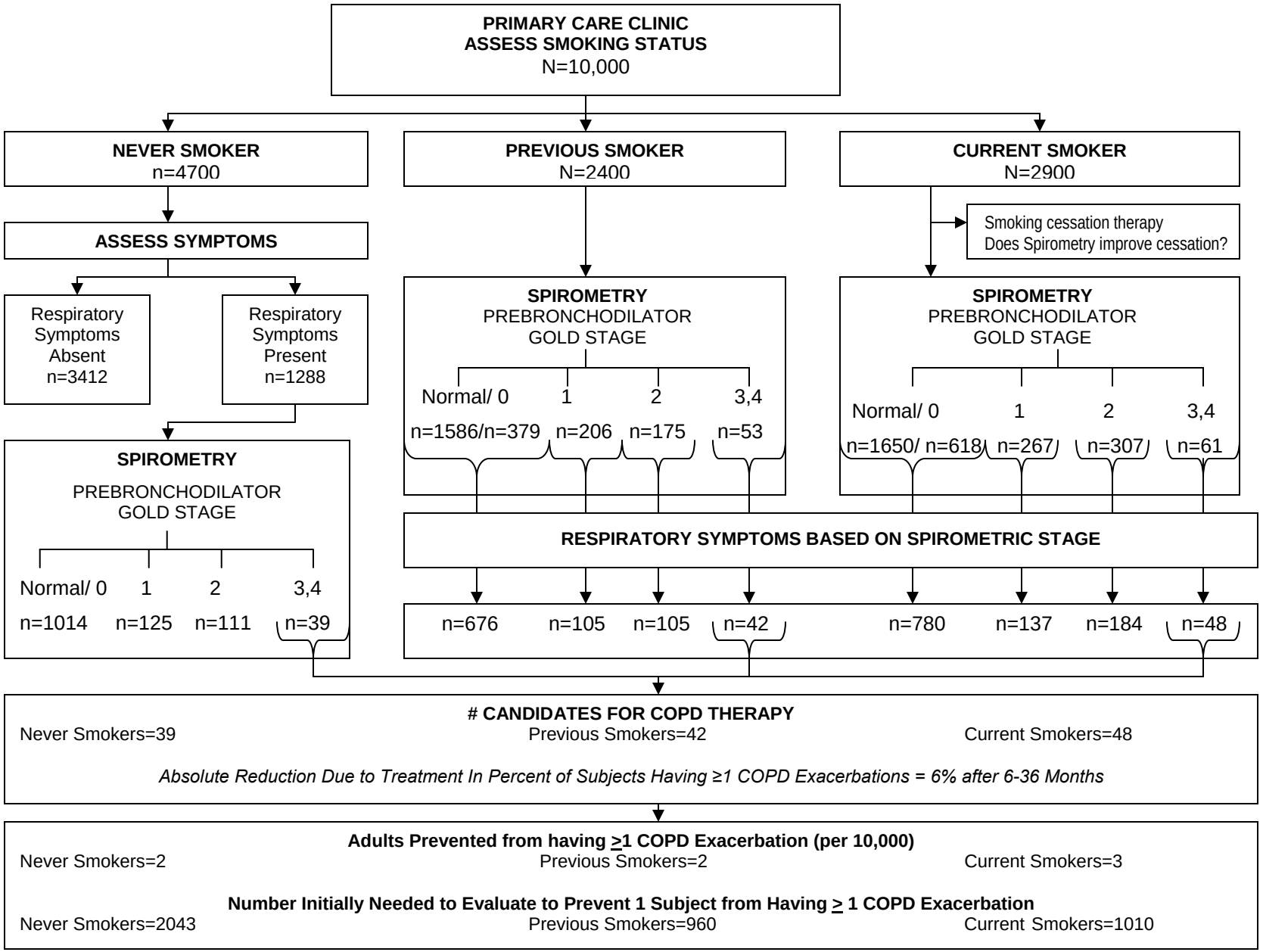


Figure 17. Number of adults evaluated, treated, and receiving benefit from spirometric in primary care clinics



Chapter 4. Discussion

Summary

Prevalence of Airflow Obstruction, Chronic Obstructive Lung Disease, and Use of Spirometry for Diagnosis and Case-Finding

COPD is a major health problem resulting in considerable morbidity, mortality, loss of productivity, and utilization of health care resources. Individuals with respiratory symptoms compatible with COPD are often not diagnosed or are misdiagnosed. Compared to clinical examination alone, spirometry, in combination with clinical examination, improves diagnostic accuracy of clinically significant disease in adults with respiratory symptoms (especially dyspnea) that are compatible with COPD. No single item or combination of items from the clinical examination rules out spirometrically determined airflow limitation. The best clinical finding associated with decreased likelihood of airflow limitation is a history of never having smoked cigarettes (especially in patients without a history of wheezing and without wheezing on examination). The best findings associated with increased likelihood of airflow limitation are objective wheezing, barrel chest, positive match test result, rhonchi, hyperresonance, forced expiratory time greater than 9 seconds, and subxyphoid apical impulse. A finding of two of the following virtually rules in airflow limitation: 70-pack years or more of smoking, decreased breath sounds, or history of COPD. Three findings predict the likelihood of airflow limitation in men: years of cigarette smoking, subjective wheezing, and either objective wheezing or peak expiratory flow rate. The clinical history, respiratory symptom status and physical examination are of limited value in determining whether an individual has airflow obstruction.

Based on NHANES results, 12.8 percent of the adult population reported a current or past clinical diagnosis of OLD. However, only 17.4 percent had 1987-ATS defined low lung function, suggesting that most individuals who report a diagnosis of emphysema or chronic bronchitis of COPD do not have airflow obstruction. Of individuals reporting a diagnosis of COPD, 25.6 percent reported chronic phlegm and 48 percent reported shortness of breath; the symptom most likely to affect quality of life and predict mortality.

The prevalence and severity of airflow obstruction in general populations vary across countries. The biggest factor in varying prevalence estimates is the criteria used to define airflow obstruction and clinically significant COPD. Within the same population the prevalence of disease defined as “at risk” or having air flow obstruction can vary more than three fold by altering definition thresholds. The prevalence of airflow obstruction and symptoms increases with age and a history of smoking. There are relatively few differences according to race or gender after accounting for age and smoking status. Increasing severity of spirometrically determined airflow obstruction is associated with respiratory symptom prevalence. However, respiratory symptoms are not unique to COPD and may be due to other medical conditions (e.g., heart failure, deconditioning) even in the presence of airflow obstruction. Many individuals with respiratory symptoms have normal airflow and nearly one-quarter of individuals with severe to very severe airflow obstruction have no respiratory symptoms. Impairment in health status is

most commonly associated with dyspnea and typically not evident until individuals have postbronchodilator airflow obstruction of GOLD 3,4 severity (FEV_1 <50 percent predicted). Less than 5 percent of the U.S. population has respiratory symptoms and moderate, severe, or very severe airflow obstruction. A substantial portion of these individuals may not have been diagnosed with COPD and many who have reported a clinical diagnosis of COPD do not have airflow obstruction. Spirometry performed in the absence of bronchodilator testing (a method likely to be encountered in primary care clinics) identifies over 20 percent of the U.S. adult population and 25 percent of current smokers as having "abnormal airflow" or being "at-risk." Prevalence increases with age and a broader definition of what constitutes airflow obstruction. The vast majority of individuals with airflow obstruction detected by case finding with spirometry have mild airflow obstruction and no dyspnea.

Spirometry, while important in determining prognosis, whether respiratory symptoms are likely due to COPD, and whether these symptoms would improve with COPD specific therapy is not an ideal test for establishing a diagnosis of clinically significant COPD. Using physiologic variables to define clinically significant COPD differs from other chronic conditions such as hypertension, diabetes, or hyperlipidemia that use laboratory values to define clinically significant disease and evaluate treatment effectiveness even in the absence of symptoms. Unlike those conditions, interventions for COPD, except for oxygen therapy in individuals with resting hypoxemia and smoking cessation have not been shown to be effective in asymptomatic adults, do not alter the laboratory parameter used to determine disease status (spirometry) acutely or over prolonged followup, and do not reduce mortality. Additionally, in subjects with COPD clinical outcomes are not associated with spirometric response to treatment and the symptom of dyspnea is a better predictor of clinical outcomes than spirometry. Instead, the benefits of COPD interventions are to improve patient's existing symptoms and functional status. Spirometric testing is of value to improve diagnostic accuracy in individuals reporting bothersome respiratory symptoms. Individuals should not be labeled as having COPD or treated with COPD-specific medications in the absence of respiratory symptoms and spirometric testing that demonstrates airflow obstruction.

Spirometry for Smoking Cessation

Smoking cessation is the most important intervention to reduce the development and/or progression of airflow obstruction and symptomatic COPD. Quitting smoking is also an important factor in reducing a wide range of other medical conditions that result in considerable morbidity, mortality, and health care costs. Thus, relatively small improvements in smoking cessation rates due to feasible interventions would be beneficial. Except for smoking cessation, no interventions have been demonstrated to reduce spirometric decline in lung function or prevent the development of respiratory symptoms in asymptomatic individuals within a 3-year period.

However, all adults should have smoking status assessed regardless of symptom or spirometric status. Counseling strategies and interventions, including pharmacologic therapy, should be offered for those willing to quit. Smoking cessation rates and motivation to quit may differ slightly according to spirometric and symptom status. However, results are inconsistent and the variability and magnitude of the difference according to these categories is unlikely to provide independent aid for clinicians in determining an individual patient's likelihood of quitting or whether targeted programs would be beneficial.

The evidence from non-randomized studies indicates that biological markers, including spirometry, may have some potential as a motivational tool as part of a multidisciplinary approach to assist patients and clinicians improve smoking cessation rates. The lack of controls makes assessment of the independent contribution of spirometry problematic. Randomized trials of other biomarkers for improving smoking cessation have generally been negative. Improvements in smoking cessation rates are generally of small magnitude and generally require multimodality therapy. Thus, there is little evidence for the biologic plausibility that spirometry would provide more than small improvements in smoking cessation.

Baseline symptom or spirometry status appears to be of limited clinical use in risk stratification and in assisting clinicians' target smoking cessation strategies. Efforts to improve smoking cessation rates in subjects with COPD have led to a modest increase in abstinence. However, because smoking has a wide range of serious adverse effects, even fairly small differences in cessation rates may be clinically important if they could be achieved feasibly in clinical settings. The only randomized trial to demonstrate a long-term improvement in smoking cessation rates among subjects with mild to moderate COPD or judged to be at increased risk used a pharmacologic intervention provided free of charge in combination with an intensive program of cessation and maintenance counseling. All subjects were provided their spirometric results. The intensity of this type of smoking cessation program may not be generalizable to primary care clinics. Differences in symptom status and baseline spirometric values between subjects who quit and those who continued to smoke were small and inconsistent in direction.

The evidence from randomized controlled trials assessing the effectiveness of obtaining spirometry and discussing results with current smokers in order to improve smoking cessation is limited and flawed. However, the evidence indicates that spirometry is unlikely to provide more than small improvements in smoking cessation rates. The intervention arms of six of the seven studies involved multiple components that are known to alter smoking cessation rates or had control groups that did not receive smoking cessation advice/therapies.[80-85] Therefore they do not allow for the independent assessment of the effects of spirometry. The only study that assessed the independent effect of spirometry failed to demonstrate a benefit (abstinence rate difference of 1.0 percent).[79] This study was relatively small, suffered from poor physician and patient compliance, and did not obtain spirometry directly in the primary care setting. Two studies approximate the independent effects of spirometry on smoking cessation. Their results are conflicting.[80,81] One showed an absolute point-prevalent abstinence rate difference of 13.3 percent at 12 months that favored the spirometry group.[80] The other had an absolute point-prevalent abstinence rate difference of 5 percent at 9 months that favored the control group.[81] None of the study results were statistically significant.

There is no information whether spirometry improves the prognosis of a subject's willingness to quit and/or addiction to tobacco. The only study of a mandated program that stratified quit rates by spirometry results reported less abstinence in patients with abnormal spirometry.[85] This suggests the possibility of recidivism among patients with abnormal spirometry. Spirometric results may theoretically provide information that enhances physician compliance and/or effectiveness in providing smoking cessation therapies. Additionally, it may motivate smokers to quit. However, there is little empiric evidence from randomized controlled trials that assesses the effectiveness and potential adverse effects of spirometry for smoking cessation.

Spirometry for Initiating, Monitoring, and Modifying Treatment

Results from NHANES indicate that the majority of individuals reporting a clinical diagnosis of COPD have normal prebronchodilator airflow on spirometry. In the absence of spirometric testing, these individuals likely were incorrectly diagnosed and may have received unnecessary and ineffective treatment. Initiating COPD specific interventions in subjects with respiratory symptoms should not be done unless spirometric testing is performed and confirms airflow obstruction.

Treatment trials typically were of short duration and enrolled subjects with an established clinical diagnosis of COPD, activity limiting and bothersome respiratory symptoms (especially frequent exacerbations), and moderate to very severe airflow obstruction on baseline spirometry. No trials adjusted interventions according to an individual's baseline or followup spirometry, spirometric response to treatment, slope of spirometric values over time, or crossing a "threshold" spirometric value. Compared to placebo inhaled corticosteroids and long-acting bronchodilators reduced the absolute percentage of individuals having at least one exacerbation over a 3 month to 5 year time period by 5-6 percent. Comparative studies suggest that long acting β agonist and long-acting anticholinergics are of similar efficacy in preventing COPD exacerbations, but inhaled corticosteroids were slightly more effective than LABA. Short-acting anticholinergics are not superior to placebo, slightly less effective than long-acting anticholinergics, and comparable to short acting β agonists. These benefits were almost exclusively limited to individuals with a previous clinical diagnosis of COPD who had activity limiting or bothersome respiratory symptoms and baseline spirometry indicating severe to very severe airflow obstruction (GOLD Stage 3,4). Treatment effectiveness did not vary according to dose of pharmacologic interventions. Hospitalization rates were rarely reported and were lower compared to placebo by 4-7 percent.

The average improvement in respiratory health status due to inhaled corticosteroids and bronchodilators did not achieve a previously determined level of clinical significance even in individuals with severe airflow obstruction. However, individual patients may obtain a large and noticeable benefit and studies of tiotropium indicated that a greater percentage of subjects receiving tiotropium achieved a clinically significant improvement than those receiving placebo. Inhaled bronchodilators and corticosteroids did not alter spirometric decline or reduce mortality in subjects with baseline spirometry indicating airflow obstruction, though the number of subjects and duration of studies may be inadequate to conclusively conclude that they are ineffective for mortality.

Interventions other than smoking cessation do not prevent the development of respiratory symptoms among individuals not reporting these symptoms at baseline. These interventions also do not reduce mortality or spirometric decline in lung function. Therefore, treatment benefits are almost exclusively due to improvement in bothersome respiratory symptoms and possibly respiratory related health status among individuals with activity limiting respiratory symptoms. Many subjects enrolled in trials with mild to moderate airflow obstruction did not have activity limiting respiratory symptoms (or reported no symptoms) or a prior diagnosis of COPD. Most were detected based on spirometry in a fashion likely to occur with broad based primary care testing. The longest trial had a followup of 5 years, and thus the effectiveness of these agents on COPD outcomes at longer duration is not known. Pooled analysis of three trials of inhaled corticosteroids enrolling approximately 2,500 subjects with a mean FEV_1 >2L (GOLD Stage 0-2) and followed for 3 or more years failed to demonstrate a benefit in clinical outcomes, although

there was a trend towards a reduction of mortality. One of these studies[114] demonstrated a statistically significant but clinically small improvement in respiratory symptoms and physician visits. In the COPE trial analysis of the subgroup of patients with a FEV_1 value less than 50 percent predicted (low FEV_1 group) suggests that the improvement in time to first exacerbation due to fluticasone is driven by this group. In subjects who smoke at baseline and have normal to moderate airflow obstruction (GOLD Normal-Stage 2), ipratropium did not prevent the development of dyspnea, cough, and sputum, or respiratory hospitalizations at 3 years regardless of presence or absence of baseline respiratory symptoms.

Long-acting monotherapies provide similar reductions in COPD exacerbations among symptomatic individuals with severe to very severe airflow obstruction. There are differences in their adverse effects. Five trials compared monotherapy using either long-acting β agonists or inhaled corticosteroids versus combination therapy and versus placebo. Compared with placebo the absolute difference of having at least one COPD exacerbation was: 3.7 percent for long-acting beta agonists, 5.2 percent for inhaled corticosteroids, and 6 percent for combination therapy of long acting β agonists and corticosteroids. Combination therapy with LABA and inhaled corticosteroids did not significantly reduce exacerbations or mortality compared to corticosteroid monotherapy. The combination of short-acting anticholinergic plus short- or long-acting β agonist is not superior to short-acting anticholinergics alone. No studies are available to determine if adding long-acting anticholinergics to inhaled corticosteroids or β agonists reduces exacerbations or improves respiratory symptoms compared to monotherapy. Pulmonary rehabilitation provides a small improvement in clinical outcomes including respiratory health status measures during the period of the rehabilitation in individuals with respiratory symptoms and severe to very severe airflow obstruction.

In symptomatic patients with severe to very severe airflow obstruction the choice of pharmacologic agents depends primarily on costs and adverse effects because effectiveness is similar. In studies that compared different doses of the same drug treatment effectiveness did not vary. The primary demonstrated benefit of these interventions is in reducing exacerbations (and possibly hospitalizations) rather than an average clinically noticeable benefit in dyspnea. Exacerbations are relatively rare and it is difficult to assess whether an average patient is achieving clinical improvement. Thus, treatment should be continued even if patients do not report symptomatic improvement. This indicates that dose titration or modification is not beneficial. However, the long-acting inhaled anti-cholinergic agent, tiotropium, is superior to the short-acting anti-cholinergic, ipratropium, in individuals with moderate to severe respiratory symptoms and airflow obstruction.

Spirometry may be useful for identifying a threshold value to initiate treatment in adults with bothersome respiratory symptoms (especially dyspnea and frequent exacerbations) with inhaled corticosteroids, bronchodilators, or pulmonary rehabilitation. This threshold appears to be at a postbronchodilator FEV_1 below approximately 50 percent predicted (GOLD Stage 3,4). There is evidence to suggest that monitoring subjects' spirometric response to therapy or change over time while on therapy does not improve outcomes. Limited data suggest that an individual's response to inhaled bronchodilators is quite variable and that spirometric response to treatment is not associated with improvement in clinical outcomes. An individual's spirometric change over time is also quite variable and except for identifying a spirometric threshold to initiate therapy does not improve treatment outcomes. Modification of therapies in the absence of adverse effects or compliance issues is not supported by evidence.

Spirometry for Prognosis

Spirometry provides independent prognostic value regarding health status, rate of exacerbations, morbidity, and mortality. However, degree of dyspnea appears to be a better predictor of mortality than FEV_1 and a multidimensional grading system that assessed body-mass index, spirometry, dyspnea, and exercise capacity (the BODE index) predicted death better than spirometry alone. Baseline spirometry predicts rate of spirometric decline over time in male smokers. The probability of survival at 28 months of followup in subjects with established COPD was 90 percent and 75 percent in subjects with ATS-1995 Stage I, II, and III disease. Four factors, when combined, provide an index that predicted the risk of death better than FEV_1 alone. These include (B) body mass index; (O) airflow obstruction; (D) dyspnea and (E) exercise capacity on 6-minute walk. The presence of current respiratory symptoms is a better predictor than spirometric value of having future respiratory symptoms. Subjects with chronic sputum production and normal spirometry (Stage GOLD 0 condition) are not at higher risk for developing airflow obstruction than individuals without COPD. Over half of these GOLD 0 subjects did not have sputum production at 10 years of followup.

Estimating the Number Needed to Evaluate with Spirometry and Symptom Assessment

The number that would need evaluation by spirometry and symptom assessment to provide clinical benefit was estimated based on data from NHANES III, as well as efficacy data from intervention trials. If a primary care clinic population was comprised of 10,000 adults with similar characteristics as NHANES III respondents (47 percent never smokers) then approximately 6,588 would undergo spirometric testing for either the presence of symptoms or because they were judged to be at increased risk due to smoking status. Thirty-nine "never smoking" adults (0.8 percent), 42 "previous smokers" (1.7 percent), and 48 "current smokers" (1.6 percent) have both respiratory symptoms and airflow obstruction severity (approximately GOLD Stage 3,4) that might make them candidates for COPD-specific treatment in addition to smoking cessation and influenza vaccination (129/10,000 or 1.3 percent of the total clinic population). Using the pooled efficacy data from treatment trials of inhaled bronchodilators or corticosteroids, it can be estimated that approximately 2,043 "never smoking" adults, 960 "previous smokers," and 1,010 "current smokers" would have to have respiratory symptom and spirometry evaluation with subsequent selective treatment to prevent one subject from having one or more COPD exacerbations over a 6-36 month period. A total of 7 out of 10,000 primary care adults would have prevention of one or more COPD exacerbations. The pooled efficacy data indicate that treatment would not reduce mortality (except for oxygen in subjects with resting hypoxemia). The average improvement in respiratory health status among treated subjects would not be of clinical significance though approximately 18 of these 129 treated patients (14 percent) would have a clinically noticeable improvement in health status. Treatment with combination therapy would not be superior to inhaled monotherapy, and, on average, therapy in asymptomatic individuals or those with mild to moderate airflow obstruction would not improve or prevent symptoms. If subjects with moderate airflow obstruction (approximately GOLD Stage 2) were also assumed to benefit in a similar fashion, then approximately 529 adults would be candidates and 32 (0.3 percent) would have reductions in exacerbations and 76 subjects (0.8% of all adults) would have noticeable improvements in respiratory health status.

The number of eligible candidates for COPD therapy would increase from these NHANES estimates if spirometric testing and symptom assessment were limited to middle age or older adults (e.g., age 50 or greater) because the risk of airflow obstruction and symptoms increases with age. However, our estimates are otherwise optimistic because they assume that adults with severe airflow obstruction and any respiratory symptom including symptoms limited to wheeze, cough, or sputum production would benefit in an amount similar to subjects enrolled in treatment trials who had known COPD, dyspnea, and experienced frequent exacerbations. Cost associated with testing and treatment would be large and include bronchodilator testing not typically performed in primary care settings as well as assessing individuals with risk exposure beyond a personal smoking history. Costs could be reduced considerably with no apparent reduction in clinical effectiveness by targeting spirometry to individuals with respiratory symptoms, especially current and former smokers 40-50 years of age or older who have bothersome dyspnea. Spirometry could improve treatment costs if it led to treatment being targeted towards individuals with bothersome respiratory symptoms, especially dyspnea and exacerbations who have severe to very severe airflow obstruction. The existing evidence indicates that spirometry is unlikely to provide more than a small improvement in sustained smoking abstinence and that it is of limited clinical use in predicting subsequent smoking cessation rates.

Spirometric testing in combination with clinical examination is useful in symptomatic individuals for improving diagnostic accuracy compared to clinical examination alone. It helps to ensure that COPD-specific therapy is not initiated in individuals who do not have at least moderate airflow obstruction. Among adults with bothersome respiratory symptoms, spirometry may be useful for determining at what threshold level of airflow obstruction to initiate therapy. Spirometric testing in symptomatic adults could improve physician use of COPD-specific treatments to subjects likely to benefit (i.e., those with bothersome respiratory symptoms and severe to very severe airflow obstruction) while reducing the cost and side effects of unnecessary or ineffective treatments. In subjects with COPD acute spirometric response to bronchodilators is variable, potentially misleading, does not predict long-term spirometric decline, and is not associated with clinical response to treatment. Responsiveness to bronchodilators in younger adults with respiratory symptoms is likely to be beneficial if asthma is suspected. However, it is not useful for assessing clinical response to therapy or determining treatment options in subjects with COPD. Periodic spirometric testing to monitor and modify treatment has not been evaluated. However, this method is unlikely to be beneficial because different types of pharmacologic management have similar efficacy, relative treatment effectiveness cannot be determined by baseline spirometry or spirometric response to treatment, there is considerable intra-individual variation in spirometric results, pharmacologic therapies do not alter the rate of spirometric decline, clinical outcomes are not associated with spirometric response to therapy, and dose titration or combination therapy is not more effective than fixed dose monotherapy. Choice of therapy should be determined by patient preference, cost, and adverse effects.

Conclusion

Irreversible airflow obstruction as determined by spirometry in individuals with respiratory symptoms is the most widely established criterion for establishing the diagnosis of COPD. It is useful for determining whether treatment is likely to be beneficial and estimating prognosis.

While respiratory symptoms are quite common in adults, the vast majority of these individuals do not have clinically significant airflow obstruction, and many who have moderate or worse airflow obstruction do not have bothersome respiratory symptoms. Spirometry in combination with clinical examination improves diagnostic accuracy in adults with respiratory symptoms compared to clinical examination alone. It is useful in determining the presence and severity of airflow obstruction prior to establishing a diagnosis or initiating disease-specific therapy. Spirometry is likely to demonstrate that some adults with a previous clinical diagnosis of COPD do not have airflow obstruction and should not be labeled or receive COPD specific therapy. Increased use of spirometry primary care settings for adults with bothersome respiratory symptoms, especially dyspnea, would identify the small percentage of individuals with severe to very severe airflow obstruction who have not received a clinical diagnosis of COPD and might benefit from disease specific therapies.

A strategy of conducting spirometric testing of all at-risk adults would require testing a large number of asymptomatic individuals or those with nonspecific and nonbothersome respiratory symptoms. It would result in considerable testing costs and health care personnel time and resources. Some individuals with abnormal airflow will have other medical conditions causing respiratory symptoms (e.g., heart failure). As criteria for defining disease expand, the number of adults labeled with disease markedly increases. If spirometric measures of airflow obstruction are used as sufficient criteria to establish disease, then the vast majority of adults newly diagnosed by spirometric testing will be asymptomatic or have nondisabling respiratory symptoms. Some may be treated unnecessarily or not receive effective interventions for other medical conditions.

Spirometric testing is unlikely to alter smoking cessation rates or be useful for monitoring response to therapy or modifying treatments. The average benefits of therapy are primarily seen in those with severe to very severe airflow obstruction (FEV_1 < 50% predicted, GOLD Stage 3,4 disease) and related to reduction in COPD exacerbations. Treatment, beyond smoking cessation and influenza vaccination, does not prevent symptom development in asymptomatic individuals over a 3 year period. None of the interventions other than smoking cessation alter the rate of decline of spirometry and clinical response to treatment is not associated with spirometric changes. Spirometry provides independent prognostic value for predicting respiratory and overall morbidity and mortality in individuals with established COPD. However, the degree of dyspnea appears to be a better predictor than spirometry. Patients with normal spirometry and chronic sputum production (GOLD 0) do not appear to be a group “at increased risk” for development of clinically significant airflow obstruction.

Future studies are required to determine if spirometry improves smoking cessation rates, if treatment effectiveness in patients with established COPD varies according to an individual’s baseline or followup spirometric value, and if treatment is effective in individuals with airflow obstruction who do not report respiratory symptoms.

Limitations

Our report has limitations. We used NHANES III population-based spirometry data performed without bronchodilator testing to estimate prevalence of airflow obstruction, symptom status, and previous reported clinical diagnosis of COPD. We did not assess the benefits or

harms of spirometry (including use of bronchoresponsiveness) for other respiratory conditions including asthma and restrictive lung disease. NHANES is a national probability sampling of adults and may not directly reflect the population to be evaluated in primary care clinics. Many NHANES respondents were younger and thus at lower risk of having COPD. We were unable to determine prevalence of specific respiratory symptoms by postbronchodilator GOLD stage category in subgroups of interest (smoking status, age, race, gender). We used estimates derived from spirometry done in the absence of bronchodilators for the total population sample. Furthermore, we could not determine the number of individuals with a diagnosis of COPD by GOLD stage nor the accuracy or methods used for diagnosis. Our report was limited to subjects with COPD. We did not assess patients with asthma or restrictive lung disease.

Failing to find a benefit that spirometry improves smoking cessation does not mean that a benefit does not exist. Available RCT evidence was limited and of poor quality. There was also no evidence that spirometric testing led to adverse effects such as lower smoking cessation, poorer quality of life, or misuse of smoking cessation interventions. As noted, even a relatively small improvement in smoking cessation could have large population benefits due to the high prevalence and large and diverse adverse health effects of smoking.

Data regarding COPD-specific treatments typically provided outcomes for the whole population enrolled and did not report results for subgroups according to respiratory or spirometric status. However, results from the few studies that provided this information suggest that interventions are most effective in individuals with the combination of activity limiting respiratory symptoms and severe to very severe airflow obstruction. While average improvement in respiratory symptoms was less than considered clinically significant (especially for dyspnea) it is likely that individual patient's response to therapy varies. Secondary analyses determined that some individuals found a clinically significant improvement in respiratory health status and likely dyspnea, cough, and sputum production. However, based on the available data, interventions appear to be most effective at reducing exacerbations rather than the patient's perception of dyspnea that most affects day-to-day health status. While mortality was not improved with these interventions, studies were typically of short duration and the confidence intervals around the point estimate for effectiveness were wide. Clinically significant improvements in mortality due to interventions beyond oxygen therapy may exist.

Our report is not a formal cost effectiveness analysis. A previous cost-effectiveness analysis concluded that inhaled corticosteroids were cost effective in subjects with ATS Stage 2-3 disease (GOLD Stage 3,4). We used the available information from NHANES regarding airflow obstruction performed in the absence of bronchodilator testing and respiratory symptom status prevalence assessed by responses to survey questions, optimistic assumptions regarding treatment efficacy, and conducted sensitivity analysis incorporating treatment of subjects with moderate airflow obstruction (FEV_1 50-80 percent predicted). Information from population based studies indicated that failure to use postbronchodilator spirometry likely resulted in only a small misclassification of subjects. We also employed widely available estimates for costs of one time spirometry and pharmacologic interventions. Our cost estimates did not include the medical and societal costs for COPD exacerbations or hospitalization that might be prevented. Nor do they consider the benefits that might occur by targeting COPD treatments to individuals who have both bothersome respiratory symptoms and severe to very severe airflow obstruction.

Future Research Needs

- Conduct randomized trials to determine if spirometry in primary care office-based settings results in improved rates of smoking cessation and long-term abstinence. Studies should evaluate rates of smoking cessation; types of smokers likely to benefit (based on smoking intensity, readiness to quit, symptom, and spirometric status); types of smoking cessation counseling; and pharmacologic interventions as well as other interventions specifically for airflow obstruction or respiratory symptoms. A conceptual trial design is shown in Figure 18 on page 99.

- Determine if inhaled treatments prevent the development of respiratory symptoms and/or improve health status in individuals with airflow obstruction not reporting bothersome respiratory symptoms. Studies should evaluate subjects across the full spirometric range of airflow obstruction severity and be at least several years in duration.

- Conduct randomized trials to determine if therapeutic thresholds exist for specific interventions according to spirometric and symptom status (especially in subjects with mild to moderate airflow obstruction).

- Conduct randomized trials to determine if therapy based on spirometric level, response to therapy, or change over time provides better clinical outcomes compared to clinical examination, fixed-dose, or symptom-driven therapy.

- Improve physician recognition of respiratory symptoms, especially dyspnea, that are compatible with COPD and may benefit from earlier detection via a combination of clinical history, physical examination, and measures of airflow (spirometry).

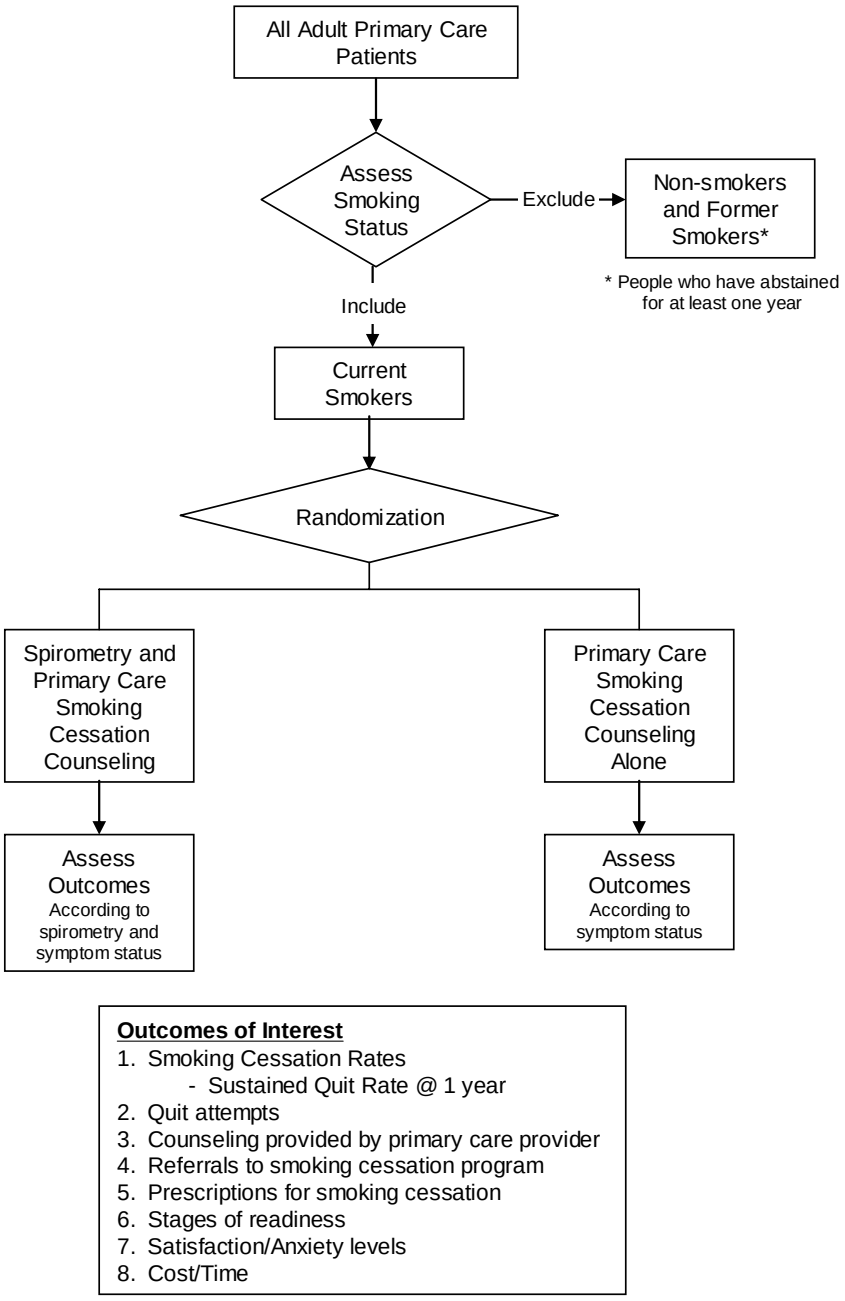
- Conduct long-term longitudinal cohort studies to better assess the associations between spirometric values, symptom status, and clinical outcomes, especially in individuals with mild disease or GOLD 0, or those who are asymptomatic.

- Estimate the costs, adverse effects, time, and personnel involved with spirometry for casefinding, diagnosis, and management including the possible harms from COPD-specific therapies or disease labeling.

- Identify better diagnostic markers for clinically significant COPD.

- Develop new therapies that can improve clinical outcomes, especially dyspnea, as well as alter the decline in spirometry.

Figure 18. Potential study design of a randomized trial to evaluate the impact of spirometric testing to alter smoking cessation rates



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Listing of Excluded Studies *(reason for exclusion is provided in italics following each reference)*

Q2—Smoking Cessation and Spirometry

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Listing of Excluded Studies *(reason for exclusion is provided in italics following each reference)*

Q3—Sin Update

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List of Acronyms/Abbreviations

AAFP	American Academy of Family Practitioners
AAP	American Academy of Pediatrics
ACP	American College of Physicians
AHRQ	Agency for Healthcare Research and Quality
ARR	Absolute Risk Reduction
ATS	American Thoracic Society
β	Beta
BODE	(B)=Body mass index; (O)=airflow Obstruction; (D)=Dyspnea; (E)=Exercise capacity
CCT	Controlled Clinical Trial
CI	Confidence Interval
CO	Carbon Monoxide
COPD	Chronic Obstructive Pulmonary Disease
CRQ	Chronic Respiratory disease Questionnaire
ED	Emergency Department
EPC	Evidence-based Practice Center
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GOLD	Global initiative for Obstructive Lung Disease
ISOLDE	Inhaled Steroids in Obstructive Lung Disease
ITT	Intention to Treat
LABA	Longacting beta agonists
LHS	Lung Health Study
LR	Likelihood Ratio
N	Number
NHANES	National Health and Nutrition Examination Survey
NIMV	Non-Invasive Mechanical Ventilation
NLHEP	National Lung Health Education Program
NRTs	Nicotine replacement therapies
OLD	Obstructive Lung Disease
OR	Odds Ratio
PFT	Pulmonary Function Test
RC	Repeat Counseling
RCT	Randomized Control Trials
RD	Risk Difference
RR	Risk Ratio
SGRQ	St. George's Respiratory Questionnaire
TEP	Technical Expert Panel
WMD	Weighted Mean Difference

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