Unnecessary inhaled corticosteroids in COPD:
understanding patient and health system complexity as contributors

Laura J. Spece

A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Science

University of Washington

2018

Committee:

Nicholas L. Smith

David H. Au

Laura C. Feemster

Program Authorized to Offer Degree:

Epidemiology

University of Washington

Abstract

Unnecessary inhaled corticosteroids in COPD:

understanding patient and health system complexity as contributors

Laura J. Spece

Chair of the Supervisory Committee:

Nicholas L. Smith

Epidemiology

Objective: To determine if patient complexity is associated with unnecessary use of inhaled corticosteroids (ICS) among patients with chronic obstructive pulmonary disease (COPD) at low risk of exacerbations and if health system complexity modifies this association.

Methods: We identified Veterans with COPD without a guideline-recommended indication for ICS from electronic health records between January 2012 and September 2016. Our primary outcome was incident prescription of ICS. We used the Care Assessment Needs (CAN) score to describe complexity at the patient-level as the primary exposure. We used a time-to-event model with time-varying exposures over one year of follow-up time. We tested for effect modification using health system data from the Strategic Analytics for Improvement and Learning (SAIL) report.

Results: We identified 8,497 patients with COPD who did not have an indication for ICS. The mean follow-up time was 4 quarters. Patient complexity by CAN was associated with unnecessary ICS (HR 1.017 per CAN unit; 95% CI 1.013 – 1.021). This association demonstrated a dose-response when examining quartiles of CAN score. Markers of health system complexity did not modify the association between patient complexity and unnecessary ICS.

Conclusions: As patient complexity increased, patients were more likely to have unnecessary ICS therapy initiated. Complexity as reflected in CAN scores may represent a marker for patients who have persistent and bothersome symptom despite appropriate therapies. Lack of effect-modification by health system complexity likely reflects the paucity of structural support and low prioritization for COPD care. Future efforts are needed to understand provider-level barriers to care quality in COPD as are efforts to prioritize complex patients with COPD.

Introduction

Inhaled corticosteroids (ICS) reduce the risk of exacerbations in chronic obstructive pulmonary disease (COPD), and are among the most commonly prescribed inhaled medications for the condition.[1-4] In both initial and subsequent trials, investigators noted an increased risk of pneumonia, while observational studies have demonstrated increased risk of osteoporotic fractures, poor diabetes control, and cataracts associated with ICS.[5-9] Comparative efficacy studies demonstrate marginal benefit of adding ICS to other inhaled treatments. Collectively, this body of evidence has led guideline authors to narrow the indications for appropriate use of ICS. With the changes to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) statement in 2017, ICS are restricted to patients with COPD and overlapping history of asthma or a history of severe and/or frequent exacerbations.

Several studies have found that the guideline recommendations for prescribing ICS in COPD are not followed in clinical practice.[10] Current estimates suggest that ICS are commonly prescribed in up to 40% of Veterans with COPD,[11] and that 47-89% of existing ICS prescriptions are unnecessary ("potential overuse").[12,13] Withdrawal of ICS in patients with a low risk of exacerbations has been shown to be safe[14,15] and thus presents a large target population for de-implementation of ICS and an opportunity to understand what drives low-value care practices in COPD.

Understanding patient and system-level factors associated with receipt of unnecessary ICS would help frame de-implementation efforts. Most patients with COPD present after more than 20 years of tobacco smoking and as a result are older and medically complex, suffering from multiple comorbidities and frailty,[16,17] in addition to mental health disorders,[18,19] lower health literacy and education,[20,21] and lower socioeconomic status.[22,23] These characteristics and risk factors lead to multiple mechanisms for dyspnea that may lead a clinician to over-prescribe unnecessary therapies,

such as ICS. The Veterans Affairs (VA) health system utilizes a unique patient complexity measure, the Care Assessment Needs (CAN) score, that encompasses these elements.[24] The CAN score ranges from 0-100 and was developed to predict, on a population basis, Veterans at greatest risk for adverse outcomes of hospitalization and death. The model is based on approximately 50 characteristics including demographics, vital signs, health factors, health service utilization, and medications dispensed. The CAN score includes not only comorbidities listed in the Deyo-Charlson index[25] but has expanded the measure to include risk adjustment categories used in the Hierarchical Condition Category (HCC) to encompass disability, mental health, and substance abuse.

The concept of complexity extends beyond the patient to the level of the healthcare system. Patients with COPD must navigate the healthcare system to obtain the necessary services to manage symptoms and prevent exacerbations. System-level complexity can be embodied by available services, wait time for appointments and services, access to allied health professionals, and COPD care volume that reflect the center's ability to deliver highly coordinated, effective care.[26-28] Patients with greater complexity are more likely to be seen at facilities with greater specialization and complexity. These systems are more likely to have clinical structure and processes to ensure consistent, high level quality of care. As patients and systems become more complex, however, the number of opportunities for failures in healthcare delivery likely increases.[29,30] Within the VA, the Strategic Analytics for Improvement and Learning (SAIL) quarterly report attempts to capture these health-system level complexity metrics.[31] The SAIL report includes data regarding structural factors including COPD-specific volume of hospitalizations and care-complexity designation. This study utilizes novel approaches to measure patient and health system complexity with the CAN score and SAIL reports to better understand unnecessary use of ICS.

In order to evaluate whether patient complexity is associated with unnecessary ICS prescription, we analyzed a nationwide cohort of Veterans with a low exacerbation risk and without

asthma or ICS therapy at cohort entry. We hypothesized that greater patient complexity is associated with more unnecessary ICS use. In light of known differences in the complexities of health care systems, we explored effect modification by center complexity designation code and COPD-specific annual volume within the association between patient-level complexity and ICS use.

Methods

Cohort and Participants

We conducted a cohort study of Veterans with COPD who received a pulmonary function test (PFT) in the Department of Veterans Affairs (VA) during the period of October 1, 2012 through September 30, 2016. Veterans were seen at 1 of 21 VA medical centers contributing PFT data to the Corporate Date Warehouse (CDW). We included patients with a clinical diagnosis of COPD by ICD9/10 code and airflow obstruction (AFO) on PFT ($FEV_1/FVC < 0.7$). The cohort entry date was the date of the first PFT during the study period and patients were followed administratively for 1 year or until death.

We excluded patients prescribed ICS in the year before cohort entry. In addition, we excluded patients with an indication for ICS at cohort entry, including patients with asthma by ICD9/10 diagnosis in the previous 10 years as well as those experiencing ≥2 outpatient and/or ≥1 inpatient exacerbations in the 12 months prior to cohort entry. Finally, we also excluded patients with a missing CAN score at baseline.

Data Collection

We collected patient demographic, comorbidity, healthcare utilization, smoking status, and spirometry data at cohort entry and for up to one year after entry using electronic health record information from the VA CDW. We used the CAN score as our primary exposure to characterize overall patient complexity.[24] The CAN score is used clinically and calculated automatically and weekly using information from the electronic health record for all patients seen in primary care clinics within VA. For these analyses, we calculated an average CAN score at baseline and over each quarter for 1 year of follow-up. For each Veteran, the average CAN score was calculated using the weekly CAN scores from the 3 months prior.

Our main outcome of interest was incident prescription of ICS. We assessed incident prescriptions of ICS in each quarter following the cohort entry date for one year of follow-up time. The outcome was categorized into a binary variable (initiated versus did not initiate) for each quarter.

The 21 healthcare systems in this study represented diverse geographic areas across the regions of the United States with near complete representation from the 23 Veterans Integrated Service Networks (VISNs). To characterize VA center complexity, we used the information from the SAIL report in 2 ways. First, we characterized medical centers as high versus low complexity (designation 1a-1c = high complexity; designation 2-3 = low complexity). Second, we characterized each center as high versus low COPD annual volume (≥1,000 annual COPD admissions = high volume; <1,000 annual COPD admissions = low volume). We used SAIL report data from the 2016 year due to its completeness for all 21 sites in that year.

Statistical Analysis

To assess whether CAN scores are associated with a first ICS prescription, we modeled a time-to-event analysis using a Cox proportional hazards model with a time-varying CAN exposure at cohort entry and updated every 3 months during follow-up. The time scale was time-in-cohort and Veterans were followed for 365 days. Failure was defined as a first prescription of ICS in each quarter of follow-up time. Veterans were censored at the time of death or at the end of follow-up, whichever came first.

We tested both a continuous CAN score, and a CAN score categorized by quartiles, given the high-score skewed distribution of the scores. We included patient age in the model and did not include additional covariates due to concerns with model overfit due to the comprehensive nature of

the CAN score. Each model was clustered by medical center to account for correlated data at the level of the health system.

To assess effect modification by health system-level complexity, we tested two models. The first model included the binary VA center complexity parameter plus an interaction term for site-complexity and a continuous CAN score. The second included the binary COPD annual volume score plus an interaction term for site COPD-volume and a continuous CAN score. The interaction term was examined for statistical significance in each model. The proportional hazards assumption was met in all models with Schoenfeld residuals.

We performed separate sensitivity analyses to address the changes in the GOLD statement recommendations regarding ICS from the 2011 to 2017 version. At the time of this cohort, the 2011 statement was in use and ICS were recommended in patients with severe COPD by FEV_1 (FEV_1 ≤50% predicted). However, the newest statement no longer recommends use of ICS in severe COPD in the absence of severe or frequent exacerbations. Therefore, patients with severe COPD by FEV_1 (FEV_1 percent predicted ≤50%) at baseline were excluded in sensitivity analyses to determine whether our findings persisted with application of recommendations in effect at the time of cohort entry.

For all analyses, we used STATA version 15 (College Station, Texas, United States). This study was conducted under the VA Quality Enhancement Research Initiative (QUERI) program and we received a waiver of informed consent to conduct this observational study.

RESULTS

Overall, 24,235 Veterans with a COPD diagnosis and airflow obstruction were available for review. Twenty-one sites contributed PFT data to the CDW and were included for analysis. We excluded 1,366 patients with an inpatient and 1,813 patients with ≥2 outpatient COPD exacerbations in the year prior to the cohort entry. An additional 5,465 patients were diagnosed with comorbid asthma and 318 with missing CAN scores. 8,056 patients received ICS at baseline and were also excluded. Exclusion criteria were not mutually exclusive. After all exclusions, 8,497 patients remained for analysis and the mean follow-up time was four quarters.

At baseline, the sample had a mean age of 68.4 years (SD 8.8). The baseline characteristics of Veterans are presented stratified by CAN score in quartiles (Table 1). Those at the highest stratum of complexity were more likely to be older and not married. Subjects with greater complexity also had a greater proportion of comorbidities, including severe COPD by FEV_1, and more utilization of healthcare services. The distribution of high complexity patients varied significantly across the 21 sites (range of proportion 9% - 32%). There were a total of 654 deaths (7.7%) during the one-year follow-up.

Over the follow-up period, we identified 1,889 patients (22.2%) with new ICS prescriptions. The prescription of ICS over follow-up varied significantly across the 21 sites (range of proportion 0% - 34%). In the model testing the CAN as a continuous measure, higher CAN score was significantly associated with a first ICS prescription (HR 1.017 per CAN unit; 95% CI 1.013 to 1.021), adjusted for age (Table 2). For each one-point increase of CAN score there was a 2% increase in the risk of prescription of ICS. This association demonstrated a dose-response when analyzing CAN scores by quartile (Table 2): compared with those in the lowest quartile of CAN scores, the risk of unnecessary ICS increased with each quartile of CAN. The risk of unnecessary ICS was 102% higher for those in the fourth quartile relative to those in first. In sensitivity analyses,

the association of CAN score and unnecessary ICS was not changed when excluding subjects with severe COPD by FEV_1.

Four sites were assigned a "low complexity" designation (complexity code 2 or 3). The annual COPD hospitalization volume ranged from 168 - 2,240, and seven sites assigned as "high site volume." When testing for effect modification with individual CAN score, neither site complexity code or COPD site volume significantly modified the association between patient complexity and unnecessary ICS (Table 3).

DISCUSSION

In this study of a large cohort of Veterans with COPD, increased patient complexity as measured by CAN score was associated with an increased risk of receipt of incident unnecessary ICS. Our markers of system-level complexity, however, did not modify the association between patient level complexity and unnecessary ICS.

Comparison to prior literature and novel findings

Our work is in general agreement with previous studies and highlights the difficulty of delivering high value care to complex patients with COPD. An analysis of SPIROMICS found that 26% of participants with COPD were overtreated and that 95% of the overtreatment was from unnecessary ICS.[10] Another study also found that overuse of ICS occurred in milder disease (GOLD-A and GOLD-B groups), despite the recommendation for use in GOLD-C and GOLD-D.[33] The authors' postulated the overlap with asthma may explain some of the unnecessary use of ICS in COPD, in addition to the notion of "clinical inertia" to changing therapy, especially when patients are clinically stable. Our results add to the existing literature by examining incident unnecessary use of ICS which limits considerations of provider persistence in prescribed therapies and avoids the possibility of clinical inertia in the setting of changing recommendations.

Possible explanations for unnecessary ICS in COPD

Why complex patients with COPD receive unnecessary therapy is likely to derive from a complex mechanism. One potential explanation for ICS in complex patients with COPD and low exacerbation risk is the severity of COPD by FEV_1. Prior to 2017, GOLD recommended the use of ICS in either frequent exacerbators or those patients with severe COPD. The new 2017 statement does not continue the recommendation to use ICS in patients with severe COPD alone.[13] However,

when we excluded patients with severe COPD by FEV_1, patient complexity remained associated with unnecessary ICS. Another hypothesis for unnecessary ICS in complex patients with COPD may stem from the barriers to referral to pulmonary rehabilitation (PR) or palliative care programs, which would be indicated and beneficial in COPD patients with worsening symptoms. A recent study found that older patients, and those with lower socioeconomic status, were less likely to be referred to PR.[34] This may overlap with our complex COPD population and could explain why unnecessary ICS were provided in substitution for an indicated therapy, such as PR. A study of referral and utilization patters of palliative care for symptom management in COPD found similar results.[35] Additional study is needed to understand the barriers to referral-based services and the processes behind delivery of rehabilitative and palliative care which are likely to differ from the barriers to prescribing medications.

Effect of health system complexity

We explored whether health system complexity would modify the association with unnecessary ICS in COPD. However, there was no evidence that our markers of health system complexity were effect modifiers. At present, no structural interventions exist to improve COPD-care quality, which is likely to explain the lack of an effect of system complexity on the delivery of high-quality care. Another explanation is also that we measured only two characteristics that fall into the "structural" domain of the Donabedian model of quality.[36] We did not measure "process" factors that reflect the actions a health system, and may provide a more accurate description of system complexity. We also did not have complexity metrics at the provider-level, which may explain the prescribing patterns of ICS in COPD. Future studies should incorporate provider-level metrics, assess provider knowledge and attitudes towards prescribing practices in COPD, and develop health system performance incentives to improve COPD care quality.

Limitations and strengths

Our study has limitations. Patients in this cohort may have become eligible for appropriate ICS treatment by suffering from an exacerbation that occurred outside of the VA system. A strength of the cohort used in this study is the availability of spirometry to confirm airflow obstruction and reduce diagnostic misclassification of COPD. This cohort does not include patients with COPD who did not receive spirometry and limits generalizability to the real-world practice setting. Another strength of this study is the nationwide capture of patients with COPD to make up this cohort. The VA system also allows for complete availability of pharmacy records to analyze prescriptions over time and is another strength of this study. The COPD-specific SAIL report measures were not time-varying in this analysis as the COPD-specific metrics were measured starting in mid-2015, after the introduction of the CMS penalty in 2014. Therefore, 2016 was the first year of complete data for COPD-specific metrics. Future studies in updated cohorts are needed to see if health-system level metrics vary with time and therefore could change the association with outcomes such as inappropriate prescribing.

Conclusion

This analysis presents evidence of an association between patient complexity and unnecessary delivery of ICS. Future work is needed to develop de-prescribing interventions in this complex group of patients and understand the processes in clinical settings that contribute to this potentially harmful practice.

Table 1. Baseline characteristics of the cohort stratified by CAN score quartiles

	Cohort (n=8,497)	CAN $_{0\text{-}25\%}$ (n=2,212)	CAN $_{25\text{-}50\%}$ (n=2,302)	CAN $_{50\text{-}75\%}$ (n=1,865)	CAN $_{75\text{-}100\%}$ (n=2,118)
Demographics					
Age at PFT, mean (SD)	68.4 (8.8)	67.4 (8.2)	68.2 (8.5)	68.4 (8.9)	69.7 (9.4)
Sex, n (%)					
Male	8,257 (97)	2,165 (98)	2,227 (98)	1,812 (97)	2,053 (97)
Race, n (%)					
White	7,055 (83)	1,870 (85)	1,928 (84)	1,543 (83)	1,714 (81)
Black	827 (10)	156 (7)	213 (9)	192 (11)	260 (12)
Marital Status					
Married	3,970 (47)	1,310 (59)	1,093 (48)	773 (42)	794 (38)
Service Connected, n (%)	4,539 (53)	1,152 (52)	1,259 (55)	1,029 (55)	31,098 (52)
Body Mass Index, n (%)					
Underweight	306 (4)	65 (3)	67 (3)	72 (4)	102 (5)
Normal	2,580 (30)	660 (30)	678 (30)	561 (30)	681 (32)
Overweight	2,744 (32)	763 (35)	741 (32)	560 (30)	680 (32)
Obese	2,840 (34)	713 (32)	806 (35)	669 (36)	652 (31)
Smoking Status, n (%)					
Current	3,367 (44)	880 (45)	932 (45)	721 (43)	834 (42)
Severe COPD by FEV_1, n (%)	2,067 (24)	511 (23)	564 (25)	431 (23)	561 (27)
Comorbidities					
Congestive Heart Failure	1,222 (14)	45 (2)	153 (7)	275 (15)	749 (35)
Diabetes	2,297 (27)	371 (17)	566 (25)	577 (31)	783 (37)
Utilization, n (%)					
Pulmonary Appointment in 1 year	750 (9)	83 (4)	159 (7)	194 (10)	314 (15)
Cardiology Appointment in 1 year	1,039 (12)	81 (4)	159 (7)	248 (13)	551 (26)
Primary care appointment in 1 year	3,651 (43)	943 (43)	994 (43)	780 (42)	934 (44)

Values are presented as mean (standard deviation) or n (%) as indicated. PFT = pulmonary function test; FEV_1 = forced expiratory volume in one second.

Table 2. Risk of unnecessary ICS use by continuous and quartile of CAN scores

CAN	Incident ICS, n	Person-time at risk, person-quarters	Incident ICS rate per person-quarter	HR
1st quartile	416	7,736	0.054	1.00 (reference)
2nd quartile	463	8,433	0.055	1.39 (1.20 – 1.61)
3rd quartile	459	6,185	0.074	1.69 (1.44 – 1.97)
4th quartile	551	6,936	0.079	2.02 (1.75 – 2.34)
CAN score (linear)	1,889	29,290	0.064	1.017 (1.013 – 1.021)

Values are presented as hazard ratios with 95% confidence intervals and are adjusted for age and clustered by site. CAN = care assessment needs score; ICS = inhaled corticosteroids

Table 3. Tests of effect modification by health system complexity and COPD-volume

Variable	HR (95% CI)	Interaction P-value
Model 1		
CAN score	1.02 (1.01 – 1.03)	
Site complexity	1.38 (0.88 – 2.16)	
CAN x site complexity	0.997 (0.99 – 1.01)	0.45
Model 2		
CAN score	1.02 (1.01 – 1.02)	
Site COPD-volume	1.38 (0.85 – 2.24)	
CAN x site COPD-volume	0.997 (0.99 – 1.00)	0.24

Values are presented as hazard ratios (HR) with 95% confidence intervals. Each model is adjusted for age and clustered by site. CAN = care assessment needs score; COPD = chronic obstructive pulmonary disease

BIBLIOGRAPHY

1. Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2012(7):CD002991.
2. Global Initiative for Chronic Obstructive Lung Disease (GOLD): global strategy for the diagnosis, management and prevention of COPD. 2018; www.goldcopd.org. Accessed May 20, 2018.
3. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ.* 2000;320(7245):1297-1303.
4. 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(8):775-789.
5. Crim C, Calverley PM, Anderson JA, et al. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. *Eur Respir J.* 2009;34(3):641-647.
6. Loke YK, Cavallazzi R, Singh S. Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies. *Thorax.* 2011;66(8):699-708.
7. Singh S, Loke YK. An overview of the benefits and drawbacks of inhaled corticosteroids in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis.* 2010;5:189-195.
8. Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and the risks of diabetes onset and progression. *Am J Med.* 2010;123(11):1001-1006.
9. Slatore CG, Bryson CL, Au DH. The association of inhaled corticosteroid use with serum glucose concentration in a large cohort. *Am J Med.* 2009;122(5):472-478.
10. Ghosh S, Anderson WH, Putcha N, et al. Alignment of Inhaled COPD Therapies with Published Strategies: Analysis of the GOLD Recommendations in SPIROMICS. *Ann Am Thorac Soc.* 2018.
11. Suissa S, Barnes PJ. Inhaled corticosteroids in COPD: the case against. *Eur Respir J.* 2009;34(1):13-16.
12. Corrado A, Rossi A. How far is real life from COPD therapy guidelines? An Italian observational study. *Respir Med.* 2012;106(7):989-997.
13. Rinne ST, Wiener RS, Chen Y, et al. Impact of Guideline Changes on Indications for Inhaled Corticosteroids Among Veterans with COPD. *Am J Respir Crit Care Med.* 2018.
14. Rossi A, Guerriero M, Corrado A, Group OAS. Withdrawal of inhaled corticosteroids can be safe in COPD patients at low risk of exacerbation: a real-life study on the appropriateness of treatment in moderate COPD patients (OPTIMO). *Respir Res.* 2014;15:77.
15. Magnussen H, Disse B, Rodriguez-Roisin R, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. *N Engl J Med.* 2014;371(14):1285-1294.
16. Weiss CO, Boyd CM, Yu Q, Wolff JL, Leff B. Patterns of prevalent major chronic disease among older adults in the United States. *JAMA.* 2007;298(10):1160-1162.
17. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med.* 2002;162(20):2269-2276.

18. Dowson C, Laing R, Barraclough R, et al. The use of the Hospital Anxiety and Depression Scale (HADS) in patients with chronic obstructive pulmonary disease: a pilot study. *N Z Med J.* 2001;114(1141):447-449.
19. Brenes GA. Anxiety and chronic obstructive pulmonary disease: prevalence, impact, and treatment. *Psychosom Med.* 2003;65(6):963-970.
20. Puente-Maestu L, Calle M, Rodriguez-Hermosa JL, et al. Health literacy and health outcomes in chronic obstructive pulmonary disease. *Respir Med.* 2016;115:78-82.
21. (CDC) CfDCaP. Chronic obstructive pulmonary disease among adults - United States, 2011. *Morbidity and Mortality Weekly Report.* 2012;2012(61):938-943.
22. Gershon AS, Dolmage TE, Stephenson A, Jackson B. Chronic obstructive pulmonary disease and socioeconomic status: a systematic review. *COPD.* 2012;9(3):216-226.
23. Gershon AS, Hwee J, Victor JC, Wilton AS, To T. Trends in socioeconomic status-related differences in mortality among people with chronic obstructive pulmonary disease. *Ann Am Thorac Soc.* 2014;11(8):1195-1202.
24. Wang L, Porter B, Maynard C, et al. Predicting risk of hospitalization or death among patients receiving primary care in the Veterans Health Administration. *Med Care.* 2013;51(4):368-373.
25. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* 1992;45(6):613-619.
26. Yen TW, Pezzin LE, Li J, Sparapani R, Laud PW, Nattinger AB. Effect of hospital volume on processes of breast cancer care: A National Cancer Data Base study. *Cancer.* 2017;123(6):957-966.
27. Landovitz RJ, Desmond KA, Gildner JL, Leibowitz AA. Quality of Care for HIV/AIDS and for Primary Prevention by HIV Specialists and Nonspecialists. *AIDS Patient Care STDS.* 2016;30(9):395-408.
28. Korom-Djakovic D, Canamucio A, Lempa M, Yano EM, Long JA. Organization Complexity and Primary Care Providers' Perceptions of Quality Improvement Culture Within the Veterans Health Administration. *Am J Med Qual.* 2016;31(2):139-146.
29. Sjoding MW, Prescott HC, Wunsch H, Iwashyna TJ, Cooke CR. Hospitals with the highest intensive care utilization provide lower quality pneumonia care to the elderly. *Crit. Care Med.* 2015;43(6):1178-1186.
30. Valley TS, Sjoding MW, Goldberger ZD, Cooke CR. ICU Use and Quality of Care for Patients With Myocardial Infarction and Heart Failure. *Chest.* 2016;150(3):524-532.
31. Affairs UDoV. VA Strategic Analytics for Learning and Improvement. https://www.va.gov/QUALITYOFCARE/measure-up/Strategic_Analytics_for_Improvement_and_Learning_SAIL.asp. Accessed July 7, 2017.
32. Bryson CL, Au DH, Young B, McDonell MB, Fihn SD. A refill adherence algorithm for multiple short intervals to estimate refill compliance (ReComp). *Med Care.* 2007;45(6):497-504.
33. Contoli M, Corsico AG, Santus P, et al. Use of ICS in COPD: From Blockbuster Medicine to Precision Medicine. *COPD.* 2017;14(6):641-647.
34. Spitzer KAS, M.S.; Priya, A.; Pack, Q.R.; Pekow, P.S.; Laqu T.; Pinto-Plata, V.M.; ZuWallack, R.L.; Lindenauer, P.K. Participation in pulmonary rehabilitation following

hosptialization for COPD among Medicare beneficiaries. *Annals of the American Thoracic Society.* 2018.
35. Brown CE, Jecker NS, Curtis JR. Inadequate Palliative Care in Chronic Lung Disease. An Issue of Health Care Inequality. *Ann Am Thorac Soc.* 2016;13(3):311-316.
36. Donabedian A. Evaluating the quality of medical care. *Milbank Mem Fund Q.* 1966;44(3):Suppl:166-206.