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Retrospective Cohort Study of Tobacco Dependence Treatment Patterns in a US Commercially Insured Population

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RETROSPECTIVE COHORT STUDY OF TOBACCO DEPENDENCE TREATMENT PATTERNS IN A US COMMERCIALLY INSURED POPULATION

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ABSTRACT

Recognizing the substantial public health impact of tobacco dependence (TD) and consequent importance of reducing tobacco use, the United States Public Health Service (USPHS) issues evidence based clinical practice guidelines (CPG) that urge "clinicians and health care delivery systems to consistently identify and document tobacco use status and treat every tobacco user seen in a health care setting". The latest guidelines, published in 2008, were written "in response to new, effective clinical treatments for tobacco dependence" identified since 1999 and contain strategies and recommendations designed to assist clinicians, administrators, insurers, and purchasers in "delivering and supporting effective treatments for tobacco use and dependence". The guidelines state that, barring contraindication or insufficient study in a specific sub-group, interventions for tobacco cessation are appropriate for all individuals who use tobacco, including patients with medical co-morbidities. Specific medical co-morbidities cited in the CPG for which pharmacologic interventions have been shown effective include cancer. Moreover, continued smoking in cancer patients can affect the pharmacokinetics of cancer treatments.

An important consideration for patients selected for treatment with smoking cessation medication (SCM) is the duration of therapy or persistence with therapy as these measures of medication adherence have been found to be associated with treatment success in clinical trials. Another important factor to consider in assessing SCM is recognition that tobacco dependence is a chronic disease that often requires repeated interventions. Patient relapse to tobacco use following a period of abstinence achieved with use of SCM is not unexpected.

Since the CPG serve as the definitive source to inform tobacco cessation practice in the US, one would expect that epidemiologic studies of smoking cessation medications (SCM) have been conducted in order to understand intervention use in routine clinical practice, both in the overall population of tobacco dependent patients and those with smoking related co-morbidities, such as cancer since epidemiologic studies are a required early step in the process toward closing gaps in care.

However, literature search for population level studies in large representative populations revealed few and most are derived from survey level data. Similarly, literature search for studies of the use of SCM in patients with cancer returned few results. Thus, real world studies describing the epidemiology of SCM in routine US clinical practice are lacking. Though they are not without limitations, adequately controlled observational studies using administrative healthcare claims data can answer important questions in a relatively inexpensive and time-efficient manner.

This dissertation utilizes the manuscript format and has three main objectives:

1) To describe the pharmacoepidemiology of SCM among smokers identified through CPT and ICD-9 codes to answer the question, "Who among smokers receives pharmacologic treatment?"

2) To describe treatment persistence in tobacco dependent patients prescribed SCM, repeat treatment with SCM and patient and prescriber characteristics associated premature discontinuation and repeat therapy.

3) Evaluation of the use of SCM among tobacco dependent patients with smoking related cancer diagnoses to answer the question, "Who receives pharmacologic treatment and who doesn't?"

The LifeLink™ Helath Plan Claims Database was employed to identify patients diagnosed or counseled for tobacco cessation (index) during a one year period and evaluate the use of SCM in the 1 year following the index date, rates of premature discontinuation and repeat therapy as well as use of SCM in patients with smoking related cancers. Predictors of the use of SCM in tobacco dependent patients, premature discontinuation and repeat therapy were assessed using logistic regression models, controlling for pre-index patient and/or treatment characteristics. The same was performed to identify predictors of SCM use in tobacco dependent patients with smoking related cancer.

Major findings reported in the first manuscript are that approximately 11% of newly diagnosed tobacco dependent patients received treatment within a year of diagnosis and that the youngest and oldest age groups were less likely to receive SCM than those at middle age. Of note, patients who may have had tobacco related co-morbidities were less likely to receive treatment than those without. The study of persistence and repeat therapy revealed that mean persistence was 36 days and that >90% of patients discontinued SCM before 12 weeks of therapy, shorter than recommendations. Patients under 50 years old and 65 years or older were more likely to discontinue prematuredly than patients aged 50-58 years. Few patients (5%) repeated therapy ≥ 26 weeks following index. The final study of the use of SCM in tobacco dependent patients with smoking related cancer revealed that tobacco

dependence of counseling/advice for smoking cessation in these patients was likely coincident or following diagnosis of comorbidity. This finding was also noted in the first study where pre-index mean Charlson Comorbidity was lower than the period following diagnosis.

The 3 studies presented provide insight into the utility of using administrative claims data to study patients who are tobacco dependent and their treatment with SCM. Taken in their entirety, these studies' findings contribute certain apparent overarching themes and other important observations that may be useful to practicing clinicians to highlight potential opportunities for treatment with SCM in patients who may benefit most. First, it seems that the health system is identifying patients as tobacco dependent co-incident with identification of other co-morbidity. Earlier intervention of management of tobacco dependence is likely the best strategy to aid patients in quitting. Second, diagnosis or counseling by a hospital related practitioner was associated with reduced likelihood of SCM treatment as an outpatient overall and in patients with smoking related cancer. Hospitalization has been identified as an opportune time for clinicians to intervene and offer assistance with smoking cessation. Diagnosis by a therapeutic specialist was associated with lower likelihood of SCM use and tobacco dependence can be a major contributor to risk of events often managed by therapeutic area specialists, e.g., cardiologists and oncologists. Rates of treatment with SCM by physician type is not widely described but literature reports and clinical practice guidelines recommend that cardiologists and oncologists are well positioned to assist patients in their quit attempts to reduce overall health risks.

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PREFACE

This thesis was written and formatted following the guidelines presented by the University of Rhode Island Graduate School. It is written in the Manuscript Format and is organized in three chapters: Epidemiology of smoking cessation medications in the United States (Chapter 1), Persistence and Repeat Use of Smoking Cessation Medications in the United States (Chapter 2), Use of Smoking Cessation Medications in Tobacco Dependent Patients with Smoking Related Cancers (Chapter 3).

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MANUSCRIPT 1

Epidemiology of Smoking Cessation Medication Use in the United States

Planned submission to Journal of Smoking Cessation

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Background

Smoking continues to be a leading contributor to morbidity and mortality in the United States[1,2](US) and intensive public health campaigns have been waged to assist smokers' quitting efforts and to educate clinicians as to the chronic relapsing nature of tobacco dependence and assist their efforts in aiding their patients to quit. Leading US based clinical practice guidelines for tobacco cessation recommend that smoking cessation medications (SCM) be offered to all patients, excepting those with specific contraindications or where evidence of efficacy may be lacking.[3] Despite these broad recommendations for employing SCM to aid smokers in quitting, little is known as to the extent of their use, nor which patient characteristics may be associated with prescription of such treatments.

Health-related databases, including claims databases, are an important data source for research. One strength of these data is that they allow researchers to examine medical care utilization as it occurs in routine clinical care or the "real world". These data sources can provide large study populations, long observation periods and allow for examination of specific sub-populations.[4] Though they are not without limitations, adequately controlled observational studies using administrative claims data can answer important questions in a relatively inexpensive and time-efficient manner.[4] Of note, current estimates suggest that 87% of the US population has health insurance coverage through employer sponsorship (48%), other private insurance (6%) , Medicaid (16%), Medicare (15%) or other public insurance (2%).[5]

Consequently, examination of nationwide US health plan data is expected to reveal useful information regarding tobacco cessation treatment in routine clinical practice. Few reports exist in the literature regarding the epidemiology of tobacco cessation therapy in routine US clinical practice. Studies with a national focus include those using national survey databases such as the National Health Interview Survey and the National Ambulatory Medical Care Survey.[6-8] Similar to Healthcare Effectiveness Data and Information Set (HEDIS) measures, these databases typically include self-reported smokers' recall of whether assistance or advice to quit smoking was given by a health care provider. Although these studies provide a broad epidemiologic perspective, their results may be affected by recall bias.

Few studies have examined administrative claims data for the purpose of understanding SCM use and examples include studies specific to varenicline and the effect of a utilization management approach and patients' copay on future dispensing of any SCM.[9,10] The aims of this research were to describe the pharmacoepidemiology of SCM in newly identified tobacco dependent patients in routine clinical practice in the US and to assess the patient and provider characteristics associated with its prescribing.

Methods

This study employed a retrospective cohort design using de-identified data from the LifeLink™ Health Plan Claims Database (formerly known as Pharmetrics) which is comprised of commercial health plan information obtained from managed care plans throughout the US. It is fully adjudicated medical and pharmaceutical claims for over 68 million unique patients from over 102 health plans across the U.S. (approximately

16 million covered lives per year). The database includes both inpatient and outpatient diagnoses (In International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] format) and procedures (in Current Procedure Terminology [CPT-4] codes and Healthcare Common Procedure Coding System [HCPCS] formats) as well as both retail and mail order prescription records. Available data on prescription records include the National Drug Code (NDC) as well as the quantity of the medication dispensed. Charge, allowed and paid amounts are available for all services rendered, as well as dates of service for all claims. Additional data elements include demographic variables (age, gender, geographic region), insurance product type (e.g., HMO, PPO), payer type (e.g., commercial, self-pay), provider specialty, and start and stop dates of health-plan enrollment.

The sample consisted of patients aged 16-76 with a diagnosis code for tobacco use disorder and/or CPT code for tobacco cessation counseling or advice (Appendix) during the period July 2010 to June 2011 (index) (n=15,000). Patients with ICD-9, CPT codes, or prescriptions related to tobacco dependence or treatment in the lookback period January 2009 through June 2010 were excluded. Pre-index Charlson Comorbidity Index (CCI) scores for each patient were calculated using the algorithm develop by Quan, et al., through identification of ICD-9 codes related to 17 co-morbidity categories in the 12 month period prior to and 12 month period following the index date (including index date) (Appendix). Weights specific to each co-morbidity category were assigned and the CCI score calculated; higher scores indicate greater co-morbidity.[11]

Statistical Analysis

Descriptive statistics were used to describe demographic and clinical characteristics and frequency of prescription of SCM defined as 1 or more claim for varenicline, bupropion SR or NRT during the 1 year period following diagnosis for tobacco use disorder or CPT code for tobacco cessation counseling, advice or treatment. Demographic characteristics included patient age at index, gender, geographic region of residence and insurance related factors such as payer type and insurance product. Clinical characteristics included 12 months pre-index CCI score and CCI categories. Provider characteristics included the practitioner type associated with diagnosis of or counseling/advice for tobacco dependence.

Patients were categorized into one of two groups, those who were prescribed SCM within 1 year of diagnosis and those who were not. Bivariate analyses including t-tests for continuous variables and chi-square tests or Fisher's Exact test for categorical variables were used to analyze differences in characteristics of those patients receiving SCM and those who did not. Assessment of factors associated with SCM prescription was performed by conducting a series of univariate logistic regression equations. To qualify for multivariate logistic regression, variables had to be associated with SCM prescription in the univariate analyses ($p<0.2$) or be otherwise clinically important. Multivariate logistic regression was used to assess relationships between the independent variables of patient and provider characteristics and the dependent variable of pharmacologic intervention for SC within a 1 year period following the diagnosis of or procedure for tobacco use disorder. The model was created using a

backward elimination process and the likelihood ratio test and AIC used to assess the model at each step, removing least statistically significant covariates ($p>0.05$) with each iteration and evaluating differences between full and reduced models for statistical significance. In advance of model inclusion, parametric form of continuous independent variables and multicollinearity among independent variables were assessed.

Multicollinearity was assessed by regressing independent variables against the independent variable of patient age at index. Main effects and two factor interactions of independent variables found significant in the model were assessed. The Hosmer-Lemeshow test was used to assess goodness of fit of the final model. The measure of effect is presented as an odds ratio with corresponding 95% confidence intervals. All analyses were conducted using SAS® Version 9.4 (SAS Institute, Cary, NC) with statistical significance defined as $p <0.05$. Analyses were performed using a 2-tailed alpha of 0.05 and 95% confidence intervals calculated.

Results

In total, 15,000 patients with ICD-9 or CPT codes indicative of tobacco dependence disorder were identified (Figure 1). Mean (SD) age at diagnosis was 46.08 (14.46) years, 54.49% were female and 70.60% resided in the Midwest. (Table 1). Mean (SD) pre-index Charlson Co-morbidity Index (CCI) was 0.540 (±1.184) with most patients having no Charlson co-morbidity (70.73%) and, of those with co-morbidity, the most frequently observed was COPD (12.61%). Most (56.95%) were diagnosed with or counseled for tobacco cessation by a general medicine practitioner

and the majority of patients (79.27%) had commercial insurance (s 1,2). Of the diagnosed sample, 1,621 (10.81%) had a prescription for SCM filled during the 1 year post-index period (Figure 1). Varenicline was the most commonly prescribed agent (69.46%) and bupropion SR the least commonly prescribed (4.38%), with NRT formulations comprising 27.76% of SCM use (Figure 2).

In treated patients, mean (SD) age was 44.56 (12.52) years and the youngest and oldest patients were least likely to be prescribed SCM while those aged 25-44 were nearly twice as likely to receive SCM. Gender and geographic region were also related to receiving SCM with females being more likely than males to have a prescription for SCM (11.33% vs. 10.18%, p=0.0243) and patients residing in the Midwest nearly 3 times more likely to receive SCM than those residing in the West. Pre-index mean CCI score was lower in SCM treated patients than untreated (0.402 vs. 0.5571, p<0.0001) with SCM treatment occurring in >20% of tobacco dependent patients with HIV/AIDS and approximately 10% of COPD patients. Less than 10% of patients with other CCI categories received treatment. Patients with commercial and Medicaid insurance types had the highest treatment rates (11.74% and 12.56%, respectively) with <10% of patients with Medicare Supplemental or Medicare Advantage receiving treatment.

The most common diagnosing practitioner type was the category of general medicine (56.95%) and more patients (14.35%) were treated with SCM who were diagnosed as tobacco dependent by a general medicine practitioner than any other specialty. The lowest rates of SCM treatment patients were in those whose diagnosis

was made by a hospital related physician (4.92%) or a therapeutic area specialist (7.06%), though these were the second and third most common diagnosing practitioner types (35.23% and 9.83%, respectively) (Table 3).

Multivariate logistic regression results indicated that patients with a pre-index co-morbidity of cancer had reduced odds of receiving SC medication (OR 0.703, 95% CI 0.504-0.980). Compared to patients age 45-54, patients between 18-24 years had lower likelihood of receiving SCM (OR 0.539, 95% CI 0.430-0.677) as did patients >56 years (OR 0.616, 95% CI 0.528-0.718). Compared to those patients diagnosed by a general medicine practitioner, those diagnosed or counseled for tobacco dependence by a hospital related practitioner (OR 0.332, 95% CI 0.285-0.386), by a therapeutic area specialist (OR 0.594, 95% CI 0.473-0.745) had lower likelihood of SC medication prescription (Table 4). We found no association of gender, geographic region or insurance related factors with prescription of SCM in the 1 year post-index. Once you have the correct amount of content on the first page, you can then move your cursor onto the next page of the template and add the rest of the content of the chapter by either typing or copying and pasting.

Discussion

Clinical practice guidelines for tobacco cessation recommend that SCM be offered to all tobacco dependent patients with few exceptions. However, little information exists regarding the extent of SCM use in broad populations of tobacco dependent persons in the US. This study observed that approximately 11% of those

diagnosed or counseled for tobacco cessation (10.18% of males, 11.3% of females) were prescribed SCM during the following year and the mean age (~46 years) was slightly older than or similar to that studied in recent clinical trials of SCM. [12 13 14] After controlling for covariates, the patient demographics of gender and geographic region were not associated with SCM treatment. However, 18-24 and 56-75 year olds had lower odds of receiving SCM than those aged 45-54, the age group with the largest proportion of treated patients. Of note, the clinical factor of comorbid cancer had a negative association, as did clinical settings of diagnosis other than general medicine.

It is difficult to compare rates of SCM prescribing and recipient patient characteristics to those reported in the current literature due to dissimilar study designs and populations studied, however comparison of results from some studies is worth noting. Huang, et al [15] used association rule mining methods to identify smokers in the United Kingdom (UK) primary care and the characteristics of those who typically do or do not receive SCM. The authors identified a population of smokers that was 46.7% male, of which 13.4% received a prescription for one or more SCM in 2008; 12.8% of males received SCM and 13.9% of females. Contrary to our finding that gender was not associated with receipt of treatment, these authors found that females were slightly more likely than males to receive SCM in multivariate analysis (OR 1.09, 95% CI 1.06-1.11).). They also found that those in age groups > 30 years were more likely to receive SCM than younger patients. Similarly, we found that the youngest patients (<24 years) were less likely to receive SCM than those patients age 45-54, however we also found that the oldest patients (>56 years) had lower odds. Of

note, a recent policy statement by the American Academy of Pediatrics states that, despite limited research in this age group, SCM is an option for tobacco-dependent adolescents based on level of dependence and readiness to change.[16] Also of note is a recent literature review of SCM in older adults in which the authors report a dearth of information regarding use in this population.[17] More study of the use in SCM in the youngest and oldest tobacco dependent patients is needed.

In the current study, patients with Medicaid and commercial insurance (primarily employer base) had the highest rates of SCM use (12.56% and 11.74%, respectively) while patients with Medicare Advantage had the lowest rate (5.08%). It should be noted that during the study period, Medicare coverage of tobacco cessation services may have been limited. In 2011, Medicare expanded coverage of tobacco cessation counseling to any Medicare recipient who wanted to quit. Before then, these services were limited to those who had a smoking-related illness or symptoms of such an illness. Similar rates of pharmacy benefit (83.5%) as rates of commercial insurance (~79.3%) were observed in this study and, while coverage specific to SCM is not known, patients with a pharmacy benefit may be more likely to fill prescriptions than those without.

Medicaid populations have a higher smoking rate than the general population[18,19] which might explain higher treatment rates than other payer types. In addition, coverage for SCM in Medicaid may be different than in other payer types. As of 2014, some SCM for some Medicaid enrollees were covered by all 50 states and the District of Columbia, but coverage for all approved SCM products for all enrollees was available in only 7 states. [20] Of note, in 2006, Massachusetts expanded coverage

to include behavioral counseling and all FDA approved medications for tobacco cessation for the Massachusetts Medicaid population and researchers found a decrease in crude smoking rate after benefit initiation.[21]

Overall, comorbidity as assessed by CCI was low but mean CCI score was higher in the follow up period compared to the 12 months pre-index. Mean pre-index CCI was 0.540 and this increased by 34% to 0.724 in the follow up period. While still low, the higher score in the follow up period suggests that diagnosis of or counseling for tobacco cessation may have been coincident with a tobacco related diagnosis or other health event. Additionally, the absence of any Charlson comorbidity pre-index was observed in 70.73% of patients, but this proportion was lower in the follow up period (60.55%) suggesting that diagnosis of a clinically significant event took place on or following the index event. Of note, certain Charlson categories were observed at considerably higher rates in the follow up period only as compared to pre-index only, e.g., COPD (4.7% pre-index only, 11.05% in follow-up only) and MI (0.59% pre-index only, 1.57% in follow-up only) (data not shown). This trend suggests that diagnosis of COPD or MI may lead practitioners to subsequently code for tobacco dependence.

We found that patients with pre-index diagnosis of HIV had the highest rates of SCM prescription while those with MI had the lowest. Individuals who are HIV-positive are more likely to smoke than the general population and HIV-positive smokers have higher mortality rates and greater likelihood of infectious comorbidities than HIV-positive non-smokers.[22-27] In addition, daily tobacco may possibly attenuate the immune and virological response to antiretroviral therapies.[28] The finding of high

rates of SCM use in patients with HIV-AIDS diagnosis in the present study reflects clinician recognition of particular risk of tobacco dependence in these patients. In contrast, the low rate of SCM prescribing in patients with MI diagnosis at baseline was surprising as stopping smoking after MI is one of the most effective actions for secondary prevention of CVD [29]. Others have described tobacco use as the forgotten cardiac risk factor, its treatment possibly receiving less attention than treatment of hypertension, hyperlipidemia or diabetes.[29] [30]

Our finding that a pre-index cancer diagnosis was associated with lower likelihood of receiving SCM is worth discussion. The USPHS reports cancer as a comorbidity in which SCM has been demonstrated as beneficial.[3] Health benefits can results from smoking cessation after a cancer diagnosis at any stage or prognosis and National Comprehensive Cancer Network (NCCN) recommends that treatment plans for smokers with cancer include pharmacotherapy as an option for intervention.[31] Of note, results of a survey by Warren et al report that physicians caring for lung cancer patients believe that current smoking affects outcomes and that tobacco cessation is a necessary part of clinical care, but few provide assistance to their patients as a routine part of cancer care.[32] Our results underscore the possible opportunity to study use and timing of SCM prescribing in patients with cancer.

Stratification of patients prescribed SCM by physician type (those diagnosing their tobacco dependence) revealed some interesting findings. The most common diagnosing specialty was the category of general medicine (56.95%) and more patients (14.35%) were treated with SCM who were diagnosed as tobacco dependent by a general medicine practitioner than any other specialty. The lowest proportions of

SCM treated patients were those whose diagnosis was made by a hospital related physician (4.92%) or a therapeutic specialist (7.06%), though these were the second and third most common diagnosing specialty (35.23% and 9.83%, respectively). Encounters with hospital related practitioners has been identified as a teachable moment to motivate individuals to risk reducing behaviors such as smoking cessation[33]

Hospitalization is an opportunity for patients to attempt to quit tobacco as they are likely to be in a smoke-free environment and may be particularly motivated by an illness caused or exacerbated by tobacco use (Fiore 2008). Patients can be encouraged to remain smoke free after discharge and begin treatment in the hospital. In a meta-analysis of randomized controlled trials of smokers hospitalized for a CVD diagnosis, a smoking cessation intervention begun in the hospital and sustained for at least 1 month post-discharge, increased cessation rates by 42% (RR: 1.42, 95% CI: 1.29–1.56) 6–12 months post-discharge and starting NRT in hospital increased quit rates over counselling alone.[34] Furthermore, in a trial of smokers hospitalized with MI, compared to usual care, intensive intervention with counseling and pharmacotherapy increased cessation rates and reduced all-cause mortality and hospital readmission.[35]

Furthermore, compared to diagnosis made by general medicine practitioner, patients diagnosed by any other practitioner type had lower odds of SCM prescription. Rates of treatment with SCM by physician type is not widely described, however Rigotti, et al state that cardiologists have a special opportunity to promote cessation since a smoker receiving a diagnosis of CHD may see the health risks of smoking suddenly personally salient and be motivated to reduce future risk. [29] As described

above, the NCCN recommends the same importance of fostering smoking cessation by oncologists. It should be noted that a patient may have received a diagnosis by multiple specialties on the same date, indicating multiple interactions with the health care system on the same date and possibly suggestive of the occurrence of an event.

This study utilized data from medical and pharmacy claims which are collected for billing and reimbursement purposes and which have inherent limitations. We used ICD-9-CM and tobacco cessation counseling specific CPT and HCPCS codes to identify smokers, excluding those with these and SCM codes in the 12 months pre-index. While this method may under-estimate the number of smokers and SCM treated patients, use of ICD-9-CM codes to identify smokers has been validated previously and the utility of administrative claims to describe SCM demonstrated.[36,9,10] The use of prescription claims exclusively in the current study may have missed the use of over the counter (OTC) products, but in an US insured population, over the counter SCM may be covered under the pharmacy benefit. It is difficult to estimate the extent to which OTC NRT is used, but results of an international survey of smokers using SCM in a quit attempt indicated that 68.3% of subjects self-report OTC NRT use. Of note, those who obtained OTC NRT appeared more likely to discontinue in the first week of use than those receiving NRT by prescription (23% vs. 13.4%, respectively.[37] As mentioned above, description of SCM coverage by Medicaid is often publicly available, but coverage by private health plans is not as widely reported and benefit designs can change frequently. However, a survey of Tennessee health plans yields some insight where researchers found wide variation in coverage of prescription and over-the counter medications with bupropion covered most often, followed by

varenicline, NRT patches and gum, then other forms of NRT. Given that the Affordable Care Act requires all new private health insurance plans to cover services recommended by the US Preventative Services Task Force including tobacco cessation treatments, future study using administrative data may yield different results. Moreover, evolution of reimbursement to incentivize physicians to intervene to aid tobacco cessation may lead to increased use of coding over time. Although data used in this study were collected from all U.S. census regions, due to geographic biases, any unprojected geographic information may not be representative of the true distribution. Finally, the small number of patients in some subgroups evaluated precludes comparisons by statistical analysis and thus, results are descriptive in nature. It is important to note that though patients were identified as smokers through diagnosis or procedure codes, this provides no insight into readiness to quit which is an important component of cessation attempts.[3]

Despite these limitations, this study adds important information regarding the epidemiology of the use of SCM in the U.S. Specifically, despite guidance describing pharmacotherapy as an option to aid most patients in quitting, approximately 11% of newly diagnosed tobacco dependent patients received treatment within a year of diagnosis, and the youngest and oldest patients were less likely to receive SCM than those at middle age. Additionally, the lowest proportions of SCM treated patients were those whose tobacco dependence diagnosis was made by a hospital related physician. Perhaps the most concerning finding was that patients with possibly tobacco related co-morbidities are less likely to receive treatment than those without. These findings suggest opportunity for more focused research with regard to use and timing of SCM

in these at risk populations. In addition to the findings regarding the epidemiology of SCM, this study suggests that diagnosis or procedure for tobacco dependence took place co-incident with occurrence of another co-morbidity and also suggests further study in the areas of systematic and early documentation of tobacco dependence which may facilitate earlier intervention.

References

1. Carter BD, Abnet CC, Feskanich D, Freedman ND, Hartge P, Lewis CE, Ockene JK, Prentice RL, Speizer FE, Thun MJ, Jacobs EJ. Smoking and mortality — Beyond established causes. *New England Journal of Medicine.* 2015*;* 372(7): 631-640.

2. Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, Anderson RN, McAfee T, Peto R. 21st-Century hazards of smoking and benefits of cessation in the United States. *New England Journal of Medicine.* 2013*;* 368(4): 341-350.

3. Fiore MC, Jaen CR, Baker TB, et al. *Treating Tobacco Use and Dependence: 2008 Update.* Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. May 2008.

4. Motheral B, Brooks J, Clark MA, Crown WH, Davey P, Hutchins D, Martin BC, Stang, P. A checklist for retrospective database studies--report of the ISPOR task force on retrospective databases. *Value in Health.* 2003 6(2): 90-97.

5. Health Insurance Coverage of the Total Population. The Henry J. Kaiser Family Foundation, 2014.

6. Bernstein, SL, Yu, S, Post LA, Dziura J, Rigotti NA. Undertreatment of tobacco use relative to other chronic conditions. *American Journal of Public Health.* 2013; 103(8).

7. Shiffman S, Brockwell SE, Pillitteri JL, Gitchell JG. Use of smoking-cessation treatments in the United States. *American Journal of Preventive Medicine.* 2008;34(2): 102-111.

8. Shiffman S, Brockwell SE, Pillitteri JL, Gitchell JG. Individual differences in adoption of treatment for smoking cessation: demographic and smoking history characteristics. *Drug and Alcohol Dependence.* 2008;93(1-2): 121-131.

9. Zeng F, Chen CI, Mastey V, Zou KH, Harnett J, Patel BV. Utilization management for smoking cessation pharmacotherapy: Varenicline rejected claims analysis. *The American Journal of Managed Care.* 2010;16(9): 667-674.

10. Zeng F, Chen CI, Mastey V, Zou KH, Harnett J, Patel BV. Effects of copayment on initiation of smoking cessation pharmacotherapy: An analysis of varenicline reversed claims. *Clinical Therapeutics.* 2011;33(2): 225-234.

11. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali, WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical Care.* 2005*;* 43(11): 1130-1139.

12. Gonzales D, Rennard SI, Nides M, Oncken, C, Azoulay S, Billing CB, Watsky EJ, Gong J, Williams KE, Reeves KR. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA: Journal of the American Medical Association.* 2006;296(1): 47-55.

13. Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, Billing CB, Gong J, Reeves, KR, Varenicline Phase 3 Study Group. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA: Journal of the American Medical Association.* 2006;296(1): 56-63.

14. Tonstad S, Tonnesen P, Hajek P, Williams KE, Billing CB, Reeves KR. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA: Journal of the American Medical Association.* 2006;296(1): 64-71.

15. Huang Y, Britton J, Hubbard R, Lewis S. Who receives prescriptions for smoking cessation medications? An association rule mining analysis using a large primary care database. *Tobacco Control.* 2013;22(4): 274-279.

16. Farber JJ, Groner J, Walley S, Nelson K, Section on Tobacco Control. Clinical practice policy to protect children from tobacco, nicotine, and tobacco smoke. *Pediatrics.* 2015; 136(5): 1008-1017.

17. Cawkwell P, Blaum C, Sherman S. Pharmacological smoking cessation therapies in older adults: A review of the evidence. *Drugs and Aging.* 2015; 32(6): 443-451.

18. Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for U.S. adults: National Health Interview Survey, 2012. National Center for Health Statistics. *Vital Health Statistics.* 2014; 10(260): 1-161.

19. Jamal A HD, O'Connor E, Babb SD, Caraballo RS, Singh T, Hu S, King BA. Current cigarette smoking among adults - United States, 2005-2014. *MMWR: Morbidity and Mortality Weekly Report.* 2015; 64(44): 1233-1240.

20. Singleterry J, Lancet E, Babb S, MacNeil A, Zhang L. State Medicaid coverage for tobacco cessation treatments and barriers to coverage — United

States, 2008–2014. *MMWR: Morbidity and Mortality Weekly Report.* 2014; 63 (12): 264-265.

21. Land T, Warner D, Paskowsky M, Cammaerts A, Wetherell L, Kaufmann R, Lei Z, Malarcher A, Pechacek T, Keithly L. Medicaid coverage for tobacco dependence treatments in Massachusetts and associated decreases in smoking prevalence. *PLoS One.* 2010;5(3): e977.

22. Burkhalter JE, Springer CM, Chhabra R, Ostroff JS, Rapkin BD. Tobacco use and readiness to quit smoking in low-income HIV-infected persons. *Nicotine and Tobacco Research.* 2005;7(4): 511-522.

23. Gritz ER, Vidrine DJ, Lazev AB, Amick BC, 3rd, Arduino RC. Smoking behavior in a low-income multiethnic HIV/AIDS population. *Nicotine and Tobacco Research.* 2004;6(1): 71-77.

24. Niaura R, Shadel WG, Morrow K, Tashima K, Flanigan T, Abrams DB. Human immunodeficiency virus infection, AIDS, and smoking cessation: the time is now. *Clinical Infectious Diseases.* 2000;31(3): 808-812.

25. Mamary EM, Bahrs D, Martinez S. Cigarette smoking and the desire to quit among individuals living with HIV. *AIDS Patient Care and STDs.* 2002;16(1): 39-42.

26. Hajjeh RA, Conn LA, Stephens DS, Baughman W, Hamill R., Graviss E, Pappas PG, Reingold TC, Rothrock G, Hutwagner LC, Schuchat A, Brandt ME, Pinner, R. W. Cryptococcosis: Population-based multistate active surveillance and risk factors in human immunodeficiency virus-infected persons. Cryptococcal Active Surveillance Group. *The Journal of Infectious Diseases.* 1999;179(2): 449-454.

27. Nuorti JP, Butler JC, Gelling L, Kool JL, Reingold AL, Vugia DJ. Epidemiologic relation between HIV and invasive pneumococcal disease in San Francisco County, California. *Annals of Internal Medicine.* 2000;132(3): 182-190.

28. Humfleet GL, Hall SM, Delucchi KL, Dilley JW. A randomized clinical trial of smoking cessation treatments provided in HIV clinical care settings. *Nicotine and Tobacco Research.* 2013;15(8): 1436-1445.

29. Rigotti NA, Clair C. Managing tobacco use: the neglected cardiovascular disease risk factor. *European Heart Journal.* 2013;34(42): 3259-3267.

30. Aboyans V, Pinet P, Lacroix P, Laskar M. Knowledge and management of smoking-cessation strategies among cardiologists in France: a nationwide survey. *Archives of Cardiovascular Diseases.* 2009;102(3): 193-199.

31. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology, Smoking Cessation v1.2015. Available at www.nccn.org. Accessed August 7, 2015.

32. Warren GW, Marshall JR, Cummings KM, Toll B, Gritz ER, Hutson, A, Dibaj S, Herbst R, Dresler, C, IASLC Tobacco Control and Smoking Cessation Committee. Practice patterns and perceptions of thoracic oncology providers on tobacco use and cessation in cancer patients. *Journal of Thoracic Oncology.* 2013;8(5): 543-548.

33. Shi Y, Warner DO. Surgery as a teachable moment for smoking cessation. *The Journal of the American Society of Anesthesiologists.* 2010;112(1): 102-107.

34. Rigotti NA, Clair C, Munafo MR, Stead LF. Interventions for smoking cessation in hospitalised patients. *The Cochrane Database of Systematic Reviews.* 2012;5:Cd001837.

35. Mohiuddin SM, Mooss AN, Hunter CB, Grollmes TL, Cloutier DA, Hilleman DE. Intensive smoking cessation intervention reduces mortality in high-risk smokers with cardiovascular disease. *Chest.* 2007;131(2): 446-452.

36. Wiley LK, Shah A, Xu H, Bush WS. ICD-9 tobacco use codes are effective identifiers of smoking status. *Journal of the American Medical Informatics Association : Journal of the American Medical Informatics Association.* 2013;20(4): 652-658.

37. Balmford J, Borland R, Hammond D, Cummings KM. Adherence to and reasons for premature discontinuation from stop-smoking medications: data from the ITC Four-Country Survey. *Nicotine and Tobacco Research.* 2011;13(2): 94-102.

Table 1.1. Rate of SCM Prescribing by Demographic Characteristics among Patients Diagnosed with Tobacco Dependence, LifeLink™ Health Plan Claims Database, (July 2010-June 2011)

	Total (N = 15,000)	No Rx for SCM in 1 yr follow up (n=13,379)	Rx for SCM in 1 yr follow up (n=1,621)	p-value
Age at index, years, mean, (SD)	46.08 (± 14.46)	46.27 (14.67)	44.56 (12.52)	<0.0001
Age Category, No. (%)				
18-24	1,598 (10.65)	1491 (93.30)	108 (6.76)	
25-34	1,984 (13.23)	1700(85.69)	284 (14.31)	<0.0001
35-44	2,590 (17.27)	2233 (86.22)	357 (13.78)	
45-54	3,965 (26.43)	3475 (87.64)	490 (12.36)	
55-64	3,533 (23.55)	3219 (91.11)	314 (8.89)	
65-75	1,283 (8.55)	1217 (94.85)	65 (5.07)	
Gender, No. (%)				
Female	8,174 (54.49)	7248(88.67)	926 (11.33)	0.0243
Male	6,826 (45.51)	6131 (89.82)	695 (10.18)	
Patient Geographic Region, No. (%)				
East	1,577 (10.51)	1403 (88.97)	174 (11.03)	
Midwest	10,590 (70.60)	9254 (87.38)	1337 (12.62)	<0.0001
South	76 (0.51)	≤75 (≤98.68)	≤5 (≤6.58)	
West	2,757 (18.38)	2647 (96.01)	110 (3.99)	
Payer Type/Benefit Design, No. (%)				
Consumer Directed	527 (3.51)	459 (87.10)	68 (12.90)	0.1145
HMO	10,342 (68.95)	9212 (89.07)	1130 (10.93)	0.4818
Indemnity	208 (1.39)	188 (90.38)	20 (9.62)	0.5773
POS	6,383 (42.55)	5589 (87.56)	794 (12.44)	<0.0001
PPO	1,133 (7.55)	1038 (91.62)	95 (8.38)	0.0063
Commercial	11,890 (79.27)	10494 (88.26)	1396 (11.74)	<0.0001
Medicaid	2054 (13.69)	1796 (87.44)	258 (12.56)	0.0058
Medicare Supplemental	452 (3.01)	416 (92.04)	36 (7.96)	0.0481
Medicare Advantage	413 (2.75)	392 (94.92)	21 (5.08)	0.0001
Self-insured	1832 (12.21)	1702 (92.90)	130 (7.10)	<0.0001

Rx=dispensed prescription, HMO=health maintenance organization, POS=place of service, PPO=preferred provider organization, SD=standard deviation, yr-year, No. = number

Table 1.2. Rate of SCM use by Clinical Characteristics in Patients Diagnosed with Tobacco Dependence, LifeLink™ Health Plan Claims Database (July 2010-June 2011)

	Total (N=15,000)	No Rx for SCM in 1 yr follow up (n=13,379)	Rx for SCM in 1 yr follow up (n=1,621)	p-value
No CCI co-morbidity (CCI=0)	10610 (70.73)	9388 (88.48)	1222 (11.52)	<0.0001
Chronic Obstructive Pulmonary Disease (COPD)	1892 (12.61)	1698 (89.75)	194 (10.25)	0.4072
Diabetes	1300 (8.67)	1189 (91.46)	111 (8.54)	0.0058
Cancer	640 (4.27)	600 (93.75)	40 (6.25)	<0.0001
Mild liver disease	442 (2.95)	405 (91.63)	37 (8.37)	0.0941
Peripheral Vascular Disease (PVD)	405 (2.70)	368 (90.86)	37 (9.14)	0.2722
Cerebrovascular Disease (CVD)	346 (2.31)	313 (90.46)	33 (9.54)	0.4417
Diabetes sequelae	272 (1.81)	254 (93.38)	18 (6.62)	0.0247
RA	239 (1.59)	219 (91.63)	20 (8.37)	ns
Congestive Heart Failure (CHF)	226 (1.51)	213 (94.25)	13 (5.75)	0.0137
Myocardial Infarction(MI)	178 (1.19)	171 (96.07)	7 (3.93)	0.0030
Renal disease	176 (1.17)	164 (93.18)	12 (6.82)	0.0865
Metastatic cancer	70 (0.47)	70 (100)	<=5 (≤7.14)	<0.01
Paralysis	51 (0.34)	46-50 (≤98.03)	≤5 (≤9.80)	ns
Ulcer	81 (0.54)	76-80 (≤98.77)	≤5 (≤6.17)	ns
Moderate to severe liver disease	31 (0.21)	26-30 (≤96.77)	≤5 (≤16.13)	ns
HIV/AIDS	32 (0.21)	25 (78.13)	7 (21.88)	0.0435
CCI, mean, (SD) in 12 months pre-index	0.540 (± 1.184)	0.5571 (1.210)	0.402 (0.936)	<0.0001
CCI, mean, (SD) during 1 year follow up period	0.774 (± 1.480)	0.780 (1.488)	0.726 (1.407)	0.1645

Rx=dispensed prescription, CCI=Charlson Co-morbidity Index, HIV/AIDS=Human immunodeficiency Virus/Acquired Immune Deficiency Syndrome

Table 1.3. SCM Prescribing Rate by Diagnosing Practitioner Type, in Patients Diagnosed with Tobacco Dependence, LifeLink™ Health Plan Claims Database, July 2010-June 2011*

	Total (N=15,000)	No Rx for SCM in 1 yr follow up (n=13,379)	Rx for SCM in 1 yr follow up (n=1,621)	p-value
General Medicine (GP/FP, Internal Medicine, NP, Ob/Gyn, Osteopath, PA)	8543 (56.95)	7317 (85.65)	1226 (14.35)	<0.0001
Hospital related (surgical, ER, hospital?, anesthesia, Orthopedics)	5285 (35.23)	5025 (95.08)	260 (4.92)	<0.0001
Specialist (e.g., cardiologist, pulm,onco, endo, ENT, gastro,ID,allergist, nephro, neuro, ophthl, optom,phys med, podiatrist, psychi,rheum,urol)	1474 (9.83)	1370 (92.94)	104 (7.06)	<0.0001
Other (DME_HH, PT, RN, SOC_WORK, MHSA_FAC)	318 (2.12)	283 (88.99)	35 (11.01)	0.9077
Pediatrics (pediatrics, neonatal)	95 (0.63)	85 (89.47)	10 (10.53)	0.9296

*Multiple specialties diagnosing the patient on the same date possible
GP=general practice, FP=family practice, NP=nurse practitioner, Ob/Gyn=obstetrics & gynecology, PA=physician's assistant, ER=emergency room, pulm=pulmonogist, onc=oncologist, endo=endocrine, ENT=ear, nose & throat, gastro=gastroenterologist, ID=infectious disease, nephro=nephrologist, neuro=neurologist, ophth=ophthalmologist, optom=optometrist, phys med= physical medicine, pscych=psychiatrist, rheum=rheumatologist, urol=urologist, DM_HH=durable medical equipment/home health, PT=physical therapist, RN=registered nurse, SOC_WORK=social worker, MHSA_FAC=mental health/substance abuse facility

Table 1.4. Summary of Logistic Regression Analysis of Predictors of Treatment with SCM in Tobacco Dependent Patients: Odds Ratios and 95% Confidence Intervals

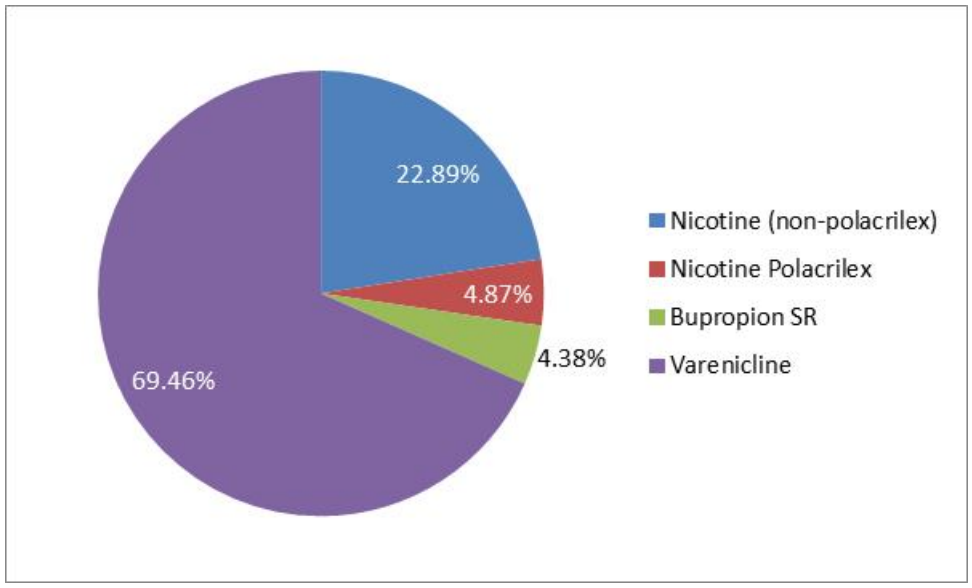
Variable	Odds Ratio	95% Wald CI
Age <18 (ref=45-54)	0.353	0.084-1.479
Age 18-24 (ref=45-54)	0.539	0.429-0.676
Age 25-34 (ref=45-54)	1.135	0.962-1.338
Age 35-44 (ref=45-54)	1.138	0.978-1.325
Age 55-64 (ref=45-54)	1.066	0.782-1.452
Age 56-75 (ref=45-54)	0.622	0.533-0.725
Diagnosis by Pediatrician (ref=general medicine)	0.880	0.447-1.735
Diagnosis by Specialist (ref=general medicine)	0.600	0.478-0.754
Diagnosis by Hospital related Practitioner (ref=general medicine)	0.332	0.285-0.386
Diagnosis by Other (non-physician) (ref=general medicine)	0.840	0.543-1.302
Pre-indexMI diagnosis	0.467	0.217-1.007
Pre-index Cancer Diagnosis	0.701	0.503-0.978
Pre-index HIV-AIDS	2.238	0.880-5.691
Hosmer and Lemeshow Test p=0.7528		

ref=reference

Figure 1.1. Sample Selection.- Tobacco Dependent Patients and Treatment with SCM, LifeLink™ Health Plan Claims Database (July 2010-June 2011)

<table>
<tr><td colspan="2">LifeLink™ Health Plan Claims Database enrolled patients: N=18,400,000 as of August 2012*</td></tr>
<tr><td colspan="2">Continuously enrolled patients January 2009 – June 2012
Patients aged 16-76 identified as having any tobacco related diagnoses or procedure, SCM or smoking related cancers
n = 117,695</td></tr>
<tr><td colspan="2">Patients identified as having any tobacco related diagnoses or procedures or smoking related cancers (Patient count without smoking cessation treatment)
n=80,486</td></tr>
<tr><td colspan="2">Patients enrolled January 2009 to June 2012 with a diagnosis or procedure indicating tobacco dependence (Patient count without smoking related cancer)
n=77,736</td></tr>
<tr><td colspan="2">Patients with a diagnosis or procedure code indicating tobacco dependence between July 2010 and June 2011 (index)
n=18,619</td></tr>
<tr><td colspan="2">Patients with a diagnosis or procedure code indicating tobacco dependence between July 2010 and June 2011 with claims activity throughout the study period (January 2009 – June 2012)
n=16,417</td></tr>
<tr><td colspan="2">Patients with no claims for SCM in the 18 month period pre-index
n=15,000</td></tr>
<tr><td>No Rx claim for SCM in 12 months post index
n = 13,379</td><td>Rx claim for SCM in 12 months post-index
n = 1,621</td></tr>
<tr><td colspan="2">*Closest estimate for continuously enrolled patients during the study period is 18.4MM patients as of August 2012. Enrollment is subject to change quarterly as updates are received from contributing health plans. Largest changes are typically seen at year beginning when patients may leave a health plan and join another. The data used for this study has been merged into a new larger database called Pharmetrics Plus which includes a larger number of contributing health plans. The database that includes the data used for this study is archived and would require data restoration to determine exact count.</td></tr>
</table>

Figure 1.2. SCM Prescribed in 1 Year Following Diagnosis, LifeLink™ Health Plan Claims Database (July 2010-June 2011) (n=1647)



MANUSCRIPT 2

Persistence and Repeat Use of Smoking Cessation Medications in the United States

Planned Submission to Journal of Smoking Cessation

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Background

Duration of use of smoking cessation medications (SCM) has been associated with treatment success in clinical trials.[1-3] However, literature reports of "real world" studies evaluating SCM treatment duration and quit outcome in clinical practice are few. One United States (US) based population survey examined the association of duration of nicotine replacement therapy (NRT) use and found no/ association with quit rates, though the population surveyed was specific to Massachusetts, which provides free NRT to interested persons.[4,5] In contrast, results of a retrospective study employing Canadian survey data which examined the association between duration of NRT use and smoking cessation indicated that NRT use for less than 4 weeks was associated with reduced likelihood of cessation, whereas use for longer periods was associated with a higher likelihood of cessation.[6] Of note, the aforementioned studies are limited to examination of NRT which is available over the counter (OTC) in the US and literature reports of US population-based studies examining the association of duration of prescription medication use with smoking cessation are scant. However, one study employed the Tobacco Use Supplement to the US Current Population Survey and results indicated that treatment with SCM for at least 5 weeks was associated with higher likelihood of successful smoking cessation.[7] No studies employing administrative claims data to assess duration of therapy (persistence) have been published.

Another important consideration in assessing SCM use is recognition that tobacco dependence is a chronic disease that often requires repeated intervention with the

average smoker making 6 to 9 lifetime quit attempts.[8] Thus, patient relapse to tobacco use following a period of abstinence achieved with use of SCM is not unexpected. Treatment guidelines encourage clinicians to prescribe/recommend medications plus counseling for each quit attempt and research suggests that smokers are willing to make repeated pharmacotherapy assisted quit attempts.[8,9] However, few reports exist in the literature that describe repeat therapy with SCM in clinical practice and none were found that use administrative data sources.

In a single center retrospective cohort study of repeat treatment for smoking, Han, et al found that patients who relapsed to smoking and returned for repeat treatment exhibited signs of higher nicotine dependence and were more likely to have a history of treatment for mental health and other behavioral problems than patients who only attended for one treatment episode.[10] Moreover, a randomized controlled trial (RCT) evaluating intensive disease management strategies for smokers over time found that smokers are willing to make repeated quit attempts using SCM, leading to progressively greater smoking abstinence.[9] Study of repeat treatment in a large national population could identify patient or provider characteristics associated with repeat treatment and inform specific approaches to management in patient subgroups. The objectives of this study were to describe treatment persistence in newly diagnosed tobacco dependent patients prescribed SCM in the 1 year following diagnosis, repeat treatment with SCM and patient and prescriber characteristics associated with premature discontinuation and repeat therapy.

Methods

Design: This study employed a retrospective cohort design using de-identified data from the LifeLink™ Health Plan Claims Database (formerly known as Pharmetrics) which is comprised of commercial health plan information obtained from managed care plans throughout the US. It is fully adjudicated medical and pharmaceutical claims for over 68 million unique patients from over 102 health plans across the U.S. (approximately 16 million covered lives per year). The database includes both inpatient and outpatient diagnoses (In International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] format) and procedures (in Current Procedure Terminology [CPT-4] codes and Healthcare Common Procedure Coding System [HCPCS] formats) as well as both retail and mail order prescription records. Available data on prescription records include the National Drug Code (NDC) as well as the quantity of the medication dispensed. Charge, allowed and paid amounts are available for all services rendered, as well as dates of service for all claims. Additional data elements include demographic variables (age, gender, geographic region), product type (e.g., HMO, PPO), payer type (e.g., commercial, self-pay), provider specialty, and start and stop dates of health-plan enrollment.

Sample Selection: The sample consisted of patients aged 16-76 newly identified as tobacco dependent through presence of a diagnosis code for tobacco use disorder and/or CPT code for tobacco cessation counseling, advice or treatment (Appendix) during the period July 2010 to June 2011 (index). Patients with ICD-9, CPT codes, or prescriptions related to tobacco dependence or treatment in the lookback period January 2009 through June 2010 were excluded. Charlson Comorbidity Index (CCI)

scores for each patient were calculated using the algorithm develop by Quan, et al., through identification of ICD-9 codes related to 17 co-morbidity categories in the 12 month period prior to (pre-index) and 12 month period following the index date (including the index date). Weights specific to each co-morbidity category were assigned and the CCI score calculated; higher CCI scores indicate greater co-morbidity.[11]

Statistical Analysis: Descriptive statistics were used to describe demographic and clinical characteristics and frequency of prescription of SCM defined as 1 or more claim for varenicline, bupropion SR or NRT during the 1 year period following tobacco dependence diagnosis or CPT code or procedure. Demographic characteristics included patient age at index, gender, geographic region of residence and insurance related factors such as payer type and insurance product. Clinical characteristics included baseline 12 month pre-index CCI score and CCI categories. Provider characteristics included the practitioner type associated with diagnosis of or counseling/advice for tobacco dependence.

Two dichotomous response variables were defined: Premature discontinuation and repeat therapy. Premature discontinuation or non-persistence was defined as duration of therapy less than 12 weeks (84 days) based on recommended duration of therapy as described in FDA approved product information for varenicline and bupropion SR and, due to multiple available formulations, expert recommendation for NRT.[12-14] Data fields employed to calculate duration of therapy included the patient identification number, product name, prescription fill date and days supply. Time to discontinuation in days was measured using a refill grace period equal to one-half the

days supplied of the previous prescription. Repeat treatment was defined based on criteria used by Han, et al.[10] Patients were identified as having repeat therapy if a span of ≥ 26 week was observed between any 2 consecutive treatment episodes in the 1 year following initiation of SCM. Bivariate analyses including t-tests for continuous variables and chi-square tests or Fisher's Exact test for categorical variables were used to analyze differences in patient and provider characteristics.

Assessment of factors associated with premature discontinuation or repeat therapy was performed by conducting a series of univariate logistic regression equations. To qualify for multivariate logistic regression, variables had to be associated with SCM prescription in the univariate analyses ($p<0.2$) or be otherwise clinically important. Two multivariate logistic regression models were constructed; the first assessed relationships between the independent variables (IVs) of patient and provider characteristics and the dependent variable (DV) of premature discontinuation of SCM therapy and the second assessed relationships between the IVs of patient and provider characteristics and the dependent variable (DV) of repeat SCM therapy as defined using Han's criteria. For modeling the DV of repeat therapy, infrequently occurring (≤5 patients) independent variable categories were combined. Each model was created using a backward elimination process and the likelihood ratio test and AIC used to assess the model at each step, removing least statistically significant covariates with each iteration and evaluating differences between full and reduced models for statistical significance. In advance of model inclusion, parametric form of any continuous independent variables and multicollinearity among independent variables were assessed. Multicollinearity was assessed by regressing independent variables

against the independent variable of patient age at index. Main effects and two factor interactions of independent variables found significant in the models were assessed. The Hosmer-Lemeshow test was used to assess goodness of fit of the final models. The measure of effect is presented as an odds ratio with corresponding 95% confidence intervals. All analyses were conducted using SAS® Version 9.4 (SAS Institute, Cary, NC) with statistical significance defined as $p < 0.05$. Analyses were performed using a 2-tailed alpha of 0.05 and 95% confidence intervals calculated.

Results

Cohort

In total, 1621 of 15,000 (10.81%) newly diagnosed tobacco dependent patients initiated therapy with SCM in the 1 year following diagnosis (Figure 1). Of treated patients, mean (SD) age was 44.56 (12.52) years, 57.13% were female and most (82.11%) resided in the Midwest. Mean (SD) pre-index Charlson Comorbidity index score (CCI) was 0.402 (0.935) and most (86.12%) had commercial insurance and an HMO insurance product (69.77%). Most (75.63%) were diagnosed by a general medicine practitioner (Table 1). Smoking cessation medication prescriptions in the 1 year post-index included 71 (4.38%) bupropion SR, 450 (27.76%) NRT and 1126 (69.46%) varenicline (Figure 2).

Persistence

Mean (SD) duration of therapy in all treated patients was 36.35 (25.74) days. Premature discontinuation, defined as duration of therapy <84 days, was observed in 1506 (92.91%) of patients. Mean (SD) age of patients who prematurely discontinued

SCM was 44.29 (12.55) years and mean (SD) pre-index baseline CCI was 0.4070 (0.9497). Differences were observed by age group with patients >50 years being less likely to discontinue prematurely than their younger counterparts (p=0.0040), and also by region (p=0.0052) with the highest rates in patients from the East (94.25%) and lowest in patients from the South (≤5) and West (84.55%) Premature discontinuation did not differ according to CCI score category (p=0.4778) with the highest rate in patients with CCI=1 (94.64%) and lowest in CCI ≥2 (92.03%) (Tables 1, 2). Overall, premature discontinuation was similar (p=0.0705) by payer type and insurance product with highest and lowest rates in patients with Medicaid (94.96%) and Medicare Supplemental (83.33%) and POS (93.71%) and PPO (88.42%), respectively. Premature discontinuation was not different (p=0.7875) by diagnosing provider type with highest reportable (count >5) rate in patients diagnosed by hospital related practitioners (93.85%) (Table 3). No difference in premature discontinuation rate was observed between in patients who ultimately repeated therapy and those who did not (p=0.8291) (Table 3). Differences were observed in rates of premature discontinuation between SCM with the highest rate in nicotine policrilex (97.47%) and lowest in bupropion SR (80.28%) (p<0.001) (Table 1).

Multivariate logistic regression analysis revealed that patients in age groups 51-64 years had slightly lower likelihood of premature discontinuation compared to patients age 41-50 (OR 0.584, 95% CI 0.354-0.962), as did patients residing in the South or West compared to those residing in the Midwest (OR 0.325, 95% CI 0.173-0.610) . Patients in Medicaid had higher likelihood of premature discontinuation

compared to those with commercial insurance (OR 2.898, 95% CI 1.179-7.122) (Table 5).

Repeat Therapy

Of the 1621 treated patients, 86 (5.3%) were identified as having repeat therapy and mean (SD) age in this group was 44.3 (12.88) years and pre-index baseline mean (SD) CCI score in patients who repeated therapy was 0.4186 (1.034). Repeat treatment rate was similar in females and males (5.62% vs 4.89%, p=0.5201). Patients in CCI score category ≥2 had the lowest rate of repeat therapy (4.35%, p=0.8379). Rates of repeat therapy by insurance product (p=0.3084), payer type (p=0.7956) and diagnosing practitioner type (p=0.2773) were similar with the lowest rates in patients with consumer directed insurance (≤5) and indemnity (≤5) and highest in patients with HMO (6.02%). Repeat treatment rate by age group was similar (p=0.4242) and lowest in the youngest and oldest age groups of 17-19 (≤5) and 65-75 (≤5) with patients 20-49 years having the highest repeat therapy rate (5.95%). Similarly, no difference was observed in repeat treatment by region with lowest counts in patients residing in the South and West (≤5) and highest in the East (5.75%). No difference in premature discontinuation rates (5.39% vs. 94.62%, p=0.6346) or mean (SD) duration of initial therapy (34.53 [20.14] days vs. 36.43 [26.02] days, p=0.5071) was observed in patients who repeated therapy compared to those who did not. Repeat therapy rates did not differ among products (p=0.919) (Table 5). Multivariate regression analysis revealed no variables that were associated with repeat therapy (Table 7).

Discussion

Population assessments of persistence with SCM are few and are derived largely from survey data with some focusing exclusively on NRT.[4,6,7,15] Though study design, data source and populations differ, our findings related to premature discontinuation can be compared most closely to a study of international survey data that used a threshold to define premature discontinuation. The authors defined premature discontinuation as self-report of <8 weeks of treatment, whether OTC or prescription, and found that most patients studied (69%) discontinued therapy prematurely.[15] These authors concluded that older age was a significant predictor of completing >8 weeks of therapy (OR 1.02, 95% CI 1.01-1.03) and that completion of a full 8 weeks of SCM was more likely among prescription SCM users (OR 1.82, 95% CI 1.29 – 2.57) and females (OR 1.16, 95% CI 0.88-1.53), though the confidence interval for the latter included 1.0. Of prescription SCM users in that study, duration of therapy 8 weeks or more was reported by 40.4%.

In the present study using administrative claims data which are exclusive to therapies dispensed by prescription, results indicate that >90% of newly diagnosed tobacco dependent patients discontinue therapy before 12 weeks. We found that 100% of patients <20 years old discontinued prematurely and those between 51 and 64 years were slightly less likely to premature discontinuation compared to those aged 41-50 (OR 0.584, 95% CI 0.354 – 0.962). We found no difference (p=0.2657) in the rate of premature discontinuation between males and females and no association of gender with premature discontinuation. Mean duration of therapy in the current study was

approximately 36 days and only 15% had duration of therapy >8 weeks (Data not shown).

We did observe regional differences (p= 0.0052) in premature discontinuation rate with the lowest rate in the West (84.55%) but comparisons were hampered by low counts of treated patients from the South. Residence in the West or South was associated with slightly lower likelihood of premature discontinuation (OR 0.354, 95% CI 0.354-0.962) compared to the Midwest, however these results are likely influenced by the lower premature discontinuation rate in the West because of low SCM utilization in the South (≤5 patients treated; ≤5 prematurely discontinuing). Literature reporting SCM persistence in different US regions has not been found. Patients with Medicaid had higher likelihood of premature discontinuation compared to those with commercial insurance (OR 2.898, 95% CI 1.179-7.122), though the confidence interval is wide. Similar to aforementioned lack of information regarding reports of SCM persistence rates by region, reports of persistence with SCM by payer type have not been found.

Differences were observed in rates of premature discontinuation between SCM with highest rate in nicotine polacrilex (97.47%) and lowest in bupropion SR (80.28%) (p<0.001). As mentioned previously, population based studies reporting SCM persistence is scant but, in a randomized controlled trial (RCT) comparing the efficacy and safety of varenicline and bupropion SR, discontinuation rates in those receiving treatment were similar with 24.12% varenicline and 29.14% of bupropion SR subjects discontinuing therapy; 10.5% due to adverse events in the varenicline group, and 12.6% in the bupropion SR group.[16] Similar results were observed in a

parallel RCT of varenicline and bupropion.[17] Differences in mechanisms of action of these two drugs could yield different responses, such as reduction in craving, nicotine withdrawal symptoms and rewarding effects of smoking.[18] Bupropion SR is indicated in both depression and as a smoking deterrent so use in patients with mental health diagnoses was possible.

Of note, in their survey of smokers or recent ex-smokers having used SCM in a quit attempt in the previous year, Balmford, et al[15] found that the most commonly reported reason for discontinuation was relapse/medication didn't work (41.6%). Interestingly, this reason was much less commonly reported among users of prescription only medication; discontinuation was described more frequently as related to side effects. The authors found no difference in proportions of patients completing treatment courses of oral NRT and the patch.[15] Of note, a considerable portion of SCM users (17%) in this study believed they no longer needed to use medication, and two thirds of those who believed the medication had worked achieved 6 months continuous abstinence.[11] The authors note that people may be able to judge the appropriate time to discontinue medication and suggest that a trial of participant point of discontinuation may be worthwhile.

Tobacco dependence is a chronic disease that often requires repeated intervention and multiple attempts to quit but few reports exist that describe repeat therapy with SCM in actual practice. In a single center retrospective cohort study, Han, et al studied the characteristics of patients who relapsed to smoking and returned to the clinic for repeat treatment.[10] The authors defined a repeat patient as one who attended clinic for two or more treatment episodes during the study period with each episode

being separated by at least 26 weeks. The study results indicated that 14.4% of patients repeated treatment which was more common between ages 25 and 64 than younger or older age groups (p=0.017) and in patients who had private insurance (56.6%, p=0.010). In the current study, repeat treatment was observed in ~5% of newly diagnosed tobacco dependent patients initiating SCM and demographic and clinical characteristics, insurance related factors, and diagnosing practitioner types in those repeating treatment were similar to those who did not. It is possible that those patients for whom providers use diagnosis codes for tobacco cessation or counsel for tobacco cessation are those with high levels of tobacco dependence and these patients have been found to have greater rates of smoking relapse following a quit attempt.[19] While not a study of routine practice, results of a randomized controlled trial of community based patients participating in a longitudinal intensive smoking cessation management program indicated that, by study end, 23%, 33% , 23%, 12% and 9% requested a total of 0,1,2,3 or 4 cycles of pharmacotherapy, respectively.[9]

This study utilized data from medical and pharmacy claims which are collected for billing and reimbursement purposes and which have inherent limitations. Data entry errors at sites of care cannot be detected or corrected in data analysis. We used ICD-9-CM and tobacco cessation counseling specific CPT and HCPCS codes to identify newly diagnosed smokers. This method may under-estimate the number of smokers, however use of ICD-9-CM codes to identify smokers has been validated previously.[20] The use of prescription claims exclusively in the current study may have missed the use of over the counter (OTC) products, but in an US insured population, over the counter SCM may be covered under the pharmacy benefit. The small number

of patients in some subgroups evaluated precludes comparisons by statistical analysis and thus, results are descriptive in nature. It is important to note that though patients were identified as smokers through diagnosis or procedure codes, this provides no insight into readiness to quit which is an important component of cessation attempts.[8] Also, as mentioned only prescription SCM could be captured and payment of a prescription claim does not mean that a patient used the medication as prescribed and does not represent those prescriptions that may have been written but not filled by the patient. Thus, treatment rates may be underestimated in this sample.

Identification of SCM use or tobacco dependence diagnosis or procedure prior to the lookback period was not possible, thus patients may have been misclassified as newly diagnosed and/or newly treated with SCM. In addition we did not identify any mental health comorbidities in which bupropion SR could have been used to treat both conditions.

Recommended duration of therapy for specific SCM can vary based on level of tobacco dependence and clinical information such as level of tobacco dependence is not ascertainable in claims data. The threshold of 12 weeks was chosen as it is the minimum recommendation for varenicline, upper limit of recommendation for bupropion SR and within recommendations for NRT.[12-14] Premature discontinuation of SCM does not mean that patients did not quit. Aforementioned population studies found that patients successfully quit using shorter than recommended durations of therapy, however cessation rates have been found to be highest among those who use prescription medication for ≥5 weeks.[6,7]

Future research using administrative claims data should focus on different persistence thresholds and include longer study periods. Additionally, long term prospective study of patients using SCM would facilitate study of persistence and repeat therapy. Important clinical information could be gained by linking administrative claims to electronic medical record data in a HIPAA compliant fashion.

Despite stated limitations, this study adds useful information regarding persistence and repeat use of prescription SCM in a US national population. Specifically, mean persistence with SCM was approximately 36 days and >90% of patients discontinued SCM before 12 weeks of therapy; shorter than recommendations. Patients under 50 years and 65 or older were more likely to discontinue prematurely than patients 50-58 years old. Few patients (5%) repeated therapy and, in this study with small sample size, no patient or provider characteristics were associated with repeat therapy.

References

1. Schnoll RA, Goelz PM, Veluz-Wilkins A, Blazekovic S, Powers L, Leone FT, Gariti P, Wiley EP, Hitsman, B. Long-term nicotine replacement therapy: a randomized clinical trial. *JAMA Internal Medicine.* 2015;175(4): 504-511.

2. Shiffman S, Sweeney CT, Ferguson SG, Sembower MA, Gitchell JG. Relationship between adherence to daily nicotine patch use and treatment efficacy: secondary analysis of a 10-week randomized, double-blind, placebo-controlled clinical trial simulating over-the-counter use in adult smokers. *Clinical Therapeutics.* 2008;30(10): 1852-1858.

3. Lee JH, Jones PG, Bybee K, O'Keefe JH. A longer course of varenicline therapy improves smoking cessation rates. *Preventive Cardiology.* 2008;11(4): 210-214.

4. Alpert HR, Connolly GN, Biener L. A prospective cohort study challenging the effectiveness of population-based medical intervention for smoking cessation. *Tobacco Control.* 2013;22(1): 32-37.

5. Quit Works Nicotine Patch Services. Available at: http://quitworks.makesmokinghistory.org/quitworks-nicotine-patch-services.html. Accessed October 20, 2015.

6. Zhang B, Cohen JE, Bondy SJ, Selby P. Duration of nicotine replacement therapy use and smoking cessation: a population-based longitudinal study. *American Journal of Epidemiology.* 2015;181(7): 513-520.

7. Siahpush M, Shaikh RA, McCarthy M, Sikora Kessler A, Tibbits M, Singh GK. Association between duration of use of pharmacotherapy and smoking cessation: findings from a national survey. *BMJ Open.* 2015;5(1).

8. Fiore MC, Jaen CR, Baker TB, et al. *Treating Tobacco Use and Dependence: 2008 Update.* Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. May 2008.

9. Ellerbeck EF, Mahnken JD, Cupertino AP, Cox, LS, Greiner, KA, Mussulman, LM, Nazir N, Shireman TI, Resnicow K, Ahluwalia, JS.. Effect of varying levels of disease management on smoking cessation: a randomized trial. *Annals of Internal Medicine.* 2009;150(7): 437-446.

10. Han ES, Foulds J, Steinberg MB, Gandhi KK, West B, Richardson DL, Zelenetz S, Dasika, J.. Characteristics and smoking cessation outcomes of patients returning for repeat tobacco dependence treatment. *International Journal of Clinical Practice.* 2006;60(9): 1068-1074.

11. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali, WA.. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical Care.* 2005;43(11): 1130-1139.

12. Chantix® (US Prescribing Information, October 2014). Pfizer Inc, New York, NY, 10017

13. Zyban® (US Prescribing Information, 2015) GlaxoSmithKline, Brentford, Middlesex, UK, TW8 9GS.

14. Kozlowski LT, Giovino GA, Edwards B, Difranza J, Foulds J, Hurt R, Niaura R, Sachs DP, Dollar KM, Bowen D, Cummings KM, Counts M, Fox B, Sweanor D, Ahern F. Advice on using over-the-counter nicotine replacement therapy-patch, gum, or lozenge-to quit smoking. *Addictive behaviors.* 2007;32(10): 2140-2150.

15. Balmford J, Borland R, Hammond D, Cummings KM. Adherence to and reasons for premature discontinuation from stop-smoking medications: data from the ITC Four-Country Survey. *Nicotine and Tobacco Research.* 2011;13(2): 94-102.

16. Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, Billing CB, Gong J, Reeves, KR, Varenicline Phase 3 Study Group. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA: Journal of the American Medical Association.* 2006;296(1): 56-63.

17. Gonzales D, Rennard SI, Nides M, Oncken, C, Azoulay S, Billing CB, Watsky EJ, Gong J, Williams KE, Reeves K R, Varenicline Phase 3 Study Group. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA: Journal of the American Medical Association.* 2006;296(1): 47-55.

18. West R, Baker CL, Cappelleri JC, Bushmakin AG. Effect of varenicline and bupropion SR on craving, nicotine withdrawal symptoms, and rewarding effects of smoking during a quit attempt. *Psychopharmacology.* 2008;197(3): 371-377.

19. Cosci F, Corlando A, Fornai E, Pistelli F, Paoletti P, Carrozzi L. Nicotine dependence, psychological distress and personality traits as possible predictors of smoking cessation. Results of a double-blind study with nicotine patch. *Addictive Behaviors.* 2009;34(1): 28-35.

20. Wiley LK, Shah A, Xu H, Bush WS. ICD-9 tobacco use codes are effective identifiers of smoking status. *JAMIA: Journal of the American Medical Informatics Association.* 2013;20(4): 652-658.

Table 2.1. Demographic Characteristics of Tobacco Dependent Patients with Premature SCM Discontinuation , LifeLink™ Health Plan Claims Database (July 2010-June 2011)

	Total (N = 1621)	Premature Discontinuation = no (n=115)	Premature Discontinuation = yes (n=1506)	p-value
Age at index, years, mean, (SD)	44.56 (12.52)	48.15 (11.59)	44.29 (12.55)	0.0014
Age Category, No. (%)				
17-19	30 (1.85)	0	30 (100)	0.0040
20-49	958 (59.06)	52 (45.22)	906 (94.57)	
50-58 (reference)	419 (25.83)	45 (39.13)	374 (89.26)	
59-64	150 (9.25)	12 (10.43)	138 (92.0)	
65-75	65 (4.01)	6 (5.22)	59 (90.77)	
Gender, No. (%)				
Female	926 (57.13)	60 (6.47)	866 (93.53)	0.2657
Male	695 (42.75)	55 (7.91)	640 (92.09)	
Region, No. (%)				
East	174 (10.73)	10 (5.75)	164 (94.25)	<0.01
Midwest	1336 (82.11)	88 (6.58)	1248 (93.41)	
South	≤5 (≤0.31)	0	≤5 (≤100)	
West (reference)	110 (6.79)	17 (15.45)	93 (84.55)	
Insurance Related, No. (%)				
Product Type Consumer Directed	68 (4.19)	≤5 (≤7.35)	63 (93.65)	ns
Product Type HMO (reference)	1131 (69.77)	81 (7.16)	1049 (92.84)	
Product Type Indemnity	20 (1.23)	≤5 (≤25.0)	18 (≤95.0)	
Product Type POS	795 (49.04)	50 (6.30)	745 (93.70)	
Product Type PPO	95 (5.86)	11 (11.58)	84 (88.42)	
Payer Type Commercial (reference)	1396 (86.12)	103 (7.37)	1293 (92.62)	ns
Payer Type Medicaid	258 (15.91)	13 (5.04)	245 (94.96)	
Payer Type Medicare	57 (3.52)	9 (15.79)	48 (84.21)	
Payer Type Self-insured	130 (8.02)	9 (6.92)	121 (93.08)	
Pharmacy Benefit	1544 (95.25)	107 (6.93)	1438 (93.07)	0.2485

PPO = Preferred Provider Organization, POS = Point of Service

Table 2.2. Clinical Characteristics of Tobacco Dependent Patients with Premature SCM Treatment Discontinuation, LifeLink™ Health Plan Claims Database (July 2010-June 2011)*

	Total (N = 1621)	Premature Discontinu-ation = no (n=115)	Premature Discontinuation = yes (n=1506)	p-value
Pre-index Charlson Comorbidity Index (CCI), mean, (SD)	0.402 (0.935)	0.3391 (0.7241)	0.4070 (0.9497)	0.4532
Pre-index CCI 0, n (%) (Reference)	1223 (75.44)	90 (7.36)	1133 (92.64)	0.4778
Pre-index CCI 1, n (%)	261 (16.10)	14 (5.36)	247 (94.64)	
Pre-index CCI ≥2, n (%)	138 (8.51)	11 (7.97)	127 (92.03)	
Chronic Obstructive Pulmonary Disease (COPD)	194 (11.97)	17 (8.76)	177 (91.24)	0.3347
Mean (SD) Duration of Therapy (days)	36.35 (25.74)			
Repeat Treatment	86 (5.30)	≤5 (≤5.81)	≤85 (≤98.84)	ns
Bupropion SR (n=71), No. (%)		14 (19.72)	57 (80.28)	<0.0001
Nicotine (n=371), No. (%)		8 (2.16)	363 (97.84)	
Nicotine Polacrilex (n=79), No. (%)		≤5 (≤6.33)	≤78 (≤98.73)	
Varenicline (n=1126), No. (%)		92 (8.17)	1034 (91.83)	

*Results presented only for Charlson Comorbidities cell counts >5

Table 2.3. Characteristics of Diagnosing Practitioners for Tobacco Dependent Patients with Premature SCM Treatment Discontinuation, LifeLink™ Health Plan Claims Database (July 2010-June 2011)

	Total (N = 1621)	Premature Discontinu-ation = no (n=115)	Premature Discontinuation = yes (n=1506)	p-value
General Medicine (GP/FP, Internal Med, NP, Ob/Gyn, Osteopath, PA)	1226 (75.63)	90 (7.34)	1136 (92.66)	ns
Hospital related (surgical, ER, hospital, anesthesia, Ortho)	260 (16.04)	16 (6.15)	244 (93.85)	
Specialist (e.g., cardiologist, pulmonol,oncol, endocrine, ent, gastro,ID,allergy, nephrol, neurol, ophthal, optom,phys med, podiatry, psychiatry,rheum,urol)	104 (6.42)	9 (8.65)	95 (91.35)	
Other (DME_HH, PT, RN, SOC_WORK, MHSA_FAC)	35 (2.16)	≤5 (≤14.28)	≤34 ≤97.14)	
Pediatrics (pediatrics, neonatal)	10 (0.62)	≤5 (≤50.0)	≤9 (≤90.0)	

GP=general practice, FP=family practice, NP=nurse practitioner, Ob/Gyn=obstetrics & gynecology, PA=physician's assistant, ER=emergency room, pulm=pulmonogist, onc=oncologist, endo=endocrine, ENT=ear, nose & throat, gastro=gastroenterologist, ID=infectious disease, nephro=nephrologist, neuro=neurologist, ophth=ophthalmologist, optom=optometrist, phys med= physical medicine, pscych=psychiatrist, rheum=rheumatologist, urol=urologist, DM_HH=durable medical

Table 2.4. Demographic Characteristics of SCM Treated Patients with Repeat Therapy LifeLink™ Health Plan Claims Database (July 2010-June 2011)

	Total (N = 1621)	No repeat ≥26 weeks (n=1535)	Repeat Rx ≥26 weeks (n=86)	p-value
Age at index, years, mean, (SD)	44.56 (12.52)	44.57 (12.51)	44.30 (12.88)	0.8431
Age Category, No. (%)**				
17-19	30 (1.85)	29 (96.67)	≤5 (≤16.67)	ns
20-49	958 (59.06)	900 (94.04)	57 (5.95)	
50-58 (reference)	419 (25.83)	403 (96.18)	16 (3.82)	
59-64	150 (9.25)	143 (95.33)	7 (4.67)	
65-75	65 (4.01)	≤64 (≤98.46)	≤5 (≤7.69)	
Gender, No. (%)				
Female	926 (57.13)	874 (94.398	52 (5.62)	0.5201
Male	695 (42.75)	661 (95.11)	34 (4.89)	
Region, No. (%)				
East	174 (10.73)	164 (94.25)	10 (5.75)	ns
Midwest	1336 (82.11)	1262 (94.46)	74 (5.54)	
South	≤5 (≤0.31)	≤5 (≤0.31)	0	
West (reference)***	110 (6.78)	108 (98.18)	≤5 (≤4.55)	
Insurance Related, No. (%)				
Consumer Directed	68 (4.19)	≤67 (≤98.53)	≤5 (≤7.35)	ns
Insurance Product HMO (reference)****	1131 (69.77)	1062 (93.98)	68 (6.02)	
Indemnity	20 (1.23)	≤19 (≤95.0)	≤5 ≤25)	
Insurance Product POS	795 (49.01)	752 (94.71)	42 (5.29)	
Insurance Product PPO	95 (5.86)	≤94 (≤98.95)	≤5 (≤5.26)	
Payer Type Commercial (reference)†	1396 (86.12)	1320 (94.56)	76 (5.44)	ns
Payer Type Medicaid	258 (15.91)	244 (94.57)	14 (5.43)	
Payer Type Medicare	57 (3.53)	≤56 (≤98.25)	≤5 (≤8.77)	
Payer Type Self-insured	130 (8.02)	124 (95.38)	6 (4.62)	
Pharmacy Benefit	1544 (95.25)	1459 (94.49)	85 (5.51)	0.1221

Repeat therapy defined if a span of ≥ 26 week was observed between any 2 consecutive treatment episodes in the 1 year following initiation of SCM. PPO = Preferred Provider Organization, POS = Point of Service

Table 2.5. Rate of Repeat Therapy by Clinical Characteristics and Diagnosing Practitioner Type in Patients Treated with SCM, LifeLink™ Health Plan Claims Database (July 2010-June 2011)

	Total (N = 1621)	No repeat ≥26 weeks (n=1535)	Repeat Rx ≥26 weeks (n=86)	p-value
Pre-index Charlson Comorbidity Index, mean, (SD)	0.402 (0.935)	0.4013 (0.9300)	0.4186 (1.034)	0.8675
Pre-index CCI 0, n (%) (Reference)	1223 (75.44)	1157 (94.68)	65 (5.32)	0.8379
Pre-index CCI 1, n (%)	261 (16.10)	246 (94.25)	15 (5.75)	
Pre-index CCI ≥2, n (%)	138 (8.51)	132 (95.65)	6 (4.35)	
Chronic obstructive pulmonary disease	194 (11.97)	183 (94.33)	11 (5.67)	0.8091
Diagnosing Practitioner Type, No (%)				
General Medicine (GP/FP, Internal Med, NP, Ob/Gyn, Osteopath, PA)	1226 (75.563)	1159 (94.54)	67 (5.46)	ns
Hospital related (surgical, ER, hospital, anesthesia, Ortho)	260 (16.04)	253 (97.31)	7 (2.69)	
Specialist (e.g., cardiologist, pulm,onc, endo, ent, gastro,ID,allergist, nephro, neuro, ophth, optom,phys med, podiatrist, psych,rheum,urol)	105 (6.42)	97 (93.27)	7 (6.73)	
Other (DME_HH, PT, RN, SOC_WORK, MHSA_FAC)	35 (2.16)	≤34 (≤97.14)	≤5 (≤14.29)	
Treatment Patterns				
Premature discontinuation (duration of therapy <84 days) No. (%)	1506 (92.91)	1425 (94.62)	81 (5.39)	0.6346
Duration of Therapy, mean (SD)	1621 (100)	36.43 (26.02)	34.53 (20.14)	0.5071
Bupropion SR (n=71)		67 (94.37)	≤5 (≤98.59)	ns
Nicotine (n=371)		355 (95.69)	16 (4.31)	
Nicotine Policrilex (n=79)		76 (96.20)	≤5 (≤98.73)	
Varenicline (n=1126)		1071 (95.03)	56 (4.97)	

*Results presented only for Charlson Comorbidities with cell counts >5; GP=general practice, FP=family practice, NP=nurse practitioner, Ob/Gyn=obstetrics & gynecology, PA=physician's assistant, ER=emergency room, pulm=pulmonogist, onc=oncologist, endo=endocrine, ENT=ear, nose & throat, gastro=gastroenterologist, ID=infectious disease, nephro=nephrologist, neuro=neurologist, ophth=ophthalmologist, optom=optometrist, phys med= physical medicine, pscych=psychiatrist, rheum=rheumatologist, urol=urologist, DM_HH=durable medical equipment/home health, PT=physical therapist, RN=registered nurse, SOC_WORK=social worker, MHSA_FAC=mental health/substance abuse facility

Table 2.6. Summary of Logistic Regression Analysis of Predictors of Premature Discontinuation of SCM: Odds Ratios and 95% Confidence Intervals

Independent Variable	OR	95% Wald CI
Age < 28 years (ref=41-50 years)	3.164	0.939-10.662
Age 28-40 (ref=41-50 years)	0.946	0.535-1.676
Age 51-64 years (ref=41-50)	0.584	0.354-0.962
Age 65-75 years (ref=41-50 years)	0.796	0.292-2.171
East Region (ref=Midwest)	1.478	0.726-3.012
South & West Regions (ref=Midwest)	0.325	0.173-0.610
Medicare and Self Insured (ref=commercial)	1.151	0.384-3.446
Medicaid (ref=commercial)	2.898	1.179-7.122
Hosmer-Lemeshow Goodness of Fit Test		p=0.8672

ref=reference

Table 2.7. Summary of Logistic Regression Analysis of Predictors of Repeat SCM Therapy: Odds Ratios and 95% Confidence Intervals

Independent Variable	OR	95% Wald CI
Indemnity (ref=HMO)	0.329	0.045-2.424
POS (ref=HMO)	0.623	0.355-1.093
Diagnosis by non-physician or pediatrician or specialist (ref=general medicine)	1.176	0.550-2.513
Diagnosis by hospital related practitioner (ref=general medicine)	0.464	0.198-1.087
Hosmer-Lemeshow Goodness of Fit Test	p=0.9775	

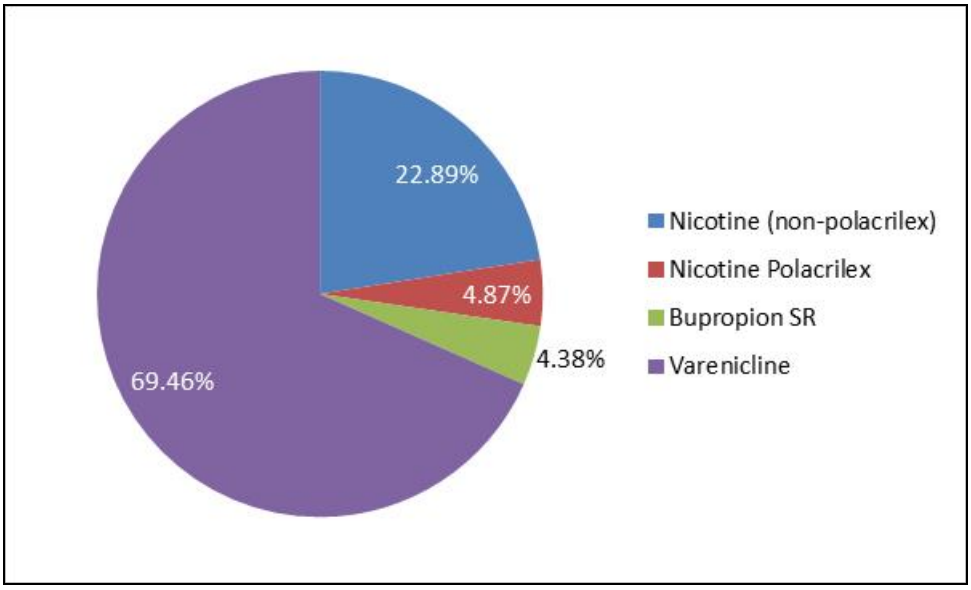
ref=reference; HMO=health maintenance organization, POS=Point of Service

Figure 2.1. Sample Selection – Tobacco Dependent Patients Treated with SCM and Repeat Therapy, LifeLink Health Plan Claims Database (July 2010-June 2011)

PharMetrics enrolled patients: N=18,400,000 as of August 2012*
Continuously enrolled patients January 2009 – June 2012 Patients aged 16-76 identified as having any tobacco related diagnoses or procedure, SCM or smoking related cancers n = 117,695
Patients identified as having any tobacco related diagnoses or procedures or smoking related cancers (Patient count without smoking cessation treatment) n=80,486
Patients enrolled January 2009 to June 2012 with a diagnosis or procedure indicating tobacco dependence (Patient count without smoking related cancer) n=77,736
Patients with a diagnosis or procedure code indicating tobacco dependence between July 2010 and June 2011 (index) n=18,619
Patients with a diagnosis or procedure code indicating tobacco dependence between July 2010 and June 2011 with claims activity throughout the study period (January 2009 – June 2012) n=16,417
Patients with no claims for SCM in the 18 month period pre-index n=15,000
Rx claim for SCM in 12 months post-index n = 1,621
Repeat Rx ≥ 26 weeks n=86

*Closest estimate for continuously enrolled in Pharmetrics during the study period is 18.4MM patients as of August 2012. Enrollment is subject to change quarterly as updates are received from contributing health plans. Largest changes are typically seen at year beginning when patients may leave a health plan and join another. The Pharmetrics data used for this study no longer exists in this form as IMS has created a new larger database called Pharmetrics Plus which includes a larger number of contributing health plans. The database that includes the data used for this study is archived offsite and would require data restoration to determine exact count.

Figure 2.2. SCM Prescribed in 1 Year Following Diagnosis of Tobacco Dependence, LifeLink Health Plan Claims Database (July 2010-June 2011)



MANUSCRIPT 3

Use of Smoking Cessation Medications in Tobacco Dependent Patients with Smoking Related Cancers

Planned manuscript submission to Journal of Community and Supportive Oncology

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Background

Smoking increases the risk of numerous cancers, and continued smoking by cancer patients and cancer survivors has been shown to have detrimental effects on health. In a recent meta-analysis, Parsons et al reported that continued smoking was associated with an increased risk of mortality, disease recurrence and development of a second primary tumor in lung cancer patients.[1] Moreover, continued smoking can alter the pharmacokinetics of chemotherapeutic drugs, leading to lower serum concentrations of the drug which may alter its therapeutic effect.[2] In 2006, the American Society for Clinical Oncology (ASCO) introduced the Quality Oncology Practice Initiative (QOPI), which has become a key component of a measurement system to promote quality cancer care. Quality measures include those related to smoking cessation (SC) such as documentation of smoking status/tobacco in the past year, smoking/tobacco use cessation counseling recommended to smokers/tobacco users in the past year, and smoking/tobacco use cessation administered appropriately in the past year.[3] It's important to note that patients with cancer who try to quit smoking often do so without formal assistance which typically yields low success rates.[4]

Further evidence of the need to foster SC in cancer patients is the issuance by the National Comprehensive Cancer Network (NCCN) of clinical practice guidelines focused on smoking cessation recommendations for patients with cancer. These guidelines recommend that treatment plans for all smokers with cancer include evidence based pharmacotherapy, behavior therapy and close follow-up with retreatment as needed.[5] However, information regarding the extent of employment of

SC interventions, including SC medications (SCM), in cancer patients is lacking. Of note, results of a survey by Warren et al report that physicians caring for lung cancer patients believe that current smoking affects outcomes and that tobacco cessation is a necessary part of clinical care, but few provide assistance to their patients as a routine part of cancer care.[6]

Health-related databases, including claims databases, are an important data source for research. One strength of these data is that they allow researchers to examine medical care utilization as it occurs in routine clinical care or the "real world". These data sources can provide large study populations, long observation periods and allow for examination of specific sub-populations.[7] Though they are not without limitations, adequately controlled observational studies using administrative claims data can answer important questions in a relatively inexpensive and time-efficient manner.[7] The utility of the LifeLink® database in studying SC interventions in patients with smoking related co-morbidities was demonstrated by Make, et al in their study of COPD in which they found that 82% of patients reported to be current smokers and 90% of current smokers in the Medicare population did not receive smoking cessation interventions within 45 days of hospitalization for exacerbation of COPD.[8]

The study of SC treatment in patients with smoking related cancers in a national population could identify potential gaps in quality care. The objective of this study was to describe the epidemiology of SCM prescribing in newly identified tobacco dependent patients with smoking related cancers and patient or provider characteristics associated with its use.

Methods

Design: This study employed a retrospective cross-sectional design using de-identified data from the LifeLink™ Health Plan Claims Database (formerly known as Pharmetrics) which is comprised of commercial health plan information obtained from managed care plans throughout the US. The database contains fully adjudicated medical and pharmaceutical claims for over 68 million unique patients from over 102 health plans across the U.S. (approximately 16 million covered lives per year). The database includes both inpatient and outpatient diagnoses (In International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] format) and procedures (in Current Procedure Terminology [CPT-4] codes and Healthcare Common Procedure Coding System [HCPCS] formats) as well as both retail and mail order prescription records. Available data on prescription records include the National Drug Code (NDC) as well as the quantity of the medication dispensed. Charge, allowed and paid amounts are available for all services rendered, as well as dates of service for all claims. Additional data elements include demographic variables (age, gender, geographic region), product type (e.g., HMO, PPO), payer type (e.g., commercial, self-pay), provider specialty, and start and stop dates of health-plan enrollment.

Sample Selection:

The sample consisted of patients aged 16-76 years newly identified as tobacco dependent who had smoking related cancer as defined by presence of a diagnosis code for tobacco use disorder and/or CPT code for tobacco cessation counseling, advice or treatment (Appendix) during the index period July 2010 to June 2011 (index).

Because of low cancer event rate and the assumption that diagnoses of smoking related cancer and tobacco dependence within approximately 2 years of each other were related, the identification period for a smoking related cancer diagnosis (Appendix) was anytime in the study period January 2009 to June 2012. Patients with ICD-9 or CPT codes related to tobacco dependence in the lookback period January 2009 through June 2010 were excluded (Figures 1, 2). Charlson Comorbidity Index (CCI) scores for each patient were calculated using the algorithm develop by Quan, et al., through identification of ICD-9 codes related to 17 co-morbidity categories in the 12 month period prior (pre-index) to and 12 month period after the index date (including index date). Weights specific to each co-morbidity category were assigned and the CCI score calculated; higher scores indicate greater co-morbidity.[9]

Statistical Analysis: Descriptive statistics were used to describe demographic and clinical characteristics and frequency of prescription of SCM defined as 1 or more claims for varenicline, bupropion SR or NRT during the study period January 1, 2009–June 30, 2012. Demographic characteristics included patient age at index, gender, geographic region of residence and insurance related factors such as payer type and insurance product. Clinical characteristics included 12 month pre-index CCI score and CCI categories. Provider characteristics included the practitioner type associated with diagnosis of or counseling/advice for tobacco dependence. Patients were categorized into one of two groups, those who were prescribed SCM at any time during the study period and those who were not. Bivariate analyses including t-tests for continuous variables and chi-square tests or Fisher's Exact test for categorical variables were used to analyze differences in patient characteristics. Assessment of

factors associated with SCM prescription was performed by conducting a series of univariate logistic regression equations. To qualify for multivariate logistic regression, variables had to be associated with SCM prescription in the univariate analyses ($p<0.2$) or be otherwise clinically important. Multivariate logistic regression was used to assess relationships between the independent variables of patient and provider characteristics and the dependent variable SCM prescription at any time during the study period. The model was created using a backward elimination process and the likelihood ratio test and AIC used to assess the model at each step, removing least statistically significant covariates ($p>0.05$) with each iteration and evaluating differences between full and reduced models for statistical significance. In advance of model inclusion, multicollinearity among independent variables was assessed. Multicollinearity was assessed by regressing independent variables against the independent variable of patient age at index. Main effects and two factor interactions of independent variables found significant in the model were assessed. The Hosmer-Lemeshow test was used to assess goodness of fit of the final model. The measure of effect is presented as an odds ratio with corresponding 95% confidence intervals. All analyses were conducted using SAS® Version 9.4 (SAS Institute, Cary, NC) with statistical significance defined as $p <0.05$. Analyses were performed using a 2-tailed alpha of .05 and 95% confidence intervals calculated.

Results

In total, 324 newly identified tobacco dependent patients with a smoking related cancer were identified. Mean (SD) age at index was 58.51 years (10.38), 56.48% were male and 66.05% resided in the Midwest. The most common payer type was commercial in 75% of patients (Table 1). Mean (SD) pre-index CCI was 2.82 (±3.07) and 43.21% were diagnosed with or counseled for tobacco cessation by a hospital related department or practitioner. The most common pre-index Charlson comorbidities were cancer in 56.48% of patients and COPD in 21.6% patients. Mean (SD) CCI score in the 12 months following diagnosis was 5.08 (±3.19) and the occurrence of the Charlson co-morbidity of cancer in the 12 months following diagnosis (data not shown) was observed in all patients (Table 2). Lung cancer was the most common tumor type in 79 patients (24.38%) (Table 3).

Of the diagnosed sample with a smoking related cancer, 46 patients (14.2%) were treated with SCM during the study period. Of treated patients, mean (SD) age was 56.30 (8.94) years and 50% were male. Patients aged 50-64 were >3 times more likely to be prescribed SCM than their younger or older counterparts (44.08% vs. 13.73% in age 20-49; 8.60% age ≥65 years). The majority of treated patients resided in the East (22.58% vs. 16.82 in the Midwest; 3.85% in the South) (Table 1). Compared to other tumor types, patients with lung cancer had the highest rate of SCM prescription (21.52%) (Table 3).

In multivariate regression analysis, patients diagnosed by a hospital related practitioner had lower odds of receiving SCM (OR 0.319, 95% CI 0.149-0.686). After

multivariate analysis, age, patient gender, pre-index CCI score and payer type were not significant.

Discussion

Tobacco smoking is known to increase the risk of numerous cancers and despite declines in smoking rates over the past few decades, recent estimates suggest that half of deaths in the US due to 12 cancer types are smoking related.[9] Clinical practice guidelines and quality measures encourage tobacco cessation efforts in patients with cancer, and this study provides data that addresses the extent to which these guidelines have been implemented.[3,5] Our results suggest that 14.2% of tobacco dependent patients with smoking related cancers were treated with SCM.

Due to paucity of data regarding rates of SCM use in cancer patients or the general population of tobacco dependent persons and differences in study designs, it is difficult to compare our findings to those of other studies. However, some insight into the rate of SCM use in cancer patients is informed by a survey of physicians caring for lung cancer patients who reported belief that tobacco cessation is a necessary part of clinical care, but who also reported low rates of providing patients with assistance in this regard.[10] Of note, >20% reported rarely or never discussing medication options with their patients during the initial visit, while approximately 15% reported always doing so and almost one-third discussing medication options some of the time.[10] However, it is not known if these physicians' patients received SCM related counseling from their non-oncology providers.

Of note, compared to general medicine practitioners, tobacco dependence diagnosis or procedure by a hospital related practitioner was associated with lower odds of treatment with SCM (OR 0.319, 95% CI 0.149-0.686). Hospitalization is an opportunity for patients to attempt to quit tobacco as they are likely to be in a smoke-free environment and may be particularly motivated by an illness caused or exacerbated by tobacco use.[11] Patients can be encouraged to remain smoke free after discharge and begin treatment in the hospital. In a meta-analysis of randomized controlled trials of smokers hospitalized for a CVD diagnosis, a smoking cessation intervention begun in the hospital and sustained for at least 1 month post-discharge, increased cessation rates by 42% (RR: 1.42, 95% CI: 1.29–1.56) during the 6-12 months period post-discharge and starting NRT in hospital increased quit rates over counseling alone.[12] Furthermore, in a trial of smokers hospitalized with MI, compared to usual care, intensive intervention with counseling and pharmacotherapy increased cessation rates and reduced all-cause mortality and hospital readmission.[13]

Of note, it appears as though diagnosis of or counseling/advice for tobacco dependence may have been co-incident with a tobacco related co-morbidity as mean CCI score post-index was nearly twice that of the pre-index mean (5.08 vs. 2.82, respectively) and the Charlson co-morbidity category of cancer was present in 56.48% of patients prior to diagnosis and 100% post-index.

Finally, it is clear that tobacco cessation efforts need to be targeted earlier to prevent clinical sequelae including cancer. Janjigian, et al found that 70% of NSCLC patients had a smoking history of >15 pack years.[14] Quitting smoking reduces cancer risk and estimates are that five years after quitting, the risk of cancers of the mouth,

throat, esophagus, and bladder is cut in half and after 10 years, the risk of dying from lung cancer is about half that of a person who is still smoking.[15] The risks of cancer of the larynx (voice box) and pancreas are also reported to decrease.[15]

This study utilized data from medical and pharmacy claims which are collected for billing and reimbursement purposes and which have inherent limitations. Data entry errors at sites of care cannot be detected or corrected in data analysis. Although data used in this study were collected from all U.S. census regions, due to geographic biases, any unprojected geographic information may not be representative of the true distribution. Finally, the small number of patients in some subgroups evaluated precludes comparisons by statistical analysis and thus, results are descriptive in nature. The requirement for continuous enrollment may bias the results due to lack of ascertainment of mortality in a population of patients with higher mortality risk than the general population. In general, expected cancer survival rates are longer when disease is detected at earlier stages but ascertainment of cancer stage is not possible in claims data. These results should be considered generalizable to an insured US population with a smoking related cancer who have been diagnosed as tobacco dependent or counseled/advised about smoking cessation and whose clinical or other circumstances may be associated with survival.

It is also important to note that though patients were identified as smokers through diagnosis or procedure codes, this provides no insight into readiness to quit which is an important component of cessation attempts.[11] Also, only prescription versus over the counter (OTC) SCM could be captured and payment of a prescription claim does not mean that a patient took the medication as prescribed. Because

medications available OTC do not commonly exist in research databases, it is difficult to estimate the extent to which OTC NRT is used. Results of an international survey of smokers indicated that 68.3% of subjects self-report OTC NRT use. Of note, those who obtained OTC NRT appeared more likely to discontinue in the first week of use than those receiving NRT by prescription (23% vs. 13.4%, respectively.)[16] These data also do not represent those prescriptions that may have been written but not filled by the patient. . Patients may have quit smoking, but clinical outcomes of this nature are not ascertainable in administrative claims data. Thus, treatment rates may be underestimated in this sample

Finally, misclassification of a cancer diagnosis as smoking related is possible, but identification of tobacco dependence diagnosis or procedure was performed to ensure that patients were smokers. Though not known, it is probable that a diagnosis of tobacco dependence does not take place in all smokers so the sample may be underrepresentative. Future research using a larger dataset could study this issue by indexing on a smoking related cancer diagnosis and exploring use of SCM in these patients. In addition, there is need for a prospective cohort study that would include real time smoking data.

Despite limitations, this study adds important information regarding the use of SCM in patients with cancer. Tobacco dependence or counseling/advice for smoking cessation in these patients was likely coincident or following diagnosis of comorbidity and earlier such intervention may be warranted. Diagnosis or counseling in a hospital could capture patients at a time when cessation efforts such as initiating SCM have been shown to be effective.

References

1. Parsons A, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. *BMJ: British Medical Journal.* 2010;340:b5569.

2. Steliga MA, Dresler C. Clinical practice and the tobacco epidemic: relevance of a global public health problem in the clinical setting. *Expert Review of Anticancer Therapy.* 2010; 10(10):1513-1515.

3. Quality Oncology Practice Initiative (QOPI®) and the QOPI Certification Program (QCP™) 2012. Available at: http://www.instituteforquality.org/qopi-qcp Accessed: August 7 2015.

4. Morgan G, Schnoll RA, Alfano CM, Evans SE, Goldstein A, Ostroff J, Park ER, Sarna L, Cox LS. National cancer institute conference on treating tobacco dependence at cancer centers. *Journal of Oncology Practice.* 2011;7(3):178-182.

5. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology, Smoking Cessation v1.2015. Available at www.nccn.org. Accessed August 7, 2015

6. Warren GW, Marshall JR, Cummings KM, Toll B, Gritz ER, Hutson, A, Dibaj S, Herbst R, Dresler, C, IASLC Tobacco Control and Smoking Cessation Committee. Practice patterns and perceptions of thoracic oncology providers on tobacco use and cessation in cancer patients. *Journal of Thoracic Oncology.* 2013;8(5):543-548.

7. Motheral B, Brooks J, Clark MA, Crown WH, Davey P, Hutchins D, Martin BC, Stang, P. A checklist for retrospective database studies--report of the ISPOR Task Force on Retrospective Databases. *Value in Health.* 2003;6(2):90-97.

8. Make B, Dutro MP, Paulose-Ram R, Marton JP, Mapel DW. Undertreatment of COPD: A retrospective analysis of US managed care and Medicare patients. *International Journal of Chronic Obstructive Pulmonary Disease.* 2012;7:1-9.

9. Siegel RL, Jacobs EJ, Newton CC, Feskanich D, Freedman ND, Prentice RL, Ahmedin J. Deaths due to cigarette smoking for 12 smoking-related cancers in the united states. *JAMA Internal Medicine.* 2015; 175 (9): 1574-1576.

10. Warren GW, Marshall JR, Cummings KM, Zevon MA, Reed R, Hysert P, Mahoney MC, Hyland AJ, Chukwumere N, Demmy T, Dexter E, Kelly M, O'Connor RJ, Houstin T, Jenkins D, Germain P, Singh AK, Epstein J, Dobson Amato KA, Reid ME. Automated tobacco assessment and cessation support for cancer patients. *Cancer.* 2014;120(4): 562-569.

11. Fiore MC, Jaen CR, Baker TB, et al. *Treating Tobacco Use and Dependence: 2008 Update.* Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. May 2008.

12. Rigotti NA, Clair C, Munafo MR, Stead LF. Interventions for smoking cessation in hospitalised patients. *The Cochrane Database of Systematic Reviews.* 2012; May 16; 5.

13. Mohiuddin SM, Mooss AN, Hunter CB, Grollmes TL, Cloutier DA, Hilleman DE. Intensive smoking cessation intervention reduces mortality in high-risk smokers with cardiovascular disease. *Chest.* 2007;131(2): 446-452.

14. Janjigian YY, McDonnell K, Kris MG, Shen R, Sima CS, Bach PB, Rizvi NA, Riely GJ. Pack-years of cigarette smoking as a prognostic factor in patients with stage IIIB/IV nonsmall cell lung cancer. *Cancer.* 2010;116(3) :670-675.

15. Benefits of quitting over time. Available at: http://www.cancer.org/healthy/stayawayfromtobacco/benefits-of-quitting-smoking-over-time. Accessed August 31. 2015.

16. Balmford J, Borland R, Hammond D, Cummings KM. Adherence to and reasons for premature discontinuation from stop-smoking medications: data from the ITC Four-Country Survey. *Nicotine and Tobacco Research.* 2011;13(2):94-102.

Table 3.1. Rate of SCM Use by Demographic Characteristics among Tobacco Dependent Patients with Smoking Related Cancer, LifeLink™ Health Plan Claims Database, (July 2010-June 2011)

	Total (N =324)	No Rx for SCM in study period (n=278)	Rx for SCM in study period (n=46)	p-value
Age at index, years, mean, (SD)	58.51 (10.38)	58.88 (10.57)	56.30 (8.94)	0.1197
Age Category, No. (%)				
Ref=20-49				
20-49	51 (15.74)	44 (86.27)	7 (13.73)	
50-58	94 (29.01)	73 (77.66)	21 (22.34)	0.0464
59-64	86 (26.54)	76 (88.37)	10 (21.74)	
65-75	93 (28.70)	85 (91.40)	8 (8.60)	
Gender, No. (%)				
Female	141 (43.52)	118 (83.69)	23 (16.31)	0.3385
Male	183 (56.48)	160 (87.43)	23 (12.57)	
Patient Geographic Region, No. (%)				
East	31 (9.57)	24 (77.42)	7 (22.58)	
Midwest	214 (66.05)	178 (83.18)	36 (16.82)	<0.05
South	≤5 (1.54)	≤5 (≤100)	0	
West	78 (24.07)	≤77 (≤98.72)	≤5 (≤6.41)	
Product Type , No. (%)*				
HMO	249 (76.85)	210 (84.34)	39 (15.66)	0.3922
POS	114 (35.19)	99 (86.84)	15 (13.16)	0.6928
Payer Type, No (%)*				
Commercial	243 (75.00)	202 (83.13)	41 (16.87)	0.0169
Medicare	64 (19.75)	34 (53.13)	30 (46.88)	ns
Self-insured	47 (14.51)	41 (87.23)	6 (12.77)	0.7610
Pharmacy Benefit	267 (82.41)	224 (83.90)	43 (16.10)	0.0333

*Results presented only for SCM Rx counts >5

Rx=dispensed prescription, HMO=health maintenance organization, POS=place of service

Table 3.2. Rate of SCM Use by Clinical Characteristics and Diagnosing Specialty among Patients Tobacco Dependent Patients with Smoking Related Cancer, LifeLink™ Health Plan Claims Database, (July 2010-June 2011)

	Total (N =324)	No Rx for SCM in study period (n=278)	Rx for SCM in study period (n=46)	p-value
Charlson Comorbidity Index (CCI), mean, (SD) in 12 months pre-index	2.82 (3.07)	2.94 (3.13)	2.09 (2.58)	0.0800
Pre-index CCI 0-1, n (%)	120 (37.04)	99 (82.50)	21 (17.50)	0.0848
Pre-index CCI 2-3, n (%)	119 (36.73)	100 (84.03)	19 (15.97)	
Pre-index CCI ≥4, n (%)	85 (26.23)	79 (92.94)	6 (7.06)	
Charlson Comorbidity Index, mean, (SD) during 1 year follow up period	5.08 (3.19)	5.08 (3.18)	5.11 (3.29)	0.9537
CCI follow up 2, n (%)	93 (28.70)	79 (84.95)	14 (15.05)	0.7150
CCI follow up 3-4 , n (%)	91 (56.79)	79 (86.81)	12 (13.19)	
CCI follow up 5-8, n (%)	72 (22.22)	64 (88.89)	8 (11.11)	
CCI follow up 9-14 , n (%)	68 (20.99)	56 (82.35)	12 (17.65)	
Pre-index CCI categories* n=324				
COPD	70 (21.60)	60 (85.71)	10 (14.29)	1.00
Cancer	183 (56.48)	163 (89.07)	20 (10.93)	0.0765
PVD	31 (9.57)	26 (83.87)	5 (16.13)	0.7861
Diagnosing Specialty Type** No. (%)				
General Medicine (GP/FP, Internal Med, NP, Ob/Gyn, Osteopath, PA)	133 (41.05)	106 (79.70)	27 (20.30)	0.0099
Hospital Related Practitioner (surgical, ER, hospital, anesthesia, Orthopedics)	140 (43.21)	128 (91.43)	12 (8.57)	0.0153
Specialist (e.g., cardiologist, pulm,onc, endo, ent, gastro,ID,allergist, nephro, neuro, ophth, optom,phys med, podiatry, psych,rheum,urol)	59 (18.21)	51 (86.44)	8 (13.56)	1.00
Other (DME_HH, PT, RN, SOC_WORK, MHSA_FAC)	12 (3.70)	12 (100)	0	
Prescription with SCM in Study Period No. (%)	46 (14.2%)			
Prescription with SCM both pre-index and post-index No. (%)	10 (0.31%)			

*Results presented only for SCM counts >5

**Multiple specialties diagnosing the patient on the same date possible, Rx=dispensed prescription, HMO=health maintenance organization, POS=place of se rvice, PPO=preferred provider organization, HIV/AIDS=Human immunodeficiency Virus/Acquired Immunodeficiency Syndrome, GP=general practice, FP=family practice, NP=nurse practitioner, Ob/Gyn=obstetrics & gynecology, PA=physician's assistant, ER=emergency room, pulm=pulmonogist, onc=oncologist, endo=endocrine, ENT=ear, nose & throat, gastro=gastroenterologist, ID=infectious disease, nephro=nephrologist, neuro=neurologist, ophth=ophthalmologist, optom=optometrist, phys med= physical medicine, pscych=psychiatrist, rheum=rheumatologist, urol=urologist, DM_HH=durable medical equipment/home health, PT=physical therapist, RN=registered nurse, SOC_WORK=social worker, MHSA_FAC=mental health/substance abuse facility

Table 3.3. Rate of SCM Use by Tumor Type in Patients Diagnosed with Tobacco Dependence, LifeLink™ Health Plan Claims Database (July 2010-June 2011) (n=324)*

	Tumor type	No SCM Rx (n=278)	SCM Rx n=46)	p-value
Any	324 (100)	278 (85.80)	46 (14.20)	0.1116
Bladder	50 (15.43)	43 (86.00)	7 (14.00)	0.9653
Colorectal cancer	59 (18.21)	53 (89.83)	6 (10.17)	0.3270
Head and Neck	50 (15.43)	44 (88.00)	6 (12.00)	0.6283
Kidney	40 (12.35)	34 (85.00)	6 (15.00)	0.8766
Lung	79 (24.38)	62 (78.48)	17 (21.52)	0.0320

*Results presented only for SCM Rx counts >5

Table 3.4. Summary of Logistic Regression Analysis of Predictors of Treatment with SCM in Tobacco Dependent Patients with Smoking Related Cancer: Odds Ratios and 95% Confidence Intervals

Independent variable	Odds Ratio	95% Wald CI	p-value
Age 50-58 years (reference = 20-49 years)	1.810	0.694-4.725	0.2254
Age 59-64 years (reference = 20-49 years)	0.828	0.288 -2.384	0.7272
Age >65 years (reference = 20-49 years)	0.539	0.179 – 1.618	0.2702
Diagnosis by disease specialist, pediatrician, non-physician	0.4670	0.232 – 1.445	0.2415
Diagnosis by hospital related practitioner	0.319	0.149 – 0.686	0.0034
Hosmer- Lemeshow Goodness of Fit Test p = 0.9016			

CI=confidence interval

Figure 3.1. Sample Selection Diagram– Tobacco Dependent Patients with Smoking Related Cancers and Treatment with SCM (January 2009-June 2012)

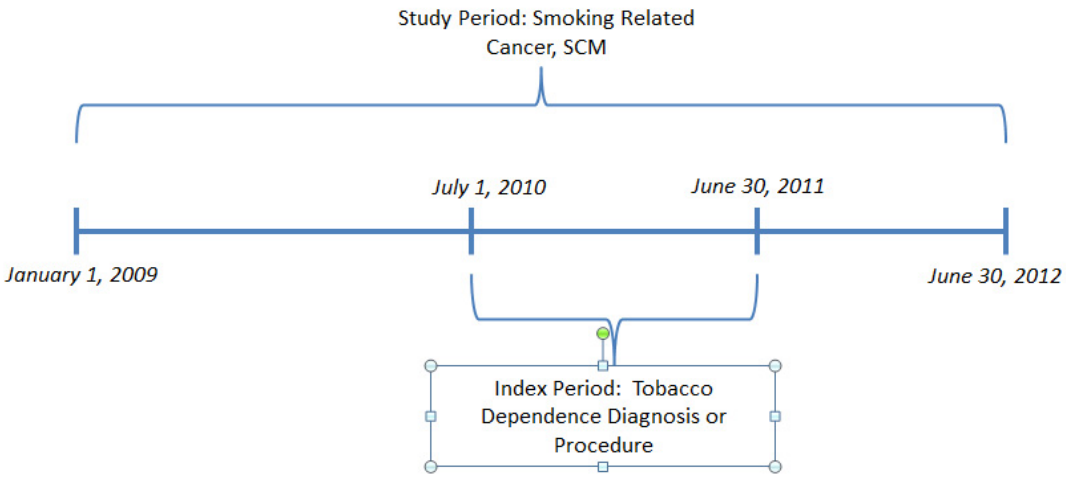

Figure 3.2. Sample Selection Flow– Tobacco Dependent Patients with Smoking Related Cancers and Treatment with SCM (January 2009-June2012)……

<table>
<tr><td colspan="2">LifeLink™ Health Plan Claims Database enrolled patients: N=18,400,000 as of August 2012*</td></tr>
<tr><td colspan="2">Continuously enrolled patients January 2009 – June 2012
Patients aged 16-76 identified as having any tobacco related diagnoses or procedure, SCM or smoking related cancers
n = 117,695</td></tr>
<tr><td colspan="2">Patients identified as having any tobacco related diagnoses or procedures or smoking related cancers (Patient count without smoking cessation treatment)
n=80,486</td></tr>
<tr><td colspan="2">Patients enrolled January 2009 to June 2012 with a diagnosis or procedure indicating tobacco dependence (Patient count without smoking related cancer)
n=77,736</td></tr>
<tr><td colspan="2">Patients with a diagnosis or procedure code indicating tobacco dependence between July 2010 and June 2011 (index)
n=18,619</td></tr>
<tr><td colspan="2">Patients with a diagnosis or procedure code indicating tobacco dependence between July 2010 and June 2011 with claims activity throughout the study period (January 2009 – June 2012)
n=16,417</td></tr>
<tr><td colspan="2">Patients with a diagnosis or procedure indicating tobacco dependence between July 2010 and June 2011 with claims activity throughout the study period (January 2009 - June 2012) and a diagnosis of smoking related cancer (January 2009 - June 2012)
n=324</td></tr>
<tr><td>No Treatment with SCM in pre or post index periods
(January 2009-June 2012)
n = 278</td><td>Treatment with SCM in pre or post index periods
(January 2009-June 2012)
n = 46</td></tr>
<tr><td colspan="2">*Closest estimate for continuously enrolled patients during the study period is 18.4MM patients as of August 2012. Enrollment is subject to change quarterly as updates are received from contributing health plans. Largest changes are typically seen at year beginning when patients may leave a health plan and join another. The data used for this study has been merged into a new larger database called Pharmetrics Plus which includes a larger number of contributing health plans. The database that includes the data used for this study is archived and would require data restoration to determine exact count.</td></tr>
</table>

CONCLUSION

The 3 studies presented herein provide insight into the utility of using administrative claims data to study patients who are tobacco dependent and their treatment with SCM. Taken in their entirety, these studies' findings contribute certain apparent overarching themes and other important observations.

Keeping in mind the stated limitation of 18 month claims history and possibility that patients may have been diagnosed, counseled or treated for tobacco dependence prior to index in these studies, it seems apparent that the health system is identifying - patients as tobacco dependent co-incident with identification of other co-morbidity. This is evident in the first manuscript through the 34% change in CCI from the pre- to the post-index period and in the third study which observed a near doubling of CCI in cancer patients after newly being identified or counseled as tobacco dependent. As stated, early intervention and management of tobacco dependence is likely the best strategy to aid patients in what is likely to be multiple attempts to quit smoking.

The second theme is related to practitioner type diagnosing or counseling patients. Diagnosis or counseling by a hospital related practitioner was associated with reduced likelihood of SCM treatment as an outpatient overall and in patients with

smoking related cancer. Joint Commission core measures include counseling for tobacco dependence in inpatients, but these efforts may not be continued after patients are discharged from the hospital. However, it is not known if patients obtained OTC NRT following discharge or if the important factor of change readiness to embark on a

quit effort was present. Though these variables are not observable in claims data, perhaps identification of patients in this manner could serve as indicators for future follow up after discharge. Similarly, diagnosis by a therapeutic area specialist was associated with lower likelihood of SCM prescription and it has been recognized in the literature that management of tobacco dependence can be a major contributor to risk of events often managed by therapeutic area specialists, e.g., cardiologists and oncologists, and that specialists are in unique position to aid patients in their quit efforts. Management of smoking cessation should not be considered a primary care issue, but an opportunity for intervention at any health care professional interaction.

Another theme is consideration of baseline co-morbidity and relationship to use of SCM. In the first study, use of SCM was low in those with cancer or MI at baseline and patients with cancer diagnosis at baseline had reduced odds of SCM prescription. Interestingly, this finding exists in parallel to the finding of reduced odds of SCM use in patients diagnosed or counseled by therapeutic area specialists. Of note, patients with HIV/AIDS had the highest rates of SCM prescription which is encouraging given the additional risk of smoking in these patients, but generalizability to a routine Medicaid population from these data obtained from commercial health plans must be considered.

The premature discontinuation rate observed in the second study exceeded 90% and studies exist that have varied designs and descriptions of the relationship of duration of therapy and quit outcomes with some studies finding quitting success with shorter durations than 12 weeks and others suggesting that longer durations of SCM therapy yields better quit outcomes. Considering that patients may experience reduced

cravings and nicotine withdrawal symptoms relatively early in SCM therapy, consideration should be given to counseling patients at the outset and throughout therapy regarding their possible perception that they no longer need therapy juxtaposed with information from labeled instructions describing recommended duration of use.

Differences in SCM use by age were also observed with the youngest and oldest patients being less likely to receive SCM prescription and patients over age 50 years having lower likelihood of premature discontinuation. Consideration of differences in readiness to change by patients who may have yet experienced a smoking related comorbidity and in those who may be resistant to changing longstanding behaviors is important. Recent action by the American Academy of Pediatrics suggests consideration of SCM use in younger people depending on their readiness to change and extent of tobacco dependence. Moreover, older patients can still be motivated to change and advanced age should not serve as a barrier to use of SCM.

Lastly, certain factors not studied here are important to consider for future study including combination use of SCM agents, exploration of mental health factors related to tobacco dependence diagnosis or counseling and SCM use and exploration of larger datasets with longer study periods.

APPENDICES

Table A.1.1 Tobacco Dependence Related Diagnosis and Procedure Codes

Diagnosis or Procedure Code	Code and Description
ICD-9	305.1 Tobacco use disorder
	989.84 Toxic effect of other substances, chiefly nonmedicinal as to source, tobacco
	649.0x Tobacco use disorder complicating pregnancy, childbirth, or puerperium
	V1582 History of tobacco use (personal history of tobacco use)
HCPCS/CPT	99406 Smoking and tobacco-use cessation counseling visit; intermediate, greater than 3 minutes up to 10 minutes.
	99407 Smoking and tobacco-use cessation counseling visit; intensive, greater than 10 minutes.
	S9075 Smoking Cessation Treatment
	S9453 Smoking Cessation Classes, non-physician provider, per session
	1032F Current tobacco smoker or currently exposed to secondhand smoke (asthma)
	1033F Current tobacco non-smoker and not currently exposed to secondhand smoke (asthma)
	1034F Tobacco - current smoker
	1035F Current smokeless tobacco user (chew, snuff)
	4000F Tobacco use cessation intervention, counseling
	4001F Tobacco use cessation intervention, pharmacologic therapy
	4004F Patient screened for tobacco use and received tobacco cessation intervention (counseling, pharmacotherapy, or both), if identified as a tobacco user
	C9801 Smoking and tobacco cessation counseling visit for the asymptomatic patient intermediate, greater than 3 minutes, up to 10
	C9802 Smoking and tobacco cessation counseling visit for the asymptomatic patient intensive, greater than 10 minutes
	G0375 Smoking and tobacco use cessation counseling visit; intermediate, greater than 3 minutes up to 10 minutes
	G0376 Smoking and tobacco use cessation counseling visit; intensive, greater than 10 minutes
	G0436 Smoking and tobacco cessation counseling visit for the asymptomatic patient; intermediate, greater than 3 minutes, up to 10 minutes
	G0437 Smoking and tobacco cessation counseling visit for the asymptomatic patient; intensive, greater than 10 minutes
	G8402 Tobacco (smoke) use cessation intervention, counseling
	G8403 Tobacco (smoke) use cessation intervention not counseled
	G8453 Tobacco use cessation intervention, counseling
	G8454 Tobacco use cessation intervention not counseled, reason not specified
	G8455 Current tobacco smoker
	G8456 Current smokeless tobacco user
	G8686 Currently a tobacco smoker or current exposure to secondhand smoke
	G8688 Currently a smokeless tobacco user (eg, chew, snuff) and no exposure to secondhand smoke
	G8690 Current tobacco smoker or current exposure to secondhand smoke

Table A.1.2. Charlson Co-morbidity Index Codes

Co-morbidity	Codes
Chronic pulmonary disease	490.x-496.x, 500.x-505.x, 416.8, 416.9, 506.4, 508.1, 508.8
Diabetes without chronic complications	250.0-250.3
Any malignancy, including lymphoma and leukemia, except neoplasm of skin	140.x-165.x, 170.x-172.x, 174.x-176.x, 179.x, 180.x-195.x, 200.x-208.x
Mild liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7
Peripheral Vascular Disease	440.x, 441.x, 0930, 4373, 443.1, 443.2, 443.8, 443.9, 447.1, 557.1, 557.9, V43.4
Cerebrovascular Disease	430.x-438.x, 362.34
Diabetes with chronic complications	250.4-250.9
Rhuematic Disease	446.5, 710.0-710.4, 714.0- 714.2, 714.8, 725
Congestive Heart Failure	428.x,425.4-425.9, 398.91, 402.91, 402.11, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93
Myocardial infarction	410.x, 412.x
Renal Disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 585.x, 586.x V56.x 583.0-583.2, 583.4, 583.6-583.7, 588.0, V420, V451
Metastatic cancer	196.x-199.x
Hemiplegia or paraplegia	334.1, 342.x, 343.x, 344.0-344.6, 344.9
Peptic ulcer disease	531.x-534.x
Moderate to severe liver disease	456.0-456.2, 572.2-572.4, 572.8
HIV/AIDS	042.x-044.x
Dementia	290.x, 294.1, 331.2

Table A.1.3. Select CCI categories Pre-index and During Follow-up Periods – All diagnosed patients (n=15000), LifeLink™ Health Plan Claims Database (July 2010-June 2011)

CCI Category, No. (%)	During 12 months pre-index only	In 1yr follow up only	Both Pre-index and Follow-up	Difference	p - value
COPD	705 (4.70)	1657 (11.05)	1187 (7.91)	135%	<0.0001
Diabetes	170 (1.13)	412 (2.75)	1130 (7.53)	142%	<0.0001
Cancer	107 (0.71)	314 (2.09)	533 (3.55)	193%	<0.0001
PVD	179 (1.19)	394 (2.63)	226 (1.51)	120%	<0.0001
CVD	183 (1.22)	394 (2.63)	163 (1.09)	115%	<0.0001
CHF	82 (0.55)	215 (1.43)	144 (0.96)	162%	<0.0001
MI	88 (0.59)	235 (1.57)	90 (0.60)	157%	<0.0001
Metastatic cancer	36 (0.24)	108 (0.72)	34 (0.23)	200%	<0.0001

Table A.1.4. Results of Test for Multicollinearity Among Independent Variables Selected for Multivariate Logistic Regression – Predictors of SCM Use in Tobacco Dependent Patients, LifeLink™ Health Plan Claims Database (July 2010-June 2011)

Regression Against Patient Age at Index		
Independent Variable	Variance Inflation Factor	Condition Index
Payer Type Medicare Supplemental	1.072	1.522
Payer Type Medicare Advantage	1.367	1.736
Payer Type Medicaid	1.994	1.774
Payer Type Self-insured	1.665	1.845
Payer Type Commercial	2.669	1.868
Diagnosing Practitioner Type General Medicine	4.399	1.900
Diagnosing Practitioner Type Hospital Related	3.808	1.912
Diagnosing Practitioner Type Pediatrics	1.097	1.922
Diagnosing Practitioner Type Therapeutic Area Specialist	1.971	1.940
Diagnosing Practitioner Type Other	1.161	1.952
CHF diagnosis in 12 months pre-index	1.087	1.992
MI diagnosis in 12 months pre-index	1.065	2.020
Cancer diagnosis in 12 months pre-index	1.025	2.065
Diabetes diagnosis in 12 months pre-index	1.208	2.129
Renal Disease diagnosis in 12 months pre-index	1.215	2.198
Mild liver disease diagnosis in 12 months pre-index	1.068	2.318
HIV-AIDS diagnosis in 12 months pre-index	1.020	2.546
Ulcer diagnosis in 12 months pre-index	1.004	7.550
CHF diagnosis in 12 months pre-index	1.005	13.569

Table A.2.1. Results of Test for Multicollinearity Among Independent Variables Selected for Multivariate Logistic Regression Model – Predictors of Premature SCM Discontinuation

Regression Against Patient Age at Index		
Independent Variable	Variance Inflation Factor	Condition Index
Payer Type Medicare Supplemental	1.205	1.637
Payer Type Medicare Advantage	1.064	1.908
Payer Type Medicaid	2.373	1.951
Payer Type Self-insured	2.187	2.123
Payer Type Commercial	2.559	2.147
Insurance Product HMO	1.630	2.157
Insurance Product PPO	2.420	2.212
Insurance Product POS	1.710	2.270
Insurance Product Consumer Directed	1.028	2.392
Insurance Product Indemnity	1.121	2.460
Diagnosing Practitioner Type General Medicine	3.412	3.198
Diagnosing Practitioner Type Therapeutic Area Specialist	1.817	4.404
Diagnosing Practitioner Type Hospital Related	2.540	6.529
Diagnosing Practitioner Type Pediatrics	1.111	9.487
Diagnosing Practitioner Type Other	1.185	15.514

Table A.2.2. . Results of Test for Multicollinearity Among Independent Variables Selected for Multivariate Logistic Regression Model - Predictors of Repeat Treatment with SCM

Regression Against Patient Age at Index		
Independent Variable	Variance Inflation Factor	Condition Index
Insurance Product HMO	1.444	1.706
Insurance Product PPO	1.084	1.824
Insurance Product POS	1.496	1.837
Insurance Product Consumer Directed	1.022	1.864
Insurance Product Indemnity	1.062	1.887
Diagnosing Practitioner Type General Medicine	3.393	1.956
Diagnosing Practitioner Type Therapeutic Area Specialist	1.784	2.000
Diagnosing Practitioner Type Hospital Related	2.536	2.486
Diagnosing Practitioner Type Pediatrics	1.108	5.586
Diagnosing Practitioner Type Other	1.177	11.413

Table A.3.1. ICD-9 Codes and Descriptions – Smoking Related Cancers

TUMOR TYPE	TUMOR SUB-TYPE	CODE	CODE	DESCRIPTION
Head & Neck Cancer		140	140	Malignant neoplasm of lip
Head & Neck Cancer		1400	140.0	Malignant neoplasm of upper lip, vermilion border
Head & Neck Cancer		1401	140.1	Malignant neoplasm of lower lip, vermilion border
Head & Neck Cancer		1403	140.3	Malignant neoplasm of upper lip, inner aspect
Head & Neck Cancer		1404	140.4	Malignant neoplasm of lower lip, inner aspect
Head & Neck Cancer		1405	140.5	Malignant neoplasm of lip, inner aspect, unspecified as to upper or lower
Head & Neck Cancer		1406	140.6	Malignant neoplasm of commissure of lip
Head & Neck Cancer		1408	140.8	Malignant neoplasm of other sites of lip
Head & Neck Cancer		1409	140.9	Malignant neoplasm of lip, vermilion border, unspecified as to upper or lower
Head & Neck Cancer		141	141	Malignant neoplasm of tongue
Head & Neck Cancer		1410	141.0	Malignant neoplasm of base of tongue
Head & Neck Cancer		1411	141.1	Malignant neoplasm of dorsal surface of tongue
Head & Neck Cancer		1412	141.2	Malignant neoplasm of tip and lateral border of tongue
Head & Neck Cancer		1413	141.3	Malignant neoplasm of ventral surface of tongue
Head & Neck Cancer		1414	141.4	Malignant neoplasm of anterior two-thirds of tongue, part unspecified
Head & Neck Cancer		1415	141.5	Malignant neoplasm of junctional zone of tongue
Head & Neck Cancer		1416	141.6	Malignant neoplasm of lingual tonsil
Head & Neck Cancer		1418	141.8	Malignant neoplasm of other sites of tongue
Head & Neck Cancer		1419	141.9	Malignant neoplasm of tongue, unspecified site
Head & Neck Cancer		143	143	Malignant neoplasm of gum
Head & Neck Cancer		1430	143.0	Malignant neoplasm of upper gum
Head & Neck Cancer		1431	143.1	Malignant neoplasm of lower gum
Head & Neck Cancer		1438	143.8	Malignant neoplasm of other sites of gum
Head & Neck Cancer		1439	143.9	Malignant neoplasm of gum, unspecified site

TUMOR TYPE	TUMOR SUB-TYPE	CODE	CODE	DESCRIPTION
Head & Neck Cancer		144	144	Malignant neoplasm of floor of mouth
Head & Neck Cancer		1440	144.0	Malignant neoplasm of anterior portion of floor of mouth
Head & Neck Cancer		1441	144.1	Malignant neoplasm of lateral portion of floor of mouth
Head & Neck Cancer		1448	144.8	Malignant neoplasm of other sites of floor of mouth
Head & Neck Cancer		1449	144.9	Malignant neoplasm of floor of mouth, part unspecified
Head & Neck Cancer		145	145	Malignant neoplasm of other and unspecified parts of mouth
Head & Neck Cancer		1450	145.0	Malignant neoplasm of cheek mucosa
Head & Neck Cancer		1451	145.1	Malignant neoplasm of vestibule of mouth
Head & Neck Cancer		1452	145.2	Malignant neoplasm of hard palate
Head & Neck Cancer		1453	145.3	Malignant neoplasm of soft palate
Head & Neck Cancer		1454	145.4	Malignant neoplasm of uvula
Head & Neck Cancer		1455	145.5	Malignant neoplasm of palate, unspecified
Head & Neck Cancer		1456	145.6	Malignant neoplasm of retromolar area
Head & Neck Cancer		1458	145.8	Malignant neoplasm of other specified parts of mouth
Head & Neck Cancer		1459	145.9	Malignant neoplasm of mouth, unspecified site
Head & Neck Cancer		146	146	Malignant neoplasm of oropharynx
Head & Neck Cancer		1460	146.0	Malignant neoplasm of tonsil
Head & Neck Cancer		1461	146.1	Malignant neoplasm of tonsillar fossa
Head & Neck Cancer		1462	146.2	Malignant neoplasm of tonsillar pillars (anterior) (posterior)
Head & Neck Cancer		1463	146.3	Malignant neoplasm of vallecula
Head & Neck Cancer		1464	146.4	Malignant neoplasm of anterior aspect of epiglottis
Head & Neck Cancer		1465	146.5	Malignant neoplasm of junctional region of oropharynx
Head & Neck Cancer		1466	146.6	Malignant neoplasm of lateral wall of oropharynx
Head & Neck Cancer		1467	146.7	Malignant neoplasm of

TUMOR TYPE	TUMOR SUB-TYPE	CODE	CODE	DESCRIPTION
				posterior wall of oropharynx
Head & Neck Cancer		1468	146.8	Malignant neoplasm of other specified sites of oropharynx
Head & Neck Cancer		1469	146.9	Malignant neoplasm of oropharynx, unspecified site
Head & Neck Cancer		147	147	Malignant neoplasm of nasopharynx
Head & Neck Cancer		1470	147.0	Malignant neoplasm of superior wall of nasopharynx
Head & Neck Cancer		1471	147.1	Malignant neoplasm of posterior wall of nasopharynx
Head & Neck Cancer		1472	147.2	Malignant neoplasm of lateral wall of nasopharynx
Head & Neck Cancer		1473	147.3	Malignant neoplasm of anterior wall of nasopharynx
Head & Neck Cancer		1478	147.8	Malignant neoplasm of other specified sites of nasopharynx
Head & Neck Cancer		1479	147.9	Malignant neoplasm of nasopharynx, unspecified site
Head & Neck Cancer		148	148	Malignant neoplasm of hypopharynx
Head & Neck Cancer		1480	148.0	Malignant neoplasm of postcricoid region of hypopharynx
Head & Neck Cancer		1481	148.1	Malignant neoplasm of pyriform sinus
Head & Neck Cancer		1482	148.2	Malignant neoplasm of aryepiglottic fold, hypopharyngeal aspect
Head & Neck Cancer		1483	148.3	Malignant neoplasm of posterior hypopharyngeal wall
Head & Neck Cancer		1488	148.8	Malignant neoplasm of other specified sites of hypopharynx
Head & Neck Cancer		1489	148.9	Malignant neoplasm of hypopharynx, unspecified site
Head & Neck Cancer		149	149	Malignant neoplasm of other and ill-defined sites within the lip, oral cavity, and pharynx
Head & Neck Cancer		1490	149.0	Malignant neoplasm of pharynx, unspecified
Head & Neck Cancer		1491	149.1	Malignant neoplasm of Waldeyer's ring
Head & Neck Cancer		1498	149.8	Malignant neoplasm of

TUMOR TYPE	TUMOR SUB-TYPE	CODE	CODE	DESCRIPTION
				other sites within the lip and oral cavity
Head & Neck Cancer		1499	149.9	Malignant neoplasm of ill-defined sites of lip and oral cavity
Gastrointestinal Cancers; Other	Esophageal Cancer	150	150	Malignant neoplasm of esophagus
Gastrointestinal Cancers; Other	Esophageal Cancer	1500	150.0	Malignant neoplasm of cervical esophagus
Gastrointestinal Cancers; Other	Esophageal Cancer	1501	150.1	Malignant neoplasm of thoracic esophagus
Gastrointestinal Cancers; Other	Esophageal Cancer	1502	150.2	Malignant neoplasm of abdominal esophagus
Gastrointestinal Cancers; Other	Esophageal Cancer	1503	150.3	Malignant neoplasm of upper third of esophagus
Gastrointestinal Cancers; Other	Esophageal Cancer	1504	150.4	Malignant neoplasm of middle third of esophagus
Gastrointestinal Cancers; Other	Esophageal Cancer	1505	150.5	Malignant neoplasm of lower third of esophagus
Gastrointestinal Cancers; Other	Esophageal Cancer	1508	150.8	Malignant neoplasm of other specified part of esophagus
Gastrointestinal Cancers; Other	Esophageal Cancer	1509	150.9	Malignant neoplasm of esophagus, unspecified site
Gastrointestinal Cancers; Other	Stomach Cancer	151	151	Malignant neoplasm of stomach
Gastrointestinal Cancers; Other	Stomach Cancer	1513	151.3	Malignant neoplasm of fundus of stomach
Gastrointestinal Cancers; Other	Stomach Cancer	1514	151.4	Malignant neoplasm of body of stomach
Gastrointestinal Cancers; Other	Stomach Cancer	1515	151.5	Malignant neoplasm of lesser curvature of stomach, unspecified
Gastrointestinal Cancers; Other	Stomach Cancer	1516	151.6	Malignant neoplasm of greater curvature of stomach, unspecified
Gastrointestinal Cancers; Other	Stomach Cancer	1518	151.8	Malignant neoplasm of other specified sites of stomach
Gastrointestinal Cancers; Other	Stomach Cancer	1519	151.9	Malignant neoplasm of stomach, unspecified site
Colorectal Cancer (CRC)		153	153	Malignant neoplasm of colon
Colorectal Cancer (CRC)		1530	153.0	Malignant neoplasm of hepatic flexure
Colorectal Cancer (CRC)		1531	153.1	Malignant neoplasm of transverse colon
Colorectal Cancer (CRC)		1532	153.2	Malignant neoplasm of descending colon
Colorectal Cancer (CRC)		1533	153.3	Malignant neoplasm of sigmoid colon
Colorectal Cancer (CRC)		1534	153.4	Malignant neoplasm of cecum

TUMOR TYPE	TUMOR SUB-TYPE	CODE	CODE	DESCRIPTION
Colorectal Cancer (CRC)		1535	153.5	Malignant neoplasm of appendix
Colorectal Cancer (CRC)		1536	153.6	Malignant neoplasm of ascending colon
Colorectal Cancer (CRC)		1537	153.7	Malignant neoplasm of splenic flexure
Colorectal Cancer (CRC)		1538	153.8	Malignant neoplasm of other specified sites of large intestine
Colorectal Cancer (CRC)		1539	153.9	Malignant neoplasm of colon, unspecified site
Colorectal Cancer (CRC)		154	154	Malignant neoplasm of rectum, rectosigmoid junction, and anus
Colorectal Cancer (CRC)		1540	154.0	Malignant neoplasm of rectosigmoid junction
Colorectal Cancer (CRC)		1541	154.1	Malignant neoplasm of rectum
Colorectal Cancer (CRC)		1548	154.8	Malignant neoplasm of other sites of rectum, rectosigmoid junction, and anus
Pancreatic Cancer		157	157	Malignant neoplasm of pancreas
Pancreatic Cancer		1570	157.0	Malignant neoplasm of head of pancreas
Pancreatic Cancer		1571	157.1	Malignant neoplasm of body of pancreas
Pancreatic Cancer		1572	157.2	Malignant neoplasm of tail of pancreas
Pancreatic Cancer		1573	157.3	Malignant neoplasm of pancreatic duct
Pancreatic Cancer		1574	157.4	Malignant neoplasm of islets of Langerhans
Pancreatic Cancer		1578	157.8	Malignant neoplasm of other specified sites of pancreas
Pancreatic Cancer		1579	157.9	Malignant neoplasm of pancreas, part unspecified
Head & Neck Cancer		160	160	Malignant neoplasm of nasal cavities, middle ear, and accessory sinuses
Head & Neck Cancer		1600	160.0	Malignant neoplasm of nasal cavities
Head & Neck Cancer		1601	160.1	Malignant neoplasm of auditory tube, middle ear, and mastoid air cells
Head & Neck Cancer		1602	160.2	Malignant neoplasm of maxillary sinus
Head & Neck Cancer		1603	160.3	Malignant neoplasm of ethmoidal sinus
Head & Neck Cancer		1604	160.4	Malignant neoplasm of frontal sinus

TUMOR TYPE	TUMOR SUB-TYPE	CODE	CODE	DESCRIPTION
Head & Neck Cancer		1605	160.5	Malignant neoplasm of sphenoidal sinus
Head & Neck Cancer		1608	160.8	Malignant neoplasm of other sites of nasal cavities, middle ear, and accessory sinuses
Head & Neck Cancer		1609	160.9	Malignant neoplasm of site of nasal cavities, middle ear, and accessory sinus, unspecified site
Head & Neck Cancer		161	161	Malignant neoplasm of larynx
Head & Neck Cancer		1610	161.0	Malignant neoplasm of glottis
Head & Neck Cancer		1611	161.1	Malignant neoplasm of supraglottis
Head & Neck Cancer		1612	161.2	Malignant neoplasm of subglottis
Head & Neck Cancer		1613	161.3	Malignant neoplasm of laryngeal cartilages
Head & Neck Cancer		1618	161.8	Malignant neoplasm of other specified sites of larynx
Head & Neck Cancer		1619	161.9	Malignant neoplasm of larynx, unspecified site
Lung Cancer		162	162	Malignant neoplasm of trachea, bronchus, and lung
Lung Cancer		1620	162.0	Malignant neoplasm of trachea
Lung Cancer		1622	162.2	Malignant neoplasm of main bronchus
Lung Cancer		1623	162.3	Malignant neoplasm of upper lobe, bronchus, or lung
Lung Cancer		1624	162.4	Malignant neoplasm of middle lobe, bronchus, or lung
Lung Cancer		1625	162.5	Malignant neoplasm of lower lobe, bronchus, or lung
Lung Cancer		1628	162.8	Malignant neoplasm of other parts of bronchus or lung
Lung Cancer		1629	162.9	Malignant neoplasm of bronchus and lung, unspecified site
Malignant Neoplasms, Other		163	163	Malignant neoplasm of pleura
Malignant Neoplasms, Other		1630	163.0	Malignant neoplasm of parietal pleura
Malignant Neoplasms, Other		1631	163.1	Malignant neoplasm of visceral pleura
Malignant Neoplasms, Other		1638	163.8	Malignant neoplasm of

TUMOR TYPE	TUMOR SUB-TYPE	CODE	CODE	DESCRIPTION
				other specified sites of pleura
Malignant Neoplasms, Other		1639	163.9	Malignant neoplasm of pleura, unspecified site
Malignant Melanoma		1720	172.0	Malignant melanoma of skin of lip
Basal Cell Carcinoma		17301	173.01	Basal Cell Carcinoma Of Skin Of Lip
Gynecological Cancer	Cervical Cancer	180	180	Malignant neoplasm of cervix uteri
Gynecological Cancer	Cervical Cancer	1800	180.0	Malignant neoplasm of endocervix
Gynecological Cancer	Cervical Cancer	1801	180.1	Malignant neoplasm of exocervix
Gynecological Cancer	Cervical Cancer	1808	180.8	Malignant neoplasm of other specified sites of cervix
Gynecological Cancer	Cervical Cancer	1809	180.9	Malignant neoplasm of cervix uteri, unspecified site
Ovarian Cancer		183	183	Malignant neoplasm of ovary and other uterine adnexa
Ovarian Cancer		1830	183.0	Malignant neoplasm of ovary
Gynecological Cancer		1838	183.8	Malignant neoplasm of other specified sites of uterine adnexa
Gynecological Cancer		1839	183.9	Malignant neoplasm of uterine adnexa, unspecified site
Bladder Cancer		188	188	Malignant neoplasm of bladder
Bladder Cancer		1880	188.0	Malignant neoplasm of trigone of urinary bladder
Bladder Cancer		1881	188.1	Malignant neoplasm of dome of urinary bladder
Bladder Cancer		1882	188.2	Malignant neoplasm of lateral wall of urinary bladder
Bladder Cancer		1883	188.3	Malignant neoplasm of anterior wall of urinary bladder
Bladder Cancer		1884	188.4	Malignant neoplasm of posterior wall of urinary bladder
Bladder Cancer		1885	188.5	Malignant neoplasm of bladder neck
Bladder Cancer		1886	188.6	Malignant neoplasm of ureteric orifice
Bladder Cancer		1887	188.7	Malignant neoplasm of urachus
Bladder Cancer		1888	188.8	Malignant neoplasm of other specified sites of

TUMOR TYPE	TUMOR SUB-TYPE	CODE	CODE	DESCRIPTION
				bladder
Bladder Cancer		1889	188.9	Malignant neoplasm of bladder, part unspecified
Kidney Cancer, Other		189	189	Malignant neoplasm of kidney and other and unspecified urinary organs
Renal Cancer		1890	189.0	Malignant neoplasm of kidney, except pelvis
Kidney Cancer, Other		1891	189.1	Malignant neoplasm of renal pelvis
Kidney Cancer, Other		1892	189.2	Malignant neoplasm of ureter
Genitourinary Cancer		1893	189.3	Malignant neoplasm of urethra
Genitourinary Cancer		1894	189.4	Malignant neoplasm of paraurethral glands
Genitourinary Cancer		1898	189.8	Malignant neoplasm of other specified sites of urinary organs
Genitourinary Cancer		1899	189.9	Malignant neoplasm of urinary organ, site unspecified
Leukemia	Acute Myeloid Leukemia (AML)	2050	205.0	Acute myeloid leukemia
Leukemia	Acute Myeloid Leukemia (AML)	20500	205.00	Acute myeloid leukemia without mention of remission
Leukemia	Acute Myeloid Leukemia (AML)	20501	205.01	Acute myeloid leukemia in remission
Leukemia	Acute Myeloid Leukemia (AML)	20502	205.02	Acute myeloid leukemia, in relapse
Endocrine Cancer		20921	209.21	Malignant carcinoid tumor of the bronchus and lung
Endocrine Cancer	Stomach Cancer	20923	209.23	Malignant carcinoid tumor of the stomach
Endocrine Cancer		20924	209.24	Malignant carcinoid tumor of the kidney

Table A.3.2. Results of Test for Multicollinearity Among Independent Variables Selected for Multivariate Logistic Regression – Predictors of SCM Use in Tobacco Dependent Patients with Smoking Related Cancer

Regression Against Patient Age at Index		
Independent Variable	Variance Inflation Factor	Condition Index
Charlson Co-morbidity Index Score in 12 months pre-index	1.067	1.889
Insurance Product HMO	1.136	1.991
Payer Type Commercial	2.896	2.111
Payer Type Medicaid	1.747	2.188
Payer Type Medicare Supplemental	1.187	2.321
Payer Type Medicare Advantage	1.960	2.665
Payer Type Self-insured	1.859	2.754
Diagnosing Practitioner Type Hospital Related	3.581	3.177
Diagnosing Practitioner Type General Medicine	3.632	5.247
Diagnosing Practitioner Type Therapeutic Area Specialist	2.254	7.809
Diagnosing Practitioner Type Other	1.400	14.917

BIBLIOGRAPHY

Aboyans V, Pinet P, Lacroix P, & Laskar M. Knowledge and management of smoking-cessation strategies among cardiologists in France: a nationwide survey. *Archives of Cardiovascular Disease.* 2009 102(3): 193-199.

Alpert HR, Connolly GN, Biener L. A prospective cohort study challenging the effectiveness of population-based medical intervention for smoking cessation. *Tobacco Control.* 2013*;* 22(1): 32-37.

Balmford J, Borland R, Hammond D, Cummings KM. Adherence to and reasons for premature discontinuation from stop-smoking medications: data from the ITC Four-Country Survey. *Nicotine and Tobacco Research.* 2011; 13(2): 94-102.

Benefits of quitting over time. Available at: http://www.cancer.org/healthy/stayawayfromtobacco/benefits-of-quitting-smoking-over-time. Accessed August 31. 2015, 2015.

Bernstein, SL, Yu, S, Post LA, Dziura J, Rigotti NA. Undertreatment of Tobacco Use Relative to Other Chronic Conditions. *American Journal of Public Health.* 2013; 103(8).

Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for U.S. adults: National Health Interview Survey, 2012. National Center for Health Statistics. *Vital Health Statistics.* 2014; 10(260): 1-161.

Burkhalter JE, Springer CM, Chhabra R, Ostroff JS, Rapkin BD. Tobacco use and readiness to quit smoking in low-income HIV-infected persons. *Nicotine and Tobacco Research.* 2005*; 7*(4): 511-522.

Chantix® (US Prescribing Information, October 2014). Pfizer Inc, New York, NY, 10017.

Carter BD, Abnet CC, Feskanich D, Freedman ND, Hartge P, Lewis CE, Ockene JK, Prentice RL, Speizer FE, Thun MJ, Jacobs EJ. Smoking and mortality — Beyond established causes. *New England Journal of Medicine.* 2015*;* 372(7): 631-640.

Cawkwell, P, Blaum, C, Sherman, S. Pharmacological smoking cessation therapies in older adults: A review of the evidence. *Drugs & Aging.* 2015; 32(6): 443-451.

Cosci, F., Corlando, A., Fornai, E., Pistelli, F., Paoletti, P., & Carrozzi, L. (2009). Nicotine dependence, psychological distress and personality traits as possible predictors of smoking cessation. Results of a double-blind study with nicotine patch. *Addictive Behaviors.* 2009; *34*(1): 28-35.

Ellerbeck EF, Mahnken JD, Cupertino AP, Cox, LS, Greiner, KA, Mussulman, LM, Nazir N, Shireman TI, Resnicow K, Ahluwalia, JS. (2009). Effect of varying levels of disease management on smoking cessation: a randomized trial. *Annals of Internal Medicine. 2009; 150*(7): 437-446.

Health Insurance Coverage of the Total Population. The Henry J. Kaiser Family Foundation, 2014.

Fiore MC, Jaen CR, Baker TB, et al. *Treating Tobacco Use and Dependence: 2008 Update.* Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. May 2008.

Gonzales D, Rennard SI, Nides M, Oncken, C, Azoulay S, Billing CB, Watsky EJ, Gong J, Williams KE, Reeves K R, Varenicline Phase 3. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA: Journal of the American Medical Association.* 2006 *296*(1): 47-55.

Gritz ER, Vidrine DJ, Lazev AB, Amick BC 3rd, Arduino RC. Smoking behavior in a low-income multiethnic HIV/AIDS population. *Nicotine and Tobacco Research.* 2004; 6(1): 71-77.

Hajjeh RA, Conn LA, Stephens DS, Baughman W, Hamill R., Graviss E, Pappas PG, Reingold TC, Rothrock G, Hutwagner LC, Schuchat A, Brandt ME, Pinner, R. W. Cryptococcosis: population-based multistate active surveillance and risk factors in human immunodeficiency virus-infected persons. Cryptococcal Active Surveillance Group. *Journal of Infectious Disease.* 1999; 179(2): 449-454.

Han ES, Foulds J, Steinberg MB, Gandhi KK, West B, Richardson DL, Zelenetz S, Dasika, J. (2006). Characteristics and smoking cessation outcomes of patients returning for repeat tobacco dependence treatment. *International Journal of Clinical Practice.* 2006*; 60*(9):1068-1074.

Huang Y, Britton J, Hubbard R, Lewis S. Who receives prescriptions for smoking cessation medications? An association rule mining analysis using a large primary care database. *Tobacco Control. 2013; 22*(4): 274-279.

Humfleet GL, Hall SM, Delucchi KL, Dilley JW. A randomized clinical trial of smoking cessation treatments provided in HIV clinical care settings. *Nicotine and Tobacco Research. 2013; 15*(8): 1436-1445.

Jamal AHD, O'Connor E, Babb SD, Caraballo RS, Singh T, Hu S, King BA. Current cigarette smoking among adults-United States, 2005-2014. *MMWR: Morbidity and Mortality Weekly Report. 2015; 64*(44): 1233-1240.

Janjigian YY, McDonnell K, Kris MG, Shen R, Sima CS, Bach PB, Rizvi NA, Riely GJ. Pack-years of cigarette smoking as a prognostic factor in patients with stage IIIB/IV nonsmall cell lung cancer. *Cancer. 2010; 116*(3): 670-675.

Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, Anderson RN, McAfee T, Peto R. 21st-Century Hazards of Smoking and Benefits o Cessation in the United States. *New England Journal of Medicine.* 2013*; 368*(4): 341-350.

Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, Billing CB, Gong J, Reeves, KR, Varenicline Phase 3 Study Group. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA: Journal of the American Medical Association.* 2006; *296*(1): 56-63.

Kozlowski LT, Giovino GA, Edwards B, Difranza J, Foulds J, Hurt R, Niaura R, Sachs DP, Dollar KM, Bowen D, Cummings KM, Counts M, Fox B, Sweanor D, Ahern F. Advice on using over-the-counter nicotine replacement therapy-patch, gum, or lozenge-to quit smoking. *Addictive Behaviors* 2007*; 32*(10): 2140-2150.

Land T, Warner D, Paskowsky M, Cammaerts A, Wetherell L, Kaufmann R, Lei Z, Malarcher A, Pechacek T, Keithly L. (2010). Medicaid coverage for tobacco dependence treatments in Massachusetts and associated decreases in smoking prevalence. *PLoS ONE.* 2010*; 5*(3): e9770.

Lee JH, Jones PG, Bybee K, O'Keefe JH. 08). A longer course of varenicline therapy improves smoking cessation rates. *Preventive Cardiology* 2008; 11(4): 210-214.

Make B, Dutro MP, Paulose-Ram R, Marton JP, Mapel DW. Undertreatment of COPD: a retrospective analysis of US managed care and Medicare patients. *International Journal of Chronic Obstructive Pulmonary Disease.* 2012 (7): 1-9.

Mamary EM, Bahrs D, Martinez S. Cigarette smoking and the desire to quit among individuals living with HIV. *AIDS Patient Care and STDS.* 2002*,* 16(1): 39-42.

Mohiuddin SM, Mooss AN, Hunter CB, Grollmes TL, Cloutier DA, Hilleman DE. Intensive smoking cessation intervention reduces mortality in high-risk smokers with cardiovascular disease. *Chest.* 2007 131(2): 446-452.

Morgan G, Schnoll RA, Alfano CM, Evans SE, Goldstein A, Ostroff J, Park ER, Sarna L, Cox LS. National cancer institute conference on treating tobacco dependence at cancer centers. *Journal of Oncology Practice.* 2011 *7*(3): 178-182.

Motheral B, Brooks J, Clark MA, Crown WH, Davey P, Hutchins D, Martin BC, Stang, P. A checklist for retrospective database studies--report of the ISPOR Task Force on Retrospective Databases. *Value in Health.* 2003 *6*(2): 90-97.

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology, Smoking Cessation v1.2015. Available at www.nccn.org. Accessed August 7, 2015.

Niaura R, Shadel WG, Morrow K, Tashima K, Flanigan T, Abrams DB. Human immunodeficiency virus infection, AIDS, and smoking cessation: the time is now. *Clinical Infectious Disease.* 2000; *31*(3): 808-812.

Nuorti JP, Butler JC, Gelling L, Kool JL, Reingold AL,Vugia DJ. Epidemiologic relation between HIV and invasive pneumococcal disease in San Francisco County, California. *Annals of Internal Medicine.* 2000 132 (3): 182-190.

Parsons A, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. *BMJ: British Medical Journal.* 2010; 340: b5569.

Quality Oncology Practice Initiative (QOPI®) and the QOPI Certification Program (QCP™) 2012. Available at: http://www.instituteforquality.org/qopi-qcp Accessed: August 7 2015.

Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali, WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical Care.* 2005*;* 43(11): 1130-1139.

Rigotti NA, Clair C. Managing tobacco use: the neglected cardiovascular disease risk factor. *European Heart Journal.* 2013; 34(42): 3259-3267.

Rigotti NA, Clair C, Munafo MR, Stead LF. Interventions for smoking cessation in hospitalised patients. *Cochrane Database Systematic Reviews*. 2012; May 16;5.

Schnoll RA, Goelz PM, Veluz-Wilkins A, Blazekovic S, Powers L, Leone FT, Gariti P, Wiley EP, Hitsman, B. Long-term nicotine replacement therapy: a randomized clinical trial. *JAMA Internal Medicine.* 2015;175(4): 504-511.

Shi Y, Warner DO. Surgery as a teachable moment for smoking cessation. *The Journal of the American Society of Anesthesiologists.* 2010; 112(1), 102-107.

Shiffman S, Brockwell SE, Pillitteri JL, Gitchell JG. Individual differences in adoption of treatment for smoking cessation: demographic and smoking history characteristics. *Drug and Alcohol Dependence.* 2008*; 93*(1-2): 121-131.

Shiffman S, Brockwell SE, Pillitteri JL, Gitchell JG. Use of smoking-cessation treatments in the United States. *American Journal of Preventive Medicine.* 2008; 34(2): 102-111.

Shiffman S, Sweeney CT, Ferguson SG, Sembower MA, Gitchell JG. Relationship between adherence to daily nicotine patch use and treatment efficacy: secondary

analysis of a 10-week randomized, double-blind, placebo-controlled clinical trial simulating over-the-counter use in adult smokers. *Clinical Therapeutics.* 2008; 30(10): 1852-1858.

Siahpush M, Shaikh RA, McCarthy M, Sikora Kessler A, Tibbits M, Singh GK. Association between duration of use of pharmacotherapy and smoking cessation: findings from a national survey. *BMJ Open.* 2015; Jan 13;*5*(1).

Siegel RL, Jacobs EJ, Newton CC, Feskanich D, Freedman ND, Prentice RL, Ahmedin J. Deaths due to cigarette smoking for 12 smoking-related cancers in the united states. *JAMA Internal Medicine*. 2015; 175 (9): 1574-1576.

Singleterry J, Lancet E, Babb S, MacNeil A, Zhang L. State Medicaid coverage for tobacco cessation treatments and barriers to coverage — United States, 2008–2014. *MMWR: Morbidity and Mortality Weekly Report.* 2014; 63 (12): 264-265.

Steliga MA, Dresler C. Clinical practice and the tobacco epidemic: relevance of a global public health problem in the clinical setting. *Expert Review of Anticancer Therapy*. 2010;10(10): 1513-1515.

Tonstad S, Tonnesen P, Hajek P, Williams KE, Billing CB, Reeves KR. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA: Journal of the American Medical Association*. 2006; *296*(1): 64-71.

Warren GW, Marshall JR, Cummings KM, Toll B, Gritz ER, Hutson, A, Dibaj S, Herbst R, Dresler, C, IASLC Tobacco Control and Smoking Cessation Committee. Practice patterns and perceptions of thoracic oncology providers on tobacco use and cessation in cancer patients. *Journal of Thoracic Oncology.* 2013 8(5): 543-548.

Warren GW, Marshall JR, Cummings KM, Zevon MA, Reed R, Hysert P, Mahoney MC, Hyland AJ, Chukwumere N, Demmy T, Dexter E, Kelly M, O'Connor RJ, Houstin T, Jenkins D, Germain P, Singh AK, Epstein J, Dobson Amato KA, Reid ME. Automated tobacco assessment and cessation support for cancer patients. *Cancer.* 2014; 120 (4): 562-569.

West R, Baker CL, Cappelleri JC, Bushmakin AG. Effect of varenicline and bupropion SR on craving, nicotine withdrawal symptoms, and rewarding effects of smoking during a quit attempt. *Psychopharmacology.* 2008;*197*(3): 371-377.

Wiley LK, Shah A, Xu H, Bush WS. ICD-9 tobacco use codes are effective identifiers of smoking status. *JAMIA: Journal of the American Medical Informatics Association.* 2013; 20(4): 652-658.

Zeng F, Chen CI, Mastey V, Zou KH, Harnett J, Patel BV. Utilization management for smoking cessation pharmacotherapy: varenicline rejected claims analysis. *The American Journal of Managed Care.* 2010; 16(9): 667-674.

Zeng F, Chen CI, Mastey V, Zou KH, Harnett J, Patel BV. Effects of copayment on initiation of smoking cessation pharmacotherapy: An analysis of varenicline reversed claims. *Clinical Therapeutics.* 2011, 33(2): 225-234

Zhang B, Cohen JE, Bondy SJ, Selby P. Duration of nicotine replacement therapy use and smoking cessation: a population-based longitudinal study. *American Journal of Epidemiology. 2015;* 181(7):513-520.