RESEARCH PROTOCOL

Reducing Diagnostic Error to Improve Patient Safety in COPD and Asthma (REDEFINE Study)

Version: 1.5
Date: 1/11/2018

Principal Investigator: Min Joo MD MPH
Division of Pulmonary, Critical Care, Sleep, and Allergy, Department of Medicine, University of Illinois at Chicago, Chicago, IL

Sponsor: AHRQ 1R01HS024964-01

SPECIFIC AIMS AND HYPOTHESIS

Aim 1: Determine the prevalence of and characteristics associated with diagnostic error (DE) in asthma and/or COPD in an underserved population

Aim 2: Evaluate the effectiveness of the REDEFINE program compared to usual care on health care utilization and patient-centered outcomes (including respiratory medication use, all-cause emergency room visits, and all-cause hospitlizations)
Hypothesis:
The REDEFINE program will reduce health care utilization and improve patien-centered outcomes compared to usual care.

Aim 3: Evaluate the cost impact and cost effectiveness of the REDEFINE program versus usual care
Hypothesis:
The REDEFINE program will be cost-effective in the management of patients with COPD and asthma compared to usual care.

BACKGROUND AND SIGNIFICANCE

Asthma and chronic obstructive pulmonary disease (COPD) are common chronic lung diseases that are diagnosed in more than 30 million adults in the United States.[1,2] However, diagnostic error (DE), considered one of the most common and harmful of patient-safety problems by the Institute of Medicine,[3,4] occur frequently with asthma and/or COPD and disproportionately affect minorities and the underserved. DE leads to lost opportunities to identify other chronic conditions, avoidable morbidity and mortality, unnecessary costs to patients and health systems, and poor quality of care.[3-6] Shortness of breath or dyspnea, which is a common symptom in asthma and COPD, is also common for many other chronic conditions such as cardiovascular disease and obesity. A better understanding of the impact of DE and interventions to improve diagnostic accuracy in asthma and COPD are of particular importance for minorities and the underserved that are disproportionately affected by conditions leading to dyspnea.

Spirometry is a simple, mobile, and essential test that is recommended by all major national and international guidelines for the diagnosis of asthma and COPD. [7-10]

However it is well known that spirometry is not routinely used in the ambulatory primary care setting[11-19] and minorities and the underserved population are less likely to have spirometry leading to greater prevalence of DE.[20-25] It has been estimated that 30-50% of people with an existing diagnosis of asthma and COPD were found to be misdiagnosed.[11,20,21,26-32] Many of these patients misdiagnosed with asthma and/or COPD receive unnecessary respiratory pharmacotherapy which can pose serious risks including pneumonia, cardiovascular events, and mortality.[33-53] In the setting of DE, these are considered avoidable and unnecessary respiratory pharmacotherapy use in minorities and the underserved that are already disproportionately affected by cardiovascular disease[54-56] increases the risk of poorer outcomes. There is also DE in the diagnosis of asthma versus COPD, as these are both clinically distinct respiratory disorders with nuances in treatment recommendations. It is reported that African-Americans are considered to have increasing COPD mortality and are disproportionately affected by asthma death rates.[57-60] However, as spirometry is not routinely performed and DE is prevalent in asthma and COPD, a component of these poor outcomes may be attributable to missed or delayed diagnoses of other chronic conditions or misdiagnosis within asthma and COPD.

Barriers to the use of spirometry in primary care exist at provider and health systems levels. Previous studies show that primary care providers (PCPs) lack knowledge in existing guidelines and in implementing spirometry into primary care clinics.[11,18,61-64] Beyond these barriers, PCPs struggle with logistical challenges such as time and workflow constraints with clinic visits lasting 15 minutes or less in patients with multiple chronic medical conditions.[62,65] These predisposing and enabling factors explain why prior studies that included interventions to educate PCPs and incorporate spirometry by training personnel in primary care clinics have had limited results.[32,63,66-68]

A new paradigm to improve guideline based care for asthma and COPD which includes spirometry is needed and can lead to a better understanding of DE and improved patient safety and patient-centered outcomes. Health Promoters or Community health workers (CHWs) have been supplementing medical care by disseminating appropriate health care practices for underserved minority populations. However, studies which include diagnostic evaluations with spirometry for asthma and COPD have not been performed. The REDEFINE program (Reducing Diagnostic Error to Improve PatieNt SafEty in COPD and Asthma) will incorporate health promoters working collaboratively with PCPs to address identified barriers to guideline based care which includes spirometry for the diagnosis of asthma and COPD for patients at risk for DE. We propose a comparative effectiveness study to better understand the epidemiology of DE and to evaluate the effectiveness and economic impact of providing the REDEFINE program to an underserved, predominantly minority population with a diagnosis of asthma and/or COPD at risk for DE.

RESEARCH DESIGN AND METHODS

1. RESEARCH DESIGN

This will be a cluster-randomized comparative effectiveness trial conducted of patients with a primary care provider (PCP) diagnosis of COPD and/or asthma seen in outpatient primary care provider clinics (i.e. Family Medicine, Miles Square Health Center, and Academic Internal Medicine) as well as the CRC (Clinical Research Center) at the University of Illinois Hospital and General Internal Medicine and Famly Medicine Clinics

at Cook County Health and Hospitals Systems (CCHHS). Providers will be randomized and their patients who fulfill the inclusion criteria will receive the intervention or be in the usual care group. Adults with a clinician-diagnosed COPD and/or asthma at high risk for diagnostic error due to lack of spirometry will undergo the REDEFINE intervention or usual care based on the PCP randomization . Outcomes will be assessed every 3 months for up to one year.

2. ELIGIBILITY CRITERIA

A. Primary care provider (PCP) eligibility criteria:

Primary care providers (PCPs) will include physicians and nurse practitioners. PCPs specializing in internal medicine or family medicine with at least one half day per week outpatient clinic session at the following clinics will be eligible for the study:

- UI Health: Family Medicine (FM) clinics, Academic Internal Medicine (AIM) clinics
- Miles Square Health Center (MSHC)
- Clinical Research Center (CRC) at UIC
- Cook County Health and Hospitals Systems (CCHHS): General Internal Medicine (GIM) and Family Medicine

B. Patient eligibility criteria:

Inclusion criteria:

1. Age ≥40 years of age
2. Use of a maintenance respiratory medication and one of the following in the past year:
    a. diagnosis of asthma
    b. diagnosis of COPD, emphysema, or chronic bronchitis
3. No spirometry test performed in the past 3 years
4. Past or current smoker

Exclusion criteria:

- Unable to perform adequate spirometry
- Non-English speaking
- Pregnancy
- Plans to move from the Chicago area within the next year
- Seen by pulmonary or allergy specialist in the past 3 years
- Any terminal illness with a life expectancy of <6 months
- Life threatening (e.g. Intensive care admission and/or use of mechanical ventilation) respiratory failure event in the past year

3. SUBJECT SELECTION, RECRUITMENT, AND INFORMED CONSENT

PCP Selection, Recruitment, and Informed consent

Primary care providers (PCPs) specializing in internal medicine or family medicine with at least one half day per week outpatient clinic will be included in the study. We

estimate a total maximum recruitment of 80 eligible PCPs from all sites (approximately 50 PCPs from UI Health and MSHC sites and approximately 30 PCPs from CCHHS). The recruitment will include a combination of paper letter and email invitations with endorsement from the clinic directors and other supervisors. A list of eligible PCPs will be obtained from each site from the clinic directors. A research introduction letter will be mailed to the qualifying practitioners as well as an email invitation sent to their email accounts. The letter and email will be sent simultaneously to ensure contact and will include a short introduction to why the research is being performed and a description of participants' roles in the study. Also included will be a contact number for those who would like to volunteer or who would like additional information. The letter will include a statement that there will be no penalty for not participating. The letter will also contain a postcard with a stamp, where the eligible PCP checks to agree to participate or decline to participate. The email will instruct them to reply by email to the same choices. If a response is not received in 2 weeks, a second recruitment letter and email will be sent followed by a postcard 2 weeks later. Once a PCP agrees to participate, informed consent will be obtained prior to initiation of any study procedures.

Patient Selection, Recruitment, and Informed consent

Approximately 500 patients will be recruited for this study from the FM, AIM, MSHC and GIM sites (A total of 250 from UI Health and MSHC sites and a total of 250 from CCHHS site). All sites use the same electronic medical record (EMR) system which is Cerner Powerchart. An Information Systems Specialists (ISS) from UI Health (including MSHC) and CCHHS will search the administrative data of their respective sites to provide a list of patients meeting the first three of the inclusion criteria listed above and are scheduled to be seen in PCP clinics or the CRC (Clinical Research Center at UIC), two weeks in the future. More specifically, using electronic health records, within the past 12 months, the following patients will initially be identified: age ≥ 40 years and using at least one maintenance respiratory medication (e.g. long acting beta agonists (LABA), long acting anticholinergics (LAA),inhaled corticosteroids (ICS), phosphodiesterase-4 inhibitors (PDE-4i), and at least one of the following 1) diagnosis of asthma (ICD-9 493.xx or ICD 10 J45.xx), 2) diagnosis of COPD, emphysema, or chronic bronchitis (ICD-9 491.xx, 492.xx, 496 or ICD 10 J41.xx, J42.xx, J43.xx, J44.xx). .In addition, our ISS will also only include those who have not had a current procedural testing (CPT) codes for spirometry (CPT codes: 94010, 94014, 94015, 94016, 94060, 94070, 94620) or completed order for spirometry testing in the past 3 years.

Medical charts of patients will be reviewed to prescreen for eligibility for the study. Participants who meet preliminary eligibility criteria will be mailed a patient recruitment letter informing them of the study and our intent to contact them by telephone to complete a phone screen approximately one week before the participants' scheduled primary care visit. The letter will be sent 2 weeks before the planned phone screen and will have a phone number to call to opt out of the study. A patient phone screen is conducted to confirm eligibility criteria and the participants' verbal consent to participate in the study is obtained. During the call, we will confirm their scheduled appointment date, go over the study, answer any questions, and if the subject agrees, conduct the phone screen to verify eligibility criteria. If eligible, they will be asked to participate in the study and if agreeable will be asked to come in 90 minutes before the clinic visit. Once a subject agrees to participate, informed consent will be obtained prior to initiation of any study procedures.

4. DESCRIPTION OF PROCEDURES

A) PCP Education and Randomization:

After obtaining PCP informed consent and prior to patient recruitment, a one hour educational session will be held for PCPs participating in the study. The purpose of this session is to provide education to PCPs about COPD, asthma, spirometry, and GOLD and GINA guidelines (GOLD=Global Initiative for Chronic Obstructive Lung Disease, GINA=Global Initiative for Asthma). The educational session will provide continuing medical education credit to those who attend. The learning objectives will be the following: 1) Review COPD and asthma disease definition, presentation, diagnosis and testing including spirometry, 2) be familiar with the GOLD and GINA guidelines and recommendations for therapy.

PCPs who consented to participate in the study and completed the education session will be randomized to have their patients who meet the study criteria receive the intervention or usual care.

B) Patient subject- Intervention:

On the day of the outpatient visit, subjects will be advised to arrive 90 minutes prior to their clinic visit in the same building as the clinic site or the CRC (Clinical Research Center at UIC). The following information will be collected and procedures will be performed:

1. Subject demographic and contact information
2. Co-morbid conditions
3. Smoking history
4. Medication history from patient and also from pharmacy used by subjects
5. A respiratory exacerbation history in the past year
6. Modified Medical Research Counsel (mMRC) dyspnea scale and COPD Assessment Test
7. Quality of life measures
8. Pre and post-bronchodilator (BD) spirometry
9. De-Escalation Spirometry Screener for patients de-escalating based on spirometry (See Based on spirometry findings)
10. De-Escalation Phone Script

<u>Based on spirometry findings:</u>

1. If the spirometry findings are consistent with COPD and/or asthma, the following will be provided to the provider and patient to have available during the clinic visit: a letter summarizing the interpretation of the findings using GOLD/GINA criteria with recommendations for initial guideline driven therapy based on GOLD/GINA guidelines. Subjects will be managed by their PCP thereafter.
2. If the spirometry findings are normal, with approval from the PCP, will de-escalate respiratory medication therapy via a stepwise process and schedule patient back for a repeat pre and post bronchodilator spirometry within 1-2 weeks at the same time and place as the PCP clinic session or the CRC (Clinical Research Center at UIC). Again with the PCP approval, this

deescalation and repeat spirometry can occur in 1-2 week intervals until all maintenance medications are discontinued as long as the pre and post spirometry continues to be normal. After each visit, the following will be provided to the provider and patient: a letter summarizing the interpretation of the findings using GOLD/GINA criteria with recommendations for initial guideline driven therapy based on GOLD/GINA guidelines, if appropriate. Subjects will be managed by their PCP thereafter.

3. All spirometry test results and the subject's assessment at the time of the test will be uploaded into the subject's electronic health record for future reference.

C) Patient subject- Usual Care:

On the day of the outpatient visit, subjects will be advised to arrive 60 minutes prior to their clinic visit in the same building as the clinic site or the CRC (Clinical Research Center). The following will be performed.

1. Subject demographic and contact information
2. Co-morbid conditions
3. Smoking history
4. Medication history from patient and also from pharmacy used by subjects
5. A respiratory exacerbation history in the past year
6. Modified Medical Research Counsel (mMRC) dyspnea scale and COPD assessment test
7. Quality of life measures

Subjects will be advised to go to their clinics and be managed by their PCP thereafter.

At the end of the 1 year followup, the patient will be scheduled for a pre and post BD spirometry and undergo the same spirometry protocol (de-escalation protocol) as the intervention group.

<u>Based on spirometry findings:</u>

1. If the spirometry findings are consistent with COPD and/or asthma, the following will be provided to the provider and patient: a letter summarizing the interpretation of the findings using GOLD/GINA criteria with recommendations for initial guideline driven therapy based on GOLD/GINA guidelines. Subjects will be managed by their PCP thereafter.
2. If the spirometry findings are normal, with approval from the PCP, will de-escalate respiratory medication therapy via a stepwise process and schedule patient back for a repeat pre and post bronchodilator spirometry within 1-2 weeks at the same time and place as the PCP clinic session. Again with the PCP approval, this deescalation and repeat spirometry can occur in 1-2 week intervals until all maintenance medications are discontinued as long as the pre and post spirometry continues to be normal. After each visit, the following will be provided to the provider and patient: a letter summarizing the interpretation of the findings using GOLD/GINA criteria with recommendations for initial guideline driven therapy based on GOLD/GINA guidelines, if appropriate. Subjects will be managed by their PCP thereafter.
3. All spirometry test results and the subject's assessment at the time of the test will be uploaded into the subject's electronic health record for future reference.

D) Outcome Measures:

1. **Primary outcome:**
   - **(i)** Accurate classification of patient as having COPD and/or asthma
   - **(ii)** All-cause and respiratory related, acute care outpatient visits, ED visits, and hospitalizations
2. **Secondary outcome:**
   - **(i)** Appropriate use of respiratory medications based on guidelines
   - **(ii)** Use of other diagnostic testing: ECG, echocardiograms, CT/CXR, stress testing, cardiac catheterization, other pulmonary function tests
   - **(iii)** Initiation of guideline based therapy
   - **(iv)** Quality of life measures

E) Data collection and follow-up

1) Baseline data collection obtained at visit zero (V_0), in addition to those listed under intervention and usual care:

1. Demographic data (gender, age, self-reported race)
2. SES related measures: median household income
3. Level of education
4. Type of health insurance or self-pay
5. Up to two emergency contacts information
6. List of current respiratory medications from subject's pharmacy and verification with patient
7. Co-morbidities
8. History of prior ED visits or hospitalizations in the past one year with associated cause
9. EQ-5D 5L +B Bolt-on
10. SF-36 short form
11. Social support survey

2) All subjects will have their medical charts reviewed every 3 months after the initial visit (MR_1, MR_2, MR_3, MR_4) up to one year. These electronic medical chart reviews will be used to obtain follow-up data since last study contact.

1. Change in type of health insurance or self-pay
2. List of current respiratory medications from subject's pharmacy and verification with patient
3. Use of diagnostic testing: ECG, echocardiograms, CT/CXR, stress testing, cardiac catheterization, other pulmonary function tests
4. Any ED visits or hospitalizations or acute outpatient care visit and associated cause.
5. Healthcare utilization outside of U of I system (e.g. testing such as spirometry, ED and hospitalizations) if available through scanned records

3) All subjects will be contacted every 3 months after the initial visit via telephone (T_1, T_2, T_3, T_4) up to one year; or they will be given the option to complete in person based on subject's convenience, for example they have a doctor appointment near time of study follow-up. These phone calls will be used to obtain follow-up data since last study contact. A reminder post-card will be mailed to the subjects a month before the next telephone contact.

1. Change in type of health insurance or self-pay

2. List of current respiratory medications from subject's pharmacy and verification with patient
3. Use of diagnostic testing: ECG, echocardiograms, CT/CXR, stress testing, cardiac catheterization, other pulmonary function tests
4. Any ED visits or hospitalizations or acute outpatient care visit and associated cause.
5. Healthcare utilization outside of U of I system (e.g. testing such as ancillary testing, ED and hospitalizations)
6. mMRC
7. A respiratory exacerbation history
8. EQ-5D 5L +B Bolt-on
9. SF-36 short form (at 3, 6 and 12 months)
10. Social support survey (at 6 months and 12 months)

F) Monetary compensation of subjects

1. PCP compensation:

UI Health and MSHC PCPs will receive $95 in cash after completion of the education session. For CCHHS PCPs, the Division or Department with receive a total of $95 per participant to be part of the divisional fund to be used by the PCP at their discretion as allowed by their institution.

2. Patient subject compensation:

Baseline visit (Vo):

Same for Intervention and usual care groups: Subjects will be provided $75 in cash for completing the initial study visit.

Telephone contact (T_1-T_3):

Same for Intervention and usual care groups. Subjects who choose to complete the follow-up in person or via telephone will receive $20 in cash at the time of the visit or at a later specified time that is convenient for the subject.

Final contact (T_4):

Intervention: Subjects will receive $95 in cash at the time of the their last visit in-person.

Usual Care Group: Subjects will receive $95 in cash at the completion of the 1 year spirometry and follow-up.

Additional spirometry visits after de-escalation of therapy:

Same for Intervention and usual care groups (except the intervention group will receive this near the beginning of the study and usual care group will receive this near the end of the study): Subjects will be provided a $50 in cash for each additional spirometry visit.

2.A. Provision to compensation: If human subject receives over $200.00 within one (1) calendar year, it is incumbent for the study staff to obtain the subjects social security number based on the OBFS guidelines. However, if human subject receives a total under $200.00 within the calendar there is no need to obtain social security number from the human subject.

5. STATISTICAL ANALYSES

All data will be stored in a secure, locked location. Data will be entered and managed through the Research Electronic Data Capture (REDCap). REDCap is a secure web-based application for building and managing online databases. REDCap is provided by

the CCTS Design Analysis Core. Data will be analyzed for clinical effectiveness using intention-to-treat principles.[69-71] For **Aim 1**, we will evaluate the misdiagnosis rates of the intervened and usual care groups separately at the first visit. Then compare rates between groups by using a generalized linear mixed model for binary outcome with two cluster levels, PCP and hospital, to account for the dependence within clusters. For the **Aim 2**, to investigate the impact of the misdiagnosis over time (4 time points: 0, 3, 6, 9, 12 months) on the quality of life and healthcare utilization, we will fit generalized linear mixed models with time, group, and their interaction as the main predictors. Two cluster levels, PCP and hospital, will be specified in the model to account for the dependence within clusters[72,73] and an appropriate link function will be used for each outcome. Clinical important confounders will also be adjusted in the models. Before these analyses we will use descriptive statistics to describe the sample, and any assumption behind each statistical method will be examined during the analysis. A two-sided p-value less than 0.05 would be considered as statistical significance. All the analyses will be conducted by using SAS 9.2 (SAS Inst., Cary, NC).

For **Aim 3:** *Costs:* The intervention costs for the study include the cost of the spirometry test, the time of the CHW/health promoter, and time of pulmonologist to provide periodic oversight of spirometry validity. In addition to estimating the costs associated with the intervention it will be important to measure the healthcare utilization for participants included in the study. It is possible that the intervention leads to use of other healthcare resources, particularly if the patient is determined to be free of respiratory disease. Therefore, we will measure both respiratory-related and overall healthcare costs. To measure these costs, we will determine overall healthcare utilization and apply unit costs to each of the events. Using chart reviews, we will examine healthcare utilization during the follow-up period. We will categorize healthcare utilization into either respiratory-related or all other healthcare use. We will apply standardized prices to each of the utilization components to estimate the overall and respiratory-related healthcare resource use during the study period. The standardize prices will be based on either the National Committee for Quality Assurance standardize price list for their relative resource use measure or Medicare reimbursement rates. For medications, we will rely on average wholesale price of medications to assign an average price to each of the COPD and asthma-related medications.

Cost-Effectiveness: The secondary outcome measures included in the study will be used to estimate the effectiveness to be used in the cost-utility analysis. We will use responses to the EQ5D to estimate patient utility and use that in calculation of quality-adjusted life-years (QALY). The area under the curve will be compared between the two groups and the difference will be the incremental effect used in the cost-utility analysis.

Cost-utility analyses: We will evaluate the cost-utility of the intervention compared to usual care over the study period using recommended methods for cost-effectiveness analysis.[74] To compare the cost-effectiveness of the intervention to usual care, the findings are summarized into a ratio that provides the results in terms of the costs per unit of effect. We will calculate the difference in intervention costs and respiratory-related healthcare resource use between groups to determine the numerator of the ratio and the denominator will be the difference in QALYs in the cost-utility analysis. These incremental cost-effectiveness ratios (ICERs) will represent the cost per gain in QALYs for the intervention compared to standard care. As part of the cost-utility analysis we will evaluate the uncertainty associated with the ICERs. We will use bootstrapping

methods to generate confidence limits for the ICERs.[75,76] We will display the results graphically on a cost-effectiveness plane and generate cost-effectiveness acceptability curves for the intervention compared to usual care.[77,78] Cost-effectiveness acceptability curves display the probability of the intervention being cost-effective given various threshold values.[78] Thus decision-makers can identify a threshold value appropriate for their setting and determine the probability that the intervention will be cost-effective. We will also conduct sensitivity analyses that use the measure of overall healthcare utilization in calculation of the costs, as there may not be perfect specificity in identifying respiratory-related costs during the follow-up assessments and the intervention may lead to differences in non-respiratory costs.

6. SAFETY MONITORING AND ASSESSMENT

Risks of intervention study

Spirometry is a breathing test commonly utilized in the outpatient primary care setting. Risks and discomforts associated with spirometry are possible. The risks include shortness of breath and on rare occasion, the subject might experience dizziness, cough, or light-headedness. A medication that can open subjects' airways may be used during spirometry testing. This medication, albuterol, is in a class of medications (i.e. short acting beta agonist) that is often used to treat subjects suspected with COPD and/or asthma as part of usual care. Albuterol may sometimes cause tremors/shaking, nervousness, dizziness, difficulty sleeping, headache, irregular heartbeats, drying or irritation of mouth, sore throat, upset stomach, and coughing. These effects usually disappear within a short time and do not require treatment.

Data Safety Monitoring Plan

The PI will review monthly data reports reviewing recruitment, consent, intervention activities, adverse events, and follow-up. Although few, if any, intervention-related adverse events are anticipated in this study, the study population is at risk for poor outcomes, including life-threatening exacerbations and death not caused by the study itself. The PI will comply with prompt reporting of any adverse event to the IRB

7. DATA MANAGEMENT

Confidentiality

To help ensure that patients' health information remains private, we will restrict access to data collected for our study to study personnel only (via use of password-protection and locked cabinets for study documents). Study ID numbers will be generated and will be used when discussing and/or reviewing data at study meetings. Also, study reports will report results in aggregate and not contain information that can be used to identify individual patients.

Storage of Data

Data will be collected from participants in the form of questionnaires and will be documented in the secure, password protected, web-based Research Electronic Data Capture (REDCap) database available only to members of the research team. The research data will be stored securely using subject ID numbers and kept for 6 years after the end of the study.

UI Health electronic medical records(EMR) (inpatient and outpatient) will be reviewed by staff from UI Health and CCHHS EMR (inpatient and outpatient) will be reviewed by staff from CCHHS . Data collected from both institutions will be input into REDCap. The crosswalk file with direct identifiers to the coded data will be created, encrypted, and kept on Dr. Joo's office computer at 840 S. Wood St. Chicago, Il and stored such that only authorized inviduals will have access to patient identifying information. Hardcopies of the data will not be made.

REFERENCES

1 National Center for Health Statistics. Chronic Obstructive Pulmonary Disease Among Adults Aged 18 and Over in the United States, 1998-2009, 2011

2 Centers for Disease C, Prevention. Vital signs: asthma prevalence, disease characteristics, and self-management education: United States, 2001--2009. MMWR Morb Mortal Wkly Rep 2011; 60:547-552.

3 In: Balogh EP, Miller BT, Ball JR, eds. Improving Diagnosis in Health Care. Washington (DC), 2015

4 Ball JR, Balogh E. Improving Diagnosis in Health Care: Highlights of a Report From the National Academies of Sciences, Engineering, and Medicine. Ann Intern Med 2016; 164:59-61.

5 Singh H, Graber ML. Improving Diagnosis in Health Care--The Next Imperative for Patient Safety. N Engl J Med 2015; 373:2493-2495.

6 Khullar D, Jha AK, Jena AB. Reducing Diagnostic Errors--Why Now? N Engl J Med 2015; 373:2491-2493.

7 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: World Health Organization and National Heart, Lung, and Blood Institute, 2016

8 Global Initiative for Asthma. Global strategy for asthma management and prevention. Bethesda, MD, USA: GINA, 2015

9 Qaseem A, Wilt TJ, Weinberger SE, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med 2011; 155:179-191.

10 National Asthma E, Prevention P. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. The Journal of allergy and clinical immunology 2007; 120:S94-138.

11 Bolton CE, Ionescu AA, Edwards PH, et al. Attaining a correct diagnosis of COPD in general practice. Respir Med 2005; 99:493-500.

12 Damarla M, Celli BR, Mullerova HX, et al. Discrepancy in the use of confirmatory tests in patients hospitalized with the diagnosis of chronic obstructive pulmonary disease or congestive heart failure. Respir Care 2006; 51:1120-1124.

13 Han MK, Kim MG, Mardon R, et al. Spirometry Utilization for COPD: How Do We Measure Up? Chest 2007; 132:403-409.

14 Lee TA, Bartle B, Weiss KB. Spirometry use in clinical practice following diagnosis of COPD. Chest 2006; 129:1509-1515.

15 Mapel DW, Picchi MA, Hurley JS, et al. Utilization in COPD: patient characteristics and diagnostic evaluation. Chest 2000; 117:346S-353S.

16 Miravitlles M, de la Roza C, Naberan K, et al. Use of spirometry and patterns of prescribing in COPD in primary care. Respir Med 2007; 101:1753-1760.

17 Mularski RA, Asch SM, Shrank WH, et al. The quality of obstructive lung disease care for adults in the United States as measured by adherence to recommended processes. Chest 2006; 130:1844-1850.

18 Walters JA, Hansen E, Mudge P, et al. Barriers to the use of spirometry in general practice. Aust Fam Physician 2005; 34:201-203.

19 O'Dowd LC, Fife D, Tenhave T, et al. Attitudes of physicians toward objective measures of airway function in asthma. Am J Med 2003; 114:391-396.

20 Ghattas C, Dai A, Gemmel DJ, et al. Over diagnosis of chronic obstructive pulmonary disease in an underserved patient population. Int J Chron Obstruct Pulmon Dis 2013; 8:545-549.

21 Prieto-Centurion V, Rolle AJ, Au DH, et al. Multi-center Study Comparing Case Definitions Used to Identify Patients with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2014

22 Han MK, Postma D, Mannino DM, et al. Gender and chronic obstructive pulmonary disease: why it matters. Am J Respir Crit Care Med 2007; 176:1179-1184.

23 Chapman KR, Tashkin DP, Pye DJ. Gender bias in the diagnosis of COPD. Chest 2001; 119:1691-1695.

24 Franks P, Clancy CM, Naumburg EH. Sex, access, and excess. Ann Intern Med 1995; 123:548-550.
25 Ohar J, Fromer L, Donohue JF. Reconsidering sex-based stereotypes of COPD. Prim Care Respir J 2011; 20:370-378.
26 Tinkelman DG, Price DB, Nordyke RJ, et al. Misdiagnosis of COPD and asthma in primary care patients 40 years of age and over. J Asthma 2006; 43:75-80.
27 Abramson MJ, Schattner RL, Sulaiman ND, et al. Accuracy of asthma and COPD diagnosis in Australian general practice: a mixed methods study. Prim Care Respir J 2012; 21:167-173.
28 Melbye H, Drivenes E, Dalbak LG, et al. Asthma, chronic obstructive pulmonary disease, or both? Diagnostic labeling and spirometry in primary care patients aged 40 years or more. Int J Chron Obstruct Pulmon Dis 2011; 6:597-603.
29 Griffiths C, Feder G, Wedzicha J, et al. Feasibility of spirometry and reversibility testing for the identification of patients with chronic obstructive pulmonary disease on asthma registers in general practice. Respir Med 1999; 93:903-908.
30 Sichletidis L, Chloros D, Spyratos D, et al. The validity of the diagnosis of chronic obstructive pulmonary disease in general practice. Prim Care Respir J 2007; 16:82-88.
31 Walters JA, Walters EH, Nelson M, et al. Factors associated with misdiagnosis of COPD in primary care. Prim Care Respir J 2011; 20:396-402.
32 Buffels J, Degryse J, Liistro G, et al. Differential diagnosis in a primary care population with presumed airway obstruction: a real-life study. Respiration 2012; 84:44-54.
33 Nelson HS, Weiss ST, Bleecker ER, et al. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006; 129:15-26.
34 Nelson HS, Weiss ST, Bleecker ER, et al. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006; 129:15-26.
35 Lee TA, Pickard AS, Au DH, et al. Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. Ann Intern Med 2008; 149:380-390.
36 Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. Jama 2008; 300:1439-1450.
37 Van den Bruel A, Gailly J, Neyt M. Does tiotropium lower exacerbation and hospitalization frequency in COPD patients: results of a meta-analysis. BMC Pulm Med 2010; 10:50.
38 Ogale SS, Lee TA, Au DH, et al. Cardiovascular events associated with ipratropium bromide in COPD. Chest 2010; 137:13-19.
39 Macie C, Wooldrage K, Manfreda J, et al. Cardiovascular morbidity and the use of inhaled bronchodilators. Int J Chron Obstruct Pulmon Dis 2008; 3:163-169.
40 Ringbaek T, Viskum K. Is there any association between inhaled ipratropium and mortality in patients with COPD and asthma? Respir Med 2003; 97:264-272.
41 Guite HF, Dundas R, Burney PG. Risk factors for death from asthma, chronic obstructive pulmonary disease, and cardiovascular disease after a hospital admission for asthma. Thorax 1999; 54:301-307.
42 Singh S, Loke YK, Enright PL, et al. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. Bmj 2011; 342:d3215.
43 Martin-Merino E, Garcia-Rodriguez LA, Masso-Gonzalez EL, et al. Do oral antimuscarinic drugs carry an increased risk of acute urinary retention? J Urol 2009; 182:1442-1448.
44 Armitage JN, Sibanda N, Cathcart PJ, et al. Mortality in men admitted to hospital with acute urinary retention: database analysis. Bmj 2007; 335:1199-1202.
45 Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007; 356:775-789.
46 Ernst P, Gonzalez AV, Brassard P, et al. Inhaled corticosteroid use in chronic obstructive pulmonary disease and the risk of hospitalization for pneumonia. Am J Respir Crit Care Med 2007; 176:162-166.
47 Kardos P, Wencker M, Glaab T, et al. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2007; 175:144-149.
48 Ferguson GT, Anzueto A, Fei R, et al. Effect of fluticasone propionate/salmeterol (250/50 microg) or salmeterol (50 microg) on COPD exacerbations. Respir Med 2008; 102:1099-1108.
49 Wedzicha JA, Calverley PM, Seemungal TA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med 2008; 177:19-26.
50 Joo MJ, Au DH, Fitzgibbon ML, et al. Inhaled corticosteroids and risk of pneumonia in newly diagnosed COPD. Respir Med 2010; 104:246-252.

51 Yawn BP, Li Y, Tian H, et al. Inhaled corticosteroid use in patients with chronic obstructive pulmonary disease and the risk of pneumonia: a retrospective claims data analysis. Int J Chron Obstruct Pulmon Dis 2013; 8:295-304.
52 McKeever T, Harrison TW, Hubbard R, et al. Inhaled corticosteroids and the risk of pneumonia in people with asthma: a case-control study. Chest 2013; 144:1788-1794.
53 Lee TA, Weiss KB. Fracture risk associated with inhaled corticosteroid use in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004; 169:855-859.
54 Mensah GA, Mokdad AH, Ford ES, et al. State of disparities in cardiovascular health in the United States. Circulation 2005; 111:1233-1241.
55 Cooper R, Cutler J, Desvigne-Nickens P, et al. Trends and disparities in coronary heart disease, stroke, and other cardiovascular diseases in the United States: findings of the national conference on cardiovascular disease prevention. Circulation 2000; 102:3137-3147.
56 Ski CF, King-Shier KM, Thompson DR. Gender, socioeconomic and ethnic/racial disparities in cardiovascular disease: a time for change. Int J Cardiol 2014; 170:255-257.
57 Akinbami LJ, Moorman JE, Bailey C, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. NCHS Data Brief 2012:1-8.
58 Morbidity & Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases. In: National Heart Lung and Blood Institute, ed, 2012
59 Dransfield MT, Bailey WC. COPD: racial disparities in susceptibility, treatment, and outcomes. Clin Chest Med 2006; 27:463-471, vii.
60 Akinbami LJ, Liu X. Chronic obstructive pulmonary disease among adults aged 18 and over in the United States, 1998-2009. NCHS Data Brief 2011:1-8.
61 Barr RG, Celli BR, Martinez FJ, et al. Physician and patient perceptions in COPD: the COPD Resource Network Needs Assessment Survey. Am J Med 2005; 118:1415.
62 Caramori G, Bettoncelli G, Tosatto R, et al. Underuse of spirometry by general practitioners for the diagnosis of COPD in Italy. Monaldi Arch Chest Dis 2005; 63:6-12.
63 Kaminsky DA, Marcy TW, Bachand M, et al. Knowledge and use of office spirometry for the detection of chronic obstructive pulmonary disease by primary care physicians. Respir Care 2005; 50:1639-1648.
64 Foster JA, Yawn BP, Maziar A, et al. Enhancing COPD management in primary care settings. MedGenMed 2007; 9:24.
65 Stange KC, Zyzanski SJ, Jaen CR, et al. Illuminating the 'black box'. A description of 4454 patient visits to 138 family physicians. J Fam Pract 1998; 46:377-389.
66 Lusuardi M, De Benedetto F, Paggiaro P, et al. A Randomized Controlled Trial on Office Spirometry in Asthma and COPD in Standard General Practice *. Chest 2006; 129:844-852.
67 Walters JA, Hansen EC, Johns DP, et al. A mixed methods study to compare models of spirometry delivery in primary care for patients at risk of Chronic Obstructive Pulmonary Disease. Thorax 2007
68 Walker PP, Mitchell P, Diamantea F, et al. Effect of primary-care spirometry on the diagnosis and management of COPD. Eur Respir J 2006; 28:945-952.
69 Little R, Yau L. Intent-to-treat analysis for longitudinal studies with drop-outs. Biometrics 1996; 52:1324-1333.
70 Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. Bmj 1999; 319:670-674.
71 Lachin JM. Statistical considerations in the intent-to-treat principle. Control Clin Trials 2000; 21:167-189.
72 Donner A, Klar N. Design and Analysis of Cluster Randomization Trials in Health Research. London, England: Oxford University Press, 2000;
73 Brown H, Prescott R. Applied mixed models in medicine.: John Wiley & Sons, 2006;
74 Gold M. Cost-Effectiveness in Health and Medicine. New York, New York: Oxford University Press, 1996;
75 Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. Health Econ 1997; 6:327-340.
76 Efron B, Tibshirani R. An Introduction to the Bootstrap. New York: Chapman and Hall, 1993;
77 Briggs A, Fenn P. Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. Health Econ 1998; 7:723-740.
78 van Hout BA, Al MJ, Gordon GS, et al. Costs, effects and C/E-ratios alongside a clinical trial. Health Econ 1994; 3:309-319.